

**STUDIES TOWARDS THE SYNTHESIS OF  
PERHYDROPYRROLO[2,1-*J*]QUINOLINE AND  
PERHYDROPYRIDO[2,1-*J*]QUINOLINE  
ASCIDIAN ALKALOIDS**

Submitted in fulfilment of the requirements  
for the degree of

**MASTER OF SCIENCE**

By

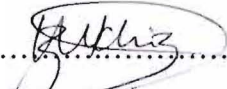
**Zimbili Mkhize**

December 2002

School of Chemical and Physical Sciences  
University of Natal  
Pietermaritzburg

## DECLARATION

I hereby certify that this research is a result of my own investigation which has not already been accepted in substance for any degree and is not being submitted in candidature for any other degree.

Signed.....

Zimbili Mkhize

I hereby certify that this statement is correct

Signed.....

pp. Doctor D. Gravestock  
Supervisor

Signed.....

Doctor R. S. Robinson  
Co-supervisor

School of Chemical and Physical Sciences  
University of Natal  
Pietermaritzburg

December 2002



# CONTENTS

|                                     |     |
|-------------------------------------|-----|
| <b>ACKNOWLEDGMENTS</b> .....        | v   |
| <b>CONFERENCE PROCEEDINGS</b> ..... | vi  |
| <b>ABBREVIATIONS</b> .....          | vii |
| <b>ABSTRACT</b> .....               | ix  |

## **CHAPTER 1: An Overview of Ascidian Alkaloids**

|   |    |
|---|----|
| <b>1.1 INTRODUCTION</b> .....   | 1  |
| <b>1.2 AN OVERVIEW OF ASCIDIAN ALKALOIDS</b> .....                                      | 2  |
| 1.2.1. Polycyclic alkaloids .....   | 3  |
| 1.2.2. Bicyclic alkaloids   |    |
| 1.2.2.1 Quinolizidine .....   | 4  |
| 1.2.2.2 Indolizidine .....  | 5  |
| 1.2.2.3 Decahydroquinoline .....  | 6  |
| 1.2.3. Tricyclic alkaloids  |    |
| 1.2.3.1. Cylindricines.....   | 7  |
| 1.2.3.2. Lepadiformine.....   | 9  |
| 1.2.3.3. Fascicularin.....  | 10 |
| <b>1.3 REPORTED SYNTHESSES OF THE CYLINDRICINES, LEPADIFORMINE AND FASCULARIN</b> ..... | 10 |
| <b>1.4 AIMS</b> .....   | 24 |

## **CHAPTER 2: Model Studies**

|   |    |
|---|----|
| <b>2.1 Attempted preparation of the azaspirocycles [111] and [112]</b>                                      |    |
| 2.1.1. 1-Methyltetrahydro-2(1 <i>H</i> )-pyridinone [104].....  | 33 |
| 2.1.2. 1-Methyl-2-pyrrolidinethione [105] and 1-methyltetrahydro-2(1 <i>H</i> )-pyridinethione[106].....    | 34 |
| 2.1.3. 1-(1-Methyl-2-pyrrolidinylidene)acetone [107] and 1-(1-methyl-2-piperidinylidene)-acetone [108]..... | 35 |
| 2.1.4. Attempted preparation of dienes [109] and [110]  |    |
| 2.1.4.1. Silylation.....  | 38 |

|                                     |    |
|-------------------------------------|----|
| 2.1.4.2. Acylation.....             | 39 |
| 2.1.4.3. Alkylation.....            | 39 |
| 2.1.4.4. Petasis methylenation..... | 43 |

### CHAPTER 3: Enantioselective Synthesis of B and C Rings of Fascicularin

|   |    |
|---|----|
| 3.1. (2 <i>S</i> )-5-Oxotetrahydro-2-furancarboxylic acid [123] .....   | 46 |
| 3.2. (5 <i>S</i> )-5-(Hydroxymethyl)dihydro-2(3 <i>H</i> )-furanone[124].....   | 47 |
| 3.3. [(2 <i>S</i> )-5-Oxotetrahydro-2-furanyl]methyl methanesulfonate [125].....  | 48 |
| 3.4. (5 <i>S</i> )-5-(Azidomethyl)dihydro-2(3 <i>H</i> )-furanone [126].....  | 48 |
| 3.5. (5 <i>S</i> )-5-Hydroxytetrahydro-2(1 <i>H</i> )pyridinone [127].....  | 49 |
| 3.6. Attempted protection of (5 <i>S</i> )-5-hydroxytetrahydro-2(1 <i>H</i> )pyridinone [127].....  | 51 |
| 3.6.1. (3 <i>S</i> )-1-Benzoyl-6-oxo-3-piperidinyl benzoate [159].....  | 52 |
| 3.6.2. (5 <i>S</i> )-5-{{ <i>tert</i> -Butyl(diphenyl)silyl}oxy}tetrahydro-2(1 <i>H</i> )-pyridinone [114].....   | 52 |
| 3.7. (5 <i>S</i> )-5-{{ <i>tert</i> -Butyl(diphenyl)silyl}oxy}tetrahydro-2(1 <i>H</i> )-pyridinethione [160].....   | 54 |
| 3.8. Attempted <i>N</i> -alkylation of (5 <i>S</i> )-5-{{ <i>tert</i> -butyl(diphenyl)silyl}oxy}tetrahydro-2(1 <i>H</i> )-<br>pyridinethione [160].....                     | 55 |
| 3.8.1. Attempted <i>N</i> -alkylation of 5-{{ <i>tert</i> -butyl(diphenyl)silyl}oxy}tetrahydro-<br>2(1 <i>H</i> )- pyridinethione [160] using methyl 2-nonenoate [117]..... | 56 |
| 3.8.2. Attempted preparation of (5 <i>S</i> )-1-benzyl-5-{{ <i>tert</i> -butyl(diphenyl)silyl}oxy}-<br>tetrahydro-2(1 <i>H</i> )- pyridinethione [161].....                 | 57 |
| 3.8.3. Methyl 3-[(5 <i>S</i> )-5-{{ <i>tert</i> -butyl(diphenyl)silyl}oxy}-2-thioxotetrahydro-1(2 <i>H</i> )-<br>pyridinyl ]propanoate [163].....                           | 59 |
| 3.9. Methyl 3-[(5 <i>S</i> )-5-{{ <i>tert</i> -butyl(diphenyl)silyl}oxy}2-[( <i>E</i> )-2-oxopropylidene] tetrahydro-<br>2(1 <i>H</i> )-pyridinyl]propanoate [164].....     | 60 |
| 3.10. Attempted diene and azabicyclo formation.....   | 62 |
| 3.11. Synthesis of (3 <i>R</i> )-1,3-nonanediol [131].....  | 66 |
| 3.12. Attempted coupling of mesylate [116] with lactam [114].....   | 70 |
| 3.13. CONCLUSION.....   | 72 |

### CHAPTER 4: Experimental

|  |    |
|--|----|
| 4.1. Attempted preparation of the azaspirocycles [111] and [112] |    |
| 4.1.1. 1-Methyltetrahydro-2(1 <i>H</i> )-pyridinone [104].....   | 75 |

|             |   |    |
|-------------|---|----|
| 4.1.2.      | 1-Methyl-2-pyrrolidinethione [105].....   | 76 |
| 4.1.3.      | 1-Methyltetrahydro-2(1 <i>H</i> )-pyridinethione [106].....   | 76 |
| 4.1.4.      | Bromoacetone.....   | 77 |
| 4.1.5.      | 1-(1-Methyl-2-pyrrolidinylidene)propanone [107].....  | 77 |
| 4.1.6.      | 1-(1-Methyl-2-piperidinylidene)propanone [108].....   | 78 |
| 4.1.7.      | Alternative method to 1-(1-methyl-2-piperidinylidene)propanone [108].....   | 78 |
| 4.1.8.      | Attempted diene formation.  |    |
| 4.1.8.1.    | Attempted silylation of vinylogous amide [107].....   | 79 |
| 4.1.8.2.    | Attempted acylation of vinylogous amide [107].....  | 79 |
| 4.1.8.3.    | Attempted alkylation of the vinylogous amide [107].....   | 80 |
| 4.1.9.      | 1-(3-Ethyl-1-methyl-2- pyrrolidinylidene))propanone [151].....  | 80 |
| 4.1.10.     | 1-(3-Ethyl-1-methyl-2-piperidinylidene)propanone [152].....   | 81 |
| 4.1.11.     | Ethyl 2-(1-methyl-2-piperidinylidene)acetate [157].....   | 82 |
| 4.1.12.     | Attempted Tebbe methylenation.....  | 82 |
| <b>4.2.</b> | <b>Construction of the B and C rings of fascicularin.</b>   |    |
| 4.2.1.      | (2 <i>S</i> )-5-Oxotetrahydro-2-furancarboxylic acid [123].....   | 83 |
| 4.2.2.      | (5 <i>S</i> )-5-(Hydroxymethyl)dihydro-2(3 <i>H</i> )-furanone [124].....   | 83 |
| 4.2.3.      | [(2 <i>S</i> )-5-Oxotetrahydro-2-furanyl]methyl methanesulfonate [125].....   | 84 |
| 4.2.4.      | (5 <i>S</i> )-5-(Azidomethyl)dihydro-2(3 <i>H</i> )-furanone [126].....   | 84 |
| 4.2.5.      | (5 <i>S</i> )-5-Hydroxytetrahydro-2(1 <i>H</i> )pyridinone [127].....   | 85 |
| 4.2.6.      | Attempted protection of (5 <i>S</i> )-5-hydroxytetrahydro-2(1 <i>H</i> )pyridinone [127]                              |    |
| 4.2.6.1.    | 1-Benzoyl-6-oxo-3-piperidinyl benzoate [159].....   | 85 |
| 4.2.6.2.    | (5 <i>S</i> )-5-{[ <i>tert</i> -Butyl(diphenyl)silyl]oxy}tetrahydro-2(1 <i>H</i> )-pyridinone [114]...                | 86 |
| 4.2.7.      | (5 <i>S</i> )-5-{[ <i>tert</i> -Butyl(diphenyl)silyl]oxy}tetrahydro-2(1 <i>H</i> )-pyridinethione [160].....          | 87 |
| 4.2.8.      | Attempted <i>N</i> -alkylation of (5 <i>S</i> )-5-{[ <i>tert</i> -butyl(diphenyl)silyl]oxy}tetrahydro-2(1 <i>H</i> )- |    |
|             | pyridinethione [160].....   | 88 |
| 4.2.8.1     | 2-(Benzylthio)-(5 <i>S</i> )-5-{[ <i>tert</i> -butyl(diphenyl)silyl]oxy}-3,4,5,6-tetrahydropyridine                   |    |
|             | [162] .....   | 88 |
| 4.2.8.2.    | Attempted conjugate addition of the thiolactam [114] to methyl-2-nonenoate  |    |
|             | [117].....  | 89 |
| 4.2.8.3.    | Methyl 3-[(5 <i>S</i> )-5-{[ <i>tert</i> -butyl(diphenyl)silyl]oxy}-2-thioxotetrahydro-1-                             |    |
|             | (2 <i>H</i> )- pyridinyl]propanoate [163].....  | 89 |
| 4.2.9.      | Methyl 3-[(5 <i>S</i> )-5-{[ <i>tert</i> -butyl(diphenyl)silyl]oxy}2-[( <i>E</i> )-2-                                 |    |

|   |    |
|---|----|
| oxopropylidene]tetrahydro-2(1 <i>H</i> )-pyridinyl]propanoate [164].....  | 90 |
| 4.2.10. 1-[(5 <i>S</i> )-5-{{ <i>tert</i> -Butyl(diphenyl)silyl}oxy}tetrahydro-2(1 <i>H</i> )- piperidinylidene]-<br>propanone [167]..... | 91 |
| 4.2.11. Synthesis of (3 <i>R</i> )-1,3-nonanediol [131].....  | 92 |
| 4.2.12. (1 <i>R</i> )-1-(2-{{ <i>tert</i> -Butyl(dimethyl)silyl}oxy}ethyl)heptyl methanesulfonate [116] .....                             | 92 |
| 4.2.13. Attempted coupling of mesylate [116] to lactam [115] .....  | 93 |
| <b>REFERENCES</b> .....   | 94 |

## ACKNOWLEDGMENTS

I would like to thank my supervisor, Dr. D. Gravestock for his assistance, encouragement and guidance throughout this project. I would also like to thank my co-supervisor, Dr. R. S. Robinson, as well as Prof. Drewes, for their contributions.

I would also like to thank the following people for their contributions to this work:

- Mr. Martin Watson, Mr. Craig Grimmer and Mr. James Ryan for assistance with NMR and mass spectra.
- Mr. Paul Forder for providing the necessary glassware.
- Mr. Raj Somaru and Wilson Zondi for their willing help in the laboratory.
- Dr. P. Boshoff of the Cape Technikon for all the high resolution mass spectrometry.
- My colleagues in the Warren laboratory for all their support.
- My family, Bheka, Mom and Dad for all their support and encouragement.

I also gratefully acknowledge the financial assistance from the National Research Foundation (NRF) and the University of Natal.



## CONFERENCE PROCEEDINGS

The following posters were presented on various aspects of this research project

1. David Gravestock and Zimbili Mkhize, *Studies Towards the Synthesis of Fascicularin*, 35<sup>th</sup> Convention of the South African Chemical Institute, Potchefstroom, September 2000.
2. David Gravestock and Zimbili Mkhize, *Progress Towards the Synthesis of Fascicularin*, 1<sup>st</sup> Binational Royal Society of Chemistry/ South African Chemical Institute, Cape Town, January 2001.
3. David Gravestock and Zimbili Mkhize, *Progress Towards the Synthesis of Fascicularin*, Royal Society of Chemistry Perkin Division 17<sup>th</sup> International Symposium: Synthesis in Organic Chemistry, Oxford, July 2001.
4. David Gravestock and Zimbili Mkhize, *Progress Towards the Enantioselective Synthesis of Fascicularin*, 36<sup>th</sup> Convention of the South African Chemical Institute, Port Elizabeth, July 2002.

## ABBREVIATIONS

(AcO)<sub>2</sub> = acetic anhydride

Ac = CH<sub>3</sub>C(O)-

Bn = benzyl

br = broad

CAN = ceric ammonium nitrate

COSY = correlation spectroscopy

Cp = cyclopentadienyl

DEPT = distortion enhancement over polarisation transfer

DMAP = 4dimethylaminopyridine

DMF = *N,N*-dimethylformamide

Et = CH<sub>3</sub>CH<sub>2</sub>-

Et<sub>3</sub>N = triethyl amine

GCMS = gas chromatography/ mass spectrometry

GHMQC = gradient heteronuclear multiple quantum coherence

GHSQC = gradient heteronuclear single quantum coherence

h = hour

HClO<sub>4</sub> = perchloric acid

K<sub>2</sub>CO<sub>3</sub> = potassium carbonate

KHMDS = potassium bis(trimethylsilyl) amide

LDA = lithium diisopropylamide

LiAlH<sub>4</sub> / LAH = lithium aluminum hydride

Me = CH<sub>3</sub>-

MOM = methoxymethyl / CH<sub>2</sub>OCH<sub>3</sub>

MOMCl = chloromethylmethyl ether / ClCH<sub>2</sub>OCH<sub>3</sub>

Ms or Mes = mesyl/ CH<sub>3</sub>SO<sub>2</sub>-

MsCl = CH<sub>3</sub>SO<sub>2</sub>Cl

MW = microwave

NaHMDS = sodium bis(trimethylsilyl) amide

NMR = nuclear magnetic resonance  
NOESY = nuclear overhauser effect spectroscopy  
Ph = phenyl  
ppm = parts per million  
PPTS = pyridinium *p*-toluenesulfonic acid  
*p*-TsOH = *p*-toluenesulfonic acid  
rt = room temperature  
*t* / *tert* = tertiary  
TBAF = tetrabutylammonium fluoride  
TBDPS = *tert*-butyldiphenyl silyl  
TBDPSCl = *tert*-butyldiphenyl silyl chloride  
TBS = *tert*-butyldimethyl silyl  
TBSCl = *tert*-butyldimethyl silyl chloride  
*t*-BuOK = potassium *tert*-butoxide  
Tf = triflate, CF<sub>3</sub>SO<sub>3</sub><sup>-</sup>  
TFAA = trifluoroacetic anhydride  
THF = tetrahydrofuran  
THP = tetrahydropyran  
TIPS = triisopropyl silyl  
TIPSTf = triisopropylsilyl trifluoromethanesulfonate  
TLC = thin layer chromatography  
TMEDA = *N, N, N', N'*-tetramethylethylenediamine  
TMSCl = trimethyl silyl chloride  
Ts = *p*-CH<sub>3</sub>PhSO<sub>2</sub><sup>-</sup>



## ABSTRACT

Cylindricines A-K [1-11], lepadiformine [12] and fascicularin [13] are tricyclic ascidian alkaloids exhibiting the perhydropyrrolo[2,1-*j*]quinoline and perhydropyrido[2,1-*j*]quinoline ring systems. The structural features and biological activity of these alkaloids make them ideal targets for total synthesis.

The first aim of this project was to construct the azabicycles [111] and [112] that resemble the spirocyclic core of these alkaloids. The synthesis began with the C ring intact and the attempted construction of the B ring using Diels-Alder methodology. A key step was the Eschenmoser coupling reaction between thiolactams [105] and [106] to give the vinylogous amides [107] and [108]. All attempts to convert the vinylogous amides to the corresponding dienes proved to be unsuccessful, due to the fact that the preferred site for deprotonation was  $\beta$  to nitrogen and not  $\alpha$  to the carbonyl group. Due to time constraints we moved to our second aim, the enantioselective synthesis of the B and C rings of fascicularin [13].

Significant progress was made towards our second goal. (5*S*)-5-Hydroxytetrahydro-2(1*H*)pyridinone [127], which represents the C ring of fascicularin, was successfully synthesized in 5 steps from L-glutamic acid [113]. This lactam was *O*-protected with *tert*-butyldiphenylsilyl group to afford (5*S*)-5-*tert*-butyldiphenylsilyloxy-2-piperidinone [114]. Thionation of lactam [114] gave the thiolactam [160]. Conjugate addition of this thiolactam to methyl acrylate gave methyl 3-[(5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}-2-thioxotetrahydro-1(2*H*)-pyridinyl]propanoate [163], which underwent a Eschenmoser coupling reaction with bromoacetone to give methyl 3-[(5*S*)-5-{{*tert*-butyl(diphenyl)-silyl}oxy}2-[(*E*)-2-oxopropylidene]tetrahydro-2(1*H*)-pyridinyl]propanoate [164]. Unfortunately conversion of [164] into the corresponding diene using KHMDS and TBSCl was unsuccessful. The reaction conditions caused the cleavage of the methyl acrylate protecting group on nitrogen, affording the secondary *E*-vinylogous amide [167]. This constituted an important serendipitous discovery - methyl acrylate can be used to protect the nitrogen atom of enaminones and can be removed by KHMDS to access secondary *E*-enaminones that are otherwise difficult to synthesise. Another route pursued was to introduce the hexyl chain in the A ring of fascicularin by means of an S<sub>N</sub>2 reaction between lactam [114] and mesylate [116]. The stereodefined (1*R*)-1-(2-{{*tert*-butyl-(dimethyl)silyl}oxy}ethyl)heptyl methanesulfonate [116] was successfully

synthesized in 5 steps from 1-octyne [115]. Unfortunately the subsequent S<sub>N</sub>2 reaction with lactam [114] failed when we using *t*-BuOK and THF and time constraints prevented us from attempting this coupling reaction using alternative conditions.

## CHAPTER 1

**An overview of ascidian alkaloids, a review of reported approaches towards the synthesis of the cylindricines, lepadiformine and fascicularin, and aims of this project.**

### 1.1 Introduction

The history of alkaloids is almost as old as civilization itself.<sup>1</sup> Humankind used drugs containing alkaloids in potions, medicines, teas, poultices and poisons for 4000 years, yet no attempts were made to isolate any of the therapeutically active reagents from the natural material until the early nineteenth century.<sup>1</sup> Opium was the first alkaloid to be isolated, from the dried latex of the poppy *Papaver somniferum* in 1805.<sup>1</sup> Cordell's definition of alkaloids is as follows: "True alkaloids are toxic; they show a wide range of physiological activity; they are almost invariably basic; they normally contain nitrogen in a heterocyclic ring; they are derived from amino acids; they are of limited taxonomic distribution, and they normally occur in plants as the salt of an organic acid."<sup>1</sup> This definition is not completely definitive because not all alkaloids contain nitrogen as part of a ring system and there has been an increasing number of examples of the occurrence of alkaloids in animal, insects, marine organisms, and microorganisms.<sup>1-4</sup>

A later definition of alkaloids proposed by Dewick is as follows: "Alkaloids are organic nitrogenous bases found mainly in plants, but also to a lesser extent in microorganisms and animals."<sup>4</sup> This definition is preferred because it does not restrict nitrogen to being present in a heterocyclic ring. The word alkaloid was originally derived from alkali.<sup>1,3,4</sup> The degree of basicity of an alkaloid depends on its structure and the effect of other functional groups.

Marine natural product chemists have enjoyed unrivaled success in the discovery of unique new compounds. However instead of just searching for new metabolites, the search has become more applied; targeting compounds which exhibit pharmacologically useful biological activities.<sup>2</sup> It has been proven that marine organisms, especially invertebrates such as ascidians, sponges, soft corals and molluscs, produce secondary metabolites that are unprecedented within the terrestrial biosphere.<sup>2</sup> A diverse array of biomedically relevant compounds have been detected, including central nervous system membrane-active toxins, ion channel effectors,



anticancer agents, tumor promoters, antiviral compounds, anti-inflammatory agents and metabolites which affect microfilament-mediated processes.

Ascidians in particular have become the target of natural product research. Ascidians are marine benthic invertebrates belonging to the phylum Chordata and subphylum Tunicates.<sup>2,5-7</sup> Ascidians are commonly referred to as tunicates, because their body is covered by a saclike case or tunic. They are also referred to as sea squirts, because many species expel streams of water through a siphon when disturbed.<sup>2</sup>

There are roughly 2000 known species of tunicate.<sup>2</sup> Adult ascidians are sessile filter feeders, either solitary or colonial. They live in regions that are free from extensive waveshock, but receive considerable freely flowing water. Solitary ascidians may be as small as 1cm or up to 15cm in length. Colonial ascidians are usually found encrusting rocks and may be extremely thin and delicate or as thick as 5cm. Some ascidians have indefinite shape, thus the contraction which causes a sea squirt to spray streams of water distinguish ascidians from other marine invertebrates, like sponges and fresh coelenterates.<sup>2</sup> The majority of the compounds produced by ascidians contain nitrogen derived from amino acids and are known to possess interesting biological activities.<sup>2,5,7-11</sup>

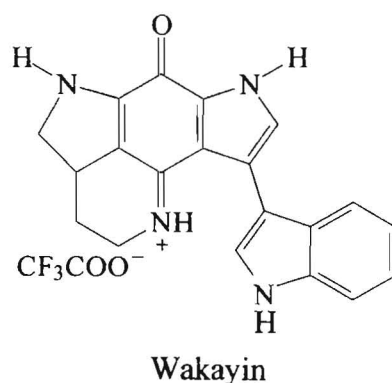
An interest in ascidian chemistry started as early as 1847.<sup>2</sup> Unusual colour changes in ascidian blood were observed upon exposure to air, when blood would turn from yellow-green to deep blue, however attention has focused, more recently on ascidians because of the biological activities of their metabolites. Between 1988 and mid-1992 an incredible surge of interest in ascidian chemistry yielded approximately 165 new ascidian metabolites.<sup>2</sup> Ascidian alkaloids are divided into a number of nitrogenous metabolites. They include peptide metabolites, polycyclic aromatic alkaloids, tryptophan-derived, lysine-derived, tyrosine- and phenylalanine-derived metabolites. Some examples of alkaloids from the *Clavelinidae* and *Nephtheis* ascidian families are reviewed in the following section.

## 1.2 An overview of ascidian alkaloids

A number of structurally interesting alkaloids have been isolated from the *Clavelinidae* family of ascidians. An unidentified *Clavelina* species gave the novel pyrroloiminoquinone alkaloid,

wakayin shown below.<sup>12</sup> *Clavelina picta* obtained in Bermuda gave quinolizidine alkaloids, clavepictines A and B,<sup>13</sup> together with indolizidine alkaloids, piclavines A, B and C.<sup>14</sup> The same species from Venezuela gave the quinolizidine alkaloid, pictamine.<sup>11</sup> Ascidian *Clavelina lepadiformis* and its predatory flatworm *Prostheceraeus villatus* obtained in the North Sea gave the decahydroquinoline alkaloids, lepadin A, B and C.<sup>15,16</sup> *Clavelina cylindrica* from Tasmania gave tricyclic alkaloids, cylindricines A-K.<sup>5,10,17</sup> *Clavelina lepadiformis* from Tunisia gave another interesting tricyclic alkaloid lepadiformine<sup>9</sup> which is structurally similar to the cylindricines. From the Micronesian ascidian *Nephteis fascicularis*, a tricyclic alkaloid similar to the cylindricines and lepadiformine, was obtained, namely fascularin.<sup>7</sup> This section will give a brief overview of the above-mentioned alkaloids and their biological activities. These alkaloids are subdivided according to the structure of the heterocyclic ring system.

### 1.2.1 Polycyclic alkaloids

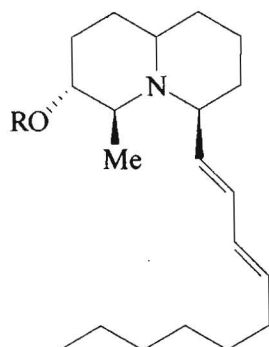


Many polycyclic aromatic alkaloids have been isolated from ascidians.<sup>12</sup> Ascidiemnin and 2-bromoleptoclinidinone from the ascidians *Leptoclinides* and *Didemnum* were the first aromatic metabolites to be isolated.<sup>2</sup> Wakayin is the first example of a reported pyrroloiminoquinone alkaloid to be isolated from an ascidian. Ireland and co-workers isolated this novel alkaloid from an unidentified *Clavelina* species in 1991.<sup>12</sup> It was first isolated and characterized as its trifluoroacetate salt. There has been no reported total synthesis of wakayin, although Cava and co-workers<sup>18</sup> and Barret and co-workers<sup>19</sup> reported a synthesis of wakayin model compounds.

Wakayin possesses a variety of biological activities. It exhibits *in vitro* cytotoxicity against the human colon tumor line (HCT116; IC<sub>50</sub> 0.5 µg/mL) and inhibition of topoisomerase II enzymes (MIC 0.3 µg/mL). Antimicrobial activity against *Bacillus subtilis* was also observed.

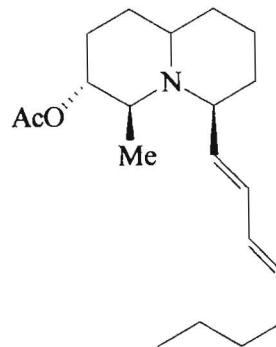
## 1.2.2 Bicyclic alkaloids

### 1.2.2.1 Quinolizidine



Clavepictine A : R = Ac

Clavepictine B : R = H



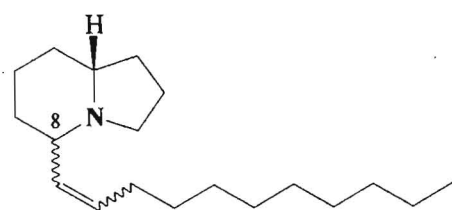
Pictamine

Clavepictines A and B were isolated in 1991 by Cardellina II and co-workers from the Bermudian ascidian *Clavelina picta*.<sup>13</sup> These alkaloids were the first quinolizidine alkaloids to be isolated from an ascidian. Momose and co-workers<sup>20</sup> reported the first total synthesis of clavepictine A and B. There are, to date, five reported syntheses of clavepictines A and B.<sup>20-24</sup>

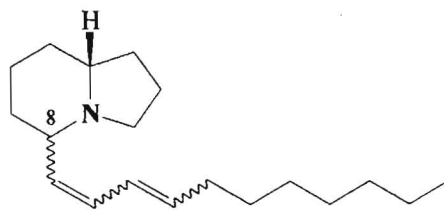
These quinolizidine alkaloids exhibit antibacterial and antifungal activities. They inhibit growth of murine leukemia and human solid tumor cell lines at concentrations less than 9  $\mu\text{g/mL}$  ( $\text{IC}_{50} = 1.8\text{-}8.5 \mu\text{g/mL}$ ) and effectively kill all cell lines at less than 25  $\mu\text{g/mL}$  ( $\text{LC}_{50} = 10.1\text{-}24.7 \mu\text{g/mL}$ ).<sup>13,20-24</sup>

Faulkner and co-workers independently isolated pictamine from the same ascidian *Clavelina picta*, collected in Venezuela.<sup>11</sup> There is only one reported total synthesis of pictamine.<sup>22</sup> Pictamine is the bis-nor analog of Clavepictine A bearing two less carbons in the side-chain.<sup>2,10,20,22</sup> It also possesses antimicrobial and antifungal activities.<sup>2,11</sup> A thorough study of the biological activity of this alkaloid has been hampered by its limited bioavailability.

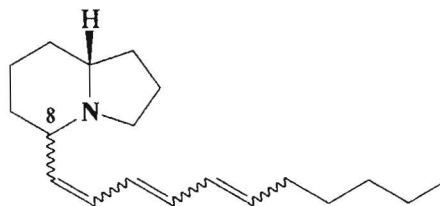
### 1.2.2.2 Indolizidine



Piclavine A



Piclavine B



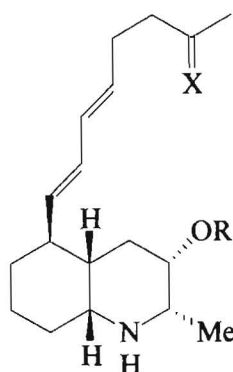
Piclavine C

Indolizidine alkaloids were previously unknown from marine sources, although similar mono-substituted indolizidines are characteristic secondary metabolites found in the skin of dendrobatid frogs.<sup>14</sup> Three series of indolizidine alkaloids (piclavines A, B and C), were isolated by Cardellina II and co-workers from the Bermudian ascidian *Clavelina picta*, in 1992.<sup>14</sup> Piclavine A was the first indolizidine alkaloid to be isolated in the marine biosphere. Each piclavine differs in the number of double bonds in the undecyl substituent. Each piclavine is composed of an inseparable mixture of isomers, which differ in stereochemistry at the C<sub>8</sub> chiral center (indolizidine numbering) and at each of the double bonds in the substituent. There are two reported syntheses of piclavine A.<sup>25,26</sup>

It was found that these compounds serve as antifouling or antiinfective agents for both tunicates and frogs.<sup>14</sup> These alkaloids are the principal antimicrobial agents of the ascidians. These alkaloids also exhibit antifungal and antibacterial activity against Gram-positive bacteria.<sup>14</sup>



### 1.2.2.3 Decahydroquinoline



Lepadin A :  
X=H<sub>2</sub>, R=COCH<sub>2</sub>OH

Lepadin B :  
X=H<sub>2</sub>, R=H

Lepadin C :  
X=O, R= COCH<sub>2</sub>OH

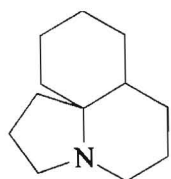
The decahydroquinolines represent one of the major classes of amphibian alkaloids. Recently these alkaloids have been found in the extracts of virgin queen myrmicine ants.<sup>27</sup> Lepadin A was the first decahydroquinoline alkaloid to be isolated from an ascidian. Lepadin A was isolated by Steffan in 1991<sup>15</sup> and lepadin B and C were later isolated by Andersen and co-workers<sup>16</sup> from the same ascidian, *Clavelina lepadiformis*, collected from the island of Hegoland in the North Sea. *Clavelina lepadiformis* is a colonial ascidian living mainly at depths between 4 and 25m on sunlit submarine rocks and soils. Their tunic is absolutely transparent allowing one to view the intestine.<sup>15</sup> The flatworm *Prostheceraeus villatus* is found seasonally in the North East Atlantic Ocean and in the North Sea. Many of these flatworms were found feeding on the tunicate *Clavelina lepadiformis*. Lepadin A, B and C were isolated from both the predatory flatworm *Prostheceraeus villatus* and its tunicate prey *Clavelina lepadiformis*.<sup>16,28</sup> There is one reported synthesis of lepadin A,<sup>27</sup> four for lepadin B<sup>27-30</sup> and one for lepadin C.<sup>27</sup>

Lepadin A and B showed significant cytotoxic activity towards a variety of murine and human cancer cell lines; murine leukemia (P338), human breast cancer (MCF7), human glioblastoma/astrocytoma (U373), human ovarian carcinoma (HEY), human colon (LOVO) and human lung cancer (A549).<sup>15,16,28-30</sup> Lepadin C was inactive towards cancer cell lines at 50 µg/mL.<sup>16</sup>

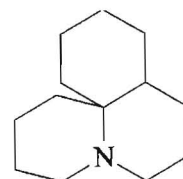


### 1.2.3 Tricyclic alkaloids

In this section the spiro-tricyclic ascidian alkaloids exhibiting the perhydropyrrolo[2,1-*j*]quinoline and perhydropyrido[2,1-*j*]quinoline ring systems will be discussed. Why an interest in these alkaloids? These are new structural classes of alkaloids, exhibiting some interesting biological activities. Their structural features make them ideal targets for total synthesis. The generic structure of these ring systems is shown below.



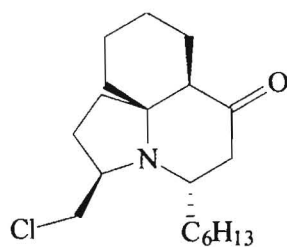
perhydropyrrolo[2,1-*j*]quinoline



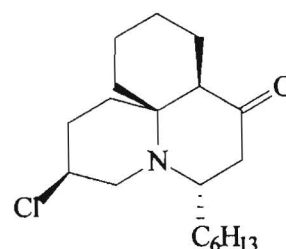
perhydropyrido[2,1-*j*]quinoline

Cylindricines A [1], C-I [3-9] and K [11] as well as lepadiformine [12] are based on the perhydropyrrolo[2,1-*j*]quinoline structural motif while cylindricines B [2] and J [10] as well as fascicularin [13] possess the perhydropyrido[2,1-*j*]quinoline ring system.

#### 1.2.3.1 Cylindricines



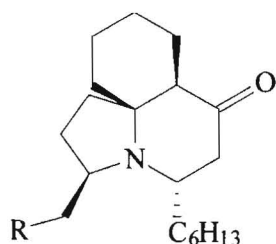
Cylindricine A [1]



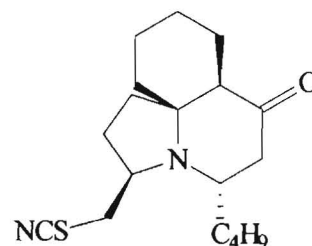
Cylindricine B [2]

Blackman and co-workers isolated eleven cylindricine alkaloids (A-K) from the Tasmanian ascidian *Clavelina cylindrica* in 1991.<sup>5,10,17</sup> They first isolated cylindricines A and B,<sup>10</sup> which were the first examples of perhydropyrrolo[2,1-*j*]quinoline and perhydropyrido[2,1-*j*]quinoline alkaloids from an ascidian. High resolution mass spectrometry (HRMS) indicated that the molecular formula of the two alkaloids is the same  $C_{19}H_{32}ClNO$ , thus they are isomeric alkaloids. The spectral data helped to elucidate the structures of the two compounds. NMR spectroscopic analysis revealed that cylindricine B had the chlorine atom attached to a methine

group while cylindricine A possessed a  $\text{CH}_2\text{Cl}$  group. Single crystal analysis helped to resolve the structures. It was found that a solution of cylindricine A [1] or B [2] both gave, after 6 days, the same equilibrium mixture of 3:2 of cylindricine A and B. Thus the two alkaloids are interconvertible.<sup>5,6</sup>

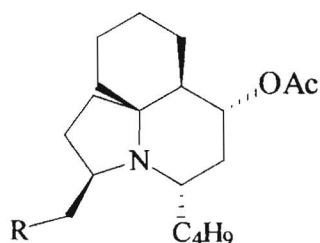


Cylindricine C : R = OH [3]  
 Cylindricine D : R = OMe [4]  
 Cylindricine E : R = OAc [5]  
 Cylindricine F : R = SCN [6]

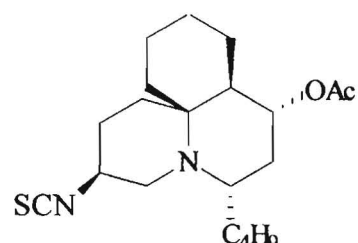


Cylindricine G [7]

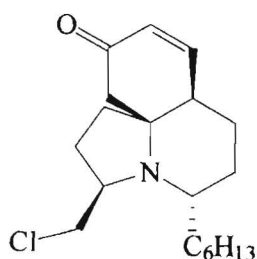
Further material yielded the minor alkaloids cylindricines C-G.<sup>5</sup> HRMS together with infrared (IR) and NMR spectroscopy revealed that cylindricines C-G were tricyclic tertiary amines with a perhydropyrrolo[2,1-*j*]quinoline skeleton similar to cylindricine A. Cylindricine C has a hydroxy group, cylindricine D has a methoxy group, cylindricine E has an acetoxy group and cylindricines F and G have a thiocyanate group. Cylindricines F and G are the first thiocyanates to be isolated from an ascidian. Cylindricines F and G are very similar in structure; the only difference is the length of the alkyl side chain; cylindricine F has a *n*-hexyl chain ( $\text{C}_6\text{H}_{13}$ ) while cylindricine G has a *n*-butyl chain ( $\text{C}_4\text{H}_9$ ).



Cylindricine H : R = SCN [8]  
 Cylindricine I : R = NCS [9]



Cylindricine J [10]

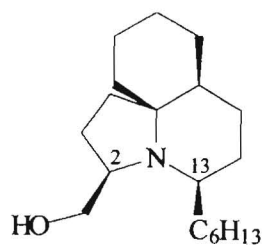


Cylindricine K [11]

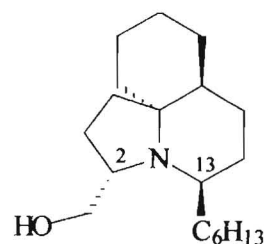
Four more alkaloids, cylindricines H-K, were isolated;<sup>17</sup> these were related to cylindricines A-G previously isolated. Their skeletons are similar to either cylindricine A or B, differences being the substituents and oxidation levels. HRMS showed that cylindricines H-J were isomeric, with the molecular formula  $C_{20}H_{32}N_2O_2S$ . They possess a *n*-butyl ( $C_4H_9$ ) side chain instead of a *n*-hexyl ( $C_6H_{13}$ ) side chain. Cylindricine H has a thiocyanate group like cylindricines F and G, while cylindricines I and J possess an isothiocyanate group. Cylindricines H and I have the cylindricine A skeleton and cylindricine J has the cylindricine B skeleton. The isothiocyanate group in cylindricine J is attached to a methine group rather than a methylene group. The major difference between cylindricines H-J and previously reported cylindricines is the replacement of the ketone functionality with an acetoxy group. Cylindricine K is unique in that it possesses a cyclohexenone ring. Snider and Liu<sup>31</sup> reported the first synthesis of ( $\pm$ ) cylindricine A [1], D [4] and E [5]. Heathcock and Liu<sup>6</sup> reported the synthesis of ( $\pm$ ) cylindricine A [1] and B [2]. Molander and Rönn<sup>32</sup> reported the first enantioselective synthesis of (-)-cylindricine C (-)-[3].

The cylindricines exhibit bioactivity against brine shrimp in a biomass and a DNA-repair-deficient yeast strain and also inhibit growth of murine leukemia and human solid tumor cell lines.<sup>10</sup>

### 1.2.3.2 Lepadiformine



Original structure  
of lepadiformine [12']

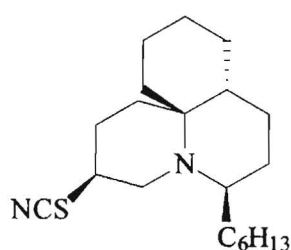


Revised structure  
of lepadiformine [12]

In 1994, Biard and co-workers isolated lepadiformine from a Tunisian ascidian *Clavelina lepadiformis*.<sup>9</sup> Its structure is similar to the cylindricines isolated from *Clavelina cylindrica*. Weinreb and co-workers<sup>33,34</sup> and Kibayashi<sup>35</sup> reported the first synthesis of the proposed

original structure of lepadiformine [12']. They found that the synthetic material was different to the natural lepadiformine. Pearson and co-workers then synthesized the remaining three diastereomers at C<sub>2</sub> and C<sub>13</sub>, however none of these compounds were found to be identical to the natural alkaloid.<sup>36,37</sup> Thus the original structure of the alkaloid had to be revised to be epimeric at the quaternary carbon and at C<sub>2</sub> thus constituting the *trans*-fused perhydroquinoline ring system. Kibayashi and co-workers reported the first synthesis of the revised structure of lepadiformine [12].<sup>8</sup> Lepadiformine shows moderate *in vitro* cytotoxic activity against various tumor cell lines.<sup>9</sup>

### 1.2.3.3 Fascicularin



Fascicularin [13]

Fascicularin is a novel marine tricyclic alkaloid isolated from the Micronesian ascidian *Nephteis fascicularis*. Its structure was reported in 1997 by Patil and co-workers.<sup>7</sup> Fascicularin possesses a perhydropyrido[2,1-*j*]quinoline ring system and is thus structurally similar to the cylindricines and lepadiformine. Little work has been done on this alkaloid. There are, to date, two reported syntheses of (±) fascicularin [13].<sup>8,38</sup> Fascicularin has selective activity against a DNA repair-deficient organism and is cytotoxic to Vero cells with an IC<sub>50</sub> of 14 µg/mL.<sup>7</sup> In the following section the approaches of other workers to assemble the spirocyclic core of the cylindricines, lepadiformine and fascicularin are reviewed.

### 1.3 Reported syntheses of the cylindricines, lepadiformine and fascicularin.

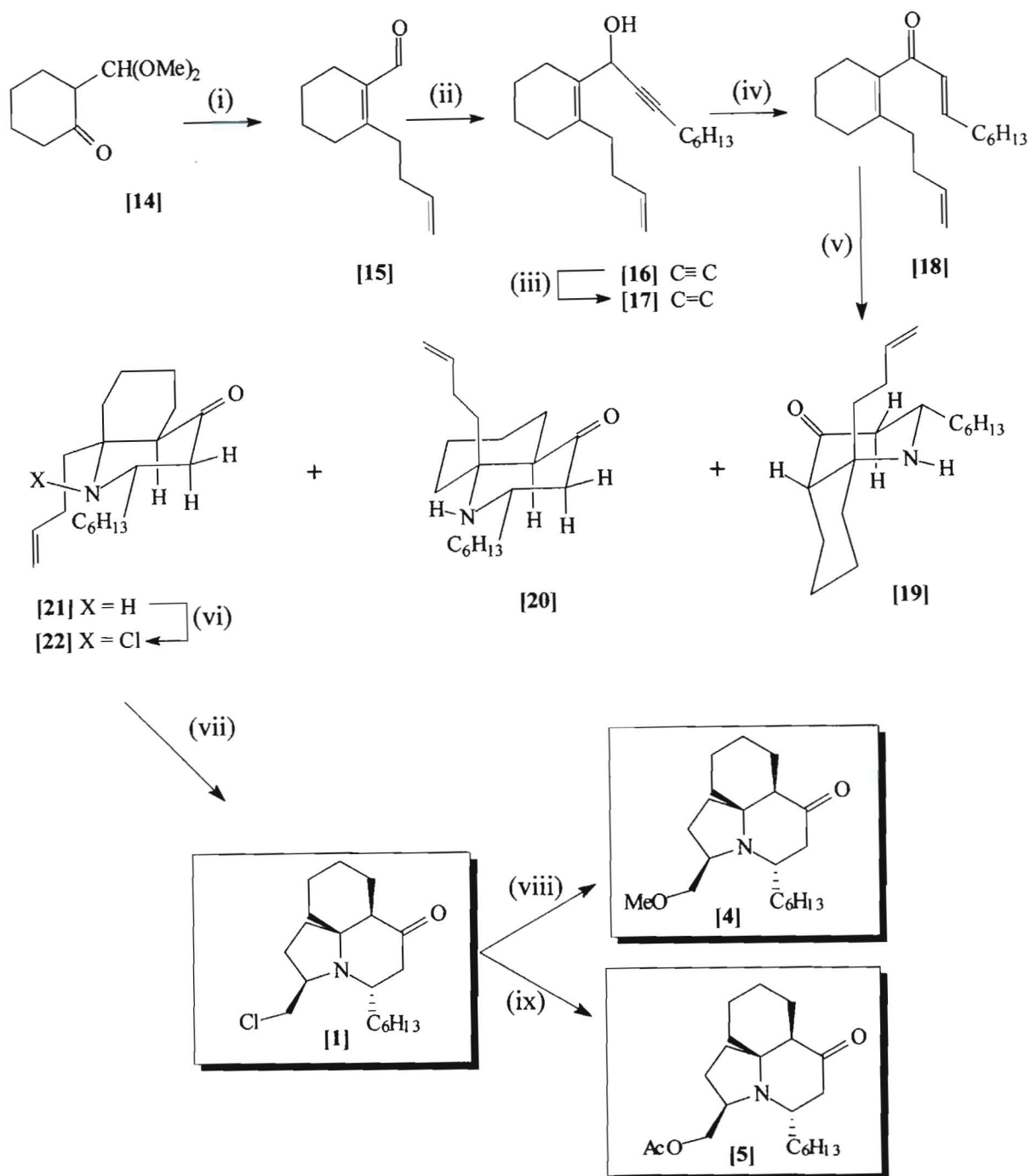
The unique structure of these alkaloids as tricyclic systems which contain an azaspirocyclic, and their interesting biological activities make them ideal targets for total synthesis. Their limited distribution in nature poses a challenge to organic chemists to synthesize more material to enable extensive biological tests to assess the bioactivity of these fascinating natural



products. Several approaches to the construction of these azatricyclic ring systems have been reported.

**Snider and Liu**<sup>31</sup> reported the synthesis of ( $\pm$ ) cylindricine A [1], D [4] and E [5]. **Heathcock and Liu**<sup>6</sup> reported the synthesis of ( $\pm$ ) cylindricine A [1] and B [2]. **Molander and Rönn**<sup>32</sup> reported the first enantioselective synthesis of (–)-cylindricine C (–)-[3]. There has been no reported total synthesis or approaches to the synthesis of cylindricines F-K. **Oppolzer** with **Bagley**<sup>39</sup> in one paper, and with **Bochet**<sup>40</sup> in another paper, reported the asymmetric synthesis of the spirocyclic core of lepadiformine and the cylindricine alkaloids. **Weinreb**<sup>33,34</sup> and **Kibayashi**<sup>35</sup> reported the first total synthesis of the putative structure of lepadiformine [12'] while **Pearson and co-workers**<sup>36,37</sup> reported the synthesis of the remaining three stereoisomers at C2 and C13. **Kibayashi and co-workers**<sup>8</sup> reported the first synthesis of the revised structure of lepadiformine ( $\pm$ )-[12] as well as the first synthesis of fascicularin ( $\pm$ )-[13]. This section will review the approaches of these workers to the synthesis of cylindricines A-E [1-5], lepadiformine [12] and fascicularin [13]. We are primarily interested for the purpose of this project in how these workers achieved the construction of the azaspirocyclic core of these alkaloids.

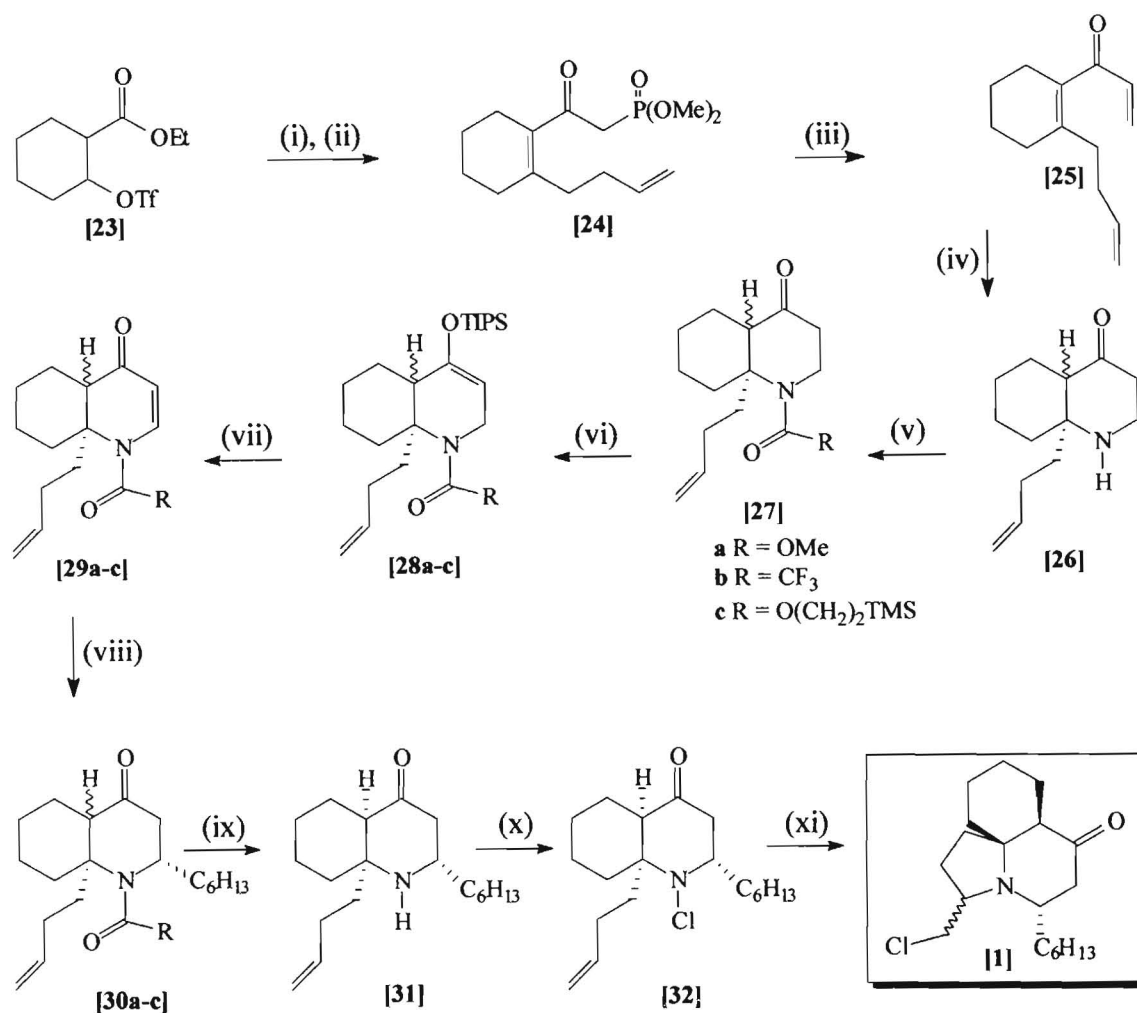
**Snider and Liu** published the first total synthesis of cylindricines A [1], D [4] and E [5] in racemic form, in 1997.<sup>31</sup> Cylindricine A [1] was synthesized in 7 steps and in 5% overall yield (Scheme 1.1). The most important feature in their route is the double Michael addition of  $\text{NH}_3$  to the dienone [18] to give the piperidinone [21] as one of the products. The first step was the Grignard addition of 3-butenylmagnesium bromide to the acetal ketone [14], followed by hydrolysis of the acetal and dehydration to give the cyclohexenecarboxaldehyde [15]. Addition of 1-octynyllithium to the aldehyde [15] gave the alcohol [16], which was further reduced with  $\text{LAH}/\text{NaOMe}$ <sup>31,41</sup> to give alcohol [17]. Alcohol [17] was very unstable and underwent allylic rearrangement on chromatography. Thus crude allylic alcohol [17] was oxidized by  $\text{MnO}_2$  to give the divinylketone [18]. The double Michael addition of  $\text{NH}_3$  to the divinylketone [18] afforded 47% of piperidinone [21], and its two isomers, 9% of [19] and 34% of [20]. Piperidinone [21] was reacted with *N*-chlorosuccinimide to give *N*-chloropiperidinone [22]. The step of paramount interest for this project is the final radical cyclization to create the spirofused ring (step vii).



**Scheme 1.1** (i) (a)  $C_4H_7MgBr$ ,  $Et_2O$ ; (b)  $HCl$ , heat, 60%; (ii)  $LiC\equiv CC_6H_{13}$ ,  $THF$ , 64%; (iii)  $LAH$ ,  $NaOMe$ ,  $THF$ ; (iv)  $MnO_2$ ,  $CH_2Cl_2$ , 71% from [16]; (v)  $NH_3$ ,  $H_2O$ ,  $MeOH$ ,  $NH_4Cl$ , 65 °C, 47%; (vi)  $N$ -chlorosuccinimide,  $CH_2Cl_2$ , 86%; (vii)  $CuCl$ ,  $CuCl_2$ ,  $THF$ ,  $AcOH$ ,  $H_2O$ , 41%; (viii)  $NaOMe$ ,  $MeOH$ , 32%; (ix)  $NaOAc$ ,  $MeOH$ , 91%.

Radical cyclization of  $N$ -chloropiperidinone [22] using  $CuCl$  and  $CuCl_2$  afforded the ( $\pm$ )-cylindricine A [1]. Treatment of ( $\pm$ )-cylindricine A [1] with  $NaOMe$  in  $MeOH$  resulted in the formation of ( $\pm$ )-cylindricine D [4]. Treatment of ( $\pm$ )-cylindricine A with  $NaOAc$  in  $MeOH$  afforded cylindricine E [5].

**Heathcock and Liu** reported the total synthesis of ( $\pm$ )-cylindricine A [1] and B [2], in 11 steps and in 19% overall yield (Scheme 1.2).<sup>6</sup> The characteristic feature of this route is the Stella's metal-coordinated radical cyclization to furnish the spirofused ring (step xi). The first step was the conversion of  $\beta$ -trifluoromethanesulfonyloxy ester [23] into  $\beta$ -substituted ester using the Gilman cuprate formed from CuCN and 4-lithio-1-butene.



**Scheme 1.2** (i)  $\text{CH}_2\text{CHCH}_2\text{CH}_2\text{Cu}(\text{CN})\text{Li}$ ,  $\text{Et}_2\text{O}$ ; (ii)  $\text{LiCH}_2\text{P}(\text{O})(\text{OMe})_2$ , THF, 95%; (iii) NaH,  $(\text{CHO})_n$ , benzene, 86%; (iv)  $\text{NH}_3$ -sat. EtOH, conc.  $\text{NH}_4\text{OH}$ , 97%; (v)  $\text{ClCO}_2\text{Me}$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ ; (or) TFAA,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; (or) TEOC-Osu,  $\text{K}_2\text{CO}_3$ ,  $\text{CH}_3\text{CN}$ , 81-96%; (vi), LDA, TIPSTf, THF, 89-97%; (vii) CAN, DMF, 90-95%; (viii)  $\text{C}_6\text{H}_{13}\text{MgBr}$ ,  $\text{CuBr}\cdot\text{Me}_2\text{S}$ ,  $\text{BF}_3\cdot\text{OEt}_2$ , THF, 77-90%; (ix) TBAF, THF; (x) *N*-chlorosuccinimide,  $\text{CH}_2\text{Cl}_2$ , 97%; (xi)  $\text{CuCl}$ ,  $\text{CuCl}_2$ , THF,  $\text{H}_2\text{O}$ , AcOH, 85%.

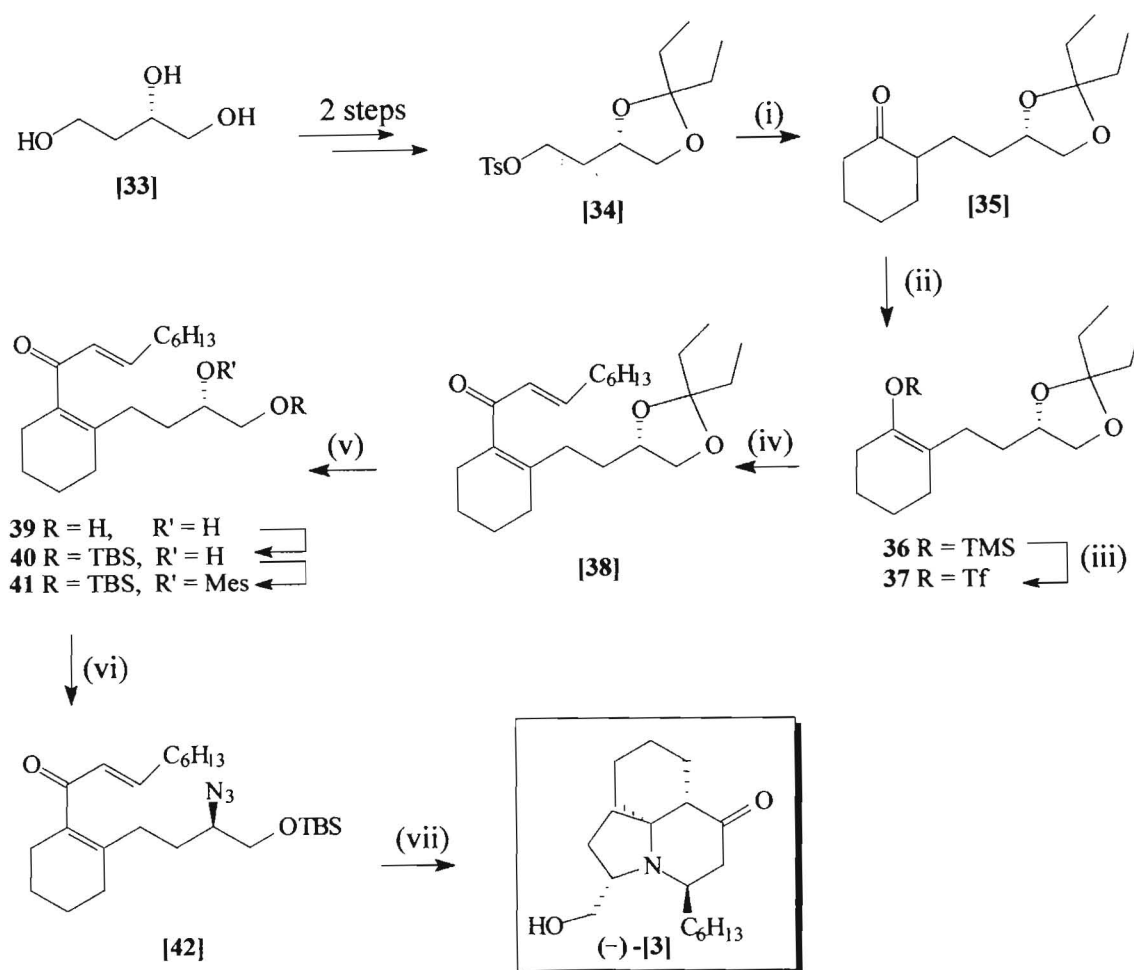
The  $\beta$ -substituted ester was subsequently converted into the  $\beta$ -ketophosphonate [24] using the lithium anion of dimethylmethylphosphonate [ $\text{LiCH}_2\text{P}(\text{O})(\text{OMe})_2$ ]. Horner-Emmons reaction



with a  $\beta$ -ketophosphonate [24] and paraformaldehyde gave the divinylketone [25] in an excellent 86% yield. Double Michael reaction on the divinylketone [25] afforded the octahydroquinolinone [26]. Nitrogen protection of the octahydroquinolinone [26] using  $\text{ClCO}_2\text{Me}$  or TFAA or TEOC-Osu gave the compounds [27a], [27b] and [27c], respectively. The next step was enolate formation and the subsequent trapping of the enolate as its triisopropylsilyl enol ether [28]. Ceric ammonium nitrate oxidation of the triisopropylsilyl enol ether [28] afforded the vinylogous amide [29].<sup>6,42,43</sup> The hexyl side chain was introduced by the conjugate addition of the cuprate formed by  $\text{C}_6\text{H}_{13}\text{MgBr}$ ,  $\text{CuBr}\cdot\text{Me}_2\text{S}$  and  $\text{BF}_3\cdot\text{OEt}_2$  to the vinylogous amide [29] to give carbamate [30].<sup>6,44,45</sup> Treatment of the carbamate [30c] with TBAF gave the desired free amine [31]. Attempted nitrogen deprotection of the other carbamates [30a] and [30b] failed; only the starting material was recovered. Treatment of the amine [31] with NCS afforded the *N*-chloroamine [32]. Stella's metal-coordinated radical cyclization<sup>6,46,47</sup> of *N*-chloroamine [32] using  $\text{CuCl}$  and  $\text{CuCl}_2$  in aqueous acetic acid afforded a mixture of cylindricine A and *epi*-cylindricine A. The two isomers were separated and cylindricine A [1] was allowed to convert to a mixture of cylindricine A [1] and B [2].

**Molander and Rönn** reported the first total synthesis of (–)-cylindricine C, in 11 steps with an overall yield of 12%.<sup>32</sup> The key feature of their route was the reduction of the azide [42] followed by the double Michael addition to form the remaining two rings and three stereocentres in one process (Scheme 1.3). The first step involved the selective protection of the 1,2-diol moiety of 1,2,4-butanetriol [33], followed by the conversion of the remaining primary alcohol into a tosylate [34]<sup>32,48</sup> using tosyl chloride and  $\text{Et}_3\text{N}$ . The tosylate [34] was coupled with the enolate of cyclohexanone to give ketone [35], this was followed by enolate formation, and the subsequent trapping of the enolate as a silyl enol ether [36]. The silyl enol ether [36] was then converted into the corresponding enol triflate [37]. Palladium-catalyzed Stille carbonylative coupling<sup>49,50</sup> of the vinyl triflate [37] with (*E*)-trimethyl-1-octenylstanne afforded the divinylketone [38]. Hydrolysis of the acetal gave the diol [39], this was followed by selective protection of the primary alcohol with the TBS group [40] and mesylation of the secondary alcohol to give the mesylate [41].

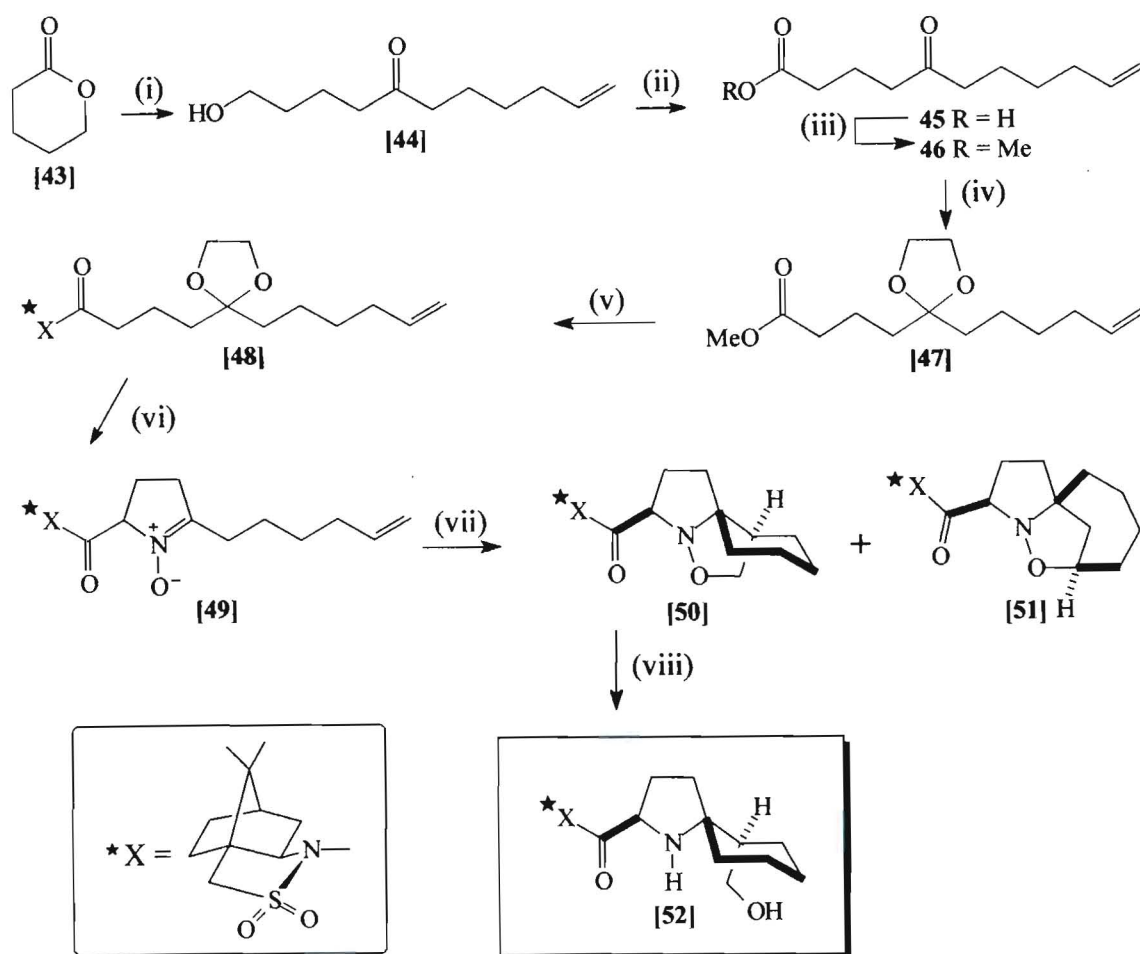




**Scheme 1.3** (i) (a) Cyclohexanone dimethylhydrazone, LDA then [34], THF; (b)  $\text{Cu}(\text{OAc})_2$ , THF/ $\text{H}_2\text{O}$ , 77%; (ii) (a)  $(i\text{-Pr})_2\text{NMgBr}$ ,  $\text{Et}_2\text{O}$ ; (b)  $\text{TMSCl}$ ,  $\text{Et}_3\text{N}$ , HMPA; (iii)  $\text{MeLi}$ , THF,  $\text{Tf}_2\text{NPh}$ , TMEDA, 86% from [35]; (iv) (*E*)-trimethyl-1-octenylstannane,  $\text{LiCl}$ ,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{CO}(\text{g})$ , 79%; (v) (a)  $\text{PdCl}_2(\text{MeCN})_2$  cat.,  $\text{MeCN}:\text{H}_2\text{O}$  9:1, 83%; (b)  $\text{TBSCl}$ ,  $\text{NEt}_3$ , DMAP,  $\text{CH}_2\text{Cl}_2$ ; (c)  $\text{MsCl}$ ,  $\text{NEt}_3$ ; (vi)  $\text{NaN}_3$ , DMF,  $60^\circ\text{C}$ , 86% from [39]; (vii) TBAF, THF, 45%.

The mesylate [41] was converted into the corresponding azide [42] using sodium azide. The azide [42] had all the carbons required for the alkaloid. The second and the third ring were formed in one process. Reduction of the azide to an amine using  $\text{CrCl}_2$ ,<sup>6,51,52</sup> followed by double Michael addition reaction and deprotection of the primary alcohol gave (-)-cylindricine C (-)-[3].

Bagley *et al.*<sup>39</sup> reported the asymmetric synthesis of the spirocyclic core of lepadiformine and the cylindricine alkaloids, in 7 steps with an overall yield of 19%.

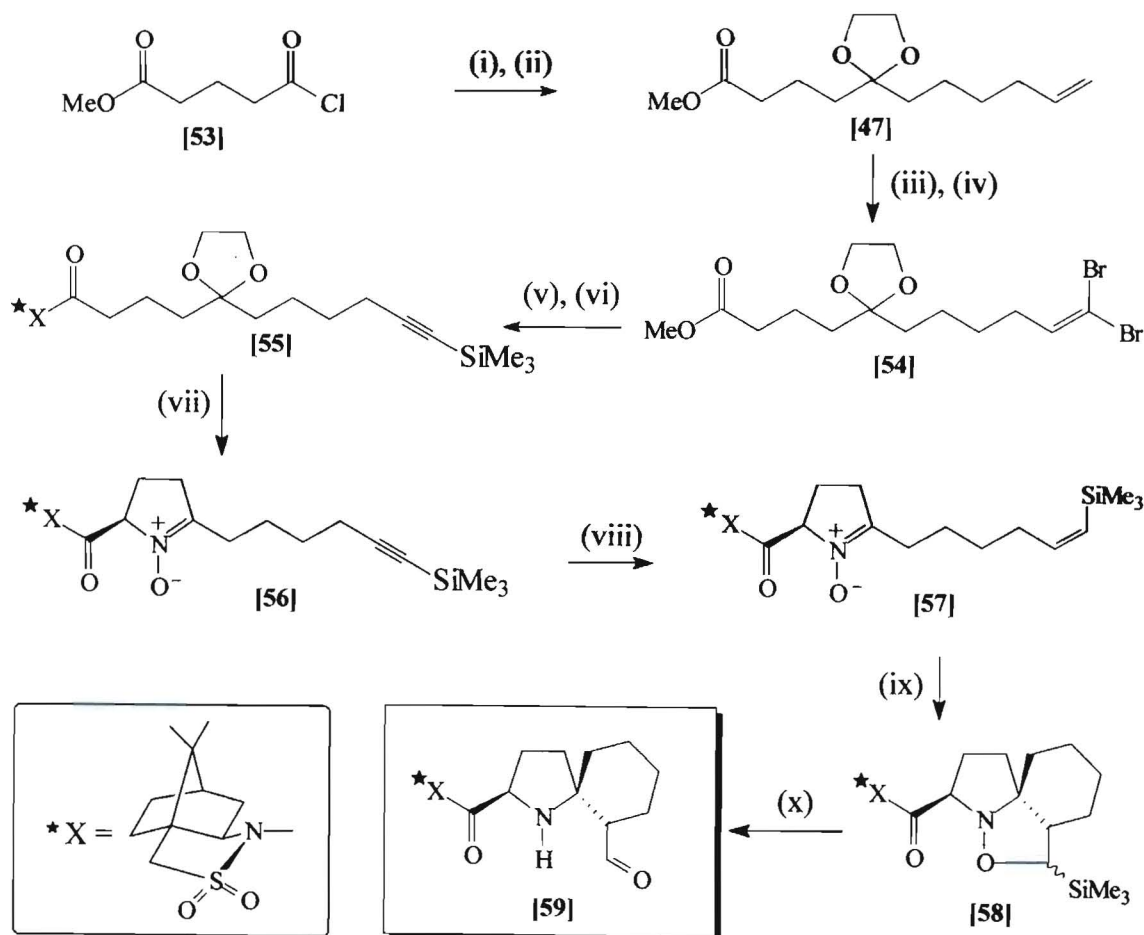


**Scheme 1.4** (i)  $\text{ClCe}(\text{CH}_2)_4\text{CH}=\text{CH}_2$ , 0.2M in THF, 0.5M HCl; (ii) PDC, DMF, 74%; (iii)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ; (iv)  $(\text{HOCH}_2)_2$ , PPTS, PhH, 98%; (v)  $\text{AlMe}_3$ , toluene, 78%; (vi) NaHMDS, THF, 1-chloro-1-nitrosocyclohexane, conc. HCl, 80%; (vii) 0.01M of [49], toluene,  $\Delta$ ; (viii) Zn, AcOH/H<sub>2</sub>O (1:1), 53%.

The key feature of this route (step vii, Scheme 1.4) and the next route (step ix, Scheme 1.5), is the intramolecular nitronediene dipolar cycloaddition, which results in the formation of the spirocyclic compounds [50] and [58], respectively, key intermediates to lepadiformine and the cylindricines. The synthesis in Scheme 1.4 begins with the four step synthesis of acetal [47] from  $\delta$ -valerolactone [43]. The first step involved the addition of 6-hex-1-enylcerium(III) to  $\delta$ -valerolactone [43] to give the undecenol [44]. Oxidation of undecenol [44] with pyridinium dichromate gave undecenoic acid [45]. Esterification and acetalisation of the keto-acid [45] gave the acetal, methyl undecenoate [47]. Acylation of (2*R*)-bornane-10,2-sultam with methyl undecenoate [47] gave acylsultam [48]. Deprotonation and subsequent trapping of the enolate with 1-chloro-1-nitrosocyclohexane followed by the acid catalysed hydrolysis of the acetal resulted in the formation of the nitrone [49]. Reflux of nitrone [49] in toluene resulted in the

fused tricycle [50] and bridged cyclo product [51], in 41% and 47% yield, respectively. N-O bond cleavage of the fused cycloadduct [50] using acetic acid and zinc metal gave 1-azaspiro[4,5]decane [52], an intermediate to the cylindricines and lepadiformine.

**Oppolzer and co-workers**<sup>40</sup> also reported an asymmetric synthesis of the spirocyclic core of the cylindricine-type alkaloids, slightly different to the route depicted in Scheme 1.4.



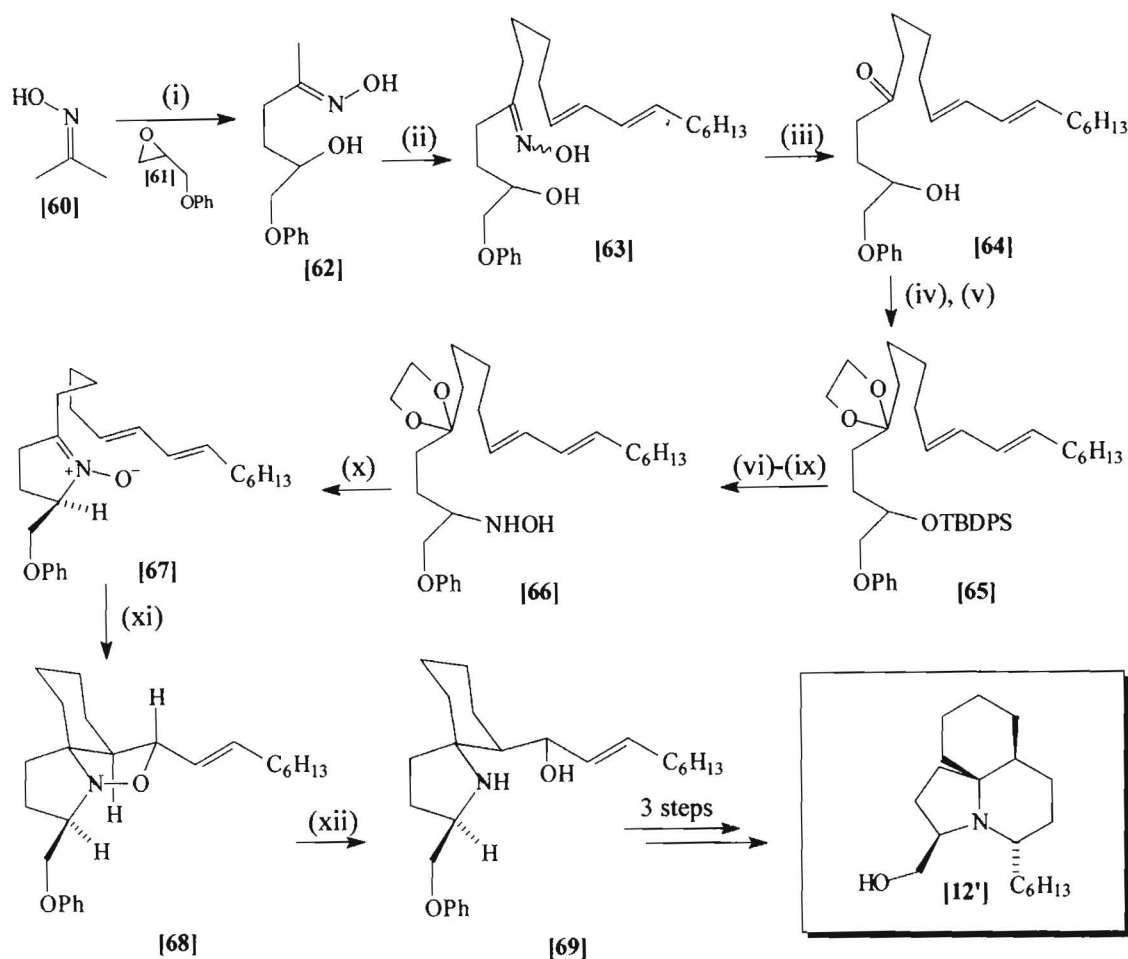
**Scheme 1.5** (i)  $C_6H_{11}MgBr$ , THF; (ii)  $(HOCH_2)_2$ , PPTS, PhH, 87% from [53]; (iii)  $O_3$ , MeOH,  $Me_2S$ , 89%; (iv)  $CBr_4$ ,  $PPh_3$ , Zn,  $CH_2Cl_2$ , 66%; (v)  $AlMe_3$ , toluene, 68%; (vi)  $t-BuLi$ ,  $TMSCl$ , 63%; (vii)  $NaHMDS$ , THF, 1-chloro-1-nitrosocyclohexane, conc. HCl, 62%; (viii)  $Ni_2B-BER$ ,  $H_2$ , MeOH, 43%; (ix) PhH, heat, 0.01M, 62%; (x) HF-pyridine,  $CH_2Cl_2$ .

In this route there is a selective formation of only the fused cycloadduct [58] with no traces of the bridged cycloadduct [51] (Scheme 1.5). The spirocyclic compound [58] (Scheme 1.5) was synthesized in 9 steps with an overall yield of 5%. The synthesis begins with the four step preparation of dibrominated compound [54] from glutaric acid chloride monoester [53].



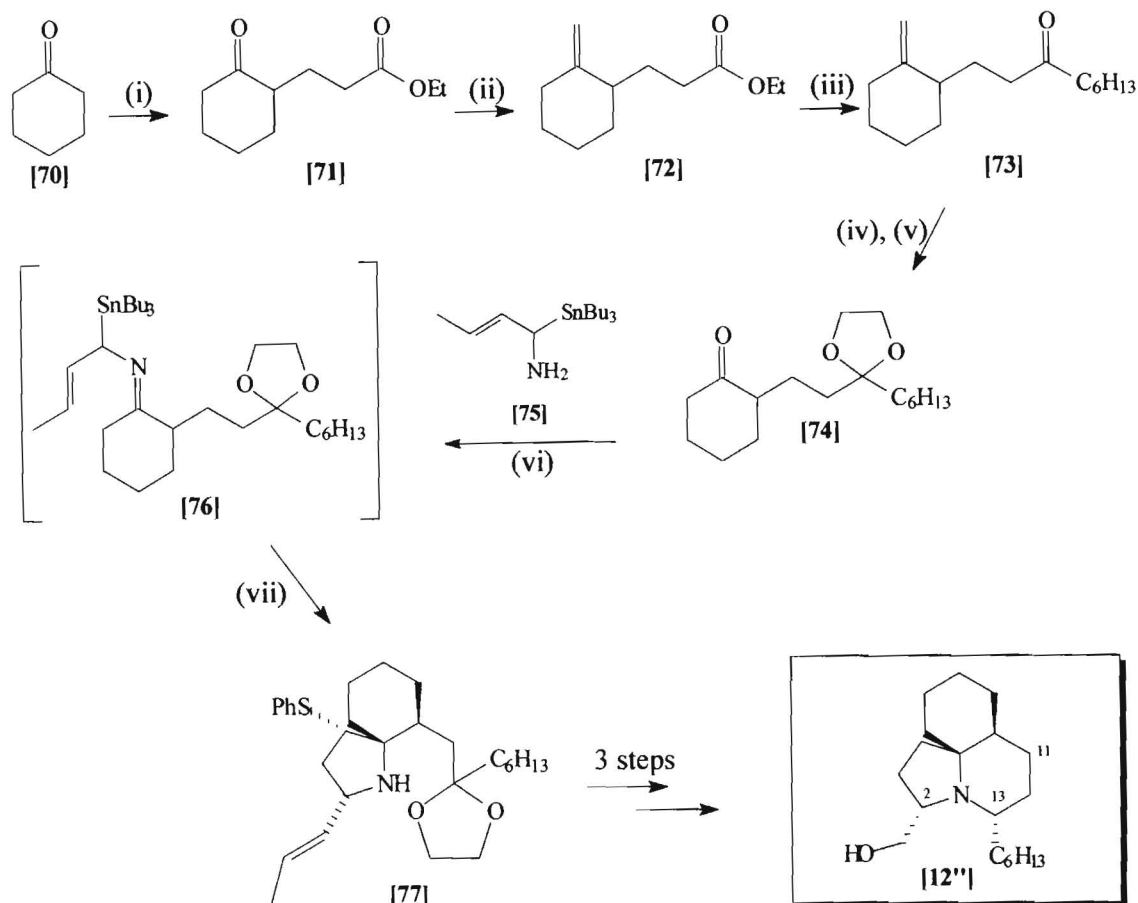
Addition of 5-hexenylmagnesium bromide followed by the ketone protection afforded the acetal [47]. Ozonolysis of the terminal olefin resulted in an aldehyde which was reacted with  $\text{CBr}_4$  and  $\text{PPh}_3$  to give vinyl dibromide [54]. Acylation of the (2*R*)-bornane-10,2-sultam with compound [54], followed by the addition of *t*-BuLi and TMSCl gave the alkynylsilane [55]. Enolate formation using NaHMDS and the subsequent trapping of the enolate using 1-chloro-1-nitrosocyclohexane followed by the acid-catalysed hydrolysis of the acetal gave a single diastereomer of the nitron [56]. Partial reduction of compound [56] with nickel boride borohydride resin ( $\text{Ni}_2\text{B-BER}$ ) gave the (*Z*)-vinylsilane [57]. Heating of [57] in benzene under reflux gave exclusively the spirocyclic product, isoxazolidine [58]. The isoxazolidine [58] was converted into the aldehyde [59], an intermediate to the cylindricalines and lepadiformine, upon treatment with HF-pyridine. This route showed the accessibility of the spirocyclic core of cylindricalines and lepadiformine by a stereo- and regio-selective 1,3-dipolar cycloaddition reaction.

**Weinreb and co-workers** reported the first synthesis of the putative structure of lepadiformine in a communication<sup>33</sup> and later in a full paper<sup>34</sup> (Scheme 1.6). Lepadiformine [12'] was synthesized in 15 steps with an overall yield of 5%. The most important feature of their route is the intramolecular dipolar cycloaddition [67]→[68] to form the spirofused core of lepadiformine. The synthesis began with the formation of (*E*)-oxime alcohol [62] from acetone oxime [60] and epoxide [61]. Subsequent regiospecific alkylation of oxime [62] with  $\text{C}_6\text{H}_{13}\text{CH}=\text{CHCH}=\text{CH}(\text{CH}_2)_3\text{I}$  afforded compound [63]. The next step was the conversion of the oxime [63] to ketone [64]. Protection of the secondary alcohol using a TBDPS group, followed by acetalisation of the ketone afforded the silyl ether acetal [65]. Removal of the silyl protecting group, oxidation of the resulting alcohol to the corresponding ketone, formation of the oxime and subsequent hydride reduction of the oxime afforded the hydroxylamine [66]. Dilute hydrochloric acid was used to convert the hydroxylamine [66] into nitron [67]. Nitron [67] was cyclized thermally to give isoxazolidine [68]. N-O bond cleavage of the isoxazolidine [68] using acetic acid and zinc gave amino alcohol [69]. Three additional steps completed the synthesis of lepadiformine [12'].



**Scheme 1.6** (i) *n*-BuLi, THF, [61] 86%; (ii) *n*-BuLi, THF,  $C_6H_{13}CH=CHCH=CH(CH_2)_3I$ , 76%; (iii)  $TiCl_3$ ,  $NH_4OAc$ ,  $H_2O/HOAc$  (1:1), dioxane, 86%; (iv)  $(HOCH_2)_2$ , *p*-TsOH, PhH, reflux, 97%; (v) TBDPSCl, imidazole,  $CH_2Cl_2$ , 92%; (vi) TBAF, THF, 99%; (vii) DMSO,  $CH_2Cl_2$ , 93%; (viii)  $NH_2OH \cdot HCl$ , pyr, EtOH, 100%; (ix)  $NaBH_3CN$ , 2N HCl, MeOH, 95%; (x) 3N HCl, THF, 92%; (xi) DMSO, 190 °C, 63%; (xii) Zn dust, HOAc, 91%.

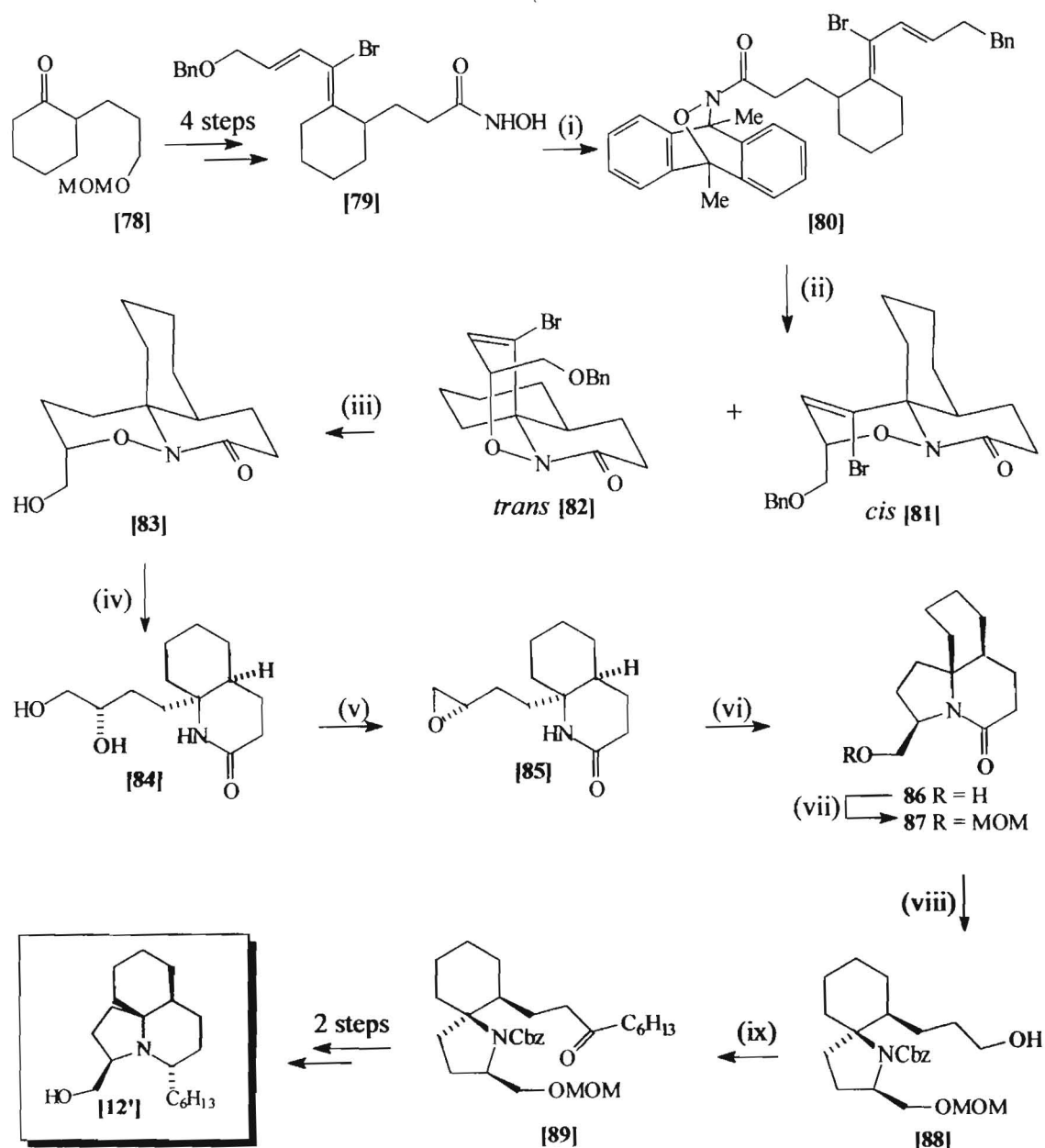
**Pearson and co-workers** reported the syntheses of the three remaining diastereomers of the putative structure of lepadiformine in both a communication<sup>37</sup> and a full paper.<sup>36</sup> Lepadiformine was synthesized in 10 steps with an overall yield of 0.4% (Scheme 1.7). The important step in this route is the formation of the spirofused compound [77] by reacting stannylimine [76] with *n*-BuLi and phenyl vinyl sulfide. The synthetic route began with a five step synthesis of 2-[2-(2-methyl-1,3-dioxonal-2-yl)ethyl]cyclohexanone [74] from cyclohexanone [70]. The first step was the preparation of the ketoester [71] from cyclohexanone [70] and ethyl acrylate using Stork's enamine method.



**Scheme 1.7** (i) (a) *p*-TsOH, pyrrolidine,  $-H_2O$ ; (b) ethyl acrylate,  $H_2O$ , 91%; (ii) Zn,  $PbCl_2$ ,  $TiCl_4$ ,  $CH_2Br_2$ , 61%; (iii)  $Me_2AlN(OMe)Me$ ,  $C_6H_{13}MgBr$ , 73%; (iv)  $(HOCH_2)_2$ ,  $TMSCl$ ,  $PhH$ , 84%; (v)  $O_3$ ,  $CH_2Cl_2$ ,  $NaHCO_3$ ,  $MeOH$ , 45%; (vi)  $AlMe_3$ ,  $PhH$ ,  $0^\circ C$ ; (vii) *n*-BuLi,  $CH_2=CHSPh$ ,  $H_2O$ , 41% from [74].

This was followed by the methylenation of the ketone to give the ester [72]. The ester was converted into the ketone [73] using  $Me_2AlN(OMe)Me$  and  $C_6H_{13}MgBr$ . Carbonyl protection and ozonolysis of alkene [73] afforded the ketone [74]. The ketone [74] was condensed with the amine [75], to give the stannylimine [76]. Without purification, treatment of the imine [76] with phenyl vinyl sulfide and *n*-BuLi afforded the spirofused azabicyclic compound [77]. Tin-lithium exchange of stannane [76] with *n*-BuLi produced the 2-azapentadienyl anion, which participated in a  $[\pi 4s + \pi 2s]$  cycloaddition reaction with phenyl vinyl sulfide to afford the spirocyclic pyrrolidine [77].<sup>37</sup> Three more steps led to the total synthesis of 2,13-diepilepadiformine [12''] or 2-*epi*-11-deoxycylindricine C. Pearson used the same methodology to synthesize the remaining two of the four diastereomers of lepadiformine.

**Kibayashi and co-workers**<sup>35</sup> reported a stereocontrolled approach to the proposed structure of lepadiformine, in 15 steps with an overall yield of 1% (Scheme 1.8).



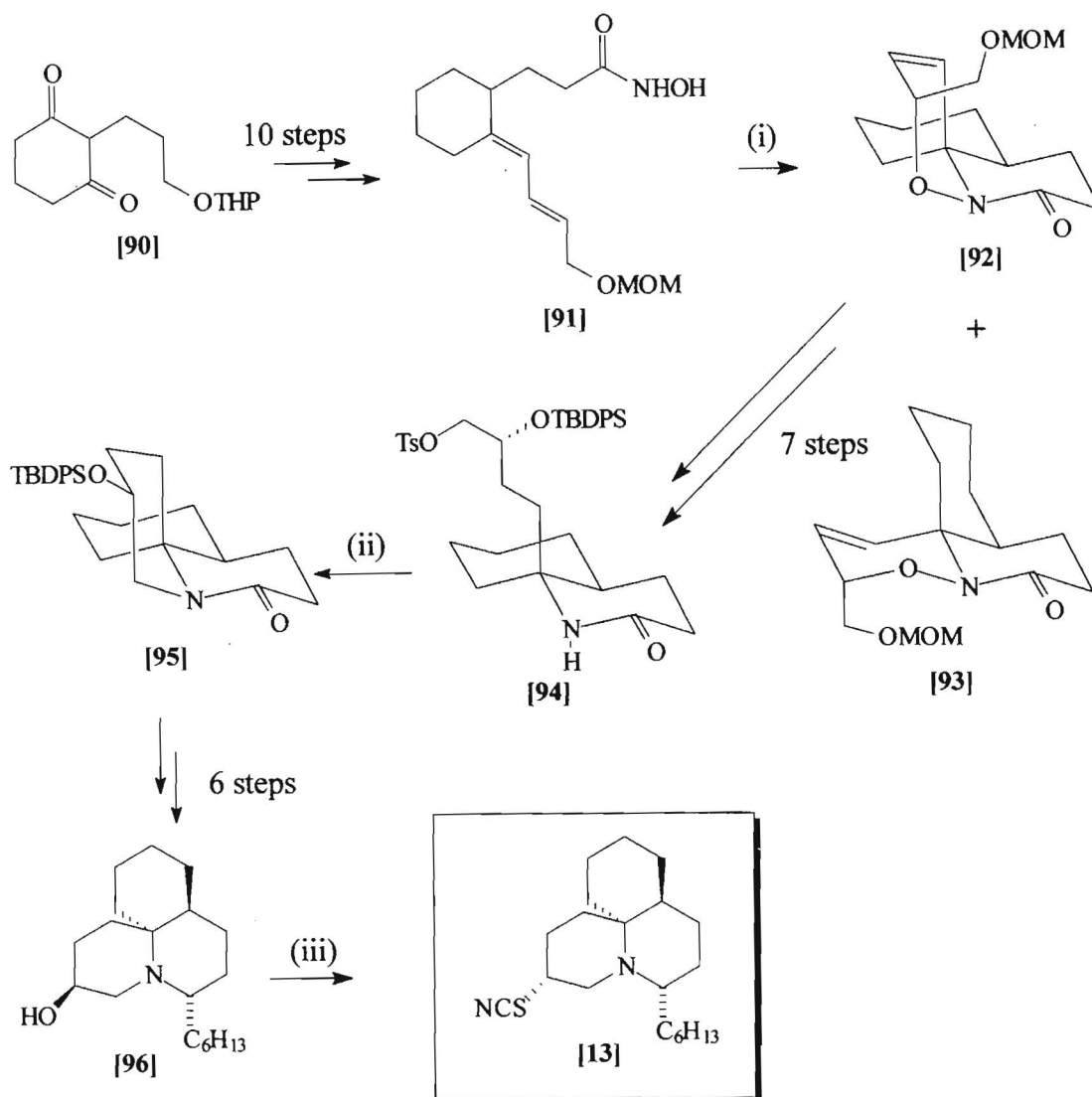
**Scheme 1.8** (i)  $Pr_4NIO_4$ ,  $CHCl_3$ , 9,10-dimethylantracene, 84%; (ii) benzene, reflux, 75%; (iii)  $H_2$ , Pd-C,  $Et_3N$ , MeOH, 63%; (iv) Na(Hg),  $Na_2HPO_4$ , EtOH, 97%; (v) MsCl, 2,4,6-collidine, NaOH, THF-MeOH, 65%; (vi) NaH, THF, 87%; (vii) MOMCl,  $i-Pr_2NEt$ , 93%; (viii) (a)  $BH_3 \cdot NH_3$ , BuLi; (b) CbzCl,  $Na_2CO_3$ , 78%; (ix) (a) DMSO,  $(COCl)_2$ ,  $Et_3N$ ,  $CH_2Cl_2$ ; (b)  $C_6H_{11}MgBr$ ,  $Et_2O$ ; (c) PCC,  $CH_2Cl_2$ , 66%.



The first important feature is the intramolecular hetero Diels-Alder reaction of [80].<sup>35</sup> The second important step is the treatment of lactam [85] with NaH in refluxing THF causing the regioselective formation of the five-membered spirofused compound [86]. Their route begins with the four step synthesis of hydroxamic acid [79] from the cyclohexanone derivative [78]. Oxidation of the hydroxamic acid [79] in the presence of 9,10-dimethylanthracene gave compound [80]. Compound [80] underwent intramolecular cyclisation to give the tricyclic diastereomeric mixture of *cis* product [81] and *trans* product [82] in a 5.5:1 ratio. Catalytic reduction of the two diastereomers gave only the *cis*-fused isomer [83]. Reductive cleavage of the N-O bond gave the diol [84]. The diol [84] was converted into the epoxide [85] via selective mesylation of the primary alcohol followed by treatment with alkali. Intramolecular cyclization with concomitant epoxide ring opening gave the tricyclic compound [86]. Compound [86] underwent lactam ring opening, followed by *N*-protection to give the alcohol [88]. Swern oxidation of alcohol [88] followed by Grignard reaction with C<sub>6</sub>H<sub>11</sub>MgBr, and PCC oxidation gave the ketone [89]. Catalytic hydrogenation of the ketone [89] and removal of the MOM protecting group gave lepadiformine [12'].

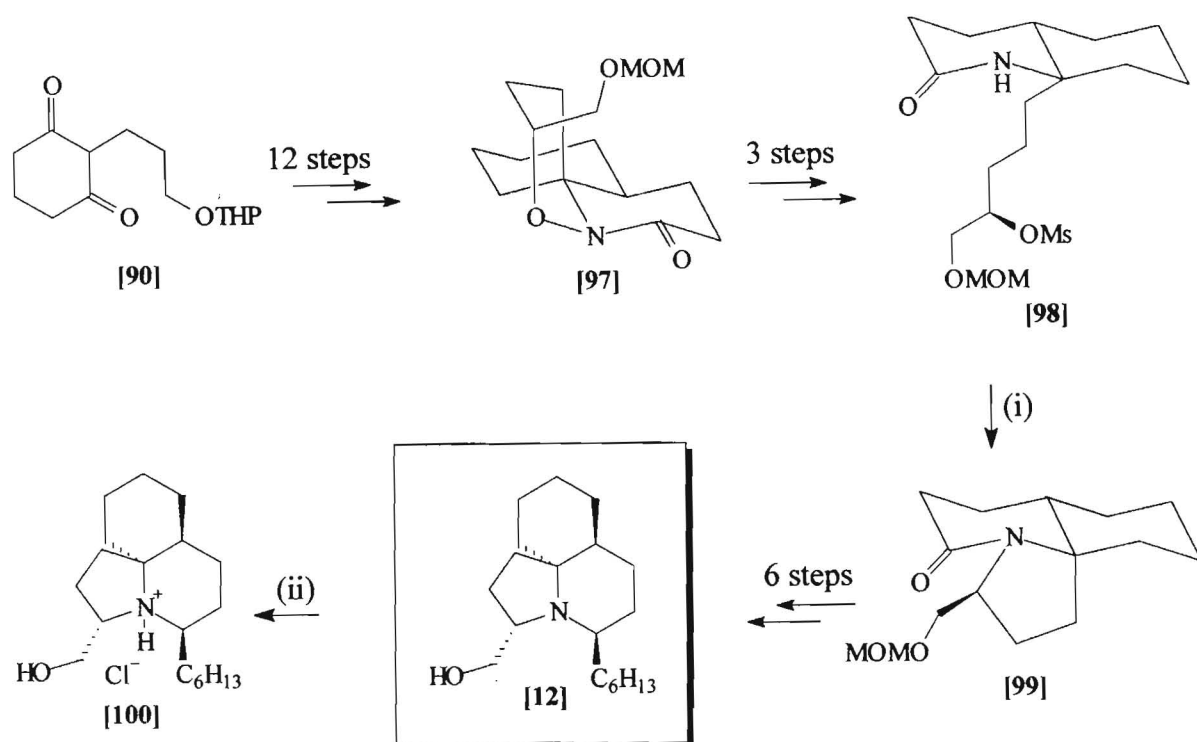
**Kibayashi and co-workers** also reported the first total synthesis of (±)-lepadiformine (±)-[12] and (±)-fasicularin (±)-[13].<sup>8</sup> The preliminary steps towards the synthesis of the two alkaloids were the same. Scheme 1.9 shows the route to the synthesis of fasicularin [13], in 25 steps with an overall yield of 2%. The most important feature in the synthesis of fasicularin [13] is the intramolecular acylnitroso-Diels-Alder reaction of diene [91], which prefers formation of the *trans*-product [92]. Tricyclic compound [92] was transformed into lactam [94] in 7 steps. Another important step is the conversion of lactam [94] into the spiro tricyclic compound [95], using NaH in refluxing THF. Lactam [95] was converted into tricycle [96] in 6 steps. The last reaction was the Mitsunobu condensation with thiocyno acid, which proceeded with complete inversion of configuration to give (±)-fasicularin (±)-[13].





**Scheme 1.9** (i)  $Pr_4NIO_4$ ,  $H_2O$ - $MeOH$  (5:1), 84%; (ii)  $NaH$ ,  $THF$ , reflux, 99%; (iii)  $HSCN$ ,  $Ph_3P$ ,  $DEAD$ , benzene, 20%.

Furthermore, **Kibayashi and co-workers** reported the first total synthesis of lepadiformine ( $\pm$ ) [12], in 22 steps with an overall yield of 4% (Scheme 1.10).<sup>8</sup> Diketone [90] was transformed into azatriacycle [97] in 12 steps. Azatriacycle [97] underwent reductive N-O bond cleavage followed by mesylation of the secondary alcohol, to provide mesylate [98]. Base treatment of mesylate [98] led to the formation of the third ring of spiro-fused tricyclic compound [99]. Six further steps resulted in the formation of ( $\pm$ )-lepadiformine ( $\pm$ )-[12]. Treatment of ( $\pm$ )-[12] with methanolic HCl resulted in the formation of hydrochloride salt [100]. The NMR data of ( $\pm$ )-[12] were different from that of natural lepadiformine, but the NMR data of the hydrochloride salt [100]

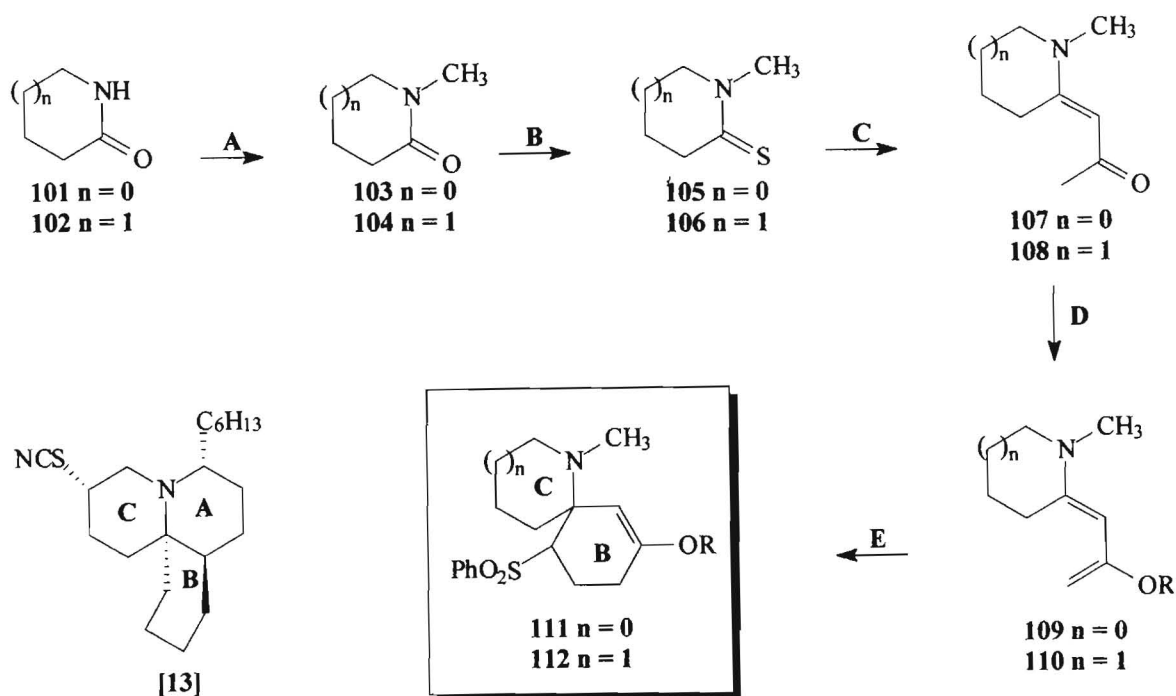


**Scheme 1.10** (i) *t*-BuOK, THF, 91%; (ii) 1N HCl-MeOH.

matched those of the isolated material. Thus lepadiformine was isolated as its hydrochloride salt (this is understandable because the isolation of the natural alkaloid was achieved by evaporation of an acidic solution [MeOH-1N HCl 99:1] of the chromatography fractions).<sup>8</sup> In the next section the specific aims of this project will be presented.

#### 1.4 Aims

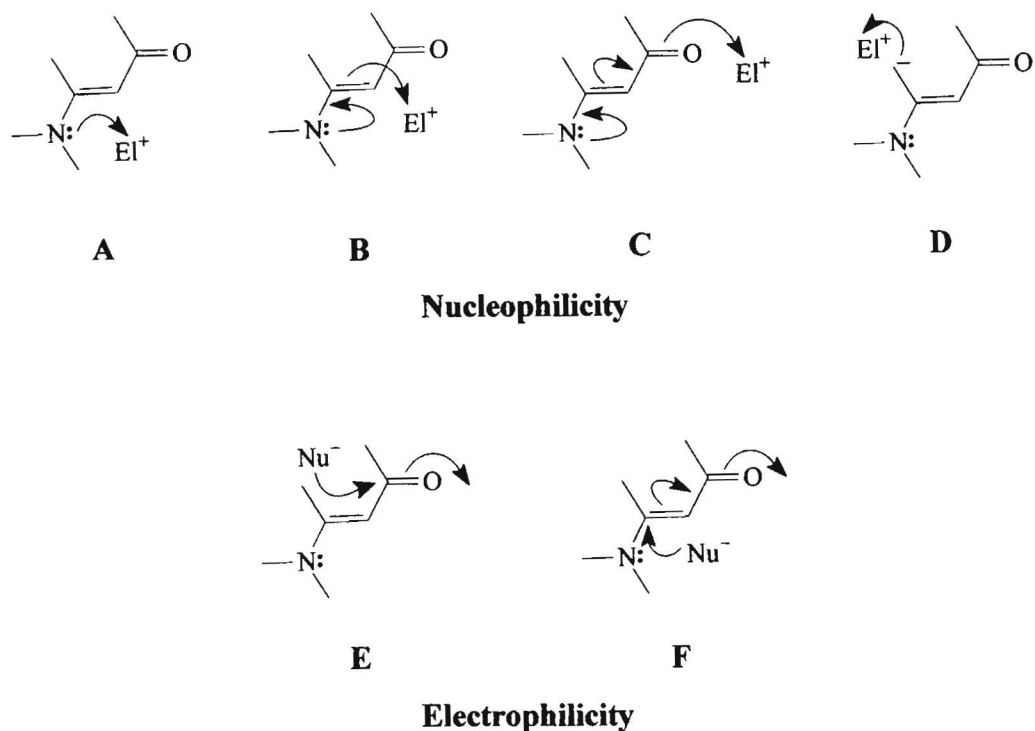
The first aim of this project is the development of methodology for the construction of model compounds that resemble the spirocyclic core of the cylindricine-like compounds (Scheme 1.11). Thus spirocycle [111] will serve as a model for cylindricines A [1], C-I [3-9] and K [11] as well as lepadiformine [12] while spirocycle [112] will serve as a model for cylindricines B [2] and J [10] as well as fascicularin [13]. Inspection of our approach will show that it is completely different to the reported approaches reviewed in Section 1.3.



Scheme 1.11

The major goal is the preparation of the azaspirocycles [111] and [112]. The first step involves the preparation of the thiolactams [105] and [106], from 2-pyrrolidinone [101] and 2-piperidinone [102], by *N*-methylation using sodium hydride and iodomethane (*step A*) and the thionation of the carbonyl group using Lawesson's reagent (*step B*). As these are model studies we chose the simplest alkyl group, namely methyl, for nitrogen. 1-Methyl-2-pyrrolidinone [103] is commercially available so there is no need for the *N*-methylation of 2-pyrrolidinone. Transformation of the thiolactams [105] and [106] into the corresponding vinylogous amides [107] and [108] is accomplished by using the Eschenmoser coupling reaction<sup>53</sup> between the thiolactam and bromoacetone (*step C*).

Vinylogous amides are versatile intermediates that combine the ambident nucleophilicity of the enamine with the ambident electrophilicity of enones (Figure 1).<sup>54,55</sup> The enamine nucleophilicity at the nitrogen and carbon can be extended to the carbonyl oxygen atom by conjugation (structures A-C). In addition, deprotonation with a strong base can provide an additional nucleophilic site  $\beta$  to nitrogen (structure D). The systems also have enone character and hence may act as electrophiles at the carbon atoms  $\alpha$  and  $\gamma$  to N (structures E and F).<sup>57</sup>



**Figure 1**

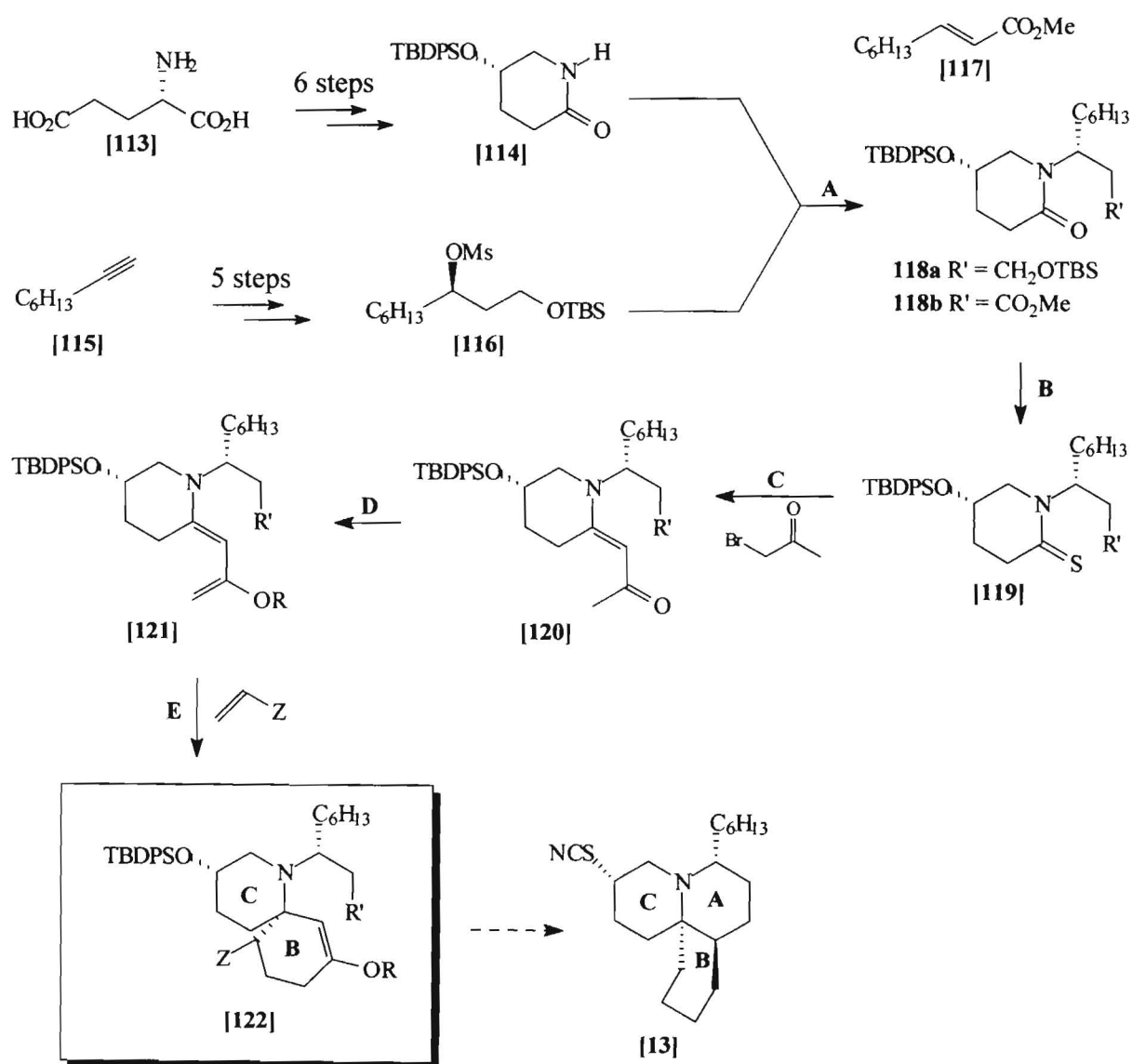
The next step (*step D*) is to convert the vinylogous amides [107] and [108], into the dienes [109] and [110] by enolate formation followed by the subsequent trapping of the enolate as the corresponding enol ethers. The final step (*step E*) is the construction of the B ring using the Diels-Alder reaction between the dienes [109] and [110] and a suitable dienophile to give the azaspirocycles [111] and [112].

Over the 70 years since its report by Diels and Alder, the synthetic potential of the Diels-Alder reaction has been greatly expanded through modifications of the diene and dienophile components.<sup>58</sup> The hetero Diels Alder reaction has emerged as a method of choice for the stereocontrolled synthesis of six-membered heterocycles, which are building blocks for a wide range of natural products.<sup>59</sup> The Diels-Alder reaction can produce from one to as many as four stereocenters in a single step. Thus in *step E* we intend to use the Diels-Alder reaction between the dienes [109] and [110] and phenyl vinyl sulfone as dienophile to assemble the B ring.

Once the first aim is achieved the synthesis will then be repeated using a modified C ring so as to incorporate the thiocyanate moiety in fascicularin [13]. The second aim is thus to develop a novel stereoselective route towards the synthesis of fascicularin. Taking the time constraints of a Masters project into account, we realistically intend to construct only the B and the C rings of



fasicularin using this route. Fasicularin was chosen in particular because at the beginning of this project (early 2000) there was no reported synthesis of this fascinating alkaloid. Scheme 1.9 shows the first reported total synthesis of fasicularin [13] by Kibayashi and co-workers.<sup>8</sup> Their route has a large number of steps (25) and is linear in design. Our route is convergent and would be shorter. Shown in Scheme 1.12 is the proposed synthetic route to our goal.



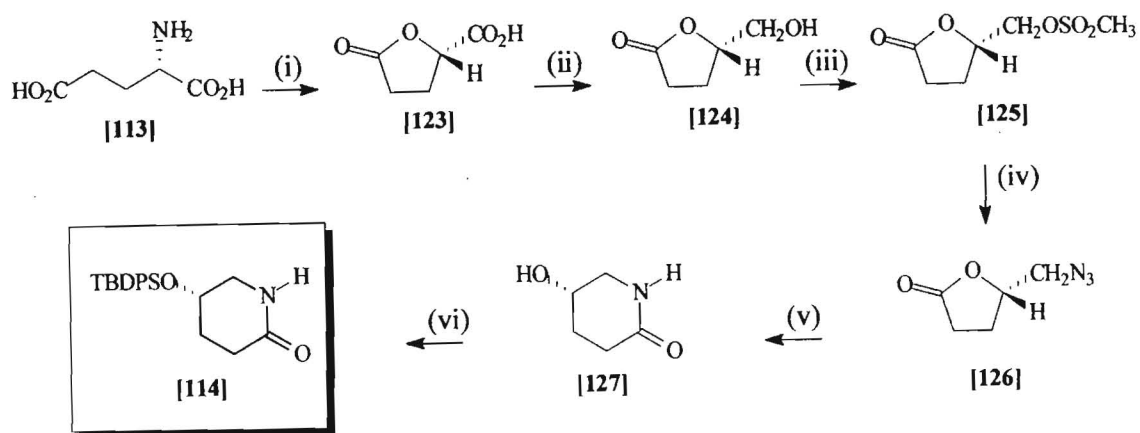
**Scheme 1.12**

(5S)-5-tert-butylidiphenylsilyloxy-2-piperidinone [114], which constitutes the C ring of fasicularin, is synthesized in 6 steps from (S)-glutamic acid [113].<sup>60-62</sup> Mesylate [116] is synthesized from 1-octyne [115] in 5 steps.<sup>63</sup> Lactam [114] and mesylate [116] are then

coupled (*step A*) to give *N*-alkylated lactam [118a]. Alternatively, lactam [114] can be added conjugatively to enoate [117] to give *N*-alkylated lactam [118b]. Methyl-2-nonenolate [117] is synthesized from methyl bromoacetate and heptanal using the Wittig reaction. The amide carbonyl is thionated (*step B*) to give the thiolactam [119]. The next reaction (*step C*) is the Eschenmoser coupling of the thiolactam [119] with bromoacetone, to give the corresponding vinylogous amide [120]. The final steps, which complete the B ring of fascicularin (*steps D and E*), are the diene [121] formation and the Diels-Alder reaction between the diene and an appropriate dienophile to give azaspirocycle [122].

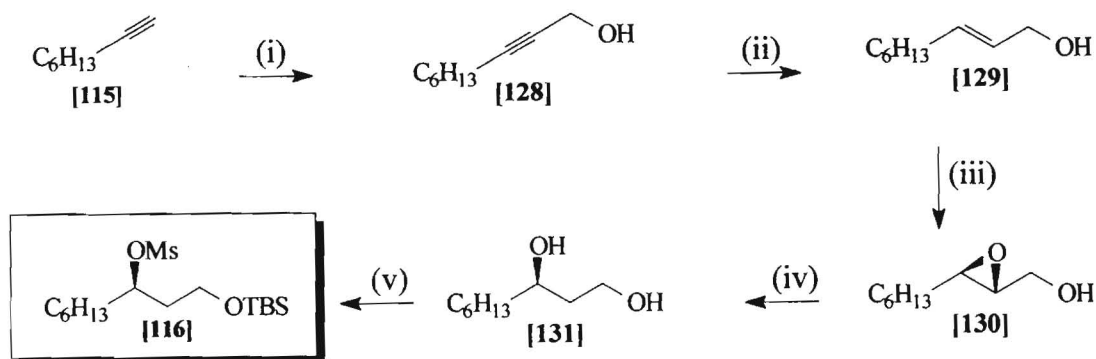
What precedents can we draw on in support of the proposed synthetic route outlined in Scheme 1.12? Many of the steps have literature precedents. The following step-by-step analysis gives an account of both the encouraging features and the potential problems that are expected in the proposed route.

Synthesis of (5*S*)-5-*tert*-butyldiphenylsilyloxy-2-piperidinone [114]: Literature precedent for the synthesis of (5*S*)-5-hydroxy-2-piperidinone [127] from *L*-glutamic acid [113] is found in the publications by Herdeis,<sup>60</sup> Silverstein<sup>61</sup> and Thompson,<sup>62</sup> therefore no problems are expected (Scheme 1.13). In this manner (*S*)-glutamic acid [113] is converted into (5*S*)-5-hydroxy-2-piperidinone [127] in an overall yield of 24% (Scheme 1.13). The first step is the transformation of (*S*)-glutamic acid [122] into the corresponding lactone [123] using hydrochloric acid and sodium nitrite. Lactone [123] is reduced to primary alcohol [124] using the borane-methyl sulfide complex. Treatment of the alcohol [124] with methane sulfonylchloride and triethylamine gives the mesylate [125]. Heating of the mesylate [125] with NaN<sub>3</sub> affords the azide [126]. Hydrogenation of the azide [126] yields (5*S*)-5-hydroxy-2-piperidinone [127]. The next step requires the selective protection of a secondary alcohol in the presence of a secondary amide and is potentially problematic. The protecting group could go to the secondary alcohol and/or the secondary amide. Thus we need to find a chemoselective method. However Herdeis and co-workers<sup>64</sup> reported the selective protection of the OH group in (5*S*)-5-hydroxy-2-piperidinone [127], using TBDPSCl and imidazole in DMF to give lactam [114]. We intend to use the same method.



**Scheme 1.13** (i)  $\text{NaNO}_2$ ,  $\text{HCl}$ ,  $\text{H}_2\text{O}$ , 55%; (ii)  $\text{H}_3\text{B}\cdot\text{S}(\text{CH}_3)_2$ ,  $\text{THF}$ ,  $\text{MeOH}$ , 72%; (iii)  $\text{CH}_3\text{SO}_2\text{Cl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 88%; (iv)  $\text{NaN}_3$ , 18-crown-6,  $\text{CH}_3\text{CN}$ , 93%; (v)  $\text{H}_2$ ,  $\text{Pd-C}$ ,  $\text{MeOH}$ , 300 kPa, 77%; (vi)  $\text{TBDPSCl}$ , imidazole,  $\text{DMF}$ , 98%.

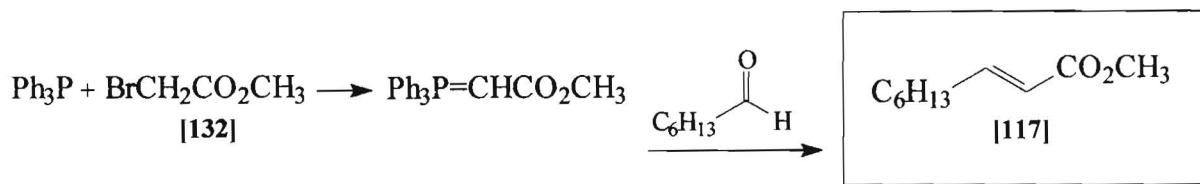
**Synthesis of (1R)-1-(2-{[tert-butyl(dimethyl)sily]oxy}ethyl)heptyl methanesulfonate [116]:** 1,3-Nonanediol [131] is synthesized in 4 steps from 1-octyne [115] (Scheme 1.14).<sup>63</sup>



**Scheme 1.14** (i)  $\text{EtMgBr}$ ,  $\text{CH}_2\text{O}$ , 86%; (ii)  $\text{LiAlH}_4$ , 76%; (iii) (-)-DET,  $\text{Ti}(\text{O}^i\text{Pr})_4$ , TBHP; (iv) Red-Al, 80% from [129]; (v) Ref 32.

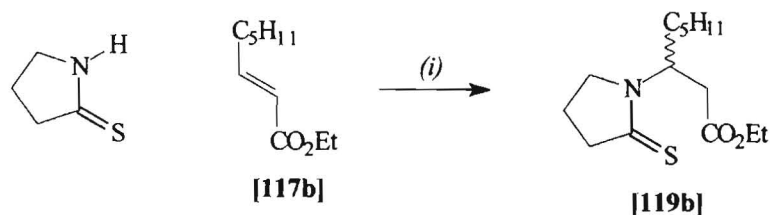
The synthesis begins with the formation of 2-nonyn-1-ol [128] by reacting 1-octyne [115] with ethyl magnesium bromide and formaldehyde. Reduction of alkyne [128] with  $\text{LiAlH}_4$  yields the allylic alcohol [129]. Sharpless epoxidation followed by reduction of epoxide [130] yields (3R)-1,3-nonanediol [131]. Close inspection of compounds [131] and [116] in Scheme 1.14 reveals similarities with compounds [39] and [41] in Scheme 1.3. Thus mesylate [116] will be synthesized from 1,3-diol [131] using the methodology reported by Molander.<sup>32</sup>

Synthesis of methyl-2-nonenoate [117]: Methyl-2-nonenoate [117] is synthesized from methyl bromoacetate [132] and heptanal using the Wittig reaction (Scheme 1.15). Methyl bromoacetate [132] is reacted with  $\text{Ph}_3\text{P}$  to give the phosphorus ylide. The ylide reacts with heptanal to produce a mixture of *E* and *Z* isomers of methyl-2-nonenoate [117].



### Scheme 1.15

Step A: Literature precedent for the conjugate addition of the lactam [114] to methyl-2-nonenoate [117] is found in the work of Michael and Gravestock.<sup>54,57,65-67</sup> Michael and Gravestock reported the conjugate addition of ethyl oct-2-enoate [117b] to pyrrolidine-2-thione in their work on the synthesis of alkaloids 209B isolated from the skins of dendrobatid frogs (Scheme 1.16).<sup>65-67</sup> They used a catalytic amount of sodium hydroxide as base and their yield was a respectable 74%. So we were confident enough to go ahead with our proposed route.



### Scheme 1.16 (i) $\text{NaOH}$ (cat), THF, rt.

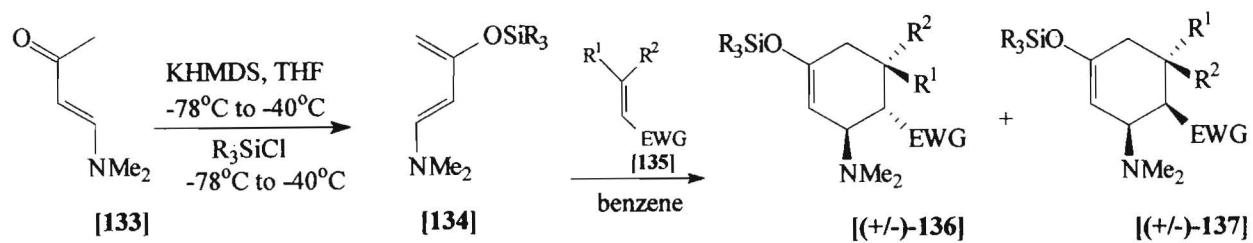
We thus intended to use their method to form lactam [118b] from lactam [114] and methyl-2-nonenoate [117]. This reaction is expected to produce a mixture of diastereomers of lactam [118b] and subsequent separation of the desired stereoisomer may be difficult. To circumvent this difficulty, it is hoped that an  $\text{S}_{\text{N}}2$  reaction between the lactam [114] and the stereodefined mesylate [117] will give alkylated lactam [118a] as a single stereoisomer.



Step B: Amides can be converted to corresponding thioamides using the Brillon method,<sup>68</sup> Belleau's<sup>69</sup> or Lawesson's reagents.<sup>70</sup> For our project we intend to use Lawesson's reagent because the method is the simplest and does not require an aqueous workup. Lawesson's reagent does the conversion selectively and efficiently, under mild conditions in the presence of other functional groups including esters.<sup>53</sup> Lactam [118] is heated at reflux with Lawesson's reagent in toluene to give the corresponding thiolactam [119]. Only 0.6 equivalents of the Lawesson's reagent are used because it has two sulfur atoms to donate. We can interchange *Steps B* and *A*, however it is better to start with *N*-alkylation (*step A*) and then perform the thionation (*step B*). Occasionally *S*-alkylation results during attempts to *N*-alkylate a secondary thioamide.<sup>71</sup>

Step C: Conversion of thioamide into a vinylogous amide is easily achieved by use of the Eschenmoser coupling reaction.<sup>53</sup> Thiolactam [119] is coupled with bromoacetone to give the vinylogous amide [120]. Bromoacetone is synthesized from acetone and bromine under aqueous acidic conditions.<sup>72</sup>

Steps D and E: Rawal and co-workers<sup>58,59,73-77</sup> have published a number of papers concerning the preparation of 1-amino-3-siloxy-1,3-butadienes [134] and their subsequent participation in Diels-Alder reactions (Scheme 1.17). These butadienes are formed by reacting the vinylogous amide [133] with potassium bis(trimethylsilyl) amide (KHMDS) followed by the subsequent trapping of the enolate with a silylating reagent (TBSCl, TIPSCl or TBDPSCl). The dienes [134] undergo the Diels-Alder reaction with various dienophiles [135] to form cycloadducts *exo*-[136] and *endo*-[137], which can be separated. Dienophiles that have been used successfully include methyl acrylate, methyl crotonate and acrylonitrile. Different ratios and yields of the *endo* and *exo* products are obtained, depending on the dienophile and the solvent used. For example methyl acrylate gave a 1.5:1 ratio of *exo:endo* diastereomers and acrylonitrile gave 4:1 ratio of *exo:endo* diastereomers. Toluene gave high yields compared to THF and CH<sub>3</sub>CN. Close inspection of structures [120] and [121] in Scheme 1.12 will reveal their similarity to compounds [133] and [134]. We thus intend to use this methodology for *steps D and E*, to construct the B ring of fascicularin [13], using TBSCl to trap the enolate and phenyl vinyl sulfone as the dienophile. Phenyl vinyl sulfone is chosen because the phenyl sulfonyl group is easily removed from the resulting product [122], using sodium amalgam in disodium hydrogen phosphate buffered methanol.<sup>78</sup>



### Scheme 1.17

The following chapter will give an account of the successes and failures incurred when applying the proposed methodology that has been discussed.

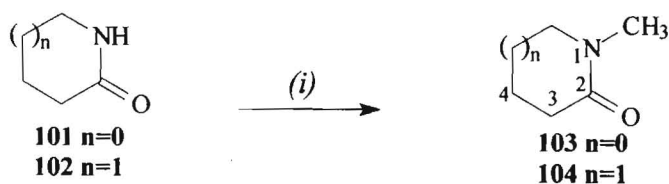
## CHAPTER 2

### MODEL STUDIES

This chapter will discuss the experimental findings for model studies towards the construction of the azaspirocycles [111] and [112] (Scheme 1.11). The first section will describe the *N*-methylation of piperidinone [102] and the thionation of lactams, 1-methyl-2-pyrrolidinone [103] and 1-methyltetrahydro-2(1*H*)-pyridinone [104]. This will be followed by subsequent sulfide contraction of the resulting thiolactams with bromoacetone to give the vinylogous amides 1-(1-methyl-2-pyrrolidinylidene)acetone [107] and 1-(1-methyl-2-piperidinylidene)-acetone [108] respectively. Attempted diene ([109] and [110]) formation, which on reacting with the dienophile results in the formation of the azabicycles [111] and [112] will also be discussed. Also to be included is the discussion of selected carbon and proton NMR spectroscopic data of some of the compounds synthesized.

#### 2.1 Attempted preparation of the azaspirocycles [111] and [112]

##### 2.1.1 1-Methyltetrahydro-2(1*H*)-pyridinone [104]



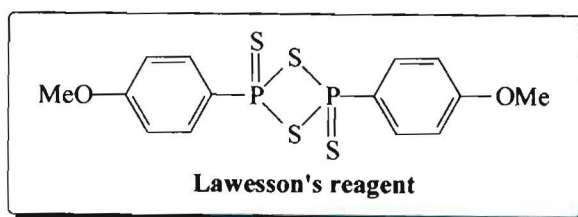
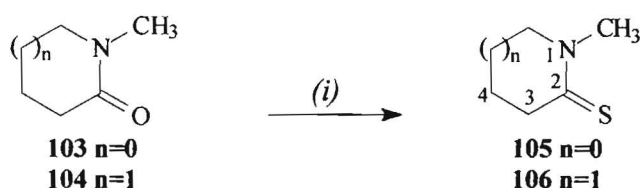
**Scheme 2.1** (i) *NaH*, *CH<sub>3</sub>I*, *THF*

1-Methyl-2-pyrrolidinone [103] is commercially available so there is no need to synthesise it from 2-pyrrolidinone [101]. However, 1-methyltetrahydro-2(1*H*)-pyridinone [104] needed to be synthesised. *N*-Methylation of 2-piperidinone [102] was achieved by reacting it with sodium hydride and iodomethane in THF. Purification by column chromatography afforded pure 1-methyltetrahydro-2(1*H*)-pyridinone [104] as a yellow oil in a 66% yield. The product was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, and GCMS. Proton NMR spectral analysis of the product shows a characteristic singlet peak at 2.9 ppm, corresponding to the three protons

on the methyl group, methylene protons at C<sub>4</sub> and C<sub>5</sub> appeared as a multiplet from 1.7-1.9 ppm and protons of the methylene groups C<sub>3</sub> and C<sub>6</sub> appeared as triplets at 2.4 ppm and 3.3 ppm respectively. In the carbon NMR the characteristic carbonyl peak at 170 ppm was observed.

### 2.1.2 1-Methyl-2-pyrrolidinethione [105] and 1-methyltetrahydro-2(1H)-pyridinethione [106]

Smith *et al.*<sup>79</sup> reported the synthesis of the two thiolactams [105] and [106] using Lawesson's reagent. The structure of Lawesson's reagent is shown below. An alternative method developed by Brillon can also be used for the thionation of amides.<sup>68</sup> Brillon's method mixes phosphorous pentasulfide and sodium carbonate in THF to form a sodium salt and carbon dioxide. The salt is then reacted with the amide in THF and after aqueous workup the desired thiolactam is obtained. We decided to use Lawesson's reagent because with Lawesson's reagent less time is required to complete the reaction, no gas is produced and no aqueous workup is required.



**Scheme 2.2** (i) Lawesson's reagent, toluene, 2h reflux.

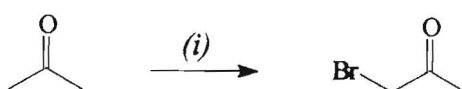
1-Methyl-2-pyrrolidinone [103] and 1-methyltetrahydro-2(1H)-pyridinone [104] were heated at reflux with 0.6 equivalents of Lawesson's reagent in toluene for 2h. Purification by column chromatography afforded 1-methyl-2-pyrrolidinethione [105] and 1-methyltetrahydro-2(1H)-pyridinethione [106] in an overall yield of 90% and 86%, respectively.



The NMR spectroscopic data showed good correlation with the data reported by Smith *et al.*<sup>79</sup> 2D NMR experiments (COSY and GHSQC) were performed to assign all the signals unambiguously. Comparing lactam [104] and its corresponding thiolactam [106], the <sup>1</sup>H NMR of [106] showed two clearly resolved multiplets corresponding to the C<sub>4</sub> and C<sub>5</sub> protons, yet the two signals overlapped in the spectrum for the lactam [104]. In the carbon NMR spectrum the absence of the carbonyl peak at 170 ppm, is an indication that reaction had taken place. A new signal at 200 ppm which corresponds to a thiocarbonyl was observed. Unfortunately this thionation reaction produces an unpleasant odour, thus it is important to work in the fume hood at all times and to dispose of the residues properly by treatment with sodium hypochlorite (bleach).

### 2.1.3 1-(1-Methyl-2-pyrrolidinylidene)acetone [107] and 1-(1-methyl-2-piperidinylidene)-acetone [108]

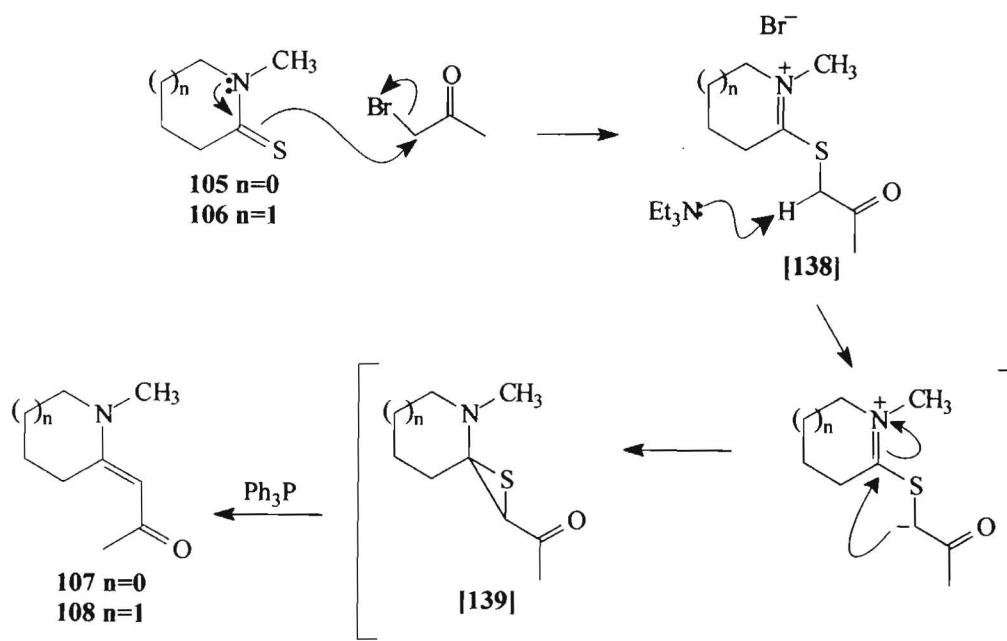
Bromoacetone was prepared by the dropwise addition of bromine to a solution of acetone, glacial acetic acid and water at 60°C.<sup>72</sup> The resultant oil was distilled twice, since the first distillate was contaminated with the dibrominated product.



**Scheme 2.3** (i)  $Br_2$ ,  $CH_3CO_2H$ ,  $H_2O$ , 60 °C.

Pure bromoacetone was obtained as a colourless liquid in 60% yield at 28-30°C (9mmHg). The distillation was performed at reduced pressure because the product decomposes at high temperatures. Bromoacetone is a strong lachrymator and thus one has to take special care when working with it. It also decomposes at high temperature, so it was prepared just before use in the Eschenmoser coupling reaction to form the vinylogous amides and was stored in a freezer between reactions.

1-(1-Methyl-2-pyrrolidinylidene)propanone [107] and 1-(1-methyl-2-piperidinylidene)propanone [108] were prepared by the Eschenmoser coupling reaction between thiolactams [105] and [106] respectively, and bromoacetone. The Eschenmoser coupling reaction is composed of two steps, which are conducted in one pot. The first step is alkylation of sulfur to form an iminium bromide salt, followed by extrusion of sulfur with a thiophile. Outlined in Scheme 2.4 is the mechanism for this reaction as proposed by Shiosaki.<sup>53</sup> Treatment of thiolactams [105] and [106] with bromoacetone, results in the *S*-alkylated  $\alpha$ -thioiminium salt [138]. Secondly, treatment of the salt [138] with base ( $\text{Et}_3\text{N}$ ) and the thiophile ( $\text{Ph}_3\text{P}$ ) results in the extrusion of the sulfur atom via the proposed episulfide intermediate [139]. Aqueous workup followed by purification by column chromatography resulted in the formation of the desired 1-(1-methyl-2-pyrrolidinylidene)propanone [107] and 1-(1-methyl-2-piperidinylidene)propanone [108] as brown oils in an overall yield of 58% and 31%, respectively.

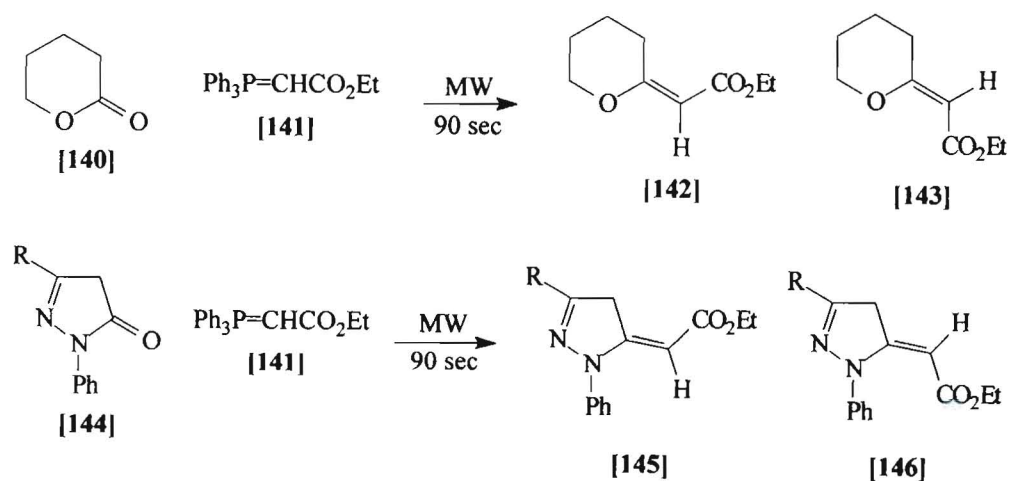


**Scheme 2.4**

The spectral data of our vinylogous amide [107] matched those reported by Michael and co-workers.<sup>80</sup> Proton NMR spectroscopic evidence of the formation of the vinylogous amide, 1-(1-methyl-2-piperidinylidene)-acetone [108] was shown by the presence of two new singlets at 4.9 ppm and 1.9 ppm, corresponding to the methine (vinyl) proton and methyl protons  $\alpha$  to the

carbonyl. The carbonyl carbon appeared at 193 ppm in the carbon NMR spectra. The disappearance of the thiocarbonyl peak at 200 ppm was further proof of the success of the reaction. We are unable to rationalize why the six-membered ring thiolactam [106] gave poorer yields than its five-membered analogue [105]. However, other solvents were investigated to try and improve the yield of the vinylogous amide [108], but without success.

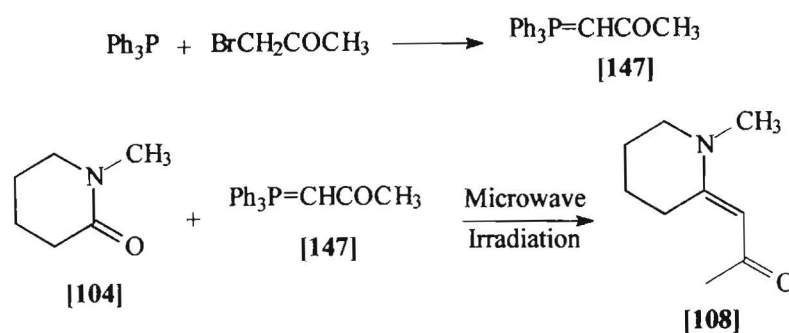
In an attempt to find an alternative route to the synthesis of the vinylogous amide [108] a paper by Sabitha and co-workers<sup>81</sup> was discovered. This reaction is worth trying because it is one step less than our initial route, and it would convert lactam [104] to a vinylogous amide [108] avoiding an intermediate thionation step. Sabitha and co-workers<sup>81</sup> reported the Wittig olefination of lactones [140] and amides [144] under microwave irradiation (Scheme 2.5). Triphenyl phosphine was reacted with ethyl bromoacetate to give the phosphorus ylide [141]. The lactone [140] was reacted with the ylide [141] at 90°C in a microwave oven, giving isomeric products [142] and [143] in an overall yield of 80%. A similar reaction was done on the amide [144] giving products [145] and [146] in an overall yield of 86%. These reactions were quick since they took less than 2 min. This method looked promising for the synthesis of the vinylogous amide [108] from the lactam [104].



**Scheme 2.5**

The above methodology was attempted by reacting the lactam [104] with the phosphorus ylide [147] (synthesised from triphenyl phosphine and bromoacetone Scheme 2.6), but no matter how long the reaction mixture was left in the microwave, there was no sign of any product

being formed. Different power settings (low, med, med-low, high) were tried, but the results were unsuccessful, with the starting material being recovered in each case.



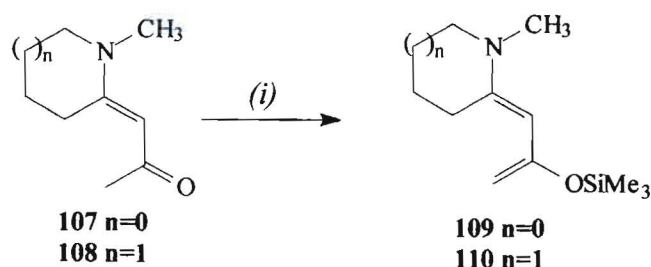
### Scheme 2.6

We then decided to persevere with the Eschenmoser coupling reaction using large quantities to get more of the desired material. Thus a more efficient method is still required to improve the low yield of this reaction.

#### 2.1.4 Attempted preparation of dienes [109] and [110]

Having successfully synthesized the vinylogous amides 1-(1-methyl-2-pyrrolidinylidene)acetone [107] and 1-(1-methyl-2-piperidinylidene)-acetone [108], the next step was to convert them into their corresponding dienes. The first reaction attempted was the formation of the silyl ethers.

##### 2.1.4.1. Silylation

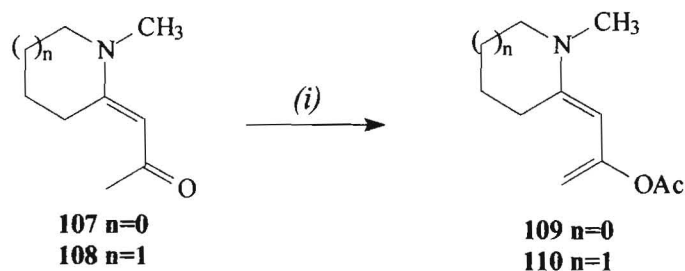


Scheme 2.7 (i) LDA, Me<sub>3</sub>SiCl, THF, -78 °C.



Silylation was initially attempted using LDA and TMSCl at  $-78^{\circ}\text{C}$ . The vinylogous amides [107] and [108] were reacted with LDA followed by the subsequent trapping of the enolate with a silylating reagent TMSCl (Scheme 2.8). The reaction did not work and starting materials were recovered. Increasing the temperature and changing bases to sodium hydride (NaH) and potassium hydride (KH) did not improve matters. Once again only the starting material was recovered. We then attempted acylation.

#### 2.1.4.2. Acylation



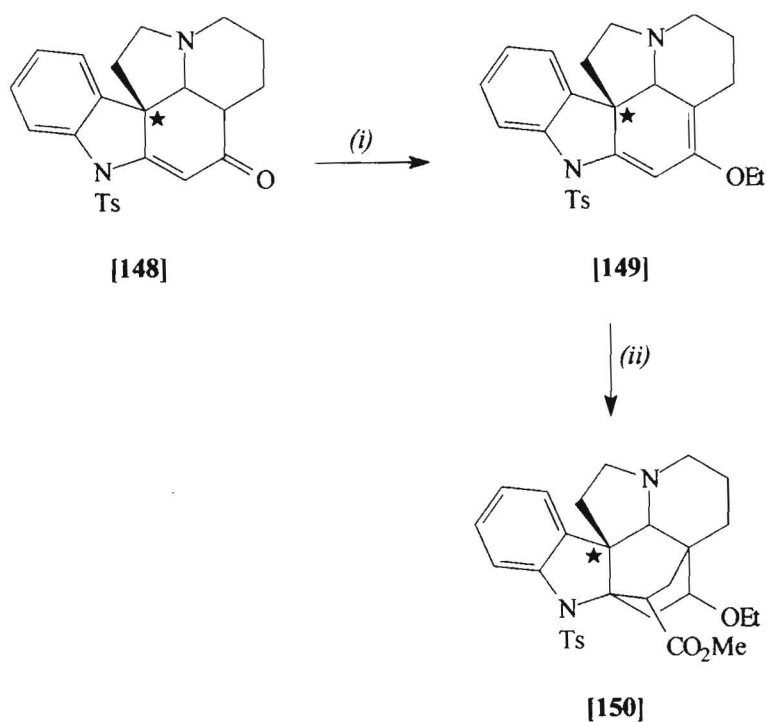
**Scheme 2.8** (i)  $(\text{AcO})_2$ , *p*-TsOH/HClO<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>.

Acylation using acetic anhydride  $(\text{AcO})_2$  and *p*-TsOH, HClO<sub>4</sub> or K<sub>2</sub>CO<sub>3</sub> as promoters, was attempted based on literature precedents,<sup>82,83,84</sup> but the results were similarly disappointing (Scheme 2.8). The starting materials were recovered in each case.

#### 2.1.4.3 Alkylation

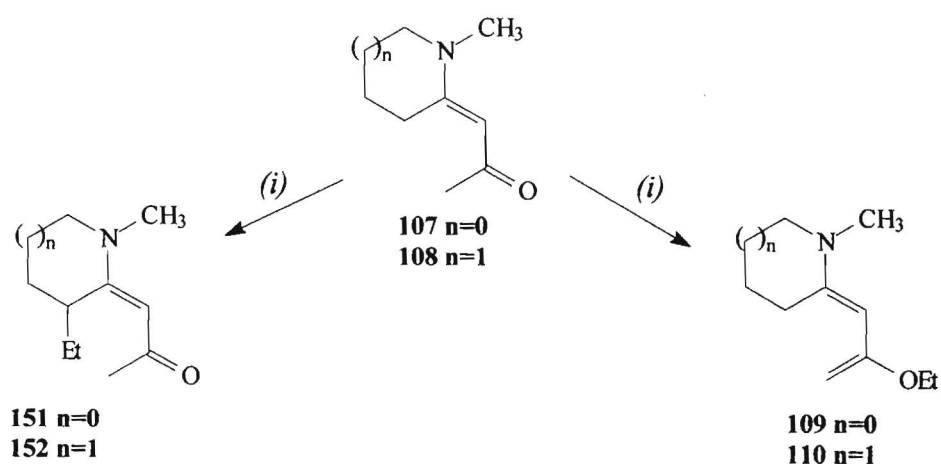
*O*-Alkylation was attempted using NaH and ethyl iodide (EtI) in ether but without success as only starting materials were recovered. Changing the solvent to DMF did not improve matters. The base was then changed to KH and ether as the solvent, based on the reaction shown below in Scheme 2.9 reported by Wenkert and Kunesch.<sup>85</sup>

Wenkert and Kunesch<sup>85</sup> in their work towards the synthesis of ( $\pm$ ) aspidofractine, reported two steps relevant to our synthetic work (Scheme 2.9). These steps were the synthesis of the diene [149] from [148], and the Diels-Alder reaction between the diene [149] and methyl acrylate to form the six-membered ring [150].



**Scheme 2.9** (i) *KH, EtI, THF, 0°C*; (ii) *CH<sub>2</sub>=CHCO<sub>2</sub>Me, CH<sub>2</sub>Cl<sub>2</sub>, rt*

Vinylogous amide [108] was reacted with *KH* to form the enolate and this was followed by the trapping of the enolate with ethyl iodide (Scheme 2.10). An excess of ethyl iodide was added to try and force the reaction to completion.

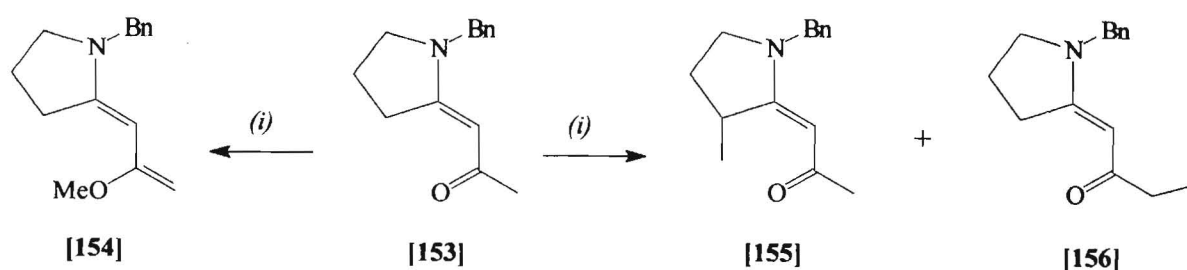


**Scheme 2.10** (i) *KH, EtI, THF, 0°C*.

GCMS data showed that the product formed had the expected mass, since the molecular formula of the obtained and the expected products is the same,  $C_{11}H_{19}NO$ .  $^1H$  and  $^{13}C$  NMR

data, DEPT and 2D NMR experiments (COSY and GHSQC) however showed that the product was not the desired diene even though it had the same mass. On observation of the carbon and proton NMR it was clear that no change had occurred in the enone functionality of the vinylogous amide. In the proton NMR the two singlets corresponding to the vinyl proton and the methyl protons were present at 5.0 ppm and 2.8 ppm respectively. There were additional signals showing that a reaction had taken place. From the DEPT spectrum we ascertained that the product had three methyl groups instead of two and two methine carbons instead of one. Instead of forming the diene [110] the vinylogous amide, 1-(3-ethyl-1-methyl-2-piperidinylidene)propanone [152] had been formed in a 92% yield. The ethyl group went to the position  $\beta$  to nitrogen instead. This result is not altogether unexpected when one considers the ambident reactivity of the enaminones depicted in Figure 1 (structure D, p. 26). Thus under these reaction conditions the preferred site for nucleophilic reactivity is  $\beta$  to nitrogen. Why did our reaction fail despite the literature precedent provided by Wenkert and Kunesch in Scheme 2.9? The major difference between our starting material and that reported by Wenkert and Kunesch is that their  $\beta$ -position was blocked\* i.e. this is a quaternary carbon and thus has no proton available to abstract (Scheme 2.9). When repeating the same reaction on the vinylogous amide [107] we obtained the same results, i.e. the ethyl group went to the carbon at the position  $\beta$  to nitrogen instead of the oxygen atom to afford the vinylogous amide, 1-(3-ethyl-1-methyl-2-piperidinylidene)propanone [151].

These results are interesting as they demonstrate that the preferred site for deprotonation is  $\beta$  to nitrogen and not  $\alpha$  to the carbonyl group.



**Scheme 2.11** (i) LDA,  $-78^{\circ}\text{C}$ , MeI.

\*  $\beta$ -position is indicated by an asterisk in Scheme 2.9.

Rawal and co-workers experienced similar problems on their work towards the total synthesis of perhydropyrrolo[2,1,*j*]quinoline alkaloids (Scheme 2.11).<sup>86</sup> From the vinylogous amide [153], Rawal and co-workers intended to form the enolate and trap it with a methyl group to form the diene [154]. Instead they discovered that the preferred position for alkylation was  $\beta$  to nitrogen [155]. Compounds [155] and [156] were obtained in 74% and 9% respectively. Variation of reaction conditions as well as the use of different bases, such as KHMDS, had little effect on the ratio of [155] to [156].<sup>86</sup>

Figures 2 and 3 show the proton and carbon NMR spectra of 1-(3-ethyl-1-methyl-2-piperidinylidene)propanone [152], respectively. In the proton NMR, the triplet at 0.92 ppm corresponding to the methyl protons ( $C_{11}$ )  $\alpha$  to the methylene group ( $C_{10}$ ) was observed, clear evidence that the ethyl group had indeed been added to the starting material, unfortunately not at the desired position. The presence of non-equivalent signals assigned to diastereotopic protons  $C_4$ ,  $C_5$ ,  $C_6$  and  $C_{10}$  is clear evidence that a chiral center at  $C_3$  has been created.

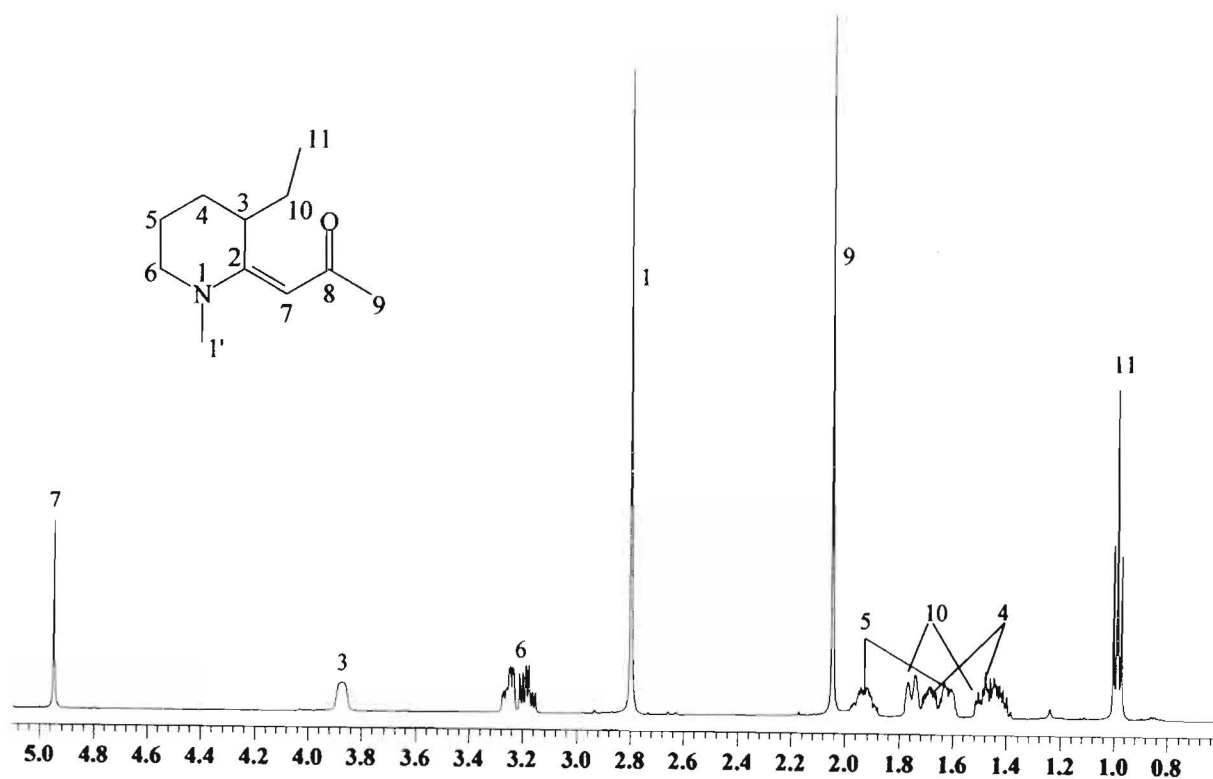
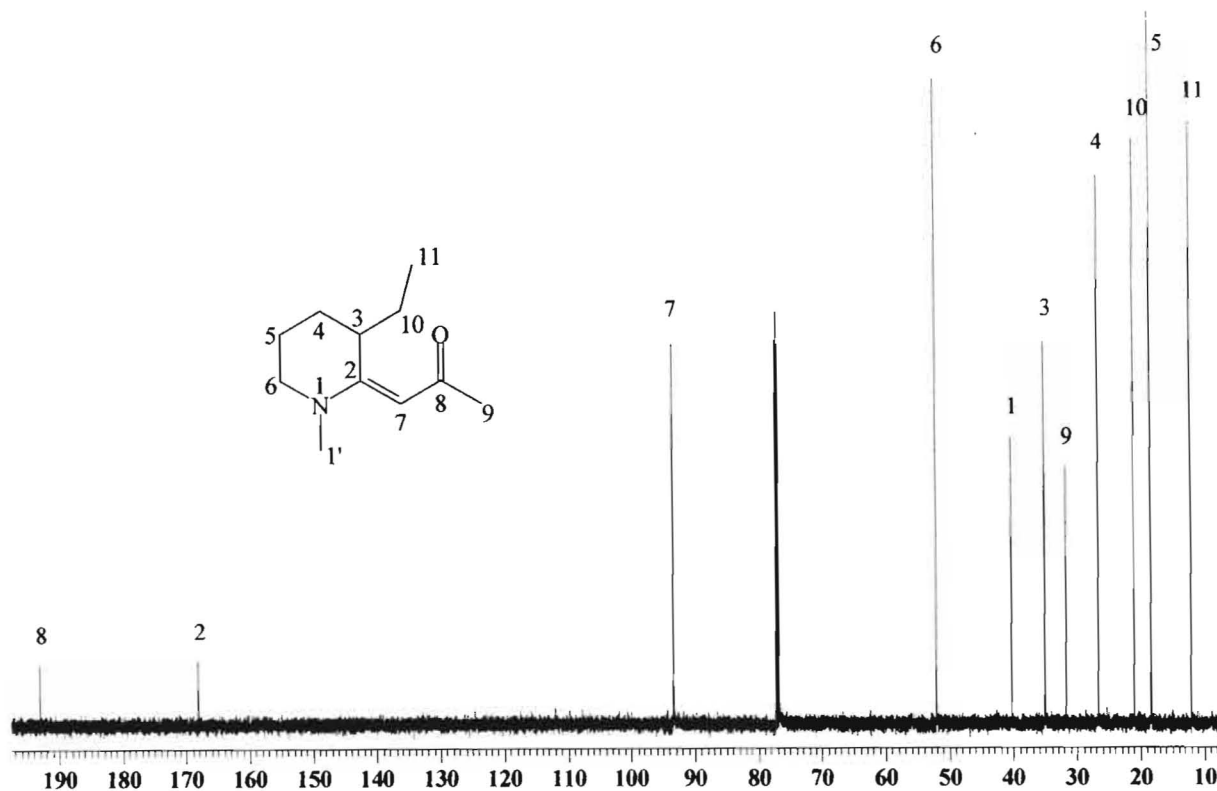


Figure 2  $^1\text{H}$  NMR spectrum of 1-(3-ethyl-1-methyl-2-piperidinylidene)propanone [152] in  $\text{CDCl}_3$



In the carbon NMR spectrum the carbonyl carbon and the quaternary carbon  $\alpha$  to nitrogen resonate at 193 ppm and 168 ppm respectively. The vinyl carbon was observed at 93 ppm and the rest of the aliphatic carbons were upfield of this signal.



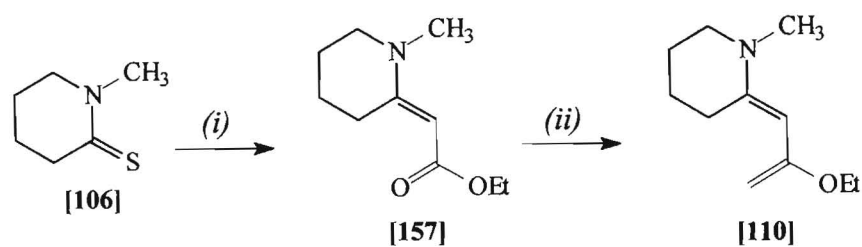
**Figure 3**  $^{13}\text{C}$  NMR spectrum of 1-(3-ethyl-1-methyl-2-piperidinylidene)propanone [152] in  $\text{CDCl}_3$

The explanation for the failure of this *O*-alkylation reaction is the fact that there is more than one set of acidic protons in the vinylogous amide and alkylation did not occur at the desired position. We have been unable to find reaction conditions that favour formation of the required diene.

#### 2.1.4.4. Petasis methylenation

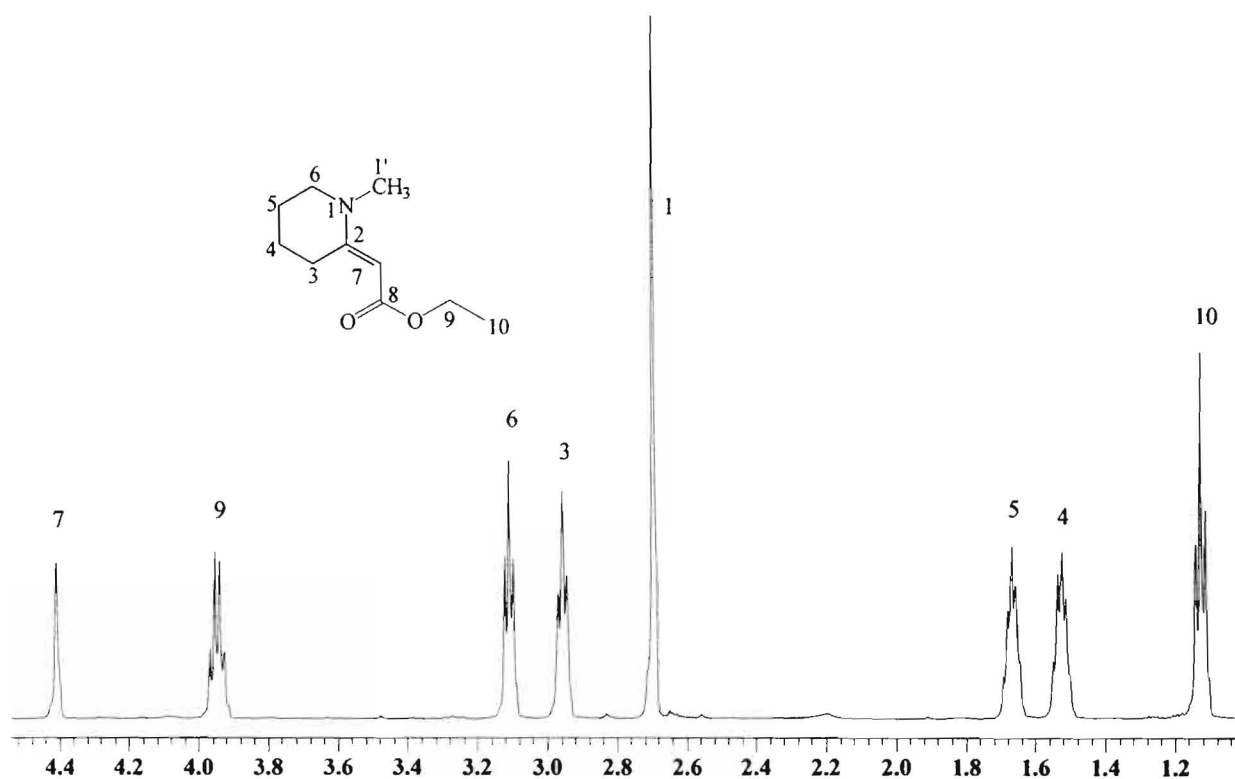
More attempts were made to synthesize the diene, this time using the Petasis methylenation.<sup>87</sup> This method uses dimethyltitanocene ( $\text{Cp}_2\text{TiMe}_2$ ) for the methylenation of carbonyl compounds including aldehydes, ketones and esters. Dimethyl titanocene is prepared from titanocene dichloride and methyl lithium. The Petasis methylenation reaction proceeds by

heating a mixture of dimethyl titanocene and the carbonyl substrate in THF or toluene at 60-75°C. The scheme below shows our proposed route towards the synthesis of the diene [110].



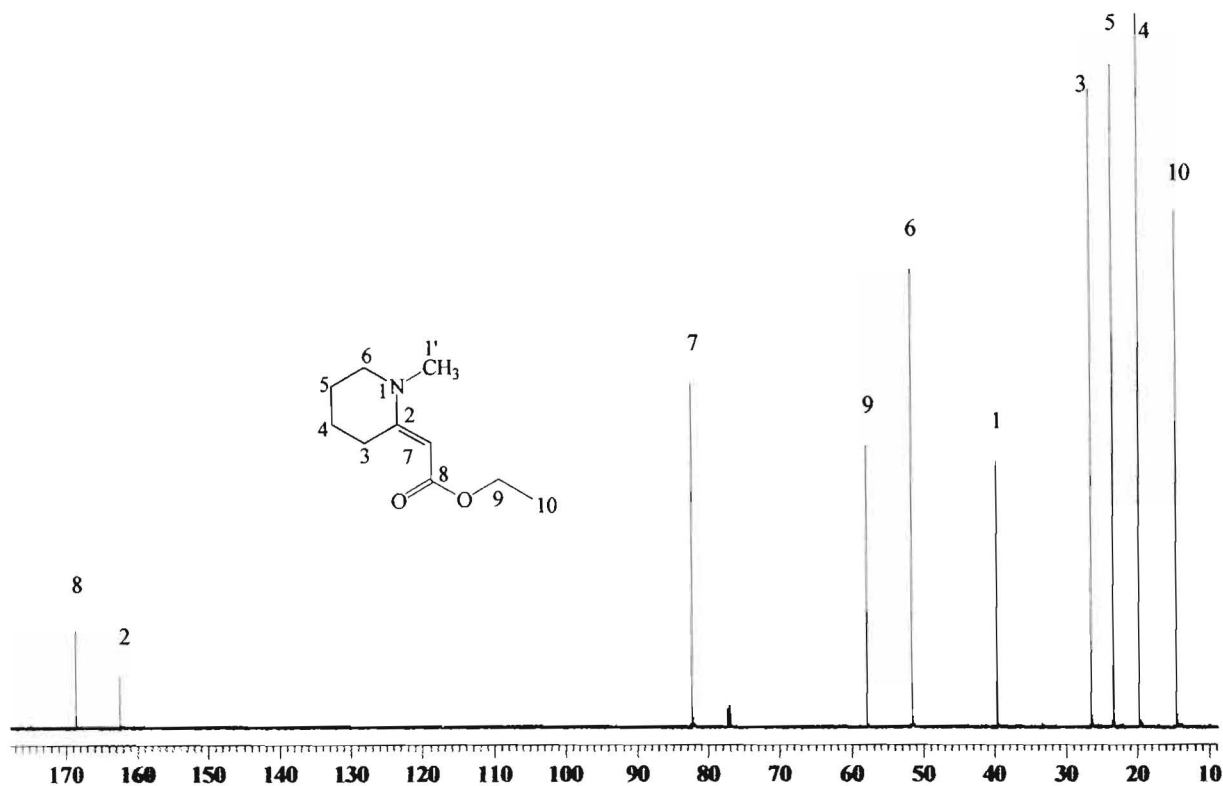
**Scheme 2.12** (i) (a)  $BrCH_2CO_2Et$ ,  $CH_2Cl_2$ ; (b)  $Ph_3P$ ,  $Et_3N$ ; (ii)  $Cp_2TiMe_2$ , THF or  $PhCH_3$ .

The vinylogous urethane [157] was successfully synthesized from the thiolactam [106] and ethyl bromoacetate in an overall yield of 90%, using the Eschenmoser coupling reaction described earlier.



**Figure 4**  $^1H$  NMR spectrum of ethyl 2-(1-methyl-2-piperidinylidene)acetate [157] in  $CDCl_3$ .

In the carbon NMR spectrum the quaternary carbon as well as the carbonyl carbon signal resonated downfield at 162 ppm and 169 ppm respectively (Figure 5). The vinyl carbon was observed at 82 ppm. In the proton NMR the vinyl proton was observed as a singlet at 4.4 ppm, all this clear evidence that the reaction did take place. The quartet and triplet corresponding to the methylene and methyl protons ( $C_9$  and  $C_{10}$ ) of the ethoxy group were observed at 1.1 ppm and 3.9 ppm respectively (Figure 4).



**Figure 5**  $^{13}\text{C}$  NMR spectrum of ethyl 2-(1-methyl-2-piperidinylidene)acetate [157] in  $\text{CDCl}_3$

Having synthesized the vinylogous urethane [157], it was then reacted with dimethyl titanocene in THF at  $60^\circ\text{C}$  as proposed in Scheme 2.12. GCMS and TLC analysis showed only the starting material so the temperature was increased to reflux, but still there was no sign of any product being formed. The solvent was changed to toluene and the mixture heated under reflux but still there was no product was detected.

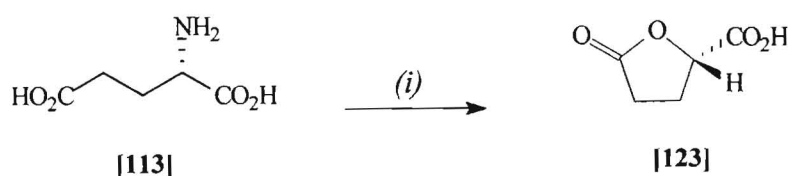
Due to time constraints and our failure to prepare the requisite diene, we then decided to focus our attention and efforts towards achieving our second aim, the enantioselective synthesis of the B and C rings of fascicularin [13].

## CHAPTER 3

### ENANTIOSELECTIVE SYNTHESIS OF THE B AND C RINGS OF FASICULARIN

To be discussed in this chapter is the stereoselective route towards the construction of the spirofused B and C rings of fascicularin [13] (Scheme 1.12). This was a major goal of this project. If the proposed methodology works, it will then be extended towards the syntheses of the other perhydropyrrolo[2,1-*j*]quinoline and perhydropyrido[2,1-*j*]quinoline alkaloids discussed in Chapter 1. To be discussed in this chapter are the successes and failures incurred *en route* to this goal.

#### 3.1 (2*S*)-5-Oxotetrahydro-2-furancarboxylic acid [123]

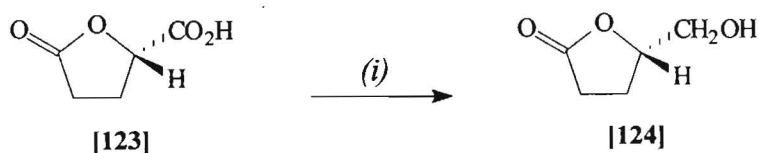


**Scheme 3.1** (i)  $\text{NaNO}_2$ ,  $\text{HCl}$ ,  $\text{H}_2\text{O}$

The synthesis of the lactone [123] is well documented.<sup>60,61,62</sup> We adapted the synthetic route reported by Herdeis.<sup>60</sup> Lactone [123] was synthesized from the commercially available and optically pure (*S*)-enantiomer of glutamic acid [113]. Aqueous HCl was added to solution of the glutamic acid [113] in water, followed by sodium nitrite. After overnight stirring the water was removed by distillation. The resultant oil was supposed to form crystals but it did not. Thus a minimum volume of chloroform was added and the flask was cooled to  $-30^\circ\text{C}$ . White crystals of analytically pure (2*S*)-5-oxotetrahydro-2-furancarboxylic acid [123] were formed in 51% yield. This yield compared favourably to the 55% obtained by Herdeis.<sup>60</sup> A melting point of  $70.8 - 72.0^\circ\text{C}$  was recorded, which agreed favourably with the literature value ( $71-73^\circ\text{C}$ )<sup>60,61</sup> and GCMS showed a *m/z* value of 130. The next step was to reduce the carboxylic acid group to a primary alcohol.



### 3.2 (5*S*)-5-(Hydroxymethyl)dihydro-2(3*H*)-furanone[124]



#### Scheme 3. 2 (i) $H_3B \cdot SMe_2$ , THF

(5*S*)-5-(Hydroxymethyl)dihydro-2(3*H*)-furanone [124] was synthesised from (5*S*)-5-oxotetrahydro-2-furancarboxylic acid [123] using a procedure reported by Silverstein.<sup>61</sup> Borane-methylsulfide complex was added to a solution of carboxylic acid [123] in THF. In their procedure, after aqueous work up with methanol, the resultant oil was distilled. We obtained better results when the crude product was purified by column chromatography. (5*S*)-5-(Hydroxymethyl)dihydro-2(3*H*)-furanone [124] was obtained as a colourless oil in 82% yield. The NMR spectroscopic data were in close agreement with those reported by Silverstein.<sup>61</sup>

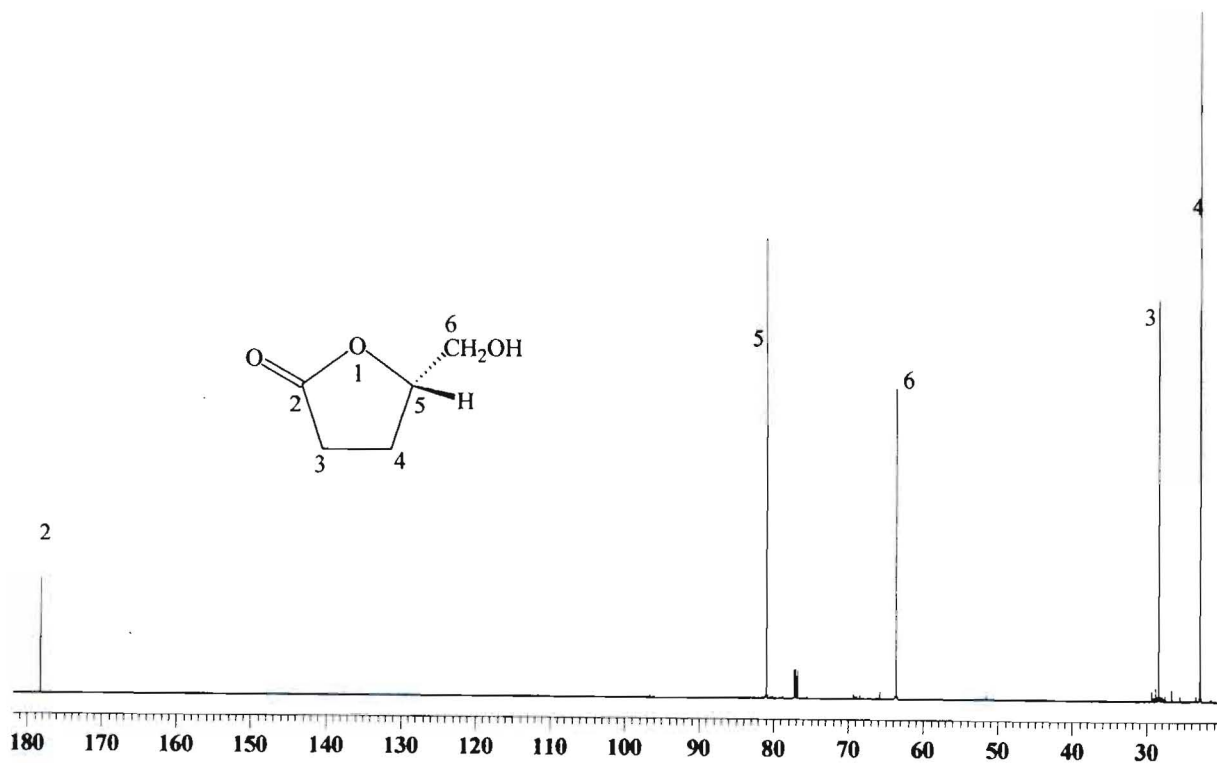
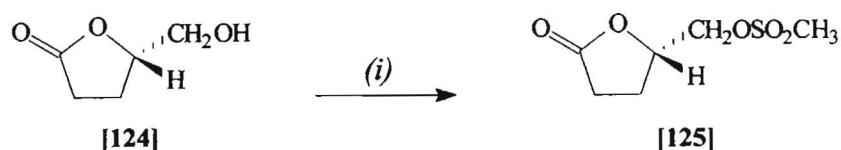


Figure 6  $^{13}C$  NMR spectrum of (5*S*)-5-(hydroxymethyl)dihydro-2(3*H*)-furanone [124] in  $CDCl_3$

Figure 6 above shows the carbon NMR spectrum of the alcohol [124]. Downfield at 178 ppm is the carbonyl signal, with the methine signal resonating further upfield at 81 ppm. The disappearance of the CO<sub>2</sub>H signal further downfield and its replacement with the methylene at 64 ppm is an indication that the desired reaction has taken place. The primary alcohol [124] was then converted into a mesylate.

### 3.3 [(2*S*)-5-Oxotetrahydro-2-furanyl]methyl methanesulfonate [125]

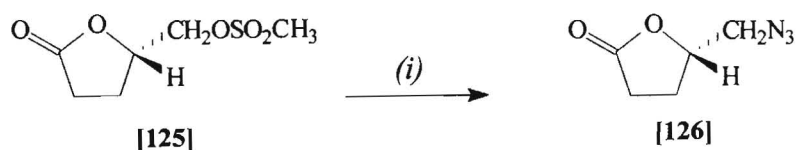


#### Scheme 3.3 (i) CH<sub>3</sub>SO<sub>2</sub>Cl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>

The alcohol [124] was converted into mesylate [125] by treatment with methanesulfonyl chloride and triethylamine in dichloromethane at -30°C. After aqueous workup with HCl the residue was purified by column chromatography. The mesylate was chosen instead of the tosylate because the tosyl derivative showed a marked lower reactivity towards sodium azide to be used in the following step.<sup>60</sup> (5*S*)-5-Oxotetrahydro-2-furanyl]methyl methanesulfonate [125] was obtained as light yellow oil in a 61% yield. GCMS and NMR spectroscopic data showed that the desired reaction had taken place and GCMS showed a *m/z* value of 194. The appearance of a new signal at 37 ppm in the carbon NMR spectrum and a singlet at 3.0 ppm in the proton NMR spectrum, both corresponding to the methyl group were clear evidence of the formation of the product [125]. The mesylate [125] was then converted into the corresponding azide.

### 3.4 (5*S*)-5-(Azidomethyl)dihydro-2(3*H*)-furanone [126]

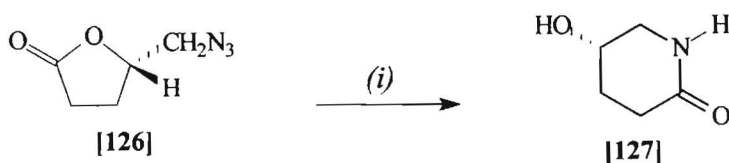
Mesylate [125] was heated at reflux with sodium azide and 18-crown-6 in acetonitrile for 12 hours. After evaporation of the solvent the residual oily suspension was filtered through silica gel using ethyl acetate as eluent.



**Scheme 3.4** (i)  $\text{NaN}_3$ , 18-crown-6,  $\text{CH}_3\text{CN}$

(5*S*)-5-(Azidomethyl)dihydro-2(3*H*)-furanone [126] was obtained as a yellow oil in an 83% yield. GCMS showed a  $m/z$  value of 141 corresponding to the mass of compound [126]. The disappearance of the methyl signal at 37 ppm showed that the mesyl ( $\text{SO}_2\text{CH}_3$ ) group had been cleaved. Further proof was the upfield shift of the methylene carbon ( $\text{CH}_2\text{OS}$ ) from 68 ppm to 54 ppm which corresponds to the  $\text{CH}_2\text{N}_3$  group. The next step involved hydrogenation of the azide functionality.

### 3.5 (5*S*)-5-Hydroxytetrahydro-2(1*H*)pyridinone [127]



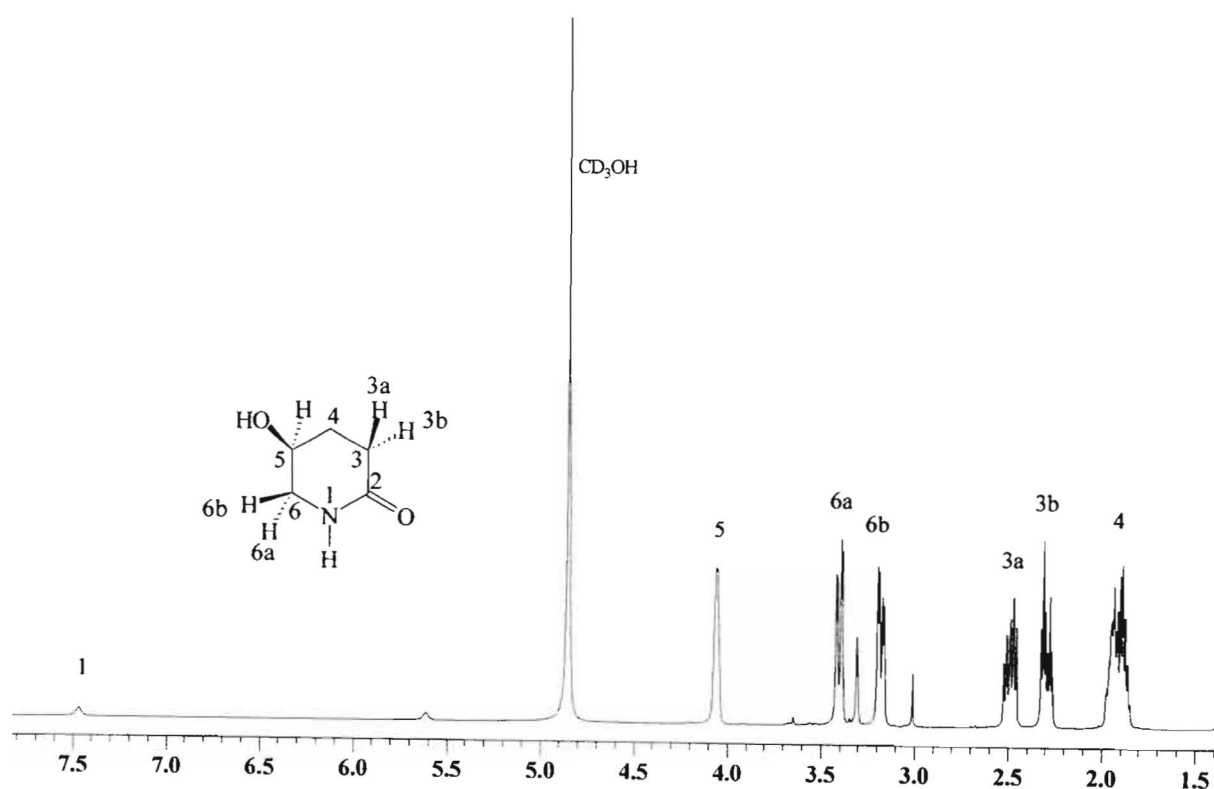
**Scheme 3.5** (i)  $\text{H}_2$ ,  $\text{Pd/C}$ ,  $\text{MeOH}$ , 3.0bar

Ring expansion, achieved by catalytic hydrogenation of the azide [126] in methanol at 3.5bar and 30°C for 4hours, using palladium on carbon catalyst, gave (5*S*)-5-hydroxytetrahydro-2(1*H*)pyridinone [127]. The catalyst was removed by filtration by passing the suspension through Celite. After evaporation of the solvent the product was purified by column chromatography. Pure (5*S*)-5-hydroxytetrahydro-2(1*H*)pyridinone [127] was obtained as white crystals in 61% yield; mp 118.5-120°C (lit.<sup>62</sup> 120-121°C). The existence of the hydroxy group will provide the synthetic handle to incorporate the thiocyanate moiety on the C ring of fascicularin [13]. The table below serves to give a comparison of our  $^{13}\text{C}$  NMR data for the hydrogenation product [127] with those reported by Huh and Thompson.<sup>62</sup> As can be seen there is favourable agreement between these data.

**Table 1. Comparison of our  $^{13}\text{C}$  NMR data for [127] with published values**

| Carbon atom | Gravestock and Mkhize | Huh and Thompson <sup>62</sup> |
|-------------|-----------------------|--------------------------------|
| C-2         | 174.6                 | 174.9                          |
| C-5         | 63.7                  | 62.5                           |
| C-6         | 49.2                  | 47.6                           |
| C-3         | 28.6                  | 26.6                           |
| C-4         | 28.0                  | 26.4                           |

In the proton NMR spectrum (Figure 7) the protons at the methylene carbon ( $\text{C}_4$ ) appear as a multiplet from 1.8 ppm to 2.0 ppm, indicating that they both exist in a similar environment. In contrast the protons at the methylene carbons  $\text{C}_3$  and  $\text{C}_6$  each have two distinct signals, showing their diastereotopic nature due to the presence of the stereogenic centre at  $\text{C}_5$ . The two  $\text{C}_3$  protons are each seen as a multiplet at around 2.3 ppm and 2.5 ppm, while the  $\text{C}_6$  protons are multiplets at 3.2 ppm and 3.5 ppm. Another signal seen is that of  $\text{CD}_3\text{OH}$  at 4.9 ppm. Finally the N-H proton is seen as a broad signal at 7.5 ppm.

**Figure 7  $^1\text{H}$  spectrum of (5*S*)-5-hydroxytetrahydro-2(1*H*)pyridinone [127] in  $\text{CD}_3\text{OD}$**



The carbon NMR spectrum shows the carbonyl carbon downfield at 174.6 ppm and the methine carbon resonates at 63.7 ppm (Figure 8). The next step was the protection of the hydroxyl group.

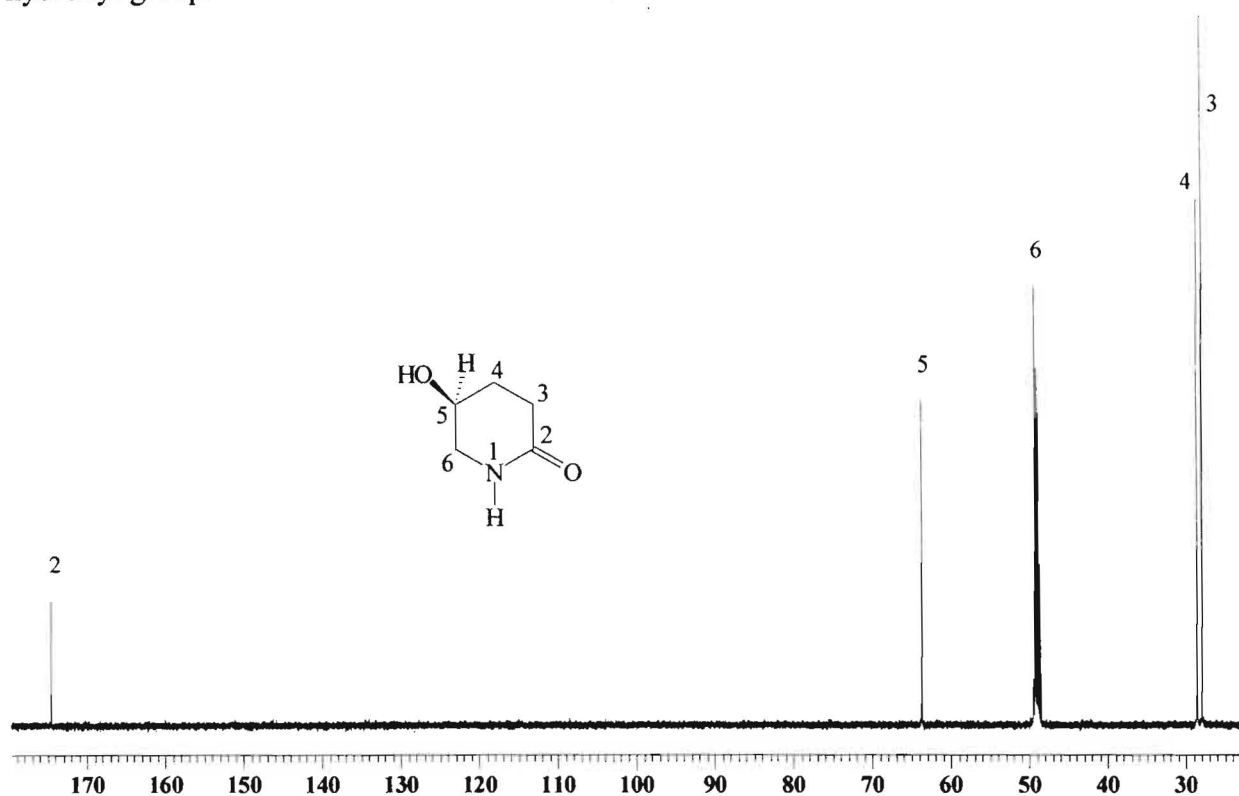
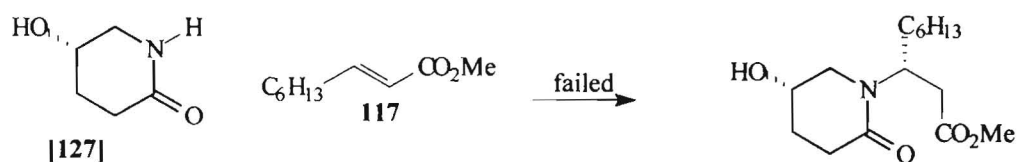


Figure 8 <sup>13</sup>C NMR spectrum of (5S)-5-hydroxytetrahydro-2(1H)pyridinone [127] in CD<sub>3</sub>OD

### 3.6 Attempted protection of (5S)-5-hydroxytetrahydro-2(1H)pyridinone [127]

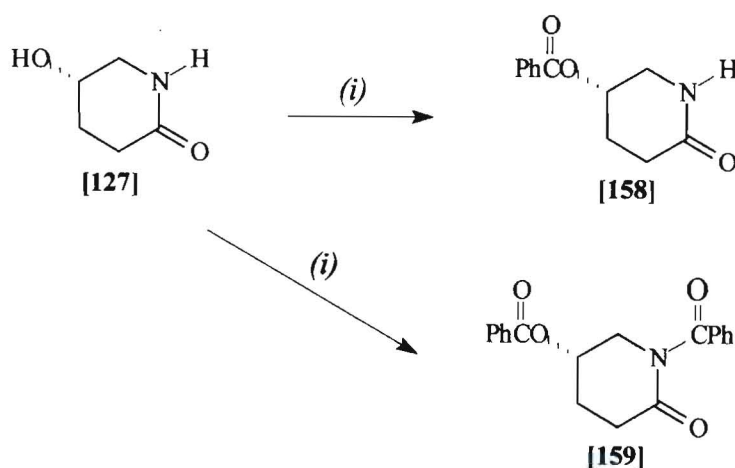
Firstly, different reactions were attempted in vain on unprotected (5S)-5-hydroxytetrahydro-2(1H)pyridinone [127].



Scheme 3.6

These reactions included the conjugate addition of the lactam [127] to methyl-2-nonenate [117] (Scheme 3.6) and thionation of the carbonyl group. These failed reactions forced us to face the difficult challenge of selectively protecting a secondary alcohol in the presence of a secondary amide. Different methods were attempted to protect the secondary alcohol. The first reaction was an attempt to protect the hydroxyl group as benzoate ester.

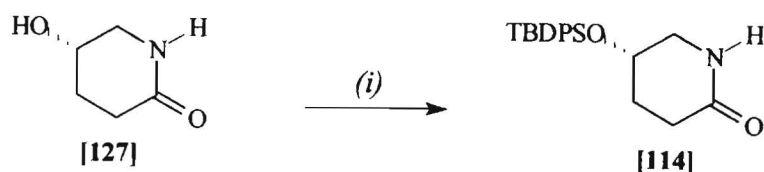
### 3.6.1 (3*S*)-1-Benzoyl-6-oxo-3-piperidiny benzoate [159]



**Scheme 3. 7** (i) Pyridine, PhCOCl, rt

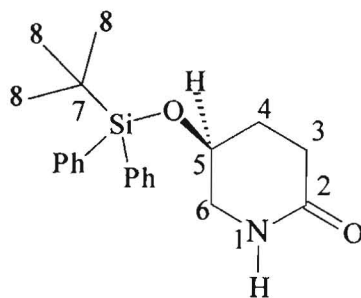
Lactam [127] was reacted with 1.5 equivalents of benzoyl chloride in excess pyridine.<sup>88</sup> Unfortunately the benzoyl group went to both the nitrogen and oxygen atoms. Instead of forming the desired lactam [158], amide [159] was formed. In the carbon NMR the three carbonyl signals at 165, 172 and 174 ppm were convincing evidence for the formation of compound [159]. In pursuit of a chemoselective method, a paper by Herdeis was found.<sup>64</sup>

### 3.6.2 (5*S*)-5-{{*tert*-Butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinone [114]



**Scheme 3.8** (i) Pyridine, TBDPSCl

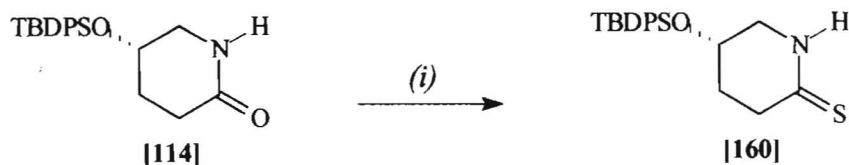
Herdeis reported the protection of (5*S*)-5-hydroxytetrahydro-2(1*H*)pyridinone [127] using imidazole and *tert*-butyldiphenylsilyl chloride in DMF.<sup>64</sup> We attempted the reaction using the same conditions without success. We checked the melting point of the imidazole we were using and found it matched the literature value and thus were reassured there was nothing wrong with it. We suspected the problem lay with the solvent, DMF. We then modified the procedure by using pyridine as both the base and the solvent. The reaction was successful and to our delight (5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinone [114] was obtained as a colourless oil in a 69% yield. Our spectroscopic data were in agreement with those reported by Herdeis.<sup>64</sup> In the proton NMR spectrum the success of the protection reaction was shown by the presence of the singlet at 1.06 ppm for the *t*-butyl group and the phenyl protons resonated between 7.34 ppm and 7.66 ppm. The aromatic carbon signals were visible in the range 128 to 136 ppm. Our spectroscopic data were in close agreement with those reported by Herdeis.<sup>64</sup> as seen in Table 2 below.



**Table 2. Comparison of selected <sup>13</sup>C NMR data for [114] with published values**

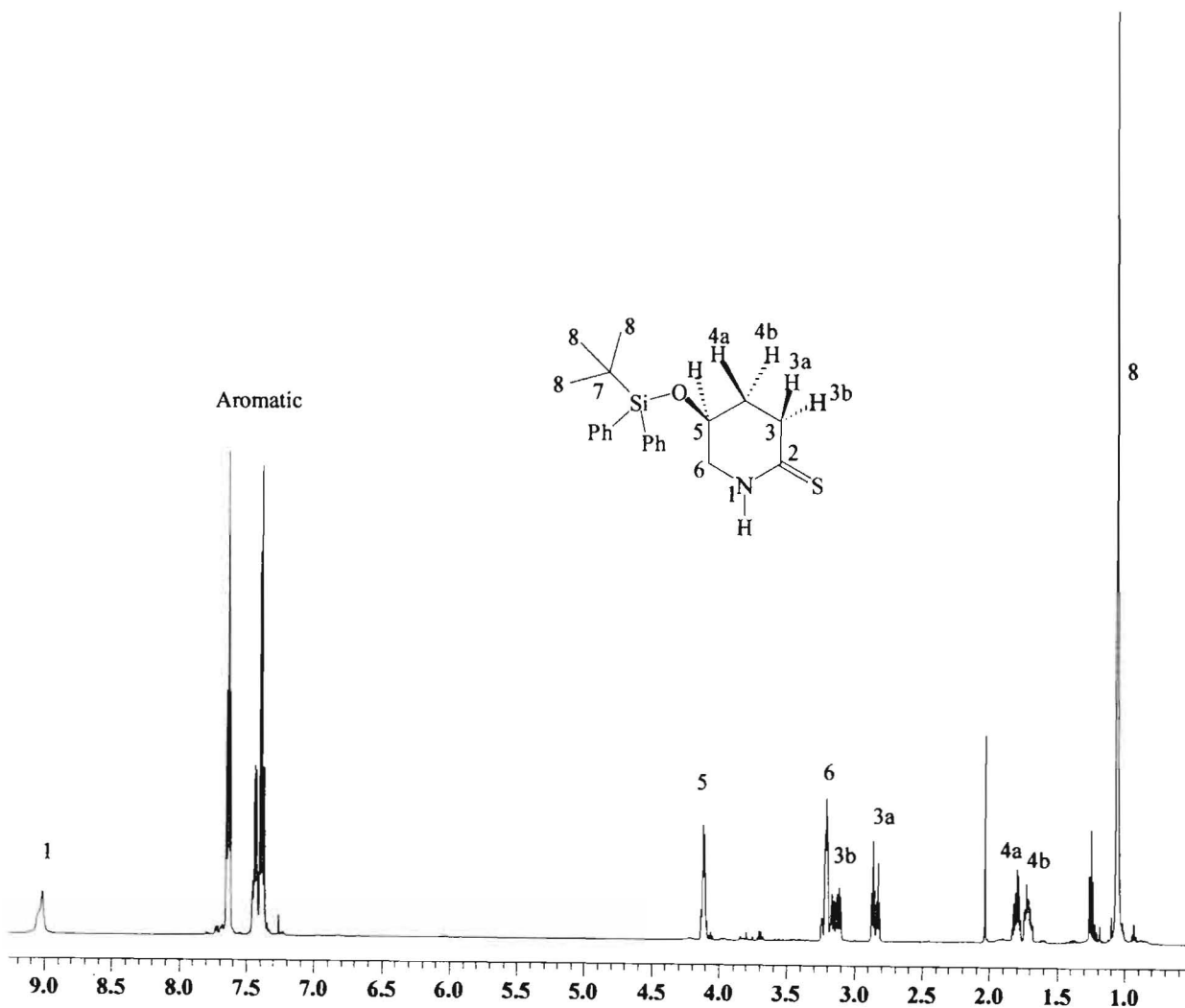
| Carbon atom | Gravestock and Mkhize | Herdeis <sup>64</sup> |
|-------------|-----------------------|-----------------------|
| C-2         | 172.1                 | 172.2                 |
| C-5         | 64.7                  | 64.8                  |
| C-6         | 48.9                  | 49.8                  |
| C-4         | 28.4                  | 28.4                  |
| C-3         | 27.3                  | 27.5                  |
| C-8         | 26.8                  | 26.9                  |
| C-7         | 19.1                  | 19.1                  |

### 3.7 (5*S*)-5-{{*tert*-Butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinethione [160]



**Scheme 3.9 (i)** Lawesson's reagent, toluene, 2h reflux

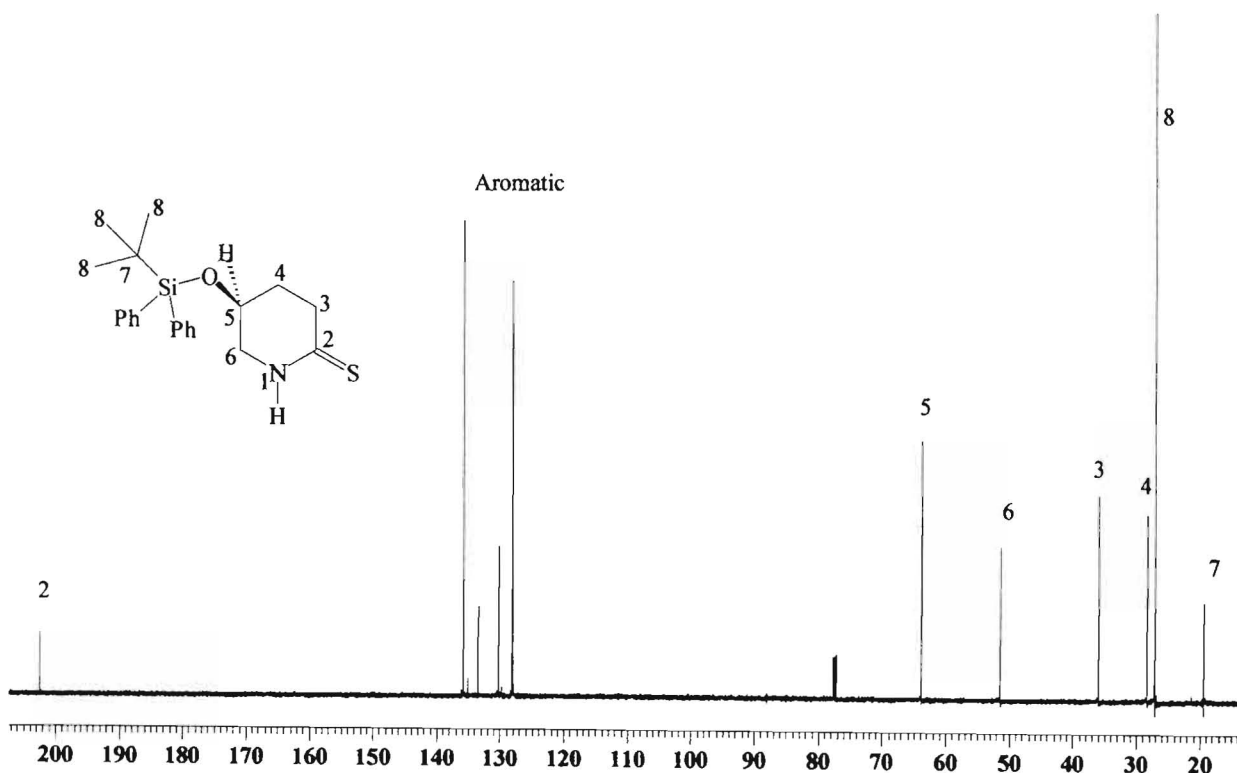
The protected lactam [114] was reacted with Lawesson's reagent to give the thiolactam [160] as yellow crystals in 96% yield. The formation of the thiolactam was confirmed by GCMS and NMR spectroscopy. GCMS showed a  $m/z$  value of 369, providing proof of the formation of the product.



**Figure 9** <sup>1</sup>H NMR spectrum of (5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinethione [160] in CDCl<sub>3</sub>



In the proton NMR spectrum (Figure 9) the diastereotopic protons at C<sub>4</sub> are each seen as a multiplet at 1.7 ppm and 1.8 ppm, while the C<sub>3</sub> protons were observed as multiplets at 2.8 ppm and 3.1 ppm. There was a larger difference in chemical shift values of the C<sub>3</sub> hydrogens than the C<sub>4</sub> hydrogens. The multiplet at 3.2 ppm accounts for both C<sub>6</sub> protons. The N-H proton appeared further downfield at 9.0 ppm. The protecting group was still intact since the aromatic and *t*-butyl signals were still evident in both the proton and carbon NMR spectra. The <sup>13</sup>C NMR spectrum of the thiolactam [160] showed clearly the appearance of the thiocarbonyl quaternary signal at 202 ppm while the carbonyl signal of the lactam precursor had disappeared from its position at 172 ppm (Figure 10).



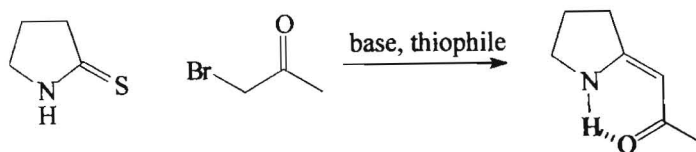
**Figure 10** <sup>13</sup>C NMR spectrum of (5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinethione [160] in CDCl<sub>3</sub>

With the thiolactam [160] in hand our next goal was to protect the nitrogen atom.

### 3.8 Attempted *N*-alkylation of (5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinethione [160]

It is necessary to protect the nitrogen atom of the secondary thiolactam because the Eschenmoser coupling reactions of tertiary amides produce higher yields of products in shorter

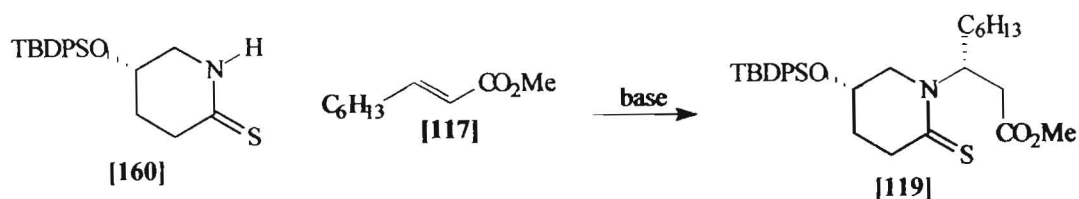
times than secondary thiolactams under similar reaction conditions.<sup>53</sup> Another problematic feature when doing Eschenmoser coupling reactions on secondary thiolactams is that *Z*-enaminones are produced which have incorrect geometry for the future Diels-Alder reaction as shown in Scheme 3.10.<sup>53</sup>



**Scheme 3.10**

Therefore for the later construction of the A ring of fascicularin we thought it a good idea to use methyl 2-nonenoate [117] as it mimics the hexyl chain of the A ring of fascicularin.

### 3.8.1 Attempted *N*-alkylation of 5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinethione [160] using methyl 2-nonenoate [117]



**Scheme 3.11**

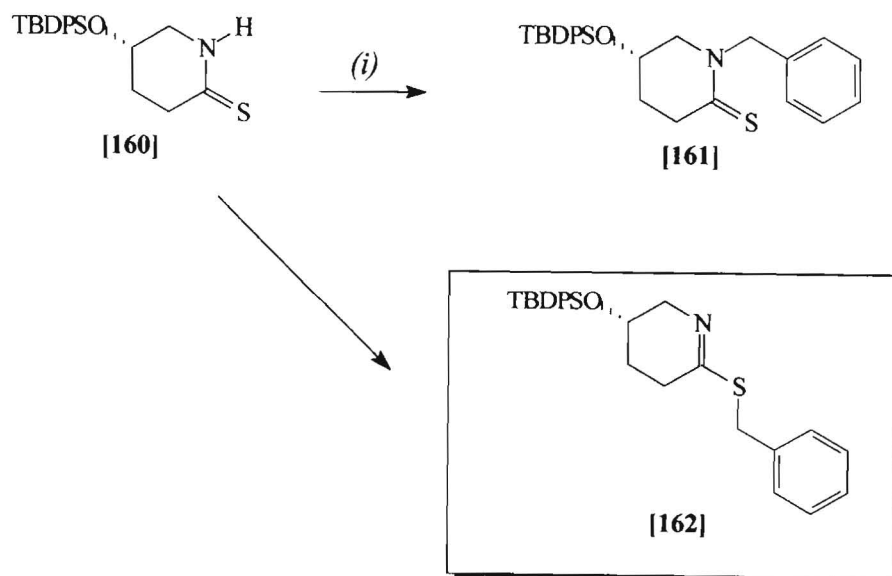
As has been said earlier, literature precedents for the conjugate addition of the lactam to alkenes are found in the work of Michael and Gravestock (Scheme 1.16).<sup>54,57,65-67</sup> Attempted conjugate addition of the thiolactam [160] to methyl 2-nonenoate [117] was carried out at room temperature in THF using a catalytic amount of sodium hydroxide as base (Scheme 3.11). However the reaction failed and only starting materials were recovered. Attempts to improve the synthesis by heating the reaction mixture under reflux and addition of greater than catalytic amounts of NaOH failed to improve matters. TLC analysis showed only unreacted starting material and there was no sign of any product. Changing the base to sodium hydride caused the cleavage of the silyl ether and the only isolated products were *tert*-butyldiphenylsilanol (TBDPSOH) as well as unprotected lactam [127]. Whilst searching for an alternative route to

*N*-alkylate the thiolactam a paper by Guarna *et al.*<sup>71</sup> was discovered. The thiolactam [160] was reacted with methyl-2-nonenoate [117] using 18-crown-6 and potassium carbonate as base. Unfortunately no matter how long the reaction mixture was stirred for, no product formed and only starting materials were recovered.

Bearing in mind that our primary interest was in the construction of the B and C rings of fascicularin, *N*-alkylation is in principle unnecessary as it introduces the molecular scaffold for assembly of the A ring. Our second attempt involved simple benzylation of the nitrogen atom. Our reasoning was that with the nitrogen atom suitably protected we would be able to couple the thiolactam with bromoacetone in an Eschenmoser sulfide contraction reaction. We would then attempt the preparation of the B ring of fascicularin and thereafter remove the benzyl group by catalytic hydrogenation.

### 3.8.2 Attempted preparation of (5*S*)-1-benzyl-5-{{*tert*-butyl(diphenyl)silyl}oxy}-tetrahydro-2(1*H*)-pyridinethione [161]

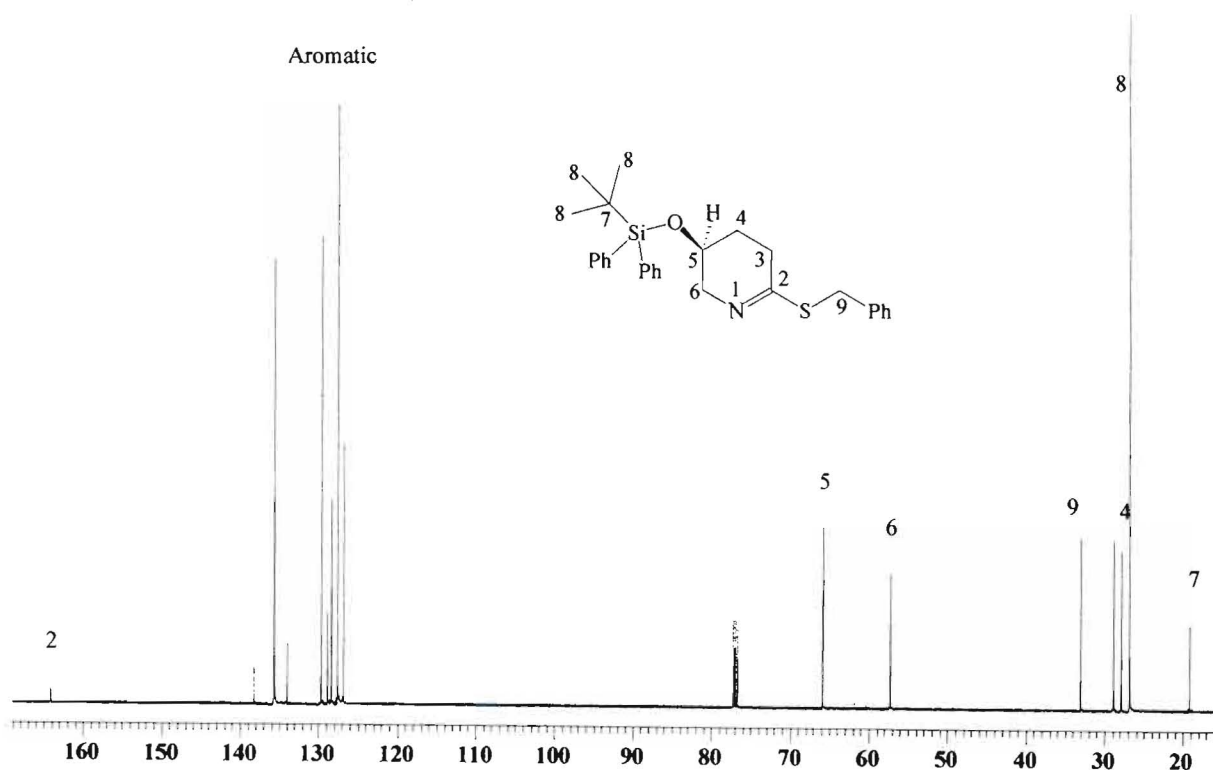
The thiolactam [160] was reacted with benzyl bromide and sodium hydride as base in THF. A reaction did take place but unfortunately not the one we wanted.



**Scheme 3.12** (i) *NaH*, *BnBr*, *THF*, *rt*

The proton NMR spectrum on its own could not tell us if the product had been formed or not.

Based on further NMR analysis we discovered that the benzyl group had bonded to the sulfur atom instead (Scheme 3.12). The *S*-alkylated product 2-(benzylthio)-5-{{*tert*-butyl-(diphenyl)silyl}oxy}-3,4,5,6-tetrahydropyridine [162] was obtained as a light yellow oil in a 63% yield. In the proton NMR spectrum the C<sub>9</sub> protons were each seen as separate doublets at 4.1 ppm and 4.2 ppm. The aromatic protons resonates between 7.21ppm and 7.70 ppm. The absence of the thiocarbonyl signal in the carbon NMR spectrum at 202 ppm attested to the fact that we had lost the C=S group (Figure 11). A signal at 164 ppm corresponded to the quaternary imidothioate carbon atom (C<sub>2</sub>). A new C<sub>9</sub> signal was also observed at 33 ppm.

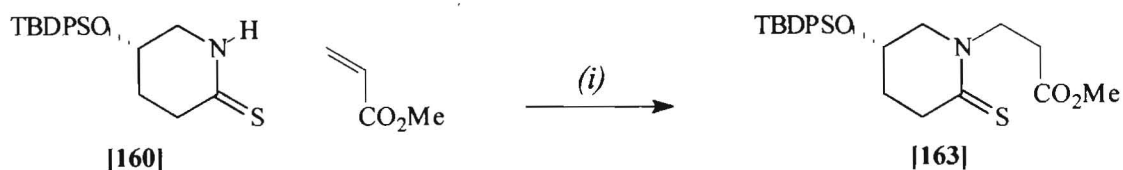


**Figure 11** <sup>13</sup>C NMR spectrum of 2-(benzylthio)-5-{{*tert*-butyl-(diphenyl)silyl}oxy}-3,4,5,6-tetrahydropyridine [162] in CDCl<sub>3</sub>

Considering our failed attempts to protect nitrogen using methyl-2-nonenolate [117] and benzyl bromide we decided to opt for a simple unsubstituted acrylate.

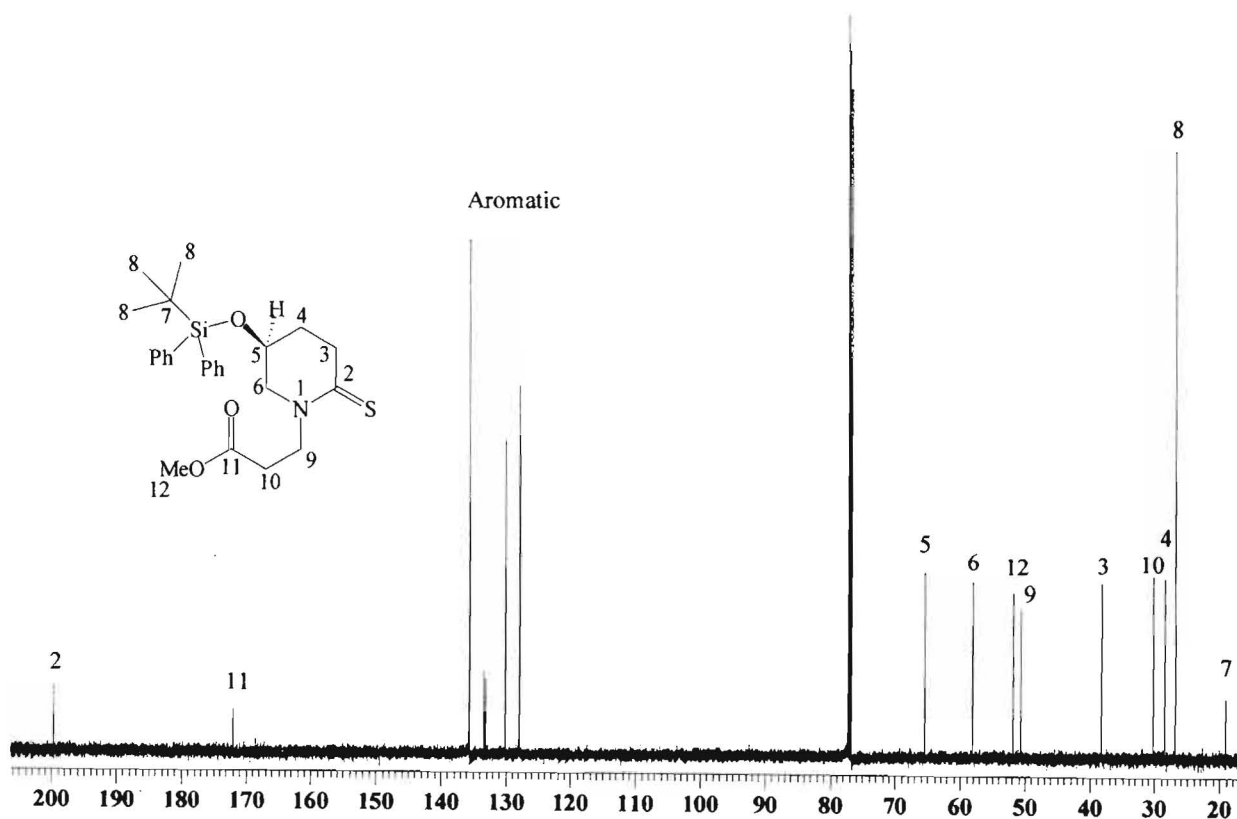


### 3.8.3 Methyl 3-[(5*S*)-5-[[*tert*-butyl(diphenyl)silyl]oxy]-2-thioxotetrahydro-1(2*H*)-pyridinyl]propanoate [163]



**Scheme 3.13** (i) *NaOH* (cat.), *THF*

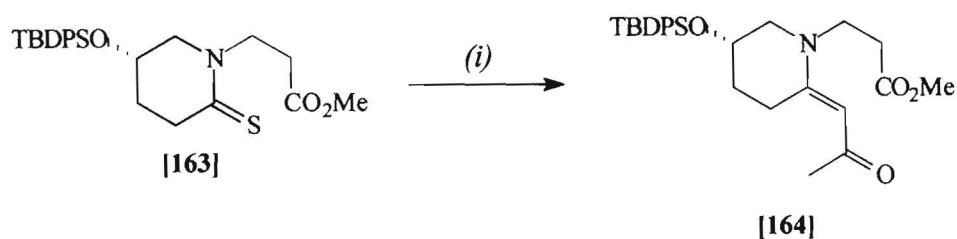
Conjugate addition of the thiolactam [160] to methyl acrylate was carried out at room temperature in *THF* using a catalytic amount of sodium hydroxide as base. This time the reaction was successful. The *N*-alkylated thiolactam [163] was obtained as a colourless oil in a 59% yield. The product was used without further purification. GCMS showed a *m/z* value of 455.



**Figure 12**  $^1\text{H}$  NMR spectrum of methyl 3-[(5*S*)-5-[[*tert*-butyl(diphenyl)silyl]oxy]-2-thioxotetrahydro-1(2*H*)-pyridinyl]propanoate [163] in  $\text{CDCl}_3$

In the  $^{13}\text{C}$  NMR spectrum (Figure 12) the appearance of a new signal downfield at 172 ppm corresponding to the ester functionality was observed and the thiocarbonyl signal at 201 ppm was still present. A singlet at 3.7 ppm in the  $^1\text{H}$  NMR spectrum corresponding to the methyl group was observed. We were unable to rationalize why the conjugate addition thiolactam [160] to methyl 2-nonenoate [117] did not work at all considering the success achieved by Michael and Gravestock (Scheme 1.16).<sup>54,57,65-67</sup> The next step was the Eschenmoser coupling of the thiolactam [160] with bromoacetone.

### 3.9 Methyl 3-[(5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}2-[(*E*)-2-oxopropylidene] tetrahydro-2(1*H*)-pyridinyl]propanoate [164]



**Scheme 3.14** (i)  $\text{BrCH}_2\text{COCH}_3$ ,  $\text{Et}_3\text{N}$ ,  $\text{Ph}_3\text{P}$ ,  $\text{CH}_3\text{CN}$

Overnight reaction of thiolactam [163] and bromoacetone in acetonitrile gave the corresponding *S*-alkylated bromide salt. Subsequent reaction with triphenylphosphine and triethylamine afforded the vinylogous amide [164] in 53% yield. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectrum were assigned with the aid of DEPT, COSY and GHSQC spectra. In the proton NMR spectrum four singlets for  $\text{C}_8$ ,  $\text{C}_{15}$ ,  $\text{C}_{12}$  and  $\text{C}_{13}$  protons were observed at 1.04 ppm, 2.05 ppm, 3.67 ppm and 5.03 ppm respectively (Figure 13). The  $\text{C}_3$ ,  $\text{C}_{10}$ ,  $\text{C}_4$  and  $\text{C}_9$  methylene protons were assigned using the COSY spectrum. The diastereotopic  $\text{C}_6$  protons are seen as separate multiplets at 3.1 ppm and 3.2 ppm. The methine  $\text{C}_5$  proton resonates at 4.0 ppm and finally the aromatic protons are seen in the region 7.36-7.65 ppm.

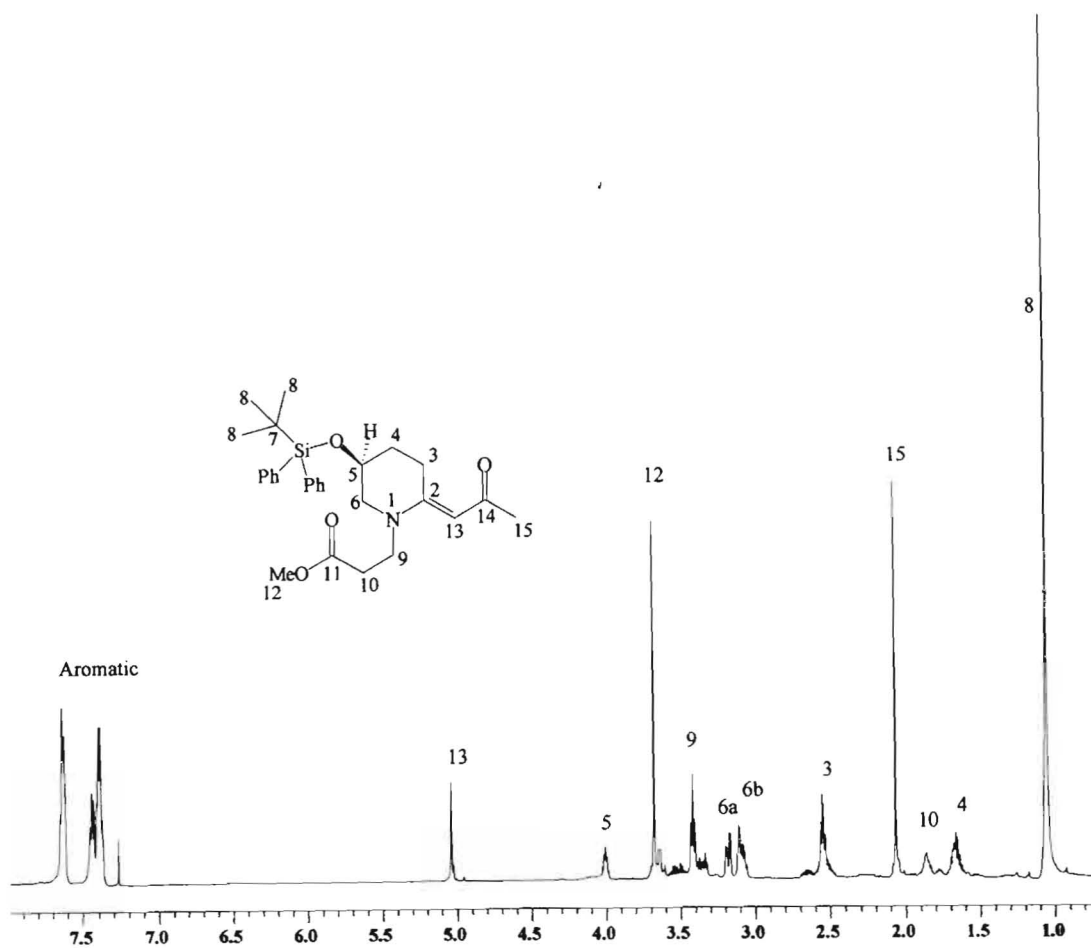


Figure 13  $^1\text{H}$  NMR spectrum of methyl 3-[(5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}2-[(*E*)-2-oxopropylidene] tetrahydro-2(1*H*)-pyridinyl]propanoate [164] in  $\text{CDCl}_3$

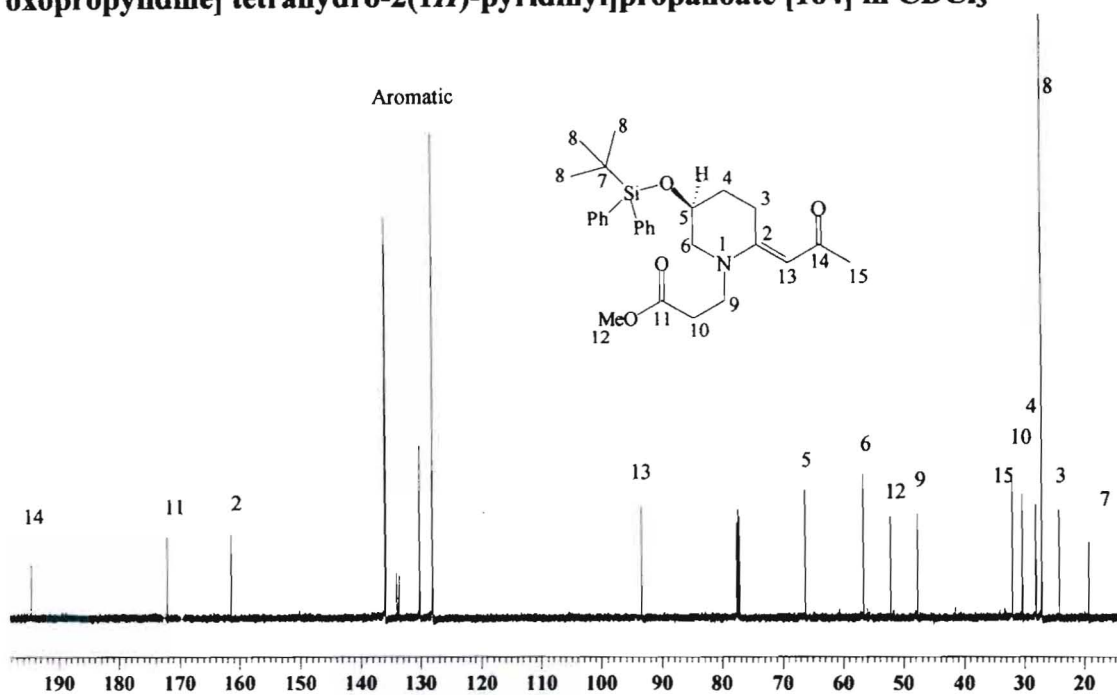
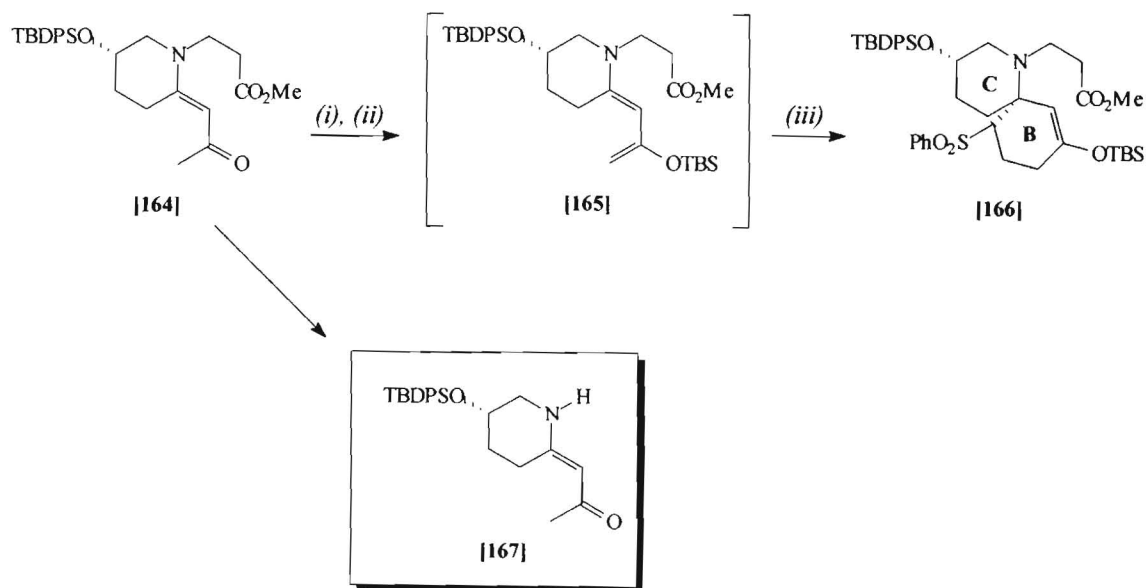


Figure 14  $^{13}\text{C}$  NMR spectrum of methyl 3-[(5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}2-[(*E*)-2-oxopropylidene] tetrahydro-2(1*H*)-pyridinyl]propanoate [164] in  $\text{CDCl}_3$

The carbon signals were assigned using DEPT and GHSQC spectra. The 3 quaternary carbons at C<sub>2</sub>, C<sub>11</sub>, and C<sub>14</sub> were observed at 161 ppm, 172 ppm and 195 ppm respectively ( Figure14). The thiocarbonyl peak at about 200 ppm is absent providing further proof of the success of the reaction.

### 3.10 Attempted diene and azabicycle formation

Our aim was to synthesise 1-amino-3-siloxy-1,3-butadiene [165], by treatment of vinylogous amide [164] with KHMDS followed by the addition of TBSCl and react it in a Diels-Alder reaction using phenyl vinyl sulfone as dienophile to afford azabicycle [166] (Scheme 3.15). This was based on the favourable results reported by Rawal and co-workers.<sup>58,59,73-77</sup> The diene formation step (164→165) is a one-pot reaction. The diene [165] can be used without further purification according to Rawal. We decided to do the reaction (164 → 166) in one pot as we were unsure of the stability of diene [165]. Thus, without purification, phenyl vinyl sulfone was then added to the reaction mixture containing the putative amino siloxy diene [165].

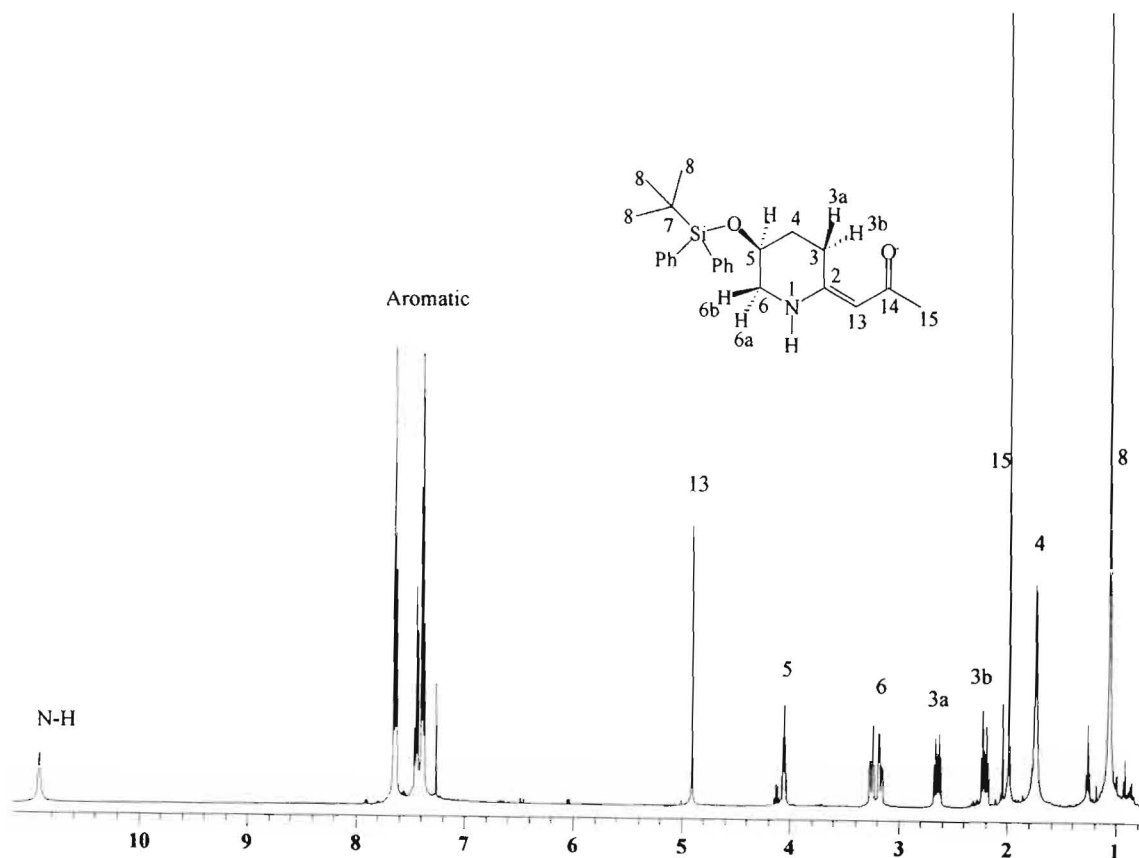


**Scheme 3.15** (i) KHMDS, THF (ii) TBSCl (iii) phenyl vinylsulfone

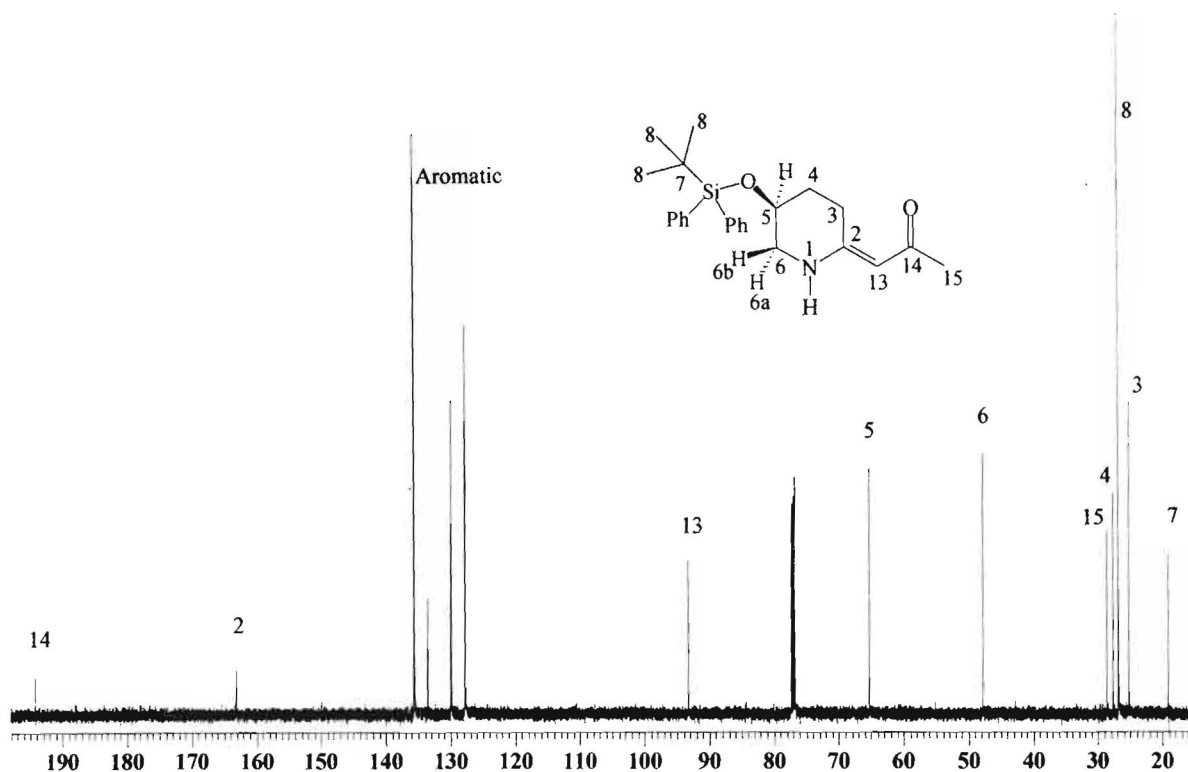
GCMS and NMR data clearly showed that the product obtained was not the desired azabicycle but instead the vinylogous amide, 1-[(5*S*)-5-{*tert*-butyl(diphenyl)silyl}oxy]tetrahydro-2(1*H*)-



piperidinylidene]propanone [167]. GCMS showed a  $m/z$  value of 393, which was less than  $m/z$  479 of the starting material. In both the proton and carbon NMR spectra there were fewer signals than observed for the starting material. A new signal in the proton NMR spectrum was observed further downfield at 10.9 ppm corresponding to the hydrogen atom on nitrogen (Figure 15). The structure was confirmed by  $^1\text{H}$ ,  $^{13}\text{C}$  and DEPT NMR experiments. COSY and GHMQC spectra proved invaluable for the unambiguous assignment of all the NMR signals. NOESY experiments were carried out in an attempt to unambiguously assign the methylene protons at  $\text{C}_3$  and  $\text{C}_6$  in the proton NMR. Figure 15 and 16 show the proton and carbon NMR of the vinylogous amide [167]. In the carbon NMR spectrum two quaternary carbons were observed similar to those of the starting material corresponding to  $\text{C}_2$  and  $\text{C}_{14}$ . The result was not what we wanted, but as is the case with most scientific endeavours, constituted a very important serendipitous discovery. As we discussed earlier on in section 3.8, secondary thiolactams usually give *Z*-enaminones under forcing conditions. This result thus constitutes a mild route to secondary *E*-enaminones.

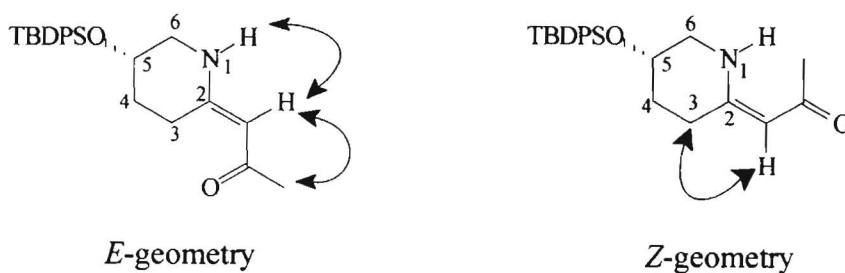


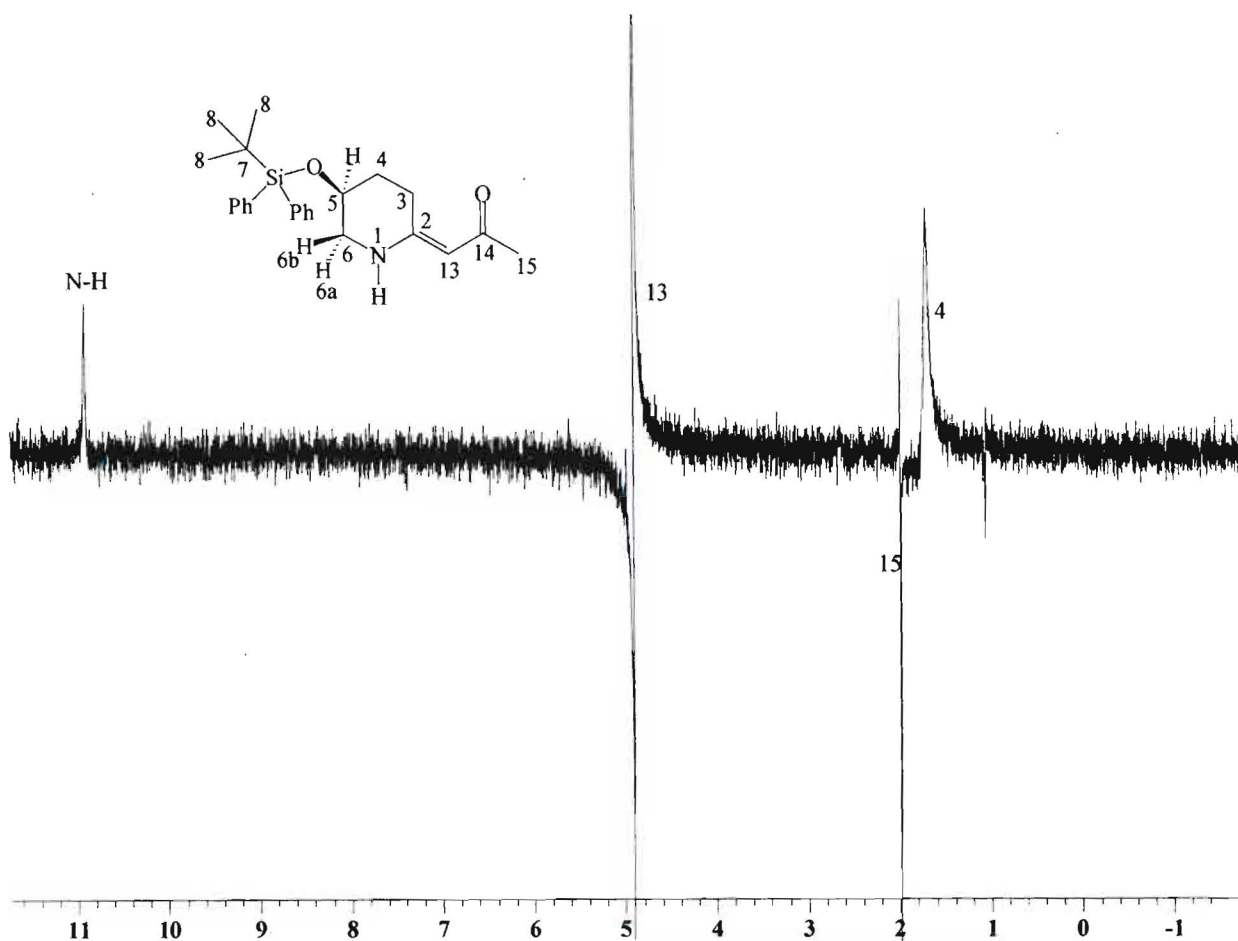
**Figure 15**  $^1\text{H}$  NMR spectrum of 1-[(5*R*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)- piperidinylidene]propanone [167] in  $\text{CDCl}_3$



**Figure 16**  $^{13}\text{C}$  NMR spectrum of 1-[(5*R*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-piperidinylidene]propanone [167] in  $\text{CDCl}_3$

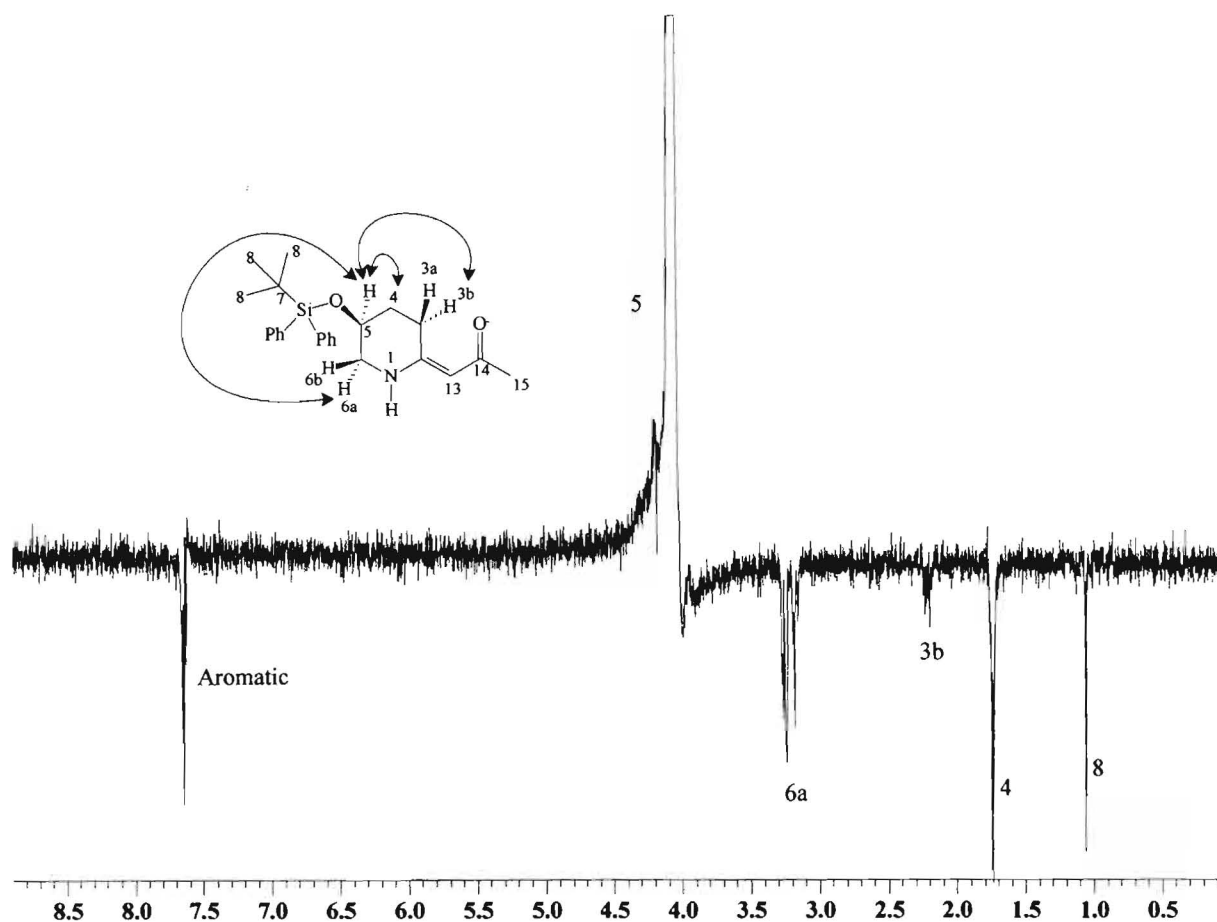
From the NOESY spectrum (Figure 17) we saw that irradiation of the vinyl proton at 4.9 ppm showed an enhancement of the NH proton at 10.9 ppm and the methylene protons at  $\text{C}_4$  as well as the methyl protons at  $\text{C}_{15}$ . There was no correlation between the vinyl proton and the  $\text{C}_3$  protons, which would be expected if the compound existed as the *Z*-isomer, providing the further proof for the *E*-geometry of the enaminone.





**Figure 17** NOESY spectrum of 1-[(5*R*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-piperidinylidene]propanone [167] showing irradiation of the vinyl proton at 4.9 ppm

Irradiation of H-5 (Figure 18) showed correlation with some of the aromatic protons, the *t*-butyl protons, the methylene protons at C<sub>4</sub>, the 6a proton as well as a small correlation to the 3b proton. This NOESY spectrum proved invaluable in the unambiguous assignment of the diastereotopic protons at C<sub>3</sub> and C<sub>6</sub>. The COSY spectrum was used to differentiate the C<sub>3</sub> protons from the C<sub>6</sub> protons.



**Figure 18** NOESY spectrum of 1-[(5*R*)-5-{*tert*-butyl(diphenyl)silyloxy}tetrahydro-2(1*H*)-piperidinylidene]propanone [167] showing irradiation of the methine (H-5) proton at 4.0 ppm.

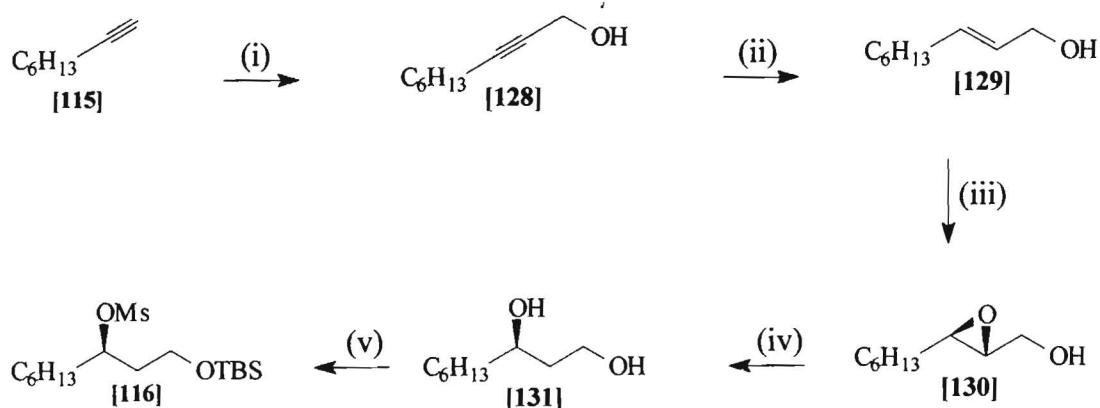
Considering our failed attempt to synthesise azaspirocycle [166] we moved to our next goal, namely the enantioselective synthesis of mesylate [116]. Mesylate [116] contains the structural features necessary for the construction of the A ring of fascicularin (Scheme 1.12).

### 3.11 Synthesis of (3*R*)-1,3-nonanediol [131]

The synthesis of (3*R*)-1,3-nonanediol [131] from 1-octyne [115] was reported by Kitching and co-workers in their work on the synthesis of the components of the rectal gland secretion of fruit flies.<sup>63</sup> The synthesis begins with the formation of the Grignard reagent ethylmagnesium bromide, synthesized from magnesium and bromoethane in ether. Ethylmagnesium bromide was then used as base to deprotonate 1-octyne [115] to give oct-1-ynylmagnesium bromide

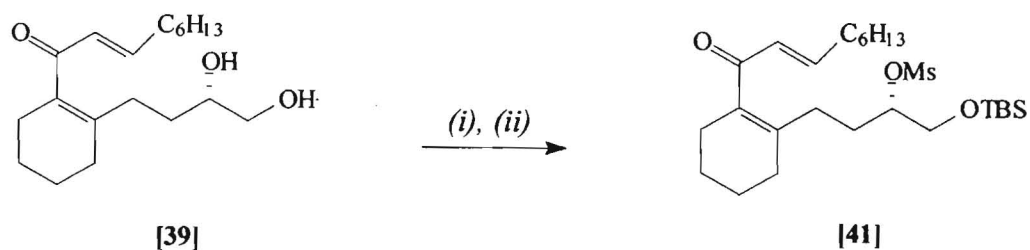


which on reaction with formaldehyde provided 2-nonyn-1-ol [128]. The alkyne was reduced with  $\text{LiAlH}_4$  to give the allylic alcohol [129] as exclusively the *E*-isomer.



**Scheme 3.16** (i)  $\text{EtMgBr}$ ,  $\text{CH}_2\text{O}$ ; (ii)  $\text{LiAlH}_4$ ; (iii)  $(-)$ -DET,  $\text{Ti}(\text{O}^i\text{Pr})_4$ , TBHP; (iv) Red-Al; (v) Ref 32.

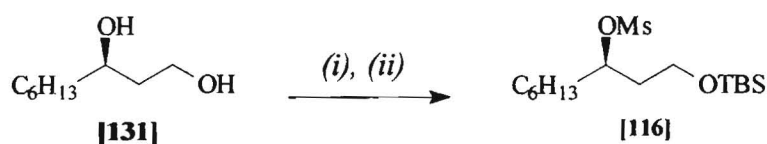
In Sharpless epoxidation, allylic alcohols are converted to optically active epoxides in better than 90% enantiomeric excess.<sup>89</sup> Sharpless epoxidation has been used during the preparation of a large number of natural products.<sup>89,90</sup> Thus treatment of the allylic alcohol [129] with  $(-)$ -diethyl tartrate, titanium tetraisopropoxide and *tert*-butyl hydroperoxide afforded epoxide [130]. Since both  $(-)$  and  $(+)$ -diethyl tartrate are readily available either enantiomer of the product could be prepared.<sup>90</sup> Reduction of the epoxide [130] with Red-Al  $\{[(\text{CH}_3\text{OCH}_2\text{CH}_2\text{O})_2\text{AlH}_2]\text{Na}\}$ , afforded (3*R*)-1,3-nonyn-1,3-diol [131]. Unfortunately the optical rotation and high resolution mass spectrum of the sample were not obtained as the sample had decomposed. The next step was the regioselective protection of the hydroxyl groups.



**Scheme 3.17** (i)  $\text{TBSCl}$ ,  $\text{Et}_3\text{N}$ , DMAP (ii)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$

Molander and Rönn reported the selective protection of a primary alcohol in the presence of a secondary alcohol using TBSCl/Et<sub>3</sub>N/DMAP, immediately followed by the mesylation of the secondary alcohol using Et<sub>3</sub>N/MsCl, in their work on the total synthesis of cylindricine C (Scheme 3.17).<sup>32</sup>

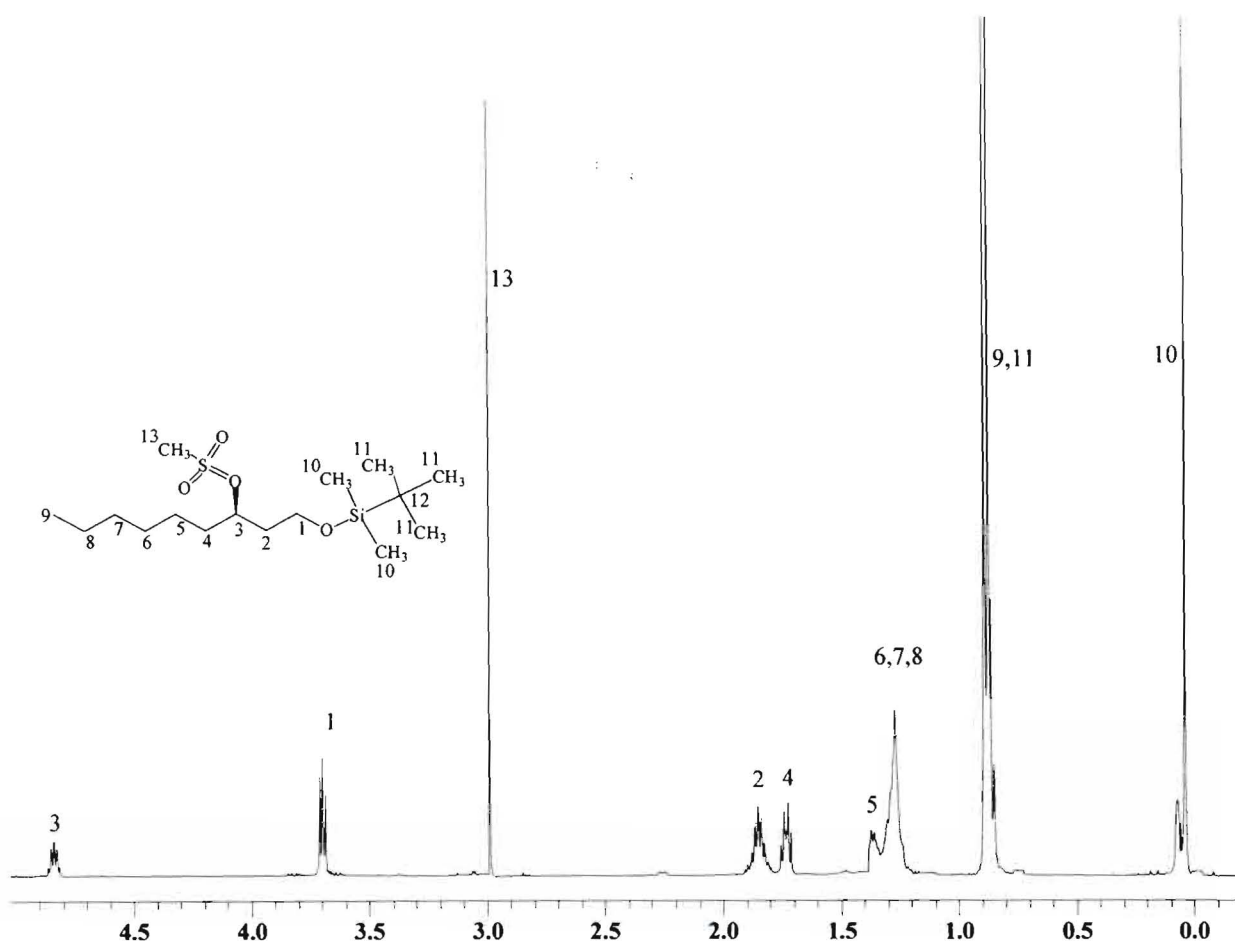
Close inspection of compound [131] and [116] in Scheme 3.18 reveals similarities with compounds [39] and [41] in Scheme 3.17. Thus we attempted the synthesis of mesylate [116] from 1,3-diol [131] using the methodology reported by Molander.<sup>32</sup>



**Scheme 3.18** (i) TBSCl, Et<sub>3</sub>N, DMAP (ii) MsCl, Et<sub>3</sub>N

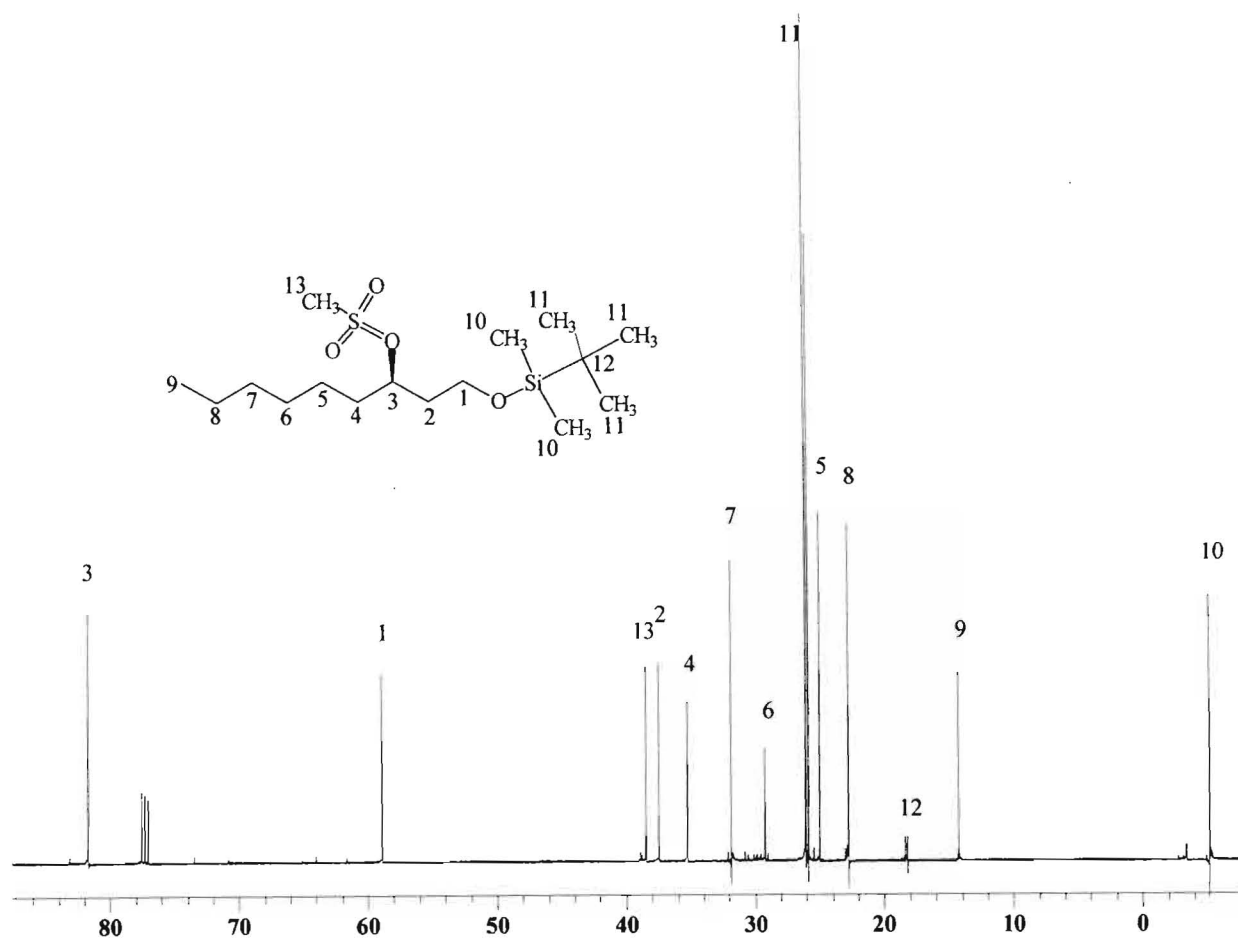
Fortuitously the protection of the two OH groups of the diol was accomplished in one pot. The primary alcohol was selectively protected by the addition of TBSCl, Et<sub>3</sub>N and DMAP to give the monoprotected alcohol. This was immediately followed by the addition of methane sulfonyl chloride and Et<sub>3</sub>N to give (1*R*)-1-(2-{{tert-butyl(dimethyl)silyl}oxy}ethyl)heptyl methanesulfonate [116] in quantitative yield.

The product was characterized by <sup>1</sup>H, <sup>13</sup>C as well as 2D NMR spectroscopy. In the proton NMR spectrum the formation of the product was confirmed by the presence of the three singlets, C<sub>10</sub>, C<sub>11</sub> which overlaps with the C<sub>9</sub> triplet and the C<sub>13</sub> singlet. The COSY spectrum was used to assign the other proton signals (Figure 19). C<sub>1</sub> appeared as a triplet at 3.7 ppm and C<sub>3</sub> appeared as a multiplet at 4.8 ppm.



**Figure 19**  $^1\text{H}$  NMR spectrum of (1*R*)-1-(2-{{tert-butyl(dimethyl)silyloxy}}-ethyl)heptyl methanesulfonate [116]

All carbon peaks were assigned unambiguously except for  $\text{C}_7$  and  $\text{C}_8$  which were assigned with help from ACD labs,<sup>91</sup> a computer program which simulates carbon and proton NMR spectra (Figure 20). From the starting material there was only one methyl group corresponding to  $\text{C}_9$ , the DEPT spectrum of the product showed four methyl signals corresponding to  $\text{C}_9$ ,  $\text{C}_{10}$ ,  $\text{C}_{11}$  and  $\text{C}_{13}$ .



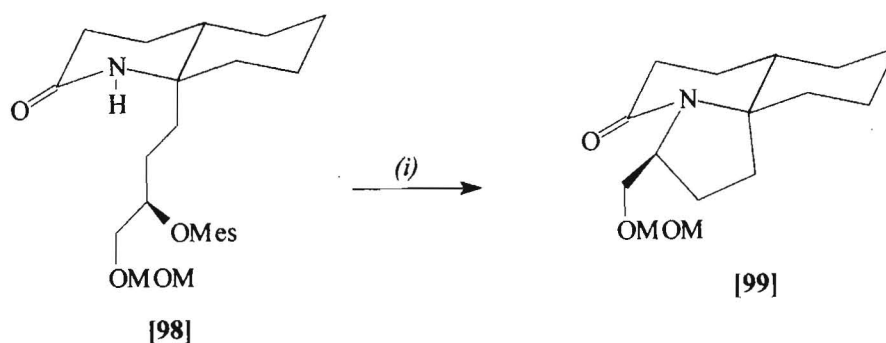
**Figure 20**  $^{13}\text{C}$  NMR spectrum of (1*R*)-1-(2-{{tert-butyl(dimethyl)silyl}oxy}-ethyl)heptyl methanesulfonate [116]

Having synthesized mesylate [116], we intended to use it for the *N*-alkylation of lactam [114].

### 3.12 Attempted coupling of mesylate [116] with lactam [114]

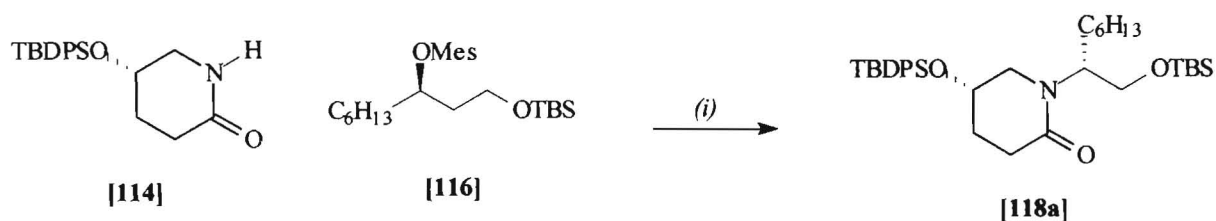
Kibayashi and co-workers reported the synthesis of tricyclic lactam [99] from the mesylate [98] in their work on the first total synthesis of lepadiformine [12] (Scheme 1.10).<sup>8</sup> *t*-BuOK was added to a solution of bicyclic lactam [98] in THF and the reaction mixture was stirred at room temperature for 30 min, followed by aqueous workup and extraction with diethyl ether. After column chromatography the tricyclic lactam [99] was obtained in a 91% yield.





**Scheme 3.19** (i) *t*-BuOK, THF

We intended to use the same method to synthesise the *N*-alkylated lactam [118a] (Scheme 3.20). We hoped an  $S_N2$  reaction between the lactam [114] and the stereodefined mesylate [116] would give alkylated lactam [118a] with the correct absolute stereochemistry found in fascicularin [13].



**Scheme 3.20** (i) *t*-BuOK, THF

The reaction was attempted using Kibayashi's method described above. Unfortunately only the starting materials were recovered. Our system is different from the work reported by Kibayashi and co-workers (Scheme 3.19). The essential difference between our reaction and Kibayashi's is that their reaction is taking place intramolecularly. In our case, the amide and the mesylate are different molecules, hence an intermolecular process. The failure of this reaction unfortunately meant that we could not couple the C ring [114] to the scaffold for the A ring [116] of our target alkaloid fascicularin [13].

### 3.13 CONCLUSION

The route towards the synthesis of the marine alkaloid described in chapter 1 looked attractive and appeared feasible based on the literature precedents already discussed in chapters 1, 2 and 3.

Unfortunately in practice our synthesis was thwarted at certain key steps. We discovered that what works for one system does not necessarily mean it will work for another. To summarise we were able to prepare the C ring of fascicularin enantioselectively. This was further modified to serve as a scaffold for constructing the B ring of fascicularin. Attempted enolate formation and trapping on oxygen was scuppered by competitive deprotonation at an alternative nucleophilic position, namely the position  $\beta$  to nitrogen. The scaffold for the A ring was prepared enantioselectively in a multistep synthesis. However the crucial N-C bond formation that would link the C ring to the A ring precursor failed.

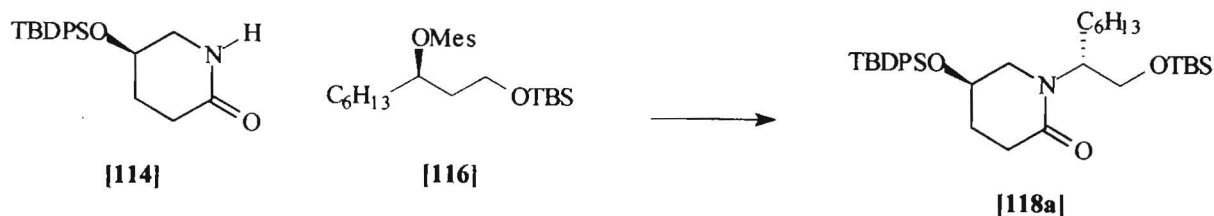
All is not doom and gloom as there are three noteworthy achievements that have emanated from this project.

In summary the achievements of the projects are as follows:

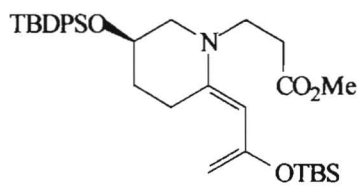
- ❖ The successful enantioselective preparation of the C ring of fascicularin.
- ❖ The successful enantioselective preparation of the scaffold for constructing the A ring of fascicularin.
- ❖ The discovery of a mild method for the preparation of secondary *E*-enaminones.

Suggestions for future work

- ❖ Different bases and solvents can be used for the  $S_N2$  reaction between the lactam [114] and the mesylate [116], to link the C ring to the A ring precursor.



- ❖ Development of an alternative route towards the construction of the diene **[167]**, since the ambident reactivity of the vinylogous amide hinders the reaction.

**[167]**

In conclusion, significant progress was made towards our goals and a number of novel compounds were synthesized *en route*.

## CHAPTER 4

### EXPERIMENTAL

Flash chromatography was performed using either column chromatography with Merck silica gel 60 (230-400 mesh; particle size 0.040-0.063 nm) or by radial chromatography on a chromatotron using Merck silica gel 60 PF<sub>254</sub>, containing gypsum. Thin layer chromatography (TLC) was performed on Merck Aluminum sheets coated with silica gel 60 PF<sub>254</sub> (layer thickness 0.2mm), with visualization of the compounds by inspection under light (254/365nm) and/or by exposure to iodine vapour and/or dipping in anisaldehyde stain.

<sup>1</sup>H and <sup>13</sup>C NMR as well as 2D NMR experiments were recorded on a Varian Gemini 200 MHz and a Varian Unity-Inova 500 MHz spectrometer. COSY, GHMQC, GHSQC and DEPT spectra were routinely recorded to facilitate the unambiguous assignment of NMR signal. For NMR samples, CDCl<sub>3</sub> was used as the solvent except for (5*S*)-5-hydroxytetrahydro-2(1*H*)pyridinone [127] where CD<sub>3</sub>OD was used. Spectra recorded in CDCl<sub>3</sub> were calibrated using solvent signal at 7.26 ppm for <sup>1</sup>H and 77.0 ppm for <sup>13</sup>C, while <sup>1</sup>H and <sup>13</sup>C spectra run in CD<sub>3</sub>OD were calibrated using the solvent signals. All chemical shift values are given in ppm and coupling constants, *J*, are given in Hz. Spectroscopic data is only given for new compounds. Abbreviations used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

GCMS spectra were recorded on a Hewlett Packard (HP5988A) using a quadrupole mass analyzer, while HRMS were recorded on a double-focusing Kratos MS 80RF mass spectrometer at the Cape Technikon Mass Spectrometry Unit. Melting points were recorded on a Kofler hot stage apparatus and are uncorrected. IR spectra were recorded with a Perkin Elmer Spectrum One spectrometer as thin films between NaCl plates. The absorptions are reported in wave number (cm<sup>-1</sup>) scale, in the range 400-4000 cm<sup>-1</sup>. A 700W National domestic microwave oven was used for microwave reactions. Optical rotations were obtained on a Perkin-Elmer polarimeter 241 at 589 nm.

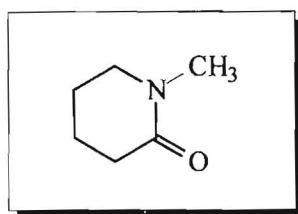
All solvents used for the reactions and preparative chromatography were distilled. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone; acetonitrile,



dichloromethane and triethylamine from calcium hydride; toluene from sodium; pyridine from potassium hydroxide.  $-78^{\circ}\text{C}$  temperatures were attained using dry ice-acetone bath. Great care was taken to ensure moisture sensitive reagents were used under inert conditions. Thus glassware was routinely heated under vacuum and the vacuum replaced with  $\text{N}_2$  gas. Concentration or evaporation *in vacuo* refers to the removal of solvent under reduced pressure (9 mmHg,  $30\text{--}40^{\circ}\text{C}$ ) using a rotary evaporator. Yields are calculated from the immediate synthetic precursor used.

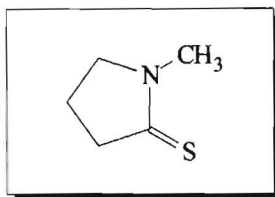
#### 4.1. Attempted preparation of the azaspirocycles [111] and [112]

##### 4.1.1. 1-Methyltetrahydro-2(1H)-pyridinone [104]



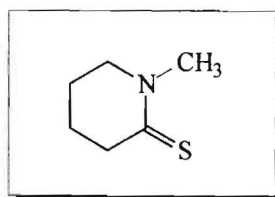
Sodium hydride (50% suspension in mineral oil, 5.80 g, 33.3 mmol) was added to a solution of piperidin-2-one [102] (3.00 g, 30.3 mmol) and iodomethane (4.73 g, 33.3 mmol) in dry THF (50 mL) at  $0^{\circ}\text{C}$ . The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (20 mL) and the organic components extracted with ethyl acetate ( $3 \times 20$  mL). The organic phase was separated and dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Purification by silica gel chromatography (ethyl acetate) afforded 1-methyltetrahydro-2(1H)-pyridinone (2.26 g, 20.0 mmol, 66%) as a yellow oil;  $R_f$  0.33 (ethyl acetate);  $m/z$  113. The spectroscopic data were in close agreement with those reported by Nabeya.<sup>93</sup>

#### 4.1.2. 1-Methyl-2-pyrrolidinethione [105]



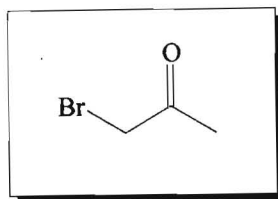
Smith *et al.* reported the synthesis of the thiolactams [105] and [106].<sup>79</sup> Lawesson's reagent (7.35 g, 18.2 mmol) was added to a solution of 1-methyl-2-pyrrolidinone [103] (3.00 g, 30.2 mmol) in toluene (120 mL). The reaction mixture was heated under reflux for 2h and the solvent was evaporated *in vacuo*. The resultant mixture was purified by silica gel chromatography (50% ethyl acetate/hexane) giving 1-methyl-2-pyrrolidinethione [105] as a yellow oil (3.14 g, 27.3 mmol, 90%);  $R_f$  0.47 (60% ethylacetate/hexane);  $m/z$  115. The spectroscopic data were in close agreement with those reported by Smith *et al.*<sup>79</sup>

#### 4.1.3. 1-Methyltetrahydro-2(1H)-pyridinethione [106]



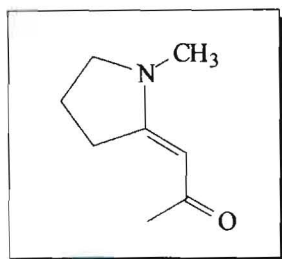
Lawesson's reagent (2.19 g, 5.42 mmol) was added to a solution of 1-methyltetrahydro-2(1H)-pyridinone [104] (1.02 g, 9.03 mmol) in toluene (40 mL). The reaction mixture was heated under reflux for 2h and the solvent was evaporated. The resultant mixture was purified by column chromatography (50% ethyl acetate/hexane) giving 1-methyltetrahydro-2-(1H)pyridinethione as the yellow oil (1.00 g, 7.77 mmol, 86%);  $R_f$  0.52 (60% ethylacetate/hexane);  $m/z$  129. The spectroscopic data were in close agreement with those reported by Smith *et al.*<sup>79</sup>

#### 4.1.4. Bromoacetone



Bromine (35.4 mL, 691 mmol) was added dropwise to a stirred solution of water (160 mL), acetone (50 mL, 0.68 mol) and glacial acetic acid (37 mL) at 65°C. The resultant solution was diluted with cold water (80 mL), cooled in an ice bath to 10°C and made neutral by portionwise addition of anhydrous sodium carbonate (80 g). The organic layer was separated and dried over anhydrous CaCl<sub>2</sub>. The remaining oil was distilled using a short path distillation apparatus to afford bromoacetone as a colourless oil (55.9 g, 408 mmol, 60%); b.p (28 - 30°C /9 mmHg) lit.<sup>72</sup> (40-42°C /13 mmHg).

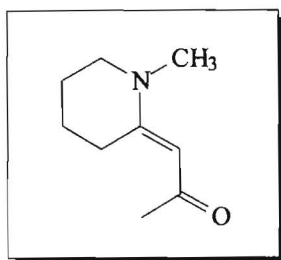
#### 4.1.5. 1-(1-Methyl-2-pyrrolidinylidene)propanone [107]



Michael co-workers reported the synthesis of 1-(1-methyl-2-pyrrolidinylidene)propanone [107].<sup>80</sup> Our synthesis begins with the addition of bromoacetone (3.60 g, 26.0 mmol) to a stirred solution of 1-methyl-2-pyrrolidinethione [105] (1.50 g, 10.0 mmol) in dichloromethane (15 mL). The reaction mixture was stirred overnight at room temperature. The volatiles were removed under vacuum and the residue was dissolved in dichloromethane (30 mL). Triphenylphosphine (3.41 g, 13.0 mmol) and triethylamine (2.70 mL, 19.5 mmol) were added and the reaction mixture was stirred for 30 minutes. Water (50 mL) was added and the organic product was extracted with ethyl acetate (3 × 50 mL). The product was purified by column chromatography (60% ethyl acetate/hexane) giving 1-(1-methyl-2-pyrrolidinylidene)propanone as an orange-brown oil (807 mg, 6.24 mmol, 58%); R<sub>f</sub> 0.13 (60%

ethylacetate/hexane);  $m/z$  139. The spectroscopic data were in close agreement with those reported by Michael and co-workers.<sup>80</sup>

#### 4.1.6. 1-(1-Methyl-2-piperidinylidene)propanone [108]



Bromoacetone (1.79 g, 12.8 mmol) was added to a stirred solution of 1-methyltetrahydro-2-(1H)pyridinethione [106] (1.50 g, 11.6 mmol) in acetone (10 mL). The reaction mixture was kept in the fridge (4°C) overnight. The solvent was evaporated and the resulting salt was dissolved in acetonitrile (40 mL) and then treated with triphenylphosphine (3.05 g, 11.6 mmol) and triethylamine (1.77 mL, 12.8 mmol). The resulting reaction mixture was stirred for 30 min, filtered and the solvent was evaporated. The resultant mixture was treated with ethyl acetate and filtered again. The solvent was evaporated and purification by column chromatography (60% ethyl acetate/hexane) gave 1-(1-methyl-2-piperidinylidene)propanone as a brown oil (551 mg, 3.59 mmol, 31%);  $R_f$  0.13 (60% ethylacetate/hexane);  $m/z$  153. The spectroscopic data were in close agreement with those reported by Leete and co-workers.<sup>94</sup>

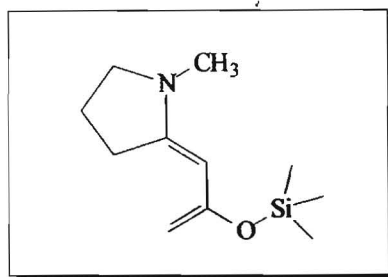
#### 4.1.7. Alternative method to 1-(1-methyl-2-piperidinylidene)propanone [108]

Bromoacetone (5.35 g, 39.1 mmol) was added dropwise to a solution of triphenylphosphine (10.0 g, 38.1 mmol) in acetone (120 mL). The resulting mixture was heated under reflux for 45 minutes. The solution was cooled to 0°C. The precipitate was filtered off and washed with ether (3 × 20 mL). The resultant salt (675 mg, 2.12 mmol) was mixed with 1-methyltetrahydro-2(1H)-pyridinone [104] (200 mg, 177 mmol) and the mixture was heated in the microwave at different power settings (low, med, med-low, high) but in each case only the starting materials were recovered.



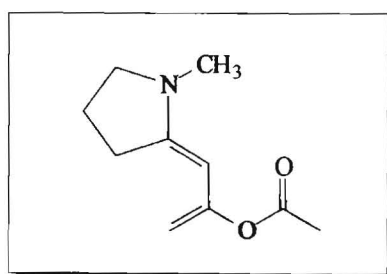
#### 4.1.8. Attempted diene formation.

##### 4.1.8.1. Attempted silylation of vinylogous amide [107]



THF (5 mL) was added into a dried flask and cooled to 0°C. Diisopropylamine (0.14 mL, 1.1 mmol) was added followed by 1M solution of butyllithium in THF (1.17 mL, 1.17 mmol). The reaction mixture was cooled to -78°C and 1-(1-methyl-2-pyrrolidinylidene)propanone [107] (125 mg, 0.898 mmol) was added. The reaction was stirred for a 15min followed by the addition of TMSCl (0.15 mL, 1.17 mol) and stirred for further 15min. The solvent was evaporated and the residue was treated with cold hexane. The GCMS showed the starting material. The reaction was repeated at a higher temperature (0°C) and left for a longer period but still no product formed and only the starting material was recovered. The base was changed to KH and NaH but these changes failed to produce the desired product.

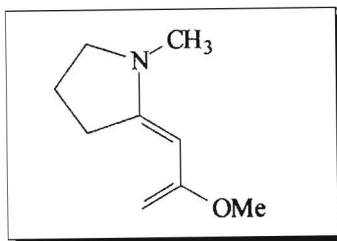
##### 4.1.8.2. Attempted acylation of vinylogous amide [107]



1-(1-Methyl-2-pyrrolidinylidene)propanone [107] (100 mg, 0.718 mmol) was added to a solution of acetic anhydride (0.14 mL, 1.4 mmol) and *p*-TsOH (411 mg, 2.16 mmol). The solution was heated to 140°C. After 3h the solution was cooled to room temperature and dichloromethane (15 mL) was added. The resulting solution was washed with water (2 × 20 mL), 5% sodium carbonate (2 × 20 mL) and dried over MgSO<sub>4</sub>. TLC analysis showed only the

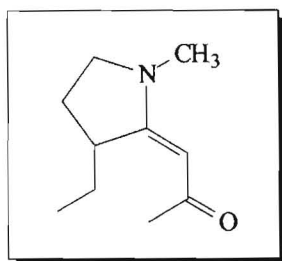
starting material and this was also confirmed by the GCMS results. The reaction was repeated using  $\text{HClO}_4$ ,  $\text{K}_2\text{CO}_3$  and  $\text{CCl}_4$ , the results were similarly fruitless.

#### 4.1.8.3. Attempted alkylation of vinylogous amide [107]



Sodium hydride (50% suspension in mineral oil, 38 mg, 0.79 mmol) was added to a solution of 1-(1-methyl-2-pyrrolidinylidene)propanone [107] (100 mg, 0.718 mmol) and iodomethane (0.05 mL, 0.8 mmol) in dry THF (5 mL) at  $0^\circ\text{C}$ . The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was monitored by TLC and no product was formed, only the starting materials were recovered.

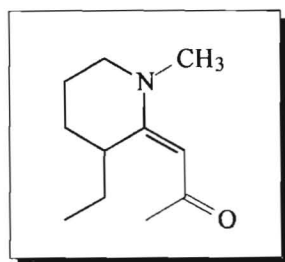
#### 4.1.9. 1-(3-Ethyl-1-methyl-2-pyrrolidinylidene) propanone [151]



A mixture of the vinylogous amide [107] (50 mg, 0.36 mmol) and potassium hydride (144 mg, 3.59 mmol, 35% mineral oil suspension, washed three times with dry ether) in ether (5 mL) was stirred at  $0^\circ\text{C}$  for 0.5h. Ethyl iodide (1.5 mL, 19 mmol) was then added dropwise and the stirring was continued for another hour. A drop of water was added cautiously and the mixture was concentrated under vacuum. The reaction was quenched with water (20 mL) and the organic components extracted with ethyl acetate ( $3 \times 20$  mL). The organic phase was dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Purification by radial chromatography (30% ethyl acetate/hexane) afforded 1-(3-ethyl-1-methyl-2-pyrrolidinylidene)propanone as an orange/brown (38 mg, 0.23 mmol, 64%);  $R_f$  0.32 (60% ethyl acetate/hexane);  $\nu_{\text{max}}$  (film)/ $\text{cm}^{-1}$

2972-2873 (C-H), 1703 (C=O), 1629 (C=C);  $\delta_{\text{H}}$  (500MHz :  $\text{CDCl}_3$ ) 0.93 (3H, t,  $J$  7.3,  $\text{CH}_3\text{CH}_2$ ), 1.22-1.29 (2H, m,  $\text{CH}_3\text{CH}_2$ ), 1.68-1.71 (1H, m,  $\text{CH}_2\text{CH}_a\text{H}_b\text{CH}$ ), 1.74-78 (1H, m,  $\text{CH}_2\text{CH}_a\text{H}_b\text{CH}$ ), 2.02 (3H, s,  $\text{COCH}_3$ ), 2.79 (3H, s,  $\text{NCH}_3$ ), 3.23 (1H, t,  $J$  9.9,  $\text{NCH}_a\text{H}_b$ ), 3.43-3.48 (1H, q,  $J$  10.0,  $\text{NCH}_a\text{H}_b$ ), 3.70 (1H, t,  $J$  8.2,  $\text{CH}_2\text{CH}_2\text{CH}$ ) 4.87 (1H, s,  $\text{C}=\text{CH}$ );  $\delta_{\text{C}}$  (125MHz :  $\text{CDCl}_3$ ) 12.16 ( $\text{CH}_2\text{CH}_3$ ), 25.27 ( $\text{CH}_2\text{CH}_3$ ), 25.39 ( $\text{NCH}_2\text{CH}_2$ ), 30.51 ( $\text{COCH}_3$ ), 32.99 ( $\text{CHCH}_2$ ), 45.08 ( $\text{NCH}_3$ ), 52.82 ( $\text{NCH}_2$ ), 88.36 ( $\text{C}=\text{CH}$ ), 169.85 (NC), 193.04 (CO);  $m/z$  167 (46%,  $\text{M}^+$ ), 145 (100), 139 (36), 72 (34) (Found:  $\text{M}^+$ , 167.1302.  $\text{C}_{10}\text{H}_{17}\text{NO}$  requires 167.1310).

#### 4.1.10. 1-(3-Ethyl-1-methyl-2-piperidinylidene)propanone [152]

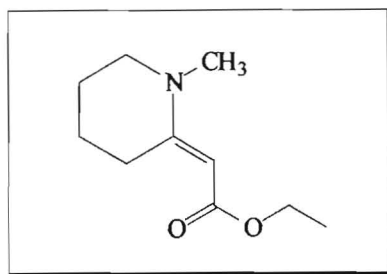


A mixture of the vinylogous amide [108] (200 mg, 1.31 mmol) and potassium hydride (530 mg, 13.1 mmol, 35% mineral oil suspension, washed three times with dry ether) in ether (5 mL) was stirred at  $0^\circ\text{C}$  for 0.5h. Ethyl iodide (5.50 mL, 68.1 mmol) was then added dropwise and the stirring was continued for a further 0.5h. A drop of water was added cautiously and the mixture was concentrated under vacuum. The reaction was quenched with water (20 mL) and the organic components extracted with ethyl acetate ( $3 \times 20$  mL). The organic layer was separated and dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Purification by radial chromatography (30% ethyl acetate/hexane) gave 1-(3-ethyl-1-methyl-2-piperidinylidene)propanone as a yellow oil (220 mg, 1.21 mmol, 92%);  $R_f$  0.43 (30% ethyl acetate/hexane);  $\nu_{\text{max}}$  (film)/ $\text{cm}^{-1}$  2922-2873 (C-H), 1667 (C=O), 1601 (C=C);  $\delta_{\text{H}}$  (500MHz :  $\text{CDCl}_3$ ) 0.98 (3H, t,  $J$  7.4,  $\text{CH}_3\text{CH}_2$ ), 1.40-1.50 (1H, m,  $\text{CH}_3\text{CH}_a\text{H}_b$  and 1H, m,  $\text{CH}_2\text{CH}_a\text{H}_b\text{CH}$ ), 1.59-1.65 (1H, m,  $\text{CH}_a\text{H}_b\text{CH}_2\text{CH}$ ), 1.74-1.77 (1H, m,  $\text{CH}_3\text{CH}_a\text{H}_b$ ), 1.66-1.71 (1H, m,  $\text{CH}_2\text{CH}_a\text{H}_b\text{CH}$ ), 1.90-1.95 (1H, m,  $\text{CH}_a\text{H}_b\text{CH}_2\text{CH}$ ), 2.05 (3H, s,  $\text{COCH}_3$ ), 2.80 (3H, s,  $\text{NCH}_3$ ), 3.15-3.24 (1H, m,  $\text{NCH}_a\text{H}_b$ ), 3.25-3.28 (1H, m,  $\text{NCH}_a\text{H}_b$ ); 3.88 (1H, br m,  $\text{CH}_2\text{CH}_2\text{CH}$ ), 4.95 (1H, s,  $\text{C}=\text{CH}$ );  $\delta_{\text{C}}$  (125MHz :  $\text{CDCl}_3$ ) 12.01 ( $\text{CH}_2\text{CH}_3$ ), 18.37 ( $\text{CH}_2\text{CH}_3$ ) 26.65 ( $\text{CH}_2\text{CH}_2\text{CH}$ ), 31.72 ( $\text{COCH}_3$ ),



35.03 (CHCH<sub>2</sub>), 40.27 (NCH<sub>3</sub>), 52.13 (NCH<sub>2</sub>), 93.41 (C=CH), 168.11(C=CH), 193.05 (CO); *m/z* 181 (52%, M<sup>+</sup>), 166 (100), 138 (82), 77 (70).

#### 4.1.11. Ethyl 2-(1-methyl-2-piperidinylidene)acetate [157]



Ethyl bromoacetate (1.92 g, 11.5 mmol) and 1-methyltetrahydro-2-(1H) pyridinethione (1.35 g, 10.5 mmol) were stirred in dichloromethane (10 mL) at room temperature overnight. When salt formation was complete (by TLC analysis), triphenylphosphine (3.02 g, 11.5 mmol) and triethylamine (1.59 mL, 11.5 mmol) were added, after which stirring was continued at room temperature for 30min. The reaction was quenched with water (50 mL) and the organic components extracted with ethyl acetate (3 × 50 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (30% ethyl acetate/hexane) afforded ethyl 2-(1-methyl-2-piperidinylidene)acetate as an orange/brown oil (1.73 g, 9.44 mmol, 90%); R<sub>f</sub> 0.60 (50% ethyl acetate /hexane); *v*<sub>max</sub> (film)/cm<sup>-1</sup> 2976-2867 (C-H), 1679 (C=O), 1144 (C(=O)-O), 1094 (C-N); δ<sub>H</sub> (500MHz : CDCl<sub>3</sub>), 1.13 (3H, t, *J* 6.9, CH<sub>2</sub>CH<sub>3</sub>) 1.52 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>) 1.67 (2H, m, CCH<sub>2</sub>CH<sub>2</sub>), 2.70 (3H, s, NCH<sub>3</sub>), 2.96 (2H, t, *J* 6.0, CCH<sub>2</sub>) 3.11 (2H, t, *J* 6.4, NCH<sub>2</sub>), 3.95 (2H, q, *J* 6.9, CH<sub>2</sub>CH<sub>3</sub>), 4.41(1H, s, CH); δ<sub>C</sub> (125MHz : CDCl<sub>3</sub>) 14.45 (CH<sub>2</sub>CH<sub>3</sub>), 19.64 (NCH<sub>2</sub>CH<sub>2</sub>), 23.28 (CCH<sub>2</sub>CH<sub>2</sub>), 26.39 (CCH<sub>2</sub>), 39.60 (NCH<sub>3</sub>), 51.47 (NCH<sub>2</sub>), 57.75 (CH<sub>2</sub>CH<sub>3</sub>), 82.18 (CH), 162.32 (C=CH), 168.50 (CO); *m/z* 183 (49%, M<sup>+</sup>), 138 (100), 111 (65), 110 (34).

#### 4.1.12. Attempted Petasis methylenation

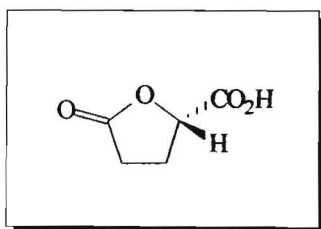
Dimethyltitanocene (0.34 g, 1.7 mmol) was added to a solution of vinylogous urethane [157] (100 mg, 0.546 mmol) in THF (20 mL). The reaction mixture was heated at 60°C overnight. The solvent was evaporated and the residue was treated with pentane to precipitate titanocene



oxide byproducts. The precipitate was filtered and the solvent was evaporated. TLC analysis and GCMS showed only the starting material. There was no sign of the desired product. The reaction was repeated at reflux temperature and for longer time period but the results were similarly disappointing. Even on changing the solvent to toluene none of the desired product formed, instead the vinylogous urethane was recovered.

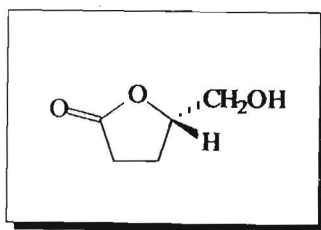
#### 4.2. Construction of the B and C rings of fascicularin

##### 4.2.1. (2*S*)-5-Oxotetrahydro-2-furancarboxylic acid [123]



A solution of  $\text{NaNO}_2$  (16.9 g, 0.243 mol) in water (120 mL) was added dropwise to a mixture of L-glutamic acid (29.4 g, 0.200 mol) in water (200 mL) and 2N HCl (120 mL) at  $0^\circ\text{C}$ . The resulting light yellow solution was stirred overnight. The solvent was evaporated and the resulting mixture was diluted with ethyl acetate (250 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated and a minimum volume of chloroform was added and the flask was cooled to  $-30^\circ\text{C}$  giving (2*S*)-5-oxotetrahydro-2-furancarboxylic acid as white crystals (13.3 g, 0.102 mmol, 51%); m.p (70.8-72.0 $^\circ\text{C}$ , lit.<sup>60,61</sup> 71-73 $^\circ\text{C}$ ); *m/z* 130.

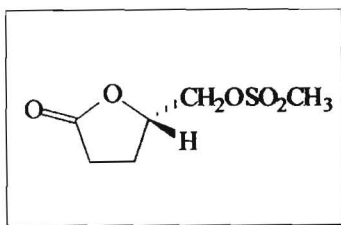
##### 4.2.2. (5*S*)-5-(Hydroxymethyl)dihydro-2(3*H*)-furanone [124]



A 5M borane-methylsulfide (10.7 mL, 53.7 mmol) solution in diethyl ether was added dropwise to a solution of (2*S*)-5-oxotetrahydro-2-furancarboxylic acid [123] (6.35 g, 48.8 mmol) in THF (50 mL). After stirring for a further 3h anhydrous MeOH (40 mL) was added

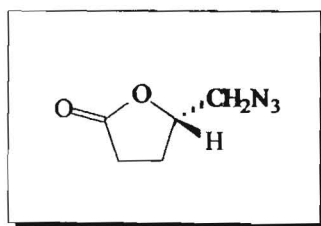
and the solvent was evaporated *in vacuo*. Purification by radial chromatography (4% ethanol/chloroform) afforded (5*S*)-5-(hydroxymethyl)dihydro-2(3*H*)-furanone as a yellow oil (4.65 g, 40.1 mmol, 82%);  $R_f$  0.27 (10% methanol/chloroform);  $m/z$  116.

#### 4.2.3. [(2*S*)-5-Oxotetrahydro-2-furanyl]methyl methanesulfonate [125]



Methane sulfonylchloride (5.72 mL, 72.8 mmol) was added to a stirred solution of (5*S*)-5-(hydroxymethyl)dihydro-2(3*H*)-furanone (7.67 g, 66.1 mmol) and triethylamine (10.1 mL, 72.7 mmol) in dichloromethane (90 mL) at  $-30^\circ\text{C}$ . The resultant solution was stirred for 5 min at  $-30^\circ\text{C}$  and then at room temperature for 2 h. The reaction was quenched with 0.5N HCl (25 mL) and the organic components extracted with dichloromethane ( $3 \times 50$  mL). The organic layer was separated, washed with water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. Purification by silica gel chromatography (60% ethyl acetate/hexane) afforded [(2*S*)-5-oxotetrahydro-2-furanyl]methyl methanesulfonate as a colourless oil (7.83 g, 40.3 mmol, 61%);  $R_f$  0.81 (60% ethyl acetate-hexane);  $m/z$  194.

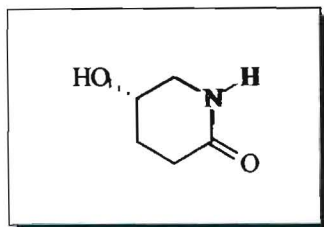
#### 4.2.4. (5*S*)-5-(Azidomethyl)dihydro-2(3*H*)-furanone [126]



To a solution of [(2*S*)-5-oxotetrahydro-2-furanyl]methyl methanesulfonate (5.20 g, 26.8 mmol) and 18-crown-6 (1.35 g) in acetonitrile (50 mL) was added sodium azide (2.49 g, 40.2 mmol). The resultant suspension was heated at reflux temperature for 12 h. The solvent was evaporated and purification by silica gel chromatography (ethyl acetate) afforded (5*S*)-5-(azidomethyl)-

dihydro-2(3*H*)-furanone as a orange/brown oil (3.13 g, 22.2 mmol, 83%);  $R_f$  0.72 (ethyl acetate);  $m/z$  141.

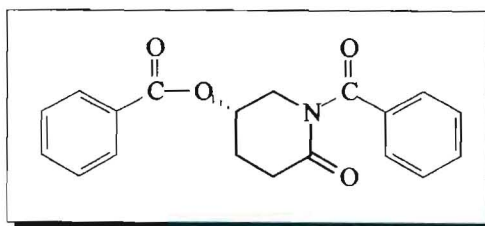
#### 4.2.5. (5*S*)-5-Hydroxytetrahydro-2(1*H*)pyridinone [127]



A mixture of (5*S*)-5-(azidomethyl)dihydro-2(3*H*)-furanone (3.90 g, 27.6 mmol) and palladium, 10wt.%, on activated carbon (100 mg) in methanol (120 mL) was hydrogenated at 300kPa at 30°C for 4h. The solution was filtered through Celite and the residue washed with hot methanol. The solvent was evaporated and purification by column chromatography (8% methanol/chloroform) afforded (5*S*)-5-hydroxytetrahydro-2(1*H*)pyridinone as white crystals (1.95 g, 16.9 mmol, 61%);  $R_f$  0.25 (10% methanol/chloroform); m.p 118 - 120°C, lit.<sup>62</sup> 120-121°C;  $m/z$  115. The spectroscopic data were in close agreement with those reported by Huh and Thompson.<sup>62</sup>

#### 4.2.6. Attempted protection of (5*S*)-5-hydroxytetrahydro-2(1*H*)pyridinone [127]

##### 4.2.6.1. 1-Benzoyl-6-oxo-3-piperidinyl benzoate [159]

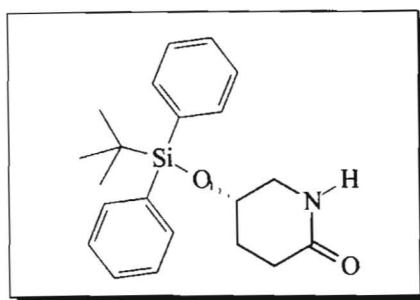


Benzoyl chloride (0.23 mL, 2.0 mmol) was added to the solution of (5*S*)-5-hydroxytetrahydro-2(1*H*)pyridinone (150 mg, 1.30 mmol) in pyridine (1mL, dried over KOH overnight and distilled). The resulting reaction mixture was stirred overnight. The reaction was quenched with 3% HCl (20 mL) and the organic components extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with water, dried over MgSO<sub>4</sub>, filtered and concentrated *in*



*vacuo*. Purification by silica gel chromatography (5% ethyl acetate/hexane) afforded 1-benzoyl-6-oxo-3-piperidinyl benzoate as white crystals (290 mg, 0.949 mmol, 69%);  $R_f$  0.88 (5% ethyl acetate/hexane);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$  2976-2867 (C-H), 1715 (C=O), 1070 (C-N);  $\delta_H$  (200MHz :  $\text{CDCl}_3$ ) 2.28-2.37 (2H, m,  $\text{CHCH}_2\text{CH}_2$ ), 2.55-2.70 (1H, m,  $\text{COCH}_a\text{H}_b$ ) 2.77-2.90 (1H, m,  $\text{COCH}_a\text{H}_b$ ), 3.90-4.01 (1H, m,  $\text{NCH}_a\text{H}_b$ ), 4.18-4.27 (1H, m,  $\text{NCH}_a\text{H}_b$ ), 5.59-5.65 (1H, m,  $\text{CH}$ ), 7.35-8.08 (aromatic protons);  $\delta_C$  (50MHz :  $\text{CDCl}_3$ ) 25.88 ( $\text{CHCH}_2\text{CH}_2$ ), 30.40 ( $\text{COCH}_2$ ), 48.94 ( $\text{NCH}_2$ ), 66.45 ( $\text{CH}$ ), 127.92-135.42 (aromatic carbons) 165.42 (OCO), 172.14 ( $\text{NCOAr}$ ); 174.02 ( $\text{CH}_2\text{NCOCH}_2$ );  $m/z$  323 (2%,  $\text{M}^+$ ), 201 (19), 105 (100), 77 (33).

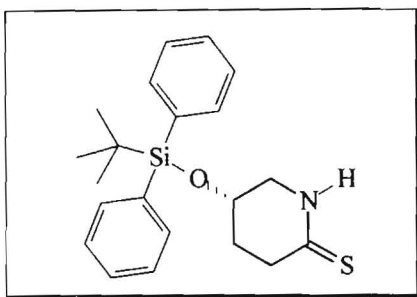
#### 4.2.6.2. (5S)-5-{{*tert*-Butyl(diphenyl)silyl}oxy}tetrahydro-2(1H)-pyridinone [114]



*tert*-Butyldiphenylsilyl chloride (0.27 mL, 1.0 mmol) was added to the solution of (5S)-5-hydroxytetrahydro-2(1H)pyridinone (100 mg, 0.869 mmol) in pyridine (2 mL, dried over KOH overnight and distilled). The reaction was quenched with 3% HCl (50 mL) and the organic components extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with water, dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated *in vacuo*. Purification by silica gel chromatography (5% methanol/dichloromethane) afforded (5S)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1H)-pyridinone as a colourless oil (212 mg, 0.600 mmol, 69%);  $R_f$  0.74 (10% methanol/dichloromethane);  $[\alpha]_D^{23}$  -12 (chloroform);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$  3071 (NH), 2931-2857 (CH), 1669 (C=O), 1112 (C-N), 1257 (SiC), 822 (SiO);  $\delta_H$  (500MHz :  $\text{CDCl}_3$ ) 1.06 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 1.76-1.81 (1H, m,  $\text{CHCH}_a\text{H}_b$ ), 1.87-1.93 (1H, m,  $\text{CHCH}_a\text{H}_b$ ) 2.24-2.30 (1H, m,  $\text{CHCH}_2\text{CH}_a\text{H}_b$ ) 2.63-2.69 (1H, m,  $\text{CHCH}_2\text{CH}_a\text{H}_b$ ), 3.20 (2H, d,  $J$  11.3,  $\text{NCH}_2$ ), 4.08 (1H, d,  $J$  3.7,  $\text{CH}$ ), 6.18 (NH), 7.34-7.66 (aromatic protons);  $\delta_C$  (125MHz :  $\text{CDCl}_3$ ) 19.13 ( $\text{SiC}(\text{CH}_3)_3$ ), 26.82 ( $\text{SiC}(\text{CH}_3)_3$ ), 27.33 ( $\text{COCH}_2$ ), 28.36 ( $\text{CHCH}_2\text{CH}_2$ ), 48.97 ( $\text{NCH}_2$ ), 64.66 ( $\text{CH}$ ), 127.77-135.63 (aromatic carbons), 172.1 (C=O);  $m/z$  354 (100%,  $(\text{M}+\text{H})^+$ ), 199 (40), 137 (33), 135 (63) (Found:  $(\text{M}+\text{H})^+$ , 354.1894.  $\text{C}_{21}\text{H}_{28}\text{NO}_2\text{Si}$  requires 354.1889).



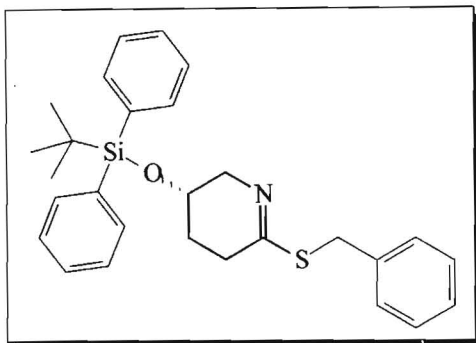
#### 4.2.7. (5*S*)-5-{{*tert*-Butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinethione [160]



Lawesson's reagent (0.688 g, 1.70 mmol) was added to a solution of (5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinone (1.00 g, 2.83 mmol) in toluene (40 mL). The reaction mixture was heated under reflux for 2h and the solvent was evaporated *in vacuo*. The resultant mixture was purified by silica gel chromatography (30% ethyl acetate/hexane) to yield 5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinethione as a yellow oil (1.00 g, 2.71 mmol, 96%);  $R_f$  0.37 (30% ethyl acetate/hexane);  $[\alpha]_D^{23}$  -28 (chloroform);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$  3071 (N-H), 2967-2851 (C-H), 1251 (SiC), 1156 (C=S), 1111 (C-N), 823 (SiO);  $\delta_H$  (500MHz :  $\text{CDCl}_3$ ) 1.06 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 1.68-1.74 (1H, m,  $\text{CHCH}_a\text{H}_b\text{CH}_2$ ), 1.77-1.83 (1H, m,  $\text{CHCH}_a\text{H}_b\text{CH}_2$ ), 2.81-2.87 (1H, m,  $\text{CSCH}_a\text{H}_b$ ), 3.10-3.18 (1H, m,  $\text{CSCH}_a\text{H}_b$ ), 3.19-3.22 (2H, m,  $\text{NCH}_2$ ), 4.09-4.13 (1H, m, *CH*), 7.35-7.65 (aromatic protons), 9.01 (NH);  $\delta_C$  (125MHz :  $\text{CDCl}_3$ ) 18.97 ( $\text{SiC}(\text{CH}_3)_3$ ), 26.72 ( $\text{SiC}(\text{CH}_3)_3$ ), 27.95 ( $\text{CHCH}_2\text{CH}_2$ ), 35.57 ( $\text{CSCH}_2$ ), 51.03 ( $\text{NCH}_2$ ), 63.49 (*CH*), 127.52-135.47 (aromatic carbons), 202.09 (C=S);  $m/z$  369 (2%,  $M^+$ ), 312 (100), 252 (63), 199 (49) (Found:  $M^+$ , 369.1576.  $\text{C}_{21}\text{H}_{27}\text{NOSSi}$  requires 369.1583)

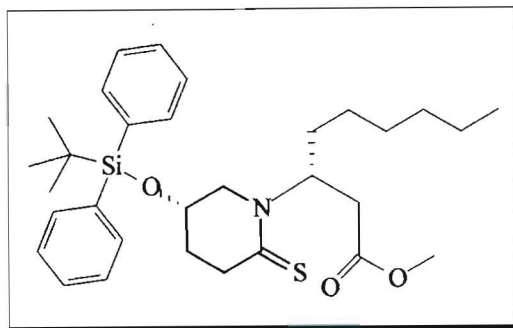
#### 4.2.8. Attempted *N*-alkylation of (5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}tetrahydro-2(1*H*)-pyridinethione [160]

##### 4.2.8.1 2-(Benzylthio)-(5*S*)-5-{{*tert*-butyl(diphenyl)silyl}oxy}-3,4,5,6-tetrahydropyridine [162]



Sodium hydride (50% suspension in mineral oil, 26 mg, 1.1 mmol) was added to a solution of thiolactam (340 mg, 0.920 mmol) and benzylbromide (1.31 mL, 1.10 mmol) in dry THF (50 mL) at 0°C. The resulting reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water (20 mL) and the organic components extracted with ethyl acetate (3 × 20 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by radial chromatography gave 2-(benzylthio)-5-{{*tert*-butyl-(diphenyl)silyl}oxy}-3,4,5,6-tetrahydropyridine (266 mg, 0.579 mmol, 63%); *R<sub>f</sub>* 0.45 (10% ethylacetate/hexane);  $[\alpha]_D^{29} - 44$  (chloroform);  $\nu_{\max}$  (film)/cm<sup>-1</sup> 2924-2853 (CH), 1494, 1453, 1234 (SiC), 829 (SiO);  $\delta_H$  (500MHz : CDCl<sub>3</sub>) 1.09 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.73-1.79 (2H, m, CHCH<sub>2</sub>CH<sub>2</sub>), 2.17-2.23 (1H, m, CHCH<sub>2</sub>CH<sub>a</sub>H<sub>b</sub>), 2.56-2.63 (1H, m, CHCH<sub>2</sub>CH<sub>a</sub>H<sub>b</sub>), 3.63-3.69 (2H, m, NCH<sub>2</sub>), 3.95-3.98 (1H, m, CH), 4.12 (1H, d, *J* 13.7, CSCH<sub>a</sub>H<sub>b</sub>Ar), 4.24 (1H, d, *J* 13.7, CSCH<sub>a</sub>H<sub>b</sub>Ar), 7.21-7.70 (aromatic protons);  $\delta_C$  (125MHz : CDCl<sub>3</sub>) 19.17 (C(CH<sub>3</sub>)<sub>3</sub>), 26.89 (C(CH<sub>3</sub>)), 27.92 (CHCH<sub>2</sub>CH<sub>2</sub>), 28.89 (CHCH<sub>2</sub>CH<sub>2</sub>), 33.07 (CSCH<sub>2</sub>), 57.31 (NCH<sub>2</sub>), 65.87 (CH), 126.84-138.24 (aromatic carbons), 164.18 (CSCH<sub>2</sub>); *m/z* 459 (7%, M<sup>+</sup>), 199 (11), 135 (23), 91 (100).

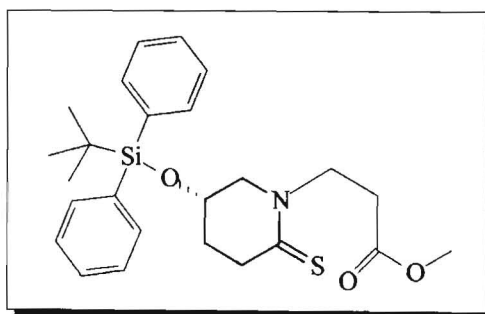
**4.2.8.2. Attempted conjugate addition of the thiolactam [114] to methyl-2-nonenoate [117]**



(i) Thiolactam [114] (100 mg, 0.271 mmol), methyl-2-nonenoate [117] (60 mg, 0.33 mmol) and a catalytic amount of finely crushed NaOH in dry THF (5 mL) were stirred overnight (a mixture of the *E*- and *Z*-isomers of methyl-2-nonenoate [117] was synthesized by means of a Wittig reaction between heptanal and ethyl bromo acetate). Based on TLC analysis the reaction had not worked. Attempts to encourage the reaction by heating the reaction under reflux and the addition of greater than catalytic amounts of NaOH failed.

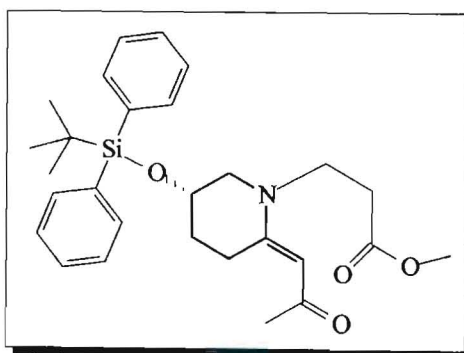
(ii) Another method was attempted: thiolactam [114] (100 mg, 0.271 mmol) and  $K_2CO_3$  (75 mg, 0.54 mmol) and 18-crown-6 (20 mg) were suspended in dry THF (15 mL). After being cooled to  $0^\circ C$ , methyl-2-nonenoate [117] (149 mg, 0.809 mmol) was added dropwise, the reaction mixture was stirred at  $0^\circ C$  for 5 minutes and then 1h at room temperature. The reaction was monitored by TLC and no new spots were observed. The starting materials were recovered.

**4.2.8.3. Methyl 3-[(5*S*)-5-{[tert-butyl(diphenyl)silyl]oxy}-2-thioxotetrahydro-1(2*H*)-pyridinyl]propanoate [163]**



A catalytic quantity of finely crushed NaOH was added to a solution of thiolactam [114] (100 mg, 0.271 mmol) and methyl acrylate (0.05 mL, 0.5 mmol) in dry THF (3 mL). Water (15 mL) was added and the organics extracted with ethyl acetate. The resulting reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (15 mL) and the organic components extracted with ethyl acetate (3 × 20 mL). The organic phase was separated and dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by radial chromatography (7% ethyl acetate/hexane) afforded a colourless oil (73 mg, 0.16 mmol, 59%). This compound was used without further purification; R<sub>f</sub> 0.36 (30% ethylacetate/hexane); [α]<sub>D</sub><sup>26</sup> -15 (chloroform); ν<sub>max</sub> (film)/cm<sup>-1</sup> 2931-2856 (C-H), 1737 (C=O), 1260 (SiC), 1112 (C-N), 823 (SiO); δ<sub>H</sub> (500MHz : CDCl<sub>3</sub>) 1.06 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.71-1.75 (2H, q, *J* 6.4, CHCH<sub>2</sub>CH<sub>2</sub>), 2.66-2.71 (1H, m, NCH<sub>2</sub>CH<sub>a</sub>H<sub>b</sub>), 2.80-2.94 (1H, m, NCH<sub>2</sub>CH<sub>a</sub>H<sub>b</sub> and 1H, m, CSCH<sub>a</sub>H<sub>b</sub>), 3.16-3.23 (1H, m, CSCH<sub>a</sub>H<sub>b</sub>), 3.32-3.40 (2H, m, NCH<sub>2</sub>CH), 3.65 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.00-4.10 (1H, m, NCH<sub>a</sub>H<sub>b</sub>CH<sub>2</sub>), 4.11-4.17 (1H, m, NCH<sub>a</sub>H<sub>b</sub>CH<sub>2</sub> and 1H, m, CH<sub>2</sub>CH), 7.38-7.64 (aromatic protons); δ<sub>C</sub> (125MHz : CDCl<sub>3</sub>) 19.06 (SiC(CH<sub>3</sub>)<sub>3</sub>), 26.82 (SiC(CH<sub>3</sub>)<sub>3</sub>), 28.50 (CH<sub>2</sub>CH<sub>2</sub>CH), 30.23 (NCH<sub>2</sub>CH<sub>2</sub>), 38.21 (CSCH<sub>2</sub>), 50.67 (NCH<sub>2</sub>CH<sub>2</sub>), 51.82 (CO<sub>2</sub>CH<sub>3</sub>) 58.07 (NCH<sub>2</sub>CH), 65.45 (CH<sub>2</sub>CH), 127.87-135.62 (aromatic carbons), 171,99 (CO<sub>2</sub>CH<sub>3</sub>) 199.74 (CS), *m/z* 455 (12%, M<sup>+</sup>), 312 (100), 234 (37), 199 (40), (Found: M<sup>+</sup>, 455.1956. C<sub>25</sub>H<sub>33</sub>NO<sub>3</sub>SSi requires 455.1950).

**4.2.9. Methyl 3-[(5*S*)-5-{*tert*-butyl(diphenyl)silyl]oxy}2-[(*E*)-2-oxopropylidene]tetrahydro-2(1*H*)-pyridinyl]propanoate [164]**

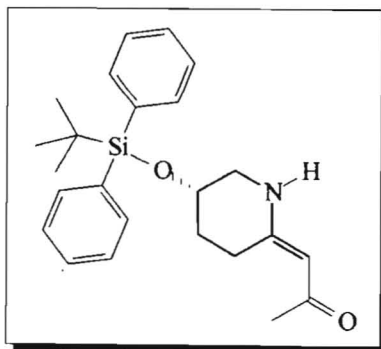


Bromoacetone (150 mg, 1.09 mmol) was added to a stirred solution of methyl 3-[(5*S*)-5-{*tert*-butyl(diphenyl)silyl]oxy}-2-thioxotetrahydro-1(2*H*)-pyridinyl]propanoate [163] (100 mg,



0.219 mmol) in acetone (10 mL). The reaction mixture was kept in the fridge (4°C) overnight. The solvent was evaporated and the salt was dissolved in acetonitrile (20 mL) and treated with triphenylphosphine (300 mg, 1.14 mmol) and triethylamine (0.15 mL, 1.14 mmol). The resulting reaction mixture was stirred for 30 min. The reaction was quenched with water (15 mL) and the organic components extracted with ethyl acetate (3 × 20 mL). The organic phase was separated and dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by radial chromatography (5% ethyl acetate/hexane) afforded methyl 3-[(5*S*)-5-[[*tert*-butyl(diphenyl)silyl]oxy}2-[(*E*)-2-oxopropylidene]tetrahydro-2(1*H*)-pyridinyl] propanoate as a brown oil (58 mg, 0.12 mmol, 53%); *R*<sub>f</sub> 0.23 (30% ethyl acetate/hexane); [α]<sub>D</sub><sup>29</sup> -3.6 (chloroform); *v*<sub>max</sub> (film)/cm<sup>-1</sup> 2953-2857 (C-H), 1737 (C=O), 1259 (SiC), 1112 (C-N), 822 (SiO); δ<sub>H</sub> (500MHz : CDCl<sub>3</sub>), 1.04 (9H, s, SiC(CH<sub>3</sub>)<sub>3</sub>), 1.61-1.69 (2H, m, CCH<sub>2</sub>CH<sub>2</sub>), 1.82-1.87 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 2.05 (3H, s, COCH<sub>3</sub>), 2.49-2.58 (2H, m, CHCH<sub>2</sub>CH<sub>2</sub>), 3.05-3.11 (1H, m, NCH<sub>a</sub>H<sub>b</sub>CH), 3.16-3.19 (1H, m, NCH<sub>a</sub>H<sub>b</sub>CH), 3.41 (2H, t, *J* 7.3, NCH<sub>2</sub>CH<sub>2</sub>), 3.67 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.99-4.02 (1H, m, CH<sub>2</sub>CH), 5.03 (1H, s, CCH), 7.36-7.65 (aromatic protons); δ<sub>C</sub> (125MHz : CDCl<sub>3</sub>) 19.31 (SiC(CH<sub>3</sub>)<sub>3</sub>), 24.19 (CHCH<sub>2</sub>CH<sub>2</sub>), 27.10 (SiC(CH<sub>3</sub>)<sub>3</sub>), 28.01 (CCH<sub>2</sub>CH<sub>2</sub>), 30.34 (NCH<sub>2</sub>CH<sub>2</sub>), 31.96 (COCH<sub>3</sub>), 47.67 (NCH<sub>2</sub>CH<sub>2</sub>), 52.15 (CO<sub>2</sub>CH<sub>3</sub>), 56.64 (NCH<sub>2</sub>CH), 66.26 (CH<sub>2</sub>CH), 93.33 (CCH), 128.02-135.89 (aromatic carbons), 161.41 (CCH), 172.01 (CO<sub>2</sub>CH<sub>3</sub>), 194.56 (COCH<sub>3</sub>); *m/z* 479 (51%, M<sup>+</sup>), 436 (44), 218 (100), (Found: M<sup>+</sup>, 479.2488. C<sub>28</sub>H<sub>37</sub>NO<sub>4</sub>Si requires 479.2492).

#### 4.2.10. 1-[(5*S*)-5-[[*tert*-Butyl(diphenyl)silyl]oxy}tetrahydro-2(1*H*)-piperidinylidene]-propanone [167]



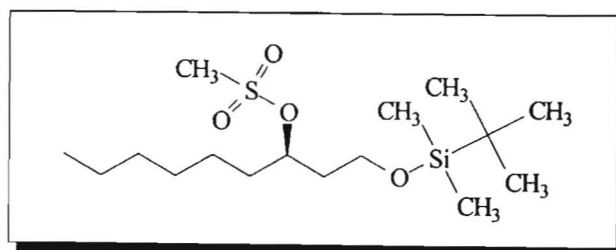
A solution of KHMDS (62 mg, 0.32 mmol) in THF (2,mL) was cooled to -78°C. To the cooled solution, was added vinylogous amide [164] (100 mg, 0.208 mmol). The temperature was allowed to warm to 0°C for 1h and then cooled to -78°C and treated with *tert*-

butyldimethylsilyl chloride (48 mg, 0.32 mmol). The reaction mixture was allowed to warm up to room temperature. The reaction mixture was cooled to 0°C, and a solution of phenyl vinyl sulfone (70 mg, 0.42 mmol) in THF (1 mL) was added. The reaction mixture was allowed to warm up to room temperature and was allowed to stir overnight. The solvent was evaporated *in vacuo* and purification was done using radial chromatography. 1-[(5*S*)-5-{[*tert*-butyl(diphenyl)silyl]oxy}-2-piperidinylidene]propanone was obtained as a brown oil (59 mg, 0.15 mmol, 71 %);  $R_f$  0.45 (40% ethyl acetate/hexane);  $[\alpha]_D^{23}$  -62 (chloroform);  $\nu_{max}$  (film)/ $\text{cm}^{-1}$  3071(N-H), 2957-2857 (C-H), 1712 (C=O), 1269 (SiC), 1112 (C-N), 822 (SiO);  $\delta_H$  (500MHz :  $\text{CDCl}_3$ ) 1.06 (9H, s,  $\text{SiC}(\text{CH}_3)_3$ ), 1.72-1.76 (2H, m,  $\text{CHCH}_2\text{CH}_2$ ), 1.99 (3H, s,  $\text{COCH}_3$ ), 2.18-2.24 (1H, m,  $\text{CCH}_a\text{H}_b\text{CH}_2$ ), 2.62-2.68 (1H, m,  $\text{CCH}_a\text{H}_b\text{CH}_2$ ), 3.15-3.19 (1H, m,  $\text{NCH}_a\text{H}_b$ ), 3.24-3.27 (1H, m,  $\text{NCH}_a\text{H}_b$ ), 4.03-4.07 (1H, m,  $\text{CH}_2\text{CH}$ ), 4.90 (1H, s,  $\text{CCH}$ ), 7.37-7.66 (aromatic protons), 10.92 (1H, s,  $\text{NH}$ );  $\delta_C$  (125MHz :  $\text{CDCl}_3$ ) 19.11 ( $\text{SiC}(\text{CH}_3)_3$ ), 25.23 ( $\text{CCH}_2\text{CH}_2$ ), 26.85 ( $\text{SiC}(\text{CH}_3)_3$ ), 27.67 ( $\text{CHCH}_2\text{CH}_2$ ), 28.62 ( $\text{COCH}_3$ ), 47.75 ( $\text{NCH}_2$ ), 65.30 ( $\text{CH}_2\text{CH}$ ), 93.23 ( $\text{CCH}$ ), 127.74-136.64 (aromatic carbons), 163.15 ( $\text{CCH}$ ), 194.27 ( $\text{COCH}_3$ );  $m/z$  393 (8%,  $\text{M}^+$ ), 352 (66), 336 (100,  $\text{M}^+ - \text{tert-butyl}$ ), 199 (26), (Found:  $\text{M}^+$ , 393.21246.  $\text{C}_{24}\text{H}_{31}\text{NO}_2\text{Si}$  requires 393.21241).

#### 4.2.11. Synthesis of (3*R*)-1,3-nonanediol [131]

(3*R*)-1,3-Nonanediol [131] was synthesised in four steps from hept-1-yne [115] using the procedure of Kitching and co-workers.<sup>63</sup>

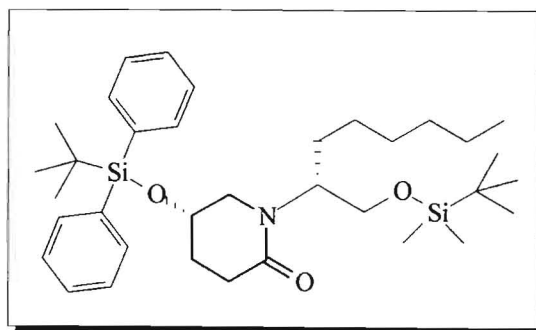
#### 4.2.12. (1*R*)-1-(2-{*tert*-Butyl(dimethyl)silyl}oxy)ethyl)heptyl methanesulfonate [116]



$\text{Et}_3\text{N}$  (0.68 mL, 4.7 mmol) followed by TBSCl (564 mg, 3.74 mmol) and DMAP (12 mg) were added to the solution of the (3*R*)-1,3-nonanediol (500 mg, 3.12 mmol) [131] in  $\text{CH}_2\text{Cl}_2$  (5 mL). The reaction mixture was stirred for 6 hours at room temperature. Additional  $\text{Et}_3\text{N}$  (0.68 mL,

4.68 mmol) and MsCl (0.29 mL, 3.7 mmol) were added and the reaction mixture was stirred for a further 3h. The solvent was evaporated and the residue dissolved in 30% ethyl acetate/hexane. The crude mixture was filtered through a plug column. The solvent was evaporated to give the mesylate **[116]** as a colourless oil (1.08 mg, 3.06 mmol, 98%);  $R_f$  0.58 (50% ethyl acetate/hexane);  $\nu_{\max}$  (film)/ $\text{cm}^{-1}$  2928-2858 (C-H), 1733, 1225 (SiC), 1137, 1012;  $\delta_H$  (500MHz :  $\text{CDCl}_3$ ) 0.04 ( $\text{Si}(\text{CH}_3)_2$ ), 0.84-0.90 (9H, s,  $\text{C}(\text{CH}_3)_3$  and 3H, m,  $\text{CH}_3\text{CH}_2$ ), 1.26-1.38 ( $4 \times 2\text{H}$ , m,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}$ ), 1.71-1.75 (2H, m,  $\text{CH}_2\text{CHCH}_2\text{CH}_2\text{OSi}$ ), 1.83-1.88 (2H, m,  $\text{CH}_2\text{CH}_2\text{OSi}$ ), 2.99 (3H, s,  $\text{CH}_3\text{O}_2\text{S}$ ), 3.70 (2H, t,  $J$  6.4,  $\text{CH}_2\text{OSi}$ ), 4.81-4.86 (1H, m,  $\text{CHOS}$ );  $\delta_C$  (125MHz :  $\text{CDCl}_3$ ) -5.20 ( $\text{Si}(\text{CH}_3)_2$ ), 14.24 ( $\text{CH}_3\text{CH}_2$ ), 18.37 ( $\text{C}(\text{CH}_3)_3$ ), 22.76 ( $\text{CH}_3\text{CH}_2$ ), 24.97 ( $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 26.06 ( $\text{C}(\text{CH}_3)_3$ ), 29.01 ( $\text{CHCH}_2\text{CH}_2\text{CH}_2$ ), 31.84 ( $\text{CH}_3\text{CH}_2\text{CH}_2$ ), 35.22 ( $\text{CH}_2\text{CHCH}_2\text{CH}_2\text{OSi}$ ), 37.44 ( $\text{CH}_2\text{CH}_2\text{OSi}$ ), 38.43 ( $\text{CH}_3\text{O}_2\text{S}$ ), 58.88 ( $\text{CH}_2\text{OSi}$ ), 81.66 ( $\text{CHOS}$ ).

#### 4.2.13. Attempted coupling of mesylate **[116]** to lactam **[115]**



Mesylate **[116]** (260 mg, 0.737 mmol) and lactam (220 mg, 0.622 mmol) **[115]** were added to a stirred solution of *t*-BuOK 1M (0.74 mL, 0.74 mmol) in THF. The resulting mixture was stirred at room temperature for 24 hours. There was no sign of the desired product even when increasing the reaction time and temperature.



## REFERENCES

1. G. A. Cordell, in "Introduction to Alkaloids", Wiley, New York, 1991.
2. B. S. Davidson, *Chem. Rev.*, 1993, **93**, 1771.
3. S. W. Pelletier, ed., in "Alkaloids: Chemical and Biological Perspectives" Vol.1, Wiley, New York, 1983.
4. P. M. Dewick, in "Medicinal Natural Products: A Biosynthetic Approach," 2<sup>nd</sup> ed., Wiley, New York, 2001, 291.
5. C. Li and A. J. Blackman, *Aust. J. Chem.*, 1994, **47**, 1355.
6. J. F. Liu and C. H. Heathcock, *J. Org. Chem.*, 1999, **64**, 8263.
7. A. D. Patil, A. J. Freyer, R. Reichwein, B. Carte, L. Faucette, L. B. Killmer, R. K. Johnson, and D. J. Faulkner, *Tetrahedron Lett.*, 1997, **38**, 363.
8. H. Abe, S. Aoyagi and C. Kibayashi, *J. Am. Chem. Soc.*, 2000, **122**, 4583.
9. J. F. Biard, s. Guyot, C. Roussakis, J. F. Verbist, J. Vercauteren, J. F. Weber and K. Boukef, *Tetrahedron Lett.*, 1994, **35**, 2691.
10. A. J. Blackman, C. Li, D. C. R. Hockless, B. W. Skelton and A. H. White, *Tetrahedron*, 1993, **49**, 8645.
11. F. Kong and D. J. Faulkner, *Tetrahedron Lett.*, 1991, **32**, 3667.
12. B. R. Copp, C. M. Ireland and L. R. Barrows, *J. Org. Chem.*, 1991, **56**, 4596.
13. M. F. Raub, J. H. Cardellina II, M. I. Choudhary, C. -Z. Ni, J. Clardy and M. C. Alley, *J. Am. Chem. Soc.*, 1991, **113**, 3178.
14. M. F. Raub, J. H. Cardellina II and T. F. Spande, *Tetrahedron Lett.*, 1992, **33**, 2257.
15. B. Steffan, *Tetrahedron*, 1991, **47**, 8729.
16. J. Kubanek, D. E. Williams, E. D. de Silva, T. Allen and R. J. Andersen, *Tetrahedron Lett.*, 1995, **36**, 6189.
17. C. Li and A. J. Blackman, *Aust. J. Chem.*, 1995, **48**, 955.
18. L. Zhang, M. P. Cava, R. D. Rogers and L. M. Rogers, *Tetrahedron Lett.*, 1998, **39**, 7677-7678.
19. R. Barret and N. Roue, *Tetrahedron Lett.*, 1999, **40**, 3889.
20. N. Toyooka, Y. Yotsui, Y. Yoshida and T. Momose, *J. Org. Chem.*, 1996, **61**, 4882.
21. D. J. Hart and V. Leroy, *Tetrahedron*, 1995, **51**, 5757.
22. N. Toyooka, Y. Yotsui, Y. Yoshida, T. Momose and H. Nemoto, *Tetrahedron*, 1999, **55**, 15209.



23. J. D. Ha, D. Lee and J. K. Cha, *J. Org. Chem.*, 1997, **62**, 4550.
24. J. D. Ha and J. K. Cha, *J. Am. Chem. Soc.*, 1999, **121**, 10012.
25. C. W. Jefford, K. Sienkiewicz and S. R. Thornton, *Helv. Chim. Acta*, 1995, **78**, 1511.
26. H. McAlonan, D. Potts, P. J. Stevenson and N. Thompson, *Tetrahedron Lett.*, 2000, **41**, 5411.
27. N. Toyooka, M. Okumura, H. Takahata and H. Nemoto, *Tetrahedron*, 1999, **55**, 10673.
28. N. Toyooka, M. Okumura and H. Takahata, *J. Org. Chem.*, 1999, **64**, 2182.
29. T. Ozawa, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 2001, **66**, 3338.
30. T. Ozawa, S. Aoyagi and C. Kibayashi, *Org. Lett.*, 2000, **2**, 2955.
31. B. B. Snider and T. Liu, *J. Org. Chem.*, 1997, **62**, 5630.
32. G. A. Molander and M. Rönn, *J. Org. Chem.*, 1999, **64**, 5183.
33. K. M. Werner, J. M. de los Santos, S. M. Weinreb and M. Shang, *J. Org. Chem.*, 1999, **64**, 686.
34. K. M. Werner, J. M. De los Santos, S. M. Weinreb and M. Shang, *J. Org. Chem.*, 1999, **64**, 4865.
35. H. Abe, S. Aoyagi and C. Kibayashi, *Tetrahedron Lett.*, 2000, **41**, 1205.
36. W. H. Pearson and Y. Ren, *J. Org. Chem.*, 1999, **64**, 688.
37. W. H. Pearson, N. S. Barta and J. W. Kampf, *Tetrahedron Lett.*, 1997, **38**, 3369.
38. R. L. Funk and J. H. Maeng, *Org. Lett.*, 2002, **4**, 331.
39. M. C. Bagley and W. Oppolzer, *Tetrahedron: Asymmetry*, 2000, **11**, 2625.
40. W. Oppolzer and C. G. Bochet, *Tetrahedron: Asymmetry*, 2000, **11**, 4761.
41. B. B. Molloy and K. L. Hauser, *Chem. Commun.*, 1968, 1017.
42. P. A. Evans, J. M. Longmire and D. P. Modi, *Tetrahedron Lett.*, 1995, **36**, 3985.
43. P. A. Evans and J. D. Nelson, *J. Org. Chem.*, 1996, **61**, 7600.
44. J. D. Brown, M. A. Foley and D. L. Comins, *J. Am. Chem. Soc.*, 1988, **110**, 7445.
45. D. L. Comins and A. Dehghani, *J. Org. Chem.*, 1995, **60**, 794.
46. J. L. Bougeois, L. Stella and J. M. Surzur, *Tetrahedron Lett.*, 1981, **22**, 61.
47. L. Stella, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 337.
48. L. Börjesson, I. Csöregi and C. J. Welch, *J. Org. Chem.*, 1995, **60**, 2989.
49. G. T. Crisp, W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, 1984, **106**, 7500.
50. B. L. Groh, A. F. Kreager and J. B. Schneider, *Synth. Commun.*, 1991, **21**, 2065.
51. D. N. Kirk and M. A. Wilson, *J. Chem. Soc. C*, 1971, 414.
52. T. Kondo, H. Nakai and T. Goto, *Tetrahedron*, 1973, **29**, 1801.

53. K. Shiosaki, Eschenmoser Coupling Reaction, in "Comprehensive Organic Synthesis", ed. B. M. Trost, Pergamon Press, New York, 1991, Vol. 2, 865.
54. J. P. Michael, C. B. de Koning, D. Gravestock, G. D. Hosken, A. S. Howard, C. M. Jungmann, R. W. M. Krause, A. S. Parsons, S. C. Pelly and T. V. Stanbury, *Pure Appl. Chem.*, 1999, **71**, 979.
55. J. P. Michael and A. S. Parsons, *Tetrahedron*, 1996, **52**, 2199.
56. J. P. Michael and C. M. Jungmann, *Tetrahedron*, 1992, **48**, 10211.
57. J. P. Michael and D. Gravestock, *Pure Appl. Chem.*, 1997, **69**, 583.
58. S. A. Kozmin, J. M. Janey and V. H. Rawal, *J. Org. Chem.*, 1999, **64**, 3039.
59. Y. Huang, T. Iwama and V. H. Rawal, *J. Am. Chem. Soc.*, 2000, **122**, 7843.
60. C. Herdeis, *Synthesis*, 1986, 232.
61. U. Ravid, R. M. Silverstein and L. R. Smith, *Tetrahedron*, 1978, **34**, 1449.
62. N. Huh and C. M. Thompson, *Tetrahedron*, 1995, **51**, 5935.
63. W. Kitching, J. A. Lewis, M. V. Perkins, R. Drew, C. J. Moore, V. Schuring, W. A. König and W. Francke, *J. Org. Chem.*, 1989, **54**, 3893.
64. C. Herdeis, C. Kaschinski, R. Karia and H. Lotter, *Tetrahedron: Asymmetry*, 1996, **7**, 867.
65. J. P. Michael and D. Gravestock, *Synlett*, 1996, 981.
66. J. P. Michael and D. Gravestock, *Eur. J. Org. Chem.*, 1998, 865.
67. J. P. Michael and D. Gravestock, *J. Chem. Soc., Perkin Trans. 1*, 2000, 4583.
68. D. Brillon, *Synth. Commun.*, 1990, **20**, 3085.
69. G. Lajoie, F. Lépine, L. Maziak and B. Belleau, *Tetrahedron Lett.*, 1983, **24**, 3815.
70. (a) M. P. Cava and M. I. Levinson, *Tetrahedron*, 1985, **41**, 5061. (b) B. S. Pedersen, S. Scheibye, N. H. Nilsson and S. Lawesson, *Bull. Soc. Chim. Belg.*, 1978, **87**, 233. (c) M. Thorsen, T. P. Andersen, U. Pederson, B. Yde and S. Lawesson, *Tetrahedron*, 1985, **41**, 5633 (d) A. A. G. Ghattas, E. A. El-Khrisy and S. Lawesson, *Sulfur Lett.*, 1982, **1**, 69. (e) B. Yde, N. M. Yousif, U.S. Pedersen, I. Thomsen and S. Lawesson *Tetrahedron*, 1984, **40**, 2047.
71. A. Guarna, E. Lombardi, F. Machetti, E. G. Occhiato and D. Scarpi, *J. Org. Chem.*, 2000, **65**, 8093.
72. A. H. Blatt, in "Organic syntheses, Collective vol. 2", Wiley, New York, 1955, 88.
73. S. A. Kozmin and V. H. Rawal, *J. Org. Chem.*, 1997, **62**, 5252.
74. S. A. Kozmin and V. H. Rawal, *J. Am. Chem. Soc.*, 1998, **120**, 13523.

75. S. A. Kozmin and V. H. Rawal, *J. Org. Chem.*, 1999, **64**, 8045.
76. S. A. Kozmin and V. H. Rawal, *J. Am. Chem. Soc.*, 1999, **121**, 9562.
77. Y. Huang and V. H. Rawal, *Org. Lett.*, 2000, **2**, 3321.
78. R. V. C. Carr, R. V. Williams and L. A. Paquette, *J. Org. Chem.*, 1983, **48**, 4976.
79. D. C. Smith, S. W. Lee and P. L. Fuchs, *J. Org. Chem.*, 1994, **59**, 348.
80. R. Ghirlando, A. S. Howard, R. B. Katz and J. P. Michael, *Tetrahedron*, 1984, **40**, 2879.
81. G. Sabitha, M. M. Reddy, D. Srinivas and J. S. Yadov, *Tetrahedron Lett.*, 1999, **40**, 165.
82. N. Sato and S. Fukuya, *J. Chem. Soc., Perkin Trans. 1*, 2000, 89.
83. J. O. Karlsson and T. Frejd, *J. Org. Chem.*, 1983, **48**, 1921.
84. P. Barbier and C. Benezra, *J. Org. Chem.*, 1983, **48**, 2705.
85. N. Kunesch, P. Le Menez, J. Sapi, E. C. Angell and E. Wenkert, *J. Org. Chem.*, 1989, **54**, 3216.
86. Prof. V. H. Rawal, Department of Chemistry, University of Chicago, personal communication. We are grateful to Professor Rawal for his assistance with a number of our queries.
87. N. A. Petasis and S. Lu, *Tetrahedron Lett.*, 1995, **36**, 165.
88. L. M. Harwood and C. J. Moody, in "Experimental Organic Chemistry: Principles and Practice", Blackwell Scientific Publications, Oxford, 1989, 663.
89. J. March, in "Advanced Organic Chemistry: Reactions, Mechanism and Structure", 4<sup>th</sup> ed., pp. 828, Wiley, New York, 1992.
90. M. B. Smith, in "Organic Synthesis", McGraw-Hill, New York, 1994, 275.
91. ACD/Labs<sup>TM</sup>, Advanced Chemistry Development Inc., 133 Richmond Street West, Suite 605, Toronto, Ontario Canada M5H 2L3.
92. D. D. Perrin, W. L. F. Armarego and D. R. Perrin, in "Purification of Laboratory Chemicals", 2<sup>nd</sup> ed. Pergamon Press, Oxford, 1980.
93. A. Nabeya and T. Endo, *J. Org. Chem.*, 1991, **56**, 3194.
94. E. Leete, J. A. Bjorklund, M. M. Couladis and S. H. Kim, *J. Am. Chem. Soc.*, 1991, **113**, 9286.