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# NEW REAGENTS FOR ASYMMETRIC ELECTROPHILIC NITROGEN TRANSFER

By

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## Abstract

This thesis describes the synthesis of new chiral *NH* oxaziridines and their uses for electrophilic amination reactions. The introduction highlights some of the most successful electrophilic amination reagents and development of systems for the formation of carbon-nitrogen bonds. Examples of the use of camphor and fenchone *NH*-oxaziridines synthesized by our group are provided towards the end of the first chapter.

The second chapter is dedicated to our efforts to synthesize new chiral *NH*-oxaziridines derived from camphor. The first part of this chapter describes the formation of 3-mono- and 3,3-disubstituted camphor nitrimine precursors. The synthesis of 3-alkyl camphor nitrimines and their attempted conversion to oxaziridines are reported in section 2.2. Section 2.3 concerns the synthesis of 3-halo-camphor oxaziridines, and the section 2.4 attempts to synthesize 3,3-dihalo-camphor oxaziridines. Investigation of the process of amination of camphor nitrimine using ammonia is discussed in section 2.5. Section 2.6 is dedicated to the attempted formation of 3,3-diacetal camphor nitrimines.

The second part of chapter two reports the synthesis of *N*-pyrrolidinyl-camphor-10-sulfonamide oxaziridine, and 3,5-dimethyl-phenyl camphor-10-sulfonate oxaziridine. Their use as electrophilic aminating reagents is also discussed.

The last part of this chapter is concerned with the formation of camphor diaziridines starting from camphor oxime. The chapter concludes with a few suggestions for the synthesis of enantiomerically pure *NH*-oxaziridines and a diaziridine derived from isobornylamine.

The third chapter is the experimental section and is dedicated to the methods of synthesis and characterization of the compounds described in the previous chapter.

X-ray reports regarding the crystallographic analysis of some structures presented in chapter two are provided in chapter four.

## Abbreviations

|              |   |                                    |
|--------------|---|------------------------------------|
| Å            | = | ångström                           |
| Ac           | = | acetyl                             |
| aq.          | = | aqueous                            |
| Ar           | = | aryl                               |
| atm.         | = | atmosphere                         |
| br           | = | broad                              |
| Bn           | = | benzyl                             |
| Bz           | = | benzoyl                            |
| Boc          | = | <i>tert</i> -butoxycarbonyl        |
| bp           | = | boiling point                      |
| <i>i</i> -Bu | = | <i>iso</i> -butyl                  |
| <i>n</i> -Bu | = | <i>n</i> -butyl                    |
| <i>t</i> -Bu | = | <i>tert</i> -butyl                 |
| cat.         | = | catalytic                          |
| conc.        | = | concentrated                       |
| d            | = | doublet                            |
| DBDMH        | = | dibromodimethylhydantoin           |
| DBU          | = | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCE          | = | dichloroethane                     |
| DCDMH        | = | dichlorodimethylhydantoin          |
| DCM          | = | dichloromethane                    |
| <i>d.e.</i>  | = | diastereomeric excess              |
| DIBAL-H      | = | diisobutylaluminium hydride        |
| DIEA         | = | diisopropylethylamine              |
| dm           | = | decimetre                          |
| DMAD         | = | dimethyl acetylenedicarboxylate    |
| DMAP         | = | 4-dimethylaminopyridine            |
| DME          | = | 1,2-dimethoxyethane                |
| DMF          | = | dimethylformamide                  |
| DMSO         | = | dimethylsulfoxide                  |
| E            | = | electrophile                       |

|                |   |  |
|----------------|---|--|
| <i>e.e.</i>    | = | enantiomeric excess                    |
| E.I.           | = | electron impact                        |
| Et             | = | ethyl                                  |
| EWG            | = | electron withdrawing group             |
| F.A.B.         | = | fast atom bombardment                  |
| HPLC           | = | high performance liquid chromatography |
| hr             | = | hour                                   |
| I.R.           | = | infra red                              |
| <i>J</i>       | = | coupling constant                      |
| KHMDS          | = | potassium hexamethyldisilazide         |
| LAH            | = | lithium aluminium hydride              |
| LDA            | = | lithium di- <i>iso</i> -propylamide    |
| LHMDS          | = | lithium hexamethyldisilazide           |
| Lit            | = | literature                             |
| M              | = | Molar                                  |
| m              | = | multiplet                              |
| <i>m</i> -CPBA | = | 4-chloroperbenzoic acid                |
| Me             | = | methyl                                 |
| MeOH           | = | methanol                               |
| Mes            | = | mesyl                                  |
| MHz            | = | megahertz                              |
| min            | = | minute                                 |
| ml             | = | millilitres                            |
| mmol           | = | millimoles                             |
| m.p.           | = | melting point                          |
| MS             | = | mass spectrum                          |
| NCS            | = | <i>N</i> -chlorosuccinimide            |
| NHMDS          | = | sodium hexamethyldisilazide            |
| NMR            | = | nuclear magnetic resonance             |
| Nu             | = | nucleophile                            |
| Pd/C           | = | palladium on carbon                    |
| Ph             | = | phenyl                                 |
| Ppm            | = | parts per million                      |
| <i>i</i> -Pr   | = | <i>iso</i> -propyl                     |

|                |   |                                       |
|----------------|---|---------------------------------------|
| <i>n</i> -Pr   | = | <i>n</i> -propyl                      |
| Py             | = | pyridine                              |
| q              | = | quartet ( <sup>1</sup> H NMR)         |
| Quat           | = | quaternary ( <sup>13</sup> C NMR)     |
| R              | = | alkyl                                 |
| rt             | = | room temperature                      |
| s              | = | singlet                               |
| t              | = | triplet                               |
| TBAF           | = | tetrabutyl ammonium fluoride          |
| TBDMS          | = | <i>tert</i> -butyldimethylsilyl       |
| TEA            | = | triethylamine                         |
| Tf             | = | trifluoromethanesulfonyl              |
| TFA            | = | trifluoroacetic acid                  |
| THF            | = | tetrahydrofuran                       |
| tlc            | = | thin layer chromatography             |
| TMS            | = | trimethylsilane                       |
| TPPP           | = | tetraphenylphosphonium peroxysulphate |
| Ts             | = | <i>para</i> -tosyl                    |
| <i>p</i> -TsOH | = | <i>para</i> -toluenesulfonic acid     |
| UV             | = | ultra violet                          |



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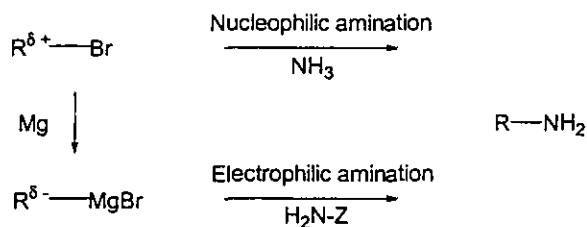
# **CHAPTER 1:**

## **INTRODUCTION**

## 1. ELECTROPHILIC AMINATION

A large number of biologically active compounds contain an amino functionality. This means that the formation of carbon-nitrogen bonds is an important chemical transformation. Numerous approaches have been made to the development of systems for the formation of carbon-nitrogen bonds, usually by attack of a nucleophilic nitrogen atom by an electrophilic carbon bearing a leaving group by an  $S_N2$  type reaction. A different approach, electrophilic amination, involves the ability to transfer an amino or substituted amino group to all kinds of nucleophiles, using a various range of different aminating reagents.

A diagram showing the two different approaches and describing the concept of electrophilic amination involving inversion of polarity is given below (**Scheme 1**). First equation is the reaction of an electrophilic alkyl halide with ammonia or amine, the second one the nucleophilic attack on an electrophilic aminating agent.



Z = Cl, Br, O-Alkyl,  $OSO_3H$ , sulfonate ester,...

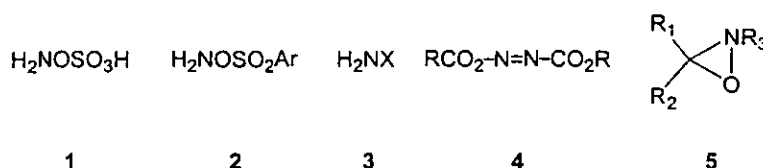
**Scheme 1:** Concept of electrophilic and nucleophilic amination

The important point in electrophilic aminating reagents is the substituent group on the nitrogen atom. This must be a good leaving group and is displaced by the nucleophile during the reaction.

## 1.1. Aminating reagents

Several aminating reagents have been reported, derived from hydroxylamine, halogeno-amine, substrates possessing nitrogen nitrogen multiple bonds, oxaziridines unsubstituted at nitrogen or *N*-protected oxaziridines (Scheme 2).

The demand for practical equivalents of the electrophilic synthon ( $\text{NH}_2^+$ ), has seen the development of many aminating reagents. The following account discusses these techniques in the area of electrophilic amination.



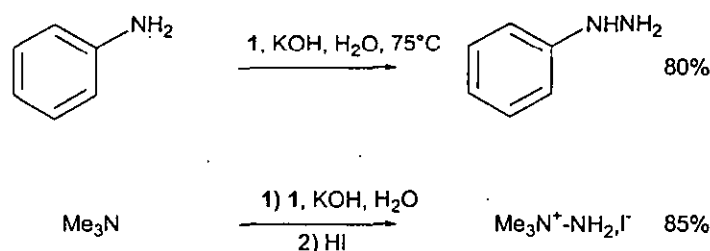
**Scheme 2:** Aminating reagents

### 1.1.1 Hydroxylamine-*O*-sulfonic acid

This commercially available reagent has been employed for many chemical reactions,<sup>1</sup> such as amination, conversion of alkenes into primary amines, hydroxymethylation,<sup>2</sup> and conversion of aldehydes to nitriles.<sup>3,4</sup>

#### 1.1.1.1 Amination of Nitrogen Nucleophiles

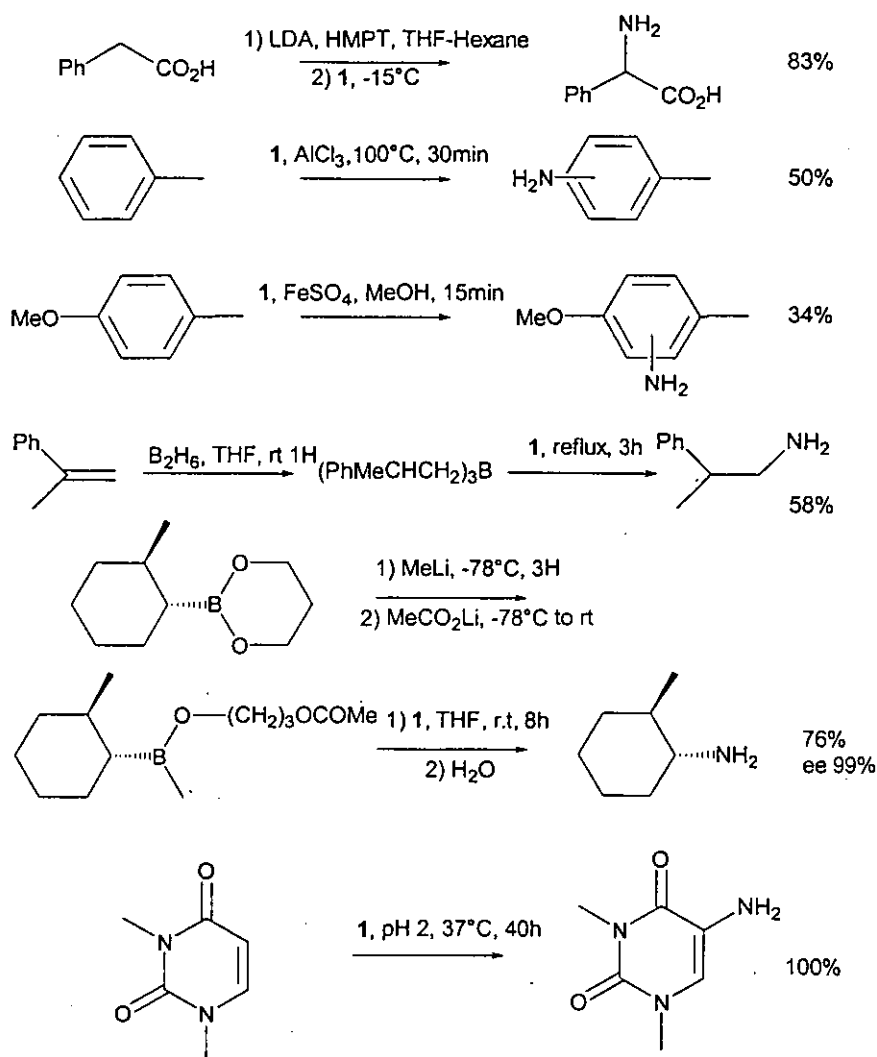
Hydroxylamine-*O*-sulfonic acid (1) reacts with primary and secondary amines, in basic aqueous solution to give mono or 1,1-disubstituted hydrazines.<sup>5,6,7</sup> Tertiary amines are transformed into 1,1,1-trisubstituted hydrazonium salts (**Scheme 3**).<sup>5,7</sup>



**Scheme 3:** Nitrogen nucleophiles

## 1.1.1.2 Amination of Carbon Nucleophiles

Lithium enolates,<sup>8</sup> aromatic rings,<sup>9,10</sup> borane,<sup>11</sup> and heterocyclic compounds,<sup>12</sup> were aminated with hydroxylamine-*O*-sulfonic acid. (Scheme 4)

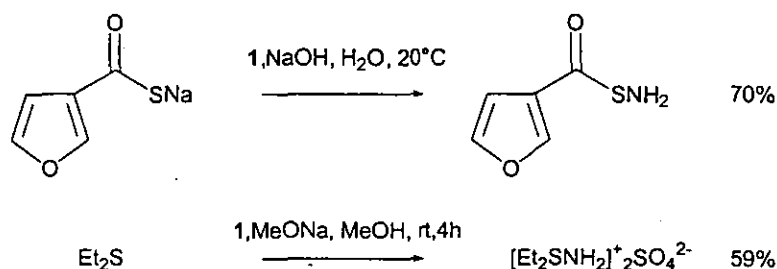


Scheme 4: Carbon nucleophiles

The direct amination of aromatic compounds can be catalysed by aluminium chloride or can be an homolytic amination procedure via an amino radical generated using iron (II).<sup>13</sup>

### 1.1.1.3 Amination of Sulfur Nucleophiles

Organosulfur compounds including thiols,<sup>14</sup> thioacids,<sup>14</sup> thioamides,<sup>15,16</sup> and thioesters undergo amination using **1**. (**Scheme 5**)

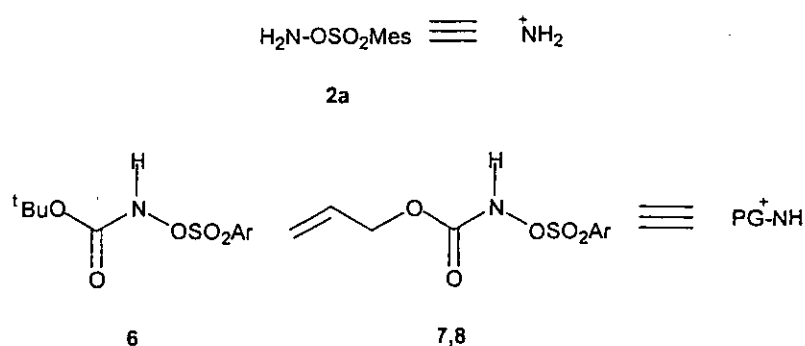


### Scheme 5: Sulfur nucleophiles

The commercially available hydroxylamine-*O*-sulfonic acid (1) has proven to be an efficient aminating reagent, in spite of its solubility. It is soluble in water and slightly soluble in methanol and ethanol and this has restricted its utilization.

### 1.1.2 Hydroxylamine Sulfonamides

A number of *N*-unsubstituted and *N*-protected hydroxylamine sulfonyl esters have also been investigated (**Scheme 6**). The first type delivers the free amino group, and the second transfer directly a *N*-protected amino group.

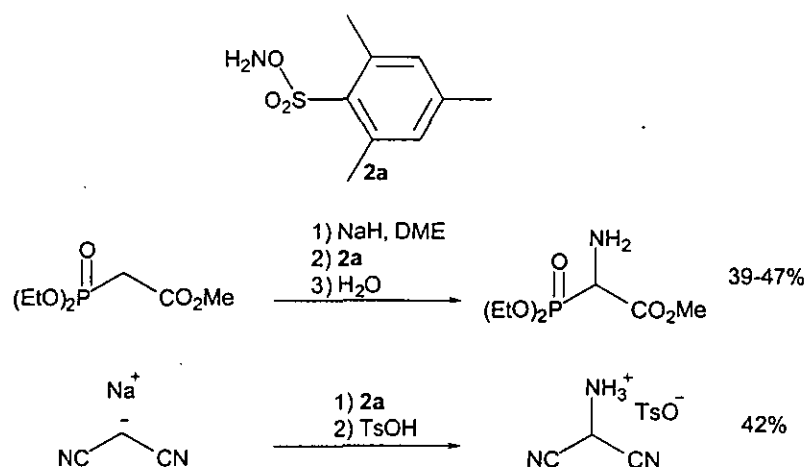


**Scheme 6:** *O*-Sulfonyloxy hydroxylamine ester derivatives



1.1.2.1 *N* Unsubstituted Type

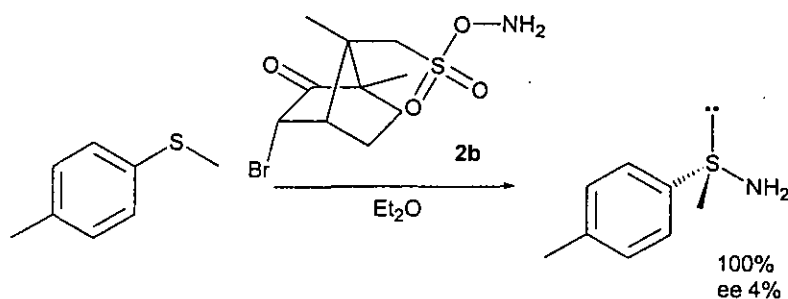
Among all the hydroxylamine-*O*-sulfonate esters developed, Tamura's reagent<sup>17</sup> *O*-mesitylsulfonyl hydroxylamine (**2a**) has been widely adopted for the amination of various nucleophiles including C-H acidic compound such as malonodinitrile,<sup>18</sup> methyl diethylphosphonoacetate (**Scheme 7**),<sup>19</sup> sulfides, sulfoxides<sup>20</sup> or nitrogen nucleophiles.<sup>21,22</sup>



Scheme 7: Free amino group transfer

However the instability of (**2a**) proved troublesome as indicated by the author. The reagents and its synthetic precursor may decompose spontaneously during drying of the solids.

An example of asymmetric amination of sulfur nucleophile using the chiral (+)-*O*-( $\alpha$ -bromocamphor- $\pi$ -sulfonyl) hydroxylamine (**2b**) has been developed by Kjaer and Malaver.(**Scheme 8**).<sup>23</sup>



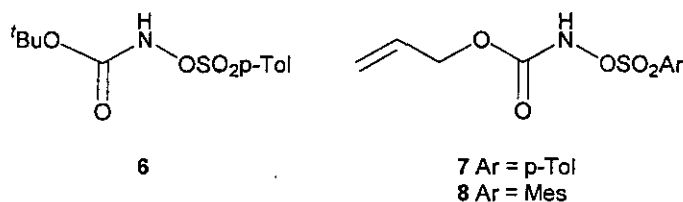
Scheme 8: Asymmetric amination

The electrophilic nitrogen is remote from the chirality, so inducing a poor selectivity during the amine transfer.

### 1.1.2.2 *N*-Protected Type

The accessibility and the stability of *N*-(aryl-sulfonyloxy) carbamates, *t*-butyl-*N*-tosyloxy carbamates (**6**) and *N*-allyl-*N*-tosyloxy and *N*-allyl-*N*-mesityl carbamates (**7,8**), (**Scheme 9**) as precursor of metalated species, increases the value of those reagents for electrophilic amination.

The allyl group is stable in acidic or basic media and is removed under neutral conditions in the presence of a palladium Pd(0) catalyst.<sup>24,25</sup> The *t*-butoxy-group is removed under acidic conditions.<sup>24</sup>

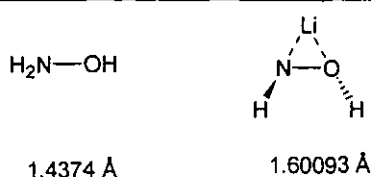


**Scheme 9:** *N*-(aryl-sulfonyloxy) carbamates

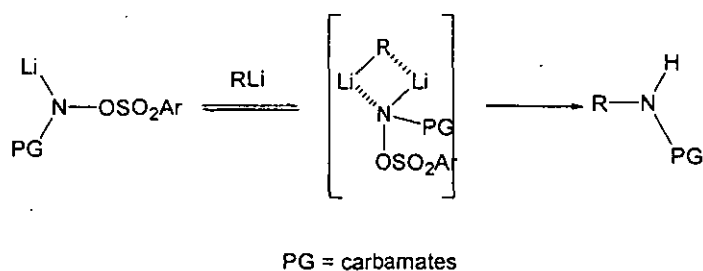
Compound (**6**) was obtained from commercially available *t*-butylcarbamate by tosylation. *N*-Allyl carbamates (**7,8**), were synthesized from hydroxylamine, first protected as a carbamate and then sulfonylated.<sup>26</sup>

The treatment of (**6,7,8**) with one equivalent of base such as *n*-BuLi, EtMgBr or KHMDS affords the metalated *N*-(aryl-sulfonyloxy) carbamates: nitrenoid precursors.

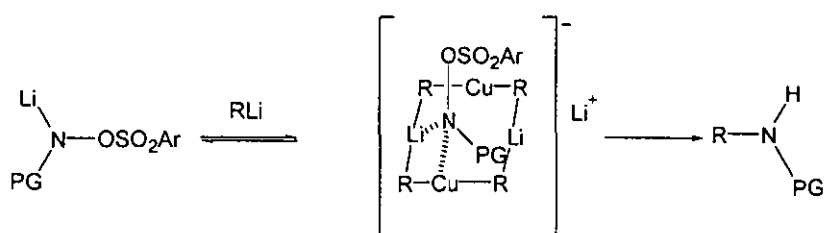
Boche and Wagner's quantum chemical calculation<sup>27</sup> revealed that the N-O bond in the metallated complex is bridged by Li, resulting in a longer bond than the non lithiated bond (**Scheme 10**). This could explain the facile cleavage of the N-O bond in the case of those nitrenoids.

**Scheme 10:** Nitrenoids

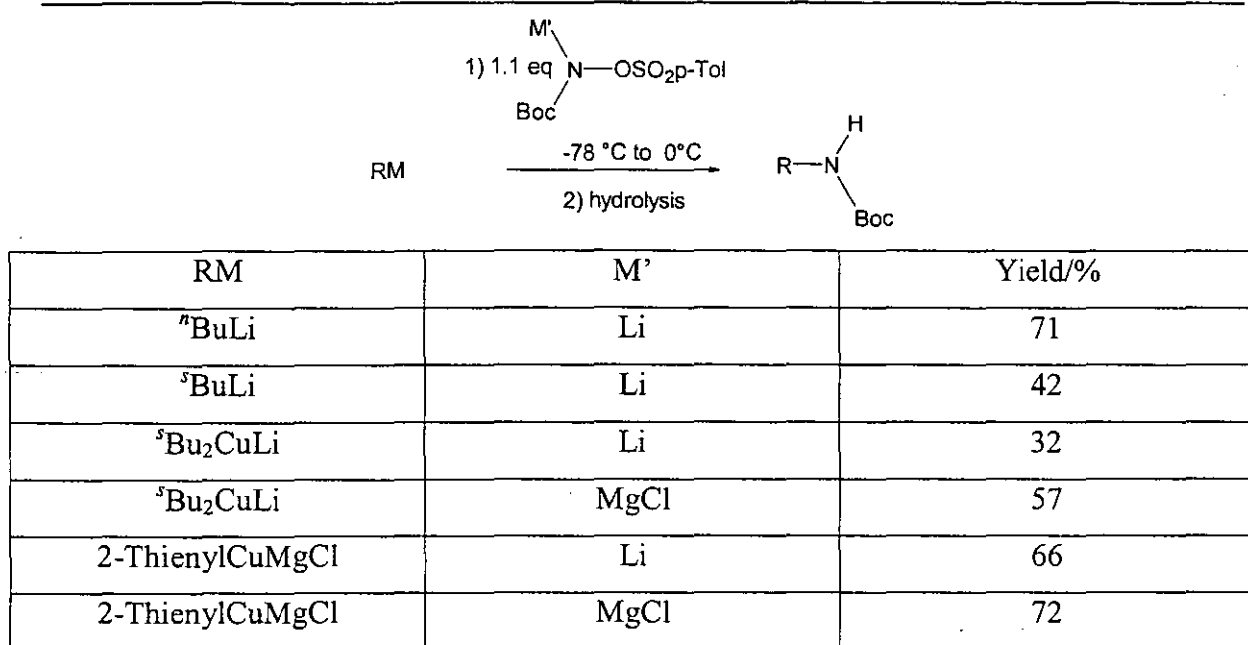
Beak proposed a transition state for the case of lithiated hydroxylamine-*O*-sulfonic ester for the amination of alkyl lithium, which could be adapted for the use of (6, 7, 8) (Scheme 11).<sup>28</sup>

**Scheme 11:** Feasible transition state

Boche has also established that lithium metalated (8) crystallized as a dimer.<sup>29</sup> In the case of amination of dialkylcuprates a chelation of the nitrogen to both Li and Cu was suggested (Scheme 12).

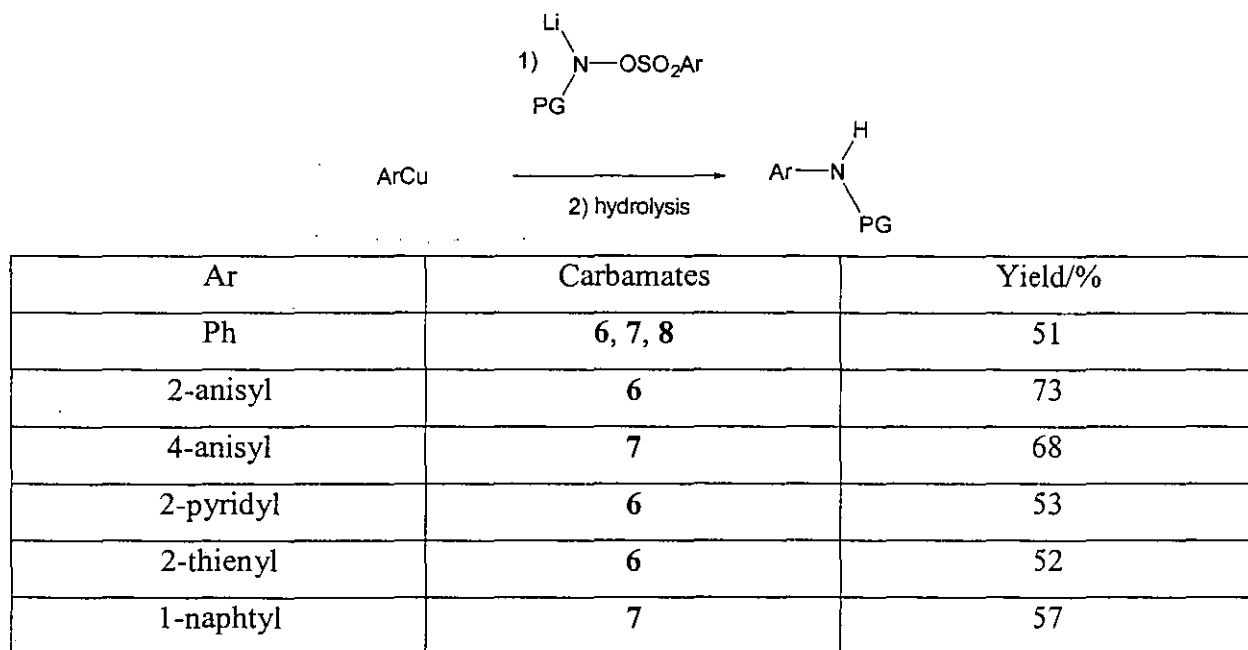
**Scheme 12:** Amination of organocuprates

Metallated *N*-(aryl-sulfonyloxy) carbamates, are good reagents for the transfer of *N*-protected amino group to organometallic compounds (Scheme 13)



Scheme 13: Amination of organometallic compounds

Aryl coppers<sup>26,30</sup> undergo amination under mild conditions using the lithiated carbamates (6, 7, 8) (Scheme 14).



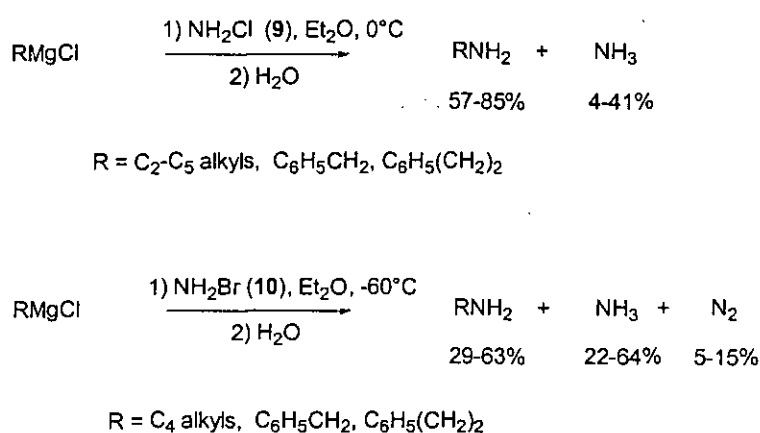
Scheme 14: Amination of aryl coppers

Nitrogen nucleophiles are aminated by *t*-butyl-*N*-tosyloxycarbamate to afford *N*-Boc-β-protected hydrazines or *N*-tert-butoxyureas from amines.<sup>31</sup>

Other carbon nucleophiles that have been reported to be aminated with this reagent include  $\alpha$ -cuprophosponates<sup>31</sup> and boranes.<sup>32</sup>

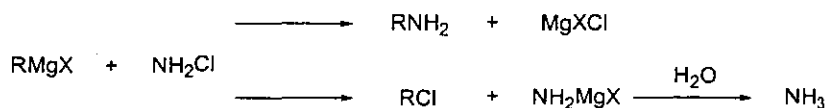
### 1.1.3 *N*-Haloamines

Monochloramine (9), monobromamine (10), dibromamine, nitrogen trichloride and mono or dialkyl-substituted chloramines have been used for the amination of numerous carbanions.<sup>33</sup> Grignard reagents react with (9) to form primary amines and ammonia as by product,<sup>34</sup> (10) leads to primary amine, ammonia and nitrogen (Scheme 15).



**Scheme 15:** Amination with mono-haloamines

The formation of ammonia during the process could, as Coleman proposed be due to the ambivalent character, acting as nucleophilic or electrophilic species, of the nitrogen (Scheme 16).



**Scheme 16:** Ambivalent character of haloamines

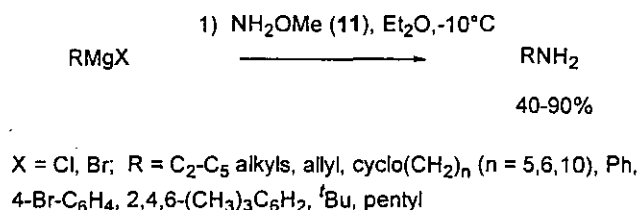
In the first reaction the nitrogen atom acts as electrophile and the chlorine as a leaving group, whereas, in the second reaction, the leaving group is the nitrogen  $\text{NH}_2^-$ . In the case of the reaction of phenyl magnesium iodide and chloramines (9), one equivalent of chlorobenzene was isolated.<sup>35</sup>

Organolithium reagents react with (9) but do not offer better yields than the corresponding Grignard reagents. The highest yield require the use of 3 equivalents of organolithium.<sup>36</sup> The difficult preparation of (9) and (10), their instability, and the poor reproducibility of the yields have limited their utilization as electrophilic amination reagents.

#### 1.1.4 *O*-Alkyl, *O*-Aryl, *O*-Acyl- Hydroxylamines

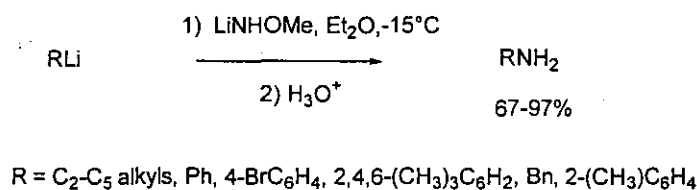
##### 1.1.4.1 *O*-alkyl hydroxylamine

*O*-Methyl-hydroxylamine (11) is by far the most widely employed reagent of this family. It reacts with alkyl and aryl-Grignard reagents in moderate to good yields (Scheme 17).<sup>37</sup>



**Scheme 17:** Amination with *O*-methyl hydroxylamine

For the amination of organolithium species the metallated form of (11) was used. Deprotonation of (11) with methyl lithium was followed by the addition of the lithium nucleophiles (Scheme 18).<sup>38</sup>

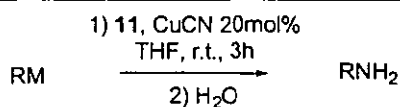


**Scheme 18:** Amination of organolithium species

Erdike and Daskapan have reported recently the amination of mono-, di- and triorganozinc species with (11) (Scheme 19).<sup>39</sup>

Original

Took on Spine



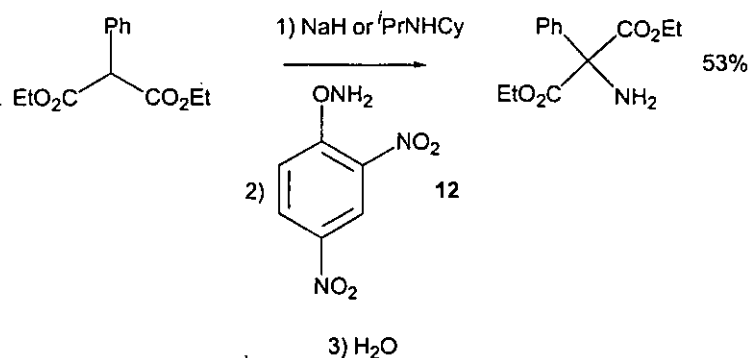
M = ZnCl (or ZnBr), 1/2Zn, 1/3ZnMgBr

| RM   | Yield/% |
|--|---------|
| C <sub>6</sub> H <sub>5</sub> ZnCl   | 7       |
| (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> Zn                                 | 82      |
| (C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> ZnMgBr                             | 95      |
| ( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> Zn      | 62      |
| ( <i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> ZnMgBr  | 70      |
| ( <i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> )ZnCl                 | 0       |
| ( <i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> Zn     | 63      |
| ( <i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> ) <sub>3</sub> ZnMgBr | 63      |

Scheme 19: Amination of mono-, di- or triorganozinc

#### 1.1.4.2 *O*-Aryl hydroxylamine

*O*-2,4-Dinitro-phenyl hydroxylamine (12) has been shown to react with stabilized carbanions such as malonates (Scheme 20).<sup>40</sup>

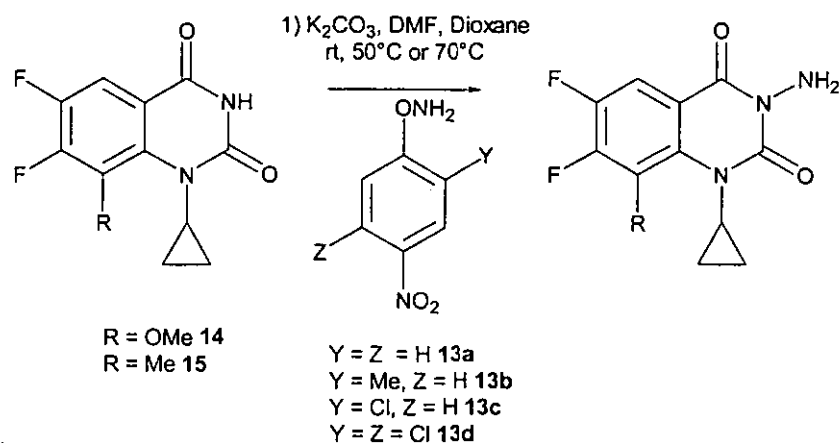


Scheme 20: Amination of stabilized carbanions

Those malonates can be hydrolysed and decarboxylated to give the corresponding amino acids. Less stabilized carbanions such as enolates of simple esters, nitriles have been shown to give lower yields.<sup>41</sup>



Curran, reported recently the amination of quinazoline-2,4-dione using a variety of substituted nitrophenyl hydroxylamines (Scheme 21).<sup>42</sup>

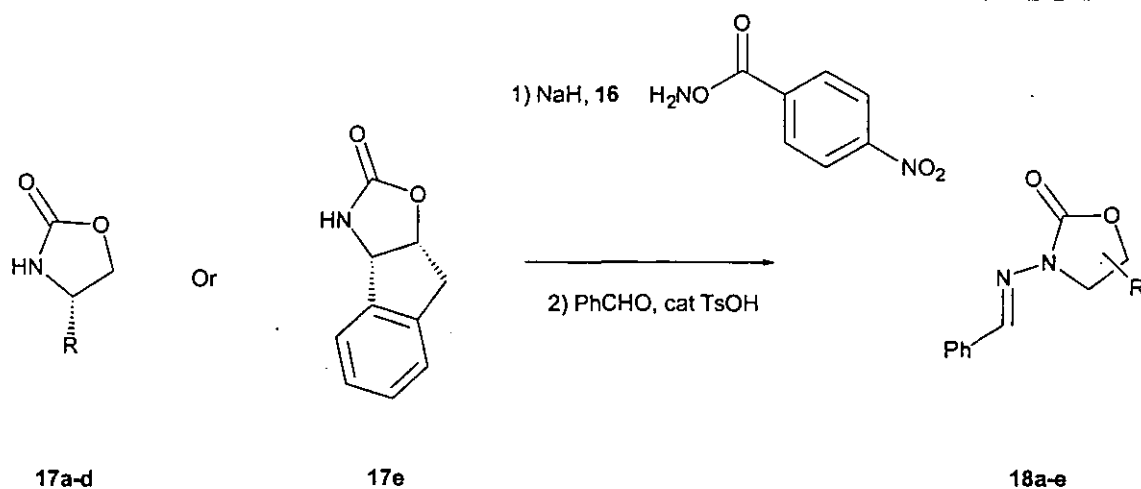


| Aminating agent | Imide 14<br>T°C, time, (yield/%) | Imide 15<br>T°C, time, (yield/%) |
|-----------------|----------------------------------|----------------------------------|
| 13a             | 72°C, 2h, (75)                   | 72°C, 2h, (79)                   |
| 13b             | 72°C, 2h, (74)                   | 72°C, 2h, (62)                   |
| 13c             | 50°C, 3.5h, (62)                 | 50°C, 3h, (51)                   |
| 13d             | 50°C, 3h, (47)                   | 50°C, 3h, (59)                   |

Scheme 21: Amination of quinazoline-2,4-dione.

#### 1.1.4.3 *O*-Acyl hydroxylamines

*O*-Acyl hydroxylamines have also been reported to react with certain nucleophiles.<sup>20</sup> Friestad have shown that the use of *O*-(*p*-nitrobenzoyl) hydroxylamine (16) and sodium hydride in dioxane was a good combination for the amination of 2-oxazolidinones (Scheme 22).<sup>22</sup>

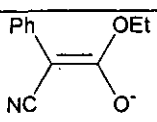
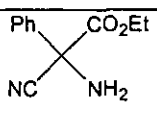
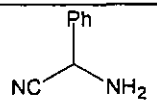


| Substrate 17a-e                 | Product 18a-e yield/% |
|---------------------------------|-----------------------|
| <b>a</b> R = CH <sub>2</sub> Ph | 80                    |
| <b>b</b> R = CHPh <sub>2</sub>  | 68                    |
| <b>c</b> R = CHMe <sub>2</sub>  | 45                    |
| <b>d</b> R = Ph                 | 95                    |
| <b>e</b>                        | 92                    |

Scheme 22: Amination of 2-oxazolidinones

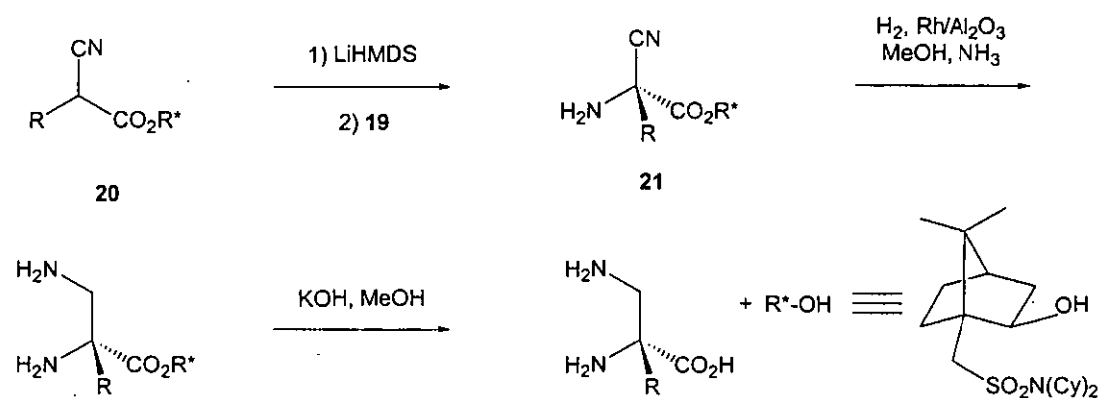
### 1.1.5 *O*-Phospinoyl Hydroxylamines

*O*-(Diphenylphospinoyl) hydroxylamine (19) aminates a number of nucleophiles including metal amides, alkyl and acyl Grignard reagents, lithium and boron enolates and doubly activated enolate compounds (Scheme 23).<sup>43</sup>

| $\text{RM} \xrightarrow[\text{THF, -20}^\circ\text{C}]{19, \text{Ph}_2\text{PO-O-NH}_2} \text{RNH}_2$ |   |         |
|---|---|---------|
| RM  | Product   | Yield/% |
| PhMgBr  | PhNH <sub>2</sub>   | 22      |
| (Ph(CH <sub>2</sub> ) <sub>2</sub> ) <sub>3</sub> B   | Ph(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>                                 | 36      |
|                      |  | >96     |
| PhCH <sub>2</sub> Li  | PhCH <sub>2</sub> NH <sub>2</sub>   | 30      |
| PhCHCN, Li  |  | 37      |

**Scheme 23:** Amination with *O*-(diphenylphosphinoyl) hydroxylamine

Badorrey has synthesized a variety of 2-alkyl-2,3 diaminopropionic acids using chiral 2-cyanopropanoates and (19) (Scheme 24).<sup>44</sup>



| R   | Yield (21/%) <sup>a</sup> | Yield (21/%) <sup>b</sup> | Isomer Ratio | Absolute configuration |
|---|---------------------------|---------------------------|--------------|------------------------|
| CH <sub>3</sub>                                   | 87                        | 67                        | 78/22        | R                      |
| CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>   | 84                        | 64                        | 76/24        | R                      |
| (CH <sub>3</sub> ) <sub>2</sub> CH                | 78                        | 60                        | 70/30        | R                      |
| (CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> | 84                        | 61                        | 77/23        | R                      |
| C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>     | 91                        | 70                        | 80/20        | R                      |

a : crude, b : isolated major diastereoisomer.

**Scheme 24:** Amination of chiral 2-cyanopropanoates

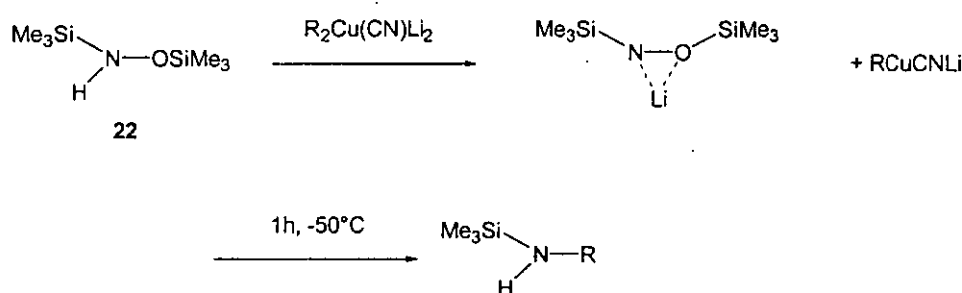
The formation of 2-amino-2-cyanopropanoates occurs in good yield and acceptable diastereoselectivity using lithium amide as base. In this case the source of chirality,<sup>45</sup> the bornane skeleton, is attached to the carbanions.

A chiral *O*-(phospinoyl) hydroxylamine derived from ephedrine has been developed and reacted with a variety of nucleophiles in poor to moderate yields.<sup>46</sup>

### 1.1.6 *O*-Trimethylsilyl hydroxylamines derivatives

#### 1.1.6.1 *N*-*O* bis-trimethylsilyl hydroxylamine

*N*-*O* bis-Trimethylsilyl hydroxylamine (**22**) reacts with higher order cuprates in good yield. These cuprates provide the base for the deprotonation as well as the ligand to transfer to the nitrogen atom (Scheme 25).

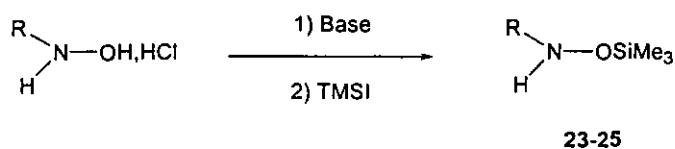


| Cuprate   | Product                                | Yield/% |
|---|--|---------|
| $\text{Ph}_2\text{CuCNLi}_2$                    | $\text{PhNH}_2$                        | 90      |
| $(4\text{-MeOC}_6\text{H}_4)_2\text{CuCNLi}_2$  | $4\text{-MeOC}_6\text{H}_4\text{NH}_2$ | 70      |
| $\left(\text{Indole}\right)_2\text{CuCNLi}_2$   | $\text{Indole-2-NSiMe}_3$              | 70      |
| $\left(\text{Pyridine}\right)_2\text{CuCNLi}_2$ | $\text{Pyridine-3-NH}_2$               | 58      |

**Scheme 25:** Amination of higher order cuprates with *N*-*O* bis-trimethylsilyl hydroxylamine

### 1.1.6.2 *N*-Alkyl-*O*-silyl hydroxylamine

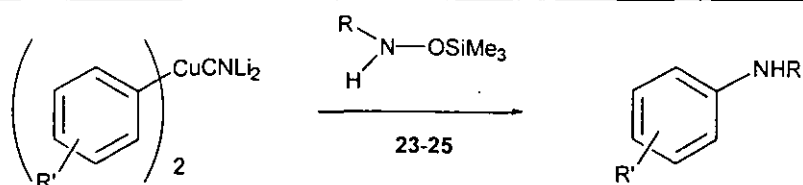
*N*-Methyl, *N*-isopropyl, and *N*-tert-butyl-*O*-silyl hydroxylamines were obtained using 1-trimethyl silyl imidazole as silylating agent with the corresponding alkyl hydroxylamines (Scheme.26).<sup>47</sup>

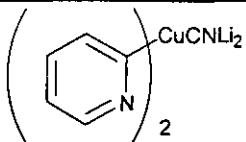
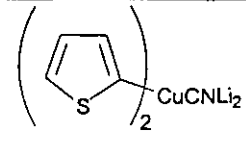


| R                      | Base                     | Yield/% |
|------------------------|--------------------------|---------|
| Me <b>23</b>           | 2,4,6-trimethyl pyridine | 68      |
| <i>i</i> -Pr <b>24</b> | Et <sub>3</sub> N        | 80      |
| <i>t</i> -Bu <b>25</b> | Et <sub>3</sub> N        | 77      |

**Scheme 26:** Formation of *N*-alkyl-*O*-silyl hydroxylamines

Compounds (23-25) react under mild condition with aryl- and heteroaryl-cyanocuprates in satisfactory to good yield (Scheme 27).



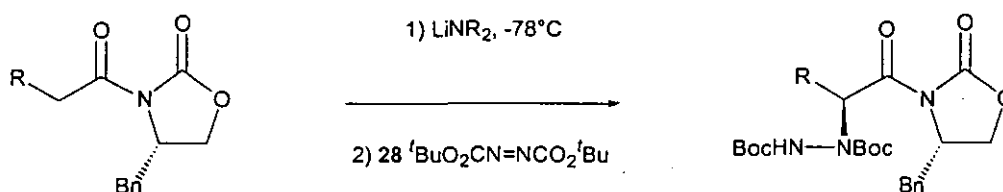
| Aminating agents | R            | R'  | Yield/% |
|------------------|--------------|---|---------|
| 23               | Me           | H   | 58      |
| 23               | Me           | <i>p</i> -Me  | 57      |
| 23               | Me           | <i>m</i> -OMe   | 59      |
| 23               | Me           | <i>p</i> -OMe   | 88      |
| 24               | <i>i</i> -Pr | H   | 64      |
| 24               | <i>i</i> -Pr | <i>p</i> -Me  | 67      |
| 24               | <i>i</i> -Pr | <i>m</i> -OMe   | 74      |
| 24               | <i>i</i> -Pr | <i>p</i> -F   | 45      |
| 25               | <i>t</i> -Bu | H   | 53      |
| 25               | <i>t</i> -Bu | <i>p</i> -Me  | 65      |
| 25               | <i>t</i> -Bu | <i>m</i> -OMe   | 73      |
| 25               | <i>t</i> -Bu | <i>p</i> -F   | 45      |
| 23               | Me           | 26  | 65      |
| 24               | <i>i</i> -Pr | 26  | 68      |
| 25               | <i>t</i> -Bu | 26  | 72      |
| 23               | Me           | 27  | 60      |
| 24               | <i>i</i> -Pr | 27  | 65      |

**Scheme 27:** Amination of higher order cuprates with *N*-alkyl-*O*-silyl hydroxylamines

This methodology permitted the synthesis of *N*-*tert*-butyl amino-pyridine and 2-(*N*-alkylamino)-thiophene derivatives.

### 1.1.7 Amination with dialkyl azodicarboxylates

Di-*tert*-butyl azodicarboxylate (**28**), by far the most employed of this family, reacts under mild conditions with carbon nucleophiles.<sup>48</sup> Moreover, (**28**) has been used for diastereoselective electrophilic amination. Dialkyl azodicarboxylates react with metal enolates derived from *N*-acyl oxazolidinones to provide the hydrazide adducts in excellent selectivity and yields.<sup>49,50</sup> The diastereoisomeric ratios were improved by increase of the bulkiness of the dialkyl substituent of the azocarboxylates. The use of the more hindered di-*tert*-butyl azodicarboxylate (**28**) DBAD gave good yields and excellent diastereoselectivities (**Scheme 28**)

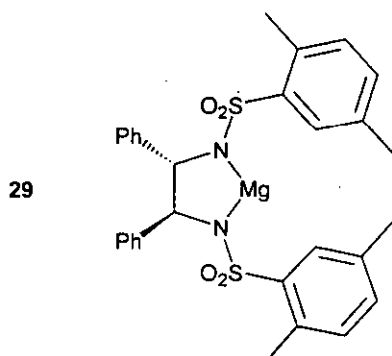
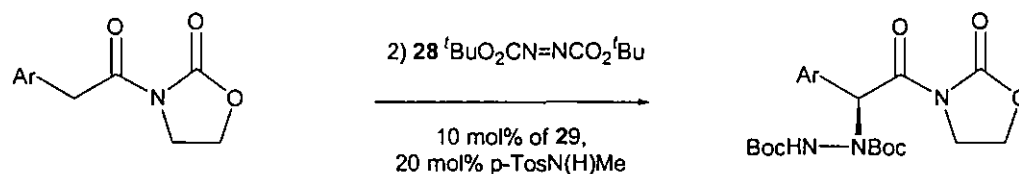


| R               | Product yield/% | Dr 2S:2R |
|-----------------|-----------------|----------|
| Me              | 92              | 98:2     |
| Allyl           | 94              | 98:2     |
| Bn              | 91              | 97:3     |
| Ph              | 96              | 97:3     |
| <sup>t</sup> Pr | 95              | 98:2     |
| <sup>t</sup> Bu | 96              | >99:1    |

**Scheme 28:** Diastereoselective amination using di-*tert*-butyl azodicarboxylate

The chiral oxazolidinones were removed either by hydrolysis, methanolysis or transesterification.<sup>49,50</sup> The conversion of the  $\alpha$ -hydrazido derivatives to  $\alpha$ -amino esters proceeded by the removal of the Boc groups, then cleavage of the *N-N* bond by hydrogenolysis over Raney nickel to generate the  $\text{NH}_2$  functionality without detectable racemization.<sup>51</sup>

Evans and Nelson demonstrated that a small amount of base such as  $\text{La}(\text{O}^t\text{Bu})_3$  or  $\text{NaO}^t\text{Bu}$  could catalyse the reactions and discovered that the hydrazide conjugate base is strong enough to catalysed the process.<sup>52</sup> Moreover the addition of 5 nmol% of a metallo-bis-sulfonamide complex (**29**) gave high yields and high stereoselectivities (**Scheme 29**).



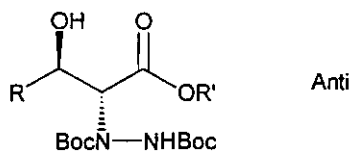
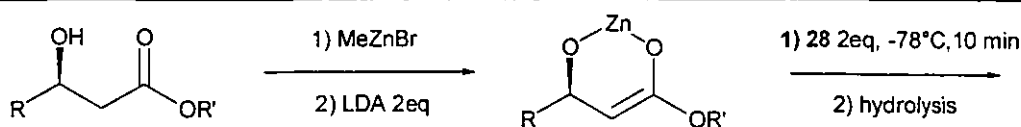
| Ar  | Reaction time/h,<br>(Temp °C) | 2S:2R ratio (yield/%) | ee <sup>a</sup> /% |
|---|-------------------------------|-----------------------|--------------------|
| C <sub>6</sub> H <sub>5</sub>                             | 48 (-75)                      | 93:7 (92)             | > 99               |
| <i>p</i> -F-C <sub>6</sub> H <sub>4</sub>                 | 48 (-65)                      | 95:5 (97)             | > 99               |
| <i>p</i> -CH <sub>3</sub> O-C <sub>6</sub> H <sub>4</sub> | 48 (-65)                      | 93:7 (93)             | 99                 |
|   | 72 (-75)                      | 91:9 (85)             | > 99               |
|   | 60 (-75)                      | 90:10 (84)            | 97                 |
|   | 48 (-65)                      | 91:9 (87)             | 96                 |

<sup>a</sup> Values reported are those for recrystallised hydrazides

**Scheme 29:** Diastereoselective amination using di-*tert*-butyl azodicarboxylate catalysed by (**29**)

This methodology was applied to the anti-diastereoselective amination of  $\beta$  hydroxy-esters.<sup>53</sup> The best results were obtained with zinc enolates prepared from methyl zinc bromide, two equivalents of base, and (**28**). The reaction occurred smoothly with no trace of the syn-diastereoisomer (**Scheme 30**).<sup>31</sup>

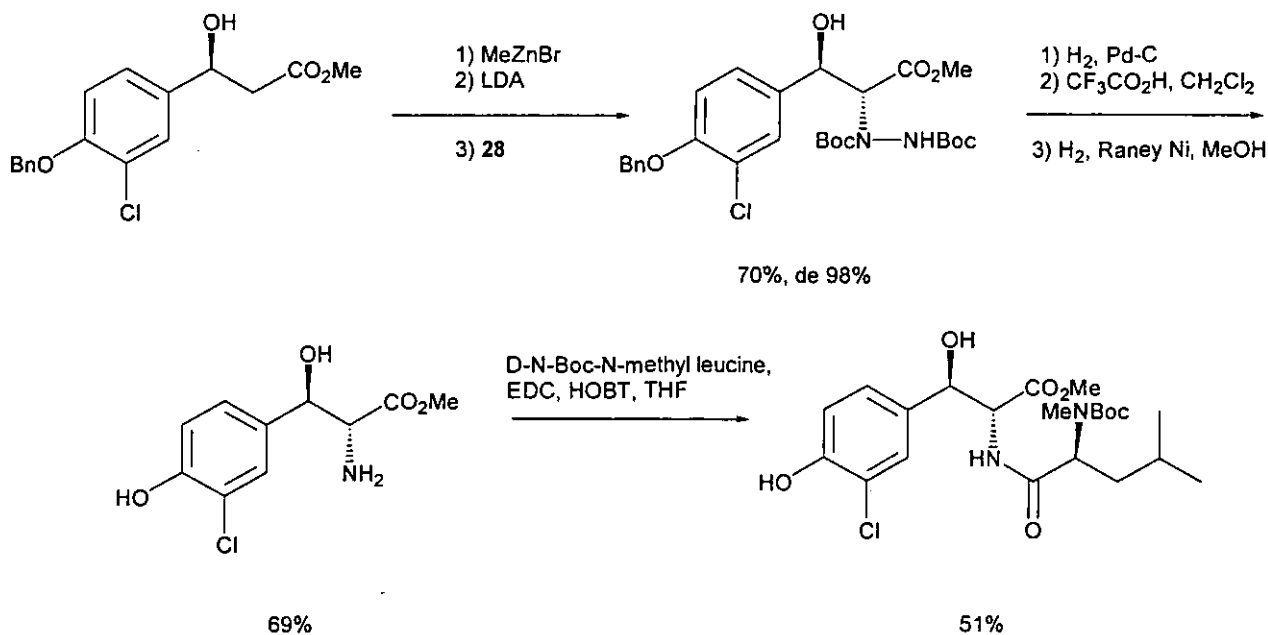




| R                              | R'                            | Yield/% |
|--------------------------------|-------------------------------|---------|
| CH <sub>3</sub>                | C <sub>2</sub> H <sub>5</sub> | 67      |
| C <sub>2</sub> H <sub>5</sub>  | CH <sub>3</sub>               | 60      |
| C <sub>5</sub> H <sub>11</sub> | CH <sub>3</sub>               | 66      |
| C <sub>6</sub> H <sub>5</sub>  | C <sub>2</sub> H <sub>5</sub> | 69      |

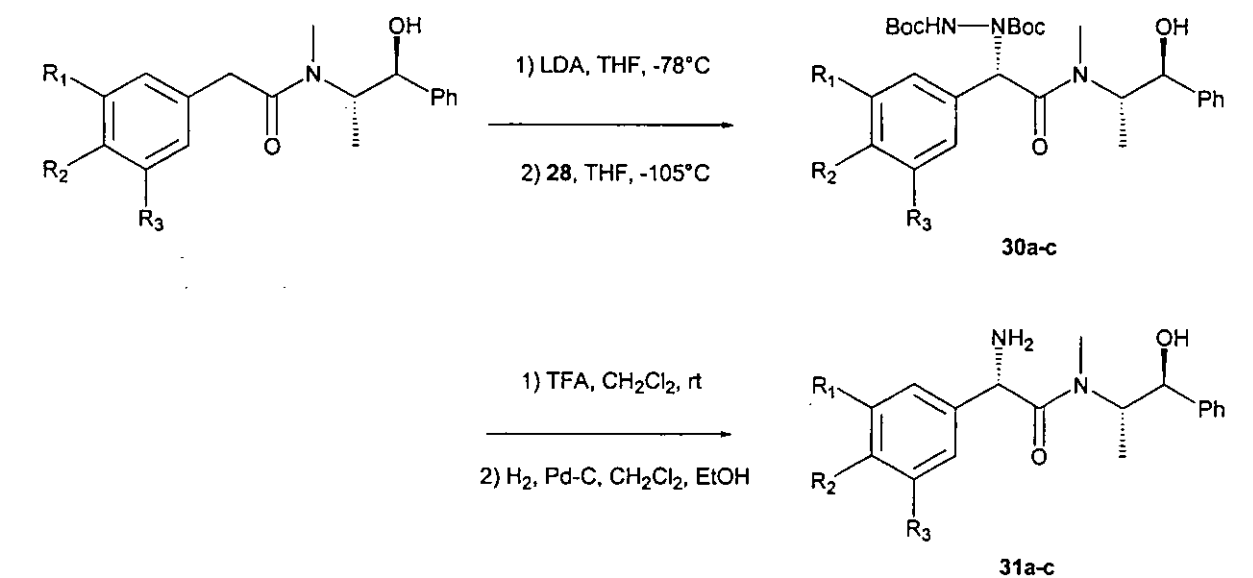
**Scheme 30:** Diastereoselective amination of zinc enolates with **27**

Synthesis of (2S,2R)-3-chloro-*p*-hydroxytyrosine, the east part of the antibiotic vancomycin proved the potential of this approach (**Scheme 31**).



**Scheme 31:** Synthesis of the East Part of Vancomycin

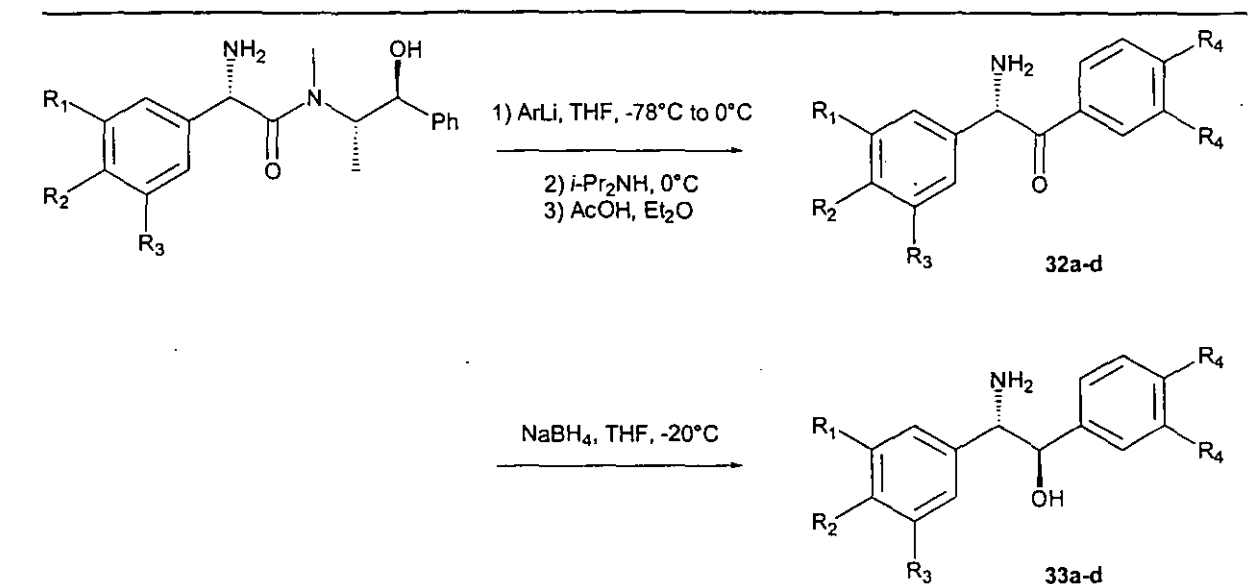
Furthermore, this straightforward procedure proved to be successful for the synthesis of 1,2-diaryl-2-amino ethanol. Aryl acetamides attached to chiral auxiliary derived from (S, S)-(+)-pseudoephedrine were aminated in good yield with (28) (Scheme 32).<sup>54</sup>



| R <sub>1</sub>     | R <sub>2</sub> | R <sub>3</sub> | 30a-c    | Yield/% | Isomers ratio | 31a-c    | Yield/% |
|--------------------|----------------|----------------|----------|---------|---------------|----------|---------|
| OMe                | OMe            | OMe            | <b>a</b> | 90      | >95:5         | <b>a</b> | 78      |
| OCH <sub>2</sub> O |                | H              | <b>b</b> | 91      | >95:5         | <b>b</b> | 79      |
| OMe                | OMe            | H              | <b>c</b> | 89      | >95:5         | <b>c</b> | 78      |

**Scheme 32:** Amination of chiral aryl acetamides

The 1,2 addition of aryl-lithium reagent to (31a-c) was followed by reduction with sodium borohydride. The reduction of the ketone proceeds with anti-diastereoselectivity (Scheme 33).



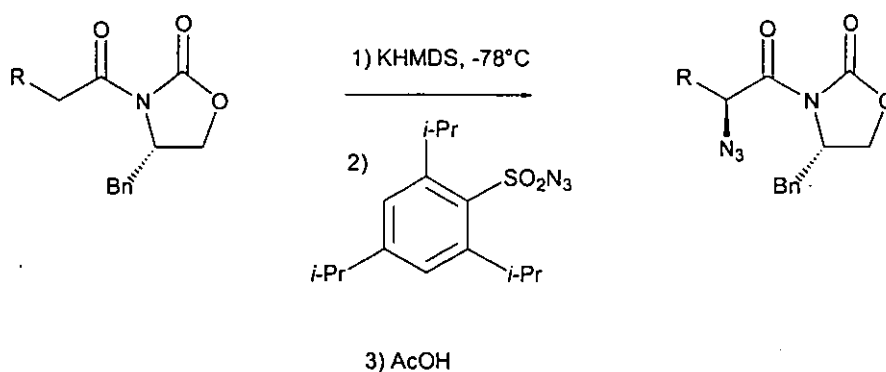
| R <sub>1</sub>     | R <sub>2</sub> | R <sub>3</sub> | R <sub>4</sub> | 32a-d    | Yield/% | 33a-d    | Yield/% | Isomers ratio |
|--------------------|----------------|----------------|----------------|----------|---------|----------|---------|---------------|
| OMe                | OMe            | OMe            | OMe            | <b>a</b> | 82      | <b>A</b> | 83      | >95:5         |
| OCH <sub>2</sub> O |                | H              | OMe            | <b>b</b> | 72      | <b>B</b> | 79      | >95:5         |
| OMe                | OMe            | H              | H              | <b>c</b> | 79      | <b>C</b> | 89      | >95:5         |
| OMe                | OMe            | H              | OMe            | <b>d</b> | 77      | <b>D</b> | 93      | >95:5         |

**Scheme 33:** Formation of 1,2-diaryl-2-aminoethanols

In addition, *N,N*-dimethyl-hydrazones are protected ketone derivatives that have been aminated with (28) in good yield.<sup>55</sup>

### 1.1.8 Electrophilic azide transfer

The use of sulfonyl azides as synthetic equivalents of the  $-N_3^+$  synthon, in reactions with *N*-acyl oxazolidinone enolates was developed by Evans.<sup>56</sup> Different acyl substituents were employed and reactions occurred in high yields and diastereoselectivities (**Scheme 34**). The amino groups were obtained after cleavage of the triazene followed by reduction with H<sub>2</sub>, Pd-C.



| R                                   | Yield/% | Isomers ratio 2S:2R <sup>a</sup> |
|-------------------------------------|---------|----------------------------------|
| CH <sub>3</sub>                     | 74      | 97:3                             |
| CH <sub>3</sub> -CH=CH <sub>2</sub> | 78      | 97:3                             |
| CH <sub>2</sub> -Ph                 | 91      | 97:3                             |
| Ph                                  | 82      | 91:9                             |
| CHMe <sub>2</sub>                   | 77      | 98:2                             |
| CMe <sub>3</sub>                    | 90      | >99:1                            |

<sup>a</sup> Ratio determined by NMR Spectroscopy

**Scheme 34:** Electrophilic azide transfer

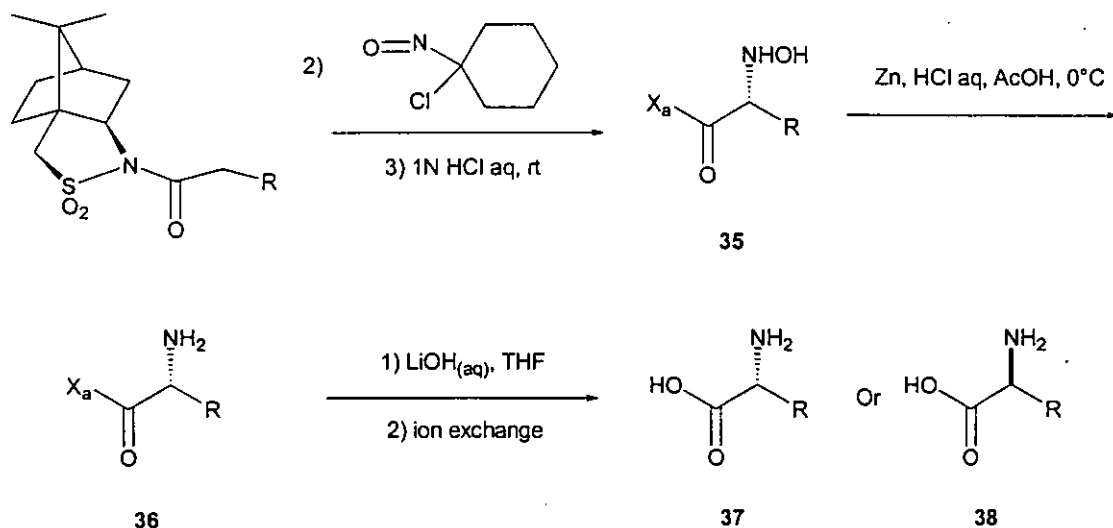
The cleavage of the oxazolidinones with lithium hydroxide or hydrogen peroxide was reported to occur without any racemization.

Hanessian described the azide transfer to chiral  $\alpha$ -alkyl phosphonamides in moderate to excellent yield and stereoselectivity,<sup>57</sup> and Denmark the transfer to chiral phosphorinanes.<sup>58</sup>

Another approach developed by Hoffman's group consists of the amination of chiral nucleophiles with retention of configuration.<sup>59</sup> The Grignard reagents bearing the chirality was generated from enantiomerically pure  $\alpha$ -chlorosulfoxide with ethyl magnesium bromide. The reaction with azidomethyl-phenyl sulfide (**34**) was quenched with acetic anhydride.<sup>60</sup> The crude acetyltriazene was cleaved with potassium hydroxide in 82% yield overall and 92% enantiomeric excess (**Scheme 35**).



1) NaHMDS

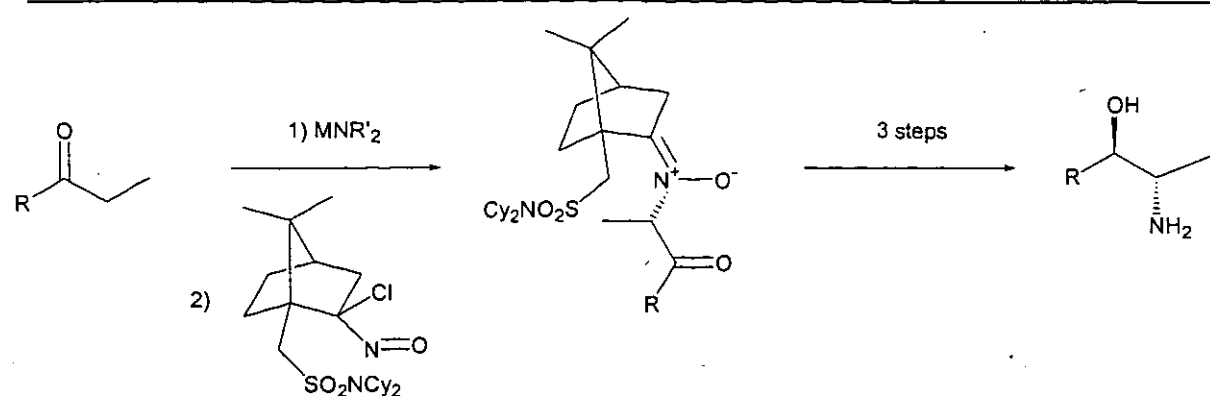


| R                                       | Amino Acids                |               |          |         |       |                     |
|---|----------------------------|---------------|----------|---------|-------|---------------------|
|   | Yield/% <sup>a</sup><br>35 | Yield/%<br>36 | 37 or 38 | Yield % | e.e/% | Absolute<br>Config. |
| CH <sub>3</sub>                         | 87 (80)                    | 83            | 37       | > 99    | > 99  | R                   |
| CH <sub>3</sub>                         | 88 (82)                    | 78            | 38       | 99      | > 99  | S                   |
| CH <sub>2</sub> =CH-<br>CH <sub>2</sub> | 88 (69)                    | 78            | 37       | > 99    | > 99  | R                   |
| Me <sub>2</sub> CH                      | 82 (70)                    | 85            | 37       | > 99    | > 99  | R                   |
| Me <sub>2</sub> CH-<br>CH <sub>2</sub>  | 97 (87)                    | 97            | 37       | > 99    | 99    | R                   |
| Ph-CH <sub>2</sub>                      | 91 (78)                    | 93            | 37       | 94      | > 99  | R                   |
| Ph                                      | 88 (77)                    | 95            | 37       | 97      | > 99  | R                   |
| <i>p</i> -MeOPh                         | - (72)                     | 84            | 37       | 97      | > 99  | R                   |
| <i>p</i> -MeOPh                         | 81 (73)                    | 90            | 38       | 99      | > 99  | S                   |

<sup>a</sup> Yields in parenthesis after crystallization (hexane/EtOAc)**Scheme 36:** Amination of *N*-acylbornylsultams.

The use of the other enantiomer of camphorsultam provides the opposite amino-acids.

Chiral  $\alpha$ -chloronitroso camphorsulfonamides prepared from oximes with *tert*-butyl hypochlorite have also been used for the amination of ketones (**Scheme 37**).<sup>62</sup>



| R  | M  | Isomers ratio<br>(nitronium) | Yield/%<br>(aminol) | Ratio<br>syn/anti | Ee aminol% |
|--|----|------------------------------|---------------------|-------------------|------------|
| Me   | Zn | <1:99                        | 68                  | 95:5              | 96         |
| 2,5-<br>(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> | Na | <1:99                        | 57                  | 90:10             | >99        |
| <sup>t</sup> Bu  | Zn | 5:95                         | 54                  | >99.9 :0.1        | >99.9      |
| <sup>i</sup> Pr  | Zn | 5:95                         | 65                  | 98:2              | >99.9      |
| Et   | Zn | 5:95                         | 65                  | 90:10             | 98.2       |

**Scheme 37:** Amination of ketones with chiral  $\alpha$ -nitroso camphorsulfonamides.

## 1.2 Electrophilic amination with oxaziridines

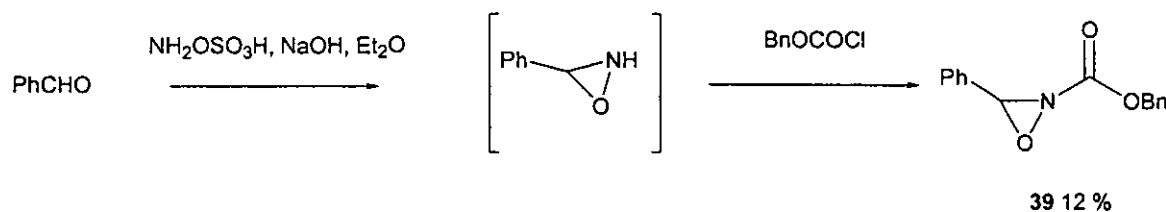
Oxaziridines are three membered rings compounds containing two heteroatoms. This strained heterocycle is remarkably reactive and the relative weak N-O bond makes oxaziridines powerful oxygenating and aminating reagents. Two groups of oxaziridines are able to transfer nitrogen to nucleophiles: *N*-acyl-oxaziridines and *N*-unsubstituted oxaziridines. In contrast *N*-sulfonyl oxaziridines are known for their ability to transfer oxygen.

### 1.2.1 *N*-protected oxaziridines

#### 1.1.2.1 Synthesis

*N*-Acyl oxaziridines can be prepared by acylation of the corresponding *NH*-oxaziridines,<sup>63</sup> or by oxidation of *N*-protected imines. The first method leads to poor yields.

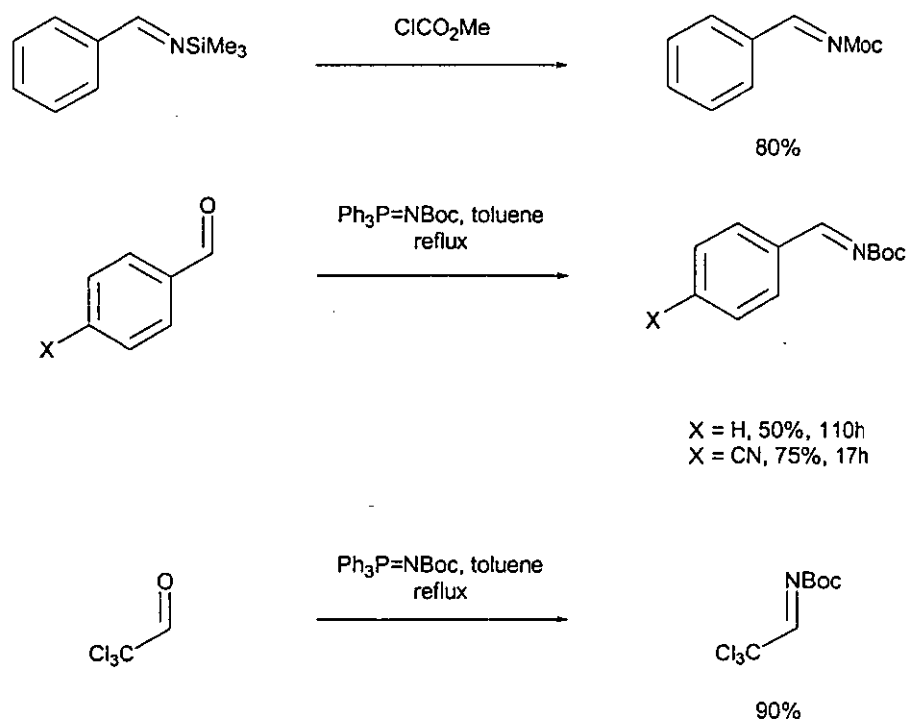
The reaction of benzaldehyde with hydroxylamine-*O*-sulfonic acid followed by direct acylation with benzyl chloroformate affords the oxaziridine (**39**) in 12% overall yield (**Scheme 38**).



**Scheme 38:** Acylation of *NH*-oxaziridine

The second method requires the preparation of *N*-protected imines. *N*-Moc protected imines were obtained by acylation of the corresponding *N*-silyl imines (**Scheme 39**).<sup>64</sup>

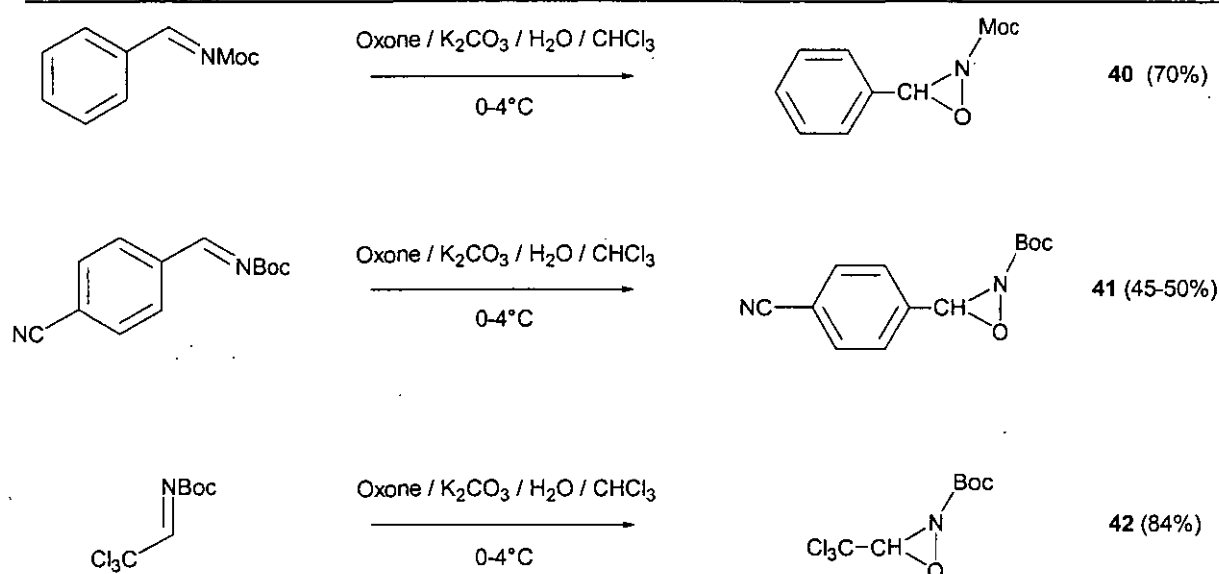
A general procedure widely employed for the formation of *N*-Boc imines consists of an aza-Wittig reaction using *N*-Boc triphenyliminophosphorane (**Scheme 39**).<sup>65</sup>



**Scheme 39:** Formation of *N*-protected imines

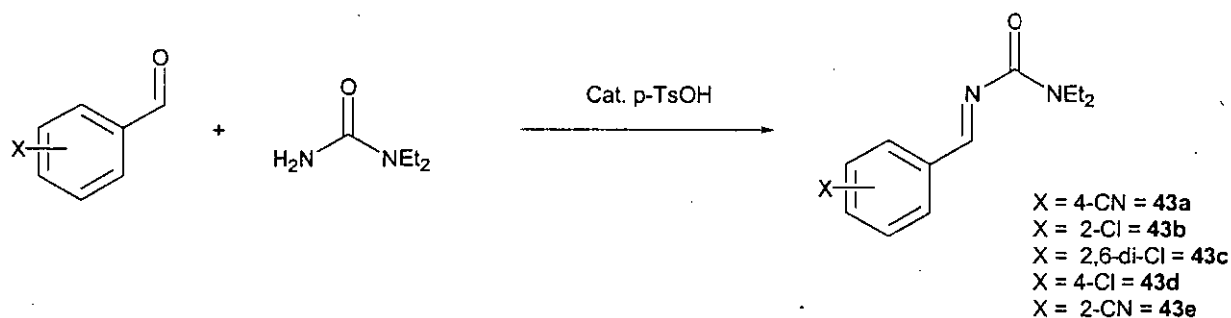
Vidal and Collet reported the use of oxone for the oxidation of the *N*-protected imines. *N*-Moc and *N*-Boc oxaziridines (**40**, **41**, **42**) were produced in moderate to good yields (**Scheme 40**).





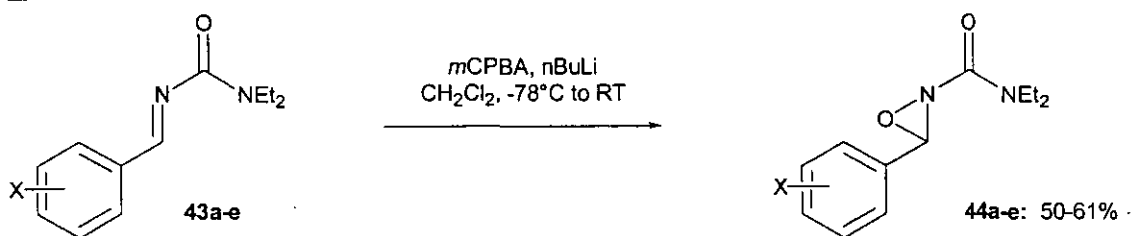
**Scheme 40:** Oxidation of *N*-protected imines with oxone

*N*-Carboxamido imines were prepared by condensation of 1,1-diethyl urea with aromatic aldehydes (**Scheme 41**).<sup>66</sup>



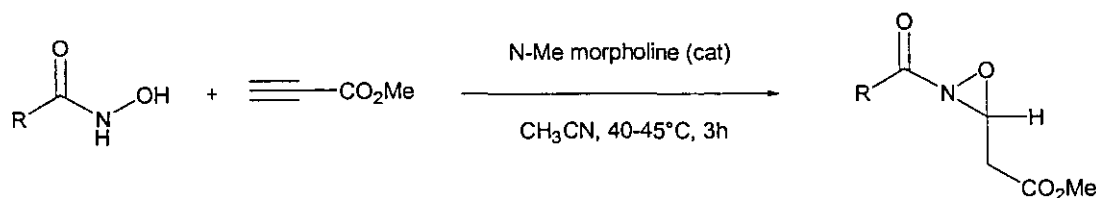
**Scheme 41:** Synthesis of *N*-carboxamido imines

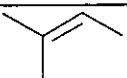
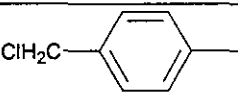
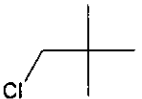
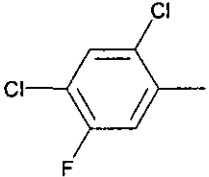
*N*-Carboxamido imines (**43a-e**) were oxidized to oxaziridines (**44a-e**) in 50-61% yields from the corresponding aryl aldehydes. The reaction proceeds in dichloromethane using *m*-CPBA and butyl lithium (**Scheme 42**). *n*-BuLi was used to form the conjugate base of the peracid under aprotic conditions.

**Scheme 42:** Oxidation of 43a-e

Schmitz reported the synthesis of 2-carbamoyl oxaziridines from *NH*-oxaziridines solutions by acylation with acetanhydride<sup>67</sup> or isocyanates<sup>68</sup> in moderate yields

Ryu, Shin and Zong produced a series of *N*-acyl-oxaziridines,<sup>69</sup> by tandem *O,N* addition of hydroxamic acids to methyl propiolate in presence of a catalytic amount of *N*-methyl morpholine (Scheme 43).



| R   | Yield/% | R   | Yield/% |
|---|---------|---|---------|
| Bu  | 92      | 2,6-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>                                   | 92      |
|  | 91      |  | 90      |
|  | 86      |  | 89      |
| Ph  | 95      | 2-F-C <sub>6</sub> H <sub>4</sub>   | 90      |

**Scheme 43:** Formation of *N*-acyl oxaziridines by *O,N* addition

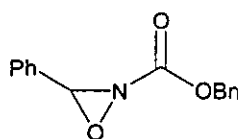
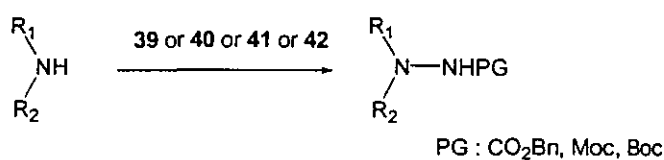
It is suggested that the hydroxyl group of the hydroxamic group is added to methyl propiolate in a 1,4 addition type reaction followed by intramolecular cyclization by the amino group to form the *N*-acyloxaziridines.

*N*-Protected oxaziridines exist as a mixture of *trans* and *cis* isomers at the nitrogen atom, normally pyramidal inversion at nitrogen are fast, this is possible in the case of oxaziridines due to the ring strain. Ratios are for examples: (9/1) for *N*-benzyloxycarbonyl-3-phenyloxaziridine (39), (88:12) for (41), (9:1) for *N*-Boc-3-(4-cyanophenyl)oxaziridine (42) and (92:8) for some of the *N*-carboxamido oxaziridines (44a-e).

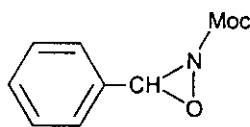
### 1.2.1.2 Reactivity of *N*-protected oxaziridines

#### 1.2.1.2.1 Amination of nitrogen nucleophiles

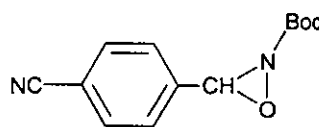
Primary and secondary amines were smoothly aminated by oxaziridines (39, 40, 41 and 42) to produce *N*-protected hydrazines (Scheme 44).



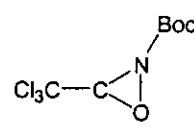
39



40

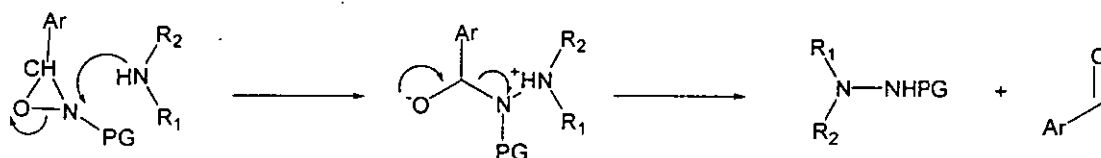


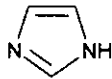
41



42

Postulated mechanism



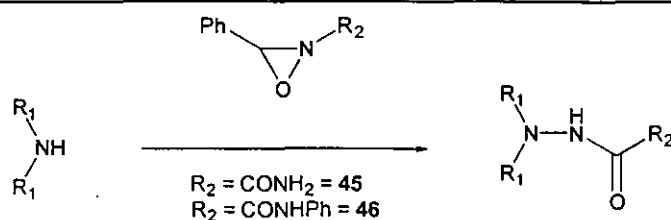
| Amines  | Oxaziridines | Yield/%      |
|---|--------------|--------------|
| N-benzyl-L-Serine ( $\text{Me}_4\text{N}^+$ salt)                                 | 39           | 41           |
| O-benzyl-L-Serine ( $\text{Me}_4\text{N}^+$ salt)                                 | 39           | 55           |
| L-Tryptophan ( $\text{Et}_4\text{N}^+$ salt)                                      | 39           | 54           |
| 2-Phenylethylamine  | 39           | 64           |
| Piperidine  | 39           | 90           |
| Morpholine  | 40           | Not detected |
|  | 40           | 76           |
| Phenylamine   | 40           | 75           |
| Morpholine  | 41           | 90           |
| Morpholine  | 42           | Quantitative |
| (-) Ephedrine   | 41           | 70           |
| Proline( $\text{BnMe}_3\text{N}^+$ salt)  | 41           | 77           |
| Alanine methyl ester  | 41           | 67           |
| Valine methyl ester   | 40           | 57           |
| Valine methyl ester   | 41           | 44           |
| Valine methyl ester   | 42           | 56           |
| Phenylalanine ( $\text{Me}_4\text{N}^+$ salt)                                     | 39           | 76           |
| Phenylalanine ( $\text{BnMe}_3\text{N}^+$ salt)                                   | 41           | 41           |

Scheme 44: Synthesis of *N*-protected hydrazines

Primary amines lead to lower yields due to a competing side reaction. Aryl-aldehydes released during the process react with primary amines to give Schiff's bases.

Proline, alanine, phenylalanine, valine, serine and tryptophan were used in this reaction as their benzyl-trimethylammonium, tetramethylammonium or tetraethylammonium salts soluble in chloroform.

In the same way 2-carbamoyl oxaziridines react smoothly with amines to give semicarbazides (Scheme 45).<sup>68</sup>

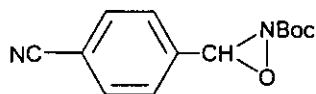
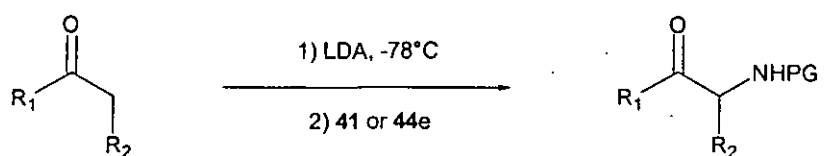
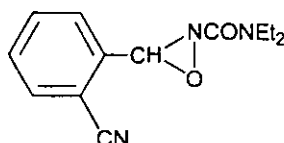


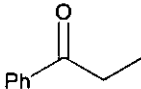
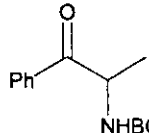
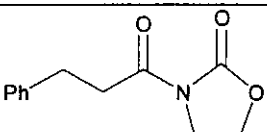
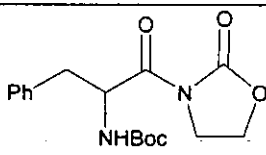
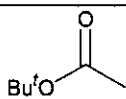
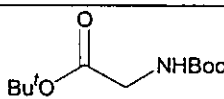
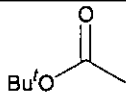
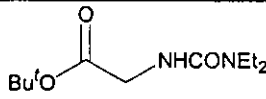
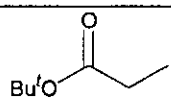
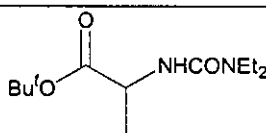
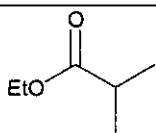
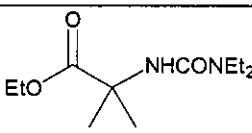
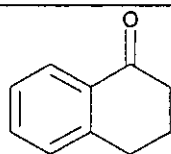
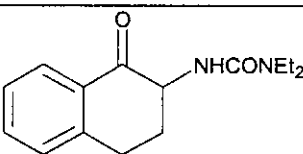
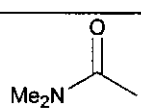
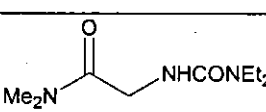
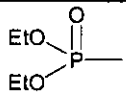
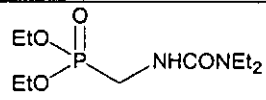
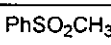

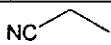
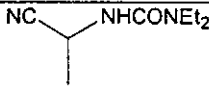
| Oxaziridines | $R_1$                                    | Yield/% |
|--------------|--|---------|
| <b>45</b>    | H  | 61      |
| <b>45</b>    | <i>c</i> -C <sub>6</sub> H <sub>11</sub> | 85      |
| <b>46</b>    | -(CH <sub>2</sub> ) <sub>5</sub> -       | 70      |
| <b>46</b>    | <i>c</i> -C <sub>6</sub> H <sub>11</sub> | 61      |

Scheme 45: Formation of semicarbazides

#### 1.2.1.2.2 Amination of carbon nucleophiles

*N*-Boc, *N*-Moc and *N*-carboxamido oxaziridines are capable of nitrogen transfer under mild conditions to: ketones, esters and amide enolates, as well as sulfone phosphonate and nitrile stabilized carbanions (Scheme 46).<sup>64,65,66</sup>

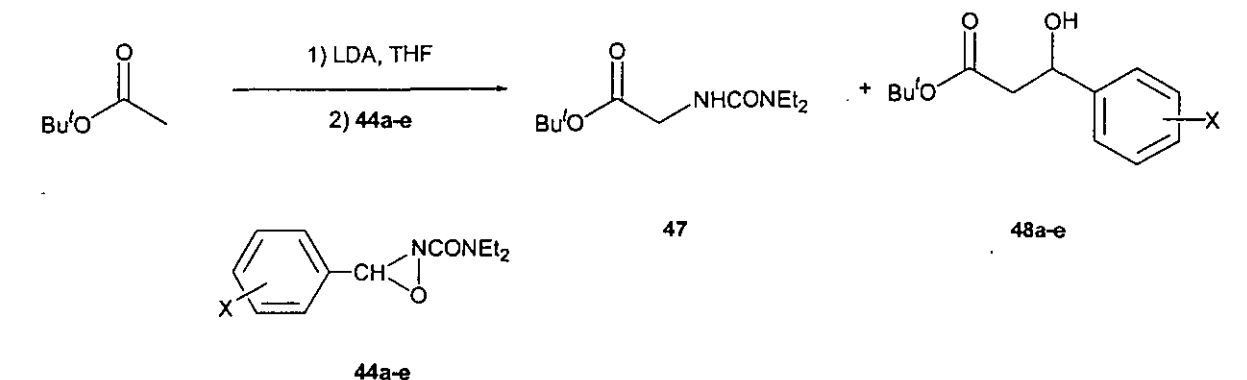
**41****44e**

| Substrates  | Oxaziridines | Products   | Yield/% |
|---|--------------|--|---------|
|    | <b>41</b>    |     | 38      |
|    | <b>41</b>    |    | 33      |
|    | <b>41</b>    |     | 35      |
|    | <b>44e</b>   |    | 55      |
|    | <b>44e</b>   |    | 55      |
|   | <b>44e</b>   |    | 53      |
|  | <b>44e</b>   |  | 60      |
|  | <b>44e</b>   |  | 59      |
|  | <b>44e</b>   |  | 51      |
|  | <b>44e</b>   |   | 43      |
|  | <b>44e</b>   |   | 56      |

Scheme 46: Amination of carbon nucleophiles

These aminations occurred in moderate to low yields. This is again due to the condensation of the enolate with the aryl-benzaldehyde released during the process in an aldol reaction.

Armstrong studied the effects that substitution on the aromatic ring of the oxaziridines **44a-e** had on the aldol condensation side reaction (Scheme 47).<sup>66</sup>



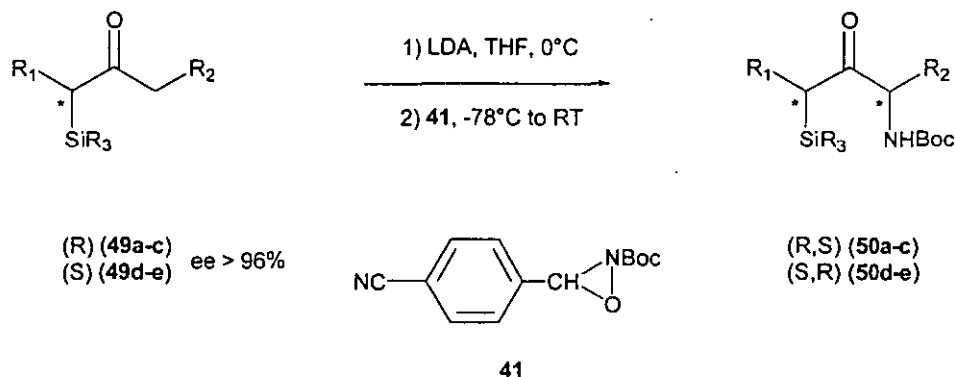
| Oxaziridine | X         | <b>47</b> yield/% | <b>48a-e</b> yield/% |
|-------------|-----------|-------------------|----------------------|
| <b>44a</b>  | 4-CN      | 39                | 20                   |
| <b>44b</b>  | 2-Cl      | <sup>a</sup>      | <sup>a</sup>         |
| <b>44c</b>  | 2,6-di-Cl | <sup>a</sup>      | <sup>a</sup>         |
| <b>44d</b>  | 4-Cl      | 31                | 10                   |
| <b>44e</b>  | 2-CN      | 55                | 7                    |

<sup>a</sup> no reaction observed

**Scheme 47:** Effects of aryl-substitution on the aldol condensation side reaction

The results show that a cyano group on the *ortho*-position reduces the competing aldol condensation in favour of the electrophilic amination.

Enders described the stereoselective synthesis of *N*-Boc  $\alpha$ -aminoketones.<sup>70</sup> Enantiopure  $\alpha$ -silyl ketones were aminated with oxaziridine (**41**) in moderate to poor yields, but with good stereoselectivities (Scheme 48).



| 49a-d    | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub>      | Yield/% | d.e./% |
|----------|----------------|----------------|---------------------|---------|--------|
| <b>a</b> | Me             | Me             | Me <sub>2</sub> Bu  | 27      | 80     |
| <b>b</b> | Et             | Et             | Me <sub>2</sub> Bu  | 37      | 87     |
| <b>c</b> | <i>n</i> -Pr   | <i>n</i> -Pr   | Me <sub>2</sub> Bu  | 29      | 88     |
| <b>d</b> | Bn             | Me             | Me <sub>2</sub> Hex | 20      | 83     |
| <b>e</b> | Me             | Bn             | Me <sub>2</sub> Bu  | 19      | 41     |

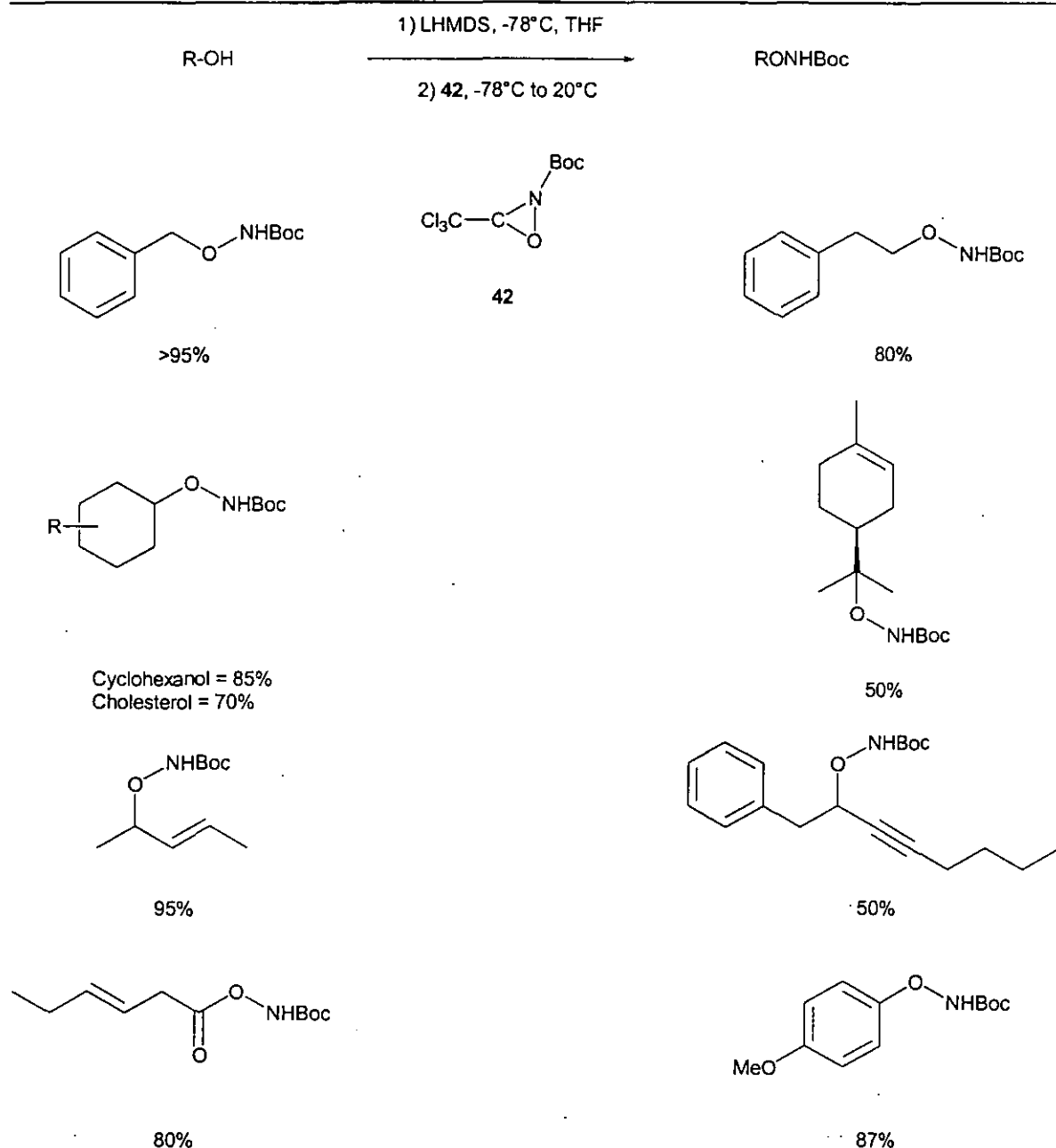
**Scheme 48:** Diastereoselective amination of  $\alpha$ -silyl ketones

Cleavage of the silyl group using TBAF resulted in complete racemisation of the  $\alpha$ -amino ketone. The use of TBAF with a buffer solution of NH<sub>4</sub>F, K<sub>2</sub>PHO<sub>4</sub>, and HF at  $-78\text{ }^{\circ}\text{C}$  to  $-20\text{ }^{\circ}\text{C}$  leads to partial racemisation.

#### 1.2.1.2.3 Amination of oxygen and sulfur nucleophiles

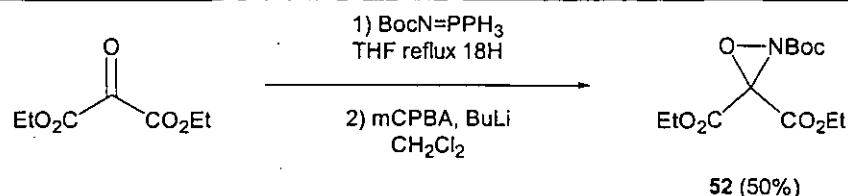
Knight and Foot have shown that a series of lithium alkoxide nucleophiles react with 3-trichloromethyl oxaziridine (**42**) to deliver *N*-protected hydroxylamines in good yields (Scheme 49).<sup>71</sup>



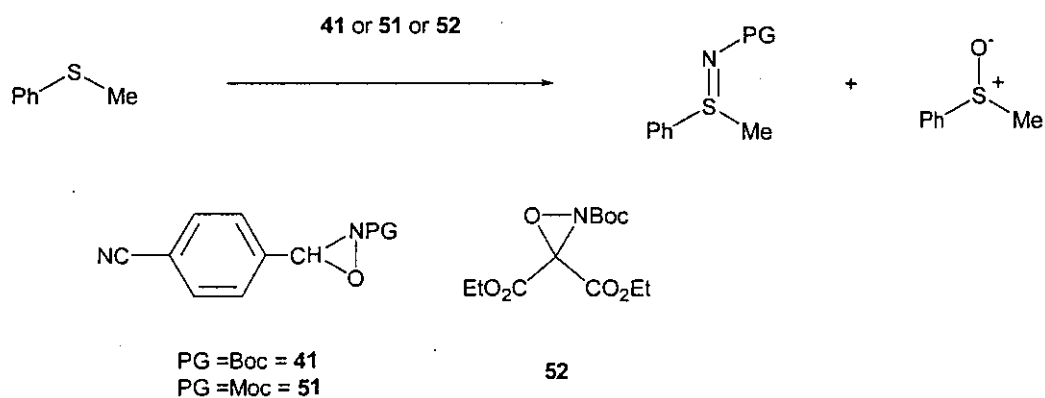


**Scheme 49:** *N*-Boc transfer to lithium alkoxides

Collet and Vidal developed the amination of sulfides with *N*-protected oxaziridines. The reaction occurred with competing oxygen transfer.<sup>72</sup> Armstrong and Cooke synthesised a ketomalonate *N*-alkoxycarbonyl oxaziridine (**52**) which gives a more selective amination of sulfides.<sup>73</sup> Oxaziridine (**52**) was prepared by an aza-Wittig reaction with *N*-Boc-triphenylimino phosphorane, followed by oxidation with *m*-CPBA in the presence of butyllithium (Scheme 50).

**Scheme 50:** Synthesis of oxaziridine **52**

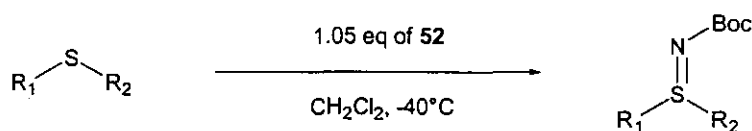
Thioanisole reacts with oxaziridines (**41**) and (**51**) to give a mixture of amination and oxidation products. The ratio in favour of the amination was improved at lower temperatures and by using a more polar solvent. In comparison oxaziridine (**52**) offers a higher level of amination even at 10 °C (**Scheme 51**).



| Oxaziridine | Solvent            | Temp/°C | Amination/Oxidation Ratio |
|-------------|--------------------|---------|---------------------------|
| <b>51</b>   | CDCl <sub>3</sub>  | 19      | 34/66                     |
| <b>51</b>   | CDCl <sub>3</sub>  | -34     | 52/48                     |
| <b>51</b>   | CH <sub>3</sub> CN | -35     | 67/33                     |
| <b>41</b>   | CDCl <sub>3</sub>  | 19      | 27/73                     |
| <b>41</b>   | CH <sub>3</sub> CN | -35     | 62/38                     |
| <b>52</b>   | CDCl <sub>3</sub>  | 10      | 90/10                     |
| <b>52</b>   | CDCl <sub>3</sub>  | 0       | 95/5                      |
| <b>52</b>   | CDCl <sub>3</sub>  | -40     | 98/2                      |

**Scheme 51:** S-Amination of thioanisole with *N*-protected oxaziridines

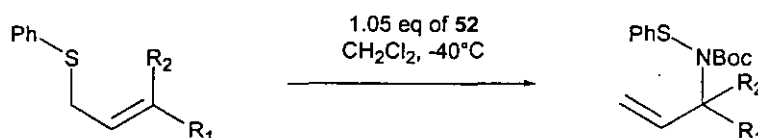
A series of sulfides was aminated by oxaziridine (**52**) in good yields with essentially no oxidation products being observed (**Scheme 52**). The low yield obtained with dimethyl sulfide is due to the poor stability of the product to chromatography on silica gel.



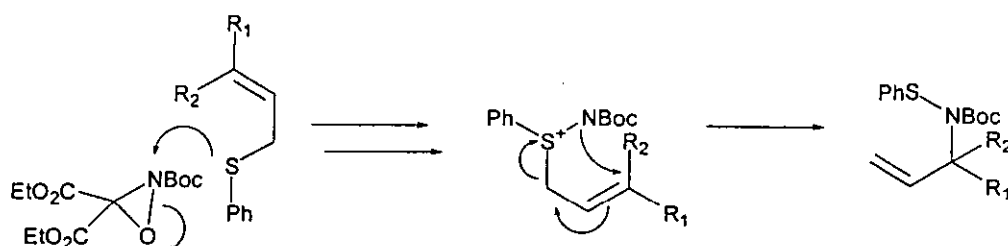
| R <sub>1</sub>  | R <sub>2</sub> | Yield/% |
|-----------------|----------------|---------|
| Ph              | Me             | 97      |
| <sup>t</sup> Bu | Me             | 75      |
| Ph              | Bn             | 77      |
| Bn              | Et             | 75      |
| Me              | Me             | 49      |

**Scheme 52:** Formation of *N*-Boc sulfimides

Allylic sulfides in the presence of oxaziridine (**52**) undergo amination followed by [2,3] sigmatropic rearrangement to give allylic *N*-protected amines in high yields (**Scheme 53**).



#### Postulated Mechanism



| R <sub>1</sub> | R <sub>2</sub>     | Yields/% |
|----------------|--------------------|----------|
| H              | Me                 | 94       |
| Me             | Me                 | 93       |
| H              | Ph                 | 73       |
| H              | CO <sub>2</sub> Me | 85       |

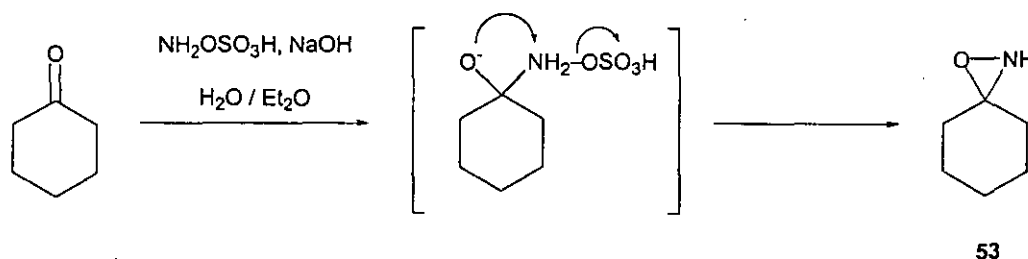
Scheme 53: Amination of allylic sulfides

### 1.2.2 *NH*-Oxaziridines.

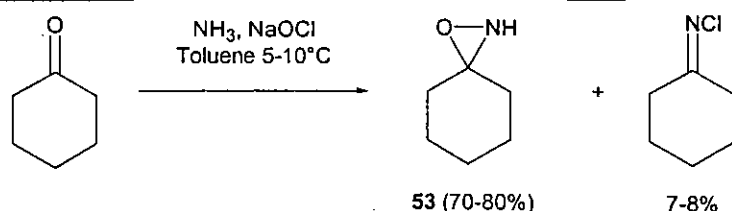
Oxaziridines bearing no substituents at nitrogen were first reported by Schmitz in 1961.<sup>74</sup> Therefrom they have been used to aminate nitrogen, oxygen, sulfur and carbon nucleophiles.<sup>75</sup> Only few *NH*-oxaziridines have been reported, due to their low stabilities.

#### 1.2.2.1 Synthesis

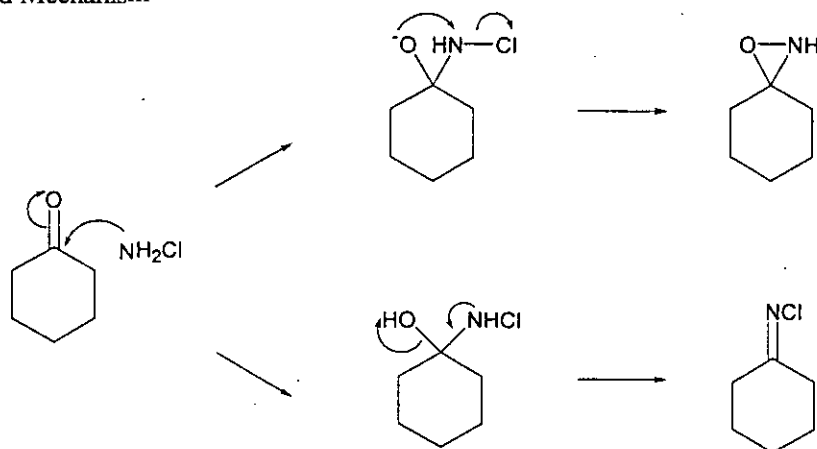
The first *NH*-oxaziridine (**53**) was formed in a fast reaction between cyclohexanone and an alkaline solution of hydroxylamine-*O*-sulfonic acid in 50% yield. The first step of this process is nucleophilic attack by hydroxylamine-*O*-sulfonic acid on the sp<sup>2</sup> carbon of the carbonyl group (Scheme 54).

Scheme 54: Formation of 3,3-pentamethylene oxaziridine **53**

Oxaziridine (**53**) is obtained in better yield from cyclohexanone by using chloramines or a solution of ammonia and sodium hypochlorite.<sup>76</sup> Formation of *N*-chlorocyclohexylimine was also observed (Scheme 55).

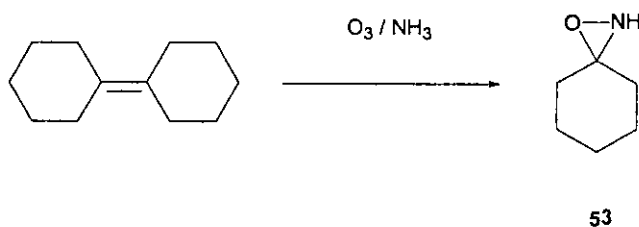


## Postulated Mechanism

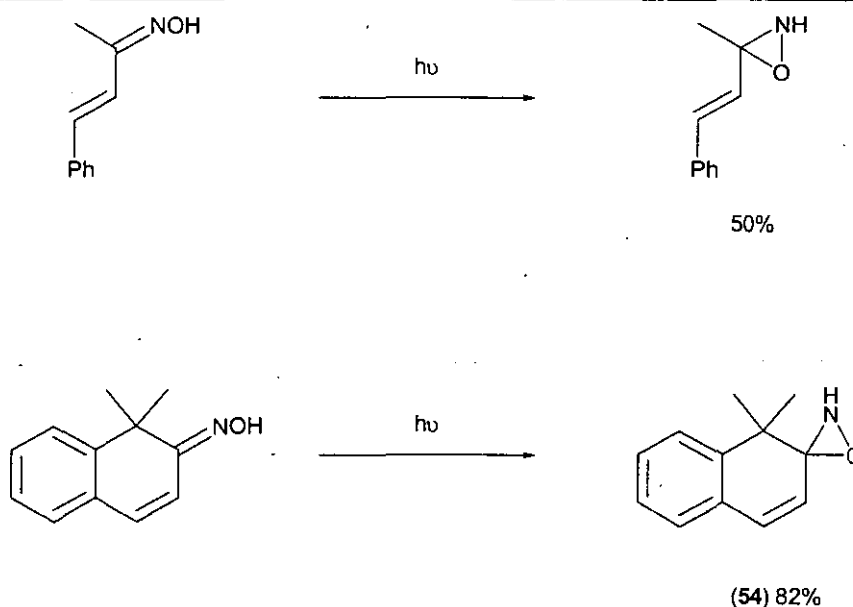
**Scheme 55:** Synthesis of **53** with chloramines

Oxaziridine (**53**) is remarkably reactive towards nucleophiles. Oxaziridine (**53**) is employed in solution without further purification and is by far the most common *NH*-oxaziridine employed.<sup>75</sup>

Formation of (**53**) was also observed on ozonolysis of cyclohexylidenecyclohexane in the presence of ammonia (**Scheme 56**).<sup>77</sup>

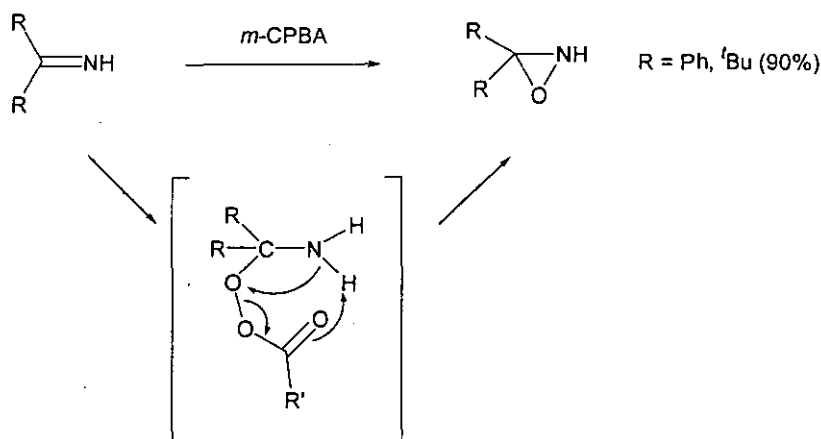
**Scheme 56:** Formation of **53** by ozonolysis

$\alpha,\beta$ -Unsaturated Oximes have been isomerised by photolysis with formation of oxaziridines. Irradiation of benzylideneacetone oxime affords the corresponding oxaziridine in (50%) yield. Similarly, oxaziridine (**54**) was obtained in 82% yield (**Scheme 57**).<sup>78</sup>



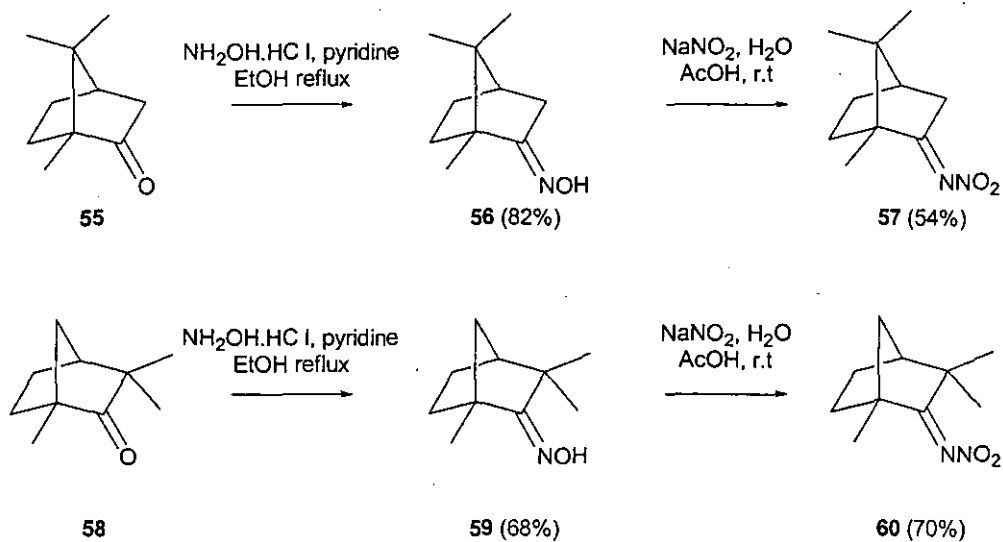
**Scheme 57:** Isomerisation of oximes into oxaziridines

*NH*-Oxaziridines can also be synthesized by the peracid oxidation method. The first *NH*-ketimines oxidized, with *m*-CPBA, derived from benzophenone and di-butyl ketone (**Scheme 58**).<sup>79</sup>



**Scheme 58:** Formation of *NH*-oxaziridines from oxidation of *NH*-ketimines

Our group employed the peracid oxidation method for the synthesis of the first chiral *N*-unsubstituted oxaziridines.<sup>80</sup> Camphor and fenchone oxaziridines were prepared by oxidation of the corresponding *NH*-imines with *m*-CPBA. Fenchone and camphor imines were prepared in three steps from the hindered ketones (**55**, **58**). The first step is the formation of the corresponding oximes (**56**, **59**) followed by nitrosation with an aqueous solution of sodium nitrite in glacial acetic acid to afford nitrimines after rearrangement (**57**, **60**) (**Scheme 59**).<sup>81</sup>



**Scheme 59:** Synthesis of nitrimines precursors

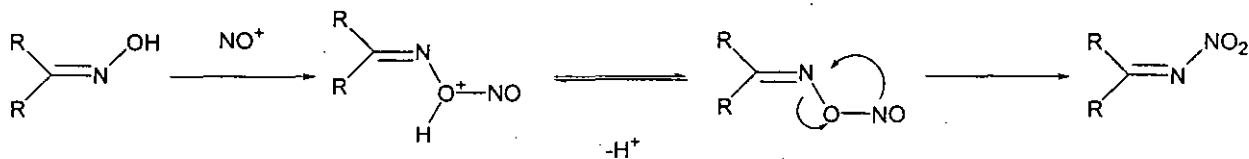
Two mechanisms have been postulated for the formation of the nitrimines, both based on a nucleophilic attack on nitrosyl cation  $\text{NO}^+$ . Guziec and Russo proposed an attack from the nitrogen atom of the oxime group, leading to a nitroso nitron intermediate, which gives after rearrangement the nitrimine (Equation 1 **Scheme 60**).<sup>82</sup>

Ridge and Gamble however suggested that the oxygen atom of the oxime group reacted with the nitrosyl cation (Equation 2 **Scheme 60**).<sup>83</sup>

Equation 1

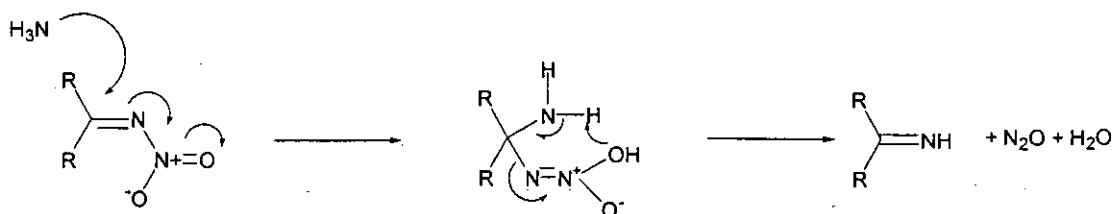


Equation 2



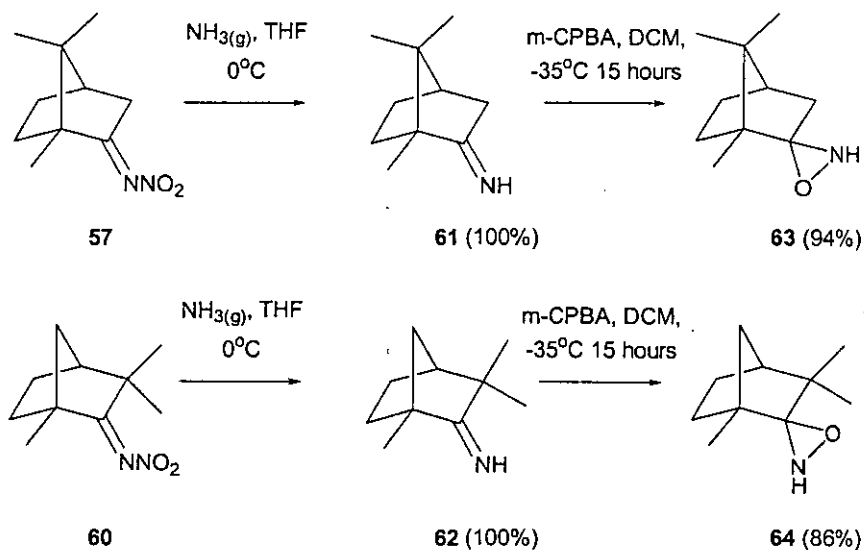
**Scheme 60:** Postulated mechanisms for the formation of nitrimines

Nitrimines are sensitive to nucleophiles. Schenone, Ramise and Bondavalli suggested that amines or ammonia react with nitrimines in a Michael addition type reaction (Scheme 61).<sup>84</sup>



**Scheme 61:** Postulated mechanism of the ammonolysis of nitrimines with ammonia

Camphor and fenchone nitrimines undergo this ammonolysis with ammonia to give the corresponding imines (**61**, **62**) in excellent yield.<sup>82</sup> Imines (**61**, **62**) are unstable if heated above 35 °C. Therefore they were oxidised with *m*-CPBA to afford camphor and fenchone oxaziridines (**63**, **64**) (Scheme 62).



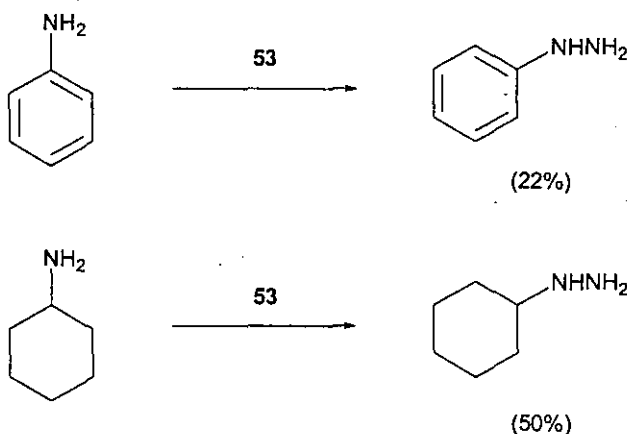
**Scheme 62:** Synthesis of camphor and fenchone oxaziridines

### 1.2.2.2 Reactivity of *N-H* oxaziridines

#### 1.2.2.2.1 Amination of nitrogen nucleophiles

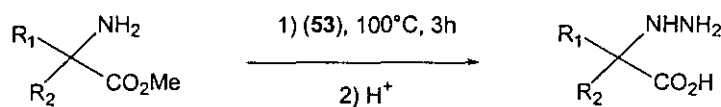


Aniline and cyclohexyl amine react with oxaziridine (**53**) to form phenyl hydrazine and cyclohexyl hydrazine in respectively 22 and 50 % yield. (**Scheme 63**).<sup>85</sup>



**Scheme 63:** Amination of primary amines with *NH*-oxaziridine

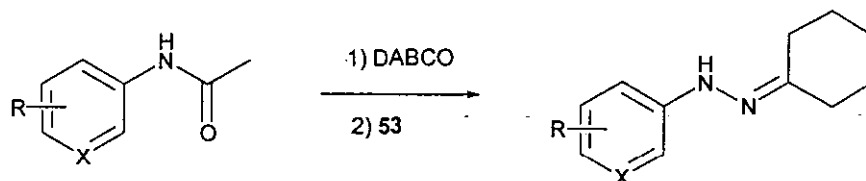
$\alpha$ -Amino acid esters were heated for three hours in a solution of oxaziridine in toluene (**53**) to give after hydrolysis  $\alpha$ -hydrazino acids in fair yields (**Scheme 64**).<sup>86</sup>



| Amino-acid ester                            | R <sub>1</sub>   | R <sub>2</sub> | Yield/% |
|---|--|----------------|---------|
| L-Alanine                                   | Me   | H              | 38      |
| L-Valine                                    | <sup>i</sup> Pr  | H              | 54      |
| L-Phenyl Glycine                            | Ph   | H              | 32      |
| DL-Phenyl Alanine                           | PhCH <sub>2</sub>  | H              | 54      |
| 3-(3,4-dimethoxy-phenyl)-2-methyl L-alanine | 3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub> | Me             | 69      |
| 3-(3,4-dihydroxy-phenyl)-2-methyl L-alanine | 3,4-(HO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CH <sub>2</sub>  | Me             | 66      |

**Scheme 64:** Amination of  $\alpha$ -amino acid esters

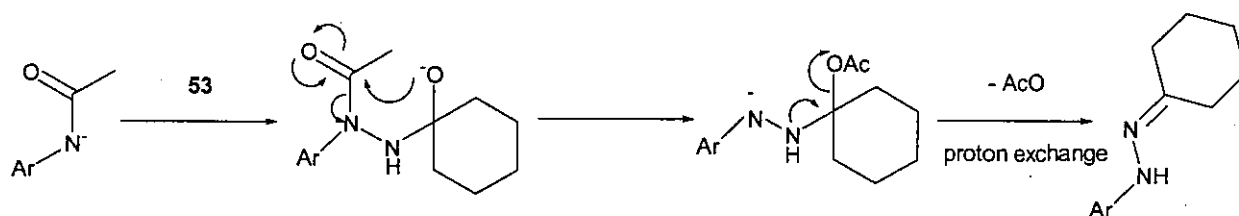
Deprotonated *N*-acyl-aryl amines react with oxaziridine (**53**) to give protected hydrazines. The reaction occurs with loss of the acetyl group and transfer of the cyclohexyl moiety (**Scheme 65**).<sup>87</sup>



| X  | R    | Base (mol/%) | Yield/% |
|----|------|--------------|---------|
| N  | 2-CN | 71           | 59      |
| N  | 2-Cl | 140          | 62      |
| NO | 2-Cl | 76           | 78      |

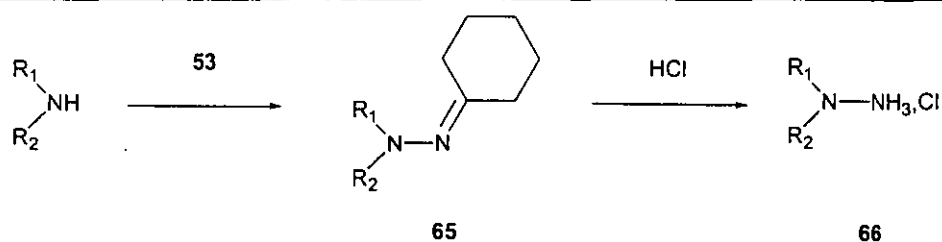
**Scheme 65:** Amination of *N*-acetyl-aryl amines

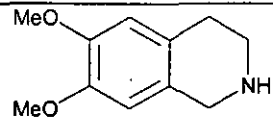
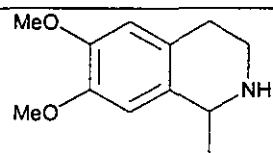
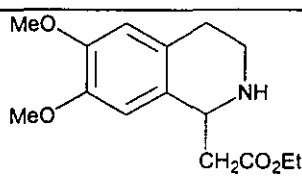
The acetyl group is thought to be lost *via* an intramolecular oxygen transfer, as indicated in (**Scheme 66**).



**Scheme 66:** Postulated mechanism for the loss of the *N*-acetyl group

Furthermore, secondary amines react similarly within few minutes with *NH*-oxaziridine (**53**) to afford protected *N,N*-dialkyl hydrazines in moderate to good yields. The cyclohexyl moiety was hydrolysed under acidic conditions (**Scheme 67**).

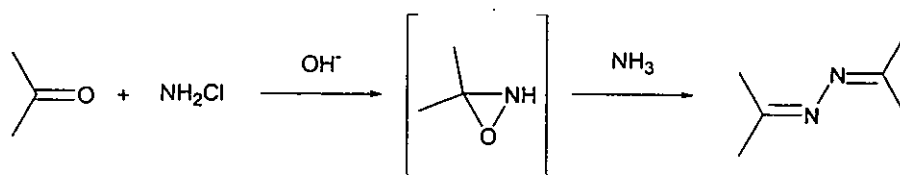


| $R_1R_2NH$   | 65 Yield/% | 66 Yield/% |
|--|------------|------------|
| $Et_2NH$   | -          | 93         |
| $Bu_2NH$   | -          | 75         |
| $(CNCH_2CH_2)_2NH$   | 71         | -          |
| Morpholine   | -          | 47         |
|   | >80        | 78         |
|   | >80        | 71         |
|  | 98         | -          |

**Scheme 67:** Amination of secondary amines with  $NH$ -oxaziridine (53)

It was found that the addition of acetone to a solution of ammonia and sodium hypochlorite resulted in a better yield of hydrazine than without the catalysis of acetone (**Scheme 68**).

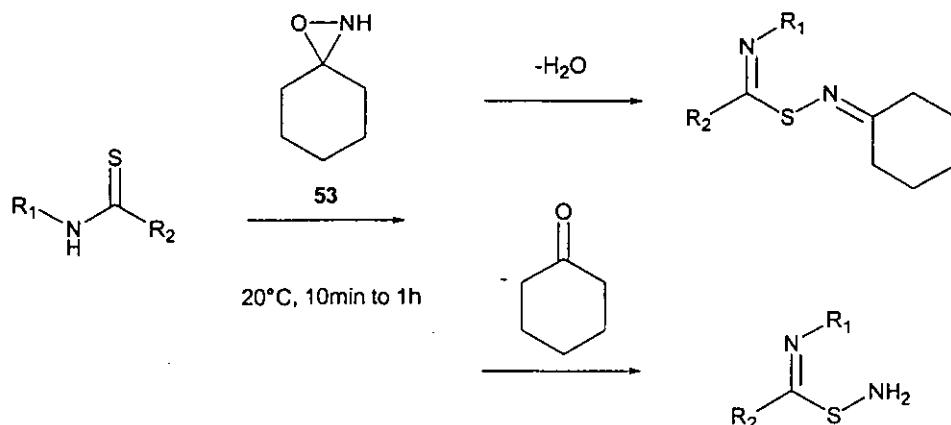
This modified Raschig's process takes place with the formation of 3,3-dimethyl oxaziridine as a key intermediate of the reaction.<sup>88</sup>



**Scheme 68:** Synthesis of hydrazine

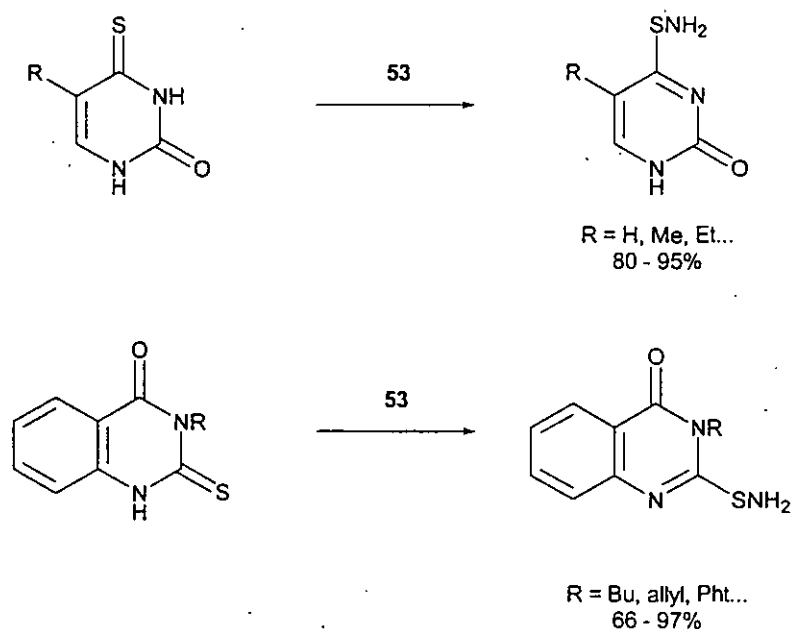
## 1.2.2.2.2 Amination of sulfur nucleophiles

Among sulfur nucleophiles, bivalent thioamides and thioureas react with *NH*-oxaziridine (**53**) to form thiooximes or sulfenamides, depending on the loss of water or cyclohexanone during the process of amination (**Scheme 69**).<sup>75</sup>



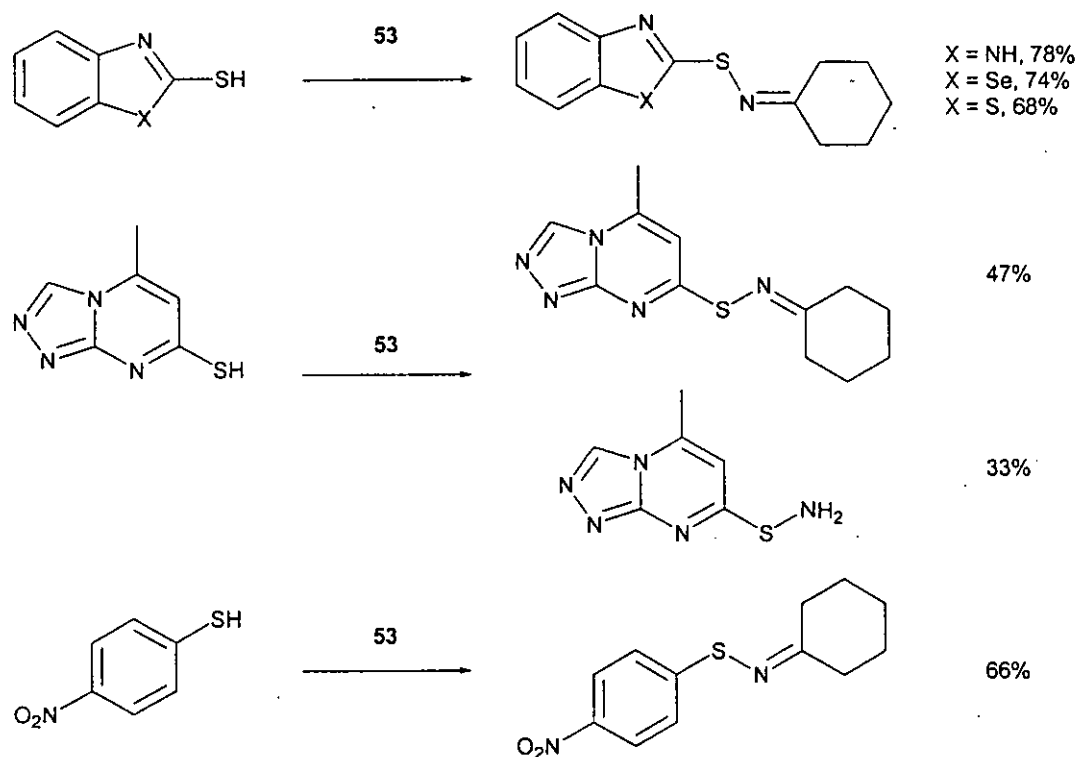
**Scheme 69:** Amination of bivalent sulphur nucleophiles

S-Alkyl-thiouracil and benzopyrimidine derivatives give sulfenamides in good yields when reacted with oxaziridine (**53**) (**Scheme 70**).



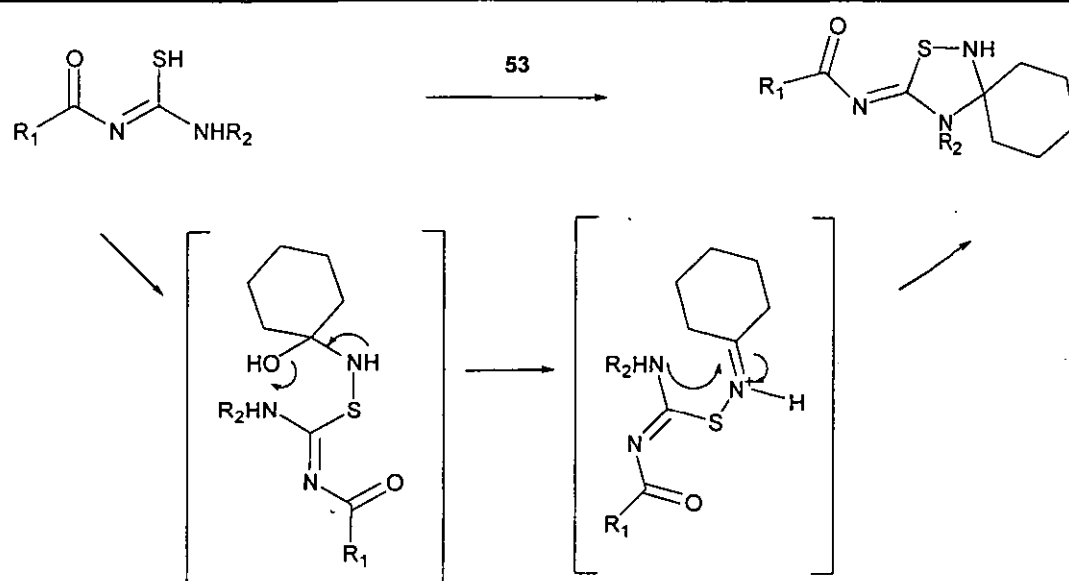
**Scheme 70:** Synthesis of sulfenamides

Further, many examples of the formation of thiooximes have been reported from heterocyclic mercaptans such as mercaptobenzazoles, thioazapurine or 4-nitrophenyl thiol (**Scheme 71**) upon reaction with (**53**). In the case of the amination of thioazapurine, the formation of thiooxime and sulfenamide was observed.



**Scheme 71:** Formation of thiooximes

In many cases, thiooximes undergo additional rearrangement, by further reaction with a functional group in the molecule, resulting in a ring closure with insertion of the cyclohexyl amine moiety (**Scheme 72**).<sup>75</sup>

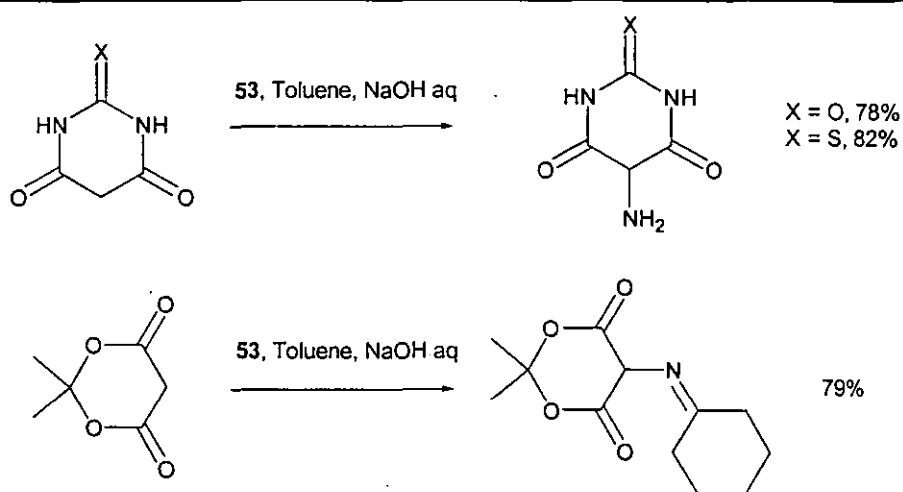


| R <sub>1</sub> | R <sub>2</sub>                     | Yield/% |
|----------------|------------------------------------|---------|
| OH             | H                                  | 75      |
| OEt            | Ph                                 | 68      |
| OEt            | 2-MeOC <sub>6</sub> H <sub>4</sub> | 63      |
| Ph             | Ph                                 | 44      |
| Ph             | 2-MeOC <sub>6</sub> H <sub>4</sub> | 42      |

Scheme 72: Rearrangement of thiooximes

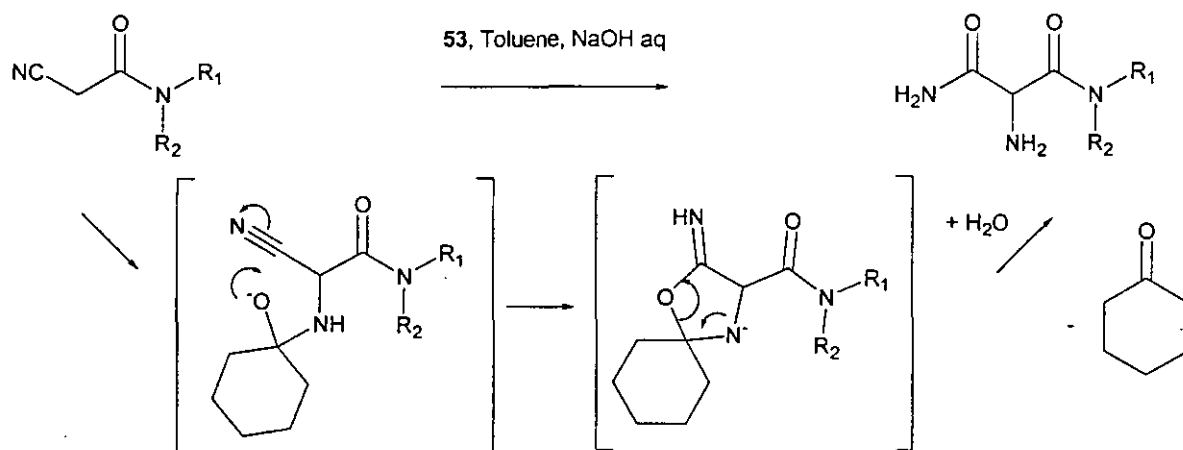
#### 1.2.2.2.3 Amination of carbon nucleophiles

*C-H* Acidic compounds were first investigated because of their ability to be deprotonated by an alkali hydroxide solution. The amination proceeds smoothly in a biphasic reaction in the presence of oxaziridine (53). Free and protected amino compounds were obtained, depending on the loss of cyclohexanone or water during the reaction (Scheme 73).



Scheme 73: Amination of C-H acidic compounds

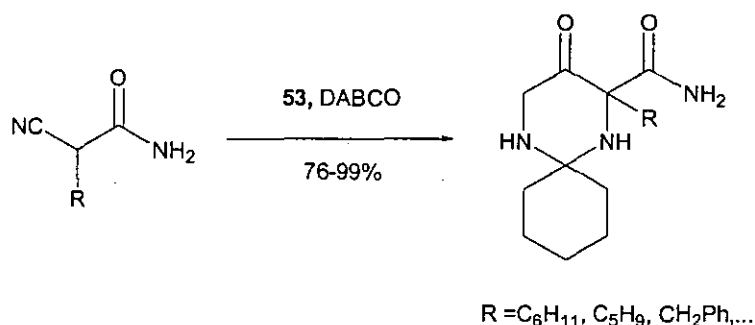
Amination of  $\alpha$ -cyano carboxamides with oxaziridine (53) occurred with the hydration of the nitrile group (Scheme 74).



| R <sub>1</sub>  | R <sub>2</sub> | Yield/% |
|---|----------------|---------|
| H   | Me             | 94      |
| Me  | Me             | 91      |
| -(CH <sub>2</sub> ) <sub>4</sub> -                                      |                | 71      |
| -(CH <sub>2</sub> ) <sub>5</sub> -                                      |                | 74      |
| -CH <sub>2</sub> -CH <sub>2</sub> -O-CH <sub>2</sub> -CH <sub>2</sub> - |                | 56      |

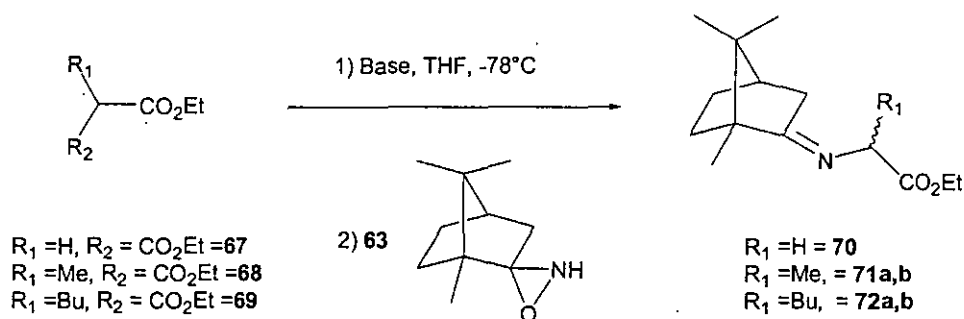
Scheme 74: Amination of  $\alpha$ -cyano carboxamides

An organic base can catalyse the nitrogen transfer. DABCO has been used for the amination of 2-cyanoalkyl amides (**Scheme 75**).



**Scheme 75:** Amination catalysed by DABCO

Chiral camphor and fenchone oxaziridines (**63**, **64**) were used by our research group for asymmetric nitrogen transfer to a range of various enolates. Unsubstituted malonate and diethyl malonates were first investigated with camphor oxaziridine (**63**) (**Scheme 76**).<sup>89</sup>



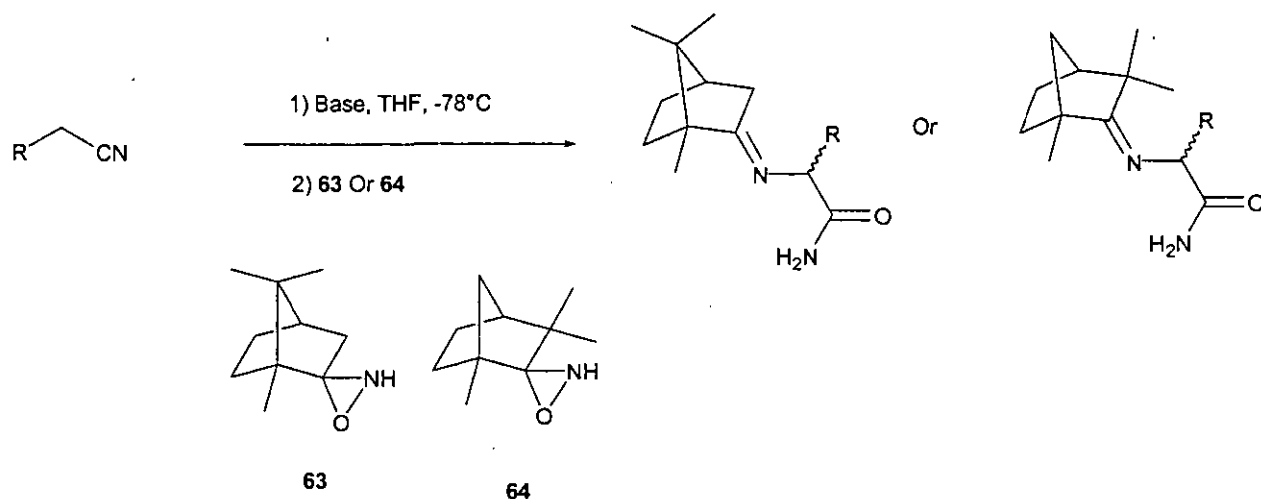
| Substrate | Base  | Product      | Yield/% |
|-----------|-------|--------------|---------|
| <b>67</b> | NaOEt | <b>70</b>    | 68      |
| <b>67</b> | LHMDS | <b>70</b>    | 50      |
| <b>68</b> | NaOEt | <b>71a,b</b> | 89      |
| <b>68</b> | LHMDS | <b>71a,b</b> | 20      |
| <b>69</b> | LHMDS | <b>72a,b</b> | 14      |

**Scheme 76:** Amination of malonate and diethyl malonates with oxaziridine **63**



The reactions occurred with loss of an ester group *via* decarboxylation and with transfer of the camphor moiety. The geometry of the imine double bond is believed to be *E*. It has been shown that the *Z* isomer is destabilized due to steric hindrance.<sup>90</sup> Compounds (71) and (72) were obtained as a 1:1 mixture of diastereoisomers.

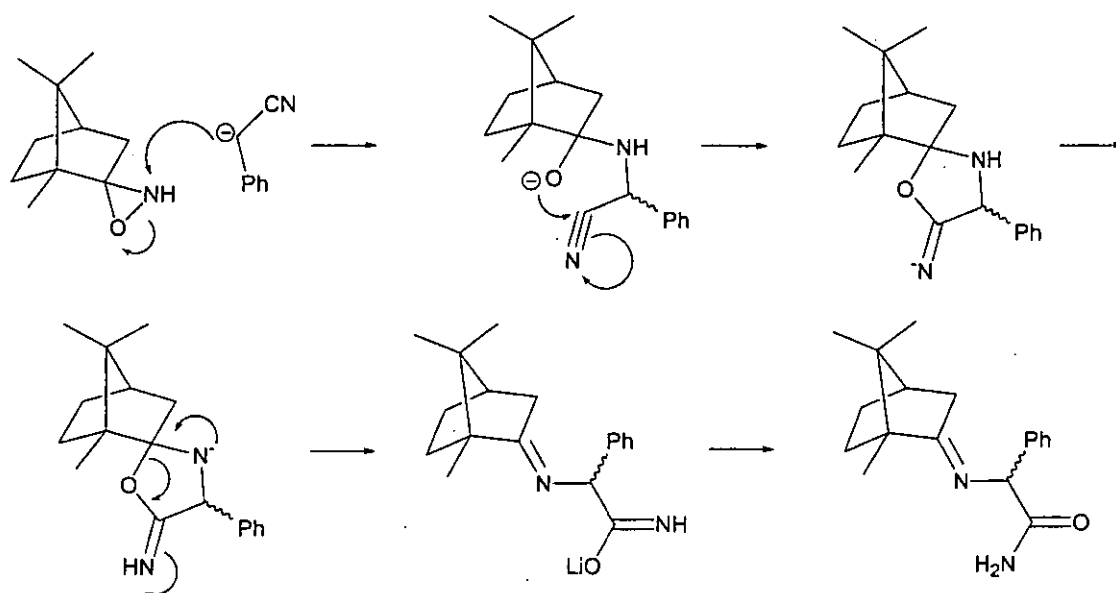
Camphor and fenchone oxaziridines (63, 64) also transfer nitrogen to nitrile carbanions in moderate to excellent yields (Scheme 77)



| Substrate  | Oxaziridine | Base  | Yield/% | d.e. /% |
|--|-------------|-------|---------|---------|
| PhCH <sub>2</sub> CN                                   | <b>63</b>   | LHMDS | 78      | 25      |
| PhCH <sub>2</sub> CN                                   | <b>63</b>   | LDA   | 62      | 3       |
| 2-Naphtyl Acetonitrile                                 | <b>63</b>   | LHMDS | 73      | 33      |
| 1-Naphtyl Acetonitrile                                 | <b>63</b>   | LHMDS | 80      | 33      |
| 4-Cl-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN  | <b>63</b>   | LHMDS | 80      | 16      |
| 4-MeO-C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CN | <b>63</b>   | LHMDS | 73      | 5       |
| CNCH <sub>2</sub> CN                                   | <b>63</b>   | LHMDS | 82      | 0       |
| PhCH <sub>2</sub> CN                                   | <b>64</b>   | LHMDS | 55      | 50      |
| 2-Naphtyl Acetonitrile                                 | <b>64</b>   | LHMDS | 31      | 52      |
| 1-Naphtyl Acetonitrile                                 | <b>64</b>   | LHMDS | 48      | 33      |
| CNCH <sub>2</sub> CN                                   | <b>64</b>   | LHMDS | 57      | 23      |

**Scheme 77:** Amination of nitrile carbanions

All the reactions were observed to occur with hydrolysis of the cyano group to primary amide. The imine double bond was proved to be in the *E* configuration by single crystal X-ray. In the case of fenchone oxaziridine (**64**) the presence of the methyl groups close to the oxaziridine ring induces a better stereoselectivity during the nitrogen transfer. The hydrolysis of the nitrile group could occur as shown below (**Scheme 78**).

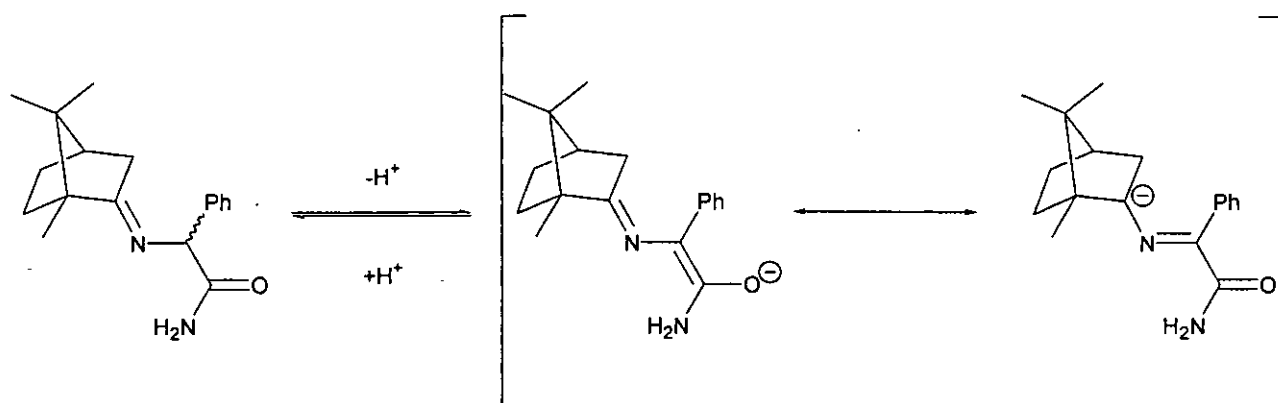


**Scheme 78:** Postulated mechanism of the nitrogen transfer

The first step involves the nucleophilic attack by the carbanion on the nitrogen atom, resulting in the cleavage of the N-O bond. The oxygen anion released could then react further with the cyano group to give a heterocyclic intermediate. The oxygen is then transferred to give the amido group, resulting in the formation of the imine double bond.

Schmitz has also observed the hydrolysis of the cyano group when oxaziridine (**53**) was reacted with nitrile carbanions.<sup>91</sup>

The diastereomeric excess were determined <sup>1</sup>H NMR of the crude reactions. However due to the nature of the product of amination, partial epimerisation of the new chiral center could occur during the reaction, as the corresponding anion would be stabilize either by the amide group, the imine or the corresponding aryl group. Which would means that any diastereoisomeric excesses observed in the final products could arise from diastereoselective protonation of these enolates, induced by the chiral camphor moiety, and not by an initial enantioselective amination of the nucleophile (**Scheme 79**).



**Scheme 79:** Possible epimerisation of the new chiral center

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## **CHAPTER 2:**

## **RESULTS AND DISCUSSION**

## 2. NEW REAGENTS FOR ASYMMETRIC ELECTROPHILIC NITROGEN TRANSFER

### 2.1 Introduction

The aim of this work is to synthesize new chiral *NH*-camphor oxaziridine derivatives. This choice was motivated by two facts.

First, the *NH*-oxaziridine obtained from camphor is relatively stable and reactive towards carbon nucleophiles.<sup>1</sup>

Secondly, Davis has shown that *N*-substituted camphorylsulfonyl oxaziridines transfer oxygen to various nucleophiles with very good stereoselectivities.<sup>2</sup> This is due to the high hindrance close to the oxaziridine ring.

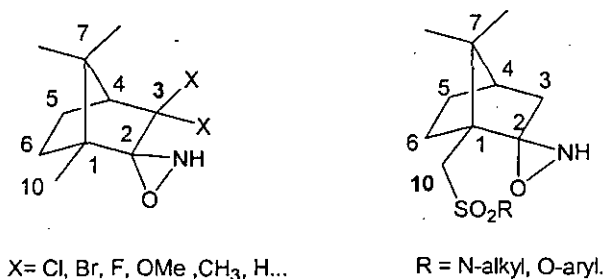
Hence our attention became focused on more elaborated camphor derivatives. The choice of the substitution on the carbon 3 of the bornane skeleton could be justified in two ways.

Steric hindrance could cause such substitution as a barrier to favour only one trajectory of approach of nucleophiles during the process of amination.

The second reason is electronic. Adding an electron-withdrawing or a chelating group could affect the stability and reactivity of the *NH*-oxaziridine ring.

In order to provide focus, we limited our interest to mono- and di-substituted alkyl, halogeno, and *O*-alkyl camphor derivatives (**Scheme 1**).

The second choice of substitution, which was interesting to us, was on carbon 10 of the bornane skeleton (**Scheme 1**). 10-Sulfonyl camphor ester derivatives have been widely used in asymmetric synthesis.<sup>3</sup>



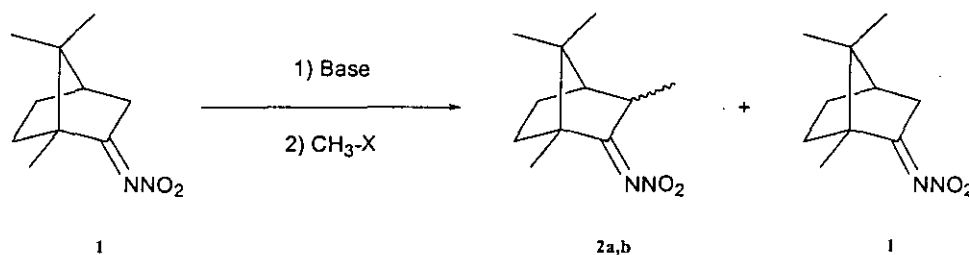
**Scheme 1:** New chiral *NH*-camphor oxaziridines

## 2.2 Synthesis of 3-mono and dialkyl precursors

We first chose substitution on carbon 3 of the bornane skeleton by alkyl groups for two reasons. First, and mainly, for the creation of high hindrance around the *NH*-oxaziridine, which we believed would favour one route of the approach of nucleophiles during the nitrogen transfer. Secondly it would reinforce the stability of the oxaziridine. Our first target was the synthesis of 3-*endo* and 3-*exo* methyl- and 3,3-dimethyl camphor derivatives starting from camphor nitrimines.

### 2.2.1 Synthesis of methyl camphor nitrimines and attempted synthesis of 3,3-dimethyl camphor nitrimine

We believed that 3-methyl and 3,3-dimethyl camphor precursors could be prepared from camphor nitrimine (**1**), via the formation of the corresponding azaenolate. Camphor nitrimine (**1**) was first treated with one equivalent of base followed by one equivalent of methylating agent (**Scheme 2**).



| Entry | Base   | Alkyl reagent                      | Products                    |
|-------|--------|------------------------------------|-----------------------------|
| 1     | LHMDS  | MeI                                | <b>2</b> (25%) <sup>a</sup> |
| 2     | LDA    | MeI                                | <b>2</b> (20%) <sup>a</sup> |
| 3     | NaHMDS | MeI                                | <b>1</b>                    |
| 4     | LHMDS  | CH <sub>3</sub> OCOCF <sub>3</sub> | <b>1</b>                    |
| 5     | LDA    | (CH <sub>3</sub> O)SO <sub>2</sub> | <b>1</b>                    |
| 6     | KOH    | MeI                                | <b>1</b>                    |
| 7     | DBU    | MeI                                | <b>1</b>                    |

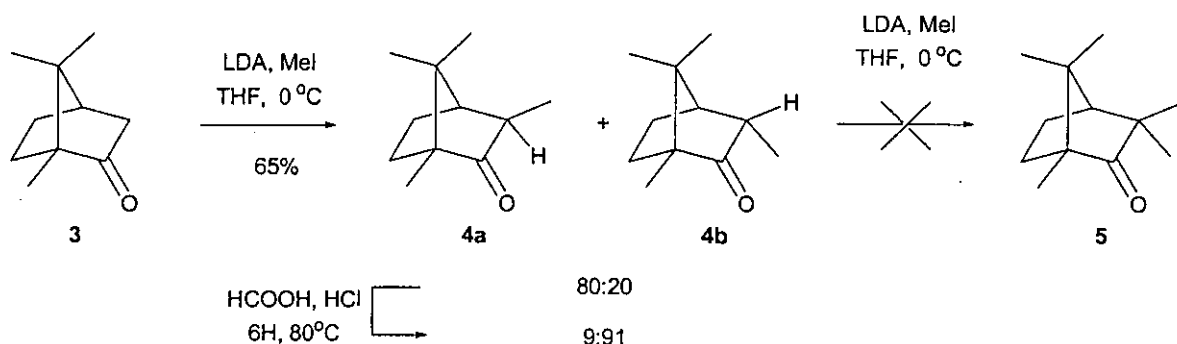
a) ratio determined by NMR of the crude

**Scheme 2:** Synthesis of 3-methyl camphor nitrimines

The deprotonation of camphor nitrimine (**1**) using a strong base (LHMDS, LDA, NaHMDS) at  $-78\text{ }^{\circ}\text{C}$  in THF, followed by the addition of the alkylating reagents, did not give satisfactory results. The  $^1\text{H}$  NMR spectrum of the crude reaction showed only 25% of the desired product (**2**) (entry 1, **Scheme 2**). Camphor nitrimine (**1**) can be deprotonated using an ethanolic solution of potassium hydroxide, or an ethanol solution of DBU. The corresponding salts were reacted with methyl iodide in ethanol but with no formation of methyl camphor nitrimines (**2**).

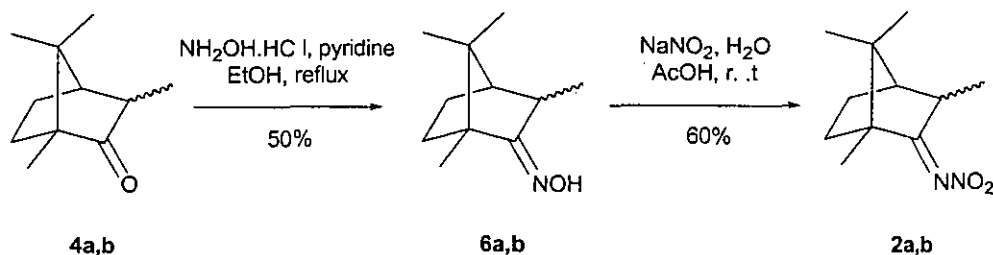
When camphor nitrimine (**1**) was reacted with two equivalents of base and two equivalents of methylating reagent, no 3,3-dimethyl camphor nitrimine was recovered and we did not observe a better yield in the synthesis of the 3-methyl camphor nitrimine (**2**).

However, Hutchinson and Money have reported the kinetic methylation of camphor.<sup>4</sup> Following their procedure, a solution of camphor (**3**) in THF was added to LDA at  $0\text{ }^{\circ}\text{C}$ . The corresponding enolate was treated with an excess of methyl iodide for 30 minutes to afford after purification by column chromatography in 66% yield a mixture of 3-*exo* and 3-*endo* methyl camphor (**4a,b**). The  $^1\text{H}$  NMR spectrum of the crude shows a ratio of 4:1 for the kinetic *exo* product. Epimerization under acidic conditions changes this ratio to 9:1 in favour of the thermodynamically more stable *endo* form (**4b**). The diastereomeric mixture was heated with acetic acid and hydrochloric acid for six hours (**Scheme 3**). Unfortunately, the separation of the two diastereomers by crystallization was not successful. Attempted syntheses of 3,3-dimethyl camphor were made from camphor (**3**) and 3-methyl camphor (**4a,b**). They were reacted with LDA at  $0\text{ }^{\circ}\text{C}$  followed by the addition of an excess of methyl iodide (**Scheme 3**). Unfortunately in both cases no 3,3-dimethyl camphor was recovered.



**Scheme 3:** Formation and epimerisation of 3-methyl camphor and attempted synthesis of 3,3-dimethyl camphor

Oximes (**6a,b**) were synthesized by reaction of (**4a,b**) with hydroxylamine hydrochloride in presence of pyridine under refluxing conditions in ethanol (Scheme 4). The ratio between the *endo* and *exo* products was 9:1, and no epimerization was observed during the oximation. The reaction of (**6a,b**) with a (5%) aqueous sodium nitrite solution in glacial acetic acid over a period of three hours afforded nitrimines (**2a,b**) in good yield (Scheme 4).



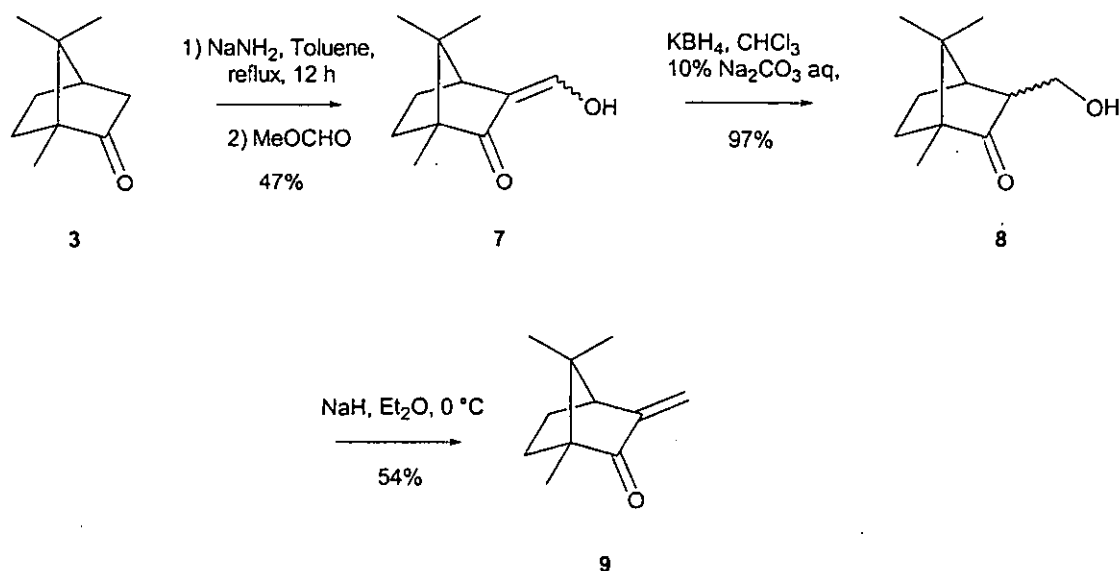
**Scheme 4:** Formation of 3-methyl camphor nitrimines

The separation of 3-*endo* methyl camphor nitrimine (**2b**) by column chromatography or crystallization from the 3-*exo* methyl nitrimines (**2a**) was not possible.

However, in order to obtain only one diastereoisomer of 3-methyl camphor nitrimine, we thought that the synthesis of 3-methylene camphor (**9**) would be important for two reasons. Firstly, hydrogenation of 3-methylene camphor (**9**) could occur stereoselectively and produce only one diastereoisomer of 3-methyl camphor. Secondly 3-methylene camphor could undergo cyclopropanation using the Simmons-Smith reagents, which after hydrogenation would give us the 3,3-dimethyl camphor precursor.

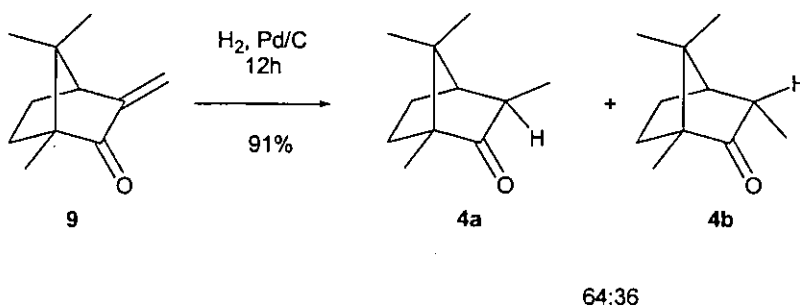
We prepared 3-methylene camphor (**9**) in three steps in moderate yield (Scheme 5).<sup>5,6</sup> Camphor (**3**) in toluene was treated with sodium amide at reflux overnight. The sodium enolate was then reacted with methyl formate to produce 3-hydroxymethylene camphor (**7**) in 47% yield. The literature procedure reported a yield of 70% using isopentyl formate, which is now not commercially available. The reduction of 3-hydroxymethylene camphor (**7**) with potassium borohydride in chloroform afforded 3-hydroxymethyl camphor (**8**) in 97% yield. Elimination of water from the alcohol (**8**) was performed under basic conditions using potassium

hydroxide under reflux conditions for five hours, to result in the formation of 3-methylene camphor (**9**) in 54% yield. We also found the elimination of water proceeds in half an hour using sodium hydride in diethyl ether in 54% yield.



**Scheme 5:** Synthesis of 3-methylene camphor

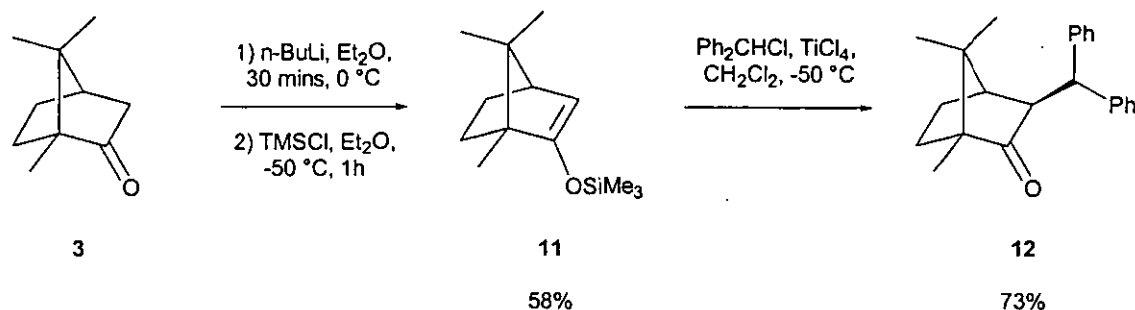
The hydrogenation of 3-methylene camphor (**9**) with hydrogen and Pd/C as catalyst afforded 3-methyl camphor in good yield. Unfortunately the  $^1\text{H}$  NMR spectrum of the crude shown that both diastereoisomers were obtained in a 64:36 ratio in favour of the 3-*exo* methyl camphor (**Scheme 6**).



**Scheme 6:** Hydrogenation of 3-methylene camphor



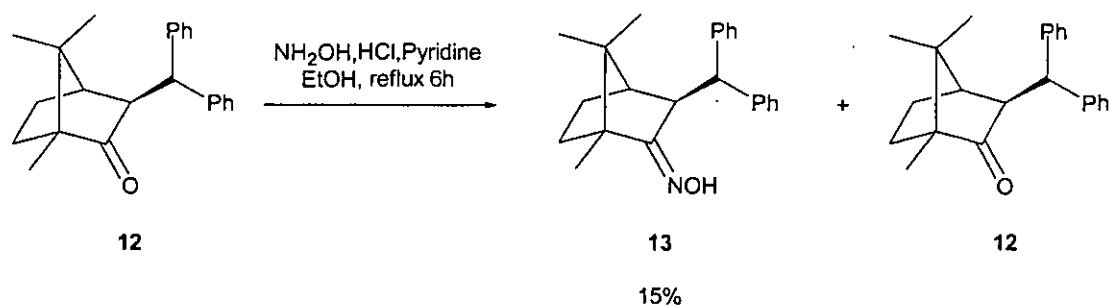
of the silyl enol ether with chlorodiphenyl methane in the presence of  $\text{TiCl}_4$  at  $-50^\circ\text{C}$  in dry dichloromethane afforded the desired product (**12**) in 73% yield (Scheme 8).



**Scheme 8:** Synthesis of 3-*exo*-(diphenylmethyl) camphor

Recrystallization from hexane afforded (1R)-3-*exo*-(diphenylmethyl) camphor. The  $^1\text{H}$  NMR spectrum showed the *endo* proton on carbon 3 as a doublet coupled to the proton attached to carbon 11 bearing the phenyl groups ( $J = 12.1$  Hz). There was no coupling observed between the *endo* proton and the proton on carbon 4, proving the stereochemistry.

The oximation of compound (**12**) using hydroxylamine hydrochloride in the presence of pyridine under reflux conditions give the desired oxime in low yield (15%) together with starting material and some decomposition products (Scheme 9).



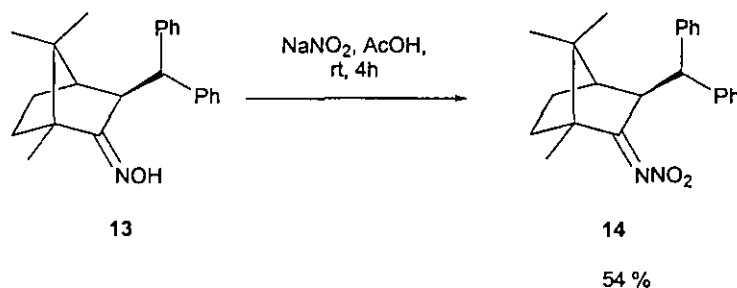
**Scheme 9:** Synthesis of (1R)-3-*exo*-(diphenylmethyl) camphor oxime.

The presence of the doublet at  $\delta$  3.35 ( $J = 9.2$  Hz) due to the coupling between the *endo* proton on carbon (3) and the proton on carbon (11) shows that no epimerization occurred during the oximation. Attempts to form the oxime (**13**) using



hydroxylamine hydrochloride and sodium acetate under reflux in ethanol, only resulted in the recovery of the starting material (12).

(1R)-3-*exo*-(diphenylmethyl) camphor nitrimine (14) was synthesized by reaction of the oxime (13) with a (5%) aqueous sodium nitrite solution in glacial acetic acid at room temperature over a period of four hours in 54% yield (Scheme 10).

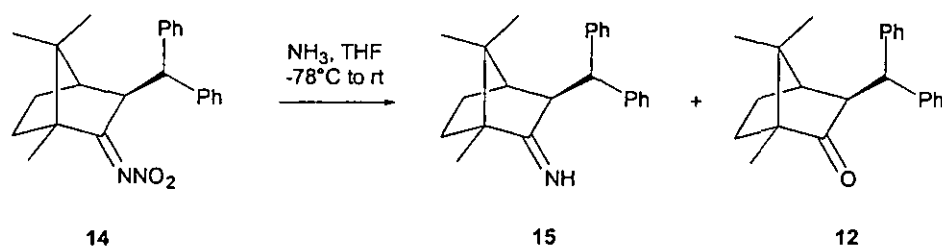


**Scheme 10:** Synthesis of 3-*exo*-(diphenylmethyl) camphor nitrimine

The attempted synthesis of 3-(diphenylmethyl) camphor nitrimine starting from (+) camphor nitrimine (1) using LHMDs and chlorodiphenyl methane did not afford the desired compound, only starting materials were recovered. Attempts using different bases such as LDA or DBU were also unsuccessful.

#### 2.2.4 Attempted synthesis of 3-*exo*-(diphenylmethyl) camphor oxaziridine

A solution of 3-*exo*-(diphenylmethyl) camphor nitrimine (14) in THF was reacted with ammonia during five hours at  $-78^{\circ}\text{C}$ , then allowed to warm up to room temperature; unfortunately the ammonolysis was not complete and the presence of the corresponding ketone (12) was observed by infrared spectroscopy. Other attempts to form the *NH*-imine by longer reaction of the nitrimine (14) with ammonia resulted in each case in some formation of the corresponding ketone (12). The separation of the imine from the ketone was not possible and so the subsequent oxidations step was not carried out (Scheme 11).

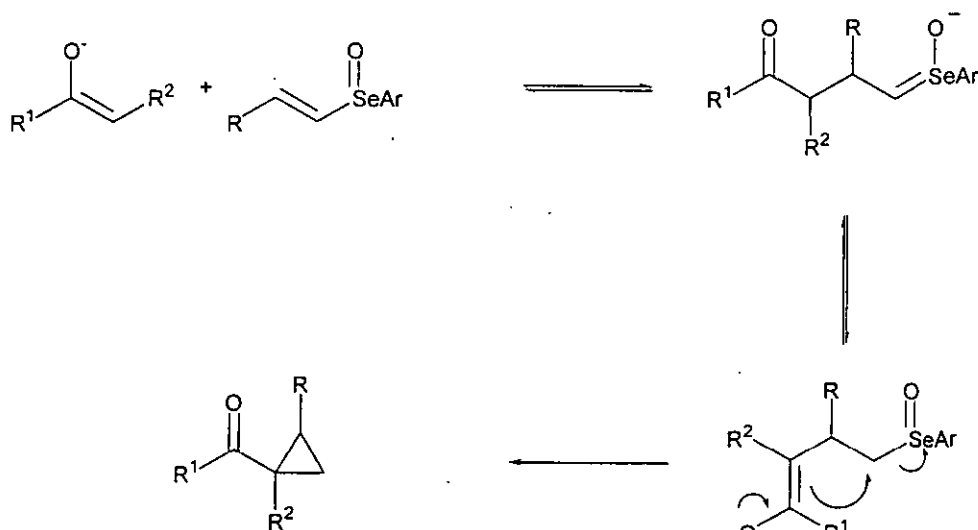


**Scheme 11:** Attempted synthesis of 3-*exo*-(diphenylmethyl) camphor imine

### 2.2.5 Synthesis of 3,3-cyclopropane camphor derivative

We next investigated the synthesis of 3,3-cyclopropane camphor, as we were interested in the effect that high hindrance on carbon 3 could have during the electrophilic amination reaction, as well as believing that it would increase the stability of the oxaziridine. 3,3-Cyclopropane camphor could also be a precursor of 3,3-dimethyl camphor after hydrogenation.

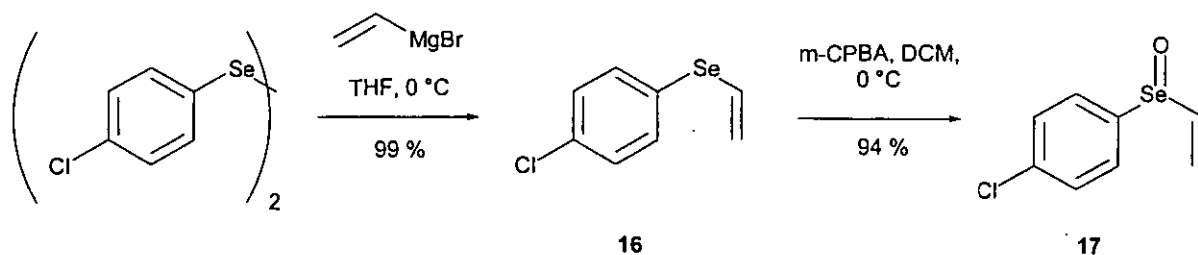
Kuwajima reported in 1984 the one step synthesis of cyclopropylcarbonyl compounds, from the reaction of enolates with vinyl selenoxides in a Michael addition type reaction followed by cyclization (**Scheme 12**).<sup>8</sup>



**Scheme 12:** Cyclopropanation of enolates with aryl vinyl selenoxides

The authors reported the cyclopropanation of camphor in 74% yield by reaction of the lithium enolate with *p*-chlorophenyl vinyl selenoxide. Following the

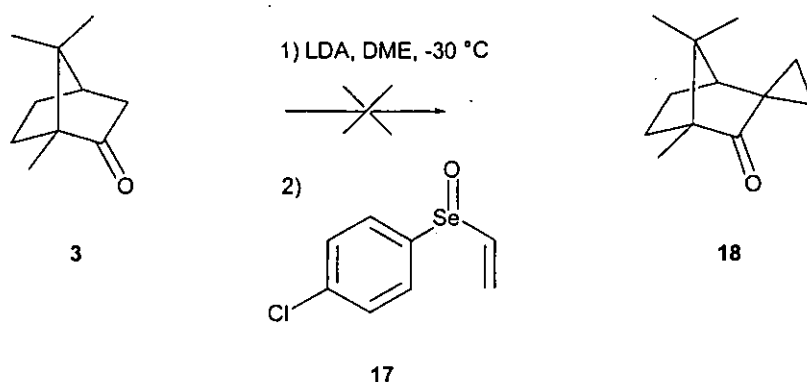
procedure of Reich, we prepared the vinyl selenoxide in two steps from bis(*p*-chlorophenyl) diselenide (**Scheme 13**).<sup>9</sup>



**Scheme 13:** Preparation of *p*-chlorophenyl vinyl selenoxide

Bis(*p*-chlorophenyl) diselenide, was subject to reaction with vinyl magnesium bromide to afford (**16**) in nearly quantitative yield, which was then oxidized with 3-chloroperoxybenzoic acid to form the selenoxide (**17**) in excellent yield. We found that the use of 3 equivalents of the Grignard reagent affords the *p*-chlorophenyl vinyl selenide (**16**) in quantitative yield.

A solution of camphor in DME at  $-30\text{ }^\circ\text{C}$  was then reacted with LDA for one hour. The lithium enolate was treated with a solution of *p*-chlorophenyl vinyl selenoxide for an additional hour at the same temperature (**Scheme 14**).



**Scheme 14:** Attempted cyclopropanation of camphor

Unfortunately only camphor was recovered, and no 3,3-cyclopropane camphor (**52**) was formed. Attempted cyclopropanation of the lithium azaenolate of camphor

nitrimine (1) with *p*-chlorophenyl vinyl selenoxide also failed. Hence an alternative route was investigated.

In 1969 Limasset and reported the synthesis of cyclopropyl ketones using the Simmons-Smith reaction on  $\alpha,\beta$ -unsaturated carbonyl compound.<sup>10</sup>

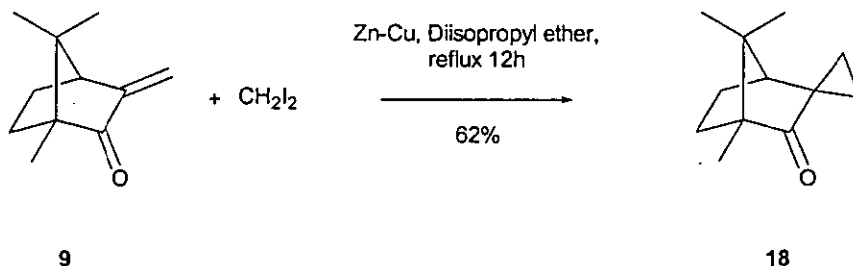
The Simmons-Smith reagent was generated by oxidative addition of diiodomethane to activated zinc-copper couple (Scheme 15)



**Scheme 15:** Formation of the Simmons-Smith reagent

We noticed that zinc-copper couple, freshly prepared by reaction of copper acetate with zinc powder in acetic acid, gave better results in the Simmons-Smith reaction than the commercially available material. We prepared 3-methylene camphor (9) in three steps in moderate yield (Scheme 5).<sup>5,6</sup>

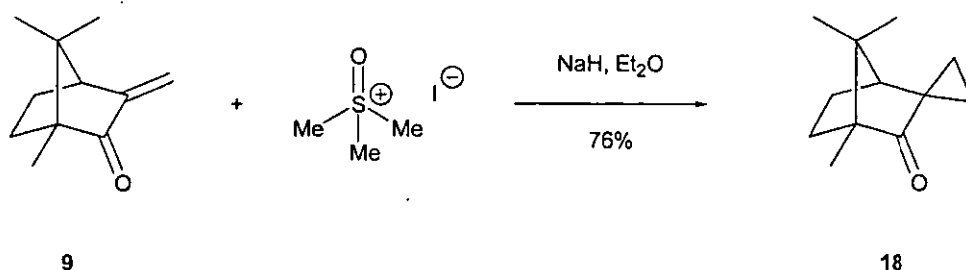
3-Methylene camphor (9) and diiodomethane in diisopropyl ether were gradually added to the zinc-copper couple in diisopropyl ether. The reaction mixture was heated under reflux for 12 hours to afford the desired 3,3-cyclopropane camphor in good yield along with some starting material (9) (Scheme 16).



**Scheme 16:** Synthesis of 3,3-cyclopropyl camphor

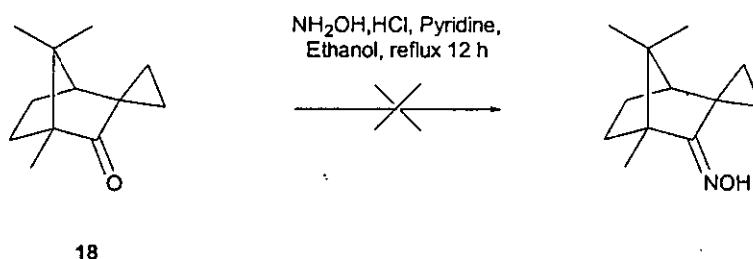
The separation of the 3,3-cyclopropyl camphor from the starting material (9) by chromatography technique was difficult, and hence the use of a stable ylide was investigated for the preparation of (18).

Corey and Chaykovsky reported in 1965 the generation of dimethyloxosulfonium methylide for the transfer of methylene group to a  $\alpha,\beta$ -unsaturated ketones, to form cyclopropyl ketones.<sup>11</sup> The ylide was prepared *in situ* by reaction between trimethyloxosulfonium iodide and sodium hydride and reacted with 3-methylene camphor (**9**) (Scheme 17). The reaction reached completion in two hours, and the 3,3-cyclopropyl camphor was isolated in 76% yield. The reaction occurs without formation of oxirane, and no starting material (**9**) was recovered.



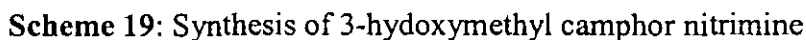
**Scheme 17:** Methylene insertion using dimethyloxosulfonium methylide

The formation of the corresponding oxime was carried out in presence of hydroxylamine hydrochloride and pyridine under reflux in ethanol. Unfortunately, only the starting material (**9**) was recovered: even after 12 hours at reflux, no oxime was formed (Scheme 18).

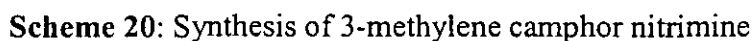


**Scheme 18:** Attempted synthesis of 3,3-cyclopropyl camphor oxime

Since the attempt at formation of the 3-cyclopropyl camphor oxime failed, the conversion of the carbonyl group to oxime was carried out from 3-hydroxymethyl camphor (**8**), which was reacted with hydroxylamine hydrochloride and pyridine to afford 3-hydroxymethyl camphor oxime (**19**) in 57% yield (Scheme 19).



3-Hydroxymethyl camphor nitrimine (**20**) was reacted with methanesulfonyl chloride in the presence of triethylamine to afford the methanesulfonate ester which was subsequently treated with DBU to afford 3-methylene camphor nitrimine (**21**) in 58% yield overall (**Scheme 20**). The methanesulfonate ester was not isolated, and the elimination reaction was performed *in situ*.



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### Conclusion of section 2.2

The alkylation of camphor nitrimine (1) using different bases and alkylating reagents resulted mainly in the recovery of the starting material (1). In order to obtain the 3-alkyl camphor nitrimines, precursors of the desired oxaziridines, the alkylation was carried out on camphor. The hindered 3-alkyl camphor nitrimines were obtained in moderate yield for 3-methyl camphor nitrimines (2a,b) and poor yield for 3-*exo*-(diphenylmethyl) camphor nitrimine (14). It was not possible to separate the two diastereoisomers of 3-methyl camphor nitrimines (2a,b) (ratio *endo/exo*: 91:9). The oximation step in the synthesis of 3-*exo*-(diphenylmethyl) camphor nitrimine (14) was the limiting step only 15% yield.

Unfortunately none of the corresponding oxaziridines have been successfully synthesized, due to the stabilities of the imine intermediates (10a,b; 15).

The synthesis of 3,3-cyclopropane nitrimine was investigated. 3,3-cyclopropane camphor (18) was synthesized from 3-methylene camphor (9) using the ylide methodology in 76% yield. Unfortunately the oximation failed resulting only in the recovery of 3,3-cyclopropane camphor. However 3-hydroxymethyl camphor (8) undergoes oximation and nitroimination to give 3-hydroxymethyl camphor nitrimine (20). The dehydration of (20) via the formation *in situ* of the corresponding mesylate afforded 3-methylene camphor nitrimine (20), which could be a key intermediate for the synthesis of 3,3-cyclopropane and 3,3-dimethyl camphor oxaziridine.

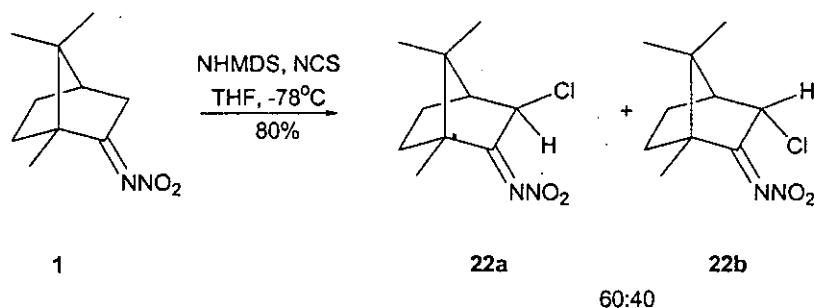
### 2.3 Synthesis of 3-halogeno precursors

The presence of electron-withdrawing groups could enhance the stability and reactivity of the *NH*-imine towards 3-chloroperoxybenzoic acid during the oxidizing steps. Davis and Weismiller noted that the presence of electronegative chlorine atoms on camphorsulfonyl oxaziridine increase its reactivity as well as the stereoinduction during the oxidation of enolates.<sup>13</sup>

The incorporation of halogen atoms would allow us to study the influence of electronegativity on the reactivity of the new *NH* oxaziridines. Substitution at the *endo* or *exo* position, which could affect the stereoinduction during the *NH* transfer reaction, could also be investigated.

### 2.3.1 Synthesis of 3-chloro camphor nitrimine

The synthesis of the 3-chlorocamphor nitrimine was first examined. Camphor nitrimine (**1**) was treated with one equivalent of NHMDS at  $-78^{\circ}\text{C}$  over an hour followed by the addition of *N*-chlorosuccinimide (NCS). The reaction was stirred at the same temperature for two additional hours (**Scheme 21**).



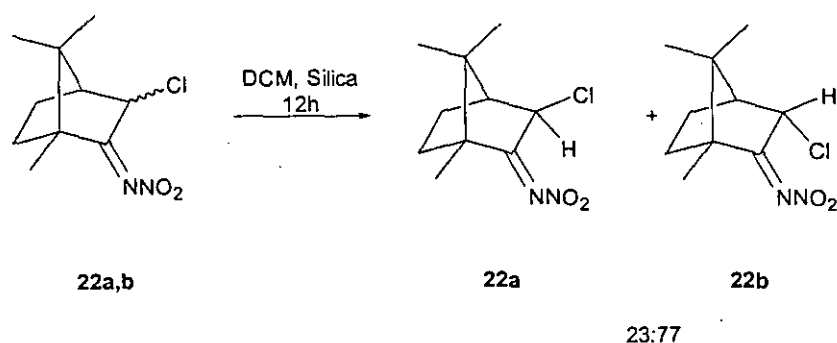
**Scheme 21:** Synthesis of 3-chlorocamphor nitrimines

The desired 3-chlorocamphor nitrimines were recovered in 80% yield after purification by flash chromatography. The *exo* and *endo* chloro nitrimines were obtained in a 60:40 ratio.

The  $^1\text{H}$  NMR spectrum of the mixture shows the presence of a doublet and a singlet for the proton on carbon 3. When the chlorine atom is on *exo* position, there is no coupling between the protons on carbons 3 and 4 due to the angle between them, approximately  $90^{\circ}$  degrees. When the proton on carbon 3 is in the *exo* configuration, it is then coupled to the proton on carbon 4 at  $\delta$  4.65 ( $J = 4.6$  Hz)

It was found that when the mixture of diastereoisomers (**22a,b**) was stirred overnight in dichloromethane with the presence of silica gel, epimerization at carbon 3 occurred in favour of the thermodynamically more stable 3-*endo* chlorocamphor nitrimine (**22b**) (**Scheme 22**). The  $^1\text{H}$  NMR spectrum showed a ratio of 77:23 of *endo*: *exo* products. The process takes place without decomposition of the nitroimine group. The two diastereoisomers were separated by crystallization in hexane.



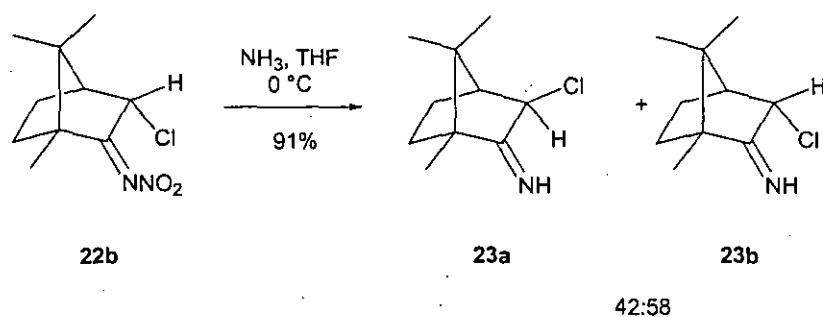


**Scheme 22:** Epimerization of 3-chlorocamphor nitrimine

### 2.3.2 Synthesis of 3-*endo* chlorocamphor oxaziridine

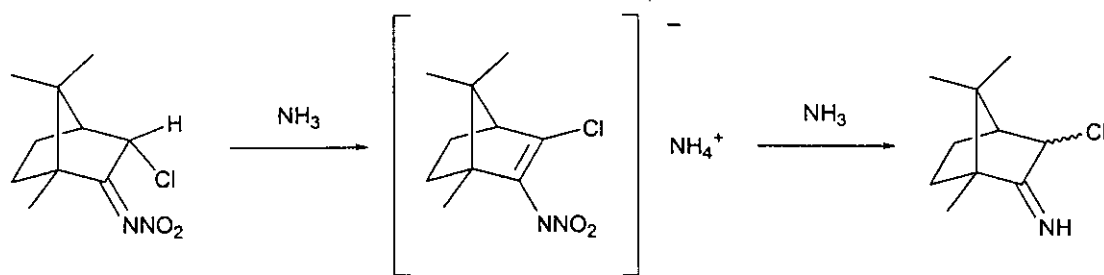
A solution of 3-*endo* chlorocamphor nitrimine (**22b**) in dry THF was treated with ammonia at 0 °C. Surprisingly after 5 minutes the solution became a gel. After further addition of ammonia, the gel disappeared. The reaction was followed by TLC and infrared spectroscopy. The desired imine was obtained in 91% yield.

The  $^1\text{H}$  NMR spectrum revealed that the reaction occurred with partial epimerization at the carbon 3 (**Scheme 23**). A singlet at  $\delta$  4.1 ppm, proving the formation of the *exo* chloro camphor imine (**23a**), and a doublet at 4.62 ppm ( $J$  11.7) were observed.



**Scheme 23:** Formation of 3-chlorocamphor imine

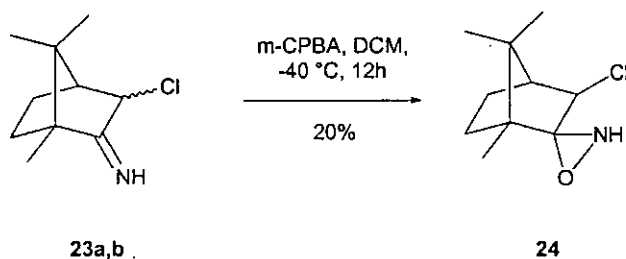
A possible mechanism to explain the formation of the two diastereoisomers and the gel is shown in **Scheme 24**.



**Scheme 24:** Epimerization of 3-chlorocamphor nitrimine and formation of 3-chlorocamphor imine

The presence of the chlorine atom and the nitrimine group make the proton attached on carbon 3 sufficiently acidic for ammonia to act as a base.

Nevertheless, a mixture of (23a/b) was treated with a solution of 3-chloroperoxybenzoic acid in DCM at  $-40^{\circ}\text{C}$  and allowed to stir overnight (**Scheme 25**). TLC and the use of an ethanol solution of potassium iodide revealed the presence of the desired *NH*-camphor oxaziridine. The oxidation of iodine anion by the oxaziridine results in the formation of an orange spot of iodine on the TLC plate. The desired 3-chlorocamphor oxaziridine (**24**) was isolated in 20% yield after purification by flash chromatography on alumina. The  $^1\text{H}$  NMR spectrum showed only a singlet at  $\delta$  4.11 ppm characteristic of the *exo* chloro substitution. Our group has proved on the basis of chemical derivatization at the nitrogen atom that the two bridgehead methyl groups induce *endo* attack of the per-acid from underneath the six-membered ring, an X-ray crystallography of *N*-chlorooxaziridine with the oxygen atom of the oxaziridine moiety *endo*.<sup>1</sup> It is thought that the *endo* chlorine substitution might slow the oxidation and therefore only the *exo* chlorocamphor oxaziridine was recovered. The  $^1\text{H}$  NMR spectrum showed the *endo* proton on carbon 3 as a singlet at 4.11 ppm. There is no coupling between the *endo* proton on carbon 3 and the proton on carbon 4, proving the stereochemistry.

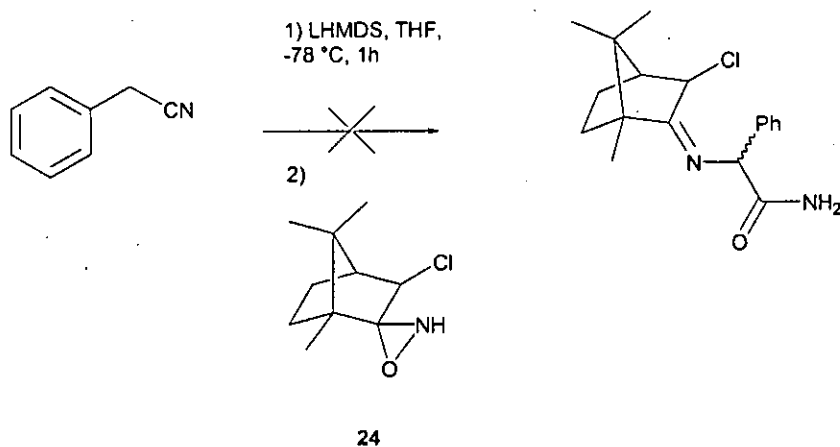


**Scheme 25:** Synthesis of 3-*exo* chlorocamphor oxaziridine

3-Chloroperoxybenzoic acid was used after purification with a solution of phosphate buffered at pH 7.4. Then the exact perbenzoic acid content (84%) was determined by oxidation of a sodium iodide solution and titration of the liberated iodine with a sodium thiosulfate solution.<sup>14</sup>

**2.3.3 Attempted electrophilic amination using 3-*exo*-chlorocamphor oxaziridine**

Our group has reported that *NH*-camphor oxaziridine shows good reactivity towards nitrile nucleophiles.<sup>15</sup> A THF solution of benzyl cyanide at  $-78^{\circ}\text{C}$  was treated with LHMDS for an hour. The freshly formed anion was then reacted with the oxaziridine (**24**) for an additional 4 hours at the same temperature (**Scheme 26**).

**Scheme 26:** Attempted *NH* transfer using 3-*exo* chlorocamphor oxaziridine

Unfortunately no amination was observed. Benzyl cyanide and 3-chlorocamphor were recovered. The benzyl cyanide anion might act as a base removing the *endo* proton on carbon 3.

**Conclusion of section 2.3**

The precursors, 3-chloro camphor nitrimines, were synthesized in good yield from camphor nitrimine (**1**). The epimerization in favour of the thermodynamically

more stable *endo* chloro nitrimine (**22b**) was performed under mild acidic conditions in order to protect the nitrimine group.

The ammonolysis of the nitrimine (**22b**) occurred with epimerization. The oxidation of the diastereoisomeric mixture affords in poor yield the *exo* chlorocamphor oxaziridine (**24**). As the oxidation proceeds underneath the six-membered ring, the *endo* chloro substitution hindrance could explain the non-formation of the corresponding oxaziridine

Unfortunately no electrophilic aminations were observed on the reaction of benzyl cyanide anion with oxaziridine (**24**), probably because deprotonation at the carbon 3 is occurring.

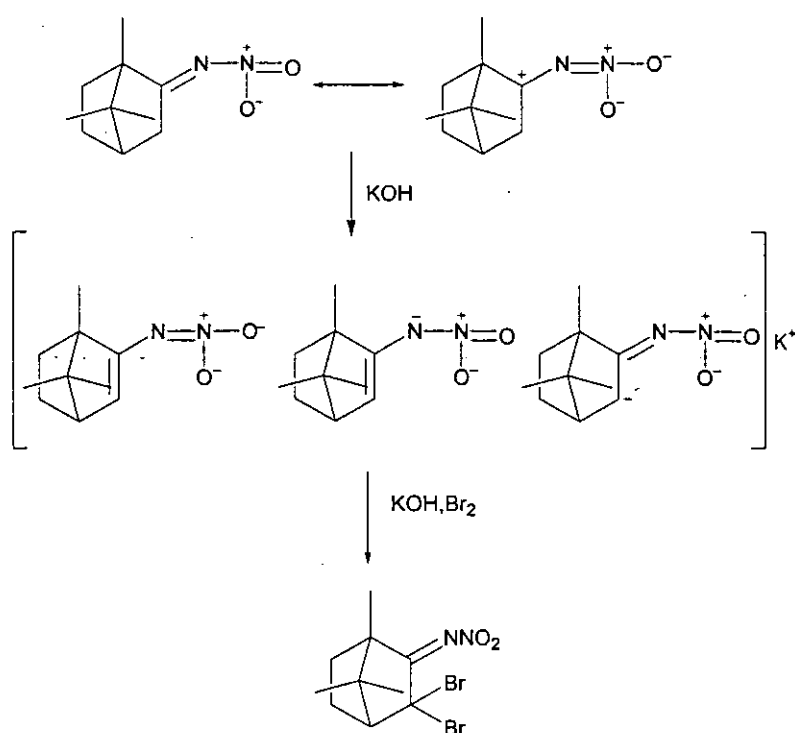
On the basis of these results, the synthesis of di-halogeno camphor oxaziridine was investigated.

## 2.4 Synthesis of di-halogenocamphor nitrimines

The presence of two halogen atoms on carbon 3 of the bornane skeleton would increase the electron-withdrawing effect on the oxaziridine ring and act as a barrier during the trajectory of approach of the nucleophiles during the process of electrophilic amination and prevents deprotonation on carbon 3. 3,3-Dibromocamphor nitrimine was the first to be investigated.

### 2.4.1 Synthesis of 3,3-dibromocamphor nitrimine

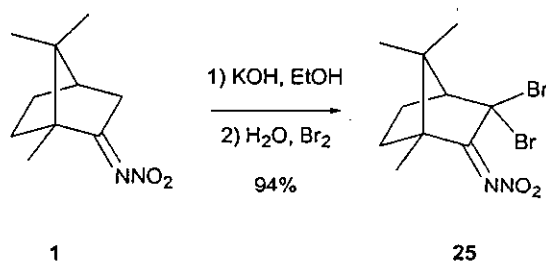
Schenone, Bondavalli and Ranise reported in 1985 the formation of the (S) 3,3-dibromocamphor nitrimine *via* the alkaline salt of camphor nitrimine (Scheme 27).<sup>16</sup>



**Scheme 27:** Formation of (S) 3,3-dibromocamphor nitrimine

Following their procedure, a warm ethanol solution of camphor nitrimine (**1**) was treated with potassium hydroxide. The freshly formed potassium salt was dissolved in the minimum of water and reacted with an excess of bromine to give in 94% yield the desired (R) 3,3-dibromocamphor nitrimine (**25**) (Scheme 28).

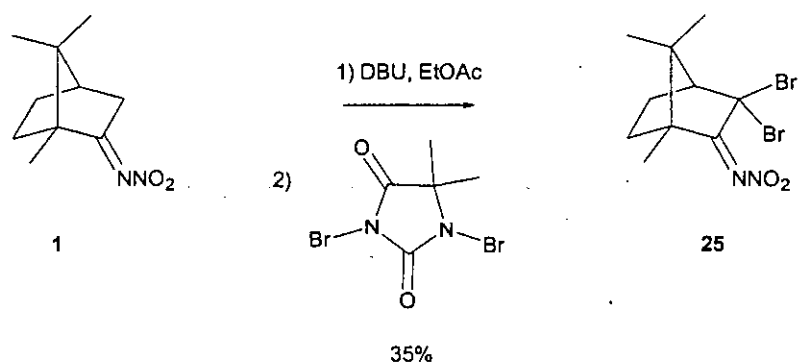
This reaction occurred at room temperature, the pale yellow potassium salt is formed within a minute, and the bromination takes place in half an hour.



**Scheme 28:** Synthesis of (R) 3,3-dibromo camphor nitrimine

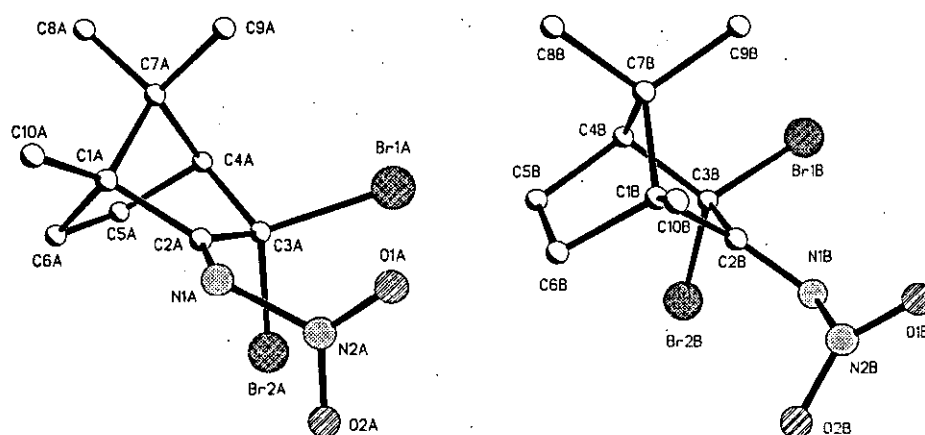
Another method for the synthesis of (**25**) gave an interesting result. Camphor nitrimine (**1**) was treated with the base DBU in ethyl acetate and then reacted with

dibromodimethylhydantoin (DBDMH). The desired 3,3-dibromocamphor nitrimine was obtained after purification by flash chromatography in 35% yield (**Scheme 29**).



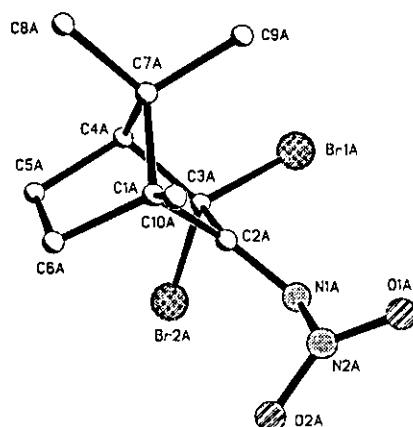
**Scheme 29:** Alternative synthesis of 3,3-dibromocamphor nitrimine

The  $^1\text{H}$  NMR spectrum of the purified material however revealed the formation of two compounds with the characteristic of the required product in a 1:1 ratio. Comparison with the data of the 3,3-dibromocamphor nitrimine obtained with the previous method proved that one of the product obtained was the same nitrimine (**25**). X-ray analysis of the crystals (**Appendix 1**) showed that both products, which crystallized together, were 3,3-dibromocamphor nitrimines but for the first time with different stereochemistry at the imine nitrogen (**Scheme 30**).



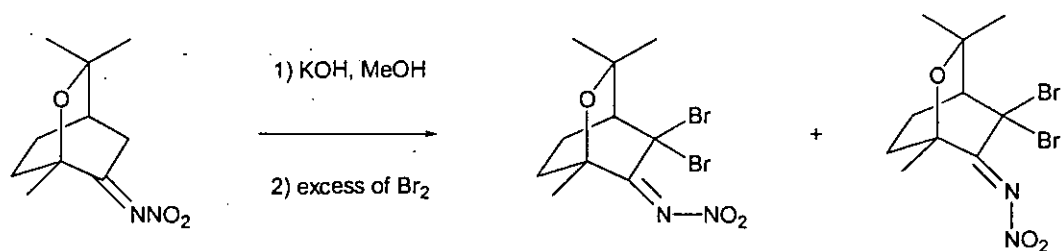
**Scheme 30:** X-ray of 3,3-dibromocamphor nitrimine

As the two diastereoisomers crystallized out together, another X-ray study (**Appendix 2**) was performed on crystals of the nitrimine (**25**) obtained by the first technique, which proved to be the thermodynamically more stable *N-trans* nitro isomer (**Scheme 31**).



**Scheme 31:** X-ray of *N-trans* nitro 3,3-dibromocamphor imine

Schenone, Bondavalli and Ranise also reported the formation of *N-(Z)* and *N-(E)* nitro 3,3-dibromocineole nitrimines when cineole nitrimine was reacted with an excess of potassium hydroxide and bromine (**Scheme 32**).<sup>17</sup>

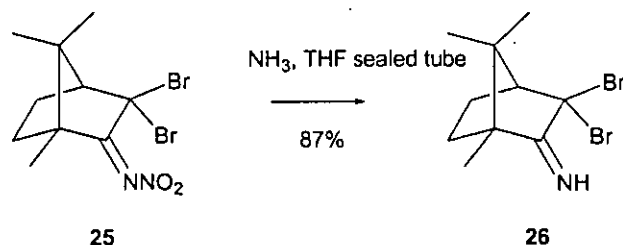


**Scheme 32:** Synthesis of *N-(Z)* and *N-(E)* nitro 3,3-dibromocineole nitrimine

#### 2.4.2 Attempted synthesis of 3,3-dibromocamphor oxaziridine

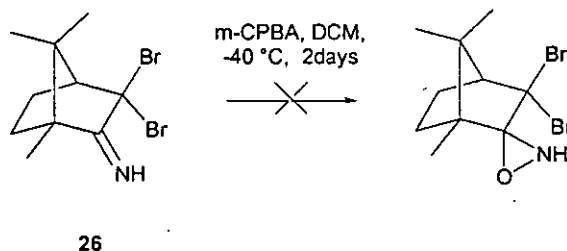
The ammonolysis of the 3,3-dibromocamphor nitrimine (**25**) was a slow process due to the steric hindrance around the nitrimine group. When a solution of the 3,3-dibromocamphor nitrimine (**25**) was treated with ammonia for four hours the

reaction did not reach completion. In order to obtain the desired imine the ammonolysis was carried out in a sealed tube. In a typical procedure, ammonia was condensed at  $-78\text{ }^{\circ}\text{C}$  into a THF solution of nitrimine (**25**). After five minutes, the flux of ammonia was stopped and the tube sealed. The reaction undergoes completion in 12 hours at room temperature (Scheme 33). 3,3-Dibromocamphor nitrimine (**25**) was first dissolved in THF because of its insolubility in liquid ammonia.



**Scheme 33:** Formation of 3,3 dibromocamphor nitrimine

Unfortunately the oxidation of the imine (**26**) in presence of purified 3-chloroperoxybenzoic acid did not occur over two days at  $-40\text{ }^{\circ}\text{C}$ . The reaction was followed by TLC, and revealed the formation of a new compound. The new product was separated by column chromatography but was not the desired oxaziridine (Scheme 34).



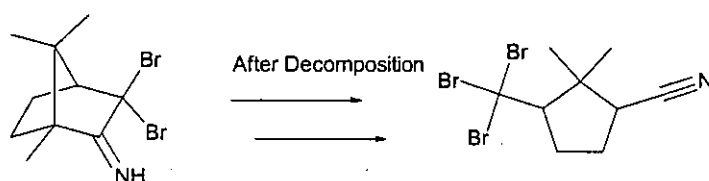
**Scheme 34:** Attempts oxidation of 3,3-dibromocamphor imine

The new compound showed oxidant properties when the TLC plates were visualized with a potassium iodide solution. The  $^1\text{H}$  NMR spectrum proved that the new product was not the corresponding 3,3-dibromocamphor. The  $^{13}\text{C}$  NMR spectrum did not show a peak around  $\delta$  100 ppm characteristic of the quaternary carbon bearing the oxaziridine ring but instead a peak at  $\delta$  184 ppm. The signal corresponding to the



carbon bearing the imine double bond was at  $\delta$  189.4 ppm. A peak at  $1610\text{ cm}^{-1}$  was present in the infrared spectrum. This compound was subject to mass spectrum analysis which revealed a mass of 310.13; the expected mass of the desired oxaziridine would be 325.04 and 3,3-dibromocamphor imine has a mass of 309.04.

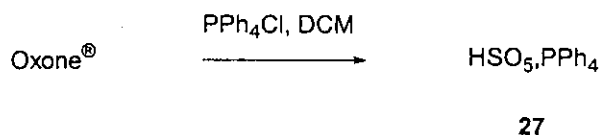
This compound crystallized in hexane at low temperature ( $-20\text{ }^{\circ}\text{C}$ ) and was submitted to X-Ray analysis. Unfortunately the initial product had decomposed to give a nitrile derivative bearing three atoms of bromine (**Scheme 35**). It is thought that the unknown compound could be the bromine salt of the protonated imine.



**Scheme 35:** Decomposition product from the oxidation of the imine

*m*-Chlorobenzoic acid, the byproduct of the oxidation with 3-chloroperoxybenzoic acid, could induce a slow decomposition of the imine or the oxaziridine. In order to avoid the presence of an acid, the use of an oxone derivative, which gives a sulfonate salt as byproduct, was employed in the reaction to oxidize the primary imine. Oxone<sup>®</sup> contains water, and it is normally used in bi-phasic (aqueous/organic) reactions. Those oxidation conditions are not suitable in our case because of the relative instability of the primary amine.

However the tetraphenyl phosphonium monoperoxysulfate TPPP (**27**), prepared from Oxone<sup>®</sup> and tetraphenyl phosphonium chloride, is soluble in dichloromethane and is water-free (**Scheme 36**).

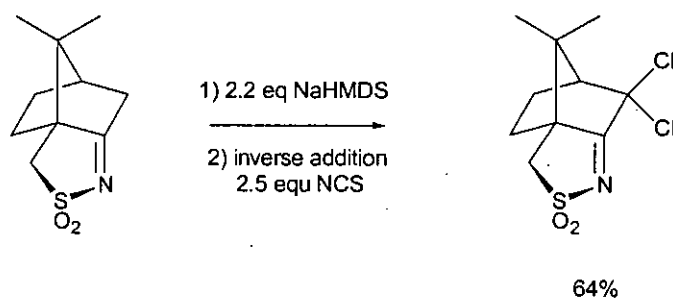


**Scheme 36:** Formation of TPPP

An attempted oxidation of the imine (**26**) with TPPP (**27**) did not reach completion after two days. The reaction led to no decomposition product. The reaction was followed by TLC, and revealed the formation of the same unidentified product. The sulfonate salt byproduct insoluble in DCM was removed by simple filtration.

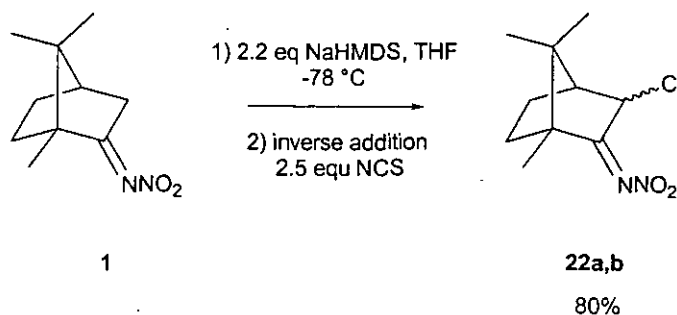
### 2.4.3 Synthesis of 3,3-dichlorocamphor nitrimine

Davis reported the synthesis of the *N*-sulfonyl 3,3-dichlorocamphor imine in 64% yield by treating *N*-(camphorylsulfonyl) imine with 2.2 equivalents of NaHMDS at  $-78\text{ }^{\circ}\text{C}$  in THF to generate the azaenolate followed by its addition, *via* a cannula, to 2.5 equivalents of *N*-chlorosuccinimide (**Scheme 37**).<sup>13</sup>



**Scheme 37:** Synthesis of the *N*-sulfonyl 3,3-dichlorocamphor imine

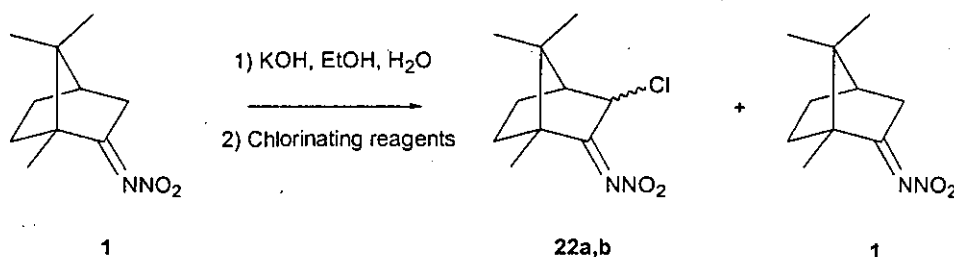
Following this method, camphor nitrimine (**1**) was treated with two equivalent of NaHMDS over one hour. The freshly formed azaenolate was then added to a solution of *N*-chlorosuccinimide (**Scheme 38**).



**Scheme 38:** Attempted synthesis of 3,3-dichlorocamphor nitrimine

Unfortunately only 3-chlorocamphor nitrimines (**22a,b**) were obtained. Other attempts using different bases such as LDA or LHMDs gave the same result. Since the dichlorination of camphor nitrimine was unsuccessful, the reaction was repeated, starting from 3-chloro camphor nitrimines. A solution of nitrimines (**22a,b**) in THF at  $-78\text{ }^{\circ}\text{C}$  was treated with LHMDs over one hour, followed by the addition to NCS, but no 3,3-dichlorocamphor nitrimine was recovered.

The use of potassium hydroxide and bromine had however proved to be successful for the formation of the 3,3-dibromocamphor nitrimine. A solution of camphor nitrimine in warm ethanol was therefore treated with potassium hydroxide followed by the addition of a number of chlorinating reagents (**Scheme 39**).



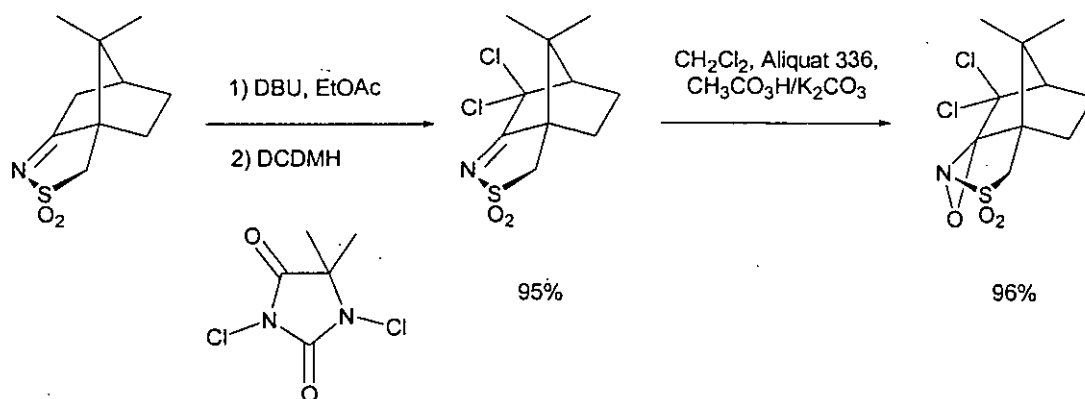
| Entry | Chlorinating reagents           | Products                                  |
|-------|---------------------------------|---|
| 1     | NCS                             | Starting material <b>1</b> + <b>22a,b</b> |
| 2     | Cl <sub>2</sub>                 | Starting material <b>1</b>                |
| 3     | SO <sub>2</sub> Cl <sub>2</sub> | Starting material <b>1</b> + <b>22a,b</b> |

**Scheme 39:** Attempted synthesis of 3,3-dichlorocamphor nitrimine using potassium hydroxide

The <sup>1</sup>H NMR spectrum of the crude reaction mixture (entry 1) showed the formation of a little amount of mono-chlorocamphor nitrimine but mainly the presence of the starting material (**1**). The potassium salt was then treated with chlorine (entry 2). The chlorine was synthesized by reaction of potassium permanganate with sodium hypochlorite and bubbled through the reaction mixture. No reaction was observed, probably due to low solubility of chlorine in ethanol, or the low polarisability of the chlorine-chlorine bond. The use of sulfuryl chloride (entry 3)

resulted in the formation of a mixture of starting material and traces of chlorocamphor nitrimine (**22a,b**). In all these cases no 3,3-dichlorocamphor nitrimine was synthesised.

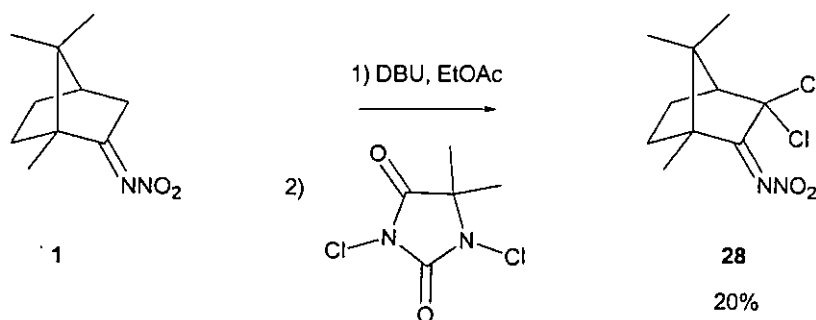
In 1992, Tanner and co-workers reported a convenient and efficient procedure for the synthesis of (-)-((8,8-dichlorocamphoryl)sulfonyl) oxaziridine from (-) (camphorylsulfonyl)imine (**Scheme 40**).<sup>18</sup>



**Scheme 40:** Synthesis of (-)-((8,8-dichlorocamphoryl)sulfonyl) oxaziridine

This improved procedure allowed the synthesis of the oxaziridine in large scale. The formation of the (-)-((8,8-dichlorocamphoryl)sulfonyl) imine was run at room temperature in ethyl acetate with the use of the inexpensive dichlorodimethylhydantoin as chlorinating reagent.

Following this method, we treated camphor nitrimine (**1**) in ethyl acetate with 2.1 equivalents of DBU, resulting in the formation of a yellow salt. Dichlorodimethylhydantoin was added gradually over five minutes. The reaction was stirred for two additional hours. The desired 3,3-dichlorocamphor nitrimine was obtained after purification by flash chromatography (**Scheme 41**).



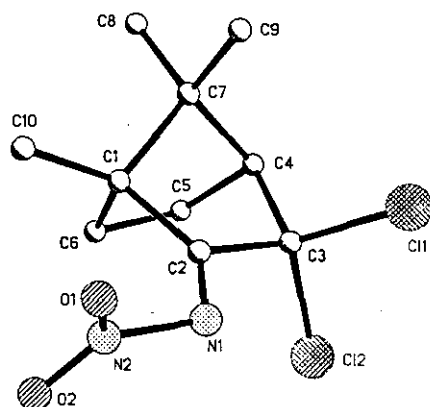
**Scheme 41:** Synthesis of 3,3-dichlorocamphor nitrimine

$^1\text{H}$  NMR spectroscopy revealed the formation of two compounds with the characteristic peaks of the desired product in a 1:1 ratio. The reaction occurred with no isolation of 3-chlorocamphor nitrimine. The two products obtained were originally thought to be the *cis* and *trans* *N*-nitro isomers, like the corresponding 3,3-dibromocamphor nitrimine synthesised using this method.

Mass spectroscopic data confirmed the presence of two chlorine atoms on both compounds. The infrared spectra of the mixture showed the absorption of (C=N) imine double bonds at  $1650\text{ cm}^{-1}$  and the nitro group at  $1578\text{ cm}^{-1}$ .

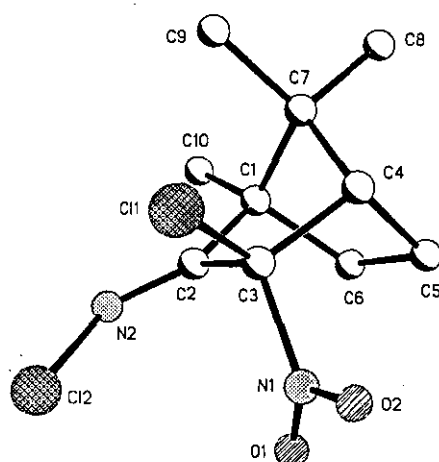
The  $^{13}\text{C}$  NMR spectrum of the mixture shows two signals at  $\delta$  181.57 ppm and at  $\delta$  177.06 ppm, characteristic of the C=N-NO<sub>2</sub> grouping. Davis and co-workers reported that the typical chemical shift of the carbon bearing the two chlorine atoms is around 60 ppm in *N*-(phenylsulfonyl) 3,3-dichlorocamphor imine.<sup>2</sup> We observed only one signal at  $\delta$  62.16 ppm. The compounds were separated by crystallization in hexane. The mass spectroscopic data of the two products were in agreement with the molecular formula C<sub>10</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub>.

The X-ray diffraction data allowed us to establish the absolute structure and configuration of both compounds. One was indeed the desired 3,3-dichlorocamphor nitrimine (28) (Scheme 42) (Appendix 3).



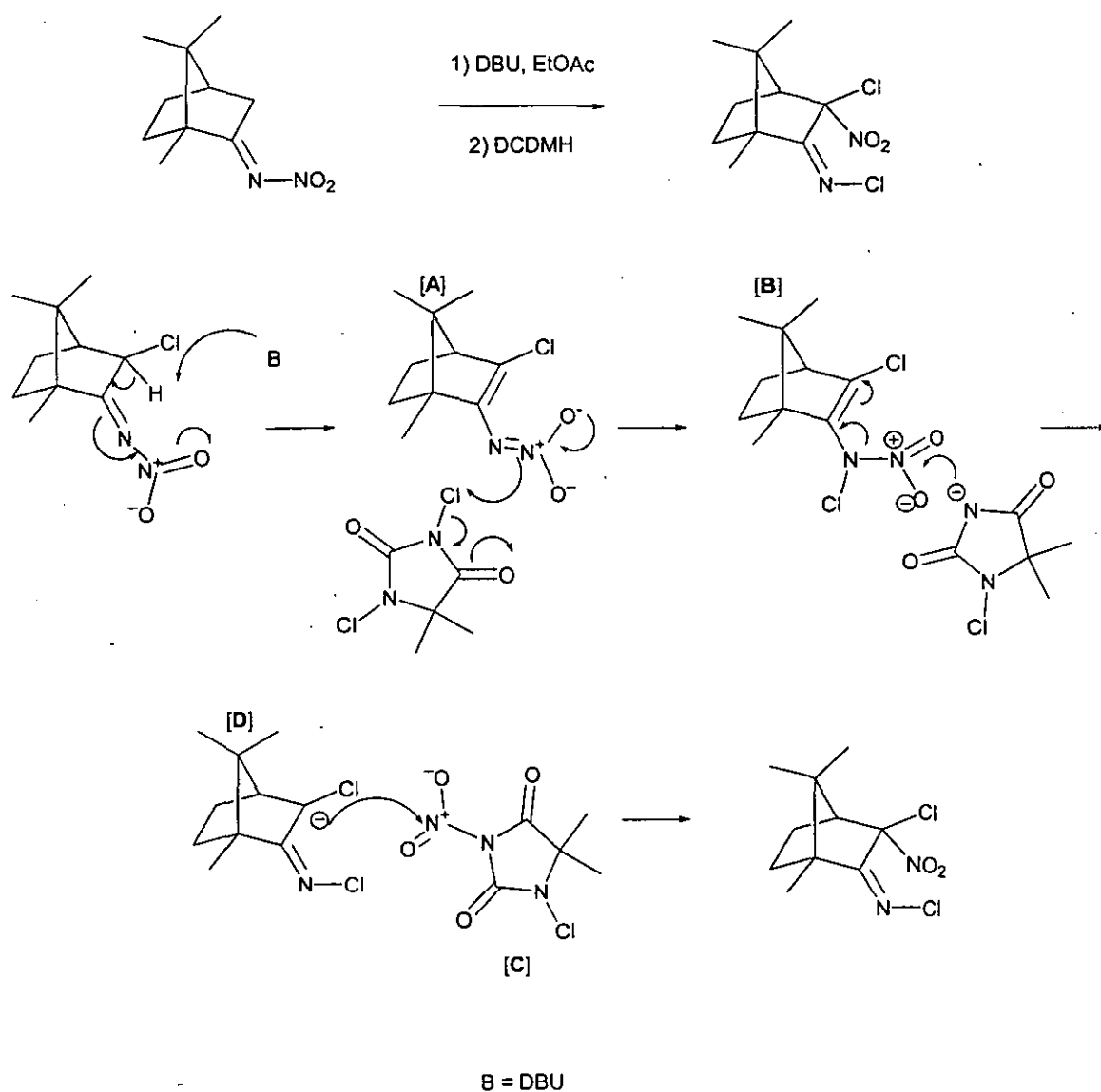
**Scheme 42:** X-ray of 3,3-dichlorocamphor nitrimine

The other compound was identified as the *N*-chloro 3-nitro 3-chlorocamphor imine (**29**) (**Scheme 43**) (**appendix 4**). The nitro group has been transferred from the imine to the carbon 3, which explains the observed chemical shift of 100.74 ppm for the quaternary carbon 3.



**Scheme 43:** X-ray of *N*-chloro 3-nitro 3 chloro camphor imine

A tentative mechanism for the formation of the imine (**29**) is shown in the **Scheme 44**.

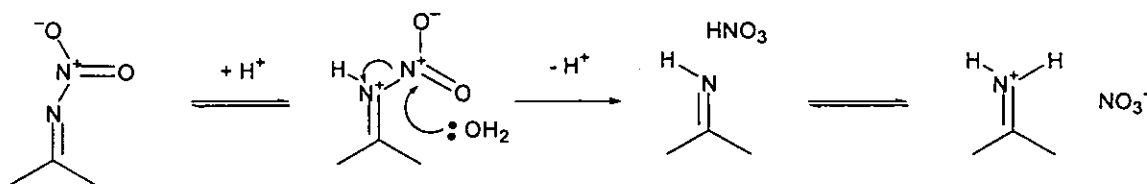


**Scheme 44:** Possible mechanism for the formation of imine (29)

It is thought that the first step would be the formation of the 3-chloro camphor nitrime. The remaining acidic proton on carbon 3 could be deprotonated by DBU to form a stabilized enamine [A], which would react further to give the *N*-chloro *N*-nitro enamine [B] weakening the nitrogen-nitro bond. The hydantoin-conjugated base may attack the nitro group to form an electrophilic nitro compound [C], which could react with the stabilised anion [D] to form the *N*-chloro imine (29).

Gamble, Hems and Ridge have proposed a mechanism for the preparation of camphor imine as a stable nitrate salt by nitrosation of camphor oxime in acidic conditions, *via* the formation of the nitrime intermediate.<sup>19</sup> They postulated under

these conditions the nitrimine is in equilibrium with its protonated form. The nitro group of this intermediate would be attacked by water, resulting in the generation of the nitrate salt (**Scheme 45**).



**Scheme 45:** Suggested mechanism for the formation of camphor imine nitrate salt

The mechanism proposed for the formation of the imine (**29**) is in accordance with this synthesis of the nitrate salt as both suggest the formation of an intermediate (intermediate **[B]** **Scheme 45**), which would result in the weakening of the imine-nitro bond and so could explain the lability of the nitro group.

The imines (**28,29**) were isolated by column chromatography on silica in 40% yield, eluting together. The separation by recrystallization was successful to allow characterization of each compound. On larger scale it was not possible to obtain the 3,3-dichlorocamphor nitrimine (**28**) uncontaminated with the imine (**29**).

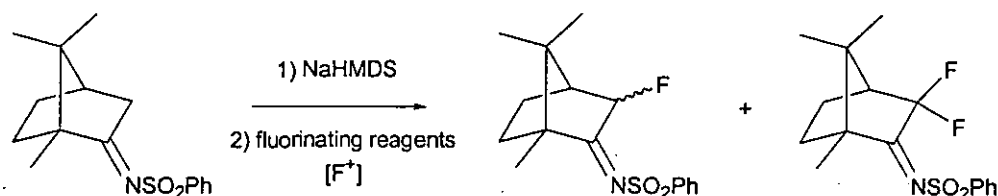
#### 2.4.4 Attempted synthesis of 3,3-difluorocamphor nitrimine

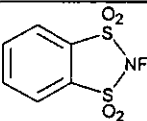
Davis reported that the synthesis of *N*-(phenylsulfonyl)-(3,3-difluorocamphoryl) oxaziridine by oxidation of the difluorosulfonylimine occurred in only three hours, due to the electron-withdrawing effect of the fluorine substitution. In comparison, the oxidation of dichloro- and dibromo-sulfonylimines required five days.<sup>2</sup>

Davis and co-workers attempted synthesis of the difluoro-sulfonylimine by treatment of *N*-phenylsulfonyl camphor imine with NHMDS followed by the addition of acyl hypofluorite ( $\text{CH}_3\text{COOF}$ ) or *N*-fluoro-*o*-benzenedisulfonimide failed, but resulted in the recovery of the monofluoro product (**Scheme 46**). In order to obtain the desired difluoro compound the aza-enolate was treated with perchloryl fluoride



( $\text{FCIO}_3$ ), to afford the *N*-phenylsulfonyl 3,3-difluorocamphor imine in 43% yield along with the monofluoro product in 28% yield (**Scheme 46**).



| $\text{F}^+$  | Monofluorosulfonylimine<br>Yield% | Difluorosulfonylimine<br>Yield% |
|---|-----------------------------------|---------------------------------|
| $\text{CH}_3\text{COOF}$  | 30                                | -                               |
|  | 65                                | -                               |
| $\text{FCIO}_3$   | 28                                | 43                              |

**Scheme 46:** Synthesis of *N*-phenylsulfonyl-3,3-difluorocamphor imine

The presence of fluorine electron-withdrawing groups could enhance reactivity of the *NH*-camphor imine towards 3-chloroperoxybenzoic acid during the oxidizing steps.

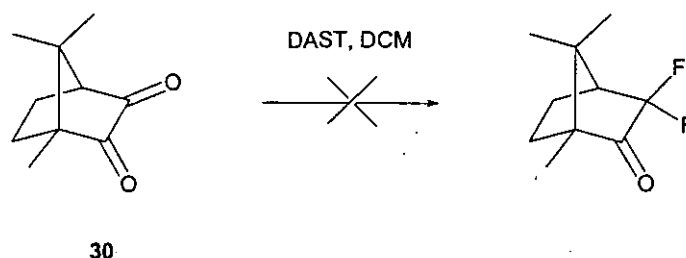
Our attempts to synthesize the 3,3-difluorocamphor nitrimine from camphor nitrimine (**1**) by treatment with different bases, such as KHMDS or DBU and *N*-fluorobenzene sulfonamide, failed resulting in recovery of starting material and monofluoro nitrimines. The use of perchloryl fluoride ( $\text{FCIO}_3$ ) was not tested, as explosions with this reagent have been reported.<sup>20</sup>

An alternative approach tested by us to obtain the difluoro product was the method developed by Middleton.<sup>21</sup> Diethylaminosulfur trifluoride (DAST) is a convenient reagent for replacing the carbonyl oxygen of ketones by two fluorine atoms (**Scheme 47**).



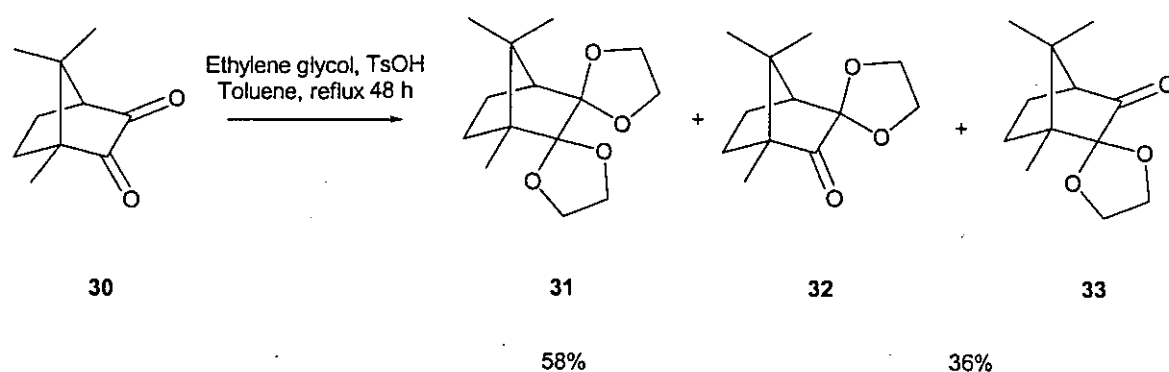
**Scheme 47:** Reaction of carbonyl compounds with DAST

First, camphorquinone (**30**) was treated with DAST in dichloromethane at room temperature for half an hour, but only starting material was recovered (**Scheme 48**). Attempts to prepare difluorocamphor with different reaction conditions as for example by stirring (**30**) with a DCM solution of DAST overnight or by refluxing (**30**) and DAST in chloroform for two days failed, producing complex mixtures. It is possible that DAST might react further with the more hindered carbonyl group on carbon 2.



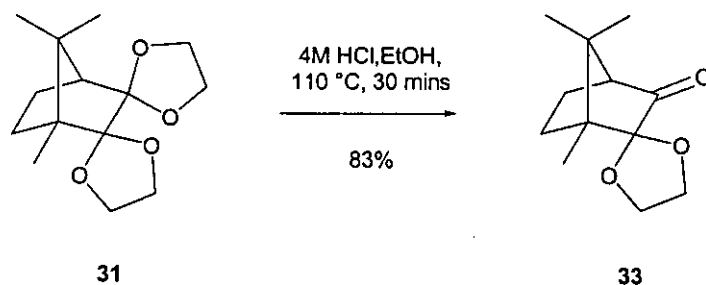
**Scheme 48:** Attempted synthesis of 3,3-difluorocamphor using DAST

Since the difluorination of camphorquinone was unsuccessful, protection of the carbonyl group on carbon 2 was investigated. Riera, Pericas and Moyano reported in 1998 the synthesis of 2,2-(ethylenedioxy) camphorquinone (**33**).<sup>22</sup> The monoacetal was prepared by chemoselective hydrolysis of the less sterically shielded 1,3 dioxolane group of camphorquinone diacetal (**31**). Following their procedure camphorquinone (**30**) was treated with ethylene glycol in a Dean-Stark device using toluene as solvent, to afford a mixture of diacetal (**31**) and monoacetals (**32**) and (**33**) after two days of reflux. Camphorquinone diacetal (**31**) was isolated in 58% yield (**Scheme 49**).



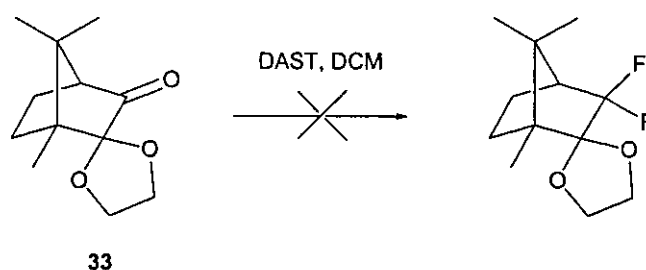
**Scheme 49:** Preparation of camphorquinone diacetal (22)

The regioselective hydrolysis of the diacetal (31) was achieved by treatment of (31) in solution in ethanol with a 4M aqueous HCl solution. The reaction mixture was heated at 110 °C for 30 minutes (TLC monitoring) to afford the monoacetal (33) in 83% yield. (Scheme 50).



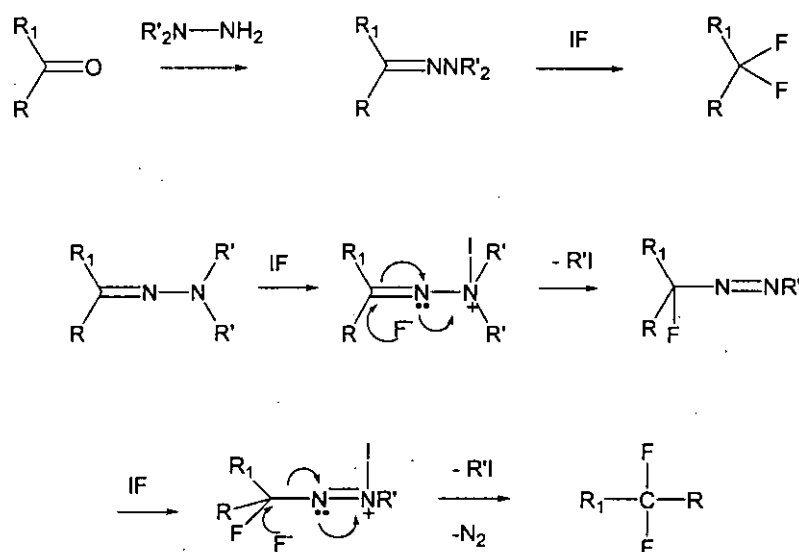
**Scheme 50:** Regioselective hydrolysis of camphorquinone diacetal

2,2-(Ethylenedioxy) camphorquinone (33) in dichloromethane was then reacted with DAST over four hours at room temperature resulting only in the recovery of the starting material (Scheme 51). When compound (33) and DAST were heated under reflux in chloroform none of the desired difluoro product was obtained only starting material was recovered.



**Scheme 51:** Attempted fluorination of 2,2-(ethylenedioxy) camphorquinone

Another method to convert carbonyl group to  $\text{CF}_2$  was developed by Rozen and Zamir.<sup>23</sup> The hydrazone derivative of the carbonyl moiety is reacted under mild conditions with iodine monofluoride (**Scheme 52**).



**Scheme 52:** Conversion of the carbonyl group to  $\text{CF}_2$  using IF.

Iodine monofluoride is formed by reaction of a source of electrophilic iodine and a source of nucleophilic fluorine. It can also be prepared by a reaction between the corresponding elements<sup>24</sup> or from iodine and silver fluoride.<sup>25</sup>

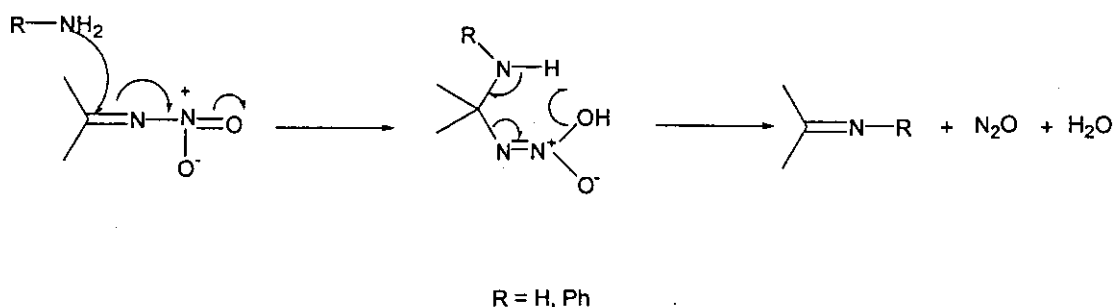
The monohydrazone of camphorquinone was prepared by stirring camphorquinone and hydrazine in ethanol for three hours at 40 °C. The hydrazone product crystallized out of the ethanol solution and was isolated in 51% yield (**Scheme 53**).<sup>26</sup> Unfortunately, attempts to prepare the corresponding 2,2-



Attempts to synthesise 3,3-difluorocamphor nitrimine, by reaction of the az-enolate of camphor nitrimine (1) with *N*-fluorobenzene sulfonamide, or by converting the carbonyl group, on carbon 3 to CF<sub>2</sub> group using DAST or IF, failed.

## 2.5 Ammonolysis of Camphor nitrimine

Schenone, Bondavalli and Ranise have proposed a mechanism for the ammonolysis of nitrimines by attack on sp<sup>2</sup> carbon bearing the nitrimine group, and oxygen transfer from the nitro group to the nucleophile, resulting in the formation of water and dinitrogen oxide (**Scheme 54**).<sup>16</sup>



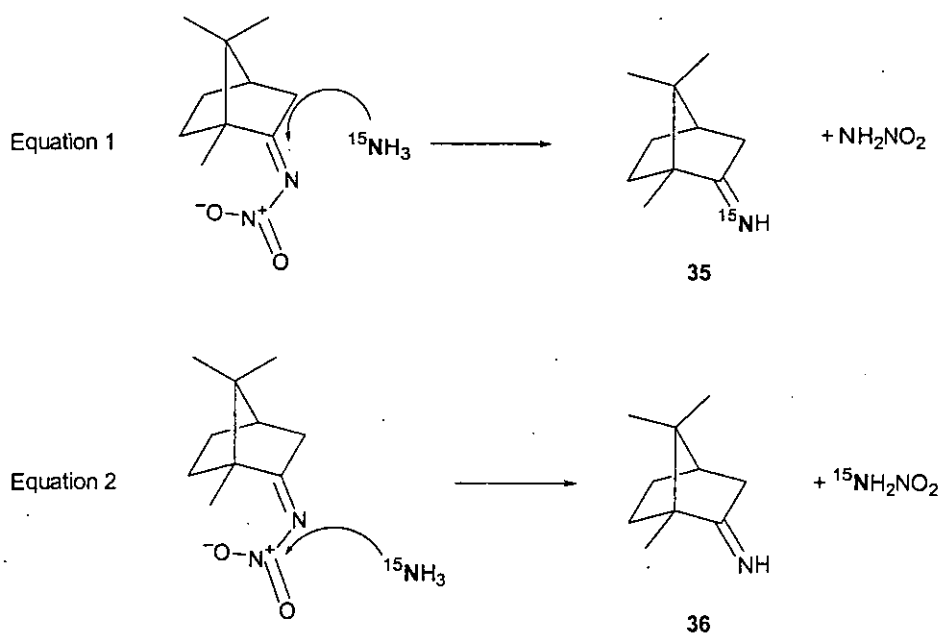
**Scheme 54:** Possible mechanism for the ammonolysis of nitrimine group

During the synthesis of 3,3-dichloro camphor nitrimine however, the nitro group attached to the imine was transferred to the carbon 3 to form the *N*-chloro-3-chloro-3-nitro camphor imine (**29**) (**Scheme 44**). It is possible that attack by the amine might occur at the nitro group instead of the carbon bearing the imine group. The trajectory of approach of the nucleophile during the process of ammonolysis could be blocked by the rigidity of the bornane skeleton.

In order to study the mechanism, the ammonolysis was investigated using <sup>15</sup>N-labelled ammonia. If indeed the nucleophilic attack takes place on the sp<sup>2</sup> carbon bearing the imine double bond, <sup>15</sup>N-camphor imine should be recovered (Equation 1, **Scheme 55**). If the process occurs at the nitro group, however <sup>14</sup>N-camphor imine would be synthesised (Equation 2, **Scheme 55**).

<sup>15</sup>N ammonia was employed, and the reaction was followed by NMR spectroscopy (<sup>15</sup>N, *I* = ½, NMR active). A sample of acetonitrile was submitted first

in order to give the reference. If the ammonolysis occurred at the  $sp^2$  carbon we would observe a signal for imine nitrogen. A solution of camphor nitrimine (1) in dry THF was added to a flask containing 100 ml of  $^{15}\text{N}$ -ammonia (97% purity) gas cooled at  $-78\text{ }^\circ\text{C}$ , and the reaction was stirred for four hours. After removal of the solvent the camphor imine was analysed. The  $^{15}\text{N}$  NMR spectrum showed a signal at  $\delta$  50 ppm. The mass spectral data were in agreement with the molecular formula  $\text{C}_{10}\text{H}_{17}^{15}\text{N}$  and confirmed the presence of an atom of  $^{15}\text{N}$  nitrogen.

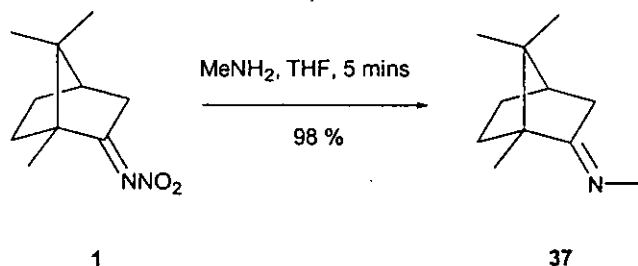


| Camphor Imine | $\delta_{\text{C}}$ ppm (C=NH) | $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$<br>(C=N) | $\delta_{\text{N}}$ $\text{CH}_3\text{-CN} = 0$<br>ppm |
|---------------|--------------------------------|--|--|
|               | 193.7                          | 1666   | -  |
|               | 194.22                         | 1651   | 50   |

**Scheme 55:** Ammonolysis of camphor nitrimine using  $^{15}\text{N}$ -ammonia

According to the data collected, the ammonolysis occurs at the  $sp^2$  carbon bearing the nitrimine group, unless transimination occurs as a subsequent process in situ.

Moreover, *N*-methyl camphor imine was obtained within five minutes when camphor nitrimine was treated with methylamine in THF (Scheme 56). The reaction occurs with formation of gas, probably dinitrogen oxide, as suggested by Schenone.<sup>16</sup>



**Scheme 56:** Synthesis of *N*-methyl camphor imine

## 2.6 Attempted synthesis of 3,3-acetalcamphor nitrimine

Davis has reported that the use of (8,8-dimethoxycamphoryl) sulfonyl oxaziridine for the asymmetric oxidation of substituted tetralones gave higher ee's than did the corresponding (8,8-dichlorocamphoryl) sulfonyl oxaziridine.<sup>27</sup>

We were interested in the synthesis of 3,3-dimethoxy camphor oxaziridine as the presence of methoxy groups, as Davis suggested, could improve the ee's due to stereoelectronic effects and the metal chelation during the amination transfer.<sup>27</sup> Besides, the presence of the bulky methoxy groups could stabilize the oxaziridine.

Our group has reported a convenient procedure for the preparation of a range of camphorsulfonyl oxaziridine 3,3-acetals by treatment of the corresponding imines with commercial aqueous hydrogen peroxide.<sup>28</sup> Syntheses of cyclic and non-cyclic acetals were therefore next investigated.

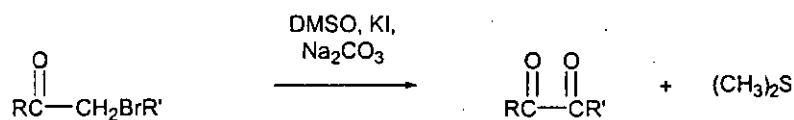
### 2.6.1 Attempted synthesis of 3,3-dimethoxycamphor nitrimine.

Following the procedure of Herzog and Scharf, 3,3-dimethoxycamphor (38) was obtained in 76% yield from camphorquinone by treatment with

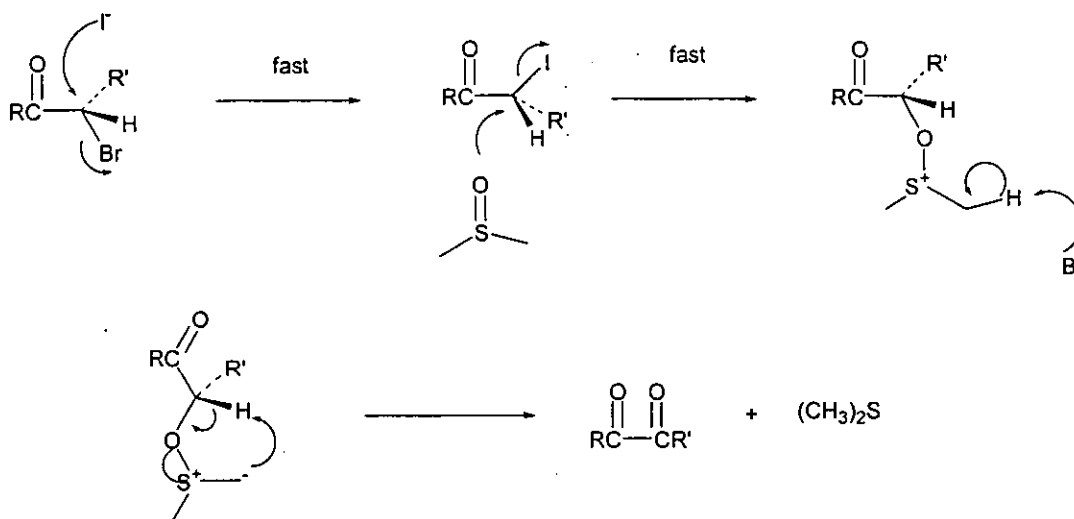




Bauer and Macomber<sup>31</sup> have reported the Kornblum<sup>32</sup> oxidation of  $\alpha$ -bromo ketone with dimethyl sulfoxide, catalysed by iodide. The mechanism is shown in (Scheme 59).

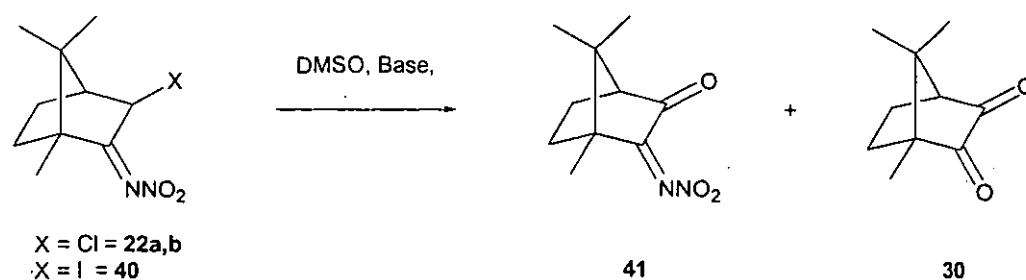


#### Postulated Mechanism



**Scheme 59:** Synthesis of  $\alpha$  diketone

Since camphor nitrimine undergoes  $\alpha$ -halogenation in good yield and the oxidation occurs at room temperature, which would prevent decomposition of the nitrimine group, this modified Kornblum oxidation was investigated with 3-halogeno camphor nitrimine (Scheme 60). The reaction was first tested on 3-chlorocamphor nitrimine.



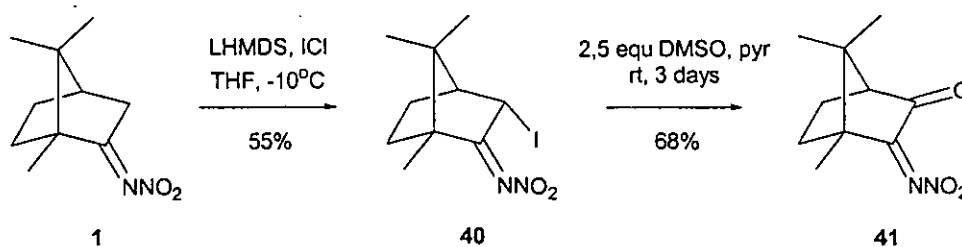
| Entry | Starting Material | Reaction Conditions                                | 30 Yield% | 41 Yield% | Starting material yield% |
|-------|-------------------|--|-----------|-----------|--------------------------|
| 1     | 22a,b             | DMSO, NaI, $\text{K}_2\text{CO}_3$ , 120 °C, 12 h. | 36        | -         | 59                       |
| 2     | 22a,b             | DMSO 2,6-lutidine, r.t., 2 days                    | 24        | -         | 65                       |
| 3     | 40                | DMSO, pyridine, 50°C, 3 days.                      | Trace     | 28        | 47                       |
| 4     | 40                | Pyridine, DMSO, r.t., 3days.                       | -         | 68        | -                        |

Scheme 60 Synthesis of 3-oxo camphor nitrimine

Following the procedure of Bauer and Macomber, 3-chloro camphor nitrimine (22a,b) (entry 1) was added to a mixture of sodium iodide, potassium carbonate and dimethyl sulfoxide at 120 °C. The oxidation step was successful but the reaction occurred with loss of the nitrimine group and the reaction did not reach completion after 12 hours. Attempts using an organic base (entry 2), failed to produce the desired 3-oxocamphor nitrimine : only starting material and camphorquinone were recovered.

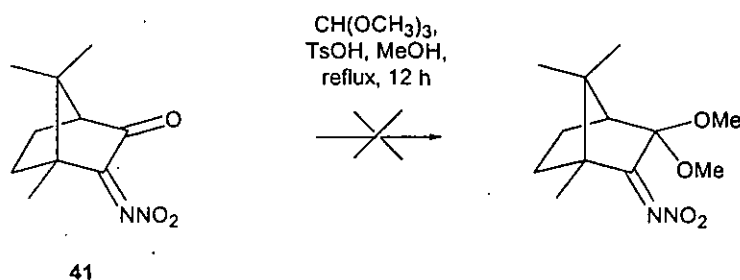
Since iodide is a better leaving group than chloride, the oxidation was also carried with 3-iodocamphor nitrimine (**40**), which was synthesized by reaction of the aza-enolate of camphor nitrimine with iodine monochloride (ICl) (**Scheme 61**). Compound (**40**), dimethyl sulfoxide and pyridine were stirred at 50 °C for three days (entry 3) to afford the desired product in 28% yield.

The above reactions were all carried out in dimethyl sulfoxide, which caused degradation of the nitrimine group. We found that when pyridine was used as solvent (entry 4), 3-oxocamphor nitrimine (**41**) was finally obtained in a good yield of 68% without formation of camphorquinone (**Scheme 61**).



**Scheme 61:** Optimised conditions for the formation of 3-oxocamphor nitrimine

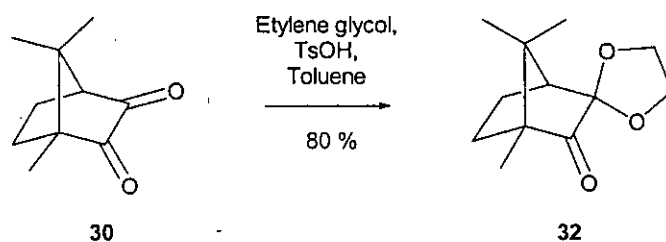
Attempts to synthesize 3,3-dimethoxycamphor nitrimine failed when 3-oxocamphor nitrimine was heated under reflux in methanol with trimethyl orthoformate in the presence of a catalytic amount of *p*-toluenesulfonic acid; only starting material was recovered (**Scheme 62**). Harsher conditions, such as using higher boiling point solvents or the use of sulfuric acid as catalyst, were not investigated because of the ease of hydrolysis of the nitrimine group.



**Scheme 62:** Attempts to synthesize 3,3-dimethoxycamphor nitrimine

### 2.6.2 Attempted synthesis of 3,3-ethylenedioxycamphor nitrimine

Cyclic acetals were next investigated, due to their higher stabilities, which might allow us to obtain the desired nitrimine by the oxime route. Selective acetalization of the less hindered carbonyl group of camphorquinone was accomplished using ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid in toluene with azeotropic removal of water to afford the desired monoacetal (**32**) in 80% yield (**Scheme 63**).<sup>33</sup> The reaction was heated under reflux for only 12 hours, longer reaction time leading to the formation of camphor quinone diacetal (**31**) (**Scheme 49**).



**Scheme 63:** Selective acetalisation of camphorquinone

Conversion of compound (**32**) into the oxime using hydroxylamine hydrochloride and pyridine afforded the desired product in a poor 25% yield, together with formation of camphor dioxime (**Scheme 64**). Several conditions were tested such as the use of a 50% aqueous hydroxylamine solution, which led to a 20% yield of the oxime (**42**). The same yield was obtained when the reaction was carried out in a sealed tube. Under basic conditions in the presence of an excess of sodium acetate and hydroxylamine in methanol the reaction gave only 26% of (**42**). The yield did not improve in ethanol solution at reflux.

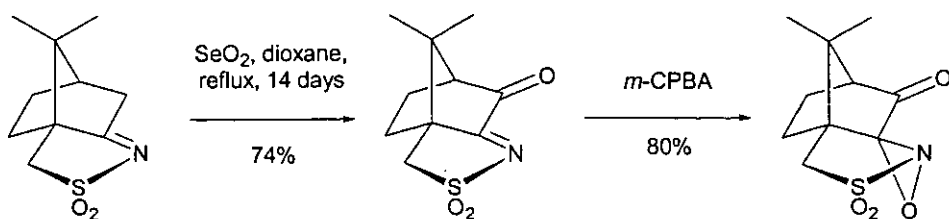
The reaction of (**42**) with 5% aqueous sodium nitrite solution in glacial acetic acid at room temperature over a period of four hours did not afford the desired nitrimine (**Scheme 64**).

Since the oxime (42) was formed in low yield, and because the synthesis of the nitrimine under the usual conditions, failed, this route was not thought to be a viable for the synthesis of new oxaziridines.

Synthesis of 3,3-dimethoxycamphor nitrimine starting from camphorquinone failed due to the low stability of the acetal group towards the oximation conditions. Only camphorquinone dioxime (**39**) and starting material were recovered.

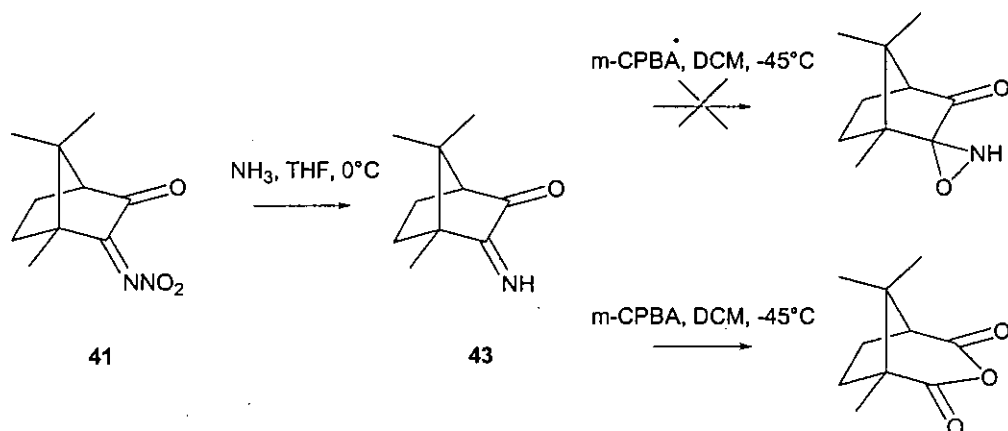
In the case of the cyclic acetal 3,3-ethylenedioxcamphor, generation of the oxime using several different reaction conditions produced the desired oxime (**42**) in poor yield. Furthermore, the transformation of (**42**) to introduce the nitrimine group failed resulting in the formation of decomposition products.

Glahsl and Herrman have reported the synthesis of 3-oxocamphorylsulfonyl oxaziridine for the oxidation of sulfides.<sup>34</sup> The presence of the oxo-group on carbon 3 can improve the selectivity. The first step of the synthesis of the 3-oxocamphorylsulfonyl oxaziridine is the selenium dioxide oxidation of the imine followed by the peracid techniques (**Scheme 65**).



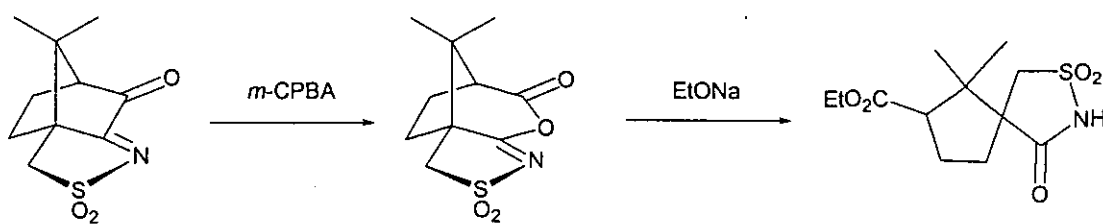
**Scheme 65:** Synthesis of 3-oxo-camphorsulfonyl oxaziridine

3-Oxocamphor nitrimine (**41**), prepared by us using the Kornblum oxidation (**Scheme 61**), was submitted to ammonolysis in THF, resulting in the formation of the desired *NH*-imine (**43**) in quantitative yield, which was oxidized using *m*-CPBA in dichloromethane at  $-45^{\circ}\text{C}$  (**Scheme 66**).



**Scheme 66:** Attempted synthesis of 3-oxo-camphor oxaziridine

Unfortunately, the 3-oxocamphor imine undergoes Bayer-Villiger oxidation under those conditions, and camphor anhydride was isolated. When the reaction was carried out with tetraphenylphosphonium peroxysulfate TPPP (**27**) at  $-45^{\circ}\text{C}$  in dichloromethane no oxaziridine was recovered. Glahsl and Herrman have also observed the formation of Bayer-Villiger product, when the pH of the solution became too acidic. The product of oxidation undergoes ethanolysis to form a spiro compound (**Scheme 67**).

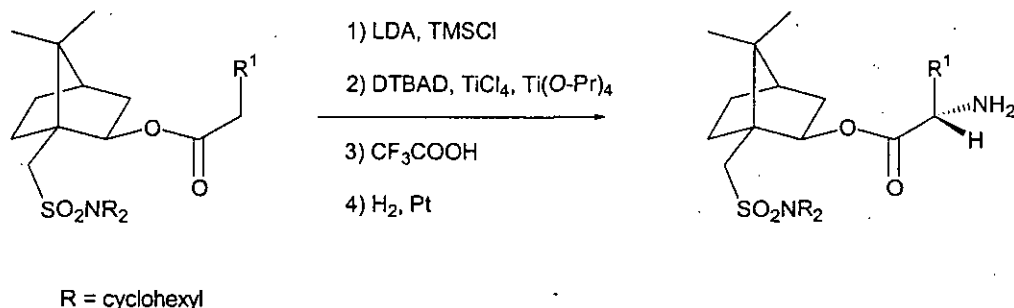


Scheme 67: Bayer-Villiger oxidation

## 2.8 Synthesis of 10-sulfonamido camphor nitrimines

Camphor-10-sulfonamide derivatives have been widely used as chiral auxiliaries for a variety of reactions.<sup>35</sup> They have been commonly employed as chiral alcohols and can be prepared in two steps from camphor-10-sulfonyl chloride by successive amidation and carbonyl reduction.<sup>36</sup>

For example camphor sulfonamide derivatives have been employed as chiral auxiliaries for the electrophilic amination of esters by treating the corresponding esters with LDA/Me<sub>3</sub>SiCl and then with di-*t*-butylazodicarboxylate (Scheme 68).<sup>37</sup> Transesterification mediated by Ti(OEt)<sub>4</sub> yielded the intact camphor auxiliary and hydrolysis of the amino esters afforded the amino acids in good yield and high ee.

Scheme 68: Preparation of  $\alpha$ -amino esters

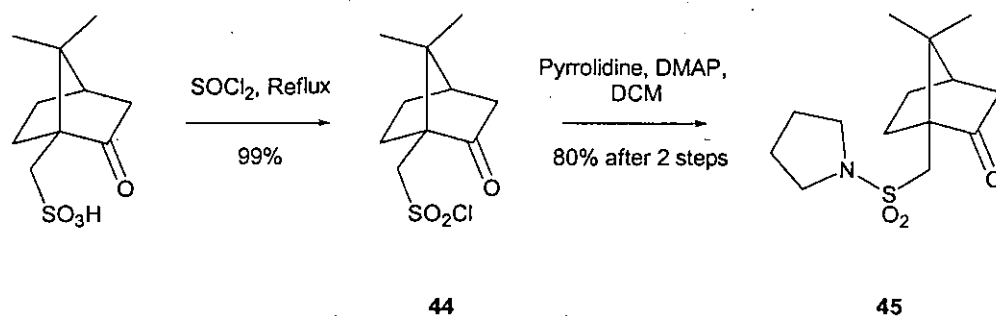
The range of camphor-10-sulfonamides that can be prepared from the sulfonyl chloride offers an opportunity to investigate the effect that substitution on carbon 10 has on the electrophilic amination process and on the asymmetric inductions. In this case the bulkiness in the system is shifted further from the oxaziridine ring. This



might more allow ready oxidation of the corresponding *NH*-imine with *m*-CPBA or tetraphenylphosphonium monoperoxysulfate TPPP (27) to reach completion.

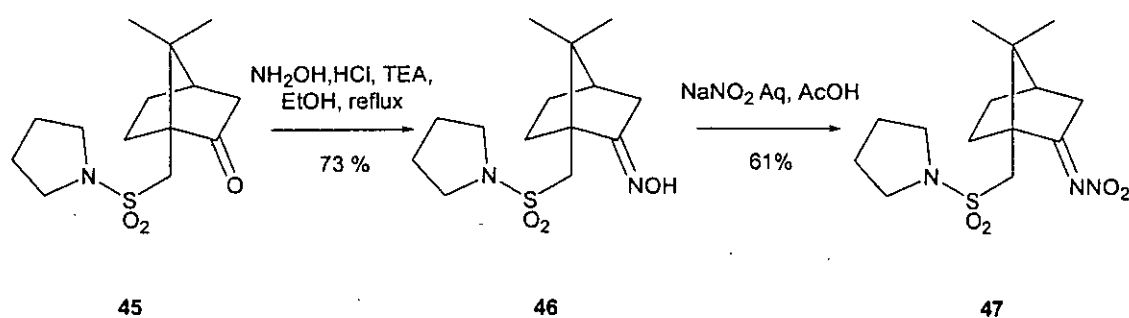
### 2.8.1 Synthesis of *N*-pyrrolidine-10-sulfonamide camphor nitrimine

The synthesis of the *N*-pyrrolidine-10-sulfonamide camphor nitrimine was the first to be investigated and took place in four steps. The first step was the formation of camphor-10-sulfonyl chloride by treatment of camphor-10-sulfonic acid with thionyl chloride in 99% yield, followed by its reaction with pyrrolidine in dichloromethane catalysed by 4-dimethylamino pyridine (DMAP). The corresponding camphor sulfonamide was isolated in 80% yield after two steps (**Scheme 69**). We have noticed that freshly prepared camphor-10-sulfonyl chloride gives better yields than the commercially available material. The presence of the pyrrolidine substitution makes the camphor derivative (45) slightly soluble in water, which can impact upon the isolated yield.



**Scheme 69:** Synthesis of *N*-pyrrolidine-camphor-10-sulfonamide

The synthesis of the corresponding nitrimine encountered no difficulties. First the corresponding oxime (46) was generated from compound (45) using hydroxylamine hydrochloride and triethylamine in 73% yield. The oxime was subsequently treated with a 5% aqueous sodium nitrite in glacial acetic acid to give *N*-pyrrolidine-10-sulfonamide camphor nitrimine in 61% yield (**Scheme 70**).



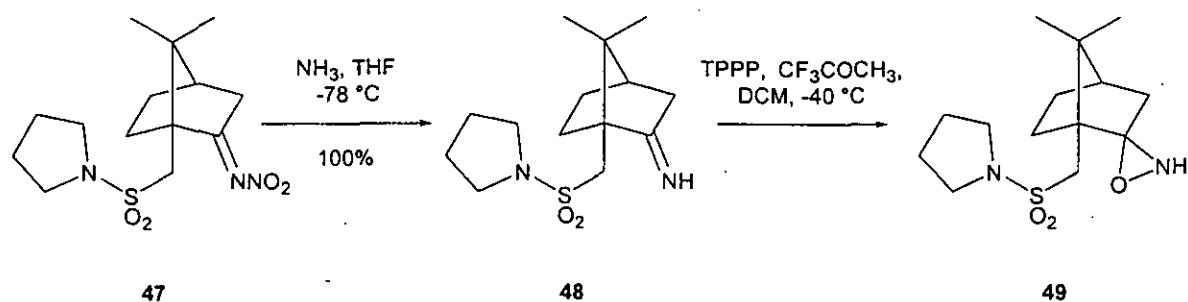
**Scheme 70:** Synthesis of camphor *N*-pyrrolidinyl-10-sulfonamide nitrimine

### 2.8.2 Synthesis of camphor *N*-pyrrolidinyl-10-sulfonamide oxaziridine

Camphor *N*-pyrrolidinyl-10-sulfonamide nitrimine was converted to the *NH*-imine by treatment with ammonia in solution in THF at  $-78\text{ }^{\circ}\text{C}$  for four hours in quantitative yield (**Scheme 71**). We found that the ammonolysis in liquid ammonia at  $-78\text{ }^{\circ}\text{C}$ , instead of bubbling ammonia gas through the reaction at  $0\text{ }^{\circ}\text{C}$  for the same amount of time, reduces the use of ammonia.

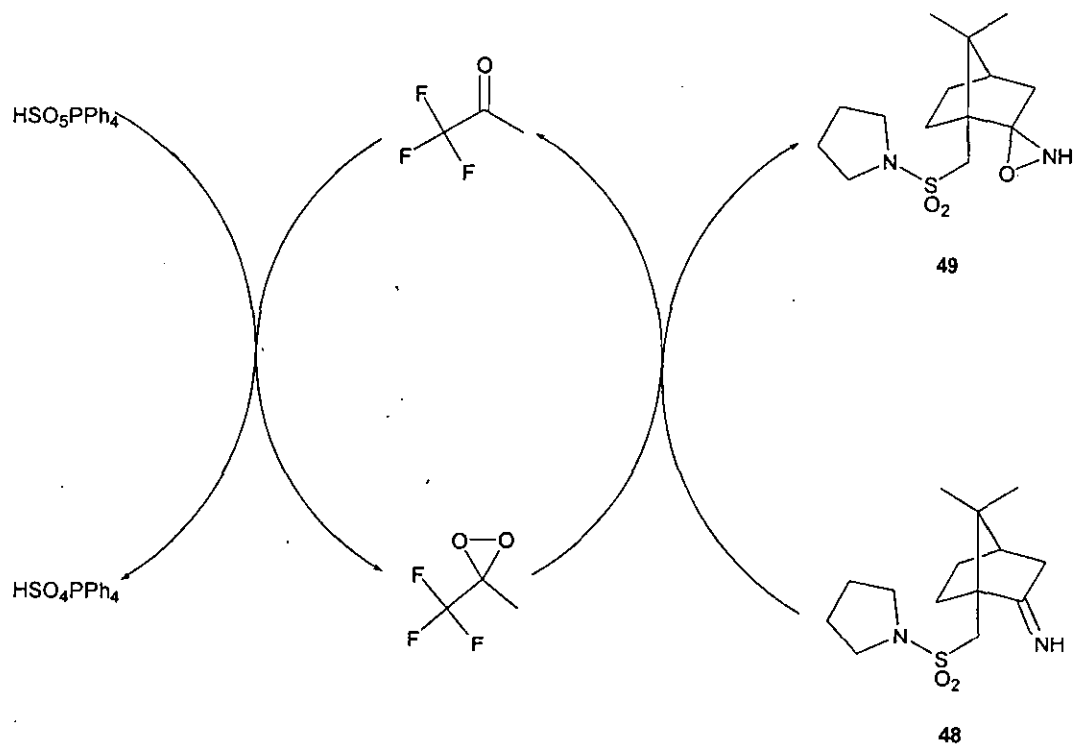
The oxidation step was carried out in the presence of purified 3-chloroperoxybenzoic acid in dichloromethane overnight at  $-40\text{ }^{\circ}\text{C}$ . The reaction was followed by TLC, and revealed the formation of oxaziridine (TLC plates visualized with a potassium iodide solution). Unfortunately the oxaziridine decomposed upon attempted purification by column chromatography.

The oxidation was then carried out using tetraphenyl phosphonium oxone (TPPP) (**27**) and a catalytic amount of trifluoroacetone (**Scheme 71**). The tetraphenyl phosphonium bisulfonate salt, byproduct of the oxidation with TPPP (**27**) crystallized out upon addition of diethyl ether, and was eliminated by filtration during the workup. Filtration through magnesium sulfate and through a small amount of silica gel were the most efficient conditions to remove the by-product.



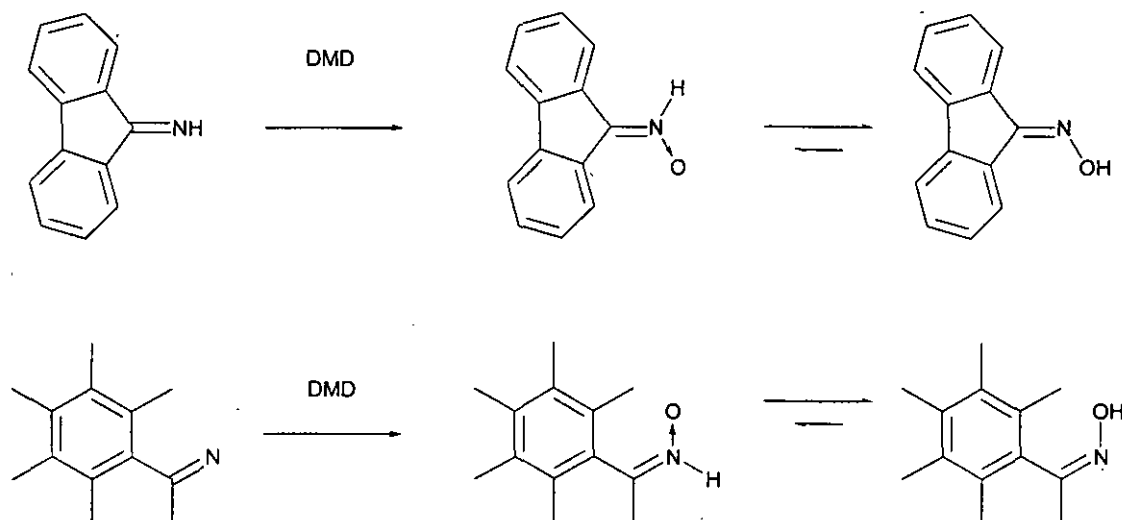
**Scheme 71:** Synthesis of *N*-pyrrolidiny-camphor-10-sulfonamide oxaziridine

The formation of the oxaziridine proceeded in three hours at  $-40^\circ\text{C}$ . In comparison, the oxidation with 3-chloroperoxybenzoic acid reaches completion in 12 hours. We believed that the reaction proceeds with formation of the trifluoro dioxirane, which then oxidizes *N*-pyrrolidiny-camphor-10-sulfonamide imine to form the desired oxaziridine (Scheme 72).



**Scheme 72:** Formation of *N*-pyrrolidine-camphor-10-sulfonamide oxaziridine

However, Boyd and coworkers have reported that the oxidation of *NH*-imines by dimethyldioxirane in dichloromethane/acetone solution yielded oximes (Scheme 73).<sup>38</sup>



**Scheme 73:** Oxidation of primary imines by dimethyl dioxirane

It is probable that the isomeric nitrones were the initial products, due to electrophilic attack at the imino nitrogen, and that these were isolated as the more stable oxime tautomers.

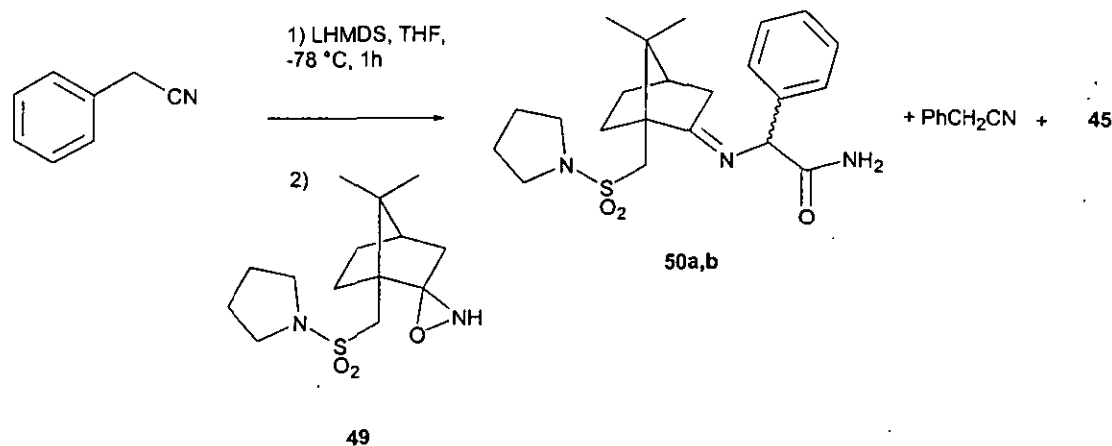
However, the  $^{13}\text{C}$  NMR spectrum of *N*-pyrrolidinyl-camphor-10-sulfonamide oxaziridine (49) shows the typical signal for the carbon bearing the oxaziridine ring at 88.4 ppm, no oxime being isolated. The oxidation of the imine (48) was not carried out without trifluoroacetone and therefore it is possible that the methyl(trifluoromethyl) dioxirane did not mediate the oxidation.

The new oxaziridine (49) decomposed quickly at room temperature and was therefore used directly after its synthesis.

### 2.8.3 Electrophilic amination using *N*-pyrrolidinyl-camphor-10-sulfonamide oxaziridine

A THF solution of benzyl cyanide at  $-78\text{ }^{\circ}\text{C}$  was treated with LHMDS for an hour. The reaction was carried out at the same time as the formation of the

oxaziridine (47). The freshly formed anion was then reacted with the oxaziridine (49) for an additional four hours at  $-78\text{ }^{\circ}\text{C}$  (Scheme 74).



**Scheme 74:** Electrophilic amination of benzyl cyanide anion with *N*-pyrrolidinyll-camphor-10-sulfonamide oxaziridine

The  $^1\text{H}$  NMR spectrum of the crude reaction mixture showed mainly the presence of benzyl cyanide and *N*-pyrrolidine-camphor-10-sulfonamide (45). The LCMS analysis of the crude, however revealed the presence of amination products with a mass of 417. The crude mixture was purified by column chromatography over silica gel to result in the isolation of benzyl cyanide and the corresponding ketone (45) along with the diastereoisomers (50a,b), in only 4% yield overall. The reaction had occurred with hydrolysis of the cyano group as we have observed previously. Other attempts of amination of benzyl cyanide anion using the oxaziridine (49) resulted in low yields of amination products (50a,b). The instability of the oxaziridine (49) is thought to be primarily the cause.

### Conclusion of Section 2.8

The synthesis of the precursor *N*-pyrrolidine-camphor-10-sulfonamide nitrimine (47) was accomplished in four steps in good yield, starting from camphor-10-sulfonic acid, which was converted to *N*-pyrrolidine-camphor-10-sulfonamide (45) in 80% yield over two steps. The oxime (46) was formed in 73% yield by reaction of the camphor *N*-pyrrolidine-10-sulfonamide (45) with hydroxylamine hydrochloride,

and was treated with 5% aqueous solution of sodium nitrite to afford *N*-pyrrolidine-camphor-10-sulfonamide nitrimine (47) in 61% yield.

The ammonolysis of (47) with ammonia, followed by the oxidation of the corresponding imine (48) using tetraphenylphosphonium monoperoxysulfate (TPPP) (27) with a small amount of trifluoroacetone provided the desired oxaziridine (49) in 75% yield overall. Unfortunately compound (49) decomposes quickly at room temperature and during the workup.

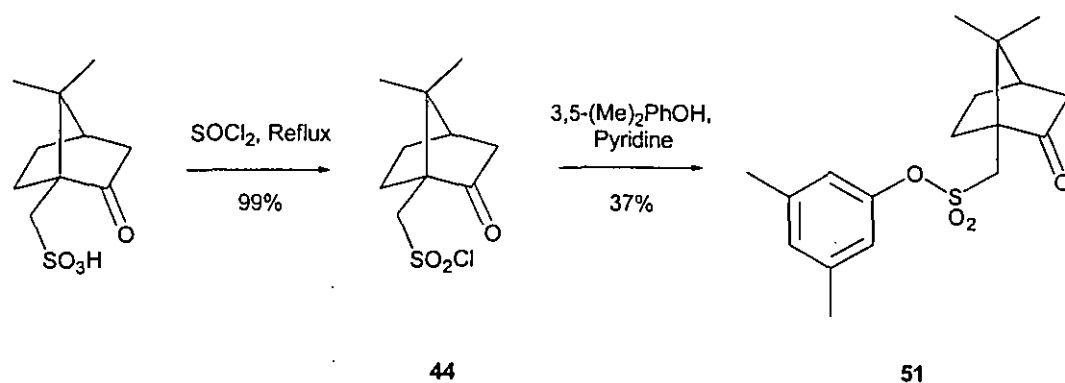
The electrophilic amination of the benzyl cyanide anion with the freshly formed oxaziridine (49) occurred in 4% yield, with hydrolysis of the cyano group. Benzyl cyanide and camphor *N*-pyrrolidine-10-sulfonamide (45) were the main products of the reaction. Since *N*-pyrrolidine-camphor-10-sulfonamide oxaziridine was easy to prepare, the synthesis of camphor-10-sulfonate esters were next investigated.

## 2.9 Synthesis of camphor aryl-10-sulfonate ester derivatives

We next investigated the synthesis of camphor aryl-10-sulfonate ester oxaziridines in order to study the effect that higher steric hindrance on carbon 10 could have during the approach of the nucleophile during the electrophilic amination process. Moreover it would be interesting to evaluate the stability of the new oxaziridines.

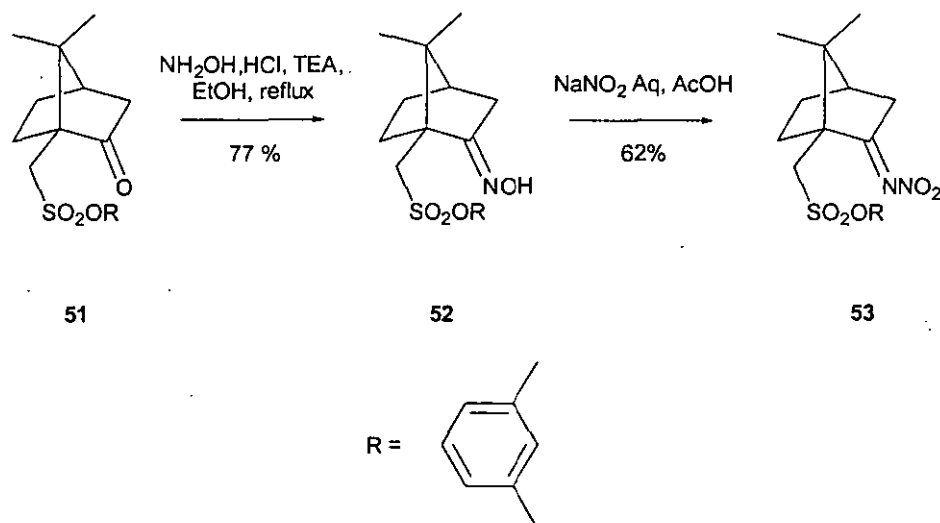
### 2.9.1 Synthesis of camphor-3,5-dimethylphenyl-10-sulfonate nitrimine

Following the procedure of Procter, 3,5-dimethylphenyl camphor-10-sulfonate (51) was synthesized in two steps from camphor-10-sulfonic acid. The first step was the formation of camphor-10-sulfonyl chloride by treatment of camphor-10-sulfonic acid with thionyl chloride in quantitative yield, followed by its reaction with 3,5-dimethyl phenol in solution in pyridine (Scheme 75).<sup>39</sup> Although the yield of the esterification was moderate 37%, the starting materials were readily available in large quantities, and isolation of the product (51) was simple.



**Scheme 75:** Synthesis of 3,5-dimethyl-phenyl camphor-10-sulfonate ester

The oxime (**52**) was synthesized in 77% yield, by reaction of (**51**) with hydroxylamine hydrochloride in presence of pyridine in ethanol under reflux conditions (**Scheme 76**). The reaction of the oxime (**52**) with a 5% aqueous sodium nitrite solution in glacial acetic acid at room temperature for three hours afforded 3,5-dimethylphenyl-camphor-10-sulfonate nitrimine (**53**) in 62% yield (**Scheme 76**).

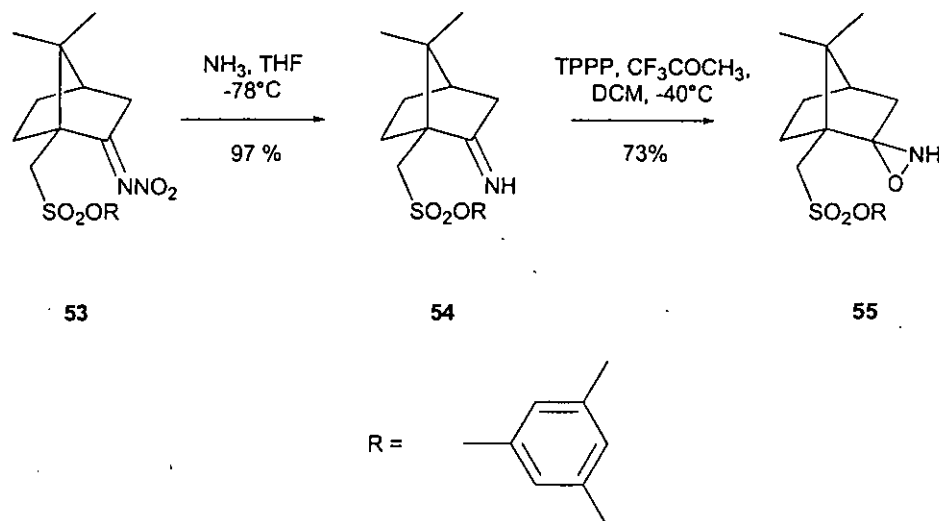


**Scheme 76:** Synthesis of 3,5-dimethylphenyl-camphor-10-sulfonate nitrimine

### 2.9.2 Synthesis of 3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine

A solution of 3,5-dimethylphenyl-camphor-10-sulfonate nitrimine (**53**) in THF at  $-78^{\circ}\text{C}$  was treated with ammonia over ten minutes. The reaction mixture was stirred at the same temperature for four hours (**Scheme 77**). The reaction was worked

up by removal of the solvent to afford the imine (**54**) in 97% yield, which was used immediately in the oxidation step. The freshly formed imine (**54**) was reacted with TPPP (**27**) and a catalytic amount of trifluoroacetone in dichloromethane for three hours at  $-40\text{ }^{\circ}\text{C}$  (TLC monitoring). The 3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine was isolated by simple filtration of the crude mixture through magnesium sulfate and a small amount of silica gel in 73% yield (**Scheme 77**).



**Scheme 77:** Synthesis of 3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine

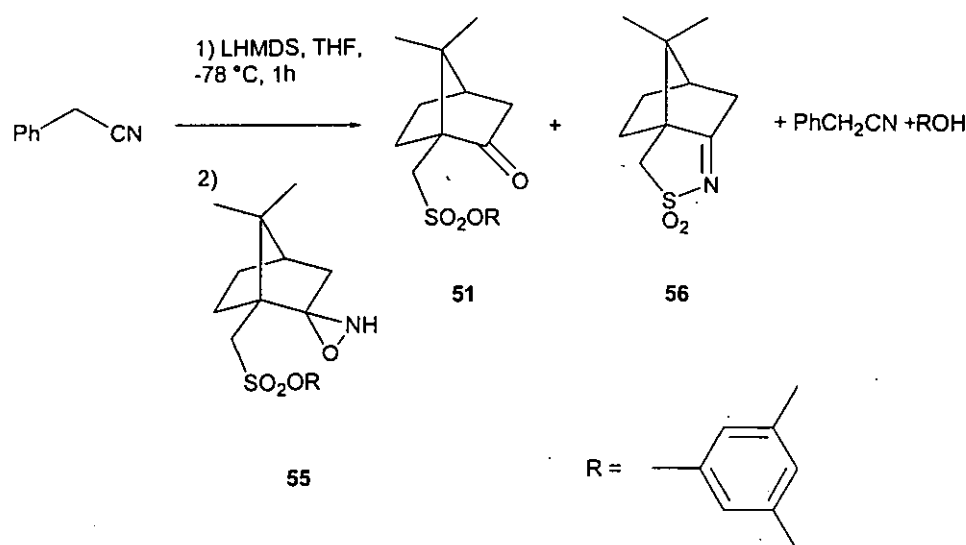
The new oxaziridine showed oxidative properties when the TLC plates were visualized with a solution of potassium iodide. The infrared spectrum of 3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine (**55**) showed the absorption of the oxaziridine ring bonds at  $1440\text{ cm}^{-1}$  and the N-H bond at  $3226\text{ cm}^{-1}$ .

The  $^{13}\text{C}$  NMR spectrum of (**55**) shows a signal at  $\delta\ 88.29\text{ ppm}$ , characteristic of the quaternary carbon bearing the oxaziridine ring.

### 2.9.3 Attempted electrophilic amination using 3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine

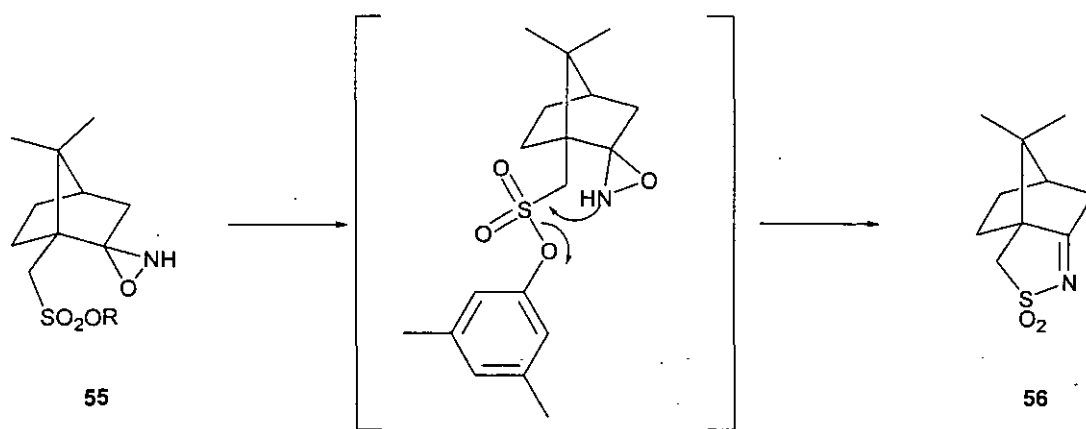
A THF solution of benzyl cyanide at  $-78\text{ }^{\circ}\text{C}$  was treated with LHMDS for one hour. The freshly formed anion was then reacted with the oxaziridine (**55**) for an additional four hours at  $-78\text{ }^{\circ}\text{C}$  (**Scheme 78**).





**Scheme 78:** Attempted electrophilic amination of benzyl cyanide anion with 3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine

Unfortunately no amination products were observed by LCMS analysis. The <sup>1</sup>H NMR spectrum of the crude reaction mixture showed only the presence of benzyl cyanide, 3,5-dimethyl-phenyl camphor-10-sulfonate ester and 10-camphorylsulfonylimine (56). The purification of the crude mixture by column chromatography on silica gel confirmed that only the starting materials benzyl cyanide, the camphor sulfonate ester (51) (62% yield) along with 10-camphorylsulfonylimine (56) (25% yield) and 3,5-dimethyl phenol (26% yield) were present. We believe that the nitrogen of the oxaziridine ring reacts with the sulfonate esters and that 3,5-dimethylphenol act as a leaving group in a cyclization type reaction to give (56) (Scheme 79).



**Scheme 79:** Possible mechanism for the formation of 10-camphorylsulfonylimine (56)

### Conclusion of Section 2.9

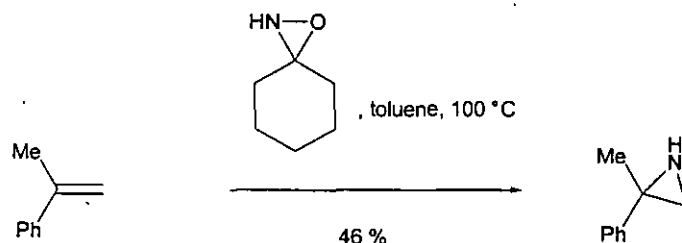
The synthesis of the precursor 3,5-dimethylphenyl-camphor-10-sulfonate nitrimine occurred in four steps but in moderate yield. Camphor-10-sulfonic chloride was converted to 3,5-dimethylphenyl-camphor-10-sulfonate in 37% yield. The formation of the corresponding oxime (52) proceeded in 77% yield, which was followed by nitrosation/rearrangement using a 5% aqueous solution of sodium nitrite to afford the nitrimine (53) in reasonable 62% yield.

The ammonolysis of (53) gave the 3,5-dimethylphenyl-camphor-10-sulfonate imine in 97% yield. The oxidation of the imine (54) with tetraphenylphosphonium monoperoxysulfate TPPP (27) and a catalytic amount of trifluoroacetone provided the oxaziridine (55) in 72% yield overall. As its homologue the *N*-pyrrolidinyl-camphor-10-sulfonamide oxaziridine (49), 3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine (55) is unstable and decomposes quickly.

The electrophilic amination was carried out straightaway after the formation of the oxaziridine (55) to result only in the recovery of the 3,5-dimethylphenyl-camphor-10-sulfonate with the formation of 10-camphorylsulfonyl imine (56). We believed that the nitrogen of the oxaziridine ring reacts intramolecularly with the sulfonate ester to give (56).

## 2.10 Diaziridines

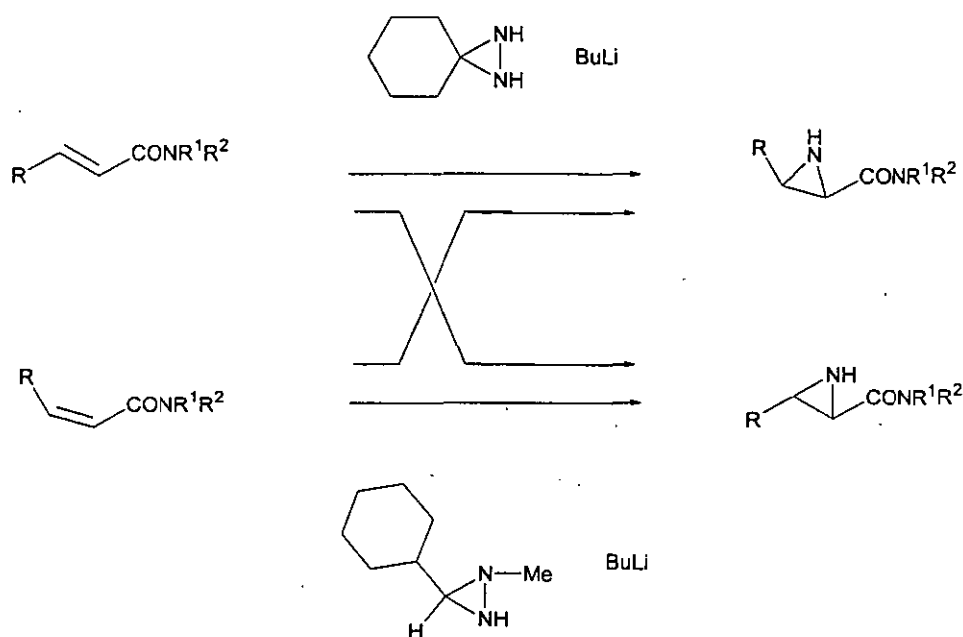
Aziridines are versatile compounds as precursors for the synthesis of a various types of nitrogen-containing compounds, which are biologically important, such as amino acid, amino alcohols, *etc.*<sup>40</sup> There are many reports on the synthesis of aziridines.<sup>41</sup> Among them, cyclohexyl oxaziridine has been reported to react with alkene to give aziridine in moderate to poor yield (**Scheme 80**).<sup>42</sup>



**Scheme 80:** Aziridination of alkene

Unfortunately our group noticed that camphor and fenchone oxaziridines were unreactive towards alkenes.

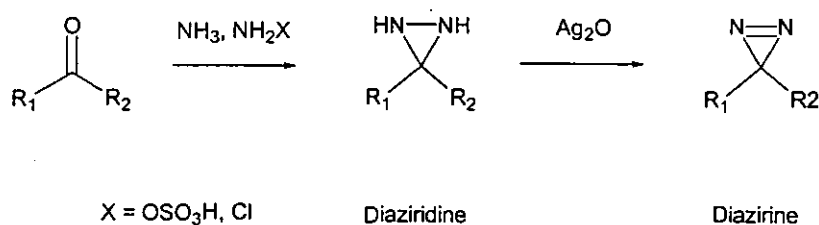
However, Katuski reported that 3,3-pentamethylenediaziridine can induce *cis* aziridination of  $\alpha,\beta$ -unsaturated amides,<sup>43</sup> and 3-monosubstituted *trans* selective aziridination (**Scheme 81**).<sup>44</sup> Aziridination with an optically active 3-monosubstituted diaziridine, prepared with (1*R*)-1-phenylethylamine, proceeded with high *trans* selectivity and high enantioselectivity.<sup>44</sup>



**Scheme 81** : Aziridination with diaziridines

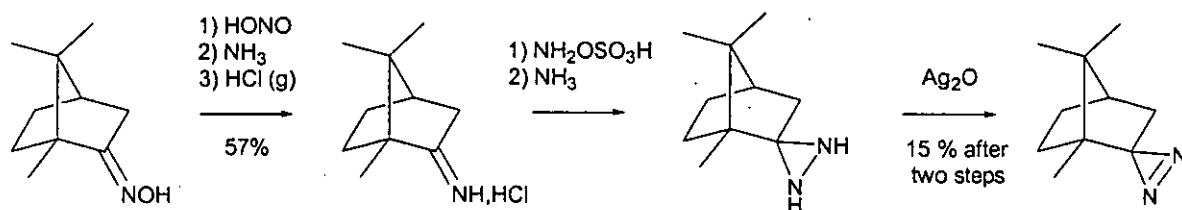
For those reasons, we decided to synthesise camphor diaziridine, as a chiral diaziridine and investigate its potency to induce aziridination to alkenes.

Diaziridines are the dinitrogen equivalents of dioxiranes and were first synthesized in 1959. They are usually prepared according to the procedure developed by Schmitz (**Scheme 82**).<sup>45</sup> Ketones are reacted with ammonia and an electrophilic aminating agent such as hydroxylamine-*O*-sulfonic acid or chloramines, to produce diaziridines. They are mostly used as precursors of diazirines. Diazirines are synthesised by oxidation of diaziridines with silver oxide.



**Scheme 82**: Synthesis of diaziridines

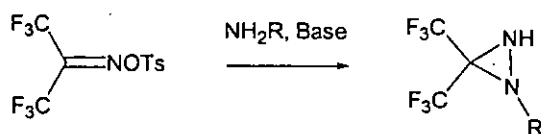
Brinker reported the synthesis of camphor diazirine by reaction of camphor imine hydrochloride with hydroxylamine-*O*-sulfonic acid and oxidation of the crude diaziridine with silver oxide.<sup>46</sup> The camphor imine chloride was prepared in 57% yield from camphor oxime (**Scheme 83**).



**Scheme 83:** Synthesis of camphor diazirine

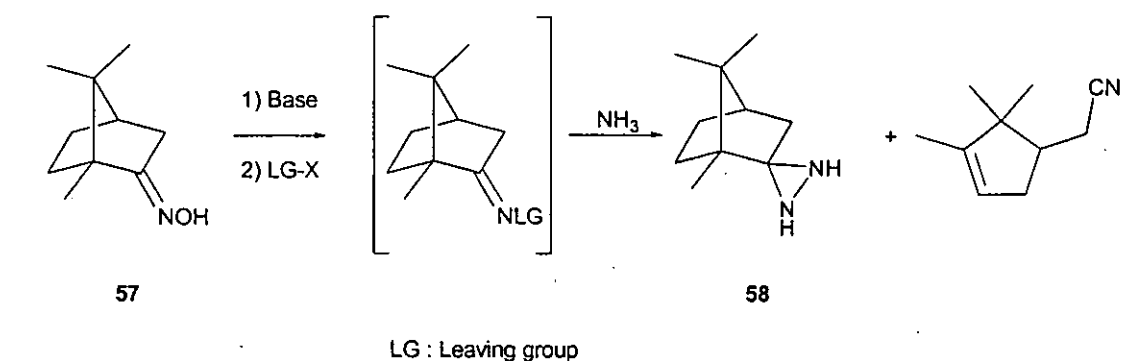
Camphor diaziridine was not isolated but oxidised to give the diazirine in 15% yield over two steps. Since the procedure involves nucleophilic attack of hydroxylamine-*O*-sulfonic acid on the hindered  $sp^2$  carbon, we were interested in an alternative route for the synthesis of camphor diaziridine starting from camphor oxime. The transformation of the hydroxyl function, of the oxime as a leaving group followed by addition of ammonia could give the corresponding diaziridine.

Kostyanovsky reported the synthesis of 3,3-bis(trifluoromethyl) diaziridine using this method.<sup>47</sup> The reaction of an *O*-tosyloxime with a primary amine afforded the diaziridine in moderate to good yield (**Scheme 84**). The presence of the electronegative  $CF_3$  group ensure the stability of the diaziridines



**Scheme 84:** Synthesis of 3,3-bis(trifluoromethyl) diaziridines

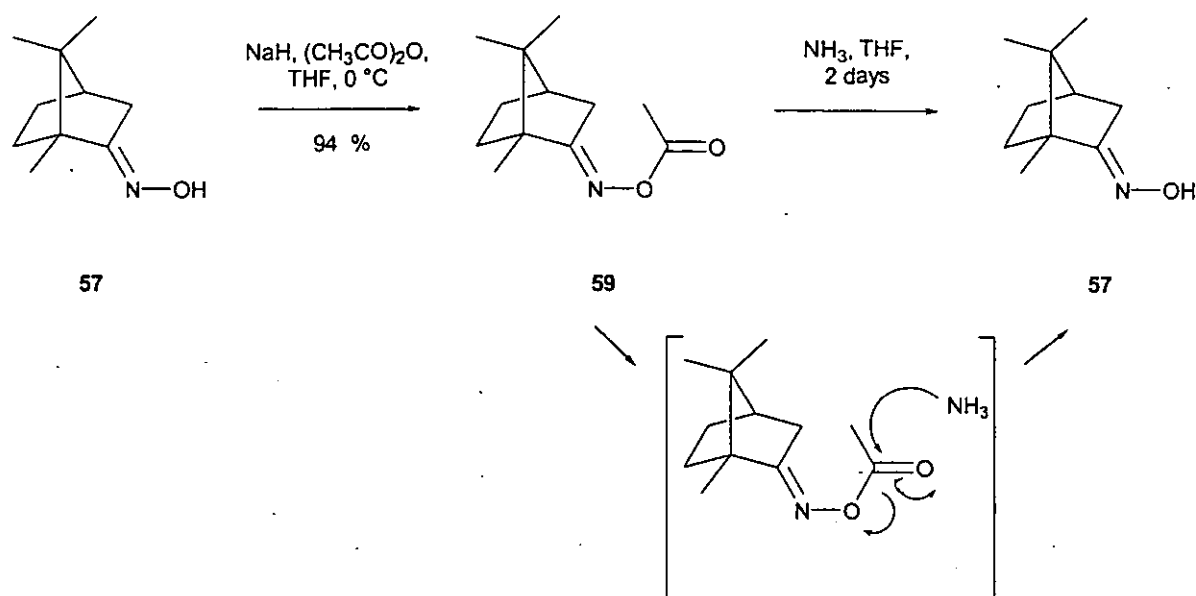
Following the Kostyanovsky method, we tested several leaving groups on camphor oxime such as *p*-toluenesulfonyl, methanesulfonyl or trifluoromethanesulfonyl group (**Scheme 85**). The corresponding sulfonylimines were not isolated, but immediately subjected to ammonolysis. (**Scheme 85**).



| LG-X, base  | 58 yield % | Decomposition product<br>yield % |
|---|------------|----------------------------------|
| MsCl, Et <sub>3</sub> N                                     | 16         | 48                               |
| TsCl, Et <sub>3</sub> N                                     | -          | 74                               |
| (CF <sub>3</sub> SO <sub>2</sub> ) <sub>2</sub> O, pyridine | -          | 87                               |

**Scheme 85:** Synthesis of camphor diaziridine

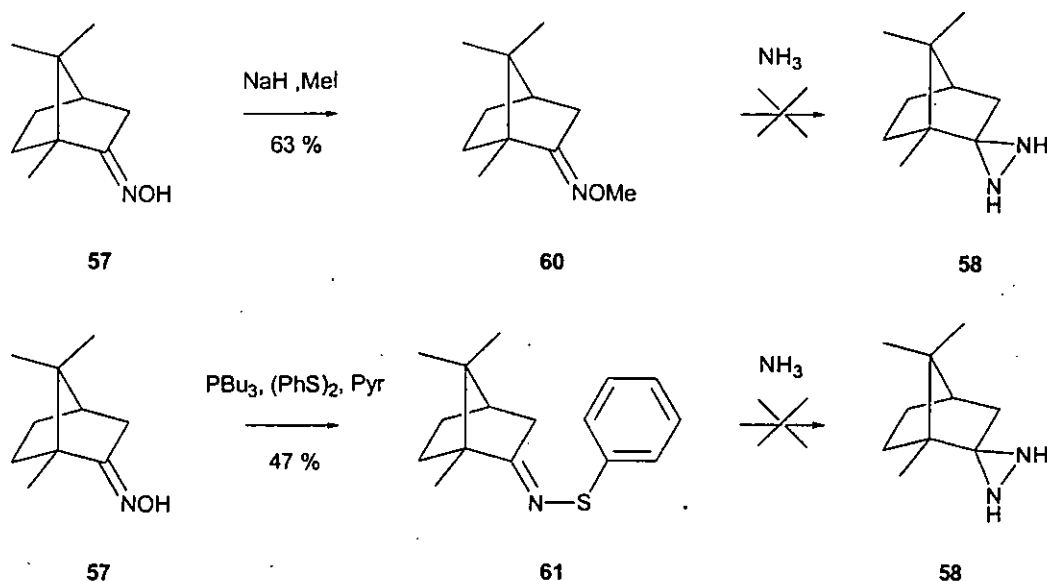
Unfortunately, only when camphor oxime was reacted with mesyl chloride followed by the addition of ammonia did we observe the formation of the desired camphor diaziridine (**58**). All reactions led to the rearrangement product, which have already been reported.<sup>48</sup> With triflate or tosylate as leaving groups, the intermediate was too unstable and only the corresponding rearrangement products were recovered. Camphor diaziridine (**58**) decomposed at room temperature and was isolated by flash chromatography on silica gel, which could induce also decomposition of the diaziridine. In attempt to suppress the rearrangement, we investigated the synthesis of camphor oxime derivatives, which with less labile leaving groups. *O*-Acetoxycamphor oxime (**59**) was prepared by reaction of camphor oxime with sodium hydride and acetic anhydride in 94% yield (**Scheme 86**). In attempt to prepare the diaziridine it was then treated with ammonia in solution in THF at  $-78\text{ }^{\circ}\text{C}$  for four hours, but unfortunately the reaction did not reach completion (TLC monitoring). The reaction reached completion when it was carried out in a sealed tube for 2 days but to afford only camphor oxime (**57**). We believe that ammonia attacks the carbonyl group resulting in the recovery of (**57**) (**Scheme 86**).



**Scheme 86:** Attempted synthesis of camphor diaziridine

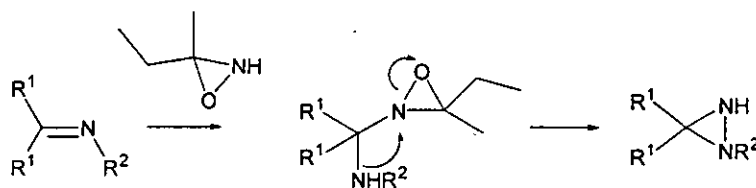
The next camphor oxime derivatives to be investigated were *O*-methylcamphor oxime (60) and *N*-sulfenyl camphor imine (61). Camphor oxime (57) in solution in THF at 0 °C was treated with sodium hydride followed by the addition of methyl iodide to afford *O*-methylcamphor oxime in 63% yield (60) (Scheme 87). *N*-sulfenyl camphor imine (61) was prepared following the procedure of Bovin.<sup>49</sup> Camphor oxime (57) in solution in pyridine was reacted with tributyl phosphine and an excess of diphenyl disulfide to provide the desired compound (59) in 47% yield (Scheme 87).

The reactions of *O*-methylcamphor oxime (60) and *N*-sulfenyl camphor imine (61) with ammonia were attempted but failed to produce camphor diaziridine. In both cases, only the starting materials were recovered (Scheme 87).



**Scheme 87:** Attempted synthesis of camphor diaziridine

Another approach was investigated next, Schmitz has reported that *NH*-oxaziridines can react with imines to give diaziridine (Scheme 88).<sup>50</sup> The *NH*-oxaziridines was prepared by reaction of the corresponding ketone with hydroxylamine-*O*-sulfonic acid and reacted with the imines.

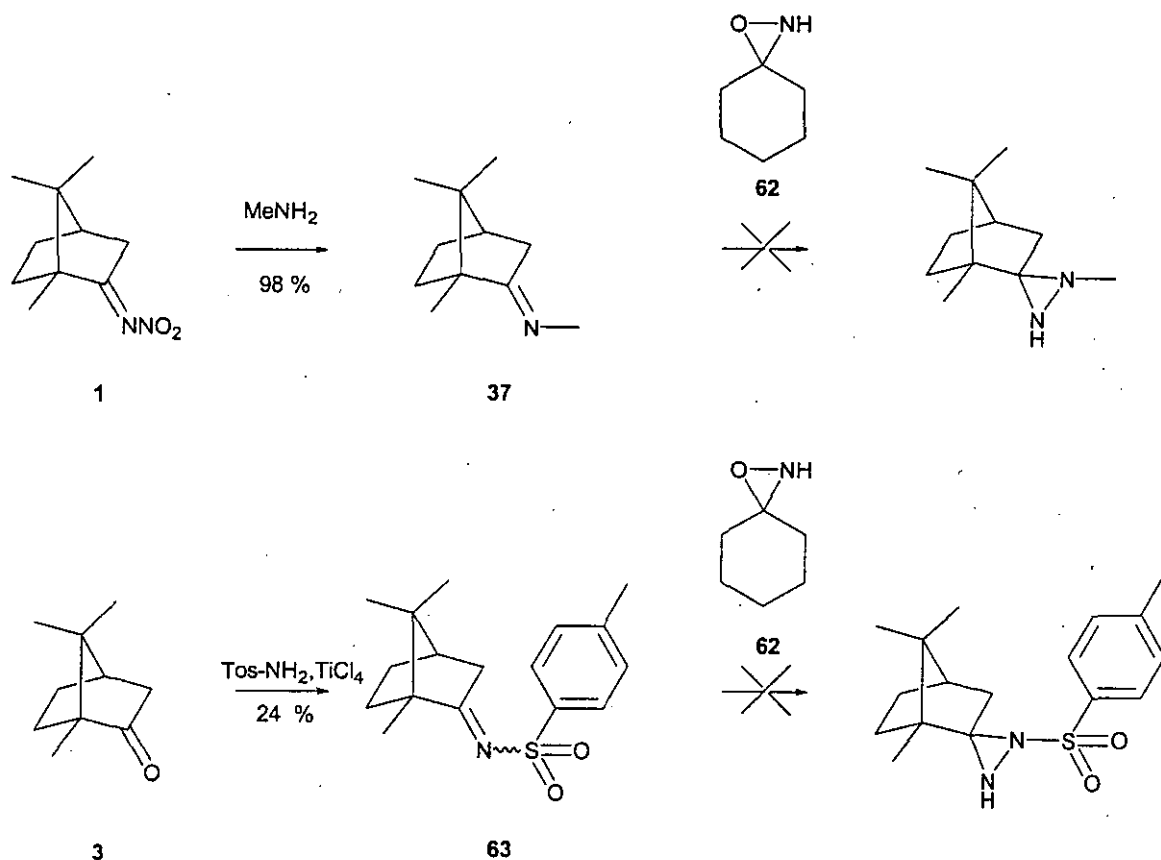


**Scheme 88:** Synthesis of diaziridine using oxaziridine

A solution of *N*-methyl camphor imine (37) and isobutyraldehyde in diethyl ether was treated with an alkaline solution of hydroxylamine-*O*-sulfonic acid for two hours at 0 °C. The isobutyraldehyde oxaziridine was synthesized *in situ*. Unfortunately only starting material was recovered. Schmitz reported also that the reaction of cyclohexanone with an alkaline solution of hydroxylamine-*O*-sulfonic affords a solution of the corresponding oxaziridine in 50% yield (62). A freshly formed oxaziridine in diethyl ether solution was added to *N*-substituted camphor imine. After two hours only the starting material and cyclohexanone were present



(Scheme 89). *N*-*p*-Methylphenylsulfonyl camphor imine (63) was prepared from camphor by reaction with *p*-methylphenyl sulfonamide in the presence of titanium chloride in 24% yield. Unfortunately the reaction of (63) with a solution of 3,3-pentamethylene oxaziridine in diethyl ether did not give the desired diaziridine (Scheme 89).



**Scheme 89:** Attempted synthesis of *N*-substituted diaziridines

We believe that the hindrance surrounding the imine double bond is the main factor responsible for the lack of reaction.

### Conclusion of Section 2.11

Camphor diaziridine (58) was prepared in 16% yield from camphor oxime (57) by treatment with mesyl chloride in presence of triethylamine followed by the addition of ammonia. However, the camphor-*O*-sulfonyl oxime derivatives investigated were found undergo mainly rearrangement.

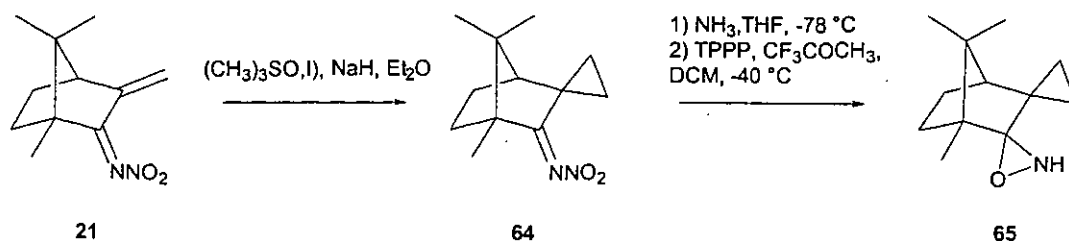
Attempted synthesis of the diaziridine from camphor oxime bearing different leaving groups such as acetoxy-, methoxy- or *N*-sulfenyl group failed. In the case of *O*-acetoxy camphor oxime treatment with ammonia afforded only the camphor oxime. We believe that ammonia attacks the carbonyl group instead of the imine double bond. When *O*-methoxy camphor oxime or *N*-sulfenyl camphor imine was reacted with ammonia only starting materials were recovered even if the reactions were carried out in a sealed tube.

A last attempt to synthesize camphor diaziridine was performed using *NH*-oxaziridine, following the Schmitz procedure. The oxaziridines were obtained by reaction of isobutyrylaldehyde or cyclohexanone with an alkaline solution of hydroxylamine-*O*-sulfonic acid. The oxaziridines were not isolated but kept in diethyl ether solution, and reacted with *N*-methyl camphor imine or *N*-*p*-methylphenylsulfonyl camphor imine. In both cases no reaction were observed, resulting in the recovery of the starting material.

### 2.1.2 Future work

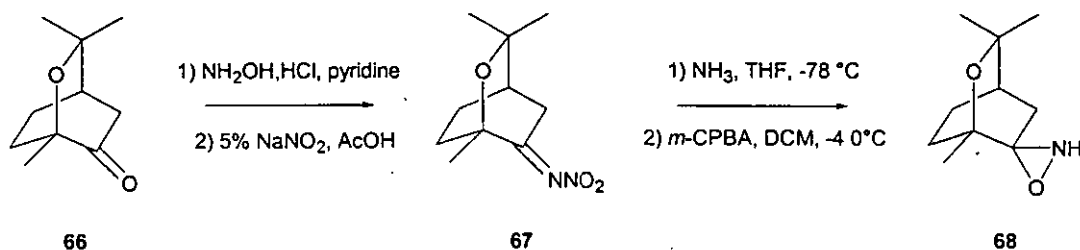
#### Oxaziridines

The synthesis of 3-cyclopropyl oxaziridine could be finished by cyclopropanation of 3-methylene camphor nitrimine (**21**) to afford 3,3-cyclopropyl camphor nitrimine (**64**). The ammonolysis of (**64**) and the oxidation of the corresponding imine with tetraphenyl phosphonium monoperoxysulfate (**27**) and a catalytic amount of trifluoroacetone would give the 3,3-cyclopropyl camphor oxaziridine (**65**) (Scheme 90)



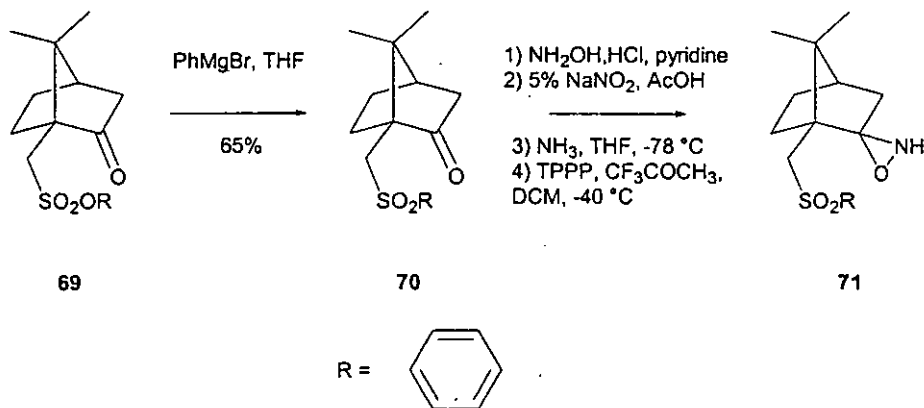
**Scheme 90:** Proposed synthesis of 3,3-cyclopropyl camphor oxaziridine

The synthesis of new *NH*-oxaziridines from natural chiral starting materials could be investigated for example from the cineole derivative (66), which could be converted to the corresponding nitrimine (67), followed by ammonolysis with ammonia and oxidation with either *m*-CPBA or tetraphenyl phosphonium monoperoxysulfate to afford the *NH*-cineole oxaziridine (68) (Scheme 91).



**Scheme 91:** Proposed synthesis of cineole oxaziridine

Procter reported the synthesis of camphor 10-phenylsulfone (70) by reaction of phenyl camphor-10-sulfonate (69) with phenyl magnesium bromide in solution in THF in 65% yield (Scheme 92). The interest in the synthesis of phenyl camphor-10-sulfonate oxaziridine would be that the nitrogen of the oxaziridine ring should not react with the sulfone group. The phenyl camphor-10-sulfonate oxaziridine (71) could be synthesised following our straightforward procedure shown in Scheme 92.

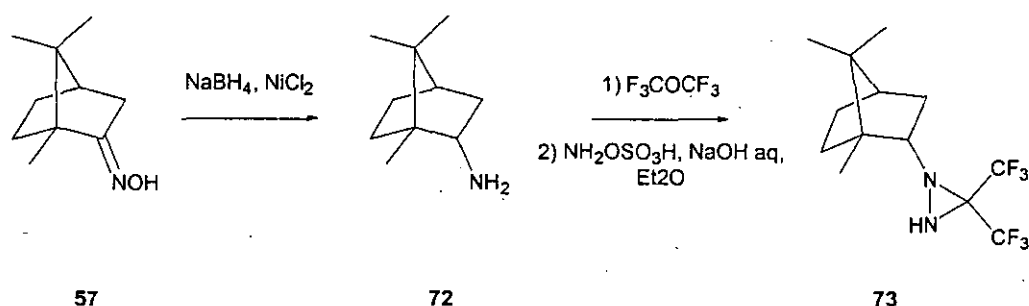


**Scheme 92:** Proposed synthesis of 10-phenylsulfone camphor oxaziridine

If phenyl camphor-10-sulfonate oxaziridine appeared to be more stable, the range of aryl- or alkyl-sulfonates that could be prepared from phenyl camphor-10-sulfonate would be interesting to investigate.

### Diaziridines

The first step of the formation of diaziridine involved nucleophilic attack on the imine  $sp^2$  carbon by the aminating reagent. Our problems with the synthesis of camphor diaziridine were probably due to the hindrance around the  $sp^2$  carbon bearing the imine double bonds. A new class of diaziridine could be investigated, from isobornylamine (**72**) by reaction with hexafluoroacetone to form the imine followed, by the addition of an electrophilic aminating agent (**Scheme 93**). Due to the presence of the electron-withdrawing  $CF_3$  groups, and the small degree of hindrance around the  $sp^2$  carbon-imine double bond, hydroxylamine-*O*-sulfonic acid or chloramines should react quickly to form the diaziridine (**73**) (**Scheme 93**). Isobornylamine (**72**) can be prepared by reduction of camphor oxime (**57**) with sodium borohydride in presence of nickel chloride (**Scheme 93**).<sup>51</sup>

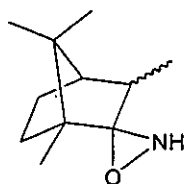


**Scheme 93:** Proposed synthesis of new diaziridine

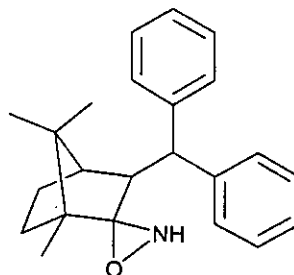
## Conclusion

The following part will resume all the oxaziridines we synthesized or attempted to synthesize, and the problem we encountered and what we learned from the studies.

### 3-Alkyl oxaziridines



3-methyl camphor oxaziridine

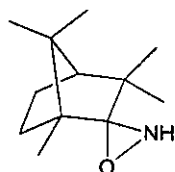


3-*exo*-(diphenylmethyl) camphor oxaziridine

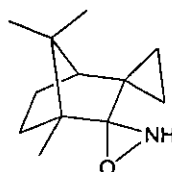
In the synthesis of 3-methyl camphor nitrimine a mixture of two diastereoisomers were isolated, this could not be separated by either column chromatography or crystallization. Attempted oxidation of 3-methyl camphor imines with *m*-CPBA resulted in the recovery of the corresponding 3-methyl camphor. We believed that the decomposition of the primary imine occur as the oxidation is a slow process.

We synthesized 3-*exo*-(diphenylmethyl) camphor nitrimine as a single diastereoisomer. The ammonolysis of 3-*exo*-(diphenylmethyl) camphor nitrimine was a slow process, resulting in the recovery of the ketone. Moreover we encountered difficulties in the synthesis of the corresponding oxime.

### 3,3 Alkyl oxazirines



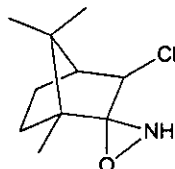
3,3-dimethyl camphor oxaziridine



3,3-cyclopropyl camphor oxaziridine

Dialkylation of camphor was the main difficulty we encountered, starting either from camphor or camphor nitrimine. Nevertheless, the synthesis of 3-methylene camphor opened the way for the synthesis of the desired 3,3-cyclopropyl nitrimine, which can be hydrogenated to give the 3,3-dimethyl camphor nitrimine.

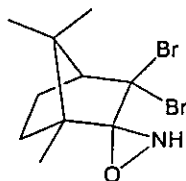
### 3-Chloro camphor oxaziridine



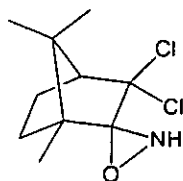
3-chloro camphor oxaziridine

The synthesis of 3-*endo*- and *exo* chloro camphor nitrimine was straightforward. However due to the electronegativity of the chlorine atom, epimerisation occurred during the ammonolysis. The oxidation of the diastereomeric mixture of 3-chloro camphor imines affords only 20% of 3-*exo*-chloro camphor oxaziridine. We believed that the attempted amination of phenyl acetonitrile anion failed, due to the abstraction of the acidic proton by the nucleophile.

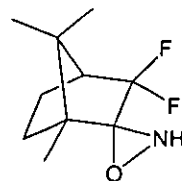
### 3,3-Dihalogeno camphor oxaziridines



3,3-dibromo camphor oxaziridine



3,3-dichloro camphor oxaziridine



3,3-difluoro camphor oxaziridine

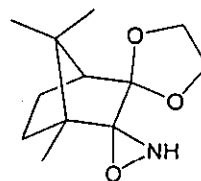
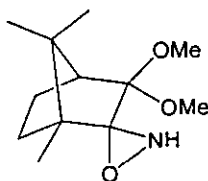
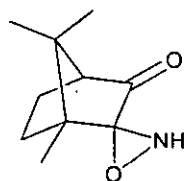
3,3-Dibromo camphor nitrimine was obtained in good yield from camphor nitrimine. We found that the corresponding imine could be obtained when the ammonolysis was carried out in a sealed tube. However, the oxidation did not give the corresponding

oxaziridine, despite the relative stability of 3,3-dibromo camphor imine, but resulted in the recovery of an unidentified product.

The synthesis of 3,3-dichloro camphor nitrimine was achieved, using DBU as base and dichlorodimethylhydantoin as a chlorinating agent. However, the reaction proceeded with formation of *N*-chloro 3-nitro 3-chloro camphor imine and it was not possible to separate the two isomers.

Different attempted synthesis of 3,3-difluoro camphor nitrimine were investigated, using DAST, iodine monofluoride or *N*-fluorobenzene sulfonamide however none were successful.

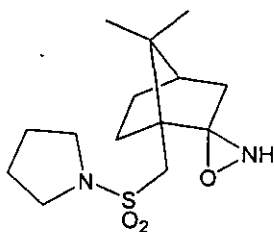
### 3-Oxo camphor oxaziridine and 3,3-diacetal oxaziridines



3-oxo camphor oxaziridine    3,3-dimethoxy camphor oxaziridine    3,3-ethylenedioxy camphor oxaziridine

3-Oxo camphor nitrimine, prepared from 3-iodo camphor nitrimine by the Kornblum oxidation was converted to the corresponding 3-oxo camphor imine, the oxidation did not afford the desired oxaziridine but only the Baeyer-Villiger product, camphor anhydride was recovered.

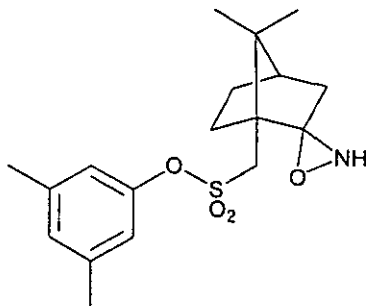
We encountered difficulties to synthesize the oxaziridine precursors 3,3-dimethoxy and 3,3-ethylenedioxy camphor nitrimine. Oximation of 3,3-dimethoxy camphor resulted in the formation of camphorquinone dioxime, and the acetalisation of 3-oxo camphor nitrimine never occurred. Secondly, 3,3-ethylenedioxy camphor oxime was obtained in low yield from 3,3-ethylene dioxy camphor and moreover the formation of the corresponding nitrimine failed.

*N*-Pyrrolidine-10-sulfonamide camphor oxaziridine

N-pyrrolidine-10-sulfonamide camphor oxaziridine

The synthesis of *N*-pyrrolidine-10-sulfonamide camphor oxaziridine was straightforward from camphor sulfonic acid. The oxidation of the primary imine using tetraphenyl phosphonium monoperoxysulfate afforded the oxaziridine in good yield. On the other hand we noticed that the new oxaziridine decomposed quickly. Consequently the amination of benzyl cyanide anion occurred in low yield.

## 3,5-Dimethylphenyl-camphor-10-sulfonate oxaziridine



3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine

Starting from camphor sulfonic acid, 3,5-dimethylphenyl-camphor-10-sulfonate oxaziridine was obtained in good yield. We noticed that the oxaziridine decomposed quickly to give camphorylsulfonylimine due, we believed, to intramolecular reaction between the nitrogen of the oxaziridine and the sulfonyl group.

Overall despite the relatively low successes in the synthesis of new chiral *NH* camphor oxaziridines, and in the electrophilic amination reaction, this study has proven to be an exciting as much as challenging experience. Confronting the



problems and applying all the analytical techniques has allowed us to assign and understand the chemistry we explored. This project merits further studies. We learned that the ammonolysis of hindered nitrimine can be carried with success in sealed tube. The synthesis of chiral 3-alkyl camphor nitrimine can be achieved from camphor trimethylsilyl enol ether. 3,3-dichloro camphor nitrimine can be synthesized and its study could be developed further in order to reduce the formation of the N-chloro-3-nitro-3-chloro camphor imine.

# **CHAPTER 3:**

## **EXPERIMENTAL**

### 3.1 General information

#### 3.1.1 Solvents and reagents

Solvents, where necessary, were dried, distilled and then stored over 4Å molecular sieves prior to use. Dichloromethane was distilled over phosphorus pentoxide; ethyl acetate and light petroleum ether (40-60 °C) were distilled over calcium chloride. Tetrahydrofuran was bought from Aldrich Chemical Company Ltd. and distilled over sodium wire. Unless otherwise stated light petroleum refers to 40-60 petroleum ether (fraction boiling between 40 and 60°C). Anhydrous dimethylformamide was purchased from Aldrich Chemical Co. Ltd. Other chemicals used in this work were obtained from Aldrich Chemical Co. Ltd, Lancaster Synthesis Ltd., Acros (Fisher) Chemicals Ltd. or Avocado.

#### 3.1.2 Chromatographic procedures

Analytical thin layer chromatography was carried out with aluminium backed plates coated with 0.2 mm of silica. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate or iodine. Flash column chromatography was carried out using Merck Kieselgel (70-230 Mesh ASTM).

#### 3.1.3 Spectra

Infrared spectroscopy was carried out using a Perkin-Elmer Fourier Transform Paragon 1000 spectrophotometer (with internal calibration), the spectra were recorded in the range 4000-600  $\text{cm}^{-1}$ . Solid samples were run as  $\text{CH}_2\text{Cl}_2$ -cast film on KBr plates and liquids as thin films. Nuclear magnetic resonance (NMR) spectra ( $^1\text{H}$  and  $^{13}\text{C}$ ) were recorded using either a Bruker AC-250 or DPX-400 instrument. All  $^1\text{H}$  resonances were assigned on the model of camphor nitrimine (1),  $\text{H}_{\text{number}}$  meaning the hydrogen attached to the corresponding carbon. Multiplicities were recorded as broad peaks (b), singlets (s), doublets (d), triplets (t), quartets (q), double doublets (dd) and multiplets (m). All NMR samples were made up in deuterated chloroform with all values quoted in ppm relative to tetramethylsilane as reference. Coupling constants ( $J$  values)

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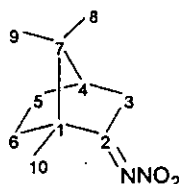
are reported in Hertz (Hz). Quaternary carbon and CH<sub>2</sub> were confirmed by DEPT 135 experiments on DPX 400 instrument. Electron Impact (E.I.) and Fast Atom Bombardment (F.A.B.) mass spectra were recorded on a Jeol (JMX)SX102 Instrument.

#### 3.1.4 Other data

Melting points were determined on a Leica Galen III instrument and are uncorrected. Optical rotations were performed where possible on a polAAR 2001 instrument using a 0.25 dm cell. All yields are for isolated pure products except where diastereomeric mixtures are noted.

### 3.2 Experimental data

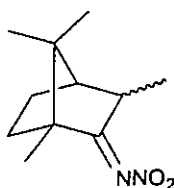
#### Camphor nitrimine<sup>1</sup>



1

Camphor oxime (40.0 g, 0.24 mol) in glacial acetic acid (1.2 ml) was treated with aqueous sodium nitrite (5%, 600 ml). A bright yellow colour developed and dispersed over 30 minutes. After 1.5 hours the crude product was precipitated as colourless solid by addition of water and isolated by filtration. After drying under reduced pressure, this crude product was crystallized from 95% ethanol to afford pure camphor nitrimine (**1**) as a white crystalline solid (25.4 g, 54%). m.p. 41-42 °C;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2968, 1642 (C=N), 1563 (NO<sub>2</sub>), 1457, 1307;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 2.69 (1H, ddd, *J* 18.6, 4.7 and 2.2, H<sub>3exo</sub>), 2.13 (1H, d, *J* 18.6, H<sub>3endo</sub>), 2.05-1.79 (3H, m, H<sub>4+5+6</sub>), 1.65-1.51 (1H, m, H<sub>6</sub>), 1.37-1.28 (1H, m, H<sub>5</sub>), 1.04 (3H, s, H<sub>10</sub>), 0.98 (3H, s, H<sub>9 or 8</sub>), 0.88 (3H, s, H<sub>9 or 8</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 10.71 (Me), 19.00 (Me), 19.84 (Me), 27.17 (CH<sub>2</sub>), 31.94 (CH<sub>2</sub>), 35.52 (CH<sub>2</sub>), 43.83 (CH), 49.21 (C<sub>quat</sub>), 54.50 (C<sub>quat</sub>), 189.86 (C=N); *m/z* (F.A.B.): (Found: 196.1210 (M<sup>+</sup>); C<sub>10</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> requires 196.1211).

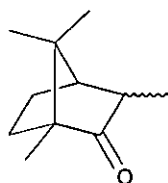
#### 3-Methyl camphor nitrimine



2a,b

3-Methyl camphor oxime (**6a/b**) (650 mg, 3.6 mmol) in glacial acetic acid (18 ml) was treated with aqueous sodium nitrite (5%, 9 ml). A bright yellow colour developed and dispersed over 30 minutes. After 4 hours the crude product was concentrated and quenched with aqueous sodium bicarbonate, extracted with diethyl ether (100 ml) and dried over magnesium sulfate. Solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate/light petroleum 5/95) to afford methyl camphor nitrimine (**2a/b**) as a colourless solid (454 mg, 60%) as a 9/1 ratio of *endo/exo* methyl camphor nitrimine. m.p. 44-46 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  1642 (C=N), 1562 (NO<sub>2</sub>);  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 2.02 (1H, s, H<sub>3</sub>), 1.82-1.80 (1H, m, H<sub>4</sub>), 1.75-1.45 (4H, m, H<sub>5+6</sub>), 1.08 (3H, d, *J* 4.5, CH<sub>3</sub>), 0.94 (3H, s, H<sub>10</sub>), 0.91 (3H, s, H<sub>9</sub> or 8), 0.84 (3H, s, H<sub>9</sub> or 8);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 11.29 (Me), 12.33 (Me), 19.02 (Me), 19.25 (Me), 20.11 (CH<sub>2</sub>), 32.01 (CH<sub>2</sub>), 38.07 (CH), 48.18 (C<sub>quat</sub>), 49.99 (CH), 55.45 (C<sub>quat</sub>), 192.13 (C=N); *m/z* (F.A.B.): (Found: 210.1361 (M<sup>+</sup>); C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub> requires 210.1362); 211 (M<sup>+</sup>), 187, 176, 165, 137, 121, 109.

### 3-Methyl camphor<sup>4</sup>

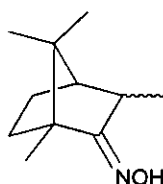


**4a/b**

Camphor (**3**) (2.0 g, 13.1 mmol) in anhydrous THF (5 ml) was added to a solution of LDA (2M in THF) (6.9 ml, 13.8 mmol) in anhydrous THF (10 ml) cooled to 0 °C and the enolate was allowed to form over 45 minutes. Methyl iodide was added and then the reaction stirred for overnight. The mixture was then quenched with hydrochloric acid (1N, 5 ml) and extracted with diethyl ether (3 × 20 ml). The combined organic layers were washed with water, brine and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography over silica gel (diethyl ether/light petroleum, 2/98) to give 3-methyl camphor (**4a,b**) as a colourless solid (1.36g, 66%) containing a mixture of the *endo* and *exo* isomers (20/80). The oily mixture was epimerised with a mixture of acetic acid/hydrochloric acid (18 ml/6 ml) over 6 hours at 85

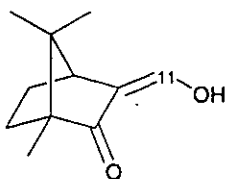
°C resulting in a in a product with an *endo/exo* ratio of (91/9) compound. m.p. 37-39 °C;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  1735 (C=O);  $\delta_{\text{H}}$  (*endo* described) (400 MHz;  $\text{CDCl}_3$ ) 2.48 (1H, dq,  $J$  7.5 and 4.5,  $\text{H}_3$ ), 1.98-1.89 (3H, m  $\text{H}_{4+5+6}$ ), 1.76-1.71 (1H, m,  $\text{H}_6$ ), 1.46-1.35 (1H, m,  $\text{H}_5$ ), 1.06 (3H, d,  $J$  7.5,  $\text{CH}_3$ ), 1.00 (3H, s,  $\text{H}_{10}$ ), 0.90 (3H, s,  $\text{H}_9$  or 8), 0.87 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (*endo* described) (100 MHz;  $\text{CDCl}_3$ ) 9.94 (Me), 16.52 (Me), 19.62 (Me), 19.84 (Me), 20.21 ( $\text{CH}_2$ ), 31.38 ( $\text{CH}_2$ ), 44.05 (CH), 45.97 ( $\text{C}_{\text{quat}}$ ), 48.87 (CH), 58.44 ( $\text{C}_{\text{quat}}$ ), 222.33 (C=O);  $m/z$  (E.I.): (Found: 166.1356 ( $\text{M}^+$ );  $\text{C}_{11}\text{H}_{18}\text{O}$  requires 166.1358); 166 ( $\text{M}^+$ ), 153, 123, 119, 108, 95, 83, 77.

### 3-Methyl camphor oxime



6a,b

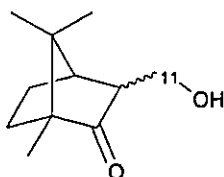
Hydroxylamine hydrochloride (1.2 g, 17.3 mmol), methyl camphor (**4a/b**) (1.19 g, 7.2 mmol) and pyridine (0.88 ml, 10.8 mmol) were heated under reflux in ethanol (10 ml) for 4 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed under reduced pressure. Water was then added and the mixture was extracted with diethyl ether (100 ml). The organic layer was washed with water, brine and dried over magnesium sulfate. Solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 20/80) to afford methyl camphor oxime (**6a/b**) as a colourless solid (653 mg, 50%). m.p. 123-125 °C;  $\delta_{\text{H}}$  8.62 (1H, br.s, OH), 2.84-2.77 (2H, m,  $\text{H}_{3+4}$ ), 1.65 (1H, m,  $\text{H}_5$ ), 1.57-1.53 (3H, m,  $\text{H}_{5+6}$ ), 1.18 (3H, d,  $J$  4.7,  $\text{CH}_3$ ), 0.88 (3H, s,  $\text{H}_{10}$ ), 0.86 (3H, s,  $\text{H}_9$  or 8), 0.74 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 11.88 (Me), 13.86 (Me), 19.16 (Me), 19.31 (Me), 20.82 ( $\text{CH}_2$ ), 32.70 ( $\text{CH}_2$ ), 36.13 (CH), 48.01 ( $\text{C}_{\text{quat}}$ ), 50.04 (CH), 53.22 ( $\text{C}_{\text{quat}}$ ), 171.63 (C=N);  $m/z$  (E.I.): (Found: 181.1475 ( $\text{M}^+$ );  $\text{C}_{11}\text{H}_{19}\text{NO}$  requires 181.1473); 181 ( $\text{M}^+$ ), 166, 153, 148, 138, 124, 109, 95, 81, 77.

3-Hydroxymethylene camphor<sup>5</sup>

7

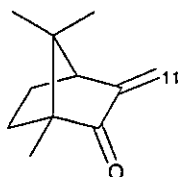
Camphor (3) (10.0 g, 65.7 mmol) in anhydrous toluene (40 ml) was slowly dropped into a suspension of sodium amide (5.12 g, 0.13 mol) in anhydrous toluene (80 ml) under nitrogen and then heated at reflux for 12 hours. The resulting orange solution was cooled in an ice bath and methyl formate (4.05 ml, 65.7 mmol) in anhydrous toluene (10 ml) was added. After 4 hours of stirring under nitrogen, the orange product was dissolved in water (80 ml) and the two phases separated. The organic phase was extracted with water (2 × 50 ml). The combined aqueous layers were washed with diethyl ether (3 × 50 ml). The organic layer was acidified with 37% HCl (5 ml) and extracted with diethyl ether (4 × 50 ml). The organic phase was washed with water, brine and dried over magnesium sulfate. After removal of the solvent, the pale yellowish oil was found to crystallize at room temperature to afford the title compound (7) as a yellow solid (5.55 g, 47%).  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3146 (OH, bs), 2959, 2874, 1748 (C=O), 1713, 1628 (C=C), 1450, 1391, 1195, 1073;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 9.33 (1H, bs), 6.75 (1H, s,  $\text{H}_{11}$ ), 2.41 (1H, d,  $J$  3.93,  $\text{H}_4$ ) 2.10-1.95 (1H, m,  $\text{H}_5$ ), 1.72-1.53 (1H, m,  $\text{H}_6$ ), 1.43-1.37 (2H, m,  $\text{H}_{5+6}$ ), 0.94 (3H, s,  $\text{H}_{10}$ ), 0.92 (3H, s,  $\text{H}_9$  or s), 0.82 (3H, s,  $\text{H}_9$  or s);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 8.94 (Me), 18.92 (Me), 20.72 (Me), 28.08 ( $\text{CH}_2$ ), 30.35 ( $\text{CH}_2$ ), 46.95 (CH), 50.19 ( $\text{C}_{\text{quat}}$ ), 58.92 ( $\text{C}_{\text{quat}}$ ), 119.78 ( $=\text{C}_{\text{quat}}$ ), 152.02 ( $=\text{CH}$ ), 213.26 (C=O);  $m/z$  (E.I.): (Found: 180.1154 ( $\text{M}^+$ );  $\text{C}_{11}\text{H}_{16}\text{O}_2$  requires 180.1150); 181 ( $\text{M}^{+1}$ ) (100), 180 ( $\text{M}^+$ ) (27), 154 (20), 136 (30); 121 (9), 105 (61).



3-Hydroxymethyl camphor<sup>6</sup>

8

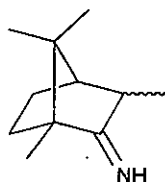
3-Hydroxymethylene camphor (7) (5.50 g, 30.5 mmol) in chloroform (91 ml) was added to a vigorously stirred solution of potassium borohydride (1.64 g, 30.5 mmol) in aqueous sodium carbonate (10 %, 15 ml) at room temperature. After stirring for 2.5 hours, the mixture was allowed to settle, and the organic aqueous layers were separated. The aqueous layer was extracted with chloroform (3 × 50 ml). The extracts were combined with the organic layer and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford 3-hydroxymethyl camphor (8) (5.35 g, 94%) in a ratio of (85/15) mixture of (*endo/exo*) hydroxymethyl diastereoisomers.  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3420 (br.s, OH), 2959, 1735 (C=O), 1391, 1329; 1270, 1034;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 3.96-3.92 (1H, m,  $\text{H}_{11}$  minor) 3.88-3.82 (1H, m,  $\text{H}_{11}$  major), 3.70-3.66 (2H, m,  $\text{H}_{11}$  major and minor), 2.71-2.66 (1H, m,  $\text{H}_3$ ), 2.22 (1H, t,  $J$  4.1,  $\text{H}_4$  minor), 2.15 (1H, t,  $J$  3.9,  $\text{H}_{4\text{major}}$ ), 1.80-1.67 (4H, m,  $\text{H}_{5+6}$  major and minor), 1.55-1.46 (2H, m,  $\text{H}_6$  major and minor), 1.38-1.35 (2H, m,  $\text{H}_5$  major and minor) 1.00 (6H, s,  $\text{H}_{10}$  major and minor), 0.94 (3H, s,  $\text{H}_9$  or 8 minor) 0.91 (3H, s,  $\text{H}_9$  or 8 major), 0.89 (3H, s,  $\text{H}_9$  or 8, major), 0.84 (3H, s,  $\text{H}_9$  or 8, minor);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 9.31 (Me), 18.83 (Me), 19.54 (Me), 20.75 ( $\text{CH}_2$ ), 31.38 ( $\text{CH}_2$ ), 45.79 (CH), 46.19 ( $\text{C}_{\text{quat}}$ ), 51.94 (CH), 59.15 ( $\text{C}_{\text{quat}}$ ), 61.59 ( $\text{CH}_2$ ), 221.87 (C=O);  $m/z$  (E.I.): (Found: 182.1306 ( $\text{M}^+$ );  $\text{C}_{11}\text{H}_{18}\text{O}_2$  requires 182.1306); 182 ( $\text{M}^+$ ) (25), 164 (4), 152 (28), 121 (21), 109 (31), 95 (100), 83 (51).

3-Methylene camphor<sup>6</sup>

9

3-Hydroxymethyl camphor (0.50 g, 2.7 mmol) and potassium hydroxide (0.92 g, 16.4 mmol) were heated under reflux in ethanol (10 ml) for 5 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed under reduced pressure. The mixture was then quenched with hydrochloric acid (1M, 5 ml) and extract with diethyl ether (3 × 20 ml). The organic layer was washed with water, brine and dried over magnesium sulfate. The crude product was purified by column chromatography over silica gel (ethyl acetate ether/light petroleum, 1/99) to give (9) as a colourless solid (0.24 g, 54%). m.p. 39-40 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2959, 1732 (C=O), 1651 (C=C), 1425, 1390, 1005;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.79 (1H, d,  $J$  0.4,  $\text{H}_{11}$ ), 5.15 (1H, d,  $J$  0.4,  $\text{H}_{11}$ ), 2.59 (1H, d,  $J$  4.4,  $\text{H}_4$ ), 2.06-2.01 (1H, m,  $\text{H}_5$ ), 1.73-1.70 (1H, m,  $\text{H}_6$ ), 1.45-1.40 (2H, m,  $\text{H}_{5+6}$ ), 0.97 (3H, s,  $\text{H}_{10}$ ), 0.96 (3H, s,  $\text{H}_9$  or 8), 0.80 (3H, s, Me,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 9.58 (Me), 18.51 (Me), 20.88 (Me), 27.23 ( $\text{CH}_2$ ), 30.23 ( $\text{CH}_2$ ), 45.98 ( $\text{C}_{\text{quat}}$ ), 51.64 (CH), 58.10 ( $\text{C}_{\text{quat}}$ ), 112.54 ( $=\text{CH}_2$ ), 150.60 ( $=\text{C}_{\text{quat}}$ ), 207.62 (C=O);  $m/z$  (E.I.): (Found: 164.1202 ( $\text{M}^+$ );  $\text{C}_{11}\text{H}_{16}\text{O}$  requires 164.1201); 165 ( $\text{M}^{+1}$ ) (12), 164 ( $\text{M}^+$ ) (57), 149 (34), 121 (72), 109 (33), 95 (100), 83 (45).

### 3-Methyl camphor imine

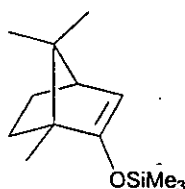


10a,b

3-Methyl camphor nitrimine (2a,b) (480 mg, 2.3 mmol) in anhydrous THF (5 ml) was treated at  $-78$  °C with a slow stream of ammonia gas for 15 minutes. The reaction was stirred for 5 hours at the same temperature. The solvent was removed under reduced pressure keeping the water bath below 30 °C to give 3-methyl camphor imine (10a,b) as a colourless oil (309 mg, 76%).  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3123 (br.s, NH), 2961, 2870, 1662 (C=N), 1450, 1370, 934;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 8.12 (1H, br.s, NH), 2.59 (1H, m,  $\text{H}_3$ ), 1.70-1.55 (3H, m,  $\text{H}_{4+5+6}$ ), 1.34-1.19 (2H, m,  $\text{H}_{5+6}$ ), 1.12 (3H, d,  $J$  10.8,  $\text{CH}_3$ ), 0.97 (3H, s,  $\text{H}_{10}$ ), 0.92 (3H, s,  $\text{H}_9$  or 8), 0.83 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$

(100 MHz;  $\text{CDCl}_3$ ) 10.91 (Me), 13.61 (Me), 19.19 (Me), 19.33 (Me), 20.43 ( $\text{CH}_2$ ), 32.72 ( $\text{CH}_2$ ), 40.68 (CH), 45.84 ( $\text{C}_{\text{quat}}$ ), 49.00 (CH), 55.43 ( $\text{C}_{\text{quat}}$ ), 197.72 ( $\text{C}=\text{N}$ ).

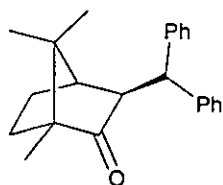
### Trimethyl-(1,7,7-trimethyl-bicyclo[2.2.1]hept-2-en-2-yloxy)-silane<sup>7</sup>



11

A 1.6 M hexane solution of *n*-BuLi (67.5 ml, 0.11 mol) was added to a solution of camphor (15.0 g, 98 mmol) in anhydrous diethyl ether (75 ml) was at 0 °C. After being stirred for 30 minutes, chlorotrimethylsilane (13.5 ml, 0.11 mol) was added to the mixture at -50 °C. The mixture was stirred for an additional hour at this temperature, filtered and evaporated under reduced pressure. Distillation from the residue gave the trimethylsilyl enol ether of camphor (**11**) as a colourless oil (12.66 g, 58%).  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 4.63 (1H, d,  $J$  3.4,  $\text{H}_3$ ), 2.18 (1H, t,  $J$  3.4,  $\text{H}_4$ ), 1.88-1.78 (1H, m,  $\text{H}_5$ ), 1.53-1.44 (2H, m,  $\text{H}_{5+6}$ ), 1.12-1.05 (1H, m,  $\text{H}_5$ ), 0.87 (6H, s, Me,  $\text{H}_{8+9}$ ), 0.72 (3H, s, Me,  $\text{H}_{10}$ ), 0.19 (9H, s,  $\text{H}_{\text{SiMe}_3}$ ).

### 3-Diphenylmethyl camphor<sup>7</sup>

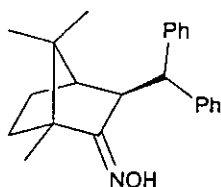


12

Titanium tetrachloride (6.18 ml, 60 mmol) was added to a solution of the trimethylsilyl enol ether of camphor (**11**) (12.66 g, 56 mmol) and chlorodiphenylmethane (9.96ml, 60 mol) in anhydrous dichloromethane (100 ml) at -50 °C. After being stirred for 1 hour, the mixture was

diluted gently with aqueous HCl (1M, 200 ml) and extracted with dichloromethane. The organic layer was washed with water, brine and dried over magnesium sulfate. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate ether/light petroleum, 2/98) to give (12) as a colourless solid (13.03 g, 73%).  $[\alpha]_D^{20} +164.6$  ( $c$  0.073,  $\text{CHCl}_3$ ); m.p. 111-112 °C (Lit.<sup>7</sup> m.p. 110 °C);  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2957, 1738 (C=O), 1493, 1450, 746;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.33-7.10 (10H, m, ArH), 4.09 (1H, d,  $J$  12.1,  $\text{H}_{11}$ ), 2.91 (1H, d,  $J$  12.1,  $\text{H}_{3\text{endo}}$ ) 2.04-1.93 (1H, m,  $\text{H}_4$ ), 1.86-1.83 (1H, m,  $\text{H}_5$ ), 1.47-1.41 (3H, m,  $\text{H}_{5+6}$ ) 1.04 (3H, s,  $\text{H}_{10}$ ), 0.87 (6H, s,  $\text{H}_{8+9}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 9.21 (Me), 20.13 (Me), 21.64 (Me), 29.12 ( $\text{CH}_2$ ), 29.33 ( $\text{CH}_2$ ), 45.69 ( $\text{C}_{\text{quat}}$ ), 46.82 (CH), 53.87 (CH), 57.15 (CH), 57.96 ( $\text{C}_{\text{quat}}$ ), 126.01 (CH), 127.57 (CH), 127.86 (CH), 128.38 (CH), 143.66 ( $\text{C}_{\text{quat}}$ ), 143.96 ( $\text{C}_{\text{quat}}$ ), 206.11 (C=O);  $m/z$  (E.I.): (Found: 318.1888 ( $\text{M}^+$ );  $\text{C}_{23}\text{H}_{26}\text{O}$  requires 318.1983); 319 ( $\text{M}^{+1}$ ) (4), 290 (4), 180 (10), 168 (100), 129 (5), 95 (5).

### 3-Diphenylmethyl camphor oxime

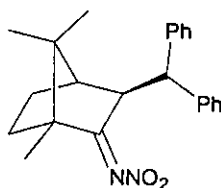


13

Hydroxylamine hydrochloride (8.6 g, 0.12 mol), 3-benzhydryl camphor (12) (8.6 g, 27.0 mmol) and pyridine (7.56 ml, 0.93 mol) were heated under reflux in ethanol (100 ml) for 6 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed under reduced pressure. Water was added and the mixture extracted with diethyl ether (100 ml). The organic layer was washed with water, brine and dried over magnesium sulfate. The solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 25/75) to afford 3-benzhydryl camphor oxime (13) as a colourless solid (1.39 g, 15%). m.p. 146-147 °C;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3289 (OH), 1661 (C=N), 1493, 1150, 910, 729;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 8.81 (1H, br.s, OH), 7.34-7.20 (10H, m, ArH), 4.32 (1H, d,  $J$  9.2,  $\text{H}_{11}$ ), 3.35 (1H, d,  $J$  9.2,  $\text{H}_{3\text{endo}}$ ) 1.88 (1H,

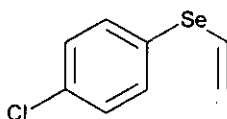
d,  $J$  4.0,  $H_4$ ), 1.83-1.74 (1H, m,  $H_5$ ), 1.65-1.49 (1H, m,  $H_6$ ), 1.43-1.29 (2H, m,  $H_{5+6}$ ) 0.91 (3H, s,  $H_{10}$ ), 0.83 (3H, s,  $H_{9 \text{ or } 8}$ ), 0.73 (3H, s,  $H_{9 \text{ or } 8}$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 11.46 (Me), 19.64 (Me), 22.05 (Me), 29.35 ( $CH_2$ ), 33.41 ( $CH_2$ ), 47.30 ( $C_{quat}$ ), 48.90 (CH), 52.97 (CH), 53.63 ( $C_{quat}$ ), 55.03 (CH), 125.21 (CH), 125.81 (CH), 127.39 (CH), 127.81 (CH), 128.41 (CH), 129.99 (CH), 145.22 ( $C_{quat}$ ), 147.80 ( $C_{quat}$ ), 169.87 (C=N);  $m/z$  (E.I.): (Found 333.2108 ( $M^+$ );  $C_{23}H_{27}NO$  requires 333.2192); 334 ( $M^{+1}$ ) (46), 167 (100), 154 (7).

### 3-Diphenylmethyl camphor nitrimine

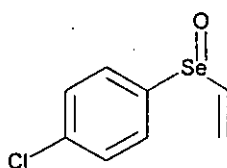


14

3-Benzhydryl camphor oxime (**13**) (950 mg, 2.8 mmol) in glacial acetic acid (15 ml) was treated with 5% aqueous sodium nitrite solution (7.5 ml). After 4 hours of stirring the crude product was concentrated and quenched with aqueous sodium bicarbonate (10 ml), extracted with ether (100 ml) and dried over magnesium sulfate. Solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) to afford 3-diphenylmethyl camphor nitrimine (**14**) as a colourless solid (557 mg, 54%).  $[\alpha]_D^{20}$  -64.5 ( $c$  0.009,  $CHCl_3$ ); m.p. 104-105 °C;  $\nu_{max}$ (film)/ $cm^{-1}$  2977, 1634 (C=N), 1522 ( $NO_2$ ), 1452, 1292, 770;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.27-7.15 (10H, m, ArH), 4.23 (1H, d,  $J$  11.5,  $H_{11}$ ), 3.26 (1H, d,  $J$  11.5,  $H_{3endo}$ ), 1.92-1.79 (2H, m,  $H_{5+6}$ ), 1.75 (1H, d,  $J$  3.5,  $H_4$ ), 1.67-1.61 (1H, m,  $H_6$ ), 1.45-1.41 (1H, m,  $H_5$ ), 1.16 (3H, s,  $H_{10}$ ), 1.05 (3H, s,  $H_{9 \text{ or } 8}$ ), 0.76 (3H, s,  $H_{9 \text{ or } 8}$ );  $\delta_C$  (100 MHz;  $CDCl_3$ ) 9.93 (Me), 20.05 (Me), 22.68 (Me), 29.51 ( $CH_2$ ), 32.03 ( $CH_2$ ), 47.03 (CH), 49.46 ( $C_{quat}$ ), 53.54 (CH), 55.59 (CH), 59.16 ( $C_{quat}$ ), 126.48 (CH), 126.56 (CH), 127.91 (CH), 128.14 (CH), 128.35 (CH), 129.00 (CH), 143.49 ( $C_{quat}$ ), 144.11 ( $C_{quat}$ ), 184.78 (C=N);  $m/z$  (F.A.B.): (Found: 362.1999 ( $M^+$ );  $C_{23}H_{26}N_2O_2$  requires 362.1994).

**1-Chloro-4-vinylselanyl-benzene , *p*-chlorophenyl vinyl selenide<sup>9</sup>****16**

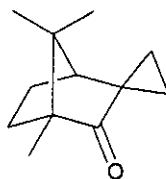
Bis(*p*-chlorophenyl) diselenide (300 mg, 0.8 mmol) in THF (10 ml) was added over 5 minutes to a solution of vinyl magnesium bromide (1N, 2.36 ml, 2.4 mmol) in THF (5 ml) at 0 °C. The reaction was stirred for one hour and allowed to reach temperature. The mixture was quenched with aqueous HCl (5M, 10 ml) and extracted with dichloromethane (3 × 20 ml). The organic layer was washed with aqueous sodium hydroxide (2M, 30 ml), water and brine and dried over magnesium sulfate. Removal of the solvent afforded the title compound (**16**) as colourless oil (340 mg, 99%).  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2900, 1601, 1471, 1390, 1373, 1009, 940;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.43 (2H, d,  $J$  8.5, ArH), 7.27 (2H, d,  $J$  8.5, ArH), 6.79 (1H, dd,  $J$  16.8 and 9.6, CHSe), 5.8 (1H, d,  $J$  9.6, =CH<sub>2</sub>), 5.54 (1H, d,  $J$  16.8, =CH<sub>2</sub>);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 120.06 (CH<sub>2</sub>), 127.16 (CH), 127.43 (C<sub>quat</sub>), 129.49 (CH), 133.83 (C<sub>quat</sub>), 134.39 (CH).

***p*-Chlorophenyl vinyl selenoxide<sup>9</sup>****17**

A solution of *p*-chlorophenyl vinyl selenide (480 mg, 2.2 mmol) in dichloromethane (6 ml) was added to a solution of 3-chloroperoxybenzoic acid (911 mg, 2.6 mmol, 50-55% purity) in dichloromethane (5 ml) at 0 °C. After standing for 30 minutes the reaction mixture was washed with 10% aqueous solution of sodium hydroxide, brine and dried over magnesium sulfate. Removal of the solvent from the organic layer gave the title compound (**17**) as colorless oil (481 mg, 94%).  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2890, 2830, 1590, 1570, 1470 1390, 1360, 1090, 940;  $\delta_{\text{H}}$  (400 MHz;

CDCl<sub>3</sub>) 7.63 (2H, d, *J* 8.4, ArH), 7.50 (2H, d, *J* 8.4, ArH), 6.86 (1H, dd, *J* 16.6 and 9.2, CHSe). 6.38 (1H, d, *J* 16.6, =CH<sub>2</sub>), 6.14 (1H, d, *J* 9.2, =CH<sub>2</sub>); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>) 124.97 (CH<sub>2</sub>), 128.11 (CH), 130.42 (CH), 138.21 (C<sub>quat</sub>), 139.68 (C<sub>quat</sub>), 140.65 (CH).

### 3,3 Cyclopropyl camphor<sup>8</sup>



18

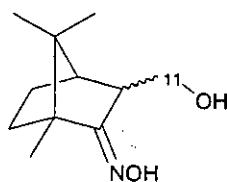
#### Method 1: Preparation of the zinc-copper couple and Simmons-Smith reaction

In a round bottom flask under nitrogen was placed copper acetate (364 mg, 1.8 mmol) in hot acetic acid (10 ml), to this solution zinc powder (2.38 g, 36.5 mmol) was added. After 5 minutes the stirring and the heating was stopped and the reaction mixture allowed to cooled to room temperature. Diethyl ether (100 ml) was poured into the mixture stirred then the organic layer removed the same operation was repeated four times. The diethyl ether was then replace by diisopropyl ether (20 ml) and the mixture was cooled to 0 °C with an ice bath followed by the addition of few drops of diiodomethane. A solution of 3-methylene camphor (9) (600 mg, 3.6 mmol) and diiodomethane (1.17 ml, 3.9 mmol) in diisopropyl ether was added gradually to the zinc-copper couple. When the addition was finished the reaction was heated under reflux for 12 hours and allowed to cool down. The reaction was then quenched by addition of water (10 ml). The organic phase was separated and the aqueous layer extracted with diethyl ether (3 × 30ml). The organic layers were washed with 10% aqueous HCl solution, water, brine and dried over magnesium sulfate. Following removal of the solvent, the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 1/99) to afford the title compound (18) (403 mg, 62%).

## Method 2: Use of the trimethyloxosulfonium methylid.

A solution of trimethyloxosulfonium ylid was prepared under nitrogen from sodium hydride (60% in mineral oil) (357 mg, 10.7 mmol) and trimethyloxosulfonium iodide (2.39 g, 10.6 mmol) in anhydrous diethyl ether (10 ml). A solution of 3-methylene camphor (**9**) (1.50 g, 8.9 mmol) in anhydrous diethyl ether (5 ml) was added, with stirring and slight cooling in water bath. The reaction mixture was stirred at room temperature for two hours and poured into cold water (50 ml). The ether extracts were washed with water, brine and dried over magnesium sulfate. Following removal of the solvent, the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 1/99) to afford the title compound (**18**) as colourless oil (1.19 g, 76%).  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3076, 2957, 2872 1734 (C=O), 1477, 1353, 1279, 1035, 956;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 1.95 (1H, tt,  $J$  11.6 and 4.4,  $\text{H}_4$ ), 1.74-1.67 (1H, td,  $J$  11.6 and 3.8,  $\text{H}_5$ ), 1.56-1.53 (2H, m,  $\text{H}_{5+6}$ ), 1.50-1.47 (1H, m,  $\text{H}_6$ ), 1.20-1.16 (1H, m,  $\text{H}_{11}$  or  $12$ ), 1.04-0.96 (2H, m,  $\text{H}_{11+12}$ ), 0.99 (6H, s,  $\text{H}_{10+9}$ ), 0.94 (3H, s,  $\text{H}_8$ ), 0.73-0.68 (1H, m,  $\text{H}_{11}$  or  $12$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 9.56 (Me), 12.08 ( $\text{CH}_2$ ), 19.24 ( $\text{CH}_2$ ), 19.79 (Me), 20.39 (Me), 25.57 ( $\text{CH}_2$ ), 31.95 ( $\text{CH}_2$ ), 35.15 ( $\text{C}_{\text{quat}}$ ), 47.93 ( $\text{C}_{\text{quat}}$ ), 50.69 (CH), 58.95 ( $\text{C}_{\text{quat}}$ ), 220.90 (C=O);  $m/z$  (E.I.): (Found: 178.1357 ( $\text{M}^+$ );  $\text{C}_{12}\text{H}_{18}\text{O}$  requires 178.1357); 178 ( $\text{M}^+$ ) (84), 163 (62), 149 (30), 135 (77), 121 (33), 109 (28), 83 (100).

## 3-Hydroxymethyl camphor oxime



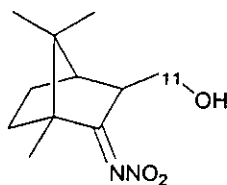
19

Hydroxylamine hydrochloride (5.5 g, 79.2 mmol), 3-hydroxymethyl camphor (**8**) (5.5 g, 30.1 mmol) and pyridine (3.15 ml, 39.2 mmol) were heated under reflux in ethanol (10 ml) for 4 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed under reduced pressure. Water was added and the solution extracted with diethyl ether



and dried over magnesium sulfate. Solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate/light petroleum, 25/75) to afford 3-hydroxymethyl camphor oxime (**19**) as a colourless solid (3.55 g, 57%) as a 3-(*endo/exo*) diastereoisomeric mixtures (85:15). m.p. 128-129 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3281 (br.s, OH), 2959, 2872, 1670 (C=N), 1444, 1390, 1375; 1207, 1026, 931, 733;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 8.64 (1H, br.s, OH), 3.84-3.72 (2H, m,  $\text{H}_{11}$ ), 2.99-2.97 (2H, m,  $\text{H}_{3+4}$ ), 1.96-1.94 (1H, m,  $\text{H}_5$ ), 1.75-1.68 (2H, m,  $\text{H}_{5+6}$ ), 1.46-1.41 (1H, m,  $\text{H}_6$ ), 1.00 (3H, s,  $\text{H}_{10}$ ), 0.93 (3H, s,  $\text{H}_9$  or 8), 0.83 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 12.35 (Me), 18.70 (Me), 19.49 (Me), 21.40 ( $\text{CH}_2$ ), 32.87 ( $\text{CH}_2$ ), 46.38 (CH), 48.04 (CH), 48.67 ( $\text{C}_{\text{quat}}$ ), 53.73 ( $\text{C}_{\text{quat}}$ ), 62.98 ( $\text{CH}_2$ ), 171.03 (C=N);  $m/z$  (E.I.): (Found: 198.1496 ( $\text{M}^{+1}$ );  $\text{C}_{11}\text{H}_{19}\text{NO}_2$  requires 198.1494); 198 ( $\text{M}^{+1}$ ) (100), 180 (7), 154 (7), 150 (6), 136 (7), 109 (15), 95 (6).

### 3-Hydroxymethyl camphor nitrimine

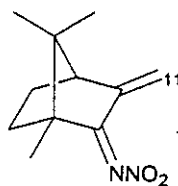


20

3-Hydroxymethyl camphor oxime (**19**) (3.10 g, 15.6 mmol) in glacial acetic acid (78 ml) was treated with aqueous sodium nitrite (5 %, 39 ml). A bright yellow colour developed and dispersed over 30 minutes. After 4 hours the crude product was concentrated and quenched with aqueous sodium bicarbonate, extracted with diethyl ether and dried over magnesium sulfate. Solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 10/90) to afford 3-hydroxymethyl camphor nitrimine (**20**) as a colourless solid (1.91 g, 54%).  $[\alpha]_{\text{D}}^{20} +104.2$  ( $c$  0.095,  $\text{CHCl}_3$ ); m.p. 107-108 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3279 (br.s, OH), 2957, 1666 (C=N), 1597 ( $\text{NO}_2$ ) 1439, 1389, 1373; 1264, 1031, 942, 740;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 3.76-3.69 (2H, m,  $\text{H}_{11}$ ), 3.33-3.29 (1H, m,  $\text{H}_3$ ), 2.13-2.11 (1H, m,  $\text{H}_4$ ), 1.84-1.74 (3H, m,  $\text{H}_{5+6}$ ), 1.60-1.57 (1H, m,  $\text{H}_6$ ), 1.02 (3H, s,  $\text{H}_{10}$ ), 1.00 (3H, s,  $\text{H}_9$  or 8), 0.92 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 10.71 (Me),

18.72 (Me), 18.79 (Me), 20.53 (CH<sub>2</sub>), 31.31 (CH<sub>2</sub>), 45.88 (CH), 47.18 (CH), 47.62 (C<sub>quat</sub>), 55.23 (C<sub>quat</sub>), 58.90 (CH<sub>2</sub>), 188.02 (C=N); *m/z* (F.A.B.): (Found: 227.1394 (M<sup>+</sup>), C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub> requires 227.1395); 227 (M<sup>+</sup>) (100), 181 (27), 180 (19), 163 (25), 154 (73), 136 (70), 109 (59), 94 (28).

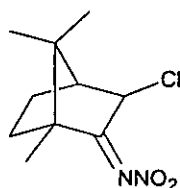
### 3-Methylene camphor nitrimine



21

To a solution of 3-hydroxymethyl camphor nitrimine (20) (1.20 g, 5.3 mmol) in dichloromethane (20 ml) was added mesyl chloride (620  $\mu$ l, 7.9 mmol) and triethylamine (1.5 ml, 10.6 mmol). The reaction mixture was stirred at room temperature overnight followed by the addition of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) (810 mg, 5.3 mmol). After two hours of additional stirring the reaction was quenched by the addition of water (20 ml). The aqueous layer was extracted with dichloromethane (3  $\times$  20 ml). The combined organic phases were washed with water, brine and dried over magnesium sulfate. Solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) to afford 3-methylene camphor nitrimine (21) as colourless oil (647 mg, 58%).  $[\alpha]_D^{20} +78.3$  (*c* 0.056, CHCl<sub>3</sub>);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2863, 2875, 1650, 1623, 1557, 1452, 1393, 1306, 1045, 928, 750;  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 5.62 (1H, d, *J* 0.67, H<sub>11</sub>), 5.27 (1H, d, *J* 0.67, H<sub>11</sub>), 2.43 (1H, d, *J* 3.86, H<sub>4</sub>), 2.00-1.92 (1H, m, H<sub>5</sub>), 1.87-1.76 (1H, m, H<sub>6</sub>), 1.62-1.41 (2H, m, H<sub>5+6</sub>), 1.03 (3H, s, H<sub>10</sub>), 0.93 (3H, s, H<sub>9 or 8</sub>), 0.87 (3H, s, H<sub>9 or 8</sub>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 11.15 (Me), 18.41 (Me), 20.57 (Me), 27.25 (CH<sub>2</sub>), 31.73 (CH<sub>2</sub>), 47.62 (C<sub>quat</sub>), 54.79 (CH), 55.60 (C<sub>quat</sub>), 118.18 (=CH<sub>2</sub>), 143.18 (=C<sub>quat</sub>), 172.38 (C=N); *m/z* (F.A.B.): (Found: 209.1345 (M<sup>+</sup>), C<sub>11</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub> requires 209.1340); 209 (M<sup>+</sup>) (45), 208 (9), 191 (12), 162 (54), 154 (47), 136 (54), 109 (23), 95 (30), 57 (100).

## 3-Chlorocamphor nitrimine



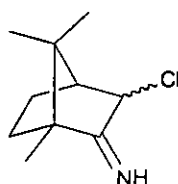
22a,b

NaHMDS (1M in THF) (13.45 ml, 13.5 mmol) was added to a solution of camphor nitrimine (1) (2.4 g, 12.2 mmol) in THF (50 ml) at  $-78^{\circ}\text{C}$ . The solution was stirred for an hour and then added to a round bottom flask containing *N*-chlorosuccinimide (NCS) (2.45 g, 18.4 mmol) in THF (60 ml) cooled to  $-78^{\circ}\text{C}$ . After the addition the reaction mixture was stirred for 2 hours and quenched by adding a saturated solution of ammonium chloride (10 ml). The organic layer was washed with water, brine, and dried over magnesium sulfate. Following the removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) to give a mixture in a ratio of 60:40 of 3-*exo/endo* chloro camphor nitrimine (22a/b) as a colourless solid (2.25 g, 80%). The 3-*exo*-chloro camphor nitrimine (22a) was crystallised from hexane.  $[\alpha]_{\text{D}}^{20} -79.6$  (*c* 0.076,  $\text{CHCl}_3$ ); m.p.  $123-123^{\circ}\text{C}$ ;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  1645 (C=N), 1578 ( $\text{NO}_2$ );  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 4.65 (1H, s,  $\text{H}_{3\text{endo}}$ ), 2.22 (1H, d, *J* 4.8,  $\text{H}_4$ ), 2.11-2.00 (1H, m,  $\text{H}_5$ ), 1.87-1.76 (1H, td, *J* 14.0 and 3.9,  $\text{H}_6$ ), 1.60-1.54 (1H, m,  $\text{H}_5$ ), 1.47-1.39 (1H, m,  $\text{H}_6$ ) 1.19 (3H, s, Me,  $\text{H}_{10}$ ), 1.10 (3H, s,  $\text{H}_9$  or 8), 1.01 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 10.80 (Me), 11.02 (Me), 19.51 (Me), 26.84 ( $\text{CH}_2$ ), 31.87 ( $\text{CH}_2$ ), 48.56 (C), 43.83 ( $\text{C}_{\text{quat}}$ ), 52.58 (CH), 55.57 (CHCl), 185.63 ( $\text{C}_{\text{quat}}$ ); *m/z* (F.A.B.): (Found: 230.0820 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{15}^{35}\text{ClN}_2\text{O}_2$  requires 230.0822).

The oily mixture of 3-*exo/endo*-chloro camphor nitrimine (22a/b) in dichloromethane was epimerised on silica gel overnight to increase the ratio to 77:23 of 3-*endo/exo*-chloro camphor nitrimine, and the 3-*endo*-chloro camphor nitrimine (22b), was crystallised from hexane.  $[\alpha]_{\text{D}}^{20} -54.9$  (*c* 0.067,  $\text{CHCl}_3$ ) m.p.  $116-118^{\circ}\text{C}$ ;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  1645 (C=N), 1579 ( $\text{NO}_2$ );  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 4.65 (1H, d, *J* 4.6,  $\text{H}_{3\text{exo}}$ ), 2.24 (1H, m,  $\text{H}_4$ ), 2.11-2.02 (1H, m,  $\text{H}_5$ ), 1.79-1.76 (1H, m,  $\text{H}_6$ ), 1.63-1.53 (1H, m,  $\text{H}_5$ ), 1.30-1.26 (1H, m,  $\text{H}_6$ ) 1.08 (3H, s, Me,  $\text{H}_{10}$ ), 1.04 (3H, s,  $\text{H}_9$  or 8), 0.95

(3H, s, H<sub>9 or 8</sub>);  $\delta_C$  (100 MHz; CDCl<sub>3</sub>) 10.80 (Me), 11.02 (Me), 19.51 (Me), 26.84 (CH<sub>2</sub>), 31.87 (CH<sub>2</sub>), 48.56 (C), 43.83 (C<sub>quat</sub>), 52.58 (CH), 55.57 (CHCl), 185.63 (C<sub>quat</sub>);  $m/z$  (F.A.B.): (Found: 230.0820 (M<sup>+</sup>); C<sub>10</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>2</sub> requires 230.0822).

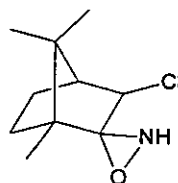
### 3-Chloro camphor imine



23a,b

A solution of 3-*endo*-chloro camphor nitrimine (**22b**) (200 mg, 0.9 mmol) in anhydrous THF (2 ml) at  $-78\text{ }^{\circ}\text{C}$  was treated with a slow stream of ammonia gas during 15 minutes. The solution was stirred for 2 hours at the same temperature. The solvent was removed under reduced pressure keeping the water bath below  $30\text{ }^{\circ}\text{C}$  to give a mixture of 3-(*endo/exo*)-chloro camphor imine (58:42) (**23a,b**) as a colourless oil (147 mg, 91%).  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  1674 (C=N);  $\delta_H$  (400 MHz; CDCl<sub>3</sub>) 4.62 (1H, d,  $J$  11.7, H<sub>3*exo*</sub>, 23b), 4.10 (1H, s, 3*endo*, 23a), 2.22-2.10 (2H, m), 2.06-1.99 (2H, m), 1.74-1.60 (2H, m), 1.44-1.35 (4H, m), 1.04 (3H, s, H<sub>10</sub>), 1.03 (6H, s, Me, H<sub>10+9 or 8</sub>), 1.02 (3H, s, H<sub>9 or 8</sub>), 0.95 (3H, s, H<sub>9 or 8</sub>), 0.88 (3H, s, H<sub>9 or 8</sub>).

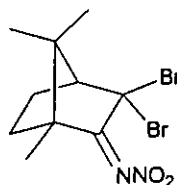
### 3-Chlorocamphor oxaziridine



24

A solution of purified 3-chloroperoxybenzoic acid (85%) (263 mg, 1.3 mmol) in anhydrous dichloromethane (5 ml) at  $-40\text{ }^{\circ}\text{C}$  was added to a solution of 3-chloro camphor imine (**23a,b**) (147 mg, 0.8 mmol) in anhydrous dichloromethane (2 ml). This reaction mixture was then stirred overnight at  $-40\text{ }^{\circ}\text{C}$ . The crude mixture was washed with aqueous sodium hydroxide (0.1M, 5 ml). The organic solution was dried over magnesium sulfate. Following removal of the solvent the crude product was purified by column chromatography over alumina eluting with light petroleum to afford the oxaziridine (**24**) as a colourless solid (35 mg, 20%).  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 4.55 (1H, br.s, NH), 4.11 (1H, s,  $\text{H}_{3\text{endo}}$ ), 2.15 (1H, d,  $J$  3.2,  $\text{H}_4$ ), 2.01-1.95 (1H, m,  $\text{H}_5$ ), 1.61-1.50 (2H, m,  $\text{H}_{5+6}$ ), 1.41-1.39 (1H, m,  $\text{H}_6$ ), 1.16 (3H, s,  $\text{H}_{10}$ ), 0.94 (3H, s,  $\text{H}_9$  or  $8$ ), 0.74 (3H, s,  $\text{H}_9$  or  $8$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 9.16 (Me), 20.64 (Me), 21.08 (Me), 27.61 ( $\text{CH}_2$ ), 29.75 ( $\text{CH}_2$ ), 47.88 (Cquat), 48.95 (Cquat), 53.02 (CH), 64.13 ( $\text{CHCl}$ ), 92.16 (O-C-N). This compound could not be further characterized due to instability.

### 3,3-Dibromocamphor nitrimine<sup>16</sup>



25

#### Method 1: Using potassium hydroxide and bromine

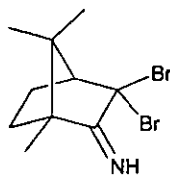
Potassium hydroxide (713 mg, 12.7 mmol) was dissolved in ethanol (1 ml) and added with vigorous stirring to a warm solution of camphor nitrimine (**1**) (1.0 g, 5.1 mmol) in ethanol (2 ml). Water (0.75 ml) was added to dissolve the precipitated potassium salt. Bromine (1 ml, 19.5 mmol) was added at room temperature until a faint orange colour persisted. The mixture was stirred for a further 10 minutes, water (30 ml) added and the excess bromine destroyed with aqueous sodium thiosulfate. The mixture was extracted with diethyl ether:light petroleum (3:1, 30 ml). The organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product purified by flash chromatography over silica gel eluting with (ethyl acetate/light petroleum, 2/98) to give the title compound (**25**) as a colourless solid

(1.72 g, 94%).  $[\alpha]_D^{20} +131.5$  ( $c$  0.019,  $\text{CHCl}_3$ ); m.p. 92-93 °C;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  1645 (C=N), 1569 ( $\text{NO}_2$ );  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 2.77 (1H, d,  $J$  3.94,  $\text{H}_4$ ), 2.37 (1H, ddd, 14.11, 9.01, 3.94,  $\text{H}_5$ ), 2.10-1.99 (1H, m,  $\text{H}_6$ ), 1.88 (1H, td, 14.11, and 3.01,  $\text{H}_5$ ), 1.69-1.54 (1H, m,  $\text{H}_6$ ), 1.36 (3H, s,  $\text{H}_{10}$ ), 1.13 (3H, s,  $\text{H}_9$  or 8), 1.08 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 10.73 (Me), 19.02 (Me), 19.88 (Me), 27.14 ( $\text{CH}_2$ ), 31.99 ( $\text{CH}_2$ ), 43.80 (CH), 49.22 ( $\text{C}_{\text{quat}}$ ), 54.54 ( $\text{C}_{\text{quat}}$ ), 66.43 ( $\text{CBr}_2$ ), 189.85 (C=N); (Found (F.A.B.): 354.9486 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2^{79,81}\text{Br}_2$  requires 354.9422); 357 (4), 356 (7), 355 ( $\text{M}^+$ ) (60), 307 (34), 154 (100), 107 (37).

#### Method 2: Using DBU and 1,3-dibromo-5,5-dimethylhydantoin

1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU) (814 mg, 5.3 mmol) was added to a solution of camphor nitrimine (**1**) (500 mg, 2.5 mmol) in ethyl acetate (5 ml). After stirring for 30 minutes at room temperature, 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) (603 mg, 3.1 mmol) was added in portions over ca.15 minutes, maintaining the temperature between 20 and 25 °C by external cooling with an ice/water bath. The reaction mixture was stirred for 2.5 hours, and quenched by the addition of aqueous HCl (1M, 10 ml). The organic layer was washed with water, brine and dried over magnesium sulfate. Following the removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 2/98) to give the desired compounds (**25**) as a mixture of *N-cis* and *N-trans* nitro-3,3-dibromocamphor nitrimine (655 mg, 35%) in a 1:1 mixture.  $\delta_{\text{H}}$  (mixture) (250 MHz;  $\text{CDCl}_3$ ) 2.76 (1H, d,  $J$  3.9,  $\text{H}_4$ ), 2.73 (1H, d,  $J$  3.9,  $\text{H}_4$ ), 2.41-2.32 (2H, m,  $\text{H}_5$  or 6), 2.15-2.01 (2H, m,  $\text{H}_5$  or 6), 1.94-1.55 (4H, m,  $\text{H}_5$  and 6), 1.35 (3H, s,  $\text{H}_{10}$ ), 1.32 (3H, s,  $\text{H}_{10}$ ), 1.13 (3H, s,  $\text{H}_9$  or 8), 1.12 (3H, s,  $\text{H}_9$  or 8), 1.06 (3H, s,  $\text{H}_9$  or 8), 1.07 (3H, s,  $\text{H}_9$  or 8).

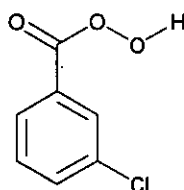
#### 3,3-Dibromocamphor imine



26

A solution of 3,3-dibromocamphor nitrimine (**25**) (200 mg, 0.6 mmol) in anhydrous THF (1 ml) was placed in a tube closed by a rubber septum under nitrogen and cooled to  $-78\text{ }^{\circ}\text{C}$ . Liquid ammonia (3 ml) was condensed by cannula into the tube, which was then sealed, and the reaction was stirred overnight while reaching room temperature. The reaction was then cooled to  $-78\text{ }^{\circ}\text{C}$  prior opening the tube. The ammonia was allowed to evaporate at room temperature under nitrogen. The solvent was removed under reduced pressure keeping the water bath below  $30\text{ }^{\circ}\text{C}$  to give 3,3-dibromo camphor imine (**26**) as a colourless oil (153 mg, 87%).  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2993, 2965, 1672 (C=NH), 1469, 1334, 1277, 1204, 798, 774;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 9.68 (1H, br.s, NH), 2.66 (1H, d,  $J$  4.4,  $\text{H}_4$ ), 2.24 (1H, td,  $J$  9.47 and 3.47,  $\text{H}_5$ ), 1.98-1.93 (1H, m,  $\text{H}_6$ ), 1.57-1.47 (2H, m,  $\text{H}_{5+6}$ ), 1.13 (3H, s,  $\text{H}_{10}$ ), 1.02 (3H, s,  $\text{H}_9$  or 8), 0.98 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 12.09 (Me), 22.74 (Me), 23.93 (Me), 29.49 ( $\text{CH}_2$ ), 30.23 ( $\text{CH}_2$ ), 47.42 ( $\text{C}_{\text{quat}}$ ), 61.01 (CH), 65.54 ( $\text{C}_{\text{quat}}$ ), 68.35 ( $\text{C}_{\text{quat}}$ ), 189.47 (C=N);  $m/z$  (F.A.B.): (Found: 306.9569 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{15}\text{N}^{79,79}\text{Br}_2$  requires 306.9571). This compound was used for the next step without further characterization.

#### Procedure for purification and titration of 3-chloroperoxybenzoic acid<sup>14</sup>



Commercially available (supplied by Aldrich Chemical) 3-chloroperoxybenzoic acid (50%, 2 g) was dissolved in the minimum amount of dichloromethane needed to obtain a homogenous solution (20 ml). This solution was then washed with aqueous phosphate buffered saline (pH 7.4,  $10 \times 20\text{ ml}$ ). The organic solution was separated, dried over magnesium sulfate. Solvents were removed under reduced pressure, keeping the water bath below  $30\text{ }^{\circ}\text{C}$  to give the title compound, which was subsequently submit to iodimetric titration methods described below. Precaution must be taken as purified 3-chloroperoxybenzoic acid can cause explosion. After purification the purified *m*-CPBA was kept in the freezer at  $-20\text{ }^{\circ}\text{C}$  or used immediately.

### Titration

Glacial acetic acid (5 ml) and chloroform (5 ml) were added to a solution of potassium iodide (1.5 g) in water (50 ml). The purified 3-chloroperoxybenzoic acid (100 mg) was then added to this solution and stirred for 5 minutes. The liberated iodine was then titrated with a standard 0.1M sodium thiosulfate solution.

1 ml of 0.1M  $\text{Na}_2\text{SO}_3$  = 0.069 g of 3-chloroperoxybenzoic acid

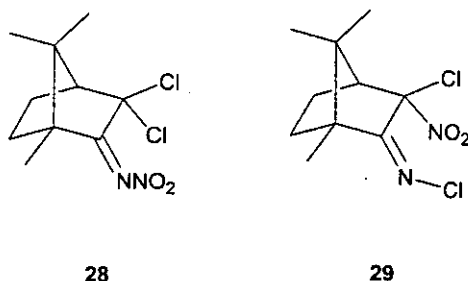
### Tetraphenylphosphonium monoperoxysulfate (TPPP)



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Oxone<sup>®</sup> triple salt (15.0 g, 48.8 mmol  $\text{KHSO}_5$ ) was dissolved in deionised water (300 ml) in a conical flask (1 L) and stirred at 10-15 °C. A solution of tetraphenyl phosphonium chloride (15.0 g, 40 mmol) in dichloromethane (300 ml) was gradually added over 5 minutes. After an additional 30 minutes, the organic layer was separated and the solvent removed under reduced pressure at room temperature. The crude colourless salt was transferred to a fritted glass funnel and washed with distilled water ( $2 \times 75$  ml). The solid was dissolved in dichloromethane (100 ml) dried over magnesium sulfate and filtered. Hexane was added to the dichloromethane solution until cloudiness developed and the flask was placed in a freezer (-20 °C) overnight producing the desired product (27) as a colourless solid (12.8 g, 70%).  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 8.92 (1H, br.s, OH), 7.89 (4H), 7.78 (8H), 7.64 (8H).



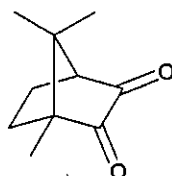
3,3-Dichlorocamphor nitrimine (**28**), *N*-chloro-3-nitro-3-chlorocamphor imine (**29**).

1,8-Diazabicyclo [5.4.0]undec-7-ene (DBU) (814 mg, 5.3 mmol) was added to a solution of camphor nitrimine (**1**) (500 mg, 2.5 mmol) in ethyl acetate (5 ml). After stirring for 30 minutes at room temperature, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) (603 mg, 3.1 mmol) was added in portions over ca.15 minutes, maintaining the temperature between 20 and 25 °C by external cooling with an ice/water bath. The reaction mixture was stirred for 2.5 hours, and quenched by the addition of aqueous HCl (1M, 10 ml). The organic layer was washed with water, brine and dried over magnesium sulfate. Following the removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 2/98) to give the desired compounds (**28**, **29**) as colourless solid (270 mg, 40%) in a 1:1 mixture. Compound (**28**) was crystallized from hexane.  $[\alpha]_D^{20} +63.5$  (*c* 0.081, CHCl<sub>3</sub>); m.p. 106-107 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  1653 (C=N), 1570 (NO<sub>2</sub>), 1454, 1324, 1294, 838;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 2.63 (1H, d, *J* 3.7, H<sub>4</sub>), 2.35-2.25 (1H, td, *J* 9.24 and 3.93, H<sub>5</sub>), 2.06-1.99 (1H, m, H<sub>6</sub>), 1.93-1.81 (1H, m, H<sub>5</sub>), 1.76-1.66 (1H, m, H<sub>6</sub>) 1.36 (3H, s, H<sub>10</sub>), 1.27 (3H, s, H<sub>9 or 8</sub>), 1.14 (3H, s, H<sub>9 or 8</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 9.73 (Me), 21.19 (Me), 23.63 (Me), 25.58 (CH<sub>2</sub>), 30.56 (CH<sub>2</sub>), 49.20 (C<sub>quat</sub>), 58.91 (C<sub>quat</sub>), 59.61 (CH), 62.16 (CCl<sub>2</sub>), 181.6 (C=N); *m/z* (F.A.B.): (Found: 265.0507 (M<sup>+</sup>); C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub><sup>35,35</sup>Cl<sub>2</sub> requires 265.0510); 265 (M<sup>+</sup>) (26), 200 (10), 154 (100), 107 (27).

Compound (**29**) was recrystallized from the mother liquor with hexane, after 3,3-dichloro camphor nitrimine (**28**) has been crystallized.  $[\alpha]_D^{20} -110.8$  (*c* 0.069, CHCl<sub>3</sub>) m.p. 93-94 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2983, 1631 (C=N), 1567 (NO<sub>2</sub>), 1494, 1396, 1184, 723;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 2.61 (1H, d, *J* 4.0, H<sub>4</sub>), 2.05-1.97 (2H, m, H<sub>5+6</sub>), 1.81-1.77 (2H, m, H<sub>5+6</sub>), 1.18 (3H, s, H<sub>10</sub>), 1.16 (3H, s, H<sub>9 or 8</sub>), 1.09 (3H, s, H<sub>9 or 8</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 11.61 (Me), 20.13 (Me), 22.18 (Me),

24.04 (CH<sub>2</sub>), 30.82 (CH<sub>2</sub>), 46.94 (C<sub>quat</sub>), 58.89 (CH), 60.34 (C<sub>quat</sub>), 100.74 (CICNO<sub>2</sub>) 179.58 (C=N-Cl); *m/z* (F.A.B.): (Found: M<sup>+</sup>, 264.0432, C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub><sup>35,35</sup>Cl<sub>2</sub> requires 264.0427).

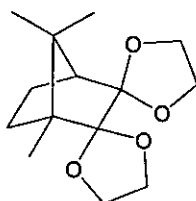
### Camphorquinone<sup>30</sup>



30

Selenium dioxide (1.36 g, 12.2 mmol) was added to a solution of camphor nitrimine (1) (2.0 g, 10.2 mmol) in dioxane (10 ml). The reaction mixture was heated under reflux for eight days and filtered hot. The residue was washed with hot dioxane. The combined solutions were dried over magnesium sulphate and were concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 10/90) to give camphorquinone (30) as a yellow solid (355 mg, 17%). m.p. 200-201 °C;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3040, 2980, 1776 (C=O), 1759 (C=O), 908, 894;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 2.63 (1H, d *J* 5.4, H<sub>4</sub>), 2.27-2.07 (1H, m, H<sub>5</sub>), 2.01-1.84 (1H, m, H<sub>6</sub>), 1.70-1.58 (2H, m, H<sub>5+6</sub>), 1.11 (3H, s, H<sub>10</sub>), 1.07 (3H, s, H<sub>9 or 8</sub>), 0.94 (3H, s, H<sub>9 or 8</sub>). This compound displayed identical spectral properties to those previously reported for the same product.

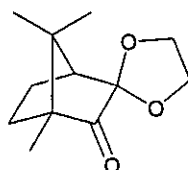
### 2,2,3,3-Bis-(ethylenedioxy) camphorquinone<sup>22</sup>



31

A mixture of camphorquinone (**30**) (10.2 g, 61.4 mmol), ethylene glycol (8.5 g, 0.14 mol), and TsOH.H<sub>2</sub>O (1.1 g, 5.8 mmol) in toluene (100 ml) was heated under reflux using a Dean-Stark trap for 48 hours. The crude mixture was washed with aqueous sodium hydroxide (5%, 2 × 25 ml), water, and brine. The organic phases were dried over magnesium sulfate, and most of the solvent was evaporated. A small amount of the compound crystallised (4.62 g) and the mother liquors were evaporated and the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 15/85) to afford the title compound (**31**) as a colourless solid (9.1 g, 58%).  $[\alpha]_D^{20} +3.8$  (*c* 0.063, CHCl<sub>3</sub>) (Lit.<sup>22</sup>  $[\alpha]_D^{20} +57$  (*c* 2, EtOH)) m.p. 63-64 °C (Lit.<sup>22</sup> m.p. 62-63 °C);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2962, 2893, 1473, 1311, 1212, 1186, 1034;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 3.97-3.74 (8H, m, CH<sub>2</sub>O), 1.98-1.91 (1H, m, H<sub>4</sub>), 1.82-1.76 (1H, m, H<sub>5</sub>), 1.68 (1H, d, *J* 4.4, H<sub>6</sub>), 1.59-1.51 (1H, m, H<sub>6</sub>), 1.34 (1H, td, *J* 12.4 and 4.4, H<sub>5</sub>), 1.17 (3H, s, H<sub>10</sub>), 0.86 (3H, s, H<sub>9</sub> or 8), 0.80 (3H, s, H<sub>9</sub> or 8);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 10.1 (Me), 20.9 (Me), 21.0 (CH<sub>2</sub>), 21.3 (Me), 29.5 (CH<sub>2</sub>), 44.7 (C<sub>quat</sub>), 52.9 (C<sub>quat</sub>), 53.5 (CH), 64.5 (CH<sub>2</sub>), 66.7 (CH<sub>2</sub>), 65.2 (CH<sub>2</sub>), 66.1 (CH<sub>2</sub>), 114.0 (C-(O)<sub>2</sub>), 114.9 (C-(O)<sub>2</sub>); *m/z* (E.I.): (Found: 254.1544 (M<sup>+</sup>); C<sub>14</sub>H<sub>22</sub>O<sub>4</sub> requires 254.1518); 254 (M<sup>+</sup>) (4), 141 (12), 113 (100), 99 (79).

### 3,3-Ethylenedioxy camphor<sup>22</sup>

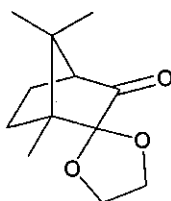


32

A mixture of camphorquinone (**30**) (10.2 g, 61.4 mmol), ethylene glycol (8.5 g, 0.14 mol) and TsOH.H<sub>2</sub>O (1.1 g, 5.8 mmol) in toluene (100 ml) was heated under reflux using a Dean-Stark trap for 12 hours. The crude mixture was washed with aqueous sodium hydroxide (5%, 2 × 25 ml), water, and brine. The organic layers were dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) to give the product (**32**) as a colourless solid (10.40 g, 80%); m.p. 83-85 °C (Lit.<sup>22</sup> m.p. 83-85 °C);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2964,

2899, 1754 (C=O), 1467, 1135;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 4.23-4.19 (1H, m,  $\text{CH}_2\text{O}$ ), 4.11-4.06 (1H, m,  $\text{CH}_2\text{O}$ ), 3.96-3.86 (2H, m,  $\text{CH}_2\text{O}$ ), 1.94-1.87 (2H, m,  $\text{H}_{4+5}$ ), 1.69 (1H, m,  $\text{H}_6$ ), 1.62-1.55 (1H, m,  $\text{H}_5$ ), 1.52-1.45 (1H, m,  $\text{H}_6$ ), 0.94 (3H, s,  $\text{H}_{10}$ ), 0.91 (3H, s,  $\text{H}_{9 \text{ or } 8}$ ), 0.82 (3H, s,  $\text{H}_{9 \text{ or } 8}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 9.51 (Me), 19.33 (Me), 21.62 ( $\text{CH}_2$ ), 21.85 (Me), 31.23 ( $\text{CH}_2$ ), 43.98 ( $\text{C}_{\text{quat}}$ ), 51.96 ( $\text{C}_{\text{quat}}$ ), 52.53 (CH), 64.76 ( $\text{CH}_2$ ), 66.44 ( $\text{CH}_2$ ), 109.13 (C-(O)<sub>2</sub>), 219.34 (C=O);  $m/z$  (E.I.): (Found: 210.1258 ( $\text{M}^+$ );  $\text{C}_{12}\text{H}_{18}\text{O}_3$  requires 210.1256); 210 ( $\text{M}^+$ ) (2), 182 (100), 165 (43), 141 (43), 141 (46).

### 2,2-Ethylenedioxy camphorquinone<sup>22</sup>

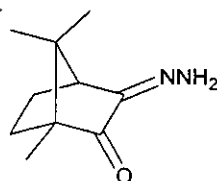


33

A solution of 2,2,3,3-bis-(ethylenedioxy) camphorquinone (**30**) (2.0 g, 7.86 mmol) in ethanol (23 ml) was added to aqueous HCl (4M, 6.15 ml) at room temperature and the resulting mixture was heated at 110 °C (TLC monitoring). When the starting material was consumed (30 minutes), the solvent was evaporated. A mixture of hexane/diethyl ether (1/1, 50 ml) was added to the residue. The resulting organic layer was washed with a saturated aqueous sodium hydrogenocarbonate, brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) to give (**33**) as a colourless solid (1.37 g, 83%).  $[\alpha]_{\text{D}}^{20}$  -60.7 ( $c$  0.074,  $\text{CHCl}_3$ ) m.p. 47-48 °C (Lit.<sup>22</sup> m.p. 47-48 °C);  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  2962, 2900, 1751 (C=O), 1465, 1219, 1157, 1034;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 4.30-4.28 (1H, m,  $\text{CH}_2\text{O}$ ), 4.16-4.14 (1H, m,  $\text{CH}_2\text{O}$ ), 4.00-3.96 (2H, m,  $\text{CH}_2\text{O}$ ), 2.16 (1H, d,  $J$  5.6,  $\text{H}_4$ ), 2.09-2.02 (1H, m,  $\text{H}_5$ ), 1.97-1.88 (1H, m,  $\text{H}_6$ ), 1.63-1.52 (2H, m,  $\text{H}_{5+6}$ ), 1.04 (3H, s,  $\text{H}_{10}$ ), 0.95 (3H, s,  $\text{H}_{9 \text{ or } 8}$ ), 0.90 (3H, s,  $\text{H}_{9 \text{ or } 8}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 9.1 (Me), 18.6 (Me), 21.8 (Me), 23.1 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 44.1 ( $\text{C}_{\text{quat}}$ ), 51.7 ( $\text{C}_{\text{quat}}$ ), 59.5(CH), 65.2 ( $\text{CH}_2$ ), 66.5 ( $\text{CH}_2$ ), 107.8 (C-(O)<sub>2</sub>), 217.0 (C=O);  $m/z$  (E.I.): (Found:

210.1258 ( $M^+$ );  $C_{12}H_{18}O_3$  requires 210.1256); 210 ( $M^+$ ) (1), 182 (81), 165 (14), 113 (100) 99 (48).

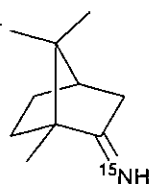
### 3-Hydrazano camphor<sup>26</sup>



34

Hydrazine hydrate (150 mg, 3 mmol) was added to a solution of camphorquinone (30) (500 mg, 3 mmol) in ethanol (5 ml). The reaction mixture was stirred for three hours at 40 °C. The crude product crystallised from the reaction mixture. It was then filtered and washed with cold ethanol to give the titled product (34) as a colourless solid (277 mg, 51%). m.p. 204-205 °C (Lit.<sup>26</sup> m.p. 206 °C);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3600, 3350, 1744 (C=O), 1641 (C=N);  $\delta_H$  (400 MHz;  $CDCl_3$ ) 6.34 (2H, m,  $NH_2$ ), 2.81 (1H, d,  $J$  3.7,  $H_4$ ), 2.2-1.2 (4H, m,  $H_{5+6}$ ), 1.02 (3H, s,  $H_{10}$ ), 1.00 (3H, s,  $H_9$  or 8), 0.86 (3H, s,  $H_9$  or 8);  $\delta_C$  (100 MHz;  $CDCl_3$ ) 9.01 (Me), 18.02 (Me), 20.42 (Me), 23.52 ( $CH_2$ ), 31.36 ( $CH_2$ ), 44.87 (CH), 45.63 ( $C_{\text{quat}}$ ), 57.98( $C_{\text{quat}}$ ), 150.35 (C=N), 204.52 (C=O);  $m/z$  (E.I.): (Found: 180.1259 ( $M^+$ );  $C_{10}H_{16}N_2O$  requires 180.1262). This compound displayed identical spectral properties to those previously reported for the same product

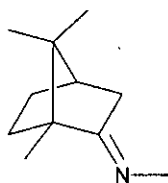
### Camphor imine<sup>1</sup>



35

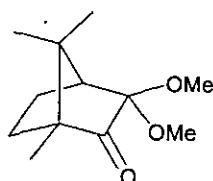
Camphor nitrimine (**1**) (25 mg, 0.1 mmol) in anhydrous THF (2 ml) was added to a flask containing 100 ml of pure  $^{15}\text{N}$  ammonia gas cooled at  $-78\text{ }^{\circ}\text{C}$ . The reaction was stirred for 4 hours at the same temperature and then allowed to reach room temperature. The solvent was removed under reduced pressure keeping the water bath below  $30^{\circ}\text{C}$  to give  $^{15}\text{N}$  camphor imine (**35**) as colourless oil.  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2959, 1650 (C=N), 1449, 1313, 1121;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 8.70 (1H, bs, NH) 2.48-2.44 (1H, m,  $\text{H}_3$ ), 2.19-2.01 (1H, m,  $\text{H}_3$ ), 1.96-1.87 (2H, m,  $\text{H}_{4+5}$ ), 1.70-1.64 (1H, m,  $\text{H}_6$ ), 1.38-1.29 (2H, m,  $\text{H}_{5+6}$ ), 0.96 (3H, s,  $\text{H}_{10}$ ), 0.95 (3H, s,  $\text{H}_9$  or 8), 0.82 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 10.86 (Me), 19.03 (Me), 20.03 (Me), 27.84 ( $2 \times \text{CH}_2$ ), 32.47 ( $\text{CH}_2$ ), 43.74 ( $\text{C}_{\text{quat}}$ ), 44.15 (CH), 54.07 ( $\text{C}_{\text{quat}}$ ). 194.22 (C= $^{15}\text{N}$ );  $\delta_{\text{N}}$  50 (C=N) ( $\text{CH}_3\text{CN} = 0$ );  $m/z$  (F.A.B.): (Found: 152.1331 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{17}\text{N}$  requires 152.1328; 153.1412 ( $\text{M}^{+1}$ ); requires 153.1409); 153 ( $\text{M}^{+1}$ ) (4), 152 ( $\text{M}^+$ ) (12), 137 (15), 109 (100), 93 (25).

#### *N*-Methyl camphor imine

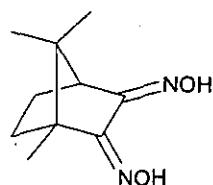


37

A 2M methylamine THF solution (1.5 ml, 3.0 mmol) was added to a solution of camphor nitrimine (**1**) (500 mg, 2.5 mmol) in anhydrous THF (2 ml). The reaction took place with production of gas. After 5 minutes of stirring (IR monitoring), the solvent was evaporated to afford the title compound as colourless oil (**37**) (418 mg, 99%).  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  1678 (C=N);  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 3.03 (3H, Me,  $\text{H}_{11}$ ), 2.32 (1H, d,  $J$  17.2,  $\text{H}_3$ ), 1.95-1.79 (3H, m,  $\text{H}_{3+4+5}$ ), 1.65 (1H, m,  $\text{H}_6$ ), 1.35-1.20 (2H, m,  $\text{H}_{5+6}$ ), 0.97 (3H, s,  $\text{H}_{10}$ ), 0.92 (3H, s,  $\text{H}_9$  or 8), 0.74 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 11.3 (Me), 19.0 (Me), 19.5 (Me), 27.4 ( $\text{CH}_2$ ), 32.0 ( $\text{CH}_2$ ), 35.2 ( $\text{CH}_2$ ), 39.1 (Me), 43.8 (CH), 47.2 ( $\text{C}_{\text{quat}}$ ), 53.6 ( $\text{C}_{\text{quat}}$ ), 189.9 (C=N);  $m/z$  (E.I.): (Found: 165.1519 ( $\text{M}^+$ );  $\text{C}_{11}\text{H}_{19}\text{N}$  requires 165.1517).

**3,3-Dimethoxy camphor<sup>29</sup>****38**

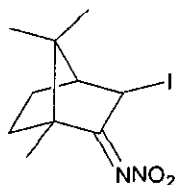
A solution of camphorquinone (**30**) (2.0 g, 12.0 mmol), trimethyl orthoformate (1.9 g, 18.0 mmol), and *p*-toluenesulfonic acid (91 mg, 0.5 mmol) in methanol (10 ml) was stirred and heated under reflux overnight. The solution was quenched with aqueous potassium carbonate and extracted with diethyl ether (3 × 50ml). The organic layer was washed with water, brine and dried over magnesium sulfate. Following the removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) to give the desired compound (**38**) as colourless oil (1.94 g, 76%).  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2836 (C-O), 1756 (C=O);  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 3.34 (3H, s, Me,  $\text{CH}_3\text{O}$ ), 3.24 (3H, s, Me,  $\text{CH}_3\text{O}$ ), 2.13 (1H, d,  $J$  3.4,  $\text{H}_4$ ), 1.70-1.63 (2H, m,  $\text{H}_{5+6}$ ), 1.52-1.40 (2H, m,  $\text{H}_{5+6}$ ), 0.92 (3H, s,  $\text{H}_{10}$ ), 0.90 (3H, s,  $\text{H}_{9 \text{ or } 8}$ ), 0.80 (3H, s,  $\text{H}_{9 \text{ or } 8}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 9.35 (Me), 20.05 (Me), 21.00 (Me), 21.82 ( $\text{CH}_2$ ), 31.23 ( $\text{CH}_2$ ), 43.88 ( $\text{C}_{\text{quat}}$ ), 49.78 (OMe), 50.59 (CH) 58.33 ( $\text{C}_{\text{quat}}$ ), 101.91 (C-OMe), 212.10 (C=O);  $m/z$  (E.I.): (Found: 212.1415 ( $\text{M}^+$ );  $\text{C}_{12}\text{H}_{20}\text{O}_3$  requires 212.1412); 199, 184, 169, 153, 137, 123, 115, 101, 95.

**Camphorquinone dioxime****39**

A solution of hydroxylamine hydrochloride (979 mg, 14.1 mmol), 3,3 dimethoxy camphor (**38**) (1.5 g, 7.1 mmol) and pyridine (1.06 ml, 10.6 mmol) in ethanol (10 ml) was heated under reflux

for 4 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed under reduced pressure. Water was then poured into the mixture followed by extraction with diethyl ether. The resulting organic layer was washed water, brine, dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 20/80) to afford camphorquinone dioxime (**39**) as a colourless solid (589 mg, 45%).  $[\alpha]_D^{20} -109.8$  ( $c$  0.025,  $\text{CHCl}_3$ ); m.p. 190-192 °C;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  1654 (C=N), 1637 (C=N);  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 11.63 (1H, br.s, OH), 8.69 (1H, br.s, OH), 3.16 (1H, d,  $J$  4.6,  $\text{H}_4$ ), 1.98-1.94 (1H, m,  $\text{H}_5$ ), 1.80 (1H, td,  $J$  12.7 and 4.6,  $\text{H}_6$ ), 1.58-1.42 (2H, m,  $\text{H}_{5+6}$ ), 1.09 (3H, s,  $\text{H}_{10}$ ), 0.94 (3H, s,  $\text{H}_{9 \text{ or } 8}$ ), 0.86 (3H, s,  $\text{H}_{9 \text{ or } 8}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 11.4 (Me), 17.9 (Me), 20.5 (Me), 23.9 ( $\text{CH}_2$ ), 33.3 ( $\text{CH}_2$ ), 47.9 ( $\text{C}_{\text{quat}}$ ), 48.1 (CH), 52.5 ( $\text{C}_{\text{quat}}$ ), 157.2(C=N), 159.0(C=N);  $m/z$  (E.I.): (Found: 196.1219 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_3$  requires 196.1212); 196 ( $\text{M}^+$ ), 179, 161, 146, 134, 121, 107, 94.

### 3-Iodocamphor nitrimine



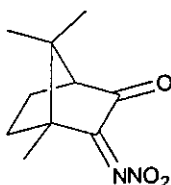
40

LiHMDS (1M in THF) (10.2 ml, 10.2 mmol) was added to a solution of camphor nitrimine (**1**) (2.0 g, 10.2 mmol) in THF (20 ml) at  $-10$  °C. The solution was stirred for 1 hour and then added to a round bottom flask containing ICl (1.65 g, 10.2 mmol) in THF (30 ml) cooled to  $-78$  °C. After the addition the reaction mixture was stirred for 2 hours and quenched by the addition of aqueous ammonium chloride (10 ml). The organic layer was washed with water, a solution of sodium sulfite, brine and dried over magnesium sulfate. Following the removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) to give a mixture of 87:13 of 3-(*endo/exo*)-iodocamphor nitrimine (**40**) as a yellow solid (1.82 g, 55%). 3-*endo*-iodocamphor nitrimine was crystallized from hexane.  $[\alpha]_D^{20} -78.3$  ( $c$  0.051,  $\text{CHCl}_3$ ) m.p. 90-91 °C;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  1652 (C=N), 1581 ( $\text{NO}_2$ );



$\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.45 (1H, d,  $J$  4.52,  $\text{H}_3$ ), 2.14-2.12 (1H, m,  $\text{H}_4$ ), 2.08-2.03 (2H, m,  $\text{H}_{5+6}$ ), 1.82-1.75 (1H, m,  $\text{H}_5$ ), 1.62-1.59 (1H, m,  $\text{H}_6$ ), 1.13 (3H, s,  $\text{H}_{10}$ ), 1.05 (3H, s,  $\text{H}_9$  or 8), 0.96 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 11.21 (Me), 19.54 (Me), 20.86 (Me), 22.14 (CH), 28.11 ( $\text{CH}_2$ ), 30.85 ( $\text{CH}_2$ ), 48.21 ( $\text{C}_{\text{quat}}$ ), 51.25 (CH), 54.26 ( $\text{C}_{\text{quat}}$ ), 186.48 ( $\text{C}=\text{N}$ );  $m/z$  (F.A.B.): (Found: 322.0179 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_2$  requires 322.0178).

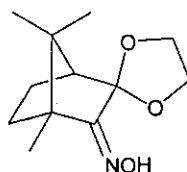
### 3-Oxocamphor nitrimine



41

Dimethyl sulfoxide (50  $\mu\text{l}$ , 0.62 mmol) was added to a solution of 3-iodocamphor nitrimine (40) (0.2 g, 0.62 mmol) in pyridine (2 ml) at room temperature. The solution was stirred for 12 hours (TLC monitoring) then another equivalent of dimethyl sulfoxide (50  $\mu\text{l}$ , 0.62 mmol) was added and the reaction was stirred for an additional two days. The reaction mixture was then poured into water and extracted with diethyl ether ( $3 \times 20$  ml). The organic layer was washed with water, a solution of sodium sulfite, brine and dried over magnesium sulfate. Following the removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 3/97) to afford the title compound (41) as a colourless solid (0.85 mg, 68%).  $[\alpha]_{\text{D}}^{20}$   $-135.7$  ( $c$  0.073,  $\text{CHCl}_3$ ); m.p. 51-52  $^{\circ}\text{C}$ ;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  1761 ( $\text{C}=\text{O}$ ) 1648 ( $\text{C}=\text{N}$ ), 1581 ( $\text{NO}_2$ ), 1308, 1195, 877;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 2.54 (1H, d,  $J$  5.02,  $\text{H}_4$ ), 2.20-2.12 (1H, m,  $\text{H}_5$ ), 2.08-2.01 (1H, td,  $J$  4.52, 13.6,  $\text{H}_6$ ), 1.85-1.78 (1H, m,  $\text{H}_5$ ), 1.70-1.63 (1H, m,  $\text{H}_6$ ), 1.19 (3H, s,  $\text{H}_{10}$ ), 1.07 (3H, s,  $\text{H}_9$  or 8), 1.02 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 10.19 (Me), 16.88 (Me), 20.81 (Me), 22.07 ( $\text{CH}_2$ ), 31.21 ( $\text{CH}_2$ ), 44.68 ( $\text{C}_{\text{quat}}$ ), 53.38 ( $\text{C}_{\text{quat}}$ ), 57.57 (CH), 170.71 ( $\text{C}=\text{N}$ ), 193.9 ( $\text{C}=\text{O}$ );  $m/z$  (F.A.B.): (Found: 210.1006 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_3$  requires 210.1004).

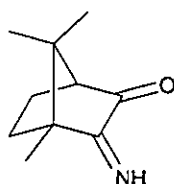
## 3,3-Ethylenedioxy camphor oxime



42

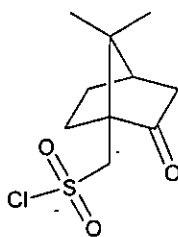
Hydroxylamine hydrochloride (1.5 g, 21.6 mmol), 3,3-(ethylenedioxy)-camphor (**32**) (1.5 g, 7.1 mmol) and pyridine (0.86 ml, 10.7 mmol) were heated under reflux in ethanol (10 ml) for 6 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed under reduced pressure. Water was then added and the mixture was extracted with diethyl ether ( $3 \times 30$  ml) and the organic phase was washed with water, brine and dried over magnesium sulfate. Solvents were removed under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate/light petroleum, 15/85) to afford the title compound (**42**) as a colourless solid (402 mg, 25%) as two diastereoisomers (66/34) at the nitrogen atom.  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3278 (OH), 2964, 2899, 1657 (C=N), 1662 (C=N);  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 9.05 (1H, bs OH major), 8.29 (1H, bs, OH minor), 4.28-4.19 (2H, m,  $\text{CH}_2\text{O}$ ), 3.94-3.90 (2H, m,  $\text{CH}_2\text{O}$ ), 1.94-1.54 (10H, m,  $\text{H}_{4+5+6}$ ), 1.34 (3H, s, major,  $\text{H}_{10}$ ), 1.10 (3H, s, minor,  $\text{H}_{10}$ ), 1.03 (3H, s, Me major,  $\text{H}_9$  or 8), 0.98 (3H, s, Me, minor,  $\text{H}_9$  or 8), 0.92 (3H, s, Me, major,  $\text{H}_9$  or 8), 0.86 (3H, s, Me, minor,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) (major) 9.95 (Me), 17.35 (Me), 19.48 ( $\text{CH}_2$ ), 21.35 ( $\text{CH}_2$ ), 21.69 (Me), 31.19 ( $\text{CH}_2$ ), 43.77 ( $\text{C}_{\text{quat}}$ ), 51.08 ( $\text{C}_{\text{quat}}$ ), 53.06 (CH), 64.31 ( $\text{CH}_2$ ), 65.01 ( $\text{CH}_2$ ), 107.55 (C-(O)<sub>2</sub>), 164.92 (C=N);  $m/z$  (E.I.): (Found: 225.1360 ( $\text{M}^+$ );  $\text{C}_{12}\text{H}_{19}\text{NO}_3$  requires 225.1365).

## 3-Oxocamphor imine



43

A solution of 3-oxo camphor nitrimine (41) (200 mg, 0.95 mmol) in anhydrous THF (3 ml) at  $-78\text{ }^{\circ}\text{C}$  was treated with a slow stream of ammonia gas over 10 minutes. The solution was stirred for four hours at the same temperature then allowed to reach room temperature to allow the ammonia to evaporate. The solvent was removed under reduced pressure keeping the water bath below  $30\text{ }^{\circ}\text{C}$  to give the title compound (43) (156 mg, 99%).  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3352 (NH, sharp), 2957, 2879, 1755 (C=O), 1667 (C=N), 1392, 1195, 928. This compound was used for the next step without further characterization.

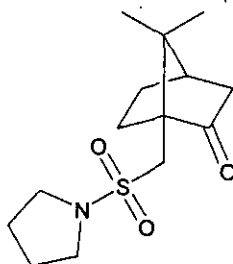
Camphor-10-sulfonyl chloride<sup>36</sup>

44

Camphor sulfonic acid (2 g, 8.61 mmol) is heated slowly in the presence of thionyl chloride (1.57 ml, 21.5 mmol). After three hours, excess thionyl chloride is evaporated under reduced pressure to give the corresponding sulfonyl chloride (44) as a yellow solid (2.16 g, 99%);  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 4.31 (1H, d,  $J$  14.6,  $\text{H}_{10}$ ), 3.75 (1H, d,  $J$  14.6,  $\text{H}_{10}$ ), 2.50-2.39 (1H, m,  $\text{H}_3$ ), 2.19-2.07 (2H, m,  $\text{H}_{3+4}$ ), 1.99 (1H, d,  $J$  18.6,  $\text{H}_5$ ), 1.82-1.74 (2H, m,  $\text{H}_{5+6}$ ), 1.54-1.46 (1H, m,  $\text{H}_6$ )

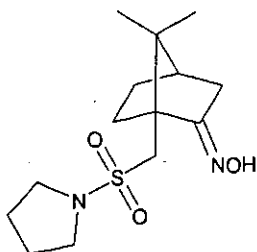
1.14 (3H, s, H<sub>9</sub> or 8), 0.93 (3H, s H<sub>9</sub> or 8). This product showed identical properties to the commercial compound.

### *N*-Pyrrolidinyl-camphor-10-sulfonamide<sup>36</sup>

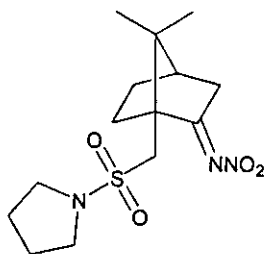


45

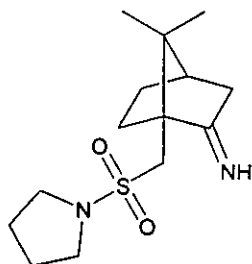
A solution of dimethylamino pyridine (DMAP) (1.05 g, 8.60 mmol) in dichloromethane (5 ml) was added to a solution of camphor-10-sulfonyl chloride (**44**) (2.16 g, 8.60 mmol) in dichloromethane (10 ml), cooled to 0°C. The mixture was stirred for 15 minutes before pyrrolidine (681 µl, 8.20 mmol) was slowly injected. The reaction mixture was stirred overnight at room temperature. The crude mixture was diluted with ethyl acetate (200 ml). The organic phase was washed with aqueous HCl (1M, 100 ml), water, brine and dried over magnesium sulfate. Following the removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 20/80) to afford the title compound (**45**) as a colourless solid (1.87 g, 80%).  $[\alpha]_D^{20} +32.3$  (*c* 0.051, CHCl<sub>3</sub>); m.p. 81-82 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2956, 2884, 1743 (C=O), 1332, 1146, 1051;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 3.45-3.34 (6H, m, CH<sub>2</sub>N, H<sub>10</sub>), 2.82 (1H, d, *J* 14.4, H<sub>3</sub>), 2.54 (1H, td, *J* 14.4 and 4.0, H<sub>3</sub>), 2.36 (1H, dt, *J* 18.4 and 4.0, H<sub>4</sub>), 2.12-1.92 (6H, m, CH<sub>2</sub>+H<sub>5+6</sub>), 1.66-1.61 (1H, m, H<sub>5</sub>), 1.46-1.40 (1H, m, H<sub>6</sub>), 1.13 (3H, s, H<sub>9</sub> or 8), 0.89 (3H, s, H<sub>9</sub> or 8);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 20.12 (Me), 20.31 (Me), 25.41 (CH<sub>2</sub>), 26.15 (2 x CH<sub>2</sub>), 27.26 (CH<sub>2</sub>), 42.96 (CH), 43.06 (CH<sub>2</sub>), 44.93 (CH<sub>2</sub>), 48.04 (2xCH<sub>2</sub>), 48.31 (C<sub>quat</sub>), 58.55 (C<sub>quat</sub>), 215.95 (C=O); *m/z* (E.I.): (Found: 286.1476 (M<sup>+</sup>); C<sub>14</sub>H<sub>23</sub>NO<sub>3</sub>S requires 286.1476); 286 (M<sup>+</sup>) (100), 215 (22), 154 (10), 151 (17), 123 (18).

***N*-Pyrrolidinyl-camphor-10-sulfonamide oxime****46**

Hydroxylamine hydrochloride (612 mg, 8.90 mmol), *N*-pyrrolidinyl-camphor-10-sulfonamide (**45**) (400 mg, 1.47 mmol) and triethylamine (942  $\mu$ l, 6.65 mmol) were heated under reflux in ethanol (10 ml) for 4 hours. The reaction vessel was cooled and the ethanol was removed under reduced pressure. The residue was diluted with dichloromethane and washed with water, brine and dried over magnesium sulfate. Following the removal of the solvent, the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 35/65) to afford the oxime (**46**) as a colourless solid (0.32 g, 73%).  $[\alpha]_D^{20}$   $-128.3$  ( $c$  0.087,  $\text{CHCl}_3$ ); m.p. 115-116  $^\circ\text{C}$ ,  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3277 (OH), 2944, 2879, 1664 (C=N);  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 8.73 (1H, b), 3.35-3.28 (5H, m,  $\text{CH}_2\text{N}$ ,  $\text{H}_{10}$ ), 2.88 (1H, d,  $J$  14.4,  $\text{H}_{10}$ ), 2.49 (1H, dt,  $J$  17.6 and 4.0,  $\text{H}_3$ ), 2.38 (1H, td,  $J$  11.6 and 4.0,  $\text{H}_4$ ), 2.01 (1H, d, 17.6,  $\text{H}_3$ ), 1.87-1.81 (6H, m,  $\text{CH}_{2\text{pyr}} + \text{H}_{5+6}$ ), 1.71-1.64 (1H, m,  $\text{H}_5$ ), 1.26-1.20 (1H, m,  $\text{H}_6$ ), 0.99 (3H, s,  $\text{H}_9$  or 8), 0.78 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 19.61 (Me), 19.85 (Me), 26.23 (2 x  $\text{CH}_2$ ), 27.53 ( $\text{CH}_2$ ), 28.38 ( $\text{CH}_2$ ), 33.22 ( $\text{CH}_2$ ), 43.78 (CH), 46.77 ( $\text{CH}_2$ ), 48.18 (2 x  $\text{CH}_2$ ), 50.30 ( $\text{C}_{\text{quat}}$ ), 52.41 ( $\text{C}_{\text{quat}}$ ), 166.66 (C=N);  $m/z$  (E.I.): (Found: 301.1587 ( $\text{M}^+$ );  $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_3\text{S}$  requires 301.1508); 301 ( $\text{M}^+$ ) (100), 230 (58), 154 (27), 136 (24).

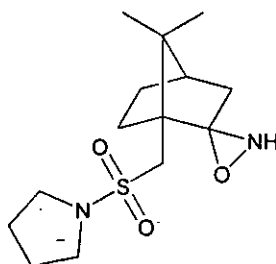
***N*-Pyrrolidinyl-camphor-10-sulfonamide nitrimine****47**

The oxime (46) (0.23 g, 0.76 mmol) in glacial acetic acid (7 ml) was treated with an aqueous solution of sodium nitrite (5%, 3.5 ml). A bright yellow colour developed and dispersed over 30 minutes. After 3 hours the crude mixture was evaporated, the residue dissolved in dichloromethane (50 ml). The organic layer was washed with water, brine and dried over magnesium sulfate. Following the removal of the solvent, the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 15/85) to afford the title compound (47) as a colourless solid (0.15 g, 61%).  $[\alpha]_D^{20} -58.2$  (*c* 0.098, CHCl<sub>3</sub>); m.p. 104-105 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2967, 2888, 1650 (C=N), 1567 (NO<sub>2</sub>), 1333, 1314, 1203, 1149, 1073, 783;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 3.47-3.36 (5H, m, CH<sub>2</sub> + H<sub>10</sub>), 2.98 (1H, d, *J* 14,8, H<sub>10</sub>), 2.73-2.65 (2H, m, H<sub>3+4</sub>), 2.20 (1H, d, *J* 18.8, H<sub>3</sub>), 2.09-1.92 (6H, m, CH<sub>2pyr</sub>+H<sub>5+6</sub>), 1.85-1.79 (1H, m, H<sub>5</sub>), 1.45-1.39 (1H, m, H<sub>6</sub>), 1.14 (3H, s, H<sub>9 or 8</sub>), 0.95 (3H, s, H<sub>9 or 8</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 19.65 (2 x Me), 26.29 (2 x CH<sub>2</sub>), 26.97 (CH<sub>2</sub>), 27.10 (CH<sub>2</sub>), 35.00 (CH<sub>2</sub>), 43.43 (CH), 46.14 (CH<sub>2</sub>), 48.11 (2 x CH<sub>2</sub>), 50.94 (C<sub>quat</sub>), 54.66 (C<sub>quat</sub>), 187.5 (C=N); *m/z* (F.A.B.): (Found: 329.1413 (M<sup>+</sup>); C<sub>14</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>S requires 329.1409).

***N*-PyrrolidinyI-camphor-10-sulfonamide imine**

48

A solution of *N*-pyrrolidinyI-camphor-10-sulfonamide nitrimine (**47**) (300mg, 0.91 mmol) in anhydrous THF (3 ml) at  $-78^{\circ}\text{C}$  was treated with a slow stream of ammonia gas over 10 minutes. The solution was stirred for four hours at the same temperature then allowed to reach room temperature to allow the ammonia to evaporate. The solvent was removed under reduced pressure keeping the water bath below  $30^{\circ}\text{C}$  to give the title compound (**48**) (259 mg, 99%).  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3261 (NH, sharp), 2856, 2885, 1671 (C=N), 1382, 1150, 779. This compound was used for the next step without further characterization.

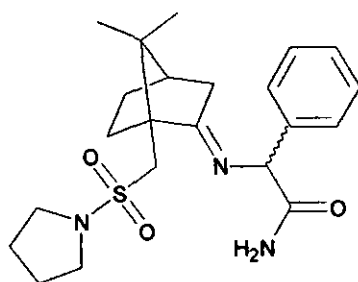
***N*-PyrrolidinyI-camphor-10-sulfonamide oxaziridine**

49

Tetraphenylphosphonium monoperoxysulfate (**27**) (982 mg, 2.3 mmol) and trifluoroacetone (10  $\mu\text{l}$ , 0.11 mmol) was added to a solution of *N*-pyrrolidine-10-sulfonamide camphor imine (**48**) (325 mg, 1.1 mmol) in dichloromethane (10 ml) at  $-40^{\circ}\text{C}$ . The reaction mixture was stirred at the same temperature for three hours (TLC monitoring). Diethyl ether (20 ml) was added to the

reaction mixture at  $-40\text{ }^{\circ}\text{C}$ , which caused precipitation of the tetraphenylphosphonium sulfone salt. The reaction mixture was filtered through a mixture of magnesium sulfate and silica. Following removal of the solvent the title compound was obtained (**49**) as a colourless solid (260 mg, 76%).  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3226 (NH, sharp), 3058, 2951) 1440, 1287, 1229, 1163, 1107, 723;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 5.63 (1H, bs, NH), 3.49-3.23 (5H, m,  $\text{CH}_2 + \text{H}_{10}$ ), 2.90 (1H, d,  $J$  16.0,  $\text{H}_{10}$ ), 2.42-2.39 (2H, m,  $\text{H}_{3+4}$ ), 2.02-1.99 (5H, m,  $\text{CH}_{2\text{pyr}} + \text{H}_3$ ), 1.85-1.69 (2H, m,  $\text{H}_{5+6}$ ), 1.47-1.39 (2H, m,  $\text{H}_{5+6}$ ), 1.04 (3H, s,  $\text{H}_{9\alpha\beta}$ ), 0.87 (3H, s,  $\text{H}_{9\alpha\beta}$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 15.26 (Me), 19.69 (Me), 25.04 ( $\text{CH}_2$ ), 25.82 ( $2\times\text{CH}_2$ ), 26.93 ( $\text{CH}_2$ ), 27.33 ( $\text{CH}_2$ ), 42.75 (CH), 44.66 ( $\text{CH}_2$ ), 47.83 ( $\text{CH}_2$ ), 47.90 ( $\text{CH}_2$ ), 53.53 ( $\text{C}_{\text{quat}}$ ), 58.25 ( $\text{C}_{\text{quat}}$ ), 88.44 (O-C-N).

#### *N*-Pyrrolidinyl-camphor-10-sulfonamide-*N*-phenyl-acetamide imine



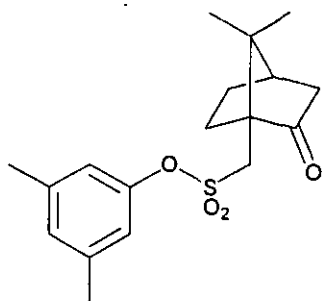
**50a,b**

A 1M solution of LiHMDS in THF (992  $\mu\text{l}$ , 0.99 mmol) was added to a solution of benzyl cyanide (96  $\mu\text{l}$ , 0.83 mmol) in THF (5 ml) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at the same temperature for 1 hour, followed by the addition of a solution of camphor *N*-pyrrolidinyl-10-sulfonamide oxaziridine (**49**) (274 mg, 0.91 mmol) in anhydrous THF (5 ml). After 4 hours of stirring at  $-78\text{ }^{\circ}\text{C}$  the reaction mixture was quenched with aqueous ammonium chloride (20 ml) and then extracted with dichloromethane ( $3 \times 40\text{ ml}$ ). The organic phase was washed with water, brine and dried over magnesium sulfate. Following the removal of the solvent, the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 35/65) to afford the title compound (**50a,b**) as a colourless solid (14.3 mg, 4%) as a mixture of diastereoisomers.  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 8.11 (1H, br.s, NH), 7.75-7.24 (11H, m, ArH), 5.39 (1H, bs, NH), 4.86 (1H, bs, NH), 4.82 (1H, s,  $\text{H}_{12}$ ), 4.79 (1H, s,  $\text{H}_{12}$ ), 3.42-3.47 (10H,



m, CH<sub>2</sub>N + H<sub>10</sub>), 3.19 (1H, d, *J* 14.0, H<sub>10</sub>, minor), 2.88, (1H, d, *J* 13.8, H<sub>10</sub>, major) 2.42 (1H, dt *J* 17.6 and 4.0, H<sub>3</sub>), 2.04-1.94 (11H, mCH<sub>2</sub><sub>pyr</sub> + H<sub>4+3</sub>), 1.85-1.70 (6H, m, H<sub>3+5+6</sub>), 1.59-1.52 (4H, m, H<sub>5+6</sub>), 1.05 (3H, s, H<sub>9 or 8</sub> minor), 0.96 (3H, s, H<sub>9 or 8</sub> major) 0.93 (3H, s, H<sub>9 or 8</sub> minor), 0.51 (3H, s, H<sub>9 or 8</sub> major); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>) 19.05 (Me), 20.13 (Me), 25.77 (CH<sub>2</sub>), 26.90 (CH<sub>2</sub>), 29.82 (CH<sub>2</sub>), 35.45 (CH<sub>2</sub>), 44.44 (CH), 47.74 (CH<sub>2</sub>), 48.48 (C<sub>quat</sub>), 56.07 (C<sub>quat</sub>), 68.63 (CH), 127.38 (CH), 128.53 (2 x CH), 132.09 (2 x CH), 139.54 (C<sub>quat</sub>), 175.42 (C=N), 180.56 (N-C=O); *m/z* (E.I.): (Found: 417.2088 (M<sup>+</sup>); C<sub>22</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>S requires 417.2086).

### 3,5-Dimethylphenyl camphor-10-sulfonate

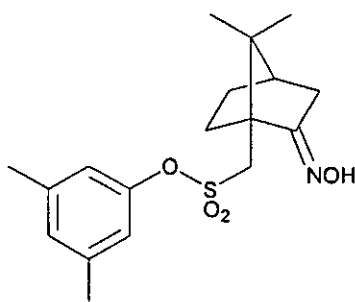


51

Camphor-10-sulfonic chloride (**44**) (5.0 g, 2.0 mmol) was gradually added to a solution of 3,5-dimethyl phenol (2.43 g, 20.0 mmol) in pyridine (50 ml) at -5 °C. The reaction mixture was stirred for two hours at 0 °C. The reaction mixture was then diluted with water (100 ml) and extracted with dichloromethane (3 × 50 ml), the organic layer was washed with water, brine and dried over magnesium sulfate. Following the removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 10/90) to afford the titled compound (**51**) as colourless oil (2.46 g, 37%); ν<sub>max</sub>(film)/cm<sup>-1</sup> 2981, 2900, 1756 (C=O), 1475; δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 6.93 (3H, s, ArH), 3.80 (1H, d, *J* 15.2, H<sub>10</sub>), 3.19 (1H, d, *J* 15.2, H<sub>10</sub>), 2.65-2.54 (1H, m, H<sub>3</sub>) 2.40 (1H, dt, *J* 18.4 and 4.0, H<sub>3</sub>) 2.32 (6H, s, ArCH<sub>3</sub>) 2.15-2.07 (2H, m, H<sub>4+5</sub>), 1.96 (1H, d, *J* 18.4, H<sub>5</sub>), 1.72-1.68 (1H, m, H<sub>6</sub>), 1.45(1H, td, *J* 5.6 and 4.0, H<sub>6</sub>), 1.15 (3H, s, H<sub>9 or 8</sub>), 0.90 (3H, s, H<sub>9 or 8</sub>); δ<sub>C</sub> (100 MHz; CDCl<sub>3</sub>) 20.07 (Me), 20.34 (Me), 21.61 (2 x Me), 25.49 (CH<sub>2</sub>), 27.24 (CH<sub>2</sub>), 42.43 (CH<sub>2</sub>), 43.22 (CH), 47.84 (CH<sub>2</sub>), 48.30 (C<sub>quat</sub>), 59.51 (C<sub>quat</sub>), 119.89 (2 x ArCH), 129.22 (ArCH), 140.22 (2 x ArC<sub>quat</sub>), 149.51 (ArC<sub>quat</sub>), 214.48

(C=O);  $m/z$  (E.I.): (Found: 336.1395 ( $M^+$ );  $C_{18}H_{24}O_4S$  requires 336.1395). 336 ( $M^+$ ) (4), 216 (70), 151 (50), 122 (100), 93 (18).

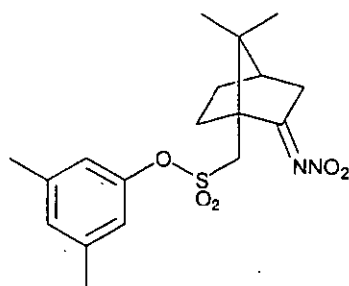
### 3,5-Dimethylphenyl camphor-10-sulfonate oxime



52

A solution of hydroxylamine hydrochloride (1.50 g, 21.6 mmol), 3,5-dimethylphenyl camphor-10-sulfonate (**51**) (1.64 g, 4.9 mmol) and pyridine (1.00 ml, 10 mmol) in ethanol (10 ml) was refluxed for 4 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed under reduced pressure. Water was then added to the mixture followed by extraction with diethyl ether. The resulting organic layer was washed water, brine, dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 20/80) to afford the desired oxime (**52**) as a colourless solid (1.32 g, 77%). m.p. 95-96 °C;  $\nu_{\max}$ (film)/ $\text{cm}^{-1}$  3420 (b, OH), 2955, 1684 (C=N), 1616, 1578, 1353, 1181, 1124, 945;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 8.72 (1H, br.s), 6.92 (3H, s, ArH), 3.80 (1H, d,  $J$  14.7,  $H_{10}$ ), 3.34 (1H, d,  $J$  14.7,  $H_{10}$ ), 2.61 (1H, dt,  $J$  18.4 and 3.7,  $H_3$ ), 2.51-2.41 (1H, m,  $H_3$ ), 2.31 (6H, s, ArCH<sub>3</sub>), 2.10 (1H, d,  $J$  18.1,  $H_5$ ), 2.05-1.79 (3H, m,  $H_{4+5+6}$ ), 1.38-1.25 (1H, m,  $H_6$ ), 1.08 (3H, s,  $H_9$  or 8), 0.87 (3H, s,  $H_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 19.59 (Me), 19.70 (Me), 21.63 (2 x Me), 27.53 (CH<sub>2</sub>), 28.38 (CH<sub>2</sub>), 33.28 (CH<sub>2</sub>), 43.97 (CH), 49.94 (CH<sub>2</sub>), 50.42 (C<sub>quat</sub>), 52.33 (C<sub>quat</sub>), 120.14 (2 x ArCH), 129.17 (ArCH), 140.13 (2 x ArC<sub>quat</sub>), 149.33 (ArC<sub>quat</sub>), 167.16 (C=N);  $m/z$  (E.I.): (Found: 351.1499 ( $M^+$ );  $C_{18}H_{25}NO_4S$  requires 351.1504); 351 ( $M^+$ ), 231 (26), 230 (100), 148 (33), 122 (95), 107 (71), 93 (33).

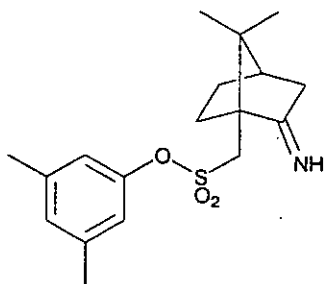
## 3,5-Dimethylphenyl camphor-10-sulfonate nitrimine



53

The oxime (**52**) (1.21 g, 3.4 mmol) in glacial acetic acid (15 ml) was treated with aqueous sodium nitrite (5%, 7 ml). A bright yellow colour developed and dispersed over 30 minutes. After 3 hours the crude was evaporated and the residue dissolved in dichloromethane (50 ml). The organic layer was washed with water, brine and dried over magnesium sulfate. Following removal of the solvent the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 10/90) to afford 3,5-dimethylphenyl camphor-10-sulfonate nitrimine (**53**) as a colourless solid (814 mg, 62%).  $[\alpha]_D^{20} -115.3$  (*c* 0.068, CHCl<sub>3</sub>); m.p. 91-92 °C;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2965, 1654 (C=N), 1569 (NO<sub>2</sub>), 1471, 1373, 1313, 1181, 1122, 941;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 6.94 (1H, s, ArH), 6.92 (2H, s, ArH), 3.84 (1H, d, *J* 15.0, H<sub>10</sub>), 3.32 (1H, d, *J* 15.0, H<sub>10</sub>), 2.78-2.68 (2H, m, H<sub>3</sub>), 2.33 (6H, s), 2.24 (1H, d, *J* 18.7, H<sub>5</sub>), 2.10-1.87 (3H, m, H<sub>4+5+6</sub>) 1.48-1.40 (1H, m, H<sub>6</sub>), 1.18 (3H, s, H<sub>9</sub> or 8), 0.97 (3H, s, H<sub>9</sub> or 8);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 19.28 (Me), 19.36 (Me), 21.23 (2 x Me), 26.57 (CH<sub>2</sub>), 26.84 (CH<sub>2</sub>), 34.64 (CH<sub>2</sub>), 43.25 (CH), 48.02 (CH<sub>2</sub>), 50.41 (C<sub>quat</sub>), 54.13 (C<sub>quat</sub>), 119.40 (2 x CH), 128.97 (CH), 139.96 (2 x C<sub>quat</sub>), 148.84 (C<sub>quat</sub>), 186.06 (C=N); *m/z* (F.A.B.): (Found: 381.1484 (M<sup>+</sup>); C<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>S requires 381.1406); 381 (M<sup>+</sup>) (67), 334 (27), 259 (7), 214 (11), 154 (18), 137 (15), 122 (100), 107 (13), 93 (7).

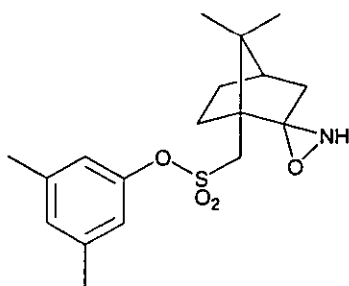
### 3,5-Dimethylphenyl camphor-10-sulfonate imine



54

A solution of 3,5-dimethylphenyl camphor-10-sulfonate nitrimine (**53**) (300 mg 0.79 mmol) in anhydrous THF (5 ml) at  $-78^{\circ}\text{C}$  was treated with a slow stream of ammonia gas for 10 minutes. The solution was stirred during four hours at the same temperature then allowed to reach room temperature for the ammonia to evaporate. The solvent was removed under reduced pressure keeping the water bath below  $30^{\circ}\text{C}$  to give the title compound (**54**) as a colourless oil (258 mg, 97%).  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3270 (NH, sharp), 2954, 2885, 1670 (C=N), 1615 1386, 1282, 1177, 1122, 1020, 943;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 8.83 (1H, bs, NH), 6.93 (3H, s, ArH), 3.88 (1H, d,  $J$  14.8,  $\text{H}_{10}$ ), 3.28 (1H, d,  $J$  14.8,  $\text{H}_{10}$ ), 2.47-2.41 (1H, m,  $\text{H}_3$ ), 2.31 (6H, s,  $\text{ArCH}_3$ ), 2.02 (1H, d,  $J$  17.6,  $\text{H}_3$ ), 2.01-1.94 (2H, m,  $\text{H}_{4+5}$ ), 1.85-1.74 (2H, m,  $\text{H}_{5+6}$ ), 1.43-1.36 (1H, m,  $\text{H}_6$ ), 1.08 (3H, s,  $\text{H}_9$ ), 0.87 (3H, s,  $\text{H}_8$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 19.91 (Me), 19.96 (Me), 21.57 (2 x Me), 27.75 ( $\text{CH}_2$ ), 27.85 ( $\text{CH}_2$ ), 40.67 ( $\text{CH}_2$ ), 44.07 (CH), 49.30 ( $\text{C}_{\text{quat}}$ ), 49.61 ( $\text{CH}_2$ ), 55.51 ( $\text{C}_{\text{quat}}$ ), 119.86 (CH), 119.92 (CH), 129.18 (CH), 140.18 (2 x  $\text{C}_{\text{quat}}$ ), 149.44 ( $\text{C}_{\text{quat}}$ ), 188.62 (C=N).

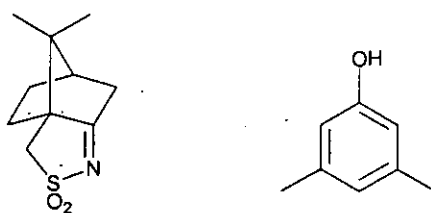
### 3,5-Dimethylphenyl camphor-10-sulfonate oxaziridine



55

Tetraphenylphosphonium monoperoxysulfate (27) (673 mg, 1.5 mmol) and trifluoroacetone (20  $\mu$ l, 0.2 mmol) was added to a solution of 3,5-dimethylphenyl camphor-10-sulfonate imine (54) (258 mg, 0.8 mmol) in dichloromethane (10 ml) at  $-40\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at the same temperature for 3 hours (TLC monitoring). Diethyl ether (30 ml) was added to the reaction mixture at  $-40\text{ }^{\circ}\text{C}$ , which caused precipitation of the tetraphenylphosphonium sulfone salt. The reaction mixture was then filtrate through a mixture of magnesium sulfate and silica. Removal of the solvent afforded the 3,5-dimethylphenyl camphor-10-sulfonate oxaziridine (55) as a colourless solid (197 mg, 73%).  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3226 (NH, br.s), 3058, 2962, 1616, 1440, 1368, 1163, 1108, 1059, 942, 753, 723;  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 6.95 (3H, s, ArH), 4.76 (1H, bs, NH), 3.48 (1H, d,  $J$  15.2,  $\text{H}_{10}$ ), 3.10 (1H, d,  $J$  15.2,  $\text{H}_{10}$ ), 2.59-2.42 (1H, m,  $\text{H}_3$ ), 2.33 (6H, s,  $\text{ArCH}_3$ ), 2.06 (1H, d,  $J$  17.8,  $\text{H}_3$ ), 1.97-1.95 (2H, m,  $\text{H}_{4+5}$ ), 1.86-1.73 (1H, m,  $\text{H}_6$ ), 1.51-1.48 (2H, m,  $\text{H}_{5+6}$ ), 1.08 (3H, s,  $\text{H}_9$  or 8), 1.01 (3H, s,  $\text{H}_9$  or 8);  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 15.28 (Me), 19.54 (Me), 21.25 (2 x Me), 25.75 ( $\text{CH}_2$ ), 27.27 ( $\text{CH}_2$ ), 37.83 ( $\text{CH}_2$ ), 43.82 (CH), 47.57 ( $\text{CH}_2$ ), 49.47 ( $\text{C}_{\text{quat}}$ ), 58.21 ( $\text{C}_{\text{quat}}$ ), 88.29 (O-C-N), 119.41 (2 x ArCH), 129.12 (ArCH), 140.05 (2 x  $\text{ArC}_{\text{quat}}$ ), 148.87 ( $\text{ArC}_{\text{quat}}$ ).

#### Camphorylsulfonyl imine, 3,5-dimethyl phenol



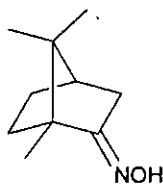
56

A 1M solution of LiHMDS in THF (34  $\mu$ l, 0.3 mmol) was added to a solution of benzyl cyanide (33  $\mu$ l, 0.3 mmol) in THF (2 ml) at  $-78\text{ }^{\circ}\text{C}$ . The reaction mixture was stirred at the same temperature for one hour, followed by the addition of a solution of 3,5-dimethyl-phenyl camphor-10-sulfonate ester oxaziridine (55) (100 mg, 0.3 mmol) in THF (2 ml). After 4 hours of stirring at  $-78\text{ }^{\circ}\text{C}$  the reaction mixture was quenched with aqueous ammonium chloride (5 ml) and extracted with dichloromethane (3  $\times$  20 ml). The organic phase was washed with water,

brine and dried over magnesium sulfate. Following removal of the solvent, the crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 20/80) to afford the title compound (**56**) (15 mg, 25%). m.p. 224–225 °C,  $\nu_{\text{max}}$ (film)/cm<sup>-1</sup> 3006, 2975, 2956, 2894, 1643 (C=N), 1487, 1394, 1380, 1294, 1260, 1106, 786;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 3.18 (1H, d, *J* 13.2, H<sub>10</sub>), 2.97 (1H, d, *J* 13.2, H<sub>10</sub>), 2.82–2.75 (1H, m, H<sub>3</sub>), 2.37 (1H, d, *J* 19.2, H<sub>3</sub>), 2.27–2.25 (1H, m, H<sub>4</sub>), 2.08–2.05 (1H, m, H<sub>5</sub>), 1.81–1.78 (2H, m, H<sub>5+6</sub>), 1.50–1.45 (1H, m, H<sub>6</sub>), 1.08 (3H, s, H<sub>9 or 8</sub>), 0.87 (3H, s, H<sub>9 or 8</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 18.47 (Me), 19.43 (Me), 26.60 (CH<sub>2</sub>), 28.37 (CH<sub>2</sub>), 35.89 (CH<sub>2</sub>), 44.58 (CH), 44.79 (C<sub>quat</sub>), 47.96 (C<sub>quat</sub>), 49.39 (CH<sub>2</sub>), 195.45 (C=N); *m/z* (E.I.): (Found: 213.0825 (M<sup>+</sup>); C<sub>10</sub>H<sub>15</sub>NO<sub>2</sub>S requires 213.0823); 213 (M<sup>+</sup>); (4), 149 (11), 134 (35), 109 (33), 108 (100), 94 (8).

3,5-Dimethyl-phenol was recovered from the crude product after column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) (9 mg, 26%).  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 6.58 (1H, s, ArH), 6.47 (2H, s, ArH), 4.58 (1H, bs), 2.27 (6H, s, ArCH<sub>3</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 21.27 (2 × Me), 113.00 (2 × CH), 122.56 (CH), 139.56 (2 × C<sub>quat</sub>), 155.40 (C<sub>quat</sub>). This product showed identical properties to the commercial compound.

### Camphor oxime<sup>1</sup>

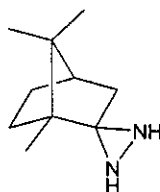


57

Hydroxylamine hydrochloride (10 g, 0.14 mol), (1R)-camphor **3** (10 g, 66 mmol) and pyridine (8.0 ml, 0.1 mmol) were heated under reflux in ethanol (100 ml) for 4 hours. The reaction vessel was then cooled and most of the ethanol in the reaction mixture was removed under reduced pressure. Water was then added and the crude oxime crashed out of the solution as white crystals, which were isolated by filtration and washed with distilled water. The product was then dried under reduced pressure and recrystallized from absolute ethanol to afford pure camphor

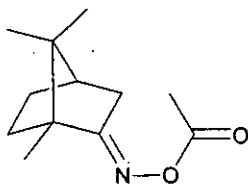
oxime (**57**) as white crystals (9.03 g, 82%). m.p. 119-121 °C;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 6.19 (1H, br.s, OH), 2.56 (1H, dt,  $J$  17.9 and 3.9,  $\text{H}_3$ ), 2.06 (1H, d,  $J$  17.9,  $\text{H}_3$ ), 1.94-1.66 (3H, m,  $\text{H}_{4+5+6}$ ), 1.51-1.41 (1H, m,  $\text{H}_5$ ), 1.20 (1H, m,  $\text{H}_6$ ), 1.03 (3H, s,  $\text{H}_{10}$ ), 0.92 (3H, s,  $\text{H}_9$  or  $8$ ), 0.81 (3H, s,  $\text{H}_9$  or  $8$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 11.28 (Me), 18.51 (Me), 19.53 (Me), 27.3 ( $\text{CH}_2$ ), 32.76 ( $\text{CH}_2$ ), 33.14 ( $\text{CH}_2$ ), 43.86 (CH), 48.20 ( $\text{C}_{\text{quat}}$ ), 51.73 ( $\text{C}_{\text{quat}}$ ), 169.52 ( $\text{C}=\text{O}$ );  $m/z$  (E.I.): (Found: 167.1309 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{17}\text{NO}$  requires 167.1310).

### Camphor diaziridine



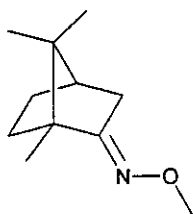
58

Mesyl chloride (1.39 ml, 18 mmol) was slowly added to a solution of camphor oxime (**57**) (2.0 g, 12 mmol) and triethylamine (3.84 ml, 28 mmol) in dichloromethane (10 ml) at 0 °C. After 30 minutes of stirring the mixture was treated with a slow stream of ammonia gas over 30 minutes. The reaction was stirred for two days at room temperature. After evaporation of ammonia, the crude mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate/light petroleum, 20/80) then with (ethyl acetate/ethanol, 50/50) to give the camphor diaziridine (**58**) as colourless oil (317mg, 16%).  $\delta_{\text{H}}$  (400 MHz;  $\text{CDCl}_3$ ) 7.22 (1H, br.s, NH), 5.71 (1H, br.s, NH), 3.40 (1H, d,  $J$  7.0,  $\text{H}_3$ ), 2.60 (1H, m,  $\text{H}_3$ ), 1.90-1.51 (5H, m,  $\text{H}_{4+5+6}$ ), 1.15 (3H, s, Me,  $\text{H}_{10}$ ), 1.02 (3H, s,  $\text{H}_9$  or  $8$ ), 0.98 (3H, s,  $\text{H}_9$  or  $8$ );  $\delta_{\text{C}}$  (100 MHz;  $\text{CDCl}_3$ ) 8.96 (Me), 18.21 (Me), 18.48 (Me), 23.73 (CH), 28.11 ( $\text{CH}_2$ ), 39.75 ( $\text{C}_{\text{quat}}$ ), 40.47 ( $\text{CH}_2$ ), 43.05 ( $\text{C}_{\text{quat}}$ ), 46.64 ( $\text{CH}_2$ ), 64.11 (C-NH);  $m/z$  (F.A.B.): (Found: 166.1473 ( $\text{M}^+$ );  $\text{C}_{10}\text{H}_{18}\text{N}_2$  requires 166.1470).

**O-Acetoxy camphor oxime**

59

Sodium hydride NaH (158 mg, 5 mmol) was added to a dry THF (5 ml) solution of camphor oxime (543 mg, 3 mmol) at 0 °C. After 30 minutes of stirring, acetic anhydride (382  $\mu$ l, 5 mmol) was added dropwise and the mixture stirred overnight. The reaction mixture was diluted with diethyl ether then washed with water and brine. The organic layers were dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 2/98) to give the desired compound (59) as colourless oil (636 mg, 94%).  $\nu_{\max}$  /cm<sup>-1</sup> 2960, 1662 (C=N), 1764 (C=O) strong, 1448, 1365, 1208, 1001, 922;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 2.59-2.53 (1H, dt, *J* 18.4 and 3.2, H<sub>3</sub>), 2.10 (3H, s, Me, CH<sub>3</sub>CO), 1.89 (1H, t, *J* 4.4, H<sub>4</sub>), 1.84-1.79 (2H, m, H<sub>3+5</sub>), 1.76-1.69 (1H, td, *J* 12.4 and 4.4, H<sub>6</sub>), 1.52-1.46 (1H, m, H<sub>5</sub>), 1.24-1.20 (1H, m, H<sub>6</sub>) 1.07 (3H, s, H<sub>9 or 8</sub>), 0.90 (3H, s, H<sub>9 or 8</sub>), 0.78 (3H, s, H<sub>9 or 8</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 11.35 (Me), 18.83 (Me), 19.87 (Me), 20.01 (CH<sub>3</sub>), 27.50 (CH<sub>2</sub>), 32.84 (CH<sub>2</sub>), 35.28 (CH<sub>2</sub>) 43.83 (CH), 48.99 (C<sub>quat</sub>), 53.34 (C<sub>quat</sub>), 169.51 (C=N), 178.06 (C=O); (Found (E.I.)  $M^{+1}$ , 209.1416, C<sub>12</sub>H<sub>19</sub>NO<sub>2</sub> requires 209.1416.

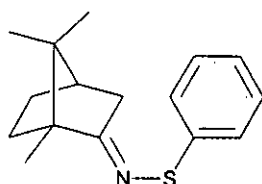
**O-Methyl camphor oxime**

60



Sodium hydride NaH (232 mg, 6 mmol) was added to a THF (5 ml) solution of camphor oxime (809 mg, 4 mmol) at 0 °C. After 30 minutes of stirring methyl iodide (390  $\mu$ l, 10 mmol) was added dropwise. Stirring was continued overnight at room temperature. The reaction mixture was diluted with diethyl ether, washed with water and brine. The organic layers were dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate/light petroleum, 2/98) to give the desired compound (**60**) as colourless oil (467 mg, 63%).  $\nu_{\max}$  /cm<sup>-1</sup> 2957, 2812, 1663 (C=N), 1764 (C=O), 1447, 1389, 1111, 1045, 886;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 3.79 (3H, s, O-CH<sub>3</sub>), 2.49-2.39 (1H, dt, *J* 17.8 and 3.3, H<sub>3</sub>), 1.97 (1H, d, *J* 17.8, H<sub>3</sub>), 1.84-1.61 (3H, m, H<sub>4+5+6</sub>), 1.47-1.37 (1H, m, H<sub>5</sub>), 1.24-1.14 (1H, m, H<sub>6</sub>), 0.98 (3H, s, H<sub>10</sub>), 0.88 (3H, s, H<sub>9 or 8</sub>), 0.76 (3H, s, Me, H<sub>9 or 8</sub>);  $\delta_{\text{C}}$  (100 MHz; CDCl<sub>3</sub>) 11.58 (Me), 18.93 (Me), 19.85 (Me), 27.85 (CH<sub>2</sub>), 33.57 (CH<sub>2</sub>), 34.23 (CH<sub>2</sub>), 44.41 (CH), 48.78 (C<sub>quat</sub>), 52.25 (C<sub>quat</sub>), 55.31 (Me), 169.76 (C=N); *m/z* (E.I.): (Found: 181.1766 (M<sup>+</sup>); C<sub>11</sub>H<sub>19</sub>NO requires 181.1770); 181 (M<sup>+</sup>), 166 (26), 150 (32), 138 (80), 94 (38).

#### *N*-Thiophenyl camphor imine<sup>45</sup>

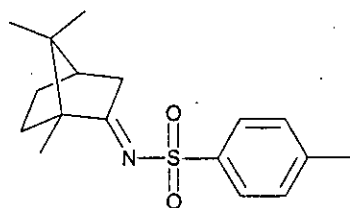


61

Diphenyldisulfide (2.15 g, 10 mmol) and tributylphosphine (1.05 ml, 4 mmol) were added successively, at 20 °C, to a solution of camphor oxime (500 mg, 3 mmol) in pyridine (12 ml). The reaction mixture was stirred for 30 minutes, and then poured into an aqueous potassium carbonate (5%, 150 ml). The crude mixture was extracted with a mixture of (4/1) pentane/dichloromethane mixture (2  $\times$  75 ml). The organic phases were washed with water and brine, dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 5/95) to give the titled compound (**61**) as colourless oil (364 mg, 47%).  $\nu_{\max}$  /cm<sup>-1</sup> 2958, 1636 (C=N), 1582, 1448, 1440, 1067, 739;  $\delta_{\text{H}}$  (400 MHz; CDCl<sub>3</sub>) 7.54-7.51 (2H, m, ArH),

7.36-7.34 (2H, m, ArH), 7.18-7.15 (1H, m, ArH), 2.54 (1H, dt,  $J$  17.6 and 3.6,  $H_3$ ), 2.08 (1H, t,  $J$  4.4,  $H_4$ ), 2.00-1.83 (2H, m,  $H_{3+5}$ ), 1.73 (1H, td,  $J$  12.1 and 3.6,  $H_6$ ), 1.47 (1H, td,  $J$  8.8 and 3.6,  $H_5$ ), 1.37-1.30 (1H, m,  $H_6$ ), 1.14 (3H, s,  $H_{10}$ ), 1.00 (3H, s,  $H_9$  or 8), 0.83 (3H, s,  $H_9$  or 8);  $\delta_C$  (100 MHz;  $CDCl_3$ ) 11.42 (Me), 19.44 (Me), 20.06 (Me), 27.81 ( $CH_2$ ), 32.57 ( $CH_2$ ), 39.82 ( $CH_2$ ), 44.97 (CH), 48.93 ( $C_{quat}$ ), 56.84 ( $C_{quat}$ ), 124.82 ( $2 \times CH$ ), 125.73 (CH), 129.16 ( $2 \times CH$ ), 140.18 ( $C_{quat}$ ) 181.65 (C=N);  $m/z$  (E.I.): (Found: 259.1397 ( $M^+$ );  $C_{16}H_{21}NS$  requires 259.1395).

### *N*-Toluenesulfonamide camphor imine



63

Titanium chloride (405 mg, 2.1 mmol) was slowly added to a solution of camphor (500 mg, 3.3 mmol) and *p*-toluene sulfonamide (563 mg, 3.3 mmol) in 1,1,2,2 tetrachloroethane (16 ml) at 0 °C. The mixture was slowly brought to room temperature and heated under reflux for 24 hours. The crude mixture was cooled down to 0 °C again and 0.65 equivalent of  $TiCl_4$  (405 mg, 2.1 mmol) was slowly added and the mixture was heated under reflux for an additional 24 hours. The crude mixture was quenched by the addition of water (20 ml) and extracted with dichloromethane ( $3 \times 20$  ml). The organic phases were washed with water, brine and dried over magnesium sulfate. The crude product was purified by column chromatography over silica gel eluting with (ethyl acetate/light petroleum, 10/90) to give the title compound (**63**) as a colourless solid (229 mg, 24%).  $\nu_{max}/cm^{-1}$  1632;  $\delta_H$  (400 MHz;  $CDCl_3$ ) 7.92 (2H, d,  $J$  8.4, ArH), 7.41 (2H, d,  $J$  8.4, ArH), 2.49 (3H, s, ArCH<sub>3</sub>), 2.35 (1H, dt,  $J$  18.0 and 4.4,  $H_3$ ), 2.09 (1H, t,  $J$  4.4,  $H_4$ ), 1.98-1.92 (1H, m,  $H_3$ ), 1.94 (1H, d,  $J$  18.0,  $H_5$ ), 1.72-1.65 (1H, m,  $H_6$ ), 1.43-1.31 (2H, m,  $H_{5+6}$ ), 0.96 (3H, s,  $H_{10}$ ), 0.91 (3H, s,  $H_9$  or 8), 0.83 (3H, s,  $H_9$  or 8);  $\delta_C$  (100 MHz;  $CDCl_3$ ) 9.26 (Me), 19.13 (Me), 19.82 (Me), 21.81 (Me), 27.16 ( $CH_2$ ), 29.94 ( $CH_2$ ), 43.18 (CH), 43.36 ( $CH_2$ ), 46.85 ( $C_{quat}$ ), 57.77 ( $C_{quat}$ ), 127.02 ( $2 \times CH$ ), 130.20 ( $2 \times CH$ ), 141.72 ( $C_{quat}$ ), 146.89 ( $C_{quat}$ ), 219.67

(C=N);  $m/z$  (E.I.): (Found: 305.1445 ( $M^{+1}$ );  $C_{17}H_{23}NO_2S$  requires 305.1449). 305 ( $M^{+1}$ ) (9), 150 (43), 109 (100), 91 (32).

### 3.3 Appendixes

The crystallographic data for the structures presented in the text are given in this section. Crystallographic analyses were carried out at Loughborough University by Professor V. McKee and Dr M. R. Elsegood.

#### Appendix 1: 3,3-dibromo camphor nitrimines

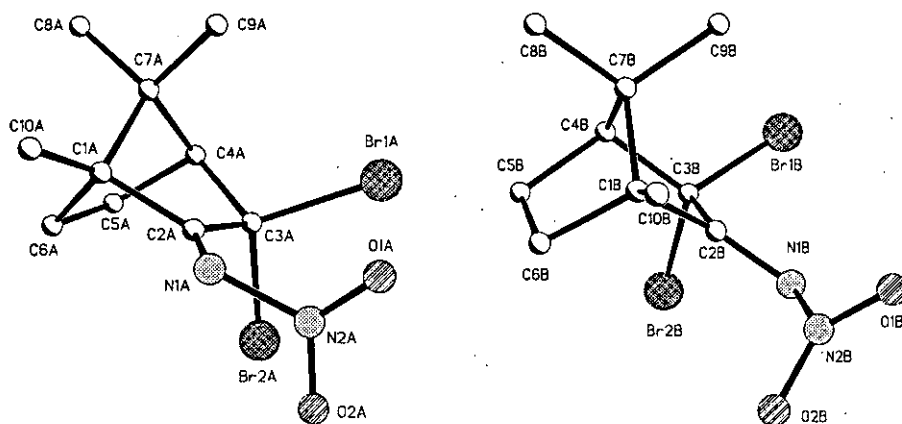


Table 1. Crystal data and structure refinement.

|                      |                          |                       |
|----------------------|--------------------------|-----------------------|
| Empirical formula    | $C_{10}H_{14}Br_2N_2O_2$ |                       |
| Formula weight       | 354.05                   |                       |
| Temperature          | 150(2) K                 |                       |
| Wavelength           | 0.71073 Å                |                       |
| Crystal system       | Orthorhombic             |                       |
| Space group          | $P2(1)2(1)2(1)$          |                       |
| Unit cell dimensions | $a = 7.1351(4)$ Å        | $\alpha = 90^\circ$ . |

|  |  |                     |
|--|--|---------------------|
|  | $b = 14.7117(8) \text{ \AA}$                                     | $\beta = 90^\circ$  |
|  | $c = 24.2379(14) \text{ \AA}$                                    | $\gamma = 90^\circ$ |
| Volume                                 | $2544.2(2) \text{ \AA}^3$  |                     |
| Z                                      | 8  |                     |
| Density (calculated)                   | $1.849 \text{ Mg/m}^3$   |                     |
| Absorption coefficient                 | $6.360 \text{ mm}^{-1}$  |                     |
| F(000)                                 | 1392   |                     |
| Crystal size                           | $0.58 \times 0.26 \times 0.13 \text{ mm}^3$                      |                     |
| Crystal description                    | Colourless trigonal prism  |                     |
| Theta range for data collection        | $1.62$ to $28.73^\circ$  |                     |
| Index ranges                           | $-9 \leq h \leq 9$ , $-19 \leq k \leq 18$ , $-31 \leq l \leq 30$ |                     |
| Reflections collected                  | 21713  |                     |
| Independent reflections                | 5999 [ $R(\text{int}) = 0.0284$ ]                                |                     |
| Completeness to $\theta = 25.00^\circ$ | 100.0 %  |                     |
| Absorption correction                  | Multiscan  |                     |
| Max. and min. transmission             | 1.00000 and 0.575022   |                     |
| Refinement method                      | Full-matrix least-squares on $F^2$                               |                     |
| Data / restraints / parameters         | 5999 / 0 / 289   |                     |
| Goodness-of-fit on $F^2$               | 1.034  |                     |
| Final R indices [ $I > 2\sigma(I)$ ]   | $R1 = 0.0261$ , $wR2 = 0.0581$                                   |                     |
| R indices (all data)                   | $R1 = 0.0301$ , $wR2 = 0.0595$                                   |                     |
| Absolute structure parameter           | 0.000(8)   |                     |
| Largest diff. peak and hole            | $0.828$ and $-0.594 \text{ e.\AA}^{-3}$                          |                     |

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

|       | x        | y         | z        | $U(\text{eq})$ |
|-------|----------|-----------|----------|----------------|
| C(1A) | -7938(4) | -10837(2) | -1571(1) | 21(1)          |
| C(2A) | -8506(4) | -9920(2)  | -1802(1) | 19(1)          |
| C(3A) | -6719(4) | -9486(2)  | -2032(1) | 21(1)          |
| C(4A) | -5295(4) | -10276(2) | -1977(1) | 21(1)          |
| C(5A) | -4736(4) | -10355(2) | -1364(1) | 27(1)          |
| C(6A) | -6573(4) | -10644(2) | -1080(1) | 27(1)          |
| C(7A) | -6567(4) | -11139(2) | -2039(1) | 22(1)          |
| C(8A) | -5508(5) | -12021(2) | -1921(1) | 33(1)          |

|        |           |           |          |       |
|--------|-----------|-----------|----------|-------|
| C(9A)  | -7568(5)  | -11270(2) | -2594(1) | 29(1) |
| C(10A) | -9559(5)  | -11456(2) | -1429(2) | 32(1) |
| N(1A)  | -10232(4) | -9693(2)  | -1807(1) | 25(1) |
| N(2A)  | -10722(4) | -8841(2)  | -2067(1) | 32(1) |
| O(1A)  | -11490(3) | -8900(2)  | -2512(1) | 42(1) |
| O(2A)  | -10509(4) | -8160(2)  | -1791(1) | 48(1) |
| Br(1A) | -6945(1)  | -9082(1)  | -2798(1) | 29(1) |
| Br(2A) | -6057(1)  | -8401(1)  | -1603(1) | 35(1) |
| C(1B)  | -12578(4) | -9683(2)  | -4386(1) | 21(1) |
| C(2B)  | -14447(4) | -10027(2) | -4608(1) | 20(1) |
| C(3B)  | -14144(4) | -11043(2) | -4744(1) | 20(1) |
| C(4B)  | -12127(4) | -11206(2) | -4544(1) | 20(1) |
| C(5B)  | -10790(4) | -10756(2) | -4959(1) | 25(1) |
| C(6B)  | -11220(4) | -9734(2)  | -4892(1) | 25(1) |
| C(7B)  | -11980(4) | -10536(2) | -4044(1) | 22(1) |
| C(8B)  | -9970(4)  | -10479(3) | -3816(1) | 32(1) |
| C(9B)  | -13272(5) | -10700(2) | -3547(1) | 29(1) |
| C(10B) | -12541(4) | -8777(2)  | -4082(1) | 31(1) |
| N(1B)  | -16052(4) | -9685(2)  | -4698(1) | 26(1) |
| N(2B)  | -16225(4) | -8721(2)  | -4584(1) | 31(1) |
| O(1B)  | -17001(4) | -8517(2)  | -4158(1) | 46(1) |
| O(2B)  | -15724(4) | -8215(2)  | -4949(1) | 48(1) |
| Br(1B) | -15951(1) | -11849(1) | -4385(1) | 30(1) |
| Br(2B) | -14560(1) | -11229(1) | -5536(1) | 30(1) |

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

|              |          |              |          |
|--------------|----------|--------------|----------|
| C(1A)-C(10A) | 1.512(4) | C(4A)-C(7A)  | 1.568(4) |
| C(1A)-C(2A)  | 1.516(4) | C(5A)-C(6A)  | 1.541(4) |
| C(1A)-C(7A)  | 1.562(4) | C(7A)-C(8A)  | 1.528(4) |
| C(1A)-C(6A)  | 1.565(4) | C(7A)-C(9A)  | 1.536(4) |
| C(2A)-N(1A)  | 1.277(4) | N(1A)-N(2A)  | 1.444(4) |
| C(2A)-C(3A)  | 1.530(4) | N(2A)-O(1A)  | 1.212(4) |
| C(3A)-C(4A)  | 1.550(4) | N(2A)-O(2A)  | 1.213(4) |
| C(3A)-Br(1A) | 1.957(3) | C(1B)-C(10B) | 1.523(4) |
| C(3A)-Br(2A) | 1.963(3) | C(1B)-C(2B)  | 1.524(4) |
| C(4A)-C(5A)  | 1.541(4) | C(1B)-C(7B)  | 1.563(4) |

|              |          |             |          |
|--------------|----------|-------------|----------|
| C(1B)-C(6B)  | 1.565(4) | C(4B)-C(7B) | 1.566(4) |
| C(2B)-N(1B)  | 1.270(4) | C(5B)-C(6B) | 1.543(4) |
| C(2B)-C(3B)  | 1.546(4) | C(7B)-C(9B) | 1.537(4) |
| C(3B)-C(4B)  | 1.537(4) | C(7B)-C(8B) | 1.540(4) |
| C(3B)-Br(1B) | 1.955(3) | N(1B)-N(2B) | 1.450(4) |
| C(3B)-Br(2B) | 1.962(3) | N(2B)-O(1B) | 1.211(4) |
| C(4B)-C(5B)  | 1.536(4) | N(2B)-O(2B) | 1.210(4) |

|                     |            |                     |            |
|---------------------|------------|---------------------|------------|
| C(10A)-C(1A)-C(2A)  | 114.6(2)   | O(2A)-N(2A)-N(1A)   | 116.5(3)   |
| C(10A)-C(1A)-C(7A)  | 118.2(3)   | C(10B)-C(1B)-C(2B)  | 118.4(2)   |
| C(2A)-C(1A)-C(7A)   | 98.8(2)    | C(10B)-C(1B)-C(7B)  | 116.2(2)   |
| C(10A)-C(1A)-C(6A)  | 114.3(2)   | C(2B)-C(1B)-C(7B)   | 99.2(2)    |
| C(2A)-C(1A)-C(6A)   | 106.6(2)   | C(10B)-C(1B)-C(6B)  | 114.2(2)   |
| C(7A)-C(1A)-C(6A)   | 102.4(2)   | C(2B)-C(1B)-C(6B)   | 104.4(2)   |
| N(1A)-C(2A)-C(1A)   | 119.7(3)   | C(7B)-C(1B)-C(6B)   | 102.0(2)   |
| N(1A)-C(2A)-C(3A)   | 133.7(3)   | N(1B)-C(2B)-C(1B)   | 135.9(3)   |
| C(1A)-C(2A)-C(3A)   | 106.4(2)   | N(1B)-C(2B)-C(3B)   | 118.2(3)   |
| C(2A)-C(3A)-C(4A)   | 101.7(2)   | C(1B)-C(2B)-C(3B)   | 105.9(2)   |
| C(2A)-C(3A)-Br(1A)  | 113.84(19) | C(4B)-C(3B)-C(2B)   | 102.4(2)   |
| C(4A)-C(3A)-Br(1A)  | 111.35(18) | C(4B)-C(3B)-Br(1B)  | 112.50(19) |
| C(2A)-C(3A)-Br(2A)  | 110.28(19) | C(2B)-C(3B)-Br(1B)  | 113.55(19) |
| C(4A)-C(3A)-Br(2A)  | 113.97(19) | C(4B)-C(3B)-Br(2B)  | 115.37(19) |
| Br(1A)-C(3A)-Br(2A) | 105.96(13) | C(2B)-C(3B)-Br(2B)  | 108.77(18) |
| C(5A)-C(4A)-C(3A)   | 108.1(2)   | Br(1B)-C(3B)-Br(2B) | 104.51(13) |
| C(5A)-C(4A)-C(7A)   | 100.4(2)   | C(5B)-C(4B)-C(3B)   | 107.9(2)   |
| C(3A)-C(4A)-C(7A)   | 102.7(2)   | C(5B)-C(4B)-C(7B)   | 101.1(2)   |
| C(6A)-C(5A)-C(4A)   | 103.4(2)   | C(3B)-C(4B)-C(7B)   | 102.0(2)   |
| C(5A)-C(6A)-C(1A)   | 103.8(2)   | C(4B)-C(5B)-C(6B)   | 103.2(2)   |
| C(8A)-C(7A)-C(9A)   | 106.7(3)   | C(5B)-C(6B)-C(1B)   | 104.6(2)   |
| C(8A)-C(7A)-C(1A)   | 114.5(2)   | C(9B)-C(7B)-C(8B)   | 106.6(2)   |
| C(9A)-C(7A)-C(1A)   | 112.4(2)   | C(9B)-C(7B)-C(1B)   | 112.3(2)   |
| C(8A)-C(7A)-C(4A)   | 112.5(2)   | C(8B)-C(7B)-C(1B)   | 113.7(3)   |
| C(9A)-C(7A)-C(4A)   | 117.1(2)   | C(9B)-C(7B)-C(4B)   | 117.9(3)   |
| C(1A)-C(7A)-C(4A)   | 93.6(2)    |                     |            |
| C(2A)-N(1A)-N(2A)   | 117.7(3)   |                     |            |
| O(1A)-N(2A)-O(2A)   | 127.2(3)   |                     |            |
| O(1A)-N(2A)-N(1A)   | 115.8(3)   |                     |            |

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|                   |          |
|-------------------|----------|
| C(8B)-C(7B)-C(4B) | 112.0(2) |
| C(1B)-C(7B)-C(4B) | 94.4(2)  |
| C(2B)-N(1B)-N(2B) | 115.6(3) |
| O(1B)-N(2B)-O(2B) | 127.4(3) |
| O(1B)-N(2B)-N(1B) | 116.4(3) |
| O(2B)-N(2B)-N(1B) | 115.9(3) |

Table 4. Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ). The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

|        | U <sup>11</sup> | U <sup>22</sup> | U <sup>33</sup> | U <sup>23</sup> | U <sup>13</sup> | U <sup>12</sup> |
|--------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| C(1A)  | 20(1)           | 20(1)           | 22(1)           | 3(1)            | 0(1)            | 0(1)            |
| C(2A)  | 22(1)           | 18(1)           | 17(1)           | -1(1)           | -1(1)           | 0(1)            |
| C(3A)  | 29(2)           | 17(1)           | 17(1)           | -4(1)           | -1(1)           | -3(1)           |
| C(4A)  | 21(1)           | 24(2)           | 19(1)           | -3(1)           | 2(1)            | -1(1)           |
| C(5A)  | 22(1)           | 37(2)           | 23(1)           | -1(1)           | -3(1)           | 1(1)            |
| C(6A)  | 27(2)           | 33(2)           | 21(1)           | 0(1)            | -3(1)           | 6(1)            |
| C(7A)  | 25(1)           | 18(1)           | 22(1)           | -1(1)           | 1(1)            | 1(1)            |
| C(8A)  | 37(2)           | 25(2)           | 39(2)           | 1(1)            | 6(2)            | 10(1)           |
| C(9A)  | 42(2)           | 23(2)           | 23(1)           | -5(1)           | -3(1)           | -7(1)           |
| C(10A) | 29(2)           | 24(2)           | 41(2)           | 13(1)           | 3(1)            | -1(1)           |
| N(1A)  | 25(1)           | 22(1)           | 26(1)           | 2(1)            | -3(1)           | 3(1)            |
| N(2A)  | 31(1)           | 26(2)           | 38(2)           | 5(1)            | -3(1)           | 10(1)           |
| O(1A)  | 42(2)           | 46(2)           | 39(1)           | 8(1)            | -14(1)          | 12(1)           |
| O(2A)  | 63(2)           | 28(1)           | 52(2)           | 2(1)            | -9(1)           | 18(1)           |
| Br(1A) | 38(1)           | 25(1)           | 24(1)           | 7(1)            | 0(1)            | -8(1)           |
| Br(2A) | 44(1)           | 23(1)           | 37(1)           | -11(1)          | -1(1)           | -9(1)           |
| C(1B)  | 20(1)           | 21(1)           | 22(1)           | -4(1)           | -1(1)           | -1(1)           |
| C(2B)  | 21(1)           | 21(1)           | 17(1)           | 1(1)            | 1(1)            | -1(1)           |
| C(3B)  | 21(1)           | 19(1)           | 20(1)           | -1(1)           | -3(1)           | -1(1)           |
| C(4B)  | 20(1)           | 23(1)           | 18(1)           | 1(1)            | -2(1)           | 4(1)            |
| C(5B)  | 20(2)           | 33(2)           | 22(1)           | -4(1)           | 3(1)            | 4(1)            |
| C(6B)  | 20(1)           | 32(2)           | 23(1)           | 0(1)            | 3(1)            | 1(1)            |
| C(7B)  | 20(1)           | 27(2)           | 18(1)           | -2(1)           | -2(1)           | 1(1)            |
| C(8B)  | 24(2)           | 44(2)           | 28(2)           | -3(2)           | -11(1)          | 3(1)            |
| C(9B)  | 38(2)           | 31(2)           | 18(1)           | -1(1)           | 3(1)            | -2(1)           |
| C(10B) | 31(2)           | 24(2)           | 38(2)           | -11(1)          | -6(1)           | -2(1)           |
| N(1B)  | 22(1)           | 18(1)           | 37(1)           | -1(1)           | -5(1)           | 3(1)            |
| N(2B)  | 26(1)           | 22(1)           | 44(2)           | -1(1)           | -5(1)           | 5(1)            |
| O(1B)  | 41(1)           | 38(2)           | 58(2)           | -13(1)          | 10(1)           | 9(1)            |
| O(2B)  | 67(2)           | 27(1)           | 49(2)           | 7(1)            | -5(1)           | 1(1)            |
| Br(1B) | 25(1)           | 21(1)           | 44(1)           | 4(1)            | -1(1)           | -4(1)           |
| Br(2B) | 38(1)           | 28(1)           | 24(1)           | -5(1)           | -14(1)          | 4(1)            |



Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ )

|        | x      | y      | z     | U(eq) |
|--------|--------|--------|-------|-------|
| H(4A)  | -4217  | -10248 | -2240 | 26    |
| H(5A1) | -3746  | -10819 | -1312 | 33    |
| H(5A2) | -4283  | -9766  | -1219 | 33    |
| H(6A1) | -7061  | -10151 | -841  | 32    |
| H(6A2) | -6384  | -11196 | -853  | 32    |
| H(8A1) | -4844  | -11967 | -1569 | 50    |
| H(8A2) | -4603  | -12134 | -2217 | 50    |
| H(8A3) | -6399  | -12527 | -1902 | 50    |
| H(9A1) | -8269  | -10718 | -2687 | 44    |
| H(9A2) | -8435  | -11785 | -2568 | 44    |
| H(9A3) | -6639  | -11391 | -2883 | 44    |
| H(10A) | -9076  | -12032 | -1284 | 47    |
| H(10B) | -10304 | -11574 | -1761 | 47    |
| H(10C) | -10349 | -11165 | -1150 | 47    |
| H(4B)  | -11826 | -11853 | -4455 | 24    |
| H(5B1) | -11051 | -10964 | -5340 | 30    |
| H(5B2) | -9466  | -10890 | -4867 | 30    |
| H(6B1) | -11828 | -9490  | -5228 | 30    |
| H(6B2) | -10058 | -9386  | -4821 | 30    |
| H(8B1) | -9092  | -10376 | -4120 | 48    |
| H(8B2) | -9655  | -11050 | -3629 | 48    |
| H(8B3) | -9885  | -9975  | -3552 | 48    |
| H(9B1) | -14574 | -10742 | -3673 | 43    |
| H(9B2) | -13151 | -10194 | -3286 | 43    |
| H(9B3) | -12916 | -11269 | -3364 | 43    |
| H(10D) | -11255 | -8640  | -3968 | 46    |
| H(10E) | -13350 | -8812  | -3756 | 46    |
| H(10F) | -12995 | -8295  | -4328 | 46    |

Table 6. Torsion angles [ $^\circ$ ].

|                          |        |
|--------------------------|--------|
| C(10A)-C(1A)-C(2A)-N(1A) | 7.2(4) |
|--------------------------|--------|

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|                          |            |
|--------------------------|------------|
| C(7A)-C(1A)-C(2A)-N(1A)  | 133.9(3)   |
| C(6A)-C(1A)-C(2A)-N(1A)  | -120.3(3)  |
| C(10A)-C(1A)-C(2A)-C(3A) | -168.1(3)  |
| C(7A)-C(1A)-C(2A)-C(3A)  | -41.4(3)   |
| C(6A)-C(1A)-C(2A)-C(3A)  | 64.4(3)    |
| N(1A)-C(2A)-C(3A)-C(4A)  | -167.2(3)  |
| C(1A)-C(2A)-C(3A)-C(4A)  | 7.2(3)     |
| N(1A)-C(2A)-C(3A)-Br(1A) | -47.3(4)   |
| C(1A)-C(2A)-C(3A)-Br(1A) | 127.0(2)   |
| N(1A)-C(2A)-C(3A)-Br(2A) | 71.6(4)    |
| C(1A)-C(2A)-C(3A)-Br(2A) | -114.0(2)  |
| C(2A)-C(3A)-C(4A)-C(5A)  | -75.7(3)   |
| Br(1A)-C(3A)-C(4A)-C(5A) | 162.7(2)   |
| Br(2A)-C(3A)-C(4A)-C(5A) | 42.9(3)    |
| C(2A)-C(3A)-C(4A)-C(7A)  | 29.9(3)    |
| Br(1A)-C(3A)-C(4A)-C(7A) | -91.7(2)   |
| Br(2A)-C(3A)-C(4A)-C(7A) | 148.48(19) |
| C(3A)-C(4A)-C(5A)-C(6A)  | 65.4(3)    |
| C(7A)-C(4A)-C(5A)-C(6A)  | -41.7(3)   |
| C(4A)-C(5A)-C(6A)-C(1A)  | 7.9(3)     |
| C(10A)-C(1A)-C(6A)-C(5A) | 158.0(3)   |
| C(2A)-C(1A)-C(6A)-C(5A)  | -74.4(3)   |
| C(7A)-C(1A)-C(6A)-C(5A)  | 28.8(3)    |
| C(10A)-C(1A)-C(7A)-C(8A) | -62.3(3)   |
| C(2A)-C(1A)-C(7A)-C(8A)  | 173.6(2)   |
| C(6A)-C(1A)-C(7A)-C(8A)  | 64.3(3)    |
| C(10A)-C(1A)-C(7A)-C(9A) | 59.6(3)    |
| C(2A)-C(1A)-C(7A)-C(9A)  | -64.5(3)   |
| C(6A)-C(1A)-C(7A)-C(9A)  | -173.7(2)  |
| C(10A)-C(1A)-C(7A)-C(4A) | -179.1(3)  |
| C(2A)-C(1A)-C(7A)-C(4A)  | 56.8(2)    |
| C(6A)-C(1A)-C(7A)-C(4A)  | -52.5(2)   |
| C(5A)-C(4A)-C(7A)-C(8A)  | -60.9(3)   |
| C(3A)-C(4A)-C(7A)-C(8A)  | -172.3(2)  |
| C(5A)-C(4A)-C(7A)-C(9A)  | 175.0(3)   |
| C(3A)-C(4A)-C(7A)-C(9A)  | 63.6(3)    |
| C(5A)-C(4A)-C(7A)-C(1A)  | 57.6(2)    |
| C(3A)-C(4A)-C(7A)-C(1A)  | -53.8(2)   |

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|                          |            |
|--------------------------|------------|
| C(1A)-C(2A)-N(1A)-N(2A)  | -175.7(2)  |
| C(3A)-C(2A)-N(1A)-N(2A)  | -1.9(5)    |
| C(2A)-N(1A)-N(2A)-O(1A)  | 106.4(3)   |
| C(2A)-N(1A)-N(2A)-O(2A)  | -81.5(4)   |
| C(10B)-C(1B)-C(2B)-N(1B) | 15.4(5)    |
| C(7B)-C(1B)-C(2B)-N(1B)  | 142.0(3)   |
| C(6B)-C(1B)-C(2B)-N(1B)  | -113.0(4)  |
| C(10B)-C(1B)-C(2B)-C(3B) | -164.9(3)  |
| C(7B)-C(1B)-C(2B)-C(3B)  | -38.3(3)   |
| C(6B)-C(1B)-C(2B)-C(3B)  | 66.7(3)    |
| N(1B)-C(2B)-C(3B)-C(4B)  | -176.3(3)  |
| C(1B)-C(2B)-C(3B)-C(4B)  | 4.0(3)     |
| N(1B)-C(2B)-C(3B)-Br(1B) | -54.7(3)   |
| C(1B)-C(2B)-C(3B)-Br(1B) | 125.5(2)   |
| N(1B)-C(2B)-C(3B)-Br(2B) | 61.2(3)    |
| C(1B)-C(2B)-C(3B)-Br(2B) | -118.6(2)  |
| C(2B)-C(3B)-C(4B)-C(5B)  | -74.0(3)   |
| Br(1B)-C(3B)-C(4B)-C(5B) | 163.77(19) |
| Br(2B)-C(3B)-C(4B)-C(5B) | 44.0(3)    |
| C(2B)-C(3B)-C(4B)-C(7B)  | 32.1(3)    |
| Br(1B)-C(3B)-C(4B)-C(7B) | -90.2(2)   |
| Br(2B)-C(3B)-C(4B)-C(7B) | 150.04(19) |
| C(3B)-C(4B)-C(5B)-C(6B)  | 66.1(3)    |
| C(7B)-C(4B)-C(5B)-C(6B)  | -40.6(3)   |
| C(4B)-C(5B)-C(6B)-C(1B)  | 7.5(3)     |
| C(10B)-C(1B)-C(6B)-C(5B) | 154.5(3)   |
| C(2B)-C(1B)-C(6B)-C(5B)  | -74.6(3)   |
| C(7B)-C(1B)-C(6B)-C(5B)  | 28.3(3)    |
| C(10B)-C(1B)-C(7B)-C(9B) | 61.4(3)    |
| C(2B)-C(1B)-C(7B)-C(9B)  | -66.7(3)   |
| C(6B)-C(1B)-C(7B)-C(9B)  | -173.7(2)  |
| C(10B)-C(1B)-C(7B)-C(8B) | -59.7(3)   |
| C(2B)-C(1B)-C(7B)-C(8B)  | 172.2(2)   |
| C(6B)-C(1B)-C(7B)-C(8B)  | 65.2(3)    |
| C(10B)-C(1B)-C(7B)-C(4B) | -176.1(2)  |
| C(2B)-C(1B)-C(7B)-C(4B)  | 55.8(2)    |
| C(6B)-C(1B)-C(7B)-C(4B)  | -51.2(2)   |
| C(5B)-C(4B)-C(7B)-C(9B)  | 174.7(3)   |

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|                         |           |
|-------------------------|-----------|
| C(3B)-C(4B)-C(7B)-C(9B) | 63.4(3)   |
| C(5B)-C(4B)-C(7B)-C(8B) | -61.1(3)  |
| C(3B)-C(4B)-C(7B)-C(8B) | -172.4(3) |
| C(5B)-C(4B)-C(7B)-C(1B) | 56.6(2)   |
| C(3B)-C(4B)-C(7B)-C(1B) | -54.7(2)  |
| C(1B)-C(2B)-N(1B)-N(2B) | 2.2(5)    |
| C(3B)-C(2B)-N(1B)-N(2B) | -177.5(2) |
| C(2B)-N(1B)-N(2B)-O(1B) | -102.3(3) |
| C(2B)-N(1B)-N(2B)-O(2B) | 84.0(4)   |

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## Appendix 2: 3,3-dibromo camphor nitrimine

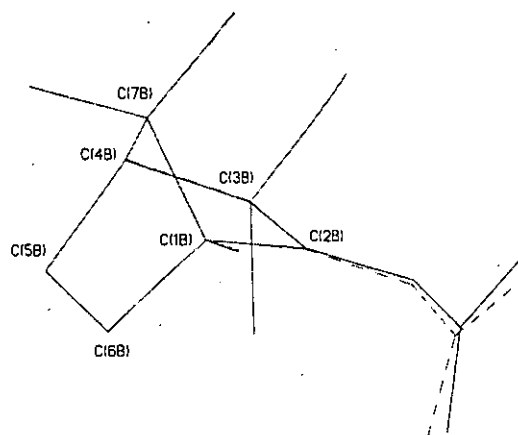
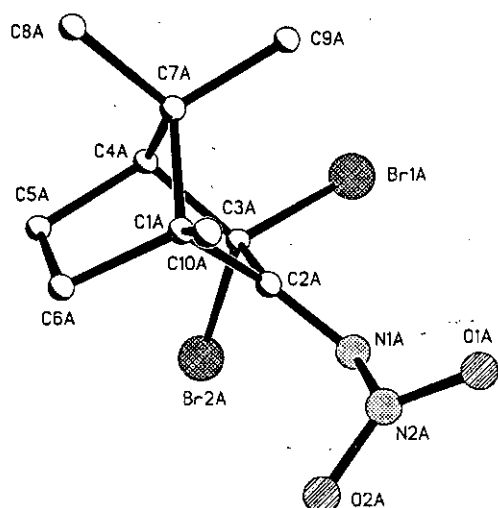


Table 1. Crystal data and structure refinement.

|                      |   |          |
|----------------------|---|----------|
| Empirical formula    | C <sub>10</sub> H <sub>14</sub> Br <sub>2</sub> N <sub>2</sub> O <sub>2</sub> |          |
| Formula weight       | 354.05  |          |
| Temperature          | 150(2) K  |          |
| Wavelength           | 0.71073 Å   |          |
| Crystal system       | Orthorhombic  |          |
| Space group          | P2(1)2(1)2  |          |
| Unit cell dimensions | a = 11.4903(5) Å  | α = 90°. |
|                      | b = 24.2947(11) Å   | β = 90°. |
|                      | c = 9.2079(4) Å   | γ = 90°. |

|                                   |   |
|-----------------------------------|---|
| Volume                            | 2570.4(2) Å <sup>3</sup>                    |
| Z                                 | 8   |
| Density (calculated)              | 1.830 Mg/m <sup>3</sup>                     |
| Absorption coefficient            | 6.296 mm <sup>-1</sup>                      |
| F(000)                            | 1392  |
| Crystal size                      | 0.29 x 0.23 x 0.10 mm <sup>3</sup>          |
| Crystal description               | Colourless block                            |
| Theta range for data collection   | 1.68 to 28.86°                              |
| Index ranges                      | -14 ≤ h ≤ 15, -32 ≤ k ≤ 30, -12 ≤ l ≤ 12    |
| Reflections collected             | 22110                                       |
| Independent reflections           | 6103 [R(int) = 0.0280]                      |
| Completeness to theta = 25.00°    | 100.0 %                                     |
| Absorption correction             | Multiscan                                   |
| Max. and min. transmission        | 1.00000 and 0.621914                        |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup> |
| Data / restraints / parameters    | 6103 / 0 / 289                              |
| Goodness-of-fit on F <sup>2</sup> | 1.042                                       |
| Final R indices [I > 2σ(I)]       | R1 = 0.0286, wR2 = 0.0645                   |
| R indices (all data)              | R1 = 0.0342, wR2 = 0.0666                   |
| Absolute structure parameter      | 0.001(9)                                    |
| Largest diff. peak and hole       | 0.902 and -0.783 e.Å <sup>-3</sup>          |

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

|        | x        | y        | z        | $U(\text{eq})$ |
|--------|----------|----------|----------|----------------|
| C(1A)  | -3219(3) | -3895(1) | 7(3)     | 22(1)          |
| C(2A)  | -2233(2) | -3588(1) | -740(3)  | 18(1)          |
| N(1A)  | -1749(2) | -3604(1) | -1979(3) | 23(1)          |
| N(2A)  | -2253(3) | -3974(1) | -3008(3) | 25(1)          |
| O(1A)  | -1710(3) | -4388(1) | -3276(3) | 40(1)          |
| O(2A)  | -3116(3) | -3814(1) | -3625(3) | 44(1)          |
| C(3A)  | -1769(3) | -3168(1) | 367(3)   | 22(1)          |
| Br(1A) | -104(1)  | -3227(1) | 705(1)   | 34(1)          |
| Br(2A) | -1995(1) | -2426(1) | -444(1)  | 31(1)          |
| C(4A)  | -2491(3) | -3304(1) | 1720(3)  | 25(1)          |

|        |          |          |         |       |
|--------|----------|----------|---------|-------|
| C(5A)  | -3746(3) | -3084(2) | 1475(4) | 28(1) |
| C(6A)  | -4189(3) | -3451(1) | 214(4)  | 27(1) |
| C(7A)  | -2690(3) | -3936(1) | 1573(4) | 26(1) |
| C(8A)  | -3531(4) | -4160(2) | 2714(4) | 35(1) |
| C(9A)  | -1613(3) | -4311(2) | 1607(4) | 33(1) |
| C(10A) | -3639(3) | -4431(1) | -661(4) | 31(1) |
| C(1B)  | -3278(3) | -1068(1) | 5086(3) | 22(1) |
| C(2B)  | -2304(2) | -1417(1) | 5727(3) | 19(1) |
| N(1B)  | -1710(2) | -1412(1) | 6887(3) | 24(1) |
| N(2B)  | -2018(3) | -1006(1) | 7954(3) | 26(1) |
| O(1B)  | -1418(2) | -596(1)  | 7999(3) | 39(1) |
| O(2B)  | -2769(3) | -1137(1) | 8804(3) | 47(1) |
| C(3B)  | -2030(3) | -1861(1) | 4589(4) | 24(1) |
| Br(1B) | -390(1)  | -1890(1) | 4075(1) | 39(1) |
| Br(2B) | -2364(1) | -2581(1) | 5464(1) | 33(1) |
| C(4B)  | -2811(3) | -1693(1) | 3315(3) | 25(1) |
| C(5B)  | -4072(3) | -1850(2) | 3693(4) | 29(1) |
| C(6B)  | -4347(3) | -1466(1) | 4985(4) | 26(1) |
| C(7B)  | -2852(3) | -1050(1) | 3466(4) | 22(1) |
| C(8B)  | -3726(3) | -788(2)  | 2420(4) | 31(1) |
| C(9B)  | -1705(3) | -731(2)  | 3288(4) | 34(1) |
| C(10B) | -3545(3) | -520(1)  | 5791(4) | 32(1) |

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

|              |          |              |          |
|--------------|----------|--------------|----------|
| C(1A)-C(2A)  | 1.520(4) | C(4A)-C(5A)  | 1.554(5) |
| C(1A)-C(10A) | 1.520(4) | C(5A)-C(6A)  | 1.550(5) |
| C(1A)-C(6A)  | 1.562(4) | C(7A)-C(8A)  | 1.528(5) |
| C(1A)-C(7A)  | 1.568(5) | C(7A)-C(9A)  | 1.538(5) |
| C(2A)-N(1A)  | 1.270(4) | C(1B)-C(10B) | 1.513(4) |
| C(2A)-C(3A)  | 1.537(4) | C(1B)-C(2B)  | 1.523(4) |
| N(1A)-N(2A)  | 1.430(4) | C(1B)-C(6B)  | 1.566(4) |
| N(2A)-O(1A)  | 1.208(4) | C(1B)-C(7B)  | 1.571(4) |
| N(2A)-O(2A)  | 1.208(4) | C(2B)-N(1B)  | 1.267(4) |
| C(3A)-C(4A)  | 1.533(4) | C(2B)-C(3B)  | 1.537(4) |
| C(3A)-Br(1A) | 1.943(3) | N(1B)-N(2B)  | 1.437(4) |
| C(3A)-Br(2A) | 1.968(3) | N(2B)-O(1B)  | 1.212(4) |
| C(4A)-C(7A)  | 1.558(5) | N(2B)-O(2B)  | 1.208(4) |

|                     |            |                     |            |
|---------------------|------------|---------------------|------------|
| C(3B)-C(4B)         | 1.533(4)   | C(4B)-C(7B)         | 1.568(5)   |
| C(3B)-Br(1B)        | 1.945(3)   | C(5B)-C(6B)         | 1.545(5)   |
| C(3B)-Br(2B)        | 1.964(3)   | C(7B)-C(8B)         | 1.530(5)   |
| C(4B)-C(5B)         | 1.539(5)   | C(7B)-C(9B)         | 1.538(5)   |
| C(2A)-C(1A)-C(10A)  | 118.3(3)   | C(10B)-C(1B)-C(7B)  | 116.5(3)   |
| C(2A)-C(1A)-C(6A)   | 104.4(2)   | C(2B)-C(1B)-C(7B)   | 98.9(2)    |
| C(10A)-C(1A)-C(6A)  | 114.5(3)   | C(6B)-C(1B)-C(7B)   | 101.8(2)   |
| C(2A)-C(1A)-C(7A)   | 99.1(2)    | N(1B)-C(2B)-C(1B)   | 135.8(3)   |
| C(10A)-C(1A)-C(7A)  | 116.1(3)   | N(1B)-C(2B)-C(3B)   | 118.0(3)   |
| C(6A)-C(1A)-C(7A)   | 102.0(3)   | C(1B)-C(2B)-C(3B)   | 106.1(2)   |
| N(1A)-C(2A)-C(1A)   | 135.8(3)   | C(2B)-N(1B)-N(2B)   | 116.7(3)   |
| N(1A)-C(2A)-C(3A)   | 117.7(3)   | O(1B)-N(2B)-O(2B)   | 126.9(3)   |
| C(1A)-C(2A)-C(3A)   | 106.5(2)   | O(1B)-N(2B)-N(1B)   | 116.6(3)   |
| C(2A)-N(1A)-N(2A)   | 116.0(3)   | O(2B)-N(2B)-N(1B)   | 115.9(3)   |
| O(1A)-N(2A)-O(2A)   | 126.7(3)   | C(4B)-C(3B)-C(2B)   | 102.4(2)   |
| O(1A)-N(2A)-N(1A)   | 116.7(3)   | C(4B)-C(3B)-Br(1B)  | 113.0(2)   |
| O(2A)-N(2A)-N(1A)   | 116.1(3)   | C(2B)-C(3B)-Br(1B)  | 113.0(2)   |
| C(4A)-C(3A)-C(2A)   | 102.0(2)   | C(4B)-C(3B)-Br(2B)  | 115.9(2)   |
| C(4A)-C(3A)-Br(1A)  | 112.8(2)   | C(2B)-C(3B)-Br(2B)  | 107.8(2)   |
| C(2A)-C(3A)-Br(1A)  | 113.5(2)   | Br(1B)-C(3B)-Br(2B) | 104.88(14) |
| C(4A)-C(3A)-Br(2A)  | 115.7(2)   | C(3B)-C(4B)-C(5B)   | 108.2(3)   |
| C(2A)-C(3A)-Br(2A)  | 108.1(2)   | C(3B)-C(4B)-C(7B)   | 102.4(3)   |
| Br(1A)-C(3A)-Br(2A) | 104.94(14) | C(5B)-C(4B)-C(7B)   | 101.5(3)   |
| C(3A)-C(4A)-C(7A)   | 102.8(3)   | C(4B)-C(5B)-C(6B)   | 102.5(3)   |
| C(3A)-C(4A)-C(5A)   | 108.1(3)   | C(5B)-C(6B)-C(1B)   | 105.0(3)   |
| C(7A)-C(4A)-C(5A)   | 100.9(3)   | C(8B)-C(7B)-C(9B)   | 106.6(3)   |
| C(6A)-C(5A)-C(4A)   | 102.5(3)   | C(8B)-C(7B)-C(4B)   | 112.2(3)   |
| C(5A)-C(6A)-C(1A)   | 104.7(3)   | C(9B)-C(7B)-C(4B)   | 117.8(3)   |
| C(8A)-C(7A)-C(9A)   | 106.5(3)   | C(8B)-C(7B)-C(1B)   | 113.8(3)   |
| C(8A)-C(7A)-C(4A)   | 112.6(3)   | C(9B)-C(7B)-C(1B)   | 112.5(3)   |
| C(9A)-C(7A)-C(4A)   | 117.7(3)   | C(4B)-C(7B)-C(1B)   | 93.9(2)    |
| C(8A)-C(7A)-C(1A)   | 114.2(3)   |                     |            |
| C(9A)-C(7A)-C(1A)   | 111.6(3)   |                     |            |
| C(4A)-C(7A)-C(1A)   | 94.2(2)    |                     |            |
| C(10B)-C(1B)-C(2B)  | 118.2(3)   |                     |            |
| C(10B)-C(1B)-C(6B)  | 114.3(3)   |                     |            |
| C(2B)-C(1B)-C(6B)   | 104.7(3)   |                     |            |

Table 4. Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ). The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

|        | U <sup>11</sup> | U <sup>22</sup> | U <sup>33</sup> | U <sup>23</sup> | U <sup>13</sup> | U <sup>12</sup> |
|--------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| C(1A)  | 24(2)           | 20(2)           | 21(2)           | -1(1)           | 1(1)            | -2(1)           |
| C(2A)  | 17(1)           | 17(1)           | 21(2)           | 3(1)            | -2(1)           | 2(1)            |
| N(1A)  | 25(1)           | 20(1)           | 23(1)           | -1(1)           | 0(1)            | 0(1)            |
| N(2A)  | 34(2)           | 21(1)           | 20(1)           | -2(1)           | 4(1)            | -1(1)           |
| O(1A)  | 46(2)           | 27(1)           | 48(2)           | -13(1)          | 8(1)            | 3(1)            |
| O(2A)  | 58(2)           | 39(2)           | 36(2)           | -7(1)           | -24(1)          | 6(1)            |
| C(3A)  | 23(1)           | 21(2)           | 23(2)           | -1(1)           | -3(1)           | -2(1)           |
| Br(1A) | 24(1)           | 47(1)           | 31(1)           | -1(1)           | -5(1)           | -8(1)           |
| Br(2A) | 46(1)           | 19(1)           | 27(1)           | 0(1)            | 2(1)            | -5(1)           |
| C(4A)  | 31(2)           | 27(2)           | 17(2)           | -3(1)           | 0(1)            | 0(1)            |
| C(5A)  | 29(2)           | 26(2)           | 28(2)           | -3(1)           | 9(1)            | 1(1)            |
| C(6A)  | 21(2)           | 31(2)           | 29(2)           | 0(1)            | 4(1)            | 3(1)            |
| C(7A)  | 30(2)           | 27(2)           | 21(2)           | 0(1)            | 1(1)            | -3(2)           |
| C(8A)  | 46(2)           | 31(2)           | 27(2)           | 5(2)            | 3(2)            | -5(2)           |
| C(9A)  | 39(2)           | 29(2)           | 32(2)           | 7(2)            | -3(2)           | 4(2)            |
| C(10A) | 33(2)           | 29(2)           | 31(2)           | -2(2)           | 1(2)            | -11(1)          |
| C(1B)  | 19(2)           | 22(2)           | 24(2)           | -1(1)           | -5(1)           | 1(1)            |
| C(2B)  | 18(1)           | 18(1)           | 22(2)           | 2(1)            | 3(1)            | -1(1)           |
| N(1B)  | 26(1)           | 20(1)           | 26(1)           | -1(1)           | -1(1)           | 1(1)            |
| N(2B)  | 28(1)           | 22(2)           | 29(2)           | -3(1)           | -8(1)           | 2(1)            |
| O(1B)  | 37(2)           | 27(2)           | 53(2)           | -10(1)          | -9(1)           | -4(1)           |
| O(2B)  | 55(2)           | 50(2)           | 35(2)           | -10(1)          | 18(1)           | -9(1)           |
| C(3B)  | 26(1)           | 19(2)           | 26(2)           | 1(1)            | 4(1)            | 2(1)            |
| Br(1B) | 31(1)           | 48(1)           | 38(1)           | 4(1)            | 9(1)            | 16(1)           |
| Br(2B) | 53(1)           | 18(1)           | 26(1)           | 1(1)            | -2(1)           | 2(1)            |
| C(4B)  | 33(2)           | 23(2)           | 18(2)           | 0(1)            | 2(1)            | 3(1)            |
| C(5B)  | 32(2)           | 27(2)           | 28(2)           | -1(1)           | -8(1)           | -5(2)           |
| C(6B)  | 22(2)           | 31(2)           | 26(2)           | 0(1)            | -3(1)           | -4(1)           |
| C(7B)  | 24(2)           | 21(2)           | 22(2)           | 1(1)            | 2(1)            | 0(1)            |



|        |       |       |       |       |       |       |
|--------|-------|-------|-------|-------|-------|-------|
| C(8B)  | 36(2) | 29(2) | 26(2) | 6(2)  | -5(2) | 2(2)  |
| C(9B)  | 31(2) | 33(2) | 38(2) | 8(2)  | 2(2)  | -4(2) |
| C(10B) | 37(2) | 27(2) | 31(2) | -7(2) | -8(2) | 10(1) |

Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).

|        | x     | y     | z     | U(eq) |
|--------|-------|-------|-------|-------|
| H(4A)  | -2128 | -3187 | 2658  | 30    |
| H(5A1) | -4230 | -3131 | 2355  | 33    |
| H(5A2) | -3740 | -2691 | 1195  | 33    |
| H(6A1) | -4292 | -3232 | -683  | 33    |
| H(6A2) | -4940 | -3626 | 469   | 33    |
| H(8A1) | -4235 | -3932 | 2733  | 52    |
| H(8A2) | -3158 | -4151 | 3670  | 52    |
| H(8A3) | -3741 | -4539 | 2469  | 52    |
| H(9A1) | -1046 | -4183 | 888   | 49    |
| H(9A2) | -1846 | -4690 | 1378  | 49    |
| H(9A3) | -1263 | -4301 | 2577  | 49    |
| H(10A) | -4268 | -4584 | -67   | 47    |
| H(10B) | -2992 | -4694 | -701  | 47    |
| H(10C) | -3926 | -4362 | -1646 | 47    |
| H(4B)  | -2540 | -1827 | 2345  | 30    |
| H(5B1) | -4130 | -2242 | 3977  | 35    |
| H(5B2) | -4602 | -1780 | 2866  | 35    |
| H(6B1) | -4434 | -1680 | 5893  | 32    |
| H(6B2) | -5073 | -1258 | 4808  | 32    |
| H(8B1) | -4476 | -978  | 2501  | 46    |
| H(8B2) | -3435 | -820  | 1423  | 46    |
| H(8B3) | -3827 | -399  | 2667  | 46    |
| H(9B1) | -1115 | -886  | 3940  | 51    |
| H(9B2) | -1832 | -343  | 3529  | 51    |
| H(9B3) | -1436 | -761  | 2281  | 51    |
| H(10D) | -4183 | -340  | 5268  | 48    |
| H(10E) | -2852 | -285  | 5757  | 48    |

|        |       |      |      |    |     |
|--------|-------|------|------|----|-----|
| H(10F) | -3774 | -579 | 6805 | 48 | Tat |
|--------|-------|------|------|----|-----|

Table 6. Torsion angles [°].

|                          |           |
|--------------------------|-----------|
| C(10A)-C(1A)-C(2A)-N(1A) | 15.5(5)   |
| C(6A)-C(1A)-C(2A)-N(1A)  | -113.2(4) |
| C(7A)-C(1A)-C(2A)-N(1A)  | 141.8(4)  |
| C(10A)-C(1A)-C(2A)-C(3A) | -164.2(3) |
| C(6A)-C(1A)-C(2A)-C(3A)  | 67.1(3)   |
| C(7A)-C(1A)-C(2A)-C(3A)  | -37.9(3)  |
| C(1A)-C(2A)-N(1A)-N(2A)  | 4.1(5)    |
| C(3A)-C(2A)-N(1A)-N(2A)  | -176.2(2) |
| C(2A)-N(1A)-N(2A)-O(1A)  | -107.3(3) |
| C(2A)-N(1A)-N(2A)-O(2A)  | 80.0(4)   |
| N(1A)-C(2A)-C(3A)-C(4A)  | -175.8(3) |
| C(1A)-C(2A)-C(3A)-C(4A)  | 4.0(3)    |
| N(1A)-C(2A)-C(3A)-Br(1A) | -54.2(3)  |
| C(1A)-C(2A)-C(3A)-Br(1A) | 125.6(2)  |
| N(1A)-C(2A)-C(3A)-Br(2A) | 61.8(3)   |
| C(1A)-C(2A)-C(3A)-Br(2A) | -118.4(2) |
| C(2A)-C(3A)-C(4A)-C(7A)  | 32.1(3)   |
| Br(1A)-C(3A)-C(4A)-C(7A) | -90.0(3)  |
| Br(2A)-C(3A)-C(4A)-C(7A) | 149.1(2)  |
| C(2A)-C(3A)-C(4A)-C(5A)  | -74.1(3)  |
| Br(1A)-C(3A)-C(4A)-C(5A) | 163.8(2)  |
| Br(2A)-C(3A)-C(4A)-C(5A) | 43.0(3)   |
| C(3A)-C(4A)-C(5A)-C(6A)  | 66.2(3)   |
| C(7A)-C(4A)-C(5A)-C(6A)  | -41.2(3)  |
| C(4A)-C(5A)-C(6A)-C(1A)  | 7.6(3)    |
| C(2A)-C(1A)-C(6A)-C(5A)  | -74.5(3)  |
| C(10A)-C(1A)-C(6A)-C(5A) | 154.6(3)  |
| C(7A)-C(1A)-C(6A)-C(5A)  | 28.3(3)   |
| C(3A)-C(4A)-C(7A)-C(8A)  | -172.7(3) |
| C(5A)-C(4A)-C(7A)-C(8A)  | -61.1(3)  |
| C(3A)-C(4A)-C(7A)-C(9A)  | 62.8(4)   |
| C(5A)-C(4A)-C(7A)-C(9A)  | 174.4(3)  |

---

|                          |           |
|--------------------------|-----------|
| C(3A)-C(4A)-C(7A)-C(1A)  | -54.3(3)  |
| C(5A)-C(4A)-C(7A)-C(1A)  | 57.3(3)   |
| C(2A)-C(1A)-C(7A)-C(8A)  | 172.1(3)  |
| C(10A)-C(1A)-C(7A)-C(8A) | -60.1(4)  |
| C(6A)-C(1A)-C(7A)-C(8A)  | 65.1(4)   |
| C(2A)-C(1A)-C(7A)-C(9A)  | -67.1(3)  |
| C(10A)-C(1A)-C(7A)-C(9A) | 60.7(4)   |
| C(6A)-C(1A)-C(7A)-C(9A)  | -174.0(3) |
| C(2A)-C(1A)-C(7A)-C(4A)  | 55.0(3)   |
| C(10A)-C(1A)-C(7A)-C(4A) | -177.2(3) |
| C(6A)-C(1A)-C(7A)-C(4A)  | -51.9(3)  |
| C(10B)-C(1B)-C(2B)-N(1B) | 12.6(5)   |
| C(6B)-C(1B)-C(2B)-N(1B)  | -116.0(4) |
| C(7B)-C(1B)-C(2B)-N(1B)  | 139.2(4)  |
| C(10B)-C(1B)-C(2B)-C(3B) | -165.9(3) |
| C(6B)-C(1B)-C(2B)-C(3B)  | 65.6(3)   |
| C(7B)-C(1B)-C(2B)-C(3B)  | -39.2(3)  |
| C(1B)-C(2B)-N(1B)-N(2B)  | 4.1(5)    |
| C(3B)-C(2B)-N(1B)-N(2B)  | -177.6(3) |
| C(2B)-N(1B)-N(2B)-O(1B)  | -100.2(4) |
| C(2B)-N(1B)-N(2B)-O(2B)  | 87.3(4)   |
| N(1B)-C(2B)-C(3B)-C(4B)  | -173.8(3) |
| C(1B)-C(2B)-C(3B)-C(4B)  | 4.9(3)    |
| N(1B)-C(2B)-C(3B)-Br(1B) | -52.0(3)  |
| C(1B)-C(2B)-C(3B)-Br(1B) | 126.8(2)  |
| N(1B)-C(2B)-C(3B)-Br(2B) | 63.4(3)   |
| C(1B)-C(2B)-C(3B)-Br(2B) | -117.8(2) |
| C(2B)-C(3B)-C(4B)-C(5B)  | -75.0(3)  |
| Br(1B)-C(3B)-C(4B)-C(5B) | 163.1(2)  |
| Br(2B)-C(3B)-C(4B)-C(5B) | 42.0(3)   |
| C(2B)-C(3B)-C(4B)-C(7B)  | 31.6(3)   |
| Br(1B)-C(3B)-C(4B)-C(7B) | -90.2(3)  |
| Br(2B)-C(3B)-C(4B)-C(7B) | 148.7(2)  |
| C(3B)-C(4B)-C(5B)-C(6B)  | 66.0(3)   |
| C(7B)-C(4B)-C(5B)-C(6B)  | -41.3(3)  |
| C(4B)-C(5B)-C(6B)-C(1B)  | 7.7(3)    |

|                          |           |
|--------------------------|-----------|
| C(10B)-C(1B)-C(6B)-C(5B) | 154.8(3)  |
| C(2B)-C(1B)-C(6B)-C(5B)  | -74.3(3)  |
| C(7B)-C(1B)-C(6B)-C(5B)  | 28.3(3)   |
| C(3B)-C(4B)-C(7B)-C(8B)  | -172.2(3) |
| C(5B)-C(4B)-C(7B)-C(8B)  | -60.5(3)  |
| C(3B)-C(4B)-C(7B)-C(9B)  | 63.5(4)   |
| C(5B)-C(4B)-C(7B)-C(9B)  | 175.2(3)  |
| C(3B)-C(4B)-C(7B)-C(1B)  | -54.5(3)  |
| C(5B)-C(4B)-C(7B)-C(1B)  | 57.3(3)   |
| C(10B)-C(1B)-C(7B)-C(8B) | -59.9(4)  |
| C(2B)-C(1B)-C(7B)-C(8B)  | 172.3(3)  |
| C(6B)-C(1B)-C(7B)-C(8B)  | 65.1(3)   |
| C(10B)-C(1B)-C(7B)-C(9B) | 61.4(4)   |
| C(2B)-C(1B)-C(7B)-C(9B)  | -66.4(3)  |
| C(6B)-C(1B)-C(7B)-C(9B)  | -173.6(3) |
| C(10B)-C(1B)-C(7B)-C(4B) | -176.3(3) |
| C(2B)-C(1B)-C(7B)-C(4B)  | 55.9(3)   |
| C(6B)-C(1B)-C(7B)-C(4B)  | -51.3(3)  |

### Appendix 3: 3,3-dichloro camphor nitrimine

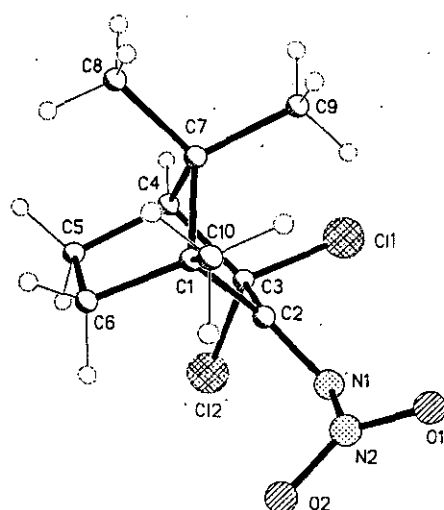


Table 1. Crystal data and structure refinement.

|                                   |   |          |
|-----------------------------------|---|----------|
| Empirical formula                 | C <sub>10</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> |          |
| Formula weight                    | 265.13  |          |
| Temperature                       | 150(2) K  |          |
| Wavelength                        | 0.71073 Å   |          |
| Crystal system                    | Orthorhombic  |          |
| Space group                       | P2(1)2(1)2(1)   |          |
| Unit cell dimensions              | a = 7.1353(6) Å   | α = 90°. |
|                                   | b = 11.2751(9) Å  | β = 90°. |
|                                   | c = 15.1164(12) Å   | γ = 90°. |
| Volume                            | 1216.13(17) Å <sup>3</sup>  |          |
| Z                                 | 4   |          |
| Density (calculated)              | 1.448 Mg/m <sup>3</sup>   |          |
| Absorption coefficient            | 0.521 mm <sup>-1</sup>  |          |
| F(000)                            | 552   |          |
| Crystal size                      | 0.17 x 0.33 x 0.40 mm <sup>3</sup>  |          |
| Crystal description               | Colourless block  |          |
| Theta range for data collection   | 2.25 to 28.74°.   |          |
| Index ranges                      | -9 ≤ h ≤ 9, -14 ≤ k ≤ 14, -20 ≤ l ≤ 20  |          |
| Reflections collected             | 9926  |          |
| Independent reflections           | 2878 [R(int) = 0.0216]  |          |
| Completeness to theta = 25.00°    | 100.0 %   |          |
| Absorption correction             | Semi-empirical from equivalents   |          |
| Max. and min. transmission        | 1.00000 and 0.918605  |          |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                   |          |
| Data / restraints / parameters    | 2878 / 0 / 145  |          |
| Goodness-of-fit on F <sup>2</sup> | 1.085   |          |
| Final R indices [I > 2σ(I)]       | R1 = 0.0310, wR2 = 0.0759   |          |
| R indices (all data)              | R1 = 0.0358, wR2 = 0.0783   |          |
| Absolute structure parameter      | 0.06(6)   |          |
| Largest diff. peak and hole       | 0.274 and -0.185 e.Å <sup>-3</sup>  |          |

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

|       | x        | y        | z       | $U(\text{eq})$ |
|-------|----------|----------|---------|----------------|
| C(1)  | 6885(3)  | -219(2)  | 5555(1) | 23(1)          |
| C(2)  | 8710(3)  | 406(1)   | 5776(1) | 20(1)          |
| N(1)  | 10285(2) | 546(1)   | 5400(1) | 25(1)          |
| N(2)  | 10468(2) | 16(2)    | 4540(1) | 30(1)          |
| O(1)  | 11422(2) | -862(2)  | 4495(1) | 50(1)          |
| O(2)  | 9795(3)  | 561(1)   | 3929(1) | 44(1)          |
| C(3)  | 8402(2)  | 1034(2)  | 6670(1) | 22(1)          |
| Cl(1) | 10081(1) | 612(1)   | 7484(1) | 32(1)          |
| Cl(2) | 8706(1)  | 2597(1)  | 6520(1) | 32(1)          |
| C(4)  | 6396(3)  | 645(2)   | 6906(1) | 24(1)          |
| C(5)  | 5037(3)  | 1323(2)  | 6302(1) | 32(1)          |
| C(6)  | 5491(3)  | 817(2)   | 5376(1) | 31(1)          |
| C(7)  | 6304(2)  | -634(2)  | 6509(1) | 22(1)          |
| C(8)  | 4318(3)  | -1154(2) | 6555(1) | 31(1)          |
| C(9)  | 7632(3)  | -1564(2) | 6888(1) | 29(1)          |
| C(10) | 6911(3)  | -1181(2) | 4851(1) | 34(1)          |

Table 3. Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ].

|                 |            |                |            |
|-----------------|------------|----------------|------------|
| C(1)-C(2)       | 1.518(2)   | C(3)-C(4)      | 1.539(3)   |
| C(1)-C(10)      | 1.521(3)   | C(3)-Cl(1)     | 1.7820(18) |
| C(1)-C(6)       | 1.558(3)   | C(3)-Cl(2)     | 1.7897(18) |
| C(1)-C(7)       | 1.571(2)   | C(4)-C(5)      | 1.535(3)   |
| C(2)-N(1)       | 1.269(2)   | C(4)-C(7)      | 1.564(2)   |
| C(2)-C(3)       | 1.541(2)   | C(5)-C(6)      | 1.546(3)   |
| N(1)-N(2)       | 1.437(2)   | C(7)-C(9)      | 1.525(3)   |
| N(2)-O(1)       | 1.203(2)   | C(7)-C(8)      | 1.535(2)   |
| N(2)-O(2)       | 1.209(2)   |                |            |
| C(2)-C(1)-C(10) | 118.34(16) | C(2)-C(1)-C(6) | 103.75(14) |

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|                  |            |
|------------------|------------|
| C(10)-C(1)-C(6)  | 114.90(17) |
| C(2)-C(1)-C(7)   | 99.37(13)  |
| C(10)-C(1)-C(7)  | 115.67(16) |
| C(6)-C(1)-C(7)   | 102.41(15) |
| N(1)-C(2)-C(1)   | 135.95(16) |
| N(1)-C(2)-C(3)   | 117.50(15) |
| C(1)-C(2)-C(3)   | 106.50(15) |
| C(2)-N(1)-N(2)   | 115.74(15) |
| O(1)-N(2)-O(2)   | 126.79(18) |
| O(1)-N(2)-N(1)   | 116.46(18) |
| O(2)-N(2)-N(1)   | 116.36(17) |
| C(4)-C(3)-C(2)   | 101.83(14) |
| C(4)-C(3)-Cl(1)  | 112.87(12) |
| C(2)-C(3)-Cl(1)  | 112.77(12) |
| C(4)-C(3)-Cl(2)  | 115.00(13) |
| C(2)-C(3)-Cl(2)  | 108.93(12) |
| Cl(1)-C(3)-Cl(2) | 105.59(9)  |
| C(5)-C(4)-C(3)   | 107.92(15) |
| C(5)-C(4)-C(7)   | 101.77(15) |
| C(3)-C(4)-C(7)   | 102.28(14) |
| C(4)-C(5)-C(6)   | 102.87(16) |
| C(5)-C(6)-C(1)   | 104.63(15) |
| C(9)-C(7)-C(8)   | 107.10(15) |
| C(9)-C(7)-C(4)   | 117.62(15) |
| C(8)-C(7)-C(4)   | 111.90(16) |
| C(9)-C(7)-C(1)   | 112.69(15) |
| C(8)-C(7)-C(1)   | 113.54(15) |
| C(4)-C(7)-C(1)   | 93.81(13)  |

Table 4. Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ). The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

|       | U <sup>11</sup> | U <sup>22</sup> | U <sup>33</sup> | U <sup>23</sup> | U <sup>13</sup> | U <sup>12</sup> |
|-------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| C(1)  | 22(1)           | 26(1)           | 21(1)           | 2(1)            | -3(1)           | -3(1)           |
| C(2)  | 23(1)           | 19(1)           | 18(1)           | 1(1)            | -3(1)           | 1(1)            |
| N(1)  | 25(1)           | 28(1)           | 21(1)           | -4(1)           | 2(1)            | -1(1)           |
| N(2)  | 29(1)           | 35(1)           | 27(1)           | -7(1)           | 5(1)            | -8(1)           |
| O(1)  | 43(1)           | 51(1)           | 56(1)           | -25(1)          | 3(1)            | 13(1)           |
| O(2)  | 66(1)           | 42(1)           | 24(1)           | 2(1)            | 2(1)            | -14(1)          |
| C(3)  | 24(1)           | 21(1)           | 22(1)           | -2(1)           | 0(1)            | -2(1)           |
| Cl(1) | 30(1)           | 43(1)           | 23(1)           | -2(1)           | -6(1)           | -4(1)           |
| Cl(2) | 38(1)           | 23(1)           | 36(1)           | -5(1)           | 8(1)            | -7(1)           |
| C(4)  | 23(1)           | 25(1)           | 25(1)           | -1(1)           | 5(1)            | -2(1)           |
| C(5)  | 23(1)           | 27(1)           | 46(1)           | 8(1)            | 4(1)            | 4(1)            |
| C(6)  | 24(1)           | 36(1)           | 34(1)           | 12(1)           | -5(1)           | -1(1)           |
| C(7)  | 23(1)           | 22(1)           | 22(1)           | 3(1)            | -1(1)           | -2(1)           |
| C(8)  | 29(1)           | 32(1)           | 33(1)           | 5(1)            | 1(1)            | -8(1)           |
| C(9)  | 34(1)           | 24(1)           | 31(1)           | 5(1)            | -5(1)           | 0(1)            |
| C(10) | 37(1)           | 38(1)           | 27(1)           | -5(1)           | -2(1)           | -12(1)          |

Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).

|       | x    | y     | z    | U(eq) |
|-------|------|-------|------|-------|
| H(4)  | 6089 | 693   | 7550 | 29    |
| H(5A) | 5271 | 2187  | 6326 | 38    |
| H(5B) | 3718 | 1165  | 6467 | 38    |
| H(6A) | 6076 | 1430  | 4996 | 37    |
| H(6B) | 4341 | 523   | 5082 | 37    |
| H(8A) | 3422 | -581  | 6313 | 47    |
| H(8B) | 3999 | -1325 | 7173 | 47    |
| H(8C) | 4265 | -1888 | 6209 | 47    |
| H(9A) | 8919 | -1261 | 6872 | 44    |



|        |      |       |      |    |
|--------|------|-------|------|----|
| H(9B)  | 7551 | -2291 | 6534 | 44 |
| H(9C)  | 7280 | -1737 | 7501 | 44 |
| H(10A) | 5647 | -1508 | 4779 | 51 |
| H(10B) | 7771 | -1815 | 5031 | 51 |
| H(10C) | 7333 | -842  | 4288 | 51 |

Table 6. Torsion angles [°].

|                      |             |
|----------------------|-------------|
| C(10)-C(1)-C(2)-N(1) | 19.3(3)     |
| C(6)-C(1)-C(2)-N(1)  | -109.3(2)   |
| C(7)-C(1)-C(2)-N(1)  | 145.3(2)    |
| C(10)-C(1)-C(2)-C(3) | -163.45(17) |
| C(6)-C(1)-C(2)-C(3)  | 67.90(17)   |
| C(7)-C(1)-C(2)-C(3)  | -37.45(16)  |
| C(1)-C(2)-N(1)-N(2)  | 1.3(3)      |
| C(3)-C(2)-N(1)-N(2)  | -175.74(15) |
| C(2)-N(1)-N(2)-O(1)  | -106.6(2)   |
| C(2)-N(1)-N(2)-O(2)  | 80.1(2)     |
| N(1)-C(2)-C(3)-C(4)  | -179.39(16) |
| C(1)-C(2)-C(3)-C(4)  | 2.78(17)    |
| N(1)-C(2)-C(3)-Cl(1) | -58.15(19)  |
| C(1)-C(2)-C(3)-Cl(1) | 124.02(13)  |
| N(1)-C(2)-C(3)-Cl(2) | 58.73(19)   |
| C(1)-C(2)-C(3)-Cl(2) | -119.10(13) |
| C(2)-C(3)-C(4)-C(5)  | -73.42(17)  |
| Cl(1)-C(3)-C(4)-C(5) | 165.41(13)  |
| Cl(2)-C(3)-C(4)-C(5) | 44.18(19)   |
| C(2)-C(3)-C(4)-C(7)  | 33.42(16)   |
| Cl(1)-C(3)-C(4)-C(7) | -87.74(15)  |
| Cl(2)-C(3)-C(4)-C(7) | 151.03(12)  |
| C(3)-C(4)-C(5)-C(6)  | 66.59(19)   |
| C(7)-C(4)-C(5)-C(6)  | -40.61(18)  |
| C(4)-C(5)-C(6)-C(1)  | 7.14(19)    |
| C(2)-C(1)-C(6)-C(5)  | -74.54(18)  |
| C(10)-C(1)-C(6)-C(5) | 154.73(17)  |

|                      |             |
|----------------------|-------------|
| C(7)-C(1)-C(6)-C(5)  | 28.49(18)   |
| C(5)-C(4)-C(7)-C(9)  | 174.50(16)  |
| C(3)-C(4)-C(7)-C(9)  | 62.97(19)   |
| C(5)-C(4)-C(7)-C(8)  | -60.89(18)  |
| C(3)-C(4)-C(7)-C(8)  | -172.42(14) |
| C(5)-C(4)-C(7)-C(1)  | 56.38(16)   |
| C(3)-C(4)-C(7)-C(1)  | -55.15(15)  |
| C(2)-C(1)-C(7)-C(9)  | -66.74(17)  |
| C(10)-C(1)-C(7)-C(9) | 61.1(2)     |
| C(6)-C(1)-C(7)-C(9)  | -173.18(15) |
| C(2)-C(1)-C(7)-C(8)  | 171.27(14)  |
| C(10)-C(1)-C(7)-C(8) | -60.9(2)    |
| C(6)-C(1)-C(7)-C(8)  | 64.83(18)   |
| C(2)-C(1)-C(7)-C(4)  | 55.37(15)   |
| C(10)-C(1)-C(7)-C(4) | -176.82(17) |
| C(6)-C(1)-C(7)-C(4)  | -51.07(16)  |

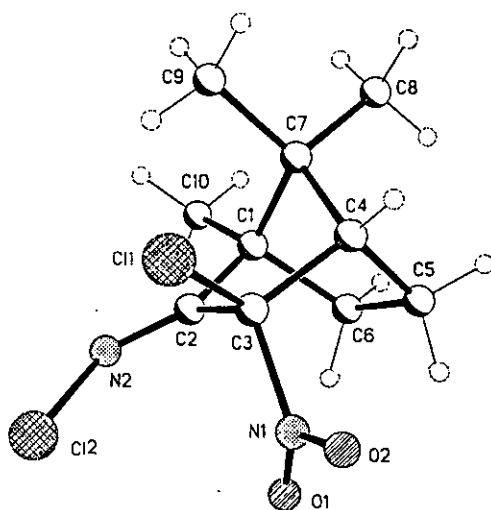
**Appendix 4: *N*-chloro-3-chloro-3-nitro camphor imine**

Table 1. Crystal data and structure refinement.

|                                   |   |                       |
|-----------------------------------|---|-----------------------|
| Empirical formula                 | C <sub>10</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub> |                       |
| Formula weight                    | 265.13  |                       |
| Temperature                       | 150(2) K  |                       |
| Wavelength                        | 0.71073 Å   |                       |
| Crystal system                    | Orthorhombic  |                       |
| Space group                       | P2(1)2(1)2(1)   |                       |
| Unit cell dimensions              | a = 8.3482(7) Å   | $\alpha = 90^\circ$ . |
|                                   | b = 10.9717(9) Å  | $\beta = 90^\circ$ .  |
|                                   | c = 12.8261(10) Å   | $\gamma = 90^\circ$ . |
| Volume                            | 1174.79(17) Å <sup>3</sup>  |                       |
| Z                                 | 4   |                       |
| Density (calculated)              | 1.499 Mg/m <sup>3</sup>   |                       |
| Absorption coefficient            | 0.539 mm <sup>-1</sup>  |                       |
| F(000)                            | 552   |                       |
| Crystal size                      | 0.50 x 0.35 x 0.13 mm <sup>3</sup>  |                       |
| Crystal description               | Colourless irregular plate  |                       |
| Theta range for data collection   | 2.44 to 28.75°.   |                       |
| Index ranges                      | -10 ≤ h ≤ 11, -14 ≤ k ≤ 14, -17 ≤ l ≤ 17                                      |                       |
| Reflections collected             | 10065   |                       |
| Independent reflections           | 2784 [R(int) = 0.0271]  |                       |
| Completeness to theta = 25.00°    | 99.9 %  |                       |
| Absorption correction             | Multiscan   |                       |
| Max. and min. transmission        | 1.000000 and 0.926502   |                       |
| Refinement method                 | Full-matrix least-squares on F <sup>2</sup>                                   |                       |
| Data / restraints / parameters    | 2784 / 0 / 145  |                       |
| Goodness-of-fit on F <sup>2</sup> | 1.062   |                       |
| Final R indices [I > 2σ(I)]       | R1 = 0.0303, wR2 = 0.0846   |                       |
| R indices (all data)              | R1 = 0.0325, wR2 = 0.0866   |                       |
| Absolute structure parameter      | 0.06(6)   |                       |
| Largest diff. peak and hole       | 0.421 and -0.176 e.Å <sup>-3</sup>  |                       |

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

|       | x        | y        | z        | $U(\text{eq})$ |
|-------|----------|----------|----------|----------------|
| C(1)  | -3358(2) | 857(2)   | -5377(1) | 20(1)          |
| C(2)  | -1727(2) | 238(2)   | -5363(1) | 19(1)          |
| C(3)  | -1664(2) | -581(2)  | -6335(1) | 21(1)          |
| C(4)  | -3304(2) | -322(2)  | -6847(1) | 22(1)          |
| C(5)  | -4587(2) | -946(2)  | -6168(1) | 25(1)          |
| C(6)  | -4564(2) | -190(2)  | -5146(1) | 24(1)          |
| C(7)  | -3582(2) | 1055(2)  | -6575(1) | 22(1)          |
| C(8)  | -5262(3) | 1486(2)  | -6878(2) | 31(1)          |
| C(9)  | -2399(3) | 1982(2)  | -7037(2) | 29(1)          |
| C(10) | -3506(2) | 1962(2)  | -4680(2) | 26(1)          |
| N(1)  | -1505(2) | -1962(1) | -6034(1) | 25(1)          |
| O(1)  | -1773(2) | -2197(1) | -5125(1) | 37(1)          |
| O(2)  | -1317(2) | -2659(1) | -6736(1) | 44(1)          |
| Cl(1) | -26(1)   | -277(1)  | -7169(1) | 33(1)          |
| N(2)  | -731(2)  | 450(1)   | -4637(1) | 23(1)          |
| Cl(2) | 1061(1)  | -368(1)  | -4695(1) | 33(1)          |

Table 3. Bond lengths [ $\text{\AA}$ ] and angles [ $^\circ$ ].

|            |            |            |            |
|------------|------------|------------|------------|
| C(1)-C(10) | 1.512(2)   | C(4)-C(5)  | 1.540(2)   |
| C(1)-C(2)  | 1.522(2)   | C(4)-C(7)  | 1.567(2)   |
| C(1)-C(6)  | 1.556(2)   | C(5)-C(6)  | 1.551(2)   |
| C(1)-C(7)  | 1.563(2)   | C(7)-C(8)  | 1.530(3)   |
| C(2)-N(2)  | 1.269(2)   | C(7)-C(9)  | 1.537(3)   |
| C(2)-C(3)  | 1.537(2)   | N(1)-O(2)  | 1.192(2)   |
| C(3)-C(4)  | 1.545(2)   | N(1)-O(1)  | 1.215(2)   |
| C(3)-N(1)  | 1.569(2)   | N(2)-Cl(2) | 1.7462(15) |
| C(3)-Cl(1) | 1.7677(18) |            |            |

|                 |            |
|-----------------|------------|
| C(10)-C(1)-C(2) | 115.07(14) |
| C(10)-C(1)-C(6) | 115.28(15) |
| C(2)-C(1)-C(6)  | 104.29(13) |
| C(10)-C(1)-C(7) | 117.42(14) |
| C(2)-C(1)-C(7)  | 100.43(13) |
| C(6)-C(1)-C(7)  | 102.25(14) |
| N(2)-C(2)-C(1)  | 120.84(15) |
| N(2)-C(2)-C(3)  | 132.80(15) |
| C(1)-C(2)-C(3)  | 106.35(14) |
| C(2)-C(3)-C(4)  | 101.94(13) |
| C(2)-C(3)-N(1)  | 111.58(13) |
| C(4)-C(3)-N(1)  | 110.91(14) |
| C(2)-C(3)-Cl(1) | 114.02(12) |
| C(4)-C(3)-Cl(1) | 113.18(12) |
| N(1)-C(3)-Cl(1) | 105.41(11) |
| C(5)-C(4)-C(3)  | 107.12(14) |
| C(5)-C(4)-C(7)  | 101.55(13) |
| C(3)-C(4)-C(7)  | 102.36(14) |
| C(4)-C(5)-C(6)  | 103.35(13) |
| C(5)-C(6)-C(1)  | 104.01(14) |
| C(8)-C(7)-C(9)  | 106.69(15) |
| C(8)-C(7)-C(1)  | 113.69(15) |
| C(9)-C(7)-C(1)  | 113.21(15) |
| C(8)-C(7)-C(4)  | 112.15(15) |
| C(9)-C(7)-C(4)  | 117.19(14) |
| C(1)-C(7)-C(4)  | 93.83(13)  |
| O(2)-N(1)-O(1)  | 127.75(17) |
| O(2)-N(1)-C(3)  | 116.47(15) |
| O(1)-N(1)-C(3)  | 115.19(14) |
| C(2)-N(2)-Cl(2) | 115.82(12) |

Table 4. Anisotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ). The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

| $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|----------|----------|----------|----------|----------|----------|
|----------|----------|----------|----------|----------|----------|

|       |       |       |       |        |       |       |
|-------|-------|-------|-------|--------|-------|-------|
| C(1)  | 19(1) | 19(1) | 21(1) | 0(1)   | 1(1)  | 1(1)  |
| C(2)  | 19(1) | 17(1) | 21(1) | 4(1)   | 3(1)  | -1(1) |
| C(3)  | 22(1) | 18(1) | 23(1) | 0(1)   | 5(1)  | 3(1)  |
| C(4)  | 23(1) | 22(1) | 20(1) | -2(1)  | -2(1) | 1(1)  |
| C(5)  | 23(1) | 24(1) | 30(1) | -3(1)  | 0(1)  | -3(1) |
| C(6)  | 18(1) | 26(1) | 27(1) | -1(1)  | 3(1)  | -3(1) |
| C(7)  | 23(1) | 21(1) | 21(1) | 2(1)   | -2(1) | 2(1)  |
| C(8)  | 30(1) | 32(1) | 31(1) | 0(1)   | -9(1) | 8(1)  |
| C(9)  | 36(1) | 23(1) | 28(1) | 9(1)   | 2(1)  | 0(1)  |
| C(10) | 26(1) | 24(1) | 28(1) | -6(1)  | -1(1) | 4(1)  |
| N(1)  | 31(1) | 15(1) | 28(1) | -1(1)  | 2(1)  | -4(1) |
| O(1)  | 39(1) | 28(1) | 43(1) | 7(1)   | -2(1) | 0(1)  |
| O(2)  | 51(1) | 30(1) | 51(1) | -10(1) | 5(1)  | 7(1)  |
| Cl(1) | 28(1) | 38(1) | 31(1) | 0(1)   | 10(1) | 2(1)  |
| N(2)  | 18(1) | 23(1) | 28(1) | 2(1)   | -1(1) | 2(1)  |
| Cl(2) | 20(1) | 36(1) | 43(1) | 7(1)   | -3(1) | 3(1)  |

Table 5. Hydrogen coordinates ( $\times 10^4$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).

|        | x     | y     | z     | U(eq) |
|--------|-------|-------|-------|-------|
| H(4)   | -3364 | -520  | -7607 | 26    |
| H(5A)  | -4307 | -1808 | -6033 | 30    |
| H(5B)  | -5652 | -910  | -6506 | 30    |
| H(6A)  | -4197 | -693  | -4551 | 28    |
| H(6B)  | -5641 | 139   | -4987 | 28    |
| H(8A)  | -6060 | 920   | -6594 | 46    |
| H(8B)  | -5354 | 1510  | -7639 | 46    |
| H(8C)  | -5448 | 2302  | -6593 | 46    |
| H(9A)  | -1300 | 1734  | -6870 | 44    |
| H(9B)  | -2609 | 2789  | -6741 | 44    |
| H(9C)  | -2532 | 2013  | -7796 | 44    |
| H(10A) | -4587 | 2303  | -4741 | 39    |
| H(10B) | -2718 | 2576  | -4891 | 39    |

|        |       |      |       |    |
|--------|-------|------|-------|----|
| H(10C) | -3309 | 1723 | -3955 | 39 |
|--------|-------|------|-------|----|

Table 6. Torsion angles [°].

|                      |             |
|----------------------|-------------|
| C(10)-C(1)-C(2)-N(2) | 16.6(2)     |
| C(6)-C(1)-C(2)-N(2)  | -110.67(16) |
| C(7)-C(1)-C(2)-N(2)  | 143.70(16)  |
| C(10)-C(1)-C(2)-C(3) | -163.15(15) |
| C(6)-C(1)-C(2)-C(3)  | 69.58(16)   |
| C(7)-C(1)-C(2)-C(3)  | -36.06(15)  |
| N(2)-C(2)-C(3)-C(4)  | -178.37(17) |
| C(1)-C(2)-C(3)-C(4)  | 1.34(16)    |
| N(2)-C(2)-C(3)-N(1)  | 63.2(2)     |
| C(1)-C(2)-C(3)-N(1)  | -117.07(14) |
| N(2)-C(2)-C(3)-Cl(1) | -56.1(2)    |
| C(1)-C(2)-C(3)-Cl(1) | 123.66(12)  |
| C(2)-C(3)-C(4)-C(5)  | -72.38(16)  |
| N(1)-C(3)-C(4)-C(5)  | 46.51(17)   |
| Cl(1)-C(3)-C(4)-C(5) | 164.73(12)  |
| C(2)-C(3)-C(4)-C(7)  | 33.99(15)   |
| N(1)-C(3)-C(4)-C(7)  | 152.88(13)  |
| Cl(1)-C(3)-C(4)-C(7) | -88.90(13)  |
| C(3)-C(4)-C(5)-C(6)  | 68.57(17)   |
| C(7)-C(4)-C(5)-C(6)  | -38.39(17)  |
| C(4)-C(5)-C(6)-C(1)  | 4.27(18)    |
| C(10)-C(1)-C(6)-C(5) | 159.99(15)  |
| C(2)-C(1)-C(6)-C(5)  | -72.87(16)  |
| C(7)-C(1)-C(6)-C(5)  | 31.40(17)   |
| C(10)-C(1)-C(7)-C(8) | -63.9(2)    |
| C(2)-C(1)-C(7)-C(8)  | 170.57(14)  |
| C(6)-C(1)-C(7)-C(8)  | 63.31(18)   |
| C(10)-C(1)-C(7)-C(9) | 58.0(2)     |
| C(2)-C(1)-C(7)-C(9)  | -67.46(17)  |
| C(6)-C(1)-C(7)-C(9)  | -174.72(14) |
| C(10)-C(1)-C(7)-C(4) | 179.85(15)  |

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|                      |             |
|----------------------|-------------|
| C(2)-C(1)-C(7)-C(4)  | 54.34(14)   |
| C(6)-C(1)-C(7)-C(4)  | -52.92(14)  |
| C(5)-C(4)-C(7)-C(8)  | -61.55(17)  |
| C(3)-C(4)-C(7)-C(8)  | -172.19(14) |
| C(5)-C(4)-C(7)-C(9)  | 174.55(15)  |
| C(3)-C(4)-C(7)-C(9)  | 63.91(18)   |
| C(5)-C(4)-C(7)-C(1)  | 55.96(15)   |
| C(3)-C(4)-C(7)-C(1)  | -54.67(14)  |
| C(2)-C(3)-N(1)-O(2)  | -174.14(17) |
| C(4)-C(3)-N(1)-O(2)  | 73.0(2)     |
| Cl(1)-C(3)-N(1)-O(2) | -49.9(2)    |
| C(2)-C(3)-N(1)-O(1)  | 13.9(2)     |
| C(4)-C(3)-N(1)-O(1)  | -98.98(18)  |
| Cl(1)-C(3)-N(1)-O(1) | 138.18(15)  |
| C(1)-C(2)-N(2)-Cl(2) | 177.67(11)  |
| C(3)-C(2)-N(2)-Cl(2) | -2.6(2)     |



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