Synthetic Studies on Canangone and β-Chamigrene

von der Fakultät für Mathematik und Naturwissenschaften
der Carl von Ossietzky–Universität Oldenburg
zur Erlangung des Grades und Titels
eines Doktors der Naturwissenschaften
(Dr. rer. nat.)
angenommene Dissertation

von

Girish Kumar Koripelly

geboren am 10. Oktober 1976 in Adilabad/Indien

Oldenburg, Dezember 2007

This work was carried out from Oct 2004 to Feb 2006 at the Institut für Organische Chemie, Universität Stuttgart and from March 2006 to Nov 2007 at the Institut für Reine und Angewandte Chemie, Carl von Ossietzky–Universität Oldenburg under the guidance of *Prof. Dr. Jens Christoffers*.

Gutachter: Prof. Dr. Jens Christoffers
Zweitgutachter: Prof. Dr. Jürgen Martens

Tag der Disputation: 04. Februar 2008

My brother...

K. Rama Krishna Reddy

Acknowledgements

I would like to express sincere gratitude to my research advisor, *Prof. Dr. Jens Christoffers* for taking me into his team and giving me an interesting topic as well as guiding me with constant encouragement and patience throughout my Ph. D.

I would like to thank *Prof. Dr. Jürgen Martens* for reviewing my doctoral thesis and giving valuable comments and suggestions.

I am grateful to all the members of the analytical department at the Institutes of Organic Chemistry, Universities of Stuttgart and Oldenburg.

I wish to express my special thanks to *Mr. Wolfgang Saak*, *Mr. Detlev Hasse* for measuring the X-ray structures and *Dr. Thomas Glatzel* for assisting me in performing the preliminary biological studies.

My heartfelt thanks to all the past and current group members, *Dr. Thomas Werner*, *Dr. Burkard Kreidler*, *Dr. Heiko Scharl*, *Dr. Sven Unger*, *Dr. Thomas Kauf*, *Dr. Anna Rosiak*, *Michael Rössle*, *Ralf M. Müller*, *Yawei Zhang*, *Claas Lüder Diedrich*, *Rebekka Pflantz*, *Dr. Herbert Frey*, *Francesco Fabretti*, *Dr. Rajamalleswaramma "Mallu" Jogireddy, Alkit Beqiraj*, *Elisabeth Jaskulska*, *and Heiko Schramm* for providing a social and stimulating work environment in Stuttgart and Oldenburg.

I would like to thank especially *Jagan*, *Banala Srinivas*, *Bantu Bhasker*, *Mahendra Gulla*, *Marthala Ramana* and *Jatin Kumar Sinha* for their support during my stay in Stuttgart and Oldenburg.

Finally and most importantly, I would like to thank my parents, brother, sister and brother-in-law for their love, effection and constant support, without them nothing would have been possible.

Table of Contents

I	**Kurzzussammenfassung**	**1**
II	**English Summary**	**4**
1	**Introduction**	**7**
1.1	Stereoselective Synthesis	8
1.2	Quaternary Stereocenters	11
1.3	Michael and Conjugate Addition Reactions	12
1.4	Spirocycles	15
1.4.1	Alkylation	16
1.4.2	Rearrangement Reactions	17
1.4.3	Cycloaddition Reactions	18
1.4.4	Conversion of Bridged Systems into Spirocycles	19
1.5	Michael Reaction/Robinson Annulation	19
1.6	Chamigrenes	22
1.6.1	Isolation of Chamigrenes	22
1.6.2	Total Syntheses of β-Chamigrene	23
1.6.2.1	Total Synthesis of (±)-β-Chamigrene by Tanaka *et al*.	23
1.6.2.2	Total Synthesis of (±)-β-Chamigrene by Ireland *et al*.	24
1.6.2.3	Total Synthesis of (±)-β-Chamigrene by Martin *et al*.	25
1.6.2.4	Total Synthesis of (±)-β-Chamigrene by Adams *et al*.	26
1.6.2.5	Total Synthesis of (±)-β-Chamigrene by Srikrishna *et al*.	27
1.6.2.6	Attempted Synthesis of β-Chamigrene From Our Group	28
2	**Goal of this Work**	**30**
2.1	Retrosynthetic Analysis for Canangone **19**	30
2.2	Retrosynthetic Pathway for β-Chamigrene **18**	32
3	**Results and Discussion**	**35**
3.1	Canangone	35
3.1.1	Synthesis of Michael Acceptors	35
3.1.1.1	Synthesis of Protected Hydroxy Acetic Acid **82**	35

3.1.1.2 Synthesis of Weinreb Amide **81** 37
3.1.1.3 Synthesis of Vinyl Ketone **9** 39
3.1.2 Synthesis of Racemic Canangone **19** 41
3.1.2.1 Synthesis of Michael Product **79a** Using Lewis Acidic Conditions 41
3.1.2.2 Under Basic Conditions 42
3.1.2.3 Regioselective Spiroannulations Using Acidic Conditions 43
3.1.2.4 Using Buffered Conditions 45
3.1.2.5 Using Lewis Acidic or LDA Conditions 45
3.1.2.6 Spiroannulations Using Enaminolactone **78** 47
3.1.2.7 Synthesis of *rac*-Spirolactone **77b** Using Enaminolactone **78** 49
3.1.2.8 Attempted Synthesis of Spirolactone **77c** from Enaminolactone **78** 50
3.1.2.9 Synthesis of Spirolactone **77d** from Enaminolactone **78** 51
3.1.2.10 Luche Reduction of Spirolactone **62a** 52
3.1.2.11 Deprotection of the 3,4-Dimethoxy Benzyl Group of Spirolactone **62a** 54
3.1.2.12 Selective Reduction of Enone **75** Using Luche Reduction 55
3.1.2.13 Selective Oxidation of Diol (5*R**,6*S**)-**74** and (*R**,*R**)-**74** 56
3.1.3 Synthesis of Optically Active Canangone **19** 58
3.1.3.1 Synthesis of Optically Active Spirolactone **77b** 59
3.1.3.2 Synthesis of Optically Active Spirolactone **75** 60
3.1.3.3 Brosylation of Spirolactone **75** 61
3.1.3.4 Synthesis of Optically Active Diol **74** 63
3.1.3.5 TEMPO Oxidation of (5*R*,6S)-**74** and (*R*,*R*)-**74** 64
3.1.4 Optically Active Synthesis of (*S*,*S*)-Canangone 65
3.1.5 Brief Introduction of Screening on Biologically Active Compounds 68
3.1.5.1 Hatching the Shrimp and Bioassay 68
3.1.5.2 Sample Preparation and the Test for Biological Activity 69
3.2 Attempted Synthesis of Chamigrene 70
3.2.1 Synthesis of Cyclic β-Ketoester **12i** 70
3.2.2 Synthesis of Dibromide **83** 70
3.2.2.1 Synthesis of β-Methyl Glutaconic Acid **87** 70
3.2.2.2 Synthesis of Glutaconic Anhydride **86** 72
3.2.2.3 Synthesis of Diol **64** 72
3.2.3 Model Study for Alkylation Using Allyl Bromide **117** 74
3.2.3.1 Attempted Synthesis for an Exclusive *C*-Allylated Product **123** 77
3.2.4 Second Retrosynthetic Analysis for β-Chamigrene **18** 79
3.2.4.1 Synthesis of Acetyl Cyclohexene **130** 80

3.2.4.2 Synthesis of Alkylated Product **129** from Acetyl Cyclohexene **130** 81
3.2.4.3 Attempted Synthesis for the Spiroannulated Product **42a** 84

4 Summary and Conclusion 87

5 Experimental Section 93

5.1 General Information 93
5.1.1 Analytical Methods 93
5.1.2 Chromatography 94
5.1.3 Solvents and Chemicals 95
5.1.4 Working techniques 95
5.2 Experimental Procedures for Canangone **19** and Their Intermediates 96
5.2.1 Synthesis of DMB Protected Vinyl Ketone **9d** 96
5.2.1.1 (3,4-Dimethoxybenzyloxy)acetic acid **(82a)** 96
5.2.1.2 2-(3,4-Dimethoxybenzyloxy)-*N*-methoxy-*N*-methylacetamide **(81a)** 97
5.2.1.3 1-(3,4-Dimethoxybenzyloxy)-3-buten-2-one **(9d)** 98
5.2.1.4 3-(3,4-Dimethoxybenzyloxymethyl)penta-1,4-dien-3-ol **(97)** 100
5.2.1.5 1-(3,4-Dimethoxybenzyloxy)-4-(methoxymethylamino)-2-butanone **(96)** 101
5.2.2 Synthesis of PMB Protected Vinyl Ketone **9e** 102
5.2.2.1 (4-Methoxybenzyloxy)acetic acid[117] **(82b)** 102
5.2.2.2 *N*-Methoxy-2-(4-methoxybenzyloxy)-*N*-methylacetamide **(81b)** 103
5.2.2.3 1-(4-Methoxybenzyloxy)-3-buten-2-one **(9e)** 104
5.2.3 Synthesis of Trityl Protected Vinyl Ketone **9f** 106
5.2.3.1 Trityloxyacetic acid[119] **(82c)** 106
5.2.3.2 *N*-Methoxy-*N*-methyl-2-trityloxyacetamide **(81c)** 107
5.2.3.3 1-Trityloxy-3-buten-2-one **(9f)** 108
5.2.4 Synthesis of Michael Product **79a** 109
5.2.4.1 Procedure 1 for the Iron Catalyzed Michael reaction 109
5.2.4.2 2,3,7,8,12,13-Hexamethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononane [128] **(99)** 111
5.2.4.3 Procedure 2 for the Base Catalyzed Michael Product **(79a)** 112
5.2.5 Attempted Synthesis of Spirolactone **75** 112
5.2.5.1 7-Hydroxy-6-methyl-2-oxaspiro[4.5]-6-decene-1,8-dione **(100)** 112
5.2.5.2 Procedure for an Attempt of Aldol Cyclization with Lewis Acid 114
5.2.5.3 7-(3,4-Dimethoxybenzyloxy)-6-methyl-2-oxaspiro[4.5]-6-decene-1,8-dione **(104)** 114

5.2.5.4 7-(3,4-Dimethoxybenzyloxy)-6-hydroxy-6-methyl-2-oxa-spiro[4.5]decane-1,8-dione **(103)** 115
5.2.5.5 *rac*-Acetyl-3-(3-oxo-4-trityloxybutyl)-4,5-dihydro-2-furanone **(79b)** 117
5.2.5.6 Procedure for an Aldol Cyclization Under Acidic (H_2SO_4) Conditions 118
5.2.6 Synthesis of Spirolactone **77a** 118
5.2.6.1 *rac*-(*Z*)-3-[1-(1-Phenylethylamino)ethylidene]-4,5-dihydro-2-furanone[129] **(78)** 118
5.2.6.2 *rac*-8-Methyl-6-(1-phenylethylimino)-2-oxaspiro[4.5]-7-decen-1-one **(109a)** [129] 120
5.2.6.3 *rac*-8-Methyl-2-oxaspiro[4.5]-7-decene-1,6-dione[42] **(77a)** 120
5.2.7 Synthesis of Spirolactone **77b** 122
5.2.7.1 *rac*-8-(3,4-Dimethoxybenzyloxymethyl)-6-(1-phenylethylimino)-2-oxaspiro[4.5]-7-decen-1-one **(109b)** 122
5.2.7.2 *rac*-8-(3,4-Dimethoxybenzyloxymethyl)-2-oxaspiro[4.5]-7-decene-1,6-dione **(77b)** 123
5.2.8 Synthesis of Sprolactone **77c** 124
5.2.8.1 *rac*-6-(1-Phenylethylimino)-8-trityloxymethyl-2-oxa-spiro[4.5]-7-decen-1-one **(109c)** 124
5.2.9 Synthesis of Spirolactone **77d** 125
5.2.9.1 *rac*-8-(4-Methoxybenzyloxymethyl)-6-(1-phenylethylimino)-2-oxaspiro[4.5]-7-decen-1-one **(109d)** 125
5.2.9.2 *rac*-8-(4-Methoxybenzyloxymethyl)-2-oxaspiro[4.5]-7-decene-1,6-dione **(77d)** 125
5.2.10 Synthesis of Canangone **19** 127
5.2.10.1 *rac*-8-(Hydroxymethyl)-2-oxaspiro[4.5]-7-decene-1,6-dione **(75)** 127
5.2.10.2 *rac*-(1,6-Dioxo-2-oxaspiro[4.5]-7-decen-8-yl)methyl-4- bromobenzene sulfonate **(112)** 129
5.2.10.3 *rac*-8-(3,4-Dimethoxybenzyloxymethyl)-6-hydroxy-2-oxaspiro[4.5]-7-decen-1-one **(76)** 130
5.2.10.4 *rac*-6-Hydroxy-8-(hydroxymethyl)-2-oxaspiro[4.5]-7-decen-1-one **(74)** 133
5.2.10.5 (*R**,*S**)-6-Hydroxy-1-oxo-2-oxaspiro[4.5]-7-decene-8-carbaldehyde **(19)** 136
5.2.10.6 (*R**,*R**)-6-Hydroxy-1-oxo-2-oxaspiro[4.5]-7-decene-8-carbaldehyde **(19)** 137
5.3 Experimental Procedures for Attempted Synthesis of Chamigrene **18** 139
5.3.1 Synthesis of Dibromide **83** 139
5.3.1.1 Ethyl 2,4-Dimethyl-6-oxo-6*H*-pyran-3-carboxylate[142] **(113)** 139
5.3.1.2 2,4-Dimethyl-6-oxo-6*H*-pyran-3-carboxylic acid[142] **(114)** 140

5.3.1.3 (*E*)- and (*Z*)-3-Methyl-2-pentenedioic acid[142] **(87)** 141
5.3.1.4 Glutaconic Anhydride[144] **(86)** 142
5.3.1.5 (*Z*)-3-Methyl-2-pentene-1,5-diol[143] **(85)** 143
5.3.1.6 3-Methylpentane-1,5-diol **(116)** 144
5.3.1.7 (*Z*)-1,5-Dibromo-3-methyl-2-pentene[151] **(83)** 145
5.3.2 Synthesis of β-Ketomethylester **12i** 146
5.3.2.1 Methyl 7-methyl-3-oxo-6-octenoate [140] **(12j)** 146
5.3.2.2 Methyl 6,6-Dimethyl-2-oxocyclohexanecarboxylate[141] **(12i)** 148
5.3.3 Synthesis of 2-Allyl Cyclohexanone **120** 149
5.3.3.1 Methyl 2-Allyloxy-6,6-dimethyl-1-cyclohexenecarboxylate[147] **(118)** 149
5.3.3.2 Methyl 1-Allyl-6,6-dimethyl-2-oxocyclohexanecarboxylate[147] **(119)** 150
5.3.3.3 2-Allyl-3,3-dimethylcyclohexanone[147] **(120)** 151
5.3.4 Synthesis of Cyclohexene Derivative **139** 152
5.3.4.1 4-Acetyl-1-methylcyclohexene[149] **(130)** 152
5.3.4.2 1-Iodo-3-methyl-2-butene[150] **(136)** 154
5.3.4.3 5-Methyl-1-(4-methyl-3-cyclohexenyl)-4-hexen-1-one **(129)** 155
5.3.4.4 5-Methyl-2-(3-methyl-2-butenyl)-1-(4-methyl-3-cyclohexenyl)-4-hexen-1-one **(131)** 156
5.3.4.5 5-Hydroxy-5-methyl-1-(4-methyl-3-cyclohexenyl)hexan-1-one **(137)** 157
5.3.4.6 2,2-Dimethyl-6-(4-methyl-3-cyclohexenyl)-3,4-dihydro-2*H*-pyran **(140)** 159

6 Data for Crystal Strucure Analysis 160

6.1 Crystal Structure Data for (5*R**,6*S**)-**74** 160
6.2 Crystal Structure Data for (*R*)-**112** 161

7 Abbreviations 163

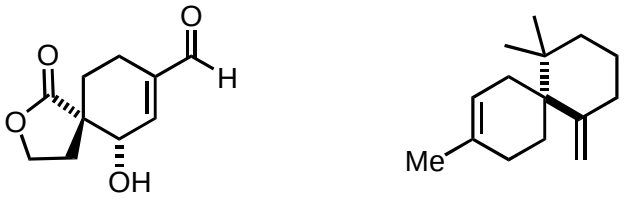
8 Bibliography 165

9 List of Synthesized Compounds 173

10 List of Publications 177

I Kurzzusammenfassung

Das Ziel dieser Arbeit war die Synthese zweier Verbindungen mit quartären Stereozentren, (+)-Canangon **19** und β-Chamigren **18** (Abbildung I). Canangon kann aus den Blättern der Pflanze *ylang-ylang* (*Cananga odorata*) aus der Familie der *annonaceae* gewonnen werden. Caloprisco *et al*. bestimmte dessen relative Konfiguration zu (*R**,*R**), wobei jedoch weiterhin die absolute Konfiguration unklar blieb. Daher diente die erste Totalsynthese von Canangon zusätzlich auch zur Klärung der absoluten Stereochemie der Verbindung. Das Terpen β-Chamigren ist ebenfalls ein Pflanzeninhaltsstoff, welcher aus den Blättern einiger Zypressenarten oder den Früchten der *Schizandra chinensis*-Liane isoliert werden kann.

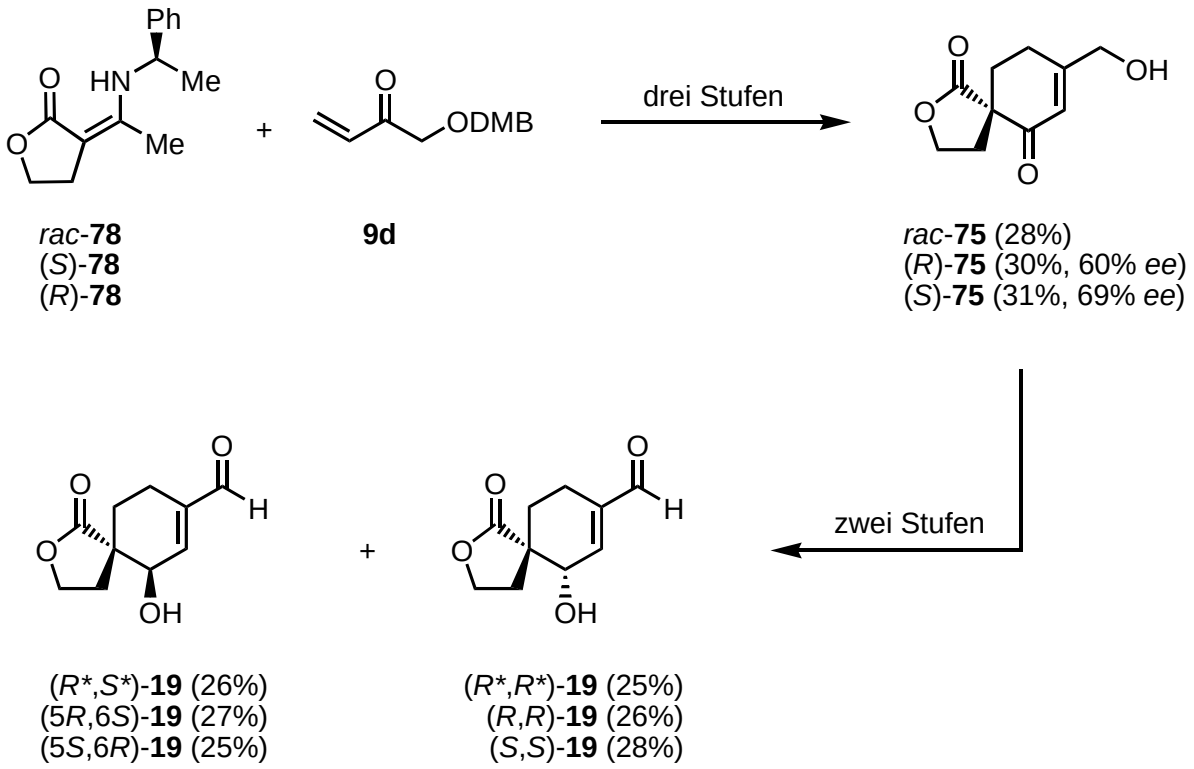


19 **18**

Abbildung I. (+)-Canangon **19** and β-Chamigren **18**.

Ausgehend von den beiden kommerziell günstig erhältlichen Verbindungen 3,4-Dimethoxybenzylalkohol **89a** und Bromessigsäure **90** wurde der Michaelakzeptor **9d** in drei Stufen *via* Williamsonsche Ethersynthese, Aminolyse und Grignardaddition dargestellt. Spirolacton **77b** wurde durch eine Robinson-Anellierung des Enaminlactons **78** mit Michaelakzeptor **9d** in einer Ausbeute von 40% über beide Stufen synthetisiert. Nach dem Entschützen mit TFA wurde Enon **75** zu den beiden diastereoisomeren Alkoholen (*R**,*R**)-**74** und (*5R**,*6S**)-**74** reduziert. Schließlich wurden diese selektiv mit O_2 zu (*R**,*R**)-Canangon **19** und (*5R**,*6S**)-*epi*-Canangon **19** oxidiert (Schema I). Die beiden optischen Antipoden (+)- und

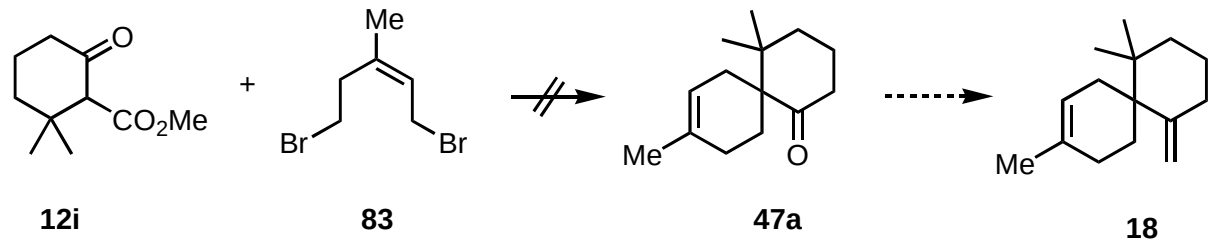
(−)-Canangon **19**, sowie deren Epimere wurden nach der gleichen Synthesestrategie erhalten.



Schema I. Synthese von Canangon **19**, sowohl racemisch als auch in optisch aktiver Form.

Um die biologische Aktivität zu evaluieren, wurden Versuchsreihen mit Salinenkrebslarven durchgeführt. Allerdings zeigten die untersuchten Verbindungen selbst bei hohen Konzentrationen keine signifikante Toxizität.

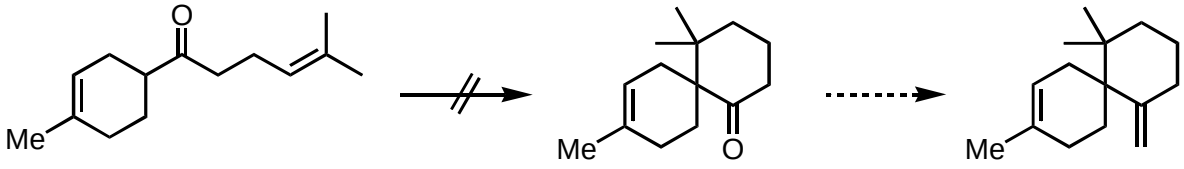
Um nun das zweite Syntheseziel, β-Chamigren **18**, zu erhalten, wurden zwei unterschiedliche Ansätze verfolgt. Zuerst sollte eine konvergente Synthese vom cyclischen β-Ketoester **12i** und von Dibromid **83** über die spirocyclische Vorstufe **47a** verlaufen (Schema II). Nach einigen erfolglosen Versuchen Verbindung **47a** darzustellen, wurde diese Strategie aufgegeben und eine Alternativroute beschritten.



12i **83** **47a** **18**

Schema II. Erster Syntheseversuch von β-Chamigren **18.**

Nach dieser sollte β-Chamigren **18** in nur vier Stufen zugänglich sein. Eine Lewis-Säure-katalysierte Diels-Alder-Reaktion von Methylvinylketon **9a** mit Isopren **45** ergab Cyclohexen **130**. Die Umsetzung mit Prenyliodid **136** führte daraufhin glatt zur monoalkylierten Verbindung **129**, welche sich allerdings nicht mehr weiter zur spirocyclischen Vorstufe **47a** cyclisieren ließ (Schema III).

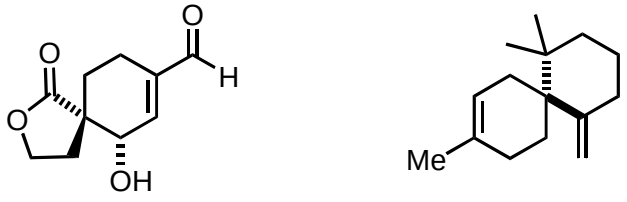


129 **47a** **18**

Schema III. Zweiter Syntheseversuch von β-Chamigren **18.**

II English Summary

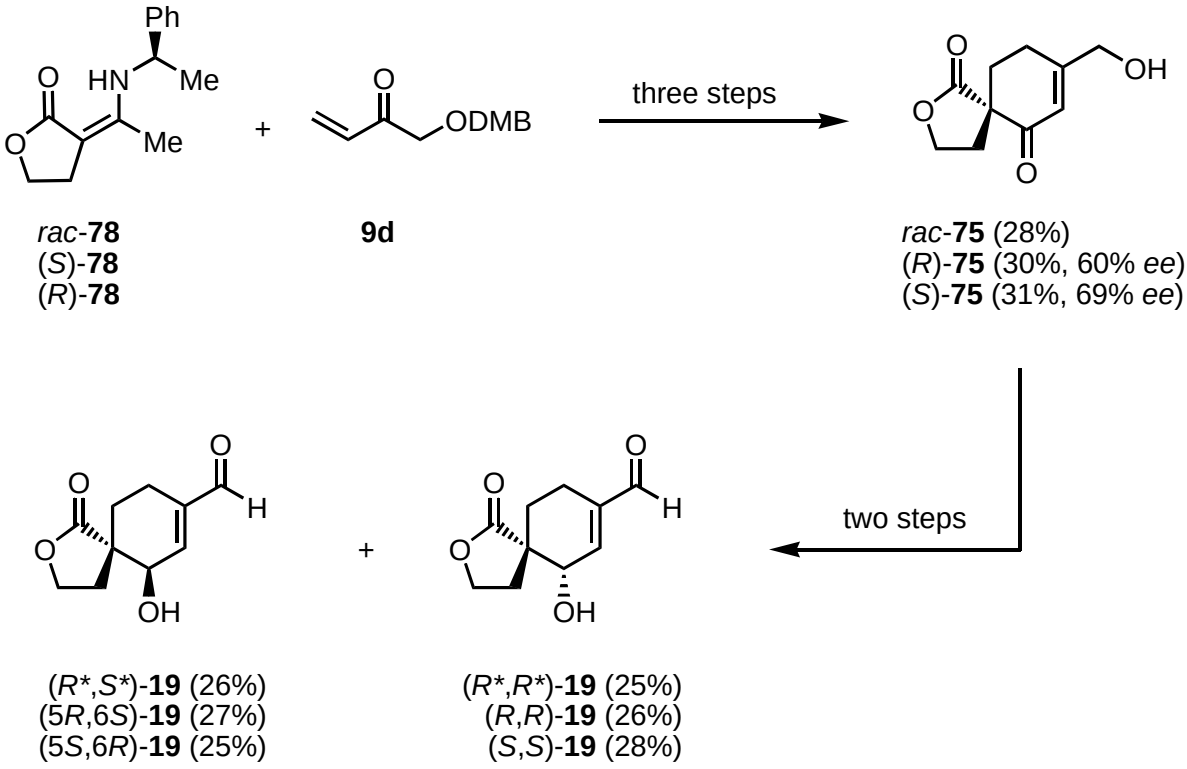
The objective of this work was to synthesize the quaternary stereocenter containing spirocycles, (+)-Canangone **19** and β-Chamigrene **18** (Figure II). Canangone was extracted from the leaves and branches of *ylang-ylang* (*Cananga odorata*), which belongs to the family of annonaceae. The relative configuration was elucidated to be (*R**,*R**) by Caloprisco and coworkers but the absolute configuration was so far unknown. The first synthesis of Canangone **19** and also its absolute stereochemistry was accomplished for the first time in this work.



19 **18**

Figure II. (+)-Canangone **19** and β-Chamigrene **18**.

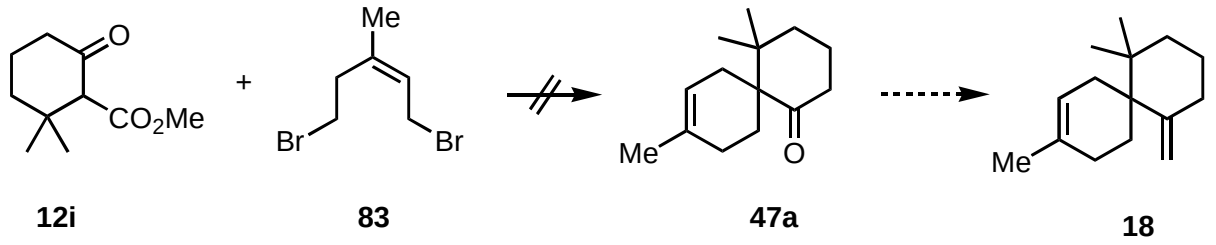
The synthesis was started with cheap and commercially available 3,4-dimethoxy benzyl alcohol **89a** and bromoacetic acid **90**. Michael acceptor **9d** was prepared in three steps over 64% yield using Williamson ether synthesis, aminolysis and Grignard reaction conditions. The Robinson annulation of enamino lactone **78** and Michael acceptor **9d** followed by hydrolysis provided the spirolactone **77b** in 40% yield over two steps. Subsequent deprotection of 3,4-dimethoxy benzyl group using TFA and Luche reduction of enone **75** furnished the diastereomeric alcohols (*R**,*R**)-**74** and (5*R**,6*S**)-**74**. The latter was further transformed to (*R**,*R**)-Canangone **19** and (5*R**,6*S**)-*epi*-Canangone **19** under selective oxidation conditions (Scheme IV). Following the same strategy, optically active (+)-Canangone and (–)-Canangone, and their epimers were synthesized.



Scheme IV. Synthesis of Canangone **19**, both in racemic as well as in optically active series.

After synthesizing the racemic as well as the optically active Canangone **19**, preliminary biological tests were carried out using brine shrimps in order to check the toxicity of the compounds. But unfortunately, the biological tests showed no significant toxicity even at higher concentrations. Nevertheless, the compounds isolated from *ylang-ylang* species can be useful in perfumery and aromatherapy.

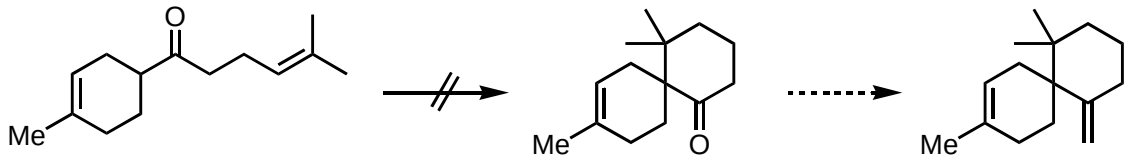
As a second target, the synthesis of β-Chamigrene **18** was attempted using a convergent synthesis from cyclic β-ketoester **12i** and dibromide **83** in order to obtain its potential precursor **47a** (Scheme V). But unfortunately, attempts to synthesize the β-Chamigrene precursor **47a** completely failed.



12i **83** **47a** **18**

Scheme V. First synthetic approach for the synthesis of β-Chamigrene **18**.

An alternative route was proposed, in which β-Chamigrene **18** could be synthesized in only four steps. The Lewis acid catalysed Diels-Alder reaction of methyl vinyl ketone **9a** and isoprene **45** using $Sc(OTf)_3$ gave acetyl cyclohexene **130**. The alkylation of the Diels-Alder product **130** using prenyl iodide **136** provided successfully the mono alkylated product **129**, but unfortunately, attempts to cyclize this product failed completely to give the desired spirocyclic compound **47a** (Scheme VI).



129 **47a** **18**

Scheme VI. Second synthetic approach for the synthesis of β-Chamigrene **18**.

1 Introduction

At the dawn of the twenty-first century, the state of the art and science of synthesis is as healthy and vigorous as ever. The birth of this exhilarating, multifaceted, and boundless science is marked by the Wöhlers' synthesis of urea in 1828. Organic synthesis is considered, to be a key technology which is essential for life science (e.g. drug discovery and drug production), high-tech materials, polymers, fertilizers, cosmetics, clothing, as well as for the development of nano devices.[1] The chemical synthesis of natural molecules without the aid of enzymes often presents formidable challenges to human ingenuity and skill. While chemical processes for the synthesis of oligonucleotides and peptides are now well developed and quite routine, nature's secondary metabolites, commonly known as natural products, are not always easy to construct in the laboratory.[2]
The syntheses of the nineteenth century were relatively simple and, with a few exceptions, were directed towards benzenoid compounds. The starting materials for these target molecules were benzenoid compounds, chosen for their resemblance to the targeted substance and the ease by which the synthetic chemist could connect them by simple functionalization chemistry. The twentieth century was destined to bring dramatic advances in the field of synthesis. The era began with impressive strides and with increasing molecular complexity and sophistication in strategy design. Some of the most notable examples of synthesis of this era were Robinson's one-step synthesis of tropinone[3] (1917) from succindialdehyde, methylamine, and acetone dicarboxylic ester and H. Fischer's synthesis of haemin[4] (1929). Both of them went on to win a Nobel Prize for Chemistry (Fischer, 1929; Robinson, 1947).

1.1 Stereoselective Synthesis

Stereoselective synthesis, also called enantioselective synthesis or diastereoselective synthesis, is the organic synthesis which introduces one or more new and desired elements of chirality. The demand for chiral compounds, often as single enantiomers, has escalated sharply in recent years, driven particularly by the demands of the pharmaceutical industry and also by other applications, including agrochemicals, flavors, fragrances and materials. Although the most obvious applications are bio-related, materials science also relies on the properties imparted by chirality, notably in chiral polymers and liquid crystals. This widespread demand for optically active compounds has stimulated intensive research to develop improved methods for synthesizing single enantiomers. This is particularly important in the field of pharmaceuticals, because the different enantiomers or diastereomers of a compound often have different biological activity. One such example is the chiral drug Thalidomide **1** (Figure 1), which was prescribed as an antiemetic to combat morning sickness and an aid to help the sleep for pregnant women.

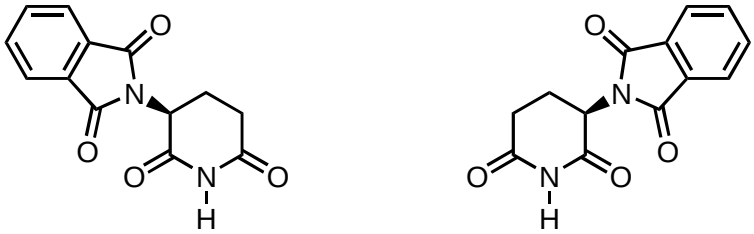
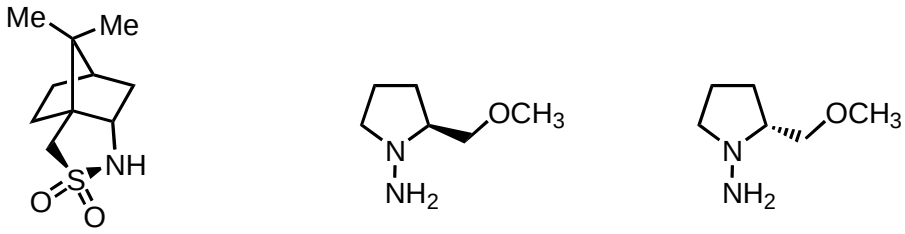


Figure 1. The two enantiomers (*S*)-**1** and (*R*)-**1** of Thalidomide having different biological effects.

However, it turned out that whereas the *S*-enantiomer had indeed this desired property, the other enantiomer was tetratogenic and caused deformities in the

children born from the women treated with the drug.[5,6] When one considers that the phrase "asymmetric synthesis" was just of mechanistic curiosity in 1965 with no one really believing that this could become an important part of molecular synthesis, the rate of progress has been remarkable. In just over 30 years the organic chemist has transformed this virtually unknown aspect of synthesis into a serious route to virtually every class of chiral organic compounds in greater than 90% enantiomeric purity.

Since the pioneering times of the mid-1970s, when the first practical and generally applicable methods in asymmetric synthesis[7] were developed, such as the sultam **2** method by Oppolzer[8] and the SAMP/RAMP **3** hydrazone method by Enders[9] (Figure 2), there has been a tremendous growth in this research field. One major driving force for this rapid development is of course the different biological activities of enantiomers and thus the need for enantiopure compounds.



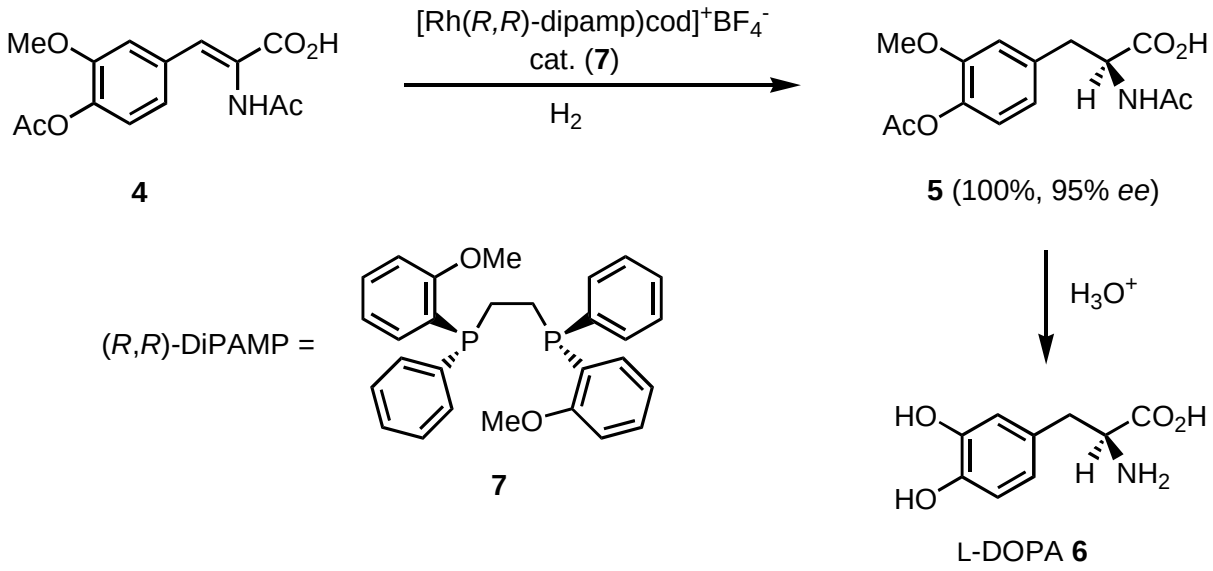
Sultam **2** SAMP (*S*)-**3** RAMP (*R*)-**3**

Figure 2. Chiral auxiliaries for asymmetric synthesis.

During the past few decades there has been intensive research into developing methods for synthesizing one of the enantiomers rather than the other. Among the significant achievements in this area are (i) asymmetric hydrogenation of dehydroamino acids, a ground-breaking work by William S. Knowles *et al.*[10] (ii) the Sharpless epoxidation by K. B. Sharpless *et al.*[11] and (iii) the second generation asymmetric hydrogenation process developed by R. Noyori *et al.*[12] deserve particular attention because of the tremendous impact that these processes have made in synthetic organic chemistry. In 2001, Nobel Prize in Chemistry has been awar-

ded to William S. Knowles, Ryoji Noyori and K. Barry Sharpless for developing chiral catalysts for hydrogenations and oxidations. The achievements of these three chemists are of great importance for academic research, for the development of new drugs and materials, and are being used in many industrial syntheses of pharmaceutical products and other biologically active substances.

The successful industrial example in the field of catalytic asymmetric synthesis is the Monsanto process for the commercial synthesis of L-DOPA **6** (Scheme 1), a rare amino acid which is effective in the treatment of Parkinson's disease.[13] Monsanto process, the first commercialized catalytic asymmetric synthesis employing a chiral transition metal complex, was introduced by W. S. Knowles and co-workers and has been in operation since 1974. This large scale process for the synthesis of L-DOPA **6** is based on a catalytic asymmetric hydrogenation. In the key step of this synthesis by Monsanto, enamide **4** is hydrogenated in the presence of a catalytic amount of [Rh(*R*,*R*)-dipamp)cod]$^+BF_4^-$ **7** affording protected amino acid **5** in quantitative yield and in 95% *ee*. A simple acid-catalyzed hydrolysis step completes the synthesis of L-DOPA **6**.



Scheme 1. The Monsanto synthesis of L-DOPA **6** using catalytic asymmetric hydrogenation.

1.2 Quaternary Stereocenters

Synthetic chemists nowadays can create almost every tertiary stereocenter with excellent levels of enantiocontrol and chemical yields. Various methodologies or series of tailor made ligands have been developed and are used commonly in organic synthesis. In contrast to tertiary stereocenters, the construction of quarternary stereocenters remains the milestone of every enantioselective procedure. However, catalytic enantioselective C–C bond formation of all-carbon quaternary stereocenters, i.e. carbon stereocenters bearing four different carbon substituents, still represents a tremendous challenge for synthetic organic chemists.[14-22] Moreover, when a carbon stereocenter is situated near a vicinal tertiary or quaternary stereocenters, the construction of these features become even more problematic. The difficulty for the construction of these motives arises often from steric hindrance and a limited amount of reliable reactions.

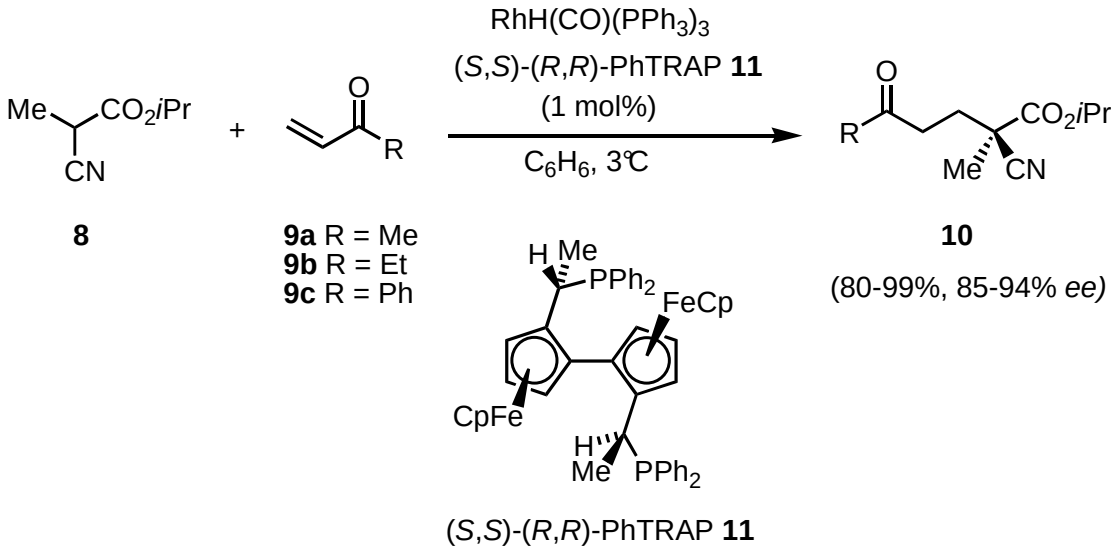
The development of efficient asymmetric methods for constructing C–C bonds have enjoyed considerable attention from the organic community in the past 30 years. The need to generate such C–C bonds has provoked the disclosure of several asymmetric methods.[14-22] In the beginning, most of the reported methods involved the use of chiral auxiliaries to induce enantioselectivity in the newly formed C–C bonds. Despite the stoichiometric use of chiral auxiliaries, this approach still boasts practical aspects. However, efficient enantioselective catalytic methods provide an access to optically active materials in large amounts using small quantities of chiral catalysts without the necessity of removing the chiral unit. As a result, research devoted towards the development of enantioselective catalytic methods is gaining in importance and major breakthroughs have recently been achieved.[23,24]

Frequently used quaternary C–C bond formation reactions are: cycloadditions like Diels-Alder reactions,[25] Pd-allylation reactions,[26,27] and Michael additions, also known as conjugate additions.[14] Asymmetric Michael reaction is the most

frequently used method for the construction of quaternary stereocenters with high selectivity, which have been developed by several groups.[14]

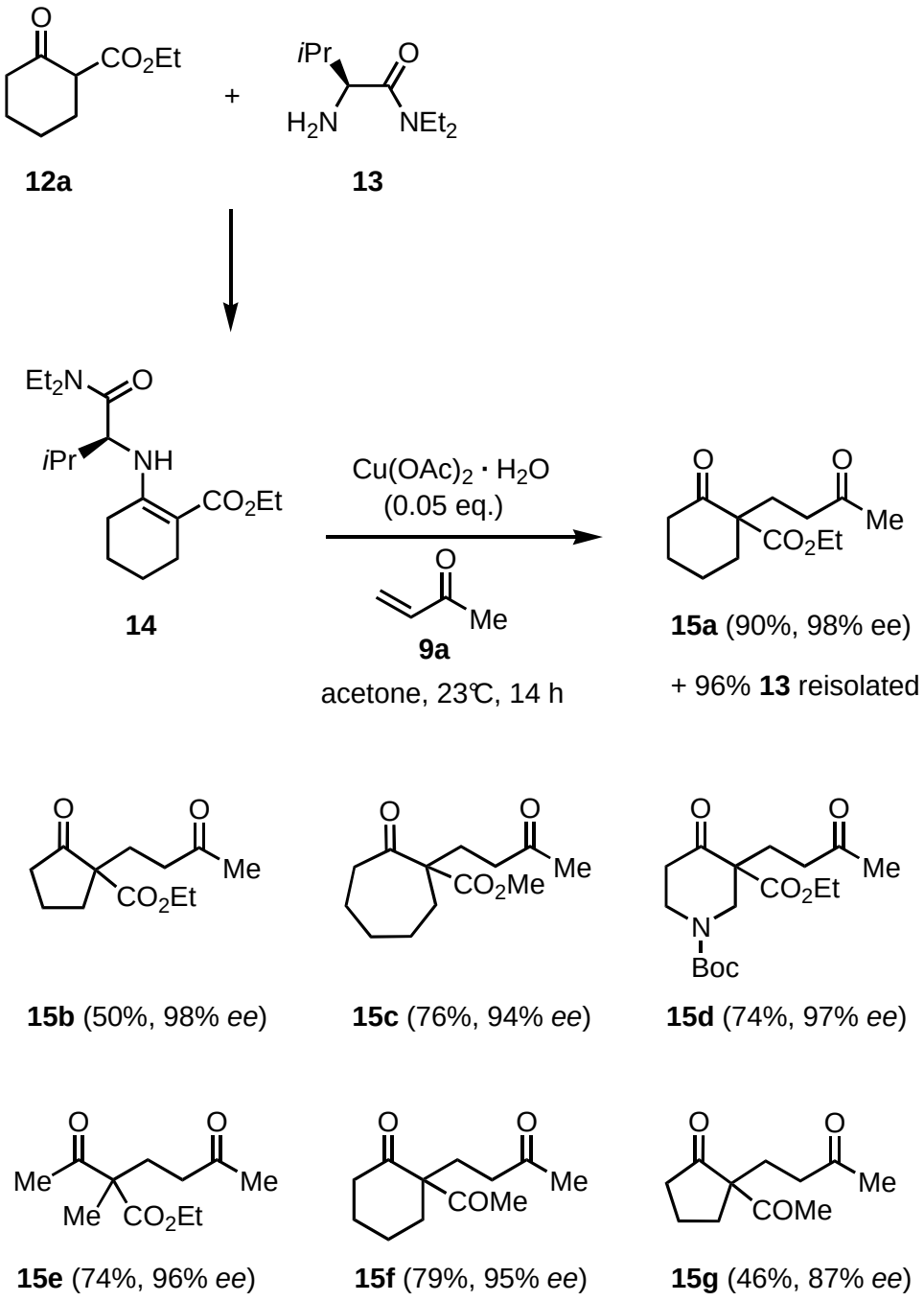
1.3 Michael and Conjugate Addition Reactions

Conjugate additions of carbon nucleophiles to acceptor activated carbon–carbon multiple bonds (the Michael addition) are very useful and versatile reactions for the synthesis of quaternary carbon centers. However, very limited success has been achieved in the development of highly enantioselective catalytic versions until recently.[15,28-30] An important breakthrough in the studies of transition metal catalyzed Michael additions came into light by the work of Ito and coworkers, who have developed an optically active diphosphanebiferrocene ligand **11** called PhTRAP with both planar and central chirality, which is a rare case of a diphosphane ligand that chelates to Pt(II), Pd(II) and Rh(I) center metals in a *trans* manner.[31-34] First studies on asymmetric Michael addition of α-cyanopropionate **8** to olefins **9** with a Rh catalyst generated *in situ* from $RhH(CO)(PPh_3)_3$ and (*S*,*S*)-(*R*,*R*)-PhTRAP **11** gave product **10** with a quaternary stereocenter in excellent yields and 85-94% *ee* selectivity.[31] (Scheme 2).



Scheme 2. Rh–catalyzed asymmetric Michael reaction using optically active PhTRAP ligand **11**.

In 1999, Christoffers' group carried out an intensive screening program with several primary chiral amines and transition metal salts catalysts, which led to the development of a highly reliable process for the formation of stereocenters by Michael reaction.[35] Transition metal catalysis of the Michael reaction of 1,3-dicarbonyl compounds with acceptor-activated alkenes is herein a valuable alternative to the classic base catalysis of this reaction. Owing the mild, neutral reaction conditions, the chemoselectivity of these processes is often superior to that offered by the base catalysis, since the latter suffers from various unwanted side- and subsequent reactions, such as aldol cyclizations and ester solvolysis. The most efficient transition-metal catalysts do not require inert or anhydrous conditions. L-Valine diethylamide **13** as chiral auxiliary combined with catalytic quantities of $Cu(OAc)_2 \cdot H_2O$ turned out to be extraordinarily efficient for this purpose. Representative results are depicted in Scheme 3.[36-42]



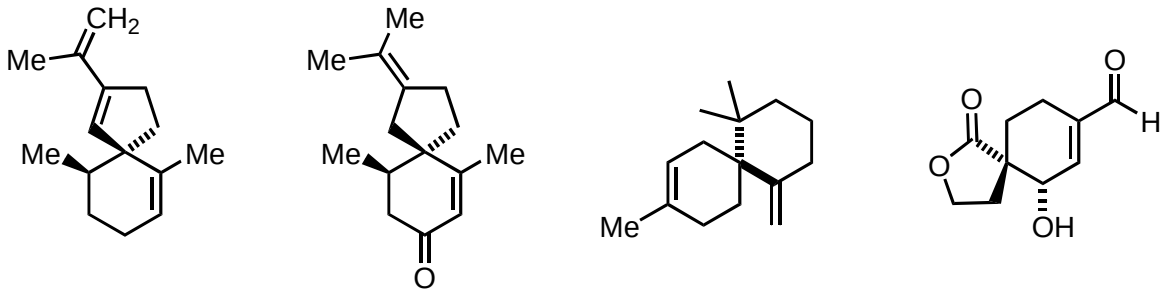
Scheme 3. Cu(II)-catalyzed asymmetric Michael reaction with L-Valine diethylamide **13** as chiral auxiliary.

The developed procedure is of practical interest: conversion of enamines such as **14** with **9a** in the presence of $Cu(OAc)_2 \cdot H_2O$ (1–5 mol%) proceeds at ambient temperature. Anhydrous or inert conditions are not required, and the solvent is simply acetone. After acidic workup, all the products were isolated in generally

good yield, with selectivities up to 95–99% *ee*. The auxiliary could be separated from the reaction mixture by extraction and recovered almost quantitatively. The selectivities obtained for these products have, to date, not been exceeded by other methods. A special feature of the copper-catalyzed reaction is the compatibility with donor functions such as the carbamate moiety in product **15d**.[38] Substrates of this type do not convert in reactions using Shibasaki's heterobimetallic catalysts.

1.4 Spirocycles

The name "spirocyclane" was first introduced by Baeyer in 1900[43,44] for those bicyclic hydrocarbons "welche ein beiden Ringen gemeinschaftliches quartärers Kohlenstoffatom enthalten: Spirocyclane, von 'spira' die Brezel". Thus the origin of spiro is from the Latin meaning spiral, which Baeyer construed to be like a pretzel. Spirocyclic compounds have attracted considerable attention recently from the standpoints of synthesis and reactivity. Spirocyclic structures are found in a wide range of natural products such as α-Vetispirene **16**,[45] β-Vetivone **17**,[46] β-Chamigrene **18**,[47] Canangone **19**,[48] isolated from various sources (Figure 3).



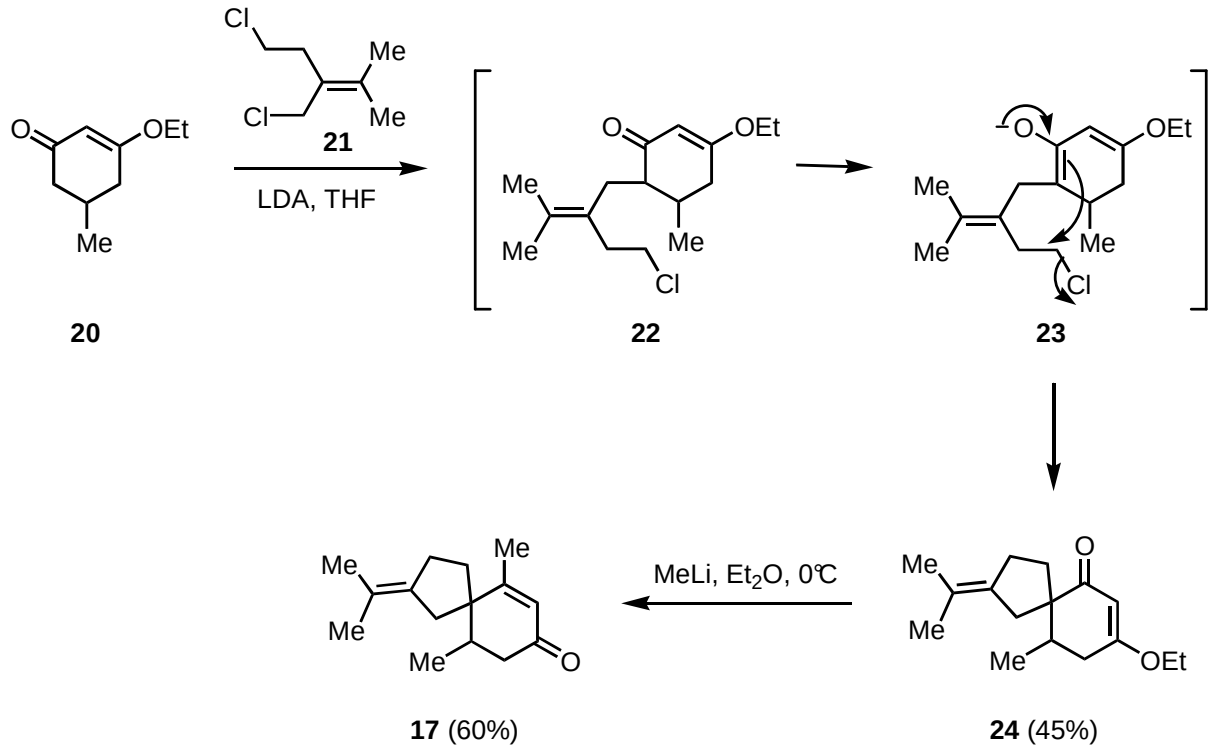
16 **17** **18** **19**

Figure 3. The structures of α-Vetispirene **16**, β-Vetivone **17**, β-Chamigrene **18**, and Canangone **19**.

(+)-Canangone **19** was isolated from the leaves and branches of *ylang-ylang* (*Cananga odorata*),[48] which belongs to the family of annonaceae, a known source for biologically active natural products like acetogenins.[49-51] Although this species has long been cultivated on a large scale for the production of essential oils from the flowers, it is chemically one of the least known of the tropical plant families. The construction of the spirocyclics can be roughly categorized into alkylation, rearrangement, cycloaddition and cleavage of bridged systems.

1.4.1 Alkylation

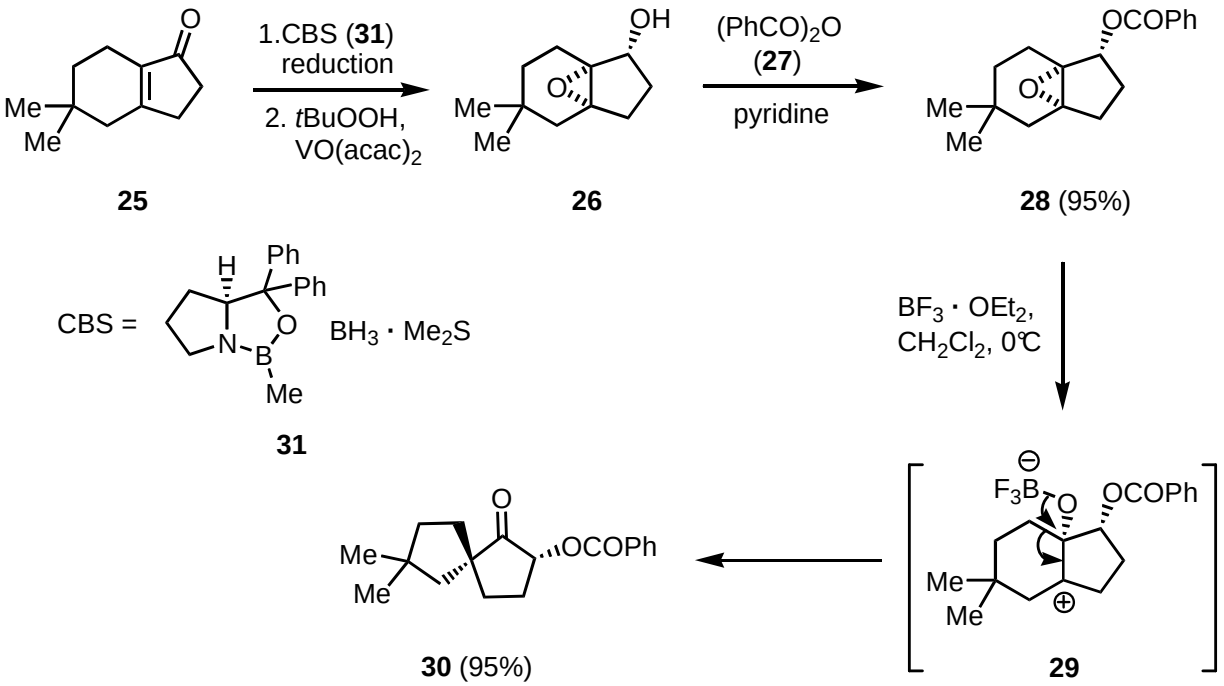
The intramolecular alkylation on a tertiary carbon to give a quaternary carbon is one of the most common methods in constructing spirocenters. Stork and co-workers[52] used the intramolecular alkylation as the key step for the racemic synthesis of the fragrant sesquiterpene, β-Vetivone **17** (Scheme 4). The spiroketone **24** was formed from enone **20** and homoallylic dichloride **21** in presence of LDA *via* an inter **22** and intra **23** molecular alkylation. Addition of methyl lithium to **24** gave (±)-β-Vetivone **17**. Eilerman and Willis[53] developed a spiroannulation technique that employs a similar dihalide for double alkylation but in a manner that use a mild base (LiCl). This method was used in the synthesis of (±)-β-Vetivone **17** and (±)-β-Vetispirene **16**.



Scheme 4. Synthesis of (±)-β-Vetivone **17** using an intramolecular alkylation as the key step.

1.4.2 Rearrangement Reactions

Rearrangement reactions have also found wide application in the synthesis of spirocycles. For example, Kita *et al.*[54] developed a stereospecific method to make spiro[4.4]nonanes by Lewis acid catalyzed rearrangement of *cis*-α,β-epoxy alcohol derivatives (Scheme 5). *cis*-Epoxy alcohol **26** was easily obtained by CBS reduction of ketone **25** followed by Sharpless epoxidation (99% *de*). The derived benzoate **28** obtained from epoxide **26** using benzoic anhydride **27** underwent Lewis acid promoted ring opening to give **29** and then rearrangement to the spiro compound **30** in 95% yield.

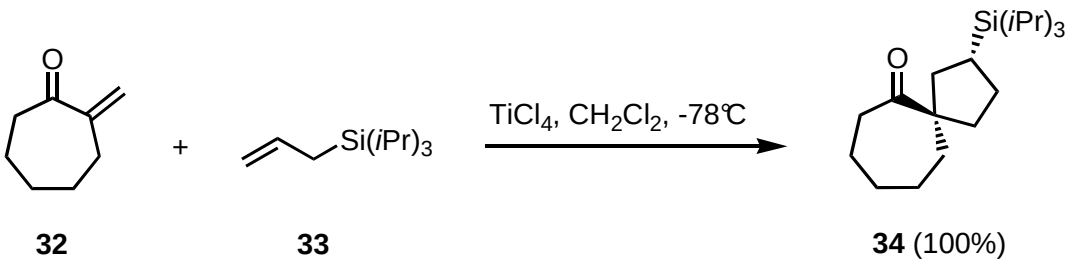


Scheme 5. Synthesis of spiro compounds using rearrangement reactions.

1.4.3 Cycloaddition Reactions

A variety of cycloadditions, such as [4+2],[55] [2+2],[56-59] [2+1],[60] [3+2],[61-63] as well as ene reactions,[64-66] have been used for the synthesis of spirocyclic moieties of natural products.

For example, Knölker *et al.*[67] used titanium tetrachloride promoted [3+2] cycloaddition of allyl silanes, such as **33**, with 2-methylenecycloheptan-1-one **32** to synthesize silylspirocyclopentane **34** as a single diastereoisomer in excellent yield (Scheme 6). Koft and Smith[68] developed a route to a spiroketone that involves intramolecular [2+2] photoaddition for the synthesis of perhydrohistrionicotoxin.

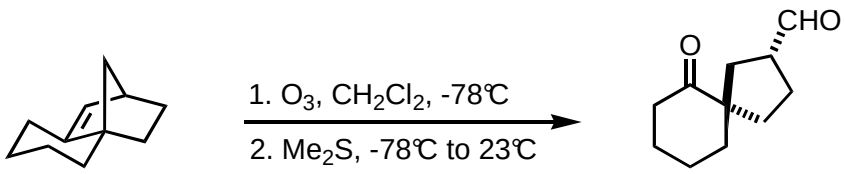


32 **33** **34** (100%)

Scheme 6. [3+2] cycloadditions for the synthesis of silyl spirocyclopentane **34**.

1.4.4 Conversion of Bridged Systems into Spirocycles

Spiro compounds can also be prepared when one of the bridges is cleaved from the appropriately constructed bridged systems. For instance, **36** can be prepared from the bridged compound **35** by ozonolysis followed by the reductive workup (Scheme 7).[69]



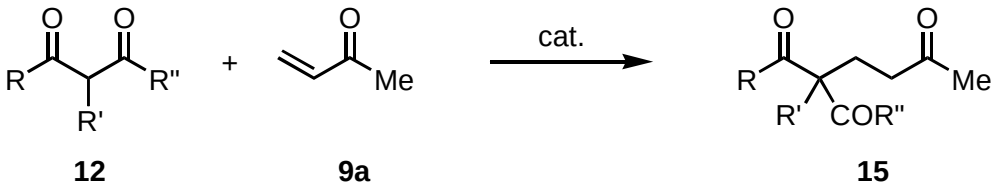
35 **36** (68%)

Scheme 7. Construction of spirocyclic ring from the bridged system.

1.5 Michael Reaction/Robinson Annulation

Among all the known C–C bond forming reactions, one of the most important and mildest method is the Michael reaction. This reaction was first observed and reported by Komnenos and Claisen,[70,71] and was later named after Arthur Michael in order to honor his early systematic investigations.[72-76] The Michael reaction is the addition of an enolate of a carbonyl derivatives to an α,β-unsa-

turated compound at the β-carbon (Scheme 8), which is usually catalysed by bases.

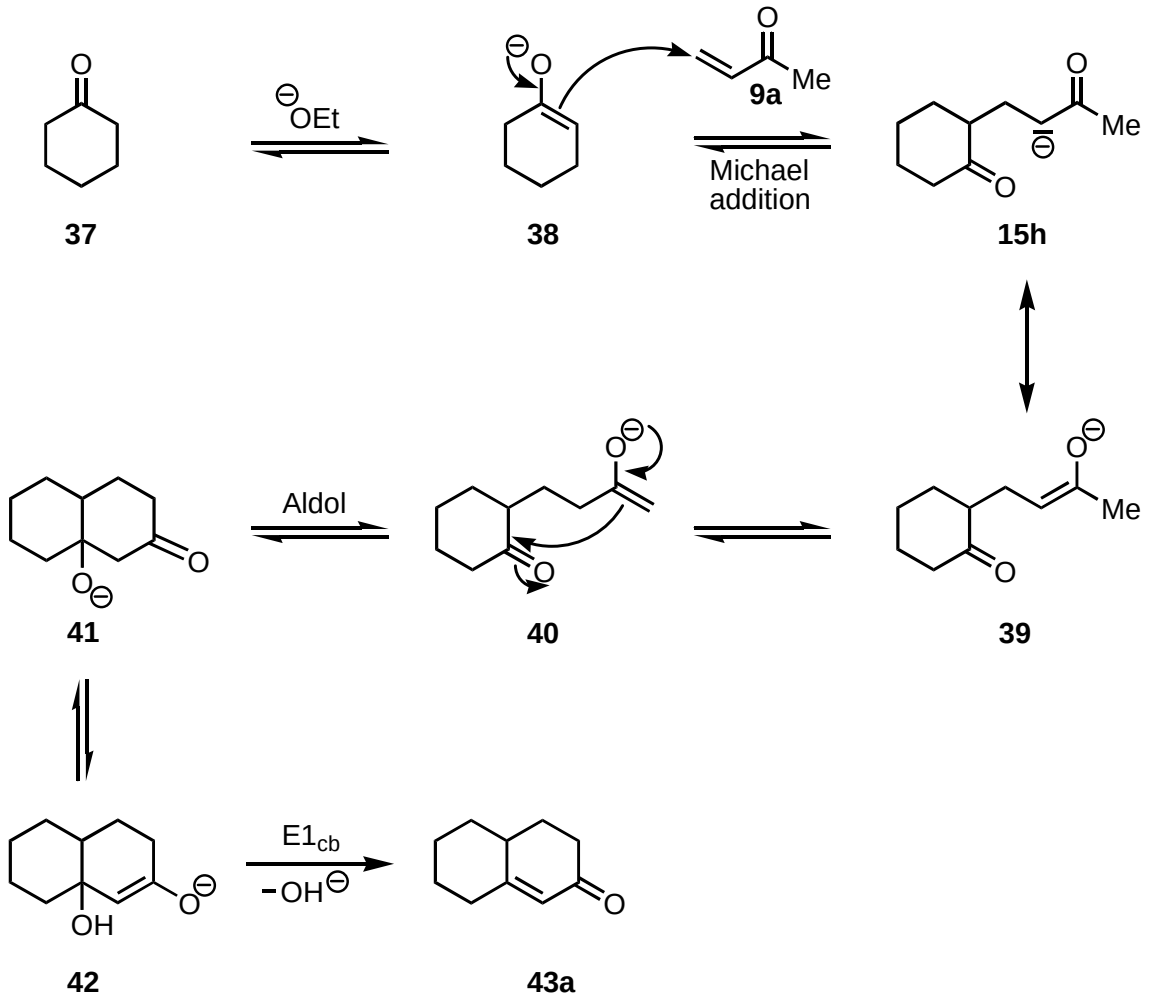


12 **9a** **15**

Scheme 8. Michael reaction of donor **12** with MVK **9a**.

However basic conditions often reduce chemoselectivity because of the undesired side or subsequent reactions such as aldol or retro Claisen reactions. In order to minimize these drawbacks, several lanthanide[77-79] and transition metal[80-82] catalyzed Michael reactions have been established in the past decades. With regard to economical and ecological considerations, the $FeCl_3 \cdot 6\ H_2O$ catalyzed Michael reaction developed by Christoffers' [83-96] seems to be optimal. The reaction conditions are very mild, can be carried out without solvent and moreover no inert conditions are required. Additionally, if a suitable chiral ligand or auxiliary is applied, these reactions may be enantioselectively performed. The Michael reaction may be used to construct a wide variety of complex molecules from relatively simple starting materials.

The Robinson annulation reaction is a Michael addition followed by an intramolecular aldol condensation (Scheme 9). This reaction was discovered in the 1930's by Sir Robert Robinson (Nobel prize winner in 1947), which allows the one pot synthesis of bicyclic ring-compounds.[97-100] The Robinson annulation reaction involves the acid- or base-induced reaction between a cyclic ketone containing an α-CH_2 group and an α,β-unsaturated ketone such as methyl vinyl ketone (MVK) **9a** with an alkyl substituent having two α-hydrogens adjacent to the carbonyl carbon.

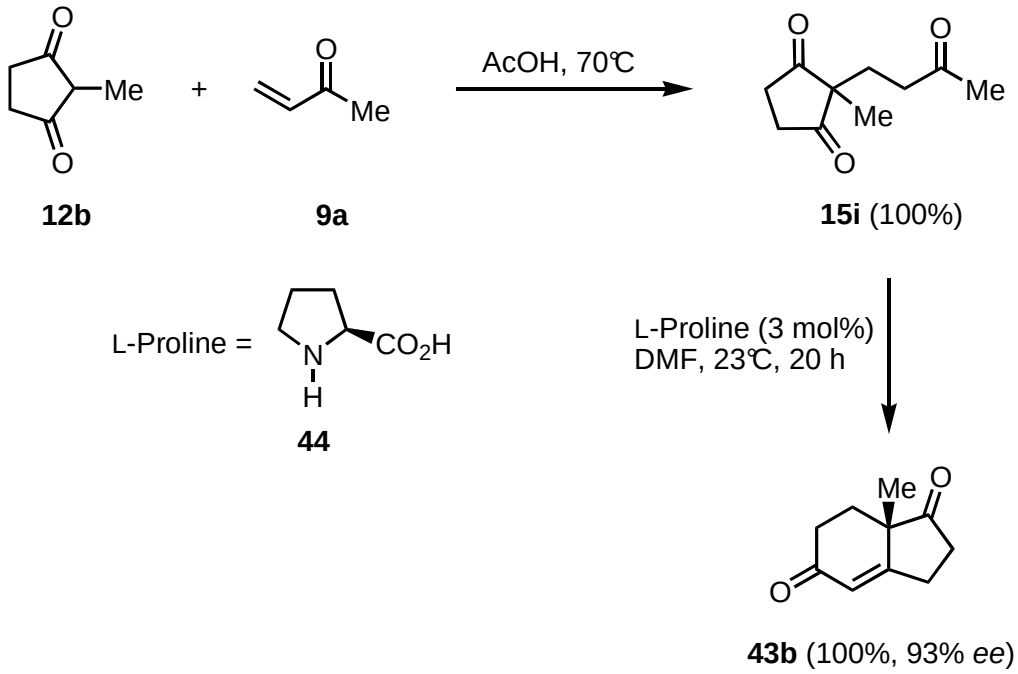


Scheme 9. Mechanism of Robinson annulation.

The Robinson annulation reaction is particularly important in the synthesis of natural products and pharmacologically active compounds such as steroids. The Wieland-Miescher Ketone[101,102] is a bicyclic diketone, a versatile building block, which has so far been employed in the total synthesis of more than fifty natural products, predominantly sequiterpenoids, diterpenes and steroids possessing exceptionally promising biological properties including anticancer, antimicrobial, antiviral, antineurodegenerative and immunomodulatory activities.

An enantioselective synthesis of Wieland-Miescher Ketone **43b** was accomplished by using L-proline **44** as a chiral auxiliary in catalytic amounts. This is known as Hajos-Parrish-Eder-Sauer-Wiechert reaction.[103-107] Achiral Michael product **15i** undergoes L-Proline **44** catalyzed Robinson annulation giving the ketone **43b** as

shown in Scheme 10. It contains the AB-ring structure of steroids and for this reason it became an attractive starting material towards the steroid skeleton, an approach which was used in one of the successful total synthesis of adrenosterone.[108]



Scheme 10. The Hajos-Parrish-Eder-Sauer-Wiechert reaction.

1.6 Chamigrenes

1.6.1 Isolation of Chamigrenes

Chamigrenes, which contain a spiro[5.5]undecane carbon framework incorporating two vicinal quaternary carbon atoms, are interesting sesquiterpene natural products isolated from plants and liverworts as well as marine sources. Chamigrenes appear to be metabolites from algae of the genus *Laurencia*. The isolation of β-Chamigrene **18** was first reported by Ito *et al.*[47] in 1967 from the leaf oil of *Chamaecyparis taiwanensis*. Subsequently, a variety of chlorine and bromine containing chamigrenes were isolated from marine sources. Over 120 chamigrenes

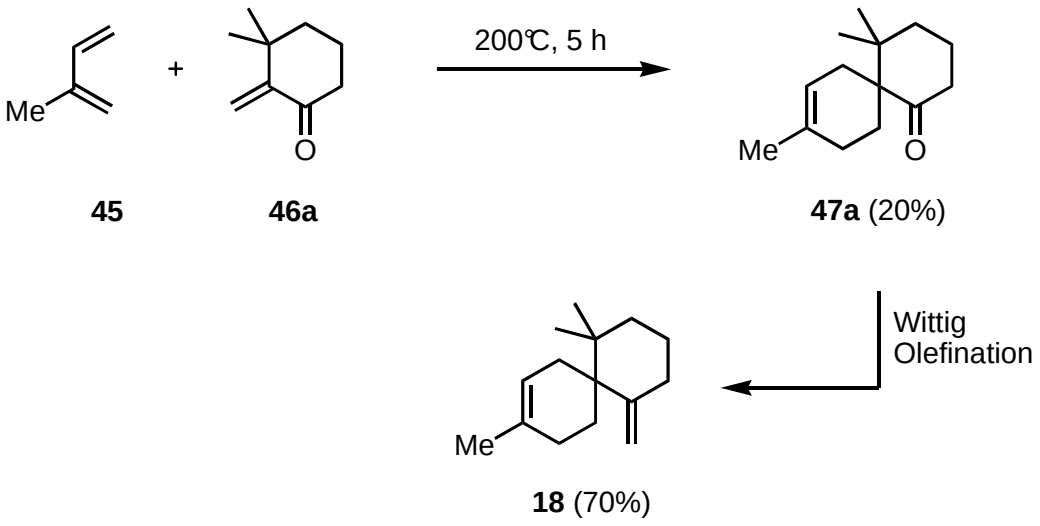
were isolated from *Laurencia* species and from sea hares grazing on them. Several halogenated chamigrenes were shown to exhibit cytostatic activity and remarkable antimicrobial activity on both Gram-positive and Gram-negative bacteria.[109]

1.6.2 Total Syntheses of β-Chamigrene

Synthesis of Chamigrenes is challenging owing to the presence of a quaternary carbon adjacent to the spirocenter. So far Tanaka *et al.*,[110] Ireland *et al.*,[111] Martin *et al.*,[109] Adams *et al.*,[112] and Srikrishna *et al.*[113] have published the synthesis of β-Chamigrene. An overview of all the total syntheses is summarized briefly.

1.6.2.1 Total Synthesis of (±)-β-Chamigrene by Tanaka *et al.*

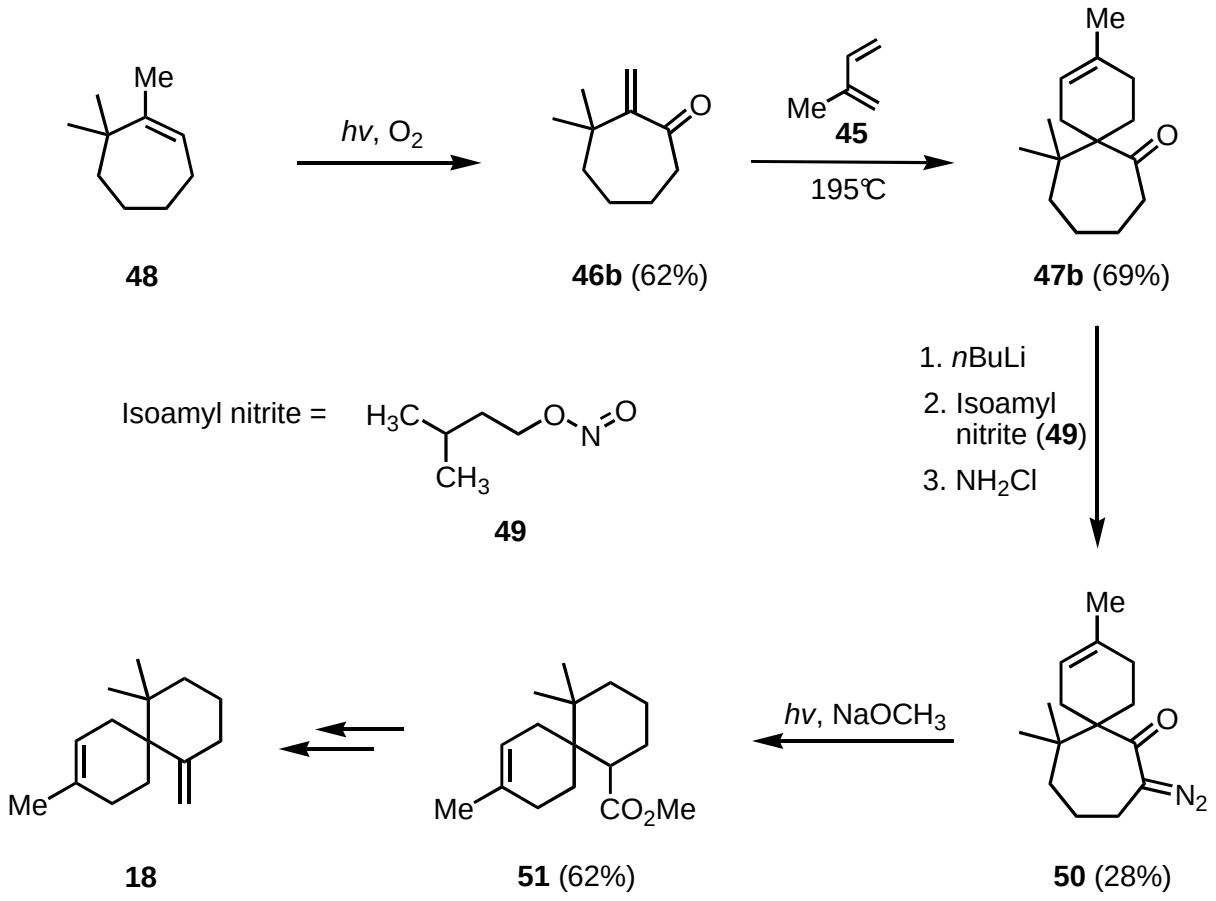
The first total synthesis of β-Chamigrene was published by Tanaka *et al.* in 1967.[110] Diels-Alder reaction of an α,β-unsaturated ketone **46a** and isoprene **45** furnished a precursor **47a** of β-Chamigrene in 20% yield. Wittig olefination of compound **47a** provided racemic β-Chamigrene **18** in 70% yield as depicted in Scheme 11.



Scheme 11. Synthesis of (±)-β-Chamigrene **18** by Tanaka *et al.*

1.6.2.2 Total Synthesis of (±)-β-Chamigrene by Ireland *et al.*

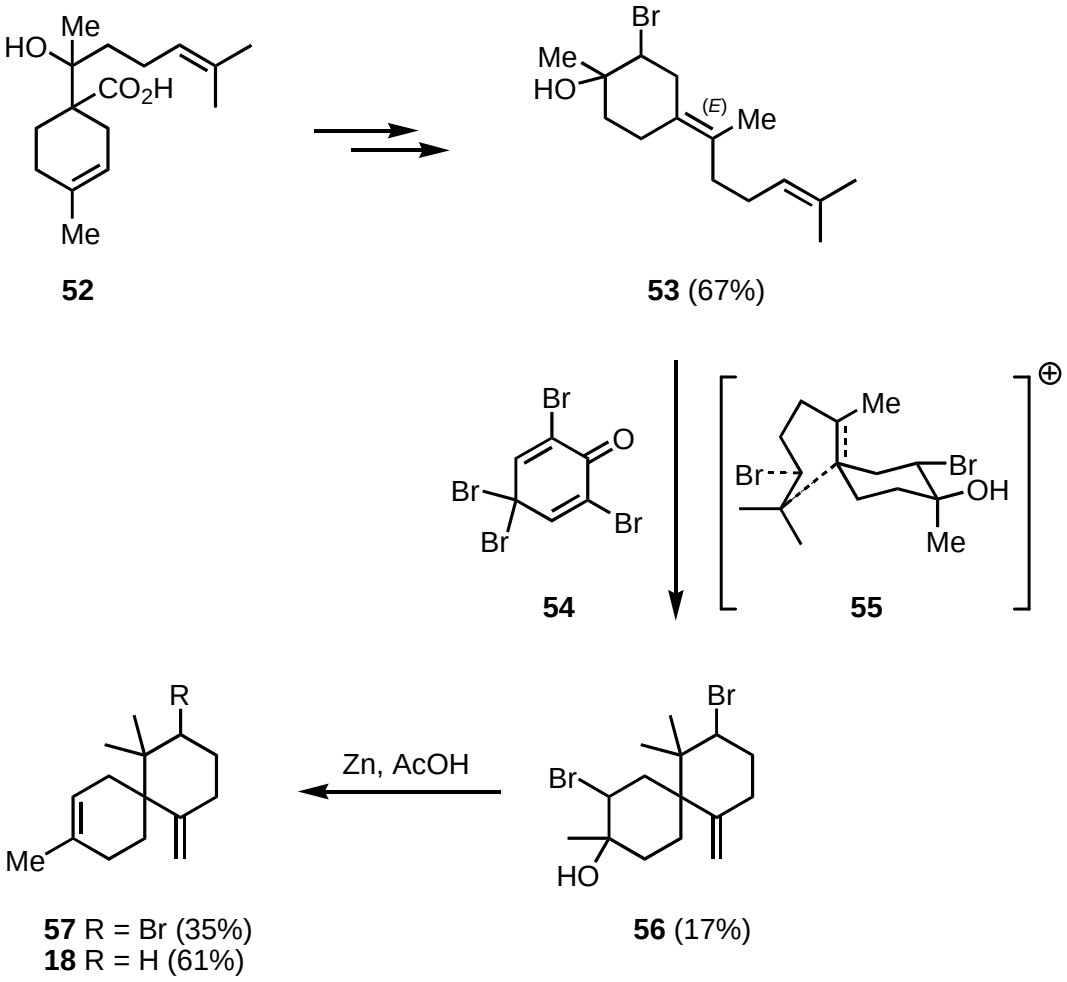
In 1984, Ireland *et al.*[111] synthesized (±)-β-Chamigrene using a Diels-Alder strategy as a key step to construct the spirocyle **47b** by following the protocol of Tanaka *et al*. The synthetic route started with photosensitized oxygenation of endocyclic olefin **48**, followed by Diels-Alder reaction between α,β-unsaturated ketone **46b** with isoprene **45** to provide compound **47b**. Diazoketone **50** was obtained in two steps from compound **47b** as shown in Scheme 12. Photolysis of the derived diazo ketone **50** provided the ester **51** followed by further transformations furnished β-Chamigrene **18** in 31% yield.



Scheme 12. Synthesis of (±)-β-Chamigrene by Ireland *et al*.

1.6.2.3 Total Synthesis of (±)-β-Chamigrene by Martin *et al*.

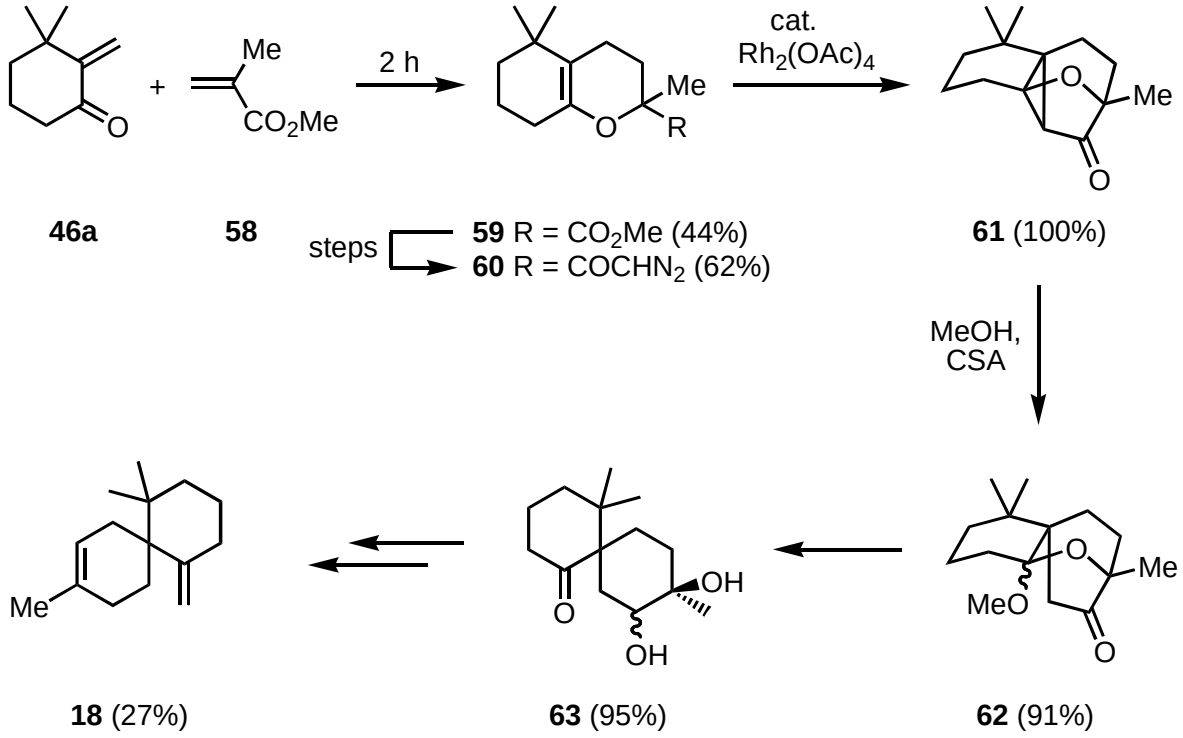
The synthesis of β-Chamigrene as well as the other sesquiterpenes was achieved by Martin *et al*.[109] in 1986. The *E*-exocyclic tetra substituted olefin **53** was the key building block for the synthesis of these sesquiterpenes, which was synthesized in eight steps from readily available[114] (±)-β-hydroxy acid **52**. Cyclization of (±)-**53** gave compound **56** in 17% yield. Treatment of **56** with Zn dust in acetic acid afforded in 35% yield of 2-bromo-β-chamigrene **57** and 61% yield of (±)-β-Chamigrene **18** as shown in Scheme 13.



Scheme 13. Total synthesis of (±)-β-Chamigrene **18** by Martin *et al*.

1.6.2.4 Total Synthesis of (±)-β-Chamigrene by Adams *et al.*

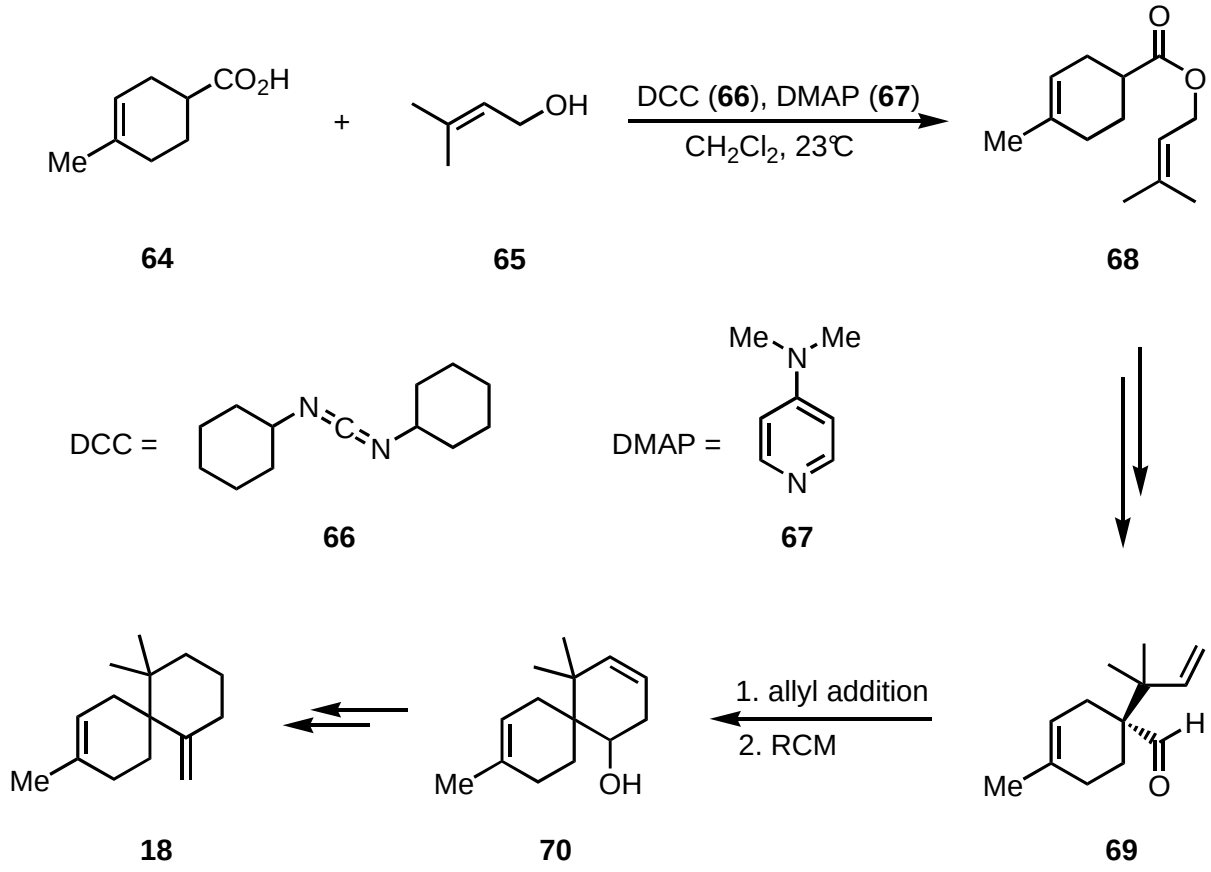
In addition to Tanaka, Ireland and Martin *et al.*, another racemic synthesis of β-Chamigrene was published by Adams *et al.*[112] in 1991. Highly substituted dihydropyran derivative **59** was prepared from α,β-unsaturated ketone **46a** and methyl methacrylate **58** by employing an Hetero–Diels–Alder strategy.[111] Saponification of the ester, followed by conversion to an acid chloride under neutral conditions with oxalyl chloride and treatment with excess CH_2N_2 afforded diazoketone **60** in 62% yield. The cyclopropanation reaction using $Rh_2(OAc)_4$ catalysis generated cyclopropane derivative **61** in quantitative yield as shown in Scheme 14. Regiospecific cleavage of the cyclopropane ring through an acid–catalyzed solvolysis of **61** using camphorsulfonic acid in MeOH gave a mixture of acetals **62** which were later reduced to isomeric mixture of diols **63** in 95% yield. Further transformations led to (±)-β-Chamigrene **18** in 27% yield.



Scheme 14. Total synthesis of (±)-β-Chamigrene by Adams *et al.*

1.6.2.5 Total Synthesis of (±)-β-Chamigrene by Srikrishna *et al*.

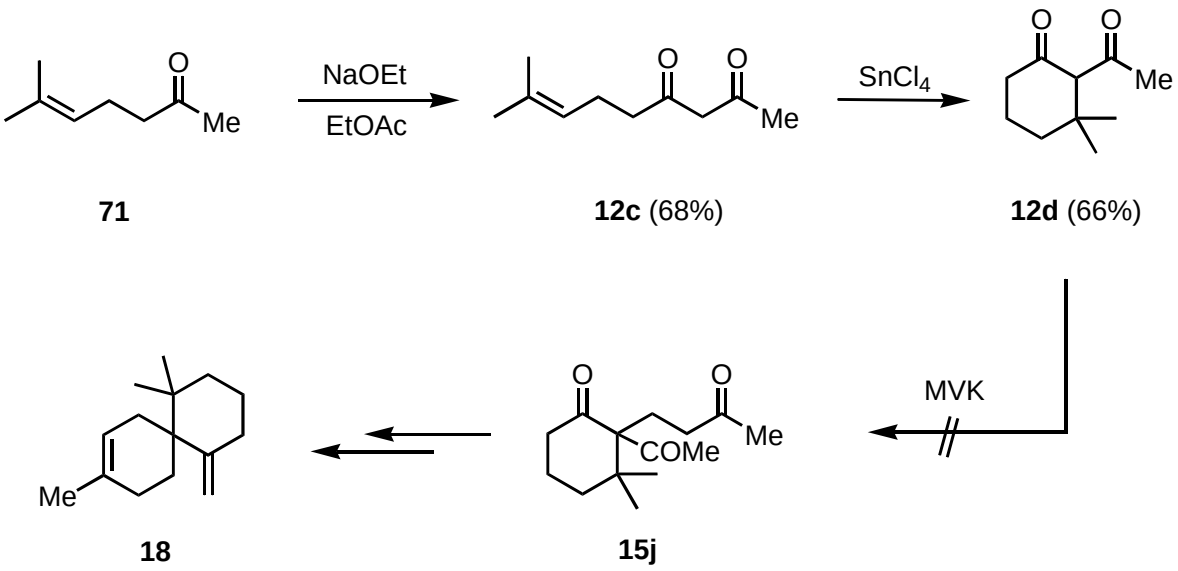
Srikrishna *et al*.[113] have accomplished a total synthesis of (±)-β-Chamigrene **18** in ten steps starting from readily available[115] Diels–Alder adduct **64**. The esterification of acid **64** with prenyl alcohol **65** provided prenyl ester **68** in 95% yield as shown in Scheme 15. Ireland–Claisen rearrangement followed by hydrolysis of the reaction mixture and esterification resulted methyl ester derivative, which in turn was converted to aldehyde **69**. Allylic addition followed by ring closing metathesis afforded alcohol **70**. Further transformations led to (±)-β-Chamigrene **18**.



Scheme 15. The synthesis of (±)-β-Chamigrene by Srikrishna *et al*.

1.6.2.6 Attempted Synthesis of β-Chamigrene From Our Group

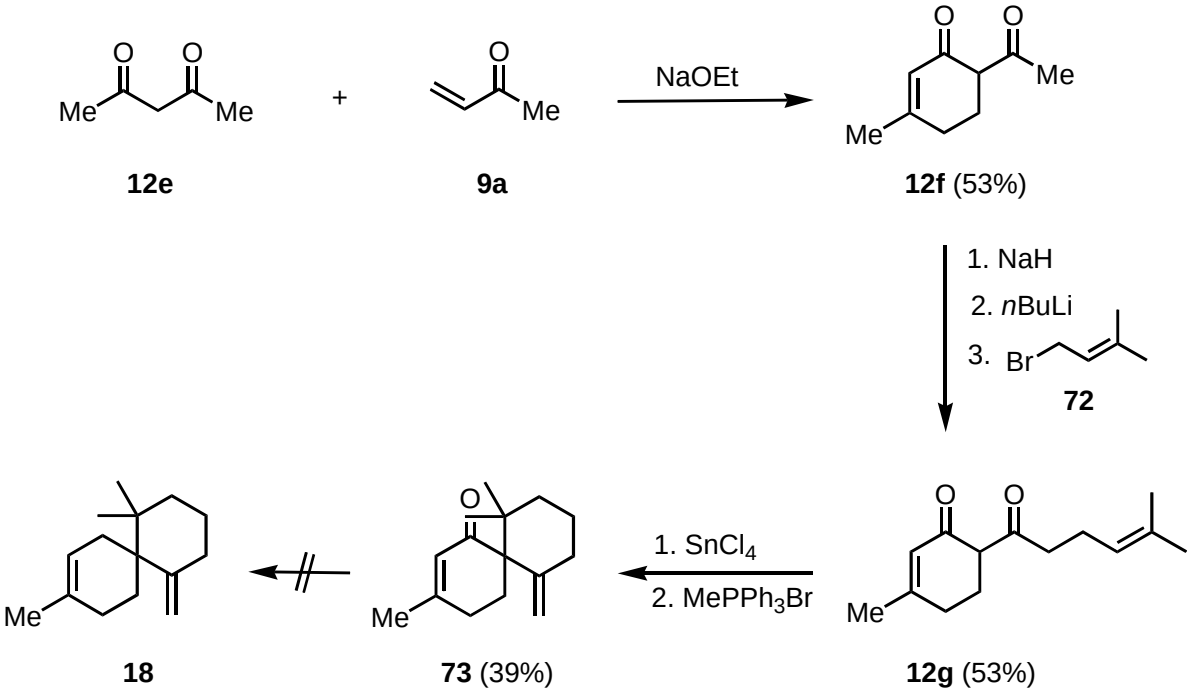
Two synthetic routes were designed for the synthesis of β-Chamigrene **18** in Sven Unger's dissertation.[116] The first route was planned using a Michael reaction as the key step. The acetylation of ketone **71** using ethyl acetate provided 1,3-dicarbonyl derivative **12c** in 68% yield. Subsequent cyclization in presence of $SnCl_4$ gave α-acetyl dimethyl cyclohexanone **12d** in 66% yield. Unfortunately the synthesis of Michael product **15j** could not be carried out neither in metal catalysis nor in basic conditions to proceed further in the synthesis of β-Chamigrene **18** (Scheme 16).



Scheme 16. First approach to the synthesis of β-Chamigrene **18**.

An alternative route was developed, which allowed the synthesis of potential precursor **73** for the target molecule in only four steps. The sequence started with the synthesis of α-acetylated cyclohexanone **12f**, prepared from simple and commercially available compounds, methyl vinyl ketone **9a** and acetyl acetone **12e** in a base catalyzed solvent free Michael reaction followed by aldol condensation in 53% yield. The Robinson annulated product **12f** was deprotonated and treated

with excess prenyl bromide **72** to afford the alkylated cyclohexanone **12g** in 53% yield. The Lewis acidic induced spirocyclization in the presence of $SnCl_4$ followed by a Wittig olefination using $MePPh_3Br$, finally led to the potential precursor **73** of the natural product β-Chamigrene. Unfortunately all the strategies to deoxygenate the α,β-unsaturated carbonyl group of a potential precursor **73** were unsuccessful (Scheme 17).



Scheme 17. The second approach for the synthesis of β-Chamigrene **18**.

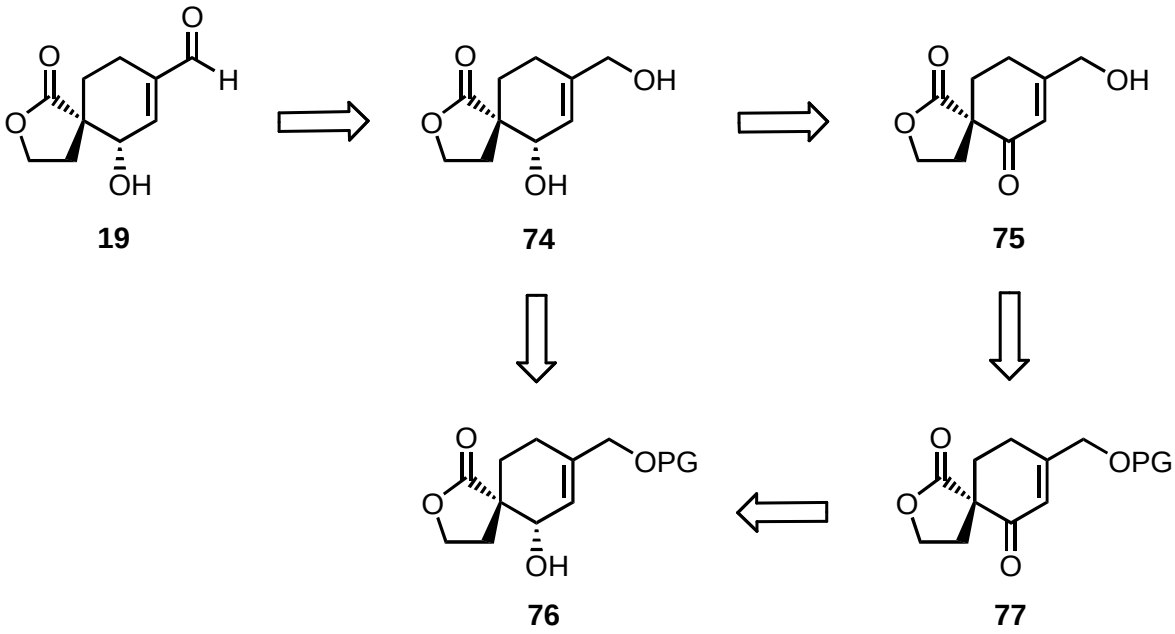
2 Goal of this Work

This dissertation includes two projects, both on stereoselective synthesis of spirocyclic compounds. The first project deals with the first enantioselective synthesis of (+)-Canangone **19** and second should be the first enantioselective synthesis of (–)-β-Chamigrene **18**.

2.1 Retrosynthetic Analysis for Canangone 19

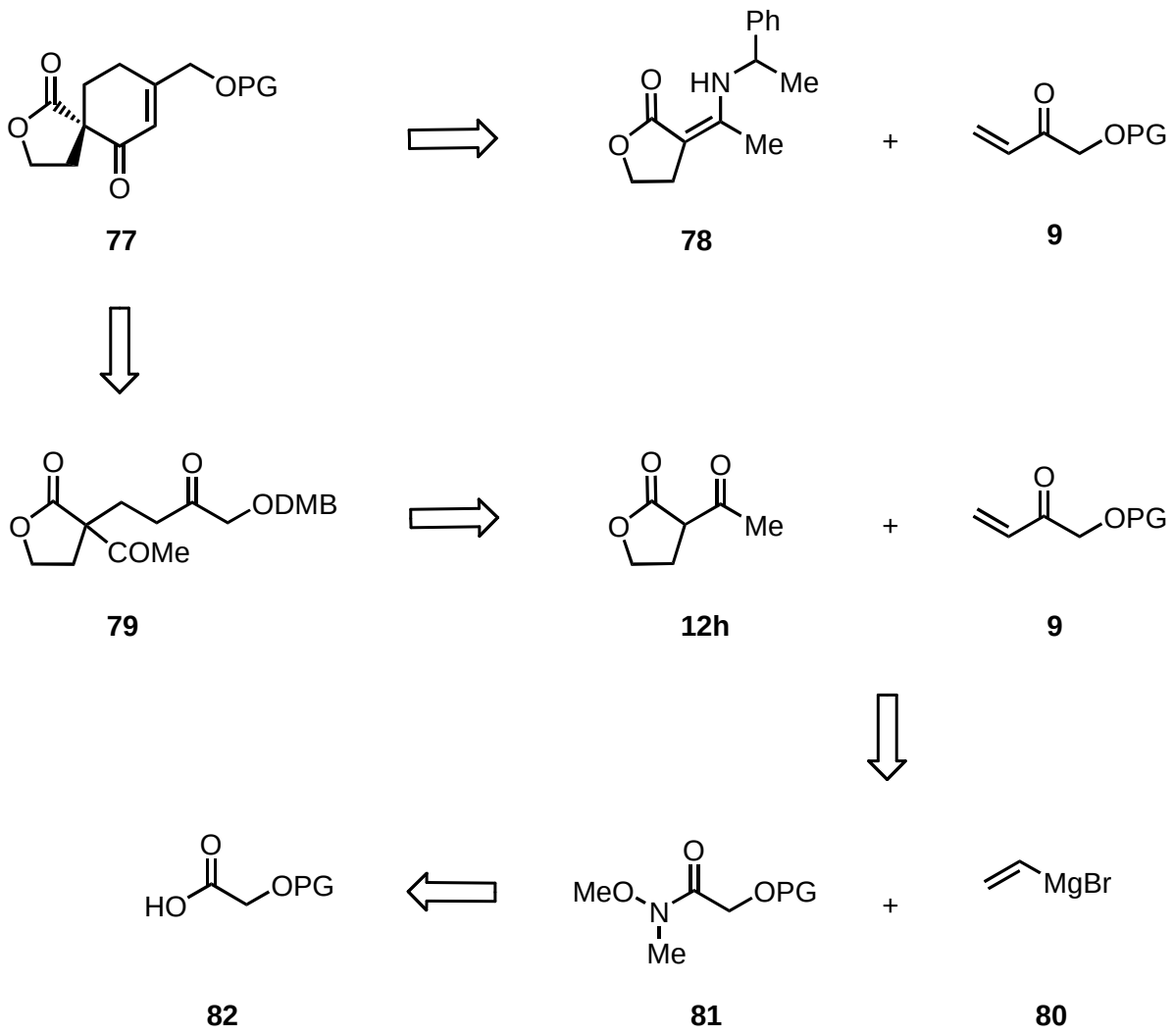
Our interest in the synthesis of Canangone **19** stems from the presence of a quaternary stereocenter,[14-22] which is a challenging task for formation of spirolactones. To date, there have been no reports on the synthesis of Canangone **19**. So far, only its relative configuration is known, but the absolute configuration is still unknown.[48] Therefore, a synthetic strategy was planned to synthesize (+)-Canangone **19** and determine its absolute configuration as well as checking the biological activities of racemic as well as the optically active Canangones.

The target molecule, Canangone **19** can be obtained by selective oxidation of primary allylic alcohol **74** as shown in Scheme 18. The primary allylic alcohol **74** can be synthesized either by stereoselective reduction of enone **75** or by deprotection of the primary alcoholic protecting group in **76**. Both enone **75** and allylic alcohol **76** can be prepared either by deprotection or selective reduction of spirolactone **77** respectively.



Scheme 18. Retrosynthetic scheme for Canangone **19** from spirolactone **77**.

Spirolactone **77** could be possibly made either by Robinson annulation of enaminolactone **78** and vinyl ketone derivative **9** or by cyclization of Michael product **79**. The Michael product **79** can be prepared from α-acetyl butyro lactone **12h** and vinyl ketone derivative **9** (Scheme 19). Grignard reaction of Weinreb amide **81** and vinyl magnesium bromide **80** would provide vinyl ketone **9**. Weinreb amide derivative **81** can be synthesized from protected glycolic acid **82** by using Weinreb amide conditions.



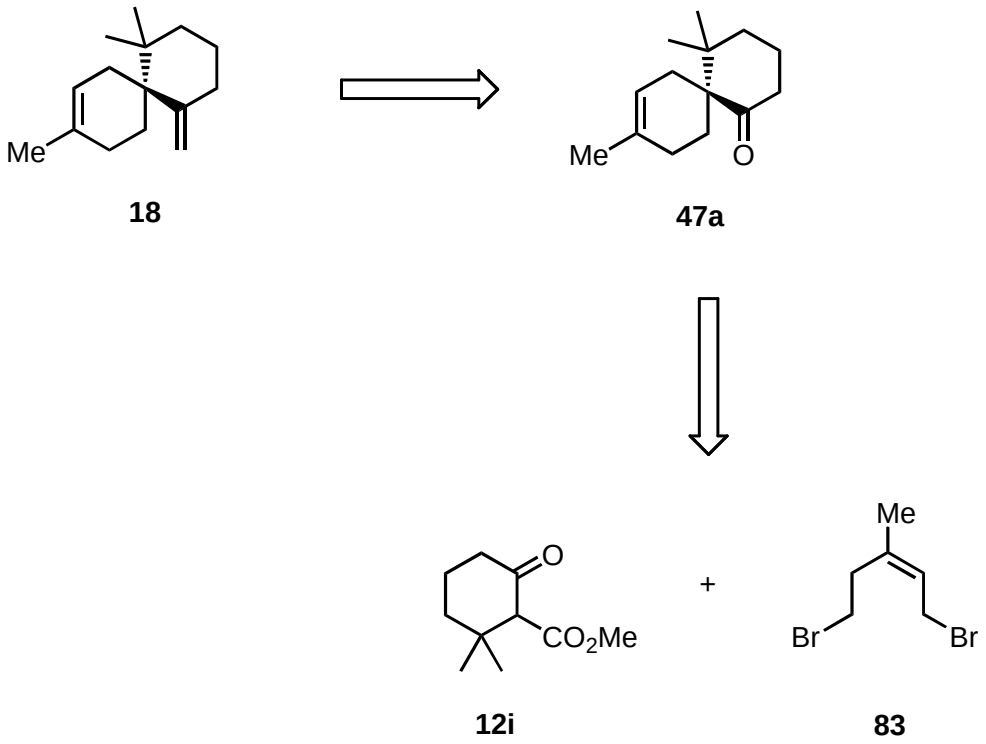
PG = 4-$MeOC_6H_4CH_2$- or 3,4-$(MeO)_2C_6H_3CH_2$ or Ph_3C

Scheme 19. Retrosynthetic pathway for the synthesis of spirolactone **77**.

2.2 Retrosynthetic Pathway for β-Chamigrene 18

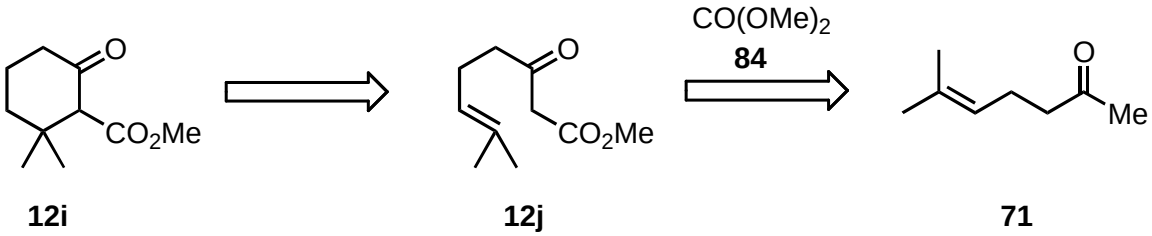
The second synthetic target is the total synthesis of β-Chamigrene **18**, isolated from the leaf oil of *Chamaecyparis taiwanensis*.[47] Although several total syntheses on β-Chamigrene **18** have been published,[109-113] most of them were too lengthy and moreover they were synthesized in a racemic form. Therefore a synthesis was planned for β-Chamigrene **18** in a very short, stereoselective and reliable pathway.

In the retrosynthetic plan as shown in Scheme 20, β-Chamigrene **18** can be synthesized from spirocyclic ketone **47a** by Wittig olefination, which in turn can be obtained by alkylation of dibromo olefin **83** and β-ketoester **12i** followed by cyclization.



Scheme 20. Retrosynthetic scheme for the synthesis of β-Chamigrene **18**.

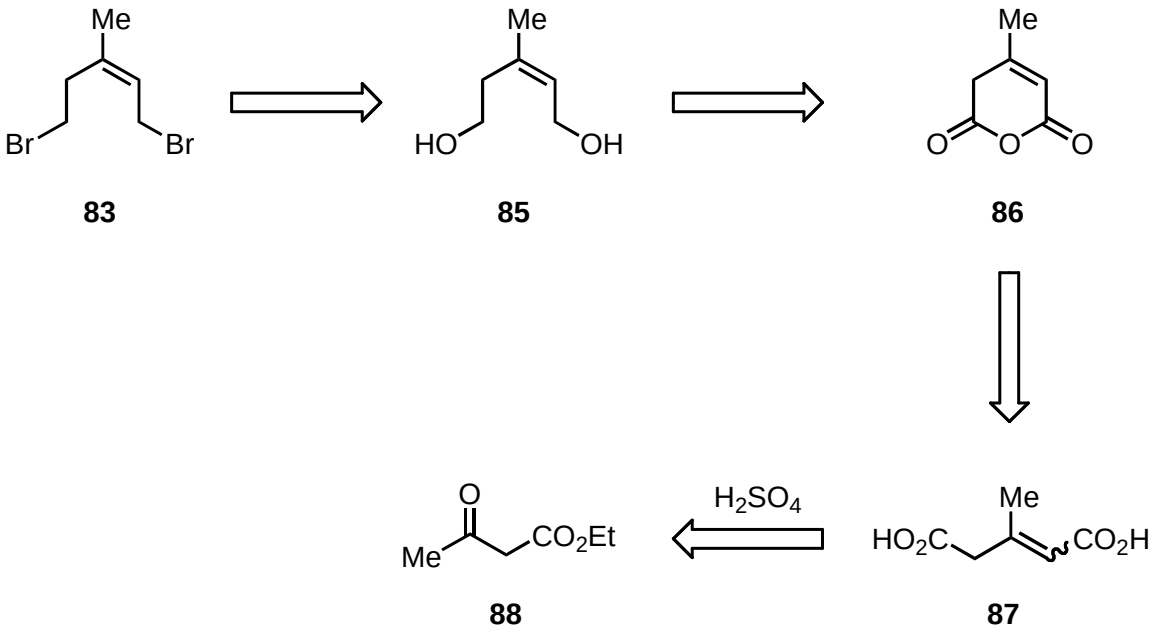
The cyclic β-keto ester **12i** can be synthesized from β-keto methyl ester **12j** by using Lewis acid mediated cyclization. β-Keto ester **12j** can be obtained by carbomethoxylation of the anion of 6-methylhept-5-en-2-one **71** with dimethyl carbonate **84** (Scheme 21).



12i **12j** **71**

Scheme 21. Retrosynthetic pathway for cyclic β-ketoester **12j**.

The dibromide **83** can be prepared by bromination of diol **85**, which in turn can be obtained by the reduction of cyclic anhydride **86**. The anhydride formation of diacid **87** would provide cyclic anhydride **86**. Condensation of ethylacetoacetate **88** with H_2SO_4 followed by hydrolysis might provide diacid **87** (Scheme 22).



83 **85** **86** **88** **87**

Scheme 22. Retrosynthetic pathway for dibromide **83**.

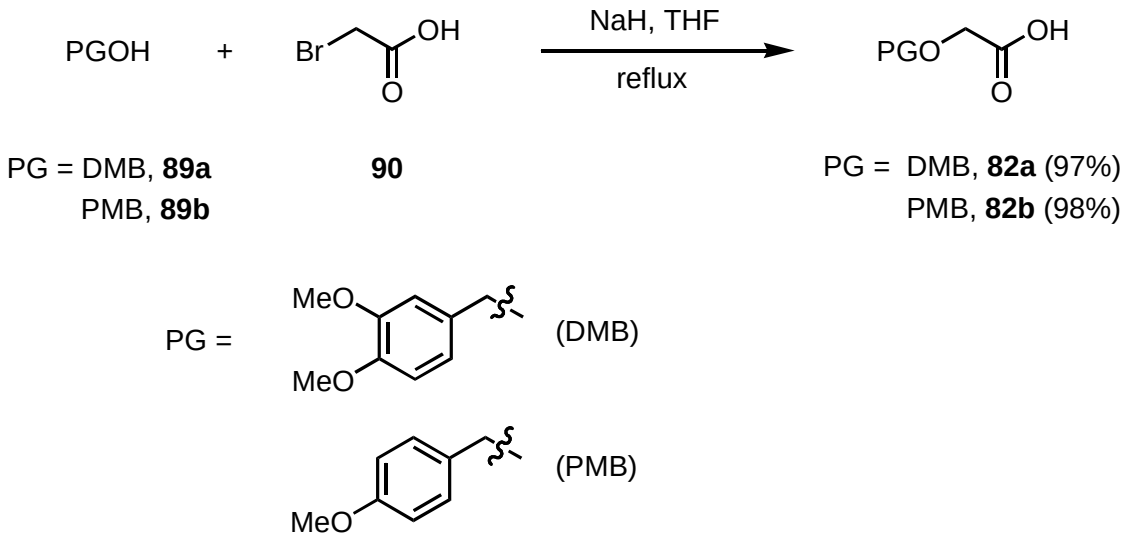
3 Results and Discussion

3.1 Canangone

3.1.1 Synthesis of Michael Acceptors

3.1.1.1 Synthesis of Protected Hydroxy Acetic Acid 82

The synthesis of Canangone (**19**) was planned with relatively cheap and commercially available starting materials. Three protecting groups were used in this synthesis, namely dimethoxy benzyl (DMB), paramethoxy benzyl (PMB), and trityl (Tr). The synthesis began with the Williamson ether synthesis with bromo-acetic acid **90** (1.0 eq) and 3,4-dimethoxy benzyl alcohol (DMB-OH) **89a** (1.0 eq) using NaH (1.0 eq) in THF[117] to give protected hydroxy acetic acid **82a** in 67% after acidic work up (Scheme 23).



Scheme 23. Synthesis of protected hydroxy acetic acid **82a** and **82b**.

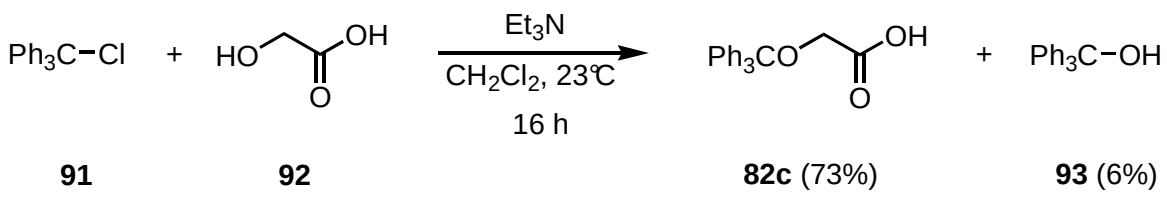
As the yield of above reaction was moderate and not satisfying, the optimization of the reaction conditions were attempted in order to obtain a maximum yield of

protected hydroxy acid **82a** (Table 1). After few attempts DMB protected hydroxy acid **82a** was obtained in quantitative yields with 1.5 eq. of bromoacetic acid **90** and 3.5 eq. of NaH. By following the same reaction conditions, PMB protected hydroxy acid **82b** was synthesized in 98% yield from 4-methoxy benzyl alcohol (PMB-OH) **89b**.

Table 1. Optimization to increase the yield of protected glycolic acid **82a**.

89a	NaH	t	Yield
1.0 eq.	2.0 eq.	1 d	67%
1.5 eq.	2.0 eq.	2 d	78%
1.5 eq.	3.5 eq.	2 d	97%

The trityl protected glycolic acid **82c** was prepared using trityl chloride **91** and hydroxy acetic acid **92** in presence of pyridine[118] as a base. But the yield of this reaction was only 12% after the acidic work up at 0°C and the remaining amount got converted to trityl alcohol **93**. The reason might be the clevage of trityl group during the acidic work up. In order to improve the yield, the work up conditions were optimized by using different acids. Finally the yield of the protected hydroxy acid **82c** was increased to 73% using Et_3N[119] as a base (Scheme 24) and 1 molar aqueous $KHSO_4$ for acidic workup.



Scheme 24. Synthesis of trityl protected hydroxy acid **82c**.

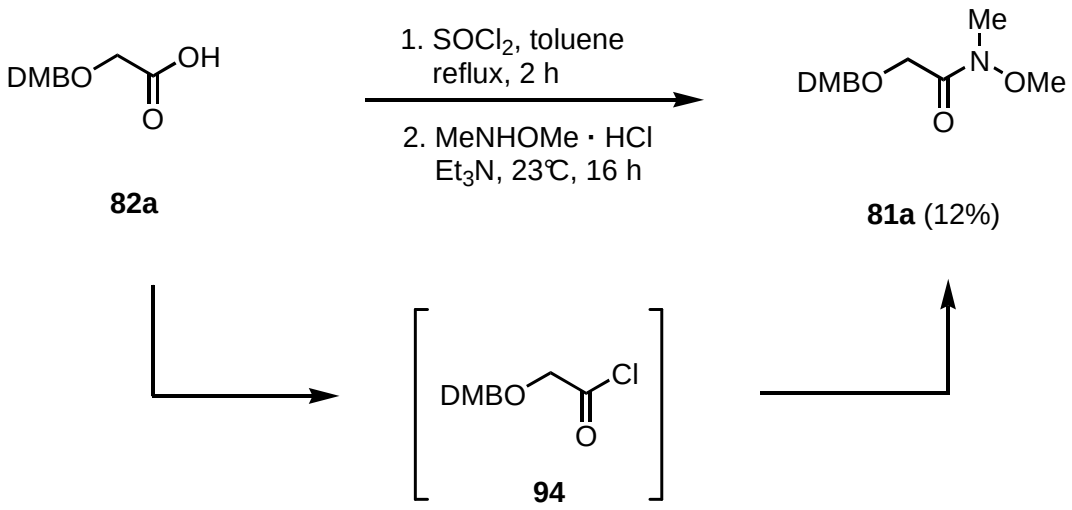
The acidic workup plays a very crucial role in this reaction. $KHSO_4$ was the reagent of choice for acidifying the organic layer and care should be taken that the pH of the organic layer should not drop below 3. If the pH of the organic layer drops below 3, the trityl alcohol was obtained as the major product (Table 2).

Table 2. Acidic workup conditions for obtaining glycolic acid derivative **82c**.

base	work up conditions	pH of the organic layer	**82c**	**93**
pyridine	1 mol/l HCl	1	12%	80%
pyridine	1 mol/l HCl	3	20%	73%
pyridine	1 mol/l $KHSO_4$	3	42%	38%
pyridine	1 mol/l $KHSO_4$	1	21%	56%
Et_3N	1 mol/l $KHSO_4$	3	73%	6%
Et_3N	1 mol/l $KHSO_4$	1	46%	30%

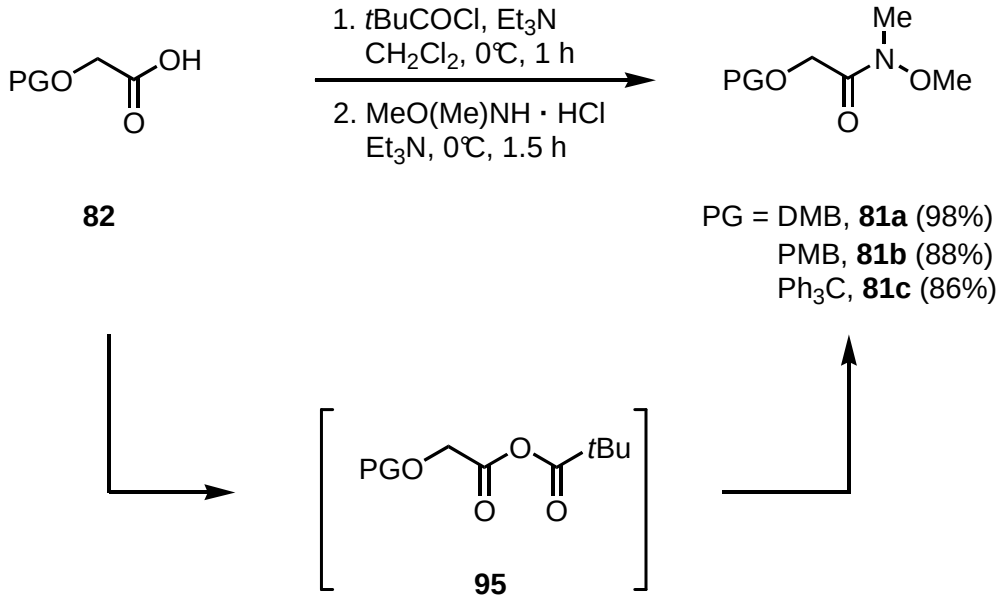
3.1.1.2 Synthesis of Weinreb Amide 81

The synthesis of Weinreb amide **81a** from protected hydroxy acetic acid **82a** was first attempted using thionyl chloride, $SOCl_2$ (for *in situ* formation of acyl chloride **94**) and then treating it with *N*-methoxy methyl hydroxyl amine hydrochloride and triethyl amine.[120] But the yield of this reaction under these conditions was only 12% (Scheme 25).



Scheme 25. Synthesis of Weinreb amide **81a** by *in situ* formation of acyl chloride **94**.

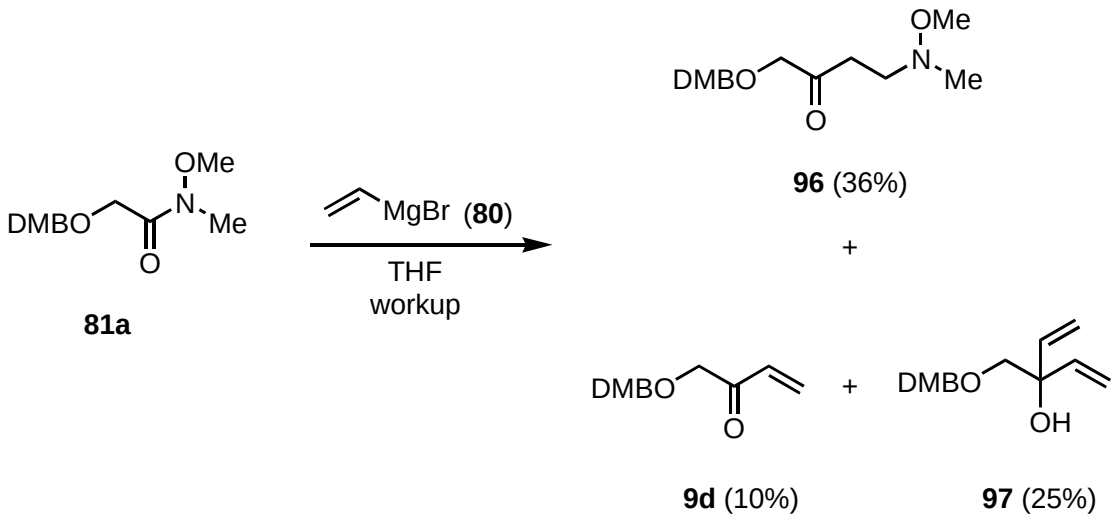
But by following a method developed by Raghuram *et al.*,[121] the protected hydroxy acetic acid **82a** was first activated to form mixed anhydride **95** using pivaloyl chloride and Et_3N in CH_2Cl_2 at 0°C. After the *in situ* formation of mixed anhydride **95** (1.5 h, monitored by TLC), the reaction mixture was then treated with more Et_3N (2.0 eq.) and $MeO(Me)NH_2Cl$ (1.0 eq.; 5°C, 1.5 h) in order to obtain Weinreb amide **81a** in 98% after aqueous acidic workup and chromatographic purification.[122-124] In analogy, PMB Weinreb amide **81b** and trityl Weinreb amide **81c** were prepared in 88% and 86% yield from PMB protected glycolic acid **82b** and trityl protected glycolic acid **82c**, respectively (Scheme 26).



Scheme 26. Synthesis of Weinreb amide **81** from mixed anhydride **95**.

3.1.1.3 Synthesis of Vinyl Ketone 9

Grignard reaction of Weinreb amide **81a** with vinyl magnesium bromide **80** initially provided vinyl ketone **9d** in very low yields (5-10%) when the reaction mixture was quenched by dropwise addition of 1 molar hydrochloric acid. The major product obtained was the conjugate addition product **96** (Scheme 26).



Scheme 26. Conjugate addition of Weinreb amine to vinyl ketone **9d**.

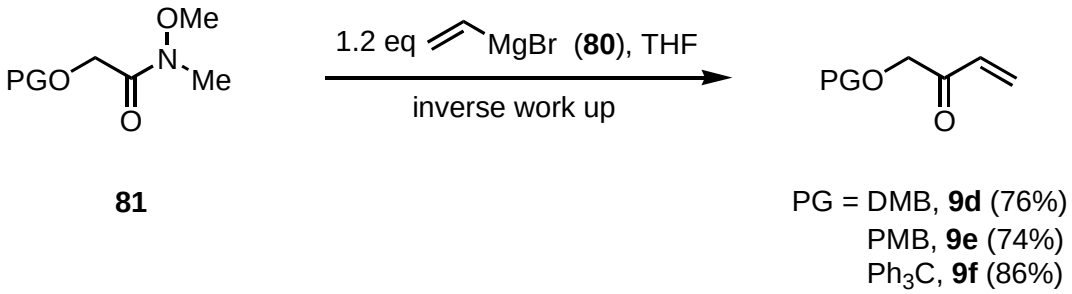
The probable reason for the formation of conjugate addition product **96** in major amounts might be that the liberated *N*,*O*-dimethyl hydroxylamine tends to attack the vinyl ketone **9d** by conjugate addition.[125] In order to trap the expelled *N*,*O*-dimethyl hydroxylamine, the reaction mixture was quenched with acetic anhydride[126] but again **96** was observed in major amounts. The optimal conditions for this reaction were achieved by attempting several work up conditions as well as the amount of vinyl magnesium bromide **80** as shown in Table 3.

Table 3. Attempts to optimize the work up conditions and amount of vinyl magnesium bromide **80**.

80	**t**	**Work up conditions**	**9d**	**96**	**97**
10.0 eq.	1 h	1 mol/l HCl	10%	36%	25%
5.0 eq.	1 h	1 mol/l HCl	15%	40%	15%
3.0 eq.	2 h	1 mol/l HCl	25%	35%	15%
1.2 eq.	4 h	1 mol/l HCl	0%	84%	9%
1.2 eq.	4 h	Ac_2O	10%	60%	8%
1.2 eq.	4 h	AcOH	8%	65%	9%
1.2 eq.	4 h	sat. aq. NH_4Cl	0%	74%	7%
1.2 eq.	4 h	1 mol/l $KHSO_4$	5%	70%	8%
1.2 eq.	4 h	Add rxn. mix. to 1 mol/l HCl	76%	0%	9%

After several optimization conditions, vinyl ketone **9d** was obtained in 76% yield by inverse workup, *i.e*. dropwise transfer of the reaction mixture into an equal volume of 1 molar hydrochloric acid at 0°C (Scheme 27). As vinyl ketone **9d** decomposes within few hours, it is highly recommended to store it by using only

2 mol% hydroquinone as a stabilizer. The success of this reaction was mainly dependent on two important factors: First, the amount of addition of vinyl magnesium bromide in order to subside considerable amounts of divinyl alcohol as a by-product **97** and, secondly, the work up conditions for quenching the reaction mixture to avoid the formation of conjugate addition product **96.** In analogy, PMB vinyl ketone **9e** and trityl vinyl ketone **9f** were obtained in 74% and 86% yield from PMB Weinreb amide **81b** and trityl Weinreb amide **81c** respectively.

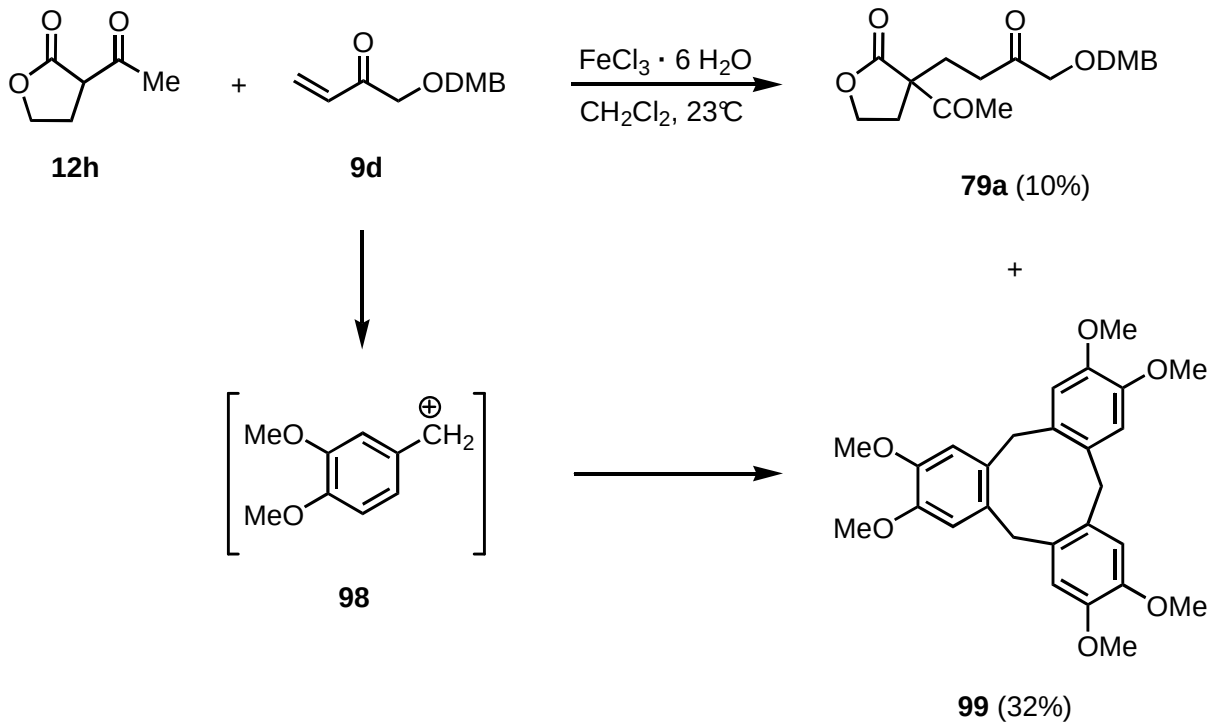


Scheme 27. Synthesis of vinyl ketone derivatives **9**.

3.1.2 Synthesis of Racemic Canangone 19

3.1.2.1 Synthesis of Michael Product 79a Using Lewis Acidic Conditions

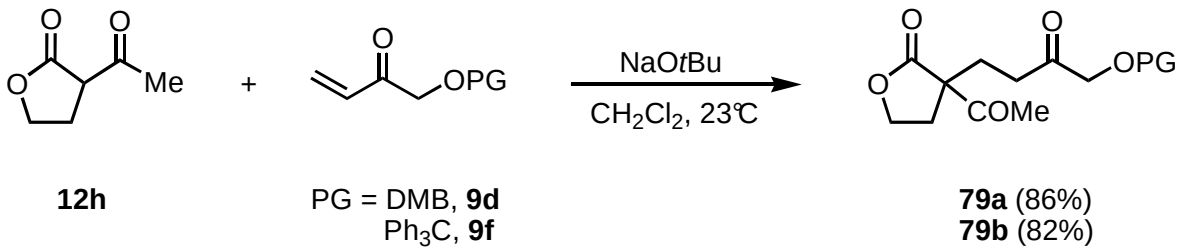
After synthesizing the Michael acceptors **9**, the Michael products **79** were prepared for spiroannulation reactions. The Michael reaction was first attempted using commercially available Michael donor **12h** and Michael acceptor **9d** in presence of catalytic amounts of $FeCl_3 \cdot 6\ H_2O$ (7 mol%).[127] But under these conditions, the yield of the desired Michael product **79a** was very low (10%). Mainly, hexamethoxytribenzocyclononane (trimerized product)[128] **99** was obtained as a by-product in 32% yield (Scheme 28), presumably due to the trimerization of liberated stable benzyl carbenium ion **98** in the presence of Lewis acid.



Scheme 28. Synthesis of Michael product **79a** using $FeCl_3 \cdot 6\ H_2O$ as a Lewis acid.

3.1.2.2 Under Basic Conditions

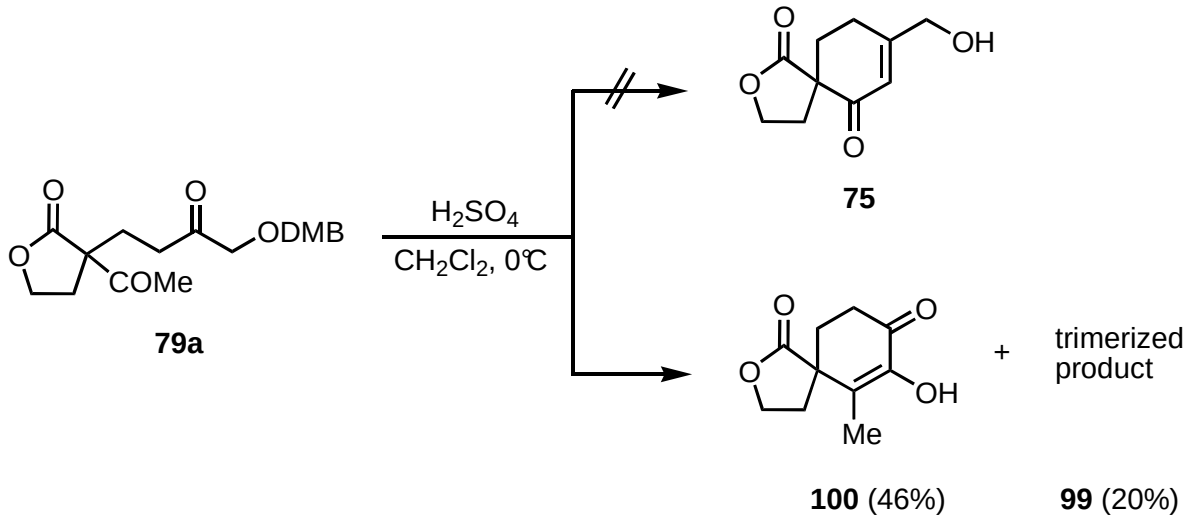
Since the yield of the Michael product **79a** was very low using $FeCl_3 \cdot 6\ H_2O$, the same reaction was carried out under basic conditions. The Michael reaction of vinyl ketone **9d** and α-acetyl butyro lactone **12h** in presence of NaO*t*Bu[127] (5 mol%) at 0°C to 23°C provided the Michael product **79a** in 86% yield (Scheme 29). In analogy, trityl protected Michael product **79b** was obtained in 82% yield from vinyl ketone **9f**.



Scheme 29. Synthesis of Michael product **79** under basic conditions.

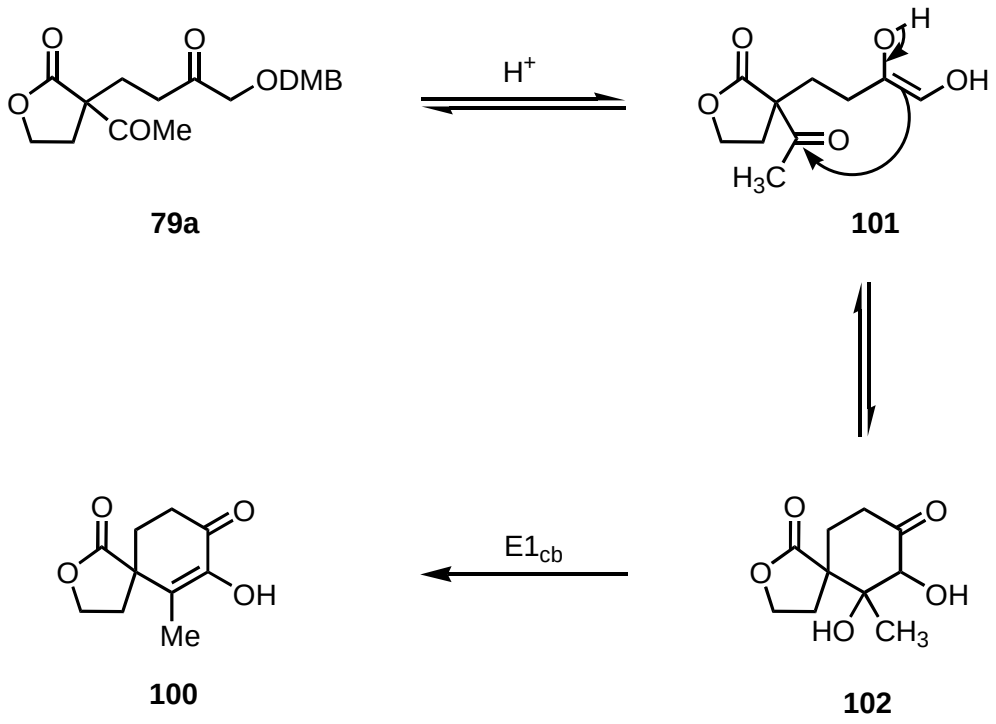
3.1.2.3 Regioselective Spiroannulations Using Acidic Conditions

Following the protocol developed by our group, the cyclization of the Michael product **79a** was tried under acidic conditions (conc. H_2SO_4)[127] in order to obtain the desired spirolactone **75**. But unfortunately, spirolactone **100** was obtained in 46% yield along with the trimerized product **99**[128] (Scheme 30).



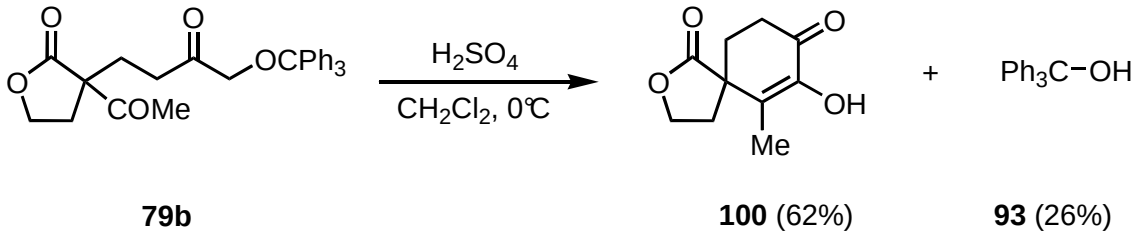
Scheme 30. Attempted synthesis of spirolactone **75**.

The formation of spirolactone **100** instead of **75** can be explained based on the enolization at the protected hydroxy acetyl group in compound **101** rather than at the acetyl group, which undergoes the aldol reaction followed by $E1_{cb}$ elimination of newly obtained alcohol **102** to afford spirolactone **100** (Scheme 31).



Scheme 31. Mechanism for the formation of spirolactone **100**.

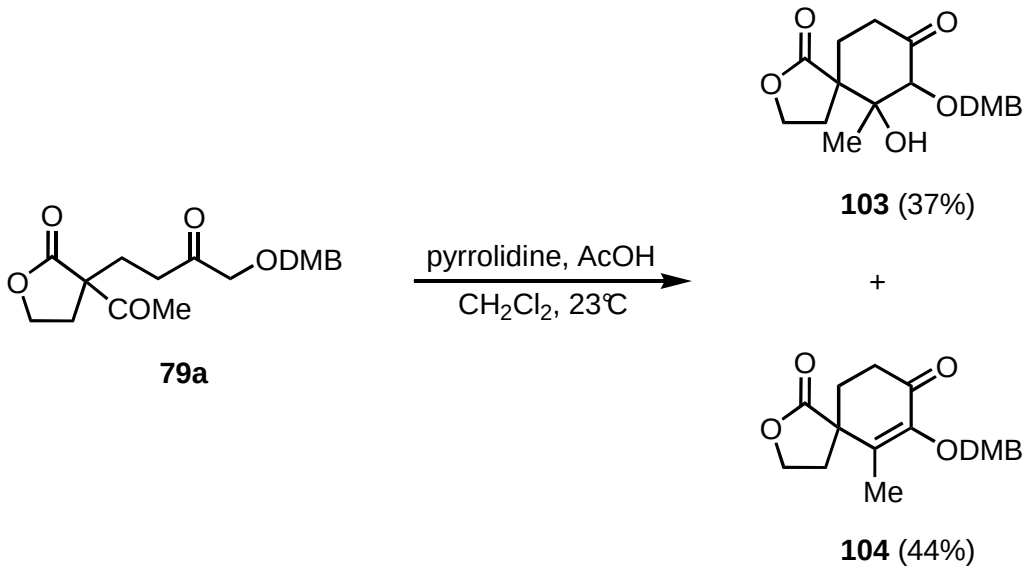
The spirocyclization was also tried with trityl protected Michael product **79b** assuming that the bulky phenyl groups might avoid the enolization at the protected hydroxy acetyl group due to steric hindrance and allowing the enolization at acetyl group. But even in this case only the undesired spirolactone **100** was obtained as a major product in 62% yield along with trityl alcohol **93** in 26% yield (Scheme 32).



Scheme 32. Spiroannulation using trityl protected Michael product **79b**.

3.1.2.4 Using Buffered Conditions

The spirolactone formation with DMB protected Michael product **79a** was also tried in buffered conditions (pyrrolidine/AcOH)[127] in order to check the feasibility of desired cyclization. Even under these conditions enolization was occuring at protected hydroxy acetyl group rather than at the acetyl group, which provided the mixture of spirolactones **103** and **104** in 37% and 44% yield respectively (Scheme 33). The same spirocyclization with trityl protected Michael product **79b** was also tried under buffered conditions (pyrrolidine/AcOH) in CH_2Cl_2 and toluene at 23°C, but only the starting material was observed on GC-MS even after 24 h. At higher temperatures only decomposed materials were detected.

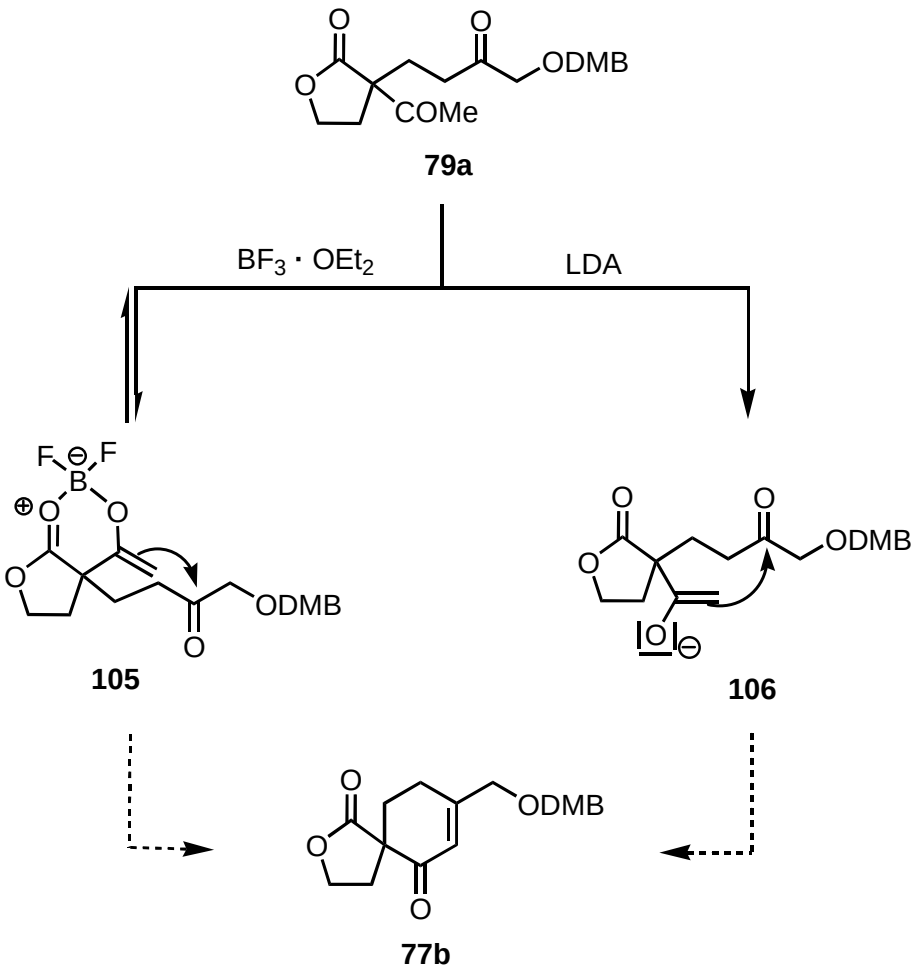


Scheme 33. Attempted synthesis of spirolactone **77b** in buffered conditions.

3.1.2.5 Using Lewis Acidic or LDA Conditions

Assuming that both Lewis acidic as well as the strong and hindered basic conditions generate the enolate at the acetyl group rather than at the protected hydroxy acetyl group, the spirocyclizations were also carried out under $BF_3 \cdot OEt_2$

and LDA conditions (Scheme 34). But none of them provided the desired product **77b**. With DMB protected Michael product **79a**, trimerized product **99** was obtained exclusively in 41% yield in presence of $BF_3 \cdot OEt_2$ and complex mixtures were obtained with no detection of desired product mass by GC-MS analysis under basic (LDA) conditions.

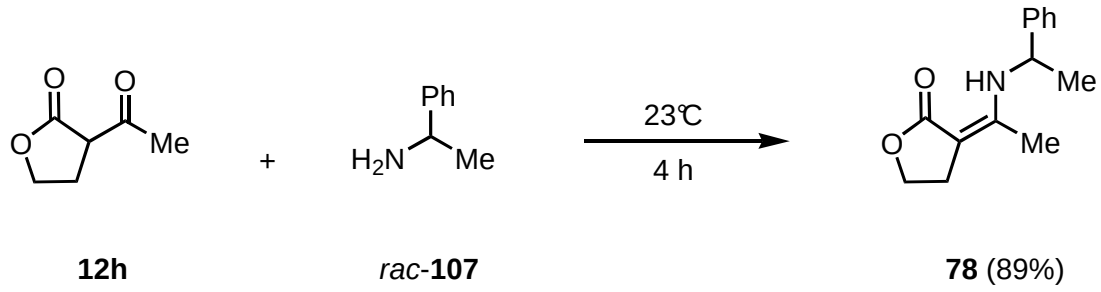


Scheme 34. Probable pathway for the synthesis of spirolactone **77b**.

Since all the attempted conditions for the synthesis of desired spiroannulated products **75** or **77** yielded either the regiomers of them or decomposition products, an enamine strategy was planned by following the Pfaus' procedure[129] who applied a method developed by Angelo *et al*.[130-135]

3.1.2.6 Spiroannulations Using Enaminolactone 78

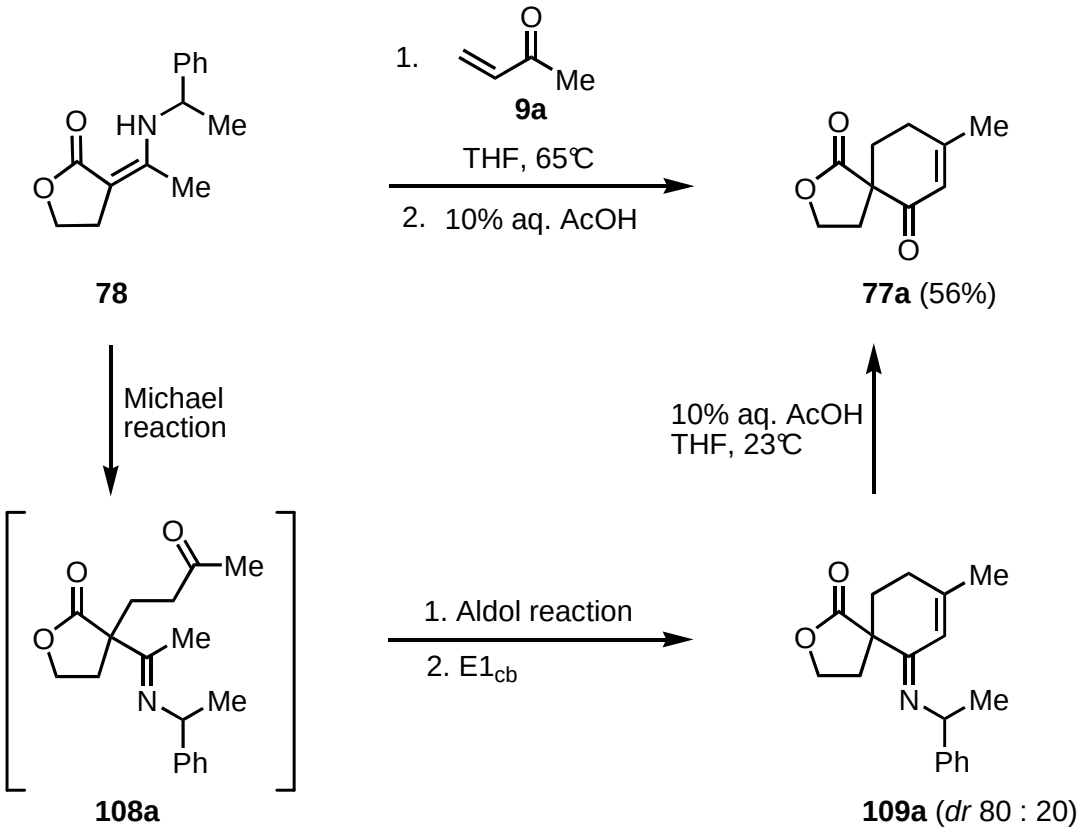
Before applying this method directly to our synthetic strategy, a model study was planned to check the feasibility of the spiroannulation process. The synthesis of model compound **77a** was started with commercially available α-acetylbutyrolactone **12h** and *rac*-phenylethylamine **107**. Both the compounds **12h** and **107** were mixed and stirred together at 23°C for 4 h to afford pure secondary enamine lactone **78** in 89% yield. GC, ^{1}H and ^{13}C-NMR of enaminolactone **78** showed the presence of a single isomer. A low field chemical shift at 8.61 ppm in the ^{1}H-NMR spectrum showed the presence of a hydrogen bonded N-H group, which determines the enamine lactone **78** to be the *Z*-isomer (Scheme 35).



12h *rac*-**107** **78** (89%)

Scheme 35. Synthesis of enamino lactone **78**.

The Michael reaction was performed in THF at 65°C for 18 h using methyl vinyl ketone **9a** (1.0 eq.) as a Michael acceptor and enaminolactone (1.0 eq.) **78** as a Michael donor. This Michael reaction did not stop at the stage of conjugate addition product **108a**, but proceeded further to give a spirocyclic imine **109a** by virtue of an imine-enamine tautomerism allowing an intramolecular aldol reaction directly followed by an $E1_{cb}$ process to provide spirolactone **77a** (Scheme 36).



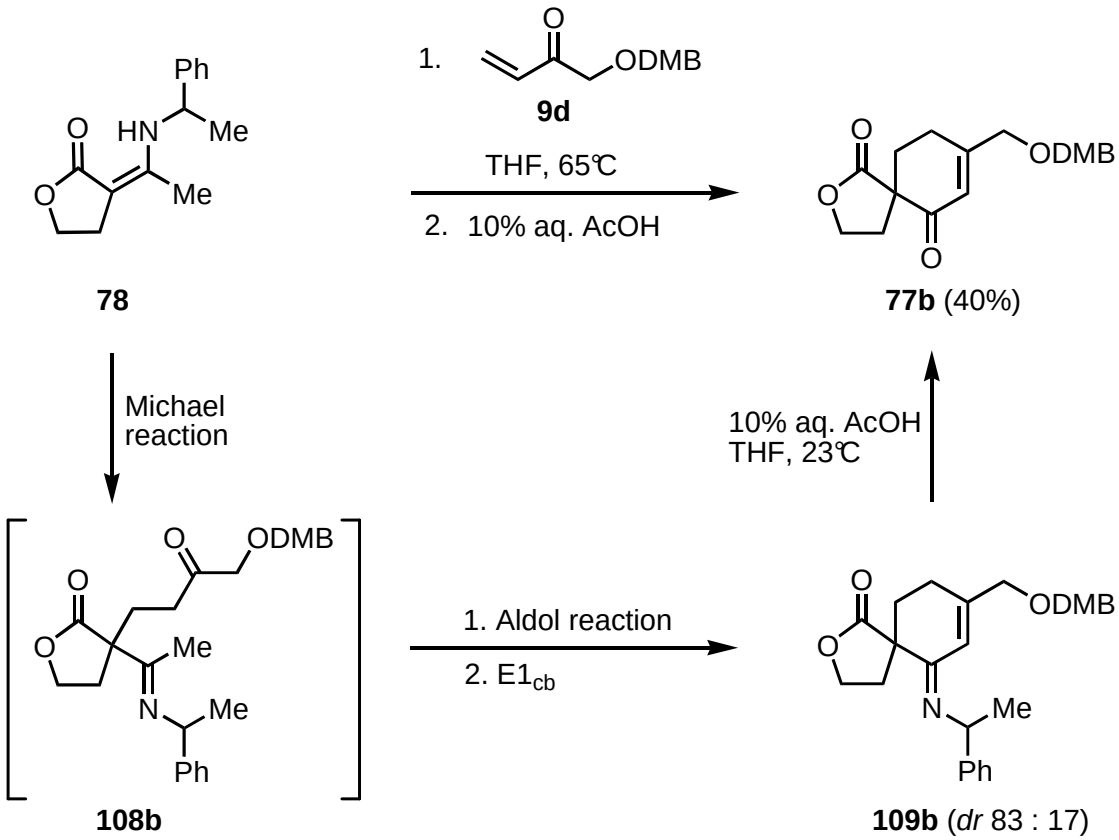
Scheme 36. Synthesis of spirolactone **77a**.

Based on the ^{1}H-NMR, the diastereomeric ratio of the spirocyclic imine **109a** was found to be 80 : 20 by integration of the two separate sp^2-CH resonances. An important point to be noticed in this reaction is the diastereomeric ratio of the imine **109a**. Pfau *et al.*[129] reported the same reaction with 93 : 7 diastereomeric ratio, but in our case only 80 : 20 *dr* was observed even after repeating the reaction for several times.

Attempt to purify spirocyclic imine **109a** by column chromatography on silica or on Al_2O_3 yielded only decomposed materials. Therefore, without further purification, the imine **109a** was subjected for hydrolysis using 10% aq. acetic acid (2 eq.) in THF at 23°C for 24 h. After work up and chromatographic purification, pure spirolactone **77a** was obtained in 56% yield.

3.1.2.7 Synthesis of *rac*-Spirolactone 77b Using Enaminolactone 78

With the optimized conditions for model study, synthesis of the spirolactone **77b** was performed in a similar manner. The whole synthesis was carried out using *rac*-phenylethylamine **107** in order to synthesize (±)-Canangone. The Michael reaction was performed using enaminolactone **78** (1.1 eq.) and methyl vinyl ketone derivative **9d** (1.0 eq.) in THF at 65°C. The Michael reaction did not stop at the stage of conjugate addition product **108b** but proceeded further to give a spirocyclic imine **109b** (Scheme 37). Since it was very difficult to monitor the reaction on TLC (due to the formation of many spots), aliquots from the reaction mixture were taken and submitted to ^{1}H-NMR for every 4 h in order to check the complete consumption of vinyl ketone **9d**.



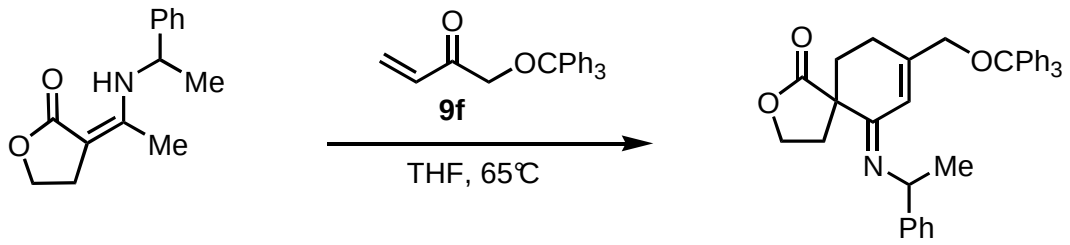
Scheme 37. Synthesis of spirolactone **77b**.

After completion of the reaction (18 h), the solvent was removed under reduced pressure and attempts to purify the residual imine **109b** by column chromatography using silica or Al_2O_3 completely failed. Only the decomposed products were detected on TLC. Therefore the diastereomeric ratio of this reaction was determined from the crude product itself, which showed 83:17 by integration of the two separate sp^2-CH resonances in the ^{1}H-NMR. The imine **109b** was subjected for hydrolysis without any further purification in order to obtain spirolactone **77b** in 40% yield. The reason for the low yield of an overall reaction is the cleavage of 3,4-dimethoxy benzyl group during the reaction and the 3,4-dimethoxy benzyl alcohol was isolated in 18% yield after chromatographic purification of the hydrolysis step. But, unfortunately the isolation of deprotected spirolactone **75** became impossible.

3.1.2.8 Attempted Synthesis of Spirolactone 77c from Enaminolactone 78

Since the yield was not satisfying with 3,4-dimethoxy benzyl as the protecting group (due to its cleavage under the reaction conditions), spirocyclization was tried with the stable trityl protected methyl vinyl ketone derivative **9f**.

The Robinson annulation was performed using enaminolactone **78** (1.1 eq.) and methyl vinyl ketone derivative **9f** (1.0 eq.) in THF at 65°C. Although the diastereomeric ratio of this reaction was high [(91 : 09), Scheme 38], the hydrolysis of imine **109c** using 10% aq. AcOH failed completely. To our surprise, no sp^2-CH peak was observed in the ^{1}H-NMR spectrum after the hydrolysis. Attempts to cleave the imine **109c** in different hydrolysis conditions (10% HCl, 10% HCO_2H, 10% TFA, 10% TosOH, 10% H_2SO_4) led to complex mixtures.

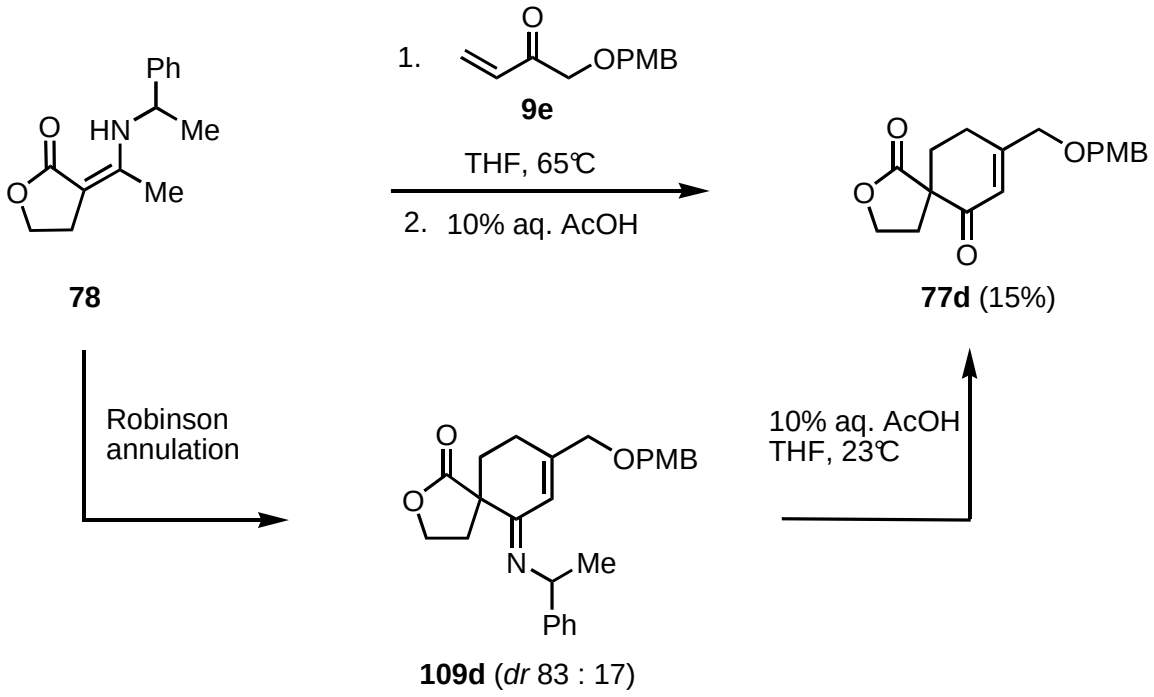


78 **109c** (*dr* 91 : 09)

Scheme 38. Synthesis of spirocyclic imine **109c**.

3.1.2.9 Synthesis of Spirolactone 77d from Enaminolactone 78

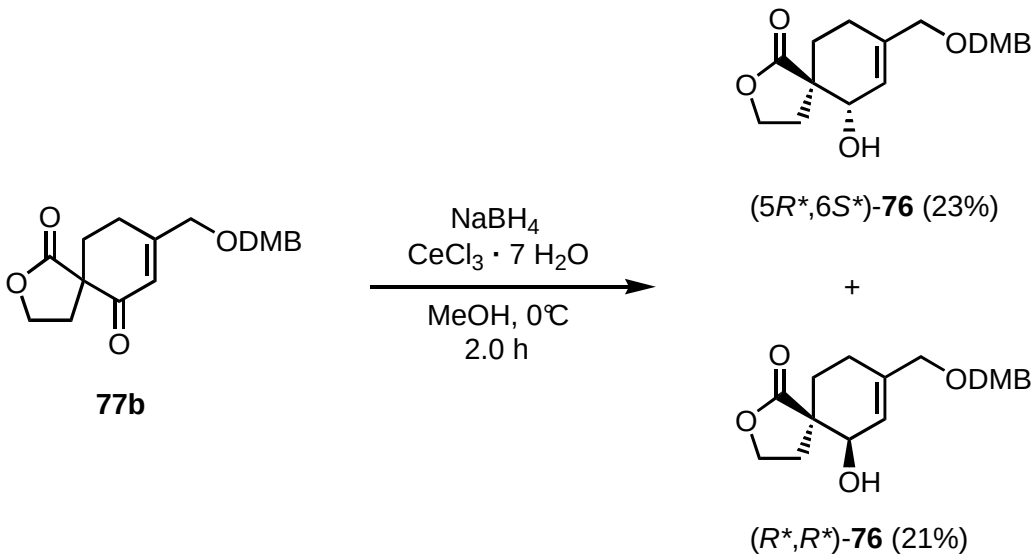
As several problems were faced in cleaving the imine in spirocyclic compound **109c**, the spiroannulation was also tried with relatively stable PMB protecting group inorder to improve the yield of spirocyclic ketone **77d**. The synthesis of spirolactone **77d** was achieved using enaminolactone **78** (1.1 eq.) and methyl vinyl ketone derivative **9e** (1.0 eq.) in THF at 65°C. The diastereomeric ratio of spirocyclic imine **109d** was found to be 83 : 17, same as that of imine **109b**, but the yield of the hydrolysis product **77d** was very low (15% yield) with 41% being the cleaved 4-methoxy benzyl alcohol (Scheme 39). Even though the yield of the spirolactone **77b** was relatively low, the synthesis of Canangone was forced to be continued using spirolactone **77b**, since the other protecting groups showed either problematic in the hydrolysis step or provided the desired spirolactone in very low yield (15%).



Scheme 39. Synthesis of spirolactone **77d**.

3.1.2.10 Luche Reduction of Spirolactone 62a

The Luche reduction was first attempted on spirolactone **77b** using $CeCl_3 \cdot 7\ H_2O$ (1.05 eq.) and $NaBH_4$ (1.05 eq.) in MeOH at 0°C to obtain alcohol **76** in 44% yield with almost 1 : 1 diastereomeric ratio. As both diastereomers did not resolve on TLC, a long bed of silica (ca. 20 cm) was used in order to purify the nonpolar isomer (5*R*,6S**)-**76** and polar isomer (*R*,R**)-**76**. The yields of these two diastereoisomers were obtained in 23% and 21% respectively (Scheme 40).



Scheme 40. Luche reduction of protected spirolactone **77b**.

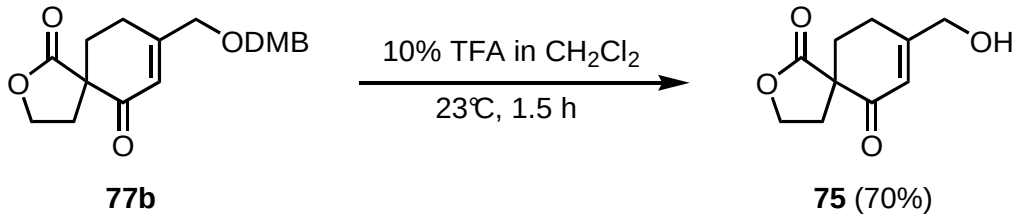
The reaction was also carried out at different temperatures in order to improve the diastereoselectivity of the reaction. When the reaction was carried out at –78°C, the reaction mixture got solidified and further stirring at the same temperature or at elevated temperatures (up to –40°C) became difficult. At 23°C, the diastereoselectivity remained almost same as that of 0°C. But at higher temperature (40°C) the reaction mixture got decomposed. Attempts were also made to improve the yield of the Luche reduction by changing the stoichiometric ratios of the reagents, but none of them were successful in giving the better yields (Table 4). As the yield of this reaction was not satisfying, the deprotection of 3,4-dimethoxy benzyl (DMB) group of alcohol **76** was not attempted, rather another pathway was opted, *i.e* first, the deprotection of DMB group and later, the Luche reduction.

Table 4. Attempted stoichiometric ratios of the reagents for Luche reduction.

$CeCl_3 \cdot 7\ H_2O$	$NaBH_4$	T	Yield
1.05 eq.	1.05 eq.	0°C	44%
		23°C	42%
3.0 eq.	3.0 eq.	0°C	39%
		23°C	40%
3.2 eq.	1.5 eq.	0°C	42%
		23°C	40%
6.0 eq.	1.5 eq.	0°C	38%
		23°C	39%

3.1.2.11 Deprotection of the 3,4-Dimethoxy Benzyl Group of Spirolactone 62a

The deprotection of the 3,4-dimethoxy benzyl group of spirolactone **77b** was first tried using conc. H_2SO_4, as these conditions already proved to be successful in deprotecting the 3,4-dimethoxy benzyl group during the acidic cyclization to provide regioisomer **100**. But unfortunately in this reaction, only trace amount (4%) of the desired product **75** was isolated**,** the major being the trimerized product **99** in 40% yield. The deprotection of the DMB group was also attempted with trifluoroacetic acid (1 eq.), but in this case too the yield of the spirolactone **75** was low (18%). Finally, the deprotection under diluted conditions of TFA (10% TFA in CH_2Cl_2, 23°C, 1.5 h][136] gave deprotected spirolactone **75** in 70% yield with minor amounts (7%) of trimerized product **99**[128] (Scheme 41) after chromatographic purification.

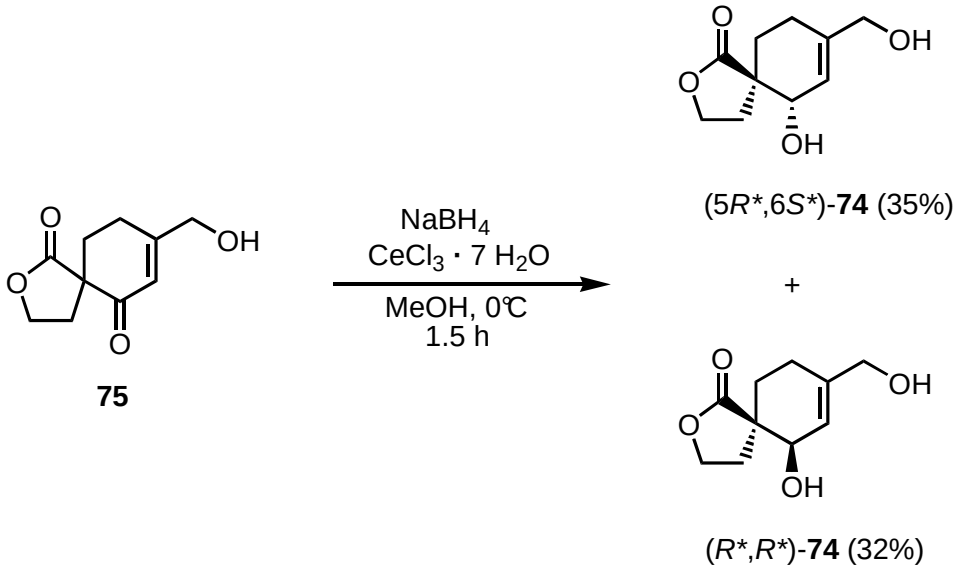


77b **75** (70%)

Scheme 41. Synthesis of deprotected spirolactone **75**.

3.1.2.12 Selective Reduction of Enone 75 Using Luche Reduction

After synthesizing enone **75,** Luche reduction was performed using $CeCl_3 \cdot 7\ H_2O$ (1.05 eq.) and $NaBH_4$ (1.05 eq.) in MeOH at 0°C. The reaction was complete within 1.5 h to give diol **74** in 67% yield with no diasteroselectivity (Scheme 42). In order to improve the diastereoselectivity of **74**, the reaction was carried out at –78°C. But at this temperature the dissolution problem occurred. At higher temperatures (above 23°C) only decomposed materials were detected on TLC. Therefore the reaction at 0°C was opted, eventhough there was no diastereoselectivity.



75 (5*R**,6*S**)-**74** (35%)

(*R**,*R**)-**74** (32%)

Scheme 42. Synthesis of diol (5*R**,6*S**)-**74** and (*R**,*R**)-**74**.

The two diastereoisomers however could be easily separated by column chromatography to give the non polar isomer (5*R**,6*S**)-**74** as a colorless solid in 35% yield and the polar isomer (*R**,*R**)-**74** as a colorless oil in 32% yield. As the non polar isomer (5*R**,6*S**)-**74** was obtained in solid form, single crystals could be grown from EA–pentane at 23°C for X-ray crystal structure analysis to prove the relative configuration. The relative configuration was confirmed to be (5*R**,6*S**) as shown in Figure 4.

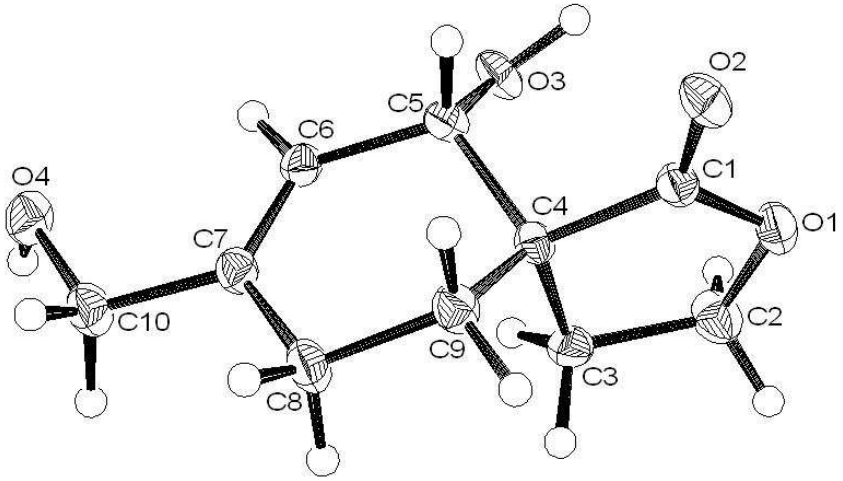
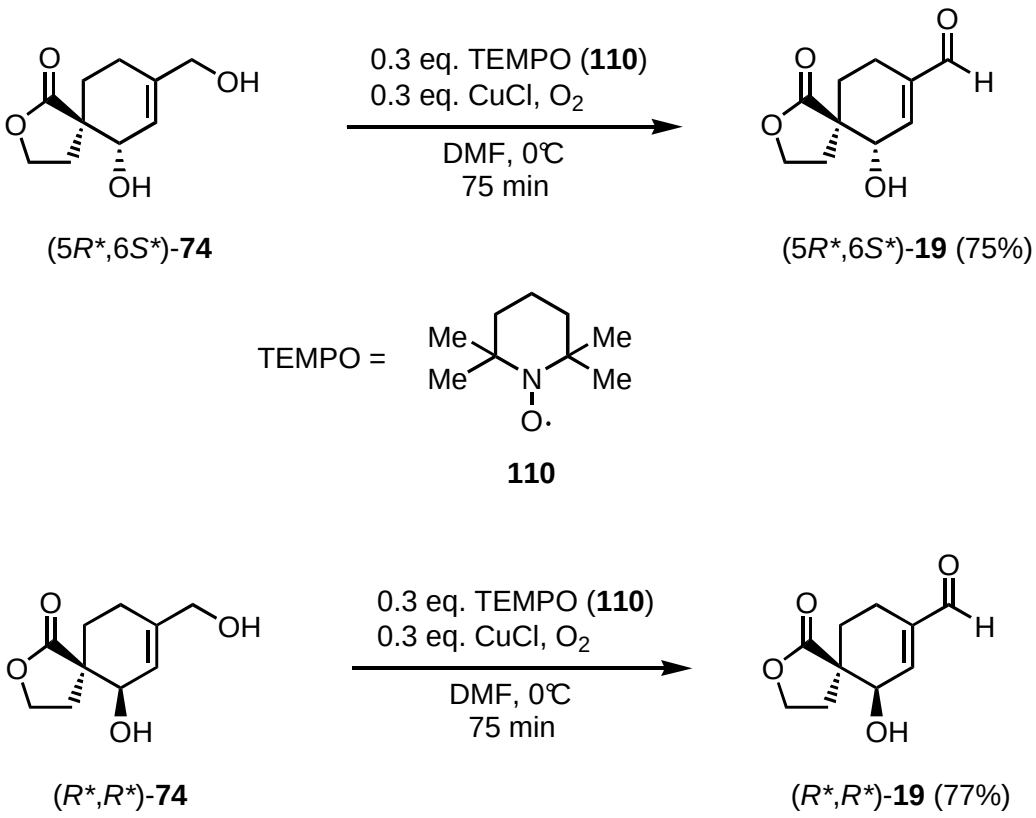


Figure 4. ORTEP view of racemic diol (5*R**,6*S**)-**74**.

3.1.2.13 Selective Oxidation of Diol (5*R**,6*S**)-74 and (*R**,*R**)-74

The selective oxidation was performed on individual diols, (5*R**,6*S**)-**74** and (*R**,*R**)-**74**, using cat. TEMPO **110** and CuCl (both 0.3 eq., 1 atm O_2, DMF, 23°C, 75 min)[137] which afforded the oxidation products (5*R**,6*S**)-**19** and (*R**,*R**)-**19** in 75% and 77% yield respectively (Scheme 43).



Scheme 43. Selective oxidation of (5*R**,6*S**)-**74** and (*R**,*R**)-**74**.

After the successful synthesis of the final products (5*R**,6*S**)-**19** and (*R**,*R**)-**19**, the ^{1}H and ^{13}C-NMR values were compared with that of the naturally occurring Canangone **19**.[48] The ^{13}C-NMR data of natural Canangone **19** and synthetic Canangones *i.e.* (5*R**,6*S**)-**19** and (*R**,*R**)-**19** are shown in Table 5. Based on the ^{1}H and ^{13}C-NMR values, the data of (*R**,*R**)-**19** was matching with that of the isolated (+)-Canangone **19** and the other isomer (5*R**,6*S**)-**19** being the epimer of it.

Table 5. Comparison of ^{13}C-NMR values of (5*R**,6*S**)-**19** and (*R**,*R**)-**19** with the natural (+)-Canangone **19**.

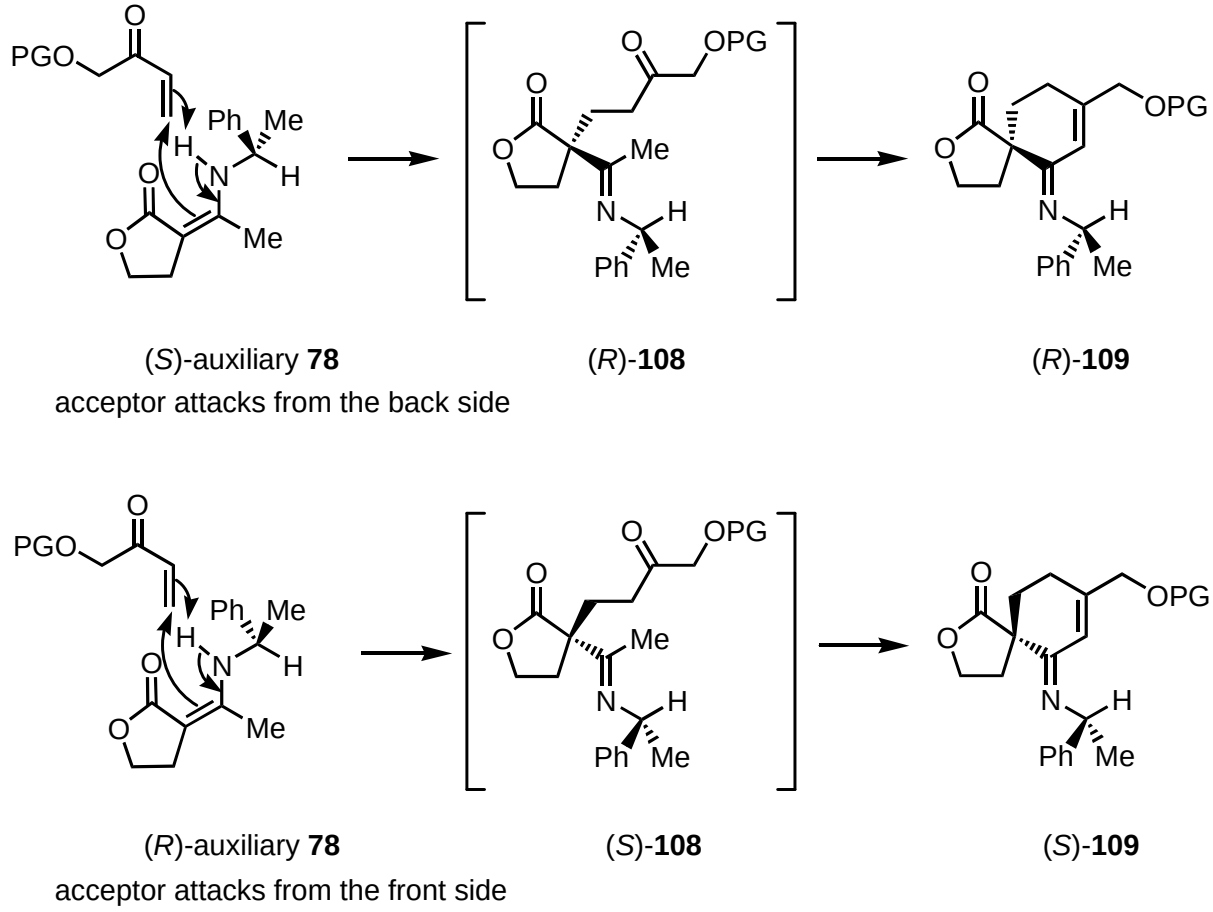
C	Natural Canangone-**19** δ ^{13}C (ppm)	(5*R**,6*S**)-**19a** δ ^{13}C (ppm)	(*R**,*R**)-**19** δ ^{13}C (ppm)
1	178.28	181.10	178.31
3	65.45	66.77	65.40
4	32.25	27.49	32.21
5	46.65	48.22	46.61
6	69.38	70.27	69.35
7	142.12	140.81	142.07
8	145.83	149.65	145.81
9	18.69	18.48	18.66
10	25.63	26.05	25.99
11	193.24	192.92	193.20

3.1.3 Synthesis of Optically Active Canangone 19

According to the structure proposed by Caloprisco *et al.*, the quaternary center of spirolactone is assumed to be *R*-configurated. The important criterion for synthesizing the optically active Canangone **19** is the chiral auxiliary, which creates the enantiomerically pure quaternary stereocenter of spirolactone **77b**. According to Pfau and Angelo *et al.*[129-135] the (*S*)-phenyl ethyl amine was supposed to be chosen in order to create (*R*)-configuration at the quaternary stereocenter of the spirocycle.

An aza-ene type mechanism was proposed for this type of reaction. In the case of the (*S*)-configured auxiliary, the phenyl group shields the front face and the acceptor attacks from the back giving the quaternary stereocenter as (*R*)-configu-

ration as shown in Scheme 44. In a similar way, the (*R*)-configured auxiliary affords the opposite product configuration.

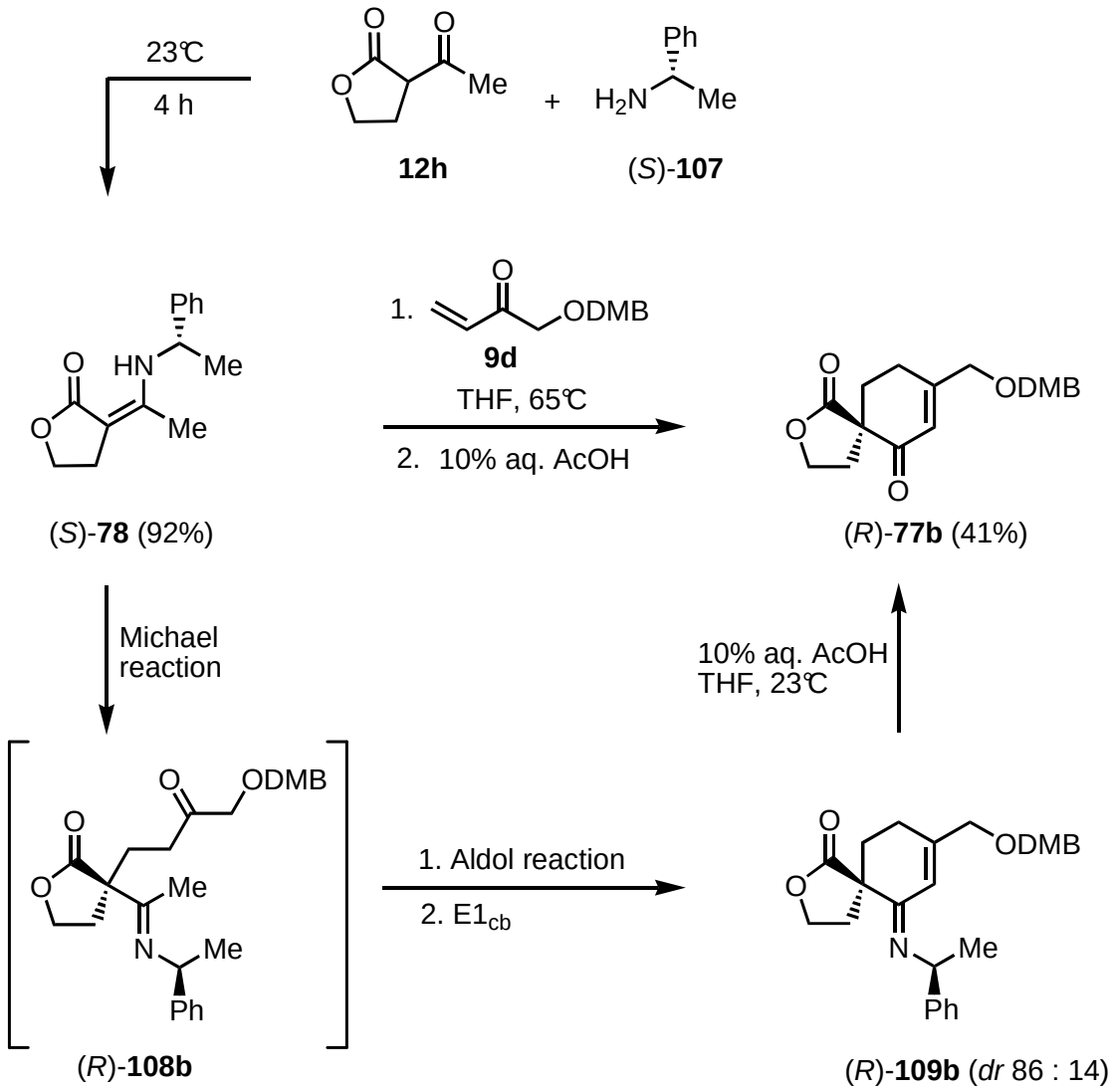


Scheme 44. Proposed model for the stereochemistry at the quaternary carbon using phenyl ethyl amine.

3.1.3.1 Synthesis of Optically Active Spirolactone 77b

The synthesis of optically active spirolactone **77b** was started with γ-butyro lactone **12h** and (*S*)-phenyl ethyl amine (*S*)-**107** to obtain enaminolactone (*S*)-**78** in 92% yield. The Michael addition of enamine lactone (*S*)-**63** and methyl vinyl ketone derivative **9d** gave *in situ* a Michael adduct (*R*)-**108b**, which was then spontaneously converted to spirocyclic imine (*R*)-**109b** with a diastereomeric ratio

of 86 : 14. The hydrolysis of the spirocyclic imine (*R*)-**109b** using 10% aq. AcOH provided the spirolactone (*R*)-**77b** in 41% yield (Scheme 45).

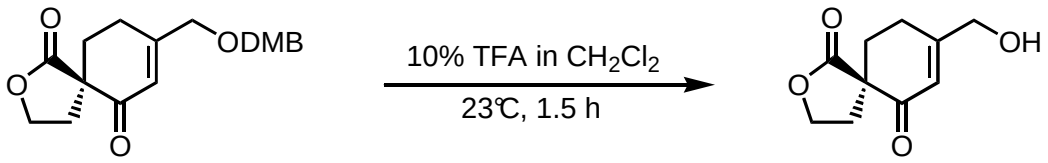


Scheme 45. Synthesis of spirolactone (*R*)-**77b**.

3.1.3.2 Synthesis of Optically Active Spirolactone 75

The deprotection of 3,4-dimethoxy benzyl group of spirolactone (*R*)-**77b** was carried out in the presence of 10% TFA in CH_2Cl_2 at 23°C to obtain allylic alcohol (*R*)-**75** in 72% yield (Scheme 46). Since the allylic alcohol (*R*)-**67** gave sufficient baseline resolution at this stage on GLC at a chiral phase, the stereoselectivity of

the Michael reaction was determined to be 60% *ee* being sensitive to the reaction conditions.



(*R*)-**77b** (*R*)-**75** (72%)

Scheme 46. Synthesis of allylic alcohol **75**.

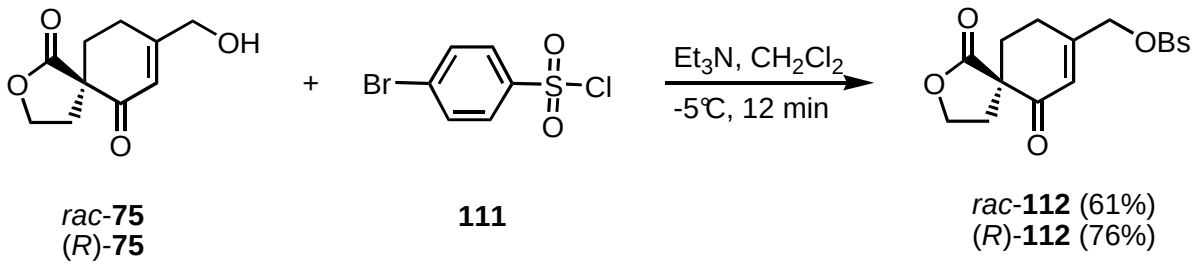
3.1.3.3 Brosylation of Spirolactone 75

In order to check the absolute configuration at the quaternary stereocenter, attempts were made to convert spirolactone (*R*)-**75** to brosylate (*R*)-**112** using different conditions as shown in the Table 6.

Table 6. Reaction conditions for brosylation of spirolactone (*R*)-**75**.

111	base	T	t	yield
1.5 eq.	pyridine (10 eq.)	0°C	4 h	–
1.2 eq.	pyridine (5 eq.)	23°C	16 h	–
1.2 eq.	Et_3N (1.5 eq.)	23°C	16 h	11%
1.2 eq.	Et_3N (1.5 eq.)	0°C	4 h	25%
1.1 eq.	Et_3N (1.5 eq.)	–5°C	1 h	48%
1.1 eq.	Et_3N (1.5 eq.)	–5°C	12 min	76%

Finally the spirolactone (*R*)-**75** was successfully converted to brosylate (*R*)-**112** using brosyl chloride **111** (1.1 eq.) and Et_3N (1.5 eq.) in CH_2Cl_2 at –5°C for 12 min[138] in 76% yield (Scheme 47).



rac-**75**
(*R*)-**75**

111

rac-**112** (61%)
(*R*)-**112** (76%)

Scheme 47. Synthesis of brosyl derivative (*R*)-**112** for determination of the absolute configuration.

The solid obtained from the brosylate (*R*)-**112** was then crystallized using CH_2Cl_2-pentane as a solvent mixture for the crystal structure analysis. The X-ray crystal structure (Figure 5) proved the configuration at quaternary center to be (*R*) as predicted by Pfau and Angelo *et al*.[129-135] The bromine and sulfur atom in this compound allowed for anomalous dispersion giving the (*R*)-configuration with an absolute structure parameter[139] of –0.009(5). The racemate of **112** was obtained as an oil.

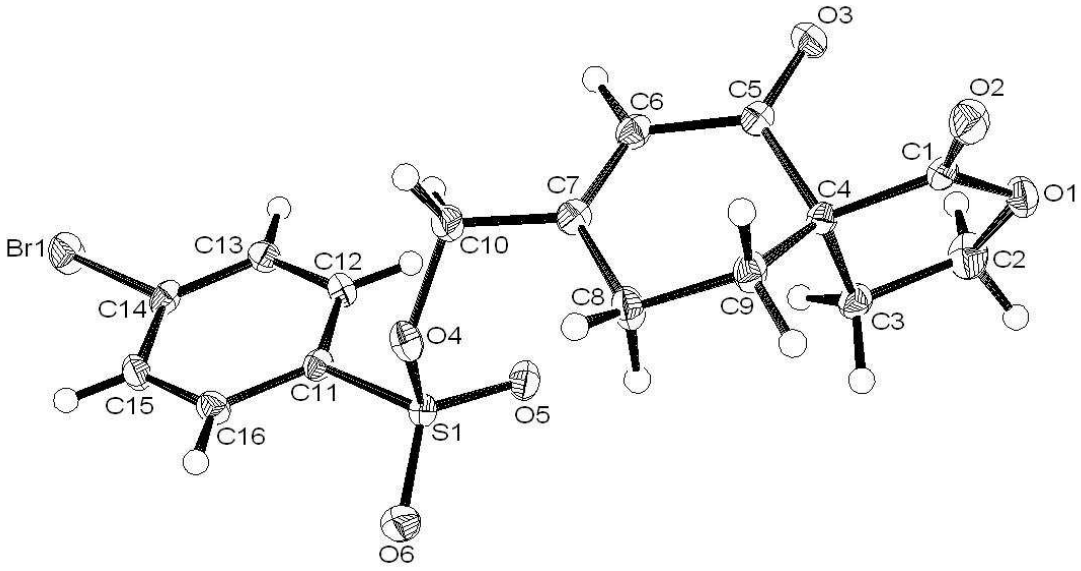
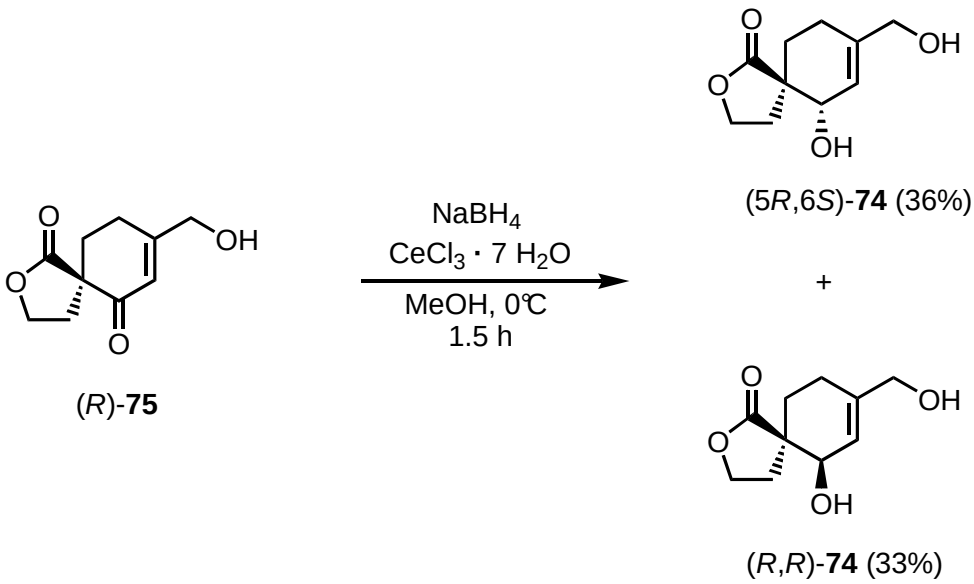


Figure 5. ORTEP view of optically active bromosulfonate **112**. The depicted enantiomer has (*R*)-configuration.

Although the stereochemistry of the quarternary stereocenter of brosylate **112** in the crystal structure anaylsis matched with the literature precedence, another experiment was carried out inorder to make sure that the right crystal was chosen for X-ray structure analysis (as the enantiomeric excess of the spirolactone was only 60%). Since the brosylate **112** was not compatible to GC-analysis, its crystalline material was taken and subjected for deprotection in batches (4 x 9 mg) by using KOH in methoxy ethanol. The obtained spirolactone **75** was then sumitted for GC analysis, which proved the right stereochemistry (*R*) in all the batches (almost 90% *ee*).

3.1.3.4 Synthesis of Optically Active Diol 74

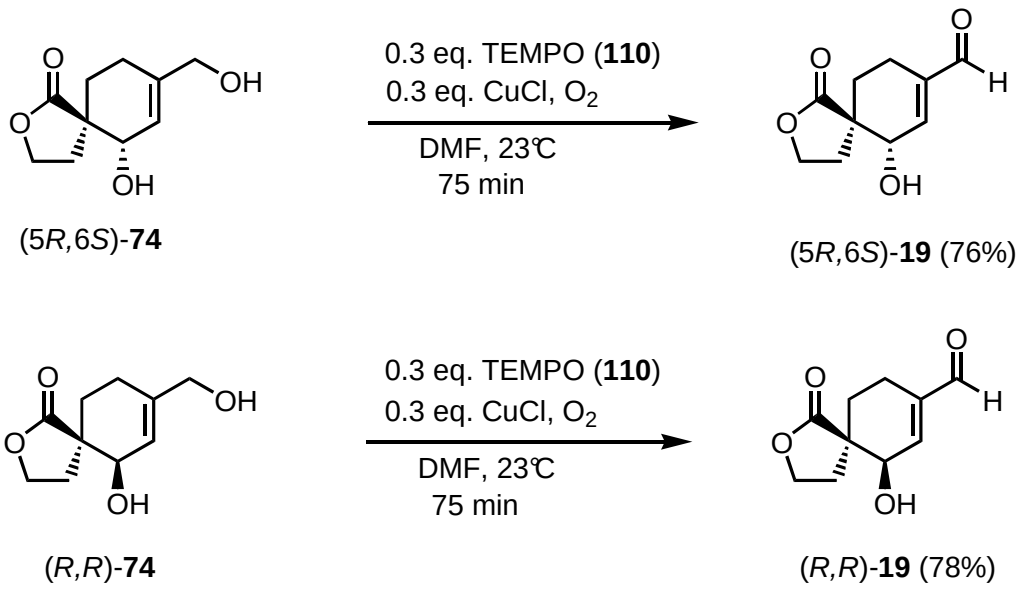
Luche reduction was performed on allylic alcohol (*R*)-**75** using $CeCl_3 \cdot 7\ H_2O$ (1.05 eq) and $NaBH_4$ (1.05 eq) in MeOH to obtain two diastereomeric diols (5*R*,6S)-**74** and (*R*,*R*)-**74** in 36% and 33% yield respectively (Scheme 48).



Scheme 48. Luche reduction to give products (5*R*,6S)-**74** and (*R*,*R*)-**74**.

3.1.3.5 TEMPO Oxidation of (5*R*,6S)-74 and (*R*,*R*)-74

After synthesizing the reduction products (5*R*,6S)-**74** and (*R*,*R*)-**74**, selective oxidation was performed individually on these two diols, using cat. TEMPO (**110**) and CuCl (each 0.3 eq.), 1 atm. oxygen in DMF at 23°C to provide aldehydes (5*R*,6S)-**19** and (*R*,*R*)-**19** in 76% and 78% yield respectively (Scheme 49).



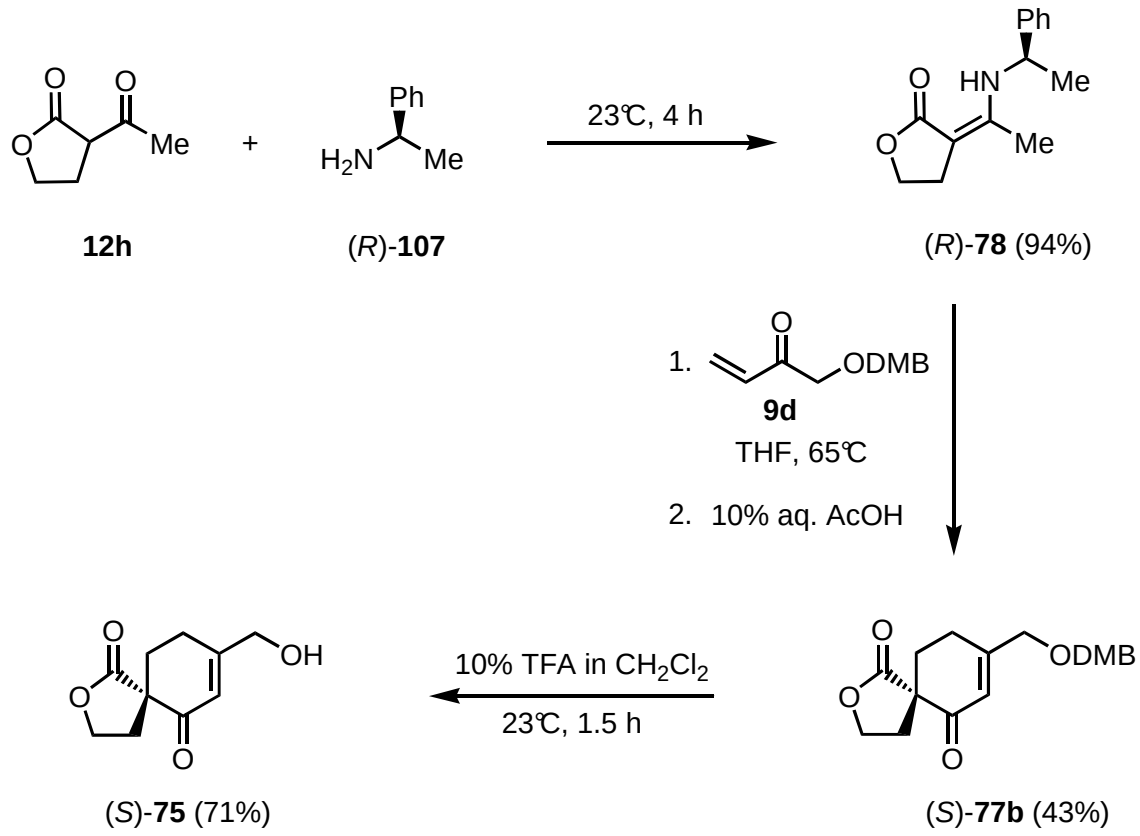
Scheme 49. Synthesis of aldehyde (5*R*,6S)-**19** and (*R*,*R*)-**19**.

After completing the synthesis of aldehydes (5*R*,6S)-**19** and (*R*,*R*)-**19**, the ^{1}H and ^{13}C-NMR values were compared with the isolated Canangone **19**. Like in racemic Canangone **19**, only aldehyde (*R*,*R*)-**19** data was matching to that of isolated Canangone. But after measuring the optical rotation, it proved that (*R*,*R*)-**19** ($[\alpha]_D^{25}$ = –67.0°) is the enantiomer of the originally isolated natural product ($[\alpha]_D^{25}$ = +58.8°).[48]

3.1.4 Optically Active Synthesis of (*S*,*S*)-Canangone

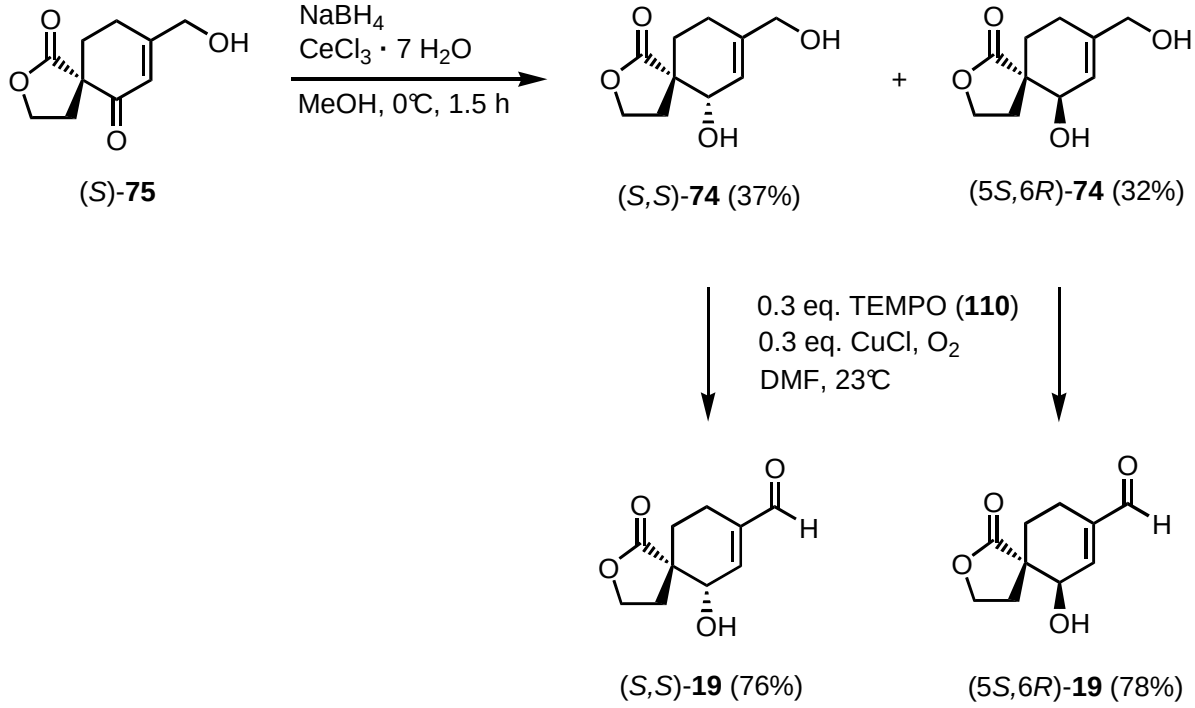
The synthetic steps were repeated using (*R*)-phenyl ethyl amine **107** as the chiral auxiliary to achieve (*S*,*S*)-Canangone. (*R*)-enaminolactone **78** was prepared from α-acetylbutyro lactone **12h** and (*R*)-phenyl ethyl amine **107** in 94% yield. Subsequent Michael reaction with methyl vinyl ketone derivative **9d** gave spirolactone (*S*)-**77b** in 43% yield (Scheme 50). The cleavage of the protective group in spirolactone (*S*)-**77b** (10% TFA in CH_2Cl_2, 23°C, 1.5 h) gave primary alcohol (*S*)-**75** in 71% yield. Since allylic alcohol (*R*)-**75** gave sufficient baseline resolution at this stage on GLC at a chiral phase, the stereoselectivity of the

Michael reaction was determined to be 69% *ee* being sensitive to the reaction conditions.



Scheme 50. Synthesis of (S)-**75** from enaminolactone (R)-**78**.

Luche reduction was performed on primary alcohol (*S*)-**75** to yield two diastereoisomers of allylic alcohols (5*S*,6*R*)-**75** and (*S*,*S*)-**74** in 32% and 37% yield respectively, which were easily separated by column chromatography. The primary alcoholic functional groups of both diastereoisomers of **74** were selectively oxidized using cat. TEMPO (**110**) and CuCl (both 0.3 eq., 1 atm O_2, DMF, 23°C, 75 min) to furnish both (5*S*,6*R*)-**19** and (*S*,*S*)-**19** in 78% and 76% yield respectively (Scheme 51).



Scheme 51. Synthesis of (*S*,*S*)-**19** and (5*S*,6*R*)-**19**.

Like in the way of racemic Canangone **19** and aldehyde (*R*,*R*)-**19,** the ^{1}H and ^{13}C-NMR data of aldehyde (*S*,*S*)-**19** were matching with that of isolated Canangone.[48] The optical rotation of the (*S*,*S*)-**19** was $[\alpha]_D^{20}$ = +107.5° (c = 1.87 in MeOH, 69% *ee*) which corresponds to the original literature value of the isolated material being $[\alpha]_D^{25}$ = +58.8° (c = 0.68 in MeOH, unknown *ee*). Deviation of the absolute value might be due to minor differences in experimental conditions. Interestingly, 6-*epi*-Canangone (*S*,*R*)-**19** showed opposite optical rotation: $[\alpha]_D^{20}$ = –71.4° (c = 1.56 in MeOH, 69% *ee*). All the $[\alpha]_D^{20}$ values of synthetic and natural Canangone are compared in Table 7.

Table 7. Comparision of $[\alpha]_D^{20}$ values of synthetic and natural Canangone **19**.

Canangone	(*S*,*S*)-**19**	(*S*,*R*)-**19**	(*R*,*S*)-**19**	(*R*,*R*)-**19**	natural-**19**
$[\alpha]_D^{20}$	+107.5°	–71.4°	+58.9°	–67.0°	+58.8°

After preparing the racemic as well as optically active epimers of Canangone **19**, and being able to prepare their enantiomers, the biological activity tests were carried out with the racemic and all four stereoisomers of this natural product.

3.1.5 Brief Introduction of Screening on Biologically Active Compounds

Desiring for a rapid, inexpensive, in-house bioassay for screening of physiologically active plant extracts, a tiny crustacean, brine shrimp, has been used as the general bioassay tool. Popularly known as sea monkeys, brine shrimps are crustaceans that live in saline environments. Their eggs can be inexpensively purchased from pet stores, hatch quickly upon being placed in a brine solution within 48 hours and the larvae (termed a nauplius or plural, nauplii) are sensitive to small doses of biologically-active chemicals. One indicator of the toxicity of a substance is LC_{50}, which refers to the lethal concentration of a substance that kills half of the test organisms. Activities are considered significant if the LC_{50} is less than 30 µg/ml.

3.1.5.1 Hatching the Shrimp and Bioassay

Brine shrimp eggs (*Artemia* franciscana) were hatched in a shallow rectangular dish (22 x 32 cm) filled with artificial sea water which was prepared with a commercial salt mixture and double-distilled water (30 g/500 ml). The eggs (ca. 50 mg) were sprinkled on the artificial sea water and after 48 hours the phototropic nauplii were collected with a pipette. Ten shrimp were transferred to each sample

vial using a disposable pipette. The nauplii can be counted macroscopically in the stem of the pipette against a lighted background. A drop of Liquizell (food for Artemia; 3 mg in 5 ml artificial sea water) was added to each vial. The vials were maintained under illumination. Survivors were counted, with the aid of a microscope after every 12 and 24 hours, and the percent deaths at each dose and control were determined. Generally the 24 hour counts were considered to be more useful for LC_{50} values.

3.1.5.2 Sample Preparation and the Test for Biological Activity

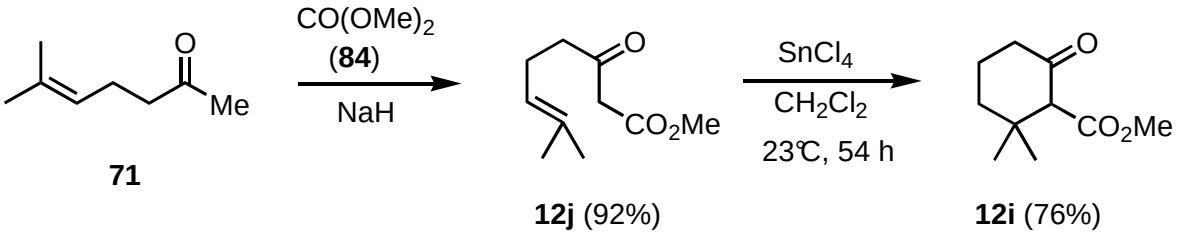
In order to check the biological activity of the synthesized Canangones and its epimers, the dilution series were prepared and 100 µl were taken from each solution, diluted with 5 ml sea water and biological tests were carried out. Only at higher conc. *i.e.* (1g/l), 3 brine shrimps were died out of 10 which indicate that the synthesized Canangones are not active to the brine shrimp bioassay.

3.2 Attempted Synthesis of Chamigrene

The second synthetic target in this work is the total synthesis of (–)-β-Chamigrene **18**, isolated from the leaf oil of *Chamaecyparis taiwanensis*.

3.2.1 Synthesis of Cyclic β-Ketoester 12i

The β-ketoester **12j**[140] was obtained from 6-methylhept-5-en-2-one **71** (1.0 eq.) and dimethyl carbonate **84** (2.0 eq.) using 2.2 eq. NaH in THF (refluxing for 2 h and allowing to stand the reaction mixture for 12 h at 23°C). With this method the yield was only 54% after distillation. But when the reaction was carried out using same amount of NaH and 10.0 eq. of dimethyl carbonate **84** under solvent free conditions, the yield was increased to 92% after aqueous acidic workup and distillation. The cyclization of β-ketoester **12j** was carried out using $SnCl_4$ (1.0 eq.) in CH_2Cl_2 at room temperature to give cyclic β-ketoester **12i**[141] in 76% yield after chromatographic purification (Scheme 52).



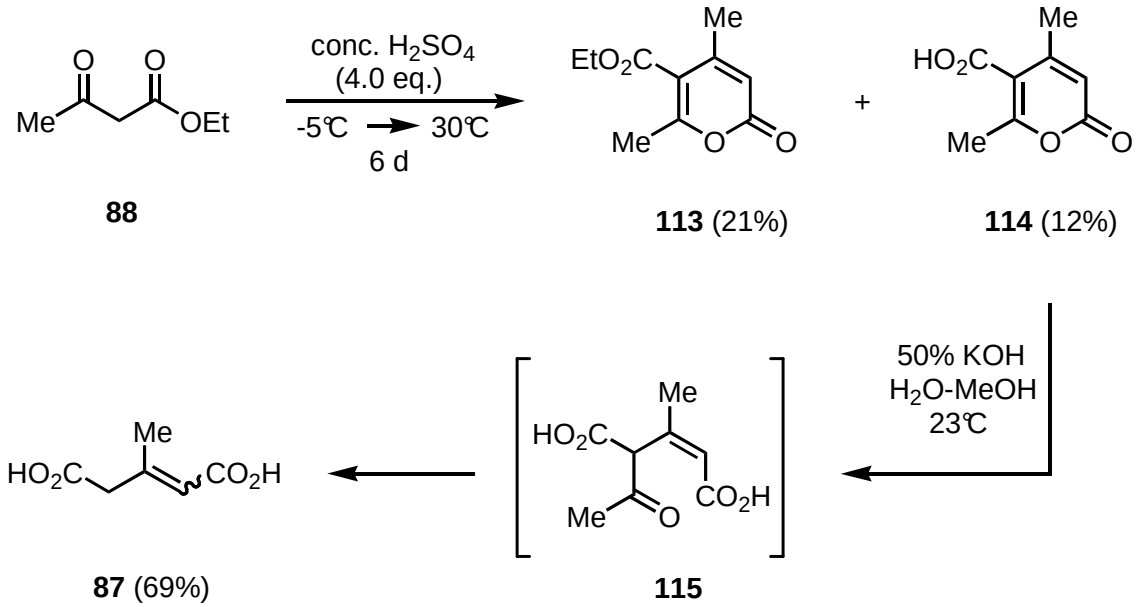
Scheme 52. Synthesis of cyclic β-ketoester **12i**.

3.2.2 Synthesis of Dibromide 83

3.2.2.1 Synthesis of β-Methyl Glutaconic Acid 87

The synthesis of β-methyl glutaconic acid **87**[142] was started with the condensation of ethyl acetoacetate **88** initially in 2.0 eq. conc. H_2SO_4. After stirring the reaction

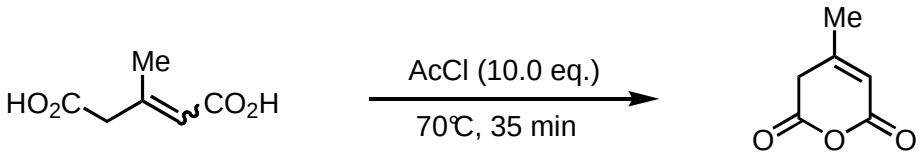
mixture for 5 d (care should be taken that the temperature of the reaction mixture does not rise above 30°C), a small aliquot from the reaction mixture was taken, and submitted for GC after aqueous work up. As the GC result showed the presence of 50% of the reactant, additional amounts of conc. H_2SO_4 (2.0 eq.) were added to the reaction mixture and stirred for an additional 5 d. After aqueous workup, a mixture of lactones **113** and **114** were obtained in 33% yield (Scheme 53). In order to increase the yield of the condensation products, the reaction time was increased (12 d), but not much improvement was observed in the yield. In the subsequent step, without further purification, the mixture of ester **113** and acid **114** were subjected for base hydrolysis using 50% aq. KOH, which resulted in a mixture of (*Z*)- and (*E*)-acids **87** in 69% yield after acidic workup and recrystallization from acetonitrile. The ratio of the *E*/*Z* mixture of acid **87** was found to be 2 : 1 based on ^{1}H-NMR.



Scheme 53. Synthesis of 3-methyl glutaconic acid **87**.

3.2.2.2 Synthesis of Glutaconic Anhydride 86

After preparing 3-methylglutaconic acid **87,** the next aim was to access 3-methyl-glutaconic anhydride **86** by cyclization in order to obtain desired *cis* geometry for further synthetic sequences. Initially the reaction was tried with acetic anhydride[143] (2-10 eq.) by heating the reaction mixture at 70°C for 1 h, but in all the cases, only complex mixtures were obtained. But when the same reaction was tried using acetyl chloride[144] (heating the reaction mixture at 70°C for 35 min), the glutaconic anhydride **86** was obtained in 72% yield after crystallization from ether (Scheme 54).

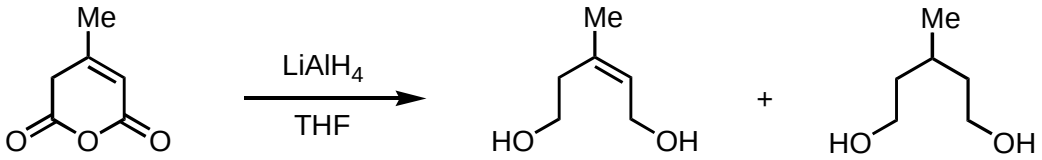


87 **86** (72%)

Scheme 54. Synthesis of glutaconic anhydride **86** from acid **87**.

3.2.2.3 Synthesis of Diol 64

The desired *cis*-configurated glutaconic anhydride **86** was then reduced to diol **85** (Scheme 55). The reaction was first tried by adding a solution of anhydride **86** in THF to an ice cooled solution of $LiAlH_4$ in THF.[143] In these conditions, always a mixture of unsaturated diol **85** and saturated diol **116** were obtained almost in equal ratio.



86 **85** (4%) **116** (56%)

Scheme 55. Reduction of glutaconic anhydride **86** to unsaturated diol **85**.

Several optimization conditions were carried out in order to obtain exclusively the desired unsaturated diol **85**, but none of them were successful (Table 8).

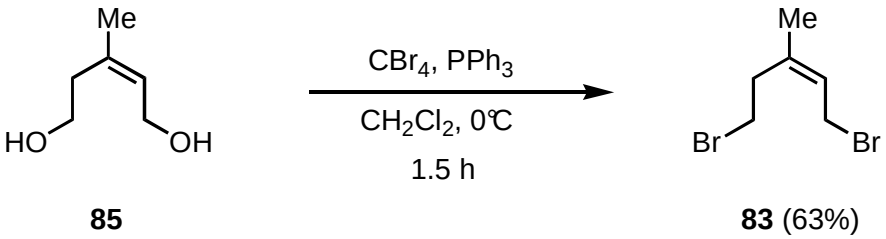
Table 8. Reduction of glutaconic anhydride using $LiAlH_4$ under different conditions.

$LiAlH_4$	T	t	**85**	**116**
4.0 eq.	reflux	4 h	4%	56%
2.0 eq.	reflux	1 h	10%	48%
1.2 eq.	reflux	30 min	15%	38%
1.2 eq.	23°C	1 h	22%	36%
1.2 eq.	–5°C	1 h	28%	30%
1.2 eq.	–5°C	30 min	34%	30%
1.2 eq.	–5°C	10 min	35%	31%
1.2 eq.	–78°C	45 min	35%	26%
1.2 eq.[a)]	–15°C	45 min	63%	8%

[a)] Inverse addition

Luche reduction [145] (1.5 eq. each $CeCl_3 \cdot 7\ H_2O$ and $NaBH_4$, MeOH, 23°C, 16 h) was also performed, but only the starting material was recovered. Even at reflux

conditions, only the starting material was recovered. Finally the desired unsaturated diol **85** was obtained in major amount when the reaction was carried out in the inverse addition manner, i.e. addition of an ice-cooled suspension of $LiAlH_4$ in THF to a cooled solution of glutaconic anhydride **86** in THF at –15°C and stirring the resulting mixture for 45 min at the same temperature. Under these conditions, the diol **85** was obtained in 63% yield with 8% being the saturated diol **116**. The unsaturated diol **85** was then subjected for nucleophilic substitution conditions to synthesize dibromide **83**. The reaction was first tried with $SOBr_2$ (1.3 eq.) in CH_2Cl_2 at 23°C as well as at 0°C, but in both the cases only decomposed products were detected. The same reaction was tried applying the Appel conditions[146] (CBr_4, PPh_3, each 4.0 eq.), this time the conversion was fruitful to obtain dibromide **83** in 63% yield (Scheme 56).



85 **83** (63%)

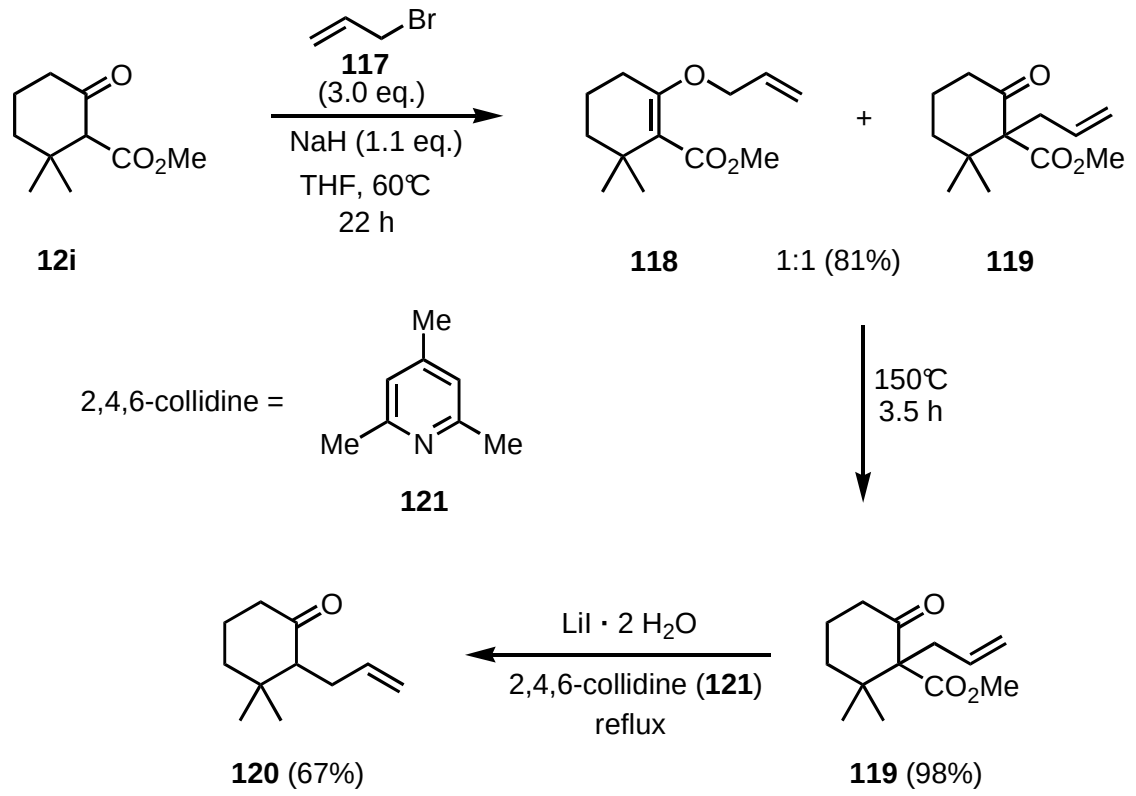
Scheme 56. Synthesis of dibromide **83**.

3.2.3 Model Study for Alkylation using Allyl Bromide 117

Before continuing further, *i.e.* performing the alkylation between dibromo compound **83** and cyclic β-ketoester **12i**, a model study was planned with commercially available allyl bromide **117** and the synthesized cyclic β-ketoester **12i** in order to check the feasibility of the reaction, optimize the reaction conditions and to apply the same conditions for dibromo compound **83.**

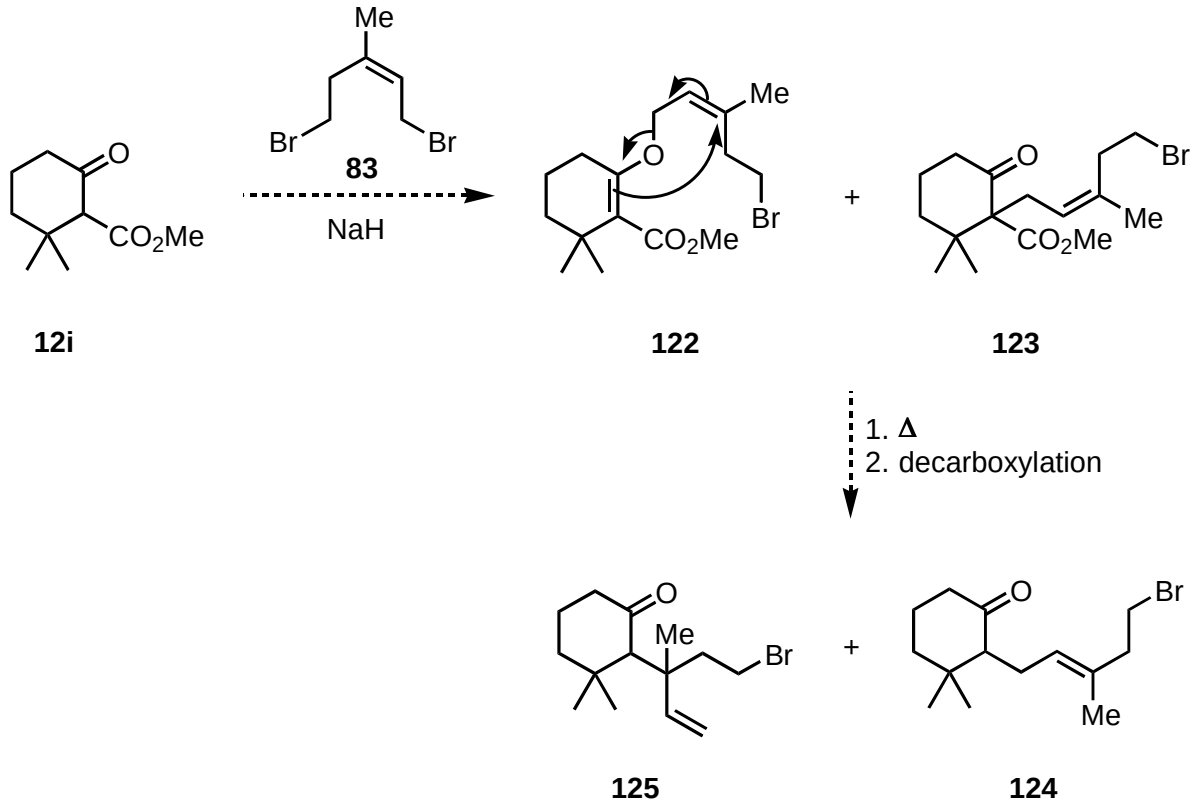
The synthesis of model compound, substituted cyclohexanone **120**[147] was started with cyclic β-ketoester **12i** and allyl bromide **117.** Treatment of **12i** with NaH (1.1 eq.) followed by an addition of allyl bromide **117** (3.0 eq.) in THF at 60°C provided

an inseparable mixture of *O*- and *C*-allylated products **118** and **119,** in almost 1 : 1 ratio respectively, as determined by ^{1}H-NMR. The ^{1}H-NMR spectrum of the inseparable mixture, exhibited three distinct singlets with the resonances at δ 0.84, 1.11 and 1.25, with the intensity of the resonance at δ 1.11 being approximately twice that of the other two resonances. The geminal dimethyl groups in the *O*-allylated product **118** might be enantiotopic because of which the two dimethyl groups are resonating at the same ppm (δ 1.11), while the geminal dimethyl groups in the *C*-allylated product **119** might be diastereotopic as a result of which they are exhibiting two distinct signals. In order to convert the *O*-allylated product **118** to *C*-allylated product **119**, the mixture of **118** and **119** were subjected to Claisen rearrangement conditions (heating and vigorous stirring at 150°C for 3.5 h). As a result of this, the *O*-allylated product **118** underwent a Claisen rearrangement to produce the *C*-allylated product **119** quantitatively. Decarboxylation of **119** using wet lithium iodide in collidine **121** under reflux, gave the substituted cyclohexanone **120** in 67% yield (Scheme 57).



Scheme 57. Synthesis of substituted cyclohexanone **120**.

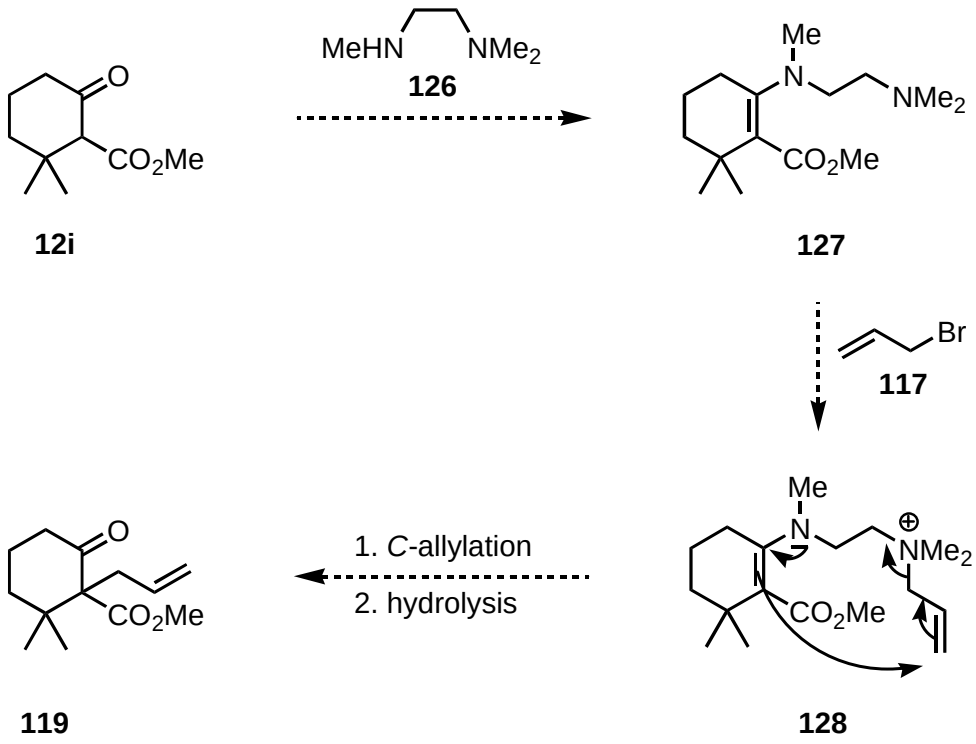
During the synthesis of model compound **120**, the *O*-allylation **118** and *C*-allylation product **119** were obtained in almost 1 : 1 ratio. If the same process continues in the original synthesis, the basic problem will be at the Claisen rearrangement. The product, which might be obtained from the Claisen rearrangement, will be the undesired alkylated product **125**, which is not useful for further synthesis (Scheme 58).



Scheme 58. Possible pathway for undesired (**125**) and desired allylated product **124**.

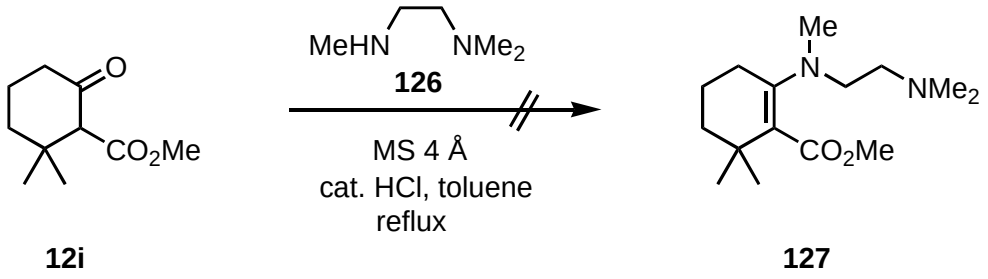
3.2.3.1 Attempted Synthesis for an Exclusive *C*-Allylated Product 123

Since the *O*-allylation product **122** could give the undesired product **125** after the Claisen rearrangement, the enamine pathway was planned to prepare exclusively *C*-allylated product **123**. Before trying the enamine pathway using cyclic β-ketoester **12i** and dibromide **83** as an allylating agent, again a model study was planned using allylbromide **117** as allylating agent in order to check the allylation conditions (Scheme 59). The enamine pathway may occur as follows: The first step would be the formation of an enamine **127** from cyclic β-ketoester **12i** and *N*,*N*,*N*′-trimethylethylenediamine[148] **126**. In the second step, the diamine **127** could attack the allyl bromide **117** to give the ammonium salt **128** and then *C*-allylation takes place simultaneously. Hydrolysis of *in situ* generated iminium salt would provide allyl substituted cyclic β-ketoester **119**.



Scheme 59. Possible reaction mechanism for the synthesis of allyl substituted cyclic β-ketoester **119**.

As proposed in Scheme **59**, the synthesis of *C*-allylated cyclic β-ketoester **119** was tried using cyclic β-ketoester **12i** (1.0 eq.), *N*,*N*,*N*′-trimethylethylenediamine **126** (1.1 eq.) and allylbromide **117** (3.0 eq.) in DMF at 80°C. The reaction did not work even after stirring the reaction mixture for 10 days at the same temperature. No fruitful result was observed even by increasing the stoichiometric amounts of the reagents. As the reaction failed in one pot sequence, a two pot procedure was followed *i.e.* first enamine formation, later the addition of the allylbromide **117** to generate the C-allylated product. For this, first the enamine formation was tried using cyclic β-ketoester **12i** (1.0 eq.), *N*,*N*,*N*′-trimethylethylenediamine **126** (1.1 eq.) in toluene at 23°C in presence of 4 Å molecular sieves and cat. hydrochloric acid (Scheme 60).



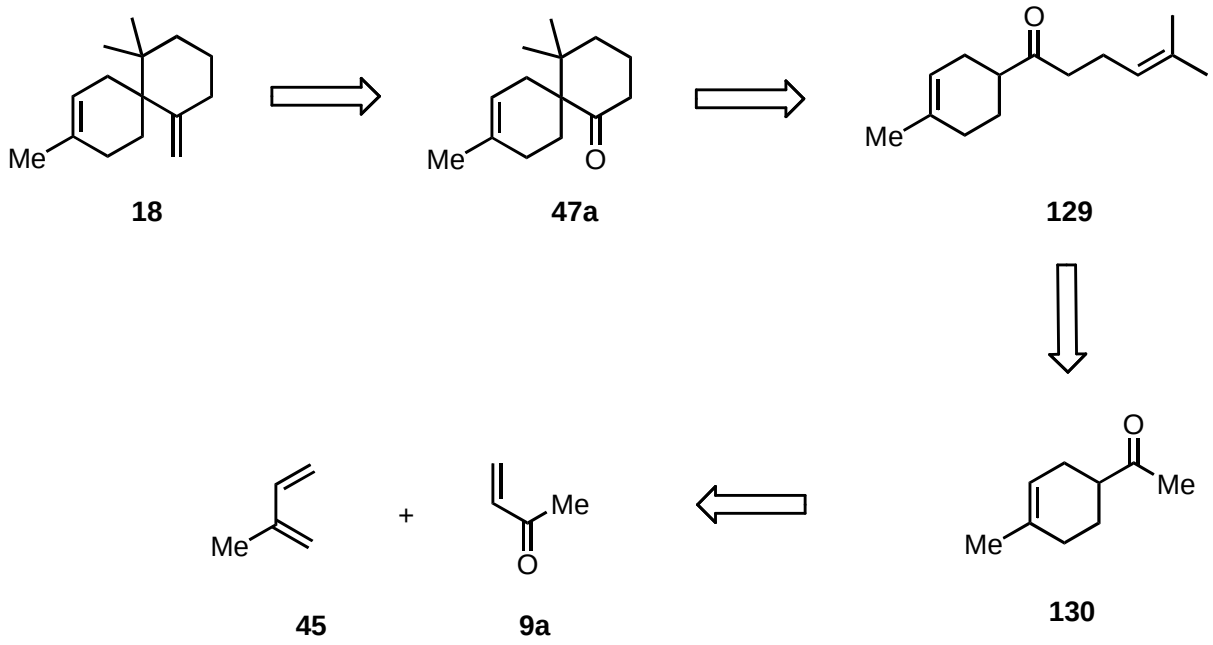
12i **127**

Scheme 60. Attempted synthesis of enamine **127**.

The reaction was checked after 24 h, but no new spot was observed on TLC. Therefore, the reaction mixture was heated to reflux and stirred for another 24 h first and then left the reaction for an additional 4 days at the same temperature as there was no new spot detected on TLC. As the reaction was not working at the enamine formation itself, it became difficult to obtain C-allylated product **123** exclusively. At this stage the present synthetic route had to be stopped and another synthetic strategy was proposed for the synthesis of β-Chamigrene **18**.

3.2.4 Second Retrosynthetic Analysis for β-Chamigrene 18

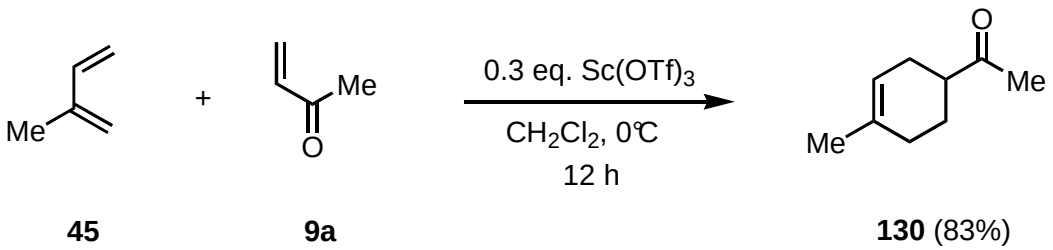
The second retrosynthetic scheme was planned in a very short (four steps) and reliable pathway for the synthesis of racemic as well as the optically active β-Chamigrene **18** (Scheme 61). In this scheme, the β-Chamigrene **18** could be possibly obtained from **129** by performing acidic cyclization followed by Wittig olefination on **47a**. The ketone derivative **129** can be synthesized by alkylation of acetyl cyclohexene **130** using prenyl bromide **72**. The Diels-Alder approach of methyl vinyl ketone **9a** and isoprene **45** would provide acetyl cyclohexene **130**.



Scheme 61. Second retrosynthetic analysis of β-Chamigrene **18**.

3.2.4.1 Synthesis of Acetyl Cyclohexene 130

The synthesis of β-Chamigrene **18** in the second approach was started with a Lewis acid catalysed Diels-Alder reaction of methyl vinyl ketone **9a** and isoprene **45** using $Sc(OTf)_3$.[149] The reaction was successful and gave only one regioisomers of acetyl cyclohexene **130** in 83% yield (Scheme 62).



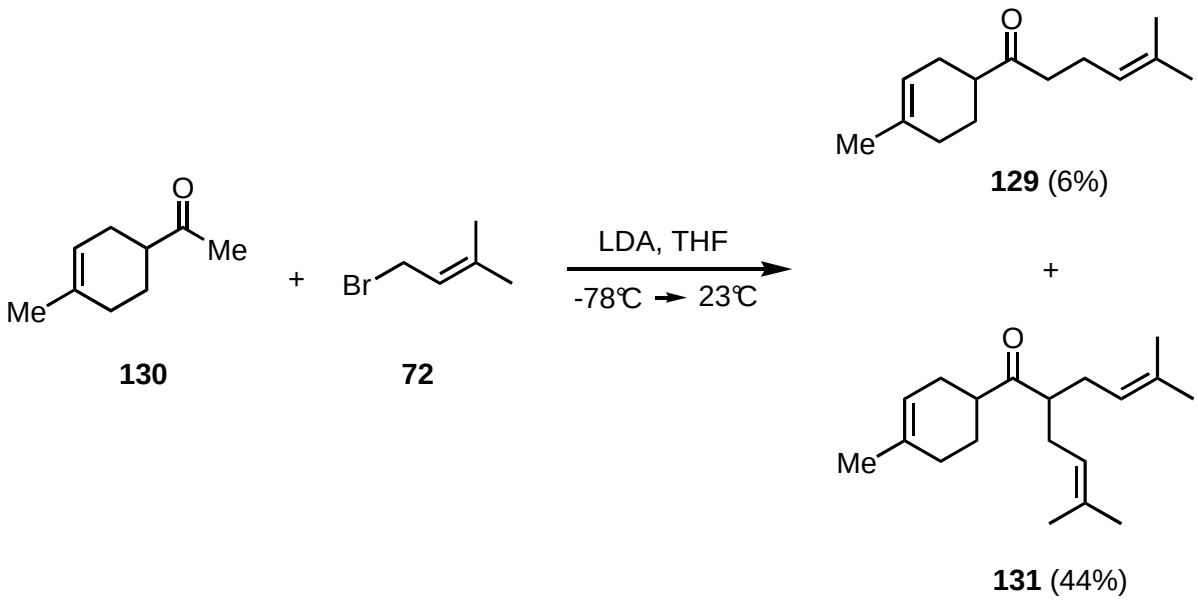
Scheme 62. Synthesis of the Diels-Alder product **130**.

As the Diels-Alder product **130** is volatile, care was taken while evaporating the solvents. The characteristic feature of $Sc(OTf)_3$ as a Lewis acid catalyst is that it can

be easily recovered and reused. After the reaction is complete and the Diels-Alder product is extracted with dichloromethane, the aqueous layer is concentrated to remove the water under reduced pressure. $Sc(OTf)_3$ is almost quantitatively recovered and the recovered catalyst also showed effective in the Diels-Alder reaction of next batches. The yields of Diels-Alder reaction using recovered catalyst in the 2nd and 3rd runs were 78% and 76% yields, respectively.

3.2.4.2 Synthesis of Alkylated Product 129 from Acetyl Cyclohexene 130

The next step was the alkylation of the Diels-Alder product **130** using prenyl bromide **72** as the alkylating agent. The acetyl cyclohexene **130** was treated with LDA (2.0 eq.) in THF and stirred for 1.5 h at –78°C for the formation of kinetic enolate, which was then treated with prenyl bromide **72** (5.0 eq) and stirred the reaction mixture at 23°C for 12 h, which provided the mono- **129** and dialkylated products **131** in 6% and 44% yields respectively (Scheme 63).



Scheme 63. Alkylation of acetyl cyclohexene **130** using prenyl bromide **72**.

In order to improve the yield of mono alkylated product **129**, several reactions conditions were tried by varying stoichiometric ratio of the reagents as shown in Table 9.

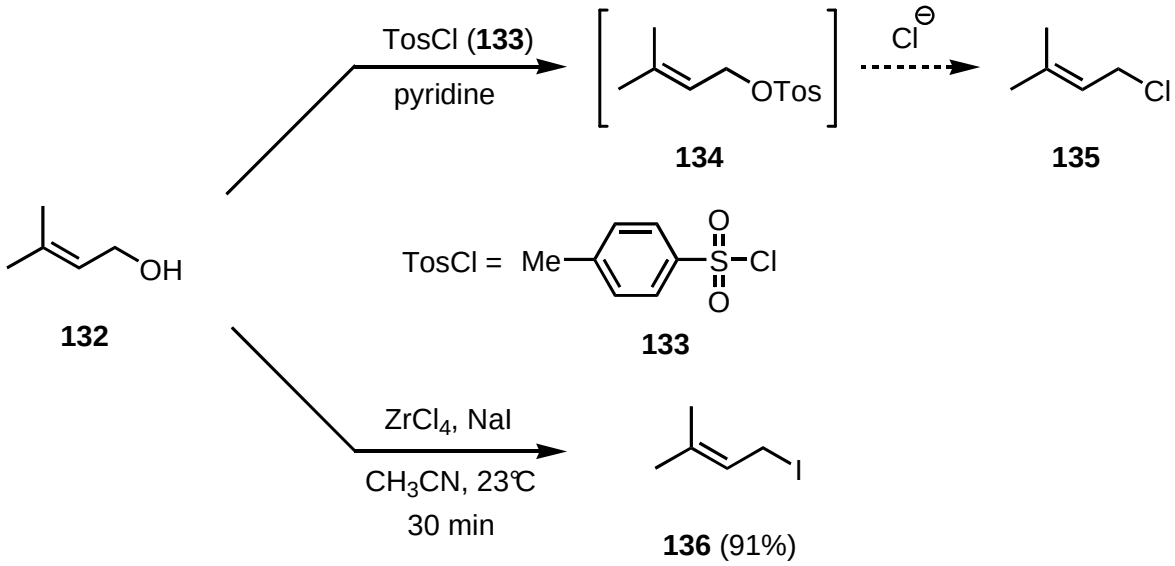
Table 9. Conditions and yields of mono-**129** and di-alkylated **131** products as well as the recovered starting material **130**.

LDA[a)]	**72**	T/t	**129**	**131**	**130**
2.0 eq.	5.0 eq.	23°C/20 h	6%	44%	12%
1.5 eq.	5.0 eq.	23°C/3 h	8%	35%	15%
1.2 eq.	3.0 eq.	23°C/3 h	6%	20%	26%
1.02 eq.	1.1 eq.	–20°C/16 h	12%	16%	28%
1.02 eq.	1.1 eq.	0°C/16 h	14%	19%	26%
1.02 eq.	1.1 eq.	23°C/16 h	17%	26%	21%
1.02 eq.	1.1 eq.	23°C/2 d	15%	32%	18%

[a)] conditions for enolate formation: –78°C/1.5 h.

As all the efforts failed to improve the yield of monoalkylated product **129** using prenyl bromide **72** as an alkylating agent, prenyl iodide **136** was used by assuming that iodides are more reactive than bromides in alkylation reactions. Since prenyl iodide **136** is not commercially available, it was planned to prepare from prenyl alcohol **132**, by formation of tosylate **134** using *p*-toluene sulfonyl chloride **133** and then a nucleophilic substitution with iodide using Finkelstein conditions. The tosylation was tried using tosyl chloride **133** and pyridine in CH_2Cl_2 at 0°C as well as at 23°C for 16 h, but none of them could provide tosylate **134**. Probably during the reaction conditions, the chloride anion must have been attacking to the tosylate **134** to form prenyl chloride **135** which might be difficult to isolate because of its high volatility (Scheme 73). Finally the prenyl iodide **136**

was obtained in 91% yield by stirring the prenyl alcohol **132**, $ZrCl_4$ (0.5 eq.) and NaI (1.5 eq.) in acetonitrile at 23°C for 30 min (Scheme 64).[150]



Scheme 64. Synthesis of prenyl iodide **136**.

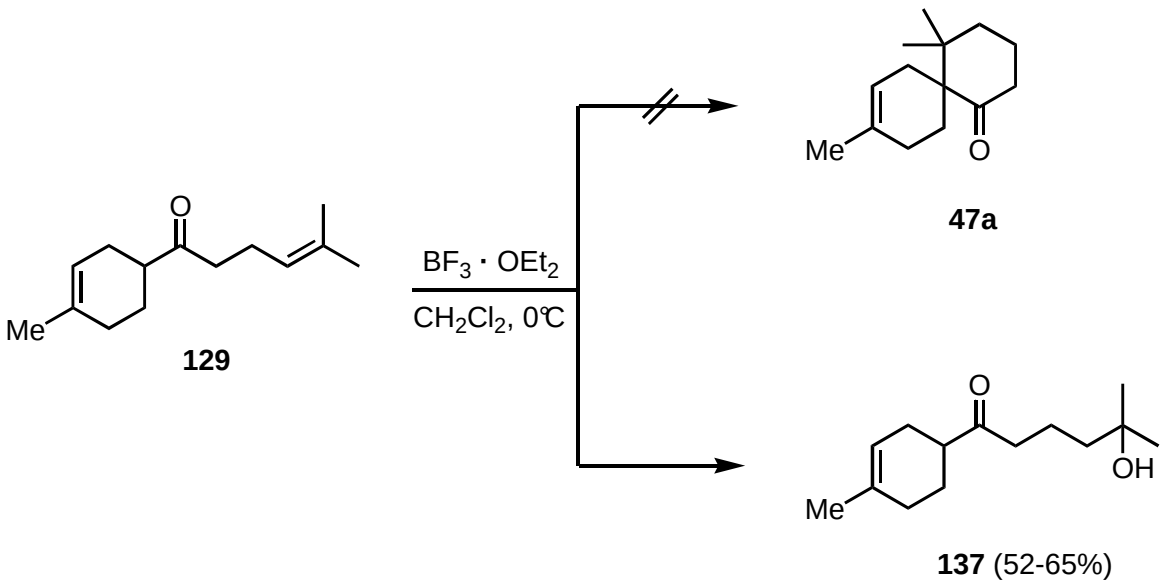
Then, the alkylation was attempted using prenyl iodide **136** in order to obtain the mono alkylated product **129** exclusively. Initially, both mono-**129** and dialkylated products **131** were obtained but after few optimizations the mono alkylated product **129** was obtained in 72% yield (Table 10).

Table 10. Alkylation conditions and their yields using prenyl iodide **136**.

LDA[a)]	**136**	T/t	**129**	**131**	**130**
1.0 eq.	1.5 eq.	–60°C/3 h	16%	8%	26%
1.2 eq.	2.5 eq.	–40°C/8 h	18%	15%	20%
1.02 eq.	1.2 eq.	0°C/8 h	20%	12%	24%
1.1 eq.	4.0 eq.	–78°C/2 h 23°C/3 h	72%	11%	8%

3.2.4.3 Attempted Synthesis for the Spiroannulated Product 42a

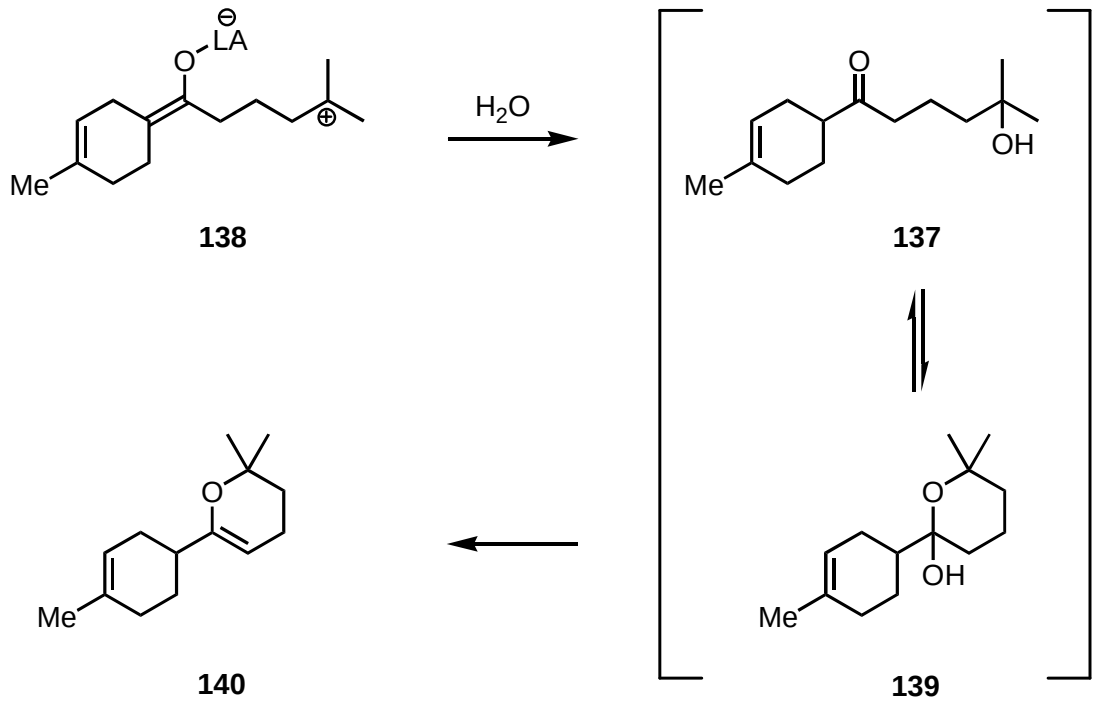
After synthesizing the mono alkylated product **129**, it was subjected for cyclization using Brønsted acid (H_2SO_4). But unfortunately, only complex mixtures were detected by GC-MS analysis. Lewis acidic spiroannulation was attempted in order to obtain desired product **47a**. First the reaction was tried in different equivalents of $BF_3 \cdot OEt_2$ (0.3 eq., 1.0 eq., 1.5 eq., 2.0 eq.) at 0°C as well as at 23°C. The only product obtained in all the cases was the alcohol **137** in 52 to 65% yield (Scheme 65). The same reaction was also tried at –78°C as well as at reflux conditions. The alcohol **137** was isolated as a sole product at –78°C and decomposed products at higher temperature (reflux).



Scheme 65. Attempted synthesis of spiroannulated product **47a**.

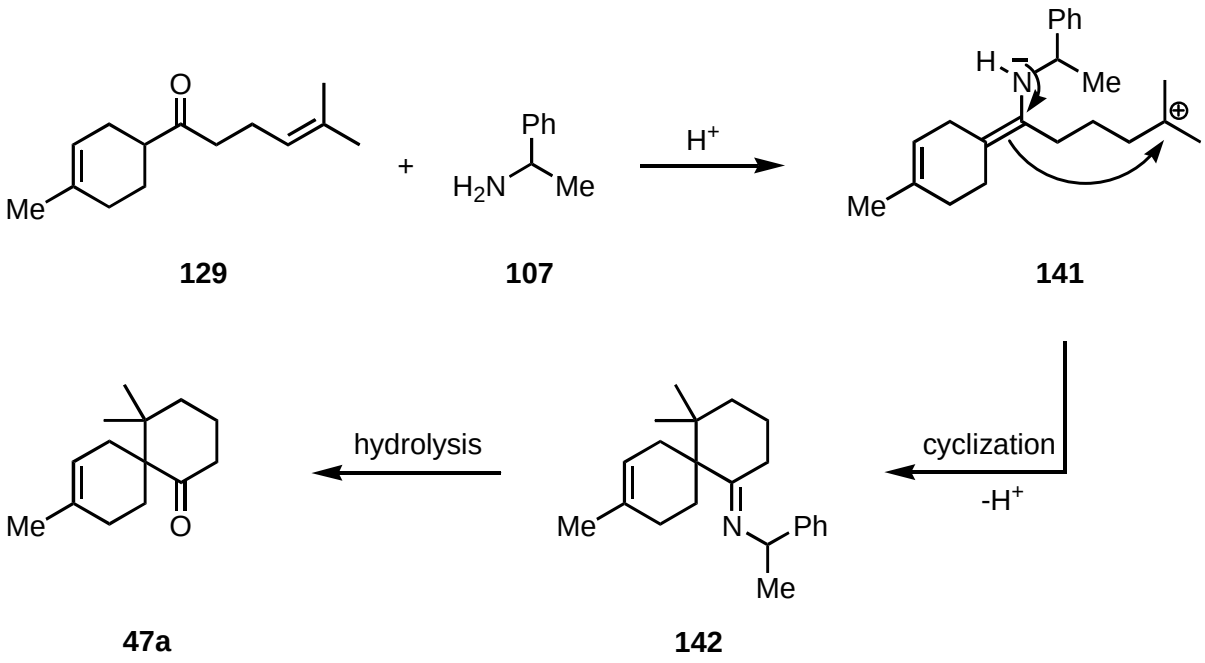
The spiroanuulation was also tried with other Lewis acids [$SnCl_4$, $Sc(OTf)_3$] at lower temperatures (–78°C, 0°C) and at 23°C. Here too, the alcohol **137** was isolated exclusively in 55% to 62% yields. In slightly acidic conditions (SiO_2, $CDCl_3$) enol ether **140** formation was observed in trace amounts. Probably this

enol ether **140** is formed *via* hemiacetal **139** from hydroxy product **137** (Scheme 66).



Scheme 66. Formation of enol ether **140** from hydroxy product **137**.

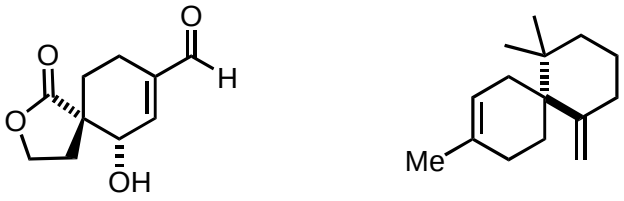
The above synthetic scheme had to be stopped at this stage because of the exclusive formation of hydroxy product **137** under Lewis acidic conditions. The enamine cyclization has to be tried in order to obtain β-Chamigrene precursor **47a** (Scheme 67).



Scheme 67. Possible strategy for the synthesis of β-Chamigrene precursor **47a**.

4 Summary and Conclusion

This dissertation includes two parts, first is total synthesis of Canangone **19** in racemic as well as optically active form, and their preliminary biological studies and the second part is the attempted synthesis of β-Chamigrene **18** (Figure 6).

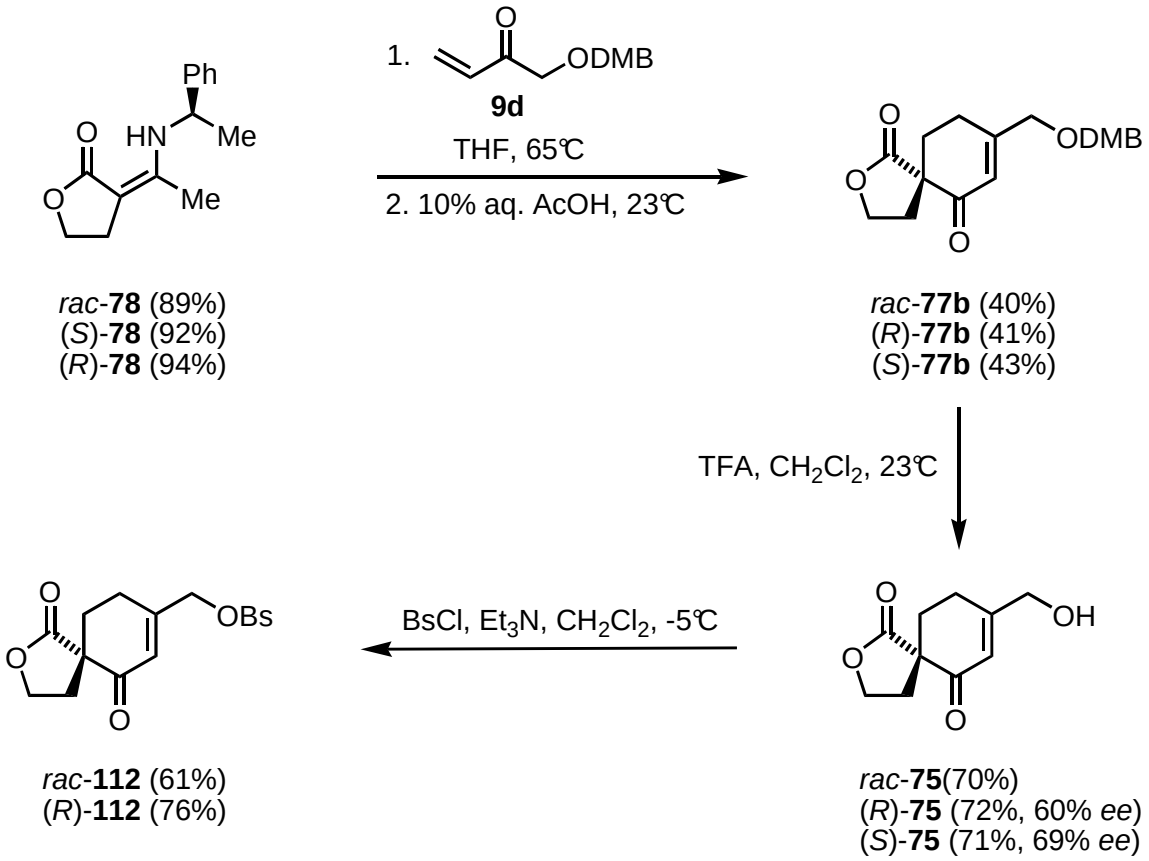


19 **18**

Figure 6. (+)-Canangone **19** and β-Chamigrene **18**.

The Michael acceptor **9d** for synthesis of Canangone was prepared in three steps. The first step was Williamson's ether synthesis of 3,4-dimethoxy benzyl alcohol **89** and bromoacetic acid **90** followed by transformation of the derived acid **73a** to Weinreb amide derivative **71a**, which was then converted to vinyl ketone **9d** under Grignard conditions. The enamines **78** were prepared from α-acetylbutyro-lactone **12h** and phenethylamine **107** in 89–94% yield (Scheme 68). Subsequent Robinson annulation using vinyl ketone **9d** gave spirocyclic ketones **77b** in 40–43%. The cleavage of the protective group with 10% TFA in CH_2Cl_2 gave primary allylic alcohol **75**. As these primary alcohols **75** gave sufficient baseline resolution at GLC on a chiral phase, the stereoselectivity of the Michael reaction was determined to be 60–69% *ee* being sensitive to the reaction conditions. The reaction sequence leading to canangone was first developed and optimized in the racemic series and applied the same to the optically active series. Work from Pfau and d'Angelo predicted the (*R*)-configuration when starting from (*S*)-phenethylamine. This was confirmed by X-ray single crystal structure

determination of the brosylate (*R*)-**112**, which was prepared using Brosyl chloride **111** and Et_3N.

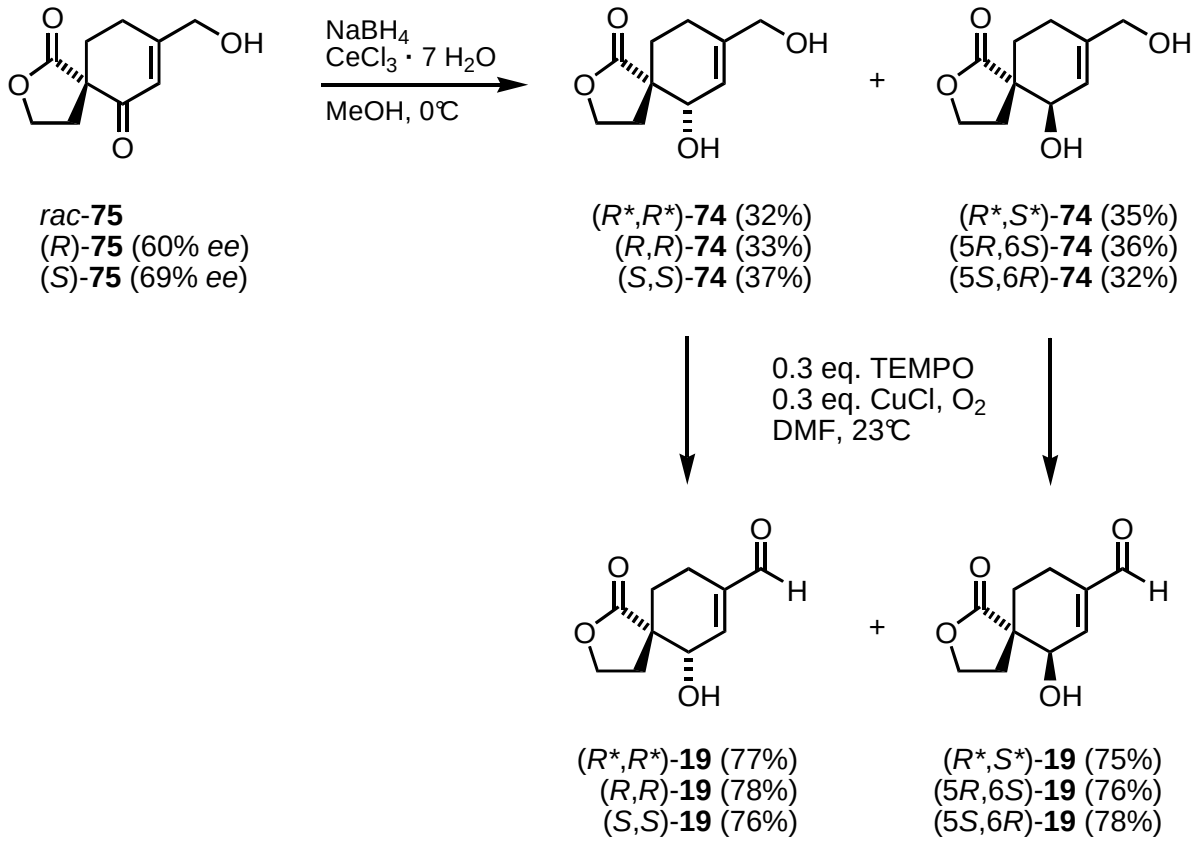


Scheme 68. Synthesis of brosylate **112** from enamino lactone **78**.

After finishing the synthesis of (*R*,*R*)-Canangone **19**, it was proved from ($[\alpha]_D^{20}$ = –67.0°, vide infra), that this was the enantiomer of the originally isolated natural product ($[\alpha]_D^{25}$ = +58.8°). Therefore, the whole synthesis had to be repeated in the (*S*)-series starting from the (*R*)-configurated chiral auxiliary.

The synthesis of Canangone **19** was finished in both, the racemic and the (*S*)-series (69% *ee* of **75**) as depicted in Scheme 69. Luche reduction of the conjugated enone moiety yielded the allylic alcohols **74** without any stereoselectivity. In the racemic series, single crystals were grown from the more unpolar isomer, which were suitable for X-ray structure analysis. This confirmed the relative (*R**,*S**)-configuration. The primary alcohol functions of both diastereoisomers of **74** could be selectively oxidized using TEMPO–CuCl (both 0.3 eq., 1 atm O_2, DMF, 23°C, 75

min) to furnish both Canangones **19** and its 6-epimer, in both, the racemic as well as the (5*S*)-series, with 75–78% yields.



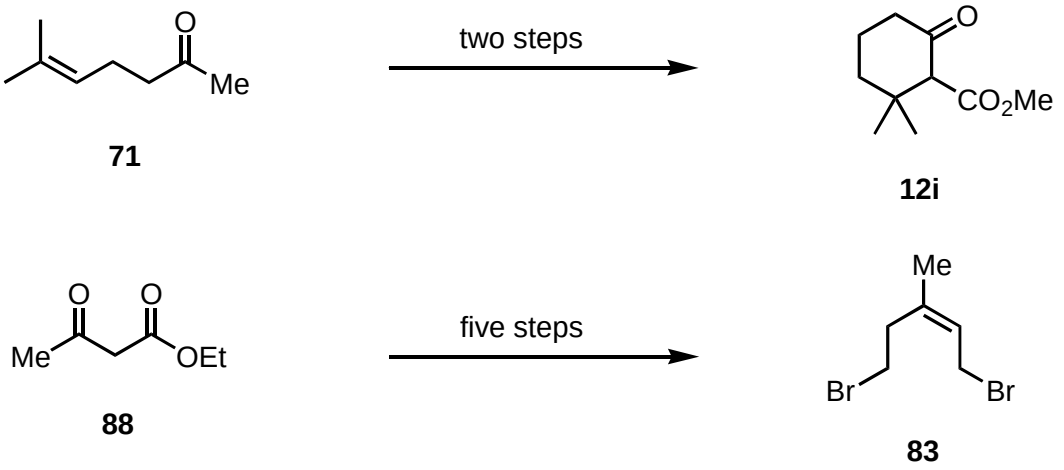
Scheme 69. Synthesis of Canangone **19**.

Comparison of ^{1}H- and ^{13}C-NMR data of (*R**,*R**)-**19** and (*R**,*S**)-**19** with the original publication confirmed the relative (*R**,*R**)-configuration of Canangone **19** as proposed by Caloprisco and coworkers. After preparing the optically active epimers of Canangone **19** and their enantiomers, the biological tests were carried out using brine shrimp bioassay. But unfortunately, none of the synthesized Canangones showed significant toxicity even at higher concentrations.

In conclusion, (+)-(*S*,*S*)-canangone **19** and its 6-epimer (5*S*,6*R*)-**19** were prepared for the first time. Absolute and relative configurations were established by X-ray crystallography. This confirmed the originally proposed relative configuration.

The so far unknown absolute configuration of this natural product is established for the first time.

The second part of this dissertation dealt with the attempted synthesis of β-Chamigrene **18**. A convergent strategy was planned for the synthesis of β-Chamigrene The β-ketoester **12i** was prepared in two steps from 6-methylhept-5-en-2-one **101** and the dibromide **83** was synthesized in five steps from ethyl acetoacetate **88** (Scheme 70).

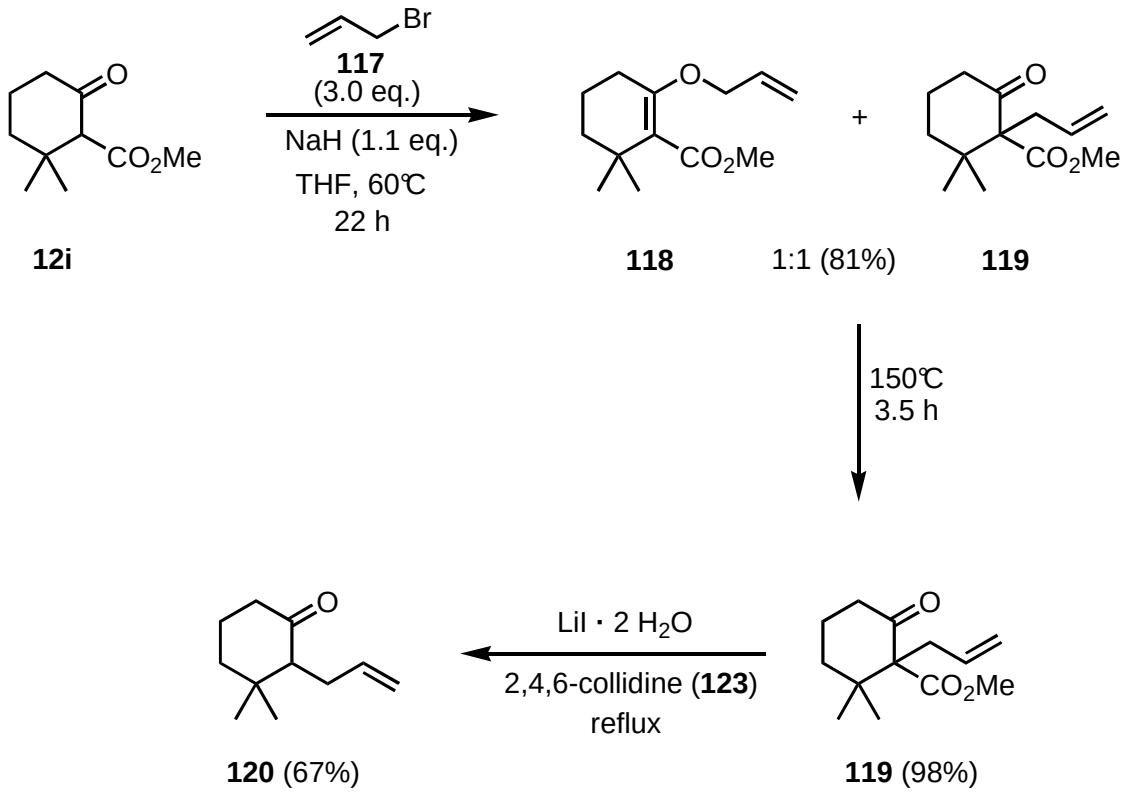


71 **12i** **88** **83**

Scheme 70. Synthesis of β-ketoester **12i** and dibromide **83** from their corresponding starting materials.

Before continuing further in the synthesis *i.e.* performing the alkylation between dibromo compound **83** and cyclic β-ketoester **12i**, a model study was planned with commercially available allyl bromide **117** and the synthesized cyclic β-ketoester **12i** in order to check the feasibility of the reaction**.** The synthesis of model compound, *i.e.* substituted cyclohexanone **120** was started with cyclic β-ketoester **12i** and allyl bromide **117** in presence of NaH. This reaction gave an inseparable mixture of *O*- and *C*- allylated products **118** and **119,** in almost 1 : 1 ratio, as determined by ^{1}H-NMR. In order to convert the *O*-allylated product **118** to *C*-allylated product **119**, the mixture was subjected to Claisen rearrangement conditions.

Decarboxylation of **119** using wet lithium iodide in collidine under reflux, gave the substituted cyclohexanone **120** (Scheme 71).

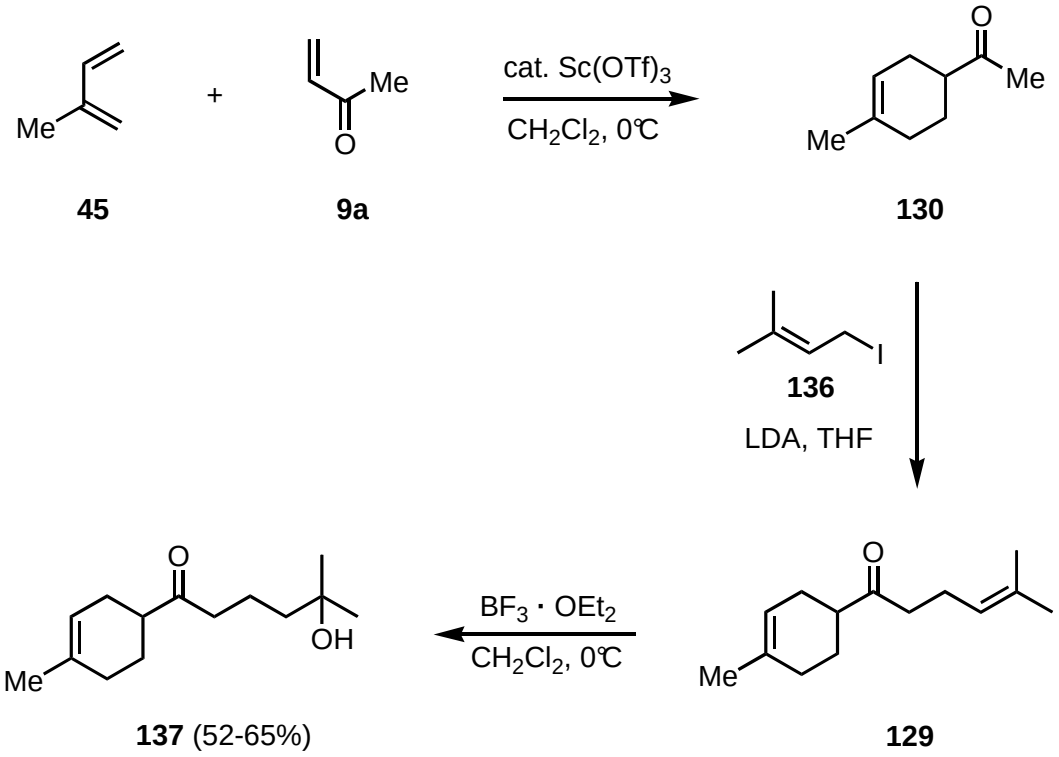


Scheme 71. Synthesis of allyl substituted cyclohexanone **120**.

As the *O*-allylation product **118** and *C*-allylation product **119** were obtained in almost 1 : 1 ratio, the synthesis was stopped by this method and an enamine strategy was planned using *N*,*N*,*N*′-trimethylethylenediamine **126** and allylbromide **117** for getting exclusively the *C*-allylation product **119**. But unfortunately in this case the reaction did not work at all. As the reaction was not working to give exclusively the *C*-allylated product **119**, the present synthetic route had to be stopped at this stage and another synthetic strategy was proposed for the synthesis of β-Chamigrene **18**.

The synthesis of β-Chamigrene **18** in the second approach, was started with Lewis acid catalysed Diels-Alder reaction of methyl vinyl ketone **9a** and isoprene **45**

using $Sc(OTf)_3$ to give acetyl cyclohexene **130** (Scheme 72). In the next step, the Diels-Alder product **130** was alkylated using prenyl iodide **136** in presence of LDA to give the mono alkylated product **129**. It was then submitted for cyclization conditions using $BF_3 \cdot OEt_2$, $SnCl_4$, and $Sc(OTf)_3$ at 0°C as well as at 23°C. But unfortunately in all the cases, the hydroxy product **137** was obtained exclusively. As an outlook an enamine strategy can be planned in order to access the potential precursor of Chamigrene **18**.



Scheme 72. Diels-Alder approach for the synthesis of β-Chamigrene **18**.

5 Experimental Section

5.1 General Information

5.1.1 Analytical Methods

NMR-Spectroscopy: ^{1}H-NMR spectra were recorded on a *Bruker AC 250* (250 MHz), *Bruker ARX 300* (300 MHz) or *Bruker ARX 500* (500 MHz). ^{13}C-NMR spectra were recorded on a *Bruker AC 250* (62 MHz), *Bruker ARX 300* (75 MHz) or *Bruker ARX 500* (125 MHz). Multiplicities were determined with distortionless enhancement by polarization transfer (DEPT) experiments. All measurements performed in $CDCl_3$ or acetone-d_6 as solvent and with tetramethylsilane (δ = 0.000) as internal standard. The chemical shifts δ are denoted in ppm, the couplings constants *J* as frequency in Hz. The signal multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartett), quint (quintet), sex (sextet), h (heptet), oct (octet), m (multiplet). Broad signals are characterized as br. (broad).

IR-Spectroscopy: IR spectra were recorded on a *Bruker Vector 22* and *Bruker Tensor 27* spectrometer affiliated with *MKII Golden Gate Signal Reflection Diamond ATR-System*. The positions of absorption bands are denoted in cm^{-1}. The intensity of the bands is abbreviated as br. (broad), vs (very strong), s (strong), m (moderate), w (weak).

Mass-Spectrometry: All mass spectra (Low Resolution and High Resolution) were measured on a *Varian MAT 711* (EI) and a *Finnigan MAT 95* (EI and CI) with direct-inlet at 70 eV. GC-MS spectra were measured on a *GC HP 5890 II* of the company *Hewlett-Packard* with mass detector *Finnigan MAT 95*, a *Varian Star 3400 CX* with mass detector *Saturn 4D* of the company *Varian* or with a *Focus DSQ*

quadrupol machine by Thermo Fisher corporation. The relative intensities were indicated in percent of the respective basis peak.

Elemental Analysis: CHN-Analyses were measured on *Jena Vario EL* and with a *Carlo Erba Strumentazione Elemental Analyzer Model 1108*, respectively.

Optical rotation: Optical rotations were measured on a *Perkin-Elmer* Polarimeter 343.

Crystal structure analysis: The measurements were performed using a Molybdenum K_α–Source with a IPDS machine from *Stoe*. For data collection and cell refinement IPDS from *Stoe* (1999) and for data reduction xred by *Stoe* (1997) was used. The structure was refined and solved with *SHELXS*-97 and *SHELXL*-97 by *Sheldrick*, 1990. The refinement of F^2 was done against all reflections. The weighted R-factor wR and the goodness of fits are based on F^2, with F set to O for negative F^2. The crystals were grown from EA, pentane or CH_2Cl_2 at 23°C.

5.1.2 Chromatography

Gas-Chromatography: GC-analysis was performed with a *Focus* equipped with *Triplus* autosampler (*Thermo Electron*) and FID on a column CP-SIL 19 *Varian* (30 m x 0.25 mm) with hydrogen (constant flow of 1.5 ml min^{-1}) as carrier gas.

Enantiomeric analysis: GLC analysis was performed with a *Focus* equipped with *Triplus* autosampler (*Thermo Electron*) and FID on a column Lipodex E (25 m x 0.25 mm, chiral phase) with hydrogen (constant flow of 1.5 ml min^{-1}) as carrier gas.

Column-Chromatography: Preparative column chromatography was carried out using Merck SiO_2 (0.035–0.070 mm, type 60 A) with PE (b.p. 40–60°C), n-hexane,

ethyl acetate (EA) or CH_2Cl_2 as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminium sheets and the spots were visualized with molybdophosphoric acid reagent.

5.1.3 Solvents and Chemicals

Solvents: The solvents were purified according to standard procedures and dried. The solvents for the column chromatography [ethyl acetate (EA), dichloromethane (CH_2Cl_2), petroleum ether (PE, bp. 30–75°C) and *n*-hexane] were distilled prior to use. The following solvents were available from the Fluka or Acros company in absolute form and used without any further purification: THF, CH_2Cl_2, DMF, and toluene.

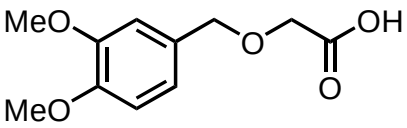
5.1.4 Working techniques

Procedures using $BF_3 \cdot OEt_2$, LDA (c = 2 mol dm^{-3} in Heptane/THF/Ethylbenzene), $NaBH_4$, NaH (60% dispersion in mineral oil) or vinyl magnesium bromide (c = 0.7 mol dm^{-3} in THF) were performed in flame dried glass-ware and with absolute solvent under nitrogen atmosphere.

5.2 Experimental Procedures for Canangone 19 and their Intermediates

5.2.1 Synthesis of DMB Protected Vinyl Ketone 9d

5.2.1.1 (3,4-Dimethoxybenzyloxy)acetic acid (82a)



A solution of 3,4-dimethoxybenzyl alcohol **89a** (14.7 g, 87.5 mmol) in abs. THF (30 ml) was added to a suspension of NaH (7.76 g, 194 mmol, 60% dispersion in mineral oil) in abs. THF (30 ml) under nitrogen at 0°C. After the mixture was stirred for 1 h, a solution of bromoacetic acid **90** (8.00 g, 57.6 mmol) in abs. THF (30 ml) was added, and the stirring was continued for 2 h at 23°C. Then more abs. THF (400 ml) was added and the mixture was heated to reflux for 2 d. It was then cooled to 0°C, diluted with ice cold water (250 ml) and extracted with CH_2Cl_2 (3 x 150 ml). The aqueous layer was acidified with conc. hydrochloric acid (15 ml) to pH 1 and extracted with CH_2Cl_2 (3 x 150 ml). The combined extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give acid **82a** (12.7 g, 56.1 mmol, 97%) as a yellow oil.

$C_{11}H_{14}O_5$ M = 226.23 g mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.78 (s, 3H), 3.80 (s, 3H), 4.05 (s, 2H), 4.49 (s, 2H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.80 (d, br., *J* = 8.1 Hz, 1H), 6.86 (s, br., 1H), 10.21 (br., s, 1H) ppm.

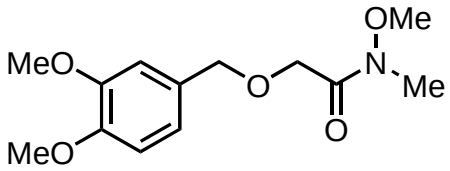
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 55.51 (CH_3), 55.56 (CH_3), 65.92 (CH_2), 72.96 (CH_2), 110.69 (CH), 111.17 (CH), 120.64 (CH), 128.89 (C), 148.69 (C), 148.79 (C), 174.87 (C) ppm.

IR (ATR): λ^{-1} = 3173 (m, br), 3085 (w), 3022 (w), 2964 (m), 2941 (w), 2870 (w), 2844 (w), 1772 (s), 1746 (s), 1609 (w), 1595 (m), 1515 (s), 1467 (m), 1456 (m), 1424 (s), 1373 (m), 1348 (w), 1322 (w), 1300 (w), 1258 (vs), 1178 (s), 1162 (vs), 1145 (vs), 1026 (vs), 969 (s), 940 (m), 927 (m), 902 (w), 816 (s), 768 (s), 744 (s) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 226 (67) [M^+], 167 (14), 151 (100), 139 (11).

Elemental analysis: calcd. C 58.40, H 6.24;
found C 58.10, H 6.41.

5.2.1.2 2-(3,4-Dimethoxybenzyloxy)-*N*-methoxy-*N*-methylacetamide (81a)



Et_3N (3.00 g, 29.6 mmol) was added to a stirred solution of acid **82a** (6.11 g, 27.0 mmol) in abs. CH_2Cl_2 (90 ml) at –5 to 0°C. The mixture was stirred for 15 min at 0°C before pivaloyl chloride (3.26 g, 27.0 mmol) was added. After 1 h further stirring at 0°C, $MeO(Me)NH_2Cl$ (2.63 g, 27.0 mmol) was added in one portion, followed by dropwise addition of Et_3N (5.5 g, 54 mmol). After additional stirring for 1.5 h at 0°C (or until the disappearance of the anhydride monitored by TLC, SiO_2, PE : EA 2 : 1, R_f = 0.43) at 0 to 5°C, the reaction mixture was washed with hydrochloric acid (20 ml, c = 1 mol dm^{-3}), sat. aq. $NaHCO_3$ soln. (20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (EA) to give Weinreb amide **81a** (6.71 g, 24.9 mmol, 92%) as a light yellow oil.

$C_{13}H_{19}NO_5$ M = 269.29 g mol^{-1}

R_f(SiO_2, EA) = 0.44.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.18 (s, 3H), 3.63 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.25 (s, 2H), 4.60 (s, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.90 (dd, *J* = 1.7 Hz, *J* = 8.1 Hz, 1H), 6.97 (d, *J* = 1.8 Hz, 1H) ppm.

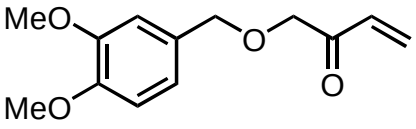
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 32.11 (CH_3), 55.68 (CH_3), 55.73 (CH_3), 61.20 (CH_3), 66.53 (CH_2), 72.95 (CH_2), 110.69 (CH), 111.25 (CH), 120.54 (CH), 129.92 (C), 148.61 (C), 148.90 (C), 170.88 (C) ppm.

IR (ATR): λ^{-1} = 3000 (w), 2939 (m), 2913 (w), 2838 (w), 1677 (s), 1609 (w), 1594 (m), 1516 (vs), 1464 (m), 1420 (m), 1393 (w), 1330 (m), 1263 (vs), 1237 (vs), 1182 (m), 1159 (vs), 1137 (vs), 1085 (s), 1027 (vs), 993 (s), 952 (m), 923 (w), 857 (m), 812 (m), 767 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 269 (8) [M^+], 167 (8), 152 (10), 151 (100), 107 (10), 103 (63), 73 (26).

Elemental analysis: calcd. C 57.98, H 7.11, N 5.20;
found C 58.40, H 7.24, N 5.39.

5.2.1.3 1-(3,4-Dimethoxybenzyloxy)-3-buten-2-one (9d)



A solution of vinyl magnesium bromide **80** (38.2 ml, 26.7 mmol, 0.7 mol dm^{-3} in THF) was added dropwise to a cooled (–5°C) solution of Weinreb amide **81a** (6.00 g, 22.3 mmol) in abs. THF (180 ml). The resulting mixture was slowly warmed and then stirred for 4 h at 23°C. Subsequently, it was transferred *via* a cannula into a cooled (0°C) solution of hydrochloric acid (140 ml, c = 1 mol dm^{-3}). The biphasic mixture was extracted with ether (3 x 30 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The

residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give a first fraction, divinyl alcohol **97** (532 mg, 2.01 mmol, 9%) as a yellow oil and a second fraction, vinyl ketone **9d** (3.80 g, 16.1 mmol, 72%) as a colorless oil.

$C_{13}H_{16}O_4$ M = 236.26 g mol^{-1}

R_f(SiO_2, PE : EA = 1 : 1) = 0.47.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.76 (s, 3H), 3.77 (s, 3H), 4.16 (s, 2H), 4.44 (s, 2H), 5.71 (d, *J* = 10.7 Hz, 1H), 6.21 (d, *J* = 17.6 Hz, 1H), 6.40 (dd, *J* = 10.7 Hz, *J* = 17.6 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.78 (d, br., *J* = 8.3 Hz, 1H), 6.84 (s, br., 1H) ppm.

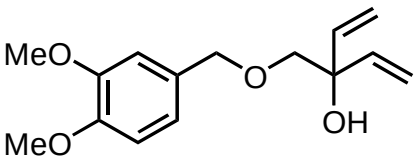
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 55.46 (CH_3), 55.51 (CH_3), 72.83 (CH_2), 73.07 (CH_2), 110.61 (CH), 110.99 (CH), 120.35 (CH), 128.73 (CH_2), 129.34 (C), 132.17 (CH), 148.54 (C), 148.75 (C), 196.78 (C) ppm.

IR (ATR): λ^{-1} = 3001 (w), 2938 (m), 2910 (w), 2866 (w), 2836 (m), 1737 (w), 1714 (m), 1697 (s), 1613 (w), 1593 (w), 1517 (vs), 1464 (m), 1419 (m), 1403 (w), 1365 (w), 1265 (s), 1237 (m), 1216 (w), 1159 (m), 1138 (m), 1066 (w), 1027 (m), 991 (w), 891 (w), 859 (w), 809 (w), 764 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 236 (5) [M$^+$], 166 (54), 151 (100), 107 (8).

HR-MS (CI, isobutane): calcd. 237.1127 for $C_{13}H_{17}O_4$,
found 237.1126 [M$^+$ + H].

5.2.1.4 3-(3,4-Dimethoxybenzyloxymethyl)penta-1,4-dien-3-ol (97)



The divinyl alcohol **97** (532 mg, 2.01 mmol, 9%) was obtained as a by-product (first fraction, yellow oil) in the synthesis of vinyl ketone **9d** from Weinreb amide **81a.** For procedure please see the page number 98-99**.**

$C_{15}H_{20}O_4$ M = 264.32 g mol^{-1}

R$_f$(SiO_2, PE : EA = 1 : 1) = 0.53.

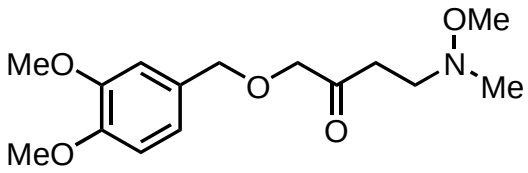
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 1H), 3.43 (s, 2H), 3.88 (s, 6H), 4.52 (s, 2H), 5.19 (dd, *J* = 1.2 Hz, *J* = 10.7 Hz, 2H), 5.35 (dd, *J* = 1.2 Hz, *J* = 17.4 Hz, 2H), 5.91 (dd, *J* = 10.7 Hz, *J* = 17.4 Hz, 2H), 6.84–6.98 (m, 3H) ppm.

IR (ATR): λ^{-1} = 3510 (br, m), 3083 (w), 3004 (m), 2956 (m), 2936 (m), 2911 (m), 2838 (m), 1717 (w), 1662 (m), 1592 (s), 1513 (vs), 1462 (s), 1453 (s), 1419 (s), 1339 (m), 1262 (vs), 1238 (vs), 1207 (m), 1151 (vs), 1135 (vs), 1093 (s), 1021 (vs), 924 (s), 866 (m), 809 (m), 782 (m), 764 (s), 732 (w), 703 (w), 626 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 264 (7) [M$^+$], 165 (7), 151 (100).

HR-MS (EI, 70 eV): calcd. 264.1362 for $C_{15}H_{20}O_4$,
found 264.1362 [M$^+$].

5.2.1.5 1-(3,4-Dimethoxybenzyloxy)-4-(methoxymethylamino)-2-butanone (96)



A solution of vinyl magnesium bromide **90** (13.0 ml, 8.90 mmol, 0.7 mol dm^{-3} in THF) was added dropwise to a cooled (–5°C) solution of Weinreb amide **81a** (2.00 g, 7.42 mmol) in abs. THF (60 ml). The resulting mixture was slowly warmed and then stirred for 4 h at 23°C. Subsequently, it was diluted with ice-cold hydrochloric acid (40 ml, c = 1 mol dm^{-3}). The biphasic mixture was extracted with ether (3 x 15 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give compound **96** (3.80 g, 16.1 mmol, 72%) as a colorless oil.

$C_{15}H_{23}NO_5$ M = 297.35 g mol^{-1}

$\mathbf{R_f}$(SiO_2, PE : EA = 1 : 1) = 0.37.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.47 (s, 3H), 2.61 (t, *J* = 6.8 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 3.35 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 4.00 (s, 2H), 4.44 (s, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.79 (dd, *J* = 1.9 Hz, *J* = 8.1 Hz, 1H), 6.84 (d, *J* = 1.8 Hz, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 36.75 (CH_2), 44.65 (CH_3), 54.52 (CH_2), 55.54 (CH_3), 55.61 (CH_3), 59.50 (CH_3), 72.91 (CH_2), 74.39 (CH_2), 110.65 (CH), 110.97 (CH), 120.34 (CH), 129.48 (C), 148.61 (C), 148.84 (C), 207.15 (C) ppm.

IR (ATR): λ^{-1} = 2951 (m), 2937 (m), 2894 (m), 2875 (m), 2852 (m), 2838 (m), 2809 (w), 1719 (s), 1607 (w), 1592 (w), 1515 (s), 1463 (m), 1442 (m), 1418 (m), 1377 (w),

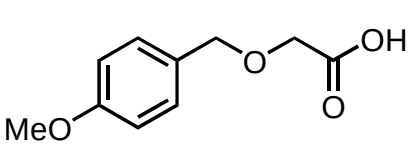
1334 (w), 1262 (vs), 1237 (s), 1195 (w), 1157 (s), 1137 (s), 1105 (m), 1043 (s), 1026 (vs), 914 (m), 855 (m), 809 (m), 765 (m), 729 (s) cm^{-1}.

MS (CI, isobutane): *m/z* (%) = 298 (73) [M^+ + H], 151 (100).

HR-MS (CI, isobutane): calcd. 298.1654 for $C_{15}H_{24}NO_5$, found 298.1654 [M^+ + H].

5.2.2 Synthesis of PMB Protected Vinyl Ketone 9e

5.2.2.1 (4-Methoxybenzyloxy)acetic acid[117] (82b)



A solution of 4-methoxybenzyl alcohol **89b** (4.54 g, 32.9 mmol) in abs. THF (10 ml) was added to a suspension of NaH (2.92 g, 73.1 mmol, 60% dispersion in mineral oil) in abs. THF (10 ml) under nitrogen at 0°C. After the mixture was stirred for 1 h at 0°C, a solution of bromoacetic acid **90** (3.00 g, 21.7 mmol) in abs. THF (10 ml) was added, and the mixture was further stirred for 2 h at 23°C, after which additional abs. THF (120 ml) was added, and the mixture heated to reflux for 2 d. It was then cooled to 0°C before it was diluted with ice cold water (50 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The aqueous layer was then acidified with conc. hydrochloric acid (5 ml) to pH 1 and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give acid **82b** (4.18 g, 21.3 mmol, 98%) as a light yellow oil.

$C_{10}H_{12}O_4$ M = 196.20 g mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.81 (s, 3H), 4.11 (s, 2H), 4.58 (s, 2H), 6.89–6.90 (m, 2H), 7.28–7.30 (m, 2H), 10.45 (br., s, 1H) ppm.

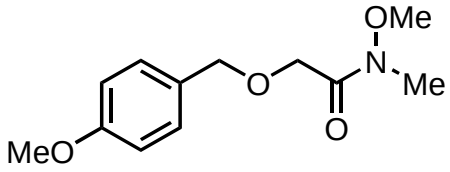
$^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 55.23 (CH_3), 66.20 (CH_2), 73.08 (CH_2), 113.96 (2CH), 128.57 (C), 129.83 (2CH), 159.62 (C), 175.27 (C) ppm.

IR (ATR): λ^{-1} = 3161 (m, br), 3002 (w), 2956 (w), 2937 (w), 2909 (w), 2838 (w), 1728 (vs), 1612 (s), 1585 (w), 1463 (w), 1441 (w), 1424 (w), 1302 (w), 1246 (vs), 1212 (m), 1175 (m), 1108 (s), 1032 (m), 948 (w), 924 (w), 848 (w), 890 (m), 761 (w), 668 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 196 (19) [M^+], 137 (78), 121 (100), 77 (8).

HR-MS (EI, 70 eV): calcd. 196.0736 for $C_{10}H_{12}O_4$,
found 196.0735 [M^+].

5.2.2.2 *N*-Methoxy-2-(4-methoxybenzyloxy)-*N*-methylacetamide (81b)



Et_3N (2.20 g, 21.8 mmol) was added to a stirred solution of acid **82b** (3.88 g, 19.8 mmol) in abs. CH_2Cl_2 (60 ml) at –5 to 0°C. The mixture was stirred for 15 min at 0°C before pivaloyl chloride (2.38 g, 19.8 mmol) was added. After 75 min stirring at 0°C MeO(Me)NH_2Cl (1.93 g, 19.8 mmol) was added in one portion, followed by dropwise addition of Et_3N (4.00 g, 39.6 mmol). After additional stirring for 2 h (or until the disappearance of anhydride monitored by TLC, SiO_2, PE : EA = 1 : 1, R_f = 0.75) at 0 to 5°C, the reaction mixture was washed with hydrochloric acid (10 ml, c = 1 mol dm^{-3}), sat. $NaHCO_3$ soln. (10 ml) and brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give Weinreb amide **81b** (4.08 g, 17.1 mmol, 86%) as a light yellow oil.

$C_{12}H_{17}NO_4$ M = 239.27 g mol^{-1}

R_f(SiO_2, PE : EA = 1 : 1) = 0.28.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.19 (s, 3H), 3.63 (s, 3H), 3.80 (s, 3H), 4.25 (s, 2H), 4.60 (s, 2H), 6.87–6.89 (m, 2H), 7.31–7.33 (m, 2H) ppm.

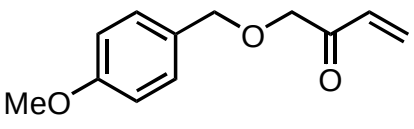
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 32.17 (CH_3), 55.20 (CH_3), 61.30 (CH_3), 66.62 (CH_2), 72.74 (CH_2), 113.70 (2CH), 129.51 (C), 129.64 (2CH), 159.28 (C), 171.04 (C) ppm.

IR (ATR): λ^{-1} = 2998 (w), 2938 (w), 2907 (w), 2872 (w), 2837 (w), 1676 (vs), 1612 (m), 1585 (w), 1512 (s), 1462 (m), 1441 (m), 1391 (w), 1327 (m), 1302 (m), 1246 (vs), 1174 (m), 1134 (m), 1112 (m), 1084 (s), 1031 (s), 992 (s), 954 (w), 930 (w), 820 (m), 759 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 239 (17) [M$^+$], 121 (100), 103 (57), 73 (14).

HR-MS (EI, 70 eV): calcd. 239.1158 for $C_{12}H_{17}NO_4$,
found 239.1159 [M$^+$].

5.2.2.3 1-(4-Methoxybenzyloxy)-3-buten-2-one (9e)



A solution of vinyl magnesium bromide **80** (6.60 ml, 4.63 mmol, 0.7 mol dm^{-3} in THF) was added dropwise to a cooled (–5°C) solution of Weinreb amide **81b** (0.930 g, 3.86 mmol) in abs. THF (30 ml). The resulting mixture was slowly warmed and then stirred for 4.5 h at 23°C. Subsequently, it was transferred via a cannula into a cooled (0°C) solution of hydrochloric acid (20 ml, c = 1 mol

dm^{-3}). The biphasic mixture was extracted with ether (3 x 10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give vinyl ketone **9e** (0.590 g, 2.86 mmol, 74%) as a colorless oil.

$C_{12}H_{14}O_3$ M = 206.24 g mol^{-1}

$\mathbf{R_f}$(SiO_2, PE : EA = 1 : 1) = 0.60.

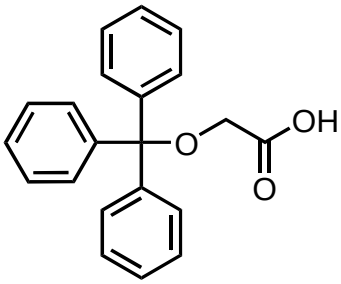
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.81 (s, 3H), 4.24 (s, 2H), 4.55 (s, 2H), 5.81 (d, *J* = 10.7 Hz, 1H), 6.33 (d, *J* = 17.6 Hz, 1H), 6.54 (dd, *J* = 10.8 Hz, *J* = 17.7 Hz, 1H), 6.88–6.90 (m, 2H), 7.28–7.30 (m, 2H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 55.24 (CH_3), 72.96 (CH_2), 73.50 (CH_2), 113.88 (2CH), 129.12 (CH_2), 129.15 (C), 129.65 (2CH), 132.46 (CH), 159.48 (C), 197.30 (C) ppm.

IR (ATR): λ^{-1} = 3057 (w), 3036 (w), 2989 (w), 2951 (w), 2932 (w), 2904 (w), 2843 (w), 2825 (w), 1722 (s), 1700 (s), 1607 (w), 1590 (w), 1521 (m), 1510 (s), 1480 (w), 1461 (m), 1442 (m), 1394 (w), 1343 (w), 1259 (vs), 1220 (s), 1194 (m), 1146 (m), 1088 (s), 1040 (w), 1026 (w), 995 (m), 940 (w), 925 (w), 881 (w), 849 (m), 739 (m) cm^{-1}.

5.2.3 Synthesis of Trityl Protected Vinyl Ketone 9f

5.2.3.1 Trityloxyacetic acid[119] (82c)



A solution of trityl chloride **91** (2.80 g, 10.0 mmol) in abs. CH_2Cl_2 (25 ml) was added dropwise to a stirred solution of glycolic acid **92** (0.806 g, 10.6 mmol) and Et_3N (3.80 g, 38.0 mmol) in abs. CH_2Cl_2 (25 ml) at –5 to 0°C. The resulting mixture was stirred at the same temperature for 1 h and then warmed to 23°C and further stirred for 16 h. The reaction mixture was acidified (pH = 3) with aqueous $KHSO_4$ (20 ml, c = 1 mol dm^{-3}). The layers were separated and the organic layer was washed with brine (2 x 10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (CH_2Cl_2 : MeOH = 4 : 1) to give acid **82c** (2.32 g, 7.29 mmol, 73%) as a colorless oil.

$C_{21}H_{18}O_3$ M = 318.37 g mol^{-1}

R_f(SiO_2, CH_2Cl_2 : MeOH = 4 : 1) = 0.40.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.87 (s, 2H), 7.23–7.26 (m, 3H), 7.30–7.33 (m, 6H), 7.45–7.47 (m, 6H), 9.95 (br., s, 1H) ppm.

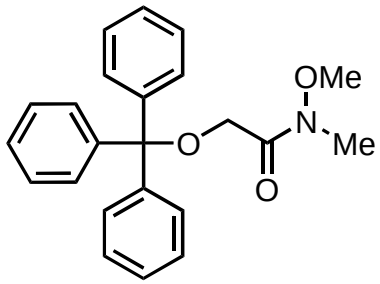
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 62.03 (CH_2), 87.83 (C), 127.43 (3CH), 128.49 (6CH), 128.58 (6CH), 142.86 (3C), 174.87 (C) ppm.

IR (ATR): λ^{-1} = 3427 (br, m), 3087 (m), 3060 (m), 3027 (m), 2922 (m), 2861 (m), 2768 (m), 2670 (m), 2570 (m), 1728 (vs), 1599 (m), 1492 (s), 1448 (vs), 1325 (m), 1220 (s), 1185 (m), 1156 (s), 1112 (vs), 1034 (m), 1013 (s), 1002 (s), 989 (s), 903 (s), 851 (w), 764 (vs), 748 (vs), 734 (vs), 698 (vs), 635 (vs) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 318 (35) [M^+], 259 (52), 243 (100), 183 (22), 165 (46), 105 (48), 77 (17).

HR-MS (EI, 70 eV): calcd. 318.1256 for $C_{21}H_{18}O_3$,
found 318.1254 [M^+].

5.2.3.2 *N*-Methoxy-*N*-methyl-2-trityloxyacetamide (81c)



Et_3N (0.770 g, 7.60 mmol) was added to a stirred solution of acid **82c** (2.20 g, 6.91 mmol) in abs. CH_2Cl_2 (30 ml) at –5 to 0°C. The mixture was stirred for 15 min at 0°C before pivaloyl chloride (0.833 g, 6.91 mmol) was added. After 2.5 h stirring at 0°C $MeO(Me)NH_2Cl$ (0.674 g, 6.91 mmol) was added in one portion, followed by dropwise addition of Et_3N (1.40 g, 13.8 mmol). After additional stirring for 2 h (or until the disappearance of the anhydride monitored by TLC, SiO_2, PE : EA 1 : 1, R_f = 0.78) at 0 to 5°C, the reaction mixture was washed with hydrochloric acid (10 ml, c = 1 mol dm^{-3}), sat. $NaHCO_3$ soln. (10 ml) and brine (10 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give Weinreb amide **81c** (2.20 g, 6.08 mmol, 88%) as a colorless oil.

$C_{23}H_{23}NO_3$ M = 361.43 g mol^{-1}

R_f(SiO_2, PE : EA = 1 : 1) = 0.56.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.12 (s, 3H), 3.42 (s, 3H), 3.91 (s, 2H), 7.21–7.25 (m, 3H), 7.29–7.32 (m, 6H), 7.51–7.53 (m, 6H) ppm.

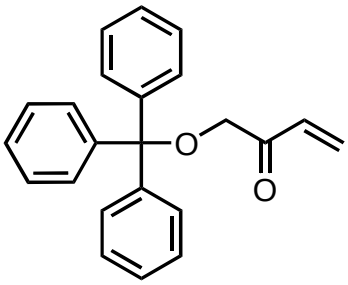
$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 32.29 (CH_3), 61.19 (CH_3), 62.08 (CH_2), 87.20 (C), 127.07 (3CH), 127.86 (6CH), 128.65 (3CH), 128.72 (3CH), 143.51 (3C), 170.49 (C) ppm.

IR (ATR): λ^{-1} = 3085 (w), 3055 (w), 3031 (w), 3023 (w), 3001 (w), 2969 (w), 2936 (w), 2906 (w), 1681 (vs), 1596 (w), 1490 (m), 1461 (m), 1447 (s), 1425 (m), 1390 (m), 1329 (m), 1219 (m), 1178 (m), 1154 (m), 1126 (m), 1079 (s), 1032 (w), 989 (m), 901 (m), 762 (m), 747 (m), 731 (m), 705 (vs) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 361 (49) [M^+], 243 (100), 164 (19).

HR-MS (EI, 70 eV): calcd. 361.1678 for $C_{23}H_{23}NO_3$,
found 361.1679 [M^+].

5.2.3.3 1-Trityloxy-3-buten-2-one (9f)



A solution of vinyl magnesium bromide **80** (8.5 ml, 5.97 mmol, 0.7 mol dm^{-3} in THF) was added dropwise to a cooled (–5°C) solution of Weinreb amide **81c** (1.80 g, 4.98 mmol) in abs. THF (50 ml). The resulting mixture was slowly warmed and then stirred for 1.5 h at 23°C. Subsequently, it was transferred via a cannula into a cooled (0°C) solution of hydrochloric acid (40 ml, c = 1 mol dm^{-3}). The biphasic mixture was extracted with ether (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was purified by column chromatography on SiO_2 (PE : EA = 4 : 1) to give vinyl ketone **9f** (1.40 g, 4.26 mmol, 86%) as a colorless oil.

$C_{23}H_{20}O_2$ M = 328.40 g mol^{-1}

R_f(SiO_2, PE : EA = 4 : 1) = 0.53.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.92 (s, 2H), 5.73 (dd, *J* = 1.4 Hz, *J* = 10.7 Hz, 1H), 6.25 (dd, *J* = 1.4 Hz, *J* = 17.5 Hz, 1H), 6.66 (dd, *J* = 10.7 Hz, *J* = 17.5 Hz, 1H), 7.23–7.26 (m, 3H), 7.29–7.32 (m, 6H), 7.45–7.47 (m, 6H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 69.06 (CH_2), 87.43 (C), 127.27 (3CH), 127.99 (6CH), 128.57 (6CH), 128.92 (CH_2), 132.32 (CH), 143.22 (3C), 196.90 (C) ppm.

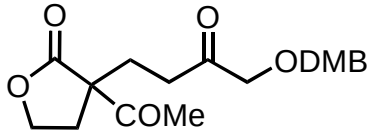
IR (ATR): λ^{-1} = 3086 (w), 3058 (w), 3032 (w), 3023 (w), 2891 (w), 2841 (w), 1715 (s), 1697 (vs), 1613 (m), 1596 (w), 1511 (w), 1490 (s), 1447 (s), 1400 (s), 1319 (w), 1288 (w), 1217 (s), 1177 (m), 1155 (m), 1065 (s), 1032 (m), 984 (m), 948 (w), 927 (w), 900 (m), 851 (w), 828 (w), 763 (s), 746 (s), 698 (vs) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 328 (12) [M^+], 243 (100), 165 (22), 105 (5).

HR-MS (EI, 70 eV): calcd. 328.1463 for $C_{23}H_{20}O_2$,
found 328.1463 [M^+].

5.2.4 Synthesis of Michael Product 79a

5.2.4.1 Procedure 1 for the Iron Catalyzed Michael Reaction 3-Acetyl-3-[4-(3,4-dimethoxybenzyloxy)-3-oxobutyl]-4,5-dihydro-2-furanone (79a)



$FeCl_3 \cdot 6\ H_2O$ (20 mg, 74 µmol) was added to a solution of vinyl ketone **9d** (250 mg, 1.06 mmol) and 2-acetylbutyrolactone **12h** (189 mg, 1.48 mmol) in CH_2Cl_2 (0.5 ml). The resulting mixture was stirred for 16 h at 23°C. Then the reaction mixture was concentrated *in vacuo* and the residue

was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give in a first fraction hexamethoxytribenzocyclononane **99** (138 mg, 0.306 mmol, 32%) as a colorless solid, mp. 225–226°C. A second fraction was Michael product **79a** (35 mg, 94 µmol, 10%), a colorless oil.

$C_{19}H_{24}O_7$ M = 364.39 g mol^{-1}

R_f(SiO_2, PE : EA = 1 : 1) = 0.31.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.98 (td, *J* = 8.5 Hz, *J* = 13.0 Hz, 1H), 2.13 (ddd, *J* = 5.9 Hz, *J* = 9.4 Hz, *J* = 14.8 Hz, 1H), 2.29 (s, 3H), 2.29–2.35 (m, 1H), 2.38–2.50 (m, 2H), 2.78 (ddd, *J* = 3.7 Hz, *J* = 7.3 Hz, *J* = 13.0 Hz, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.00 (s, 2H), 4.14 (dt, *J* = 7.4 Hz, *J* = 8.9 Hz, 1H), 4.28 (dt, *J* = 3.7 Hz, *J* = 8.8 Hz, 1H), 4.49 (s, 2H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.85 (dd, *J* = 1.7 Hz, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 1.5 Hz, 1H) ppm.

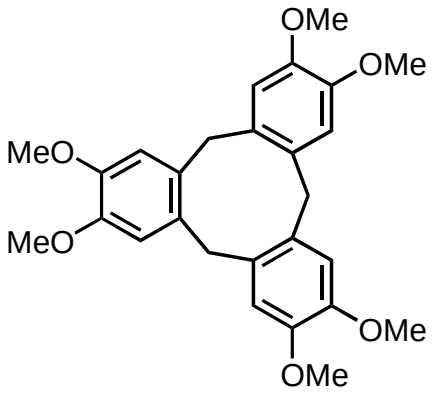
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 25.68 (CH_3), 27.11 (CH_2), 29.80 (CH_2), 34.06 (CH_2), 55.83 (CH_3), 55.87 (CH_3), 60.19 (C), 65.99 (CH_2), 73.42 (CH_2), 74.54 (CH_2), 110.89 (CH), 111.26 (CH), 120.71 (CH), 129.32 (C), 148.97 (C), 149.11 (C), 175.22 (C), 202.38 (C), 206.90 (C) ppm.

IR (ATR): λ^{-1} = 2999 (w), 2936 (m), 2918 (m), 2868 (w), 2838 (w), 1762 (s), 1712 (vs), 1607 (w), 1593 (m), 1516 (s), 1464 (m), 1455 (m), 1419 (m), 1371 (m), 1363 (m), 1337 (w), 1264 (s), 1238 (s), 1159 (vs), 1139 (s), 1107 (m), 1090 (m), 1026 (vs), 949 (w), 856 (w), 812 (m), 765 (m), 747 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 364 (17) [M$^+$], 166 (42), 151 (100), 87 (12).

HR-MS (EI, 70 eV): calcd. 364.1522 for $C_{19}H_{24}O_7$,
found 364.1521 $[M^+]$.

5.2.4.2 2,3,7,8,12,13-Hexamethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononane[128] (99)



The hexamethoxytribenzocyclononane **99** (138 mg, 0.306 mmol, 32%) was obtained as the by-product (first fraction, colorless solid) in the synthesis of Michael product **79a** from vinyl ketone **9d.** For procedure please see the page numbers 109-110.

$C_{27}H_{30}O_6$ M = 450.52 g mol^{-1}

$\mathbf{R_f}$(SiO_2, PE : EA = 1 : 1) = 0.34.

Melting point: 225–226°C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.54 (d, *J* = 13.8 Hz, 3H), 3.84 (s, 18H), 4.76 (d, *J* = 13.7 Hz, 3H), 6.83 (s, 6H) ppm.

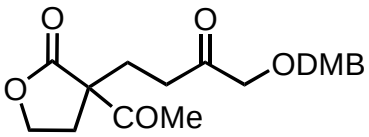
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 36.43 ($3CH_2$), 55.99 ($6CH_3$), 113.11 (6CH), 131.75 (6C), 147.68 (6C) ppm.

IR (ATR): nu(tilde) = 3059 (w), 3001 (w), 2936 (m), 2912 (m), 2958 (w), 2836 (m), 1714 (s), 1697 (s), 1610 (m), 1593 (m), 1514 (vs), 1463 (s), 1418 (s), 1403 (m), 1366 (w), 1333 (w), 1261 (vs), 1236 (vs), 1194 (m), 1157 (vs), 1137 (vs), 1109 (s), 1065 (s), 1025 (vs), 989 (s), 855 (m), 809 (s), 764 (s), 732 (s), 700 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 450 (100) [M^+], 419 (78), 299 (68), 281 (22), 268 (18), 151 (22), 69 (15).

HR-MS (EI, 70 eV): calcd. 450.2042 for $C_{27}H_{30}O_6$, found 450.2041 [M^+].

5.2.4.3 Procedure 2 for the Base Catalyzed Michael Product 79a

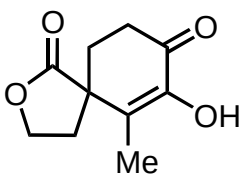


NaO*t*Bu (12 mg, 0.125 mmol) was added to a cooled (–5°C) solution of vinyl ketone **9d** (600 mg, 2.54 mmol) and 2-acetylbutyrolactone **12h** (357 mg, 2.79 mmol) in CH_2Cl_2 (5 ml). The resulting mixture was slowly warmed to 23°C and then stirred for 18 h. Then the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1, R_f = 0.31) to give Michael product **79a** (796 mg, 2.18 mmol, 86%) as a colorless oil.

For analytical data please see the page numbers 110-111.

5.2.5 Attempted Synthesis of Spirolactone 75

5.2.5.1 7-Hydroxy-6-methyl-2-oxaspiro[4.5]-6-decene-1,8-dione (100)



Ice-cold conc. H_2SO_4 (354 mg, 3.61 mmol) was added to a solution of a Michael product **79a** (88 mg, 0.241 mmol) in CH_2Cl_2 (1 ml) at –5°C. The resulting mixture was stirred at the same temperature for 1 h. It was then diluted with sat. aq. $NaHCO_3$ soln. (40 ml) and extracted with CH_2Cl_2 (4 x 15 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to obtain a first

fraction, hexamethoxytribenzocyclononane **99** (22 mg, 0.048 mmol, 20%, R_f = 0.34) as a colorless solid (For the analytical data please see the page number 111-112). As a second fraction, cyclized product **100** (22 mg, 0.111 mmol, 46%, R_f = 0.28) was obtained as a colorless solid.

$C_{10}H_{12}O_4$ M = 196.20 g mol^{-1}

R_f(SiO_2, PE : EA = 1 : 1) = 0.28.

Melting point: 122–123°C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.88 (s, 3H), 2.09 (ddd, *J* = 5.0 Hz, *J* = 6.1 Hz, *J* = 13.6 Hz, 1H), 2.31–2.37 (m, 2H), 2.49–2.58 (m, 2H), 2.76 (ddd, *J* = 4.9 Hz, *J* = 6.1 Hz, *J* = 17.7 Hz, 1H), 4.34 (dt, *J* = 7.3 Hz, *J* = 9.3 Hz, 1H), 4.46 (dt, *J* = 3.1 Hz, *J* = 9.2 Hz, 1H), 6.30 (s, 1H, OH) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 12.83 (CH_3), 29.51 (CH_2), 31.47 (CH_2), 31.56 (CH_2), 48.25 (C), 65.60 (CH_2), 126.96 (C), 145.61 (C), 177.76 (C), 191.99 (C) ppm.

IR (ATR): λ^{-1} = 3351 (br., m), 2989 (m), 2962 (m), 2939 (m), 2920 (m), 2878 (w), 2855 (w), 1745 (vs), 1672 (vs), 1650 (vs), 1479 (w), 1449 (m), 1420 (m), 1378 (vs), 1362 (s), 1343 (m), 1322 (m), 1284 (m), 1266 (m), 1218 (s), 1203 (s), 1191 (s), 1175 (vs), 1148 (vs), 1128 (m), 1074 (w), 1059 (m), 1019 (vs), 987 (s), 975 (m), 960 (w), 942 (w), 911 (w), 869 (m), 822 (w), 797 (w), 736 (m), 687 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 196 (100) [M$^+$], 152 (42), 137 (14), 124 (44), 109 (48), 95 (27), 67 (15).

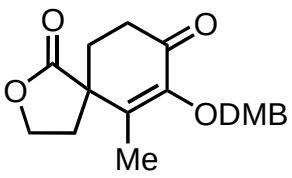
HR-MS (EI, 70 eV): calcd. 196.0736 for $C_{10}H_{12}O_4$,
found. 196.0735 [M$^+$].

5.2.5.2 Procedure for an Attempt of Aldol Cyclization with Lewis Acid:

$BF_3 \cdot OEt_2$ (24 mg, 0.169 mmol) was added to a cooled (–78°C) solution of Michael product **79a** (55 mg, 0.151 mmol) and the mixture stirred for 6 h at the same temperature. It was then diluted with sat. aq. $NaHCO_3$ soln. (2 ml) and extracted with CH_2Cl_2 (3 x 2 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1, R_f = 0.34), to give hexamethoxytribenzocyclononane **99** (21 mg, 0.061 mmol, 41%) as a colorless solid.

For the analytical data please see the page numbers 111–112.

5.2.5.3 7-(3,4-Dimethoxybenzyloxy)-6-methyl-2-oxaspiro[4.5]-6-decene-1,8-dione (104)



Pyrrolidine (15 mg, 0.211 mmol) and acetic acid (13 mg, 0.216 mmol) were subsequently added to a solution of Michael product **79a** (76 mg, 0.208 mmol) in CH_2Cl_2 (2.5 ml) at 0°C. The resulting mixture was warmed to 23°C and stirred for 18 h and then the volatile materials were removed *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 4 : 1) to give as a first fraction, enolether **104** (32 mg, 0.092 mmol, 44%, R_f = 0.25), and as a second fraction, alcohol **103** (28 mg, 0.08 mmol, 37%, R_f = 0.20), both as a colorless oils.

$C_{19}H_{22}O_6$ M = 346.37 g mol^{-1}

R_f(SiO_2, PE : EA = 4 : 1) = 0.25.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.80 (s, 3H), 2.05 (td, *J* = 5.1 Hz, *J* = 13.5 Hz, 1H), 2.31–2.38 (m, 2H), 2.40–2.44 (m, 1H), 2.51 (ddd, *J* = 4.8 Hz, *J* = 12.1 Hz, *J* = 17.0 Hz,

1H), 2.72 (td, *J* = 5.0 Hz, *J* = 17.2 Hz, 1H), 3.88 (s, 3H), 3.91 (s, 3H), 4.33 (dt, *J* = 7.5 Hz, *J* = 9.2 Hz, 1H), 4.44 (dt, *J* = 3.4 Hz, *J* = 9.2 Hz, 1H), 4.76 (d, *J* = 10.9 Hz, 1H), 4.95 (d, *J* = 10.9 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.91 (dd, *J* = 1.8 Hz, *J* = 8.1 Hz, 1H), 7.00 (d, *J* = 1.7 Hz, 1H) ppm.

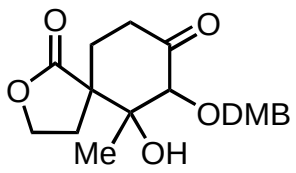
$^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 13.85 (CH_3), 29.54 (CH_2), 31.47 (CH_2), 34.36 (CH_2), 49.04 (C), 55.88 (CH_3), 56.09 (CH_3), 65.56 (CH_2), 73.97 (CH_2), 110.81 (CH), 111.98 (CH), 121.33 (CH), 129.61 (C), 142.84 (C), 148.89 (C), 149.04 (C), 149.47 (C), 177.47 (C), 192.34 (C) ppm.

IR (ATR): λ^{-1} = 2996 (m), 2938 (m), 2875 (m), 2837 (m), 1762 (vs), 1680 (vs), 1620 (w), 1608 (w), 1528 (m), 1515 (vs), 1463 (s), 1453 (s), 1419 (m), 1378 (s), 1349 (w), 1335 (w), 1307 (m), 1265 (vs), 1239 (s), 1212 (m), 1193 (s), 1169 (vs), 1159 (vs), 1077 (w), 1025 (vs), 989 (s), 918 (w), 858 (w), 813 (w), 732 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 346 (80) [M^+], 151 (100).

HR-MS (EI, 70 eV): calcd. 346.1416 for $C_{19}H_{22}O_6$,
found 346.1415 [M^+].

5.2.5.4 7-(3,4-Dimethoxybenzyloxy)-6-hydroxy-6-methyl-2-oxaspiro[4.5]decane-1,8-dione (103)



The alcohol **103** (28 mg, 0.08 mmol, 37%) was obtained as a second fraction (colorless oil) in the spiroannulation reaction of Michael product **79a** using pyrrolidine and acetic acid. For procedure please see the page number 114.

$C_{19}H_{24}O_7$ M = 346.39 g mol^{-1}

R_f(SiO_2, PE : EA = 4 : 1) = 0.20.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.18 (s, 3H), 1.81 (ddd, *J* = 5.4 Hz, *J* = 11.8 Hz, *J* = 17.2 Hz, 1H), 2.05 (ddd, *J* = 4.4 Hz, *J* = 7.7 Hz, *J* = 12.6 Hz, 1H), 2.18 (ddd, *J* = 4.2 Hz, *J* = 6.4 Hz, *J* = 14.2 Hz, 1H), 2.44 (ddd, *J* = 4.5 Hz, *J* = 5.3 Hz, *J* = 14.4 Hz, 1H), 2.77 (td, *J* = 8.4 Hz, *J* = 13.1 Hz, 1H), 2.84 (s, 1H), 2.91 (ddd, *J* = 6.5 Hz, *J* = 12.0 Hz, *J* = 18.5 Hz, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 4.27 (dt, *J* = 7.9 Hz, *J* = 8.7 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.41 (dt, *J* = 4.4 Hz, *J* = 8.8 Hz, 1H), 4.79 (d, *J* = 11.1 Hz, 1H), 4.92 (s, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.91 (dd, *J* = 1.5 Hz, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 1.4 Hz, 1H) ppm.

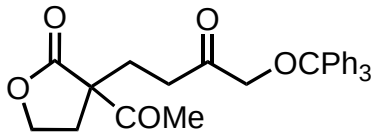
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 19.47 (CH_3), 29.30 (CH_2), 31.12 (CH_2), 35.71 (CH_2), 50.33 (C), 55.90 ($2CH_3$), 65.79 (CH_2), 73.41 (CH_2), 77.42 (C), 85.04 (CH), 110.97 (CH), 111.62 (CH), 120.90 (CH), 130.01 (C), 148.94 (C), 149.01 (C), 179.01 (C), 206.73 (C) ppm.

IR (ATR): λ^{-1} = 3493 (br. m), 2982 (w), 2938 (m), 2918 (m), 2875 (w), 2837 (w), 1753 (vs), 1725 (vs), 1608 (w), 1592 (w), 1515 (vs), 1464 (m), 1454 (m), 1421 (m), 1379 (m), 1320 (w), 1264 (s), 1238 (s), 1158 (s), 1137 (vs), 1119 (s), 1070 (m), 1028 (vs), 964 (w), 915 (w), 890 (w), 861 (w), 810 (w), 731 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 364 (10) [M^+], 166 (37), 151 (100).

HR-MS (EI, 70 eV): calcd. 364.1522 for $C_{19}H_{24}O_7$,
found 364.1521 [M^+].

5.2.5.5 *rac*-Acetyl-3-(3-oxo-4-trityloxybutyl)-4,5-dihydro-2-furanone (79b)



NaO*t*Bu (5 mg, 0.052 mmol) was added to a cooled (–5°C) solution of vinyl ketone **9f** (320 mg, 0.974 mmol) and 2-acetylbutyrolactone **12h** (137 mg, 1.07 mmol) in abs. CH_2Cl_2 (5 ml). The resulting mixture was slowly warmed and then stirred for 18 h at 23°C. The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give Michael product **79b** (365 mg, 7.99 mmol, 82%) as a colorless oil.

$C_{29}H_{28}O_5$ M = 456.53 g mol^{-1}

$\mathbf{R_f}$(SiO_2, PE : EA = 1 : 1) = 0.37.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.95 (td, *J* = 8.6 Hz, *J* = 13.0 Hz, 1H), 2.06–2.12 (m, 1H), 2.26 (td, *J* = 7.2 Hz, *J* = 8.1 Hz, 1H), 2.30 (s, 3H), 2.44–2.47 (m, 2H), 2.80 (ddd, *J* = 3.6 Hz, *J* = 7.2 Hz, *J* = 12.9 Hz, 1H), 3.79 (s, 2H), 4.15 (dt, *J* = 7.4 Hz, *J* = 8.7 Hz, 1H), 4.28 (dt, *J* = 3.7 Hz, *J* = 8.8 Hz, 1H), 7.24–7.27 (m, 3H), 7.30–7.33 (m, 6H), 7.40–7.42 (m, 6H) ppm.

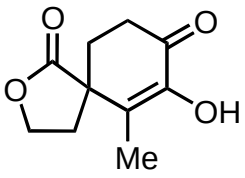
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 25.75 (CH_3), 27.17 (CH_2), 29.67 (CH_2), 34.42 (CH_2), 60.28 (C), 66.03 (CH_2), 69.80 (CH_2), 87.63 (C), 127.40 (3CH), 128.06 (6CH), 128.47 (3CH), 128.53 (3CH), 143.01 (3C), 175.22 (C), 202.38 (C), 206.78 (C) ppm.

IR (ATR): λ^{-1} = 3086 (w), 3058 (w), 3031 (w), 2917 (w), 2899 (w), 2840 (w), 1764 (s), 1711 (vs), 1596 (w), 1490 (m), 1448 (m), 1371 (m), 1448 (m), 1371 (m), 1360 (m), 1319 (w), 1283 (w), 1218 (m), 1153 (s), 1083 (m), 1030 (s), 1001 (w), 982 (w), 891 (w), 947 (w), 908 (s), 765 (s), 746 (vs), 705 (vs) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 456 (8) [M^+], 243 (100), 165 (17).

HR-MS (EI, 70 eV): calcd. 456.1937 for $C_{29}H_{28}O_5$,
found 456.1936 [M^+].

5.2.5.6 Procedure for an Aldol Cyclization Under Acidic (H_2SO_4) Conditions

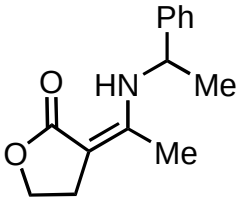


Ice-cold conc. H_2SO_4 (393 mg, 4.01 mmol) was added to a solution of a Michael product **79b** (122 mg, 0.267 mmol) in CH_2Cl_2 (3 ml) at –5°C. The resulting mixture was stirred at the same temperature for 1 h, it was then diluted with sat. aq. $NaHCO_3$ soln. (50 ml) and extracted with CH_2Cl_2 (4 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give cyclized product **100** (33 mg, 0.17 mmol, 62%) as a colorless solid.

For analytical data please see the page number 113.

5.2.6 Synthesis of Spirolactone 77a

5.2.6.1 *rac*-(*Z*)-3-[1-(1-Phenylethylamino)ethylidene]-4,5-dihydro-2-furanone[129] (78)



A mixture of 2-Acetylbutyrolactone **12h** (1.00 g, 7.80 mmol) and *rac*-phenyl ethylamine **107** (945 mg, 7.80 mmol) was stirred at 23°C for 4 h. It was then diluted with CH_2Cl_2 (20 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give enamino lactone **78** (1.60 g, 6.91 mmol, 89%) as a colorless oil.

$C_{14}H_{17}NO_2$ M = 231.29 g mol^{-1}

R_f(SiO_2, PE : EA = 1 : 1) = 0.45.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 6.8 Hz, 3H), 1.78 (s, 3H), 2.73–2.84 (m, 2H), 4.23–4.30 (m, 2H), 4.63 (pent, *J* = 7.0 Hz, 1H), 7.22–7.26 (m, 3H) 7.32–7.34 (m, 2H), 8.61 (d, br., *J* = 5.7 Hz, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 16.78 (CH_3), 24.87 (CH_3), 26.36 (CH_2), 52.95 (CH), 65.10 (CH_2), 86.10 (C), 125.42 (2CH), 127.10 (CH), 128.79 (2CH), 145.02 (C), 156.41 (C), 174.04 (C) ppm.

IR (ATR): λ^{-1} = 3285 (w), 3223 (w), 3083 (w), 3061 (w), 3028 (w), 2971 (w), 2922 (w), 2907 (w), 2865 (w), 1769 (w), 1686 (s), 1618 (vs), 1476 (w), 1453 (m), 1408 (w), 1371 (m), 1279 (w), 1225 (vs), 1156 (w), 1099 (m), 1026 (m), 999 (w), 966 (m), 894 (w), 767 (m), 702 (m) cm^{-1}.

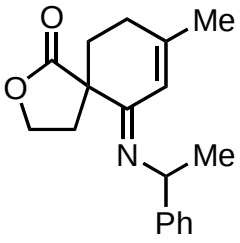
MS (EI, 70 eV): *m/z* (%) = 231 (82) [M$^+$], 216 (55) [M$^+$ – Me], 145 (10), 127 (24), 105 (100).

HR-MS (CI, isobutane): calcd. 232.1337 for $C_{14}H_{18}NO_2$, found 232.1338 [M$^+$ + H].

In analogy, (*R*)-phenyl ethylamine (*R*)-**107** (2.36 g, 19.5 mmol) was converted to (*R*)-**78** (4.26 g, 18.4 mmol, 94%) as a colorless solid, mp. 72–73°C. $[\alpha]_D^{20}$ = –512.4° (c = 1.15 in MeOH).

In analogy, (*S*)-phenyl ethylamine (*S*)-**107** (1.89 g, 15.6 mmol) was converted to (*S*)-**78** (3.31 g, 14.3 mmol, 92%) as a colorless solid, mp. 71–72°C. $[\alpha]_D^{20}$ = +474.9° (c = 0.86 in MeOH).

5.2.6.2 *rac*-8-Methyl-6-(1-phenylethylimino)-2-oxaspiro[4.5]-7-decen-1-one[129] (109a)

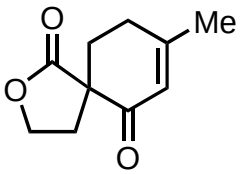


A solution of methyl vinyl ketone **9a** (170 mg, 2.42 mmol) was added to a solution of enamino lactone **78** (350 mg, 1.51 mmol) in abs. THF (5 ml). The mixture was stirred at 65°C for 18 h. The solvent was then removed under reduced pressure to give an orange colored residue **109a** (412 mg, 1.45 mmol, 96%). A ^{1}H-NMR spectrum shows two separate sp^2-CH resonances at δ = 6.24 and 6.21 ppm, which integrate to *dr* = 80 : 20.

$C_{18}H_{21}NO_2$ M = 283.36 g mol^{-1}

R$_f$(SiO_2, PE : EA = 1 : 1) = 0.50.

5.2.6.3 *rac*-8-Methyl-2-oxaspiro[4.5]-7-decene-1,6-dione[42] (77a)



The imine **109a** (524 mg, 1.85 mmol) was dissolved in a mixture of THF (5 ml) and 10% aqueous acetic acid (1.8 ml). The mixture was stirred at room te[42]mperature for 24 h. Subsequently, the solvent was removed *in vacuo*, the residue diluted with hydrochloric acid (2 ml, c = 1 mol dm^{-3}) and extracted with CH_2Cl_2 (4 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give ketone **77a** (152 mg, 0.843 mmol, 56%) as a light yellow solid.

$C_{10}H_{12}O_3$ M = 180.20 g mol^{-1}

R_f(SiO_2, PE : EA = 1 : 1) = 0.37.

Melting point: 63–64°C.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.98 (ddd, *J* = 5.2 Hz, *J* = 6.8 Hz, *J* = 13.8 Hz, 1H), 1.98 (d, *J* = 1.3 Hz, 3H), 2.10 (td, *J* = 8.6 Hz, *J* = 12.9 Hz, 1H), 2.28 (td, *J* = 5.9 Hz, *J* = 18.7 Hz, 1H), 2.40 (ddd, *J* = 5.2 Hz, *J* = 7.3 Hz, *J* = 13.6 Hz, 1H), 2.64 (ddd, *J* = 4.0 Hz, *J* = 6.9 Hz, *J* = 12.8 Hz, 1H), 2.69 (td, *J* = 6.0 Hz, *J* = 19.0 Hz, 1H), 4.32 (dt, *J* = 4.0 Hz, *J* = 8.8 Hz, 1H), 4.35 (dt, *J* = 7.0 Hz, *J* = 8.8 Hz, 1H), 5.87 (sextet, *J* = 1.3 Hz, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 24.31 (CH_3), 27.83 (CH_2), 30.56 (CH_2), 32.49 (CH_2), 52.67 (C), 65.81 (CH_2), 124.10 (CH), 164.13 (C), 175.72 (C), 194.31 (C) ppm.

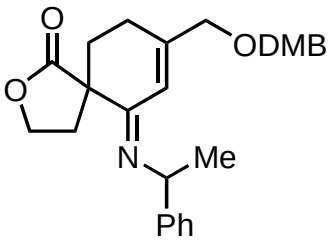
IR (ATR): λ^{-1} = 3058 (w), 2979 (w), 2928 (m), 2872 (w), 2832 (w), 1767 (vs), 1657 (vs), 1631 (s), 1478 (w), 1428 (m), 1378 (s), 1346 (m), 1324 (w), 1305 (w), 1283 (m), 1217 (s), 1186 (s), 1163 (m), 1140 (s), 1101 (w), 1061 (m), 1026 (s), 986 (m), 960 (m), 931 (m), 890 (w), 865 (m), 837 (w), 783 (w), 746 (w), 705 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 180 (19) [M$^+$], 152 (36), 134 (32), 121 (13), 82 (100).

HR-MS (EI, 70 eV): calcd. 180.0786 for $C_{10}H_{12}O_3$,
found 180.0789 [M$^+$].

5.2.7 Synthesis of Spirolactone 77b

5.2.7.1 *rac*-8-(3,4-Dimethoxybenzyloxymethyl)-6-(1-phenylethylimino)-2-oxaspiro[4.5]-7-decen-1-one (109b)



A solution of vinyl ketone **9d** (1.30 g, 5.50 mmol) in abs. THF (10 ml) was added to a solution of enamino lactone **78** (1.40 g, 6.05 mmol) in abs. THF (10 ml). The mixture was stirred at 65°C for 18 h. The solvent was then removed under reduced pressure, to give an orange colored residue **109b** (2.22 g, 4.94 mmol, 90%). A ^{1}H-NMR spectrum shows two separate sp^2-CH resonances at δ = 6.54 and 6.51 ppm, which integrate to *dr* = 83 : 17.

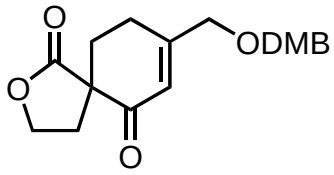
$C_{27}H_{31}NO_5$ M = 449.54 g mol^{-1}

R$_f$(SiO_2, PE : EA = 1 : 1) = 0.45.

In analogy, (*S*)-enamino lactone (*S*)-**78** (2.10 g, 9.10 mmol) was converted to (*R*)**–109b** (3.82 g, 8.50 mmol, 93%) with product *dr* = 86:14 from ^{1}H-NMR by integration of two separate sp^2-CH resonances.

In analogy, (*R*)-enamino lactone (*R*)-**78** (3.33 g, 14.4 mmol) was converted to (*S*)**–109b** (6.24 g, 13.9 mmol, 96%) with product *dr* = 87:13 from ^{1}H-NMR by integration of two separate sp^2-CH resonances.

5.2.7.2 *rac*-8-(3,4-Dimethoxybenzyloxymethyl)-2-oxaspiro[4.5]-7-decene-1,6-dione (77b)



The cyclized imine *rac*-**109b** (3.36 g, 7.47 mmol) was dissolved in a mixture of THF (15 ml) and 10% aqueous acetic acid (5.5 ml). The mixture was stirred at room temperature for 24 h, and then the solvent was removed *in vacuo*, the residue diluted with hydrochloric acid (5 ml, c = 1 mol dm^{-3}) and extracted with CH_2Cl_2 (4 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (CH_2Cl_2 : EA = 4 : 1) to give ketone **77b** (760 mg, 2.19 mmol, 40%) as a colorless oil.

$C_{19}H_{22}O_6$ M = 346.37 g mol^{-1}

R_f(SiO_2, CH_2Cl_2 : EA = 4 : 1) = 0.52.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.01–2.10 (m, 1H), 2.10 (dt, *J* = 13.1 Hz, *J* = 8.5 Hz, 1H), 2.29 (dt, *J* = 18.5 Hz, *J* = 5.8 Hz, 1H), 2.45 (ddd, *J* = 5.2 Hz, *J* = 6.4 Hz, *J* = 13.6 Hz, 1H), 2.71–2.78 (m, 2H), 3.88 (s, 3H; OCH_3), 3.89 (s, 3H; OCH_3), 4.11 (s, 2H; 8-CH_2), 4.36 (dt, *J* = 3.9 Hz, *J* = 8.7 Hz, 1H; H-3), 4.42 (dt, *J* = 7.1 Hz, *J* = 8.7 Hz, 1H; H-3), 4.50 (s, 2H; $ArCH_2$), 6.20 (pent, *J* = 1.5 Hz, 1H; H-7), 6.86–6.89 (m, 3H; ArH) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 23.27 (CH_2), 30.39 (CH_2), 32.41 (CH_2), 53.36 (C), 55.76 (CH_3), 55.80 (CH_3), 65.80 (CH_2), 71.12 (CH_2), 72.70 (CH_2), 110.88 (CH), 111.01 (CH), 120.36 (CH), 122.19 (CH), 129.75 (C), 148.73 (C), 148.97 (C), 162.79 (C), 175.38 (C), 194.24 (C) ppm.

IR (ATR): λ^{-1} = 3058 (w), 2997 (w), 2935 (m), 2920 (w), 2866 (w), 2837 (w), 1770 (vs), 1715 (w), 1663 (vs), 1607 (w), 1593 (w), 1516 (s), 1464 (m), 1452 (m), 1420 (m), 1375 (m), 1341 (w), 1264 (s), 1238 (m), 1217 (m), 1187 (m), 1158 (s), 1139 (s), 1101 (w), 1083 (w), 1059 (w), 1027 (s), 961 (w), 914 (w), 869 (w), 811 (w), 765 (w), 731 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 346 (40) [M^+], 167 (29), 151 (100).

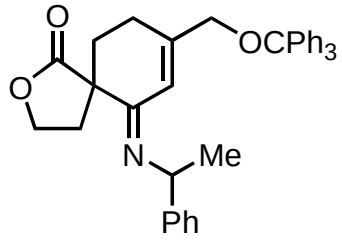
HR-MS (EI, 70 eV): calcd. 346.1416 for $C_{19}H_{22}O_6$,
found 346.1415 [M^+].

In analogy, cyclized imine (*R*)**–109b** (2.10 g, 9.10 mmol) was converted to (*R*)-**77b** (1.17 g, 3.37 mmol, 41%). $[\alpha]_D^{20}$ = –36.6° (c = 1.63 in MeOH).

In analogy, cyclized imine (*S*)**–109b** (3.33 g, 14.4 mmol) was converted to (*S*)-**77b** (1.94 g, 5.60 mmol, 43%). $[\alpha]_D^{20}$ = +47.2° (c = 3.14 in MeOH).

5.2.8 Synthesis of Sprolactone 77c

5.2.8.1 *rac*-6-(1-Phenylethylimino)-8-trityloxymethyl-2-oxaspiro[4.5]-7-decen-1-one (109c)



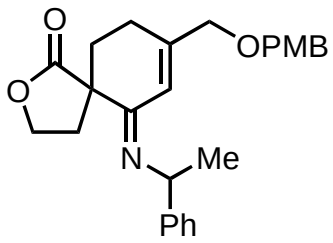
A solution of vinyl ketone **9f** (1.13 g, 3.45 mmol) in abs. THF (10 ml) was added to a solution of enamino lactone **78** (878 mg, 3.80 mmol) in abs. THF (5 ml). The mixture was stirred at 65°C for 18 h. The solvent was then removed under reduced pressure to give an orange colored residue **109c** (1.56 g, 2.87 mmol, 84%). A ^{1}H-NMR spectrum shows two separate sp^2-CH resonances at δ = 6.71 and 6.66 ppm, which integrate to *dr* = 91 : 9.

$C_{37}H_{35}NO_3$ M = 541.68 g mol^{-1}

R$_f$(SiO_2, PE : EA = 1 : 1) = 0.50.

5.2.9 Synthesis of Spirolactone 77d

5.2.9.1 *rac*-8-(4-Methoxybenzyloxymethyl)-6-(1-phenylethylimino)-2-oxaspiro[4.5]-7-decen-1-one (109d)

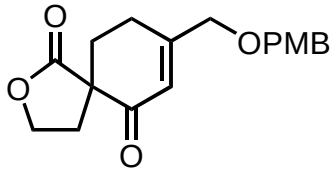


A solution of vinyl ketone **9e** (420 mg, 2.04 mmol) in abs. THF (4 ml) was added to a solution of enamino lactone **78** (517 mg, 2.24 mmol) in abs. THF (4 ml). The mixture was stirred at 65°C for 18 h. The solvent was then removed under reduced pressure to give an orange colored residue **109d** (0.796 g, 1.90 mmol, 93%). A ^{1}H-NMR spectrum shows two separate sp^2-CH resonances at δ = 6.46 and 6.42 ppm, which integrate to *dr* = 83 : 17.

$C_{26}H_{29}NO_4$ M = 419.51 g mol^{-1}

R$_f$(SiO_2, PE : EA = 1 : 1) = 0.45.

5.2.9.2 *rac*-8-(4-Methoxybenzyloxymethyl)-2-oxaspiro[4.5]-7-decene- 1,6-dione (77d)



The cyclized imine **109d** (1.01 g, 2.40 mmol) was dissolved in a mixture of THF (8 ml) and 10% aqueous acetic acid (2.8 ml). The mixture was stirred at room temperature for 24 h, and then the solvent was removed *in vacuo*, the residue diluted with hydrochloric acid (3 ml, c = 1 mol dm^{-3}) and extracted with CH_2Cl_2 (4 x 5 ml). The combined organic layers were dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (CH_2Cl_2 : EA = 4 : 1) to give ketone **77d** (98 mg, 0.309 mmol, 15%) as a light yellow oil.

$C_{18}H_{20}O_5$ M = 316.35 g mol^{-1}

R_f(SiO_2, CH_2Cl_2 : EA = 4 : 1) = 0.54.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.04 (ddd, *J* = 5.2 Hz, *J* = 7.1 Hz, *J* = 13.5 Hz, 1H), 2.11 (td, *J* = 8.6 Hz, *J* = 12.9 Hz, 1H), 2.28 (td, *J* = 6.0 Hz, *J* = 18.7 Hz, 1H), 2.45 (ddd, *J* = 5.2 Hz, *J* = 6.9 Hz, *J* = 13.6 Hz, 1H), 2.68–2.73 (m, 2H), 3.81 (s, 3H), 4.10 (s, 2H), 4.36 (dt, *J* = 3.8 Hz, *J* = 8.7 Hz, 1H), 4.40 (dt, *J* = 7.3 Hz, *J* = 8.7 Hz, 1H), 4.49 (s, 2H), 6.18 (pent, *J* = 1.8 Hz, 1H), 6.88–6.90 (m, 2H), 7.26–7.27 (m, 2H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 22.37 (CH_2), 30.55 (CH_2), 32.57 (CH_2), 53.43 (C), 55.30 (CH_3), 65.91 (CH_2), 71.22 (CH_2), 72.57 (CH_2), 113.88 (2CH), 122.36 (CH), 129.37 (2CH), 129.41 (C),159.42 (C), 162.87 (C), 175.43 (C), 194.31 (C) ppm.

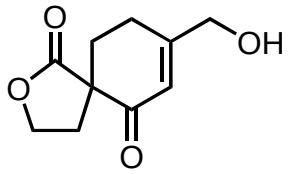
IR (ATR): λ^{-1} = 2997 (w), 2935 (w), 2916 (w), 2865 (w), 2840 (w), 1770 (s), 1724 (w), 1662 (vs), 1613 (m), 1587 (w), 1514 (s), 1455 (m), 1447 (m), 1426 (w), 1377 (m), 1346 (w), 1322 (w), 1301 (m), 1248 (s), 1217 (s), 1184 (s), 1177 (s), 1162 (m), 1144 (m), 1083 (m), 1060 (m), 1030 (vs), 998 (m), 963 (m), 911 (m), 872 (w), 821 (m), 731 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 316 (4) [M^+], 180 (15), 137 (50), 121 (100), 82 (8).

HR-MS (EI, 70 eV): calcd. 316.1311 for $C_{18}H_{20}O_5$,
found 316.1311 [M^+].

5.2.10 Synthesis of Canangone 19

5.2.10.1 *rac*-8-(Hydroxymethyl)-2-oxaspiro[4.5]-7-decene-1,6-dione (75)



TFA (34 ml of a 10% solution in CH_2Cl_2) was added to a solution of compound **77b** (213 mg, 0.614 mmol) in CH_2Cl_2 (2 ml) at 23°C. After stirring for 1.5 h at the same temperature, the reaction mixture was filtered through a pad of silica (5 cm) and washed with CH_2Cl_2 (15 ml). The volatile materials were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (CH_2Cl_2 : EA = 1 : 1) to give as first fraction hexamethoxytribenzocyclononane **99** (10 mg, 0.022 mmol, 4%, R_f = 0.75) as a light yellow solid. (For analytical data please see the page numbers 111–112). A second fraction was allylic alcohol **75** (84 mg, 0.428 mmol, 70%, R_f = 0.13), a light yellow oil.

$C_{10}H_{12}O_4$ M = 196.20 g mol^{-1}

R_f (SiO_2,CH_2Cl_2 : EA = 1 : 1) = 0.13.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.89 (t, *J* = 6.1 Hz, 1H; OH), 2.03–2.11 (m, 1H), 2.11 (dt, *J* = 13.0 Hz, *J* = 8.5 Hz, 1H), 2.27 (dt, *J* = 18.5 Hz, *J* = 5.5 Hz, 1H), 2.46 (ddd, *J* = 5.4 Hz, *J* = 6.2 Hz, *J* = 13.6 Hz, 1H), 2.69–2.80 (m, 2H), 4.25 (B part of an ABX–system, J_{BX} = 6.3 Hz, J_{AB} = 16.7 Hz, 1H; 8–CH*H*), 4.27 (A part of an ABX–system, J_{AX} = 5.6 Hz, J_{AB} = 16.7 Hz, 1H; 8–C*H*H), 4.36 (dt, *J* = 4.0 Hz, *J* = 8.7 Hz, 1H; H–3), 4.43 (dt, *J* = 7.1 Hz, *J* = 8.7 Hz, 1H; H–3), 6.20 (pent, *J* = 1.5 Hz, 1H; H–7) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 23.03 (CH_2), 30.49 (CH_2), 32.51 (CH_2), 53.65 (C), 64.49 (CH_2), 66.07 (CH_2), 120.71 (CH), 166.26 (C), 175.94 (C), 194.67 (C) ppm.

IR (ATR): λ^{-1} = 3447 (br, m), 2982 (w), 2927 (w), 2873 (w), 2842 (w), 1756 (vs), 1656 (vs), 1513 (w), 1479 (w), 1427 (m), 1377 (m), 1347 (m), 1323 (w), 1295 (m), 1216 (s), 1188 (s), 1159 (m), 1146 (m), 1127 (m), 1098 (w), 1052 (s), 1028 (vs), 997 (m), 960 (m), 930 (m), 866 (w), 791 (w), 731 (w), 707 (w) cm^{-1}.

MS (CI, isobutane): *m/z* (%) = 197 (100) $[M^+ + H]$.

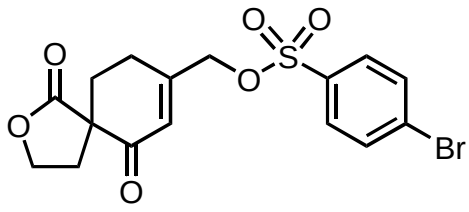
HR-MS (EI, 70 eV): calcd. 196.0735 for $C_{10}H_{12}O_4$, found. 196.0735 $[M^+]$.

GLC on Lipodex E (2 min at 60°C, then with 0.5 K min^{-1} to 160°C, then 1 min at 160°C, then with 0.2 K min^{-1} to 185°C, finally 150 min at 185°C): t_R(*R*) = 325 min, t_R(*S*) = 454 min.

In analogy, (*R*)-**77b** (1.80 g, 5.19 mmol) was converted to (*R*)-**75** (740 mg, 3.77 mmol, 72%) as a light yellow oil. GLC on Lipodex E (2 min at 60°C, then with 0.5 K min^{-1} to 160°C, then 1 min at 160°C, then with 0.2 K min^{-1} to 185°C, finally 150 min at 185°C): t_R(*R*) = 325 min (major), t_R(*S*) = 454 min (minor), 60% *ee*. $[\alpha]_D^{20}$ = –60.8° (c = 1.54 in MeOH).

In analogy, (*S*)-**77b** (1.50 g, 4.33 mmol) was converted to (*S*)-**75** (600 mg, 3.05 mmol, 71%) as a light yellow solid, mp. 84–85°C. GLC on Lipodex E (2 min at 60°C, then with 0.5 K min^{-1} to 160°C, then 1 min at 160°C, then with 0.2 K min^{-1} to 185°C, finally 150 min at 185°C): t_R(*R*) = 326 min (minor), t_R(*S*) = 446 min (major), 69% *ee*. $[\alpha]_D^{20}$ = +84.8° (c = 1.19 in MeOH).

5.2.10.2 *rac*-(1,6-Dioxo-2-oxaspiro[4.5]-7-decen-8-yl)methyl-4- bromobenzene sulfonate (112)



Et_3N (39 mg, 0.382 mmol) and brosyl chloride **111** (72 mg, 0.281 mmol) were subsequently added to a cooled solution of allylic alcohol *rac*-**75** (50 mg, 0.255 mmol) in CH_2Cl_2 (1 ml) at –5°C and the resulting mixture was stirred for 12 min at the same temperature. It was then washed with hydrochloric acid (1 ml, c = 1 mol dm^{-3}), sat. $NaHCO_3$ soln. (1 ml) and brine (1 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 1 : 1) to give *rac*-**112** (65 mg, 0.156 mmol, 61%) as a light yellow oil.

$C_{16}H_{15}BrO_6S$ M = 415.26 g mol^{-1}

R_f(SiO_2, PE : EA = 2 : 1) = 0.29.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.02 (ddd, *J* = 5.2 Hz, *J* = 7.6 Hz, *J* = 13.8 Hz, 1H), 2.08 (dt, *J* = 12.9 Hz, *J* = 8.4 Hz, 1H), 2.28 (dt, *J* = 18.7 Hz, *J* = 5.3 Hz, 1H), 2.40 (ddd, *J* = 5.3 Hz, *J* = 6.2 Hz, *J* = 13.7 Hz, 1H), 2.66–2.71 (m, 2H), 4.31–4.39 (m, 2H), 4.65 (A–part of an AB–system, *J* = 14.7 Hz, 1H), 4.67 (B–part of an AB–system, *J* = 15.0 Hz, 1H), 6.03 (pent, *J* = 1.3 Hz, 1H, H–7), 7.70–7.73 (m, 2H), 7.76–7.77 (m, 2H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 22.94 (CH_2), 30.16 (CH_2), 32.26 (CH_2), 53.13 (C), 65.93 (CH_2), 70.07 (CH_2), 123.91 (CH), 129.33 (2CH), 129.63 (C), 132.82 (2CH), 134.36 (C), 156.30 (C), 174.79 (C), 193.51 (C) ppm.

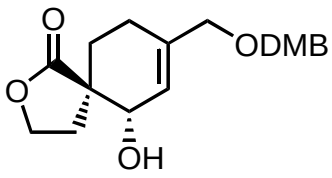
IR (ATR): λ^{-1} = 3102 (w), 3082 (w), 3063 (w), 3017 (w), 2983 (w), 2950 (w), 2915 (w), 2890 (w), 2872 (w), 2825 (w), 1759 (s), 1662 (s), 1632 (m), 1575 (m), 1471 (m), 1454 (w), 1443 (w), 1421 (w), 1393 (m), 1385 (m), 1363 (s), 1347 (m), 1284 (m), 1260 (m), 1217 (m), 1178 (vs), 1135 (m), 1091 (m), 1070 (m), 1057 (m), 1032 (s), 997 (m), 957 (vs), 931 (m), 889 (m), 872 (m), 792 (vs), 774 (vs), 731 (m), 721 (m), 655 (m) cm^{-1}.

MS (CI, isobutane): *m/z* (%) = 415 (100) [M^+ + H], 259 (14), 179 (19).

HR-MS (CI, isobutane): calcd. 414.9851 for $C_{16}H_{16}BrO_6S$,
found 414.9850 [M^+ + H].

In analogy, (*R*)-**75** (200 mg, 1.02 mmol) was converted to (*R*)-**112** (325 mg, 0.782 mmol, 76%) as a light yellow solid, mp. 126°C, $[\alpha]_D^{20}$ = –44.8° (c = 0.59 in MeOH). Singe crystals were grown from CH_2Cl_2–pentane at 23°C.

5.2.10.3 *rac*-8-(3,4-Dimethoxybenzyloxymethyl)-6-hydroxy-2-oxaspiro[4.5]-7-decen-1-one (76)



$CeCl_3 \cdot 7\ H_2O$ (248 mg, 0.666 mmol) was added to a cooled solution of ketone **77b** (220 mg, 0.635 mmol) in MeOH (4 ml) at –5°C. After stirring the reaction mixture for 30 min at –5 to 0°C, $NaBH_4$ (25 mg, 0.67 mmol) was added portionwise and the resulting mixture was stirred for 2 h at the same temperature. Then the reaction mixture was diluted with water (2 ml) and the solvent was removed *in vacuo*. The residue was extracted with EtOAc (4 x 2 ml). The combined organic layers were dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was purified by column chromatography on SiO_2 (CH_2Cl_2 : EA = 1 : 1) to obtain two fractions, first, (*R**,*S**)-diastereomer **76** (50 mg, 0.143

mmol, 23%, R_f = 0.50) and secondly, (*R**,*R**)-diastereomer **76** (47 mg, 0.13 mmol, 21%, R_f = 0.46), both as a colorless oils.

(*R,*S**)-Diastereomer (76)**

$C_{19}H_{24}O_6$ M = 348.39 g mol^{-1}

R_f(SiO_2, CH_2Cl_2 : EA = 1 : 1) = 0.50.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.77 (ddd, *J* = 1.9 Hz, *J* = 5.6 Hz, *J* = 13.6 Hz, 1H), 1.90–1.95 (m, 1H), 1.97 (ddd, *J* = 6.5 Hz, *J* = 8.7 Hz, *J* = 14.9 Hz, 1H), 2.03–2.10 (m, 1H), 2.17 (dd, *J* = 5.7 Hz, *J* = 17.5 Hz, 1H), 2.48–2.53 (m, 2H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 2H), 4.29 (dt, *J* = 6.0 Hz, *J* = 8.6 Hz, 1H), 4.36 (dt, *J* = 6.4 Hz, *J* = 8.6 Hz, 1H), 4.41 (s, 2H), 4.60 (s, 1H), 5.63 (s, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 1.8 Hz, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 1.8 Hz, 1H) ppm.

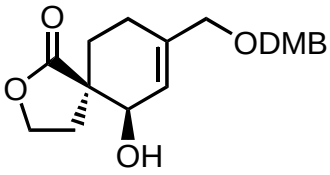
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 22.75 (CH_2), 26.55 (CH_2), 28.13 (CH_2), 47.82 (C), 55.85 (CH_3), 55.90 (CH_3), 66.54 (CH_2), 70.09 (CH), 72.01 (CH_2), 72.75 (CH_2), 110.92 (CH), 111.11 (CH), 120.34 (CH), 126.58 (CH), 130.53 (C), 136.73 (C), 148.66 (C), 149.01 (C), 181.58 (C) ppm.

IR (ATR): λ^{-1} = 3497 (br m), 2993 (m), 2933 (m), 2862 (m), 2839 (m), 1757 (vs), 1669 (w), 1607 (w), 1593 (w), 1515 (vs), 1463 (s), 1452 (s), 1419 (m), 1379 (m), 1340 (w), 1262 (vs), 1236 (vs), 1189 (vs), 1156 (vs), 1138 (vs), 1084 (s), 1052 (s), 1026 (vs), 951 (w), 913 (m), 855 (m), 810 (m), 765 (m), 728 (s) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 348 (27) [M$^+$], 166 (93), 151 (100).

HR-MS (EI, 70 eV): calcd. 348.1573 for $C_{19}H_{24}O_6$,
found. 348.1572 $[M^+]$.

(*R,*R**)-Diastereomer (76)**



The (*R**,*R**)-diastereomer **76** (47 mg, 0.13 mmol, 21%) was obtained as a second fraction (colorless oil) in the Luche reduction of ketone **77b** using $CeCl_3 \cdot 7\ H_2O$ and $NaBH_4$.

$C_{19}H_{24}O_6$ M = 348.39 g mol^{-1}

$\mathbf{R_f}$(SiO_2, CH_2Cl_2 : EA = 1 : 1) = 0.46.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.71 (td, *J* = 5.9 Hz, *J* = 13.5 Hz, 1H), 2.05–2.11 (m, 2H), 2.17–2.23 (m, 1H), 2.25–2.31 (m, 2H), 2.98 (d, *J* = 5.5 Hz, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 3.92 (s, 2H), 4.13 (t, *J* = 5.1 Hz, 1H), 4.28 (dt, *J* = 7.7 Hz, *J* = 8.1 Hz, 1H), 4.34 (dt, *J* = 4.5 Hz, *J* = 8.8 Hz, 1H), 4.40 (d, *J* = 11.5 Hz, 1H), 4.43 (d, *J* = 11.5 Hz, 1H), 5.80 (pent. *J* = 1.7 Hz, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 2.0 Hz, *J* = 8.1 Hz, 1H), 6.88 (d, *J* = 2.0 Hz, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 22.90 (CH_2), 24.94 (CH_2), 32.03 (CH_2), 45.77 (C), 55.82 (CH_3), 55.86 (CH_3), 65.22 (CH_2), 68.62 (CH), 71.95 (CH_2), 72.94 (CH_2), 110.88 (CH), 111.14 (CH), 120.35 (CH), 123.24 (CH), 130.59 (C), 138.95 (C), 148.59 (C), 148.95 (C), 179.49 (C) ppm.

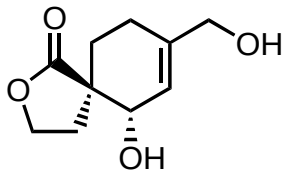
IR (ATR): λ^{-1} = 3486 (br m), 3000 (m), 2934 (m), 2917 (m), 2857 (m), 2840 (m), 1759 (vs), 1609 (w), 1594 (m), 1516 (vs), 1465 (s), 1454 (s), 1421 (m), 1377 (s), 1332 (w),

1263 (vs), 1237 (vs), 1220 (m), 1158 (vs), 1140 (vs), 1066 (s), 1026 (vs), 964 (w), 944 (w), 914 (s), 858 (m), 812 (m), 767 (m), 729 (vs), 647 (m)
cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 348 (72) [M^+], 166 (50), 151 (100), 87 (18).

HR-MS (EI, 70 eV): calcd. 348.1573 for $C_{19}H_{24}O_6$,
found. 348.1572 [M^+].

5.2.10.4 *rac*-6-Hydroxy-8-(hydroxymethyl)-2-oxaspiro[4.5]-7-decen-1-one (74)



$CeCl_3 \cdot 7\ H_2O$ (874 mg, 2.36 mmol) was added to a cooled solution of allylic alcohol **75** (443 mg, 2.26 mmol) in MeOH (8 ml) at –5°C. After stirring the reaction mixture for 30 min at –5 to 0°C, $NaBH_4$ (89 mg, 2.4 mmol) was added portionwise and the resulting mixture was stirred for 1.5 h at the same temperature. It was then diluted with water (5 ml) and ca. 80% of the solvent was removed *in vacuo*. The residue was extracted with EtOAc (4 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (EA) to obtain two fractions, first, (*R**,*S**)-diastereomer **74** (155 mg, 0.782 mmol, 35%, R_f = 0.28) as a colorless solid (single crystals were grown from EA–pentane at 23°C) and secondly, (*R**,*R**)-diastereomer **74** (142 mg, 0.716 mmol, 32%, R_f = 0.20) as a colorless oil.

(*R,*S**)-Diastereomer 74**

$C_{10}H_{14}O_4$ M = 198.22 g mol^{-1}

R_f(SiO_2, EA) = 0.28.

Melting point: 99–101°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.59 (s, br., 1H; OH), 1.79 (ddd, *J* = 2.8 Hz, *J* = 5.2 Hz, *J* = 13.4 Hz, 1H), 1.90–2.03 (m, 2H), 2.07–2.15 (m, 2H), 2.20–2.23 (m, 1H), 2.51 (ddd, *J* = 6.2 Hz, *J* = 8.5 Hz, *J* = 14.6 Hz, 1H), 4.06 (s, 2H; 8–CH_2), 4.30 (dt, *J* = 6.1 Hz, *J* = 8.5 Hz, 1H; 3–H), 4.38 (dt, *J* = 6.3 Hz, *J* = 8.6 Hz, 1H; 3–H), 4.62 (s, br., 1H; 6–H), 5.63 (sex, *J* = 1.7 Hz, 1H; 7–H) ppm.

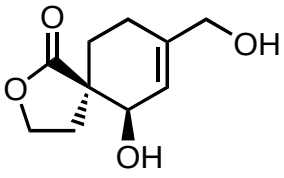
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 22.36 (CH_2), 26.65 (CH_2), 28.22 (CH_2), 47.90 (C), 65.42 (CH_2), 66.75 (CH_2), 70.11 (CH), 123.99 (CH), 139.30 (C), 181.99 (C) ppm.

IR (ATR): λ^{-1} = 3395 (br, s), 2987 (w), 2925 (m), 2867 (w), 1745 (vs), 1450 (w), 1434 (w), 1382 (m), 1344 (w), 1271 (w), 1220 (s), 1193 (s), 1060 (m), 1028 (s), 893 (w), 830 (w), 745 (w), 704 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 198 (8) [M^+], 180 (22), 134 (18), 99 (43), 84 (100), 82 (50), 49 (65).

HR-MS (CI, isobutane): calcd. 199.0970 for $C_{10}H_{15}O_4$, found 199.0970 [$M^+ + H$].

(*R,*R**)-Diastereomer (74)**



The (*R**,*R**)-diastereomer **74** (142 mg, 0.716 mmol, 32%) was obtained as a second fraction (colorless oil) in the Luche reduction of allylic alcohol **75** using $CeCl_3 \cdot 7\ H_2O$ and $NaBH_4$.

$C_{10}H_{14}O_4$ M = 198.22 g mol^{-1}

R_f(SiO_2, EA) = 0.20.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, br., 1H; OH), 1.69–1.78 (m, 1H), 2.00–2.13 (m, 1H), 2.10 (ddd, *J* = 4.5 Hz, *J* = 7.1 Hz, *J* = 12.8 Hz, 1H), 2.24 (ddd, *J* = 5.0 Hz, *J* = 8.7 Hz, *J* = 19.5 Hz, 1H), 2.19–2.30 (m, 2H), 3.04 (d, *J* = 5.6 Hz, 1H; 6–OH), 4.06–4.09 (m, 2H; 8–CH_2), 4.15 (t, *J* = 4.4 Hz, 1H; 6–H), 4.31 (dt, *J* = 7.5 Hz, *J* = 8.8 Hz, 1H; 3–H), 4.37 (dt, *J* = 4.5 Hz, *J* = 8.8 Hz, 1H; 3–H), 5.80–5.84 (m, 1H; 7–H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 22.55 (CH_2), 25.20 (CH_2), 32.24 (CH_2), 45.95 (C), 65.40 (CH_2), 65.77 (CH_2), 68.75 (CH), 121.01 (CH), 141.51 (C), 179.73 (C) ppm.

IR (ATR): λ^{-1} = 3387 (br s), 2922 (m), 2863 (w), 1749 (vs), 1486 (w), 1450 (w), 1431 (w), 1377 (m), 1259 (w), 1215 (s), 1188 (s), 1167 (s), 1056 (s), 1028 (vs), 962 (w) cm^{-1}.

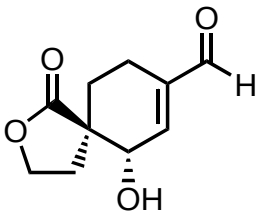
MS (CI, isobutane): *m/z* (%) = 199 (2) [M^+ + H], 181 (100), 163 (27), 87 (5).

HR-MS (CI, isobutane): calcd. 199.0970 for $C_{10}H_{15}O_4$,
found 199.0969 [M^+ + H].

In analogy, (*R*)-**75** (450 mg, 2.29 mmol) was converted to (5*R*,6*S*)-**74** (165 mg, 0.832 mmol, 36%) as a colorless oil (slowly solidifying at 5°C), $[\alpha]_D^{20}$ = +30.6° (c = 0.47 in MeOH), and (*R*,*R*)-**74** (150 mg, 0.756 mmol, 33%) as a colorless solid, mp. 105°C, $[\alpha]_D^{20}$ = –53.2° (c = 0.88 in MeOH).

In analogy, (*S*)-**75** (300 mg, 1.51 mmol) was converted to (5*S*,6*R*)-**74** (96 mg, 0.48 mmol, 32%) as a colorless solid, mp. 78–79°C, $[\alpha]_D^{20}$ = –32.8° (c = 0.71 in MeOH), and (*S*,S)-**74** (110 mg, 0.554 mmol, 37%) as a colorless oil (slowly solidifying at 5°C), $[\alpha]_D^{20}$ = +66.4° (c = 1.02 in MeOH).

5.2.10.5 (*R**,*S**)-6-Hydroxy-1-oxo-2-oxaspiro[4.5]-7-decene-8-carbaldehyde (19)



TEMPO **110** (3 mg, 18 µmol) and CuCl (2 mg, 18 µmol) were added to a stirred solution of (*R**,*S**)-diol **74** (12 mg, 61 µmol) in abs. DMF (1 ml) at 23°C under nitrogen atmosphere. The reaction mixture flask was then cooled with N_2 (l), evacuated, filled with O_2 (1 atm, balloon), and the mixture was stirred at 23°C for 75 min. Subsequently, it was diluted with sat. aq. $CuSO_4$ soln. (1 ml) and extracted with EtOAc (4 x 1 ml). The combined organic layers were washed with water (2 ml) and brine (2 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (EA) to obtain (*R**,*S**)-6-*epi*-Canangone **19** (9 mg, 0.046 mmol, 75%) as a colorless oil.

$C_{10}H_{12}O_4$ M = 196.20 g mol^{-1}

$\mathbf{R_f}$(SiO_2, EA) = 0.60.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.80–1.94 (m, 2H), 1.97 (ddd, *J* = 6.1 Hz, *J* = 8.4 Hz, *J* = 14.4 Hz, 1H), 2.14–2.22 (m, 1H), 2.43–2.50 (m, 1H), 2.50 (ddd, *J* = 6.4 Hz, *J* = 8.6 Hz, *J* = 14.8 Hz, 1H), 3.44 (d, *J* = 6.1 Hz, 1H; 6–OH), 4.34 (dt, *J* = 6.3 Hz, *J* = 8.6 Hz, 1H; 3–H), 4.42 (dt, *J* = 6.1 Hz, *J* = 8.7 Hz, 1H; 3–H), 4.83–4.87 (m, 1H; 6–H), 6.64–6.66 (m, 1H), 9.51 (s, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 18.48 (CH_2), 26.05 (CH_2), 27.49 (CH_2), 48.22 (C), 66.77 (CH_2), 70.27 (CH), 140.81 (C), 149.65 (CH), 181.10 (C), 192.92 (C) ppm.

IR (ATR): λ^{-1} = 3437 (br, m), 2986 (w), 2930 (m), 2870 (w), 2849 (w), 1759 (vs), 1683 (vs), 1485 (w), 1451 (w), 1433 (w), 1381 (m), 1342 (w), 1221 (m), 1193 (s), 1167 (m),

1059 (m), 1030 (s), 1005 (m), 954 (w), 899 (w), 871 (w), 821 (w), 784 (w), 748 (w), 707 (w) cm^{-1}.

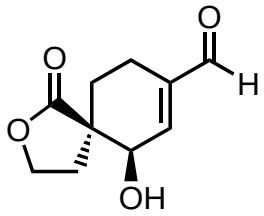
MS (EI, 70 eV): *m/z* (%) = 196 (14) [M^+], 178 (14), 167 (9), 150 (12), 134 (23), 121 (40), 105 (55), 99 (100), 91 (44), 77 (73), 62 (36), 51 (27), 41 (35).

HR-MS (CI, isobutane): calcd. 197.0814 for $C_{10}H_{13}O_4$, found. 197.0814 [$M^+ + H$].

In analogy, (5*R*,6*S*)-**74** (40 mg, 0.202 mmol) was converted to (5*R*,6*S*)-**19** (30 mg, 0.153 mmol, 76%) as a colorless oil (slowly solidifying at 5°C), $[\alpha]_D^{20}$ = +58.9° (c = 0.43 in MeOH).

In analogy, (5*S*,6*R*)-**74** (44 mg, 0.222 mmol) was converted to (5*S*,6*R*)-**19** (34 mg, 0.173 mmol, 78%) as a colorless oil (slowly solidifying at 5°C), $[\alpha]_D^{20}$ = –71.4° (c = 1.56 in MeOH).

5.2.10.6 (*R**,*R**)-6-Hydroxy-1-oxo-2-oxaspiro[4.5]-7-decene-8-carbaldehyde (19)



TEMPO **110** (4 mg, 26 µmol) and CuCl (3 mg, 26 µmol) were added to a stirred solution of (*R**,*R**)-diol **74** (17 mg, 86 µmol) in abs. DMF (1 ml) at 23°C under nitrogen atmosphere. The reaction mixture flask was then cooled with N_2 (l), evacuated, filled with O_2 (1 atm, balloon), and the mixture was stirred at 23°C for 75 min. Subsequently, it was diluted with sat. aq. $CuSO_4$ soln. (1 ml) and extracted with EtOAc (4 x 1 ml). The combined organic layers were washed with water (2 ml) and brine (2 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (EA) to obtain (*R**,*R**)-Canangone **19** (13 mg, 0.07 mmol, 77%) as a colorless oil.

$C_{10}H_{12}O_4$ M = 196.20 g mol^{-1}

R_f(SiO_2, EA) = 0.40.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.76 (ddd, *J* = 6.0 Hz, *J* = 8.0 Hz, *J* = 14.0 Hz, 1H; 10–H), 2.07 (ddd, *J* = 3.6 Hz, *J* = 7.1 Hz, *J* = 12.8 Hz, 1H; 4–H), 2.21 (dt, *J* = 14.0 Hz, *J* = 5.6 Hz, 1H; 10–H), 2.29 (dtt, *J* = 18.7 Hz, *J* = 5.7 Hz, *J* = 1.4 Hz, 1H; 9–H), 2.39 (dddt, *J* = 18.7 Hz, *J* = 7.9 Hz, *J* = 5.8 Hz, *J* = 2.1 Hz, 1H; 9–H), 2.47 (dt, *J* = 12.8 Hz, *J* = 8.9 Hz, 1H; 4–H), 3.11 (t, *J* = 7.8 Hz, 1H; 6–OH), 4.33 (dt, *J* = 7.1 Hz, *J* = 9.1 Hz, 1H; 3–H), 4.39 (dt, *J* = 3.6 Hz, *J* = 9.1 Hz, 1H; 3–H), 4.36–4.40 (m, 1H; 6–H), 6.68 (dt, *J* = 3.4 Hz, *J* = 1.8 Hz, 1H; 7–H), 9.51 (s, 1H; 8–CHO) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 18.66 (CH_2), 25.59 (CH_2), 32.21 (CH_2), 46.61 (C), 65.40 (CH_2), 69.35 (CH), 142.07 (C), 145.81 (CH), 178.31 (C), 193.20 (C) ppm.

IR (ATR): λ^{-1} = 3432 (br, m), 2924 (m), 2854 (w), 2726 (w), 1750 (s), 1674 (vs), 1485 (w), 1451 (w), 1429 (w), 1378 (m), 1256 (w), 1215 (m), 1176 (s), 1124 (s), 1091 (w), 1061 (m), 1024 (vs), 998 (m), 962 (m), 902 (m), 869 (w), 826 (w), 783 (w), 769 (w), 711 (m), 658 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 196 (3) [M^+], 167 (4), 149 (12), 134 (100), 121 (19), 105 (100), 99 (88), 91 (58), 77 (65), 65 (19), 53 (28), 41 (32). HRMS (CI, isobutane): calcd. 197.0814 (for $C_{10}H_{13}O_4$), found: 197.0814 [M^+ + H].

HR-MS (CI, isobutane): calcd. 197.0814 for $C_{10}H_{13}O_4$, found. 197.0814 [M^+ + H].

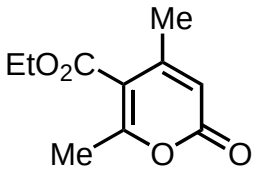
In analogy, (*R*,*R*)-**74** (40 mg, 0.202 mmol) was converted to (*R*,*R*)-**19** (31 mg, 0.158 mmol, 78%) as a colorless solid, mp. 92–93°C, $[\alpha]_D^{20}$ = –67.0° (c = 1.25 in MeOH).

In analogy, (*S*,*S*)-**74** (48 mg, 0.242 mmol) was converted to (*S*,*S*)-**19** (36 mg, 0.183 mmol, 76%) as a colorless solid, mp. 98–99°C, $[\alpha]_D^{20}$ = +107.5° (c = 1.87 in MeOH).

5.3 Experimental Procedures for Attempted Synthesis of Chamigrene 18

5.3.1 Synthesis of Dibromide 83

5.3.1.1 Ethyl 2,4-Dimethyl-6-oxo-6*H*-pyran-3-carboxylate[142] (113)



Ethyl acetoacetate **88** (133 g, 1.02 mol) was added dropwise to cooled (–5°C) conc. H_2SO_4 (184 g, 1.88 mol) over a period of 1 h (Caution: the temperature of the reaction mixture should be kept below 30°C). The resulting mixture was then stirred for 6 d at 23°C. It was then poured onto ice (500 g) and extracted with ether (3 x 500 ml). The combined organic layers were washed with H_2O (200 ml) and dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a mixture of **113** and **114** [61.8 g, ratio **113**/**114** = 2 : 1 by ^{1}H-NMR; *i.e.* **113** (41.2 g, 0.210 mmol, 21%), **114** (20.6 g, 0.123 mmol, 12%)], as a light yellow oil.

$C_{10}H_{12}O_4$ M = 196.20 g mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.2 Hz, 3H), 2.23 (d, *J* = 0.9 Hz, 3H), 2.41 (s, 3H), 4.35 (q, *J* = 7.1 Hz, 2H), 6.03 (br. s, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 14.16 (CH_3), 19.58 (CH_3), 21.27 (CH_3), 61.78 (CH_2), 110.39 (C), 112.07 (CH), 155.28 (C), 160.81 (C), 165.46 (C), 167.12 (C) ppm.

IR for **113** and **114** (ATR): λ^{-1} = 3466 (br, m), 3052 (m), 2982 (br, m), 2933 (m), 2906 (m), 2873 (m), 2762 (m), 2600 (m), 2485 (m), 2339 (w), 1719 (vs), 1676 (vs), 1661 (vs), 1620 (s), 1542 (s), 1443 (m), 1400 (s), 1375 (s), 1369 (s), 1301 (m), 1292 (m), 1243 (vs),

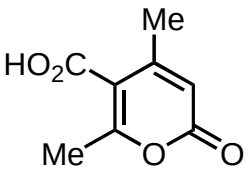
1218 (s), 1163 (m), 1081 (vs), 1048 (m), 1033 (s), 962 (m), 911 (m), 884 (s), 877 (s), 858 (s), 844 (vs), 779 (m), 753 (s), 735 (s), 703 (w), 666 (w), 634 (s) cm^{-1}.

GC-MS (EI, 70 eV): *m/z* (%) = 196 (100) [M^+], 168 (84), 151 (91), 140 (65), 125 (17), 122 (39), 109 (22), 98 (13), 43 (41).

HR-MS was performed with a mixture of compounds (ratio **113/114** = 2 : 1 by ^{1}H-NMR).

HR-MS (CI, isobutane):	calcd. 197.0814	for $C_{10}H_{13}O_4$,
	found 197.0815	[M^+ + H].

5.3.1.2 2,4-Dimethyl-6-oxo-6*H*-pyran-3-carboxylic acid[142] (114)



The carboxylic acid **114** (20.6 g, 0.123 mmol, 12%) was obtained as a light yellow oil along with the ester **113** in the condensation reaction of ethylacetoacetate **88** in presence of H_2SO_4. (For procedure please see page number 139).

$C_8H_8O_4$ M = 168.15 g mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.33 (d, *J* = 1.1 Hz, 3H), 2.53 (s, 3H), 6.05 (br. s, 1H), 11.87 (br. s, 1H) ppm.

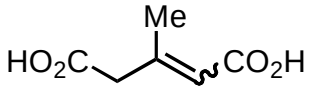
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 20.34 (CH_3), 21.92 (CH_3), 106.90 (C), 111.88 (CH), 154.83 (C), 161.19 (C), 164.64 (C), 169.19 (C) ppm.

GC-MS (EI, 70 eV): *m/z* (%) = 168 (73) [M^+], 140 (100), 125 (16), 122 (31), 94 (14), 43 (39).

HR-MS was performed with a mixture of compounds (ratio **113**/**114** = 2 : 1 by ^{1}H-NMR).

HR-MS (CI, isobutane): calcd. 169.0501 for $C_8H_9O_4$,
found 169.0501 $[M^+ + H]$.

5.3.1.3 (*E*)- and (*Z*)-3-Methyl-2-pentenedioic acid[142] (87)



A solution of KOH (24.7 g, 0.440 mol) in 24.7 ml H_2O was dropwise added over a period of 30 min to a cooled (–5°C) solution of **113** and **114** (10.0 g, 550 mmol) in MeOH (14 ml) (Caution: the temperature of the reaction mixture should be kept below 15°C). The resulting mixture was stirred for 1 h at 23°C. Then it was diluted with H_2O (140 ml), acidified to pH = 1 using conc. hydrochloric acid (35 ml) and extracted with EtOAc (4 x 150 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by recrystallization from CH_3CN (18 ml) to give diacid **87** (5.43 g, 0.038 mol, 69%) as a colorless solid. The ^{1}H-NMR shows two diastereoisomers in (A/B = 1.5 : 1) ratio. The absolute configuration (*E*/*Z*) could not be assigned.

$C_6H_8O_4$ M = 144.13 g mol^{-1}

Melting point: 118–119°C.

^{1}H-NMR (500 MHz, acetone-d_6),
isomer A: δ = 2.21 (d, *J* = 1.3 Hz, 3H), 3.20 (d, *J* = 1.0 Hz, 2H), 5.82–5.83 (m, 1H), 10.69 (s, 2H) ppm;
isomer B: δ = 1.97 (d, *J* = 1.5 Hz, 3H), 3.77 (s, 2H), 5.83–5.86 (m, 1H), 10.69 (s, 2H) ppm.

$^{13}C\{^{1}H\}$-NMR (125 MHz, acetone-d_6),

isomer A: δ = 25.56 (CH_3), 38.36 (CH_2), 119.25 (CH), 153.10 (C), 167.67 (C), 171.34 (C) ppm.

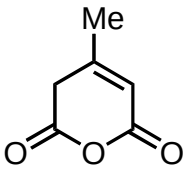
isomer B: δ = 18.80 (CH_3), 45.62 (CH_2), 119.74 (CH), 153.02 (C), 167.43 (C), 171.46 (C) ppm.

IR (ATR): λ^{-1} = 3452 (br, m), 3021 (m), 2988 (br, m), 2951 (m), 2934 (m), 2758 (w), 2695 (w), 2643 (w), 2611 (w), 2576 (w), 2510 (w), 1702 (vs), 1681 (vs), 1640 (vs), 1561 (w), 1408 (s), 1380 (w), 1346 (w), 1314 (w), 1302 (w), 1278 (w), 1221 (vs), 1179 (vs), 1168 (vs), 1153 (s), 1086 (w), 1046 (w), 1026 (w), 919 (s), 903 (s), 872 (s), 851 (s), 839 (s), 750 (w), 718 (m) cm^{-1}.

MS (CI, isobutane): *m/z* (%) = 145 (20) [M^+ + H], 127 (100), 126 (28), 98 (18), 41 (10).

Elemental analysis: calcd. C 50.00, H 5.60;
found C 50.07, H 5.59.

5.3.1.4 Glutaconic Anhydride[144] (86)



Acetyl chloride (34.6 g, 441 mmol) was added dropwise to diacid **87** (6.36 g, 44.1 mmol) and the resulting mixture stirred for 30 min at 70°C. The excess acetyl chloride and other volatile materials were then removed *in vacuo* and the residue was crystallized from Et_2O (30 ml) to give glutaconic anhydride **86** (4.12 g, 33.0 mmol, 72%) as a colorless solid.

$C_6H_6O_3$ M = 126.11 g mol^{-1}

Melting point: 84–85°C.

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.07 (td, *J* = 1.0 Hz, *J* = 1.4 Hz, 3H), 3.43 (dq, *J* = 1.8 Hz, *J* = 1.0 Hz, 2H), 6.08 (tq, *J* = 1.7 Hz, *J* = 1.5 Hz, 1H) ppm.

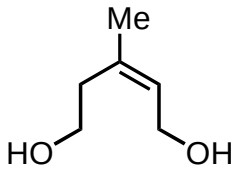
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 22.20 (CH_3), 36.32 (CH_2), 114.78 (CH), 155.39 (C), 159.73 (C), 164.72 (C) ppm.

IR (ATR): λ^{-1} = 3077 (m), 2991 (m), 2932 (m), 2912 (m), 2882 (m), 2611 (w), 1795 (s), 1705 (vs), 1684 (vs), 1669 (vs), 1640 (vs), 1446 (m), 1435 (m), 1413 (s), 1392 (s), 1372 (w), 1317 (s), 1278 (vs), 1219 (vs), 1161 (s), 1125 (s), 1050 (w), 1042 (w), 1011 (s), 954 (vs), 930 (vs), 910 (vs), 876 (vs), 858 (vs), 742 (w), 718 (vs) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 126 (71) [M^+], 100 (14), 98 (100), 82 (20), 53 (23), 45 (18).

HR-MS (EI, 70 eV): calcd. 126.0317 for $C_6H_6O_3$,
found 126.0317 [M^+].

5.3.1.5 (*Z*)-3-Methyl-2-pentene-1,5-diol[143] (85)



An ice-cooled suspension of $LiAlH_4$ (240 mg, 6.34 mmol) in THF (5 ml) was added dropwise to a cooled solution of glutaconic anhydride **86** (800 mg, 6.34 mmol) in THF (5 ml) at –15°C and the resulting mixture was stirred for 45 min at this temperature. The reaction mixture was then diluted with ice cold water (8 ml) and extracted with CH_2Cl_2 (4 x 8 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vaccuo*. The residue was purified by column chromatography on SiO_2 (EA) to give as a first fraction **85** (465 mg, 4.00 mmol, 63%, R_f = 0.27) and as a second fraction **116** (61 mg, 0.51 mmol, 8%, R_f = 0.22), both as colorless oils.

$C_6H_{12}O_2$ M = 116.16 g mol^{-1}

R_f(SiO_2, EA) = 0.27.

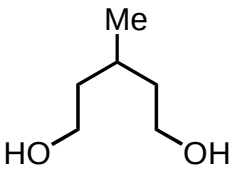
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.76 (dt, *J* = 0.7 Hz, *J* = 1.5 Hz, 3H), 2.34 (t, *J* = 5.8 Hz, 2H), 3.26 (br. s, 2H), 3.67 (t, *J* = 5.8 Hz, 2H), 4.01 (d, *J* = 7.5 Hz, 2H), 5.70 (t, *J* = 7.5 Hz, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 23.20 (CH_3), 34.68 (CH_2), 57.61 (CH_2), 58.97 (CH_2), 126.45 (CH), 138.15 (C) ppm.

IR (ATR): λ^{-1} = 3299 (br, s), 3066 (m), 2961 (s), 2932 (s), 2916 (s), 2877 (s), 1738 (w), 1727 (w), 1666 (m), 1443 (s), 1378 (s), 1232 (m), 1216 (m), 1161 (w), 1100 (w), 1042 (vs), 1000 (vs), 916 (w), 864 (m) cm^{-1}.

GC-MS (EI, 70 eV): *m/z* (%) = 98 (48) [M^+ – H_2O], 83 (100), 71 (64), 67 (60), 55 (27).

5.3.1.6 3-Methylpentane-1,5-diol (116)



The saturated diol **116** (61 mg, 0.51mmol, 8%,) was obtained as a by-product (second fraction, colorless oil) in the synthesis of unsaturated diol **85** from Glutaconic anhydride **86.** (For procedure please see the page number 143).

$C_6H_{14}O_2$ M = 118.17 g mol^{-1}

R_f(SiO_2, EA) = 0.22.

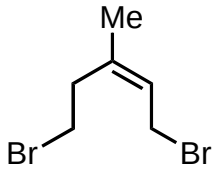
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.7 Hz, 3H), 1.41 (tdd, *J* = 6.2 Hz, *J* = 7.7 Hz, *J* = 13.8 Hz, 2H), 1.56–1.62 (m, 2H), 1.77 (octet, *J* = 6.7 Hz, 1H), 2.49 (br. s, 2H), 3.66 (ddd, *J* = 6.2 Hz, *J* = 7.1 Hz, *J* = 10.7 Hz, 2H), 3.70 (td, *J* = 6.3 Hz, *J* = 10.7 Hz, 2H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 19.87 (CH_3), 25.94 (CH), 39.43 ($2CH_2$), 60.55 ($2CH_2$) ppm.

IR (ATR): λ^{-1} = 3315 (br, s), 2955 (s), 2929 (s), 2875 (s), 1459 (m), 1432 (m), 1380 (m), 1219 (w), 1190 (w), 1142 (w), 1108 (w), 1054 (vs), 1011 (s), 968 (m), 914 (w), 850 (w), 766 (w) cm^{-1}.

GC-MS (EI, 70 eV): *m/z* (%) = 100 (10) [$M^+ - H_2O$], 82 (22), 70 (61), 67 (100).

5.3.1.7 (*Z*)-1,5-Dibromo-3-methyl-2-pentene[151] (83)



CBr_4 (570 mg, 1.72 mmol) and PPh_3 (451 mg, 1.72 mmol) were subsequently added to a cooled solution of diol **85** (50 mg, 0.43 mmol) in CH_2Cl_2 at –5°C and the resulting mixture was stirred for 1.5 h at 23°C. It was then diluted with sat. aq. $NaHCO_3$ soln. (2 ml) and the mixture extracted with CH_2Cl_2 (3 x 2 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 9 : 1) to give **83** (104 mg, 0.27 mmol, 63%) as a light yellow oil. The ^{1}H-NMR shows two diastereoisomers in (A/B = 4 : 1) ratio. The absolute configuration (*Z*/*E*) could not be assigned.

$C_6H_{10}Br_2$ M = 241.95 g mol^{-1}

R_f(SiO_2, PE : EA = 9 : 1) = 0.70.

^{1}H-NMR (500 MHz, $CDCl_3$),

isomer B: δ = 1.75 (d, *J* = 1.3 Hz, 3H), 2.61 (dt, *J* = 0.8 Hz, *J* = 7.3 Hz, 2H), 3.45 (t, *J* = 7.3 Hz, 2H), 3.99–4.01 (m, 2H), 5.62 (qt, *J* = 1.3 Hz, *J* = 8.4 Hz, 1H) ppm;

isomer A: δ = 1.81 (td, *J* = 0.8 Hz, *J* = 1.5 Hz, 3H), 2.71 (dt, *J* = 0.9 Hz, *J* = 7.4 Hz, 2H), 3.46 (t, *J* = 7.4 Hz, 2H), 4.00 (qd, *J* = 0.8 Hz, *J* = 8.5 Hz, 2H), 5.69 (tqt, *J* = 0.8 Hz, *J* = 1.5 Hz, *J* = 8.5 Hz, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$),

isomer B: δ = 15.52 (CH_3), 28.39 (CH_2), 30.27 (CH_2), 31.19 (CH_2), 123.42 (CH), 139.55 (C) ppm;

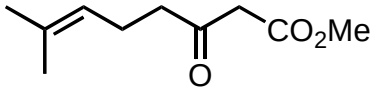
isomer A: δ = 22.94 (CH_3), 28.19 (CH_2), 29.62 (CH_2), 34.86 (CH_2), 124.27 (CH), 139.16 (C) ppm.

IR (ATR): λ^{-1} = 3012 (w), 2970 (m), 2936 (m), 2913 (m), 2876 (w), 2867 (w), 1738 (m), 1657 (m), 1441 (s), 1378 (s), 1366 (m), 1355 (m), 1306 (w), 1273 (m), 1226 (s), 1201 (vs), 1114 (w), 1016 (w), 997 (w), 912 (w), 898 (w), 856 (m), 669 (s) cm^{-1}.

GC-MS (EI, 70 eV): *m/z* (%) = 240 (25) [M^+], 161 (51), 119 (10), 81 (100), 67 (19), 55 (13).

5.3.2 Synthesis of β-Ketomethylester 12i

5.3.2.1 Methyl 7-methyl-3-oxo-6-octenoate[140] (12j)



6-Methyl-5-heptene-2-one **71** (6.31 g, 50.0 mmol) was dropwise added with a syringe pump over a period of 3 h to a suspension of dimethyl carbonate **84** (45.1 g, 500 mmol) and NaH (4.41 g, 110 mmol, 60% dispersion in mineral oil) under nitrogen at 0°C. The resulted mixture was heated to 60°C and stirred for 2 h. It was then allowed to stand for 12 h at 23°C. The reaction mixture was then cooled

to 0°C, diluted with ice cold water (20 ml) and extracted with Et_2O (3 x 20 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by distillation to give **12i** (8.49 g, 46.0 mmol, 92%) as a mixture of keto and enol tautomer (ratio, keto/enol 4 : 1), as a colorless oil.

$C_{10}H_{16}O_3$ M = 184.23 g mol^{-1}

Boiling point: 65–70°C at 1.5 Torr.

Keto isomer:

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.61 (d, *J* = 0.8 Hz, 3H), 1.68 (d, *J* = 1.1 Hz, 3H), 2.28 (q, *J* = 7.3 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 3.45 (s, 2H), 3.74 (s, 3H), 5.06 (thept, *J* = 7.2 Hz, *J* = 1.4 Hz, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 17.56 (CH_3), 22.15 (CH_2), 25.57 (CH_3), 42.97 (CH_2), 49.01 (CH_2), 52.53 (CH_3), 122.13 (CH), 133.06 (C), 167.56 (C), 202.38 (C) ppm.

Enol isomer:

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.63 (d, *J* = 0.6 Hz, 3H), 1.69 (d, *J* = 1.2 Hz, 3H), 2.28 (q, *J* = 7.3 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H), 3.43–3.46 (m, 1H), 3.73 (s, 3H), 5.02 (thept, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H), 12.01 (s, 1H) ppm.

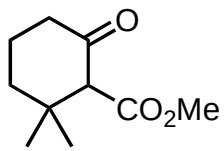
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 17.65 (CH_3), 25.65 (CH_3), 26.95 (CH_2), 35.11 (CH_2), 50.97 (CH_3), 88.78 (CH), 122.38 (CH), 132.91 (C), 169.97 (C), 178.44 (C) ppm.

IR (ATR): λ^{-1} = 3090 (m), 2968 (m), 2957 (m), 2918 (m), 2861 (s), 1747 (vs), 1717 (vs), 1653 (w), 1631 (w), 1438 (s), 1409 (m), 1378 (w), 1319 (s), 1241 (s), 1200 (m), 1174 (m), 1155 (m), 1111 (m), 1080 (m), 1040 (w), 1002 (w), 835 (w), 677 (m), 658 (m), 630 (s) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 184 (12) [M$^+$], 116 (27), 86 (56), 84 (92), 69 (94), 55 (19), 49 (100), 41 (61).

HR-MS (EI, 70 eV): calcd. 184.1099 for $C_{10}H_{16}O_3$,
found 184.1100 $[M^+]$.

5.3.2.2 Methyl 6,6-Dimethyl-2-oxocyclohexanecarboxylate[141] (12i)



$SnCl_4$ (0.562 g, 2.16 mmol) was dropwise added to a solution of **12j** (2.00 g, 10.8 mmol) in CH_2Cl_2 (20 ml) at 0°C. After stirring the reaction mixture for 54 h at 23°C, it was poured onto ice (10 g) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 9 : 1) to give **12i** (1.51 g, 8.20 mmol, 76%) as a mixture of keto and enol tautomer (ratio, keto/enol = 5 : 1), as a colorless oil.

$C_{10}H_{16}O_3$ M = 184.23 g mol^{-1}

$\mathbf{R_f}$(SiO_2, PE : EA = 9 : 1) = 0.42.

Keto isomer:

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 0.99 (s, 3H), 1.05 (s, 3H), 1.44–1.52 (m, 1H), 1.80–1.96 (m, 3H), 2.23–2.30 (m, 1H), 2.60–2.65 (m, 1H), 3.16 (s, 1H), 3.67 (s, 3H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$); Keto isomer δ = 21.84 (CH_2), 24.72 (CH_3), 28.13 (CH_3), 36.45 (CH_2), 38.81 (C), 39.35 (CH_2), 51.62 (CH_3), 67.28 (CH), 169.17 (C), 206.66 (C) ppm.

Enol isomer:

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.16 (s, 6H), 1.60–1.65 (m, 1H), 1.80–1.96 (m, 3H), 2.23–2.30 (m, 1H), 2.60–2.65 (m, 1H), 3.75 (s, 3H), 12.83 (s, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 17.57 (CH_2), 24.72 (CH_3), 28.73 (CH_3), 30.54 (CH_2), 31.82 (C), 41.00 (CH_2), 50.91 (CH_3), 105.95 (C), 173.43 (C), 174.10 (C) ppm.

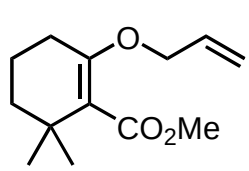
IR (ATR): λ^{-1} = 3010 (w), 2953 (m), 2920 (m), 2874 (m), 1750 (s), 1731 (s), 1708 (vs), 1636 (m), 1600 (m), 1460 (m), 1453 (s), 1388 (w), 1369 (m), 1347 (s), 1333 (m), 1311 (s), 1290 (w), 1272 (m), 1239 (s), 1222 (s), 1193 (s), 1159 (vs), 1133 (s), 1079 (m), 1040 (m), 1015 (w), 968 (w), 942 (w), 907 (w), 852 (w), 805 (w), 738 (w), 676 (m), 628 (s) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 184 (37) [M^+], 169 (16), 153 (32), 137 (53), 100 (51), 84 (87), 69 (25), 49 (100), 41 (29).

HR-MS (EI, 70 eV): calcd. 184.1099 for $C_{10}H_{16}O_3$,
found 184.1099 [M^+].

5.3.3 Synthesis of 2-Allyl Cyclohexanone 120

5.3.3.1 Methyl 2-Allyloxy-6,6-dimethyl-1-cyclohexenecarboxylate[147] (118)



A solution of **12i** (1.20 g, 6.51 mmol) in abs. THF (8 ml) was added to a suspension of NaH (0.285 g, 7.16 mmol, 60% dispersion in mineral oil) in abs. THF (5 ml) under N_2 at 0°C. After the mixture was stirred for 1 h at 23°C, allyl bromide **117** (1.97 g, 16.3 mmol) was dropwise added and the mixture was then heated to 60°C and stirred for 22 h at the same temperature. It was then cooled to 0°C, diluted with ice cold water (20 ml) and extracted with Et_2O (3 x 10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : EA = 9 : 1) to give inseparable mixtures of enol ether **118** and ketone **119** [(ratio, 1 : 1), 1.18 g, 5.26 mmol, 81%)], as colorless oil.

$C_{13}H_{20}O_3$ M = 224.30 g mol^{-1}

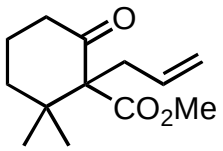
R_f(SiO_2, PE : EA = 9 : 1) = 0.27.

Enol ether 125:

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.11 (s, 6H), 1.42–1.45 (m, 2H), 1.72–1.78 (m, 2H), 2.17 (t, *J* = 6.6 Hz, 2H), 3.74 (s, 3H), 4.26 (dt, *J* = 5.1 Hz, *J* = 1.6 Hz, 2H), 5.16 (dq, *J* = 10.1 Hz, *J* = 1.5 Hz, 1H), 5.29 (dq, *J* = 17.3 Hz, *J* = 1.7 Hz, 1H), 5.88 (ddt, *J* = 17.1 Hz, *J* = 10.7 Hz, *J* = 5.0 Hz, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 18.70 (CH_2), 24.93 (CH_2), 28.50 ($2CH_3$), 33.16 (C), 38.11 (CH_2), 51.26 (CH_3), 68.62 (CH_2), 116.53 (CH_2), 120.95 (C), 134.03 (CH), 152.65 (C), 169.84 (C) ppm.

5.3.3.2 Methyl 1-Allyl-6,6-dimethyl-2-oxocyclohexanecarboxylate[147] (119)



Both the inseparable mixtures of enol ether **118** and ketone **119** (1.1 g, 4.90 mmol) were stirred vigorously at 150°C for 3.5 h under nitrogen atmosphere to convert completely to ketone **119** (1.08 g, 4.82 mmol, 98%)**.**

$C_{13}H_{20}O_3$ M = 224.30 g mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.84 (s, 3H), 1.25 (s, 3H), 1.44–1.52 (m, 1H), 1.77–1.87 (m, 3H), 2.37 (dd, *J* = 8.6 Hz, *J* = 13.6 Hz, 1H), 2.34–2.42 (m, 1H), 2.64 (ddt, *J* = 13.6 Hz, *J* = 5.6 Hz, *J* = 1.6 Hz, 1H), 2.80–2.89 (m, 1H), 3.65 (s, 3H), 4.95 (d, br., *J* = 10.0 Hz, 1H), 5.01 (d, br., *J* = 17.1 Hz, 1H), 5.16 (dddd, *J* = 5.6 Hz, *J* = 9.0 Hz, *J* = 10.1 Hz, *J* = 16.8 Hz, 1H) ppm.

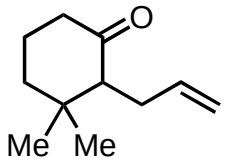
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 21.48 (CH_2), 23.53 (CH_3), 26.54 (CH_3), 33.90 (CH_2), 37.17 (CH_2), 39.92 (CH_2), 41.01 (C), 51.33 (CH_3), 68.42 (C), 117.16 (CH_2), 135.33 (CH), 171.53 (C), 208.35 (C) ppm.

IR (ATR): λ^{-1} = 3078 (w), 2971 (m), 2951 (m), 2880 (w), 1746 (s), 1712 (vs), 1639 (w), 1457 (m), 1433 (m), 1395 (w), 1374 (w), 1351 (w), 1314 (m), 1289 (m), 1217 (s), 1197 (s), 1181 (m), 1154 (m), 1129 (w), 1103 (w), 1077 (w), 1043 (m), 1002 (m), 915 (s), 854 (w), 798 (w), 669 (s), 632 (vs) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 224 (100) [M^+], 209 (15), 195 (30), 192 (53), 168 (35), 149 (38), 136 (94), 123 (83), 109 (29), 95 (49), 69 (56), 55 (55), 41 (42).

Elemental analysis: calcd. C 69.61, H 8.99;
found C 69.53, H 9.19.

5.3.3.3 2-Allyl-3,3-dimethylcyclohexanone[147] (120)



A solution of ketoester **119** (110 mg, 0.490 mmol) in 2,4,6-collidine (1 ml) was added dropwise to a mixture of LiI · 2 H_2O (112 mg, 0.666 mmol) and 2,4,6-collidine (1 ml) and the mixture was heated to reflux for 19 h. It was then cooled to 23°C and poured into a mixture of hydrochloric acid (2 ml, c = 6 mol dm^{-3}), ice-cold water (1 ml) and Et_2O (4 ml). The aqueous layer was extracted with Et_2O (3 x 3 ml) and the combined organic layers were washed with hydrochloric acid (2 x 2 ml, c = 6 mol dm^{-3}), Na_2CO_3 soln. (2 x 2 ml, c = 2 mol dm^{-3}) and brine (2 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give **120** (54 mg, 0.324 mmol, 67%) as a colorless oil.

$C_{11}H_{18}O$ M = 166.26 g mol^{-1}

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.79 (s, 3H), 1.07 (s, 3H), 1.59–1.69 (m, 2H), 1.77–1.94 (m, 2H), 2.04–2.09 (m, 1H), 2.21–2.36 (m, 3H), 2.42–2.49 (m, 1H), 4.93 (dq, *J* =

10.1 Hz, *J* = 1.5 Hz, 1H), 5.00 (dq, *J* = 17.0 Hz, *J* = 1.7 Hz, 1H), 5.16 (ddt, *J* = 17.0 Hz, *J* = 10.1 Hz, *J* = 7.0 Hz, 1H) ppm.

$^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 22.07 (CH_3), 23.11 (CH_2), 28.62 (CH_2), 29.46 (CH_3), 39.19 (CH_2), 39.70 (C), 41.26 (CH_2), 60.98 (CH), 115.19 (CH_2), 137.88 (CH), 212.65 (C) ppm.

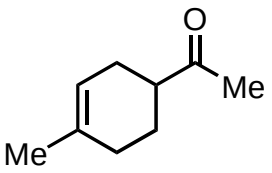
IR (ATR): λ^{-1} = 3074 (w), 2960 (m), 2928 (m), 2898 (m), 2871 (m), 2850 (m), 1705 (vs), 1457 (m), 1430 (w), 1388 (w), 1368 (m), 1259 (s), 1123 (vs), 1077 (vs), 1026 (vs), 843 (w), 803 (m), 737 (w), 718 (w), 699 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 166 (100) [M^+], 151 (40), 123 (26), 109 (50), 96 (64), 81 (26), 69 (50), 55 (28), 41 (35).

HR-MS (CI, isobutane): calcd. 167.1436 for $C_{11}H_{19}O$, found 167.1436 [$M^+ + H$].

5.3.4 Synthesis of Cyclohexene Derivative 139

5.3.4.1 4-Acetyl-1-methylcyclohexene[149] (130)



A mixture of methyl vinyl ketone **9a** (2.96 g, 42.3 mmol) and isoprene **45** (0.960 g, 14.1 mmol) in CH_2Cl_2 (6 ml) was added to a cooled solution of $Sc(OTf)_3$ (2.08 g, 4.23 mmol) in CH_2Cl_2 (50 ml) at 0°C. The mixture was stirred at the same temperature for 18 h, then diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : Et_2O = 1 : 1) to give **130** (1.62 g, 11.7 mmol, 83%) as a colorless oil. The

$Sc(OTf)_3$ can be recovered quantitatively by concentrating the aqueous layer and drying the residue at high vacuum (0.7 mbar).

$C_9H_{14}O$ M = 138.21 g mol^{-1}

R_f(SiO_2, PE : Et_2O = 2 : 1) = 0.42.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.53–1.61 (m, 1H), 1.62–1.63 (m, 3H), 1.92–1.94 (m, 1H), 1.95–2.02 (m, 2H), 2.10–2.14 (m, 2H), 2.14 (s, 3H), 2.50 (dddd, *J* = 2.8 Hz, *J* = 5.9 Hz, *J* = 9.1 Hz, *J* = 11.8 Hz, 1H), 5.36–5.38 (m, 1H) ppm.

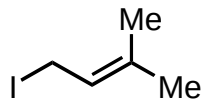
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 23.33 (CH_3), 24.86 (CH_2), 27.00 (CH_2), 27.90 (CH_3), 29.44 (CH_2), 47.18 (CH), 119.21 (CH), 133.76 (C), 211.76 (C) ppm.

IR (ATR): λ^{-1} = 3011 (w), 2965 (m), 2917 (m), 2859 (m), 2837 (m), 1708 (vs), 1440 (m), 1377 (m), 1354 (s), 1301 (w), 1283 (w), 1252 (w), 1240 (w), 1225 (m), 1167 (s), 1157 (m), 1117 (w), 1055 (w), 1024 (w), 949 (m), 914 (m), 801 (m), 758 (w), 682 (m), 644 (m), 630 (s) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 138 (94) [M$^+$], 123 (50), 95 (100), 84 (28), 79 (23), 67 (39), 55 (20), 49 (33), 43 (74).

HR-MS (EI, 70 eV): calcd. 138.1045 for $C_9H_{14}O$,
found. 138.1046 [M$^+$].

5.3.4.2 1-Iodo-3-methyl-2-butene[150] (136)



$ZrCl_4$ (2.03 g, 8.71 mmol) was added portionwise to a solution of prenyl alcohol **132** (1.50 g, 17.4 mmol) and NaI (3.91 g, 26.1 mmol) in CH_3CN (30 ml) at 23°C and the resulting mixture was stirred for 30 min at the same temperature. It was then diluted with Et_2O (10 ml) and H_2O (10 ml). The organic layer was washed with a 10% aqueous solution of $Na_2S_2O_3$ (10 ml) and H_2O (10 ml) dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (pentane : Et_2O = 9 : 1) to give **136** (3.12 g, 15.9 mmol, 91%) as a dark brown oil.

C_5H_9I M = 196.03 g mol^{-1}

R_f(SiO_2, Pentane : Et_2O = 9 : 1) = 0.56.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.64 (d, *J* = 1.6 Hz, 3H), 1.72 (d, *J* = 1.5 Hz, 3H), 3.91 (d, *J* = 8.8 Hz, 2H), 5.51 (thept, *J* = 8.8 Hz, *J* = 1.4 Hz, 1H) ppm.

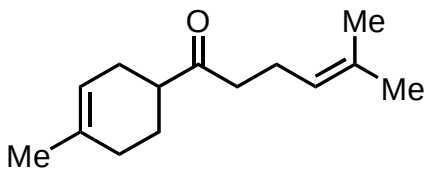
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 4.00 (CH_2), 17.36 (CH_3), 25.85 (CH_3), 122.01 (CH), 138.75 (C) ppm.

IR (ATR): λ^{-1} = 3033 (w), 3026 (w), 3016 (w), 2970 (m), 2928 (s), 2910 (m), 2879 (w), 2853 (w), 1655 (s), 1446 (s), 1376 (s), 1340 (w), 1223 (w), 1143 (vs), 1096 (w), 1004 (w), 977 (w), 856 (m), 837 (s), 752 (m), 663 (m), 628 (s) cm^{-1}.

GC-MS (EI, 70 eV): *m/z* (%) = 196 (13) [M$^+$], 127 (10), 69 (100).

HR-MS (EI, 70 eV): calcd. 195.9749 for C_5H_9I
found 195.9749 [M$^+$].

5.3.4.3 5-Methyl-1-(4-methyl-3-cyclohexenyl)-4-hexen-1-one (129)



A solution of LDA (2.10 ml, 4.15 mmol, 2.0 mol dm^{-3} in THF/pentane/ethylbenzene) was added to a cooled (–78°C) solution of ketone **130** (0.522 g, 3.77 mmol) in abs. THF (10 ml). After stirring the reaction mixture for 1 h at –78°C, prenyl iodide **136** (2.96 g, 15.1 mmol) was added dropwise. The resulting mixture was stirred for 2 h at the same temperature and then at 23°C for 3 h. It was then diluted with sat. aq. NH_4Cl soln. (5 ml) and extracted with Et_2O (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : Et_2O = 9 : 1) to give as a first fraction compd. **131** (0.112 g, 0.410 mmol, 11%, R_f = 0.83) and as a second fraction compd. **129** (0.562 g, 2.72 mmol, 72%, R_f = 0.78), both as light yellow oils.

$C_{14}H_{22}O$ M = 206.32 g mol^{-1}

R_f(SiO_2, PE : Et_2O = 9 : 1) = 0.78.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.56 (dddd, *J* = 6.0 Hz, *J* = 10.6 Hz, *J* = 11.5 Hz, *J* = 13.0 Hz, 1H), 1.59 (s, 3H), 1.62–1.63 (m, 3H), 1.65 (d, *J* = 1.1 Hz, 3H), 1.88–1.93 (m, 1H), 1.95–2.05 (m, 2H), 2.09–2.12 (m, 2H), 2.19–2.25 (m, 2H), 2.41–2.52 (m, 1H), 2.47 (dt, *J* = 6.0 Hz, *J* = 7.4 Hz, 2H), 5.04 (thept, *J* = 7.2 Hz, *J* = 1.4 Hz, 1H), 5.35–5.38 (m, 1H) ppm.

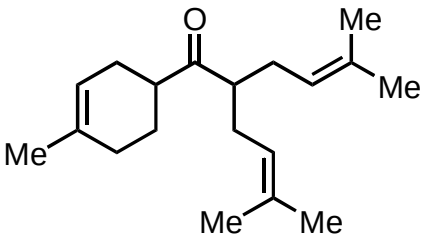
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 17.57 (CH_3), 22.40 (CH_2), 23.34 (CH_3), 24.93 (CH_2), 25.59 (CH_3), 27.09 (CH_2), 29.54 (CH_2), 40.69 (CH_2), 46.53 (CH), 119.36 (CH), 122.97 (CH), 132.43 (C), 133.67 (C), 213.51 (C) ppm.

IR (ATR): λ^{-1} = 3010 (w), 2964 (m), 2913 (s), 2856 (m), 2835 (m), 1707 (vs), 1675 (w), 1439 (s), 1407 (w), 1376 (s), 1342 (w), 1299 (w), 1280 (w), 1250 (w), 1217 (w), 1154 (w), 1108 (w), 1088 (m), 1065 (w), 1049 (w), 1007 (w), 984 (w), 954 (w), 915 (w), 830 (m), 798 (m), 760 (w), 675 (m), 628 (s) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 206 (49) [M^+], 189 (9), 123 (21), 95 (100), 81 (20), 69 (44), 55 (23), 41 (26).

HR-MS (EI, 70 eV): calcd. 206.1671 $C_{14}H_{22}O$,
found. 206.1670 [M^+].

5.3.4.4 5-Methyl-2-(3-methyl-2-butenyl)-1-(4-methyl-3-cyclohexenyl)-4-hexen-1-one (131)



The dialkylated cyclohexenone **131** (0.112 g, 0.410 mmol, 11%) was obtained as a by-product (first fraction, light yellow oil) in the synthesis of the monoalkylated cyclohexene **129** from acetyl cyclohexene **130.** (For procedure please see the page number 155).

$C_{19}H_{30}O$ M = 274.44 g mol^{-1}

$\mathbf{R_f}$(SiO_2, PE : Et_2O = 9 : 1) = 0.83.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.49 (dddd, *J* = 6.3 Hz, *J* = 10.6 Hz, *J* = 11.6 Hz, *J* = 13.0 Hz, 1H), 1.57 (d, *J* = 0.6 Hz, 3H), 1.58 (s, 3H), 1.65 (s, 3H), 1.66 (s, 6H), 1.82–1.86 (m, 1H), 1.94–2.00 (m, 2H), 2.04–2.10 (m, 4H), 2.20–2.29 (m, 2H), 2.54 (dddd, *J* = 2.8 Hz, *J* = 5.4 Hz, *J* = 8.5 Hz, *J* = 12.6 Hz, 1H), 2.69 (tt, *J* = 6.0 Hz, *J* = 7.9 Hz, 1H), 5.00–5.04 (m, 2H), 5.37–5.40 (m, 1H) ppm.

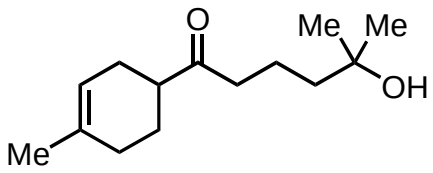
$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 17.71 ($2CH_3$), 23.42 (CH_3), 24.64 (CH_2), 25.74 (CH_3), 25.76 (CH_3), 26.91 (CH_2), 29.74 (CH_2), 30.18 (CH_2), 30.36 (CH_2), 46.90 (CH), 51.04 (CH), 119.63 (CH), 121.70 (CH), 121.85 (CH), 133.27 (C), 133.33 (C), 133.57 (C), 217.13 (C) ppm.

IR (ATR): λ^{-1} = 3009 (w), 2964 (m), 2913 (s), 2855 (m), 2727 (w), 1706 (vs), 1674 (w), 1449 (s), 1439 (s), 1377 (s), 1347 (w), 1300 (w), 1275 (w), 1247 (w), 1232 (w), 1215 (w), 1180 (w), 1155 (w), 1120 (m), 1108 (m), 1090 (m), 1049 (w), 1037 (w), 1009 (w), 984 (w), 953 (w), 915 (w), 841 (m), 825 (m), 798 (m), 758 (m), 699 (m) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 274 (68) [M^+], 205 (100), 123 (15), 109 (27), 95 (49), 69 (42), 41 (27).

HR-MS (EI, 70 eV): calcd. 274.2297 for $C_{19}H_{30}O$,
found. 274.2296 [M^+].

5.3.4.5 5-Hydroxy-5-methyl-1-(4-methyl-3-cyclohexenyl)hexan-1-one (137)



$BF_3 \cdot OEt_2$ (302 mg, 2.13 mmol) was added to a cooled solution of alkylated ketone **129** (200 mg, 0.97 mmol) in CH_2Cl_2 (10 ml) at –5°C and the resulting mixture was stirred at 23°C for 52 h. It was then diluted with sat. aq. $NaHCO_3$ soln. (5 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 (PE : Et_2O = 1 : 3) to give **137** (104 mg, 0.270 mmol, 63%) as a light yellow oil.

$C_{14}H_{24}O_2$ M = 224.34 g mol^{-1}

R_f(SiO_2, PE : Et_2O = 1 : 3) = 0.27.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.27 (s, 6H), 1.42–1.45 (m, 2H), 1.52–1.68 (m, 4H), 1.64–1.65 (m, 3H), 1.89–1.94 (m, 1H), 1.96–2.06 (m, 2H), 2.09–2.13 (m, 2H), 2.44–2.55 (m, 3H), 5.37–5.40 (m, 1H) ppm.

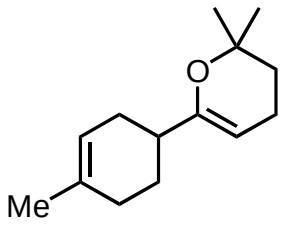
^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 18.46 (CH_2), 23.39 (CH_3), 25.02 (CH_2), 27.19 (CH_2), 29.18 ($2CH_3$), 29.56 (CH_2), 40.89 (CH_2), 43.20 (CH_2), 46.55 (CH), 70.84 (C), 119.32 (CH), 133.76 (C), 213.90 (C) ppm.

IR (ATR): λ^{-1} = 3439 (br. m), 2965 (s), 2926 (s), 1704 (vs), 1671 (w), 1453 (m), 1440 (m), 1405 (w), 1377 (s), 1366 (s), 1301 (w), 1279 (w), 1216 (m), 1206 (m), 1154 (m), 1146 (m), 1119 (w), 1092 (w), 1065 (w), 1051 (w), 1009 (w), 943 (w), 913 (m), 863 (w), 798 (m), 760 (w), 740 (w), 726 (w) cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 206 (22) [M^+ – H_2O], 123 (18), 95 (29), 84 (87), 69 (17), 49 (100), 41 (13).

HR-MS (EI, 70 eV): calcd. 206.1671 for ($C_{14}H_{24}O$ – H_2O),
found. 206.1671 [M^+ – H_2O].

5.3.4.6 2,2-Dimethyl-6-(4-methyl-3-cyclohexenyl)-3,4-dihydro-2*H*-pyran (140)



The enol ether **140** was slowly formed from the hydroxy product **137** in an attempt of the synthesis of β-Chamigrene precursor **47a**.

$C_{14}H_{22}O$ M = 206.32 g mol^{-1}

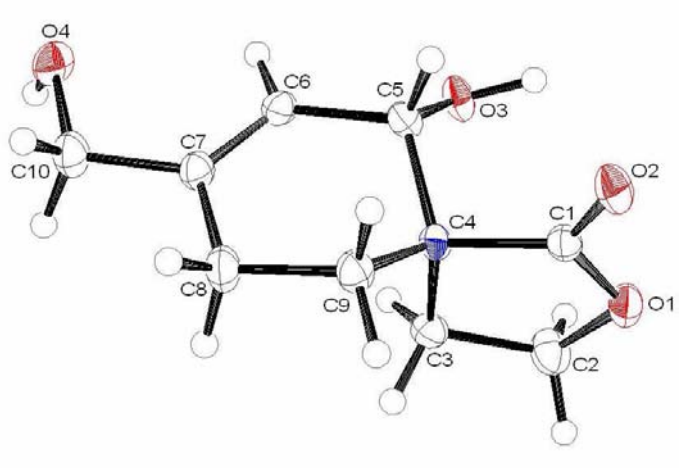
R$_f$(SiO_2, PE : Et_2O = 1 : 3) = 0.43.

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.18 (s, 3H), 1.19 (s, 3H), 1.43–1.51 (m, 1H), 1.54 (t, *J* = 6.6 Hz, 2H), 1.63–1.64 (m, 3H), 1.79–1.84 (m, 1H), 1.92–1.96 (m, 1H), 1.99 (ddt, *J* = 1.0 Hz, *J* = 3.7 Hz, *J* = 6.6 Hz, 3H), 2.00–2.05 (m, 2H), 2.06–2.11 (m, 1H), 4.42 (t, *J* = 3.7 Hz, 1H), 5.35–5.38 (m, 1H) ppm.

^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 18.42 (CH_2), 23.55 (CH_3), 26.28 (CH_3), 26.45 (CH_3), 27.01 (CH_2), 29.72 (CH_2), 30.31 (CH_2), 32.92 (CH_2), 38.34 (CH), 72.72 (C), 91.21 (CH), 120.56 (CH), 133.55 (C), 156.36 (C) ppm.

6 Data for Crystal Strucure Analysis

6.1 Crystal Structure Data for (5*R**,6*S**)-74



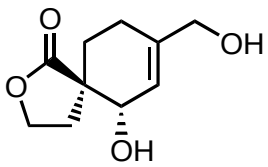


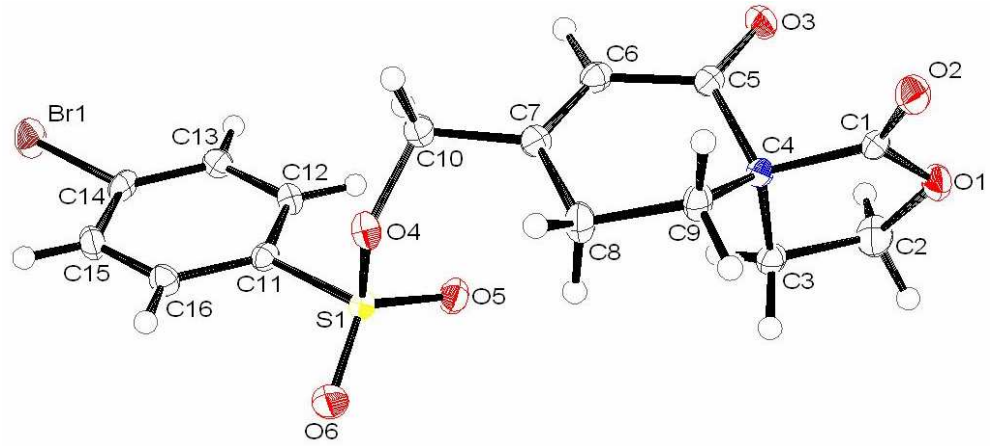
Table 11. Crystal structure data for (5*R**,6*S**)-**74**.

Empirical formula	$C_{10}H_{14}O_4$
Formula weight	198.21 g mol^{-1}
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 8.3347(10) Å, α= 90°
	b = 11.5682(11) Å, β= 104.266(12)°
	c = 10.2659(9) Å, γ = 90°
Volume,	959.29(17) $Å^3$
Z	4
Density (calculated)	1.372 mg m^{-3}
Absorption coefficient	0.106 mm^{-1}
F(000)	424
Crystal size	0.60 x 0.36 x 0.28 mm^3
θ-range for data collection	2.52 to 26.24°
Index ranges	$-10 \le h \le 10$, $-14 \le k \le 14$, $-12 \le l \le 12$
Reflections collected	10169
Independent reflections	1808 [R(int) = 0.0558]
Observed reflections	1241 [I>2sigma(I)]
Completeness to θ = 25.00°	95.0%

Absorption correction	None
Max. and min. transmission	0.9710 and 0.9392
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1808 / 0 / 135
Goodness-of-fit on F^2	0.879
Final R indices [I>2sigma(I)]	R1 = 0.0320, wR2 = 0.0727
R indices (all data)	R1 = 0.0517, wR2 = 0.0795
Largest diff. peak and hole	0.238 and –0.196 e/Å^3

CCDC-647100 for (*R**,*S**)-**74** contain the supplementary crystallographic data. It can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

6.2 Crystal Structure Data for (*R*)-112



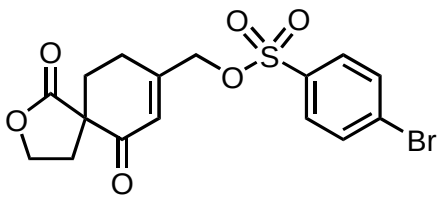


Table 12. Crystal structure data for (*R*)-**112**.

Empirical formula	C_{16} H_{15} Br O_6 S
Formula weight	415.25 g mol^{-1}
Temperature	153(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 6.0232(3) Å, α= 90°.
	b = 14.8372(10) Å, β= 104.959(7)°
	c = 9.3893(7) Å, β = 90°
Volume	810.66(9) $Å^3$
Z	2
Density (calculated)	1.701 mg m^{-3}
Absorption coefficient	2.694 mm^{-1}
F(000)	420
Crystal size	0.30 x 0.24 x 0.20 mm^3
θ-range for data collection	2.75 to 26.11°
Index ranges	-7 ≤ h ≤ 7, -18 ≤ k ≤ 18, -11 ≤ l ≤ 11
Reflections collected	9753
Independent reflections	3045 [R(int) = 0.0368]
Observed reflections	2790 [I>2sigma(I)]
Completeness to θ = 25.00°	94.7%
Absorption correction	Numerical
Max. and min. transmission	0.6148 and 0.4987
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3045 / 1 / 217
Goodness-of-fit on F^2	0.954
Final R indices [I>2sigma(I)]	R1 = 0.0212, wR2 = 0.0444
R indices (all data)	R1 = 0.0243, wR2 = 0.0450
Absolute structure parameter	–0.009(5)
Largest diff. peak and hole	0.315 and –0.296 e/$Å^3$

CCDC-647101 for (*R*)-**112** contain the supplementary crystallographic data. It can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

7 Abbreviations

Å	Ångström
Ac	acetyl
acac	acetylacetonato
ATR	attenuated total reflection
aq.	aqueous
Bs	4-bromophenylsulfonyl
calc.	calculated
CSA	camphor sulfonic acid
cat.	catalytic
CI	chemical ionization
δ	chemical shift
cod	1,5-cyclooctadiene
c	concentration
conc.	concentrated
CBS	Corey Bakshi Shibata
de	diastereomeric excess
DCC	dicyclohexylcarbodiimide
DOPA	dihydroxyphenylalanine
DMB	dimethoxybenzyl
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DEPT	distortionless enhancement by polarisation transfer
d	doublet
ee	enantiomeric excess
EI	electron impact
eV	electron volt
EA	ethyl acetate
eq.	equivalent
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry coupling
h	heptet
HR-MS	high resolution mass spectrometry
IR	infra red
J	coupling constant
LDA	lithiumdiisopropylamide
m/z	mass/charge
MS	mass spectrometry

MVK	methyl vinyl ketone
m	medium (IR), multiplet (NMR)
NMR	nuclear magnetic resonance
oct	octet
PMB	paramethoxybenzyl
ppm	parts per million
PE	petroleum ether
q	quartett
quin	quintet
RAMP	(*R*)-1-amino-2-methoxymethylpyrrolidine
rac	racemic
R_f	*ratio of fronts*
RCM	ring closing metathesis
SAMP	(*S*)-1-amino-2-methoxymethylpyrrolidine
sat.	saturated
soln.	solution
sex	sextet
s	singulet (NMR), strong (IR)
T	temperature
THF	tetrahydrofuran
t	time, triplet (NMR)
TLC	thin layer chromatography
TFA	trifluoroacetic acid
TMS	tetramethylsilane
Tos	*p*-toluenesulfonyl
UV	ultraviolet
vs	very strong
w	weak
λ	wavelength

8 Bibliography

[1] K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, *Wiley*-VCH, Weinheim, **1996**.

[2] K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem.* **2000**, *112*, 46–126; *Angew. Chem. Int. Ed.* **2000**, *39*, 44–122.

[3] R. Robinson, *J. Chem. Soc.* **1917**, *111*, 762–768.

[4] H. Fischer, K. Zeile, *Liebigs. Ann. Chem.* **1929**, *468*, 98–116.

[5] W. Lenz, R. A. Pfeiffer, W. Kosenow, D. J. Hayman, *The Lancet* **1962**, *279*, 45-46.

[6] W. G. Mcbride, *The Lancet* **1961**, *278*, 1358.

[7] D. Enders, R. W. Hoffmann, *Chemie in Unserer Zeit* **1985**, *19*, 177–190.

[8] W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther, *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772.

[9] A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329.

[10] W. S. Knowles, *Angew. Chem.* **2002**, *114*, 2096–2107; *Angew. Chem. Int. Ed.* **2002**, *41*, 1998–2007.

[11] K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2126–2135; *Angew. Chem. Int. Ed.* **2002**, *41*, 2024–2032.

[12] R. Noyori, *Angew. Chem.* **2002**, *114*, 2108–2123; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008–2022.

[13] I. Ojima, *Catalytic Asymmetric Synthesis*, *Wiley*-VCH, Weinheim, **2000**.

[14] J. Christoffers, A. Baro, Eds., *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*, *Wiley*-VCH, Weinheim, **2005**.

[15] J. Christoffers, A. Baro, *Angew. Chem.* **2003**, *115*, 1726–1728; *Angew. Chem. Int. Ed.* **2003**, *42*, 1688–1690.

[16] J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482.

[17] J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597.

[18] E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 389–401.

[19] K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066.

[20] S. F. Martin, *Tetrahedron* **1980**, *36*, 419–460.

[21] E. A. Peterson, L. E. Overman, *Proc. Natl. Acad. Sci. USA,* **2004**, *101*, 11943–11948.

[22] B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396.

[23] R. Noyori, *Asymmetric Catalysis in Organic Synthesis; Wiley: New York* **1994**.

[24] B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed.* **1995**, *34*, 259–281.

[25] E. J. Corey, *Angew. Chem.* **2002**, *41*, 1724–1741; *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667.

[26] B. M. Trost, *Chem. Pharm. Bull.* **2002**, *50*, 1–14.

[27] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.

[28] J. Christoffers, *in Encyclopedia of Catalysis, Vol. 5, ed. I. Horvath, J. Wiley & Sons, New York,* **2003**, pp. 99–118.

[29] J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279–1300.

[30] N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171–196.

[31] M. Sawamura, H. Hamashima, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 8295–8296.

[32] M. Sawamura, H. Hamashima, Y. Ito, *Tetrahedron* **1994**, *50*, 4439–4454.

[33] M. Sawamura, H. Hamashima, H. Shinoto, Y. Ito, *Tetrahedron Lett.* **1995**, *36*, 6479–6482.

[34] M. Sawamura, H. Hamashima, Y. Ito, *Tetrahedron: Asymmetry* **1991**, *2*, 593–596.

[35] J. Christoffers, *Chem. Eur. J.* **2003**, *9*, 4862–4867.

[36] J. Christoffers, A. Mann, *Angew. Chem.* **2000**, *112*, 2871–2874; *Angew. Chem. Int. Ed.* **2000**, *39*, 2752–2754.

[37] J. Christoffers, A. Mann, *Chem. Eur. J.* **2001**, *7*, 1014–1027.

[38] J. Christoffers, H. Scharl, *Eur. J. Org. Chem.* **2002**, 1505–1508.

[39] J. Christoffers, H. Scharl, W. Frey, A. Baro, *Eur. J. Org. Chem.* **2004**, 2701–2706.

[40] J. Christoffers, H. Scharl, W. Frey, A. Baro, *Org. Lett.* **2004**, *6*, 1171–1173.

[41] J. Christoffers, K. Schuster, *Chirality* **2003**, *15*, 777–782.

[42] J. Christoffers, B. Kreidler, H. Oertling, S. Unger, W. Frey, *Synlett* **2003**, 493–496.

[43] A. P. Krapcho, *Synthesis* **1976**, 425–444.

[44] A. P. Krapcho, *Synthesis* **1974**, 383–419.

[45] N. H. Andersen, M. S. Falcone, D. D. Syrdal, *Tetrahedron Lett.* **1970**, 1759–1762.

[46] J. A. Marshall, P. C. Johnson, *J. Org. Chem.* **1970**, *35*, 192–196.

[47] S. Ito, K. Endo, T. Yoshida, M. Yatagai, M. Kodama, *J. Chem. Soc., Chem. Commun.* **1967**, 186–188.

[48] E. Caloprisco, J.-D. Fourneron, R. Faure, F.-E. Demarne, *J. Agric. Food Chem.* **2002**, *50*, 78–80.

[49] F. Q. Alali, X.-X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504–540.

[50] M. S. Tempesta, G. R. Kriek, R. B. Bates, *J. Org. Chem.* **1982**, *47*, 3151–3153.

[51] L. Zeng, Q. Ye, N. H. Oberlies, G. Shi, Z. M. Gu, K. He, J. L. McLaughlin, *Nat. Prod. Rep.* **1996**, *13*, 275–306.

[52] G. Stork, R. L. Danheiser, B. Ganem, *J. Am. Chem. Soc.* **1973**, *95*, 3414–3415.

[53] R. G. Eilerman, B. J. Willis, *J. Chem. Soc., Chem. Commun.* **1981**, 30–32.

[54] H. Fujioka, S. Kitagaki, R. Imai, M. Kondo, S. Okamoto, Y. Yoshida, S. Akai, Y. Kita, *Tetrahedron Lett.* **1995**, *36*, 3219–3222.

[55] J. N. Marx, L. R. Norman, *J. Org. Chem.* **1975**, *40*, 1602–1606.

[56] W. Oppolzer, F. Zutterman, K. Bättig, *Helv. Chim. Acta* **1983**, *66*, 522–533.

[57] M. Duc Do Khac, J. Ecoto, M. Fetizon, H. Colin, J. C. Diez-Masa, *J. Chem. Soc., Chem. Commun.* **1981**, 953–955.

[58] W. Oppolzer, L. Gorrichon, T. G. Bird, *Helv. Chim. Acta* **1981**, *64*, 186–187.

[59] T. R. Hoye, S. J. Martin, D. R. Peck, *J. Org. Chem.* **1982**, *47*, 331–337.

[60] J. F. Ruppert, M. A. Avery, J. D. White, *J. Chem. Soc., Chem. Commun.* **1976**, 978.

[61] Y. Tokunaga, M. Yagihashi, M. Ihara, K. Fukumoto, *J. Chem. Soc., Chem. Commun.* **1995**, 955–956.

[62] K. Takai, Y. Hotta, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1698–1702.

[63] L. Lombardo, *Org. Synth.* **1987**, *65*, 81–89.

[64] J. Cossy, A. Bouzide, *Tetrahedron Lett.* **1992**, *33*, 2505–2508.

[65] J. Cossy, A. Bouzide, M. Pfau, *Tetrahedron Lett.* **1992**, *33*, 4883–4884.

[66] J. Cossy, A. Bouzide, M. Pfau, *J. Org. Chem.* **1997**, *62*, 7106–7113.

[67] H. J. Knölker, P. G. Jones, R. Graf, *Synlett* **1996**, 1155–1158.

[68] E. R. Koft, A. B. Smith, III, *J. Org. Chem.* **1984**, *49*, 832–836.

[69] J. E. Nystrom, T. D. McCanna, P. Helquist, R. S. Iyer, *Tetrahedron Lett.* **1985**, *26*, 5393–5396.

[70] T. Komnenos, *Liebigs Ann. Chem.* **1883**, *218*, 145–149.

[71] L. Claisen, *J. Prakt. Chem.* **1887**, *35*, 413–415.

[72] A. Michael, *J. Prakt. Chem.* **1887**, *36*, 113–114.

[73] A. Michael, *J. Prakt. Chem.* **1887**, *35*, 349–356.

[74] A. Michael, *Chem. Ber.* **1894**, *27*, 2126–2130.

[75] A. Michael, *Chem. Ber.* **1900**, *33*, 3731–3769.

[76] A. Michael, O. Schulthess, *J. Prakt. Chem.* **1892**, *45*, 55–63.

[77] F. Bonadies, A. Lattanzi, L. R. Orelli, S. Pesci, A. Scettri, *Tetrahedron Lett.* **1993**, *34*, 7649–7650.

[78] E. Keller, B. L. Feringa, *Tetrahedron Lett.* **1996**, *37*, 1879–1882.

[79] A. Soriente, A. Spinella, M. De Rosa, M. Giordano, A. Scettri, *Tetrahedron Lett.* **1997**, *38*, 289–290.

[80] C. P. Fei, T. H. Chan, *Synthesis* **1982**, 467–468..

[81] H. Brunner, B. Hammer, *Angew. Chem.* **1984**, *96*, 305–306; *Angew. Chem. Int. Ed.* **1984**, *23*, 312–313.

[82] P. Kočovský, D. Dvořák, *Tetrahedron Lett.* **1986**, *27*, 5015–5018.

[83] J. Christoffers, *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141–3150.

[84] J. Christoffers, *Chem. Commun.* **1997**, 943–944.

[85] J. Christoffers, *Tetrahedron Lett.* **1998**, *39*, 7083–7084.

[86] J. Christoffers, *Eur. J. Org. Chem.* **1998**, 1259–1266.

[87] J. Christoffers, *J. Org. Chem.* **1998**, *63*, 4539–4540.

[88] J. Christoffers, *Eur. J. Org. Chem.* **1998**, 759–761.

[89] J. Christoffers, *Synlett* **2001**, 723–732.

[90] J. Christoffers, H. Oertling, N. Önal, *J. Prakt. Chem.* **2000**, *342*, 546–553.

[91] J. Christoffers, A. Mann, *Eur. J. Org. Chem.* **2000**, 1977–1982.

[92] J. Christoffers, H. Oertling, M. Leitner, *Synlett* **2000**, 349–350.

[93] J. Christoffers, H. Oertling, *Tetrahedron* **2000**, *56*, 1339–1344.

[94] S. Pelzer, T. Kauf, C. van Wüllen, J. Christoffers, *J. Organomet. Chem.* **2003**, *684*, 308–314.

[95] M. Bauer, T. Kauf, J. Christoffers, H. Bertagnolli, *Phys. Chem. Chem. Phys.* **2005**, *7*, 2664–2670.

[96] J. Christoffers, Y. Zhang, W. Frey, P. Fischer, *Synlett* **2006**, 624–626.

[97] W. S. Rapson, R. Robinson, *J. Chem. Soc.* **1935**, 1285–1288.

[98] J. W. Cornforth, R. Robinson, *J. Chem. Soc.* **1949**, 1855–1865.

[99] M. E. Jung, *Tetrahedron* **1976**, *32*, 3–31.

[100] R. E. Gawley, *Synthesis* **1976**, 777–794.

[101] P. Wieland, K. Miescher, *Helv. Chim. Acta* **1950**, *33*, 2215–2228.

[102] N. Cohen, *Acc. Chem. Res.* **1976**, *9*, 412–417.

[103] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed.* **1971**, *10*, 496–497.

[104] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.

[105] J. Gutzwiller, P. Buchschacher, A. Fürst, *Synthesis* **1977**, 167–168.

[106] C. Agami, F. Meynier, C. Puchot, J. Guilhem, C. Pascard, *Tetrahedron* **1984**, *40*, 1031–1038.

[107] S. Terashima, S. Sato, K. Koga, *Tetrahedron Lett.* **1979**, 3469–3472.

[108] C. D. Dzierba, K. S. Zandi, T. Moellers, K. J. Shea, *J. Am. Chem. Soc.* **1996**, *118*, 4711–4712.

[109] J. D. Martin, C. Perez, J. L. Ravelo, *J. Am. Chem. Soc.* **1986**, *108*, 7801–7811.

[110] A. Tanaka, H. Uda, A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.* **1967**, 188–189.

[111] R. E. Ireland, W. C. Dow, J. D. Godfrey, S. Thaisrivongs, *J. Org. Chem.* **1984**, *49*, 1001–1013.

[112] J. Adams, C. Lepine-Frenette, D. M. Spero, *J. Org. Chem.* **1991**, *56*, 4494–4498.

[113] A. Srikrishna, B. V. Lakshmi, M. Mathews, *Tetrahedron Lett.* **2006**, *47*, 2103–2106.

[114] L. E. Wolinsky, D. J. Faulkner, J. Finer, J. Clardy, *J. Org. Chem.* **1976**, *41*, 697–699.

[115] A. P. Krapcho, E. G. E. Jahngen, jr., *J. Org. Chem.* **1974**, *39*, 1322–1324.

[116] S. Unger, "Aufbau quartärer Stereozentren in spirocyclischen Verbindungen", Dissertation, Universität Stuttgart, **2005**.

[117] M. Ollivault-Shiflett, D. B. Kimball, L. A. P. Silks, *J. Org. Chem.* **2004**, *69*, 5150–5152.

[118] M. Antopolsky, E. Azhayeva, U. Tengvall, A. Azhayev, *Tetrahedron Lett.* **2002**, *43*, 527–530.

[119] D. T. S. Rijkers, J. W. M. Höppener, G. Posthuma, C. J. M. Lips, R. M. J. Liskamp, *Chem. Eur. J.* **2002**, *8*, 4285–4291.

[120] E. R. Ottosen, M. D. Sørensen, F. Björkling, T. Skak-Nielsen, M. S. Fjording, H. Aaes, L. Binderup, *J. Med. Chem.* **2003**, *46*, 5651–5662.

[121] T. Raghuram, S. Vijaysaradhi, I. Singh, J. Singh, *Synth. Commun.* **1999**, *29*, 3215–3219.

[122] M. Mentzel, H. M. R. Hoffmann, *J. Prakt. Chem.* **1997**, *339*, 517–524.

[123] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

[124] J. Singh, N. Satyamurthi, I. S. Aidhen, *J. Prakt. Chem.* **2000**, *342*, 340–347.

[125] A. Gomtsyan, *Org. Lett.* **2000**, *2*, 11–13.

[126] N. Papaioannou, J. T. Blank, S. J. Miller, *J. Org. Chem.* **2003**, *68*, 2728–2734.

[127] J. Christoffers, H. Oertling, W. Frey, *Eur. J. Org. Chem.* **2003**, 1665–1671.

[128] T. Brotin, V. Roy, J.-P. Dutasta, *J. Org. Chem.* **2005**, *70*, 6187–6195.

[129] A. Felk, G. Revial, B. Viossat, P. Lemoine, M. Pfau, *Tetrahedron: Asymmetry* **1994**, *5*, 1459–1462.

[130] D. Desmaële, S. Delarue-Cochin, C. Cavé, J. d'Angelo, G. Morgant, *Org. Lett.* **2004**, *6*, 2421–2424.

[131] D. Desmaële, K. Mekouar, J. d'Angelo, *J. Org. Chem.* **1997**, *62*, 3890–3901.

[132] M. Pfau, G. Revial, A. Guingant, J. d'Angelo, *J. Am. Chem. Soc.* **1985**, *107*, 273–274.

[133] M. Pizzonero, F. Dumas, J. d'Angelo, *Heterocycles* **2005**, *66*, 31–37.

[134] M. Pizzonero, F. Hendra, S. Delarue-Cochin, M.-E. Tran Huu-Dau, F. Dumas, C. Cavé, M. Nour, J. d'Angelo, *Tetrahedron: Asymmetry* **2005**, *16*, 3853–3857.

[135] J. d'Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, *3*, 459–505.

[136] L. Yan, D. Kahne, *Synlett* **1995**, 523–524.

[137] G. Mehta, S. C. Pan, *Org. Lett.* **2004**, *6*, 3985–3988.

[138] K. Kraehenbuehl, S. Picasso, P. Vogel, *Helv. Chim. Acta* **1998**, *81*, 1439–1479.

[139] G. Bernardinelli, H. D. Flack, *Acta Crystallogr., Sect. A* **1985**, *41*, 500–511.

[140] J. D. White, R. W. Skeean, G. L. Trammell, *J. Org. Chem.* **1985**, *50*, 1939–1948.

[141] M. T. Reetz, I. Chatziiosifidis, K. Schwellnus, *Angew. Chem.*, **1981**, *93*, 716–717; *Angew. Chem. Int. Ed.* **1981**, *20*, 687–689.

[142] K. I. Kuchkova, A. B. Morari, P. F. Vlad, *Synthesis* **1993**, 1221–1222.

[143] A. Nangia, B. M. Rao, G. Prasuna, *Synth. Commun.* **1992**, *22*, 593–602.

[144] R. Adams, B. L. Van Duuren, *J. Am. Chem. Soc.* **1953**, *75*, 2377–2379.

[145] A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

[146] T. W. Baughman, J. C. Sworen, K. B. Wagener, *Tetrahedron* **2004**, *60*, 10943–10948.

[147] C. V. Magatti, J. J. Kaminski, I. Rothberg, *J. Org. Chem.* **1991**, *56*, 3102–3108.

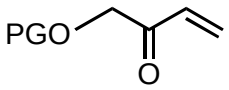
[148] H. Nakamura, H. Yamamoto, *Chem. Commun.* **2002**, 1648–1649.

[149] S. Kobayashi, I. Hachiya, M. Araki, H. Ishitani, *Tetrahedron Lett.* **1993**, *34*, 3755–3758.

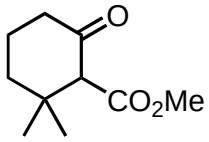
[150] H. Firouzabadi, N. Iranpoor, M. Jafarpour, *Tetrahedron Lett.* **2004**, *45*, 7451–7454.

[151] J. W. Cornforth, R. H. Cornforth, K. K. Mathew, *J. Chem. Soc.* **1959**, 112–127.

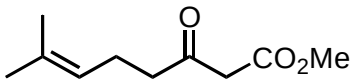
9 List of Synthesized Compounds



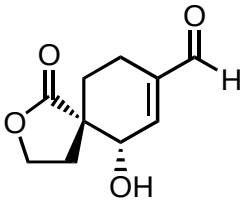
9d, PG = DMB
9e, PG = PMB
9f, PG = Ph_3C



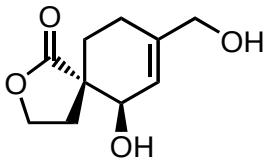
12j



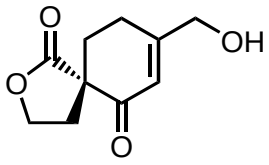
12k



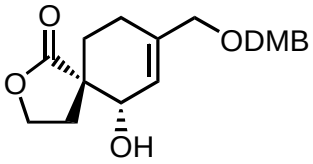
19



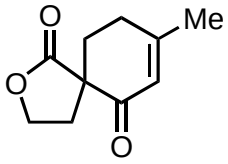
74



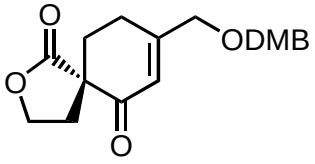
75



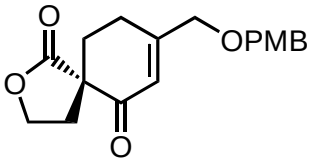
76



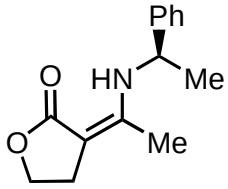
77a



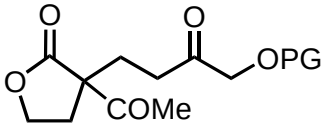
77b



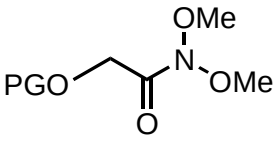
77d



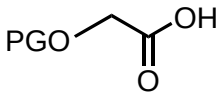
78



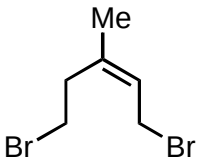
79a, PG = DMB
79b, PG = Ph_3C



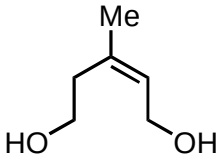
81a, PG = DMB
81b, PG = PMB
81c, PG = Ph_3C



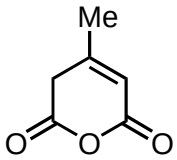
82a, PG = DMB
82b, PG = PMB
82c, PG = Ph_3C



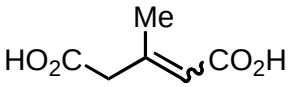
83



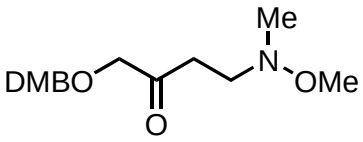
85



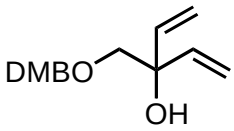
86



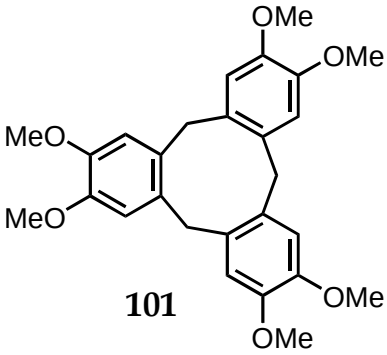
87



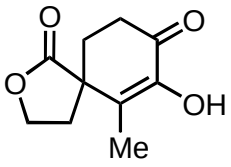
98



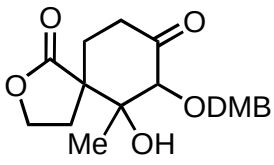
99



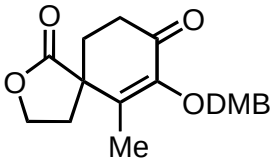
101



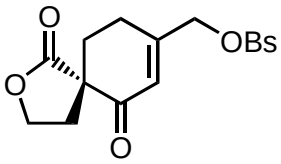
102



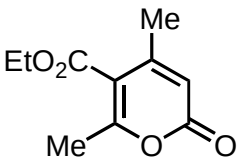
105



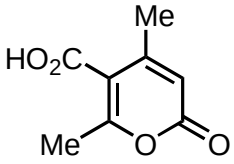
106



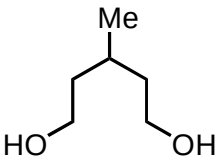
114



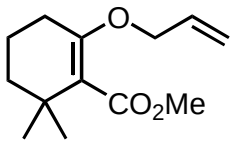
115



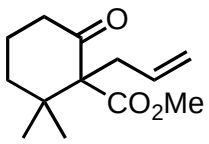
116



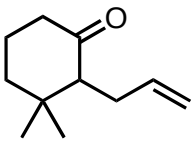
118



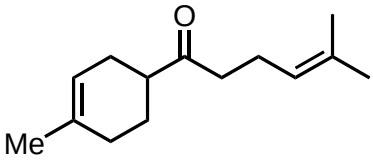
120



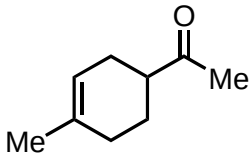
121



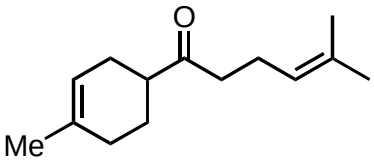
122



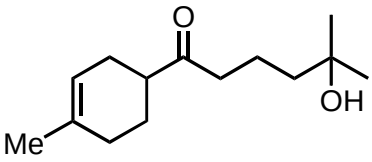
131



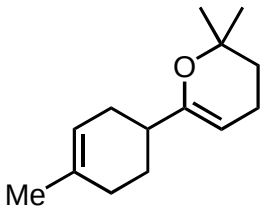
132



133



139



142

10 List of Publications

G. Koripelly, W. Saak, J. Christoffers, "Synthesis of Optically Active (+)-Canangone, Its 6-Epimer and Determination of Absolute Configuration" *Eur. J. Org. Chem.* **2007**, 5840–5846.

J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, "Recent Advances in Metal-Catalyzed Asymmetric Conjugate Additions" *Synthesis* **2007**, 1279–1300.

Curriculum Vitae

Girish Kumar Koripelly

Personal Data

Date of Birth	10/10/1976
Marital Status	Single
Nationality	Indian

Education

1982–1994	School education
1995–1998	B. Sc. (Botany, Zoology, Chemistry) Osmania University, Hyderabad, India
1998–1999	B. Ed. (Chemistry & Biology) Osmania University, Hyderabad, India
2000–2002	M. Sc. (Chemistry) University of Hyderabad, India

Research Experience

09/2002–08/2003	Research Student, Institute of Organic Chemistry, University of Fribourg, Switzerland, Research Advisor: Prof. Titus A. Jenny Title: Synthesis of self assembled organic molecules e.g. HBC with different substituents for understanding the liquid crystalline properties.
05/2004–09/2004	Research Student, Institut für Organische Chemie, Universität Kiel, Germany, Research Advisor: Dr. Anke Krüger Title: Synthesis of cage structures with sulphur containing functional groups for the production of self organised monolayers on gold substrates.
10/2004–02/2006	Ph. D. Student, Institut für Organische Chemie, Universität Stuttgart, Germany, Research Advisor: Prof. Dr. Jens Christoffers Title: Synthetic Studies on Canangone and β–Chamigrene.
from 03/2006	Movement with Prof. Dr. Jens Christoffers to the Institute für Reine und Angewandte Chemie, Universität Oldenburg

Oldenburg, 04. Februar 2008