Synthetic and Structural Studies on the Novel Formation of Bicyclo[\textit{n.2.0}]alkan-1-ols

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Submitted in fulfillment of the requirements of the Degree of Doctor of Philosophy

September 2003
Statement of Originality

This work has not previously been submitted for a degree or diploma in any university.

To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

Michelle M'Cleary BSc(Hons)
Preface

Unless otherwise stated the results in this thesis are those of the author. Parts of this work have appeared elsewhere. Refereed Journal Publications are submitted with the dissertation and are presented in Appendix Two.

Refereed Journal Publications


Conference Posters

*The Structure of Fused Bicyclo Ring Systems via a Novel Cyclisation Process*

*The Generation of Fused Bicyclo Ring Systems via a Novel Cyclisation Process: A Scope and Selectivity Study*
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List of Supplementary Material

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CD-ROM (1)

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<td>Heteronuclear Single Quantum Correlation</td>
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<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
</tbody>
</table>
sec  second

T  triplet

TBDMSCI  \textit{tert}-butyldimethylsilyl chloride

TBDMSO\textsubscript{TF}  \textit{tert}-butyldimethylsilyl trifluoromethanesufonate

\textit{tert}-  tertiary

THF  tetrahydrofuran

T.L.C  thin-layer chromatography

TMSI  trimethylsilyl iodide

(TMS)\textsubscript{2}NH  1,1,1,3,3,3-hexamethyldisilizane

TMSO\textsubscript{TF}  trimethylsilylmethyl trifluoromethanesufonate

Tol  tolyl

Ts  tosyl

\(\delta\)  chemical shift

\(\Delta\)  heat

\(\nu_{\text{max}}\)  Infrared absorbance maximum

\(\%\)  percent

\(\lambda\)  wavelength
Acknowledgements

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Abstract

Reaction of phenyl vinyl sulfoxide with the lithium enolates of simple ketones of varying ring size (cyclopentanone, cycloheptanone and cyclooctanone) under controlled cyclisation conditions followed by subsequent oxidation resulted in the formation of the bicyclo[\(n.2.0\)]alkan-1-ols 253-255, 262, 263, 265, 268 and 269 in conjunction with alkylated species 256, 257, 264, 266 and 267. The ratio of bicyclo[\(n.2.0\)]alkan-1-ols to alkylated ketone formation observed was dependent on a number of factors including the variation of enolate reactivity between the different ring sizes, conversion of phenyl vinyl sulfoxide, time, temperature and concentration of reaction and the stability and steric strain observed in the final bicyclo[\(n.2.0\)]alkan-1-ol product. X-ray crystal structures of 253, 262 and 265 were obtained and a structural study showed that as the overall steric strain in the bicyclo[\(n.2.0\)]alkan-1-ol product is decreased there is a corresponding increase in product distribution in favour of bicyclo[\(n.2.0\)]alkan-1-ol formation in conjunction with increased yields.

Selected substituted and functionalised ketones (2-methylcyclopentanone, 2,6-dimethylecyclohexanone, 2-methylcyclohexanone and 1,4-cyclohexanedione monoethylene ketal) also reacted in the cyclisation reaction to give bicyclo[\(n.2.0\)]alkan-1-ols 270, 271, 277, 278, 281, 282, 285 and 286 in conjunction with alkylated products 272, 279, 280, 283, 284 and 287. Incorporation of substitution at the bridgehead and C2 position had a role in the preference of the major stereochemical isomer observed for a bicyclo[\(n.2.0\)]alkan-1-ol (\(n = 3, 4\)). A structural comparison of the X-ray crystal structures of 278, 281 and 286 indicated that the pseudo chair conformation of the six-membered ring influenced ring torsion and bond angles in the bicyclo[4.2.0]octanol ring system. Two model studies were selected to illustrate the potential application of the cyclisation process as methodology towards natural product synthesis or complex ring
systems. No bicyclo[2.2.0]alkan-1-ol formation was evident in an intramolecular example using the starting ketone 291 in which the electrophile is tethered to the ketone. 2,6-Dimethyl-2-cyclohexen-1-one 301 considered as a model study towards the synthesis of the antibiotic mellolide, upon reaction with phenyl vinyl sulfoxide and oxidation displayed poor reactivity. The novel bicyclo[2.2.2]octanones 303, 304 and 305 were formed in very low yields. The lack of reactivity of the ketones 2,6-dimethyl-2-cyclohexen-1-one, 1,2-cyclohexanedione and 1,4-cyclohexanedione towards bicyclo[2.2.0]alkan-1-ol formation suggested that conjugation in the enolate prior to reaction with phenyl vinyl sulfoxide was not favourable. The non-reactivity of these ketones and the hindered ketone camphor indicated the potential limitations to the cyclisation methodology. However, conversion of the ketal functionality of 286 to a ketone resulted in the formation of the functionalised bicyclo[4.2.0]octanol 288 providing positive indications for further synthetic applications.
**Introduction**

Bicyclo[n.2.0]alkanols possessing a bridgehead hydroxy group, such as the parent compounds 1-4 are contained within a variety of natural products. These structures pose as key components in synthetic pathways and are components of solvolysis, mechanism and structural studies. In addition, synthetic and natural compounds containing a bicyclo[n.2.0]alkanol moiety are found within classes of compounds which exhibit biological activity. Synthetic access to such diverse compounds is challenged by the structural complexity of carbocyclic frameworks that include the bicyclo[n.2.0]alkanol moiety. Herein approaches to the formation of four membered rings and the formation of bicyclo[n.2.0]alkanols within the context of multifunctional compounds will be presented. This will form the introduction to the novel synthetic approach to bicyclo[n.2.0]alkanols presented in this dissertation.

Current methodologies for obtaining four membered rings or cyclobutanes predominantly rely on thermal or photochemical [2+2] cycloaddition reactions. As cycloadditions have been reviewed elsewhere a précis of [2+2] cycloadditions using examples incorporating cyclobutanol formation wherever possible will be discussed here. [2+2] Cycloadditions can occur by three pathways; a concerted pathway (mechanism A), the dimerisations of alkenes via 1,4-diradicals (mechanism B) or via zwitterionic intermediates (mechanism C) (scheme 1). These will be briefly discussed.
Mechanism A

Mechanism B

Mechanism C

Scheme 1

1.0 Photochemical Cycloadditions

Photochemical [2+2] cycloaddition reactions of alkenes to yield cyclobutanes potentially offer the advantage of the formation of two new carbon-carbon bonds and the generation of a maximum of four new stereocenters. Cyclobutane adducts are believed to arise from excitation of the alkene to a short lived singlet $A^*$, followed by crossing to a longer-lived triplet $A^*$ which forms eventually a triplet diradical then singlet diradical which closes to the cyclobutane. However, aspects of the mechanism of photochemical [2+2] cycloaddition still are not well understood. Photochemical cycloadditions can occur via inter or intramolecular processes with varying degrees of regiochemical and stereochemical control due to steric and electronic effects in the reactants as well as factors such as solvent polarity and temperature of the reaction.

1.1 Intermolecular Photocycloadditions

Use of unsymmetrical alkenes in [2+2] cycloadditions gives rise to regiochemical issues. Two regiochemical isomers are often observed when unsymmetrical alkenes undergo [2+2] photocycloaddition, the head-to-head or the head-to-tail isomers. For example, both the head-to-tail and head-to-head regioisomers, 5 and 6 respectively, are formed when cyclohexenone is irradiated in the presence of isobutylene (scheme 2).
The formation of the preferred head-to-tail isomer is accounted for by favourable electronic interactions.

\[ \text{Scheme 2} \]

Steric interactions can also have an influential role on the outcome of regioselectivity. For example, cyclohexenone 7 reacts with vinyl acetate 8 to exclusively yield the head-to-tail regioisomer 10, whereas reaction with the substituted vinyl acetate 9 yields a 1:4 mixture of regioisomers 11 and 12 (scheme 3).

\[ \text{Scheme 3} \]

Both solvent polarity and temperature can be altered to bring about regioselectivity. A notable change in product ratios can be observed upon use of solvents of different polarity. Use of a nonpolar solvent drives the reaction to favour the head-to-head regioisomer such as in the formation of ketone 14 (scheme 4). Likewise by lowering the temperature it is observed that selectivity towards the head-to-head regioisomer increases such as in the formation of ester 16 (scheme 5).

\[ \text{Scheme 4} \]
In conjunction with potential to generate regioisomers, the stereochemistry of addition needs to be considered as well. Cycloaddition processes can yield up to four new stereogenic centers. Whereas acyclic cases typically produce a nonselective mixture of products, the presence of a pre-existing stereogenic centre alters the outcome. A pre-existing stereogenic center on either the excited state or ground-state alkene will affect the stereochemistry of addition. Addition of the excited state of the enone 17 occurs to the sterically more accessible face of the ground-state of the alkene 18 in a low yield as illustrated in the formation of the ketone 19 in the synthesis of acorenone (scheme 6).\(^\text{13}\)

Although many advances have been made in the area of asymmetric synthesis, there are few reports on the control of absolute stereochemistry in [2+2] photochemical cycloadditions. However, examples of enantioselective [2+2] photochemical cycloadditions do exist. The stereogenic center of the pyrrolooxazolone 20 controls the diastereoselectivity of the cycloaddition and gives excellent facial selectivity in the formation of the pyrrolooxazolone derivative 21.\(^\text{14}\) The heterocyclic moiety can be
removed from the pyrrolooxazolone derivative 21 after subsequent steps to yield grandisol in high enantiomeric purity (scheme 7).\textsuperscript{14}

\[
\begin{align*}
\text{20} & \quad \text{hv sensitiser} \quad \text{21} \\
& \quad \text{8 steps} \\
\end{align*}
\]

grandisol, (88 \% ee)

\textbf{Scheme 7}

\subsection{1.2 Intramolecular Photocycloadditions}

In intermolecular photochemical [2+2] cycloadditions, regiochemical and stereochemical control can often be readily achieved, however there are a large number of examples where selectivity is low. By the inclusion of the two sites of unsaturation into the same molecule low selectivity may be overcome. In intramolecular photocycloaddition reactions, regioselectivity is often observed to be both higher and more predictable as opposed to intermolecular examples. The higher selectivity is observed owing to the geometric constraints placed on the transition states during initial ring closure. For example, in the formation of the polycyclic ketone 23 from the diketone 22 (scheme 8),\textsuperscript{15} in the initial ring formation, the generation of the five-membered ring is favoured by the attack of the excited-state on the ground-state alkene. Though it is not an exclusive rule this empirical observation was named ‘the rule of five’.\textsuperscript{16} This rule is similar to the observation that the 5-hexenyl radical cyclizes to the cyclopentylmethyl radical faster than the cyclohexyl radical.\textsuperscript{17} After formation of the five-membered ring, the subsequent diradical intermediate ring closes to form the ketone 23 and create the four-membered ring.
Scheme 8

The tethering of the alkene components within the one molecule can also influence the resulting stereoselectivity of cycloaddition. To date one of the more important advancements in intramolecular [2+2] photocycloadditions has been the stereochemical control in generating complex polycyclic systems. For example, in the photochemical [2+2] addition of the enone 24, the stereochemistry observed about the cyclobutane in the photoadduct 25 is cis (scheme 9).\textsuperscript{18}

Scheme 9

There are exceptions to this observation, though these usually are a result of when the cycloalkenone is larger than a six membered ring or when the tethering chain can easily accommodate the trans cyclobutane. Illustrative of this, the photochemical [2+2] cycloaddition of the enone 26 gave the polycyclic ketones 27 and 28 (scheme 10).\textsuperscript{19}
The [2+2] cycloadditions that occur via a concerted process are generally believed to be almost exclusively between that of a ketene with an olefin or acetylene. Exceptions include when a stable intermediate is formed as in the reaction between ketenes and enamines. Taking into consideration orbital symmetry rules, ketene 29 could undergo cycloaddition to 1,3-pentadiene (acting as a ketenophile) in either a $[\pi^2 + \pi^2]$ or a $[\pi^4 + \pi^2]$ manner to yield the adducts 30 and 31 respectively (scheme 11). However, with cyclopentadiene and other non-hetero 1,3-dienes studied, the [2+2] adduct, such as 30, is the exclusive product.

1.3 Thermal Cyclobutane Ring Formation

Despite being well documented, thermal [2+2] cycloadditions are frequently overlooked from a synthetic viewpoint. However insight into the mechanism of thermal cycloadditions is emerging, thus paving the way for more widespread use of this method. One of the initial examples of thermal [2+2] cycloadditions was the dimerisation of monosubstituted ethylenes, which gave the cyclobutanes 33 and 34 (scheme 12). It was hypothesised the [2+2] cycloadditions occur via an initial carbon-carbon bond forming step, yielding the more stable 1,4-disubstituted 1,4 diradical 32.
The diradical mechanism was reinforced by the Woodward-Hoffman theory.\textsuperscript{24} Through orbital symmetry considerations, Woodward and Hoffman recognised that the [2+2] cycloaddition of two ethylenes would not be favoured. In the Woodward-Hoffman theory a \([\pi2\pi+\pi2\pi]\) process is thermally not allowed while the alternative \([\pi2\pi+\pi2\pi]\) process was normally geometrically inaccessible. Thus the idea that [2+2] thermal cycloadditions proceeded via a tetramethylene diradical such as 32 or possibly zwitterionic intermediates was favoured. Regiochemistry may be predicted when structural features that may destabilize an alkene and stabilize a 1,4-diradical intermediate are introduced. Based on this proposed simple theory, a number of quantitative techniques in the prediction and rationalization of regiochemistry have been developed.\textsuperscript{25}

Stereochemical studies have supported the theory that [2+2] cycloadditions go via a tetramethylene diradical intermediate. The \textit{cis} or \textit{trans} stereochemistry in the alkene reactants is either partially or completely lost. As shown in the study of the dimerisation of \textit{cis}-1,2-dideuteriocyanomethylenes six distinct [2+2] adducts are obtained, the deuterated cyclobutanes 35a- f (scheme 13).\textsuperscript{26}

\[
\begin{align*}
\text{D} & \text{D} \quad \text{(CN)} \\
\text{CN} & \text{C} \text{N} \\
\hline
\text{246 °C, 2 hr} & \text{10 %} \\
\end{align*}
\]


\textbf{Scheme 13}
The changes in regiochemistry are more obvious when two different alkenes are used. Activating substituents such as a conjugated vinyl or phenyl group on an acyclic substrate (hydrocarbon) promotes the occurrence of intramolecular [2+2] cycloadditions. For example the tetraene 36 undergoes cycloaddition via a radical intermediate to yield the bicyclic adducts 37, 38 and 39 (scheme 14).\textsuperscript{27}

![Scheme 14](image)

The C1 and C4 substituents on intermediate tetramethylene diradicals can affect the relative stability of these intermediates. This and geometrical constraints can thus dictate the regiochemistry of thermal intramolecular [2+2] cycloadditions.\textsuperscript{28}

Different products arise from mixtures of dienes existing as $s$-cis and $s$-trans conformational isomers. The [2+2] products arise via a diradical intermediate from the reaction of the $s$-trans isomer.\textsuperscript{29} Alternatively the [2+2] adduct may result from the generation of a diradical from the $s$-cis form or the $s$-cis form may react in a competing pericyclic [4+2] addition (scheme 15).\textsuperscript{30} The mechanism of the competition between [2+2] and [4+2] additions has been extensively studied.\textsuperscript{31} This mechanistic rivalry can cause a synthetic challenge, as many alkenes reactive in [2+2] additions also prove to be excellent dieneophiles in Diels-Alder reactions.

![Scheme 15](image)
When the conformation of the diene is restricted such as the diene 40, only [2+2] adducts are formed (scheme 16). Alternatively when conformationally mobile dienes such as 41 react intramolecularly the formation of the [2+2] products via a diradical intermediate are in competition with the formation of the [4+2] adducts. In the case of the diene 41 a ratio of 3:2 of [4+2] to [2+2] adducts are observed (scheme 17).

\[
\begin{align*}
\text{Scheme 16} & \\
\begin{array}{c}
& \text{NC} \\
\text{40} & + & \text{NC} \\
& \text{CN} & \text{CN} \\
& \text{CN} & \text{CN} \\
\end{array} & \xrightarrow{4.5 \text{ hr, rt}} & \begin{array}{c}
\text{CN} \\
\text{CN} \\
\text{CN} \\
\text{CN} \\
\text{CN} \\
\text{CN} \\
\end{array} \\
\text{71%} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 17} & \\
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{41} & \xrightarrow{390 \degree C, 12 \text{ sec}} & \begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \\
\end{array} \\
20\% & + & 30\% \\
\end{array} \\
\end{align*}
\]

The formation of the 1,4-tetramethylene diradical intermediate and its comparison to zwitterionic intermediates has been the subject of a large range of theoretical investigations. From a theoretical viewpoint when substituted with a donor group such as methoxy and an acceptor group such as cyano a tetramethylene intermediate can be viewed as a resonance hybrid. It is a resonance hybrid of a singlet diradical canonical form 42 and a zwitterionic form 43.

\[
\begin{align*}
\text{42} & \quad \text{43} \\
\end{align*}
\]

Being of lower energy it would be valid to assume that an extensive range of these hybrids exists in between a pure diradical and a real zwitterion. Whether the intermediate is in a radical or zwitterionic form is of importance to a synthetic organic chemist as it can imply different chemical reactivities and thus affect synthetic planning.
and the outcome of observed product mixtures. The nature of the donor and acceptor substituents, other structural factors, conformation and solvent can all influence the relative weight of the diradical and zwitterionic forms.

A theoretical correlation study of reactive alkenes with a range of powerful donor and acceptor substituents indicated the potential points at which the transition between diradical and zwitterionic addition occurs. Noteworthy from this and other theoretical studies was that diradical intermediates predominate. Experimentally this has been supported where the diradical was successfully trapped using the 2,2,6,6-tetramethyl-1-piperidinylxyloxy free radical.

A review that comprehensively discusses the detail of evidence and theoretical studies towards diradical and zwitterionic intermediates in the formation of cyclobutanes is given elsewhere.

2.0 Bicyclo[n.2.0]alkanols

With a précis of cyclobutane formation now presented, the formation of the target moiety, a bicyclo[n.2.0]alkanol with the context of multi-functional compounds now will be discussed. Upon reviewing the literature, some synthetic methods were applied to more than one bicyclo[n.2.0]alkanol system and thus the examples presented herein are interleaved and cross-referenced for a more succinct discussion. This review is restricted to bicyclo[3.2.0]heptan-1-ols, bicyclo[4.2.0]octan-1-ols, bicyclo[5.2.0]nonan-1-ols and bicyclo[6.2.0]decan-1-ols.
2.1 Bicyclo[3.2.0]heptan-1-ols

2.1.1 Simple functionalised bicyclo[3.2.0]heptan-1-ols

Derivatives of the simplest bicyclo[3.2.0]heptan-1-ol has been the subject of solvolysis studies. In these studies, the rates and products of solvolysis were determined for both cis- and trans-fused derivatives of bicyclo[3.2.0]heptan-1-ols and bicyclo[4.2.0]octan-1-ols. The bicycloalkanols 45 and 46 gave similar product mixtures that contain cyclobutanols 47 and 48 and cyclopropylcarbinols such as 49 and 50 respectively (scheme 18). The formation of the cyclopropylcarbinols 49 and 50 was accounted for by the possibility of carbon migration.

Scheme 18

Bicyclo[3.2.0]heptan-1-ols, such as cis-bicyclo[3.2.0]heptan-1-ol 47, and bicyclo[4.2.0]octan-1-ols such as bicyclo[4.2.0]octan-1-ol 48 have been accessed via rearrangement of the 2-(1-cyclopenten-1-yl)ethyl and 2-(1-cyclohexen-1-yl)ethyl derivatives 51 and 53 respectively (schemes 19 and 20). Cis-bicyclo[3.2.0]heptan-1-ol 47 can be prepared from the tosylate 51 in the presence of calcium carbonate (scheme 19). The ratio of 47 to 3-methylene cyclohexanol 52 obtained was very similar to that found by Closson and Kwiatkowski when they treated spiro[2.4]heptan-4-ol with p-nitrobenzoic acid. Similarly, cis-bicyclo[4.2.0]octan-1-ol 48 was prepared from the tosylate 53 in the presence of calcium carbonate with an unstirred reaction mixture (scheme 20). Calcium carbonate was believed to act as a buffer and control the ratio of 48 and 50. The ratio of 48 and 50 was altered significantly when the reaction was stirred, promoting the formation of the spiro 50.
Scheme 19

$$\text{51} \xrightarrow{20 \% \text{ aqueous acetone}} \text{CaCO}_3 \xrightarrow{} \text{47 (65\%)} + \text{52 (24\%)} + \text{53 (11\%)}$$

Scheme 20

Alternatively, trans-bicyclo[3.2.0]heptan-l-ol 55, was prepared in 41% yield by the lithium aluminum hydride reduction of 8-oxatricyclo[3.2.1.0^{1,5}]octane 54 (scheme 21). The trans isomer 55 was formed in conjunction with the cis isomer 47 (8%), cyclopropylcarbinol 49 (19%), and cycloheptanol (32%). Trans-bicyclo[4.2.0]octan-l-ol 56 was prepared in a similar manner to that used for trans-bicyclo[3.2.0]heptan-l-ol 55.

Scheme 21

Other solvolysis studies included treatment of 49 with p-nitrobenzoic acid in the solvent aqueous acetone which resulted in the formation of bicyclo[3.2.0]heptan-l-ol 1 (64%) and alcohol 52 (37%) via carbocation intermediates (scheme 22).
The solvolysis was conducted under a variety of conditions including buffered and unbuffered solvolysis of the \( p \)-nitobenzoate of the alcohol 49, and change of solvent. With a change of solvent conditions (dioxane-water, with perchloric acid 0.5 M) a large number of products resulted with the major products being 1 (78%) and 52 (11%). Similar to the work in schemes 19 and 20, solvolysis of cyclohepten-1-yl, cycloocten-1-yl and cyclononen-1-yl ethyl amines gave a mixture of products including the bicyclo[\( n.2.0 \)]alkan-1-ols 1-3.\(^{44} \) The cis and trans (1:1) product ratio of the bicyclo[\( n.2.0 \)]alkanols 1-3 was controlled by the pH of the reaction.

Although the bicyclo[3.2.0]heptan-1-ol 1 was observed to be the major product from the above mentioned solvolysis studies, the large number and complexity of side products detract from this approach when synthesising bicyclo[3.2.0]heptan-1-ols. This is further illustrated in the following example.

### 2.1.2 Polycyclic bicyclo[3.2.0]heptan-1-ols

The solvolysis of the substituted alcohol 57 in aqueous dioxane with perchloric acid resulted in a reaction mixture including alcohol 58 which possesses a bicyclo[3.2.0]heptan-1-ol moiety.\(^{45} \) Even with variation in reaction time it was seen that a number of products are obtained including the ring enlargement product 58, ring opening product 59, dimeric product 60 and a product lacking the alcohol group 61 (scheme 23). A study of the reaction mixture over time at a constant temperature showed that very low yields of 3 – 10.1% are obtained for the alcohol 58.
Apart from solvolysis studies, the samarium diiodide-mediated pinacolisation of diketones has been used to construct polycyclic frameworks. In an example of the synthesis of a norpinane-1,5-diol (bicyclo[2.1.1]hexane-1,5-diol), the β-acylated cyclopentanone 62 when treated with samarium (II) iodide gave the strained norpinane-1,5-diol 64 in a typically moderate yield (scheme 24). Similar to the preparation of 64, the homologous pinane skeleton 65 was accessible from 3-acetylcyclohexanone 63.

In another approach, the synthesis of polycyclic cyclopentanone derivatives such as 67 and 68 has been achieved by condensation of ketone enolates in an aprotic solvent with cyclohexadienes generated in situ from 1-chlorocyclohexene 66 (scheme 25). This type of condensation is related to arynic condensation. A fuller discussion of arynic condensation is reserved to section 2.2.1 which is on polycyclic bicyclo[4.2.0]octan-1-ols.
In a photochemical approach, irradiation of α,β-unsaturated ketone 69 in 1,3-dioxalane in the presence of the sensitizer anthraquinone led to the acetal 70. Upon irradiation of the acetal 70, photocyclisation occurred and the alcohol 71 was obtained in poor yield (25%) (scheme 26). It was suggested that hydrogen bonding between the hydroxyl group and the acetal group of the diradical intermediate arising from 70 maintains the conformation required for cyclisation of 70 and formation of 71.

Photochemical approaches have been used to generate sesquiterpenes. In the first example, a tricyclic hydrocarbon skeleton, a quirogadiene 72 derived from longipinene, was irradiated in 1,4-dioxane and the pentacyclic sesquiterpene 73 was obtained, in which a bicyclo[3.2.0]heptan-1-ol subunit is observed (scheme 27).

In the next example, the 2-hydroxy-1-methyltricyclo[5.4.0.0\(^{2,6}\)]undecan-8-one 76 was used as a precursor in the synthesis of the sesquiterpene α-himachalene. The [2+2] photoaddition of cyclohexenone 74 with 1-methyl-2-trimethylsiloxy-1-cyclopentene 75 in benzene, gave photoadducts which were deprotected with dilute hydrochloric acid
and a stereoisomeric mixture of the tricycloundecanone 76 was obtained in 33% yield (scheme 28). An accompanying product was the retroaldol product 77 (27%) formed via a de Mayo reaction.

![Scheme 28](image)

The trans-transoid-cis isomers are the predominant photoadducts in the photoaddition. In these studies, the trans-transoid-cis isomer 78 was isomerised to the more stable cis-transoid-cis isomer 79 by treatment with a base (scheme 29).

![Scheme 29](image)

Aside from incorporation of bicyclo[3.2.0]heptan-1-ols as synthons in the synthesis of natural product targets, the bicyclo[3.2.0]heptan-1-ol ring system is also observed to be a constituent component of more complex systems such as cage compounds. Examples are singular and varied in their mode of formation. In the first example, treatment of dione 80 with zinc and acetic acid leads to the formation of the tetracyclic diketone 81, followed by reduction to the adduct 82 by treatment with amalgamated zinc and hydrochloric acid (scheme 30).

![Scheme 30](image)
Whereas, reaction of 83 led mainly to the pinacol adduct 86 (30%) and the alcohol 84 (45%) in conjunction with 85 and 87 (scheme 31). It was shown that two competing reactions were involved in the Clemmensen reduction of 83 and that 86 arose via 85.

\[
\text{Cage molecules were accessed via an intramolecular ketyl-olefin reductive coupling using samarium(II) iodide to generate the ketyl moiety.}\]

In the next example, cage molecules were accessed via an intramolecular ketyl-olefin reductive coupling using samarium(II) iodide to generate the ketyl moiety. Treatment of the undecane 95 with samarium(II) iodide gave the functionalised undecane 96 (70%) as a single product (scheme 32). The formation of 96 proceeds via a 4-\textit{exo-trig} closure or a 5-\textit{endo-trig} closure of 95.
The formation of polycyclic ring systems can also be accessed via the tandem intramolecular Michael-aldol reaction of α,β-unsaturated esters carrying a ketone function at an appropriate position. For example, treatment of the cyclopentanone derivative 97 with tert-butyldimethylsilyl triflate (TBDMSOTf) and triethylamine gave the cyclised product, the ester 98 in 11% yield together with TBDMS ether 99 in 45% yield (scheme 33). Reduction of the ester 98 with DIBALH, followed by removal of the TBDMS group with tetrabutylammonium fluoride (n-Bu₄NF) afforded the functionalised bicycloheptanol 100. The four membered ring results from intramolecular conjugate addition to the ester side chain of 97 followed by intramolecular cyclisation of the resulting enolate to give the four member ring in the cyclized product 98. The regioselectivity of enolate formation of the ketone 97 was not an issue as it is an α,α-diblocked substrate.
In a complementary approach, the cyclohexanone derivative 101 was treated with trimethylsilyl iodide (TMSI) in the presence of excess hexamethyldisilazane ((TMS)₂NH) to afford the cyclised product 102 in 68% yield (scheme 34). When the methyl group of the α,β-unsaturated ester 101 was replaced with (-)-8-phenylmenthyl group as a chiral auxiliary, optically pure polycyclic compounds related to the cyclized product 102 were obtained.

![Scheme 34](image)

In another polycyclic example, epoxide alcohol 105, was an intermediate in a model study towards the enantiospecific synthesis of isodaucane sesquiterpenes. Irradiation of 103 with cyclopentene gave the cis-anti-cis photoadduct 104 in 69% yield (scheme 35). Treatment of 104 with dimethyloxosulfonium methylide followed by removal of the benzoyl group with sodium ethoxide solution resulted in the formation of alcohol 105.

![Scheme 35](image)

In two final examples, the reduction of the bridgehead tosylate 106 with lithium aluminium hydride afforded a 5:3 mixture of tricyclo[3.2.1.0³⁶]octan-6-ol 107 and endo-bicyclo[3.2.1]octan-6-ol 108 respectively (scheme 36). In a study of bridgehead substituted polycyclic compounds, derivatives of tricyclo[3.1.1.0³⁶]heptane were sought. In these studies attempted conversion of tricyclo-6-methanol 109 into the
corresponding tosylate 110 gave the tosylate 106 as the unexpected rearrangement product.

![Scheme 36](image)

2.1.3 Bicyclo[3.2.0]heptan-1-ols - Natural products and analogues

Exemplary of the incorporation into natural products are functionalised bicyclo[3.2.0]heptan-1-ols contained within diterpenes and sesquiterpenes. For example, alcohol 111 is a spatan diterpene, isolated from the algae, *Dilophus okamurae* (Dawson collection), which has feeding-deterrent activity against abalone.60 Compounds 112 and 113 are lactones related to bourbonene isolated from aerial parts of *Vernonia arkansana*.61 Alternatively, functionalised bicyclo[3.2.0]heptan-1-ols are present in photoadducts arising from possible *in vivo* formation of colchicine.62

![compounds 111, 112, 113](image)

As already discussed bicyclo[3.2.0]heptan-1-ols can serve as key intermediates towards natural products with different ring systems. A further example is where optically active cyclobutenols have been employed in the synthesis of biologically active natural sesquiterpenes such as spatanes63 and as intermediates towards sesquiterpene antibiotics
such as siliphinene.\textsuperscript{64} The ZrCl\textsubscript{4} promoted [2+2] cycloaddition of the silyl enol ether of cyclopentanone with chiral propynoates resulted in the formation of cyclobutene esters 114 and 115 (scheme 37).\textsuperscript{63} The esters 114 and 115 were separated by resolution techniques prior to further synthetic transformations.

\begin{equation}
\begin{array}{c}
\text{OSiMe}_3 \\
\text{CO}_2\text{R} \\
\end{array} + \begin{array}{c}
\text{ZrCl}_4 \\
\end{array} \rightarrow \begin{array}{c}
\text{CO}_2\text{R} \\
\text{OH} \\
\end{array} + \begin{array}{c}
\text{OSiMe}_3 \\
\text{CO}_2\text{R} \\
\text{OH} \\
\end{array} \\
\text{R} = \text{menthyl, bornyl}
\end{equation}

Scheme 37

2.2 Bicyclo[4.2.0]octan-1-ols

2.2.1 Polycyclic bicyclo[4.2.0]octan-1-ols

Selected approaches to the synthesis of simple functionalised bicyclo[4.2.0]octan-1-ols have been already presented in section 2.1. Additional to these examples, a successful strategy to the synthesis of benzocyclobutenol derivatives has been the arynic condensation of ketone enolates in an aprotic solvent. For example, elimination of hydrohalide acid by the complex base NaNH\textsubscript{2}-t-BuONa from an aryl halide to generate benzyne was followed by condensation with an enolate and gave benzocyclobutenols such as compound 116 as the major product (scheme 38).\textsuperscript{65} Analogous products were observed for the enolates of cyclopentanone, cycloheptanone,\textsuperscript{65} and cyclooctanone.\textsuperscript{66}

\begin{equation}
\begin{array}{c}
\text{ONa} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{O} \\
\end{array} \rightarrow \begin{array}{c}
\text{OH} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{H} \\
\end{array} + \begin{array}{c}
\text{Ph} \\
\text{O} \\
\end{array}
\end{equation}

Scheme 38

This methodology has been used extensively to gain access to polycyclic aromatic compounds such as the alcohol 117 from bromobenzene and 1-tetralone,\textsuperscript{67} the
phenanthrocyclobutenol 118 from 9-phenanthryne and the polycyclic aromatic compounds 119 and 120 from bromonaphthalene and 1-tetralone.

Other products have included phenylethanolamines 121 where \( n = 1 - 3 \), and benzocyclobutenols 122 where \( n = 1 - 4, 7 \) and 8, which can be transformed into benzocyclobutenones using protecting group chemistry for the alcohol functionality.

Cyclobutenols possessing functionality on the saturated ring and on the \( \alpha \)-position relative to the hydroxyl group also have been accessed via arynic condensation.

Control of product ratios was achieved through use of starting ketones such as cyclohexan-1,2-dione monoketals which gave benzocyclobutenols such as 123 and 124 as the only products (scheme 39). The sodium ion stabilized the intermediate cyclobutanol anion by chelating the oxygen atoms of the ketal group.

\[
\text{Scheme 39}
\]
The main difficulties with the general strategy of arylic condensation can be the preparation of the starting cyclic ketones such as 1,2-ketones, and the size of the starting ketone, which has been shown to be limited to $5 \leq n \leq 7$. In addition, with a few exceptions linear ketone enolates did not lead to cyclic alcohols. Also low yields can be obtained. For example, the synthesis of polycyclic phenylethanolamines results in yields typically of 15-30%.

Non-aromatic analogues of benzocyclobutenols have been obtained by substituting halobenzenes with a halocyclohexene, such as 66 in the reaction with the sodium enolate of cyclohexanone (scheme 40). The formation of the tricyclic product 125 was favoured when the reaction was carried out in THF. A 63:37 mixture of 125 and 126 was obtained in DME. The tricyclic compound 125 is a useful synthetic intermediate and has been converted to the furan 127, the tricyclic ketone 128 and the $\alpha$-hydroxyketone 129.

Alternatively when 3-bromohydropyran 130 was treated with a complex base, dehydrodihydropyran 131 can be generated. Condensation with ketone enolates such as the enolate of cyclohexanone, gave the alcohols 132 and 134 and ketone 135 (scheme 41). Structural studies on related compounds such as the alcohol 133 allowed
interpretation of the reaction products and showed that the presence of the oxygen atom influences the reactivity of the diene intermediate 131.

![Scheme 41](image)

Arynic condensation methodology also has been used to access biologically active compounds containing the bicyclo[4.2.0]octan-1-ol component. For example compound 116 has demonstrated anticonvulsant properties.\(^8^0\) The amino substituted analogue 136 relaxes tracheobronchial smooth muscle.\(^8^1\) The polycyclic indoles 137-140 are cytotoxic towards L1210 leukaemia cell line and 138, 139 and 140 induced accumulation of cells in the G\(_2\)+M phase of the cell cycle.\(^8^2\)

![Compounds 116, 136, 137, 138, 139, 140](image)

As previously discussed, benzocyclobutenols 142 can be obtained via arynic condensation but the ring size is limited to 5-7 membered rings.\(^8^3\) As an alternative procedure, the irradiation of benzocycloalkenones such as 141 has been examined in
tert-butyl alcohol,\textsuperscript{83} the solvent being used to diminish the classical photoreduction\textsuperscript{84} products observed with these ketones.\textsuperscript{85} Cyclisation of ketones \textbf{141} into benzocyclobutenols \textbf{142} (n = 7 - 9) was observed in conjunction with formation of the unsaturated alcohol \textbf{143} for the n = 7 case (scheme 42). However, recovered ketone \textbf{141} was obtained for the n = 6 case.

![Scheme 42](image)

By comparison, on irradiation, substituted benzocycloalkenones \textbf{144} cyclised by either an exo cyclic mechanism or by an endo cyclic mechanism to yield mixtures of the tricyclic benzocyclobutenols \textbf{147} in conjunction with varying yields of the alcohols \textbf{145} and \textbf{146}. The ratio of these products was shown to be dependent on the ring size and nature of the alkyl substitution and was related to the mechanism of photoenolisation requiring the presence of the aromatic ring.\textsuperscript{86} Examples are given in scheme 43 for the formation of bicyclooctanols (n = 6) and bicyclodecanols (n = 8).

![Scheme 43](image)
In a different photochemical approach, bicyclo[4.2.0]octan-1-ol systems have been obtained through Norrish type II chemistry.\textsuperscript{87} An illustrative example is presented here.\textsuperscript{88} The cyclopropyl-naphthoquinones 148a-d gave the cyclobutanols 150a-d and the products 151a-d upon irradiation (scheme 44).\textsuperscript{89} A solvent system of benzene/tert-butanol (1:1) and short reaction time (< 1 hour) favoured formation of the cyclobutanol products 150a-d. The formation of both products 150a-d and 151a-d can be explained in terms of Norrish Type II chemistry. The intramolecular abstraction of the gamma-hydrogen in 148a-d followed by cleavage of the resulting diradicals 149a-d (a secondary reaction) results in the formation of 150a-d via cyclisation of the diradical 149a-d, or 151a-d by the reverse disproportionation of the diradicals 149a-d. When the starting cyclopropyl-naphthoquinone was diphenyl (R\textsubscript{2} = R\textsubscript{3} = Ph) rather than dimethyl (R\textsubscript{2} = R\textsubscript{3} = CH\textsubscript{3}) (148a, 148c), the corresponding cyclobutanol was the only product formed (53%),\textsuperscript{90} as the absence of an abstractable proton precluded the formation of the reverse disproportionation product.

\begin{itemize}
  \item a: R\textsubscript{1} = H, R\textsubscript{2} = R\textsubscript{3} = CH\textsubscript{3}
  \item b: R\textsubscript{1} = R\textsubscript{2} = H, R\textsubscript{3} = CH\textsubscript{3}
  \item c: R\textsubscript{1} = R\textsubscript{2} = R\textsubscript{3} = CH\textsubscript{3}
  \item d: R\textsubscript{1} = R\textsubscript{2} = CH\textsubscript{3}, R\textsubscript{3} = H
  \item e: R\textsubscript{1} = R\textsubscript{2} = R\textsubscript{3} = H
\end{itemize}

Further transformation of the cyclobutanols 150 obtained utilising this chemistry also has been explored.\textsuperscript{88} Irradiation of 148e in benzene/tert-butanol (1:1) for 45 minutes
gave the cyclobutanol 150e (60%) and the two rearranged products 152 (17%) and 153 (5%) (scheme 45). Separate irradiation of 150e for 3 hours resulted in the formation of 152 (51%) and 153 (20%), indicating that 152 and 153 were the secondary photoproducts derived from 149e.

A related Norrish/Yang type II photochemical cyclisation has been observed with the spiroketone 154. Irradiation of ketone 154 in both the solid and solution state gave the cyclobutanol product 155, which arises from the Norrish/Yang type II cyclisation (scheme 46). An analogous cyclobutanol 157 was formed under similar photochemical conditions from the spirocyclic ketone 156 (scheme 47). With the geometry displayed by the ketones 154 and 156, the Norrish/Yang type II photocyclisation predominates for the intermediate 1,4-hydroxy biradicals as these biradicals are well aligned for closure and poorly aligned for cleavage.
Bicyclo[4.2.0]octan-1-ols incorporated as moieties in complex and functionalised ring systems are useful intermediates in the synthesis of natural products and their analogues. In a model study towards the synthesis of saudin,\textsuperscript{93} of interest due to its hypoglycaemic activity, a bicyclooctanol ring was installed from \textbf{158} via an intramolecular dioxenone photochemical cycloaddition in acetonitrile and acetone and the photoadducts \textbf{159} and \textbf{160} were obtained in 97\% yield (scheme 48). The relative stereochemistry of the C13 and C16 centres was attributable to the orientation of the trisubstituted double bond of the photosubstrate \textbf{158}. Upon heating photoadduct \textbf{160} in methanol and catalytic \(p\)-toluenesulfonic acid, ester \textbf{162} was afforded in a 61\% yield. Treatment of \textbf{159} under the same reaction conditions instead afforded the cyclobutanol product \textbf{161} (54\%).

![Scheme 48](image)

Another example of the importance of bicyclo[4.2.0]octan-1-ol moiety in intermediates to natural products is the multistep synthesis of taxol and its analogues.\textsuperscript{94} Taxol is well known for its use in the treatment of refractory ovarian and metastatic breast cancers.
and significant synthetic efforts are concentrated on providing access to taxol and its analogues.\textsuperscript{94} Taxol precursors such as the taxane AB-ring analog \textbf{166} can be accessed via the versatile synthon pinene \textbf{163}, which can supply 10 of the 20 carbons and the chirality of the taxane core (scheme 49). The trimethylsilyl ether \textbf{164} is accessed via pinene \textbf{163} in 6 steps.\textsuperscript{94} Conjugate addition of Me$_2$CuLi to the trimethylsilyl ether \textbf{164} introduced the C8 methyl group and in turn generated a carbanion at C3, which underwent addition to the C2 carbonyl group. As a result of the intramolecular C2-C3 bond formation, the bicyclooctanol framework was installed in the intermediate subunit \textbf{165} in 97\% yield from the trimethylsilyl ether \textbf{164} upon cleavage of the trimethylsilyl protecting group.

\begin{center}
\textbf{Scheme 49}
\end{center}

In a unusual approach to bicyclooctanols and bicyclonals, the diol \textbf{167} underwent a tandem 4-exo-dig carbopalladation/Stille cross-coupling reaction to obtain the intermediate bicyclo[4.2.0]octenediol and bicyclo[5.2.0]nonenediol \textbf{168} (scheme 50). The strained compounds \textbf{168} slowly underwent a thermal rearrangement via a cascade reaction to give the bicyclic systems \textbf{169} and \textbf{170}.\textsuperscript{95}
2.2.2 Bicyclo[4.2.0]octan-1-ols - Natural products and analogues

Functionalised bicyclo[4.2.0]octan-1-ols are contained within a range of natural products and examples include sesquiterpenoids, diterpenes, and penitrems. Selected examples are presented now.

Punctatins A 171, D 172, E 173 and F 174 are isomeric sesquiterpene alcohols from the dung fungus, Poronia puctata (Linnaeus ex Fries) (Whalley collection). The structures of the acetonide derivatives of punctatin D 172 and E 173 have been determined by X-ray crystallography. Punctatin D 172 is marginally active (1ppm) in vitro against a mycelial form of Candida albicans, and punctatin E 173 was inhibitory to Trichomonas vaginalis at 100ppm in vitro.

Atlanticone D 175 was isolated from the fruiting bodies of Lactarius altanticus, a Mediterranean mushroom. It was proposed that Atlanticone D 175 arose from the enzymatic conversion of the protoilludane sesquiterpene 176 into the free hydroxyl derivative 175.
The following natural products are also sesquiterpenoids possessing a bicyclo[4.2.0]octan-1-ol functionality. Sterpuric acid 177 was isolated from the silver leaf disease causing fungus, *Stereum purpureum*. The sesquiterpenoid aromatic esters, melleolides K 178, L 179 and M 180 were obtained from the cultured mycelia of *Armillariella mellea* (Vahl. Ex Fr.) (Karst collection) and were shown to exhibit antimicrobial activities. Also isolated from *Armillariella mellea*, were sesquiterpene aryl esters such as armillane and 10α-hydroxyarmillarin. Armillane and 10α-hydroxyarmillarin displayed limited activity against *Phytophthora cinnamomi*. A further example of a functionalised bicyclo[4.2.0]octan-1-ol is in the lindenane sesquiterpene, chloranthalactone A photodimer, which was obtained from the leaves of *Chloranthus glaber*.

Diterpenoid examples are the feeding-deterrents 181, 182 and 183, which were isolated from the red algae *Laurencia saitoi* collected in the Sea of Japan. Structurally related to the polycyclic compounds 181, 182 and 183 and containing a bicyclooctanol moiety, isoparguerol and isoparguerol 16-acetate were obtained from the extracts of the sea hare *Aplysia dactilomela*. The brominated diterpenes isoparguerol and isoparguerol 16-acetate exhibited cytotoxicity. The novel diterpenoid cyclobutatusin 184 was isolated.
from the leaves of the Brazilian plant, *Coleus barbatus* (*Labiatae*), which has been used in the practice of folk medicine against intestinal disorders.\(^\text{105}\)

![Chemical structures](image)

In a final example, penitrem A \(^\text{185}\) is a tremorgenic (tremor causing) mycotoxin first isolated from the cultures of *Penicillium cyclopium*.\(^\text{106}\) The neurochemical effects of penitrem A \(^\text{185}\) have been investigated and presynaptic transmission in central synapses was affected.\(^\text{107}\)

![Chemical structure](image)

As already discussed, bicyclooctanols have been used as synthetic intermediates towards natural products. In a further example, bicyclo[5.3.1]undecane derivatives \(^\text{190}\) and \(^\text{191}\), which are important structural elements of taxane diterpenes,\(^\text{108}\) were prepared by photochemical cycloaddition of bicyclo[3.2.1]dione \(^\text{186}\) to allene in methanol followed by base induced cyclobutane ring opening (scheme 51). Addition of allene to the triplet excited state of the enol form \(^\text{187}\) of the 1,3 dione \(^\text{186}\) resulted in a mixture of the two regioisomers \(^\text{188}\) and \(^\text{189}\) in a 1:4 ratio respectively. Related work on photochemical approaches towards taxanes incorporating bicyclo[3.2.0]octan-1-ol moieties has been reported.\(^\text{109}\)
2.3 Bicyclo[5.2.0]nonan-1-ols

2.3.1 Simple functionalised bicyclo[5.2.0]nonan-1-ols

Selected approaches to the synthesis of simple functionalised bicyclo[5.2.0]nonan-1-ols have been already presented in section 2.2. Additional to these examples the solvolysis of epimeric 2-hydroxy-trans-bicyclo[6.1.0]nonanes in lutidine buffered aqueous dioxane was shown to yield a complex mixture of rearrangement products including a bicyclononanol 3 in 10% yield (scheme 52). The study showed that compounds 192, 193 and 194 were the primary products present in the early stage of solvolysis at 230 °C, whereas, the bicyclononanol 3 arose from the rearrangement of 193 under the buffered conditions.
A functionalised bicyclo[5.2.0]nonanol has been accessed via a hydrolytic approach. Irradiation of the vinylcarbonate 195 in acetone at -65 °C with bubbling ethylene, gave carbonate 196 (scheme 53).\textsuperscript{111} Hydrolysis of carbonate 196 in 2N KOH-50% methanol gave the diol 197. The analogous reaction was carried out for the formation of the corresponding bicyclooctanediol.\textsuperscript{111}

\begin{center}
\textbf{Scheme 53}
\end{center}

2.3.2 Polycyclic bicyclo[5.2.0]nonan-1-ols

Examples of polycyclic molecules possessing the bicyclo[5.2.0]nonan-1-ol moiety have been presented in the preceding sections (2.2.1). Mentioned were the formation of the cyclobutanol 157 via a Yang cyclisation of a spirocyclic ketone 156,\textsuperscript{91} arynic condenations,\textsuperscript{70} a tandem 4\textendash exo\textendash dig carbopalladation/Stille cross-coupling,\textsuperscript{95} and samarium diiodide-mediated pinacolization of 1,4-diketones.\textsuperscript{112} Further examples are presented below.

The simple bicyclononanol 198 was obtained from arynic condensation of chlorocyclohexene and the enolate of cycloheptane.\textsuperscript{75} In heterocyclic examples, polycyclic aryl derivatives 199 and 200 were obtained from the arynic condensation of 3,4-pyridine with the enolates of 1,2-diketone monoketals,\textsuperscript{113} and the nucleophilic condensation of cycloalkanones with 3,4-dehydrodihydropyran gave pyran derivatives such as 201.\textsuperscript{114} Triol derivatives also were obtained via arynic condensation followed by bis hydroxylation of the methylenecyclobutanols to give bicyclononanols such as 202.\textsuperscript{77}
In a further example of Norrish type I and type II photochemical processes of ketones, the photolysis of 203 resulted in the formation of the type II cyclisation products 204 in good yields along with traces of type I and type II side products (scheme 54).\textsuperscript{115}

Scheme 54

In a similar photochemical approach to that previously discussed, bicyclononanols have been accessed from the triplet sensitised [2+2] photocycloaddition of the trimethylsilyl enol ether of β-suberone 205 with acrylonitrile (scheme 55).\textsuperscript{116} A mixture of photoadducts 206 and 208 were obtained in low yield. Subsequent acidic hydrolysis gave the cyclobutanol 207 and its isomer 209 in 10% and 7% yield respectively. Using this procedure on β-tetralone and β-indanone, the corresponding bicycloheptanols and bicyclooctanols also were obtained.\textsuperscript{116}
Polycyclic functionalised bicyclonananol ring systems incorporating other bicycloalkanols such as a bicycloheptanol ring as in 210 and 211, have served as synthetic intermediates in model studies towards the preparation of the ingenane diterpene skeleton.\textsuperscript{117}

Alternatively, polycyclic functionalised bicyclonananol ring systems have been the oxidation products of the natural products β-lumicolchicine 212. Active manganese (IV) oxide adds a hydroxyl group to the tetrasubstituted double bond of β-lumicolchicine 212 and the acetamido side chain is used to form a 2-oxazoline ring by ring closure to give 213 (scheme 56).\textsuperscript{118}

\textbf{2.3.3 Bicyclo[5.2.0]nonan-1-ols - Natural products and analogues}

Examples of functionalised bicyclo[5.2.0]nonan-1-ols contained within natural products are limited. In particular, an example of a sesquiterpenoid includes paesslerins A 214 and B 215. Isolated from the subAntarctic soft coral \textit{Alcyonium paessleri}, a rich source of novel sesquiterpenoids, paesslerins A 214 and B 215 displayed moderate cytotoxicity.\textsuperscript{119}
2.4 Bicyclo[6.2.0]decan-1-ols

2.4.1 Simple functionalised bicyclo[6.2.0]decan-1-ols

Approaches to the synthesis of simple functionalised bicyclo[6.2.0]decanols are limited. Medium sized ring diametric diketones in which the carbonyl groups are separated by an equal number of methylene groups undergo Norrish/Yang type II photochemical cyclisation.\textsuperscript{120} The 1,2-cyclodecane-dione 216 gave two photoproducts 217 and 218 upon irradiation through pyrex in benzene (scheme 57). The outcome of the photochemistry is dependent on the reaction medium. Functionalisation of the ketone group in the photoproduct 217 has been studied and gave further simple functionalised bicyclo[6.2.0]decanols.\textsuperscript{121}

\[
\text{216} \xrightarrow{hν, \text{C}_6\text{H}_5, \lambda > 340 \text{ nm}} \text{217} + \text{218}
\]

Scheme 57

In a different approach to simple bicyclo[6.2.0]decanol systems, the acetylisation and hydrolysis of 3,4-cyclononadien-1-yl tosylate and 4,3-vinylidencycloalkyl tosylates have been investigated. Radical mechanisms based on vinylium ions were proposed to explain the formation of bridged cyclobutanols, such as 219 and fused cyclopropyl ketones.\textsuperscript{122}
2.4.2 Polycyclic bicyclo[6.2.0]decan-1-ols

Examples of polycyclic molecules possessing the bicyclo[6.2.0]decan-1-ol moiety have been presented in the preceding sections (2.3.2). Mentioned were arynic condensations$^{123}$ and Norrish type I/II photochemical reactions.$^{115}$ Further examples are presented below.

More recent work has extended arynic condensation methodology to the preparation of polycyclic alcohols with larger rings such as 220,$^{124}$ polycyclic oxygen containing heterocycles such as 221,$^{114}$ and aromatic polycyclic compounds such as 222.$^{125}$

In addition the samarium diiodide-mediated pinacolisation of the 1,4-diketone 223 has been used to construct tricyclic bicyclobutane diols 224 and 225, where a mixture of the meso and racemic diastereomers were obtained (scheme 58).$^{112}$

Scheme 58

Bicyclodecanols as part of polycyclic systems have been incorporated in the products derived from synthetic transformations of natural products. For example, photolysis of the tetrahydro zexbrevin 226 followed by subsequent Huang-Minlon reduction of the photoisomerisation product gave the polycyclic product 227 (scheme 59).$^{126}$
2.4.3 Bicyclo[6.2.0]decan-1-ols - Natural products and analogues

Examples of functionalised bicyclo[6.2.0]decan-1-ols contained within natural products in the absence of any other bicycloalkanol rings as previously mentioned, are limited. In particular, an example of a sesquiterpene is the novel tetracyclic hemisuccinate punctaporonin C $^{228}$, which was isolated from the culture medium of the fungus *Poronia punctata*. The *Poronia* species occurs exclusively on dung.

\[ R' = HOOC(CH_2)_2CO \]

3.0 Project Impetus

The study and development of a novel cyclisation methodology for the synthesis of bicyclo[\(n.2.0\)]alkan-1-ols was stimulated by two literature reports of interesting by-products. In the first report, as part of a study towards intermediates in the synthesis of Vitamin D, the reaction between the cyclopentanone lithium enolate $^{229}$ and phenyl vinyl sulfoxide gave the unexpected products bicyclo[3.2.0]heptan-1-ols $^{230}$ and $^{231}$ (scheme 60).$^{128}$ This unexpected result has not been explored since being reported.
Upon consideration of this result, the phosphine oxide side chain in 229 may have played a role in the transition state and hence the outcome of the reaction.

![Scheme 60](image)

In the second report, ‘variable amounts’ of bicycloalkanol intermediates were reported from the Michael addition of the lithium enolates of cyclohexanone, 1,4-cyclohexanedione *mono*-ethylene ketal and cyclopentanone to phenyl vinyl sulfoxide.\(^{129}\)

The bicycloalkanol intermediates were not described or characterised, rather the reaction conditions were used to effect ring opening of any bicycloalkanols formed. Thus the reaction mixture was allowed to warm to room temperature during the five hours reaction time and aqueous sodium hydroxide workup gave the alkylated ketones 232 (scheme 61), 233 and 234 respectively.

![Scheme 61](image)

In our research group, it was anticipated the formation of a bicyclic system incorporating a four membered ring, under mild conditions in good yield from a ketone
enolate and phenyl vinyl sulfoxide, might be applied to the synthesis of simple bicyclo[4.2.0]octan-1-ols. Recent preliminary experiments\textsuperscript{130} showed that the reaction between the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide under mild conditions did indeed result in the formation of simple bicyclo[4.2.0]octan-1-ol compounds \textbf{235} (scheme 62). At the time however, full characterisation of all novel compounds formed in the reaction and complete analysis of the results of the preliminary experiments was not carried out. Nevertheless, the preliminary results suggested that this reaction was an example of an intermolecular route to a bicyclo[4.2.0]octan-1-ol system.

\[
\text{Scheme 62}
\]

In the context of these three reports (schemes 60, 61 and 62), it is clear that an understanding of enolate chemistry and the use of phenyl vinyl sulfoxide as an electrophile is important.

Enolate chemistry has been extensively reviewed elsewhere\textsuperscript{131} thus a brief overview of important factors in enolate chemistry is presented. An unsymmetrical ketone can generate two possible regioisomeric enolates on deprotonation, as shown in scheme 63.\textsuperscript{132} Control over regioselectivity can be achieved through the choice of: solvent and thus aggregation state of the enolate, the base, cation, reaction time and temperature. The regioisomers of an enolate mixture may be governed by kinetic and thermodynamic factors. Kinetic control (less substituted enolate) is favoured by aprotic solvents, strong bases, cations such as lithium which complex oxygen, low reaction temperature and short reaction times. Whereas thermodynamic control (more substituted enolate) is
favoured by protic solvents, nucleophilic bases, cations which form ionic M-O bonds, higher temperatures and longer reaction times.

\[
\begin{align*}
\text{O} & \quad \longrightarrow \quad \text{O}^- \\
\text{ketonic control (LDA, DME)} & \quad 1 : 99 \\
\text{thermodynamic control (Et}_3\text{N, DMF)} & \quad 78 : 22
\end{align*}
\]

Scheme 63

Stereoselectivity of enolate formation can also be controlled to some extent, either by kinetic or thermodynamic conditions. Other important factors in enolate chemistry include the presence of electron withdrawing groups, which affect enolate formation, the ratio of E/Z enolate isomers in acyclic ketones and the control of C-alkylation versus O-alkylation.

Reactions of enolate anions with electrophiles tend to fall under the categories of displacement reactions with alkyl halides or other suitable electrophiles and nucleophilic addition to carbonyl compounds or the β-carbon of the electrophile in a Michael addition process. In particular, α,β-unsaturated sulfoxides can be Michael acceptors in conjugate addition reactions with a variety of nucleophiles. For example, asymmetric addition of an ester enolate to the optically active α-carbonyl-α,β-unsaturated sulfoxides \textbf{236} gave the ketone \textbf{237} in 70% enantiomeric excess following removal of the sulfoxide from the addition product. The same methodology has been applied using ketone enolates. In these cases, both carbonyl and sulfoxide groups activated the β-carbon to nucleophilic attack. The sulfoxide chiral auxiliary was removed from the Michael adduct having served its purpose in asymmetric induction.
Many cycloaddition reactions involving ketone enolates where the two carbon atoms of the enolate π bond become part of a carbo cyclic or heterocyclic ring in the product have been reported elsewhere.\textsuperscript{136} Included are reports of \([4+2]\) cycloaddition reactions,\textsuperscript{137} \([3+2]\) cycloadditions,\textsuperscript{138} \([4+3]\) cycloadditions,\textsuperscript{139} \([2+2+2]\) cycloadditions or Michael-Michael-Ring Closure (MIMIRC).\textsuperscript{140} A selected example is the reaction between the lithium enolate of cyclohexanone and methyl styryl sulfone \(238\), which resulted in the formation of the β-hydroxy sulfone \(239\).\textsuperscript{141}

Another important example is the \([2+2]\) photochemical cycloaddition of phenyl vinyl sulfoxide with an aluminium enolate.\textsuperscript{142} The cycloadduct \(240\) was isolated as a mixture of sulfur epimers (scheme 64). \([2+2]\) Cycloaddition occurred in preference to the formation of the expected Diels-Alder adduct. Similarly, a regioisomeric cyclohexanone aluminium dienolate reacted with phenyl vinyl sulfoxide to give the cycloadduct \(241\). The aluminium enolate of cyclopentanone gave the \([2+2]\) adduct \(242\) in addition to the product of monoalkylation \(232\).

\[ \begin{align*}
\text{Scheme 64} \\
1. \text{hν, THF/Et}_2\text{O, -30 °C} \\
2. \text{2M aqueous } \text{HCl} \\
(64 \%) \\
\end{align*} \]
3.1 Project Aims

Access to a bicyclo\([n.2.0]\)alkan-1-ol skeleton directly from a ketone enolate and phenyl vinyl sulfoxide in one step is a potential alternative to the current literature methods. Preliminary experiments\(^{143}\) in the research group had shown that compounds with a bicyclo\([4.2.0]\)octan-1-ol carbocyclic skeleton could be obtained from the reaction between the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide (scheme 62). The major aim of the current project was to develop, and to establish the scope of this methodology outlined in scheme 26 as an alternative synthetic approach to bicyclo\([n.2.0]\)alkan-1-ol systems as previously reviewed. As the current study was carried out in conjunction with a mechanistic study into the formation of bicyclo\([4.2.0]\)octan-1-ols\(^{143}\) the focus of the present choice of ketone synthons is towards bicyclo\([n.2.0]\)alkanols where the ring size may produce fused bicyclo\([2.2.0]\)hexan-1-ol, bicyclo\([3.2.0]\)heptan-1-ol, bicyclo\([5.2.0]\)nonan-1-ol and bicyclo\([n.2.0]\)decan-1-ol ring systems. The scope of this methodology will be examined with respect to simple ring size, substitution on the starting ketone and thus tolerance of substitution in the resulting bicyclo\([n.2.0]\)alkan-1-ol, and the introduction of simple functionality with the ketone ring. The latter two points will be explored with cyclohexanone derivatives due to commercial availability of these ketones. Phenyl vinyl sulfoxide was considered a useful reagent for this project because of the ready availability of the racemic compound and the potential for using optically active vinyl sulfoxides in the reaction. Furthermore, the sulfoxide functionality incorporated in
resultant products could be removed or used as a handle for further synthetic transformation.

Throughout this project, the isolation, purification and characterisation of the products formed in the exploratory reactions will form the basis for structural studies on bicyclo[\(n.2.0\)]alkan-1-ols. Thus, structural aspects of any bicyclo[\(n.2.0\)]alkan-1-ol products obtained will be studied where possible, to assist in the development of an understanding of the limitations of ketone substrates suitable for the cyclisation methodology. With the overall aims of the study identified, the initial point of the investigation was the reaction between the lithium enolate of simple ketones, such as cyclobutanone, cyclopentanone, cycloheptanone and cyclooctanone and phenyl vinyl sulfoxide (chapter one).
The undiscovered country, from whose borne

No traveller returns, puzzles the will,

And makes us rather bear those ills we have,

Than fly to others that we know not of?

Shakespeare
Chapter One
Isolation and Characterisation of Bicyclo[n.2.0]alkan-1-ols

Described within this chapter are the investigations into the reaction of the lithium enolates of simple ketones with (±)-phenyl vinyl sulfoxide and the formation of bicyclo[n.2.0]alkan-1-ols under the one set of reaction conditions. From here on in the (±) descriptor will be omitted, as it will be assumed that the phenyl vinyl sulfoxide is racemic. A preliminary experiment within the group had shown that reaction between the lithium enolate of cyclohexanone and phenyl vinyl sulfoxide under mild conditions resulted in the formation of a simple bicyclo[4.2.0]octan-1-ol such as 244. The initial conditions were a reaction temperature of –30 °C warming to 0 °C then stirred for 45 minutes prior to quenching. However the complete characterisation of all products and analysis of reaction conditions was not carried out at the time of the preliminary experiment. It was at this point that the current project commenced. Subsequent to this in conjunction with the current project, characterisation of the products from the reaction under slightly different reaction conditions eventuated (scheme 65). In addition, upon oxidation with m-CPBA the sulfonylbicyclo[4.2.0]octan-1-ols 246 and 247 were obtained (scheme 65). The relative stereochemistries of 243-247 were established by X-ray structural determination.
In the present study the potential scope of this cyclisation reaction was explored, with respect to the ring size of the starting ketone and thus the formation of bicyclo[\(n.2.0\)]alkan-1-ols. Four representative ketones were chosen, cyclobutanone, cyclopentanone, cycloheptanone and cyclooctanone, all of which are commercially available. Throughout these studies oxidation of the sulfoxide products was carried out to simplify and assist in product characterisation. In an overview, generation of the lithium enolate of cyclobutanone, cyclopentanone, cycloheptanone or cyclooctanone from LDA and using a reaction concentration of 0.155 M, was followed by reaction with phenyl vinyl sulfoxide (dropwise addition) at –30 °C. The reaction mixture was warmed to 0 °C and the temperature maintained for 45 minutes, under normal laboratory light. These set of conditions were defined as method A. This reaction was carried out concurrently with the initial mechanistic and synthetic studies for cyclohexanone, hence the choice of a 45 minute reaction time, reaction lighting and mode of addition of phenyl vinyl sulfoxide. Upon workup, and subsequent oxidation with \(m\)-CPBA in chloroform, novel bicyclo[\(n.2.0\)]alkan-1-ols were identified. All yields are calculated on conversion of phenyl vinyl sulfoxide, as the starting ketones were generally volatile.

1.0 Reaction with Cyclobutanone – Method A

In the first example, the lithium enolate of cyclobutanone was reacted with phenyl vinyl sulfoxide using method A and the crude sulfoxide mixture oxidised with \(m\)-CPBA. Upon workup and isolation by column chromatography followed by HPLC, analytically pure samples of two products were obtained. Analysis by \(^1\)H nmr, \(^{13}\)C nmr and two-dimensional nmr spectroscopy confirmed the structures of the compounds as being the cyclohexanone \(248\) (5.5%) and monoalkylated cyclobutanone \(249\) (38.5%) (scheme 66). No bicyclo[2.2.0]hexan-1-ols in the crude product mixture were evident by HPLC
analysis or in the $^1$H nmr spectrum of the crude material. In the latter, key peaks in the region of $\delta$ 2.5-4.0 ppm indicating the presence of a bicyclo[2.2.0]alkan-1-ol structure were absent. The low recovery of starting material was attributed to apparent polymerisation of the phenyl vinyl sulfoxide. Supporting this, during the workup polymeric material was observed.

![Scheme 66](image)

Method A: (i) LDA, THF, -78 °C, (ii) PhS(O)CH=CH$_2$ dropwise, -30 °C (iii) 0 °C, 45 min

The rationale supporting the structures of the products will be discussed prior to the next ketone example. Due to the simplicity of the spectra of 249, and other related alkylated products obtained in the remaining studies, discussion of the structural elucidation of the alkylated compounds will not be given. Instead the discussion will focus on the elucidation of the bicyclo[2.2.0]alkan-1-ols and any unusual side products.

The cyclohexanone 248 was an unexpected product and was unambiguously determined from the following spectral information. Mass spectrometry and microanalysis results indicated a molecular mass of 238 amu, which was consistent with a molecular formula of C$_{12}$H$_{14}$O$_3$S and the formation of either cyclohexanone 248 or monoalkylated cyclobutanone 249. The FTIR spectrum displayed a strong absorption band at 1710 cm$^{-1}$ attributed to the carbonyl group, the presence of which also was confirmed by $^{13}$C nmr ($\delta$ 202.3 ppm). Absorptions at 1309 cm$^{-1}$ and 1149 cm$^{-1}$ in the FTIR, were both indicative of a sulfonyl group. However, in the $^1$H nmr spectrum of the cyclohexanone 248 the side chain protons due to H2’ and H1’ adjacent to the sulfonyl group, as in
monoalkylated cyclobutanone 249, were absent. Furthermore, the signal at $\delta$ 3.82 ppm (H2) was shifted downfield, as would be expected for a proton alpha to a carbonyl and a sulfonyl group. Further support for the structure of cyclohexanone 248 was obtained from two-dimensional nmr analysis. Observed in the gHSQC nmr spectrum was a CH signal assigned as C2-H2, in conjunction with four contiguously arranged CH$_2$ groups and a quaternary carbon in addition to a mono-substituted aromatic ring. The key correlation between the carbonyl carbon and H2 was observed in the gHMBC nmr spectrum. From this, the connectivity between the four CH$_2$ groups and correlation to the carbonyl group and CH allowed the connectivity of the cyclohexanone ring of cyclohexanone 248 to be established.

The unexpected product, cyclohexanone 248 can be rationalised by the possibility of a bicyclohexanolide intermediate 250. It was established in the concurrent study on cyclohexanone that an ionic mechanism was operating for the formation of bicyclo[4.2.0]octan-1-ols.$^{147}$ Assuming an ionic mechanism for the present example, addition of the enolate of cyclobutanone to the electrophile phenyl vinyl sulfoxide to give 251 and ring closure of 251 could give the intermediate 250. Ring opening of the intermediate 250 to break the strained bridgehead bond could give rise to an anion 252 which could deprotonate itself (or cyclobutanone) that upon quenching and oxidation would give the cyclohexanone 248.

With the unexpected formation of the ketone 248 from cyclobutanone, the five-membered case was considered next.
2.0 Reaction with Cyclopentanone – Method A

The lithium enolate of cyclopentanone was reacted with phenyl vinyl sulfoxide using method A and the crude sulfoxide mixture oxidised with \textit{m}-CPBA. Upon workup and isolation by column chromatography followed by HPLC, analytically pure samples of monoalkylated cyclopentanone 257 (55.5%), in conjunction with minor amounts of dialkylated cyclopentanone 256 (2.5%), bicyclo[3.2.0]heptan-1-ols 253 (3%) and 254 (2.5%) and the unexpected bicyclo[3.2.0]heptan-1-ol 255 (1.5%) were obtained (scheme 67). Analysis by $^1$H nmr, $^{13}$C nmr and two-dimensional nmr spectroscopy allowed characterisation of the bicyclo[3.2.0]heptan-1-ols 253, 254 and 255 and the alkylated compounds 256 and 257. In the first instance, the two bicyclo[3.2.0]heptan-1-ols 253 and 254, will be comprehensively discussed to illustrate the structural elucidation of a bicyclo[\textit{n}.2.0]alkan-1-ol. Subsequent to this, the discussion of further examples will focus on key spectral information.

\textbf{Scheme 67}

Mass spectrometry and microanalysis results for 253 and 254 indicated a molecular mass of 252 amu which was consistent with the formation of either bicyclo[3.2.0]heptan-1-ols 253 or 254 or the monoalkylated cyclopentanone 257. A strong absorption due to the alcohol functionality at 3536 cm\(^{-1}\) for 253 and 3457 cm\(^{-1}\)
for 254 and the absence of a carbonyl stretch in the FTIR spectra aided in establishing the functionality of the ring. Absorptions at 1291 cm\(^{-1}\) and 1144 cm\(^{-1}\) for 253 and 1295 cm\(^{-1}\) and 1147 cm\(^{-1}\) for 254 were each indicative of a sulfonyl group.

Next, the connectivity of the cyclobutyl ring system of bicyclo[3.2.0]heptan-1-ol 253 was established by one-dimensional and two-dimensional nmr analysis. Key assignments and \(\delta\) values from the \(^1\)H and \(^{13}\)C nmr spectra of the bicyclo[3.2.0]heptan-1-ols 253-255 are reported in table 1. The connectivity of the cyclobutyl ring of bicyclo[3.2.0]heptan-1-ol 253 can be accounted for by correlations between the signals due to H7 (\(\delta\) 3.62 ppm) and H6 (\(\delta\) 2.62-2.72 ppm) and H6 (\(\delta\) 1.46-1.60 ppm) in the COSY nmr spectrum. In the HMQC nmr spectrum, CH signals were observed for C7-H7 and C5-H5 with the carbon signals for C7 and C5 occurring at \(\delta\) 64.2 and \(\delta\) 46.3 ppm respectively. The quaternary carbon for C1 at \(\delta\) 83.6 ppm in the \(^{13}\)C nmr spectrum of 253, was identified by its absence in the HMQC nmr spectrum. In the HMBC nmr spectrum, \(^2\)J and \(^3\)J correlations were observed between C1 and H7, H6 and H5. Three contiguously arranged CH\(_2\) groups were observed in the COSY nmr spectrum. The connectivity of the three CH\(_2\) groups to the cyclobutyl ring was established though correlations observed in the HMBC nmr spectrum.

Likewise, for the bicyclo[3.2.0]heptan-1-ol 254 signals due to H7 (\(\delta\) 3.79 ppm) and H6 (\(\delta\) 2.04-2.22 ppm) and H6 (\(\delta\) 1.68-1.95 ppm) were evident in the COSY nmr spectrum. In the gHSQC nmr spectrum, CH signals were observed for C7-H7 and C5-H5 with the carbon signals for C7 and C5 occurring at \(\delta\) 65.3 and \(\delta\) 44.6 ppm respectively. The quaternary carbon for C1 at \(\delta\) 85.3 ppm was also identified in the \(^{13}\)C nmr spectrum of 254, by its absence in the gHSQC nmr spectrum. In the gHMBC nmr spectrum, \(^2\)J and \(^3\)J correlations were observed between C1 and H7, H6 and H5. Three contiguously
arranged CH₂ groups were observed in the COSY nmr spectrum and the connectivity to the cyclobutyl ring established through correlations observed in the gHMBC nmr spectrum.

Table 1 Key assignments and δ values (ppm) from the ¹H and ¹³C nmr spectra of bicyclo[3.2.0]heptan-1-ols 253, 254 and 255

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C7</th>
<th>C5</th>
<th>H7</th>
<th>H6</th>
<th>H6</th>
<th>H5</th>
</tr>
</thead>
<tbody>
<tr>
<td>253</td>
<td>83.6</td>
<td>64.2</td>
<td>46.3</td>
<td>3.62 (ddd, 9.5, 5.5, &lt;1 Hz)</td>
<td>2.62-2.72</td>
<td>1.46-1.60</td>
<td>2.62-2.72</td>
</tr>
<tr>
<td>254</td>
<td>85.3</td>
<td>65.3</td>
<td>44.6</td>
<td>3.79 (ddd, 10, 10, 1 Hz)</td>
<td>2.04-2.22</td>
<td>1.68-1.95</td>
<td>2.45-2.54</td>
</tr>
<tr>
<td>255</td>
<td>83.4</td>
<td>62.2</td>
<td>49.2</td>
<td>3.50 (dd, 10, 7 Hz)</td>
<td>2.20</td>
<td>1.60-1.74</td>
<td>-</td>
</tr>
</tbody>
</table>

With the connectivity established for the bicyclo[3.2.0]heptan-1-ols 253 and 254, the relative stereochemistry of the sulfonyl group, hydroxyl group and bridgehead proton (H5) was determined using ¹H nmr spectral information. NOESY and ROESY two-dimensional nmr spectroscopy was considered unsuitable due to the small size and the proximity of the protons within compounds 253-255. However it was noted that the ¹H nmr spectrum displayed characteristic couplings and shifts for H7, depending on the epimer observed at C7. The following rationale for assignment of stereochemistry was applied to other bicyclo[n.2.0]alkan-1-ols isolated, as discussed later.

A relative upfield δ value of H7 (δ 3.62 ppm) was indicative of a cis relationship between the hydroxyl and sulfonyl groups (Figure 1a). For bicyclo[n.2.0]alkan-1-ol 253, couplings of 9.5 Hz to H6, 5.5 Hz to H6 and a long range coupling of <1 Hz, typical of cyclobutyl ring systems,¹⁴⁸ to H5 was observed for H7. The long range coupling between H7 and H5 was correlated with a trans relationship of H7 and H5 in bicyclo[n.2.0]alkan-1-ol 253 (Figure 1a). From these correlations it was implied that the hydroxyl group and H5 were in a cis relationship. Thus it was determined that bicyclo[3.2.0]heptan-1-ol 253 was the (1RS, 5SR, 7SR)-isomer.
A relative downfield $\delta$ value of H7 ($\delta$ 3.79 ppm) was indicative of a *trans* relationship between the hydroxyl and sulfonyl groups (Figure 1b). For bicyclo[n.2.0]alkan-1-ol 254, couplings of 10 Hz to H6 and 10 Hz to H6 were observed for H7. The absence of the 1 Hz coupling between H7 and H5 was correlated with a *cis* relationship of H7 and H5 (Figure 1b) and thus a *trans* relationship between the hydroxyl and sulfonyl groups in bicyclo[n.2.0]alkan-1-ol 254. The additional 1 Hz coupling observed for H7 of bicyclo[3.2.0]heptan-1-ol 254 was assigned to a W-coupling between H7 and H2 in the cyclopentyl ring. Thus, it was determined that bicyclo[3.2.0]heptan-1-ol 254 was the (1RS, 5SR, 7RS)-isomer.

The assignment of the relative stereochemistries of 253 and 254 were correlated by X-ray crystallography of the bicyclo[3.2.0]heptan-1-ol 253. Single crystals of the bicyclo[3.2.0]heptan-1-ol 253 were obtained by slow diffusion of diethyl ether into a solution of pure bicyclo[3.2.0]heptan-1-ol 253 in dichloromethane and the X-ray crystal structure obtained from these crystals. The relative stereochemistry of (1RS, 5SR, 7SR)-253 was assigned using the X-ray crystal structure. This confirmed the assignments of stereochemistry for bicyclo[3.2.0]heptan-1-ol 253 obtained from the solution state structure. The ORTEP plot for bicyclo[3.2.0]heptan-1-ol 253 is displayed in figure 2a. To facilitate later discussion, a non-IUPAC numbering will be used here and elsewhere in the ORTEP plots contained within the discussion. Proper IUPAC numbering of such structures is reserved for appendix one. In the X-ray structure of 253 the S-O3 bond is

![Figure 1](https://example.com/figure1.png)
directed away from the bicyclo[3.2.0]alkan-1-ol ring whereas the S-O2 bond is oriented towards this ring, resulting in intramolecular hydrogen bonding interactions with the hydroxyl proton with O1···O2 distances of 2.954 Å for bicyclo[3.2.0]heptan-1-ol 253. The five-membered ring displays a pseudo-‘half-chair’ conformation with a minor distortion from planarity for a plane through C4-C1-C7-C6. Further discussion of the structure of the bicyclo[3.2.0]heptan-1-ol 253 is reserved for chapter two.

Single crystals of the monoalkylated cyclopentanone 257 were also obtained by slow evaporation of a hexane-ethyl acetate (60:40) solution and the X-ray crystal structure obtained from these crystals. The ORTEP plot of monoalkylated cyclopentanone 257 is displayed in figure 2b.

![ORTEP diagram of bicyclo[3.2.0]heptan-1-ol 253](image)

![ORTEP diagram of monoalkylated cyclopentanone 257](image)

**Figure 2** ORTEP diagrams of the molecular structures of (a) bicyclo[3.2.0]heptan-1-ol 253 and (b) monoalkylated cyclopentanone 257. The thermal ellipsoids are drawn at the 30% probability level

One further substituted bicyclo[3.2.0]heptan-1-ol had been isolated, albeit in low yield. The structure of the substituted bicyclo[3.2.0]heptan-1-ol 255 was unambiguously determined from the following spectral information. Mass spectrometry and microanalysis results indicated a molecular mass of 420 amu, which was consistent with a molecular formula of C_{21}H_{34}S_{2}O_{5} and the formation of either bicyclo[3.2.0]heptan-1-
ol 255 or dialkylated cyclopentanone such as 256. Absence of a carbonyl stretch within the FTIR spectrum and an absorption at 3451 cm\(^{-1}\) attributed to the hydroxyl group supported the bicyclo[3.2.0]heptan-1-ol 255 structure. Absorptions at 1305 cm\(^{-1}\) and 1147 cm\(^{-1}\) were indicative of a sulfonyle group.

The substituted bicyclo[3.2.0]heptan-1-ol 255 possessed an extra side-chain as shown in scheme 67 and figure 3. The connectivity of the cyclobutyl ring was assigned using the methodology described previously, however presented herein are the key correlations. A three-proton connectivity for the cyclobutyl ring was apparent from correlations between the signals due to H7 (δ 3.50 ppm) and H6 (δ 2.20 ppm) and H6 (δ 1.60-1.74 ppm) in the gCOSY nmr spectrum and the coupling constants observed for these signals in the \(^1\)H nmr spectrum (Table 1). The four proton connectivity of the side chain was apparent from correlations between the signals due to H2' (δ 3.01-3.15 ppm) and H1' (δ 2.11 ppm) and H1' (δ 1.88 ppm) in the gCOSY nmr spectrum. A signal at δ 49.2 ppm in the \(^{13}\)C nmr spectrum was determined to be a quaternary carbon by its absence in the gHSQC nmr spectrum and thus assigned as C5. In the HMBC nmr spectrum, \(^2\)J correlations between C5 and H1' (δ 1.88, 2.11 ppm), H6 (δ 1.60-1.74, 2.20 ppm), and \(^3\)J correlations between C5 and H7 (δ 3.50 ppm), H2' (δ 3.01-3.15 ppm), between C4 (δ 35.9 ppm) and H1' (δ 1.88, 2.11 ppm), and between C1 (δ 83.4 ppm) and H6 (δ 1.60-1.74, 2.20 ppm), H1' (δ 1.88, 2.11 ppm) were observed (Figure 3). It was inferred from the 10 and 7 Hz couplings of H7 and the upfield shift of H7 (δ 3.50 ppm) that a cis relationship existed between the hydroxyl and sulfonyle groups (Figure 3). The relative stereochemistry at C5 was not established by two-dimensional nmr spectroscopy methods. However, upon comparison of the shifts of H1' for bicyclo[3.2.0]heptan-1-ol 255 (δ 1.88, 2.11 ppm) and monoalkylated cyclopentanone 257 (δ 1.67-1.83, 1.93-2.00 ppm) it was inferred that the side chain at C5 was proximal to an oxygen and thus the
ring junction was *cis* (Figure 3). Thus it was established that bicyclo[3.2.0]heptan-1-ol 255 was the (1RS, 5RS, 7SR)-isomer as shown (scheme 67).

![Figure 3](image)

**Figure 3** Representation of the relative stereochemistry for substituted bicyclo[3.2.0]heptan-1-ol 255

The formation of substituted bicyclo[3.2.0]heptan-1-ol 255 albeit in very low yield was unexpected. As observed in scheme 67, the reaction between cyclopentanone and the electrophile phenyl vinyl sulfoxide via method A also resulted in the formation of the symmetrical dialkylated adduct 256. Kinetic versus thermodynamic product formation in the polyalkylation of non-symmetrical ketone enolates is dependent on the nature of the substrate, the base, the cation and the solvent. The more substituted enolate is considered the thermodynamic intermediate. Assuming an ionic mechanism for the lithium enolate of cyclopentanone, reaction with phenyl vinyl sulfoxide will give the monoalkylated anion 258a (scheme 68). Further reaction of the monoalkylated anion 258a with phenyl vinyl sulfoxide was not observed. Rather dialkylation occurred at the sites of enolate formation on the cyclopentanone ring (C2, C5). Given the pKₐ difference between a proton alpha to a sulfoxide (∼ -2) or a ketone (∼ 20-25), the formation of dialkylated species on the cyclopentanone ring could be attributed to the presence of base. This would lead to the formation of dianion 258b, which must be equilibrating to some extent to give the dianion 258c (scheme 69). Alkylation of 258b with another equivalent of phenyl vinyl sulfoxide then results in the formation of the dialkylated intermediate 259 ultimately leading to 256. Whereas alkylation of 258c with phenyl vinyl sulfoxide would give the 2,2-dialkylated intermediate 260. Cyclisation of
the 2,2-dialkylated intermediate 260, perhaps promoted by conformational effects arising from the presence of two alkyl side chains at position two results in the formation of the corresponding sulfinylbicyclo[3.2.0]heptan-1-olide intermediate 261 which upon quenching and oxidation would give the substituted bicyclo[3.2.0]heptan-1-ol 255.

![Scheme 68](image1)

Scheme 68

At this point, the four and five membered ketones, cyclobutanone and cyclopentanone had been examined. As previously mentioned, synthetic and mechanistic studies were conducted within the group with the six membered ketone cyclohexanone. Thus cyclohexanone was not considered for the current study on the scope of simple ring ketones in the cyclisation reaction. Therefore the next example examined was the seven-membered ketone, cycloheptanone.

![Scheme 69](image2)

Scheme 69
3.0 Reaction with Cycloheptanone – Method A

The lithium enolate of cycloheptanone was reacted with phenyl vinyl sulfoxide using method A and upon oxidation of the crude sulfoxide mixture gave monoalkylated cycloheptanone \( \text{264} \)\(^{153} \) (41%) as the major product, in conjunction with the bicyclo[5.2.0]nonan-1-ols \( \text{262} \) (26%) and \( \text{263} \) (8%) (scheme 70). Isolation by column chromatography followed by HPLC, gave analytically pure samples of monoalkylated cycloheptanone \( \text{264} \) and bicyclo[5.2.0]nonan-1-ols \( \text{262} \) and \( \text{263} \).

![Diagram](image)

Method A: (i) LDA, THF, -78 °C, (ii) PhS(O)CH=CH\(_2\) dropwise, -30 °C (iii) 0 °C, 45 min

Scheme 70

Mass spectrometry and microanalysis results for bicyclo[5.2.0]nonan-1-ols \( \text{262} \) and \( \text{263} \) indicated a molecular mass of 280 amu which is consistent with the formation of the bicyclo[5.2.0]nonan-1-ols \( \text{262} \) or \( \text{263} \) and the monoalkylated cycloheptanone \( \text{264} \). Absorptions of 3505 cm\(^{-1}\) and 3452 cm\(^{-1}\) in the FTIR spectra for bicyclo[5.2.0]nonan-1-ol \( \text{262} \) and bicyclo[5.2.0]nonan-1-ol \( \text{263} \) were attributable to a hydroxyl group. Absence of a carbonyl stretch in either FTIR spectrum supported the formation of the bicyclo[5.2.0]nonan-1-ols \( \text{262} \) and \( \text{263} \). Absorptions, indicative of a sulfonyl group at 1307 cm\(^{-1}\) and 1148 cm\(^{-1}\) for \( \text{262} \) and 1300 cm\(^{-1}\) and 1143 cm\(^{-1}\) for \( \text{263} \) were evident.
Next, the connectivity of the cyclobutyl ring system of bicyclo[5.2.0]nonan-1-ols 262 and 263 was established by one-dimensional and two-dimensional nmr analysis. Key assignments and δ values from the 1H and 13C nmr spectra of the bicyclo[5.2.0]nonan-1-ols 262 and 263 are reported in table 2. The connectivity of the cyclobutyl ring was assigned using the methodology described previously. Based on the shifts and couplings observed for H9, H7 and H8 (Table 2) using the rationalisation presented above it was established that, bicyclo[5.2.0]nonan-1-ol 262 was the (1RS, 7SR, 9SR)-isomer and bicyclo[5.2.0]nonan-1-ol 263 was the (1RS, 7SR, 9RS)-isomer.

Table 2 Key assignments and δ values (ppm) from the 1H and 13C nmr spectra of bicyclo[5.2.0]nonan-1-ols 262 and 263

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C9</th>
<th>C7</th>
<th>H9</th>
<th>H8</th>
<th>H8</th>
<th>H7</th>
</tr>
</thead>
<tbody>
<tr>
<td>262</td>
<td>78.9</td>
<td>64.1</td>
<td>48.7</td>
<td>3.53 (ddd, 9.5, 5.5, 1 Hz)</td>
<td>2.48-2.66</td>
<td>1.54-1.80</td>
<td>2.48-2.66</td>
</tr>
<tr>
<td>263</td>
<td>81.8</td>
<td>66.0</td>
<td>45.0</td>
<td>3.60 (dd, 10, 9 Hz)</td>
<td>1.90-2.07</td>
<td>1.65-1.78</td>
<td>2.17-2.30</td>
</tr>
</tbody>
</table>

Single crystals of the bicyclo[5.2.0]nonan-1-ol 262 were obtained by slow diffusion of diethyl ether into a solution of pure bicyclo[5.2.0]nonan-1-ol 262 in dichloromethane and the X-ray crystal structure obtained from these crystals. The relative stereochemistry of (1RS, 7SR, 9SR)-262 was assigned using the X-ray crystal structure. This confirmed the assignments of stereochemistry for bicyclo[5.2.0]nonan-1-ol 262 obtained from the solution state structure. The ORTEP plot for bicyclo[5.2.0]nonan-1-ol 262 is displayed in figure 4. In the X-ray structure of bicyclo[5.2.0]nonan-1-ol 262 the S-O3 bond is directed away from the bicyclo[n.2.0]alkan-1-ol ring whereas the S-O2 bond is oriented towards this ring, resulting in intramolecular hydrogen bonding interactions with the hydroxyl proton with O1⋅⋅⋅O2 distances of 2.972 Å for bicyclo[5.2.0]nonan-1-ol 262. In the seven-membered ring of 262 the ring adopts a pseudo-‘twist-chair’ conformation. The plane through C5-C6-C8-C9 shows a minor distortion from planarity but in the plane through C1-C4-C5-C9 the distortion is more
pronounced. Further discussion of the structure of the bicyclo[5.2.0]nonan-1-ol 262 is reserved for chapter two.

Figure 4 ORTEP diagram of the molecular structure of bicyclo[5.2.0]nonan-1-ol 262. The thermal ellipsoids are drawn at the 30% probability level

4.0 Reaction with Cyclooctanone – Method A

In the final example, the lithium enolate of cyclooctanone was reacted with phenyl vinyl sulfoxide using method A and upon oxidation of the crude sulfoxide mixture gave monoalkylated cyclooctanone 266\textsuperscript{153} (65%) as the major product in conjunction with the dialkylated cyclooctanone 267 (14.5%) and bicyclo[6.2.0]decan-1-ol 265 (2%) (scheme 71). Isolation by column chromatography followed by HPLC, resulted in analytically pure samples of monoalkylated cyclooctanone 266, dialkylated cyclooctanone 267 and bicyclo[6.2.0]decan-1-ol 265. Unlike the simple ketones cyclobutanone, cycloheptanone, cyclohexanone and cycloheptanone, reaction with cyclooctanone using method A resulted in the formation of only one bicyclo[n.2.0]alkan-1-ol, the bicyclo[6.2.0]decan-1-ol 265.
Method A: (i) LDA, THF, -78 °C, (ii) Ph(S)OCH=CH₂ dropwise, -30 °C (iii) 0 °C, 45 min

**Scheme 71**

Similar to that observed for cyclopentanone, a dialkylated adduct 267 was obtained for the reaction between the lithium enolate of cyclooctanone and phenyl vinyl sulfoxide (method A). Compared to the results obtained for cyclopentanone (dialkylated cyclopentanone 256, 2.5%) a larger percentage of the reaction mixture was attributed to the dialkylated product 267 (14.5%). This was attributed to a difference in reactivity of the cyclooctanone enolate and monoalkylated cyclooctanone enolate with phenyl vinyl sulfoxide and also may have been due to the presence of base.

Mass spectrometry and microanalysis results for bicyclo[6.2.0]decan-1-ol 265 indicated a molecular mass of 294 amu, which was consistent with the formation of the bicyclo[6.2.0]decan-1-ol 265 and the monoalkylated cyclooctanone 266. Absence of the carbonyl stretch in the FTIR spectrum and the presence of a hydroxyl (3527 cm⁻¹) in conjunction with stretches at 1282 cm⁻¹ and 1155 cm⁻¹ indicative of a sulfonyl group supported the bicyclo[6.2.0]decan-1-ol 265 structure.

Key assignments and δ values from the ¹H and ¹³C nmr spectra of the bicyclo[6.2.0]decan-1-ol 265 are reported in table 3. Using the methodology previously
described in the structural elucidation of the bicyclo[\textit{n}.2.0]alkan-1-ols \textit{253}, \textit{254}, \textit{255}, \textit{262}, and \textit{263}, bicyclo[6.2.0]decan-1-ol \textit{265} was assigned based on the shifts and couplings observed for H10, H8 and H9 (Table 3). Using the rationalisation presented above it was established that, bicyclo[5.2.0]decan-1-ol \textit{265} was the (1\textit{RS}, 8\textit{SR}, 10\textit{SR})-isomer.

\textbf{Table 3} Key assignments and $\delta$ values (ppm) from the $^1\text{H}$ and $^{13}\text{C}$ nmr spectra of bicyclo[6.2.0]decan-1-ol \textit{265}

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C10</th>
<th>C8</th>
<th>H10</th>
<th>H9</th>
<th>H9</th>
<th>H8</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{265}</td>
<td>78.3</td>
<td>65.3</td>
<td>48.1</td>
<td>3.44 (ddd, 10, 6, 1 Hz)</td>
<td>2.61</td>
<td>1.39-1.60</td>
<td>2.30-2.39</td>
</tr>
</tbody>
</table>

Single crystals of the bicyclo[6.2.0]decan-1-ol \textit{265} were obtained by slow diffusion of diethyl ether into a solution of pure bicyclo[6.2.0]decan-1-ol \textit{265} in dichloromethane and the X-ray crystal structure obtained from these crystals. The relative stereochemistry of (1\textit{RS}, 8\textit{SR}, 10\textit{SR})-\textit{265} was assigned using the X-ray crystal structure. This confirmed the assignments of stereochemistry for bicyclo[6.2.0]decan-1-ol \textit{265} obtained from the solution state structure. The ORTEP plot of bicyclo[6.2.0]decan-1-ol \textit{265} is displayed in figure 5. In the X-ray structure of bicyclo[6.2.0]decan-1-ol \textit{265} the S-O3 bond is directed away from the bicyclo[\textit{n}.2.0]alkan-1-ol ring whereas the S-O2 bond is oriented towards this ring, resulting in intramolecular hydrogen bonding interactions with the hydroxyl proton with O1...O2 distances of 2.888 Å for bicyclo[6.2.0]decan-1-ol \textit{265}. In the eight-membered ring of \textit{265} the ring adopts a pseudo-‘chair-boat’\textsuperscript{155} conformation. The plane of C1-C10-C7-C8 in the ‘chair’ shows a minor deviation from planarity but the plane of C1-C4-C6-C7 in the ‘boat’ shows a significant deviation from planarity. Further discussion of the structure of bicyclo[6.2.0]decan-1-ol \textit{265} is reserved for chapter two.
Figure 5 ORTEP diagram of the molecular structure of bicyclo[6.2.0]decan-1-ol 265. The thermal ellipsoids are drawn at the 30% probability level.

In summary, the key assignments and δ values for the bicyclo[n.2.0]alkan-1-ols 253, 254, 255, 262, 263 and 265 are collated in table 4, using non-IUPAC labels (Figure 6) to aid comparison. Throughout the series for all the cis compounds 253, 262 and 265 the relative configurations were established by $^1$H nmr and X-ray crystallography. This comparison supports the trends and conclusions drawn from the δ shift values as discussed previously for 253, 255, 262 and 265 and thus those for compounds 254 and 263.

Table 4 Summary of key assignments and δ values (ppm) from the $^1$H and $^{13}$C nmr spectra of bicyclo[3.2.0]heptan-1-ols 253, 254 and 255, bicyclo[5.2.0]nonan-1-ols 262 and 263, and bicyclo[6.2.0]decan-1-ol 265

<table>
<thead>
<tr>
<th></th>
<th>$\text{C}_a$</th>
<th>$\text{C}_b$</th>
<th>$\text{C}_d$</th>
<th>$\text{H}_b$</th>
<th>$\text{H}_c$</th>
<th>$\text{H}_d$</th>
<th>$\text{H}_e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>253</td>
<td>83.6</td>
<td>64.2</td>
<td>46.3</td>
<td>3.62 (ddd, 9.5, 5.5, &lt;1 Hz)</td>
<td>2.62-2.72</td>
<td>1.46-1.60</td>
<td>2.62-2.72</td>
</tr>
<tr>
<td>254</td>
<td>85.3</td>
<td>65.3</td>
<td>44.6</td>
<td>3.79 (ddd, 10, 10, 1 Hz)</td>
<td>2.04-2.22</td>
<td>1.68-1.95</td>
<td>2.45-2.54</td>
</tr>
<tr>
<td>255</td>
<td>83.4</td>
<td>62.2</td>
<td>49.2</td>
<td>3.50 (dd, 10, 7 Hz)</td>
<td>2.20</td>
<td>1.60-1.74</td>
<td>-</td>
</tr>
<tr>
<td>262</td>
<td>78.9</td>
<td>64.1</td>
<td>48.7</td>
<td>3.53 (ddd, 9.5, 5.5, 1 Hz)</td>
<td>2.48-2.66</td>
<td>1.54-1.80</td>
<td>2.48-2.66</td>
</tr>
<tr>
<td>263</td>
<td>81.8</td>
<td>66.0</td>
<td>45.0</td>
<td>3.60 (dd, 10, 9 Hz)</td>
<td>1.90-2.07</td>
<td>1.65-1.78</td>
<td>2.17-2.30</td>
</tr>
<tr>
<td>265</td>
<td>78.3</td>
<td>65.3</td>
<td>48.1</td>
<td>3.44 (ddd, 10, 6, 1 Hz)</td>
<td>2.61</td>
<td>1.39-1.60</td>
<td>2.30-2.39</td>
</tr>
</tbody>
</table>
Figure 6 Correlation of IUPAC numbering and generalised label for bicyclo[\(n.2.0\)]alkan-1-ols

With method A results complete for the simple ketones cyclobutanone, cyclopentanone, cycloheptanone and cyclooctanone and the structural elucidation of six novel bicyclo[\(n.2.0\)]alkan-1-ols completed attention now was focussed on some simple synthetic variations of the reaction conditions.
Enthusiasm is the genius of sincerity, and truth accomplishes no victories without it

*Lord Bulwer-Lytton*
Chapter Two

Formation of Bicyclo[n.2.0]alkan-1-ols, Selected Variations in Reaction Conditions

With the elucidation of the structures of the bicyclo[n.2.0]alkan-1-ols established in chapter one it was next sought to improve the ratio of the bicyclo[n.2.0]alkan-1-ols to alkyalted products. Initial results within the study on bicyclo[4.2.0]octan-1-ols running concurrently within the group with the current exploration of ring size showed that provided accurate control of temperature, concentration and reaction time the formation of the desired novel bicyclo[n.2.0]alkan-1-ols could be improved. A reaction temperature of -10 °C and reaction time of 10 minutes were considered optimal for bicyclo[4.2.0]octan-1-ols. However at the time of the body of work carried out in chapter two the bicyclo[4.2.0]octan-1-ol work was still in progress. As a consequence a shorter reaction time of 5 minutes, reaction temperature of –30 °C and dark reaction conditions were chosen for the first variation in the present study. The exclusion of light was introduced in order to remove potential competing pathways that may be light promoted, and the rapid addition of phenyl vinyl sulfoxide was employed to decrease the time for potential equilibration of intermediates. A reaction time of less than 15 minutes was shown to favour bicyclo[4.2.0]octan-1-ol formation over monoalkylation. For consistency the remaining present studies were carried out with the chosen reaction time of 5 minutes, absence of light and phenyl vinyl sulfoxide addition. However in light of the final results of the bicyclo[4.2.0]octan-1-ol study it is acknowledged that the conditions of the present study probably represents unoptimised conditions. Thus in an overview, the lithium enolate of the simple ketones, cyclobutanone, cyclopentanone, cycloheptanone or cyclooctanone were reacted rapidly with phenyl vinyl sulfoxide at –30 °C for 5 minutes in the dark (method B, Table 5).
Oxidation of the crude sulfoxide mixtures with m-CPBA resulted in the formation of the corresponding sulfonyl products.

1.0 Reaction with Cyclobutanone - Method B

The lithium enolate of cyclobutanone was reacted with phenyl vinyl sulfoxide using method B. Upon workup and subsequent oxidation of the sulfoxide mixture, analysis of the crude mixture by $^1$H nmr indicated the presence of the cyclohexanone 248 (6%) and the monoalkylated cyclobutanone 249 (18%) in low yields. Key peaks in the region of $\delta$ 2.5-4.0 ppm indicating the presence of a bicyclo[2.2.0]alkan-1-ol structure again were absent. The product yields obtained for the reaction of cyclobutanone and phenyl vinyl sulfoxide from methods A and B are summarised in table 5.

![Structures 248 and 249]

**Table 5** Product yields for the reaction of the lithium enolate of cyclobutanone and phenyl vinyl sulfoxide from methods A and B after m-CPBA oxidation

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Reaction Method</th>
<th>A (%) Yield</th>
<th>B (%) Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobutanone</td>
<td></td>
<td>5.5</td>
<td>6</td>
</tr>
<tr>
<td>248</td>
<td></td>
<td>38.5</td>
<td>18</td>
</tr>
<tr>
<td>249</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVS$^b$</td>
<td></td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

$^a$ Method A (0.155M, 45 min, -30 °C to 0 °C, laboratory light); Method B (0.155M, 5 min, -30 °C, dark); $^b$ combined recovery of phenyl vinyl sulfoxide and/or yield of phenyl vinyl sulfone.

It was apparent from the results of method A and B that the formation of a bicyclo[2.2.0]hexan-1-ol was unlikely, even under the more favourable conditions of method B. The formation of cyclohexanone 248 was discussed in chapter one. The isolation of 248 from two different sets of reaction conditions and in very poor yields
suggested that no further change in conditions would effect isolation of a bicyclo[2.2.0]hexan-1-ol. Thus no further experiments were carried out with cyclobutanone and attention was turned to cyclopentanone.

2.0 Reaction with Cyclopentanone - Methods B-D

The lithium enolate of cyclopentanone and phenyl vinyl sulfoxide were reacted together using method B, and the crude sulfoxide mixture subsequently oxidised by \textit{m}-CPBA. Analysis of the crude sulfone mixture by $^1$H nmr showed an increase in the formation of the major bicyclo[3.2.0]heptan-1-ol 253 from 3\% to 18.5\% with a corresponding decrease in monoalkylated cyclopentanone 257 from 55.5\% to 19.5\% (Table 6). The minor products 254, 255 and 256 also were observed in marginal yields (< 1\%) with a slight decrease in the overall conversion of phenyl vinyl sulfoxide (6\% recovery).

Having established an improvement in the ratio of bicyclo[3.2.0]heptan-1-ols to alkylated products, next it was sought to explore the effects of total concentration of the reaction mixture on the product outcome. A dilute set of reaction conditions of 0.01 M (method C, Table 6) and a more concentrated set of conditions of 0.31 M (method D, Table 6) were investigated to determine the concentration effects on the cyclisation of cyclopentanone. Thus the lithium enolate of cyclopentanone was reacted with phenyl vinyl sulfoxide using methods C and D respectively. The crude sulfoxide mixtures obtained were then separately oxidised using \textit{m}-CPBA and the product distribution
yields are reported in table 6. To aid in the comparison of the effect in change of reaction concentration, the ratio of bicyclo[3.2.0]heptan-1-ols 253 and 254 to alkylated products 256 and 257 are shown in table 7. The methods in which the only variable was the change in concentration are shown, methods B, C and D.

**Table 6** Product yields for the reaction of the lithium enolate of cyclopentanone and phenyl vinyl sulfoxide from methods A-D after \( m \)-CPBA oxidation

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Product</th>
<th>Reaction Method(^a)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclopentanone</td>
<td>253</td>
<td>0.01</td>
<td>55.5</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>254</td>
<td>0.01</td>
<td>55.5</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>255</td>
<td>0.01</td>
<td>55.5</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>256</td>
<td>0.01</td>
<td>55.5</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>257</td>
<td>0.01</td>
<td>55.5</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>PVS(^b)</td>
<td>0</td>
<td>0.01</td>
<td>55.5</td>
<td>0.5</td>
<td>1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\(^a\) Method A (0.155M, 45 min, -30 °C to 0 °C, laboratory light); Method B (0.155M, 5 min, -30 °C, dark); Method C (0.01M, 5 min, -30 °C, dark); Method D (0.31M, 5 min, -30 °C, dark); \(^b\) combined recovery of phenyl vinyl sulfoxide and/or yield of phenyl vinyl sulfone.

**Table 7** Product ratios for the reaction of the lithium enolate of cyclopentanone and phenyl vinyl sulfoxide from methods B-D after \( m \)-CPBA oxidation

<table>
<thead>
<tr>
<th>Reaction Method(^a)</th>
<th>Reaction Concentration (M)</th>
<th>Product Ratio 253 : 254 : 256 : 257</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>0.01</td>
<td>56:44</td>
</tr>
<tr>
<td>B</td>
<td>0.155</td>
<td>49:51</td>
</tr>
<tr>
<td>D</td>
<td>0.31</td>
<td>48:52</td>
</tr>
</tbody>
</table>

\(^a\) Method B (0.155M, 5 min, -30 °C, dark); Method C (0.01M, 5 min, -30 °C, dark); Method D (0.31M, 5 min, -30 °C, dark)

Over the concentration range 0.01 M, 0.155 M and 0.31 M it can be seen that the approximate ratio of the major bicyclo[3.2.0]heptan-1-ol isomer 253 and bicyclo[3.2.0]heptan-1-ol 254 to alkylated cyclopentanones 256 and 257 is approximately 50:50. Taking into consideration recovery of phenyl vinyl sulfoxide
(26.5%) and overall yield of bicyclo[3.2.0]heptan-1-ols (27.5%) the optimal reaction concentration chosen from the present set of conditions (methods B-D) was of dilute conditions, 0.01 M. A fuller discussion is reserved for the end of the chapter.

3.0 Reaction with Cycloheptanone - Methods B-D

Previously reaction of the lithium enolate of cycloheptanone with phenyl vinyl sulfoxide via method A resulted in the formation of the bicyclo[5.2.0]nonan-1-ols 262 (61.5%) and 263 (8.5%) and monoalkylated cycloheptanone 264 (3%). Reaction of the lithium enolate of cycloheptanone and phenyl vinyl sulfoxide using method B followed by oxidation of the crude sulfoxide mixture resulted, in addition to the above mentioned products, the substituted bicyclo[5.2.0]nonan-1-ol 268 in very low yield (1%) (Table 9).

The substituted bicyclo[5.2.0]nonan-1-ol 268 was isolated by column chromatography followed by HPLC. An analytically pure sample was obtained and analysis by high resonance mass spectrometry, FTIR, $^1$H nmr, $^{13}$C nmr and two-dimensional nmr spectroscopy confirmed the structure to be that of the substituted bicyclo[5.2.0]nonan-1-ol 268. High resolution mass spectrometry indicated a molecular mass of 448 amu, which is consistent with the formation of the substituted bicyclo[5.2.0]nonan-1-ol 268 and dialkylated cycloheptanone. However absence of a carbonyl stretch in the FTIR spectrum and the presence of a hydroxyl stretch at 3536 cm$^{-1}$ removed the possibility of the dialkylated product. Absorptions attributable to a sulfonyl group at 1302 cm$^{-1}$ and
1149 cm$^{-1}$ also were observed. Key assignments and $\delta$ values from the $^1$H and $^{13}$C nmr spectra of the bicyclo[5.2.0]heptan-1-ol 268 are reported in table 8.

**Table 8** Key assignments and $\delta$ values (ppm) from the $^1$H and $^{13}$C nmr spectra of substituted bicyclo[5.2.0]nonan-1-ol 268

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C9</th>
<th>C7</th>
<th>H9</th>
<th>H8</th>
<th>H8</th>
<th>H7</th>
</tr>
</thead>
<tbody>
<tr>
<td>268</td>
<td>81.7</td>
<td>62.7</td>
<td>49.6</td>
<td>3.74 (dd, 10.5, 4 Hz)</td>
<td>2.47-2.62</td>
<td>1.27-1.46</td>
<td>2.47-2.62</td>
</tr>
</tbody>
</table>

**Figure 7** Representation of the relative stereochemistry about the cyclobutanol ring for bicyclo[5.2.0]nonan-1-ol 268

The substituted bicyclo[n.2.0]alkan-1-ol 268 displayed an extra signal due to a CH in the HSQC nmr spectrum. It was assigned as C2-H2 on the cycloheptyl ring. A $^2$J correlation between C1 and H2 and $^2$J and $^3$J correlations between C2 and H1' and H2' respectively were observed in the HMBC nmr spectrum. The four proton connectivity of the side chain also was apparent in the signals due to H2' ($\delta$ 3.09, 2.97 ppm) and H1' ($\delta$ 1.27-1.46, 1.46-1.91 ppm) in the gCOSY nmr spectrum. It was inferred from the 10.5 and 4 Hz couplings of H9 and the shift of H9 that a cis relationship existed between the hydroxyl and C9 sulfonyl group and H7 and the C9 sulfonyl group. The relative stereochemistry at C2 was unable to be established by two-dimensional nmr spectroscopy methods. A NOESY nmr spectrum of 268 was obtained but the correlations observed were too ambiguous to permit the stereochemistry at C2 to be assigned. However, the upfield shift of H1' ($\delta$ 1.27-1.46, 1.46-1.91 ppm) for bicyclo[5.2.0]nonan-1-ol 268 compared to that for H1’ in compounds bicyclo[3.2.0]heptan-1-ol 255 and monoalkylated cyclopentanone 257 as previously
discussed (chapter one, section 2.0) suggested that the side chain at C2 and the hydroxyl group were on opposite sides of the bicyclo[5.2.0]alkan-1-ol ring. Thus, it was established that bicyclo[5.2.0]nonan-1-ol 268 was the (1RS, 2RS, 7SR, 9SR)-isomer.

Next the lithium enolate of cycloheptanone was reacted with phenyl vinyl sulfoxide using methods C and D respectively followed by oxidation of the crude sulfoxide mixture with m-CPBA. The product distribution yields obtained are collated in table 9 and the product ratios summarised in table 10.

Table 9 Product yields for the reaction of the lithium enolate of cycloheptanone and phenyl vinyl sulfoxide from methods A-D after m-CPBA oxidation

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Product</th>
<th>Reaction Method(^a)</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycloheptanone</td>
<td>262</td>
<td></td>
<td>26</td>
<td>61.5</td>
<td>42</td>
<td>43.5</td>
</tr>
<tr>
<td></td>
<td>263</td>
<td></td>
<td>8</td>
<td>8.5</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>268</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>264</td>
<td></td>
<td>41</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>PVS(^b)</td>
<td></td>
<td></td>
<td>0</td>
<td>5</td>
<td>13.5</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^a\) Method A (0.155M, 45 min, -30 °C to 0 °C, laboratory light); Method B (0.155M, 5 min, -30 °C, dark); Method C (0.01M, 5 min, -30 °C, dark); Method D (0.31M, 5 min, -30 °C, dark); \(^b\)combined recovery of phenyl vinyl sulfoxide and/or yield of phenyl vinyl sulfone.

Whereas an approximate 50:50 ratio of bicyclo[5.2.0]alkan-1-ol to alkylated product was observed for the cyclopentanone example, the bicyclo[5.2.0]nonan-1-ols 262 and 263 were obtained as the major products in preference to the alkylated cycloheptanone 264 and in an approximate 90:10 ratio. Notably from the present set of conditions (methods B-D) the best ratio of 96:4 for the bicyclo[5.2.0]nonan-1-ols 262 and 263 to alkylated cycloheptanone 264 and a combined 70% yield for 262 and 263 was obtained from the intermediate concentration (0.155 M). A fuller discussion is reserved for the end of this chapter.
Table 10 Product ratios for the reaction of the lithium enolate of cycloheptanone and phenyl vinyl sulfoxide from methods B-D after m-CPBA oxidation

<table>
<thead>
<tr>
<th>Reaction Method(^a)</th>
<th>Reaction Concentration (M)</th>
<th>Product Ratio 262 : 263 : 264</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>0.01</td>
<td>89:11</td>
</tr>
<tr>
<td>B</td>
<td>0.155</td>
<td>96:4</td>
</tr>
<tr>
<td>D</td>
<td>0.31</td>
<td>86:14</td>
</tr>
</tbody>
</table>

\(^a\) Method B (0.155M, 5 min, -30 \(^\circ\)C, dark); Method C (0.01M, 5 min, -30 \(^\circ\)C, dark); Method D (0.31M, 5 min, -30 \(^\circ\)C, dark)

4.0 Reaction with Cyclooctanone - Methods B-D

In the final example reaction of the lithium enolate of cyclooctanone with phenyl vinyl sulfoxide using method B resulted in the formation of the bicyclo[6.2.0]decan-2-ol 269 (3.5%) in addition to the products 265 (19%), 266 (49.5%) and 267 (9%) previously observed in method A. Oxidation of the crude sulfoxide mixture from method B followed by column chromatography and HPLC resulted in an analytically pure sample of bicyclo[6.2.0]decan-2-ol 269 being obtained.

A molecular mass of 294 amu was obtained by mass spectrometry. This and the microanalysis results were consistent with a molecular formula of C\(_{16}\)H\(_{22}\)O\(_3\)S and the formation of a bicyclo[5.2.0]decan-1-ol or monoalkylated cyclooctanone 266. Previous elucidation (chapter one, section 4.0) of the bicyclo[5.2.0]decan-1-ol 265 and monoalkylated cyclooctanone 266 allowed direct comparison to the \(^1\)H nmr spectra of bicyclo[6.2.0]decan-1-ol 269. Adding further support to the formation of bicyclo[6.2.0]decan-2-ol 269 absence of a carbonyl stretch and the presence of a
The connectivity of the cyclobutyl ring was assigned using the methodology previously described in chapter one. Key assignments and δ values from the $^1$H and $^{13}$C nmr spectra of the bicyclo[6.2.0]decan-1-ol 269 are reported in table 11. Based on the shifts and couplings observed for H10, H8 and H9 and using the rationalisation presented in chapter one, section 2.0, it was established that, bicyclo[6.2.0]decan-1-ol 269 was the (1RS, 8SR, 10RS)-isomer.

### Table 11 Key assignments and δ values (ppm) from the $^1$H and $^{13}$C nmr spectra of bicyclo[6.2.0]decan-1-ol 269

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C10</th>
<th>C9</th>
<th>H10 (ppm)</th>
<th>H9</th>
<th>H9 (ppm)</th>
<th>H8 (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>269</td>
<td>81.4</td>
<td>67.3</td>
<td>44.6</td>
<td>3.58 (dd, 10.5, 9 Hz)</td>
<td>1.86-1.95</td>
<td>1.62-1.77</td>
<td>1.96-2.05</td>
</tr>
</tbody>
</table>

Next the lithium enolate of cyclooctanone was reacted with phenyl vinyl sulfoxide using methods C and D, and the crude sulfoxide mixtures oxidised using $m$-CPBA. The product distribution yields obtained are given in table 12 and the product ratios summarised in table 13.

### Table 12 Product yields for the reaction of the lithium enolate of cyclooctanone and phenyl vinyl sulfoxide from methods A-D after $m$-CPBA oxidation

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Product</th>
<th>Reaction Method$^a$</th>
<th>A (% Yield)</th>
<th>B</th>
<th>C (% Yield)</th>
<th>D (% Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclooctanone</td>
<td>265</td>
<td></td>
<td>2</td>
<td>19</td>
<td>6</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>269</td>
<td></td>
<td>0</td>
<td>3.5</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>266</td>
<td></td>
<td>65</td>
<td>49.5</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>267</td>
<td></td>
<td>14.5</td>
<td>9</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>PVS$^b$</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>0.5</td>
</tr>
</tbody>
</table>

$^a$ Method A (0.155M, 45 min, -30 °C to 0 °C, laboratory light); Method B (0.155M, 5 min, -30 °C, dark); Method C (0.01M, 5 min, -30 °C, dark); Method D (0.31M, 5 min, -30 °C, dark); $^b$ combined recovery of phenyl vinyl sulfoxide and/or yield of phenyl vinyl sulfone.
The use of cyclooctanone gave yet a different product ratio. The alkylated products 266 and 267 were obtained in preference to the bicyclo[6.2.0]decan-1-ols 265 and 269 in all concentrations studied. The ratio changed to increase the yield of bicyclo[6.2.0]decan-1-ols at higher concentration. Thus at 0.31 M the best ratio of 35:65 for bicyclo[6.2.0]decan-1-ols 265 and 269 to alkylated cyclooctanones 266 and 267 was observed.

**Table 13** Product ratios for the reaction of the lithium enolate of cyclooctanone and phenyl vinyl sulfoxide from methods B-D after m-CPBA oxidation

<table>
<thead>
<tr>
<th>Reaction Method&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Reaction Concentration (M)</th>
<th>Product Ratio 265 + 269: 266 + 267</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>0.01</td>
<td>12:88</td>
</tr>
<tr>
<td>B</td>
<td>0.155</td>
<td>28:72</td>
</tr>
<tr>
<td>D</td>
<td>0.31</td>
<td>35:65</td>
</tr>
</tbody>
</table>

<sup>a</sup> Method B (0.155M, 5 min, -30 °C, dark); Method C (0.01M, 5 min, -30 °C, dark); Method D (0.31M, 5 min, -30 °C, dark)

5.0 Comments

A comparative examination of the results for methods B-D for cyclopentanone, cycloheptanone and cyclooctanone reveals an interesting perspective. To assist the discussion, tables 14 and 15 collate the results presented within each simple ketone. For the simple ketones, cyclopentanone, cycloheptanone and cyclooctanone a comparison of the distribution of product ratios over the concentrations 0.01 M, 0.155 M and 0.31 M resulted in a notable change in trends for each. From the present set of conditions (methods B-D) bicyclo[3.2.0]heptan-1-ol formation was favoured under a dilute reaction concentration (0.01 M), bicyclo[5.2.0]nonan-1-ol formation was favourable at the intermediate concentration of 0.155 M and bicyclo[6.2.0]decan-1-ol formation favourable at the higher concentration of 0.31 M. However it is important to note that the trends reported in table 14 may be affected by the conversion of phenyl vinyl sulfoxide. It was noted that at the lower concentration of 0.01 M (method C), phenyl
vinyl sulfoxide conversion was lower than that observed for methods B (0.155 M) and D (0.31 M).

Table 14 Product yields for the reaction of the lithium enolates of cyclobutanone, cyclopentanone, cycloheptanone or cyclooctanone and phenyl vinyl sulfoxide from methods A-D after m-CPBA oxidation

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Product</th>
<th>Reaction Method(^a) (%) Yield</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclobutanone</td>
<td>248</td>
<td>5.5</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>249</td>
<td>38.5</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVS(^b)</td>
<td>0</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Cyclopentanone</td>
<td>253</td>
<td>3</td>
<td>18.5</td>
<td>26.5</td>
<td>22.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>254</td>
<td>2.5</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>257</td>
<td>55.5</td>
<td>19.5</td>
<td>22</td>
<td>25.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>256</td>
<td>2.5</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>255</td>
<td>1.5</td>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVS(^b)</td>
<td>0</td>
<td>6</td>
<td>26.5</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Cycloheptanone</td>
<td>262</td>
<td>26</td>
<td>61.5</td>
<td>42</td>
<td>43.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>263</td>
<td>8</td>
<td>8.5</td>
<td>5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>268</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>264</td>
<td>41</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVS(^b)</td>
<td>0</td>
<td>5</td>
<td>13.5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Cyclooctanone</td>
<td>265</td>
<td>2</td>
<td>19</td>
<td>6</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>269</td>
<td>0</td>
<td>3.5</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>266</td>
<td>65</td>
<td>49.5</td>
<td>44</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td></td>
<td>267</td>
<td>14.5</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVS(^b)</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Method A (0.155M, 45 min, -30 °C to 0 °C, laboratory light); Method B (0.155M, 5 min, -30 °C, dark); Method C (0.01M, 5 min, -30 °C, dark); Method D (0.31M, 5 min, -30 °C, dark); \(^b\) combined recovery of phenyl vinyl sulfoxide and/or yield of phenyl vinyl sulfone.
Table 15 Product ratios for the reaction of cyclopentanone, cycloheptanone or cyclooctanone and phenyl vinyl sulfoxide from methods B-D after m-CPBA oxidation

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Products</th>
<th>Reaction Method&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(product ratio)</td>
</tr>
<tr>
<td>Cyclopentanone</td>
<td>253 + 254: 256 + 257</td>
<td>56:44</td>
</tr>
<tr>
<td>Cycloheptanone</td>
<td>262 + 263: 264</td>
<td>89:11</td>
</tr>
</tbody>
</table>

<sup>a</sup>Method B (0.155M, 5 min, -30 °C, dark); Method C (0.01M, 5 min, -30 °C, dark); Method D (0.31M, 5 min, -30 °C, dark)

Comparison of the yields of bicyclo[3.2.0]heptan-1-ols 253, 254 and 255 to alkylated cyclopentanones 256 and 257 over the concentrations 0.01 M, 0.155 M and 0.31 M are shown in figure 8. Relative to cycloheptanone and cyclooctanone, the reaction of the lithium enolate of cyclopentanone under methods B-D, generally resulted in a lower conversion of phenyl vinyl sulfoxide being observed. Over the concentration range, combined yields of 39-49% for bicyclo[3.2.0]heptan-1-ols 253 and 254, substituted bicyclo[3.2.0]heptan-1-ol 255 and alkylated cyclopentanones 256 and 257 were observed.

![Figure 8](image-url)  
**Figure 8** Reaction Concentration vs. % Composition of product in total reaction products with cyclopentanone enolate for the products, monoalkylated cyclopentanone 257 (■), dialkylated cyclopentanone 256 (□), bicyclo[3.2.0]heptan-1-ol 253 (●), bicyclo[3.2.0]heptan-1-ol 254 (○), and bicyclo[3.2.0]heptan-1-ol 255 (▲).
Next, comparison of the yields of bicyclo[5.2.0]nonan-1-ols 262, 263 and 268 to alkylationed cycloheptanone 264 over the concentrations 0.01 M, 0.155 M and 0.31 M are shown in figure 9. Overall conversion of phenyl vinyl sulfoxide for the reaction of the lithium enolate of cycloheptanone using methods B-D was improved (53-73%) relative to the smaller cyclic ketone, cyclopentanone. Of the three ketones examined in the concentration study, cycloheptanone resulted in the best ratio of bicyclo[n.2.0]alkan-1-ol to alkylationed ketones (96:4) being observed. Throughout the concentration study, cycloheptanone consistently gave the highest yields of bicyclo[n.2.0]alkan-1-ols.

![Figure 9](image)

**Figure 9** Reaction Concentration vs. % Composition of product in total reaction products with cycloheptanone enolate for the products, monoalkylated cycloheptanone 264 (□), bicyclo[5.2.0]nonan-1-ol 262 (●), bicyclo[5.2.0]nonan-1-ol 263 (○), and substituted bicyclo[5.2.0]nonan-1-ol 268 (X).

Finally, comparison of the yields of bicyclo[6.2.0]decan-1-ols 265 and 269 to alkylationed cyclooctanones 266 and 267 over the concentrations 0.01 M, 0.155 M and 0.31 M are shown in figure 10. Conversion of phenyl vinyl sulfoxide was improved (52-80%) compared to the smaller ring sizes. However this was not associated with increased bicyclo[n.2.0]alkan-1-ol formation but instead increased alkylationed cyclooctanone.
Figure 10 Reaction Concentration vs. % Composition of product in total reaction products with cyclooctanone enolate for the products, monoalkylated cyclooctanone 266 (■), dialkylated cyclooctanone 267 (□), bicyclo[6.2.0]decan-1-ol 265 (●), and bicyclo[6.2.0]decan-1-ol 269 (○).

Trends in product distribution over concentration for each ketone and comparison of the yields of bicyclo[n.2.0]alkan-1-ols to alkylated ketones at each concentration (0.01 M, 0.155 M, 0.31 M) was carried out. Figure 11 shows the comparison for the 0.31 M series and is illustrative of the distinct trend observed at all concentrations.

Figure 11 Ketone ring size vs. % Composition of product in total reaction products using Method D (0.31 M) for the products, monoalkylated ketone (■), dialkylated ketone (□), bicyclo[n.2.0]alkan-1-ols (●), and substituted bicyclo[n.2.0]alkan-1-ol (X).
The product distribution observed for each ketone in the concentration study can be accounted for by the stability and steric interactions observed for the final bicyclo[n.2.0]alkan-1-ols formed. As reported in chapter one, the X-ray structures for the bicyclo[n.2.0]alkan-1-ols 253, 262 and 265 were obtained (Figure 12).

![Figure 12](image)

**Figure 12** Representation of the molecular structures of (a) bicyclo[3.2.0]heptan-1-ol 253 (b) bicyclo[5.2.0]nonan-1-ol 262 and (c) bicyclo[6.2.0]decan-1-ol 265

Comparison of the solid state structures show that the torsion angle at the ring junction varies between the different bicyclo[n.2.0]alkan-1-ols formed. Non-IUPAC nomenclature (chapter one, Figure 6) will be used to aid the comparison of structures 253, 262 and 265. The angular geometries about the bridgehead carbons C1 and C4 show considerable variation across the series of compounds. As can be seen in table 16, the interior angle about C4 (C1-C4-C5) increases with increasing ring size (108.1(3)-
123.7(5)°). The corresponding angles about C1(C4-C1-Cx) (x = 7, 9 or 10) show a similar trend with increasing ring size however, these angles are about 1-6° smaller than those observed for C1-C4-C5 in the five-, seven- and eight-membered rings. The conformational structure of the rings adjacent to the bond between the bridgehead atoms, C1 and C4 appeared to have the greatest effect on the interior angles. For the five-, seven- and eight-membered ring systems, the C1-Cx and C4-C5 bonds adopt pseudo-eclipsed conformations.

Examination of the torsion angles C5-C4-C1-Cx (table 16) showed an increase in the series, seven-membered 262 to five-membered 253 to eight-membered 265. The four-membered ring shows similar distortion from planarity for C3-C4-C1-C2 (table 16). This conformational arrangement is illustrated in figure 12 for 253, 262 and 265.

<table>
<thead>
<tr>
<th>Bicyclo[n.2.0]alkan-1-ol</th>
<th>Relevant geometric parameters: bond angles (°)</th>
<th>Relevant geometric parameters: torsion angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C1-C4-C5</td>
<td>C4-C1-Cx a</td>
</tr>
<tr>
<td>253</td>
<td>108.1(3)</td>
<td>105.0(2)</td>
</tr>
<tr>
<td>262</td>
<td>119.3(3)</td>
<td>118.8(3)</td>
</tr>
<tr>
<td>265</td>
<td>123.7(5)</td>
<td>116.4(5)</td>
</tr>
</tbody>
</table>

a x = 7, 9, 10 for the five-, seven- and eight-membered ring systems respectively

In overview of the three compounds, bicyclo[5.2.0]nonan-1-ol 262 displayed the least amount of overall steric strain, whereas bicyclo[3.2.0]heptan-1-ol 253 and bicyclo[6.2.0]decan-1-ol 265 both showed an increased amount of overall steric strain approximately equal to each other. Interestingly the product yields obtained for the bicyclo[n.2.0]alkan-1-ols at the higher concentrations (0.155 M and 0.31 M) reflect this trend, and were in the order, bicyclo[3.2.0]heptan-1-ol 253 ≡ bicyclo[6.2.0]decan-1-ol
Likewise, at the lower concentration of 0.01 M the corresponding yields were in the order bicyclo[6.2.0]decan-1-ol 265 < bicyclo[3.2.0]heptan-1-ol 253 < bicyclo[5.2.0]nonan-1-ol 262. As the overall steric strain in the bicyclo[n.2.0]alkan-1-ol product is decreased there is a corresponding increase in product distribution in favour of bicyclo[n.2.0]alkan-1-ol formation in conjunction with increased yields. Thus the cycloheptanone example in all cases showed a preference towards bicyclo[5.2.0]nonan-1-ol formation over alkylation.

This rationale also was applied to account for the preference of formation of the bicyclo[n.2.0]alkan-1-ols in which the isomer with a cis relationship between the hydroxyl and sulfonyl groups (253, 262 and 265) is favoured over the trans counterpart (254, 263 and 269). The bicyclo[n.2.0]alkan-1-ols 254, 263 and 269 were typically obtained in low yields (1-10%). The trans relationship between the hydroxyl and sulfonyl group observed in 254, 263 and 269 must alter the ring strain and the hydrogen bonding that occurs in the product which may in turn contribute to the low yields observed.

Other factors would have an influence on the yields observed. Changes in concentration affected the ratio of bicyclo[n.2.0]alkan-1-ols to alkylated species observed for each individual ketone. This is consistent with an ionic mechanism. Stabilisation of the transition states and or intermediates leading to the final bicyclo[n.2.0]alkan-1-ol products by the reaction solvent (THF) or lithium chelation may contribute to the product ratios observed. Also the basicity of the carbonyl groups of the individual ketones (cyclopentanone pK_a –7.5, 157 cycloheptanone pK_a -6.6 157 and cyclooctanone, pK_a -6.2 157) may contribute to the preference for the formation of the final bicyclo[n.2.0]alkan-1-ol product.
From above it is seen that variances occur at each reaction concentration for each ketone. This suggests that prediction of whether or not a change in concentration would result in favourable formation of bicyclo$[n.2.0]$alkan-1-ol products is not singularly reflected in the product outcome.

In conclusion, reaction of phenyl vinyl sulfoxide with the lithium enolates of ketones of varying ring size (cyclopentanone, cycloheptanone and cyclooctanone) followed by subsequent oxidation resulted in the formation of the bicyclo[3.2.0]heptan-1-ols 253 and 254, bicyclo[5.2.0]nonan-1-ols 262 and 263 and bicyclo[6.2.0]decan-1-ols 265 and 269. Control of the reaction conditions including time, temperature and concentration of the reaction resulted in partially optimised yields of bicyclo$[n.2.0]$alkan-1-ols. The ring junction in the bicyclo$[n.2.0]$alkan-1-ols formed within this concentration study were generated with apparent selectivity. Also of note was that the generation of the bicyclo$[n.2.0]$alkan-1-ols was from a convergent approach from readily available synthons, a cyclic ketone and phenyl vinyl sulfoxide. From the set of reaction conditions chosen within this study no bicyclo[2.2.0]hexan-1-ols were obtained. The ratio of bicyclo$[n.2.0]$alkan-1-ols to alkylated ketone formation observed was dependent on a number of factors including the variation of enolate reactivity between the different ring sizes, conversion of phenyl vinyl sulfoxide, time, temperature and concentration of reaction. A critical balance of these factors helped promote bicyclo$[n.2.0]$alkan-1-ol formation. However the stability and steric strain observed in the final bicyclo$[n.2.0]$alkan-1-ols formed appeared to significantly influence the total yields observed under the present set of conditions. With the potential scope of the cyclisation reaction between simple ketones of varying ring size and phenyl vinyl sulfoxide examined, a study on the effects that substitution and the introduction of other functionality on the ketone ring was carried out (chapter three).
Only the soul that knows the mighty grief

can know the mighty rapture

*Edwin Markham*
Chapter Three

Synthesis of Substituted and Functionalised Bicyclo\[n.2.0\]alkan-1-ols

From the preceding chapters it was established that simple unsubstituted ketones could be used in the cyclisation procedure to form bicyclo\[n.2.0\]alkan-1-ols. In terms of the potential synthetic applications of the cyclisation, now it was relevant to extend the scope of the study. In doing so, the current chapter sought to focus on the ketone used and examine the effects of substitution and introduction of other functionality on the ketone ring. When considering this, the possibilities for substitution and functionality on a simple ketone are wide and to include all variants is understandably an enormous task. Thus, the simple substituted ketones chosen for the current study were selected on the basis of commercial availability, the exploration of the extent of steric crowding at the bridgehead of the resultant bicyclo\[n.2.0\]alkan-1-ol, and testing of introduction of functionality that could permit further synthetic transformations. The ketones chosen to demonstrate these points were 2-methylcyclopentanone, 2,6-dimethylcyclohexanone, 2-methylcyclohexanone, 1,4-cyclohexanedione and 1,2-cyclohexanedione. A further example, an optically active ketone that may impart a degree of stereoselectivity, (1R)-(+)-camphor, also was examined.

Figure 13 Substituted and functionalised ketones
In the previous chapter it was concluded that the variables of enolate reactivity, conversion of phenyl vinyl sulfoxide, time, temperature and concentration of reaction, and stability and steric strain observed in the final bicyclo[n.2.0]alkan-1-ol product influenced the product outcomes and distribution when a ketone was reacted with phenyl vinyl sulfoxide under the cyclisation conditions. In addition it was noted that the prediction of whether increasing or decreasing the reaction concentration to prefer bicyclo[n.2.0]alkan-1-ols from a ketone enolate was not singularly reflective of the product outcome.

The initial work into substituted ketones as substrates for the cyclisation reaction was carried out concurrently with the concentration studies for the simple ketones, cyclopentanone, cycloheptanone and cyclooctanone. As a consequence of this choice, initial experiment conditions for the ketones discussed in this chapter show variance from the conclusions derived from the simple ketone study (chapter two). Selected variations in the reaction conditions are not meant to represent total exploration for optimisation but rather partial optimisation for bicyclo[n.2.0]alkan-1-ol formation. The discussion for this chapter is focused on the synthetic aspects of the simple substituted ketone study. The structural elucidation and characterisation of products arising from the reactions of simple substituted ketones contained within this chapter are reported in chapter four. However to assist the present discussion, the assigned stereochemistries of such products concluded from the structural study in chapter four are used in this chapter with reference to chapter four.

1.0 Reaction with 2-Methylcyclopentanone

The first ketone examined was 2-methylcyclopentanone. Initially, generation of the lithium enolate from 2-methylcyclopentanone and LDA at –78 °C was followed by
reaction with phenyl vinyl sulfoxide at −30 °C for a 45 minute reaction time, under normal laboratory light (entry 1, Table 17). A 0.168M concentration of the ketone was used in this instance, and phenyl vinyl sulfoxide was added dropwise. This reaction was carried out concurrently with the concentration studies for the simple ketones, hence the choice of a 45 minute reaction time, reaction lighting and mode of addition of phenyl vinyl sulfoxide.

**Table 17** Description of experimental procedures for the reaction of the lithium enolate of 2-methylcyclopentanone and phenyl vinyl sulfoxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>LDA T(°C)</th>
<th>Enolate Generation T(°C)</th>
<th>Conc. (M)*</th>
<th>Lighting conditions</th>
<th>PVS(O) addition T(°C)</th>
<th>PVS(O) addition</th>
<th>Reaction Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-10</td>
<td>-78</td>
<td>warm*</td>
<td>normal</td>
<td>-30</td>
<td>drop-wise</td>
<td>45@ -30 °C</td>
</tr>
<tr>
<td>2</td>
<td>-10</td>
<td>-78</td>
<td>0.01</td>
<td>dark</td>
<td>-30</td>
<td>rapid</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>-10</td>
<td>-78</td>
<td>0.172</td>
<td>dark</td>
<td>-30</td>
<td>rapid</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>-10</td>
<td>-78</td>
<td>0.31</td>
<td>dark</td>
<td>-30</td>
<td>rapid</td>
<td>5</td>
</tr>
</tbody>
</table>

‡ 1 equivalent of LDA  * ketone in total reaction volume  † 1 equivalent of phenyl vinyl sulfoxide  *warm denotes reaction warmed from −78 °C to −30 °C generally over a period of 10-30 min

Upon workup, and subsequent oxidation with m-CPBA four novel compounds, substituted bicyclo[3.2.0]heptan-1-ols 270 and 271 and a diastereomeric mixture of monoalkylated 2-methylcyclopentanone 272 were identified by ¹H nmr analysis of the crude sulfone mixture (entry 1, Table 18). Analytically pure samples of bicyclo[3.2.0]heptan-1-ols 270 and 271 and monoalkylated 2-methylcyclopentanone 272 were isolated and the structural characterisation is reported in chapter four, section 1.0. Substituted bicyclo[3.2.0]heptan-1-ol 270 was determined to be the (1RS, 2RS, 5SR, 7SR) isomer and substituted bicyclo[3.2.0]heptan-1-ol 271 the (1RS, 2SR, 5SR, 7SR) isomer as shown in scheme 72.
Analysis by $^1$H nmr showed that the use of racemic 2-methylcyclopentanone led to the formation of two diastereomers of monoalkylated 2-methylcyclopentanone 272 in a 70:30 ratio and thus it was assumed that all four enantiomers of monoalkylated 2-methylcyclopentanone were present. The monoalkylated 2-methylcyclopentanone 272 was isolated and characterised as a diastereomeric mixture and in a 86:14 ratio upon isolation where the major diastereomer was designated monoalkylated 2-methylcyclopentanone 272a and the minor diastereomer as monoalkylated 2-methylcyclopentanone 272b (scheme 73). The enantiomers of 272a and 272b would be indistinguishable by $^1$H nmr spectroscopy. The relative stereochemistry was unable to be assigned from the $^1$H nmr spectrum. However upon simple modelling and for the purpose of this discussion the major and minor diastereomers 272a and 272b respectively have been assigned on the basis of favourable/unfavourable steric interactions. We noted the unexpected ratio of the major diastereomer 272a and minor
diastereomer 272b in the crude $^1$H nmr spectrum. In conjunction with this, when attempting to grow crystals for the structural studies (chapter four) related to this work it was observed that the substituted bicyclo[3.2.0]heptan-1-ols 270 and 271 ring opened. Substituted bicyclo[3.2.0]heptan-1-ol 270 upon standing in ether for 30 days ring opened to the monoalkylated products in a ratio of 70:30 for 272a:272b. Likewise when substituted bicyclo[3.2.0]heptan-1-ol 271 was left upon standing in ether for 30 days a ratio of 68:32 for 272a:272b was obtained (scheme 73).

\[
\begin{align*}
\text{Scheme 73}
\end{align*}
\]

Due to the similar ratios of monoalkylated products 272a to 272b observed in the ring opening of both substituted bicyclo[3.2.0]heptan-1-ols 270 and 271 it was assumed that the ring opening followed by epimerisation through a common intermediate occurs. It was proposed that it could occur via either enol 273 or enolate 274. Inspection of the $^1$H nmr spectra of the products indicated that no enol species were present, as H2 peaks were evident and no peak attributable to an alcohol was observed in CDCl$_3$. The amount of enol present at equilibrium would be expected to be higher in a non polar solvent such as CDCl$_3$.$^{158}$

\[
\begin{align*}
\text{Scheme 73}
\end{align*}
\]

It is proposed that the ring opening of, for example, 270 generates the anion 276a as a result of hydrogen bonding of the hydroxyl group to the sulfone oxygens with these...
atoms acting as a base to promote ring opening (scheme 74). Under the conditions used, further equilibration via an anion such as 276b, even if it occurs in low percentage could lead to racemisation at C2 and/or C4 via a catalytic cycle over time. The conformational preference of the intermediate anion such as 276b and 276c is presumed to dictate the face from which protonation can occur and thus the final product ratio of the major monoalkylated isomer 272a to the minor isomer 272b.

Scheme 74

The use of simple models showed that the pseudo trans relationship of the methyl group and the side chain in monoalkylated 2-methylcyclopentanone 272 showed less steric crowding than the cis isomer. This could explain why a 50:50 ratio was not observed and why the ratio favoured the trans isomer 272a. Likewise under the reaction conditions, alkylation of the enolate 275 could occur from either face of the enolate to produce upon oxidation monoalkylated 2-methylcyclopentanone 272 in a similar ratio due to steric constraints (entry 1, Table 18). The variance in the ratios observed for 272a:272b for the experiments listed in table 18 could be accounted for by the kinetic conditions employed.

The reaction conditions used for the 2-methylcyclopentanone case were varied further. At this point, from the simple ketone study, it was found that rapid addition of phenyl
vinyl sulfoxide in the dark and a reaction time of 5 minutes resulted in the improved formation of bicyclo[\textit{n}.2.0]alkan-1-ols. Using these general conditions in the second reaction, the lithium enolate of 2-methylcyclopentanone (ketone concentration 0.172M) was reacted with phenyl vinyl sulfoxide at –30 °C and 5 minutes in the dark (entry 3, Tables 17 and 18). In addition the results from the concentration studies of the simple ketones (chapter two) indicated a concentration variation from the above general conditions could bring about a change in product ratios. In the study of the simple ketones, it was concluded for cyclopentanone from the reactions attempted, that the best conditions were 5 minutes at –30 °C in the dark with the rapid addition of the electrophile and a ketone concentration of 0.01M (method C). Thus, the lithium enolate of 2-methylcyclopentanone (ketone concentration 0.01M) was reacted with phenyl vinyl sulfoxide using method C (entry 2, Tables 17 and 18). A further concentration of ketone (0.31M, method D) was examined at this point to complete the study on 2-methylcyclopentanone. The lithium enolate of 2-methylcyclopentanone (ketone concentration 0.31M) was reacted with phenyl vinyl sulfoxide using method D (entry 4, Tables 17 and 18).

As can be seen in table 18 there is a considerable difference in the product ratios of substituted bicyclo[3.2.0]heptan-1-ols \textit{270} and \textit{271} to monoalkylated 2-methylcyclopentanone \textit{272}. These changes corresponded with a variance in ketone concentration (entries 2-4, Table 17) and reaction time, electrophile addition and reaction lighting (entries 1 and 3, Table 17). With an increased reaction time in combination with dropwise addition of electrophile under normal laboratory light (entries 1 and 3, Table 17) the ratio of substituted bicyclo[3.2.0]heptan-1-ols \textit{270} and \textit{271} to monoalkylated 2-methylcyclopentanones \textit{272} changed from 81:19 (entry 3, Table 18) to 68:32 (entry 1, Table 18). Although there are differences in the electrophile
addition and reaction lighting, the major contributing factor for this change in ratio was the reaction time.

The increased formation of monoalkylated product 272 associated with a longer reaction time was consistent with results from our group found in a time-course study using cyclohexanone to form bicyclo[4.2.0]octan-1-ols. Bicyclo[4.2.0]octan-1-ols were seen to slowly ring open to the monoalkylated cyclohexanone over 24 hours (scheme 75). However, at 5.25 hours reaction time the ratio of bicyclo[4.2.0]octan-1-ols to monoalkylated cyclohexanone was 53:47. Likewise, here in the current study substituted bicyclo[3.2.0]heptan-1-ols 270 and 271 appear to slowly ring open to the monoalkylated product 272 with the longer reaction time of 45 minutes.

When comparing the concentrations of 0.01 M, 0.172 M and 0.31 M (entries 2-4, Tables 17 and 18) there was a notable change in the trend for product distribution. The formation of substituted bicyclo[3.2.0]heptan-1-ols was favoured as the concentration was decreased. Thus at the lower concentration of 0.01M (entry 2, Table 18) the ratio of substituted bicyclo[3.2.0]heptan-1-ols 270 and 271 to monoalkylated 2-methylcyclopentanone 272 was 91:9. Notably, there was decreased conversion for the dilute conditions (entry 2, Table 18) where 18% of phenyl vinyl sulfoxide was recovered. For entries 1-3, table 18 the trends in product yields and conversion of phenyl vinyl sulfoxide were consistent with those observed from the concentration study for cyclopentanone as discussed in chapter two. We noted the diversion from
bicyclo[\textit{n}.2.0]alkan-1-ol formation for entry 4. Typically overall product yields of 47-54.5\% (entries 2-4 Table 18) were observed for 2-methylcyclopentanone. These yields were comparable to those obtained for the cyclopentanone case (~50\%). However a 56:44 ratio of bicyclo[3.2.0]heptan-1-ols 253 and 254 to alkylated cyclopentanones 256 and 257 as compared to a 91:9 ratio of substituted bicyclo[3.2.0]heptan-1-ols 270 and 271 to monoalkylated 2-methylcyclopentanone 272 was observed with a ketone concentration of 0.01M under the same reaction conditions otherwise. The notable improvement in bicyclo[3.2.0]heptan-1-ol formation for the 2-methylcyclopentanone case must be attributed to the presence of the C2 methyl group.

Assuming an ionic mechanism, formation of the bicyclo[3.2.0]heptan-1-ol could proceed via a transition state such as that in figure 14. The presence of the C5 methyl group may place favourable steric interactions to tighten the transition state as compared to that observed for the cyclopentanone case. This could account for the improved yield of bicyclo[3.2.0]heptan-1-ols 270 and 271 from the 2-methylcyclopentanone case. Likewise in the most concentrated reaction (entry 4, Table 18) a decrease in participation of the solvent THF in the transition state and perhaps an increase in intermolecular interactions may promote alkylation and formation of 272.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure14}
\caption{Possible transition structure leading to bicyclo[3.2.0]heptan-1-ol 271}
\end{figure}
2.0 **Reaction with 2,6-Dimethylcyclohexanone**

In the next example the extent of steric crowding at the bridgehead of the resultant bicyclo[4.2.0]alkan-1-ol was explored by using 2,6-dimethylcyclohexanone as the starting ketone. Due to the commercial availability, 2,6-dimethylcyclohexanone was chosen for the study instead of 2,5-dimethylcyclopentanone.

At the time of this work the optimal conditions employed in the formation of bicyclo[4.2.0]octan-1-ols using cyclohexanone was rapid addition of phenyl vinyl sulfoxide in the dark, reaction time of 5 minutes and a reaction concentration of 0.141 M. Thus the lithium enolate of 2,6-dimethylcyclohexanone was reacted with phenyl vinyl sulfoxide using this set of reaction conditions (entry 1, Table 19). Analysis of the crude mixture by $^1$H nmr indicated polymerised phenyl vinyl sulfoxide and unreacted starting ketone were present. Due to the substitution pattern of 2,6-dimethylcyclohexanone there may have been insufficient time to allow the generation of the lithium enolate to occur. Thus to accommodate this, a longer enolate generation of one hour was attempted.

**Table 19** Description of experimental procedures for the reaction of the lithium enolate of 2,6-dimethylcyclohexanone and phenyl vinyl sulfoxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>LDA T(°C)</th>
<th>Enolate Generation$^2$ T(°C)</th>
<th>Conc. (M)*</th>
<th>Lighting conditions</th>
<th>PVS(O) addition T(°C)</th>
<th>Reaction Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-10</td>
<td>-78 warm$^b$</td>
<td>0.141</td>
<td>dark</td>
<td>-30</td>
<td>rapid</td>
</tr>
<tr>
<td>2</td>
<td>-10</td>
<td>-78 1</td>
<td>0.141</td>
<td>dark</td>
<td>-30</td>
<td>rapid</td>
</tr>
<tr>
<td>3</td>
<td>-10</td>
<td>0 1</td>
<td>0.141</td>
<td>dark</td>
<td>-30</td>
<td>rapid</td>
</tr>
<tr>
<td>4</td>
<td>-10</td>
<td>0 1</td>
<td>0.141</td>
<td>dark</td>
<td>-10</td>
<td>rapid</td>
</tr>
</tbody>
</table>

$^b$ 1 equivalent of LDA  
$^* ketone in total reaction volume  
$^† 1 equivalent of phenyl vinyl sulfoxide  
$^b$ warm denotes reaction warmed from –78 °C to –30 °C generally over a period of 10-30 min
In the second reaction the lithium enolate (ketone concentration 0.141M) was generated at −78 °C for one hour with 2,6-dimethylcyclohexanone and LDA. This was then reacted with phenyl vinyl sulfoxide at −30 °C for 5 minutes in the dark (entry 2, Table 19). Analysis of the crude mixture by $^1$H nmr indicated polymerised phenyl vinyl sulfoxide and unreacted starting ketone were present. Not only insufficient time but also temperature may have limited the generation of the lithium enolate of 2,6-dimethylcyclohexanone. Thus the same enolate generation conditions employed for entry 2, table 19 were attempted, however this time at a warmer temperature of 0 °C (entry 3, Table 19). In comparison, generation of the lithium enolate of 2,6-dimethylcyclohexanone at 0 °C in a different solvent, DME has been reported. The lithium enolate (ketone concentration 0.141M) was generated at 0 °C for one hour with 2,6-dimethylcyclohexanone and LDA. This was subsequently reacted with phenyl vinyl sulfoxide at −30 °C for 5 minutes in the dark. This was followed by oxidation of the crude sulfoxide mixture with $m$-CPBA (scheme 76). Peaks indicative of the formation of bicyclo[$n$.2.0]alkan-1-ols and monoalkylated ketone in the region of δ 2.5-4.0 ppm were evident in the $^1$H nmr spectrum. The products were identified as substituted bicyclo[4.2.0]octan-1-ols 277 and 278 and monoalkylated 2,6-dimethylcyclohexanones 279 and 280 as shown in scheme 76 (entry 3, Table 20).

Scheme 76
Table 20

<table>
<thead>
<tr>
<th>Entry</th>
<th>277 (% Yield)</th>
<th>278</th>
<th>279</th>
<th>280</th>
<th>277 + 278:279 + 280 (Product Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>11</td>
<td>34.5</td>
<td>4.5</td>
<td>26:74</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>15.5</td>
<td>41.5</td>
<td>14</td>
<td>25:75</td>
</tr>
</tbody>
</table>

Further work within our group on the effects of temperature and concentration on the cyclisation reaction for the formation of bicyclo[4.2.0]octan-1-ols using cyclohexanone concluded at this point that a reaction temperature of −10 °C favoured bicyclo[4.2.0]octan-1-ol formation. This example was more applicable to the 2,6-dimethylcyclohexanone case than the cyclopentanone, cycloheptanone and cyclooctanone examples. Thus, in the present study the lithium enolate of 2,6-dimethylcyclohexanone (ketone concentration 0.141M) was generated for one hour at 0 °C and then reacted with phenyl vinyl sulfoxide at −10 °C for 5 minutes in the dark followed by oxidation of the crude sulfoxide mixture by m-CPBA (entry 4, Table 19). Analytically pure samples of substituted bicyclo[4.2.0]octan-1-ols 277 and 278 and monoalkylated 2,6-dimethylcyclohexanones 279 and 280 were isolated and the structural characterisation is reported in chapter four. Substituted bicyclo[4.2.0]octan-1-ol 277 was determined to be the (1RS, 2RS, 6SR, 8SR) isomer, and substituted bicyclo[4.2.0]octan-1-ol 278 the (1RS, 2SR, 6SR, 8SR) isomer as shown in scheme 76.

As can be seen in table 20, the product ratio of substituted bicyclo[4.2.0]octan-1-ols 277 and 278 to monoalkylated 2,6-dimethylcyclohexanones 279 and 280 was not improved with an increase in reaction temperature (entries 3-4, Table 20). However, an increase in overall yield from 52.5% to 74% is observed when the reaction temperature was
increased from –30 °C to –10 °C (entries 3-4, Table 20). The increase in yield was a result of increased conversion of phenyl vinyl sulfoxide. Notably, the substituted bicyclo[4.2.0]octan-1-ols 277 and 278 formed in an approximate 17:83 ratio that favoured the one with lesser steric constraints, bicyclo[4.2.0]octan-1-ol 278.

3.0 Reaction with 2-Methylcyclohexanone

The ketone 2-methylcyclohexanone was chosen next as a valid comparison to 2,6-dimethylcyclohexanone to illustrate the effects of the absence of steric bulk at the bridgehead within the same ring system. The initial set of conditions attempted were those found from the simple ketone study to be at the time favourable (method B, 5 minute reaction time at –30 °C and a ketone concentration of 0.155M). The lithium enolate of 2-methylcyclohexanone (ketone concentration 0.155M) was reacted with phenyl vinyl sulfoxide at –30 °C and 5 minutes in the dark (entry 1, Table 21). Upon workup the crude sulfoxide mixture was oxidised with m-CPBA. Peaks indicative of the formation of bicyclo[4.2.0]alkan-1-ols and the monoalkylated ketone in the region of δ 2.5-4.0 ppm were evident in the 1H nmr spectra. These were identified as substituted bicyclo[4.2.0]octan-1-ols 281 and 282 and the monoalkylated products 283 and 284 as shown in scheme 77 (entry 1, Table 22).
Next, using the general conditions of rapid addition of electrophile in the dark and a ketone concentration of 0.085M, the lithium enolate of 2-methylcyclohexanone was reacted with phenyl vinyl sulfoxide at −10 °C for 10 minutes. Upon workup the sulfoxide mixture was oxidised with \textit{m}-CPBA (entry 2, Table 21). Interestingly under the same reaction conditions as those found favourable in the formation of bicyclo[4.2.0]octan-1-ols from cyclohexanone only the monoalkylated products \ref{283} and \ref{284} were evident in the $^1\text{H}$ nmr spectrum (entry 2, Table 22).

In the present case this may be an anomalous result when compared to later experiments (entries 3 and 4, Tables 21 and 22). Key peaks in the region of δ 2.5-4.0 ppm indicating the presence of the bicyclo[4.2.0]octan-1-ols \ref{281} and \ref{282} were absent. Analytically pure samples of monoalkylated 2-methylcyclohexanones \ref{283} and \ref{284} were isolated and the structural characterisation is reported in chapter four. Monoalkylated 2-methylcyclohexanone \ref{283} was determined to be the (2\textit{RS}, 6\textit{RS}) isomer and monoalkylated 2-methylcyclohexanone \ref{284} the (2\textit{RS}, 6\text{SR}) isomer as shown in scheme 77.
Table 22 Product yields and ratios for the reaction of the lithium enolate of 2-methylcyclohexanone and phenyl vinyl sulfoxide (entries 1-4, Table 21) after m-CPBA oxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>281 (% Yield)</th>
<th>282 (% Yield)</th>
<th>283 (% Yield)</th>
<th>284 (% Yield)</th>
<th>281 + 282:283 + 284 (Product Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6.5</td>
<td>5</td>
<td>0.5</td>
<td>5</td>
<td>68:32</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
<td>37</td>
<td>40.5</td>
<td>0:100</td>
</tr>
<tr>
<td>3</td>
<td>16.5</td>
<td>11</td>
<td>28</td>
<td>22</td>
<td>35:65</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.5</td>
<td>3</td>
<td>9</td>
<td>14.5</td>
<td>19:81</td>
</tr>
</tbody>
</table>

<sup>a</sup>12.5% and <sup>b</sup>31% combined recovery of phenyl vinyl sulfoxide and/or phenyl vinyl sulfone

At this point from the 2,6-dimethylcyclohexanone example it was indicated that due to the presence of the methyl group at C2, enolate generation required a longer time at a warmer temperature. The next two reactions attempted were to compare the reaction time of 10 minutes at –10 °C (entry 3, Table 21) and the reaction time of 5 minutes at –30 °C (entry 4, Table 21) under the more favourable enolate generation conditions. Thus with enolate generation for an hour at 0 °C and a reaction time of 10 minutes at –10 °C followed by subsequent oxidation with m-CPBA (entry 3, Table 21), analytically pure samples of substituted bicyclo[4.2.0]octan-1-ols 281 and 282 were isolated and the structural characterisation is reported in chapter four. Substituted bicyclo[4.2.0]octan-1-ol 281 was determined to be the (1RS, 2RS, 6SR, 8SR) isomer, and substituted bicyclo[4.2.0]octan-1-ol 282 the (1RS, 2SR, 6SR, 8SR) isomer as shown in scheme 77. Product ratios for all variations are summarised in table 22.

A dramatic increase in overall product yield from 29% to 77.5% is observed when the reaction time and temperature was changed from 5 minutes at –30 °C to 10 min at –10 °C (entries 3-4, Tables 21 and 22). These results are consistent with previous results from the ketones, cyclohexanone and 2,6-dimethylcyclohexanone. Interestingly upon comparison to the 2,6-dimethylcyclohexanone case where one substituted bicyclo[4.2.0]octan-1-ol was favoured the substituted bicyclo[4.2.0]octan-1-ols 281 and
formed in a more equal ratio of approximately 55:45 of 281:282. In summary bicyclo[4.2.0]octan-1-ols can form with incorporation of substitution at the C5 bridgehead and C2 position on the six-membered ring. However the presence or absence of a group at these positions has a role in the preference of the major stereochemical isomer observed for a bicyclo[4.2.0]octan-1-ol.

4.0 Reaction with 1,4-Cyclohexanedione

The ketone 1,4-cyclohexanedione, was chosen next to introduce functionality that could permit further synthetic transformations. The initial set of reaction conditions chosen were those which at the time were favourable for the formation of bicyclo[4.2.0]octanols. Thus the lithium enolate of 1,4-cyclohexanedione was reacted with phenyl vinyl sulfoxide at –10 °C for 10 minutes at a reaction concentration of 0.085 M (entry 1, Table 23). Analysis of the crude mixture by 1H nmr indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione were present. It was noted during the reaction that a precipitate formed. The solubility of the diketone in THF at –78 °C was tested and the ketone was soluble. However upon addition of LDA a precipitate formed presumably due to the lithium enolate.

Table 23 Description of experimental procedures for the reaction of the lithium enolate of 1,4-cyclohexanedione and phenyl vinyl sulfoxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>LDA T(°C)</th>
<th>Enolate Generation T(°C)</th>
<th>Conc. (M)*</th>
<th>Lighting conditions</th>
<th>PVS(O) addition T(°C)</th>
<th>Reaction Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-10</td>
<td>-78</td>
<td>0.085</td>
<td>dark</td>
<td>-10</td>
<td>rapid</td>
</tr>
<tr>
<td>2</td>
<td>-10</td>
<td>0</td>
<td>0.085</td>
<td>dark</td>
<td>-10</td>
<td>rapid</td>
</tr>
<tr>
<td>3</td>
<td>-10</td>
<td>1</td>
<td>0.085</td>
<td>dark</td>
<td>5</td>
<td>rapid</td>
</tr>
<tr>
<td>4</td>
<td>-10</td>
<td>0</td>
<td>0.04</td>
<td>dark</td>
<td>-10</td>
<td>rapid</td>
</tr>
<tr>
<td>5</td>
<td>-10</td>
<td>0</td>
<td>0.04</td>
<td>dark</td>
<td>-10</td>
<td>rapid</td>
</tr>
</tbody>
</table>

‡ 1 equivalent of LDA * ketone in total reaction volume † 1 equivalent of phenyl vinyl sulfoxide \"sonication \" 2 equivalents of LDA ‡ warm denotes reaction warmed from –78 °C to –10 °C generally over a period of 10-30 min
Next, a longer time for enolate generation was employed to ensure that formation of the lithium enolate of 1,4-cyclohexanedione was occurring. Reaction with phenyl vinyl sulfoxide was carried out despite the heterogeneous nature of the reaction on the premise that any reaction intermediates maybe soluble. Thus the enolate was allowed to form at 0 °C for an hour prior to reaction with phenyl vinyl sulfoxide at –10 °C for 10 minutes (entry 2, Table 23). Analysis of the crude mixture by 1H nmr indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione were present. Once again it was noted during the reaction that a precipitate formed.

In an effort to overcome the solubility problems observed 1,4-cyclohexanedione was added dropwise to a solution of LDA in THF at –10 °C and allowed to stir for 30 minutes at 0-5 °C (reaction concentration 0.085 M). The system was then sonicated for a further 30 minutes and the temperature maintained between 0 °C and 5 °C. Phenyl vinyl sulfoxide was added at 5 °C, the temperature maintained and the reaction mixture sonicated for 10 minutes (entry 3, Table 23). As observed in the previous cases a precipitate formed during the reaction. Analysis of the crude mixture by 1H nmr indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione were present. In another attempt to address the solubility problems observed a dilute reaction concentration of 0.04 M was used (entry 4, Table 23). Again, a precipitate was observed during the reaction. Analysis of the crude mixture by 1H nmr revealed unreacted phenyl vinyl sulfoxide in conjunction with unreacted 1,4-cyclohexanedione were present.

In a final attempt to ensure enolate formation, excess base was used under dilute reaction conditions (0.04 M) with a longer reaction time (entry 5, Table 23). Analysis of the crude mixture by 1H nmr indicated a complex mixture of compounds was obtained
which included polymerised phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanone, No signals in the region δ 2.5-4 ppm attributable to bicyclo[n.2.0]alkan-1-ols were observed. Given the problems encountered with 1,4-cyclohexanone it was decided to protect one of the carbonyl groups, thus 1,4-cyclohexanone mono-ethylene ketal was considered next.

5.0 Reaction with 1,4-Cyclohexanone mono-ethylene ketal

The initial set of reaction conditions chosen for 1,4-cyclohexanone mono-ethylene ketal were those that were favourable for the formation of bicyclo[4.2.0]octan-1-ols. Thus the lithium enolate of 1,4-cyclohexanone mono-ethylene ketal was reacted with phenyl vinyl sulfoxide at −10 °C for 10 minutes (entry 1, Table 24). Analysis of the crude mixture by $^1$H nmr indicated that unreacted phenyl vinyl sulfoxide in conjunction with unreacted starting ketone were present. Signals in the region δ 2.5-4 ppm indicated bicyclo[n.2.0]alkan-1-ol products may be present (<5%).

Table 24 Description of experimental procedures for the reaction of the lithium enolate of 1,4-cyclohexanone mono-ethylene ketal and phenyl vinyl sulfoxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>LDA T(°C)</th>
<th>Enolate Generation$^2$ T(°C)</th>
<th>Conc. (M)$^*$</th>
<th>Lighting conditions</th>
<th>PVS(O) addition T(°C)</th>
<th>Reaction Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-10</td>
<td>-78 warm$^6$</td>
<td>0.085</td>
<td>dark</td>
<td>-10 rapid</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>-10</td>
<td>0</td>
<td>0.085</td>
<td>dark</td>
<td>-10 rapid</td>
<td>10</td>
</tr>
</tbody>
</table>

$^\dagger$ 1 equivalent of LDA $^*$ ketone in total reaction volume $^\dagger$ 1 equivalent of phenyl vinyl sulfoxide

warm denotes reaction warmed from −78 °C to −10 °C generally over a period of 10-30 min

To help promote the formation of the bicyclo[n.2.0]alkan-1-ols the longer enolate generation at 0 °C for an hour prior to addition of phenyl vinyl sulfoxide at −10 °C for 10 minutes (reaction concentration 0.085 M) was employed (entry 2, Table 24). Upon workup, and subsequent oxidation with $m$-CPBA three novel compounds, the functionalised bicyclo[4.2.0]octanols 285 and 286 and monoalkylated 1,4-
cyclohexanedione mono-ethylene ketal 287 were identified in the $^1$H nmr spectrum (entry 2, Table 25). Analytically pure samples of functionalised bicyclo[4.2.0]octanols 285 and 286 and monoalkylated 1,4-cyclohexanedione mono-ethylene ketal 287 were isolated and the structural characterisation is reported in chapter four, section 4.0. Functionalised bicyclo[4.2.0]octanol 285 was determined to be the (1’RS, 6’SR, 8’RS) isomer and functionalised bicyclo[4.2.0]octanol 286 the (1’RS, 6’S R, 8’S R) isomer as shown in scheme 78.

Scheme 78

Table 25 Product yields and ratios for the reaction of the lithium enolate of 1,4-cyclohexanedione mono-ethylene ketal and phenyl vinyl sulfoxide (entries 1-2, Table 24) after m-CPBA oxidation

<table>
<thead>
<tr>
<th>Entry</th>
<th>285 (% Yield)</th>
<th>286 (%)</th>
<th>287 (%)</th>
<th>285 + 286: 287 (Product Ratio)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2a</td>
<td>7</td>
<td>17.5</td>
<td>17.5</td>
<td>58:42</td>
</tr>
</tbody>
</table>

*a17.5% combined recovery of phenyl vinyl sulfoxide and/or phenyl vinyl sulfone

As moderate yields of functionalised bicyclo[4.2.0]octanols 285 and 286 in conjunction with a reasonable product ratio of bicyclo[4.2.0]octanol to monoalkylated species was observed no further reaction variations were carried out.
Instead, removal of the protecting group of the functionalised bicyclo[4.2.0]octanol 286 was examined in order to access the ketone functionality. Functionalised bicyclo[4.2.0]octanol 286 was treated with PPTS in ethanol for 21 hours at 55 °C followed by further treatment with PPTS in acetone/water (95:5) for 16 hours at 55 °C to afford the functionalised bicyclo[4.2.0]octanol 288 (scheme 79). An analytically pure sample of functionalised bicyclo[4.2.0]octanol 288 was isolated and the structural characterisation is reported in chapter four, section 4.0. Functionalised bicyclo[4.2.0]octan-1-ol 288 was determined to be the (1RS, 6SR, 7SR) isomer as shown in scheme 79. Acetal cleavage is a well known reaction but notably the bicyclo[4.2.0]octanol ring was stable to the acidic cleavage conditions. This example successfully demonstrates incorporation of a functional group into a bicyclo[n.2.0]alkan-1-ol that could permit further synthetic transformations to be carried out.

\[
\begin{align*}
\text{OH} & \quad \text{SO}_2\text{Ph} \\
\text{H} & \quad \text{OH} \\
\end{align*}
\]

1. PPTS, ethanol
21 hr, 55 °C
2. PPTS, acetone:H₂O (95:5)
16 hr, 55 °C

Scheme 79

6.0 Reaction with 1,2-Cyclohexanedione

Running concurrently with the investigation into the cyclisation reaction with 1,4-cyclohexanedione, work also was being carried out with 1,2-cyclohexanedione. The starting ketone 1,2-cyclohexanedione, present as both the enol and keto form, upon treatment with base would result in formation of the mono-enolate. Treatment of this enolate was carried out using the same reaction conditions resulting in the favoured formation of bicyclo[4.2.0]octan-1-ols\(^{145}\) (entry 1, Table 26). Unlike 1,4-
cyclohexanedione no solubility problems were encountered with these set of reaction conditions. However analysis of the crude product mixture by $^1$H nmr indicated recovered phenyl vinyl sulfoxide and 1,2-cyclohexanedione and showed no sign of bicyclo[4.2.0]octanol products as evidenced by a lack of signals in the key region $\delta$ 2.5-4 ppm.

Table 26 Description of experimental procedures for the reaction of the lithium enolate of 1,2-cyclohexanedione and phenyl vinyl sulfoxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>LDA T(°C)</th>
<th>Enolate Generation$^\ddagger$ T(°C)</th>
<th>Conc. (M)$^*$</th>
<th>Lighting conditions</th>
<th>PVS(O) addition T(°C)</th>
<th>PVS(O) addition</th>
<th>Reaction Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-10</td>
<td>-78</td>
<td>warm$^a$</td>
<td>0.085</td>
<td>dark</td>
<td>-10</td>
<td>rapid</td>
</tr>
<tr>
<td>2</td>
<td>-10</td>
<td>-10</td>
<td>1.5$^a$</td>
<td>0.085</td>
<td>dark</td>
<td>-10</td>
<td>rapid</td>
</tr>
<tr>
<td>3</td>
<td>-10</td>
<td>0</td>
<td>1</td>
<td>0.085</td>
<td>dark</td>
<td>-10</td>
<td>rapid</td>
</tr>
</tbody>
</table>

$\ddagger$ 1 equivalent of LDA  * ketone in total reaction volume  † 1 equivalent of phenyl vinyl sulfoxide  $^a$addition of ketone over 30 minutes followed by 1 hour stirring  $^\ddagger$ warm denotes reaction warmed from $-78$ °C to $-10$ °C generally over a period of 10-30 min

To ensure that enolate generation was occurring, 1,2-cyclohexanedione was added dropwise over a half hour period and stirred for a further hour at $-10$ °C, followed by addition of phenyl vinyl sulfoxide at $-10$ °C and a reaction time of one hour (entry 2, Table 26). Analysis of the crude mixture by $^1$H nmr indicated that polymerised phenyl vinyl sulfoxide in conjunction with unreacted starting ketone were present. The final set of reaction conditions were an enolate generation at 0 °C for an hour followed by addition of phenyl vinyl sulfoxide at $-10$ °C for 10 minutes (entry 3, Table 26). Analysis of the crude mixture by $^1$H nmr indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,2-cyclohexanedione were present in conjunction with traces (<5%) of a complex mixture of products. 1,2-Cyclohexanedione was not pursued further as the 1,4-cyclohexanedione mono-ethylene ketal example had illustrated a functional transformation of a bicyclo[4.2.0]octanol. The non-reactivity of the lithium enolate of
1,2-cyclohexanedione may be a consequence of a disrupted transition state due to the presence of the second carbonyl group, which would be able to chelate to lithium. In addition a poorly reactive site for C-alkylation in the enolate due to electronic effects may contribute to the absence of products, even those of simple alkylation. This example indicates a potential limitation of the cyclisation methodology.

7.0 Reaction with Camphor

The final ketone to be examined was the optically active (1R)-(+) -camphor. The initial work into camphor was run concurrently with that of the ketones previously discussed. Thus the enolate of camphor was generated at 0 °C for one hour followed by phenyl vinyl sulfoxide addition at –30 °C and a reaction time of 5 minutes (entry 1, Table 27). Analysis of the crude mixture by 1H nmr indicated that polymerised phenyl vinyl sulfoxide and unreacted camphor were present.

**Table 27** Description of experimental procedures for the reaction of the lithium enolate of camphor and phenyl vinyl sulfoxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>LDA T(°C)</th>
<th>Enolate Generation T(°C)</th>
<th>Conc. (M)*</th>
<th>Lighting conditions</th>
<th>PVS(O) addition T(°C)</th>
<th>Reaction Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-10</td>
<td>0</td>
<td>1</td>
<td>dark</td>
<td>-30</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>-10†</td>
<td>-78</td>
<td>1.5</td>
<td>dark</td>
<td>-10</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>-10</td>
<td>-78</td>
<td>1.5</td>
<td>dark</td>
<td>-10</td>
<td>10</td>
</tr>
</tbody>
</table>

‡ 1 equivalent of LDA
* ketone in total reaction volume
† 1 equivalent of phenyl vinyl sulfoxide
1.1 equivalent of LDA

In many reported examples, a slight excess of base is often employed in the formation of lithium enolates of camphor at –78 °C for 90 minutes. Thus the enolate of camphor was generated with 1.1 equivalents of base at -78 °C for 90 minutes. The remaining conditions used were those found favourable for the formation of bicyclo[4.2.0]octan-1-ols from cyclohexanone. Phenyl vinyl sulfoxide addition at the favourable
temperature of –10 °C and a reaction time of 10 minutes was chosen (entry 2, Table 27). Analysis of the crude mixture by $^1$H nmr indicated that polymerised phenyl vinyl sulfoxide and unreacted camphor were present. To prevent polymerisation of the electrophile, the same reaction conditions were employed however the equivalent of base reduced from 1.1 to 1 (entry 3, Table 27). Once again polymerised phenyl vinyl sulfoxide and unreacted camphor were recovered.

To ensure formation of the lithium enolate of camphor was occurring, phenyl vinyl sulfoxide was replaced with benzaldehyde.$^{161}$ Similar reaction conditions as those set out in entry 3, table 27 were employed with the only variance being a reaction time of 15 minutes instead of 10 minutes (scheme 80). Analysis of the crude mixture by weight and $^1$H nmr indicated that ketone 289$^{161}$ was present in >95% purity and 58% yield. The signals in the $^1$H nmr for the ketone 289 were consistent with literature values. The formation of the ketone 289 in such high yield confirmed formation of the lithium enolate of camphor.

![Scheme 80](image)

With confirmation of the formation of the lithium enolate of camphor the non-reactivity of phenyl vinyl sulfoxide with the enolate and polymerisation of phenyl vinyl sulfoxide was unexpected. Polymerisation of the electrophile may have been catalysed by the enolate itself and thereby effectively competing with alkylation of camphor and bicyclo[n.2.0]alkan-1-ol formation. Another optically active ketone such as the commercially available (R)-(+-)3-methylcyclohexanone may be a more appropriate example for future investigations.
8.0 Comments

From the ketones examined within this chapter, it can be seen that the introduction of a substituent alpha to the ketone can affect the formation of the lithium enolate and consequently the formation of bicyclo[n.2.0]alkan-1-ols. Due to the variations in reaction conditions a direct comparison of the results cannot be carried out, however the following general conclusions can be made. With increased substitution of the ketone enolate generation generally required a longer time of one hour and a warmer temperature of 0 °C compared to the conditions used with the simple ketones. In some cases, such as 2,6-dimethylcyclohexanone, bicyclo[n.2.0]alkan-1-ol formation was not observed unless these longer enolate conditions were employed. Solubility of the enolate was required for subsequent reaction with phenyl vinyl sulfoxide as seen in the contrasting results for the 1,4-cyclohexanedione and 1,4-cyclohexanedione mono-ethylene ketal examples. In conjunction with the improved enolate conditions, improved yields of bicyclo[n.2.0]alkan-1-ols were observed for 2-methylocyclohexanone and 1,4-cyclohexanedione mono-ethylene ketal when modified conditions of a reaction concentration of 0.085 M and rapid phenyl vinyl sulfoxide addition at –10 °C for 10 minutes were used. The non reactivity of the hindered ketone camphor, 1,2-cyclohexanediol and 1,4-cyclohexanediol indicate potential limitations of the cyclisation methodology. However that bicyclo[n.2.0]alkan-1-ols could be formed in unoptimised yields even in the presence of a bridgehead substituent and that conversion of a ketal functional group to a ketone in the presence of the bicyclo[n.2.0]alkan-1-ol could be carried out provides positive indications for further synthetic applications. The next chapter focuses on the structural elucidation and structural aspects of the bicyclo[n.2.0]alkan-1-ols discussed in the present chapter.
In examinations the foolish ask questions that the wise cannot answer

*Oscar Wilde*
Chapter Four

Structural Elucidation and Characterisation of Substituted Bicyclo[n.2.0]alkan-1-ols

In the preceding chapter the effects that substitution and introduction of functionality on the ketone can have in the formation of bicyclo[n.2.0]alkan-1-ols was examined. Reported in this chapter is the structural elucidation and characterisation of products arising from the reactions of the simple substituted ketones 2-methylcyclopentanone, 2-methylcyclohexanone, 2,6-dimethylcyclohexanone, 1,4-cyclohexanedione mono-ethylene ketal and the functionalised bicyclo[4.2.0]octan-1-ol 288 that arose from the cleavage of the functionalised bicyclo[4.2.0]octan-1-ol 286 (chapter three). The connectivity of the cyclobutyl ring systems of the substituted bicyclo[n.2.0]alkan-1-ols presented in this chapter was assigned using the methodology described in chapters one and two in the elucidation of bicyclo[3.2.0]heptan-1-ols 253, 254 and 255, bicyclo[5.2.0]nonan-1-ols 262, 263 and 268 and bicyclo[6.2.0]decan-1-ols 265 and 269. Focus will be placed on key spectral information in the present chapter. A structural comparison of selected substituted bicyclo[n.2.0]alkan-1-ols also is reported.

1.0 2-Methylcyclopentanone

As reported in chapter three, section 1.0 the lithium enolate of 2-methylcyclopentanone was reacted with phenyl vinyl sulfoxide using method A and the crude sulfoxide mixture was oxidised. Analytically pure samples of substituted bicyclo[3.2.0]heptan-1-ols 270 and 271 and a diastereomeric mixture of monoalkylated methylcyclopentanone 272 were obtained. Mass spectrometry and microanalysis results for 270 and 271 indicated a molecular mass of 266 amu which was consistent with the molecular formula C₁₄H₁₈SO₃ and the formation of substituted bicyclo[3.2.0]heptan-1-ols 270 or 271 or monoalkylated 2-methylcyclopentanone 272. In the FTIR spectra a strong
absorbance at 3507 cm\(^{-1}\) and 3512 cm\(^{-1}\) for \(\mathbf{270}\) and \(\mathbf{271}\) respectively was attributable to the hydroxyl group and the absence of a carbonyl stretch in either spectra aided in establishing the functionality of the cyclobutyl ring. The presence of a sulfonyl group was indicated by stretches at 1293 cm\(^{-1}\) and 1145 cm\(^{-1}\) for \(\mathbf{270}\) and 1305 cm\(^{-1}\) and 1141 cm\(^{-1}\) for \(\mathbf{271}\).

Key assignments and \(\delta\) values from the \(^1\)H and \(^{13}\)C nmr spectra of the substituted bicyclo[3.2.0]heptan-1-ols \(\mathbf{270}\) and \(\mathbf{271}\) are reported in table 28. The connectivity of the cyclobutyl ring in \(\mathbf{270}\) and \(\mathbf{271}\) were assigned based on the rationale previously described in chapter one. For example in the gHSQC nmr spectrum of \(\mathbf{270}\), CH signals were observed for C7-H7, C5-H5 and C2-H2 with the carbon signals for C7, C5 and C2 occurring at \(\delta\) 64.2 ppm, \(\delta\) 45.9 ppm and \(\delta\) 44.0 ppm respectively. Only one quaternary carbon at \(\delta\) 84.2 ppm in the \(^{13}\)C nmr spectrum of \(\mathbf{270}\), was identified by its absence in the gHSQC nmr spectrum and was assigned as C1 thereby indicating that the methyl group was in the C2 position on the cyclopentyl ring rather than the C5 position.

**Table 28** Key assignments and \(\delta\) values (ppm) from the \(^1\)H and \(^{13}\)C nmr spectra of substituted bicyclo[3.2.0]heptan-1-ols \(\mathbf{270}\) and \(\mathbf{271}\)

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C7</th>
<th>C5</th>
<th>H7</th>
<th>H6</th>
<th>H6</th>
<th>H5</th>
<th>H2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\mathbf{270})</td>
<td>84.2</td>
<td>64.2</td>
<td>45.9</td>
<td>3.59 (ddd, 9, 6, &lt;1 Hz)</td>
<td>2.62-2.78</td>
<td>1.48-1.60</td>
<td>2.62-2.78</td>
<td>1.78-1.92</td>
</tr>
<tr>
<td>(\mathbf{271})</td>
<td>85.7</td>
<td>59.0</td>
<td>45.7</td>
<td>3.70 (ddd, 10, 7.5, 1 Hz)</td>
<td>2.81</td>
<td>1.54</td>
<td>2.61-2.69</td>
<td>1.72-1.92</td>
</tr>
</tbody>
</table>

Based on the shifts and couplings observed for H7, H5 and H6 (Table 28) for substituted bicyclo[3.2.0]heptan-1-ol \(\mathbf{270}\) it was established that a \textit{cis} relationship existed between the sulfonyl group, hydroxyl group and the bridgehead proton (H5) as
shown. A correlation was observed between the signals due to the hydroxyl group proton, the methyl group and H5 in the ROESY nmr spectrum, thereby inferring a \textit{cis} relationship between the hydroxyl group and C2 methyl and confirming the \textit{cis} ring junction. The presence of a correlation between signals due to H7 and H2 in the ROESY nmr spectrum also indicated that the sulfonyl group and C2 methyl lie on the same face of the molecule. It was therefore established that the substituted bicyclo[3.2.0]heptan-1-ol 270 was the (1RS, 2RS, 5SR, 7SR)-isomer.

Based on the shifts and couplings observed for H7, H5 and H6 (Table 28) using a similar rationalisation presented above it was established that the hydroxyl group, sulfonyl group and bridgehead proton (H5) in bicyclo[3.2.0]heptan-1-ol 271 all existed in a \textit{cis} relationship. The key correlation in the ROESY nmr spectrum between the signals due to H7 and the methyl group was indicative of the methyl group being on the opposite face of the ring to the hydroxyl group, sulfonyl group and bridgehead proton H5. This was confirmed by the absence of a correlation between the signals due to the methyl group and either the hydroxyl group proton or H5. It was therefore established that the substituted bicyclo[3.2.0]heptan-1-ol 271 was the (1RS, 2SR, 5SR, 7SR)-isomer.

A direct comparison of the $^1$H nmr spectra of monoalkylated cyclopentanone 257 to that of monoalkylated 2-methylecyclopentanone 272 aided in establishing the connectivity of 272. Formation of the kinetic alkylated product 272 was confirmed by the presence of a second CH assigned as C5-H5 (δ 44.1 ppm) in conjunction with C2-H2 (δ 46.8 ppm). Only one quaternary carbon was evident by its absence in the gHSQC nmr spectrum and it was thus assigned as C1 (δ 220.7 ppm).
Crystals of the substituted bicyclo[3.2.0]heptan-1-ols 270 and 271 were grown for example by the slow evaporation of a hexane/ethyl acetate (90:10) solution of pure 270 or 271, and from the slow diffusion of diethyl ether into a solution of 270 or 271 in dichloromethane in an attempt to obtain an X-ray crystal structure, however the crystals obtained were unsolvable. The remaining part of the chapter will focus on the bicyclo[4.2.0]octan-1-ol examples only.

2.0 2,6-Dimethylcyclohexanone

As previously discussed (chapter three, section 2.0) the lithium enolate of 2,6-dimethylcyclohexanone was reacted with phenyl vinyl sulfoxide under a variety of reaction conditions and the crude sulfoxide mixture oxidised. Analytically pure samples of substituted bicyclo[4.2.0]octan-1-ols 277 and 278 and monoalkylated 2,6-dimethylcyclohexanones 279 and 280 were obtained.

Mass spectrometry and microanalysis results for the substituted bicyclo[4.2.0]octan-1-ols 277 and 278 indicated a molecular mass of 294 amu which is consistent with the formation of the bicyclo[4.2.0]octan-1-ols 277 or 278 or the monoalkylated 2,6-dimethylcyclohexanones 279 or 280. Absence of a carbonyl stretch in the FTIR spectra and the presence of an absorption attributable to an alcohol group at 3527 cm\(^{-1}\) for 277 and 3471 cm\(^{-1}\) for 278 respectively confirmed the functionality of the cyclobutyl ring.
Absorptions, indicative of a sulfonyl group at 1301 cm\(^{-1}\) and 1143 cm\(^{-1}\) for 277 and 1305 cm\(^{-1}\) and 1139 cm\(^{-1}\) for 278 were evident.

Key assignments and \(\delta\) values from the \(^1\)H and \(^1^3\)C nmr spectra of the substituted bicyclo[4.2.0]octan-1-ols 277 and 278 are reported in table 29. The connectivity of the cyclobutyl ring was assigned using the methodology described previously in chapter one. In addition, in the gHSQC nmr spectrum of 277, the absence of signals attributable to two carbons observed in the \(^1^3\)C nmr at \(\delta\) 42.4 ppm and \(\delta\) 78.5 ppm allowed these signals to be assigned as C6 and C1 respectively. Also in the gHSQC nmr spectrum CH signals were observed for C8-H8 and C2-H2 with the carbon signals for C8 and C2 occurring at \(\delta\) 64.6 ppm and \(\delta\) 35.5 ppm respectively. In the HMBC nmr spectrum of 277, \(^2\)J correlations were observed between the signals due to C6 and the protons of the C6-methyl group (\(\delta\) 19.9 ppm) and between the signals due to C2 and the protons of the C2-methyl group (\(\delta\) 13.6 ppm). Likewise the connectivity of the substituted bicyclo[4.2.0]octan-1-ol 278 was established as above.

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C8</th>
<th>C6</th>
<th>H8</th>
<th>H7</th>
<th>H7</th>
<th>H2</th>
</tr>
</thead>
<tbody>
<tr>
<td>277</td>
<td>78.5</td>
<td>64.6</td>
<td>42.4</td>
<td>3.665 (dd, 9.5, 6.5 Hz)</td>
<td>2.36</td>
<td>1.92</td>
<td>1.58-1.69</td>
</tr>
<tr>
<td>278</td>
<td>83.2</td>
<td>57.3</td>
<td>40.9</td>
<td>3.72 (dd, 9, 9 Hz)</td>
<td>2.29</td>
<td>1.76</td>
<td>1.54-1.65</td>
</tr>
</tbody>
</table>

Table 29 Key assignments and \(\delta\) values (ppm) from the \(^1\)H nmr and \(^1^3\)C nmr spectra of substituted bicyclo[4.2.0]octan-1-ols 277 and 278

Based on the shifts and couplings observed for H8 and H7 (Table 29) it was established that a *cis* relationship existed between the hydroxyl and sulfonyl group for both substituted bicyclo[4.2.0]octan-1-ols 277 and 278. The use of simple models showed that a *cis* relationship between the C6 bridgehead methyl and the hydroxyl group displayed less steric strain in the cyclobutyl ring than in a *trans* relationship. Thus it was
inferred that the C6 methyl group was in a *cis* position relative to the hydroxyl and sulfanyl groups in both substituted bicyclo[4.2.0]octan-1-ols 277 and 278. The relative stereochemistry of 278 also was assigned by X-ray crystallography. Single crystals of the substituted bicyclo[4.2.0]octan-1-ol 278 were obtained by slow evaporation of a hexane/ethyl acetate (90:10) solution of pure 278 and the X-ray crystal structure obtained from these crystals. The relative stereochemistry of (1RS, 2SR, 6SR, 8SR)-278 was assigned using the X-ray crystal structure. The ORTEP plot for substituted bicyclo[4.2.0]octan-1-ol 278 is displayed in figure 15.

![ORTEP diagram of the molecular structure of substituted bicyclo[4.2.0]octan-1-ol 278.](image)

**Figure 15** ORTEP diagram of the molecular structure of substituted bicyclo[4.2.0]octan-1-ol 278. The thermal ellipsoids are drawn at the 30% probability level.

In the X-ray structure of 278 the S-O2 and S-O3 bonds are directed away from the bicyclo[n.2.0]alkan-1-ol ring whereas the phenyl group is oriented towards this ring. Intramolecular hydrogen bonding interactions with the hydroxyl proton with O1⋯O2 distances of 2.759 Å are observed for substituted bicyclo[4.2.0]octan-1-ol 278. The six-membered ring displays a pseudo-chair conformation. In the reported simple cyclohexanone case of bicyclo[4.2.0]octan-1-ol 290, orientation of the six-membered ring allows intermolecular ‘bifurcated’ H-bonding between the hydroxyl hydrogen and the sulfone oxygen atoms. However in substituted bicyclo[4.2.0]octan-1-ol 278 the
presence of the methyl in the C8 position now disrupts this and intermolecular H-bonding is not observed in the solid state structure of 278. Further discussion and comparison of the X-ray structure of the bicyclo[4.2.0]octan-1-ol 278 and other bicyclo[4.2.0]octan-1-ols formed is reserved for the end of this chapter.

With confirmation of the relative stereochemistry of 278 the relative stereochemistry of the C2 methyl group in 277 was established through comparison of the $^1$H nmr spectra of 277 and 278 and two-dimensional nmr analysis of 277. The hydroxyl proton and H8 were noted to be coincident in the $^1$H nmr of 277 thereby making any correlations to these signals ambiguous. A correlation in the ROESY nmr spectrum between the signals at H8 and H7a at δ 1.92 ppm infers that H7a is on the opposite face to the hydroxyl, sulfonyl and C6 methyl groups (Figure 16). The signal due to H7a displayed a weak correlation to H2 indicating that the C2 methyl group is in a cis relationship with the hydroxyl, sulfonyl and C6 methyl groups. This is confirmed by the absence of a correlation in the ROESY nmr spectrum between H7a and the C2 methyl group. Thus it was determined that substituted bicyclo[4.2.0]octan-1-ol 277 was the (1RS, 2RS, 6SR, 8SR)-isomer.

Figure 16 Representation of the relative stereochemistry about the cyclobutanol ring for substituted bicyclo[4.2.0]octan-1-ol 277

Due to the simplicity of the spectra of monoalkylated 2,6-dimethylcyclohexanones 279 and 280 and other related products obtained in the remainder of this chapter, discussion
of the solution state structural elucidation of the connectivity of the alkylated compounds will not be given.

Single crystals of the monoalkylated 2,6-dimethylcyclohexanone 280 were obtained by slow evaporation of a hexane-ethyl acetate (80:20) solution and the X-ray crystal structure obtained from these crystals. The ORTEP plot of monoalkylated 2,6-dimethylcyclohexanone 280 is displayed in figure 17. Thus the relative stereochemistry of 280 was assigned as being the (2RS, 6RS)-isomer. Monoalkylated 2,6-dimethylcyclohexanone 280 could exist as a conformational isomer where the C2 alkyl and C6 methyl substituents are in the axial orientation. However this was considered unlikely due to unfavourable 1,3-diaxial interactions. Instead monoalkylated 2,6-dimethylcyclohexanone 279 must be the isomer with a trans relationship between the C2 alkyl and C6 methyl groups. In the $^1$H nmr spectrum of 279, H6 displayed an axial-axial coupling of 12.5 Hz to H5 and was therefore in the axial position, thus the C6 methyl group must be equatorial and the C2 alkyl equatorial. Thus monoalkylated 2,6-dimethylcyclohexanone 279 was assigned as the (2RS, 6SR)-isomer.

Figure 17 ORTEP diagram of the molecular structure of monoalkylated 2,6-dimethylcyclohexanone 280. The thermal ellipsoids are drawn at the 30% probability level.
3.0 2-Methylcyclohexanone

As a comparison to 2,6-dimethylcyclohexanone, 2-methylcyclohexanone was examined next. Reported in chapter three, section 3.0 reaction of the lithium enolate of 2-methylcyclohexanone with phenyl vinyl sulfoxide under a variety of reaction conditions was followed by oxidation of the crude sulfoxide mixture by \textit{m}-CPBA. Analytically pure samples of substituted bicyclo[4.2.0]octan-1-ols \textbf{281} and \textbf{282} and monoalkylated 2,6-dimethylcyclohexanones \textbf{283} and \textbf{284} were obtained.

One-dimensional and two-dimensional nmr analysis revealed that the kinetic alkylated products were formed. A key indication was the presence of two CH signals in the $^{13}$C nmr spectrum of \textbf{283} at $\delta$ 49.0 ppm and $\delta$ 45.6 ppm due to C2 and C6. Likewise in the $^{13}$C nmr spectrum of \textbf{284} two CH signals at $\delta$ 46.0 ppm and $\delta$ 43.5 ppm were assigned C2 and C6 respectively. In the $^1$H nmr spectrum of \textbf{284}, H2 displayed an axial-axial coupling to H3 of 9 Hz and was assigned as being in an axial orientation. Upon consideration of possible stereoisomers and conformational isomers and using a similar rationale to that explained in section 2.0 it was established that the monoalkylated 2-methylcyclohexanone \textbf{283} was the (2\textit{RS}, 6\textit{RS}) isomer and the monoalkylated 2-methylcyclohexanone \textbf{284} the (2\textit{RS}, 6\textit{SR}) isomer.
Mass spectrometry and microanalysis results for 281 and 282 indicated a molecular mass of 280 amu which was consistent with the formation of either substituted bicyclo[4.2.0]octan-1-ols 281 or 282 or the monoalkylated 2-methylecyclohexanones 283 or 284. A strong absorption due to the alcohol functionality at 3514 cm\(^{-1}\) for 281 and 3521 cm\(^{-1}\) for 282 and the absence of a carbonyl stretch in the FTIR spectra aided in establishing the functionality of the ring. Absorptions at 1283 cm\(^{-1}\) and 1143 cm\(^{-1}\) for 281 and 1295 cm\(^{-1}\) and 1138 cm\(^{-1}\) for 282 were each indicative of a sulfonyl group.

Next, the connectivity of the cyclobutyl ring system of substituted bicyclo[4.2.0]octan-1-ols 281 and 282 was established by one-dimensional and two-dimensional nmr analysis. Key assignments and \(\delta\) values from the \(^1\)H and \(^{13}\)C nmr spectra are reported in table 30. The connectivity of the cyclobutyl ring was assigned using the methodology described previously in chapter one and for the 2-methylcyclopentanone case (section 1.0). Based on the shifts and couplings observed for H8, H7 and H6 it was established that the hydroxyl group, sulfonyl group and bridgehead proton (H5) existed in a cis relationship in both substituted bicyclo[4.2.0]octan-1-ols 281 and 282.

### Table 30 Key assignments and \(\delta\) values (ppm) from the \(^1\)H and \(^{13}\)C nmr spectra of substituted bicyclo[4.2.0]octan-1-ols 281 and 282

<table>
<thead>
<tr>
<th></th>
<th>C1</th>
<th>C8</th>
<th>C6</th>
<th>H8</th>
<th>H7</th>
<th>H7</th>
<th>H6</th>
<th>H2</th>
</tr>
</thead>
<tbody>
<tr>
<td>281</td>
<td>75.5</td>
<td>67.0</td>
<td>44.6</td>
<td>3.48 (ddd, 9, 3, 1 Hz)</td>
<td>2.35</td>
<td>1.86</td>
<td>2.89-3.00</td>
<td>1.44-1.55</td>
</tr>
<tr>
<td>282</td>
<td>80.5</td>
<td>58.6</td>
<td>41.5</td>
<td>3.75 (ddd, 9.5, 8, &lt;1 Hz)</td>
<td>2.65</td>
<td>1.50-1.75</td>
<td>2.37</td>
<td>1.50-1.75</td>
</tr>
</tbody>
</table>

The relative stereochemistry of 281 was assigned by X-ray crystallography. Single crystals of the substituted bicyclo[4.2.0]octan-1-ol 281 were obtained by slow evaporation of hexane/ethyl acetate (80:20) into a solution of pure substituted 281 and the X-ray crystal structure obtained from these crystals. The relative stereochemistry of
(1RS, 2RS, 6SR, 8SR)-281 was assigned using the X-ray crystal structure. This confirmed the assignments of stereochemistry for substituted bicyclo[4.2.0]octan-1-ol 281 obtained from the solution state structure by nmr spectroscopy. The ORTEP plot for 281 is displayed in figure 18. In the X-ray structure of 281 the S-O3 bond in conjunction with the phenyl group is directed away from the bicyclo[n.2.0]alkan-1-ol ring whereas the S-O2 bond is oriented towards this ring, resulting in intramolecular hydrogen bonding interactions with the hydroxyl proton with O1⋯O2 distances of 2.898 Å for substituted bicyclo[4.2.0]octan-1-ol 281. The six-membered ring displays a pseudo-chair conformation. As was observed with substituted bicyclo[4.2.0]octan-1-ol 278 intermolecular ‘bifurcated’ H-bonding between the hydroxyl hydrogen and the sulfone oxygen atoms is disrupted by the presence of the methyl group and no intermolecular H-bonding is observed in the solid state structure of 281. Further discussion is reserved for the end of this chapter.

Figure 18 ORTEP diagram of the molecular structure of substituted bicyclo[4.2.0]octan-1-ol 281. The thermal ellipsoids are drawn at the 30% probability level

The assignment of the relative stereochemistry of the C2 methyl group of 282 was determined by a positive correlation in the ROESY nmr spectrum between the signals due to the C2 methyl group and H8. This inferred that the methyl group is on the
opposite face of the hydroxyl, sulfonyl group and bridgehead proton H6 (Figure 19).

Absence of a correlation between the signals due to the C2 methyl group and H6 confirmed this assignment. Thus it was determined that the substituted bicyclo[4.2.0]octan-1-ol 282 was the (1RS, 2SR, 6SR, 8SR) isomer.

**Figure 19** Representation of the relative stereochemistry about the cyclobutanol ring for substituted bicyclo[4.2.0]octan-1-ol 282

**4.0 1,4-Cyclohexanedione mono-ethylene ketal**

The next ketone examined that resulted in the formation of bicyclo[4.2.0]alkan-1-ols was 1,4-cyclohexanedione mono-ethylene ketal. The lithium enolate of 1,4-cyclohexanedione mono-ethylene ketal was reacted with phenyl vinyl sulfoxide under selected conditions and the crude sulfoxide mixture oxidised with m-CPBA (chapter three, section 5.0). Analytically pure samples of the functionalised bicyclo[4.2.0]octanols 285 and 286 and monoalkylated 1,4-cyclohexanedione mono-ethylene ketal 287 were obtained.

Mass spectrometry and microanalysis results indicated a molecular mass of 324 amu for 285 and 286 which is consistent with the formation of the functionalised bicyclo[4.2.0]octanols 285 or 286 or monoalkylated 1,4-cyclohexanedione mono-ethylene ketal 287. Absorbances in the FTIR spectra due to an alcohol group at 3470 cm$^{-1}$ and 3500 cm$^{-1}$ for bicyclo[4.2.0]octanols 285 and 286 respectively were observed
in addition to the absence of a carbonyl stretch. Peaks indicative of a sulfonyl group were observed at 1300 cm\(^{-1}\) and 1142 cm\(^{-1}\) for bicyclo[4.2.0]octanol 285 and at 1302 cm\(^{-1}\) and 1142 cm\(^{-1}\) for bicyclo[4.2.0]octanol 286.

The connectivity of the cyclobutyl ring system of substituted bicyclo[4.2.0]octanols 285 and 286 was established using the methodology previously discussed in chapter one. Key assignments and \(\delta\) values from the \(^1\)H and \(^{13}\)C nmr spectra are reported in table 31. Based on the shifts and couplings observed for H8’, H7’ and H6’ it was established that functionalised bicyclo[4.2.0]octanol 285 was the (1’RS, 6′SR, 8′RS) isomer and functionalised bicyclo[4.2.0]octanol 286 the (1’RS, 6′SR, 8′SR) isomer. Two-dimensional nmr analysis confirmed the assignment of relative stereochemistry of functionalised bicyclo[4.2.0]octanol 285. The key correlation between H6’ and H8’ was observed in the ROESY nmr spectrum of 285 thereby establishing H6’ and H8’ were on the same face of the ring and that there was a \textit{trans} relationship between the sulfonyl group and the hydroxyl group.

<table>
<thead>
<tr>
<th></th>
<th>C1’</th>
<th>C8’</th>
<th>C6’</th>
<th>H8’</th>
<th>H7’</th>
<th>H7’</th>
<th>H6’</th>
</tr>
</thead>
<tbody>
<tr>
<td>285</td>
<td>75.5</td>
<td>66.9</td>
<td>39.5</td>
<td>3.47 (dd, 10.5, 8 Hz)</td>
<td>2.15-2.26</td>
<td>1.79-1.96</td>
<td>2.27-2.36</td>
</tr>
<tr>
<td>286</td>
<td>72.7</td>
<td>67.3</td>
<td>43.8</td>
<td>3.52 (ddd, 9, 3, 1 Hz)</td>
<td>2.32</td>
<td>2.12</td>
<td>3.03-3.13</td>
</tr>
</tbody>
</table>

The assignment of the relative stereochemistries of 285 and 286 were correlated by X-ray crystallography of the functionalised bicyclo[4.2.0]octanol 286. Single crystals of 286 were obtained by slow evaporation of a hexane-ethyl acetate (50:50) solution of pure 286 and the X-ray crystal structure obtained from these crystals. The relative stereochemistry of (1’RS, 6′SR, 8′SR)-286 was assigned using the X-ray crystal...
structure. This confirmed the assignments of stereochemistry for functionalised bicyclo[4.2.0]octanol 286 obtained from the solution state structure by nmr spectroscopy. The ORTEP plot for 286 is displayed in figure 20. In the X-ray structure of 286 the S-O2 bond is directed away from the bicyclo[n.2.0]alkan-1-ol ring whereas the S-O3 bond is oriented towards this ring, resulting in intramolecular hydrogen bonding interactions with the hydroxyl proton with O1⋯O3 distances of 2.928 Å for functionalised bicyclo[4.2.0]octan-1-ol 286. The six-membered ring displays a pseudo-chair conformation. The conformation of 286 is stabilised by three-centred ‘bifurcated’ intra- and intermolecular hydrogen bonds between the hydroxyl hydrogen and the sulfone oxygen atoms. Upon comparison to the reported simple cyclohexanone144 case, bicyclo[4.2.0]octanol 290, it was seen that in the functionalised bicyclo[4.2.0]octanol 286 the stereochemistry and molecular packing of the molecule is not significantly affected by the addition of the dioxolane ring to the system (Figure 21).

Figure 20 ORTEP diagram of the molecular structure of functionalised bicyclo[4.2.0]octanol 286. The thermal ellipsoids are drawn at the 30% probability level.
In the final example, functionalised bicyclo[4.2.0]octanol 288 was obtained from the cleavage of the ketal functionality on the bicyclo[4.2.0]octanol 286 with PPTS (chapter three, section 5.0). An analytically pure sample of 288 was obtained from semi-preparative HPLC.

Mass spectrometry and microanalysis results for functionalised bicyclo[4.2.0]octanol 288 indicated a molecular mass of 280 amu which was consistent with the cleavage of the ketal group of 286 and formation of 288 or consistent with the formation of a ring opening product, monoalkylated diketone. A stretch at 3373 cm\(^{-1}\) attributable to an alcohol was observed in the FTIR spectrum in conjunction with a strong carbonyl stretch at 1698 cm\(^{-1}\), the presence of which was also confirmed by \(^{13}\)C nmr (\(\delta\) 209.7 ppm). Stretches at 1306 cm\(^{-1}\) and 1146 cm\(^{-1}\) in the FTIR spectrum were indicative of a sulfonyl group.
The connectivity of the cyclobutyl ring system of functionalised bicyclo[4.2.0]octanol 288 was established using the methodology previously discussed in chapter one and comparison to functionalised bicyclo[4.2.0]octanol 286. Key assignments and δ values from the $^1$H and $^{13}$C nmr spectra are reported in table 32. Based on the shifts and couplings observed for H7, H8 and H1 it was established that the hydroxyl, sulfonyl group and bridgehead proton (H1) existed in a cis relationship. Thus the relative stereochemistry for the functionalised bicyclo[4.2.0]octanol 288 was determined to be the (1RS, 6SR, 7SR) isomer.

**Table 32** Key assignments and δ values (ppm) from the $^1$H and $^{13}$C nmr spectra of functionalised bicyclo[4.2.0]octanol 288

<table>
<thead>
<tr>
<th></th>
<th>C6</th>
<th>C7</th>
<th>C1</th>
<th>H7</th>
<th>H8</th>
<th>H8</th>
<th>H1</th>
</tr>
</thead>
<tbody>
<tr>
<td>288</td>
<td>73.0</td>
<td>64.7</td>
<td>42.4</td>
<td>3.75 (ddd, 10, 4.5, 1 Hz)</td>
<td>2.71</td>
<td>1.69</td>
<td>2.98-3.07</td>
</tr>
</tbody>
</table>

5.0 Structural Comparison of the solid state structures of 278, 281 and 286

With the solid state structures of substituted bicyclo[4.2.0]octan-1-ols 278 and 281 and functionalised bicyclo[4.2.0]octanol 286 in hand and data from the unsubstituted simple cyclohexanone case 290 available, this allowed qualitative measure of the effects of substitution of the cyclohexanone ring to be carried out. Comparison of the X-ray crystal data from 278, 281, 286 and 290 shows that the torsion angle at the ring junction varies between the different bicyclo[n.2.0]alkan-1-ols formed. (Figure 22, Table 33).

For the six-membered ring systems of 278, 281, 286 and 290, the pseudo chair conformational structure necessitates an increase in the C5-C4-C1-C8 torsion angle to values greater than 30° (34.0(4)° for 278, -34.5(7)° for 281 and -31.2(7)° for 286, Table 33). A distortion of similar magnitude is not possible for the constrained four membered ring system where C3-C4-C1-C2 increases only to 22.3(3)° for 278, -17.5(4)° for 281
and $-17.6(6)^\circ$ for 286. These differences, illustrated in figure 22, for 278, 281 and 286 result in the observed differences in the C3-C4-C5 and C2-C1-C8 angles.

**Figure 22** Representation of the molecular structures of (a) substituted bicyclo[4.2.0]octan-1-ol 278 (b) substituted bicyclo[4.2.0]octan-1-ol 281 and (c) functionalised bicyclo[4.2.0]octanol 286
Table 33: The bond angles (°) and torsion angles (°) for bicyclo[n.2.0]alkan-1-ols 278, 281, 286 and 290

<table>
<thead>
<tr>
<th>Relevant geometric parameters: bond angles (°)</th>
<th>Relevant geometric parameters: torsion angles (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-C4-C5</td>
<td>C4-C1-C8</td>
</tr>
<tr>
<td>278</td>
<td>112.0(3)</td>
</tr>
<tr>
<td>281</td>
<td>118.7(6)</td>
</tr>
<tr>
<td>286</td>
<td>119.0(6)</td>
</tr>
<tr>
<td>290</td>
<td>117.3(6)</td>
</tr>
</tbody>
</table>

Notably the magnitude of the exterior angle about C4 (C3-C4-C5) for 281 and 286 and the exterior angle about C1 (C2-C1-C8) for 278 are relatively large. The origin of this effect is primarily a result of the conformational structure of the rings adjacent to the bond between the bridgehead atoms C1 and C4. The introduction of a methyl substituent at the C4 in 278 appears to change the direction of torsion within the molecules compared to the simpler structures 281 and 290 but not the magnitude of relative torsion angles and bond angles. For example a value of 34.0(4)° and –34.5(7)° is observed for the C5-C4-C1-C8 torsion angle for 278 and 281 respectively. Likewise a value of 121.0(3)° for C2-C1-C8 and 122.9(5)° for C3-C4-C5 for the exterior angles about C1 for 278 and C4 for 281 respectively are observed. As previously mentioned 286 displays a three-centred ‘bifurcated’ intra- and intermolecular hydrogen bonding between the hydroxyl proton and the sulfone oxygen atoms. Whereas in 278 and 281 the methyl group at C8 disrupts the intermolecular hydrogen bonding. The presence or absence of the intermolecular hydrogen bonding appears to have no influence on the conformation of the four-six membered ring system. Correlations between the solid state structures observed for 278, 281 and 286 and the product distributions and yields observed in chapter three were not drawn due to the variations in reaction conditions used.
We live in deeds, not years; in thoughts, not breaths

*Philip James Bailey*
Chapter Five
Potential Applications of the Novel Cyclisation Process

In the preceding chapters, simple ketones, simple functionalised and substituted ketones were examined. In most cases, bicyclo[n.2.0]alkan-1-ols were obtained in varying unoptimised yields. Now, further application of the cyclisation process as methodology that could be used in the synthesis of natural product structures or complex ring systems was examined. Two selected model studies were used to illustrate these potential applications.

1.0 2-(3’-Phenylsulfinyl-2’-propenyl)cyclohexanone 291

The examples of the previous chapters were ones in which the ketone synthon and phenyl vinyl sulfoxide was reacted in an intermolecular fashion. Next it was sought to examine an example in which the electrophile is tethered to the starting ketone such as the ketone 291. In doing so a fused ring structure such as 292 might be generated (scheme 81).

Ketone 291 is commercially unavailable and was prepared as follows. Phenylthio ketone 293 was prepared in 27.5% yield by treating the trimethylsilyl ether of cyclohexanone with $N,N$-diisopropylethylamine and trimethylsilylmethyl trifluoromethanesulfonate (TMSOTf) followed by allyl phenyl vinyl sulfoxide at $–78\,^{\circ}\mathrm{C}$ (scheme 82). Upon workup the ketone 293 was obtained as the trans isomer (>$90\%$) as determined by $^1\mathrm{H}$ nmr and partially purified by silica column chromatography and
then used directly in the next step. The sulfide 293 was oxidised to the corresponding sulfoxide by one equivalent of \textit{m}-CPBA to afford predominantly the \textit{trans} isomer of phenylsulfinylketone 291 in 25\% yield (scheme 82). The major isomer was \(>95\%\) \textit{trans} as determined by analysis of the \(\textsuperscript{1}H\) nmr spectrum of 291. An analytically pure sample of 291 was obtained by semi-preparative HPLC and characterised using microanalysis, one-dimensional and two-dimensional nmr spectroscopy, mass spectrometry and FTIR spectroscopy.

![Scheme 82]

With the sulfoxide in hand, the conditions chosen for the cyclisation reaction were those found optimal for the formation of bicyclo[4.2.0]octan-1-ols from cyclohexanone.\textsuperscript{145} However comparison of the simple ketones to the substituted ketones in the preceding chapters showed that a longer enolate generation is required when a substituent is placed on the ketone. Due to the electrophile already being tethered to the ketone 291 it was not feasible to allow lengthy enolate generation. Thus phenylsulfinyl ketone 291 was added to LDA dropwise at \(-10\) °C to ensure rapid enolate formation and the temperature maintained for 10 minutes. Upon workup and analysis of the crude mixture by \(\textsuperscript{1}H\) nmr spectroscopy and T.L.C, a complex mixture of products was obtained. No signals in the region \(\delta\ 2.5-4\) ppm attributable to bicyclo[\(n.2.0\)]alkan-1-ols were
observed. The lack of formation of bicyclo[4.2.0]alkan-1-ols from the ketone 291 may be a consequence of the trans geometry of the double bond. A cis geometry of this double bond may provide a favourable transition state. However, with the inherent problems with enolate generation no further work was carried out on the ketone 291.

### 2.0 Model ketone Study

A long-term aim of synthetic methodology development could be applications towards the synthesis of bioactive natural products. As mentioned in the introduction, many bicyclo[4.2.0]alkan-1-ols are contained as moieties within natural products. One example is melleolide.\(^{163}\) Melleolide is an antibiotic from Armillaria mellea that exhibits inhibitory activity against gram-positive bacteria. The partial or total synthesis of melleolide and its derivatives, such as armillaric acid, which also displays antibiotic activity, have not been reported at the time of this work. The novel cyclisation reaction would provide a unique and potentially expedient entry into these systems.

A proposed preliminary route to a model compound for melleolide is shown in scheme 83. The ester ketone 294 under cyclisation conditions could give the bicyclo[4.2.0]octan-1-ol 295. Subsequent conversion of the sulfoxide group to a hydroxyl group perhaps could be achieved using trimethyl phosphite\(^{164}\) or alternatively thermal elimination of the sulfoxide followed by hydroxylation of the resultant double bond via a hydroboration and cleavage sequence. Reduction of 296 could give diol 297 (scheme 83).
Scheme 83

The ester ketone 294 is not commercially available and the synthesis of 294 was attempted as follows. The dianion generated from methyl propionylacetate 298 upon treatment with sodium hydride followed by butyllithium was reacted with commercially available dioxolanyl bromide 299 which resulted in the formation of dioxolanyl ketoester 300 in 41.5% yield (scheme 84).165 Dioxolanyl ketoester 300 was purified by column chromatography and used directly in the next step. Treatment of dioxolanyl ketoester 300 with 50% aqueous acetic acid resulted in the formation of the ketoester 294 in 65% yield (scheme 84).165 Extensive attempts at purification by either short path reduced pressure distillation or fractional reduced pressure distillation or column chromatography or HPLC chromatography resulted in decomposition of ketoester 294.

Given the problems encountered with the purification of the ketoester 294, 2,6-dimethyl-2-cyclohexen-1-one 301 was considered next. This ketone was chosen to examine whether a double bond could be present in the starting ketone when using the cyclisation reaction.
3.0 2,6-Dimethyl-2-cyclohexen-1-one 301

2,6-Dimethyl-2-cyclohexen-1-one 301 is not commercially available. Thus 2,6-dimethylcyclohexanone was treated with N-bromosuccinimide and AIBN to afford enone 301 in 45% yield (scheme 85).166 2,6-Dimethyl-2-cyclohexen-1-one 301 was partially purified by short path distillation and used directly in the next step.

The conditions chosen for the reaction between ketone 301 and phenyl vinyl sulfoxide were those found to be optimal for 2,6-dimethylcyclohexanone and 2-methylcyclohexanone (chapter 3, sections 2.0 and 3.0). Thus the lithium enolate of ketone 301 was generated at 0 °C for one hour, followed by addition of phenyl vinyl sulfoxide at –10 °C and the temperature maintained for 10 minutes. The crude sulfoxide mixture was subsequently oxidised with m-CPBA. Analysis of the crude \(^1\)H nmr spectrum indicated that unreacted 2,6-dimethyl-2-cyclohexen-1-one 301 (37.5%) in
conjunction with monoalkylated 2,6-dimethyl-2-cyclohexen-1-one \(302\) (7%) and bicyclo[2.2.2]octanones \(303\) (1.5%), \(304\) (1.5%) and \(305\) (1%) and polymerised phenyl vinyl sulfoxide were present (scheme 86). The remainder of the starting ketone was assumed to be volatile under the workup conditions. Isolation by column chromatography followed by HPLC resulted in analytically pure samples of bicyclo[2.2.2]octanones \(303\), \(304\) and \(305\) and monoalkylated 2,6-dimethyl-2-cyclohexen-1-one \(302\) being obtained. Structural elucidation of monoalkylated 2,6-dimethyl-2-cyclohexen-1-one \(302\) by microanalysis, one-dimensional and two-dimensional nmr spectroscopy, mass spectrometry and FTIR spectroscopy was straightforward and will not be discussed further.

**Scheme 86**

Mass spectrometry and microanalysis results for \(303\), \(304\) and \(305\) indicated a molecular mass of 292 amu which was consistent with the formation of either bicyclo[4.2.0]octan-1-ols, bicyclo[2.2.2]octanones \(303\), \(304\) or \(305\) or the monoalkylated 2,6-dimethyl-2-cyclohexen-1-one \(302\). The carbonyl group functionality was confirmed by strong absorptions at 1720 cm\(^{-1}\) for \(303\) and 1727 cm\(^{-1}\) for \(305\) in the FTIR spectra in conjunction with signals at \(\delta\) 217.0 ppm and \(\delta\) 217.3 ppm for \(303\) and \(305\) in the \(^{13}\)C nmr spectra. Due to the low product yield a FTIR spectrum was unable to be obtained for \(304\) however the presence of a carbonyl group was confirmed by a signal at \(\delta\) 216.1
ppm in the $^{13}$C nmr. In the FTIR spectra absorptions at 1305 cm$^{-1}$ and 1145 cm$^{-1}$ for 303 and 1303 cm$^{-1}$ and 1153 cm$^{-1}$ for 305 were each indicative of a sulfonyl group.

Analysis of the $^1$H nmr spectra of bicyclo[2.2.2]octanones 303, 304 and 305 showed the absence of an alkene proton in the region $\delta$ 5-7 ppm in conjunction with the absence of H1’ and H2’ protons associated with the alkylated product 302. The connectivity of the bicyclo[2.2.2]octanones 303, 304 and 305 was determined by two-dimensional nmr analysis. In the gHSQC nmr spectrum of bicyclo[2.2.2]octanone 305, CH signals were observed for C3-H3, C4-H4 and C5-H5 with the carbon signals for C3, C4 and C5 occurring at $\delta$ 47.5 ppm, $\delta$ 34.7 ppm and $\delta$ 57.9 ppm respectively. For compound 305 C3 was identified by its correlation in the gCOSY nmr spectrum to the C3-methyl group. Due to its proximity to a sulfonyl group, C5-H5 would be expected to be further downfield in the $^1$H and $^{13}$C nmr spectra compared to C4-H4. Two quaternary carbons, C1 and C2 at $\delta$ 42.5 ppm and $\delta$ 217.3 ppm respectively were identified in the $^{13}$C nmr spectrum of 305 and by the absence of these signals in the gHSQC nmr spectrum. Key correlations were observed in the gHMBC nmr spectrum where a $^2$J coupling was observed between the signals due to C2 and H3 as well as C1 and H7, C1 methyl group and H6 and $^3$J couplings were observed between the signals due to C2 and H4, H6 and H7. The remaining connectivity of compound 305 was established thorough key gCOSY nmr spectrum correlations. For example H5 ($\delta$ 3.28 ppm) correlated to H4 ($\delta$ 2.42 ppm) and H6 ($\delta$ 2.21, 1.53-1.68 ppm) whereas H4 correlated to H3 ($\delta$ 2.30 ppm), H5 and H8 ($\delta$ 2.56-2.65 ppm). The structural elucidation of bicyclo[2.2.2]octanones 303 and 304 were established using the same methodology as discussed above.

With four stereocentres present eight diastereomers each with an enantiomeric isomer could potentially form in a non-selective reaction process. However the individual
stereochemistry of bicyclo[2.2.2]octanones 303, 304 and 305 was unable to be assigned. Two-dimensional ROESY nmr spectra of 303, 304 and 305 provided ambiguous information. Likewise $^1\text{H}-^1\text{H}$ coupling information drawn from the $^1\text{H}$ nmr spectra was inconclusive. The formation of the bicyclo[2.2.2]octanones 303, 304 and 305, albeit in very low yield, can be accounted for by intramolecular attack of the intermediate anion 306 via a Michael addition to the double bond (scheme 87). The resultant enolate then upon quenching forms, for example, ketone 303.

The lack of reactivity of 2,6-dimethylcyclohexanone towards bicyclo[4.2.0]octan-1-ol formation was disappointing but perhaps consistent with the results observed for 1,2-cyclohexanedione and 1,4-cyclohexanedione. For bicyclo[4.2.0]octan-1-ol formation from the latter ketones this may be a consequence of a combination of stereo and electronic effects in the enolate intermediate. These results suggest that conjugation in the enolate intermediate prior to reaction with phenyl vinyl sulfoxide is not favourable for bicyclo[n.2.0]alkan-1-ol formation. This indicates that future work on model studies towards natural products such as melleolide will need to consider introduction of the double bond in a masked form.

Scheme 87
‘Game over man, game over……’

Aliens
Chapter Six
Concluding Comments

Exploration of the potential scope of the novel cyclisation reaction between a cyclic ketone and phenyl vinyl sulfoxide has revealed some interesting results. The simple cyclic ketones, cyclopentanone, cycloheptanone and cyclooctanone upon cyclisation and oxidation gave bicyclo[n.2.0]alkan-1-ols 253-255, 262, 263, 265, 268, 269 in conjunction with alkylated species 256, 257, 264, 266 and 267 respectively (scheme 88). Whereas cyclobutanone gave no bicyclo[2.2.0]hexan-1-ols rather the cyclohexanone 248 and monoalkylated cyclobutanone 249. The cyclohexanone 248 was an unexpected product and was thought to form through the ring opening of a strained bicyclic intermediate 250 that upon quenching and oxidation would give 248. In chapter one the solution state structural elucidation of the bicyclo[n.2.0]alkan-1-ols in addition to solid state structural elucidation for 253, 262 and 265 showed that a cis ring junction occurred in all the bicyclo[n.2.0]alkan-1-ols that formed.

![Scheme 88](image)

Selected variations in reaction conditions including reaction temperature and time, concentration and mode of electrophile addition were reported in chapter two. For the simple ketones, cyclopentanone, cycloheptanone and cyclooctanone a comparison of the
distribution of product ratios over the concentrations 0.01 M, 0.155 M and 0.31 M
resulted in a notable change in trends for each. Bicyclo[3.2.0]heptan-1-ol formation was
favoured under a dilute reaction concentration (0.01 M), bicyclo[5.2.0]nonan-1-ol
formation was favourable at the intermediate concentration of 0.155 M and
bicyclo[6.2.0]decan-1-ol formation favourable at the higher concentration of 0.31 M. It
was noted that these reported trends may have been affected by the conversion of
phenyl vinyl sulfoxide. Of the three ketones examined in the concentration study,
cycloheptanone resulted in the best ratio of bicyclo[n.2.0]alkan-1-ol to alkylated ketones
(96:4) being observed. Throughout the concentration study, cycloheptanone consistently
gave the highest yields of bicyclo[n.2.0]alkan-1-ols. For the cyclooctanone case
conversion of phenyl vinyl sulfoxide was improved compared to the smaller ring sizes.
However this was not associated with increased bicyclo[n.2.0]alkan-1-ol formation but
instead increased alkylated cyclooctanone.

The product distribution observed for each ketone in the concentration study was
accounted for by the stability and steric interactions observed for the final
bicyclo[n.2.0]alkan-1-ols formed. As reported in chapter one, the X-ray structures for
the bicyclo[n.2.0]alkan-1-ols 253, 262 and 265 were obtained. Examination of the
torsion angle at the ring junction and angular geometries about the bridgehead carbons
C1 and C4 between the different bicyclo[n.2.0]alkan-1-ols formed showed that of the
three compounds, bicyclo[5.2.0]nonan-1-ol 262 displayed the least amount of overall
steric strain, whereas bicyclo[3.2.0]heptan-1-ol 253 and bicyclo[6.2.0]decan-1-ol 265
both showed an increased amount of overall steric strain approximately equal to each
other. Interestingly the product yields obtained for the bicyclo[n.2.0]alkan-1-ols at the
higher concentrations (0.155 M and 0.31 M) reflected this trend, and were in the order,
bicyclo[3.2.0]heptan-1-ol 253 ≅ bicyclo[6.2.0]decan-1-ol 265 < bicyclo[5.2.0]nonan-1-
ol 262. Likewise, at the lower concentration of 0.01 M the corresponding yields were in the order bicyclo[6.2.0]decan-1-ol 265 < bicyclo[3.2.0]heptan-1-ol 253 < bicyclo[5.2.0]nonan-1-ol 262. As the overall steric strain in the bicyclo[n.2.0]alkan-1-ol product was decreased there was a corresponding increase in product distribution in favour of bicyclo[n.2.0]alkan-1-ol formation in conjunction with increased yields. Thus the cycloheptanone example in all cases showed a preference towards bicyclo[5.2.0]nonan-1-ol formation over alkylation.

Changes in concentration also affected the ratio of bicyclo[n.2.0]alkan-1-ols to alkylated species observed for each individual ketone. This was consistent with an ionic mechanism which supported work in a concurrent study in which it was established that an ionic mechanism was operating for the formation of bicyclo[4.2.0]octan-1-ols from cyclohexanone.145 Stabilisation of the transition states and or intermediates leading to the final bicyclo[n.2.0]alkan-1-ol products by the reaction solvent (THF) may contribute to the product ratios observed. Also the basicity of the carbonyl groups of the individual ketones may contribute to the preference for the formation of the final bicyclo[n.2.0]alkan-1-ol product. Thus, prediction of whether or not a changed in concentration would result in favourable formation of bicyclo[n.2.0]alkan-1-ol products was not singularly reflected in the product outcome. The ratio of bicyclo[n.2.0]alkan-1-ols to alkylated ketone formation observed was dependent on a number of factors including the variation of enolate reactivity between the different ring sizes, conversion of phenyl vinyl sulfoxide, time, temperature and concentration of reaction. A critical balance of these factors helped promote bicyclo[n.2.0]alkan-1-ol formation.

Further scope of the cyclisation reaction was considered next (chapter three). The extent of steric crowding at the bridgehead of the resultant bicyclo[n.2.0]alkan-1-ol, and
testing of introduction of functionality that could permit further synthetic transformations was examined. The ketones chosen to demonstrate these points were 2-methylcyclopentanone, 2,6-dimethylcyclohexanone, 2-methylcyclohexanone, 1,4-cyclohexanedione, 1,2-cyclohexanedione and an optically active example (1R)-(+)camphor. Selected variations in the reaction conditions were not meant to represent total exploration for optimisation but rather partial optimisation for bicyclo[n.2.0]alkan-1-ol formation. Substituted ketones 2-methylcyclopentanone, 2,6-dimethylcyclohexanone and 2-methylcyclohexanone upon cyclisation and oxidation gave the substituted bicyclo[n.2.0]alkan-1-ols 270, 271, 277, 278, 281 and 282 in conjunction with the alkylated products 272, 279, 280, 283 and 284 (scheme 89). Comparison of these substituted ketones to the simple cases showed that the introduction of a substituent alpha to the ketone affected the formation of the lithium enolate and consequently the formation of bicyclo[n.2.0]alkan-1-ols. It was observed that a longer enolate generation of one hour at the warmer temperature of 0 °C was required with increased substitution compared to the conditions used with the simple ketones. In some cases, such as 2,6-dimethylcyclohexanone, bicyclo[n.2.0]alkan-1-ol formation was not observed unless these longer enolate conditions were employed.

Scheme 89
The next examples 1,4-cyclohexanedione, 1,2-cyclohexanediione and camphor, non-reactivity under selected cyclisation conditions was observed. The non-reactivity of 1,4-cyclohexanedione was attributed to poor solubility of the lithium enolate of 1,4-cyclohexanedione under the reaction conditions. The non-reactivity of the lithium enolate of 1,2-cyclohexanedione was attributed to a disrupted transition state due to the presence of the second carbonyl group, which would be able to chelate to lithium and also a poorly reactive site for C-alkylation in the enolate. In the chiral example although the lithium enolate of camphor reacted successfully with benzaldehyde the non-reactivity of the lithium enolate of camphor under the cyclisation conditions resulted in polymerisation of phenyl vinyl sulfoxide. The polymerisation of the electrophile may have been catalysed by the enolate itself and thereby effectively competing with alkylation of camphor and bicyclo[n.2.0]alkan-1-ol formation. A further example, 1,4-cyclohexanedione mono-ethylene ketal was considered. Under the cyclisation conditions followed by oxidation with m-CPBA functionalised bicyclo[4.2.0]octanols 285 and 286 were obtained in conjunction with alkylated product 287. In order to access the ketone functionality the protecting group was removed from functionalised bicyclo[4.2.0]octanol 286 to yield the functionalised bicyclo[4.2.0]octanol 288.

The next chapter focused on the structural elucidation and structural aspects of the bicyclo[n.2.0]alkan-1-ols formed from 2-methylcyclopentanone, 2,6-dimethylycyclohexanone, 1,4-cyclohexanediione mono-ethylene ketal and the deprotected functionalised bicyclo[4.2.0]octanol 288. From the solution state structural elucidation of the bicyclo[n.2.0]alkan-1-ols in addition to solid state structural elucidation for 278,
281 and 286 it was determined that as a cis ring junction occurred in all the bicyclo[n.2.0]alkan-1-ols formed. From the solid state structures of 278, 281 and 286 a pseudo chair conformation was observed for the six-membered ring system. The introduction of a methyl substituent at the C4 in 278 appears to change the direction of torsion within the molecules compared to the simpler structures 281 and 290 but not the magnitude of relative torsion angles and bond angles. Functionalised bicyclo[4.2.0]octanol 286 notably displayed a three-centred ‘bifurcated’ intra- and intermolecular hydrogen bonding between the hydroxyl proton and the sulfone oxygen atoms. Whereas in 278 and 281 the methyl group at C8 disrupts the intermolecular hydrogen bonding. The presence or absence of the intermolecular hydrogen bonding appears to have no influence on the conformation of the four-six membered ring system. Correlations were not drawn between the solid state structures observed for 278, 281 and 286 and the product distributions and yields observed in chapter three due to the variations in reaction conditions used.

In the future it would be interesting to explore further examples, such as the ketone 307, which may provide in situ ring opening of bicyclo[6.2.0]decanolide intermediates to lead to macrocyclic compounds such as ketone 308. Other issues that need to be examined are the selective removal or conversion of the sulfoxide or sulfone functional group in bicyclo[n.2.0]alkan-1-ols and use of optically active ketones or phenyl vinyl sulfoxide to impart stereoselectivity.

![Scheme 89](image-url)
In summary, the range of ketones used in the current study effectively illustrates potential scope and limitations of the novel cyclisation reaction. Whereas application of the cyclisation reaction was successful in simple ketones and simply functionalised ketones, the introduction of a double bond to the starting ketone was a limitation. The latter may prevent application of the cyclisation process to the synthesis of a natural product such as melleolide. However that bicyclo[n.2.0]alkan-1-ols could be formed in unoptimised yields even in the presence of a bridgehead substituent and that conversion of a ketal functional group to a ketone in the presence of the bicyclo[n.2.0]alkan-1-ol could be carried out provides positive indication for further synthetic applications.
Experimental

1.0 General Procedures

$^1$H nmr and $^{13}$C nmr spectra were obtained using a 200 MHz (Varian Gemini 200) or a 400 MHz (Varian Unity 400) spectrometer, with the samples dissolved in CDCl$_3$ or as indicated. $^1$H nmr and $^{13}$C nmr signals are recorded in terms of chemical shift ($\delta$ in ppm) referenced with respect to CDCl$_3$ at 7.24 ppm and 77.0 ppm respectively. Example of abbreviations for multiplicities used are: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; m, multiplet. Mass spectra were recorded on a Fisons VG-Platform II spectrometer, using electrospray as the ionisation technique. Mass Lynx Version I (IBM) software was used to acquire and process the data. Fourier Transform Infrared (FTIR) spectra were recorded in the range 4000-400 cm$^{-1}$ on a Perkin-Elmer FTIR 1725X spectrophotometer. All spectra were recorded as either KBr disc or Nujol as indicated. Melting points were measured on a GallenKamp Variable Temperature Apparatus and are uncorrected. Microanalyses were carried out by the Microanalytical Service, Department of Chemistry at the University of Queensland. High Resolution Mass Spectrometry (HRMS) were carried out at the University of Tasmania.

Analytical thin-layer chromatography (T.L.C) was carried out on Merck precoated aluminium T.L.C plates coated with silica gel 60 F$_{254}$ (0.2 mm). T.L.C fractions were visualised by means of vanillin dip (vanillin, 2 g; ethanol, 200 ml; sulphuric acid, 1 ml) followed by heating of the plate or by ultra-violet light. Analytical HPLC was carried out using a Waters Spherisorb® silica analytical column, Waters 486 tunable absorbance detector set at 265 nm and a Waters 600 controller. Semi-preparative HPLC utilised a Waters Spherisorb® 25 mm Module semi-preparative column, Waters 486 tunable absorbance detector set at 265 nm and a Waters 600 controller. A pressure of 800-1000
psi was typically observed. Millenium HPLC software was used to acquire and process data.

1.1 Reagents and Solvents
Butyllithium as a solution in hexane and lithium diisopropylamide as a solution in heptane/THF/ethylbenzene or heptane were both standardised by titration against 2,5-dimethoxybenzylalcohol. Tetrahydrofuran and diethyl ether were predried over sodium and distilled from sodium using benzophenone as indicator. Both solvents were dispensed from the still under nitrogen immediately prior to use. Other solvents and commercially available reagents were purified in the standard manner.

1.2 Note on nomenclature
The nomenclature and numbering used within the experimental is in accordance with IUPAC nomenclature of organic chemistry. Below are selected examples of numbering systems.

![Figure 23 Representation of IUPAC numbering of selected examples](image)

1.3 $^1$H nmr product analysis and determination of percentage composition
The crude product mixtures from oxidation were dried under high vacuum, and the mass of the crude product determined. The $^1$H nmr (400 MHz) spectra were obtained using CDCl$_3$ as solvent. Integration of the baseline resolved key peaks (to ± 1%) in the region $\delta$ 2.5-4 ppm, for bicyclo[n.2.0]alkan-1-ol, monoalkylated and dialkylated products and in the region $\delta$ 5.80-6.80 ppm unreacted phenyl vinyl sulfoxide as phenyl...
vinyl sulfoxide and/or phenyl vinyl sulfone, was used to calculate the percentage composition of these components if present from the integral of the total crude mixture. Crude yields greater than theoretical 100% were found to include water and this was included in calculations.

1.4 Published Novel Compounds

The characterisation data on compounds 249,253,254-257,262,263,265,267-269,280,286 have been published elsewhere but are reported here for continuity of this body of work.

2.0 General synthesis of bicyclo[n.2.0]alkan-1-ol sulfoxides

Reactions done in the dark were carried out with the reaction vessel thoroughly covered in aluminium foil. Dark conditions were applied before electrophile addition and were maintained until after the reaction was quenched. Table 34 summarises the variables of procedures A–F. Descriptions of procedures A–F are given for conditions that were used multiple times. All other single variations are indicated in the individual experimental heading description.

<table>
<thead>
<tr>
<th>Method</th>
<th>LDA T(°C)</th>
<th>Enolate Generation† T(°C)</th>
<th>Conc. (M)*</th>
<th>Lighting conditions</th>
<th>PVS(O) addition T(°C)</th>
<th>Reaction Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-10</td>
<td>-78 warm</td>
<td>0.155</td>
<td>normal</td>
<td>-30 drop-wise</td>
<td>45 @ 0 °C</td>
</tr>
<tr>
<td>B</td>
<td>-10</td>
<td>-78 warm</td>
<td>0.155</td>
<td>dark</td>
<td>-30 rapid</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>-10</td>
<td>-78 warm</td>
<td>0.01</td>
<td>dark</td>
<td>-30 rapid</td>
<td>5</td>
</tr>
<tr>
<td>D</td>
<td>-10</td>
<td>-78 warm</td>
<td>0.31</td>
<td>dark</td>
<td>-30 rapid</td>
<td>5</td>
</tr>
<tr>
<td>E</td>
<td>-10</td>
<td>-78 warm</td>
<td>0.085</td>
<td>dark</td>
<td>-10 rapid</td>
<td>10</td>
</tr>
<tr>
<td>F</td>
<td>-10</td>
<td>0</td>
<td>0.085</td>
<td>dark</td>
<td>-10 rapid</td>
<td>10</td>
</tr>
</tbody>
</table>

† 1 equivalent of LDA
* ketone in total reaction volume
† 1 equivalent of phenyl vinyl sulfoxide
§ warm denotes reaction warmed from –78 °C to –30 °C generally over a period of 10-30 min
Procedure A

Lithium diisopropylamide (1 equivalent, 1.27–1.95 M) was added to THF under an atmosphere of nitrogen at -10 °C and the solution cooled to -75-78 °C. The ketone (0.155M, using 3.796 mmoles – 7.134 mmoles according to ketone used) was added over 5 minutes and the temperature maintained between -70-78 °C. The system was allowed to warm to -30 °C and phenyl vinyl sulfoxide (1 equivalent) was added over 5 minutes. The reaction mixture was warmed to 0 °C, stirred for 45 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was extracted with ethyl acetate (3 x 40 ml) and the combined organic layers were washed with water (2 x 50 ml), brine (50 ml) and dried (MgSO₄, anhydrous). The solvent was removed under reduced pressure to afford the crude sulfoxide mixture which was oxidised to the corresponding sulfone mixture according to the general procedures.

Procedure B

The lithium enolate of the ketone was generated according to procedure A using lithium diisopropylamide (1 equivalent, 1.27–1.95 M), THF and ketone (0.155M, using 2.261 mmoles – 8.915 mmoles according to ketone used). The system was shielded from light and allowed to warm to -30 °C. Phenyl vinyl sulfoxide (1 equivalent) was added rapidly. The reaction mixture was maintained at -30 °C, stirred for 5 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. The crude sulfoxide mixture was oxidised to the corresponding sulfone mixture according to the general procedures.

Procedure C

The lithium enolate of the ketone was generated according to procedure A using lithium diisopropylamide (1 equivalent, 1.27–1.70 M), THF and ketone (0.01M, using 0.759
mmoles – 1.869 mmoles according to ketone used). The system was shielded from light and allowed to warm to -30 °C. Phenyl vinyl sulfoxide (1 equivalent) was added rapidly. The reaction mixture was maintained at -30 °C, stirred for 5 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. The crude sulfoxide mixture was oxidised to the corresponding sulfone mixture according to the general procedures.

Procedure D
The lithium enolate of the ketone was generated according to procedure A using lithium diisopropylamide (1 equivalent, 1.40–1.95 M), THF and ketone (0.31M, using 3.796 mmoles – 5.653 mmoles according to ketone used). The system was shielded from light and allowed to warm to -35 °C. Phenyl vinyl sulfoxide (1 equivalent) was added rapidly. The reaction mixture was stirred for 5 minutes. The temperature was maintained at -30 °C during this time. The reaction was quenched with aqueous ammonium chloride (40 ml) and worked up according to procedure A. The crude sulfoxide mixture was oxidised to the corresponding sulfone mixture according to the general procedures.

Procedure E
The lithium enolate of the ketone was generated according to procedure A using lithium diisopropylamide (1 equivalent, 1.27–2.0 M), THF and ketone (0.085M, using 3.201 mmoles – 8.237 mmoles according to ketone used). The system was shielded from light and allowed to warm to -10 °C. Phenyl vinyl sulfoxide (1 equivalent) was added rapidly. The reaction mixture was maintained at -10 °C, stirred for 10 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up
according to procedure A. The crude sulfoxide mixture was oxidised to the corresponding sulfone mixture according to the general procedures.

**Procedure F**

Lithium diisopropylamide (1 equivalent, 1.4 M) was added to THF under an atmosphere of nitrogen at -10 °C and the solution warmed to 0 °C. The ketone (0.085M, using 3.201 mmoles – 4.459 mmoles according to ketone used) was added over 5 minutes and the temperature maintained at 0 °C for an hour. The system was shielded from light and cooled to -10 °C. Phenyl vinyl sulfoxide (1 equivalent) was added rapidly. The reaction mixture was maintained at -10 °C, stirred for 10 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. The crude sulfoxide mixture was oxidised to the corresponding sulfone mixture according to the general procedures.

**Oxidation of bicyclo[n.2.0]alkan-1-ol sulfoxide mixtures**

The crude sulfoxides (1 mole, based on assumed 100% conversion to monoalkylated product) dissolved in chloroform (10 or 20 ml) were added to a vigorously stirred solution of m-CPBA (1.0-1.1 mole) and chloroform (10 or 20 or 30 ml) at 0 °C, over 20 minutes. The mixture was stirred at room temperature for 16 hours and the solvent removed under reduced pressure. The residue was dissolved in ethyl acetate (50 ml) and the combined organic layers washed with aqueous sodium hydrogen carbonate (3 x 40 ml), brine (40 ml) and dried (MgSO₄, anhydrous). The solvent was removed under reduced pressure and dried under high vacuum to afford the crude sulfone mixture.
2.1 Reaction between Cyclobutanone and phenyl vinyl sulfoxide

**Cyclobutanone: Procedure A**

Cyclobutanone (0.53 ml, 7.134 mmole), lithium diisopropylamide (1.4 M, 5.1 ml, 7.134 mmole) and phenyl vinyl sulfoxide (0.95 ml, 7.134 mmole) in THF (39.5 ml), were reacted together according to procedure A. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.408 g). The crude sulfoxide mixture (1.408 g, 6.334 mmole) in chloroform (20 ml) was reacted with \( m \)-CPBA (6.334 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of \( m \)-chlorobenzoic acid was obtained as a yellow oil (0.877 g). Analysis of the crude mixture by \(^1\)H nmr spectroscopy indicated that cyclohexanone 248 (5.5%) and monoalkylated cyclobutanone 249 (38.5%) were present. The crude mixture was purified by silica column chromatography (hexane: ethyl acetate, 60:40). The first fraction (64 mg) contained cyclohexanone 248. The second fraction (693 mg) contained monoalkylated cyclobutanone 249. Analytically pure samples were obtained by semi-preparative HPLC of cyclohexanone 248 from fraction one (hexane: ethyl acetate, 70:30) and monoalkylated cyclobutanone 249 from fraction two (hexane: ethyl acetate, 50:50).

2-(Phenylsulfonyl)cyclohexanone 248 was isolated from fraction 1 as a white solid, mp 65.7-66.6 °C‡ (ethyl acetate-hexane) (87 °C from CCl₄).\(^1\)\(^4\)\(^6\) (Rt 13.0 min, 3 ml/min) (Found: C, 60.53; H, 6.11. Calc. for C₇H₁₄SO₃: C, 60.48; H, 5.92%); \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\) 1710, (CO), 1309, (SO\(_2\)), 1149, (SO\(_2\)); \( \delta_{\text{H}} \) (400 MHz, CDCl₃) 7.85–7.90 (2 H, m, \( o \)-C\(_₆\)H\(_₅\)), 7.61–7.67 (1 H, m, \( p \)-C\(_₆\)H\(_₅\)), 7.51–7.57 (2 H, m, \( m \)-C\(_₆\)H\(_₅\)), 3.82 (1 H, ddd, \( J_{2,3} \) 5.5, \( J_{2.5} \) 5.5, \( J_{2,4 \text{ or } 6} \) 1.5, 2-H), 2.80 (1 H, ddd, \( J_{6,6} \) 15, \( J_{6,5} \) 9.5, \( J_{6,5} \) 5, 6-H), 2.47-2.60 (1 H, m, 3-H), 2.37-2.45 (1 H, m, 6-H), 2.13-2.28 (2 H, m, 3-H, 4-H), 1.93-2.05 (1 H, m, 3-H, 4-H).

\(^1\)\(^1\)H nmr and IR spectra were in agreement with reported literature values.
5-H), 1.67-1.87 (2 H, m, 4-H, 5-H); δC (50 MHz, CDCl₃) 202.3 C-1; 138.4 i-C₆H₅; 134.2 p-C₆H₅; 129.3 m-C₆H₅; 129.1 o-C₆H₅; 72.9 C-2; 41.9 C-6; 27.8 C-3; 26.7 C-5; 22.3 C-4; (ESMS+) 245 (MLi⁺, 24%), 261 (MNa⁺, 100%).

2-[2′-(Phenylsulfonyl)ethyl]cyclobutanone 249 was isolated from fraction 2 as a white solid, mp 40.5-41.8 °C (ethyl acetate-hexane). (Rt 9.4 min, 3 ml/min) (Found: C, 60.31; H, 6.05; S, 13.30. Calc. for C₁₂H₁₄SO₃: C, 60.48; H, 5.92; S, 13.45%); νmax(KBr)/cm⁻¹ 1776, (CO), 1294, (SO₂), 1144, (SO₂); δH (400 MHz, CDCl₃) 7.86–7.91 (2 H, m, o-C₆H₅), 7.63–7.69 (1 H, m, p-C₆H₅), 7.51–7.60 (2 H, m, m-C₆H₅), 3.36 (1 H, dddddd, J₂,3 10.5, J₂,1' 7.5, J₂,1 7.5, J₂,4 2.5, J₂,2 2.5, 2-H), 3.26 (1 H, ddd, J₂,2' 14, J₂,1' 10, J₂,1' 6, 2'-H), 3.12 (1 H, ddd, J₂,2' 14, J₂,1' 10, J₂,1' 6, 2'-H), 3.05 (1 H, dddd, J₄,₄ 18.5, J₄,3 10, J₄,4 7.5, J₄,2 2.5, 4-H), 2.90 (1 H, dddd, J₄,4 18, J₄,3 9.5, J₄,3 5, J₄,2 3, 4-H), 2.22 (1 H, dddd, J₃,₃ 10.5, J₃,4 10.5, J₃,2 10.5, J₃,4 5, 3-H), 1.90-2.08 (2 H, m, 2 x 1'-H), 1.62 (1 H, dddd, J₃,₃ 11, J₃,4 9.5, J₃,4 8, J₃,2 8, 3-H); δC (50 MHz, CDCl₃) 209.3 C-1; 139.9 i-C₆H₅; 133.8 p-C₆H₅; 129.3 m-C₆H₅; 128.0 o-C₆H₅; 57.9 C-2; 53.7 C-2'; 44.8 C-4; 22.8 C-1'; 16.9 C-3; (ESMS+) 245 (MLi⁺, 40%), 261 (MNa⁺, 100%).

Cyclobutanone: Procedure B

Cyclobutanone (0.53 ml, 7.134 mmole), lithium diisopropylamide (1.4 M, 5.1 ml, 7.134 mmole) and phenyl vinyl sulfoxide (0.95 ml, 7.134 mmole) in THF (39.5ml), were reacted together according to procedure B. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.365 g). The crude sulfoxide mixture (1.365 g, 6.141 mmole) in chloroform (20 ml) was reacted with m-CPBA (6.141 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.503 g). Analysis of the crude
mixture by $^1$H nmr spectroscopy indicated that phenyl vinyl sulfoxide (1%),
cyclohexanone 248 (6%) and monoalkylated cyclobutanone 249 (18%) were present.

2.2 Reaction between Cyclopentanone and phenyl vinyl sulfoxide

Cyclopentanone: Procedure A

Cyclopentanone (0.55 ml, 6.220 mmole), lithium diisopropylamide (1.95 M, 3.2 ml, 6.220 mmole) and phenyl vinyl sulfoxide (0.83 ml, 6.220 mmole) in THF (35.5 ml), were reacted together according to procedure A. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.365 g). The crude sulfoxide mixture (1.365 g, 5.775 mmole) in chloroform (20 ml) was reacted with m-CPBA (5.775 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (1.139 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that monoalkylated cyclopentanone 257 (55.5%) and dialkylated cyclopentanone 256 (2.5%), bicyclo[3.2.0]heptan-1-ols 253 (3%) and 254 (2.5%), and substituted bicyclo[3.2.0]heptan-1-ol 255 (1.5%) were present. The crude mixture was purified by silica column chromatography (hexane:ethyl acetate, 60:40). The first fraction (62 mg) contained bicyclo[3.2.0]heptan-1-ol 253. The second fraction (514 mg) contained monoalkylated cyclopentanone 257. The third fraction (154 mg) contained a mixture of bicyclo[3.2.0]heptan-1-ol 254 and monoalkylated cyclopentanone 257. The fourth fraction (245 mg) contained monoalkylated cyclopentanone 257, dialkylated cyclopentanone 256 and substituted bicyclo[3.2.0]heptan-1-ol 255. Analytically pure samples were obtained by semi-preparative HPLC of bicyclo[3.2.0]heptan-1-ol 253 from fraction one (hexane:ethyl acetate, 60:40), bicyclo[3.2.0]heptan-1-ol 254 from fraction three (hexane:ethyl acetate, 70:30), monoalkylated cyclopentanone 257 from fraction four (hexane:ethyl acetate, 60:40), dialkylated cyclopentanone 256 from fraction four (hexane:ethyl acetate, 60:40)
and substituted bicyclo[3.2.0]heptan-1-ol 255 from fraction four (hexane:ethyl acetate, 60:40).

2-[(2’-(Phenylsulfonyl)ethyl)cyclopentanone 257 was isolated from fraction 4 as a white solid mp, 75.2-76.0 °C (ethyl acetate-hexane). (Rt 10.7 min, 4 ml/min) (Found: C, 61.98; H, 6.43. Calc. for C_{13}H_{16}SO_3: C, 61.87; H, 6.39%); ν_{max}(KBr)/cm^{-1} 1733, (CO), 1299, (SO_2), 1143, (SO_2); δ_{H} (400 MHz, CDCl_3) 7.85–7.93 (2 H, m, o-C_6H_5), 7.60–7.68 (1 H, m, p-C_6H_5), 3.16 (1 H, ddd, J_{2',2'} 7, J_{2',1'} 5.5, J_{2',1'} 3, 2'-H), 3.16 (1 H, ddd, J_{2',2'} 7, J_{2',1'} 5.5, J_{2',1'} 3, 2'-H), 2.00–2.15 (4 H, m, 2-H, 3-H, 2 x 5-H), 1.93–2.00 (2 H, m, 4-H, 1'-H), 1.67–1.83 (2 H, m, 4-H, 1'-H), 1.42–1.52 (1 H, m, 3-H); δ_{C} (50 MHz, CDCl_3) 219.7 C-1; 139.3 i-C_6H_5; 133.7 p-C_6H_5; 129.7 m-C_6H_5; 128.3 o-C_6H_5; 54.0 C-2'; 47.5 C-2; 37.4 C-5; 29.3 C-3; 22.8 C-1'; 20.5 C-4; (ESMS+) 259 (MLi^+, 94%), 275 (MNa^+, 100%). HRMS (Found: 253.08844. C_{13}H_{17}SO_3 requires 253.0898).

2,5-Bis[(2’-(Phenylsulfonyl)ethyl)cyclopentanone 256 was isolated from fraction 4 as a tacky solid. (Rt 15.7 min, 4 ml/min) (Found: C, 59.67; H, 5.96. Calc. for C_{21}H_{24}S_2O_5: C, 59.96; H, 5.75%). ν_{max}(KBr)/cm^{-1} 1738, (CO), 1305, (SO_2), 1150, (SO_2); δ_{H} (400 MHz, CDCl_3) 7.80–7.94 (4 H, m, o-C_6H_5), 7.63–7.73 (2 H, m, p-C_6H_5), 7.53–7.63 (4 H, m, m-C_6H_5), 2.80–3.12 (4 H, m, 2 x 2’-H, 2 x 2''-H), 2.17–2.30 (2 H, m, 2-H, 5-H), 1.67–2.00 (8 H, m, 2 x 3-H, 2 x 4-H, 2 x 1’-H, 2 x 1”-H); δ_{C} (50 MHz, CDCl_3) 219.3 C-1; 138.8 i-C_6H_5; 134.0 p-C_6H_5; 129.5 m-C_6H_5; 128.0 o-C_6H_5; 51.1 C-2’, C-2’’; 37.5 C-2, C5; 25.7 C-1’, C-1’’; 18.4 C-3, C-4; (ESMS+) 427 (MLi^+, 100%), 443 (MNa^+, 100%); (ESMS-) 419 (M-H 54%).
(1RS, 5SR, 7SR)-7-(Phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol 253 was isolated from fraction 1 as a white solid, mp 89.1-92.6 °C (ethyl acetate-hexane). (Rt 8.9 min, 3 ml/min) (Found: C, 61.82; H, 6.34. Calc. for C_{13}H_{16}SO_3: C, 61.87; H, 6.39%); \nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} 3536 (OH), 1291 (SO_2), 1144 (SO_2); \delta_H (400 MHz, CDCl_3) 7.92–7.99 (2 H, m, \text{o}-C_6H_5), 7.60–7.68 (1 H, m, \text{p}-C_6H_5), 7.51–7.60 (2 H, m, \text{m}-C_6H_5), 3.62 (1 H, ddd, J_{7,6} 9.5, J_{7,6} 5.5, J_{7,5} < 1, 7-H), 3.40 (1 H, br s, W_{h/2} 136, OH), 2.62–2.72 (2 H, m, 5-H, 6-H), 1.74–1.89 (2 H, m, 3-H, 4-H), 1.60–1.84 (3 H, m, 3-H, 2 x 2-H), 1.46–1.60 (2 H, m, 4-H, 6-H); \delta_C (50 MHz, CDCl_3) 139.5 \text{i}-C_6H_5; 133.6 \text{p}-C_6H_5; 129.2 \text{m}-C_6H_5; 127.9 \text{o}-C_6H_5; 83.6 C-1; 64.2 C-7; 46.3 C-5; 40.1 C-2; 31.4 C-4; 24.2 C-3; 20.1 C-6; (ESMS+) 259 (M{\text{Li}}^+, 100%), 275 (M{\text{Na}}^+, 30%).

(1RS, 5SR, 7RS)-7-(Phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol 254 was isolated from fraction 3 as a white solid, mp 94.9-95.8 °C (ethyl acetate-hexane) (Rt 28.7 min, 3 ml/min) (Found: C, 61.84; H, 6.45; S, 12.35. Calc. for C_{13}H_{16}SO_3: C, 61.87; H, 6.39; S, 12.72%); \nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} 3457, (OH), 1295, (SO_2), 1147, (SO_2); \delta_H (400 MHz, CDCl_3) 7.82–7.92 (2 H, m, \text{o}-C_6H_5), 7.58–7.68 (1 H, m, \text{p}-C_6H_5), 7.48–7.58 (2 H, m, \text{m}-C_6H_5), 3.79 (1 H, ddd, J_{7,6} 10, J_{7,6} 10, J_{7,2} 1, 7-H), 2.90 (1 H, ddd, J_{2,2} 14 , J_{2,3} 7, J_{2,3} 4, 2-H), 2.45–2.54 (1 H, m, 5-H), 2.04–2.22 (2 H, m, 3-H, 6-H), 1.68–1.95 (3 H, m, 3-H, 4-H, 6-H), 1.53–1.68 (2 H, m, 2-H, 4-H), OH not observed; \delta_C (50 MHz, CDCl_3) 140.2 \text{i}-C_6H_5; 133.4 \text{p}-C_6H_5; 129.2 \text{m}-C_6H_5; 127.6 \text{o}-C_6H_5; 85.3 C-1; 65.3 C-7; 44.6 C-5; 36.8 C-2; 31.3 C-4; 25.6 C-3; 20.8 C-6; (ESMS+) 275 (M{\text{Na}}^+, 100%).

(1RS, 5RS, 7SR)-7-(Phenylsulfonyl)-5-[2-(phenylsulfonyl)ethyl]bicyclo[3.2.0]heptan-1-ol 255 was isolated from fraction 4 and after extensive drying was as a hygroscopic gum. (Rt 16.2 min, 4 ml/min). (Found: C, 58.84; H, 5.67. Calc. for C_{21}H_{24}S_2O_5.1/2H_2O: C, 58.72; H, 5.87%). \nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} 3451, (OH), 1305, (SO_2), 1147, (SO_2); \delta_H (400
MHz, CDCl₃) 7.84–7.96 (4 H, m, o-C₆H₅), 7.50–7.70 (6 H, m, p-C₆H₅, m-C₆H₅), 4.27 (1 H, br s, W½/2 1.5, OH), 3.50 (1 H, dd, J₇,₆ 10, J₇,₆ 7, 7-H), 3.01–3.15 (2 H, m, 2 x 2'-H), 2.20 (1 H, dd, J₆,₆ 14 , J₆,₇ 7, 6-H), 2.11 (1 H, ddd, J₁',₁' 13.5, J₁',₂' 11, J₁',₂' 6, 1'-H), 1.88 (1 H, ddd, J₁',₁' 13.5, J₁',₂' 11, J₁',₂' 5.5, 1'-H), 1.75–1.82 (1 H, m, 3-H), 1.60–1.74 (2 H, m, 2-H, 6-H), 1.36–1.59 (4 H, m, 2-H, 3-H, 2 x 4-H); δC (100 MHz, CDCl₃) 139.7, 138.7 i-C₆H₅; 133.9, 133.8 p-C₆H₅; 129.4, 129.3 m-C₆H₅; 128.2, 127.9 o-C₆H₅; 83.4, C-1; 62.2, C-7; 52.3, C-2'; 49.2 C-5; 40.1 C-2; 35.9 C-4; 26.7 C-1'; 26.6 C-6; 21.8 C-3; (ESMS+) 427 (MLi⁺, 100%), 443 (MNa⁺, 100%).

Cyclopentanone: Procedure B

Cyclopentanone (0.2 ml, 2.261 mmole), lithium diisopropylamide (1.27 M, 1.78 ml, 2.261 mmole) and phenyl vinyl sulfoxide (0.3 ml, 2.261 mmole) in THF (12.3 ml), were reacted together according to procedure B. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (0.372 g). The crude sulfoxide mixture (0.372 g, 1.574 mmole) in chloroform (10 ml) was reacted with m-CPBA (1.574 mmole) in chloroform (15 ml). Upon workup, the crude sulfone mixture containing m-chlorobenzoic acid was obtained as a yellow oil (0.303 g). Analysis of the crude mixture by ¹H nmr spectroscopy indicated that phenyl vinyl sulfoxide (6%), monoalkylated cyclopentanone 257 (19.5%), dialkyated cyclopentanone 256 (0.5%), bicyclo[3.2.0]heptan-1-ols 253 (18.5%) and 254 (0.5%), and substituted bicyclo[3.2.0]heptan-1-ol 255 (0.5%) were present.

Cyclopentanone: Procedure C

Cyclopentanone (0.1 ml, 1.131 mmole), lithium diisopropylamide (1.70 M, 0.67 ml, 1.131 mmole) and phenyl vinyl sulfoxide (0.15 ml, 1.131 mmole) in THF (113 ml), were reacted together according to procedure C. Upon workup, the crude sulfoxide
mixture was obtained as a yellow oil (0.278 g). The crude sulfoxide mixture (0.278 g, 1.176 mmole) in chloroform (10 ml) was reacted with \textit{m}-CPBA (0.176 mmole) in chloroform (15 ml). Upon workup, the crude sulfone mixture was obtained as a yellow oil (0.220 g). Analysis of the crude mixture by \textsuperscript{1}H nmr spectroscopy indicated that phenyl vinyl sulfoxide (23%), phenyl vinyl sulfone (3.5%), monoalkylated cyclopentanone \textbf{257} (22%), bicyclo[3.2.0]heptan-1-ols \textbf{253} (26.5%) and \textbf{254} (1%) and substituted bicyclo[3.2.0]heptan-1-ol \textbf{255} (0.5%) were present.

**Cyclopentanone: Procedure D**

Cyclopentanone (0.5 ml, 5.653 mmole), lithium diisopropylamide (1.95 M, 2.9 ml, 5.653 mmole) and phenyl vinyl sulfoxide (0.76 ml, 5.653 mmole) in THF (14.2 ml), were reacted together according to procedure D. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.149 g). The crude sulfoxide mixture (1.149 g, 4.862 mmole) in chloroform (20 ml) was reacted with \textit{m}-CPBA (4.862 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of \textit{m}-chlorobenzoic acid was obtained as a yellow oil (0.873 g). Analysis of the crude mixture by \textsuperscript{1}H nmr spectroscopy indicated that phenyl vinyl sulfoxide (6.5%), monoalkylated cyclopentanone \textbf{257} (25.5%), bicyclo[3.2.0]heptan-1-ols \textbf{253} (22.5%) and \textbf{254} (1%) and substituted bicyclo[3.2.0]heptan-1-ol \textbf{255} (0.5%) were present.

2.3 **Reaction between Cycloheptanone and phenyl vinyl sulfoxide**

**Cycloheptanone: Procedure A**

Cycloheptanone (0.5 ml, 4.239 mmole), lithium diisopropylamide (1.40 M, 3.0 ml, 4.239 mmole) and phenyl vinyl sulfoxide (0.57 ml, 4.239 mmole) in THF (23 ml), were reacted together according to procedure A. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.074 g). The crude sulfoxide mixture (1.074 g, 4.063
mmole) in chloroform (20 ml) was reacted with \( m \)-CPBA (4.063 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture was obtained as a yellow oil (0.890 g). Analysis of the crude mixture by \(^1\)H nmr spectroscopy indicated that monoalkylated cycloheptanone 264 (41%), bicyclo[5.2.0]nonan-1-ols 262 (26%) and 263 (8%) were present. The crude mixture was purified by silica column chromatography (hexane:ethyl acetate, 60:40). The first fraction (257 mg) contained bicyclo[5.2.0]nonan-1-ol 262. The second fraction (170 mg) contained monoalkylated cycloheptanone 264 which included bicyclo[5.2.0]nonan-1-ol 262 (<5%). The third fraction (240 mg) contained a mixture of bicyclo[5.2.0]nonan-1-ol 263 and monoalkylated cycloheptanone 264, and the last fraction (71 mg) contained monoalkylated cycloheptanone 264. Analytically pure samples were obtained by semi-preparative HPLC of bicyclo[5.2.0]nonan-1-ol 262, from fraction one (hexane: ethyl acetate, 70:30), bicyclo[5.2.0]nonan-1-ol 263 from fraction three (hexane:ethyl acetate, 60:40) and monoalkylated cycloheptanone 264 from fraction three (hexane:ethyl acetate, 60:40).

2-[2'-(Phenylsulfonyl)ethyl]cycloheptanone 264\(^{153}\) was isolated from fraction 3 as an oil. (Rt 10.0 min, 3 ml/min) \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\): 1702, (CO), 1306, (SO\(_2\)), 1148, (SO\(_2\)); \( \delta_{\text{H}} \) (200 MHz, CDCl\(_3\)) 7.80–7.92 (2 H, m, o-C\(_6\)H\(_5\)), 7.47–7.70 (3 H, m, m-C\(_6\)H\(_5\), p-C\(_6\)H\(_5\)), 2.95–3.23 (2 H, m, 2 x 2'-H), 2.62–2.80 (1 H, m, 2-H), 2.30–2.55 (2 H, m, 2 x 7-H), 1.07–2.10 (10 H, m, 2 x 3-H, 2 x 4-H, 2 x 5-H, 2 x 6-H, 2 x 1'-H); \( \delta_{\text{C}} \) (50 MHz, CDCl\(_3\)) 214.3 C-1; 139.1 i-C\(_6\)H\(_5\); 133.6 p-C\(_6\)H\(_5\); 129.2 m-C\(_6\)H\(_5\); 127.9 o-C\(_6\)H\(_5\); 54.0 C-2'; 49.8 C-2; 43.2 C-7; 31.8, 29.1, 28.8, 25.0, 23.8 C-3, C-4, C-5, C-6, C-1'; (ESMS+) 287 (MLi\(^+\), 44%), 303 (MNa\(^+\), 100%).

(1RS, 7SR, 9SR)-9-(Phenylsulfonyl)bicyclo[5.2.0]nonan-1-ol 262 was isolated from fraction 1 as a white solid mp, 99.3–101.1 °C (ethyl acetate-hexane). (Rt 8.8 min, 3
Cycloheptanone: Procedure B

Cycloheptanone (0.530 ml, 4.458 mmole), lithium diisopropylamide (1.74 M, 2.56 ml, 4.458 mmole) and phenyl vinyl sulfoxide (0.6 ml, 4.458 mmole) in THF (25ml), were reacted together according to procedure B. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.063 g). The crude sulfoxide mixture (1.063 g, 4.021
mmole) in chloroform (20 ml) was reacted with m-CPBA (4.021 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (1.043 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that phenyl vinyl sulfoxide (4%), phenyl vinyl sulfone (1%), monoalkylated cycloheptanone 264 (3%), bicyclo[5.2.0]nonan-1-ols 262 (61.5%) and 263 (8.5%) and substituted bicyclo[5.2.0]nonan-1-ol 268 (1%) were present. The crude mixture was purified by silica column chromatography (hexane: ethyl acetate, 60:40). The first fraction (653 mg) contained bicyclo[5.2.0]nonan-1-ol 262, which included phenyl vinyl sulfoxide (<5%). The second fraction (20 mg) contained monoalkylated cycloheptanone 264, bicyclo[5.2.0]nonan-1-ol 263, bicyclo[5.2.0]nonan-1-ol 262 (<5%) and phenyl vinyl sulfone. The third fraction (87 mg) contained bicyclo[5.2.0]nonan-1-ol 263. The fourth fraction (46 mg) contained substituted bicyclo[5.2.0]nonan-1-ol 268 and phenyl vinyl sulfone (<5%). An analytically pure sample of substituted bicyclo[5.2.0]nonan-1-ol 262 was obtained by semi-preparative HPLC from fraction four (hexane: ethyl acetate, 70:30).

$(1RS, 2RS, 7SR, 9SR)$-9-(Phenylsulfonyl)-2-[2(phenylsulfonyl)ethyl]bicyclo[5.2.0]non-
an-1-ol 268 was isolated from fraction 4 as a cream solid mp, 123.3-126.1 °C (ethyl acetate-hexane). Minor inseparable impurities (<5%) were present. (Rt 20.4 min, 3 ml/min); $v_{\text{max}}$(KBr)/cm$^{-1}$ 3536, (OH), 1302, (SO$_2$), 1149, (SO$_2$); $\delta_H$ (400 MHz, CDCl$_3$) 7.80–7.86 (4 H, m, o-C$_6$H$_5$), 7.60–7.63 (2 H, m, p-C$_6$H$_5$), 7.44–7.60 (4 H, m, m-C$_6$H$_5$), 3.74 (1 H, dd, $J_{9,8}$ 10.5, $J_{9,8}$ 4, 9-H), 3.09 (1 H, ddd, $J_{2',2'}$ 14, $J_{2',1'}$ 8, $J_{2',1'}$ 6, 2'-H), 2.97 (1 H, ddd, $J_{2',2'}$ 14.5, $J_{2',1'}$ 8, $J_{2',1'}$ 7, 2'-H), 2.47–2.62 (2 H, m, 2-H, 4-H, 8-H, 6-H, 3'-H), 1.27–1.46 (2 H, m, 8-H, 1'-H), 1.06–1.27 (4 H, m, 3-H, 4-H, 5-H, 6-H), OH not observed; $\delta_C$ (50 MHz, CDCl$_3$) 138.9 i-C$_6$H$_5$; 133.7, 133.5 p-C$_6$H$_5$; 129.2 m-C$_6$H$_5$; 128.2, 127.8 o-C$_6$H$_5$; 81.7 C-1; 62.7 C-9; 54.3 C-2'; 49.6
Cycloheptanone: Procedure C

Cycloheptanone (0.1 ml, 0.848 mmole), lithium diisopropylamide (1.70 M, 0.5 ml, 0.848 mmole) and phenyl vinyl sulfoxide (0.11 ml, 0.848 mmole) in THF (85 ml), were reacted together according to procedure C. Upon workup, the crude sulfoxide mixture was obtained as a yellow solid (0.222 g). The crude sulfoxide mixture (0.222 g, 0.840 mmole) in chloroform (10 ml) was reacted with m-CPBA (0.840 mmole) in chloroform (15 ml). Upon workup, the crude sulfone mixture containing m-chlorobenzoic acid was obtained as a yellow oil (0.158 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that phenyl vinyl sulfoxide (13.5%), monoalkylated cycloheptanone 264 (6%) and bicyclo[5.2.0]nonan-1-ols 262 (42%) and 263 (5%) were present.

Cycloheptanone: Procedure D

Cycloheptanone (0.5 ml, 4.239 mmole), lithium diisopropylamide (1.95 M, 2.2 ml, 4.239 mmole) and phenyl vinyl sulfoxide (0.56 ml, 4.239 mmole) in THF (10.6 ml), were reacted together according to procedure D. Upon workup, the crude sulfoxide mixture was obtained as a yellow solid (1.211 g). The crude sulfoxide mixture (1.211 g, 4.598 mmole) in chloroform (20 ml) was reacted with m-CPBA (4.598 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing a trace of m-chlorobenzoic acid was obtained as a yellow oil (0.920 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that phenyl vinyl sulfoxide (12%),
monoalkylated cycloheptanone 264 (9%) and bicyclo[5.2.0]nonan-1-ols 262 (43.5%) and 263 (12%) were present.

2.4 Reaction between Cyclooctanone and phenyl vinyl sulfoxide

Cyclooctanone: Procedure A

Cyclooctanone (0.5 ml, 3.796 mmole) in THF (2 ml), lithium diisopropylamide (1.95 M, 1.95 ml, 3.796 mmole) and phenyl vinyl sulfoxide (0.51 ml, 3.796 mmole) in THF (19.5 ml), were reacted together according to procedure A. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.128 g). The crude sulfoxide mixture (1.128 g, 4.051 mmole) in chloroform (20 ml) was reacted with m-CPBA (4.051 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (1.021 g).

Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that monoalkylated cyclooctanone 266 (65%), dialkylated cyclooctanone 267 (14.5%) and bicyclo[6.2.0]decan-1-ol 265 (2%) were present. The crude mixture was purified by silica column chromatography (hexane: ethyl acetate, 60:40). The first fraction (20 mg) contained bicyclo[6.2.0]decan-1-ol 265. The second fraction (502 mg) contained monoalkylated cyclooctanone 266. The last fraction (317 mg) contained dialkylated cyclooctanone 267. Analytically pure samples were obtained by semi-preparative HPLC of bicyclo[6.2.0]decan-1-ol 265 from fraction one (hexane: ethyl acetate, 70:30), monoalkylated cyclooctanone 266 from fraction two (hexane: ethyl acetate, 60:40) and dialkylated cyclooctanone 267 from fraction three (hexane: ethyl acetate, 70:30).

2-[2'-(Phenylsulfonyl)ethyl]cyclooctanone 266$^{153}$ was isolated from fraction 2 as an oil. (Rt 9.5 min, 3 ml/min) $v_{\text{max}}$(KBr)/cm$^{-1}$ 1698, (CO), 1306, (SO$_2$), 1151, (SO$_2$); $\delta_H$ (400 MHz, CDCl$_3$) 7.80–7.91 (2 H, m, o-C$_6$H$_5$), 7.57–7.80 (1 H, m, p-C$_6$H$_5$), 7.48–7.57 (2 H,
2,5-Bis[2'-(phenylsulfonyl)ethyl]cyclooctanone 267 was isolated from fraction 3 as a white solid mp, 122.8-124.1 °C (ethyl acetate-hexane). (Rt 25.8 min, 3 ml/min) (Found: C, 62.44; H, 6.59; S, 13.72. Calc. for C_{24}H_{30}S_2O_5: C, 62.31; H, 6.54; S, 13.86%). ν_{\text{max}}(KBr)/cm^{-1} 1690, (CO), 1305, (SO_2), 1144, (SO_2); δ_{\text{H}} (400 MHz, CDCl_3) 7.80–7.89 (4 H, m, o-C_6H_5), 7.45–7.70 (6 H, m, m-C_6H_5, p-C_6H_5), 3.05 (2 H, ddd, J_{2'/2'',2'/2''} 14, J_{2'/2'',1'/1''} 6.5, 2'-H, 2''-H), 2.91 (2 H, ddd, J_{2'/2'',2'/2''} 14, J_{2'/2'',1'/1''} 9.5, J_{2'/2'',1'/1''} 6.5, 2'-H, 2''-H), 2.53–2.66 (2 H, m, 2-H, 8-H), 1.72–1.95 (4 H, m, 2 x 1’-H, 2 x 1”-H), 1.43–1.72 (6 H, m, 2 x 3-H, 2 x 4-H or 2 x 6-H, 2 x 7-H), 1.10–1.43 (4 H, m, 2 x 5-H, 2 x 4-H or 2 x 6-H); δ_{\text{C}} (50 MHz, CDCl_3) 218.9 C-1; 138.8 i-C_6H_5; 133.8 p-C_6H_5; 129.4 m-C_6H_5; 128.0 o-C_6H_5; 53.8 C-2’, C-2”; 48.4 C-2, C-8; 32.5 C-3, C-7; 26.1 C-4, C-6; 25.7 C-1’, C-1”; 24.5 C-5; (ESMS+) 469 (MLi^+, 100%), 485 (MNa^+, 100%).

(1RS, 8SR, 10SR)-10-(Phenylsulfonyl)bicyclo[6.2.0]decan-1-ol 265 was isolated from fraction 1 as a white solid mp 98.1–100.2 °C (ethyl acetate-hexane). (Rt 7.70 min, 3 ml/min) (Found: C, 65.05; H, 7.61; S, 10.89. Calc. for C_{16}H_{22}SO_3: C, 65.26; H, 7.53; S, 10.90%); ν_{\text{max}}(KBr)/cm^{-1} 3527, (OH), 1282, (SO_2), 1155, (SO_2); δ_{\text{H}} (400 MHz, CDCl_3) 7.87–7.93 (2 H, m, o-C_6H_5), 7.57–7.64 (1 H, m, p-C_6H_5), 7.48–7.57 (2 H, m, m-C_6H_5), 3.44 (1 H, ddd, J_{10.9} 10, J_{10.9} 6, J_{10.8} 1, 10-H), 2.61 (1 H, ddd, J_{9.9} 13, J_{9.9} 10 10.5, J_{9.8} 6, 9-H), 2.30–2.39 (1 H, m, 8-H), 1.60–1.79 (2 H, m, 2-H, 3-H), 1.39–1.60 (8 H, m, 2-H, 4-
H, 2 x 5-H, 6-H, 7-H, 9-H), 1.27–1.37 (2 H, m, 3-H, 6-H), 1.15–1.26 (1 H, m, 4-H), OH not observed; $\delta_C$ (50 MHz, CDCl$_3$) 139.7 $i$-C$_6$H$_5$; 133.5 $p$-C$_6$H$_5$; 129.1 $m$-C$_6$H$_5$; 128.0 o-C$_6$H$_5$; 78.3 C-1; 65.3 C-10; 48.1 C-8; 35.4 C-2; 29.9 C-7; 28.3 C-6; 24.9 C-4; 24.6 C-5; 23.7 C-3; 22.8 C-9; (ESMS$^+$) 301 (MLi$^+$, 100%), 317 (MNa$^+$, 100%).

**Cyclooctanone: Procedure B**

Cyclooctanone (0.5 ml, 3.796 mmole) in THF (2 ml), lithium diisopropylamide (1.95 M, 1.95 ml, 3.796 mmole) and phenyl vinyl sulfoxide (0.51 ml, 3.796 mmole) in THF (19.5 ml), were reacted together according to procedure B. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.033 g). The crude sulfoxide mixture (1.033 g, 3.710 mmole) in chloroform (20 ml) was reacted with $m$-CPBA (3.710 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of $m$-chlorobenzoic acid was obtained as a yellow oil (0.933 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that monoalkylated cyclooctanone 266 (49.5%), dialkylated cyclooctanone 267 (9%) and bicyclo[6.2.0]decan-1-ols 265 (19%) and 269 (3.5%) were present. The crude mixture was purified by silica column chromatography (hexane: ethyl acetate, 60:40). The first fraction (182 mg) contained bicyclo[6.2.0]decan-1-ol 265. The second fraction (319 mg) contained a mixture of bicyclo[6.2.0]decan-1-ol 269 and monoalkylated cyclooctanone 266. The third fraction (14 mg) contained a mixture of monoalkylated cyclooctanone 266 and dialkylated cyclooctanone 267. The fourth fraction (179 mg) contained dialkylated cyclooctanone 267. An analytically pure sample of bicyclo[6.2.0]decan-1-ol 269 was obtained by semi-preparative HPLC using (hexane: ethyl acetate, 75:25).
(IRS, 8SR, 10RS)-10-(Phenylsulfonyl)bicyclo[6.2.0]decan-1-ol 269 was isolated from fraction 2 as a white solid mp, 132.6-134.5 °C (ethyl acetate-hexane). (Rt 19.7 min, 3 ml/min).  (Found: C, 65.12; H, 7.54; S, 10.60. Calc. for C_{16}H_{22}SO_{3}: C, 65.26; H, 7.53; S, 10.90%); ν_{max}(KBr)/cm^{-1}: 3448, (OH), 1284, (SO_{2}), 1143, (SO_{2}); δH (400 MHz, CDCl_{3}) 7.77–7.84 (2 H, m, o-C_{6}H_{5}), 7.57–7.64 (1 H, m, p-C_{6}H_{5}), 7.49–7.55 (2 H, m, m-C_{6}H_{5}), 3.58 (1 H, dd, J_{10,9} 10.5, J_{10,9} 9, 10-H), 2.45 (1 H, br s, W_{1/2} = 2.5 Hz, OH), 2.40 (1 H, ddd, J_{2,2} 15.5, J_{2,3} 4.5, J_{2,3} 3.5, 2-H), 2.24 (1 H, ddd, J_{2,2} 15.5, J_{2,3} 13, J_{2,3} 3, 2-H) 1.96–2.05 (1 H, m, 8-H), 1.86-1.95 (1 H, m, 9-H), 1.62–1.77 (6 H, m, 3-H, 4-H, 6-H, 2 x 7-H, 9-H), 1.45–1.58 (2 H, m, 3-H, 6-H), 1.28–1.40 (2 H, m, 2 x 5-H), 1.07–1.18 (1 H, m, 4-H); δC (50 MHz, CDCl_{3}) 139.9 i-C_{6}H_{5}; 133.4 p-C_{6}H_{5}; 129.2 m-C_{6}H_{5}; 127.7 o-C_{6}H_{5}; 81.4 C-1; 67.3 C-10; 44.6 C-8; 29.7 C-2; 28.5 C-6; 27.1 C-5; 24.7 C-4; 24.4 C-7; 24.2 C-3; 22.6 C-9; (ESMS+) 301 (MLi^+ 100%), 317 (MNa^+ 100%).

**Cyclooctanone: Procedure C**

Cyclooctanone (0.1 ml, 0.759 mmole) in THF (2 ml), lithium diisopropylamide (1.70 M, 0.45 ml, 0.759 mmole) and phenyl vinyl sulfoxide (0.1 ml, 0.759 mmole) in THF (76 ml), were reacted together according to procedure C. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (0.225 g). The crude sulfoxide mixture (0.225 g, 0.808 mmole) in chloroform (10 ml) was reacted with m-CPBA (0.808 mmole) in chloroform (15 ml). Upon workup, the crude sulfone mixture was obtained as a yellow oil (0.164 g). Analysis of the crude mixture by ^1H nmr spectroscopy indicated that phenyl vinyl sulfoxide (21%), monoalkylated cyclooctanone 266 (44%), dialkylated cyclooctanone 267 (2%) and bicyclo[6.2.0]decan-1-ol 265 (6%) were present.
Cyclooctanone: Procedure D

Cyclooctanone (0.5 ml, 3.796 mmole) in THF (2 ml), lithium diisopropylamide (1.95 M, 1.95 ml, 3.796 mmole) and phenyl vinyl sulfoxide (0.51 ml, 3.796 mmole) in THF (7.3 ml), were reacted together according to procedure D. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.088 g). The crude sulfoxide mixture (1.088 g, 3.908 mmole) in chloroform (20 ml) was reacted with m-CPBA (3.908 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing traces of m-chlorobenzoic acid was obtained as a yellow oil (0.940 g). Analysis of the crude mixture by ¹H nmr spectroscopy indicated that phenyl vinyl sulf oxide (0.5%), monoalkylated cyclooctanone 266 (47%), dialkylated cyclooctanone 267 (7%) and bicyclo[6.2.0]decan-1-ols 265 (23%) and 269 (6%) were present.

2.5 Reaction between 2-Methylcyclopentanone and phenyl vinyl sulfoxide

2-Methylcyclopentanone: Procedure A with 0.168 M of ketone and 45 minute reaction time at –30 °C

2-Methylcyclopentanone (1.09 ml, 10.19 mmole), lithium diisopropylamide (1.27 M, 8.04 ml, 10.19 mmole) and phenyl vinyl sulfoxide (1.36 ml, 10.19 mmole) in THF (50 ml), were reacted together according to procedure A using rapid addition of phenyl vinyl sulfoxide and a reaction time of 45 minutes. The reaction mixture was maintained at -30 °C and stirred for 45 minutes. The reaction was quenched with aqueous ammonium chloride (40 ml) and the mixture worked up according to procedure A. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (2.367 g). The crude sulfoxide mixture (2.367 g, 9.455 mmole) in chloroform (30 ml) was reacted with m-CPBA (9.455 mmole) in chloroform (40 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (2.270 g). Analysis of the crude mixture by ¹H nmr spectroscopy indicated that
substituted bicyclo[3.2.0]heptan-1-ols 270 (15%) and 271 (39%) and a diastereomeric mixture of monoalkylated 2-methylcyclopentanone 272 (25%, 70:30) were present. The crude mixture was purified by silica column chromatography (hexane:ethyl acetate, 60:40). The first fraction (880 mg) contained substituted bicyclo[3.2.0]heptan-1-ols 270 and 271. The second fraction (687 mg) contained a diastereomeric mixture of monoalkylated 2-methylcyclopentanone 272. Analytically pure samples were obtained by semi-preparative HPLC of substituted bicyclo[3.2.0]heptan-1-ol 270 from fraction one (hexane: ethyl acetate, 90:10), substituted bicyclo[3.2.0]heptan-1-ol 271 from fraction one (hexane: ethyl acetate, 90:10) and monoalkylated 2-methylcyclopentanone 272 from fraction two (hexane: ethyl acetate, 80:20).

(1RS,2RS,5SR,7SR)-2-Methyl-7-(phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol 270 was isolated from fraction one as a white solid mp, 95.3–96.7 °C (ethyl acetate-hexane). (Rt 27.3 min, 3 ml/min) (Found: C, 63.18; H, 7.00; S, 11.75. Calc. for C_{14}H_{18}SO_3: C, 63.13; H, 6.81; S, 12.04%); ν max (KBr)/cm⁻¹ 3507, (OH), 1293, (SO₂), 1145, (SO₂); δ H (400 MHz, CDCl₃) 7.90–7.96 (2H, m, o-C₆H₅), 7.60–7.66 (1H, m, p-C₆H₅), 7.49–7.56 (2H, m, m-C₆H₅), 3.89 (1H, br s, W₁/₂ 1.5, OH), 3.59 (1H, ddd, J₇,6 9, J₇,6 6, J₇,5 < 1, 7-H), 2.62–2.78 (2H, m, 5-H, 6-H), 1.93–2.06 (1H, m, 4-H), 1.78–1.92 (2H, m, 2-H, 3-H), 1.48–1.60 (2H, m, 3-H, 6-H), 1.32–1.42 (1H, m, 4-H), 0.88 (3H, d, J₂-Me₂ 7, 2-Me); δ C (100 MHz, CDCl₃) 139.5 i-C₆H₅; 133.6 p-C₆H₅; 129.1 m-C₆H₅; 128.0 o-C₆H₅; 84.2 C-1; 64.2 C-7; 45.9 C-5; 44.0 C-2; 32.7 C-3; 29.7 C-4; 22.2 C-6; 13.2 2-Me; (ESMS+) 273 (MLi⁺, 100%), 289 (MNa⁺, 72%).

(1RS,2SR,5SR,7SR)-2-Methyl-7-(phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol 271 was isolated from fraction one as a white solid mp, 107.2–108.5 °C (ethyl acetate-hexane). (Rt 29.7 min, 3 ml/min) (Found: C, 63.09; H, 6.84; S, 11.88. Calc. for C_{14}H_{18}SO_3: C,
2-Methyl-5-[2′-(phenylsulfonyl)ethyl]cyclopentanone 272 was isolated as a 86:14 diastereomeric mixture (\(^\ddagger\) denotes minor isomer) from fraction two as a white solid, mp 69.6–70.1 °C (ethyl acetate-hexane). (Rt 30.4 min, 3 ml/min) (Found: C, 63.33; H, 7.00; S, 11.99. Calc. for C\(_{14}\)H\(_{18}\)SO\(_3\): C, 63.13; H, 6.81; S, 12.04%); \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 1725, (CO), 1291, (SO\(_2\)), 1148, (SO\(_2\)); \(\delta_{\text{H}}\) (400 MHz, CDCl\(_3\)) 7.86–7.95 (2H, m, \(o\)-C\(_6\)H\(_5\)), 7.62–7.71 (1H, m, \(p\)-C\(_6\)H\(_5\)), 7.52–7.62 (2H, m, \(m\)-C\(_6\)H\(_5\)), 3.34 (1H, ddd, \(J_{2',2'}\) 14, \(J_{2',1'}\) 10.5, \(J_{2',1'}\) 5.5, 2′-H), \(^\ddagger\) 3.31 (1H, ddd, \(J_{2',2'}\) 14, \(J_{2',1'}\) 10.5, \(J_{2',1'}\) 5.5, 2′-H), 3.17 (1H, ddd, \(J_{2',2'}\) 14, \(J_{2',1'}\) 10.5, \(J_{2',1'}\) 5, 2′-H), \(^\ddagger\) 3.12-3.20 (1H, m, 2′-H), 2.10–2.26 (3H, m, 2-H, 3-H, 4-H), 1.98–2.10 (2H, m, 5-H, 1′-H), 1.72–1.84 (1H, m, 1′-H), 1.32–1.44 (2H, m, 3-H, 4-H), 1.07 (3H, d, \(J_{5-5\text{-Me}}\) 7, 5-Me), \(^\ddagger\) 1.02 (3H, d, \(J_{5-5\text{-Me}}\) 7, 5-Me); \(\delta_{\text{C}}\) (100 MHz, CDCl\(_3\)) 220.7 C-1; 138.9 \(i\)-C\(_6\)H\(_5\); 133.7 \(p\)-C\(_6\)H\(_5\); 129.3 \(m\)-C\(_6\)H\(_5\); 128.0 \(o\)-C\(_6\)H\(_5\); 54.1 C-2′; 46.8 C-2; 44.1 C-5; 29.7, 27.8 C-3, C-4; 23.6 C-1′; 14.5 5-Me; (ESMS+) 273 (MLi\(^+\), 100%), 289 (MNa\(^+\), 100%).
2-Methylcyclopentanone: Procedure B with 0.172 M of ketone

2-Methylcyclopentanone (0.55 ml, 5.094 mmole), lithium diisopropylamide (1.55 M, 3.3 ml, 5.094 mmole) and phenyl vinyl sulfoxide (0.7 ml, 5.094 mmole) in THF (25 ml), were reacted together using procedure B. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.004 g). The crude sulfoxide mixture (1.004 g, 4.011 mmole) in chloroform (20 ml) was reacted with m-CPBA (4.011 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.721 g). Analysis of the crude mixture by \(^1\)H nmr spectroscopy indicated that substituted bicyclo[3.2.0]heptan-1-ols **270** (16.5%) and **271** (23.5%) and a diastereomeric mixture of monoalkylated 2-methylcyclopentanone **272** (9.5%, 71:29) were present.

2-Methylcyclopentanone: Procedure C

2-Methylcyclopentanone (0.2 ml, 1.869 mmole), lithium diisopropylamide (1.27 M, 1.47 ml, 1.869 mmole) and phenyl vinyl sulfoxide (0.25 ml, 1.869 mmole) in THF (185 ml), were reacted together using procedure C. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (0.441 g). The crude sulfoxide mixture (0.441 g, 1.762 mmole) in chloroform (10 ml) was reacted with m-CPBA (1.762 mmole) in chloroform (15 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.371 g). Analysis of the crude mixture by \(^1\)H nmr spectroscopy indicated that phenyl vinyl sulfoxide (16.5%), phenyl vinyl sulfoxide (1.5%), substituted bicyclo[3.2.0]heptan-1-ols **270** (20%) and **271** (29.5%) and a diastereomeric mixture of monoalkylated 2-methylcyclopentanone **272** (5%, 57:43) were present.
2-Methylcyclopentanone: Procedure D

2-Methylcyclopentanone (0.5 ml, 4.671 mmole), lithium diisopropylamide (1.4 M, 3.34 ml, 4.671 mmole) and phenyl vinyl sulfoxide (0.63 ml, 4.671 mmole) in THF (10.5 ml), were reacted together using procedure D. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (0.799 g). The crude sulfoxide mixture (0.799 g, 3.192 mmole) in chloroform (20 ml) was reacted with m-CPBA (3.192 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.630 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that substituted bicyclo[3.2.0]heptan-1-ols 270 (4%) and 271 (11%) and a diastereomeric mixture of monoalkylated 2-methylcyclopentanone 272 (32%, 53:47) were present.

Ring opening of substituted bicyclo[3.2.0]heptan-1-ols 270 and 271

(a) A sample of substituted bicyclo[3.2.0]heptan-1-ol 270 in ether was allowed to stand at room temperature for 30 days. Upon evaporation of the solvent, analysis of the residue by $^1$H nmr spectroscopy in CDCl$_3$ indicated that the monoalkylated 2-methylcyclopentanone products 272a and 272b were present in a ratio of 70:30 respectively.

(b) A sample of substituted bicyclo[3.2.0]heptan-1-ol 271 in ether was allowed to stand at room temperature for 30 days. Upon evaporation of the solvent, analysis of the residue by $^1$H nmr spectroscopy in CDCl$_3$ indicated that the monoalkylated methylcyclopentanone products 272a and 272b were present in a ratio of 68:32 respectively.
2.6 Reaction between 2,6-Dimethylcyclohexanone and phenyl vinyl sulfoxide

2,6-Dimethylcyclohexanone: Procedure B with 0.141 M of ketone

2,6-Dimethylcyclohexanone (0.54 ml, 3.962 mmole), lithium diisopropylamide (1.55 M, 2.56 ml, 3.962 mmole) and phenyl vinyl sulfoxide (0.53 ml, 3.962 mmole) in THF (25 ml), were reacted together using procedure B. Upon workup, the crude mixture was obtained as a yellow oil (0.608 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that polymerised phenyl vinyl sulfoxide and unreacted 2,6-dimethylcyclohexanone were present. Some loss of 2,6-dimethylcyclohexanone was observed upon evaporation of the crude mixture.

2,6-Dimethylcyclohexanone: Procedure B with a variance in enolate generation and 0.141 M of ketone

Lithium diisopropylamide (1.55 M, 2.56 ml, 3.962 mmole) was added to THF (25 ml) under an atmosphere of nitrogen at -10 °C and the solution cooled to -75-78 °C. 2,6-Dimethylcyclohexanone (0.55 ml, 3.962 mmole) was added over 5 minutes and the temperature maintained between -70–78 °C for an hour. The system was shielded from light and allowed to warm to -30 °C. Phenyl vinyl sulfoxide (0.53 ml, 3.962 mmole) was added rapidly. The reaction mixture was maintained at -30 °C, stirred for 5 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. Upon workup, the crude mixture was obtained as a yellow oil (0.699 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that polymerised phenyl vinyl sulfoxide and unreacted 2,6-dimethylcyclohexanone were present. Some loss of 2,6-dimethylcyclohexanone was observed upon evaporation of the crude mixture.
2,6-Dimethylcyclohexanone: Procedure F with -30 °C reaction temperature, 5 minute reaction time and 0.141 M of ketone

2,6-Dimethylcyclohexanone (0.55 ml, 3.962 mmole), lithium diisopropylamide (1.55 M, 2.56 ml, 3.962 mmole) and phenyl vinyl sulfoxide (0.55 ml, 3.962 mmole) in THF (25 ml) were reacted together according to procedure F using a reaction temperature of -30 °C and a 5 minute reaction time. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (0.777 g). The crude sulfoxide mixture (0.777 g, 2.791 mmole) in chloroform (20 ml) was reacted with m-CPBA (2.791 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.669 g). Analysis of the crude mixture by \(^1\)H nmr spectroscopy indicated that substituted bicyclo[4.2.0]octan-1-ols 277 (2.5%) and 278 (11%) and monoalkylated 2,6-dimethylcyclohexanones 279 (34.5%) and 280 (4.5%) were present.

2,6-Dimethylcyclohexanone: Procedure F with 5 minute reaction time and 0.141 M of ketone

2,6-Dimethylcyclohexanone (0.55 ml, 3.962 mmole), lithium diisopropylamide (1.55 M, 2.56 ml, 3.962 mmole) and phenyl vinyl sulfoxide (0.55 ml, 3.962 mmole) in THF (25 ml) were reacted together according to procedure F using a reaction time of 5 minutes. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.077 g). The crude sulfoxide mixture (1.077 g, 3.869 mmole) in chloroform (20 ml) was reacted with m-CPBA (3.869 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.911 g). Analysis of the crude mixture by \(^1\)H nmr spectroscopy indicated that substituted bicyclo[4.2.0]octan-1-ols 277 (3%) and 278 (15.5%) and monoalkylated 2,6-dimethylcyclohexanones 279 (41.5%) and 280 (14%) were present. The crude
mixture was purified by silica column chromatography (hexane: ethyl acetate, 80:20). The first fraction (42 mg) contained substituted bicyclo[4.2.0]octan-1-ol 277. The second fraction (197 mg) contained substituted bicyclo[4.2.0]octan-1-ol 278. The third fraction (449 mg) contained a mixture of monoalkylated 2,6-dimethylcyclohexanones 279 and 280. The fourth fraction (128 mg) contained monoalkylated 2,6-dimethylcyclohexanone 280. Analytically pure samples were obtained by semi-preparative HPLC of substituted bicyclo[4.2.0]octan-1-ol 277 from fraction one (hexane: ethyl acetate, 90:10), substituted bicyclo[4.2.0]octan-1-ol 278 from fraction two (hexane: ethyl acetate, 90:10) and monoalkylated 2,6-dimethylcyclohexanone 279 from fraction three (hexane: ethyl acetate, 80:20). Monoalkylated 2,6-dimethylcyclohexanone 280 crystallised from fraction three upon standing over a few days.

(1RS,2RS,6SR,8SR)-2,6-Dimethyl-8-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol 277 was isolated from fraction one as a white solid mp, 84.4-85.7 °C (ethyl acetate-hexane). (Rt 14.1 min, 3 ml/min) (Found: C, 65.23; H, 7.59. Calc. for C_{16}H_{22}SO_3: C, 65.27; H, 7.53; \nu_{\text{max}} (\text{KBr})/\text{cm}^{-1} 3527, (\text{OH}), 1301, (\text{SO}_2), 1143, (\text{SO}_2); \delta_{\text{H}} (400 MHz, CDCl_3) 7.89–7.93 (2H, m, o-C_6H_5), 7.59–7.64 (1H, m, p-C_6H_5), 7.50–7.55 (2H, m, m-C_6H_5), 3.664 (1H, s, OH), 3.665 (1H, dd, J_{8,7} 9.5, J_{8,7} 6.5, 8-H), 2.36 (1H, dd, J_{7,7} 13, J_{7,8} 6.5, 7-H), 1.92 (1H, dd, J_{7,7} 13, J_{7,8} 10, 7-H), 1.58-1.69 (1H, m, 2-H), 1.36–1.54 (5H, m, 3-H, 2 x 4-H, 2 x 5-H), 1.26–1.35 (1H, m, 3-H), 1.24 (3H, s, 6-Me), 0.55 (3H, d, J_{2,Me,2} 7, 2-Me); \delta_{\text{C}} (100 MHz, CDCl_3) 140.0 i-C_6H_5; 133.8 p-C_6H_5; 129.3 m-C_6H_5; 128.5 o-C_6H_5; 78.5 C-1; 64.6 C-8; 42.4 C-6; 35.5 C-2; 34.1 C-5; 32.1 C-7; 25.5 C-3; 19.9 6-Me; 17.4 C-4; 13.6 2-Me; (ESMS+) 317 (MNa^+ , 100%), 301 (MLi^+, 93%).
(1RS,2SR,6SR,8SR)-2,6-Dimethyl-8-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol 278 was isolated from fraction two as a white solid mp, 108.5-109.1 °C (ethyl acetate-hexane). (Rt 17.4 min, 3 ml/min) (Found: C, 65.34; H, 7.64; O, 16.36. Calc. for C\textsubscript{16}H\textsubscript{22}SO\textsubscript{3}: C, 65.27; H, 7.53; O, 16.30%) \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 3471, (OH), 1305, (SO\textsubscript{2}), 1139, (SO\textsubscript{2}); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.83–7.92 (2H, m, o-C\(_6\)H\(_5\)), 7.58–7.66 (1H, m, p-C\(_6\)H\(_5\)), 7.49–7.57 (2H, m, m-C\(_6\)H\(_5\)), 4.29 (1H, br s, W\(_{h/2}\) 61, OH), 3.72 (1H, dd, J\(_{8,7}\) 8, J\(_{8,7}\) 7, 8-H), 2.29 (1H, dd, J\(_{7,7}\) 7, J\(_{7,8}\) 7, 7-H), 1.76 (1H, dd, J\(_{7,7}\) 11.5, J\(_{7,8}\) 9.5, 7-H), 1.67–1.74 (1H, m, 5-H), 1.54–1.65 (2H, m, 2-H, 3-H), 1.43–1.53 (1H, m, 4-H), 1.22–1.38 (2H, m, 4-H, 5-H), 1.11 (3H, s, 6-Me), 0.94–1.07 (1H, m, 3-H), 0.68 (3H, d, J\(_{2,6-Me}\) 6.5, 2-Me); \(\delta_C\) (100 MHz, CDCl\(_3\)) 139.2 i-C\(_6\)H\(_5\); 133.7 p-C\(_6\)H\(_5\); 129.1 m-C\(_6\)H\(_5\); 128.3 o-C\(_6\)H\(_5\); 83.2 C-1; 57.3 C-8; 40.9 C-6; 36.5 C-2; 36.3 C-5; 32.5 C-7; 30.3 C-3; 20.2 6-Me; 19.9 C-4; 15.6 2-Me; (ESMS+) 317 (MNa\(^+\), 100%), 301 (MLi\(^+\), 48%).

(2RS,6RS)-2,6-Dimethyl-2-[2'-(phenylsulfonyl)ethyl]cyclohexanone 280 was isolated from fraction three upon standing as a white solid, mp 131.3–132.2 °C (ethyl acetate-hexane). (Found: C, 65.45; H, 7.71; S, 11.03. Calc. for C\textsubscript{16}H\textsubscript{22}SO\textsubscript{3}: C, 65.27; H, 7.53; S, 10.89%) \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 1695, (CO), 1299, (SO\textsubscript{2}), 1148, (SO\textsubscript{2}); \(\delta_H\) (400 MHz, CDCl\(_3\)) 7.86–7.95 (2H, m, o-C\(_6\)H\(_5\)), 7.60–7.66 (1H, m, p-C\(_6\)H\(_5\)), 7.52–7.60 (2H, m, m-C\(_6\)H\(_5\)), 3.28 (1H, ddd, J\(_{2',2'}\) 14, J\(_{2',1'}\) 11.5, J\(_{2',1'}\) 5.5, 2'-H), 3.13 (1H, ddd, J\(_{2',2'}\) 13.5, J\(_{2',1'}\) 13.5, J\(_{2',1'}\) 11.5, J\(_{2',1'}\) 5.5, 2'-H), 2.52–2.63 (1H, m, 6-H), 1.96–2.04 (1H, m, 5-H), 1.47–1.90 (6H, m, 2 x 3-H, 2 x 4-H, 2 x 1'-H), 1.24 (1H, dddd, J\(_{5,5}\) 13, J\(_{5,6}\) 13, J\(_{5,4}\) 13, J\(_{5,4}\) 4, 5-H), 1.15 (3H, s, 2-Me), 0.91 (3H, d, J\(_{6-Me,6}\) 6.5, 6-Me); \(\delta_C\) (50 MHz, CDCl\(_3\)) 215.6 C-1; 148.3 i-C\(_6\)H\(_5\); 133.5 p-C\(_6\)H\(_5\); 129.2 m-C\(_6\)H\(_5\); 127.9 o-C\(_6\)H\(_5\); 52.2 C-2'; 47.4 C-2; 41.0 C-6; 39.4 C-3; 36.5 C-5; 31.5 C-1'; 22.9 2-Me; 21.1 C-4; 14.8 6-Me; (ESMS+) 317 (MNa\(^+\), 100%), (ESMS-) 293 (M-H, 21%).
(2RS,6SR)-2,6-Dimethyl-2-[2'-(phenylsulfonyl)ethyl]cyclohexanone 279 was isolated from fraction three as a white solid mp, 87.6–88.9 °C (ethyl acetate-hexane). (Rt 13.3 min, 3 ml/min) (Found: C, 65.20; H, 7.67; S, 10.82. Calc. for C_{16}H_{22}SO_{3}: C, 65.27; H, 7.53; S, 10.89); ν_{max} (KBr)/cm^{-1} 1710, (CO), 1305, (SO_{2}), 1152, (SO_{2}); δ_{H} (400 MHz, CDCl_{3}) 7.82–7.89 (2H, m, o-C_{6}H_{5}), 7.63–7.69 (1H, m, p-C_{6}H_{5}), 7.49–7.60 (2H, m, m-C_{6}H_{5}), 3.02 (1H, ddd, J_{2',2'} 14, J_{2',1'} 12.5, J_{2',1'} 5, 2'-H), 2.61 (1H, ddd, J_{2',2'} 14, J_{2',1'} 12.5, J_{2',1'} 4, 2'-H), 2.32–2.42 (1H, ddq, J_{6,5} 12.5, J_{6,5} 6, J_{6,6-Me} 6, 6-H), 2.30 (1H, ddd, J_{1',1'} 13, J_{1',2'} 12.5, J_{1',2'} 4, 1'-H), 1.96–2.04 (1H, m, 5-H), 1.71–1.85 (3H, m, 3-H, 4-H, 1'-H), 1.47–1.66 (2H, m, 3-H, 4-H), 1.30 (1H, dddd, J_{5,5} 13, J_{5,6} 13, J_{5,4} 13, J_{5,4} 4, 5-H), 0.92 (3H, d, d_{6-Me} 6.5, 6-Me), 0.90 (3H, s, 2-Me); δ_{C} (100 MHz, CDCl_{3}) 215.5 C-1; 138.9 i-C_{6}H_{5}; 133.8 p-C_{6}H_{5}; 129.4 m-C_{6}H_{5}; 127.9 o-C_{6}H_{5}; 51.7 C-2'; 47.6 C-2; 41.3 C-6; 40.5 C-3; 36.2 C-5; 29.5 C-1'; 22.0 2-Me; 20.8 C-4; 14.9 6-Me; (ESMS+) 317 (MNa^{+}, 100%), 301 (MLi^{+}, 100%).

2.7 Reaction between 2-Methylcyclohexanone and phenyl vinyl sulfoxide

2-Methylcyclohexanone: Procedure B

2-Methylcyclohexanone (1.08 ml, 8.915 mmole), lithium diisopropylamide (1.74 M, 5.12 ml, 8.915 mmole) and phenyl vinyl sulfoxide (1.19 ml, 8.915 mmole) in THF (50 ml), were reacted together using procedure B. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.255 g). The crude sulfoxide mixture (1.255 g, 4.747 mmole) in chloroform (20 ml) was reacted with m-CPBA (4.747 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.754 g). Analysis of the crude mixture by \textsuperscript{1}H nmr spectroscopy indicated that phenyl vinyl sulfoxide (8.5%), phenyl vinyl sulfone (4%), substituted bicyclo[4.2.0]octan-1-ols 281 (6.5%) and 282 (5%) and monoalkylated 2-methylcyclohexanones 283 (0.5%) and 284 (5%) were present.
2-Methylcyclohexanone: Procedure E

2-Methylcyclohexanone (1 ml, 8.237 mmole), lithium diisopropylamide (2.0 M, 4.12 ml, 8.237 mmole) and phenyl vinyl sulfoxide (1.1 ml, 8.237 mmole) in THF (90.7 ml), were reacted together using procedure E. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (2.134 g). The crude sulfoxide mixture (2.134 g, 8.072 mmole) in chloroform (30 ml) was reacted with m-CPBA (8.072 mmole) in chloroform (40 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (1.834 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that monoalkylated 2-methylcyclohexanones 283 (37%) and 284 (40.5%) were present. The crude mixture was purified by silica column chromatography (hexane: ethyl acetate, 70:30). The first fraction (356 mg) contained monoalkylated 2-methylcyclohexanone 283. The second fraction (550 mg) contained monoalkylated 2-methylcyclohexanones 283 and 284. The third fraction (168 mg) contained monoalkylated 2-methylcyclohexanone 284 which included minor amounts of contaminants. Analytically pure samples were obtained by semi-preparative HPLC of monoalkylated 2-methylcyclohexanone 283 from fraction two (hexane: ethyl acetate, 75:25) and monoalkylated 2-methylcyclohexanone 284 from fraction two (hexane: ethyl acetate, 75:25).

$(2RS,6RS)-2$-Methyl-6-$\text{2'}$-(phenylsulfonyl)ethyl$cyclohexanone$ 283$ was isolated from fraction two as a white solid mp, 86.6–87.3 °C (ethyl acetate-hexane). (Rt 14.3 min, 3 ml/min) (Found: C, 64.26; H, 7.26; S, 11.44. Calc. for $\text{C}_{15}\text{H}_{20}\text{SO}_3$: C, 64.25; H, 7.19; S, 11.43%); $\nu_{\text{max}}$ (KBr)/cm$^{-1}$ 1704, (CO), 1307, (SO$_2$), 1147, (SO$_2$); $\delta_H$ (400 MHz, CDCl$_3$) 7.86–7.93 (2H, m, $\text{o-C}_6\text{H}_5$), 7.60–7.66 (1H, m, $\text{p-C}_6\text{H}_5$), 7.52–7.58 (2H, m, $\text{m-C}_6\text{H}_5$), 3.28 (1H, ddd, $J_{2',2'}/14$, $J_{2',1'}/9.5$, $J_{2',1'}/5.5$, 2'-H), 3.08 (1H, ddd, $J_{2',2'}/14$, $J_{2',1'}/9.5$, $J_{2',1'}/6$, 2'-H), 2.43-2.54 (1H, m, 2-H), 2.29-2.40 (1H, m, 6-H), 2.04–2.14 (2H, m, 3-H, 5-H),
1.94–2.02 (1H, m, 1'-H), 1.76–1.86 (2H, m, 2 x 4-H), 1.61–1.75 (1H, m, 1'-H), 1.22–1.37 (2H, m, 3-H, 5-H), 0.94 (3H, d, J6-Me 6.5, 6-Me); δC (100 MHz, CDCl3) 213.1 C-1; 139.2 i-C6H5; 133.6 p-C6H5; 129.3 m-C6H5; 127.9 o-C6H5; 54.0 C-2'; 49.0 C-2; 45.6 C-6; 37.2 C-5; 35.4 C-3; 25.3 C-4; 23.2 C-1’; 14.3 6-Me; (ESMS+) 287 (MLi+ , 78%), 303 (MNa+, 100%).

(2RS,6SR)-2-Methyl-6-[2'-(phenylsulfonyl)ethyl]cyclohexanone 284 was isolated from fraction two as a white solid mp, 67.5-68.1 °C (ethyl acetate-hexane). (Rt 16.2 min, 3 ml/min) (Found: C, 64.33; H, 7.31; S, 11.22. Calc. for C15H20SO3: C, 64.25; H, 7.19; S, 11.43%); νmax (KBr)/cm⁻¹ 1694, (CO), 1308, (SO2), 1148, (SO2); δH (400 MHz, CDCl3) 7.84–7.90 (2H, m, o-C6H5), 7.60–7.66 (1H, m, p-C6H5), 7.50–7.58 (2H, m, m-C6H5), 3.02-3.15 (2H, m, 2'-H), 2.54 (1H, dddd, J2,3 9, J2,1' 9, J2,3 5.5, J2,1' 5.5, 2-H), 2.41-2.48 (1H, m, 6-H), 1.98-2.09 (1H, m, 1’-H), 1.88–1.98 (1H, m, 3-H), 1.81–1.88 (1H, m, 5-H), 1.63–1.80 (3H, m, 2 x 4-H, 1’-H), 1.54–1.63 (1H, m, 5-H), 1.44–1.63 (1H, m, 3-H), 1.06 (3H, d, J6-Me 6, 6-Me); δC (100 MHz, CDCl3) 215.3 C-1; 139.0 i-C6H5; 133.7 p-C6H5; 129.3 m-C6H5; 127.9 o-C6H5; 54.0 C-2'; 46.0 C-2; 43.5 C-6; 34.1 C-5; 33.1 C-3; 23.4 C-1’; 20.1 C-4; 16.0 6-Me; (ESMS+) 287 (MLi+, 70%), 303 (MNa+, 100%).

2-Methylcyclohexanone: Procedure F

2-Methylcyclohexanone (0.5 ml, 4.119 mmole), lithium diisopropylamide (1.4 M, 2.95 ml, 4.119 mmole) and phenyl vinyl sulfoxide (0.55 ml, 4.119 mmole) in THF (44.5 ml), were reacted together using procedure F. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (1.074 g). The crude sulfoxide mixture (1.074 g, 4.062 mmole) in chloroform (20 ml) was reacted with m-CPBA (4.062 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.910 g). Analysis of the crude mixture by 1H nmr
spectroscopy indicated that substituted bicyclo[4.2.0]octan-1-ols **281** (16.5%) and **282** (11%) and monoalkylated 2-methylcyclohexanones **283** (28%) and **284** (22%) were present. The crude mixture was purified by silica column chromatography (hexane: ethyl acetate, 60:40). The first fraction (119 mg) contained substituted bicyclo[4.2.0]octan-1-ols **281** and **282**. The second fraction (539 mg) contained monoalkylated 2-methylcyclohexanones **283** and **284**. Analytically pure samples were obtained by semi-preparative HPLC of substituted bicyclo[4.2.0]octan-1-ol **281** from fraction one (hexane:ethyl acetate, 80:20) and substituted bicyclo[4.2.0]octan-1-ol from fraction one (hexane:ethyl acetate, 80:20).

**281** was isolated from fraction one as a white solid mp, 110.2–111.6 °C (ethyl acetate-hexane). (Rt 11.8 min, 3 ml/min) (Found: C, 64.52; H, 7.36; S, 11.32. Calc. for C_{15}H_{20}SO_{3}: C, 64.25; H, 7.19; S, 11.43%); ν_{max} (KBr)/cm^{-1} 3514, (OH), 1283, (SO_{2}), 1143, (SO_{2}); δ_{H} (400 MHz, CDCl_{3}) 7.89–7.98 (2H, m, o-C_{6}H_{5}), 7.57–7.66 (1H, m, p-C_{6}H_{5}), 7.49–7.57 (2H, m, m-C_{6}H_{5}), 3.48 (1H, ddd, J_{8,7} 9, J_{8,6} 3, J_{8,6} 1, 8-H), 2.89–3.00 (1H, m, 6-H), 2.35 (1H, ddd, J_{7,7} 13, J_{7,6} 10.5, J_{7,8} 2.5, 7-H), 1.86 (1H, ddd, J_{7,7} 13, J_{7,6} 11, J_{7,8} 9, 7-H), 1.55–1.67 (2H, m, 4-H, 5-H), 1.44–1.55 (1H, m, 2-H), 1.30–1.44 (3H, m, 3-H, 4-H, 5-H), 1.12–1.28 (1H, m, 3-H), 0.72 (3H, d, J_{2-Me,2} 7, 2-Me), OH not observed; δ_{C} (100 MHz, CDCl_{3}) 139.8 i-C_{6}H_{5}; 133.5 p-C_{6}H_{5}; 129.1 m-C_{6}H_{5}; 128.1 o-C_{6}H_{5}; 75.5 C-1; 67.0 C-8; 44.6 C-6; 38.2 C-2; 27.8 C-3; 23.6 C-5; 21.7 C-4; 19.6 C-7; 13.8 2-Me; (ESMS+) 287 (MLi^+, 76%), 303 (MNa^+, 100%).

**282** was isolated from fraction one as a white solid mp, 95.3-96.5 °C (ethyl acetate-hexane). (Rt 9.5 min, 3 ml/min) (Found: C, 64.28; H, 7.30. Calc. for C_{15}H_{20}SO_{3}: C, 64.25; H,
7.19%); ν max (KBr)/cm −1 3521, (OH), 1295, (SO2), 1138, (SO2); δH (400 MHz, CDCl3) 7.86–7.92 (2H, m, o-C6H5), 7.64–7.80 (1H, m, p-C6H5), 7.49–7.56 (2H, m, m-C6H5), 4.27 (1H, br s, W 1/2 1.5, OH), 3.75 (1H, ddd, J8,7 9.5, J8,7 8, J8,6 <1, 8-H), 2.65 (1H, ddd, J7,7 12.5, J7,6 10, J7,8 8, 7-H), 2.37 (1H, dddddd, J6,7 7, J6,5 6, J6,7 5, J6,8 <1, 6-H), 1.92 (1H, ddd, J5,5 14, J5,4 7.5, J5,6 7, J5,4 7, 5-H), 1.50–1.75 (4H, m, 2-H, 3-H, 4-H, 7-H), 1.30–1.43 (1H, m, 4-H), 1.23 (1H, m, 5-H), 0.93–1.10 (1H, m, 3-H), 0.65 (3H, d, J2, Me,2 6.5, 2-Me); δC (100 MHz, CDCl3) 139.1 i-C6H5; 133.7 p-C6H5; 129.1 m-C6H5; 128.3 o-C6H5; 80.5 C-1; 58.6 C-8; 41.5 C-6; 36.6 C-2; 28.5 C-3; 26.0 C-5; 23.6 C-7; 19.5 C-4; 15.0 2-Me; (ESMS+) 287 (MLi+, 47%), 303 (MNa+, 89%).

2-Methylcyclohexanone: Procedure F at -30 °C reaction temperature and 5 minute reaction time

2-Methylcyclohexanone (0.5 ml, 4.119 mmole), lithium diisopropylamide (1.4 M, 2.95 ml, 4.119 mmole) and phenyl vinyl sulfoxide (0.55 ml, 4.119 mmole) in THF (44.5 ml) were reacted together according to procedure F using a reaction temperature of -30 °C and 5 minute reaction time. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (0.846 g). The crude sulfoxide mixture (0.846 g, 3.200 mmole) in chloroform (20 ml) was reacted with m-CPBA (3.200 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of m-chlorobenzoic acid was obtained as a yellow oil (0.693 g). Analysis of the crude mixture by 1H nmr spectroscopy indicated that phenyl vinyl sulfoxide (24%), phenyl vinyl sulfone (7%), substituted bicyclo[4.2.0]octan-1-ols 281 (2.5%) and 282 (3%) and monoalkylated 2-methylcyclohexanones 283 (9%) and 284 (14.5%) were present.
2.8 Reaction between 1,4-Cyclohexanedione and phenyl vinyl sulfoxide

1,4-Cyclohexanedione: Procedure E

1,4-Cyclohexanedione (0.5 g, 4.459 mmole) in THF (5 ml), lithium diisopropylamide (1.4 M, 3.19 ml, 4.459 mmole) and phenyl vinyl sulfoxide (0.6 ml, 4.459 mmole) in THF (43.7 ml), were reacted together using procedure E. Upon workup, the crude mixture was obtained as a yellow oil (0.890 g). Analysis of the crude mixture by \(^1\)H nmr spectroscopy indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione were present. Some loss of 1,4-cyclohexanedione was observed upon evaporation of the crude mixture.

1,4-Cyclohexanedione: Procedure F

1,4-Cyclohexanedione (0.5 g, 4.459 mmole) in THF (5 ml), lithium diisopropylamide (1.4 M, 3.19 ml, 4.459 mmole) and phenyl vinyl sulfoxide (0.6 ml, 4.459 mmole) in THF (43.7 ml), were reacted together using procedure F. Upon workup, the crude mixture was obtained as a yellow oil (0.792 g). Analysis of the crude mixture by \(^1\)H nmr spectroscopy indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione were present. Some loss of 1,4-cyclohexanedione was observed upon evaporation of the crude mixture.

1,4-Cyclohexanedione: Procedure F with -5 °C reaction temperature and sonication

Lithium diisopropylamide (1.07 M, 4.17 ml, 4.459 mmole) was added to THF (42.7 ml) under an atmosphere of nitrogen at -10 °C and the solution warmed to 0-5 °C. 1,4-Cyclohexanedione (0.5 g, 4.459 mmole) in THF (5 ml) was added over 5 minutes and the temperature maintained between 0-5 °C for 30 minutes. The system was then sonicated for a further 30 minutes and the temperature maintained between 0-5 °C. The
system was shielded from light and kept at 5 °C. Phenyl vinyl sulfoxide (0.6 ml, 4.459 mmole) was added rapidly. The reaction mixture was maintained at 5 °C, stirred and sonicated for 10 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. Upon workup, the crude mixture was obtained as a yellow oil (0.950 g). Analysis of the crude mixture by \textsuperscript{1}H nmr spectroscopy indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione were present.

1,4-Cyclohexanedione: Procedure F with 0.04 M of ketone

1,4-Cyclohexanedione (0.5 g, 4.459 mmole) in THF (5 ml), lithium diisopropylamide (1.27 M, 3.51 ml, 4.459 mmole) and phenyl vinyl sulfoxide (0.60 ml, 4.459 mmole) in THF (102.4 ml), were reacted together using procedure F. Upon workup, the crude mixture was obtained as a yellow oil (1.006 g). Analysis of the crude mixture by \textsuperscript{1}H nmr spectroscopy indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione were present.

1,4-Cyclohexanedione: Procedure F with 2 equivalents of LDA, 45 minute reaction time and 0.04 M of ketone

The lithium enolate of the ketone was generated using 1,4-cyclohexanedione (0.5 g, 4.459 mmole) in THF (5 ml) and lithium diisopropylamide (1.27 M, 7.02 ml, 8.918 mmole) in THF (98.9 ml) according to procedure F. The system was shielded from light and cooled to -10 °C. Phenyl vinyl sulfoxide (0.6 ml, 4.459 mmole) was added rapidly. The reaction mixture was maintained at -10 °C, stirred for 45 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. Upon workup, the crude mixture was obtained as a yellow oil (0.918 g). Analysis of the crude mixture by \textsuperscript{1}H nmr spectroscopy indicated a complex mixture of
compounds was obtained which included polymerised phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione. No signals in the region $\delta$ 2.5-4 ppm attributable to bicyclo[4.2.0]alkanol products were observed.

### 2.9 Reaction between 1,4-Cyclohexanedione mono-ethylene ketal and phenyl vinyl sulfoxide

#### 1,4-Cyclohexanedione mono-ethylene ketal: Procedure E

1,4-Cyclohexanedione mono-ethylene ketal (0.5 g, 3.201 mmole) in THF (2 ml), lithium diisopropylamide (1.4 M, 2.3 ml, 3.201 mmole) and phenyl vinyl sulfoxide (0.43 ml, 3.201 mmole) in THF (33 ml), were reacted together using procedure E. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (0.871 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,4-cyclohexanedione mono-ethylene ketal were present. Signals in the region $\delta$ 2.5-4 ppm indicated that bicyclo[n.2.0]alkan-1-ol products may be present (<5%). Some loss of 1,4-cyclohexanedione mono-ethylene ketal was observed upon evaporation of the crude mixture.

#### 1,4-Cyclohexanedione mono-ethylene ketal: Procedure F

1,4-Cyclohexanedione mono-ethylene ketal (0.5 g, 3.201 mmole) in THF (2 ml), lithium diisopropylamide (1.4 M, 2.3 ml, 3.201 mmole) and phenyl vinyl sulfoxide (0.43 ml, 3.201 mmole) in THF (33 ml), were reacted together using procedure F. Upon workup, the crude sulfoxide mixture was obtained as a yellow oil (0.833 g). The crude sulfoxide mixture (0.833 g, 2.701 mmole) in chloroform (20 ml) was reacted with $m$-CPBA (2.701 mmole) in chloroform (30 ml). Upon workup, the crude sulfone mixture containing minor amounts of $m$-chlorobenzoic acid was obtained as a yellow oil (0.671 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that phenyl vinyl
sulfoxide (15.5%), phenyl vinyl sulfone (2%), functionalised bicyclo[4.2.0]octanols 285 (7%) and 286 (17.5%) and monoalkylated 1,4-cyclohexanedione mono-ethylene ketal 287 (17.5%) were present. The crude mixture was purified by silica column chromatography (hexane: ethyl acetate, 70:30). The first fraction (94 mg) contained phenyl vinyl sulfoxide. The second fraction (9 mg) contained 1,4-cyclohexanedione mono-ethylene ketal. The third fraction (14 mg) contained phenyl vinyl sulfone. The fourth fraction (485 mg) contained functionalised bicyclo[4.2.0]octanols 285 and 286 and monoalkylated 1,4-cyclohexanedione mono-ethylene ketal 287. Analytically pure samples were obtained by semi-preparative HPLC of functionalised bicyclo[4.2.0]octanol 285 from fraction four (hexane:ethyl acetate, 50:50), functionalised bicyclo[4.2.0]octanol 286 from fraction four (hexane:ethyl acetate, 50:50) and monoalkylated 1,4-cyclohexanedione mono-ethylene ketal 287 from fraction four (hexane:ethyl acetate, 50:50).

(1’RS,6’SR,8’RS)-Spiro[1,3-dioxolane-2,4’-[8]phenylsulfonylbicyclo[4.2.0]octan-1’-ol] 285 was isolated from fraction four after extensive drying as a hygroscopic oil (Rt 21.6 min, 3 ml/min). (Found: C, 57.84; H, 6.15; S, 9.42. Calc. for C_{16}H_{20}SO_5 \cdot \frac{1}{2}H_2O: C, 57.64; H, 6.35; S, 9.62%); ν_{max} (KBr)/cm^{-1} 3470, (OH), 1300, (SO_2), 1142, (SO_2); δ_{H} (400 MHz, CDCl_3) 7.82–7.88 (2H, m, o-C_6H_5), 7.64–7.58 (1H, m, p-C_6H_5), 7.49–7.57 (2H, m, m-C_6H_5), 3.85–4.00 (4H, m, 2 x 4-H, 2 x 5-H), 3.47 (1H, dd, J_{8'7'} 10.5, J_{8'7'} 8, 8'-H), 2.98 (1H, ddd, J_{2'2'} 15, J_{2'3'} 11.5, J_{2'3'} 7, 2'-H), 2.79 (1H, br s, W_{1/2} 1.5, OH), 2.27-2.36 (1H, m, 6'-H), 2.15-2.26 (1H, m, 7'-H), 1.79–1.96 (3H, m, 2'-H, 5'-H, 7'-H), 1.62-1.71 (2H, m, 2 x 3'-H), 1.51-1.60 (1H, m, 5'-H); δ_{C} (50 MHz, CDCl_3) 140.4 i-C_6H_5; 133.5 p-C_6H_5; 129.2 m-C_6H_5; 127.6 o-C_6H_5; 108.5 C-2,4'; 75.5 C-1'; 66.9 C-8'; 64.6, 63.9 C-4, C-5; 39.5 C-6'; 32.6 C-5'; 28.7 C-3'; 27.9 C-2'; 22.0 C-7'; (ESMS+) 331 (MLi^+, 100%), 347 (MNa^+, 83%).
(1R'S,6'SR,8'SR)-Spiro[1,3-dioxolane-2,4'-8'phenylsulfonylbicyclo[4.2.0]octan-1-ol] 286 was isolated from fraction four as a white solid mp, 117.4–119.1 °C (ethyl acetate-hexane). (Rt 12.9 min, 3 ml/min) (Found: C, 59.30; H, 6.32; S, 9.70. Calc. for C_{16}H_{20}SO_5: C, 59.24; H, 6.21; S, 9.88%); \nu_{\text{max}} \text{(KBr)/cm}^{-1} 3500, (OH), 1302, (SO_2), 1142, (SO_2); \delta_{\text{H}} (400 MHz, CDCl_3) 7.87–7.95 (2H, m, o-C_6H_5), 7.57–7.65 (1H, m, p-C_6H_5), 7.48–7.57 (2H, m, m-C_6H_5), 3.84–3.94 (4H, m, 2 x 4-H, 2 x 5-H), 3.52 (1H, ddd, J_8',7' 9, J_8',6' 3, J_8',5' 1, 8'-H), 3.03–3.13 (1H, m, 6'-H), 2.32 (1H, ddd, J_7',7' 10, J_7',6' 10, J_7',8' 3, 7'-H), 2.12 (1H, ddd, J_7',7' 11, J_7',6' 9, J_7',8' 9, 7'-H), 1.91–1.98 (2H, m, 2 x 3'-H), 1.85 (1H, dd, J_5',5' 15, J_5',6' 7, 5'-H), 1.68–1.77 (1H, m, 2'-H), 1.49–1.58 (2H, m, 2'-H, 5'-H), OH not observed; \delta_{\text{C}} (50 MHz, CDCl_3) 139.8 i-C_6H_5; 133.5 p-C_6H_5; 129.2 m-C_6H_5; 127.9 o-C_6H_5; 108.4 C-4',2; 72.7 C-1'; 67.3 C-8'; 64.4, 63.9 C-4, C-5; 43.8 C-6'; 33.4 C-2'; 32.8 C-5'; 29.4 C-3'; 20.4 C-7'; (ESMS+) 331 (MLi^+, 100%), 347 (MNa^+, 83%).

7-[2'-(Phenylsulfonyl)ethyl]-1,4-dioxaspiro[4.5]decan-8-one 287 was isolated from fraction four as an oil (Rt 13.9 min, 3 ml/min). (Found: C, 59.30; H, 6.32; S, 10.06. Calc. for C_{16}H_{20}SO_5: C, 59.24; H, 6.21; S, 9.88%); \nu_{\text{max}} \text{(KBr)/cm}^{-1} 1712, (CO), 1304, (SO_2), 1150, (SO_2); \delta_{\text{H}} (400 MHz, CDCl_3) 7.89–7.90 (2H, m, o-C_6H_5), 7.57–7.64 (1H, m, p-C_6H_5), 7.44–7.57 (2H, m, m-C_6H_5), 3.90–4.02 (4H, m, 2 x 2-H, 2 x 3-H), 3.23 (1H, ddd, J_2',2' 14, J_2',1' 10.5, J_2',1' 5, 2'-H), 3.02 (1H, ddd, J_2',2' 14, J_2',1' 10.5, J_2',1' 5, 2'-H), 2.69–2.80 (1H, m, 7-H), 2.54 (1H, dddd, J_9,9 14, J_9,10 14, J_9,10 6, J_9,7 <1, 9-H), 2.21–2.30 (1H, ddd, J_9,9 14, J_9,10 5, J_9,10 3, 9-H), 1.91–2.03 (3H, m, 6-H, 10-H, 1'-H), 1.78–1.91 (1H, m, 10-H), 1.54–1.68 (2H, m, 6-H, 1'-H); \delta_{\text{C}} (50 MHz, CDCl_3) 210.1 C-8; 139.0 i-C_6H_5; 133.6 p-C_6H_5; 129.2 m-C_6H_5; 128.0 o-C_6H_5; 106.9 C-5; 64.9, 64.7 C-2, C-3; 53.9 C-2'; 44.9 C-7; 40.9 C-6; 38.2 C-9; 34.7 C-10; 22.8 C-1'; (ESMS+) 331 (MLi^+, 100%), 347 (MNa^+, 100%).
Cleavage of mono-ethylene ketal group in functionalised bicyclo[4.2.0]octanol 286

PPTS was prepared from p-toluenesulfonic acid monohydrate (5.70 g) and pyridine (12.1 ml). A solution of functionalised bicyclo[4.2.0]octanol 286 (60.0 mg, 0.185 mmole) and PPTS (4.6 mg, 0.018 mmole) in ethanol (3 ml) was stirred for 3 hours at 55 °C. The solvent was removed under reduced pressure. Analysis by 1H nmr spectroscopy indicated incomplete cleavage. The crude mixture in ethanol (3 ml) was treated with PPTS (5 mg, 0.020 mmole) and stirred for a further 18 hours at 55 °C. The solvent was removed under reduced pressure. Analysis by 1H nmr spectroscopy indicated incomplete cleavage. The crude mixture was dissolved in acetone and water (95:5) and stirred for 16 hours at 55 °C. The solvent was removed under reduced pressure. An analytically pure sample of functionalised bicyclo[4.2.0]octanol 288 was obtained by semi-preparative HPLC (hexane:ethyl acetate, 50:50).

(1RS,6SR,7SR)-6-Hydroxy-7-(phenylsulfonyl)bicyclo[4.2.0]octan-3-one 288 was obtained as a white solid mp, 116.2–117.1 °C (ethyl acetate-hexane). (Rt 21.5 min, 3 ml/min) (Found: C, 59.97; H, 5.81. Calc. for C_{14}H_{16}SO_{4}: C, 59.98; H, 5.75); ν_{max} (KBr)/cm^{-1} 3373, (OH), 1698 (CO), 1306, (SO_{2}), 1146, (SO_{2}); δH (400 MHz, CDCl_{3}) 7.88–7.96 (2H, m, o-C_{6}H_{5}), 7.60–7.68 (1H, m, p-C_{6}H_{5}), 7.51–7.60 (2H, m, m-C_{6}H_{5}), 3.75 (1H, ddd, J_{7,8} 10, J_{7,1} 4.5, J_{7,1} 1, 7-H), 2.98–3.07 (1H, m, 1-H), 2.71 (1H, ddd, J_{8,8} 14, J_{8,7} 11, J_{8,1} 4.5, 8-H), 2.65 (1H, dd, J_{8,8} 15, J_{2,2} 17, J_{2,1} 7, 2-H), 2.53 (1H, ddd, J_{4,4} 18, J_{4,5} 9, J_{4,5} 5, 4-H), 2.28 (1H, dd, J_{2,2} 17, J_{2,1} 4.5, 2-H), 2.17–2.24 (1H, m, 4-H), 2.06–2.15 (1H, m, 5-H), 1.97 (1H, ddd, J_{5,5} 14, J_{5,4} 9, J_{5,4} 5, 5-H), 1.69 (1H, ddd, J_{8,8} 14, J_{8,7} 9.5, J_{8,1} 8.5, 8-H), OH not observed; δC (50 MHz, CDCl_{3}) 209.7 C-3; 139.1 i-C_{6}H_{5}; 133.9 p-C_{6}H_{5}; 129.4 m-C_{6}H_{5}; 128.0 o-C_{6}H_{5}; 73.0 C-6; 64.7 C-7; 42.4 C-1; 41.4 C-2; 34.7 C-4; 32.4 C-5; 22.1 C-8; (ESMS+) 287 (MLi^{+}, 100%), 303 (MNa^{+}, 100%).
2.10 Reaction between 1,2-Cyclohexanedione and phenyl vinyl sulfoxide

1,2-Cyclohexanedione: Procedure E

1,2-Cyclohexanedione (0.5 g, 4.459 mmole) in THF (5 ml), lithium diisopropylamide (1.27 M, 3.51 ml, 4.459 mmole) and phenyl vinyl sulfoxide (0.6 ml, 4.459 mmole) in THF (43 ml), were reacted together using procedure E. Upon workup, the crude mixture was obtained as a yellow oil (0.985 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,2-cyclohexanedione were present.

1,2-Cyclohexanedione: Procedure E with a variance in enolate generation and 1 hr reaction time

Lithium diisopropylamide (1.27 M, 7.02 ml, 8.919 mmole) was added to THF (40 ml) under an atmosphere of nitrogen at -10 °C. 1,2-Cyclohexanedione (0.5 g, 4.459 mmole) in THF (5 ml) was added over 30 minutes and the temperature maintained at -10 °C for an hour. The system was shielded from light and phenyl vinyl sulfoxide (0.66 ml, 4.905 mmole) was added rapidly. The reaction mixture was maintained at -10 °C, stirred for an hour and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. Upon workup, the crude mixture was obtained as a yellow oil (0.973 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that polymerised phenyl vinyl sulfoxide and unreacted 1,2-cyclohexanedione were present.

1,2-Cyclohexanedione: Procedure F

1,2-Cyclohexanedione (0.5 g, 4.459 mmole) in THF (5 ml), lithium diisopropylamide (1.27 M, 3.51 ml, 4.459 mmole) and phenyl vinyl sulfoxide (0.6 ml, 4.459 mmole) in THF (43 ml) were reacted together using procedure F. Upon workup, the crude mixture
was obtained as a yellow oil (0.911 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that unreacted phenyl vinyl sulfoxide and unreacted 1,2-cyclohexanedione were present in conjunction with traces of a complex mixture of products. Some loss of 1,2-cyclohexanedione was observed upon evaporation of the crude mixture.

2.11 Reaction between Camphor and phenyl vinyl sulfoxide

**Camphor: Procedure B with a variance in enolate generation and 0.15 M of ketone**

Lithium diisopropylamide (1.4 M, 2.35 ml, 3.284 mmole) was added to THF (17.1 ml) under an atmosphere of nitrogen at $-10\, ^\circ\mathrm{C}$ and the solution warmed to 0 °C. Camphor (0.5 g, 3.284 mmole) in THF (2 ml) was added dropwise and the temperature maintained at 0 °C for one hour. The system was shielded from light and cooled to $-30\, ^\circ\mathrm{C}$. Phenyl vinyl sulfoxide (0.44 ml, 3.284 mmole) was added rapidly. The reaction mixture was maintained at $-30\, ^\circ\mathrm{C}$, stirred for 5 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. Upon workup, the crude mixture was obtained as a yellow oil (0.709 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that polymerised phenyl vinyl sulfoxide and unreacted camphor were present. Some loss of camphor was observed upon evaporation of the crude mixture.

**Camphor: Procedure E with 1.1 equivalents of LDA and a variance in enolate generation**

Lithium diisopropylamide (1.27 M, 2.85 ml, 3.613 mmole) was added to THF (33.5 ml) under an atmosphere of nitrogen at $-10\, ^\circ\mathrm{C}$ and the solution cooled to $-78\, ^\circ\mathrm{C}$. Camphor (0.5 g, 3.284 mmole) in THF (2 ml) was added dropwise and the temperature maintained at $-78\, ^\circ\mathrm{C}$ for 90 minutes. The system was shielded from light and allowed
to warm to –10 °C. Phenyl vinyl sulfoxide (0.44 ml, 3.284 mmole) was added rapidly. The reaction mixture was maintained at –10 °C, stirred for 10 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. Upon workup, the crude mixture was obtained as a yellow oil (0.919 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that polymerised phenyl vinyl sulfoxide and unreacted camphor were present.

**Camphor: Procedure E with a variance in enolate generation**

Lithium diisopropylamide (1.27 M, 2.59 ml, 3.284 mmole) was added to THF (30.5 ml) under an atmosphere of nitrogen at –10 °C and the solution cooled to –78 °C. Camphor (0.5 g, 3.284 mmole) in THF (5 ml) was added dropwise and the temperature maintained at –78 °C for 90 minutes. The system was shielded from light and allowed to warm to –10 °C. Phenyl vinyl sulfoxide (0.44 ml, 3.284 mmole) was added rapidly. The reaction mixture was maintained at –10 °C, stirred for 10 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A. Upon workup, the crude mixture was obtained as a yellow oil (0.959 g). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that polymerised phenyl vinyl sulfoxide and unreacted camphor were present.

**Reaction between Camphor and Benzaldehyde**

**Camphor: Procedure E with a variance in enolate generation and 15 minute reaction time**

Lithium diisopropylamide (1.27 M, 2.59 ml, 3.284 mmole) was added to THF (30.7 ml) under an atmosphere of nitrogen at –10 °C and the solution cooled to –78 °C. Camphor (0.5 g, 3.284 mmole) in THF (5 ml) was added dropwise and the temperature maintained at –78 °C for 90 minutes. The system was shielded from light and allowed
to warm to –10 °C. Benzaldehyde (0.33 ml, 3.284 mmole) was added rapidly. The reaction mixture was maintained at –10 °C, stirred for 15 minutes and quenched with aqueous ammonium chloride (40 ml). The mixture was worked up according to procedure A using diethyl ether as the extraction solvent. Upon workup, the crude mixture was obtained as a yellow oil (0.469 g, 58%). Analysis of the crude mixture by $^1$H nmr spectroscopy indicated that 3-[hydroxyphenylmethyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one 289$^{172}$ was present. The data was in agreement with reported literature values.

2.12 Synthesis of phenylsulfinyl ketone 291

(a) 1-Trimethylsilyloxy cyclohexene (1.50 ml, 7.706 mmole) was added to dichloromethane (15 ml) under an atmosphere of nitrogen and cooled to –78 °C. Diisopropylethylamide (1.75 ml, 10.02 mmole) was added, followed by the dropwise addition of TMSOTf (1.82 ml, 10.02 mmole) and the addition of allyl phenyl sulfoxide (1.48 ml, 10.02 mmole) over a period of 20 minutes. The temperature was maintained at –78 °C and the reaction monitored by T.L.C (hexane: ethyl acetate 70:30). After 2 hours the reaction mixture was quenched with hydrochloric acid (0.1 M, 6 ml). The mixture was diluted with water (30 ml), extracted with dichloromethane (3 x 75 ml) and the combined organic layers dried (MgSO$_4$, anhydrous). The solvent was removed under reduced pressure to afford a yellow oil (3.487 g). Analysis by $^1$H nmr indicated that 2-(3’-phenylthio-2’-propenyl)cyclohexanone 293$^{162}$ (27.5%) as the trans isomer (>90%) in conjunction with diisopropylethylamide (54% recovered yield), allyl phenyl sulfoxide (52.5% recovered yield) and TMSOTf (6% recovered yield) were present. Phenylthio ketone 293 was partially purified by silica column chromatography (hexane: dichloromethane, 70:30) and then used directly in step (b).
(b) *m*-CPBA (1.542 mmole) was added to a solution of phenylthio ketone 293 (0.380 g, 1.542 mmole) in dichloromethane (10 ml) under an atmosphere of nitrogen at –78 °C. The reaction mixture was warmed to 30 °C and stirred for a further hour. The mixture was poured into sodium hydrogen carbonate (aqueous, saturated, 30 ml), extracted with dichloromethane (3 x 30 ml) and the combined organic layers were washed with water (3 x 30 ml) and dried (MgSO₄, anhydrous). The solvent was removed under reduced pressure to afford crude phenylsulfenyl ketone 291 as a diastereomeric mixture (50:50) of *trans* isomers with minor impurities. An analytically pure sample of phenylsulfenyl ketone 291 (0.10 g, 25%) was prepared by semi-preparative HPLC (ethyl acetate: hexane, 80:20).

2-(3’-Phenylsulfenyl-2’-propenyl)cyclohexanone 291 was isolated as a 50:50 diastereomeric mixture (*denotes isomer A, †denotes isomer B) after extensive drying as a white waxy solid. (Rt 7.8 min, 4 ml/min) (Found: C, 68.39; H, 7.20. Calc. for C₁₅H₁₈SO₂: C, 68.67; H, 6.92); ²νmax (nujol)/cm⁻¹ 1704 (CO), 1042 (SO); δH (400 MHz, CDCl₃) 7.63–7.56 (2H, m, o-C₆H₅), 7.42–7.55 (3H, m, p-C₆H₅, m-C₆H₅), 6.51–6.62 (1H, m, 2’-H), *6.24 (1H, ddd, J₃’,2’ 15, J₃’,1’ 1.5, J₂’,1’ 1.5, 3’-H), †6.23 (1H, ddd, J₃’,2’ 15, J₃’,1’ 1.5, J₂’,1’ 1.5, 3’-H), 2.60-2.72 (1H, m, 1’-H), 2.24–2.48 (3H, m, 2-H, 2 x 6-H), 1.20–2.36 (7H, m, 2 x 3-H, 2 x 4-H, 2 x 5-H, 1’-H); δC (50 MHz, CDCl₃) 211.3, 211.2 (C-1; 139.1, 138.7 C-2’; 136.6, 136.4 C-3’; 130.92, 130.89 p-C₆H₅; 129.3 m-C₆H₅; 124.5, 124.4 o-C₆H₅; 49.7, 49.6 C-2; 42.1, 42.0 C-6; 33.9, 33.6 C-3 or C-4 or C-5; 32.2, 31.9 C-1’; 27.8, 27.7 C-3 or C-4 or C-5; 25.11, 25.09 C-3 or C-4 or C-5; (ESMS+) 269 (MLi⁺, 100%), 285 (MNa⁺, 100%).

³ FTIR signal intensity was very weak, due to inability to prepare sample in high enough concentration.
Reaction of phenyl sulfinyl ketone 291

Lithium diisopropylamide (1.27 M, 0.30 ml, 0.381 mmole) was added to THF (3.7 ml) under an atmosphere of nitrogen at –10 °C. Phenylsulfinyl ketone 291 (0.085 M, 0.100 g, 0.381 mmole) in THF (0.5 ml) was added dropwise at –10 °C and the temperature maintained for a further 10 minutes. The reaction mixture was quenched with aqueous ammonium chloride (10 ml) and extracted with ethyl acetate (3 x 20 ml). The combined organic layers were washed with water (2 x 25 ml), brine (25 ml) and dried (MgSO₄, anhydrous). The solvent was removed under reduced pressure. Upon workup the crude mixture was obtained as a yellow oil (0.101 g). Analysis of the crude mixture by ¹H nmr spectroscopy indicated a complex mixture of products.

2.13 Synthesis of 5-methyl-6-oxo-1-cyclohexene-1-carboxylic acid, methyl ester 294

(a) NaH (0.421 g, 17.53 mmole) in THF (50 ml) under nitrogen was cooled to 0 °C. Methyl propionylacetate (2.0 ml, 15.94 mmole) was added dropwise to the suspension with stirring over 20 minutes and stirred for a further 15 minutes. Butyllithium (0.634 M, 27.6 ml, 17.53 mmole) was then added dropwise over 15 minutes and stirred for a further 30 minutes. A solution of 2-(2-bromoethyl)-1,3-dioxolane (2.06 ml, 17.53 mmole) in THF (2 ml) was added rapidly and the mixture allowed to warm slowly to room temperature and stirred for a further 3 hours. The reaction mixture was quenched with aqueous ammonium chloride (50 ml) and extracted with diethyl ether (3 x 50 ml). The combined organic layers were washed with water (70 ml), brine (50 ml), dried (MgSO₄, anhydrous) and the solvent removed under reduced pressure to afford a yellow oil (3.570 g). Analysis of the crude mixture by ¹H nmr spectroscopy indicated that dioxolanyl ketoester 300 (41.5 %) was present in conjunction with unreacted methyl propionylacetate (24.5% recovered yield) and unreacted 2-(2-bromoethyl)-1,3-dioxolane (48% recovered yield). Dioxolanyl ketoester 300 was purified by silica
column chromatography (diethyl ether:hexane, 35:65). The first fraction (1.984 g) contained methyl propionylacetate and 2-(2-bromoethyl)-1,3-dioxolane. The second fraction (1.258 g) contained dioxolanyl ketoester 300 as a yellow oil which was used directly in step (b).

(b) A solution of dioxolanyl ketoester 300 (1.258 g, 5.464 mmole) and 50% aqueous acetic acid (65 ml) was stirred at room temperature for 16 hours under nitrogen, and then diluted with water (65 ml). The aqueous solution is saturated with sodium chloride and extracted with diethyl ether (4 x 60 ml). The combined organic layers were washed with saturated sodium bicarbonate (5 x 50 ml), water (100 ml), brine (100 ml) and dried (MgSO₄, anhydrous). Analysis of the crude product by ¹H nmr spectroscopy indicated the presence of cyclohexenecarboxylate 294 (0.596 g, 65%). Attempted purification by either short path reduced pressure distillation or fractional reduced pressure distillation or column chromatography (diethyl ether:hexane, 50:50) or HPLC chromatography (ethyl acetate:hexane, 10:90) resulted in decomposition of cyclohexenecarboxylate 294.

2.14 Reaction between 2,6-Dimethyl-2-cyclohexen-1-one 301 and phenyl vinyl sulfoxide

Synthesis of 2,6-Dimethyl-2-cyclohexen-1-one 301

N-Bromosuccinimide (14.351 g, 80.630 mmole) and AIBN (15 mg, 0.091 mmole) was added to a suspension of 2,6-dimethylcyclohexanone (9.250 g, 73.300 mmole) in carbon tetrachloride (60 ml). The reaction was heated at reflux for 22 hours, at which time an aliquot, which was analysed by ¹H nmr spectroscopy, showed the reaction to be complete. The reaction mixture was allowed to cool to room temperature, poured onto saturated sodium bicarbonate solution (70 ml), and extracted into chloroform (3 x 70
ml). The combined organic layers were washed with water (2 x 70 ml) and dried (MgSO₄, anhydrous). The solvent was removed under reduced pressure to afford 2,6-dimethyl-2-cyclohexen-1-one 301 (15.316 g) as confirmed by ¹H nmr spectroscopy. Partial purification by short path distillation (125 °C, 40-60 mmHg) gave 2,6-dimethyl-2-cyclohexen-1-one 301 as a colourless liquid (4.06 g, 44.5%).

2,6-Dimethyl-2-cyclohexen-1-one 301: Procedure F with 0.141 M of ketone

2,6-Dimethyl-2-cyclohexen-1-one 301 (1.0 ml, 8.053 mmole), lithium diisopropylamide (1.27 M, 6.34 ml, 8.053 mmole) and phenyl vinyl sulfoxide (1.08 ml, 8.053 mmole) in THF (49.7 ml), were reacted together using procedure F. Upon workup the crude sulfoxide mixture was obtained as a yellow oil (2.190 g). The crude sulfoxide mixture (2.190 g, 7.924 mmole) in chloroform (40 ml) was reacted with m-CPBA (7.924 mmole) in chloroform (60 ml). Upon workup, the crude sulfone mixture, containing minor amounts of m-chlorobenzoic acid, was obtained as a yellow oil (1.405 g). Analysis of the crude mixture by ¹H nmr spectroscopy indicated that polymerised phenyl vinyl sulfoxide, unreacted 2,6-dimethyl-2-cyclohexen-1-one (37.5%), bicyclo[2.2.2]octanones 305 (1%), 303 (1.5%) and 304 (1.5%) and monoalkylated 2,6-dimethyl-2-cyclohexen-1-one 302 (7%) were present. The crude mixture was purified by silica column chromatography (hexane:ethyl acetate, 80:20). The first fraction (370 mg) contained 2,6-dimethyl-2-cyclohexen-1-one. The second fraction (181 mg) contained monoalkylated 2,6-dimethyl-2-cyclohexen-1-one 302, bicyclo[2.2.2]-octanones 303, 304 and 305. The third fraction (540 mg) contained m-chlorobenzoic acid and ethyl acetate. Analytically pure samples were obtained by semi-preparative HPLC of bicyclo[2.2.2]octanone 305 from fraction two (hexane:ethyl acetate, 80:20) followed by semi-preparative HPLC (hexane:ethyl acetate, 70:30), monoalkylated 2,6-dimethyl-2-cyclohexen-1-one 302 from fraction two (hexane:ethyl acetate, 80:20),
bicyclo[2.2.2]octanone 303 from fraction two (hexane:ethyl acetate, 80:20) followed by semi-preparative HPLC (hexane:ethyl acetate, 70:30) and bicyclo[2.2.2]octanone 304 from fraction two (hexane:ethyl acetate, 80:20).

1,3-Dimethyl-5-(phenylsulfonyl)bicyclo[2.2.2]octan-2-one 305 was isolated from fraction three after extensive drying as a colourless hygroscopic oil. (Rt 16.2 min, 2.5 ml/min) (Found: C, 65.59; H, 7.14. Calc. for C_{16}H_{20}SO_3: C, 65.72; H, 6.90); \(\nu_{\text{max}}\) (nujol)/cm\(^{-1}\) 1727 (CO), 1303 (SO_2), 1153 (SO_2); \(\delta_H\) (400 MHz, CDCl_3) 7.86–7.90 (2H, m, \(o\)-C_6H_5), 7.62–7.68 (1H, m, \(p\)-C_6H_5), 7.54–7.59 (2H, m, \(m\)-C_6H_5), 3.28 (1H, dddd, \(J_5,6\) 10.5, \(J_{5,6}\) 7.5, \(J_{5,3}\) or \(J_{5,4}\) 1.5, 5-H), 2.56–2.65 (1H, m, 8-H), 2.42 (1H, dddd, \(J_{4,3}\) 2.5, \(J_{4,5}\) 2.5, \(J_{4,8}\) 2.5, \(J_{4,8}\) 2.5, 4-H), 2.30 (1H, dq, \(J_{3,3-Me}\) 7.5, \(J_{3,4}\) 2.5, 3-H), 2.21 (1H, dd, \(J_{6,6}\) 14, \(J_{6,5}\) 7.5, 6-H), 1.78–1.88 (1H, m, 7-H), 1.53–1.68 (3H, m, 6-H, 7-H, 8-H), 1.04 (3H, d, \(J_{3-Me}\) 7.5, 3-Me), 0.96 (3H, s, 1-Me); \(\delta_C\) (50 MHz, CDCl_3) 217.3 C-2; 138.7 \(i\)-C_6H_5; 133.8 \(p\)-C_6H_5; 129.4 \(m\)-C_6H_5; 128.2 \(o\)-C_6H_5; 57.9 C-5; 47.5 C-3; 42.5 C-1; 34.7 C-4; 31.8 C-6; 29.3 C-7; 21.6 C-8; 19.8 3-Me; 12.6 1-Me; (ESMS+) 299 (MLi\(^+\), 100%), 315 (MNa\(^+\), 100%).

2,6-Dimethyl-6-[2’-(phenylsulfonyl)ethyl]cyclohex-2-en-1-one 302 was isolated from fraction three after extensive drying as a white waxy solid. (Rt 17.3 min, 4 ml/min) (Found: C, 65.65; H, 7.03; S, 10.86. Calc. for C_{16}H_{20}SO_3: C, 65.72; H, 6.90; S, 10.97); \(\nu_{\text{max}}\) (nujol)/cm\(^{-1}\) 1659 (CO), 1635, (C=C), 1304 (SO_2), 1150 (SO_2); \(\delta_H\) (400 MHz, CDCl_3) 7.86–7.91 (2H, m, \(o\)-C_6H_5), 7.61–7.66 (1H, m, \(p\)-C_6H_5), 7.52–7.58 (2H, m, \(m\)-C_6H_5), 6.58-6.62 (1H, m, 3-H), 3.0–3.15 (2H, m, 2 x 2’-H), 2.29–2.36 (2H, m, 2 x 4-H), 1.81–1.92 (3H, m, 5-H, 2 x 1’-H), 1.71–1.78 (1H, m, 5-H), 1.68 (3H, m, 2-Me), 1.03 (3H, s, 6-Me); \(\delta_C\) (50 MHz, CDCl_3) 202.1 C-1; 143.9 C-3; 139.0 \(i\)-C_6H_5; 133.9 C-2;
133.6 p-C6H5; 129.3 m-C6H5; 128.0 o-C6H5; 52.1 C-2'; 43.4 C-6; 34.1 C-5; 29.4 C-1'; 22.6 C-4; 21.7 6-Me; 16.3 2-Me; (ESMS+) 299 (MLi+, 100%), 315 (MNa+, 100%).

1,3-Dimethyl-5-(phenylsulfonyl)bicyclo[2.2.2]octan-2-one 303 was isolated from fraction three after extensive drying as a colourless hygroscopic oil (Rt 16.3 min, 2.5 ml/min) (Found: C, 65.78; H, 7.12. Calc. for C16H20SO3: C, 65.72; H, 6.90); νmax (nujol)/cm−1 1720 (CO), 1305 (SO2), 1145 (SO2); δH (400 MHz, CDCl3) 7.86–7.90 (2H, m, o-C6H5), 7.64–7.69 (1H, m, p-C6H5), 7.55–7.60 (2H, m, m-C6H5), 3.17 (1H, ddd, J3,3-Me 7, J3,4 2, J3,5 or 8 2, 3-H), 2.46–2.51 (1H, m, 4-H), 2.19 (1H, ddd, J6,6 14, J6,5 8.5, J6,4 or 7 2.5, 6-H), 1.78–1.84 (1H, m, 8-H), 1.69 (1H, ddd, J6,6 14, J6,5 10, 6-H), 1.46–1.63 (3H, m, 2 x 7-H, 8-H), 1.12 (3H, d, J3-Me,3 7, 3-Me), 0.97 (3H, s, 1-Me); δC (50 MHz, CDCl3) 217.0 C-2; 138.5 i-C6H5; 133.9 p-C6H5; 129.4 m-C6H5; 128.4 o-C6H5; 61.9 C-5; 43.1 C-1; 41.7 C-3; 35.1 C-4; 31.1 C-7; 30.8 C-6; 22.0 C-8; 19.6 1-Me; 12.6 3-Me; (ESMS+) 299 (MLi+, 100%), 315 (MNa+, 100%).

1,3-Dimethyl-5-(phenylsulfonyl)bicyclo[2.2.2]octan-2-one 304 was isolated from fraction three after extensive drying as a colourless hygroscopic oil (Rt 20.1 min, 3 ml/min) δH (400 MHz, CDCl3) 7.84–7.88 (2H, m, o-C6H5), 7.61–7.67 (1H, m, p-C6H5), 7.53–7.58 (2H, m, m-C6H5), 3.30–3.38 (1H, m, 5-H), 2.82–2.88 (1H, m, 4-H), 2.29 (1H, dq, J3,3-Me 7.5, J3,4 2, 3-H), 2.21 (1H, ddd, J6,6 14, J6,5 8.5, J6,4 or 7 2.5, 6-H), 1.78–1.84 (2H, m, 2 x 8-H), 1.70 (1H, dd, J6,6 14, J6,5 10, 6-H), 1.56–1.64 (2H, m, 2 x 7-H), 1.48 (3H, d, J3-Me,3 7.5, 3-Me), 0.98 (3H, s, 1-Me); δC (50 MHz, CDCl3) 216.1 C-2; 136.4 i-C6H5; 133.6 p-C6H5; 129.4 m-C6H5; 128.0 o-C6H5; 63.1 C-5; 46.9 C-3; 42.6 C-1; 35.0 C-4; 32.6 C-6; 29.9 C-8; 28.4 C-7; 19.7 1-Me; 15.1 3-Me; HRMS (Found: 292.11338. C16H20SO3 requires 292.1133).
References


Appendix One

X-ray Crystallography

Data collection, structure solution and refinement.

Unique data sets for compounds 253, 257, 262, 265, 278, 280, 281 and 286 were measured at 295 K within $2\theta_{\text{max}} = 50^\circ$ using a Rigaku AFC7R four circle diffractometer ($\omega$-2$\theta$ scan mode, monochromated Mo-K$_\alpha$ radiation $\lambda = 0.71069$ Å) yielding $N$ independent reflections, $N_o$ with $I > 2\sigma(I)$ being considered 'observed'. The structures were solved by direct methods and refined by full matrix least squares refinement on $|F|$. Positional and anisotropic thermal parameters were refined for non-hydrogen atoms. Positions of hydrogen atoms were geometrically calculated and included in refinement and constrained with estimated isotropic thermal parameters. The hydroxyl hydrogens were located from difference Fourier maps except for compound 278, in which the hydroxyl hydrogen atom was not included. Weights derivative of $w = 1/[\sigma^2(F)]$ were employed. Conventional residuals $R$, $R_w$, on $|F|$ at convergence are quoted. Neutral atom complex scattering factors were employed; computation used the teXsan crystallographic software package for Windows version 1.06 of the Molecular Structure Corporation,\textsuperscript{1} ORTEP-3\textsuperscript{2} and PLATON.\textsuperscript{3}

\textsuperscript{3}Spek AL, PLATON for Windows version 121201. Utrecht, University of Utrecht.
(1RS, 5SR, 7SR)-7-(Phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol 253 crystals formed from slow diffusion of diethyl ether into a solution of 253 in dichloromethane, mp 89.1-92.6 °C. C_{13}H_{16}O_{3}S M = 252.3, monoclinic, space group P2_1/c (C_{2h}^5 No. 14), a = 10.538(3), b = 10.148(2), c = 11.840(2) Å, β = 98.34(2)°, V = 1252.7(4) Å^3, Z = 4, D_c = 1.34 g cm^{-3}, µ(Mo Kα) = 2.52 cm^{-1}, Crystal size: 0.60 x 0.50 x 0.20 mm, N = 2365, N_o = 1803; R = 0.045, R_w = 0.048.
2-[2’-(Phenylsulfonyl)ethyl]cyclopentanone 257 crystals isolated by slow evaporation of a hexane-ethyl acetate (60:40) solution, mp 75.2-76.0 °C. C_{13}H_{16}O_{3}S \ M = 252.33, monoclinic, space group \( P2_1/n \) (\( C_{2v}^5 \) No. 14 variant), \( a = 11.986(2) \), \( b = 12.387(6) \), \( c = 9.2183(13) \AA \), \( \beta = 110.29(2)^o \), \( V = 1283.7(7) \AA^3 \), \( Z = 4 \), \( D_c = 1.31 \) g cm\(^{-3}\), \( \mu(\text{Mo K}_{\alpha}) = 2.50 \) cm\(^{-1}\), Crystal size: 0.40 x 0.30 x 0.30 mm, \( N = 2943 \), \( N_o = 2167 \); \( R = 0.042 \), \( R_w = 0.130 \).
(1RS, 7SR, 9SR)-9-(Phenylsulfonyl)bicyclo[5.2.0]nonan-1-ol 262 crystals formed from slow diffusion of diethyl ether into a solution of 262 in dichloromethane, mp 99.3-101.1 °C. C\textsubscript{15}H\textsubscript{20}O\textsubscript{3}S \( M = 280.4 \), monoclinic, space group \( P2_1/n \), \( a = 12.032(5) \), \( b = 10.385(4) \), \( c = 12.640(4) \) Å, \( \beta = 111.78(2)^\circ \), \( V = 1467(1) \) Å\textsuperscript{3}, \( Z = 4 \), \( D_c = 1.27 \) g cm\textsuperscript{-3}, \( \mu(\text{Mo } K\alpha) = 2.22 \) cm\textsuperscript{-1}, Crystal size: 0.50 x 0.40 x 0.10 mm, \( N = 2572, N_o = 1430; R = 0.042, R_W = 0.045. \)
(1RS, 8SR, 10SR)-10-(Phenylsulfonyl)bicyclo[6.2.0]decan-1-ol 265 crystals formed from slow diffusion of diethyl ether into a solution of 265 in dichloromethane, mp 98.1-100.2 °C. C_{16}H_{22}O_3S M = 294.9, monoclinic, space group P2_1/c (C_{2h} \text{ No. 14}), a = 13.289(7), b = 10.275(7), c = 11.539(7) Å, \( \beta = 104.29(4)^\circ \), V = 1527(2) Å\(^3\), Z = 4, \( D_c = 1.28 \text{ g cm}^{-3} \), \( \mu(\text{Mo K}_\alpha) = 2.17 \text{ cm}^{-1} \), Crystal size: 0.50 x 0.30 x 0.10 mm, N = 2855, \( No = 1213; R = 0.055, R_w = 0.040. \)
(1RS, 2SR, 6SR, 8SR)-2,6-Dimethyl-8-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol 278

crystals isolated by slow evaporation of a hexane-ethyl acetate (90:10) solution, mp 108.5-109.1 °C. C$_{16}$H$_{22}$O$_3$S $M = 294.41$, monoclinic, space group $P2_1/c$, $a = 11.340(3)$, $b = 18.026(6)$, $c = 7.844(2)$ Å, $\beta = 106.79(2)^\circ$, $V = 1535.2(7)$ Å$^3$, $Z = 4$, $D_c = 1.27$ g cm$^{-3}$, $\mu$(Mo K$_\alpha$) = 2.15 cm$^{-1}$, Crystal size: 0.40 x 0.35 x 0.20 mm, $N = 3643$, $N_o = 1896$; $R = 0.052$, $R_w = 0.040$. 
(2RS, 6RS)-2,6-Dimethyl-2-[2’-(phenylsulfonyl)ethyl]cyclohexanone crystals isolated by slow evaporation of a hexane-ethyl acetate (80:20) solution, mp 131.3-132.2 °C. C₁₆H₂₂O₃S $M = 294.41$, orthorhombic, space group $P2_12_12_1$ ($D_2^4$ No. 19), $a = 12.641(3)$, $b = 20.240(5)$, $c = 6.051(2)$ Å, $V = 1548.2$ Å³, $Z = 4$, $D_c = 1.26$ g cm⁻³, $\mu$(Mo $K_{\alpha}) = 2.10$ cm⁻¹, Crystal size: 0.60 x 0.40 x 0.20 mm, $N = 2094$, $N_o = 1316$; $R = 0.042$, $R_w = 0.125$. 
(1RS, 2RS, 6SR, 8SR)-2-Methyl-8-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol crystals isolated by slow evaporation of a hexane-ethyl acetate (80:20) solution, mp 110.2-111.6 °C. C_{15}H_{20}O_3S M = 280.38, monoclinic, space group \textit{P}2_1/n, a = 12.328(6), b = 10.362(4), c = 12.149(2) Å, \(\beta = 99.60(3)\)°, \(V = 1530.4(8)\) Å\(^3\), \(Z = 4\), \(D_c = 1.21\) g cm\(^{-3}\), \(\mu(\text{Mo K}\alpha) = 2.13\) cm\(^{-1}\), Crystal size: 0.30 x 0.20 x 0.10 mm, \(N = 3516\), \(N_o = 1712\); \(R = 0.058\), \(R_W = 0.055\).
(1’RS, 6’SR, 8’SR)-Spiro[1,3-dioxolane-2,4’-[8]phenylsulfonylbicyclo[4.2.0]octan[1]-ol] 286 crystals isolated by slow evaporation of a hexane-ethyl acetate (50:50) solution, mp 117.4-119.1 °C. C_{16}H_{20}O_{5}S M = 324.39, triclinic, space group P-1, a = 5.736(3), b = 11.468(5), c = 12.095(4) Å, α = 81.1(6), β = 98.83(3), γ = 98.03(3)°, V = 771(1) Å³, Z = 2, D_c = 1.40 g cm⁻³, μ(Mo Kα) = 2.30 cm⁻¹, Crystal size: 0.60 x 0.20 x 0.15 mm, N = 3537, N_o = 2637; R = 0.045, R_w = 0.130.
Appendix 2 consists of previously published papers, which are not included in the digital version of the thesis.


