A New Synthetic Pathway to Epothilone Analogues and an Efficient Approach to Cyclohexenylamines as Precursors for the Total Synthesis of Epibatidine

Ein neuer Syntheseweg zu Epothilon-Analoga und ein effizienter Zugang zu Cyclohexenylaminen als Vorstufen in der Totalsynthese von Epibatidin

DISSERTATION

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Tz. Lapeva, M. Bugl, M. E. Maier, An Efficient Approach to Epothilone Analogues, 37th IUPAC Congress: Frontiers in Chemistry; 27th GDCh General Meeting, Berlin (Germany), 14. - 19. August **1999**.

My Parents

Abbreviations

p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
APT	attached proton test
9-BBN	9-borabicyclo[3.3.1]nonane
(*R*)-BINAP	(*R*)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthaline
(*S*)-BINOL	(*S*)-(-)-1,1'-bi-2-naphtol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
b.p.	boiling point
Bu	butyl
*t*Bu	*tert*-butyl
*t*BuOH	*tert*-butyl alcohol
CAN	ceric ammonium nitrate
calc.	calculate
Cbz	benzyloxycarbonyl
COSY	corelated spectroskopy
m-CPBA	*meta*-chloroperoxybenzoic acid
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
de	diastereomeric excess
DEPT	distortionless enhancement by polarization transfer
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DHP	dihydropyran
DIBAL	diisobutylaluminium hydride
4-DMAP	dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
Dppf	1,1'-bis(diphenylphosphanyl)ferrocene
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EI	electron-impact
eq.	equivalent
ESI	electrospray ionization
EtOH	ethanol
FAB	fast-atom bombardment

FD	field-desorption
FT-ICR	Fourier transform ion cyclotron resonance
GC	gass chromatography
glyme	1,2-dimethoxyethane
GTP	guanosine triphosphate
HMBC	heteronuclear multiple bond correlation
HMDS	bis(trimethylsilyl)amide
HMPA	hexamethylphosphoric triamide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
HYTRA	2-hydroxy-1,2,2-triphenylethyl acetate
Ipc	isopinocampheyl
IR	infrared
LDA	lithium diisopropyl amide
MAPs	microtubule-associated proteins
MeOH	methanol
MOM	methoxymethyl
m.p.	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroskopy
OTf	trifluoromethanesulfonate
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium-4-toluenesulfonate
i-Pr	isopropyl
Py	pyridine
rBSM	recovered based starting material
RCM	ring closing metathesis
*R*f	retention factor

SAMP	(*S*)-(-)-1-amino-2-(methoxymethyl)pyrolidine
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TOCSY	total corelation spectroscopy
TPAP	tetra-*n*-propylammonium perruthenate
Troc	2,2,2-trichloroethyl oxycarbonyl
Ts	*para*-toluenesulfonyl, “tosyl”
*p*TsOH	*para*-toluenesulfonic acid
UV	ultraviolet

Contents

1 Introduction

Since the earliest time mankind was using extracts from natural sources like plants, animals and fungi for treatment of different diseases without knowing the relation between chemical structures and biological activity. During the enlightenment many of the old therapy methods were condemned but with the further development of the modern natural sciences it was found out that many of the earlier used natural extracts contain in fact biological active compounds which can be used as drugs or therapeutics and applied in medicine. An important milestone was the discovery of penicillin in 1928 by Sir Alexander Fleming.[1] Since this time isolation, characterization and finally synthesis of natural molecules with biological activity became one of the main aims in modern organic chemistry.

In the present work two topics concerning natural product synthesis are discussed. The first topic represents a novel convergent synthetic way to epothilone analogues, whereas the second has as purpose the synthesis of cyclohexenylamines which represents a formal total synthesis of the alkaloid epibatidine.

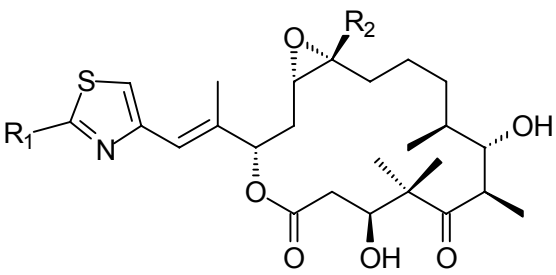
Since the discovery that the epothilones (see Scheme 1.1) possess a very high activity against cancer cells,[2] as well as some advantages compared to the billion dollar anticancer drug Taxol® in terms of potency and effectiveness against drug-resistant tumor cells, their total synthesis, structural modification and biological investigation became a very interesting synthetic target for many scientists all over the world. The epothilones and their analogues appeared as the most promising candidates for cancer chemotherapy in the present days.

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells that invade and disrupt other tissues and spread to other areas of the body. If the spread is not controlled, it can result in death. There are two classes of factors, which can be responsible for the development of cancer, external factors (for example, chemicals, radiation, and viruses) and internal factors (for example, hormones, immune conditions, and inherited genes). Causal factors may act together or in sequence, to initiate or promote carcinogenesis.[3]

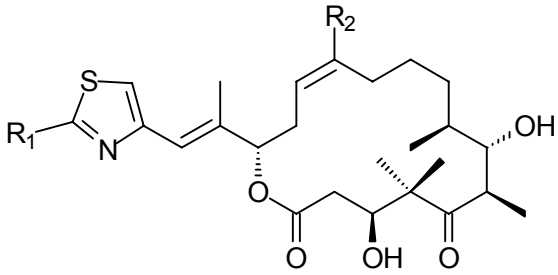
At the beginning of the last century the word “cancer” was not even mentioned as a known disease in medicine, but today cancer is a growing public health problem, and in middle Europe and USA it is the second leading cause of death, after the cardiovascular diseases.[4] According to studies of the American Cancer Society (ACS) in 1997 in the USA died alone around 560 000 people of different cancer diseases. That is more than 1 500 people a day, averaging approximately one death per minute.[5] These fearful facts motivated many research groups around the world to search, to investigate, and to

produce drugs against these diseases in an intradisciplinary and intensive way. Very often the quantity of biologically active products obtained from natural sources is not enough, that's why the main task of the synthetic chemists is to develop and to optimize convergent total syntheses with maximum yields, good stereoselectivity and the fewest possible reaction steps. Through a convergent synthesis it is possible to keep the basic structure of the desired molecule and at the same time to introduce new functional groups, which can promote a higher biological activity. An important issue in the synthesis of natural products is furthermore the stereoselectivity. Quite often enantiomeric molecules show different biological activities. One example for this, which became known to the public in an extreme dramatical way, was the CONTERGAN-affair in 1961. The active compound of the analgesic CONTERGAN was thalidomide[6] a chiral molecule, which was used as racemic mixture in this drug. Whereas one enantiomeric form had the desired activity, the other form damaged very seriously human embryos. Many children born by women who had used this analgesic during pregnancy stayed handicapped for their whole life.

In completion to the known ways of epothilone synthesis, the new alternative synthetic route, represented in this work, allows the insertion of an additional number of different residues in the epothilone scaffold. This will be important for the finding of the epothilone analogue with the most suitable properties to become a drug.



epothilone A (R_1 = Me, R_2 = H)
epothilone B (R_1 = Me, R_2 = Me)
epothilone E (R_1 = CH_2OH, R_2 = H)

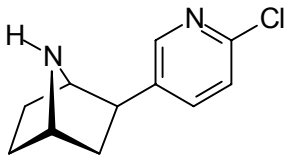


epothilone C (R_1 = Me, R_2 = H)
epothilone D (R_1 = Me, R_2 = Me)
epothilone F (R_1 = CH_2OH, R_2 = H)

Scheme 1.1: *Structures of the natural occurring epothilones A-F.*

The second part of this work represents a formal total synthesis of the natural alkaloid epibatidine through a straightforward synthesis of cyclohexenylamine as starting material. Epibatidine (see Scheme 1.2) occurs as a very potent analgesic agent which shows in two assays about 200-500 times stronger activity than those of morphine. The most interesting

fact found for this compound is that epibatidine posses a non-opiate mechanism of action.[7] Because of the undesired strong side effects known for opiates used as analgesic agents, the interest in epibatidine as a potential drug was extremely growing in the last ten years. The epibatidine can be isolated from the natural source in very small amounts (1mg isolated from the skin of 750 frogs), which stimulated considerable interest in its total synthesis.



(-) - epibatidine

Scheme 1.2: *Structure of the natural compound (-)-epibatidine.*

Both classes of compounds represented in this work have several stereocenters which play an important role for their biological activity (epothilone has seven, epibatidine has three stereocenters). Therefore a main focus was directed on the stereoselective synthesis of these compounds and their analogues.

2 The Family of Epothilones

2.1 The Macrolactones Epothilone A and B

The epothilones A and B (see Scheme 1.1) were discovered in the late 1980s, by Höfle, Reichenbach, and their coworkers at the Gesellschaft für Biotechnologische Forschung (GBF) in Braunschweig, Germany.[8] These compounds were isolated from culture extracts of the cellulose-degrading myxobacterium *Sorangium cellulosum* (Myxococcales; strain So ce90), first found in soil collected from the banks of the Zambesi River in South Africa. Initially the investigations of these compounds were focused on the activity of the epothilones against fungi, bacteria, and a variety of animal cell lines.[9] It was found that the pure substances show a large spectrum of activity against eukaryotic cells whereupon the epothilone B was more active than epothilone A, minimum with factor 2 in the most cases. The studies revealed only a narrow spectrum of antifungal activity and the field experiments indicated a rather high phytotoxicity of the epothilones.[8-10] These facts discouraged an early interest in the epothilones as pesticide agents as well as their potential application in agriculture.

Some years later in 1995, a team from MERCK in the USA independently isolated epothilones A and B and they found that these compounds kill tumor cells through a mechanism of action similar to that of taxol (paclitaxel), namely through induction of tubulin polymerization to microtubules and microtubule stabilization.[2] Thereafter this observation was confirmed by the GBF scientists.[9] A special merit in this work had D. M. Bollag and coworkers, who established a new very sensitive filtration-calorimetric assay to detect microtubule nucleating activity.[2] During a high-throughput screening program to discover taxol-like tubulin polymerization agents, the MERCK group subjected tens of thousands of compounds to biological assays and their only hits were epothilones A and B.[2] So the interest of the family of epothilones resumed, this time with much more excitement and momentum.

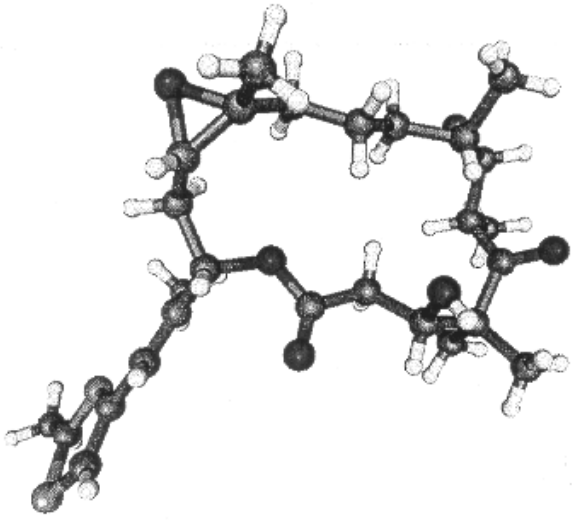
Nearly twenty years after the discovery of the mechanism of action of taxol by Horwitz et al. (1979)[11] this new class of cytotoxic agents, the epothilones, were found which exhibit an almost identical biological activity. By comparison of this activity, it was established that the potency of epothilones as tubulin polymerization agents is higher than this of taxol (epothilone B > epothilone A > taxol). Both compounds, epothilone and taxol, probably compete for the same receptor and replace each other.[2, 12] They are “equipotent” in *in vitro* tests (filtration, light scattering, sedimentation, and electron microscopy), show similar kinetics, and provide closely similar microscopic pictures of microtubule structure and cell damage. Perhaps the most exciting property of the

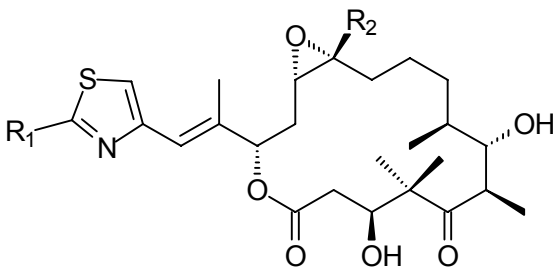
epothilones is their superiority over taxol as a killer of tumor cells, particularly multiple drug resistant (MDR) cell lines, including a number resistant to taxol.[2, 12] Additionally, they are slightly soluble in water, while the insolubility of taxol is notorious, which may also prove an advantage in their clinical application. MERCK scientists found in displacement experiments that epothilones A and B were competitive inhibitors of [^{3}H]-labelled taxol with almost identical IC_{50} values (inhibiting concentration which stops growth in 50% of cells) to that of non-labelled taxol, from which it may be deduced that the binding site for epothilones is located on the *β*–tubulin subunit as it is in the case of taxol.[2, 12] In some of the cytotoxicity experiments, epothilone B demonstrated a 2000–5000-fold higher potency than taxol.[2] For example, Table 2.1 shows some test results from treating of tumor cells with epothilones and taxol. The cytotoxicity is determined based on the growing rate of human leukemia cells CCRF-CEM as well the taxol resistant subtribe CCRF-CEM/VBL and the etoposide resistant subtribe CCRF-CEM/VM1.[13]

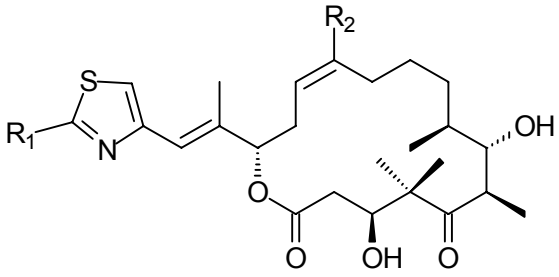
Table 2.1: *Activity of epothilones and taxol against human leukemia cells*.

Compound	CCRF-CEM IC_{50} (μM)	CCRF-CEM/VBL IC_{50} (μM)	CCRF-CEM/VM1 IC_{50} (μM)
Epothilone A	0.003	0.020	0.003
Epothilone B	0.022	0.012	0.013
Epothilone C	0.0004	0.003	0.002
Epothilone D	0.009	0.017	0.014
Taxol®	0.002	3.390	0.002

Although the chemical structures of the epothilones were reported in the first papers by Höfle et al.[8] in 1993 as well as by the MERCK group[2] in 1995, the absolute stereochemistry of these natural products was not explained until July 1996.[9] The structural assignments were made on the basis of spectroscopic[9, 14] and X-ray crystallographic data,[9] and the compounds were named *epothilones* after their structural subunits, *epo*xide, *thi*azo*l*e and ket*one*. The determination of the absolute configuration of the seven stereocenters in epothilone B was made through X-ray measurements (Figure 2.1) and chemical degradation of the fragment C13-C16 to (*S*)-hydroxy succinic acid. As it is possible to see from Figure 2.1, the carbon backbone of the macrocycle is largely flat, and the side-chain with the thiazol moiety adopts an equatorial position.







epothilone A (R_1 = Me, R_2 = H)
epothilone B (R_1 = Me, R_2 = Me)
epothilone E (R_1 = CH_2OH, R_2 = H)

epothilone C (R_1 = Me, R_2 = H)
epothilone D (R_1 = Me, R_2 = Me)
epothilone F (R_1 = CH_2OH, R_2 = H)

Figure 2.1: *X-ray structure of epothilone B and chemical structures of the natural epothilones.*

Because of the assumption that the epothilones have the same or partly the same binding position on tubulin as the taxol, some structural similarities, in spite of their significant differences were investigated. Several pharmacophore models, have been formulated to explain the interaction of epothilone and tubulin at an atomic level.[15] Based on conformational analysis Winkler and Axelsen have developed a model for the taxol-epothilone-pharmacophore (see Figure 2.2).[16]

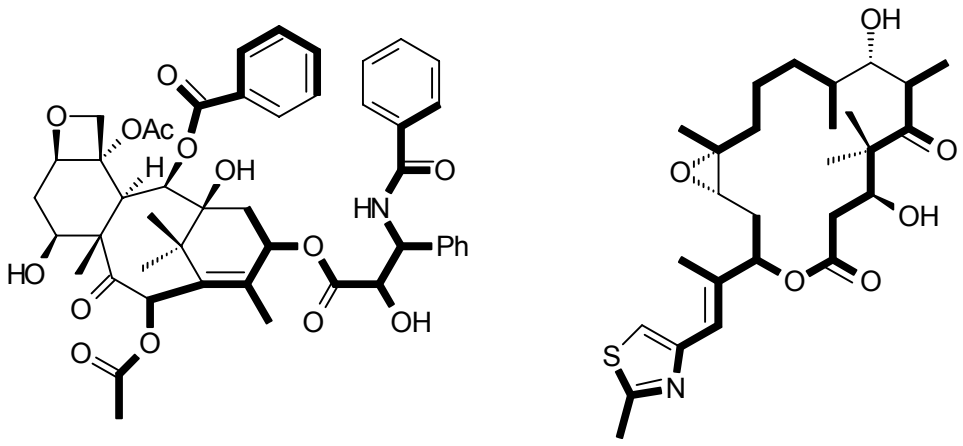


Figure 2.2: *Pharmacophore-model studies based on conformational analysis.*

2.2 Biological Properties of Epothilones

The cytoskeleton of eukaryotic cells is an extremely complex system possessing a multitude of individual components with a whole range of different functions. It is not only principally responsible for cell shape, but also plays an essential part in cell movement, in nuclear and cell division, and in intracellular transport processes. It is involved in the reception of signals from the cell's environment, as well as for their transformation into chains of intracellular signals. Basically the cytoskeleton consists of two distinct but mutually interacting and complementary systems, the actin skeleton and the tubulin skeleton. In the case of epothilone, it is principally the tubulin skeleton, which is affected.

The tubulin skeleton is formed through polymerization of protein dimers, consisting of one molecule each of globular α- and β–tubulin subunits. Dimer and polymer are in a state of dynamic equilibrium, so that the network can respond flexibly and quickly to functional requirements. The polymer forms a fine, unbranched cylinder, usually with internal and external diameters of 14 and 28 nm, respectively, the so-called microtubule.[17, 18] Assembly is initiated by the association of α/β–tubulin dimers to form short protofilaments, thirteen of which – as a rule – subsequently arrange themselves side by side and bind to form the microtubule (Figure 2.3).[18]

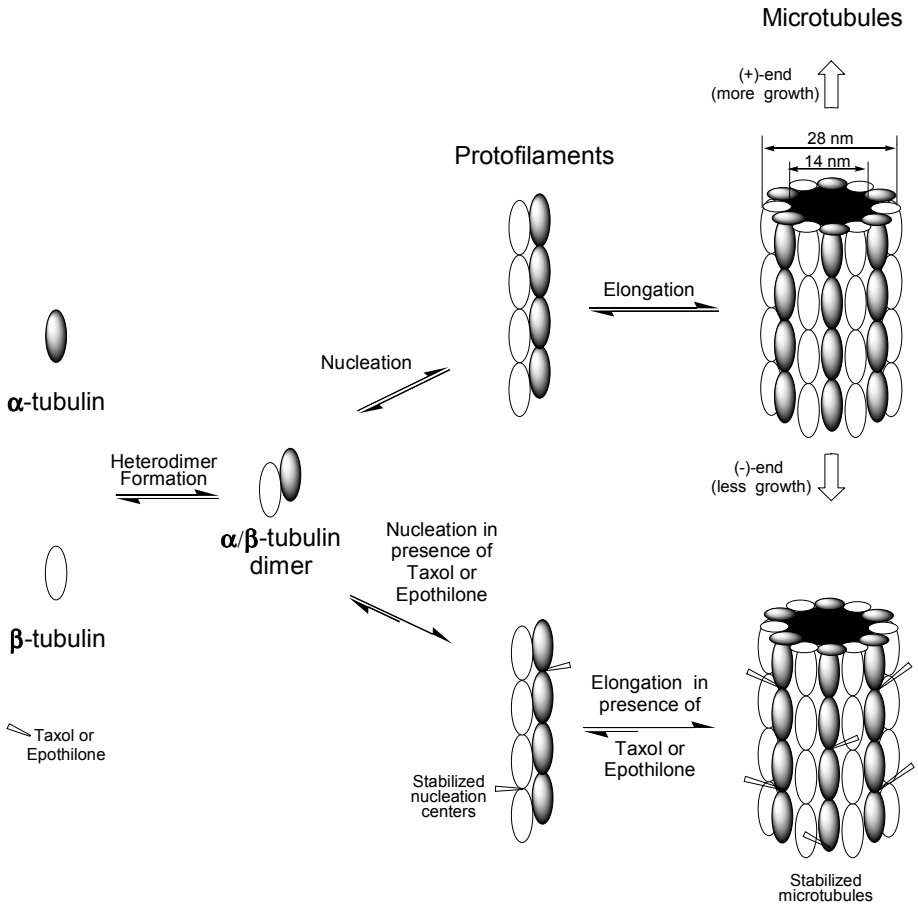


Figure 2.3: *Schematically representation of the microtubule formation from α- and β- tubulin proteines.*

Formation of microtubules proceeds by a nucleation-elongation mechanism.[19, 20] Nucleation is the initial phase of the process in which preformed heterodimers of *α*- and *β*-tubulin assemble in the presence of magnesium ions, guanosine triphosphate (GTP), and microtubule-associated proteins (MAPs). This process is relatively slow until a short microtubule is formed. Thereafter follows the much faster elongation phase, which involves extension of the microtubule nucleus at both ends by a reversible, noncovalent addition of tubulin heterodimers to form polymers. The *α*/*β*–tubulin dimers within the protofilaments are held together by stronger bonds compared to the ones formed during the microtubule assembly between the single protofilaments. The structure of the microtubules is dipolar, containing (+)-end, which is kinetically more dynamic, and (-)-end, which is less dynamic. Although both ends can either grow or dissociate, it is the (+)-end that usually grows faster than the (-)-end, and net growth occurs at the (+)-end, while net shortening takes place at the (-)-end.[21]

Subsequent growth of the microtubules occurs through the addition of further dimers, which involves GTP molecules. Each tubulin dimer carries two GTP molecules, but only the one on the *β*-subunit appears to function.[22] The growth and the dissolution of microtubules are regulated by adding (for growth) or hydrolyzing (for shrinkage) GTP on the ends of the microtubule. Consequently, microtubules are in a constant state of flux responding to the needs of the cell. This state is called “dynamic instability” and is controlled by regulatory processes within the cell.[19, 23] Thus, microtubule growth is promoted in a dividing or moving cell, but more controlled in a stable polarized cell. The half-life of microtubules is about 10-20 min.

The tubulin skeleton appears to be modulated at two levels. On the one hand there are a number of different genes for tubulin, at least five of which are expressed in the mammalian brain, and which are possibly activated according to the tissue or organ they occur in, or depending on the stage of development, so that from situation to situation it may react differently to the signals it receives. In addition, there are a number of proteins, the MAPs, which bind to microtubules and affect their behavior. Varying expression and constitution of MAP patterns facilitate the cell’s differential influence over its tubulin skeleton in different tissues, organs and stages of development.[17]

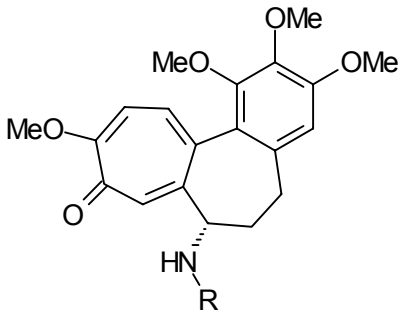
As major components of the cellular apparatus known as the mitotic spindle, the microtubules play an important role in the mitosis, the process during cell replication in which the duplicated genetic material in the form of chromosomes is partitioned equally between the two daughter cells.[24] During the transition from metaphase to anaphase, in the stage of the active cell division, the fast growing microtubules literally pull the cell chromosomes apart pushing them into the two emerging daughter cells. Because of the rapid dynamic growth of the microtubules (length increases by 20- to 100-fold compared with the interphase) during the active phase, their sensitiveness is extremely high against compounds, which can interact with the tubulin.[23, 25] Such antimitotic agents, which take action in these stage of the cell cycles inhibit mitosis and lead to cell death (apoptosis).

A wide range of compounds, including a number of natural products interact with the tubulin system, of which some have found practical application. They bind either to the tubulin itself or to the MAPs. The antimitotic agents known so far can be classified in four main classes, based on their binding place as well as on their mechanism of action:

Class I: Colchicine like binding agents

This group of compounds include the well-established chemotherapeutic agents colchicine,[26] and colcemide,[27] obtained from meadow saffron *Colchicum antumnale* (see Scheme 2.1). Colchicine first binds to free tubulin and the formed complexes are incorporated into the microtubules at the growing ends in relatively low concentrations, but

show profound effects on the microtubule dynamics, and inhibit the formation of the mitotic spindle.

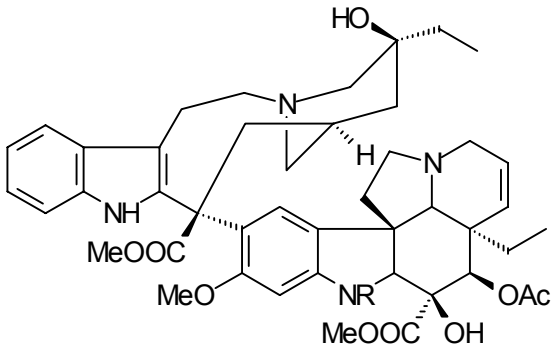


Colchicine (R = Ac)
Colcemide (R = Me)

Scheme 2.1: *Cholchicine like binding agents promoting depolymerization of tubulin.*

Class II: GTP binding agents

Here belongs the group of the vinca alkaloids, like vinblastine and vincristine [19, 28] (see Scheme 2.2), which were isolated from the plant *Catharanthus* (formerly *Vinca*) *roseus*. Their binding place is central situated near to the GTP-binding place of the *β*–tubulin, whereby the tubulin polymerization is prevented. The vinca alkaloids have been used for many years in cancer therapy.



Vinblastine (R = Me)
Vincristine (R = CHO)

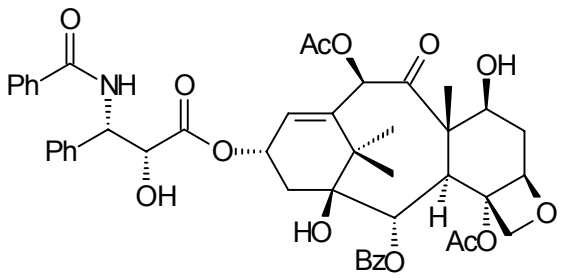
Scheme 2.2: *GTP binding agents promoting depolymerization of tubulin*.

Class III: Microtubules stabilizing agents

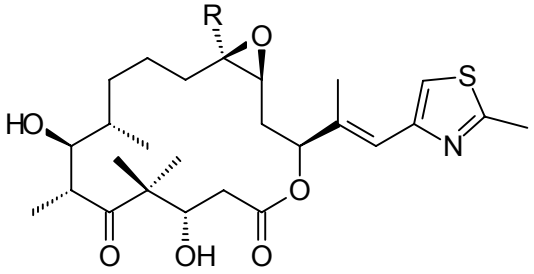
The most known substance in this class of compounds is Taxol® (registered with the trade mark from Bristol-Myers Squibb) as well known as paclitaxel, which was discovered from the Pacific Yew Tree (*Taxus brevifolia*) in 1971.[29] In the meantime this compound is also semi-synthetically available and is mainly used for the treatment of a variety of solid tumors commonly encountered with ovarian and breast cancer.[30] In contrast to the antimitotic drugs described above, taxol disturbs the polymerization-depolymerization dynamics of microtubules *in vitro*. The mechanism of action is based on a stabilization of the microtubules against depolymerization so that the mitosis cannot take its regular course, which finally results in apoptosis. To this class of compounds belong also the epothilones A-F,[31] discodermolide,[32] eleutherobin,[33] sarcodictyn A,[34] and laulimalide[35] (see Scheme 2.3). Although the epothilones displace taxol from its receptor, they must bind in a slightly different manner to microtubules as suggested by their action against taxol-resistant tumor cells, which contain mutated tubulin.

Class IV: Microtubules-Network-destabilizing agents

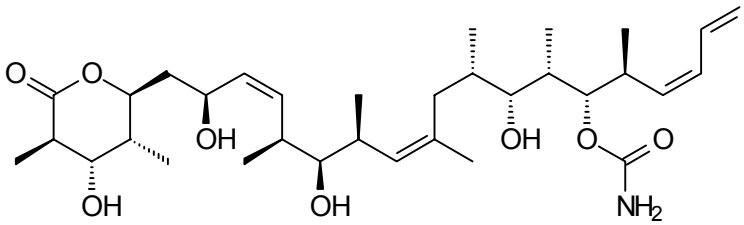
To this class belong for example the ecteinascidin 743, isolated from snails, which reorganize completely the microtubules-network which leads to cell death.



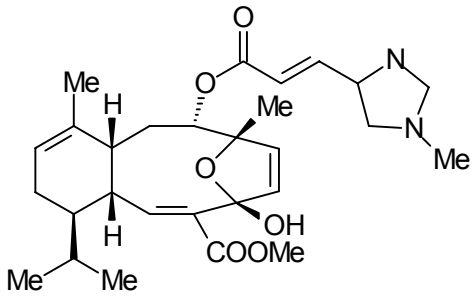
taxol



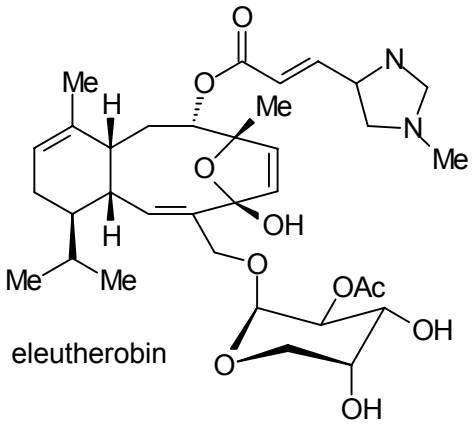
epothilone A (R = H)
epothilone B (R = Me)



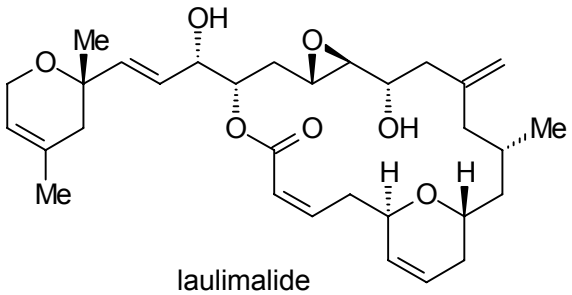
discodermolide



sarcodictyin A



eleutherobin



laulimalide

Scheme 2.3: *Selected natural products with tubulin polymerization and microtubule stabilization properties.*

2.3 Structure and Activity Relationships of Epothilones

Through investigations of the isolated natural epothilones as well as their synthetically obtained large number of derivates, it was possible to find and to explain some structural requirements for the biological activity within the epothilone structure.[31] The cytotoxicity data for many of the epothilone analogues were compatible with those of the natural epothilones, which hold a considerable promise to find the compounds with the best properties as a drug candidates. The cytotoxicity investigations were made by measurements of the tubulin polymerization through Filtrations-Colorimetric-Assays methods.[2, 36] On Figure 2.4 is represented the chemical structure of epothilone, divided on four regions A-D, which may easier to explain many relationships between the structure and the effect on biological action.

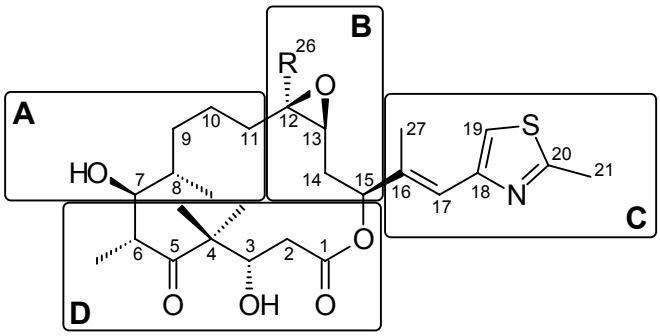


Figure 2.4: *Structure and activity releationships of the epothilones.*

Region A includes the C7-C11 part from the carbon skeleton and is relative sensitive against modifications. For example the change of the ring size or the stereochemistry of C8, as well as the addition or removal of a methyl group on this position, resulted in considerable loss of biological activity.

In contrast, changes in region B (C12-C15) are well tolerated. It was found that the absolute configuration of the epoxides had a small influence on the biological activity and that both stereoisomers exhibit actually high activity. The derivates of epothilones C and D with a double bound are also active and additionally it was proved that changes in the geometry of the double bound as well as the epoxide derivates obtained from an *E*-olefin, had little effect on the activity. Since the discovery that epothilone B is more active than A, the role of the C12 substituent was extensively studied, whereby other alkyl substituents were also accepted and the resulting derivates showed high activity. The (*S*)-configuration at C15 seems to play an important role, because inversion of this configuration leads to a significant decrease of tubulin polymerization activity.

Modifications in region C reveal less tolerance than in region B. Specifically, depletion or direct attachment of the aromatic moiety at C15, as well as replacement of the C20 methyl group with bulkier alkyl or aryl substituents, resulted in a loss of cytotoxic properties. On the other hand only a hydrogen atom as a substituent at C20 lead to a small positive changes in the activity. Furthermore, replacement of the C16 methyl group with an ethyl group, and the thiazole ring by a number of structurally diverse aromatic moieties turned out to be, in general, detrimental to biological activity. The only exceptions were *N*-containing aromatic compounds like oxazoles, 2-pyridyl or 2-thiazoyl-containing compounds, where the nitrogen is on the same position as in the natural epothilones and the properties of these analogues are comparable to those of the natural products.

The region D is also relative sensitive towards structural changes. For example, inversion of the C3 stereochemistry resulted in significantly reduced potency, as did a cyclopropane substitution on C4-position instead of geminal dimethyl moiety. Similar loss of activity was observed, when the C5, C6 and C7 sbstituents were removed or when the ketone at C5 was reduced. An interesting fact was found when an *E*-olefin was introduced at C2-C3 bound. The resulting compounds retained considerable potency.

2.4 Chemistry of the Epothilones

Soon after the recognition of the importance of the epothilones, a number of groups around the world began to pursue strategies for their total synthesis. Only few months after the structure of these macrolides was published the working groups of S. J. Danishefsky,[37] K. C. Nicolaou,[38] and D. Schinzer[39] were able to present independently successful total syntheses of epothilones A and B. In the following time many other working groups have published contributions to the existing synthetic strategies as well as new total syntheses, and essays[31, 40] about the biological role of epothilones.

Within the scope of the general introduction of this thesis it is not possible to present the entire existing literature on this field. Therefore only a short selection of the first total syntheses is compiled. For a more comprehensive representation of the chemistry and biological activity of epothilones the review of K. C. Nicolaou[31] is recommended.

2.4.1 The Danishefsky Strategies to the Synthesis of Epothilones

The first total synthesis of both epothilones A and B including their desoxy precursors epothilones C and D respectively, were carried out in the working group of S. J. Danishefsky, who made major contributions in the field of epothilone research. In the published synthesis a number of interesting reactions and sequences were used as a means to install functionality and control stereochemistry. For the construction of the macrocycle, Danishefsky and co-workers applied three main strategies, which include a macroaldolization reaction,[41] an olefin metathesis approach[42] and a macrolactonization procedure.[41] In their first published total synthesis of epothilone A and later also of epothilone B two key-step reactions were employed, namely a stereospecific SUZUKI-type cross-coupling for combining two synthetically obtained fragments, and a macrocyclization-aldol reaction for the ring formation (see Figure 2.5). This synthesis was taken as an example and is schematically presented in the following discussion.

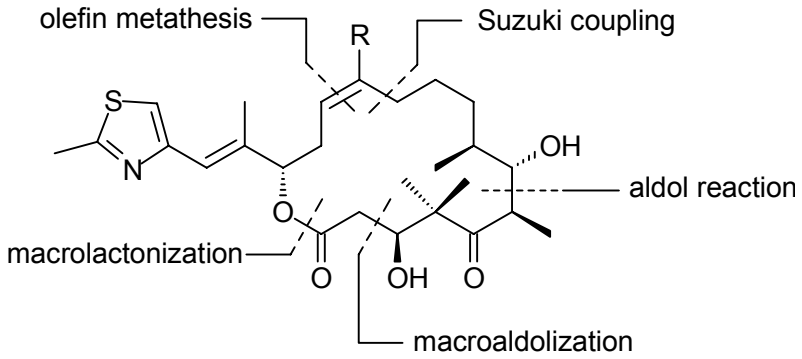
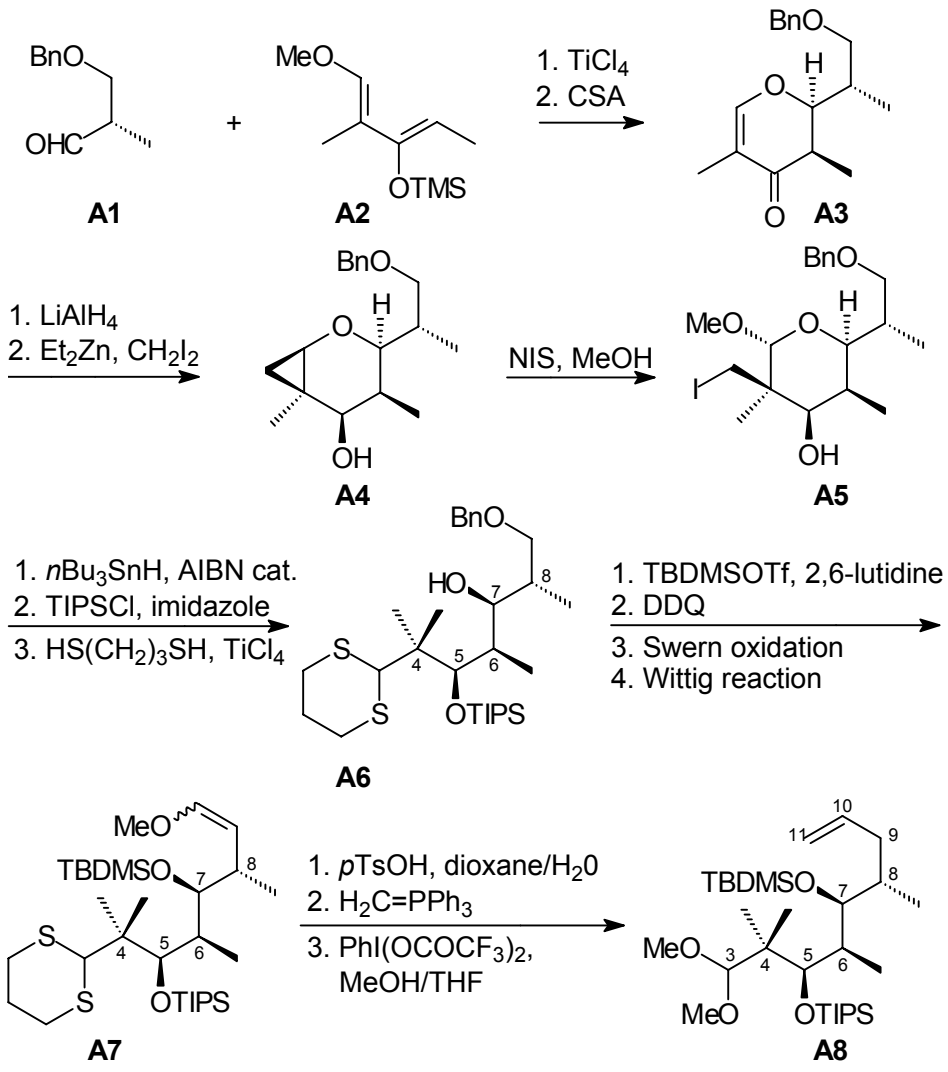


Figure 2.5: *Strategic bond disconnections applied in the total syntheses of epothilone A and B by Danishefsky et al.*

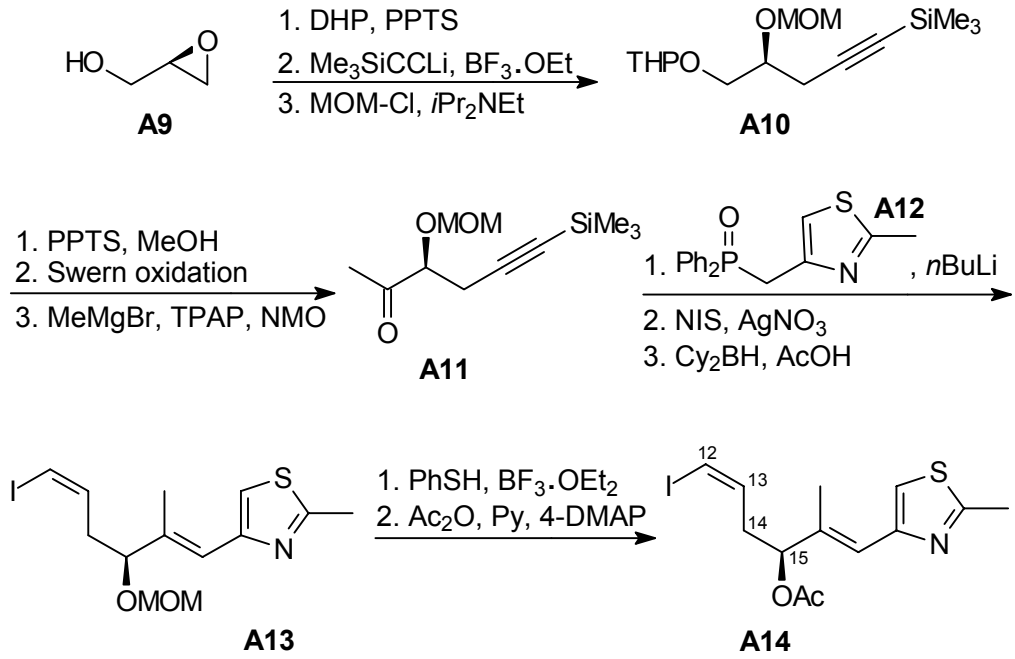
The synthesis of fragment C3-C11 was started with formation of the dihydropyran ring **A3** by a Lewis acid catalyzed stereoselective cyclocondensation of the enatiomerically pure aldehyde **A1** with the Danishefsky diene **A2** (see Scheme 2.4). The chirality of aldehyde **A1** determines the configuration of the new stereocentres in the condensation product **A3**. Thereafter followed a stereoselective reduction of the keto group with lithium aluminium hydride and the double bound was converted via a SIMMONS-SMITH reaction to the cyclopropane derivative **A4**. The opening of the cyclopropane ring was done with *N*-iodosuccinimide (NIS) in methanol, which leads to product **A5**. Compound **A6** was obtained after subsequent radical dehalogenation of iodide **A5** followed by protection of the hydroxy moiety, and thioacetalization of the intermediary formed aldehyde. The

product **A6** includes the centers C6 and C8, which were prepared in the correct configuration, as it was necessary according to the structure of the target molecule. Additionally, **A6** was a key building block, because it was also suitable for the alternative synthetic routes to epothilone and its analogues, reported later by Danishefsky et al. Further silyl protection of the new formed hydroxyl group in **A6**, followed by cleavage of the benzyl group, then SWERN oxidation and WITTIG reaction transformed the key building block **A6** to the methoxyvinyl ether **A7**. Later this vinyl ether was hydrolysed with *p*-toluenesulfonic acid to the aldehyde which was reacted with methlytriphenyl-phosphonium bromide and through a subsequent transacetalization the acetal **A8** was obtained. Compound **A8** represents the C3-C11 fragment of the desired carbon skeleton, which is one of the two main building blocks necessary for the synthesis of the epothilone A and B as well. Sequential formation and opening of the dihydropyran system was the key tactic for introduction of the stereochemistry into the final open-chain intermediate **A8**.



Scheme 2.4: *Synthesis of the C3-C11 key fragment **A8**.*

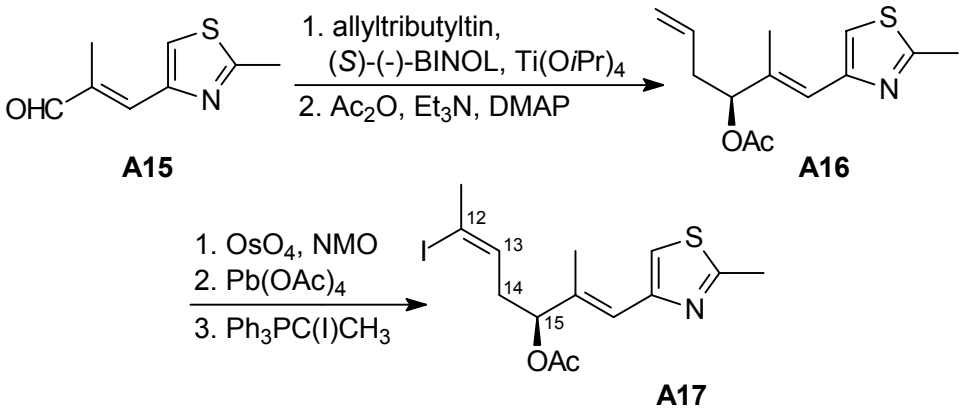
The second building block C12-C15, employed in the macroaldolization strategy of Danishefsky et al, contained the side chain with the aromatic moiety. Initially for the synthesis of epothilone A the (*R*)-glycidol **(A9)** was used as a starting material, where the hydroxyl group was protected with dihydropyran (see Scheme 2.5). Subsequent opening of the epoxide leads to a secondary alcohol, which was protected as methoxymethyl ether and the compound **A10** was formed. After cleavage of the tetrahydropyrane moiety, followed by SWERN oxidation and subsequent GRIGNARD reaction the methylketone **A11** was obtained. This compound was reacted with the EMMONS reagent **A12** and the silyl group was replaced with iodine with the help of *N*-iodosuccinimide. Thereafter followed hydroboration whereby the (*Z*)-iodoalkene **A13** was received. At the end, the methoxymethyl ether **A13** was cleaved, and the resulting compound was acetylated to give the product **A14**. The desired stereochemistry of the C12-C15 fragment was established through the use of the enantiomerically pure starting material **A9**.



Scheme 2.5: *Synthesis of the C12-C15 key fragment **A14**.*

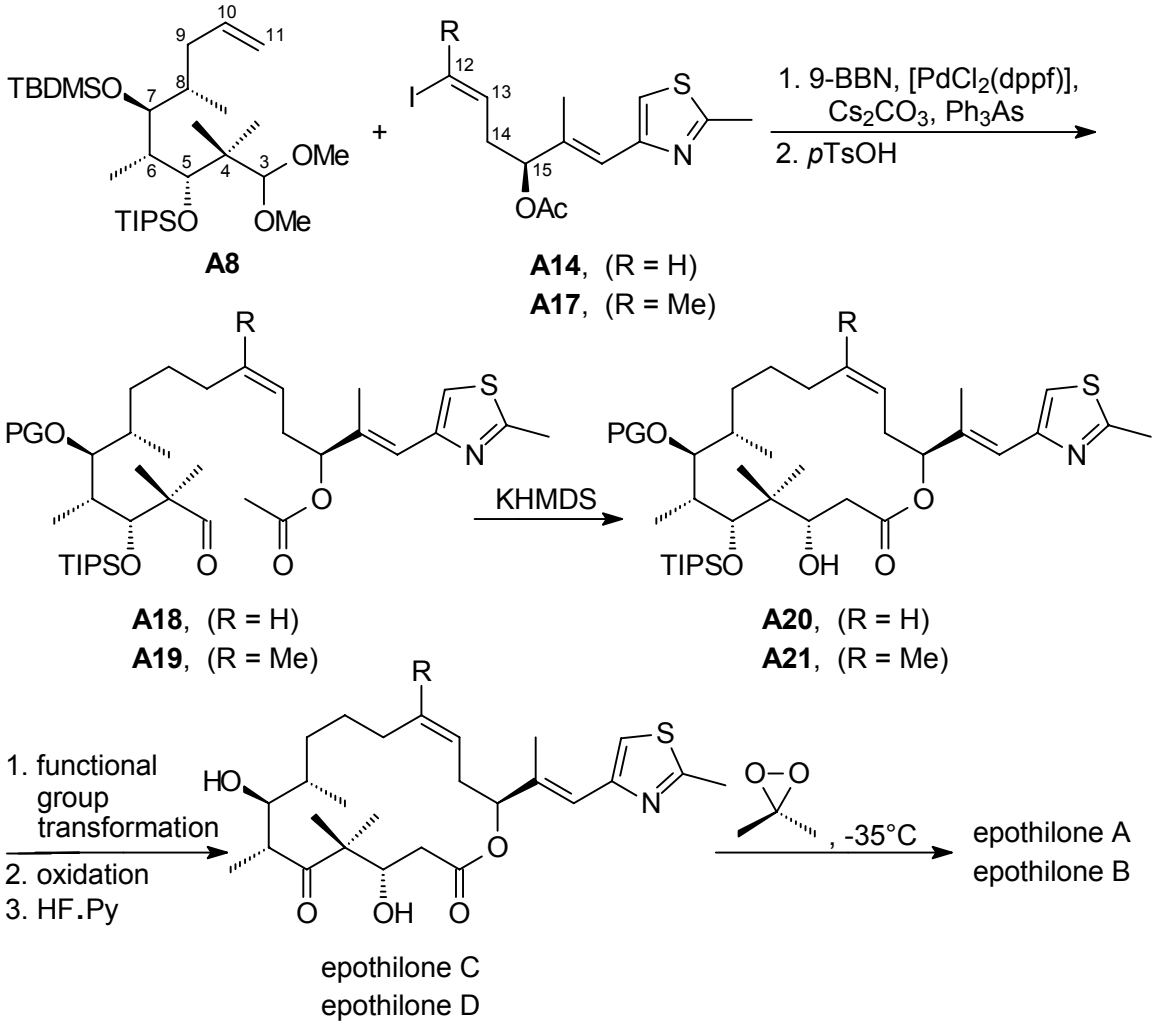
Short time after the successful synthesis of epothilone A, Danishefsky et al. have published also a convergent total synthesis of epothilone B, in which they applied the same macroaldolization strategy for the ring formation. This time, the second building block C12-C15 was synthesized starting from the aldehyde **A15**, which was reacted with allyltributyltin under enantioselective catalysis and subsequently acetylated to give the compound **A16** (see Scheme 2.6). Thereafter this compound was dihydroxylated and after

glycol cleavage transferred to the vinyl iodide **A17** by WITTIG reaction. The product **A17** was an analogue to the above described compound **A14** and had an additional methyl group at C12, which was obligatory for the synthesis of epothilone B.



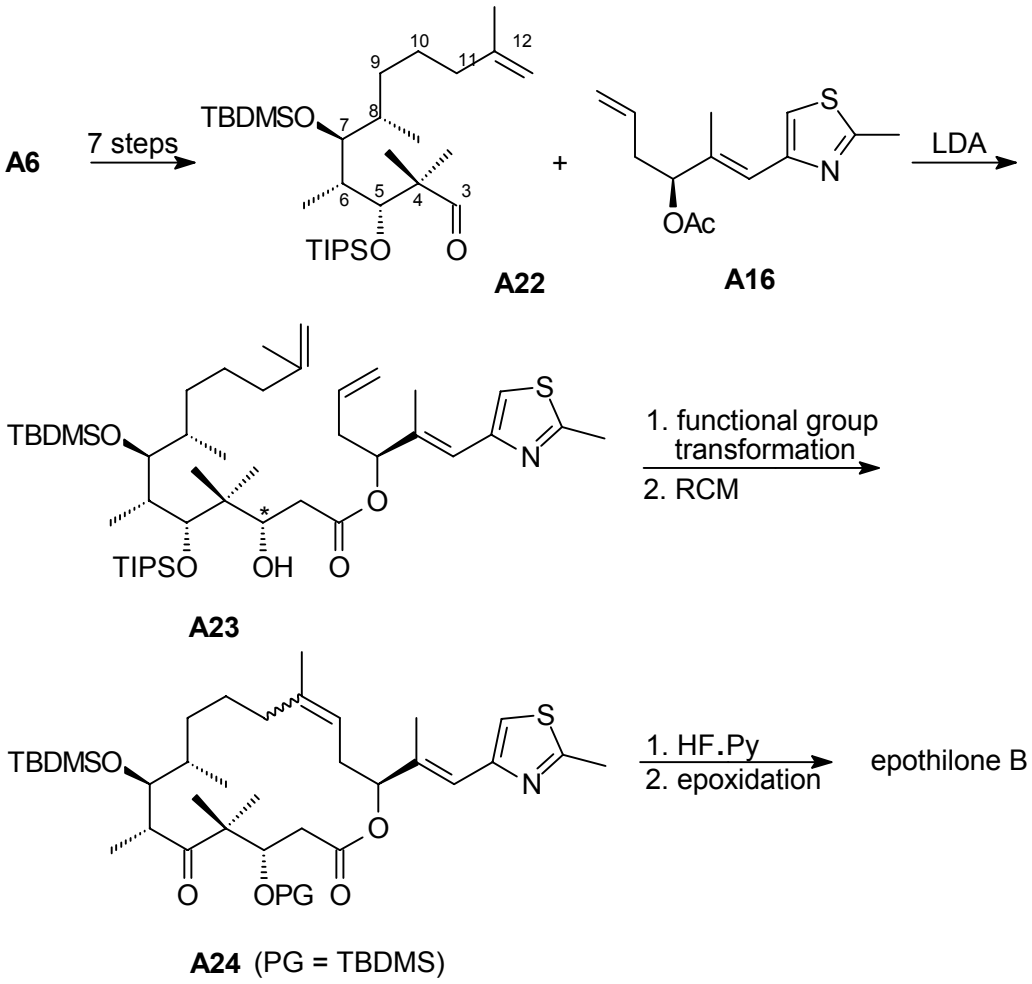
Scheme 2.6: *Synthesis of olefin **A17** as a starting material for the Suzuki-coupling.*

In assembling both fragments, a stereospecific SUZUKI coupling allowed the union of intermediates **A8** and **A14** for epothilone A or **A8** and **A17** for epothilone B to form after an acetal cleavage compound **A18** or **A19**, respectively (see Scheme 2.7). These intermediates underwent a stereoselective ring closure through an intramolecular aldol reaction to give the desired macrocycles **A20** with yield of 51% (stereoselectivity ca. 6:1) and **A21** with yield of 64% (stereoselectivity ca. 3:2), respectively. Subsequent functional group transformations led to the desoxy precursors epothilone C and D, and finally after stereoselective epoxidation the epothilones A and B were obtained.



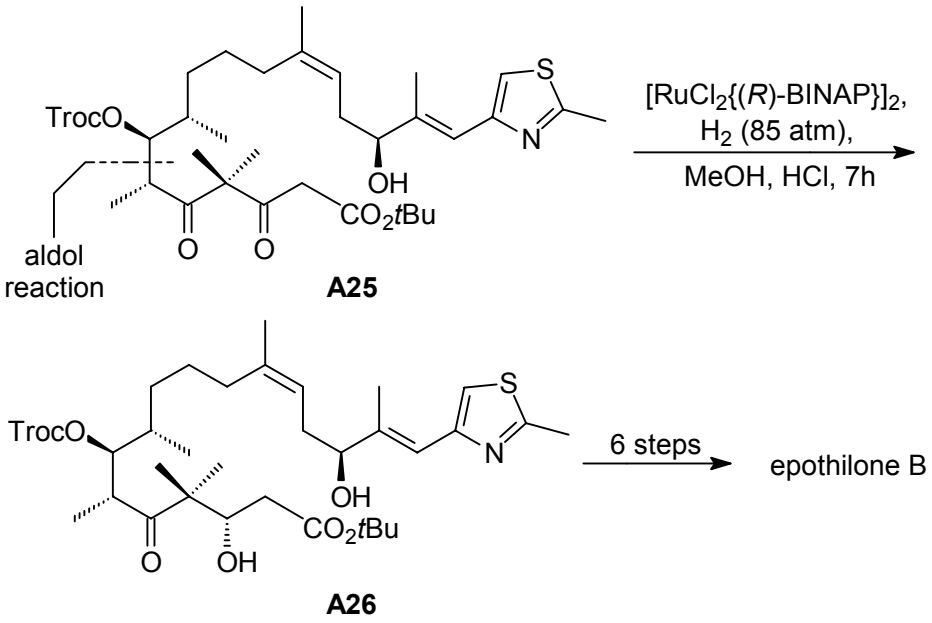
Scheme 2.7: *Suzuki-coupling and macroaldolization reaction for preparation of epothilone A and B.*

The already mentioned olefin metathesis strategy to obtain epothilone B starts also from the key building block **A6** (see Scheme 2.8). After removing of the benzyl group the hydroxy moiety was oxidized to obtain an aldehyde, which appeared as a starting material for the chain elongation. In this way compound **A22** was synthesized in several steps. Coupling of **A22** with compound **A16** via aldol addition results in compound **A23**. After several modifications the ring was closed through an olefin metathesis reaction and the macrocycle **A24** was obtained. For the olefin metathesis the molybdenum-based SCHROCK catalyst was used.[43] In this case, however, the C12-C13 double bond was formed as a mixture of *Z*:*E* isomers in an approximately 1:1 ratio. After cleavage of the protecting groups, epothilone D was obtained and final stereoselective epoxidation led to epothilone B.



Scheme 2.8: *Synthesis of epothilone B through an olefin metathesis approach*.

Because of the low stereoselectivity in the olefin metathesis approach, as well as the poor yields in the case of the macrocyclization-aldol reaction, there was a high motivation in establishing alternative methods for ring closure.[44] The third route established by Danishefsky et al. was the macrolactonization strategy. For that purpose compound **A25** was synthesized (see Scheme 2.9). The most remarkable part of this route was the subsequent regio- and stereoselective NOYORI reduction[45] of the keto moiety at C3 to obtain compound **A26**. This was carried out by the use of a ruthenium-binaphtol-complex as a catalyst under a hydrogen pressure of 85 atm. The stereoselectivity was higher than 95%. From compound **A26**, the epothilones were prepared in several steps including the macrolactonization reaction.



Scheme 2.9: *Regio- and stereoselective Noyori-reduction.*

2.4.2 The Nicolaou Strategies to the Synthesis of Epothilones

On the field of epothilone synthesis K. C. Nicolaou and co-workers have made a remarkable work. The special merits of Nicolaou et al. were to establish different synthetic routes not only to the known natural epothilones A-F, but also to a big number of epothilone analogues. Additionally, in the working group of Nicolaou experiments on solid phase for the construction of epothilone libraries were carried out.[46] Through combinatorial methods it was possible to synthesize different single fragments, which were used later for the formation of the macrocycles. The synthesis of a big number of epothilone derivatives allowed the investigation and understanding of the relationships between structure and biological activity.

Amongst many strategies, Nicolaou et al. considered the olefin metathesis approach[47] for constructing of the macrocycle and simultaneously applied as well a second strategy based on macrolactonization[38, 46]. Both methods were similar to that presented in the work of Danishefsky et al. The first total synthesis made in the working group of Nicolaou led to epothilone A and its desoxy precursor epothilone C employing the olefin metathesis strategy (see Figure 2.6).

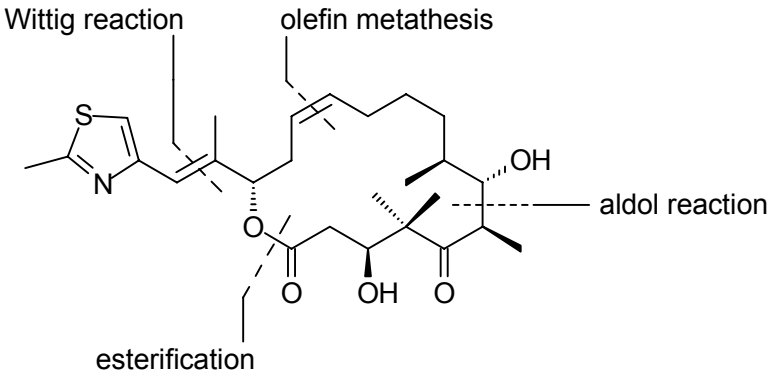
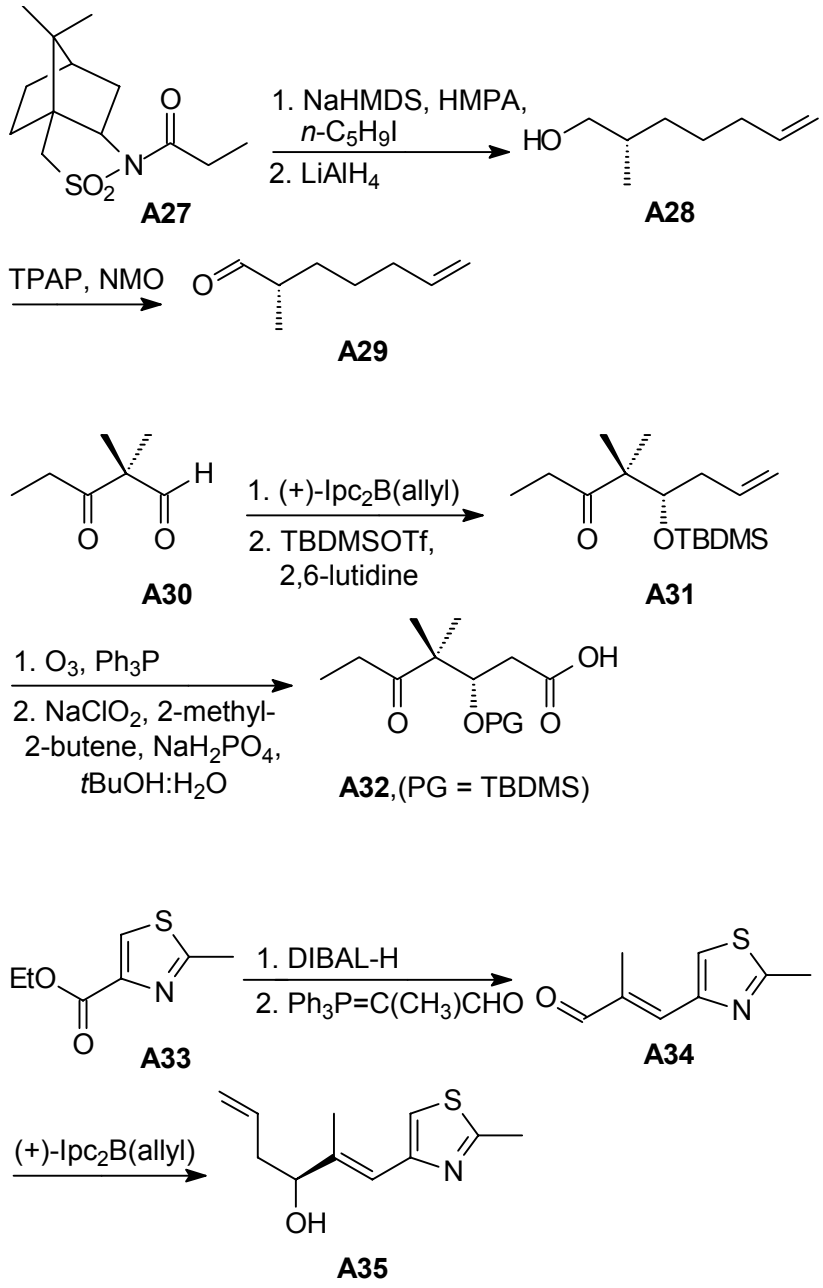


Figure 2.6: *Strategic bond disconnections applied in the total synthesis of epothilone A by Nicolaou et al.*

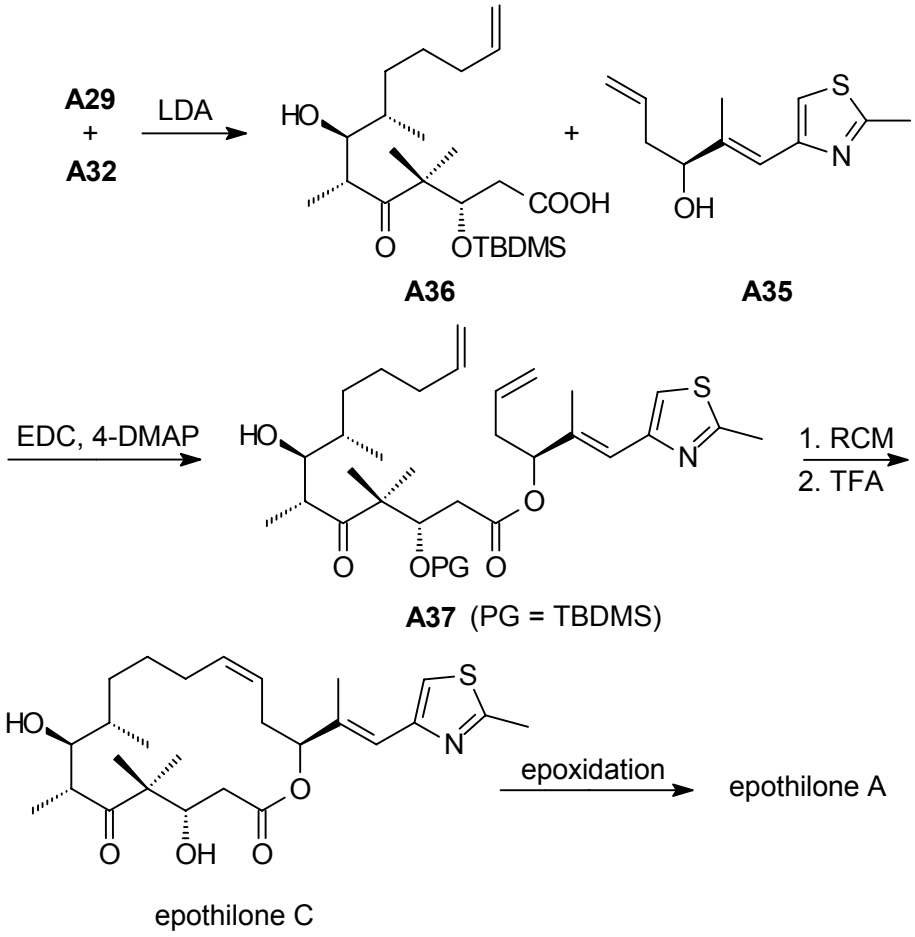
After a retrosynthetic analysis the target molecule was divided in three key building blocks, which were synthesized independently, following different synthetic pathways than the ones described by Danishefsky et al. The C7-C12 building block **A29** was obtained starting from *N*-propionyl bornyl sulfonamide **A27**, which was alkylated with ω-iodo-pentene and the resulting product was subsequently reduced to alcohol **A28** by cleavage of the bornyl sulfonamide residue (see Scheme 2.10). Further oxidation with *N*-methylmorpholin-*N*-oxide and tetra-*n*-propylammoniumperruthenate led to aldehyde **A29**. The synthesis of the C1-C6 fragment **A32** began with the stereoselective allylation of the keto aldehyde **A30** using the BROWN reagent allylisopinocamphenylborane. The new-formed hydroxy moiety was protected with a silyl group and the compound **A31** was obtained. An oxidative degradation of the double bound to a carboxyl group provided the desired product **A32**. The thiazol-fragment **A35** was synthesized starting from the carboxylic ester **A33**, which was reduced with diisobutylaluminium hydride to the corresponding aldehyde. Subsequent WITTIG olefination gave the aldehyde **A34**, which was further transformed through a BROWN allylation[48] to the compound **A35**.



Scheme 2.10: *Synthesis of the key fragments for the olefin metathesis approach of Nicolaou et al.*

The two fragments **A29** and **A32** were combined through an aldol condensation with lithiumdiisopropyl amide (LDA) to form the acid **A36**, which through an esterification with the thiazol alcohol **A35** gave the starting material **A37** for the olefin metathesis reaction for constructing of the macrocycle (see Scheme 2.11). For the ring closing metathesis (RCM), Nicolaou et al. used the GRUBBS catalyst $[RuCl_2(=CHPh)(PCy_3)_2]$.[49] Thereafter, similar to the methods established from Danishefsky et al., the double bound of the desoxy

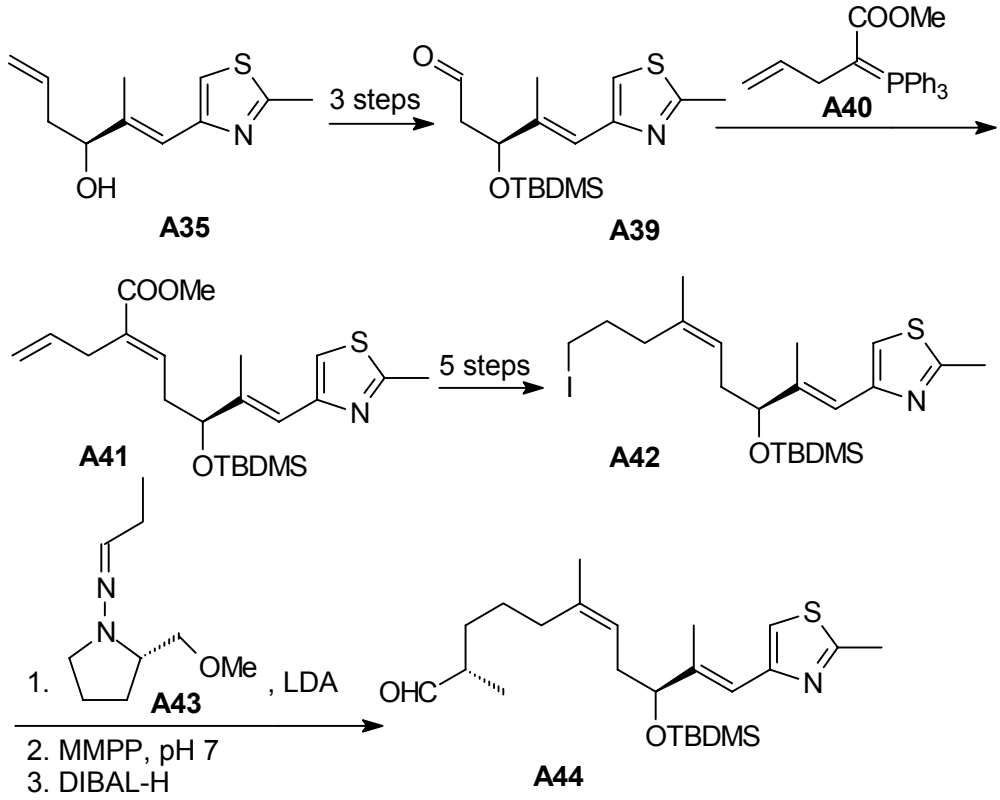
precursor epothilone C was stereoselectively oxidized to an epoxide, to give the end product, in this case epothilone A. As stereoselective oxidation reagents were applied 3,3-dimethyldioxirane (65% yield, diastereoselectivity ca. 3:1), 3,3-methyl-(triflouromethyl)-dioxirane (75% yield, diastereoselectivity ca. 5:1), or *m*-chloroperbenzoic acid (48% yield, diastereoselectivity ca. 3:1).



Scheme 2.11: *Aldol reaction and olefin metathesis for preparation of epothilone A.*

Short time after establishing the first strategy for the building of the ring system, Nicolaou and co-workers published their second route, which applied an YAMAGUCHI macrolactonization procedure[50] for the ring formation. In this way they carried out the stereoselective syntheses of both epothilones A and B, whereas here is schematically presented the synthesis of epothilone B. The construction of the carbon-chain starts with the formation of the fragments C1-C6 **A38** and C7-C15 **A43**, which were assembled through an aldol reaction with LDA to give the ring closure precursor **A44**. The first building block C1-C6 **A38** was synthesized starting from compound **A31**. After ozonolysis of **A31** followed by reduction to the corresponding alcohol, which was further protected,

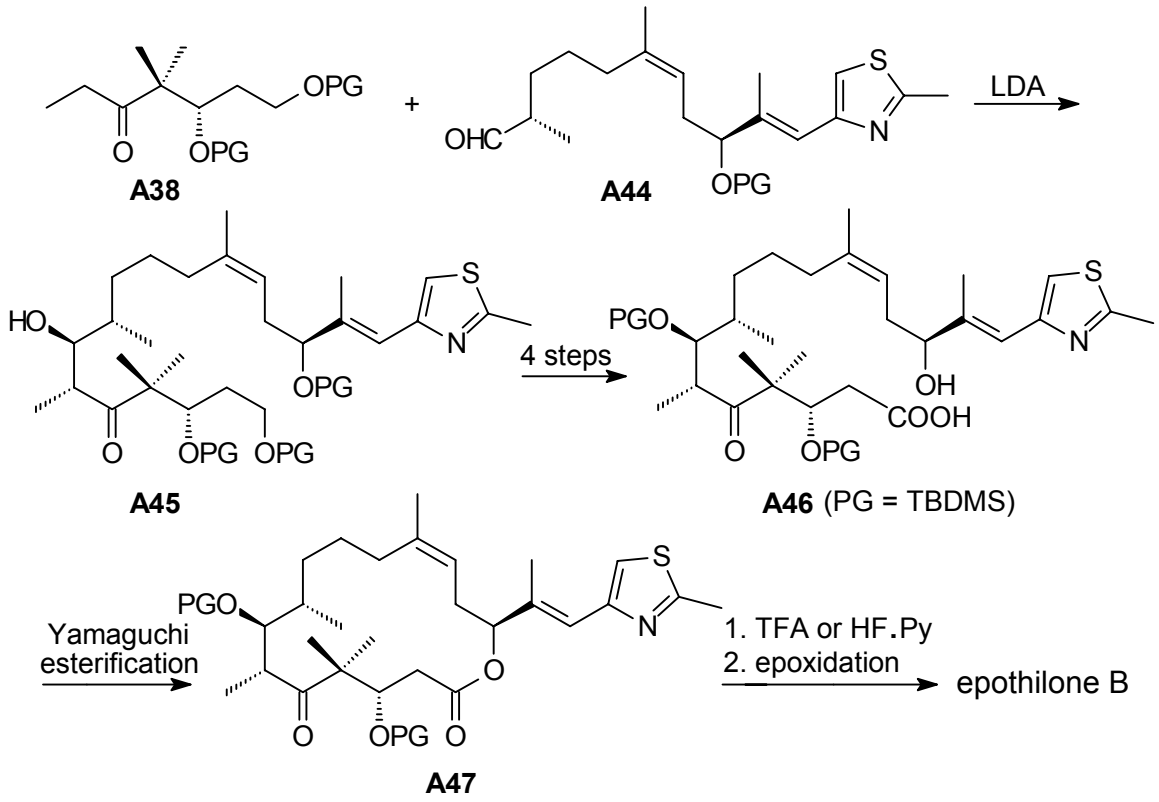
the key fragment C1-C6 **A38** was obtained. For the formation of the other building block C7-C15 **A43**, the alcohol **A35** was used as a starting material. In three steps, including an oxidation, **A35** was transformed to the thiazol aldehyde **A39** (Scheme 2.12). Thereafter, followed a *Z*-selective WITTIG reaction with the ylide **A40** which lead to the chain-elongated product **A41**. The ester function was reductively removed and after a hydroboration of the terminal double bond, the primary-formed hydroxy function was replaced by iodine to give **A42**. The configuration at C7 was controlled by a stereoselective ENDERS alkylation with SAMP-hydrazone **A43**.[51] After an oxidative cleavage of the chiral auxiliary group and subsequent reduction the desired key building block **A44** was obtained.



Scheme 2.12: *Preparation of the C7-C15 fragment **A44** for further synthesis of epothilone B.*

The applied aldol reaction for formation of compound **A45** with the new stereocenters at C7 and C6 occurs with a stereoselectivity of approximately 3:1 (Scheme 2.13). Thereafter the ring closure precursor **A45** was transformed in several steps to the carboxylic acid **A46**. The macrolactonization was carried out using the YAMAGUCHI procedure. After cleavage of the silyl protecting groups in **A47** the desoxy precursor

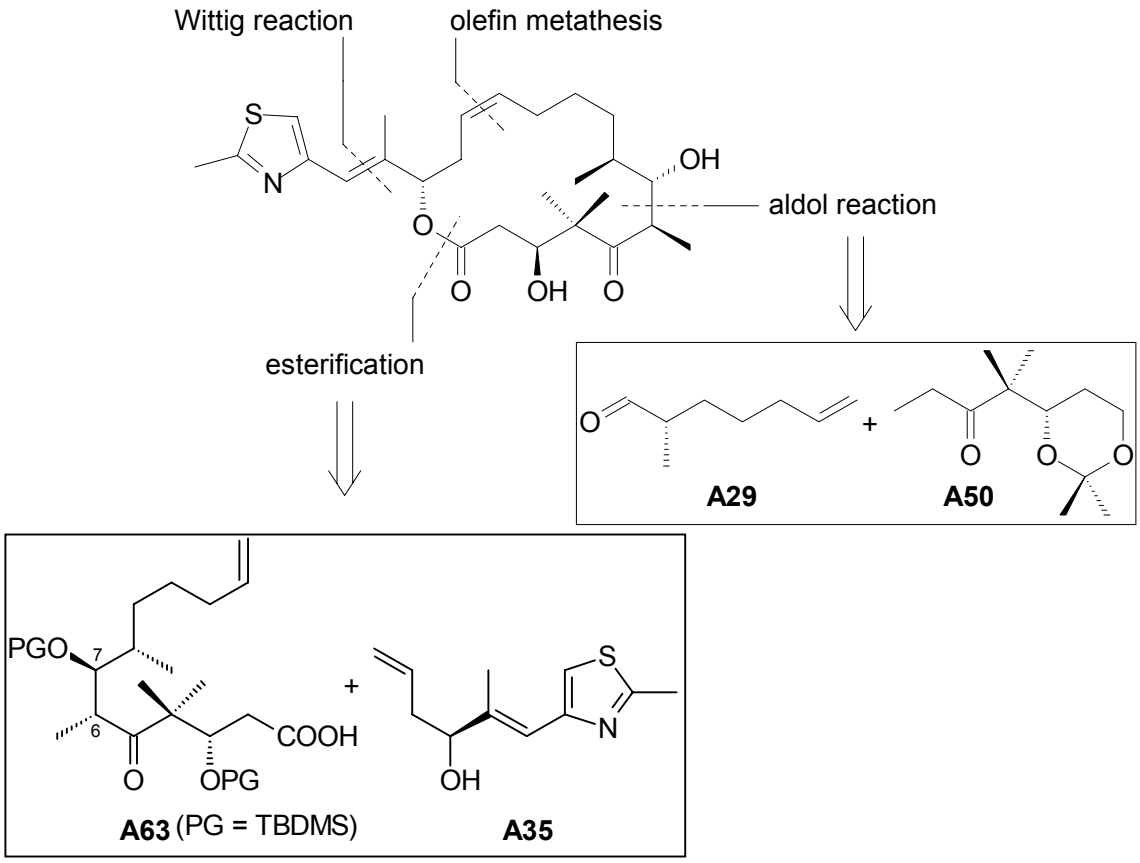
epothilone D was received. By the following stereoselective epoxidation to obtain the end-product epothilone B, diastereoselectivity of approximately 5:1 was achieved.



Scheme 2.13: *Ring formation via Yamaguchi macrolactonization*.

2.4.3 The Schinzer Strategies to the Synthesis of Epothilones

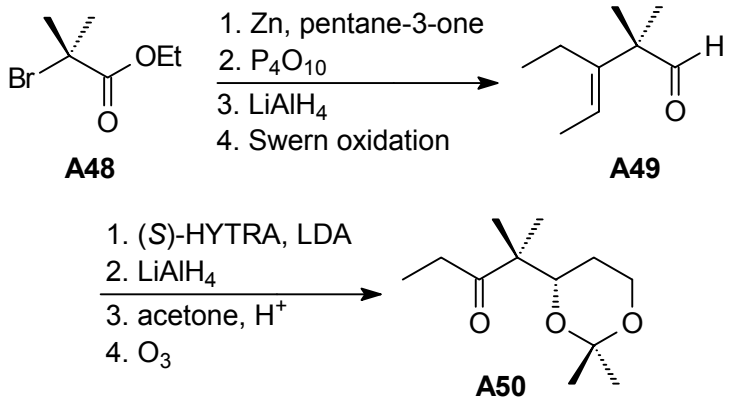
Another working group with big contributions in the field of the epothilone synthesis is the group of D. Schinzer. At the beginning of 1997, Schinzer et al. published their independently developed olefin metathesis approach to epothilones A and C.[39] Their design required three key intermediates **A50**, **A29** and **A35**, which were obtained by asymmetric synthesis (see Scheme 2.14). Compounds **A29** and **A35** were also used in the total synthesis of Nicolaou et al. The formation of the single (6*R*,7*S*) diastereomer in the aldol condensation of the ethyl ketone **A50** with the aldehyde **A29** under the influence of LDA was most impressive, and was attributed to the influence of the acetonide moiety. Attachment of the side-chain **A35** by esterification, ring closure through olefin metathesis, and epoxidation with 3,3-dimethyldioxirane, led to the desired products epothilone C and A respectively. Like Nicolaou et al., the group of Schinzer also applied the GRUBBS catalyst [$RuCl_2(=CHPh)(PCy_3)_2$], for the ring closing metathesis reaction.



Scheme 2.14: *The Schinzer et al. strategic bond disconections and retrosynthetic analysis for preparation of epothilone A.*

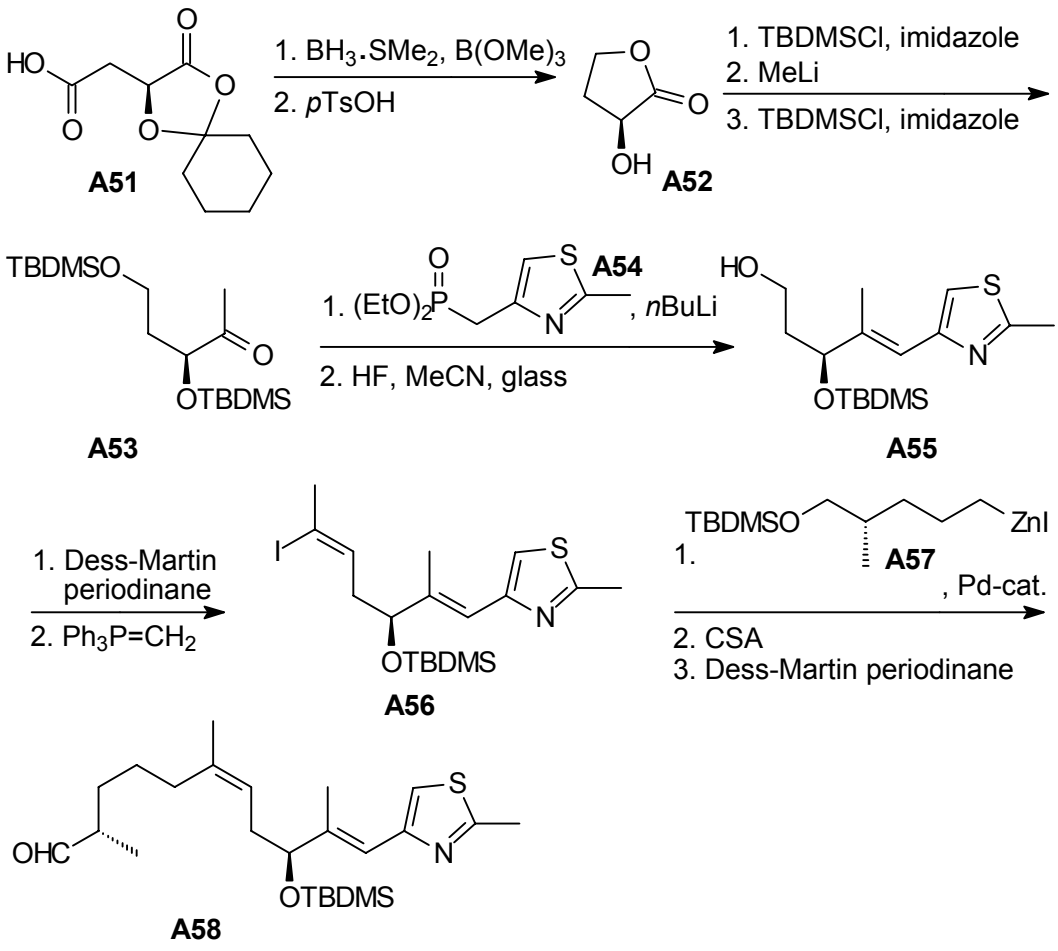
In 1998, Schinzer et al. established as well a new synthetic route[52] to epothilone B using also the macrolactonization strategy as a key reaction step for the ring formation, which is presented in the following. The most innovative steps in this synthesis are the successful introduction of the correct chiralities at the stereocentres C3, C6 and C7 via stereoselective aldol reactions. The main key intermediates were the C1-C6 fragment **A50** and the C7-C15 fragment **A58**.

The synthesis of the C1-C6 fragment was started from the α-bromoester **A48**, which was condensed through a REFORMATSKY reaction with pentane-3-one (see Scheme 2.15). After subsequent reduction and oxidation the coupling product was transformed to the appropriate aldehyde **A49**. Thereafter followed a stereoselctive aldol reaction with (*S*)-HYTRA [(*S*)-2-hydroxy-1,2,2-triphenylethylacetate] according to the method of M. Braun[53] and the correct chirality at C3 was introduced. The condensation product was further reduced, the resulting 1,3-diol moiety was protected as an acetal and the double bound was ozonized to give the key compound **A50**.



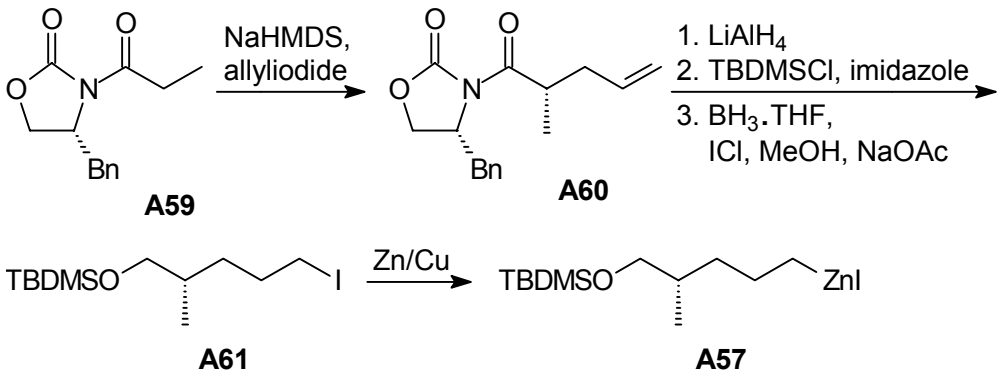
Scheme 2.15: *Synthesis of C1-C6 building block **A50**.*

The synthesis of the C7-C15 fragment was beginning from the (*S*)-hydroxy succinic acid derivative **A51**, which after reduction and cleavage of the protecting group was transformed to the hydroxy butyrolactone **A52** (see Scheme 2.16). Further silyl protection of the hydroxy moiety, ring opening with methyl lithium and subsequent protection of the resulting hydroxyl group led to the ketone **A53**. The thiazol-containing residue was introduced by a WITTIG-WADSWORTH-HORNER reaction with **A54**, and after deprotection of the chain-elongated product, the compound **A55** was obtained. DESS-MARTIN oxidation and WITTIG reaction gave the vinyl iodide **A56**. Thereafter followed a palladium-catalyzed coupling of **A56** with the alkyl zinc compound **A57** and the resulting product was deprotected and oxidized to give the desired C7-C15 key fragment **A58**. The coupling reaction presented by Schintzer et al. appeared as an alternative to the SUZUKI-cross coupling used by Danishefsky et al.



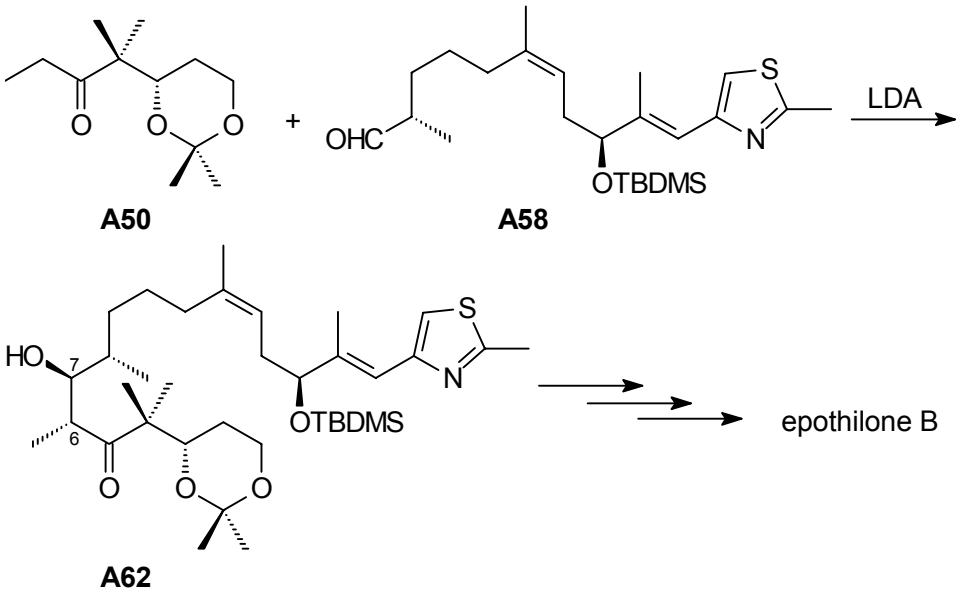
Scheme 2.16: *Synthesis of C7-C15 building block **A58**.*

The alkyl zinc compound **A57** contains the stereocenter C8 in the later macrocycle (see Scheme 2.17). The synthesis of **A57** began with the EVANS auxiliary **A59**, which allowed the introduction of the correct chirality.[54] For that purpose the EVANS auxiliary **A59** was combined in a stereoselective reaction with allyl iodide and the compound **A60** was obtained. The oxazolidinone group was cleaved by reduction with lithiumaluminium hydride and after protection of the resulting hydroxy moiety, the terminal double bond was degraded by using a mixture of borane-THF complex, iodine chloride and sodium acetate and the corresponding iodide **A61** was obtained. Compound **A61** was coupled with zinc-copper mixture to the alkyl zinc compound **A57**.



Scheme 2.17: *Synthesis of compound **A57**.*

The compound **A62** was formed via stereoselective aldol reaction with LDA of the C7-C15 fragment **A58** with the C1-C6 fragment **A50** (see Scheme 2.18). This reaction step introduced the correct configurations at C6 and C7 stereocenters. The high stereoselectivity (*de* 9:1) was reached by the chelation ability of the C1-C6 fragment, because of the acetal-protecting group. After cleavage of the acetal group the synthesis to epothilone B proceeded similar to the synthesis presented in the work of Nicolaou et al.



Scheme 2.18: *Aldol reaction and macrolactonization for synthesis of epothilone B.*

2.4.4 Further Strategies to the Synthesis of Epothilones and Analogues

As it was mentioned already there are plenty of publications in the field of epothilones syntheses and it is not possible to discuss all of them in the present thesis. Therefore, only a short overview of some important publications is given in the following in addition to the first three important strategies described schematically above.

Similar to the strategy of Schinzer and Nicolaou, the working group of Mulzer described independently their syntheses of epothilones.[55] Herein, the key reaction steps were also an aldol reaction and macrolactonization. However, for highly stereoselective construction of the carbon chain they have used an asymmetric MUKAIYAMA aldol reaction. The further synthesis was carried out according to the strategy of Nicolaou et al., whereby the KECK-variant of the STEGLICH esterification was applied for the macrolactonization. The chiral hydroxyl group at C3-atom from the carbon skeleton was introduced by BROWN allylation. The main difference between the strategy of Mulzer compared to the earlier published syntheses was the formation of the oxirane ring before the final macrocyclization reaction. This allowed a better determination of its absolute configuration.

Furthermore, the total synthesis of S. Sinha and R. A. Lerner has to be mentioned in which aldol and retroaldol reactions was used by employing monoclonal aldolase-antibodies.[56] Another total synthesis was presented also from the working group of P. A. Grieco which is based on the olefin metathesis strategy from Danishefsky et al., and the correct configuration at C7 and C8 stereocenters was introduced via a ROUSH crotylation.[57] A further interesting total synthesis of epothilone B was presented by J. D. White, whereby the hydroxyl group at C15-stereocenter was built through an oxazolidinone-controlled hydroxylation reaction by using the DAVIS reagent which allows the reaction to proceed with high stereoselectivity.[58] One of the newest work concerning the syntheses of epothilone A and B was published by Carreira et al.[59] Here, a C13-C15 bridging nitrile oxide unite plays the central role.

3 The Natural Alkaloid Epibatidine

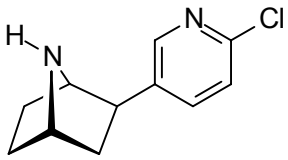
3.1 Isolation and Biological Activity

The alkaloid (-)-epibatidine (see Scheme 3.1) was isolated for the first time in 1992 from Daly and co-workers[60] from the skin of the Ecuadorian poison frog *Epipedobates tricolor*. This amphibian belongs to the family *Dendrobatidae* that inhabits the rain forest of South and Central America. To this family belong approximately 160 species and more than 200 different alkaloids were isolated from the skin of these small, often colorful frogs.[61] Most of these alkaloids show strong pharmacological activity against muscle cells and the nervous system.[62] For this reason the skin-secret from these animals has been used, until the present days, by the native people in the tropic regions of America as a source for their arrow poisons. Presumably the biological occurrence of these often extremely poisonous compounds is for the passive protection of the frogs against rapacious animals or as well for protection of their humid and sensitive skin against microbes.[63] However, the amounts of the alkaloids isolated from the natural sources are very low. For example for the isolation of 80 mg of a mixture of alkaloids, the skins of 750 frogs from *Epipedobates tricolor* was necessary, whereby the amount of the alkaloid epibatidine only, was below 1 mg.[60]

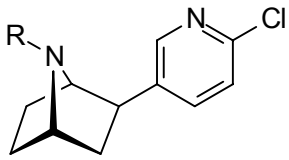
Initially, the crude alkaloid mixture isolated from the *Epipedobates tricolor* was investigated because of the observed STRAUB-phenomenon, when mice were treated with this skin-extract.[64] In general it was known, that when the STRAUB-phenomenon appeared an opiate-like analgesic activity should be expected. Actually it was found, that the special activity of the crude alkaloid mixture is due to the natural substance epibatidine.[60] In the applied mice Hot-Plate Test, epibatidine showed about 200-fold higher activity than morphine.[65] However, further pharmacological investigations were made, which assumed that the natural product epibatidine is a very potent analgesic agent and has a non-opiate mechanism of action.[66] Strong hints for this were the facts that the general opiate-antagonist naloxone is ineffectual against the symptoms caused by epibatidine and that the affinity of epibatidine to the known natural opiate receptors is 2000 times lower than those of morphine.[66]

The chemical structure of epibatidine represents an azabicyclic system and contains the 7-azabicyclo[2,2,1]heptane unit with an *exo*-oriented 5-(2-chloropyridyl) substituent (see Scheme 3.1).[61, 67, 68] The structure and activity relationship studies show that the nucleophilic character of the nitrogen and the configuration of the aromatic substituted carbon play a crucial role for the high biological activity.[69] This was proven by comparing the activity data of the *N*-acetyl derivative **B1**, the *N*-methyl derivative **B2**, and the *endo*-

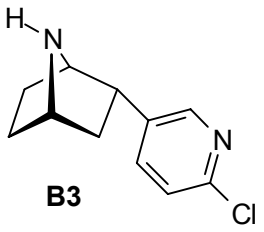
epimer of epibatidine **B3** with those from the natural compound. The activity, tested on mice, was almost the same in the case of epibatidine and its *N*-methyl derivative **B2**, whereas the *N*-acetyl derivative **B1** and the *endo*-epimer **B3** were inactive. A less important role for the biological activity plays the configuration of the bridged carbons on the molecule. The activity of non-natural (+)-epibatidine was nearly the same as of its natural enantiomer.



(-)-Epibatidine



R = Ac **B1**
R = Me **B2**



B3

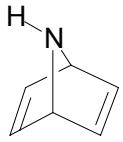
Scheme 3.1: *The natural alkaloid (-)-epibatidine and structurally related compounds.*

In the case of mice the subcutaneous dose of 10 µg/kg epibatidine leads to poisoning symptoms like cramps and difficulties in breathing, whereas higher than 10-fold doses are lethal. The same doses of the inactive *endo*-epimere **B3** and *N*-acetyl epibatidine **B1** cause no poisoning symptoms or other effects.[69]

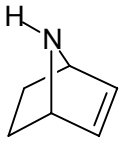
Qian et al.[70] pointed out the structural similarities of epibatidine with nicotine and compared their activities. In fact epibatidine was 120 times more active than nicotine. Furthermore, it was found out that epibatidine shows a selective and the strongest so far known affinity to the acetylcholine receptors, which are the targets of nicotine as well.[70, 71] The acetylcholine receptors play an important role in many diseases like PARKINSON- and ALZHEIMER- disease, addiction to nicotine, special forms of colon inflammation and various disorders of the central nervous system.[72] Therefore, selective agonists of the acetylcholine receptors like epibatidine are promising candidates for the use in therapy of these diseases. In spite of symptoms like decrease of body temperature, cramps and difficulties in breathing observed in the animal tests, the epibatidine plays also an important role as a lead structure for the development of new, extremely effective analgesics. Bannon et al.[73] were able to demonstrate that the analgesic activity of epibatidine can be partly separated from the undesired side effects. Herewith it was proved that the analgesic activity is not a fictitious activity or a consequence of poisoning.

3.2 Chemistry of the Epibatidine

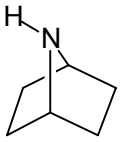
The synthesis of 7-azabicyclo[2.2.1]hepta-2,5-diene, 7-azabicyclo[2.2.1]hept-2-ene, and 7-azabicyclo[2.2.1]heptane (see Figure 3.1) systems has been the subject of numerous synthetic studies which have resulted in the development of several methods for the construction of these novel azabicyclic systems.[74] The synthesis of such bicyclic structures was only of academic interests until no natural occurring compound was known that contains this ring systems.[61, 67] Due to the novel biological activity associated with epibatidine and its paucity in nature its total synthesis has aroused the interest of many working groups around the world.



7-azabicyclo[2.2.1]hepta-2,5-diene



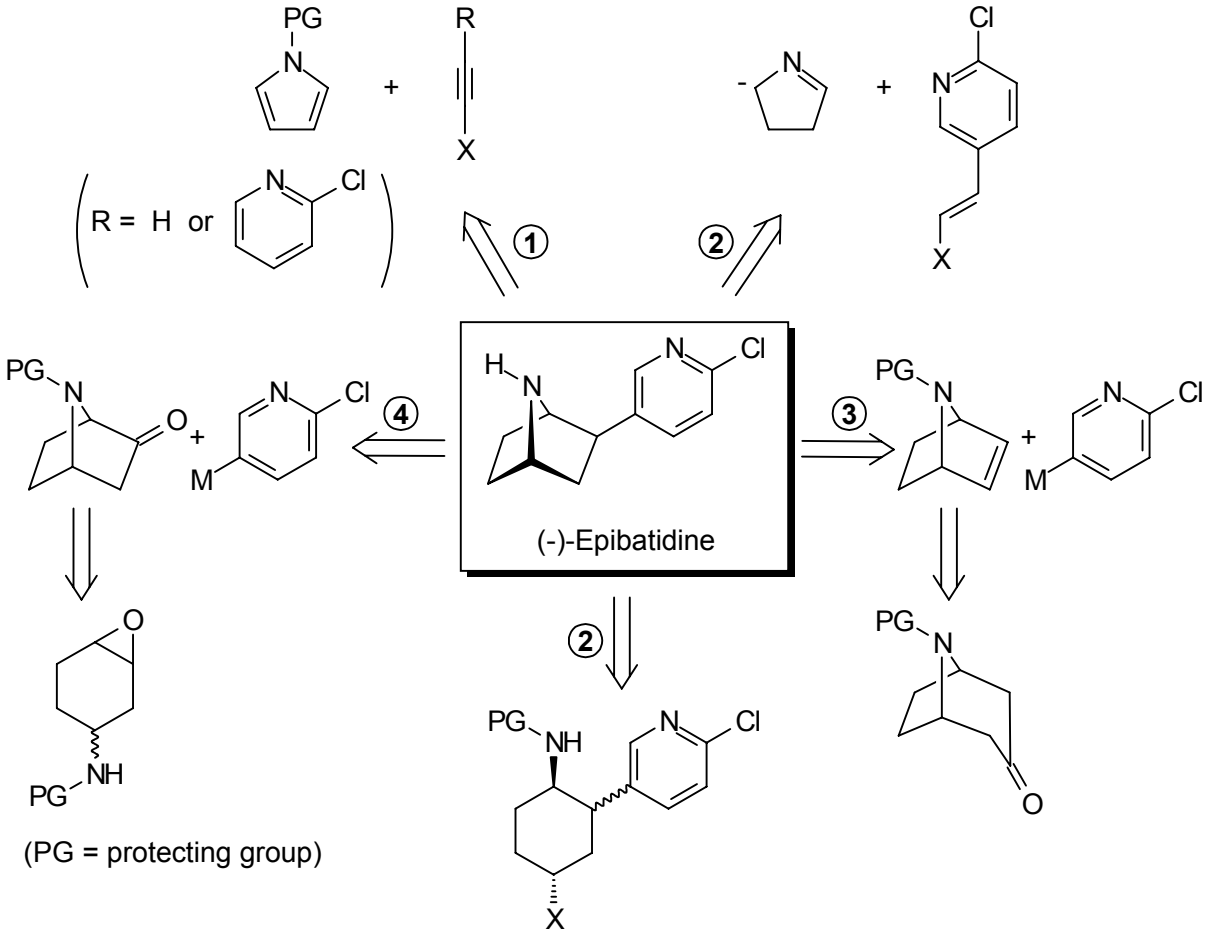
7-azabicyclo[2.2.1]hept-2-ene



7-azabicyclo[2.2.1]heptane

Figure 3.1: *7-azabicyclo[2.2.1]heptane derivatives.*

The first total synthesis was achieved by Broka and co-workers[75] and was published in 1993, nearly one year after the discovery of epibatidine by Dally et al.[61] Thereafter, almost simultaneously were reported several synthetic approaches to the epibatidine structure from different working groups. Because the absolute configuration of epibatidine was not determined until this point many of the publications described the synthesis of the both possible enantiomers (±)-epibatidine.[74] The basic strategies used for the epibatidine total syntheses are presented in Scheme 3.2.



Scheme 3.2: *Retrosynthetic pathways to epibatidine.*

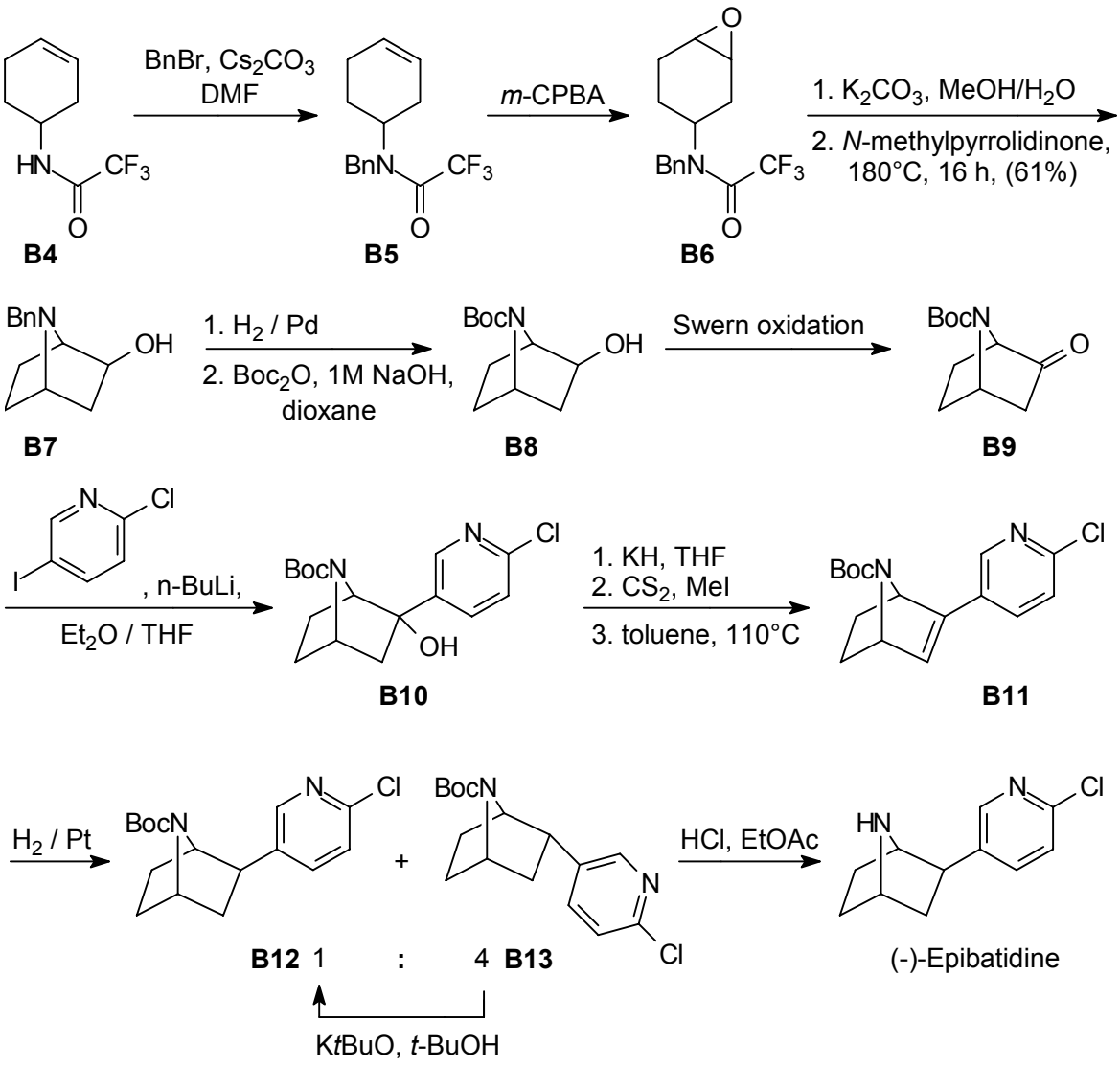
1) DIELS-ALDER reaction between an activated pyrrole derivate and an activated alkyne. The pyridyl residue can be introduced by using a suitable activated pyridyl alkyne[76, 77] or by subsequent reductive HECK reaction with a 3-metallated pyridine.[78, 79]
2) 1,3-Dipolar cycloaddition of an azomethine ylide to an activated pyridyl alkene.[80]
3) Ring contraction of 8-azabicyclo[3.2.1]octane derivative to give 7-azabicyclo[2.2.1]hept-2-ene. The pyridyl residue was introduced via a reductive Pd-catalyzed HECK-type coupling.[81]
4) Addition of 3-metallated pyridine to 7-azabicyclo[2.2.1]hept-2-one, which was obtained from a 3,4-epoxycyclohexane derivative.[62, 82, 83]
5) Ring closure of 2-pyridyl cyclohexylamine with a suitable leaving group (X) at C4 (transannular cyclization reaction).[75, 84-88]

From the big amount of published total syntheses of epibatidine only the total synthesis of Fletcher et al.[68] is discussed in the present work. This synthetic strategy includes the preparation of *N*,*N*-benzyltrifluoroacetyl-3-cyclohexenylamine **B5** (see Scheme 3.3) which was as well one of the target compounds in our straightforward synthesis of cyclohexenylamines by olefin metathesis reaction (compound **63d**, see Section 6.3). In this context our synthetic pathway represent also a formal total synthesis of epibatidine.

3.2.1 The Fletcher Strategy to the Synthesis of Epibatidine

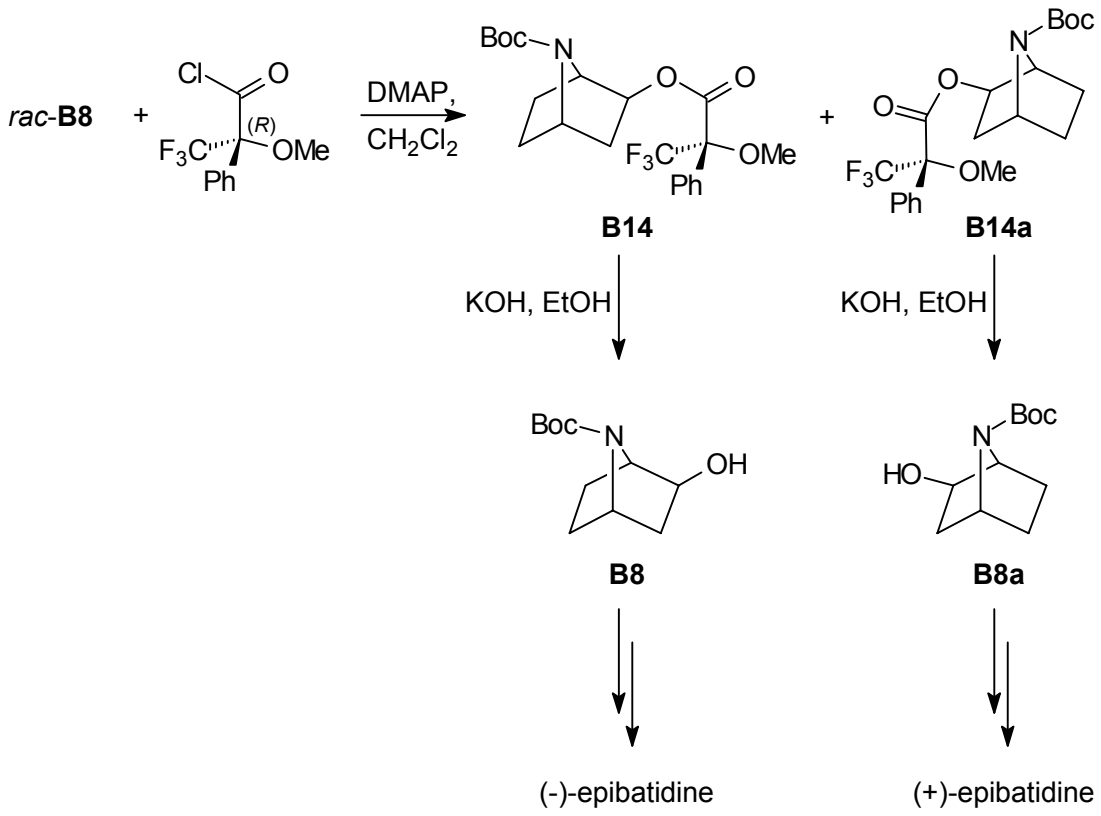
In the following the total synthesis of epibatidine by Fletcher et al.[68] is presented which at first applied the synthetic strategy described above in point 4. Additionally it has to be mentioned that in 1993 Fletcher et al. first reported the absolute configuration of the natural (-)-epibatidine and determined it to be 1*R*,2*R*,4*S*.[82]

This synthesis used as starting material the racemic *N*-trifluoroacetyl-3-cyclohexenylamine **B4** (see Scheme 3.3) which was obtained from 4-cyclohexenylcarboxylic acid chloride via a CURTIUS-degradation reaction. Compound **B4** was protected at the N-H by reaction with benzyl bromide under basic conditions to give *N*,*N*-benzyltrifluoroacetyl-3-cyclohexenylamine **B5**. Epoxidation with *m*-CPBA led to epoxide **B6**. Basic hydrolysis and subsequent transannular cyclization reaction in the polar solvent 1-methyl-2-pyrrolidinone gave the desired *N*-benzyl-7-aza-2-hydroxy bicyclo[2.2.1]heptane **B7**. Reductive cleavage of the benzyl group followed by introduction of the *tert*-butyloxycarbonyl moiety provided compound **B8**. Thereafter followed a SWERN oxidation which gave the ketone **B9**. The subsequent reaction with 5-lithium-2-chloro pyridine proceeded stereoselective and only the endo-alcohol **B10** was obtained. The compound **B10** was then converted to the coresponding *S*-methyl xanthate by treatment with potassium hydride, carbon disulfide and methyl iodide and thereafter thermolysis in toluene resulted in elimination to give the bicyclic olefin **B11**. After catalytic hydrogenation a mixture of two products was obtained, namely the *N*-protected natural epibatidine (the *exo*-isomer) **B12** and the *N*-protected *endo*-epibatidine **B13**, in approximately 1:4 ratio. Epimerisation of compound **B13** to compound **B12** was achieved in 50% yield by longer heating (30 h) of the reaction mixture in *tert*-butanol in the presence of potassium *tert*-butoxide. Then the Boc protecting group was cleaved by using hydrogen chloride in ethylacetate and the racemic epibatidine was obtained in quantitative yield.



Scheme 3.3: *The Fletcher et al. total synthesis of epibatidine.*

It was reported that epibatidine analogues were also prepared from the key intermediate ketone **B9** following the same synthetic route. Nevertheless, a mixture of *exo*/*endo* products was always obtained which requires a separation and subsequent epimerization of the *endo*-isomer.



Scheme 3.4: *Determination of the absolute configuration of epibatidine.*

To investigate the absolute configuration of the natural product, Fletcher et al.[82] have transformed compound **B8** to the corresponding Moscher's esters **B14** and **B14a** using (*R*)-(-)-Mosher's acid chloride (see Scheme 3.4). The resulting diastereomeric mixture was separated by HPLC and the absolute configuration of the natural compound was determined to be (-)-(1*R*,2*R*,4*S*)-epibatidine. Confirmation for this was obtained by X-ray analysis of the crystalline compound **B14a** and the subsequent transformation reactions which led to the non-natural (+)-epibatidine.

4 Formulation of the Problem

Within the scope of the present work two different projects are independently presented. The first and as well the main part of the following work concerns the development of an alternative strategy to epothilone analogues. Epothilones and their related compounds are promising candidates to become chemotherapeutics with outstanding relevance, because of their high biological activity against tumour cells and interesting mechanism of action as microtubule-stabilizing agents. The structures of epothilones are considerably less complex than that of taxol. Nevertheless, the epothilones posed a considerable challenge to synthetic chemist and, most importantly, offered opportunities for the discovery and development of new synthetic technologies and strategies. Variation of the different functional groups in the natural molecule should make it possible to find an analogue with higher activity and/or easier applicability for large-scale synthesis.

The purpose of our project is the development of a synthetic strategy that also allows rapid access to epothilone analogues.[31] A key feature is the creation of stereocenters by aldol reactions. In searching for new and alternative reactions for the synthesis of the target molecule it was generally noticed that until now in the all published total syntheses the coupling of the key building blocks was accomplished mainly between C6 and C7 using an aldol reaction. Thereby the desired configuration of the methyl group at C6 was often obtained with low stereoselectivity, and the methyl group at C8 had normally to be introduced in advance trough a stereoselective alkylation reaction. Therefore we wanted to apply a new strategy using an asymmetric EVANS aldol reaction[89] for formation of the C7-C8 bond, whereby it would be possible to establish the new stereocenters at C7 and C8 with higher stereoselectivity (Scheme 5.1). One of the key fragments should carry the methyl group at C6 with the desired configuration, which could be achieved also with an asymmetric aldol reaction. For the ring formation we planned to use the YAMAGUCHI macrolactonization,[50] which seemed to be the best method for obtaining the 16-membered macrolide.

As it was mentioned above, in the present work is also discussed a second project which includes the straightforward synthesis of cyclohexenylamines by ring closing metathesis reaction (RCM) of 4-amino-1,7-octadiene derivatives.[90] This route would provide a valuable alternative to the DIELS-ALDER strategy to cyclohexenes with an electron donating substituent in the homoallylic position. It was planned to study a transannular cyclization reaction for obtaining of bicyclic structures which appear often in natural products. Additionally, the present work also constitutes a formal total synthesis of

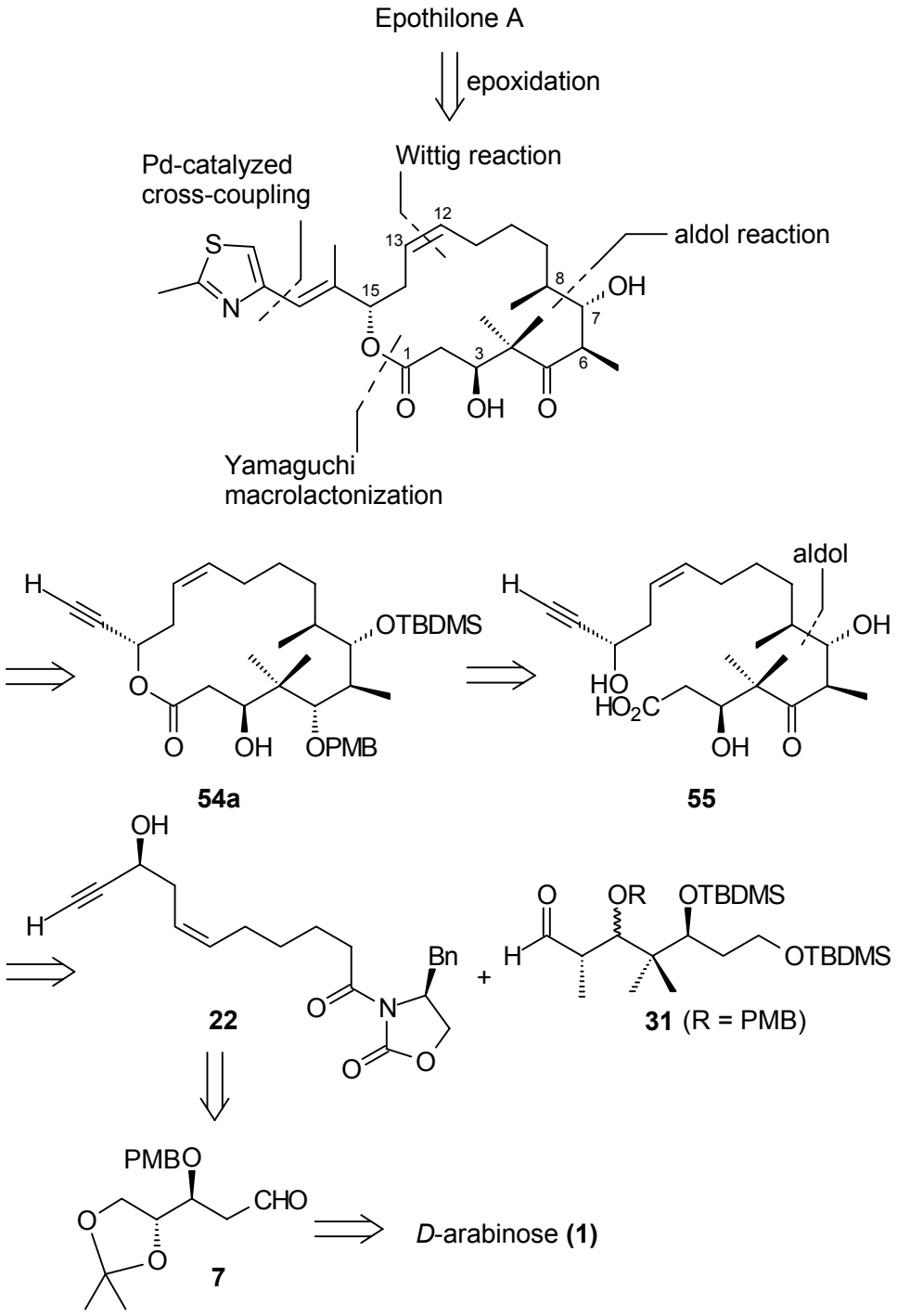
racemic epibatidine,[91] because the compound **63d** obtained by our new synthetic route using the RCM, has been already used in the total synthesis of this alkaloid.[68] Epibatidine is a natural product which is a very potent analgesic agent and its chemical structure contains a 7-azabicyclo[2.2.1]heptane ring plus a 5-(2-chloropyridyl) substituent.

5 Synthetic Pathway for Preparation of Epothilone Analogues

5.1 Retrosynthetic Analysis

According to the other published total synthesis of epothilones we have also planned to introduced the epoxide function at a late stage of the synthesis by a conformationally controlled reaction. Molecular modelling indicates that the epoxide is exposed to the outside of the macrocycle. A similar conformation is found also for the corresponding *cis*-olefin.

In our initial retrosynthetic analysis for constructing of the epothilone core structure were planned three key reaction steps namely a WITTIG reaction for formation of the double bound which would represent later the desoxy precursor epothilone C; then an asymmetric aldol reaction for formation of the C7-C8 bond, which required the synthesis of the two key fragments C1-C7 and C8-C15; and macrolactonization reaction for formation of the macrocycle, whereupon a YAMAGUCHI procedure was envisioned (see Scheme 5.1). The attachment of the thiazol ring was planned to be done using a palladium-catalyzed cross-coupling reaction between a vinylmetal species and a 4-bromo-thiazole. This approach would allow for the preparation of aryl analogous of the target molecule. The vinylmetal species in turn would arise from a carbometallation reaction.[92] For this purpose it would be necessary to introduce the alkyne moiety using the SEYFERTH/GILBERT reagent.[93] One could also think about putting on the thiazole at an earlier stage of the synthesis. Selective removal of the PMB group, oxidation, epoxidation of the double bond, and final deprotection would provide the title compound, namely epothilone A.



Scheme 5.1 *Retrosynthetic analysis for synthesis of epothilone A*.

After opening of the macrolactone to the hydroxy acid **55** a retrosynthetic cut between atoms 7 and 8 by a stereoselective aldol reaction leads to compounds such as **22** and **31**. Thus, the methyl group at C8 would originate ultimately from a carboxylic group.[94] Compounds **22** and **31** represent the two key fragments in our retrosynthesis. The C6 and C3 stereocenters in the originally assigned aldehyde **31** might be established by an

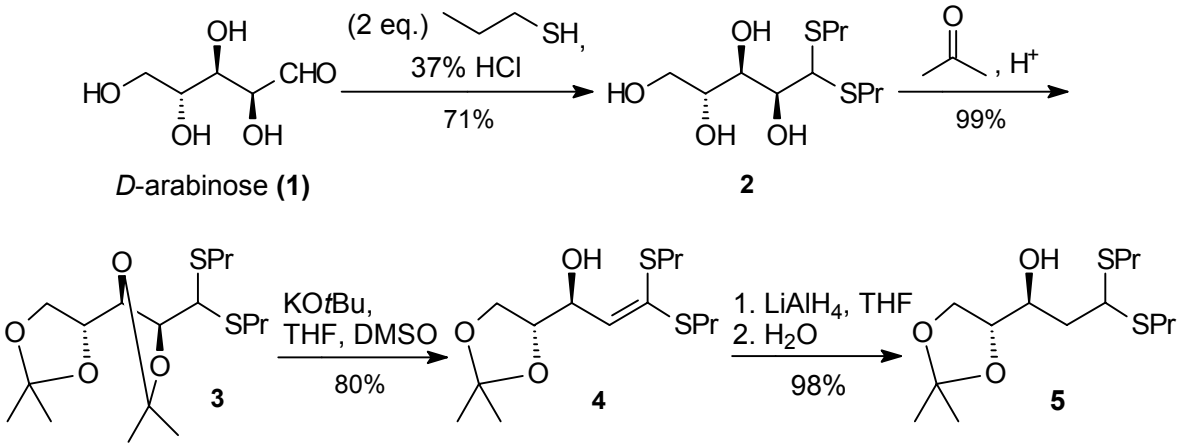
acylation and subsequent stereoselective aldol reaction. However, according to our experiments, it became necessary to replace the initially chosen aldehyde **31** with an analogue aldehyde **44** which contains only the stereocenter C6.

The alkyne moiety in the C8-C15 key fragment would be obtained through reaction of the appropriate aldehyde with the SEYFERTH/GILBERT reagent. The *cis* double bond of the oxazolidinone **22**, in turn would be fashioned by a WITTIG reaction between a 6-carbon building block and the aldehyde **7**. This aldehyde contains the future C15 stereocenter of the target molecule which might be obtained starting from the optically pure and commercially available *D*-arabinose **(1)**. The choice of protecting groups is not casual and suited to the further planned selective deprotections and the oxidation at the end of the synthesis.

5.2 Synthesis of the C8-C15 Fragment

5.2.1 Preparation of 2-Deoxy-3-O-(4-methoxybenzyl)-4,5-O-isopropylidene-D-erythro-pentose (7)

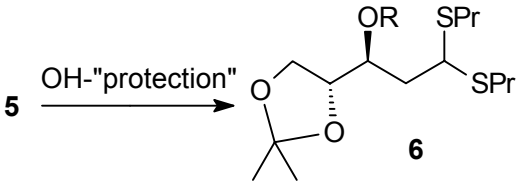
The first step in our research work was to obtain the aldehyde **7**, which was later used as a precursor for the chain elongation through a WITTIG olefination reaction. As a starting material we used the optically pure *D*-arabinose **(1)**, which can function as a source of the desired chirality for the stereocenter C15 in the target product. According to the literature[95] the aldehyde function of *D*-arabinose **(1)** was converted to a dipropyl mercaptal, through reaction with 2 equivalents of propyl mercaptan in concentrated hydrochloric acid and compound **2** was obtained in 71% yield (see Scheme 5.2). The reason for the use of the dipropyl instead of the more common diethyl mercaptal was the considerably reduced solubility of the *D*-arabinose dipropyl mercaptal which makes purification by recrystallization easier.[95] The hydroxyl groups of the resulting tetraol were protected as acetals, which led to compound **3**. For this purpose, a standard procedure under acidic conditions and acetone was applied. Treatment of compound **3** with 1.5 equivalents of potassium *tert*-butoxide in water free THF/DMSO (3:1) mixture resulted in abstraction of the acidic hydrogen and concomitant elimination of acetone to give the ketene dithioacetal **4** in 80% yield.



Scheme 5.2: *Synthesis of 2-deoxy-4,5-O-isopropylidene-D-erythro-pentose di-1-propyl dithioacetal **(5)**.*

Because of the instability of **4** under acidic conditions,[96] for the further reduction lithium aluminum hydride in dry THF instead of the known protonation hydride transfer sequence with trifluoroacetic acid / triethyl silane was used.[97] Compound **5** was obtained after work up under aqueous conditions in excellent yield of 98%. In the mechanism of this reduction, aluminum coordinates to the oxygen of the free hydroxyl group and a five membered cyclic transition state is formed in which the hydride is transferred to the carbon of the double bond.[98]

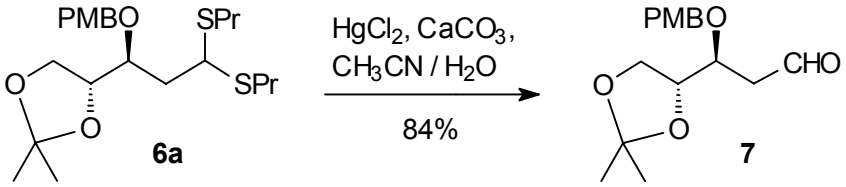
Thereafter followed a protection of the free hydroxy moiety of **5** and compounds **6a-d** were obtained (see Scheme 5.3). For that purpose were made several experiments with different protecting groups. The interesting fact however was, that in the case of benzyl (Bn) and *tert*-butyl(diphenyl)silyl (TBDPS) protecting groups the yields were very poor, whereas with *p*-methoxybenzyl (PMB) and *tert*-butyl(dimethyl)silyl (TBDMS) groups the yields were nearly quantitative. According to our initial synthetic strategy the PMB-ether **6a** was used for the next studies, which would allow a selective deprotection at the end of the synthesis. In a later phase of this synthetic route, during an aldol reaction for combining the two key fragments, we observed that the PMB protecting group was not stable and we had to exchange it with the more bulky triisopropylsilyl (TIPS) group (see Section 5.2.4). Further experiments with the TBDMS-ether **6b**, were also made until the first key reaction, namely the WITTIG reaction for the chain-elongation, whereupon after working up and/or purification a substantial part of the desired product decomposed and the yield unfortunately was only 5%.



product	R	reagent	yield (%)
6a	PMB	PMB-Cl, NaH in DMF	99
6b	TBDMS	TBDMS-Cl, imidazole, DMAP in CH_2Cl_2	100
6c	Bn	BnBr, NaH, KI in THF	23
6d	TBDPS	TBDPS-Cl, imidazole, in DMF	38

Scheme 5.3: *Protection of the hydroxy moiety of compound **5**.*

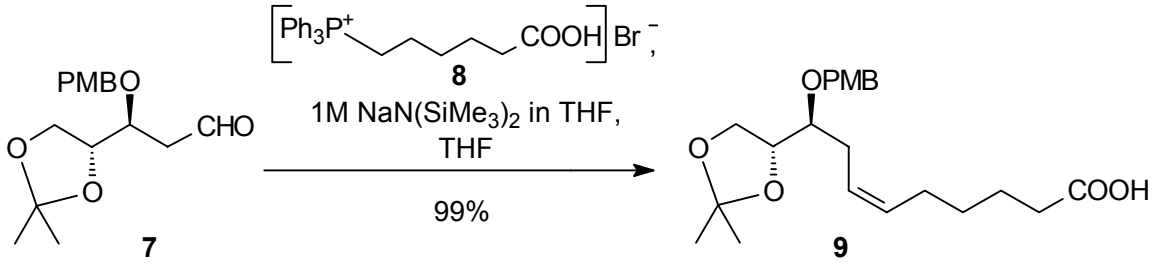
The desired 2-deoxy-3-*O*-(4-methoxybenzyl)-4,5-*O*-isopropylidene-*D*-erythro-pentose **(7)**, was obtained after dithioacetal cleavage of **6a**, with mercuric (II) chloride and calcium carbonate in a mixture of acetonitrile / water (4:1) using the known procedure of Kende et al.[99] The aldehyde **7** was obtained in 84% yield as a pure product and further purification was not necessary (see Scheme 5.4).



Scheme 5.4: *Cleavage of the dithioacetal to aldehyde **7**.*

*5.2.2 WITTIG Reaction for Formation of the Carboxylic Acid **9***

To form the double bound it was planned to apply a WITTIG olefination, which was as well our first key reaction for the preparation of the chain-elongated product **9**, containing the C8-C15 part of the carbon skeleton of the 16-membered macrocycle. For that purpose the aldehyde **7** was reacted with the non-stabilized ylide, prepared in advance from (5-carboxypentyl)triphenylphosphonium bromide **(8)** and sodium bis(trimethylsilyl)amide (see Scheme 5.5).[100] The phosphonium bromide **8** was easily synthesized by heating equimolar quantities of triphenylphosphine and 6-bromohexanoic acid in toluene for 24 h and under inert atmosphere.[101]

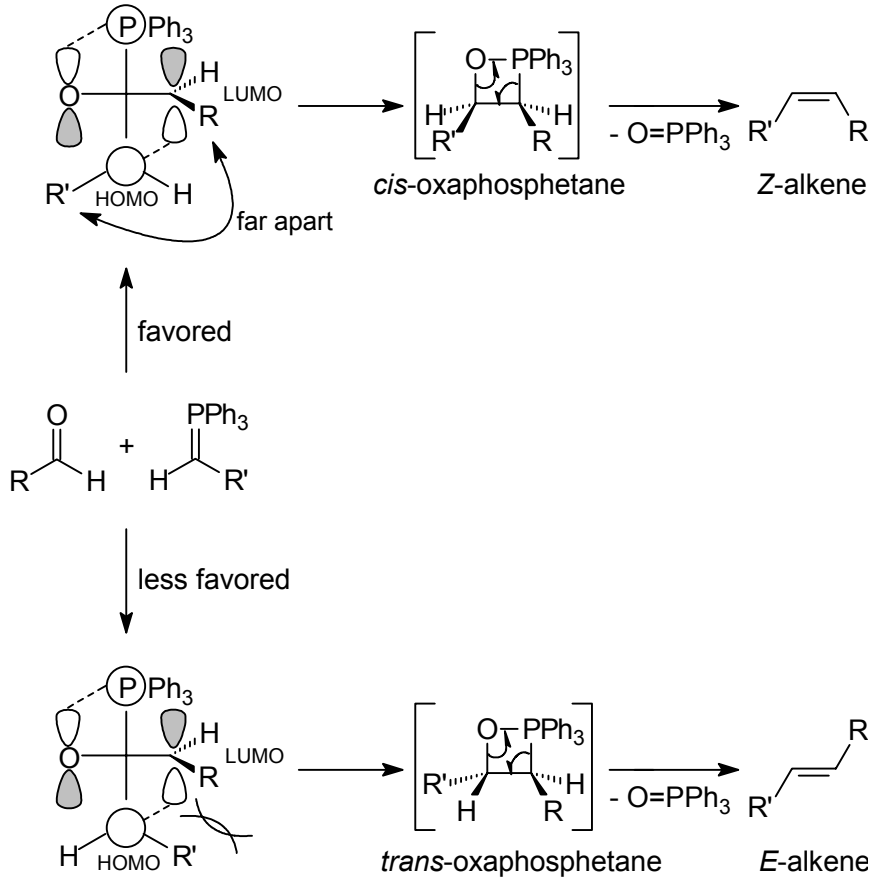


Scheme 5.5: *Chain elongation by WITTIG reaction*.

The resulting unsaturated carboxylic acid **9** was obtained in an excellent yield of 99% as a single isomer. Unfortunately it was not possible to confirm the *Z*-configuration by ^{1}H NMR, because both signals from the olefinic protons were overlapping and therefore the value of the coupling constant could not be determined. For proving isomeric purity, the product **9** was treated with diazomethane to give the corresponding methyl ester and after GC-MS only one product was detected. Based on literature precedence it was assumed to be the *Z*-isomer.

Thus, it is known from the literature that non-stabilized triphenylphosphorus ylides generally react with aldehydes to afford mainly *Z*-alkenes, by a process suggested to involve oxaphosphetane intermediates.[102] The stereochemistry of the WITTIG reaction can be affected by solvent, cation, temperature, and type of aldehyde. *Z* stereoselectivity is maximized by polar aprotic solvents, exclusion of lithium salts, and low reaction temperatures.[100] To explain the stereochemistry it is necessary to look at the mechanism of the WITTIG olefination reaction (see Scheme 5.6).[103] At the beginning occurs a [2+2]-cycloaddition of the ylide to the aldehyde, which can result in a *cis*- or *trans*-configuration of the oxaphosphetane. Because of the 4 participating electrons, the thermal cycloaddition has to occur via a MÖBIUS transition state or a [π^2s + π^2a] approach, respectively. The two double bonds approach each other in a perpendicular fashion with the R groups as far as possible apart from each other. Therefore, the transition state leading to the *cis*-oxaphosphetane is favored. The four-membered ring collapses to give the alkene and triphenylphosphine oxide. Triphenylphosphine oxide is exceptionally stable, and the conversion of triphenylphosphine to triphenylphosphine oxide provides the driving force for the WITTIG reaction. The collapse of the four-membered ring is stereoselective and the *cis*-oxaphosphetane exclusively forms a *cis*-olefin, and respectively the *trans*-oxaphosphetane forms only a *trans*-olefin. The formation of the 1,2-substituted oxaphosphetane is kinetically controlled. This process is very fast and irreversible. When stabilized ylides are used the thermodynamic stability of the resulting oxaphophetanes is

increased and therefore, the selectivity to form the *cis*-oxaphosphetane is decreased. Consequently, in this case the *E*-alkene can be obtained also, whereas non-stabilized ylides, especially under lithium salt-free conditions, give *Z*-alkenes with high selectivity.



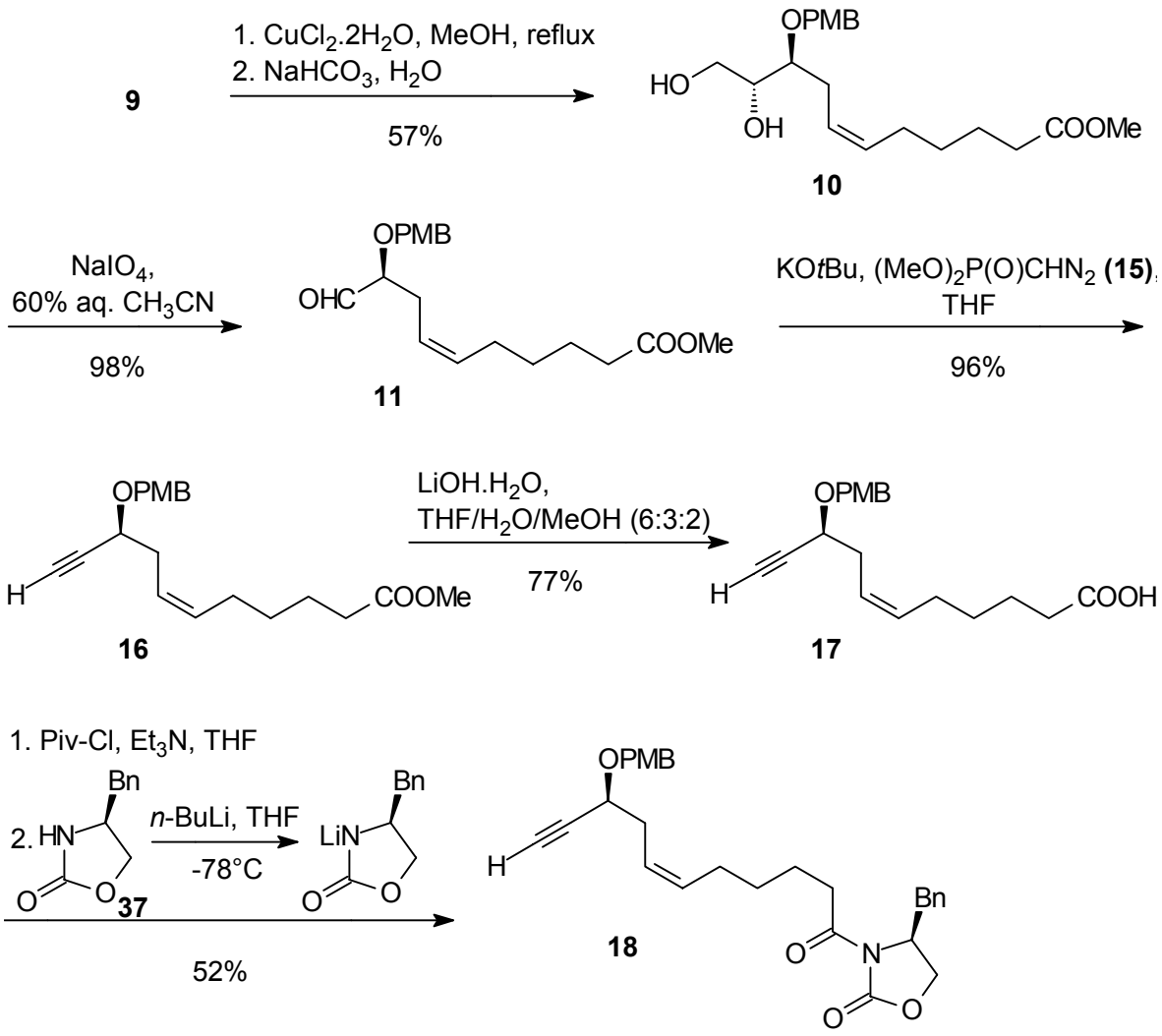
Scheme 5.6: *Mechanism of the WITTIG reaction***.**

*5.2.3 Introduction of the EVANS Auxiliary and Synthesis of Compound **18***

With the WITTIG olefination the carbon skeleton of the C8-C15 fragment was complete. Because of the subsequently planned stereoselective EVANS aldol reaction[104] for combining the two key fragments, it was necessary to introduce a chiral auxiliary in the molecule. In the present work two alternative routes for introducing the EVANS auxiliary, namely the oxazolidinone moiety, are presented. Additionally, the acetal group was cleaved and the terminus modified to obtain an alkyne residue, which is needed for the future attachment of the thiazole group by a cross-coupling reaction.

Route A: Removal of the isopropylidene group from the unsaturated acid **9** was achieved using 5 equivalents of copper(II) chloride dihydrate in refluxing methanol for 1.5 h (see Scheme 5.7). Additionally, as a side effect of this reaction, esterification of the free

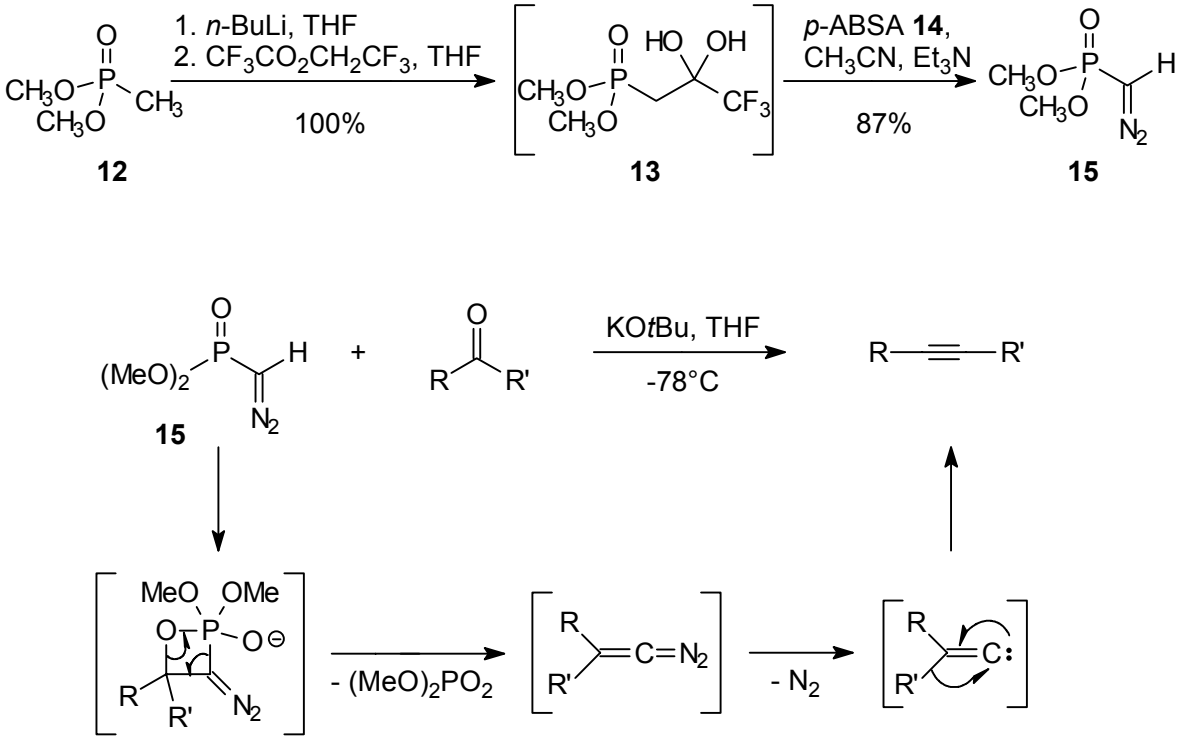
carboxyl group was observed and the dihydroxyester **10** was obtained. Subsequent glycol cleavage was carried out by using of sodium(meta)periodate in 60% aqueous acetonitrile solution to give the unstable aldehyde **11**, which was used immediately for the next reaction step. According to the literature[99] the aldehyde was used directly without further purification, because otherwise an undesired racemization at C15 has to be expected. Small racemization was always observed, which was evident from GC-MS at the stage of compound **22** and thereby the ratio was determined to be approximately 96:4. Thereafter the aldehyde moiety was transformed to an alkyne group by using the SEYFERTH/GILBERT reagent **15**,[93] and potassium *tert*-butoxide as a base.[105] The reaction was carried out at –78°C in anhydrous THF and under inert atmosphere and the desired product **16** was obtained in excellent yield of 96%. Further saponification of the methyl ester with lithium hydroxide at room temperature in a mixture of THF/H_2O/MeOH (6:3:2) gave the alkynoic acid **17** as colorless oil in 77% yield. Thereafter followed the attachment of the chiral auxiliary, which was done with the EVANS's protocol.[106, 107] Thus, the chiral oxazolidinone **37** was deprotonated with *n*-butyllithium at –78°C in THF and the resulting lithio derivative was reacted at –78°C with the mixed anhydride derived from the alkynoic acid **17**, pivaloyl chloride, and triethylamine. The desired carboximide **18** was obtained after a silica gel chromatography in 52% yield.



Scheme 5.7: *Route A for formation of compound **18**.*

The dimethyl(diazomethyl)phosphonate **(15)** (SEYFERTH/GILBERT reagent) was synthesized in advance[93] and it turned out that the reagent was stable for a longer time, when stored under inert atmosphere and at –18°C. For the preparation of the SEYFERTH/GILBERT reagent the commercially available dimethyl methylphosphonate **(12)** was used, which was temporarily trifluoroacetylated to give the intermediate **13**, existing as a ketone hydrate (see Scheme 5.8). This was used directly without purification in the diazo/trifluoroacetyl exchange to give the dimethyl(diazomethyl)phosphonate **(15)**. According to the original literature the most convenient reagent for the diazo/trifluoroacetyl exchange was the *p*-acetamidobenzenesulfonyl azide **(14)** (*p*-ABSA) and the reaction was performed at 0°C in acetonitrile with triethylamine as a base.[108] Comparable to the WITTIG reaction the SEYFERTH/GILBERT reagent forms with the aldehyde in the first step an

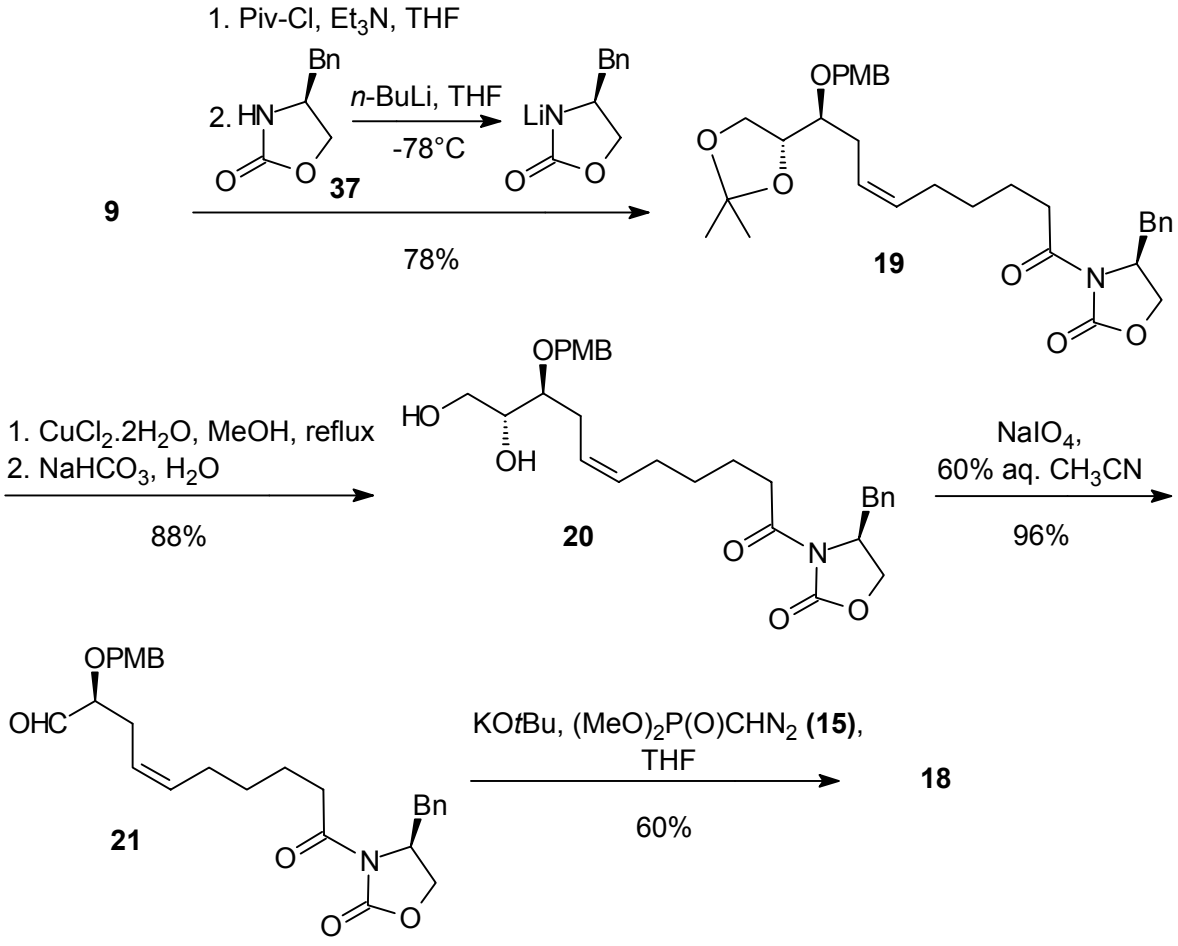
oxaphosphetane, which collapses under loss of dimethyl phosphate to give the unstable diazo alkene. The diazo alkene decomposes to nitrogen and a vinylidene carbene intermediate, which stabilizes itself through a migration of the alkyl residue to the electrophilic carbon and formation of a triple bond.



Scheme 5.8: *Preparation of the SEYFERTH/GILBERT reagent and mechaism of the alkyne formation.*

Route B: In comparison to route A, the introduction of the EVANS auxiliary was done at the first step after the WITTIG olefination reaction. This had as advantage the formation of the caboximide function at the beginning, which prevented the methyl ester formation and the saponification step was not necessary. The introduction of the oxazolidinone auxiliary was made using the EVANS procedure as was described above whereupon the mixed anhydride was prepared this time from the carboxylic acid **9**, pivaloyl chloride and triethylamine (see Scheme 5.9). The desired product **19** was purified by silica gel chromatography and was obtained in 78% yield as a colorless oil. The isopropylidene group was removed as before using 5 equivalents of copper(II) chloride dihydrate in refluxing methanol and the glycol **20** was obtained in 88% yield. Subsequent treatment of **20** with sodium(meta)periodate in 60% aqueous acetonitrile solution gave the aldehyde **21** as a highly viscous oil, which was used directly without further purification for the same

reason as it was described above, namely undesired racemization at C15. Thereafter followed reaction of the aldehyde **21** with the SEYFERTH/GILBERT reagent **15** for formation of the alkyne moiety and the oxazolidinone **18** was obtained in 60% yield.

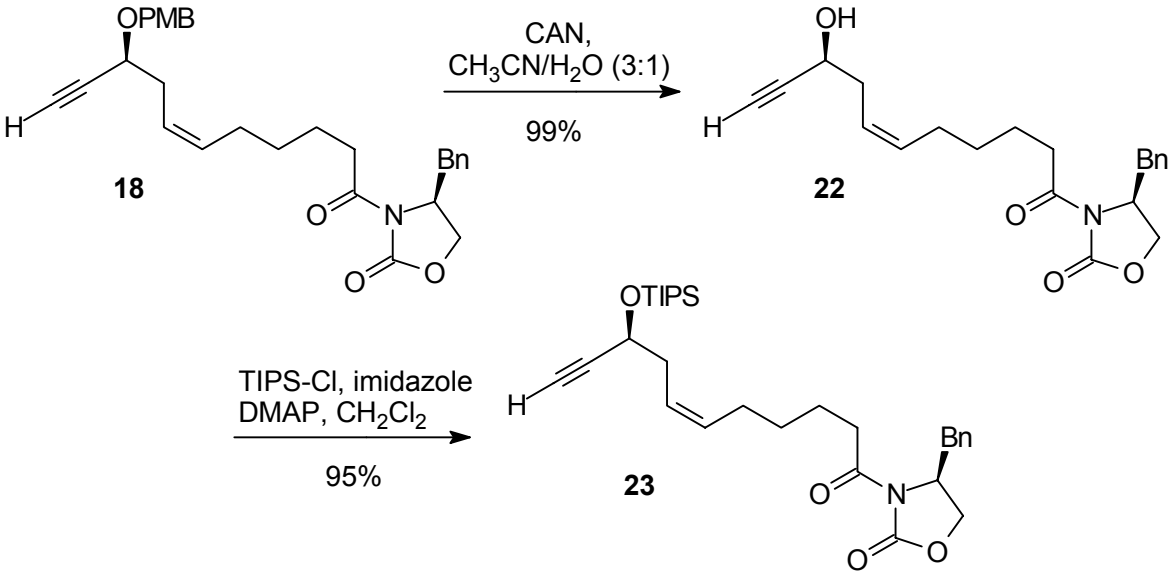


Scheme 5.9: *Route B for formation of compound **18**.*

5.2.4 Protecting Group Exchange

Compound **18**, which carries the chiral oxazolidinone moiety, was the starting material for the subsequent stereoselective aldol reaction. For this aldol reaction we used the conditions established by Evans et al. with *n*-Bu_2BOTf as a Lewis acid and triethylamine or diisopropylethyl amine (HÜNIG base) as a base.[104] Unfortunately, the experiments with this substrate and different test aldehydes were not successful and a mixture of recovered starting material and deprotected product was always obtained. That's why we considered a new strategy, where the PMB group was exchanged with the more bulky TIPS protecting group. For this purpose compound **18** was treated with 3

equivalents of ceric ammonium nitrate in acetonitrile / water (3:1) mixture and the desired deprotected product **22** was obtained in almost quantitative yield (99%) as a colorless oil, which solidified on standing as a white solid (see Scheme 5.10).[99] Here it is important to mention that the work up and the purification of this reaction step have to be done immediately, because otherwise decomposition of the product was observed. The secondary hydroxyl group of **22** was further protected with triisopropylsilyl chloride in anhydrous CH_2Cl_2 in the presence of imidazole as a base and dimethylaminopyridine as a catalyst. The reaction was followed by TLC and after 3 days no more starting material was presented and compound **23** was obtained in excellent yield of 95% as a colorless oil.



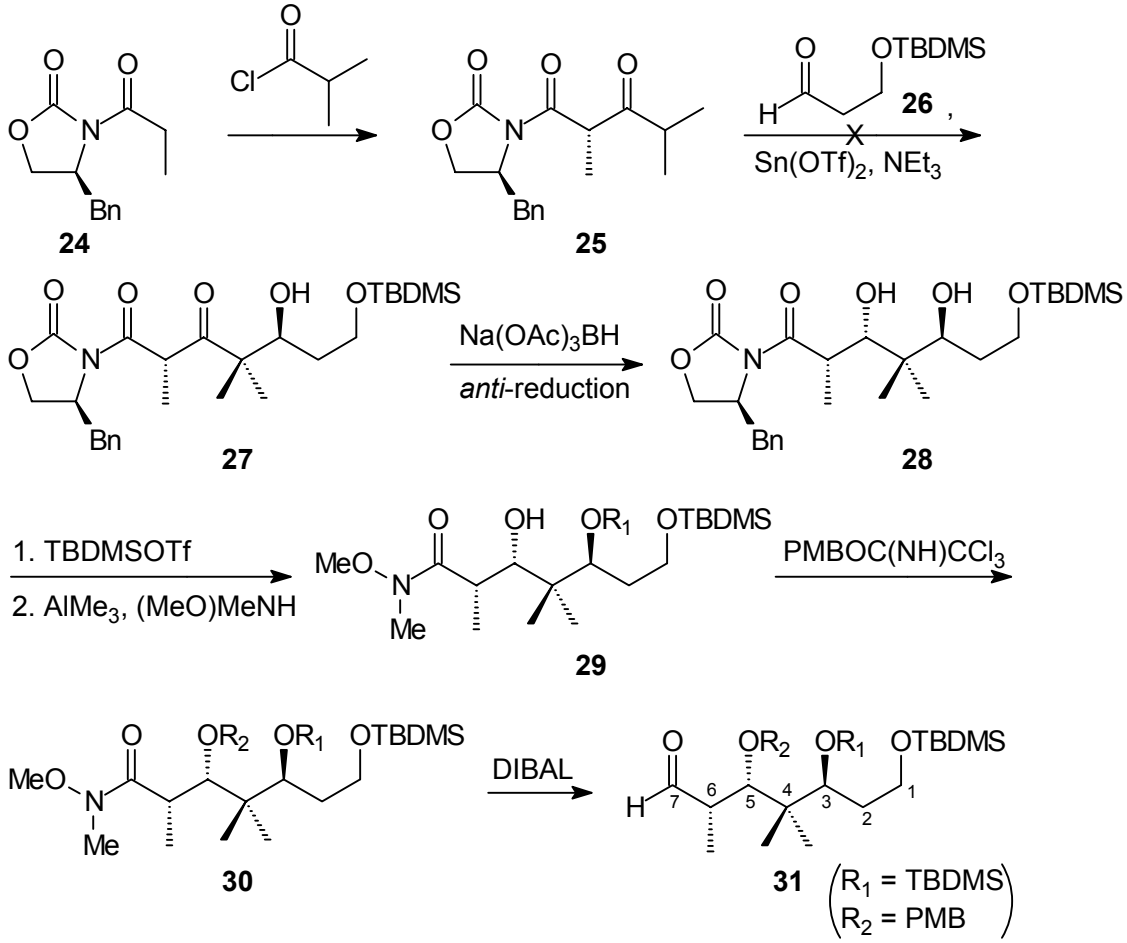
Scheme 5.10: *Protecting group exchange for obtaining the suitable C8-C15 fragment **23**.*

The TIPS protected β-keto imide **23** represents the fragment C8-C15 of the target carbon skeleton from the natural epothilones and is the first key intermediate applied in our synthesis.

5.3 Synthesis of the C1-C7 Fragment

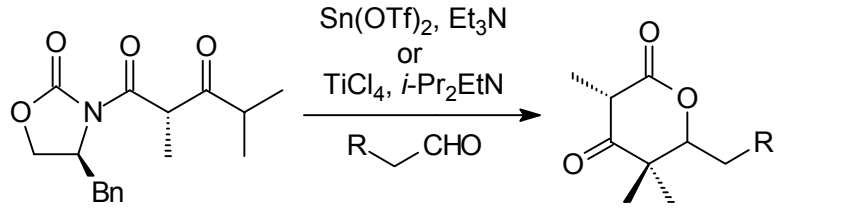
*5.3.1 Initial Experiments for Synthesis of the Aldehyde **31***

The fragment C1-C7 was actually an aldehyde molecule, which according to the carbon skeleton of the natural product required an *anti*-relationship between C3 and C6, and a protecting group at C5 that can be removed selectively. We have thought of several options to reach a compound like **31**. Our initial route was thought to start from oxazolidinone **24**, which had to be acetylated to the keto imide **25** (see Scheme 5.11). A subsequent aldol reaction with the aldehyde **26** in presence of stannous triflate should give compound **27** with the indicated stereochemistry.[109, 110] Treatment of **27** with triacetoxyborohydride[111] would lead to the *anti*-1,3-diol **28**. Although the compound **28** carries two similar hydroxyl groups, a regioselective monosilylation could be expected according to the literature.[110] After that, it was planned to convert **28** via a transamination to the WEINREB amide **29**, protect the remaining hydroxyl function and finally to reduce the WEINREB amide **30** with DIBAL, to provide the aldehyde **31**.



Scheme 5.11: *Initial considerations for synthesis of aldehyde **31**.*

Following this synthetic strategy compound **25** was obtained in excellent yield (90% over two steps) after an asymmetric EVANS aldol reaction with *n*-Bu_2BOTf and triethylamine, and subsequent oxidation of the new formed hydroxyl group with SO_3-Py complex in anhydrous DMSO.[109] The first problem appeared during the aldol reaction in the presence of stannous triflate for preparation of compound **27**. Unfortunately, all the experiments with different aldehydes and different Lewis acids for obtaining the desired product **27** were not successful and in all cases oxazolidinone cleavage, followed by 6-membered lactone formation was observed (see Scheme 5.12). It seems likely that the lactonization is favored by the geminal dialkyl effect of the substrate. The structures of the resulting products were determined by NMR- and MS analysis.



25

32a ($CH_2OTBDMS$)
32b (R = CH_2OBn)
32c (R = H)

Scheme 5.12: *Observed lactonization by using compound **25** as a starting material for aldol reaction.*

From the NMR spectroskopic data it can be assumed, that the keto form is the mainly occurring one. The ^{13}C shifts of the carbonyl signals C1 and C3, as well as the C2 signal gave no hints for enolization. This is also confirmed by the integration of the signal of the acidic proton at C2 from the ^1H-NMR spectra. As an example, the NMR data of compound **32a** are presented in Table 5.1.

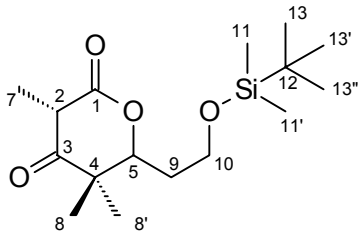
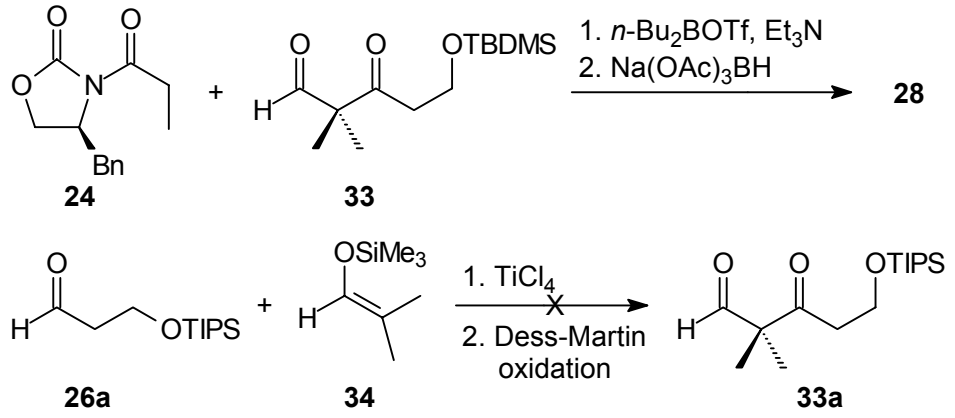


Table 5.1: *NMR data of compound **32a**.*

Position	^{1}H [ppm]	^{13}C [ppm]
1	-	169.9
2	3.56 (q, 1H, *J* = 7 Hz)	49.3
3	-	207.6
4	-	46.3
5	4.64 – 4.68 (m, 1 H)	78.1
7	1,28 (d, 3 H, *J* = 7 Hz)	8.1
8, 8´	1.08 ; 1.04 (s, 2 x 3 H)	21.3 ; 18.0
9	1.72 –1.79 (m, 2H)	31.7
10	4.64 - 4.68 (m, 2H)	58.4
11, 11´	0.01 (s, 6H)	-5.2
12	-	18.3
13, 13´, 13´´	0.84 (s, 9H)	25.9

To circumvent this problem, we have thought of an alternative way to reach the *anti*-I,3-diol **28** by applying an Evans aldol reaction between the oxazolidinone **24** and the ketoaldehyde **33** (see Scheme 5.13). Unfortunately, the synthesis of the ketoaldehyde **33a** was also problematic. For its preparation a MUKAIYAMA cross-aldol reaction between the silyl enol ether **34** and a C3-aldehyde, for example **26a**, was examined.[112] It was not possible to purify the resulting aldol product. Therefore, the subsequent DESS-MARTIN oxidation was performed on the crude product. However, only decomposition was observed. Therefore, this rout was not further investigated.



Scheme 5.13: *Further considerations for obtaining aldehyde **33** through MUKAIYAMA aldol reaction.*

From the experiments toward an aldehyde of type **31** the following conclusions could be drawn. First, a free hydroxyl group at C3 (epothilone numbering) is not possible with a carboxylic group at C7 due to lactonization. Second, an aldol reaction forming the C5-C6 bond is very difficult due to steric hindrance (quaternary center at C4, see Figure 5.1). Thus, other routes were developed.[113] In this work, we therefore concentrated on a less complicated C1-C7 fragment.

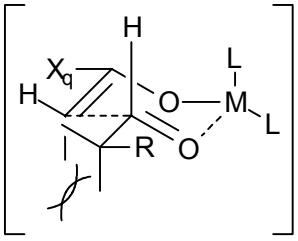
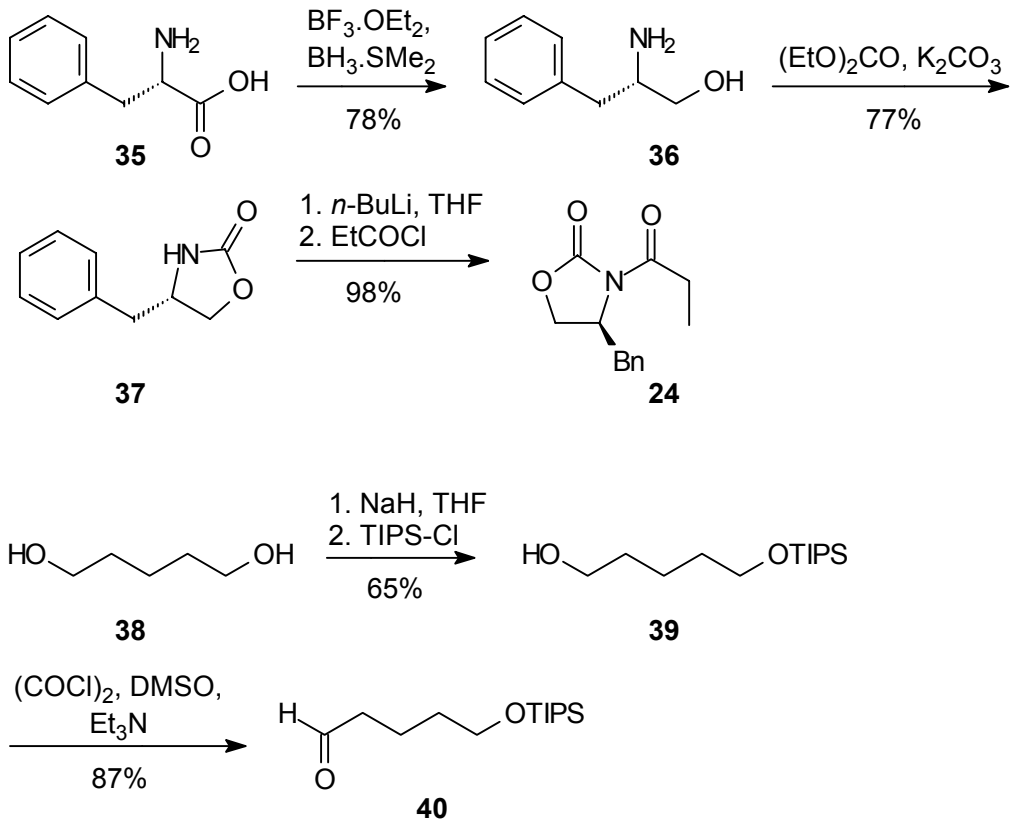


Figure 5.1: *Steric hindrance between the methyl groups at C4 and C6 in the assumed transition state.*

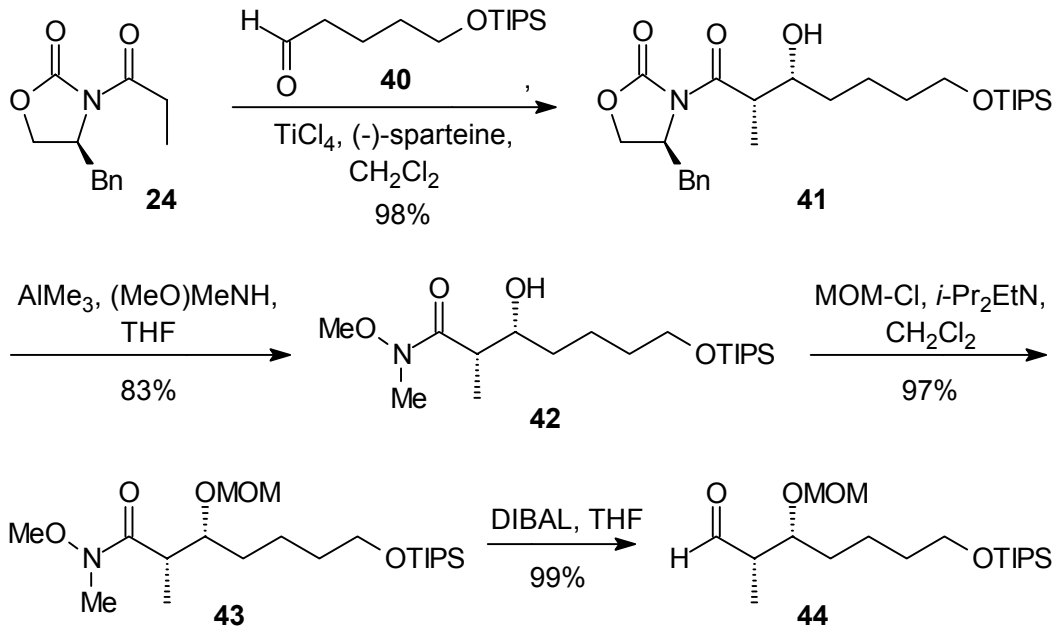
*5.3.2 Preparation of Aldehyde **44***

After the unsuccessful experiments for the synthesis of aldehyde **31** we chose a third option this time for preparation of the analogue compound **44**. For that purpose we started again from the carboximide **24**, which was synthezised from (*S*)-phenylalanine **(35)**, according to the EVANS procedure,[114] as it is shown on Scheme 5.14. The (*S*)-phenylalanol **(36)** was obtained in 78% yield after a direct reduction of the α-amino acid with a borane. The resulting β-amino alcohol **36** can be transformed into oxazolidinone **37** using 2 equivalents of diethylcarbonate and catalytic amounts of potassium carbonate. Further depotonation with *n*-butyllithium at –78°C and subsequent acylation with freshly distilled propionyl chloride gave the desired carboximide **24** in 98% yield.



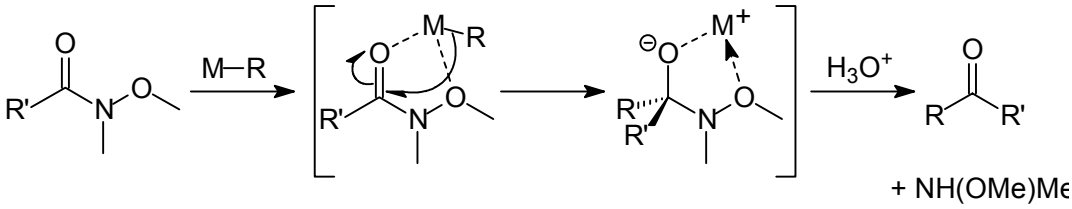
Scheme 5.14: *Preparation of oxazolidinone **24** and aldehyde **40** as a starting materials for the further synthesis of C1-C7 fragment.*

The C1-C7 chain from the desired molecule was built through a *syn*-aldol reaction with the formed titanium enolate of **24** and the aldehyde **40**, whereby as a base the commercially available (-)-spartein was used (see Scheme 5.15).[115] The aldol product **41** was obtained as a single diastereomer in excellent yield of 98%. The stereochemical outcome of this reaction is discussed in the next Section 5.4. The aldehyde **40** was obtained in two steps starting from 1,5-pentanediol **(38)**, which was monosilylated according to the literature[116] to give the compound **39**. Subsequent SWERN oxidation with oxalyl chloride, anhydrous DMSO and triethylamine led to the aldehyde **40** (see Scheme 5.14).



Scheme 5.15: *Synthesis of C1-C7 fragment **44**.*

Thereafter was prepared *in situ* a dimethylaluminum amide intermediate by treatment of *N*,*O*-dimethylhydroxylamine hydrochloride (WEINREB salt) with trimethylaluminum and evolution of methane was an evident. This reagent was necessary for converting the oxazolidinone moiety of the aldol product **41** to the WEINREB amide **42** (see Scheme 5.15). The free hydroxyl function was than protected with chloromethyl methyl ether in the presence of diisopropylethylamine to give the MOM-ether **43** in 97% yield. This protecting group was chosen because the experiments for introduction of the more convenient PMB-group were unsuccessful and always led to unknown products, either using the standard procedure with NaH in dry DMF or applying the procedure with *p*-methoxybenzyl trichloroacetimidate[117] and trifluoromethanesulfonic acid as a catalyst.[118] Further reduction of the protected WEINREB amide **43** with DIBAL gave the desired end-aldehyde **44** in almost quantitative yield as a colorless syrup. The mechanism of this transformation is represented on the following Scheme 5.16. The WEINREB amide is attacked by a metallorganic compound (methyllithium or DIBAL) which leads to formation of a stable tetrahedral-intermediate, whereas (MeO)MeN$^-$ - moiety represents an extremely bad leaving group. At the same time the metal atom is chelated by the methoxy group which additionally stabilizes the Weinreb-intermediate. Thus, the two-fold reaction by excess amounts of metallorganic reagent is prevented. The intermediate collapses to the corresponding aldehyde or ketone after work up under aqueous conditions.



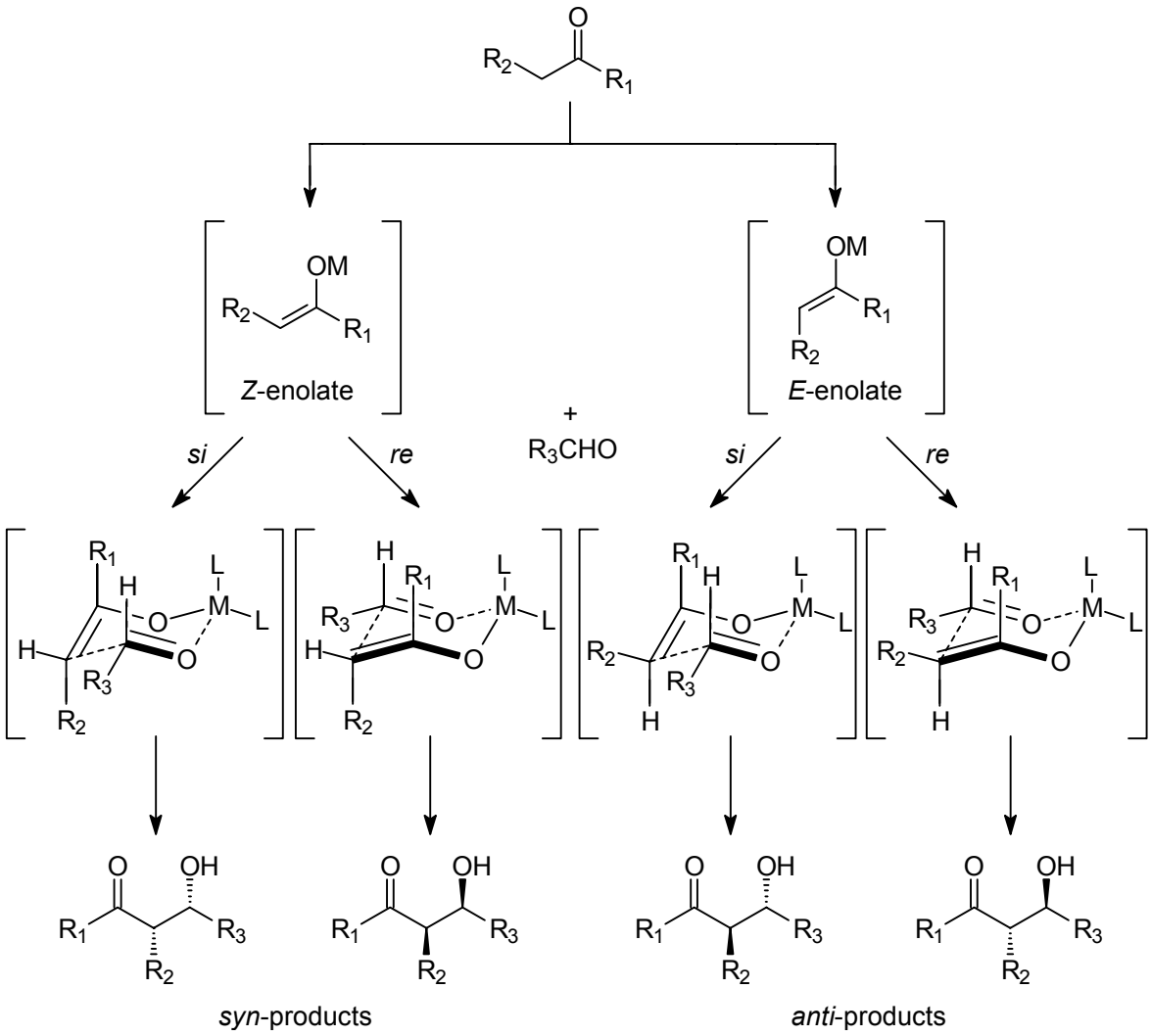
Scheme 5.16: *Mechanism of the WEINREB amide reduction .*

The aldehyde **44** represents our simplified C1-C7 key fragment that was used in the main asymmetric aldol reaction for the combination of the two fragments. Comparing with the structure of the natural product, here the methyl group at the C3 stereocenter is missing as well as the two methyl groups at C4, which will lead to the synthesis of an epothilone analogue.

5.4 Combination of the Fragments via an Asymmetric Aldol Reaction

One of the most important reactions used in our work was the asymmetric EVANS aldol reaction[89] for formation of a new C-C bond and two new stereocenters. This type of reaction was applied two times in our synthetic strategy. Once it was used in the synthesis of the C1-C7 fragment and as a key reaction for combination of the two fragments C1-C7 and C8-C15 which formed the precursor for the further macrocyclization step.

To explain the stereochemical outcome of this reaction it is necessary to present its mechanism. The aldol reactions are one of the most common reactions that utilize enolate chemistry. A substituted carbonyl compound can form to enolates, the *Z*- or *E*-enolates (neglecting regioisomers). Each isomer then reacts with the electrophile (*re*- or *si*-face attack) to give two different products. The geometry of the resulting enolate plays an important role in determining the stereochemical outcome of the aldol reaction, which proceeds via a cyclic transition state (Zimmerman-Traxler-model). In general, the *Z*-enolate reacts further with the aldehyde to produce *syn*-products whereas the *E*-enolate is responsible for the formation of the *anti*-products (see Scheme 5.17).

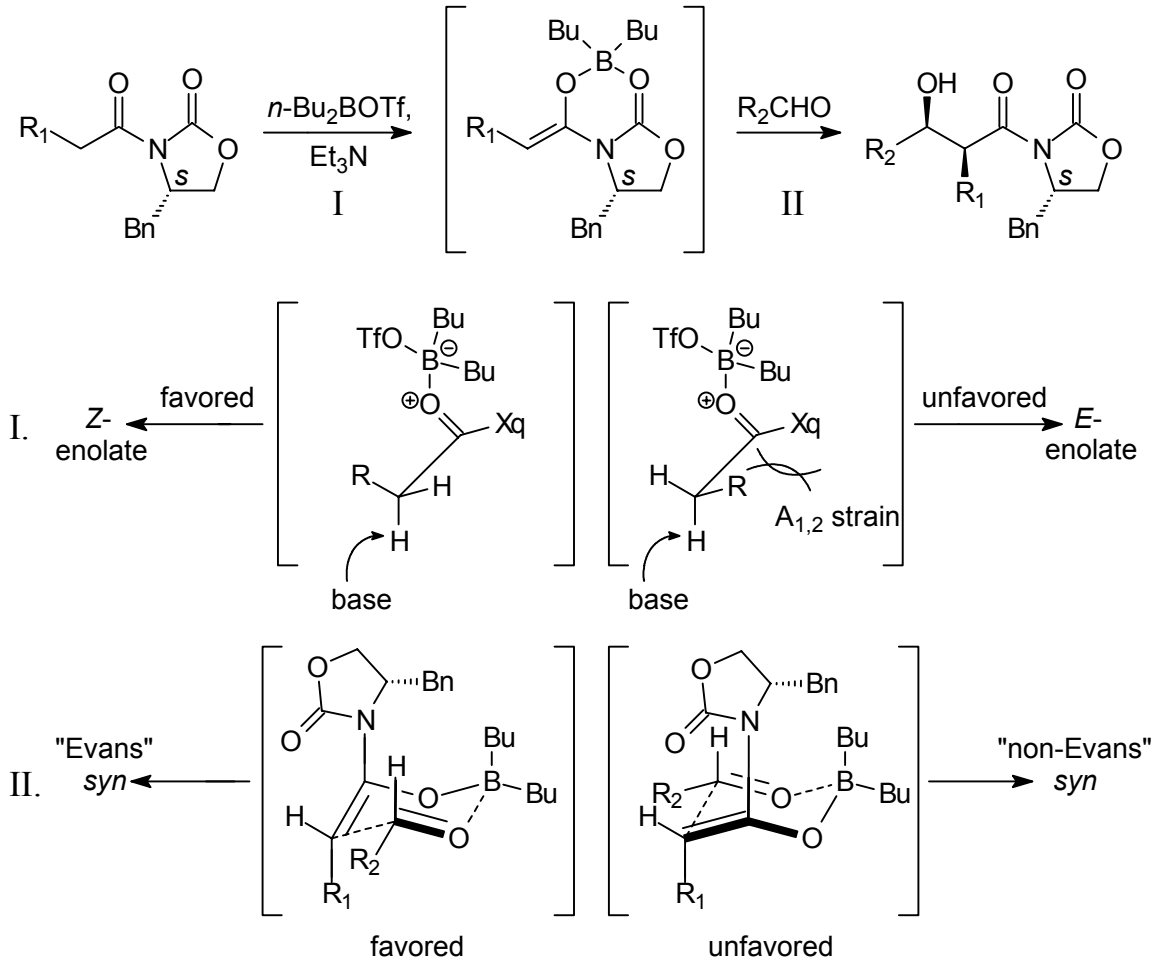


Scheme 5.17: *(Z)- and (E)-enolate formation and the corresponding stereochemical outcome after aldol reaction.*

Within *syn*- or *anti*-aldol products, enantioselection can be obtained via a chiral auxiliary or a chiral ligand based enolate. A good chiral auxiliary should have the following properties: to be suitable for easy introduction with high yield and high optical purity; stable under enolate reaction conditions; to induce high diastereofacial selectivity; and to be easily removed and when possible recovered.[89] The most popular auxiliary which was used also in our synthesis, is the EVANS oxazolidinone prepared from an α-amino acid as it was described above in Section 5.3.2.

For a typical EVANS aldol reaction, the starting carbonyl derivative reacts at -78°C with *n*-Bu_2BOTf and Et_3N or *i*-Pr_2NEt as a base to give the *Z*-enolate which further reacts with the aldehyde to give the *syn*-aldol product (commonly known as "Evans" *syn*) with a high diastereofacial (>250:1, >99% de) selectivity.[104] The favored formation of the *Z*-enolate

can be explained by the fact, that the intarmolecular steric hindrance between the auxiliary group and the reasidue R is much bigger in the transition state which leads to the *E*-enolate compared to this which results in *Z*-enolate. The reaction is believed to proceed via a Zimmerman-Traxler-type cyclic transition state, in which the *re*-face of the enolate is hindered by the chiral auxiliary leading to attack from the *si*-face of the enolate giving "Evans" *syn* product. The unfavored transition state leads to the "non-Evans" *syn* product (see Scheme 5.18). For electronic reasons (dipol alignment) the C=O of the oxazolidinone and the C-O of the enolate point in opposite directions.



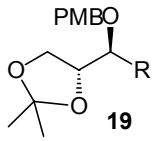
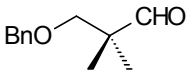
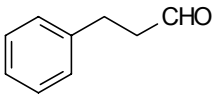
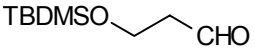
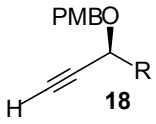
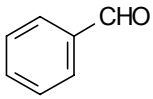
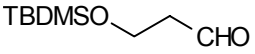
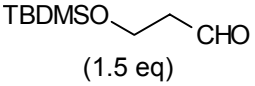
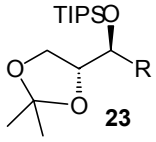
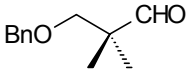
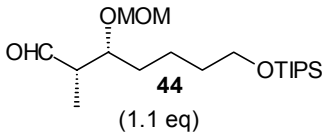
Scheme 5.18: *Transition states of the EVANS aldol reaction.*

Titanium[118-120] and tin[121] metal centers have also been reported to be effective in creating well-ordered transition states for aldol reactions. Because in our particular synthetic route the experiments with *n*-Bu_2BOTf were in a large part unsuccessful, as it is described later, we have looked for an alternative way to obtain the same stereoselective results in agreement with the stereochemistry of the target molecule. For this purpose we

used $TiCl_4$ as a Lewis acid and (-)-sparteine as a base even though it was reported that titanium enolates of the EVANS acyl oxazolidinones are less selective than the boron enolates.[122] According to the literature[115] the transition state has been proposed for the titanium enolate to give the "Evans" *syn* aldol product. An additional important point is that $TiCl_4$ and (-)-sparteine could be used directly as received without further purification in contrast with *n*-Bu_2BOTf, which was prepared in advance in two steps[123, 124] (see Experimental part) and even freshly distilled was stable only for a short time as a 1M solution in anhydrous CH_2Cl_2.

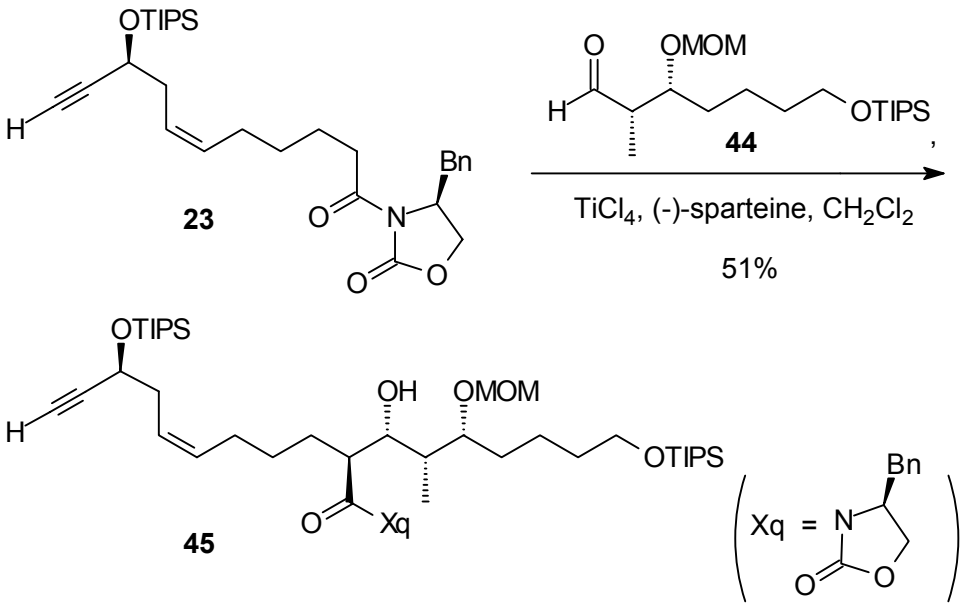
In our synthesis the first test EVANS aldol reactions were studied with the building block **19**, which carries the isopropylidene moiety and the PMB-ether functionality using a freshly prepared *n*-Bu_2BOTf and Et_3N or HÜNIG base in presence of different aldehydes (see Table 5.1). Unfortunately, the isopropylidene and the PMB groups were not stable under different reaction conditions and in all cases no desired products were obtained. Then we have thought to apply the asymmetric aldol reaction after modification of the isopropylidene group to a triple bond but our test experiments failed again and a mixture of recovered starting material and starting material with cleaved PMB group was always obtained (Table 5.2). To circumvent the problems with the cleavage of the PMB group we exchanged it with the more bulky TIPS group as it was described above in Section 5.2.4, and the desired boron enolate mediated aldol reaction was applied again whereby only deprotection was observed (Table 5.2).

Table 5.2: *Studies on test aldol reactions.*

Starting material	Reagent and reaction conditions	Aldehyde	Remarks
 **19**	1.2 eq. *n*-Bu_2BOTf, 1.3 eq. Et_3N in CH_2Cl_2 0°C → -78°C, 30 min	 (1.5 eq) -78°C → 0°C, 1h	decomposition
19	1.2 eq. *n*-Bu_2BOTf, 1.3 eq. *i*-Pr_2EtN in CH_2Cl_2 0°C, 45 min	 (1.5 eq) -78°C, 30 min; RT, 2h	decomposition
19	1.2 eq. *n*-Bu_2BOTf, 1.3 eq. *i*-Pr_2EtN in CH_2Cl_2 0°C, 45 min	 (1.5 eq) -78°C, 30 min; RT, 2h	decomposition
 **18**	1.2 eq. *n*-Bu_2BOTf, 1.3 eq. Et_3N in toluene -60°C, 1h → -38°C, 1.5 h	 (1.5 eq) -78°C → RT, 2 d	recovered starting material (93%) and cleavage of the PMB-group (7%)
18	1.2 eq. *n*-Bu_2BOTf, 1.3 eq. *i*-Pr_2EtN in CH_2Cl_2 0°C, 45 min	 (1.5 eq) -78°C, 30 min; RT, 2h	recovered starting material (100%)
18	3 eq. *n*-Bu_2BOTf, 3.3 eq. Et_3N in CH_2Cl_2 0°C, 2 h	 (1.5 eq) -78°C, 1 h; RT, 2h	cleavage of the PMB-group (100%)
 **23**	7.5 eq. *n*-Bu_2BOTf, 8.25 eq. Et_3N in CH_2Cl_2 0°C, 1 h	 (1.5 eq) -78°C, 1 h; RT, 2h	cleavage of the TIPS-group and decomposition
23	1.2 eq. *n*-Bu_2BOTf, 1.3 eq. *i*-Pr_2EtN in CH_2Cl_2 0°C, 2 h	 **44** (1.1 eq) -78°C, 1 h; RT, 2h	cleavage of the TIPS-group (100%)

Summarising this results we came to the conclusion that our particular substrates including the C8-C15 part of the main carbon skeleton and the oxazolidinone chiral auxiliary, are not suitable for this reaction using the standard EVANS procedure, because of the deprotection of the hydroxyl group at C15, which interferes with the boran enolate formation or aldol reaction.

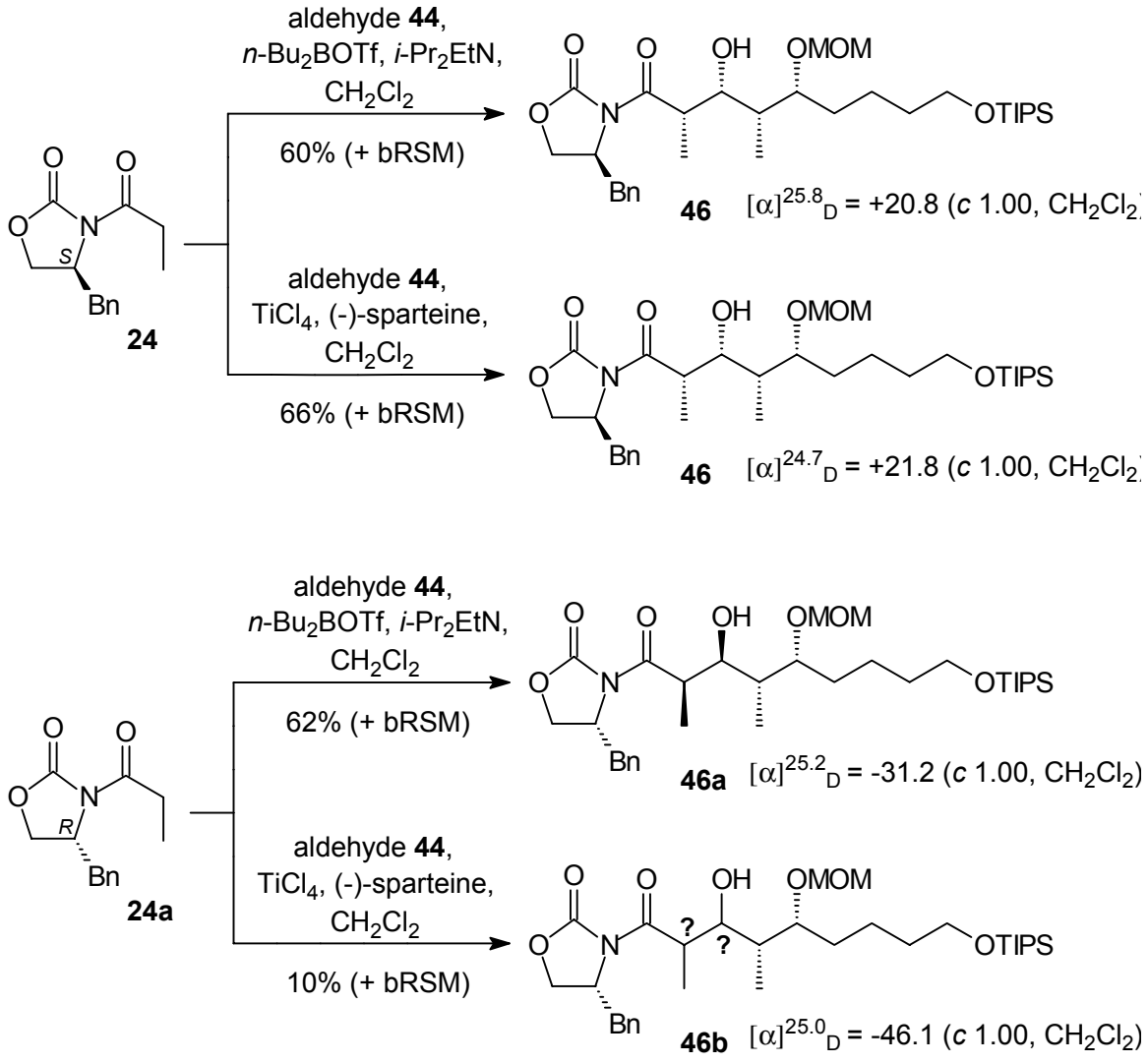
To solve this problem, we then exploited a recent modification of the EVANS procedure in the aldol addition which according to the literature also results in "Evans"-type *syn* products.[115]. Enolization of the C8-C15 key fragment **23** with (1 eq.) $TiCl_4$, and (2.5 eq.) (-)-sparteine at –78°C, followed by addition of the freshly prepared (1.2 eq.) aldehyde **44** (the C1-C7 building block), produced the desired aldol adduct **45** with excellent diastereoselectivity (>95% *de*) (see Scheme 5.19). This established the C7 and C8 stereocenters for the future analogues of the target natural compound. The two diastereomers could be separated by flash column chromatography and the yield was 51% based on recovered starting material.



Scheme 5.19: *Combination of the fragments C1-C7 and C8-C15 via aldol reaction.*

To confirm this stereochemical outcome some investigations on test aldol reactions with aldehyde **44** were made by using either the (*S*) or the (*R*) enantiomer of the oxazolidinone auxiliary, namely compound **24** and **24a** respectively. In both cases we made the boron enolate following the EVANS protocol[104] with *n*-Bu_2BOTf and HÜNIG base, and additionally the titanium enolate formation with $TiCl_4$ and (-)-sparteine. According to the literature for obtaining "Evans" *syn* product an equimolar amount of $TiCl_4$ and 2.5 eq.

of (-)-sparteine was employed.[115] The summarised results are presented on Scheme 5.20. In all cases we obtained single aldol products with exception of the example where the titanium enolate of the (*R*)-auxiliary was used in presence of (-)-sparteine. Here a mixture of aldol products and undetermined by-products was obtained which could be separated by flash column chromatography.



Scheme 5.20: *Test aldol reactions for investigation of the stereochemical outcome.*

When the (*S*)-auxiliary was used the same aldol product was obtained by applying both different conditions. Within the scope of measurement accuracy the optical rotation values were the same, and ^{1}H- and ^{13}C-NMR spectra were identical. Different results were observed when the (*R*)-auxiliary was applied. Because of the obviously different optical rotation values measured from the two received compounds we concluded that the obtained compounds from this aldol reactions are different. This result was difficult to

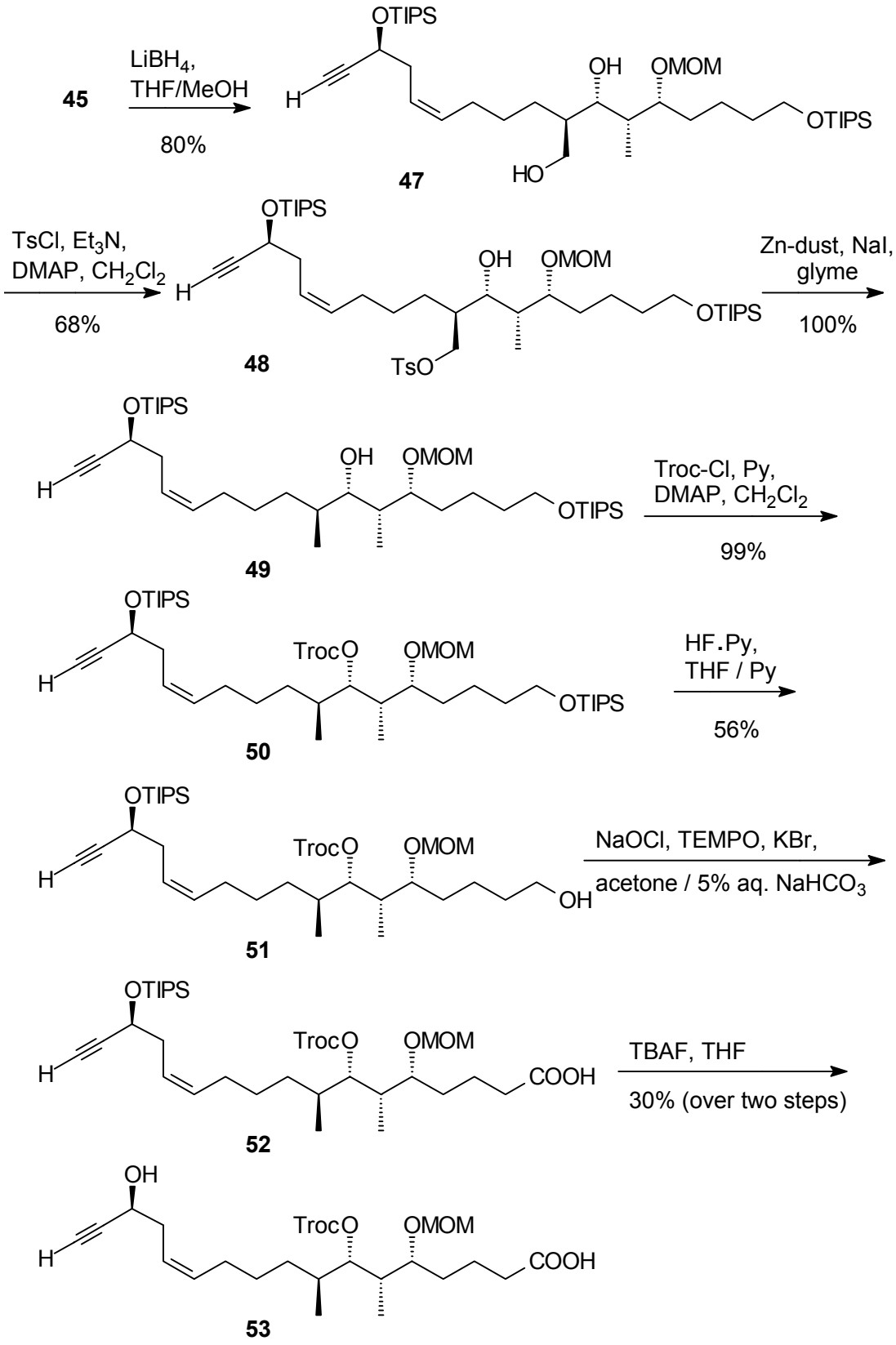
confirm by ^{1}H-NMR, because the significant signals were overlapped and by ^{13}C-NMR it was not possible to determine clear differences in the chemical shifts. However, it was visible from the NMR-experiments, that the compounds obtained from the (*R*)-auxiliary are definitively different from the compound resulting from the (*S*)-auxiliary. It is difficult to explain the seemingly strange result from the two aldol reactions with the (*R*)-auxiliary. One might speculate that the different stereochemical outcome when using $TiCl_4$ and (-)-sparteine is due to the chiral nature of the base. The low yield obtained in this aldol reaction as compared to the otherones can serve as a hint for a low compatibility of the base to the (*R*) auxiliary. It is known from various investigations reported in the literature[104] that when *n*-Bu_2BOTf and HÜNIG base are used an "Evans" *syn* product can be expected. Based on this and comparing our results it can be assumed that when the titanium enolate of the (*S*)-auxiliary was formed in presence of (-)-sparteine, the "Evans" *syn* product is also obtained whereas the titanium enolate of the (*R*)-auxiliary gives under the same conditions the "non-Evans" *syn* product or an *anti* product. Further investigations concerning the stereochemical outcome in the case of the (*R*)-auxiliary were not made within the scope of the present work.

5.5 Further Synthesis and Final Macrolactonization

The next task was the generation of the methyl group from the side chain which carries the chiral auxiliary and this was accomplished as follows. At first the oxazolidinone moiety from the aldol product **45** was reduced to the primary alcohol **47** (see Scheme 5.21). The best yield (80%) was obtained with lithium borohydride in anhydrous THF and traces of absolute methanol,[125] whereas by using a system of absolute ether and traces of water the maximum obtained yield was only 56%.[126] The primary hydroxyl group was further tosylated with *p*-toluenesulfonyl chloride, triethylamine and catalytic amounts of DMAP to give the product **48** as a colorless oil in 68% yield. Very important for the performance of this reaction was the presence of the catalytic amounts of DMAP, because in the experiments without it, only recovered starting material was isolated, even after longer reaction time (more than 24 h). Thereafter it was planned to apply the standard procedure for reduction of the tosylate to a methyl group with the superhydride triethyllithium borohydride in anhydrous THF.[126] However, this reaction always resulted in a mixture of unknown cyclization by-products and a small amount of the desired product (14% yield). This forced us to search for a new method for preparation of this compound and we found that when a mixture of 10 eq. zinc dust and 5 eq. sodium iodide refluxing in glyme for 2.5 h[127] was used, the desired product **49** was obtained without any problems

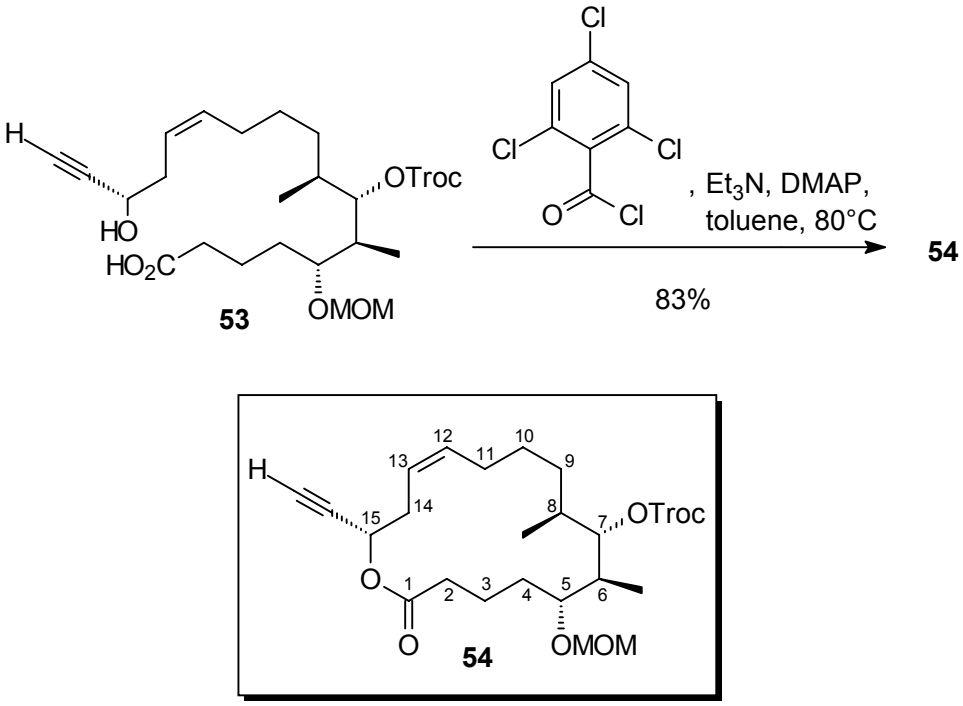
in quantitative yield. Thus, compound **49**, which carries the methyl group, was always obtained as a single product according to the ^{1}H- and ^{13}C-NMR, and therefore was used without further purification for the next step.

To continue the synthesis it was necessary to protect the free secondary hydroxyl group resulting from the *syn*-aldol reaction. According to our initial considerations, the requirements for the new protecting group were to be stable under acidic conditions, which does not allow to use a PMB group (not stable at pH ≤ 2[128]); to be stable under the conditions for cleavage of the already existing MOM group; to be different from a silicone group, because of the necessary selective deprotection of the TIPS moiety; and to be possibly to be removed without disturbing the later formed macrolactone. Consequently we chose the 2,2,2-trichloroethyl carbonate (Troc) group. For this reason compound **49** was treated with 2,2,2-trichloroethyl chloroformate at 0°C in the presence of absolute pyridine and catalytic amounts of DMAP to give the Troc-protected product **50** in excellent yield of 99% (see Scheme 5.22).[129] Thereafter, as it is described also in the literature the silicone protecting groups can be removed selectively.[130] Thus, treatment of **50** with HF in pyridine liberated the primary hydroxyl group and compound **51** was obtained in 56% yield together with recovered starting material (42%). Subsequent oxidation of the primary hydroxyl group with aqueous sodium hypochlorite solution in acetone / 5% aqueous $NaHCO_3$ mixture and in presence of potassium bromide and TEMPO provided the desired carboxylic acid **52**.[131] This reaction also gave an unknown by-product, which could not be separated at this step of the synthesis. Therefore, the whole crude material was used for the desilylation of the secondary TIPS-protecting group with 1M solution of TBAF in THF. The reaction was successful and gave the hydroxy acid **53** in 30% yield (over two steps). Here, it was possible to isolate the by-product and after some investigations, we concluded that during the oxidation step a concurrent reaction appeared, probably involving an addition of chlorine and water to the triple bond resulting in an α-chloroketone moiety. Evidence for this was the disappearance of the alkyne signals at 66.3, 85.0 ppm in the ^{13}C NMR and the appearance of an additional carbonyl signal at 210.0 ppm. The ESI-MS spectrum shows the typical isotopes pattern of a molecule containing four chlorines instead of the corresponding three chlorines from the Troc-moiety. The molecule peak [M-H^{+}] measured by the HRMS (FT-ICR-ESI) was found to be 609.1194910 m/z, which fits well with the theoretical mass of 609.1197172 m/z for the assumed by-product $C_{24}H_{37}O_9Cl_4$ [M-H^{+}].



Scheme 5.21: *Synthesis of the hydroxy acid **53** as precursor for the macrolactonization.*

Nevertheless, with the obtained purified product **53** in hands we made our next key reaction toward formation of the macrocycle via the very efficient YAMAGUCHI macrolactonization method.[130] For that purpose we used the commercially available YAMAGUCHI reagent (2,4,6-trichlorobenzoyl chloride), which formed with our starting material the mixed anhydride in the presence of a base. The lactonization by means of the mixed anhydride consists of two steps: the formation of the mixed anhydride, and the alcoholysis of the anhydride. Normally the reaction is performed when the solution of the mixed anhydride was diluted with toluene and added slowly to a hot solution of DMAP in toluene [refluxing or as in our particular case 80°C (see the Experimental section)] under high-dilution conditions to prevent the unwanted formation of polymers. In our case after flash column chromatography the expected 16-membered ring lactone **54** was isolated in excellent yield of 83% as colorless oil (see Scheme 5.22).



Scheme 5.22: *YAMAGUCHI macrolactonization to epothilone analogue **54**.*

Compound **54** was the target molecule in the represented synthetic strategy for preparation of epothilone analogues. After some functional group transformations, which include the cleavage of the MOM ether, subsequent oxidation and removal of the Troc-moiety an epothilone analogue compound should be obtained.

*5.5.1 Characterization of the Macrolactone **54** and Conformational Studies*

For characterization of the macrolactone **54** two-dimensional NMR experiments, such as H-H COSY, TOCSY, HMBC, HSQC and NOESY were used. In the following the H-H COSY and the NOESY are presented. As it is possible to see from the H-H COSY (Figure 5.2), all expected couplings between protons bounded to neighbouring carbons could be confirmed in accordance to the structure. For conformational analysis the macrolactone **54** was investigated by NOESY (Figure 5.3). Besides the expected interactions between vicinal and geminal protons, the most remarkable result was the prominent NOESY cross-peak observed between H-2/H-5.

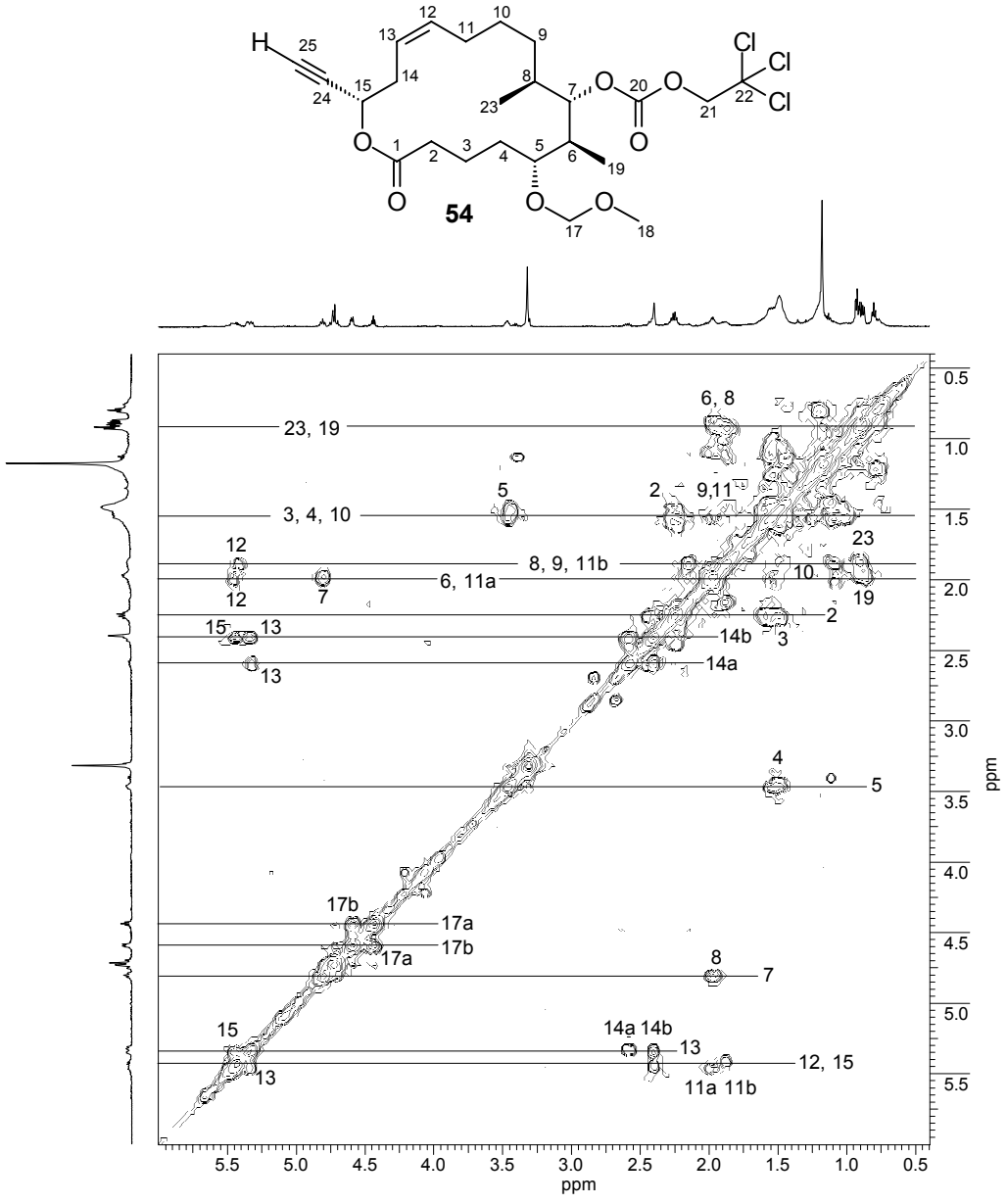


Figure 5.2: *H-H COSY of compound **54**.*

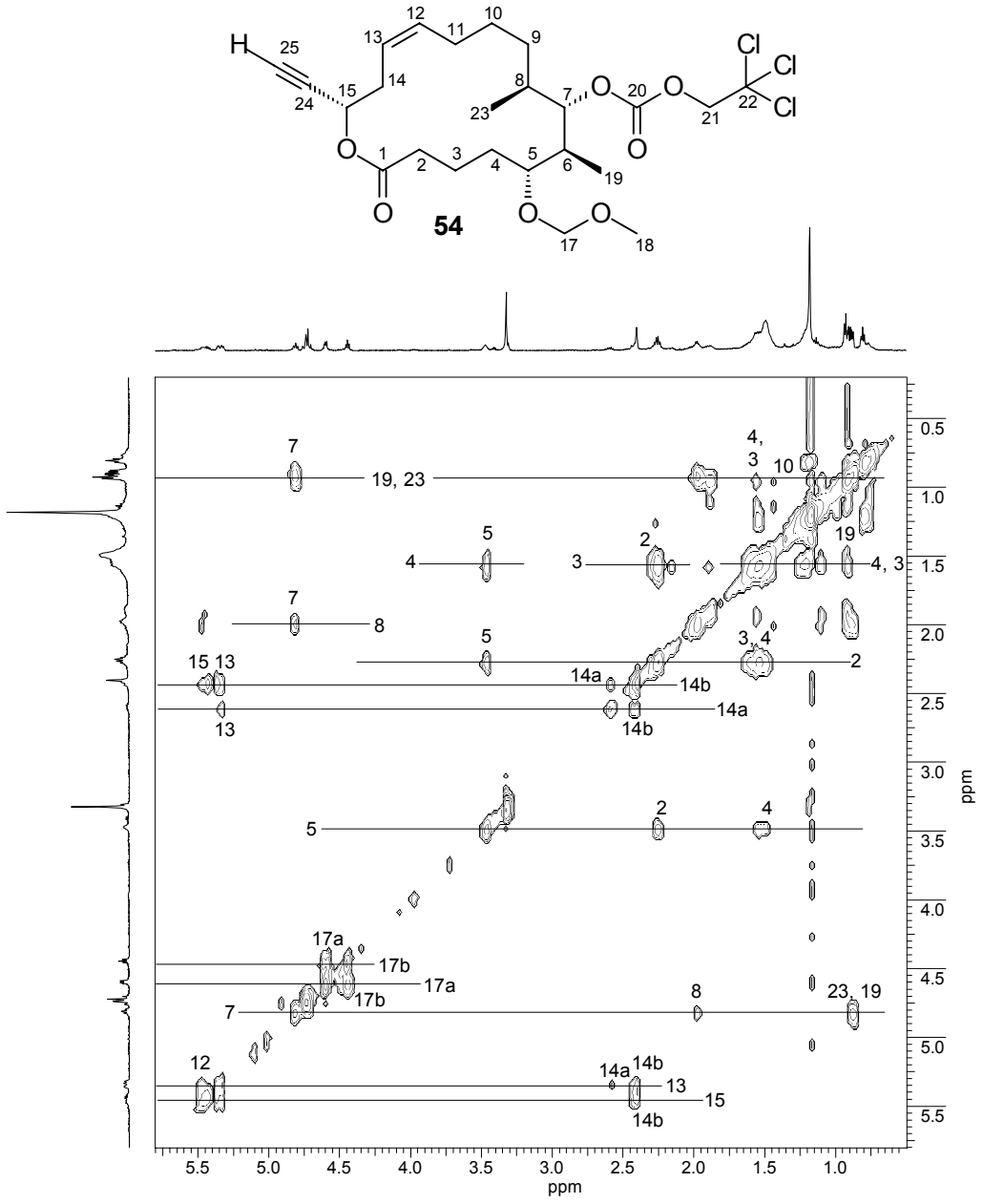
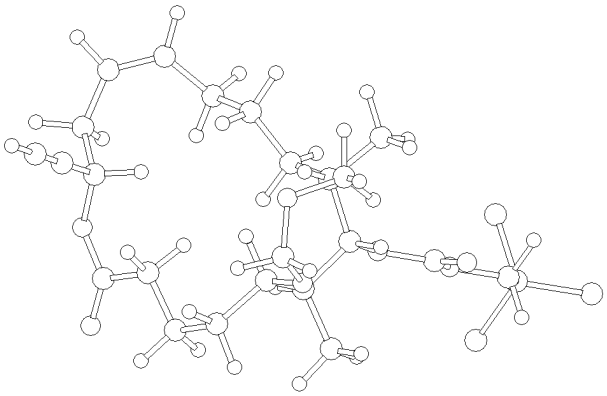


Figure 5.3: *NOESY of compound **54**.*

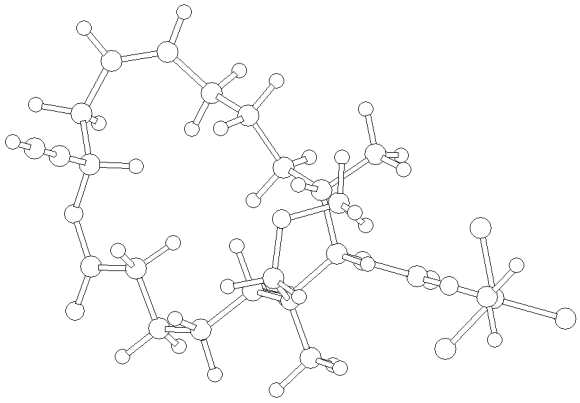
For a better understanding of the topology of the single conformations of compound **54** a conformational search was carried out by using MacroModel 7.0 (10 000 starting conformations, 50 kJ/mol cutoff, MM* force field). From the obtained set of conformations the five energy-minimised average conformations with the lowest energies were selected and presented on Figure 5.4. Comparison of the topology of this conformations shows, that the conformations E1 (97.98 kJ/mol), E2 (98.02 kJ/mol) and E3 (101.79 kJ/mol) differs only in the alignment of side chains, but not in the topology of the cyclic system.

Accordances in the topology of the cyclic system were found also for the conformations E4 (101.94 kJ/mol) and E5 (101.95 kJ/mol).

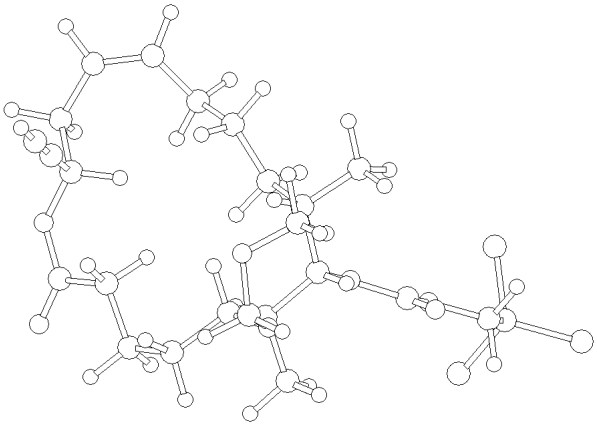
In all cases, the distances between the protons at C2 and C5 were found to be < 3 Å. Therefore, interaction between this protons can be observed for all examined conformations. The results of the NOESY are in accordance to the global minimum conformation E1.



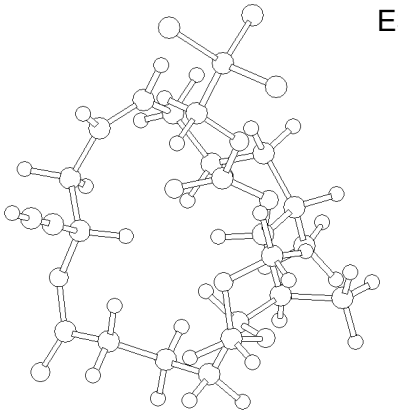
E1 = 97.979 kJ/mol



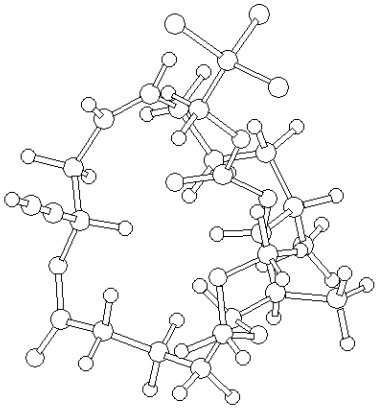
E2 = 98.020 kJ/mol



E3 = 101.79 kJ/mol



E4 = 101.94 kJ/mol



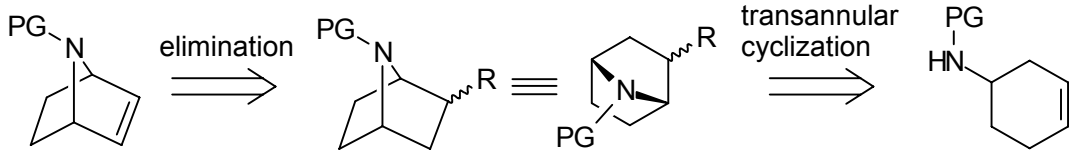
E5 = 101.95 kJ/mol

Figure 5.4: *Calculated conformations of **54**.*

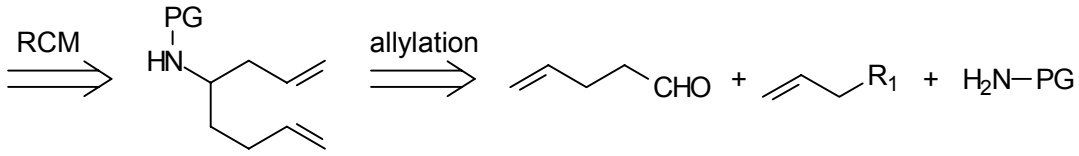
6 Synthetic Pathway for Preparation of Functionalized Cyclic Olefins by RCM

6.1 Retrosynthetic Analysis

The natural alkaloid epibatidine contains a 7-azabicyclic structure which provided our initial interest to this type of compounds. After a retrosynthetic analysis we have determined our synthetic route for preparation of 7-azabicyclo[2.2.1]hept-2-enes (see Scheme 6.1). It was planned to apply an elimination reaction of the appropriate 7-azabicyclo[2.2.1]heptane derivative, which in turn would be fashioned by a transannular cyclization reaction of cyclohexenylamines with possibilities for using different protecting groups for the amine function. The cyclic structure would be obtained by performing a RCM reaction of the appropriate dienes. An allylation reaction would be used to obtain the protected homoallyl amines, possibly applying a one-pot synthesis with 5-pentenaldehyde, appropriate carbamates and the commercially available allyl(trimethyl)silane under the influence of borontrifluoride etherate.



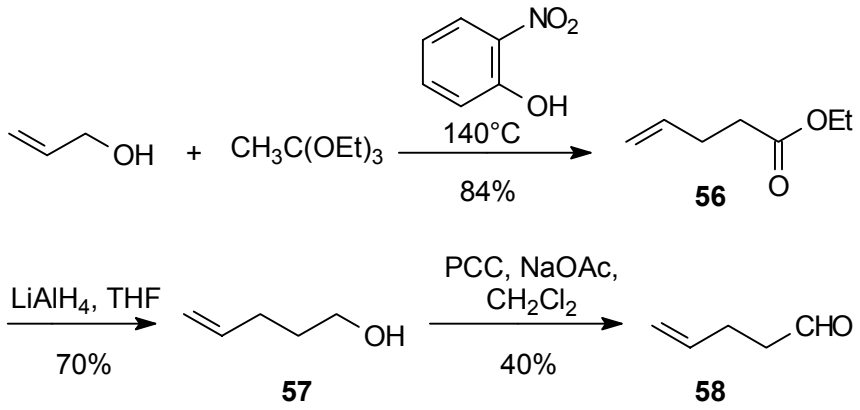
PG = Cbz, Boc, $COCF_3$, Tos



Scheme 6.1: *Retrosynthetic analysis for 7-azabicyclo[2.2.1]heptane derivatives*.

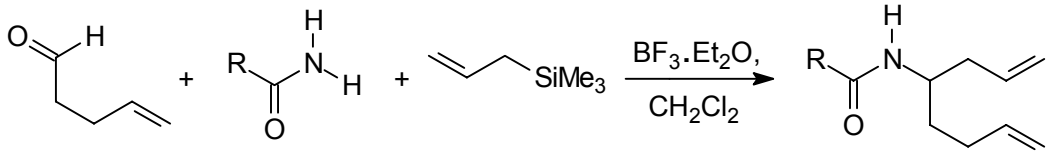
6.2 Preparation of Diene Intermediates as Precursors for the RCM

For the planned allylation reaction it was necessary first to synthesized the 5-pentenaldehyde **58**. For this purpose, according to the literature,[132] allyl alcohol was reacted with triethyl ortoacetate in the presence of catalytic amounts of *o*-nitrophenol at 140°C and the desired ester **56** was obtained after distillation in 86% yield (see Scheme 6.2). Thereafter followed reduction of the ester function with $LiAlH_4$ in anhydrous THF and the primary alcohol **57** was obtained as a colourless liquid in 70% yield. Subsequent oxidation with PCC in presence of anhydrous sodium acetate gave the desired aldehyde **58** in 40% yield.[133] The low yield can be explained with the high volatility of this product.



Scheme 6. 2: *Preparation of 4-pentenal **(58)**.*

The corresponding substrates, 1-allyl-4-pentenylamines were available by addition of an allyl anion equivalent to a suitable 4-pentenylimine. According to this strategy, the 1,7-octadien-4-amine derivatives **59a-d** were prepared. The urethanes **59a,b** were synthesized in analogy to a published procedure (see Scheme 6.3).[134] Thus, addition of borone trifluorid etherate to a mixture of 4-pentenal **(58)**, benzyl carbamate and allyl(trimethyl)silane followed by stirring of the reaction mixture over night gave the urethane **59a** in 60% yield. In a similar manner the urethane **59b** was prepared by using *tert*-butyl carbamate instead. However, when trifluoroacetamide was used as starting material for the same reaction with aldehyde **58**, no product was obtained.

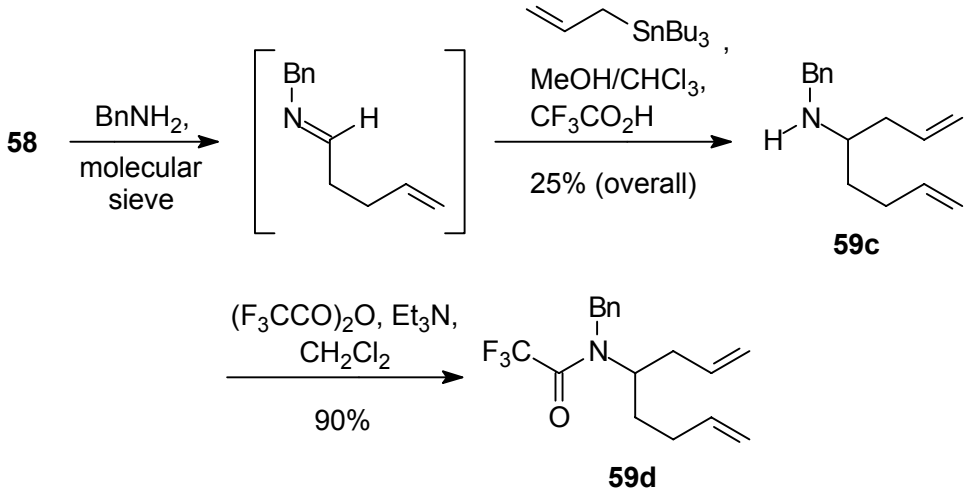


58 **59**

product	R	yield (%)
59a	BnO	60
59b	*t*BuO	48

Scheme 6.3: *One-pot synthesis of protected homoallyl amines.*

It was also of interest to study the influence of different substituents at the amino function upon the further planned RCM reaction. Therefore the secondary amine **59c** was synthesized in a simple two-step operation by first converting the aldehyde **58** with benzylamine to the corresponding imine followed by addition of allyl(tributyl)stannane and trifluoroacetic acid.[135, 136] Treatment of the benzyl amine **59c** with triflouroacetic acid anhydride in the presence of triethylamine furnished the protected aminodiene **59d** (see Scheme 6.4).

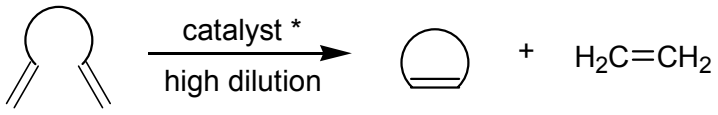


59c **59d**

Scheme 6.4: *Synthesis of protected homoallyl amines by using allyl(tributyl) stannane.*

6.3 Synthesis of Cyclohexenylamines by Ring Closing Metathesis

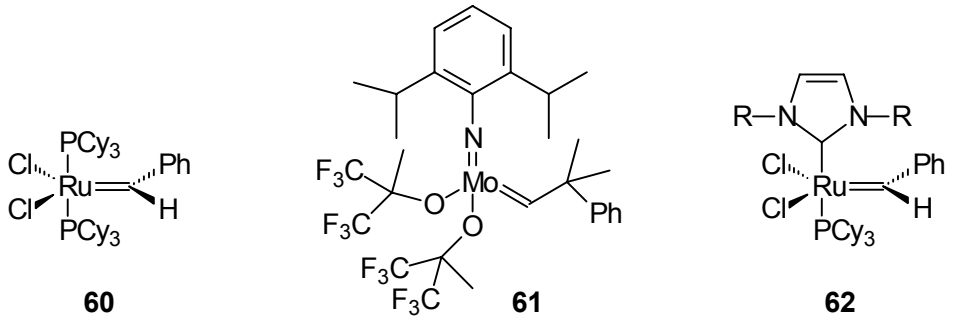
The ring closing methatesis (RCM) is one of a few reactions that form a double bond in the cyclization step (see Scheme 6.5). In contrast to the intramolecular WITTIG reaction or the MCMURRY cyclization, the starting materials, acyclic nonconjugated dienes, are stable entities and usually easily accessible. It is thus logical that the RCM reaction has found widespread use[137] since the discovery of carbene complexes that are able to mediate this reaction efficiently. In addition, some of these complexes are easily available.[138] The RCM reaction allows the formation of cyclic olefins with various ring sizes. However, as with other cyclization reactions, entropic factors and ring strain make the formation of medium-sized cycloolefins by this route difficult. Other well-known ways to some cyclic olefins include cycloaddition reactions. While, for example, cyclohexenes can be obtained by DIELS-ALDER reactions, not all substitution patterns are suitable for this strategy. Examples include cyclohexenes with a hetero atom at the homoallylic position. They require the use of special dienophilles, such as vinylboranes[139] or rearrangement reactions on a carboxylic substituent.[140] A grate advantage of the RCM is the involvement of relatively stable double bonds. This facilitates synthesis and handeling of the cyclization precursors.



* metal-carbene compelex

Scheme 6.5: *Ring closing metathesis (RCM)*

The commonly used catalysts for the RCM reaction are the ruthenium carbene complexes **60** and **61** developed by Grubbs,[138] and the Schrock molybdenum-based catalyst **62** (see Figure 6.1).[141] The GRUBBS catalyst **60** is very easy to prepare, commercially available, and air stable. On the other hand, the preparation of the SCHROCK catalyst **61** is a more elaborate undertaking, but is also commercially available. Recently, novel air- and water-tolerant ruthenium complex like **62** were introduced and shown to exhibit increased methatesis activity as compared to **60**.[142] These complexes are even able to induce cyclization to tetrasubstituted cycloalkenes.

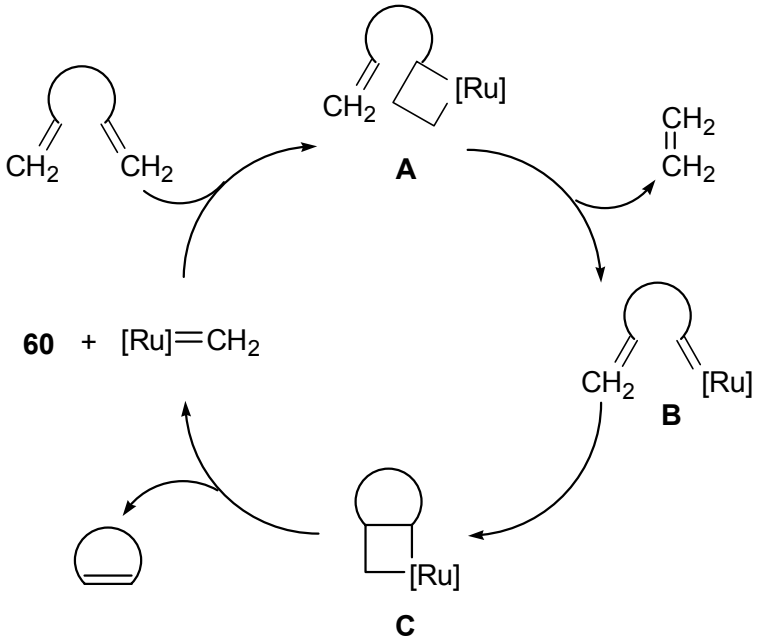


60 **61** **62**

Cy = cyclohexyl R = C_6H_2-2,4,6-(CH_3)

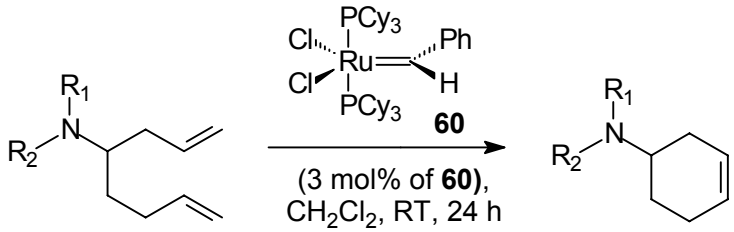
Figure 6.1: *Metal carbene complexes as catalysts for RCM.*

The RCM reaction is generally believed to proceed via a sequence of formal [2+2] cycloaddition and cycloreversion steps between metal alkylidene and metallacyclobutane species (see Scheme 6.6).[137] In the first turn of the catalytic cycle, the alkene cut-off by-product depends on the substituent in the original catalyst, while in second and subsequent catalytic cycles it depends on the substrate. For terminal alkene substrates the reaction by-product is ethene, and a partial vacuum may be used to drive the reaction to completion. Alkene substitution in both substrate and product can dramatically influence the reaction rate and outcome. Fürstner and co-workers have found some key parameters for successful proceeding of the RCM reaction.[143] These are: the presence of a functional group which serves as a relay entity that assembles the reacting sites; an appropriate distance between this polar group and the reacting alkenes; and low steric congestion near the double bonds.



Scheme 6.6: *Mechanism of RCM.*

In the present work the crucial RCM reactions were performed by stirring a solution of the dienes **59a-d** in CH_2Cl_2 in presence of 3 mol% of the GRUBBS ruthenium carbene **60** catalyst at room temperature for 24 h. As can be seen from Scheme 6.7, the 1,7-octadiene-4-amine derivatives **59a,b** and **59d** cyclized in almost quantitative yield to the coresponding cyclohexenylamines **63a,b** and **63d**. In contrast, the unprotected amine **59c** was recovered unchanged. This negative result supports the observation of Fürstner et al., mentioned above that a chelating substituent in close proximity to one of the double bonds shuts down the catalytic cycle.[143]

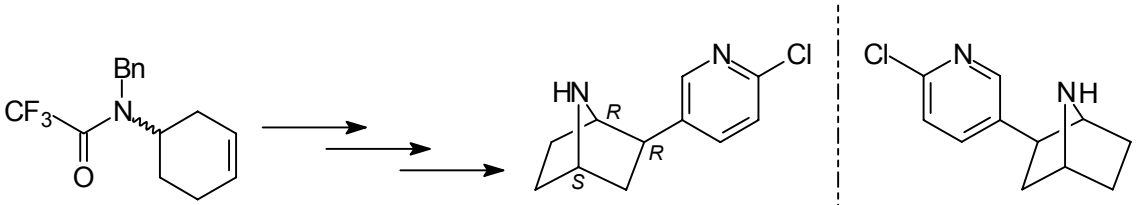


59 **63**

starting material	product	R_1	R_2	yield (%)
59a	**63a**	H	Cbz	95
59b	**63b**	H	Boc	91
59c	**63c**	Bn	H	0
59d	**63d**	Bn	F_3CCO	98

Scheme 6.7: *Preparation of cyclohexenylamines **63a-d** via RCM.*

Since compound **63d** had been used in the total synthesis of the alkaloid epibatidine by Fletcher et al.[68] (compound **B5,** see Section 3.2.1) the present work also constitutes a formal total synthesis of racemic epibatidine (Scheme 6.8).[91]

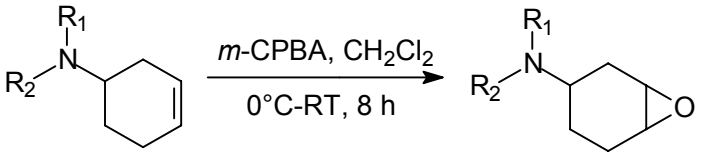


64d = B5 (-)-epibatidine (1*R*,2*R*,4*S*) (+)-epibatidine

Scheme 6.8: *Formal total synthesis of racemic epibatidine according to the synthesis of Fletcher et al.*

6.4 Transannular Cyclization

To achieve structural analogues of the natural compound epibatidine, we continued our experiments with an epoxidation reaction according to the total synthesis of Fletcher et al.[68] The substrates **63a,b,d**, dissolved in anhydrous dichloromethane, were treated with *m*-CPBA at 0°C and the desired products **64a,b,d** were obtained (see Scheme 6.9).

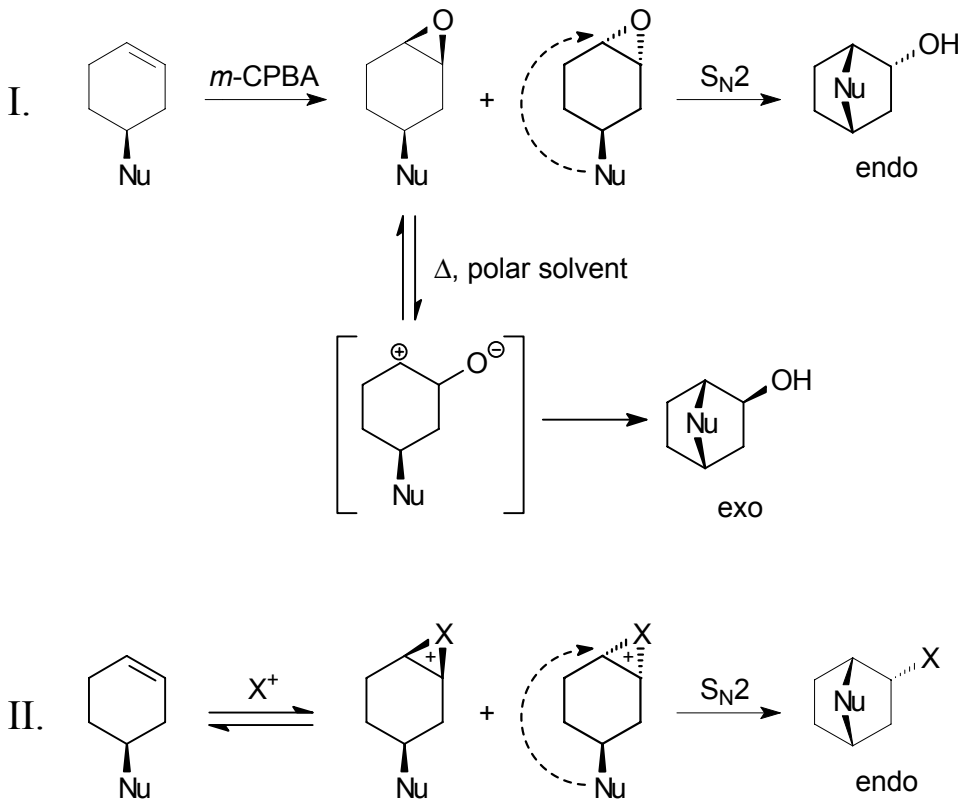


63 **64**

starting material	product	R_1	R_2	yield (%)
63a	**64a**	H	Cbz	55
63b	**64b**	H	Boc	35
63d	**64d**	Bn	F_3CCO	74

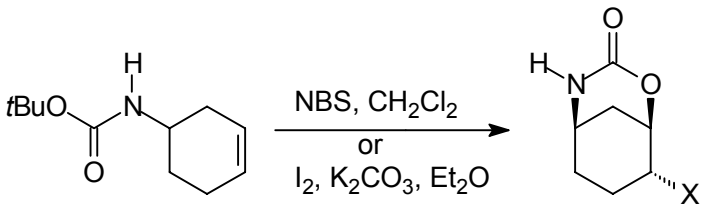
Scheme 6.9: *Epoxidation for obtaining precursors for the transannular cyclization reaction.*

Thereafter it was planned to perform an transannular cyclization reaction for constructing of the bicyclic system. The mechanism of this reaction is presented in Scheme 6.10. As can be seen there are two cyclization modes, *exo* and *endo*, which can be involved in this mechanism. By ring opening of an *anti*-epoxide the nucleophilic attack of the nitrogen occurs from the back side and the mechanism is proposed to be concerted. Therefore the *anti*-epoxide leads to an *endo*-product, whereas the *exo*-product can be obtained from the corresponding *syn*-epoxide. The mechanism of this cyclization is believed to proceed through a opening of the epoxide function to give a carbenium ion. Such examples have been relative rarely reported[144] and one of them was presented by Fletcher et al.[68] in the total synthesis of epibatidine.



Scheme 6.10: *Mechanism of the transannular cyclization.*

The transannular cyclization reaction used by Fletcher et al. was performed with compound **64d** at 180°C for 16 h in presence of a catalytic amount of 1-methyl-2-pyrrolidinone. In our synthetic route the same reaction conditions were also applied to substrates **64a** and **64b**, but no products were obtained even after prolongation of the reaction time. Another possibility to establish this bicyclic structure is the use of transannular cyclization reaction of cyclic olefins involving electrophilic halogen atoms. The proposed mechanism is present in Scheme 6.10 and is similar to the one described above. However, treatment of cyclohexenylamine derivative **63b** with 1.2 eq. *N*-bromosuccinimide (NBS) in dichloromethane[145] provided the bicyclic urethane **65a** in good yield instead of the initially assigned 7-azabicyclo[2.2.1]heptane derivative (see Scheme 6.11). Similarly, reaction of **63b** with 2 eq. iodine and 2 eq. potassium carbonate in diethyl ether gave the corresponding iodo compound **65b**.[146]



63b

65a X = Br (60% yield
65b X = I (74% yield)

Scheme 6.11: *Bicyclic urethanes **65a,b** obtained by transannular cyclization.*

However, from the observed results it has to be considered that the nitrogen itself dose not react as nucleophile. Instead, the oxygen of the carbamate moiety functions as nucleophile because of the good leaving group properties of Boc and Cbz groups. Therefore another bicyclic system was obtained containing a six- and an eight-membered ring. This method represents another alternative way for obtaining bicyclic structures.

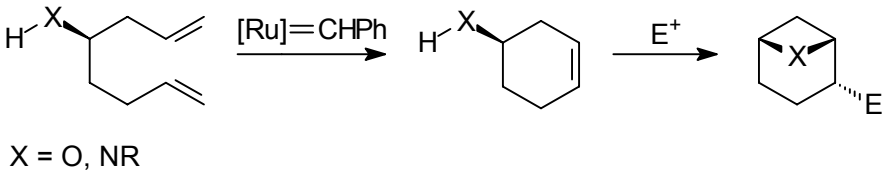
7 Summary and Conclusion

The first goal of the present thesis was to find an efficient approach to epothilone analogues. Herein was described the formal synthesis of epothilone A analogue as exemplified with compound **54**. The present synthetic route contains in the longest reaction sequence 22 isolated intermediates and represents a novel strategy for generation of epothilone analogues. The overall yield was determined to be 1.3%, which corresponds to an average yield of 82% per reaction step.

The innovative step in this synthesis was the formation of the C7-C8 bond via a stereoselective aldol reaction between the key fragments C1-C7 (compound **44**) and C8-C15 (compound **23**) with *de* > 95%. This required the synthesis of two building blocks. As it was mentioned already, the so far published total syntheses of epothilones and analogues describe the formation of the C-C bond through an aldol reaction only between C6 and C7 atoms of the main carbon-skeleton. The cyclization step was made via an YAMAGUCHI macrolactonization reaction and the end product **54** from our synthesis was obtained. Unfortunately, the small amount of this product has limited our practical possibilities for continuing the further planned synthetic strategy for obtaining the completely deprotected and oxidized compound. Nevertheless, compound **54** might show already some biological activity. Further experiments and investigations are planned. It should be mentioned that the present work illustrates a flexible and convergent synthetic route to epothilone analogues.

The use of optically pure and commercially available *D*-arabinose as a starting material had the purpose to introduce the desired chirality at C15 of the main carbon-skeleton. The *cis* double bond of the C8-C15 building block **23** was obtained by a WITTIG reaction and contained the EVANS auxiliary, which was necessary for the asymmetric aldol reaction. The product **23** carries also a triple bond which was introduced through a SEYFERTH/GILBERT reagent. This should make possible the attachment of the thiazol moiety through a palladium-catalysed cross-coupling reaction and would allow the preparation of aryl analogues of the natural compound. An EVANS-type modified aldol reaction was used for the synthesis of the C1-C7 building block **44**, which determined the stereochemistry of the methyl group at C6. The desired configuration of C7 and C8 stereocenters also was secured by a stereoselective EVANS type aldol reaction. Here it is necessary to mention that the natural compound contains 7 stereocenteres, whereas our expected product would have 5. Another synthetic strategy for obtaining a derivative with 7 stereocenters is currently by developed.

The second goal of the present thesis was the synthesis of cyclohexenylamines by ring closing metathesis reaction. This method represents a useful alternative to the DIELS-ALDER strategy. Such cyclohexenes are of interest for the synthesis of bicyclic heterocycles by transannular reactions (see Scheme 7.1).



X = O, NR

Scheme 7.1: *Synthesis of bicyclic heterocycles by transannular reactions from cyclohexenes.*

The combination of the RCM reaction with transannular cyclization should provide access to interesting natural products. It should be mentioned that our synthetic route to compound **63d** represents a formal total synthesis of the alkaloid epibatidine. In addition, the bicyclic urethane **65a** obtained by electrophilic transannular cyclization reaction has been of interest to the National Cancer Institute (NCI) and was tested in a disease-orientated *in vitro* anticancer screening program.[147] The compound **65a** has been evaluated in a one-dose primary anticancer assay[148] against a 3 cell line panel consisting of MCF7 (Breast), NCI-H460 (Lung), and SF-268 (CNS), but unfortunately the activity was found to be too low for further investigations.

8 Experimental Part

8.1 General Remarks

8.1.1 Chemicals and Working Technique

All required fine chemicals were received from the firms ACROS (Ulm), ALDRICH (Steinheim), FLUKA (Buchs, Switzerland) and MERCK (Darmstadt). They were used directly without further purification if nothing else was mentioned. All solvents were distilled and/or dried before use. The applied petrol ether fraction had a b.p. of 40-60°C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; dimethylformamide and dimethylsulfoxide by vacuum distillation from calcium hydride; acetone by distillation from phosphor(V)-oxide. Absolute triethylamine and pyridine were distilled from calcium hydride prior to use. Hünig's base was stored over potassium hydroxide and was used without further distillation. Aqueous sodium hypochlorite (6-14% active chlorine, «RIEDEL-DEHAEN» Sigma Aldrich Laborchemikalien) was calculated as a 2M aqueous solution. For preparation of phosphate buffer (pH 7) was used a standard procedure: 85.0 g KH_2PO_4 and 14.5 g NaOH in 1 l H_2O.

Unless mentioned, all the reactions were carried out under an argon atmosphere and the glass material was pre-dried by flame drying under high vacuum (oil pump RV 5, EDWARDS). All the chemicals, which were air or water sensitive, were stored under inert atmosphere.

Compounds which are not described in the experimental part, were prepared according to the literature.

8.1.2 NMR-Spectroscopy

^{1}H and ^{13}C NMR spectra were measured on a BRUKER AC 250 (250 or 62.9 MHz, respectively) or unity 400 VARIAN (400 or 100 MHz, respectively). All two-dimensional spectra (COSY, TOCSY, HSQC, HMBC, NOESY) were measured on BRUKER AMX 400 (400 or 100 MHz, respectively) or BRUKER AMX 600 (600 or 150 MHz, respectively). As solvents were used chloroform-*d* or benzene-d_6. TMS (δ = 0) was used as an internal standard. Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, m =multiplet, br = broadened), coupling constant (Hz), integration, peak

assignment]. For the ^{13}C NMR spectra the signal multiplicity is determined by means of the APT or DEPT-135 technique: + for CH or CH_3, - for CH_2, # for C.

8.1.3 Mass Spectrometry

Mass spectra were recorded on a Triple-Stage-Quadrupol Spectrometer TSQ-70 from the FINNIGAN-MAT (Bremen) or on an Intectra AMD 402 mass spectrometer. High-resolution mass spectra were measured on an Intectra AMD MAT-711A mass spectrometer from the same firm. The used mass spectrometric ionization methods were electron-impact (EI), fast-atom bombardment (FAB) or field-desorption (FD). FT-ICR-mass spectrometry and HR-FT-ICR mass spectra were measured on an APEX^{TM} II spectrometer from the firm BRUKER DALTONIK (Bremen) with electrospray ionization method (ESI). Some of the mass spectra were measured also on a FINNIGAN MAT SFQ 710 C (Electrospray ionization 4.5 kV, $T_{capillary}$ = 250°C, solvent methanol/water = 90/10). Significant fragments are reported as follows: *m/z* (relative intensity).

8.1.4 Infrared Spectroscopy

Infrared spectra (IR) were recorded on a FT-IR-430 spectrometer from the firm JACSO or on a FT-IR-1000 from the firm PERKIN ELMER. The percent transmittance (T%) of liquid or oily substances was measured in film between potassium bromide tablets. Solid substances were pulverized with potassium bromide and percent reflection (R%) was measured. Absorption band frequencies are reported in cm^{-1}.

8.1.5 Polarimetry

Optical rotations were measured on a JASCO Polarimeter P-1020. They are reported as follows: $[\alpha]^{temperature}_{D}$ (concentration, solvent). The unit of c is g/100 ml. As a solvent was used anhydrous CH_2Cl_2. For the measurement was used the sodium D line = 589 nm.

8.1.6 Melting Points

Melting points were taken with a BÜCHI B-540 apparatus or BOETIUS-melting point-microscope and were not corrected.

8.1.7 Elemental Analysis

Elemental analyses were recorded with a LECO CHNS-932 or a HEREAUS INSTRUMENTS ELEMENTAL ANALYSIS system Vario EL.

8.1.8 Chromatographic Methods

Analytical thin-layer chromatography (TLC) was performed on pre-coated silica gel 60 F_{254} plates (MERCK) or Polygram Sil G/UV_{254} (MACHEREY-NAGEL), and pre-coated aluminum oxide ALOX N/UV_{254} (MACHEREY-NAGEL). The compounds were visualised by UV_{254} light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or aqueous solution of potassium permanganate (heating on a hot-plate). For preparation of the molybdate solution were used 20 g ammonium molybdate [$(NH_4)_6Mo_7O_{24}$ x $4H_2O$] and 0.4 g $Cer(SO_4)_2$ x $4H_2O$ dissolved in 400 ml 10% H_2SO_4. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g Na_2CO_3 in 250 ml H_2O.

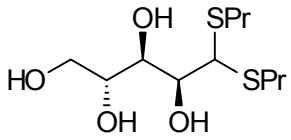
Flash column chromatography was performed using J. T. BAKER flash silica gel (40-63 μm, 230-400 mesh ASTM) or silica gel 60 M (40-63 μm) from the firms MERCK and MACHEREY-NAGEL, and aluminum oxide Typ 507 C neutral (0.05-0.15 mm, pH 7.0±0.5) from the firm FLUKA.

Gaschromatography was performed on a CHROMPACK CP 9000 using a flame ionization detector, and carrier gas H_2. For GC-MS coupled chromatography, GC-system from Series 6890 with an Injector Series 7683 and MS-detector Series 5973 from the HEWLETT PACKARD was used, with EI method, and carrier gas He.

Analytical HPLC was performed on a HEWLETT PACKARD HP 1100 system.

8.2 General Procedures for Preparation of Epothilone Analogues

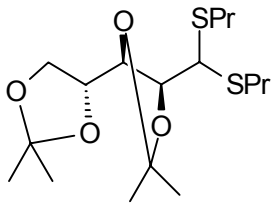
*D-Arabinose di-1-propyl dithioacetal **(2)**:*[95]



D-Arabinose (50 g, 0.33 mol) was dissolved in concentrated hydrochloric acid (51 ml) in a 1l three-necked flask with mechanical stirring and ice cooling. To the cold, stirred solution was added a slow stream of propyl mercaptan (60.4 ml, 50.7 g, 0.66 mol). The solution quickly thickened and solidified, and a white solid mass was obtained within 10 min. After 1 min, chilled water was layered on top of the precipitate, which prevents discoloration. The reaction mixture was allowed to remain in the ice bath for 5 min. Thereafter the resulting white mass was broken up to small pieces, mixed with additional water (200 ml) and stirred until a homogeneous slurry was obtained, which was filtered under suction. The white cake was washed with chilled water and the resulting moist solid was recrystallized by dissolving it in hot iso-propanol (300 ml) and adding water (500 ml). Filtration, washing with cold water and drying over potassium hydroxide in vacuum desiccator for 45 h gave the dithioacetal **2** as fine, white needles 67.3 g (71% yield). - m.p.: 131.4 – 131.7°C (lit. [95]: 131.0 – 131.5°C).

MS (EI): *m/z* (%) = 284 (5) [M^+], 163 (100).

*2,3-4,5-Di-O-isopropylidene-D-arabinose di-1-propyl dithioacetal **(3)**:*



D-Arabinose di-1-propyl dithioacetal **(2)** (67.3 g, 0.24 mol) was suspended in freshly distilled acetone (600 ml). The mechanically stirred mixture was cooled to 0°C and concentrated sulphuric acid (9 ml) was added dropwise. After 10 min of stirring at 0°C the

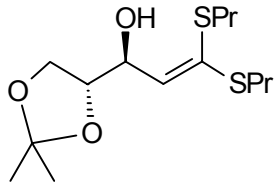
reaction mixture was allowed to reach room temperature and was stirred for additional 18 h, during which time the colour changed from colorless to yellow. Thereafter the solution was neutralized by addition of powdered, anhydrous sodium carbonate (21 g) and the vigorously stirring was continued for 2 days. The resulting suspension was filtered and the filtrate was evaporated under reduced pressure. The residue was taken up in toluene (300 ml), dried over $MgSO_4$, filtered again, and concentrated in vacuo to provided 85.1 g (99% yield) of 2,3-4,5-Di-*O*-isopropylidene-*D*-arabinose di-1-propyl dithioacetal **(3)** as a straw-colored syrup. The crude material is suitable for the next step without further purification. - TLC (*n*-hexane/ethyl acetate, 4:1): *R*f = 0.86.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.98, 1.00 (2 t, *J* = 7.3 Hz each, 3 H each, propyl-CH_3), 1.32, 1.36, 1.40, 1.44 (4 s, 3 H each, isopropylidene-CH_3), 1.55-1.69 (m, 4 H, $SCH_2C\underline{H}_2CH_3$), 2.59-2.75 (m, 4 H, $SC\underline{H}_2CH_2CH_3$), 4.24-4.28 [m, 1 H, $C\underline{H}CH(SPr)_2$], 3.91-4.15 (m, 5 H, CH_2, 3 CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.6 (propyl-CH_3), 22.7 ($SCH_2\underline{C}H_2CH_3$), 25.3, 26.6, 27.1, 27.3 (isopropylidene-CH_3), 33.0, 33.3 ($S\underline{C}H_2CH_2CH_3$), 53.0 [$\underline{C}H(SPr)_2$], 67.8 ($OCH_2$), 77.2, 79.6, 84.5 (OCH), 109.7, 110.2 (isopropylidene-C).

MS (EI): *m/z* (%) = 364 (5) [M^+], 231 (20), 163 (100), 143 (50).

*2-Deoxy-4,5-O-isopropylidene-D-erythro-pent-1-enose di-1-propyl dithioacetal **(4)**:*



To a solution of potassium *tert*-butoxide (13.9 g, 124 mmol) in absolute THF (300 ml) and anhydrous DMSO (150 ml) at room temperature and inert atmosphere was added dropwise over period of 40 min a solution of **3** (30 g, 82 mmol) in THF (150 ml). After stirring for 1 h at room temperature, the brown reaction mixture was poured onto ice (600 g). The aqueous layer was extracted with ethyl acetate (4 x 400 ml) and the combined organic layers were washed once with ice-cold water (400 ml), brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 4:1) to yield 20 g (80%) of **4** as a yellow oil. - TLC (petroleum ether/ethyl acetate, 4:1): *R*f = 0.56.

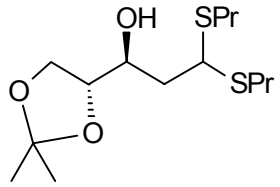
^{1}H NMR (250 MHz, benzene-d_6): δ = 0.79, 0.81 (2 t, *J* = 7.3 Hz each, 3 H each, propyl-CH_3), 1.24, 1.39 (2 s, 3 H each, isopropylidene-CH_3), 1.41-1.51 (m, 4 H, $SCH_2C\underline{H}_2CH_3$), 2.27 (br, 1 H, OH), 3.37-2.80 (m, 4 H, $SC\underline{H}_2CH_2CH_3$), 3.80-4.15 (m, 3 H, OCH_2, C<u>H</u>OH), 5.00-5.07 (m, 1 H, $CH_2C\underline{H}O$), 6.11 [d, *J* = 8.1 Hz, 1 H, C<u>H</u>C(SPr)$_2$].

^{13}C NMR (62.9 MHz, benzene-d_6): δ = 13.3 (+, propyl-CH_3), 22.4, 23.4 (2 -, $SCH_2\underline{C}H_2CH_3$), 25.4, 26.6 (2 +, isopropylidene-CH_3), 35.0, 35.4 (2 -, $S\underline{C}H_2CH_2CH_3$), 65.8 (-, OCH_2), 70.4 (+, <u>C</u>HOH), 78.6 (+, $CH_2\underline{C}HO$), 109.4 (#, isopropylidene-C), 135.0 [-, <u>C</u>HC(SPr)$_2$], 135.8 [#, <u>C</u>(SPr)$_2$].

IR (neat): $\tilde{\nu}$ = 3454 cm^{-1} (OH), 2961 cm^{-1} (alkyl), 1583 cm^{-1} (C=C).

MS (EI): *m/z* (%) = 306 (2) [M$^+$], 291 (3), 205 (100).

*2-Deoxy-4,5-O-isopropylidene-D-erythro-pentose di-1-propyl dithioacetal **(5)**:*



To a stirred suspension of lithium aluminium hydride (6.63 g, 175 mmol) in anhydrous THF (450 ml) was added at room temperature dropwise over period of 1 h a solution of **4** (13.3 g, 43 mmol) in THF (120 ml). After 4.5 h of stirring at room temperature, the reaction mixture was cooled to 0°C and quenched by careful addition of ice-cold water (60 ml). Then the resulting mixture was neutralized by addition of 1M aqueous hydrochloric acid (420 ml) and was stirred vigorously at ambient temperature over night. Thereafter the bulk of THF was removed on the rotatory evaporator and the rest was extracted with ethyl acetate (3 x 250 ml). The combined organic layers were washed with brine (200 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 2:1) to give 12.95 g (98%) of the compound **5** as colorless oil. - TLC (petroleum ether/ethyl acetate, 2:1): *R*f = 0.66.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 6 H, propyl-CH_3), 1.32, 1.38 (2 s, 3 H each, isopropylidene-CH_3), 1.52-1.66 (m, 4 H, $SCH_2C\underline{H}_2CH_3$), 1.81-1.95 [m, 2 H, $C\underline{H}_2CH(SPr)_2$], 2.45-2.71 [m, 5 H, C<u>H</u>(SPr)$_2$], 3.87-4.02 (m, 4 H, OCH_2, OCH, C<u>H</u>OH).

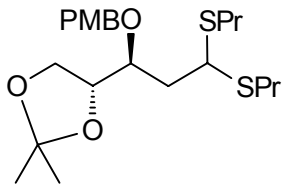
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7 (+, propyl-CH_3), 22.7, 22.8 (2 -, $SCH_2\underline{C}H_2CH_3$), 25.3, 26.6 (2 +, isopropylidene-CH_3), 31.9, 32.5 (2 -, $S\underline{C}H_2CH_2CH_3$), 39.0 [-,

$\underline{C}H_2CH(SPr)_2$], 48.8 [+, $\underline{C}H(SPr)_2$], 65.6 (-, OCH_2), 70.0 (+, $\underline{C}HOH$), 78.4 (+, OCH), 109.3 (#, isopropylidene-C).

IR (neat): $\tilde{\nu}$ = 3465 cm^{-1} (OH), 2961 cm^{-1} (alkyl).

MS (EI): *m/z* (%) = 308 (10) [M^+], 233 (15), 215 (10), 175 (50), 157 (55), 89 (100).

*2-Deoxy-3-O-(4-methoxybenzyl)-4,5-O-isopropylidene-D-erythro-pentose di-1-propyl dithioacetal **(6a)**:*



To a solution of alcohol **5** (7.17 g, 23 mmol) in dry DMF (250 ml) was added at once sodium hydride (60% mineral oil dispersion, 1.96 g, 49 mmol) and the resulting suspension was stirred at ambient temperature for 3 h. Thereafter the reaction mixture was cooled to 0°C and freshly distilled *p*-methoxybenzyl chloride (3.80 ml, 28 mmol) was added dropwise over a period of 10 min. The brown solution was allowed to reach room temperature and was stirred for 16 h. Then the reaction mixture was poured into ice-cold water (700 ml) and extracted with ethyl acetate (3 x 400 ml). The combined organic layers were washed with water (4 x 150 ml), and brine (1 x 150 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The yellow crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to afford **6a** as colorless oil (9.76 g, 99% yield). - TLC (petroleum ether/ethyl acetate, 6:1): *R*f = 0.61. - $[\alpha]^{25}_D$ = +1.3 (*c* 0.25, $CHCl_3$).

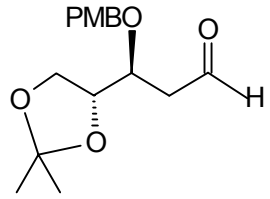
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.97, 0.98 (2 t, *J* = 7.4 Hz each, 3 H each, propyl-CH_3), 1.34, 1.43 (2 s, 3 H each, isopropylidene-CH_3), 1.53-1.64 (m, 4 H, $SCH_2\underline{C}H_2CH_3$), 1.89-1.96 [m, 2 H, $\underline{C}H_2CH(SPr)_2$], 2.46-2.62 [m, 5 H, $\underline{C}H(SPr)_2$], 3.79 (s, 3 H, OCH_3), 3.81-4.11 (m, 4 H, OCH_2, OCH, $\underline{C}HOPMB$), 4.54, 4.69 (2 d, *J* = 11.1 Hz each, 2 H, PMB-$\underline{C}H_2$), 6.86, 7.25 (2 d, *J* = 8.7 Hz each, 2 H each, aromatic-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.7, 13.8 (propyl-CH_3), 22.8 ($SCH_2\underline{C}H_2CH_3$), 25.3, 26.5 (isopropylidene-CH_3), 31.5, 32.5 ($S\underline{C}H_2CH_2CH_3$), 39.0 [$\underline{C}H_2CH(SPr)_2$], 48.2 [$\underline{C}H(SPr)_2$], 55.3 ($OCH_3$), 66.1 ($OCH_2$), 73.2 (PMB-$\underline{C}H_2$), 76.6 ($\underline{C}HOPMB$), 78.4 (OCH), 109.2 (isopropylidene-C), 113.8, 129.5 (aromatic-CH), 130.7, 159.3 (aromatic-C).

IR (neat): $\tilde{\nu}$ = 2960 cm^{-1} (alkyl), 1613 cm^{-1}, 1514 cm^{-1} (C=C).

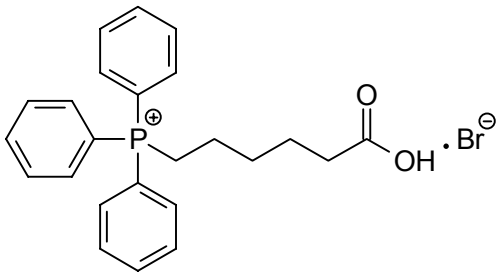
MS (EI): *m/z* (%) = 428 (10), [M^+], 352 (5), 307 (5), 276 (2), 217 (10), 121 (100).
HRMS (EI): calc. for $C_{22}H_{36}O_4S_2$: 428.20557, found: 428.20588.

*2-Deoxy-3-O-(4-methoxybenzyl)-4,5-O-isopropylidene-D-erythro-pentose **(7)**:*



To a solution of the *p*-methoxybenzyl ether **6a** (9.81 g, 23 mmol) in acetonitrile (320 ml) and water (64 ml) was added calcium carbonate (10.61 g, 106 mmol) and mercuric (II) chloride (25 g, 92 mmol). The heterogeneous reaction mixture was stirred vigorously at ambient temperature for 4.5 h. Then the mixture was filtered through a pad of Celite and washed several times with acetonitrile. The filtrate was concentrated *in vacuo* and the residue was dissolved in diethyl ether (1 l). This ether solution was washed with 1M potassium iodide solution (4 x 120 ml) and once with brine (240 ml), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to afford 5.66 g of aldehyde **7** (84% yield) as a pale yellow liquid. The crude material is suitable for the next step without further purification. - TLC (petroleum ether/ethyl acetate, 1:1): *R*f = 0.64.
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32, 1.39 (2 s, 3 H each, isopropylidene-CH_3), 2.72-2.69 (m, 2 H, C$\underline{H}_2$CHO), 3.78 (s, 3 H, OCH_3), 3.81-3.87 (m, 1 H, C$\underline{H}$OPMB), 4.02-4.15 (m, 3 H, OCH_2, OCH), 4.49, 4.56 (2 d, *J* = 11.1 Hz each, 2 H, PMB-C$\underline{H}_2$), 6.86, 7.21 (2 d, *J* = 8.7 Hz each, 2 H each, aromatic-CH), 9.79 (t, *J* = 2.0 Hz, 1 H, CHO).
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 25.1, 26.5 (isopropylidene-CH_3), 45.9 (C$\underline{H}_2$CHO), 55.3 (OCH_3), 66.9 (OCH_2), 72.3 (PMB-C$\underline{H}_2$), 75.0 (C$\underline{H}$OPMB), 76.6 (OCH), 109.7 (isopropylidene-C), 113.9, 129.6 (aromatic-CH), 129.8, 159.5 (aromatic-C), 200.6 (CHO).
IR (neat): $\tilde{\nu}$ = 2987 cm^{-1} (alkyl), 2730 cm^{-1}, 1725 cm^{-1} (CHO), 1612 cm^{-1}, 1514 cm^{-1} (C=C).

*(5-Carboxypentyl)triphenylphosphonium bromide **(8)**:*[101]



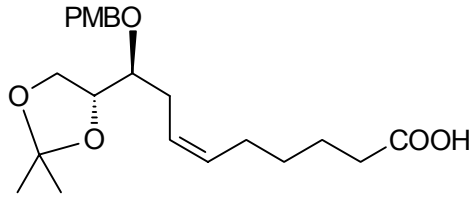
A solution of triphenylphosphine (6.72 g, 25.6 mmol) and 6-bromohexanoic acid (5 g, 256 mmol) in absolute toluene (70 ml) was heated to reflux (140°C oil bath) under inert atmosphere for 24 h during which time the mixture became inhomogeneous. Thereafter the reaction mixture was cooled to ambient temperature under an atmosphere of argon and the solvent removed under reduced pressure. The glasslike heavy oil was triturated with dry chloroform and diluted with diethyl ether, which resulted in the formation of a white solid. After recrystallization from chloroform / diethyl ether (1:10) and drying under vacuum for several hours, the pure salt **8** (7.87 g, 67% yield) was obtained as a white crystalline solid. - m.p.: 192.4 – 192.6°C (lit. [101]: 188.0 – 191.0°C).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28-1.78 [m, 6 H, $(C\underline{H}_2)_3CH_2COOH$], 2.20-2.35 (m, 2 H, $C\underline{H}_2COOH$), 3.32-3.53 (m, 2 H, $Ph_3PC\underline{H}_2$), 7.62-7.79 (m, 15 H, aromatic-CH), 8.87 (br, 1 H, COOH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 22.1 [-, $\underline{C}H_2(CH_2)_3COOH$], 22.9 (-, Ph_3PCH_2), 24.1 (-, $\underline{C}H_2CH_2COOH$), 29.7 [-, $\underline{C}H_2(CH_2)_2COOH$], 34.3 (-, $\underline{C}H_2COOH$), 117.4, 118.8 (2 #, aromatic-C), 130.7, 133.7, 135.2 (3 +, aromatic-CH), 175.8 (#, COOH).

IR (KBr): $\tilde{\nu}$ = 2938 cm^{-1} (alkyl), 1705 cm^{-1} (COOH).

*(6Z,9S)-9-[(4R)-2,2-Dimethyl-1,3-dioxolan-4-yl]-9-[(4-methoxybenzyl)oxy]-6-nonenoic acid **(9)**:*



A suspension of (5-carboxypentyl)triphenylphosphonium bromide **(8)** (4.35 g, 10 mmol) in absolute THF (20 ml) was treated dropwise over period of 15 min with 1M solution of sodium bis(trimethylsilyl)amide in THF (21 ml, 21 mmol). The resulting red colored reaction mixture was stirred for 30 min at ambient temperature and then cooled to –60°C. Thereafter was added slowly the aldehyde **7** (5.66 g, 19 mmol) dissolved in 10 ml of THF. After complete addition, the reaction mixture was warmed up to –50°C and stirred for additional 15 min and then was allowed slowly to reach room temperature and to stir for 1 h more. Thereafter the solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (160 ml), and washed several times with saturated aqueous solution of $NaHCO_3$ (15 x 100 ml). The combined aqueous layers were acidified to pH 2 using concentrated hydrochloric acid and extracted with ethyl acetate (3 x 500 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 1:1) to give the acid **9** (3.69 g, 99% yield) as yellow oil. - TLC (petroleum ether/ethyl acetate, 1:1): *R*f = 0.63. - $[\alpha]^{22.4}_D$ = +27.1 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33, 1.41 (2 s, 3 H each, isopropylidene-CH_3), 1.36-1.45 [m, 2 H, C$\underline{H}_2(CH_2)_2COOH$], 1.57-1.69 (m, 2 H, C$\underline{H}_2CH_2COOH$), 2.03-2.11 [m, 2 H, C$\underline{H}_2(CH_2)_3COOH$], 2.26-2.37 (m, 4 H, C$\underline{H}_2COOH$, C$\underline{H}_2CH$=CH), 3.48-3.55 (m, 2 H, C$\underline{H}$OPMB), 3.79 (s, 3 H, OCH_3), 3.83-3.90 (m, 1 H, OCH), 3.97-4.15 (m, 2 H, OCH_2), 4.50, 4.57 (2 d, *J* = 11.1 Hz each, 2 H, PMB-C$\underline{H}_2$), 5.41-5.55 (m, 2 H, olefin-CH), 6.86, 7.24 (2 d, *J* = 8.7 Hz each, 2 H each, aromatic-CH).

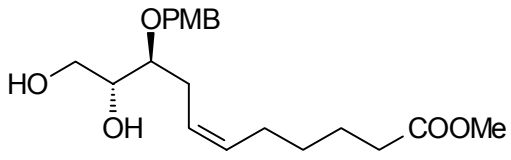
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.4 (-, $\underline{C}H_2CH_2COOH$), 25.4, 26.7 (+, isopropylidene-CH_3), 27.0 [-, $\underline{C}H_2(CH_2)_3COOH$], 29.0 (-, $\underline{C}H_2CH$=CHCH_2CH_2), 33.9 (-, $\underline{C}H_2COOH$), 55.3 (+, OCH_3), 66.6 (-, OCH_2), 72.2 (-, PMB-$\underline{C}H_2$), 77.6 (+, OCH), 78.9 (+, $\underline{C}$HOPMB), 109.1 (#, isopropylidene-C), 113.8 (+, aromatic-CH), 125.2 (+, olefin-CH), 129.4 (+, aromatic-CH), 130.6 (#, aromatic-C), 131.7 (+, olefin-CH), 159.2 (#, aromatic-C), 179.4 (#, COOH).

IR (neat): $\tilde{\nu}$ = 2936 cm^{-1} (alkyl), 2680 cm^{-1}, 1738 cm^{-1}, 1709 cm^{-1} (COOH), 1613 cm^{-1}, 1586 cm^{-1}, 1514 cm^{-1} (C=C).

MS (EI): *m/z* (%) = 392 (1) [M^+], 377 (3), 334 (3), 291 (10), 273 (12), 121 (100).

HRMS (EI): calc. for $C_{22}H_{32}O_6$: 392.21989, found: 392.21630.

*Methyl (6Z,9S,10R)-10-hydroxy-9-[(4-methoxybenzyl)oxy]-6-dodecenoate **(10)**:*



To a solution of acid **9** (826 mg, 2.11 mmol) in methanol (40 ml) was added at once cupric(II) chloride dihydrate (1.96 g, 11.5 mmol) and the green reaction mixture was refluxed for 1.5 h. The reaction was cooled to ambient temperature and 2.6 g $NaHCO_3$ was added. After the evolution of carbon dioxide ceased, 20 ml of water was added and the resulting blue precipitate was filtered off trough a pad of Celite and the pad was washed several times with ethyl acetate. The combined filtrate was washed once with brine (70 ml) and dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (ethyl acetate) gave 439 mg (57% yield) of diol **10** as colorless oil. - TLC (ethyl acetate): *R*f = 0.56.

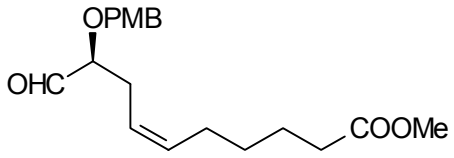
^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30-1.42 [m, 2 H, C$\underline{H}_2$(CH_2)$_2$COOMe], 1.55-1.67 (m, 2 H, C$\underline{H}_2$$CH_2$COOMe), 1.97-2.10 [m, 2 H, C$\underline{H}_2$(CH_2)$_3$COOMe], 2.26-2.48 (m, 4 H, C$\underline{H}_2$COOMe, C$\underline{H}_2$CH=CH), 2.52, 2.80 (2 br, 1 H each, 2 OH), 3.49-3.58 (m, 1 H, C$\underline{H}$OPMB), 3.64 (s, 3 H, COOC$\underline{H}_3$), 3.69-3.74 (m, 3 H, C$\underline{H}_2$OH, C$\underline{H}$OH), 3.78 (s, 3 H, OCH_3), 4.42, 4.58 (2 d, *J* = 11.1 Hz each, 2 H, PMB-C$\underline{H}_2$), 5.38-5.52 (m, 2 H, olefin-CH), 6.85, 7.23 (2 d, *J* = 8.7 Hz each, 2 H each, aromatic-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.6 (C$\underline{H}_2$$CH_2$COOMe), 27.1 [C$\underline{H}_2$($CH_2$)$_3$COOMe], 28.4 (C$\underline{H}_2$CH=CH), 29.0 [C$\underline{H}_2$($CH_2$)$_2$COOMe], 33.9 (C$\underline{H}_2$COOMe), 51.6 (COOC$\underline{H}_3$), 55.3 ($OCH_3$), 63.5 (C$\underline{H}_2$OH), 72.1 (PMB-C$\underline{H}_2$), 72.4 (C$\underline{H}$OH), 80.5 (C$\underline{H}$OPMB), 114.0 (aromatic-CH), 125.2 (olefin-CH), 129.5 (aromatic-CH), 130.2 (aromatic-C), 131.9 (olefin-CH), 159.4 (aromatic-C), 174.3 (C$\underline{O}$$OCH_3$).

IR (neat): $\tilde{\nu}$ = 3446 cm^{-1} (OH), 2935 cm^{-1} (alkyl), 1739 cm^{-1} (C=O), 1612 cm^{-1}, 1586 cm^{-1}, 1514 cm^{-1} (C=C).

MS (FAB): *m/z* (%) = 367 (60) [M+H^+], 307 (100), 289 (75).

*Methyl (6Z,9S)-9-[(4-methoxybenzyl)oxy]-10-oxo-6-decenoate **(11)**:*

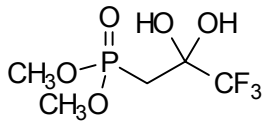


The diol **10** (300 mg, 0.82 mmol) was dissolved in 60% aqueous acetonitrile (7.5 ml) and treated with sodium(meta)periodate (263 mg, 1.23 mmol); a white precipitate was formed immediately. The reaction mixture was stirred at ambient temperature for 1.5 h and filtered through a glass funnel. The filtrate was mixed with water (10 ml) and extracted thoroughly with chloroform (5 x 10 ml). The combined organic layers were washed once with water (20 ml), dried with $MgSO_4$, filtered, and concentrated under reduced pressure to afford aldehyde **11** (268 mg, 98% yield) as colorless syrup. The crude material is suitable for the next step without further purification. - TLC (petroleum ether/ethyl acetate, 1:1): *R*f = 0.71.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28-1.41 [m, 2 H, C$\underline{H}_2$(CH$_2$)$_2$COOMe], 1.54-1.66 (m, 2 H, C$\underline{H}_2$CH$_2$COOMe), 1.95-2.06 [m, 2 H, C$\underline{H}_2$(CH$_2$)$_3$COOMe], 2.24-2.30 (m, 2 H, C$\underline{H}_2$COOMe), 2.36-2.45 (m, 2 H, C$\underline{H}_2$CH=CH), 3.64 (s, 3 H, COOC$\underline{H}_3$), 3.70-3.77 (m, 1 H, C$\underline{H}$OPMB), 3.78 (s, 3 H, OCH$_3$), 4.50, 4.58 (2 d, *J* = 11.5 Hz each, 2 H, PMB-C$\underline{H}_2$), 5.33-5.54 (m, 2 H, olefin-CH), 6.86, 7.26 (2 d, *J* = 8.7 Hz each, 2 H each, aromatic-CH), 9.60 (d, *J* = 2.1 Hz, 1 H, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.6 (C$\underline{H}_2$CH$_2$COOMe), 27.0 [C$\underline{H}_2$(CH$_2$)$_3$COOMe], 28.4 (C$\underline{H}_2$CH=CH), 28.9 [C$\underline{H}_2$(CH$_2$)$_2$COOMe], 33.9 (C$\underline{H}_2$COOMe), 51.5 (COOC$\underline{H}_3$), 55.3 (OCH$_3$), 72.3 (PMB-C$\underline{H}_2$), 82.8 (C$\underline{H}$OPMB), 114.0 (aromatic-CH), 123.3 (olefin-CH), 129.4 (aromatic-CH), 129.7 (aromatic-C), 132.8 (olefin-CH), 159.6 (aromatic-C), 174.1 (C$\underline{O}$OCH$_3$), 203.4 (CHO).

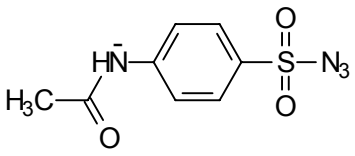
Dimethyl (3,3,3-trifluoro-2,2-dihydroxypropyl)phosphonate ***(13)****:*[93]



To a cooled (–78°C) solution of dimethyl methylphosphonate (2.00 ml, 18.5 mmol) in anhydrous THF (40 ml) was added dropwise over period of 5 min a 2.7M solution of *n*-butyllithium in heptane (7 ml, 18.5 mmol). The resulting mixture was stirred at the same temperature for 35 min and 2,2,2-trifluoroethyl trifluoroacetate (3.71 ml, 27.7 mmol) was added rapidly (1-2 s). The reaction mixture was stirred for additional 15 min at –78°C and was then allowed to warm to room temperature and diluted with diethyl ether (250 ml) followed by the addition of 3% aqueous hydrochloric acid (10 ml). The layers were separated and the organic phase was washed with saturated aqueous solution of $NaHCO_3$ (10 ml) and brine (10 ml), dried over $MgSO_4$, filtered and concentrated on rotatory evaporator to give 4.42 g of **13** (100% yield) as a pale yellow oil. The crude product was suitable for the next step without further purification and was used immediately. - TLC (ethyl acetate): *R*f = 0.68.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.33 (d, *J* = 19.2 Hz, 1 H, CH_2), 3.82 (d, *J* = 11.2 Hz, 1 H, CH_2), 5.50 (s, 6 H, CH_3).

p-Acetamidobenzenesulfonyl azide ***(14)****:*[93]

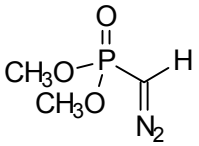


A suspension of sodium azide (3.0 g, 46 mmol) and dry acetone (500 ml) was cooled to 0°C (ice bath) and *N*-acetylsulfonyl chloride (10.5 g, 45 mmol) was added slowly, portionwise over a period of 10 min. The reaction mixture was stirred at 0°C for 2 h and was then allowed to warm up to room temperature and to stir for additional 72 h. Thereafter the resulting slurry was filtered off through a glass funnel and the filtrate was concentrated under reduced pressure to give the desired product **14**(10.8 g, 100% yield)

as a yellow oil which solidified on standing. The crude product was suitable for the next step without further purification.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.23 (s, 3H, CH_3), 7.78, 7.87 (2 d, *J* = 9.0 Hz each, 4 H, aromatic-CH), 8.09 (s, 1H, HN).

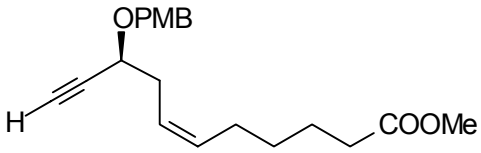
*Dimethyl (diazomethyl)phosphonate **(15)**:*[93]



The crude **13** (4.42 g, 18.5 mmol) was dissolved in dry acetonitrile (45 ml) and treated with *p*-acetamidobenzenesulfonyl azide **(14)** (4.46 g, 18.5 mmol). The resulting solution was cooled to 0°C and treated slowly over a period of 5 min with absolute triethylamine (2.58 ml, 18.5 mmol). Thereafter the reaction mixture was allowed to warm to room temperature and stirred for 18 h. The solvent was removed under reduced pressure and the residual orange oily solid was suspended in chloroform and filtered through a coarse glass frit to remove the *p*-acetamidobenzenesulfonamide, which was washed with several small portions of chloroform. Then the resulting filtrate was concentrated *in vacuo* and the crude product was purified by flash column chromatography (ethyl acetate/dichloromethane, 4:1) to afford 2.42 g of **15** (87% yield) as an intensive yellow-colored mobile liquid. - TLC (ethyl acetate/dichloromethane, 4:1): *R*f = 0.58.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.70, 3.75 (2 s, 6 H, CH_3), 3.72, 3.76 (2 s, 1 H, N_2CH).

*Methyl (6Z,9S)-9-[(4-methoxybenzyl)oxy]-6-undecen-10-ynoate **(16)**:*



A magnetically stirred slurry of potassium *tert*-butoxide (96 mg, 0.85 mmol) in absolute THF (2 ml) was cooled to –78°C and was added dropwise over a period of 5 min to a solution of dimethyl (diazomethyl)phosphonate **(15)** (128 mg, 0.85 mmol) in THF (2.5

ml). The reaction mixture was stirred at –78°C for 30 min and during this time the color turned from yellow to brown, indicating formation of the anion of **15**. Subsequently, the aldehyde **11** (259 mg, 0.78 mmol) dissolved in THF (2.5 ml) was added slowly over 2 min and nitrogen evolution was an evident. The resulting reaction mixture was stirred at –78°C for 26 h and was then allowed to warm up to room temperature. The stirring was continued for an additional 4 h. Thereafter the reaction mixture was quenched with water (30 ml) and extracted with dichloromethane (3 x 40 ml). The combined organic layers were washed with brine (30 ml), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on the rotatory evaporator to provide the product **16** as a pale yellow oil (245 mg, 96% yield), which was used without further purification in the next step. - TLC (petroleum ether/ethyl acetate, 6:1): *R*f = 0.41.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.30-1.42 [m, 2 H, C*H*$_2$(CH_2)$_2$COOMe], 1.55-1.67 (m, 2 H, C*H*$_2$$CH_2$COOMe), 2.01-2.09 [m, 2 H, C*H*$_2$(CH_2)$_3$COOMe], 2.25-2.31 (m, 2 H, C*H*$_2$COOMe), 2.46-2.51 (m, 3 H, alkyne-CH, C*H*$_2$CH=CH), 3.65 (s, 3 H, $COOCH_3$), 3.89 (s, 3 H, OCH_3), 4.01-4.07 (m, 1 H, C*H*OPMB), 4.44, 4.72 (2 d, *J* = 11.4 Hz each, 2 H, PMB-C*H*$_2$), 5.40-5.55 (m, 2 H, olefin-CH), 6.87, 7.28 (2 d, *J* = 8.7 Hz each, 2 H each, aromatic-CH).

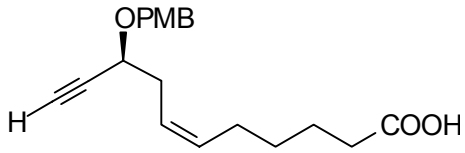
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.6 (C$H_2$$CH_2$COOMe), 27.1 [C$H_2$($CH_2$)$_3$COOMe], 29.0 [C$H_2$($CH_2$)$_2$COOMe], 33.7 (C$H_2$CH=CH), 34.0 (C$H_2$COOMe), 51.5 (COOC$H_3$), 55.3 ($OCH_3$), 67.9 (CHOPMB), 70.2 (PMB-CH_2), 74.0 (alkyne-CH), 82.7 (alkyne-C), 113.8 (aromatic-CH), 124.4 (olefin-CH), 129.7 (aromatic-CH), 129.9 (aromatic-C), 132.3 (olefin-CH), 159.3 (aromatic-C), 174.1 (COCH_3).

IR (neat): $\tilde{\nu}$ = 3284 cm^{-1} (alkyne-CH), 3010 cm^{-1} (alkyl), 2111 cm^{-1} (C≡C), 1739 cm^{-1} (C=O), 1613 cm^{-1}, 1586 cm^{-1}, 1514 cm^{-1} (C=C).

MS (ESI): *m/z* (%) = 369 (50) [M+K$^+$], 353 (100) [M+Na$^+$], 331 (50) [M+H$^+$].

HRMS (FT-ICR-ESI): calc. for $C_{20}H_{27}O_4$: 331.1897990, found: 331.1903858.

*(6Z,9S)-9-[(4-Methoxybenzyl)oxy]-6-undecen-10-ynoic acid **(17)**:*



The methyl ester **16** (240 mg, 0.73 mmol) was dissolved in 14 ml of a mixture of THF-water-methanol (6:3:2). To this solution was added at once lithium hydroxide monohydrate (180 mg, 4.29 mmol). The reaction mixture was stirred at ambient temperature for 18 h and thereafter was diluted with water (8 ml). Then the pH value of the solution was adjusted to 2-3 by adding of 1M aqueous hydrochloric acid. The aqueous phase was extracted with ethyl acetate (4 x 20 ml) and the combined organic layers were washed with water (30 ml) and brine (30 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave the expected acid **17** (176 mg, 77% yield) as colorless oil. - TLC (petroleum ether/ethyl acetate, 1:1): *R*f = 0.63.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.32-1.45 [m, 2 H, C$\underline{H}_2$(CH$_2$)$_2$COOH], 1.51-1.68 (m, 2 H, C$\underline{H}_2$CH$_2$COOH), 2.02-2.10 [m, 2 H, C$\underline{H}_2$(CH$_2$)$_3$COOH], 2.29-2.36 (m, 2 H, C$\underline{H}_2$COOH), 2.47-2.51 (m, 3 H, alkyne-CH, C$\underline{H}_2$CH=CH), 3.79 (s, 3 H, OCH_3), 4.01-4.08 (m, 1 H, C$\underline{H}$OPMB), 4.44, 4.73 (2 d, *J* = 11.4 Hz each, 2 H, PMB-C$\underline{H}_2$), 5.41-5.56 (m, 2 H, olefin-CH), 6.86, 7.28 (2 d, *J* = 8.7 Hz each, 2 H each, aromatic-CH).

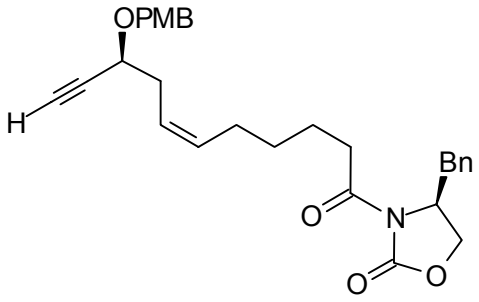
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.3 (C$\underline{H}_2$CH$_2$COOH), 27.1 [C$\underline{H}_2$(CH$_2$)$_3$COOH], 28.9 [C$\underline{H}_2$(CH$_2$)$_2$COOH], 33.7 (C$\underline{H}_2$CH=CH), 33.9 (C$\underline{H}_2$COOH), 55.3 (OCH_3), 67.8 (C$\underline{H}$OPMB), 70.2 (PMB-C$\underline{H}_2$), 74.1 (alkyne-CH), 82.7 (alkyne-C), 113.8 (aromatic-CH), 124.4 (olefin-CH), 129.7 (aromatic-CH), 129.8 (aromatic-C), 132.3 (olefin-CH), 159.3 (aromatic-C), 179.5 (COOH).

IR (neat): $\tilde{\nu}$ = 3290 cm^{-1} (alkyne-CH), 2934 cm^{-1} (alkyl), 2111 cm^{-1} (C≡C), 1708 cm^{-1} (COOH), 1612 cm^{-1}, 1586 cm^{-1}, 1514 cm^{-1} (C=C).

MS (EI): *m/z* (%) = 316 (5) [M$^+$], 135 (80), 121 (100).

HRMS (EI): calc. for $C_{19}H_{24}O_4$: 316.16746, found: 316.16137.

*(4S)-4-Benzyl-3-{(6Z,9S)-9-[(4-methoxybenzyl)oxy]-6-undecen-10-ynoyl}-1,3-oxazolidin-2-one **(18)**:*



Method A: To a stirred solution of acid **17** (171 mg, 0.54 mmol) in dry THF (3.5 ml) at –15°C was added anhydrous triethylamine (144 µl, 1.04 mmol) followed by trimethylacetyl chloride (72 µl, 0.59 mmol). After 20 min of stirring the reaction mixture was allowed to warm up to 0°C (over 15 min) and then was recooled to –78°C. In a separate flask was dissolved (4S)-4-benzyl-1,3-oxazolidin-2-one **(37)** (96 mg, 0.58 mmol) in absolute THF (5 ml) and the resulting solution was cooled to –70°C, and treated dropwise with a 2.7M solution of *n*-butyllithium in heptane (218 µl, 0.59 mmol). After the reaction mixture was stirred for 15 min the yellow solution was taken up in a syringe and added to the white slurry prepared as described above. The resulting mixture was stirred for 1.5 h at –78°C and quenched with 1M aqueous solution of $NaHSO_4$ (2.2 ml). Then the reaction mixture was allowed to reach room temperature and concentrated under reduced pressure. The residue was extracted with ethyl acetate (3 x 4 ml) and the combined organic extracts were washed with brine (5 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 2:1) provided 134 mg of the oxazolidinone **18** (52% yield) as a thick colorless oil. - TLC (petroleum ether/ethyl acetate, 2:1): *R*f = 0.52. - $[\alpha]^{26.6}_D$ = -1.1 (c 1.00, CH_2Cl_2).

Method B: A magnetically stirred slurry of potassium *tert*-butoxide (871 mg, 7.76 mmol) in absolute THF (20 ml) was cooled to –78°C and added dropwise over a period of 10 min to a solution of dimethyl (diazomethyl)phosphonate **(15)** (1.16 g, 7.76 mmol) in THF (25 ml). The reaction mixture was stirred at –78°C for 30 min and during this time the colour turned from yellow to brown, indicating formation of the anion of **15**. Subsequently the aldehyde **21** (3.38 g, 7.05 mmol) dissolved in THF (25 ml) was added slowly over 10 min and nitrogen evolution was evident. The resulting reaction mixture was stirred at –78°C for 17 h and then allowed to warm up to room temperature (over 1 h). Stirring was continued for an additional 4 h. Thereafter the reaction mixture was quenched with water

(250 ml) and extracted with dichloromethane (3 x 150 ml). The combined organic layers were washed with brine (250 ml), dried over anhydrous $MgSO_4$, filtered and the solvent was removed on the rotatory evaporator. Purification by flash column chromatography (petroleum ether/ethyl acetate, 2:1) provided 2.01 g of the oxazolidinone **18** (60% yield) as a thick colorless oil. - TLC (petroleum ether/ethyl acetate, 2:1): *R*f = 0.52. - $[\alpha]^{26.6}_{D}$ = -1.1 (c 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.31-1.43 [m, 2 H, C$\underline{H}_2$(CH$_2$)$_2$CO], 1.56-1.68 (m, 2 H, C$\underline{H}_2$CH$_2$CO), 1.99-2.07 [m, 2 H, C$\underline{H}_2$(CH$_2$)$_3$CO], 2.41-2.46 (m, 3 H, alkyne-H, C$\underline{H}_2$CH=CH), 2.68 (dd, ^2J = 13.3 Hz, ^3J = 9.6 Hz, 1 H, C$_6$H$_5$C$\underline{H}_2$), 2.76-2.88 (m, 2 H, C$\underline{H}_2$CO), 3.21 (dd, ^2J = 13.3 Hz, ^3J = 3.2 Hz, 1 H, C$_6$H$_5$C$\underline{H}_2$), 3.72 (s, 3 H, OCH$_3$), 3.96-4.15 (m, 3 H, C$\underline{H}$OPMB, oxazolidinone-CH$_2$), 4.38 (d, 1 H, *J* = 11.3 Hz, PMB-C$\underline{H}_2$), 4.53-4.61 (m, 1 H, oxazolidinone-CH), 4.66 (d, 1 H, *J* = 11.3 Hz, PMB-C$\underline{H}_2$), 5.35-5.51 (m, 2 H, olefin-CH), 6.80 (d, 2 H, *J* = 8.6 Hz, PMB-C$\underline{H}$), 7.11-7.29 (m, 7 H, aromatic-CH).

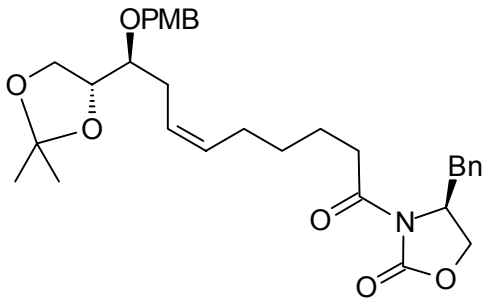
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.0 ($\underline{C}$H$_2$CH$_2$CO), 27.3 [$\underline{C}$H$_2$(CH$_2$)$_3$CO], 29.0 [$\underline{C}$H$_2$(CH$_2$)$_2$CO], 33.7 ($\underline{C}$H$_2$CH=CH), 35.4 ($\underline{C}$H$_2$CO),38.0 (C$_6$H$_5\underline{C}$H$_2$), 55.2 (oxazolidinone-CH), 55.3 (OCH$_3$), 66.2 (oxazolidinone-CH$_2$), 67.9 ($\underline{C}$HOPMB), 70.2 (PMB-$\underline{C}$H$_2$), 74.0 (alkyne-CH); 82.8 (alkyne-C), 113.8 (PMB-aromatic-$\underline{C}$H), 124.4 (olefin-CH), 129.0, 129.4, 129.6 (aromatic-CH), 130.0 (PMB-aromatic-$\underline{C}$), 132.3 (olefin-CH), 135.4 (aromatic-C), 153.5 (oxazolidinone-CO), 159.3 (PMB-aromatic-$\underline{C}$), 173.2 (amide-CO).

IR (neat): $\tilde{\nu}$ = 3283 cm^{-1} (alkyne-CH), 2934 cm^{-1} (alkyl), 2110 cm^{-1} (C≡C), 1784 cm^{-1}, 1699 cm^{-1} (C=O), 1612 cm^{-1}, 1585 cm^{-1}, 1514 cm^{-1} (C=C).

MS (FD): *m/z* (%) = 475 (100) [M$^+$].

HRMS (FT-ICR-ESI): calc. for $C_{29}H_{34}NO_5$ [M+H$^+$]: 476.24315, found: 476.2300;
calc. for $C_{29}H_{33}NO_5Na$ [M+Na$^+$]: 498.22509, found: 498.2140;
calc. for $C_{29}H_{33}NO_5K$ [M+K$^+$]: 514.19903, found: 514.1903.

*(4S)-4-Benzyl-3-{(6Z,9S)-9-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-9-[(4-methoxybenzyl)oxy]-6-nonenoyl}-1,3-oxazolidin-2-one **(19)**:*



A magnetically stirred solution of acid **9** (13.7 g, 35 mmol) in anhydrous THF (200 ml) was cooled to –15°C under argon, and was treated with dry triethylamine (9.24 ml, 67 mmol) followed by dropwise addition of trimethylacetyl chloride (4.70 ml, 38 mmol). Thereafter the resulting slurry was stirred for 20 min and was allowed to warm up to 0°C (over 15 min) and was again recooled to –78°C. In a separate flask a solution of (4*S*)-4-benzyl-1,3-oxazolidin-2-one **(37)** (6.8 g, 39 mmol) in absolute THF (350 ml) was cooled to –70°C and treated dropwise with a 2.5M solution of *n*-butyllithium in hexane (15,4 ml, 39 mmol). After being stirred for 15 min, the yellow reaction mixture was transported via double needle to a dropping funnel and added dropwise over 30 min to the white slurry prepared as described above. Then the resulting reaction mixture was stirred for 2.5 h at –78°C and quenched with 1M aqueous solution of $NaHSO_4$ (140 ml). Thereafter the reaction mixture was allowed to reach room temperature and the bulk of THF was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 150 ml) and the combined organic extracts were washed with brine (100 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Pure oxazolidinone **19** (15.1 g, 78% yield) was obtained by flash column chromatography (petroleum ether/ethyl acetate, 2:1) as colorless oil. - TLC (petroleum ether/ethyl acetate, 2:1): *R*f = 0.52. . - $[\alpha]^{22.0}_D$ = +53.3 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.27, 1.34 (2 s, 3 H each, isopropylidene-CH_3), 1.38-1.44 [m, 2 H, C$\underline{H}_2(CH_2)_2CO$], 1.58-1.67 (m, 2 H, C$\underline{H}_2CH_2CO$), 2.00-2.08 [m, 2 H, C$\underline{H}_2(CH_2)_3CO$], 2.27-2.30 (m, 2 H, C$\underline{H}_2CH$=CH), 2.68 (dd, ^2J = 13.3 Hz, ^3J = 9.6 Hz, 1 H, $C_6H_5C\underline{H}_2$), 2.82-2.90 (m, 2 H, C$\underline{H}_2CO$), 3.22 (dd, ^2J = 13.3 Hz, ^3J = 3.2 Hz, 1 H, $C_6H_5C\underline{H}_2$), 3.42-3.49 (m, 1 H, C$\underline{H}$OPMB), 3.72 (s, 3 H, OCH_3), 3.77-3.82 (m, 1 H, OCH), 3.92-4.01 (m, 2 H, OCH_2), 4.07-4.12 (m, 2 H, oxazolidinone-CH_2), 4.44, 4.52 (2 d, *J* = 11.1 Hz each, 2 H, PMB-C$\underline{H}_2$), 4.56-4.61 (m, 1 H, oxazolidinone-CH), 5.37-5.50 (m, 2 H, olefin-CH), 6.79 (d, *J* = 8.7 Hz, 2 H, aromatic-CH), 7.12-7.30 (m, 7 H, aromatic-CH).

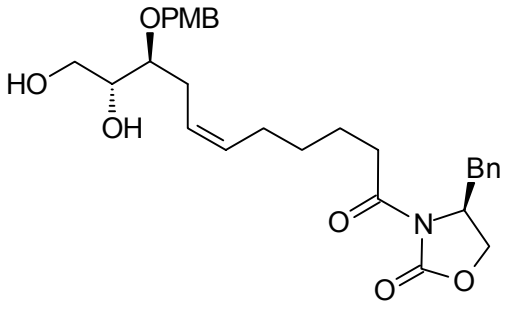
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 24.0 ($\underline{C}H_2CH_2CO$), 25.4, 26.7 (isopropylidene-CH_3), 27.2 [$\underline{C}H_2(CH_2)_3CO$], 29.1 ($\underline{C}H_2CH{=}CHCH_2\underline{C}H_2$), 35.5 ($\underline{C}H_2CO$), 38.0 ($C_6H_5\underline{C}H_2$), 55.2 (oxazolidinone-CH), 55.3 (OCH_3), 66.2 (oxazolidinone-CH_2), 66.6 (OCH_2), 72.2 (PMB-$\underline{C}H_2$), 77.3 (OCH), 79.0 ($\underline{C}$HOPMB), 109.0 (isopropylidene-C), 113.8 (PMB-aromatic-$\underline{C}$H), 125.2 (olefin-CH), 127.4, 129.0, 129.4 (aromatic-CH), 130.7 (PMB-aromatic-$\underline{C}$), 131.8 (olefin-CH), 135.4 (aromatic-C), 153.5 (oxazolidinone-CO), 159.2 (PMB-aromatic-$\underline{C}$), 173.2 (amide-CO).

IR (neat): $\tilde{\nu}$ = 2934 cm^{-1} (alkyl), 1783 cm^{-1}, 1699 cm^{-1} (C=O), 1613 cm^{-1}, 1586 cm^{-1}, 1514 cm^{-1} (C=C).

MS (EI): *m/z* (%) = 551 (1) [M^+], 493 (2), 432 (3), 337 (10), 121 (100).

HRMS (EI): calc. for $C_{32}H_{41}NO_7$: 551.28830, found: 551.29155.

*(4S)-4-Benzyl-3-{(6Z,9S,10R)-10,11-dihydroxy-9-[(4-methoxybenzyl)oxy]-6-undecenoyl}-1,3-oxazolidin-2-one **(20)**:*



To a solution of oxazolidinone **19** (5.00 g, 9.06 mmol) in methanol (170 ml) was added at once cupric(II) chloride dihydrate (1.96 g, 11.5 mmol). The resulting green reaction mixture was refluxed for 1.5 h and then allowed to cool to ambient temperature and 9.76 g $NaHCO_3$ was added. After the evolution of carbon dioxide had ceased, 85 ml of water was added and the resulting blue precipitate was filtered off trough a pad of Celite and washed intensively with ethyl acetate. The combined filtrate was washed once with brine (300 ml) and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (diethyl ether/ethanol, 10:0.5) gave 4.07 g (88% yield) of diol **20** as colorless oil. - TLC (diethyl ether/ethanol, 10:0.5): *R*f = 0.56. - $[\alpha]^{25.0}_D$ = +50.0 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.41-1.50 [m, 2 H, $C\underline{H}_2(CH_2)_2CO$], 1.63-1.75 (m, 2 H, $C\underline{H}_2CH_2CO$), 2.07-2.15 [m, 2 H, $C\underline{H}_2(CH_2)_3CO$], 2.31-2.49 (m, 2 H, $C\underline{H}_2CH{=}CH$), 2.74 (dd, ^2J = 13.3 Hz, ^3J = 9.6 Hz, 1 H, $C_6H_5C\underline{H}_2$), 2.88-2.96 (m, 2 H, $C\underline{H}_2CO$), 3.27 (dd, ^2J = 13.3

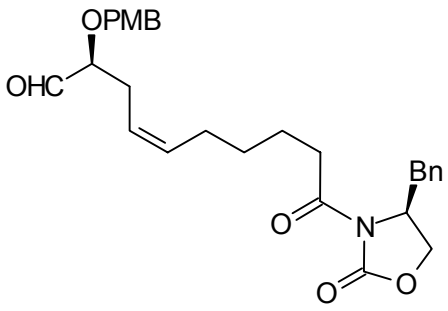
Hz, ^3J = 3.2 Hz, 1 H, $C_6H_5C\underline{H}_2$), 3.55-3.61 (m, 1 H, C<u>H</u>OPMB), 3.65-3.74 (m, 3 H, C<u>H</u>$_2$OH, C<u>H</u>OH), 3.78 (s, 3 H, OCH_3), 4.13-4.18 (m, 2 H, oxazolidinone-CH_2), 4.44, 4.60 (2 d, J = 11.1 Hz each, 2 H, PMB-C<u>H</u>$_2$), 4.64-4.68 (m, 1 H, oxazolidinone-CH), 5.44-5.53 (m, 2 H, olefin-CH), 6.86 (d, J = 8.7 Hz, 2 H, aromatic-CH), 7.17-7.36 (m, 7 H, aromatic-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.8 (<u>C</u>H$_2$CH$_2$CO), 27.2 [<u>C</u>H$_2$(CH$_2$)$_3$CO], 28.4 (<u>C</u>H$_2$CH=CH), 28.9 [<u>C</u>H$_2$(CH$_2$)$_2$CO], 35.4 (<u>C</u>H$_2$CO), 38.0 ($C_6H_5\underline{C}H_2$), 55.2 (oxazolidinone-CH), 55.3 (OCH_3), 63.5 (<u>C</u>H$_2$OH), 66.3 (oxazolidinone-CH_2), 72.2 (PMB-<u>C</u>H$_2$), 72.4 (<u>C</u>HOH), 80.6 (<u>C</u>HOPMB), 113.9 (PMB-aromatic-*C*H), 125.2 (olefin-CH), 127.4, 129.0, 129.4, 129.5 (aromatic-CH), 130.2 (PMB-aromatic-<u>C</u>), 132.0 (olefin-CH), 135.3 (aromatic-C), 153.8 (oxazolidinone-CO), 159.4 (PMB-aromatic-<u>C</u>), 173.4 (amide-CO).

IR (neat): $\tilde{\nu}$ = 3413 cm^{-1} (OH), 2933 cm^{-1} (alkyl), 1781 cm^{-1}, 1700 cm^{-1} (C=O), 1612 cm^{-1}, 1586 cm^{-1}, 1514 cm^{-1} (C=C).

MS (FD): *m/z* (%) = 511 (100) [M$^+$], 177 (10).

*(2S,4Z)-10-[(4S)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-[(4-methoxybenzyl)oxy]-10-oxo-4-decenal **(21)**:*



The diol **20** (3.98 g, 7.78 mmol) was dissolved in 60% aqueous acetonitrile (73 ml) and treated with sodium(meta)periodate (2.49 g, 11.7 mmol); a white precipitate was formed immediately. The reaction mixture was stirred at room temperature for 3.5 h and filtered through a glass funnel. The filtrate was mixed with water (100 ml) and extracted thoroughly with chloroform (4 x 100 ml). The combined organic layers were washed once with water (200 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford aldehyde **21** (3.58 g, 96% yield) as colorless high viscose oil. The crude material is suitable for the next step without further purification. - TLC (petroleum ether/ethyl acetate, 1:1): *R*f = 0.57. - $[\alpha]^{21.0}_D$ = +19.8 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40-1.49 [m, 2 H, C<u>H</u>$_2$(CH$_2$)$_2$CO], 1.62-1.74 (m, 2 H, C<u>H</u>$_2$CH$_2$CO), 2.03-2.12 [m, 2 H, C<u>H</u>$_2$(CH$_2$)$_3$CO], 2.43-2.48 (m, 2 H, C<u>H</u>$_2$CH=CH), 2.75 (dd,

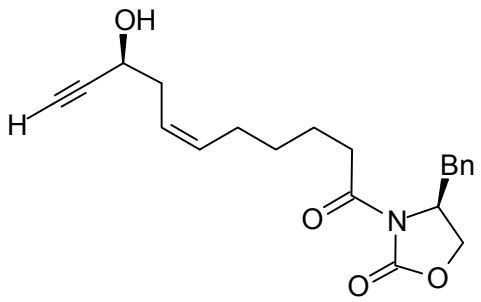
^2J = 13.3 Hz, ^3J = 9.6 Hz, 1 H, $C_6H_5C\underline{H_2}$), 2.83-2.95 (m, 2 H, $C\underline{H_2}CO$), 3.28 (dd, ^2J = 13.3 Hz, ^3J = 3.2 Hz, 1 H, $C_6H_5C\underline{H_2}$), 3.74-3.77 (m, 1 H, C<u>H</u>OPMB), 3.79 (s, 3 H, OCH_3), 4.12-4.22 (m, 2 H, oxazolidinone-CH_2), 4.52, 4.59 (2 d, J = 11.3 Hz each, 2 H, PMB-$C\underline{H_2}$), 4.62-4.69 (m, 1 H, oxazolidinone-CH), 5.39-5.55 (m, 2 H, olefin-CH), 6.87 (d, J = 8.7 Hz, 2 H, aromatic-CH), 7.18-7.36 (m, 7 H, aromatic-CH), 9.62 (d, J = 2.1 Hz, 1 H, CHO).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.9 ($\underline{C}H_2CH_2CO$), 27.1 [$\underline{C}H_2(CH_2)_3CO$], 28.4 ($\underline{C}H_2CH{=}CH$), 28.9 [$\underline{C}H_2(CH_2)_2CO$], 35.4 ($\underline{C}H_2CO$), 38.0 ($C_6H_5\underline{C}H_2$), 55.2 (oxazolidinone-CH), 55.3 (OCH_3), 66.2 (oxazolidinone-CH_2), 72.3 (PMB-$\underline{C}H_2$), 82.9 (<u>C</u>HOPMB), 114.0 (PMB-aromatic-<u>C</u>H), 123.4 (olefin-CH), 127.4, 129.0, 129.4, (aromatic-CH), 129.7 (PMB-aromatic-<u>C</u>), 132.8 (olefin-CH), 135.4 (aromatic-C), 153.5 (oxazolidinone-CO), 159.6 (PMB-aromatic-<u>C</u>), 173.2 (amide-CO), 203.3 (CHO).

IR (neat): $\tilde{\nu}$ = 2935 cm^{-1} (alkyl), 1719 cm^{-1} (CHO), 1790 cm^{-1}, 1732 cm^{-1}, 1699 cm^{-1} (C=O), 1612 cm^{-1}, 1585 cm^{-1}, 1514 cm^{-1} (C=C).

MS (FD): *m/z* (%) = 479 (100) [M^+], 451 (80).

(4S)-4-Benzyl-3-[(6Z,9S)-9-hydroxy-6-undecen-10-ynoyl]-1,3-oxazolidin-2-one ***(22)****:*



The *p*-methoxybenzyl ether **18** (900 mg, 1.89 mmol) was dissolved in acetonitrile (30 ml) and cooled to 0°C. To this solution was added ceric ammonium nitrate (3.11 g, 5.68 mmol) dissolved in water (9 ml). The yellow reaction mixture was stirred at 0°C for 5 min and then was allowed to reach room temperature. After 1 h of stirring the mixture was diluted with ethyl acetate (115 ml) and the layers were separated. The organic phase was dried over $MgSO_4$, filtered, and concentrated on the rotatory evaporator. Purification of the residue by flash column chromatography (petroleum ether/ethyl acetate, 3:2) gave 668 mg (99% yield) of the alcohol **22** as colorless oil, which solidified on standing. - TLC (petroleum ether/ethyl acetate, 3:2): *R*f = 0.45. – m.p.: 87 - 88°C. - $[\alpha]^{26.8}_D$ = +37.9 (*c* 1.10, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.43-1.52 [m, 2 H, C$\underline{H}_2$(CH_2)$_2$CO], 1.64-1.73 (m, 2 H, C$\underline{H}_2$$CH_2$CO), 2.08-2.14 [m, 2 H, C$\underline{H}_2$(CH_2)$_3$CO], 2.40-2.53 (m, 3 H, alkyne-H, C$\underline{H}_2$CH=CH), 2.75 (dd, ^2J = 13.3 Hz, ^3J = 9.6 Hz, 1 H, $C_6H_5C\underline{H}_2$), 2.89-2.97 (m, 2 H, C$\underline{H}_2$CO), 3.27 (dd, ^2J = 13.3 Hz, ^3J = 3.3 Hz, 1 H, $C_6H_5C\underline{H}_2$), 4.13-4.19 (m, 2 H, oxazolidinone-CH_2), 4.38-4.44 (m, 1 H, C$\underline{H}$OH), 4.61-4.69 (m, 1 H, oxazolidinone-CH), 5.51-5.64 (m, 2 H, olefin-CH), 7.18-7.36 (m, 5 H, aromatic-CH).

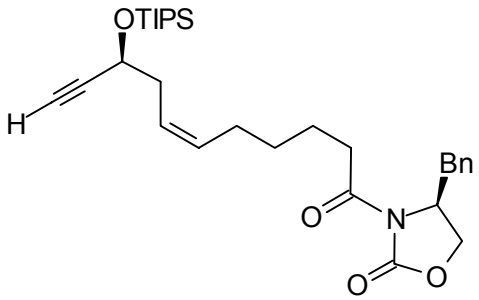
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 23.9 ($\underline{C}H_2CH_2CO$), 27.2 [$\underline{C}H_2$(CH_2)$_3$CO], 28.9 [$\underline{C}H_2$(CH_2)$_2$CO], 35.4 ($\underline{C}H_2CO$), 35.5 ($\underline{C}H_2CH$=CH), 38.0 ($C_6H_5\underline{C}H_2$), 55.2 (oxazolidinone-CH), 61.9 ($\underline{C}HOH$), 66.3 (oxazolidinone-CH_2), 73.2 (alkyne-CH); 84.4 (alkyne-C), 123.7 (olefin-CH), 127.4, 129.0, 129.5 (aromatic-CH), 133.7 (olefin-CH), 135.3 (aromatic-C), 153.6 (oxazolidinone-CO), 173.4 (amide-CO).

IR (neat): $\tilde{\nu}$ = 3503 cm^{-1} (OH), 3285 cm^{-1} (alkyne-CH), 2932 cm^{-1} (alkyl), 2116 cm^{-1} (C≡C), 1786 cm^{-1}, 1701 cm^{-1} (C=O), 1604 cm^{-1}, 1584 cm^{-1} (C=C).

MS (EI): *m/z* (%) = 356 (2) [M^+], 338 (1), 178 (100), 117 (90), 91 (55).

HRMS (EI): calc. for $C_{21}H_{25}NO_4$: 355.17836, found: 355.17625.

*(4S)-4-Benzyl-3-{(6Z,9S)-9-[(triisopropylsilyl)oxy]-6-undecen-10-ynoyl}-1,3-oxazolidin-2-one **(23)**:*



A mixture of **22** (730 mg, 2.06 mmol), imidazol (350 mg, 5.14 mmol) and dimethylaminopyridine (50 mg, 0.41 mmol) in anhydrous dichloromethane (20 ml) was cooled to 0°C and stirred for 30 min. Thereafter triisopropylsilyl chloride (0.66 ml, 3.08 mmol) was added and the reaction mixture allowed to warm slowly to room temperature, and to stir under an atmosphere of argon until complete consumption of the starting material (3 days). The reaction mixture was quenched by addition of saturated aqueous solution of NaCl (15 ml) followed by separation of the layers. The organic layer was washed with 1M aqueous hydrochloric acid (2 x 15 ml), saturated solution of $NaHCO_3$ (15 ml), brine (15 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

Flash column chromatography (petroleum ether/ethyl acetate, 5:1) provided 998 mg of **23** (95% yield) as colorless oil. - TLC (petroleum ether/ethyl acetate, 5:1): *R*f = 0.53. - $[\alpha]^{25.4}_{D}$ = +31.7 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03-1.17 (m, 21 H, TIPS), 1.42-1.48 [m, 2 H, C$\underline{H}_2$(CH$_2$)$_2$CO], 1.67-1.73 (m, 2 H, C$\underline{H}_2$CH$_2$CO), 2.07-2.13 [m, 2 H, C$\underline{H}_2$(CH$_2$)$_3$CO], 2.39-2.40 (m, 2 H, C$\underline{H}_2$CH=CH, alkyne-H), 2.45-2.50 (m, 1 H, C$\underline{H}_2$CH=CH), 2.75 (dd, ^2J = 13.3 Hz, ^3J = 9.6 Hz, 1 H, C$_6$H$_5$C$\underline{H}_2$), 2.88-2.97 (m, 2 H, C$\underline{H}_2$CO), 3.28 (dd, ^2J = 13.3 Hz, ^3J = 3.3 Hz, 1 H, C$_6$H$_5$C$\underline{H}_2$), 4.13-4.19 (m, 2 H, oxazolidinone-CH$_2$), 4.42-4.46 (m, 1 H, C$\underline{H}$OTIPS), 4.62-4.70 (m, 1 H, oxazolidinone-CH), 5.45-5.54 (m, 2 H, olefin-CH), 7.18-7.36 (m, 5 H, aromatic-CH).

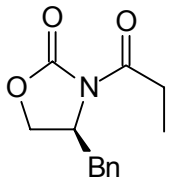
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.3 (TIPS-$\underline{C}$H), 18.0 (TIPS-$\underline{C}$H$_3$), 24.0 ($\underline{C}$H$_2$CH$_2$CO), 27.4 [$\underline{C}$H$_2$(CH$_2$)$_3$CO], 29.2 [$\underline{C}$H$_2$(CH$_2$)$_2$CO], 35.5 ($\underline{C}$H$_2$CO), 36.9 ($\underline{C}$H$_2$CH=CH), 38.0 (C$_6$H$_5$$\underline{C}H_2$), 55.2 (oxazolidinone-CH), 62.8 ($\underline{C}$HOTIPS), 66.2 (oxazolidinone-CH$_2$), 72.3 (alkyne-CH); 85.5 (alkyne-C), 124.6 (olefin-CH), 127.4, 129.0, 129.5 (aromatic-CH), 132.1 (olefin-CH), 135.4 (aromatic-C), 153.5 (oxazolidinone-CO), 173.2 (amide-CO).

IR (neat): $\tilde{\nu}$ = 3290 cm^{-1} (alkyne-CH), 2944 cm^{-1} (alkyl), 2113 cm^{-1} (C≡C), 1790 cm^{-1}, 1699 cm^{-1}, (C=O), 1605 cm^{-1} (C=C).

MS (EI): *m/z* (%) = 511 (1) [M$^+$], 468 (100), 157 (40), 117 (40), 91 (75).

HRMS (EI): calc. for $C_{30}H_{45}NO_4Si$: 511.311755, found: 511.313806.

*(4S)-4-Benzyl-3-propionyl-1,3-oxazolidin-2-one **(24)**:*[114]



Compound **37** (10 g, 56 mmol) was dissolved in absolute THF (170 ml). The resulting solution was cooled to –78°C and treated dropwise over a period of 10 min with a 2.7M solution of *n*-butyllithium in heptane (21 ml, 56.6 mmol). Thereafter, the yellow reaction mixture was treated with propionyl chloride (5.4 ml, 62 mmol) and stirred for 1 h at –78°C. Then the reaction mixture was allowed to warm to ambient temperature over 1 h and quenched with saturated aqueous solution of ammonium chloride (35 ml), which resulted in the formation of a white precipitate. The bulk of THF was removed under reduced pressure and the residue taken up in water (20 ml) and extracted with dichloromethane (2

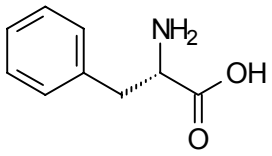
x 50 ml). The combined organic layers were washed with 1M aqueous solution of sodium hydroxide (50 ml), brine (50 ml), dried over $MgSO_4$, filtered and evaporated on the rotatory evaporator to a afford thick yellow oil (13.47 g), which was placed in a refrigerator over night to crystallize. The resulting crystalline solid was pulverized and triturated with a minimum quantity of cold hexane (50 ml). After filtration and drying for several hours with a vacuum pump, 12.91 g (98% yield) of the desired product **24** was obtained as a colorless crystalline solid. – m.p.: 43.9 – 44.4°C (lit. [114]: 44 – 46°C).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.3 Hz, 3 H, CH_3), 2.76 (dd, ^2J = 13.4 Hz, ^3J = 9.6 Hz, 1 H, $C_6H_5C\underline{H}_2$), 2.85-3.07 (m, 2 H, $C\underline{H}_2CH_3$), 3.29 (dd, ^2J = 13.4 Hz, ^3J = 3.3 Hz, 1 H, $C_6H_5C\underline{H}_2$), 4.12-4.23 (m, 2 H, oxazolidinone-CH_2), 4.62-4.71 (m, 1 H, oxazolidinone-CH), 7.19-7.36 (m, 5 H, aromatic-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.3 (CH_3), 29.2 ($\underline{C}H_2CH_3$), 38.0 ($C_6H_5\underline{C}H_2$), 55.2 (oxazolidinone-CH), 66.3 (oxazolidinone-CH_2), 127.4, 129.0, 129.5 (aromatic-CH), 135.4 (aromatic-C), 153.5 (oxazolidinone-CO), 174.1 (amide-CO).

MS (EI): *m/z* (%) = 234 (80) [M+H$^+$], 233 (100) [M$^+$], 91 (30).

*(S)-Phenylalanol **(36)**:*[114]



L-Phenylalanine (40 g, 0.24 mol) was dissolved in absolute THF (120 ml) and was treated by dropwise addition over a 25 min period with boron trifluoride etherate (31 ml, 0.24 mol). After complete addition, the reaction mixture was heated to reflux for 2 h and the resulting solution became colorless and homogeneous. Thereafter to the vigorously refluxed reaction mixture was added carefully and dropwise over a 35 min period borane-dimethyl sulphide complex (26.4 ml, 0.28 mol). During the course of the addition there was continuous evolution of dimethyl sulphide and hydrogen gas, and the solution turns from orange to light brown. Because of the vigorous exothermic reaction, which occurs, heating was reduced so that the reaction mixture could the whole time maintained at gentle reflux. Thereafter the reaction mixture was stirred for additional 6 h under reflux and was then allowed to cool to ambient temperature. The excess borane was quenched by the slowly addition of a 1:1 mixture of THF / water (30 ml) followed by addition of 5M aqueous solution of sodium hydroxide (180 ml). The resulting two-phase mixture was

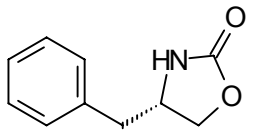
heated to reflux for additional 12 h, cooled to room temperature and filtered through a glass funnel. The residual solid was washed with small portions of THF and the filtrate was concentrated under reduced pressure to remove the bulk of the THF. The resulting slurry was then extracted with dichloromethane (4 x 100 ml) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crystalline solid residue was recrystallized from boiling ethyl acetate (145 ml) to give 28.5 g (78% yield) of the desired product **36** as white needles. – m.p.: 91 - 92°C (lit. [114]: 88.5 – 91°C).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.47-2.56 (m, 4 H, NH_2, OH, $C_6H_5C\underline{H}_2$), 2.78 (dd, ^2J = 13.4 Hz, ^3J = 5.2 Hz, 1 H, $C_6H_5C\underline{H}_2$), 3.05-3.15 (m, 1 H, $NH_2C\underline{H}$), 3.37 (dd, ^2J = 10.8 Hz, ^3J = 7.2 Hz, 1 H, $C\underline{H}_2OH$), 3.63 (dd, ^2J = 10.8 Hz, ^3J = 7.2 Hz, 1 H, $C\underline{H}_2OH$), 7.16-7.33 (m, 5 H, aromatic-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 40.6 ($C_6H_5\underline{C}H_2$), 54.3 ($NH_2\underline{C}H$), 66.0 (CH_2OH), 126.5, 128.6, 129.3 (aromatic-CH), 138.6 (aromatic-C).

MS (EI): *m/z* (%) = 152 (100) [M+H$^+$], 120 (85), 91 (70), 60 (90).

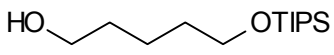
*(4S)-4-Benzyl-1,3-oxazolidin-2-one **(37)**:*[114]



A mixture of (*S*)-Phenylalanol **(36)** (26.1 g, 0.17 mol), anhydrous potassium carbonate (2.4 g, 0.017 mol) and diethyl carbonate (43.4 ml, 0.36 mol) was placed into a round bottom flask equipped with a VIGREUX column and distillation head, and heated to 135°C with an oil bath. The distillation receiver was cooled in an ice bath and the ethanol (21 ml) formed in the reaction over 1.5 h of stirring was collected. After the distillation of ethanol had ceased, the reaction mixture was allowed to cool to room temperature under an atmosphere of argon and was then diluted with dichloromethane (130 ml), and washed with water (130 ml). The resulting organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated on the rotatory evaporator to afford 37.8 g of the crude material which was recrystallized from a hot 2:1 mixture of ethyl acetate / hexane (105 ml) to give 23.5 g of pure **37** (77% yield) as fine white crystals. – m.p.: 87.9 – 88.3°C (lit. [114]: 84.5 – 86.5°C).

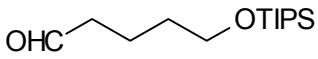
^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.78-2.95 (m, 2 H, $C_6H_5C\underline{H}_2$), 4.02-4.15 (m, 2 H, CH_2O), 4.35-4.45 (m, 1 H, NHC<u>H</u>), 6.21 (br. s, 1 H, NH), 7.13-7.36 (m, 5 H, aromatic-CH).
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 41.4 ($C_6H_5\underline{C}H_2$), 53.8 (NH<u>C</u>H), 69.6 (CH_2O), 127.2, 129.0, 129.1 (aromatic-CH), 136.0 (aromatic-C), 159.7 (CO).
MS (EI): *m/z* (%) = 177 (30) [M^+], 92 (100), 86 (70).

*5-[(Triisopropylsilyl)oxy]-1-pentanol **(39)**:*



To a suspension of sodium hydride (2.81 g, 117 mmol, washed with hexane) in anhydrous THF (230 ml) at room temperature was added 1,5-pentanediol (12.3 ml, 117 mmol). The resulting reaction mixture was stirred at ambient temperature for 45 min during which time a large amount of an opaque white precipitate has formed. Subsequently, the triisopropylsilyl chloride (25.0 ml, 117 mmol) was added dropwise over 5 min and the vigorous stirring was continued for additional 45 min. Thereafter the homogeneous white reaction mixture was poured into diethyl ether (1.1 l), washed with 10% aqueous potassium carbonate (600 ml) and brine (400 ml), dried over $MgSO_4$, filtered, and concentrated on the rotatory evaporator to afford 28.3 g of crude material as a pale yellow oil. The purification was made by flash column chromatography (petroleum ether/ethyl acetate, 2/1) to give 18.6 g (65% yield) of monosilylated alcohol **39** as colorless mobile oil. - TLC (petroleum ether/ethyl acetate, 2:1): *R*f = 0.47.
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.96-1.04 (m, 21 H, TIPS), 1.30-1.39 [m, 2 H, $C\underline{H}_2(CH_2)_2OH$], 1.43-1.56 (m, 4 H, $HOCH_2C\underline{H}_2CH_2C\underline{H}_2CH_2OTIPS$), 1.78 (br, 1 H, OH), 3.53-3.62 (m, 4 H, $C\underline{H}_2OH$, $C\underline{H}_2OTIPS$).
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.1 (TIPS-<u>C</u>H), 18.0 (TIPS-<u>C</u>H_3), 22.1 [$\underline{C}H_2(CH_2)_2OH$], 32.6, 32.7 ($\underline{C}H_2CH_2OH$, $\underline{C}H_2CH_2OTIPS$), 63.0 ($\underline{C}H_2OH$), 63.3 ($\underline{C}H_2OTIPS$).
IR (neat): $\tilde{\nu}$ = 3341 cm^{-1} (OH), 2941 cm^{-1}, 2866 cm^{-1} (alkyl).
MS (EI): *m/z* (%) = 217 (20) [M^+], 131 (40), 119 (70), 103 (60), 69 (100).
HRMS (EI): calc. for $C_{11}H_{25}O_2Si$: 217.162377, found: 217.163187.

*5-[(Triisopropylsilyl)oxy]pentanal **(40)**:*



Freshly distilled oxalyl chloride (4.31 ml, 49 mmol) was dissolved in anhydrous dichloromethane (100 ml). The solution was cooled to –78°C and then absolute DMSO (6.97 ml, 98 mmol), dissolved in 20 ml of dichloromethane was added dropwise; gas evolution was evident. The colorless reaction mixture was stirred for 30 min and then treated dropwise over a period of 25 min with a solution of alcohol **39** (10.3 g, 42 mmol) in dichloromethane (100 ml). After the mixture was stirred for 1.5 h at –78°C, absolute triethylamine (16.8 ml, 121 mmol) was added dropwise. Thereafter the resulting thick reaction mixture was allowed to warm slowly to room temperature over 3 h and was quenched with water (110 ml). The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 100 ml). The combined organic layers were washed with 1M aqueous hydrochloric acid (120 ml) then with water (120 ml) followed by saturated aqueous solution of $NaHCO_3$ (120 ml) and at the end again with water (120 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (petroleum ether/diethyl ether, 10:1) gave 9.5 g (87% yield) of the aldehyde **40** as colorless mobile liquid. - TLC (petroleum ether/diethyl ether, 10:1): *R*f = 0.42.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.98-1.09 (m, 21 H, TIPS), 1.52-1.61 (m, 2 H, C$\underline{H}_2$CH$_2$CHO), 1.66-1.78 (m, 2 H, C$\underline{H}_2$CH$_2$OTIPS), 2.45 (dt, $^3J_1$ = 1.8 Hz, $^3J_2$ =7.4 Hz, 2 H, C$\underline{H}_2$CHO), 3.69 (t, *J* = 6.0 Hz, 2 H, C$\underline{H}_2$OTIPS), 9.75 (t, *J* = 1.8 Hz, 1 H, CHO).

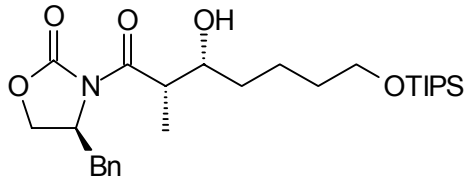
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.0 (TIPS-$\underline{C}$H), 18.0 (TIPS-$\underline{C}$H$_3$), 18.7 ($\underline{C}$H$_2$CH$_2$CHO), 32.3 ($\underline{C}$H$_2$CH$_2$OTIPS), 43.7 ($\underline{C}$H$_2$CHO), 62.9 ($\underline{C}$H$_2$OTIPS), 202.6 (CHO).

IR (neat): $\tilde{\nu}$ = 2943 cm^{-1}, 2867 cm^{-1} (alkyl), 2715 cm^{-1}, 1729 cm^{-1} (CHO).

MS (EI): *m/z* (%) = 215 (50) [M$^+$], 173 (90), 103 (100), 75 (80).

HRMS (EI): calc. for $C_{11}H_{23}O_2Si$: 215.146726, found: 215.148025.

*(4S)-4-Benzyl-3-{(2S,3R)-3-hydroxy-2-methyl-7-[(triisopropylsilyl)oxy]heptanoyl}-1,3-oxazolidin-2-one **(41)**:*



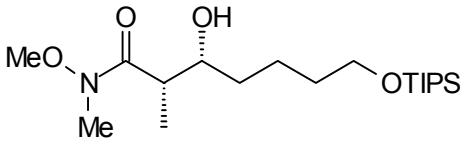
The oxazolidinone **24** (2.80 g, 12 mmol) was dissolved in anhydrous dichloromethane (60 ml) and cooled to –78°C. Titanium tetrachloride (1.30 ml, 12 mmol) was added dropwise and the resulting mixture was stirred for 10 min. Thereafter the reaction mixture was treated dropwise with (-)-sparteine (6.90 ml, 30 mmol) and the dark red solution was stirred at –78°C for 2 h. A solution of 5-[(triisopropylsilyl)oxy] pentanal **(40)** (9.13 g, 35 mmol) in dichloromethane (20 ml) was added dropwise and stirring was continued at –78°C for 1.5 h. The reaction was quenched at –78°C with half-saturated aqueous solution of ammonium chloride (60 ml) and was allowed to warm up to room temperature, during which time the colour changed to yellow and a precipitate was formed. The resulting mixture was filtered through a pad of Celite and the salts were washed with several small portions of dichloromethane. Thereafter the layers were separated and the aqueous phase was extracted with dichloromethane (3 x 60 ml). The combined organic extracts were washed with brine (80 ml), dried over anhydrous $MgSO_4$, filtered and the solvent was removed under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate, 5:1) afforded 5.78 g of alcohol **41** (98% yield) as a colorless oil. - TLC (petroleum ether/ethyl acetate, 5:1): *R*f = 0.28. - $[\alpha]^{22.1}_D$ = +39.4 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93-1.05 (m, 21 H, TIPS), 1.19 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.34-1.53 (m, 6 H, 3 CH_2), 2.48 (br, 1 H, OH), 2.71 (dd, ^2J = 13.3 Hz, ^3J = 9.4 Hz, 1 H, $C_6H_5C\underline{H}_2$), 3.18 (dd, ^2J = 13.3 Hz, ^3J = 3.3 Hz, 1 H, $C_6H_5C\underline{H}_2$), 3.62 (t, *J* = 6.2 Hz, 2 H, $C\underline{H}_2$OTIPS), 3.69 (dq, $^3J_1$ = 7.0 Hz, $^3J_2$ = 2.7 Hz, 1 H, $C\underline{H}CH_3$), 3.87-3.90 (m, 1 H, $C\underline{H}$OH), 4.09-4.20 (m, 2 H, oxazolidinone-CH_2), 4.60-4.67 (m, 1 H, oxazolidinone-CH), 7.12-7.30 (m, 5 H, aromatic-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.4 (CH_3), 12.1 (TIPS-$\underline{C}$H), 18.1 (TIPS-$\underline{C}H_3$), 22.4 [$\underline{C}H_2(CH_2)_2$OTIPS], 32.9 ($\underline{C}H_2CH_2$OTIPS), 33.7 [$\underline{C}H_2(CH_2)_3$OTIPS], 37.9 ($C_6H_5\underline{C}H_2$), 42.2 ($\underline{C}HCH_3$), 55.1 (oxazolidinone-CH), 63.3 ($\underline{C}H_2$OTIPS), 66.2 (oxazolidinone-CH_2), 71.5 (CHOH), 127.5, 129.0, 129.4 (aromatic-CH), 135.1 (aromatic-C), 153.0 (oxazolidinone-CO), 177.6 (amide-CO).

IR (neat): $\tilde{\nu}$ = 3525 cm^{-1} (OH), 2942 cm^{-1}, 2866 cm^{-1} (alkyl), 1784 cm^{-1}, 1697 cm^{-1} (C=O).
MS (FD): *m/z* (%) = 491 (5) [M^+], 448 (100) [M^+ - *i*-Pr].
MS (EI): *m/z* (%) = 492 (2) [M+H^+], 448 (100) [M^+ - *i*-Pr], 430 (5), 173 (70).
HRMS (EI): calc. for $C_{24}H_{38}NO_5Si$ [M^+ - *i*-Pr]: 448.25193, found: 448.23909.

*(2S,3R)-3-Hydroxy-N-methoxy-N,2-dimethyl-7-[(triisopropylsilyl)oxy]heptanamide **(42)**:*



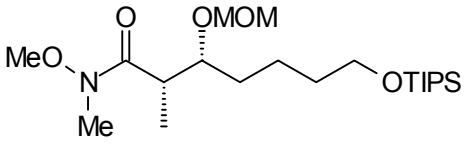
A suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (8.95 g, 91.8 mmol) in anhydrous THF (30 ml) was cooled to –30°C and treated dropwise, over a period of 10 min with a 2M solution of trimethylaluminium in heptane (45.9 ml, 91.8 mmol), and vigorous gas evolution was observed. After complete addition, the clear reaction mixture was allowed to warm to ambient temperature and to stir for 15 min. The resulting aluminium amide solution was recooled to –10°C and the aldol adduct **41** (5.15 g, 10.5 mmol) dissolved in absolute THF (30 ml) was added slowly over a 10 min period (gas evolution). Stirring was continued for 17 h and then the reaction mixture was warmed to 0°C, and stirred for additional 5 h. Thereafter the reaction mixture was transferred carefully by cannula into a rapidly stirred and cooled to 0°C, 1:1 mixture of dichloromethane / 0.1M aqueous solution of $NaHSO_4$ (440 ml), and the resulting two-phase mixture was stirred at 0°C for 1.5 h. After diluting with dichloromethane (700 ml) and water (300 ml), the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 200 ml). The combined organic layers were washed with brine (550 ml), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography (diethyl ether/petroleum ether, 5:1) to provide 3.28 g of pure amide **42** (83% yield) as colorless oil. - TLC (diethyl ether/petroleum ether, 5:1): *R*f = 0.40. - $[\alpha]^{23.0}_D$ = +3.0 (*c* 1.00, CH_2Cl_2).
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.93-1.06 (m, 21 H, TIPS), 1.12 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.28-1.53 (m, 6 H, 3 CH_2), 2.80 (br, 1 H, OH), 3.13 (s, 3 H, NCH_3), 3.58-3.65 (m, 6 H, OCH_3, $C\underline{H}_2$OTIPS, $C\underline{H}_2CH_3$), 3.76-3.82 (m, 1 H, C<u>H</u>OH).
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.0 (CH_3), 12.0 (TIPS-<u>C</u>H), 18.0 (TIPS-<u>C</u>H_3), 22.3 [<u>C</u>$H_2(CH_2)_2$OTIPS], 32.0 (NCH_3), 33.0 (<u>C</u>H_2CH_2OTIPS), 33.7 [<u>C</u>$H_2(CH_2)_3$OTIPS], 38.6 (<u>C</u>HCH_3), 61.5 (OCH_3), 63.3 (<u>C</u>H_2OTIPS), 71.5 (<u>C</u>HOH).

IR (neat): $\tilde{\nu}$ = 3455 cm^{-1} (OH), 2942 cm^{-1}, 2866 cm^{-1} (alkyl), 1640 cm^{-1} (C=O).

MS (EI): *m/z* (%) = 376 (5) [M+H^+], 332 (100) [M^+ - *i*-Pr].

HRMS (EI): calc. for $C_{16}H_{36}NO_4Si$ [M^+ - *i*-Pr]: 332.22571, found: 332.21851

*(2S,3R)-N-Methoxy-3-(methoxymethoxy)-N,2-dimethyl-7-[(triisopropylsilyl)oxy] heptanamide **(43)**:*



A mixture of the alcohol **42** (3.14 g, 8.38 mmol) in absolute dichloromethane (17 ml) and diisopropylethylamine (13.27 ml, 77.5 mmol) was cooled to 0°C. Chloromethyl methyl ether (2.92 ml, 38.5 mmol) was added dropwise and the reaction mixture was stirred at 0°C for 1 h, and then allowed to warm to ambient temperature and to stir 16 h longer. Thereafter water (50 ml) was added and the two phases were separated. The aqueous layer was extracted with dichloromethane (3 x 80 ml) and the combined organic extracts were washed with 1M aqueous hydrochloric acid (3 x 50 ml), water (50 ml), brine (50 ml), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (diethyl ether/petroleum ether, 5:1) to give the ether **43** (3.39 g, 97% yield) as colorless easy mobile oil. - TLC (diethyl ether/petroleum ether, 5:1): *R*f = 0.58. - $[\alpha]^{22.0}_D$ = +2.7 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.95-1.05 (m, 21 H, TIPS), 1.12 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.28-1.53 (m, 6 H, 3 CH_2), 2.95-3.02 (m, 1 H, C<u>H</u>CH_3), 3.12 (s, 3 H, NCH_3), 3.31 (s, 3 H, OCH_3), 3.58-3.62 (m, 5 H, $NOCH_3$, C<u>H$_2$</u>OTIPS), 3.69-3.75 (m, 1 H, C<u>H</u>OMOM), 4.59 (s, 2 H, MOM-C<u>H$_2$</u>).

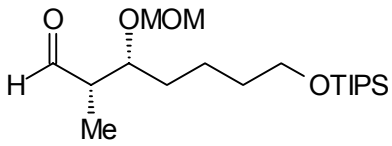
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 11.9 (TIPS-<u>C</u>H), 13.3 (CH_3), 18.0 (TIPS-<u>C</u>H_3), 21.6 [<u>C</u>H_2(CH_2)$_2$OTIPS], 32.3 (NCH_3), 32.9 (<u>C</u>H_2CH_2OTIPS), 33.1 [<u>C</u>H_2(CH_2)$_3$OTIPS], 39.4 (<u>C</u>HCH_3), 55.8 (OCH_3), 61.2 (NO<u>C</u>H_3), 63.2 (<u>C</u>H_2OTIPS), 79.5 (<u>C</u>HOMOM), 96.6 (MOM-<u>C</u>H_2).

IR (neat): $\tilde{\nu}$ = 2942 cm^{-1}, 2866 cm^{-1} (alkyl), 1666 cm^{-1}(C=O), 1039 cm^{-1} (C-O-C).

MS (EI): *m/z* (%) = 376 (100) [M^+ - *i*-Pr], 314 (30).

HRMS (EI): calc. for $C_{18}H_{38}NO_5Si$ [M^+ - *i*-Pr]: 376.251902, found: 376.255542.

*(2S,3R)-3-(Methoxymethoxy)-2-methyl-7-[(triisopropylsilyl)oxy]heptanal **(44)**:*



A cooled (–78°C) solution of WEINREB amide **43** (2.0 g, 4.77 mmol) in dry THF (50 ml) was treated dropwise, over a 5 min period, with a 1M solution of di*iso*butylaluminium hydride in hexane (11.9 ml, 11.9 mmol). The reaction mixture was stirred at this temperature for 2 h and then acetone (1.2 ml) was introduced. The resulting solution was taken up in a syringe and added at 0°C to a vigorously stirred 1:1 mixture of 0.1M aqueous ROCHELLE'S salt / diethyl ether (500 ml). After the solution was warmed to room temperature and stirred for 30 min, additional diethyl ether (150 ml) and water (100 ml) were added, and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 150 ml) and the combined organic extracts were washed with brine (200 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification was performed by flash column chromatography (petroleum ether/diethyl ether, 3:1) to give the desired aldehyde **44** (1.70 g, 99% yield) as colorless syrup. - TLC (petroleum ether/diethyl ether, 3:1): *R*f = 0.53. - $[\alpha]^{25.9}_{D}$ = +3.4 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.98-1.00 (m, 21 H, TIPS), 1.04 (d, *J* = 7.0 Hz, 3 H, CH_3), 1.29-1.61 (m, 6 H, 3 CH_2), 2.48 (dq, $^3J_1$ = 6.8 Hz, $^3J_2$ = 2.9 Hz, 1 H, C<u>H</u>CH_3), 3.25 (s, 3 H, OCH_3), 3.62 (t, *J* = 6.0 Hz, 2 H, C<u>H</u>$_2$OTIPS), 3.91-3.98 (m, 1 H, C<u>H</u>OMOM), 4.54, 4.62 (2 d, *J* = 7.0 Hz each, 2 H, MOM-C<u>H</u>$_2$), 9.71 (s, 1 H, CHO).

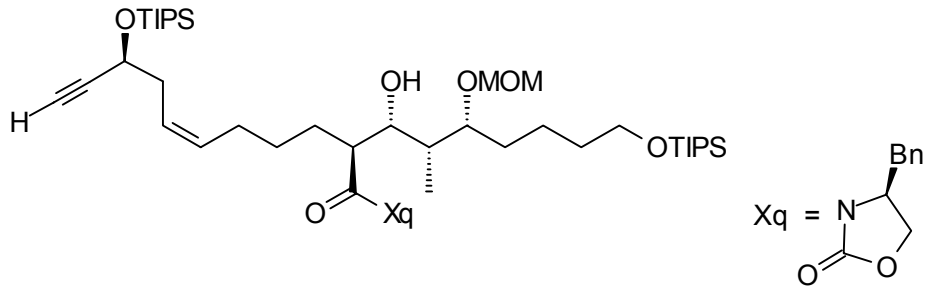
^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.7 (CH_3), 12.0 (TIPS-<u>C</u>H), 18.0 (TIPS-<u>C</u>H_3), 22.3 [<u>C</u>$H_2(CH_2)_2$OTIPS], 32.0 (<u>C</u>H_2CH_2OTIPS), 32.9 [<u>C</u>$H_2(CH_2)_3$OTIPS], 49.9 (<u>C</u>HCH_3), 55.7 (OCH_3), 63.1 (<u>C</u>H_2OTIPS), 77.5 (<u>C</u>HOMOM), 96.3 (MOM-<u>C</u>H_2), 204.3 (CHO).

IR (neat): $\tilde{\nu}$ = 2943 cm^{-1}, 2866 cm^{-1} (alkyl), 2725 cm^{-1}, 1727 cm^{-1} (CHO), 1039 cm^{-1} (C-O-C).

MS (EI): *m/z* (%) = 329 (5) [M^+-OCH_3], 215 (100), 173 (90), 145 (30).

HRMS (EI): calc. for $C_{18}H_{37}O_3Si$ [M^+-OCH_3]: 329.251187, found: 329.253845.

*(4S)-4-Benzyl-3-{(2S,6Z,9S)-2-{(1R,2R,3R)-1-hydroxy-3-(methoxymethoxy)-2-methyl-7-[(triisopropylsilyl)oxy]heptyl}-9-[(triisopropylsilyl)oxy]-6-undecen-10-ynoyl}-1,3-oxazolidin-2-one **(45)**:*



To a cooled to –78°C solution of oxazolidinone **23** (500 mg, 0.98 mmol) in dry dichloromethane (5 ml) was added dropwise titanium tetrachloride (0.11 ml, 0.98 mmol) and the resulting mixture was stirred for 10 min under an argon atmosphere. (-)-Sparteine (0.56 ml, 2.45 mmol) was added dropwise and the dark red solution was stirred at –78°C for 1.5 h. Thereafter the aldehyde **44** (423 mg, 1.17 mmol) dissolved in anhydrous dichloromethane (1 ml) was added dropwise, and the resulting mixture was stirred for additional 3 h at –78°C, before it was treated with a half saturated aqueous solution of ammonium chloride (7 ml). The reaction mixture was allowed to warm to ambient temperature and filtered through a pad of Celite and the salts were washed with small portions of dichloromethane. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 5 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave 165 mg of the desired product **45** (20 %) as a colorless oil together with 309 mg (62 %) of recovered starting material. - TLC (petroleum ether/diethyl ether, 1:1): *R*f = 0.38. - $[\alpha]^{24.1}_D$ = +6.5 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 7.1 Hz, 3 H, CH_3), 0.94-1.10 (m, 42 H, 2 TIPS), 1.21-1.64 [m, 9 H, CH=CHCH$_2$C$\underline{H}_2$, (C$\underline{H}_2$)$_3$CH$_2$OTIPS, C$\underline{H}$CH$_3$], 1.75-1.85 [m, 2 H, CH=CH(CH$_2$)$_2$C$\underline{H}_2$], 1.94-2.08 (m, 2 H, CH=CHC$\underline{H}_2$), 2.30-2.34 (m, 2 H, alkyne-CH, C$\underline{H}_2$CH=CH), 2.37-2.42 (m, 1 H, C$\underline{H}_2$CH=CH), 2.60 (dd, ^2J = 13.3 Hz, ^3J = 9.6 Hz, 1 H, C$_6$H$_5$C$\underline{H}_2$), 3.26-3.34 (m, 4 H, C$_6$H$_5$C$\underline{H}_2$, OCH$_3$), 3.59-3.64 (m, 3 H, C$\underline{H}$OMOM, C$\underline{H}_2$OTIPS), 4.00 (dd, $^3J_1$ = 7.5 Hz, $^3J_2$ = 2.5 Hz, 1 H, C$\underline{H}$OH), 4.07-4.19 (m, 3 H, C$\underline{H}$CON, oxazolidinone-CH$_2$), 4.31-4.41 (m, 1 H, C$\underline{H}$OTIPS), 4.54-4.67 (m, 3 H, MOM-C$\underline{H}_2$, oxazolidinone-CH), 5.41-5.46 (m, 2 H, olefin-CH), 7.15-7.31 (m, 5 H, aromatic-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.2 (+, CH_3), 12.0, 12.2 (2 +, TIPS-CH), 18.1 (+, TIPS-CH_3), 22.2 [-, $CH_2(CH_2)_2$OTIPS], 26.7 [-, CH=CH$(CH_2)_2CH_2$], 27.9 (-, CH=CHCH_2), 29.1 (-, CH=CHCH_2CH_2), 31.8 (-, CH_2CH_2OTIPS), 33.1 [-, $CH_2(CH_2)_3$OTIPS], 36.9 (-, CH_2CH=CH), 38.1 (-, $C_6H_5CH_2$), 38.2 (+, $CHCH_3$), 45.9 (+, CHCON), 55.6 (+, oxazolidinone-CH), 55.9 (+, OCH_3), 62.8 (+, CHOTIPS), 63.2 (-, CH_2OTIPS), 65.9 (-, oxazolidinone-CH_2), 72.3 (-, alkyne-CH), 74.7 (+, CHOH), 82.7 (+, CHOMOM), 85.4 (#, alkyne-C), 96.1 (-, MOM-CH_2), 124.6 (+, olefin-CH), 127.4, 129.0, 129.4 (3 +, aromatic-CH), 132.1 (+, olefin-CH), 135.3 (#, aromatic-C), 152.9 (#, oxazolidinone-CO), 176.0 (#, amide-CO).

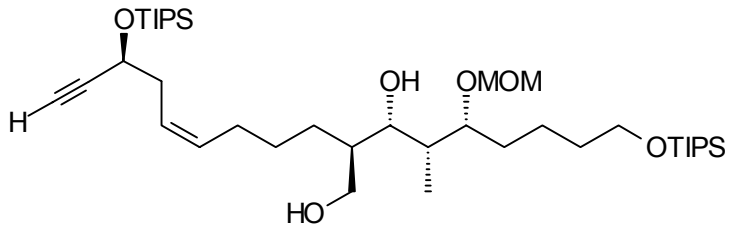
IR (neat): $\tilde{\nu}$ = 3515 cm^{-1} (OH), 3310 cm^{-1} (alkyne-CH), 2943 cm^{-1}, 2866 cm^{-1} (alkyl), 2113 cm^{-1} (C≡C), 1785 cm^{-1}, 1694 cm^{-1} (C=O), 1463 cm^{-1}, 1384 cm^{-1} (C=C), 1036 cm^{-1} (C-O-C).

MS (EI): *m/z* (%) = 829 (2) [M^+ - *i*-Pr], 785 (1) [M^+ - 2(*i*-Pr)], 468 (95), 215 (60), 173 (100).

MS (ESI): *m/z* (%) = 895 (50) [M+Na^+], 841 (50) [M^+-OCH_3^-], 534 (100).

HRMS (FT-ICR-ESI): calc. for $C_{49}H_{85}NO_8Si_2Na$ [M+Na^+]: 894.5705930, found: 894.5692011.

*(2R,3S,4R,5R)-5-(Methoxymethoxy)-4-methyl-9-[(triisopropylsilyl)oxy]-2-{(4Z,7S)-7-[(triisopropylsilyl)oxy]-4-nonen-8-ynyl}-1,3-nonanediol **(47)**:*



The aldol adduct **45** (165 mg, 0.19 mmol) was dissolved in anhydrous THF (2 ml) which contained absolute methanol (15 µl). The resulting solution was cooled to 0°C and then treated dropwise with a 2M solution of lithium borohydride in THF (0.2 ml, 0.40 mmol). After being stirred for 4.5 h at 0°C, the reaction mixture was quenched carefully with saturated aqueous ammonium chloride solution (4 ml) and the two-phase mixture was allowed to reach ambient temperature. The bulk of the THF was removed under reduced pressure and the residue extracted with ethyl acetate (3 x 4 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated on the rotatory evaporator. The residue was purified by flash column chromatography (petroleum

ether/ethyl acetate, 3:2) to give compound **47** (105 mg, 80% yield) as colorless oil. - TLC (petroleum ether/ethyl acetate, 3:2): *R*f = 0.54. - $[\alpha]^{25.5}_{D}$ = -22.4 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 7.2 Hz, 3 H, CH_3), 0.93-1.05 (m, 42 H, 2 TIPS), 1.19-1.57 [m, 9 H, CH=CHCH$_2$C$\underline{H}_2$, (C$\underline{H}_2$)$_3$CH$_2$OTIPS, C$\underline{H}$CH$_3$],1.65-1.72 (m, 1 H, C$\underline{H}$CH$_2$OH), 1.77-1.84 [m, 2 H, CH=CH(CH$_2$)$_2$C$\underline{H}_2$], 2.00-2.03 (m, 2 H, CH=CHC$\underline{H}_2$), 2.30-2.34 (m, 2 H, alkyne-CH, C$\underline{H}_2$CH=CH), 2.38-2.43 (m, 1 H, C$\underline{H}_2$CH=CH), 3.32 (s, 3 H, OCH_3), 3.53-3.55 (m, 1 H, C$\underline{H}$OMOM), 3.59-3.69 (m, 4 H, C$\underline{H}_2$OTIPS, C$\underline{H}_2$OH), 3.81 (dd, $^3J_1 \approx {}^3J_2$ = 5.0 Hz, 1 H, C$\underline{H}$OH), 4.36-4.39 (m, 1 H, C$\underline{H}$OTIPS), 4.55, 4.62 (2 d, *J* = 6.8 Hz each, 2 H, MOM-C$\underline{H}_2$), 5.40-5.47 (m, 2 H, olefin-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 8.2 (+, CH_3), 12.0, 12.3 (2 +, TIPS-$\underline{C}$H), 18.0 (+, TIPS-$\underline{C}H_3$), 22.3 [-, $\underline{C}H_2$(CH$_2$)$_2$OTIPS], 25.1 [-, CH=CH(CH$_2$)$_2\underline{C}H_2$], 27.7 (-, CH=CH$\underline{C}H_2$), 28.0 (-, CH=CHCH$_2\underline{C}H_2$), 31.4 (-, $\underline{C}H_2CH_2$OTIPS), 33.1 [-, $\underline{C}H_2$(CH$_2$)$_3$OTIPS], 36.9 (-, $\underline{C}H_2$CH=CH), 37.2 (+, $\underline{C}HCH_3$), 43.0 (+, $\underline{C}HCH_2$OH), 55.9 (+, OCH_3), 62.8 (+, $\underline{C}$HOTIPS), 63.1 (-, $\underline{C}H_2$OTIPS), 64.3 (-, CH_2OH), 72.3 (-, alkyne-CH), 77.1 (+, CHOH), 82.0 (+, $\underline{C}$HOMOM), 85.5 (#, alkyne-C), 95.7 (-, MOM-$\underline{C}H_2$), 124.6, 132.1 (2 +, olefin-CH).

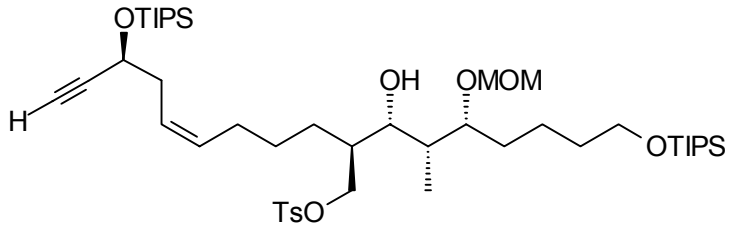
IR (neat): $\tilde{\nu}$ = 3425 cm^{-1} (OH), 3311 cm^{-1} (alkyne-CH), 2943 cm^{-1}, 2866 cm^{-1} (alkyl), 2113 cm^{-1} (C≡C), 1464 cm^{-1} (C=C).

MS (FD): *m/z* (%) = 1398 (100) [2M+H$^+$], 699 (80) [M$^+$], 679 (50).

MS (ESI): *m/z* (%) = 668 (100) [M$^+$-OCH$_3^-$], 1398 (10) [2M+H$^+$].

HRMS (FT-ICR-ESI): calc. for $C_{38}H_{75}O_5Si_2$ [M$^+$-OCH$_3^-$]: 667.5147550, found: 667.5156360.

(2R,6Z,9S)-2-{(1S,2R,3R)-1-Hydroxy-3-(methoxymethoxy)-2-methyl-7-[(triisopropylsilyl) oxy] heptyl}-9-[(triisopropylsilyl)oxy]-6-undecen-10-ynyl 4-methylbenzenesulfonate ***(48)****:*



To a solution of diol **47** (105 mg, 0.15 mmol) in anhydrous dichloromethane (1 ml) was added at once *p*-toluenesulfonyl chloride (30 mg, 0.15 mmol), followed by absolute triethylamine (22 µl, 0.16 mmol) and catalytic amounts of dimethylaminopyridine (2 mg, 16 µmol). The resulting reaction mixture was stirred at ambient temperature for 18 h. Then the solvent was removed under reduced pressure and the residue was taken up in diethyl ether (3 ml), and water (1 ml) was added. The layers were separated and the organic phase was washed with water (2 x 1 ml), dried over $MgSO_4$ filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography (petroleum ether/ethyl acetate, 6:1) to give 87 mg of the desired product **48** (68% yield) as colorless oil. - TLC (petroleum ether/ethyl acetate, 6:1): *R*f = 0.25. - $[\alpha]^{25.8}_D$ = -18.7 (*c* 1.00, CH_2Cl_2).

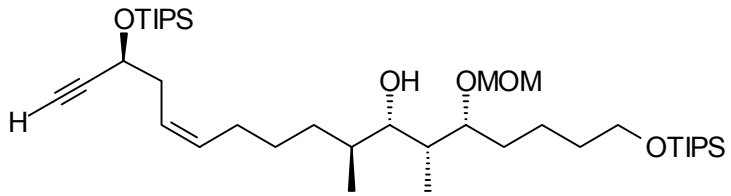
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.96-1.08 (m, 42 H, 2 TIPS), 1.13-1.56 [m, 9 H, CH=CHCH$_2$C$\underline{H}_2$, (C$\underline{H}_2$)$_3$CH$_2$OTIPS, C$\underline{H}$CH$_3$], 1.67-1.71 (m, 1 H, C$\underline{H}$CH$_2$OTs), 1.87-1.93 [m, 4 H, CH=CH(CH$_2$)$_2$C$\underline{H}_2$, CH=CHC$\underline{H}_2$], 2.31-2.38 (m, 6 H, alkyne-CH, C$\underline{H}_2$CH=CH, Ts-C$\underline{H}_3$), 3.21 (s, 3 H, OCH_3), 3.51-3.59 (m, 1 H, C$\underline{H}$OMOM), 3.60-3.65 (m, 4 H, C$\underline{H}_2$OTs, C$\underline{H}_2$OTIPS), 3.93 (dd, $^3J_1 \approx {}^3J_2$ = 5.0 Hz, 1 H, C$\underline{H}$OH), 4.32-4.41 (m, 1 H, C$\underline{H}$OTIPS), 4.54, 4.62 (2 d, *J* = 6.7 Hz each, 2 H, MOM-C$\underline{H}_2$), 5.34-5.42 (m, 2 H, olefin-CH), 7.28, 7.71 (2 d, *J* = 8.1 Hz each, 4 H, aromatic-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 7.2 (+, CH_3), 12.1, 12.3 (2 +, TIPS-C$\underline{H}$), 18.1 (+, TIPS-C$\underline{H}_3$), 21.7 (+, Ts-C$\underline{H}_3$), 22.1 [-, C$\underline{H}_2$(CH$_2$)$_2$OTIPS], 26.0 [-, CH=CH(CH$_2$)$_2$C$\underline{H}_2$], 27.2 (-, CH=CHC$\underline{H}_2$), 27.8 (-, CH=CHCH$_2$C$\underline{H}_2$), 31.5 (-, C$\underline{H}_2$CH$_2$OTIPS), 33.1 [-, C$\underline{H}_2$(CH$_2$)$_3$OTIPS], 36.9 (-, C$\underline{H}_2$CH=CH), 37.0 (+, C$\underline{H}$CH$_3$), 41.2 (+, C$\underline{H}$CH$_2$OTs), 56.0 (+, OCH_3), 62.8 (+, C$\underline{H}$OTIPS), 63.1 (-, C$\underline{H}_2$OTIPS), 70.1 (-, C$\underline{H}_2$OTs), 72.3 (-, alkyne-CH), 74.3 (+, CHOH), 82.2 (+, C$\underline{H}$OMOM), 85.5 (#, alkyne-C), 95.7 (-, MOM-C$\underline{H}_2$), 124.5 (+, olefin-CH), 127.9, 129.9 (2 +, aromatic-CH), 132.1 (+, olefin-CH), 133.1, 144.8 (2 #, aromatic-C).

IR (neat): $\tilde{\nu}$ = 3502 cm^{-1} (OH), 3310 cm^{-1} (alkyne-CH), 2943 cm^{-1}, 2866 cm^{-1} (alkyl), 2113 cm^{-1} (C≡C), 1464 cm^{-1} (C=C), 1365 cm^{-1}, 1178cm^{-1} (SO_2-OR).

MS (FD): *m/z* (%) = 809 (100) [M^+ - *i*-Pr], 224 (30).

*(9R,10R,11S,12S,16Z,19S)-19-Ethynyl-3,3,21,21-tetraisopropyl-9-(methoxymethoxy)-2,10,12,22-tetramethyl-4,20-dioxa-3,21-disilatricos-16-en-11-ol **(49)**:*



A mixture of **48** (57 mg, 67 μmol), sodium iodide (50 mg, 0.34 mmol), zinc dust (44 mg, 0.67 mmol) and glyme (6 ml) was stirred, and heated to reflux for 2.5 h. Then the reaction mixture was cooled to ambient temperature and filtered through a small glass funnel. The filtrate was diluted with water (4 ml) and extracted with ethyl acetate (3 x 8 ml). The combined organic extracts were concentrated under reduced pressure to give 45 mg of the desired product **49** (100% yield) as colorless oil, which was used in the next step without further purification. - TLC (petroleum ether/ethyl acetate, 6:1): *R*f = 0.51. - $[\alpha]^{27.2}_D$ = -20.3 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.73 (d, *J* = 6.7 Hz, 3H, $CH_2CHC\underline{H}_3$), 0.84 (d, *J* = 7.1 Hz, 3 H, $CHC\underline{H}_3$), 0.95-1.10 (m, 42 H, 2 TIPS), 1.19-1.51 [m, 9 H, $CH{=}CHCH_2C\underline{H}_2$, $(C\underline{H}_2)_3CH_2OTIPS$, $C\underline{H}CH_3$], 1.59-1.80 [m, 3 H, $CH_2C\underline{H}CH_3$, $CH{=}CH(CH_2)_2C\underline{H}_2$], 1.92-2.02 (m, 2 H, $CH{=}CHC\underline{H}_2$), 2.32-2.33 (m, 2 H, alkyne-CH, $C\underline{H}_2CH{=}CH$), 2.38-2.43 (m, 1 H, $C\underline{H}_2CH{=}CH$), 3.30-3.33 (m, 4 H, $C\underline{H}OMOM$, OCH_3), 3.59-3.64 (m, 4 H, $C\underline{H}_2OTIPS$, $C\underline{H}OH$), 4.34-4.41 (m, 1 H, $C\underline{H}OTIPS$), 4.57, 4.68 (2 d, *J* = 6.7 Hz each, 2 H, MOM-$C\underline{H}_2$), 5.39-5.49 (m, 2 H, olefin-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.8 (+, $CH\underline{C}H_3$), 12.0, 12.3 (2 +, TIPS-$\underline{C}H$), 15.7 (+, $CH_2CH\underline{C}H_3$), 18.0, 18.1 (2 +, TIPS-$\underline{C}H_3$), 22.1 [-, $\underline{C}H_2(CH_2)_2OTIPS$], 26.8 [-, $CH{=}CH(CH_2)_2\underline{C}H_2$], 27.0 (-, $CH{=}CH\underline{C}H_2$), 28.1 (-, $CH{=}CHCH_2\underline{C}H_2$), 31.3 (-, $\underline{C}H_2CH_2OTIPS$), 33.1 [-, $\underline{C}H_2(CH_2)_3OTIPS$], 36.1 (+, $CH_2\underline{C}HCH_3$), 36.3 (+, $\underline{C}HCH_3$), 36.9 (-, $\underline{C}H_2CH{=}CH$), 56.0 (+, OCH_3), 62.9 (+, $\underline{C}HOTIPS$), 63.2 (-, $\underline{C}H_2OTIPS$), 72.2 (-, alkyne-CH), 79.6 (+, CHOH), 83.3 (+, $\underline{C}HOMOM$), 85.6 (#, alkyne-C), 95.6 (-, MOM-$\underline{C}H_2$), 124.1, 132.9 (2 +, olefin-CH).

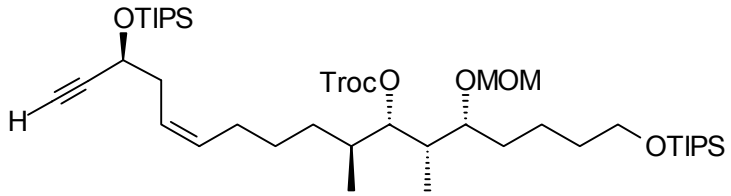
IR (neat): $\tilde{\nu}$ = 3507 cm^{-1} (OH), 3312 cm^{-1} (alkyne-CH), 2942 cm^{-1}, 2866 cm^{-1} (alkyl), 2113 cm^{-1} (C≡C), 1463 cm^{-1}, 1383 cm^{-1} (C=C).

MS (FD): *m/z* (%) = 1367 (100) [2M+H^+], 640 (80) [M^+ - *i*-Pr].

MS (ESI): *m/z* (%) = 705 (30) [M+Na$^+$], 651 (40) [M$^+$-OCH$_3$].

HRMS (FT-ICR-ESI): calc. for $C_{38}H_{75}O_4Si_2$ [M$^+$-OCH$_3^-$]: 651.5198404, found: 651.5208080; calc. for $C_{39}H_{78}O_5Si_2Na$ [M+Na$^+$]: 705.5279998, found:705.5268340.

*(1S,2S,6Z,9S)-1-{(1S,2R)-2-(Methoxymethoxy)-1-methyl-6-[(triisopropylsilyl)oxy] hexyl}-2-methyl-9-[(triisopropylsilyl)oxy]-6-undecen-10-ynyl 2,2,2-trichloroethyl carbonate **(50)**:*



To a stirred solution of **49** (67 mg, 98 μmol) in anhydrous dichloromethane (2 ml) was added absolute pyridine (143 μl, 1.77 mmol) and dimethylaminopyridine (2 mg, 16 μmol). The resulting mixture was cooled to 0°C, treated by dropwise addition with 2,2,2-trichloroethyl chloroformate (79 μl, 0.60 mmol) which resulted in the formation of a white precipitate. Thereafter the reaction mixture was allowed to warm to ambient temperature and to stir for 18 h. To destroy the excess of the chloroformate, water (2 ml) was added carefully and gas evolution was evident. The layers were separated and the aqueous phase was extracted with dichloromethane (3 x 2 ml). The combined organic extracts were washed once with 1M aqueous hydrochloric acid (2 ml) and water (2 ml), dried over $MgSO_4$, filtrated and evaporated on a rotatory evaporator. The crude crystalline material was purified by flash column chromatography (petroleum ether/dichloromethane, 5:1 → dichloromethane) to give 83 mg of the desired product **50** (99% yield) as colorless oil. - TLC (petroleum ether/dichloromethane, 5:1): *R*f = 0.15. - $[\alpha]^{23.4}_D$ = -3.3 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.8 Hz, 3H, CH_2CHCH_3), 0.90 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 0.95-1.10 (m, 42 H, 2 TIPS), 1.14-1.58 [m, 9 H, $CH=CHCH_2CH_2$, $(CH_2)_3CH_2OTIPS$, $CHCH_3$], 1.81-2.08 [m, 5 H, CH_2CHCH_3, $CH=CH(CH_2)_2CH_2$, $CH=CHCH_2$], 2.30-2.42 (m, 3 H, alkyne-CH, $CH_2CH=CH$), 3.31 (s, 3 H, OCH_3), 3.39-3.41 (m, 1 H, CHOMOM), 3.61 (t, *J* = 6.1 Hz, 2 H, CH_2OTIPS), 4.35-4.41 (m, 1 H, CHOTIPS), 4.56, 4.58 (2 d, *J* = 7.0 Hz each, 2 H, MOM-CH_2), 4.72-4.77 (m, 3 H, CHOTroc, Troc-CH_2), 5.41-5.45 (m, 2 H, olefin-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 9.9 (+, $CHCH_3$), 12.0, 12.2 (2 +, TIPS-CH), 16.3 (+, CH_2CHCH_3), 18.1 (+, TIPS-CH_3), 22.0 [-, $CH_2(CH_2)_2OTIPS$], 27.2 [-, $CH=CH(CH_2)_2CH_2$], 27.8 (-, $CH=CHCH_2$), 30.3 (-, $CH=CHCH_2CH_2$), 31.3 (-, CH_2CH_2OTIPS), 33.1 [-,

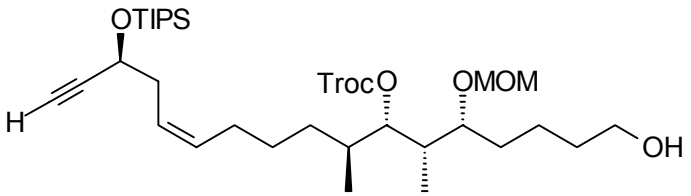
$\underline{C}H_2(CH_2)_3OTIPS]$, 34.6 (+, $CH_2\underline{C}HCH_3$), 36.8 (+, $\underline{C}HCH_3$), 36.9 (-, $\underline{C}H_2CH=CH$), 55.9 (+, OCH_3), 62.8 (+, $\underline{C}HOTIPS$), 63.2 (-, $\underline{C}H_2OTIPS$), 72.3 (-, alkyne-CH), 76.6 (-, Troc-$\underline{C}H_2$), 79.2 (+, $\underline{C}HOMOM$), 85.0 (+, $\underline{C}HOTroc$), 85.5 (#, alkyne-C), 94.9 (#, CCl_3), 96.0 (-, MOM-$\underline{C}H_2$), 124.5, 132.4 (2 +, olefin-CH), 154.5 (#, CO).

IR (neat): $\tilde{\nu}$ = 3311 cm^{-1} (alkyne-CH), 2925 cm^{-1}, 2867 cm^{-1} (alkyl), 2113 cm^{-1} (C≡C), 1760 cm^{-1} (carbonate-CO), 1463 cm^{-1}, 1383 cm^{-1} (C=C).

MS (FD): *m/z* (%) = 881 (100) / 879 (80) [$M+Na^+$].

MS (FAB): *m/z* (%) = 881 (100) / 879 (100) [$M+Na^+$], 859 (20) / 857 (30) [M^+].

(1S,2S,6Z,9S)-1-[(1S,2R)-6-Hydroxy-2-(methoxymethoxy)-1-methylhexyl]-2-methyl-9-[(triisopropylsilyl)oxy]-6-undecen-10-ynyl 2,2,2-trichloroethyl carbonate **(51)**:



To a cooled (0°C) solution of silyl ether **50** (83 mg, 97 μmol) in anhydrous THF (1.5 ml) was added dropwise a mixture of HF·pyridine complex in dry pyridine / THF mixture [HF·pyridine complex (228 μl), pyridine (0.62 ml), THF (1.09 ml)]. The resulting reaction mixture was allowed to warm to room temperature and to stir at inert atmosphere for 7 h (TLC monitoring). Thereafter the reaction was diluted with ethyl acetate (2 ml) and quenched by careful addition of saturated aqueous $NaHCO_3$ (2 ml). The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 3 ml). The combined organic extracts were washed once with 1M aqueous hydrochloric acid (2 ml) and water (2 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ethyl acetate, 3:2) of the residue provided pure alcohol **51** (38 mg, 56% yield) as a colorless oil together with recovered starting material **50** (19 mg, 42%). - TLC (petroleum ether/ethyl acetate, 3:2): *R*f = 0.48. - $[\alpha]^{25.6}_D$ = -1.9 (*c* 1.00, CH_2Cl_2).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.8 Hz, 3H, $CH_2CHC\underline{H}_3$), 0.91 (d, *J* = 6.9 Hz, 3 H, $CHC\underline{H}_3$), 1.01-1.09 (m, 21 H, TIPS), 1.14-1.53 [m, 9 H, $CH=CHCH_2C\underline{H}_2$, $(C\underline{H}_2)_3CH_2OH$, $C\underline{H}CH_3$], 1.82-2.05 [m, 5 H, $CH_2C\underline{H}CH_3$, $CH=CH(CH_2)_2C\underline{H}_2$, $CH=CHC\underline{H}_2$], 2.31-2.42 (m, 3 H, alkyne-CH, $C\underline{H}_2CH=CH$), 3.32 (s, 3 H, OCH_3), 3.39-3.44 (m, 1 H, $C\underline{H}OMOM$), 3.58 (t, *J*

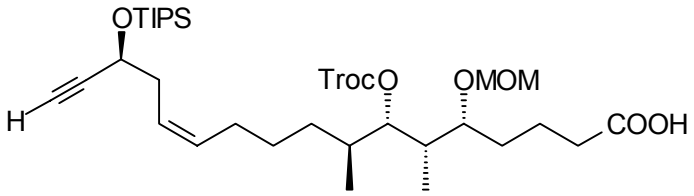
= 6.3 Hz, 2 H, CH_2OH), 4.35-4.41 (m, 1 H, CHOTIPS), 4.53, 4.58 (2 d, *J* = 7.0 Hz each, 2 H, MOM-CH_2), 4.72-4.77 (m, 3 H, CHOTroc, Troc-CH_2), 5.41-5.45 (m, 2 H, olefin-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.0 (+, CHCH_3), 12.2 (+, TIPS-CH), 16.2 (+, CH_2CHCH_3), 18.0 (+, TIPS-CH_3), 21.8 [-, $CH_2(CH_2)_2OH$], 27.1 [-, $CH=CH(CH_2)_2CH_2$], 27.8 (-, $CH=CHCH_2$), 30.3 (-, $CH=CHCH_2CH_2$), 31.3 (-, CH_2CH_2OH), 32.7 [-, $CH_2(CH_2)_3OH$], 34.7 (+, CH_2CHCH_3), 36.9 (+, $CHCH_3$), 37.0 (-, $CH_2CH=CH$), 56.0 (+, OCH_3), 62.6 (-, CH_2OH), 62.8 (+, CHOTIPS), 72.3 (-, alkyne-CH), 76.5 (-, Troc-CH_2), 79.3 (+, CHOMOM), 84.8 (+, CHOTroc), 85.5 (#, alkyne-C), 94.9 (#, CCl_3), 96.1 (-, MOM-CH_2), 124.5, 132.4 (2 +, olefin-CH), 154.5 (#, CO).

IR (neat): $\tilde{\nu}$ = 3507 cm^{-1} (OH), 3310 cm^{-1} (alkyne-CH), 2942 cm^{-1}, 2867 cm^{-1} (alkyl), 2113 cm^{-1} (C≡C), 1757 cm^{-1} (carbonate-CO), 1463 cm^{-1}, 1383 cm^{-1} (C=C).

MS (FAB): *m/z* (%) = 725 (4) / 723 (4) [M+Na$^+$], 221 (100).

*(5R,6S,7S,8S,12Z,15S)-5-(Methoxymethoxy)-6,8-dimethyl-7-{[(2,2,2-trichloroethoxy) carbonyl]oxy}-15-[(triisopropylsilyl)oxy]-12-heptadecen-16-ynoic acid **(52)**:*



The alcohol **51** (33 mg, 47 μmol) was dissolved in acetone (1 ml) and treated with a 5% aqueous solution of $NaHCO_3$ (0.2 ml). This magnetically stirred heterogeneous reaction mixture was cooled to 0°C and treated at once with potassium bromide (1 mg, 8.4 μmol) followed by TEMPO (8 mg, 49 μmol). Thereafter was added dropwise an aqueous sodium hypochlorite solution (30 μl, 59 μmol) and the resulting mixture was vigorously stirred at 0°C for 1 h. Then a new portion of sodium hypochlorite (12 μl, 23 μmol) was added and stirring continued for additional 2 h. The reaction mixture was quenched with 5% aqueous solution of $NaHCO_3$ (0.5 ml) and the acetone was removed under reduced pressure. The residue was acidified to pH 6 using a 10% aqueous solution of citric acid and extracted with ethyl acetate (4 x 2 ml). The combined organic layers were washed once with water (2 ml), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The excess of TEMPO was removed by flash column chromatography (petroleum ether/ethyl acetate, 4:1) and 34 mg of a mixture of desired acid **52** with an unknown by-product was obtained (100 % yield) as a pale yellow thick oil. The resulting material was

used in the next step without further purification. - TLC (petroleum ether/ethyl acetate, 4:1): *R*f = 0.26. - $[\alpha]^{27.8}_{D}$ = -5.2 (*c* 1.00, CH_2Cl_2).

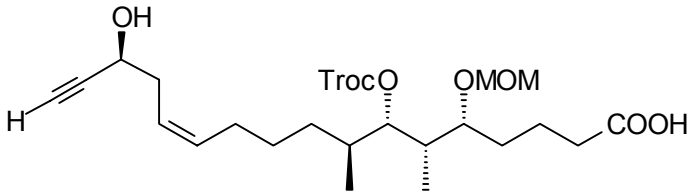
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.9 Hz, 3H, CH_2CHCH_3), 0.91 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 1.02-1.10 (m, 21 H, TIPS), 1.13-1.68 (m, 7 H, $CH{=}CHCH_2CH_2$, $(CH_2)_2CH_2COOH$, $CHCH_3$], 1.70-2.08 [m, 5 H, CH_2CHCH_3, $CH{=}CH(CH_2)_2CH_2$, $CH{=}CHCH_2$], 2.38-2.45 (m, 5 H, CH_2COOH, alkyne-CH, $CH_2CH{=}CH$), 3.32 (s, 3 H, OCH_3), 3.39-3.48 (m, 1 H, CHOMOM), 4.35-4.48 (m, 1 H, CHOTIPS), 4.54, 4.58 (2 d, *J* = 7.0 Hz each, 2 H, MOM-CH_2), 4.67-4.78 (m, 3 H, CHOTroc, Troc-CH_2), 5.41-5.47 (m, 2 H, olefin-CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 10.1 (+, $CHCH_3$), 12.3 (+, TIPS-CH), 16.2 (+, CH_2CHCH_3), 18.1 (+, TIPS-CH_3), 20.7 (-, CH_2CH_2COOH), 27.1 [-, $CH{=}CH(CH_2)_2CH_2$], 29.7 (-, $CH{=}CHCH_2$), 30.1 (-, $CH{=}CHCH_2CH_2$), 30.7 [-, $CH_2(CH_2)_2COOH$], 33.8 (-, CH_2COOH), 34.7 (+, CH_2CHCH_3), 37.0 (-, $CH_2CH{=}CH$), 37.1 (+, $CHCH_3$), 56.0 (+, OCH_3), 62.9 (+, CHOTIPS), 72.3 (-, alkyne-CH), 76.5 (-, Troc-CH_2), 79.1 (+, CHOMOM), 84.3 (+, CHOTroc), 84.4 (#, alkyne-C), 94.9 (#, CCl_3), 96.2 (-, MOM-CH_2), 124.5, 132.3 (2 +, olefin-CH), 154.3 (#, CO), 178.5 (#, COOH).

IR (neat): $\tilde{\nu}$ = 3308 cm^{-1} (alkyne-CH), 2961 cm^{-1}, 2922 cm^{-1} (alkyl), 2857 cm^{-1} (COOH), 2113 cm^{-1} (C≡C), 1756 cm^{-1} (carbonate-CO), 1715 cm^{-1} (COOH).

MS (FAB): *m/z* (%) = 739 (2) / 737 (3) [M+Na^+], 207 (100).

*(5R,6S,7S,8S,12Z,15S)-15-Hydroxy-5-(methoxymethoxy)-6,8-dimethyl-7-{[(2,2,2 trichloro ethoxy)carbonyl]oxy}-12-heptadecen-16-ynoic acid **(53)**:*



To a solution of **52** (34 mg, 47 μmol) in anhydrous THF (0.8 ml) was added dropwise a 1M solution of tetrabutylammoniumfluoride in THF (0.29 mmol, 290 μl) at 0°C. After complete addition, the reaction mixture was allowed to warm up to room temperature and stirred for 20 h. Thereafter the mixture was diluted with ethyl acetate (2 ml) and the resulting solution was washed once with saturated aqueous solution of ammonium chloride (1 ml). The layers were separated and the aqueous phase was extracted thoroughly with ethyl acetate (4 x 1 ml). The combined organic layers were washed with

brine (1 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) afforded 8 mg of compound **53** (30% yield, over two steps) as colorless oil. - TLC (petroleum ether/ethyl acetate, 1:1): *R*f = 0.46.

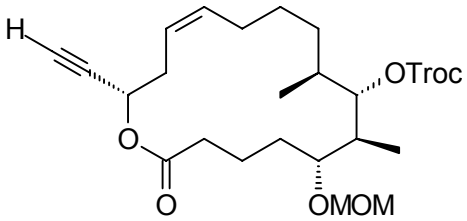
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.9 Hz, 3H, CH_2CHCH_3), 0.93 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 1.14-1.67 (m, 7 H, $CH{=}CHCH_2CH_2$, $(CH_2)_2CH_2COOH$, $CHCH_3$], 1.80-2.06 [m, 5 H, CH_2CHCH_3, $CH{=}CH(CH_2)_2CH_2$, $CH{=}CHCH_2$], 2.25-2.38 (m, 2 H, CH_2COOH), 2.39-2.63 (m, 3 H, alkyne-CH, $CH_2CH{=}CH$), 3.32 (s, 3 H, OCH_3), 3.37-3.46 (m, 1 H, CHOMOM), 4.31-4.35 (m, 1 H, CHOH), 4.52-4.59 (m, 2 H, MOM-CH_2), 4.72-4.78 (m, 3 H, CHOTroc, Troc-CH_2), 5.43-5.52 (m, 2 H, olefin-CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.3 ($CHCH_3$), 16.5 (CH_2CHCH_3), 21.1 (CH_2CH_2COOH), 27.2 [$CH{=}CH(CH_2)_2CH_2$], 30.1 ($CH{=}CHCH_2$), 30.6 ($CH{=}CHCH_2CH_2$), 31.1 [$CH_2(CH_2)_2COOH$], 34.0 (CH_2COOH), 34.9 (CH_2CHCH_3), 35.9 ($CH_2CH{=}CH$), 37.3 ($CHCH_3$), 56.4 (OCH_3), 62.2 (CHOH), 66.3 (alkyne-CH), 75.5 (Troc-CH_2), 79.2 (CHOMOM), 84.9 (CHOTroc), 85.0 (alkyne-C), 95.2 (CCl_3), 96.4 (MOM-CH_2), 123.9, 134.3 (olefin-CH), 154.9 (CO), 177.8 (COOH).

MS (ESI): *m/z* (%) = 559 (100) /557 (80) [M-H$^+$], 443 (35), 425 (35).

HRMS (FT-ICR-ESI): calc. for $C_{24}H_{36}O_8Cl_3$ [M-H$^+$]: 557.1481310, found: 557.1481248.

*(6R,7S,8S,9S,16S)-16-Ethynyl-6-(methoxymethoxy)-7,9-dimethyl-2-oxooxacyclohexadec-13-en-8-yl 2,2,2-trichloroethyl carbonate **(54)**:*



To a solution of hydroxy acid **53** (5 mg, 8.9 μmol) in anhydrous THF (0.3 ml) was added dropwise absolute triethylamine (4 μl, 28.8 μmol) and the resulting mixture was stirred for 10 min at room temperature before 2,4,6-trichlorobenzoyl chloride (2 μl, 12.8 μmol) was added. The reaction mixture was stirred for 2 h at ambient temperature during which time some fine precipitation was obtained. In a separate flask, connected with a reflux condenser and under inert atmosphere, was dissolved dimethylaminopyridine (3 mg, 19.7 μmol) in anhydrous toluene (6 ml) and the resulting solution was heated to 78°C

(oil bath). After the temperature was constant, the solution of the mixed anhydride, dissolved in additional toluene (0.7 ml) was added slowly to the amine solution over a period of 2 h using a syrange pump. Stirring was continued for 1 h at the same temperature. Thereafter the reaction mixture was allowed to cool to ambient temperature and diluted with diethyl ether (5 ml), washed successively with 1M aqueous hydrochloric acid (4 ml), saturated aqueous solution of $NaHCO_3$ (5 ml) and water (5 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (petroleum ether/diethyl ether, 2:1) gave 4.15 mg of the desired macrolacton **54** (86% yield) as colorless oil. - TLC (petroleum ether/diethyl ether, 2:1): *R*f = 0.35. - $[\alpha]^{28.2}_D$ = -9.6 (*c* 0.377, CH_2Cl_2).

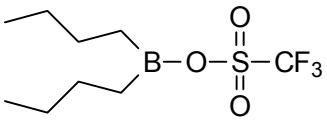
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 7.0 Hz, 3H, $CH_2CHC\underline{H}_3$), 0.94 (d, *J* = 6.7 Hz, 3 H, $CHC\underline{H}_3$), 1.43-1.70 (m, 7 H, $CH=CHCH_2C\underline{H}_2$, $(C\underline{H}_2)_2CH_2CO$, $CH=CHC\underline{H}_2$], 1.84-2.07 [m, 5 H, $CH_2C\underline{H}CH_3$, $CH=CH(CH_2)_2C\underline{H}_2$, $C\underline{H}CH_3$], 2.22-2.30 (m, 2 H, CH_2CO), 2.38-2.47 (m, 2 H, alkyne-CH, $C\underline{H}_2CH=CH$), 2.55-2.64 (m, 1 H, $C\underline{H}_2CH=CH$), 3.32 (s, 3 H, OCH_3), 3.45-3.50 (m, 1 H, $C\underline{H}OMOM$), 4.43-4.46 (m, 1 H, MOM-$C\underline{H}_2$), 4.59-4.61 (m, 1 H, MOM-$C\underline{H}_2$), 4.70-4.77 (m, 2 H, Troc-$C\underline{H}_2$), 4.79-4.85 (m, 1 H, $C\underline{H}OTroc$), 5.31-5.39 (m, 2 H, CHOCO, olefin-CH), 5.43-5.52 (m, 1 H, olefin-CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.4 ($CH\underline{C}H_3$), 17.2 ($CH_2CH\underline{C}H_3$), 21.7 ($\underline{C}H_2CH_2CO$), 27.9 [$CH=CH(CH_2)_2\underline{C}H_2$], 29.1 ($CH=CH\underline{C}H_2$), 29.7 ($CH=CHCH_2\underline{C}H_2$), 30.3 [$\underline{C}H_2(CH_2)_2CO$], 34.2 ($\underline{C}H_2CO$), 34.8 ($CH_2\underline{C}HCH_3$), 36.3 ($\underline{C}H_2CH=CH$), 36.5 ($\underline{C}HCH_3$), 55.9 ($OCH_3$), 62.2 ($\underline{C}HOCO$), 62.7 (alkyne-CH), 73.6 (Troc-$\underline{C}H_2$), 77.2 ($\underline{C}HOMOM$), 85.7 ($\underline{C}HOTroc$), 86.5 (alkyne-C), 95.4 (CCl_3), 95.5 (MOM-$\underline{C}H_2$), 123.6, 133.7 (olefin-CH), 154.8 (carbonate-CO), 171.7 (lactone-CO).

MS (ESI): *m/z* (%) = 565 (100) / 563 (100) [M+Na^+].

HRMS (FT-ICR-ESI): calc. for $C_{24}H_{35}O_7Cl_3Na$ [M+Na^+]: 563.1335320, found: 563.1340577.

Typical procedure for preparation of the di-n-butylboron triflate:[123, 124]

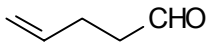


To a Gringard solution, prepeared from magnesium (17 g, 0.7 mol) and *n*-butyl bromide (75 ml, 0.7 mol) in anhydrous diethyl ether (250 ml) was added dropwise a solution of boron triflouride etherate (8.8 ml, 0.07 mol) in dry diethyl ether (23 ml) at a rate sufficient to cause gentle refluxing (40 min). After complete addition, the resulting mixture was refluxed for 2.5 h and then cooled to room temperature under an atmosphere of argon. Subsequently, a solution of concentrated hydrochloric acid (45 ml) in water (135 ml) was added carefully. The ether layer was separated, washed with water (100 ml); saturated aqueous solution of $NaHCO_3$ (100 ml), and again with water (100 ml), dried over $MgSO_4$, filtered and the solvent was removed by distillation under inert atmosphere. The residue was distilled under reduced pressure to provide 9.79 g (78% yield) of pure tri-*n*-butylborane with b.p.: 106-110°C / 20 Torr (lit. [123]: 108-110°C / 20 Torr) as a colorless mobile liquid that undergoes oxidation rapidly in the air.

Trifluoromethanesulfonic acid (4.31 ml, 0.05 mmol) was added dropwise to the tri-*n*-butylborine (8.86 g, 0.05 mmol) at room temperature under argon and the color changed to dark yellow (exothermic reaction). The reaction mixture was stirred for 3 h and then distilled in vacuum under inert atmosphere to afford 12.3 g (92% yield) of di-*n*-butylboron triflate with b.p.: 40-42°C / 0.7 Torr (lit. [124]: 37°C / 0.12 Torr) as a colorless to pale yellow liquid. According to the literature [124] the product was stored as a 1M solution in dichloromethane.

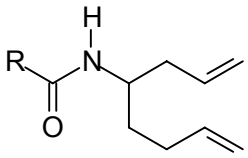
8.3 General Procedures for Preparation of Cyclohexenylamines

4-Pentenal **(58)**:



Procedure according to the literature.[132,133] Purification by distillation provided **58** as a colorless liquid (3.9 g, 40%) with b.p.: 100-105°C (lit.:[133] 104°C).
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36-2.40 (m, 2 H, CH_2), 2.52-2.56 (m, 2 H, CH_2), 5.00-5.08 (m, 2 H, olefinic-H), 5.77-5.86 (m, 1 H, olefinic-H), 9.77 (t, *J* = 1.7 Hz, 1 H, CHO). – **IR** (neat): $\tilde{\nu}$ = 1737 cm^{-1}, 1642.

*Typical procedure for preparation of N1-(allyl-4-pentenyl)-carbamates **(59a, 59b)***:



59a (R = BnO)
59b (R = *t*BuO)

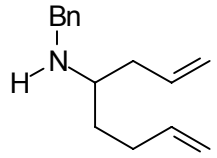
Under inert atmosphere a stirred solution of aldehyde **58** (1.0 g, 12 mmol), allyltrimethylsilane (1.37 g, 12 mmol) and carbamate (12 mmol) in 20 ml dichloromethane was cooled to 0-5°C. At this point borontrifluoride etherate (1.48 ml, 12 mmol) was added at once. After 30 min of stirring the reaction mixture was allowed to warm up to room temperature and stirred for 12 h. Then the mixture was poured into saturated aqueous $NaHCO_3$ and diluted with 30 ml toluene. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by flash column chromatography on silica gel.

N1-(1-allyl-4-pentenyl)-benzylcarbamate **(59a)**: Chromatography (eluent: heptane/ethyl acetate; 7:1) provided **59a** as a white solid (1.87 g, 60%). – TLC (heptane/ethyl acetate, 7:1): *R*f = 0.41. – m.p.: 26-28°C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44-1.61 (m, 2 H, CH_2), 2.06-2.17 (m, 2 H, CH_2), 2.19-2.30 (m, 2 H, CH_2), 3.71-3.74 (m, 1

H, CH), 4.57 (d, *J* = 7.4 Hz, 1 H, NH), 4.93-5.04 (m, 4H, olefinic H), 5.07 (s, 2 H, aryl-CH_2), 5.70-5.83 (m, 2 H, olefinic-H), 7.29-7.36 (m, 5 H, aryl-H). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.1, 33.8, 39.4 (3 CH_2), 50.3 (CH), 66.5 (aryl-CH_2), 115.0, 117.9 (2 olefinic-CH_2), 128.0, 128.5 (5 aryl-CH), 134.0 (olefinic-CH), 136.6 (aryl-CH), 137.8 (olefinic-CH), 155.9 (CO). – MS (EI): *m/z* (%): 218 (15) [M^+ - allyl], 174 (20), 91 (100). – $C_{16}H_{21}NO_2$ (259.35): calc. C 74.10, H 8.10, N 5.40; found C 73.96, H 7.82, N 5.42.

N1-(1-allyl-4-pentenyl)-tert-butylcarbamate **(59b)**: Chromatography (petroleum ether/ethyl acetate; 5:1) provided **59b** as a colorless oil (1.3 g, 48%).– TLC (petroleum ether/ethyl acetate, 5:1): *R*f = 0.51. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *tert*-butyl), 1.46-1.58 (m, 2 H, CH_2), 2.03-2.40 (m, 4 H, CH_2), 3.64 (m, 1 H, CH), 4.33 (s, 1 H, NH), 4.94-5.09 (m, 4 H, olefinic-H), 5.71-5.85 (m, 2 H, olefinic-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (C($\underline{C}H_3)_3$), 31.2, 34.9, 40.5 (3 CH_2), 50.7 (CH), 64.8 ($\underline{C}(CH_3)_3$), 115.9, 118.7 (2 olefinic-CH_2), 135.5, 139.2 (2 olefinic-CH), 156.8 (CO). – MS (ESI): *m/z* (%): 248 (100) $[M + Na]^+$. – $C_{13}H_{23}NO_2$ (225.33): calc. C 69.30, H 10.29, N 6.22; found C 69.01, H 9.94, N 6.38.

N4-Benzyl-1,7-octadien-4-amine **(59c)**:



Under inert atmosphere, freshly distilled benzylamine (1.29 g, 12 mmol) was combined with 4Å molecular sieves (1.08 g) and cooled to 0°C. Thereafter the aldehyde **58** (1 g, 12 mmol) was added dropwise and the reaction mixture stirred for 1 h and then was allowed to warm up to room temperature and stirred for additional 30 min. Anhydrous diethyl ether (3 ml) was added and the organic layer separated. The aqueous layer was extracted with ether and the combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. The obtained crude 4-pentenyl-(benzyl)-imine was used without further purification. To a stirred solution of crude 4-pentenyl-(benzyl)-imine in absolute methanol-chloroform (1/1 : v/v, 32 ml) was added a 0.3M solution of trifluoroacetic acid in absolute methanol (44 ml, 13 mmol) followed by allyltributyl stannane (4.48 g, 14 mmol). The reaction mixture was stirred 48 h at room temperature,

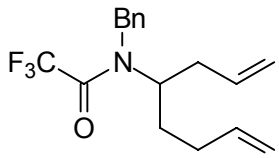
and thereafter was quenched with 1M hydrochloric acid and extracted with hexane/ethyl ether (4/1). Then the pH of the resulting solution was adjusted to pH = 7 with 1M solution of potassium hydroxide and the aqueous phase was again extracted with ether. The last organic layer was dried (K_2CO_3), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on aluminum oxide (eluent: petroleum ether/ethyl acetate; 5:1) to provide **59c** as a brown liquid (0.65 g, 25% from the aldehyde **58**, > 99% by GC area % analysis). – TLC (aluminum oxide plate; petroleum ether/ethyl acetate, 5:1): *R*f = 0.79.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50-1.58 (m, 2 H, CH_2), 2.09-2.29 (m, 4 H, CH_2), 2.62-2.67 (m, 1 H, CH), 3.76 (s, 2 H, aryl-CH_2), 4.92-5.09 (m, 4 H, olefinic-H), 5.73-5.84 (m, 2 H, olefinic-H), 7.20-7.35 (m, 5 H, aryl-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.0, 33.2, 38.3 (3 CH_2), 51.1 (aryl-CH_2), 44.8 (CH), 114.4, 117.2 (2 olefinic-CH_2), 126.8, 128.1, 128.3 (5 aryl-CH), 135.6, 138.8 (2 olefinic-CH), 140.8 (aryl-C).

MS (ESI): *m/z* (%): 216 (100) $[M + H]^+$.

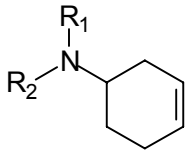
N1-(1-Allyl-4-pentenyl)-N1-benzyl-2,2,2-trifluoracetamide **(59d)**:



A stirred solution of amine **59c** (100 mg, 0.46 mmol) and triethylamine (278 mg, 2.78 mmol) in dichloromethane (2 ml) was cooled to -10°C and treated with trifluoracetic acid anhydride (293 mg, 1.39 mmol) in a dropwise fashion. The reaction mixture was stirred for 10 min, and then allowed to warm up to room temperature and stirred for additional 1½ h. Thereafter the reaction was quenched by addition of phosphate puffer pH 7 (3 ml) and methanol (6 ml) and stirring was continued for 15 min. Most of the solvent was removed under reduced pressure and the residue was extracted three times with ether and the combined extract was washed with a saturated solution of $NaHCO_3$, 1M hydrochloric acid and brine. The combined organic layer was dried (Na_2SO_4), filtered, and evaporated and the crude product was purified by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate; 5:1) to afford **59d** as a colorless liquid (130 mg, 90%, >98% by GC area % analysis). – TLC (petroleum ether/ethyl acetate, 5:1): *R*f = 0.68.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.89 (m, 4 H, CH_2), 2.30-2.33 (m, 2 H, CH_2), 3.58-4.03 (m, 1 H, CH), 4.41-4.72 (m, 2 H, aryl-CH_2), 4.83-5.08 (m, 4 H, olefinic-H), 5.52-5.64 (m, 2 H, olefinic-H), 7.26-7.37 (m, 5 H, aryl-H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.1, 31.6, 31.7, 33.0, 37.1, 39.3, 46.7, 52.5, 58.9, 60.6, 116.3, 116.5, 118.9, 119.7, 128.6, 129.4, 129.7, 129.8, 134.3, 135.7, 136.5, 137.8, 138.1, 138.5, 159.3, 159.6.
MS (EI): *m/z* (%): 311 (M^+), 270 (M^+ - allyl).
- $C_{17}H_{20}F_3NO$ (311.20): calc. C 65.61, H 6.43, N 4.50; found C 65.98, H 6.28, N 4.50.

*General procedure for preparation of cyclohexenylamines **(63a, b, d)** using RCM*:



63a (R_1 = H; R_2 = Cbz)
63b (R_1 = H, R_2 = Boc)
63d (R_1 = Bn, R_2 = F_3CCO)

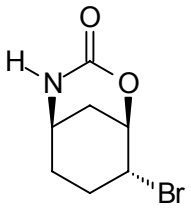
Under inert atmosphere a solution of diene (0.5 mmol) in absolute and degassed dichloromethane (90 ml) and ruthenium carbene **60** (14 mg, 0.015 mmol, 3 mol%), was stirred for 24 h at room temperature. Subsequently, the solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel.

N1-(3-cyclohexenyl)benzylcarbamate **(63a)**: Chromatography (eluent: heptane/ethyl acetate; 7:1) provide **63a** as a white crystals (212 mg, 95%). – TLC (heptane/ethyl acetate, 7:1): *R*f = 0.26. – m.p.: 61-63°C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49-1.59 (m, 2 H, CH_2), 1.86-1.98 (m, 2 H, CH_2), 2.12-2.13 (m, 2 H, CH_2), 2.38 (d, *J* = 15.6 Hz, 1 H, NH), 3.84 (s, 1 H, CH), 5.08 (s, 2 H, aryl-CH_2), 5.58-5.67 (m, 2 H, olefinic-H), 7.29-7.35 (m, 5 H, aryl-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 28.1, 31.9 (3 CH_2), 46.1 (CH), 66.5 (aryl-CH_2), 124.3, 127.1 (2 olefinic-CH), 128.16, 128.21, 128.6 (5 aryl-CH), 136.7 (aryl-C), 158.8 (CO). – IR (KBr): $\tilde{\nu}$ = 3322 cm^{-1}, 1687, 1542. – MS (ESI): *m/z* (%): 254 (100) $[M + Na]^+$. – $C_{14}H_{17}NO_2$ (231.16): calc. C 72.70, H 7.41, N 6.06; found C 72.93, H 7.54, N 6.13.

N1-(3-cyclohexyl)tert-butylcarbamate **(63b)**: Chromatography (eluent: petroleum ether/ethyl acetate; 5:1) provide **63b** as a pale violet crystals (160 mg, 91%). – TLC (petroleum ether/ethyl acetate, 5:1): *R*f = 0.57. – m.p.: 53-55°C. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29-1.60 (m, 2 H, CH_2), 1.44 (s, 9 H, *tert*-butyl), 1.80-1.89 (m, 2 H, CH_2), 2.06-2.18 (m, 2 H, CH_2), 2.37 (dd, *J* = 1.5, 17.2 Hz, 1 H, NH), 3.77 (s, 1 H, CH), 5.56-5.69 (m, 2 H, olefinic-H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (CH_2), 29.4 ($C(\underline{C}H_3)_3$), 33.1, 45.0 (2 CH_2), 47.5 (CH), 81.5 ($\underline{C}(CH_3)_3$), 125.6, 128.1 (2 olefinic-CH), 157.5 (CO). – IR (KBr): $\tilde{\nu}$ = 3315 cm^{-1}, 1676, 1534. – MS (EI): *m/z* (%): 141 (57) [M^+ - $C(CH_3)_3$], 80 (100), 57 (100). – MS (ESI): *m/z* (%): 220 (30) $[M + Na]^+$, 198 (10) $[M + H]^+$. – $C_{11}H_{19}NO_2$ (197.13): calc. C 67.02, H 9.64, N 7.11; found C 66.85, H 9.64, N 6.92.

N1-benzyl-N1-(3-cyclohexenyl)-2,2,2-trifluoracetamide **(63d)**: Chromatography (eluent: petroleum ether/ethyl acetate; 5:1) provide **63d** as a pale yellow oil which solidified on standing (82 mg, 98%). – TLC (petroleum ether/ethyl acetate, 5:1): *R*f = 0.68. – m.p.: 39-40°C (lit.:[68] 41-44°C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67-1.78 (m, 2 H, CH_2), 1.88-2.39 (m, 4 H, CH_2), 4.02-4.21 (m, 1 H, CH), 4.62 (s, 2 H, aryl-CH_2), 5.49-5.65 (m, 2 H, olefinic-H), 7.18-7.36 (m, 5 H, aryl-H). – $C_{15}H_{16}F_3NO$ (283.17): calc. C 63.62, H 5.69, N 4.94; found C 63.39, H 6.02, N 4.91.

8-Bromo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one **(65a)**:



To a cooled to -78°C solution of cyclohexenylamine **63b** (20 mg, 0.10 mmol) in dichloromethane (2 ml) was added at once *N*-bromosuccinimide (22 mg, 0.12 mmol) under inert atmosphere. After 18 h of stirring at this temperature the reaction mixture was allowed to warm up to room temperature. The reaction was controlled by TLC and after complete consumption of the starting material (3 days), the reaction mixture was quenched by addition of saturated aqueous Na_2SO_3. The mixture was diluted with ether, washed with brine and saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to

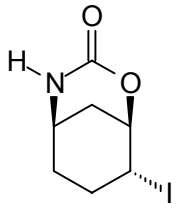
give a pale yellow oil which solidified on standing. Recrystallization from pentane/ether provided **65a** as a white crystals (13 mg, 60%). – m.p.: 157°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (d, *J* = 13.6 Hz, 1 H), 1.92-2.01 (m, 3 H, CH_2), 2.28-2.38 (m, 1 H), 2.53 (dd, *J* = 2.9, 13.8 Hz, 1 H), 3.64 (s, br., 1 H, CHN), 4.46 (s, 1 H, CHBr), 4.64 (s, 1 H, CH-O), 6.04 (s, br., 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 24.7, 26.9 (3 CH_2), 45.2 (CNH), 48.1 (CHBr), 75.4 (C-O), 154.0 (C=O).

MS (ESI): *m/z* (%): 244 (40) $[M + Na]^+$, 221 (98) $[M + H]^+$.

8-Iodo-2-oxa-4-azabicyclo[3.3.1]nonan-3-one **(65b)**:



To a stirred suspension of cyclohexenylamine **63b** (20 mg, 0.10 mmol), potassium carbonate (28 mg, 0.20 mmol) in anhydrous diethyl ether (3 ml) was added at once iodine (52 mg, 0.20 mmol) at room temperature. The reaction was controlled by TLC and after complete consumption of the starting material (3 days) ethyl acetate (10 ml) and saturated aqueous Na_2SO_3 (10 ml) was added. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and the solvent was evaporated *in vacuo*. Flash column chromatography (eluent: ethyl acetate/ethanol; 10:1) afford **65b** as a pale yellow crystals (20 mg, 74%). – TLC (ethyl acetate/ethanol, 10:1): *R*f = 0.46. – m.p.: 158-162°C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65-1.80 (m, 1 H), 1.92-2.05 (m, 3 H, CH_2), 2.18-2.30 (m, 1 H), 2.67 (d, *J* = 12.0 Hz, 1 H), 3.62 (s, br., 1 H, CHN), 4.69 (s, 1 H, CHI), 4.62 (s, 1 H, CH-O), 6.48 (s, br., 1 H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 27.3, 28.6 (3 CH_2), 28.7 (CHI), 46.2 (CNH), 77.8 (C-O), 155.7 (C=O).

IR (KBr): $\tilde{\nu}$ = 3232 cm^{-1}, 3114, 2942, 1732.

MS (ESI): *m/z* (%): 290 (100) $[M + Na]^+$, 268 (45) $[M + H]^+$.

- $C_7H_{10}INO_2$ (266.99): calc. C 31.48, H 3.77, N 5.24; found C 31.62, H 4.07, N 4.96.

9 Literature

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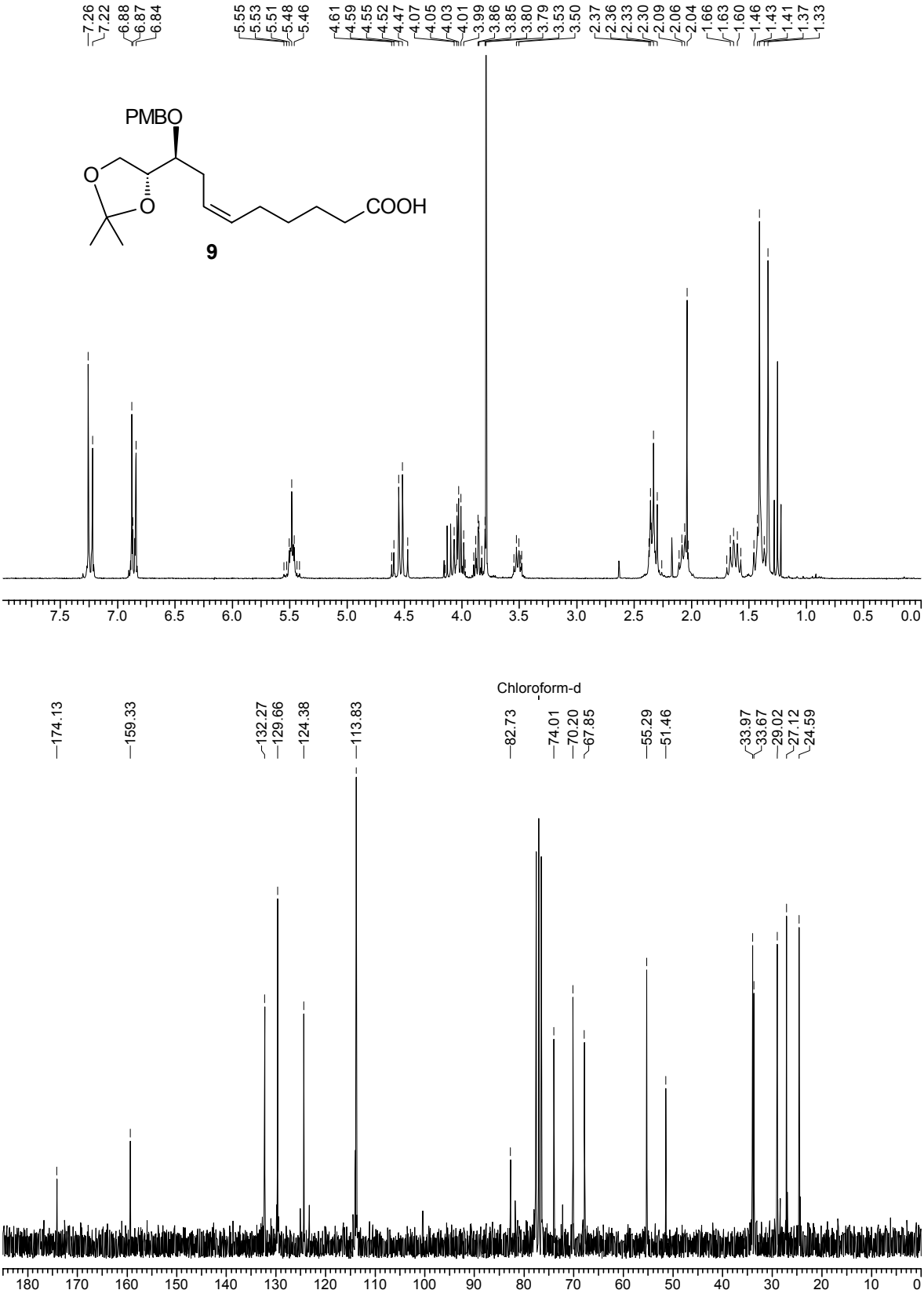
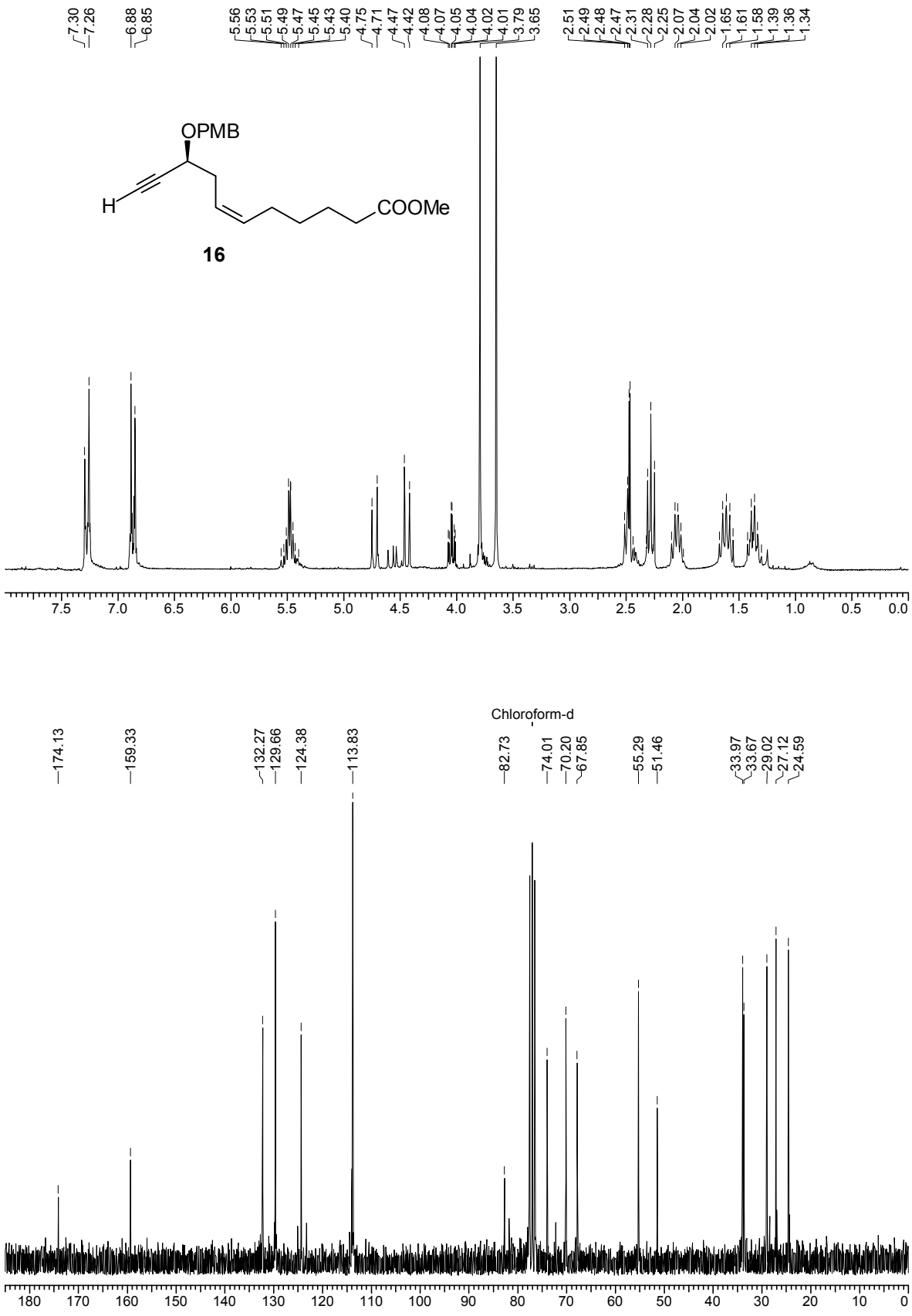
10 Appendix



^{1}H- and ^{13}C-NMR spectra of compound **9**.



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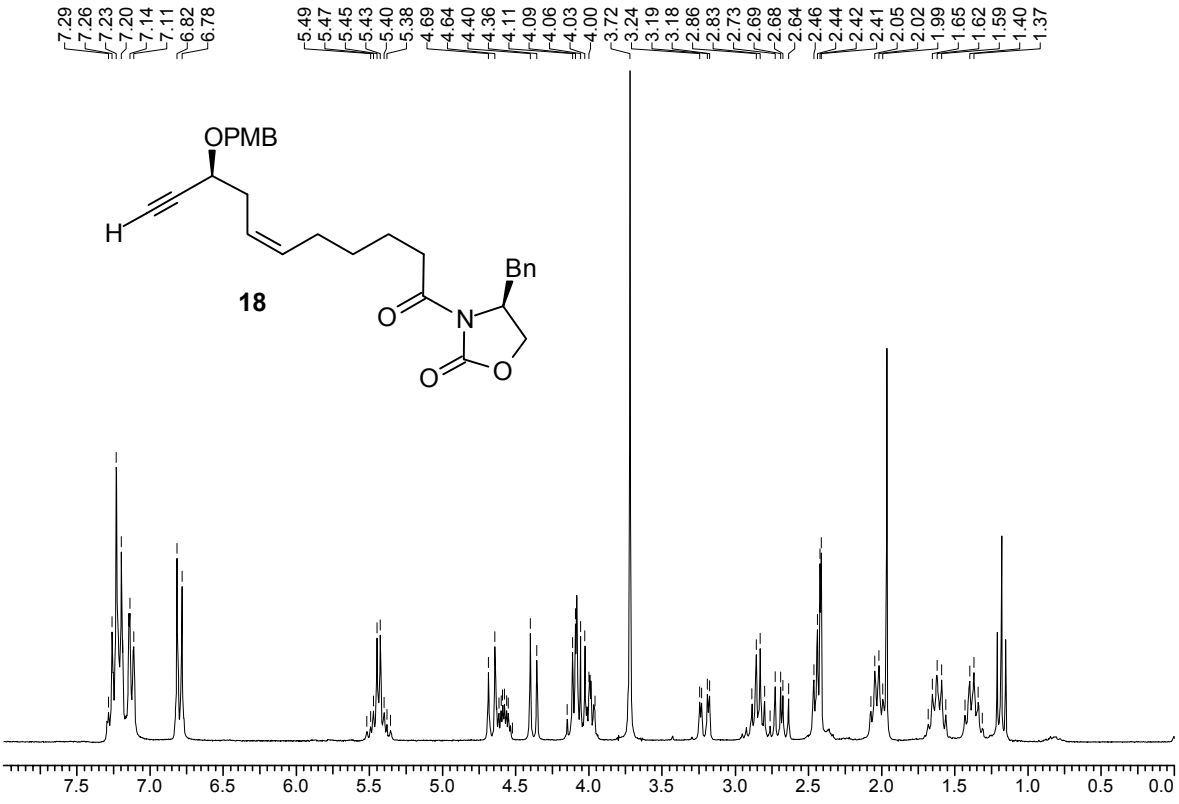

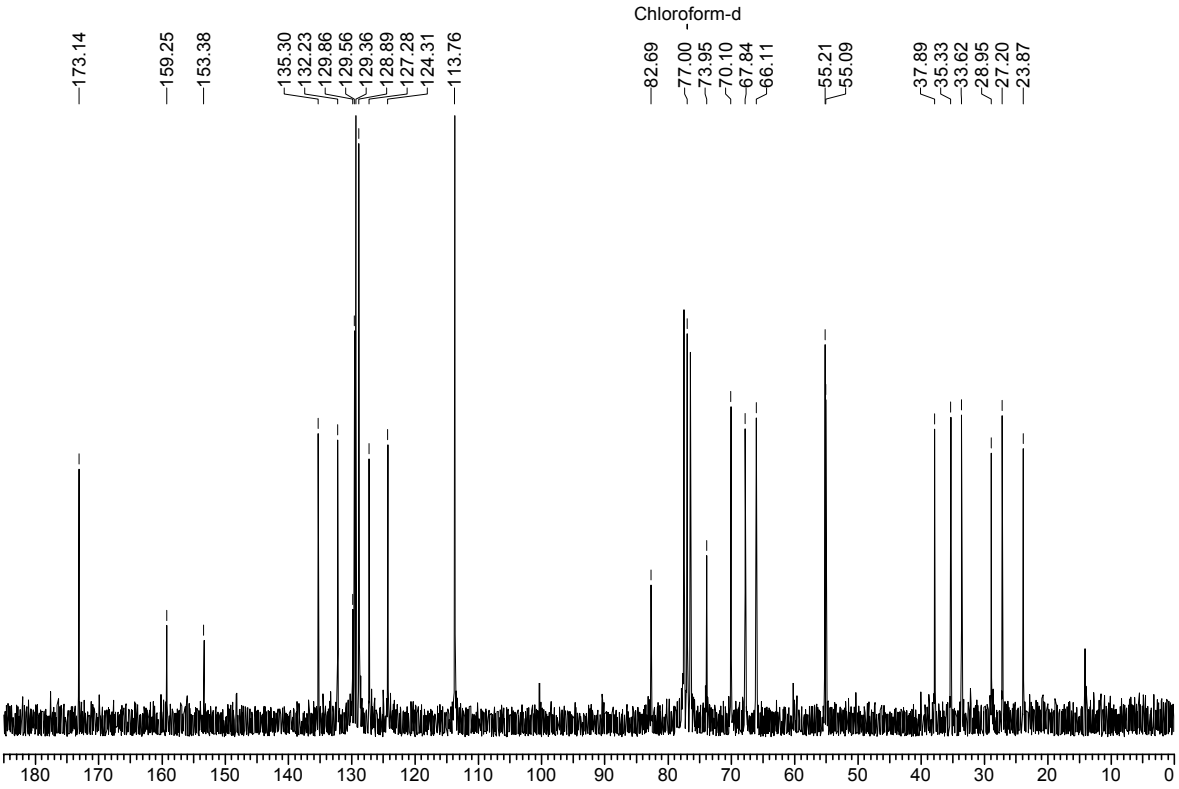

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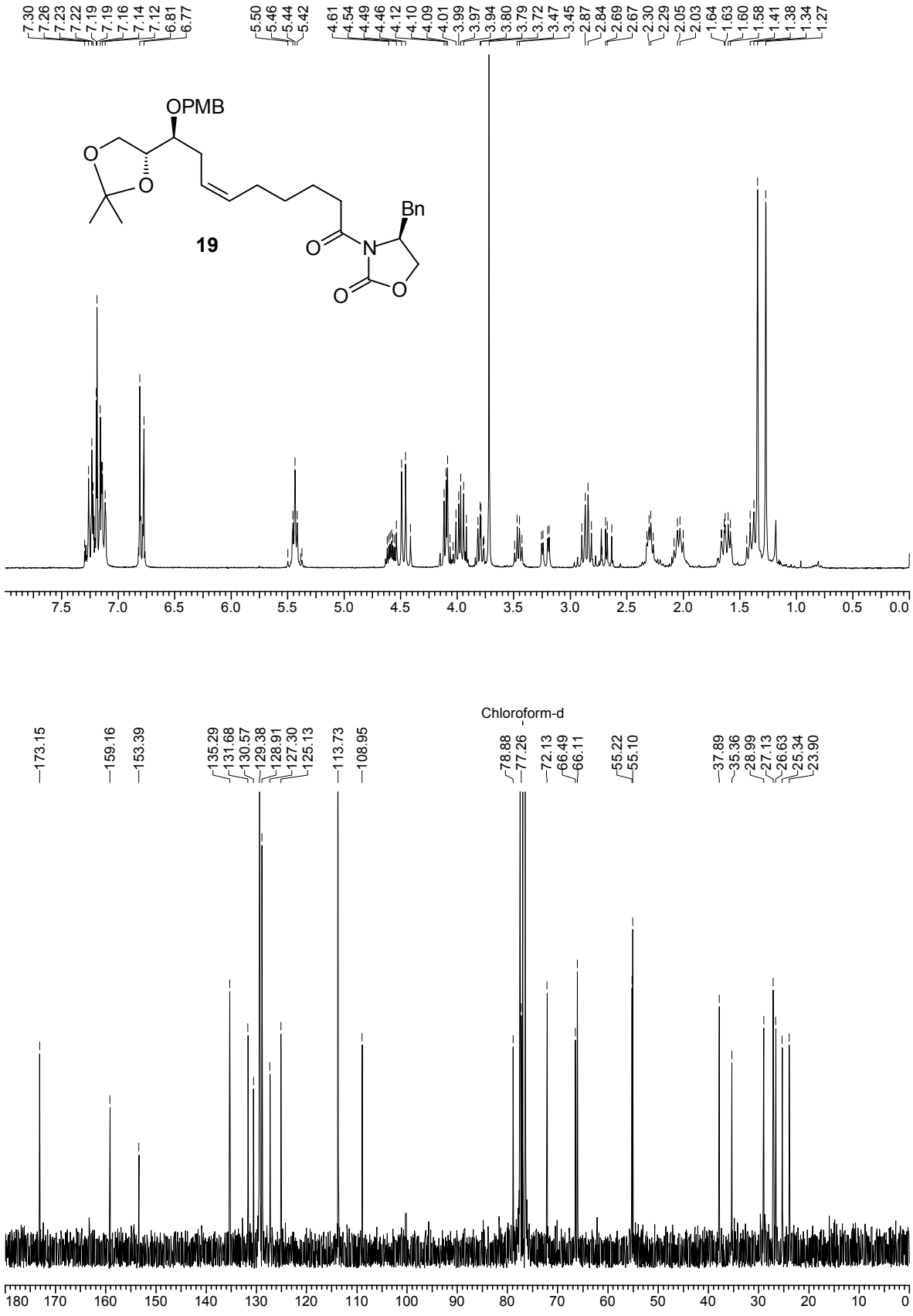
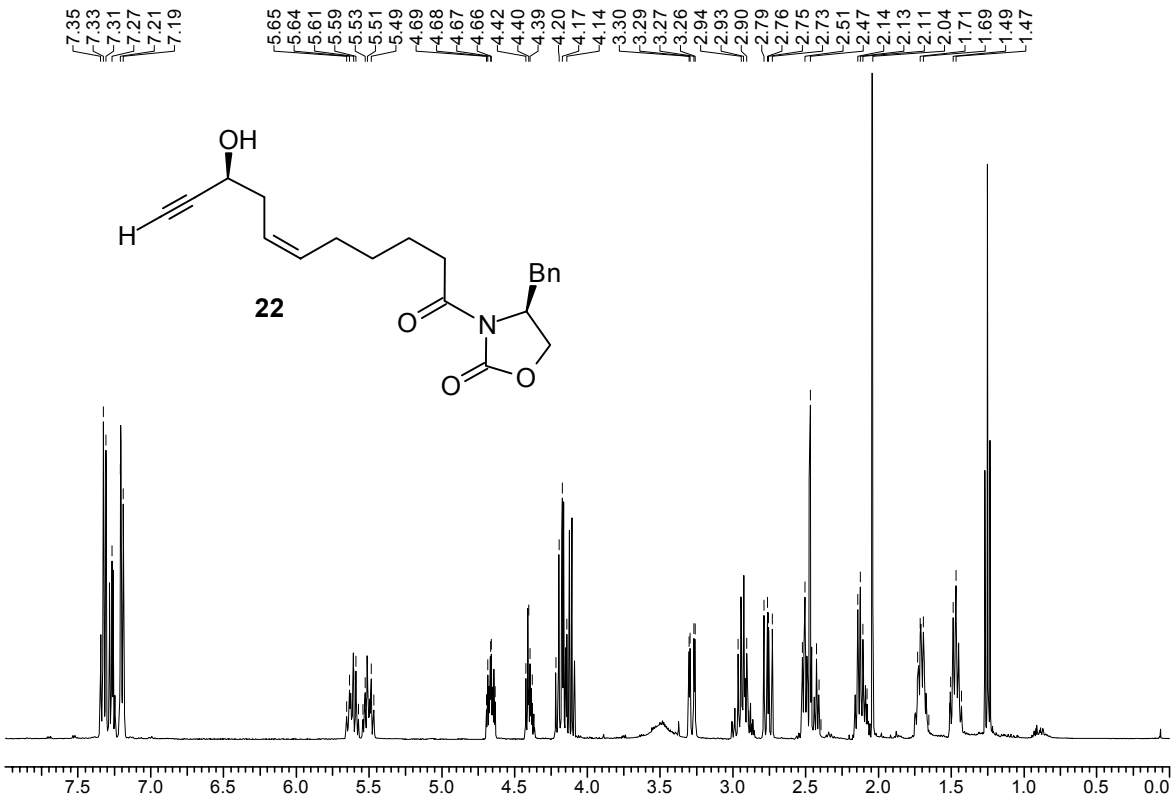
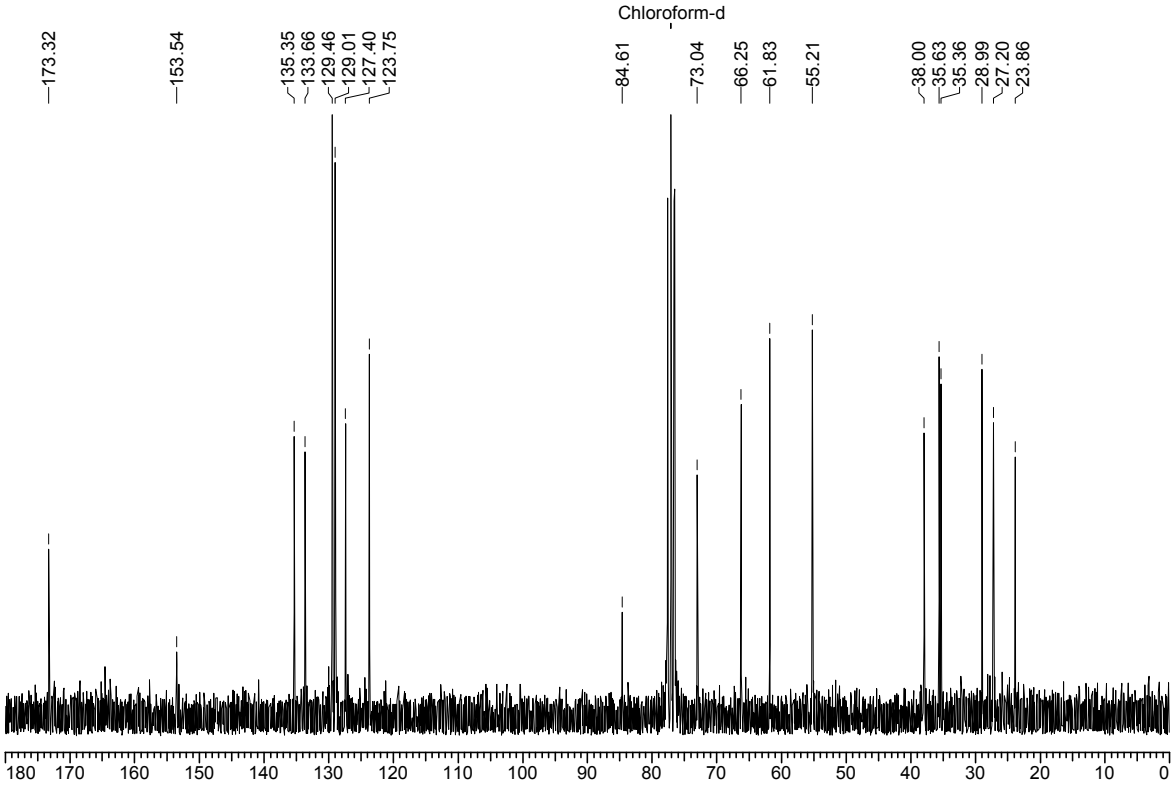
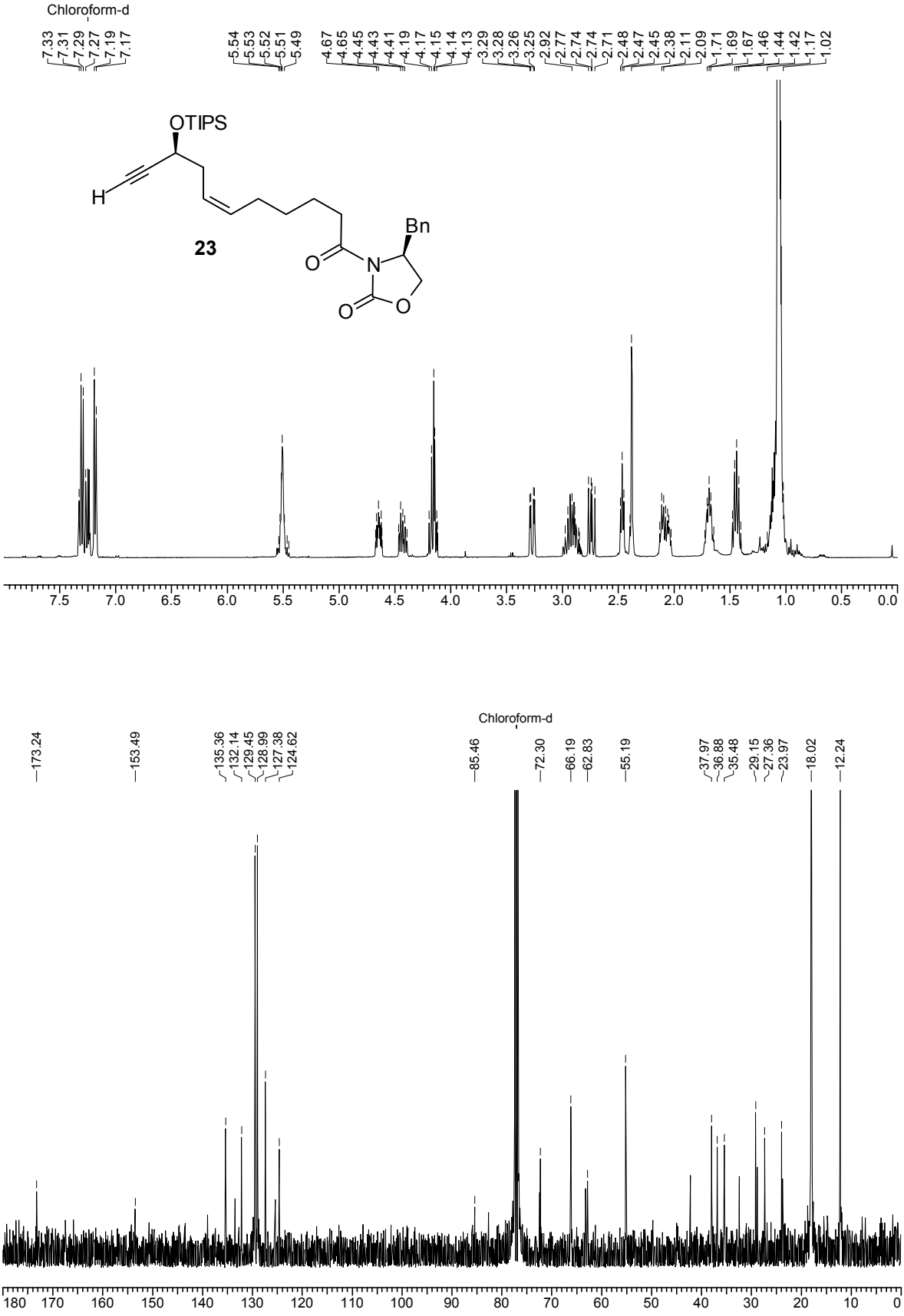


^{1}H- and ^{13}C-NMR spectra of compound **19**.





^{1}H- and ^{13}C-NMR spectra of compound **22**.



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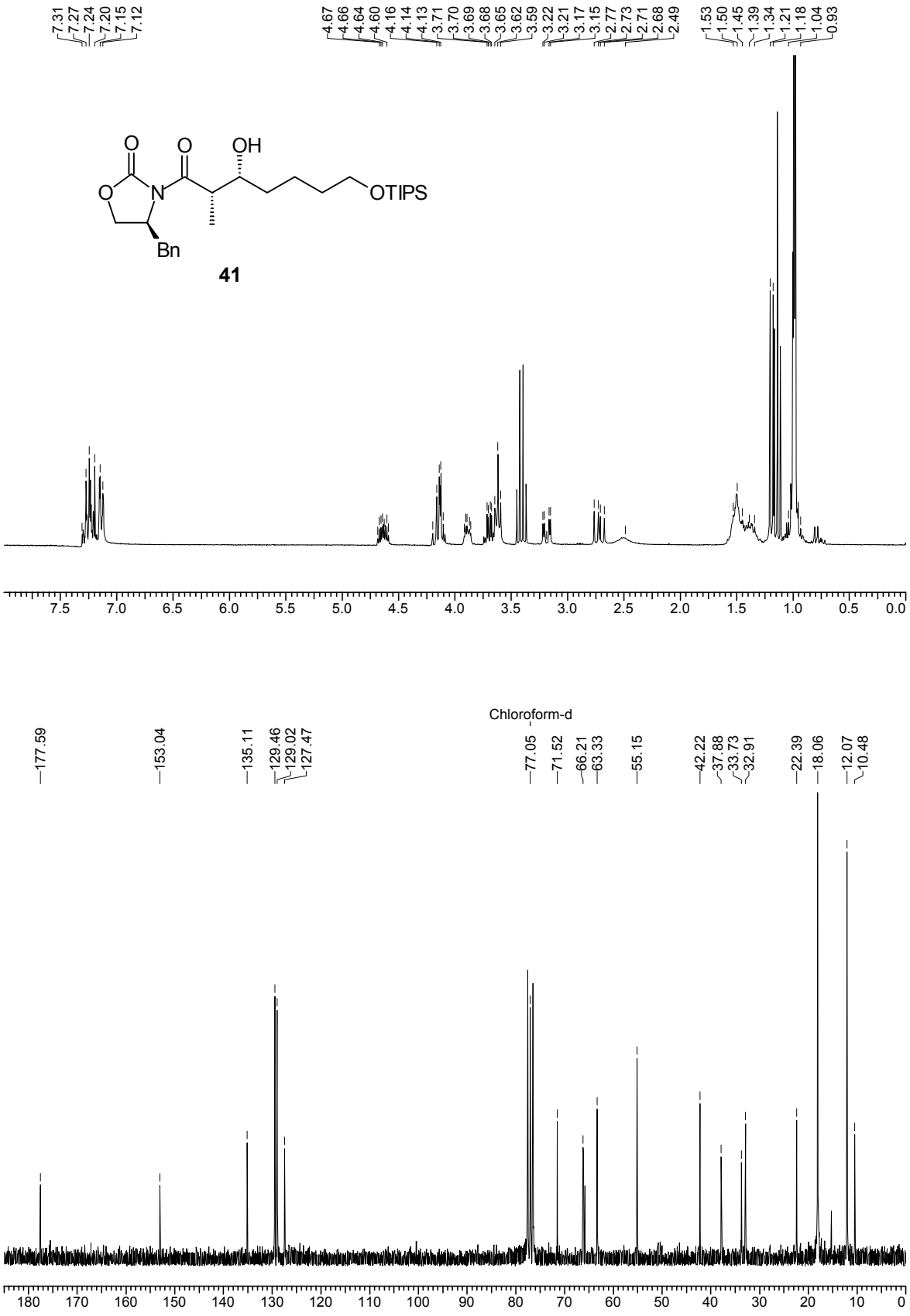

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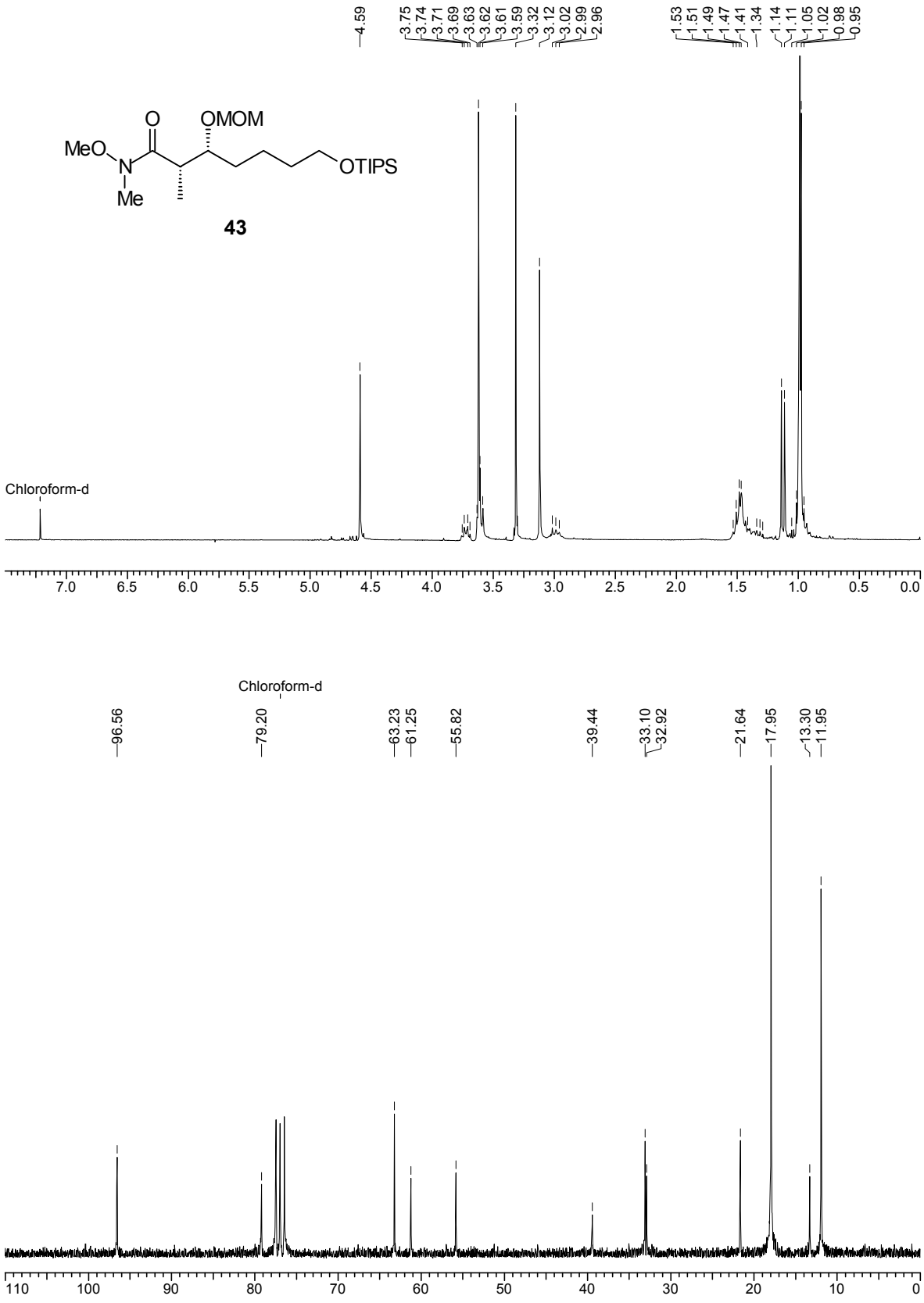

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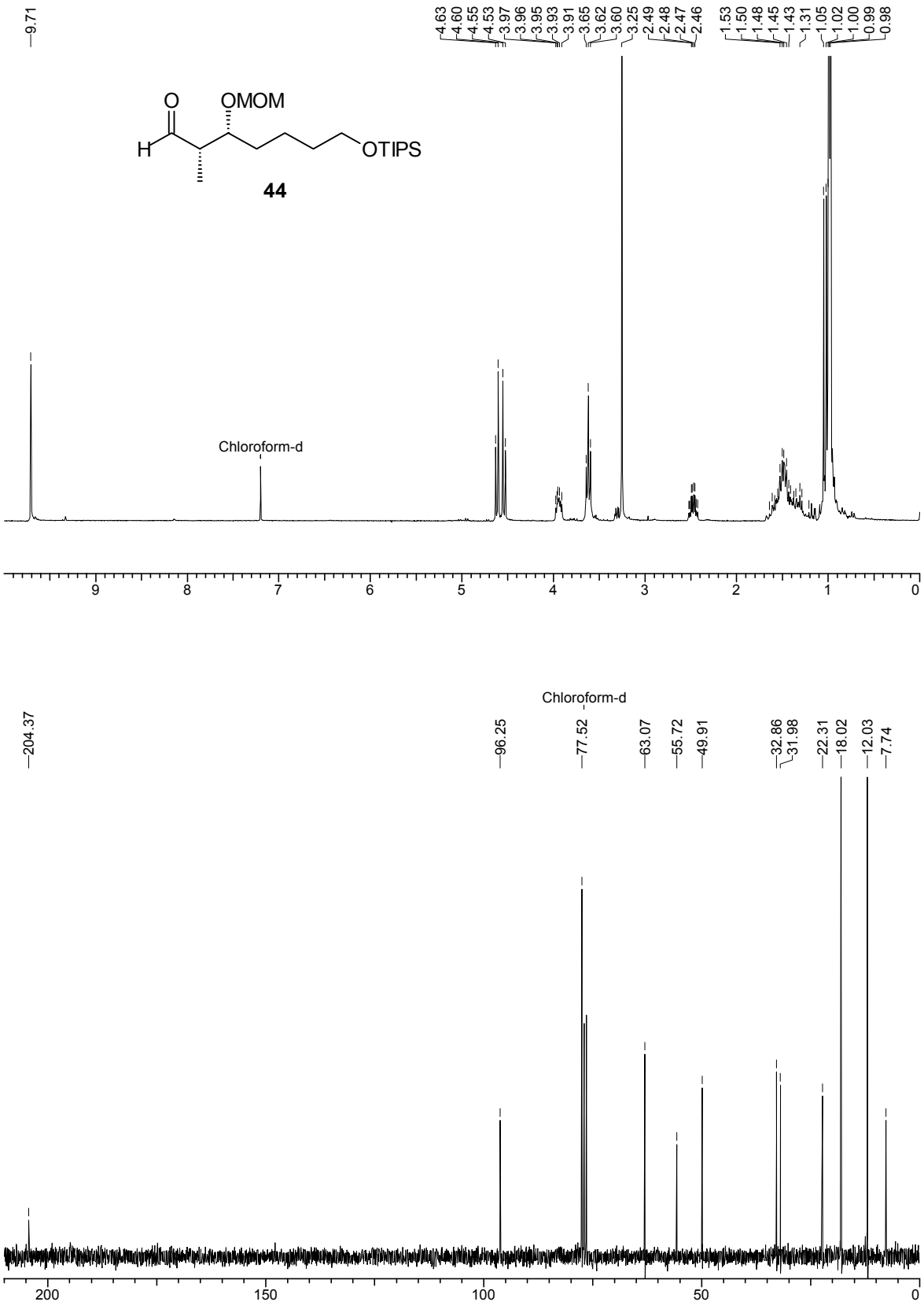

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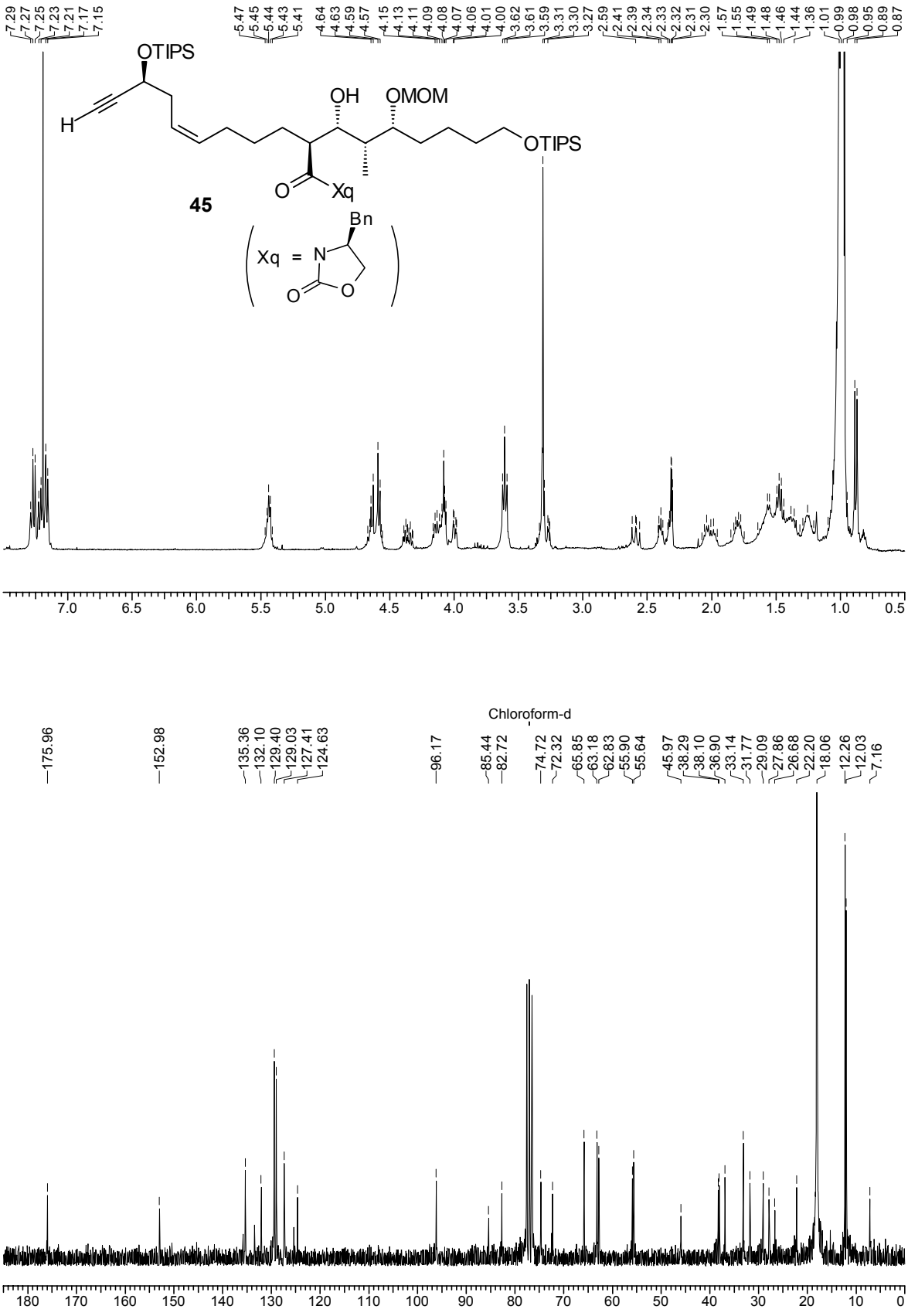
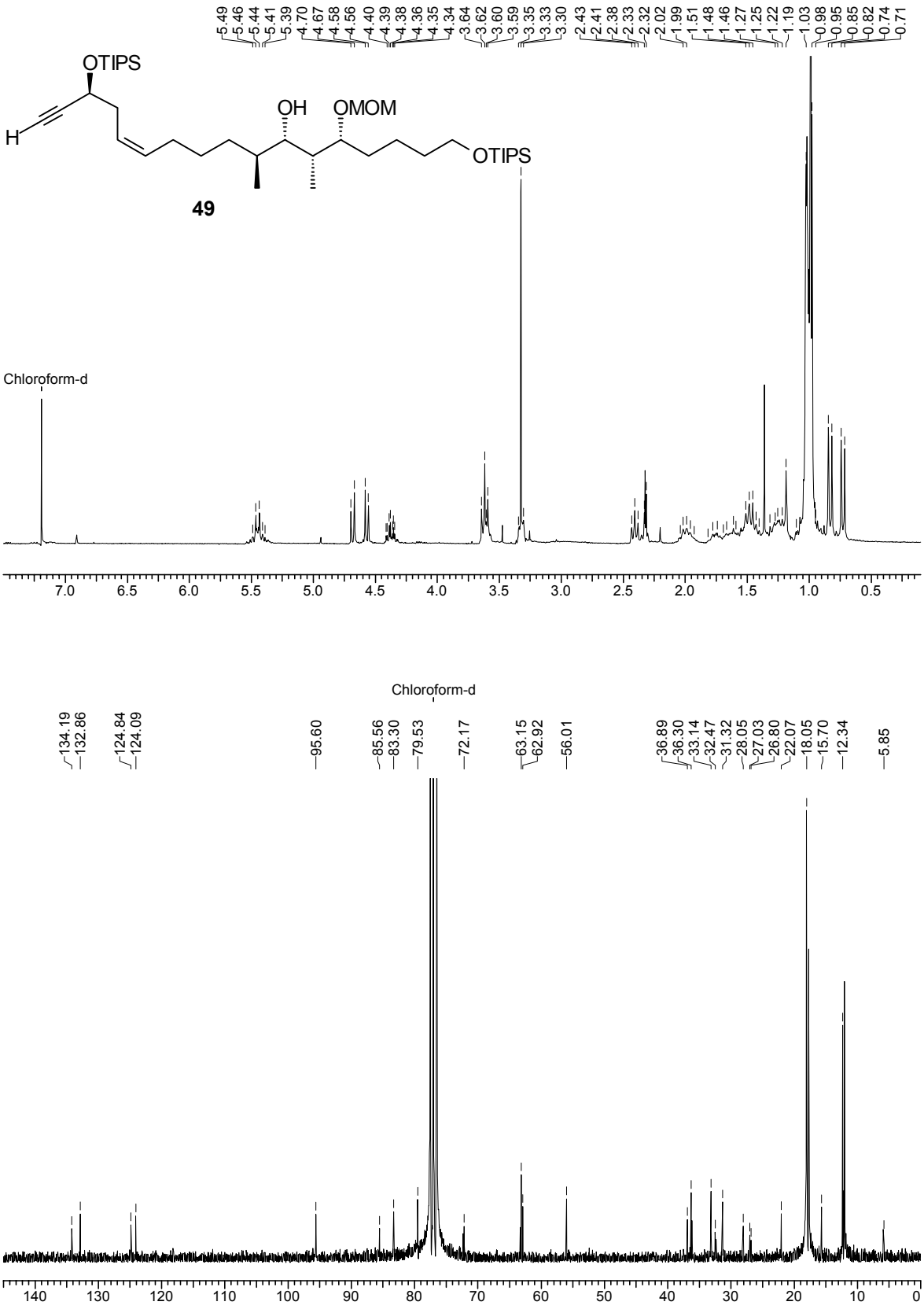
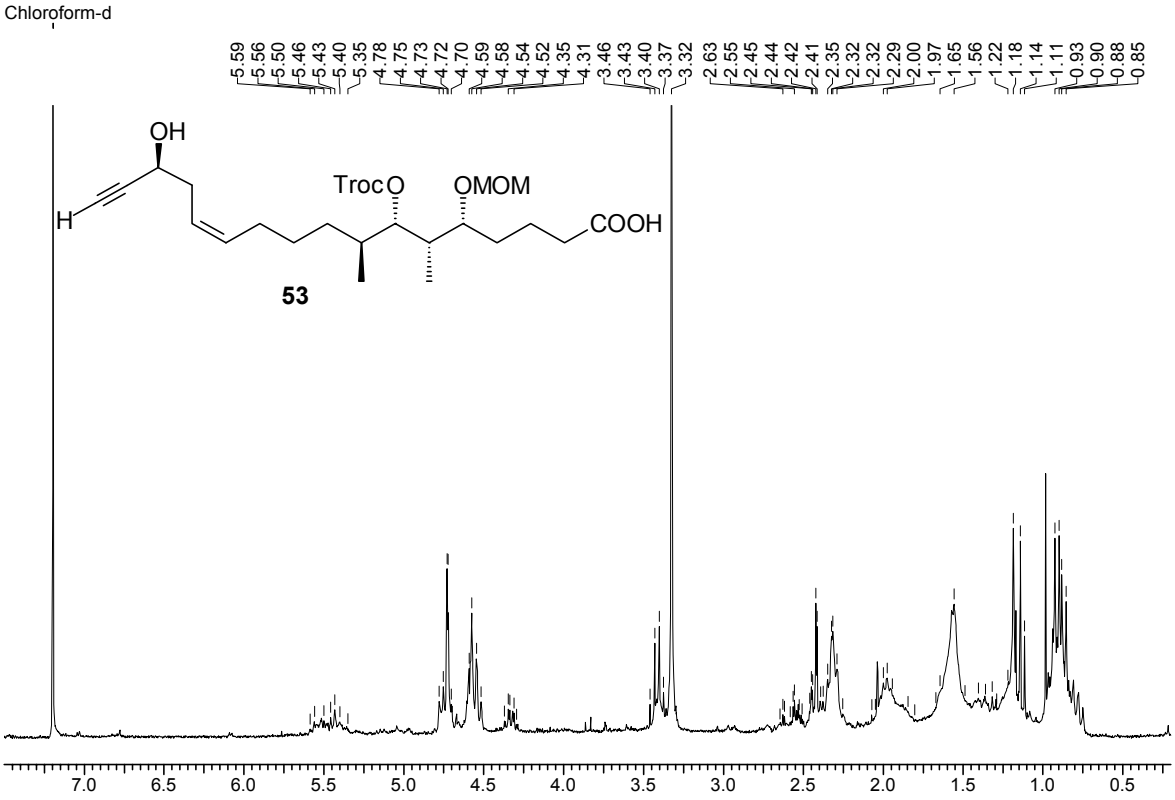
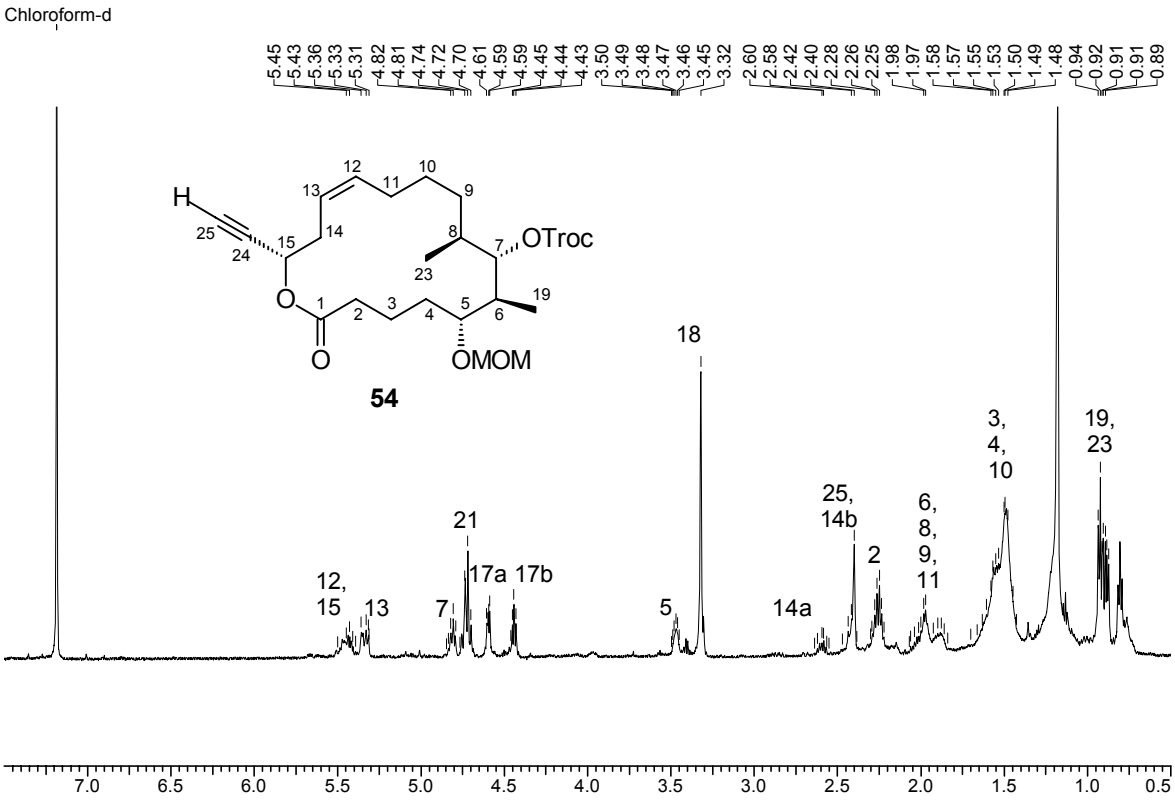


^{1}H- and ^{13}C-NMR spectra of compound **45**.



^{1}H- and ^{13}C-NMR spectra of compound **49**.





^{1}H-NMR spectra of compounds **53** and **54**.

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