Total Synthesis of Sordaricin

A Thesis Submitted for
the Degree of
Doctor of Philosophy
of

The Australian National University

Research School of Chemistry

Regan J. Thomson

2003

THE AUSTRALIAN
LIBRARY
NATIONAL UNIVERSITY

Declaration

This thesis contains no material previously submitted for a degree in any other University, and to the best of the author's knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

Regan J. Thomson

2003

In loving memory of my father, Alan James Thomson

26-10-1950 to 27-10-2002

Acknowledgements

The research conducted for this thesis would not have been possible without the support and guidance of my supervisor - Professor Lewis N. Mander. Not only have I benefited greatly from his awesome knowledge of chemistry, but his overall philosophy and approach to science has profoundly shaped my own outlook. More important than this, I would like to thank Lew for accepting me as I am and for encouraging me in my own ideas. I cannot think of a single bad moment in the time of our association, not even when I lost the bicycle you lent me.

I would like to express my thanks to the Mander group's omnipotent research officer and lynch pin - Bruce Twitchin. Not only for his expertise within the lab, but also for his friendship outside of it. Another group member leaves as a disciple of the Brawn Principle.

Like everybody at the Research School I am grateful for the help of the support staff. Special mention must be made to Tony Herlt – the local separations guru – for his help with GC and HPLC techniques, and to Chris Blake for running crucial NMR experiments for me when in dire need. I also wish to express a sincere thanks to Christine Sharrad, who was always willing to help with the formatting of this document.

The friendship of the past and present members of the Research School are what made the hard parts bearable. This usually involved large scale alcohol consumption with the Mander Boys - Matthew McLachlan and Oliver Hutt - whose enduring friendships I am grateful for, especially during my frequent mood swings. A particular thank you must be made to Kenneth McRae, for being the person who introduced me to 'bass promoted synthesis'. Amongst all the others, the Banwell Rant Boys – David Lupton and Daniel Beck – require a mention for their friendship and fine conversation, and Kelly Ann Fairweather, for her friendship and proof reading skills.

The friendship and support of the people I have lived with over the past few years cannot be understated. Firstly – Angela Gregory and Sarah Strapps – for all of their 'encouragement' and for always not believing a word I said. A big shout out to the MacArthur Massive, especially Andrej Mihajlovski – an Urban Buddha if ever I saw one – and Adam Perriman – your advice as my attorney has been most invaluable. To the Pallarenda Posse – you guys rocked my world.

Thanks to my remaining friends in New Zealand – Garrath Cadness, Russell Mitchell and Larry DeLacey – for not selling out and stagnating like the rest of them.

Finally, to my family in New Zealand for their love and support – especially when it seemed as if I wasn't interested in it.

Abstract

The sordarins are an emerging class of antifungal diterpene glycosides, of which sordarin (**1**), isolated in 1971 from the ascomycete *Sordaria araneosa* Cain, is the structural prototype. Interest in the sordarins stems primarily from their potent broad spectrum antifungal activity, which is induced by selective inhibition of fungal protein synthesis. From a synthetic standpoint, it is the tetracyclic diterpene moiety, named sordaricin (**3**), that is of most interest. This dissertation describes a convergent, enantioselective total synthesis of sordaricin (**3**), from the two enantiomers of enone **54**.

Chapter One provides an overview of the isolation and structural characterisation of the sordarins and, in particular, sordaricin (**3**). Aspects of the postulated biosynthesis of sordaricin (**3**) are introduced. Brief mention is made of the sordarins biological activity, *i.e.* antifungal properties, molecular mode of action, and to the pharmaceutical industries' attempts to produce more potent analogues and derivatives. Previous synthetic endeavours aimed at the total synthesis of sordaricin (**3**) are detailed.

Chapter Two provides a detailed outline regarding the synthetic strategy proposed for the total synthesis of sordaricin (**3**). Key concepts, such as the intramolecular [4+2] cycloaddition and convergent alkylation strategy are discussed. Possible starting materials are examined and a rationale for the choice of (+)-**54** and (−)-**54** is put forward. The possibility of performing a tandem cycloreversion/intramolecular [4+2] cycloaddition is described. Aldehyde **60** and iodide **62** (**158** for P = MOM) are identified as key initial subtargets. The flexibility of the synthetic plan is detailed with respect to the study of the postulated biosynthetic intramolecular cycloadditon and the synthesis of C1-alkyl analogues for biological evaluation.

Chapter Three describes the synthesis of aldehyde **60** from (−)-**54**. An initial, but unsuccessful approach, that relied upon the elaboration of ester **81** is discussed. The development of an alternative approach utilising 1,4-addition, acylation and a higher order cuprate in key steps is detailed. As a model for the alkylation of **60** with iodide **158**, aldehyde **60** was successfully alkylated with isobutyl iodide.

Chapter Four deals with the synthesis of iodide **158** from (+)-**54**. Synthesis of the *syn*-4,5-disubstituted cyclopentenone **132** is explained. Several possible routes to **158** from **132** are examined, and the development of a successful route to **158** *via* **124** is described.

Chapter Five provides details of the unsuccessful attempts to alkylate aldehyde **60** and dimethylhydrazone **160** with iodide **158**. An alternative approach utilising nitrile **163** is put forward, and the successful alkylation of **163** with **158** is described. Elaboration of the resulting adduct **168** to ketone **172**, a key intermediate, is detailed. A discussion of the C-acylation of sterically hindered enolates is given, and based upon this analysis, the acylation of **172** is carried out. The synthesis of aldehyde **64**, the precursor to the planned cycloreversion/intramolecular [4+2] cycloaddition, is then detailed.

Chapter Six describes efforts that culminated in the total synthesis of sordaricin (**3**). The outcomes of the tandem cycloreversion/cycloaddition process for diol **182** and aldehyde **64** are given, and the unanticipated formation of *iso*-**41** from **64** is detailed. An alternative approach, leading to aldehyde **65**, is described, as well as the cyclisation of **65** to afford **41**. Demethylation then rendered the target natural product, sordaricin (**3**).

Chapter Seven deals with the issues associated with the differences in regiochemisty obtained for the cycloaddition substrates produced during the synthesis of sordaricin (**3**). In particular, an explanation is provided for the selective formation of **41** at 40 °C from **65** *versus* the apparent poor selectivity obtained from **64** at 180 °C. Frontier orbitals and thermodynamic stabilities were used to aid in this explanation. Speculation as to the biosynthesis of sordaricin (**3**) is put forward based on these results.

Chapter Eight provides a summary of the results obtained during research for this Ph.D. and provides direction for possible future work and an overall conclusion.

Chapter Nine contains the experimental procedures conducted during this research, as well as all the spectroscopic data.

Glossary

The following abbreviations have been used throughout this thesis:

°C	degrees Celsius
µL	microlitre
µmol	micromole
ν_{max}	infrared absorption maxima (cm^{-1})
AIBN	2,2´-azo*bis*isobutyronitrile
APT	attached proton test (^{13}C NMR spectroscopy)
Bu	butyl
^{t}Bu	*tertiary*-butyl
^{t}BuOK	potassium *tertiary*-butyloxide
c	concentration (g/100mL)
cat.	catalyst
COSY	correlation spectroscopy
δ	chemical shift (parts per million)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d.e.	diastereomeric excess
Dess-Martin periodinane	1,1,1-triacetoxy-1,1-dihydro-1,2-benzido-3(1*H*)-one
DIBAL-H	diisobutylaluminum hydride
DIPEA	*N,N*-diisopropylethylamine
DMAP	4-(*N,N*-diemthylamino)pyridine
DMF	*N,N*-dimethylformamide
2D NMR	two-dimensional nuclear magnetic resonance
e.e.	enantiomeric excess
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoric triamide
HMQC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
^{i}Pr	isopropyl
IR	infrared
J	coupling constant (Hz)
KHMDS	potassium hexamethyldisilazide

LDA	lithium diisopropylamine
LiHMDS	lithium hexamethyldisilazide
LUMO	lowest unoccupied molecular orbital
$M^{+\cdot}$	molecular ion (mass spectra)
m-CPBA	*m*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
MHz	mega Hertz
min(s)	minute(s)
mmol	millimole
mol	mole
MOM	methoxymethoxymethyl
MOMCl	methoxymethoxymethyl chloride
m.p.	melting point (°C)
MS	mass spectrum
m/z	mass-to-charge ratio (mass spectroscopy)
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
$PhNTf_2$	*N*-phenyltrifluoromethanesulfonimide
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
R_f	retention factor
TBAF	tetrabutylammonium fluoride
TBS	*tertiary*-butyldimethylsilyl
TBSCl	*tertiary*-butyldimethylsilyl chloride
Tf	trifuoromethanesulfonyl (triflate)
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TsOH	*p*-toluenesulfonic acid

Table of Contents

Chapter One
The Sordarins

1.1 Introduction 1

1.2 The Sordarins 1

1.2.1 Isolation of sordarin 1

1.2.2 Other sordarins 3

1.3 Biosynthesis 3

1.3.1 The cycloaraneosene connection 3

1.3.2 Possible biosynthetic pathways 4

1.4 An Emerging Class of Antifungal Agents 5

1.4.1 Biological activity 5

1.4.2 Mode of action 6

1.4.3 Semi-synthetic analogues 7

1.5 Studies on the Synthesis of Sordaricin 8

1.5.1 Mander and Robinson's model study 8

1.5.2 Kato and coworker's model study 9

1.5.3 Kato and coworker's total synthesis of sordaricin methyl ester 10

1.6 Aims of the Research Described in this Thesis 11

1.7 References 12

Chapter Two
Synthetic Strategy

2.1 Introduction 15

2.2 A Convergent Approach to Sordaricin 15

2.2.1 Intramolecular [4+2] cycloaddition 15

2.2.2 Alkylation based convergent strategy 16

2.3 Dicyclopentadiene – A Versatile Synthon 20

2.3.1 Sordaricin total synthesis 20

2.3.2 Intramolecular [4+2] cycloaddition study 23

2.3.3 Structural variation for analogue synthesis 24

2.4 Conclusions 25

2.5 References 25

Chapter Three
Synthesis of the Aldehyde 60

3.1 Introduction 27

3.2 Synthesis of the Aldehyde 60 27

3.2.1 Initial approach 27

3.2.2 A modified approach 34

3.3.3 Successful synthesis of the aldehyde 35

3.3.4 Model alkylation 37

3.3 Summary 38

3.4 References 38

Chapter Four
Synthesis of the Iodide 158

4.1 Introduction 41

4.2 Synthesis of the Iodide 158 41

4.2.1 Synthesis of the key cyclopentenone 41

4.2.2 Successful synthesis of the iodide 45

4.3 Summary 51

4.4 References 52

Chapter Five
Alkylations Leading to Sordaricin

5.1 Introduction 55

5.2 Attempted alkylations 55

5.2.1 The aldehyde 55

5.2.2 The dimethylhydrazone 56

5.3 A successful alkylation 56

5.4 Elaboration to the tandem cycloreversion/intramolecular [4+2] cycloaddition precursor 60

5.4.1 Installation of the carboxy group 60

5.4.2 Installation of the isopropyl group 64

5.4.3 Synthesis of the precursor to the tandem cycloreversion/intramolecular [4+2] cycloaddition 65

5.5 Summary 65

5.6 References 66

Chapter Six
Total Synthesis of Sordaricin

6.1 Introduction 67

6.2 Sequential cycloreversion/intramolecular [4+2] cycloadditions 67

6.2.1 The diol 67

6.2.2 The aldehyde 68

6.3 An alternative reaction sequence 72

6.3.1 Synthesis of the intramolecular [4+2] cycloaddition precursors 72

6.3.2 Total synthesis of sordaricin 74

6.4 Summary 75

6.5 References 75

Chapter Seven
Cycloadditions Related to Sordaricin

7.1 Introduction 77

7.2 Intramolecular cycloadditions 77

7.2.1 Regioselectivity 77

7.2.2 Explaining the differences in rate and regioselectivity 78

7.3 The tandem cycloreversion/intramolecular [4+2] cycloaddition 80

7.3.1 Explaining the regioselectivity 80

7.4 Some conclusions on the cycloaddition studies 84

7.4.1 Unification of the kinetic and thermodynamic data 84

7.4.2 Speculations regarding sordaricin biosynthesis 85

7.5 References 89

Chapter Eight
Summary and Conclusions

8.1 Summary 91

8.1.1 Total synthesis of sordaricin 91

8.1.2 Cycloaddition studies 91

8.2 Conclusions 92

8.2.1 Future work 92

8.2.2 Overall conclusions 92

Chapter Nine
Experimental

9.1 General experimental 95

9.2 Notes on nomenclature 96

9.3 Experimental procedures 98

9.3.1 Chapter Three – Synthesis of the Aldehyde **60** 98

9.3.2 Chapter Four – Synthesis of the Iodide **158** 114

9.3.3 Chapter Five – Alkylations Leading to Sordaricin 125

9.3.4 Chapter Six – Total Synthesis of Sordaricin 143

9.3.5 Chapter Seven – Cycloadditions Related to Sordaricin 154

9.4 References 156

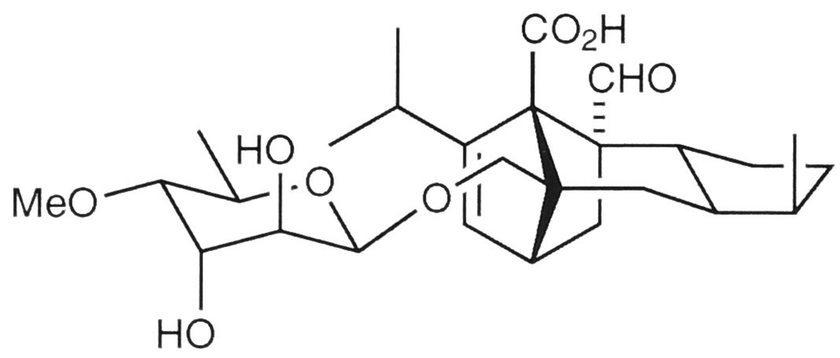
Chapter One

The Sordarins

1.1 Introduction

The incidence of invasive infections caused by opportunistic fungal pathogens has increased dramatically in the past two decades, and is seen most acutely in patients with severely compromised immune systems.[1] For the majority of cases, these conditions are due to intensive chemotherapy, organ or bone marrow transplant, and the rise of HIV infections to global epidemic proportions.[2] Unfortunately, despite the obvious need for an increase in the number of compounds available to treat such infections, medical practitioners are limited in their choices of clinically approved antifungal agents.[3] As such, the pharmaceutical industry is particularly interested in the discovery of new antifungal compounds displaying novel modes of action and improved pharmacological properties, *i.e.* increased efficacy and lowered cytotoxicity.[4]

The sordarins[5] are an emerging class of antifungal diterpene glycosides, of which sordarin (**1**),[6] isolated from the ascomycete *Sordaria araneosa* Cain, is the structural prototype. Much of the interest in sordarins stems from their demonstrated potent, broad spectrum antifungal activity and their novel mode of action. The major classes of antifungal agents *e.g.* the polyenes, azoles and allylamines,[7] are targeted against ergosterol, the major fungal sterol present in the plasma membrane. The sordarins are distinct from these classes in that they exert their influence through highly selective inhibition of fungal protein synthesis.



1

1.2 The Sordarins

1.2.1 Isolation of sordarin

Sordarin (**1**) was first isolated from the terrestrial fungus *Sordaria araneosa* Cain in 1971, by Hauser and Sigg.[6] Degradation studies on the isolated material rendered two compounds of molecular formula $C_{20}H_{28}O_4$ and $C_7H_{14}O_5$, respectively (Figure 1.2.1). The C_7 portion, named sordarose (**2**), was shown by ^1H NMR spectroscopy to be 6-desoxyaltrose. Structural elucidation of the C_{20} diterpene fragment, known as sordaricin (**3**), was achieved one year later by Vasella.[8]

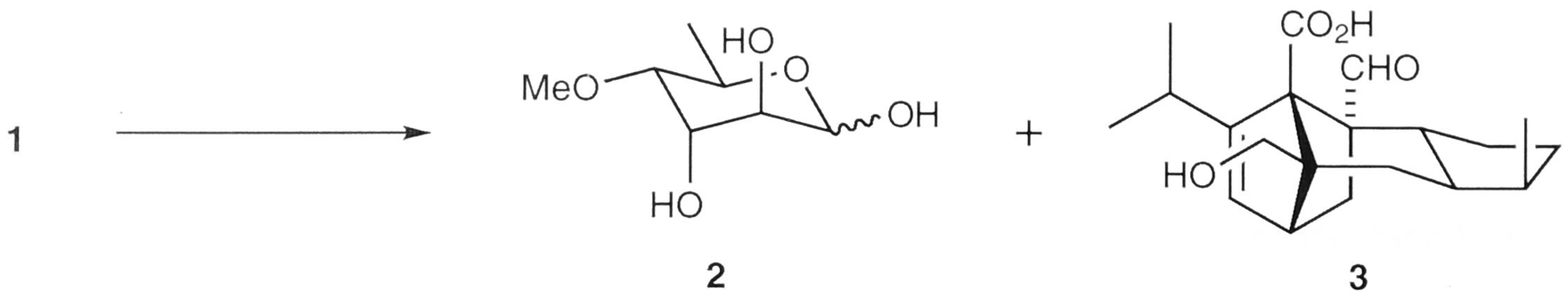


Figure 1.2.1 *Degradation of sordarin.*

Vasella's extensive studies on the C_{20} compound led ultimately to the preparation of diol **4**, that underwent a series of rearrangements to afford the tricyclic compound **5**. Ozonolysis and subsequent oxidative workup then gave the two carboxylic acids, **6** and **7** (Figure 1.2.2), of which the latter was thought to be related to nepetic acid (**8**). Synthesis of both **7** and **8** from a common precursor (**9**) was conducted, thereby confirming the absolute stereochemistry to be that shown.

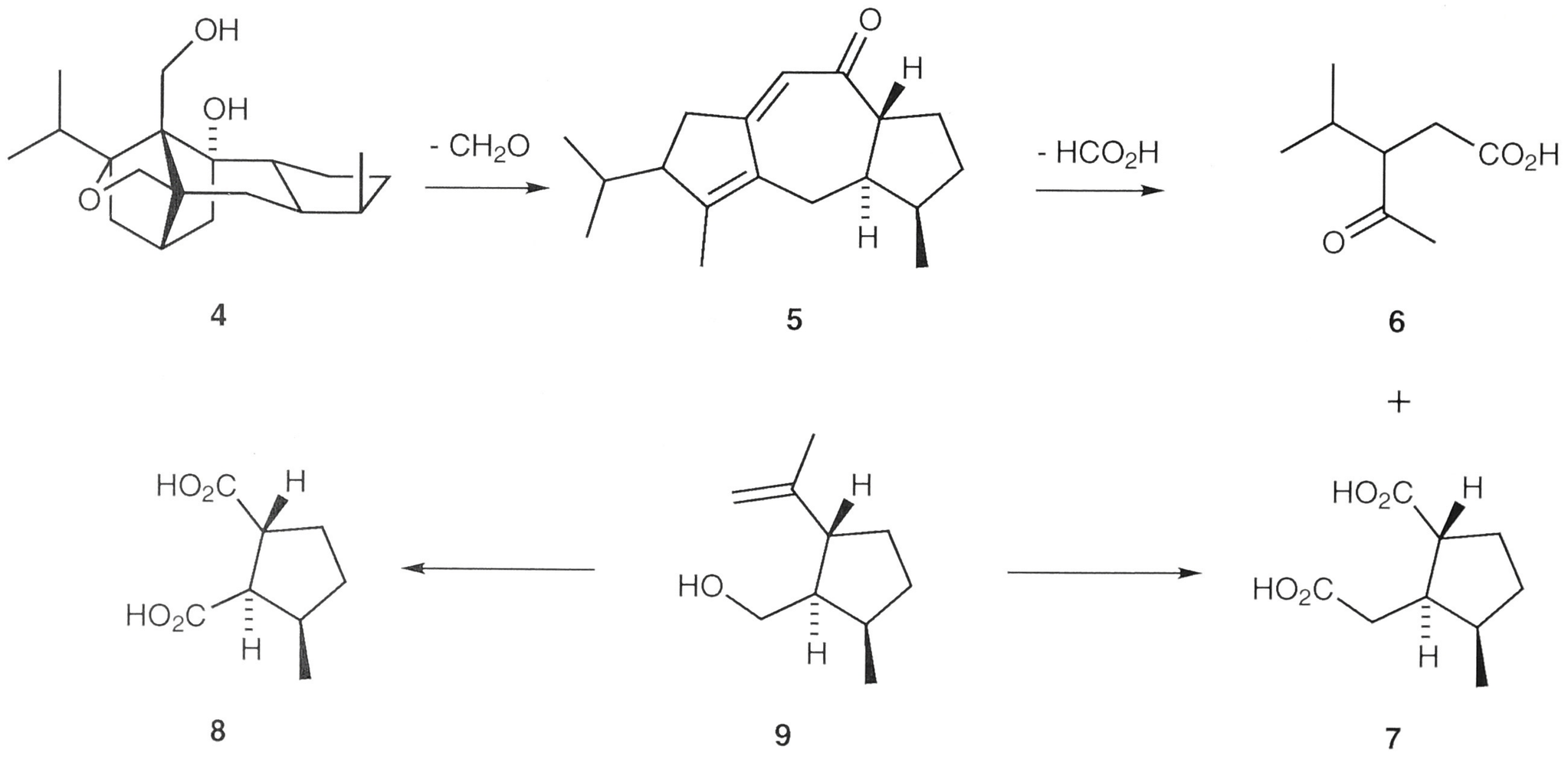
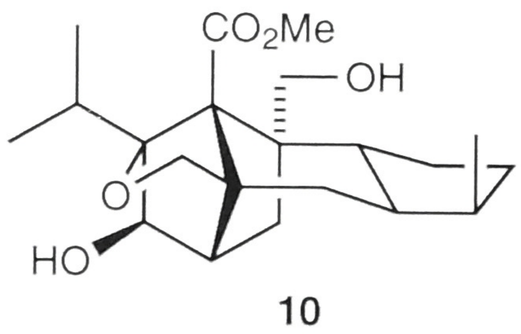


Figure 1.2.2 *Vasella's degradation studies.*

The combination of these studies, coupled with an X-ray crystal structure of diol **10**, led to the assignment of structure **3** to sordaricin, thereby showing sordarin to possess the structure given by **1**.



1.2.2 Other sordarins

Since the initial isolation of sordarin (**1**), several other compounds possessing related structures have been isolated from a wide variety of fungi.[9] All possess the same diterpene portion, *i.e.* sordaricin (**3**), with the only difference being the nature of the appended glycosidic residue (Figure 1.2.3). A large number of semi-synthetic sordarin derivatives have been produced by several pharmaceutical companies and will be discussed briefly in Section 1.4.

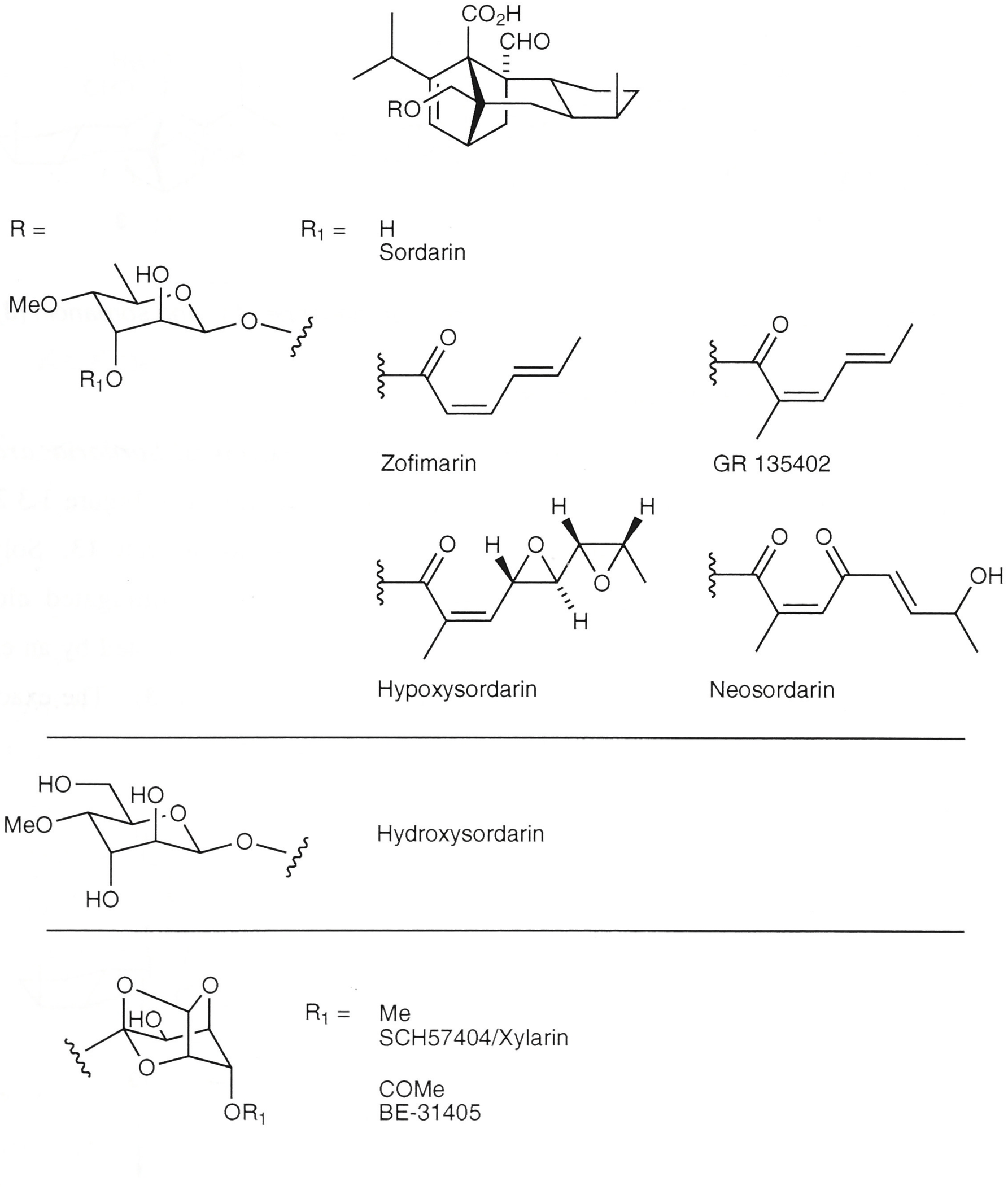


Figure 1.2.3 *Representative sordarins.*

1.3 Biosynthesis

1.3.1 The cycloareneosene connection

Following the research carried out by Vasella, Borschberg[10] conducted a study of the non-saponifiable portions of the *Sordaria araneosa* extracts. He was able to show, by GC/MS,

that most of these substances belonged to a class of compounds with the general molecular formula $C_{20}H_{32}$. The major constituent was isolated by column chromatography and shown to be cycloaraneosene (**11**), a compound similar to tricycle **5**, isolated previously during Vasella's degradation studies (see Figure 1.2.2). Comparison between the structures of sordaricin (**3**) and cycloaraneosene (**11**) lead to the speculation that cycloaraneosene (**11**) might be a biosynthetic precursor to the sordarins (Figure 1.3.1).

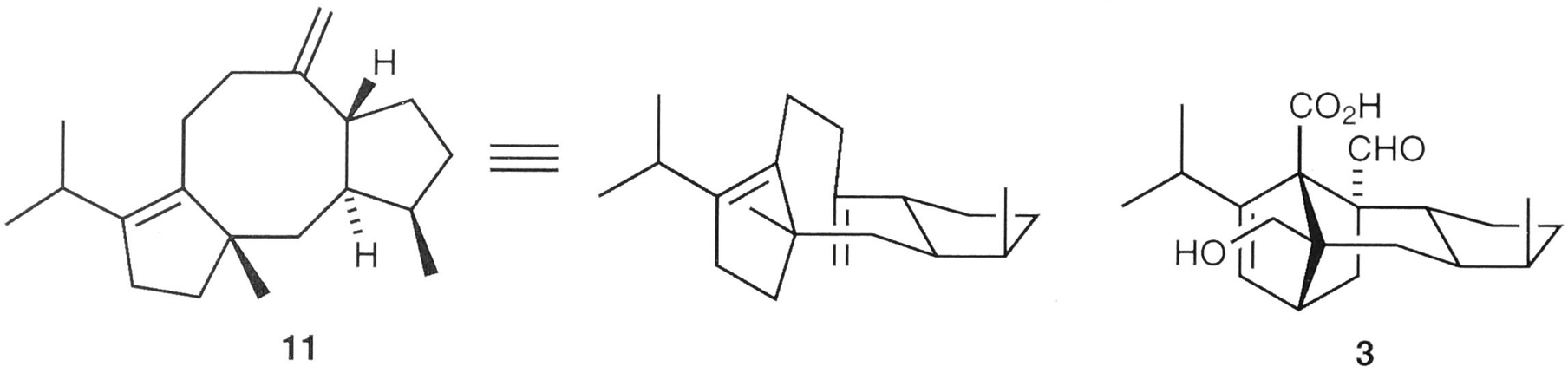


Figure 1.3.1 *Structural comparison between cycloaraneosene (**11**) and sordaricin (**3**).*

1.3.2 Possible biosynthetic pathways

The isolation of allylic alcohol **12** from the neutral extracts of *Sordaria araneosa* prompted Borschberg to formulate the speculative biosynthesis outlined in Figure 1.3.2. The hypothetical cascade would be initiated by oxidation of **12** at C12 to generate **13**. Solvolysis then triggers an English-Zimmerman-like[11] cleavage, leading to the conjugated aldehyde intermediate **14**. Subsequent ring closure, rendering **15**, would then be initiated by an external electrophile, and further oxidative processes would then lead to sordaricin (**3**). The exact stage at which glycosylation occurs was not considered, and is still unknown.

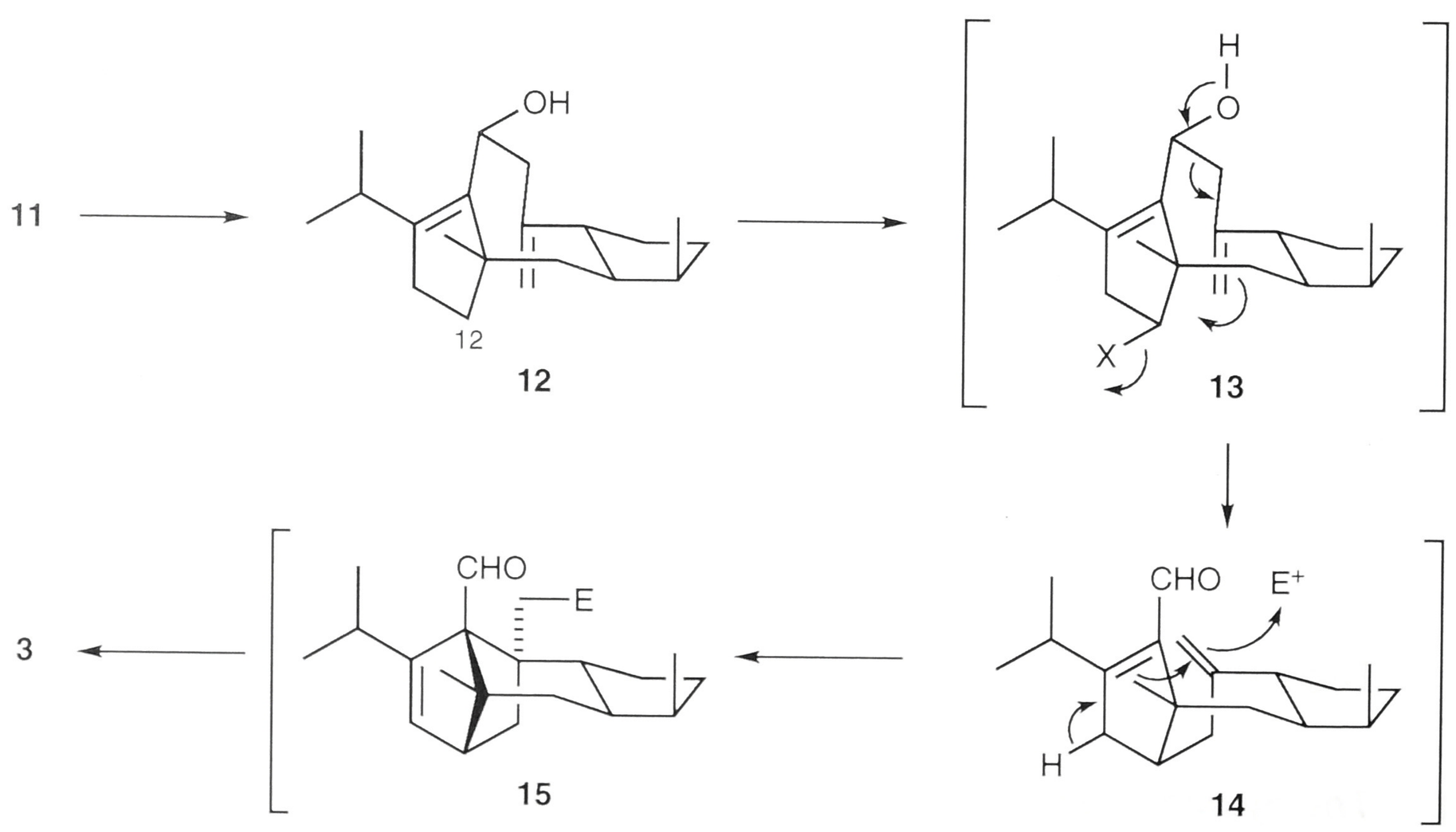
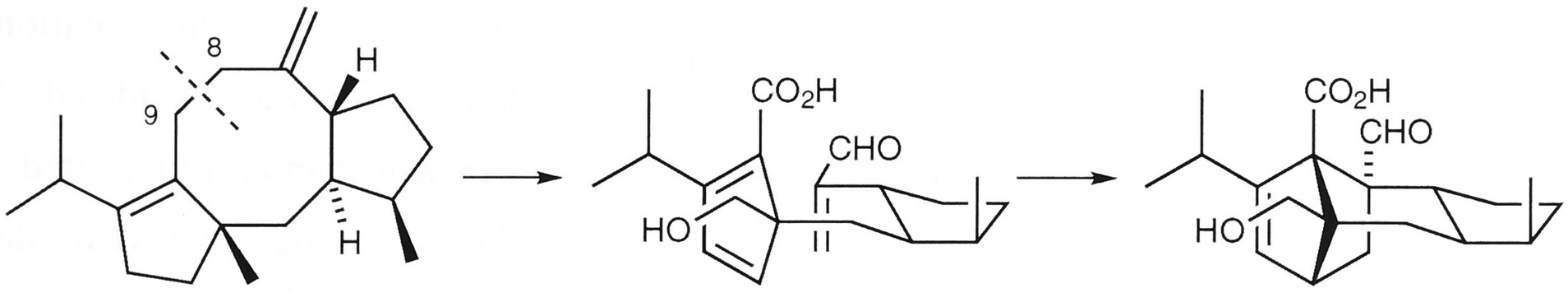


Figure 1.3.2 *Borschberg's postulated biosynthesis.*

Another, more provocative, hypothesis involving a possible [4+2] cycloaddition has also been put forward (Figure 1.3.3).[12] It requires oxidative fission of the C8-C9 bond, possibly by a *retro*-ene process, eventually affording **16**. Spontaneous or enzyme mediated cyclisation would then generate the requisite carbon skeleton. Evidence that such a biosynthetic process might exist has been produced in the form of two independent synthetic studies (see Section 1.5).



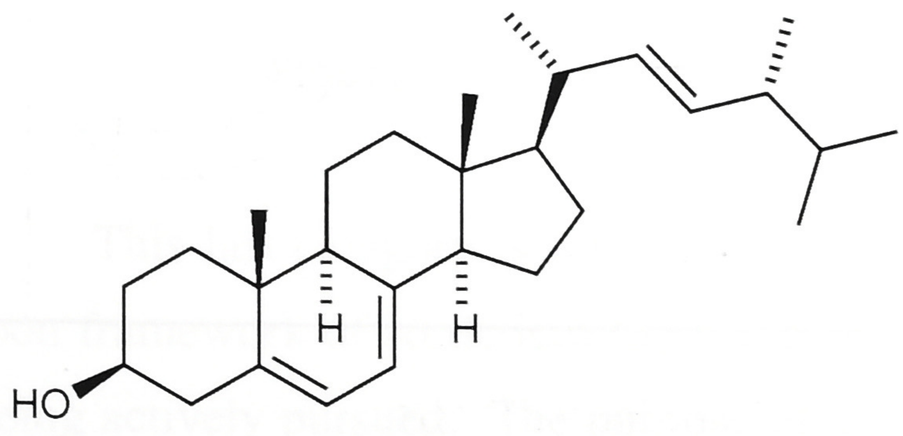
11 **16** **3**

Figure 1.3.3 *A speculative biosynthetic [4+2] cycloaddition.*

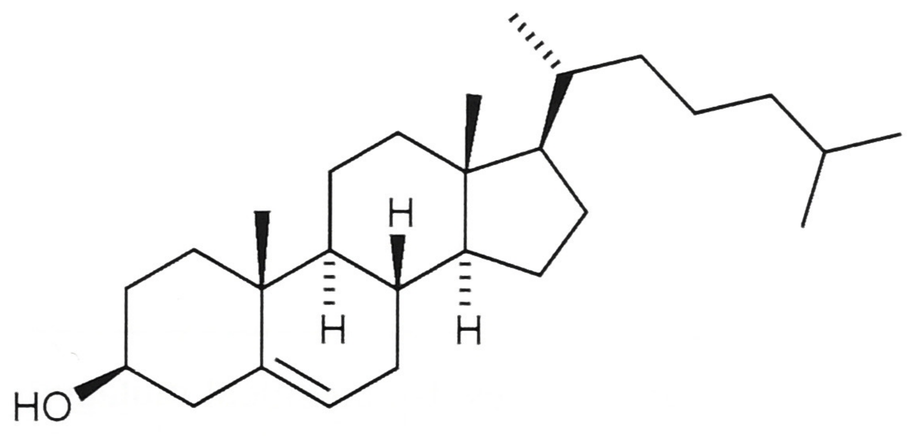
1.4 An Emerging Class of Antifungal Agents

1.4.1 Biological activity

The sordarins are potent antifungal compounds that exhibit remarkable *in vitro* activity against a wide range of fungal pathogens,[5] including *Candida albicans*, the organism responsible for the common thrush infection. They also show high levels of *in vitro* activity against several strains of emerging fungal pathogens, such as *Candida glabrata*, *C. kefyr*, *C.parapsilosis*, *C. tropicalis*, *Cryptococcus neoformans* and *Pneumocystis carinii*. Potent fungicidal activity is also observed against several endemic fungi, such as *Histoplasma capsulatum* and *Blastomyces dermatitidis*. Additionally, sordarins show encouraging *in vivo* activity against several pathogenic fungi when administered either subcutaneously or orally. Importantly, in this group is *P. carinii*, the major cause of lethal pneumonia in immunocompromised patients. This last result is particularly significant in that the major classes of antifungals in clinical use, are ineffective against *P. carinii*. These compounds target ergosterol (**17**), which leads to ill-formed cellular membranes, resulting in decreased growth rates and the inability to form invasive mycelia. Unlike most fungi, *P. carinii* utilises cholesterol (**18**) instead of ergosterol (**17**), thus rendering most antifungals ineffective.



17



18

It is the sordarins' novel mode of action (*vide infra*) that enables them to succeed where others fail, but most significantly the sordarins are non-cytotoxic and display no evidence of genotoxicity in the Ames assay.† They are not clastogenic* in cultured human lymphocytes and are well tolerated in animals.[5] As such, the sordarins are considered to be important lead targets in the search for new antifungal agents.

1.4.2 Mode of action

The antifungal properties of the sordarins have been known since the isolation of sordarin (**1**) in 1971, but it was not until recently that the mode of action was elucidated. The first report of the sordarins' mode of action came in 1998, when Kinsman *et. al* reported that GR 135402 (see Figure 1.2.3) inhibited fungal protein synthesis.[9] Later that year, detail regarding the molecular mechanism for this inhibition was published. Briefly, the molecular target was determined using two complementary approaches: identification of the sordarin binding protein in *C. albicans,* and the characterisation of genes imparting resistance in *Saccharomyces cerevisiae*. The first approach led to the discovery that elongation factor 2 (EF2) was the only protein that binds sordarin derivatives and that this binding is enhanced in the presence of ribosomes.[13] The second approach revealed that resistance was imparted by mutations in EF2[14] and mutations encoding the ribosomal protein, rpP0.[15] This led researchers to the conclusion that EF2 is the primary sordarin binding protein, and that the EF2-ribosome complex is the functional target. Further research into the link that the sordarins provide between these two proteins may lead to new insights into the mechanism of protein synthesis.

EF2 is a highly conserved protein, highlighted by the fact that *Saccharomyces cerevisiae* EF2 and human EF2 share a 66% sequence identity and 85% structural homology. In light of this information, it may seem unusual that the of action of the sordarins is highly selective for fungi and not higher order Eukaryotes. However, from the complex interactions described above, it is not unreasonable to suggest that the combination of these events leads to the observed high selectivity. Not only does this discovery have implications for antifungal compounds, it may also impact on drug discovery and design in a much broader sense. As Nielsen of Merck observed "These findings show that homology between essential proteins and processes in the host and pathogen does not necessarily exclude them as potential targets for selective chemotherapy." [14]

---

† A simple and effective test for chemical mutagens.

* Clastogenic substances cause damage to chromosomes.

1.4.3 Semi-synthetic sordarin analogues

Although the naturally derived sordarins display significant antifungal activity, most recent research has been invested in the synthesis and screening of semi-synthetic derivatives. This research has a two-fold agenda: access to new, enhanced sordarin derivatives, and the establishment of structure-activity-relationships to gain insight into the sordarin/EF2 interaction.

Fermentation of the producing fungus can provide substantial quantities (200 mg/L) of the natural product for modification, which falls into two broad categories: alteration of the glycosidic residue,[16] and derivatisation of sordaricin (**3**) (Figure 1.4.1).[17]

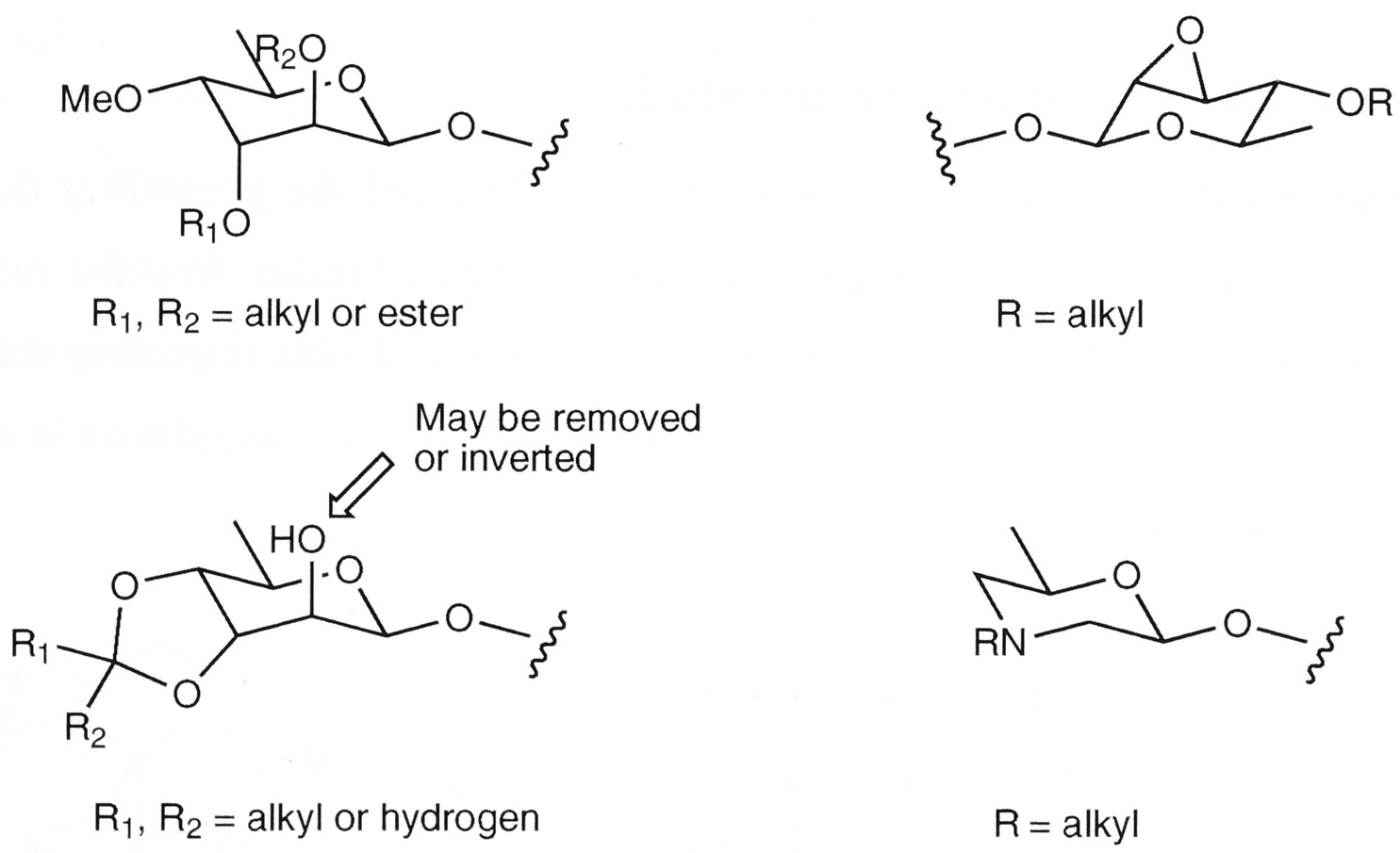
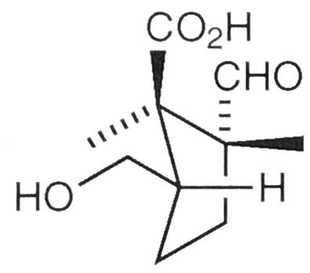


Figure 1.4.1 *Representative sordarin and sordaricin analogues.*

This last category is limited by the fact that it is extremely difficult to alter the actual carbon framework of sordaricin (**3**) and as such, the construction of a bioactive pharmacophore is being actively pursued. The purpose of this research is to provide an active compound with a

vastly simplified structure, thereby facilitating synthesis. The synthesis of only one possible pharmacophore (**19**) has been published to date, and unfortunately there was no assessment of bioactivity reported.[18]



19

1.5 Studies on the Synthesis of Sordaricin

1.5.1 Mander and Robinson's model study

Intrigued by the unique structure of sordaricin (**3**), and the possibility that it might be biosynthesised by means of an intramolecular [4+2] cycloaddition, Mander and Robinson[19] undertook the synthetic study outlined in Figure 1.5.1. Initial doubts regarding the feasibility of the proposed cycloaddition led them to study the intramolecular cycloaddition in a more readily prepared model system (**25**).

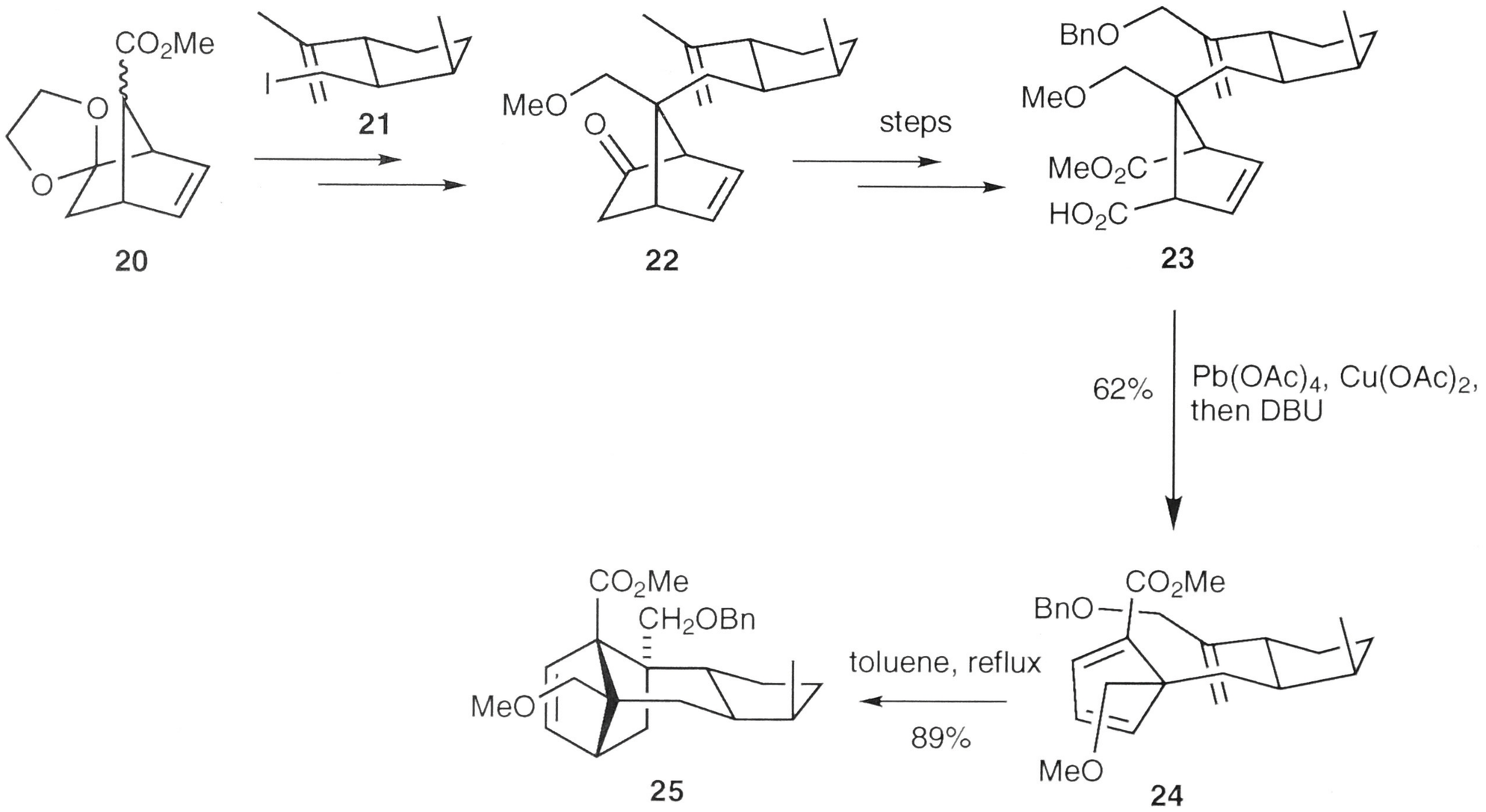


Figure 1.5.1 *Mander and Robinson's model study.*

The basic premise of the synthesis is that a highly convergent alkylation of ester **20**, with iodide **21**, would lead to compound **22**. Elaboration of the norbornene moiety, to **23**, followed by oxidative decarboxylation then gave cyclopentadiene **24**, the precursor to the planned cycloaddition. In the event, the [4+2] cycloaddition proceeded in excellent yield to

furnish **25**, as a single isomer. In an attempt to convert **25** into sordaricin (**3**), oxazoline **26** was synthesised in the hope that a directed metallation could be carried out, for the purpose of installing the requisite isopropyl group (Figure 1.5.2).[20] Although this approach did produce **28**, it required multiple steps, and the oxazoline group proved resistant to hydrolysis. Other research efforts aimed at introducing the isopropyl substituent at an earlier stage in the synthesis, were likewise unsuccessful in producing sordaricin (**3**).[21]

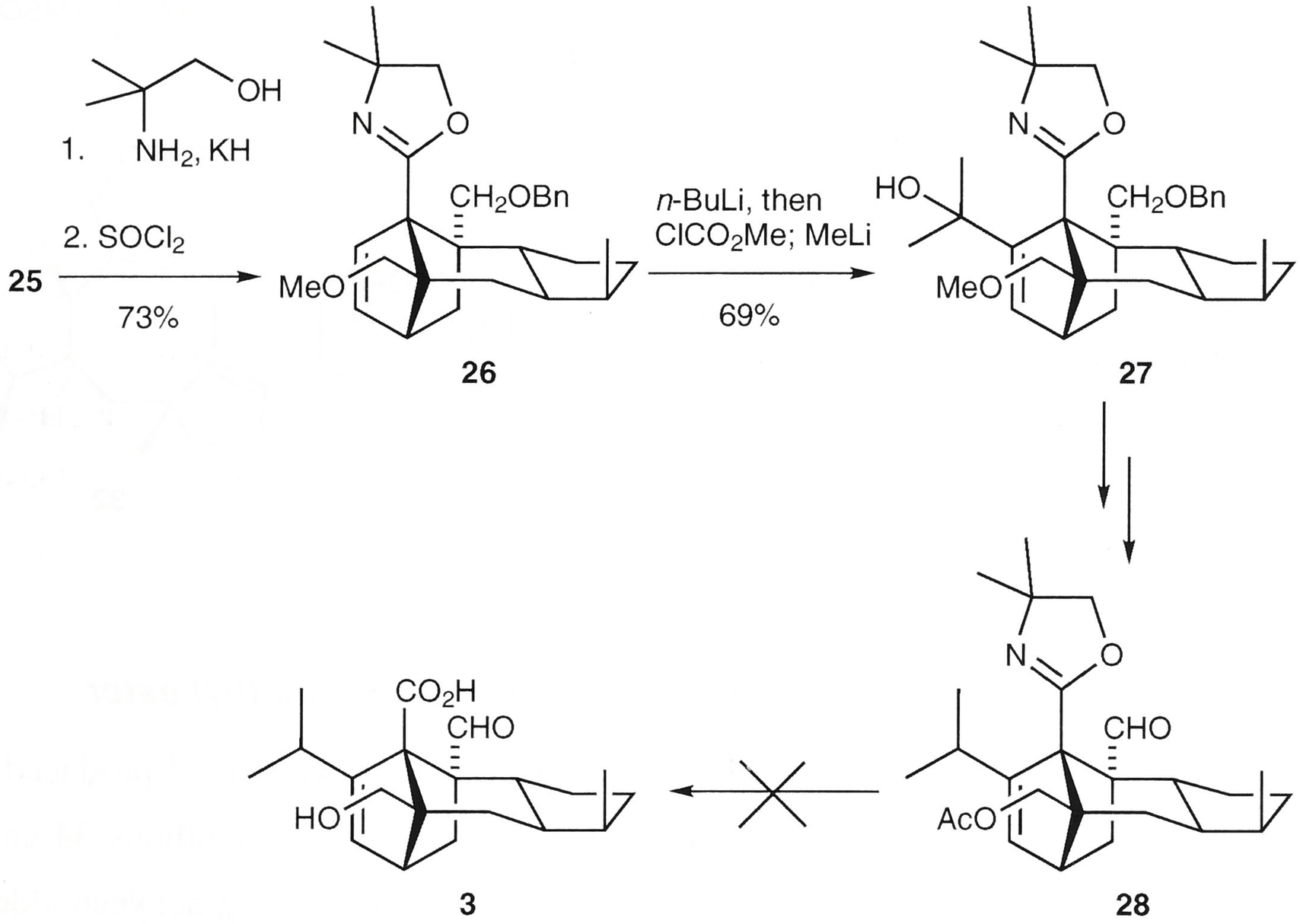


Figure 1.5.2 *Oxazoline directed isopropyl installation.*

1.5.2 Kato and co-worker's model study

Contemporaneously with Mander and Robinson, Kato and co-worker's[22] published a model study demonstrating the potential of the intramolecular [4+2] cycloaddition approach to sordaricin (**3**). During their total synthesis of hydroxycycloaraneosene (**29**), Kato *et al.* had prepared the functionalised ring B-*seco*-cycloaraneosene compound **30**,[23] which they showed could be transformed into the sordaricin derivative **33** (Figure 1.5.3).

Although the yield of the final conversion was very poor (10%), the cycloaddition occurred spontaneously after formation of the intermediate α,β-unsaturated aldehyde, suggesting that this transformation would be very facile within a biosynthetic context.

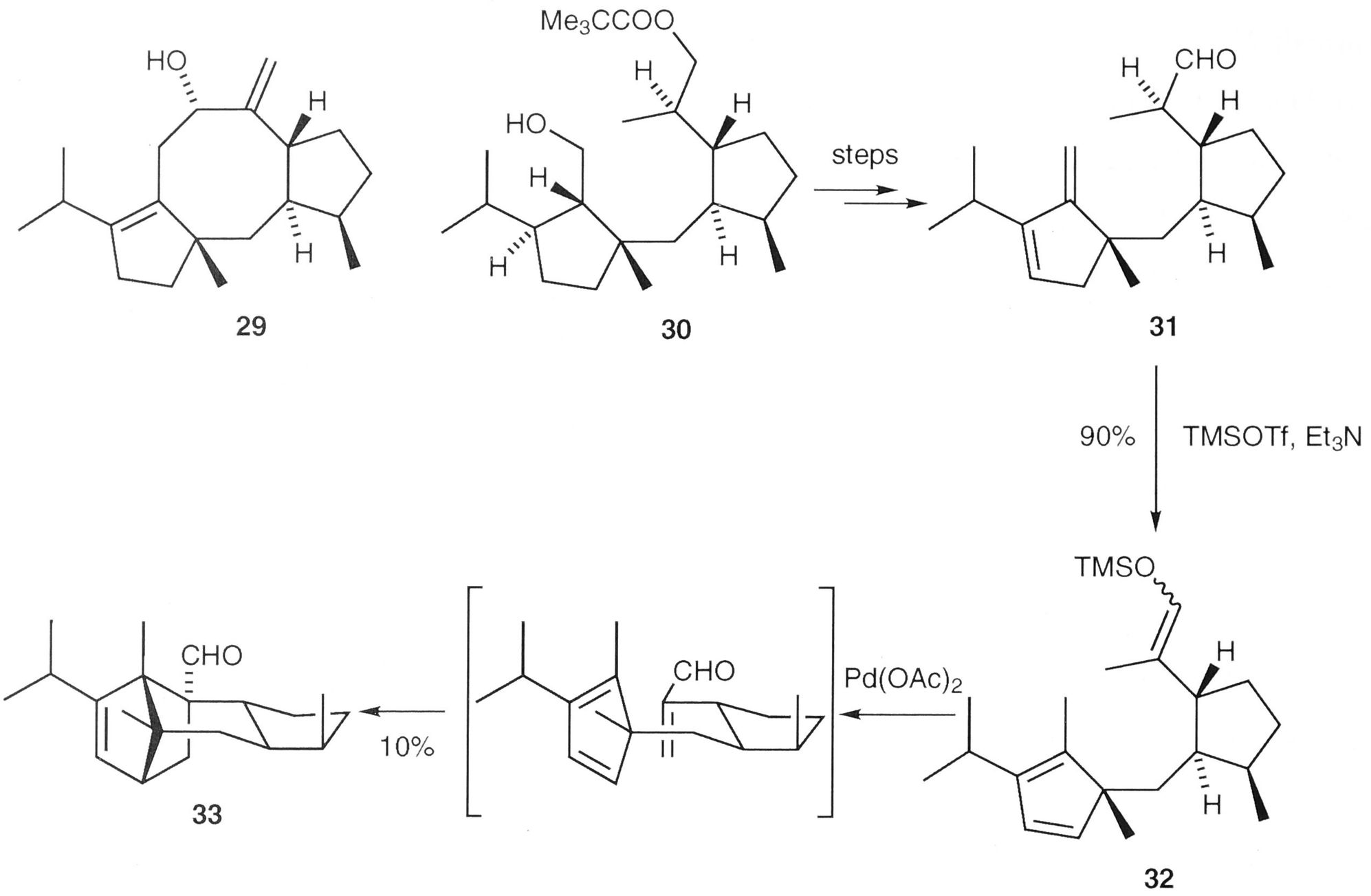


Figure 1.5.3 *Kato and co-worker's model study.*

1.5.3 Kato and co-worker's total synthesis of sordaricin methyl ester

Following the success of their model study, Kato and co-worker's[24] produced the first total synthesis of sordaricin methyl ester (**41**), which utilised iridoid synthons **34** and **35**, as starting materials (Figure 1.5.4). An initial chromium mediated coupling between aldehyde **34** and chloride **35**, followed by methylation, produced diene **36** in excellent yield (82%). Heating **36** at 200 °C induced a Cope rearrangement, thereby forming the pivotal enol ether **37**. Several manipulations then rendered cyclopentadiene **38**, which was transformed over three steps to the key silyl enol ether **39**, in moderate overall yield (26%). Saegusa oxidation readily formed the desired aldehyde, which, as in the model system (Figure 1.5.4), underwent *in situ* cyclisation to afford the MOM protected sordaricin derivative **40**. Removal of the MOM group then gave sordaricin methyl ester (**41**) in good yield (62%). The paper makes no reference to any attempts at demethylation of **41**, to form sordaricin (**3**) itself, and since this publication there have been no other reported total syntheses of sordaricin (**3**), or derivatives thereof.

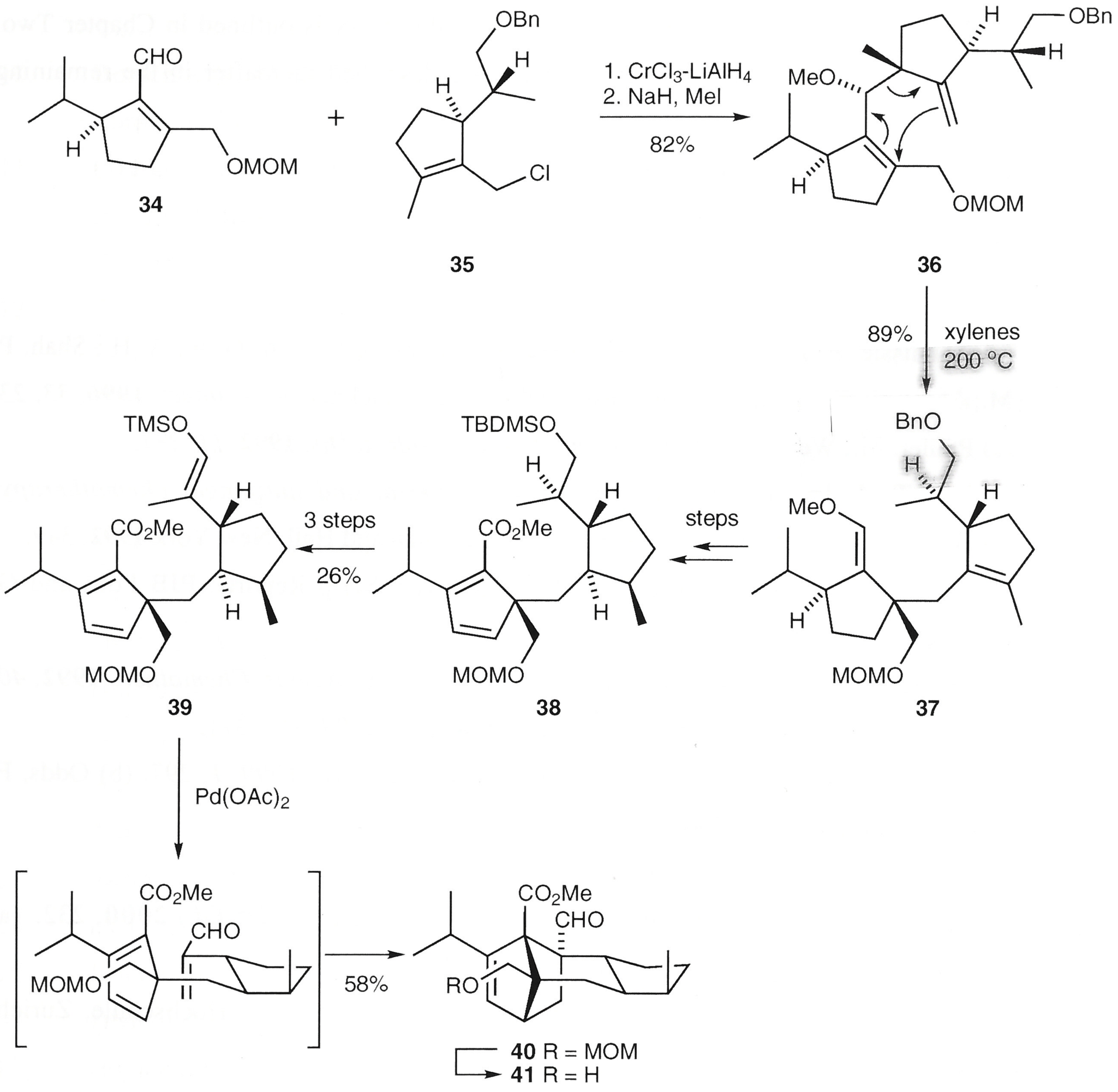


Figure 1.5.4 *Kato and co-worker's total synthesis of sordaricin methyl ester (**41**).*

1.6 Aims of the Research Described in this Thesis

In light of the foregoing discussion, it is apparent that the sordarins offer excellent potential as research targets. Their potent antifungal activity, and unique mode of action have led researchers to produce a wide variety of semi-synthetic analogues, in the pursuit of finding a suitable candidate for clinical development. The challenge of sordaricin's (**3**) complex and highly congested skeleton, coupled with biosynthetic speculations, has also produced two serious synthetic studies directed towards total synthesis.

The major aim of the research described in this thesis was to produce a concise total synthesis of sordaricn (**3**). The synthesis was planned to be flexible enough to accommodate the production of several analogues, with changes being possible in areas inaccessible by derivatisation of the natural product. A further goal was to investigate the effect of various substituents on the postulated biosynthetic [4+2] cycloaddition, in order to gain insights into

sordaricin biosynthesis. The synthetic strategy used in this work is outlined in Chapter Two, and the success or otherwise of the research goals are described thereafter in the remaining chapters.

1.7 References

1. (a) Annaissie, E. J. *Clin. Infect. Dis.* **1992**, *14* (Suppl 1), S43. (b) Groll, A. H.; Shah, P. M.; Mentzel, C.; Schneider, M.; Just-Nuebling, G.; Huebner, K. *J. Infect.* **1996**, *33*, 23. (c) Pfaller, M.; Wenzel, R. *Eur. J. Clin. Microbiol. Infect. Dis.* **1992**, *11*, 287.
2. Walsh, T. J. In *Emerging targets in antibacterial and antifungal chemotherapy*; Sutcliffe, J.; Georgopapadakou, N. H. (Eds); Chapman and Hall, New York **1992**, 349.
3. Halls, G. In *The Complete Guide to Anti-infectives*; Scrip Reports; PJB Pubs and G. Halls: UK **1999**, 111.
4. (a) Georgopapadakou, N. H.; Walsh, T. J. *Antimicrob. Agents Chemother.* **1992**, *40*, 279. (b) Georgopapadakou, N. H.; Walsh, T. J. *Science* **1994**, *265*, 371.
5. (a) Gargolla-Viola, D. *Curr. Opin. Anitinfect. Invest. Drugs* **1999**, *1*, 297. (b) Odds, F. C. *Exp. Opin. Ther. Pat.* **2001**, *11*, 283.
6. Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 1178.
7. (a) Espinel-Ingroff, A. In *Encyclopedia of Microbiology (2nd Ed.)* **2000**, 232. (a) Hartman, P. G.; Sanglard, D. *Curr. Pharm. Des.* **1997**, *3*, 177.
8. Vasella, A. T. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1972.
9. Zofimarin: Ogita, T.; Hiyashi, A.; Sato, S.; Furutani, W. JP Patent 6240292, 1987; *Chem. Abstr.* **1987**, *107*, 5745. GR135402: (a) Kinsman, O. S.; Chalk, P. A.; Jackson, H. C.; Middleton, R. F.; Shuttleworth, A.; Rudd, B. A. M.; Jones, C. A.; Noble, H. M.; Wildman, H. G.; Dawson, M. J.; Stylli, C.; Sidebottom, P. J.; Lamont, B.; Lynn, S.; Hayes, M. V. *J. Antibiotics***1998**, *51*, 41. (b) Kennedy, T. C.; Webb, G.; Cannell, R. J. P.; Kinsman, O. S.; Middleton, R. F.; Sidebottom, P. J.; Taylor, N. L.; Dawson, M. J.; Buss, A. D. *J. Antibiotics* **1998**, *51*, 1012. Hypoxysordarin: Daferner, M.; Mensch, S.; Anke, T.; Sterner, O. *Z. Naturforsch.* **1999**, *54c*, 474. Neosordarin and Hydroxysordarin: Davoli, P.; Engel, G.; Werle, A.; Sterner, O.; Anke, T. *J. Antibiotics* **2002**, *55*, 377.SCH57404/Xylarin: (a) Coval, S. J.; Puar, M. S.; Phife, D. W.; Terracciano, J. S.; Patel, M. *J. Antibiotics* **1995**, *48*, 1171. (b) Schneider, G.; Anke, H.; Sterner, O. *Nat. Prod. Lett.* **1995**, *7*, 309. BE-31405: Okada, H.; Kamiya, S.; Shiina, Y.; Suwa, H.; Nagashima, M.; Nakajima, S.; Shimokawa, H.; Sugiyama, E.; Kondo, H.; Kojiri, K.; Suda, H. *J. Antibiotics* **1998**, *51*, 1081.

10. Borschberg, H. J. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1975.

11. (a) English, J. Jr.; Zimmermann, H. E. *J. Am. Chem. Soc.* **1954**, *76,* 2285. (b) English, J. Jr.; Zimmermann, H. E. *J. Am. Chem. Soc.* **1954**, *76,* 2291. (c) English, J. Jr.; Zimmermann, H. E. *J. Am. Chem. Soc.* **1954**, *76,* 2294.

12. For other examples regarding biogenetic intramolecular [4+2] cycloadditions, see; (a) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981,** *46*, 1509. (b) Roush, W. R.; Peseckis, S. M.; Walts, A. E. *J. Org. Chem.* **1984**, *49*, 3429. (c) Takeda, S.; Sato, M.; Yoshii, E. *Tetrahedron Lett.* **1996**, *27*, 3903. (d) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748. (e) Katayama, K.; Kobayashi, T.; Oikawa, H.; Honma, M.; Ichihara, A, A. *Biochim. Biophys. Acta* **1998**, *1384*, 387. (f) Stocking, E. M.; Sanz-Cervera, J. E.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1675. (g) Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Van denHeever, J. P.; Hutchinson, C. R.; Vederas, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11519 (h) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552. (i) Evans, D. A.; Starr, J. T. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787. (j) Johansson, M.; Köpcke, B.; Anke, H.; Sterner, O. *Angew. Chem. Int. Ed.* **2002**, *41*, 2158 and references cited therein.

13. Dominguez, J. M.; Martin, J. J. *Antimicrob. Agents Chemother.* **1998**, *42*, 2279.

14. Justice, M. C.; Hsu, M. J.; Tse, B.; Balkovec, J.; Schmatz, D.; Nielsen, J. *J. Biol. Chem.* **1998**, *273*, 3148.

15. Gómez-Lorenzo, M.G.; García-Bustos, J. F. *J. Biol. Chem.* **1998**, *273*, 25041.

16. For examples, see: (a) Herreros, E.; Almela, M. J.; Lozano, S.; de las Heras, F. G.; Gargallo-Viola, D. *Antimicrob. Agents Chemother.* **2001**, *45*, 3132. (b)Arribas, E. M.; Castro, J.; Clemens, I. R.; Cuevas, J. C.; Chicharro, J.; Fraile, M. T.; García-Ochoa, S.; de las Heras, F. G.; Ruiz, J. R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 117. (c) Bueno, J. M.; Cuevas, J. C.; Fiandor, J. M.; García-Ochoa, S.; de las Heras, F. G. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 121. (d) Dawson, M.; Hall, R.; Castro, P. J. Eur. Pat. Appl. 1996 and references cited therein.

17. For examples, see: (a) Tse, B.; Balkovec, J. M.; Blazey, C. M.; Hsu, M.; Nielsen, J.; Schmatz, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2269. (b) Kaneko, S.; Uchida, T.; Shibuya, S.; Honda, T.; Kawamoto, I.; Harasaki, T.; Fukuoka, T.; Konosu, T. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 803. (c) Serrano-Wu, M.; St. Laurent, D. R.; Mazzucco, C. E.; Stickle, T. M.; Barret, J. F.; Vyas, D. M.; Balasubramanian, B. N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 943 and references cited therein.

18. Cuevas, J. C.; Martos, J. L. *Tetrahedron Lett.* **1998**, *39*, 8553.

19. Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595.

20. Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 5718.

21. (a) Smith, R. A. J. Unpublished results, 1988. (b) Whalley, J. L. Ph. D. Dissertation, Australian National University, 1995.

22. Kato, N.; Wu, X.; Takeshita, H. *Chem. Express* **1991**, *6*, 687.

23. (a) Kato, N.; Wu, X.; Tanaka, S.; Takeshita, H. *Chem. Lett.* **1989**, 91. (b)) Kato, N.; Wu, X.; Tanaka, S.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1729.

24. Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002.

Chapter Two

Synthetic Strategy

2.1 Introduction

The sordarins are attractive targets for total synthesis due to their complex molecular architecture and well established biological activity. From a synthetic standpoint, it is the diterpene aglycone, sordaricin (**3**), which poses the most significant challenge in this area. To date, only two research groups, those of Kato[1] and Mander,[2] have produced publications pertaining to the total synthesis of sordaricin (**3**). Of these groups, only Kato's has produced a successful total synthesis. Research for this thesis was primarily concerned with developing a total synthesis of sordaricin (**3**), with the added goals of obtaining insight into sordaricin biosynthesis and the production of analogues for biological evaluation. As such, the synthesis was required to be concise and efficient, but flexible enough to allow formation of several analogues. Moreover, in order to obtain information regarding biosynthesis, the synthesis needed to incorporate the putative biosynthetic intramolecular [4+2] cycloaddition.

2.2 A Convergent Approach to Sordaricin

2.2.1 Intramolecular [4+2] cycloaddition

Sordaricin (**3**) possesses a formidable carbon skeleton, containing four rings and three contiguous quaternary carbon stereocentres. Moreover, the ring appended substituents, in particular the isopropyl and carboxyl groups, generate significant steric strain through non-bonding interactions. Regardless of biosynthetic considerations, application of the Diels-Alder and alkylation transforms[3] to **3** leads to a vastly simplified pair of precursors, *i.e.* **42** and **43** (Figure 2.2.1).

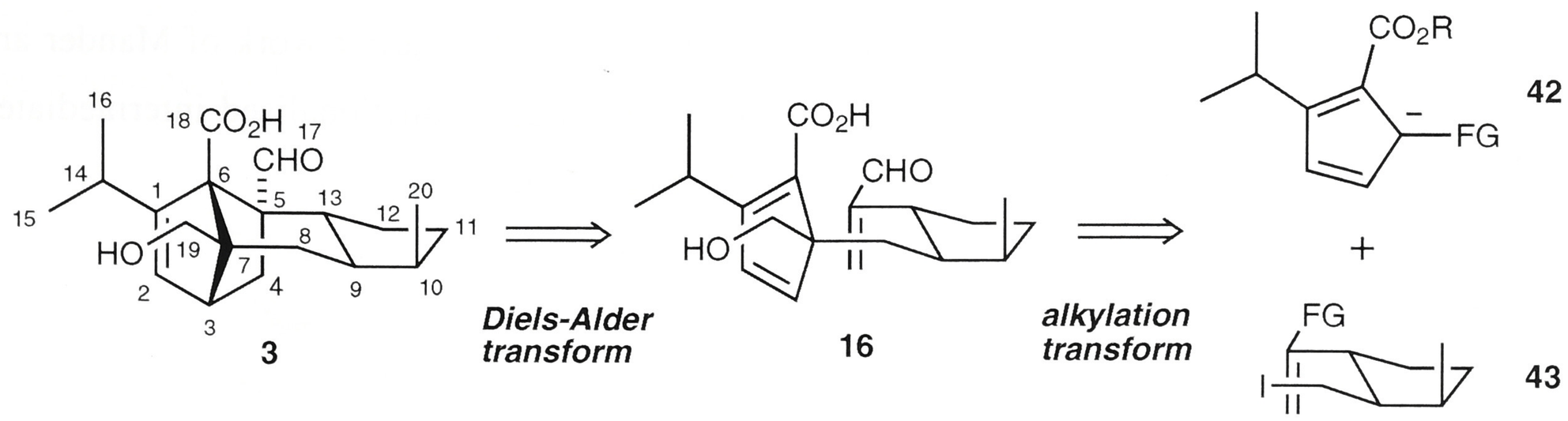


Figure 2.2.1 *Key Diels-Alder transform.*

In a forward sense this intramolecular Diels-Alder reaction produces two rings and two adjacent quaternary stereocentres (C5 and C6), in a stereodefined manner and in a single operation. Although there is a possibility that the Diels-Alder reaction could produce *iso*-**3**,

through the alternative orientation of the dienophile, this was thought to be an unlikely outcome in light of the previous work of both Kato and Mander. Both of these studies make no mention of any isomeric products being formed during the key intramolecular cycloadditions. Geometrical considerations (formation of *iso*-**3** requires the C-ring to adopt a boat conformation) and analysis of the frontier orbitals† of **16**, also leads to the prediction that **3** would be formed preferentially over *iso*-**3** (Figure 2.2.2). It may also be worthwhile to note that no structures possessing the carbon skeleton of *iso*-**3** have been isolated from any natural sources.

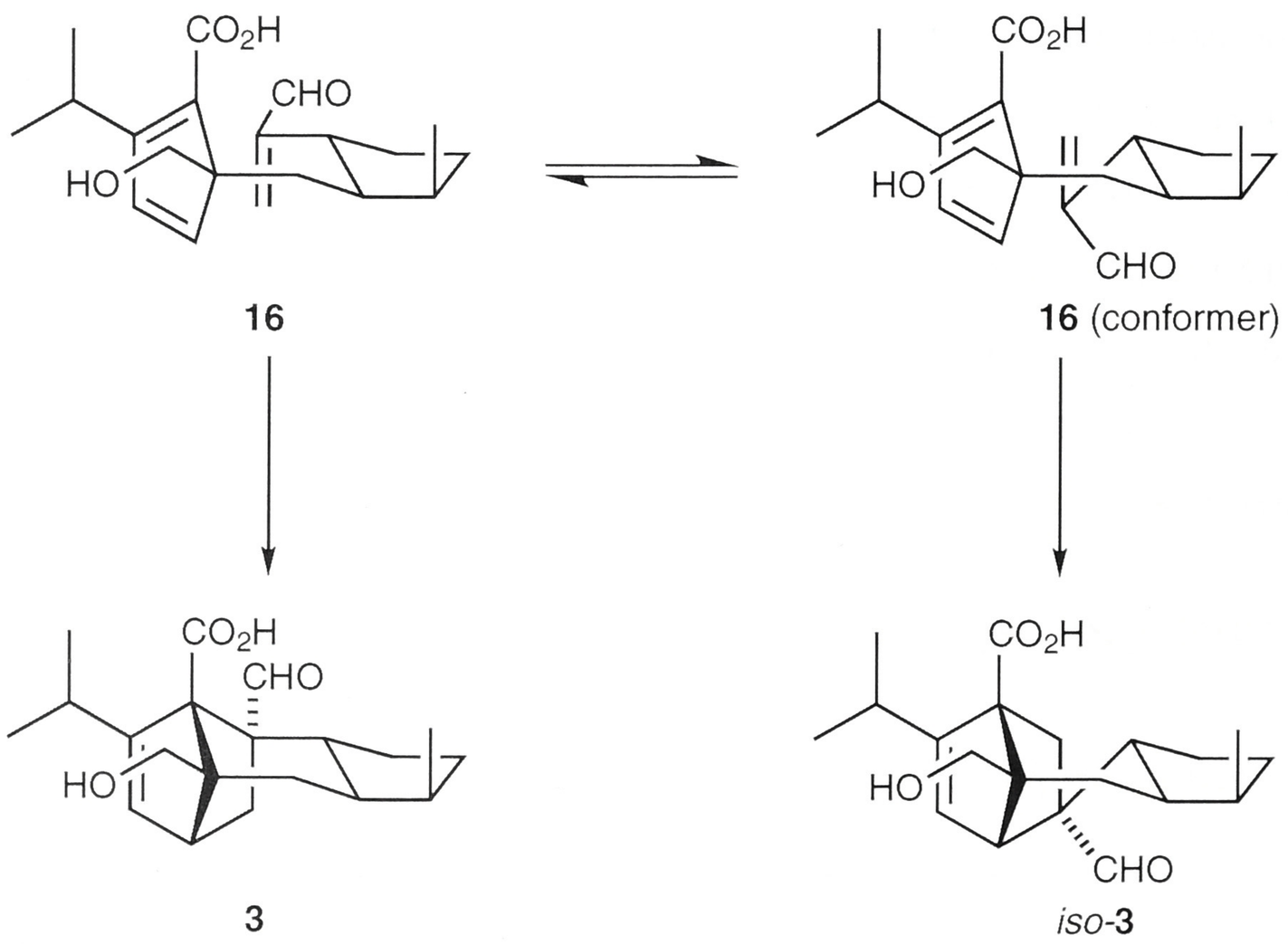


Figure 2.2.2 *Possible outcomes of the Diels-Alder cyclisation.*

2.2.2 Alkylation based convergent strategy

Having established that the Diels-Alder cycloaddition would be utilised in the synthesis, the next goal was to develop a strategy for an efficient synthesis of its precursor, namely, cyclopentadiene **16**. To this end, the present strategy parallels the earlier work of Mander and Robinson,[2] whereby a convergent alkylation between two highly functionalised intermediates, would lead to **16** in a concise and effective manner (Figure 2.2.3).

† For a discussion of the generalised frontier orbitals involved in Diels-Alder reactions: see Chapter Seven.

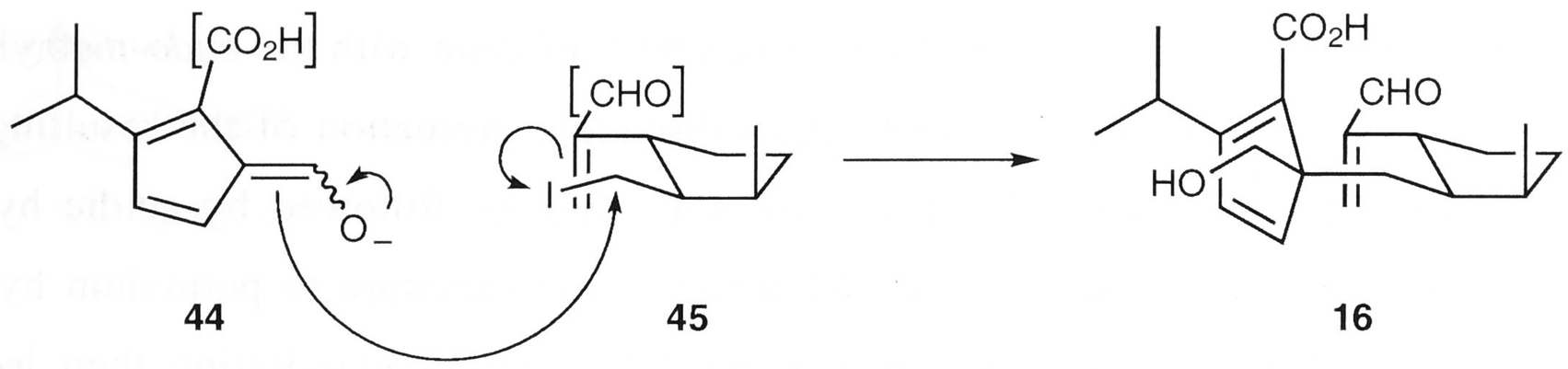


Figure 2.2.3 *Convergent alkylation strategy.*

Any direct attempt to alkylate enolate **44** could, however, be expected to suffer from lack of both regio- and stereochemical control, and therefore, the reaction indicated in Figure 2.2.3 was not considered. As such, use of a compound that is 'operationally equivalent' to this cyclopentadienyl enolate was necessary. In Mander and Robinson's model study, norbornadiene derivative **20**, was used to control the diastereoselectivity of the alkylation with iodide **21**. The norbornenyl moiety of **46**, was then converted to the appropriately functionalised cyclopentadiene, in this instance, **24** (Figure 2.2.4).

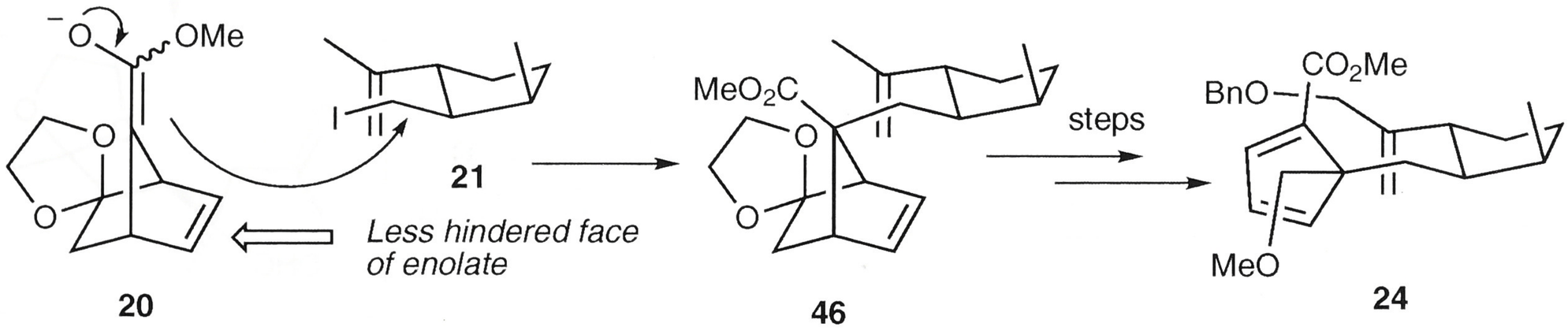


Figure 2.2.4 *Mander and Robinson's use of a norbornenyl operational equivalent.*

Therefore, in order to synthesise **16**, or a derivative thereof, it was necessary to find a method for constructing five membered rings containing a quaternary carbon stereocentre. A brief survey of the literature revealed two appropriate methods for this task. The first of these approaches was developed, and has been extensively utilised by, Meyers.[4] In principal, an amino acid derived bicyclic lactam (**47**) serves as the operational equivalent for a dienolate of cyclopentenone (**48**, Figure 2.2.5).

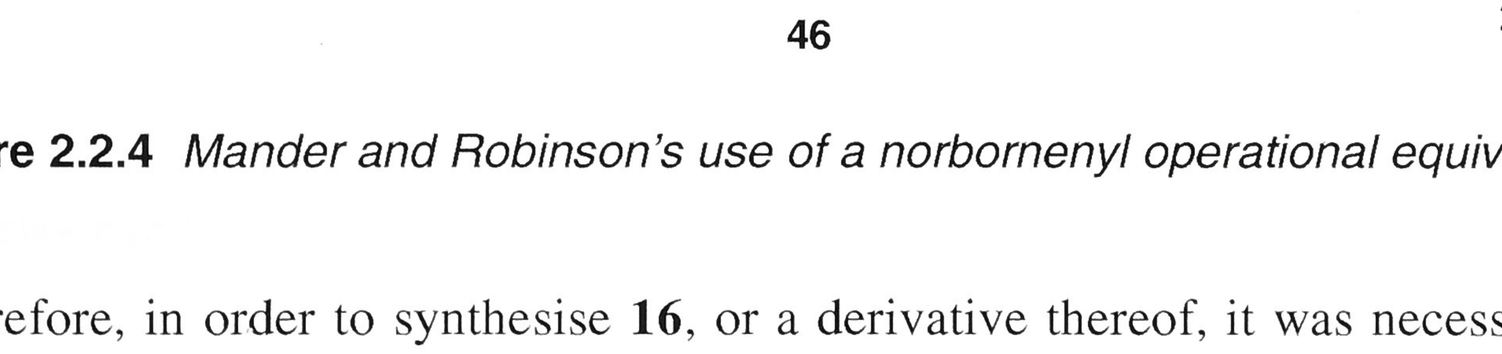


Figure 2.2.5 *Meyers' bicyclic lactam (**47**) – an operational equivalent of anion **48**.*

An example of this concept, applied to the total synthesis of (+)-$\Delta^{9(12)}$-capnellane (**53**), is given in Figure 2.2.6.[5] Lactam **47** was first alkylated with prenyl iodide, followed by methyl

iodide, to give **49** in good yield (74%, 2 steps) as a 91:9 mixture with the *endo*-methyl product predominating.† Ozonolysis of the olefin, and subsequent protection of the resulting ketone rendered lactam **50**, in good yield. Reduction with Red-Al, followed by acidic hydrolysis resulted in formation of acyclic aldehyde **51** which, upon exposure to potassium hydroxide, afforded the desired 4,4-dialkyl-2-cyclopentenone, **52**. Further elaboration then led to the formation of (+)-$\Delta^{9(12)}$-capnellane (**53**), in an overall yield of 14.1%.

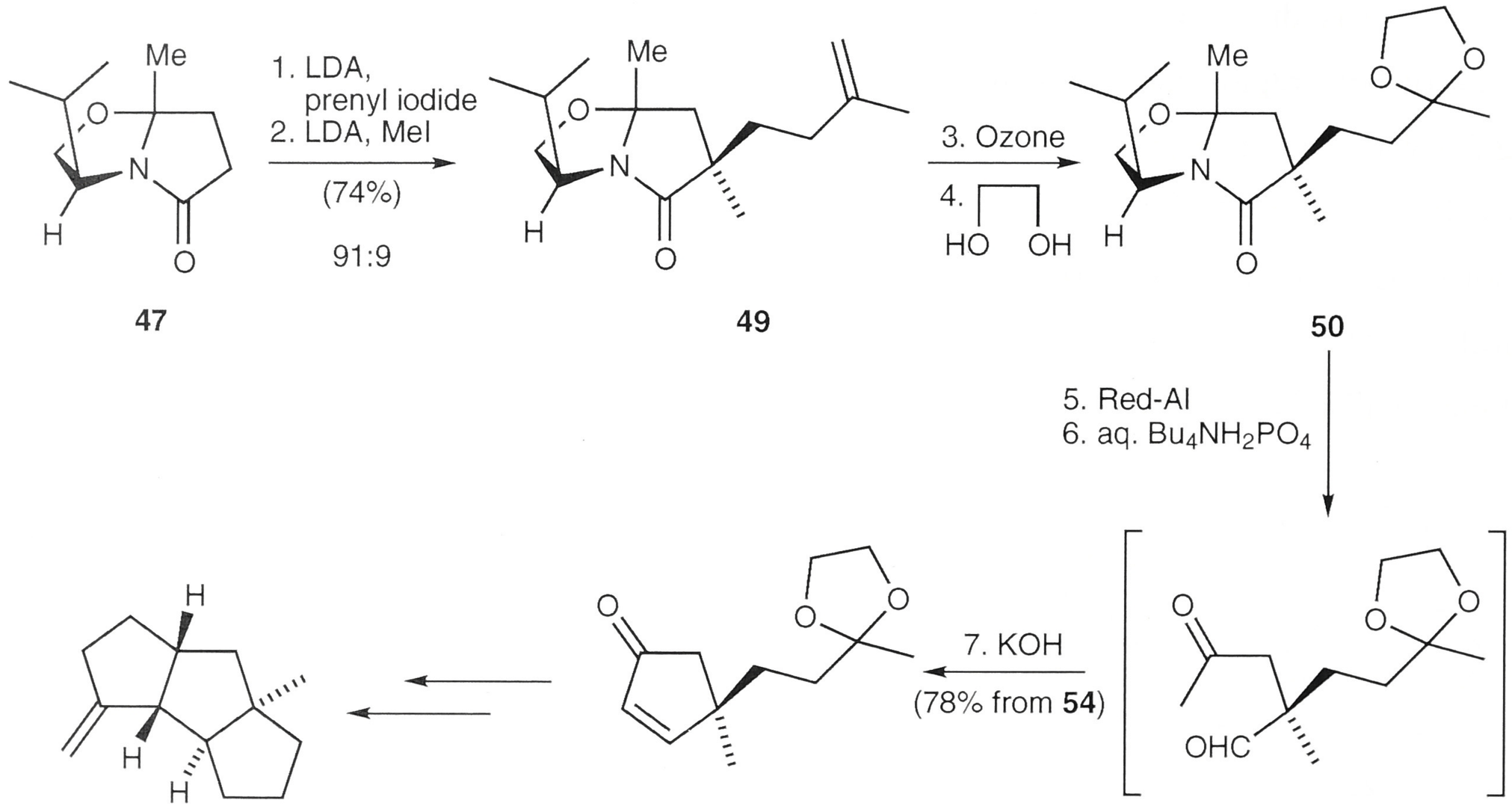


Figure 2.2.6 *Meyers' and Bienz's total synthesis of (+)-$\Delta^{9(12)}$-capnellane (**53**).*

Another widely utilised method for producing functionalised cyclopentenones in a stereodefined manner involves the use of dicyclopentadienone (**54**).[6] The concave α-face of the tricycle directs nucleophiles and electrophiles to the more exposed *exo*-face, allowing for a wide range of diastereoselective reactions to be carried out (Figure 2.2.7).

† The stereoselectivity of such alkylations has been rationalised on the basis of torsional and steric effects in the transition states: see Ando, A.; Green, N. S.;Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1999,** *121*, 5334.

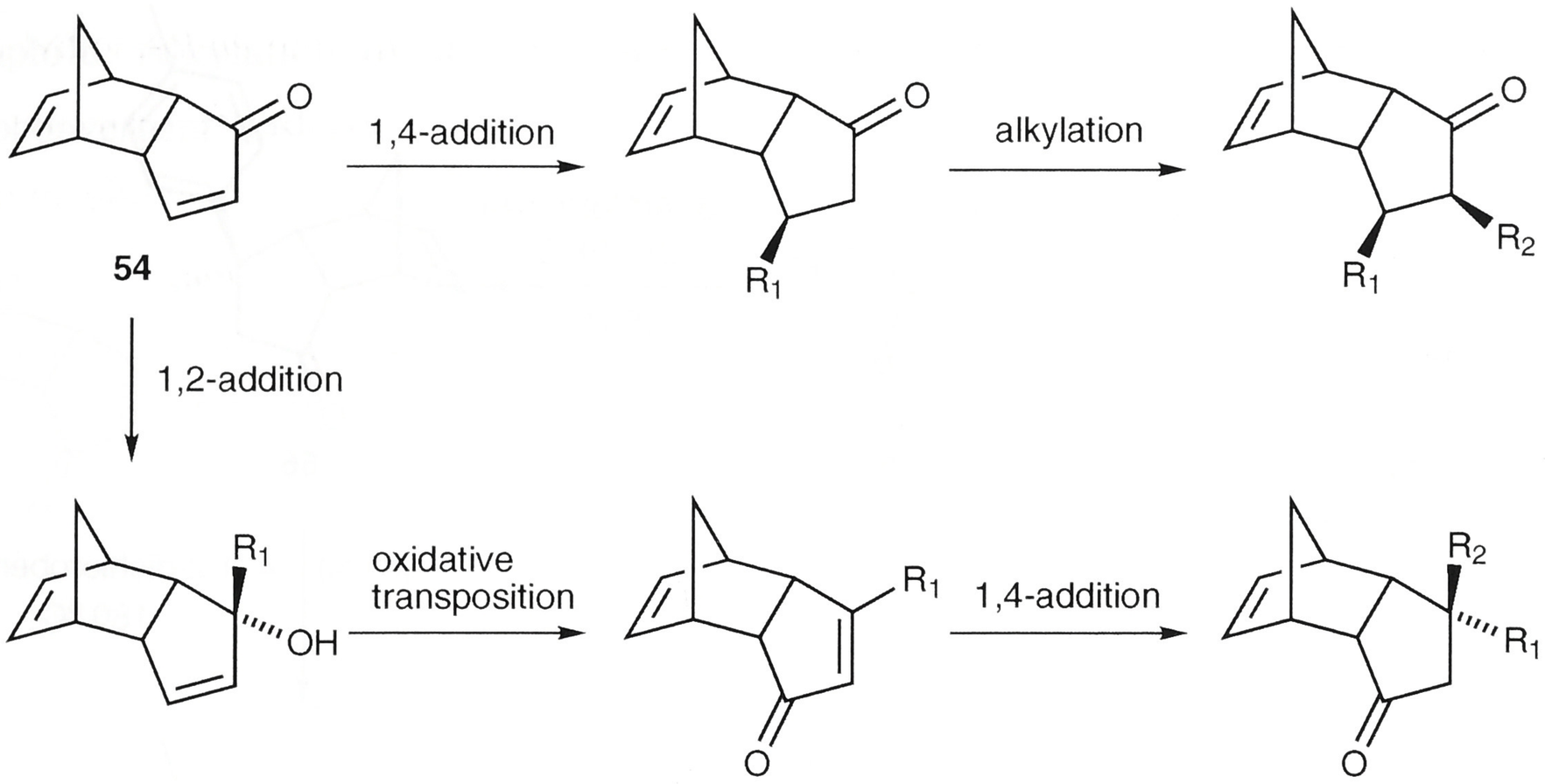


Figure 2.2.7 *Versatility of dicyclopentadienone (**54**).*

Generation of the required substituted five membered ring is achieved by means of a thermally activated *retro*-Diels-Alder reaction,[7] with loss of cyclopentadiene (Figure 2.2.8).

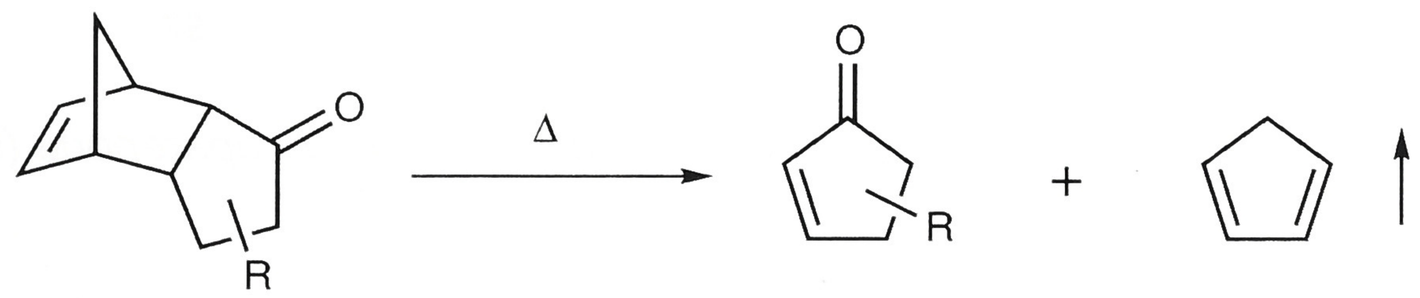


Figure 2.2.8 retro-*Diels-Alder reaction to generate functionalised cyclopentenones.*

An illustrative use of dicyclopentadienone (**54**), in the context of natural product total synthesis, is seen in Takano and co-worker's concise synthesis of (+)-α-cuparenone (**58**) (Figure 2.2.9).[8] 1,2-Addition of methyl lithium to ketone (+)-**54**, followed by 1,3-oxidative transposition with pyridinium chlorochromate, furnished β–substituted enone **55** in moderate yield (41% over two steps). Subsequent 1,4-addition of the cuprate derived from *p*-tolylmagnesium bromide rendered ketone **56**, as a single diastereomer and in reasonable yield (63%). Heating **56** in *o*-dichlorobenzene, at reflux, then effected a smooth cycloreversion to afford the key 4,4-dialkylcyclopentenone **57** in 61% yield. Methylation, followed by reduction, gave (+)-α-cuparenone (**58**) in 60% overall yield.

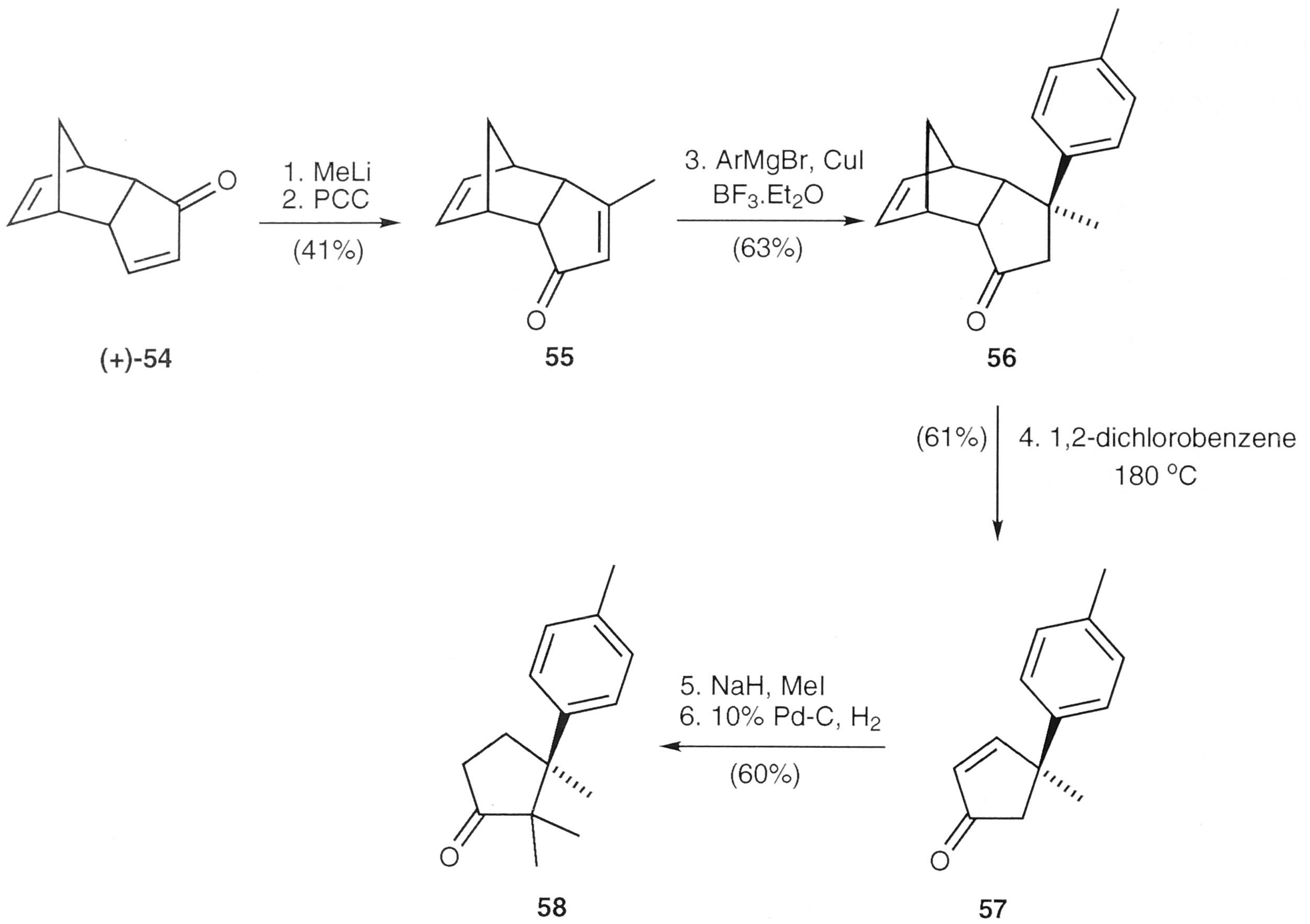


Figure 2.2.9 *Takano and co-worker's synthesis of (+)-α-cuparenone (**58**).*

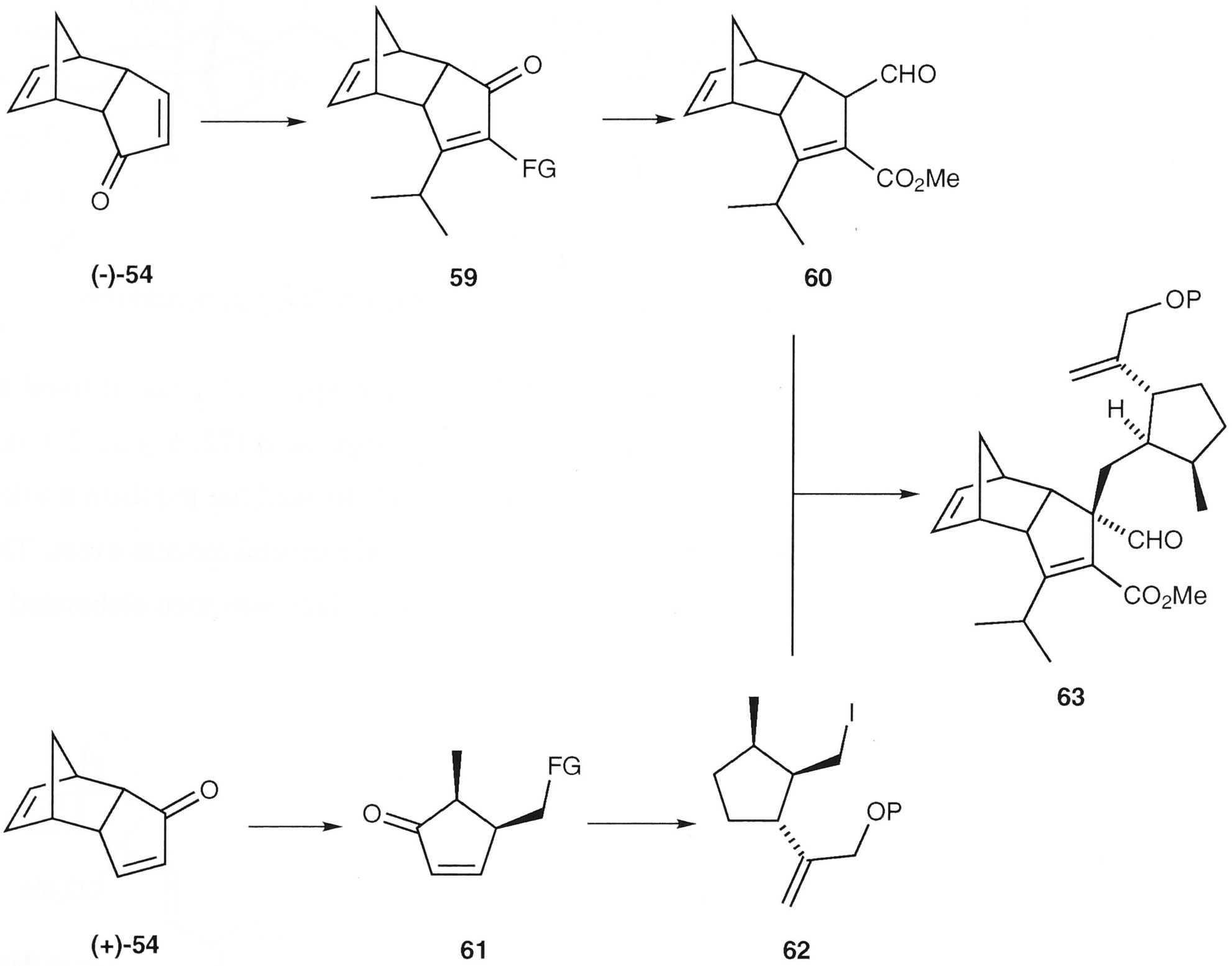
For the purpose of synthesising sordaricin (**3**), dicyclopentadienone (**54**) was considered an excellent candidate for use as a starting material.

2.3 Dicyclopentadienone – A Versatile Synthon

2.3.1 Sordaricin total synthesis

The proposed use of dicyclopentadienone (**54**) as a starting material led to two key targets, aldehyde **60** and iodide **62** which, in principle, could be generated from (–)-**54** and (+)-**54**, respectively (Figure 2.3.1).[9] Ketone **59** was considered as a good subtarget towards aldehyde **60**, with the expectation that the ketone moiety could be transformed into the required aldehyde by a Wittig reaction. It was hoped that iodide **62** could be synthesised from cyclopentenone **61**, following an *anti*-selective conjugate addition of an appropriate

nucleophile. Alkylation of aldehyde **60** with iodide **62**, would then generate **63**, in an enantioconvergent* fashion.



(-)-54 59 60 63

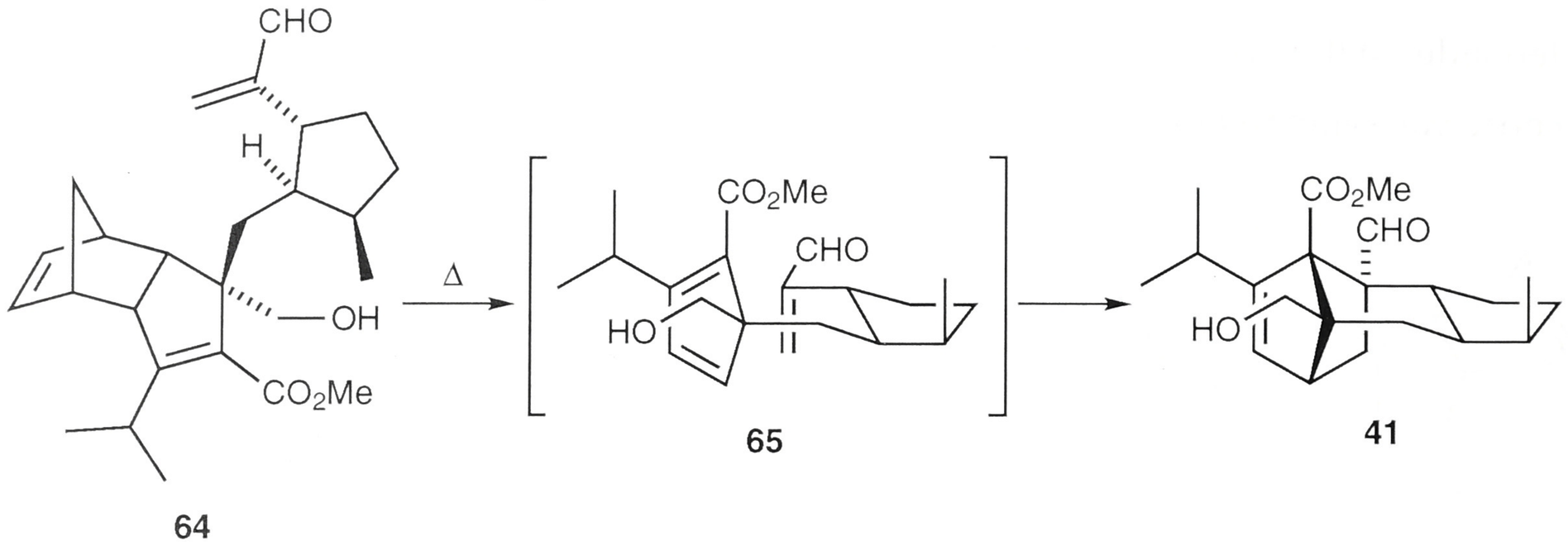
(+)-54 61 62

Figure 2.3.1 *An enantioconvergent assembly of ester **63**.*

Use of the dicyclopentadiene scaffold not only allows absolute and relative stereocontrol, but also the possibility of performing a tandem[10] cycloreversion/intramolecular [4+2] cycloaddition, to generate the sordaricin skeleton in a single step (Figure 2.3.2).

---

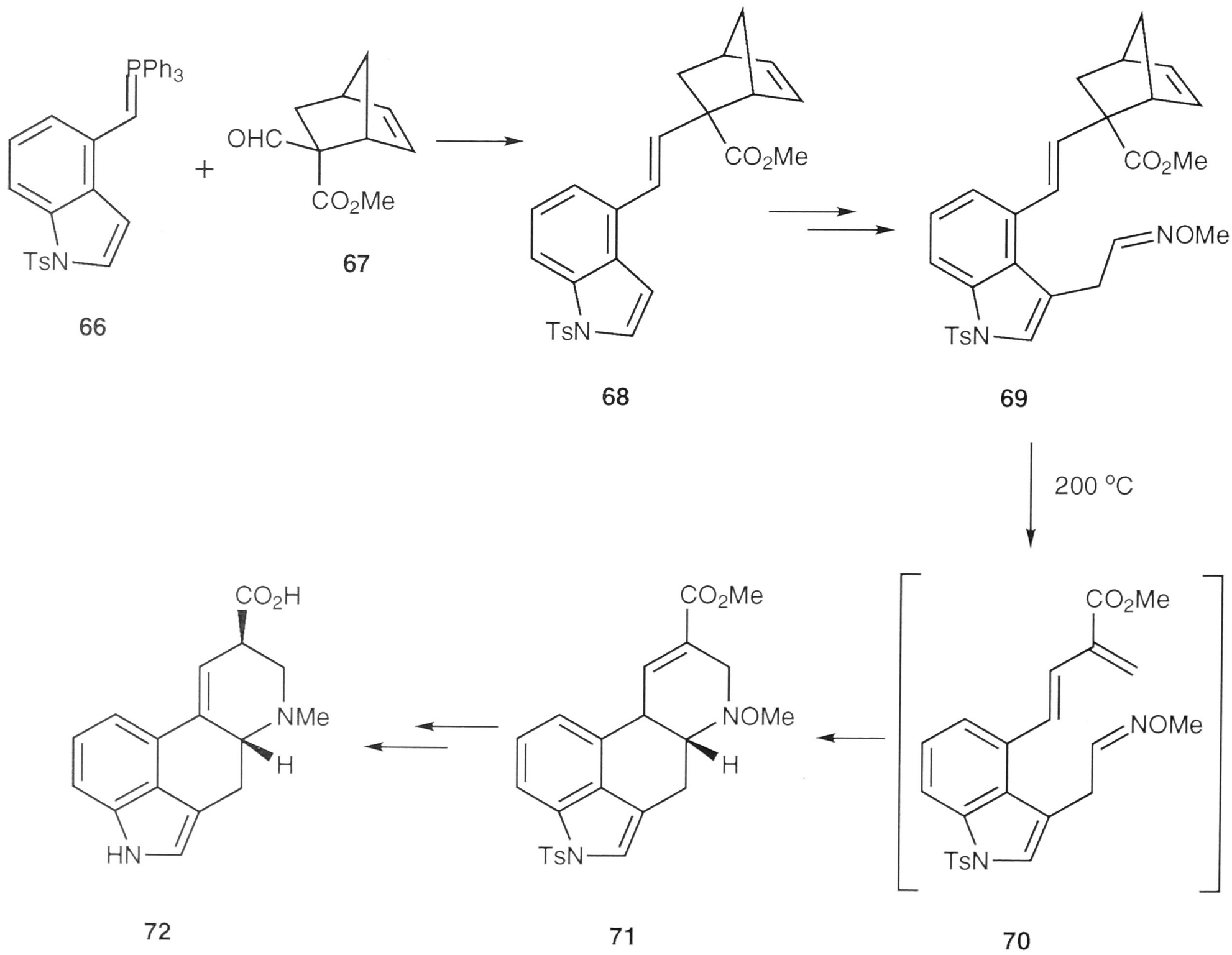
* The term 'enantioconvergent' refers to a process in which both enantiomers of a racemic substrate are ultimately converted into a single enantiomeric series: Saddler, J. C.; Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981,** *103*, 2110. The term itself was first used by Trost: Trost, B. M.; Timko, J. M.; Stanton, J. L. *J. Chem. Soc., Chem. Commun.* **1978**, 436.



64 65 41

Figure 2.3.2 *A potential tandem cycloreversion/intramolecular [4+2] cycloaddition.*

A similar type of tandem *retro*-Diels-Alder/Diels-Alder approach was utilised by Oppolzer and co-worker's in their elegant total synthesis of lysergic acid (**72**, Figure 2.3.3).[11] In this case, a Wittig reaction between ylide **66** and aldehyde **67**, formed the requisite masked diene **68**. Further elaboration to oxime **69** then set the scene for the crucial tandem event. This process proceeded, *via* **70**, at 200 °C to afford a good yield of **71**, which was then elaborated to the natural product (**72**).



66 67 68 69 70 71 72

Figure 2.3.3 *Oppolzer and co-worker's synthesis of lysergic acid (**72**).*

Although such an approach would be highly desirable in terms of producing a concise and efficient synthesis of sordaricin (**3**), it is unsuitable for studying the intramolecular [4+2] cycloaddition, as the precursor would presumably be a transient intermediate in the tandem process. Moreover, use of this strategy for analogue production would be laborious and inefficient. Introduction of diversity would occur at an early stage in the synthesis, which would necessitate carrying several analogues through essentially the same sequence of reactions. In order for analogue production to be efficient, introduction of diversity at the latest possible stage in the synthesis is highly desirable.

2.3.2 Intramolecular [4+2] cycloaddtion study

For the purpose of studying the putative biosynthetic [4+2] cycloaddtion, a strategy was required whereby the cycloaddition precursor (**65** or similar) could be isolated. Such a synthesis was deemed possible by a modification of the approach outlined in Section 2.2, as shown in Figure 2.3.4.

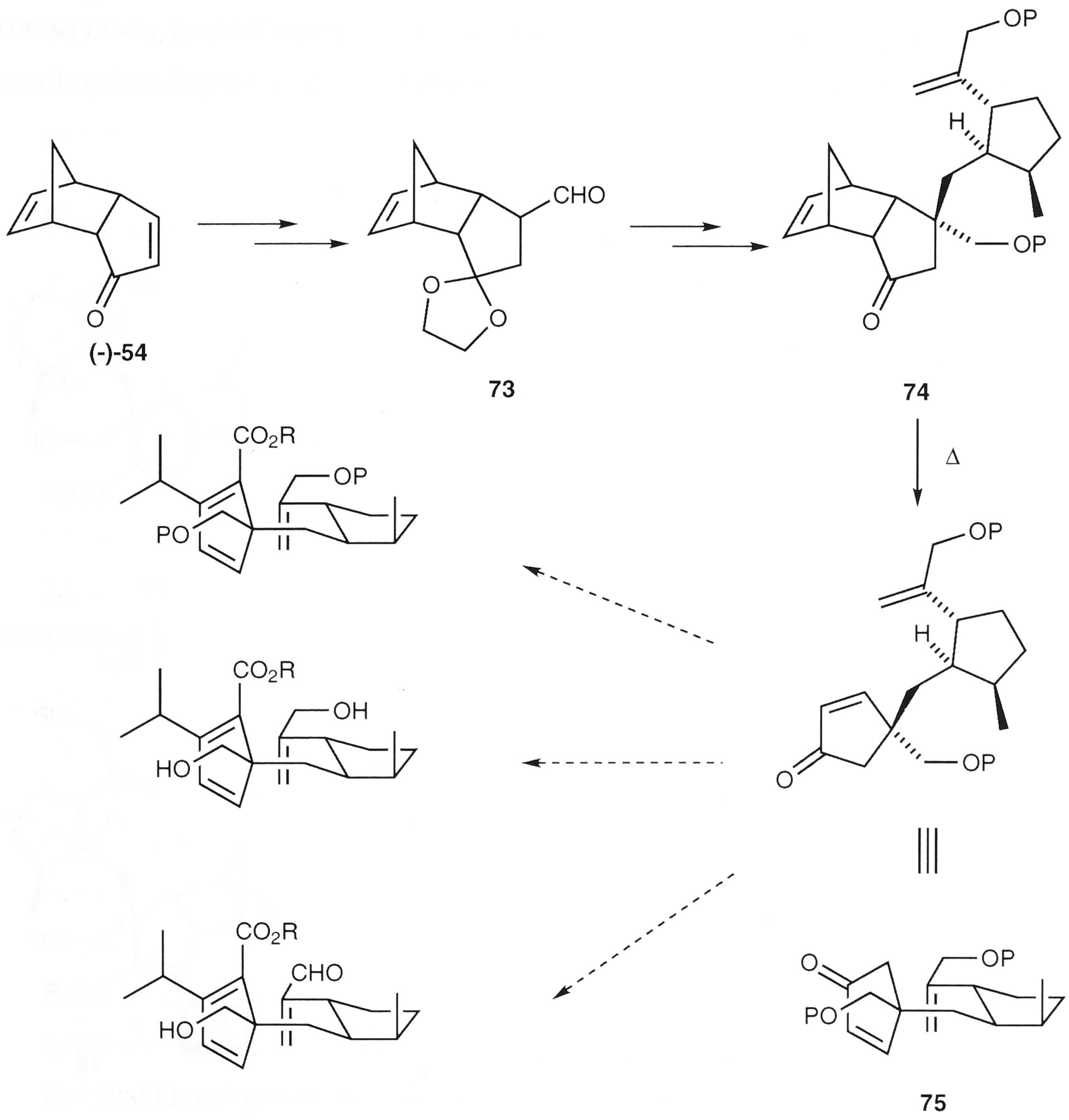


Figure 2.3.4 *Generation of intramolecular [4+2] cycloaddition precursors.*

A less convergent alkylation would lead to a compound such as **74** which, upon heating, would undergo a cycloreversion *without a subsequent intramolecular cyclisation*. Elaboration of the resultant 4,4-dialkylcyclopentenone **75**, would then give rise to suitable substrates for study.

2.3.3 Structural variation for analogue synthesis

As discussed in Chapter One, analogues of sordaricin have been produced with variations of the C5 aldehyde and C7 hydroxymethyl substituents by modification of naturally obtained sordaricin (**3**). Use of naturally obtained sordaricin (**3**) precludes any attempts to vary the C1 isopropyl and C10 methyl substituents, whereas a total synthesis could be easily adapted to produce changes at these unactivated positions.

The convergent approach detailed in Figure 2.3.1, would not be appropriate in terms of late stage introduction of structural diversity. However, the modified approach for the cycloaddition study (Figure 2.3.4) was considered ideal for these purposes. Although, variation of the C10 methyl group would be possible, to do so in a convergent fashion would be difficult. Thus, only the C1 alkyl group was considered. The general strategy for generating diversity at C1 is shown in Figure 2.3.5.

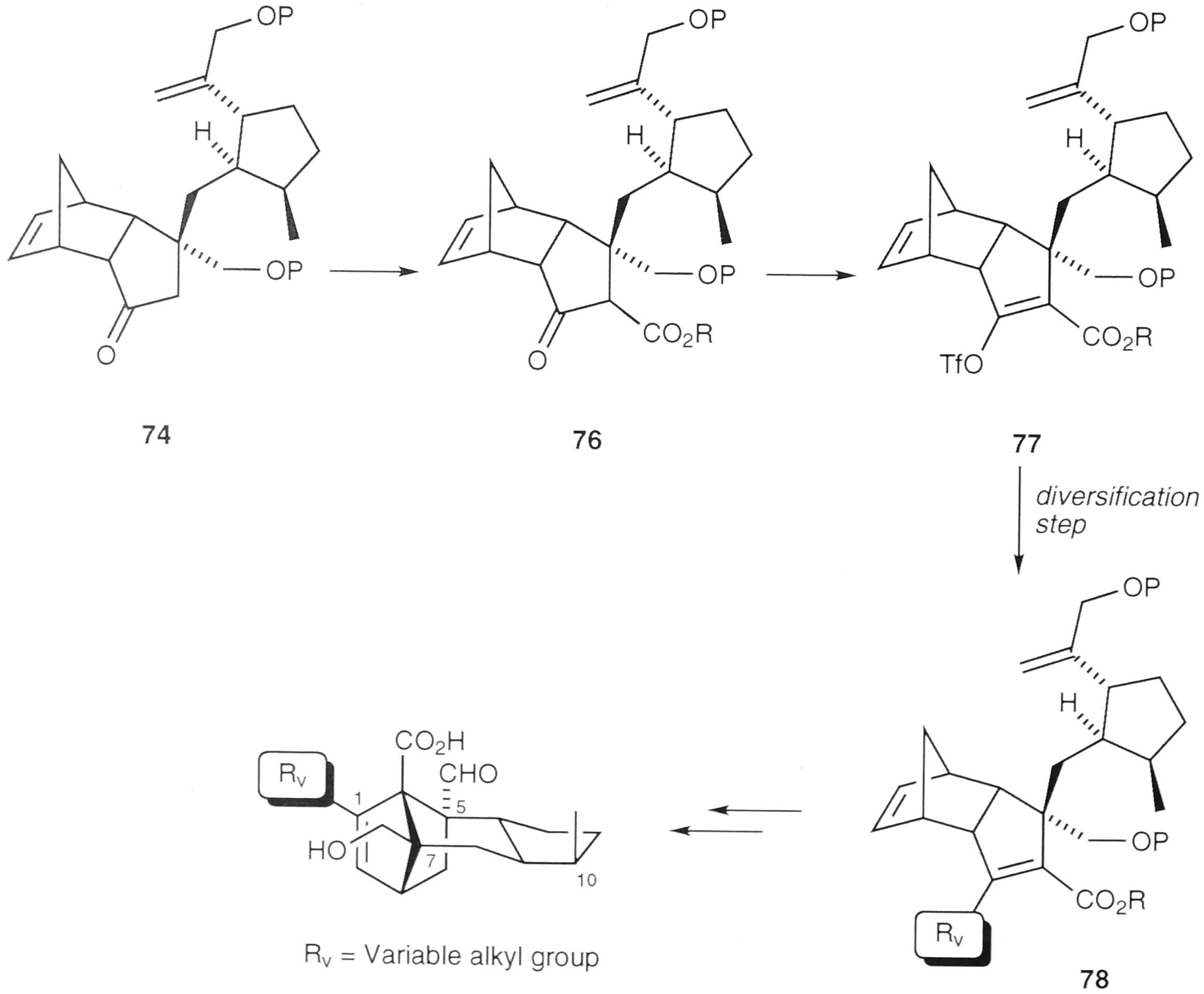


Figure 2.3.5 *Strategy for analogue production.*

Triflate **77**, obtained *via* ester **76**, was considered to be an excellent substrate for diversification by either palladium mediated cross coupling[12] or cuprate addition.[13] Further elaboration of **78** would then provide the desired sordaricin C1-alkyl analogues.

2.4 Conclusions

The strategy described above provides a flexible framework with which to approach synthetic studies related to the construction of sordaricin (**3**). The use of dicyclopentadienone (**54**) as a starting material has the potential to produce a convergent and concise synthesis of sordaricin (**3**). Simple modification of this strategy should also allow for a detailed study of the postulated biosynthetic [4+2] cycloaddition, and enable the production of some sordaricin C1-alkyl analogues for biological evaluation.

2.5 References

1. Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002.
2. Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595.
3. Corey, E. J.; Cheng, X. *The Logic of Chemical Synthesis*, John Wiley and Sons: New York, **1989**.
4. See: Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843 and references cited therein.
5. Meyers, A. I.; Bienz, S. *J. Org. Chem.* **1990**, *55*, 791.
6. For a recent review on the use of cyclopentadienone (**54**) and similar substrates in synthesis, see: Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **1999**, *99*, 1163.
7. For a recent review on retro Diels-Alder reactions, see: Rickborn, B. *Org. React.* **1998**, *52*, 1.
8. Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1989**, 271.
9. For preparation of (+)- and (–)-**54**, see: (a) Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett.* **1991**, 636. (b) Tanako, S.; Moriya, M.; Tanaka, K.; Ogasawara, K. *Synthesis* **1994**, 687.
10. For examples of tandem processes in synthesis, see: Ho, T. –L. *Tandem organic reactions*, Wiley: New York, **1992** and references cited therein.
11. Oppolzer, W.; Fiancotte, E.; Bättig, K. *Helv. Chim. Acta.* **1981**, *64*, 478.
12. For leading references, see: *Handbook of organopalladium chemistry for organic synthesis*, Negishi, E. –I.; de Meijere, A. (Eds), Wiley: New York, **2002**.
13. For leading references, see: *Modern organocopper chemistry,* Krause, N. (Ed), Wiley-VCH: Weinheim, **2002**.

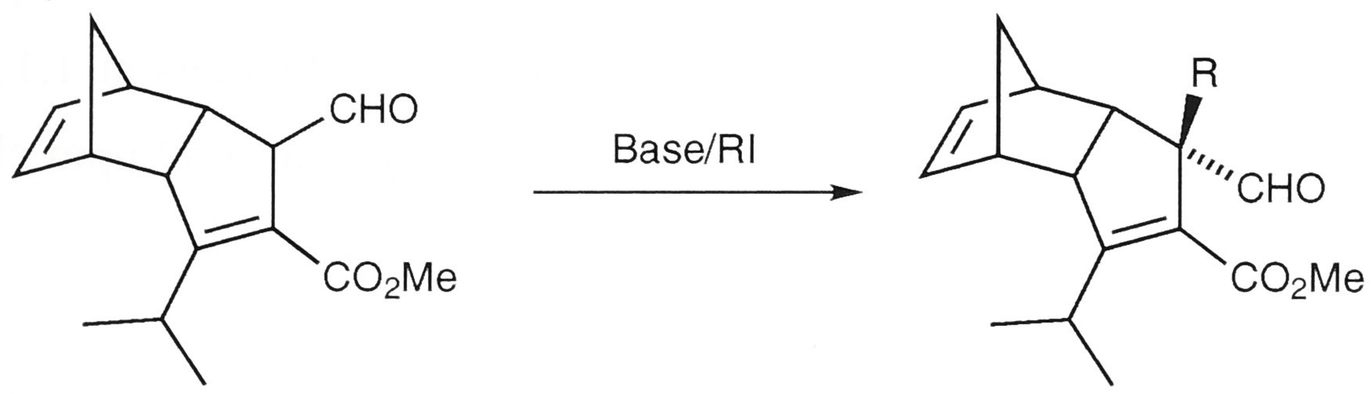
Chapter Three

Synthesis of the Aldehyde 60

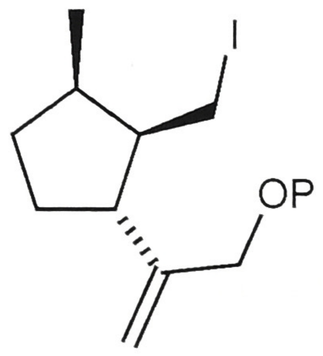
3.1 Introduction

The previous chapter outlined the synthetic strategy that was to be applied to the total synthesis of sordaricin (**3**), and showed how a modification of this strategy would enable a study of the putative biosynthetic [4+2] cycloaddition. This modified strategy could also be used to achieve a late stage diversification at C1 for the purpose of producing sordaricin analogues.

The first goal was to achieve a concise total synthesis of sordaricin (**3**), the success of which relied upon the construction of the two key fragments, aldehyde **60** and iodide **62**. Before committing to the synthesis of **62**, it was considered prudent to construct the aldehyde **60** first and carry out a test alkylations (*e.g.* RI = isobutyl iodide) as a model for the critical alkylation.



60 **79**



62

3.2 Synthesis of the Aldehyde 60

3.2.1 Initial approach

Inspection of **60** leads to several possible strategies which should lead to its rapid construction. The most obvious route involves formation of the aldehyde **60** by means of a Wittig reaction (or similar) performed on ketone **81** (Figure 3.2.1). Formation of ketone **81**, would come from C-acylation of β–substituted enone **80** which, in turn, could be derived from dicyclopentadienone [(±)-**54**].

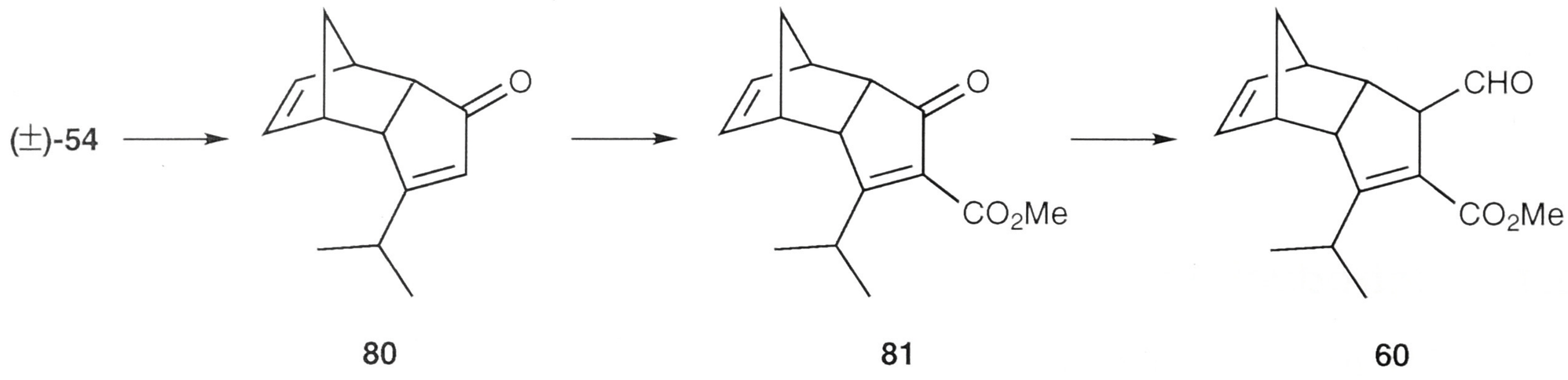


Figure 3.2.1 *Strategy for the synthesis of aldehyde **60**.*

Introduction of the requisite isopropyl group was achieved by means of a cerium trichloride mediated 1,2-addition of isopropylmagnesium chloride[1] to enone (±)-**54**, prepared according to the literature procedure.*[2] A single stereoisomer was obtained, assumed to be the *exo*-adduct **82**, from addition of the reagent to the less exposed face of the carbonyl group. No attempt was made to confirm this assumption, as the formed stereocentre is destroyed in the subsequent oxidative transposition (Figure 3.2.2). Thus, exposure of **82** to Jones' reagent[3] gave the desired β–substituted enone **80**, in good overall yield (58%, over two steps). Key signals present in the ^{1}H NMR spectra of enone **80** were two sets of doublets at 1.13 and 1.16 ppm, corresponding to the diastereotopic methyl groups, and a singlet at 5.69 ppm clearly associated with H2.

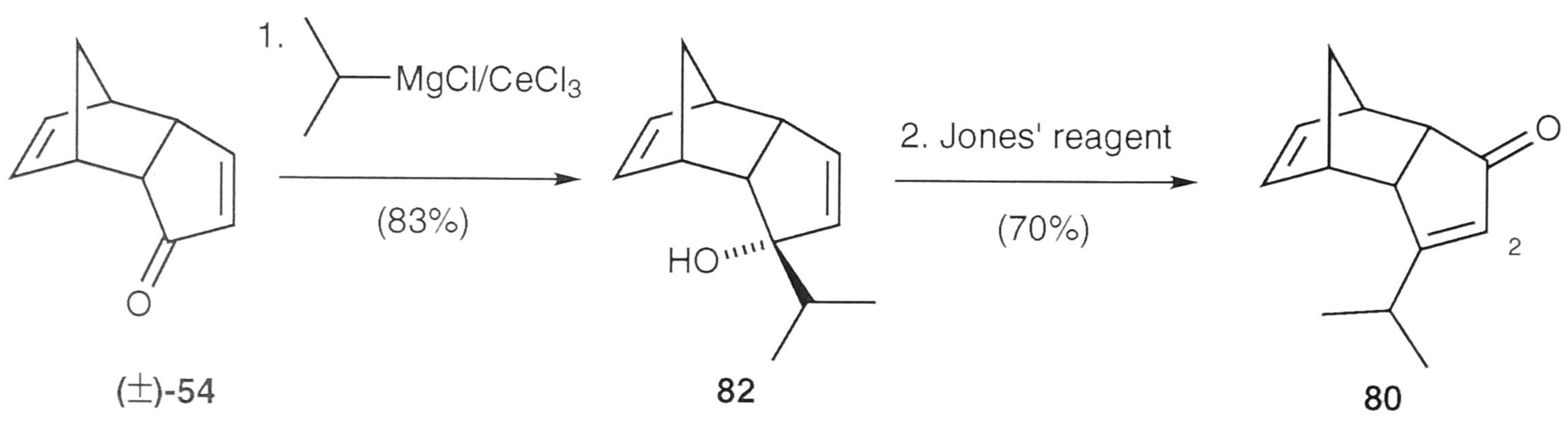


Figure 3.2.2 *Formation of enone **80**.*

Interestingly, initial attempts to use the Grignard reagent on its own resulted in complete 1,4-addition, giving rise to **83** (100%, single stereoisomer. Figure 3.2.3). Also worthy of note is the fact that the use of CuBr.DMS complex or CuI in THF, resulted in lower yields of the 1,4-adduct (80% and 65% respectively). Mehta *et al.* recently achieved an identical 1,4-addition in their approach toward the total synthesis of the diterpene antibiotic Guanacastepene A (**84**).[4] They report the eventual discovery of a simple and high yielding procedure utilising isopropylmagnesium iodide in conjunction with CuI in diethyl ether, but noted that initial

---

* The work detailed in Sections 3.2.1 and 3.2.2 was carried out on racemic **54**. Thereafter, all work was carried out on (+) or (−)-**54** as indicated for the structures and within the text.

efforts employed TMSCl and HMPA. Presumably these attempts led to poor results, which would agree with the variable results obtained during the research for this thesis.

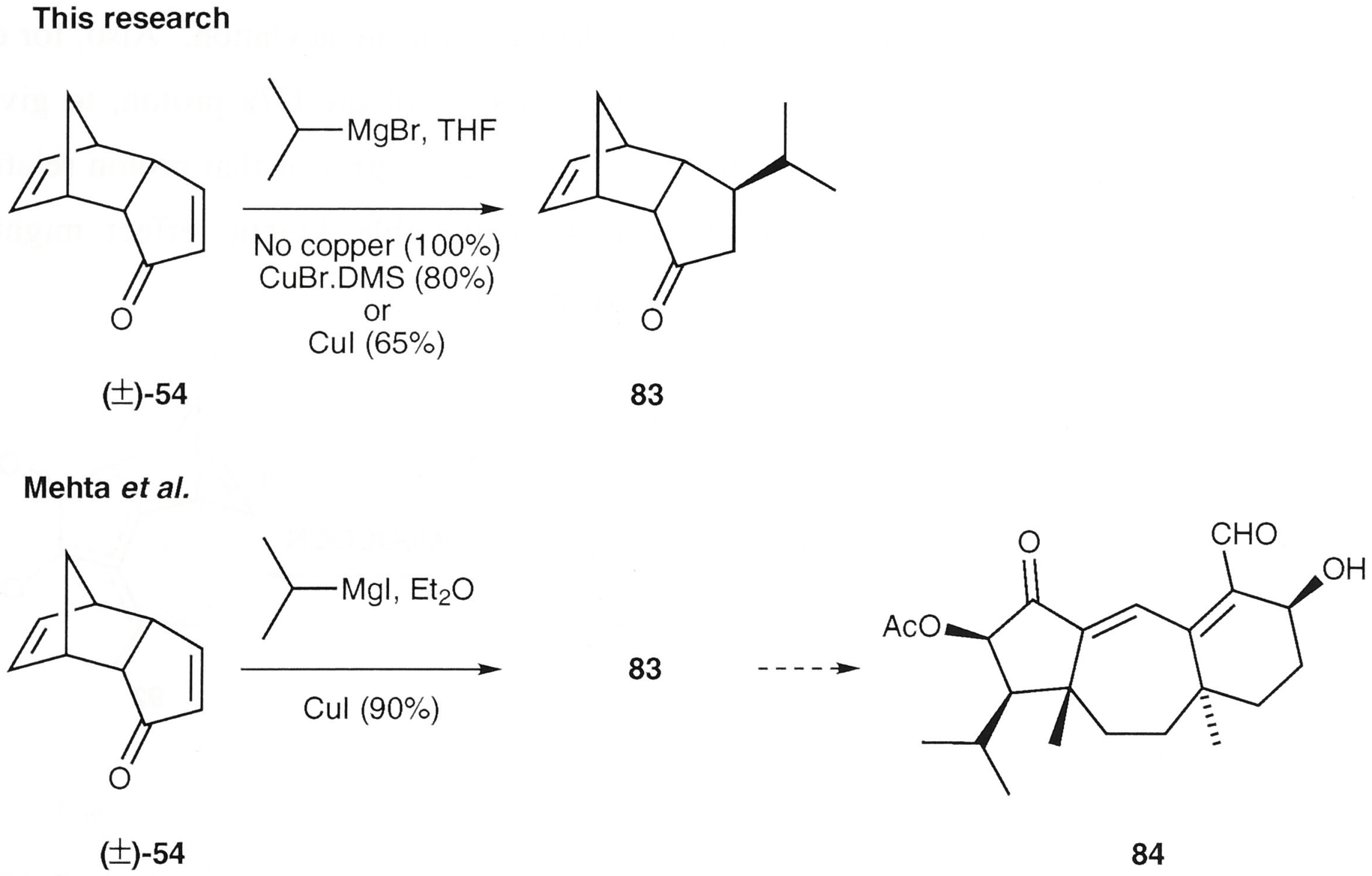


Figure 3.2.3 *1,4-additions to dicyclopentadienone* ***54****.*

With the issues of 1,2- *vs.* 1,4-addition resolved and the enone **80** successfully synthesised, the question of acylation could be addressed. The reagent of choice for the direct C-selective acylation of preformed enolates is methyl cyanoformate.[5] At the time of this research there were, however, no reported examples of its use in acylating the C2 position of an enone, as required for the synthesis of **81** (Figure 3.2.4). Usually, treatment of an enone with a strong base results in the formation of the cross-conjugated enolate (**88**), which upon acylation gives the C5 acylated product **89**.[6]

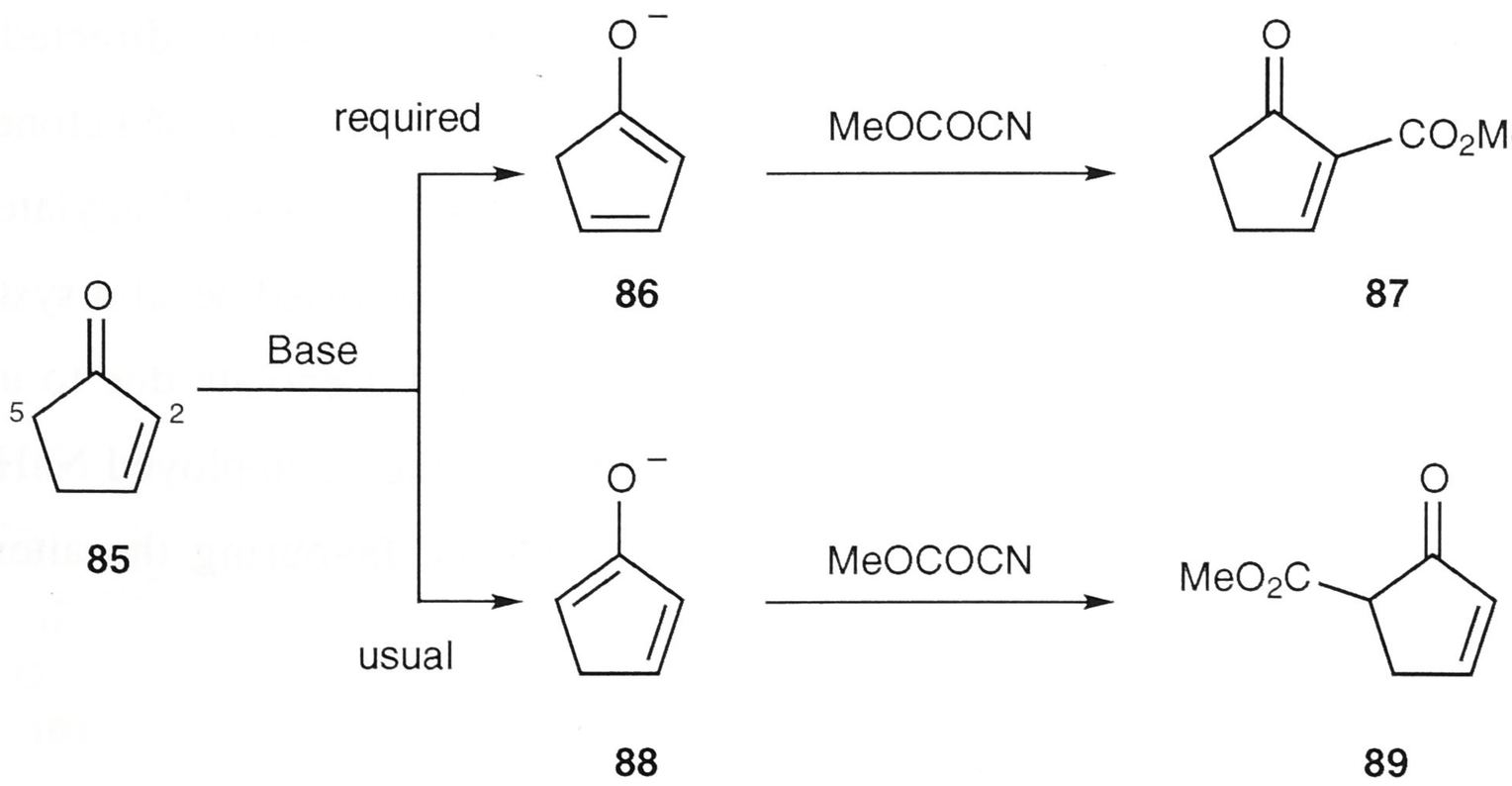


Figure 3.2.4 *Acylation of dienolates.*

The linear dienolate **86** should, however, be more stable than the cross-conjugated enolate **88**, by virtue of better delocalisation of the negative charge into the conjugated π-system. Therefore, under reversible deprotonation conditions, formation of the linear dienolate **86** should predominate, leading to the desired regioselectivity for the acylation. Also, for enone **80** this situation should be enhanced by the fact that removal of the C7a proton, to give **93**, would result in severe torsional strain, which should increase the pKa of that proton relative to simple monocyclic compounds. It was considered that this possible 'kinetic' effect, might well negate any necessary 'thermodynamic' equilibration (Figure 3.2.5)

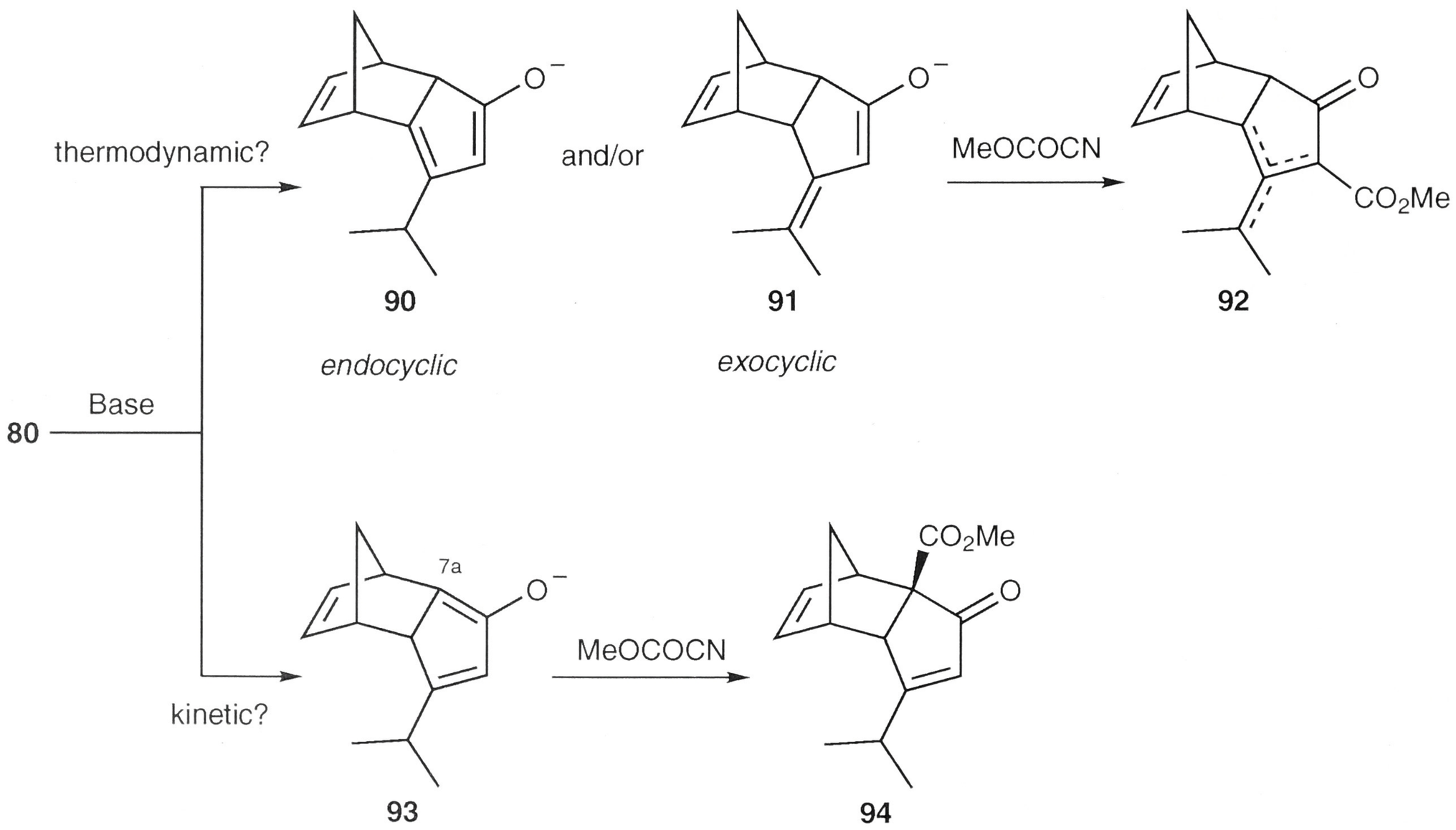
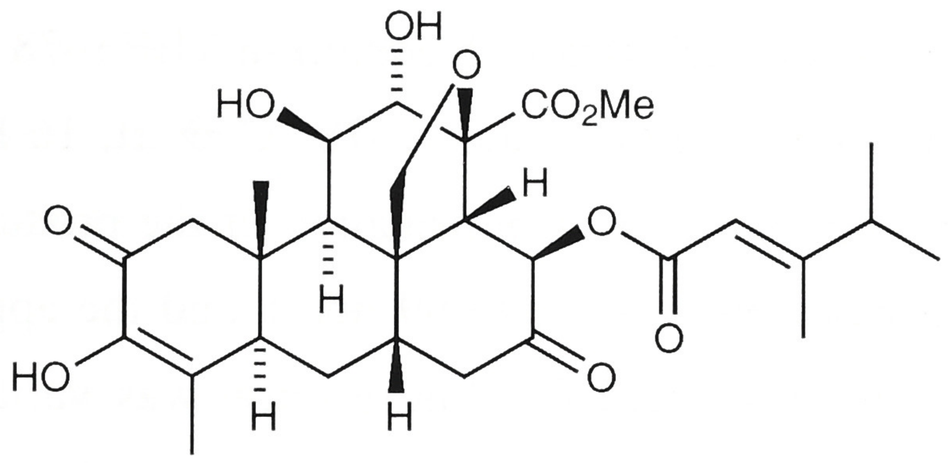
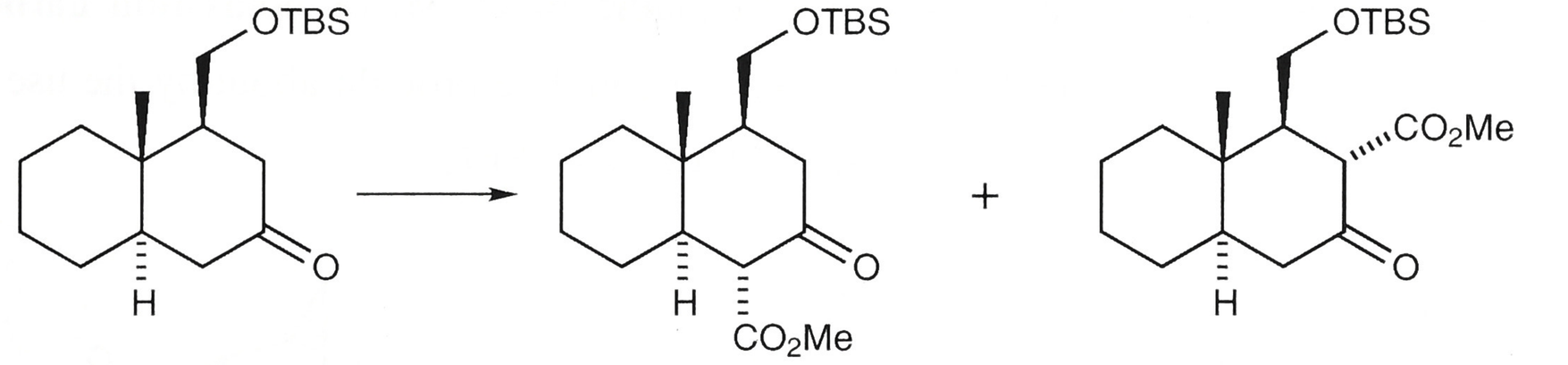


Figure 3.2.5 *Possible outcomes of C-acylation.*

Although the acylation of a linear dienolate, such as **90/91**, had not been reported, there were two examples of the acylation of an enolate generated under reversible thermodynamic conditions. The first of these was a study by Ziegler and co-worker's[7] directed toward the synthesis of bruceantin (**95**), which called for a regioselective acylation of ketone **96** (Figure 3.2.6). Use of LDA, under kinetic conditions afforded a 4:1 ratio of C-acylated products, favouring the undesired **97**. It is well known, however, that *trans*-fused decalin systems display a high thermodynamic preference for the 2,3-enolate over the 1,2-enolate due to unfavourable nonbonded interactions in the latter.[8] Thus, Ziegler and co-worker's employed NaHMDS under thermodynamic conditions, obtaining a 7:1 ratio of products, favouring the alternative, and required regioisomer **98**.



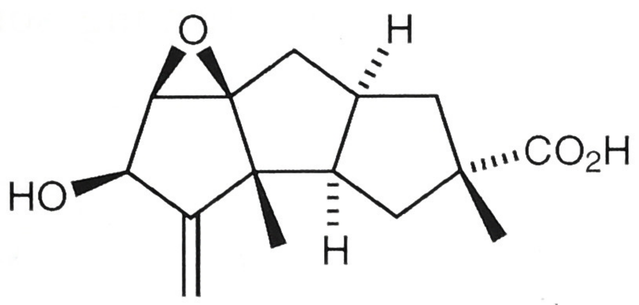
95



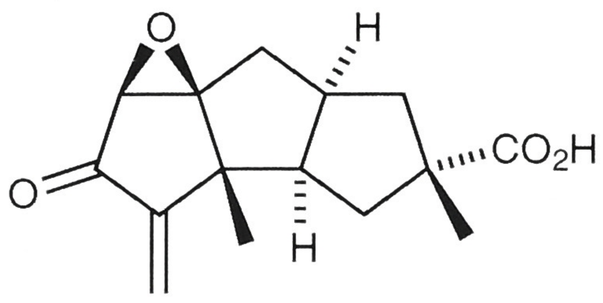
96 **97** **98**

Figure 3.2.6 *Ziegler and co-worker's acylation studies.*

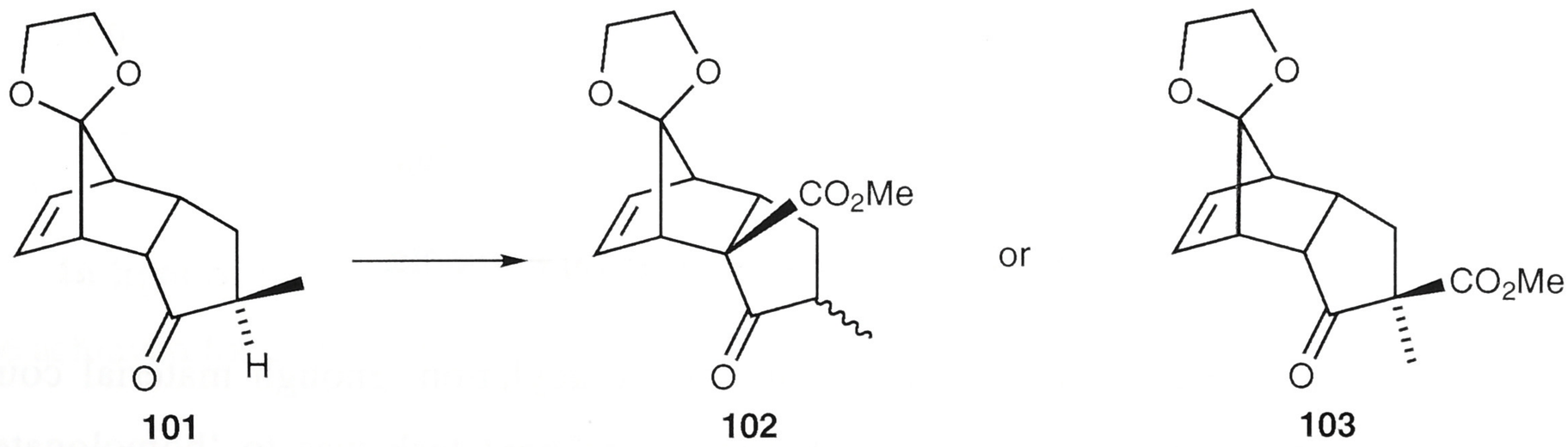
The same sort of kinetic *vs.* thermodynamic enolisation/acylation was employed by Schuda *et al.* in their total syntheses of hirsutic acid (**99**) and complicatic acid (**100**).[9] The reaction of importance here is the acylation of ketone **101** (Figure 3.2.7), a substrate quite similar to enone **80**. Generation of the enolate using LDA, followed by acylation with CO_2/CH_2N_2 gave the undesired product, **102**. Generation of the enolate using KHMDS, and acylation with methyl cyanoformate resulted in a reversal in the regioselectivity, allowing for a 58% yield of the desired product **103**, along with 24% of the corresponding enol carbonate (not shown).



99



100



101 **102** **103**

Figure 3.2.7 *Acylation studies by Schuda* et al.

Treatment of enone **80** with NaHMDS (1.5 equiv.) in THF (–78 °C → rt, 3 h), followed by the addition of methyl cyanoformate (1.5 equiv., -78 °C → rt, 16 h) gave a 32% isolated yield of the desired ester **81** (Figure 3.2.8). Confirmation of the product's identity was easily achieved by the observed disappearance of H2 (5.69 ppm), and the appearance of a singlet at 3.78 ppm for the methyl ester. The yield for this reaction was variable, and the ^{1}H NMR spectra of the crude reaction mixture indicated the presence of another acylated product, which was attributed to the unconjugated ester **104**. Although several attempts to convert this mixture into the desired conjugated ester using triethylamine in DCM, or potassium carbonate in methanol, were unsuccessful, the desired conversion could be brought about by the use of DBU in THF at reflux. Unfortunately, the isolated yield was only 40%.

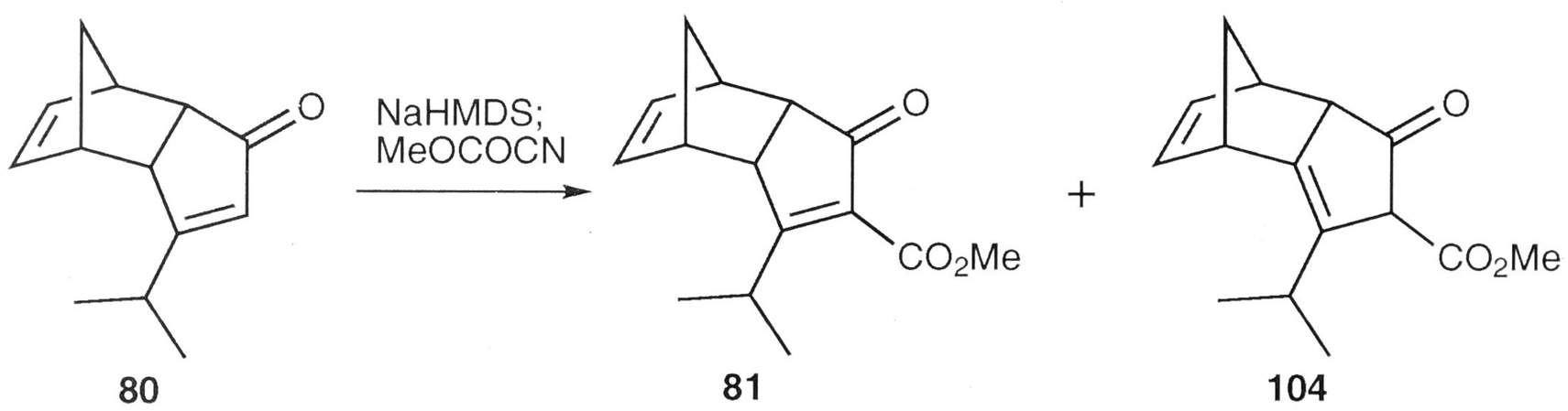


Figure 3.2.8 *Products of the acylation of enone **80**.*

Extensive experimentation led to the discovery that if the reaction mixture was kept at –78 °C after the addition of methyl cyanoformate, and was not allowed to warm to room temperature, then the only observed product was **81**. Despite a very clean looking ^{1}H-NMR spectrum, the isolated yield after chromatography was a disappointing 54%. Also worthy of note is that TMSCl trapping experiments showed that the linear enolate **91** is, in fact, both the thermodynamic and kinetically favoured product of deprotonation, confirming some earlier speculation (Figure 3.2.9).

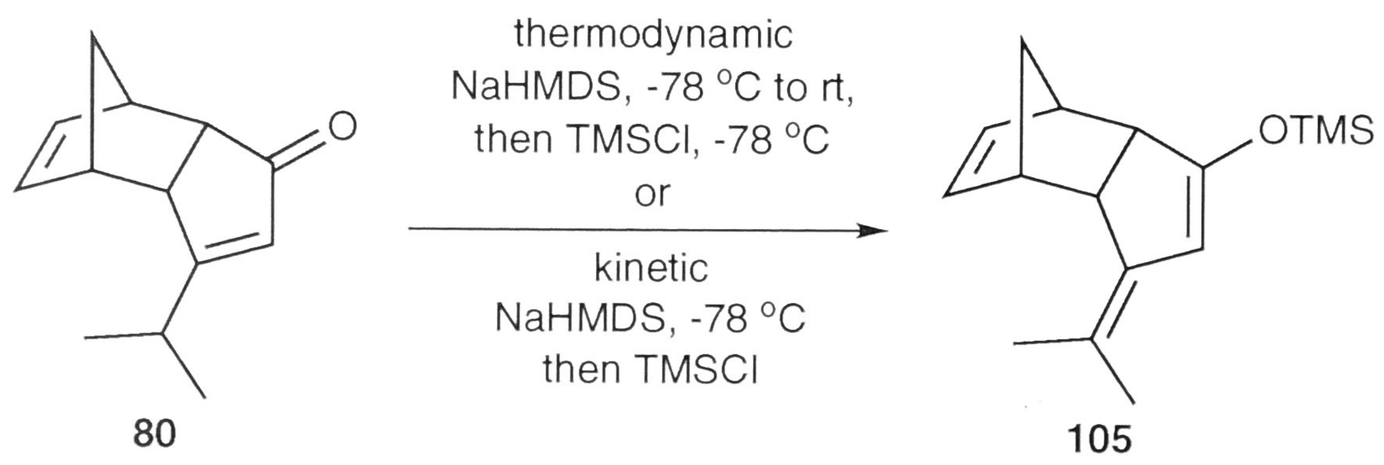


Figure 3.2.9 *Enolate trapping experiments.*

Despite the somewhat capricious nature of the acylation, enough material could be easily obtained for the synthesis to proceed. Thus, the next task was to 'homologate' the ketone, in order to generate the target aldehyde **60**. The general idea was to carry out a Wittig reaction using methoxymethylenetriphenylphosphorane,[10] with hydrolysis of the resultant enol

ethers **106** rendering the key aldehyde **60**. Unfortunately, the initial Wittig reaction proved to be highly unreliable with a maximum yield of 50% (as a 1:1 mixture of isomers) being obtained on only one occasion; ^{t}BuOK was used to generate the ylide in diethyl ether (Figure 3.2.10). Several other unidentified by-products were also isolated from the reaction mixture. Purification of the enol ethers was also very difficult due to the presence of large quantities of triphenylphosphine oxide which co-eluted with the products in a variety of solvent mixtures. Despite this, key signals could be seen in ^{1}H NMR spectra of the partially purified material, thus allowing some degree of structural assignment.

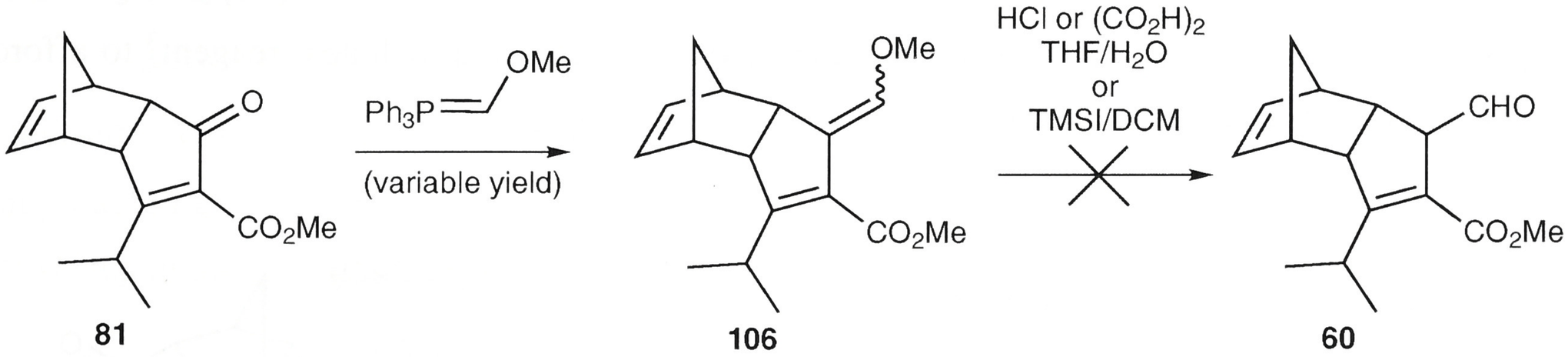


Figure 3.2.10 *Attempted formation of the key aldehyde **60**.*

Worse still, attempted hydrolysis of the enol ethers led to multiple products, none of which appeared to be the requisite aldehyde. In fact, one major product formed during this hydrolysis was the starting ketone **81**, which was presumably formed by aerial oxidation of the enol ether as shown in Figure 3.2.11. Careful exclusion of oxygen did little to improve the desired transformation. Further investigation, using the Horner-Wittig reaction[11] was unsuccessful.

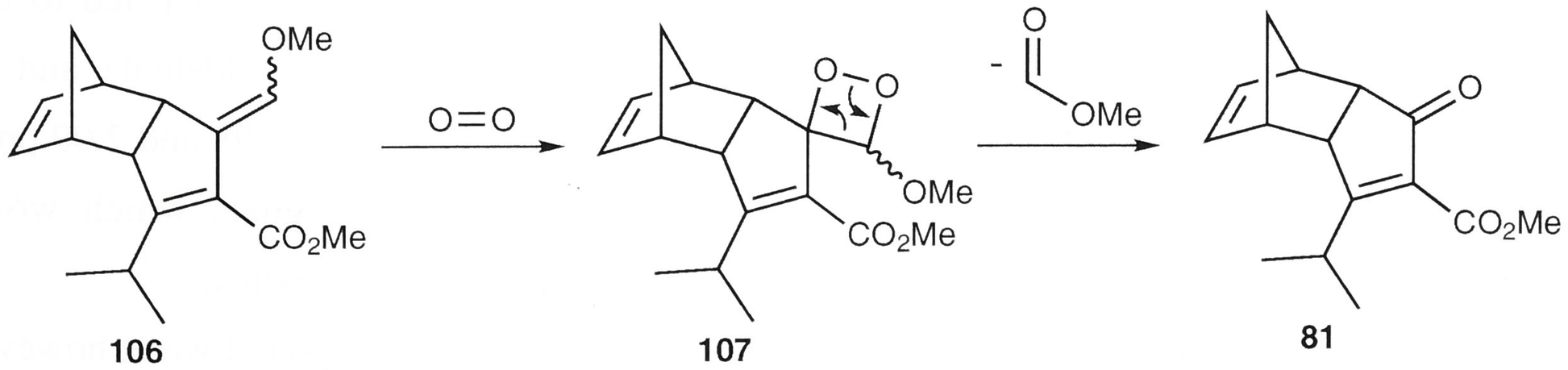


Figure 3.2.11 *An interesting, but unwanted side reaction.*

In light of the increasing body of evidence suggesting that the desired conversion could not be achieved for compound **81**, a new approach was implemented.

3.2.2 A modified approach

Reduction of the ester function in **81** to give the equivalent protected alcohol was considered as a possible way to attenuate the reactivity of the homologation substrate. Selective reduction of the ester function in **81** was not expected to be an easily performed reaction, so an alternative synthesis was developed (Figure 3.2.12). Accordingly, conversion of (±)-**54** to the known Baylis-Hillman adduct **108** was achieved according to the literature procedure.[12] Next, protection of the primary alcohol as a methoxymethyl ether[13] was carried out (91% yield) as a prelude to a 1,2-addition/1,3-oxidative transposition sequence, akin to that used previously to prepare enone **80**. Thus, treatment of **109** with cerium trichloride/isopropylmagnesium chloride,[1] gave an allylic alcohol which was immediately subjected to Jones' reagent[3] to afford the desired disubstituted enone **110** in 50% yield over two steps.

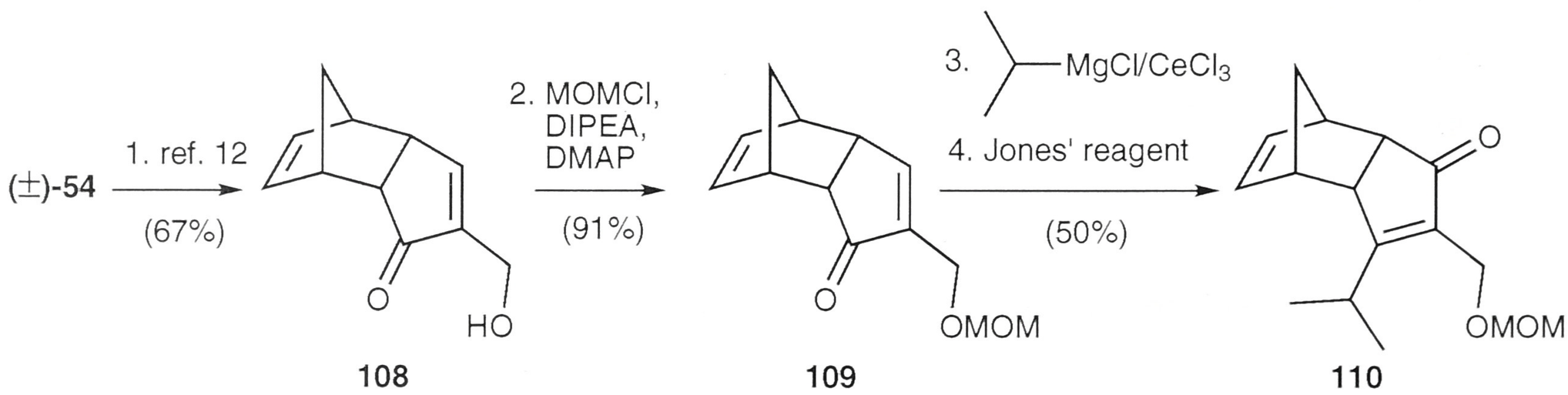


Figure 3.2.12 *Preparation of enone **110**.*

With the desired enone **110** in hand, the Wittig reaction was attempted. Once again formation of the enol ethers **111** was poor, and hydrolysis under a variety of conditions did not yield any of the desired product. In one instance of hydrolysis (MeOH/water, conc. HCl), it appeared that the compound had undergone oxidation to afford conjugated aldehyde **112** (Figure 3.2.13). Key signals in the ^{1}H NMR spectrum of compound **112** which led to this assignment were the presence of a singlet at 10.09 ppm corresponding to an aldehyde, and the strong downfield shift of the resonances associated with the methyl groups (1.98 and 2.00 ppm) which now appeared as singlets. Also, the spectra contained no signals which would correspond to the C*H*Me$_2$ group present in the starting material, or desired product.

Attempts to optimise this hydrolysis and utilise the resulting compound were, however, unproductive.

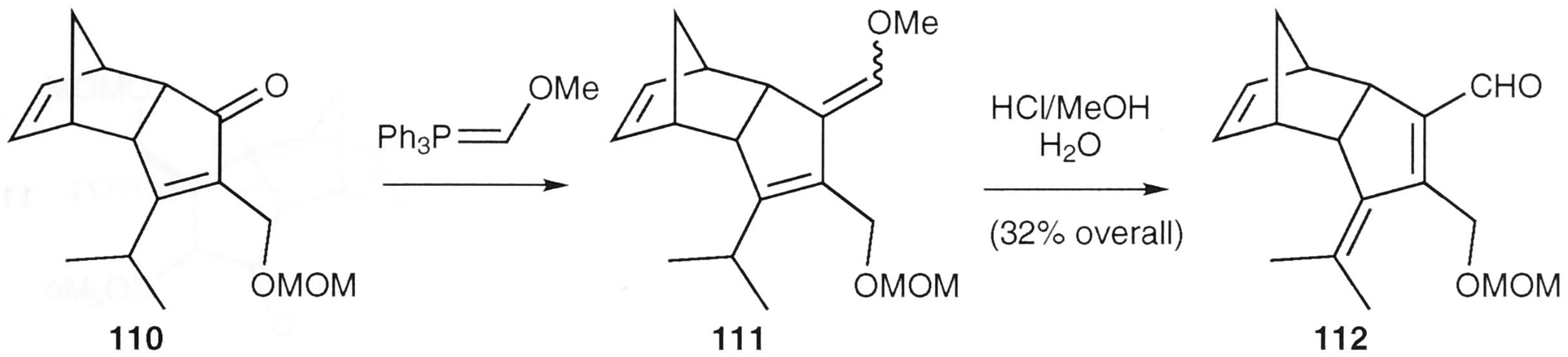


Figure 3.2.13 *Formation of aldehyde **112**.*

3.2.3 Successful synthesis of the aldehyde

With the failure of the attempts described above, a new route to aldehyde **60** was devised. This new route, outlined in Figure 3.2.14, is essentially the reverse of the initial approach, *i.e.* installation of the aldehyde group (or an operationally equivalent group), is the first step in the synthesis, not the last.

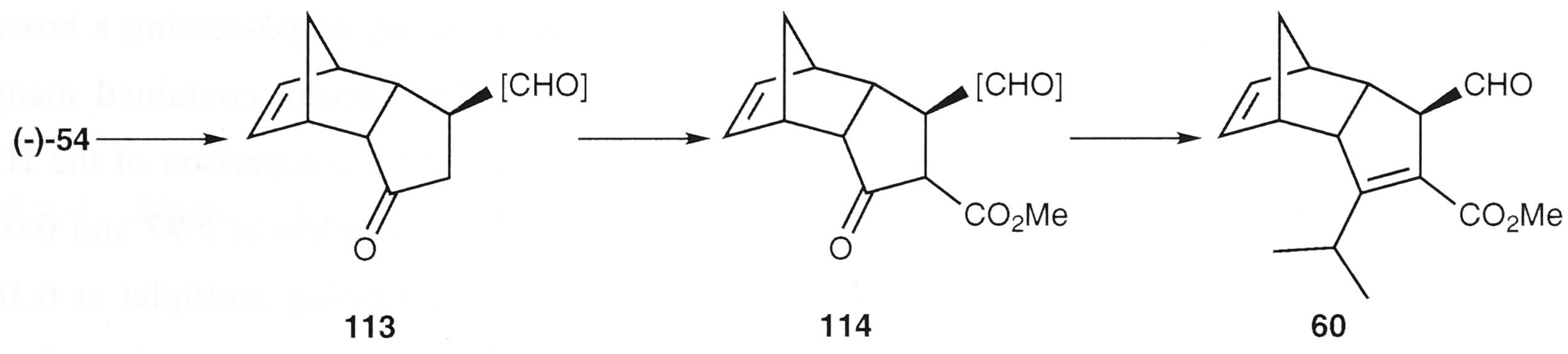


Figure 3.2.14 *New approach to the aldehyde **60**.*

There are several widely used nucleophillic carbonyl equivalents reported in the literature, such as 2-lithio-1,3-dithiane.[14] For the purpose of this synthesis the hydroxymethyl equivalent derived from *n*-BuLi and *n*-Bu_3SnCH_2OMOM (*i.e.* $LiCH_2OMOM$, **115**)[15] was considered to be the preferred choice, as eventual removal of the MOM group, followed by oxidation would render the desired aldehyde under mild conditions. The MOM protected primary alcohol would also be suitably unreactive for the intermediate substrate manipulations.

Implementation of the strategy outlined above began with the 1,4-addition of **115** to enone (–)-**54** (Figure 3.2.15), using CuI/TMEDA and TMSCl[16] to afford silyl enol ether **116** which was subjected to flash chromatography for immediate use in the next reaction. Formation of **116** was clearly seen in ^1H NMR spectra by the appearance of a broad singlet at 4.36 ppm corresponding to the silyl enol ether olefinic proton. The stereochemistry of the hydroxymethyl group was expected to be *exo* and this was proven by 1D NOESY experiments carried out on **116**.

Treatment of the silyl enol ether **116** with 1.4 M MeLi in THF, regenerated the parent enolate which, after addition of methyl cyanoformate,[17] gave the C-acylated products **117** and **118** (1:6) in good overall yield (65-75%, 2 steps).

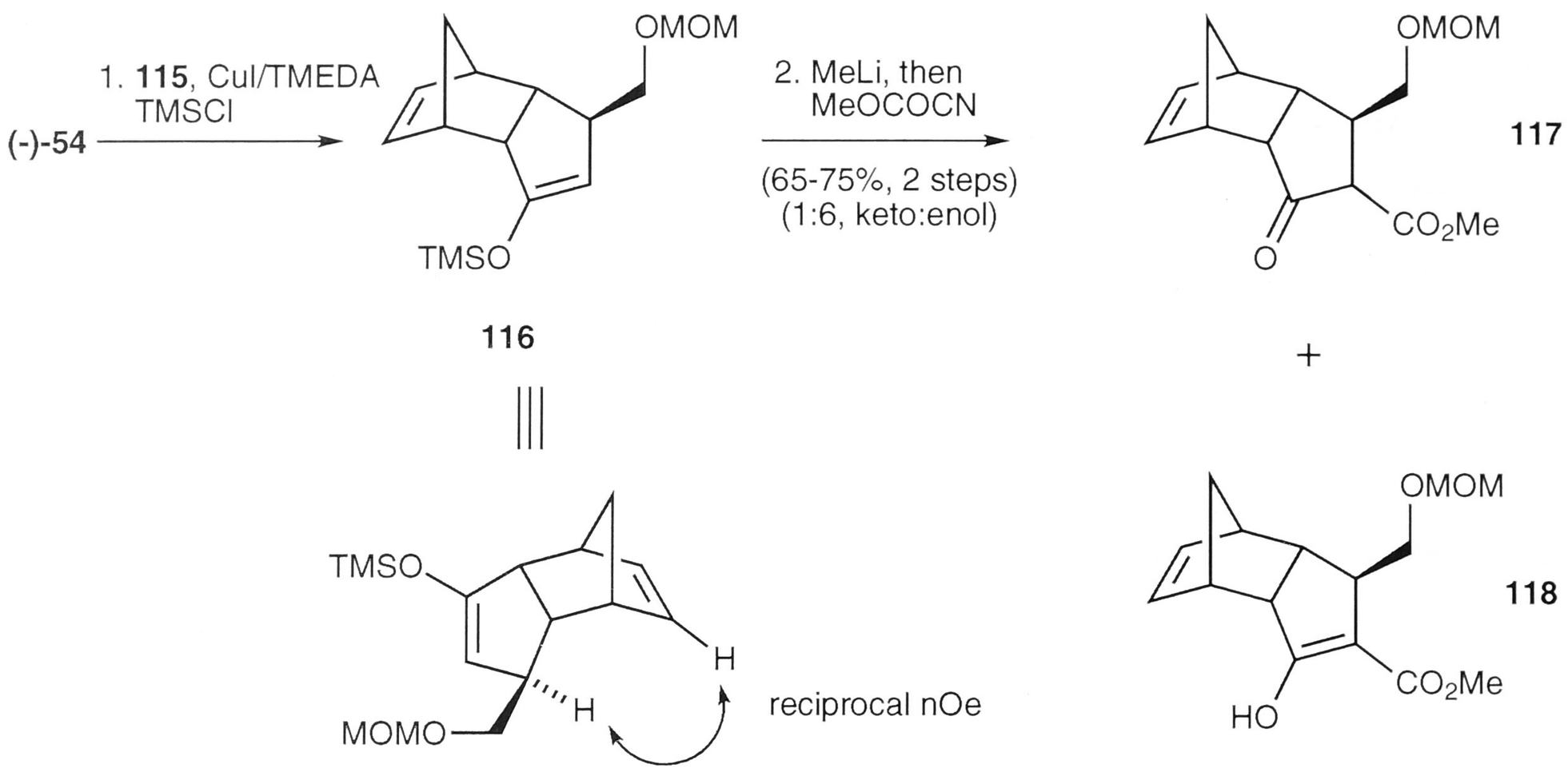


Figure 3.2.15 *Initial stages of aldehyde synthesis and 1D NOESY experiment.*

The major tautomer was clearly seen by ^{1}H NMR spectroscopy as possessing a broad singlet at 10.40 ppm, corresponding to the enol OH proton. The spectra contained many overlapping resonances, but the tautomeric ratio could be calculated by comparison of the H5 and H6 olefin signals. For the major tautomer, these appeared as multiplets at 5.97 and 6.02 ppm, whereas in the minor keto tautomer they appeared as an overlapping multiplet at 6.16 ppm.

Completion of the aldehyde synthesis (Figure 3.2.16) was then initiated by converting the inseparable mixture of tautomers **117/118** to the corresponding enol triflate **119**, using NaH and *N*-phenyltrifluoromethanesulfonimide (77%).[18] Next, treatment of triflate **119** with the higher order cuprate derived from 2-thienyl(cyano)copper lithium (2-ThCu(CN)Li)[19] and isopropylmagnesium chloride afforded **120** in good yield (73%). Formation of the product was clearly seen by the appearance of an apparent triplet at 1.10 ppm associated with the two diastereotopic methyl groups, and a septet at 3.54 ppm corresponding to the C*H*Me$_2$ resonance.

Removal of the MOM group was most effectively carried out using magnesium bromide etherate and 1-butanethiol[20] (83%), with subsequent oxidation using Dess-Martin periodinane,[21] thereby affording the key aldehyde **60** in good yield (72%), as observed by the appearance of a doublet (J = 2.8 Hz) at 9.57 ppm (CHO).

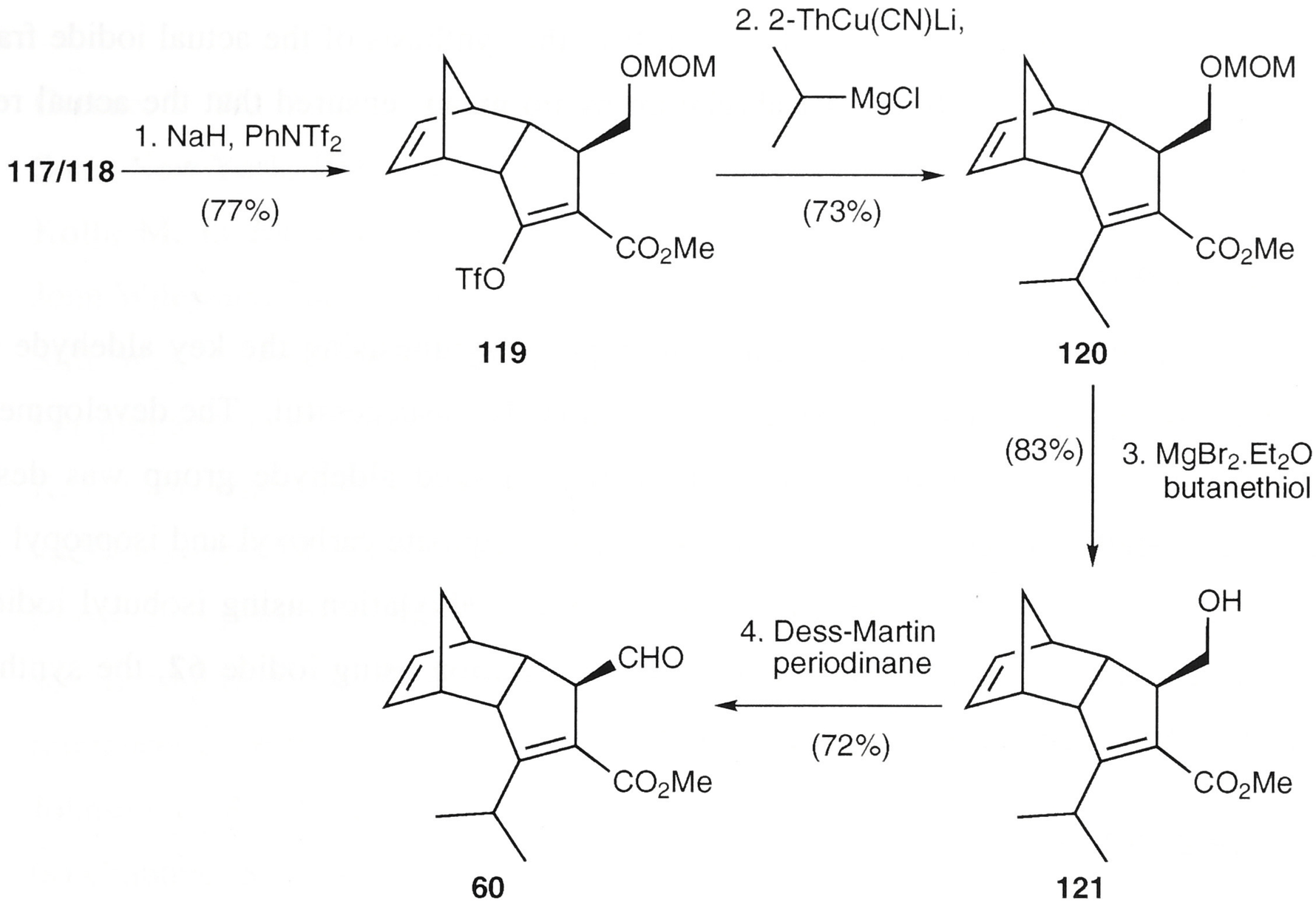


Figure 3.2.16 *Completion of the aldehyde synthesis.*

3.2.4 Model alkylation

With the key aldehyde **60** in hand, a model alkylation was performed using isobutyl iodide. Thus, treatment of aldehyde **60** with 1.0 M ^{t}BuOK/THF in THF at 0 °C followed by the addition of isobutyl iodide (3 equiv.), gave the desired alkylated substrate **122** in a moderate yield (50%) as a single stereoisomer (Figure 3.2.17). The appearance of two doublets at 0.76 and 0.94 ppm associated with the isobutyl methyl groups confirmed that alkylation had taken place. The aldehyde resonance now occurred as a singlet at 9.61 ppm and displayed reciprocal nOe signals with the olefin proton at 5.88 ppm, thereby confirming the assigned stereochemistry.

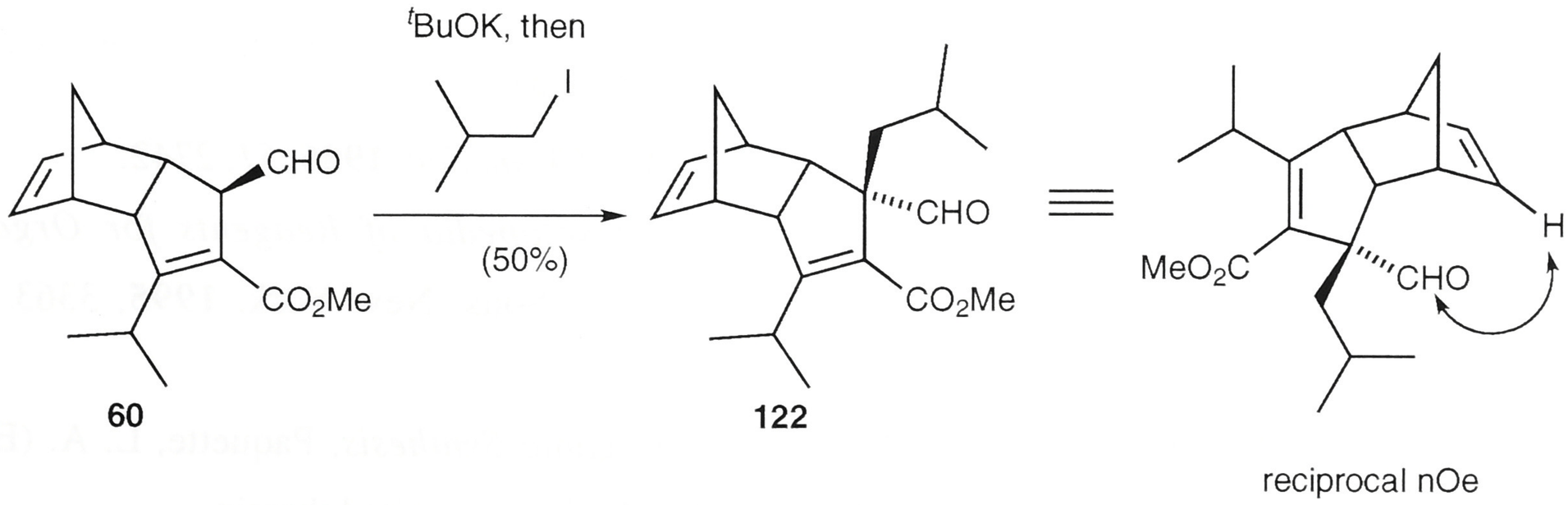


Figure 3.2.17 *Successful model alkylation and proof of stereochemistry.*

The focus of the research could now shift to the synthesis of the actual iodide fragment **62**, although the success of the model alkylation by no means ensured that the actual reaction would work as well.

3.3 Summary

This chapter outlined several initial attempts at synthesising the key aldehyde **60**, by means of a carbonyl homologation, which were ultimately unsuccessful. The development of a successful route, which utilised a 1,4-addition of a masked aldehyde group was described subsequently. Methodology for the introduction of the requisite carboxyl and isopropyl groups necessary for sordaricin (**3**) was also outlined. A model alkylation using isobutyl iodide was successfully carried out, as a model for the actual alkylation using iodide **62**, the synthesis of which will be described in the following chapter.

3.4 References

1. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
2. For preparation of (+)- and (–)-**54**, see: (a) Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett.* **1991**, 636. (b) Tanako, S.; Moriya, M.; Tanaka, K.; Ogasawara, K. *Synthesis* **1994**, 687.
3. Freeman, F. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 1261 and references cited therein.
4. Mehta, G.; Umarye, J. D. *Org. Lett.* **2002**, *4*, 1063.
5. Mander, L. N. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 3466 and references cited therein.
6. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.
7. Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T. –F.; *J. Am. Chem. Soc.* **1985**, *107*, 2730.
8. House H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341.
9. Schuda, P. F.; Phillips, J. L.; Morgan, T. M. *J. Am. Chem. Soc.* **1986**, *51*, 2742.
10. Soderquist, J. A.; Ramos-Veguilla, J. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 3363 and references cited therein.
11. Wallis, C. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 3360 and references cited therein.
12. Sugahara, T.; Ogasawara, K. *Synlett.* **1999**, 419.

13. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley and Sons: New York, **1991** and references cited therein.

14. Kolb, M. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 2983 and references cited therein.

15. Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

16. For preparation of the cuprate reagent **115**, see: Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495. For seminal discussions on the role of TMSCl in 1,4-additions, see: (a) Corey, E. J.; Boaz, N. W, *Tetrahedron Lett.* **1985**, *26*, 6015. (b) Corey, E. J.; Boaz, N. W, *Tetrahedron Lett.* **1985**, *26*, 6019. For more a recent report, see: Lipshultz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283 and references cited therein. For the use of TMEDA in TMSCl promoted 1,4-additions, see: Johnson, C. R.; Marren, T. J. *Tetrahedron Lett.* **1987**, *28*, 27

17. (a) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, 169. (b) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256.

18. Houpis, I. N. *Tetrahedron Lett.* **1991**, *32*, 6675. See also: Zeller, W. E. in *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 4096 and references cited therein.

19. Lipshultz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

20. Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett.* **1991**, 183.

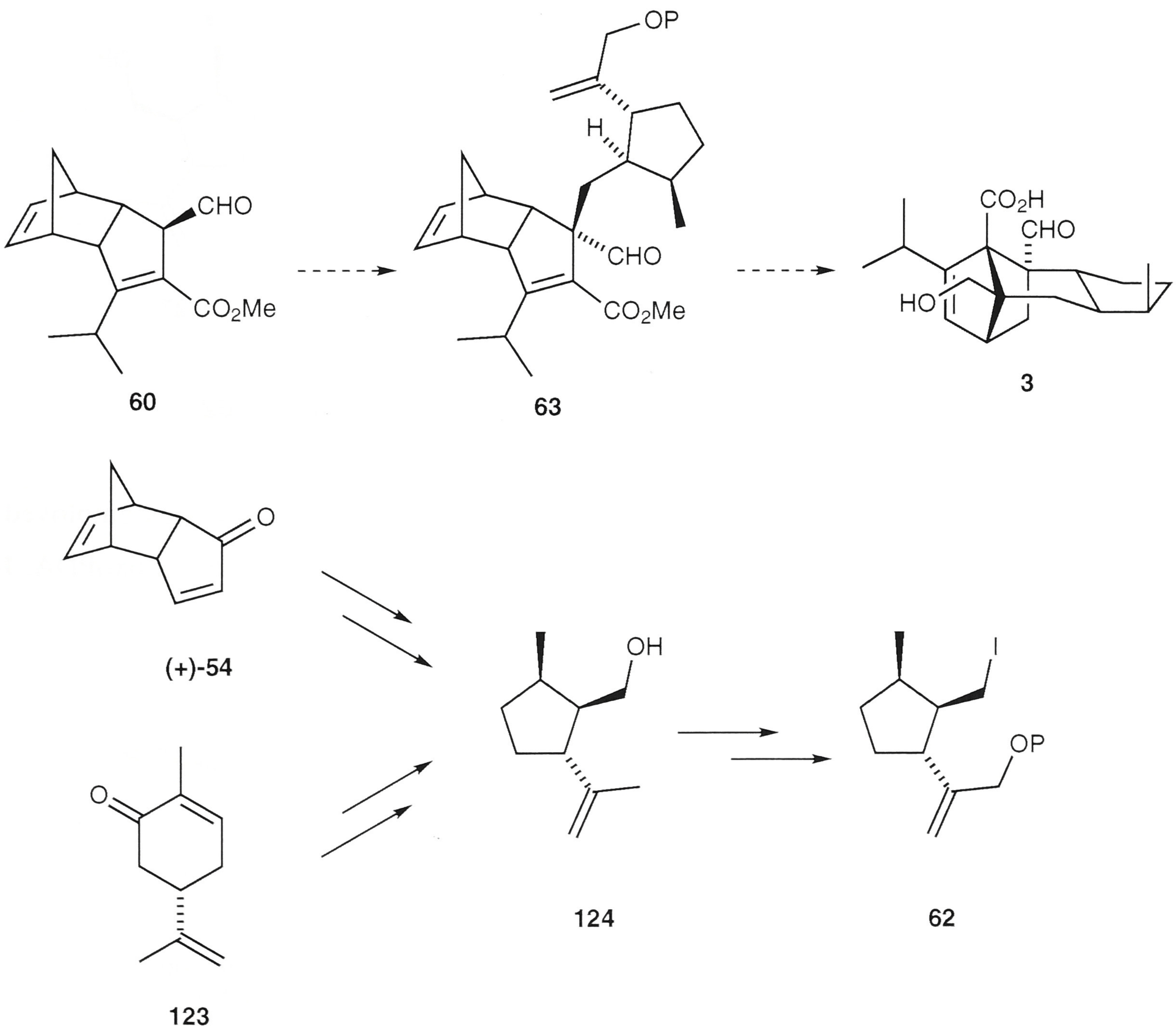
21. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C.; *J. Am. Chem. Soc.* **1991**, *113*, 7277 and references cited therein. For improved protocols for the preparation of IBX, see: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537. For an improved procedure for the preparation of Dess-Martin periodinane from IBX, see: Boeckman, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141.

Chapter Four

Synthesis of the Iodide 158

4.1 Introduction

Chapter Three outlined the successful synthesis of the key aldehyde fragment **60** from (–)-**54** and as a model study for the convergent alkylation it was also shown that **60** could be regio- and diastereoselectively alkylated with isobutyl iodide. The projected synthesis of sordaricin (**3**) called for the alkylation of aldehyde **60**, with a suitably protected cyclopentyl iodide derivative, *i.e.* **62**. This chapter will describe the synthesis of iodide **62** from (+)-**54**, *via* alcohol **124** – a compound previously prepared from (*S*)-(+)-carvone (**123**).[1]



60 **63** **3**

(+)-**54**

123 **124** **62**

4.2 Synthesis of the Iodide

4.2.1 Synthesis of the key cyclopentenone

As already discussed in Chapter Two, dicyclopentadienone (**54**) is a versatile substrate for the synthesis of a wide variety of compounds. In particular, use of **54** as a synthon for the enantio- and diastereoselective construction of substituted cyclopentenones has been

widespread within the discipline of total synthesis.[2] In planning the synthesis of iodide **62**, it was recognised that the requisite *syn,anti*-relationship of the ring substituents might be formed by a conjugate addition of a suitable group to a *syn*-4,5-subsituted enone such as **126** (Figure 4.2.1). Formation of the desired enone **126** was expected to be achieved, *via* **125**, by using dicyclopentadienone [(+)-**54**] as a starting material.

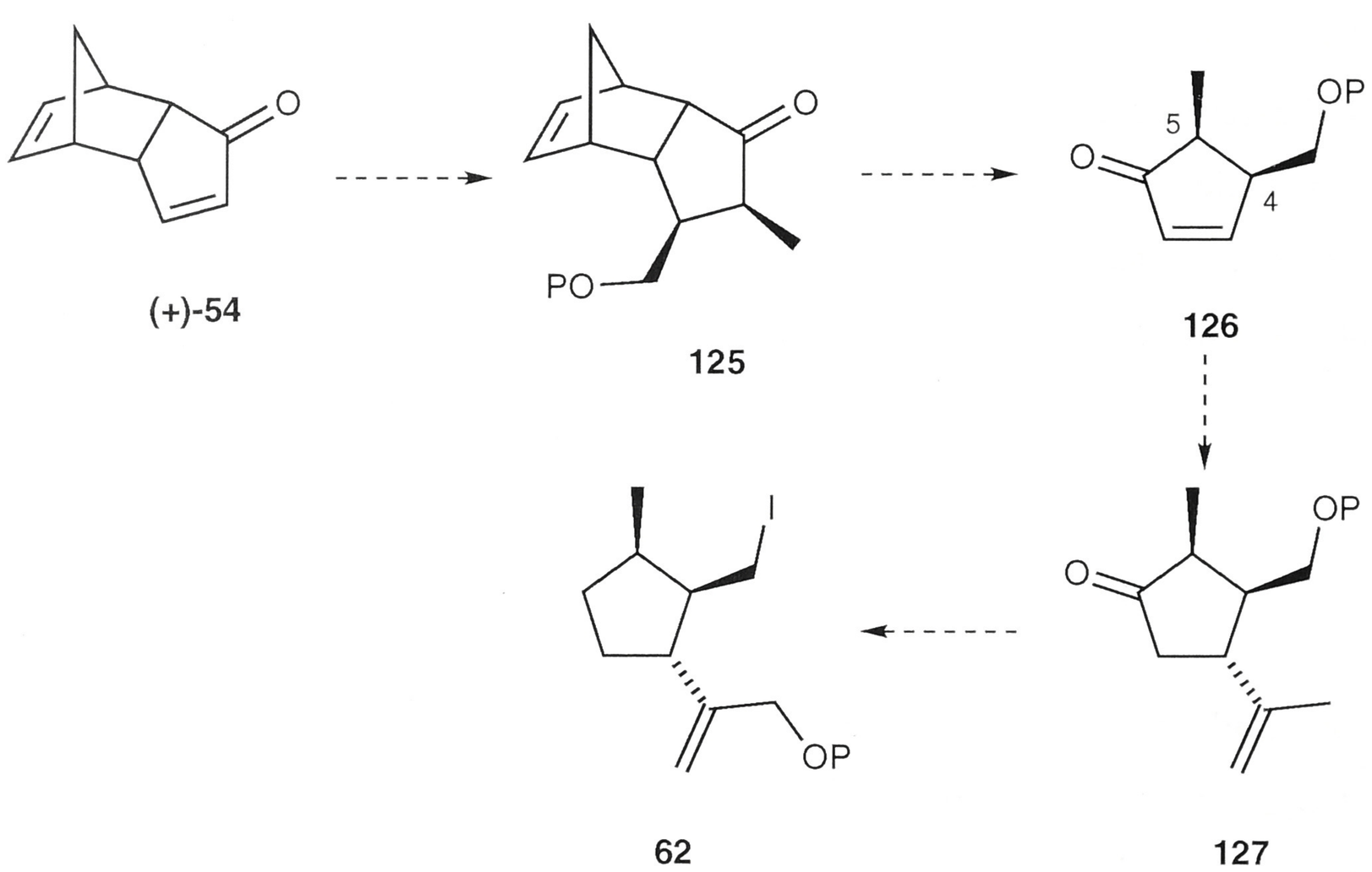


Figure 4.2.1 *Strategy for the synthesis of iodide* ***62****.*

Such a strategy for the formation of a *syn*-4,5-substituted enone was employed by Grieco and Abood[3] in their very concise synthesis of 12-oxophytodienic acid (12-oxoPDA, **130**, Figure 4.2.2); an extremely sensitive cyclopentenone found widely in plants.

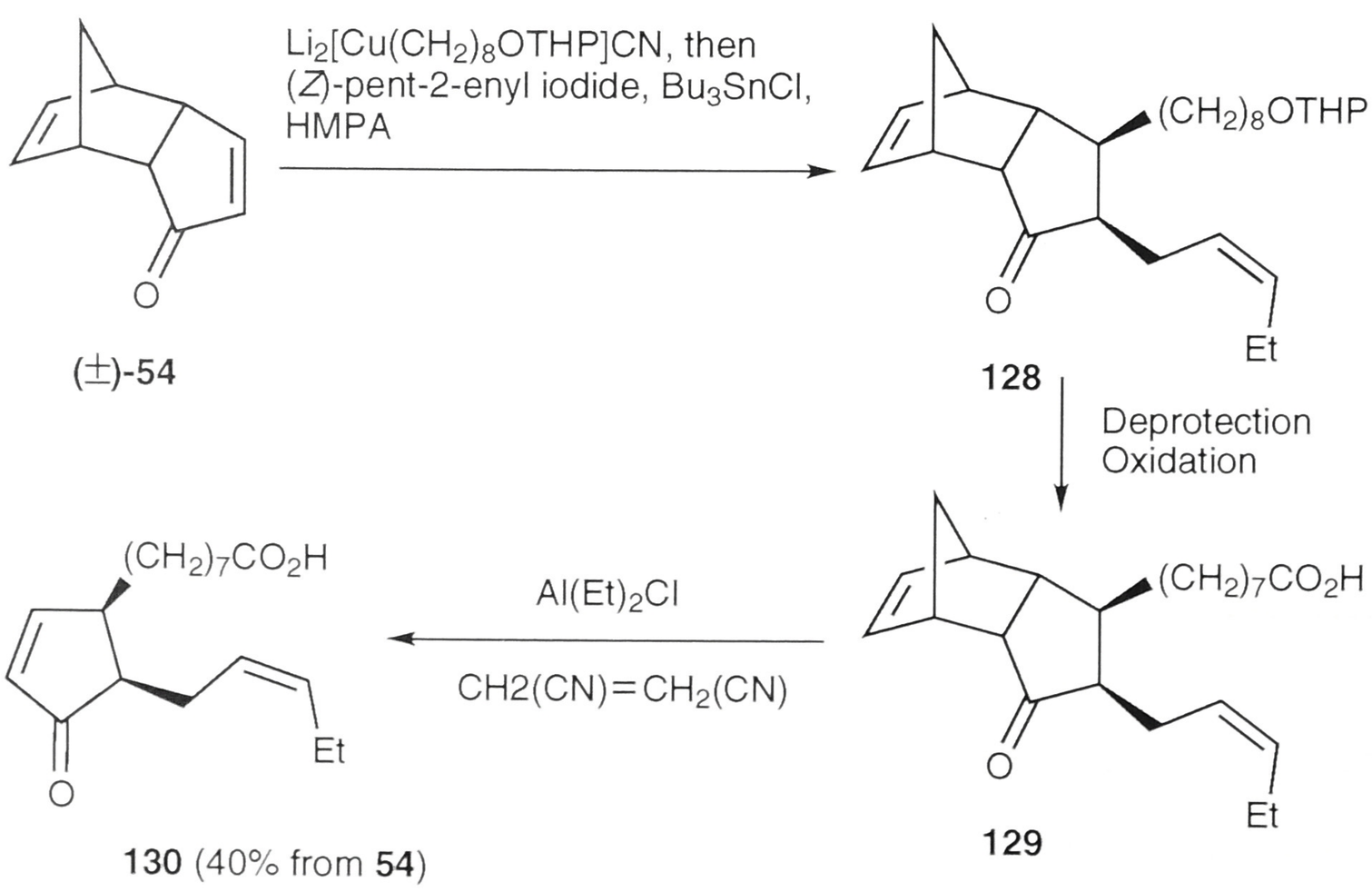


Figure 4.2.2 *Grieco and Abood's synthesis of 12-oxoPDA (****130****).*

Typically, *syn*-4,5-substituted enones are almost inaccessible owing to rapid isomerisation to the more thermodynamically stable *anti*-isomer. This problem was avoided by Grieco and Abood by the use of a three component coupling of (±)-**54**, $Li_2[Cu(CH_2)_8OTHP]CN$ and (*Z*)-pent-2-enyl iodide to afford the *syn*-substituted compound **128**. Deprotection and oxidation then gave **129**, which upon treatment with diethylaluminum chloride in 1,2-dichloroethane and fumaronitrile readily afforded the requisite target compound **130** by means of a [4+2] cycloreversion. The *syn*-stereochemistry is a consequence of the concave nature of the tricycle (±)-**54** having a greater steric influence than the *exo* β–substituent.

The first step in the sequence towards iodide **62** was the 1,4-addition of an appropriate carbon nucleophile which, in the final product, would become the iodomethyl substituent. The use of an hydroxymethyl equivalent was favoured, as there is ample literature on the conversion of primary hydroxy groups into iodide substituents.[4] The synthesis of aldehyde fragment **60**, as described in Chapter Three (Figure 3.2.14), made use of the hydroxymethyl anion equivalent (**115**) derived from *n*-BuLi and *n*-Bu_3SnCH_2OMOM.[5] Use of this reagent was deemed highly desirable due to the fact that the required reaction had already been established as high yielding and reliable, and the MOM group was considered to be a suitable protecting group for subsequent manipulations. Choice of this reagent necessitates the use of TMSCl,[6] and as a consequence, the possibility of a one-pot 1,4-addition followed by alkylation of the resultant enolate with methyl iodide was precluded. Despite this, regeneration of the enolate from the silyl enol ether had also been shown previously in the acylation of **116** with methyl cyanoformate (Figure 4.2.3, see also Chapter Three, Figure 3.2.14). Thus, the question was simply: could this enolate be alkylated with methyl iodide, and what would the diastereofacial selectivity be ?

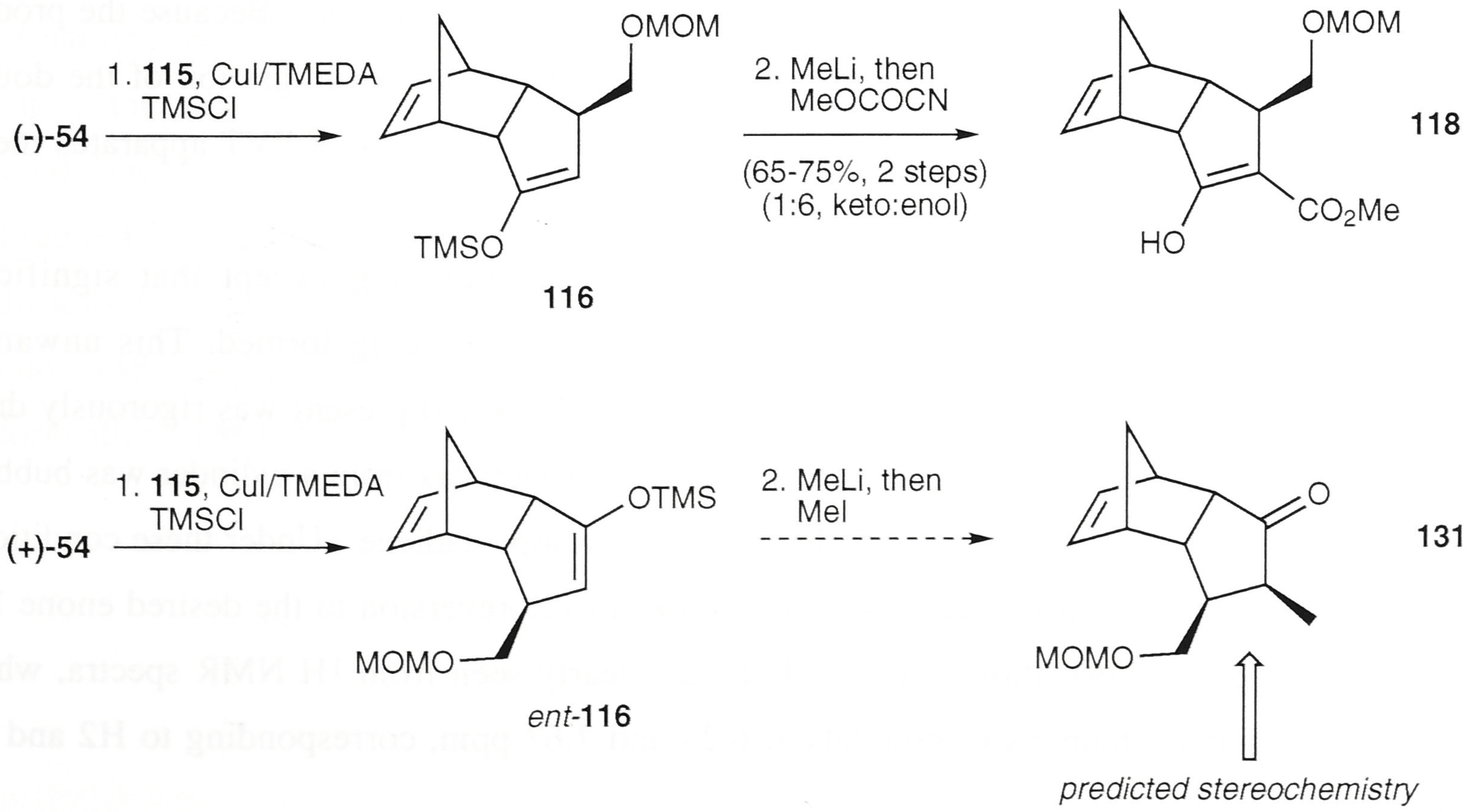


Figure 4.2.3 *Possible synthesis of* syn-*substituted cyclopentanone* ***131****.*

Initial attempts at forming **131**, with the enolate derived from *ent*-**116**, indicated that the alkylation with methyl iodide was incredibly sluggish and did not proceed appreciably at room temperature. Results were minimal until it was discovered that the addition of five equivalents of HMPA[7] to the enolate prior to the addition of methyl iodide, and subsequent warming to about 50 °C, gave a good yield (60%) of the desired α–methyl ketone **131** in 90-95% d.e. The major diastereomer displayed a doublet at 0.95 ppm corresponding to the newly installed α–methyl group.

It was expected that confirmation of the stereochemistry could be achieved by 1D NOESY experiments, but these proved to be somewhat inconclusive. However, on the basis of Grieco and Abood's work[3] (Figure 4.2.2) the major product was considered to be that with the desired *syn*-stereochemisty, *i.e.* **131**, and the synthesis was continued with the expectation that concrete confirmation would be achieved in due course.

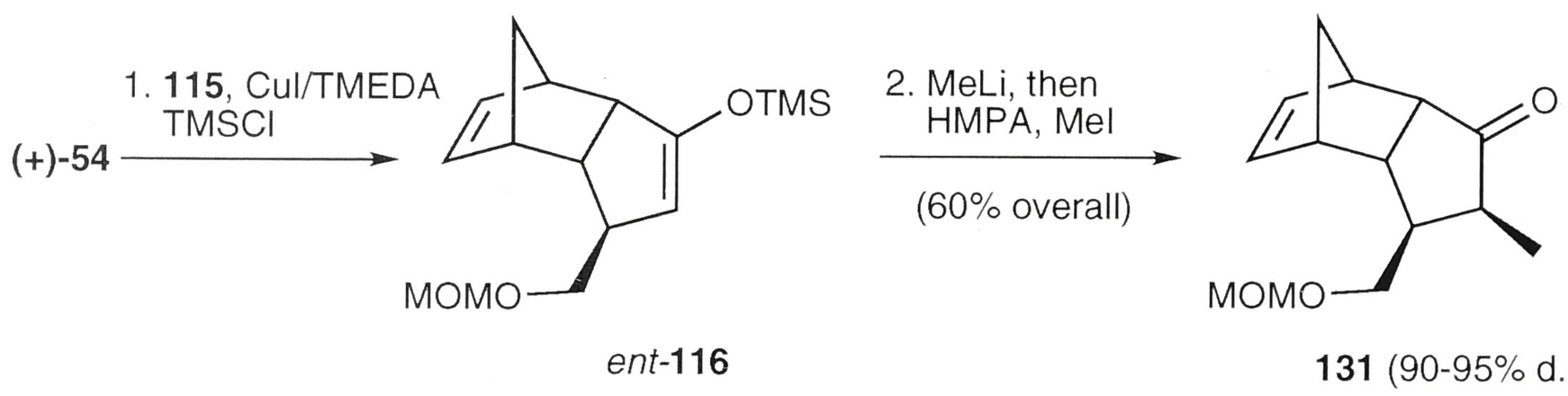
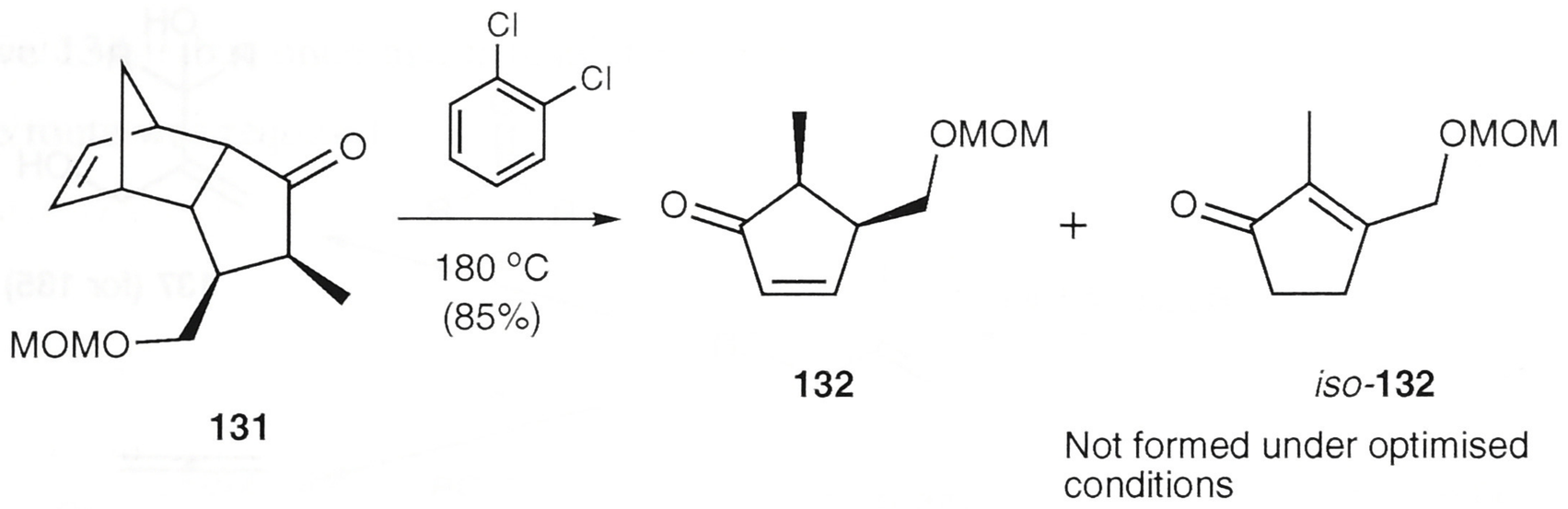


Figure 4.2.4 *Synthesis of the* syn*-substituted cyclopentanone* ***131****.*

There were several choices of possible conditions for use in the [4+2] cycloreversion of **131** to the key *syn*-4,5-substituted cyclopentenone **132**, such as: flash-vacuum-thermolysis (FVT), heating at reflux in 1,2-dichlorobenzene or diphenyl ether, the use of a dienophile to trap the formed cyclopentadiene, and the possible use of Lewis acid catalysis.[2] Because the product was expected to be prone to epimerisation of the α–substituent and/or migration of the double bond, the use of Lewis acids was immediately dismissed, and the lack of FVT apparatus meant that simple thermal cracking was the first option pursued.

Initial results using 1,2-dichlorobenzene were encouraging except that significant amounts of the isomerised tetrasubstituted enone *iso*-**132** were being formed. This unwanted process could be suppressed if the reaction vessel with compound present was rigorously dried under high vacuum before solvent addition, and if dry nitrogen gas from a cylinder was bubbled through the reaction mixture to carry off the formed dicyclopentadiene. Under these conditions, heating at 180 °C for about 6 hours resulted in smooth cycloreversion to the desired enone **132** in high yield (85%). Formation of enone **132** was clearly seen from ^{1}H NMR spectra, which displayed two sets of doublets of doublets at 6.24 and 7.67 ppm, corresponding to H2 and H3 respectively.

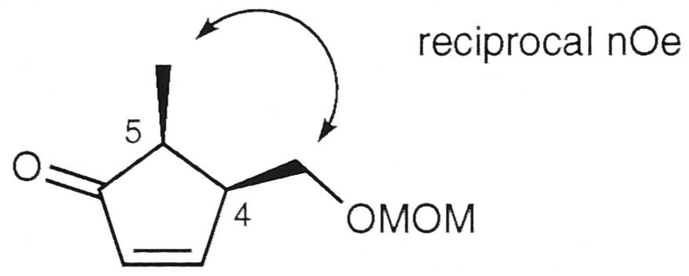


131 **132** *iso*-**132**

Not formed under optimised conditions

Figure 4.2.5 *Cycloreversion of* ***131*** *to form* syn-*4,5-substituted enone* ***132***.

Confirmation of the *syn*-relationship between the ring substituents was readily achieved at this juncture using 1D NOESY experiments, with the key nOe signal shown below in Figure 4.2.6. Further confirmation of this stereochemistry was given in the distinct lack of any nOe signals corresponding to H4 when the methyl group was irradiated, and H5 when the alkoxy methyl substituent was irradiated.



132

Figure 4.2.6 *Confirmation of* syn-*stereochemical relationship between ring substituents.*

4.2.2 Successful synthesis of the iodide

With the key cyclopentenone **132** now in hand, efforts were directed towards installing the final ring substituent which, ultimately, would become a protected hydroxylated isopropenyl group in the target iodide **62**. Ideally, the addition of a nucleophillic species carrying all the desired functionality would lead to the most efficient synthesis. Compounds of the type shown in Figure 4.2.7 are known, but usually the derived alkyllithium is used directly to carry out 1,2-addtitions to carbonyl groups (path *a*). Typically, such reactions are performed using the dianion **135**,[8] as protected hydroxy derivatives, such as **136**, tend to undergo facile elimination to form allene **138** (path *b*).[9]

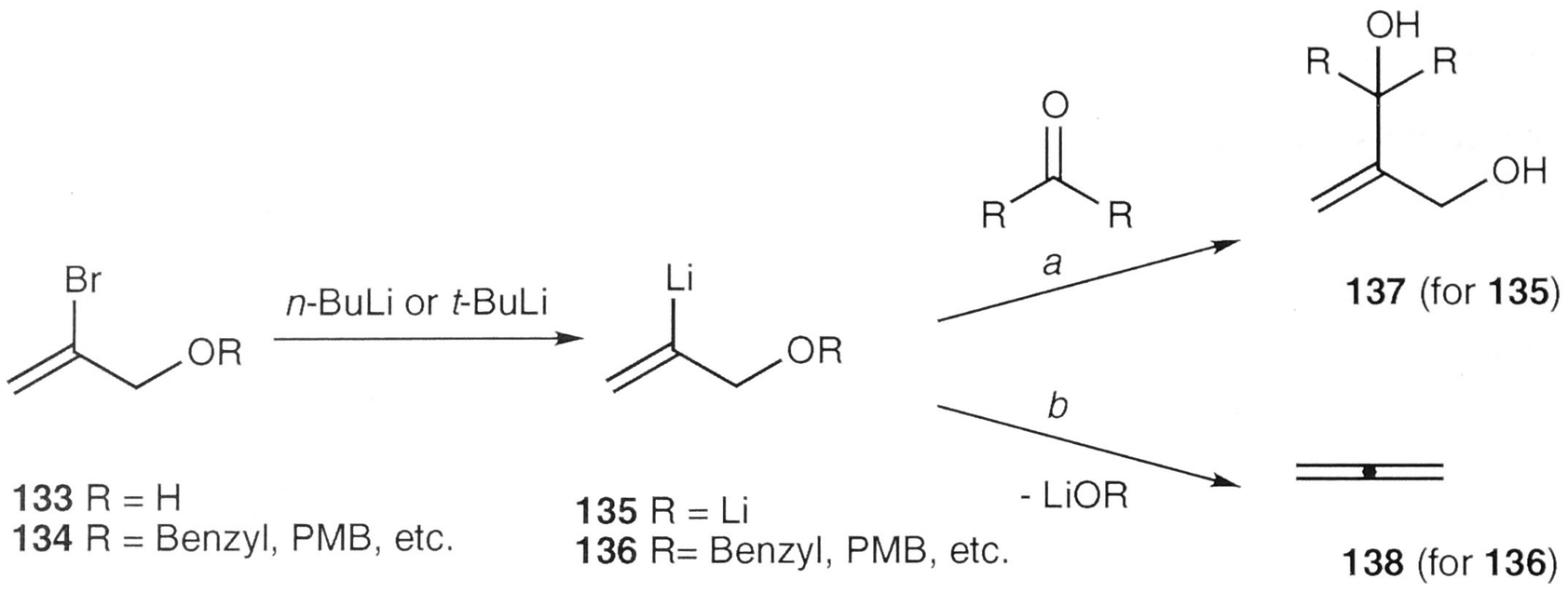


Figure 4.2.7 *Reactions of functionalised isopropenyl carbanions.*

Overman and co-worker's[10] employed the cuprate derived from the dianion of **139** to install the requisite (*Z*)-ethylidene unit into cyclopentenone *en route* to the *Strychnos* alkaloid (±)-dehydrotubifoline (**141**, Figure 4.2.8). Sequential treatment of (*Z*)-2-bromo-2-buten-1-ol with 3 equivalents of *t*.-BuLi, 1 equivalent of lithium thienylcyanocuprate, 2 equivalents of TMSCl and 1 equivalent of cyclopentenone afforded the desired product **140** in a rather low 40-45% yield. This result was acceptable for Overman and co-worker's due to the ready availability and low cost of the starting materials, but it was hoped that the equivalent reaction of dianion **135** with enone **132** would proceed with a higher yield.

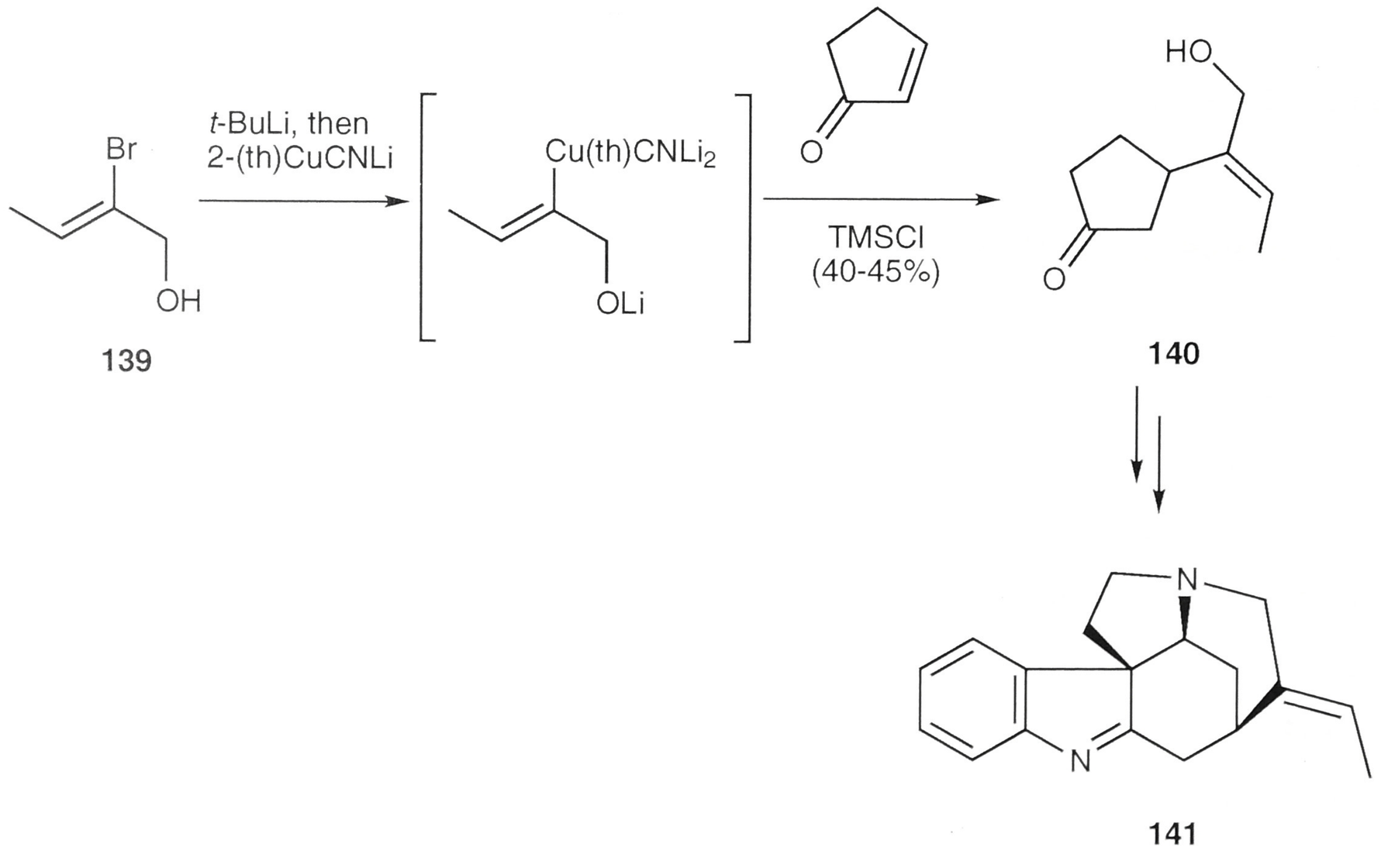


Figure 4.2.8 *Overman and co-worker's synthesis of (±)-dehydrotubifoline (**141**).*

Unfortunately, treatment of 2-bromopropene-1-ol (**133**) with ^{t}BuLi and subsequent use of Overman and co-worker's conditions for 1,4-addition to **132** gave rise to little or no observed product (**144**, Figure 4.2.9). The same reaction conditions were used on the PMB protected

derivative **134**,[11] but once again results were poor. Clearly a less direct, but hopefully more effective route was required.

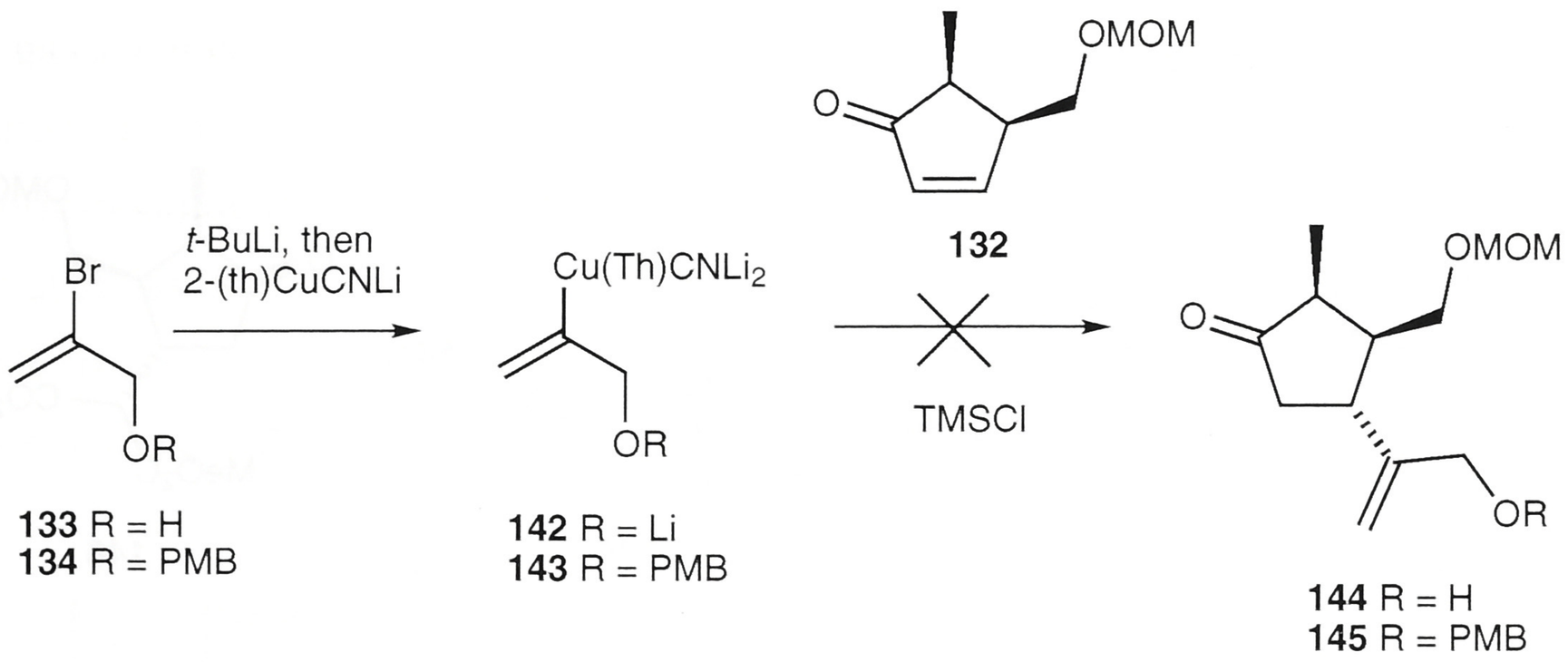
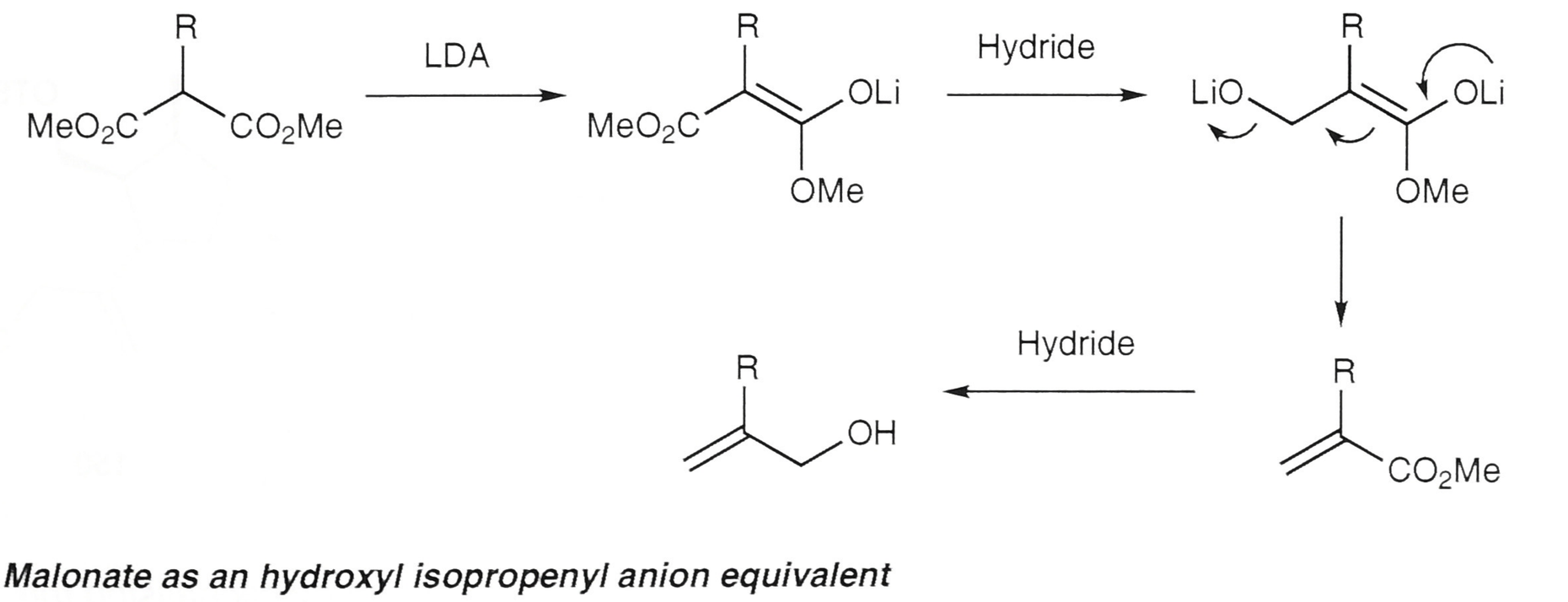


Figure 4.2.9 *Attempted direct installation of the requisite functionalised isopropenyl group.*

The Marshall reduction[12] is a procedure by which the enolate of a malonate diester is converted, in a one-pot operation, into the corresponding allylic alcohol. Thus, the use of dimethyl malonate in a 1,4-addition, followed by Marshall reduction leads to the formal conjugate addition of an hydroxyisopropenyl anion to an enone (Figure 4.2.10).

Marshall reduction



Malonate as an hydroxyl isopropenyl anion equivalent

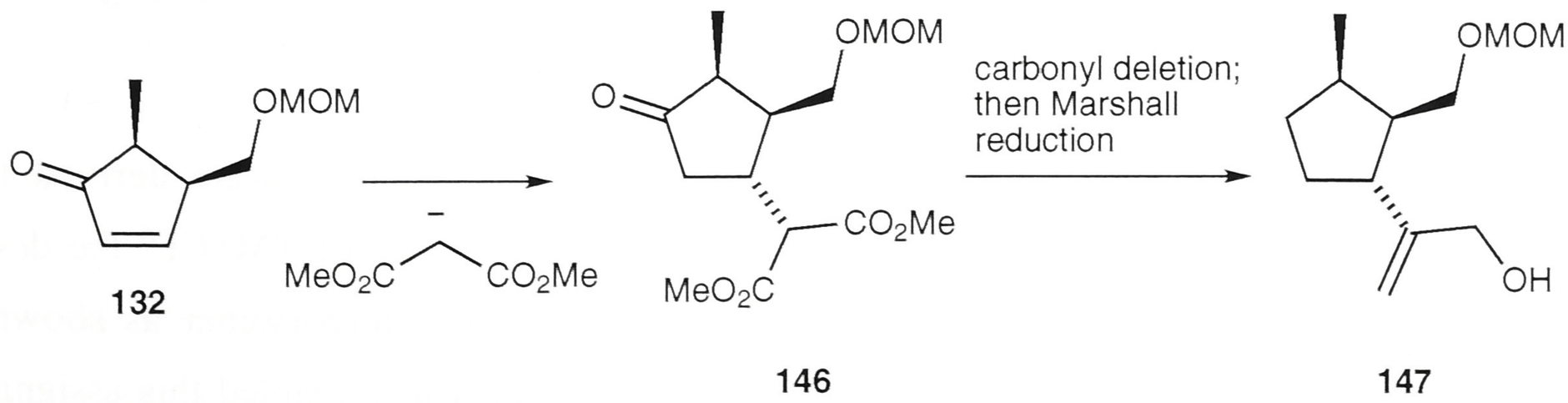


Figure 4.2.10 *Marshall reduction and malonate equivalence.*

Exposure of the enone **132** to dimethyl malonate/Na in MeOH at 0 °C for 30 minutes resulted in clean formation of a product resulting from 1,4-addition (Figure 4.2.11). The

stereochemistry was assumed to be that required for iodide **62** (*i.e.* **146**), but subsequent analysis led to the realisation that complete epimerisation of the α–methyl group had occurred. No attempts were made to discover conditions where this epimerisation was suppressed, but instead an alternative approach was sought.

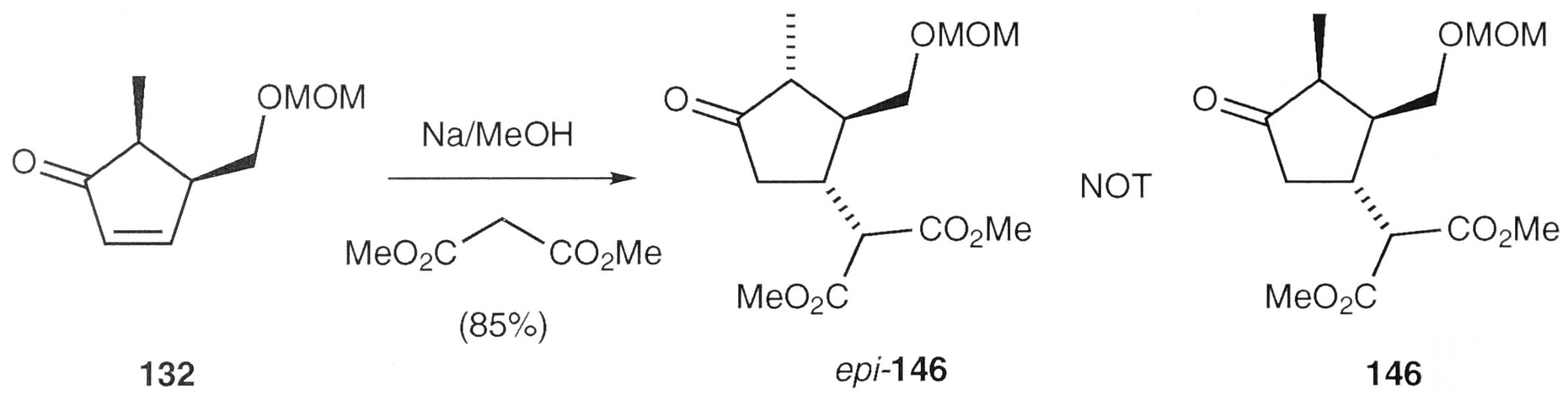


Figure 4.2.11 *Addition of dimethylmalonate to enone **132** – unwanted epimerisation.*

Some previous work within the research group had demonstrated the use of alcohol **124** in a model study[13] related to sordaricin (**3**, see Chapter One, section 1.5.1). Alcohol **124** was accessible in enantiopure form from (*S*)-(+)-carvone (**123**) in 7 steps, as described in the literature.[1] Unpublished results[14] of this research had shown that the TBS ether **148** could be transformed into alcohol **150** *via* epoxide **149** (Figure 4.2.12). Thus, it was expected that MOM ether **154** should behave in a similar manner to afford the desired alcohol **147**.

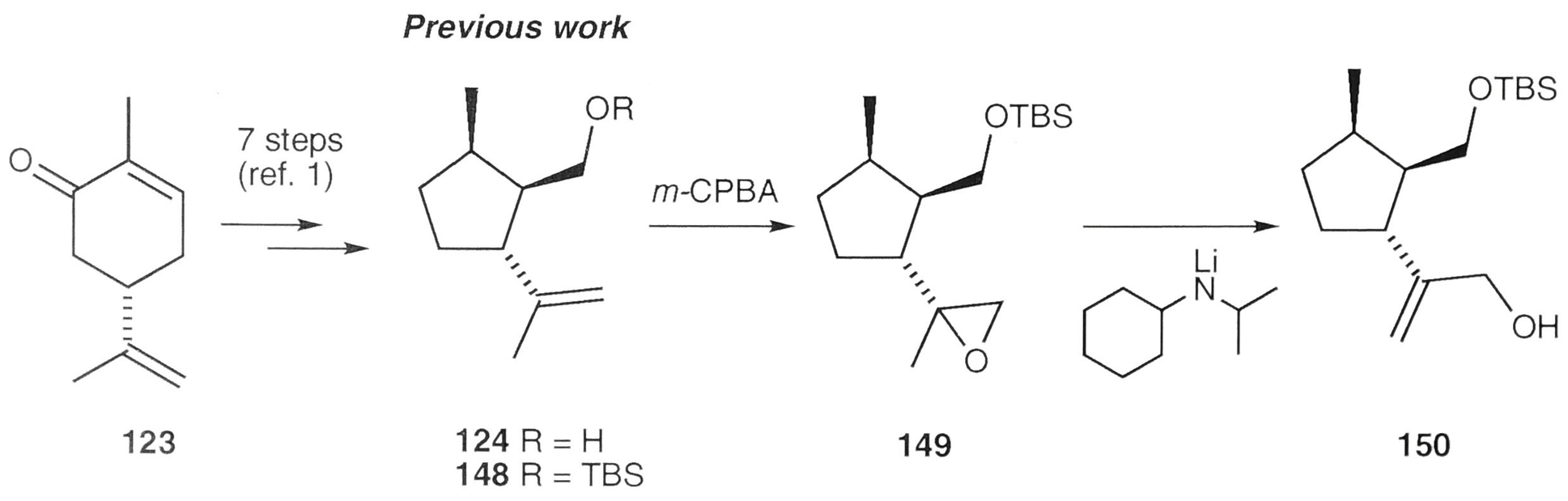


Figure 4.2.12 *Previous and unpublished work within the group on functionalising the isopropenyl unit of **148**.*

Addition of the enone **132** to a preformed solution of the cuprate derived from isopropenylmagnesium bromide and CuI,[15] delivered, in the presence of TMSCl,[6] the desired ketone **151** in good yield (70%, Figure 4.2.13) and as a single stereoisomer as shown by ^{1}H NMR spectroscopy. Key signals in the ^{1}H NMR spectrum which enabled this assignment were the signal at 1.78 ppm corresponding to the isopropenyl methyl group, and the two olefinic signals at 4.76 and 4.82 ppm. The ^{13}C NMR spectrum clearly indicated that 1,4-addtion had occurred over 1,2-addition by the presence of a carbonyl resonance at 219.4 ppm.

The diastereofacial selectivity of this process was not determined at this stage, as confirmation would be achieved readily by deletion of the carbonyl group and removal of the MOM group, thereby affording the known alcohol **124**. Thus, reduction of the ketone **151** with $NaBH_4$ gave a mixture of alcohols **152** which were used directly in the next step without purification. Removal of the hydroxy groups was achieved by first converting the alcohols **152** to the corresponding thionocarbonates **153** (88%) which, when treated with *n*-Bu_3SnH/AIBN in benzene at reflux for 1 h, gave the deoxygenated product **154** in excellent yield (100%).[16] A ^{13}C NMR spectrum clearly revealed that deoxygenation had occurred by the distinct lack of any resonances corresponding to carbonyl or hydroxylated cyclopentyl carbons.

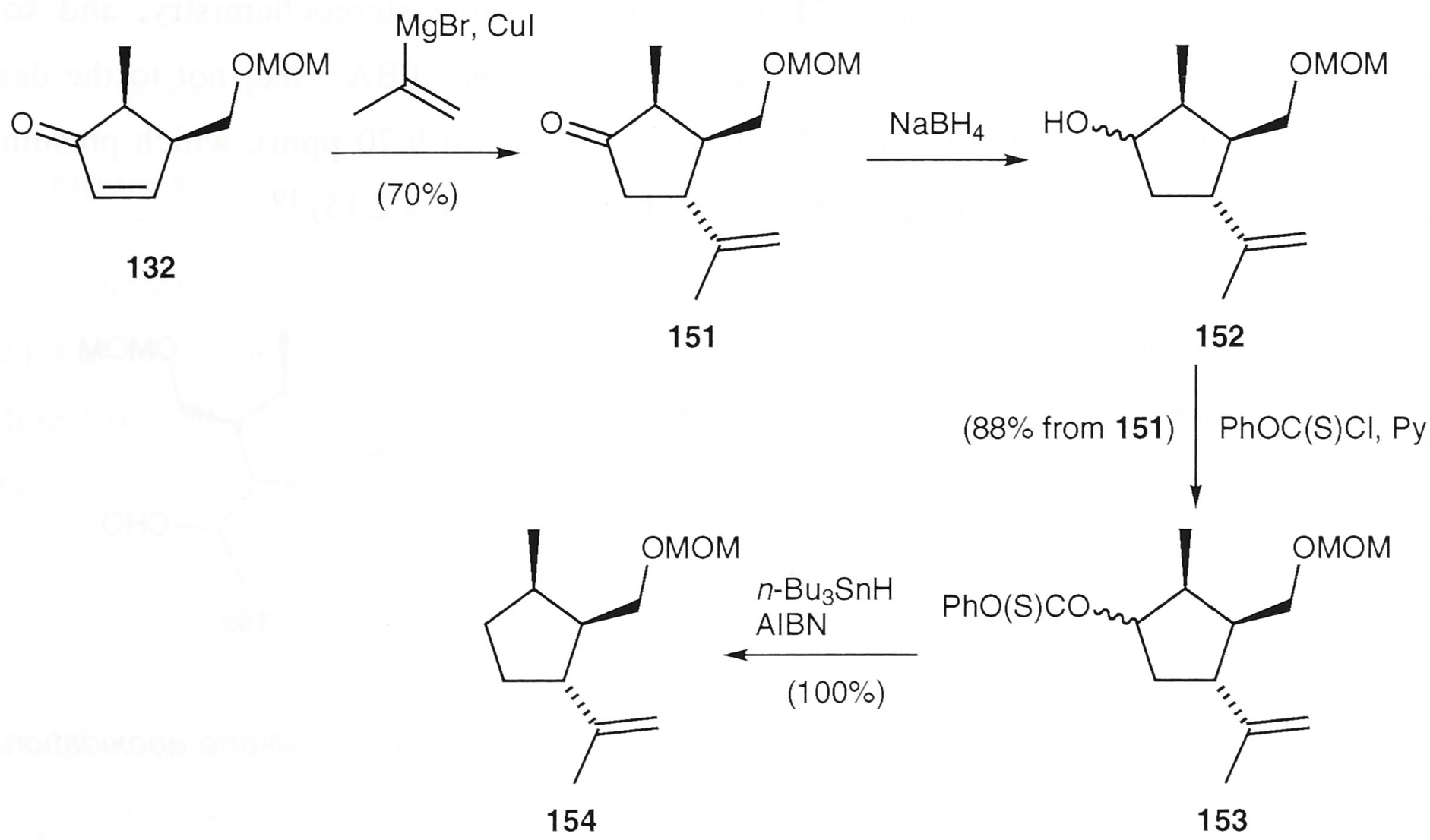


Figure 4.2.13 *Formation of cyclopentane **154**.*

At this point, before attempting the epoxidation/fragmentation sequence, the MOM group was removed using PPTS/*t*BuOH[17] to afford the known alcohol **124** in good yield (80%). Comparisons of ^1H NMR spectra and GCMS data between the carvone derived (**123**)[1] and that produced from dicyclopentadienone [(+)-**54**] were identical, thus confirming the relative stereochemistry of all the substituents. Key signals in the ^1H NMR spectra allowing this comparison were: the doublet at 0.91 ppm corresponding to the methyl substituent; the singlet at 1.73 ppm for the isopropenyl methyl group; the multiplet at 3.62 ppm associated with the hydroxy methyl substituent; and the pair of olefinic resonances at 4.71 and 4.78 ppm. The absolute stereochemistry of **124** was then confirmed by comparison of the $[\alpha]_D$ values, which were: -24.1° (*c* 0.80 $CHCl_3$) and –22.8° (*c* 0.85 $CHCl_3$) for the enone (+)-**54** and (*S*)-(+)-carvone (**123**) derived samples respectively. Thus, compound **124** was shown to have the absolute and relative stereochemical configuration depicted in Figure 4.2.14.

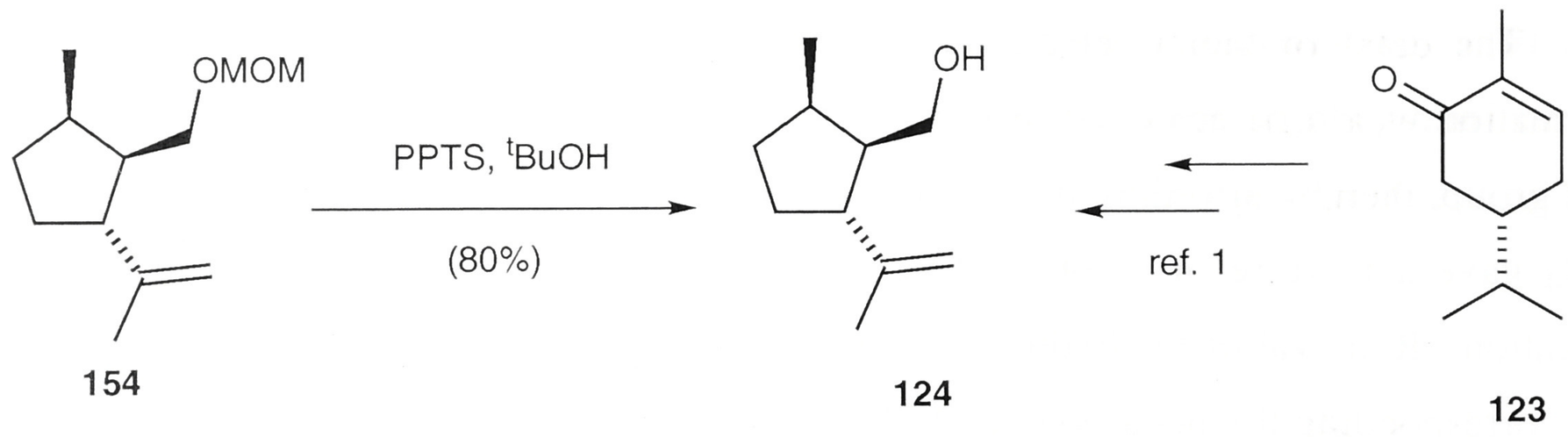


Figure 4.2.14 *Preparation of alcohol **124** for structural comparisons.*

Having established the absolute and relative stereochemistry of **124**, it seemed reasonable to consider MOM ether **154** as having the same stereochemistry, and so the epoxidation was attempted. Treatment of alkene **154** with *m*-CPBA[18] led, not to the desired epoxide, but to the saturated aldehyde **156** (CHO resonance at 9.70 ppm), which presumably forms by a facile *in situ* [1,2] hydride shift of epoxide **155** (Figure 4.2.15).[19]

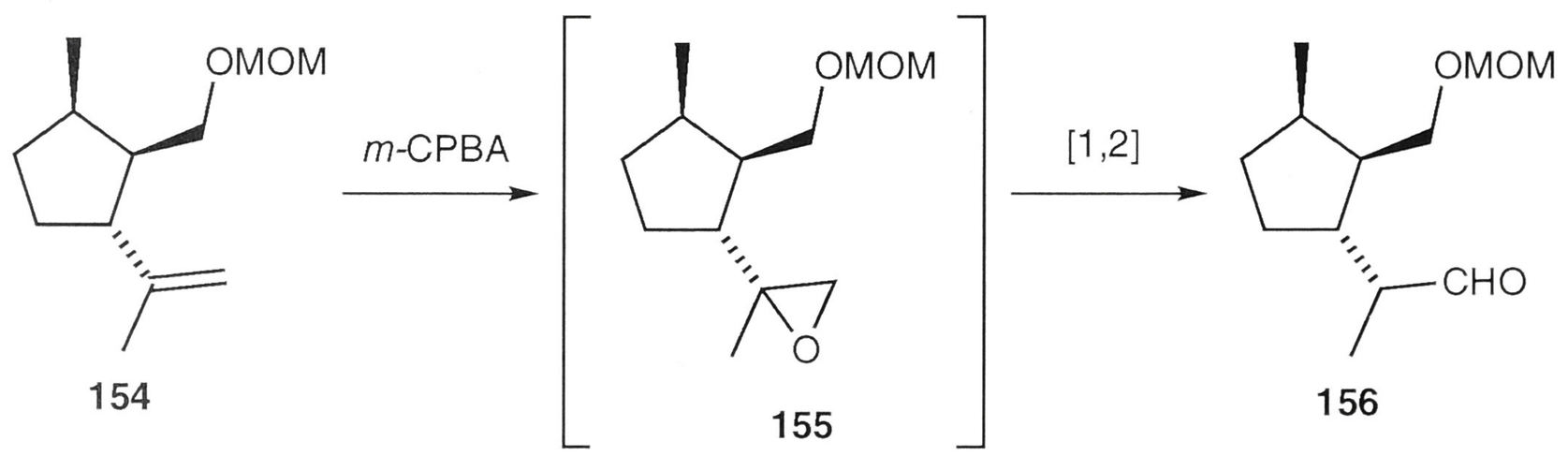


Figure 4.2.15 *Unexpected formation of saturated aldehyde **156** from alkene epoxidation.*

In an effort to suppress this unwanted rearrangement the epoxidation was carried out in the presence of excess $NaHCO_3$, but still the major product was aldehyde **156**. Even oxidation using dimethyl dioxirane,[20] which should ensure neutral conditions, lead to about a 1:1 mixture of epoxide **155** and aldehyde **156**. It is difficult to rationalise why this rearrangement is so facile, even under mild neutral conditions, when the epoxide formed from TBS derivative **148** is stable to silica gel chromatography. One possible explanation could be that rearrangement was an artifact of aqueous workup, caused by protonation of the epoxide assisted by the MOM group, but no effort was made to test this hypothesis.

Given the failure of this epoxidation, and the other approaches described above, the MOM group was removed as before and replaced with the TBS group,[21] to give the TBS ether **148** in moderate overall yield (77%).

It was discovered that yields of the epoxidation of **148** were generally higher than previously seen within the group when the reaction was buffered with $NaHCO_3$. Now, exposure of the epoxide **149** to lithium cyclohexylisopropylamide in diethyl ether[22] readily gave the required allylic alcohol **150** in good yield (64%, Figure 4.2.16). Indicative resonances in the

^{1}H NMR spectra of **150** were the broad singlet at 2.54 ppm for the hydroxyl proton, the apparent triplet at 4.10 ppm for the allylic hydroxy methyl group, and the olefinic signals at 4.90 and 5.00 ppm.

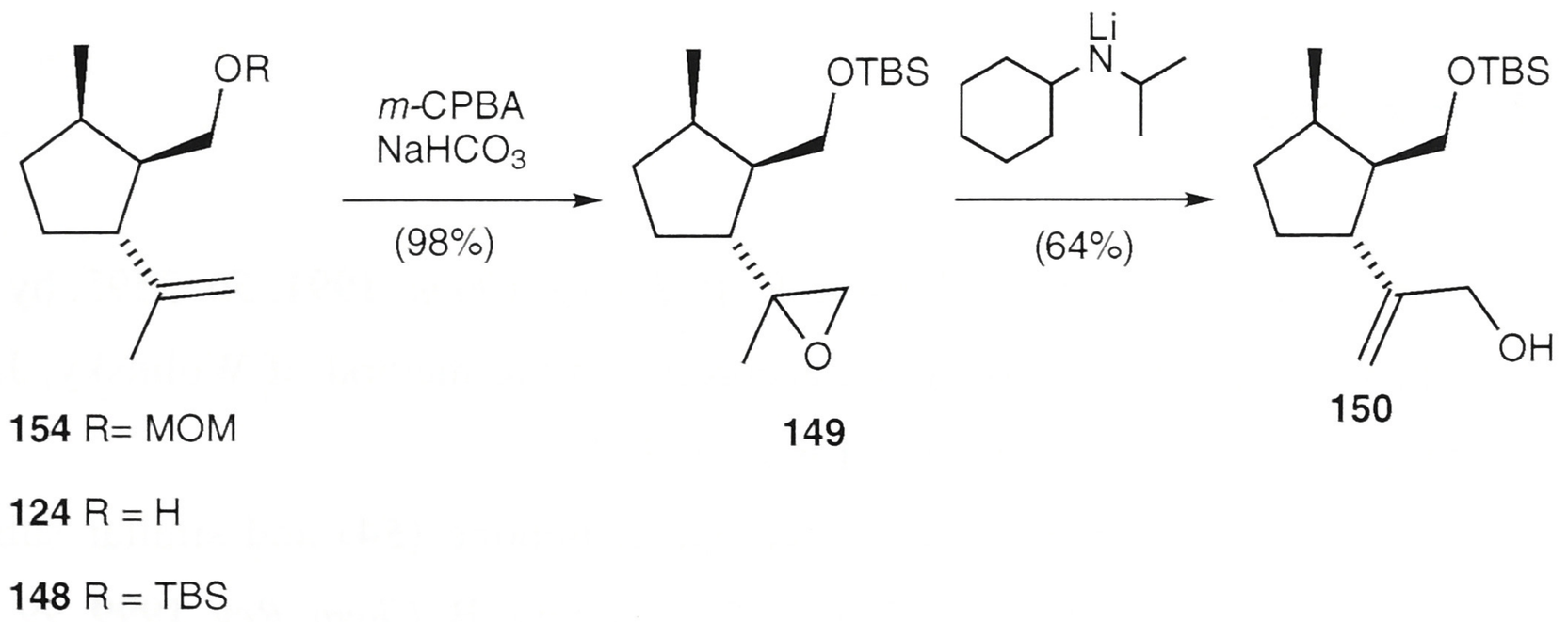


Figure 4.2.16 *Epoxidation/fragmentation sequence for the formation of alcohol **150**.*

Choice of the protecting group for the allylic alcohol was important, and the MOM group was seen as an ideal candidate due to its reliable stability and small steric demand. Thus, treatment of **150** with MOMCl, DIPEA and DMAP (cat.),[21] afforded the MOM ether **157** in virtually quantitative yield (94%). Completion of the synthesis of iodide **158** (equivalent to **62** when P = MOM) was then readily achieved after TBAF[21] mediated removal of the TBS group (93%), and subsequent transformation of the resulting primary alcohol into the iodide **158** using iodine, Ph_3P and imidazole (96%, Figure 4.2.17).[23] The ^{1}H NMR spectra of compound **158** clearly showed iodide incorporation by the signals at 2.93 and 3.28 ppm which corresponded to the iodomethyl substituent. Further evidence was seen by the ^{13}C NMR APT spectra which displayed an upfield CH_2 resonance at 7.3 ppm, for the iodomethyl group..

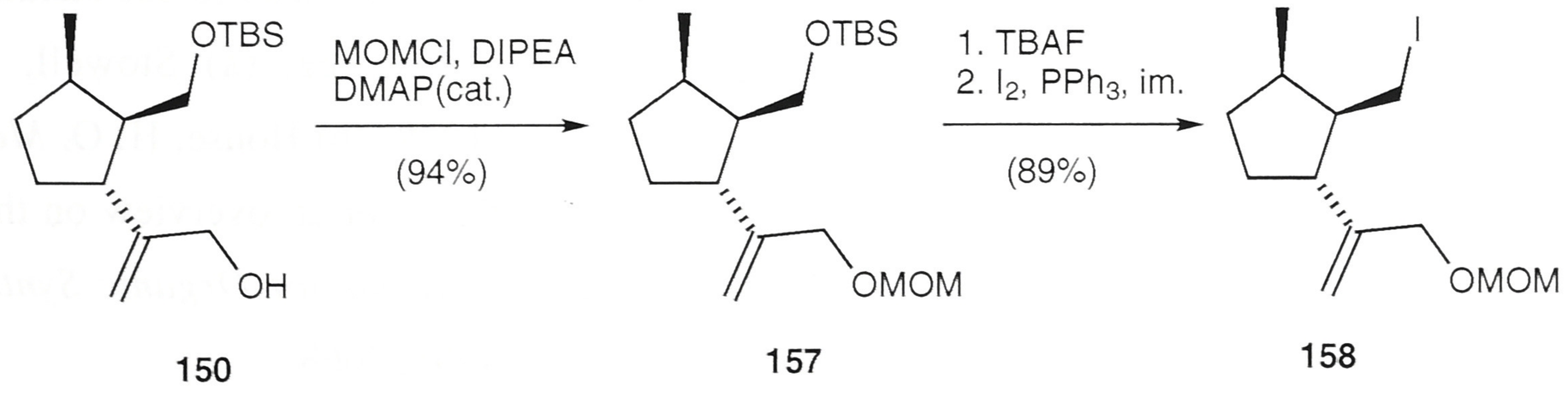


Figure 4.2.17 *Completion of the synthesis of the key iodide fragment **158**.*

4.3 Summary

Synthesis of the key *syn*-4,5-substituted enone **132** has been described, and elaboration of this intermediate into several trisubstituted cyclopentane derivatives was detailed. Several unsuccessful attempts to transform these intermediates into iodide **158** (**62** when P = MOM) have also been discussed.

An efficient synthesis of the key iodide fragment **158** was developed, and having established this route, and confirmed all necessary stereochemical assignments the alkylation of aldehyde **60** with the iodide **158** could be attempted and will be discussed in the following chapter.

4.4 References

1. Prepared by Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595, by reduction of the parent methyl ester, obtained according to the method of Wolinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron* **1965**, *21*, 1247.
2. For a recent review on the use of cyclopentadienone (**54**) and similar substrates in synthesis, see: Klunder, A. J. H.; Zhu, J.; Zwanenburg, B. *Chem. Rev.* **1999**, *99*, 1163.
3. Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008.
4. (a) Tipson, R. S.; Clapp, M. A.; Cretcher, L. H. *J. Org. Chem.* **1947**, *12*, 133. (b) Chambers, R. D.; James, S. R. In *Comprehensive Organic Chemistry*, Barton, D.; Ollis, W. D. (Eds), Pergamon: New York, **1979**, Vol. 1, 513. See also, Dormoy, J. –R.; Castro, B. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 5393 and references cited therein.
5. (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Linderman, R. J.; Godfrey, A.; Horne, K. *Tetrahedron* **1989**, *45*, 495.
6. (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019. For a more recent explanation of the role of TMSCl in Gilman cuprate 1,4-additions, see: Lipshultz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283 and references cited therein
7. Studies have shown that polar aprotic solvents like HMPA can lead to substantial rate enhancements in the electrophilic trapping of enolates, see: (a) Stowell, J. C. *Carbanions in Organic Chemistry*, Wiley: New York, **1979**. (b) House, H. O. *Modern Synthetic Reactions*, 2nd Ed, Benjamin: New York, **1972**. For an overview on the use of HMPA, see: Dykstra, R. R. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 2668.
8. Corey, E. J.; Widiger, G. N.; *J. Org. Chem.* **1975**, *40*, 2975.
9. The reaction of magnesium with ethers of 2-bromoallyl alcohol lead to allene formation, see: (a) Ficini, J.; Sarrade-Loucheur, G.; Normant, H. *Bull. Chim. Soc. Fr.* **1962**, 1219. (b) Ficini, J.; Depezay, J.-C. *Tetrahedron Lett.* **1969**, 4797.
10. Fevig, J. M.; Marquis, R. W. Jr.,; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085.
11. Hoshi, H.; Ohnuma, T.; Aburaki, S.; Konishi, M.; Oki, T. *Tetrahedron Lett.* **1993**, *34*, 1047.

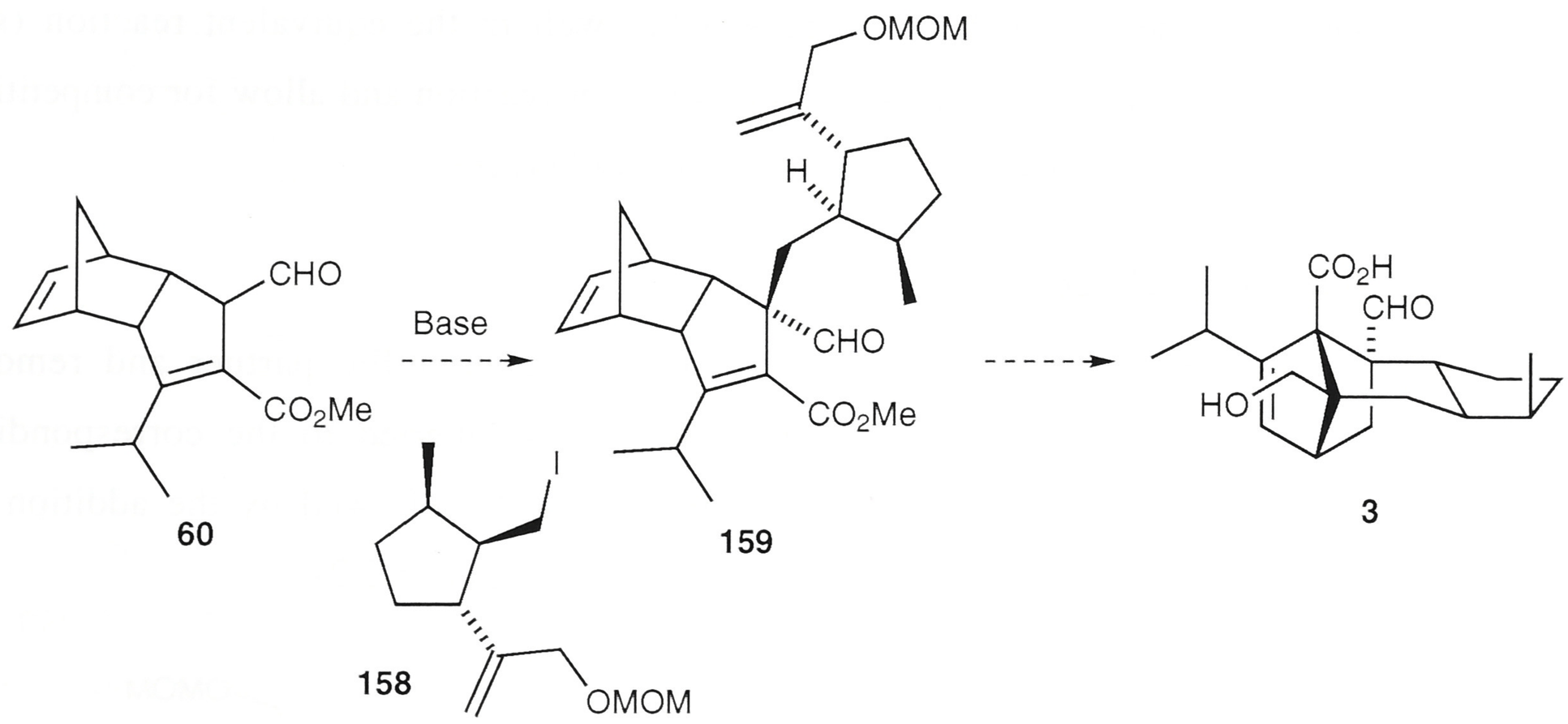
12. Marshall, J. A.; Andersen, N. H.; Hochstetlet, A. R. *J. Org. Chem.* **1967**, *32*, 113. For a useful modification, see: Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron* **1994**, *50*, 12829.
13. Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595.
14. Robinson, R. P. Unpublished results, 1985.
15. (a) House, H. O.; Latham, R. A.; Slater, C. D. *J. Org. Chem.* **1966**, *31*, 2667. (b) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736.
16. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
17. Monti, H.; Léandri, G.; Klos-Ringuet, M.; Corriol, C. *Synth. Commun.* **1983**, *13*, 1021.
18. Rao, A. S.; Mohan, H. R. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 1192 and references cited therein.
19. Such rearrangements usually require the addition of a Lewis acid, see: Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.
20. Crandall, J. K. In *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 2061 and references cited therein.
21. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley and Sons: New York, **1991** and references cited therein.
22. Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345.
23. Corey, E. J.; Pyne, S. G.; Su, W.; *Tetrahedron Lett.* **1983**, *24*, 4883.

Chapter Five

Alkylations Leading to Sordaricin

5.1 Introduction

The previous two chapters described research efforts which culminated in the successful synthesis of the two key compounds **60** and **158**, that were to partake in an alkylation based, convergent strategy leading to sordaricin (**3**). A model alkylation of **60**, using isobutyl iodide, showed some promise, but a successful outcome using the iodide **158** was far from assured. This chapter will detail attempts to alkylate the aldehyde **60** with iodide **158**, and the ultimate development of an alternative and successful alkylation strategy.



5.2 Attempted alkylations

5.2.1 The aldehyde

Having already established a procedure for the alkylation of **60** with isobutyl iodide (see Chapter Three), these conditions were the first choice for the initial attempt using iodide **158** (Figure 5.2.1). Accordingly, a solution of 1.0 M ^{t}BuOK was added to a stirred solution of the aldehyde **60** in THF at 0 °C. After 10 min a solution of the iodide **158** in THF was carefully added and the mixture allowed to warm to room temperature for 24 h. Consumption of the aldehyde **60** was clearly observable by TLC, but ^{1}H NMR spectra of the crude reaction mixture showed only unchanged iodide **158**, and no signals corresponding to the desired product **159** or aldehyde **60**. Further experimentation did not improve this situation.

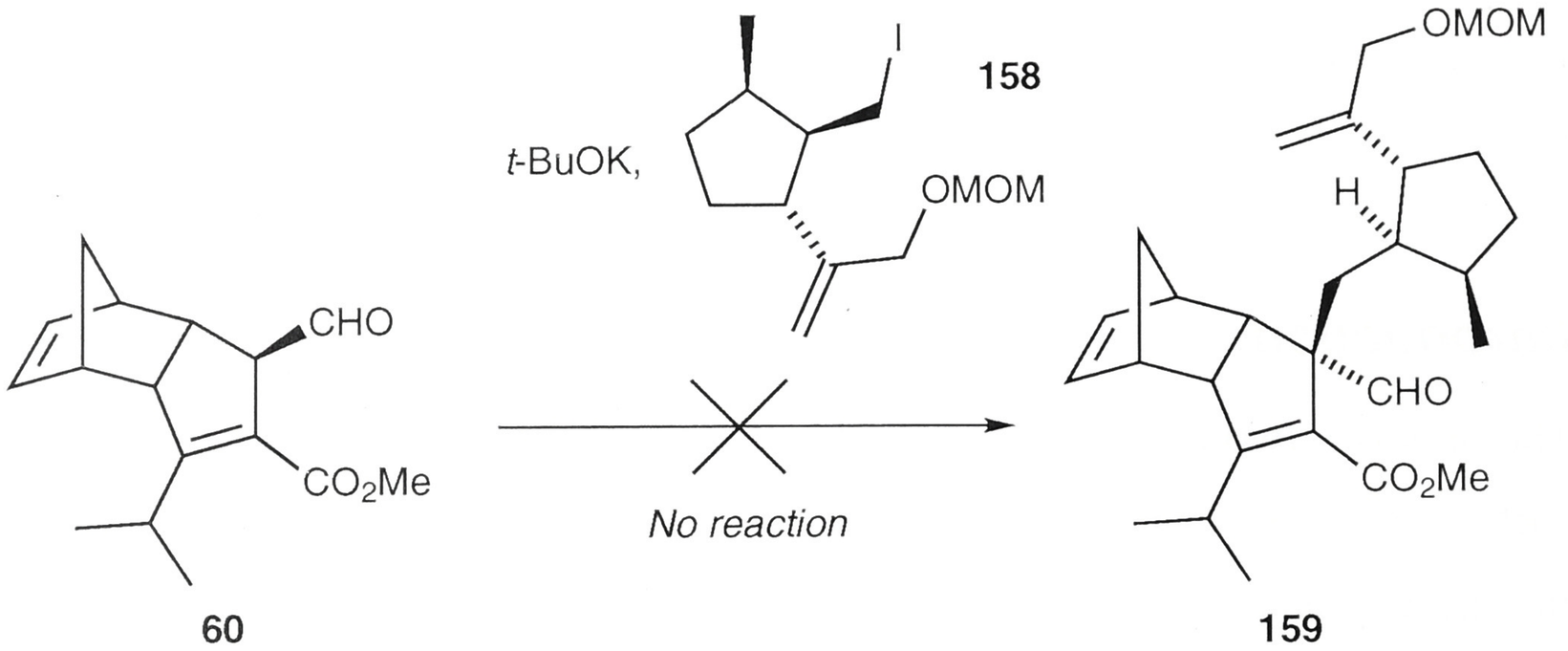


Figure 5.2.1 *Failure of the planned alkylation.*

This failure might possibly have been due to the increased steric demand of iodide **158** relative to isobutyl iodide, which behaved reasonably well in the equivalent reaction (see Chapter Three). This increased bulk might lead to a slower reaction and allow for competitive side reactions, such as the self-condensation of **60** by an aldol process.

5.2.2 The dimethylhydrazone

In an attempt to increase the reactivity of the nucleophillic partner and remove unwanted self-condensation products, aldehyde **60** was converted to the corresponding dimethylhydrazone **160** (95%).[1] Treatment of **160** with LDA, followed by the addition of iodide **158** however, did not lead to any of the desired product (Figure 5.2.2).

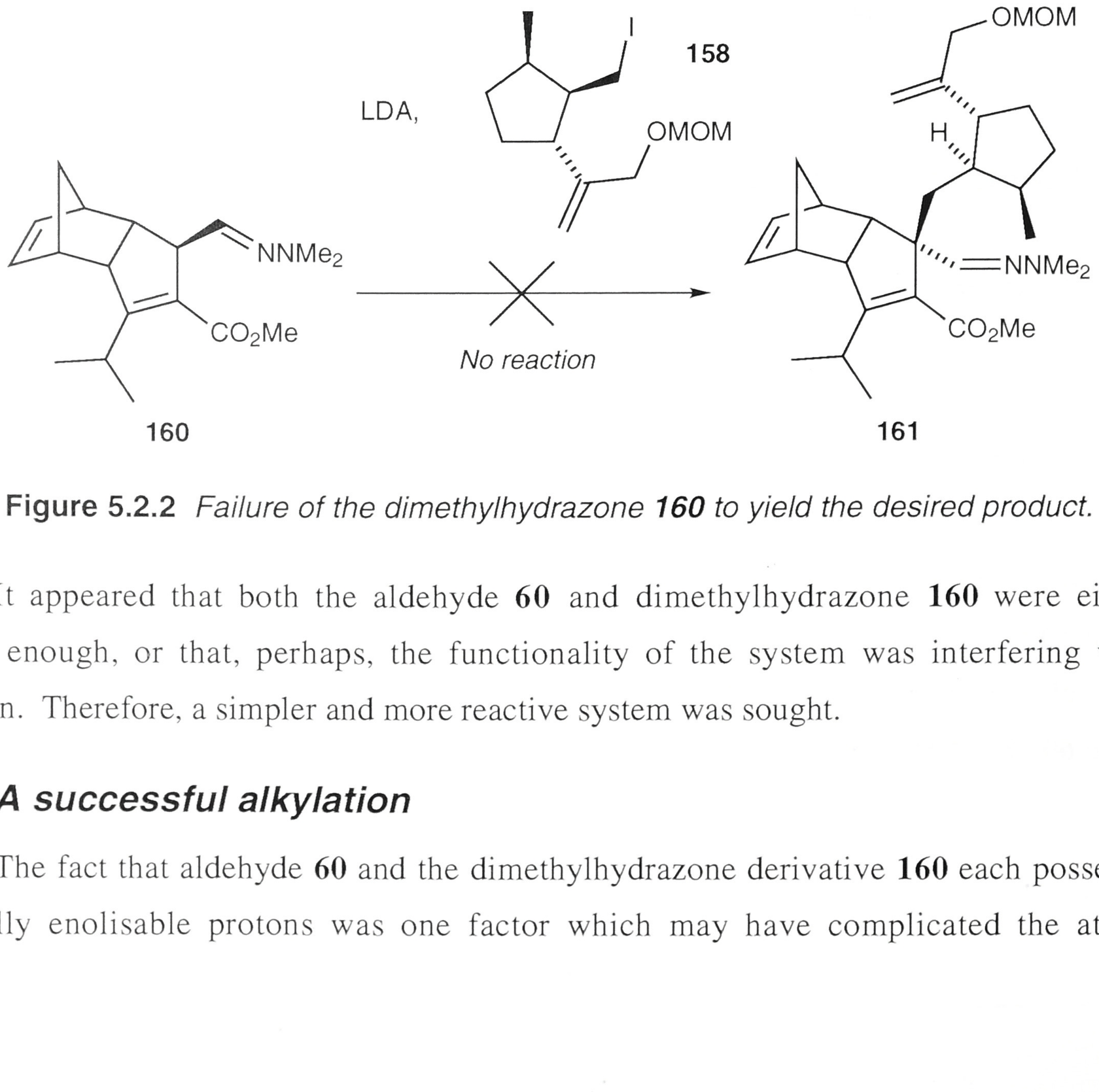


Figure 5.2.2 *Failure of the dimethylhydrazone **160** to yield the desired product.*

It appeared that both the aldehyde **60** and dimethylhydrazone **160** were either not reactive enough, or that, perhaps, the functionality of the system was interfering with the alkylation. Therefore, a simpler and more reactive system was sought.

5.3 A successful alkylation

The fact that aldehyde **60** and the dimethylhydrazone derivative **160** each possess three potentially enolisable protons was one factor which may have complicated the attempted

alkylations. Removal of both the isopropyl substituent and the ester group would give rise to a simplified substrate, of general type **162** (Figure 5.3.1), which might participate in the desired alkylation. Of course, this simplification leads to a less convergent synthesis and necessitates the installation of the remaining functional groups post-alkylation. However, use of the previously developed chemistry for ester and isopropyl group addition (see Chapter Three) should be applicable to this modified approach. With these goals in mind, nitrile **163** seemed to be an obvious candidate for development; nitrile anions are reactive species which readily participate in alkylations[2] and, moreover, cyanide itself is an excellent acyl anion equivalent allowing for a potentially rapid construction of the desired nitrile **163** from enone (–)-**54**.

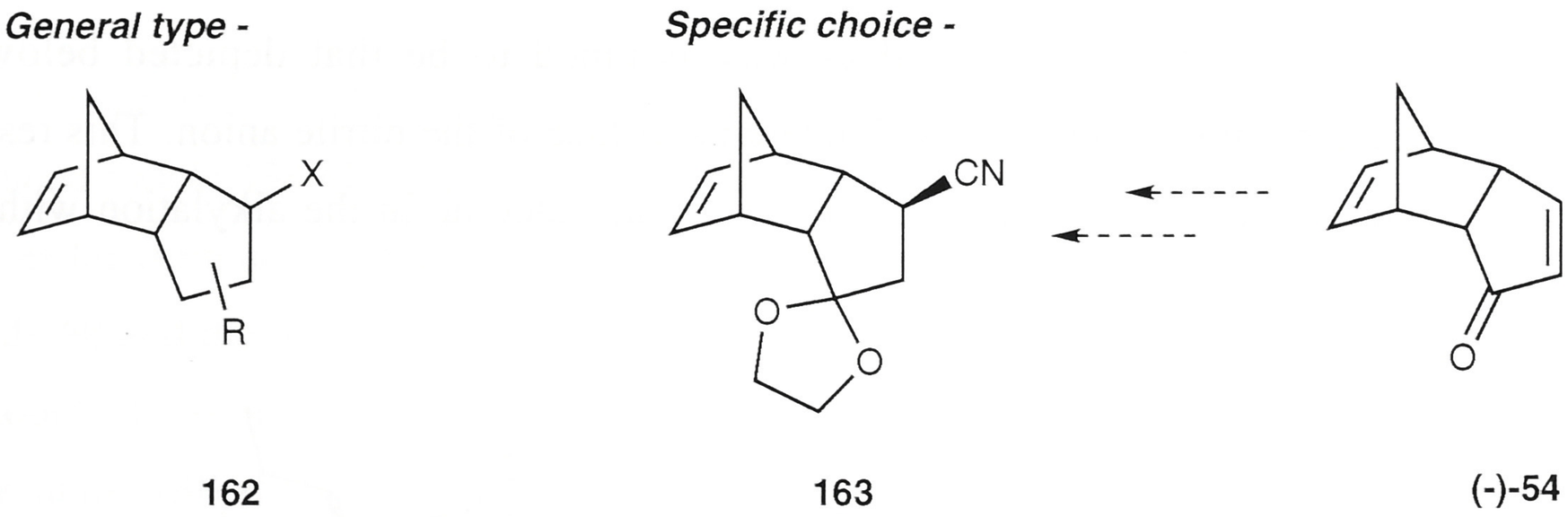


Figure 5.3.1 *Potential simplified alkylation substrates.*

Nitrile **164**, resulting from 1,4-addition of cyanide anion to enone (–)-**54** was easily prepared according to the literature procedure reported for the corresponding racemate.[3] Conversion of **164** to the dioxolane derivative **163** was then achieved using Dowex 50W resin and ethylene glycol (85%, Figure 5.3.2).[4]

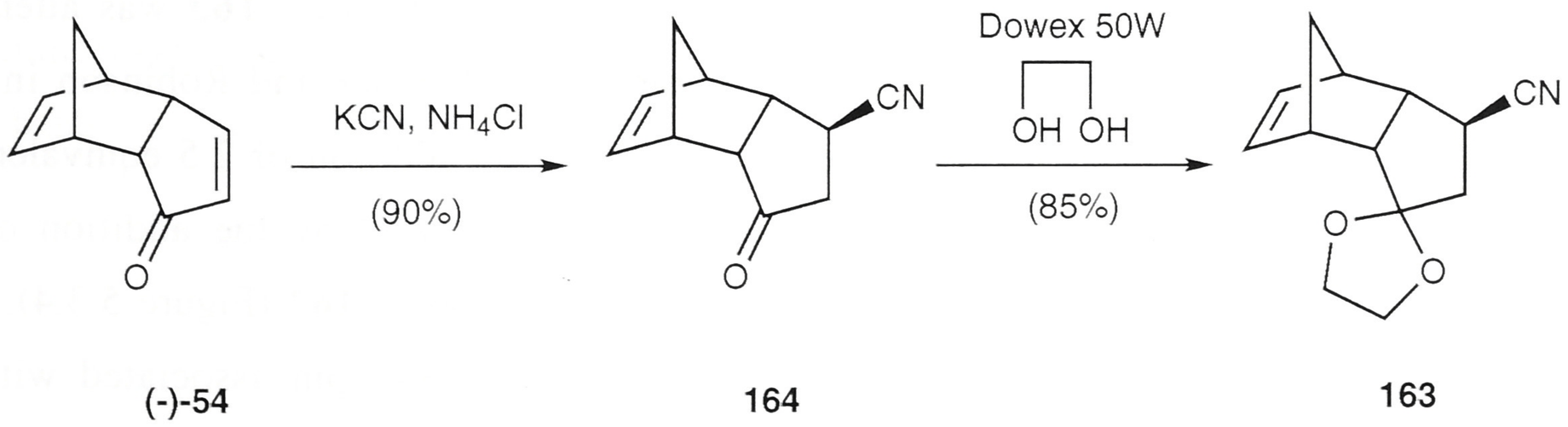
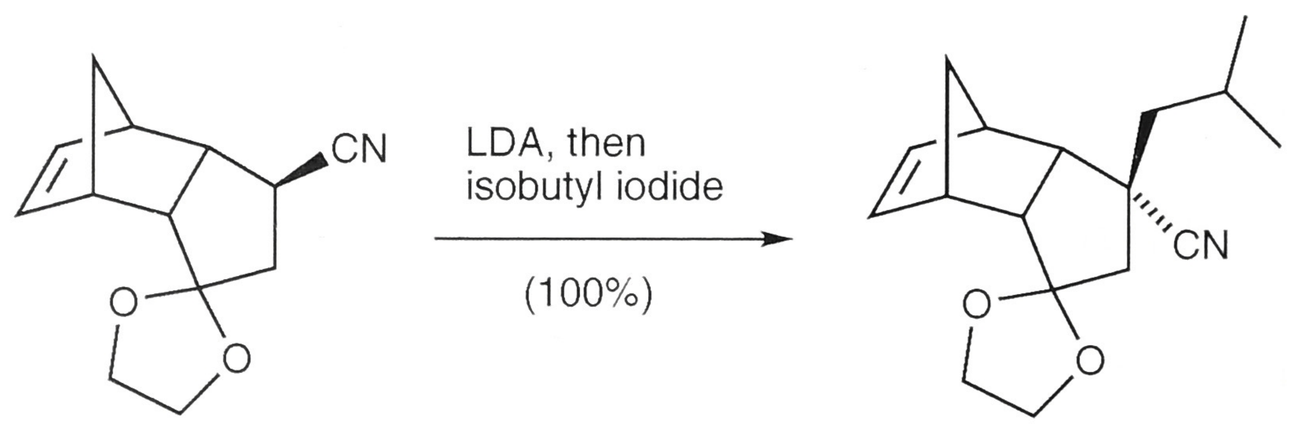


Figure 5.3.2 *Synthesis of the nitrile **163**.*

Key signals in the ^{1}H NMR spectra of nitrile **163** were a resonance at 2.42 ppm corresponding to H1, and a complex multiplet at 3.80-4.00 ppm associated with the dioxolane ring. ^{13}C NMR spectra showed the expected nitrile resonance at 122.6 ppm, and a quaternary carbon signal at 115.6 ppm corresponding to the C3 spiro ketal centre. Further evidence for the formation of **163** was seen in the IR spectra, by the presence of a diagnostic nitrile stretching band at 2231 cm^{-1}.

Alkylation of a racemic sample of nitrile **163** with isobutyl iodide was attempted in order to find suitable conditions for deprotonation, and as a useful guide for the important reaction with iodide **158**. The nitrile **163** in THF was added to a stirred solution of 2.5 equivalents of LDA in THF at –78 °C and allowed to warm to room temperature. After 30 min the reaction mixture was cooled to –78 °C and 2.0 equivalents of isobutyl iodide added. Warming to room temperature and further stirring, afforded the desired alkylated nitrile **165** as a single stereoisomer in essentially quantitative yield (Figure 5.3.3). Confirmation of the product structure was easily achieved by inspection of the ^{1}H NMR spectra, which showed two doublets at 0.99 ppm and 1.03 ppm, respectively, which can be attributed to the diastereotopic methyl groups of the isobutyl substituent.

The stereochemistry of the product was assumed to be that depicted below, with approach of the electrophile from the less hindered *exo*-face of the nitrile anion. This result was by no means interpreted as a guarantee for a successful outcome in the alkylation with iodide **158**, but the excellent yield was encouraging.

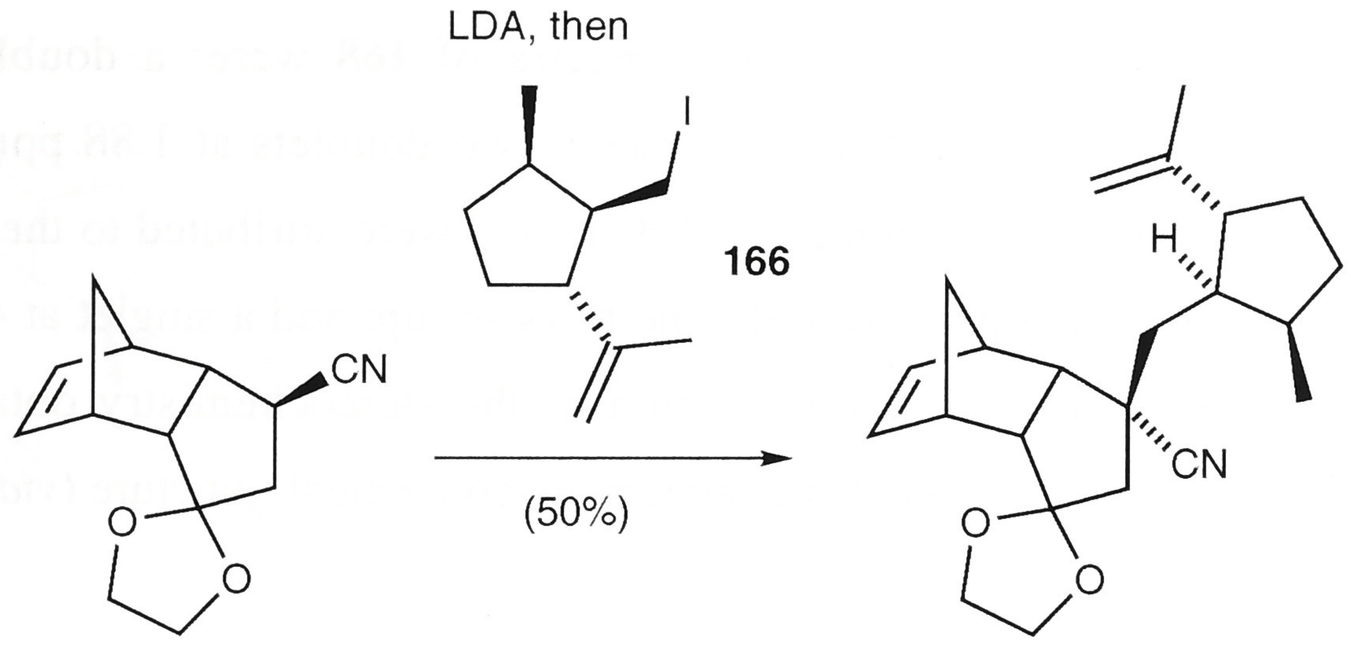


163 **165**

Figure 5.3.3 *Alkylation of nitrile **163** with isobutyl iodide.*

Working now in the enantiopure series, the alkylation of nitrile **163** was attempted using the iodide **166**[5] – which was previously employed by Mander and Robinson in their approach towards sordaricin (**3**) (see Chapter One). Now, the addition of 2.5 equivalents of 1.0 M LDA to a stirred solution of nitrile **163** in THF, followed by the addition of 1.2 equivalents of iodide **166** led to a 50% yield of the desired product **167** (Figure 5.3.4). Key signals in the ^{1}H NMR spectra of **167** were: a doublet at 0.89 ppm associated with the cyclopentane methyl substituent; a broad singlet at 1.72 ppm for the vinyl methyl group; and two singlets at 4.74 ppm and 4.77 ppm corresponding to the terminal olefinic protons of the isopropenyl group.

No attempt was made to optimise this reaction, and instead the alkylation using the fully functionalised iodide **158** was attempted.

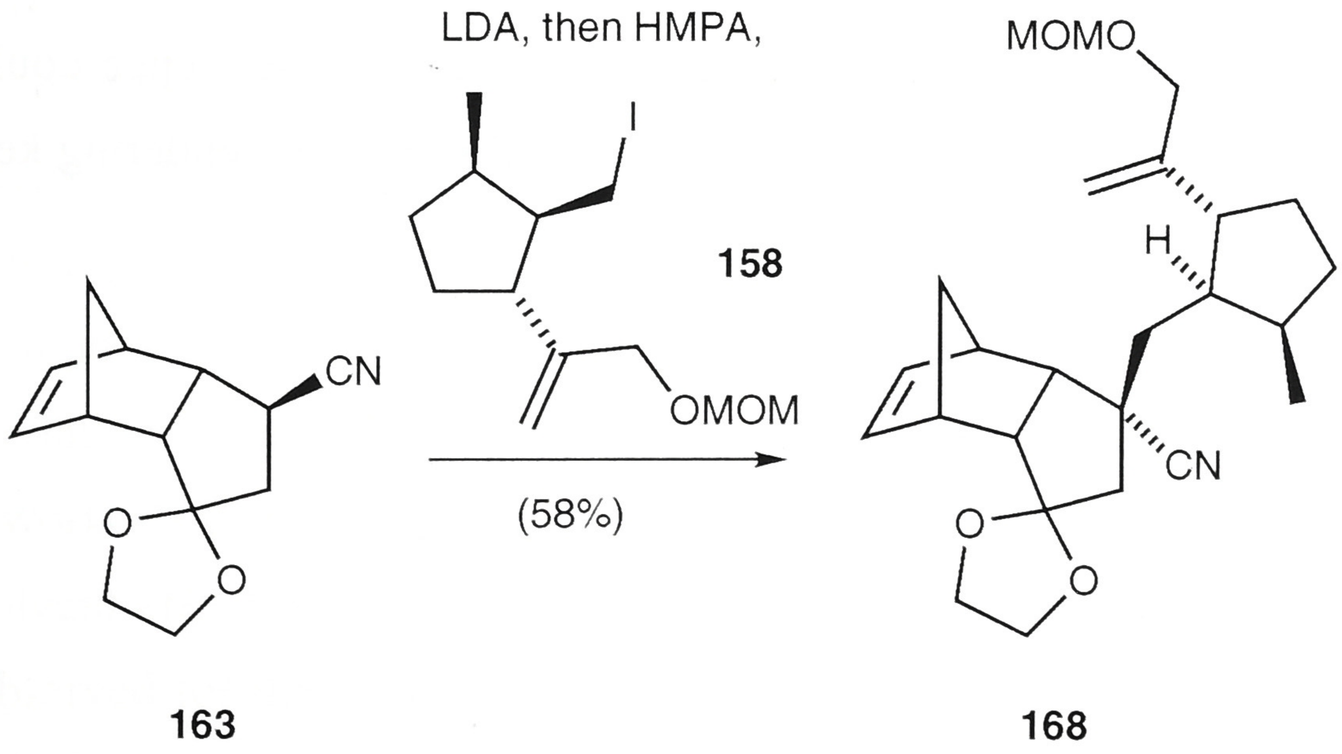


163 167

Figure 5.3.4 *Alkylation of nitrile **163** with iodide **158**.*

Under the conditions described above for the alkylation with iodide **166**, the oxygenated iodide **158** (1.5 equiv) gave only a 40% yield of the desired product. Although this yield was far from acceptable, it was a marked improvement over the previous alkylations using aldehyde **60** and the dimethylhydrazone **160**. This yield may have been improved by increasing the amount of iodide **158** used during the reaction, but this was considered wasteful as, of the two reactants, **158** is more difficult to obtain. The opposite situation, however, where an excess of nitrile **163** would be employed, was seen as a distinct possibility.

After extensive experimentation, a set of reliable conditions was found whereby the desired product **168** could be obtained in yields between 55% and 67% based on iodide consumption (Figure 5.3.6). Most of the unchanged nitrile **163** could be readily recovered during purification on silica gel. Typical conditions are as follows: nitrile **163** (2.0 g, 9.25 mmol) was treated with 1.0 M LDA (2.5 equiv, 23.1 mmol) at –78 °C and allowed to stir at room temperature for 1 h. Cooling to –78 °C followed by the addition of HMPA (1.0 equiv, 9.25 mmol) and iodide **158** (1.5 g, 4.63 mmol) afforded the desired product **168** in 58% isolated yield based on consumed iodide **158**. For the nitrile **163**, the yield was 73%.



163 168

Figure 5.3.6 *Alkylation of nitrile **163** with fully functionalised iodide fragment **158**.*

Key signals present in the 1H NMR spectra of **168** were: a doublet at 0.89 ppm associated with the cyclopentane methyl substituent; two doublets at 1.88 ppm and 2.14 ppm which possessed a large geminal coupling of 13.8 Hz and were attributed to the isolated protons attached to C2; a singlet at 3.38 ppm from the methoxy group; and a singlet at 4.04 ppm clearly derived from the allyloxy protons. Confirmation of the stereochemistry obtained during the alkylation was expected to be confirmed at a later, more convenient, juncture (*vide infra*).

5.4 Elaboration to the tandem cycloreversion/intramolecular [4+2] cycloaddition precursor

5.4.1 Installation of the carboxy group

With an efficient route to the key nitrile **168** now established, efforts focussed on elaborating this intermediate into a suitable precursor for the proposed tandem [4+2] cycloreversion/intramolecular cycloaddition.

First, the nitrile group, which was to become the primary hydroxy group in sordaricin (**3**), would have to be reduced to the appropriate oxidation level and the dioxolane group removed. These transformations were achieved in a straightforward manner (Figure 5.4.1) by initial conversion of **168** into the aldehyde **169** by exposure to DIBAL-H,[6] followed by a mild acidic hydrolysis of the resultant imine with 1.0 M oxalic acid. Use of strongly acidic solutions, such as aqueous H_2SO_4 or aqueous $KHSO_4$, led to facile hydrolysis of the dioxolane protecting group. This outcome may be a consequence of assisted hydrolysis by protonation of the formed aldehyde group. The aldehyde group displayed characteristic chemical shifts of 9.54 ppm and 204.9 ppm in ^{1}H and ^{13}C NMR spectra, respectively.

Next, reduction of the aldehyde **169** to the corresponding alcohol **170** was achieved in excellent yield using $NaBH_4$. Protection of the hydroxy group as a MOM ether was carried out, using the standard conditions of MOMCl, DIPEA and DMAP (cat.)[7] then, liberation of the ketone **172** was achieved using TsOH in acetone.[7] This entire sequence could be carried out without the need for chromatography until after the final step, thus rendering ketone **172** in 90% yield from nitrile **168**.

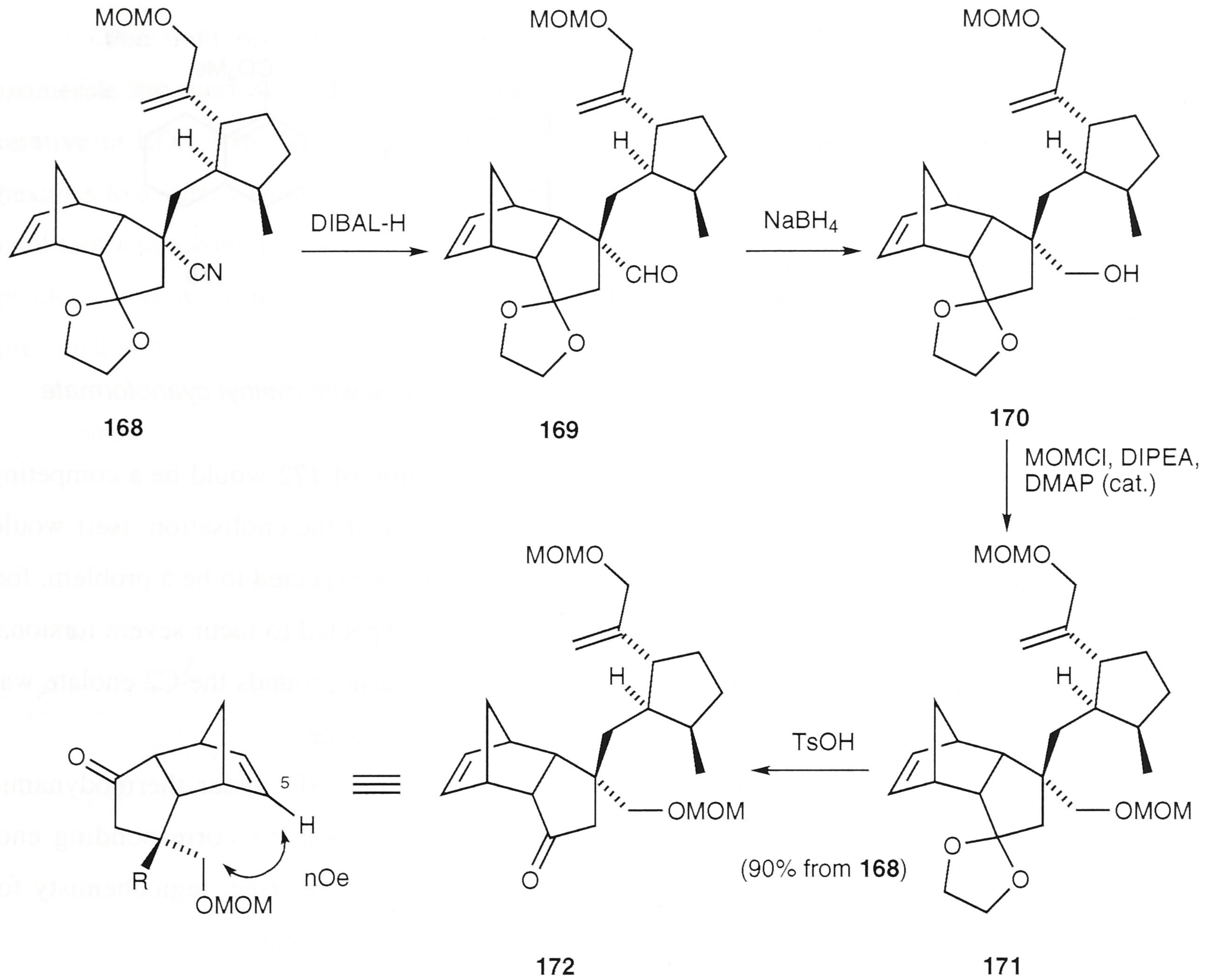


Figure 5.4.1 *Some functional group manipulations and proof of stereochemistry.*

Key signals in the ^{1}H NMR spectra of ketone **172** were: two singlets at 3.36 ppm and 3.39 ppm from the methoxy groups associated with the two MOM protecting groups; an AB doublet at 3.40 ppm from one of the protons attached to the C3 hydroxymethyl substituent; and a singlet at 3.97 ppm corresponding to the allyloxy group. The carbonyl group displayed a characteristic signal at 220.1 ppm in ^{13}C NMR spectra. Also, a 2D NOESY carried out on an Inova 500 spectrometer showed an nOe between H5 and the alkoxymethyl protons, thereby proving the stereochemistry of the earlier alkylation.

The next goal was to install the ester group required at C2. It is well established in the literature that the regiochemistry of the acylation of enolates is highly dependent upon the degree of steric hindrance arising from substituents attached to the β-carbon.[8] For hindered substrates, O-acylation usually becomes a competing process over the desired C-acylation. Mander and co-worker's discovered that the ratio of C *vs.* O-acylated products was profoundly influenced by solvent effects.[8] A pertinent example is seen in the dramatic solvent dependent site switching observed for the acylation of enolate **173** (Figure 5.4.2). By changing the solvent from THF to diethyl ether the ratio of **174**:**175** was effectively reversed.

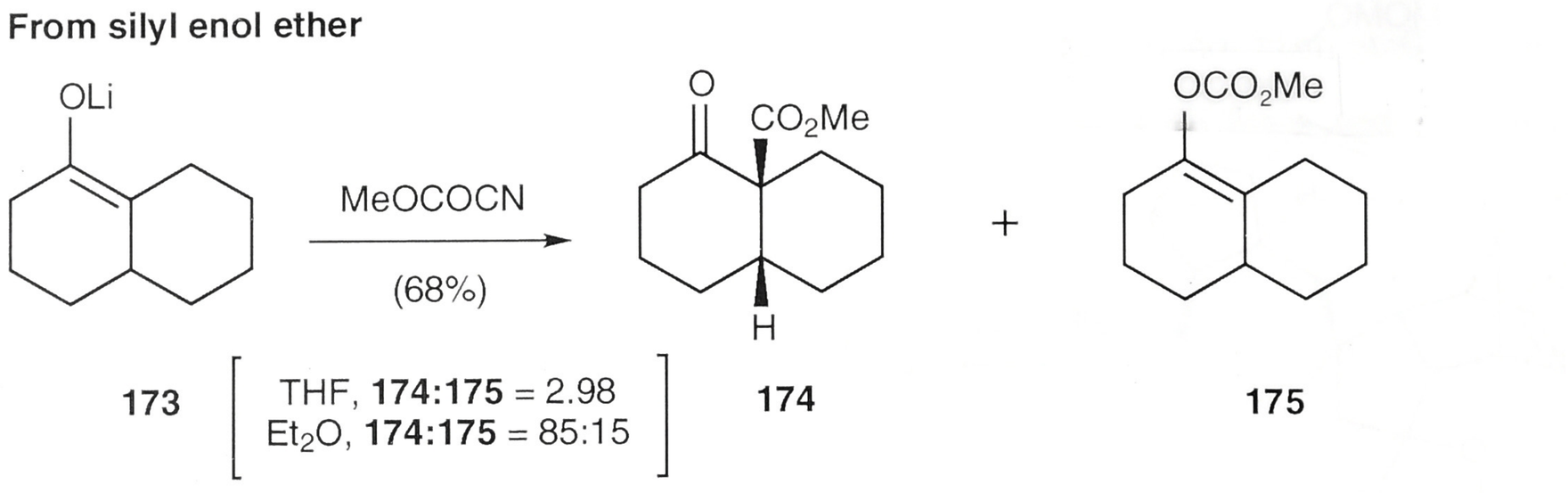


Figure 5.4.2 *Solvent effects in the acylation of lithium enolates with methyl cyanoformate.*

Based on this precedence it was assumed that O-acylation of **172** would be a competing process over the required C-acylation. Also, the regiochemistry of the enolisation itself would have to be addressed. Formation of the undesired enolate was not expected to be a problem, for, as discussed in Chapter Three, removal of the H7a proton was expected to incur severe torsional strain, leading to decreased acidity of H7a relative to H2. On these grounds the C2 enolate was also expected to be more thermodynamically stable than the C7a enolate.

As expected, treatment of **172** with 1.0 M NaHMDS in THF, under thermodynamic conditions, did not give the β–keto ester **177** but, instead, afforded the corresponding enol carbonate **176** (Figure 5.4.3). Although this product possessed the incorrect regiochemisty for the acylation, it did indicate that enolisation had occurred in the desired sense.

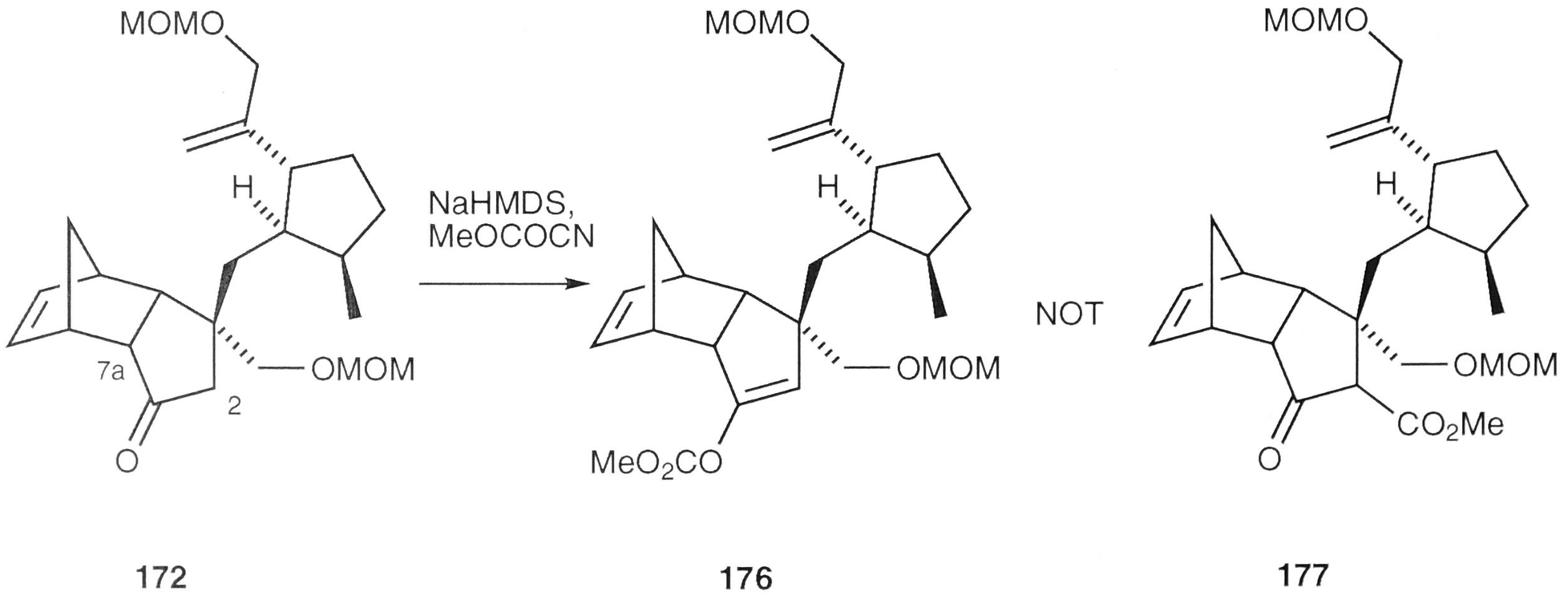


Figure 5.4.3 *The correct regiochemistry of enolisation with the* incorrect *regiochemistry of acylation.*

The logical solution to this problem was to use diethyl ether as the solvent. Accordingly, the acylation was attempted using LDA and methyl cyanoformate in diethyl ether, but it was discovered that at low temperatures (-78 °C) enolisation was slow and the reaction did not go to completion even with a large excess of LDA (5 equivalents). Allowing the enolisation to occur at room temperature led to the isomerisation of the allylic ether group into a vinyl ether group.

The next base of choice was LiHMDS, which was expected to be less likely to isomerise the methylene double bond in **172** due to its increased bulk and decreased basicity relative to LDA.† Initially, addition of a large excess (up to 5 equivalents) of 1.0 LiHMDS in hexanes to a stirred solution of ketone **172** in diethyl ether gave low yields of the ester **178** (only enol tautomer observed), with the major product being the silyl enol ether **179**. This unexpected product was assumed to be formed by removal of a TMS group from the amide base, presumably by the mechanism outlined below (Figure 5.4.4).

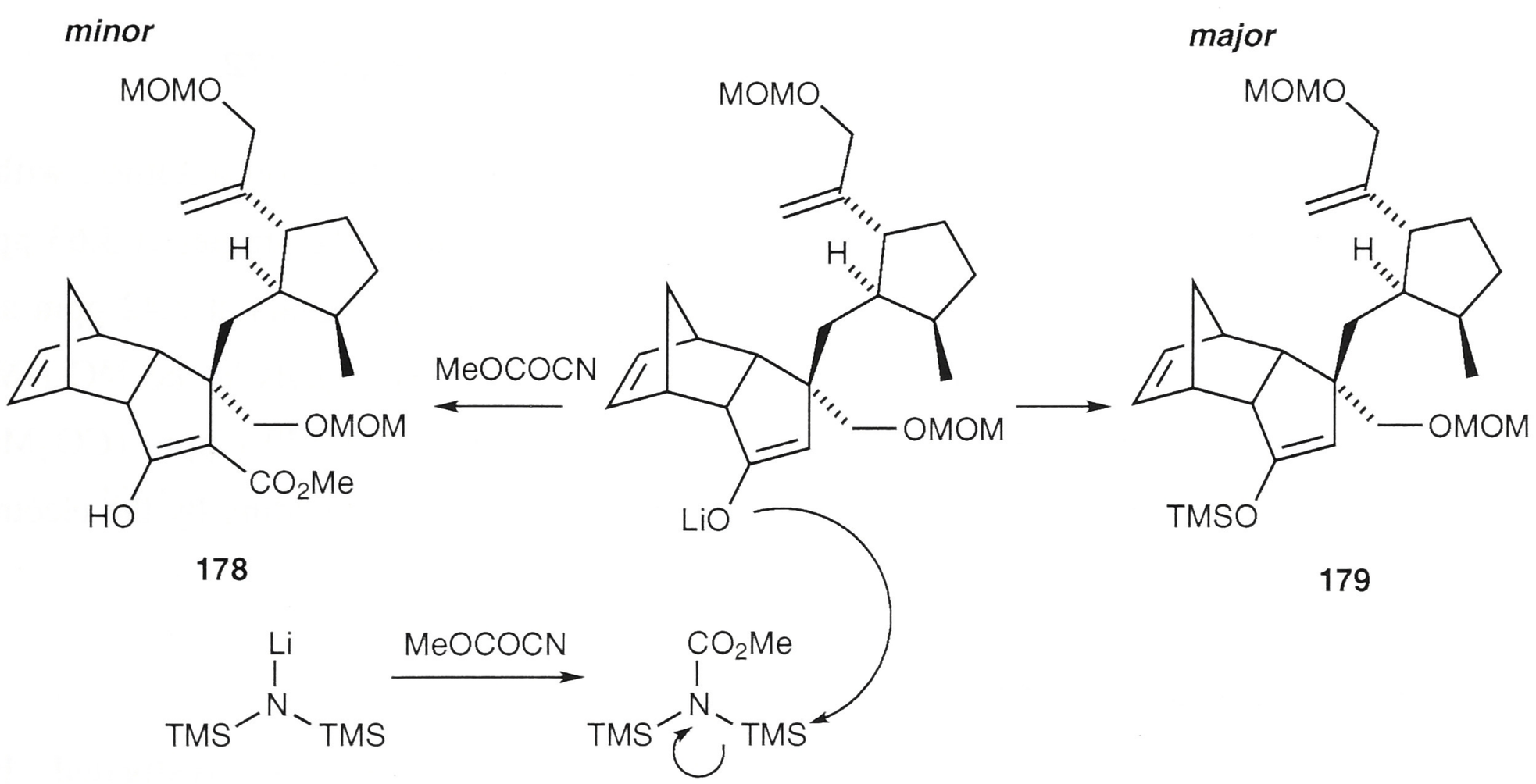


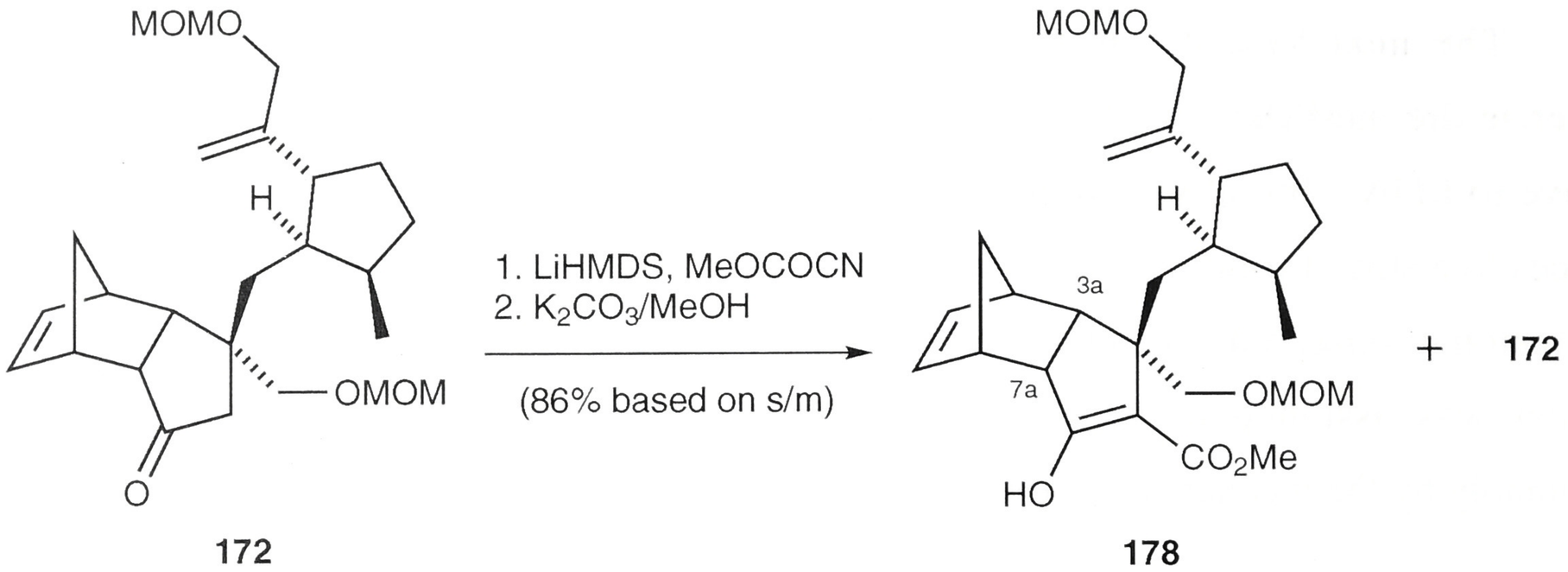
Figure 5.4.4 *Possible mechanism for the formation of silyl enol ether **179**.*

The use of a large excess of LiHMDS was considered necessary to ensure complete enolisation of the very hindered ketone **172**, but extensive experimentation showed that as little as 1.5 equivalents were needed if the reaction mixture was allowed to stir for 3 h at room temperature* before the addition of methyl cyanoformate. Still, these optimised conditions did not remove **179** completely, and also the formation of enol carbonate **176** was still occurring, although to a lesser extent (6:1 C:O). An isolated yield of 53% of **178** could, however, be obtained when this mixture was purified by chromatography. The unwanted by-products could then be recycled by hydrolysis back to **172** using K_2CO_3/MeOH. Ultimately, the crude mixture of all three products was exposed to K_2CO_3/MeOH before chromatography, and in this manner an 86% yield of **178** could be obtained, based on recovered ketone **172** (Figure 5.4.5).

---

† pKa values in DMSO: iPr$_2$NH = 36; TMS$_2$NH = 30.

* No isomerisation of the double bond was observed under these conditions.



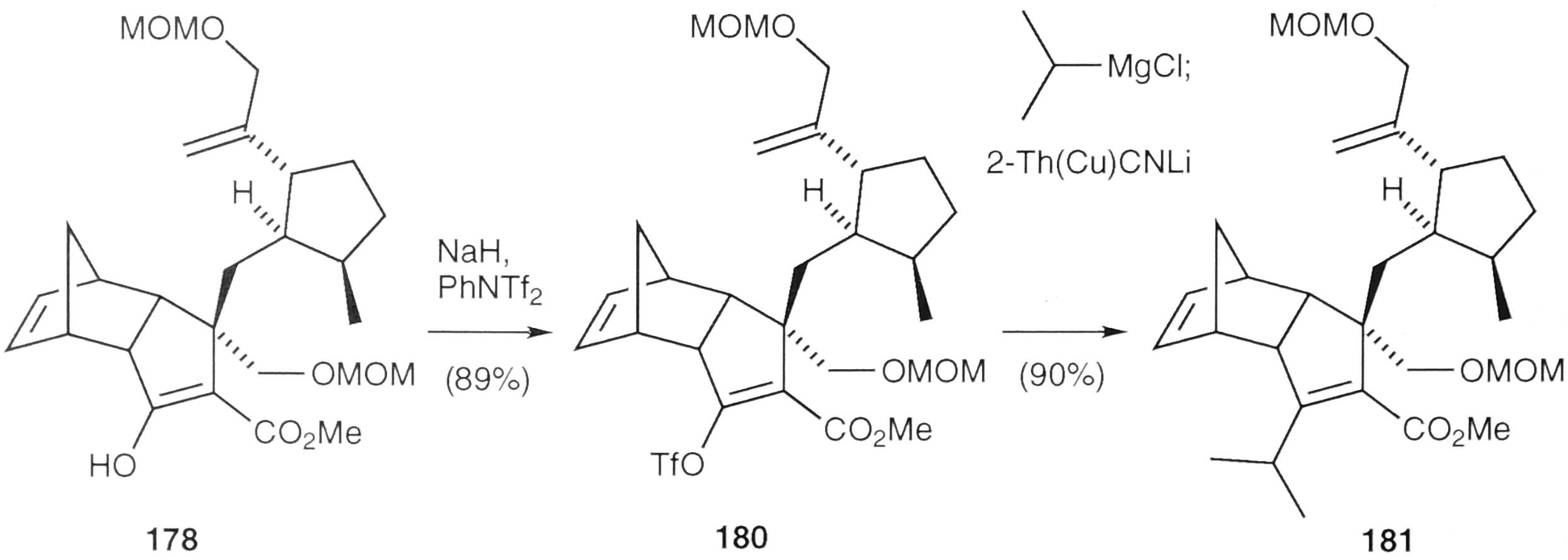
172 **178**

Figure 5.4.5 *Optimised conditions for the acylation of ketone* ***172****.*

As seen from its ^{1}H NMR spectra, ester **178** exists only as the enol tautomer, with a diagnostic enol OH resonance at 10.96 ppm. Other key signals were the singlet at 3.63 ppm corresponding to the methoxy group of the ester, and the presence of signals at 2.42 ppm and 3.34 ppm, which were attributed to H7a and H3a respectively. Key signals in the ^{13}C NMR spectra of compound **178** were: 104.5 ppm (C2), 170.5 ppm (C3) and 179.1 ppm (CO_2Me). The upfield chemical shift of C2 is typical of enols, due to significant shielding by the electron donating hydroxy substituent at C3.

5.4.2 Installation of the isopropyl group

With ester **178** now in hand, installation of the isopropyl group was investigated. For this task, it was envisaged that an equivalent sequence to that used for the synthesis of aldehyde **60** could be used (see Chapter Three). Accordingly, conversion of **178** to the enol triflate **180** was achieved in high yield (89%) using NaH and *N*-phenyltrifluoromethanesulfonimide (Figure 5.4.6).[9] 1,4-addition of the cuprate derived from isopropylmagnesium chloride and 2-thienyl(cyano)copper lithium (2-ThCu(CN)Li)[10] then gave the required isopropyl substituted ester **181** in excellent yield (90%).



178 **180** **181**

Figure 5.4.6 *Installation of the isopropyl group.*

The addition of the isopropyl group was clearly seen by inspection of the ^{1}H NMR spectra which displayed two doublets associated with the diastereotopic methyl groups (1.06 ppm and 1.10 ppm) and a downfield septet (3.17 ppm) corresponding to the isopropyl methine proton.

5.4.3 Synthesis of the precursor for the tandem cycloreversion/intramolecular [4+2] cycloaddition

To complete the synthesis of the precursor **64** for the tandem [4+2] cycloreversion/intramolecular cycloaddition, it was necessary to remove the MOM groups and for the resulting allylic alcohol function to be selectively oxidised. Removal of both MOM groups in **181** was readily achieved in high yield (92%) by stirring for 24 h with $MgBr_2.Et_2O$ and 1-butanethiol.[11] Next, selective oxidation of the allylic alcohol in diol **182** was performed using MnO_2 in diethyl ether[12] to afford pure aldehyde **64** after filtration and removal of the solvent (Figure 5.4.7).

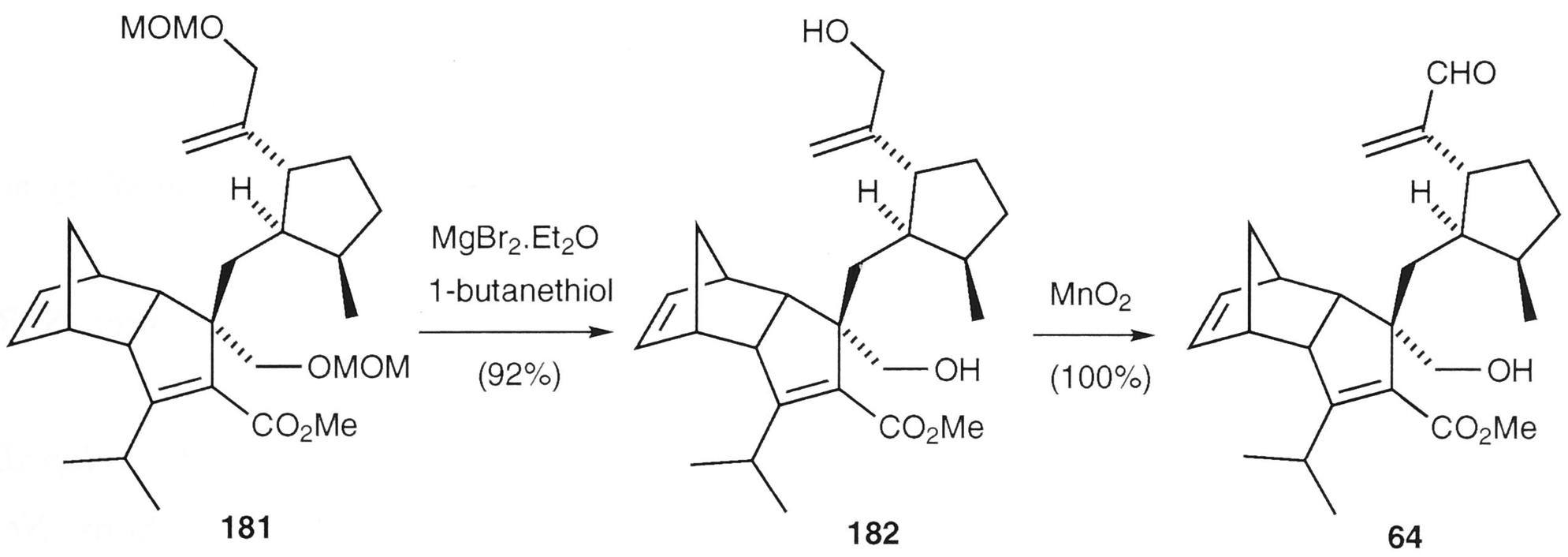


Figure 5.4.7 *Synthesis of the key aldehyde **64**.*

The formation of aldehyde **64** was clearly shown by inspection of the ^{1}H NMR spectra, which displayed a singlet at 9.43 ppm corresponding to the aldehyde proton. The downfield shift of the terminal olefinic protons from 4.78 ppm and 5.03 ppm for diol **182**, to 5.88 ppm and 6.15 ppm for the aldehyde **64** clearly indicated that the allylic hydroxy group in **182** had be oxidised. The selectivity for this oxidation was further confirmed by both the presence of a broad OH resonance in the ^{1}H NMR spectra and a broad absorption at 3467 cm^{-1} in the IR spectra. The ^{13}C NMR spectra also served to confirm these assignments, displaying a resonance at 194.3 ppm, which is typical for α,β–unsaturated aldehydes.

5.5 Summary

Details of the unsuccessful attempts to alkylate the aldehyde **60** and dimethylhydrazone **160** with iodide **158** have been provided in this chapter, as well as the development of a

successful alkylation strategy utilising nitrile **163**. Alkylated nitrile **168** was elaborated to the key aldehyde **64**, the precursor for the tandem cycloreversion/intramolecular cycloaddition.

The following chapter will discuss further research efforts that resulted in the completion of a total synthesis of sordaricin (**3**).

5.6 References

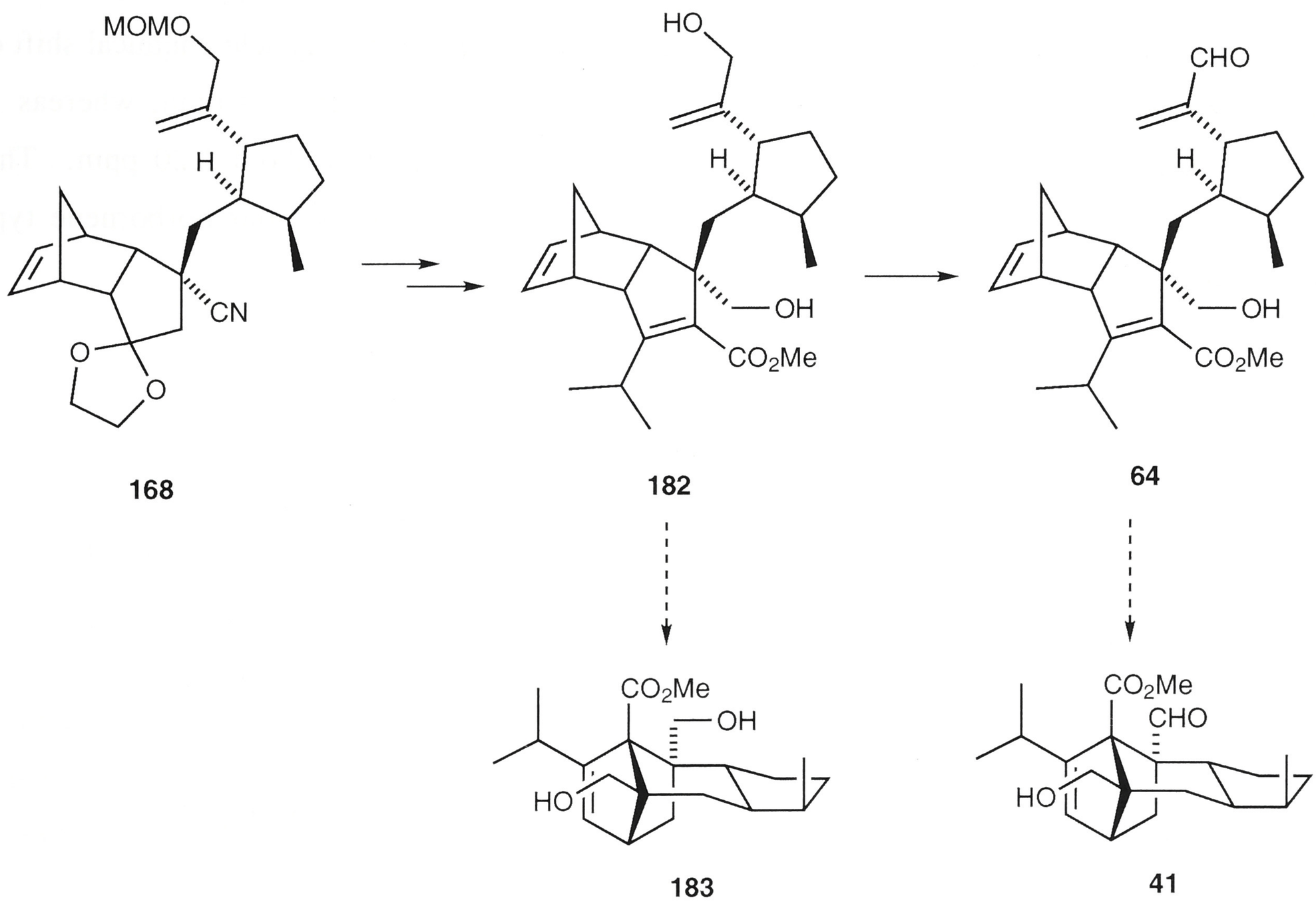
1. Chelucci, G.; Cossu, S.; Scano, G.; Soccolini, F. *Heterocycles* **1990**, *31*, 1397.
2. For a review on the reaction of nitrile stabilised carbanions, see: Arseniyadis, S.; Kyler, K. S. *Org. React.* **1984**, *31*, 1.
3. Bugel, J. P.; Ducos, P.; Gringore, O.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1972**, 4371. For an alternative synthesis of **164**, see: Zhiyu, L.; Shi, W.; Zhang, L. *Synthesis* **1990**, 235.
4. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley and Sons: New York, **1991** and references cited therein.
5. Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595.
6. Marshall, J. A.; Andersen, N. H.; Schlicher, J. W. *J. Org. Chem.* **1970**, *35*, 858.
7. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, John Wiley and Sons: New York, **1991** and references cited therein.
8. (a) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, 169. (b) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256.
9. Houpis, I. N. *Tetrahedron Lett.* **1991**, *32*, 6675. See also: Zeller, W. E. in *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 4096 and references cited therein.
10. Lipshultz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945
11. Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett.* **1991**, 183.
12. Babler, J. H.; Martin, M. J. *J. Org. Chem.* **1977**, *42*, 1799. MnO_2 (<5 micron, activated, ~85%) purchased from Aldrich Chemical Company was used without further purification or activation.

Chapter Six

Total Synthesis of Sordaricin

6.1 Introduction

The previous chapter described a successful alkylation strategy which led to nitrile **168**. Elaboration of **168** to the key intermediate **64** for the proposed sequential cycloreversion/intramolecular [4+2] cycloaddtion was also detailed. This chapter discusses the outcome of the planned sequence for compounds **182** and **64**. The development of a superior alternative reaction sequence leading to sordaricin (**3**) is also detailed.



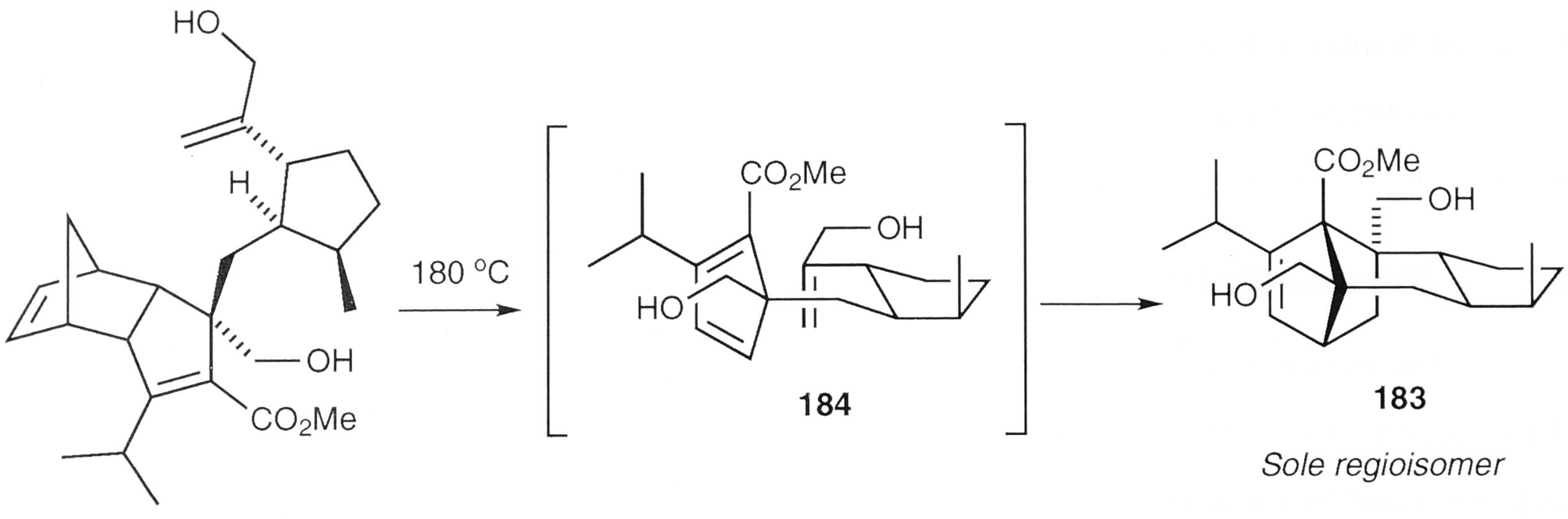
168 **182** **64**

183 **41**

6.2 Sequential cycloreversion/intramolecular [4+2] cycloaddtions

6.2.1 The diol

As a prelude to the key sequential cycloreversion/intramolecular [4+2] cycloaddition to be carried out on aldehyde **64**, the diol **182** was subjected to heating at 180 °C in dichlorobenzene. After 3 h, all starting material had been consumed and diol **183** was obtained as a single regioisomer in 64% yield (Figure 6.2.1). Diol **183** displayed identical ^{1}H and ^{13}C NMR spectra to those of an authentic sample derived by reduction ($NaBH_4$) of sordaricin methyl ester (**41**).[1]

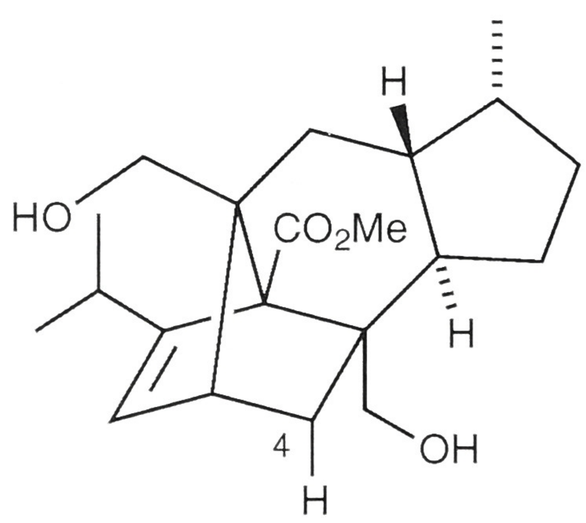


182 **184** **183**

Sole regioisomer

Figure 6.2.1 *Formation of Diol **183**.*

An interesting aspect of the ^{1}H NMR spectra of diol **183** is the upfield chemical shift of *endo*-H4 (Figure 6.2.2). In **183** this proton occurs as a doublet at 0.20 ppm, whereas in sordaricin methyl ester (**41**) it is shifted downfield and obscured at about 1.20 ppm. This chemical shift is consistent with data reported in the literature on similar norbornene type compounds.[2]



183

endo-H4 - 0.20 ppm

Figure 6.2.2 *Diol **183** – the unusual chemical shift of* endo*-H4.*

6.2.2 The aldehyde

Having achieved the successful conversion of diol **182** to **183**, the key aldehyde **64** was subjected to heating at 180 °C in dichlorobenzene (Figure 6.2.3). In this instance the reaction time was shorter (1 h), and the formation of what appeared to be one compound was observed by TLC of the reaction mixture. Subjection of the purified material (76% yield) to ^{1}H NMR spectroscopy revealed the presence of *two* compounds in a ratio of about 4:1.* Key signals for the major product were a singlet at 9.64 ppm and a multiplet at 6.08 ppm, which correspond to H17 (CHO) and H2 (=CH) in sordaricin methyl ester (**41**), as proven by comparison with an

* Increased reaction times gave a lower ratio of the two products.

authentic sample derived from natural sordaricin.[1] The minor compound showed a singlet at 9.54 ppm corresponding to an aldehyde resonance, and a multiplet at 5.55 ppm which appeared to be an olefinic resonance. It appeared that the minor product was that resulting from the alternate regiochemistry in the intramolecular [4+2] cycloaddition, *i.e. iso*-**41**.

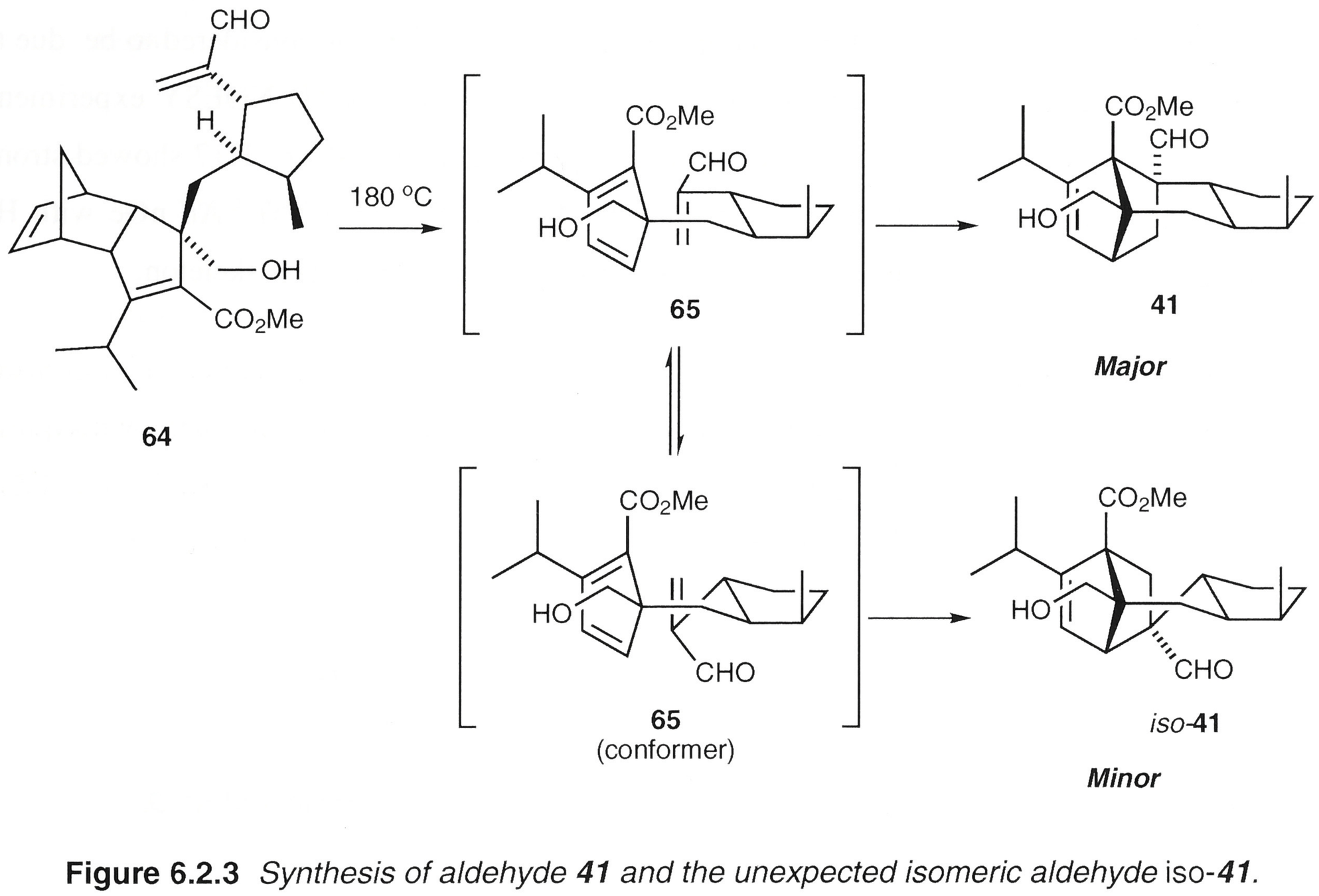


Figure 6.2.3 *Synthesis of aldehyde* ***41*** *and the unexpected isomeric aldehyde* iso-***41***.

The methyl esters were inseparable by HPLC, so a 1:1 mixture was converted into the corresponding free acids in order to facilitate separation. Demethylation could be achieved easily by the use of propanethiolate in HMPA,[3] to afford the free acids (Figure 6.2.4). Semi-preparative HPLC then gave the pure acids, **3** (38%) and *iso*-**3** (25%).

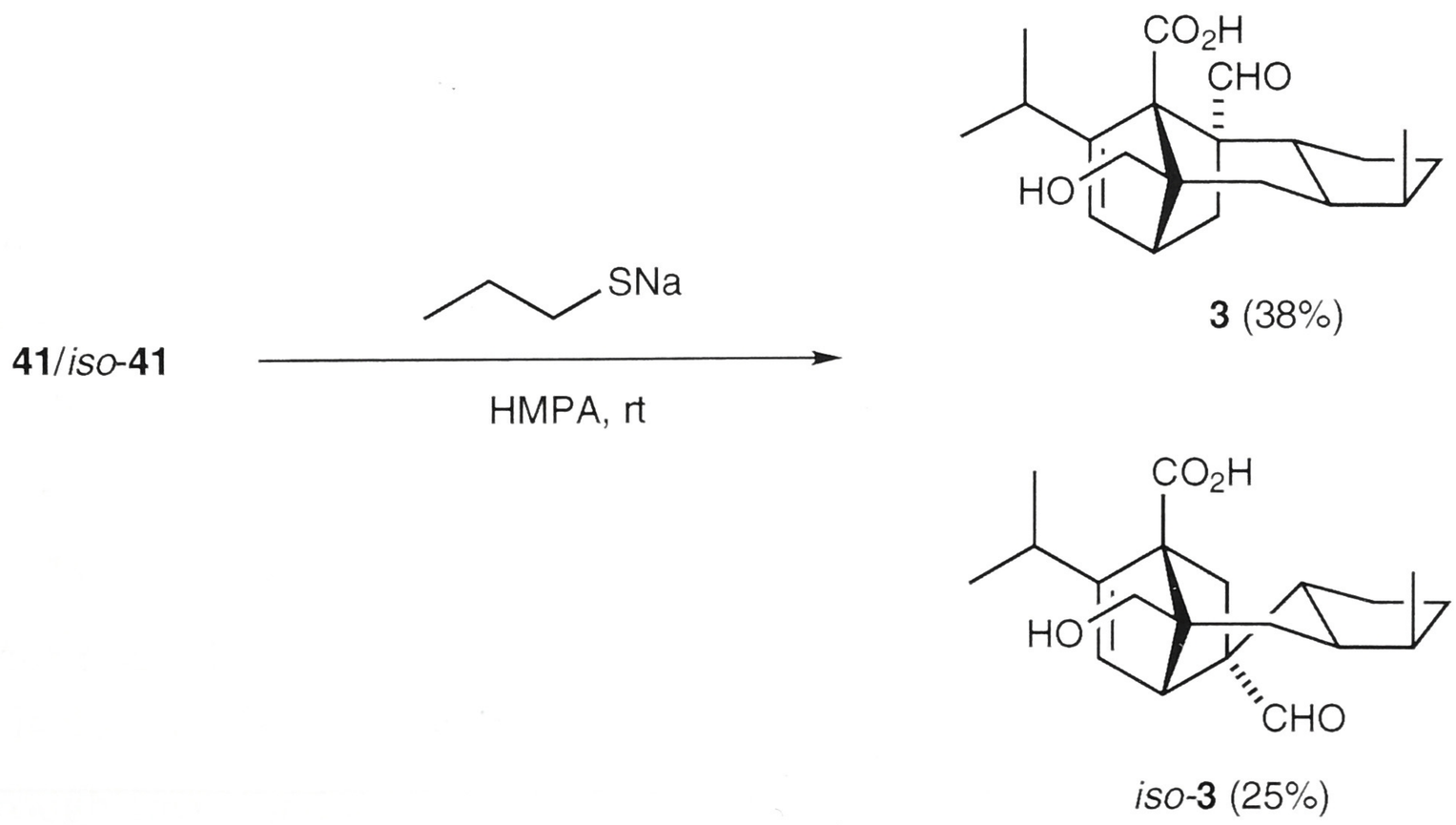


Figure 6.2.4 Preparation of sordaricin (**3**) and iso-sordaricin (iso-**3**).

The spectra of synthetic sordaricin (**3**) were identical in all respects to those of an authentic sample.*

Confirmation of the structure of *iso*-**3** was achieved using a combination of NMR spectroscopy techniques. The first piece of evidence was seen by the presence of an AB spin system due to the now isolated protons on C5 (2.49 and 2.84 ppm, J = 12.7 Hz). Also, H2 is shifted upfield from 6.13 ppm in **3**, to 5.68 ppm in *iso*-**3**. This shift was considered to be due to the close proximity of the aldehyde group, which was verified by a 1D NOESY experiment, carried out using a Varian Inova 600 spectrometer, operating at 600 MHz. H17 showed strong reciprocal nOe signals with H2 and, more importantly, H3 (Figure 6.2.5). An nOe with H3 would clearly not occur if the compound still possessed the sordaricin carbon skeleton.

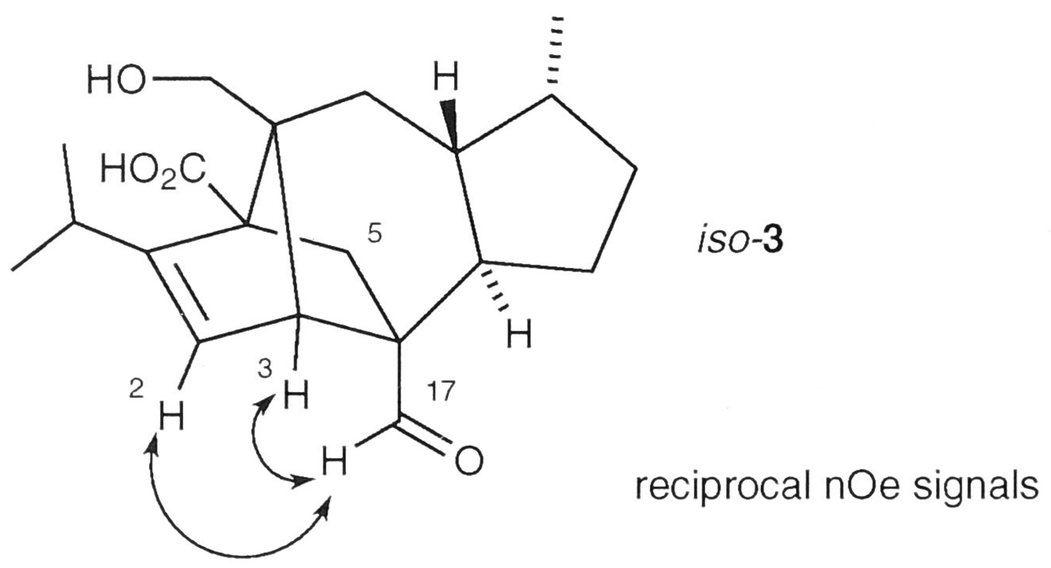


Figure 6.2.5 *Key nOe signals allowing the structural assignment of* iso-***3.***

Based on the work described by Kato and co-worker's[4] formation of *iso*-**41** was unexpected. During their total synthesis of sordaricin methyl ester (**41**), Kato and co-worker's reported the generation of aldehyde **185**, by a Saegusa oxidation of enol ether **39**. In this case, the aldehyde was not isolated, but instead underwent the desired intramolecular [4+2] cycloaddition over 3 days in benzene at 40 °C (Figure 6.2.6). The paper makes no reference to any other product(s) being formed during the reaction sequence.

---

* The author wishes to thank Dr. J. Balkovec of Merck Laboratories for the kind donation of 1 g of pure natural sordaricin (**3**).

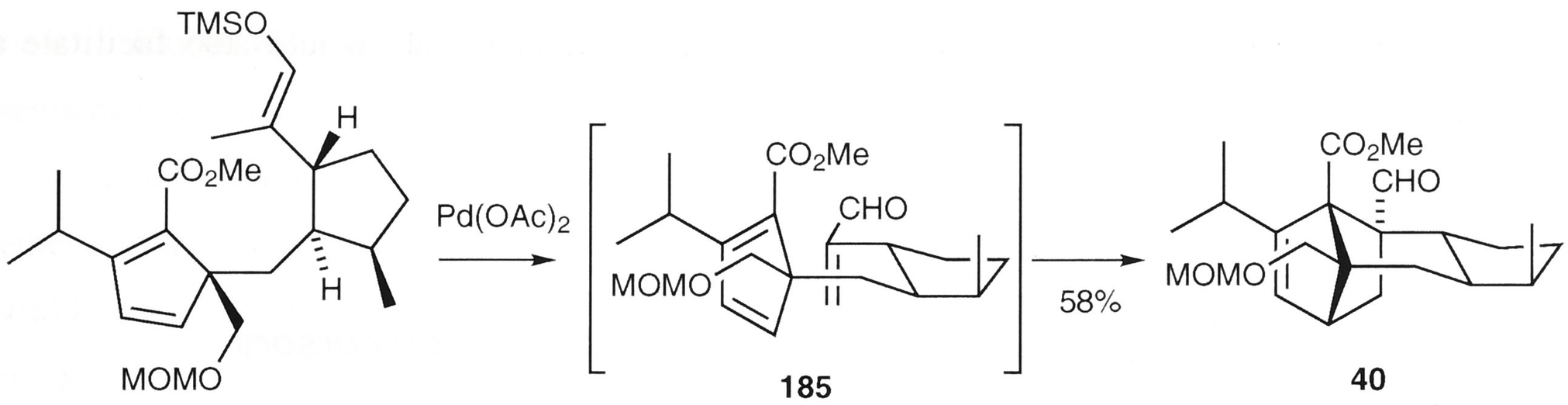


Figure 6.2.6 *Kato and co-worker's intramolecular [4+2] cycloaddition.*

These results were consistent with those reported by Mander and Robinson[5] during their model studies towards sordaricin (**3**), in which intramolecular [4+2] cycloaddition of compounds **186** and **24** gave only the desired regioisomers, **187** and **25** respectively (Figure 6.2.7).

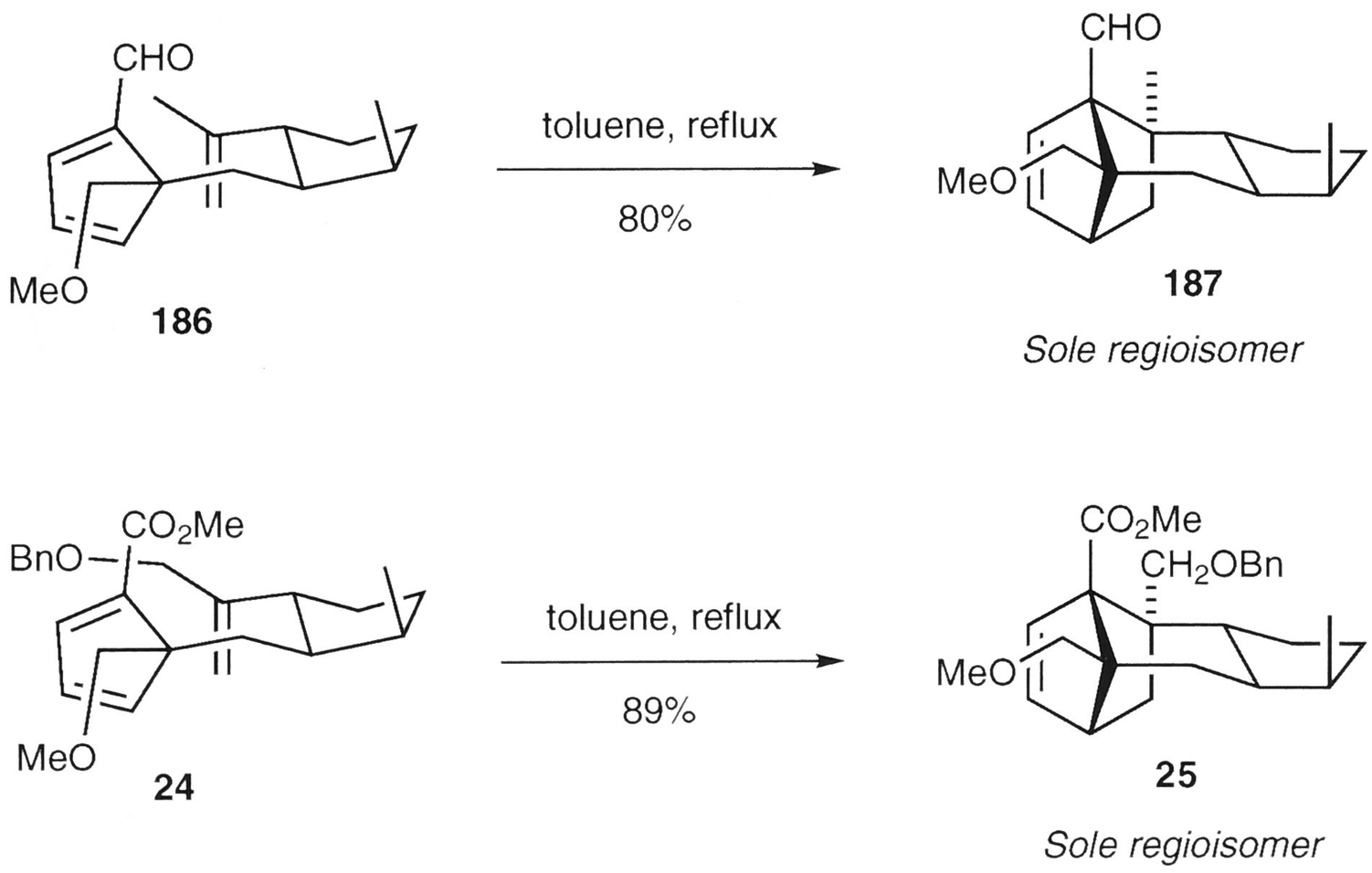


Figure 6.2.7 *Mander and Robinson's model [intramolecular [4+2] cycloadditions.*

Clearly, for this work, it would be desirable to isolate the intermediates **184** and **65** formed after the initial cycloreversion, and carry out the intramolecular [4+2] cycloaddition as a separate step under milder conditions. Unfortunately, due to the high temperature necessary to effect the cycloreversion of **182** and **64**, the respective intermediates **184** and **65** could not be isolated. In order to circumvent this problem, an alternative sequence was developed which would allow the generation of the 'intermediates' **184** and **65** under conditions that would permit their isolation. This would give confirmation of Kato and co-worker's results and enable a more thorough investigation into the intramolecular [4+2] cycloaddition. If the sordaricin

skeleton could be formed selectively over the isomeric skeleton, this would also facilitate a more efficient total synthesis.

6.3 An alternative reaction sequence

6.3.1 Synthesis of the intramolecular [4+2] cycloaddtion precursors

An alternative synthesis that would allow for the isolation and study of **184** and **65** was introduced in Chapter Two, Section 2.3.2. In this approach, ketone **172** was to be subjected to the conditions of cycloreversion and the resulting enone **188** elaborated into the target compounds (Figure 6.3.1).

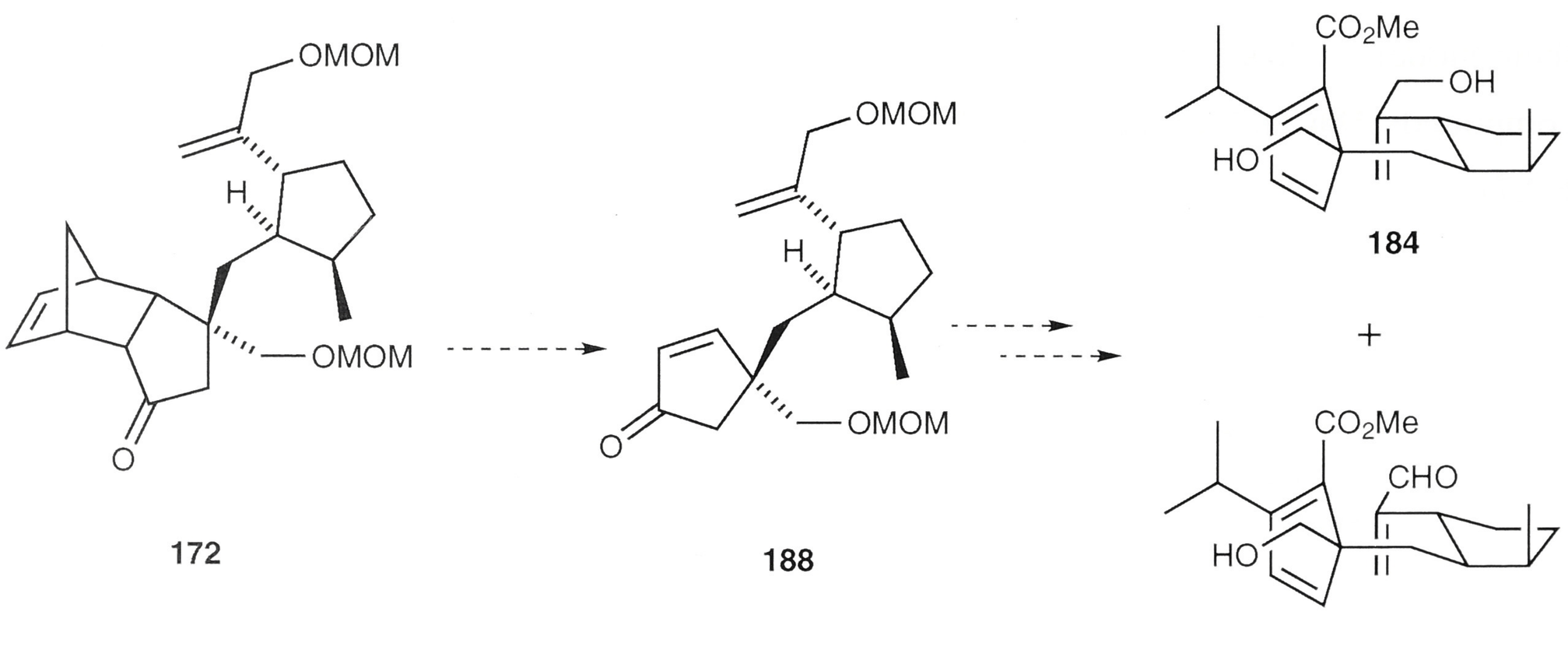


Figure 6.3.1 *Alternative reaction sequence.*

Thus, heating of ketone **172** at 180 °C in 1,2-dichlorobenzene under a stream of nitrogen for 24 hours led to the formation of the desired enone **188** in quantitative yield (Figure 6.3.2).

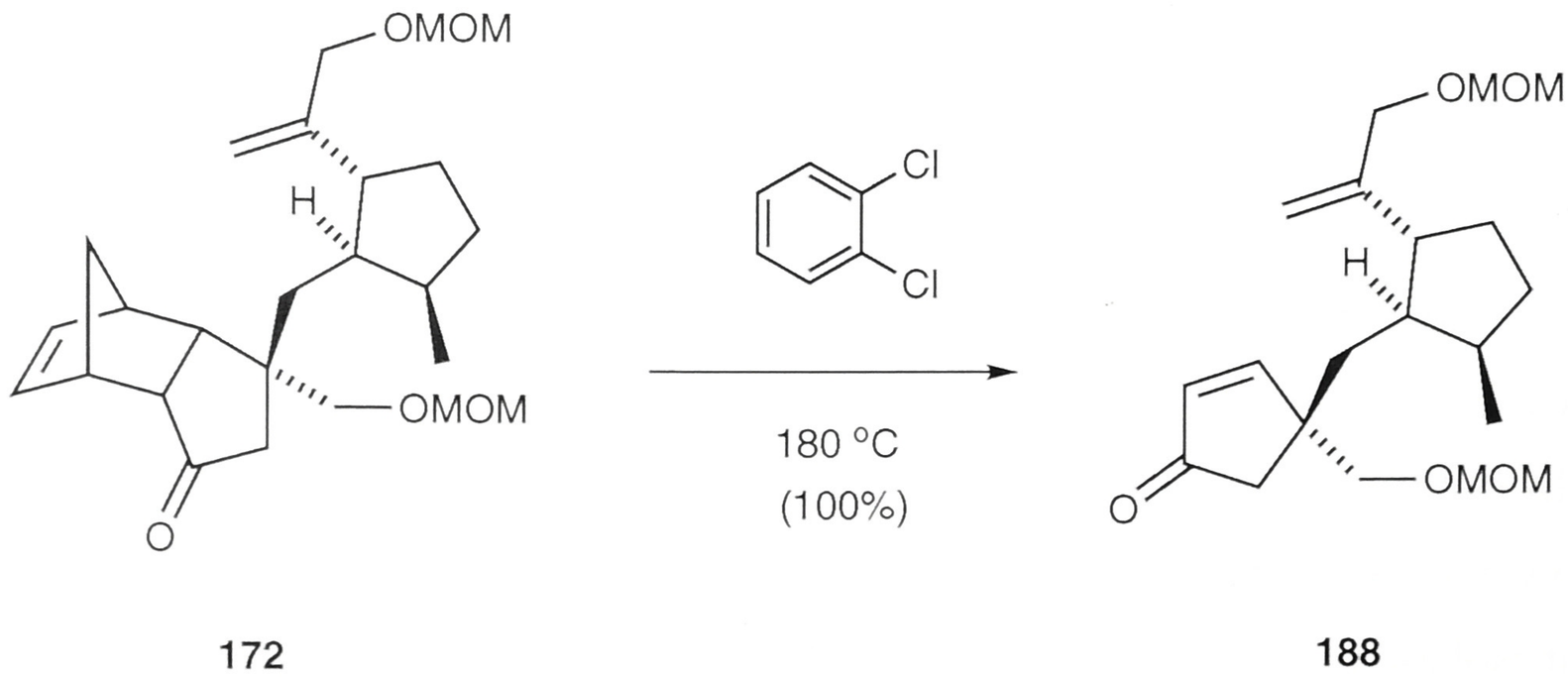
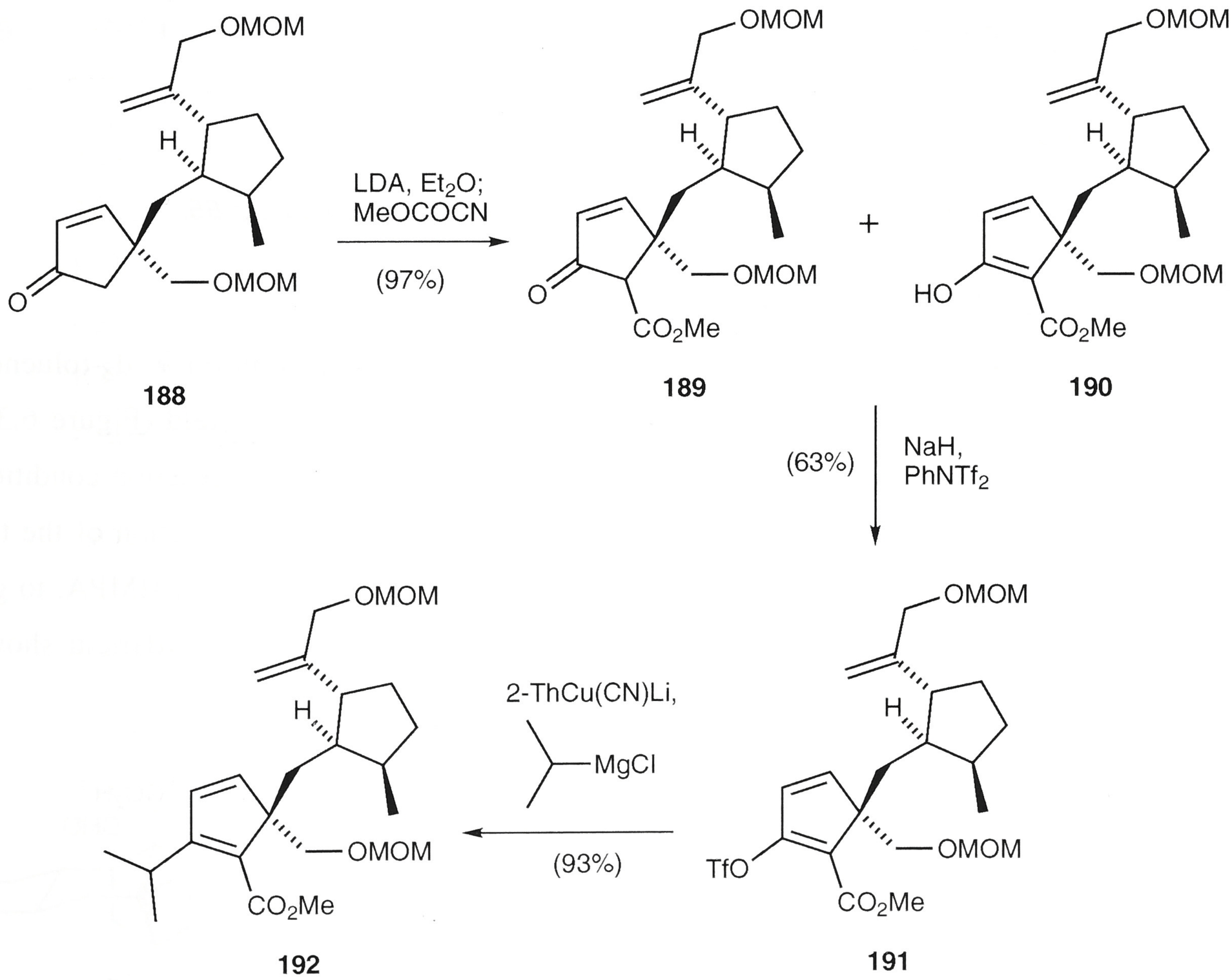


Figure 6.3.2 *Cycloreversion of ketone **172** to enone **188**.*

Elaboration of **188** to the target intermediates would now follow the analogous sequence outlined in Chapter Five for the formation of **182** and **64**.

Selective C-acylation of enone **188** was carried out by enolisation with LDA in diethyl ether and subsequent addition of methyl cyanoformate,[6] to afford the acylated compound (97% yield) as a 1:1 mixture of keto and enol tautomers (**189** and **190**, respectively). Next, installation of the isopropyl group was carried out by first converting **189/190** into the corresponding enol triflate **191** using NaH and *N*-phenyltrifluoromethanesulfonimide (62% yield).[7] Next, treatment of triflate **191** with the higher order cuprate derived from 2-thienyl(cyano)copper lithium (2-ThCu(CN)Li)[8] and isopropylmagnesium chloride afforded **192** in excellent yield (93%, Figure 6.3.3).



188 **189** **190** **191** **192**

Figure 6.3.3 *Elaboration of enone **188**.*

Removal of both MOM protecting groups using $MgBr_2.Et_2O$ and 1-butanethiol[9] gave the diol **184**, in excellent yield (86%). Selective oxidation of the allylic alcohol function in **184** was then achieved using MnO_2 in diethyl ether[10] to afford the aldehyde **65** in quantitative yield (Figure 6.3.4).

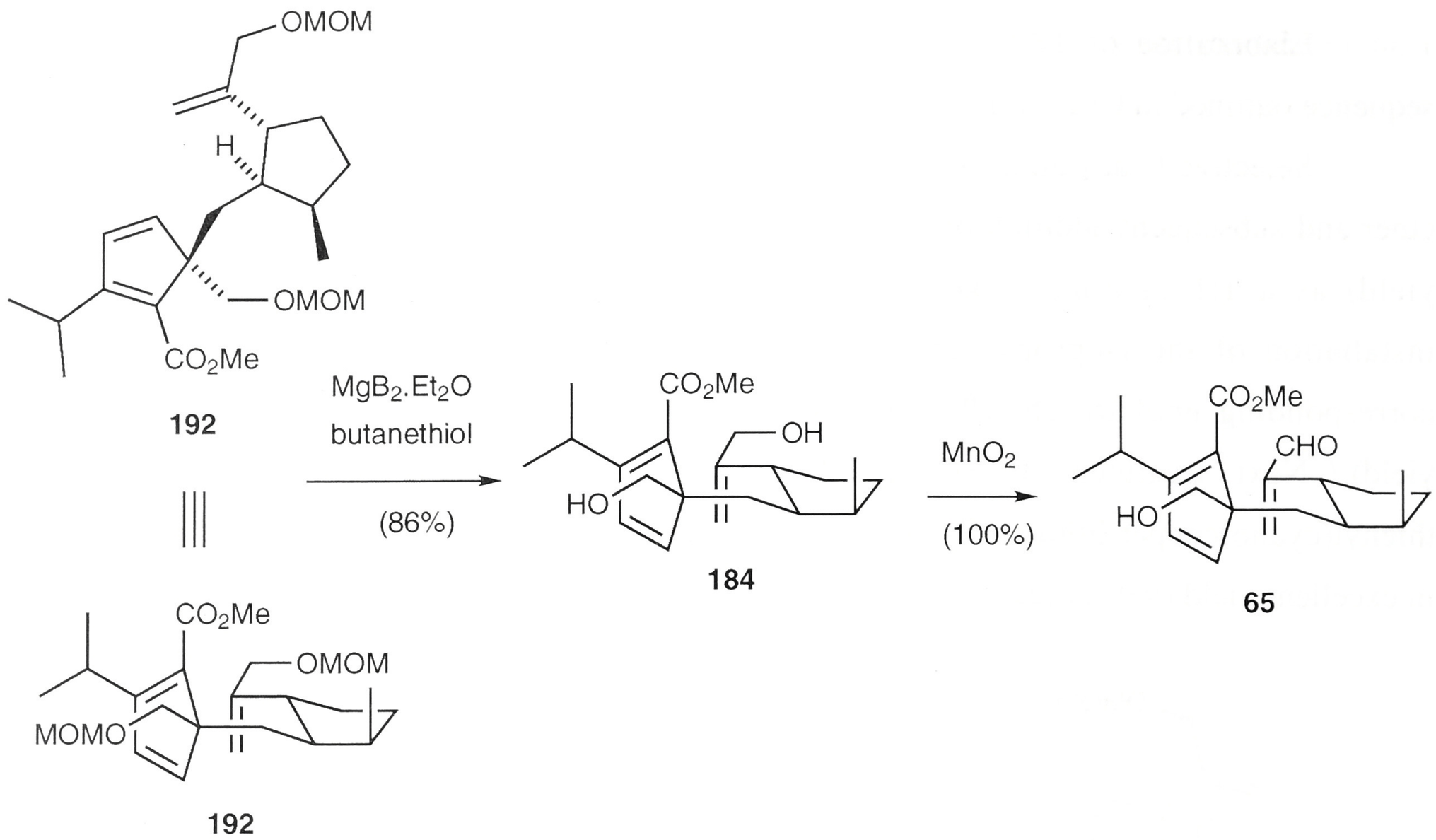


Figure 6.3.4 *Synthesis of the [4+2] cycloaddition precursor **65**.*

6.3.2 Total synthesis of sordaricin

Aldehyde **65** underwent smooth intramolecular [4+2] cycloaddition in d_8-toluene at 40 °C over 3 days, to afford sordaricin methyl ester (**41**) in quantitative yield (Figure 6.3.5). Formation of the isomeric compound *iso*-**41** was not observed under these reaction conditions, the implications of which will be addressed in the following chapter. Completion of the total synthesis was then readily achieved by demethylation using propanethiolate in HMPA, to give sordaricin (**3**) in 79% yield. Comparisons between synthetic and natural sordaricin showed them to be essentially* identical in all respects.

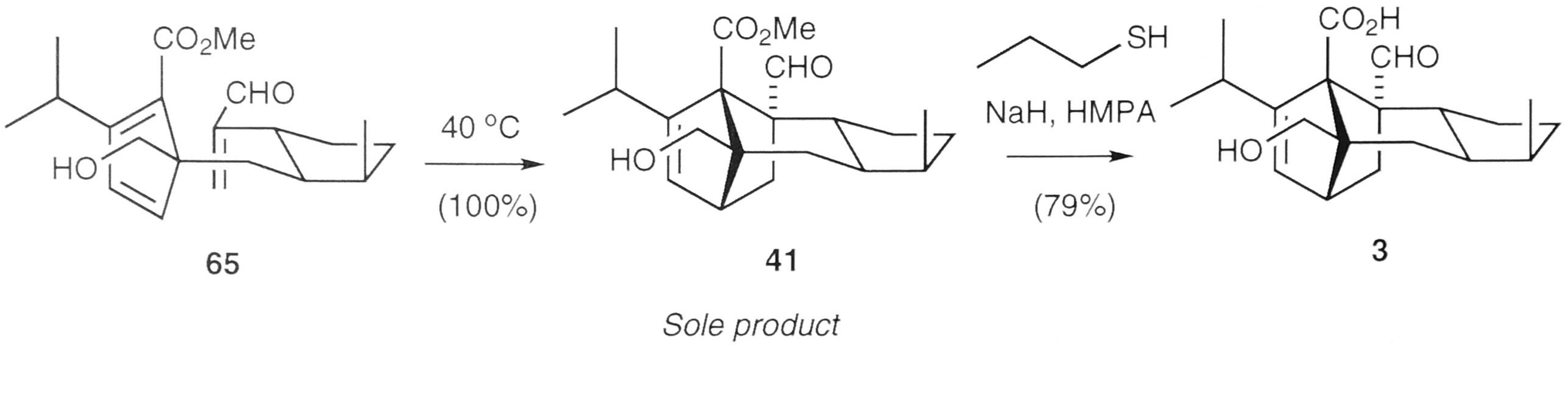


Figure 6.3.5 *Total synthesis of sordaricin (**3**).*

* Optical rotations differ slightly, see Chapter Nine.

6.4 Summary

This short chapter has detailed the successful outcome of the sequential cycloreversion/intramolecular [4+2] cycloaddition approach towards sordaricin skeleton. The unexpected formation of the isomeric compound *iso*-**41** prompted the development of an alternative reaction sequence that avoided the formation of this product, thus allowing for the completion of a total synthesis of the natural product, sordaricin (**3**).

The following chapter will discuss efforts directed at understanding the apparent differences in regiochemistry between the sequential cycloreversion/intramolecular [4+2] cycloaddtion and the intramolecular [4+2] cycloaddition. Some aspects of the possible biosynthesis of the sordarins are also discussed.

6.5 References

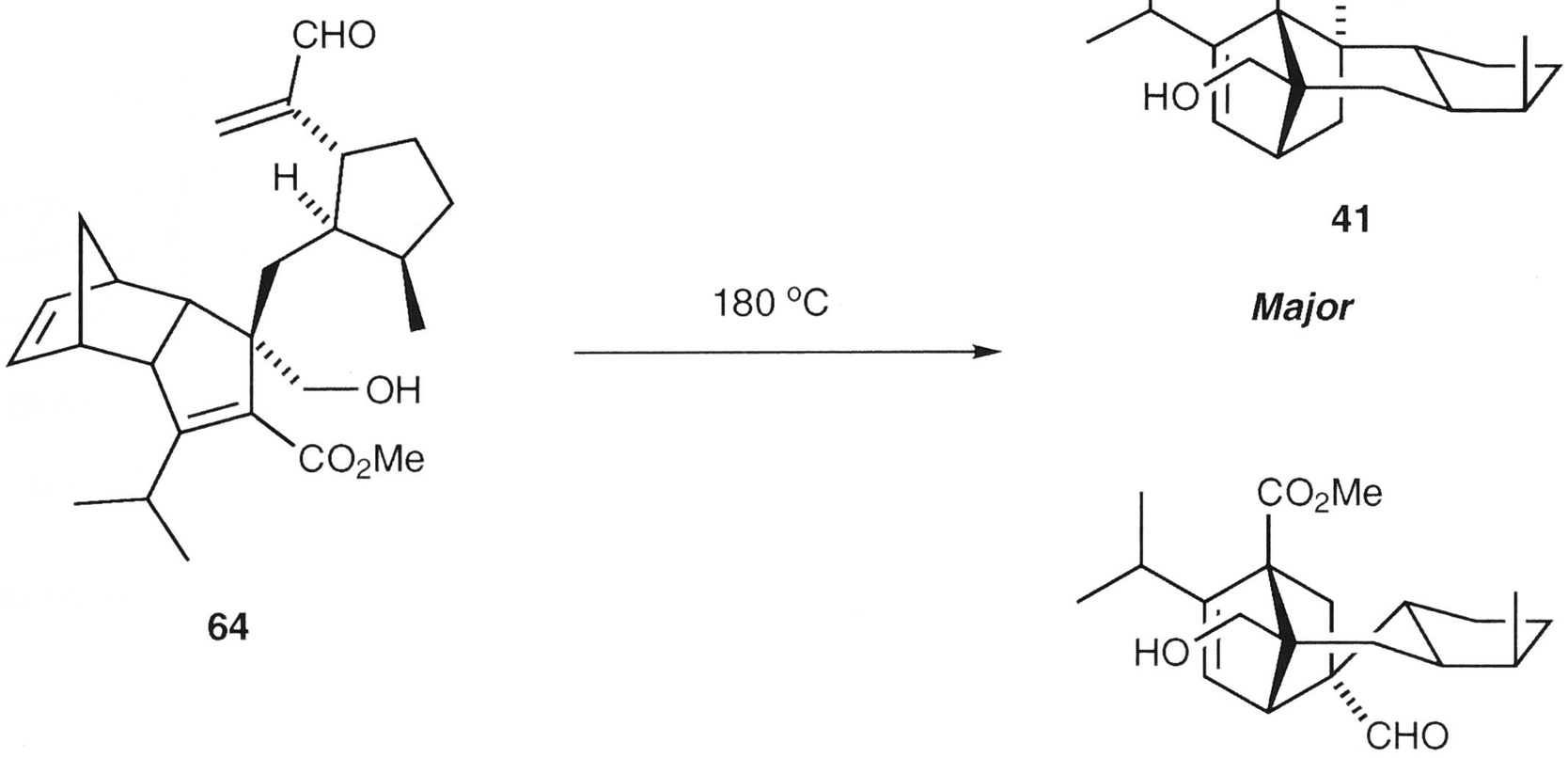
1. Vasella, A. T. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1972.
2. Fisher, J.; Gradwell, M. J. *Magn. Reson. Chem.* **1991**, *29*, 1068.
3. Chen, A.; MacMillan, J.; Willis, C. L. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3235.
4. Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002.
5. Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595.
6. (a) Mander, L. N.; Sethi, S. P.; *Tetrahedron Lett.* **1983**, *24*, 5425. (b) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, 169. (c) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1991**, *70*, 256.
7. Houpis, I. N. *Tetrahedron Lett.* **1991**, *32*, 6675. See also: Zeller, W. E. in *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A. (Ed.), John Wiley and Sons: New York, **1995**, 4096 and references cited therein.
8. Lipshultz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945
9. Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett.* **1991**, 183.
10. Babler, J. H.; Martin, M. J. *J. Org. Chem.* **1977**, *42*, 1799. MnO_2 (<5 micron, activated, ~85%) purchased from Aldrich Chemical Company was used without further purification or activation.

Chapter Seven

Cycloadditions Related to Sordaricin

7.1 Introduction

The previous chapter detailed the outcomes of a tandem [4+2] cycloreversion/intramolecular [4+2] cycloaddition approach towards the total synthesis of sordaricin (**3**). The pivotal transformation of **64** resulted in the formation of *two* products, namely, **41** and the unanticipated regioisomer, *iso*-**41**. An alternative approach, which avoided the formation of the unwanted *iso*-**41**, was developed which resulted in an improved total synthesis of sordaricin (**3**). This chapter discusses the outcomes of several studies aimed at elucidating the differences in regioselectivity for the two cases mentioned above. Some speculation regarding the biosynthesis of sordaricin (**3**) is also made.



64

41

Major

iso-**41**

Minor

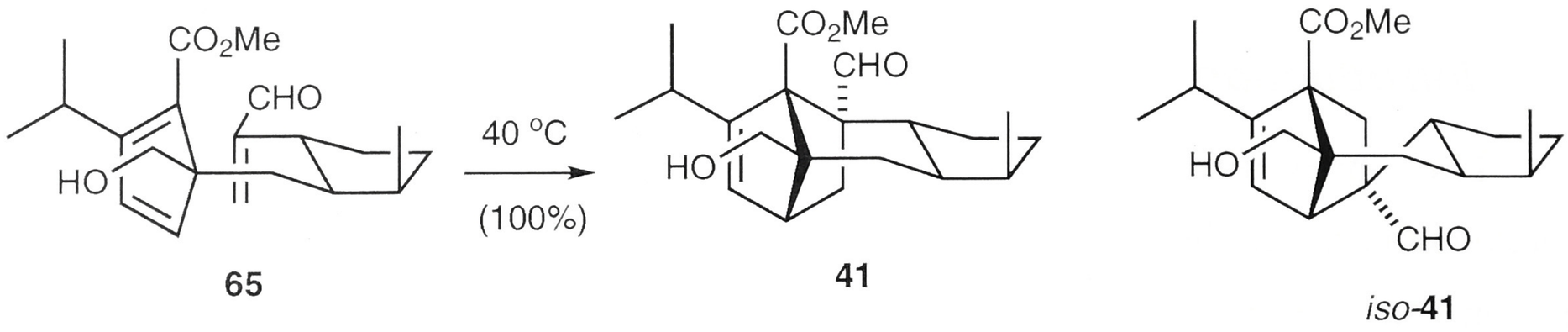
7.2 Intramolecular cycloadditions

7.2.1 Regioselectivity

For the purpose of developing an efficient synthesis of sordaricin (**3**) that avoided the formation of *iso*-**41**, an alternative reaction sequence was developed that gave rise to diol **184** and aldehyde **65** (see Chapter Six). Access to these compounds allowed for a comparison between the regioselectivities of the tandem processes and the intramolecular [4+2] cycloaddtions carried out under control conditions.

As explained in the previous chapter, the heating of aldehyde **65** in d_8-toluene at 40 °C resulted in a quantitative yield of sordaricin methyl ester (**41**, Figure 7.2.1). Formation of the

alternative regioisomer *iso*-**41** was not observed under these conditions, an outcome which mirrors the results of Kato and co-worker's.[1]

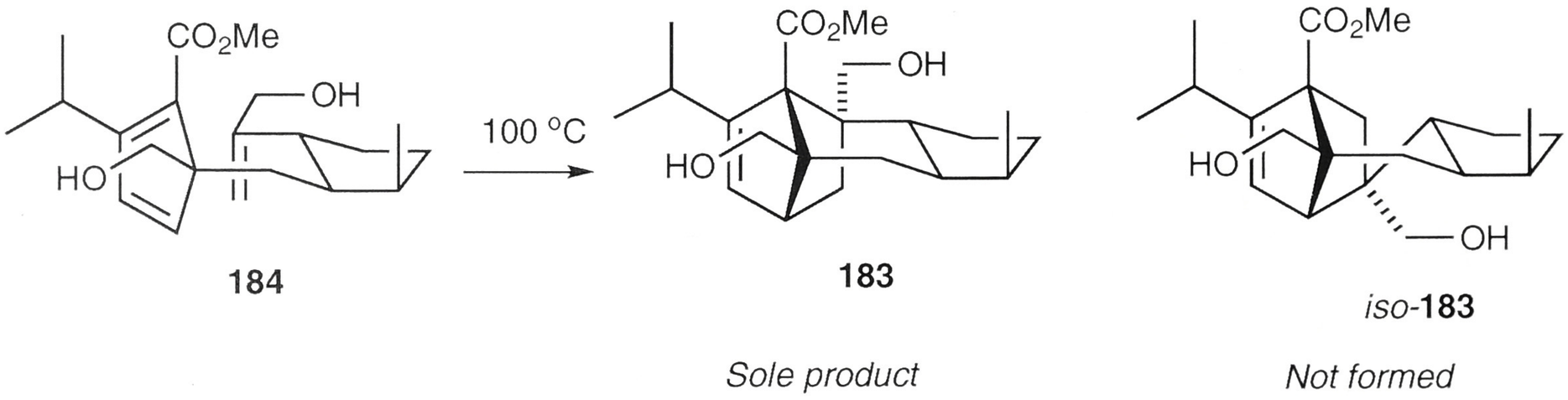


65 — **41** — *iso*-**41**

Sole product — *Not formed*

Figure 7.2.1 *Intramolecular cycloaddition of **65** - completely selective formation of **41**.*

The equivalent reaction was carried out on diol **184**, although it was necessary to heat the solution at 100 °C in order to induce a significant reaction rate, indicating a much higher barrier of activation. As expected, diol **183** was the sole product of the reaction, with no observed formation of *iso*-**183** (Figure 7.2.2).



184 — **183** — *iso*-**183**

Sole product — *Not formed*

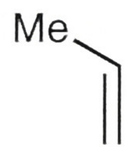
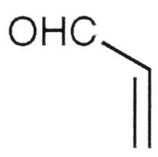
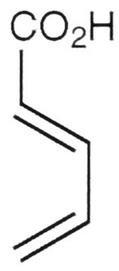
Figure 7.2.2 *Intramolecular cycloaddition of **184** - completely selective formation of **183**.*

7.2.2 Explaining the differences in rate and regioselectivity

The differences in rates of cyclisation for diol **184** and aldehyde **65**, and the regioselectivity of the cyclisations, can be rationalised by examining the frontier orbital interactions of simple model dienes and dienophiles. Houk, in his seminal publication 'Generalized Frontier Orbitals of Alkenes and Dienes. Regioselectivity in Diels-Alder Reactions',[2] laid down the foundations of what is now a generalised method for predicting and explaining the products of, *inter alia*, [4+2] cycloadditions.[3]

For the purpose of this thesis, the diene portion of **65** and **184** will be represented by sorbic acid, and the dienophile portion of **65** and **184**, by acrolein and propene, respectively. The first step in the approach is to calculate the energies of the HOMO and LUMO of the diene and dienophile (Figure 7.2.3). Houk[2] states, that 'The principal stabilization of the transition state will arise from interaction of the HO-LU pair of addended frontier orbitals which are closest in energy'. By inspection of Figure 7.2.3, it is clear that the favoured interactions in both cases, will be the HOMO of the diene and the LUMO of the dienophile (-11.21 eV for

$HOMO_{(sorbic\ acid)}$-$LUMO_{(propene)}$, and -10.01 eV for $HOMO_{(sorbic\ acid)}$-$LUMO_{(acrolein)}$, compared with -12.27 eV and -12.88 eV, respectively, for the alternative arrangement.).

	Frontier orbital energies (eV)[a]	
	HOMO	***LUMO***
	**-9.88**	**1.80**
	**-10.89**	**0.60**
	**-9.41**	**1.99**

[a] Values taken from Smith, M. B., *Organic Synthesis*, McGraw-Hill Book Co.: Singapore, **1994**.

Figure 7.2.3 *Frontier orbital energies.*

From these data it is clear that the reaction of acrolein and sorbic acid is more favourable, due to a smaller energy gap between the participating orbitals, and hence would proceed at a lower temperature than the equivalent reaction involving propene and sorbic acid. Therefore, from these models, it would be predicted that **65** should cyclise at a lower temperature than diol **184**, as observed experimentally.

Having established which orbitals are involved in the reaction, the next step is to examine the orbital coefficients in order to predict the regioselectivity. The orbital coefficients for the appropriate model fragments are indicated in Figure 7.2.4. The most important point here is that only termini with the same phase will become bonded, as to do otherwise would lead to a forbidden or disallowed transition state. The size of the co-efficient only becomes important when both termini are of the same phase.

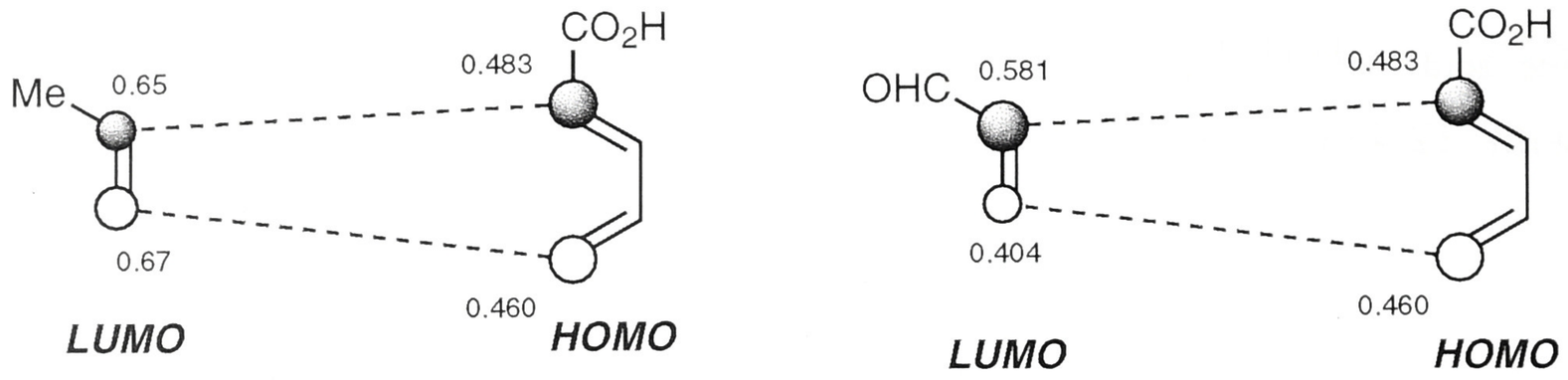


Figure 7.2.4 *Absolute values of the frontier orbital co-efficients associated with Diels-Alder reactions – Regioselectivity explained.*

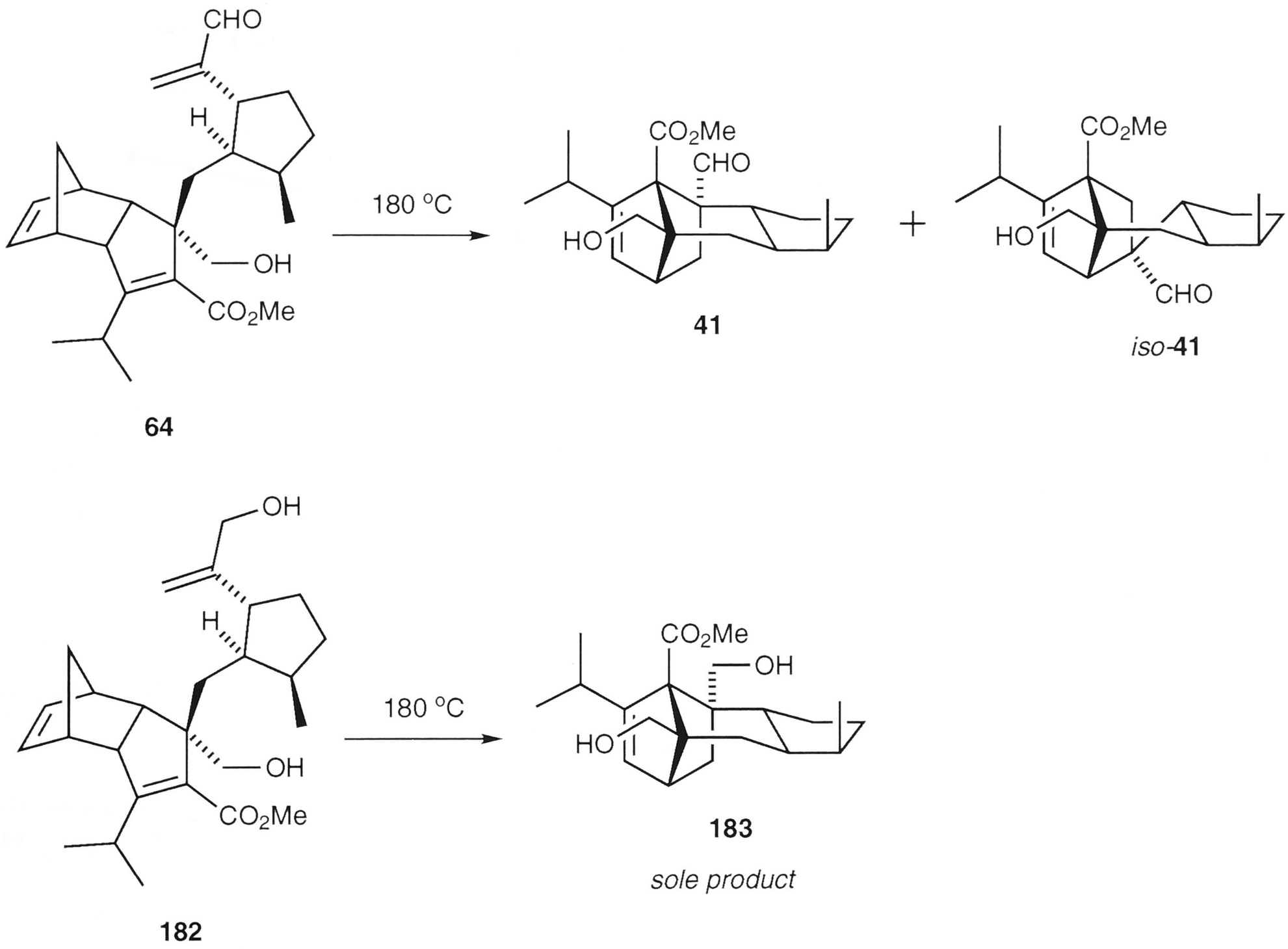
In the cases shown above, this would led to the formation of the so-called 'ortho' product. This is the experimentally observed outcome for the cyclisation of both **65** and **184**. It should be noted, however, that for electron poor 1-substituted butadienes the coefficients of the termini are nearly always equal, so that the regioselectivity should be lower. This is contrary to much experimental evidence, including the results of this research, and indicates the importance of secondary orbital interactions. Such interactions will not be dealt with here.

According to Houk,[2] the 'meta' orientation (leading to the formation of *iso*-**41** when **64** is heated at 180 °C) should only be favoured when both the diene and dienophile are electron rich. This is not so for **65**, the intermediate formed after cycloreversion of **64**, and as has been observed and explained, selective formation of **41** occurs at low temperatures by a kinetically controlled interaction of the frontier orbitals. So, in order to rationalise the formation of *iso*-**41**, the thermodynamic properties of the compounds must be examined.

7.3 The tandem cycloreversion/intramolecular [4+2] cycloaddition

7.3.1 Explaining the regioselectivity

The experiments detailed above in Section 7.2 clearly demonstrate that for aldehyde **65** and diol **184**, formation of **41** and **183**, respectively, occurs with complete selectivity. None of the other possible regioisomer was observed in either case. Whereas for aldehyde **64**, formation of *iso*-**41** is a significant competing process during the tandem reaction sequence. Conversely, diol **182** affords only **183** under the same reaction conditions (Figure 7.3.1).



64 **41** *iso*-**41**

182 **183**

sole product

Figure 7.3.1 *The two tandem reaction outcomes.*

These outcomes were rationalised in Section 7.2.2, in terms of a kinetically controlled cyclisation, governed by interactions of the frontier orbitals. It was therefore speculated that, during the tandem sequence, formation of *iso*-**41** was occurring due to reversibility of the intramolecular cycloaddition at 180 °C. For this to be true, *iso*-**41** would have to be thermodynamically more stable than **41**. Semi-empirical calculations performed using Spartan v5.0.3 (RH/PM3 level) predict heats of formation of –131.88 kcal/mol and –137.11 kcal/mol for **41** and *iso*-**41** respectively. Clearly, from these results it would be anticipated that *iso*-**41** would be the more stable of the two isomers by about 5.23 kcal/mol.

To test this hypothesis and validate the theoretical calculations, a sample of sordaricin methyl ester (**41**) was heated at 180 °C in 1,2-dichlorobenzene for 2.5 h. Inspection of the ^{1}H NMR spectra of the product revealed the presence of both **41** and *iso*-**41** in a 1:2 ratio, proving the earlier speculation. A second reaction was carried out in toluene at 120 °C (sealed tube), which showed only **41** after 6 h. A third reaction was performed, once again in toluene, but this time at 150 °C which showed a slow conversion of **41** into *iso*-**41** indicating that the temperature for conversion is somewhere between 120 °C and 150 °C.

To find the position of this equilibrium the percent conversion to the isomer *vs.* time was plotted, and is shown in Figure 7.3.2.

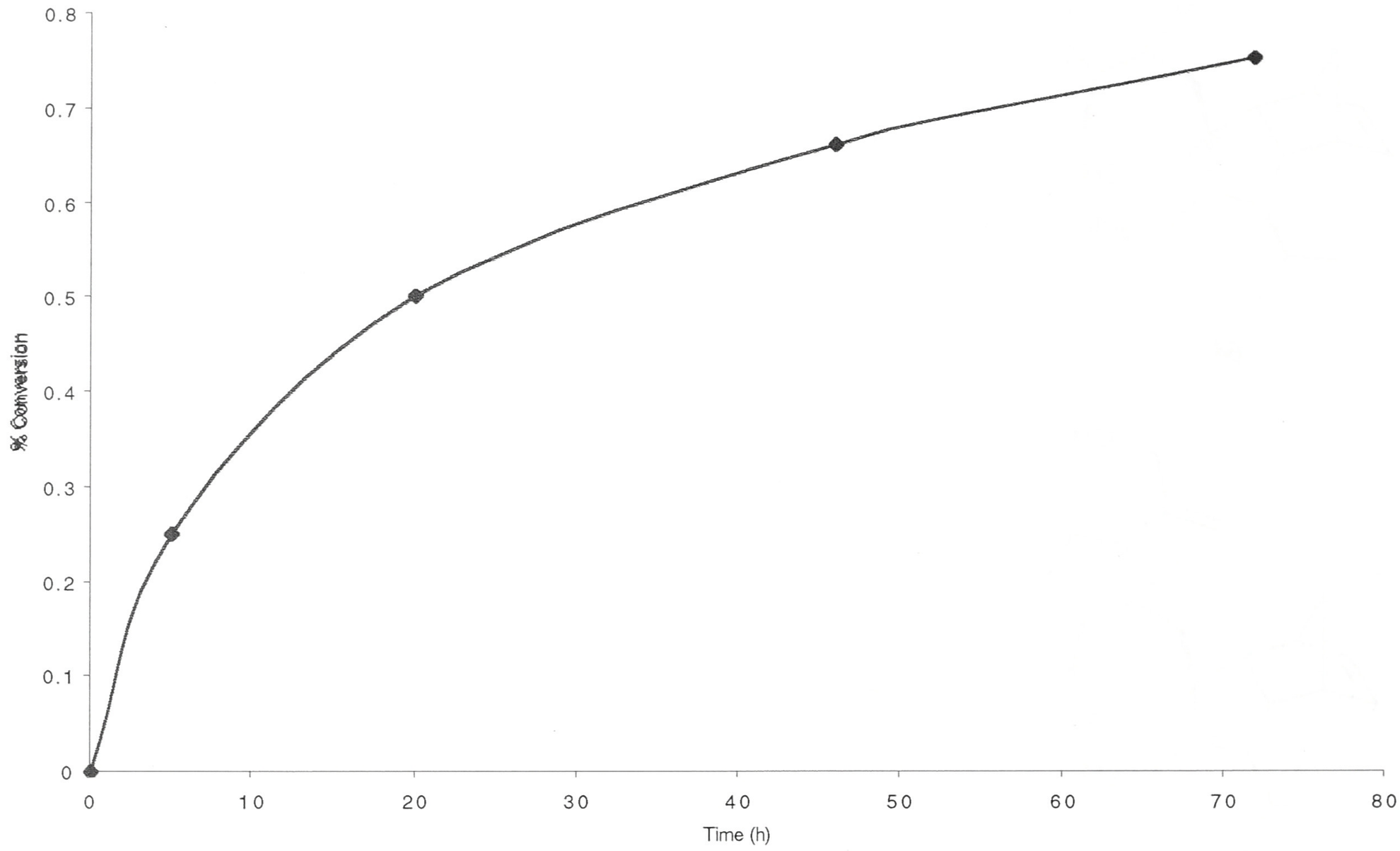


Figure 7.3.2 *Isomerisation of* ***41*** *into* iso-***41.***

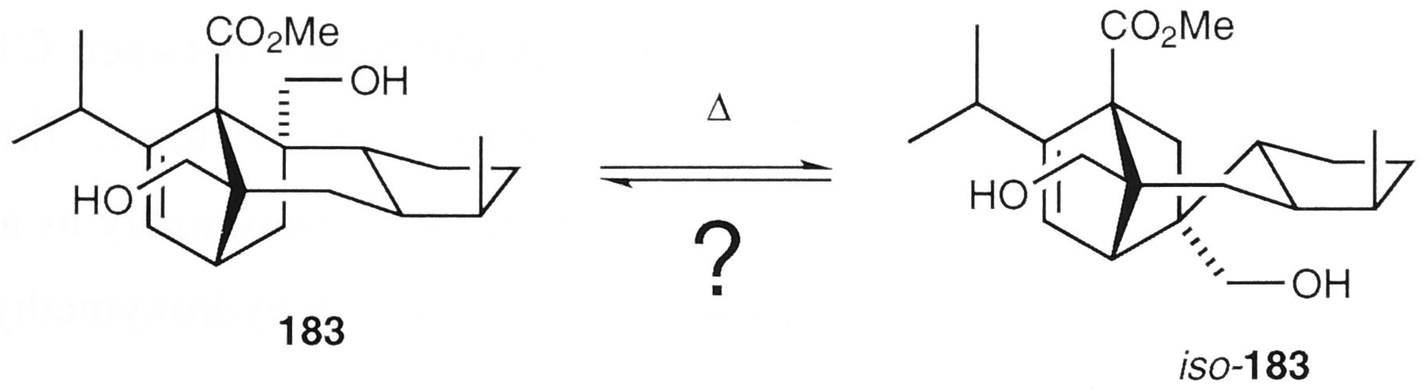
From this graph it appears that the equilibrium position lies at about 80:20 indicating an experimentally derived energy difference of approximately 1.2 kcal/mol at 150 °C.* This value is somewhat less than the calculated value of 5.23 kcal/mol, which may reflect inaccuracies in the modelling program.

The reverse experiment, where pure *iso*-**41** was heated at 150 °C in toluene for 24 h, gave a similar distribution of *iso*-**41** and **41** (80:20), giving some weight to the projected equilibrium position indicated above.

The question then arose; will diol **183** undergo the same sort of isomerisation? Obviously, the barrier would be higher because *iso*-**183** was not observed during the tandem cycloreversion/intramolecular [4+2] cycloaddition of **182**. This result makes sense given that the activation energy for the intramolecular cycloaddition is greater for diol **184** than for aldehyde **65**, and hence the reverse reaction would also have a much higher barrier.

---

* Calculated using $\Delta G = -RT\ln K$.

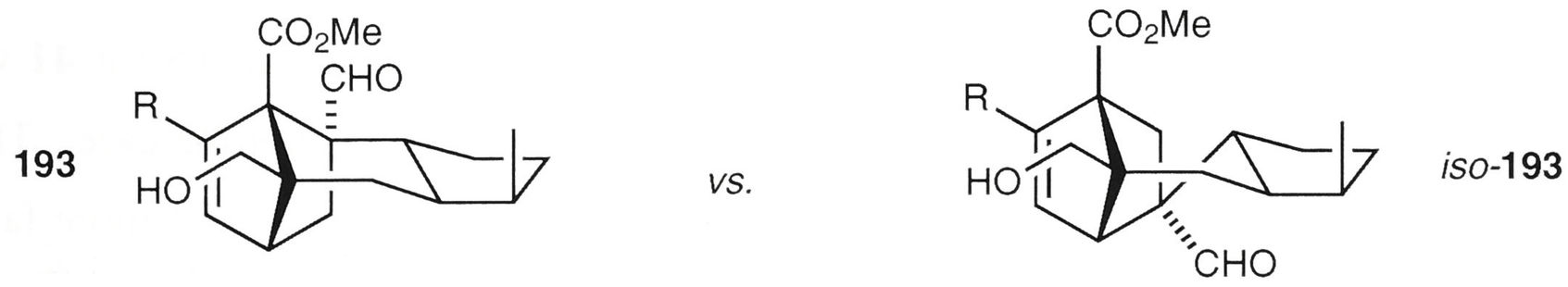


183 *iso*-**183**

Figure 7.3.3 *Possible isomerisation of diol **183.***

In the event, heating of diol **184** in dichlorobenzene at 200 °C (sealed tube) for 4 h did not show any formation of *iso*-**183** (Figure 7.3.3). Only products resulting from decomposition were observed, so this reaction was not investigated further.

It is not intuitively obvious why *iso*-**41** should be more stable than **41**, since this isomer forces the C-ring to adopt an unfavourable boat conformation. However, **41** possesses three contiguous quaternary stereocentres that, together, cause a significant amount of non-bonding interactions, which are clearly minimised by the formation of *iso*-**41**. Based on this analysis, it would seem fair to suggest that the energy difference between the two isomers would be dependent upon the size of both the C1 substituent and the C18 ester group. Using the synthetic route for C1 variation outlined in Chapter Two, it would have been possible to synthesise several derivatives and test this hypothesis experimentally, but due to lack of material this was not attempted. Instead, theoretical calculations were made using Spartan v5.0.3, as detailed for **41** and *iso*-**41**. The results are tabulated below in Table 7.3.1.



193 *iso*-**193**

R	$H_{(formation)}$ **193** (kcal/mol)	$H_{(formation)}$ ***iso*-193** (kcal/mol)	$\Delta H_{(formation)}$ (kcal/mol)
H	-118.91	-119.63	0.72
Me	-123.69	-127.66	3.97
Et	-127.79	-131.03	3.24
^{i}Pr	-131.88	-137.11	5.23
^{t}Bu	-134.42	-140.49	6.06

Table 7.3.1 *Energy differences for **193** and* iso-***193.***

The table above shows the expected trend that, as the R-group at C1 increases in bulk from a hydrogen substituent to a *t*-butyl group, the energy gap between **193** and *iso*-**193** increases.

Similarly, calculations indicated that the energy difference between C18 *t*-butyl ester derivatives of sordaricin was 4.83 kcal/mol in favour of the isomeric form. Interestingly, this difference is less than that for the methyl esters (5.23 kcal/mol), presumably as a result of more complex steric interactions with both the C1 substituent and the C19 hydroxymethyl group.

7.4 Some Conclusions on the Cycloadditon Studies

7.4.1 Unification of the kinetic and thermodynamic data

The above discussion was aimed at describing the outcome of several investigations into the intramolecular [4+2] cycloadditions employed during research for this Ph.D. thesis. From the collected information it can be concluded that: (a) cycloadducts **41** and **183** are the result of kinetically controlled intramolecular [4+2] cycloadditons of **65** and **184**, respectively. This regiochemical outcome was rationalised in terms of more favourable interactions of the molecular orbitals associated with the HOMO and LUMO of the diene and dienophile, and that (b) cycloadduct *iso*-**41** is the result of a thermodynamically driven isomerisation of the initially formed adduct, **41** which only occurs at temperatures above about 150 °C. The stability of *iso*-**41** relative to **41** can be attributed to the relief of severe non-bonding interactions that are present in **41**. The relief of these interactions in forming *iso*-**41** must be greater than the increase in energy due to the C-ring being forced into a boat conformation.

Ultimately, it is the barrier to the transition states (TS) which gives rise to the kinetic preference for **41** over the regioisomer, *iso*-**41**. It is tempting to suggest that if the stability of the products was reflected in the transition states leading to them, then the TS for **41** would be higher in energy than the isomeric TS leading to *iso*-**41**. Clearly this is not the case. Therefore, it must be that formation of **41** proceeds through an early transition state where more favourable orbital interactions leads to the formation of the less stable product (Figure 7.4.1)

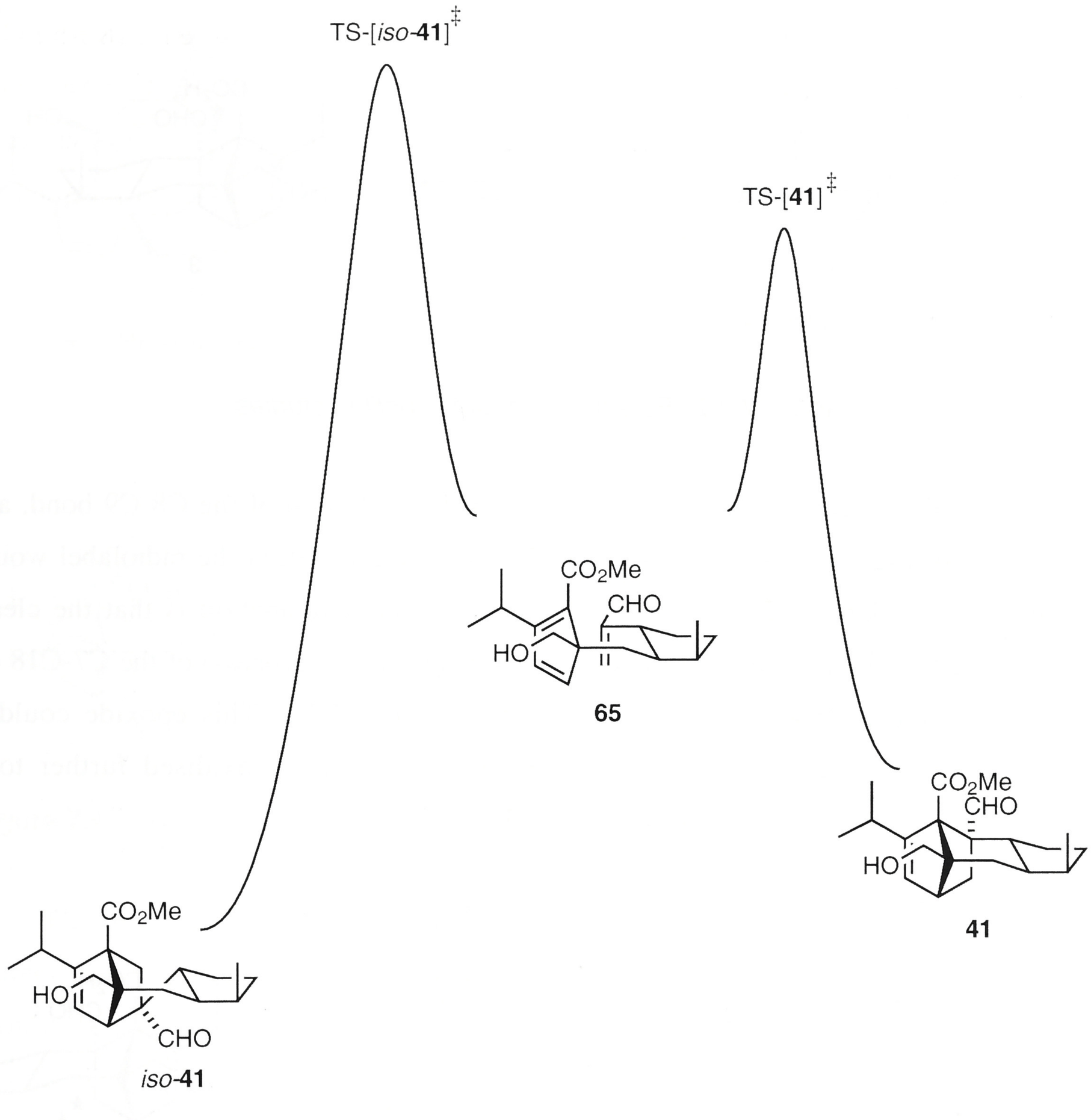


Figure 7.4.1 *Energy diagram for the intramolecular [4+2] cycloaddition.*

7.4.2 Speculations regarding sordaricin biosynthesis

One of the goals at the outset of this research was to gain some insight into what was proposed as being a biogenetic intramolecular [4+2] cycloaddition, *i.e.* the conversion of **65** into **41**.

As described in Chapter One, Borschberg[4] showed that the sordarins are biosynthetically derived from cycloaraneosene (**11**), by oxidative fission of the C8-C9 bond. The mechanism of this oxidative fission is not fully known, but Borschberg's labelling studies shed some light on the matter. He showed that incorporation of a radiolabel at C18 of **11** results in C17 of sordaricin (**3**) becoming labelled (Figure 7.4.2).

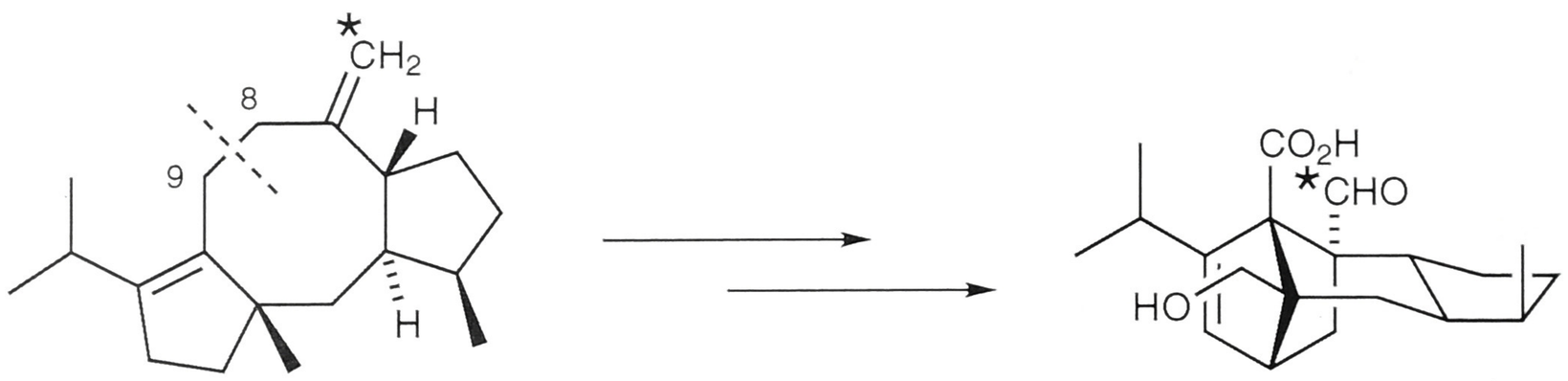


Figure 7.4.2 *Borschberg's radiolabelling studies*

Clearly, the bioconversion is not a simple oxidative fission of the C8-C9 bond, as this would result in oxygen incorporation at C8, and thus after cyclisation the radiolabel would be located at C4 of sordaricin (**3**, Figure 7.4.3). One possible explanation is that the cleavage might be initiated by the epoxidation (or some other electrophillic process) of the C7-C18 olefin in a substrate such as **194** to give epoxide **195** (Figure 7.4.4). This epoxide could then fragment, as shown, to give allylic alcohol **196** which would be oxidised further to give aldehyde **16**, the proposed precursor to sordaricin (**3**).

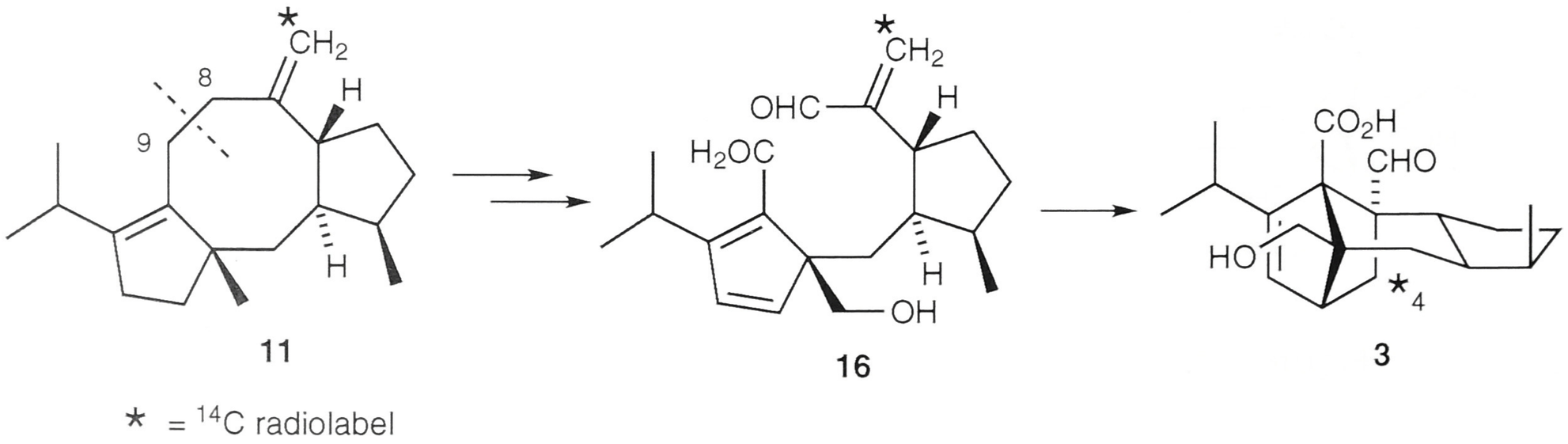


Figure 7.4.3 *The outcome of radiolabel incorporation if the C8-C9 bond was oxidatively cleaved in a direct process.*

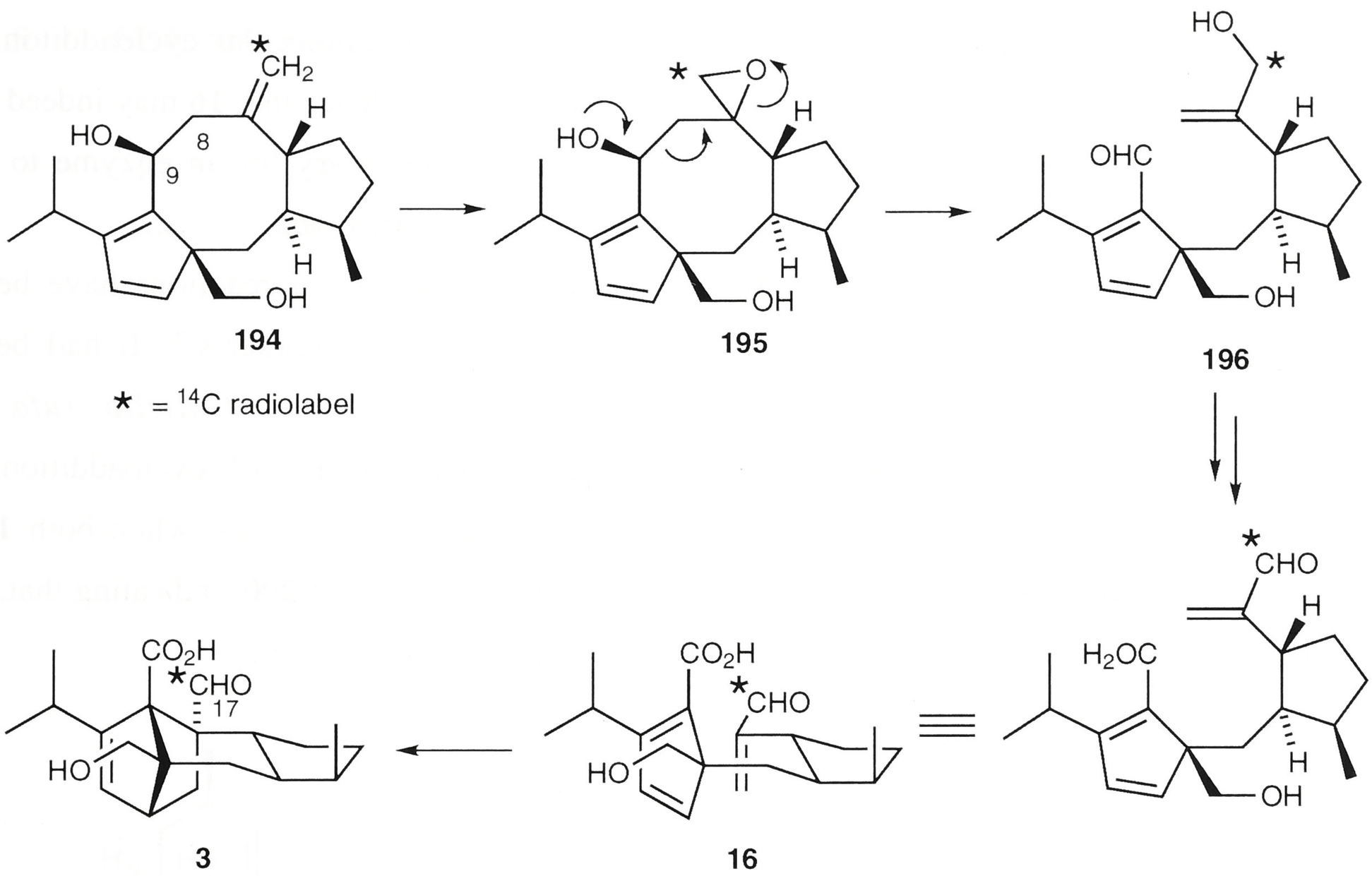


Figure 7.4.4 *A possible biosynthetic pathway to account for radiolabel incorporation at C17.*

The direct oxidative cleavage of the C8-C9 bond would generate an aldehyde such as **16** directly and there would be no need to speculate on the role of an allylic alcohol in the biosynthesis. The fact that this mechanism seems unlikely, provides good evidence for the presence of an allylic alcohol intermediate. It should be noted that neither Borchberg's research, or that of any others, has provided information on the exact timing of the glycosidation event leading to the formation of sordarin (**1**).

If the formation of sordaricin (**3**) occurs by means of an intramolecular [4+2] cycloaddition, then the precursor is more likely to be an aldehyde such as **16**, and not a diol such as **197** (Figure 7.4.5). The experiments carried out on the methyl ester derivatives of these compounds (**65** and **184**) clearly show that diol **184** does not undergo the required cycloaddition at temperatures likely to be found in the native organism, or its local environment. However, based on the aforementioned radiolabel studies, an allylic alcohol similar to diol **197** is probably the biosynthetic precursor to the aldehyde **16**.

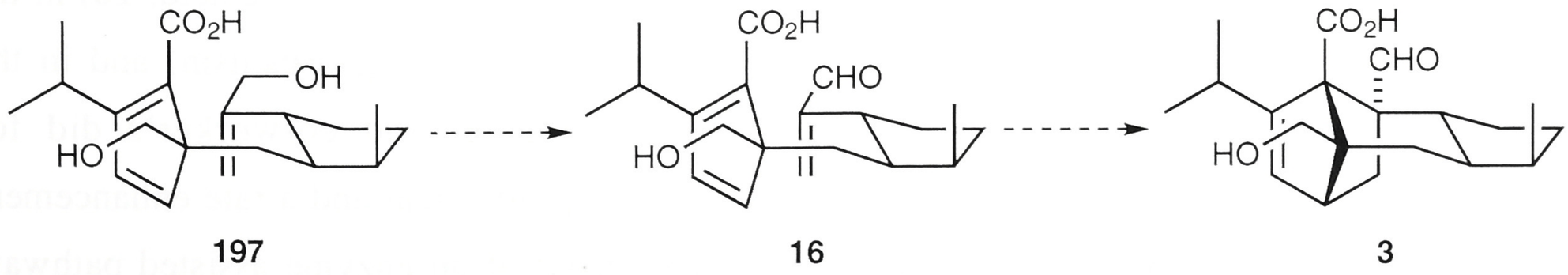
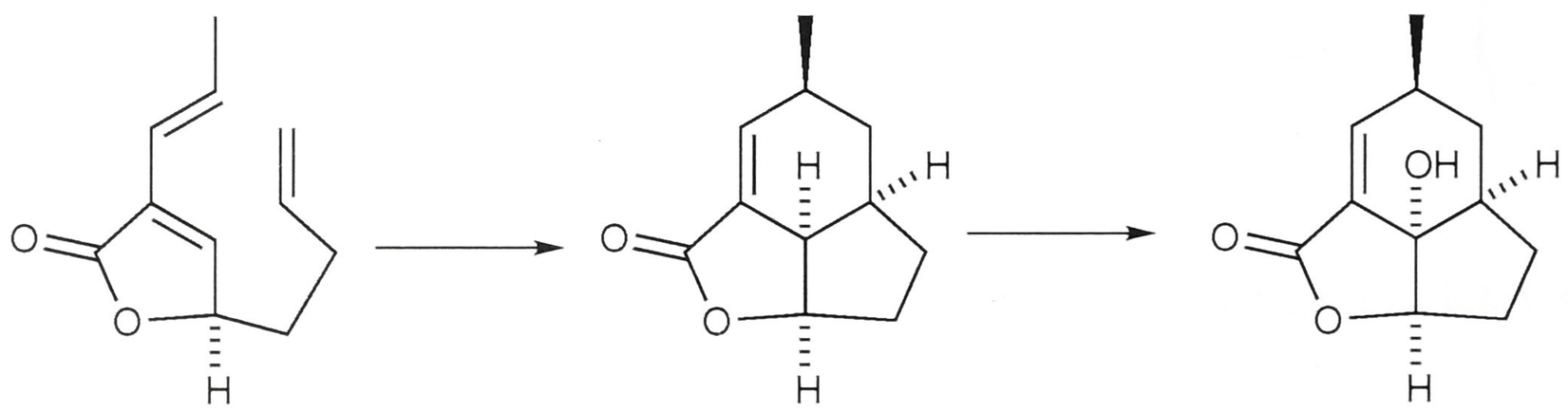


Figure 7.4.5 *Possible biosynthetic pathway to sordaricin (**3**).*

The observation that the aldehyde **65** undergoes the intramolecular cycloadditon at room temperature, in the absence of any catalyst, provides good evidence that **16** may indeed be the biosynthetic precursor to sordaricin (**3**) and that it is not necessary for an enzyme to be involved. However, this does not prove that there is not an enzyme involved.

To date, only three enzyme-catalysed biosynthetic Diels-Alder reactions have been reported,[5,6,7] the most recent being that reported by Sterner and co-worker's.[7] It had been proposed that (–)-galiellalactone (**200**), a metabolite of the fungus *Galiella rufa*, is biosynthesised *via* **199** which, in turn, is produced by an intramolecular [4+2] cycloaddition of (–)-pregaliellalactone (**198**, Figure 7.4.6). Feeding studies demonstrated that when both **198** and **199** were fed to the mycelium of *Galiella rufa* they are converted to **200**, indicating that, *in vivo*, the conversion of **198** to **199** proceeds through two discrete steps.



198 **199** **200**

Figure 7.4.6 *Biosynthetic pathway for the formation of (–)-galiellalactone (**200**).*

To probe whether or not the cyclisation event might be enzyme-mediated a series of feeding experiments were carried out, whereby **198** was fed to the mycelium of *Galiella rufa*. Compared with an abiotic control (**198** in saline solution), a rate enhancement was observed in the presence of living mycelia (control experiment was 8 times slower). The mycelium was then autoclaved before conducting the next experiment, which showed no rate enhancement for the cyclisation. Clearly, this research shows that the rate enhancement is the result of a specific interaction with a well defined macromolecule and they report that further work is underway to isolate and characterise the responsible factor. Interestingly, cyclisation of the non-natural enantiomer of **198** was not accelerated by the mycelium.

To prove that an enzyme is involved in the formation of sordaricin (**3**), one would have to compare the rate of the cyclisation of **65** (or the equivalent free acid, **16**) in the presence of active *Sordaria araneosa* (or another sordarin producing organism) and in the presence of an inactive form of the organism – as Sterner and co-worker's did for (–)-pregaliellalactone (**198**). If all other conditions were kept identical and a rate enhancement was observed, then maybe that could be considered as proof of an enzyme assisted pathway. Due to time restraints and scarcity of material, this speculation was not investigated.

7.5 References

1. Kato, N.; Kusakabe, S.; Wu, X.; Kamitamari, M.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1993**, 1002.
2. Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092.
3. For an excellent text on frontier orbital theory: see, Fleming, I., *Frontier Orbitals and Organic Chemical Reactions*, Wiley-Interscience: Chicester, **1996**.
4. Borschberg, H. J. Ph.D. Dissertation, Eidgenossischen Technischen Hochschule, Zurich, 1975.
5. (a) Oikawa, H.; Kobayashi, T.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Org. Chem.* **1998**, *63*, 8748. (b) Katayama, K.; Kobayashi, T.; Oikawa, H.; Honma, M.; Ichihara, A, A. *Biochim. Biophys. Acta* **1998**, *1384*, 387.
6. (a) Auclair, K.; Sutherland, A.; Kennedy, J.; Witter, D. J.; Van denHeever, J. P.; Hutchinson, C. R.; Vederas, J. C. *J. Am. Chem. Soc.* **2000**, *122*, 11519. (b) Witter, D. J.; Vederas, J. C. *J. Org. Chem.* **1996**, *61*, 2613.
7. Johansson, M.; Köpcke, B.; Anke, H.; Sterner, O. *Angew. Chem. Int. Ed.* **2002**, *41*, 2158.

Chapter Eight

Summary and Conclusions

8.1 Summary

8.1.1 Total synthesis of sordaricin

The main focus of the research conducted for this thesis was directed at producing a concise an efficient synthesis of sordaricin (**3**). Sordaricin (**3**) is the diterpene aglycone common to a family of antifungal glycosides known as the sordarins, of which sordarin (**1**) is the structural prototype. Interest in the sordarins stems from their demonstrated potent and broad spectrum antifungal activity against a wide range of common fungal pathogens.

The initial synthetic plan, outlined in Chapter Two, relied upon a planned alkylation between aldehyde **60** and iodide **62** (**158**, when P = MOM). The synthesis of these two subtargets was to be achieved using (–)- and (+)-**54**, respectively.

Although both the aldehyde **60** and iodide **158** were readily synthesised (Chapters Three and Four, respectively), attempts to bring about an alkylation were met with failure. Conversion of **60** into a dimethylhydrazone derivative did not improve this situation.

The nitrile **163** was synthesised from (–)-**54** and upon treatment with LDA, followed by the addition of HMPA and iodide **158** afforded the desired product, **168**. Some straightforward functional group manipulations then gave the required precursor (**64**) for the proposed tandem cycloreversion/intramolecular [4+2] cycloaddition. Heating of **64** in 1,2-dichlorobenzene gave rise to the desired product, **41** and the unexpected isomeric product, *iso*-**41** in a combined yield of 76%. The inseparable mixture of esters was converted to the corresponding mixture of free acids, which were separated by semi-preparative HPLC, thereby affording the natural product, sordaricin (**3**). The structure of *iso*-**3** was assigned by the use of appropriate NMR spectroscopy experiments.

8.1.2 Cycloaddition studies

In an effort to increase the efficiency of the synthesis and to understand the formation of *iso*-**41**, an alternative reaction sequence was developed. The ketone **172** was heated in 1,2-dichlorobenzene to give cyclopentenone **188** in quantitative yield. After several relatively simple manipulations, aldehyde **65** could be synthesised. Upon heating **65** at 40 °C for three days, sordaricin methyl ester (**41**) was formed in quantitative yield. Formation of the isomeric product was not observed under these conditions. Demethylation then gave the pure natural product (**3**). Selective formation of only **41** was rationalised in terms of frontier orbital considerations.

Based on these kinetic results and some modelling that predicted *iso*-**41** to be more stable that **41**, it was thought that *iso*-**41** was being formed as a result of the reversibility of the intramolecular [4+2] cycloaddition. To prove this, pure sordaricin methyl ester (**41**) was subjected to a variety of thermal conditions. At 150 °C **41** isomerised to *iso*-**41**, to give a ratio of *iso*-**41** to **41** of about 80:20, at equilibrium. The same product distribution was observed when pure *iso*-**41** was subjected to the same conditions.

Based on the obvious energetic differences required for the cyclisation of diol **184** and **65**, and Borschberg's previous work, some speculations into the possible biosynthesis of the sordaricins were made.

8.2 Conclusions

8.2.1 Future work

As stated in Chapter Two, the synthetic plan towards sordaricin (**3**) should allow for the possibility for variation of the C1-alkyl substituent. Such variation might lead to a sordaricin analogue with enhanced biological activity, and, in the very least, would give some insight into structure activity relationships. However, due to the length of the synthetic sequence, it is unlikely that such derivatives would be of value as pharmaceuticals.

The formation of *iso*-**41** logically leads to speculation as to whether it, or derivatives thereof, would possess any significant biological activity. Research efforts are presently being directed in this area.

8.2.2 Overall conclusions

Two major driving forces behind the total synthesis of complex molecules are the development of convergent strategies and tandem reaction sequences. Such strategies allow highly functionalised molecules to be prepared in a concise and efficient manner.

The synthesis described in this thesis utilised a diastereoselective alkylation between two reasonably large molecules, allowing the convergent construction of an advanced intermediate, **168**. Further elaboration of **168** gave rise to aldehyde **64**, which underwent a tandem cycloreversion/intramolecular [4+2] cycloaddition to generate sordaricin's carbon skeleton in a single operation. Although the tandem process was not entirely selective in generating **41**, it highlights the large degree of molecular complexity that can be generated from simpler precursors. Flexibility in the overall synthetic strategy allowed for an alternative synthesis of sordaricin (**3**) to be carried out, whereby the cycloreversion step was performed on a substrate unable to undergo a subsequent cyclisation. Such flexibility in synthetic design enables the researcher to make critical adjustments an ensure success of the project.

Total synthesis also offers the opportunity to gain insight into natural product biosynthesis by exploring the viability of proposed transformations. Although previous work

by Kato and co-worker's indicated that an intramolecular [4+2] cycloaddition seemed a viable biosynthetic process, this thesis provides a detailed rationale as to the formation of sordaricin (**3**) over the alternative regioisomer of the cycloaddition, which has not been isolated from natural sources. This research also suggests that such a cycloaddition does not have to be enzyme mediated and that it is necessary for C17 to be a formyl substituent prior to cyclisation.

Endeavours in total synthesis often lead to unanticipated discoveries, such as the formation of *iso*-**41** during the tandem process used to construct the sordaricn (**3**) carbon framework. Such discoveries enrich the researcher, often providing useful information into chemical reaction pathways and sometimes allow practical applications for the research.

Overall, the research conducted towards this thesis was a success, in that a total synthesis of sordaricin (**3**) was achieved. More importantly, the undertaking of such a total synthesis provided many stimulating challenges and gave rise to some interesting discoveries.

Chapter Nine

Experimental

9.1 General experimental

Most proton (^1H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300, Varian Mercury 300 or Varian Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. Also used were an Inova 500 and Inova 600 spectrometer operating at 500 and 600 MHz, respectively for proton, and 125 and 150 MHz, respectively for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterochloroform ($CDCl_3$) at 20 ^oC unless otherwise stated. For ^1H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. ^1H NMR spectra are reported as follows: chemical shift (δ) [multiplicity (where multiplicity is defined as: br = broad; s = singlet; d = doublet; t = triplet; q = quartet; sep = septet; m = multiplet, or combinations thereof), coupling constant(s) *J* (Hz), relative integral, and assignment (where possible)]. ^{13}C NMR spectra were conducted using the attached proton test (APT) and the central peak (δ 77.0) of the $CDCl_3$ triplet was used as the internal reference. For ^{13}C NMR spectra, the data are reported as: chemical shift (δ) [protonicity (where protonicity is defined as: C = quaternary; CH = methine; CH_2 = methylene; Me = methyl); assignment (where possible)]. The assignments of various NMR spectra were often assisted by homonuclear ($^1H/^1H$) correlation spectroscopy (COSY), nuclear Overhauser effect (nOe, 1D NOESY) and/or heteronuclear ($^1H/^{13}C$) correlation spectroscopy experiments (HMQC and HMBC). For ^1H NMR spectra recorded in d_5-pyridine, the most downfield residual pyridine peak was used as a reference (δ 8.60). For ^{13}C NMR spectra, the most downfield triplet was used as a reference (δ 149.9).

Infrared spectra (υ_{max}) were recorded on a Perkin-Elmer Spectrum *One* instrument. Samples were analysed as thin films on NaCl discs.

Low and high resolution mass spectra were recorded on a VG Fisions AutoSpec three sector (E/B/E) double focussing mass spectrometer, using positive-ion electron impact techniques (unless otherwise stated). Mass spectra data are listed as follows: mass-to-charge ratio (*m/z*) (assignment [where possible]; intensity as relative % of base peak).

Optical rotations were measured at 20 ^oC with a Perkin-Elmer 241 polarimeter at the sodium D-line (589 nm) using the spectroscopic grade solvents specified and at the concentrations (*c*) (g/100 mL) indicated. The measurements were carried out in a cell with a path length of 1 dm. Specific rotations ($[\alpha]_D^{20}$) were calculated using the equation $[\alpha]_D = (100.\alpha)/(c.1)$ and are given in $10^{-1}.deg.cm^2.g^{-1}$.

Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected.

Elemental analyses were preformed by the Australian National University Microanalytical Services Unit based in the Research School of Chemistry, The Australian National University, Canberra, Australia.

Analytical thin layer chromatography (TLC) was conducted on aluminum backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the chromatographs visualised under a 254 nm UV lamp and/or by treatment with a vanillin dip (1.7 g vanillin, 225 mL ethanol, 45 mL acetic acid and 15 mL conc. sulfuric acid), followed by heating. The retention factor (R_f) quoted is rounded to the nearest 0.05. Flash chromatography was conducted according to the method of Still and co-workers[1] using silica gel 60 (mesh size 0.040-0.063 mm) as the stationary phase and the analytical (AR) grade solvents indicated. Unless otherwise stated, petroleum spirits refers to petroleum spirits 60-80 °C.

Many materials and reagents were available from the Aldrich Chemical Company and were used as supplied or simply dried and distilled. Magnesium sulfate for drying was purchased from the Aldrich Chemical Company, and other inorganic salts were purchased from BDH or Asia Pacific Specialty Chemicals. Reactions employing air and moisture sensitive reagents and intermediates were conducted under an atmosphere of dry, oxygen free nitrogen in flame dried apparatus.

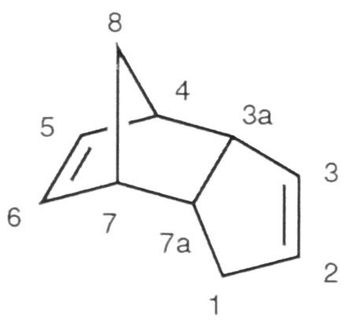
Room temperature is assumed to be *ca.* 18 °C.

THF and diethyl ether were dried using sodium metal and then distilled, as required, from sodium benzophenone ketyl. DCM and benzene were distilled from calcium hydride.

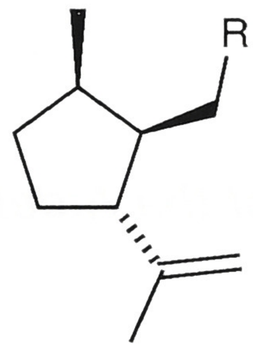
Organic solutions obtained from the work-up of reaction mixtures were dried with magnesium sulfate ($MgSO_4$). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator with the water bath generally not exceeding 40 °C. Samples were then subjected to high vacuum to remove any remaining solvent.

9.2 Notes on nomenclature

The compounds in this dissertation are named according to IUPAC conventions. The common ring systems of compounds synthesised during the course of this research are indicated below:



3a,4,7,7a-Tetrahydro-1*H*-4,7-methano-indene

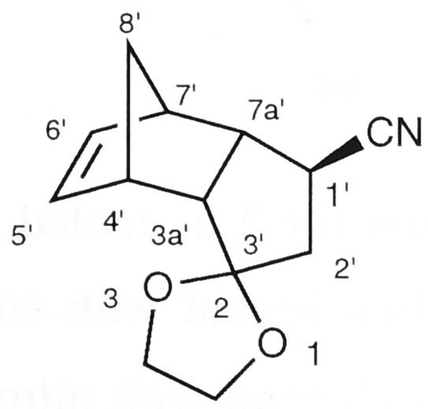


When R = OMOM or I, compounds named as cyclopentane derivatives.

When R = OH, compounds named as cyclopentyl derivatives of methanol.

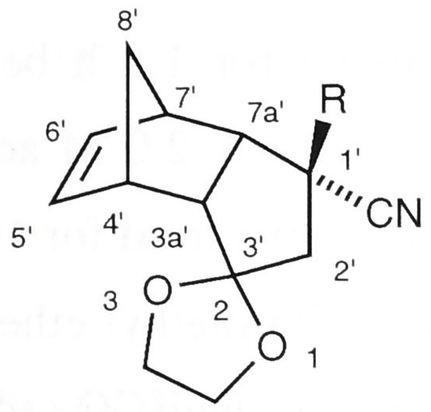
When R = OTBS, compounds named as cyclopentyl derivatives of *tert.*-butyl-dimethylsilane.

The numbering of compounds will vary depending upon substituent precedence.



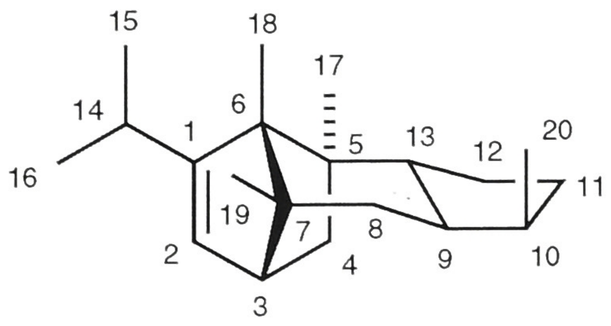
2',3',3a',4',7',7a'-Hexahydro-1*H*-4',7'-methano-indene-1'-cyano-3'-spiro-2-[1,3]dioxolane

The dioxolane group takes precedence over the indene ring system.

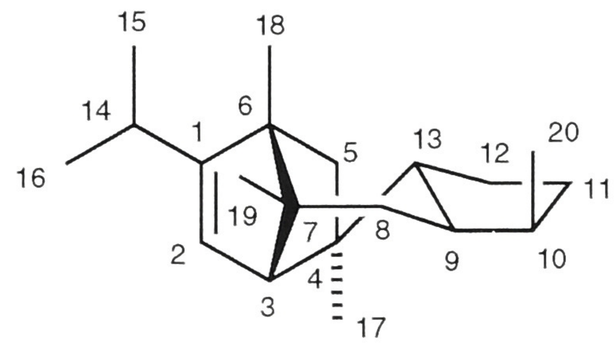


1'-Alkyl-2',3',3a',4',7',7a'-hexahydro-1*H*-4',7'-methano-indene-1'-cyano-3'-spiro-2-[1,3]dioxolane

The alkyl group (R) at C1′ is subordinate to the indene ring system.



sordaricane



iso-*sordaricane*

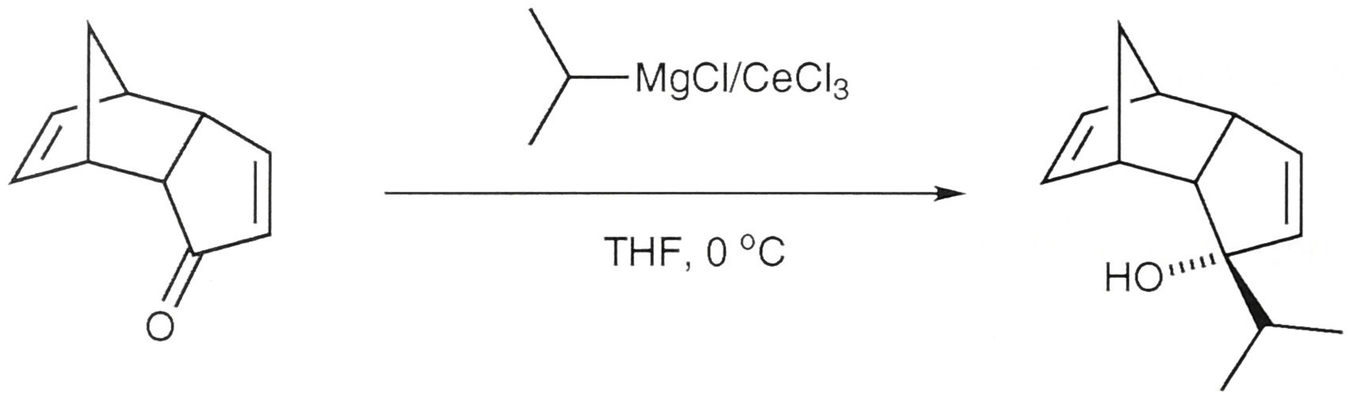
The trivial name sordaricane[2] is used for the carbon skeleton of sordaricin derivatives. The numbering used follows that used by Vasella.[3] The numbering of the isomeric sordaricane is as shown above.

The stereochemistry of compounds was determined using IUPAC rules.[4] For racemic compounds, the first stereocentre is labelled (*RS*) and the others (*RS*) or (*SR*) according to whether they are *R* or *S* when the first is *R*. For single enantiomer compounds, the structure shown corresponds with the descriptors given in the compound name.

9.3 Experimental procedures

9.3.1 Chapter Three – Synthesis of the Aldehyde 60

(*1RS*,3a*RS*,4*SR*,7*RS*,7a*SR*)-1-Isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-inden-1-ol (82)



(±)-54 **82**

$CeCl_3.7H_2O$ (7.0 g, 18.7 mmol) was heated at 130 °C under vacuum for 2 h, cooled to room temperature and crushed into a fine powder. The powder was then heated with stirring at 130 °C under vacuum for two days, after which time the flask was charged with nitrogen gas and cooled to room temperature. THF (130 mL) was added in a single volume and the suspension stirred for 5 h. Isopropylmagnesium chloride/THF (2.0 M, 9.4 mL, 18.7 mmol) was added dropwise to the stirred suspension at 0 °C and stirring continued for 1.5 h before a solution of ketone (±)-**54** (2.5 g, 17.0 mmol) in THF (20 mL) was added. A 2.0 M aqueous acetic acid solution (25 mL) was added after 30 min and the reaction mixture stirred for 10 min. When all the solid had dissolved the solution was extracted three times with diethyl ether (100 mL). The combined organic extracts were washed with a saturated aqueous $NaHCO_3$ solution (100 mL), brine (100 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 25% ethyl acetate in petroleum spirits as the eluant, afforded the alcohol **82** (2.7 g, 83%) as a colourless oil.

R_f 0.75 (3:1, petroleum spirits:ethyl acetate)

IR υ_{max} 3480, 3044, 2962, 2874, 1468, 1370, 1341, 1166, 1075, 1024, 774 cm^{-1}.

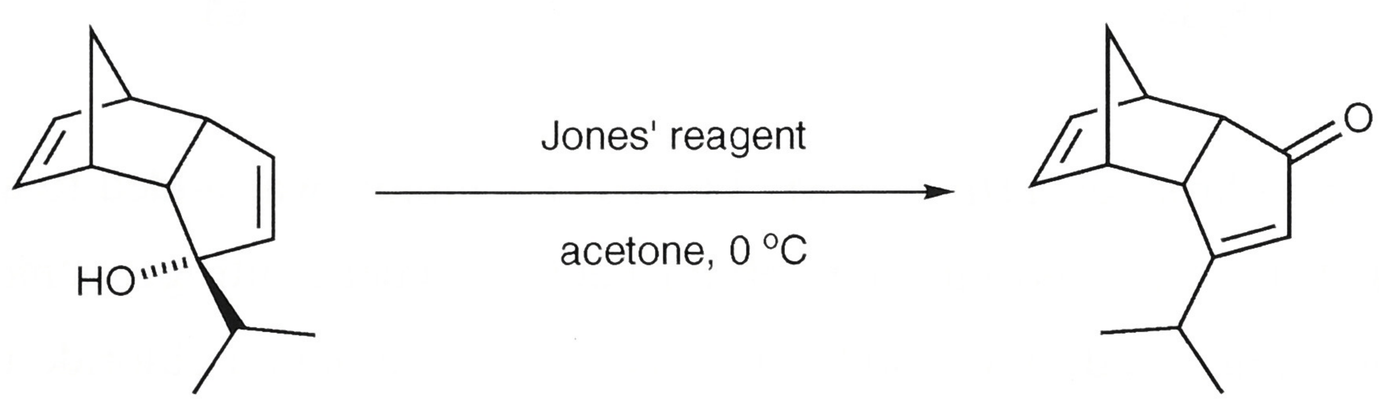
^{1}H NMR: 0.88 (d, 3 H, *J* = 6.8 Hz, CH*Me*), 0.93 (d, 3 H, *J* = 6.7 Hz, CH*Me*), 1.36 (s, 1 H, OH), 1.46 (d, 1 H, *J* = 8.1 Hz, H8), 1.58 (dt, 1 H, *J* = 7.7, 1.6 Hz, H8′), 1.74 (sep, 1 H, *J* = 6.9 Hz, C*H*Me_2), 2.65 (dd, 1 H, *J* = 7.8, 3.0 Hz, H3a or H7a), 2.86 (m, 2 H, H4 + H7), 3.19 (m, 1 H, H7a or H3a), 5.43 (dd, 1 H, *J* = 5.8, 1.7 Hz, H3), 5.55 (dd, 1 H, *J* = 5.7, 2.0 Hz, H2), 5.86 (dd, 1 H, *J* = 5.6, 3.2 Hz, H5 or H6), 6.18 (dd, 1 H, *J* = 5.6, 2.8 Hz, H6 or H5).

^{13}C NMR: 16.5 (Me), 17.1 (Me), 37.5 (CH), 45.4 (CH), 46.3 (CH), 49.5 (CH), 52.4 (CH_2), 53.7 (CH), 86.3 (C), 133.2, 134.4, 134.5, 136.8 (4 × =CH).

MS: *m/z* 190 ($M^{+\cdot}$, 14%), 172 (32), 157 (37), 147 (52), 129 (38), 124 (45), 119 (24), 109 (100), 91 (40), 81 (46).

HRMS: calcd for $C_{13}H_{18}O_1$ 190.1358, found 190.1355.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-3-Isopropyl-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one (80)



82 **80**

Jones' reagent was added dropwise to a stirred solution of alcohol **82** (1.4 g, 7.2 mmol) in acetone (70 mL) at 0 °C, until no starting material remained by TLC. Propan-2-ol (5 mL) was added and the resulting blue-green solution diluted with water (100 mL) and extracted twice with ethyl acetate (100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography on a column of silica gel using 50% ethyl acetate in petroleum spirits as the eluant, afforded the enone **80** (940 mg, 70%) as a colourless oil.

R_f 0.30 (3:1, petroleum spirits:ethyl acetate)

IR υ_{max} 2966, 2872, 1694, 1601, 1466, 1337, 1267, 1180, 770 cm^{-1}.

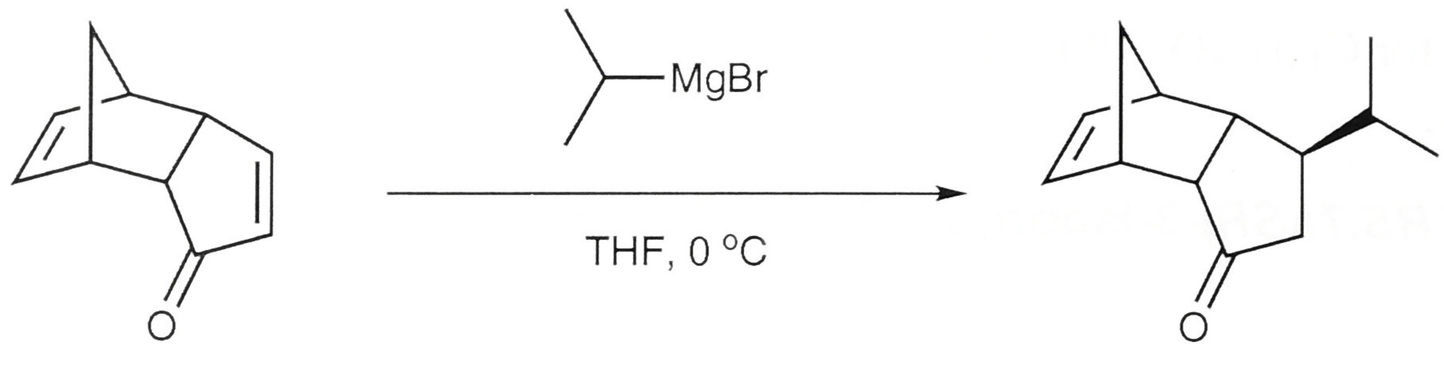
^{1}H NMR: 1.13 (d, 1 H, *J* = 6.9 Hz, CH*Me*), 1.16 (d, 1 H, *J* = 7.0 Hz, CH*Me*), 1.58 (br d, 1 H, *J* = 8.4 Hz, H8), 1.75 (dt, 1 H, *J* = 8.4, 1.2 Hz, H8´), 2.45 (sep, 1 H, *J* = 6.7 Hz, C*H*Me_2), 2.85 (t, 1 H, *J* = 5.2 Hz, H7a), 3.00 (m, 1 H, H4), 3.18 (m, 1 H, H7), 3.37 (td, 1 H, *J* = 4.4, 1.1 Hz, H7a), 5.69 (s, 1 H, H2), 5.75 (dd, 1 H, *J* = 5.5, 3.1 Hz, H5 or H6), 5.98 (dd, 1 H, *J* = 5.5, 3.1 Hz, H6 or H5).

^{13}C NMR: 20.3 (Me), 21,1 (Me), 30.9 (CH), 43.8 (CH), 43.9 (CH), 48.3 (CH), 51.2 (CH), 52.1 (CH_2), 130.0 (CH, C2), 131.6, 133.1 (2 × =CH), 133.1 (C, C3), 210.0 (C, CO).

MS: *m/z* 188 ($M^{+\cdot}$, 48%), 173 (46), 160 (21), 145 (48), 123 (34), 117 (48), 105, 17), 91 (32), 77 (27), 66 (100).

HRMS: calcd for $C_{13}H_{16}O_1$ 188.1201, found 188.1199.

(3*RS*,3a*RS*,4*RS*,7*SR*,7a*RS*)-3-Isopropyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (83)



(±)-54 83

Isopropylmagnesium bromide/THF (2.5 M, 3.0 mL, 7.5 mmol) was added to a stirred solution of enone (±)-**54** (1.0 g, 6.8 mmol) in THF (50 mL) at 0 °C under a nitrogen atmosphere. After 1 h the reaction was quenched by the addition of aqueous ammonium chloride (10 mL), diluted with 1.0 M HCl (50 mL) and extracted two times with ethyl acetate (100 mL). The combined organic extracts were washed with brine (75 mL) and dried ($MgSO_4$). Concentration *in vacuo* afforded the ketone **83** (1.29 g, 100%) as a colourless oil.

R_f 0.65 (3:1, petroleum spirits:ethyl acetate)

IR υ_{max} 2960, 1733, 1468, 1404, 1386, 1340, 1233, 1198, 1168, 835 cm^{-1}.

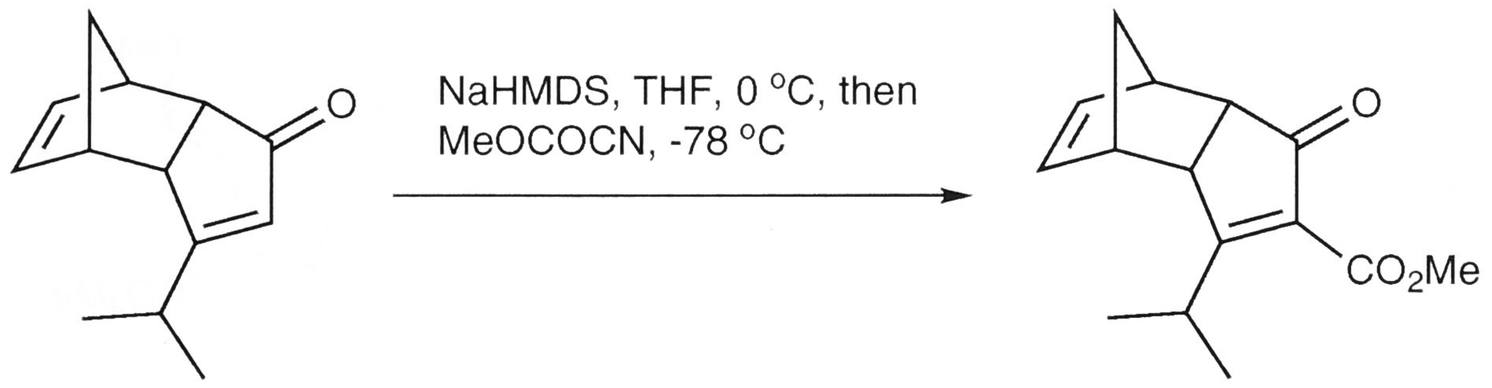
^{1}H NMR: 0.85 (d, 3 H, *J* = 6.6 Hz, CH*Me*), 0.94 (d, 3 H, *J* = 6.6 Hz, CH*Me*), 1.42-1.66 (m, 4 H), 2.02 (ddd, 1 H, *J* = 18.5, 7.8, 1.9 Hz, H2), 2.16 (dd, 1 H, *J* = 18.5, 9.1 Hz, H2´), 2.69 (m, 1 H, H4), 2.92 (ddd, 1 H, *J* = 9.8, 4.7, 1.8 Hz, 7aH), 3.00, 3.15 (m, 2 × 1 H, H4 + H7), 6.14 (m, 2 H, H5 + H6).

^{13}C NMR: 20.0 (Me), 20.1 (Me), 34.1 (CH), 43.7 (CH), 45.6 (CH), 46.0 (CH_2), 46.2 (CH), 47.3 (CH), 52.1 (CH_2), 55.1 (CH), 134.9, 135.7 (2 × =CH), 219.8 (CO).

MS: *m/z* 190 ($M^{+\cdot}$, 1%), 147 (8), 125 (84), 109 (15), 89 (44), 66 (100).

HRMS: calcd for $C_{13}H_{18}O_1$ 190.1358, found 190.1356.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-Methyl-3-isopropyl-1-oxo-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (81)



80 **81**

NaHMDS/THF (1.0 M, 15.1 mL, 15.1 mmol) was added dropwise to a stirred solution of enone **80** (1.9 g, 10 mmol) in THF (100 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1.5 h, cooled to -78 °C and methyl cyanoformate (2.4 mL, 30 mmol) added. After 30 min, water (25 mL) was carefully added and the reaction mixture allowed to warm to room temperature, then diluted with water (75 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 30% ethyl acetate in petroleum spirits as the eluant, to afford ester **81** (1.8 g, 73%) as an oil.

R_f 0.40 (3:1, petroleum spirits:ethyl acetate)

IR υ_{max} 2971, 2876, 1739, 1703, 1606, 1468, 1432, 1335, 1288, 1234, 1187, 1125, 1028 cm^{-1}.

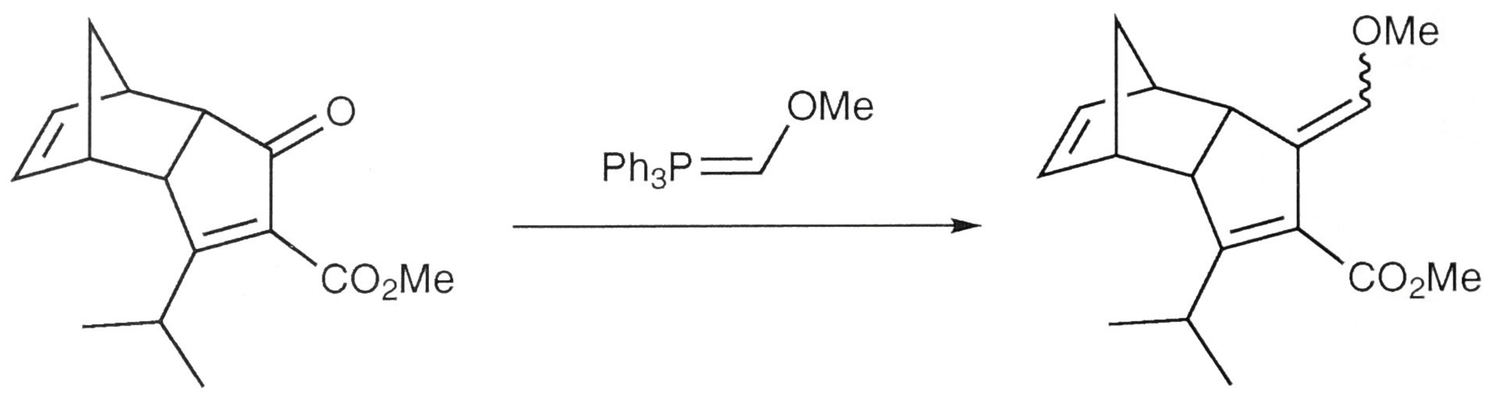
^{1}H NMR: 1.19 (d, 3 H, *J* = 7.4 Hz, CH*Me*), 1.22 (d, 3 H, *J* = 7.4 Hz, CH*Me*), 1.62 (br d, 1 H, *J* = 8.5 Hz, H8), 1.77 (dt, 1 H, *J* = 8.5, 1.8 Hz, H8´), 2.9 (dd, 1 H, *J* = 4.8, 4.8 Hz, H7a), 3.14 (m, 1 H, H4), 3.24 (m, 1 H, H7), 3.36 (sep, 1 H, *J* = 7.4 Hz, C*H*Me_2), 3.42 (dd, 1 H, *J* = 5.8, 4.1 Hz, H3a), 3.78 (s, 3 H, CO_2*Me*), 5.78 (dd, 1 H, *J* = 5.6, 2.6 Hz, H5), 6.05 (dd, 1 H, *J* = 5.6, 3.0 Hz, H6).

^{13}C NMR: 20.9 (Me), 21.2 (Me), 30.6 (CH), 44.4 (CH), 46.0 (CH), (51.2 (CH), 51.9 (OMe), 52.8 (CH_2), 132.1, 134.0 (2 × =CH), 134.6 (C, C2), 164.1 (C, *C*O_2Me), 190.7 (C, C3), 204.2 (C, CO).

MS: *m/z* 246 ($M^{+\cdot}$, 25%), 214 (26), 181 (40), 171 (26), 149 (100), 122 (21), 115 (15), 91 (26), 66 (81).

HRMS: calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1254.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-Methyl-3-isopropyl-1-methoxymethylene-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (106)



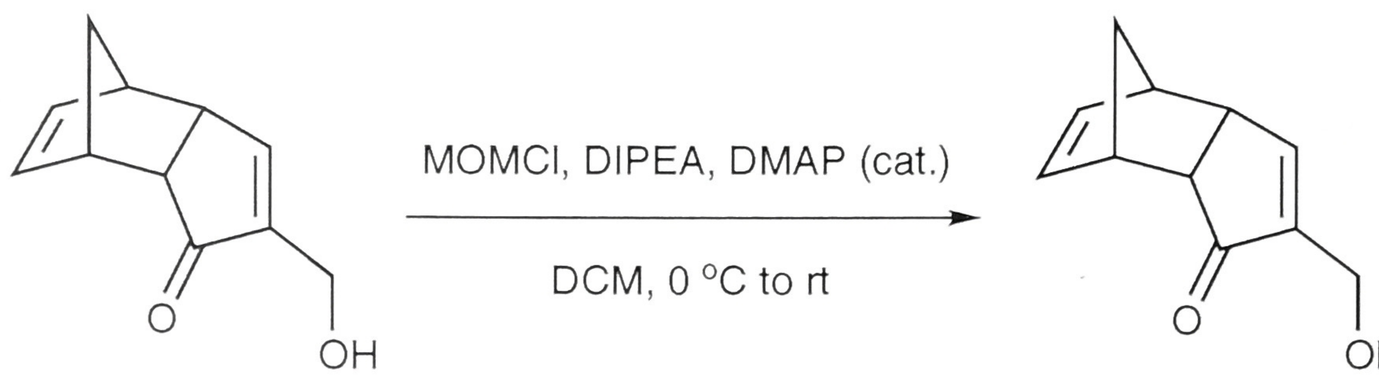
81 **106**
(~1:1 mixture of *E*- and *Z*-isomers)

^{t}BuOK/^{t}BuOH (1.0 M, 1.0mL, 1.0 mmol) was added to a stirred suspension of methoxymethyltriphenylphosphonium chloride (343 mg, 1.0 mmol) in diethyl ether (9.0 mL) at room temperature under a nitrogen atmosphere. To the resulting bright orange solution was added a solution of enone **81** (50mg, 0.2 mmol) in diethyl ether (1.0 mL) and the reaction mixture allowed to stir for 15 h before water (5 mL) was carefully added. The resulting mixture was further diluted with water (15 mL) and extracted twice with diethyl ether (15 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 5% ethyl acetate in petroleum spirits as the eluant, to give a 1:1 mixture of enol ethers **106** (20 mg, 37%) as an oil. This sample was contaminated with triphenylphosphine oxide residues.

$\mathbf{R}_f$ 0.80 (3:1, petroleum spirits:ethyl acetate)

^{1}H NMR: Key signals of isomers: 5.81 (s, 1 H, =C*H*OMe); 6.39 (s, 1 H, =C*H*OMe).

(3a*RS*,4*SR*,7*RS*,7a*SR*)-2-Methoxymethoxymethyl-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one (109)



108 **109**

To a stirred solution of alcohol **108** (730 mg, 4.1 mmol) and DMAP (51 mg, .41 mmol) in DCM (40 mL) at 0 °C under a nitrogen atmosphere was added DIPEA (1.4 mL, 8.2 mmol) and MOMCl (472 μL, 6.15 mmol). After stirring at room temperature for 16 h, a further 1.0 equiv. of DIPEA and MOMCl were added, and the mixture stirred for 5 h. The reaction mixture was diluted with 1.0 M HCl (50 mL) and extracted three times with DCM (20 mL). The combined

organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 20%, increasing to 50% ethyl acetate in petroleum spirits as the eluant, to afford **109** (820 mg, 91%) as a pale yellow oil.

R_f 0.55 (3:1, petroleum spirits:ethyl acetate)

IR υ_{max} 2936, 1697, 1634, 1454, 1392, 1338, 1150, 1114, 1040, 918 cm^{-1}.

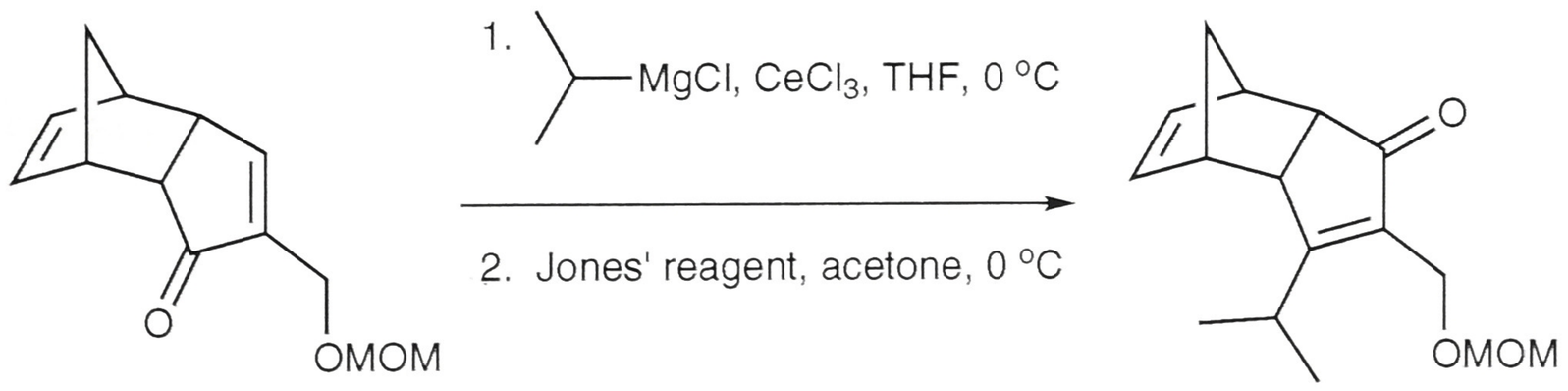
^{1}H NMR: 1.62 (d, 1 H, *J* = 8.5 Hz, H8), 1.75 (dt, 1 H, *J* = 8.4, 1.8 Hz, H8´), 2.88 (t, 1 H, *J* = 4.8 Hz, H7a), 2.96 (m, 1 H, H4), 3.33 (m, 1 H, H3a), 3.34 (s, 3 H, OMe), 4.06, 4.13 (AB d, 2 H, *J* = 13.8 Hz, CH_2OMOM), 4.60 (s, 2 H, OCH_2OMe), 5.77 (dd, 1 H, *J* = 5.6, 2.9 Hz, H5 or H6), 5.90 (dd, 1 H, *J* = 5.6, 2.9 Hz, H6 or H5), 7.26 (m, 1 H, H3).

^{13}C NMR: 43.8 (CH), 44.8 (CH), 45.5 (CH), 51.0 (CH), 52.5 (CH_2), 55.0 (OMe), 60.5 (CH_2), 95.6 (CH_2), 132.0, 132.1 (2 × =CH), 145.3 (C, C2), 159.1 (CH, C3), 208.0 (C, CO).

MS: *m/z* 220 ($M^{+\cdot}$, 9%), 188 (65), 158 (100), 130 (75), 115 (47), 88 (47), 73 (37), 66 (93).

HRMS: calcd for $C_{15}H_{16}O_3$ 220.1099, found 220.1100.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-3-Isopropyl-2-methoxymethoxymethyl-3a,4,7,7a-tetrahydro-4,7-methano-inden-1-one (110)



109 **110**

$CeCl_3.7H_2O$ (1.35 g, 3.6 mmol) was heated at 130 °C under vacuum for 2 h, before being cooled to room temperature and crushed into a fine powder. The powder was then heated with stirring at 130 °C under vacuum for two days, after which time the flask was charged with nitrogen gas and cooled to room temperature. THF (10 mL) was added in a single volume and the suspension stirred for 5 h. Isopropylmagnesium chloride/THF (2.0M, 909 μL, 1.8 mmol) was added dropwise to the stirred suspension at 0 °C and stirring continued for 1.5 h before a solution of ketone **109** (200 mg, 0.9 mmol) in THF (2 mL) was added. 1.0 M HCl (30 mL) was carefully added after 30 min and the reaction mixture stirred for 10 min. When all the solid had dissolved the solution was extracted three times with diethyl ether (20 mL). The combined

organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). Concentration *in vacuo* afforded a crude alcohol (240mg, 100 %) as a colourless oil which was used directly in the next reaction.

Jones' reagent was added dropwise to a stirred solution of the alcohol (240 mg, 0.9 mmol) in acetone (10 mL) at 0 °C, until no starting material remained by TLC. Propan-2-ol (5 mL) was added and the resulting blue-green solution diluted with water (50 mL) and extracted three times with diethyl ether (20 mL). The combined organic extracts were washed with brine (30mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography on a column of silica gel using 40% ethyl acetate in petroleum spirits as the eluant, afforded the enone **110** (120 mg, 50% over 2 steps) as a colourless oil.

R_f 0.60 (3:1, petroleum spirits:ethyl acetate)

IR υ_{max} 2966, 1695, 1627, 1468, 1391, 1333, 1200, 1149, 1102, 1031cm^{-1}.

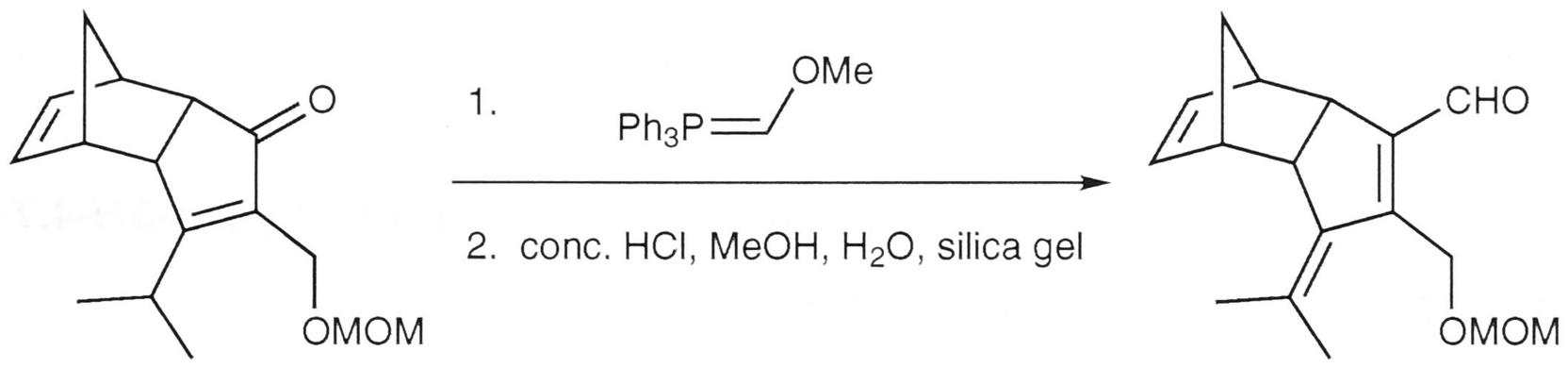
^{1}H NMR: 1.17 (d, 3 H, *J* = 7.2 Hz, CH*Me*), 1.22 (d, 3 H, *J* = 7.2 Hz, CH*Me*), 1.62 (d, 1 H, *J* = 8.4 Hz, H8), 1.76 (dt, 1 H, *J* = 8.4, 1.8 Hz, H8´), 2.85 (t, 1 H, *J* = 4.8 Hz, H7a), 3.07 (m, 1 H, H4 or H7), 3.10 (sep, 1 H, *J* = 7.2 Hz, C*H*Me$_2$), 3.19 (m, 1 H, H7 or H4), 3.36 (m, 1 H, H3a), 3.36 (s, 3 H, OMe), 4.05 (s, 2 H, C*H*$_2$OMOM), 4.55 (s, 2 H, OC*H*$_2$OMe), 5.72 (dd, 1 H, *J* = 5.6, 2.9 Hz, H5 or H6), 5.95 (dd, 1 H, *J* = 5.6, 2.8 Hz, H6 or H5).

^{13}C NMR: 21.1 (2 × Me), 29.5 (CH), 43.7 (CH), 45.1 (CH), 45.4 (CH), 50.4 (CH), 52.6 (CH_2), 55.2 (OMe), 57.1 (CH_2), 95.7 (CH_2), 131.8, 133.2 (2 × =CH), 138.2 (C, C2), 183.2 (C, C3), 208.2 (C, CO).

MS: *m/z* 262 ($M^{+\cdot}$, 27%), 230 (33), 200 (100), 185 (40), 172 (58), 157 (51), 135 (83), 107 (27), 91 (39), 66 (68).

HRMS: calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1567.

(3a*RS*,4*SR*,7*RS*,7a*SR*)-3-Isopropylidene-2-methoxymethoxymethyl-3a,4,7,7a-tetrahydro-3*H*-4,7-methano-indene-1-carbaldehyde (112)



110 **112**

NaHMDS/THF (1.0 M, 12.1 mL, 12.1 mmol) was added dropwise to a stirred suspension of methoxymethyltriphenylphosphonium chloride (4.1 g, 12.1 mmol) in THF (40 mL) at 0 °C under a nitrogen atmosphere. After 10 min, a solution of ketone **110** (790 mg, 3.0 mmol) in THF (10 mL) was added and the reaction mixture allowed to warm to room temperature. After 24 h, the mixture was diluted with water (100 mL) and extracted three times with diethyl ether (60 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting residue was partially purified by flash chromatography on a column of silica gel, using 10%, then 20% ethyl acetate in petroleum spirits as the eluant, to afford a mixture of enol ethers **111** (440 mg) which were used in the next reaction.

To a stirred solution of enol ethers **111** (250 mg, 0.86 mmol) in methanol (10 mL) and water (2 mL) was added silica gel (1 spatula tip) and conc. HCl (5 drops). After 2 days the reaction mixture was diluted with water (30 mL) and extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting residue was purified by flash chromatography on a column of silica gel, using 5% ethyl acetate in petroleum spirits to afford the aldehyde **112** (75 mg, 32%).

R_f 0.70 (3:1, petroleum spirits:ethyl acetate)

IR υ_{max} 2970, 1715, 1620, 1436, 1343, 1230, 1122, 1035 cm^{-1}.

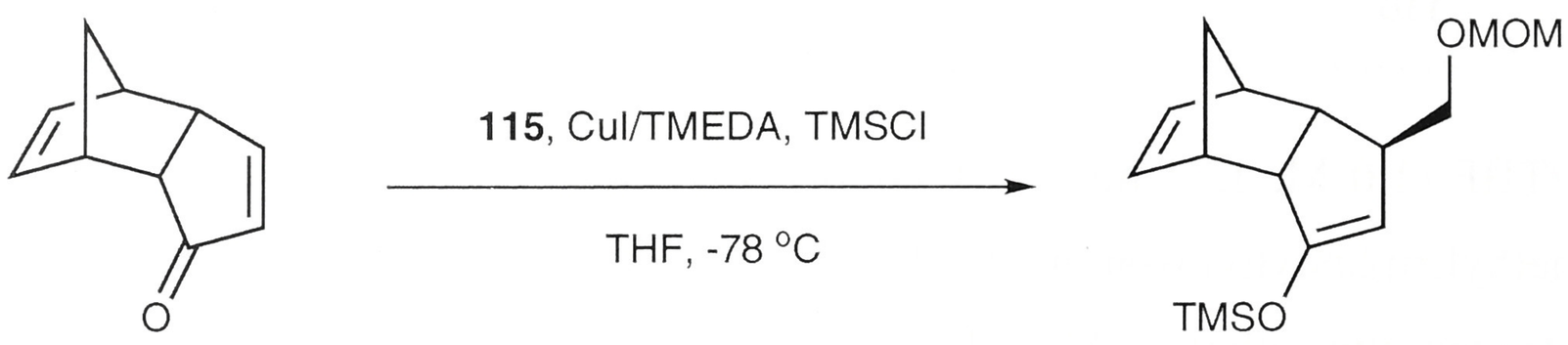
^{1}H NMR: 1.35 (br d, 1 H, *J* = 8.2 Hz, H8), 1.47 (dt, 1 H, *J* = 8.2, 1.6 Hz,H8´), 1.98 (s, 3 H, Me), 2.00 (s, 3 H, Me´), 3.17 (br s, 1 H), 3.21 (br s, 2 H), 3.36 (s, 3 H, OMe), 3.37 (obscured br s, 1 H), 4.56 (s, 2 H, OCH_2OMe), 4.62 (AB d, 2 H, *J* = 6.7 Hz, CH_2OMOM), 5.69 (m, 1 H, H5 or H6), 5.79 (m, 1 H, H6 or H5), 10.09 (s, 1 H, CHO).

^{13}C NMR: 21.4 (Me), 25.4 (Me), 45.2 (CH), 46.0 (CH), 46.6 (CH), 46.8 (CH), 49.5 (CH_2), 55.5 (OMe), 59.3 (CH_2), 94.9 (CH_2), 132.9, 134.3 (2 × =CH), 136.0, 140.1, 146.8, 154.7 (4 × =C), 189.8 (CHO).

MS: *m/z* 274 ($M^{+\cdot}$, 8%), 245 (19), 208 (22), 187 (58), 163 (63), 146 (47), 122 (66), 91 (69), 77 (44), 66 (100).

HRMS: calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1566.

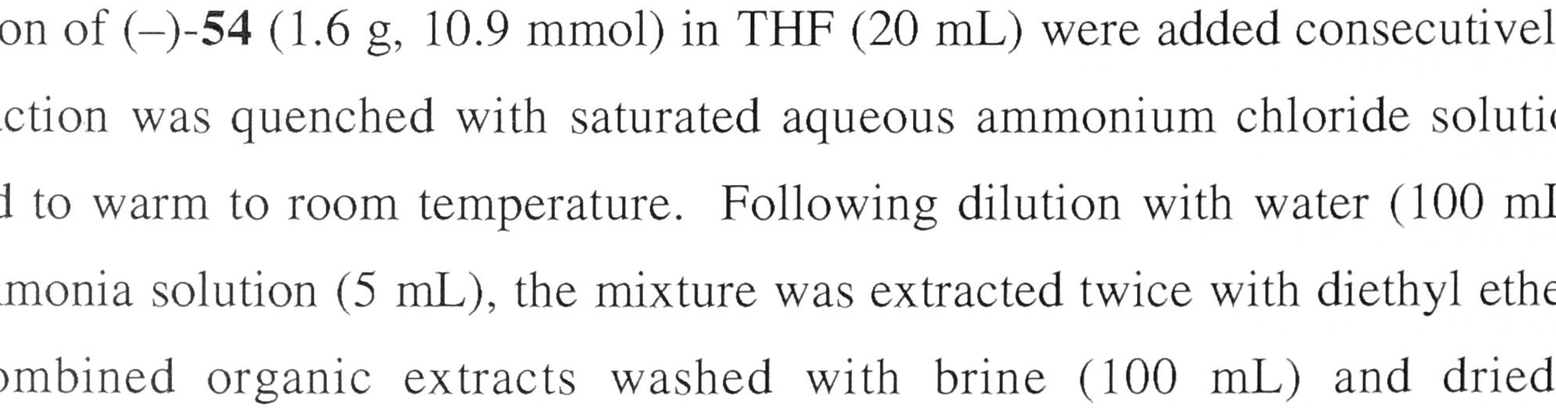
(3*S*,3a*R*,4*R*,7*S*,7a*R*)-(3-Methoxymethoxymethyl-3a,4,7,7a-tetrahydro-3*H*-4,7-methano-inden-1-yloxy)-trimethyl-silane (116)



(-)-54 116

n-BuLi/hexanes (1.6 M, 13.7 mL, 21.8 mmol) was added dropwise to a stirred solution of *n*-Bu_3SnCH_2OMOM (8.0 g, 21.8 mmol) in THF (60 mL) at –78 °C under a nitrogen atmosphere. After 5 min the reaction mixture was transferred *via* a cannula to a stirred solution of CuI (2.1 g, 10.9 mmol) and TMEDA (5.0 mL, 32.7 mmol) in THF (20 mL) at –78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 min before TMSCl (4.2 mL, 32.7 mmol) and a solution of (–)-**54** (1.6 g, 10.9 mmol) in THF (20 mL) were added consecutively. After 45 min the reaction was quenched with saturated aqueous ammonium chloride solution (10 mL) and allowed to warm to room temperature. Following dilution with water (100 mL) and 10% aqueous ammonia solution (5 mL), the mixture was extracted twice with diethyl ether (150 mL) and the combined organic extracts washed with brine (100 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using petroleum spirits, then 5% ethyl acetate in petroleum spirits as the eluant, afforded the unstable silyl enol ether **116** (2.23 g, 73%) which was used immediately in the next reaction.

(3*R*,3a*S*,4*R*,7*S*,7a*R*)-3-Methoxymethoxymethyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (201)



116 201

For the purposes of characterisation a small amount of **116** was hydrolysed to the corresponding ketone **201** by stirring in 1.0 M HCl in THF.

$\mathbf{R}_f$ 0.60 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –155.4° (*c* 0.68 $CHCl_3$)

IR υ_{max} 3434, 2920, 1729, 1642, 1450, 1400, 1338, 1183, 1150, 1107, 1038, 916 cm^{-1}.

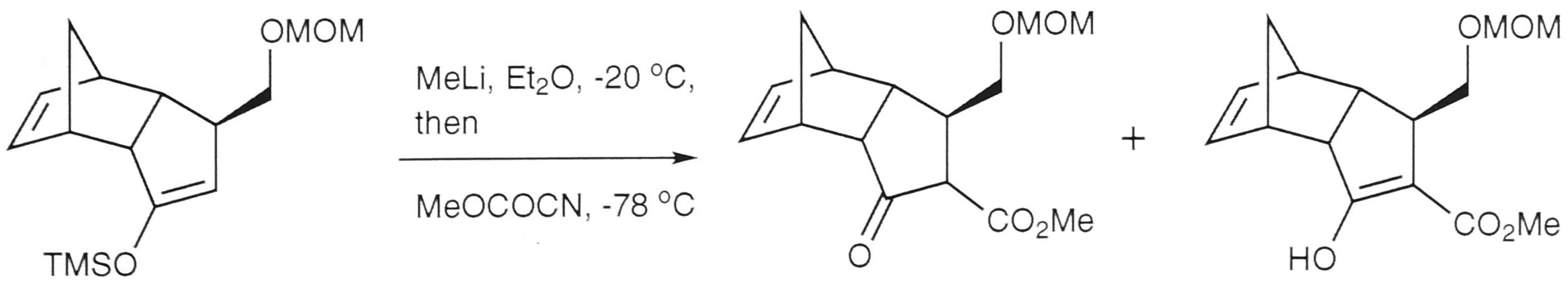
^{1}H NMR: 1.42 (d, 1 H, *J* = 8.4 Hz, H8), 1.54 (dt, 1 H, *J* = 8.3 Hz, H8´), 2.05 (m, 2 H, H2 + H3), 2.19 (dd, 1 H, *J* = 19.5, 10.6 Hz, H4´), 2.75 (m, 1 H, H3a,), 2.93 (dd, 1 H, *J* = 9.2, 4.7 Hz, H7a), 3.07 (m, 1 H, H4), 3.19 (m, 1 H, H7), 3.35 (s, 3 H, OMe), 3.46 (AB d, 2 H, *J* = 5.6 Hz, C*H*$_2$OMOM), 4.60 (s, 2 H, OC*H*$_2$OMe), 6.13 (dd, 1 H, *J* = 5.6, 2.9 Hz, H6), 6.20 (dd, 1 H, *J* = 5.6, 3.0 Hz, H5).

^{13}C NMR: 36.5 (CH), 44.6 (CH_2), 45.5 (CH), 46.6 (CH), 46.9 (CH), 52.0 (CH_2), 54.5 (CH), 55.1 (OMe), 72.1 (CH_2), 96.3 (CH_2), 134.7, 136.0 (2 × =CH), 220.6 (C, CO).

MS: *m/z* 222 ($M^{+\cdot}$, 2%), 157 (56), 117 (7), 97 (38), 95 (45), 79 (8), 66 (100).

HRMS: calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1257.

(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-1-methoxymethoxymethyl-3-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methano-indene-2-carboxylate (117, keto tautomer)
(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-3-hydroxy-1-methoxymethoxymethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (118, enol tautomer)



116 **117** **118**

MeLi/diethyl ether (1.0 M, 6.2 mL, 8.8 mmol) was added dropwise to a solution of silyl enol ether **116** (2.23 g, 8.0 mmol) in THF (70 mL) at –20 °C under a nitrogen atmosphere. Stirring was continued at –20 °C for 30 min, then after cooling to –78 °C methyl cyanoformate (1.3 mL, 16.0 mmol) was added. After 20 min water (10 mL) was carefully added and the solution allowed to warm to room temperature. The mixture was further diluted with water (100 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 10%, increasing to 20% ethyl

acetate in petroleum spirits as the eluant, to afford **117/118** (1.6 g, 71%) as an inseparable mixture of enol:keto (6:1) tautomers.

$\mathbf{R}_f$ 0.65 and 0.75 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –131.0° (*c* 0.78 $CHCl_3$)

IR υ_{max} 2952, 1756, 1731, 1661, 1619, 1445, 1358, 1342, 1243, 1217, 1150, 1111, 1041, 917cm^{-1}.

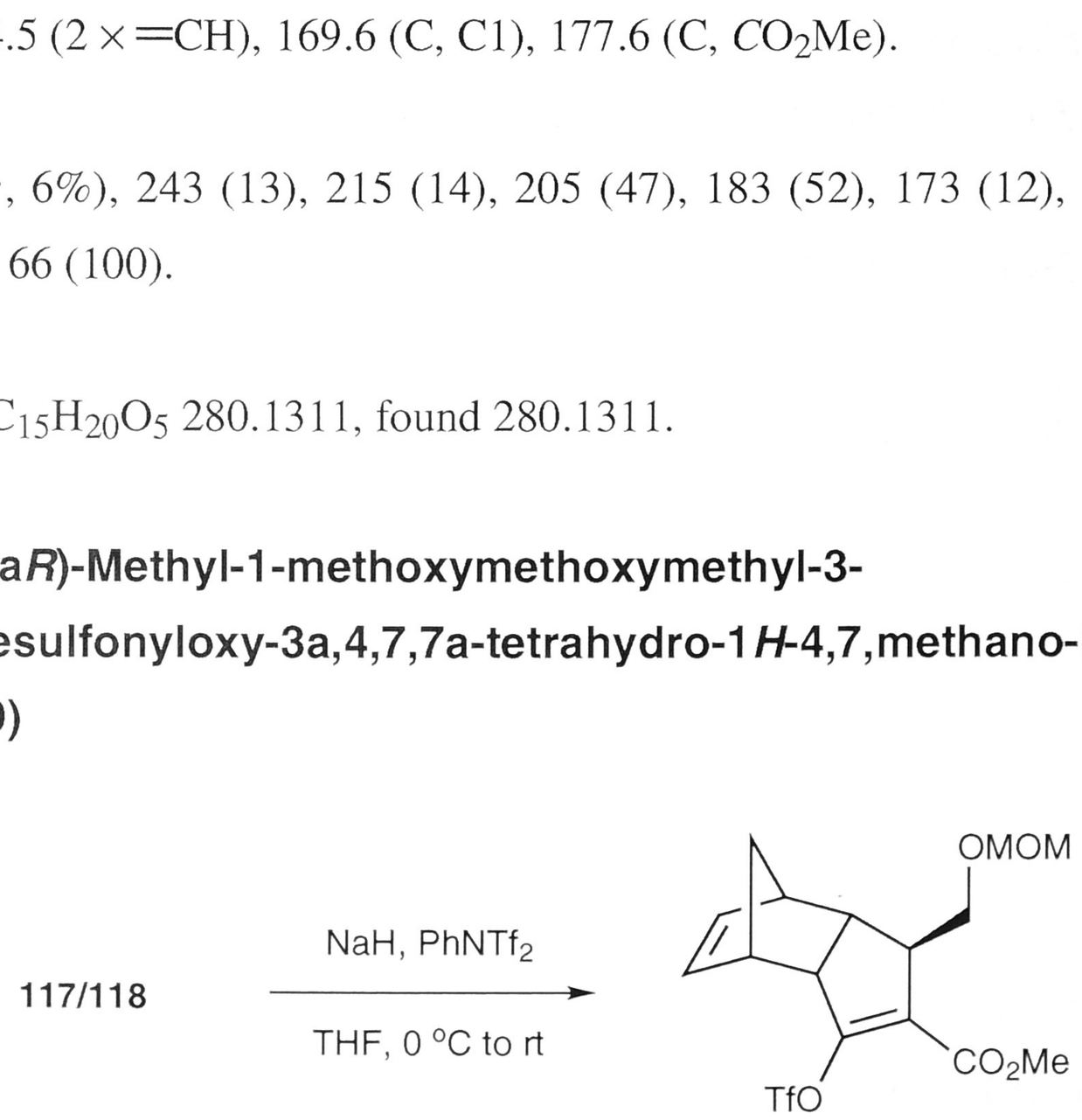
^{1}**H NMR:** Key signals **117**: 1.47 (d, 1 H, H8), 1.62 (d, 1 H, H8´), 6.16 (m, 2 H, H5 + H6). Key signals **118**: 1.30 (d, 1 H, *J* = 8.2 Hz, H8), 1.52 (d, 1 H, *J* = 8.2 Hz, H8´), 2.37 (m, 1 H, H3a or H7a), 2.55 (m, 1 H, H7a or 3a), 3.00 (br s, 1 H, H4 or H7), 3.08 (br s, 1 H, H7 or H4), 3.29 (t, 1 H, *J* = 8.2 Hz, H3), 3.34 (s, 3 H, OMe), 3.69 (m, 5 H, CO_2Me + CH_2OMOM), 4.60 (AB d, 2 H, *J* = 6.6 Hz, OCH_2OMe), 5.97 (m, 1 H, H5 or H6), 6.02 (m, 1 H, H6 or H5), 10.40 (br s, 1 H, OH).

^{13}**C NMR:** Key signals **117**: 52.5 (CH_2), 69.2 (CH_2), 96.1 (CH_2), 135.2, 136.4 (2 × =CH), 168.0 (C, CO_2Me), 209.7 (C, CO). Key signals **118**: 50.0 (CH_2), 70.8 (CH_2), 96.3 (CH_2), 101.1 (C, C2), 133.5, 134.5 (2 × =CH), 169.6 (C, C1), 177.6 (C, CO_2Me).

MS: *m/z* 280 ($M^{+\cdot}$, 6%), 243 (13), 215 (14), 205 (47), 183 (52), 173 (12), 154 (71), 139 (70), 122 (46), 107 (66), 66 (100).

HRMS: calcd for $C_{15}H_{20}O_5$ 280.1311, found 280.1311.

(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-1-methoxymethoxymethyl-3-trifluoromethanesulfonyloxy-3a,4,7,7a-tetrahydro-1*H*-4,7,methano-indene-2-carboxylate (119)



119

NaH (60% w/w in oil, 214 mg, 5.4 mmol) and *N*-phenyltrifluoromethanesulfonimide (1.4 g, 4.0 mmol) were carefully added to a stirred solution of **117/118** (1.0 g, 3.6 mmol) in THF (36 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room

temperature and stirred for 4 h after which time water (5 mL) was carefully added at 0 °C. The resulting mixture was further diluted with water (80 mL) and extracted twice with diethyl ether (75 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was subjected to flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, to afford **119** (1.14 g, 77%) as a colourless oil.

$\mathbf{R}_f$ 0.65 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –13.6° (*c* 0.96 $CHCl_3$)

IR υ_{max} 3440, 2953, 2887, 1725, 1660, 1661, 1427, 1343, 1231, 1212, 1143, 1041, 947cm^{-1}.

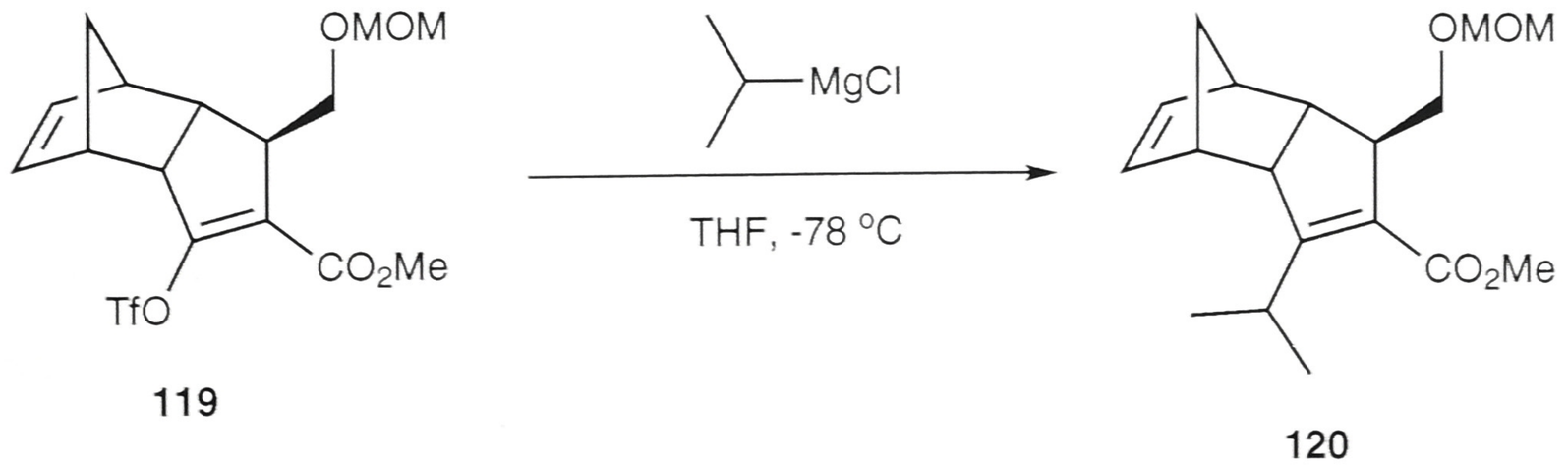
^{1}**H NMR:** 1.28 (d, 1 H, *J* = 8.5 Hz, H8), 1.60 (d, 1 H, *J* = 8.5 Hz, H8´), 2.57 (m, 1 H, H3a or H7a), 2.67 (m, 1 H, H7a or H3a), 3.06 (br s, 2 H, H4 + H7), 3.33 (s, 3 H, OMe), 3.52 (m, 2 H, H1 + C*H*$_2$OMOM), 3.66 (dd, 1 H, *J* = 5.6, 3.9 Hz, C*H*$_2$OMOM´), 3.74 (s, 3 H, CO_2*Me*), 4.59 (AB d, 2 H, *J* = 6.7 Hz, OC*H*$_2$OMe), 6.07 (m, 1 H, H5 or H6), 6.11 (m, 1 H, H6 or H5).

^{13}**C NMR:** 42.1 (CH), 44.7 (CH), 44.7 (CH), 46.0 (CH), 49.6 (CH_2), 51.6, 51.8 (CH + OMe), 55.1 (CO_2*Me*), 69.5 (CH_2), 96.4 (CH_2), 118.3 (C, q, *J* = 320 Hz, *C*F_3), 123.6 (C, C2), 134.1, 134.9 (2 × =CH), 156.2 (C, C3), 162.2 (*C*O_2Me).

MS: *m/z* 412 ($M^{+\cdot}$, 3%), 380 (3), 347 (40), 315 (67), 285 (44), 153 (24), 66 (100).

HRMS: calcd for $C_{16}H_{19}O_7F_3S$ 412.0804, found 412.0805

(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-3-isopropyl-1-methoxymethoxymethyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (120)



119 **120**

n-BuLi/hexanes (1.6 M, 5.2 mL, 8.2 mmol) was added to a stirred solution of thiophene (660 µL, 8.2 mmol) in THF (10 mL) at 0 °C under a nitrogen atmosphere. After 20 min the resulting solution was transferred *via* a cannula to a stirred suspension of CuCN (738 mg, 8.2 mmol) in

THF (10 mL) at –78 °C. The mixture was allowed to slowly warm to –40 °C and stirred for a further 30 min, after which time the solution was cooled to –78 °C. Isopropylmagnesium chloride/THF (2.0 M, 4.12 mL, 8.2 mmol) was added, followed by the addition of a solution of triflate **119** (1.7 g, 4.1 mmol) in THF (15 mL). After 1 h aqueous ammonium chloride solution (10 mL) was added and the mixture allowed to warm to room temperature. The mixture was diluted with water (100 mL) and 10% aqueous ammonia solution (5 mL), then extracted three times with diethyl ether (150 mL). The combined organic extracts were washed with 1.0 M HCl (200 mL), brine (200 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, afforded **120** (919 mg, 73%) as a colourless oil.

R_f 0.70 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –110.2° (*c* 0.68 $CHCl_3$)

IR υ_{max} 2949, 1707, 1618, 1465, 1434, 1337, 1231, 1150, 1111, 1041 cm^{-1}.

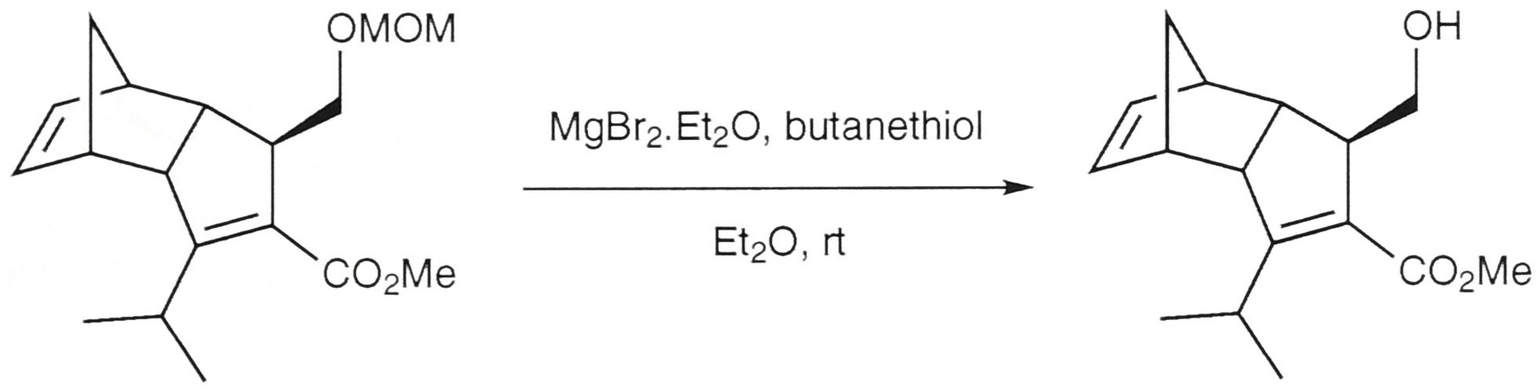
^{1}H NMR: 1.10 (apparent t, 6 H, 2 × CH*Me*), 1.29 (m, 1 H, H8), 1.50 (dt, 1 H, *J* = 8.1, 1.9 Hz, H8´), 2.52 (m, 2 H, H1 + H7a), 3.05 (m, 2 H, H4 + H7), 3.29 (d, 1 H, *J* = 7.8 Hz, CH_2OMOM), 3.35 (s, 3 H, OMe), 3.40 (m, 1 H, H3a), 3.54 (sep, 1 H, *J* = 7.0 Hz, C*H*Me$_2$), 3.64 (m, 1 H, CH_2OMOM´), 3.66 (s, 3 H, CO_2*Me*), 4.60 (AB d, 2 H, *J* = 6.6 Hz, OCH_2OMe), 5.90 (dd, 1 H, *J* = 5.7, 2.8 Hz, H5 or H6), 6,04 (dd, 1 H, *J* = 5.7, 2.9 Hz, H6 or H5).

^{13}C NMR: 21.3 (Me), 21.5 (Me), 27.8 (CH), 43. ((CH), 45.7 (CH), 45.7 (CH), 47.1 (CH), 48.9 (CH), 50.2 (CH_2), 50.8 (CH), 54.7, 54.9 (OMe + CO_2*Me*), 71.4 (CH_2), 96.3 (CH_2), 127.3 (C, C2), 133.5, 135.2 (2 × =CH), 165.8, 166.0 (*C*O_2Me + C3).

MS: *m/z* 306 ($M^{+\cdot}$, 27%), 274 (13), 260 (45), 243 (33), 231 (24), 180 (100), 165 (24), 134 (28), 105 (26). 66 (15).

HRMS: calcd for $C_{18}H_{27}O_4$ ([M+H]+)307.1909, found 307.1904.

(1*R*,3a*R*,4*S*,7*R*,7a*R*)-Methyl-1-hydroxymethyl-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (121)



120 **121**

A solution of MOM ether **120** (160 mg, 0.52 mmol), $MgBr_2.Et_2O$ (1.35 g, 5.2 mmol) and 1-butanethiol (504 μL, 4.7 mmol) in diethyl ether (5 mL) was stirred at room temperature for 24 h. The resulting solution was then diluted with 1.0 M HCl (10 mL) and extracted three times with ethyl acetate (10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 50% ethyl acetate in hexanes as the eluant, to afford **121** (113 mg, 83%) as a colourless oil.

R_f 0.30 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –104.0° (*c* 0.65 $CHCl_3$)

IR υ_{max} 3401, 2963, 1697, 1615, 1434, 1338, 1231, 1100, 1035 cm^{-1}.

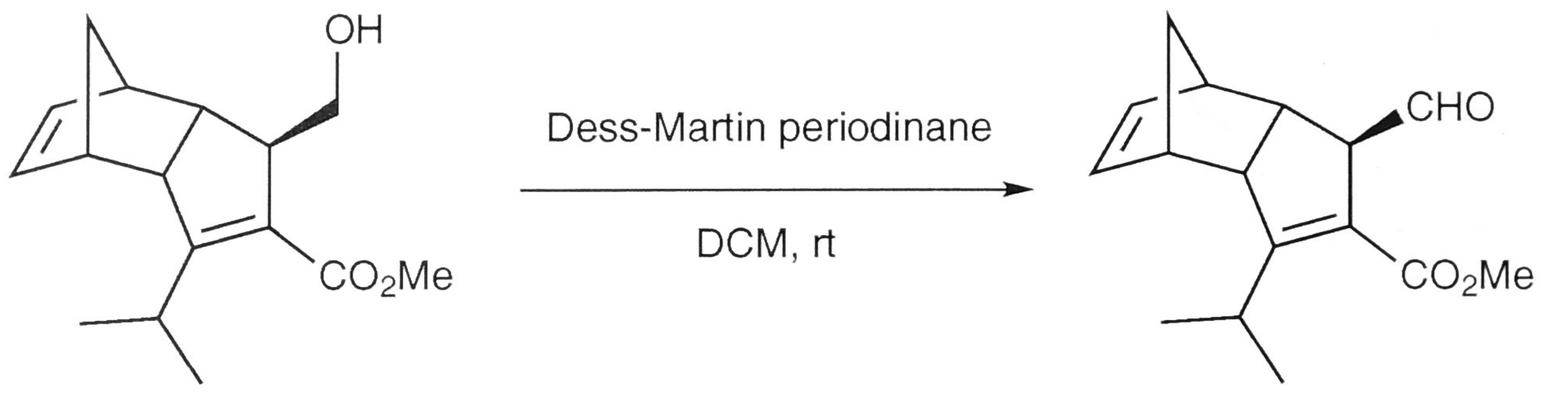
^{1}H NMR: 1.10 (m, 6 H, 2 × CH*Me*), 1.29 (d, 1 H, *J* = 8.1 Hz, H8), 1.51 (dt, 1 H, *J* = 8.2, 1.8 Hz, H8´), 2.39 (m, 1 H, H7a), 2.46 (m, 1 H, H1), 3.00 (br s, 2 H, H4 + H7), 3.39 (m, 1 H, H3a), 3.46 (m, 1 H, C*H*Me_2), 3.59 (m, 2 H, CH_2OMOM), 3.70 (s, 3 H, CO_2Me), 5.90 (dd, 1 H, *J* = 5.7, 2.9 Hz, H5 or H6), 6.02 (dd, I H, *J* = 5.9, 2.9 Hz, H6 or H5).

^{13}C NMR: 21.5 (Me), 21.7 (Me), 28.4 (CH), 43.4 (CH), 45.6 (CH), 47.2 (CH), 50.1 (CH_2), 51.2 (CH + OMe), 54.5 (OMe), 67.3 (CH_2), 127.9 (C, C2), 133.6, 135.5 (2 × =CH), 167.0 (C3 + CO_2Me).

MS: *m/z* 262 ($M^{+\cdot}$, 4%), 231 (4), 196 (40), 178 (29), 166 (100), 151 (44), 135 (19), 119 (51), 91 (36), 66 (28).

HRMS: calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1567.

(1*S*,3a*R*,4*S*,7*R*,7a*S*)-Methyl-1-formyl-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (60)



121 **60**

Dess-Martin periodinane (366 mg, 0.86 mmol) was added to a stirred solution of alcohol **121** (113 mg, 0.43 mmol) in DCM (5 mL) at room temperature. After 1 h the reaction mixture was diluted with DCM (5 mL), then treated with 1.0 M sodium thiosulfate (5 mL) and saturated aqueous sodium bicarbonate (5 mL). After vigorous stirring for 10 min the reaction mixture was diluted with water (20 mL) and extracted three times with DCM (20 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 15% ethyl acetate in hexanes as the eluant, to afford **60** (80 mg, 72%) as a colourless oil.

R_f 0.60 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –18.7° (*c* 0.46 $CHCl_3$)

IR υ_{max} 2967, 1719, 1619, 1467, 1434, 1344, 1228, 1193, 1109, 1030 cm^{-1}.

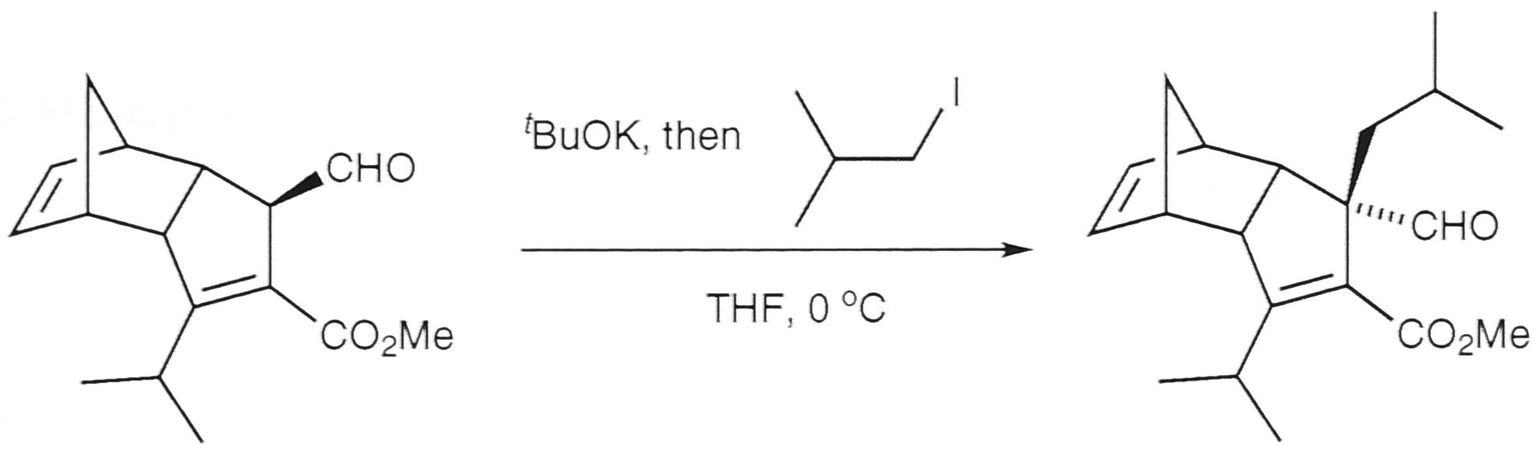
^{1}H NMR: 1.13 (m, 6 H, 2 × CH*Me*), 1.35 (d, 1 H, *J* = 8.4 Hz, H8), 1.57 (dt, 1 H, *J* = 8.2 Hz, H8´), 2.76 (m, 1 H, H7a), 3.04 (br s, 1 H, H7), 3.07 (br s, 1 H, H4), 3.12 (d, 1 H, *J* = 3.1 Hz, H1), 3.44(m, 1 H, H3a), 3.66 (m, 1 H, C*H*Me_2), 3.67 (s, 3 H, CO_2*Me*), 5.96 (dd, 1 H, *J* = 6.0, 2.6 Hz, H6), 6.05 (dd, 1 H, *J* = 5.7, 2.9 Hz, H5), 9.57 (d, 1 H, *J* = 2.8 Hz, CHO).

^{13}C NMR: 21.4 (Me), 21,7 (Me), 28.2 (CH), 40.0 (CH), 45.5 (CH), 47.1 (CH), 50.4 (CH_2), 51.3 (CH), 55.2 (CO_2*Me*), 61.0 (CH), 124.3 (C, C2), 133.4, 135.8 (2 × =CH), 164.8 (C, C3), 170.2 (*C*O_2Me), 201.7 (CHO).

MS: *m/z* 260 ($M^{+\cdot}$, 5%), 233 (20), 195 (76), 166 (100), 151 (85), 133 (48), 119 (52), 107 (56), 91 (66), 77 (38), 66 (97).

HRMS: calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1410.

(1*R*,3a*R*,4*S*,7*R*,7a*S*)-Methyl-1-formyl-1-isobutyl-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (122)



60 122

^{t}BuOK/THF (1.0 M, 115 µL, 115 µmol) was added to a stirred solution of aldehyde **60** (25 mg, 96 µmol) in THF (1.0 mL) at 0 °C under a nitrogen atmosphere. After 5 min, isobutyl iodide (33 µL, 288 µmol) was added and the reaction mixture allowed to warm to room temperature. After 2.5 h the mixture was diluted with water (10 mL) and extracted twice with diethyl ether (10 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 5% ethyl acetate in hexanes as the eluant, to afford **122** (15 mg, 50%) as a single stereoisomer.

R_f 0.80 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –78.4° (*c* 0.26 $CHCl_3$)

IR υ_{max} 2917, 1715, 1606, 1466, 1342, 1226, 1082, 1024 cm^{-1}.

^{1}H NMR: 0.76 (d, 3 H, *J* = 6.6 Hz, CH*Me*´), 0.94 (d, 3 H, *J* = 6.7 Hz, CH*Me*´), 1.15 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.16 (d, 3 H, *J* = 6.9 Hz, CH*Me*), 1.31 (d, 1 H, *J* = 8.4 Hz, H8), 1.41 (m, 1 H, C*H*Me_2´), 1.58 (br d, 1 H, *J* = 8.2 Hz, H8´), 1.74 (m, 2 H, CH_2C*H*Me_2), 2.59 (dd, 1 H, *J* = 8.1, 4.0 Hz, H7a), 2.97 (br s, 1 H, H4 or H7), 3.14 (br, s, 1 H, H7 or H4), 3.52 (dd, 1 H, *J* = 8.2, 4.3 Hz, H3a), 3.66 (sep, 1 H, *J* = 7.0 Hz, C*H*Me_2), 3.68 (s, 3 H, CO_2*Me*), 5.80, 5.88 (2 × m, 1 H, H5 + H6), 9.61 (s, 1 H, CHO).

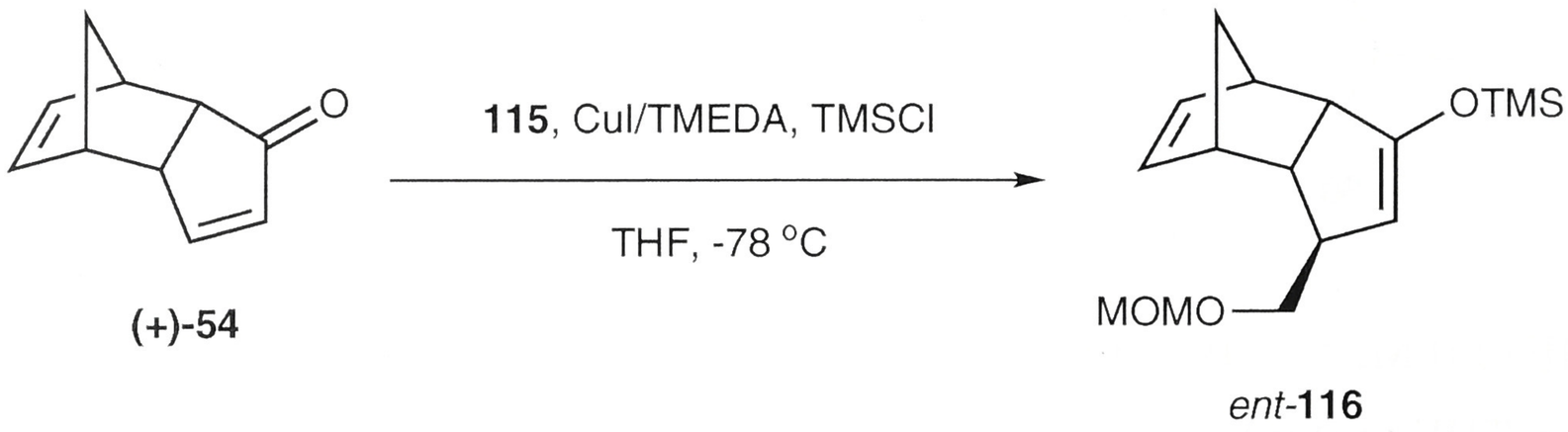
^{13}C NMR: 21.3 (Me), 21.5 (Me), 24.3 (Me), 24.5 (Me), 25.5 (CH), 28.6 (CH), 45.2 (CH), 45.7 (CH_2), 47.5 (CH), 50.6 (CH), 51.5 (CH), 51.5 (CH), 51.5 (CH_2), 52.6 (OMe), 63.5 (C, C1), 129.2 (C, C2), 134.3, 135.3 (2 × =CH), 169.4 (C3 + *C*O_2Me), 205.9 (CHO).

MS: *m/z* 316 ($M^{+\cdot}$, 10%), 298 (10), 260 (28), 248 (20), 222 (100), 207 (20), 179 (88), 147 (50), 119 (50), 91 (42), 66 (38).

HRMS: calcd for $C_{20}H_{26}O_3$ 316.2038, found 316.2037.

9.3.2 Chapter Four - Synthesis of the Iodide 158

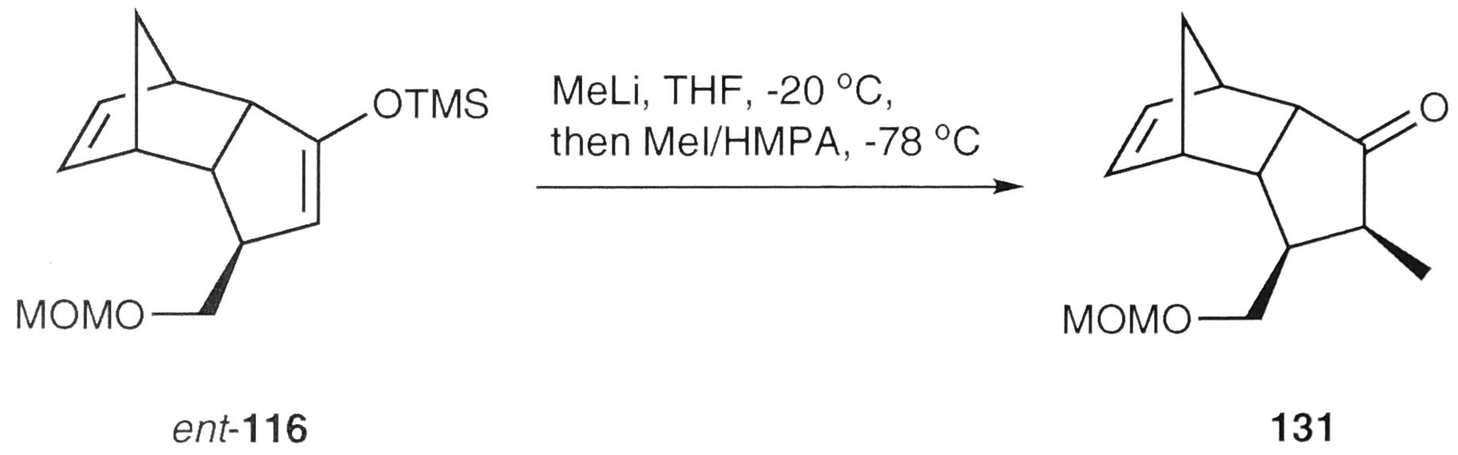
(3*R*,3a*S*,4*S*,7*R*,7a*S*)-(3-Methoxymethoxymethyl-3a,4,7,7a-tetrahydro-3*H*-4,7-methano-inden-1-yloxy)-trimethyl-silane (*ent*-116)



(+)-54 *ent*-116

Procedure as described previously for the synthesis of **116** from (–)-**54**.

(2*S*,3*S*,3a*S*,4*S*,7*R*,7a*S*)-3-Methoxymethoxymethyl-2-methyl-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (131)



ent-116 131

MeLi/diethyl ether (1.0 M, 6.4 mL, 6.4 mmol) was added dropwise to a solution of silyl enol ether *ent*-**116** (1.87 g, 6.4 mmol) in THF (50 mL) at –20 °C under a nitrogen atmosphere. Stirring was continued at –20 °C for 30 min, then after cooling to –78 °C, HMPA (5.5 mL, 32 mmol) and MeI (1.98mL, 32 mmol) were added. After 30 min the reaction mixture was allowed to gradually warm to –20 °C and stirred for a further 1 h before aqueous ammonium chloride solution (10 mL) was carefully added. The mixture was allowed to warm to room temperature, diluted with water (100 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (75 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, gave the ketone **131** (95:5 diastereoselection, 881 mg, 60 %) as a colourless oil.

$\mathbf{R}_f$ 0.50 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ +131.7° (*c* 0.67 $CHCl_3$)

IR υ_{max} 2933, 1730, 1455, 1182, 1149, 1108, 1052, 917 cm^{-1}.

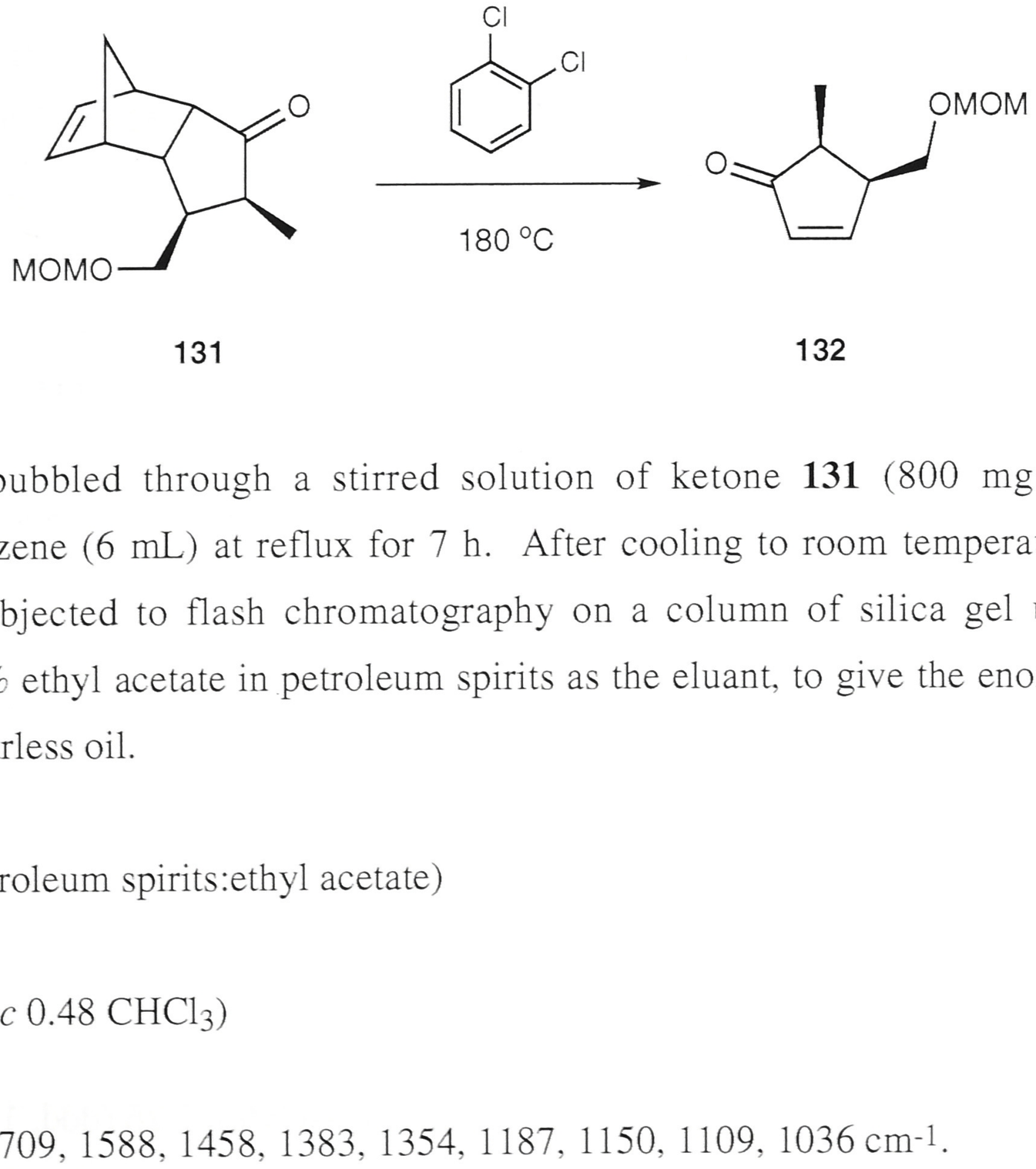
^{1}H NMR: 0.95 (d, 3 H, *J* = 7.3 Hz, CH*Me*), 1.41 (dt, 1 H, *J* = 8.2, 1.4 Hz, H8), 1.53 (dt, 1 H, *J* = 8.2, 1.6 Hz, H8´), 2.01 (m, 1 H, H3), 2.18 (m, 1 H, H2), 2.70 (ddd, 1 H, *J* = 9.2, 4.1, 2.2 Hz, H3a), 2.91 (dd, 1 H, *J* = 9.2, 4.7 Hz, H7a), 3.05 (m, 1 H, H4), 3.18 (m, 1 H, H7), 3.34 (s, 3 H, OMe), 3.45, 3.53 (AB d, 2 H, *J* = 9.3 Hz, CH_2OMOM), 4.55 (s, 2 H, OCH_2OMe), 6.07 (dd, 1 H, *J* = 5.6, 2.9 Hz, H6), 6.22 (dd, 1 H, *J* = 5.6, 3.0 Hz, H5).

^{13}C NMR: 9.5 (Me), 39.7 (CH), 44.1 (CH), 46.9 (CH), 47.1 (CH), 47.3 (CH), 52.4 (CH_2), 53.4 (CH), 55.3 (OMe), 69.3 (CH_2), 96.5 (CH_2), 134.6, 136.0 (2 × =CH), 220.8 (C, CO).

MS: *m/z* 236 ($M^{+\cdot}$, 5%), 191 (3), 171 (48), 139 (50), 109 (47), 91 (32), 81 (39), 66 (100).

HRMS: calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1415.

(4*S*,5*S*)-*4*-Methoxymethoxymethyl-5-methyl-cyclopent-2-enone (132)



131 **132**

Nitrogen was bubbled through a stirred solution of ketone **131** (800 mg, 3.4 mmol) in 1,2-dichlorobenzene (6 mL) at reflux for 7 h. After cooling to room temperature the reaction mixture was subjected to flash chromatography on a column of silica gel using petroleum spirits, then 50% ethyl acetate in petroleum spirits as the eluant, to give the enone **132** (507 mg, 85 %) as a colourless oil.

R_f 0.30 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ +234.9° (*c* 0.48 $CHCl_3$)

IR υ_{max} 2883, 1709, 1588, 1458, 1383, 1354, 1187, 1150, 1109, 1036 cm^{-1}.

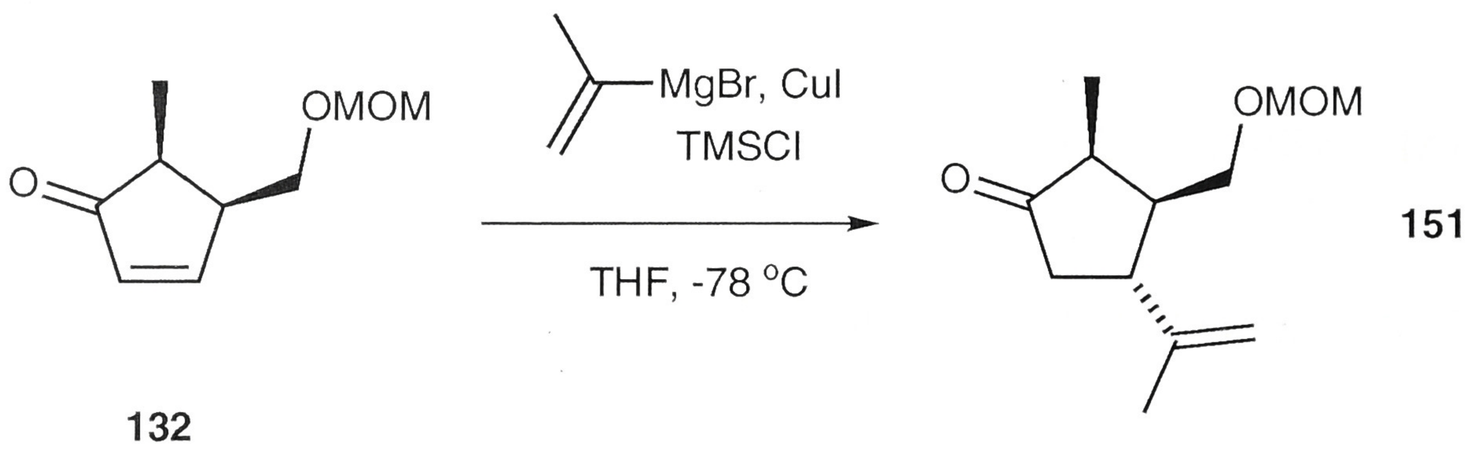
^{1}H NMR: 1.15 (d, 3 H, *J* = 7.6 Hz, CH*Me*), 2.52 (m, 1 H, H5), 3.52 (m, 1 H, H4), 3.35 (s, 3 H, OMe), 3.55 (dd, 1 H, *J* = 10.5, 7.0 Hz, CH_2OMOM), 3.70 (dd, 1 H, *J* = 9.6, 6.9 Hz, CH_2OMOM´), 4.60 (s, 2 H, OCH_2OMe), 6.24 (dd, 1 H, *J* = 5.9, 2.0 Hz, H2), 7.67 (dd, 1 H, *J* = 5.9, 2.6 Hz, H3).

^{13}**C NMR:** 10.5 (Me), 42.1 (CH), 45.) (CH), 55.4 (OMe), 67.0 (CH_2), 96.5 (CH_2), 133.5 (CH, C2), 164.2 (CH, C3), 211.8 (C, CO).

MS: *m/z* 170 ($M^{+\cdot}$, 15%), 140 (100), 125 (5), 108 (34), 95 (21), 81 (51), 75 (39), 67 (29).

HRMS: calcd for $C_9H_{14}O_3$ 170.0943, found 170.0943.

(2*S*,3*S*,4*R*)-4-Isopropenyl-3-methoxymethoxymethyl-2-methyl-cyclopentanone (151)



132 **151**

Isopropenylmagnesium bromide/THF (0.5 M, 345 mL, 2.4 mmol) was added to a stirred suspension of CuI (224 mg, 1.2 mmol) in THF (10 mL) at –78 °C under a nitrogen atmosphere. After 5 min TMSCl (298 μL, 2.4 mmol) and a solution of enone **132** (345 mg, 2.0 mmol) in THF (5 mL) were added dropwise. After stirring for 15 min, a solution of aqueous ammonium chloride (5 mL) was added and the reaction mixture allowed to warm to room temperature. The solution was diluted with water (50 mL) and 10% aqueous ammonia (2 mL), then extracted three times with ethyl acetate (30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, to afford olefin **151** (300 mg, 70%) as a single diastereoisomer.

$\mathbf{R}_f$ 0.55 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ -19.2° (*c* 1.02 $CHCl_3$)

IR υ_{max} 2933, 1740, 1645, 1454, 1377, 1149, 1108, 1042 cm^{-1}.

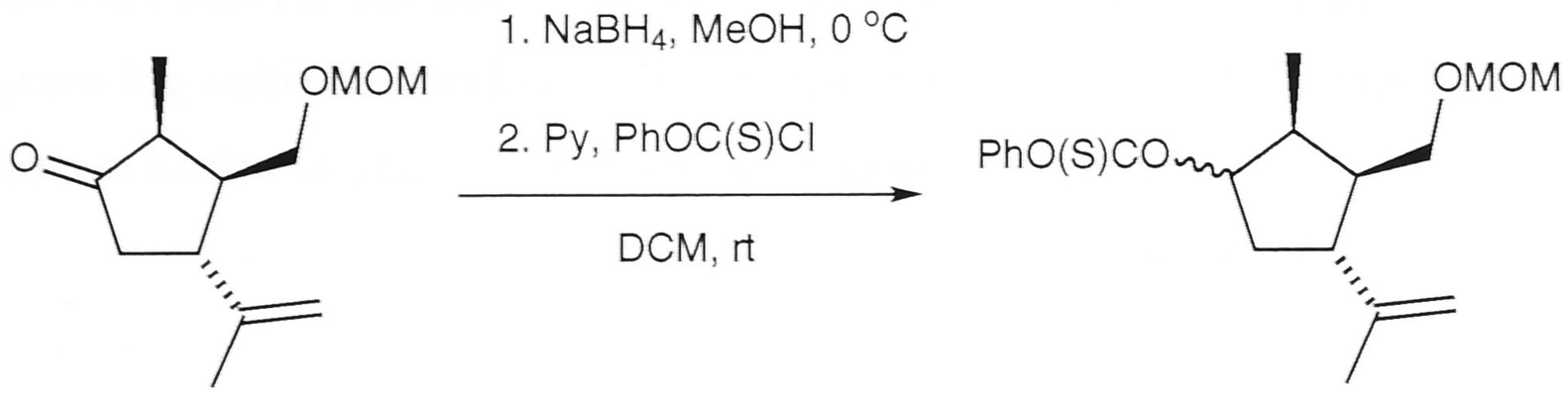
^{1}**H NMR:** 1.07 (d, 3 H, *J* = 7.3 Hz, CH*Me*), 1.78 (m, 3 H, =C*Me*), 2.26 (ddd, 1 H, *J* = 18.8, 7.5, 1.5 Hz, H5), 2.40-2.60 (m, 3 H, H2, H3 + H5'), 2.72 (dd, 1 H, *J* = 14.4, 6.9 Hz, H4), 3.35 (s, 3 H, OMe), 3.56 (AB d, 2 H, *J* = 5.6 Hz, CH_2OMOM), 4.58 (s, 2 H, OCH_2OMe), 4.76, 4.82 (m, 2 × 1 H, =CH_2).

^{13}C NMR: 9.8 (Me), 20.2 (=C*Me*), 41.8 (CH_2), 42.9 (CH), 43.5 (CH), 43.8 (CH), 55.3 (OMe), 67.3 (CH_2), 96.5 (CH_2), 110.8 (=CH_2), 145.3 (=*C*Me), 219.4 (CO).

MS: *m/z* 212 ($M^{+\cdot}$, 55%), 180 (40), 167 (39), 152 (41), 137 (53), 121 (56), 107 (82), 93 (74), 81 (62), 68 (92), 55 (100).

HRMS: calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1410.

A 1-epimeric mixture of (2*S*,3*R*,4*R*)-thiocarbonic acid *O*-(4-isopropenyl-3-methoxymethoxymethyl-2-methyl-cyclopentyl) ester *O*-phenyl ester (153)



151 **153**

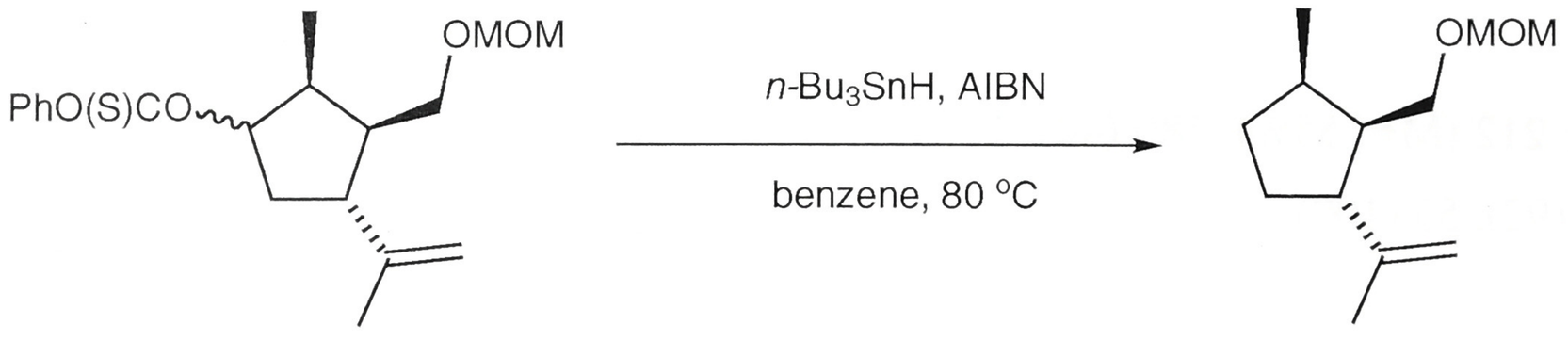
$NaBH_4$ (106 mg, 2.8 mmol) was added to a stirred solution of ketone **151** in MeOH (10 mL) at 0 °C. After 20 min water (5 mL) was added and the mixture stirred for a further 5 min. The reaction mixture was diluted with water (20 mL) and extracted three times with ethyl acetate (25 mL). The combined organic extracts were then washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford a 2:1 mixture of crude diastereomeric alcohols which were used in the next reaction without further purification.

^{1}H NMR: (major) 1.04 (d, 3 H, *J* = 7.2 Hz, CH*Me*), 1.70 (m, 3 H, =C*Me*), 3.39 (s, 3 H, OMe), 3.98 (m, 1 H, C*H*OH). (minor) 0.94 (d, 3 H, *J* = 7.2 Hz, CH*Me*), 1.73 (m, 3 H, =CHC*Me*), 3.35 (s, 3 H, OMe), 3.87 (q, 1 H, *J* = 5.7 Hz, C*H*OH).

Pyridine (280 µL, 3.5 mmol) and phenyl chlorothionoformate (211 µL, 1.5 mmol) were added successively to a stirred solution of the crude alcohols in DCM (5 mL) at room temperature under a nitrogen atmosphere. After 2 h the reaction mixture was diluted with a 1.0 M aqueous HCl solution (30 mL) and extracted three times with DCM (20 mL). The combined organic extracts were washed with aqueous sodium bicarbonate (25 mL), brine (25 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, afforded an inseparable 2:1 mixture of thionocarbonates **153** (435 mg, 88%).

^{1}H NMR: (major) 5.59 (m, 1 H, C*H*OC(S)OPh). (minor) 5.28 (m, 1 H, C*H*OC(S)OPh).

(1*R*,2*R*,3*R*)-1-Isopropenyl-2-methoxymethoxymethyl-3-methyl-cyclopentane (154)



153 **154**

n-Bu_3SnH (398 μL) and AIBN (cat.) were added to a stirred solution of thionocarbonates **153** (435 mg, 1.2 mmol) in benzene (5 mL) at reflux under a nitrogen atmosphere. After 30 min the reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using petroleum spirits and then 10% ethyl acetate in petroleum spirits as the eluant, to afford cyclopentane **154** (258 mg, 100%) as a colourless oil.

R_f 0.90 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ -42.8° (*c* 0.80 $CHCl_3$)

IR υ_{max} 2950, 1642, 1454, 1377, 1213, 1147, 1110, 1048 cm^{-1}.

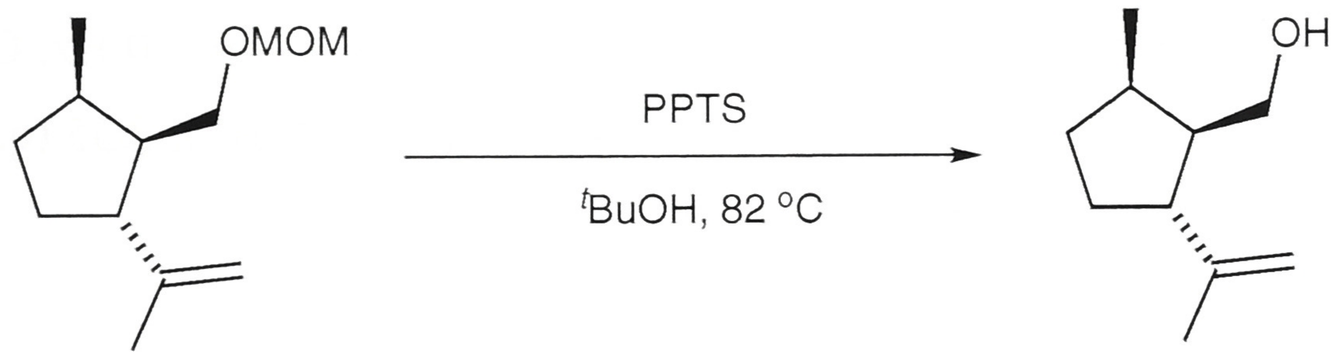
^{1}H NMR: 0.93 (d, 3 H, *J* = 7.2 Hz, CH*Me*), 1.24-1.38 (m, 1 H), 1.42-1.58 (m, 1 H), 1.70 (m, 3 H, =C*Me*), 1.78-1.90 (m, 2 H), 2.02-2.12 (m, 1 H, H1), 2.20-2.36 (m, 2 H, H2 + H3), 3.37 (s, 3 H, OMe), 3.44 (m, 2 H, CH_2OMOM), 4.60 (AB d, 2 H, *J* = 6.4 Hz, OCH_2OMe), 4.69 (m, 2 H, =CH_2).

^{13}C NMR: 15.5 (Me), 19.2 (=C*Me*), 29.7 (CH_2), 33.4 (CH_2), 35.0 (CH), 45.7 (CH), 48.2 (CH), 55.2 (OMe), 68.0 (CH_2), 96.6 (CH_2), 110.0 (=CH_2), 147.5 (=*C*Me).

MS: *m/z* 198 ($M^{+\cdot}$, 1%), 167 (11), 153 (15), 136 (68), 123 (100), 107 (55), 95 (62), 81 (84), 67 (35).

HRMS: calcd for $C_{12}H_{22}O_2$ 198.1620, found 198.1620.

(1*R*,2*R*,5*R*)-(2-Isopropenyl-5-methyl-cyclopentyl)-methanol (124)

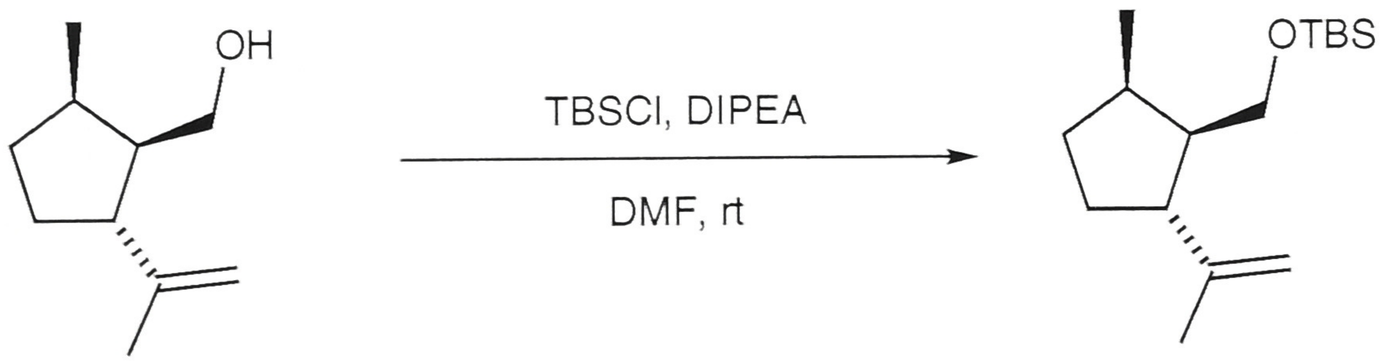


154 **124**

A solution of ether **154** (80 mg, 0.4 mmol) and PPTS (624 mg, 2.4 mmol) in ^{t}BuOH (8 mL) was heated at reflux for 20 h. After cooling to room temperature the reaction mixture was diluted with a 1.0 M aqueous HCl solution (10 mL) and extracted three times with ethyl acetate (15 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was subjected to flash chromatography on a column of silica gel using 40% ethyl acetate in petroleum spirits as the eluant, to give alcohol **124** (50 mg, 80%) as a pale yellow oil.

Identical with spectra obtained from (*S*)-(+)-carvone.[5]

(1*R*,2*R*,5*R*)-*tert.*-Butyl-[2-isopropenyl-5-methyl-cyclopentylmethoxy)-dimethyl-silane (148)



124 **148**

TBSCl (3.5 g, 23.3 mmol) was added to a stirred solution of alcohol **124** (3.0 g, 19.4 mmol) and DIPEA (4.7 mL, 27.2 mmol) in DMF (50 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stir for 12 h, after which time the mixture was diluted with water (250 mL) and 1.0 M HCl (250 mL), then extracted three times with diethyl ether (100 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was subjected to flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, to give **148** (5 g, 96%) as an oil.

$\mathbf{R}_f$ 0.95 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ +10.1° (*c* 0.24 $CHCl_3$)

IR υ_{max} 2954, 2858, 1643, 1471, 1462, 1387, 1255, 1098 cm^{-1}.

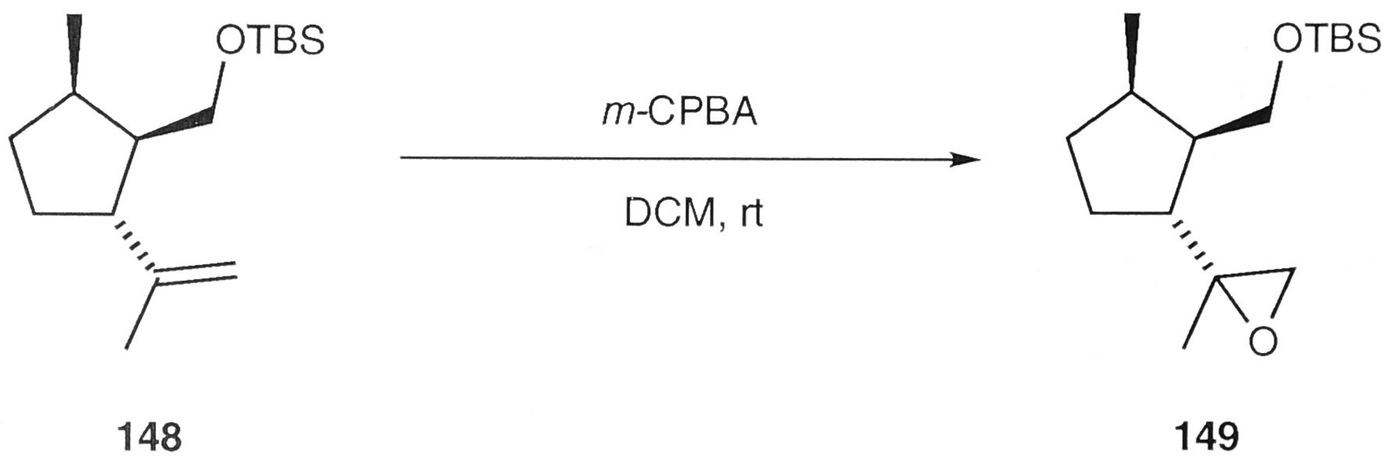
^{1}H NMR: 0.03 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Si^{t}Bu), 0.94 (d, 3 H, J = 7.0 Hz, CH*Me*), 1.22-1.50 (m, 2 H), 1.70 (m, 3 H, =C*Me*), 1.75-1.98 (m, 3 H), 2.21 (m, 1 H, H5), 2.35 (q, 1 H, J = 8.8 Hz, H2), 3.53 (m, 2 H, CH_2OTBS), 4.67 (m, 2 H, $=CH_2$).

^{13}C NMR: -5.3 ($SiMe_2$), 15.5 (Me), 18.3 (Si*C*Me_3), 19.5 (=C*Me*), 26.0 (SiC*Me*$_3$), 30.1 (CH_2), 33.7 (CH_2), 35.4 (CH), 48.0 (2 × CH), 62.8 (CH_2), 109.5 ($=CH_2$), 148.2 (=*C*Me).

MS: *m/z* 211 ([M-^{t}Bu]$^{+\cdot}$, 45%), 193 (5), 181 (8), 169 (18), 135 (12), 89 (18), 75 (100).

HRMS: calcd for $C_{12}H_{23}OSi$ 211.1518, found 211.1516.

(1*R*,2*R*,5*R*)-*tert.*-Butyl-dimethyl-[2-methyl-5-(2´-methyl-oxiranyl)-cyclopentylmethoxy]-silane (149)



148 **149**

To a stirred solution of olefin **148** (7.5 g, 28.8 mmol) and $NaHCO_3$ (25 g) in DCM (300 mL) was added small portions of *m*-CPBA (57-86%) until all the starting material was consumed, as judged by TLC. A solution of Na_2SO_3 (15 g) in water (150 mL) was added and the resulting mixture stirred vigorously for 10 min. The reaction mixture was diluted with diethyl ether (200 mL) and washed twice with 3% aqueous NaOH solution (500 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 5% ethyl acetate in petroleum spirits as the eluant, to afford an inseparable mixture of epoxides **149** (7.6 g, 98 %) as a colourless oil.

R_f 0.70 (5:1, petroleum spirits:ethyl acetate)

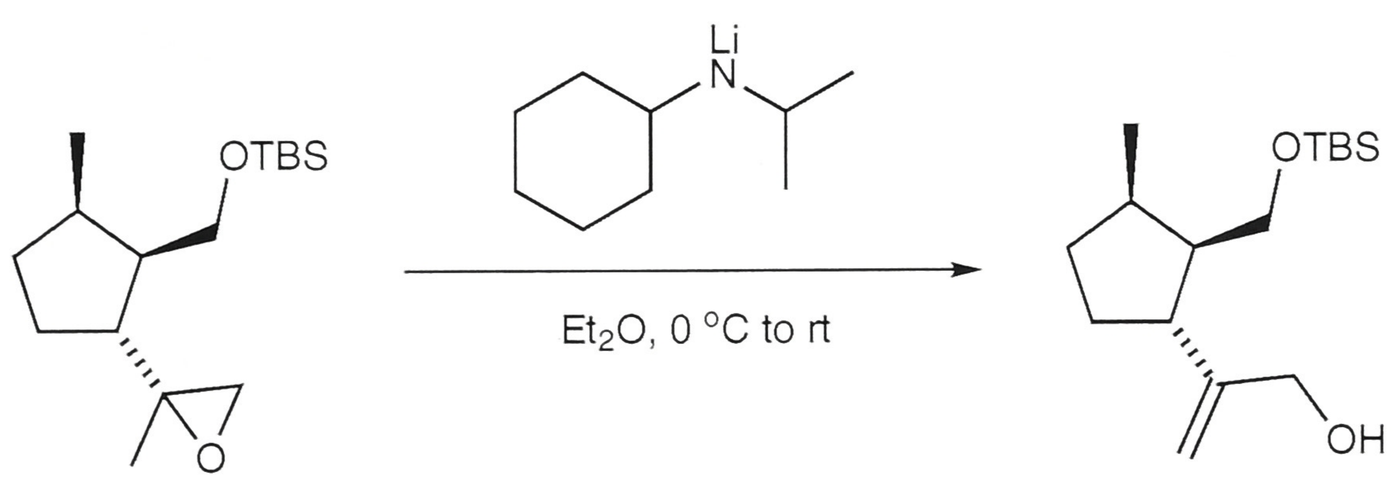
IR υ_{max} 2954, 2858, 1472, 1387, 1255, 1094cm^{-1}.

^{1}H NMR: (key signals) 0.04 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Si^{t}Bu), 0.92 (m, 3 H, CH*Me*), 1.30 (s, 3 H, Me´), 1.30-1.90 (m, 6 H), 2.10 (m 1 H, H2), 2.53, 2.61 (AB d, 2 H, J = 7.2 Hz, CH_2OTBS), 3.57 (m, 2 H, H1´).

MS: *m/z* 284 ([M+H]$^{+\cdot}$, 2%), 267 (8), 227 (52), 209 (8), 197 (17), 153 (12), 135 (100), 121 915), 93 (30), 75 (70).

HRMS: calcd for $C_{12}H_{23}O_2Si$ 227.1467, found 227.1469.

(1´*R*,2´*R*,3´*R*)-[2´-(*tert.*-Butyl-dimethyl-silanyloxymethyl)-3´-methyl-cyclopentyl]-prop-2-en-1-ol (150)



149 **150**

A solution of the epoxides **149** (2.0 g, 7.0 mmol) in diethyl ether (20 mL) was transferred *via* a cannula into a stirred solution of LICA, prepared by addition of *n*-BuLi/hexane (1.6 M, 26.4 mL, 42.0 mmol) to a solution cyclohexylisopropylamine (6.9 mL, 42.0 mmol) in diethyl ether (100 mL) at 0 °C. The mixture was stirred at room temperature for 6.5 h, cooled to 0 °C and quenched with saturated aqueous ammonium chloride solution (25 mL). The resulting mixture was diluted with water (125 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were then washed with 1.0 M HCl (150 mL), brine (150 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, afforded allylic alcohol **150** (1.28 g, 64%) as a colourless oil.

R$_f$ 0.70 (2:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –30.6° (*c* 0.32 $CHCl_3$)

IR υ_{max} 3369, 2953, 1647, 1471, 1462, 1388, 1254, 1096, 1056 cm^{-1}.

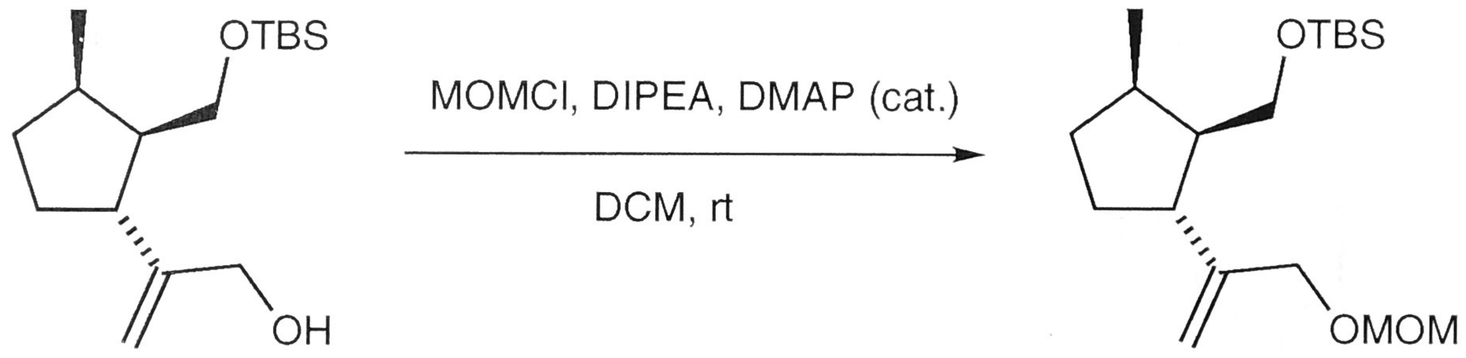
^{1}H NMR: 0.05 (s, 6 H, $SiMe_2$), 0.89 (s, 9 H, Si^{t}Bu), 0.90 (obscured d, 3 H, CH*Me*), 1.28 (m, 1 H), 1.51 (m, 1 H), 1.78-2.50 (m, 4 H), 2.47 (m, 1 H), 2.54 (br s, 1 H, OH), 3.52 (dd, 1 H, *J* = 10.0, 7.2 Hz, CH_2OTBS), 3.65 (dd, 1 H, *J* = 9.8, 6.0 Hz, CH_2OTBS´), 4.10 (apparent t, 2 H, *J* = 13.6 Hz, C*H*$_2$OH), 4.90, 5.00 (br s, 2 × 1 H, =CH_2).

^{13}C NMR: -5.5, -5.4 ($SiMe_2$), 15.3 (Me), 18.2 (C, Si*C*Me_3), 25.9 (SiC*Me*$_3$), 31.2 (CH_2), 33.5 (CH_2), 35.4 (CH), 44.5 (CH), 49.0 (CH), 63.6 (CH_2), 65.1 (CH_2), 108.5 (=CH_2), 152.1 (=C).

MS: *m/z* 227 ([M-^{t}Bu]$^{+\cdot}$, 22%), 135 (35), 107 (46), 93 (85), 75 (100).

HRMS: calcd for $C_{12}H_{23}O_2Si$ 227.1467, found 227.1465.

(1*R*,2*R*,5*R*)-*tert.*-Butyl-[2-(1´-methoxymethoxymethyl-vinyl)-5-methyl-cyclopentylmethoxy]-dimethyl-silane (157)



150 **157**

To a stirred solution of alcohol **150** (4.5 g, 16.0 mmol) and DMAP (193 mg, 1.6 mmol) in DCM (150 mL) at 0 °C under a nitrogen atmosphere, was added DIPEA (6.06 mL, 35.2 mmol) and MOMCl (2.4 mL, 32.0 mmol). The reaction mixture was allowed to stir at room temperature for 13 h, then diluted with 1.0 M HCl (100 mL) and extracted twice with diethyl ether (150 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, to give **157** (5.0 g, 94 %) as a colourless oil.

R_f 0.90 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –40.3° (*c* 0.33 $CHCl_3$)

IR υ_{max} 2953, 1647, 1471, 1463, 1388, 1255, 1151, 1100, 1055 cm^{-1}.

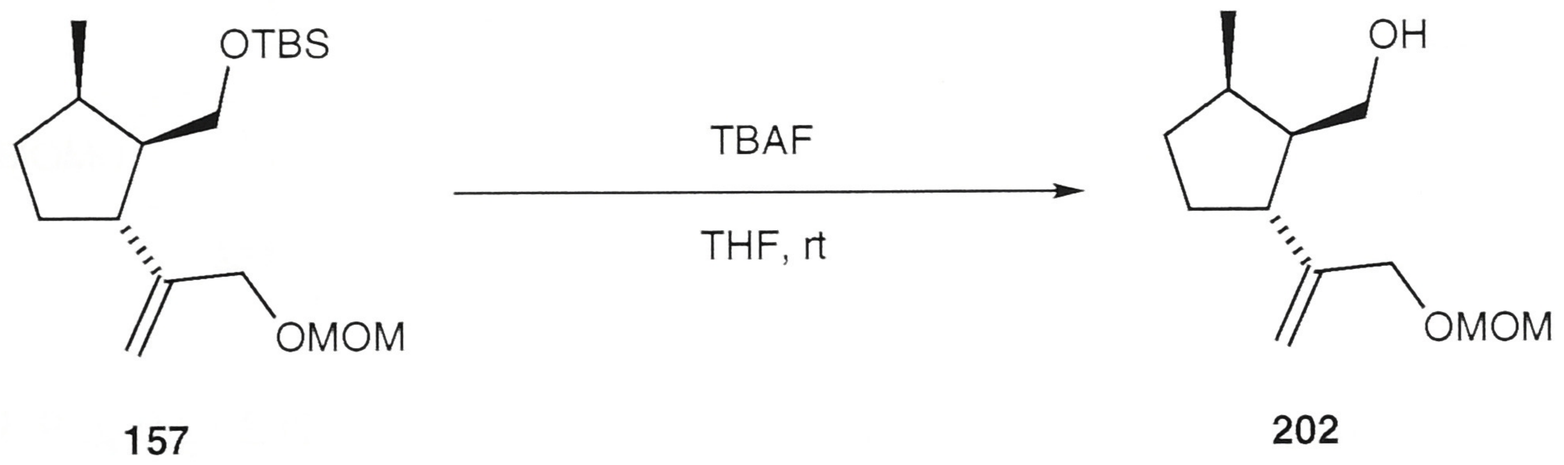
^{1}H NMR: 0.03 (s, 6 H, $SiMe_2$), 0.88 (s, 9 H, Si^{t}Bu), 0.94 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.22 (m, 1 H), 1.47 (m, 1 H), 1.75-2.04 (m, 4 H), 2.23 (sep, 1 H, *J* = 7.3 Hz, H5), 2.40 (q, 1 H, *J* = 8.6 Hz, H2), 3.38 (s, 3 H, OMe), 3.55 (m, 2 H, CH_2OTBS), 4.02 (s, 2 H, CH_2OMOM), 4.64 (s, 2 H, OCH_2OMe), 4.94, 5.05 (br s, 2 × 1 H, =CH_2).

^{13}C NMR: -5.5, -5.4 ($SiMe_2$), 15.4 (Me), 18.1 (C, Si*C*Me_3), 25.9 (SiC*Me*$_3$), 31.1 (CH_2), 33.6 (CH_2), 35.3 (CH), 44.2 (CH), 48.6 (CH), 55.1 (OMe), 62.6 (CH_2), 69.1 (CH_2), 95.4 (CH_2), 109.7 (=CH_2), 148.6 (=C).

MS: *m/z* 297 ([M-OMe]$^{+\cdot}$, 2%), 267 (20), 209 (18), 179 (20), 147 (95), 135 (30), 119 (75), 105 (70), 89 (80), 75 (100).

HRMS: calcd for [M+H] $C_{18}H_{37}O_3Si$ 329.2512, found 329.2521.

(1*R*,2*R*,5*R*)-[2-(1´-Methoxymethoxymethyl-vinyl)-5-methyl-cyclopentyl]-methanol (202)



157 **202**

TBAF/THF (1.0 M, 45.6 mL, 45.6 mmol) was added dropwise to a stirred solution of TBDMS ether **157** (5.0 g, 15 mmol) in THF (50 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to stir at room temperature for 16 h, then diluted with water (150 mL) and extracted three times with diethyl ether (100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 50% ethyl acetate in petroleum spirits as the eluant, to give **202** (3.1 g, 93 %) as an oil.

R_f 0.20 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –40.7° (*c* 0.70 $CHCl_3$)

IR υ_{max} 3435, 2950, 2874, 1649, 1456, 1399, 1214, 1150, 1050 cm^{-1}.

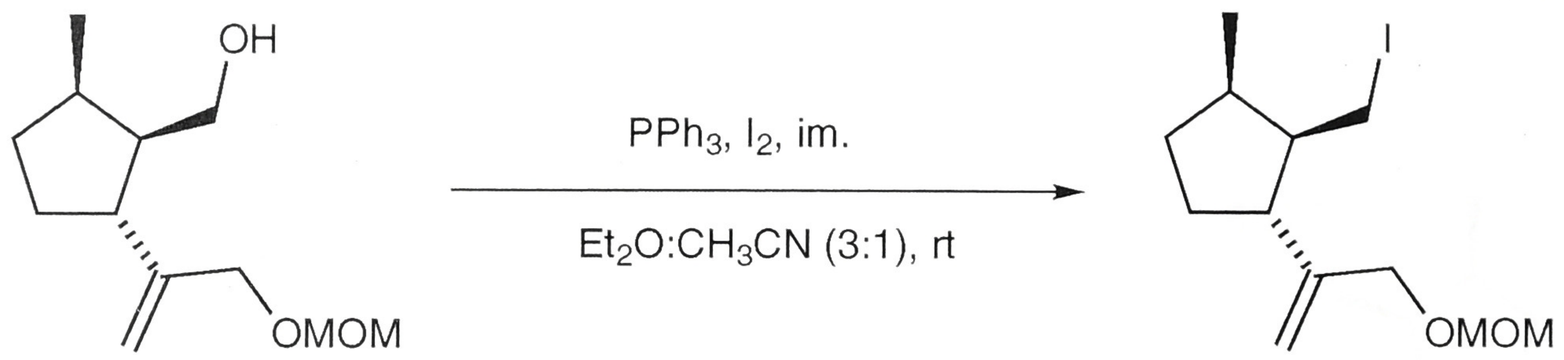
^{1}H NMR: 0.92 (d, 3 H, *J* = 7.2 Hz, CH*Me*), 1.24-1.36 (m, 1 H), 1.42-1.58 (m, 1 H), 1.8-2.25 (m, 3 H), 1.85 (br s, 1 H, OH), 2.26 (sep, 1 H, *J* = 6.7 Hz, H5), 2.41 (q, 1 H, *J* = 8.8 Hz, H2), 3.38 (s, 3 H, OMe), 3.62 (m, 2 H, C*H*$_2$OH), 4.04 (s, 2 H, C*H*$_2$OMOM), 4.64 (s, 2 H, OC*H*$_2$OMe), 5.02, 5.08 (br s, 2 × 1 H, =CH_2).

^{13}C NMR: 15.3 (Me), 31.2 (CH_2), 33.3 (CH_2), 34.9 (CH), 44.6 (CH), 49.3 (CH), 55.1 (OMe), 62.9 (CH_2), 69.5 (CH_2), 95.4 (CH_2), 110.9 (=CH_2), 148.5 (=C).

MS: *m/z* 183 ([M-MeOH]$^{+\cdot}$, 3%), 169 (10), 151 (49), 137 (35), 123 9100), 107 (65), 91 (38), 81 (74), 67 (45).

HRMS: calcd for [M-MeOH] $C_{11}H_{18}O_2$ 182.1307, found 182.1309.

(1*R*,2*R*,3*R*)-2-Iodomethyl-1-(1´-methoxymethoxymethyl-vinyl)-3-methyl-cyclopentane (158)



202 **158**

Iodine (3.6 g, 14.0 mmol) was added to a stirred solution of alcohol **202** (2.0 g, 9.3 mmol) and triphenylphosphine (3.7 g, 14.0 mmol) in 3:1 diethyl ether:acetonitrile (80 mL) at room temperature under a nitrogen atmosphere. After 30 min the mixture was diluted with saturated aqueous sodium bicarbonate solution (100 mL) and extracted twice with diethyl ether (100mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting residue was taken up in diethyl ether, and the insoluble triphenylphosphine oxide removed by filtration. The mother liquor was evaporated and the residue subjected to flash chromatography on a column of silica gel using 5% diethyl ether in hexanes as the eluant, to give **158** (2.9 g, 96%) as a colourless oil.

R_f 0.90 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –64.7° (*c* 0.30 $CHCl_3$)

IR υ_{max} 2953, 1646, 1464, 1428, 1378, 1211, 1150, 1104, 1052 cm^{-1}.

^{1}H NMR: 0.88 (d, 3 H, *J* = 6.7 Hz, CH*Me*), 1.37 (m, 1 H), 1.60 (m, 1 H), 1.86 (m, 1 H), 2.05 (m, 1 H), 2.31 (m, 3 H), 2.93 (apparent t, 1 H, *J* = 9.8 Hz, CH_2I), 3.28 (dd, 1 H, *J* = 9.5, 3.5 Hz, CH_2I´), 3.39 (s, 3 H, OMe), 4.01 (s, 2 H, CH_2OMOM), 4.64 (s, 2 H, OCH_2OMe), 4.97, 5.13 (br s, 2 × 1 H, =CH_2).

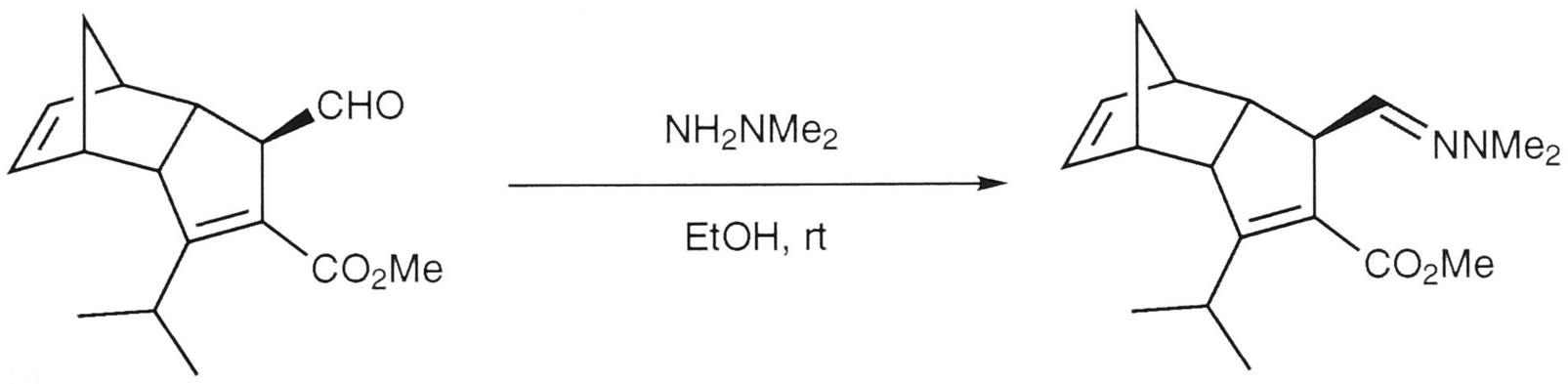
^{13}C NMR: 7.3 (CH_2I), 14.7 (Me), 31.5 (CH_2), 31.6 (CH_2), 36.0 (CH), 47.0 (CH), 50.2 (CH), 55.4 (OMe), 69.0 (CH_2), 95.6 (CH_2), 111.5 (=CH_2), 147.2 (=C).

MS: *m/z* 279 ([M-45]$^{+\cdot}$, 27%), 264 (6), 235 (36), 165 (18), 147 (42), 135 (64), 121 (32), 107 (64), 95 (90), 81 (100), 67 (59).

HRMS: calcd for $C_{12}H_{21}O_2I$ 324.0586, found 324.0590.

9.3.3 Chapter Five – Alkylations Leading to Sordaricin

(1*S*,3a*R*,4*S*,7*R*,7a*S*)-Methyl-1-(dimethyl-hydrazonomethyl)-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (160)



60 160

Dimethylhydrazine (48 μL, 0.63 mmol) was added to a stirred solution of aldehyde **60** (110 mg, 0.42 mmol) in ethanol (2.0 mL) at room temperature under a nitrogen atmosphere. After 2 h the reaction mixture was diluted with water (20 mL) and extracted three times with ethyl acetate (20 mL). The combined organic extracts were washed with brine (60 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 50% ethyl acetate in petroleum spirits as the eluant, afforded hydrazone **160** (130 mg, 100%) as a pale yellow oil.

R_f 0.20 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ +51.87° (*c* 0.38 $CHCl_3$)

IR υ_{max} 2961, 2870, 2781, 1712, 1621, 1468, 1434, 1339, 1253, 1230, 1196, 1106, 1027 cm^{-1}.

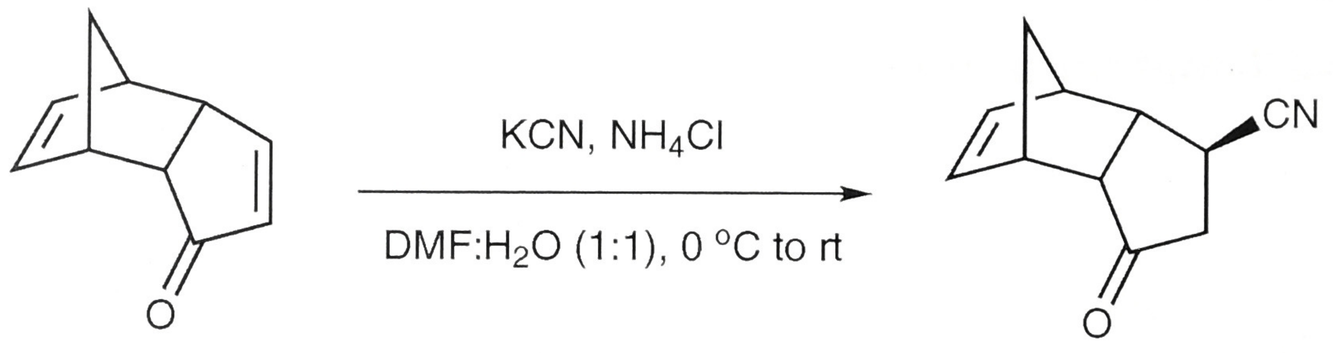
^{1}H NMR: 1.09 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.12 (d, 3 H, *J* = 7.0 Hz, CH*Me´*), 1.28 (br d, 1 H, *J* = 8.2 Hz, H8), 1.51 (dt, 1 H, *J* = 8.2, 1.8 Hz, H8´), 2.61 (m, 1 H, H7a), 2.68 (s, 6 H, N*Me*$_2$), 2.70, 3.01 (br s, 2 × 1 H, H4 + H7), 3.09 (m, 1 H, H1), 3.40 (m, 1 H, H3a), 3.56 (sep, 1 H, *J* = 7.0 Hz, C*H*Me_2), 3.61 (s, 3 H, OMe), 5.92 (dd, 1 H, *J* = 5.7, 2.9 Hz, H5 or H6), 6.06 (dd, 1 H, *J* = 5.7, 2.9 Hz, H6 or H5), 6.46 (d, 1 H, *J* = 6.6 Hz, C(*H*)=NNMe_2).

^{13}C NMR: 21.4 (Me), 21.8 (Me), 28.0 (CH), 43.5, 44.8, 45.4, 47.1, 50.7, 51.9 (5 × CH + NMe_2), 50.4 (CH_2), 55.0 (OMe), 128.3 (C, C2), 133.8, 135.2 (2 × =CH), 142.2 (=CH), 165.9 (C3 + *C*O_2Me).

MS: *m/z* 302 ($M^{+\cdot}$, 70%), 271 (13), 256 (20, 236 (81), 221 (35), 204 (100), 189 (49), 176 (33), 160 (24), 149 (29), 134 (38), 105 (22), 91 (42), 66 (54).

HRMS: calcd for $C_{18}H_{26}N_2O_2$ 302.1994, found 302.1993.

(1*S*,3a*R*,4*S*,7*R*,7a*S*)-3-Oxo-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-methano-indene-1-carbonitrile (164)



(-)-54 **164**

To a stirred solution of potassium cyanide (2.23 g, 34.2 mmol) and ammonium chloride (1.54 g, 28.8 mmol) in water (35 mL) at 0 °C under a nitrogen atmosphere, was added a solution of enone (–)-**54** (2.5 g, 17.1 mmol) in DMF (35 mL). The reaction mixture was stirred at room temperature for 48 h, then diluted with water (400 mL) and extracted three times with ethyl acetate (200 mL). The combined organic extracts were washed with water (300 mL), brine (300 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 60% ethyl acetate in petroleum spirits as the eluant, afforded nitrile **164** (2.8 g, 95%) as a white solid.

R_f 0.25 (3:1, petroleum spirits:ethyl acetate)

m.p. 48-50 °C (petroleum spirits, ethyl acetate)

$[\alpha]^{20}_D$ –149.5° (*c* 0.66 $CHCl_3$)

IR υ_{max} 2977, 223,. 1735, 1453, 1404, 1332, 1228, 1186, 1133, 840 cm^{-1}.

^{1}H NMR: 1.52 (d, 1 H, *J* = 8.6 Hz, H8), 1.67 (dt, 1 H, *J* = 8.6, 1.6 Hz, H8´), 2.42 (dd, 1 H, *J* = 18.5, 10.1 Hz, H2), 2.56 (ddd, 1 H, *J* = 18.5, 6.9, 1.6 Hz, H4´), 2.66 (m, 1 H, H1), 3.11, 3.35 (m, 2 × 1 H, H4 +H7), 3.23, 3.35 (m, 2 × 1 H, H3a + H7a), 6.17 (dd, 1 H, *J* = 5.7, 3.1 Hz, H5 or H6), 6.23 (dd, 1 H, *J* = 5.7, 3.1 Hz, H6 or H5).

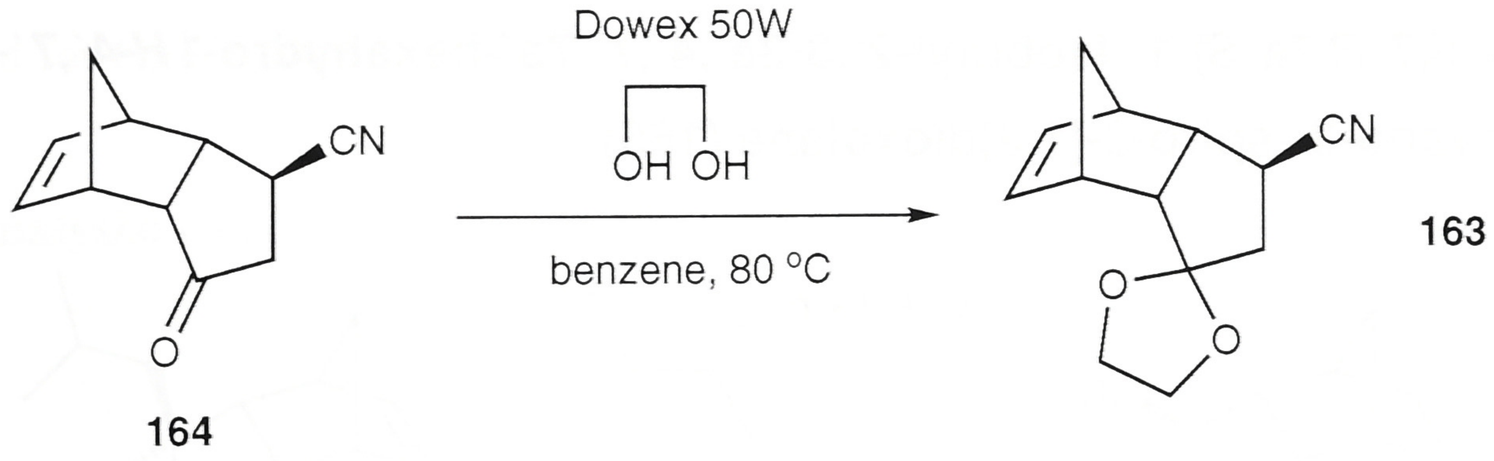
^{13}C NMR: 25.6 (CH), 44.5 (CH_2), 46.2 (CH), 46.3 (CH), 46.6 (CH), 52.1 (CH_2), 53.6 (CH), 121.9 (CN), 133.5, 137.5 (2 × =CH), 214.1 (CO).

MS: *m/z* 173 ($M^{+\cdot}$, 5%), 144 (10), 130 (32), 117 (12), 103 (20), 92 (30), 91 (100), 77 (36).

HRMS: calcd for $C_{11}H_{11}NO$ 173.0841, found 173.0834.

Elemental analysis: calcd. for $C_{11}H_{11}NO$: C, 76.3; H, 6.4; N, 8.1. Found: C, 76.0; H, 6.1; N, 8.0.

(1´*S*,3a´*R*,4´*S*,7´*R*,7a´*S*)-2´,3´,3a´,4´,7´,7a´-Hexahydro-1*H*-4´,7´-methano-indene-1´-cyano-3´-spiro-2-[1,3]dioxolane (163)



164 **163**

A solution of nitrile **164** (950 mg, 5.5 mmol), ethylene glycol (766 μL, 13.8 mmol) and Dowex-50W resin (285 mg, 30% w/w) in benzene (50 mL) was heated at reflux through a soxhlett apparatus ($MgSO_4$) under a nitrogen atmosphere. After 6 h the reaction mixture was cooled to room temperature, filtered and the solvent removed *in vacuo*. The remaining residue was taken up in ethyl acetate (100 mL), washed twice with water (100 mL) then the combined aqueous extracts extracted with ethyl acetate (100 mL). The combined organic extracts were washed with brine (100 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 50% ethyl acetate in petroleum spirits as the eluant, afforded ketal **163** (1.02 g, 85%) as a white solid.

R_f 0.40 (3:1, petroleum spirits:ethyl acetate)

m.p. 106 °C (petroleum spirits, ethyl acetate)

$[\alpha]^{20}_D$ –38.0° (*c* 1.15 $CHCl_3$)

IR υ_{max} 2985, 2231, 1479, 1430, 1338, 1140, 1107, 1067, 901 cm^{-1}.

^{1}H NMR: 1.33 (d, 1 H, *J* = 8.4 Hz, H´8), 1.50 (dt, 1 H, *J* = 8.4, 1.8 Hz, H´8´), 1.96 (apparent d, 2 H, H´4, 4´), 2.42 (td, 1 H, *J* = 6.7 Hz, H´1), 2.80 (dd, 1 H, *J* = 9.2, 4.1 Hz, H´3a), 2.90, 2.95 (m, 2 × 1 H, H´4+ H´7), 3.03 (m, 1 H, H´7a), 3.80-4.00 (m, 4 H, H4, 4´ + H5, 5´), 6.05 (dd, 1 H, *J* = 5.6, 2.9 Hz, H´5 or H´6), 6.23 (dd, 1 H, *J* = 5.7, 3.1 Hz, H´6 or H´5).

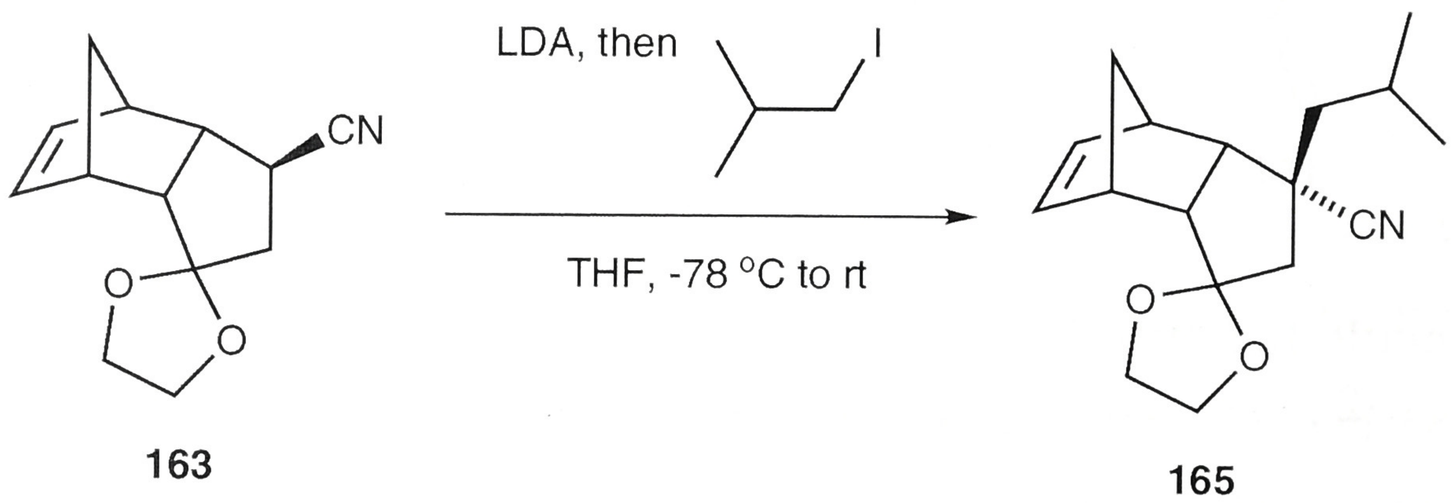
^{13}C NMR: ´27.2 (CH), 41.5 (CH_2), 44.9 (CH), 45.2 (CH_2), 48.9 (CH), 51.8 (CH_2), 53.7 (CH), 63.7 CH_2), 64.6 (CH_2), 115.6 (C, C´3), 122.6 (CN), 132.0, 138.5 (2 × =CH).

MS: *m/z* 217 ($M^{+\cdot}$, 56%), 177 (11), 164 (33), 151 (40), 124 (65), 99 (69), 88 (60), 66 (100).

HRMS: calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1104.

Elemental analysis: calcd. for $C_{13}H_{15}NO_2$: C, 71.9; H, 7.0; N, 6.5. Found: C, 72.2; H, 7.0; N, 6.4.

(1´*R*,3a´*R*,4´*S*,7´*R*,7a´*S*)-1´-Isobutyl-2´,3´3a´,4´,7´,7a´-hexahydro-1*H*-4´,7´-methano-indene-1´-cyano-3´-spiro-2-[1,3]dioxolane (165)



163 **165**

A solution of nitrile **163** (50 mg) in THF (1.5 mL) under a nitrogen atmosphere was added to a stirred solution of LDA at –78 °C, prepared by the addition of *n*-BuLi/hexane (1.6 M, 360 μL, 0.58 mmol) to a stirred solution of diisopropylamine (81 μL, 0.58 mmol) in THF (1.0 mL) at 0 °C. After 30 min the reaction mixture was warmed to room temperature and stirred for a further 30 min, then cooled to –78 °C. Isobutyliodide (53 μL, 0.46 mmol) was added, the solution warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with 1.0 M HCl (20 mL) and extracted three times with diethyl ether (20 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, afforded ketal **165** (65 mg, 100%) as a white solid..

R_f 0.65 (3:1, petroleum spirits:ethyl acetate)

m.p. 90 °C (petroleum spirits, ethyl acetate)

IR υ_{max} 2963, 2876, 2224, 1468, 1429, 1331, 1143, 1111, 1020 cm^{-1}.

^{1}H NMR: 0.99 (d, 3 H, J = 6.6 Hz, CH*Me*), 1.03 (d, 3 H, CH*Me´*), 1.29 (br d, 1 H, J = 8.2 Hz, H´8), 1.49 (dt, 1 H, J = 8.2, 1.8 Hz, H´8´), 1.66 (m, 2 H, CH_2CHMe$_2$), 1.84 (m, 1 H, C*H*Me$_2$), 1.89 (d, 1 H, J = 13.7 Hz, H´2´), 2.13 (d, 1 H, J = 13.8 Hz, H´2´), 2.72 (m, 2 H, H´3a + H´7a), 2.95, 3.12 (br s, 2 × 1 H, H´4 + H´7), 3.80-3.95 (m, 4 H, H4, 4´ + H5, 5´), 6.22 (dd, 1 H, J = 5.6, 3.0 Hz, H´5 or H´6), 6.42 (dd, 1 H, J = 5.6, 3.0 Hz, H´6 or H´5).

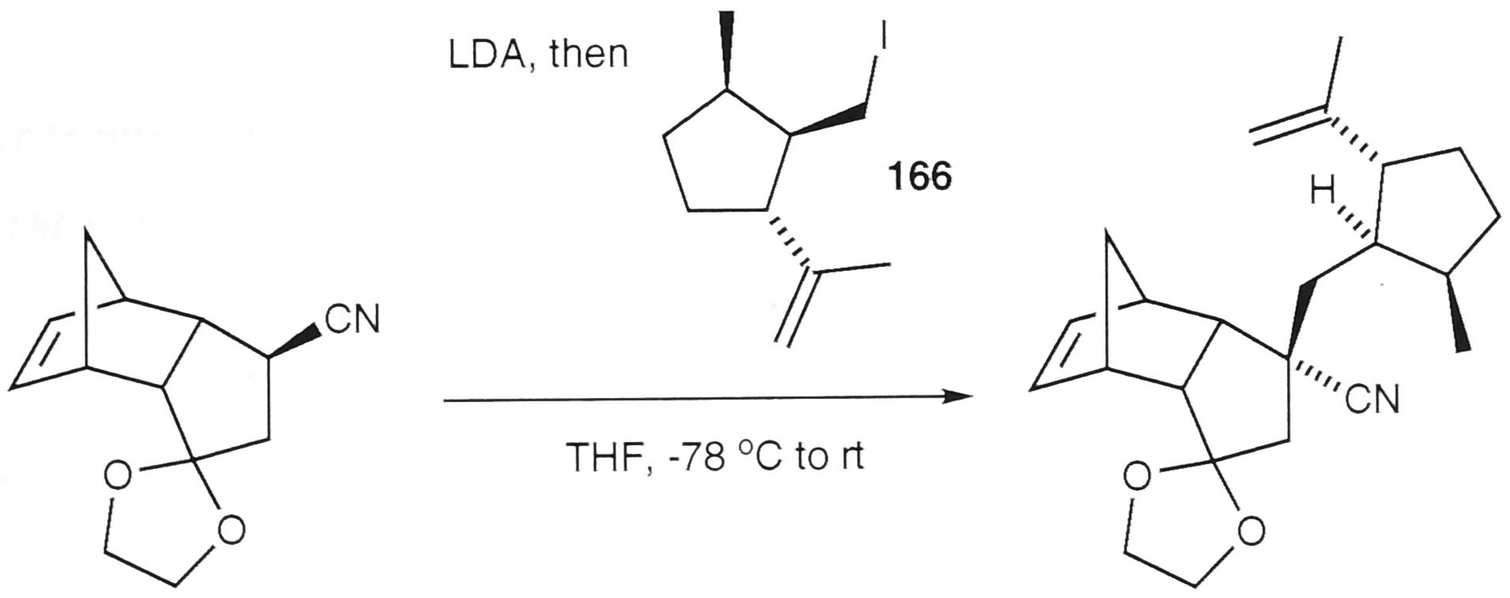
^{13}C NMR: 23.4 (Me), 24.0 (Me), 25.7 (CH), 39.4 (C, C´1), 46.1 (CH), 46.6 (CH), 46.7 (CH_2), 47.5 (CH_2), 51.1 (CH_2), 53.7 (CH), 55.0 (CH), 63.7 (CH_2), 64.3 (CH_2), 115.9 (C, C´3), 124.1 (CN), 133.6, 137.7 (2 × =CH).

MS: *m/z* 273 ($M^{+\cdot}$, 37%), 258 (40), 230 (18), 217 (49), 208 (30), 180 (26), 84 (37), 66 (100).

HRMS: calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1727.

Elemental analysis: calcd. for $C_{17}H_{23}NO_2$: C, 74.7; H, 8.5; N, 5.1. Found: C, 74.5; H, 8.3; N, 5.0.

(1´*R*,3a´*R*,4´*S*,7´*R*,7a´*S*,1´´*R*,2´´*R*,5´´*R*)-1´-(2´´-Isopropenyl-5´´-methyl-cyclopentylmethyl)-2´,3´,3a´,4´,7´,7a´-hexahydro-1*H*-4´,7´-methano-indene-1´-cyano-3´-spiro-2-[1,3]dioxolane (167)



163 167

A solution of LDA/THF (1.0 M, 600 μL, 0.58 mmol) was added dropwise to a stirred solution of nitrile **163** (50 mg, 0.23 mmol) in THF (1.3 mL) at –78 °C under a nitrogen atmosphere. After 15 min the reaction mixture was allowed to warm to room temperature and stir for 15 min before being cooled to –78 °C. A solution of iodide **166** (50 mg, 2.8 mmol) in THF (1.0 mL) was added and the mixture stirred at –78 °C for 30 min, then room temperature for 1 h. A saturated solution of aqueous ammonium chloride (1.0 mL) was added and the mixture warmed to room temperature, diluted with 1.0 M HCl (30 mL) and extracted three times with diethyl ether (15 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, afforded the desired product **167** (40 mg, 50%) as a viscous oil.

R_f 0.80 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –5.10° (*c* 0.98 $CHCl_3$)

IR υ_{max} 2947, 2234, 1741, 1638, 1466, 1427, 1380, 1337, 1148, 1114, 1063 cm^{-1}.

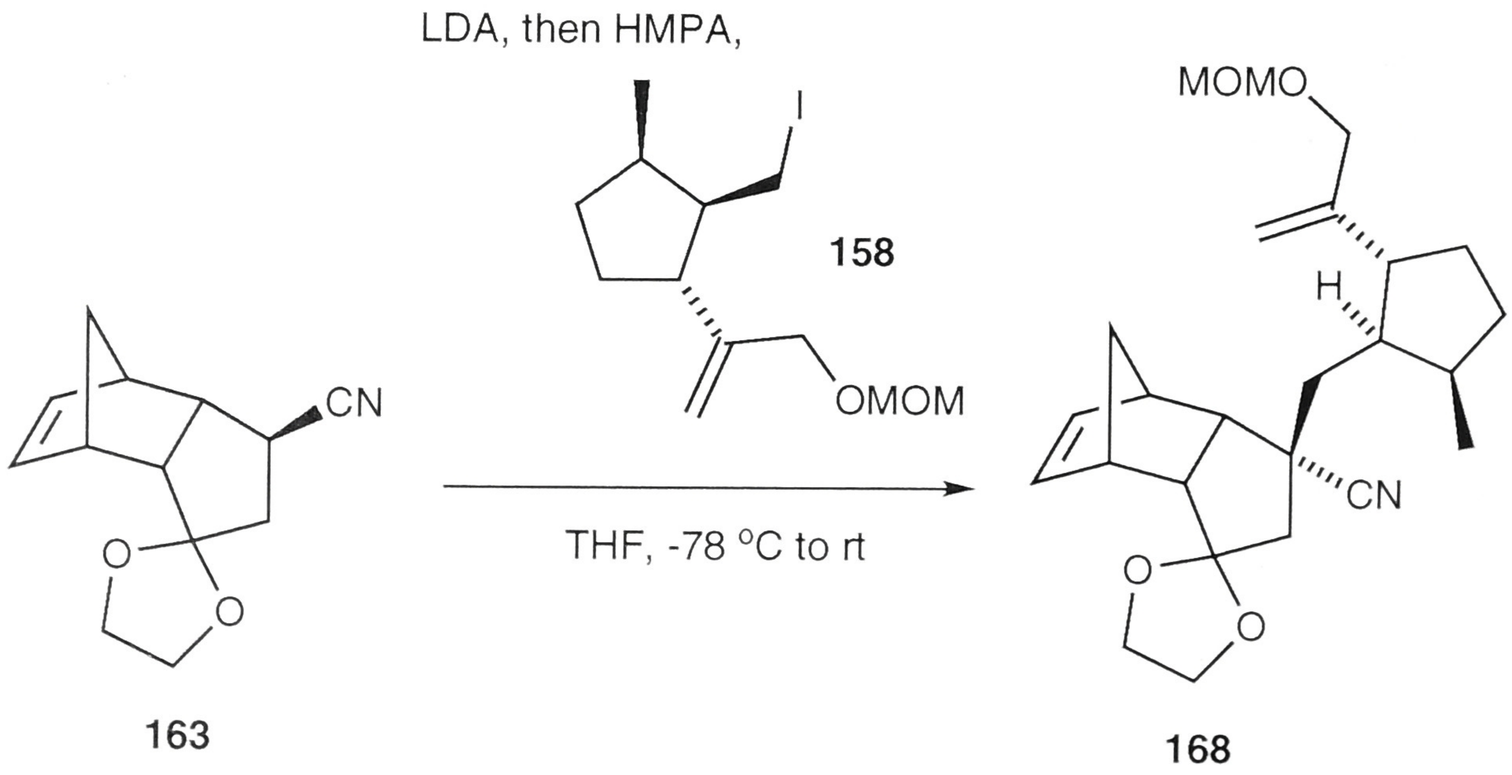
^{1}H NMR: 0.89 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.26 (d, 1 H, *J* = 8.2 Hz, H´8), 1.30-1.95 (m, 9 H), 1.72 (s, 3 H, =C*Me*), 2.12 (d, 1 H, *J* = 13.6 Hz, H´2), 2.30 (m, 2 H), 2.68 (m, 2 H), 2.94, 3.11 (br s, 2 × 1 H, H´4 + H´7), 3.8-4.0 (m, 4 H, H4, 4´ + H5, 5´), 4.74, 4.77 (s, 2 × 1 H, $=CH_2$), 6.23 (dd, 1 H, *J* = 5.7, 3.1 Hz, H´5 or H´6), 6.41 (dd, 1 H, *J* = 5.6, 2.9 Hz, H´6 or H´5).

^{13}C NMR: 15.1 (Me), 18.6 (Me), 26.9 (CH_2), 33.3 (CH_2), 35.4 (CH), 37.6, 40.8 (CH_2 + C), 44.0 (CH), 47.0 (CH), 47.4 (CH), 51.2 (CH + CH_2), 54.0 (CH), 54.9 (CH), 63.8 (CH_2), 64.4 (CH_2), 111.6 ($=CH_2$), 133.7, 137.7 (2 × =CH), 146.9 (=*C*Me).

MS: *m/z* 353 ($M^{+\cdot}$, 27%), 338 (10), 324 (42), 310 (15), 288 (25), 260 (15), 229 (52), 216 (44), 152 (27), 137 (60), 66 (100).

HRMS: calcd for $C_{23}H_{31}NO_2$ 353.2355, found 353.2353.

(1´*R*,3a´*R*,4´*S*,7´*R*,7a´*S*,1´´*R*,2´´*R*,5´´*R*)-1´-[2´´-(1´´´-Methoxymethoxymethyl-vinyl)-5´´-methyl-cyclopentylmethyl]-2´,3´,3a´,4´,7´,7a´-hexahydro-1*H*-4´,7´-methano-indene-1´-cyano-3´-spiro-2-[1,3]dioxolane (168)



163 168

A solution of LDA/THF (1.0 M, 23.1 mL, 23.1 mmol) was added dropwise to a stirred solution of nitrile **163** (2.0 g, 9.25 mmol) in THF (60 mL) at –78 °C under a nitrogen atmosphere. After 30 min the reaction mixture was allowed to warm to room temperature and stir for 1 h before being cooled to –78 °C. HMPA (1.6 mL, 9.25 mmol) and a solution of iodide **158** (1.5 g, 4.63 mmol) in THF (40 mL) were added and the mixture stirred at –78 °C for 2 h. A saturated solution of aqueous ammonium chloride (10 mL) was added and the mixture warmed to room temperature, diluted with 1.0 M HCl (300 mL) and extracted three times with diethyl ether (150 mL). The combined organic extracts were washed with brine (500 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 15% ethyl acetate in petroleum spirits as the eluant, afforded the desired product **168** (1.1 g, 58%

based on iodide) as a pale yellow oil. Further elution afforded recovered nitrile **163** (1.2 g, 5.53 mmol). Product yield based on recovered nitrile **163** was 73%.

$\mathbf{R}_f$ 0.50 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –19.9° (*c* 0.84 $CHCl_3$)

IR υ_{max} 2951, 2230, 1646, 1431, 1334, 1210, 1150, 1113, 1052 cm^{-1}.

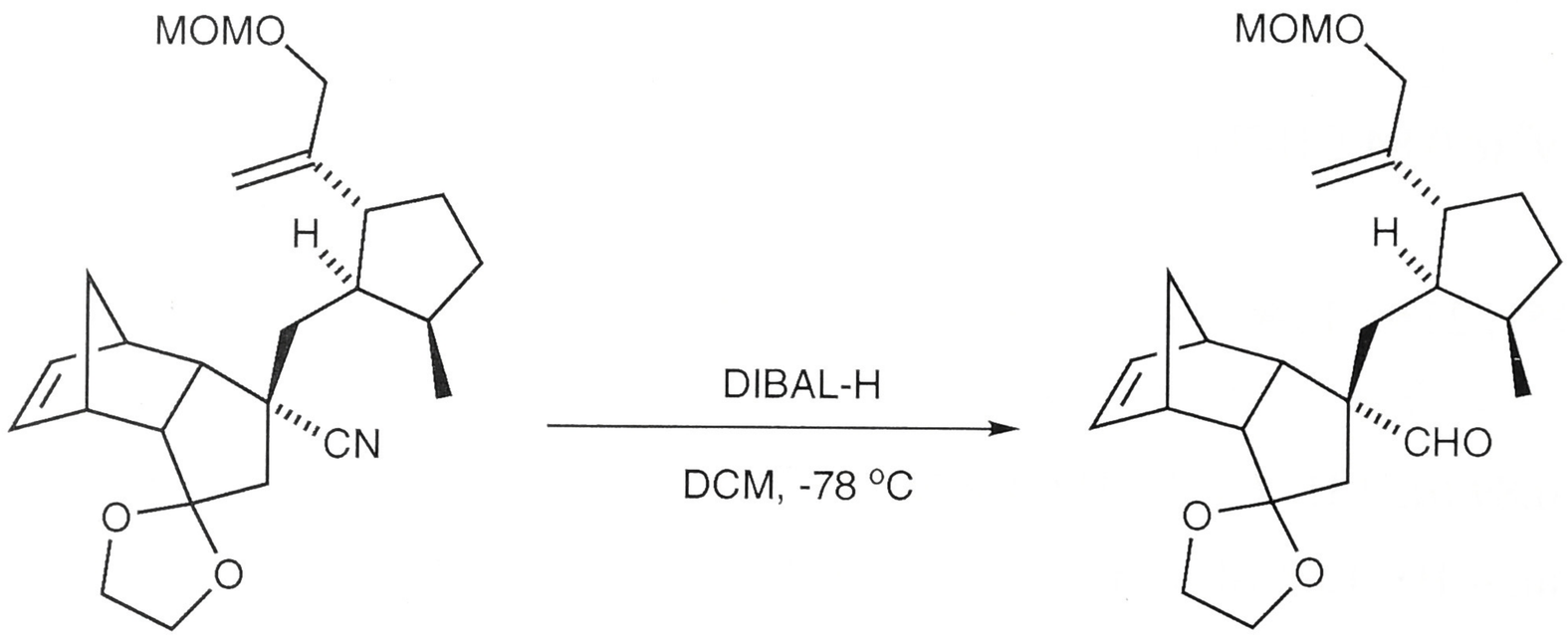
^{1}H NMR: 0.89 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.27 (d, 1 H, *J* = 8.2 Hz, H´8), 1.34-1.54 (m, 4 H), 1.68-2.08 (m, 4 H), 1.88 (d, 1 H, *J* = 13.8 Hz, H´2), 2.14 (d, 1 H, *J* = 13.9 Hz, H´2´), 2.28-2.46 (m, 2 H), 2.71 (m, 2 H), 2.93, 3.09 (s, 2 × 1 H, H´4 + H´7), 3.38 (s, 3 H, OMe), 3.78-3.94 (m, 4 H, H4,4´ + H5, 5´), 4.04 (s, 2 H, CH_2OMOM), 4.65 (s, 2 H, OCH_2OMe), 5.01, 5.15 (s, 2 × 1 H, =CH_2), 6.22 (dd, 1 H, *J* = 5.7, 3.1 Hz, H´5 or H´6), 6.41 (dd, 1 H, *J* = 5.6, 2.9 Hz, H´6 or H´5).

^{13}C NMR: 15.0 (Me), 28.2 (CH_2), 32.9 (CH_2), 35.0 (CH), 37.3 (C), 44.4 (CH), 46.0 (CH), 46.8 (CH), 47.5 (CH), 47.6 (CH_2), 51.0 (CH_2), 53.7 (CH), 54.3 (CH), 55.1 (OMe), 63.6 (CH_2), 64.2 (CH_2), 68.6 (CH_2), 95.4 (CH_2), 1115.5 (=CH_2), 115.8 (C, C2), 123.7 (CN), 133.4, 137.6 (2 × =CH), 147.3 (=C).

MS: *m/z* 413 ($M^{+\cdot}$, 3.2%), 284 (14), 268 (83), 352 (55), 316 (23), 286 (100), 261 (35), 229 (64), 216 (39), 164 912), 89 (30), 66 (78).

HRMS: calcd for $C_{25}H_{36}NO_4$ 414.2622, found 414.2643

(1´*R*,3a´*R*,4´*S*,7´*R*,7a´*S*,1´´*R*,2´´*R*,5´´*R*)-1´-[2´´-(1´´´-Methoxymethoxymethyl-vinyl)-5´´-methyl-cyclopentylmethyl]-2´,3´,3a´,4´,7´,7a´-hexahydro-1*H*-4´,7´-methano-indene-1´-formyl-3´-spiro-2-[1,3]dioxolane (169)



168 **169**

To a stirred solution of nitrile **168** (1.5 g, 3.6 mmol) in DCM (50 mL) at -78 °C under a nitrogen atmosphere was added DIBAL-H/hexane (1.0 M, 9.0 mL, 9.0 mmol). After 30 min the reaction mixture was quenched with 0.5 M aqueous oxalic acid (5.0 mL) and allowed to warm to room temperature. The mixture was further diluted with 0.5 M aqueous oxalic acid (50 mL) and extracted three times with ethyl acetate (100 mL). The combined organic extracts were washed with a saturated solution of potassium sodium tartrate (300 mL), brine (300 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford the crude aldehyde **169** (1.5 g, 100%) which was used in the next reaction without further purification. For the purpose of characterisation a portion of the aldehyde **169** was subjected to flash chromatography on a column of silica gel using 15% ethyl acetate in petroleum spirits as the eluant, to afford analytically pure aldehyde **169**.

R$_f$ 0.60 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –28.1° (*c* 0.76 $CHCl_3$)

IR υ_{max} 2954, 1720, 1645, 1454, 1435, 1333, 1244, 1211, 1150, 1111, 1052 cm^{-1}.

^{1}H NMR: 0.83 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.18 (d, 1 H, *J* = 8.1 Hz, H´8), 1.26-2.10 (m, 9 H), 2.20 (m, 1 H), 2.62 (dd, 1 H, *J* = 8.8, 4.0 Hz, H´3a or H´7a), 2.75 (m, 1 H, H´7a or H´3a), 2.88, 2.98 (br s, 2 × 1 H, H´4 + H´7), 3.37 (s, 3 H, OMe), 3.75-3.90 (m, 6 H), 4.63 (s, 2 H, OC*H*$_2$OMe), 4.89, 5.10 (br s, 2 × 1 H, =CH_2), 5.76 (dd, 1 H, *J* = 5.7, 2.9 Hz, H´5 or H´6), 6.10 (dd, 1 H, *J* = 5.6, 2.9 Hz, H´6 or H´5), 9.54 (s, 1 H, CHO).

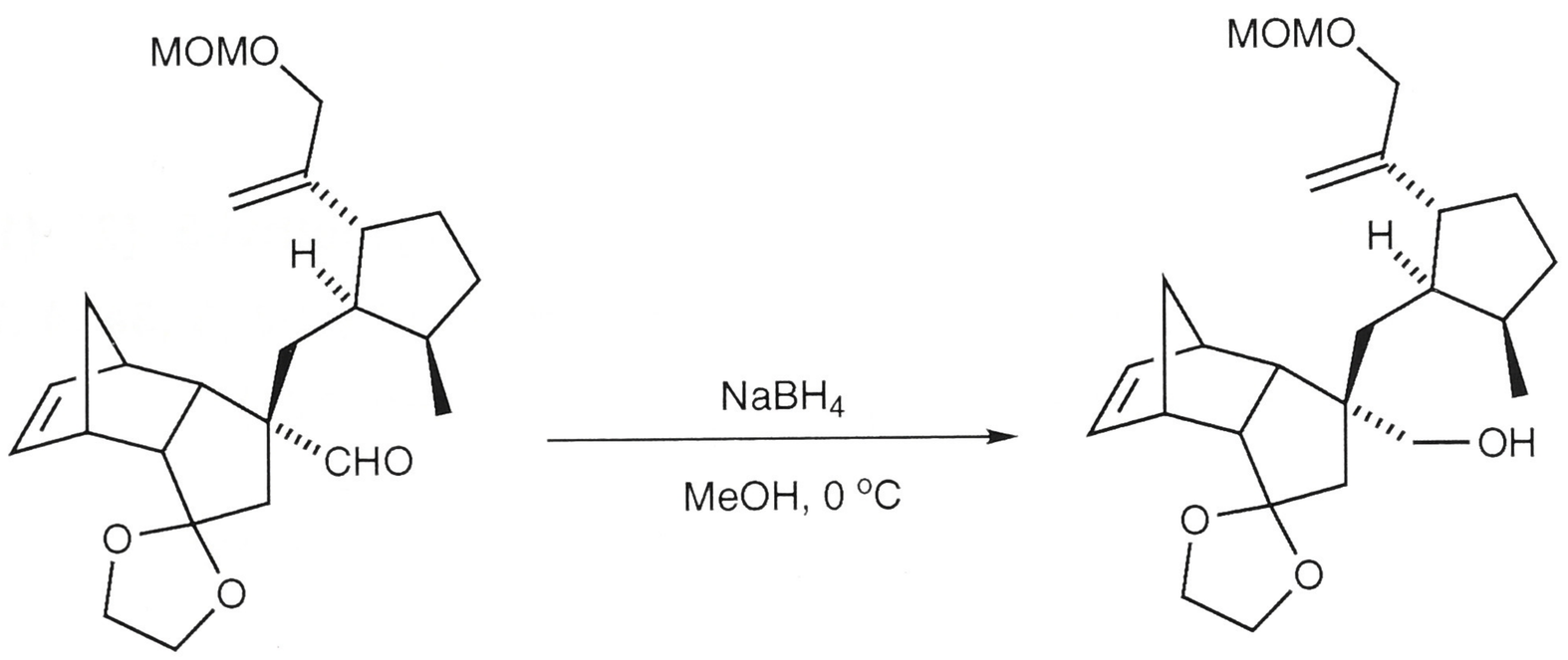
^{13}C NMR: 14.6 (Me), 28.3 (CH_2), 32.9 (CH_2), 35.8 (CH_2 or C), 36.0 (CH), 41.0 (C or CH_2), 43.7 (CH), 44.4 (CH), 44.8 (CH), 47.9 (CH), 51.3 (CH_2), 53.4 (CH), 54.0 (CH), 55.2 (OMe),

56.6 (CH_2), 63.4 (CH_2), 64.2 (CH_2), 68.6 (CH_2), 95.6 (CH_2), 111.5 ($=CH_2$), 116.3 (C, C2), 132.5, 147.8 (2 × =CH), 147.8 (=C), 204.9 (CHO).

MS: *m/z* 371 ([M-CH_2OMe]$^{+\cdot}$, 5%), 327 (10), 310 (100), 295 (20), 267 (58), 250 (48), 220 (66), 206 (25), 176 (20), 148 (78), 121 (40), 66 (32).

HRMS: calcd for ([M-CH_2OMe]$^{+\cdot}$ $C_{25}H_{31}O_4$ 371.2222, found 371.2221.

(3´*S*,3a´*S*,4´*R*,7´*S*,7a´*R*,1´´*R*,2´´*R*,5´´*R*)-3´-Hydroxymethyl-3´-[2´´-(1´´´-methoxymethoxymethyl-vinyl)-5´´-methyl-cyclopentylmethyl]-2´,3´,3a´,4´,7´,7a´-hexahydro-4´,7´-methano-indene-1´-spiro-2-[1,3]dioxolane (170)



169 **170**

To a stirred solution of aldehyde **169** (1.5 g, 3.6 mmol) in MeOH (50 mL) at 0 °C was added $NaBH_4$ (275 mg, 7.2 mmol) in portions. After 30 min the reaction was quenched with water (15 mL) and stirred for 10 min. The reaction mixture was further diluted with water (50 mL) and extracted three times with ethyl acetate (60 mL). The combined organic extracts were washed with brine (500 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford the crude alcohol **170** (1.46 g, 97%) which was used directly in the next reaction. For the purpose of characterisation a portion of the alcohol **170** was subjected to flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, to afford pure **170**.

R_f 0.30 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –50.1 ° (*c* 0.63 $CHCl_3$)

IR υ_{max} 3498, 2950, 1644, 1470, 1334, 1211, 1150, 1110, 1048 cm^{-1}.

^{1}H NMR: 0.92 (d, 3 H, *J* = 6.9 Hz, CH*Me*), 1.18-1.26 (m, 2 H), 1.36-1.53 (m, 5 H), 1.69-1.98 (m, 4 H), 2.10 (m, 1 H), 2.36-2.44 (m, 3 H), 2.79 (m, 1 H), 2.84, 3.01 (m, 2 × 1 H, H´4 + H´7),

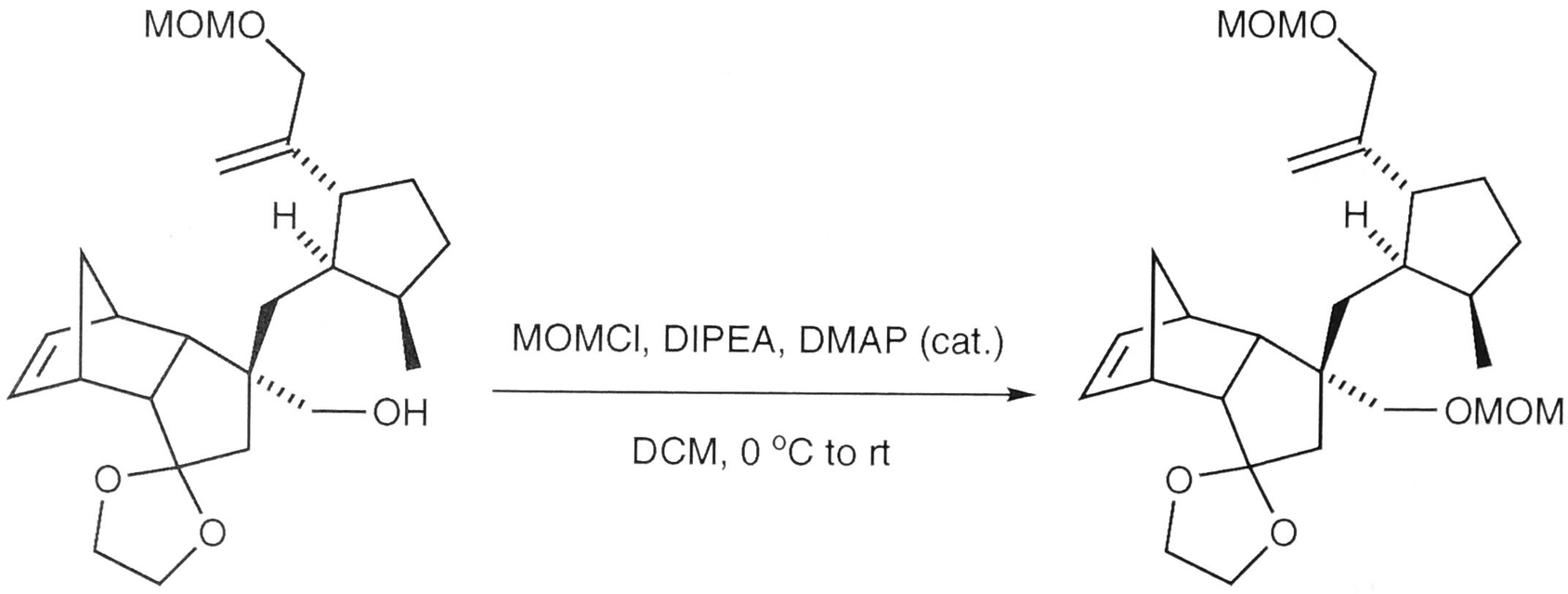
3.23 (d, 1 H, J = 11.7 Hz, CH_2OH), 3.40 (s, 3 H, OMe), 3.45 (d, 1 H, J = 11.7 Hz, CH_2OH´), 3.76-3.98 (m, 4 H, H4, 4´ + H5, 5´), 4.04 (m, 2 H, CH_2OMOM), 4.67 (s, 2 H, OCH_2OMe), 5.06, 5.16 (br s, 2 × 1 H, =CH_2), 6.15 (apparent t, 2 H, J = 1.9 Hz, 2 × =CH).

^{13}C NMR: 14.3 (Me), 27.5, 33.5, 34.1 (2 × CH_2 + C), 36.7 (CH), 43.6 (CH_2), 43.8 (CH), 45.2 (CH), 45.4 (CH), 45.6 (CH_2), 49.0 (CH), 52.1 (CH_2), 54.0 (CH), 55.4 (OMe), 56.0 (CH), 63.3 (CH_2), 63.8 (CH_2), 64.9 (CH_2), 68.5 (CH_2), 95.9 (CH_2), 114.4 (, =CH_2), 117.1 (C, C2), 133.3, 137.1 (2 × =CH), 148.5 (=C).

MS: *m/z* 418 ($M^{+\cdot}$, 13%), 387 (28), 373 (12), 357 (18), 321 (35), 291 (27), 277 (15), 234 (20), 221 (77), 157 (25), 139 (34), 91 (64), 66 (100).

HRMS: calcd for ($[M+H]^{+\cdot}$ $C_{25}H_{39}O_5$ 419.2798, found 419.2789.

(3´*S*,3a´*S*,4´*R*,7´*S*,7a´*R*,1´´*R*,2´´*R*,5´´*R*)-3´-Methoxymethoxymethyl-3´-[2´´-(1´´´-methoxymethoxymethyl-vinyl)-5´´-methyl-cyclopentylmethyl]-2´,3´,3a´,4´,7´,7a´-hexahydro-4´,7´-methano-indene-1´-spiro-2-[1,3]dioxolane (171)



170 **171**

To a stirred solution of alcohol **170** (1.46g, 3.5 mmol) and DMAP (64 mg, 0.53 mmol) in DCM (35 mL) at 0 °C under a nitrogen atmosphere, was added DIPEA (3.3 mL, 19.3 mmol) and MOMCl (1.33 mL, 17.5 mmol). The reaction mixture was allowed to stir at room temperature for 24 h, then diluted with 1.0 M HCl (100 mL) and extracted twice with diethyl ether (150 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting crude ether **171** (1.58 g, 97%) was used directly in the next reaction. For the purpose of characterisation a portion of the ether **171** was subjected to flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, to afford pure **171**.

R_f 0.70 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –47.9 ° (*c* 0.40 $CHCl_3$)

IR υ_{max} 2949, 1646, 1466, 1335, 1211, 1149, 1107, 1050 cm^{-1}.

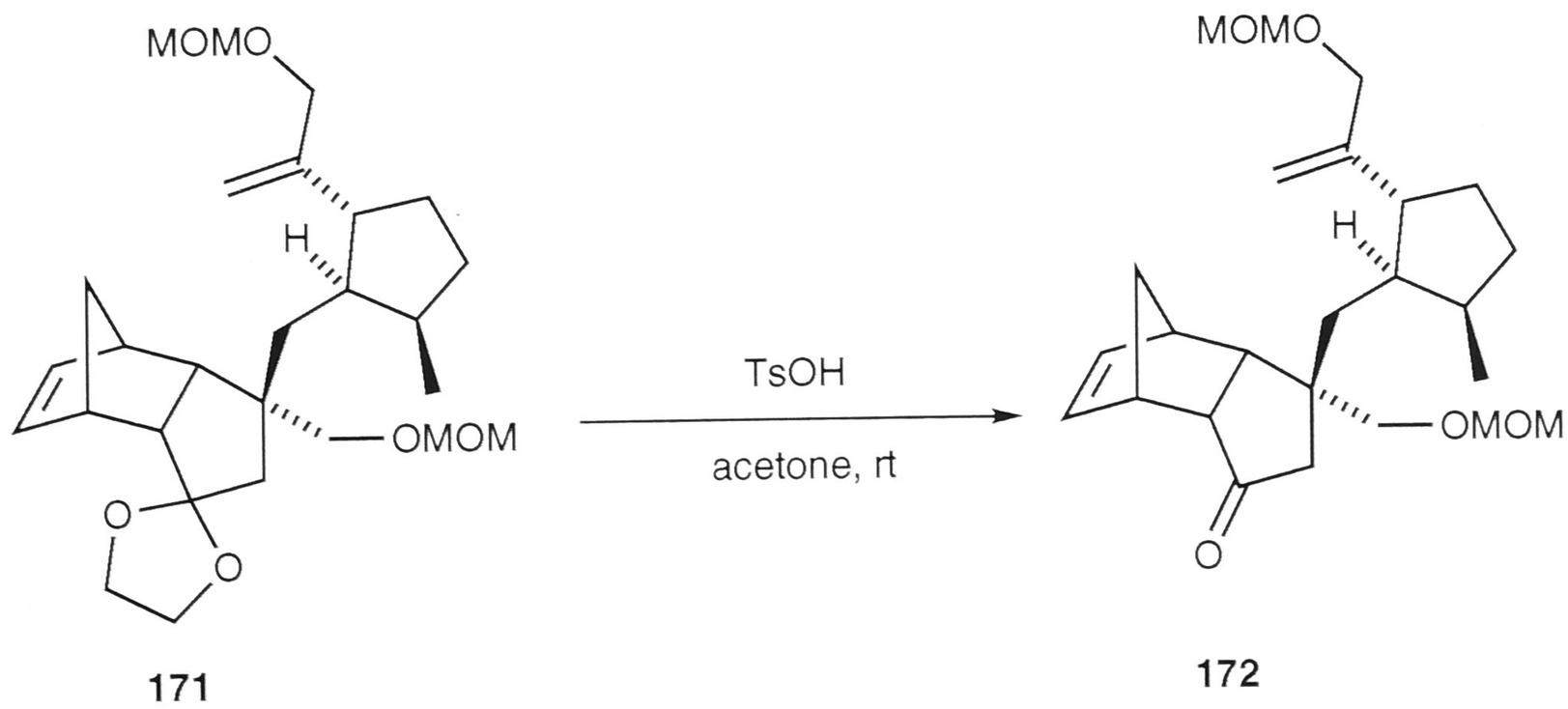
^{1}H NMR: 0.88 (d, 3 H, *J* = 6.9 Hz, CH*Me*), 1.19 (d, 1 H, *J* = 7.6 Hz, H´8), 1.36-2.14 (m, 14 H), 2.32 (m, 1 H), 2.45 (dd, 1 H, *J* = 8.9, 3.7 Hz, H´3a or H´7a), 2.73 (dd, 1 H, *J* = 8.9, 4.5 Hz, H´7a or H´3a), 2.82 (br s, 2 × 1 H, H´4 + H´7), 3.32 (AB d, 2 H, *J* = 9.4 Hz, CH_2OMOM), 3.37, 3.38 (s, 2 × 3 H, 2 × OMe), 3.76-3.84 (m, 4 H, H4, 4´ + H5, 5´), 4.03 (s, 2 H, =CCH_2OMOM), 4.58, 4.64 (s, 2 × 2 H, 2 × OCH_2OMe), 4.99, 5.10 (br s, 2 × 1 H, =CH_2), 6.09 (dd, 1 H, *J* = 5.6, 2.9 Hz, H´5 or H´6), 6.15 (dd, 1 H, *J* = 5.4, 2.9 Hz, H´6 or H´5).

^{13}C NMR: 15.0 (Me), 28.3, 33.4, 35.4 (2 × CH_2 + C), 36.5 (CH), 44.0 (CH), 44.2 (CH_2), 45.1 (2 × CH), 46.7 (CH_2), 47.7 (CH), 52.1 (CH_2), 54.0 (CH), 54.3 (CH), 55.2 (OMe), 55.4 (OMe), 63.4 (CH_2), 63.8 (CH_2), 68.9 (CH_2), 71.8 (CH_2), 95.6 (CH_2), 96.9 (CH_2), 110.6 (=CH_2), 117.1 (C, C2), 133.0, 137.4 (2 × =CH), 148.5 (=C).

MS: *m/z* 462 ($M^{+\cdot}$, 10%), 421 (5), 417 (15), 401 (40), 387 (64), 365 (20), 321 (50), 265 (64), 201 (25), 89 (84), 66 (100).

HRMS: calcd for ($[M+H]^{+\cdot}$ $C_{27}H_{43}O_6$ 463.3060, found 463.3065.

(3´*S*,3a´*S*,4´*R*,7´*S*,7a´*R*,1´´*R*,2´´*R*,5´´*R*)-3-Methoxymethoxymethyl-3-[2´-(1´´-methoxymethoxymethyl-vinyl)-5´-methyl-cyclopentylmethyl]-2,3,3a,4,7,7a-hexahydro-4,7-methano-inden-1-one (172)



171 172

A solution of bisMOM ether **171** (1.6 g, 3.4 mmol) and toluene-4-sulfonic acid (1.29 g, 6.8 mmol) in acetone (50 mL) was stirred at room temperature for 30 min. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed twice with saturated aqueous sodium bicarbonate solution (100 mL). The combined aqueous residues were washed three times with ethyl acetate (75 mL), and the combined organic extracts washed with brine (200 mL) and dried

($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 20% ethyl acetate in petroleum spirits as the eluant, afforded the ketone **172** (1.35g, 90% over 4 steps) as a pale yellow oil.

R_f 0.30 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –150.5 ° (*c* 0.50 $CHCl_3$)

IR υ_{max} 2948, 1732, 1645, 1465, 1404, 1213, 1149, 1108, 1047 cm^{-1}.

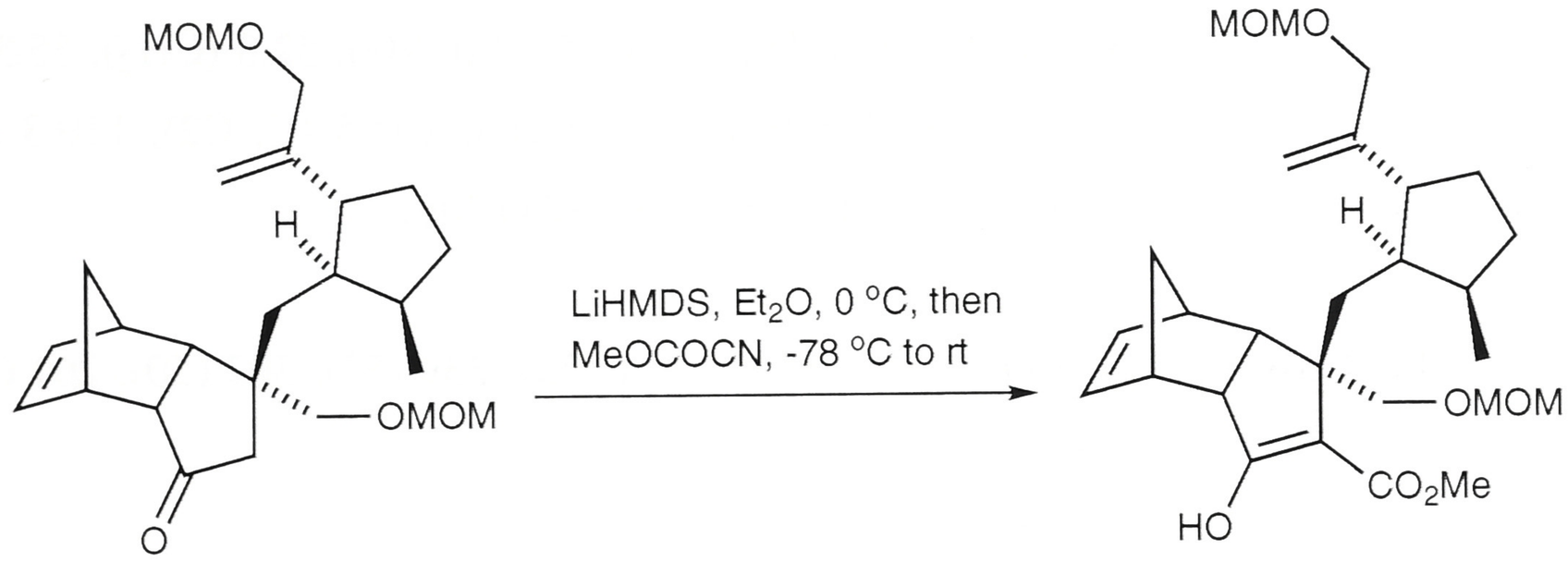
^{1}H NMR: 0.80 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.30-1.55 (m, 6 H), 1.70-2.30 (m, 8 H), 2.63 (dd, 1 H, *J* = 8.5, 3.5 Hz, H3a), 2.93 (dd, 1 H, *J* = 8.5, 3.5 Hz, H7a), 3.06, 3.14 (br s, 2 × 1 H, H4 + H7), 3.36, 3.39 (s, 2 × 3 H, 2 × OMe), 3.40 (AB d, 2 H, *J* = 9.4 Hz, CH_2OMOM), 3.97 (s, 2 H, =CCH_2OMOM), 4.62 (s, 4 H, 2 × OCH_2OMe), 4.92, 5.09 (br s, 2 × 1 H, =CH_2), 6.02 (dd, 1 H, *J* = 5.7, 3.1 Hz, =CH), 6.20 (dd, 1 H, *J* = 5.4, 2.8 Hz, =CH).

^{13}C NMR: 15.5 (Me), 28.1, 33.2, 37.8 (2 × CH_2 + C), 35.8 (CH), 42.9 (CH), 45.5 (CH), 46.5 (CH), 48.2 (CH), 50.2 (CH), 50.2 (CH_2), 52.9 (CH_2), 53.8 (CH), 55.2 (OMe), 55.5 (OMe), 68.7 (CH_2), 71.9 (CH_2), 95.6 (CH_2), 96.6 (CH_2), 111.3 (=CH_2), 134.6, 135.6 (2 × =CH), 147.7 (=C), 220.1 (CO).

MS: *m/z* 418 ($M^{+\cdot}$, <1%), 373 (1), 321 (54), 291 (22), 229 (15), 187 (17), 159 (23), 121 (30), 107 (39), 91 (44), 66 (100).

HRMS: calcd for ($[M+H]^{+\cdot}$ $C_{25}H_{39}O_5$ 419.2798, found 419.290.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1´*R*,2´*R*,5´*R*)-Methyl-3-hydroxy-1-methoxymethoxymethyl-1-[2´-(1´´-methoxymethoxymethyl-vinyl)-5´-methyl-cyclopentylmethyl]-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (178)



172 **178**

LiHMDS/hexanes (1.0 M, 2.15 mL, 2.15 mmol) was added to a stirred solution of ketone **172** (600 mg, 1.43 mmol) in diethyl ether (2.0 mL) at 0 °C under a nitrogen atmosphere. After 3 h the solution was cooled to –78 °C, diluted with diethyl ether (4 mL) and methyl cyanoformate (1.1 mL, 14.4 mmol) added. After 20 min the reaction mixture was allowed to warm to room temperature and stirred for a further 30 min. The reaction mixture was diluted with water (100 mL) and extracted three times with diethyl ether (50 mL). The combined organic residues were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was dissolved in methanol (15 mL) and potassium carbonate (500mg) added. After 30 min the reaction mixture was diluted with ethyl acetate (50 mL) and washed with 1.0 M HCl (50 mL). The aqueous layer was extracted twice with ethyl acetate (50 mL) and the combined organic extracts washed with brine (100 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, afforded the ester **178** (360 mg , 86% based on recovered starting material) as an oil. Increasing to 20% ethyl acetate in petroleum spirits as the eluant, afforded starting material **172** (230 mg).

R_f 0.75 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –111.7 ° (*c* 0.41 $CHCl_3$)

IR υ_{max} 2952, 1766, 1651, 1609, 1443, 1342, 1281, 1256, 1230, 1208, 1107, 1047 cm^{-1}.

^{1}H NMR: 0.90 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.25-1.55 (m, 7 H), 1.60-2.20 (m, 7 H), 2.42 (dd, 1 H, *J* = 8.5, 3.7 Hz, H7a), 3.10, 3.30 (br s, 2 × 1 H, H4 + H7), 3.34 (m, 1 H, H3a), 3.36 (s, 3 H, OMe), 3.40 (m, 1 H, C*H*$_2$OMOM), 3.44 (s, 3 H, OMe), 3.63 (s, 3 H, CO_2Me), 3.65 (m, 1 H, C*H*$_2$OMOM´), 3.85 (AB d, 2 H, *J* = 13.0 Hz, =CC*H*$_2$OMOM), 4.60, 4.66 (s, 2 × 2 H, 2 ×

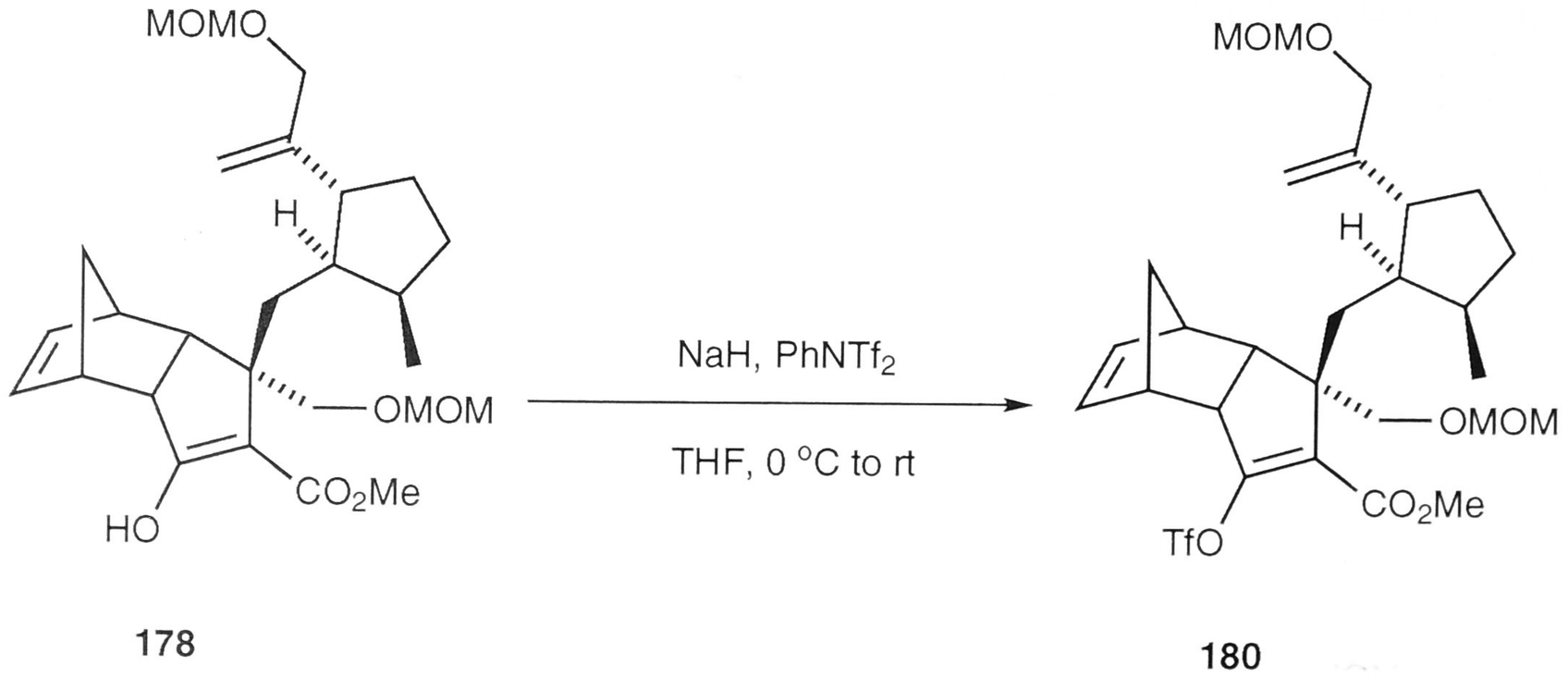
OCH_2OMe), 4.76, 4.98 (br s, 2 × 1 H, =CH_2), 5.93 (dd, 1 H, J = 5.7, 3.1 Hz, H5 or H6), 6.08 (dd, 1 H, J = 5.4, 2.5 Hz, H6 or H5), 10.96 (br s, 1 H, OH).

^{13}C NMR: 16.4 (Me), 28.8, 29.8, 33.5, 36.1 (3 × CH_2 + C), 36.5 (CH), 42.8 (CH), 45.2 (CH), 46.0 (CH), 47.7 (CH), 48.5 (CH), 49.1 (CH_2), 50.8 (CH), 51.3 (OMe), 52.0 (CH_2), 55.3 (OMe), 55.6 (OMe), 68.9 (CH_2), 73.6 (CH_2), 95.7 (CH_2), 97.3 (CH_2), 104.5 (C, C2), 110.3 (=CH_2), 133.8, 134.4 (2 × =CH), 148.2 (=C), 170.5 (C, C3), 179.1 (CO_2Me).

MS: *m/z* 445 ([M-OMe]$^{+\cdot}$, 7%), 399 (14), 369 (37), 351 (23), 339 (53), 307 (50), 261 (60), 229 (69), 191 (56), 159 (76), 91 (100).

HRMS: calcd for ([M-OMe]$^{+\cdot}$ $C_{26}H_{37}O_6$ 445.2590, found 445.2584.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1′*R*,2′*R*,5′*R*)-Methyl-1-methoxymethoxymethyl-1-[2′-(1′′-methoxymethoxymethyl-vinyl)-5′-methyl-cyclopentylmethyl]-3-trifuoromethanesulfonyloxy-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (180)



178 **180**

NaH (60% w/w in oil, 277 mg, 7.0 mmol) and *N*-phenyltrifluoromethanesulfonimide (1.2 g, 2.8 mmol) were carefully added to a stirred solution of **178** (660 mg, 1.4 mmol) in THF (20 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, after which time water (5 mL) was carefully added at 0 °C. The resulting mixture was further diluted with water (80 mL) and extracted twice with diethyl ether (100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 5%, increasing to 10% ethyl acetate in petroleum spirits as the eluant, to afford **180** (740 mg, 89%) as a colourless oil.

R_f 0.75 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_{D}$ –17.8 ° (*c* 1.02 $CHCl_3$)

IR υ_{max} 2952, 2251, 1723, 1647, 1426, 1337, 1292, 1212, 1144, 1048 cm^{-1}.

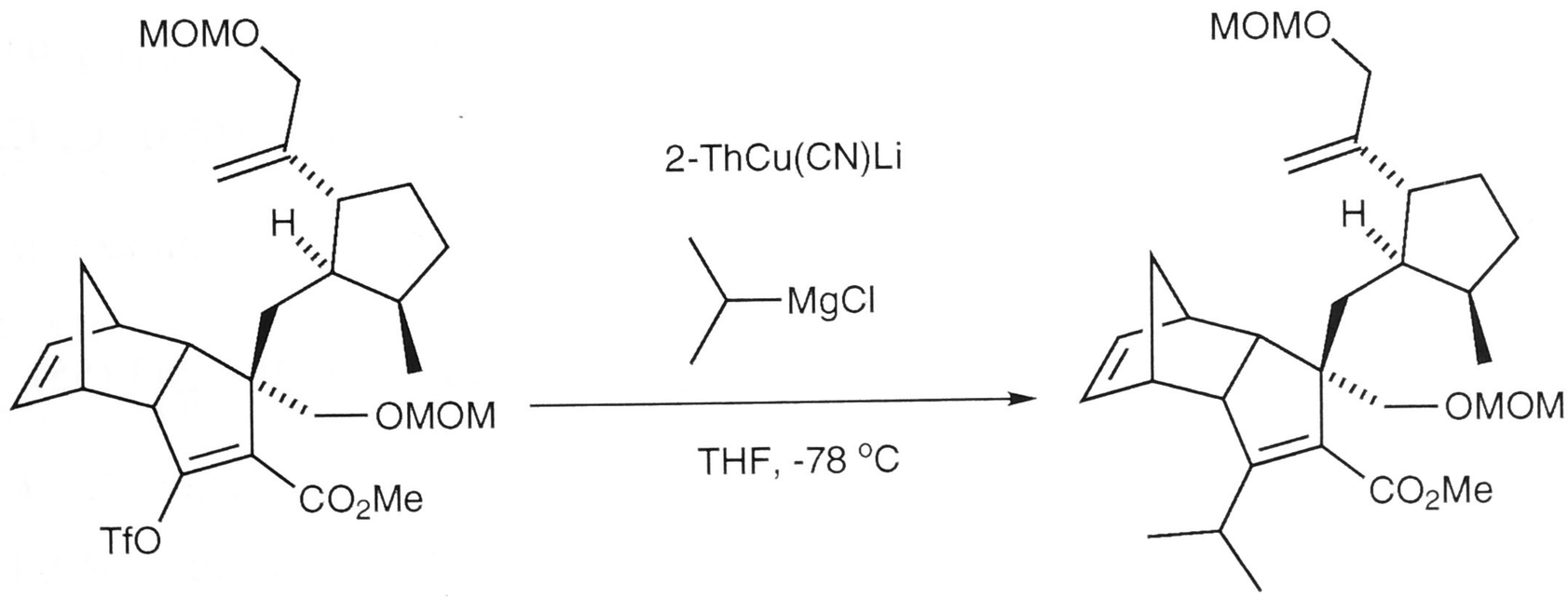
^{1}H NMR: 0.88 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.28 (d, 1 H, *J* = 8.4 Hz, H8), 1.34-1.62 (m, 4 H), 1.76-2.00 (m, 4 H), 2.16 (m, 2 H), 2.58 (dd, 1 H, *J* = 8.4, 3.7 Hz, H7a), 3.08, 3.25 (br s, 2 × 1 H, H4 + H7), 3.37 (s, 3 H, OMe), 3.42 (s, 3 H, OMe), 3.53 (m, 2 H, H3a +CH_2OMOM), 3.67 (s, 3 H, CO_2Me), 3.78 (d, 1 H, *J* = 9.7 Hz, CH_2OMOM´), 3.92 (AB d, 2 H, *J* = 13.2 Hz, =CCH_2OMOM), 4.63, 4.64 (s, 2 × 2 H, 2 × OCH_2OMe), 4.87, 5.04 (br s, 2 × 1 H, =CH_2), 5.96 (dd, 1 H, *J* = 5.6, 2.9 Hz, H5 or H6), 6.17 (dd, 1 H, *J* = 5.7, 2.8 Hz, H6 or H5).

^{13}C NMR: 15.8 (Me), 28.4 (C or CH_2), 33.3 (CH), 36.3 (CH), 36.7 (CH_2 or C), 43.2 (CH), 45.4 (CH), 46.0 (CH), 47.7 (CH), 47.9 (CH), 50.6 (OMe), 51.0 (CH_2), 51.5 (CH), 51.6 (CH_2), 55.2 (OMe), 55.7 (OMe), 68.9 (CH_2), 72.1 (CH_2), 95.5 (CH_2), 97.3 (CH_2), 111.0 (=CH_2), 118.1 (q, *J* = 319.3 Hz, CF_3), 126.6 (C, C2), 134.1, 135.1 (2 × =CH), 147.9 (=C), 156.6 (C, C3), 161.9 (*C*O2Me).

MS: *m/z* 607 ($M^{+\cdot}$, 2%), 501 (12), 434 (12), 369 (20), 348 (58), 301 (41), 241 (40), 215 (41), 79 (40), 66 (100).

HRMS: calcd for ($[M+H]^{+\cdot}$ $C_{28}H_{39}O_9F_3S$ 608.2267, found 608.2266.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1´*R*,2´*R*,5´*R*)-Methyl-3-isopropyl-1-methoxymethoxymethyl-1-[2´-(1´´-methoxymethoxymethyl-vinyl)-5´-methyl-cyclopentylmethyl]-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (181)



180 **181**

n-BuLi/hexanes (1.6 M, 357 μL, 0.58 mmol) was added to a stirred solution of thiophene (91 μL, 0.58 mmol) in THF (1.0 mL) at 0 °C under a nitrogen atmosphere. After 20 min the resulting solution was transferred *via* a cannula to a stirred suspension of CuCN (51 mg, 0.58 mmol) in THF (2.0 mL) at –78 °C. The mixture was allowed to slowly warm to –40 °C and

stirred for a further 30 min, after which time the solution was cooled to –78 °C. Isopropylmagnesium chloride/THF (2.0 M, 285 μL, 0.58 mmol) was added, followed by the addition a solution of triflate **180** (170 mg, 0.29 mmol) in THF (3.0 mL). After 1 h aqueous ammonium chloride solution (2.0 mL) was added and the mixture allowed to warm to room temperature. The mixture was diluted with water (20 mL) and 10% aqueous ammonia solution (10mL), then extracted three times with diethyl ether (25 mL). The combined organic extracts were washed with 1.0 M HCl (50 mL), brine (50 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by flash chromatography on a column of silica gel using 10% ethyl acetate in petroleum spirits as the eluant, afforded **181** (130 mg, 90%) as a pale yellow oil.

R_f 0.80 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –110.5 ° (*c* 0.76 $CHCl_3$)

IR υ_{max} 2952, 1705, 1645, 1604, 1434, 1229, 1150, 1107, 1047 cm^{-1}.

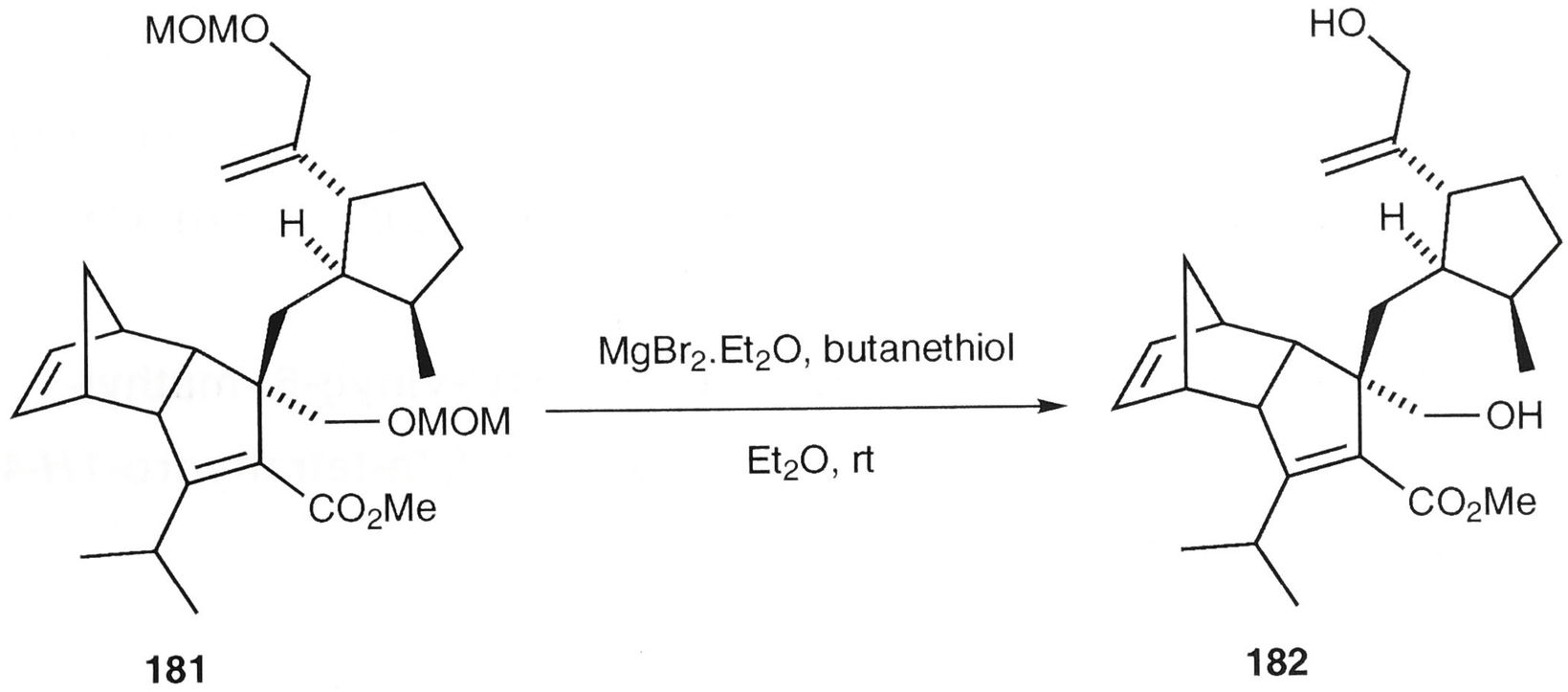
^{1}H NMR: 0.88 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.06 (d, 3 H, *J* = 7.2 Hz, CH*Me*$_2$), 1.10 (d, 3 H, *J* = 7.2 Hz, CH*Me*$_2$´), 1.20-2.00 (m, 9 H), 2.18 (m, 2 H), 2.44 (dd, 1 H, *J* = 8.4, 3.7 Hz, H7a), 3.04, 3.12 (br s, 2 × 1 H, H4 + H7), 3.17 (sep, 1 H, *J* = 6.7 Hz, C*H*Me$_2$), 3.33, 3.34 (s, 2 × 3 H, 2 × OMe), 3.36 (m, 1 H, H3a), 3.45 (d, 1 H, *J* = 9.5 Hz, C*H*$_2$OMOM), 3.56 (s, 3 H, CO_2Me), 3.60 (d, 1 H, *J* = 9.5 Hz, C*H*$_2$OMOM´), 3.87 (AB d, 2 H, *J* = 13.9 Hz, =CC*H*$_2$OMOM), 4.59, 4.60 (s, 2 × 2 H, 2 × OC*H*$_2$OMe), 4.80, 5.00 (br s, 2 × 1 H, =CH_2), 5.75 (dd, 1 H, *J* = 5.7, 2.9 Hz, H5 or H6), 6.06 (dd, 1 H, *J* = 5.6, 2.8 Hz, H6 or H5).

^{13}C NMR: 16.0 (Me), 21.6 (Me), 21.7 (Me), 28.4 (C), 28.8 (CH), 33.6 (CH_2), 36.5 (CH_2), 37.0 (CH_2), 43.1 (CH), 45.8 (CH), 47.8 (CH), 48.2 (CH), 48.3 (CH), 50.5 (CH), 52.2 (CH_2), 53.3 (OMe), 53.7 (CH_2), 55.2 (OMe), 55.5 (OMe), 68.6 (CH_2), 73.2 (CH_2), 95.6 (CH_2), 97.3 (CH_2), 110.6 (=CH_2), 131.2 (C, C2), 134.5, 135.2 (2 × =CH), 148.1 (=C), 165.0 (C, C3), 166.1 (*C*O_2Me).

MS: *m/z* 502 ($M^{+\cdot}$, 3%), 404 (37), 374 (52), 342 (100), 300 (90), 269 (39), 243 (55), 119 (40), 81 (40), 66 (52).

HRMS: calcd for $C_{30}H_{46}O_6$ 502.3294, found 502.3298.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1´*R*,2´*R*,5´*R*)-Methyl-1-hydroxymethyl-1-[2´-(1´´-hydroxymethyl-vinyl)-5´-methyl-cyclopentylmethyl]-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (182)



181 **182**

A solution of MOM ether **181** (200 mg, 0.4 mmol), $MgBr_2.Et_2O$ (823 mg, 3.2 mmol) and 1-butanethiol (299 μL, 2.8 mmol) in diethyl ether (10 mL) was stirred at room temperature for 24 h. A further portion of reagents was added and the mixture stirred a further 24 h. The resulting solution was then diluted with 1.0 M HCl (50 mL) and extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 20%, increasing to 70% ethyl acetate in hexanes as the eluant, to afford **182** (153 mg, 92%) as a colourless oil.

R_f 0.15 (2:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –78.6 ° (*c* 0.59 $CHCl_3$)

IR υ_{max} 3429, 2955, 1765, 1702, 1436, 1252, 1121, 1042 cm^{-1}.

^{1}H NMR: 0.88 (d, 1 H, *J* = 7.0 Hz, CH*Me*), 1.05 (d, 3 H, *J* = 7.0 Hz, CH*Me*$_2$), 1.13 (d, 3 H, *J* = 7.0 Hz, CH*Me*$_2$´), 1.26 (d, 1 H, *J* = 8.1 Hz, H8), 1.38 (m, 2 H), 1.50 (d, 1 H, *J* = 8.1 Hz, H8´), 1.60-1.90 (m, 5 H), 2.20 (m, 2 H), 2.43 (dd, 1 H, *J* = 8.4, 3.8 Hz, H7a), 2.97, 3.07 (br s, 2 × 1 H, H4 + H7), 3.23 (sep, 1 H, *J* = 6.9 Hz, C*H*Me$_2$), 3.39 (dd, 1 H, *J* = 8.4, 4.5 Hz, H3a), 3.56 (d, 1 H, *J* = 11.3 Hz, C*H*$_2$OH), 3.66 (s, 3 H, OMe), 3.75 (d, 1 H, *J* = 11.3 Hz, C*H*$_2$OH´), 3.98 (AB d, 2 H, *J* = 14.4 Hz, =CC*H*$_2$OH), 4.78, 5.03 (br s, 2 × 1 H, =CH$_2$), 5.73 (dd, 1 H, *J* = 5.7, 2.9 Hz, H5 or H6), 6.04 (dd, 1 H, *J* = 5.7, 2.9 Hz, H6 or H5).

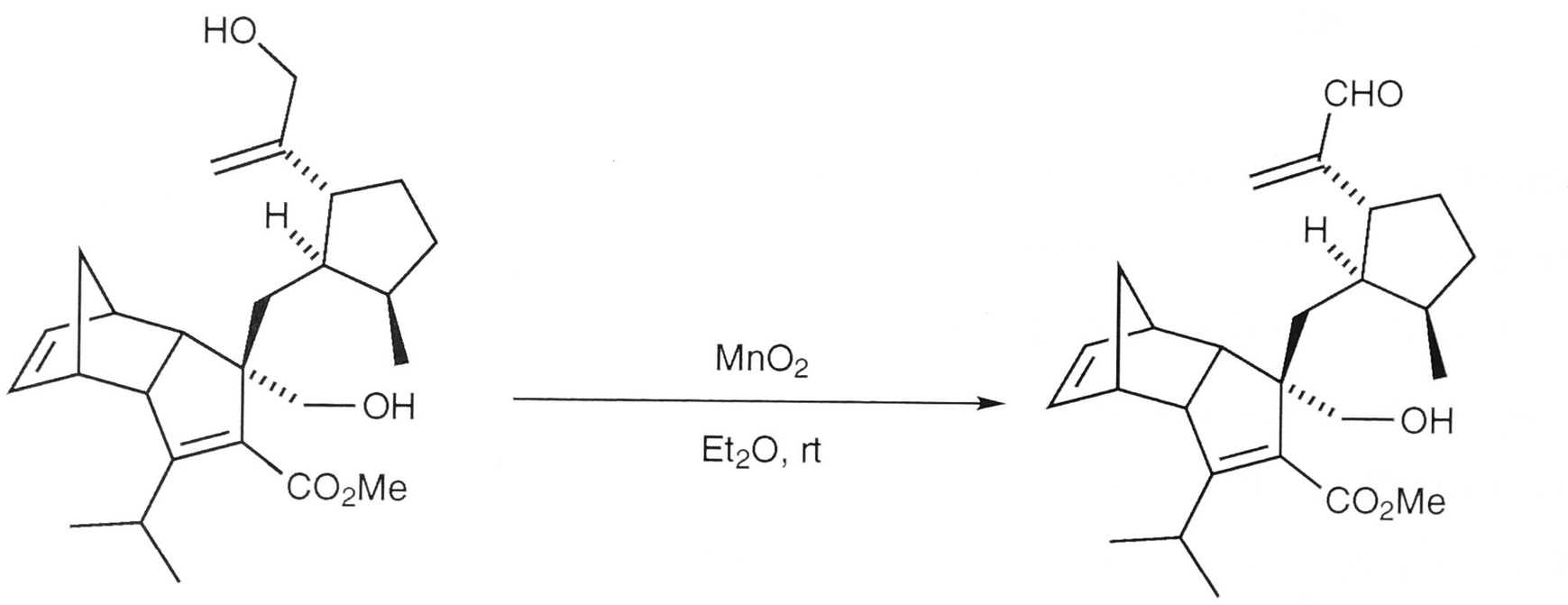
^{13}C NMR: 16.2 (Me), 21.6 (Me), 21.8 (Me), 28.0 (C or CH$_2$), 28.9 (CH), 33.6, 35.7 (2 × CH$_2$ or CH$_2$ + C), 36.5 (CH), 42.4 (CH), 45.3 (CH), 47.8 (CH), 48.5 (2 × CH), 51.4 (CH), 52.5

(CH_2), 52.8 (Me), 54.6 (CH_2), 64.0 (CH_2), 66.9 (CH_2), 109.4 ($=CH_2$), 132.0 (C, C2), 134.1, 134.3 (2 × =CH), 151.9 (=C), 165.0 (C, C3), 168.1 (CO_2Me).

MS: *m/z* 382 ([M-MeOH]$^{+\cdot}$, 17%), 357 (13), 287 (26), 244 (83), 215 (42), 197 (48), 121 (50), 109 (75), 91 (100), 66 (75).

HRMS: calcd for ([M-MeOH]$^{+\cdot}$ $C_{25}H_{34}O_3$ 382.2508, found 382.2505.

(1*S*,3a*R*,4*S*,7*R*,7a*S*,1′*R*,2′*R*,5′*R*)-Methyl-1-[2′-(1′′-formyl-vinyl)-5′-methyl-cyclopentylmethyl]-1-hydroxymethyl-3-isopropyl-3a,4,7,7a-tetrahydro-1*H*-4,7-methano-indene-2-carboxylate (64)



182 **64**

Manganese dioxide (600 mg) was added to a solution of diol **182** (120 mg, 29.0 mmol) in diethyl ether (3 mL) at room temperature. After 30 min the solution was filtered through a pad of celite and the solvent removed *in vacuo* to afford pure **64** (120 mg, 100%).

R$_f$ 0.50 (2:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –133.8° (*c* 0.50 $CHCl_3$)

IR υ_{max} 3467, 2957, 1694, 1601, 1466, 1434, 1345, 1233, 1122, 1016 cm^{-1}.

^{1}**H NMR:** 0.90 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.04 (d, 3 H, *J* = 7.0 Hz, CH*Me*$_2$), 1.13 (d, 3 H, *J* = 7.0 Hz, CH*Me*$_2$′), 1.23 (d, 1 H, *J* = 7.2 Hz, H8), 1.40-1.52 (m, 4 H), 1.73 (dd, 1 H, *J* = 14.4, 8.4 Hz), 1.80-1.98 (m, 3 H), 2.24 (m, 1 H), 2.37 (dd, 1 H, *J* = 8.5, 3.8 Hz, H7a), 2.58 (m, 1 H), 2.91, 3.06 (br s, 2 × 1 H, H4 + H7), 3.20 (sep, 1 H, *J* = 7.0 Hz, C*H*Me$_2$), 3.28 (br s, 1 H, OH), 3.36 (dd, 1 H, *J* = 8.4, 4.4 Hz, H3a), 3.49 (br d, 1 H, C*H*$_2$OH), 3.64 (s, 3 H, OMe), 3.70 (d, 1 H, *J* = 11.3 Hz, C*H*$_2$OH′), 5.71 (dd, 1 H, *J* = 5.7, 2.9 Hz, H5 or H6), 5.88, 6.12 (br s, 2 × 1 H, =CH$_2$), 6.00 (dd, 1 H, *J* = 5.6, 2.9 Hz, H6 or H5), 9.43 (s, 1 H, CHO).

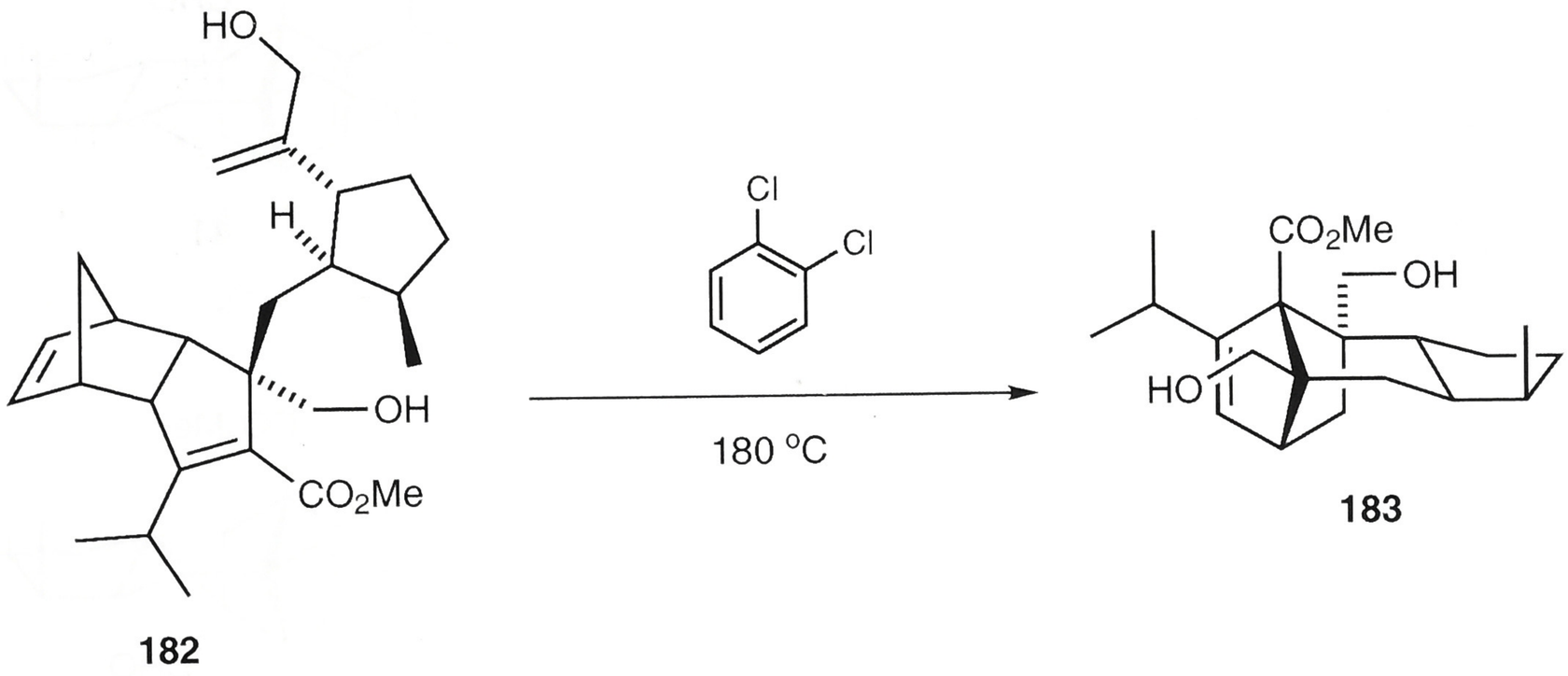
^{13}C NMR: 15.8 (Me), 21.5 (Me), 21.8 (Me), 28.7 (CH_2), 28.9 (CH), 29.7, 33.6, 35.9 (2 × CH_2 + C), 37.1 (CH), 43.4 (CH), 43.5 (CH), 45.1 (CH), 47.9 (CH), 48.4 (CH), 51.2 (CH), 52.5 (CH_2), 52.6 (OMe), 54.4 (CH_2), 66.6 (CH_2), 132.1 (=CH_2), 134.1 (2 × =CH), 153.5 (C, =*C*CHO), 165.6 (C, C3), 167.8 (*C*O_2Me), 194.3 (CHO).

MS: *m/z* 412 ($M^{+\cdot}$, <1%), 380 (5), 346 (9), 328 (45), 284 (100), 256 (30), 180 (35), 147 (55), 119 (50), 91 (52), 66 (56).

HRMS: calcd for $C_{26}H_{36}O_4$ 412.2614, found 412.2615.

9.3.4 Chapter Six – Total Synthesis of Sordaricin

Methyl 17,19-Dihydroxysodaric-1-en-18-oate (183)



A solution of diol **182** (15 mg, 36 μmol) in 1,2-dichlorobenzene (1.0 mL) was heated at 180 °C under a stream of nitrogen gas from a cylinder for 3 h. After cooling to room temperature the mixture was subjected to flash chromatography on a column of silica gel using 100% hexanes then 30%, increasing to 50% ethyl acetate in hexanes as the eluant, to afford diol **183** (8 mg, 64%) as a white solid.

R_f 0.30 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –70.4 ° (*c* 0.27 $CHCl_3$)

IR υ_{max} 3400, 2953, 1718, 1697, 1435, 1295, 1270, 1028 cm^{-1}.

^{1}H NMR: 0.21 (d, 1 H, *J* = 12.5 Hz, H4α), 0.76 (d, 3 H, *J* = 6.7 Hz, H20), 0.87, 1.12 (d, 2 × 3 H, *J* = 6.6 Hz, H15 + H16), 1.20 (obscured m, 3 H), 1.60-2.10 (m, 9 H), 2.47 (sep, 1 H, *J* = 6.6 Hz, H14), 2.55 (t, 1 H, *J* = 4.3 Hz, H3), 3.24, 3.37 (AB d, 2 × 1 H, *J* = 12.2 Hz, H17), 3.67, 3.72 (AB d, 2 × 1 H, H19), 3.78 (s, 3 H, OMe), 5.95 (d, 1 H, *J* = 2.2 Hz, H2).

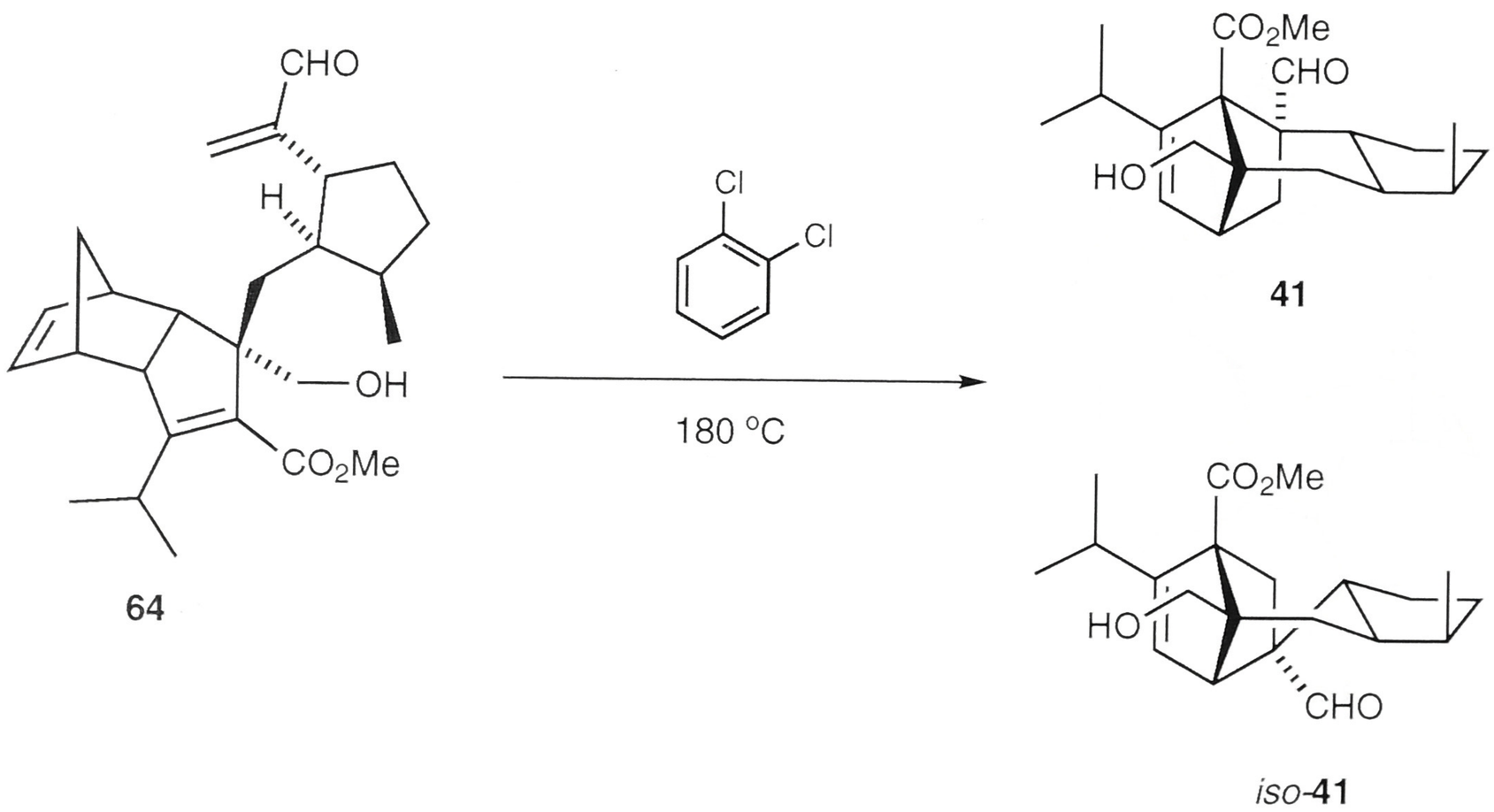
^{13}C NMR: 17.5 (Me, C20), 20.9, 22.4 (2 × Me, C15 + C16), 26.2 (CH_2, C11), 27.7 (CH, C14), 28.9 (CH_2, C12), 31.8 (CH, C10), 31.9, 32.2 (2× CH_2, C4 + C8), 41.5, 42.5, 45.0 (3 × CH, C3, C9 + C13), 50.4 (C, C5), 52.2 (OMe), 67.1, 67.2, 68.4, 71.4 (2 × C + 2 × CH_2, C6, C7, C17 + C19), 128.7 (CH, C2), 149.0 (C, C1), 176.7 (C, C18).

MS: *m/z* 348 ($M^{+\cdot}$, 5%), 330 (70), 317 (46), 299 (59), 285 (100), 257 (40), 225 (26), 197 (32), 147 (70), 119 (78), 105 (70), 91 (86), 81 (75).

HRMS: calcd for $C_{21}H_{32}O_4$ 348.2301, found 348.2298.

Methyl 19-Hydroxy-17-oxo-sordaric-1-en-18-oate (41)

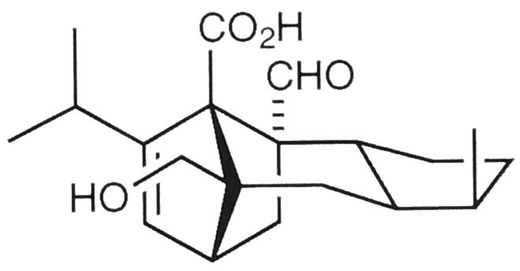
iso-Methyl 19-Hydroxy-17-oxo-sordaric-1-en-18-oate (*iso*-41)



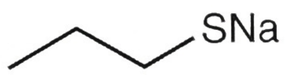
A solution of aldehyde **64** (30 mg, 73 μmol) in dichlorobenzene (1.0 mL) was heated at 180 °C under a stream of nitrogen gas from a cylinder for 1 h. After cooling to room temperature the mixture was subjected to flash chromatography on a column of silica gel using 100% hexanes then 15% ethyl acetate in hexanes as the eluant, to afford an inseparable 4:1 mixture of **41** and *iso*-**41** (19 mg, 76%) as a white solid. The mixture was then used in the next reaction.

Sordaricin (3)

iso-Sordaricin (*iso*-3)

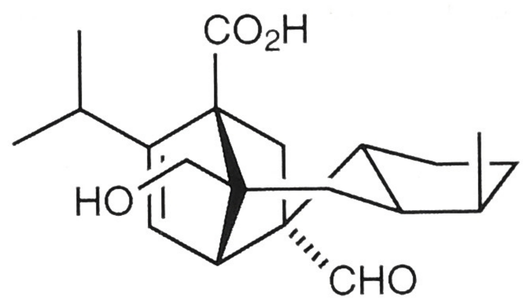


3



41/*iso*-**41**

HMPA, rt



iso-**3**

Freshly distilled propanethiol (700 μL, 7.72 mmol) was added to a stirred suspension of hexane washed NaH (240 mg, 10 mmol) in HMPA (5.0 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 2 h, then allowed to stand for 1 h to give a 1.35 M solution of propanethiolate. To a dried flask containing a 1:1 mixture of **41** and *iso***41** (70 mg, 0.2 mmol) and a stirrer bar, was added a solution propanethiolate/HMPA (1.35 M, 2.5 mL, 3.4 mmol) and the solution stirred under a nitrogen atmosphere for 48 h. The reaction mixture was diluted with ethyl acetate (15 mL) and washed twice with water (50 mL). The combined aqueous extracts were extracted twice with ethyl acetate (15 mL), then the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by flash chromatography on a column of silica gel using 20% ethyl acetate in hexanes, then 60% ethyl acetate in hexane as the eluant afforded a mixture of sordaricin (**3**) and *iso*-sordaricin (*iso*-**3**, 50 mg combined). The mixture was dissolved in HPLC grade acetonitrile (3 mL) and 50:50:0.05 water:acetonitrile:acetic acid (5 drops) and subjected to semi preparative HPLC separation using a mixture of 55% acetonitrile (containing 0.005% acetic acid) and 45% water (containing 0.005% acetic acid), at a flow rate of 5.0 mL/min on a Waters 510 HPLC pump. The column used was an Alltima C18 5 μm, 300 × 10 mm. The compounds were detected at 210 nm using a Waters Lambda-Max Model 481 LC spectrophotometer. Concentration of the fractions containing the first eluting compound afforded *iso*-sordaricin (*iso*-**3**, 17 mg, 25% from mixture of esters). Concentration of the fractions containing the second eluting compound afforded sordaricin (**3**, 25 mg, 38%).

iso-Sordaricin (*iso*-3)

$\mathbf{R}_f$ 0.15 (1:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –35.7 ° (*c* 0.23 $CHCl_3$)

IR υ_{max} 3413, 2956, 1703, 1649, 1465, 1255, 1096, 1017, 800 cm^{-1}.

^{1}H NMR: d_5-pyridine: 0.73 (d, 3 H, *J* = 7.0 Hz, H20), 1.07, 1.09 (2 × d, 2 × 3 H, *J* = 6.7 Hz, H15 + H16), 1.11 (obscured m, 2 H), 1.40 (m, 1 H), 1.55 (m, 1 H), 1.75-2.08 (m, 6 H), 2.39 (d, 1 H, *J* = 12.7 Hz), 2.49 (d, 1 H, *J* = 12.7 Hz, *exo*-H5), 2.84 (d, 1 H, *J* = 12.7 Hz, *endo*-H5), 2.95 (m, 1 H, H14), 3.50 (d, 1 H, *J* = 3.2 Hz, H3), 4.26, 4.41 (2 × AB d, 2 × 1 H, *J* = 10.5 Hz, H19,19´), 5.68 (br s, 1 H, H2), 6.85 (variable br s, 1 H, CO_2H), 9.80 (s, 1 H, H17).

^{13}C NMR: d_5-pyridine: 17.7 (Me, C20), 20.9, 22.1 (2 × Me, C15 + C16), 26.2 (CH_2), 28.4 (CH, C14), 28.6 (CH_2), 29.8 (CH, C10), 34.3 (CH_2), 37.8 (C, C6), 46.3 (CH), 46.4 (CH2, C5), 46.8 (CH), 49.6 (CH), 58.3 (C, C4), 65.3 (CH_2, C19), 69.5 (C, C7), 121.3 (CH, C2), 158.4 (C, C1), 175.8 (C, C18), 203.9 (CH, C17).

MS: *m/z* 332 ($M^{+\cdot}$, 7%), 314 (25), 302 (72), 284 (100), 274 (44), 256 (40), 241 (34), 227 (25), 166 (51), 147 (62), 133 (37), 105 (50), 91 (66).

HRMS: calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.1985.

Sordaricin (3)

R_f 0.15 (1:1, petroleum spirits:ethyl acetate, 1 drop acetic acid)

m.p. 189-191 °C (diethyl ether, DCM and hexanes), lit.[3] 190-191 °C

$[\alpha]^{20}_D$ synthetic:–55.3 ° (*c* 0.19 MeOH), natural: -58.4 ° (*c* 0.19 MeOH), lit.[3] –64° (*c* 0.374 MeOH),

IR υ_{max} 3350, 2954, 2868, 1712, 1446, 1378, 1289, 1234, 1017 cm^{-1}.

^{1}H NMR: d_5-pyridine: 0.80 (d, 3 H, *J* = 6.6 Hz, H20), 1.08 (m, 6 H, H15 + H16), 1.48 (d, 1 H, *J* = 12.5 H, H4α), 1.74 (m, 1 H), 1.95 (m, 5 H), 2.20-2.50 (m, 3 H), 2.72 (sep, 1 H, *J* = 6.7 Hz, H14), 2.97 (t, 1 H, *J* = 3.8 Hz, H3), 4.20, 4.37 (AB d, 2 × 1 H, *J* = 10.5 Hz, CH_2OH), 6.13 (d, 1 H, *J* = 3.1 Hz, H2), 8.85 (variable br s, 1 H, CO_2H), 10.24 (s, 1 H, CHO).

^{13}C NMR: d_5-pyridine: 17.7 (Me, C20), 21.3, 22.7 (2 × Me, C15 + C16), 26.9 (CH_2, C11), 28.2 (CH, C14), 29.1, 29.7 (2 × CH_2, C8 + C12), 31.6 (CH, C10), 32.4 (CH_2, C4), 41.9, 42.0, 47.1 (3

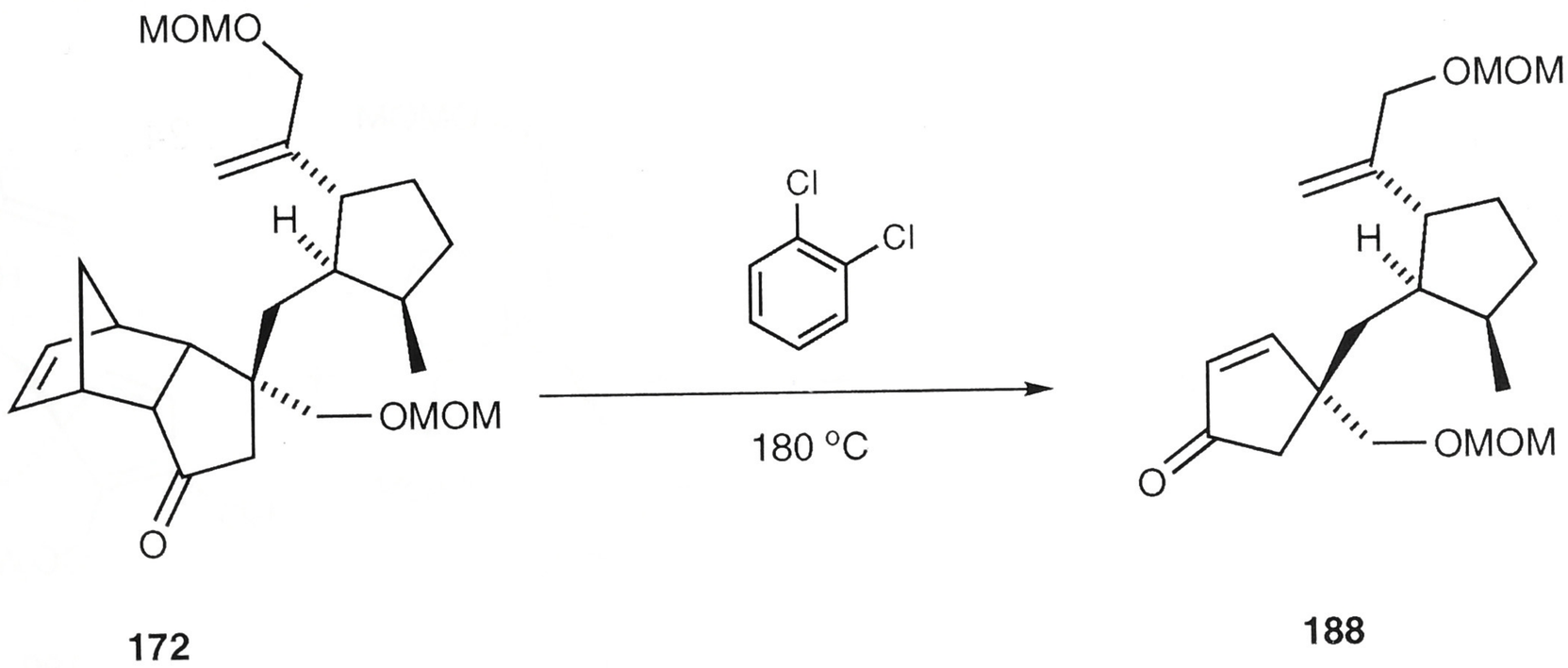
× CH, C3, C9 + C13), 59.4 (C, C5), 66.9, 67.5 (2 × C, C6 + C7), 73.8 (CH_2, C19), 130.9 (CH, C2), 148.9 (C, C1), 176.0 (C, C18), 204.8 (CH, C17).

MS: *m/z* 332 ($M^{+\cdot}$, 24%), 314 (33), 302 (40), 284 (90), 256 (37), 241 (40), 227 (35), 166 (64), 147 (67), 119 (64), 105 (72), 91 (100).

HRMS: calcd for $C_{20}H_{28}O_4$ 332.1988, found 332.1986.

Elemental analysis: calcd. for $C_{20}H_{28}O_4$: C, 72.3; H, 8.5. Found: C, 70.9; H, 8.7. Calcd. for $C_{20}H_{29}O_{4.5}$: C, 70.4; H, 8.6.

(4*S*,1′*R*,2′*R*,5′*R*)-4-Methoxymethoxymethyl-4-[2′-(1′′-methoxymethoxymethyl-vinyl)-5′-methyl-cyclopentylmethyl]-cyclopent-2-enone (188)



172 **188**

A solution of ketone **172** (300 mg, 0.72 mmol) in 1,2-dichlorobenzene (3.0 mL) was heated at 180 °C under a stream of nitrogen gas from a cylinder for 24 h. After cooling to room temperature the mixture was subjected to flash chromatography on a column of silica gel using 40% ethyl acetate in hexanes as the eluant, to afford enone **188** (243 mg, 96%) as an oil.

$\mathbf{R}_f$ 0.30 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –31.3 ° (*c* 0.75 $CHCl_3$)

IR υ_{max} 2949, 1715, 1675, 1587, 1465, 1442, 1379, 1213, 1150, 1109, 1044 cm^{-1}.

^{1}H NMR: 0.80 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.25-2.10 (m, 8 H), 2.23 (m, 1 H), 2.24 (s, 2 H, H5), 3.30 (s, 3 H, OMe), 3.34 (s, 3 H, OMe), 3.45 (AB d, 2 H, *J* = 9.2 Hz, CH_2OMOM), 3.94 (s, 2 H, =CCH_2OMOM), 4.55, 4.60 (s, 2 × 2 H, 2 × OCH_2OMe), 4.89, 5.08 (s, 2 × 1 H, =CH_2), 6.11 (d, 1 H, *J* = 5.7 Hz, H2), 7.50 (d, 1 H, *J* = 5.7 Hz, H3).

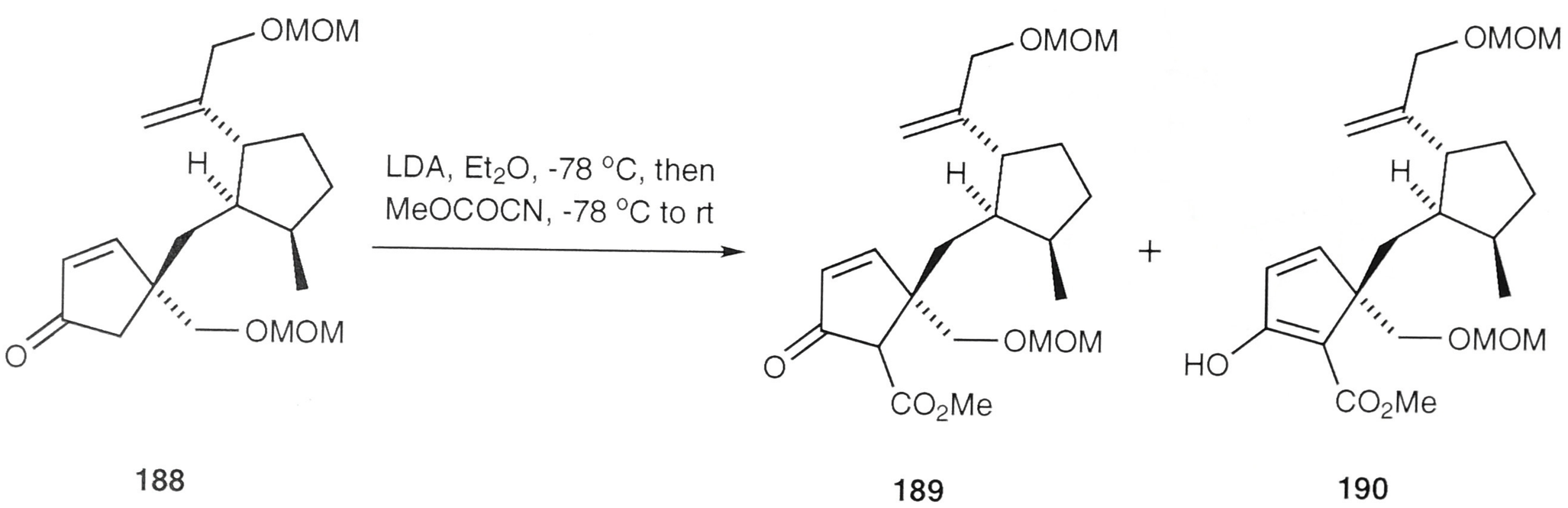
^{13}C NMR: 15.6 (Me), 28.8 (CH_2), 32.9 (CH_2), 33.0 (CH_2), 35.2 (CH), 42.9 (C), 43.3 (CH_2), 47.6 (CH), 49.7 (CH_2), 55.4 (2 × OMe), 68.9 (CH_2), 73.7 (CH_2), 95.7 (CH_2), 96.5 (CH_2), 112.1(=CH_2), 134.0 (CH, C2), 147.5 (=C), 169.0 (CH, C3), 209.0 (CO).

MS: *m/z* 352 ($M^{+\cdot}$, 1%), 291 (10), 277 (65), 217 (50), 159 (45), 122 (78), 107 (98), 95 (100), 67 (45).

HRMS: calcd for $C_{20}H_{32}O_5$ 352.2250, found 352.2247.

(2*S*,1′*R*,2′*R*,5′*R*)-Methyl-2-methoxymethoxymethyl-2-[2′-(1′′-methoxymethoxymethyl-vinyl)-5′-methyl-cyclopentylmethyl]-5-oxo-cyclopent-3-enecarboxylate (189, keto tautomer)

(5*S*,1′*R*,2′*R*,5′*R*)-Methyl-2-hydroxy-5-methoxymethoxymethyl-5-[2′-(1′′-methoxymethoxymethyl-vinyl)-5′-methyl-cyclopentylmethyl]-cyclopenta-1,3-dienecarboxylate (190, enol tautomer)

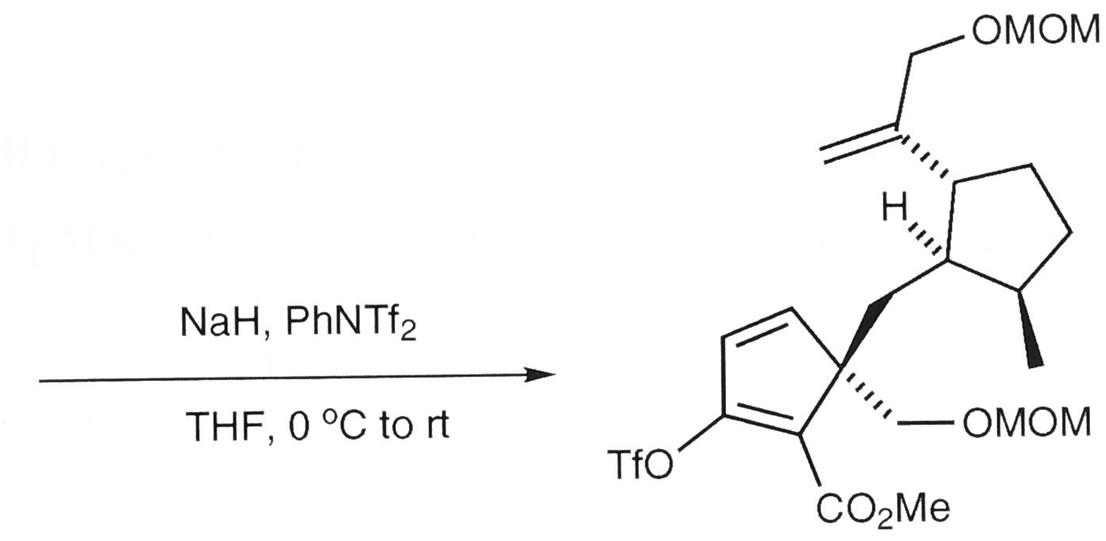


188 **189** **190**

LDA/diethyl ether (1.0 M, 2.76 mL, 27.6 mmol) was added to a stirred solution of enone **188** (243 mg, 6.9 mmol) in diethyl ether (7.0 mL) at –78 °C under a nitrogen atmosphere. After 2 h methyl cyanoformate (438 μL, 27.6 mmol) was added, the mixture allowed to warm to room temperature and stir for 1 h. The reaction mixture was quenched with water (2 mL), and after further dilution with water (20 mL) extracted three times with diethyl ether (15 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). Concentration *in vacuo*, followed by flash chromatography on a column of silica gel using 20%, increasing to 40% ethyl acetate in hexanes as the eluant, afforded an inseparable mixture of **189** and **190** (280 mg, 97%) as a pale yellow oil.

^{1}H NMR: 3.69, 3.73 (s, 3 H, 2× CO_2Me), 6.19 (d, 1 H, J = 5.7 Hz, **189**), 6.28 (d, 1 H, J = 5.7 Hz, **190**), 6.86 (d, 1 H, J = 5.7 Hz, **190**), 7.53 (d, 1 H, J = 5.7 Hz, **189**).

(5*S*,1´*R*,2´*R*,5´*R*)-Methyl-5-methoxymethoxymethyl-5-[2´-(1´´-methoxymethoxymethyl-vinyl)-5´-methyl-cyclopentylmethyl]-2-trifluoromethanesulfonyloxy-cyclopenta-1,3-dienecarboxylate (191)



NaH (60% w/w in oil, 137 mg, 3.4 mmol) and *N*-phenyltrifluoromethanesulfonimide (488 mg, 1.36 mmol) were carefully added to a stirred solution of **189/190** (280 mg, 0.68 mmol) in THF (7.0 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, after which time water (5 mL) was carefully added at 0 °C. The resulting mixture was further diluted with water (80 mL) and extracted twice with ethyl acetate (100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 5%, increasing to 10% ethyl acetate in hexanes as the eluant, to afford **191** (230 mg, 62 %) as a colourless oil.

R_f 0.60 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –62.6 ° (*c* 0.74 $CHCl_3$)

IR υ_{max} 2953, 1713, 1615, 1535, 1431, 1375, 1213, 1143, 1108, 1044 cm^{-1}.

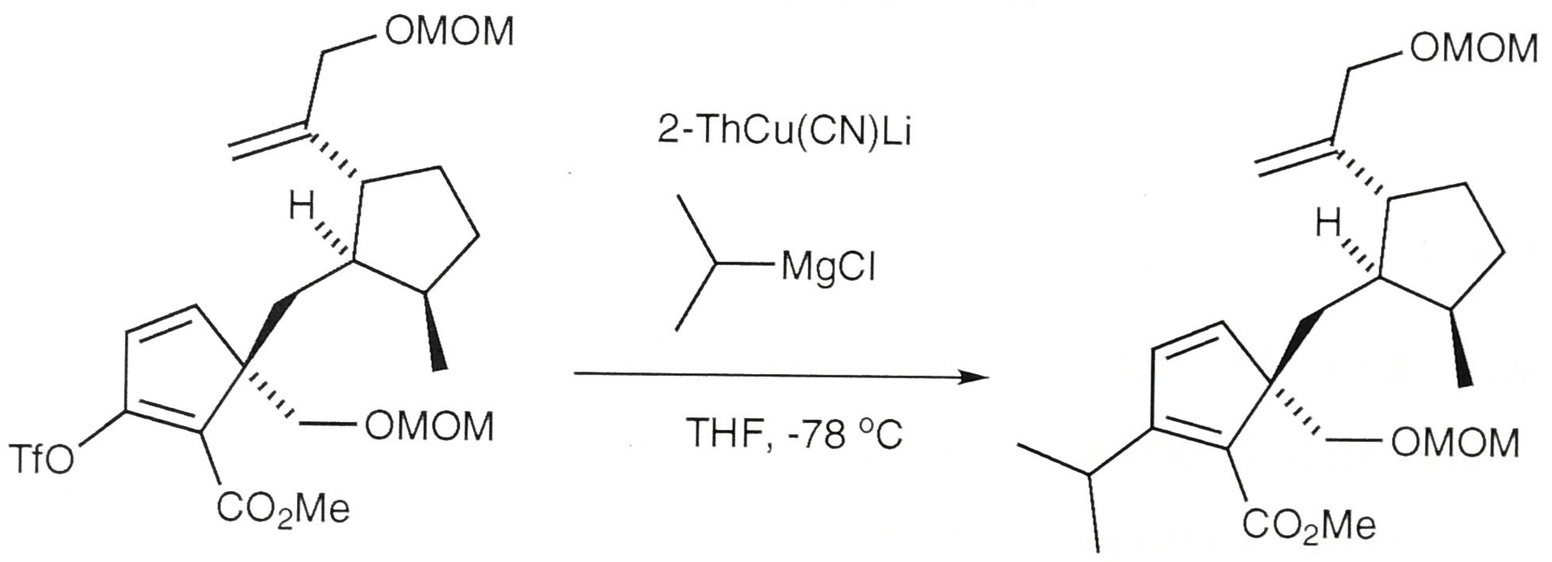
^{1}H NMR: 0.75 (d, 3 H, CH*Me*), 1.20-1.40 (m, 3 H), 1.60-2.20 (m, 6 H), 3.26 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 3.51 (d, 1 H, C*H*$_2$OMOM), 3.76 (s, 3 H, CO_2Me), 3.87 (AB d, 2 H, *J* = 13.2 Hz, =CC*H*$_2$OMOM), 4.00 (d, 1 H, *J* = 8.9 Hz, C*H*$_2$OMOM´), 4.50, 4.60 (s, 2 × 2 H, 2 × OC*H*$_2$OMe), 4.78, 5.02 (br s, 2 × 1 H, =CH_2), 6.32 (d, 1 H, *J* = 5.7 Hz, H3), 6.96 (d, 1 H, *J* = 5.7 Hz, H4).

^{13}C NMR: 14.7 (Me), 28.9, 29.4, 32.7 (2 × CH_2 + C), 35.8 (CH), 43.4 (CH), 47.1 (OMe), 51.4 (OMe), 55.2 (OMe), 60.8 (CH_2), 68.9 (CH_2), 71.6 (CH_2), 95.6 (CH_2), 96.6 (CH_2), 110.7 (=CH_2), 118.4 (q, *J* = 319.9 Hz, CF_3), 125.8 (C, C1), 129.4 (CH, C3), 147.6 (=C), 151.6 (C, C4), 153.7 (C, C2), 160.9 (*C*O_2Me).

MS: *m/z* 542 ($M^{+\cdot}$, <1%), 448 (10), 435 (32), 333 (85), 301 (100), 271 (70), 241 (86), 213 (88), 121 (55), 93 (62), 67 (41).

HRMS: calcd for $C_{26}H_{33}O_9F_3S$ 542.1797, found 542.1792.

(5*S*,1´*R*,2´*R*,5´*R*)-Methyl-2-isopropyl-5-methoxymethoxymethyl-5-[2´-(1´´-methoxymethoxymethyl-vinyl)-5´-methyl-cyclopentylmethyl]-cyclopenta-1,3-dienecarboxylate (192)



191 **192**

n-BuLi/hexanes (1.6 M, 398 μL, 0.63 mmol) was added to a stirred solution of thiophene (76 μL, 0.63 mmol) in THF (1.0 mL) at 0 °C under a nitrogen atmosphere. After 20 min the resulting solution was transferred *via* a cannula to a stirred suspension of CuCN (57 mg, 0.63 mmol) in THF (2.0 mL) at –78 °C. The mixture was allowed to slowly warm to –40 °C and stirred for a further 30 min after which time the solution was cooled to –78 °C. Isopropylmagnesium chloride/THF (2.0 M, 318 μL, 0.63 mmol) was added, followed by the addition a solution of triflate **191** (230 mg, 0.42 mmol) in THF (3.0 mL). After 1 h aqueous ammonium chloride solution (2.0 mL) was added and the mixture allowed to warm to room temperature. The mixture was diluted with water (20 mL) and 10% aqueous ammonia solution (10mL), then extracted three times with diethyl ether (25 mL). The combined organic extracts were washed with 1.0 M HCl (50 mL), brine (50 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by flash chromatography on a column of silica gel using 10% ethyl acetate in hexanes as the eluant, afforded **192** (170 mg, 93%) as an oil.

R_f 0.70 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –88.2 ° (*c* 0.68 $CHCl_3$)

IR υ_{max} 2950, 1698, 1647, 1603, 1530, 1465, 1435, 1377, 1238, 1150, 1106, 1046 cm^{-1}.

^{1}H NMR: 0.71 (d, 3 H, *J* = 7.0 Hz, CH*Me*), 1.07 (d, 3 H, CH*Me*$_2$), 1.08 (d, 3 H, *J* = 6.9 Hz, CH*Me*$_2$´), 1.10-1.35 (m, 6 H), 1.56 (m, 1 H), 1.70-2.16 (m, 5 H), 3.24 (s, 3 H, OMe), 3.30

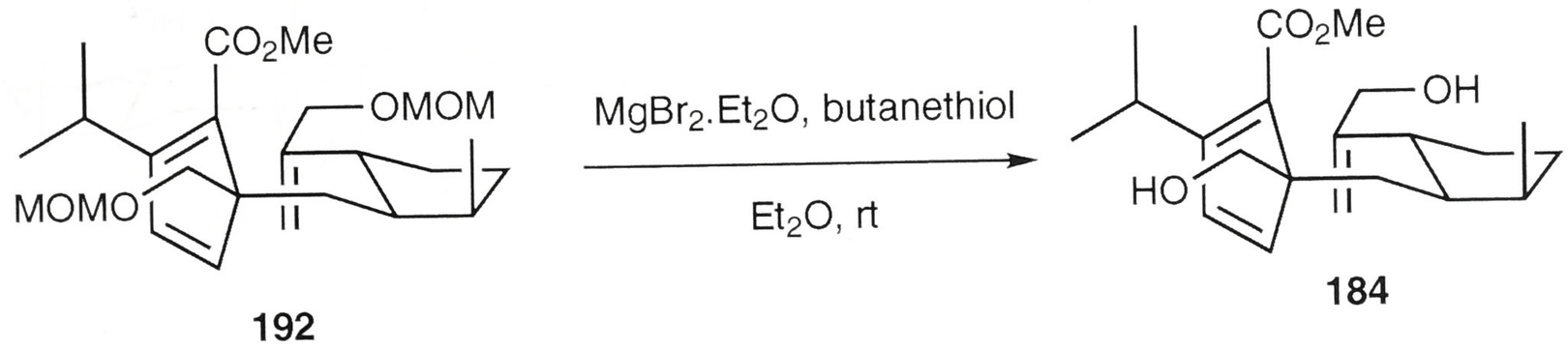
(obscured d, 1 H, CH_2OMOM), 3.31 (s, 3 H, OMe), 3.65 (s, 3 H, CO_2Me), 3.70-3.80 (m, 2 H), 3.83 (d, 1 H, J = 7.6 Hz, =CCH_2OMOM), 3.98 (d, 1 H, J = 8.9 Hz, =CCH_2OMOM´), 4.49 (AB d, 2 H, J = 7.0 Hz, OCH_2OMe), 4.56 (AB d, 2 H, J = 6.6 Hz, OCH_2OMe´), 4.73, 4.98 (br s, 2 × 1 H, =CH_2), 6.42 (d, 1 H, J = 5.4 Hz, H3), 6.75 (d, 1 H, J = 5.4 Hz, H4).

^{13}C NMR: 14.7 (Me), 21.5 (Me), 21.8 (Me), 27.2 (CH), 28.8, 29.2, 32.7 (2 × CH_2 + C), 35.6 (CH), 43.5 (CH), 47.2 (CH), 50.4 (OMe), 55.0 (OMe), 55.1 (OMe), 62.5 (CH_2), 68.7 (CH_2), 73.1 (CH_2), 95.5 (CH_2), 96.5 (CH_2), 110.1 (=CH_2), 129.3 (CH, C3), 129.8 (C, C1), 147.8 (=C), 149.9 (CH, C4), 164.3 (C, C2), 167.2 (CO_2Me).

MS: *m/z* 436 ($M^{+\cdot}$, 5%), 404 915), 374 (26), 342 (73), 329 (83), 297 (99), 269 (78), 253 (55), 179 (54), 147 (94), 133 (86), 119 (100), 91 (87).

HRMS: calcd for $C_{25}H_{40}O_6$ 436.2825, found 436.2826.

(5*S*,1´*R*,2´*R*,5´*R*)-Methyl-5-hydroxymethyl-5-[2´-(1´´-methoxymethoxymethyl-vinyl)-5´-methyl-cyclopentylmethyl]-2-isopropyl-cyclopenta-1,3-dienecarboxylate (184)



192 **184**

A solution of bisMOM ether **192** (160 mg, 0.37 mmol), $MgBr_2.Et_2O$ (948 mg, 3.7 mmol) and 1-butanethiol (472 μL, 4.4 mmol) in diethyl ether (10 mL) was stirred at room temperature for 24 h. A further portion of reagents was added and the mixture stirred a further 24 h. The resulting solution was then diluted with 1.0 M HCl (50 mL) and extracted three times with ethyl acetate (50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography on a column of silica gel using 20%, increasing to 70% ethyl acetate in hexanes as the eluant, to afford **184** (110 mg, 86%) as a colourless oil.

R_f 0.10 (2:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –143.3 ° (*c* 0.81 $CHCl_3$)

IR υ_{max} 3400, 2952, 1674, 1601, 1527, 1464, 1436, 1377, 1325, 1244, 1192, 1055 cm^{-1}.

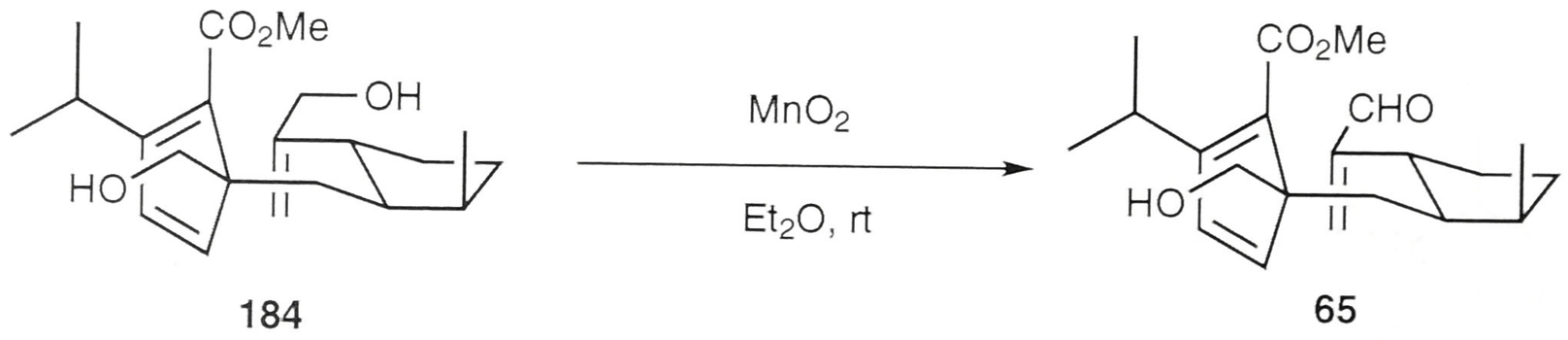
^{1}H NMR: 0.76 (d, 3 H, J = 7.0 Hz, CH*Me*), 1.09 (d, 3 H, J = 6.7 Hz, CH*Me*$_2$), 1.13 (d, 3 H, J = 6.7 Hz, CH*Me*$_2$´), 1.10-1.36 (m, 3 H), 1.56-1.86 (m, 4 H), 2.02-2.18 (m, 2 H), 2.71 (br s, 2 H, 2 × OH), 3.63 (obscured m, 1 H, C*H*Me$_2$), 3.67 (AB d, 2 H, J = 10.4 Hz, C*H*$_2$OH), 3.74 (s, 3 H, OMe), 3.92 (AB d, 2 H, J = 14.4 Hz, =CC*H*$_2$OH), 4.73, 5.02 (br s, 2 × 1 H, =CH$_2$), 6.47 (d, 1 H, J = 5.4 Hz, H3), 6.59 (d, 1 H, J = 5.4 Hz, H4).

^{13}C NMR: 15.2 (Me), 21.8 (Me), 21.9 (Me), 27.6 (CH), 28.4, 28.6, 23.9 (2 × CH$_2$ + C), 35.9 (CH), 43.7 (CH), 47.5 (CH), 51.3 (OMe), 64.0 (CH$_2$), 64.6 (CH$_2$), 67.4 (CH$_2$), 108.8 (=CH$_2$), 130.3 (CH, C3), 131.1 (C, C1), 149.3 (CH, C4), 151.5 (=C), 166.4 (C, C2), 167.0 (*C*O$_2$Me).

MS: *m/z* 348 (M$^{+\cdot}$, 5%), 330 (40), 300 (42), 285 (57), 241 (45), 225 (37), 178 (47), 133 (70), 119 (100), 105 (94), 91 (91).

HRMS: calcd for $C_{21}H_{32}O_4$ 348.2301, found 348.2301.

(5*S*,1´*R*,2´*R*,5´*R*)-Methyl-5-[2´-(1´´-formyl-vinyl)-5´-methyl-cyclopentylmethyl]-5-hydroxymethyl-2-isopropyl-cyclopenta-1,3-dienecarboxylate (65)



184 65

Manganese dioxide (250 mg) was added to a solution of diol **184** (50 mg, 0.15 mmol) in diethyl ether (2 mL) at room temperature. After 30 min the solution was filtered through a pad of celite and the solvent removed *in vacuo* to afford pure **65** (50 mg, 100%).

R$_f$ 0.30 (3:1, petroleum spirits:ethyl acetate)

$[\alpha]^{20}_D$ –180.0° (*c* 0.38 $CHCl_3$)

IR υ_{max} 3435, 2954, 1639, 1527, 1464, 1435, 1377, 1324, 1241, 1191, 1096 cm^{-1}.

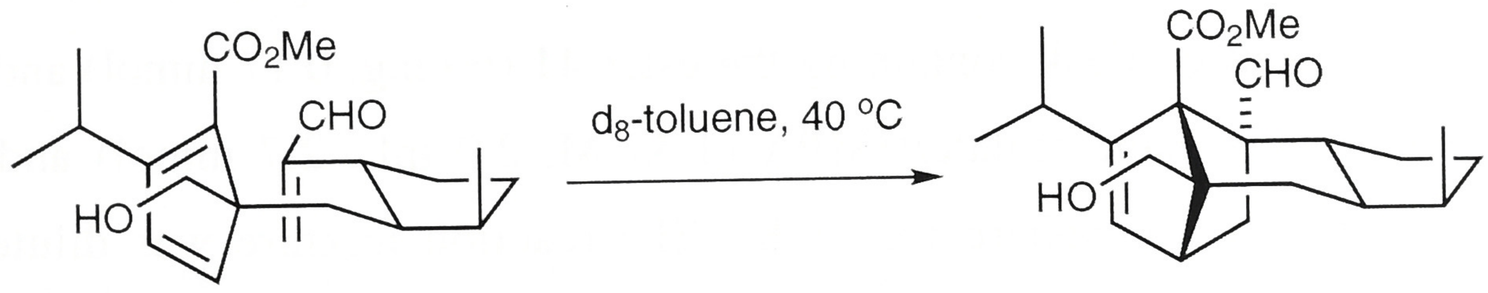
^{1}H NMR: 0.80 (d, 3 H, J = 6.9 Hz, CH*Me*), 1.11 (d, 3 H, J = 6.7 Hz, CH*Me*$_2$), 1.15 (d, 3 H, J = 6.7 Hz, CH*Me*$_2$´), 1.20-1.42 (m, 3 H), 1.64-2.00 (m, 5 H), 2.55 (m, 1 H), 3.54 (d, 1 H, J = 10.4 Hz, C*H*$_2$OH), 3.65 (obscured m, 1 H, C*H*Me$_2$), 3.74 (s, 3 H, OMe), 3.75 (obscured d, 1 H, C*H*$_2$OH´), 5.91 (s, 1 H, =CH$_2$), 6.09 (s, 1 H, =CH$_2$´), 6.49 (d, 1 H, J = 5.4 Hz, H3), 6.58 (d, 1 H, J = 5.4 Hz, H4), 9.48 (s, 1 H, CHO).

^{13}C NMR: 14.7 (Me), 21.7 (Me), 21.9 (Me), 27.6 (CH), 28.7, 29.3, 32.9 (2 × CH_2 + C), 36.1 (CH), 41.9 (CH), 44.1 (CH), 51.1 (OMe), 62.5 (CH_2), 67.3 (CH_2), 130.3 (CH, C3), 131.1 (=CH_2), 133.4 (C, C1), 149.2 (CH, C4), 153.3 (=C), 166.0 (CO_2Me), 166.8 (C, C2), 194.4 (CHO).

MS: *m/z* 346 ($M^{+\cdot}$, 13%), 328 (38), 316 (40), 284 (100), 269 (36), 256 (44), 241 (34), 180 (57), 147 (83), 133 (57), 119 (79), 105 (65), 91 (72).

HRMS: calcd for $C_{21}H_{30}O_4$ 346.2144, found 346.2147.

Methyl 19-Hydroxy-17-oxo-sordaric-1-en-18-oate (41)



65 **41**

A solution of aldehyde **65** (60 mg, 0.17 mmol) in d_8-toluene (1.5 mL) was heated at 40 °C for 3 days after which time the solvent was removed, *in vacuo* to give pure ester **41** (60 mg, 100%).

R_f 0.35 (2:1, ethyl acetate:petroleum spirits)

$[\alpha]^{20}_D$ synthetic: -65.1 ° (*c* 0.38 $CHCl_3$), natural: -66.4 ° (*c* 0.38 $CHCl_3$)

IR υ_{max} 3434, 2955, 2869, 1721, 1435, 1382, 1291, 1268, 1066 cm^{-1}.

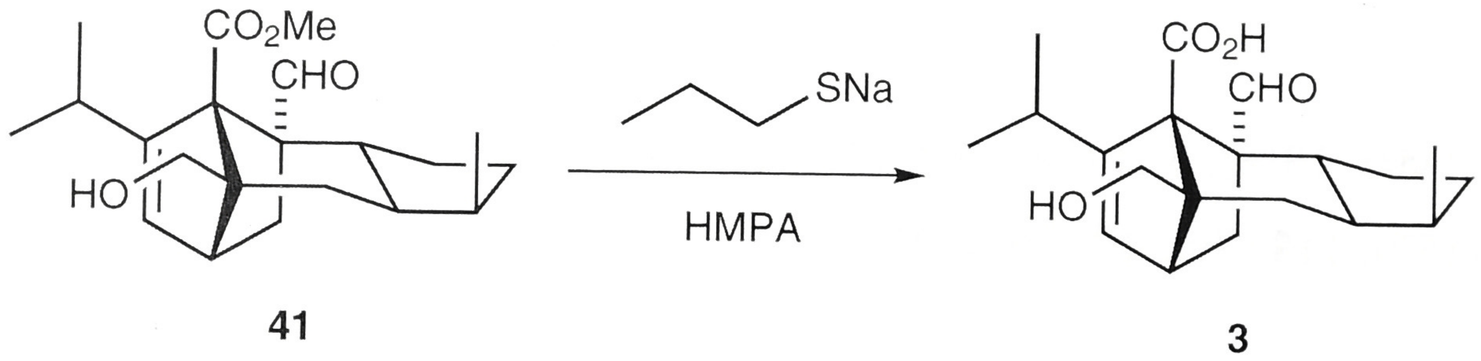
^{1}H NMR: 0.79 (d, 3 H, *J* = 7.2 Hz, H20), 0.89, 1.05 (d, 2 × 3 H, *J* = 6.9 Hz, H15 + H16), 1.24 (m, 3 H), 1.70-1.80 (m, 3 H), 1.90-2.12 (m, 5 H), 2.25 (sep d, 1 H, *J* = 6.9, 1.0 Hz, H14), 2.58 (t, 1 H, *J* = 4.1 Hz, H3), 3.53, 3.90 (AB d, 2 × 1 H, *J* = 11.3 Hz, CH_2OH), 3.80 (s, 3 H, OMe), 6.08 (dd, 1 H, *J* = 3.5, 1.3 Hz, H2), 9.64 (s, 1 H, CHO).

^{13}C NMR: 17.4 (Me, C20), 21.0, 22.1 (2 × Me, C15 + C16), 26.5 (CH_2, C11), 27.8 (CH, C14), 27.9, 30.0 (2 × CH_2, C8 + C12), 31.1 (CH, C10), 32.0 (CH_2, C4), 41.3, 41.4, 47.0 (3 × CH, C3, C9 + C13), 52.3 (C, C5), 66.8, 66.9 (2 × C, C6 + C7), 72.6 (CH_2, C19), 130.5 (CH, C2), 147.8 (C, C1), 173.6 (C, C18), 203.7 (CH, C17).

MS: *m/z* 346 ($M^{+\cdot}$, 34%), 328 (36), 315 (50), 284 (100), 269 (32), 255 (37), 239 (24), 180 (48), 147 (84), 133 (50), 119 (74), 105 (60), 91 (74).

HRMS: calcd for $C_{21}H_{30}O_4$ 346.2144, found 346.2144.

Sordaricin (3)

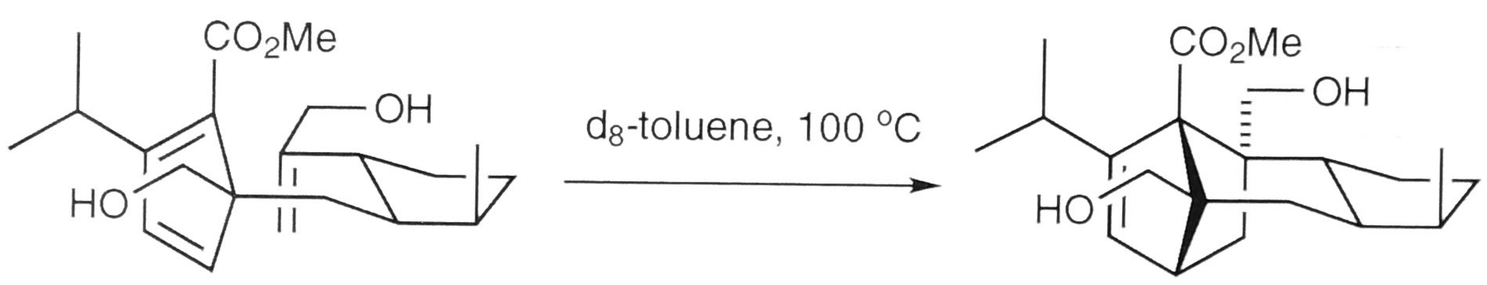


41 **3**

Freshly distilled propanethiol (700 μL, 7.72 mmol) was added to a stirred suspension of NaH (240 mg, 10 mmol) in HMPA (5.0 mL) at room temperature under a nitrogen atmosphere. The solution was stirred for 2 h, then allowed to stand for 1 h to give a 1.35 M solution of propanethiolate. To a dried flask containing the ester **41** (60 mg, 0.17 mmol) and a stirrer bar, was added a solution propanethiolate/HMPA (1.35 M, 2.0 mL, 2.7 mmol) and the solution stirred under a nitrogen atmosphere for 48 h. The reaction mixture was diluted with ethyl acetate (20 mL) and washed twice with water (30 mL). The combined aqueous extracts were extracted twice with ethyl acetate (20 mL), then the combined organic extracts were washed with brine (25 mL) and dried ($MgSO_4$). Concentration *in vacuo* followed by flash chromatography on a column of silica gel using 20% ethyl acetate in hexanes, then 60% ethyl acetate in hexane as the eluant afforded sordaricin (**3**) (45 mg, 79%) as a white solid that was identical in all respects to the sample of sordaricin (**3**) produced previously from **64** (see above).

9.3.5 Chapter Seven – Cycloadditions Related to Sordaricin

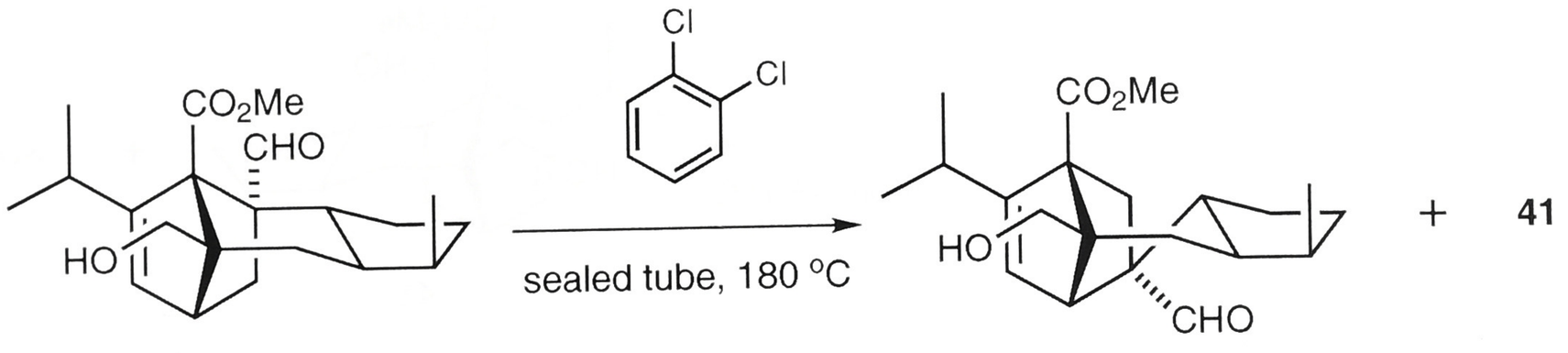
Methyl 17,19-Dihydroxysodaric-1-en-18-oate (183)



184 **183**

A solution of diol **184** (6 mg, 17 μmol) in d_8-toluene (1.5 mL) was heated at 100 °C for 3 days, during which time the reaction progress was monitored by ^1H NMR spectroscopy. The forming product was identical in all respects to the compound obtained by thermolysis of **182**, as described previously (see above).

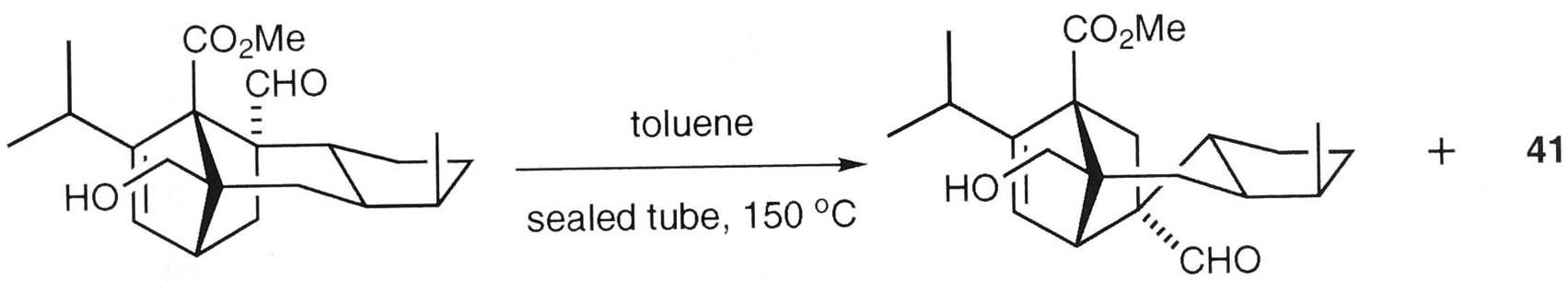
iso-Sordaricin methyl ester (*iso*-41) – Isomerisation experiments



41 *iso*-**41**

In a sealed tube, a degassed solution of ester **41** (15 mg, 43 μmol) in 1,2-dichlorobenzene (1.5 mL) was heated at 180 °C for 2.5 h. The solution was passed through a short column of silica gel using hexanes, then 35% ethyl acetate in hexanes as the eluant to afford an inseparable mixture of *iso*-**41** and **41** (6 mg, 40%). The ratio, *iso*-**41**:**41**, was determined to be 2:1 by ^{1}H NMR spectroscopy.

iso-Sordaricin methyl ester (*iso*-41) – The equilibrium position



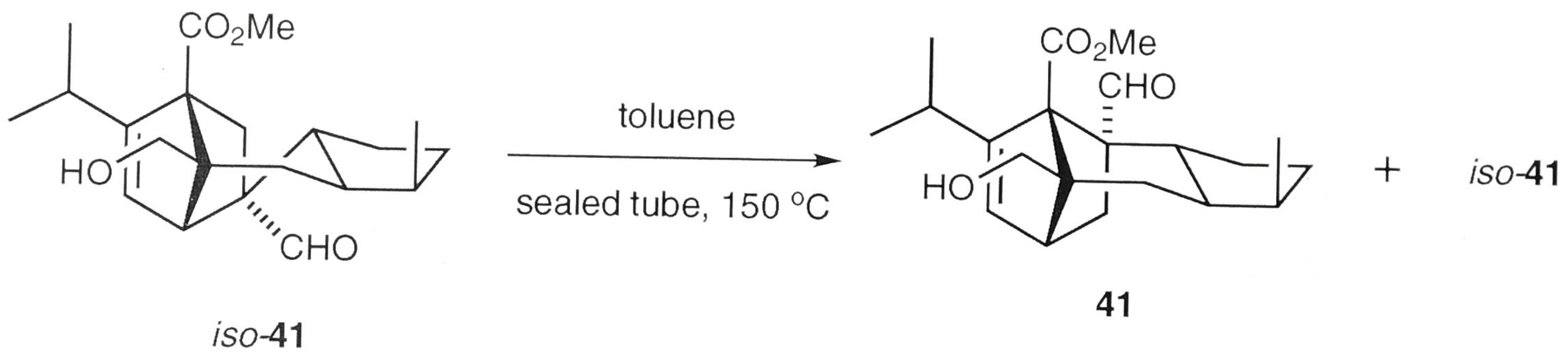
41 *iso*-**41**

In a sealed tube, a degassed solution of ester **41** (15 mg, 43 μmol) in toluene (1.5 mL) was heated at 150 °C. At intervals the reaction mixture was cooled and an aliquot removed in order to determine the isomer ratio by ^{1}H NMR spectroscopy. The data obtained are tabulated below:

Time (h)	% Conversion to *iso*-41
0	0
5	25
20	50
46	66
72	72

These data are represented in a graphical form in Figure 7.3.2 in Chapter Seven.

Sordaricin methyl ester (41) – The reverse case



In a sealed tube, a degassed solution of ester *iso*-**41** (6 mg, 17 μmol) in toluene (1.5 mL) was heated at 150 °C. After approximately 24 h, the reaction mixture was allowed to cool to room temperature and the solvent removed *in vacuo*. By ^{1}H NMR spectroscopy the ratio of *iso*-**41** to **41** was determined to be 4:1.

9.4 References

1. Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
2. Mander, L. N.; Robinson, R. P. *J. Org. Chem.* **1991**, *56*, 3595.
3. Vasella, A. T. Ph.D. Dissertation. Eidgenossischen Technischen Hochschule, Zurich, 1972.
4. *Nomenclature of Organic Chemistry*, Rigaudy, J., Klesney, S. P. (Eds.), Pergamon Press: Oxford, **1979**.
5. Obtained by reduction of the parent methyl ester, which was prepared by the method of Wolinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron* **1965**, *21*, 1247.