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# MASTERARBEIT

Titel der Masterarbeit

## Toward the Asymmetric Total Syntheses of Caribenols A and B

verfasst von

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**Eidesstattliche Erklärung:**

Diese Masterarbeit wurde eigenständig und ohne Verwendung unerlaubter Hilfsmittel erarbeitet.

Wien, am

(Lucas Schreyer)

# ABSTRACT

The West Indian gorgonian octocoral *Pseudopterogorgia elisabethae* has been a source of numerous diterpenoid secondary metabolites, which have exhibited a variety of biological activities, including anti-inflammatory, anticancer, antitubercular and general antibacterial activities. Due to the limited availability of these diterpenoids from their natural sources and their complex structural architectures, they have become interesting targets for synthetic chemists. Among these natural products are the two *nor*-diterpenoids (+)-caribenol A (**I**) and caribenol B (**II**, Figure A).

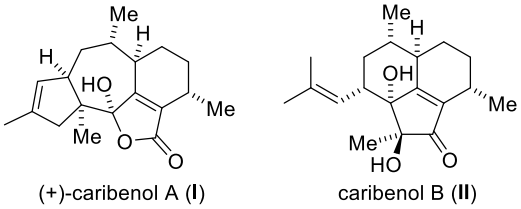
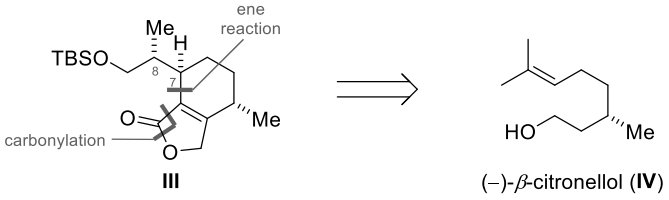



**Figure A** Two *nor*-diterpenoids from *P. elisabethae*: caribenols A (**I**) and B (**II**).

Both compounds feature unprecedented carbon skeletons, and exhibit strong inhibitory activity against *Mycobacterium tuberculosis.* In addition, (+)-caribenol A (**I**) possesses weak antiplasmodial activity. So far, only one total synthesis has been developed for (+)-caribenol A (**I**), while caribenol B (**II**) has not yet been accessed by total synthesis. Therefore, its absolute configuration still awaits confirmation.

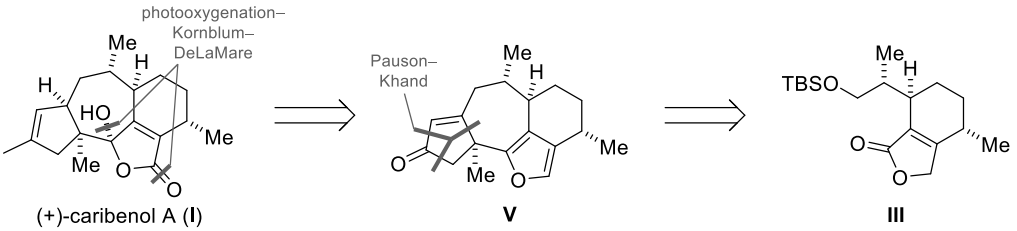
In the course of this master thesis, we envisioned the asymmetric total syntheses of both natural products *via* a common building block, butenolide **III**. This intermediate would be accessible by an *ex-chiral-pool* strategy from (–)-*β*-citronellol (**IV**, Scheme A). Chapter 2 describes the multigram scale preparation of common precursor **III**, following a route previously developed by Ingrid T. Chen in the group of Prof. Dr. Dirk Trauner. The stereogenic centers at C-7 and C-8 were established in a diastereoselective fashion, by a Lewis-acid catalyzed intramolecular ene reaction, and a highly regio- and stereoselective epoxide opening, respectively. Furthermore, this Chapter features the successful implementation of a novel carbonylation methodology for the key intramolecular alkoxycarbonylation, making use of *in situ* generated carbon monoxide instead of carbon monoxide from a gas cylinder. This improvement allows a safer yet equally efficient preparation of butenolide **III**.




**Scheme A** Retrosynthetic analysis of butenolide **III**.

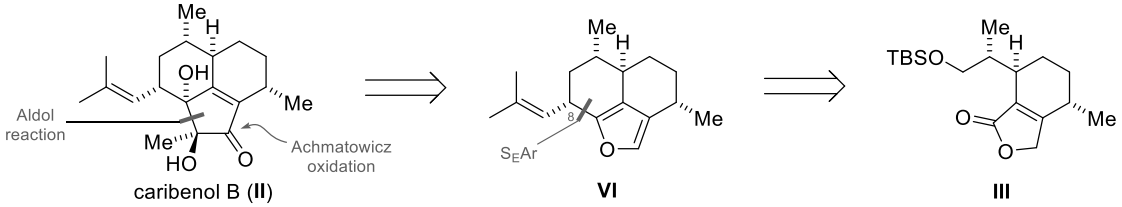
Chapter 3 outlines the progress made toward the total synthesis of (+)-caribenol A (**I**). We envisaged installing its hydroxybutenolide moiety by photooxygenation of the corresponding furan, followed by a Kornblum–DeLaMare rearrangement (Scheme B). Prior to this transformation, we intended to construct

the natural product's tetracyclic framework by an intramolecular Pauson–Khand reaction, giving access to intermediate **V**. This Chapter focuses on the two strategies investigated in the aimed synthesis of a suitable precursor for the Pauson–Khand key step from butenolide **III**.




**Scheme B** Retrosynthetic analysis of (+)-caribenol A (**I**).

Finally, Chapter 4 describes the progress toward the total synthesis of caribenol B (**II**). We aimed at accessing this natural product in a few steps from furan **VI**, implementing an Achmatowicz oxidation, followed by an intramolecular Aldol reaction (Scheme C). The synthesis of an inseparable mixture of both C-8 epimers of compound **VI** had previously been reported by Ingrid T. Chen. We therefore envisaged an enantioselective synthesis of the desired 8$\alpha$-epimer from a suitable precursor by an asymmetric Friedel–Crafts allylation. This chapter features the successful development of a concise route toward a new Friedel–Crafts allylation precursor from butenolide **III**.




**Scheme C** Retrosynthetic analysis of caribenol B (**II**).

# ABSTRACT (GERMAN)

Die zu den westindischen Gorgonien gehörende Oktokoralle *Pseudopterogorgia elisabethae* ist eine Quelle zahlreicher Diterpenoid-Sekundärmetaboliten, die eine Vielzahl verschiedener biologischer Aktivitäten aufweisen, darunter entzündungs-, krebs- und tuberkulosehemmende sowie allgemein antibakterielle Aktivitäten. Aufgrund der begrenzten Verfügbarkeit dieser Diterpenoide aus deren natürlichen Quellen, sowie der Komplexität ihrer Strukturen stellen sie interessante Ziele für Synthesechemiker dar. Zu diesen Naturstoffen gehören die zwei *nor*-Diterpenoide (+)-Caribenol A (**I**) und Caribenol B (**II**, Abb. A).

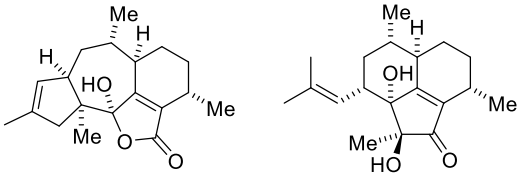
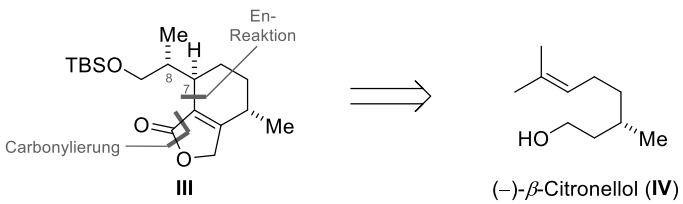



**Abb. A** Zwei *nor*-Diterpenoide aus *P. elisabethae*: Caribenole A (**I**) und B (**II**).

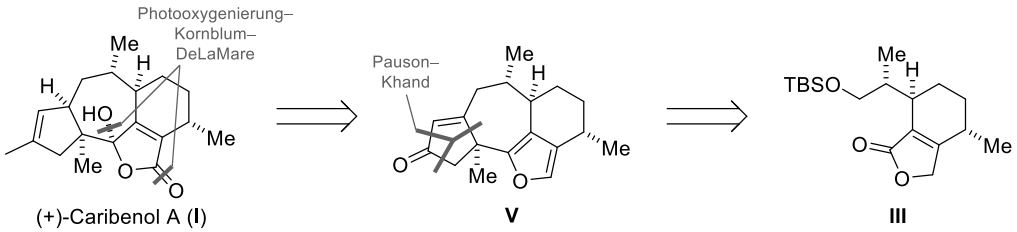
Beide Verbindungen verfügen über bisher unbekannte Kohlenstoffgerüste, und weisen eine stark hemmende Wirkung gegen *Mycobacterium tuberculosis* auf. (+)-Caribenol A (**I**) besitzt zudem schwach antiplasmodiale Eigenschaften. Bisher wurde erst eine Totalsynthese von (+)-Caribenol A (**I**) entwickelt. Caribenol B (**II**) war bislang durch keine Totalsynthese zugänglich, weshalb auch seine Absolutkonfiguration erst bestimmt werden muss.

Im Zuge dieser Masterarbeit strebten wir die asymmetrischen Totalsynthesen beider Naturstoffe durch einen gemeinsamen Synthesebaustein, Butenolid **III**, an. Dieses Intermediat würde einer *ex-chiral-pool* Strategie zufolge ausgehend von (–)-*β*-Citronellol (**IV**, Schema A) zugänglich sein. Kapitel 2 beschreibt die Darstellung des gemeinsamen Bausteins **III** im Multigramm-Maßstab, anhand der von Ingrid T. Chen in der Gruppe von Prof. Dr. Dirk Trauner entwickelten Route. Dabei wurden die stereogenen Zentren an C-7 und C-8 jeweils diastereoselektiv durch eine Lewissäure-katalysierte intramolekulare En-Reaktion bzw. eine hochgradig regio- und stereoselektive Epoxidöffnung aufgebaut. Darüber hinaus beschreibt dieses Kapitel die erfolgreiche Anwendung einer neuen Carbonylierungsmethode auf die entscheidende intramolekulare Alkoxycarbonylierung, in welcher *in situ* erzeugtes Kohlenmonoxid anstelle von Kohlenmonoxid aus einer Gasflasche eingesetzt wird. Diese Verbesserung erlaubt eine sicherere und dennoch gleichermaßen effiziente Synthese des Butenolids **III**.



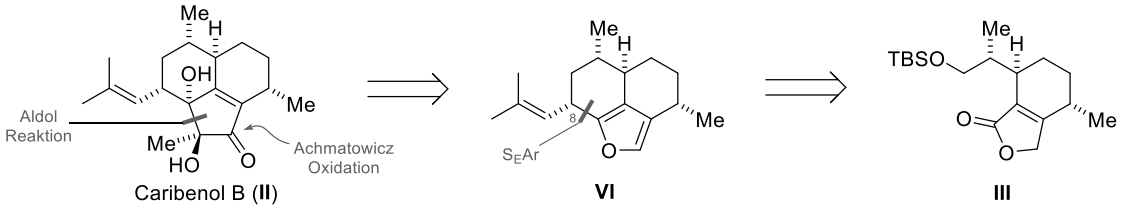

**Schema A** Retrosynthese von Butenolid **III**.

Kapitel 3 behandelt die Fortschritte, die in Richtung der Totalsynthese von (+)-Caribenol A (**I**) gemacht wurden. Wir planten die Errichtung seiner Hydroxybutenolid-Einheit aus dem entsprechenden Furan durch eine Photooxygenierung, gefolgt von einer Kornblum–DeLaMare Umlagerung (Schema B). Zuvor sollte das tetrazyklische Grundgerüst des Naturstoffs im Zuge einer intramolekularen Pauson–Khand Reaktion aufgebaut werden, was zunächst zu Intermediat **V** führen würde. Dieses Kapitel befasst sich eingehend mit zwei Strategien, die zur geplanten Synthese einer geeigneten Vorstufe des Pauson–Khand Schlüsselschritts, ausgehend von Butenolid **III**, verfolgt wurden.




**Schema B** Retrosynthese von (+)-Caribenol A (**I**).

Zuletzt umfasst Kapitel 4 die erzielten Fortschritte in Richtung der Totalsynthese von Caribenol B (**II**). Wir hatten das Ziel, diesen Naturstoff innerhalb weniger Schritte ausgehend von Furan **VI** zu erreichen, unter Anderem durch eine Achmatowicz-Oxidation und eine anschließende intramolekulare Aldolreaktion (Schema C). Ingrid T. Chen hatte bereits zuvor die Synthese einer nicht trennbaren Mischung beider C-8 Epimere von Verbindung **VI** beschrieben. Aus diesem Grund peilten wir eine enantioselektive Synthese des gewünschten 8$\alpha$-Epimers durch eine asymmetrische Friedel–Crafts Allylierung, ausgehend von einer geeigneten Vorstufe, an. Dieses Kapitel widmet sich in erster Linie der erfolgreichen Entwicklung einer kurzen Syntheseroute zu einer neuen Allylierungs-Vorstufe, ausgehend von Butenolid **III**.




**Schema C** Retrosynthese von Caribenol B (**II**).

## ACKNOWLEDGEMENTS

First of all, I would like to thank Prof. Dr. Dirk Trauner for giving me the opportunity to work on my master thesis in his group at the Ludwig-Maximilians-Universität München. I am grateful for my interesting synthesis project, and all the help and support I was provided with by Prof. Trauner himself and his entire group. The six months of my stay have certainly been a profound contribution to my skills and knowledge in the field of organic chemistry.

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Last but not least, I would like to thank my parents, who have supported and believed in me throughout my life, and thanks to whom I have been able to pursue my desired studies in chemistry.

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **4**-DMAP | 4-(dimethylamino)pyridine |
| **a** | year(s) |
| Ac | acetyl |
| acac | acetylacetonate |
| ADP | adenosine diphosphate |
| AIBN | azabisisobutyronitrile |
| aq. | aqueous |
| ATCC | American type culture collection® |
| atm | atmosphere (pressure unit) |
| ATP | adenosine triphosphate |
| ATR | attenuated total reflection (IR spectroscopy) |
| **B**ARF | tetrakis(3,5-bis(trifluoromethyl)phenyl)borate |
| BHT | 2,6-di-*tert*-butyl-4-methylphenol |
| bp | boiling point |
| br | broad (IR spectroscopy) |
| br s | broad singlet (NMR spectroscopy) |
| Bu | butyl |
| **c** | concentration |
| *c* | concentration [10 mg/mL] |
| cat. | catalytic |
| CDI | 1,1'-carbonyldiimidazole |
| CDP | cytidine diphosphate |
| CMP | cytidine monophosphate |
| CoA | coenzyme A |
| COSY | homonuclear correlation spectroscopy |
| CSA | camphorsulfonic acid |
| CTP | cytidine triphosphate |
| **d** | day(s) |
| d | dublet (NMR spectroscopy) |
| *D* | sodium D line ($\lambda$ = 589 nm) |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DIBAL-H | diisobutylaluminum hydride |
| DIPA | diisopropylamine |

| | |
|---|---|
| DMAPP | 3,3-dimethylallyl diphosphate |
| DMPU | *N,N'*-dimethylpropylene urea |
| d.r. | diastereomeric ratio |
| | |
| ***e****e* | enantiomeric excess |
| EI | electron impact ionization (mass spectrometry) |
| eq. | equivalents |
| ESI | electrospray ionization (mass spectrometry) |
| Et | ethyl |
| | |
| **F**CC | flash column chromatography |
| FT-IR | Fourier transform infrared spectroscopy |
| | |
| **g** | gram(s) |
| | |
| **h** | hour(s) |
| HIV | human immunodeficiency virus |
| HMBC | heteronuclear multiple bond coherence |
| HMPA | *N,N,N',N',N'',N''*-hexamethylphosphoramide |
| HPLC | high-performance liquid chromatography |
| HRMS | high-resolution mass spectrometry |
| HSQC | heteronuclear single quantum coherence |
| Hz | hertz (frequency) |
| | |
| **I**$C_{50}$ | half maximal inhibitory concentration |
| IPP | isopentenyl diphosphate |
| IR | infrared |
| IUPAC | International Union of Pure and Applied Chemistry |
| | |
| **K**HMDS | potassium hexamethyldisilazide |
| | |
| **L**A | lewis acid |
| LDA | lithium diisopropylamide |
| LiHMDS | lithium hexamethyldisilazide |
| lit. | literature |
| Ln | ligand(s) |
| L-selectride® | lithium tri-*sec*-butylborohydride |
| | |
| **m** | medium (IR spectroscopy) |
| m | multiplet (NMR spectroscopy) |

| | |
|---|---|
| *M* | molar mass [g/mol] |
| M | mol/L |
| $m_C$ | centrosymmetric multiplet (NMR spectroscopy) |
| Me | methyl |
| MEP | methylerythritol phosphate |
| Mes | mesityl |
| mp | melting point |
| Ms | methanesulfonyl |
| MS | mass spectrometry |
| $\mu$ | micro |
| | |
| **N**ADH/$NAD^+$ | nicotinamide adenine dinucleotide (reduced/oxidized form) |
| NADPH/$NADP^+$ | nicotinamide adenine dinucleotide phosphate (reduced/oxidized form) |
| NaHMDS | sodium hexamethyldisilazide |
| NMP | *N*-methyl-2-pyrrolidinone |
| NMR | nuclear magnetic resonance |
| NOESY | nuclear Overhauser enhancement correlation spectroscopy |
| | |
| ***p*** | pressure |
| *p*- | *para* (isomer) |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| $P_i$ | (inorganic) phosphate |
| $PP_i$ | (inorganic) diphosphate |
| ppm | parts per million |
| py | pyridine |
| | |
| **q** | quartet (NMR spectroscopy) |
| | |
| **R** | undefined substituent |
| $R_f$ | retardation factor |
| RP | reversed phase |
| rt | room temperature |
| | |
| **s** | singlet (NMR spectroscopy) |
| s | strong (IR spectroscopy) |
| s.m. | starting material |
| | |
| **t** | triplet (NMR spectroscopy) |
| *t* | time |

| | |
|---|---|
| *T* | temperature |
| *t*- | (*tert*-), tertiary (isomer) |
| TBAF | tetrabutylammonium fluoride |
| TBS | *tert*-butyldimethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| TFAA | trifluoroacetic anhydride |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TLC | thin layer chromatography |
| TMEDA | *N,N,N′,N′*-tetramethylethylenediamine |
| TMS | trimethylsilyl |
| Ts, (*p*-Ts) | *p*-toluenesulfonyl |
| | |
| **U**V | ultraviolet |
| | |
| **w** | weak (IR spectroscopy) |
| w/w | weight *per* weight |

# TABLE OF CONTENTS

# 1 INTRODUCTION

The large class of terpenoids*, comprising over 35,000 distinct molecules known to date, occurs in all domains of life, *i.e.* archaea, bacteria and eukarya. They fulfill a variety of essential biological functions, such as electron transport in bacteria and hormone-based signaling, and act as membrane constituents or stabilizers, as well as protective pigments in plants.[1] According to the 'isoprene rule', established by Wallach[2] and Ruzicka[3], all terpenoids are (formally) composed of a specific number of isoprene (**1**) units (Figure 1.1).[4] For over 4500 years, humans made use of terpenoids, *e.g.* in the form of plant oils in traditional medicine. Today, many terpenoids are applied in medicine, agriculture, and as flavors and fragrances.[5] Two important examples are depicted in Figure 1.1: (–)-Menthol (**2**) is a cooling and flavoring agent naturally occurring in field mint (*Mentha arvensis*), and is widely used in toothpastes, mouthwashes, sweets, salves and shower gels. It is won both from its natural sources, and by chemical processes, *e.g.* the Takasago-process, which bears the worldwide biggest industrial application of homogeneous asymmetric catalysis (run on 9 t scales).[6] The highly functionalized diterpenoid paclitaxel (**3**) naturally occurs in the pacific yew (*Taxus brevifola*), and is used as an anticancer drug under the trade name "Taxol®",[5] primarily against "metastatic carcinoma of the ovary, metastatic breast cancer and non-small cell lung cancer as well as in second-line treatment of AIDS-related Kaposi's sarcoma".[7] For many years, the total market value for Taxol® has been in the billion dollar range.[7]

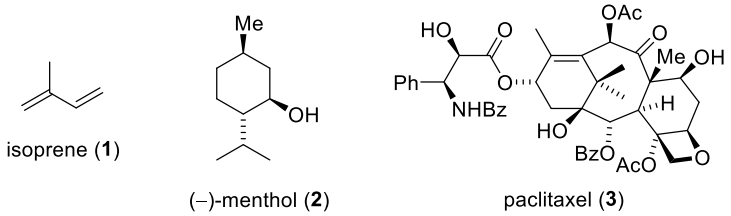



**Figure 1.1** Isoprene (**1**), and two examples for widely applied terpenoids: (–)-menthol (**2**) and paclitaxel (**3**).

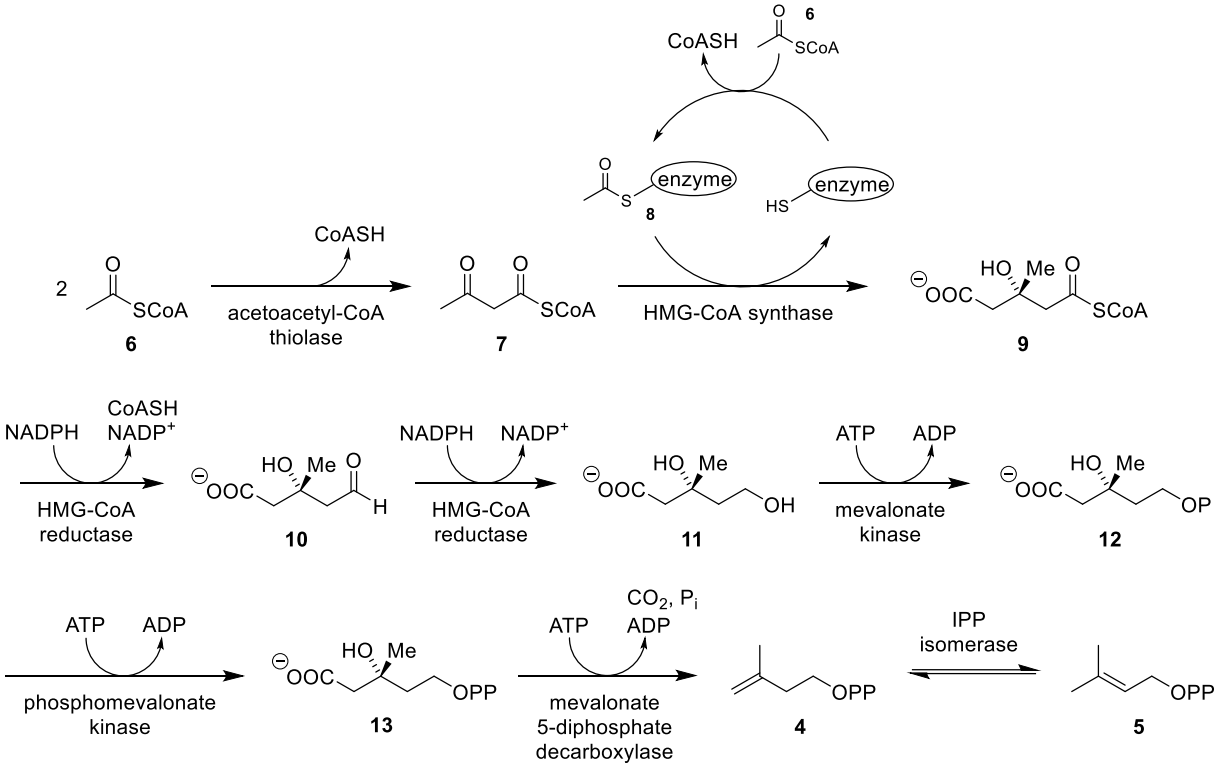
## 1.1 Biosynthesis of Terpenoids

The biosynthetic equivalents of the formal building block isoprene (**1**) are isopentenyl diphosphate (IPP, **4**) and 3,3-dimethylallyl diphosphate (DMAPP, **5**, Scheme 1.1). They are derived by either of two biosynthetic pathways, the mevalonate or the methylerythritol phosphate (MEP)-pathway.[5,8]

The biosynthesis of IPP (**4**) and DMAPP (**5**) *via* the mevalonate pathway begins with the acetoacetyl-CoA thiolase catalyzed condensation of two acetyl-CoA units (**6**), giving rise to acetoacetyl-CoA (**7**).[9] The synthesis of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA, **9**) is catalyzed by the HMG-CoA synthase, which forms acetyl-*S*-enzyme intermediate **8** with another molecule of acetyl-CoA (**6**). The corresponding thioester enolate is subsequently added to acetoacetyl-CoA (**7**), and

* The IUPAC defines 'terpenes' as "hydrocarbons of biological origin having carbon skeletons formally derived from isoprene", and 'terpenoids' (also known as 'isoprenoids') as oxygenated derivatives thereof. They further state that "the skeleton of terpenoids may differ from strict additivity of isoprene units by the loss or shift of a fragment, generally a methyl group." (Moss, G. P. *et al. Pure & Appl. Chem.* **1995**, *67*, 1307–1375.).
In this master thesis, the terms 'terpenes', 'terpenoids' and 'isoprenoids' will be used synonymously.

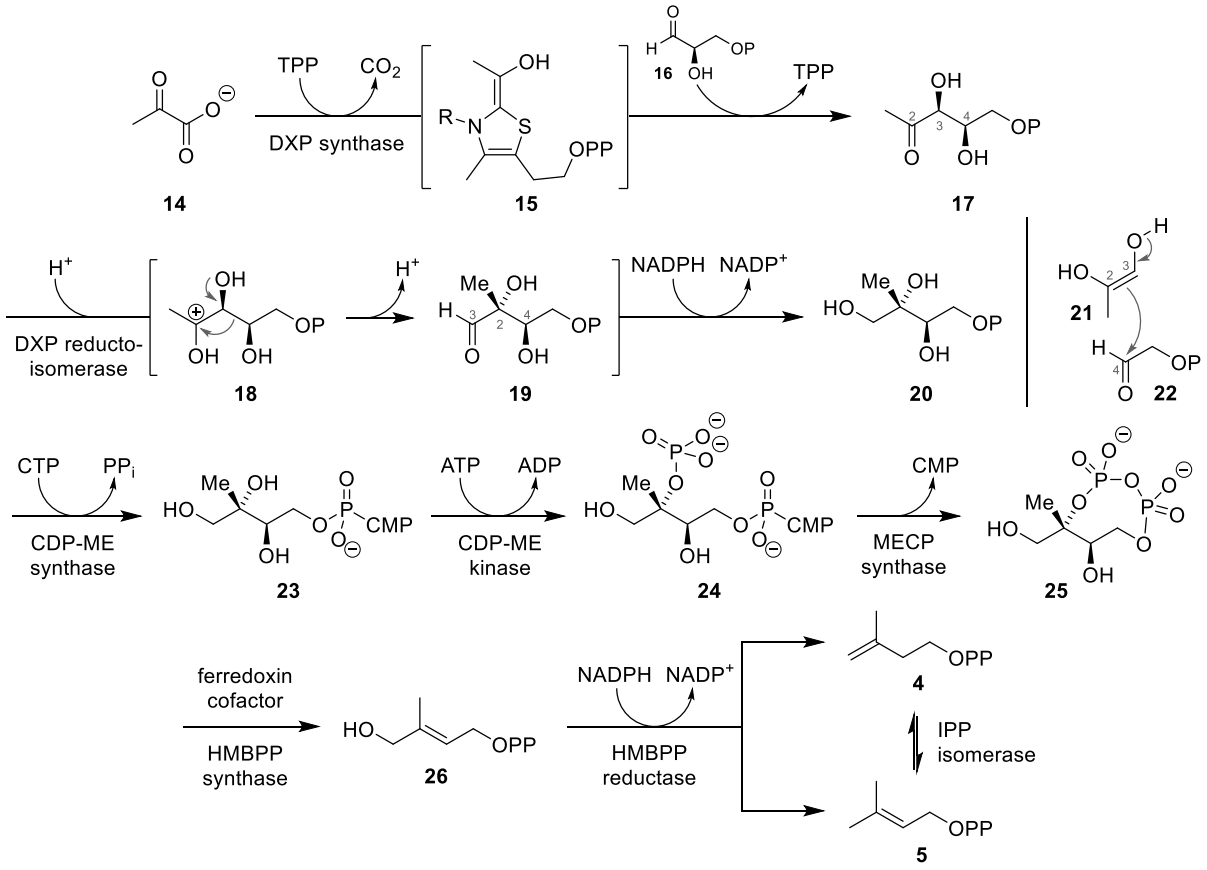
the enzyme is released upon hydrolysis.[8] Reduction of the thioester of HMG-CoA (**9**) by HMG-CoA reductase with the cofactor NADPH furnishes mevalonate (**11**) *via* mevaldate (**10**). The carbonyl group of each substrate is presumably activated by a crucial protonated lysine of the enzyme prior to hydride addition. Stepwise phosphorylation of mevalonate (**11**) by mevalonate and phosphomevalonate kinase sequentially affords mevalonate-5-phosphate (**12**) and mevalonate-5-diphosphate (**13**). In each step, one molecule of ATP is consumed. IPP (**4**) is formed through subsequent decarboxylation of intermediate **13**, catalyzed by the mevalonate-5-diphosphate decarboxylase under consumption of ATP. The mechanism of this step is not yet fully understood,[8] though studies with substrate analogues support a phosphorylation of the 3-hydroxyl group of mevalonate-5-diphosphate (**13**) prior to decarboxylation.[10] DMAPP (**5**) presumably arises from IPP (**4**) through cationic 1,3-allylic rearrangement, catalyzed by IPP isomerase.[8]




**Scheme 1.1** Biosyntheses of IPP (**4**) and DMAPP (**5**) by the mevalonate pathway.

The biosyntheses of IPP (**4**) and DMAPP (**5**) *via* the MEP pathway (also called non-mevalonate or deoxyxylulose phosphate (DXP) pathway) begins with the condensation of pyruvate (**14**) and D-glyceraldehyde 3-phosphate (**16**), affording 1-deoxy-D-xylulose 5-phosphate (DXP, **17**, Scheme 1.2). This reaction is catalyzed by the DXP synthase and proceeds *via* ketene thioaminal **15**, obtained by addition of the cofactor thiamine diphosphate (TPP) to pyruvate (**14**) and a subsequent decarboxylation. The DXP synthase was found to catalyze a rate-limiting step, as determined by gene overexpression experiments in *Escherichia coli (E. coli)*. A pinacol-type rearrangement of DXP (**17**), followed by reduction of the presumably formed aldose **19** with NADPH furnishes 2-methyl-D-erythritol 4-phosphate (MEP, **20**). Both steps are catalyzed by the DXP reductoisomerase and take place on the same active site of the enzyme.[8] An alternative mechanism proposed for the biosynthesis of aldose **19** comprises a retroadol–aldol sequence involving intermediates **21** and **22**.[11] Under the consumption of

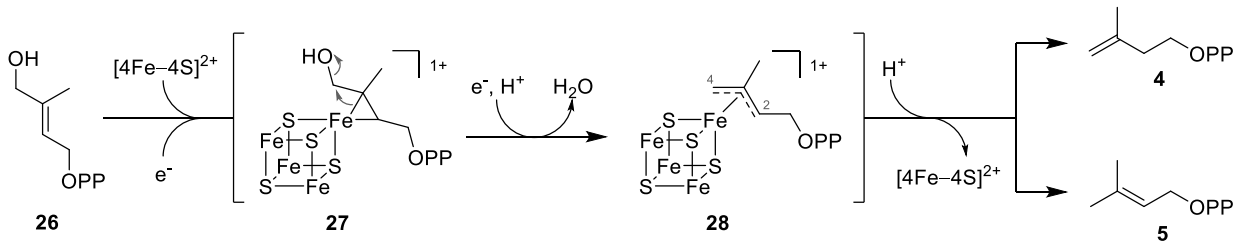
cytidine triphosphate (CTP), the enzyme 4-diphosphocytidyl-2-methyl-D-erythritol synthase catalyzes the formation of the corresponding intermediate (CDP-ME, **23**) and diphosphate. The 4-diphosphocytidyl-2-methyl-D-erythritol kinase catalyzed phosphorylation of CDP-ME (**23**) affords 4-diphosphocytidyl-2-methyl-D-erythritol 2-phosphate (CDP-ME2P, **24**), which is cyclized by the enzyme 2-methyl-D-erythritol-2,4-cyclodiphosphate synthase, forming 2-methyl-D-erythritol-2,4-cyclodiphosphate (MECP, **25**) and cytidine monophosphate (CMP). This reaction requires $Zn^{2+}$ and either $Mn^{2+}$ or $Mg^{2+}$ as cofactors, which polarize the diphosphate of the CDP residue and may also stabilize the presumed pentacoordinate transition state generated by a nucleophilic attack of the 2-phosphate on the $\beta$-phosphate of CDP-ME2P (**24**).[12]




**Scheme 1.2** Biosyntheses of IPP (**4**) and DMAPP (**5**) by the MEP pathway.

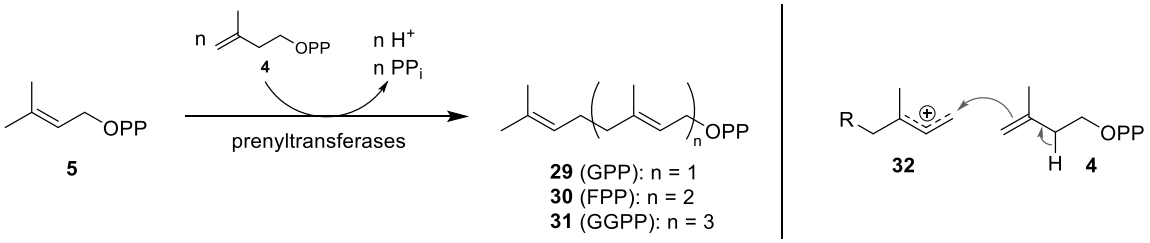
Cyclodiphosphate **25** is transformed into (*E*)-4-hydroxy-3-methylbut-2-enyl diphosphate (HMBPP, **26**) by the iron–sulfur protein HMBPP synthase in the presence of the cofactor ferredoxin.[11,13] This reaction still requires mechanistic elucidation, but is assumed to proceed through a radical intermediate, generated by single electron transfer from the enzyme's [4Fe–4S] cluster to the substrate.[11] The final step comprises the HMBPP reductase catalyzed reduction of HMBPP (**26**) to either IPP (**4**) or DMAPP (**5**). This enzyme also contains a [4Fe–4S] cluster, which upon stepwise reduction using two electrons (originating from NADPH[13]) is assumed to first form $\eta^2$-alkenyl complex **27** with HMBPP (**26**), followed by either simultaneous or consecutive reduction–elimination, furnishing $\pi$-allyl complex **28** (Scheme 1.3). Protonation of the formal allyl anion of **28** at C-2 or C-4 may then give rise to IPP (**4**) or DMAPP (**5**),

respectively.[14] Most bacteria employing the MEP pathway do not make use of an IPP isomerase. One exception is *E. coli*, for which the enzyme is nonessential though.[5]




**Scheme 1.3** Proposed mechanism of the HMBPP reductase catalyzed synthesis of IPP (**4**) and DMAPP (**5**) from HMBPP (**26**).

Prenyltransferases catalyze the elongation of DMAPP (**5**) with one or more IPP units (**4**, Scheme 1.4), giving rise to the precursors of different classes of terpenoids, such as geranyl diphosphate (GPP, **29**), farnesyl diphosphate (FPP, **30**) and geranylgeranyl diphosphate (GGPP, **31**). The elongations supposedly proceed *via* allyl cation **32**, generated by dissociation of the diphosphate from the corresponding starter units, and a subsequent addition–elimination of IPP (**4**). Bulky amino acids surrounding the active site of the enzyme limit the size to which a polyprenyl chain can grow.[8]




**Scheme 1.4** Prenyltransferase catalyzed biosynthesis of the terpenoid precursors GPP (**29**), FPP (**30**) and GGPP (**31**).

The specific classes of terpenoids arise from either the mevalonate or MEP pathway. The cytosolic mevalonate pathway, employed for example in mammals, plants and archaea, produces sesquiterpenoids, triterpenoids and sterols (Figure 1.2). The plastid-bound MEP pathway mainly leads to the formation of mono- and diterpenoids, as well as tetraterpenoids (carotenoids), and the phytol residues of chlorophylls and tocopherols (vitamin E).[5,8]

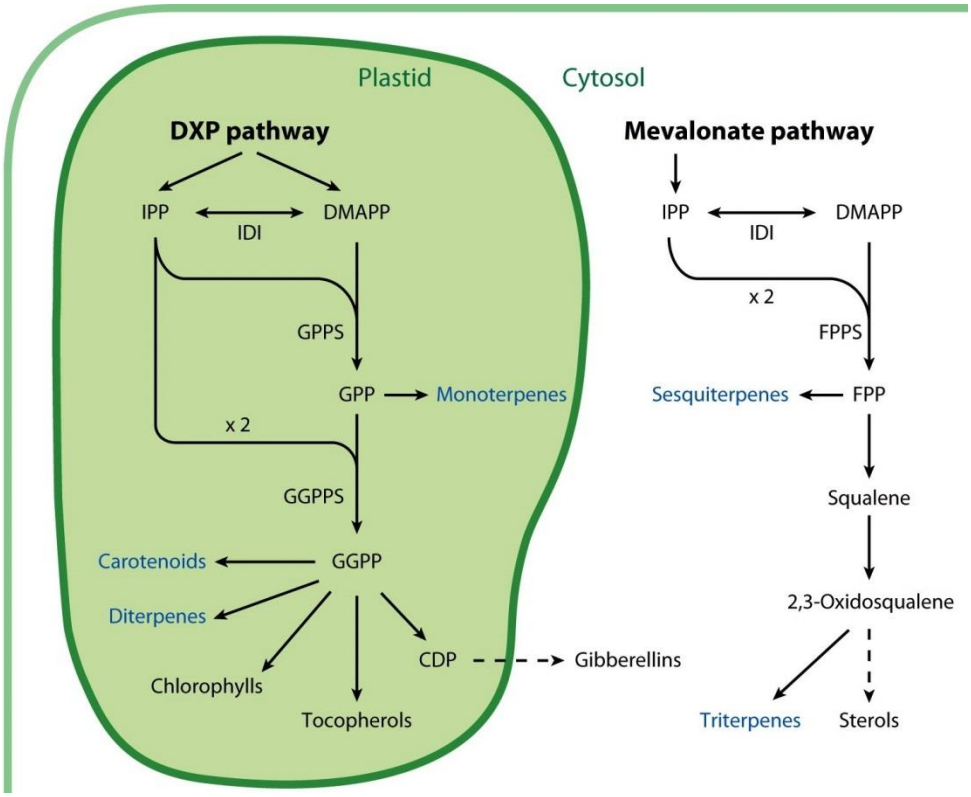



**Figure 1.2** Location of the mevalonate and MEP (DXP) pathway, and the classes of terpenoids that arise from either of them. IDI = IPP isomerase.

The hemiterpenoid ($C_5$) isoprene (**1**) is not only the hypothetical building block of all terpenoids, but actually produced from DMAPP (**5**) and emitted by many plants in large quantities (Figure 1.3[15], estimated global isoprene emissions: $6.2 \cdot 10^{11}$ kg·a$^{-1}$).[16,8] Monoterpenoids ($C_{10}$) arise from GPP (**29**), and are the major, odorous constituents of essential oils and resins of many plants. Two representatives of this class are (–)-*β*-citronellol (**33**), which is found in various geranium and rose oils, and (–)-carvone (**34**), the primary constituent of the essential oil of spearmint.[17,18]

Many different classes of diterpenoids ($C_{20}$) are synthesized from GGPP (**31**): The tetracyclic diterpenoid Prostratin (**35**), isolated from *Homalanthus nutans* (a small tree growing in Samoa), exhibits significant activities against HIV.[5,19] Gibberellins, such as $GA_{12}$ (**37**), are a large class of diterpenoids that are produced *via* copalyl diphosphate (CDP, **36**) and function as plant growth hormones.[8] Phytyl residues are reduced geranylgeranyl groups and are found in most chlorophylls, *e.g.* chlorophyll a (**38**), and tocopherols, *e.g.* *α*-tocopherol (**40**).[8,20] GGPP (**31**) also gives rise to tetraterpenoids ($C_{40}$), such as *β*-carotene (**39**).[5]

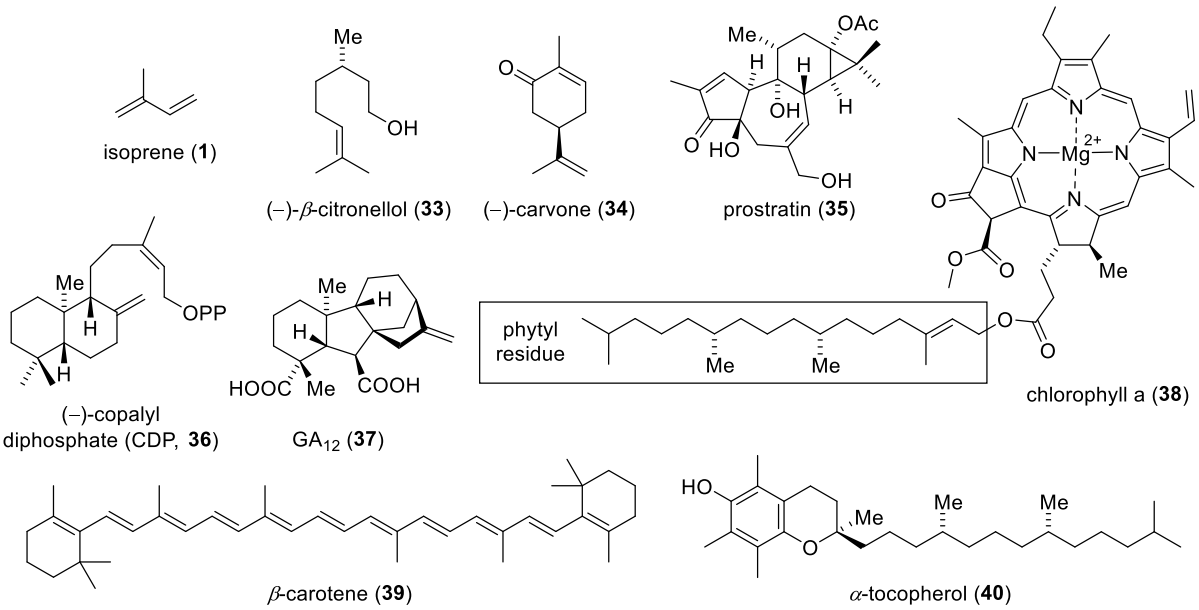



**Figure 1.3** Examples for terpenoids derived from the MEP pathway.

FPP (**30**) is the precursor of sesqui- ($C_{15}$) and triterpenoids ($C_{30}$), as well as sterols. The latter two substance classes are formed *via* two common triterpenoid precursors, squalene (**42**) and 2,3-oxidosqualene (**43**, Figure 1.4). The sesquiterpenoid artemisinin (**41**), which naturally occurs in *Artemisia annua*, is used for the treatment of malaria.[5,8,21] Ursolic acid (**44**) is a triterpenoid that was recently isolated from the leaves of *Catharanthus roseus*, and exhibited various pharmacological activities, including anti-inflammatory, antitumor and antimicrobial properties.[22] The oxidosqualene cyclase catalyzes the transformation of 2,3-oxidosqualene (**43**) into lanosterol (**45**), a protosterol which, upon oxidative demethylations, gives rise to cholesterol (**46**),[23] an important metabolite in mammals and substrate for the biosynthesis of steroid hormones and bile acids.[24]

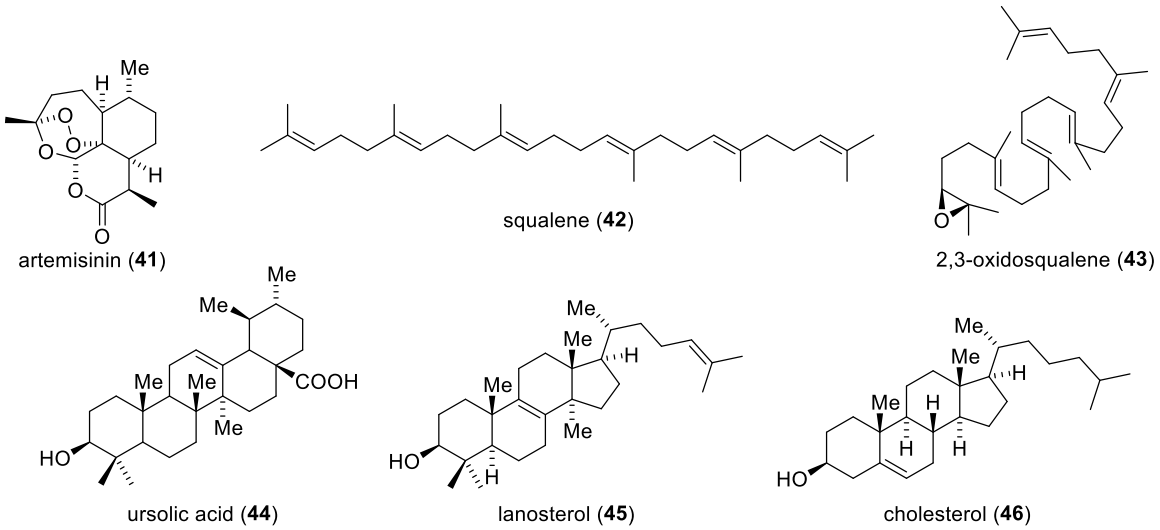



**Figure 1.4** Examples for terpenoids derived from the mevalonate pathway.

## 1.2 Diterpenoids from *P. elisabethae*: Interesting Targets for Total Synthesis

Since 1986, numerous diterpenoid secondary metabolites, which exhibited a variety of biological activities, including anti-inflammatory, anticancer, antitubercular and general antibacterial activities, have been isolated from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*.[25,26,27] Due to the limited availability of these diterpenoids from their natural source and their complex structural architectures, they have become interesting targets for synthetic chemists. [27,28,29]

The large group of pseudopterosins consists of three distinctly glycosylated and partly acetylated stereoisomeric diterpenoids: the enantiomeric aglycons of pseudopterosins A–F & Z (**47**) and K & L (**49**), as well as the diastereomeric aglycon of pseudopterosins G–J & P–Y (**48**, Figure 1.5).[25,30,31,32] With 11 different total syntheses reported as of 2013, significant synthetic effort was put into pseudopterosin aglycon **47** (or specifically glycosylated derivatives).[33a–k]

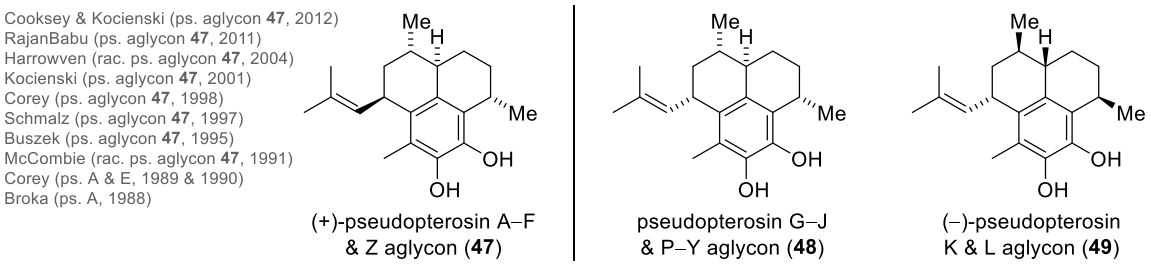



**Figure 1.5** The aglycons of pseudopterosins A–F & Z (**47**), G–J & P–Y (**48**), and K & L (**49**), and the groups which successfully synthesized aglycon **47** (or specifically glycosylated derivatives) so far. The optical rotation of aglycon **48** has not been reported. ps. = pseudopterosin, rac. = racemic.

Several total syntheses of the tetracyclic diterpenoids (–)-colombiasin A (**50**) and (–)-elisapterosin B (**51**) have been reported, partly accessing both natural products *via* common precursors (Figure 1.6).[34a–f] Two total syntheses of elisabethin A (**52**) were reported by the groups of Mulzer[35] and Rawal[36] in 2003, but the correctness of the relative configurations of both synthetic natural products was later doubted by Zanoni and Franzini.[37] In 2013, the first total syntheses of *nor*-diterpenoid ($C_{19}$) sandresolide B (**53**) and tris-*nor*-diterpenoid ($C_{17}$) amphilectolide (**54**) were reported by Trauner and coworkers.[38] The common synthetic route that gave access to both natural products was partly improved and applied in this master thesis, for the aimed total syntheses of the *nor*-diterpenoids caribenol A (**55**) and B (**56**). While the latter natural product has not been accessed by total synthesis yet, one total synthesis of (+)-caribenol A (**55**) was reported by Yang and coworkers in 2010, which also clarified the absolute configuration of the natural product.[39]

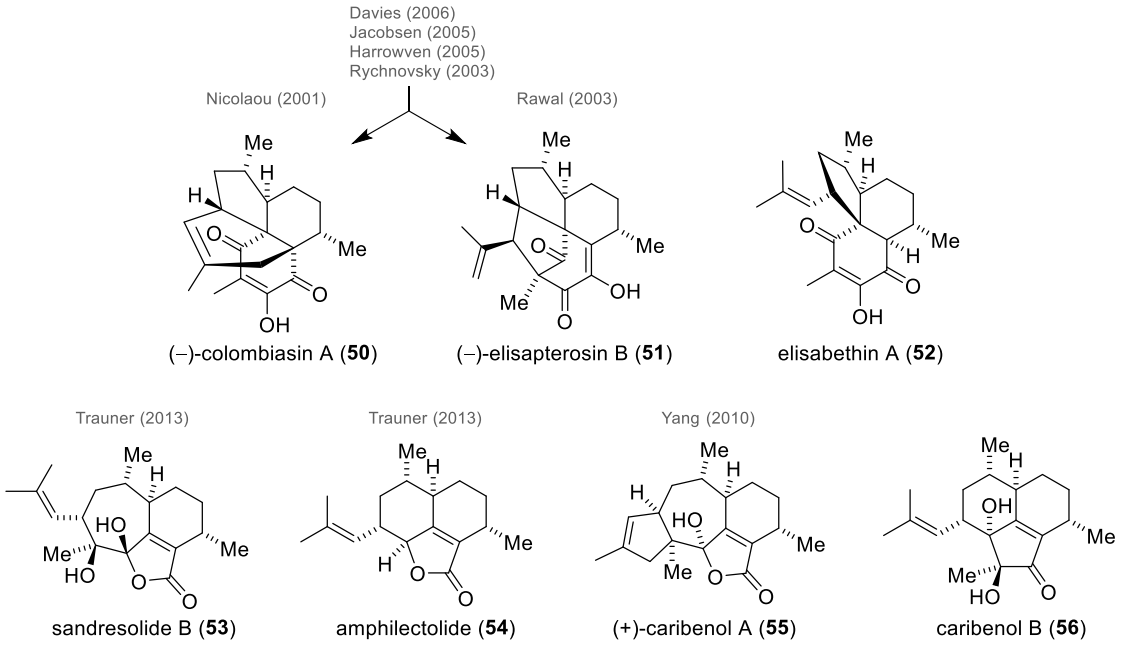
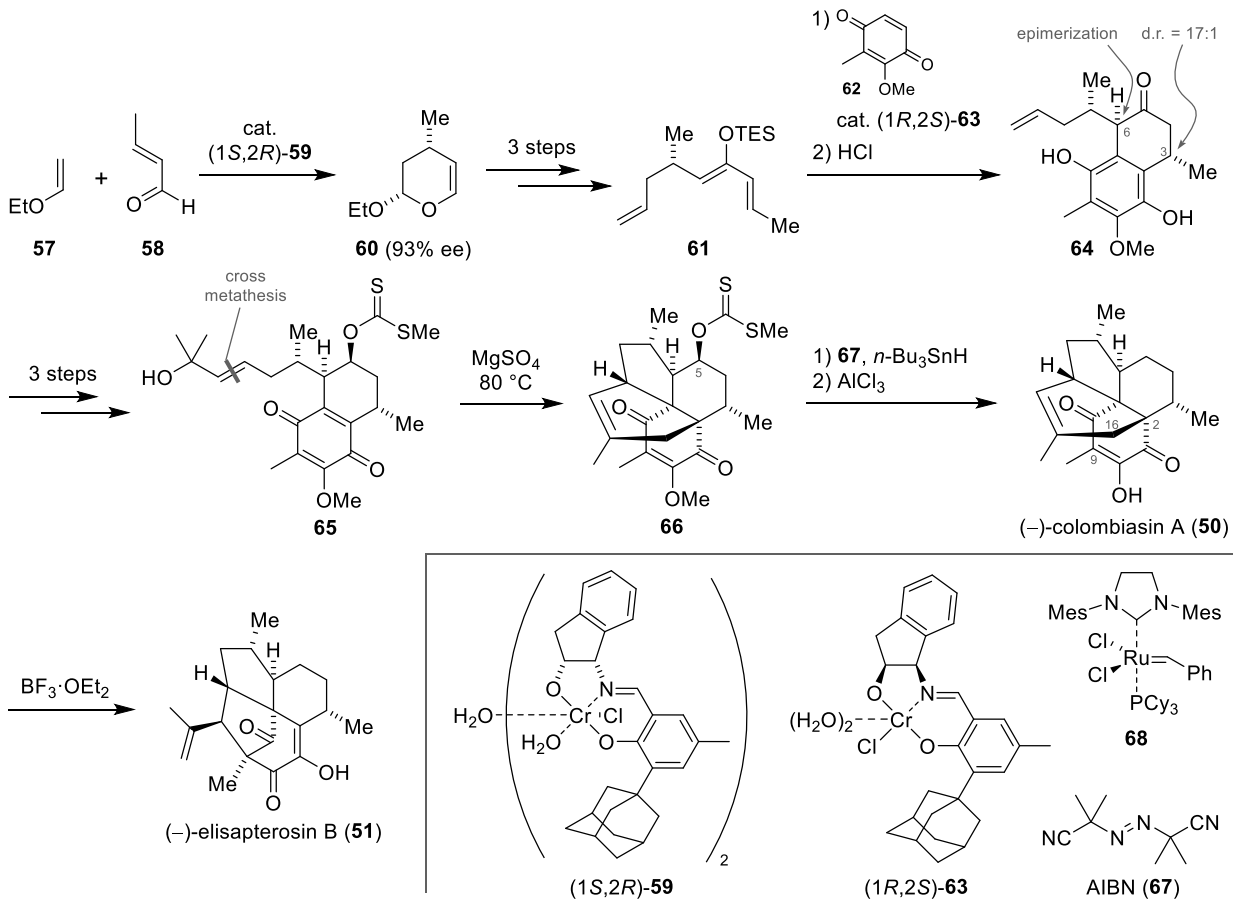



**Figure 1.6** *Nor-* (**53**–**56**) and diterpenoids (**50**–**52**) from *P. elisabethae*, partly accessed by total synthesis.

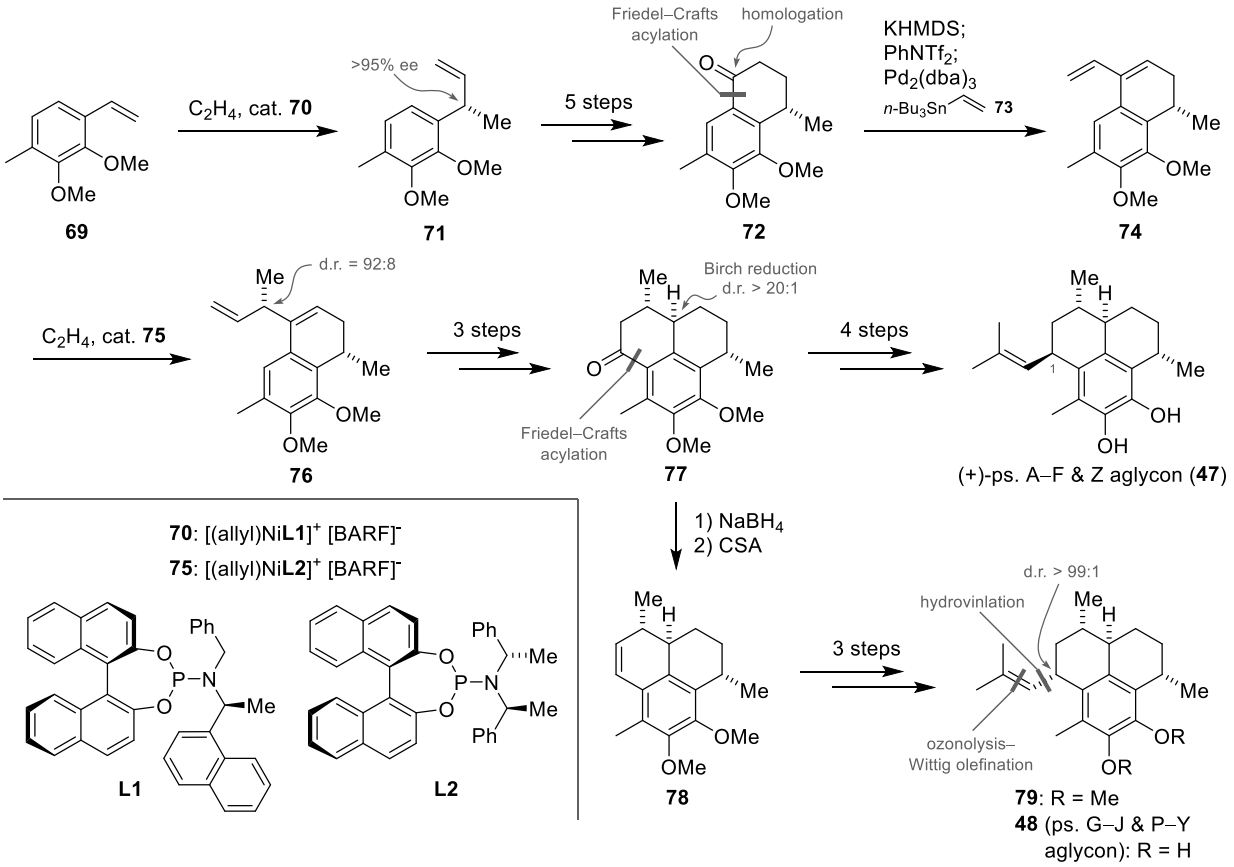
In 2005, the group of Jacobsen reported an asymmetric total synthesis of (–)-elisapterosin B (**51**) *via* (–)-colombiasin A (**50**), in a remarkable overall yield of 11%, featuring two Cr-catalyzed asymmetric Diels–Alder reactions (Scheme 1.5). The synthesis started with an asymmetric hetero-Diels–Alder reaction of ethyl vinyl ether (**57**) and (*E*)-crotonaldehyde (**58**), using $Cr^{III}$ catalyst (1*S*,2*R*)-**59**, furnishing dihydropyran **60**. Within three transformations triene **61**, the substrate for an asymmetric quinone Diels–Alder (qDA) reaction, was synthesized. This proceeded with high regio- (10:1) and diastereoselectivity (d.r. = 17:1) using quinone **62** and catalytic amounts of $Cr^{III}$ complex (1*R*,2*S*)-**63**. The initially misconfigured stereogenic center at C-6 was epimerized during the subsequent, acidic desilylation, which afforded cyclohexanone **64**. In three more steps, including cross metathesis using the 2$^{nd}$ generation Grubbs' catalyst (**68**), dimethylallyl alcohol **65** was prepared. The remaining three steps to (–)-colombiasin A (**50**) were initiated by a "tandem dehydration–intramolecular qDA reaction", which diastereoselectively established the core tetracyclic structure, followed by defunctionalization at C-5 with AIBN (**67**) and *n*-$Bu_3SnH$. Finally, demethylation of the enol ether using $AlCl_3$ constructed the natural product. Under application of a large excess of $BF_3{\cdot}OEt_2$, (–)-colombiasin A (**50**) was smoothly converted into (–)-elisapterosin B (**51**) in an excellent 94% yield. Though the mechanism of this transformation is not yet fully understood, it was proposed to either proceed by fragmentation of the bond between C-2 and C-16, followed by trapping of the intermediate allyl cation by C-9 of the enol moiety, or a retro Diels–Alder reaction and a subsequent [5+2] cycloaddition.[34b]




**Scheme 1.5** Jacobsen's asymmetric total synthesis of (–)-colombiasin A (**50**) and (–)-elisapterosin B (**51**), featuring an extensive use of asymmetric Diels–Alder reactions.

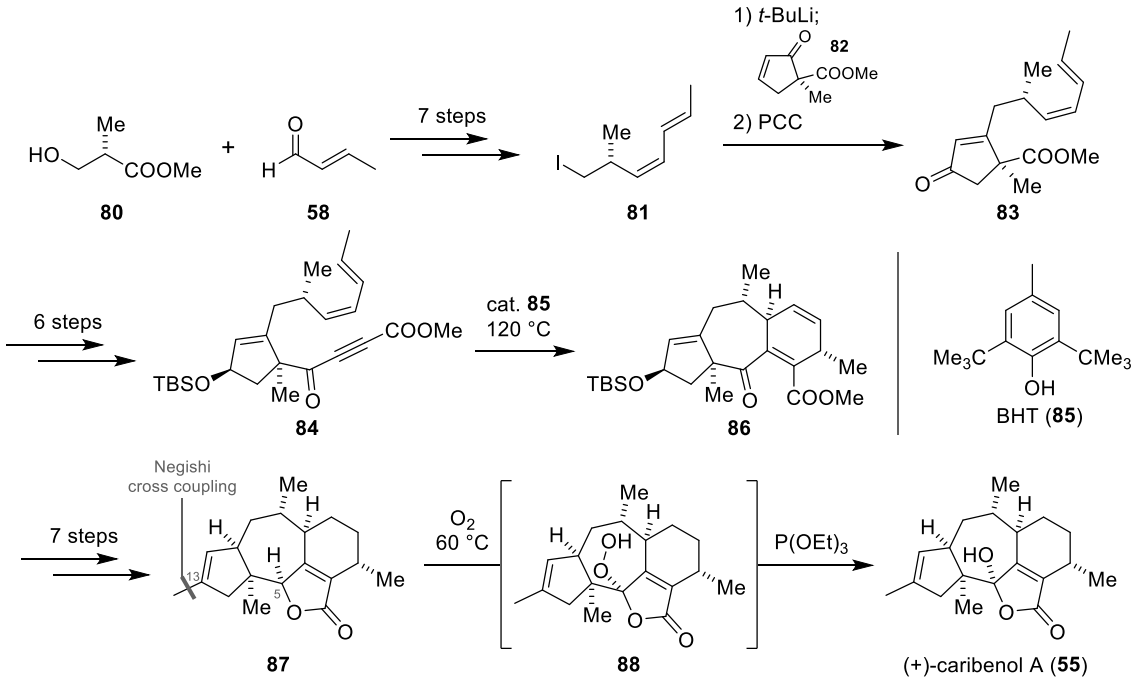
While many existing asymmetric total syntheses of (+)-pseudopterosin A–F & Z aglycon (**47**) are based on enantiopure monoterpenoids from the chiral carbon pool, RajanBabu and coworkers, in 2011, accomplished the asymmetric total syntheses of pseudopterosin aglycon **47** and the dimethyl ether of aglycon **48** from an achiral starting material, featuring an asymmetric, Ni-catalyzed hydrovinylation (Scheme 1.6).[40] The synthesis commenced with the asymmetric hydrovinylation of literature-known catechol **69**,[41] using 1 atm of ethene and catalytic amounts of $Ni^{II}$ complex **70**. The reaction afforded olefin **71** in >95% *ee*, which was converted into ketone **72** in 5 steps, including hydroboration–oxidation, homologation by substitution with cyanide, and Friedel–Crafts acylation. Hydrovinylation precursor **74** was formed *via* Stille cross coupling of tri-*n*-butyl(vinyl)tin (**73**) and the corresponding vinyl triflate of ketone **72** (not shown), which was prepared *in situ* with KHMDS and $PhNTf_2$. The asymmetric hydrovinylation was conducted with 1 atm of ethene and catalytic amounts of $Ni^{II}$ complex **75** and furnished catechol **76** in a diastereomeric ratio of 92:8. Ketone **77** was synthesized from catechol **76** by hydroboration–oxidation of the terminal olefin, diastereoselective reduction of the internal olefin under Birch conditions (d.r. > 20:1), and Friedel–Crafts acylation. From this intermediate, both the pseudopterosin aglycon **47** and the dimethyl ether of aglycon **48** could each be accessed in 4 more steps:[33k] The synthesis of aglycon **47** from ketone **77** was previously reported by Buszek and Bixby and features a diastereoselective introduction of the missing 2-methylpropenyl unit at C-1 *via* Corey–Chaykovsky epoxidation, $BF_3{\cdot}OEt_2$ induced rearrangement to the aldehyde, Wittig olefination and

demethylation of the catechol moiety with TMSI.[33f] The synthesis of pseudopterosin G–J & P–Y aglycon dimethyl ether **79** comprised the reduction–elimination of the carbonyl group of ketone **77**, a highly regio- and stereoselective (d.r. > 99:1) hydrovinylation of the resulting olefin **78** with 1 atm of ethene and catalytic amounts of $Ni^{II}$ complex **75**, and finally a sequence of ozonolysis–Wittig olefination to furnish the required trisubstituted olefin.[33k]




**Scheme 1.6** RajanBabu's asymmetric total syntheses of ps. aglycon **47** and ps. aglycon dimethyl ether **79**. ps. = pseudopterosin.

In 2010, the first total synthesis of (+)-caribenol A (**55**) was reported by Yang and coworkers.[39] The synthesis made use of a highly diastereoselective intramolecular Diels–Alder reaction to establish the core tricyclic carbon framework (Scheme 1.7). The synthesis started with (+)-Roche ester (**80**) and (*E*)-crotonaldehyde (**58**), which, within seven steps, were fused to form iodide **81**. Transmetalation with *t*-BuLi and 1,2-addition to literature-known[42] cyclopentenone **82**, and a following PCC-mediated Dauben–Michno oxidative rearrangement resulted in triene **83**. After alkyne **84** had been prepared in six steps, the subsequent key intramolecular Diels–Alder reaction gave rise to the tricyclic intermediate **86** as a single diastereomer. The reaction was conducted at an elevated temperature in the presence of a catalytic amount of BHT (**85**), which was assumed to suppress peroxide or $O_2$ initiated polymerization of the diene. Seven more steps were required to synthesize butenolide **87**, including hydrogenation of the two di- and trisubstituted double bonds, carbonyl reduction–butenolide formation and introduction of the methyl substituent at C-13 *via* Negishi cross coupling. The synthesis of (+)-caribenol A (**55**) was completed by oxidation of butenolide **87** at C-5 with $O_2$, and reduction of the resulting peroxide **88** with $P(OEt)_3$.[39]



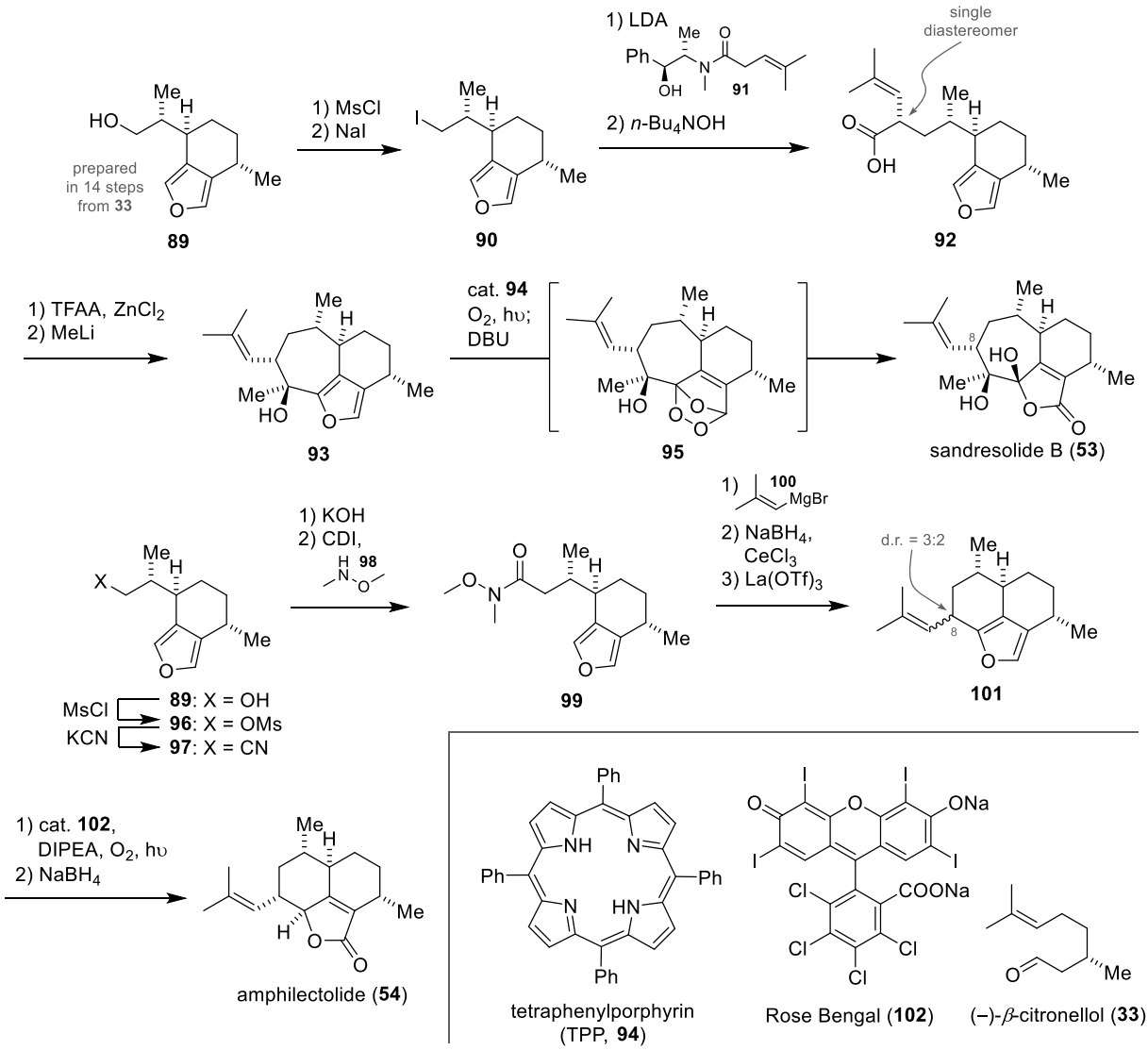

**Scheme 1.7** Yang's asymmetric total synthesis of (+)-caribenol A (**55**) featuring a key intramolecular Diels–Alder reaction.

The first, asymmetric total syntheses of sandresolide B (**53**) and amphilectolide (**54**) were developed by Ingrid T. Chen in 2011 as part of her Ph.D. thesis under the supervision of Prof. Dr. Dirk Trauner,[43] and published in 2013 after further optimizations within the Ph.D. thesis of Irina Albrecht[44] as well as this master thesis.[38] These primarily substrate controlled syntheses proceeded through a common building block, furan **89**, prepared in 14 steps from (–)-*β*-citronellol (**33**, Scheme 1.8). The synthetic route to furan **89** was reproduced and partly optimized during this master thesis, and is explained in detail in Chapters 2 and 4.

From furan **89**, the synthesis of sandresolide B (**53**) commenced with a mesylation–Finkelstein reaction to furnish iodide **90**. The isobutenyl residue at C-8 of the natural product was stereospecifically installed by a Myers asymmetric alkylation of iodide **90** with literature known amide **91**.[45] Hydrolysis of the resulting amide afforded carboxylic acid **92**, which was used for a Friedel–Crafts acylation, conducted with a stoichiometric amount of each TFAA and $ZnCl_2$. Addition of MeLi to the resulting ketone (not shown) diastereoselectively yielded the unstable furfuryl alcohol **93**, which was directly subjected to photooxygenation, using tetraphenylporphyrine (**94**) as a photosensitizer. Finally, a DBU-induced Kornblum–DeLaMare rearrangement of the intermediate endo-peroxide **95** gave rise to sandresolide B (**53**).[38,43]

For the synthesis of amphilectolide (**54**), furan **89** was transformed into mesylate **96** and homologated *via* substitution with KCN, furnishing nitrile **97**. Weinreb amide **99** was synthesized from intermediate **97** by hydrolysis of the nitrile group under basic conditions (KOH), and a CDI-mediated amidation of the resulting carboxylic acid with the Weinreb amine (**98**). Addition of Grignard reagent **100**, Luche reduction of the resulting enone and Friedel–Crafts allylation afforded furan **101** as an inseparable 3:2 mixture of both C-8 epimers (IUPAC numbering). Photooxygenation of this mixture in the presence of

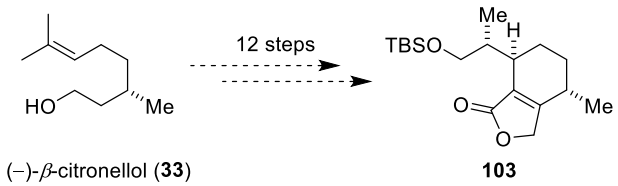
Rose Bengal (**102**) as a photosensitizer, and subsequent reduction with $NaBH_4$ gave rise to amphilectolide (**54**).[38,43]




**Scheme 1.8** Trauner's asymmetric total syntheses of sandresolide B (**53**) and amphilectolide (**54**) *via* a common building block, furan **89**.

## 1.3 Project Objectives

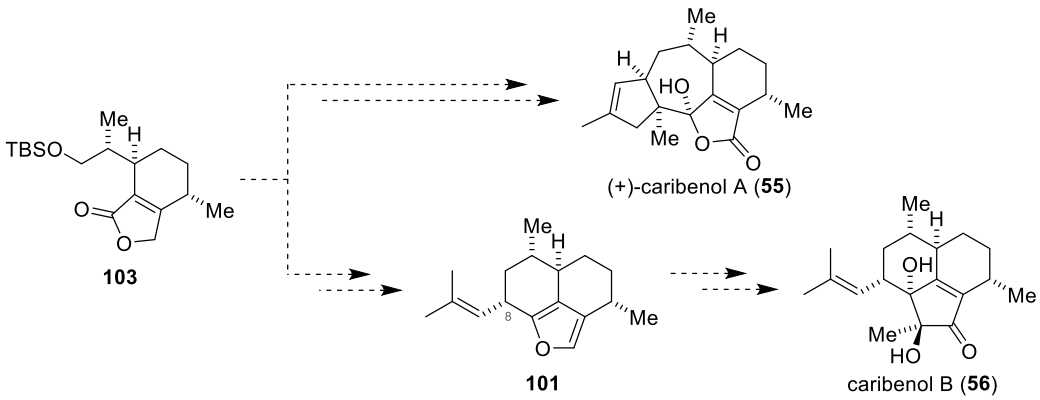
The first goal of this master thesis would be the multigram scale preparation of butenolide **103**, the last common building block in the aimed total syntheses of the *nor*-diterpenoids caribenol A (**55**) and B (**56**). This key intermediate **103** would be accessible starting from (–)-$\beta$-citronellol (**33**), thus offering a potential access to the natural products following an *ex-chiral-pool* strategy. This route was established by Ingrid T. Chen during her Ph.D. thesis in the laboratories of Prof. Dr. Dirk Trauner.[43]




**Scheme 1.9** The first goal of this master thesis: the large-scale synthesis of butenolide **103**.

With sufficient quantities of butenolide **103** available, the focus would be put on synthetic approaches to caribenols A (**55**) and B (**56**) (Scheme 1.10). Both natural products contain intriguing new carbon skeletons and have exhibited interesting biological activities: Caribenols A (**55**) and B (**56**) "were found to have strong inhibitory activity (61% and 94%, respectively) against *Mycobacterium tuberculosis* ($H_{37}Rv$) (ATCC 27294) at a concentration range of 128–64 $\mu$g/mL". (+)-Caribenol A (**55**) also "demonstrated weak *in vitro* antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* W2 ($IC_{50}$ 20 $\mu$g/mL)". In addition, the total synthesis of caribenol B (**56**) would serve to determine its absolute configuration, which was suggested to be the one depicted in Scheme 1.10, based on the proposed common biosynthetic ancestry of both caribenols.[27]

In the aimed synthesis of (+)-caribenol A (**55**), one major target would comprise the synthesis of a suitable precursor for an intended Pauson–Khand key step, by means of which the core tetracyclic system of that natural product should be elaborated. The first goal in the aimed synthesis of caribenol B (**56**) would be the development of a concise, stereoselective new route toward the crucial intermediate **101**, which previously could only be synthesized as an inseparable mixture of both C-8 epimers (IUPAC numbering, *cf.* Chapter 1.2, Scheme 1.8).

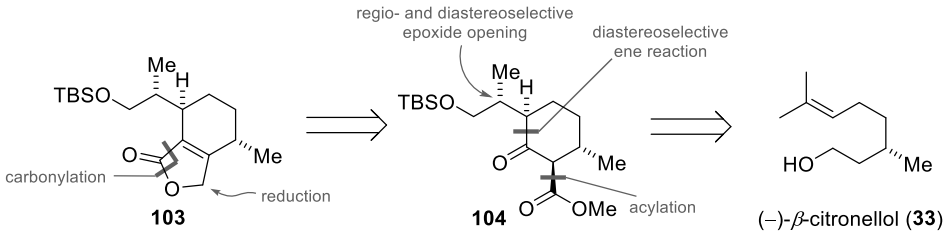



**Scheme 1.10** Aimed syntheses of caribenols A (**55**) and B (**56**) from butenolide **103**.

# 2 SYNTHESIS OF BUTENOLIDE 103

## 2.1 Retrosynthetic Analysis

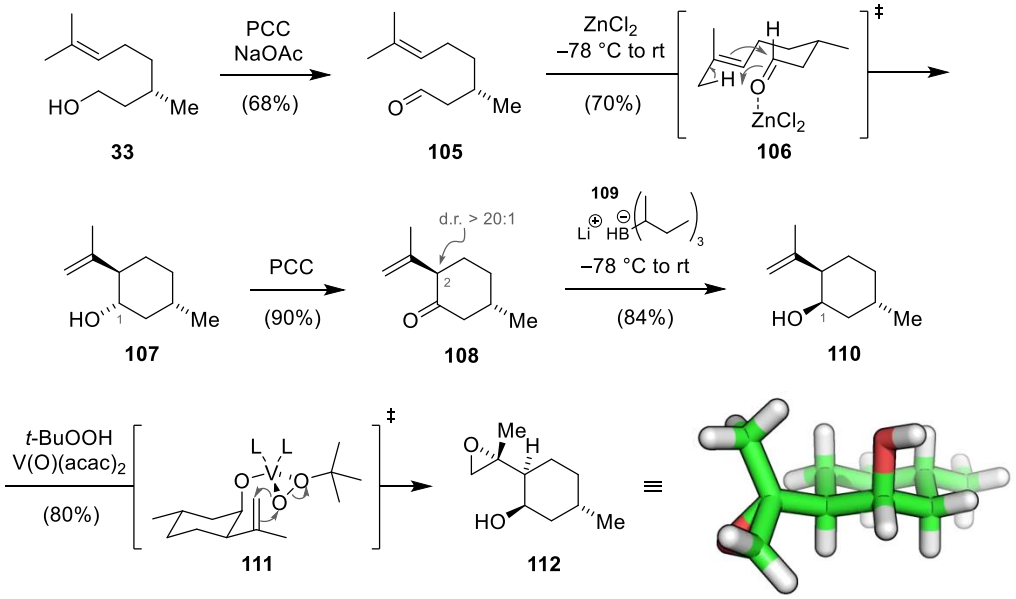
As mentioned before, the first objective of this master thesis was the multigram scale preparation of butenolide **103**. Retrosynthetically, the $\alpha,\beta$-unsaturated $\gamma$-lactone moiety of bicycle **103** would be formed in a key intramolecular alkoxycarbonylation (Scheme 2.1),[43] the precursor of which would be derived from literature-known $\beta$-keto ester **104**[53] by formation of the corresponding vinyl triflate and subsequent reduction of the ester functionality.[43] $\beta$-keto ester **104** could be synthesized in 9 steps from (–)-$\beta$-citronellol (**33**) according to previously established protocols.




**Scheme 2.1** Retrosynthetic analysis of butenolide **103**.

## 2.2 Synthesis of $\beta$-Keto Ester 104

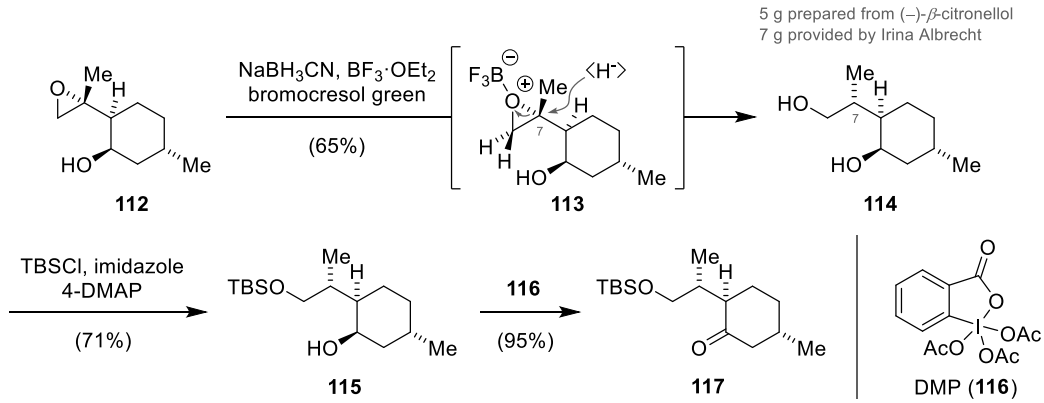
The synthesis of butenolide **103** commenced with the PCC-mediated oxidation of commercially available (–)-$\beta$-citronellol (**33**) to (–)-citronellal (**105**) on a 40 g scale according to the procedure of Corey and Suggs (Scheme 2.2).[46] The reaction was carried out in the presence of NaOAc as a buffer and delivered the desired aldehyde **105** in 68% yield. Subsequently, exposure of (–)-citronellal (**105**) to catalytic amounts of $ZnCl_2$ triggered a diastereoselective intramolecular ene reaction to provide access to (+)-isopulegol (**107**).[33c,47] Mechanistically, this reaction supposedly proceeds *via* *trans*-decalin-like transition state **106**, in which all substituents of the later cyclohexanol **107** are placed in the equatorial position. A diastereoselective epoxidation of the olefin required inversion of the stereogenic center at C-1. Thus, (+)-isopulegol (**107**) was converted into its oxidized congener (+)-isopulegone (**108**) by subjection to PCC,[48] yielding 90% of a >20:1 mixture of both C-2 epimers on a 12 g scale. With ample amounts of ketone **108** in hands, reaction with the bulky reducing agent L-selectride® (**109**) exclusively furnished (–)-neoisopulegol (**110**), resulting from an equatorial (*si*-side) hydride delivery.[48] With its hydroxyl function in the axial position of C-1 (IUPAC numbering), intermediate **110** was a suitable precursor for a diastereoselective homoallylic epoxidation, which was conducted with *t*-BuOOH and catalytic amounts of $V(O)(acac)_2$, affording epoxide **112** in a yield of 67% over two steps on a 9 g scale.[49] The corresponding transition state **111** depicted in Scheme 2.2 was suggested by Kocienski and features a *"*hydroxy-directed delivery of oxygen to the alkene […]*"*.[33c] The relative configuration of epoxide **112**, obtained as a single diastereomer according to NMR spectroscopy, was confirmed by X-ray crystallography.




**Scheme 2.2** Synthesis of epoxide **112** from (–)-$\beta$-citronellol (**33**).

Having ample quantities of epoxide **112** prepared, the intermediate **112** was reduced to diol **114** with $NaBH_3CN$ by repeated addition of $BF_3{\cdot}OEt_2$ (Scheme 2.3).[33c] Mechanistically, the epoxide of compound **112** undergoes complexation with the Lewis acid $BF_3{\cdot}OEt_2$, and the oxirane moiety of the resulting intermediate **113** is regioselectively opened with a hydride anion "at the site best able to accommodate a carbonium ion", *i.e.* at C-7.[50] The exact mechanism of the oxirane opening remains ambiguous though, since the reaction reportedly proceeds with high stereoselectivity *via* inversion of the configuration, in analogy to a substitution following an $S_N2$ rather than the expected $S_N1$ mechanism.[33c,50].

Diol **114** was obtained as a single diastereomer (according to NMR spectroscopy). With the configuration at C-7 inverted, the third stereogenic center assigned for both caribenols was correctly installed. On the largest scale, 5 g of diol **114** were prepared, and further material (7 g) was generously provided by Irina Albrecht.[44]

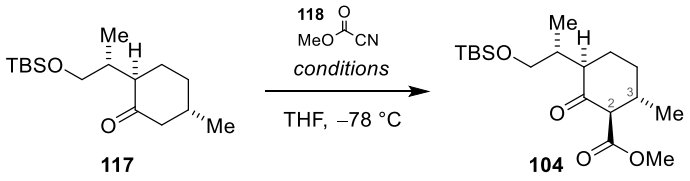



**Scheme 2.3** Synthesis of cyclohexanone **117** from epoxide **112**.

In order to pursue the envisaged route toward the caribenols, the sterically less hindered primary alcohol within diol **114** was chemoselectively protected as its TBS ether.[51] The remaining free hydroxyl

functionality of intermediate **115** was then oxidized to the corresponding ketone **117** in almost quantitative yield under mild conditions, utilizing Dess-Martin periodinane (DMP, **116**).[52] Although literature-known, the subsequent $C_1$ elongation with Mander's reagent (**118**) turned out to be unexpectedly troublesome. The corresponding procedure was described by Yadav in 2010, treating ketone **117** with freshly prepared LDA (1.50 eq.) in THF and a small excess of Mander's reagent (1.05 eq.), to yield 87% of $\beta$-keto-ester **104** on a 4.0 g scale.[53] As an initial attempt to reproduce Yadav's procedure on a smaller scale (70 mg) only provided compound **104** in a poor yield of 49% (Table 2.1, Entry 1), and Ingrid T. Chen reported a moderate yield of 65% on a 1.0 g scale (Entry 2),[43] using a greater excess of reagents and the strongly donating cosolvent HMPA (generally used to enhance the reactivity of organolithium species by breaking up their aggregates),[54] further efforts were made to improve this transformation.

**Table 2.1** $C_1$ elongation of ketone **117** with Mander's reagent (**118**): optimization of reaction conditions.




| Entry | Base (eq.) | Cosolvent (eq.) | Eq. Mander's reagent (118) | Scale [mg] | c(ketone 117) in THF [mol/L] | *t* [h] | Yield after FCC[a] [%] |
|---|---|---|---|---|---|---|---|
| 1 | LDA[b] (1.5) | - | 1.05 | 70 | 0.36 | 1.5 | 49 |
| 2[c] | LDA[b] (3.0) | HMPA (3.0) | 3.0 | 1000 | 0.03 | 1 | 65 |
| 3 | LDA[b] (3.0) | DMPU (17) | 3.0 | 50 | 0.03 | 4 | 32 |
| 4 | LiHMDS (1.2) | HMPA (1.2) | 1.4 | 50 | 0.08 | 2 | 57 |
| 5 | LiHMDS (1.5) | HMPA (1.5) | 1.75 | 100 | 0.09 | 2 | 83[d] |
| 6 | LiHMDS (1.5) | DMPU (1.5) | 1.75 | 100 | 0.09 | 2 | 73[d] |
| 7 | LiHMDS (1.5) | DMPU (4.5) | 1.75 | 100 | 0.08 | 1.5 | 55[d] |
| 8 | LiHMDS (1.5) | HMPA (1.5) | 1.75 | 1044 | 0.09 | 2 | 73[d] |
| 9 | LiHMDS (1.5) | HMPA (1.5) | 1.75 | 1500 | 0.09 | 3 | 75[d,e] |

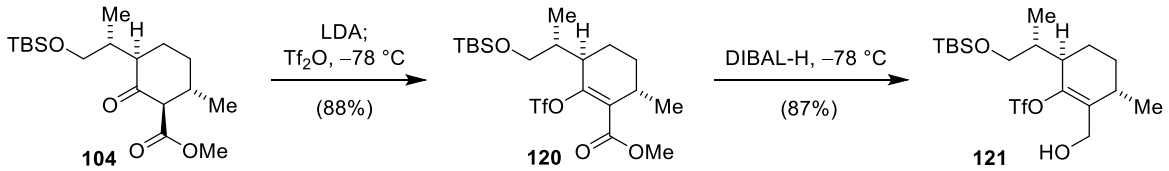
(*a*) FCC = flash column chromatography. (*b*) LDA was freshly prepared from DIPA and *n*-BuLi. (*c*) Procedure described and yield reported by Ingrid T. Chen.[43] (*d*) Eluent for flash column chromatography contained 1% $Et_3N$. (*e*) Yield of 4 parallel batches (each 1500 mg) combined during workup and commonly purified.

Our investigations initiated with a procedure reported by Shing and co-workers (Entry 3).[55] Therein, ketone **117** was exposed to 1.5 eq. of LDA and the resulting lithium enolate was reacted with Mander's reagent (**118**) in the presence of a large excess of DMPU as cosolvent. However, these conditions resulted in a poor 32% yield of $\beta$-keto ester **104**. Next, a protocol by Winkler and Axten was examined (Entry 4),[56] using a small excess of each LiHMDS and HMPA, furnishing compound **104** in a yield of 57%. This result was surprisingly poor, considering that full and rather clean conversion into the

desired product was observed by both TLC analysis of the reaction mixture, and $^{1}$H NMR spectroscopy of the crude product. Thus, we decided to carefully optimize these reaction conditions, finding that a slight increase in equivalents of the reagents as well as deactivation of the silica used for flash column chromatography by adding 1% $Et_3N$ to the eluent afforded $\beta$-keto ester **104** as a single diastereomer (according to $^{1}$H NMR spectroscopy) in yields up to 83% (Entry 5). Two more experiments were performed to investigate, whether less toxic DMPU could replace the carcinogenic HMPA, as demonstrated for a variety of reactions by Mukhopadhyay and Seebach in 1982.[57] The best yield accomplished was 73% when applying 1.5 eq. of DMPU (Entry 6), thus was 10% lower than with an equal amount of HMPA. A significant drop of the yield to 55% was noted when a 3-fold amount of DMPU was used (Entry 7). Having all these results in mind, the scale-up of the reaction was carried out according to the reaction conditions of Entry 5, providing $\beta$-keto ester **104** in 73 to 75% yields on gram scales (Entries 8 and 9). In Entry 9, the substrate (in total 6.0 g of ketone **117**) was split into four equal batches, since Ingrid T. Chen reported problems during scale-up beyond 1 g scales. The relative configuration of the newly formed stereogenic center at C-2 was determined by the strong coupling of the 2-H to the neighbored axial 3-H ($^{3}J_{2/3}$ = 12.2 Hz).

## 2.3 Synthesis of Butenolide 103

The synthesis of carbonylation precursor **121** was conducted within two further steps, the triflation of $\beta$-keto ester **104** with each 3 equivalents of LDA and $Tf_2O$, followed by the reduction of the ester group of vinyl triflate **120** with DIBAL-H (Scheme 2.3).[43] Each step proved robust to upscaling, yielding both vinyl triflate **120** and alcohol **121** in excellent yields (77% over two steps) on multigram scale.




**Scheme 2.3** Synthesis of carbonylation precursor **121**.

The key step of the synthesis of butenolide **103**, an intramolecular alkoxycarbonylation, was originally conducted with $Pd(PPh_3)_4$ (12 mol-%), $Bu_3N$ (2.0 eq.) and LiCl (1.1 eq.) in an autoclave at 85 °C under an elevated pressure of CO (2.5 bar), as described by Ingrid T. Chen (Table 2.2, Entry 1). In spite of an excellent reported yield of 97% on a multigram scale,[43] efforts were put into a modification of the original procedure that would allow avoidance of the critical handling of a CO gas cylinder. A promising new carbonylation method was therefore applied, as published by Ryu and coworkers in 2013:[58] The reaction was run in a reactor consisting of two connected chambers (Figure 2.1), one of which contained

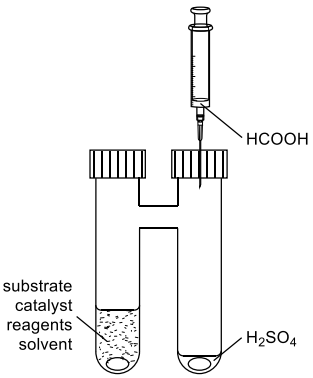
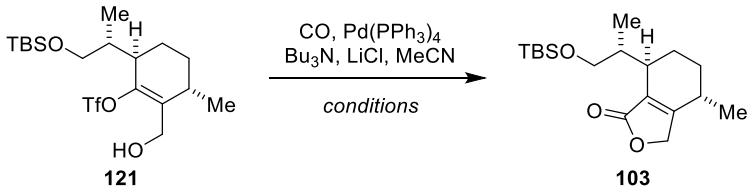



**Figure 2.1** Carbonylation in a two-chamber reactor

the carbonylation precursor, catalyst and further reagents, the other contained $H_2SO_4$. At an elevated temperature, CO was produced by addition of an equimolar amount of HCOOH to the $H_2SO_4$ *via* syringe, which through diffusion could reach the other chamber and hence enable the carbonylative coupling.[58] To our delight, using this two-chamber reactor ("COware", purchased from *SyTracks*), 3.0 equivalents of HCOOH and $H_2SO_4$, each, and otherwise the same catalyst and reagents as previously applied by Ingrid T. Chen[43] successfully converted carbonylation precursor **121** into butenolide **103** in a 55% yield on a 30 mg scale (Entry 2). Encouraged by this positive first result, the reaction was repeated on a larger scale (740 mg, Entry 3) including a prolonged reaction time to furnish butenolide **103** in a significantly higher yield of 87%. This result was still surpassed by two further experiments, each conducted on a 2.7 g scale, yielding 98 and 96% of butenolide **103** (Entries 4 and 5).

**Table 2.2** Application of *in situ* generated CO to the key alkoxycarbonylation.[a,b]

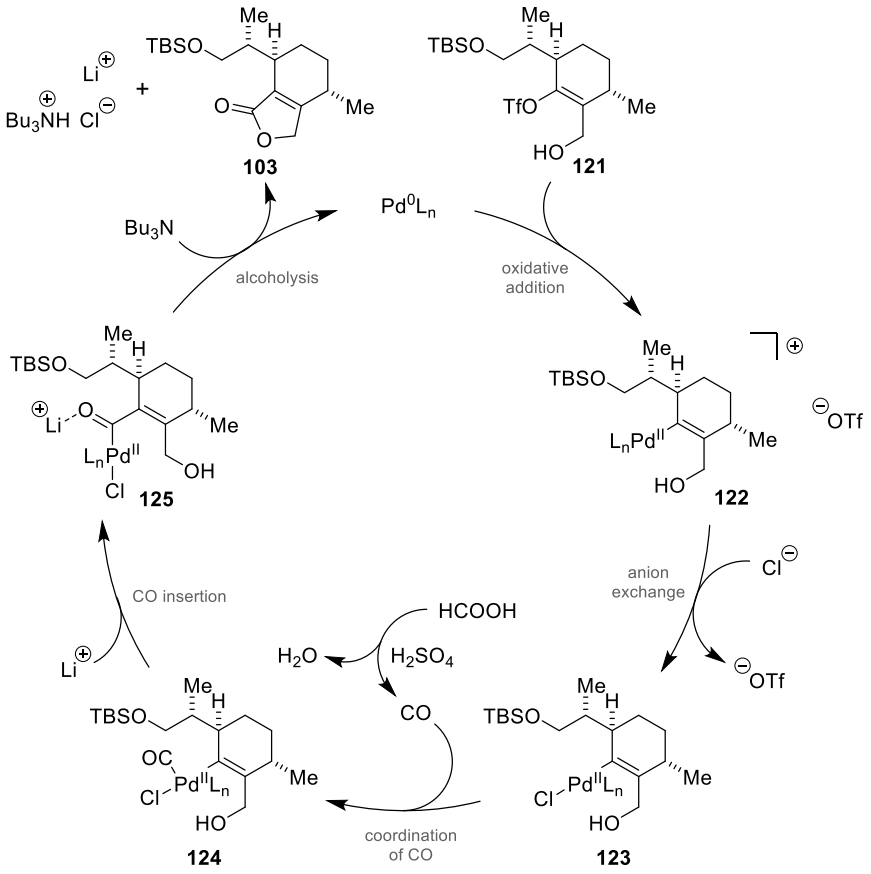



| Entry | CO source | *T* [°C] | Scale [g] | *t* [h] | Yield after FCC[c] [%] |
|---|---|---|---|---|---|
| 1[d] | gas cylinder | 85 | 2.8 | 48 | 97 |
| 2[e] | $HCOOH/H_2SO_4$ | 75 | 0.03 | 3.5 | 55 |
| 3[e] | $HCOOH/H_2SO_4$ | 75 | 0.7 | 18 | 87 |
| 4[f] | $HCOOH/H_2SO_4$ | 75 | 2.7 | 23 | 98 |
| 5[f] | $HCOOH/H_2SO_4$ | 75 | 2.7 | 17 | 96 |

(*a*) The concentration of precursor **121** in all Entries was 0.06M in MeCN. (*b*) Entries 2–5: CO was generated from 3.0 equivalents of HCOOH and $H_2SO_4$, each. (*c*) FCC = flash column chromatography. (*d*) Procedure described and yield reported by Ingrid T. Chen. 2.5 bar of CO was applied.[43] (*e*) Reactions were conducted in "COware" of appropriate size purchased from *SyTracks*. (*f*) Reactions were conducted in tightly closed Schlenk tubes behind a blast shield (*cf.* Chapter 6.2, Figure 6.1).

Mechanistically, the carbonylation commences with the oxidative addition of vinyl triflate **121** to the $Pd^0$ catalyst (Scheme 2.4).[59] Generally, in the case of vinyl triflates as substrates, this step requires the presence of chloride anions, as they enable the formation of the stable, neutral $Pd^{II}$ complex **123**, either directly or *via* anion exchange of the labile, cationic intermediate **122**.[60] CO, which was generated *in situ* by dehydration of HCOOH with $H_2SO_4$ (Morgan reaction),[58] then coordinates to the $Pd^{II}$ center of intermediate **123**, furnishing $Pd^{II}$-carbonyl complex **124**. The subsequent insertion of CO into the $Pd^{II}$-C bond gives rise to (acyl)$Pd^{II}$ complex **125**.[59] This step may be facilitated by binding of present $Li^+$ ions to the CO ligand.[61] The alcoholysis of intermediate **125**, upon which butenolide **103** is released could proceed by a direct attack of the hydroxyl group on the acyl group of intermediate **125**. Alternatively, butenolide **103** could either arise by a reductive elimination of complex **125**, followed by esterification of the resulting acyl chloride intermediate, or by precoordination–deprotonation of the

hydroxyl group and a subsequent reductive elimination. In either case, the catalytically active $Pd^0$ complex is restored.[62]



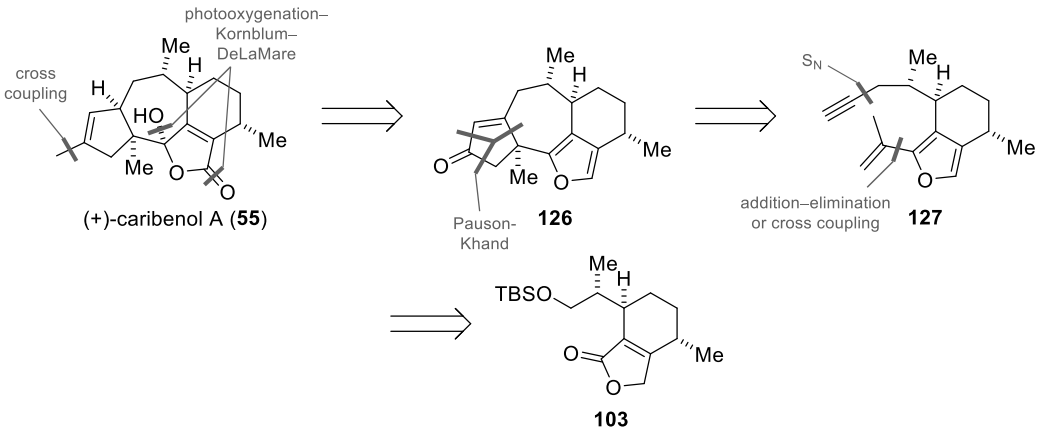

**Scheme 2.4** Proposed catalytic cycle of the Pd-catalyzed intramolecular alkoxycarbonylation of vinyl triflate **121**, furnishing butenolide **103**. $L_n$ = varying number of $PPh_3$ ligands.

It was proven that carbonylations can be accomplished in almost quantitative yields using as little as approximately 3 equivalents of *in situ* generated CO, even in the case of sophisticated substrates like vinyl triflate **121**, which reportedly did not react under 'typical' carbonylation conditions (bubbling CO through the reaction mixture, then keeping up a CO atmosphere).[43]

# 3 TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF (+)-CARIBENOL A

## 3.1 Retrosynthetic Analysis

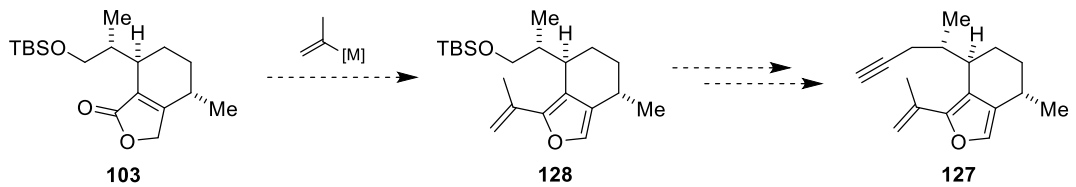
Having successfully completed the synthesis of butenolide **103**, the attention was next turned to the total synthesis of (+)-caribenol A (**55**). This natural product was envisaged to be accessed from cyclopentenone **126** in a few steps, including 1,4-reduction of the cyclopentenone moiety and subsequent cross coupling of the trapped enolate (*e.g.* an vinyl triflate), as well as photooxygenation of the furan moiety, followed by a Kornblum–DeLaMare rearrangement. Tetracycle **126** could be accessed *via* a key Pauson–Khand reaction, making enyne **127** the logical precursor. Further retrosynthetic simplification, *i.e.* introduction of the ethynyl group *via* substitution, and the formation of the isopropenylfuran moiety, either by a 1,2-addition–elimination sequence or *via* cross coupling of a trapped 2-hydroxyfuran, would trace enyne **127** back to butenolide **103**.




**Scheme 3.1** Retrosynthetic analysis of (+)-caribenol A (**55**).

## 3.2 Efforts toward the Synthesis of Enyne 127

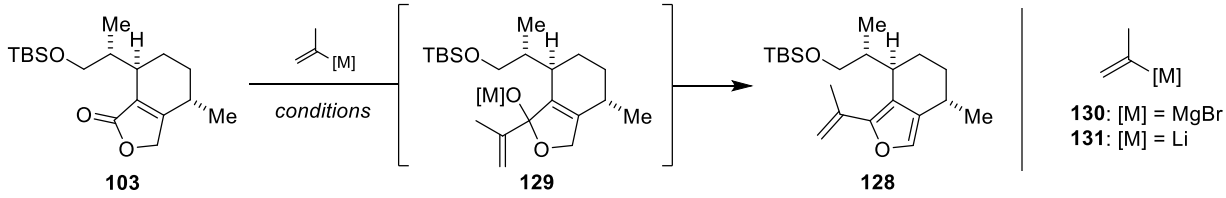
According to our proposed retrosynthesis, the first task required was the installation of an isopropylene substituted furan. As outlined in Scheme 3.2, we assumed that the addition of an appropriate organometallic species to butenolide **103** followed by aromatization could give rise to intermediate **128**, which then could be further transformed to Pauson-Khand precursor **127**.




**Scheme 3.2** Aimed synthesis of enyne **127**.

To this end, the use of isopropenylmagnesium bromide for an 1,2-addition to butenolide **103** was investigated first. The formed hemiacetal **129** was expected to readily undergo dehydration under acidic conditions, furnishing isopropenylfuran **128**. Using 3.0 equivalents of Grignard reagent **130** and 1.0M aqueous HCl for workup,[63] only decomposition of the starting material was observed (Table 3.1, Entry 1). In contrast, a slight excess of Grignard reagent **130** in the presence of anhydrous $CeCl_3$ resulted in the recovery of the starting material (Entry 2).[64]

**Table 3.1** Attempted synthesis of isopropenylfuran **128**.[a]




| Entry | reaction conditions | Workup conditions | Scale [mg] | Observation |
|---|---|---|---|---|
| 1 | **130** (3.0 eq.), rt to 40 °C | 1.0M aq. HCl | 10 | decomposition |
| 2[b] | **103** (1.0 eq.), $CeCl_3$ (1.2 eq.), rt, 1 h then **130** (1.2 eq.), 0 °C, 5 h | 10% aq. HOAc | 10 | s.m. |
| 3[c] | **131** (2.0 eq.), –78 °C, 2 h | 2.0M aq. HCl | 10 | possibly traces of **128**[d] |
| 4[c] | **131** (2.0 eq.), –78 °C, 2 h then $Tf_2O$ (2.1 eq.), –78 °C, 0.5 h | saturated aq. $NaHCO_3$ | 10 | decomposition |
| 5[c] | **131** (2.0 eq.), –78 °C, 2 h | 2.0M aq. HCl | 20 | possibly small amount of **128**[d] |
| 6[c] | **131** (5.0 eq.), –78 °C, 2 h | 2.0M aq. HCl | 10 | possibly small amount of **128**[d] |

(*a*) Entries 1–6: Reactions were conducted in THF, and were 0.02 to 0.04M in butenolide **103** (*b*) $CeCl_3$ was obtained from drying $CeCl_3 \cdot 7\ H_2O$ *in vacuo* for 2.5 h at 140 °C prior to use. (*c*) A 0.4M solution of isopropenyllithium (**131**) in pentane/$Et_2O$ was freshly prepared from 2-bromopropene and *t*-BuLi prior to use, following a procedure described by Swenton and coworkers.[65] (*d*) Based on $^1$H NMR spectra of substance mixtures obtained from flash column chromatography. In each case, the crude product still contained major amounts of butenolide **103**, as determined by $^1$H NMR spectroscopy.

The first promising result was obtained after butenolide **103** was treated with 2.0 equivalents of isopropenyllithium (**131**, Entry 3):[66] a $^1$H NMR spectrum of the most non-polar product fraction ($R_f$ = 0.45 in hexanes) recovered from flash column chromatography (using silica) contained several weak signals that may have arisen from isopropenylfuran **128**. The newly formed substance however was very impure and appeared to be unstable, since none of the characteristic signals were found in a second $^1$H NMR spectrum recorded a few hours after the first one (Figure 3.1).

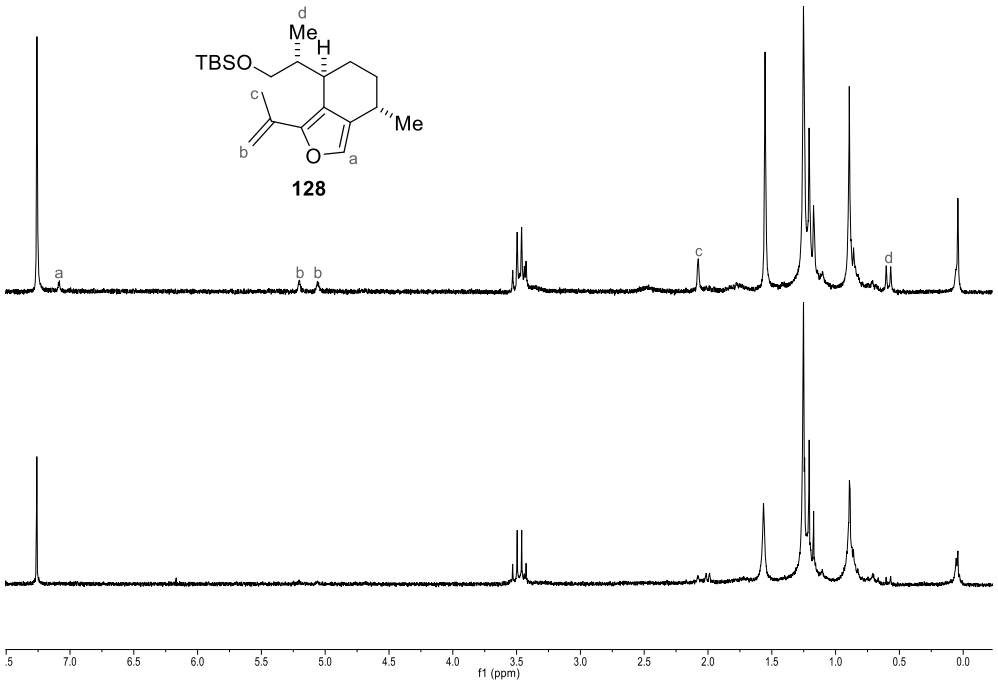



**Figure 3.1** Top: $^{1}$H NMR spectrum containing potential signals of isopropenylfuran **128**. Those signals were not found in a $^{1}$H NMR spectrum of the same sample recorded a few hours after the first one (bottom). Both spectra were recorded at 200 MHz in $CDCl_3$.

In order to prevent a possible degradation of isopropenylfuran **128** under the strongly acidic workup conditions of Entry 3, an elimination of the hemiacetal **129** to isopropenylfuran **128** was attempted under basic conditions (Entry 4). Therefore, butenolide **103** was treated with isopropenyllithium (**131**, 2.0 eq.), followed by $Tf_2O$ (2.1 eq.) with the intention to form an *O*-sulfonylated hemiacetal which would readily eliminate to isopropenylfuran **128** during workup with saturated aqueous $NaHCO_3$. Since these conditions only resulted in decomposition of starting material, modified reaction conditions of Entry 3 were applied (Entries 5 and 6), using 2.0 and 5.0 equivalents isopropenyllithium (**131**), respectively. In each case, both the reaction and purification were conducted under exclusion of light.[67] As in Entry 3, both reactions furnished small quantities of the assumed isopropenylfuran **128**, which again were co-eluted with large amounts of unknown byproducts (according to $^{1}$H NMR spectroscopy). The $^{1}$H NMR spectra of the product fractions of both experiments resembled each other, though the ratio of peak intensities of the presumed isopropenylfuran **128** to byproducts was greater in Entry 5 (spectrum depicted in Figure 3.2).

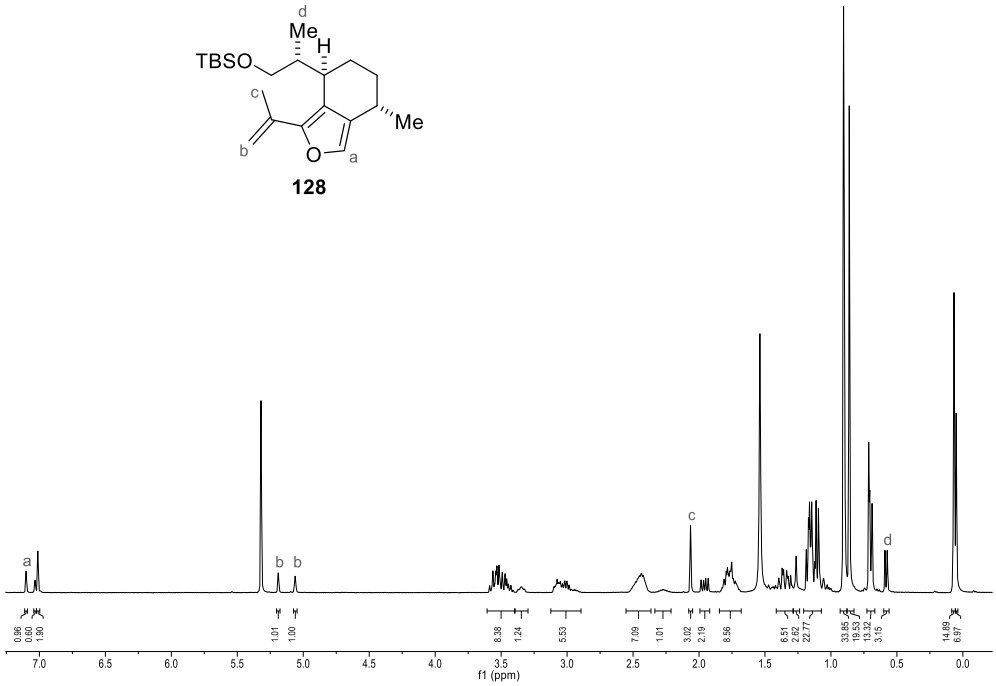
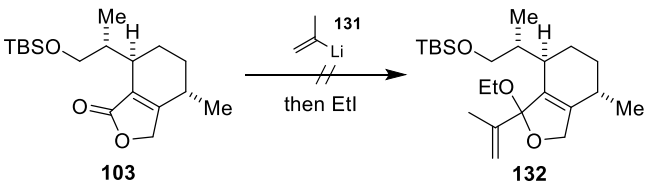



**Figure 3.2** $^{1}$H NMR spectrum (400 MHz, $CD_2Cl_2$) of the product mixture obtained in Entry 5. It was speculated whether the assigned signals may have arisen from the corresponding protons of isopropenylfuran **128**.

Attempts to separate the product mixture obtained from flash column chromatography in Entry 5 *via* RP-HPLC failed, as no substance eluted, even when washing the column with a 95:5 mixture of MeCN/$H_2O$ + 1% TFA for several minutes after the applied gradient ended.

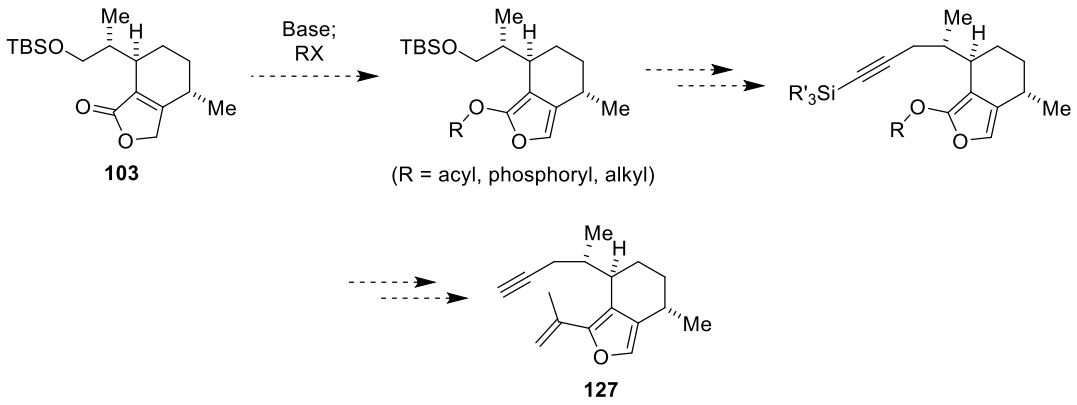
Though under the careful conditions applied (exclusion of light, NMR spectra recorded in $CD_2Cl_2$) the presumably formed isopropenylfuran **128** was more stable than before (Entry 3), it was still considered too labile to carry on with the attempted synthesis of enyne **127**, which would have required at least three more steps from this point (cleavage of the TBS group, sulfonylation of the formed alcohol and substitution by ethynyllithium). Another problem faced in all three cases (Entries 3, 5, and 6) was the incomplete conversion of butenolide **103**, as major amounts of it were still present in the crude product mixtures, according to $^{1}$H NMR spectroscopy. It should also once more be emphasized, that the formation of isopropenylfuran **128** in Entries 3, 5, and 6 was the matter of conjecture on the basis of NMR spectroscopy. The expected mass was not detected in EI-HRMS.

An attempt to form acetal **132** by subsequently treating butenolide **103** with isopropenyllithium (**131**, 2.0 eq.) and iodoethane (5.0 eq.)[66,68] did not meet with success (Scheme 3.3). Instead, the same mixture of byproducts as described in Entries 5 and 6 of Table 3.1 was found, in addition to remaining substrate.




**Scheme 3.3** Attempted synthesis of acetal **132**.

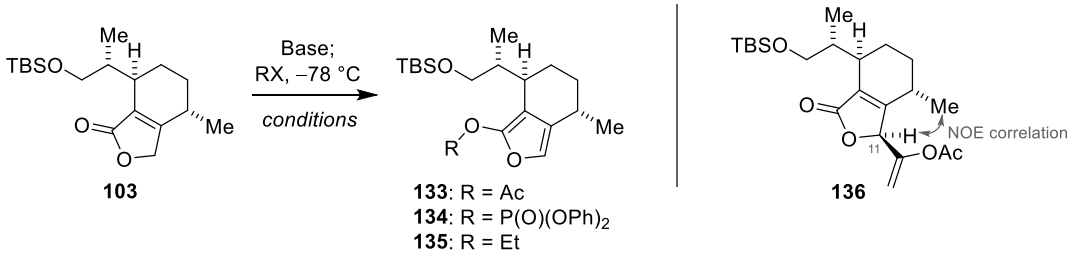
Due to the drawbacks encountered in the aimed synthesis of isopropenylfuran **128**, a second strategy toward enyne **127** was pursued which involved the formation of the critical isopropenylfuran moiety at a later stage (Scheme 3.4). Protection of the butenolide as an *O*-substituted 2-hydroxyfuran was to be followed by cleavage of the TBS group and introduction of the alkyne *via* substitution. Finally, the isopropenylfuran moiety could be formed either by an addition–elimination sequence with isopropenyllithium (as before), or possibly by cross-coupling of the derivatized 2-hydroxyfuran.




**Scheme 3.4** Alternative strategy toward enyne **127**.

First efforts were put into the synthesis of *O*-acetylated 2-hydroxyfuran **133**. While no reaction was observed when treating butenolide **103** with 1.2 equivalents of $Et_3N$ and AcCl, each (Table 3.2, Entry 1),[69] traces of the desired acetate **133** were formed using a slight excess of LDA and $Ac_2O$ (Entry 2). With increased amounts of both reagents (2.0 and 5.0 equivalents, respectively), acetate **133** was obtained in a yield of each 44% (Entries 3 and 4) on 10 mg scales.[70] In both cases, slightly lower amounts of vinyl acetate **136** (32–40%) were isolated. This unexpected product, isolated as a single diastereomer, could be unambiguously identified by NMR spectroscopy and mass spectrometry.[71] The relative configuration of the new stereogenic center at C-11 was determined by NOE spectroscopy. Upon scale-up from 10 to 50 mg (Entry 5), the yields of both compounds decreased significantly, and 13 mg of a third, highly non-polar product was isolated by flash column chromatography, the structure of which could not be elucidated by NMR spectroscopy.

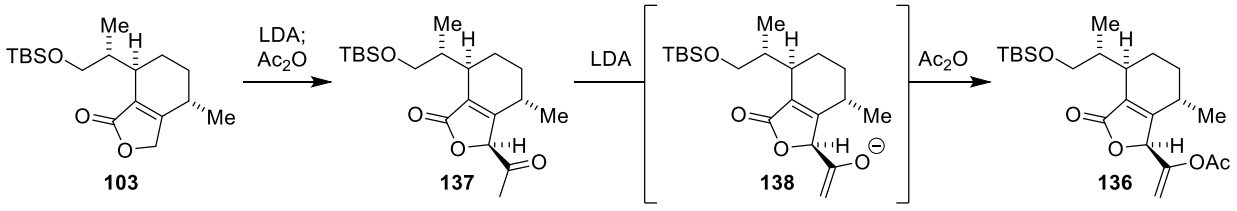
**Table 3.2** Endeavors to synthesize the trapped 2-hydroxyfurans **133** to **135**.[a]




| Entry | Base (eq.) | RX (eq.) | *t* [h] | Scale [mg] | Observation (Yields after FCC) |
|---|---|---|---|---|---|
| 1[b] | $Et_3N$ (1.2) | AcCl (1.2) | 5 | 10 | s.m. |
| 2 | LDA[c] (1.1) | $Ac_2O$ (1.1) | 3 | 10 | traces of **133** |
| 3 | LDA[c] (2.0) | $Ac_2O$ (2.0) | 2 | 10 | **133** (44%), **136** (32%) |
| 4 | LDA[c] (5.0) | $Ac_2O$ (5.0) | 2 | 10 | **133** (44%), **136** (40%) |
| 5 | LDA[c] (2.0) | $Ac_2O$ (2.0) | 1.5 | 50 | **133** (27%), **136** (21%) and a 3rd byproduct (13 mg) |
| 6[e] | NaHMDS (1.1) | $(PhO)_2P(O)Cl$ (1.1) | 1.5 | 10 | mixture of **134** (64%) and **103** (traces) |
| 7[e] | NaHMDS (1.3) | $(PhO)_2P(O)Cl$ (1.3) | 1.5 | 10 | mixture of **134** (69%) and **103** (20%)[f] |
| 8[e] | NaHMDS (1.4) | $(PhO)_2P(O)Cl$ (1.1) | 1.5 | 19 | mixture of **134** (42%) and **103** (26%)[f] |
| 9 | LDA[c] (1.1) | Iodoethane (1.1) | 2 | 10 | s.m. |

(*a*) All reactions conducted in THF, except for Entry 1 (MeCN used instead). (*b*) Reaction run at *T* = 20–60 °C (*c*) Freshly prepared from DIPA and *n*-BuLi. (*d*) Degassed by 3 freeze–pump–thaw cycles. (*e*) Phosphate **134** was exclusively characterized by NMR spectroscopy ($^1H$, $^{13}C$, HSQC, HMBC and COSY). (*f*) Eluent for FCC contained 1% $Et_3N$.

Presumably, the formation of vinyl acetate **136** proceeds *via* γ-acetylation of butenolide **103**, followed by kinetic deprotonation of the resulting ketone **137** with LDA and *O*-acetylation of the intermediate enolate **138** with $Ac_2O$ (Scheme 3.5).




**Scheme 3.5** Proposed mechanism for the formation of vinyl acetate **136**.

Due to the lacking regioselectivity of the acetylation (Entries 3 to 5), a phosphorylation was targeted by subsequently treating butenolide **103** with NaHMDS and diphenylphosphoryl chloride ($(PhO)_2P(O)Cl$).[70] Application of 1.1 equivalents of both reagents resulted in a mixture of phosphate **134** (64%) and traces

of substrate (**103**), which could not be separated by flash column chromatography (Entry 6, conversion could still be monitored *via* TLC analysis, as both compounds stained differently with *p*-anisaldehyde). In contrast to acetate **133**, phosphate **134** turned out to be quite unstable, as both the phosphate and TBS group were cleaved after a 12 h drying period in high vacuum at rt (according to $^{1}$H NMR spectroscopy, *cf.* Figure 3.3).

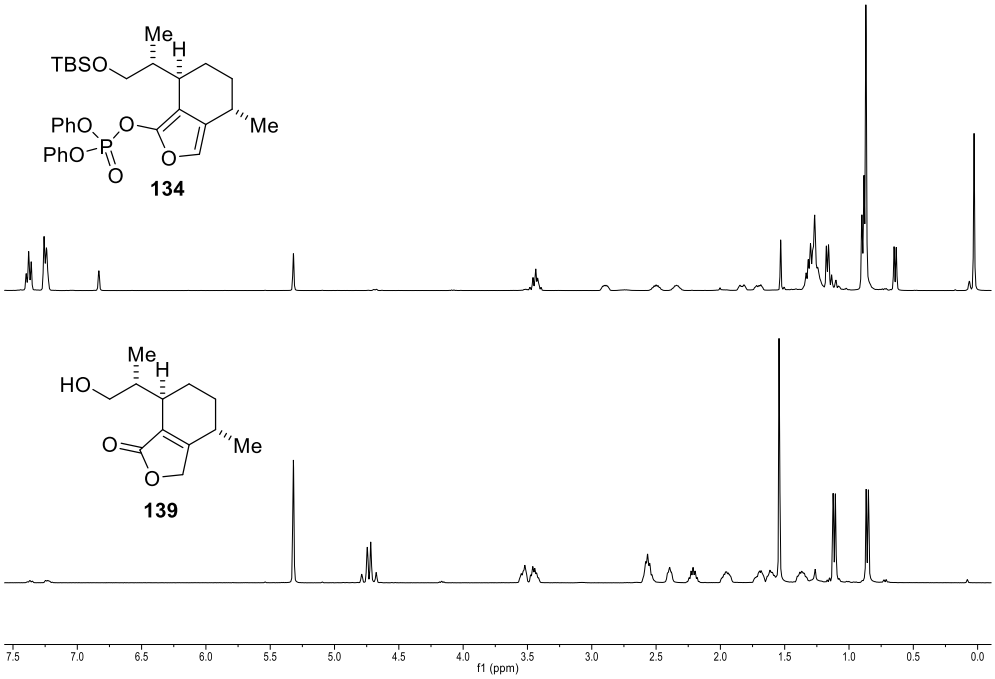
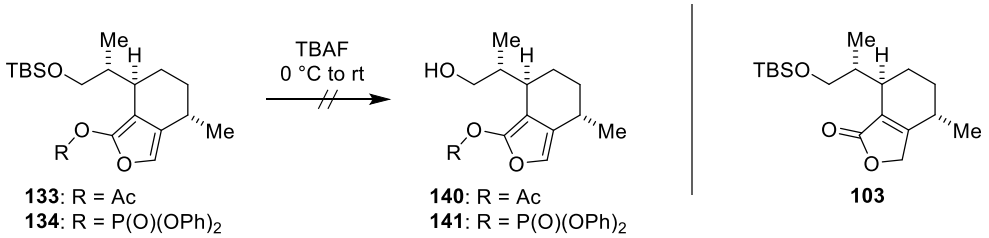



**Figure 3.3** $^{1}$H NMR spectra (recorded at 400 MHz in $CD_2Cl_2$) of phosphate **134** and the presumed product of hydrolysis (**139**), obtained in Entry 6 (purified by flash column chromatography).

Further efforts to achieve complete conversion of butenolide **103** into phosphate **134** remained unsuccessful (Entries 7 and 8). In fact, the products obtained under those conditions were contaminated with even greater amounts of substrate. No conversion was observed in one attempt to furnish ketene acetal **135** using 1.1 equivalents of LDA and iodoethane, each (Entry 9).[70]

With regard to the problems encountered in the endeavors to synthesize trapped 2-hydroxyfurans (**133** to **135**), and since treatment of acetate **133** and phosphate **134** (the 7:2 mixture with butenolide **103** obtained in Entry 7) with TBAF (1.5 eq.)[43] only resulted in the formation of butenolide **103** (Scheme 3.6) instead of the desired desilylated products **140** and **141**, respectively, this strategy was abandoned.

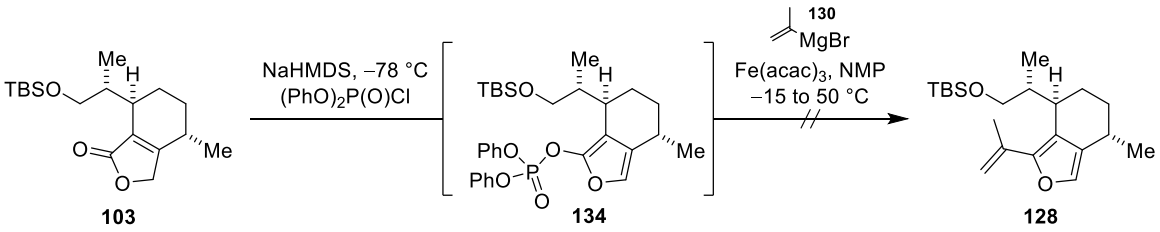



**133**: R = Ac
**134**: R = P(O)(OPh)$_2$

**140**: R = Ac
**141**: R = P(O)(OPh)$_2$

**Scheme 3.6** Attempted cleavage of the TBS group with TBAF only resulted in butenolide **103**.

Phosphate **134** was once more synthesized (applying the conditions of Table 3.2, Entry 6) and used *in situ* for an aimed synthesis of isopropenylfuran **128** via Fe-catalyzed cross-coupling. Following a procedure described by Cahiez and coworkers,[72] applying $Fe(acac)_3$ (5 mol-%), NMP (9.0 eq.) and isopropenylmagnesium bromide (**130**, 1.3 eq.) to the freshly prepared phosphate **134** (synthesis monitored by TLC analysis) did not lead to the formation of the desired product. Instead, only butenolide **103** could be reisolated (Scheme 3.7).



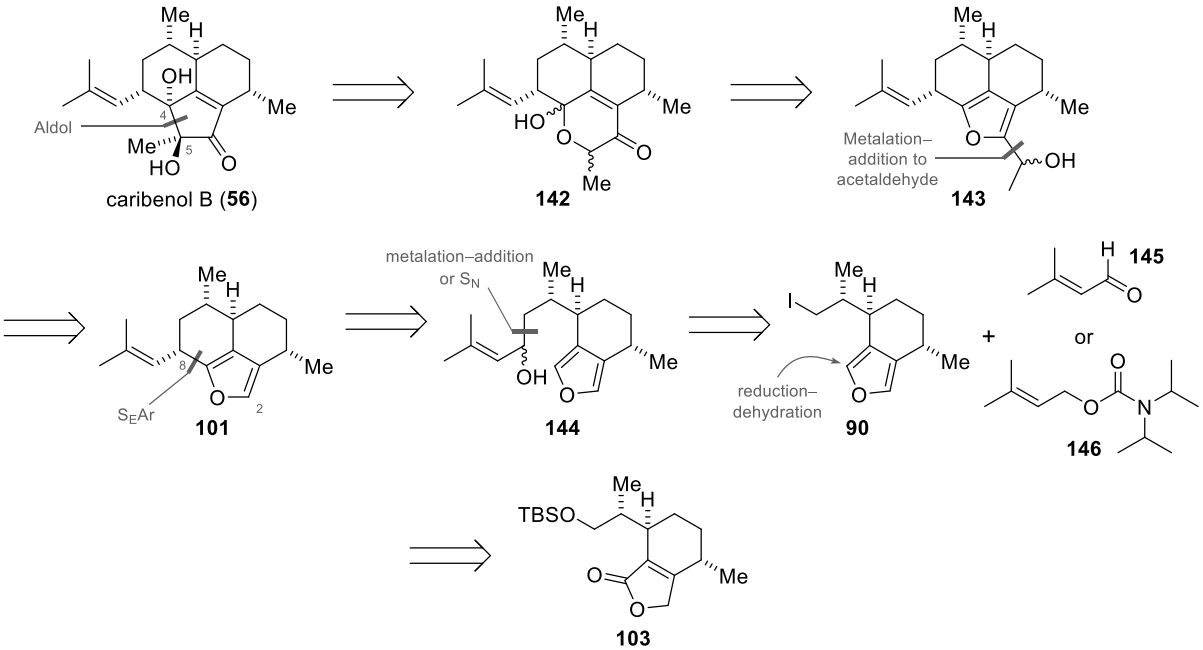

**Scheme 3.7** Attempted formation of isopropenylfuran **128** *via* Fe-catalyzed cross-coupling.

# 4 TOWARD THE ASYMMETRIC TOTAL SYNTHESIS OF CARIBENOL B

## 4.1 Retrosynthetic Analysis

Caribenol B (**56**) should be accessible from pyranone **142**, *e.g.* by a Lewis acid-mediated opening of the hemiacetal and a following aldol formation (Scheme 4.1). The stereogenic centers at C-4 and C-5 were expected to be formed in the same configurations as described for the isolated natural product,[73] as these were anticipated to be thermodynamically favored. This substrate **142** in turn should be accessible from furfuryl alcohol **143** *via* an Achmatowicz oxidation. **143** would be accessible from furan **101** by metalation of C-2 and addition to acetaldehyde.

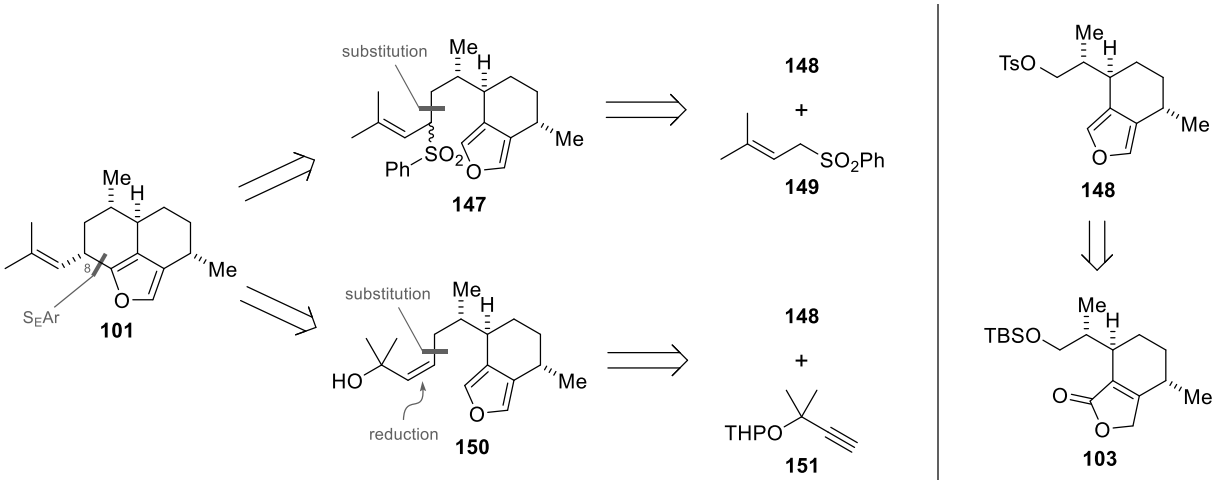
Since the formation of furan **101** from either diastereomer of allylic alcohol **144** reportedly proceeded with poor diastereoselectivity (*cf.* Chapter 1.2, Scheme 1.8),[43] one major goal would be the elaboration of an asymmetric Friedel–Crafts allylation, selectively giving rise to the 8$\alpha$-epimer of furan **101**. For example, this could involve the use of Lewis acids with chiral ligands,[74] or chiral phosphoric acid derivatives as for instance applied by List and coworkers[75]. A preceding goal was the development of a new route from butenolide **103** to allylic alcohol **144** that would involve fewer steps than the original one (*cf.* Chapter 1.2, Scheme 1.8).[43] Iodide **90** was considered as a suitable intermediate to achieve this goal, either by *in situ* metalation and 1,2-addition to prenal (**145**), or by substitution with *in situ* $\alpha$-metalated prenyl carbamate **146**, followed by reduction. Iodide **90** would be accessible from butenolide **103** within 5 steps, along the lines of the Ph.D. thesis of Ingrid T. Chen.[43]




**Scheme 4.1** Retrosynthetic analysis of caribenol B (**56**).

In addition to allylic alcohol **144**, two alternative Friedel–Crafts allylation precursors (Scheme 4.2) were envisioned: Sulfone **147** should be accessible from tosylate **148** by substitution with *in situ* $\alpha$-metalated prenyl sulfone **149**. The analogous allylic alcohol **150** could arise from tosylate **148** by substitution with

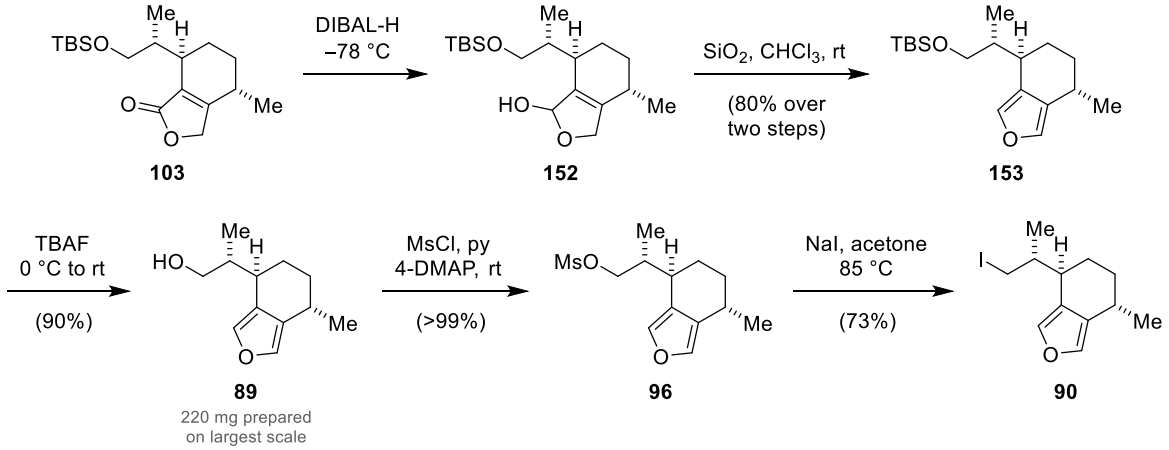
the Li-acetylide of dimethylpropargyl THP ether **151** and reduction of the alkyne with a poisoned catalyst. Tosylate **148** would be derived from butenolide **103** within three steps, in analogy to the reported preparation of mesylate **96** (*cf.* Scheme).




**Scheme 4.2** Alternative precursors of furan **101**, potentially accessible *via* tosylate **148**.

## 4.2 Toward the Synthesis of Allylic Alcohol 144

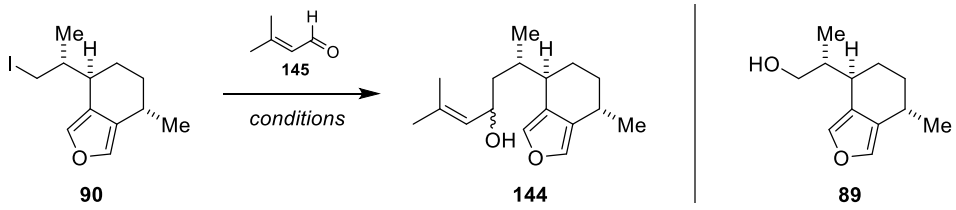
In order to examine our first envisaged route, the synthesis of alkyl iodide **90** was required. Therefore, butenolide **103** was exposed to DIBAL-H at low temperatures and the resulting lactol **152** smoothly underwent dehydration upon treatment with silica in $CHCl_3$. Overall, this two-step procedure provided access to furan **153** in a good yield of 80% on a 500 mg scale. Subsequently, the focus was turned to set the stage for the envisaged chain elongation. First, the primary alcohol functionality in silyl ether **153** was unmasked under fluoride conditions using TBAF. Next, intermediate **89** was converted into its mesylate (**96**) in almost quantitative yield. An ensuing Finkelstein reaction applying a large excess of NaI in acetone at elevated temperatures and pressure finally provided iodide **90** in 73% yield.[43]




**Scheme 4.3** Preparation of iodide **90** from butenolide **103**.

With iodide **90** in hands, the metalation and a subsequent 1,2-addition to prenal (**145**) was examined first (Table 4.1). Our investigations commenced with the attempt to convert iodide **90** into the corresponding Grignard reagent by treatment with Mg in diethyl ether and gentle heating to reflux (Entry 1).[76] When no reaction was observed *via* TLC analysis after a mini-quench with anhydrous acetone, catalytic amounts of each TMSCl and 1,2-dibromoethane were added, but had no effect. This reaction presumably failed at the formation of the Grignard reagent, as among an unknown compound, some starting material was isolated. A lithiation of iodide **90** with *t*-BuLi and subsequent addition to prenal (**145**) was attempted twice: The first conditions applied (Entry 2)[77] resulted in the formation of alcohol **89**, as determined by comparison of its $^1$H NMR spectrum with that of authentic material. Though considered unlikely, this surprising observation could only be explained by a substitution of the iodide by a hydroxide anion, *e.g.* during the strongly basic workup with 1.0M aqueous NaOH. This result however clearly indicated failure of the attempted lithiation, which in another experiment was attempted with *t*-BuLi at higher temperatures (Entry 3). A different procedure was therefore applied,[78] which also involved smoother workup conditions (saturated aqueous $NH_4Cl$), but only resulted in the decomposition of the starting material.

**Table 4.1** Attempted metalation of iodide **90** and addition to prenal (**145**).[a]

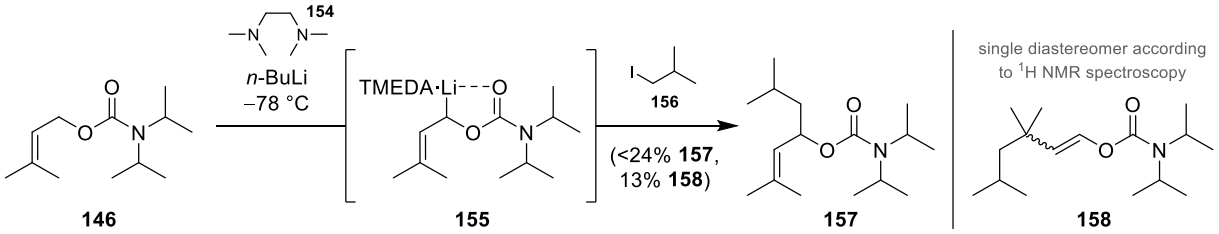



| Entry | reaction conditions | *T* [°C] | Solvent | Scale [mg] | Observation |
|---|---|---|---|---|---|
| 1 | I. Mg (1.2 eq.), cat. TMSCl cat. 1,2-dibromoethane, 4 h<br>II. **145** (3.0 eq.), 1.5 h | I. rt to reflux<br>II. rt | $Et_2O$ | 19 | s.m. + unknown product[b] |
| 2 | I. *t*-BuLi (2.0 eq.), 1.5 h<br>II. **145** (2.5 eq.), 3 h | I. –78<br>II. –78 to rt | $Et_2O$ | 12 | s.m. (traces) and **89** (71%)[c] |
| 3[d] | I. *t*-BuLi (2.1 eq.), 1.5 h<br>II. **145** (2.5 eq.), 3 h | I. –78 to 0<br>II. –78 to 0 | $Et_2O$ | 10 | decomposition |
| 4[e] | I. $SmI_2$ (2.0 eq.), HMPA (2.9 eq.), 40 min<br>II. **103** (1.0 eq.), **145** (2.0 eq.), 21 h | rt | THF | 15 | s.m. (40%)[f] and partial decomposition |

(*a*) Prenal (**145**) was distilled *in vacuo* prior to the first use and stored over molecular sieves under an Ar atmosphere and under exclusion of light. All reactions were conducted under protection from light. (*b*) Based on a $^1$H NMR spectrum of a substance mixture eluted from flash column chromatography (FCC). (*c*) Alcohol **89** was recovered from FCC and identified by comparison of its $^1$H NMR spectrum with that of authentic material. (*d*) *t*-BuLi was titrated against diphenylacetic acid prior to use. Iodide **90** was dried prior to use by repeated solvation in anhydrous benzene and subsequent removal of the solvent *in vacuo* (3 × in total). $Et_2O$ was degassed prior to use by 3 freeze–pump–thaw cycles. (*e*) A solution of $SmI_2$ in THF was purchased from Sigma-Aldrich and titrated against $I_2$ prior to use. (*f*) Pure material recovered from FCC.

The last method tested was a Kagan–Molander $SmI_2$-mediated coupling, conducted in the manner of a Barbier reaction (Entry 4):[79] a mixture of iodide **90** (1.0 eq.) and prenal (**145**, 2.0 eq.) was added to a mixture of $SmI_2$ (2.0 eq.) and HMPA (2.9 eq.). However, this reagent combination resulted in partial decomposition and recovery of iodide **90** (40% after purification by flash column chromatography).

Due to the drawbacks encountered in the metalation–addition strategy (Table 4.1), the introduction of an appropriate prenyl fragment *via* nucleophilic displacement next took center stage. Following a procedure described by Hoppe and coworkers,[80] prenyl carbamate **146** was $\alpha$-lithiated with *n*-BuLi in the presence of TMEDA (**154**), and a substitution of the resulting nucleophile **155** was tested with commercially available 1-iodo-2-methylpropane (**156**, Scheme 4.4). Two products were isolated after purification by flash column chromatography: The desired alkylation product **157** was part of a mixture containing minor amounts of unknown byproducts (yield of **157** < 24%) and identified by NMR spectroscopy ($^1$H, $^{13}$C, HSQC, HMBC, and COSY). The second compound was the product of $\gamma$-alkylation, vinyl carbamate **158**, which was obtained in a 13% yield and identified by NMR spectroscopy ($^1$H, $^{13}$C, HSQC, HMBC, and COSY) and ESI-HRMS.




**Scheme 4.4** Substitution with *in situ* metalated prenyl carbamate **146**, tested on 1-iodo-2-methlpropane (**156**).

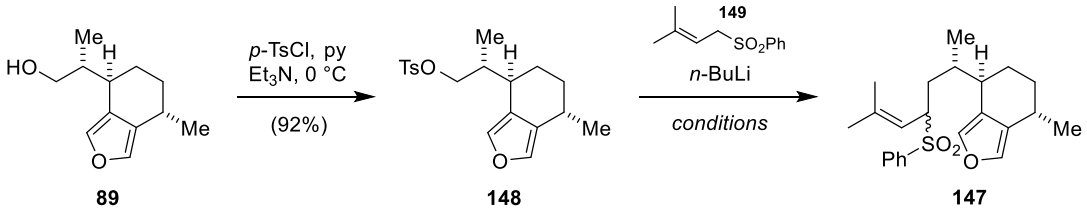
The lack of regioselectivity and the overall low yield of <37% of both products despite the usage of an excess of prenyl carbamate **146** (2.0 eq.) drove us to investigate the synthesis of an alternative Friedel–Crafts allylation precursor (*cf.* Scheme 4.2).

## 4.3 Toward the Synthesis of Sulfone 147

We next envisioned the synthesis of an alternative Friedel–Crafts allylation precursor, sulfone **147**, which should be accessed from tosylate **148** *via* substitution. Intermediate **148** was furnished from alcohol **89** in a good 92% yield upon treatment with *p*-TsCl in the presence of $Et_3N$ and pyridine (Table 4.2).[81] The substitution with $\alpha$-lithiated prenyl sulfone **149** was first attempted with 4.0 equivalents of sulfone **149** and *n*-BuLi, each, in a temperature range from –78 °C to rt.[33c] When a TLC analysis of the reaction mixture revealed that almost no conversion had taken place, HMPA (1.5 eq.) was added and the mixture was heated to 40 °C (Table 4.2, Entry 1). Since the crude product obtained after a total of 18 h almost exclusively consisted of tosylate **148** and prenyl sulfone **149**, the reaction was repeated at an elevated temperature. This change of conditions was based on the fact, that the reported synthesis of nitrile **97** (*cf.* Chapter 1.2, Scheme 1.8) also required elevated temperatures, presumably due to the

sterically congested environment at the reaction site.[43] In the event, a large excess of prenyl sulfone **149** and *n*-BuLi (20 eq., each) was used to create the corresponding $\alpha$-lithiated sulfone at rt, and the attempted substitution was conducted in 1,4-dioxane in a pressure tube at 130 °C (Entry 2). These conditions provided a complex mixture of substances which could only partly be separated by flash column chromatography (using EtOAc/hexanes, additionally a variety of binary mixtures of EtOAc, hexanes, PhMe, $Et_2O$ and $CH_2Cl_2$ was tested). The diastereomers of the desired sulfone **147** were neither isolated, nor clearly identified *via* $^1$H NMR spectroscopy.

**Table 4.2** Preparation of tosylate **148** and attempted substitution with prenyl sulfone **149**.[a]




**89** **148** **147**

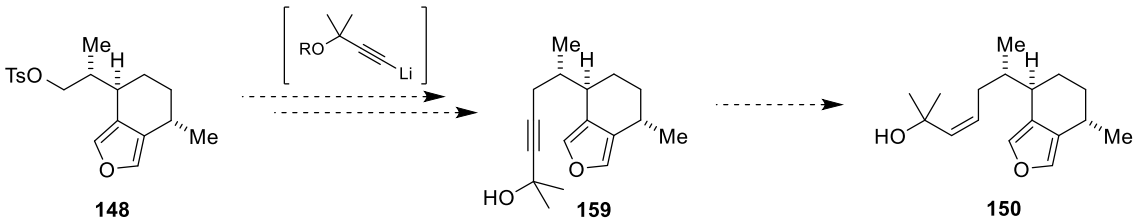
| Entry | Eq. of 149 and *n*-BuLi (each) | Solvent | *t* [h] | *T* [°C] | Observation |
|---|---|---|---|---|---|
| 1[b] | 4.0 | THF | 18 | –78 to 40 | s.m. |
| 2 | 20 | 1,4-dioxane | 5 | rt to 130 | complex mixture of compounds |

(*a*) Each experiment was conducted on a 20 mg scale and was 0.03 to 0.05M in tosylate **148**. (*b*) HMPA (1.5 eq.) was added after 4 h at rt.

In the following, no further avenues along the lines of a sulfone displacement were pursued, since promising progress in a different approach was achieved. These results will be discussed in the following subchapter.

## 4.4 Synthesis of Allylic alcohol 150

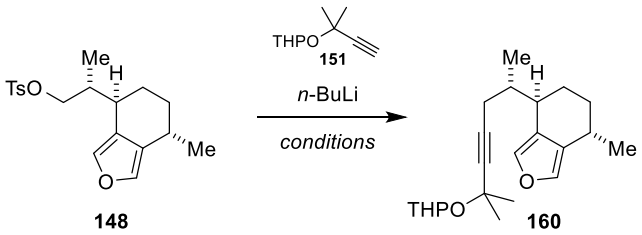
Inspired by the facile synthesis of nitrile **97** *via* substitution (*cf.* Chapter 1.2, Scheme 1.8),[43] we aimed to utilize a slim $C_5$ nucleophile which could overcome the sterical hindrance. Thus, we opted to use an sp-hybridized carbanion, *i.e.* the use of an alkyne as substrate. In particular, we were interested to examine the reactivity of the Li-acteylide derived from an *O*-protected dimethylpropargyl alcohol (Scheme 4.5). This is due to the fact that an ensuing selective hydrogenation of the alkyne group of the resulting intermediate **159** to the (*Z*)-alkene under Lindlar conditions would provide allylic alcohol **150**, which was expected to be as suitable for the subsequent Friedel–Crafts allylation as the reported, analogous allylic alcohol **144**.




**Scheme 4.5** Aimed introduction of the missing $C_5$ fragment as a slim Li-acetylide and subsequent reduction to allylic alcohol **150**.

On the basis of a procedure described by Michalak and Wicha,[82] tosylate **148** was treated with a large excess (18 eq.) of *in situ* lithiated dimethylpropargyl THP ether **151** in 1,4-dioxane and heated to reflux for 3 d. A small amount of a new, impure compound was obtained from flash column chromatography, which according to $^1$H NMR spectroscopy was conjectured to be alkyne **160** (Table 4.3, Entry 1). Only traces of the presumed alkyne **160** were obtained when the reaction was run at rt in the presence of HMPA (Entry 2). While no reaction took place after 12 h at 80 °C (according to TLC analysis, Entry 3), complete consumption of tosylate **148** was observed after the same time at 130 °C and an elevated pressure (Entry 4). The latter conditions provided 40% of pure alkyne **160** after purification by flash column chromatography. A 20% increase in yield was achieved on a 240 mg scale when applying the conditions of Entry 4 but reducing the reaction time to 5 h (Entry 5), indicating that the formed product is not indefinitely stable under the reaction conditions. However, no pathway of the degradation could be deduced, since the prolonged reaction times mostly led to intractable product mixtures.

**Table 4.3** Synthesis of alkyne **160** *via* substitution with *in situ* lithiated dimethylpropargyl THP ether **151**.[a]

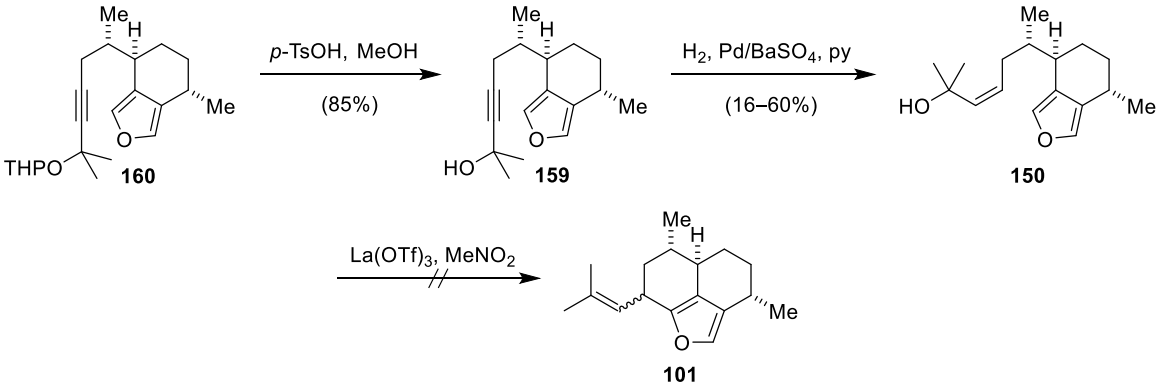



| Entry | Eq. 151 | Eq. *n*-BuLi | *T* [°C][b] | *t* [h][b] | Scale [mg] | Observation/yield of 160 after FCC [%][c] |
|---|---|---|---|---|---|---|
| 1 | 20 | 18 | 130 | 76 | 50 | <14 |
| 2[d] | 20 | 18 | rt | 21 | 20 | traces of **160**[e] |
| 3 | 20 | 18 | 80 | 12 | 25 | no conversion[f] |
| 4 | 20 | 18 | 130 | 12 | 25 | 40 |
| 5 | 20 | 18 | 130 | 5 | 240 | 60 |

(*a*) All reactions were conducted in 1,4-dioxane and were 0.04–0.08M in tosylate **148**. *n*-BuLi was added to **151** at 8 °C and the formed Li-acetylide was then brought to rt. Entries 1, 4 and 5: Reactions conducted in a pressure tube. (*b*) After addition of tosylate **148** to the *in situ* formed Li-acetylide. (*c*) FCC = flash column chromatography. (*d*) HMPA (18 eq.) was applied as a cosolvent. (*e*) Found in the $^1$H NMR spectrum of the crude product. (*f*) According to TLC analysis of the reaction mixture.

Encouraged by this result, the subsequent cleavage of the THP protecting group was investigated. To our delight, the reaction proceeded smoothly, employing catalytic amounts of *p*-TsOH in MeOH and

providing propargylic alcohol **159** in 85% yield (Scheme 4.6).[81] The hydrogenation of intermediate **159** to form allylic alcohol **150** was conducted in pyridine under an atmosphere of $H_2$, using $Pd/BaSO_4$ as a poisoned catalyst.[83] An initial experiment on a 10 mg scale provided allylic alcohol **150** in a 60% yield. When repeated on an 80 mg scale, a dramatically lower yield of 16% was obtained, which may have been the result of too harsh workup conditions, involving removal of excessive pyridine from the product containing organic layer (consisting of EtOAc/hexanes) by extraction with 1.0M aqueous HCl. One experiment was made to test the Friedel–Crafts allylation of allylic alcohol **150**, using catalytic amounts of $La(OTf)_3$ in $MeNO_2$, as reported for the cyclization of allylic alcohol **144** (*cf.* Chapter 1.2, Scheme 1.8).[43] No reaction was observed in this case, possibly due to an impaired quality of the $La(OTf)_3$, which barely (if at all) dissolved in $MeNO_2$. Unfortunately, time constrictions prevented us from improving the reaction and workup conditions of the hydrogenation of propargylic alcohol **159**, as well as the subsequent Friedel–Crafts allylation supposed to give rise to furan **101**.

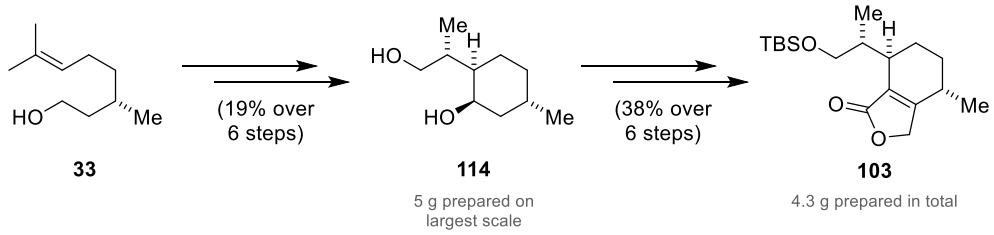



**Scheme 4.6** Synthesis of allylic alcohol **150** and attempted Friedel–Crafts allylation under reported conditions.

# 5 CONCLUSIONS AND OUTLOOK

## 5.1 Synthesis of Butenolide 103

The known route toward butenolide **103** was successfully reproduced on a multigram scale, providing diol **114** in a yield of 19% over 6 steps from (–)-*β*-citronellol (**33**, 5 g on largest scale), as well as a total of 4.3 g of butenolide **103** (38% over 6 steps on largest scale from diol **114**, Scheme 5.1).

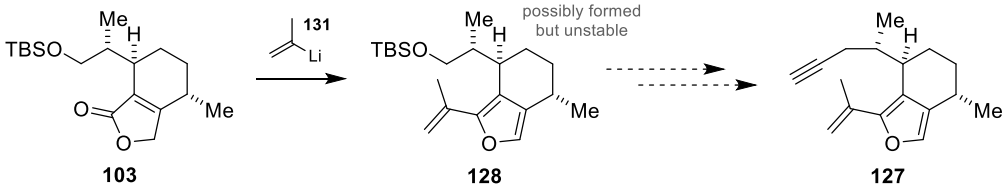



**Scheme 5.1** Overall results of the synthesis of butenolide **103**.

The synthesis of *β*-keto ester **104** worked best using LiHMDS instead of LDA, and was shown to require HMPA as a cosolvent. The synthesis of butenolide **103**, following a carbonylation method that involves *in situ* generated CO was shown to be as efficient as the originally reported procedure, in which a high pressure (2.5 bar) CO atmosphere was applied in an autoclave.

## 5.2 Toward the Asymmetric Total Synthesis of (+)-Caribenol A

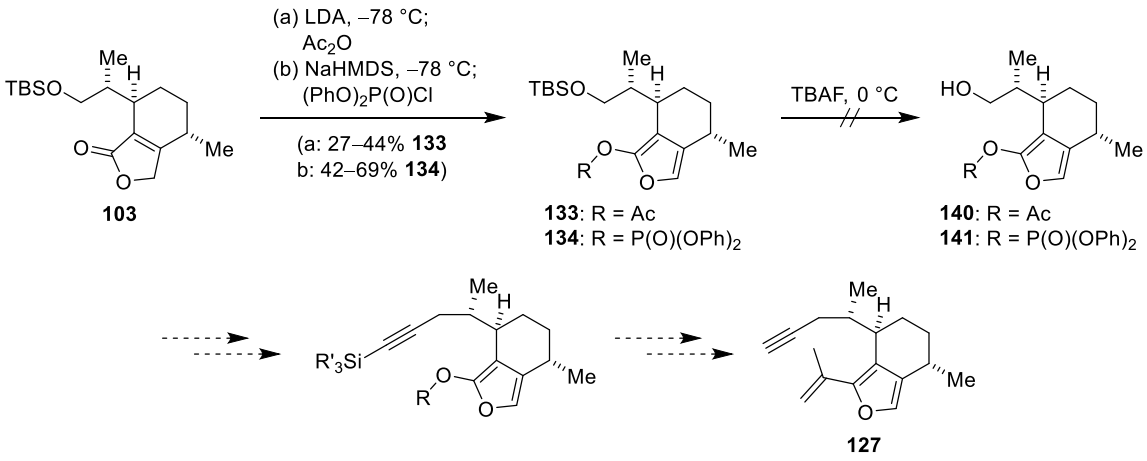
For the envisaged total synthesis of (+)-caribenol A (**55**) *via* a Pauson–Khand key step, the focus was put on the development of a synthetic route to the logical precursor **127**. Originally, the synthesis of this intermediate should have proceeded through isopropenylfuran **128**, whose formation was conjectured after treating butenolide **103** with isopropenyllithium (**131**) and applying acidic workup conditions, but could not be verified by complete analytical characterization of pure, isolated material (Scheme 5.2). The presumed isopropenylfuran **128** was only a minor component of an inseparable mixture of compounds, and proved to be quite unstable.




**Scheme 5.2** Original route toward enyne **127** failed at the synthesis of isopropenylfuran **128**.

An alternative route aimed for the formation of the critical isopropenylfuran moiety after introduction of the ethynyl group (Scheme 5.3). The protection of the butenolide moiety of intermediate **103** as a trapped 2-hydroxyfuran only worked with modest success, since acetylation was lacking regioselectivity

(*O*- vs. *C*-acetylation), and phosphorylation afforded a labile phosphate (**134**), which could not be separated from residual substrate (**103**) *via* flash column chromatography. This route was abandoned after attempts to selectively cleave the TBS group of both the phosphate (**134**) and acetate (**133**) had only furnished butenolide **103**.

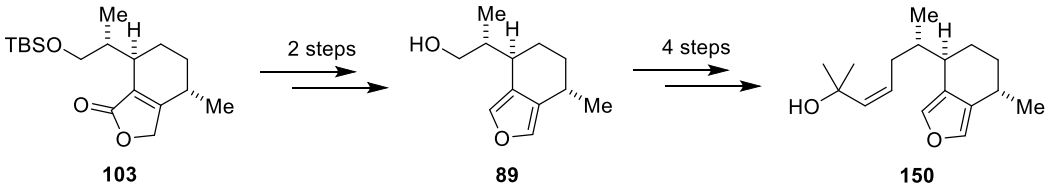



**Scheme 5.3** The alternative route toward enyne **127** was abandoned due to the failure to selectively desilylate the primary alcohol functionality of both the acetate **133** and the phosphate **134**.

The elaboration of a Pauson-Khand key step in the aimed synthesis of (+)-caribenol A (**55**) remains a challenge: On the one hand, the retrosynthetically most suitable precursor, enyne **127**, supposedly could not be synthesized due to the insufficient stability of the isopropenylfuran moiety. On the other hand, the number of alternative Pauson-Khand precursors potentially accessible from butenolide **103** is very limited, and would probably require a temporary opening of the butenolide. This would involve many more steps than planned for the synthesis of enyne **127**, and would also diverge from the original idea to complete the tetracyclic core of (+)-caribenol A (**55**) within the Pauson-Khand key step. It thus seems plausible to continue to explore further reaction and workup conditions in attempts to synthesize isopropenylfuran **128**, or acetal **132**. Most importantly, the ambiguous results obtained so far in the synthesis of isopropenylfuran **128** must be clarified, *e.g.* by trying to purify its desilylated analogue.

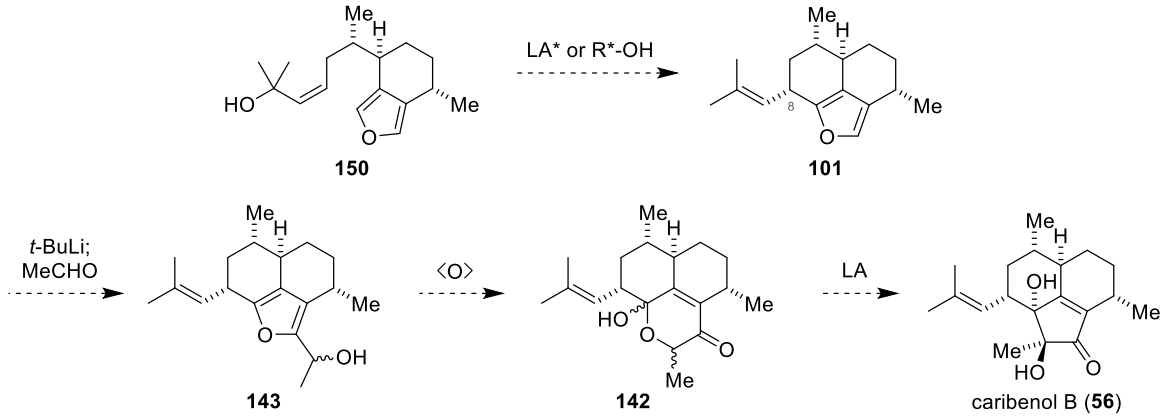
## 5.3 Toward the Asymmetric Total Synthesis of Caribenol B

The synthetic efforts toward caribenol B (**56**) commenced with the preparation of alcohol **89** in 2 steps from 500 mg of butenolide **103**. A new route has been developed to access the alternative Friedel–Crafts allylation precursor **150** in 4 steps from alcohol **89**, which is 2 steps less than required for the reported synthesis of the analogous allylic alcohol **144**.[43] Though the overall yield of the new route is not competitive yet, it could become so by optimization of the substitution and hydrogenation. On the one hand, the substitution may be further improved by reduction of the reaction time. On the other hand, application of smoother workup conditions may be the key to good yields in the hydrogenation, which showed clean and almost complete conversion of the substrate according to TLC analysis.




**Scheme 5.4** Synthesis of Friedel–Crafts allylation precursor **150** in 6 steps from butenolide **103**.

The cyclization of allylic alcohol **150** should be tested applying further reported conditions for the cyclization of allylic alcohol **144** (including another attempt with a new batch of $La(OTf)_3$).[43] The subsequent goal would be the development of an asymmetric Friedel-Crafts allylation (under the usage of a chiral Lewis or Brønsted acid) to selectively furnish the 8$\alpha$-epimer of furan **101**, which could then be used for endeavors to complete the final 3 steps in the aimed total synthesis of caribenol B (**56**, Scheme 5.5).




**Scheme 5.5** Remaining 4 steps to be accomplished in the aimed total synthesis of caribenol B (**56**) from allylic alcohol **150**.

# 6 EXPERIMENTAL SECTION

## 6.1 General Working Methods[†]

Unless noted otherwise, all reactions were magnetically stirred and conducted in anhydrous solvents under a positive pressure of Ar, applying standard Schlenk techniques. Glassware was either oven-dried for ≥ 12 h at 120 °C or dried *in vacuo* at 350 °C prior to usage. Solvents and liquid reagents, as well as solutions of solid or liquid reagents were added *via* syringes or oven-dried stainless steel cannulas through rubber septa. Solid reagents were added under a weak Ar counter-flow. Cooling baths were prepared in Dewar vessels, filled with ice/water (0 °C) or dry ice/acetone (−78 °C). Heated oil baths were used for reactions requiring elevated temperatures. Unless noted otherwise, all given yields are isolated yields of chromatographically and NMR spectroscopically pure materials.

*Solvents and reagents*

Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were freshly distilled under a nitrogen atmosphere from Na/benzophenone as a drying agent prior to use. Triethylamine ($Et_3N$), diisopropylamine (DIPA), *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and triflic anhydride ($Tf_2O$) were freshly distilled under a nitrogen atmosphere from $CaH_2$ as a drying agent prior to use. Alternatively, $Tf_2O$ was used directly from a previously unopened ampule. Further anhydrous solvents and reagents, including dichloromethane ($CH_2Cl_2$), acetonitrile (MeCN), toluene (PhMe), *N,N,N',N',N'',N''*-hexamethylphosphoramide (HMPA), *N,N*'-dimethylpropylene urea (DMPU), *N*-methyl-2-pyrrolidinone (NMP), 1,4-dioxane, acetone, $MeNO_2$ and pyridine were purchased dry and over molecular sieves from either *Acros Organics* or *Sigma-Aldrich* and used as received. Solvents for extraction, crystallization and flash column chromatography were purchased in technical grade and distilled under reduced pressure prior to use. Ratios and percentages of solvents, liquids and solutions are reported as volume *per* volume (v/v) unless otherwise noted. $Pd(PPh_3)_4$ was purchased from *Sigma-Aldrich* and stored in a UNIlab glovebox from *MBRAUN*. Solutions of $BF_3{\cdot}OEt_2$ in dry THF were prepared immediately prior to use. All other reagents and solvents were purchased from chemical suppliers (*Sigma-Aldrich*, *Acros Organics*, *Alfa Aesar*, *Merck*, *Strem*, *ABCR*, *TCI Europe*) and were used as received. The following reagents/building blocks were synthesized from commercially available starting materials according to literature procedures: Dess–Martin periodinane (DMP, **116**),[84] prenyl carbamate **146**,[85] prenyl sulfone **149**,[86] and dimethylpropargyl THP ether **151**.[87]

*Note: dimethylpropargyl THP ether **151** was purified by flash column chromatography (silica, EtOAc/hexanes = 1:8), since distillation according to the literature procedure resulted in acetal pyrolysis.*

[†] Most of the general working methods applied in this master thesis are consistent with those of Dr. Daniel T. Hog, former Ph.D. student in the group of Prof. Dr. Dirk Trauner, who granted me permission to adopt the corresponding parts of the Chapter 'General Working Methods' of his Ph.D. thesis.

*Chromatography*

Reactions and chromatography fractions were monitored by qualitative thin-layer chromatography (TLC) on silica gel $F_{254}$ TLC plates from *Merck KGaA*. Analytes on the glass plates were visualized by irradiation with UV-light ($\lambda$ = 254 and 366 nm) and/or by immersion of the TLC plate in an appropriate staining solution followed by heating with a hot-air gun (350 °C). Staining solutions that were applied were either a *p*-anisaldehyde staining solution (3.7 mL *p*-anisaldehyde, 5.0 mL concentrated aqueous $H_2SO_4$, 1.5 mL glacial AcOH and 135 mL EtOH) or a CAM staining solution (5.0 g $Ce(SO_4)_2$, 25 g $(NH_4)_6Mo_7O_{24}{\cdot}4\ H_2O$, 50 mL concentrated aqueous $H_2SO_4$, 450 mL $H_2O$). Flash column chromatography was performed on Geduran® Si60 (40–63 $\mu$m) silica gel from *Merck KGaA*. All fractions containing a desired substance were combined and concentrated *in vacuo*, then dissolved in either *n*-pentane or $Et_2O$ and filtered through a dabber to remove silica residues. The solvent was removed under reduced pressure and each compound was dried *in high vacuo* ($10^{-1}$ to $10^{-3}$ mbar).

*NMR spectroscopy*

NMR spectra were either self-recorded on a *Bruker* Avance III HD 400 spectrometer, operating at 400 and 100 MHz for $^1H$ and $^{13}C$ nuclei, respectively. Alternatively, NMR spectra were recorded by the analytical section of the Department of chemistry of the *Ludwig-Maximilians-Universität München* using *Varian* VNMRS 400 and INOVA 400 spectrometers, operating at 400 MHz for $^1H$ nuclei, and 100 MHz for $^{13}C$ nuclei, and a *Varian* VNMRS 600 spectrometer, operating at 600 MHz for $^1H$ nuclei, and 150 MHz for $^{13}C$ nuclei. $^{19}F$ NMR spectra were recorded on a Varian VNMRS 300 spectrometer, operating at 282 MHz for $^{19}F$ nuclei. The chemical shifts ($\delta$) in $^1H$ and $^{13}C$ NMR spectra are reported in parts per million (ppm), relative to the chemical shift of tetramethylsilane. All spectra were recorded in $CDCl_3$ (purchased from *Euriso-top*) and calibrated to the residual solvent signals at 7.26 ($^1H$) and 77.16 ($^{13}C$) ppm, or to external $CFCl_3$ ($^{19}F$, 0.00 ppm). $^1H$ NMR spectroscopic data are reported as follows: chemical shift in ppm (multiplicity, coupling constants *J*, integration intensity, assignment to the location in the molecule). The multiplicities are abbreviated with s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and $m_C$ (centrosymmetric multiplet). In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. Except for multiplets, the chemical shift of all signals (including centrosymmetric multiplets) is reported as the center of the resonance range. In addition to $^1H$ and $^{13}C$ NMR spectroscopy, 2D NMR techniques, including homonuclear correlation spectroscopy (COSY), heteronuclear single quantum coherence (HSQC), heteronuclear multiple bond coherence (HMBC) and nuclear Overhauser enhancement correlation spectroscopy (NOESY) were used to assign signals. Thereby, the numbering of the carbon skeleton does not correspond to the IUPAC nomenclature. If two signals could not be unambiguously assigned by these methods, the assigned protons or carbon atoms are marked as '*', '**', etc. and the assignment is interchangeable. Coupling constants $^nJ_{AB}$ between protons A and B across n bonds are reported in hertz (Hz), if an assignment of the two coupling partners was possible. Otherwise, coupling constants are given as *J* in Hz. Diastereotopic protons were labeled as $H_A$ and $H_B$, with $H_A$ corresponding to the more

downfield-shifted signal. All NMR spectra were analyzed using the program *MestRe NOVA 8.1.0* from *Mestrelab Research S. L*.

*Mass spectrometry*

All mass spectra were measured by the analytical section of the Department of Chemistry of the *Ludwig-Maximilians-Universität München*. Mass spectra were either recorded on an MAT 95 (EI-MS) or an LTQ FT (ESI-MS) mass spectrometer from *Thermo Finnigan GmbH*. Mass spectra were recorded in high-resolution and only the characteristic molecule ion peaks are indicated for each analyte. The method used is reported in the analytical section of the corresponding experimental procedure.

*X-ray crystallography*

The data collections were performed on a Bruker D8Venture diffractometer at 173 K using Mo K$\alpha$-radiation ($\lambda$ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41)[88] was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97[89] and refined by least-squares methods against *F*2 with SHELXL-97[90]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms.

*IR spectroscopy*

IR spectra were recorded on a *PerkinElmer* Spectrum BX II FT-IR system. All substances were dissolved in $CH_2Cl_2$ and directly applied on the ATR unit. The measured wavenumbers ($\tilde{\upsilon}$) are reported in $cm^{-1}$ and the band intensities are described with br (broad), s (strong), m (medium) and w (weak).

*Melting points*

Melting points were measured on a *Stanford Research Systems* EZ-Melt Automated Melting Point Apparatus and are uncorrected.

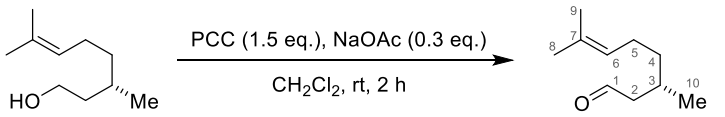
*Optical rotation*

Optical rotation values were recorded on a PerkinElmer 241 polarimeter. The specific optical rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\theta} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

The wavelength $\lambda$ is reported in nm and the measured temperature $\theta$ in °C. [$\alpha$] represents the recorded optical rotation at the apparatus, *c* the concentration of the analyte in 10 mg/mL and *d* the length of the cuvette in dm. Thus, the specific optical rotation is given in $10^{-1}$ deg·cm$^2$·g$^{-1}$. Usage of the sodium D line ($\lambda$ = 589 nm) is indicated by *D* instead of the wavelength in nm. The respective concentration and the solvent are denoted in the analytical part of the corresponding experimental procedure.

## 6.2 Experimental Procedures




**33**

(–)-citronellal (**105**)
$C_{10}H_{18}O$
*M* = 154.25 g/mol

**(–)-Citronellal (105)**. To a stirred suspension of PCC (89.9 g, 417 mmol, 1.5 eq.) and NaOAc (6.84 g, 83.4 mmol, 0.3 eq.) in $CH_2Cl_2$ (360 mL) was added a solution of (–)-*β*-citronellol (**33**) (43.5 g, 278 mmol, 1.0 eq.) in $CH_2Cl_2$ (360 mL) *via* cannula at rt (the flask containing the reaction mixture was kept in a water bath to prevent warming). After 2 h, silica gel and $Et_2O$ (300 mL) were added to the dark suspension, which was subsequently filtered through a plug of silica. The residual dark sludge in the flask was extracted with $Et_2O$ (3 × 100 mL) and the extracts were filtered through the same plug of silica, which was subsequently washed with further $Et_2O$ (3 × 50 mL). Removal of the solvent *in vacuo* gave a greenish-brown oil, which was purified by flash column chromatography (silica, EtOAc/hexanes = 1:40 to 1:30) to yield (–)-citronellal (**105**, 29.0 g, 188 mmol, 68%) as a colorless liquid.

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 9.75 (dd, $^3J_{1/2B}$ = 2.6 Hz, $^3J_{1/2A}$ = 2.1 Hz, 1H, 1-H), 5.08 ($m_C$, 1H, 6-H), 2.41 (ddd, $^2J_{2A/2B}$ = 16.0 Hz, $^3J_{2A/3}$ = 5.6 Hz, $^3J_{2A/1}$ = 2.1 Hz, 1H, 2-$H_A$), 2.23 (ddd, $^2J_{2B/2A}$ = 16.0 Hz, $^3J_{2B/3}$ = 8.0 Hz, $^3J_{2B/1}$ = 2.6 Hz, 1H, 2-$H_B$), 2.07 ($m_C$, 1H, 3-H), 2.00 ($m_C$, 2H, 5-H), 1.68 ($m_C$, 3H, 8-H)*, 1.60 ($m_C$, 3H, 9-H)*, 1.41–1.22 (m, 2H, 4-H), 0.97 (d, $^3J_{10/3}$ = 6.7 Hz, 3H, 10-H) ppm.

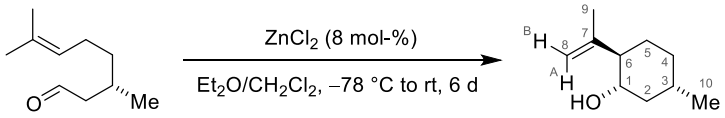
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 203.2 (C-1), 131.9 (C-7), 124.2 (C-6), 51.2 (C-2), 37.1 (C-4), 27.9 (C-3), 25.9 (C-8), 25.5 (C-5), 20.0 (C-10), 17.8 (C-9) ppm.

EI-MS for $C_{10}H_{18}O^{+\cdot}$ [$M^{+\cdot}$]: calcd. 154.1352
found 154.1348.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2962 (s), 2913 (s), 2875 (s), 2853 (s), 2715 (w), 1724 (s), 1453 (w), 1377 (w).

$[\alpha]_D^{21}$ = –17.9 (*c* 0.62, $CH_2Cl_2$).

The NMR and IR spectroscopic data matched those reported previously.[91]




**105**

(+)-isopuegol (**107**)
$C_{10}H_{18}O$
*M* = 154.25 g/mol

**(+)-Isopulegol (107)**. $ZnCl_2$ (1.39 g, 10.2 mmol, 8 mol-%) was dried in vacuo at 200 °C for 22 h, then dissolved in $Et_2O$ (50 mL), diluted with $CH_2Cl_2$ (200 mL) and cooled to −78 °C. A solution of (−)-citronellal (**105**) (20.0 g, 130 mmol, 1.0 eq.) in $CH_2Cl_2$ (200 mL) was cooled to −78 °C and added to the stirred $ZnCl_2$-solution *via* cannula over 15 min. Stirring was continued for 2 h at −78 °C, then the cooling bath was allowed to reach rt within 6 h. After stirring for a total of 6 d, the reaction mixture was washed with aqueous ammonia (1.5M, 3 × 50 mL). The organic layer was washed with saturated aqueous NaCl (100 mL), dried over $Na_2SO_4$, filtered and evaporated to dryness. Pure (+)-isopulegol (**107**, 14.0 g, 90.7 mmol, 70%) was obtained from fractional vacuum distillation (product fraction: bp = 22–30 °C, $p = 5 \times 10^{-2}$ to $7 \times 10^{-2}$ mbar) as a clear, colorless liquid.

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 4.90 (dq, $^2J_{8A/8B}$ = 2.2 Hz, $^4J_{8A/9}$ = 1.5 Hz, 1H, 8-$H_A$)*, 4.87–4.84 (m, 1H, 8-$H_B$)*, 3.46 ($m_C$, 1H, 1-H), 2.04 ($m_C$, 1H, 2-$H_A$), 1.88 ($m_C$, 1H, 6-H), 1.71 (dd, $^4J_{9/8A}$ = 1.5 Hz, $^4J$ = 0.9 Hz, 3H, 9-H), 1.71–1.63 (m, 2H, 4-$H_A$, 5-$H_A$), 1.56–1.43 (m, 1H, 3-H), 1.39–1.26 (m, 1H, 5-$H_B$), 1.03–0.87 (m, 2H, 2-$H_B$, 4-$H_B$), 0.95 (d, $^3J_{10/3}$ = 6.6 Hz, 3H, 10-H) ppm.

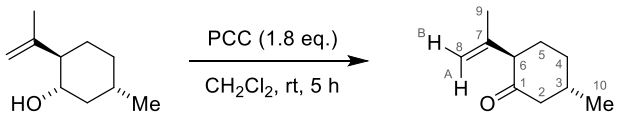
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 146.8 (C-7), 113.0 (C-8), 70.5 (C-1), 54.3 (C-6), 42.8 (C-2), 34.5 (C-4), 31.6 (C-3), 29.8 (C-5), 22.4 (C-10), 19.4 (C-9) ppm.

EI-MS for $C_{10}H_{18}O^{+\cdot}$ [$M^{+\cdot}$]: calcd. 154.1352
found 154.1356.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3406 (br w), 3072 (w), 2948 (s), 2921 (s), 2868 (s), 1645 (w), 1455 (m), 1027 (w), 885 (w).

$[\alpha]_D^{21}$ = +8.8 (*c* 0.64, $CH_2Cl_2$).

The $^1$H NMR spectroscopic data matched those reported previously.[92]




**107**

(+)-isopulegone (**108**)
$C_{10}H_{16}O$
*M* = 152.24 g/mol

**(+)-Isopulegone (108)**. To a stirred suspension of PCC (31.0 g, 144 mmol, 1.8 eq.) in $CH_2Cl_2$ (220 mL) was added a solution of (+)-isopulegol (**107**) (12.3 g, 80.0 mmol, 1.0 eq.) in $CH_2Cl_2$ (150 mL) *via* cannula at rt (the flask containing the reaction mixture was kept in a water bath to prevent warming). After stirring for 5 h, the reaction was diluted with $Et_2O$ (200 mL) and the mixture was filtered through a plug of a mixture of celite, silica and charcoal. The plug was washed with further $Et_2O$, and the filtrate was

evaporated to dryness. The crude product was purified by fractional vacuum distillation (product fraction: bp = 24–33 °C, $p$ = 8 × $10^{-3}$ to 1.6 × $10^{-2}$ mbar), yielding (+)-isopulegone (**108**, 10.9 g, 71.7 mmol, 90%) as a clear, colorless liquid.

$^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ = 4.94 (dq, $^2J_{8A/8B}$ = 1.6 Hz, $^4J_{8A/9}$ = 1.6 Hz, 1H, 8-$H_A$)*, 4.72 ($m_C$, 1H, 8-$H_B$)*, 2.95 ($m_C$, 1H, 6-H), 2.41 (ddd, $^2J_{2A/2B}$ = 13.3 Hz, $J$ = 4.0 Hz, 2.1 Hz, 1H, 2-$H_A$), 2.07–2.02 (m, 2H, 2-$H_B$, 5-$H_A$), 1.95–1.85 (m, 2H, 3-H, 4-$H_A$), 1.79 ($m_C$, 1H, 5-$H_B$), 1.75 (dd, $^4J_{9/8A}$ = 1.6 Hz, $^4J$ = 0.9 Hz, 3H, 9-H), 1.43 ($m_C$, 1H, 4-$H_B$), 1.04 (d, $^3J_{10/3}$ = 6.4 Hz, 3H, 10-H) ppm.

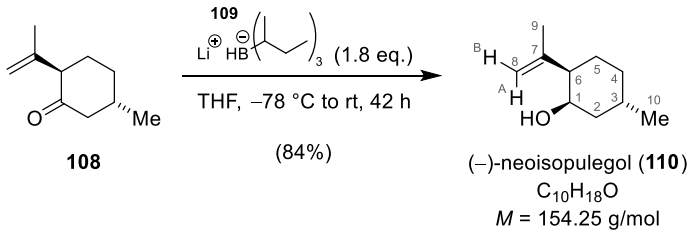
$^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ = 210.4 (C-1), 143.6 (C-7), 113.0 (C-8), 57.9 (C-6), 50.7 (C-2), 35.5 (C-3), 34.0 (C-4), 31.3 (C-5), 22.5 (C-10), 21.5 (C-9) ppm.

EI-MS for $C_{10}H_{16}O^{+\cdot}$ [$M^{+\cdot}$]: calcd. 152.1196
found 152.1191.

IR (ATR): $\tilde{\nu}$/$cm^{-1}$ = 3075 (w), 2954 (s), 2928 (s), 2870 (s), 1711 (s), 1648 (w), 1456 (w), 1375 (w), 1192 (w), 1126 (w), 890 (w).

$[\alpha]_D^{23}$ = +1.7 ($c$ 0.75, $CH_2Cl_2$).

The NMR and IR spectroscopic data matched those reported previously.[48]




**(–)-Neoisopulegol (110)**. To a solution of (+)-isopulegone (**108**, 10.8 g, 70.9 mmol, 1.0 eq.) in THF (220 mL) at –78 °C was added L-selectride® (**109**, 128 mL of a 1.0M solution in THF, 128 mmol, 1.8 eq.) *via* cannula within 1 h and the reaction mixture was allowed to warm to rt in 16 h. After a total of 42 h, the mixture was cooled to 0 °C, and aqueous $H_2O_2$ (30% w/w, 44 mL) and aqueous NaOH (15% w/w, 30 mL) were added slowly. After 1.5 h at rt, the formed precipitate was filtered off and washed with $CH_2Cl_2$ (3 × 30 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over $MgSO_4$, filtered and evaporated to dryness. Fractional vacuum distillation of the crude product yielded (–)-neoisopulegol (**110**, 9.22 g, 59.8 mmol, 84%) as a colorless liquid (product fraction: bp = 55–61 °C, $p$ = 5.3–5.7 mbar), sufficiently pure for the subsequent epoxidation.

An analytically pure sample of alcohol **110** was obtained from purification by flash column chromatography (silica, EtOAc/hexanes = 1:15).

$^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 4.95 ($m_C$, 1H, 8-$H_A$)*, 4.78 ($m_C$, 1H, 8-$H_B$)*, 3.98 ($m_C$, 1H, 1-H), 2.01–1.94 (m, 2H, 6-H, 2-$H_A$), 1.85–1.65 (m, 3H, 3-H, 4-$H_A$, 5-$H_A$), 1.79 ($m_C$, 3H, 9-H), 1.48 ($m_C$, 1H, *O*H), 1.47–1.41 (m, 1H, 5-$H_B$), 1.12 ($m_C$, 1H, 2-$H_B$), 1.00–0.91 (m, 1H, 4-$H_B$), 0.88 (d, $^{3}J_{10/3}$ = 6.5 Hz, 3H, 10-H) ppm.

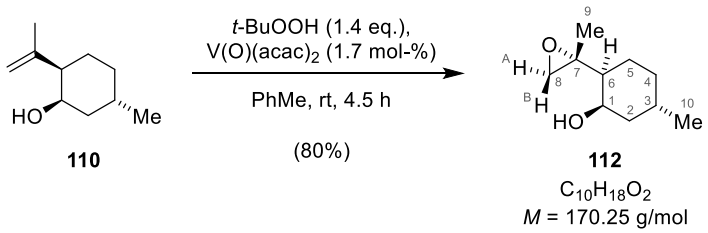
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 147.5 (C-7), 111.4 (C-8), 66.4 (C-1), 48.5 (C-6), 41.0 (C-2), 34.9 (C-4), 26.0 (C-3), 24.1 (C-5), 22.9 (C-9), 22.4 (C-10) ppm.

EI-MS for $C_{10}H_{18}O^{+\cdot}$ [$M^{+\cdot}$]: calcd. 154.1352
found 154.1358.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3465 (br w), 3085 (w), 2947 (s), 2924 (s), 2867 (s), 2844 (s), 1643 (w), 1456 (w), 1374 (w), 1235 (w), 1123 (w), 1023 (w), 955 (w), 938 (w), 889 (w).

$[\alpha]_D^{23}$ = –31.8 (*c* 0.55, $CH_2Cl_2$).

The NMR and IR spectroscopic data matched those reported previously.[48]




**Epoxide 112**. The reaction was not run under inert conditions. To a stirred solution of (–)-neoisopulegol (**110**) (9.22 g, 59.8 mmol, 1.0 eq.) in PhMe (110 mL) were added $V(O)(acac)_2$ (270 mg, 1.02 mmol, 1.7 mol-%) and aqueous *t*-BuOOH (80% w/w, 10.5 mL, 83.7 mmol, 1.4 eq.). After 4.5 h, the reaction was diluted with $Et_2O$ (100 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ (200 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed with aqueous $FeCl_2$ (10% w/w, 4 × 50 mL) to destroy residual *t*-BuOOH, and the combined washing solutions were re-extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were then washed with saturated aqueous NaCl (100 mL), dried over $Na_2SO_4$, filtered and the solvents were removed *in vacuo*. Flash column chromatography (silica, EtOAc/hexanes = 1:8 to 1:5 to 1:2) of the crude product gave epoxide **112** (8.13 g, 47.7 mmol, 80%) as colorless crystals, sufficiently pure for the subsequent epoxide opening. An analytical sample of epoxide **112** was obtained by recrystallization from *n*-pentane, yielding crystals suitable for X-ray analysis.

$R_f$ = 0.25 (EtOAc/hexanes = 1:5).

$^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ = 4.33–4.28 (m, 1H, 1-H), 2.79 (dd, $^2J_{8A/8B}$ = 4.5 Hz, $^4J_{8A/9}$ = 0.7 Hz, 1H, 8-$H_A$)*, 2.61 (br s, 1H, *O*H), 2.48 (d, $^2J_{8B/8A}$ = 4.5 Hz, 1H, 8-$H_B$)*, 1.90–1.82 (m, 1H, 2-$H_A$), 1.79 ($m_C$, 1H, 3-H), 1.76–1.68 (m, 1H, 5-$H_A$), 1.56–1.43 (m, 2H, 4-$H_A$, 6-H), 1.43–1.24 (m, 1H, 4-$H_B$), 1.39 (d, $^4J_{9/8A}$ = 0.7 Hz, 3H, 9-H), 1.04 ($m_C$, 1H, 2-$H_B$), 0.96–0.87 (m, 1H, 5-$H_B$), 0.85 (d, $^2J_{10/3}$ = 6.6 Hz, 3H, 10-H) ppm.

$^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ = 68.0 (C-1), 60.4 (C-7), 51.5 (C-8), 44.3 (C-6), 42.1 (C-2), 34.6 (C-5), 25.6 (C-3), 22.3 (2C, C-4, C-10), 21.9 (C-9) ppm.

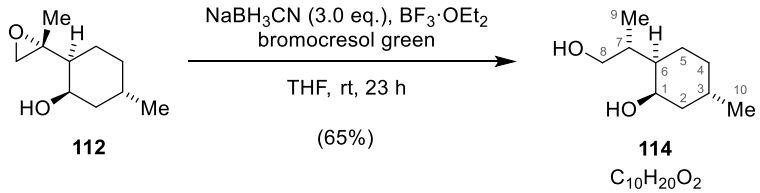
ESI-MS for $C_{20}H_{36}NaO_4^+$ [$(2M+Na)^+$]: calcd. 363.2506
found 363.2510.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3487 (s), 2944 (s), 2922 (s), 2885 (s), 2863 (s), 2843 (s), 1446 (w), 1373 (w), 1178 (w), 1084 (w), 1022 (w), 962 (w), 854 (w), 797 (w), 758 (w).

$[\alpha]_D^{23}$ = –55.4 (*c* 0.85, $CH_2Cl_2$).

Melting point = 55–56 °C (*n*-pentane; lit.[53] mp = 55–56 °C).

The NMR spectroscopic data matched those reported previously.[49]




**112** **114**

$C_{10}H_{20}O_2$

*M* = 172.27 g/mol

**Diol 114**. To a stirred solution of epoxide **112** (7.63 g, 44.8 mmol, 1.0 eq.) and bromocresol green (one spatula tip) in THF (23 mL) was added $NaBH_3CN$ (8.44 g, 134 mmol, 3.0 eq.) in one portion. To the resulting blue mixture was added $BF_3{\cdot}OEt_2$ (0.8M in THF) dropwise until the color changed from blue to yellow. Further $BF_3{\cdot}OEt_2$ solution was added whenever the mixture turned green (total amount added: 24 mL of the 0.8M solution in THF, 19.2 mmol, 0.4 eq.). After the final addition, the mixture was stirred for another 19 h at rt, at which point the reaction was quenched by the addition of saturated aqueous NaCl (100 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (5 × 50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and evaporated to dryness. The crude product was purified *via* flash column chromatography (silica, EtOAc/hexanes = 1:4 to 1:2 to 1:1) to yield diol **114** (4.98 g, 28.9 mmol, 65%) as a clear, colorless oil.

$R_f$ = 0.26 (EtOAc/hexanes = 1:1).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 4.12 ($m_C$, 1H, 1-H), 3.66 (dd, $^2J_{8A/8B}$ = 10.8 Hz, $^3J_{8A/7}$ = 2.9 Hz, 1H, 8-$H_A$), 3.54 (dd, $^2J_{8B/8A}$ = 10.8 Hz, $^3J_{8B/7}$ = 5.9 Hz, 1H, 8-$H_B$), 3.34 (br s, 2H, 2 *O*H), 1.87–1.81 (m, 1H, 2-$H_A$), 1.81–1.70 (m, 2H, 3-H, 4-$H_A$), 1.69–1.60 (m, 1H, 7-H), 1.55 ($m_C$, 1H, 5-$H_A$), 1.50–1.41 (m, 1H, 5-$H_B$), 1.25–1.17 (m, 1H, 6-H), 1.17–1.06 (m, 1H, 2-$H_B$), 0.98 (d, $^3J_{9/7}$ = 7.1 Hz, 3H, 9-H), 0.96–0.88 (m, 1H, 4-$H_B$), 0.86 (d, $^3J_{10/3}$ = 6.5 Hz, 3H, 10-H) ppm.

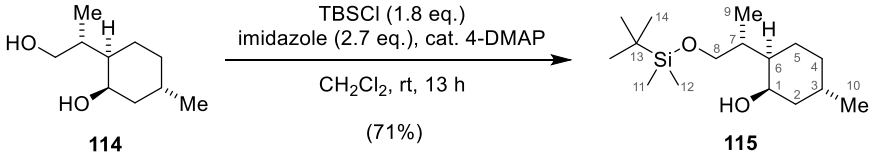
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 66.6 (C-1), 65.1 (C-8), 46.1 (C-6), 42.4 (C-2), 38.3 (C-7), 35.5 (C-4), 26.3 (C-3), 25.6 (C-5), 22.5 (C-10), 16.0 (C-9) ppm.

EI-MS for $C_{10}H_{20}O_2^{+\cdot}$ [$M^{+\cdot}$]: calcd. 172.1458
found 172.1451.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3286 (br s), 2946 (s), 2917 (s), 2868 (s), 1455 (w), 1373 (w), 1035 (w).

$[\alpha]_D^{22}$ = –25.0 (*c* 0.54, $CH_2Cl_2$).

The NMR spectroscopic data matched those reported previously, with the only exception being the chemical shift of the two hydroxy-Hs (reported as a broad singlet at 3.84 ppm).[53]




**114** **115**

$C_{16}H_{34}O_2Si$
*M* = 286.53 g/mol

**Alcohol 115**. To a solution of diol **114** (7.05 g, 40.9 mmol, 1.0 eq.), imidazole (7.52 g, 110 mmol, 2.7 eq.) and one spatula tip of 4-DMAP in $CH_2Cl_2$ (100 mL) was slowly added a solution of TBSCl (11.1 g, 73.6 mmol, 1.8 eq.) in $CH_2Cl_2$ (40 mL) at rt. After 13 h, EtOAc (300 mL) and saturated aqueous NaCl (200 mL) were added to the reaction mixture. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and evaporated to dryness. Purification of the crude product by flash column chromatography (silica, EtOAc/hexanes = 1:20) yielded alcohol **115** (8.28 g, 28.9 mmol, 71%) as a clear, colorless oil.

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 4.07 ($m_C$, 1H, 1-H), 3.68 (dd, $^3J_{OH/1}$ = 2.5 Hz, $^4J$ = 1.9 Hz, 1H, *O*H), 3.65 (dd, $^2J_{8A/8B}$ = 10.3 Hz, $^3J_{8A/7}$ = 2.4 Hz, 1H, 8-$H_A$), 3.52 (dd, $^2J_{8B/8A}$ = 10.3 Hz, $^3J_{8B/7}$ = 6.3 Hz, 1H, 8-$H_B$), 1.93–1.77 (m, 2H, 2-$H_A$, 3-H), 1.72 ($m_C$, 1H, 4-$H_A$), 1.65–1.52 (m, 2H, 7-H, 5-$H_A$), 1.42 ($m_C$, 1H,

5-$H_B$), 1.16 ($m_C$, 1H, 6-H), 1.04 ($m_C$, 1H, 2-$H_B$), 0.94 (d, $^3J_{9/7}$ = 7.1 Hz, 3H, 9-H), 0.93–0.87 (m, 1H, 4-$H_B$), 0.91 (s, 9H, 14-H), 0.85 (d, $^3J_{10/3}$ = 6.5 Hz, 3H, 10-H), 0.08 ($m_C$, 6H, 11-H, 12-H) ppm.

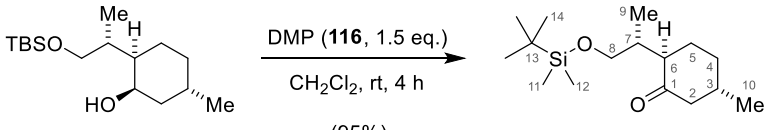
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 66.3 (C-8), 66.1 (C-1), 46.9 (C-6), 42.0 (C-2), 38.5 (C-7), 35.7 (C-4), 26.4 (C-3), 26.0 (C-14), 25.8 (C-5), 22.6 (C-10), 18.4 (C-13), 16.3 (C-9), –5.5 (2C, C-11, C-12) ppm.

ESI-MS for $C_{16}H_{35}O_2Si^+$ [$(M+H)^+$]: calcd. 287.2401
found 287.2404.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3436 (br w), 2948 (s), 2926 (s), 2857 (s), 1462 (w), 1389 (w), 1361 (w), 1252 (w), 1071 (w), 1049 (w), 1003 (w), 834 (s), 775 (w).

$[\alpha]_D^{21}$ = –8.6 (*c* 0.58, $CH_2Cl_2$).

The analytical data from NMR and IR spectroscopy as well as ESI-MS matched those reported previously.[53]




**115** **117**

$C_{16}H_{32}O_2Si$
*M* = 284.51 g/mol

**Ketone 117**. To a stirred solution of alcohol **115** (7.66 g, 26.7 mmol, 1.0 eq.) in $CH_2Cl_2$ (220 mL) was added DMP (**116**, 17.0 g, 40.1 mmol, 1.5 eq.) at rt, and the resulting mixture was stirred for 4 h. The reaction mixture was quenched by addition of aqueous $Na_2S_2O_3$ (10% w/w, 100 mL). After vigorous stirring, the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were consecutively washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried over $Na_2SO_4$, filtered and evaporated to dryness. The crude product was purified by flash column chromatography, providing ketone **117** (7.24 g, 25.4 mmol, 95%) as a clear, colorless oil.

$R_f$ = 0.33 (EtOAc/hexanes = 1:20).

$^1$H NMR ($CDCl_3$, 600 MHz): $\delta$ = 3.47 (dd, $^2J_{8A/8B}$ = 9.9 Hz, $^3J_{8A/7}$ = 5.7 Hz, 1H, 8-$H_A$), 3.41 (dd, $^2J_{8B/8A}$ = 9.9 Hz, $^3J_{8B/7}$ = 7.5 Hz, 1H, 8-$H_B$), 2.47–2.42 (m, 1H, 6-H), 2.37 (ddd, $^2J_{2A/2B}$ = 13.3 Hz, $^3J_{2A/3}$ = 4.0 Hz, $^4J$ = 2.2 Hz, 1H, 2-$H_A$), 2.28 ($m_C$, 1H, 7-H), 2.03–1.96 (m, 2H, 5-$H_A$, 2-$H_B$), 1.92–1.79 (m, 2H, 3-H, 4-$H_A$), 1.42–1.31 (m, 2H, 4-$H_B$, 5-$H_B$), 1.01 (d, $^3J_{10/3}$ = 6.5 Hz, 3H, 10-H), 0.88 (s, 9H, 14-H), 0.80 (d, $^3J_{9/7}$ = 7.0 Hz, 3H, 9-H), 0.03 (s, 3H, 12-H)*, 0.02 (s, 3H, 11-H)* ppm.

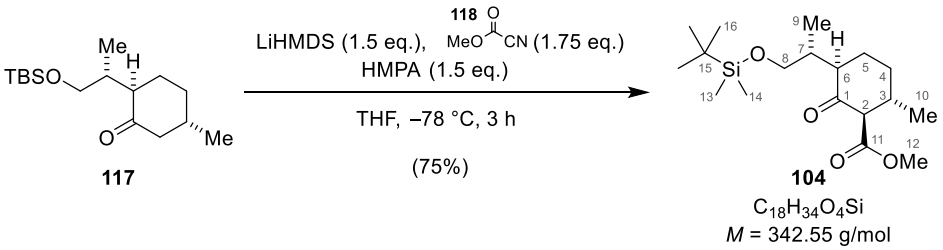
$^{13}$C NMR ($CDCl_3$, 150 MHz): $\delta$ = 212.6 (C-1), 66.1 (C-8), 51.0 (C-2), 50.0 (C-6), 35.4 (C-3), 34.1 (C-4), 33.3 (C-7), 27.0 (C-5), 26.1 (C-14), 22.5 (C-10), 18.4 (C-13), 13.0 (C-9), –5.2 (C-12)*, –5.3 (C-11)* ppm.

EI-MS for $C_{16}H_{32}O_2Si^{+\cdot}$ [$M^{+\cdot}$]: calcd. 284.2166
found 284.2183.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2953 (s), 2927 (s), 2856 (s), 1709 (s), 1472 (w), 1462 (w), 1387 (w), 1251 (w), 1086 (m), 835 (s), 774 (w).

$[\alpha]_D^{21}$ = +25.0 (*c* 0.20, $CH_2Cl_2$).

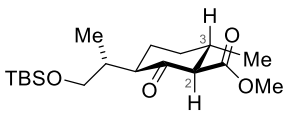
The NMR and IR spectroscopic data matched with those reported previously.[33c]




***β*-Keto ester 104**. Four experiments were set up in parallel, each with the quantities of substrate/reagents mentioned below.

A solution of ketone **117** (1.50 g, 5.27 mmol, 1.0 eq.) in THF (20 mL) was slowly added to a stirred solution of LiHMDS (7.90 mL of a 1.0M solution in THF, 7.90 mmol, 1.5 eq.) in THF (30 mL) at –78 °C, and stirring was continued for 30 min. HMPA (1.40 mL, 7.90 mmol, 1.5 eq.) was added, followed by the addition of Mander's reagent (**118**, 0.73 mL, 9.23 mmol, 1.75 eq.), 20 min later. Stirring was continued for another 1.5 h at –78 °C. The mixture was diluted with *n*-pentane (20 mL) and the reaction was quenched by the addition of $H_2O$ (40 mL). The layers of the combined four reaction mixtures were separated and the aqueous layer was extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and evaporated to dryness. Purification *via* flash column chromatography (silica, EtOAc/hexanes = 1:15 + 1% $Et_3N$) gave *β*-keto ester **104** (5.43 g, 15.9 mmol, 75%) as a pale yellow oil and a single diastereomer, according to $^1$H NMR spectroscopy.

The relative configuration of the newly formed stereogenic center at C-2 was determined by the strong coupling of the 2-H to the neighbored axial 3-H ($^3J_{2/3}$ = 12.2 Hz), as depicted aside.




$R_f$ = 0.20 (EtOAc/hexanes = 1:15 + 1% $Et_3N$).

$^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.76 (s, 3H, 12-H), 3.49 (dd, $^{2}J_{8A/8B}$ = 9.9, $^{3}J_{8A/7}$ = 5.5 Hz, 1H, 8-$H_A$), 3.37 (dd, $^{2}J_{8B/8A}$ = 9.9, $^{3}J_{8B/7}$ = 7.8 Hz, 1H, 8-$H_B$), 3.04 (dd, $^{3}J_{2/3}$ = 12.2, $^{4}J$ = 1.2 Hz, 1H, 2-H), 2.53 ($m_C$, 1H, 6-H), 2.33–2.17 (m, 2H, 3-H, 7-H), 2.07–1.91 (m, 2H, 4-$H_A$, 5-$H_A$), 1.51–1.38 (m, 2H, 4-$H_B$, 5-$H_B$), 1.02 (d, $^{3}J_{10/3}$ = 6.4 Hz, 3H, 10-H), 0.87 (s, 9H, 16-H), 0.80 (d, $^{3}J_{9/7}$ = 7.0 Hz, 3H, 9-H), 0.02 (s, 3H, 13-H)*, 0.01 (s, 3H, 14-H)* ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 207.0 (C-1), 170.5 (C-11), 65.8 (C-2), 65.7 (C-8), 52.0 (C-12), 50.0 (C-6), 37.6 (C-3), 33.3 (C-7), 33.1 (C-4), 26.5 (C-5), 26.1 (C-16), 21.2 (C-10), 18.4 (C-15), 12.8 (C-9), –5.2 (C-13)*, –5.3 (C-14)* ppm.

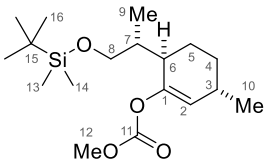
ESI-MS for $C_{18}H_{34}O_4SiNa^+$ [$(M+Na)^+$]: calcd. 365.2119
found 365.2121.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2955 (s), 2930 (s), 2857 (s), 1749 (s), 1711 (s), 1463 (w), 1360 (s), 1253 (w), 1210 (w), 1094 (w), 837 (w), 776 (w).

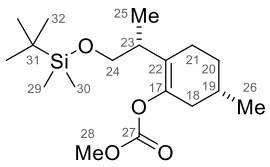
$[\alpha]_D^{23}$ = +18.5 (*c* 0.73, $CH_2Cl_2$).

The NMR and IR spectroscopic data matched with those reported previously.[53]

Beside the desired product, 548 mg of an inseparable mixture of compounds was isolated. According to NMR spectroscopy ($^{1}$H, $^{13}$C, HSQC, HMBC, COSY), this mixture consisted of regioisomeric carbonates **161** and **162** and starting material in a molar ratio of approximately 3:3:1. The yields of carbonates **161** and **162** (each 241 mg, 0.70 mmol, 3%), as well as the amount of recovered starting material (**117**, 66 mg, 0.23 mmol, 1%) were calculated on the basis of $^{1}$H NMR peak intensities.



**161**
$C_{18}H_{34}O_4Si$
*M* = 342.55 g/mol



**162**
$C_{18}H_{34}O_4Si$
*M* = 342.55 g/mol

$R_f$ = 0.45 (EtOAc/hexanes = 1:15 + 1% $Et_3N$).

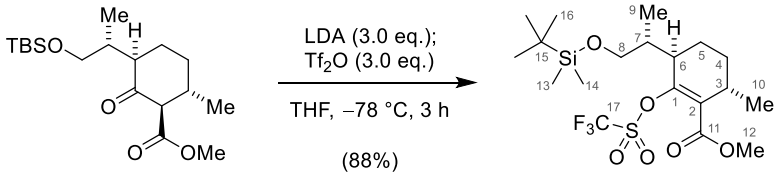
ESI-MS for $C_{18}H_{34}O_4SiNa^+$ [$(M+Na)^+$]: calcd. 365.2119
found 365.2122.

$^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 5.40 ($m_C$, 1H, 2-H), 3.79 (s, 3H, 12-H), 3.79 (s, 3H, 28-H), 3.54–3.38 (m, 2H, 8-$H_A$, 8-$H_B$), 3.51 (dd, $^{2}J_{24A/24B}$ = 9.8, $^{3}J_{24A/23}$ = 6.1 Hz, 1H, 24-$H_A$), 3.41 (dd, $^{2}J_{24B/24A}$ = 9.8 Hz, $^{3}J_{24B/23}$ = 7.7 Hz, 1H, 24-$H_B$), 2.85–2.74 (m, 2H, 6-H, 23-H), 2.33–2.22 (m, 1H, 3-H), 2.17 ($m_C$, 1H, 18-$H_A$), 2.08–1.96 (m, 3H, 21-$H_A$, 21-$H_B$, 7-H), 1.96–1.86 (m, 1H, 18-$H_B$), 1.86–1.63 (m, 4H, 4-$H_A$*, 5-$H_A$, 19-H, 20-$H_A$*), 1.45–1.32 (m, 1H, 5-$H_B$), 1.24–1.11 (m, 2H, 4-$H_B$*, 20-$H_B$*), 1.00 (d, $^{3}J_{10/3}$ = 7.1 Hz, 3H, 10-H), 0.97 (d, $^{3}J_{26/19}$ = 6.7 Hz, 3H, 26-H), 0.96 (d, $^{3}J_{25/23}$ = 7.1 Hz, 3H, 25-H), 0.88 (s, 9H, 16-H),

0.88 (s, 9H, 32-H), 0.76 (d, $^{3}J_{9/7}$ = 6.9 Hz, 3H, 9-H), 0.03 ($m_C$, 6H, 13-H**, 29-H**), 0.02 ($m_C$, 6H, 14-H**, 30-H**) ppm.
*Note: the peaks corresponding to the substrate are not mentioned.*

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 154.1 (C-11), 154.1 (C-27), 150.1 (C-1), 142.2 (C-17), 126.1 (C-22), 122.5 (C-2), 66.3 (C-24), 66.1 (C-8), 55.0 (C-12), 55.0 (C-28), 37.0 (C-6)*, 35.4 (C-23)*, 35.2 (2C, C-7, C-18), 30.7 (C-4)**, 30.5 (C-20)**, 30.1 (C-3), 29.2 (C-19), 26.1 (2C, C-16, C-32), 23.7 (C-21), 22.2 (C-5)***, 21.8 (C-10)***, 21.4 (C-26), 18.4 (2C, C-15, C-31), 14.3 (C-25), 11.4 (C-9), –5.2 (C-13)****, –5.3 (2C, C-14, C-29)****, –5.3 (C-30)**** ppm.
*Note: the peaks corresponding to the substrate are not mentioned.*

Since carbonates **161** and **162** were obtained as a mixture, no IR spectroscopy and specific optical rotation were measured.




**104** **120**
$C_{19}H_{33}F_3O_6SSi$
*M* = 474.61 g/mol

**Vinyl triflate 120**. Two experiments were set up in parallel, each with the quantities of substrate/reagents mentioned below.
To a solution of DIPA (3.50 mL, 25.0 mmol, 3.2 eq.) in THF (200 mL) was added *n*-BuLi (9.40 mL of a 2.5M solution in hexanes, 23.5 mmol, 3.0 eq.) at 0 °C. The resulting solution was stirred for 30 min, then cooled to –78 °C and a solution of *β*-keto ester **104** (2.68 g, 7.84 mmol, 1.0 eq.) in THF (30 mL) was added *via* syringe pump (1.5 mL/min). After 1.5 h, $Tf_2O$ (4.0 mL, 23.8 mmol, 3.0 eq.) was added *via* syringe pump (0.7 mL/min). The resulting orange solution was stirred for another 50 min at –78 °C, at which point the dry ice/acetone bath was replaced by an ice/water bath. After 10 min, the reaction mixture was diluted with *n*-pentane (100 mL) and quenched by addition of saturated aqueous $NaHCO_3$ (100 mL). The layers of the combined two reaction mixtures were separated, the aqueous layer was extracted with *n*-pentane (3 × 100 mL), and the combined organic layers were dried over $Na_2SO_4$, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (silica, EtOAc/hexanes = 1:30 + 1% $Et_3N$), yielding 7.92 g of a pale yellow oil. This material consisted of a mixture of vinyl triflate **120** and residual DIPA in a molar ratio of 1.0:1.0 according to $^{1}$H NMR spectroscopy (calcd. amount of compound **120**: 6.55 g, 13.8 mmol, 88%). The DIPA containing product was directly used for the subsequent reduction. An analytical sample of vinyl triflate **120** was obtained by prolonged drying of 50 mg of the product at $10^{-1}$ to $10^{-2}$ mbar.

$R_f$ = 0.21 (EtOAc/hexanes = 1:30 + 1% $Et_3N$).

$^{1}$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 3.81 (s, 3H, 12-H), 3.53 (dd, $^{2}J_{8A/8B}$ = 10.0, $^{3}J_{8A/7}$ = 6.0 Hz, 1H, 8-$H_A$), 3.41 ($m_C$, 1H, 8-$H_B$), 2.86 ($m_C$, 1H, 6-H), 2.75 ($m_C$, 1H, 3-H), 2.20 ($m_C$, 1H, 7-H), 1.87–1.75 (m, 2H, 5-$H_A$, 4-$H_A$), 1.58–1.47 (m, 1H, 5-$H_B$), 1.37–1.24 (m, 1H, 4-$H_B$), 1.11 (d, $^{3}J_{10/3}$ = 6.9 Hz, 3H, 10-H), 0.88 (s, 9H, 16-H), 0.76 (d, $^{3}J_{9/7}$ = 7.0 Hz, 3H, 9-H), 0.03 (s, 6H, 13-H, 14-H) ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 165.5 (C-11), 152.1 (C-1), 131.2 (C-2), 118.5 (q, $^{1}J_{17/F}$ = 320.2 Hz, C-17), 65.2 (C-8), 52.1 (C-12), 37.9 (C-6), 35.5 (C-7), 32.2 (C-3), 28.6 (C-5), 25.9 (C-16), 20.3 (C-4), 20.1 (C-10), 18.3 (C-15), 11.5 (C-9), –5.4 (C-13)*, –5.6 (C-14)* ppm.

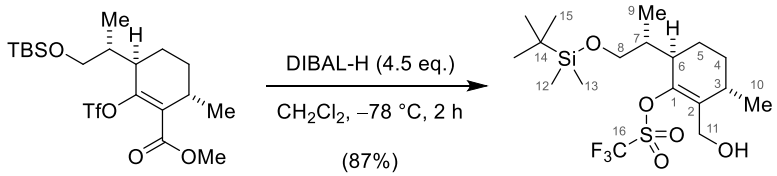
$^{19}$F NMR ($CDCl_3$, 282 MHz): $\delta$ = –74.4 (s, $CF_3$) ppm.

ESI-MS for $C_{19}H_{33}F_3O_6SSiNa^+$ [$(M+Na)^+$]: calcd. 497.1611
found 497.1617.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2955 (s), 2932 (s), 2858 (s), 1735 (s), 1423 (s), 1374 (w), 1246 (m), 1206 (s), 1141 (s), 1094 (w), 977 (w), 893 (w), 837 (w), 777 (w).

$[\alpha]_D^{23}$ = –28.9 (*c* 0.66, $CH_2Cl_2$).

The analytical data from NMR and IR spectroscopy as well as ESI-MS matched those reported previously.[43]




**120** **121**

$C_{18}H_{33}F_3O_5SSi$
*M* = 446.60 g/mol

**Carbonylation precursor 121**. To a stirred solution of ester **120** (6.55 g, 13.8 mmol, 1.0 eq.) in $CH_2Cl_2$ (420 mL) was added DIBAL-H (52 mL of a 1.2M solution in toluene, 62.4 mmol, 4.5 eq.) at –78 °C *via* syringe pump (1.5 mL/min). After stirring for an additional 1.5 h, the mixture was warmed to rt within 10 min and the reaction was quenched by the addition of half-saturated aqueous Rochelle salt (200 mL). The mixture was diluted with $CH_2Cl_2$ and stirred vigorously until no emulsion was present. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl, dried over $Na_2SO_4$, filtered and the solvent was removed *in vacuo*. Purification of the crude product by flash column chromatography (silica, EtOAc/hexanes = 1:10 to 1:6, each + 1% $Et_3N$) afforded 5.71 g of a pale yellow oil, consisting of a mixture of alcohol **121** and residual $Et_3N$ in a molar ratio of 3.0:0.9 according to $^{1}$H NMR spectroscopy

(calcd. amount of product **121**: 5.34 g, 12.0 mmol, 87%). The $Et_3N$ containing product was directly used for the subsequent carbonylation. An analytical sample of alcohol **121** was obtained by prolonged drying of 50 mg of the product at $10^{-1}$ to $10^{-2}$ mbar.

$R_f$ = 0.33 (EtOAc/hexanes = 1:6 + 1% $Et_3N$).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 4.36 (d, $^2J_{11A/11B}$ = 12.7 Hz, 1H, 11-$H_A$), 4.24 (dd, $^2J_{11B/11A}$ = 12.7, $J$ = 1.9 Hz, 1H, 11-$H_B$), 3.50 (dd, $^2J_{8A/8B}$ = 10.0, $^3J_{8A/7}$ = 6.2 Hz, 1H, 8-$H_A$), 3.42 (dd, $^2J_{8B/8A}$ = 10.0, $^3J_{8B/7}$ = 8.8 Hz, 1H, 8-$H_B$), 2.85 ($m_C$, 1H, 6-H), 2.55 ($m_C$, 1H, 3-H), 2.17 ($m_C$, 1H, 7-H), 1.87–1.65 (m, 3H, 4-$H_A$, 5-$H_A$, *O*H), 1.51–1.39 (m, 1H, 5-$H_B$), 1.34–1.24 (m, 1H, 4-$H_B$), 1.19 (d, $^3J_{10/3}$ = 7.0 Hz, 3H, 10-H), 0.88 (s, 9H, 15-H), 0.74 (d, $^3J_{9/7}$ = 7.0 Hz, 3H, 9-H), 0.04–0.02 (m, 6H, 12-H, 13-H) ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 147.4 (C-1), 136.4 (C-2), 118.5 (q, $^1J_{16/F}$ = 319.9 Hz, C-16), 65.4 (C-8), 58.4 (C-11), 38.5 (C-6), 35.2 (C-7), 32.3 (C-3), 29.9 (C-4), 25.9 (C-15), 21.2 (C-5), 19.6 (C-10), 18.3 (C-14), 11.2 (C-9), –5.4 (C-12)*, –5.5 (C-13)* ppm.

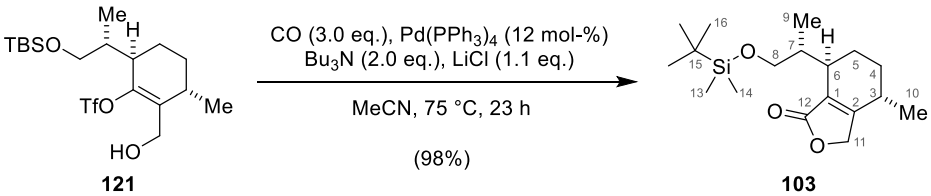
$^{19}$F NMR ($CDCl_3$, 282 MHz): $\delta$ = –74.3 (s, $CF_3$) ppm.

ESI-MS for $C_{19}H_{34}F_3O_7SSi^-$ [$(M+HCO_2)^-$]: calcd. 491.1752
found 491.1746.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3351 (br w), 2956 (s), 2930 (s), 2858 (s), 1472 (w), 1415 (m), 1248 (s), 1207 (s), 1141 (s), 1091 (s), 1019 (w), 973 (w), 885 (s), 836 (s), 775 (w).

$[\alpha]_D^{22}$ = –45.9 (*c* 0.58, $CH_2Cl_2$).

The NMR and IR spectroscopic data matched those reported previously.[43]




**121** **103**

$C_{18}H_{32}O_3Si$

$M$ = 324.54 g/mol

**Butenolide 103**. To a stirred solution of vinyl triflate **121** (2.67 g, 5.98 mmol, 1.0 eq.) in MeCN (95 mL, previously degassed by three freeze–pump–thaw cycles) in a 300 mL Schlenk tube was sequentially added $Bu_3N$ (2.80 mL, 11.8 mmol, 2.0 eq.), $Pd(PPh_3)_4$ (829 mg, 720 $\mu$mol, 12 mol-%) and LiCl (279 mg, 6.58 mmol, 1.1 eq.; previously dried *in vacuo* at 200 °C overnight). $H_2SO_4$ (1.00 mL, 96% w/w,

18.0 mmol, 3.0 eq.) was placed in a 50 mL Schlenk tube. Both Schlenk tubes were connected with each other by a plastic tube (1.5 cm outer diameter, 0.2 cm thickness). The septa on both Schlenk tubes were sealed with Teflon® tape, Parafilm® and secured with springs (see Figure 6.1[93]). A blast shield was placed in front of the reaction setup as a precautionary measure. Both Schlenk tubes were then heated to 75 °C, at which point HCOOH (710 $\mu$L, 95% w/w, 17.9 mmol, 3.0 eq.) was added to the stirred $H_2SO_4$ *via* syringe. After 23 h, both Schlenk tubes were cooled to room temperature and the reaction mixture was filtered through a silica pad, which was washed with EtOAc. The solvents were removed *in vacuo*, and the crude product was purified by flash column chromatography (silica, EtOAc/hexanes = 1:10 to 1:7 to 1:5), yielding butenolide **103** (1.90 g, 5.85 mmol, 98%) as a colorless oil. In a second experiment on the same scale, vinyl triflate **121** (2.67 g, 5.98 mmol, 1.0 eq.) was converted to butenolide **103** (1.87 g, 5.76 mmol) in a yield of 96%.


**Figure 6.1** Carbonylation setup.

*Note: carbonylation precursor **121** and butenolide **103** are co-polar on TLC, but stain differently with p-anisaldehyde (**121**: dark violet, **103**: green)*

$R_f$ = 0.26 (EtOAc/hexanes = 1:7).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 4.73 (ddd, $^2J_{11A/11B}$ = 17.1 Hz, $J$ = 3.3 Hz, 1.0 Hz, 1H, 11-$H_A$) 4.66 (ddd, $^2J_{11B/11A}$ = 17.1 Hz, $^4J$ = 2.6 Hz, $J$ = 1.5 Hz, 1H, 11-$H_B$), 3.52 (dd, $^2J_{8A/8B}$ = 10.0 Hz, $^3J_{8A/7}$ = 6.5 Hz, 1H, 8-$H_A$), 3.48 (dd, $^2J_{8B/8A}$ = 10.0 Hz, $^3J_{8B/7}$ = 8.3 Hz, 1H, 8-$H_B$), 2.87–2.70 (m, 2H, 6-H, 7-H), 2.51 ($m_C$, 1H, 3-H), 1.98 ($m_C$, 1H, 4-$H_A$), 1.78 ($m_C$, 1H, 5-$H_A$), 1.43 ($m_C$, 1H, 5-$H_B$), 1.28 ($m_C$, 1H, 4-$H_B$), 1.11 (d, $^3J_{10/3}$ = 7.1 Hz, 3H, 10-H), 0.88 (s, 9H, 16-H), 0.65 (d, $^3J_{9/7}$ = 6.9 Hz, 3H, 9-H), 0.05 (s, 3H, 13-H)*, 0.04 (s, 3H, 14-H)* ppm.

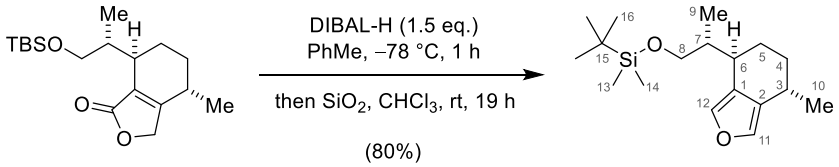
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 173.7 (C-12), 166.3 (C-2), 127.7 (C-1), 70.0 (C-11), 66.0 (C-8), 34.1 (C-7), 33.4 (C-6), 30.9 (C-4), 30.5 (C-3), 26.1 (C-16), 21.4 (C-5), 18.8 (C-10), 18.4 (C-15), 11.5 (C-9), –5.2 (C-13)*, –5.3 (C-14)* ppm.

ESI-MS for $C_{18}H_{32}O_3SiNa^+$ [$(M+Na)^+$]: calcd. 347.2013
found 347.2018.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2954 (s), 2928 (s), 2855 (s), 1751 (s), 1661 (w), 1462 (w), 1256 (w), 1088 (w), 1020 (w), 835 (w), 775 (w).

$[\alpha]_D^{24}$ = +44.1 (*c* 0.58, $CH_2Cl_2$).

The NMR and IR spectroscopic data matched those reported previously.[43] The carbonylation setup was a modified variant of Ryu and coworker's protocol.[58]




**103**

**153**

$C_{18}H_{32}O_2Si$

$M$ = 308.54 g/mol

**Furan 153**. To a stirred solution of butenolide **103** (514 mg, 1.58 mmol, 1.0 eq.) in PhMe (15 mL) was slowly added DIBAL-H (1.60 mL of a 1.2M solution in toluene, 1.90 mmol, 1.2 eq.) at –78 °C. After 30 min, further DIBAL-H (0.20 mL of a 1.2M solution in toluene, 0.24 mmol, 0.15 eq.) was added, and this was repeated another 5 min later. Stirring was continued for 15 min, at which point the reaction was quenched by addition of a 1:1 mixture of saturated aqueous Rochelle salt/$H_2O$ (30 mL), diluted with $CH_2Cl_2$ (30 mL) and stirred vigorously until no emulsion was present. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over $Na_2SO_4$, filtered and the solvent was removed *in vacuo*, to yield a crude lactol (491 mg of a colorless oil), which was used without further purification.

To a solution of the resulting crude lactol in $CHCl_3$ (25 mL) was added silica (3.17 g), and the suspension was stirred for 19 h at rt. The silica was filtered off and the filtrate was evaporated to dryness. The crude product was purified by flash column chromatography (silica, EtOAc/*n*-pentane = 1:10) to obtain pure furan **153** (390 mg, 1.26 mmol, 80%) as a clear, colorless oil.

$R_f$ = 0.89 (EtOAc/*n*-pentane = 1:10).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.18 (dd, $^4J_{11/12}$ = $^4J_{11/3}$ = 1.6 Hz, 1H, 11-H), 7.14 (dd, $^4J_{12/11}$ = $^4J_{12/6}$ = 1.6 Hz, 1H, 12-H), 3.58 (dd, $^2J_{8A/8B}$ = 10.0, $^3J_{8A/7}$ = 7.6 Hz, 1H, 8-$H_A$), 3.54 (dd, $^2J_{8B/8A}$ = 10.0, $^3J_{8B/7}$ = 6.5 Hz, 1H, 8-$H_B$), 2.92 ($m_C$, 1H, 6-H), 2.58 ($m_C$, 1H, 3-H), 2.08 ($m_C$, 1H, 7-H), 1.89 ($m_C$, 1H, 4-$H_A$), 1.73 ($m_C$, 1H, 5-$H_A$), 1.31 ($m_C$, 1H, 5-$H_B$), 1.23–1.13 (m, 1H, 4-$H_B$), 1.20 (d, $^3J_{10/3}$ = 6.7 Hz, 3H, 10-H), 0.90 (s, 9H, 16-H), 0.79 (d, $^3J_{9/7}$ = 7.0 Hz, 3H, 9-H), 0.06 ($m_C$, 6H, 13-H, 14-H) ppm.

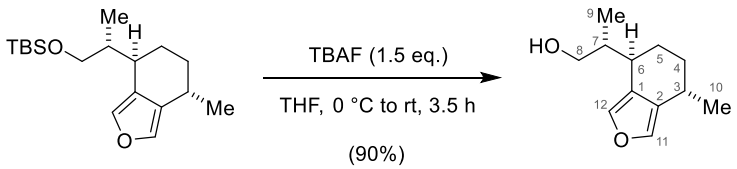
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 137.4 (C-11)*, 137.3 (C-12)*, 128.9 (C-2), 125.2 (C-1), 66.3 (C-8), 39.3 (C-7), 33.6 (C-6), 32.9 (C-4), 28.0 (C-3), 26.1 (C-16), 23.5 (C-5), 21.3 (C-10), 18.5 (C-15), 12.1 (C-9), –5.1 (C-13)**, –5.2 (C-14)** ppm.

EI-MS for $C_{18}H_{32}O_2Si^{+\cdot}$ [$M^{+\cdot}$]: calcd. 308.2166
found 308.2159.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2956 (s), 2928 (s), 2857 (s), 1472 (w), 1462 (w), 1256 (w), 1112 (w), 1091 (m), 1045 (w), 837 (m), 776 (m).

$[\alpha]_D^{23}$ = +55.9 (*c* 0.57, $CH_2Cl_2$).

The analytical data from NMR spectroscopy as well as EI-MS matched those reported previously.[43]




**153** **89**

$C_{12}H_{18}O_2$
*M* = 194.27 g/mol

**Alcohol 89**. To a stirred solution of furan **153** (390 mg, 1.26 mmol, 1.0 eq.) in THF (12 mL) was added TBAF (1.60 mL of a 1.0M solution in THF, 1.60 mmol, 1.3 eq.) at 0 °C. After stirring for 2 h, further TBAF (0.25 mL of a 1.0M solution in THF, 0.25 mmol, 0.2 eq.) was added to the mixture. After another 1.5 h, the mixture was diluted with $Et_2O$ (10 mL) and the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over $Na_2SO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (silica, EtOAc/*n*-pentane = 1:20 to 1:10 to 1:4) afforded volatile alcohol **89** (220 mg, 1.13 mmol, 90%) as a cloudy, colorless oil.

$R_f$ = 0.27 (EtOAc/*n*-pentane = 1:4).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.18 (dd, $^4J_{11/12}$ = $^4J_{11/3}$ = 1.6 Hz, 1H, 11-H), 7.15 (dd, $^4J_{12/11}$ = $^4J_{12/6}$ = 1.6 Hz, 1H, 12-H), 3.66 (dd, $^2J_{8A/8B}$ = 10.6 Hz, $^3J_{8A/7}$ = 7.3 Hz, 1H, 8-$H_A$), 3.60 (dd, $^2J_{8B/8A}$ = 10.6 Hz, $^3J_{8B/7}$ = 6.7 Hz, 1H, 8-$H_B$), 2.90 ($m_C$, 1H, 6-H), 2.58 ($m_C$, 1H, 3-H), 2.10 ($m_C$, 1H, 7-H), 1.89 ($m_C$, 1H, 4-$H_A$), 1.75 ($m_C$, 1H, 5-$H_A$), 1.43 (br s, 1H, *O*H), 1.35 ($m_C$, 1H, 5-$H_B$), 1.24–1.13 (m, 1H, 4-$H_B$), 1.20 (d, $^3J_{10/3}$ = 6.7 Hz, 3H, 10-H), 0.85 (d, $^3J_{9/7}$ = 7.0 Hz, 3H, 9-H) ppm.

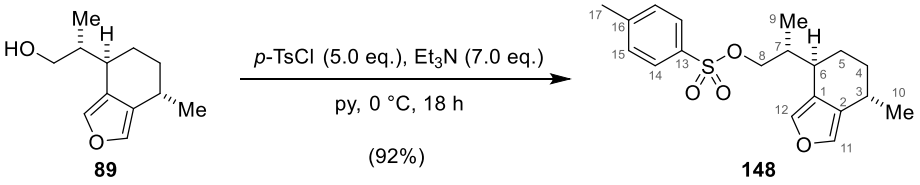
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 137.5 (C-11), 137.3 (C-12), 128.9 (C-2), 124.7 (C-1), 66.4 (C-8), 39.5 (C-7), 33.9 (C-6), 32.8 (C-4), 28.0 (C-3), 23.8 (C-5), 21.3 (C-10), 12.3 (C-9) ppm.

EI-MS for $C_{12}H_{18}O_2^{+\cdot}$ [$M^{+\cdot}$]: calcd. 194.1301
found 194.1294.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3344 (br s), 2957 (s), 2926 (s), 2871 (s), 1538 (w), 1454 (w), 1375 (w), 1130 (w), 1043 (s), 891 (w), 779 (w).

$[\alpha]_D^{24}$ = +94.2 (*c* 0.83, $CH_2Cl_2$).

The analytical data from $^{13}C$ NMR and IR spectroscopy as well as EI-MS matched those reported previously.[43]




**Tosylate 148**. To a stirred solution of alcohol **89** (220 mg, 1.13 mmol, 1.0 eq.) in pyridine (2.7 mL) were added $Et_3N$ (660 $\mu$L, 4.74 mmol, 4.2 eq.) and a solution of *p*-TsCl (648 mg, 3.40 mmol, 3.0 eq.) in pyridine (1.0 mL). The red, cloudy mixture was stirred for 12 h at 0 °C, then further $Et_3N$ (440 $\mu$L, 3.16 mmol, 2.8 eq.) and a solution of *p*-TsCl (432 mg, 2.26 mmol, 2.0 eq.) in pyridine (1.0 mL) were added. After 6 h the mixture was poured in 1.0M aqueous HCl (100 mL), to which was added $Et_2O$ (30 mL). After vigorous stirring, the layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (30 mL), dried over $Na_2SO_4$, filtered and evaporated to dryness. Purification by flash column chromatography (silica, EtOAc/*n*-pentane = 1:15 to 1:10 to 1:6) gave tosylate **148** (364 mg, 1.04 mmol, 92%) as a clear, colorless oil.

$R_f$ = 0.71 (EtOAc/*n*-pentane = 1:4).

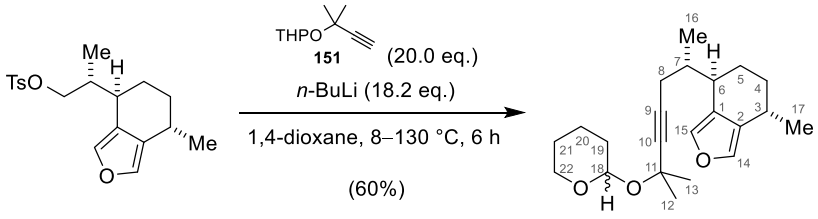
$^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.80 ($m_C$, 2H, 14-H), 7.36 ($m_C$, 2H, 15-H), 7.16 (dd, $^4J_{11/12} = {}^4J_{11/3}$ = 1.6 Hz, 1H, 11-H), 7.04 (dd, $^4J_{12/11} = {}^4J_{12/6}$ = 1.6 Hz, 1H, 12-H), 4.01 (dd, $^2J_{8A/8B}$ = 9.7 Hz, $^3J_{8A/7}$ = 7.7 Hz, 1H, 8-$H_A$), 3.96 (dd, $^2J_{8B/8A}$ = 9.7 Hz, $^3J_{8B/7}$ = 6.5 Hz, 1H, 8-$H_B$), 2.81 ($m_C$, 1H, 6-H), 2.52 ($m_C$, 1H, 3-H), 2.46 (s, 3H, 17-H), 2.23 ($m_C$, 1H, 7-H), 1.82 ($m_C$, 1H, 4-$H_A$), 1.58–1.51 (m, 1H, 5-$H_A$), 1.24 ($m_C$, 1H, 5-$H_B$), 1.18 (d, $^3J_{10/3}$ = 6.7 Hz, 3H, 10-H), 1.10 ($m_C$, 1H, 4-$H_B$), 0.81 (d, $^3J_{9/7}$ = 7.0 Hz, 3H, 9-H) ppm.

$^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ = 144.9 (C-16), 137.7 (C-11), 137.2 (C-12), 133.2 (C-13), 130.0 (C-15), 128.7 (C-2), 128.1 (C-14), 123.7 (C-1), 73.1 (C-8), 36.3 (C-7), 33.5 (C-6), 32.4 (C-4), 27.8 (C-3), 23.5 (C-5), 21.8 (C-17), 21.2 (C-10), 12.0 (C-9) ppm.

EI-MS for $C_{19}H_{24}O_4S^{+\cdot}$ [$M^{+\cdot}$]: calcd. 348.1390
found 348.1395.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2957 (s), 2927 (s), 2870 (w), 1598 (w), 1454 (w), 1359 (s), 1189 (s), 1176 (s), 1098 (w), 1042 (w), 974 (m), 960 (m), 892 (w), 841 (w), 814 (w), 792 (w), 667 (w).

$[\alpha]_D^{23}$ = +42.8 (*c* 1.47, $CH_2Cl_2$).




**Alkyne 160**. To a stirred solution of dimethylpropargyl THP ether **151** (2.33 g, 13.8 mmol, 20.0 eq.) in 1,4-dioxane (2 mL) in a pressure tube was slowly added *n*-BuLi (5.0 mL of a 2.5M solution in hexanes, 12.6 mmol, 18.2 eq.) at 8 °C. After stirring for 30 min at rt, a solution of tosylate **148** (241 mg, 690 $\mu$mol, 1.0 eq.) in 1,4-dioxane (1.5 mL) was added. The pressure tube was sealed, heated to 130 °C and kept at that temperature for 4.5 h. The cooled, dark brown mixture was diluted with hexanes (10 mL) and quenched with $H_2O$ (20 mL). The layers were separated and the aqueous layer was extracted with hexanes (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over $Na_2SO_4$, filtered and evaporated to dryness. Excess dimethylpropargyl THP ether **151** was removed *in vacuo* ($10^{-1}$ to $10^{-2}$ mbar) at 40 °C overnight. Alkyne **160** (144 mg, 420 $\mu$mol, 60%) was obtained from flash column chromatography (silica, EtOAc/hexanes = 1:30 to 1:20 to 1:15 to 1:5) as a clear, orange oil. The product, consisting of both C-18 epimers, was directly used for the subsequent THP deprotection.

*Note: Alkyne **160** (both epimers) and dimethylpropargyl THP ether **151** are co-polar on TLC, but stain differently with p-anisaldehyde.*

$R_f$ = 0.56 (EtOAc/hexanes = 1:7).

$^1$H NMR ($CDCl_3$, 400 MHz, both diastereomers quoted): $\delta$ = 7.19–7.17 (m, 1H, 14-H), 7.17–7.15 (m, 1H, 15-H), 5.09–5.00 (m, 1H, 18-H), 3.99–3.88 (m, 1H, 22-$H_A$), 3.53–3.41 (m, 1H, 22-$H_B$), 2.86 ($m_C$, 1H, 6-H), 2.57 ($m_C$, 1H, 3-H), 2.27–2.22 (m, 2H, 8-$H_A$, 8-$H_B$), 2.07 ($m_C$, 1H, 7-H), 1.94–1.64 (m, 4H, 4-$H_A$, 5-$H_A$, 19-$H_A$, 20-$H_A$), 1.59–1.44 (m, 4H, 19-$H_B$, 20-$H_B$, 21-$H_A$, 21-$H_B$), 1.51 (s, 3H, 12-H)*, 1.47 (s, 3H, 13-H)*, 1.37–1.26 (m, 1H, 5-$H_B$), 1.23–1.12 (m, 1H, 4-$H_B$), 1.20 (d, $^3J_{17/3}$ = 6.7 Hz, 3H, 17-H), 0.91 (d, $^3J_{16/7}$ = 6.9 Hz, 3H, 16-H) ppm.

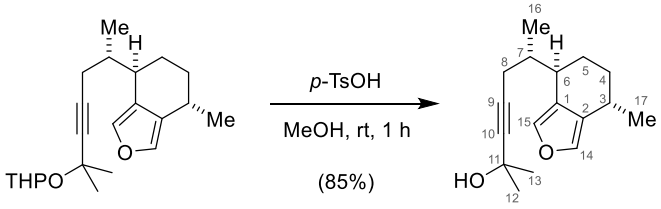
$^{13}$C NMR ($CDCl_3$, 100 MHz, both diastereomers quoted): $\delta$ = 137.5 (2C, C-14), 137.4 (2C, C-15), 128.8 (2C, C-2), 124.7 (2C, C-1), 96.4 (2C, C-18), 84.0 (2C, C-10), 83.4 (2C, C-9), 71.6 (2C, C-11), 63.7 (2C, C-22), 36.7 (C-7), 36.6 (C-7), 36.3 (2C, C-6), 32.7 (2C, C-4), 32.3 (C-19), 32.2 (C-19), 31.2 (2C,

C-12)*, 30.3 (2C, C-13)*, 27.9 (2C, C-3), 25.5 (2C, C-21), 24.2 (2C, C-8), 23.7 (C-5), 23.6 (C-5), 21.3 (2C, C-17), 20.9 (2C, C-20), 15.3 (2C, C-16) ppm.

EI-MS for $C_{22}H_{32}O_3^{+\cdot}$ [$M^{+\cdot}$]: calcd. 344.2346
found 344.2352.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2932 (m), 2869 (m), 1454 (w), 1378 (w), 1259 (w), 1159 (w), 1126 (s), 1109 (w), 1075 (w), 1022 (s), 985 (s), 779 (w).

Since alkyne **160** consisted of a mixture of 2 diastereomers, no specific optical rotation was determined.




**160** **159**

$C_{17}H_{24}O_2$
$M$ = 260.38 g/mol

**Propargylic alcohol 159**. To a stirred solution of alkyne **160** (144 mg, 420 $\mu$mol, 1.0 eq.) in MeOH (4.0 mL) was added *p*-TsOH (16 mg, 80 $\mu$mol, 20 mol-%), and the resulting mixture was stirred for 1 h at rt. $H_2O$ (4 mL) and $Et_2O$ (5 mL) were then added, the layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried over $Na_2SO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography (silica, EtOAc/*n*-pentane = 1:20 to 1:15 to 1:10), yielding propargylic alcohol **159** (92 mg, 350 $\mu$mol, 85%) as a yellow oil.

$R_f$ = 0.22 (EtOAc/*n*-pentane = 1:10).

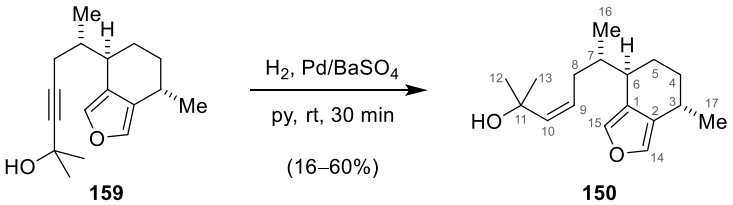
$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.18 (dd, $^4J_{14/15}$ = $^4J_{14/3}$ = 1.6 Hz, 1H, 14-H), 7.16 (dd, $^4J_{15/14}$ = $^4J_{15/6}$ = 1.6 Hz, 1H, 15-H), 2.84 ($m_C$, 1H, 6-H), 2.57 ($m_C$, 1H, 3-H), 2.29–2.17 (m, 2H, 8-$H_A$, 8-$H_B$), 2.07 ($m_C$, 1H, 7-H), 1.94–1.86 (m, 1H, 4-$H_A$), 1.82–1.71 (m, 1H, 5-$H_A$), 1.50 (s, 6H, 12-H, 13-H), 1.37–1.25 (m, 1H, 5-$H_B$), 1.24–1.12 (m, 1H, 4-$H_B$), 1.20 (d, $^3J_{10/3}$ = 6.7 Hz, 3H, 17-H), 0.91 (d, $^3J_{16/7}$ = 6.9 Hz, 3H, 16-H) ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 137.5 (2C, C-14, C-15), 128.8 (C-2), 124.7 (C-1), 86.4 (C-10), 81.7 (C-9), 65.5 (C-11), 36.6 (C-7), 36.4 (C-6), 32.7 (C-4), 31.9 (2C, C-12, C-13), 27.9 (C-3), 24.0 (C-8), 23.6 (C-5), 21.3 (C-17), 15.3 (C-16) ppm.

EI-MS for $C_{17}H_{24}O_2^{+\cdot}$ [$M^{+\cdot}$]: calcd. 260.1771
found 260.1763.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3373 (br w), 2958 (s), 2928 (s), 1455 (w), 1374 (w), 1165 (w), 1043 (w), 949 (w), 886 (w).

$[\alpha]_D^{25}$ = +54.6 (*c* 0.37, $CH_2Cl_2$).




**159** **150**

$C_{17}H_{26}O_2$
*M* = 262.39 g/mol

**Allylic alcohol 150**. Through a suspension of Pd/$BaSO_4$ (5% Pd basis, 2 mg) in pyridine (1 mL) $H_2$ was bubbled for 5 min, turning the suspension from ocher to dark grey. The mixture was kept under a positive pressure of $H_2$, and a solution of propargylic alcohol **159** (10 mg, 40 $\mu$mol) in pyridine (0.5 mL) was added. After 30 min, the mixture was filtered through a silica pad, which was then washed with a 1:4 mixture of EtOAc/hexanes (10 mL). The filtrate was washed with 1.0M aqueous HCl (5 mL), $H_2O$ (5 mL), saturated aqueous NaCl (5 mL), dried over $Na_2SO_4$, filtered and evaporated to dryness. The crude product was purified *via* flash column chromatography (silica, EtOAc/*n*-pentane = 1:20), giving allylic alcohol **150** (6 mg, 20 $\mu$mol, 60%) as a clear, colorless oil. In a second experiment on a larger scale, compound **159** (80 mg, 0.31 mmol) was converted to allylic alcohol **150** (13 mg, 50 $\mu$mol) in a low yield of 16%.

$R_f$ = 0.44 (EtOAc/*n*-pentane = 1:4).

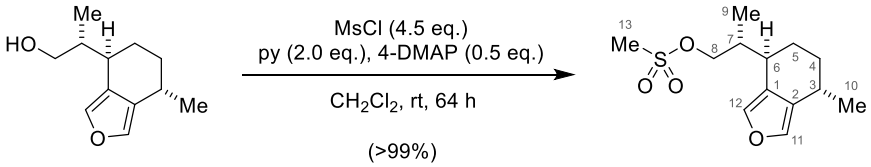
$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.18 (dd, $^4J_{14/15}$ = $^4J_{14/3}$ = 1.6 Hz, 1H, 14-H), 7.14 (dd, $^4J_{15/14}$ = $^4J_{15/6}$ = 1.6 Hz, 1H, 15-H), 5.53 (ddd, $^3J_{10/9}$ = 11.9, $^4J_{10/8A}$ = $^4J_{10/8B}$ = 1.6 Hz, 1H, 10-H), 5.37 (ddd, $^3J_{9/10}$ = 11.9, $^3J_{9/8A}$ = $^3J_{9/8B}$ = 7.3 Hz, 1H, 9-H), 2.73 ($m_C$, 1H, 6-H), 2.57 ($m_C$, 1H, 3-H), 2.47–2.30 (m, 2H, 8-$H_A$, 8-$H_B$), 1.96–1.86 (m, 2H, 4-$H_A$, 7-H), 1.78 ($m_C$, 1H, 5-$H_A$), 1.39–1.28 (m, 1H, 5-$H_B$), 1.38 (s, 6H, 12-H, 13-H), 1.22–1.10 (m, 1H, 4-$H_B$), 1.20 (d, $^3J_{17/3}$ = 6.7 Hz, 3H, 17-H), 0.85 (d, $^3J_{16/7}$ = 6.9 Hz, 3H, 16-H) ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 137.6 (C-10), 137.4 (C-14)*, 137.3 (C-15)*, 130.2 (C-9), 128.9 (C-2), 125.3 (C-1), 71.9 (C-11), 37.7 (C-7), 37.2 (C-6), 33.0 (C-8)**, 32.9 (C-4)**, 31.4 (2C, C-12, C-13), 28.1 (C-3), 23.7 (C-5), 21.3 (C-17), 15.2 (C-16) ppm.

EI-MS for $C_{17}H_{16}O_2^{+\cdot}$ [$M^{+\cdot}$]: calcd. 262.1927
found 262.1938.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 3379 (br w), 2958 (s), 2927 (s), 2868 (s), 1456 (w), 1374 (w), 1128 (w), 1043 (w), 955 (w), 890 (w), 778 (w).

$[\alpha]_D^{22}$ = +66.6 (*c* 0.65, $CH_2Cl_2$).




**89** **96**

$C_{13}H_{20}O_4S$
*M* = 272.36 g/mol

**Mesylate 96**. To a stirred solution of alcohol **89** (20 mg, 0.10 mmol, 1.0 eq.) in $CH_2Cl_2$ (2 mL) were sequentially added pyridine (16 $\mu$L, 0.20 mmol, 2.0 eq.), MsCl (12 $\mu$L, 0.16 mmol, 1.6 eq.) and 4-DMAP (2 mg, 20 $\mu$mol, 20 mol-%). Further MsCl (12 $\mu$L, 0.16 mmol, 1.6 eq.) and 4-DMAP (2 mg, 20 $\mu$mol, 20 mol-%) were added after 25 h. Additional portions of MsCl (12 $\mu$L, 0.16 mmol, 1.6 eq.) and 4-DMAP (1 mg, 10 $\mu$mol, 10 mol-%) were added 24 h later. Stirring was continued for another 15 h, at which point the mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and evaporated to dryness. Purification *via* flash column chromatography afforded mesylate **96** (28 mg, 0.10 mmol, >99%) as a clear, colorless oil.

$R_f$ = 0.36 (EtOAc/pentane = 1:4).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.19 (dd, $^4J_{11/12}$ = $^4J_{11/3}$ = 1.6 Hz, 1H, 11-H), 7.16 (dd, $^4J_{12/11}$ = $^4J_{12/6}$ = 1.6 Hz, 1H, 12-H), 4.23 (dd, $^2J_{8A/8B}$ = 9.7 Hz, $^3J_{8A/7}$ = 7.4 Hz, 1H, 8-H$_A$), 4.16 (dd, $^2J_{8B/8A}$ = 9.7 Hz, $^3J_{8B/7}$ = 6.8 Hz, 1H, 8-H$_B$), 3.02 (s, 3H, 13-H), 2.91 (m$_C$, 1H, 6-H), 2.58 (m$_C$, 1H, 3-H), 2.34 (m$_C$, 1H, 7-H), 1.91 (m$_C$, 1H, 4-H$_A$), 1.77 (m$_C$, 1H, 5-H$_A$), 1.38 (m$_C$, 1H, 5-H$_B$), 1.25–1.14 (m, 1H, 4-H$_B$), 1.21 (d, $^3J_{10/3}$ = 6.7 Hz, 3H, 10-H), 0.94 (d, $^3J_{9/7}$ = 7.0 Hz, 3H, 9-H) ppm.

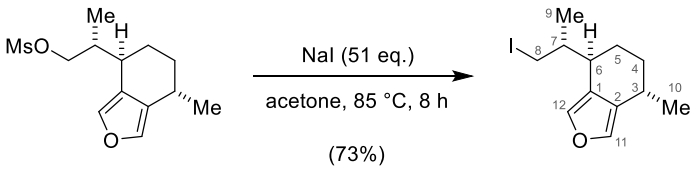
$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 137.8 (C-11), 137.3 (C-12), 128.7 (C-2), 123.6 (C-1), 72.5 (C-8), 37.5 (C-13), 36.6 (C-7), 33.8 (C-6), 32.5 (C-4), 27.8 (C-3), 23.9 (C-5), 21.2 (C-10), 12.3 (C-9) ppm.

EI-MS for $C_{13}H_{20}O_4S^{+\cdot}$ [$M^{+\cdot}$]: calcd. 272.1077
found 272.1093.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2958 (s), 2929 (s), 2870 (m), 1457 (w), 1354 (m), 1175 (s), 1042 (w), 958 (m), 892 (w), 821 (w).

$[\alpha]_D^{23}$ = +44.6 (*c* 0.77, $CH_2Cl_2$).

The NMR spectroscopic data matched those reported previously.[43]




**96** **90**

$C_{12}H_{17}IO$

*M* = 304.17 g/mol

**Iodide 90**. To a stirred solution of mesylate **96** (27 mg, 0.10 mmol, 1.0 eq.) in acetone (4 mL) in a pressure tube was added NaI (760 mg, 5.07 mmol, 51 eq.) in one portion, and the mixture was heated to 85 °C. After 8 h, the mixture was cooled to rt and $H_2O$ (10 mL) and $Et_2O$ (5 mL) were added. The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried over $Na_2SO_4$, filtered and evaporated to dryness. The crude product was purified by flash column chromatography (silica, EtOAc/*n*-pentane = 1:10), giving iodide **90** (22 mg, 73 $\mu$mol, 73%) as a light sensitive, colorless oil.

$R_f$ = 0.83 (EtOAc/*n*-pentane = 1:10).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 7.18 (dd, $^4J_{11/12}$ = $^4J_{11/3}$ = 1.6 Hz, 1H, 11-H), 7.15 (dd, $^4J_{12/11}$ = $^4J_{12/6}$ = 1.6 Hz, 1H, 12-H), 3.26 (dd, $^2J_{8A/8B}$ = 9.8 Hz, $^3J_{8A/7}$ = 7.1 Hz, 1H, 8-$H_A$), 3.23 (dd, $^2J_{8B/8A}$ = 9.8 Hz, $^3J_{8B/7}$ = 7.1 Hz, 1H, 8-$H_B$), 2.95 ($m_C$, 1H, 6-H), 2.57 ($m_C$, 1H, 3-H), 2.12 ($m_C$, 1H, 7-H), 1.94–1.87 (m, 1H, 4-$H_A$), 1.79–1.71 (m, 1H, 5-$H_A$), 1.36–1.18 (m, 2H, 4-$H_B$, 5-$H_B$), 1.21 (d, $^3J_{10/3}$ = 6.7 Hz, 3H, 10-H), 0.99 (d, $^3J_{9/7}$ = 6.9 Hz, 3H, 9-H) ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 137.6 (C-11), 137.4 (C-12), 128.7 (C-2), 124.2 (C-1), 39.8 (C-7), 36.8 (C-6), 32.4 (C-4), 27.9 (C-3), 23.3 (C-5), 21.3 (C-10), 16.1 (C-9), 13.6 (C-8) ppm.

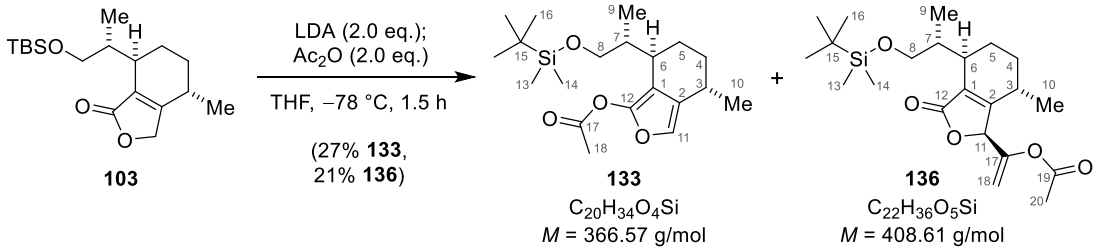
EI-MS for $C_{12}H_{17}IO^{+\cdot}$ [$M^{+\cdot}$]: calcd. 304.0319

found 304.0321.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2958 (s), 2928 (s), 2855 (m), 1454 (w), 1376 (w), 1194 (w), 1130 (w), 1044 (w), 889 (w), 782 (w).

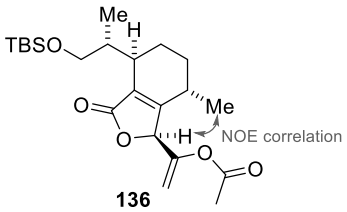
$[\alpha]_D^{25}$ = +52.3 (*c* 0.40, $CH_2Cl_2$).

The analytical data from NMR and IR spectroscopy as well as EI-MS matched those reported previously.[43]




**Acetate 133**. An LDA stock solution (0.3M in THF) was prepared as follows: To a stirred solution of DIPA (degassed by three freeze-pump-thaw cycles; 160 $\mu$L, 1.16 mmol, 7.7 eq.) in THF (3.4 mL; degassed by three freeze-pump-thaw cycles) was added *n*-BuLi (460 $\mu$L of a 2.5M solution in hexanes, 1.16 mmol, 7.7 eq.) at −78 °C, and the resulting mixture was stirred for 15 min.

To an aliquot of the prepared LDA solution (1.1 mL, 0.31 mmol, 2.0 eq.) was added a solution of butenolide **103** (50 mg, 0.15 mmol, 1.0 eq.) in THF (0.4 mL; previously degassed by 3 freeze-pump-thaw cycles) at −78 °C. After 30 min, $Ac_2O$ (29 $\mu$L, 0.31 mmol, 2.0 eq.) was added and stirring was continued at −78 °C for 1 h. The cooling bath was removed, and to the solution were added saturated aqueous $NH_4Cl$ (10 mL) and $Et_2O$ (5 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried over $Na_2SO_4$, filtered and the solvents were removed in vacuo. Purification by flash column chromatography (silica, EtOAc/*n*-pentane = 1:20 to 1:5) gave acetate **133** (15 mg, 40 $\mu$mol, 27%) as a colorless oil, as well as 15 mg of a mixture of vinyl acetate **136** and starting material, in a molar ratio of approximately 1.0:0.2 (according to $^1$H NMR spectroscopy). The yield of vinyl acetate **136** (13 mg, 30 $\mu$mol, 21%), obtained as a single diastereomer, as well as the amount of recovered starting material (**103**, 2 mg, 0.01 mmol, 4%), were calculated on the basis of $^1$H NMR peak intensities. The relative stereochemistry of C-11 of compound **136** was determined by NOE spectroscopy, as depicted aside. A third, highly nonpolar compound (13 mg, $R_f$ = 0.84 in EtOAc/*n*-pentane = 1:20) was isolated but could not be structurally elucidated by NMR spectroscopy.




Analytical data of acetate **133**:

$R_f$ = 0.44 (EtOAc/*n*-pentane = 1:20).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 6.87 (d, $^4J_{11/3}$ = 1.9 Hz, 1H, 11-H), 3.52 (dd, $^2J_{8A/8B}$ = 10.1 Hz, $^3J_{8A/7}$ = 8.1 Hz, 1H, 8-$H_A$), 3.48 (dd, $^2J_{8B/8A}$ = 10.1 Hz, $^3J_{8B/7}$ = 6.6 Hz, 1H, 8-$H_B$), 2.91 ($m_C$, 1H, 6-H), 2.51 ($m_C$, 1H, 3-H), 2.26 (s, 3H, 18-H), 2.16 ($m_C$, 1H, 7-H), 1.87–1.79 (m, 1H, 4-$H_A$), 1.75–1.66 (m, 1H,

5-$H_A$), 1.31 ($m_C$, 1H, 5-$H_B$), 1.24–1.13 (m, 1H, 4-$H_B$), 1.18 (d, $^3J_{10/3}$ = 6.7 Hz, 3H, 10-H), 0.89 (s, 9H, 16-H), 0.71 (d, $^3J_{9/7}$ = 7.0 Hz, 3H, 9-H), 0.05 ($m_C$, 6H, 13-H, 14-H) ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 168.2 (C-17), 144.9 (C-12), 130.8 (C-2), 130.5 (C-11), 106.4 (C-1), 66.1 (C-8), 36.9 (C-7), 32.6 (C-6)*, 32.5 (C-4)*, 28.6 (C-3), 26.1 (C-16), 22.4 (C-5), 20.5 (C-10)**, 20.4 (C-18)**, 18.4 (C-15), 11.2 (C-9), –5.1 (C-13)***, –5.2 (C-14)*** ppm.
*Note: The $^{13}$C NMR spectrum illustrated below contains peaks of residual n-pentane (34.3, 22.5, 14.2 ppm) and $Et_2O$ (66.0, 15.4 ppm). The $^1$H NMR spectrum shown corresponds to the solvent free product, which was obtained after prolonged drying in vacuo ($10^{-1}$ to $10^{-2}$ mbar).*

EI-MS for $C_{20}H_{34}O_4Si^{+\cdot}$ [$M^{+\cdot}$]: calcd. 366.2221
found 366.2230.

IR (ATR): $\tilde{\nu}$/cm$^{-1}$ = 2957 (s), 2929 (s), 2858 (s), 1790 (s), 1640 (w), 1563 (w), 1472 (w), 1462 (w), 1388 (w), 1370 (w), 1256 (w), 1177 (s), 1149 (w), 1115 (w), 1092 (m), 1008 (w), 837 (m), 776 (w).

$[\alpha]_D^{23}$ = +48.8 (*c* 0.50, $CH_2Cl_2$).

Analytical data of vinyl acetate **136**:

$R_f$ = 0.61 (EtOAc/*n*-pentane = 1:5).

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 5.26 ($m_C$, 1H, 11-H), 5.24 (d, $^2J_{18A/18B}$ = 2.3 Hz, 1H, 18-$H_A$), 5.22 (d, $^2J_{18B/18A}$ = 2.3 Hz, 1H, 18-$H_B$), 3.53 (dd, $^2J_{8A/8B}$ = 9.9 Hz, $^3J_{8A/7}$ = 6.4 Hz, 1H, 8-$H_A$), 3.47 (dd, $^2J_{8B/8A}$ = 9.9 Hz, $^3J_{8B/7}$ = 8.3 Hz, 1H, 8-$H_B$), 2.90–2.71 (m, 2H, 6-H, 7-H), 2.49 ($m_C$, 1H, 3-H), 2.09 (s, 3H, 20-H), 1.96 ($m_C$, 1H, 4-$H_A$), 1.82–1.71 (m, 1H, 5-$H_A$), 1.44–1.32 (m, 1H, 5-$H_B$), 1.30–1.18 (m, 1H, 4-$H_B$), 1.15 (d, $^3J_{10/3}$ = 7.1 Hz, 3H, 10-H), 0.89 (s, 9H, 16-H), 0.66 (d, $^3J_{9/7}$ = 6.9 Hz, 3H, 9-H), 0.05 (s, 3H, 13-H)*, 0.04 (s, 3H, 14-H)* ppm.

$^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ = 172.1 (C-12), 168.4 (C-19), 165.2 (C-2), 147.9 (C-1), 130.0 (C-17), 107.9 (C-18), 80.3 (C-11), 65.8 (C-8), 34.1 (C-7), 33.5 (C-6), 30.9 (C-4), 30.0 (C-3), 26.1 (C-16), 21.1 (C-20)*, 21.0 (C-5)*, 18.6 (C-10)*, 18.4 (C-15)*, 11.2 (C-9), –5.2 (C-13)**, –5.3 (C-14) ppm.

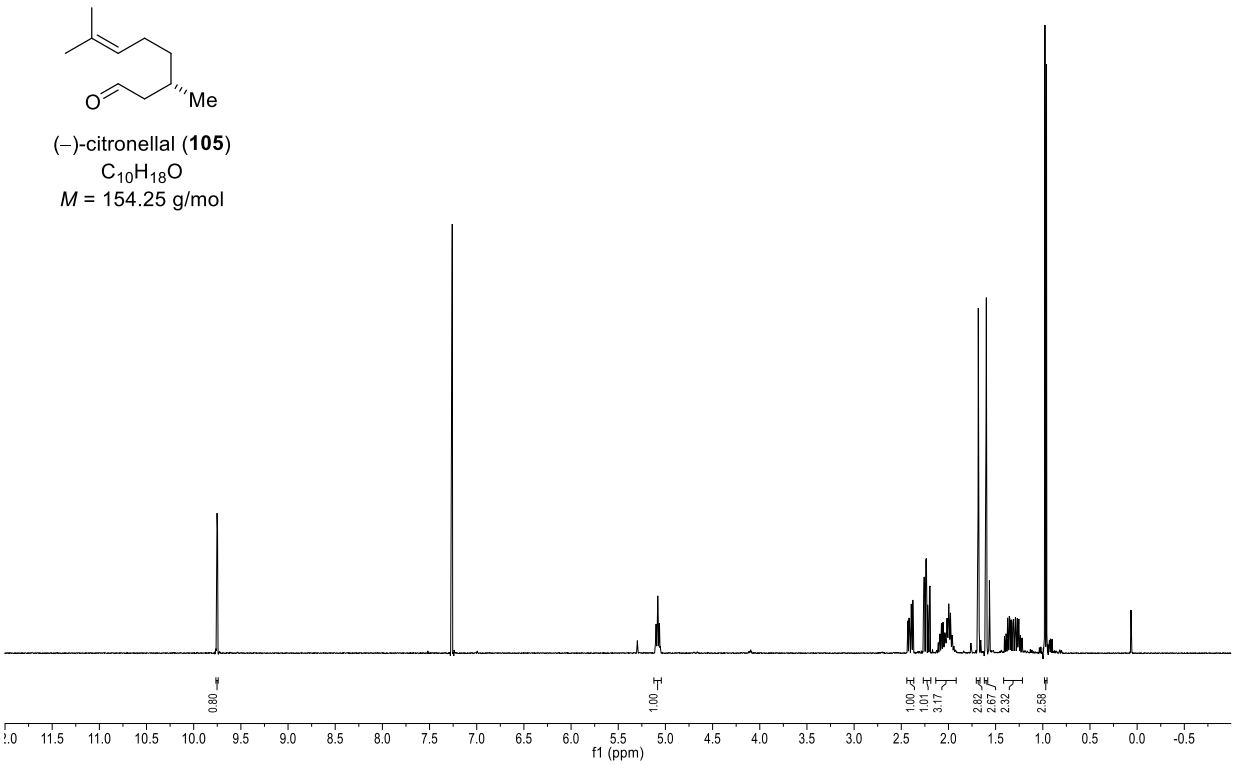
EI-MS for $C_{22}H_{36}O_5Si^{+\cdot}$ [$M^{+\cdot}$]: calcd. 408.2327
found 408.2316.

Since vinyl acetate **136** was contaminated by substrate, no IR spectrum and specific optical rotation were measured.

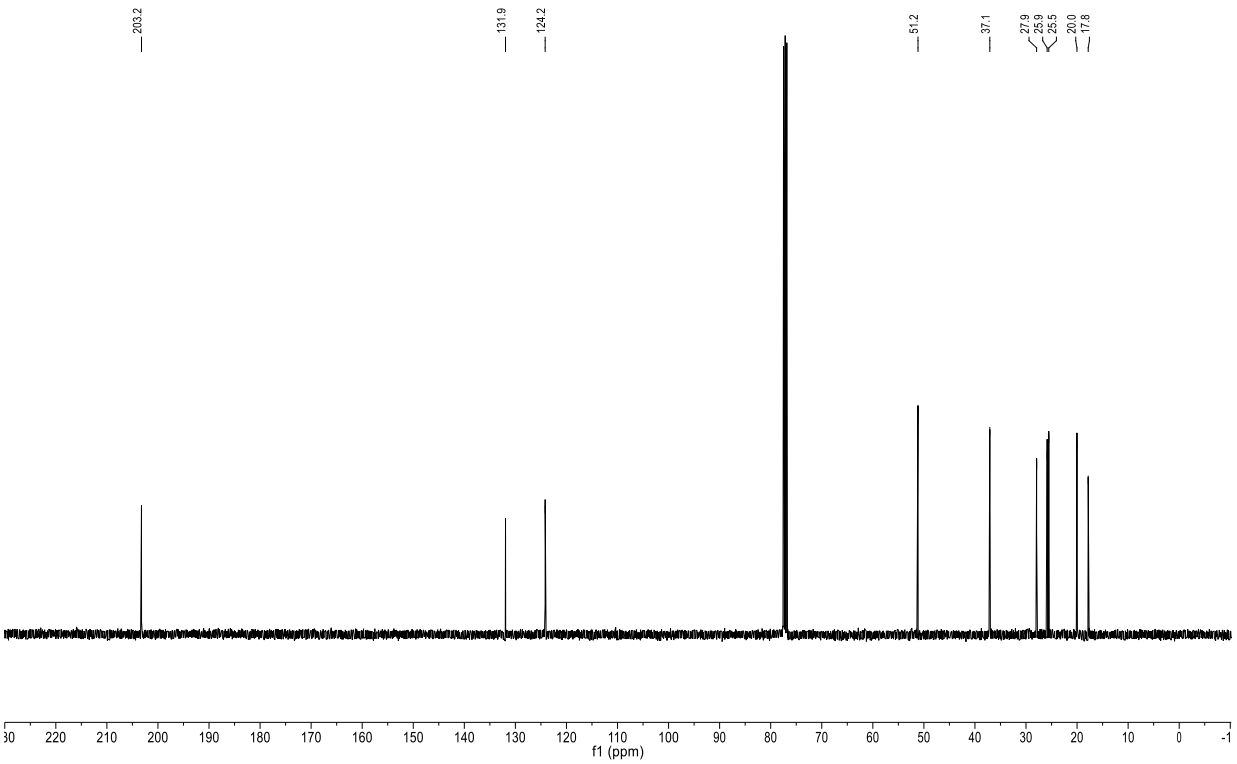
# 7 APPENDIX

## 7.1 NMR Spectra and X-Ray Crystallographic Data

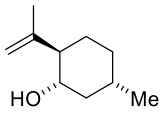
$^{1}$H NMR ($CDCl_3$, 400 MHz):




$^{13}$C NMR ($CDCl_3$, 100 MHz):



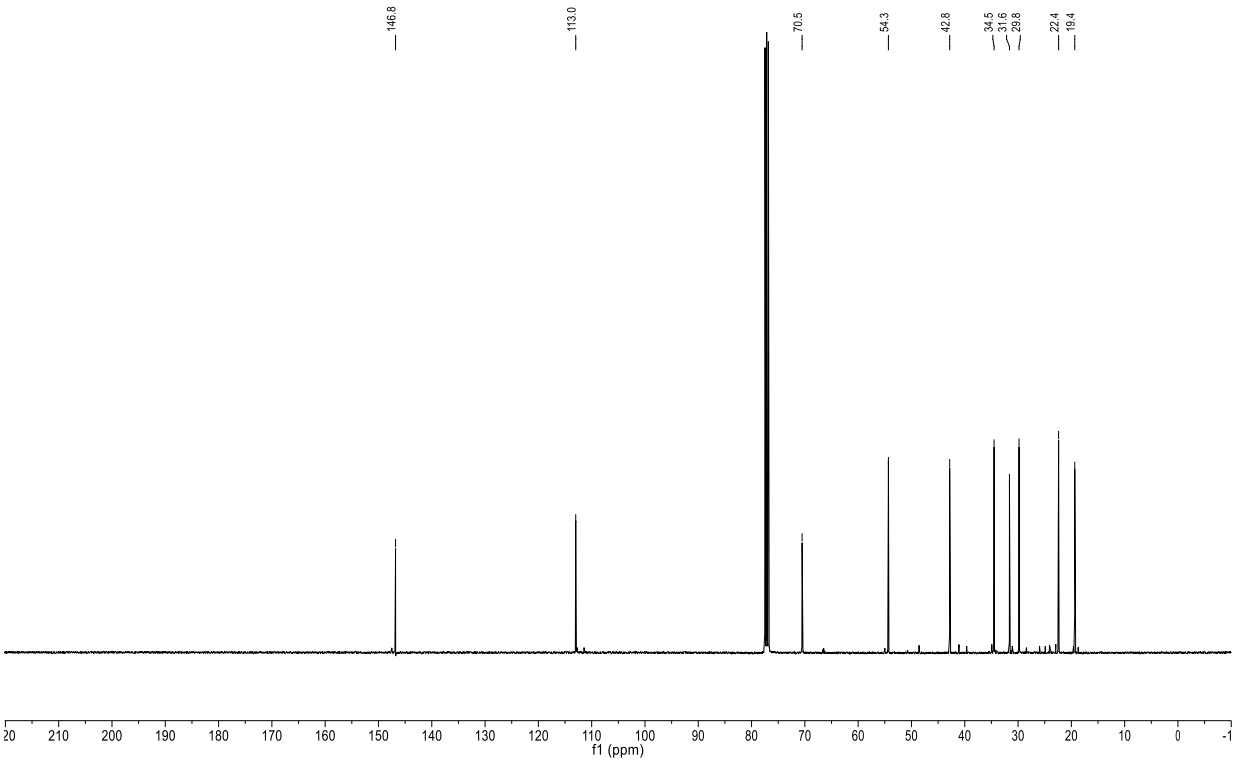
$^{1}$H NMR ($CDCl_3$, 400 MHz):



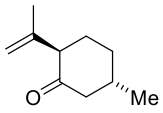

(+)-isopuegol (**107**)
$C_{10}H_{18}O$
*M* = 154.25 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



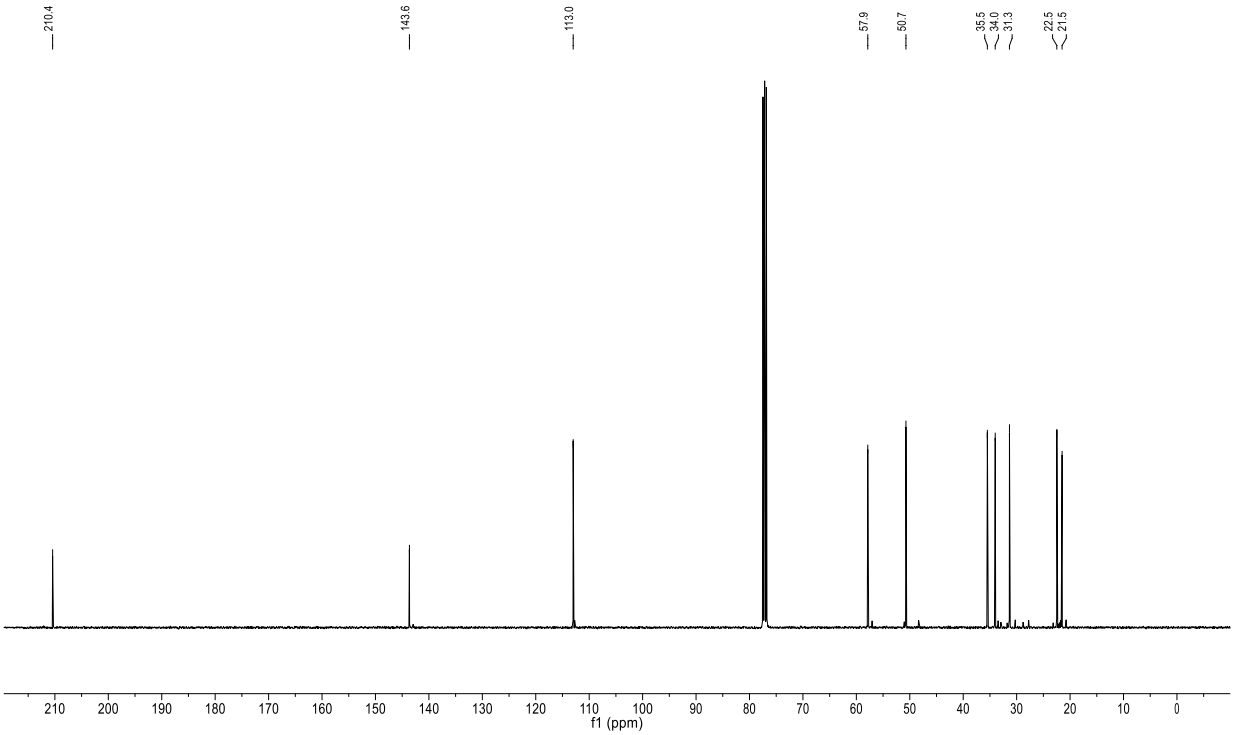
$^{1}$H NMR ($CDCl_3$, 600 MHz):



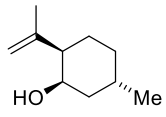

(+)-isopulegone (**108**)
$C_{10}H_{16}O$
*M* = 152.24 g/mol




$^{13}$C NMR ($CDCl_3$, 150 MHz):



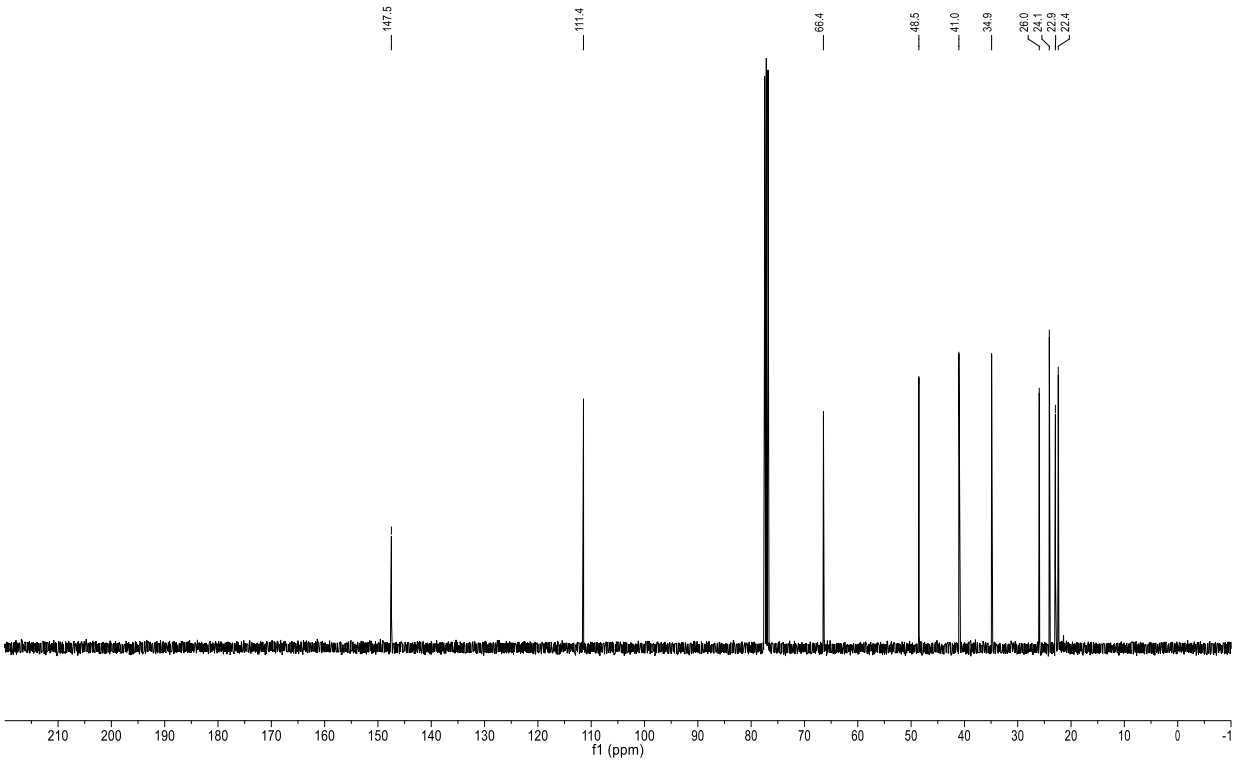
$^{1}$H NMR ($CDCl_3$, 400 MHz):



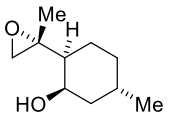

(–)-neoisopulegol (**110**)
$C_{10}H_{18}O$
*M* = 154.25 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



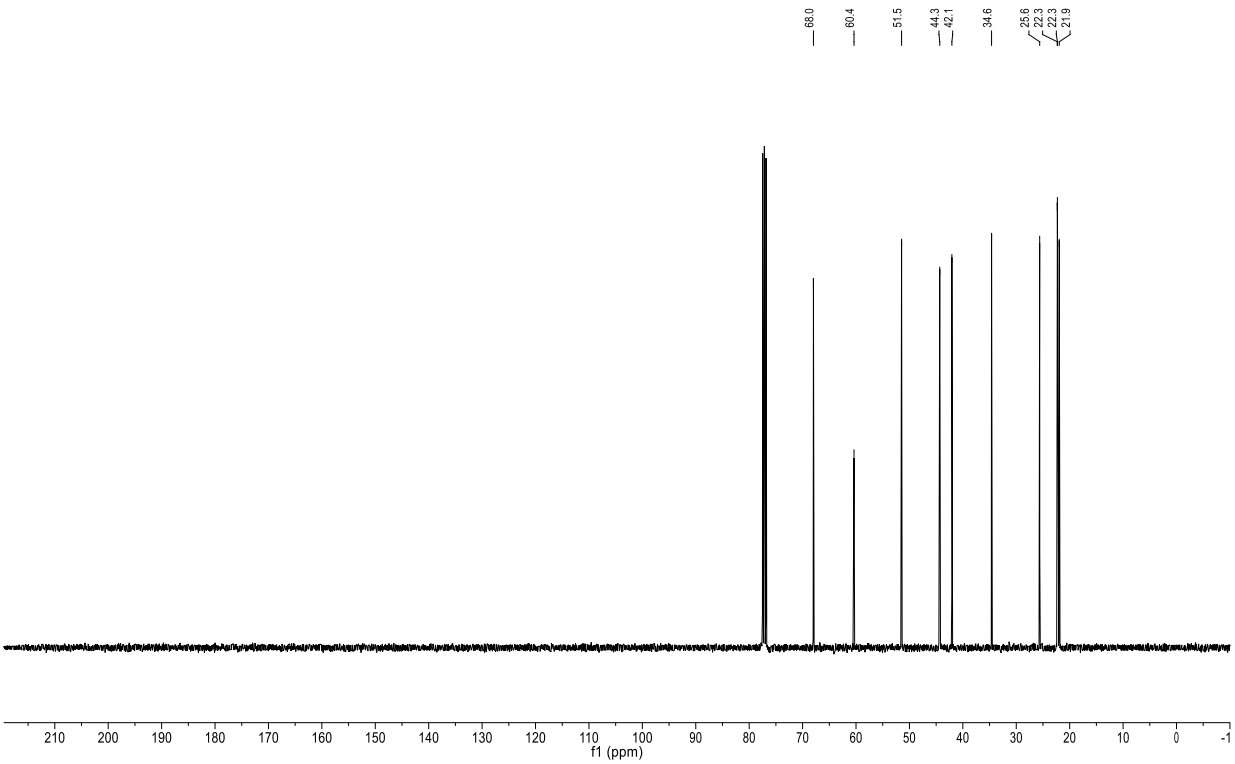

**112**

$C_{10}H_{18}O_2$

*M* = 170.25 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



X-ray crystallography (epoxide **112**):

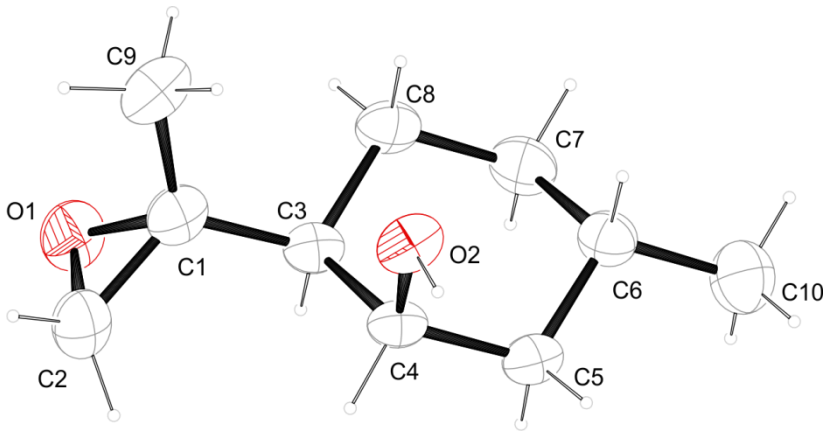
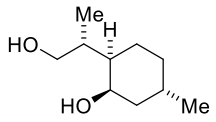



**Table 7.1** Crystallographic data for epoxide **112**.

| | |
|---|---|
| net formula | $C_{10}H_{18}O_2$ |
| $M_r$/g·mol$^{-1}$ | 170.249 |
| crystal size/mm | 0.196 × 0.157 × 0.083 |
| *T*/K | 173 |
| radiation | Mo Kα |
| diffractometer | 'Bruker D8Venture' |
| crystal system | orthorhombic |
| space group | $P2_12_12_1$ |
| *a*/Å | 6.4438(5) |
| *b*/Å | 9.6494(8) |
| *c*/Å | 15.9422(14) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| *V*/Å$^3$ | 991.27(14) |
| *Z* | 4 |
| calc. density/g·cm$^{-3}$ | 1.14079(16) |
| μ/mm$^{-1}$ | 0.077 |
| absorption correction | multi-scan |
| transmission factor range | 0.8978–0.9580 |
| refls. measured | 14309 |
| $R_{int}$ | 0.0375 |
| mean σ(*I*)/*I* | 0.0190 |
| θ range | 3.31–25.46 |
| observed refls. | 1662 |
| *x*, *y* (weighting scheme) | 0.0293, 0.2460 |
| hydrogen refinement | mixed |
| Flack parameter | 0.5(15) |
| refls in refinement | 1820 |
| parameters | 115 |
| restraints | 0 |
| $R(F_{obs})$ | 0.0356 |
| $R_w(F^2)$ | 0.0835 |
| *S* | 1.114 |
| shift/error$_{max}$ | 0.001 |
| max electron density/e Å$^{-3}$ | 0.127 |
| min electron density/e Å$^{-3}$ | −0.138 |

Flack test meaningless. Correct structure derived from synthesis. C-bound H: constr, O-bound H: refall.

$^{1}$H NMR ($CDCl_3$, 400 MHz):



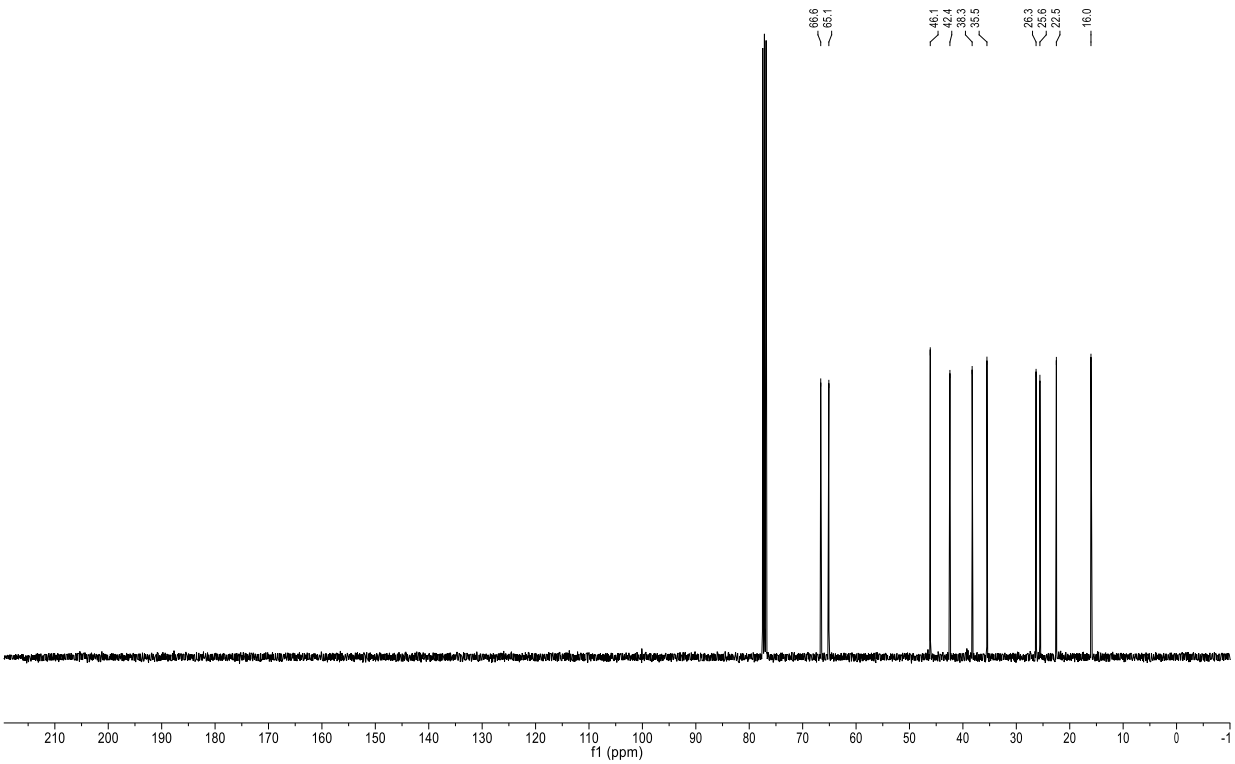

**114**

$C_{10}H_{20}O_2$

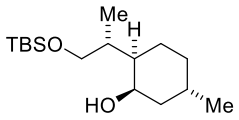
*M* = 172.27 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



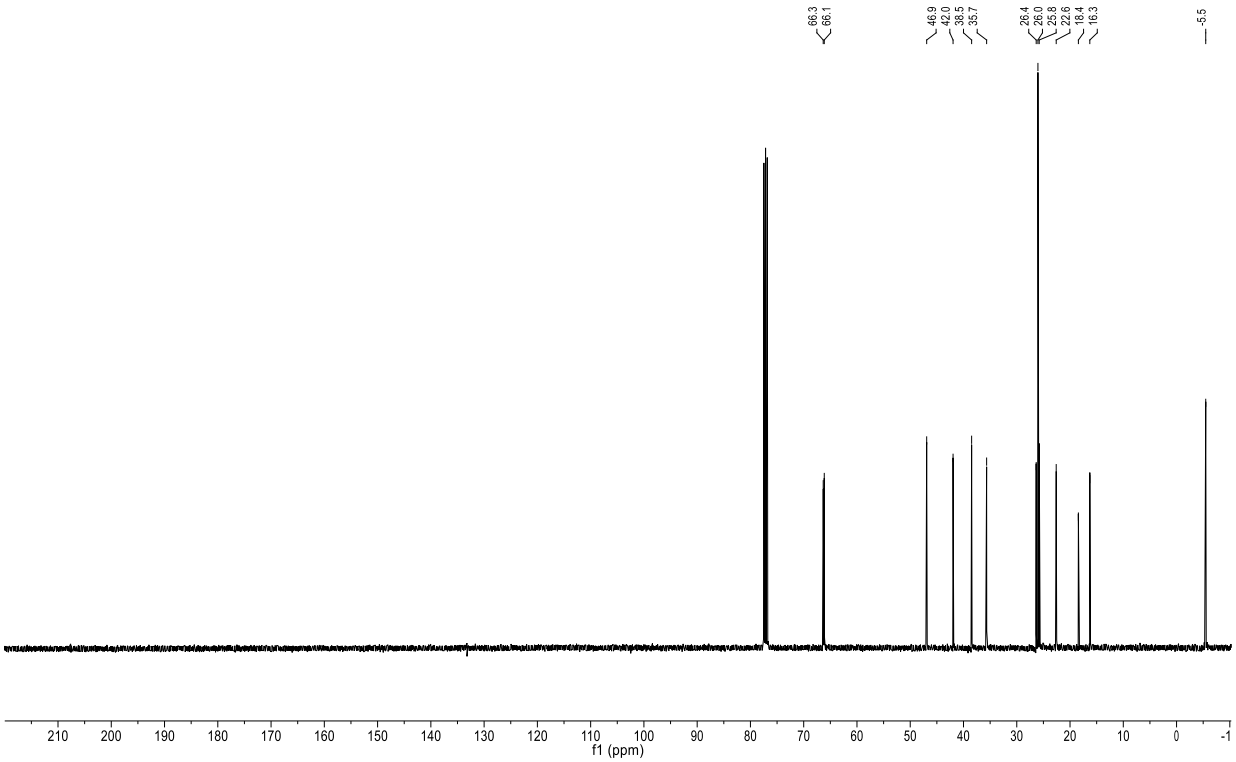

**115**

$C_{16}H_{34}O_2Si$

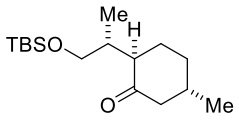
*M* = 286.53 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 600 MHz):



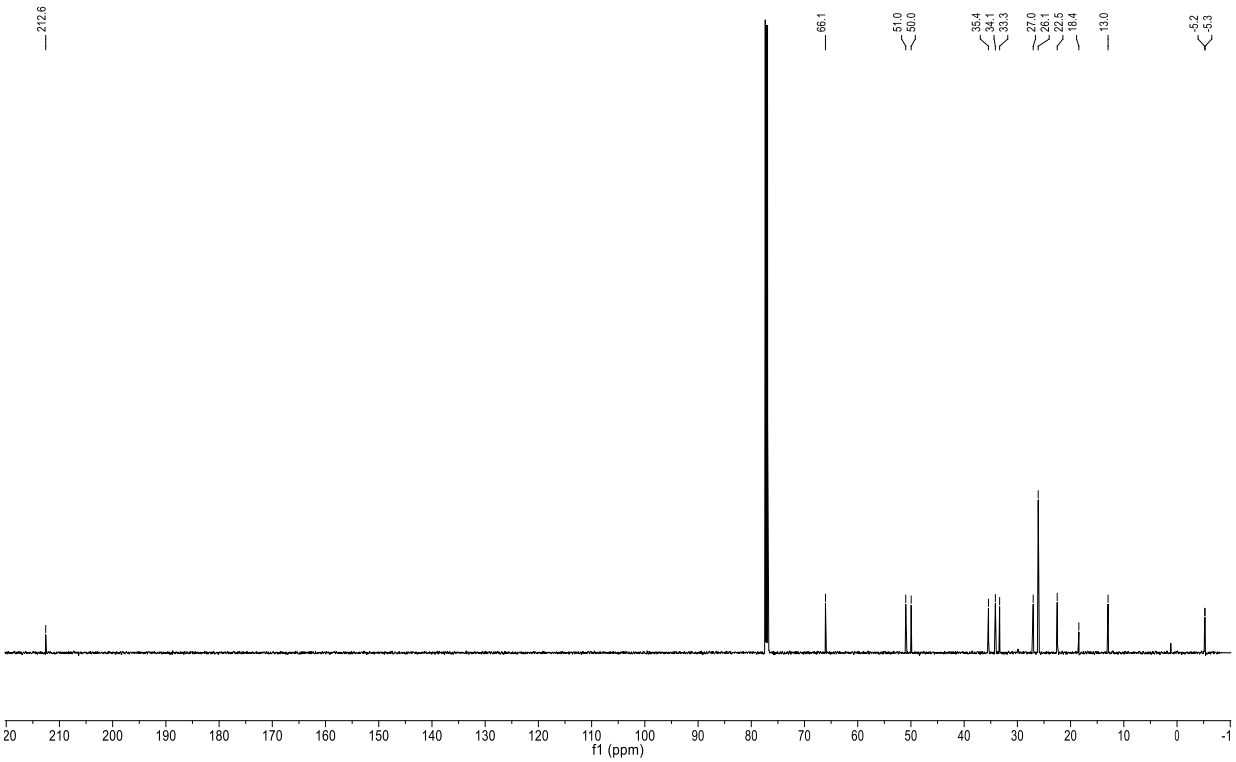

**117**

$C_{16}H_{32}O_2Si$

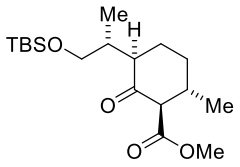
*M* = 284.51 g/mol




$^{13}$C NMR ($CDCl_3$, 150 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



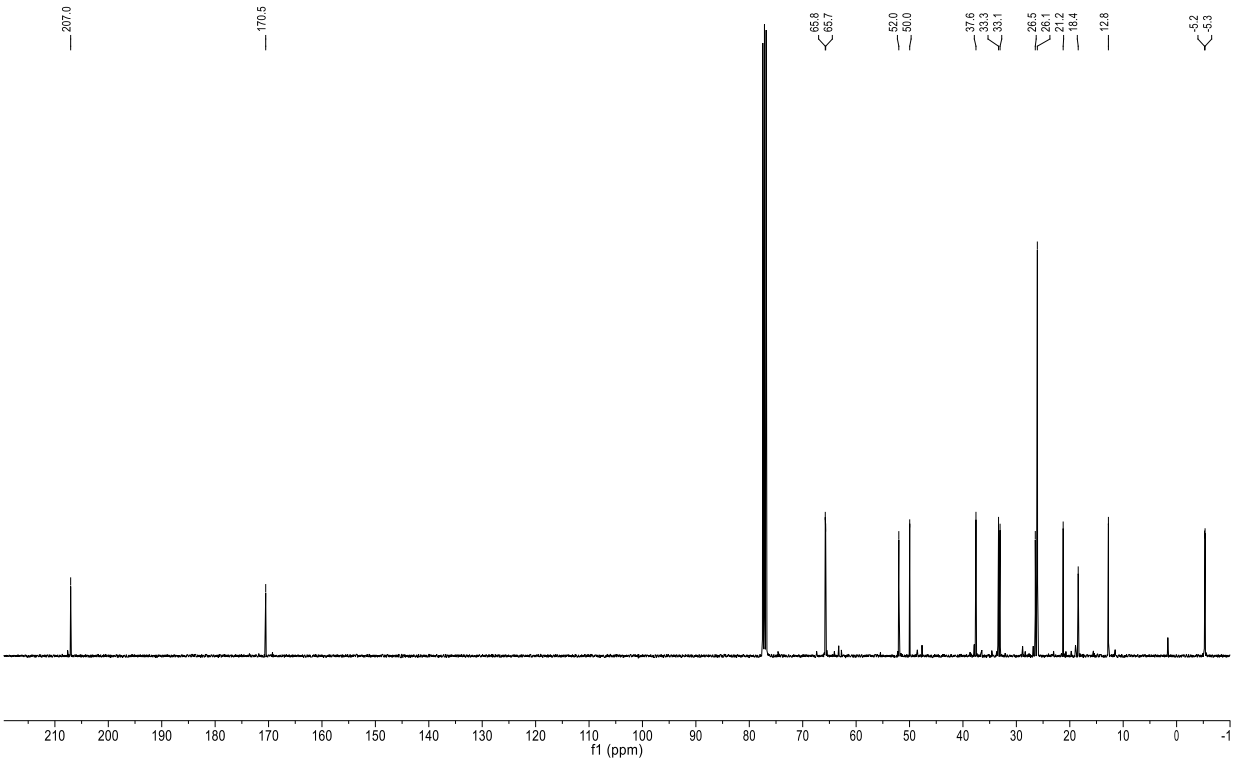

**104**

$C_{18}H_{34}O_4Si$

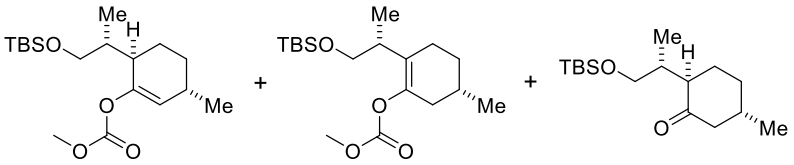
*M* = 342.55 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):




**161**
$C_{18}H_{34}O_4Si$
*M* = 342.55 g/mol

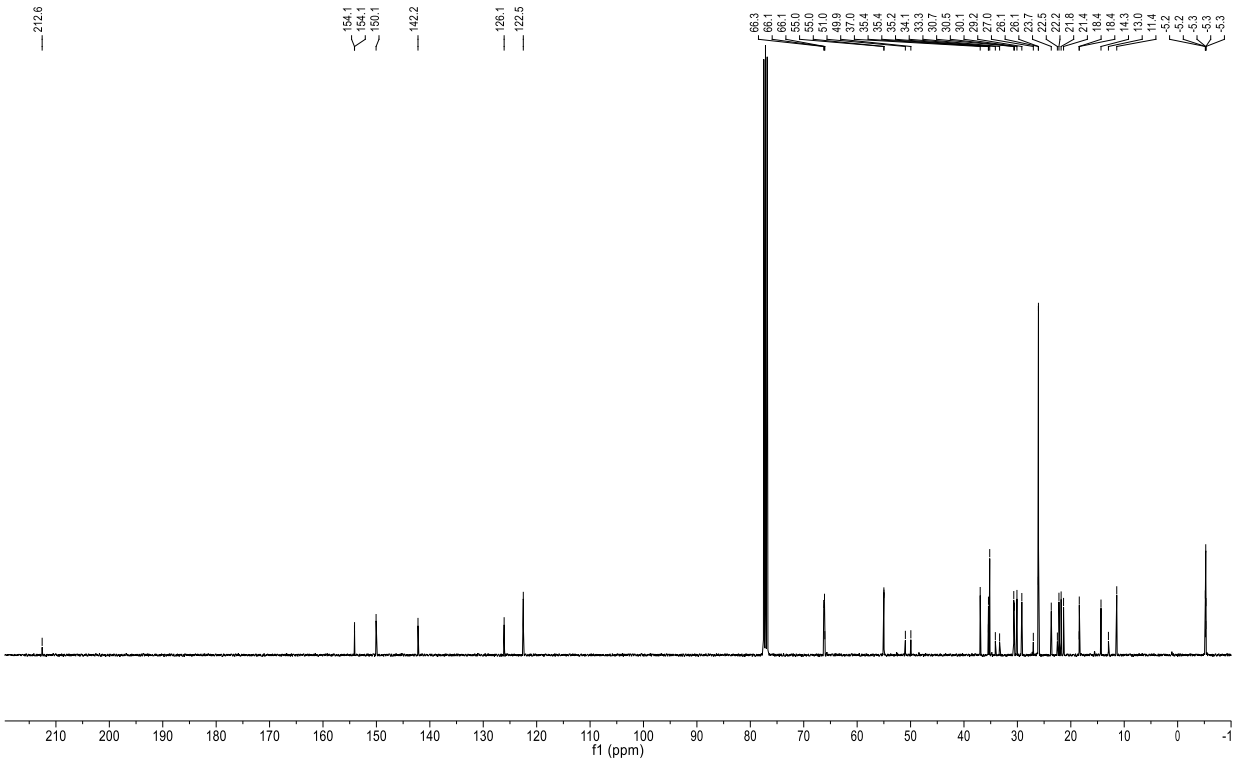
**162**
$C_{18}H_{34}O_4Si$
*M* = 342.55 g/mol

**117**
$C_{16}H_{32}O_2Si$
*M* = 284.51 g/mol

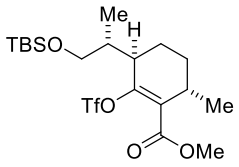
3 : 3 : 1




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



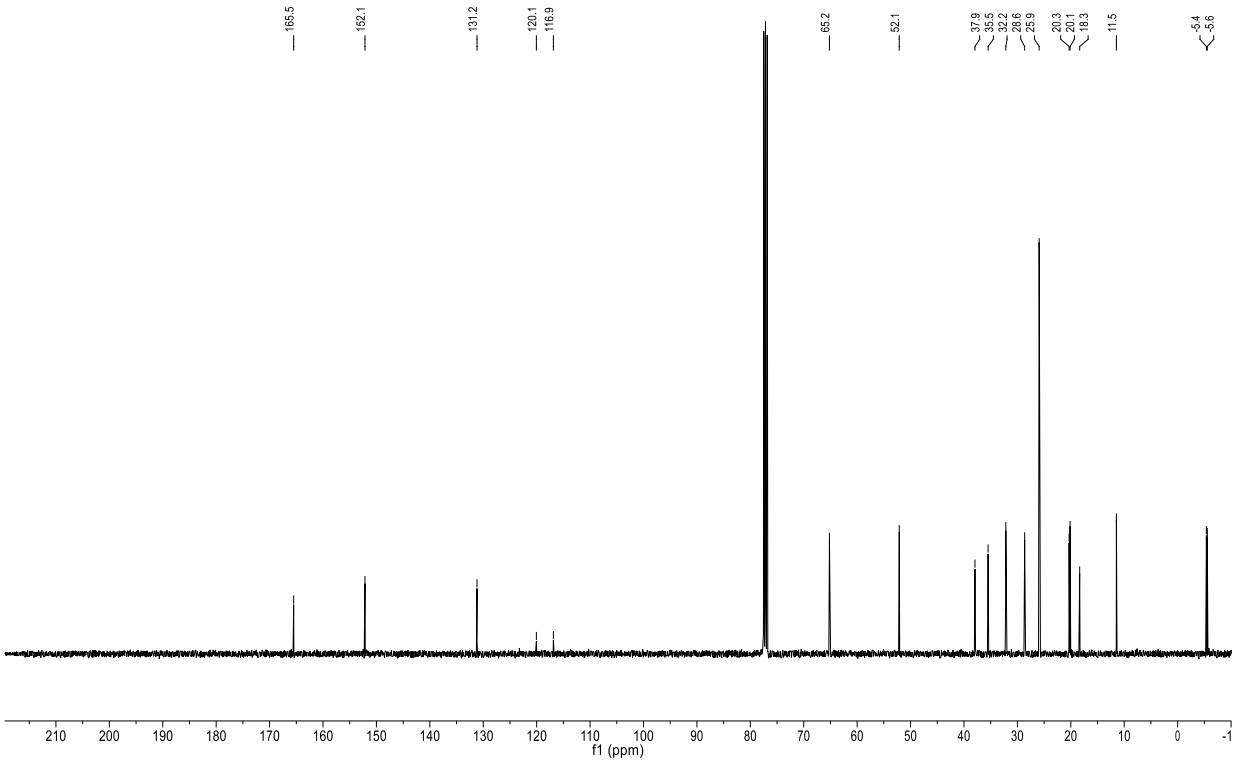

**120**

$C_{19}H_{33}F_3O_6SSi$

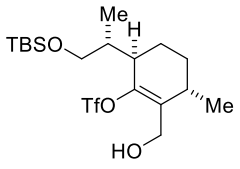
*M* = 474.61 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



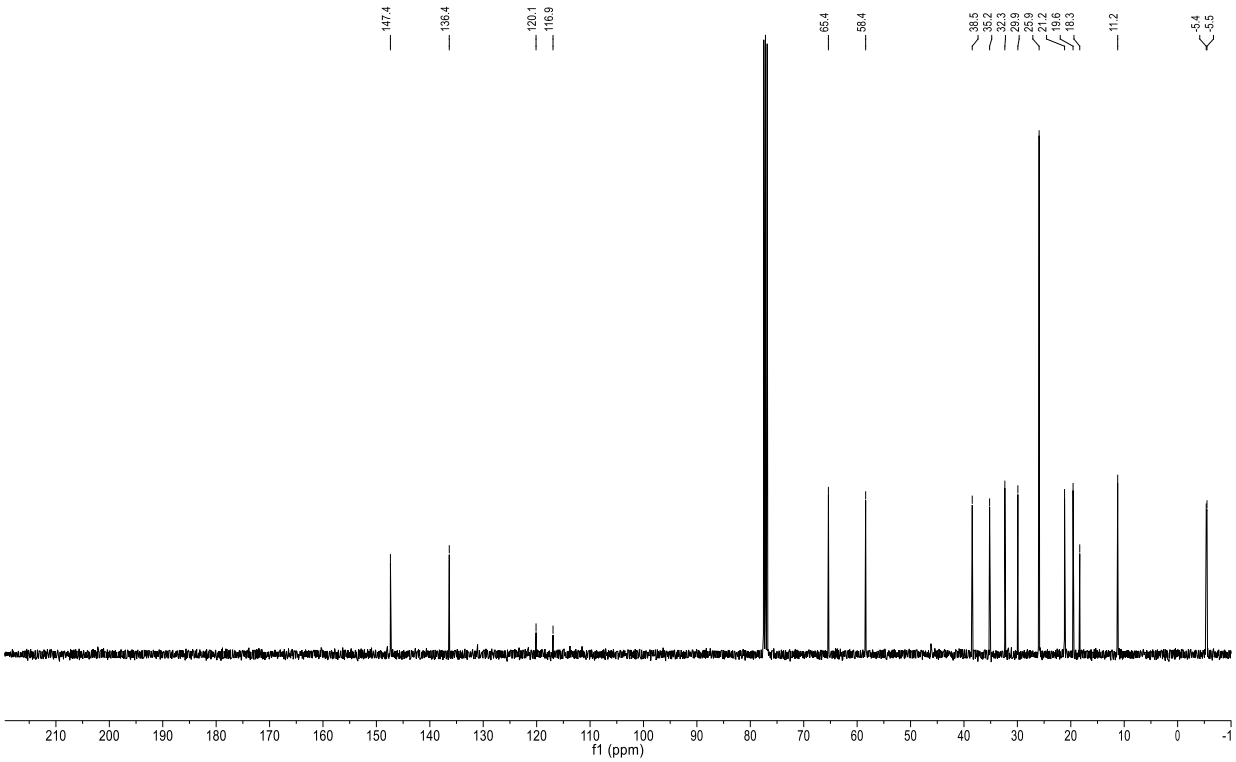

**121**

$C_{18}H_{33}F_3O_5SSi$

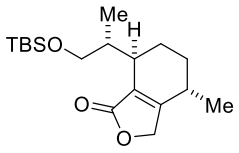
*M* = 446.60 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



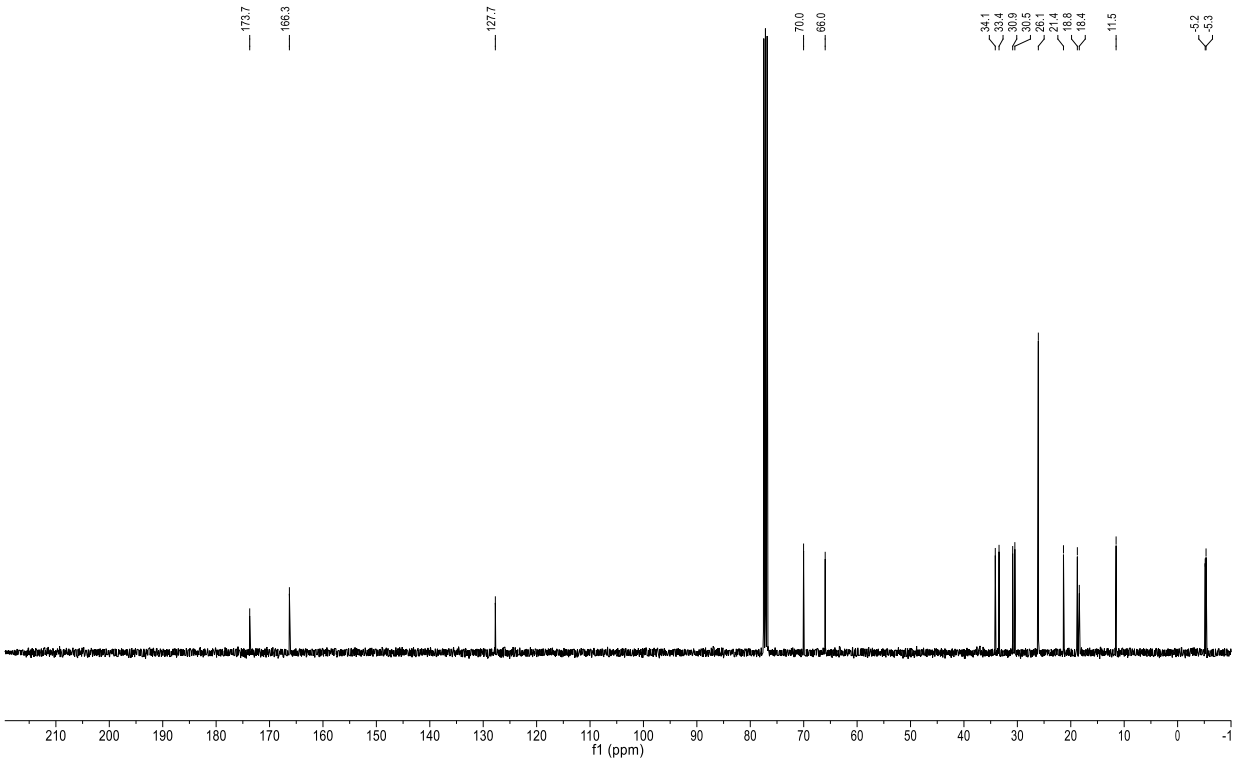

**103**

$C_{18}H_{32}O_3Si$

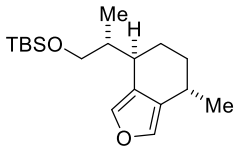
*M* = 324.54 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



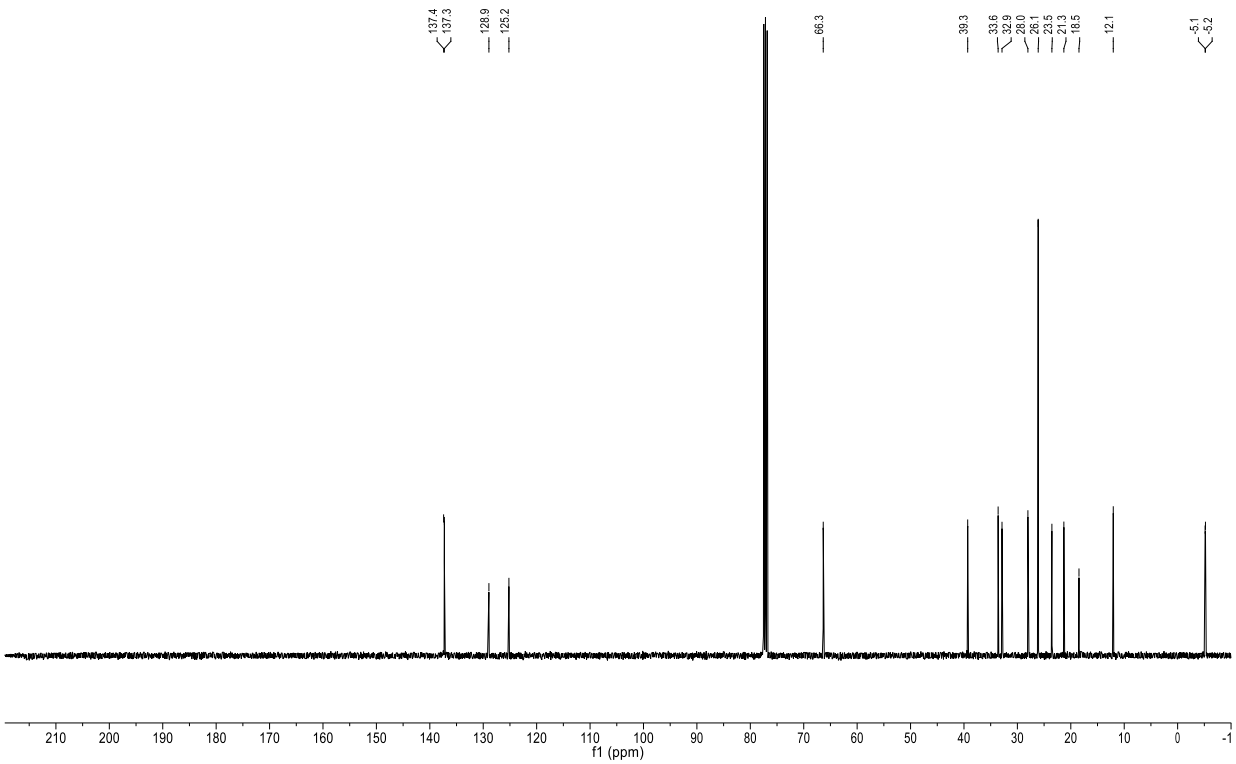
$^{1}$H NMR ($CDCl_3$, 400 MHz):



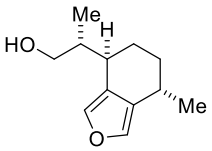

**153**
$C_{18}H_{32}O_2Si$
*M* = 308.54 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



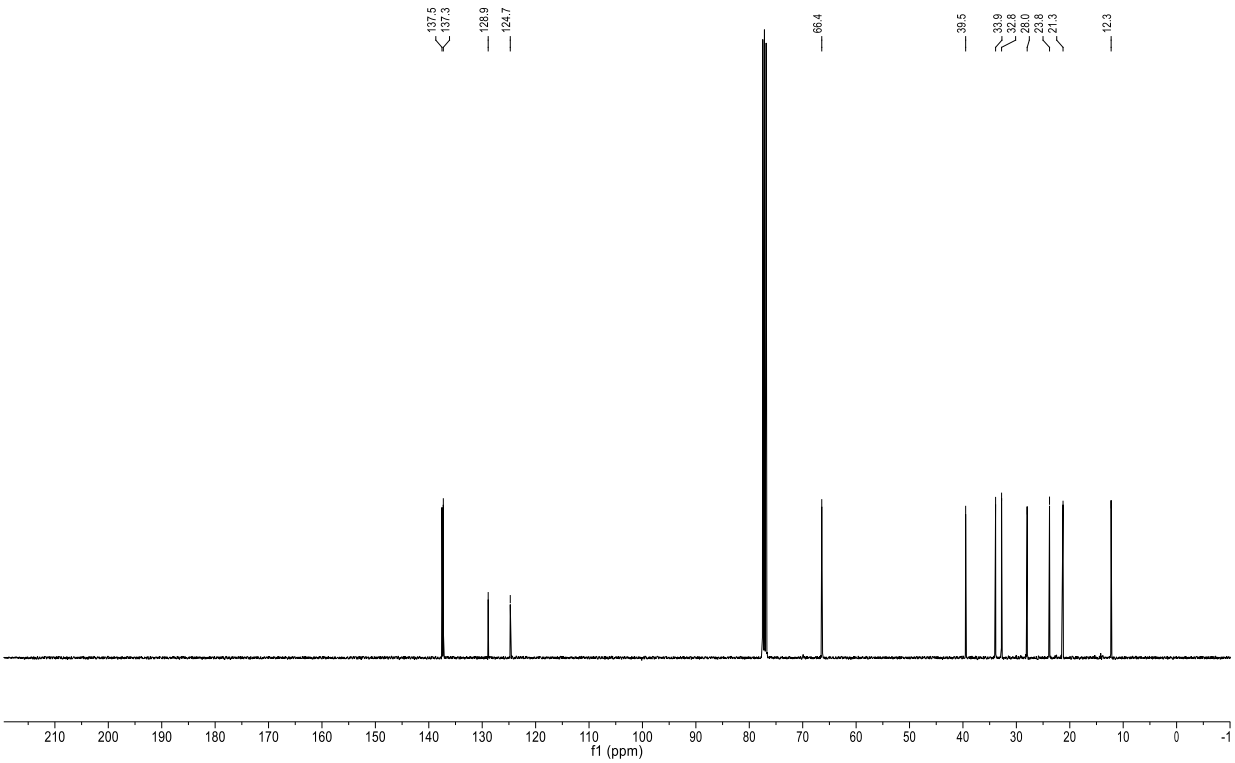

**89**

$C_{12}H_{18}O_2$

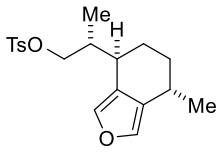
*M* = 194.27 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



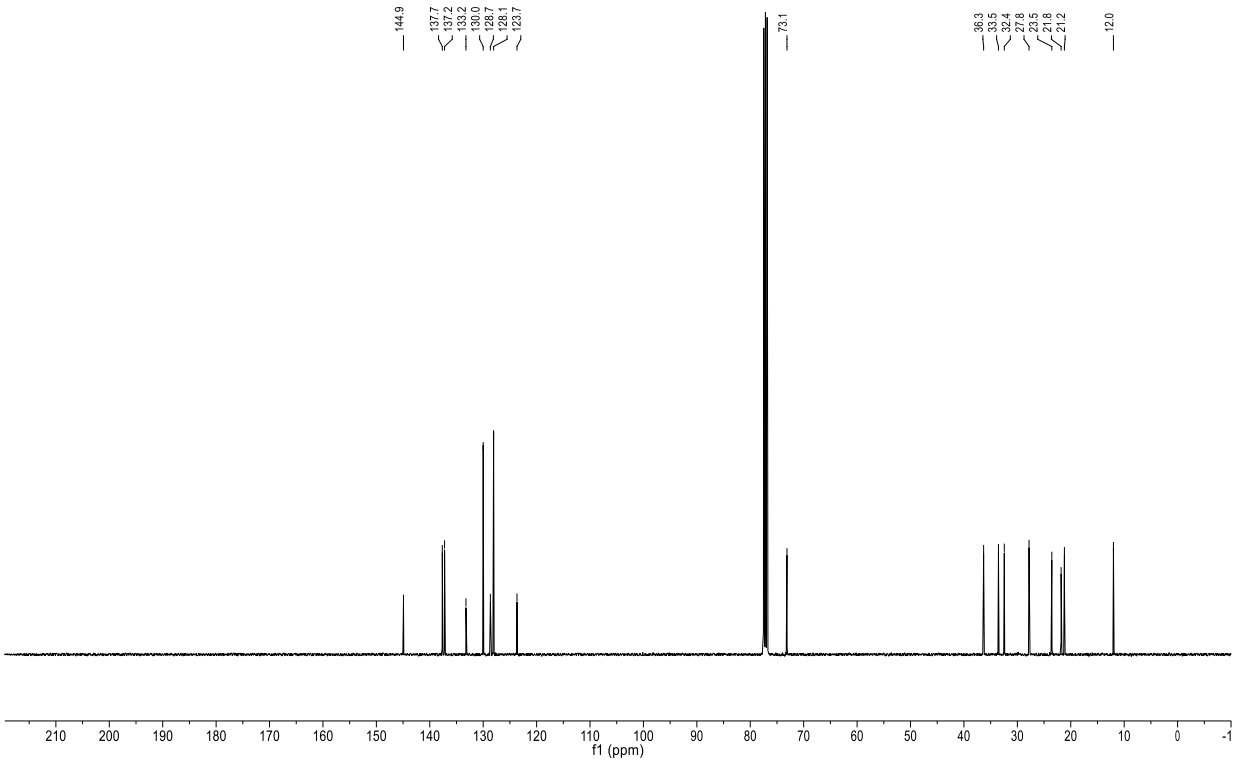
$^{1}$H NMR ($CDCl_3$, 400 MHz):



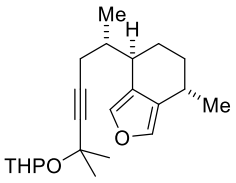

**148**
$C_{19}H_{24}O_4S$
*M* = 348.46 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



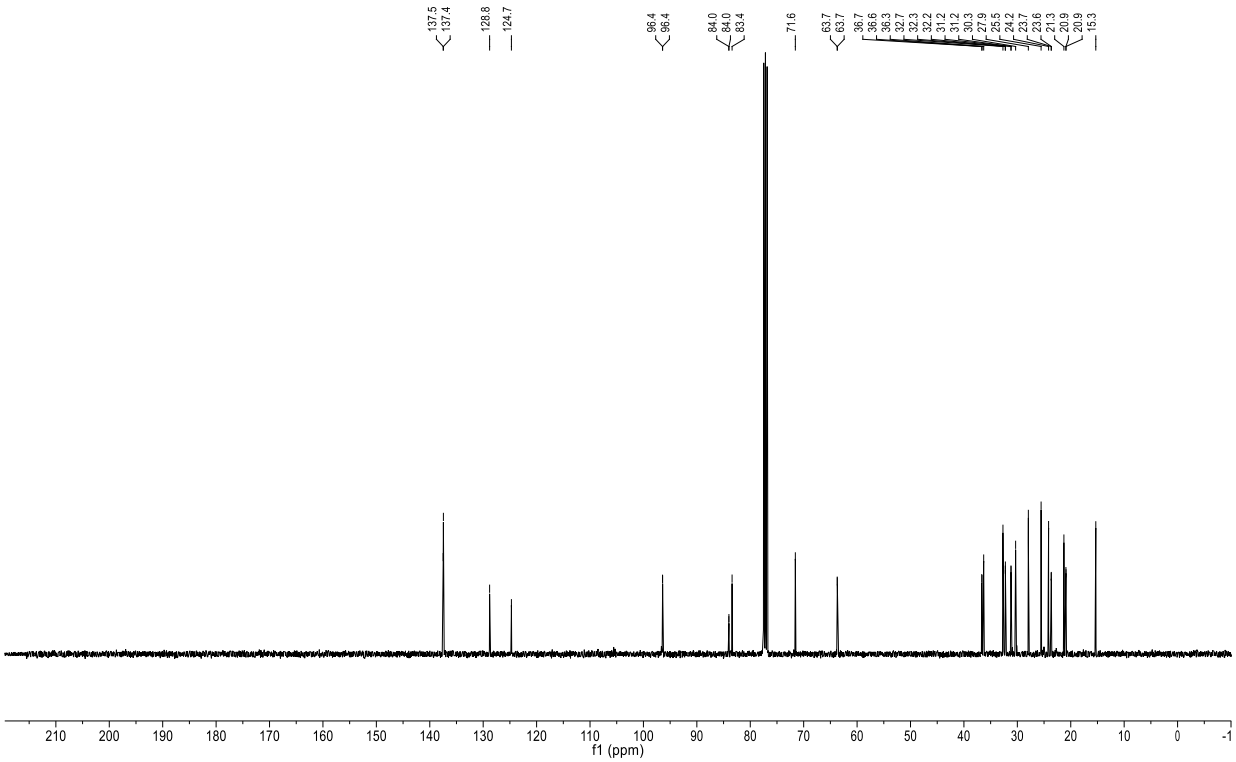

**160**

$C_{22}H_{32}O_3$

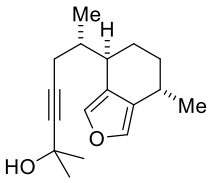
*M* = 344.49 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



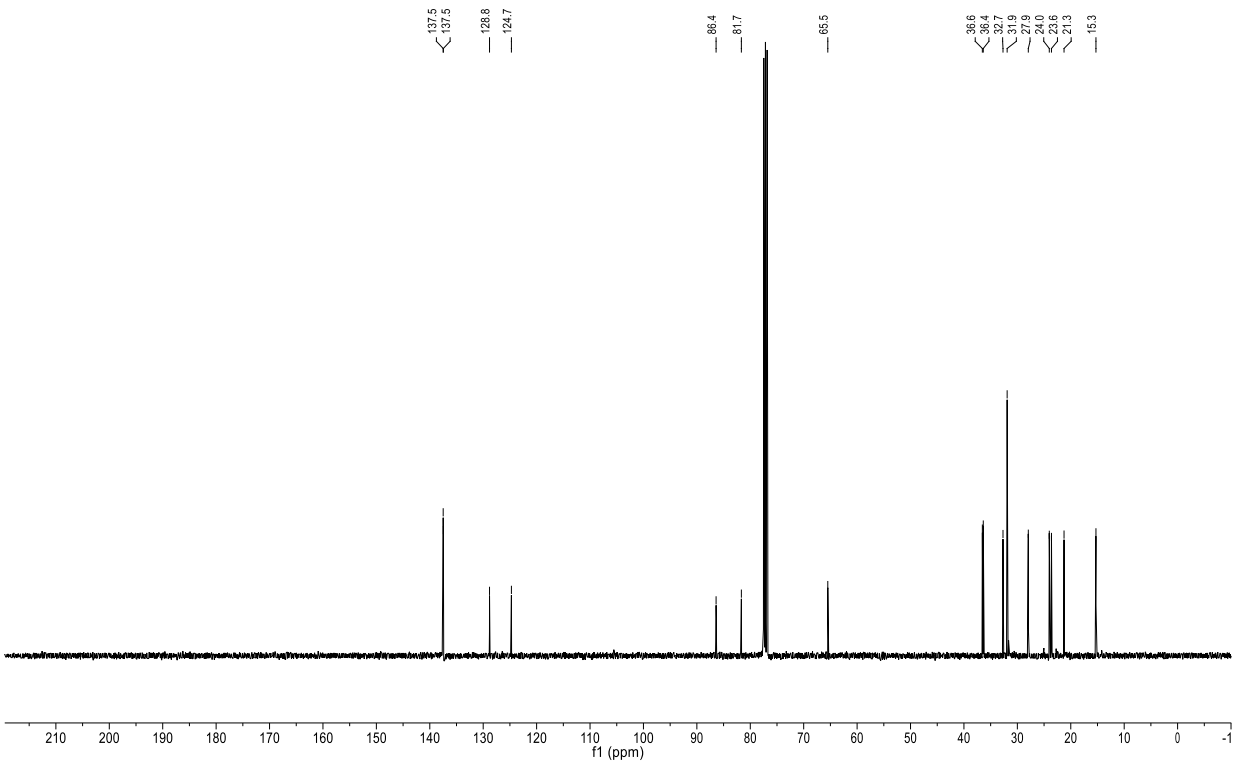

**159**

$C_{17}H_{24}O_2$

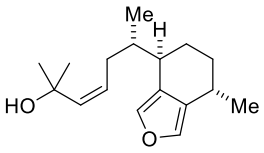
*M* = 260.38 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



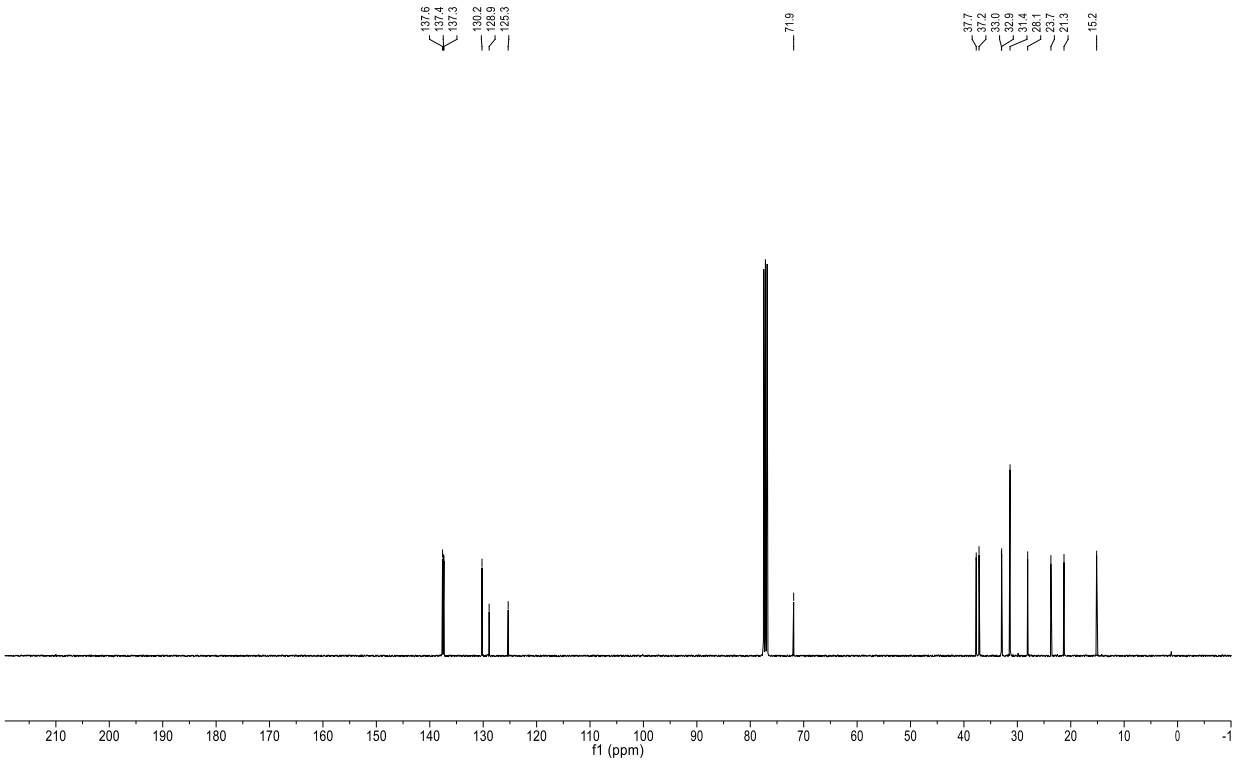

**150**

$C_{17}H_{26}O_2$

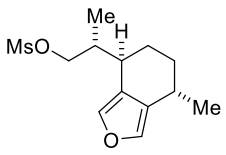
*M* = 262.39 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



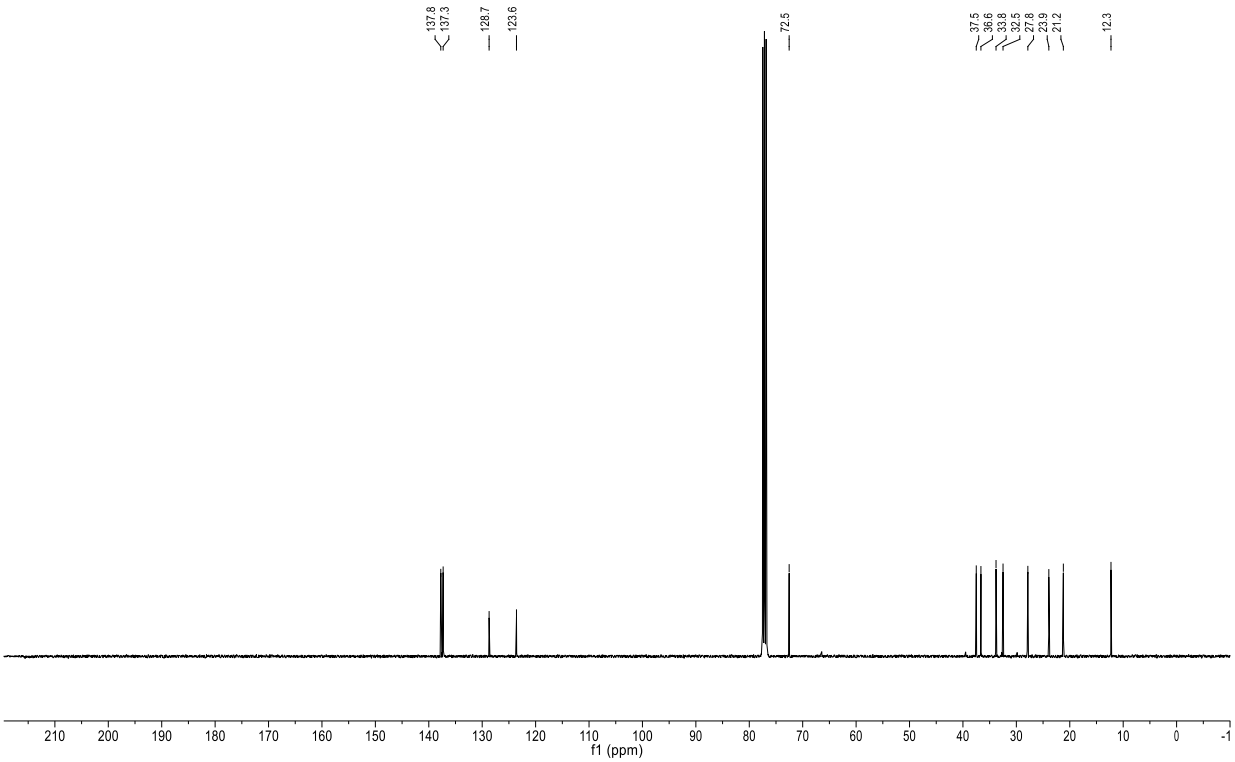

**96**

$C_{13}H_{20}O_4S$

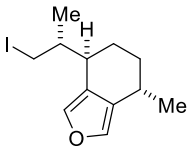
*M* = 272.36 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



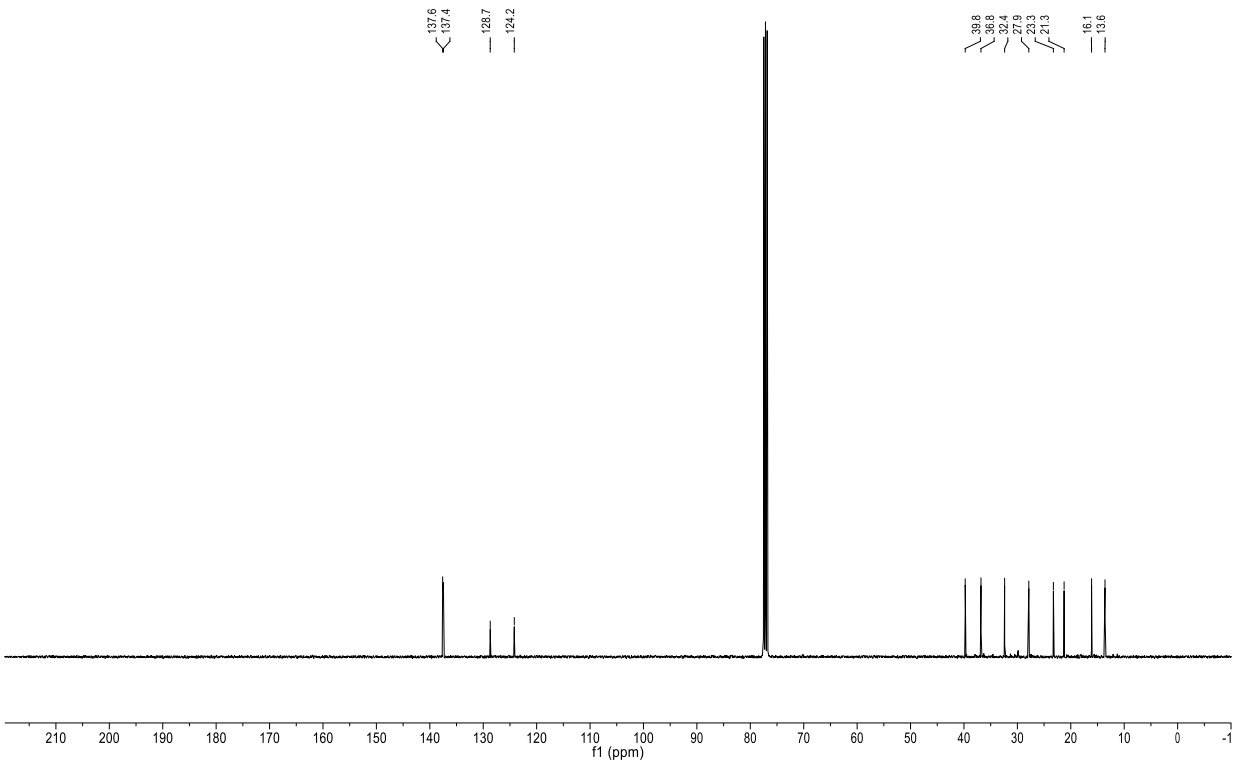

**90**

$C_{12}H_{17}IO$

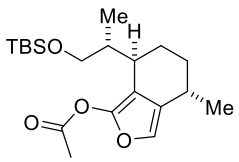
*M* = 304.17 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



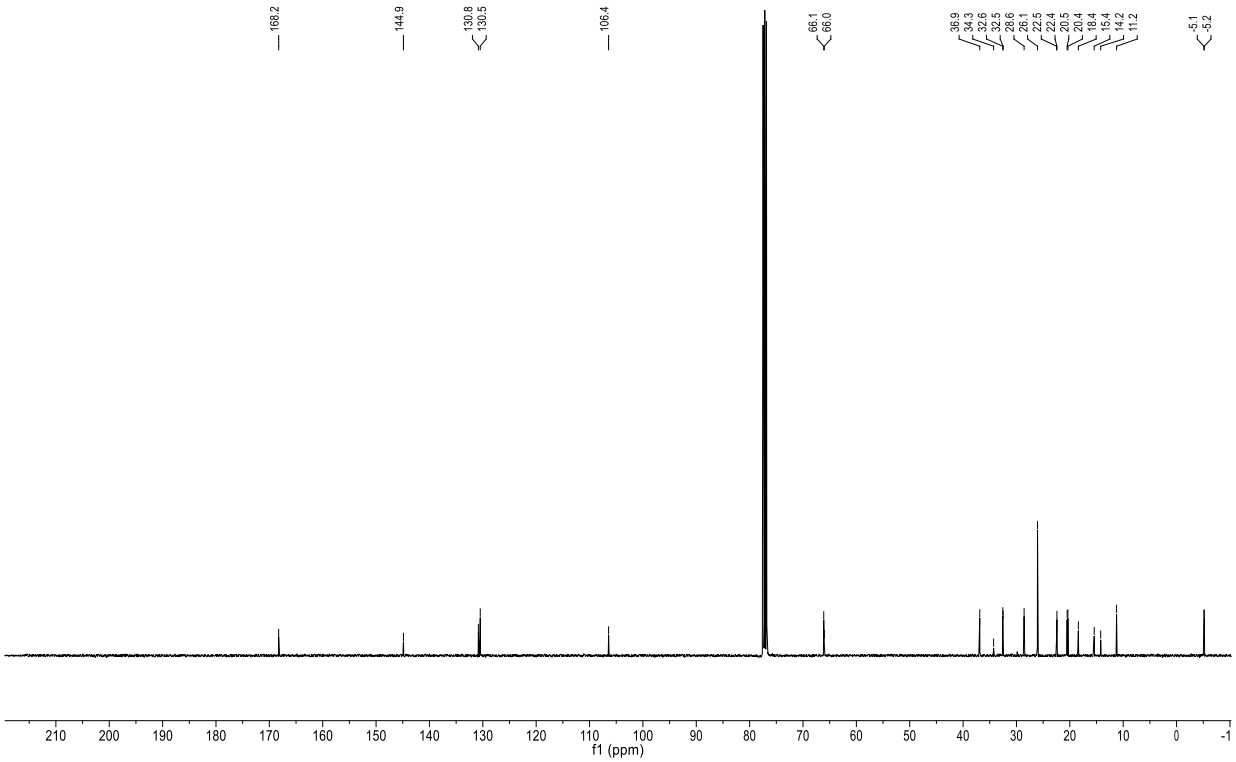
$^{1}$H NMR ($CDCl_3$, 400 MHz):



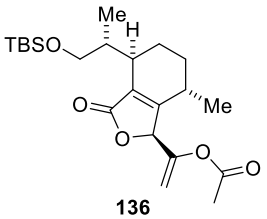

**133**
$C_{20}H_{34}O_4Si$
*M* = 366.57 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



$^{1}$H NMR ($CDCl_3$, 400 MHz):



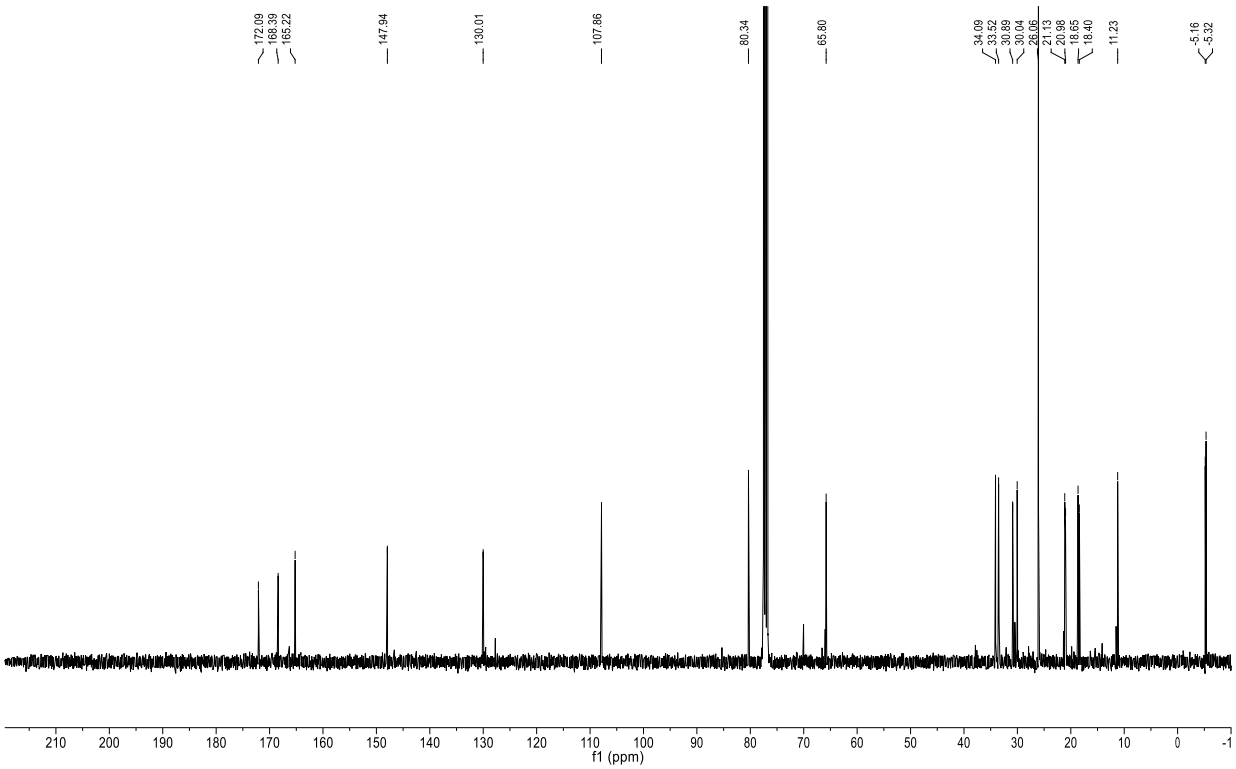

**136**

$C_{22}H_{36}O_5Si$

*M* = 408.61 g/mol




$^{13}$C NMR ($CDCl_3$, 100 MHz):



## 7.2 References


[1] Heuston, S.; Begley, M.; Gahan, C. G. M.; Hill, C. *Microbiology* **2012**, *158*, 1389–1401.

[2] Wallach, O. *Liebigs Ann. Chem.* **1887**, *239*, 1–54.

[3] (*a*) Ruzicka, L. Angew. Chem. **1938**, 38, 5–11. (*b*) Ruzicka, L. *Experimentia* **1953**, *9*, 357–367.

[4] Eschenmoser, A.; Arigoni, D. *Helv. Chim. Acta* **2005**, *88*, 3011–3050.

[5] Kirby, J.; Keasling, J. D. *Annu. Rev. Plant Biol.* **2009**, *60*, 335–355.

[6] Schäfer, B. *Chem. unserer Zeit* **2013**, *47*, 174–182.

[7] Malik, S.; Cusidó, R. M.; Mirjalili, M. H.; Moyano, E.; Palazón, J.; Bonfill, M. *Process Biochem.* **2011**, *46*, 23–34.

[8] Dewick, P. M. *Nat. Prod. Rep.* **2002**, *19*, 181–222.

[9] Soto, G.; Stritzler, M.; Lisi, C.; Alleva, K.; Pagano, M. E.; Ardila, F.; Mozzicafreddo, M.; Cuccioloni, M.; Angeletti, M.; Ayub, N. D. *J. Exp. Bot.* **2011**, *62*, 5699–5711.

[10] Dewick, P. M. *Nat. Prod. Rep.* **1997**, *14*, 111–144.

[11] Gräwert, T.; Groll, M.; Rohdich, F.; Bacher, A.; Eisenreich, W. *Cell. Mol. Life Sci.* **2011**, *68*, 3797–3814.

[12] Hunter, W. N. *J. Biol. Chem.* **2007**, *282*, 21573–21577.

[13] Vranová, E.; Coman, D.; Gruissem, W. *Annu. Rev. Plant Biol.* **2013**, *64*, 665–700.

[14] Janthawornpong, K.; Krasutsky, S.; Chaignon, P.; Rohmer, M.; Poulter, C. D.; Seemann, M. *J. Am. Chem. Soc.* **2013**, *135*, 1816–1822.

[15] Figure from: Kirby, J.; Keasling, J. D. *Annu. Rev. Plant Biol.* **2009**, *60*, 335–355.

[16] Monson, R. K.; Grote, R.; Niinemets, Ü.; Schnitzler, J.-P. *New Phytologist* **2012**, *195*, 541–559.

[17] Turner, G. W.; Croteau, R. *Plant Physiology* **2004**, *136*, 4215–4227.

[18] Ravid, U.; Putievsky, E.; Katzir, I.; Ikan, R.; Weinstein, V. *Flavour and Fragrance Journal* **1992**, *7*, 235–238.

[19] Gustafson, K. R.; Cardellina, J. H.; McMahon, J. B.; Gulakowski, R. J.; Ishitoya, J.; Szallasi, Z.; Lewin, N. E.; Blumberg, P. M.; Weislow, O. S.; Beutler, J. A.; *et al. J. Med. Chem.* **1992**, *35*, 1978–1986.

[20] Fiedor, L.; Kania, A.; Myśliwa-Kurdziel, B.; Orzeł, Ł.; Stochel, G. *Biochimica et Biophysica Acta* **2008**, *1777*, 1491–1500.

[21] World Health Organization. *Guidelines for the treatment of malaria – 2nd edition*; **2002**; ISBN: 9789241547925.

[22] Huang, L.; Li, J.; Ye, H.; Li, C.; Wang, H.; Liu, B.; Zhang, Y. *Planta* **2012**, *236*, 1571–1581.

[23] Summons, R. E.; Bradley, A. S.; Jahnke, L. L.; Waldbauer, *J. R. Phil. Trans. R. Soc. B* **2006**, *361*, 951–968.

[24] Pikuleva, I. A. *Pharmacology & Therapeutics* **2006**, *112*, 761–773.

[25] Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140–5145.

[26] Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485–2490.

[27] Wei, X.; Rodríguez, I. I.; Barnes, C. L.; Rodríguez, A. D. *J. Org. Chem.* **2007**, *72*, 7386–7389.

[28] Rodriguez, A. D.; Ramirez, C. *Org. Lett.* **2000**, *2*, 507–510.

[29] Heckrodt, T. J.; Mulzer, J. *Top. Curr. Chem.* **2005**, *244*, 1–41.

[30] Roussis, V.; Wu, Z.; Fenical, W.; Strobel, S. A.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 4916–4922.

[31] Lazerwith, S. E.; Johnson, T. W.; Corey, E. *J. Org. Lett.* **2000**, *2*, 2389–2392.

[32] Rodríguez, I. I.; Shi, Y.-P.; García, O. J.; Rodríguez, A. D.; Mayer, A. M. S.; Sánchez, J. A.; Ortega Barria, E.; González, J. *J. Nat. Prod.* **2004**, *67*, 1672–1680.

[33] (*a*) Cooksey, J. P.; Kocienski, P. J.; Schmidt, A. W.; Snaddon, T. N.; Kilner, C. A. *Synthesis* **2012**, *44*, 2779–2785. (*b*) Harrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2004**, *45*, 2089–2091. (*c*) Kocienski, P. J.; Pontiroli, A.; Qun, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2356–2366. (*d*) Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777–12782. (*e*) Majdalani, A.; Schmalz, H.-G. *Synlett* **1997**, 1303–1305. (*f*) Buszek, K. R.; Bixby, D. L. *Tetrahedron Lett.* **1995**, *36*, 9129–9132. (*g*) McCombie, S. W.; Cox, B.; Lin, S.-I.; Ganguly, A. K. *Tetrahedron Lett.* **1991**, *32*, 2087–2090. (*h*) Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 3857–3858. (*i*) Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472–5474. (*j*) Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584–1586. (*k*) Mans, D. J.; Cox, G. A.; Rajanbabu, T. V. *J. Am. Chem. Soc.* **2011**, *133*, 5776–5779.

[34] (*a*) Davies, H. M. L.; Dai, X.; Long, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 2485–2490. (*b*) Boezio, A. A.; Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6046–6050. (*c*) Harrowven, D. C.; Pascoe, D. D.; Demurtas, D.; Bourne, H. O. *Angew. Chem. Int. Ed.* **2005**, *44*, 1221–1222. (*d*) Kim, A. I.; Rychnovsky, S. D. *Angew. Chem. Int. Ed.* **2003**, *42*, 1267–1270. (*e*) Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc.* **2003**, *125*, 13022–13023. (*f*) Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem. Int. Ed.* **2001**, *40*, 2482–2486.

[35] Heckrodt, T. J.; Mulzer, J. *J. Am. Chem. Soc.* **2003**, *125*, 4680–4681.

[36] Waizumi, N.; Stankovic, A. R.; Rawal, V. H. *J. Am. Chem. Soc.* **2003**, *125*, 13022–13023.

[37] Zanoni, G.; Franzini, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4837–4841.

[38] Chen, I. T.; Baitinger, I.; Schreyer, L.; Trauner, D. *Org. Lett.* **2014**, *16*, 166–169.

[39] Liu, L.-Z.; Han, J.-C.; Yue, G.-Z.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 13608–13609.

[40] For a review on asymmetric hydrovinylation reactions, see: RajanBabu, T. V. *Chem. Rev.* **2003**, *103*, 2845–2860.

[41] Werle, S.; Fey, T.; Neudörfl, J. M.; Schmalz, H.-G. *Org. Lett.* **2007**, *9*, 3555–3558.

[42] Kato, K.; Suzuki, H.; Miyasaka, T. *Tetrahedron: Asymmetry* **1998**, *9*, 911–914.

[43] Chen, I. T. Total Synthesis of Amphilectolide, Sandresolide B, Archazolid B and towards Archazolid A and Caribenol A. Ph.D. Thesis, University of California, Berkeley, CA, **2011**.

[44] Irina Albrecht (*born Baitinger*), PhD student under the supervision of Prof. Dr. Dirk Trauner, Ludwig Maximilians-Universität München, Germany.

[45] Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 3734–3735.

[46] Corey, E. J.; Suggs J. W. *Tetrahedron Lett*. **1975**, *31*, 2647–2650.

[47] Buschmann, H.; Scharf, H.-D. *Synthesis* **1988**, 827–830.

[48] Moreira, J. A.; Corrêa, A. G. *Tetrahedron: Asymmetry* **2003**, *14*, 3787–3795.

[49] Friedrich, D.; Bohlmann, F.; *Tetrahedron* **1988**, *44*, 1369–1392.

[50] Hutchins, R. O.; Taffer, I. M.; Burgoyne, W. *J. Org. Chem.* **1981**, *46*, 5214–5215.

[51] Han, Y.; Zhu, L.; Gao, Y.; Lee, C.-S. *Org. Lett.* **2011**, *13*, 588–591.

[52] Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053–4065.

[53] Yadav, J. S.; Vijaya Bhasker, E.; Srihari, P. *Tetrahedron* **2010**, *66*, 1997–2004.

[54] Reich, H. J. *Chem. Rev.* **2013**, *113*, 7130–7178.

[55] Shing, T. K. M.; Zhu, X. Y.; Yeung, Y. Y. *Chem. Eur. J.* **2003**, *9*, 5489–5500.

[56] Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425–6426.

[57] Mukhopadhyay, T.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 385–391.

[58] Brancour, C.; Fukuyama, T.; Mukai, Y.; Skrydstrup, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 2794–2797.

[59] Liu, J.; Liang, B.; Shu, D.; Hu, Y.; Yang, Z.; Lei, A. *Tetrahedron* **2008**, *64*, 9581–9584.

[60] Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810–1817.

[61] Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans.* **2010**, *39*, 10442–10446.

[62] Lin, Y.-S.; Yamamoto, A. *Organometallics* **1998**, *17*, 3466–3478.

[63] Johnson, J. C.; Akdag, A.; Zamadar, M.; Chen, X.; Schwerin, A. F.; Paci, I.; Smith, M. B.; Havlas, Z.; Miller, J. R.; Ratner, M. A.; Nozik, A. J.; Michl, J. *J. Phys. Chem. B* **2013**, *117*, 4680–4695.

[64] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

[65] Stern, A. J.; Rohde, J. J.; Swenton, J. S. *J. Org. Chem.* **1989**, *54*, 4413–4419.

[66] Zhang, X.; Jackson, E. U.; Schultz, A. G. *J. Heterocyclic Chem.* **2006**, *43*, 223–228.

[67] Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693–11712.

[68] Castelhano, A.; McKibben, B.; Steinig, A. Pyrrolopyrimidine A2b selective antagonist compounds, their synthesis and use. US Patent US2003229067 (A1), December 11, **2003**.

[69] Dhananjeyan, M. R.; Milev, Y. P.; Kron, M. A.; Nair, M. G. *J. Med. Chem.* **2005**, *48*, 2822–2830.

[70] Schmidt, B.; Geißler, D. *Eur. J. Org. Chem.* **2011**, 7140–7147.

[71] Thanks to Dr. Thomas Magauer for helping with the structural elucidation of compound **136** *via* NMR spectroscopy.

[72] Cahiez, G.; Gager, O.; Habiak, V. *Synthesis* **2008**, *16*, 2636–2644.

[73] Wei, X.; Rodríguez, I. I.; Rodríguez, A. D.; Barnes, C. L. *J. Org. Chem.* **2007**, *72*, 7386–7389.

[74] Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194–6198.

[75] Čorić, I.; Kim, J. H.; Vlaar, T.; Patil, M.; Thiel, W.; List, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 3490–3493.

[76] Gan, Y.; Blank, D. H.; Ney, J. E.; Spencer, T. A. *J. Org. Chem* **2006**, *71*, 5864–5869.

[77] Kenndoff, M.; Singer, A.; Szeimies, G. *J. prakt. Chem.* **1997**, *339*, 217–232.

[78] Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569–572.

[79] Gu, Q.; Zheng, Y.-H.; Li, Y.-C. *Steroids* **2006**, *71*, 96–101.

[80] Heimbach, D. K.; Fröhlich, R.; Wibbeling, B.; Hoppe, D. *Synlett* **2000**, *7*, 950–954.

[81] Fürst, A.; Labler, L.; Meier, W. *Helv. Chim. Acta* **1982**, *65*, 1499–1521.

[82] Michalak, K.; Wicha, J. *J. Org. Chem.* **2011**, *76*, 6906–6911.

[83] Duan, J. J.-W.; Smith III, A. B. *J. Org. Chem.* **1993**, *58*, 3703–3711.

[84] Schröckeneder, A.; Stichnoth, D.; Mayer, P.; Trauner, D. *Beilstein J. Org. Chem.* **2012**, *8*, 1523–1527.

[85] Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; van Hülsen, E. *Chem. Ber.* **1985**, *118*, 2822–2851.

[86] Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396–405.

[87] Salomon, R. G.; Basu, B.; Roy, S.; Sachinvala, N. D. *J. Am. Chem. Soc.* **1991**, *113*, 3096–3106.

[88] CrysAlisPro, Oxford Diffraction Ltd., version 1.171.33.41 (release 06 May 2009 CrysAlis171.NET).

[89] Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.

[90] Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.

[91] Sakurai, K.; Ikeda, K.; Mori, K. *Agric. Biol. Chem.* **1988**, *52*, 2369–2371.

[92] Cheon, C. H.; Yamamoto, H.; *Tetrahedron* **2010**, *66*, 4257–4264.

[93] Figure 6.1 was personally created.

## 7.3 Curriculum Vitae

### Personal Data

| | |
|---|---|
| Name | Lucas Schreyer |
| Date and Place of Birth | 14 Feb 1989, Vienna, Austria |
| Nationality | Austrian |
| Languages | German (native), English (fluent), French (six years), Latin (four years) |
| E-Mail Address | lucasschreyer@gmx.at |

### Education

| | |
|---|---|
| Mar 2013 – Jan 2014 | **Master thesis** in the group of Prof. Dr. Dirk Trauner, Faculty of Chemistry and Pharmacy, LMU Munich, Germany: 'Toward the Asymmetric Total Syntheses of Caribenols A and B'. Supervisor at the home institution, Faculty of Chemistry, University of Vienna, Austria: Univ.-Prof. Mag. Dr. Walther Schmid. |
| Mar 2012 – present | **MSc program**, Chemistry, University of Vienna, Austria. |
| Oct 2008 – Dec 2011 | **BSc program**, Chemistry, University of Vienna, Austria (graduated with distinction). |
| Jun 2007 | **Graduation** from secondary school, Gymnasium am GRG 19, Billrothstr. 73, Vienna, Austria (trilingual – German, English, French). |
| Sept 1999 – Jun 2007 | Secondary school, Gymnasium am GRG 19, Billrothstr. 73, Vienna, Austria. |
| Sept 1995 – Jun 1999 | Elementary school, Celtesg. 2, Vienna, Austria. |

### Work Experience

| | |
|---|---|
| Jan 2012 | Tutor (lab course in basic biochemistry), University of Vienna, Austria. |
| Jan 2008 – Sept 2008 | Paramedic at the "Johanniter Unfall-Hilfe", Vienna, Austria (civilian service). |

### Scientific Interests

- Total synthesis of natural products
- Enantioselective catalysis
- NMR spectroscopy

### Publications

Chen, I. T.; Baitinger, I.; Schreyer, L.; Trauner, D. 'Total Synthesis of Sandresolide B and Amphilectolide'. *Org. Lett.* **2014**, *16*, 166–169.