Total Synthesis Of 8,9-Dehydro-Epothilone C

Total Synthese von 8,9-Dehydro-Epothilon C

Dissertation

zur Erlangung des akademischen Grades

doctor rerum naturalium
(Dr. rer. nat.)

von M.Sc. Noviandi Meta Adityawarman

geboren am 19.11.1979 in Jakarta, Indonesien

genehmight durch die Fakultät für Verfahrens-und Systemtechnik
der Otto-von-Guericke Universität Magdeburg

Gutachter: Prof. Dr. Dieter Schinzer
Junior-Prof. Edgar Haak

eingericht am: 09.04.2010

Promotionskolloquium am: 31.05.2010

Total Synthesis Of 8,9-Dehydro-Epothilone C

Total Synthese von 8,9-Dehydro-Epothilon C

DISSERTATION

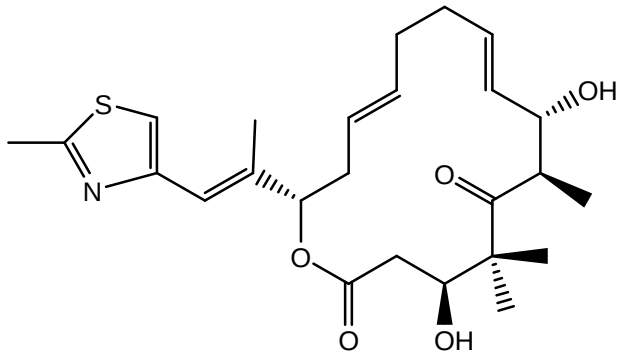
Der Fakultät für Verfahrens- und Systemtechnik
der Otto-von-Guericke-Universität Magdeburg
zur Erlangung des akademischen Grades

doctor rerum naturalium
(Dr. rer. nat.)

2010

Von Noviandi Meta Adityawarman
Aus Indonesien

ABSTRAKT / ABSTRACT:



98

The total synthesis of 8,9-dehydro-epothilone C (**98)** is reported. Compound **98** has been prepared employing a convergent strategy that is based on the consecutive assembly of building blocks **41**, **58**, and **88** into diene **95** and subsequent RCM-mediated macrocycle formation. The aldol reaction between aldehyde **88** and ketone **58** delivered the required 6*R*, 7*S* diastereoisomer **89** with moderate selectivity. RCM with diene **95** was highly *E* selective giving efficient access to 8,9-dehydro epothilone C (**98**).

Innerhalb des Projekts gelang die Totalsynthese von 8,9-dehydro-epothilon C. Die im rahmen des Projekts synthesierte Verbindung kommt in der natur nicht vor, besitz jedoch auf Grund der Doppelbindung in 8,9 eine Vorzugkonformation für tubulin, so dass von einer interesanten biologischen Wirkung ausgegangen werden kann. Für die Synthese waren die Schlüsselbausteine **41**, **58**, und **88** erforderlich. Die bildung eines einzigen 6*R*,7*S*-Diastereoisomers bei der Aldol-kondensation des Ethylketone **58** mit dem Aldehyde **88** erhalten wurden. Ringschluß durch Olefin-Metathese führten dann zu den 8,9-dehydro-epothilon C (**98**).

This doctoral thesis was carried out from April 2005 until January 2010 at the Otto-Von-Guericke Universität Magdeburg under guidance of Professor Dr. Dieter Schinzer.

First of all, I would like to thank Professor Dr. Dieter Schinzer for the interesting and challenging projects of my doctoral thesis, and his confidence towards me.

Further, I would like to thank Dr. Andrew Goss for reviewing my doctoral thesis.

For various measurements I would like to thank Frau Dr. S. Busse, Frau Dr. Liane Hilfert, Fraus S.Preiß and Frau Ines Sauer. Also I would like to thank my colleges from the working group of Professor Dr. Dieter Schinzer especially Frau Nadya Dimitrova, Hernn Jörg Moritz, Herrn Lars Michaelis, Hernn Mario Walter, Herrn Zahid Iqbal and Herrn Kumeneger Belayneh for good collaboration, interesting discussions, and suggestions in all chemical questions.

Last but not least, I would like to thank to Herrn Dr. Muharram Pasma for teaching preparative organic synthesis, my parents and my family in law for their constant and loving support which I have obtained during my study and my doctoral thesis, although they are leaving far away from me, and my wife Astrid Wiriadidjaja, M.Sc for her permanent help, love and understanding.

Abbreviations

Ar	Aryl
Ac	Acetyl
AIBN	2,2’-azobisisobutyronitrile
arom	Aromatic
aq.	Aqueous
AcOH	Ethyl Acetate
9-BBN	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
tBu	tert-butyl
tBuOH	tert-butyl alcohol
CAN	Ceric ammonium nitrate
calcd.	Calculate
Cbz	Benzyloxycarbonyl
CH_3CN	Acetonitrile
COSY	Corelated spectroscopy
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

DMAP	Dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EI	Electron-impact
Eqv	Equivalent
ESI	Electrospray ionization
Et_2O	Diethyl ether
EtOH	Ethanol
FAB	Fast-atom bombardment
FD	Field-desorption
FT-ICR	Fourier transforms ion cyclotron resonance
GC	Gass chromatography
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
Me	Methyl
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
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
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulphonate
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”
pTsOH	para-toluenesulfonic acid
UV	Ultraviolet

Contents

To My Beloved Wife
For the permanent help, love
und understanding

Chapter 1

Introduction

1.1. Background

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 Europe and USA it is the second leading cause of death, after the cardiovascular disease.[1] According to studies from the American Cancer Society (ACS) in 1997 in the USA alone around 560.000 people died of different cancers: that is more than 1.500 people a day, averaging approximately one death per minute.[2] These fearful facts motivated many interdisciplinary research groups around the world to investigate, and produce drugs against these diseases. More often the quantity of biologically active products obtained from natural sources are insufficient, that’s why the main task of the synthetic chemists is to develop and to optimize convergent total syntheses with maximum yields, high stereoselectivity in the fewest possible reaction steps.

A major share of the anticancer drug market is commanded by the complex diterpene taxol® (paclitaxel), whose discovery from the Pacific Yew Tree in 1971 and the culmination of years of research into a billion dollar drug today represents a remarkable story. Developed and sold by Bristol-Myers Squibb in the 1990s, taxol® is currently available in more than 60 countries. It is mainly used for the treatment of a variety of solid tumors commonly encountered e.g ovarian and breast cancers.[3,4] The success story of taxol demonstrated once again the wealth of mother nature in terms of biologically active molecules as cures for disease.[5,6] These stories will certainly not be the last: in the late 1980s, a new tale of cytotoxic natural products began to unfold. The epothilones A and B (see figure 1) were discovered by Höfle, Reichenbach, and their coworkers at the Gesellschaft für Biotechnologische Forschung (GBF) in Germany.[7]

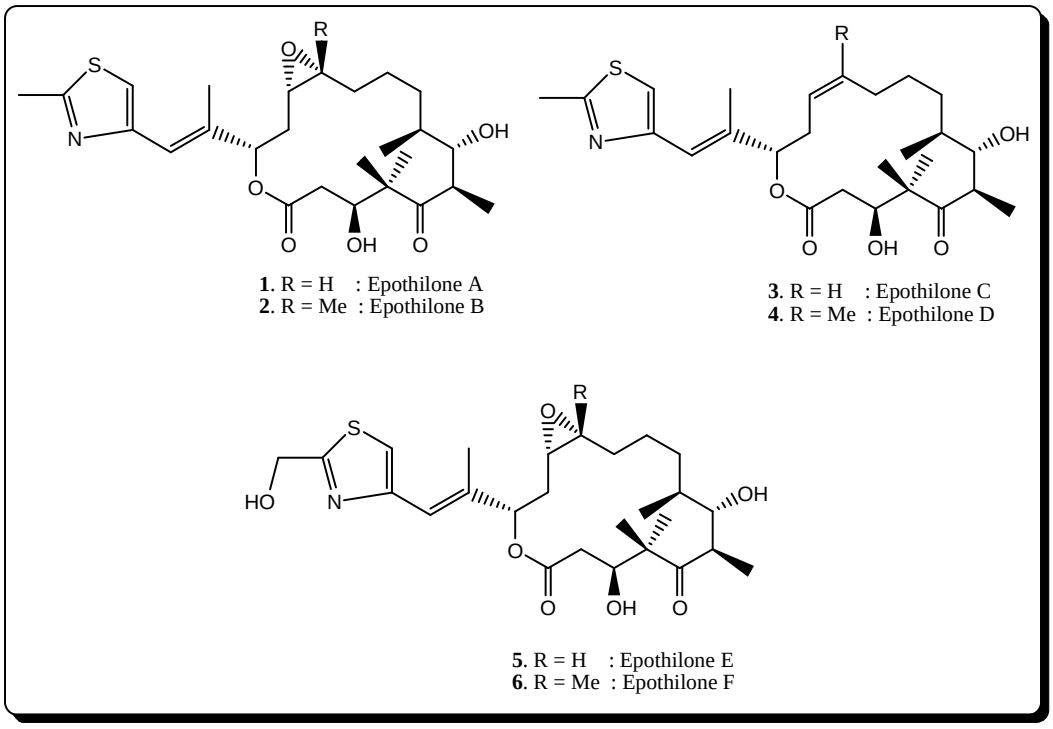


Figure 1. Structures of The Naturally Occurring Epothilones.

The structural modification and biological investigation of the epothilone became a very interesting synthetic target for many scientists all over the world due to the fact that they extremely possess a high activity against certain cancertypes, [8] as well as the advantages compared to the billion dollar anticancer drug Taxol® in terms of potency and effectiveness against drug-resistant tumor cells of the epothilone and their complexity in terms of synthesis. Currently the epothilones and their analogues appeared as one of the most promising candidates for cancer chemotherapy.

Several research group started efforts on the total synthesis of epothilones which dominated with Danishefsky, Nicolau and Schinzer publishing their synthesis a few weeks apart.[9] An improved route for the totalsynthesis of the epothilones was further investigated by Schinzer *et al*.: the retrosynthetic analysis showed that aldol reactions play an important role in the stereoselective synthesis of the epothilones.

1.2. Epothilone and Their Biological Activity

The epothilones A and B (see figure 1) were discovered in the late 1980s, by Höfle, Reichenbach, and their coworkers at the Gesellschaft für Biotechnologische Forschung (GBF) in Braunschweig, Germany.[7] 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 (see figure 2). Although the gross structures of the epothilones were revealed in the original German patent by Höfle *et al*. in the early 1990´s [10] and by the Merck group in 1995,[11] it was not until July 1996 that the absolute stereochemistry of the epothilones A and B was reported by the GBF scientist. [11] The structural assignments were made on the basis of spectroscopic[12,13] and X-ray crystallographic data,[12] and the compounds were named epothilone after their structural subunits, epoxide, thiazole and ketone.

The epothilone possess both *in vitro* and *in vivo*, a remarkable antifungal effect against Oomyceten, e.g. Phytophtora infestans, the causative agents of the dreaded potato-blight disease. But the antifungal activity was coupled with substantial plant toxicity, so that further studies were stopped. Soon it was discovered that the compounds also had powerful activities against mouse fibroblast and leukemia cells and strong immunosuppressive action as revealed by their cytotoxicity against human T-cells. It was not until 1995, when a team from Merck in the USA reported their findings on the mode of action of epothilone, that interest in these compounds resurfaced again, this time with much more excitement and momentum. 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.

Further investigation of compounds showing homology to the epothilones, such as the 16-mebered macrocyclic substances like podophyllotoxine, chalcomycin and vinblastine, revealed no active compounds. The uniqueness of the epothilones immedietly placed them in the same class as taxol, whose tubulin-binding mechanism of action was discovered by Horwitz in 1979. The Merck group compared the effects of the epothilones and taxol on tubulin and microtubules and reported higher potencies for both epothilones A and B as tubulin polymerization agents (epothilone B > epothilone A > taxol).

Most significantly, all three compounds were shown to compete for the same binding site within their target protein.[12,14] Furthermore, the epothilones were found to exhibit similar kinetics of taxol in their induction of tubulin polymerization, and gave rise to microscopic pictures of stabilized microtubules and damaged cells.[12] Perhaps the most exciting property of the epothilones is their superiority compared to taxol® as a chemotherapeutic agent, particularly MDR cell lines, including those resistant to taxol. In some of the cytotoxicity experiments, epothilone B demonstrated a 2000 ± 5000-fold higher potency than taxol, a striking enough observation to awaken and stimulate the interest of many in the academic community and the pharmaceutical industry.

(a) (b)

Figure 2. (a). Myxobacterium *Sorangium cellulosum* (Epothilone)
(b). *Taxus Breviola* (Taxol®)

1.3. Structure and Activity Relations of Epothilones

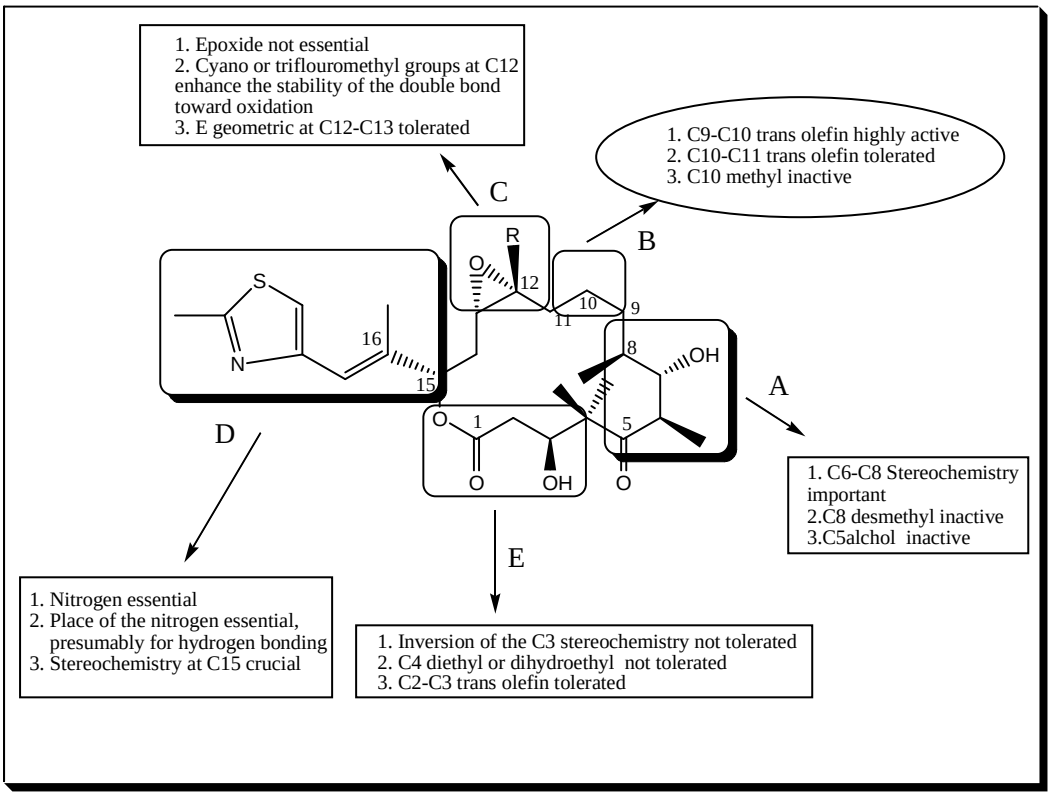


Figure 3. Structure- Activity Relationship of The Epothilones

The structure-activity relationship (SAR) of the epothilones has been extensively studied. [15-19] Since the first synthesis of epothilone in 1996, hundreds of analogues have been reported and tested. [20] Figure 3 represents epothilone, divided in five regions A-E, in order to simplify the SAR discussion.

Region A (C5-C8) is highly sensitive to any kind of modification: epimerization at C8 [21] or addition/removal of the methyl group at C8 [21] will considerably lower the cytotoxicity. Removal of C6 or C7 substituents or reduction of the ketone at C5 also leads to loss of biological activity. The sensitivity of region A suggests that it plays an important role in the binding to the active site. [22]

Region B (C9-C11) is also important as region A which is highly sensitive to any kind of modification: the C10-methyl analogue was found to be inactive [23], but hydroxyl [24] and fluoro [25] groups are tolerated at C11. Except in the case of the 18-membered ring analogue of epothilone A (which led to significant tubulin polymerization [26]), change in the ring size results in considerable loss of biological activity. [26] The C10-C11 olefin analogue, also known as epothilone 490 (Figure 4), gives very promising results *in vitro* but has disappointing results *in vivo*, due to the hydrolysis of the lactone. [27] Recently, Danishefsky *et al*. reported a C9-C10 *trans* analogue of epothilone D, which was nearly three times as active as the parent compound. This can be rationalized by the impact of the *trans* double bond on the polypropionate region.

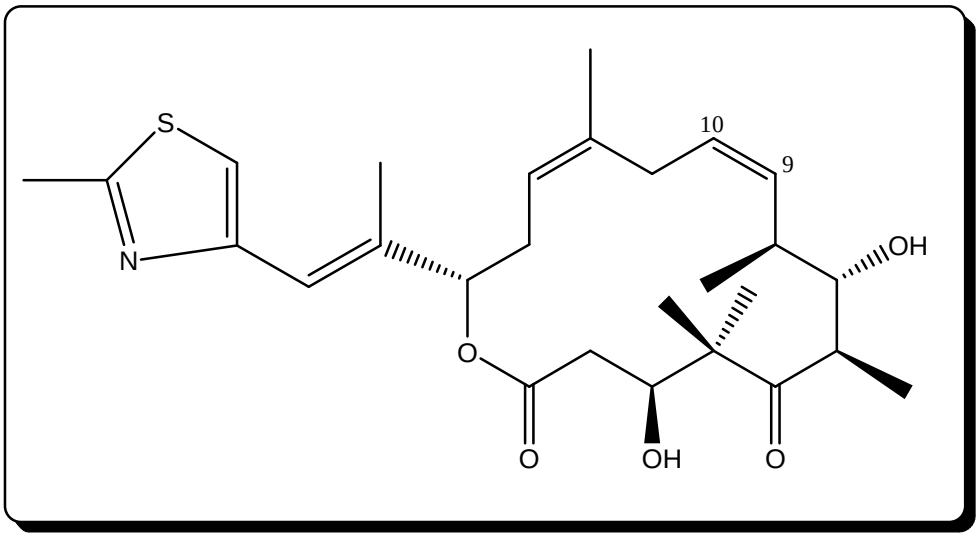


Figure 4. Epothilone **490**

In contrast, changes in Region C (C12-C14) are well tolerated: both epoxide and olefin analogues are active [27, 28]. However, epothilone A and B (C12-C13 epoxide) are about four to 20 times more active than the corresponding olefinic compounds (epothilone C and D). However, Nicolaou et al reported a variety of active cyclopropane (both cis and trans) and cyclobutane analogues [29-31], proving that the hydrogen bond between the epoxide and the C3 hydroxyl is not crucial for activity, thus the role of the epoxide is mainly conformational.

The side chain (Region D) is revealing less tolerance than region C analogues. The direct attachment of the aromatic moiety at C15, or replacement of the methyl group at C20 with bulkier substituents, results in the loss of cytotoxicity. Furthermore, the replacement of the C16 methyl group with an ethyl group, and replacement of the thiazole ring turned out to have negative effects. In particular, a methylsulfanyl replacement for the methyl group on the thiazole moiety (Figure 5) enhances the potency compare to the natural epothilone.[31,33] Recently, Nicolaou [30] reported a 12,13-*cis* cyclopropane methylsulfanyl analogue of epothilone B (Figure 6), that is six times more active than epoB against the 1A9 ovarian carcinoma cells. Finally, change of the C15 stereochemistry leads to loss of the biological activity. [32]

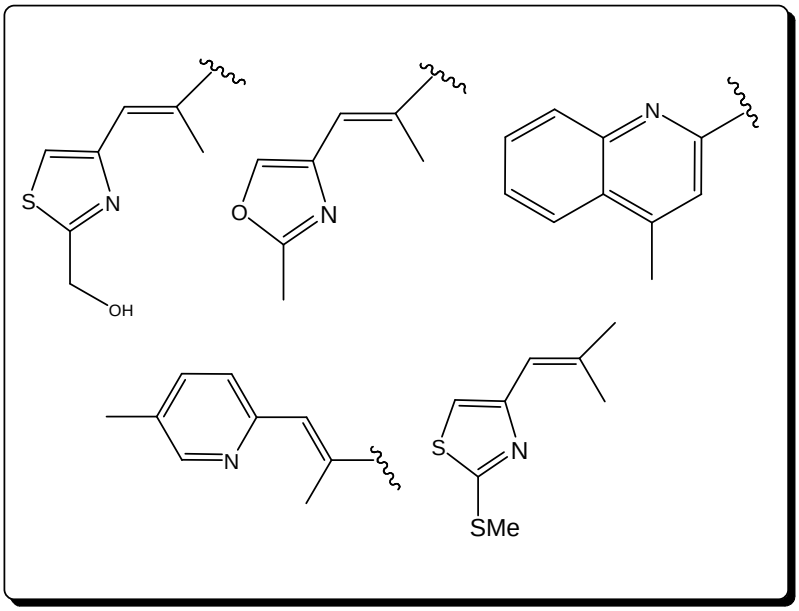


Figure 5. Side Chain Modifications with the Nitrogen at the Same Position as The Natural Product

Region E (O16-C4) hardly tolerates any changes. Indeed, inversion of the C3 stereochemistry [21] or substitution of the gem dimethyl group at C4 by a cyclopropane [34] both resulted in significant loss of activity. Moreover, the presence of an *E*-olefin at C2-C3, which is believed to rigidify the C1-C3 backbone, considerably reduces the biological activity.

It has been proposed that a hydrogen bond between the C3 hydroxyl and C1 ketone plays an important role from a conformational point of view. [19]

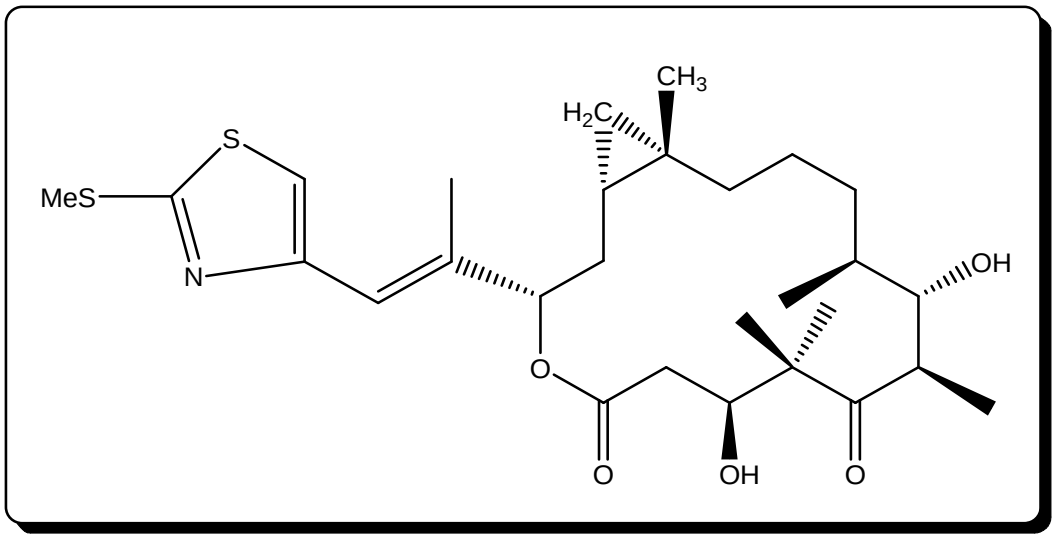


Figure 6. 12,13- *cis* Cyclopropane Methylsulfanyl EpoB

However, when the C3 hydroxyl is replaced by a cyano group [35], the analogues are active in both tubulin polymerization and cytotoxicity assays. Thus, the hydrogen bond, if present, is not crucial for cytotoxicity. Lactam analogues usually have clearly inferior tubulin polymerizing and cytotoxic potencies than the corresponding lactone. One important exception is 15-(*S*)-aza-epoB (Figure 7), which has comparable properties to Taxol® in both assays[36] and has been launched to clinical trials.[37] In fall of 2007 the FDA (Food and Drug Administration) released it to the market. BMS (Bristol Meyer Squibb) is selling it as Ixempra® against breast cancer and this is the first epothilone on the market. The lactam seems to be more stable than the lactone toward metabolic cleavage.

Several other epothilones are in late clinical trials at the moment. Novartis has just finished phase III clinical trials with epothilone B (Patupilone®) and Bayer Schering Pharma has placed ZK-Epo (Sagopilone®), a fully synthetic epothilone, in phase II clinical trials.

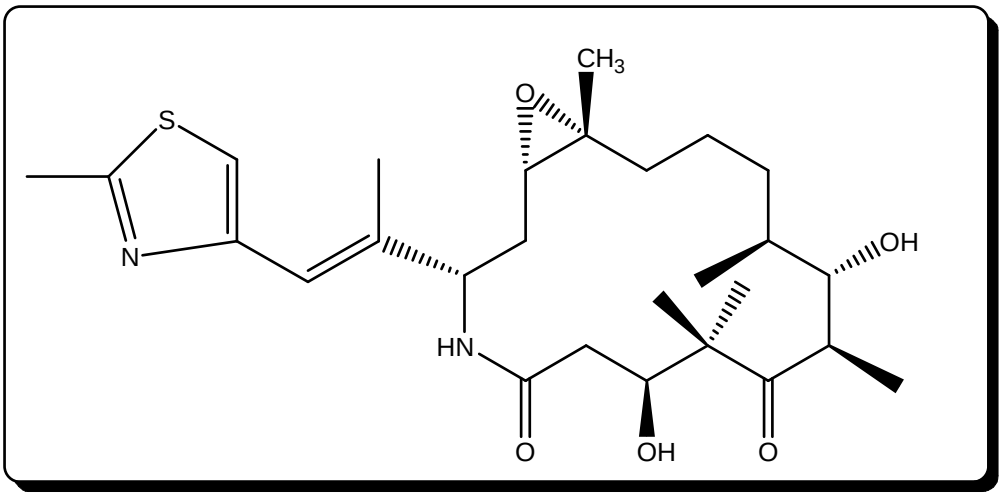


Figure 7. 15- (*S*)- aza-epoB.

1.4. 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 research groups of S. J. Danishefsky,[38] K. C. Nicolaou,[39] and D. Schinzer[40] were able to present independently successful total syntheses of epothilones A and B. Thereafter many other research groups have published contributions to the existing synthetic strategies as well as new total syntheses, and assays [41] of the biological role of epothilones. Within the scope of the general introduction of this thesis it is not possible to represent complete scope of literature on this field. Therefore only a short selection of the first total syntheses is included.

1.4.1. The Danishefsky Strategies to Epothilones

The first total synthesis of both epothilones A and B including the 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 synthetic 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[42], an olefin metathesis approach and a macrolactonization procedure.[42] 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 8).

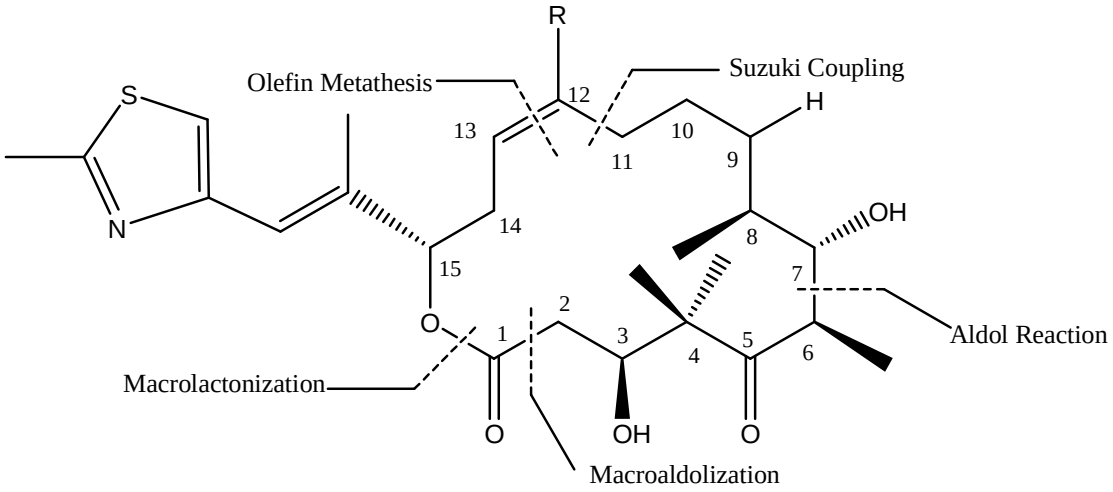


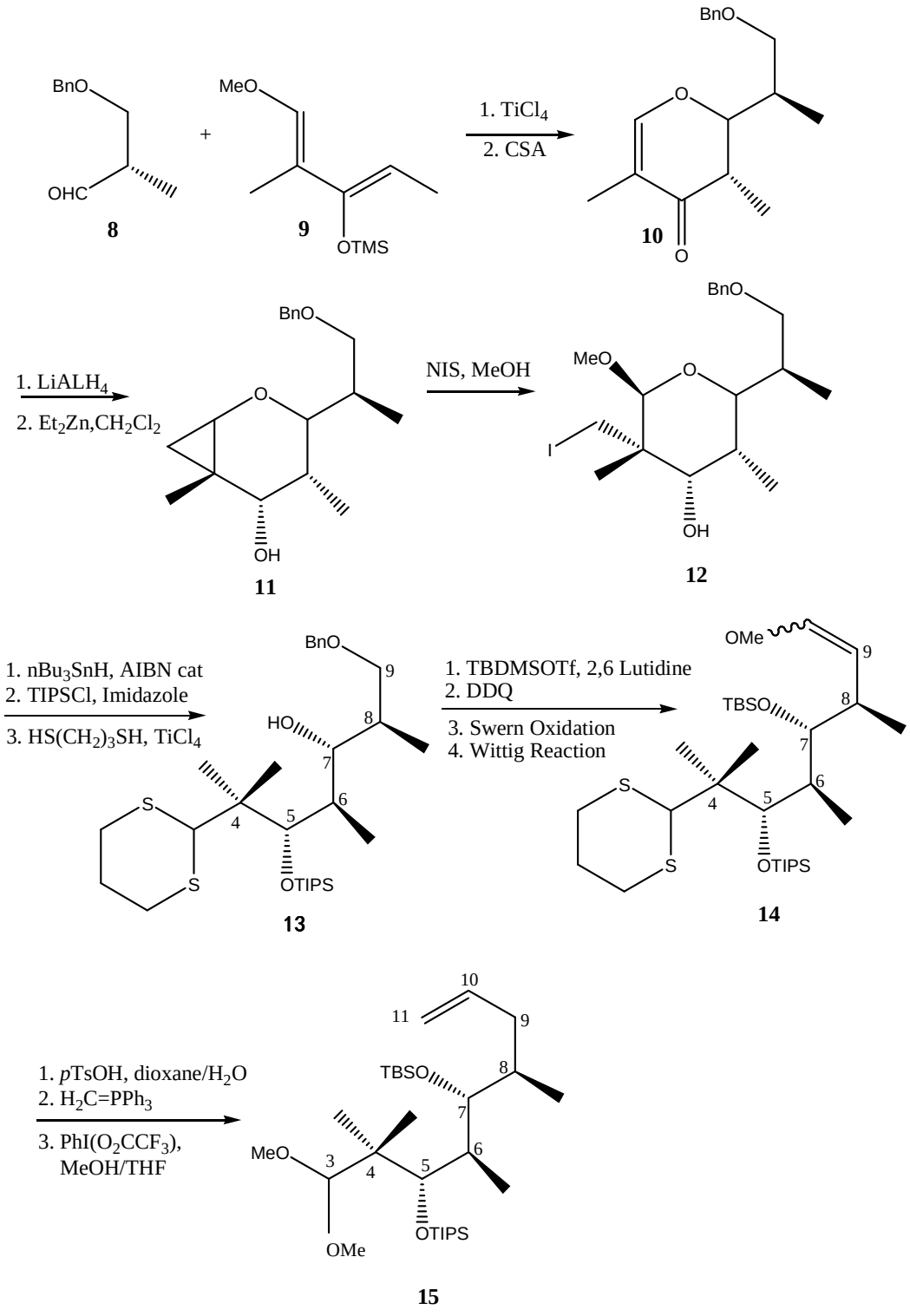
Figure 8. Danishefsky *et al*. Strategic Bond Disconnections Applied in the Total Synthesis of The Epothilone A and B

The synthesis of fragment C3-C11 started with the formation of the dihydropyran ring **10** by a $TiCl_4$ catalyzed stereoselective cyclocondensation of an enantiomerically pure aldehyde **8** with the Danishefsky diene **9** (see Scheme 1). The chirality of aldehyde **8** determines the configuration of the new stereocenters in the condensation product **10**. 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 **11**. The opening of the cyclopropane ring was performed using iodomethyl N-iodosuccinimide (NIS) in methanol, which leads to

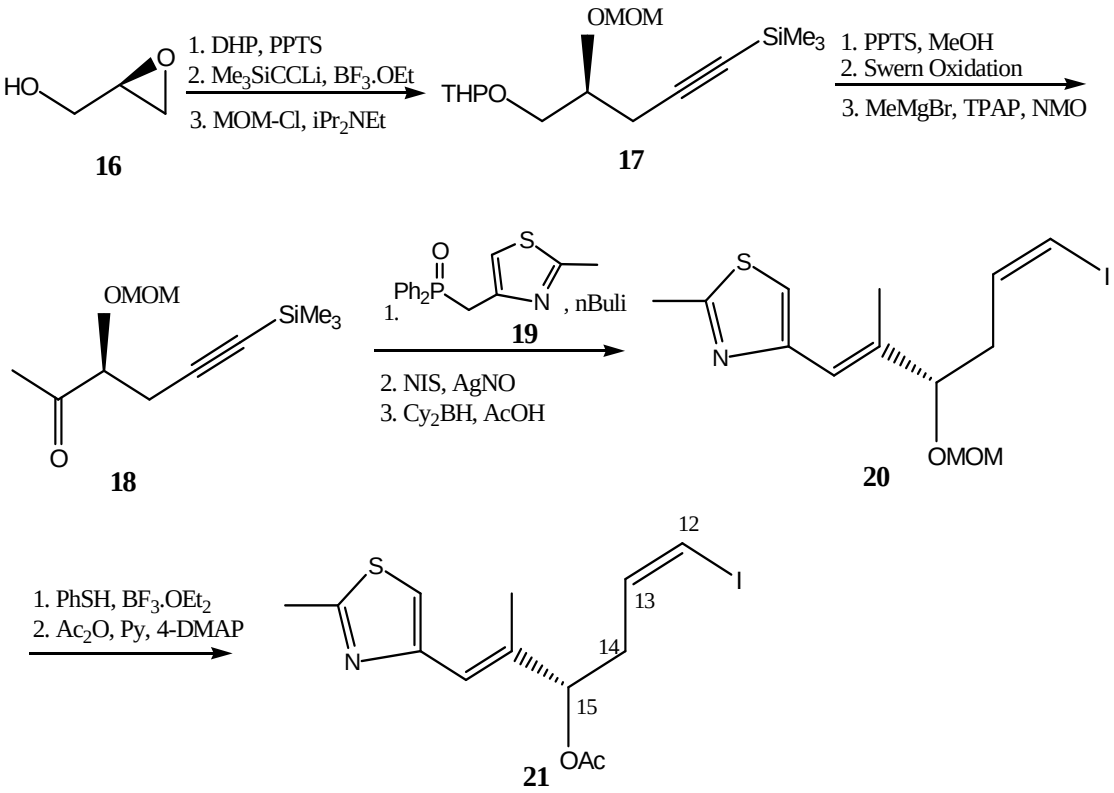
intermediate **12**. Compound **13** was obtained after subsequent radical dehalogenation of iodide **12** to introduce the geminal methyl groups followed by protection of the hydroxy moiety, and thioacetalization of the intermediary formed aldehyde.

Additionally, **13** 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 **13**, followed by cleavage of the benzyl group, then Swern oxidation and Wittig reaction transformed the key building block **13** to the methoxyvinyl ether **14**. The product **14** includes the centers C6 and C8, which have been set in the correct configuration of the target molecule. Later this vinyl ether was hydrolysed with p-toluenesulfonic acid to the aldehyde which was reacted with methlytriphenyl-phosphonium bromide and the acetal **15** was obtained through a subsequent transacetalization. Compound **15** represents the C3-C11 fragment of the desired carbon skeleton, which is one of the two main building blocks necessary for the synthesis of both 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 **15**.

The second building block C12-C15, employed in the macroaldolization strategy of Danishefsky *et al*., contains the side chain with the aromatic moiety. Initially the desired stereochemistry of the C12-C15 fragment was established through the use of the enantiomerically pure starting material *(R)*-glycidol **16** as a starting material, where the primary hydroxyl group was protected with dihydropyran (see Scheme 2). Subsequent opening of the epoxide leads to a secondary alcohol, which was protected as methoxymethyl ether giving compound **17**. Cleaving of the tetrahydropyran moiety, followed by Swern oxidation and subsequent Grignard reaction, yielded the methylketone **18** after a second oxidation. This compound was reacted with the Emmons reagent **19** and the silyl group was exchanged with iodine using N-iodosuccinimide. Thereafter followed hydroboration whereby the (*Z*)-iodoalkene **20** was produced. Finally, the methoxymethyl ether **20** was cleaved, and the resulting compound was acetylated to give the product **21**.

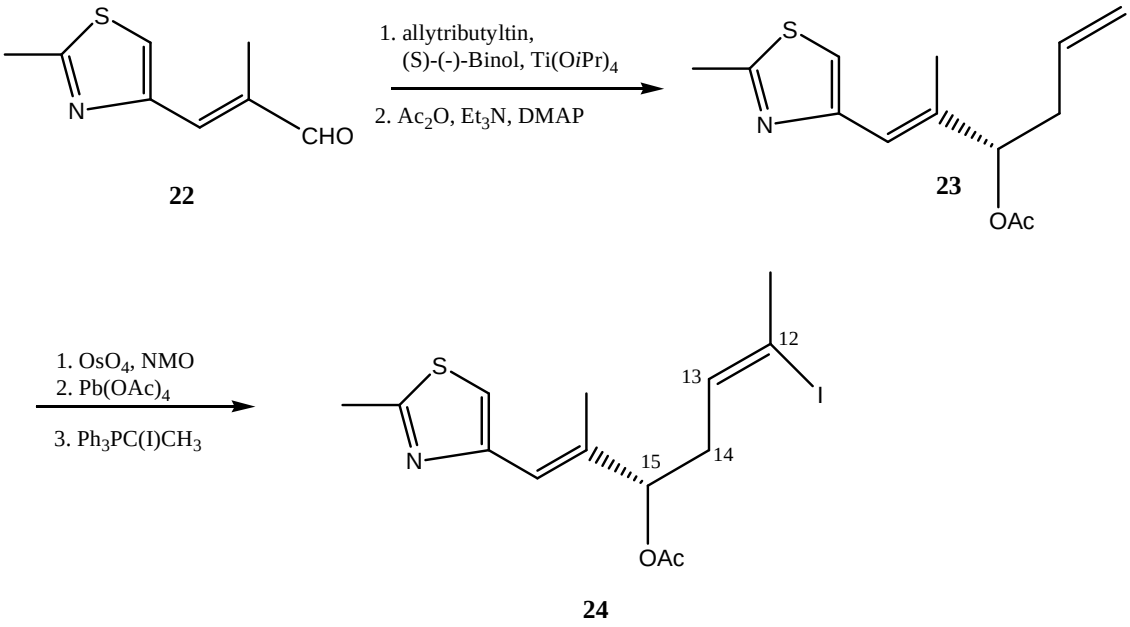


Scheme 1. Synthesis of The C3-C11 Key Fragment **15**



Scheme 2. Synthesis of The C12-C15 Key Fragment **21**

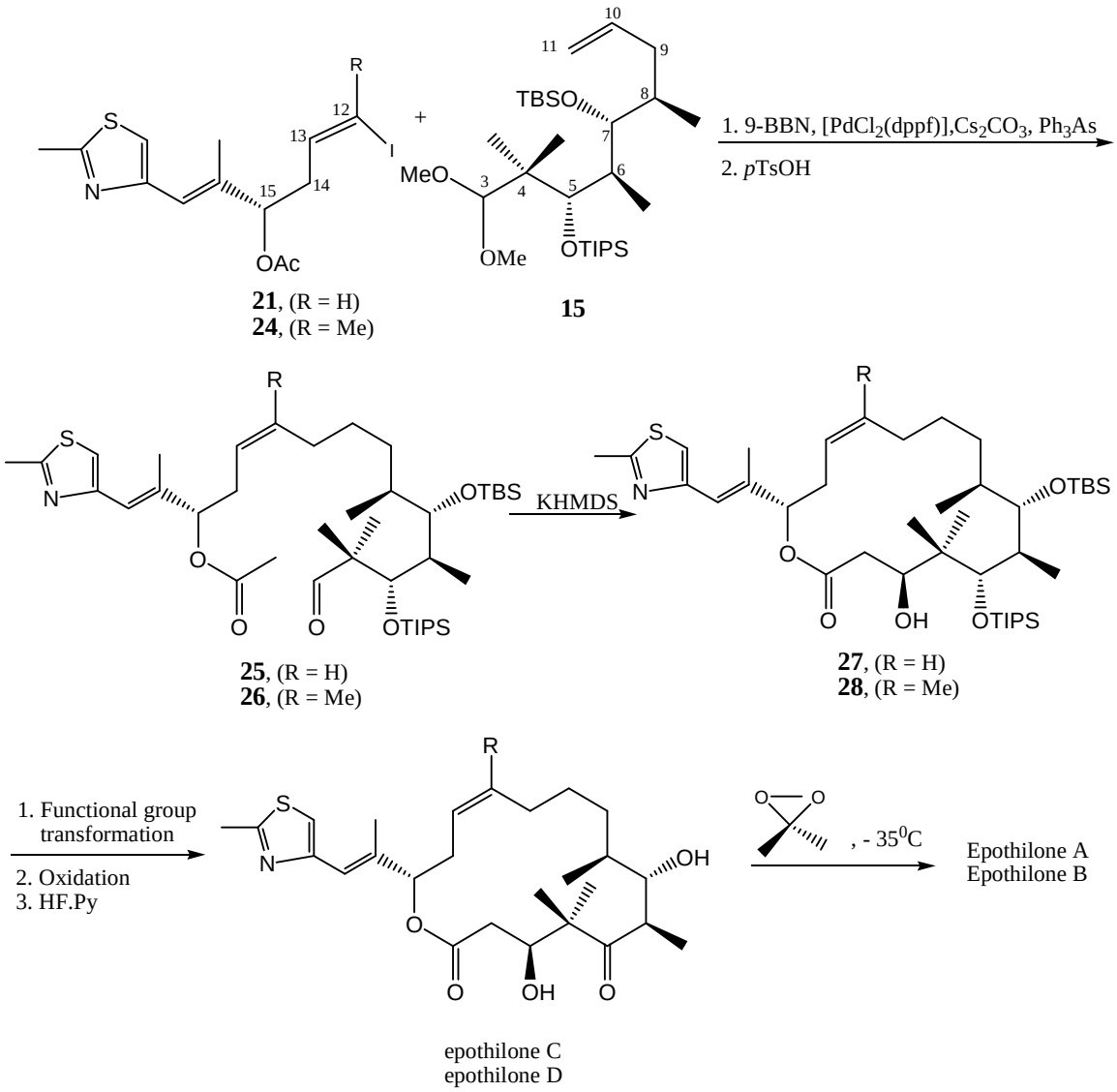
Shortly afterwards the successful synthesis of epothilone A, Danishefsky *et al*. also published also a convergent total synthesis of epothilone B, applying the same macroaldolization strategy for ring formation. In this synthesis, the second building block C12-C15 was synthesized starting from the aldehyde **22**, which was enantioselectively allylated with allyltributyltin and subsequently acetylated to give the compound **23** (see Scheme 3). Thereafter this compound was dihydroxylated and after glycol cleavage transformed to the vinyl iodide **24** by Wittig reaction. The product **24** was an analogue to the above described compound **21** and had an additional methyl group at C12, necessary for the synthesis of epothilone B.



22 **23** **24**

Scheme 3. Synthesis of Vinylolefin **24** as an Intermediate for the Suzuki Coupling

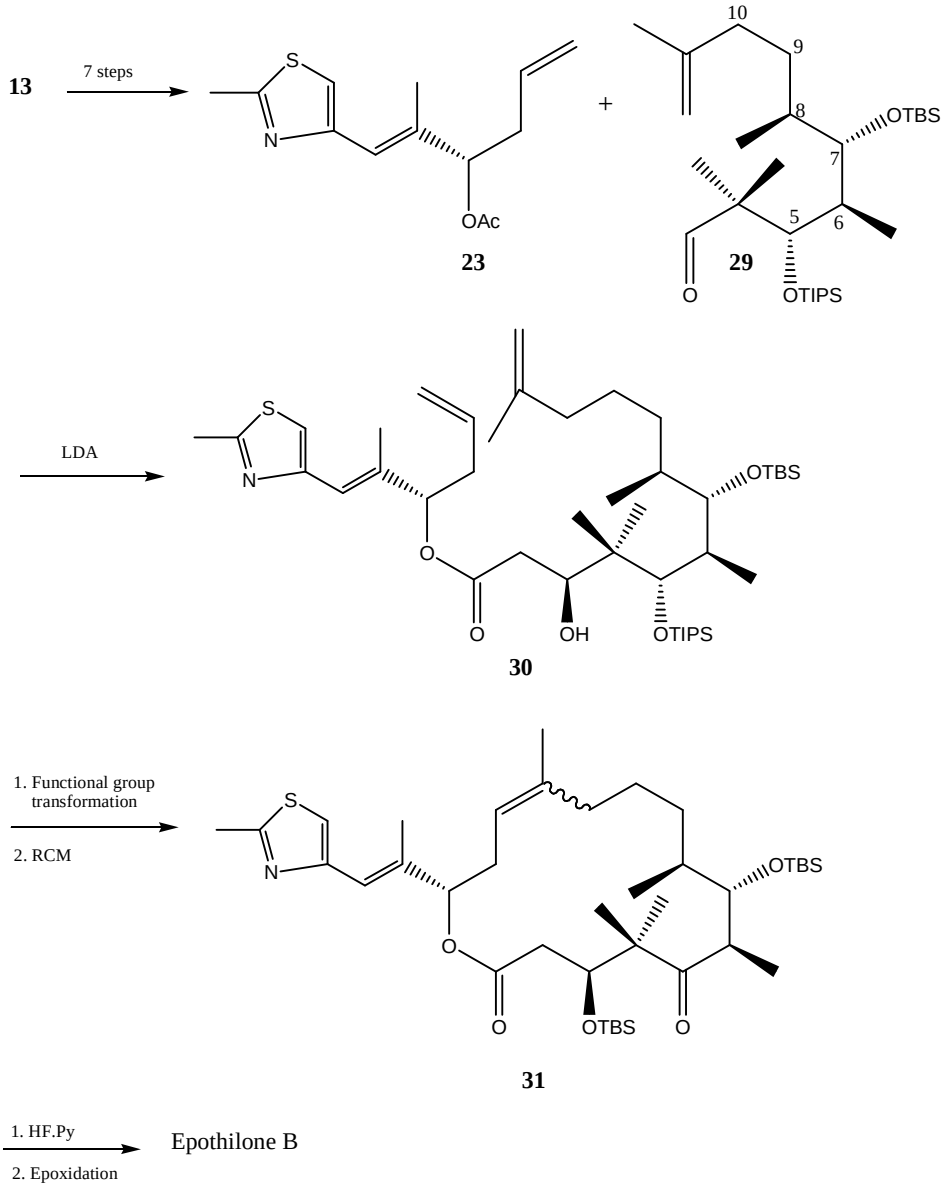
In assembling both fragments, a regiospecific Suzuki coupling allowed the union of intermediates **15** and **21** for epothilone A or **15** and **24** for epothilone B to form after an acetal cleavage compound **25** or **26**, respectively (see Scheme 4). These intermediates underwent a stereoselective ring closure through an intramolecular aldol reaction to give the desired macrocycles **27** with yield of 51% (stereoselectivity ca. 6:1) and **28** with yield of 64% (stereoselectivity ca. 3:2), respectively. Subsequent functional group transformations led to the desoxy precursor's epothilone C and D, and finally after stereoselective epoxidation the epothilones A and B were obtained.



Scheme 4. Suzuki Coupling and Macroaldolization Reaction for the Preparation of Epothilone A and B.

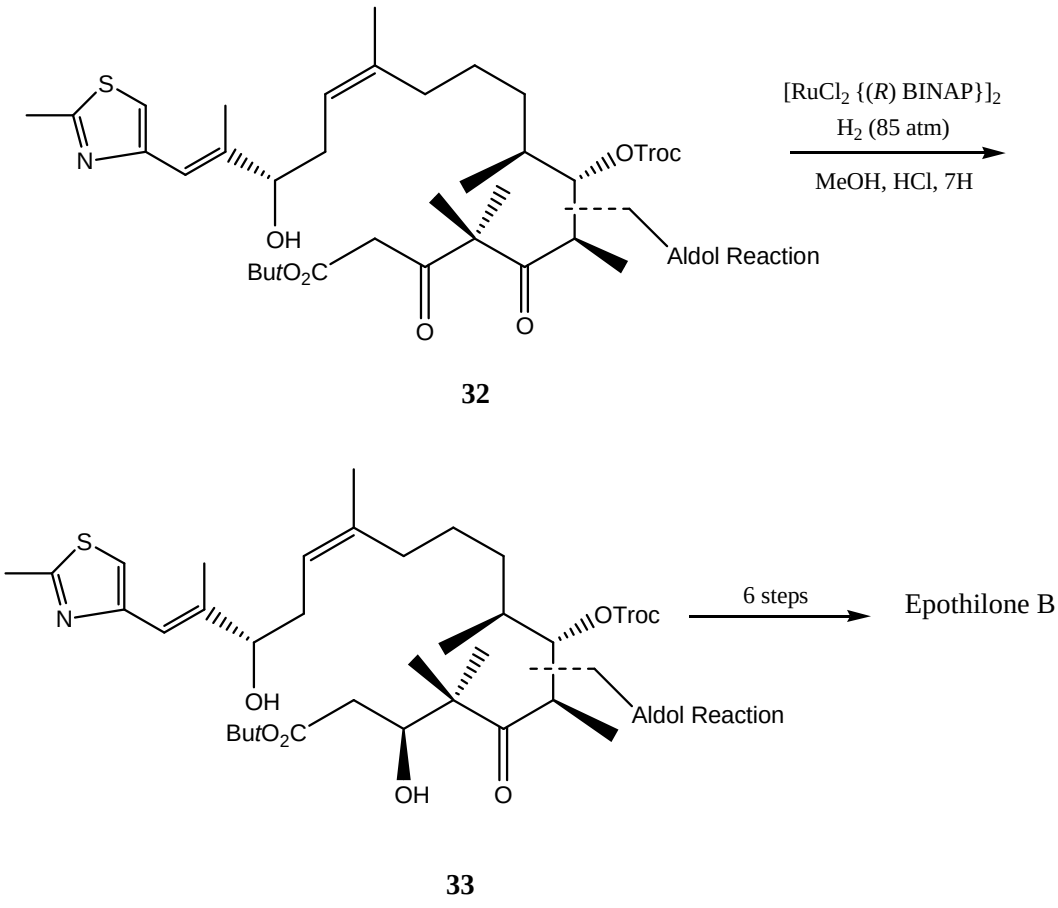
The already mentioned olefin metathesis strategy to obtain epothilone B starts also from the key building block **13** (see Scheme 5). After removing of the benzyl group the hydroxy moiety was oxidized to obtain an aldehyde, which is the starting material for the chain elongation. In this way aldehyde **29** was synthesized in several steps. Coupling of **23** with aldehyde **29** via aldol addition results in diene **30**.

After several modifications the ring was closed through an olefin metathesis reaction and the macrocycle **31** obtained. For the olefin metathesis the molybdenum-based Schrock catalyst was used.[44] 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.



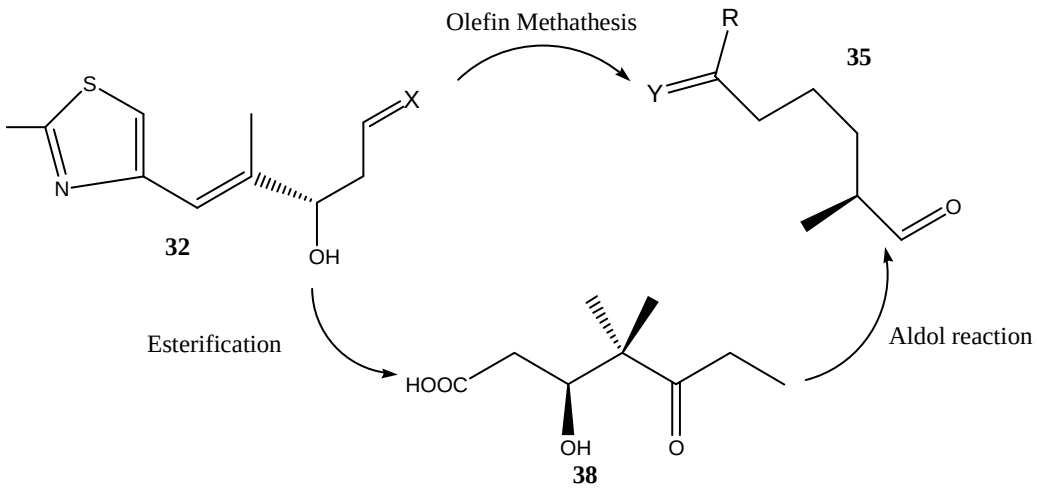
Scheme 5. Synthesis of Epothilone B through an Olefin Metathesis Approach

Due to 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 lot of pressure in establishing alternative methods for ring closure.[44] The third route established by Danishefsky *et al*. was the macrolactonization strategy. For that purpose compound **32** was synthesized (see Scheme 6). The most remarkable part of this route was the subsequent regio- and stereoselective Noyori reduction [46] of the keto moiety at C3 to obtain hydroxyl ester **33**. 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 **33**, the epothilones were prepared in several steps including the macrolactonization reaction.



Scheme 6. Regio and Stereoselective Noyori Reduction

1.4.2. The Nicolaou Strategies to Epothilones



Ring Closing	Target Molecule
Olefin-Metathesis	Epothilone A R = H, X = CH_2, Y = CH_2
Macrolactonization	Epothilone A R = H, X = PPh_3, Y = O Epothilone B R = Me, X = PPh_3, Y = O

Figure 8. Strategic Bond Disconnections applied in the Total Synthesis of the Epothilones

In the field of epothilone synthesis K. C. Nicolaou and co-workers have done 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 large number of epothilone analogues. The group carried out experiments on solid phase synthesis for the construction of epothilone libraries. [47] 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 large number of epothilone derivatives allowed the investigation and understanding of the relationships between structure and biological activity.

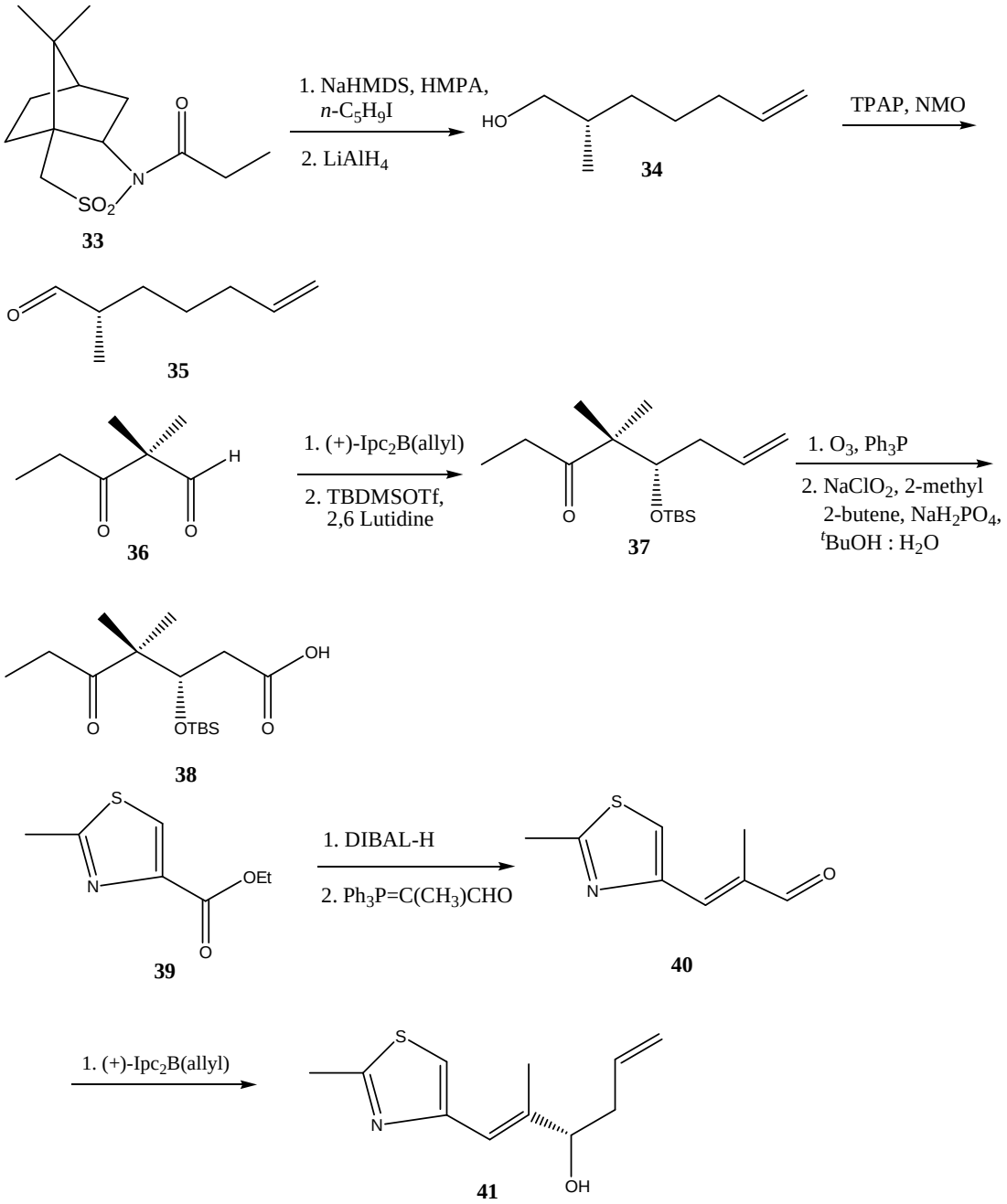
Amongst many strategies, Nicolaou *et al*. considered the olefin metathesis approach[48] for constructing the macrocycle and simultaneously applied as well a second strategy based on macrolactonization [39,47]. Both methods were similar to that presented in the work of Danishefsky *et al*.. The first total synthesis in Nicolaou's group led to epothilone A and its desoxy precursor epothilone C employing the olefin metathesis strategy (see Figure 8).

The retrosynthetic analysis divides the target into three key building blocks, which were synthesized independently, following divergent synthetic pathways to Danishefsky *et al*.. The C7-C12 building block **35** was obtained starting from *N*-propionyl bornyl sulfonamide **33**, which was alkylated with ω-iodo-pentene and the resulting product was subsequently reduced to alcohol **34** by cleavage of the bornyl sulfonamide residue (see Scheme 7). Further oxidation with *N*-methylmorpholine-*N*-oxide and tetra propylammoniumperruthenate led to aldehyde **35.** The synthesis of the C1-C6 fragment **38** began with the stereoselective allylation of the keto aldehyde **36** using the Brown reagent allylisopinocamphenylborane. The newly-formed hydroxy moiety was protected with a silyl group and provided **37**. An oxidative degradation of the double bound to a carboxyl group gave the desired product **38**. The thiazol-fragment **41** was synthesized starting from the carboxylic ester **39**, which was reduced with diisobutylaluminium hydride to the corresponding aldehyde. Subsequent Wittig olefination gave the aldehyde **40**, which was further transformed through a allylation[49] to the compound **41**.

The two fragments **35** and **38** were combined through an aldol condensation with lithiumdiisopropyl amide (LDA) to form the acid **42**, which through an esterification with the thiazol alcohol **43** gave the starting material **45** for the olefin metathesis reaction for the final stages of macrocycle generation (see Scheme 8). For the ring closing metathesis (RCM), Nicolaou *et al*. used the Grubbs catalyst $[RuCl_2(=CHPh)(PCy_3)_2]$.[50]

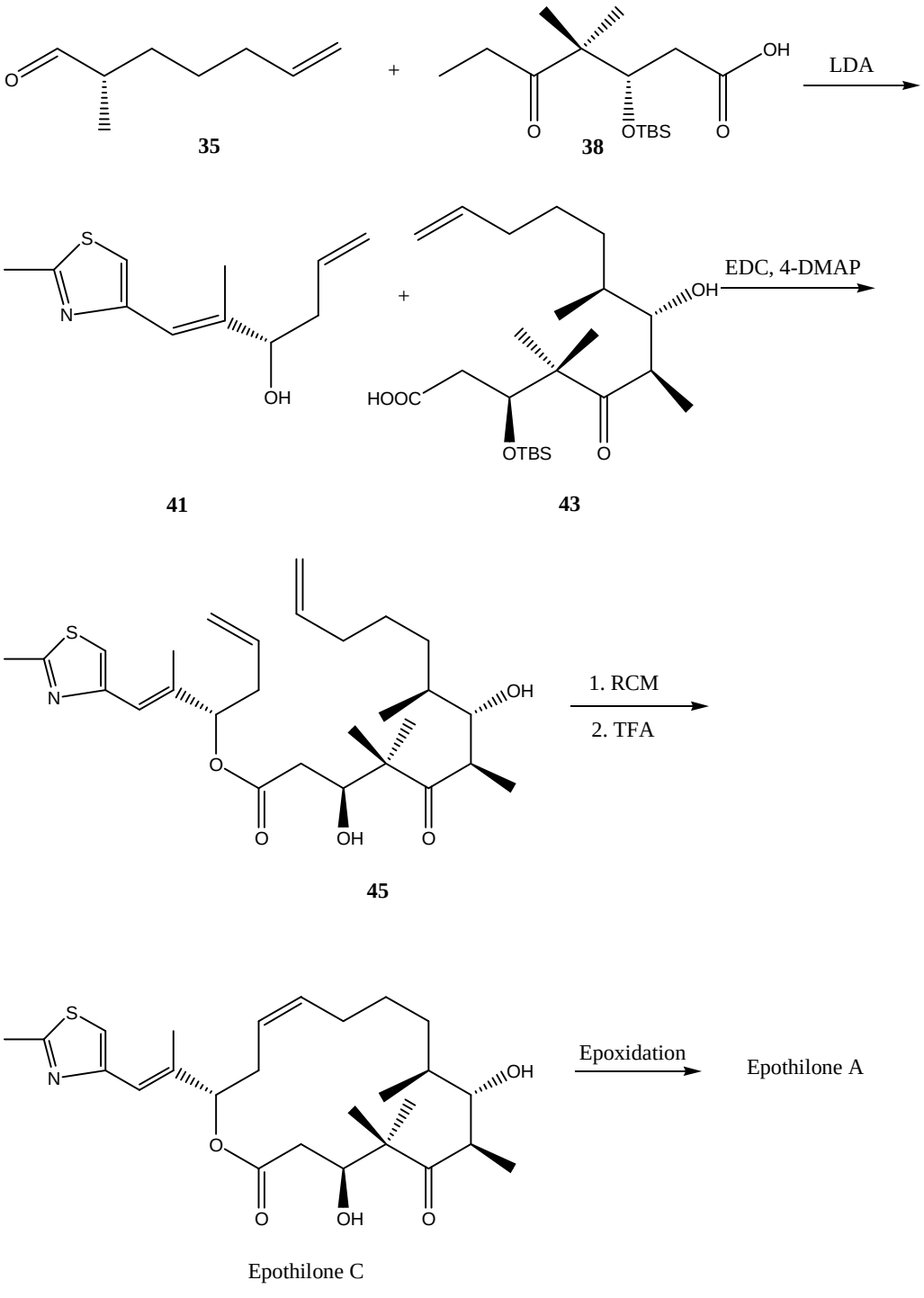
Thereafter, similar to the methods established by Danishefsky *et al*., the double bound of the desoxy precursor epothilone C was stereoselectively oxidized to the epoxide, giving the end product, in this case epothilone A.

A series of oxidants were tested: (3,3-dimethyldioxirane), (3,3-methyl (triflouromethyl)-dioxirane) and (m-chloroperbenzoic acid) were used for the stereoselective oxidation, yielding epothilone A in 65% (*de* 3:1), 75% (5:1) and 48% (3:1) respectively.



33 **34** **35** **36** **37** **38** **39** **40** **41**

Scheme 7. Synthesis of the Key Fragment for the Olefin Metathesis Approach of Nicolaou *et al*.



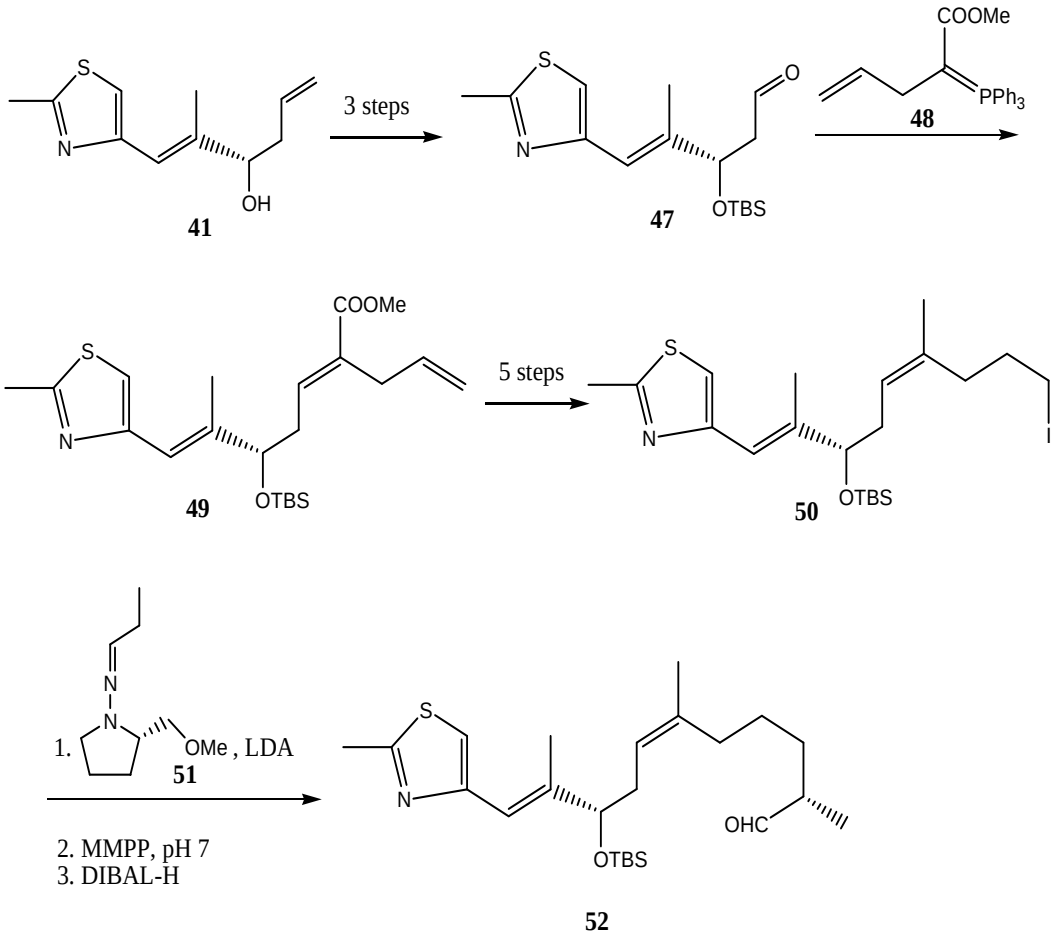
Scheme 8. The Preparation of Epothilones A via Aldol Reaction and Olefin Metathesis

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 method [51] for the ring formation. They used this approach for the stereoselective synthesis of both epothilones A and B, the schemes 10 depicts the synthesis of epothilone B. The construction of the carbon-chain starts with the formation of the fragments C1-C6 (**46**) and C7-C15 (**52**), which were assembled through an aldol reaction with LDA to give the ring closure precursor **53**. The first building block C1-C6 46 was synthesized starting from compound **37**.

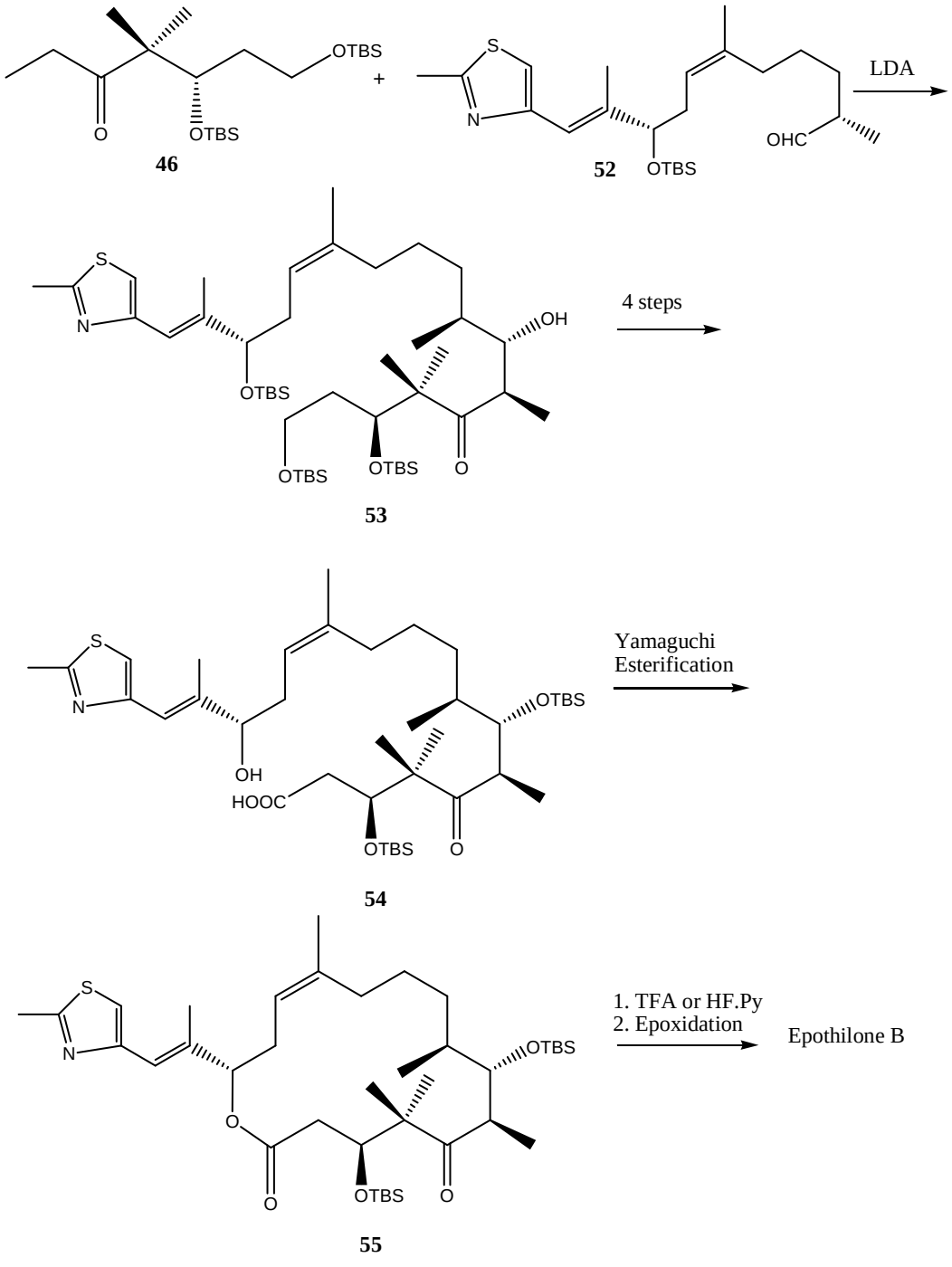
After ozonolysis of olefin **37** followed by reduction to the corresponding alcohol, which was further protected, the key fragment C1-C6 **46** was obtained. The homoallylic alcohol **41** for the formation at the C7-C15 building block was used as a starting material. In three steps, including an oxidation of the olefin, 41 were transformed to the thiazol aldehyde **47** (Scheme 9). Thereafter, followed a *Z*-selective Wittig reaction with the ylide **48** which lead to the chain-elongated product **49**. 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 **50**. Chain elongation with a stereo controlled introduction of the C8-Methyl, epothilone numbering, was achieved using an Enders alkylation with the SAMP-hydrazone **51**.[52] After oxidative cleavage of the chiral auxiliary group and subsequent reduction the desired key building block **52** was obtained.

The aldol reaction was utilized for formation of compound **53** establishing the new stereocenters at C7 and C6 occurs with a stereoselectivity of approximately 3:1 (Scheme 10). Thereafter the ring closure precursor **53** was transformed in several steps to the carboxylic acid **54**.

The macrolactonization was carried out using the Yamaguchi procedure. After cleavage of the silyl protecting groups in **55** the desoxy precursor epothilone D was isolated. The end-product, EPO B, was obtained using a stereoselective epoxidation (*de* 5:1).

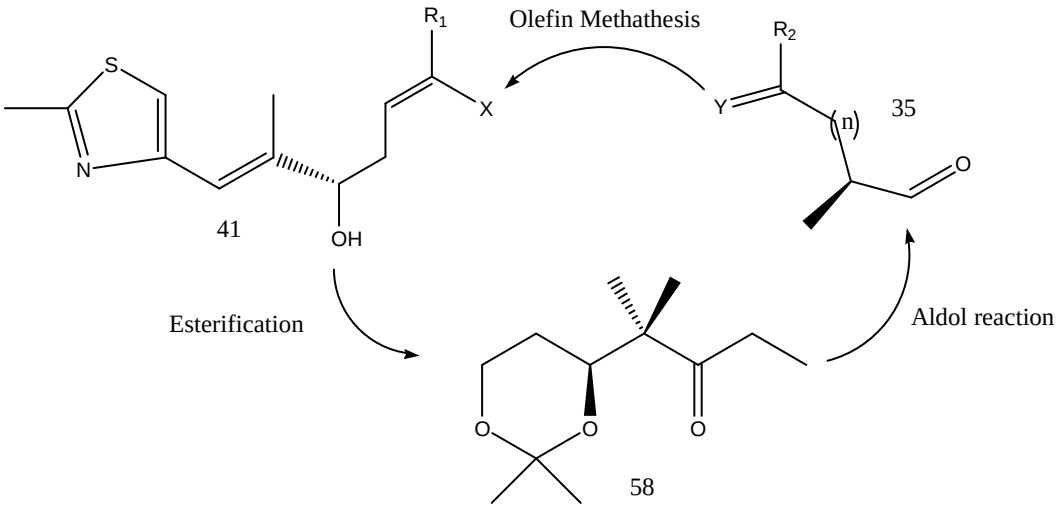


Scheme 9. Preparation of The C7-C15 Fragment **52** for Further Synthesis of Epothilone B



Scheme 10. Ring Formation via Yamaguchi Macrolactonization

1.4.2. The Schinzer Strategies to Epothilones



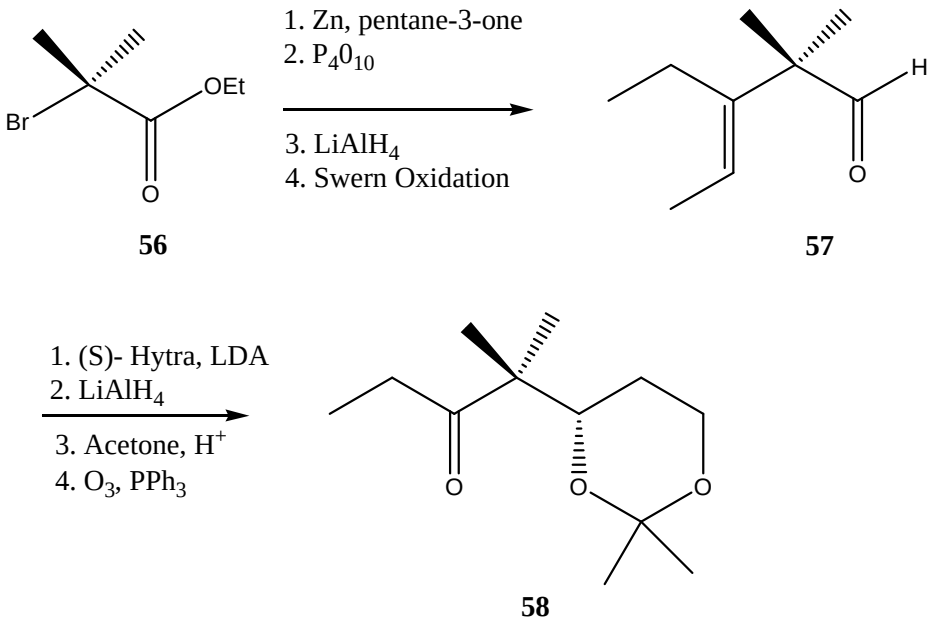
Ring Closing	Target Molecule
Olefin Metathesis - Epoxidation	Epothilone A R_1 = H, R_2 = H, X = H,Y = CH_2, n = 3 Epothilone B R_1 = H, R_2 = CH_3, X = H,Y = CH_2, n = 3
Macrolactonization	Epothilone B R_1 = CH_3, R_2 = H, X = I,Y = I, n = 1

Figure 9. The Schinzer *et al*. Strategic Bond Disconections and Retrosynthetic Analysis for the Preparation of Epothilone A

Another research group which made big contributions in the field of the epothilone synthesis is that of D. Schinzer. At the beginning of 1997, Schinzer *et al.* published their independently developed olefin metathesis approach to epothilones A and C.[40] Their design required three key intermediates **58**, **35** and **41**, which were obtained by asymmetric synthesis (see figure 9). Compounds **35** and **41** 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 **58** with the aldehyde **35** via a lithium enolate was most impressive, and was attributed to the influence of the acetonide moiety. Attachment of the side-chain **41** (figure 9) 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.

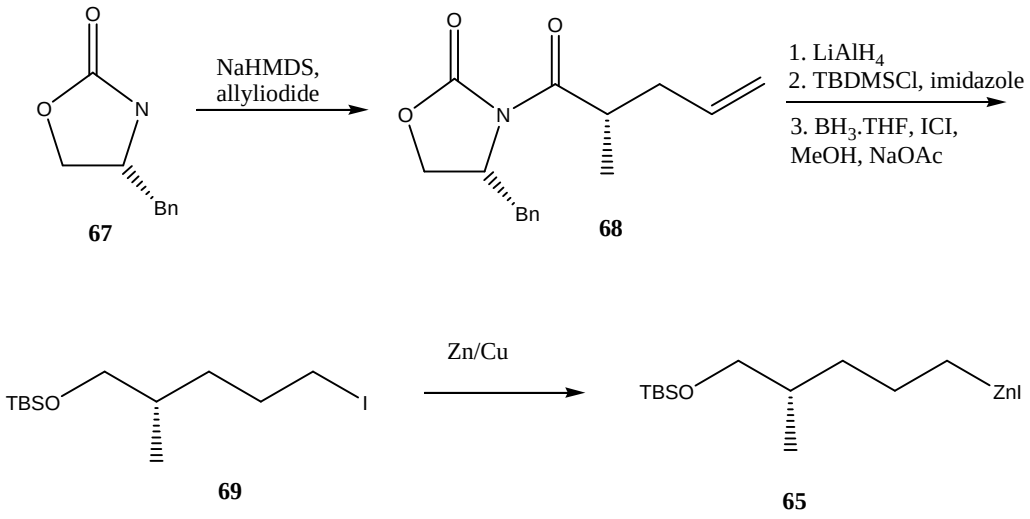
In 1998, Schinzer *et al.* established another new synthetic route [53] to epothilone B using a macrolactonization strategy as a key reaction step for the ring formation. The most innovative steps in this synthesis are the successfully introduction of the correct chiralities at the stereocenters C3, C6 and C7 via stereoselective aldol reactions. The main key intermediates were the C1-C6 fragment **58** and the C7-C15 fragment **66**.



56 **57** **58**

Scheme 11. Synthesis of C1-C6 Building Block **58**

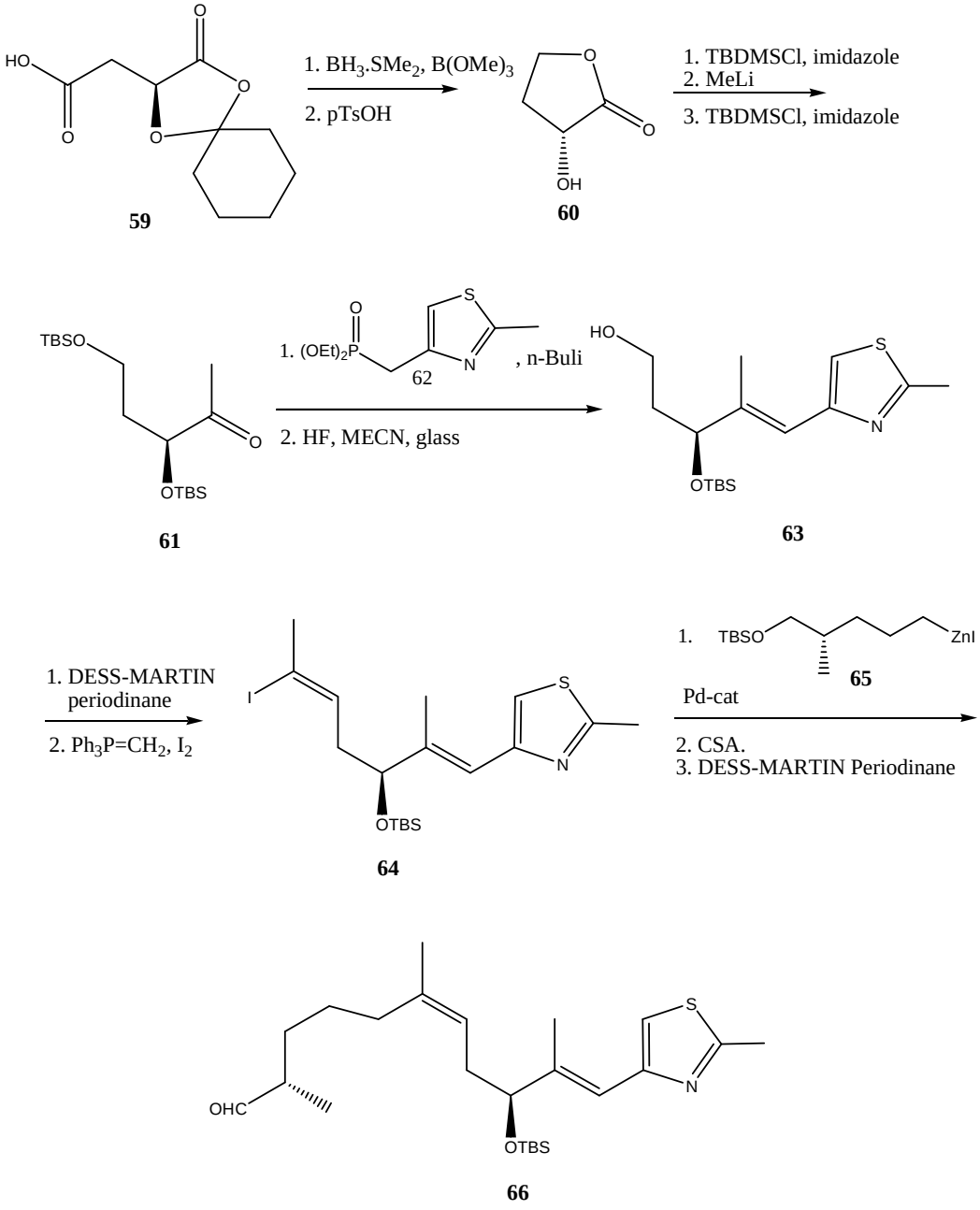
The synthesis of the C1-C6 fragment started from the α-bromoester **56**, which was combined with pentane-3-one through a Reformatsky reaction giving ß-hydroxyester as intermediate (see Scheme 11). After subsequent reduction and oxidation the coupling product was transformed to the appropriate aldehyde **57**. Thereafter a stereoselective aldol reaction with (*S*)-HYTRA [(*S*)-2-hydroxy-1,2,2-triphenylethylacetate] followed according to the method of M. Braun *et al.*[54] introducing the correct chirality at C3. The condensation product was further reduced, the resulting 1,3-diol moiety was protected as an acetal and the double bound was oxidized to give the ketone **58**.



Scheme 12. Synthesis of Compound **65**

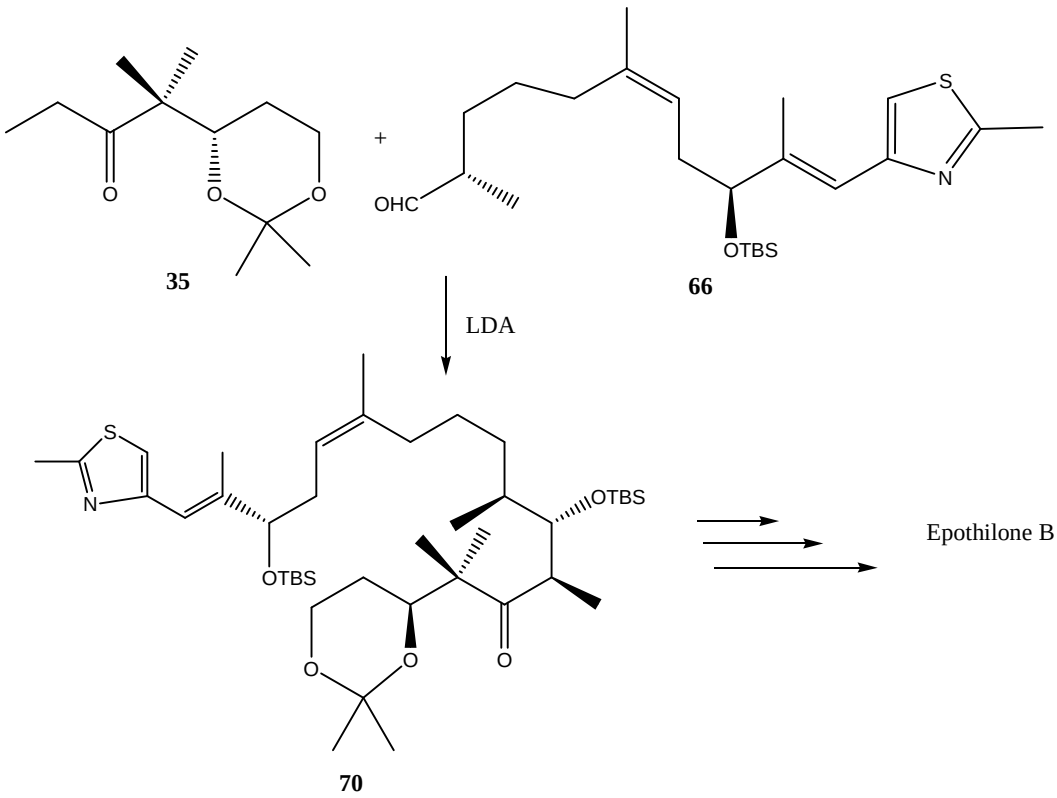
The alkyl zinc compound **65** contains the stereocenter C8 in the later macrocycle (see Scheme 12). The synthesis of **65** starts with the Evans auxiliary **67**, which allowed the introduction of the correct chirality.[55] For that purpose, the Evans auxiliary **67** was alkylated in a stereoselective reaction with allyl iodide obtaining compound **68**. The oxazolidinone group was cleaved by reduction with lithiumaluminium hydride and after protection of the resulting hydroxy moiety, the terminal double bond was reduced using a of borane-THF

complex, and then oxidized with iodine chloride and sodium acetate to the corresponding alkyliodide **69**. Compound **69** was coupled with zinc copper mixture giving the alkyl zinc compound **65**.



Scheme 13. Synthesis of C7-C15 Building Block **66**

The synthesis of the C7-C15 fragments begins with (*S*)-hydroxy succinic acid derivative **59**, which after reduction and cleavage of the protecting group was transformed to the hydroxy butyrolactone **60** (see Scheme 13). After TBS protection of the hydroxy moiety, ring opening with methyl lithium to give the lactol and subsequent protection of the resulting hydroxyl group, the ketone **61** was isolated. The thiazol-containing residue was introduced by a Wadsworth-Emmons reaction with **62**, and after deprotection of the chain-elongated product, the compound **63** was obtained. Dess-Martin oxidation and Wittig reaction gave the vinyl iodide **64** which was coupled with the alkyl zinc compound **65** in a palladium-catalyzed coupling. The resulting product was deprotected and oxidized to give the desired C7-C15 key fragment **66**. The coupling reaction presented by Schinzer *et al.* appeared as an alternative to the Suzuki-cross coupling used by Danishefsky *et al.*.



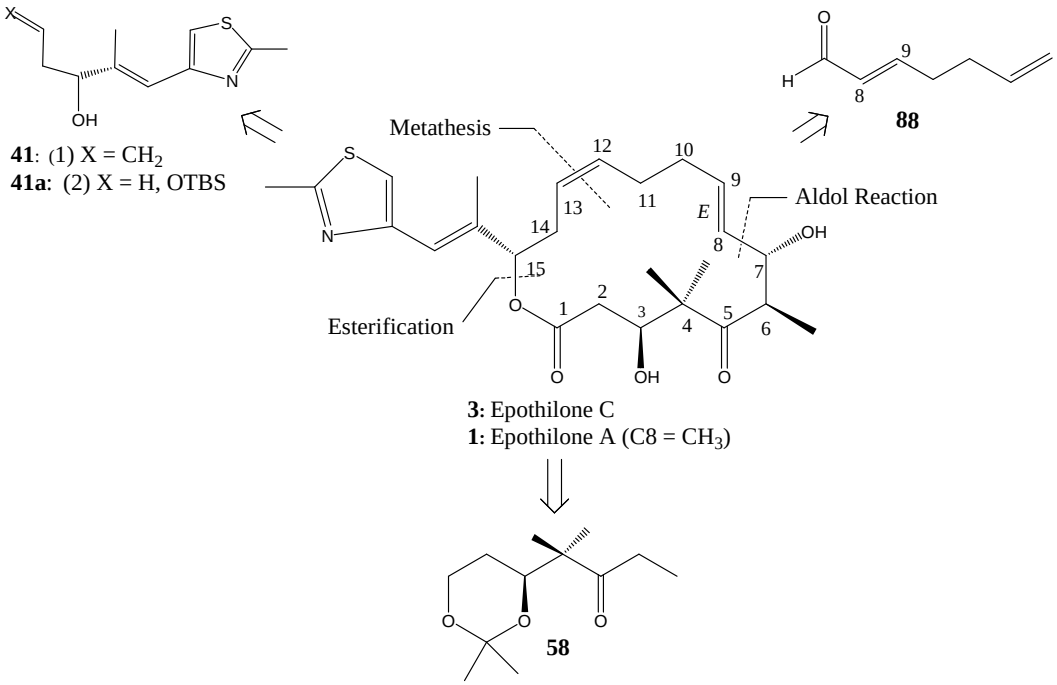
Scheme 14. Aldol Reaction and Macrolactonization for Synthesis of Epothilone B

The compound **70** was formed via stereoselective Aldol reaction with LDA of the C7-C15 fragment **66** with the C1-C6 fragment **35** (see Scheme 14), introducing the correct configurations at the C6 and C7 stereocenters. The high stereoselectivity (*de* 9:1) was reached via the strong chelating abilities of the C1-C6 fragment, reinforced by the acetal-protecting group. After cleavage of the acetal group the synthesis of epothilone B proceeded similar to the synthesis presented in the work of Nicolaou *et al*..

Chapter 2

Aims

Since 1996 The Schinzer group has been working on the total synthesis of the epothilones. Although the group has been working on numerous epothilones and their derivatives, there are still some novel epothilone analogues to be synthesized. It has been predicted that some of these analogues show high activity against tumor cells and a unique mechanism of action as microtubule-stabilizing agents. Nevertheless, the epothilone pose a considerable challenge to the synthetic chemist and, most importantly, offered opportunities for the discovery and development of new synthetic technologies and strategies. The variations of the different functional groups in the natural molecule have made it possible to find an analogue with higher activity and or an improved process chemistry profile.



Scheme 15. Retrosynthetic Analysis of 8,9 Dehydro Epothilone C

The purpose of my project is the development of a new analogue of epothilone C with a double bond between the C8 – C9 atom carbon (see scheme 15). Loose of the methyl group at position C8 resulted in considerable loss of biological activity, but still this compound is an interesting analogue for further investigation and until today this compound was unknown. The conformation of this analogue also fits very nicely in the pharmacophoric model of the active conformation of epothilone and tubulin. It could even increase the fit. Also this molecule posed new challenge for the synthetic methods developed by Schinzer *et al*. for the total synthesis of Epothilone A.

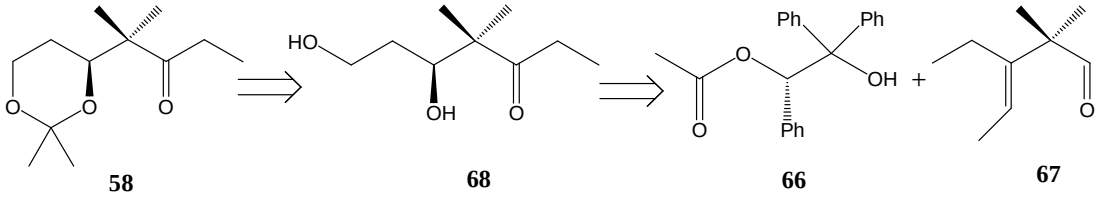
This is a convergent synthetic route which is selective and flexible. Using the previous Schinzer *et al*. retrosynthetic methods for Epothilone A, the following retron are required (see scheme 15): **41**, **58** and **88**. For the novel olefinic aldehyde **88**, the *E* configuration is necessary.

Chapter 3

Results and Discussion

3.1. Synthesis of (*S*)- Ethyl Ketone Fragments **58**

The retrosynthetic analysis relies on the late stage ozonolysis to install the ketone from an olefin and an aldol reaction to introduce the chirality. The olefinic aldehyde was constructed using a Reformatsky reaction, elimination and an oxidation adjustment sequence.

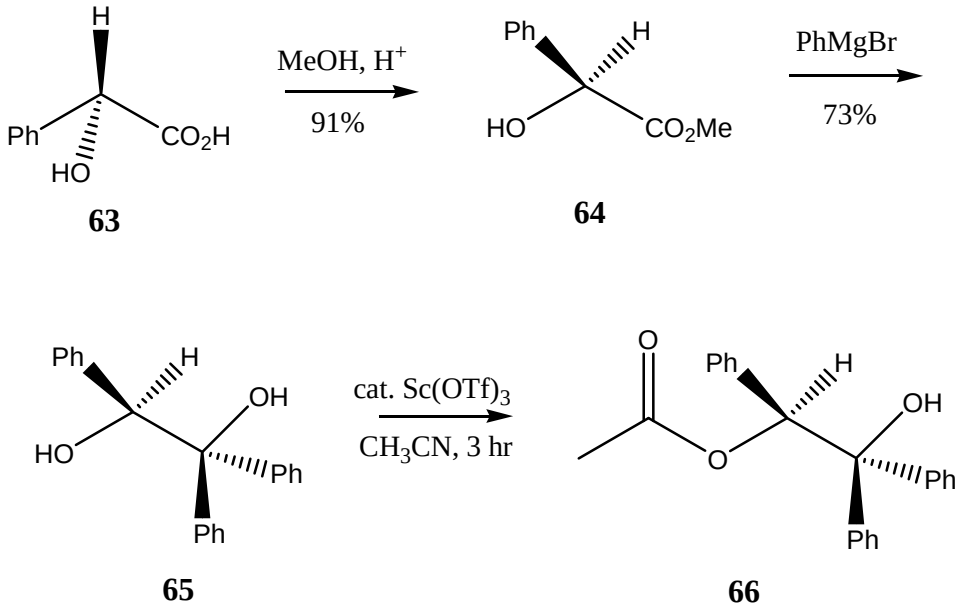


58 **68** **66** **67**

Scheme 16. Retrosynthetic of (*S*)- Ethyl Ketone Fragments **58**

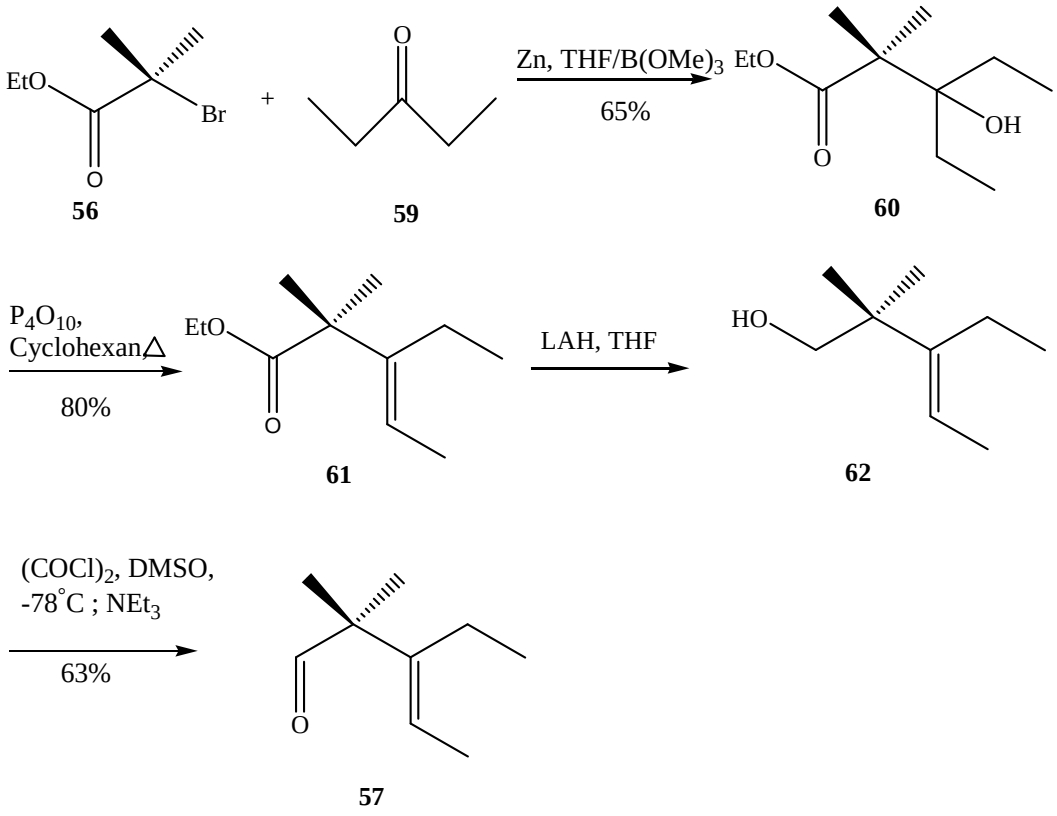
The construction of the stereocenter at C3 in the epothilone macrocycle was achieved by a diastereoselective aldol reaction with the chiral acetate equivalent (*S*)-(-)-HYTRA (1,1,2- triphenyl-1,2-ethanediol acetate) **66**. (*S*)-HYTRA was synthesized starting from (*S*)-(+)-Mandelic acid **63** by the method of Braun *et al*. in three steps (see scheme 17).[54] In the next steps the (*S*)-(+)-Mandelic acid **63** was further transformed using catalytic acid in methanol to yield the ester **64** in 91% yields, which was reacted with PhMgBr to give the diol **65**. The primary alcohol **65**, was then acylated to give the acetic anhydride **66** in the presence of catalytic amounts of scandium (III) triflate in 78% yield (Scheme 17).[56] This method is differs from that of Braun *et al.* who used acetiyl chloride in the presence of a pyridine catalyst.

The reason behind this change in the protocol was due to the fact that the aldol reaction between compound **66** and **57** failed. Our observation with Braun methode has been proved which are from 10 batch of the aldol reaction only one is succeeded. The procedure that we used is very simple by direct filtration of the reaction mixture avoiding the extensive drying necessary when using Braun`s methode, also the yields are comparable.



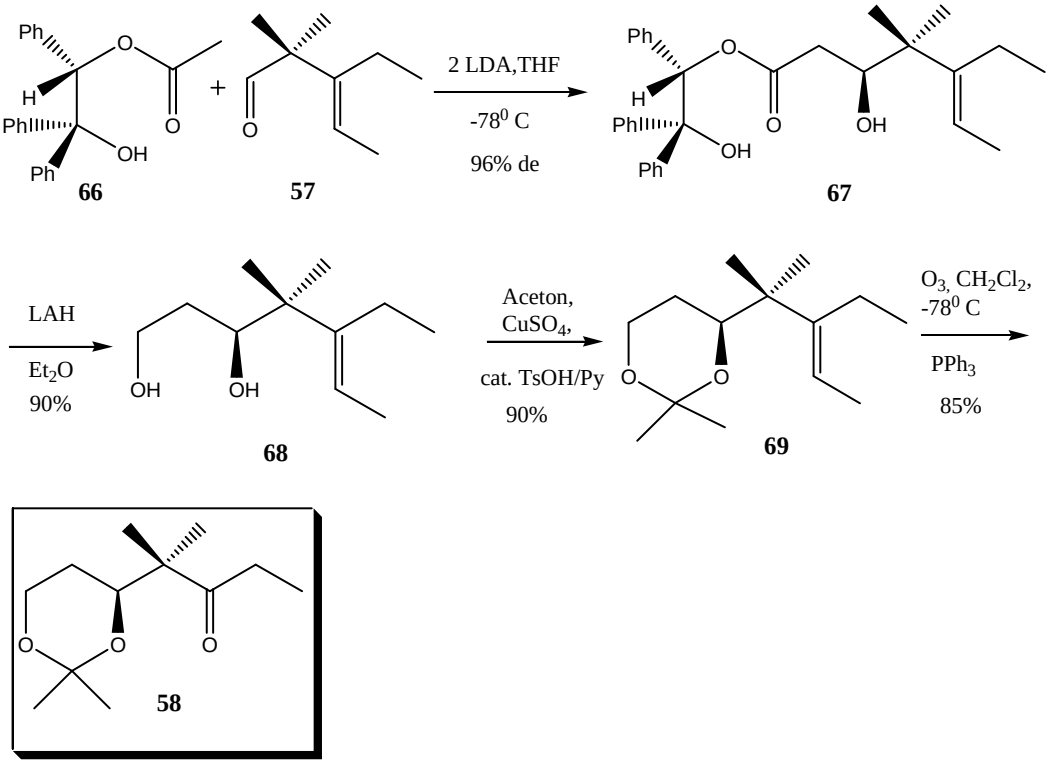
Scheme 17. Synthesis of (*S*)-HYTRA **66**

Aldehyde **57** required for the aldol reaction was obtained using a Reformatsky reaction between α–bromo ester and 3-pentanone which furnished β- hydroxyester **60** in 65% yield.[57] Dehydration with P_4O_{10} gave the olefinic ester (80%, only the *E* isomer was detected by ^{1}H and ^{13}C NMR spectroscopy), which then was converted to the aldehyde by a reduction with lithium aluminium hydride and subsequent Swern oxidation in 63% yields (scheme 18) respectively.



Scheme 18. Synthesis of Aldehyde **57**

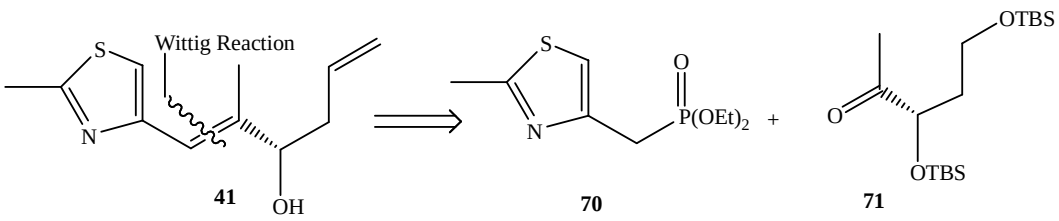
Addition of the dianion of **66** to **57** with 2 eqv LDA in THF at -78°C resulted in the formation of crystalline ester **67** in excellent diastereoselectivity (96% *de*, by HPLC) and good yield (75%). $LiAH_4$ reduction allowed the auxiliary to be removed nearly quantitatively and led to the diol **68** in 90% yield with the recovery diol **65**. Finally, **68** was protected using acetone and $CuSO_4$ in presence of TsOH and pyridine as catalyst yielding the acetonide **69** in 90% yield. Finally, ozonolysis gave the desired ß-olefinic aldehyde **58** in 85% yield (scheme 19).



Scheme 19. Synthesis of (*S*)- Ethyl Ketone Fragment **58**

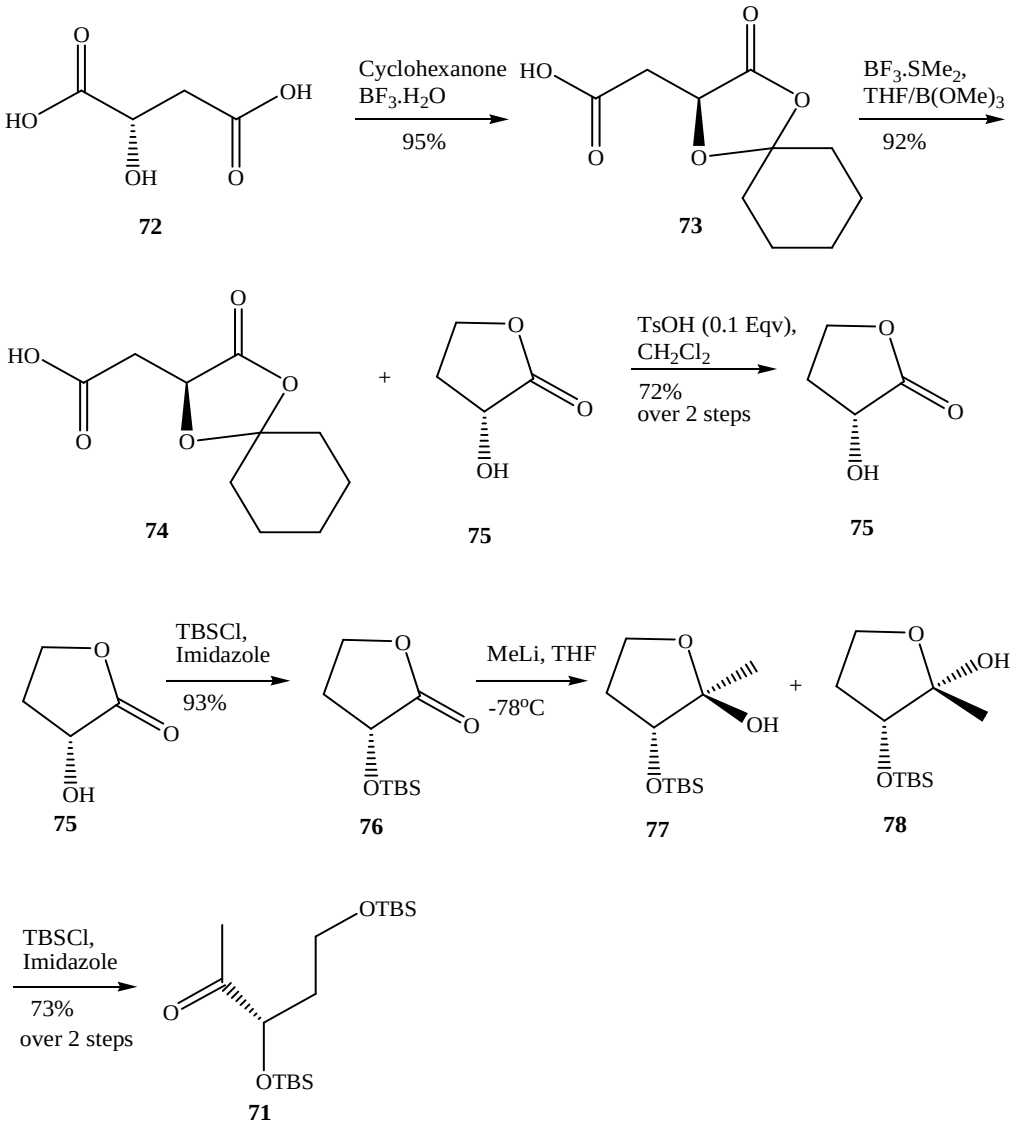
3.2. Synthesis of Thiazole Fragment **41**

The Thiazole building block **41** is derived from two key fragments: Phosponate **70** and methyl ketone **71** by means of Horner-Emmons reaction (see scheme below).



Scheme 20. Retrosynthetic Analysis of Thiazol Fragment **41**.

In the previous total synthesis of epothilone B [58], the stereocenter of the metyl ketone **71** had been established by a Sharpless resolution which gave **71** in 80% *ee* (see scheme 13).

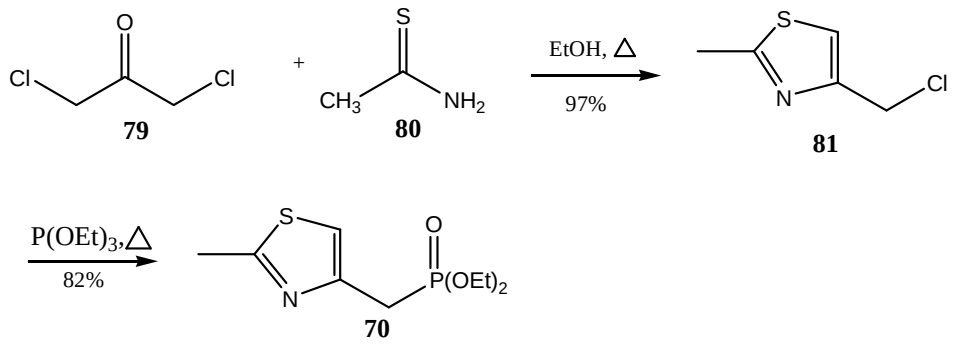


Scheme 21. Synthesis of Methyl Ketone **71**

In this sequence, (*S*)-Malic acid was chosen as the source of chirality. Its cyclohexylidine ketal **73** [59] was selectively reduced with $BH_3.Me_2S$. The alcohol product was cyclised into the known lactone **75** [60] by using 0.1 Eqv TsOH in

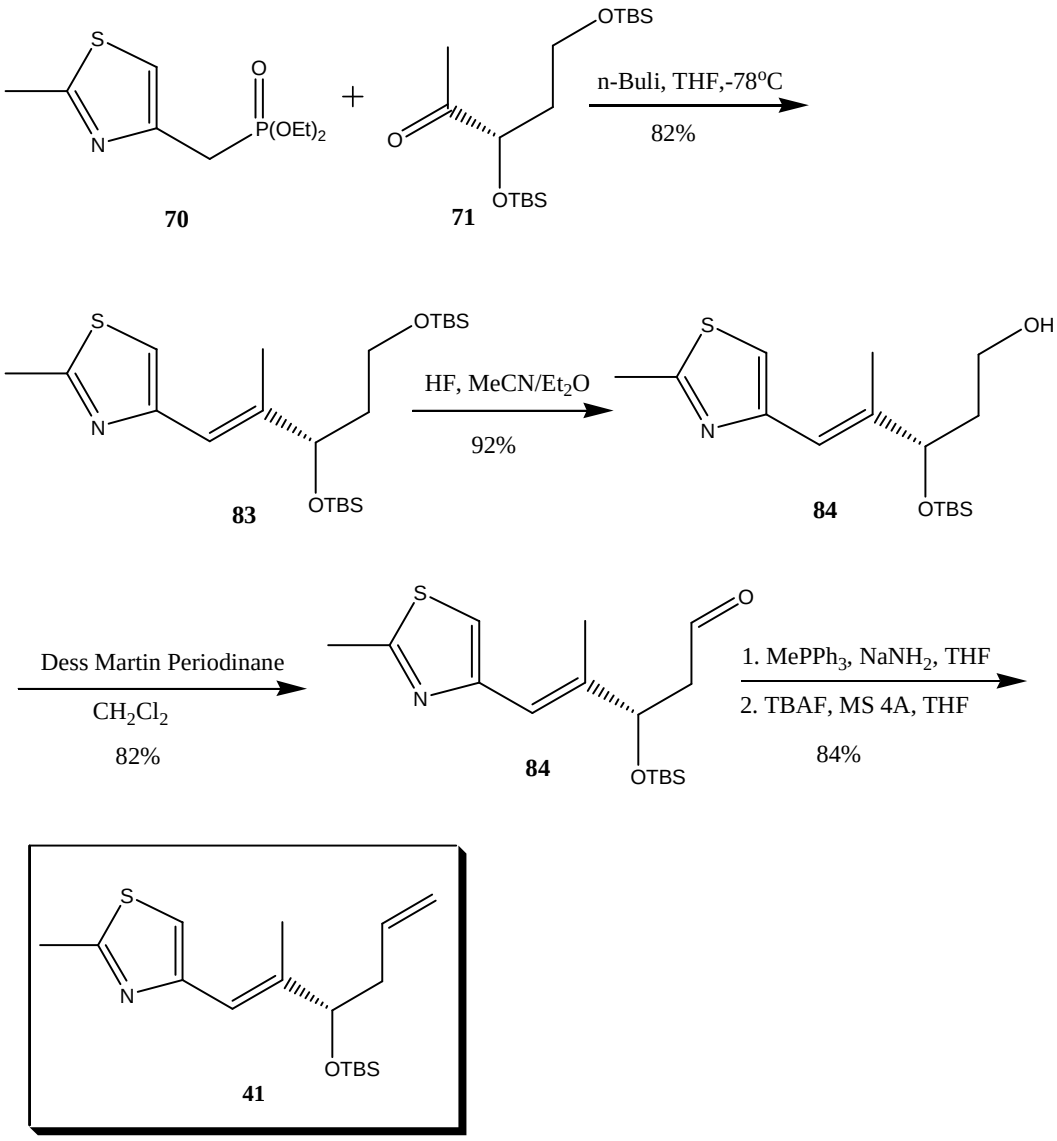
dichloromethane. Protection of compound **75** using a standard procedure afforded silyl ether **76** in 93% yield. Addition of MeLi gave the lactols **77** and **78** which were protected without purification as the TBS-ethers under standard conditions to give enantiomerically pure ketone **71** (73% yield over 2 steps).

The phosphonate **70** which is required in the Horner-Emmons reaction with methyl ketone **71** was synthesized over 2 steps using the commercially available compounds: 1,3-Dichloroacetone **79** and thioacetamide **80** which were reacted under Hantzsch condition affording the 4-chloromethyl-2-methythiazole **81**. An Arbuzov reaction then gave phosphonate **70** (see scheme 22).



Scheme 22. Synthesis of Phosphonate **70**

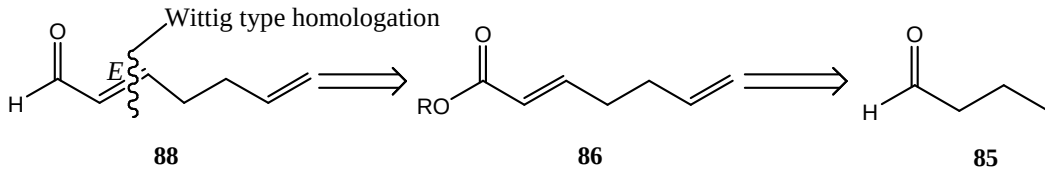
Deprotonation of phosphonate **70** with n-Buli and subsequent reaction with methyl ketone **71** under Horner-Emmons conditions (see scheme 23) yielded the desired trisubstituted olefin **82** as a single stereoisomer in good yield (79%). Selective desilylation of the primary hydroxyy group from **82** was achieved by the action of aqueous HF in $MeCN/Et_2O$, leading to hydroxyl compound **83** in 90% yield. Dess-Martin oxidation then gave aldehyde **84** in 84% yield, which was converted to the required thiazole alcohol **41** by the action of the Wittig reagent $Ph_3P{=}CH_2$ and subsequent desilylation with TBAF in 84% yield over two steps.



Scheme 23. Synthesis of The Thiazol Fragments **41**

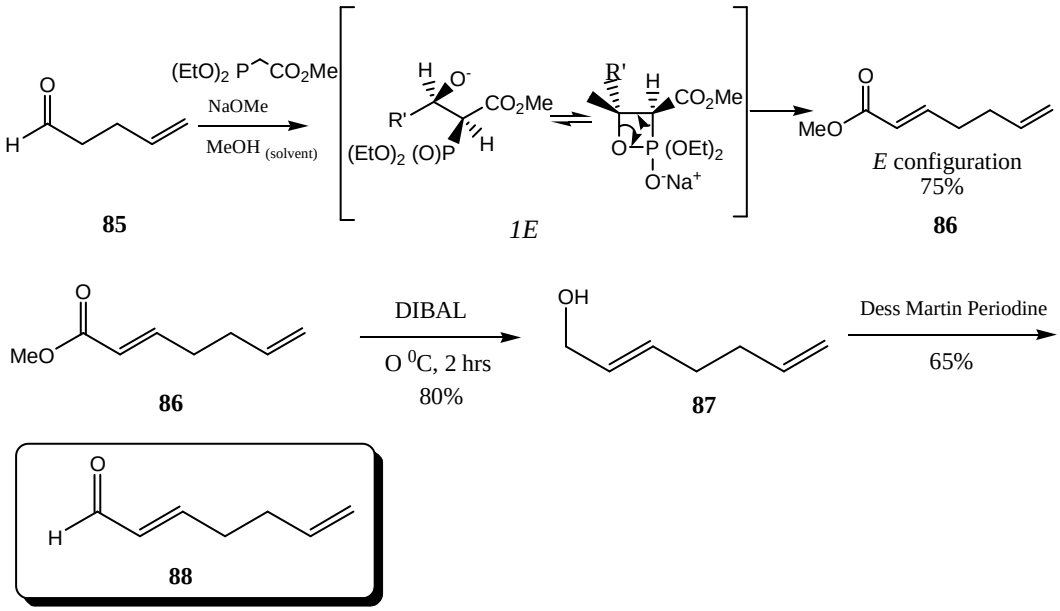
3.3. Synthesis of Aldehyde Fragment **88**

Aldehyde bulding block **88** was prepared by again employing an Horner-Wadsworth-Emmons reaction using methoxide in the methanol as the base (see scheme 24).



Scheme 24. Retrosynthetic Analysis Aldehyde **88**

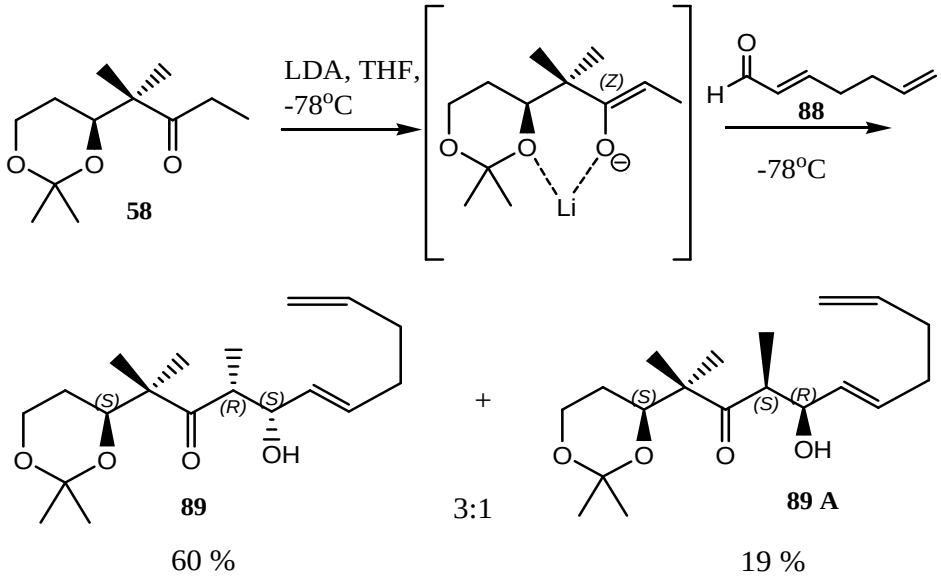
Thus, ester **86**[62] was obtained from 4-Pentenal **85** and carbomethoxymethyl diethyl phosphonate (stabilzed phosphonate). This reaction proceeds in high stereoselectivity and delivers only the *E* isomer in 70%. The transtion state of this reaction favours only the formation of the thermodynamically more stable intermediates *1E* which leads to the *E*-alkene (see scheme 25). The by-product dialkylphosphate salt was readily removed by aqueous extraction. Treatment of **86** with DIBAL-H afforded alcohol **87**[63] in 80% yield and via oxidation of compound **82** with Dess-Martin-Periodinane the pure aldehyde **88** with the desired *E* configuration was isolated in 65% yield.



Scheme 25. Synthesis of Aldehyde **88**

3.4. Total synthesis of 8,9-dehydro Epothilone C

The aldehyde **88** and ethyl ketone fragment **58** were reacted under aldol condition to produce the C1-C12 building block of the novel epothilone C analogue. The optimum conditions for this coupling reaction required the generation of the *syn*-lithium enolate of ethyl ketone **58** with 0.98 equivalents of LDA in THF at -78°C, followed by the addition of aldehyde **88** (see scheme 17).



Scheme 26. Aldol reaction of Fragment **88** and **58**

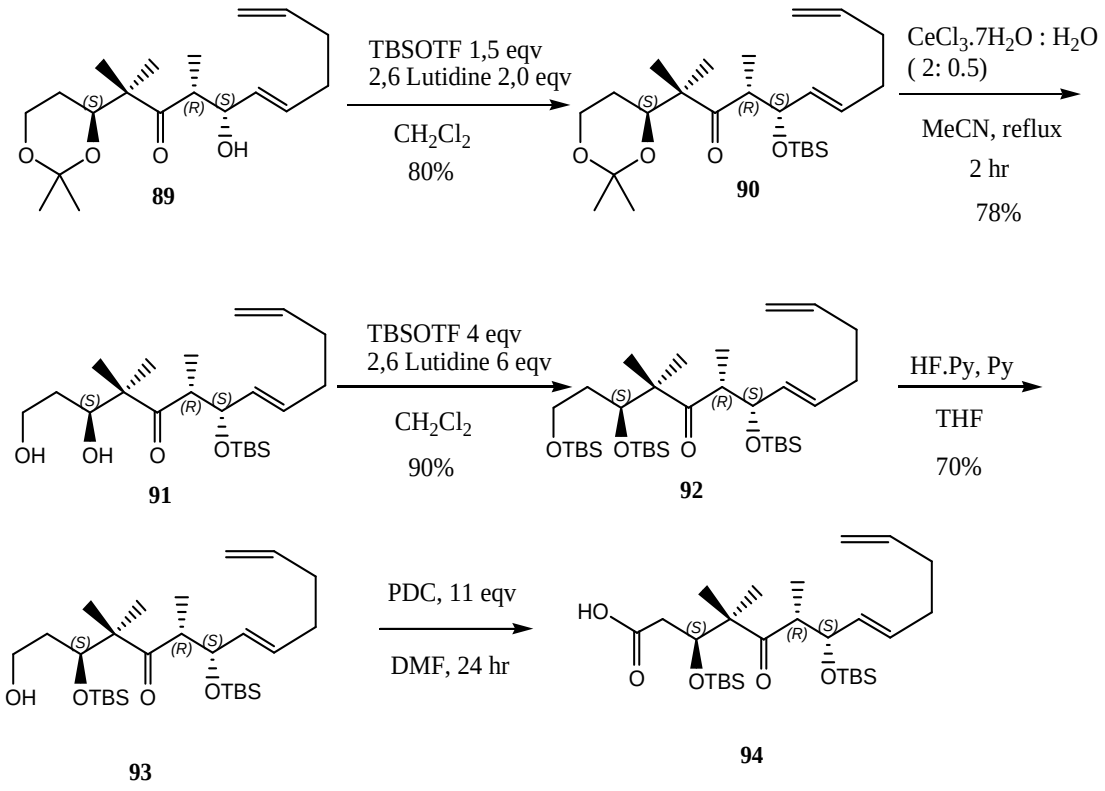
The procedure of aldol reaction for this compound had been introduced by Anja Limberg[64]. With aldehyde **88** it proceeds with moderate diastereoselectivity (3:1) in favor of the desired *syn* (6*R*,7*S*) isomer **89** in 60% yield (see scheme 26). The diastereoselectivity of this reaction was decreased compared to previous publications from Schinzer *et al*., due to the use of the achiral aldehyde (α,β-unsaturated olefin). The result just reflects the inherent selectivity of the enolate (scheme 26). The second chiral element in the aldehyde is missing and therefore no double stereoselection can be obtained.

The Aldol adduct **89** was protected with TBSOTf giving the silylether **90** in 80% yield. Cleavage of acetonide **90** has been successful by modified procedure [64] using the lewis acid $CeCl_3.7H_2O$[65] with water (2:0.5) in acetonitrile under reflux instead of CSA in MeOH. The conditions yielded diol **91** in 78% yield and no cyclization by-product was detected. Before we discovered this combination of reagents, several methods were tested to cleave acetonide including using mixtures of HCl in MeOH, PPTS in MeOH, and p-TSOH in CH_2Cl_2 at -20°C. All these methods failed to produce the desired compound leading only to decomposition (see table 1). This is probably due to the instability of this compound in the presence of acids in methanol.

Reagent, Condition	Results
PPTS in MeOH, O°C, 24 Hr	Decomposition
PPTS (0.2 Eqv) in MeOH, RT, 20 Hr	Decomposition
p-TsOH (0.2 Eqv)in CH_2Cl_2, -20 °C, 4 hr	Decomposition
1M HCl : MeOH (1:9), RT, 3 Hr	Decomposition
HCl :THF:H_2O (0.5:1:2), RT, 2 Hr	Decomposition

Table 1. Methods Test Conditions for the Cleavage of Acetonide **85**

Treating **91** with excess TBSOTf and 2,6 lutidine gave tris-silyl ether **97** almost quantitatively (90%). Selective deprotection of the primary TBS ether, **92**, was achieved by the action of mixture of HF complex and pyridine in THF leading to mono alcohol **93** in 70% yield. Finally, acid **94** was obtained from **93** by oxidation with PDC in DMF in 69% yield (see scheme 27).[58]



Scheme 27. Synthesis of Acids **94**

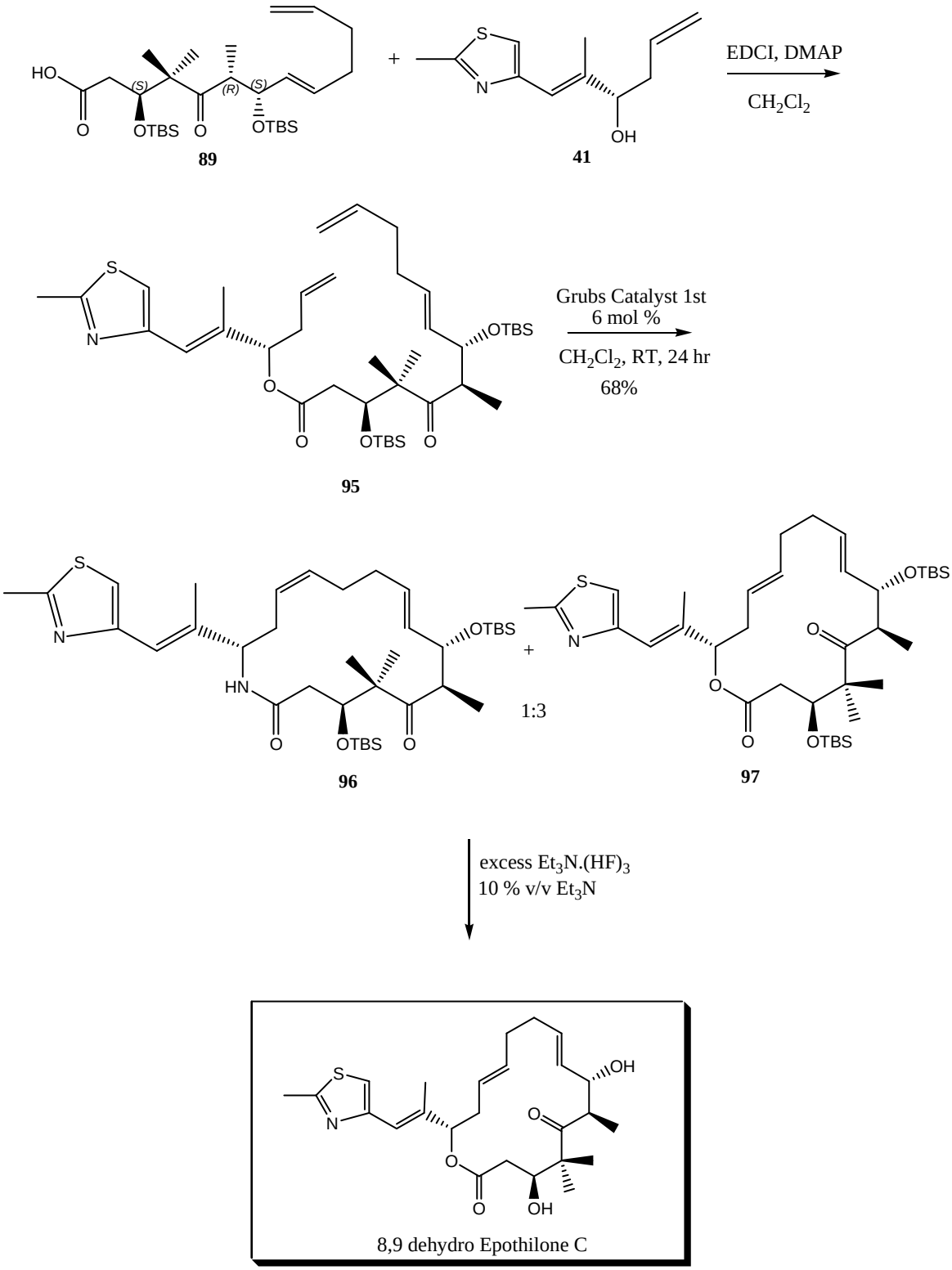
Reaction Conditions (89:63: DCC/ EDCI: DMAP) eqv	Results
1: 1: 1.3: 0.2	56 % + side product
1: 1.2: 1.3: 0.2	57% + side Product
1: 1: 1.3 (EDCI): 0.2	70% of ester **95**
1: 1.2: 1.3 (EDCI): 0.2	78 – 80% of ester **95**

Table 2. Optimization Esterification of Fragment Acids **94** and Thiazole **41**

Initials attempts for the esterification of thiazole fragment **41** and acid **89** with DCC and DMAP gave the desired diene **95** only in moderate yield (25-57%) and were not regularly reproducible. A significant improvement in the efficiency of the reaction could be realized, however, by drying of starting material, the use of EDCI instead of DCC and a 20% excess of the thiazole fragment **41**. Thus under optimized conditions (1.0 eqv acid **94**, 1.2 eqv alcohol **41**, 1.3 eqv EDCI, 0.3 eqv DMAP) ester **90** was consistently obtained in yields between 76 and 83% (see table 2).

With diene **95** as metathesis precusor in hand, we successfully carried out the RCM olefin-metathesis reaction of **95** with Grubbs catalyst (first generation) (see scheme 28). The reaction provided 2 mixture **96** and **97** which could be separated under normal chromatography, the desired *E* ($^3J_{12,13}$ = 15.5) isomer being slightly favored with (*Z*/*E* = 3:1, based on % of the yield). These phenomena probably can be explained that the double bond in C8 and C9 with *E*-geometric promotes a favorable conformation for the formation of *E*-isomer during the RCM reaction or increases the final thermodynamic stability of the *E*-isomer versus the *Z*-isomer.

The conversion of the fully protected macrolide **97** to our target structure **98** then required the selective removal of the TBS protecting groups. This transformation could be achieved in moderate yield (50%) by treatment of **97** with excess amount of $Et_3N.(HF)_3$ in acetonitrile in the presence of 10% v/v triethylamine. [66]



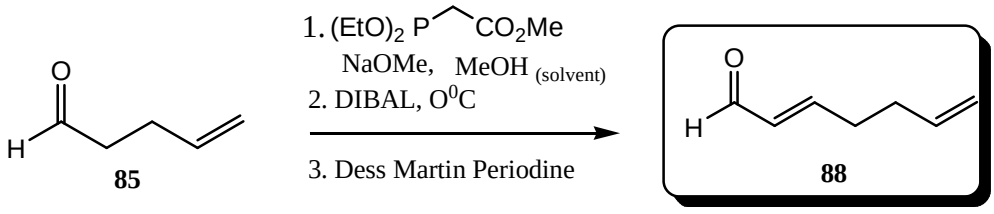
Scheme 28. Ring Closing Methatesis of 8,9-dehydro Epothilone C

Chapter 4

Summary

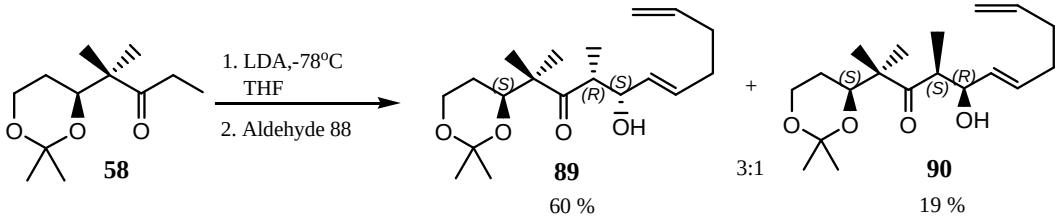
The purpose of this project was the development of a new analogue of epothilone C with a double bond between the C8 – C9 carbon atom. Herein a novel synthesis of 8,9-dehydro epothilone C was described (scheme 28). A convergent synthetic route which was stereoselective, robust and quite flexible was employed. The construction of the stereocenter at C3 in the epothilone macrocycle is achieved by a diastereoselective aldol reaction with the chiral acetate equivalent (*S*)-(-)-HYTRA (1,1,2- triphenyl-1,2-ethanediol acetate) **66**. Due to the fact that the aldol reaction between compound **66** and **57** failed, we were developed a new protocol by employing catalytic amounts of scandium (III) triflate instead of acetiyl chloride in presence of a pyridine catalyst used by Braun *et al*..

Aldehyde bulding block **88** was obtained from 4-pentenal **85** by employing a Horner-Wadsworth-Emmons reaction using methoxide in the methanol as the base. This reaction delivers only the *E* isomer in 75% yield (scheme 29).



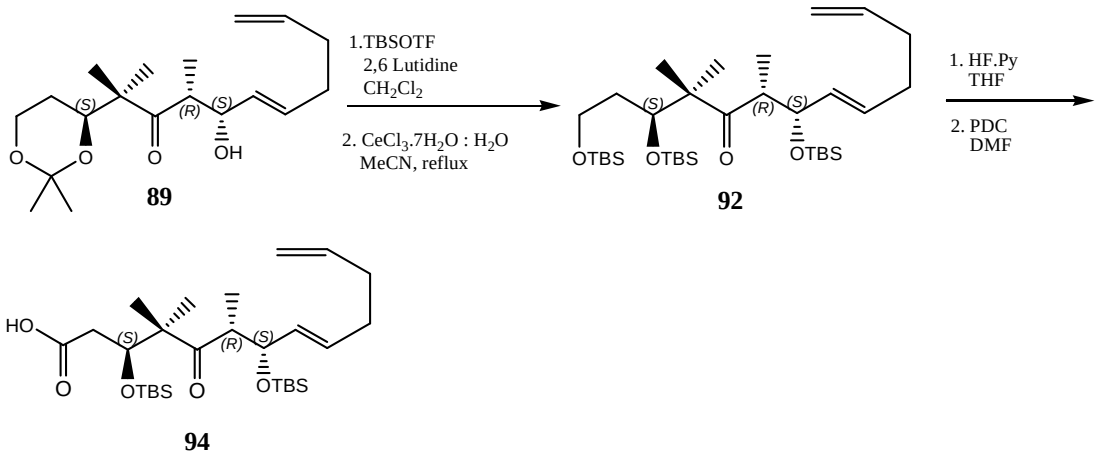
Scheme 29. Synthesis of Aldehyde **88**

The aldol reaction of aldehyde **88** and ethyl ketone **58** (for building the C1-C12 fragment of epothilone) are giving moderate diastereoselectivity (3:1) in favor of the desired *syn* (6*R*,7*S*) isomer **89** in 60% yield (scheme 30).



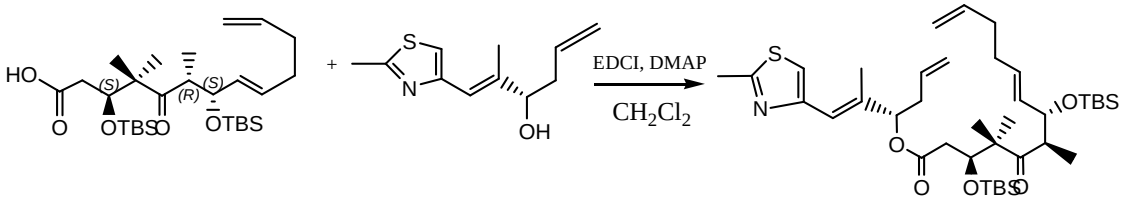
Scheme 30. Aldol Reaction of Aldehyde **88** and Ketone **58**

After protection of secondary alcohol **89**, subsequent cleavage of acetonide with $CeCl_3.7H_2O$ the intermediate **92** as isolated. Deprotection of the primary TBS group and oxidation of the alcohol with PDC in DMF to yield acid **89** (69%) (see scheme 31).



Scheme 31. Synthesis of Acids **89**

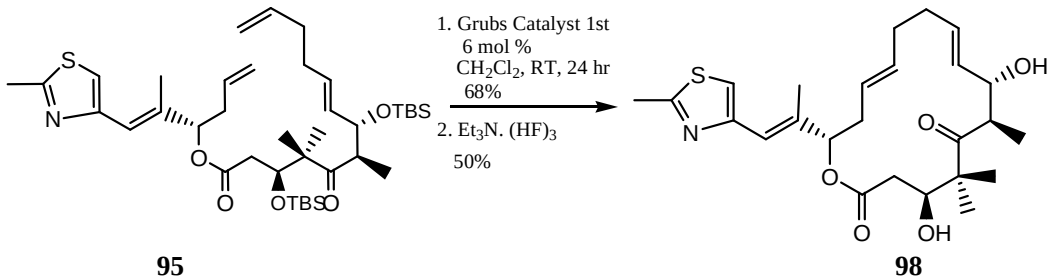
The esterification reaction of thiazole fragment **41** with acid **89** has been successfully in good yield by the use of EDCI instead of DCC and a 20% excess of the thiazole fragment **63**.



89 **41** **95**

Scheme 32. Synthesis of Diene **95**

At the end, we successfully carried out the RCM olefin-metathesis reaction of **95** with Grubbs catalyst (first generation) giving the mixture of macrolide **96** and **97** which was separable under standard chromatography. Finally, a global deprotection of marolide **96/97** proceeded by employing a much milder desylation reagent, $Et_3N.(HF)_3$. The desired *E* (**98**) isomer is being slightly favored.



95 **98**

Scheme 33. Ring Closing Metathesis of 8,9-dehydro Epothilone C.

In summary, the Schinzer *et al.* synthetic strategy offers the possibility to synthesize a new epothilone analogue with good overall selectivity.

Chapter 5

Experimental Part

5.1.1. Chemicals and Working Technique

All required fine chemicals were received from the firms ACROS , ALDRICH , FLUKA and MERCK. 4-Pentenal that has been used for aldehyde **88** precursor was purchased form Alfa Aesar in 97% purity. They were used directly without further purification if nothing else was mentioned. All solvents were distilled and/or dried before use. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform. Unless mentioned, all the reactions were carried out under a nitrogen 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.[40,53,58]

5.1.2 NMR-Spectroscopy

^{1}H , ^{13}C NMR and two-dimensional spectra (COSY, TOCSY, HSQC, HMBC, NOESY) were measured on BRUKER DPX 400, AMX 200, AMX 400 and BRUKER AMX 600 (600 or 150 MHz, respectively). As solvents was used chloroform-d or benzene-d6. TMS ($\delta = 0$) 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: d for CH, q for CH_3, t for CH_2, and s for C.

5.1.3. Mass Spectrometry

Mass spectra were recorded on a Finnigan SSQ 7000 from the FINNIGAN-MAT (Bremen). High-resolution mass spectra were measured on an Intectra Finnigan MAT-95 mass spectrometer from the same firm. The used mass spectrometric ionization methods were electron-impact (EI) with 70eV ionization potential, chemical ionization (CI) with NH_3 as gas reactant, fast-atom bombardment (FAB) or field-desorption (FD). Significant fragments are reported as follows: m/z (relative intensity).

5.1.4. Infrared Spectroscopy

Infrared spectra (IR) were recorded on a FT-IR-2000 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}.

5.1.5. Polarimetry

Optical rotations were measured on a Perkin-Elmer Polarimeter P-341. They are reported as follows: $[\alpha]_D^{Temperature}$ (concentration, solvent). The unit of c is g/100 ml. As a solvent was used anhydrous CH_2Cl_2.

5.1.6 Melting Points

Melting points were taken with a BÜCHI B-540 point microscope apparatus or digital Electrothermal IA 9100 from Kleinfeld firma and were not corrected.

5.1.7. Elemental Analysis

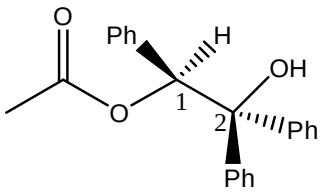
Elemental analyses were recorded with a LECO CHNS-932.

5.1.8 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 visualized by UV_{254} light and the chromatography plates were developed with a vanillin solution or aqueous solution of potassium permanganate (heating on a hot-plate). For preparation of the vanillin solution were used 8.6 g vanillin dissolved in 200 ml ethanol and put 2.5 ml 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 and 5 ml 5%NaOH. Flash column chromatography was performed using flash silica gel 60 M (40-63 µm) from the firm FLUKA.

5.1.9. Synthesis of (*S*)-Ethyl Ketone Fragments **58**

(*S*)-(-)-2-Hydroxy-1,2,2-triphenylethyl acetate [(*S*)-HYTRA] (**66**):



66

To a stirred solution of (*S*)-(-)-1,1,2-triphenyl-1,2-ethanediol 58 (35.0 g, 0.121 mol, prepared by braun methode and acetic anhydride (17.1 mL, 0.181 mol, 1.5 eq) in anhydrous acetonitrile (500 mL, at room temperature under nitrogen is added a solution of scandium (III) trifluoromethanesulfonate (1.23 g, 2.5 mmol, 2 mol%) ; The order of addition of the reagents has a significant effect on the yield of the reaction. The optimal order of addition of reagents is described above i.e., addition of Sc[III](OTf)$_3$ slowly, last. Continual addition of the scandium (III) triflate during the course of the reaction maintained the pace of the process. Bolus addition of the catalyst resulted in a reaction that slowed down or stopped part way, resulting in lower yields; in anhydrous acetonitrile (125 mL) over approximately 35 min. After about 8 min a white precipitate begins to appear, and the resulting mixture is stirred at room temperature under nitrogen for a total of 3 hr. The solid is filtered, washed with acetonitrile (2 × 25 mL), and dried under vacuum at 40°C overnight to afford (*S*)-(-)-2-hydroxy-1,2,2-triphenylethyl acetate **66** (31.36 g, 78%) as a white solid.

General data: $C_{22}H_{20}O_3$, MW: 332.39, mp 225-230°C (crude product). $[\alpha]_D^{20}$ = -196° (pyridine, crude product, *c* = 1); DC: R_f = 0.40 (Pentan/Et2O 2:1), UV (+), vanillin: yellow

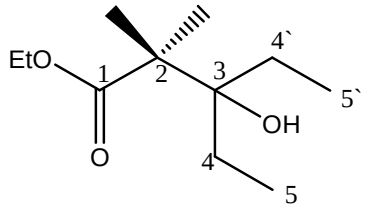
^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.98 (s, 3 H, CH_3CO_2CH), 2.80 (s, 1 H, $Ph_2CO\mathit{H}$), 6.66 (s, 1 H, $PhC\mathit{H}$), 7.04-7.42 (m, 13 H, H_{arom}), 7.55-7.57 (m, 2 H, H_{arom}) ;

^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.1 (q, $\mathit{C}H_3CO_2CH$), 78.5 (d, PhCh), 80.3 (s, Ph_2C), 126.2 (d, Ph-2), 126.3 (d, Ph-3), 127.0 (d, Ph-4), 127.3 (d, Ph-4), 127.5 (d, Ph-2), 127.8 (d, Ph-3), 127.9 (d, Ph-4), 128.4 (d, Ph-2), 128.5 (d, Ph-3), 135.9 (s, Ph-1), 142.7 (s, Ph-1), 144.8 (s, Ph-1) , 169.7 (s, $\mathit{C}H_3CO_2CH$).

IR ($CHCl_3$) cm^{-1}: 3064, 3024, 1737, 1495, 1372, 1239, 1168, 779;

HRMS calcd for $C_{22}H_{19}O_2$ ($[M+H^+]-H_2O$), m/z 315.1385,
found 315.1386

Ethyl 3-ethyl-3-hydroxy-2,2-dimethylpentanoate (**60**):



60

A suspension of zinc dust (10.79 g, 0.165 mol) in THF (40 mL) and $B(OMe)_3$ (40 mL) was activated with 1,2-dibromoethane (0.26 mL, 3.0 mmol) and TESOTf (0.34 mL, 1.5 mmol). A mixture of 3-pentanone (15.9 mL, 0.15 mmol) and ethyl 2-bromo-2-methylpropanoate (23.4 mL, 0.165 mol) was added slowly to the activated

zinc suspension. The reaction mixture was heated gently in a hot air stream until the reaction started. The addition was performed at such a rate that the mixture gently refluxed. After addition of the reactants, the mixture was refluxed for 2 h and stirred at room temperature for 20 h. The reaction was quenched by addition of 25 % aqueous NH_3 solution (45 mL) at 0°C. Glycerine (45 mL) and Et_2O (40 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 mL). The combined organic layers were dried over MgSO4 and concentrated in vacuo. Purification of the residue by vacuum distillation afforded β-hydroxy ester **60** (19.72 g, 65 %) as a colorless liquid.

General Data: $C_{11}H_{22}O_3$, MW: 209.29.: bp: 108-110°C (10 mbar); DC: R_f = 0.48 (Pentan/Et2O 1:1), UV (-), Vanillin: dark blue

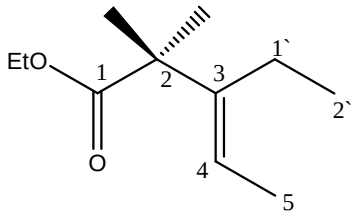
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17 (q, ^3J = 7.1 Hz, 2 H, CH_3CH_2OCO), 3.78 (s, 1 H, OH), 1.56 (m, 4 H, H-4), 1.29 (t, ^3J = 7.1 Hz, 3 H, CH_3CH_2OCO), 1.22 (s, 6 H, C2-CH_3), 0.93 (t, ^3J = 7.5 Hz, 6 H, H-5) ;

^{13}C NMR (100 MHz, CDCl3): δ = 179.2 (s, C-1), 76.2 (s, C-3), 60.9 (t, CH_3CH_2OCO), 50.3 (s, C-2), 28.2 (t, C-4, C-4`), 21.6 (q, C-5, C-5`), 14.1 (q, CH_3CH_2OCO), 8.9 (q, C2-$(CH_3)_2$);

MS (PCI, CH_4): m/z (%): 203.4 (100) $[M+H]^+$, 185.4 (78) $[M+H - H_2O]^+$, 171.1 (11), 155.1 (23), 145.1 (24),111.1 (16) ; $C_{11}H_{22}O_3$ (202.3):

HRMS calcd : C 65.31, H 10.96
found : C 65.09, H 11.35.

Ethyl -(*E*)-3-ethyl-2,2-dimethyl-3-pentenoate (**61**):



61

Hydroxy ester **60** (9.74 g, 48.1 mmol) was heated under reflux with Sicapent (11.84 g) in cyclo-hexane (40 mL) for 20 min. The solvent was removed by distillation. Vacuum distillation of the residue afforded ester **61** (7.10 g, 80 %) as a colorles liquid.

General Data: $C_{11}H_{20}O$, MW: 184.28; bp: 60-63°C (3 mbar); DC: R_f = 0.75 (Pentan/Et_2O 2:1), UV (-), Vanillin: pale blue.

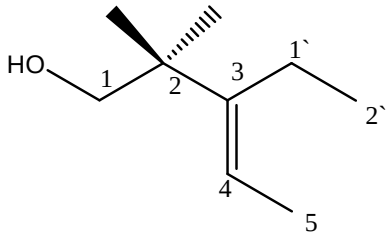
^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.41 (q, ^3J = 6.8 Hz, 1 H, H-4), 4.11 (q, ^3J = 7.2 Hz, 2 H, CH_3CH_2OCO), 2.06 (q, ^3J = 7.6 Hz, 2 H, CH_3CH_2C=C), 1.65 (d, ^3J = 6.8 Hz, 3 H, H-5), 1.28(s,6 H, C_2-CH_3), 1.23 (t, ^3J =7.1 Hz, 3 H, CH_3CH_2OCO), 0.97 (t, ^3J =7.5 Hz, 3 H, CH3CH2C=C) ;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2 (s, C-1), 144.1 (s, C-3), 118.5 (d, C-4), 60.3 (t, CH_3CH_2OCO), 48.4 (s, C-2), 24.9 (q, C2-$(CH_3)_2$), 21.7 (t, C-1`), 14.1, 13.9,13.5 (q, C-5, $CH_3CH_2OCO$, C-1`) ;

MS (PCI, CH_4): m/z (%): 185.1 (69) $[M+H]^+$, 169.1 (14), 157.1 (100), 153.0 (16), 139.0 (9), 124.9 (15), 111.0(30), 57.0 (38) ;

HRMS (EI): calcd for $C_{11}H_{20}O_2$ 184.1463,
found 184.146.

(*E*)-3-Ethyl-2,2-dimethyl-3-pentenal (**62**):



62

LAH (2.95 g, 77.6 mmol, 2.0 equiv) was added to a solution of ester 7 (7.15 g, 38.8 mmol) in THF (40 mL). The mixture was refluxed for 2 h. After cooling to 0°C, Et_2O (30 mL) was added, and the mixture was quenched by dropwise addition of water (2.95 mL), 15% aqueous NaOH (2.95 mL), and water (4.50 mL). Celite (400 mg) was added, and the mixture was stirred for 30 min at room temperature. The precipitate was filtered off by suction and washed with Et_2O (4 x 40 mL). The filtrate and the washings were combined and concentrated in vacuo to furnish crude (*E*)-3-ethyl-2,2-dimethyl-3-penten-1-ol as a colorless liquid, which was used for the preparation of aldehyde **57** without further purification. An analytical sample of the alcohol was obtained by vacuum distillation.

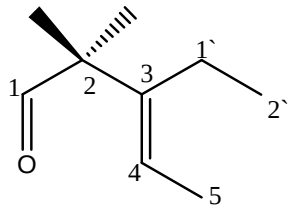
General Data: $C_9H_{18}O$, MW: 142.24; bp: 105-106°C (30 mbar); DC: R_f = 0.40 (Pentan/Et2O 5:1), UV (-), Vanillin : dark blue.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (q, ^{3}J = 6.7 Hz, 1 H, H-4), 3.35 (s, 2 H, H-1), 2.07 (q, ^{3}J = 7.6 Hz, 2 H, CH_3CH_2C=C), 1.67 (d, ^{3}J = 6.7 Hz, 3 H, H-5), 1.34 (brs,1 H, OH), 1.04 (s, 6 H, C2-CH_3), 1.00 (t,^{3}J = 7.5 Hz, 3 H, CH_3CH_2C=C) ;

^{13}C NMR (100 MHz, CDCl3): δ = 145.2 (s. C-3), 120.5 (d, C-4), 69.7, 42.0 (s, C-2), 24.0 (q, C2-CH_3), 20.0 (t, C-1`), 14.2, 13.6 (q, C-5, C-2´).

MS (70 eV, EI): m/z (%): 142.1 (7) $[M]^+$, 125.1 (48), 111.0 (34), 96.2 (14), 83.0 (35), 71.1 (37), 69.1 (100), 57.0 (42), 55.0 (66).

(*E*)-3-Ethyl-2,2-dimethyl-3-pentenal (**57**):



57

DMSO (6.59 mL, 93.0 mmol, 2.0 equiv) in CH_2Cl_2 (20 mL) was added dropwise at -78°C to a stirred solution of $(COCl)_2$ (3.71 mL, 42.7 mmol, 1.1 equiv) in CH_2Cl_2 (97 mL) within 5 min. The mixture was stirred for 10 min at -78°C. The crude (*E*)-3-ethyl-2,2-dimethyl-3-penten-1-ol dissolved in CH_2Cl_2 (38 mL) was added dropwise within 5 min. The mixture was then stirred for 1 h at -78°C. The reaction was quenched by dropwise addition of NEt_3 (27 mL, 194.0 mmol, 5.0 equiv). The mixture was warmed to room temperature within 45 min. Water (97 mL) was added, and the mixture was stirred for 10 min. The organic layer was separated and

the aqueous layer was extracted with CH_2Cl_2 (3x100 mL). The combined organic extracts were dried over MgSO4 and concentrated in vacuo. Purification of the residue by vacuum distillation afforded aldehyde **57** (3.43 g, 65 % over two steps) as a colorless liquid.

General Data: $C_9H_{16}O$, MW: 140.22; bp: 85-86 °C (28 mbar); DC: R_f= 0.75 (Penta/Et2O 5:1), UV (-), Vanillin: dark blue.

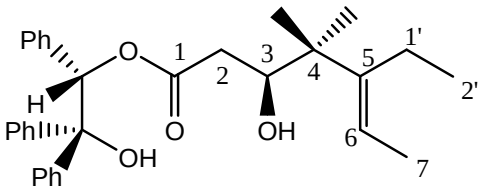
^{1}H NMR (400 MHz, CDCl3): δ =9.27 (s, 1 H, H-1), 5.41 (q, ^3J =6.8 Hz, 1 H, H-4), 2.02 (q, ^{3}J =7.6 Hz, 2 H, CH_3CH_2C=C), 1.69 (d, ^3J = 6.9 Hz, 3 H, H-5), 1.17 (s, 6 H ; C2-CH_3), 0.96 (t, ^3J = 7.6 Hz, 3 H, CH_3CH_2C=C) ;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5 (s, C-1), 141.4 (s, C-3), 122.6 (d, C-4), 52.7 (s, C-2), 24.2 (t, C-1`), 14.1, 13.8 (q, C-5, C-2`) ;

MS (PCI, CH4): m/z (%): 141.0 (29) $[M+H]^+$, 127.1 (98), 111.1 (100), 97.1 (2), 83.1 (3) ;

HRMS (EI): calcd for C_9H1_6O 140.1201,
found 140.116

(1*S*)-2-Hydroxy-1,2,2-triphenylethyl (3*S*,5*E*)-5-ethyl-3-hydroxy-4,4-di-methyl-5-heptenoate (**67)**:



67

nBuLi (3.20 mL, 8.0 mmol, 2.5 m solution in hexanes) was added at -78 °C to a solution of diisopropylamine (1.28 mL, 8.0 mmol) in THF (10 mL) cooled to-78 °C. This LDA solution was stirred for 30 min at 0 8C and added dropwise to a solution of (*S*)-(-)-2-hydroxy-1,2,2-triphenyl acetate **66** (1.330 g, 4.0 mmol) in THF (25 mL) at -78°C. The mixture was stirred for 1 h at 0°C. The resulting orange-red solution was cooled to 78 °C, and a solution of aldehyde **57** (673 mg, 4.8 mmol, 1.2 equiv) in THF (5.0 mL) was added dropwise. The mixture was stirred for 90 min. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 3:1) afforded β-hydroxy ester **67** (1.41 g, 75 %, 94 % *de*) as a colorless crystalline solids.

General Data: $C_{31}H_{36}O_4$, MW: 472.62; bp: 144-145 °C; $[\alpha]_D^{20}$ = - 252.5 (*c* = 1.0, $CHCl_3$); DC: R_f = 0.43 (Pentan/Et_2O 2:1), UV (+), Vanillin: green.

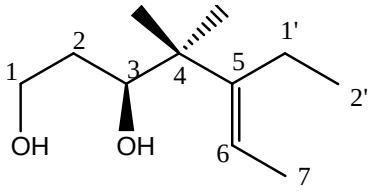
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 - 7.54 (m, 2H, Harom.), 7.38 - 7.02 (m, 13H, Harom.), 6.70 (s, 1 H, PhCH), 5.30 (q, ^{3}J = 6.8 Hz, 1H, H-6), 3.78 (ddd, ^{3}J = 10.0 Hz, ^{3}J = 2.7 Hz, ^{3}J = 2.5 Hz, 1H, H-3), 2.86 (s, 1H, Ph_2COH), 2.31 (dd, ^{2}J = 15.7 Hz, ^{3}J = 2.2 Hz, 1H, H-2), 2.21 (dd, ^{2}J = 15.7 Hz, ^{3}J = 10.0 Hz, 1 H, H-2), 2.03 (d, ^{3}J = 3.1 Hz, 1H, C3-OH), 1.98 (dq, ^{4}J = 2.2 Hz, ^{3}J = 7.5 Hz, 2H, CH_3CH_2C=C), 1.60 (d, ^{3}J = 6.8 Hz, 3H, H-7), 0.98, 0.91 (2 s, 2 3H, C2-CH_3), 0.91 (t, ^{3}J = 7.6 Hz, 3H, CH_3CH_2C=C) ;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (s, C-1), 146.0, 144.7 (s, Ph-1), 142.6 (s, C-5), 135.6 (s, Ph-1), 128.4, 128.3 (d, Ph-2, Ph-3), 128.0 (d, Ph-4), 127.8, 127.5 (d, Ph-2, Ph-3), 127.3, 127.1 (d, Ph-4), 126.3, 126.2 (d, Ph-2, Ph-3), 120.3 (d, C-6), 80.4 (s, Ph_2C), 78.9 (d, Ph*C*H), 72.3 (d, C-30), 44.0 (s, C-4), 37.4 (t, C-2), 22.9 (q, C4-CH_3), 21.3 (q, C4-CH_3), 20.2 (t, C-1`), 14.3, 13.6 (q, C-7, C-2') .

MS (70eV, EI): m/z (%): 472.3 (<0.4) $[M]^+$, 455.2 (0.4), 290.3 (4), 273.1 (70), 256.1 (12), 195.1 (17), 183.1 (100), 167.2 (12), 112.0 (16), 105.0 (26), 69.2 (10) ;

HRMS (EI) : calcd C 78.78, H 7.68 ;
found C 78.87,H 7.73.

(3*S*,5*E*)-5-Ethyl-4,4-dimethyl-5-heptene-1,3-diol (68)



68

LAH (1.325 g,35.0 mmol, 7.0 equiv) was added portionwise to a refluxing solution of ester **67** (2.364 g, 5.0 mmol) in Et_2O (50 mL) within a period of 2 h. Refluxing was continued for 30 min. After cooling to 0°C, the reaction was quenched by dropwise addition of water (1.35 mL) and 15 % aqueous NaOH (1.35 mL). Et_2O (40 mL) and water (1.35 mL) were added. The mixture was stirred for 1 h at room temperature until a white precipitate formed which was filtered off by suction through a small plug of celite. The precipitate was washed with Et_2O (4 x 40 mL). The filtrate and washings were combined and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et2O 2 :1) afforded (S)-2,2,1-triphenyl-ethane-1,2-diol **65** (912 mg, 90 %) as a colorless crystalline solid, and alcohol **68** (836 mg, 90 %) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (q, ^3J = 6.8 Hz, 1 H ; H-6), 3.86 - 3.76 (m, 2H, H-1), 3.68 (dd, ^3J = 10.3 Hz, ^3J = 2.1 Hz, 1H, H-3), 3.00 (brs, 1H, OH), 2.20 (br s, 1H, OH), 2.17 - 2.02 (m, 2H, CH_3CH_2C=C),1.67 (d, ^3J = 6.8 Hz, 3H, H-7), 1.71 - 1.52 (m, 2H, H-2), 1.03, 1.01 (2 s, 2x3H, C4-CH_3), 0.91 (t, ^{3}J = 7.6 Hz, 3H, CH_3CH_2C=C).

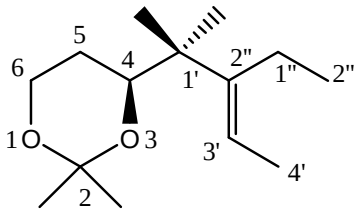
General Data: $C_{11}H_{22}O_2$, MW: 186.29, $[\alpha]_D^{20}$ = -30.7 (*c* = 1.0, $CHCl_3$); DC: R_f = 0.3 (Et_2O 2:1), UV (-), Vanillin: dark blue.

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2 (s, C-5), 121.1 (d, C-6), 75.8 (d, C-3), 62.6 (s, C-1), 44.4 (s, C-4), 32.7 (t, C-2), 22.8, 21.1 (q, C4-$(CH_3)_2$), 20.1 (t, C-1'), 14.3, 13.6 (q, C-7, C-2');

MS (70 eV, EI): m/z (%): 186.0 (0.6) $[M]^+$, 177.0 (1), 141.0 (3), 112.0 (100), 96.9 (19), 83.0 (75), 74.9 (13), 68.9 (60), 54.9 (34).

HRMS (EI): calcd for $C_{11}H_{22}O_2$ 186.1620,
found 186.157.

(4*S*)-4-[(*E*)-2-Ethyl-1,1-dimethyl-2-butenyl]-2,2-dimethyl-1,3-dioxane (**69**):



69

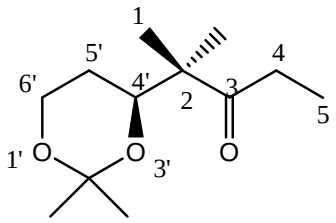
Anhydrous $CuSO_4$ (478 mg, 3.0 mmol, 1.5 equiv), pTsOH . H_2O (76 mg, 0.4 mmol, 0.2 equiv), and pyridine (24 mL, 0.3 mmol, 0.15 equiv) was added to a solution of diol **68** (372 mg, 2.0 mmol) in acetone (30 mL). The mixture was stirred for 24 h at room temperature. Saturated aqueous $NaHCO_3$ solution (40 mL) was added and the aqueous layer was extracted with Et_2O (4x60 mL). The combined organic extracts were dried over $MgSO_4$ and carefully concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 40:1) gave acetonide **69** (812 mg, 90%) as a colorless oil.

General Data: $C_{14}H_{26}O_2$, MW: 226.36; $[\alpha]_D^{20}$ = +14.3 (*c* = 1.0, $CHCl_3$); DC: R_f = 0.84 (Et_2O), UV (-), Vanillin: black

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.32 (q, ^3J = 6.8 Hz, 1H, H-3'), 3.88 (dt, ^2J = 11.8 Hz, ^3J = 2.9 Hz, 1H, H-6), 3.80 (ddd, ^2J = 11.6 Hz, ^3J = 5.5 Hz, ^3J = 2.0 Hz, 1H, H-6), 3.70 (dd, ^3J = 11.6 Hz, ^{3}J = 2.5 Hz, 1H, H-4), 2.18 - 2.00 (m, 2H, CH_3CH_2C=C), 1.62 (d, ^3J = 6.8 Hz, 3H, H-4'), 1.59 - 1.46 (m, 1 H ; H-5), 1.41, 1.35 (2 s, 23H, C2-CH_3), 1.18 (ddd, ^2J = 13.1 Hz, ^3J = 4.7 Hz, ^3J = 2.6 Hz, 1 H ; H-5), 1.03, 1.00 (2 s, 23H, C1'-CH_3), 0.98 (t, ^3J = 7.5 Hz, 3H ; CH_3CH_2C=C) ;

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1 (d, C-3'), 119.2 (d, C-4'), 98.3 (s, C-2), 74.2 (d, C-4), 60.4 (t, C-6), 42.9 (s, C-1'), 29.9 (q, C2-CH_3), 26.1 (t, C-5), 24.2, 21.2, 19.1, (q, C2-CH_3, C1'-CH_3) 14.4, 13.6 (q, C-4', C-2').

2-[(4*S*)-2,2-dimethyl-1,3-dioxan-4-yl]-2-methyl-3-pentanone (**58**):

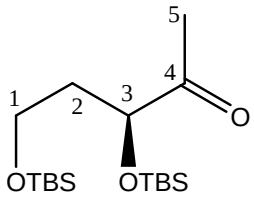


58

A stream of ozone in oxygen was bubbled through a solution of acetonide **69** (226 mg, 1.0 mmol) in CH_2Cl_2 (40 mL) at -78°C until the blue color of the solution persisted. PPh_3 (262 mg, 1.2 equiv) was added at -78°C, the mixture was allowed to warm to room temperature within 4 h and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 5:1) furnished ethyl ketone **58** (182

mg, 85 %) as colorless crystals, m.p. 378 °C, identical, IR, ^{1}H NMR, ^{13}C NMR) with substance obtained from the previously described prenyl borane protocol.[64, 40d]

(*S*)-3,5-Di-(tert-butyldimethylsilyloxy)-2-pentanone (**71**):



71

A solution of hemiacetal **77**/**78** (146 mg, 0.424 mmol); prepared by previous armin bauer methode[58]; in CH_2Cl_2 (70 mL) was cooled to -78 °C. A stream of ozone in oxygen was bubbled through the solution until the blue color persisted, then the excess of ozone was removed by bubbling N_2 through the solution. PPh_3 (333 mg, 1.27 mmol, 3.0 equiv) was added, and the mixture was allowed to warm to room temperature. Stirring was continued until TLC indicated conversion of the intermediate product. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (pentane/Et_2O 19:1) to yield methyl ketone **71** (101 mg, 69 %) as a colorless oil.

General Data: $C_{17}H_{38}O_3Si_2$, MW: 346.24; $[\alpha]_D^{20}$ = -11.8 (*c* = 1.0, $CHCl_3$); DC: R_f = 0.24 (CH_2Cl_2/Et_2O), UV (-), Vanillin: first red then change into black.

1H NMR (400 MHz, CDCl3): δ = 4.15 (dd, ^{3}J = 6.8 Hz, ^{3}J = 5.3 Hz, 1H, H-3), 3.75 - 3.58 (m, 2H, H-1), 2.16 (s, 3H, H-5), 1.88 - 1.70 (m, 2H, H-2), 0.92, 0.88 (2 s, 2 x 9H, $OSiC(CH_3)_3$), 0.06, 0.06, 0.04, 0.03 (4 s, 4 x 3H, $OSi(CH_3)_2$).

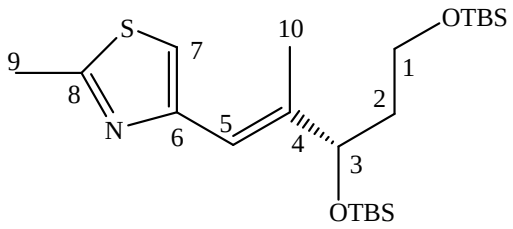
^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.0 (s, C-4), 75.8 (d, C-3), 58.4 (t, C-1), 37.8 (t, C-2), 25.9 , 25.7 (q, Si*t*Bu), 25.4 (q, C-5), 18.3 , 18.1 (s, Si*C*$(CH_3)_3$), - 5.0, - 5.1, - 5.4 (q, $SiCH_3$).

MS (PCI, NH_3): m/z (%): 347 (100) $[M+H]^+$, 324 (17), 279 (93), 231 (4), 215 (7), 157 (8), 94 (11) ;

HRMS (EI): calcd for $C_{17}H_{38}O_3Si_2$ 346.2360,
found 346.235.

5.2.0. Synthesis of Thiazole Fragment **41**

(3*S*,4*E*)-1,3-Di-(tert-butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-pentene (82):



82

nBuLi (23.5 mL, 58.7 mmol, 1.2 equiv of a 2.5 m solution in hexanes) was added dropwise to a stirred solution of phosphonate **70** (14.64 g, 58.7 mmol, 1.2 equiv) in THF (150 mL) cooled to -78°C. After the mixture was stirred at -78 °C for 1 h, a solution of methyl ketone **71** (16.96 g, 48.9 mmol, 1.0 equiv) in THF (100 mL) was added dropwise at -78 °C. The mixture was allowed to warm to room temperature within 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100

mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3x100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated

in vacuo. Flash chromatography (CH_2Cl_2, then Et_2O) yielded unconverted methyl ketone **71** (3.22 g, 22 %) and *E* olefin **82** (17.07 g, 79 %) as colorless oils.

General Data: $C_{22}H_{43}NOSSi_2$, MW: 441.82; $[\alpha]_D^{20}$ = -0.7 (*c* = 1.0, $CHCl_3$); DC: R_f = 0.18 (CH_2Cl_2/Et_2O 3:2), UV (+), Vanillin: dark green

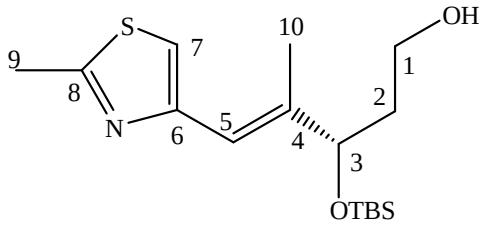
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (s, 1H, H-7), 6.47 (s, 1H, H-5), 4.31 (dd, ^3J = 8.0 Hz, ^3J = 4.6 Hz, 1 H ; H-3), 3.71 - 3.58 (m, 2 H, H-1) 2.70 (s, 3 H ; H-9), 1.99 (d, ^4J = 1.1 Hz, 3 H, H-10), 1.83 - 1.75 (m, 2 H, H-2), 0.89, 0.88 (2 s, 2x 9 H , $OSiC(CH_3)_3$), 0.06, 0.00 (2s, 2x3H, $OSi(CH_3)_2$), 0.03 (s, 6H, $OSi(CH_3)_2$)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (s, C-8), 153.2 (s, C-6), 142.6 (s, C-4), 118.6 (d, C-5), 115.0 (d, C-7), 75.0 (d, C-3), 59.6 (t, C-1), 39.8 (t, C-2), 25.9, 25.8 (q, Si*t*Bu), 19.2, 18.2 (s, Si*C*$(CH_3)_3$), 13.8, - 4.6, - 5.1, - 5.3, - 5.4 (q, $SiCH_3$).

MS (70 eV, EI): m/z (%): 441.2 (35) $[M]^+$, 384.1 (89) $[M - tBu]^+$, 356.1 (80), 309.1 (49), 282.1 (65) $[C_{14}H_{24}NOSSi]^+$, 252.0 (70),178.0 (38), 147.0 (71), 73.1 (100) ;

HRMS (EI): calcd for $C_{22}H_{43}NO_2SSi_2$ 441.2553,
found 441.255

(3*S*,4*E*)-3-(tert-Butyldimethylsilyloxy)-4-methyl-5-(2-methyl--thiazol-4-yl)-4-penten-1-ol (**83**):



83

In a PE bottle, silyl ether **82** (13.255 g, 30.0 mmol) was dissolved in a mixture of Et_2O (120 mL) and MeCN (120 mL). Aqueous 40 % hydrofluoric acid (20 mL) and finely ground splinters of glass (133 mg) were added at 0 8C to the vigorously stirred mixture. The mixture was stirred for 2 h at 0°C. Hydrofluoric acid (20 mL) was added and stirring was continued for 1 h at 0°C. The reaction was quenched by carefully adding solid $NaHCO_3$ (84.0 g, 1.0 mol) within 15 min at 0°C. After the mixture was stirred for 30 min at 0°C, water was added until the solids dissolved (the pH was adjusted to 6-8 by further addition of $NaHCO_3$, if necessary). The mixture was extracted with CH_2Cl_2 (4 x200 mL). The combined organic extracts were washed with brine (100mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue by flash chromatography (pentane/Et_2O 4:1) afforded alcohol **83** (9.041 g, 92 %) as viscous colorless oil.

General Data: $C_{16}H_{29}NOSSi_2$, MW: 327.56; $[\alpha]_D^{20}$ = -32.0 (*c* = 1.0, $CHCl_3$); DC: R_f = 0.52 (Et_2O), UV (+), Vanillin: dark green.

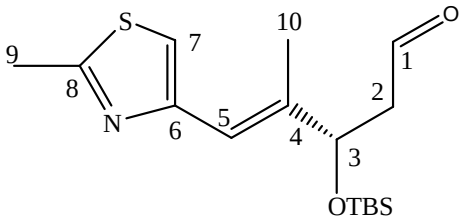
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 6.92 (s, 1H, H-7), 6.52 (s, 1H, H-5), 4.38 (dd, ^{3}J = 7.4 Hz, ^{3}J = 4.5 Hz, 1 H, H-3), 3.80-3.67 (m, 2H, H-1), 2.70 (s, 3 H, H-9), 2.40 (s, 1H, OH), 2.01 (d, ^{4}J = 1.2 Hz, 3 H, H-10), 1.93-1.76 (m, 2 H, H-2), 0.91 (s, 9 H ,$OSiC(CH_3)_3$), 0.10, 0.03 (2s, 2x3 H, $OSi(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ= 164.5 (s, C-8), 152 (s, C-6), 141.53 (s, C-4), 118.77 (d, C-5), 115.35 (d, C-7), 77.42 (d, C-3), 60.35 (t, C-1), 38.12 (t, C-12), 25.77 (q, Si*t*Bu), 19.16 (q, C-9), 18.08 (s, Si*C*$(CH_3)_3$), 14.33 (q, C-10), -4.66, -5.26 (q, $SiCH_3$).

MS (70 eV, EI): m/z (%): 327 (18) $[M]^+$, 282 (39), 270 (94), $[M + tBu]^+$, 268 (29), 252 (12), 240 (14), 178 (41), 168 (100), 164 (23), 105 (27), 75 (59), 73 (42) ;

HRMS (EI): calcd for $C_{16}H_{29}NO_2SSi$ 327.1688,
found 327.168.

(3*S*,4*E*)-3-(tert-Butyldimethylsilyloxy)-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)-4-pentenal (**84**)



84

Dess-Martin periodinane (478 mg, 2.91 mmol, 1.3 equiv) was added to a solution of alcohol **83** (732 mg, 2.24 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 30 min at room temperature. The solvent was removed under reduced pressure. Flash

chromatography (pentane/Et2O 4:1) yielded aldehyde **84** (614 mg, 84 %) as a pale yellow oil.

General Data: $C_{16}H_{27}NO_2SSi_2$, MW: 325.54; $[\alpha]_D^{20}$ = -19.2 (*c* = 1.0, $CHCl_3$); DC: R_f = 0.68 (Et_2O), UV (+), Vanillin: dark green

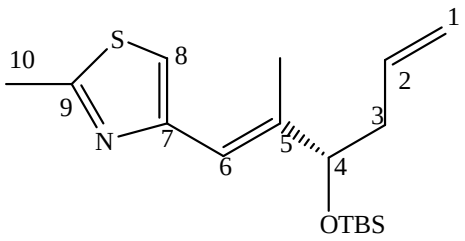
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.79 (t, ^3J = 2.7 Hz, 1 H, H-1), 6.94 (s, 1 H, H-7), 6.56 (s, 1 H, H-5), 4.69 (dd, ^3J = 8.2 Hz, ^3J =4.0 Hz, 1 H ; H-3), 2.75 (ddd, ^2J = 15.5 Hz, ^3J = 7.7 Hz, ^3J = 2.9 Hz, 1 H, H-2), 2.70 (s, 3 H, H-9), 2.51 (ddd, ^2J =15.5 Hz, ^3J = 4.0 Hz, ^3J = 2.1 Hz, 1 H ; H-2), 2.04 (d, ^4J = 1.2 Hz, 3 H, H-10), 0.88 (s, 9 H, $OSiC(CH_3)_3$), 0.08,0.03 (2 s, 2 x3H, $OSi(CH_3)_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 201.5 (d, C-1), 164.8 (s, C-8), 152.6 (s, C-6), 140.5 (s, C-4), 119.3 (d, C-5), 115.9 (d, C-7), 73.9 (d, C-3), 50.1 (t, C-2), 25.7 (q, Si*t*Bu), 19.2 (q, C-9), 18.1 (s, Si*C*$(CH_3)_3$), 14.1, - 4.6, - 5.2 (q, $SiCH_3$);

MS (70 eV, EI): m/z (%): 325 (6) $[M]^+$, 282 (24), 268 (98) $[M - tBu]^+$, 250 (17), 194 (13), 176 (100), 164 (19), 135 (15), 101 (20), 75 (32), 73 (31) ;

HRMS (EI): calcd for $C_{16}H_{27}NO_2SSi$ 325.1532,
found 325.153

(4*S*,6*E*)-4-(3-(tert-butyldimethylsilyloxy)-2-methylhexa-1,5-dienyl)-2-methylthiazole (**84a**):

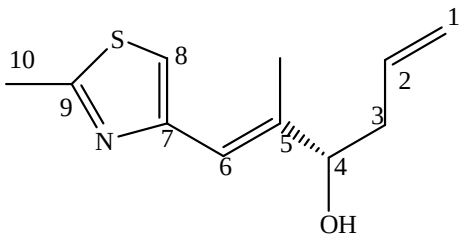


84a

A mixture of methyl triphenyl phosphoniumbromide (1.197 g, 3.35 mmol, 1.85 equiv), $NaNH_2$ (131 mg, 3.35 mmol, 1.85 equiv), and THF (10 mL) was stirred for 30 min at room temperature. A solution of aldehyde **84** (589 mg, 1.81 mmol) in THF (5 mL) was added dropwise over 10 min. The mixture was stirred for 15 min at room temperature, poured into saturated aqueous $NaHCO_3$ solution (60mL), and extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$. After removal of the solvents under reduced pressure, flash chromatography (pentane/Et_2O 19:1) of the residue afforded olefin

84a (498 mg, 85 %) as a pale yellow oil, identical (IR, ^1H NMR, ^{13}C NMR) with substance obtained from the previously described by armin bauer protocol.[58].

(1*E*,3*S*)-3-(tert-Butyldimethylsilyloxy)-2-methyl-1-(2-methyl-1,3-thiazol-4-yl)-1,5-hexadiene (**41**):



41

TBAF (4.0 mL, 1.0 M in THF, 4 mmol, 3 equiv) was added at 0°C to freshly activate molecular sieves 4°A in THF (16 mL). The mixture was stirred for 45 min at room temperature. A solution of silyl ether **84a** (444 mg, 1.37 mmol) in THF (2 mL) was added, and stirring was continued for 80 min at 0°C. The mixture was poured into saturated aqueous NH_4Cl solution (35 mL) and extracted with Et_2O (4X). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure, followed by flash filtration with Et_2O over a short silica gel column afforded alcohol **41** (283 mg, 99 %) as a colorless oil.

General Data: $C_{11}H_{15}NOS$, MW: 209.31; $[\alpha]_D^{20}$ = -18.5 (*c* = 1.0, $CHCl_3$); DC: R_f = 0.42 (Et_2O), UV (+), Vanillin: dark blue.

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 6.92 (s, 1 H, H-8), 6.46 (s, 1 H, H-6), 5.83-5.72 (m, 1 H, H-2), 5.08-4.97 (m, 2 H, H-1), 4.15 (t, ^3J = 6.4 Hz, 1 H, H-4), 2.70 (s, 3 H, H10-CH_3), 2.40 - 2.25 (m, 2 H, H-3), 2.00 (d, ^4J = 1.0 Hz, 3 H, H-11).

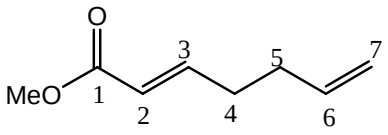
^{13}C NMR (100 MHz, CDCl3): δ(ppm) = 164.4 (s,C-9), 153.1 (s, C-7), 142.0 (s, C-5), 135.3 (d, C-2), 118.8 (d, C-6), 116.5 (t, C-1), 115.1 (d, C-8), 78.5 (d, C-4), 41.4 (t, C-3), 25.8 (q, C-13), 19.2 (q. C-10) , 13.9 (q, C-11).

MS (PCI, NH_3): m/z (%): 324 (100) $[M+H]^+$, 308 (1) $[M - CH3]^+$, 282 (7), 266 (1) $[M-tBu]^+$, 192 (4), 94 (3) ;

HRMS (EI): calcd for $C_{17}H_{29}NOSSi$ 323.1739,
found 323.173.

5.2.1. Total Synthesis of 8,9-dehydro Epothilone C

Methyl *trans*-Hepta-2,6-dienoate (**86**):



86

Based on Crandal procedure [63], sodium metal (1.09, 47.6 mmol) was dissolved in 60 ml of anhydrous methanol while cooling in ice bath to 0°C. A vigorous reaction ensued and the temperature rose to 40°C. When reaction mixture returned to 0°C, methyl diethylphosphonoacetate (10.0 g, 47.64 mmol) was added. The reaction mixture was stirred for 15 minutes at room temperature, and was again cooled to 0°C. 4-Pentenal **85** (3.36 ml, 34.0 mmol) was added via syringe. The mixture was stirred at room temperature for 1.5 h, after which 60 ml of water was added and the mixture was extracted with ether (3x60 ml). The organic phase was washed with brine (60 ml), dried over $MgSO_4$, filtered and concentrated giving 3.35 g (70% yield) of the title compound as light yellow oil.

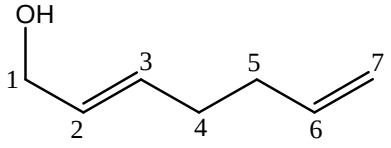
General Data: $C_8H_{12}O_2$, MW: 140.18; DC: R_f = 0.7 (Pentene/Et_2O 1:1), UV (+), Cerium: blue.

IR (film) $\tilde{V}$ (cm^{-1}): 2860 (m), 2750 (s), 1720 (s), 1680 (s), 1650 (s),

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 6.98 (dt, ^3J = 16.0 Hz, ^3J = 6.5, 1H, H-3), 5.84 (d, ^3J = 16.0 Hz, 1H, H-2), 5.79 (ddt, ^3J = 16.5 Hz, 10.0 Hz, 6.5 Hz, 1H, H-6), 5.05 (dd, ^3J = 16.5 Hz, 2.0Hz, 1H, H-7), 5.00 (dd, ^3J = 10.0 Hz, 2.0 Hz, 1H, H-7), 3.72 (s, 3H, $CH_{3)}$, 2.31-2.29 (m, 2H, H-4), 2.24-2.21 (m, 3H, H-5).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) = 167. 1 (s, C-1), 148.7 (C-3, d), 137.1 (C-6, d), 121.4 (C-2, d), 115.7 (C-7, t), 51.5 (CH_3, q), 32.1 (C-4, t), 31.6 (C-5, t)

(*E*)-hepta-2,6-dien-1-ol (**87**) [63] :



87

A solution of Methyl *trans*-Hepta-2,6-dienoate **86** (1.5 g, 10.8 mmol) in 36 ml anhydrous THF was cooled to -78°C and DIBAL-H (1.0 M solution in Hexan fraction, 28.06 ml, 28.06 mmol) was added slowly. The mixture was stirred for 2 hr at -78°C. The mixture was chilled in ice bath and then quenched by sequential addition of 1.2 ml 15% NAOH, 3.0 ml H_2O, and 1.2 ml Et_2O. The mixture was stirred at room temperature for 30 minutes and the dried over $MgSO_4$ and filtered. After removal of the solvents under reduced pressure, flash chromatography (pentane/Et_2O 15:1) of the residue afforded alcohol **87** (0.96 g, 80 %) as a pale yellow oil and the spectral data were consistent to the previous report [63].

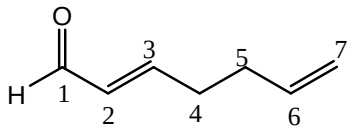
General Data: $C_7H_{12}O$, MW: 112.17; DC: R_f = 0.21 (Pentene/Et_2O 3:1), UV (-), vanillin: black

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.71-5.85 (m, 1H, H-6), 5.21-4.75 (m, 2H, H-2, H-3), 5.00-5.06(m, 1H, H-7), 4.81-4.90 (m, 1H, H-7), 4.08(d, 3J = 4.8 Hz, 2H, H-1), 2.10-2.15 (m, 4H, H-4, H-5),1.42 (br s, OH)

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) = 138.90 (d, C-6), 129.8 (d, C-2), 128.0 (d, C-3), 116.4 (t, C-7), 65.4 (t, C-1), 35.9 (t, C-5), 34.4 (t, C-4)

HRMS (EI): calcd for $C_7H_{12}O$ 112.1701,
found 112.1702.

(*E*)- 2,6-Heptadienal (**88**):



88

To a solution of **87** (1.0315 gr, 9.2894 mmol) in dry CH_2Cl_2 (15 ml) was added Dess-Martin periodinane reagent (4.334 g, 10.2183 mmol) at 0°C in several portion, and the reaction mixture was stirred at room temperature for 1 hr. The mixture was diluted with Et_2O and the former precipitate was filtered off and the filtrate was concentrated under reduced pressure without heat and the residue was purified by flash chromatography (pentene/Et_2O 10:1) to give **88** (0.8915 g, 86%) as colorless liquid.

General Data: $C_7H_{10}O$, MW: 110.15; DC: R_f = 0.36 (Pentene/Et_2O 4:1), UV (+), vanillin: black.

IR (film) $\tilde{V}$ (cm^{-1}): 1700 (C=O) cm^{-1}

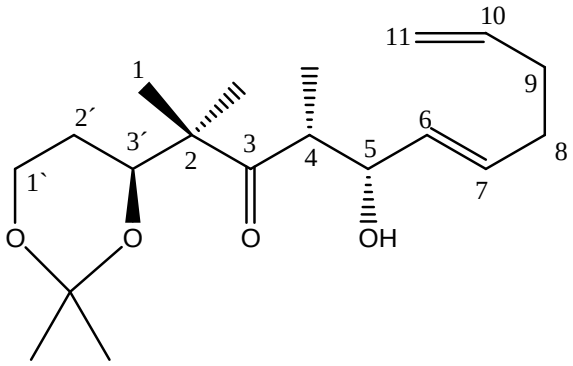
^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.40 (d, ^3J = 8Hz,1H, H-1), 6.80-6.91 (m, 1H, , H-3), 6.10-6.21 (m, 1H, H-2), 5.70-5.19 (m, 1H, H-6), 5.11-5.02 (m, 2H, H-7), 2.10-2.50 (m, 4H, H-4, H-5).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm) = 193.90 (d, C-1), 157.59 (d, C-3), 134.3 (d, C-6), 133.1 (d, C-2), 115.94 (t, C-7), 31.82 (t, C-5), 31.77 (t, C-4).

MS (70 eV, EI): m/z (%): 110 (4, $[M]^+$), 109 (14), 95 (32), 81 (100), 79 (42), 41 (71).

HRMS (EI): calcd for $C_7H_{10}O$ 110.1701,
found 110.1702.

(*E*)-(4*R*,5*S*,4'*S*)-2-(-2,2-dimethyl-1,3-dioxan-4-yl)-5-hydroxy-2,4-dimethylundeca-6,10-dien-3-one (**89**):



89

A solution of ethyl ketone **58** (1.55 g, 7.26 mmol) in THF (2.0 mL) was added to a freshly prepared solution of LDA [n-BuLi (4.3 mL, 1.6 m solution in hexanes, 6.97 mmol, 0.96 equiv) was added to a solution of diisopropylamine (0.977 mL, 6.97 mmol) in THF (11.0 mL) at 0°C] dropwise at - 78°C. The solution was stirred for 1 h at - 78°C. Aldehyde **88** (800 mg, 7.2628 mmol, 1.0 equiv) was added dropwise and stirring was continued for 45 min at at -78°C. The reaction mixture was quenched by dropwise addition of saturated aqueous NH_4Cl solution at -78°C. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (pentane/Et_2O 10:1) of the residue afforded major diastereoisomer **89** (0.92 g, 60%) as colorless oils.

General Data: $C_{19}H_{32}O_4$, MW: 324.45; DC: R_f = 0.2 (Pentene/Et_2O 3:1), UV (-), vanillin: black.

IR (film) $\tilde{V}$ (cm^{-1}): 3409 (w), 2956 (s), 2938 (s), 2876 (m), 1694 (s), 1467 (m), 1381(s), 1372 (w), 1255 (s), 1094 (m), 971(m), 882 (w) cm

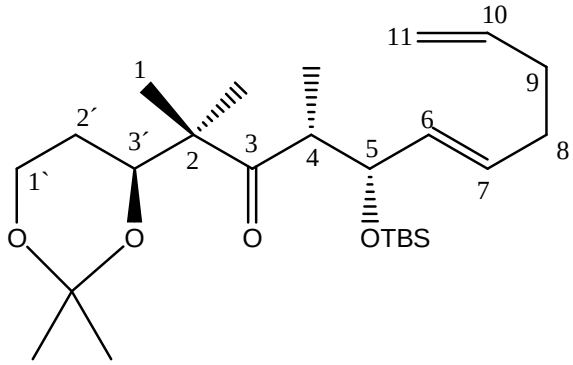
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 5.77-5.84 (m, 1H, H-10), 5.67-5.76 (dt, 1H, ^{3}J=8 Hz, ^{3}J= 2.0 Hz, H-7), 5.37-5.43 (dd, 1H, ^{3}J = 21.3, ^{3}J = 5.2, H-6), 4.92-5.31 (m, 2H, H-11), 4.23-4.28 (m, 1H, H-5), 4.02-4.07 (dd, ^{3}J= 11.9 Hz, ^{3}J= 2.5, 1H, H-4`), 3.94 (dt, $^{2}J$= 11.8 Hz, $^{2}J$= 2.7 Hz, 1H, H-6`), 3.85 (ddd, ^{3}J= 11.2 Hz, ^{3}J= 4.1 Hz, ^{3}J= 1.5 Hz, H-6`), 3.39 (s, 1H, OH), 3.02-3.10 (dq, $^{3}J$= 7.1 Hz, $^{3}J$= 2.6 Hz, 1H, H-4), 2.11-2.14 (m, 4H, H-8, H-9), 1.6-1.69 (m, 2H, H-5`), 1.4 (s, 3H, C2`-$CH_3$), 1.31 (s, 3H, H-1), 1.2 (s, 3H, C2`-CH_3), 1.1 (s, 3H, C2-CH_3), 1.03-1.07 (d, ^{3}J= 7.0 Hz, 3H, C4-CH_3).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 138,115 (d, C-10), 131.590 (d, C-6), 129. 763 (d, C-7), 114.77 (t, C-11), 98.468 (s, C-2`), 74.73 (d, C-4`), 71.9 (d-C-5), 59.73 (t, C-6`), 51.34 ( s, C-2), 45.5 (d, C-4), 33.31 (t, C-9), 31.7 (t, C-8), 29.71 (q, C2`-CH_3), 25.03 (t, C-5`), 21.24 (q, C-1), 19.00 (q, C2-CH_3), 18.05 (q, C2-CH_3), 10.094 (q, C4-CH_3).

MS (70 eV, EI): m/z (%): 324 (1<, $[M]^+$), 306 (26, $[M^+-H_2O]$, 266 (3), 248 (20), 198 (8), 169 (20), 167 (14) , 143 (86), 131 (72), 117 (38), 99 (82), 93 (63), 83 (28).

HRMS (EI): calcd for $C_{19}H_{32}O_4$ 324.230,
found 324.241.

(*E*)-(4*R*,5*S*,4'*S*)-5-(tert-butyldimethylsilyloxy)-2—(2,2-dimethyl-4,6-dioxan-4-yl)-2,4-dimethylundeca-6,10-dien-3-one (**85**):



90

2,6-Lutidine (0.515 ml, 3.7 mmol, 2.0 equiv) and TBSOTf (0.7644 mL, 3.69 mmol, 1.5 equiv) were slowly added at - 78°C to a solution of alcohol 84 (700 mg, 2.21 mmol) in CH_2Cl_2 (20 ml). The mixture was stirred at -78° C for 30 min and at 0°C for 1 h. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Silyl ether 85 (774 mg, 80%) was obtained as a colorless oil after purification of the residue by flash chromatography (pentane/Et_2O 20:1).

General Data: $C_{25}H_{46}O_{4Si}$, MW: 438.72; DC: R_f = 0.62 (Pentene/Et_2O 1:1), UV (-), vanillin: black.

IR (film) $\tilde{V}$ (cm^{-1}): 2957 (s), 2931 (m), 2886 (w), 2858 (m), 1697(s), 1473(w) , 1256 (m), 1103 (m), 987 (w), 836 (s) , 775 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 5.79-5.87 (m, 1H, H-10), 5.70-5.76 (dq, 1H, ^3J=9 Hz, ^3J= 2.0 Hz, H-7), 5.37-5.43 (dd, 1H, ^3J = 21.3, ^3J = 5.2, H-6), 5.02-5.31 (m, 2H, H-11), 4.29-4.38 (ddd, ^3J = 7.5, ^3J =*3.9*, ^3J= *3.6*, 1H, H-5), 4.10-4.17 (dd, ^3J=

11.9 Hz, ^{3}J= 2.5, 1H, H-4`), 3.94 (dt, $^{2}J$= 11.8 Hz, $^{2}J$= 2.7 Hz, 1H, H-6`), 3.85 (ddd, ^{3}J= 11.2 Hz, ^{3}J= 4.1 Hz, ^{3}J= 1.5 Hz, H-6`), 3.12-3.20 (dq, $^{3}J$= 7.1 Hz, $^{3}J$= 2.6 Hz, 1H, H-4), 2.11-2.14 (m, 4H, H-8, H-9), 1.6-1.69 (m, 2H, H-5`), 1.4 (s, 3H, C2`-$CH_3$), 1.31 (s, 3H, H-1), 1.2 (s, 3H, C2`-CH_3), 1.1 (s, 3H, C2-CH_3), 1.03-1.07 (d, ^{3}J= 7.0 Hz, 3H, C4-CH_3), 0.91 (s, 1x9H; OSiC$(CH_3)_3$), 0.09, 0.1 (2s, 2x3H; OSi$(CH_3)_2$).

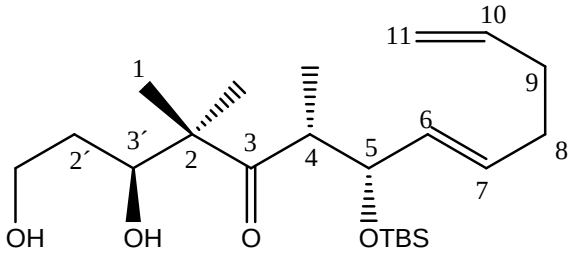
^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 215,84 (s, C-3), 138,99 (d, C-10), 133.590 (d, C-6), 130. 763 (d, C-7), 114.34 (t, C-11), , 74.73 (d, C-4`), 71.9 (s,C-5), 59.73 (t, C-6`), 51.34 (s, C-2), 45.5 (d, C-4), 33.31 (t, C-9), 31.7 (t, C-8), 29.71 (q, C2`-$CH_3$), 27.08 (q, OSiC($CH_3$)$_3$, 25.03 (t, C-5`), 23.24 (q, C-1), 21.00 (q, C2-CH_3), 20.05 (q, C2-CH_3), 18.5, 18.4 (s, OSi$C$$(CH_3)_3$), 15.094 (q, C4-$CH_3$), -4.9 , -4.0 (q, OSi$(CH_3)_2$).

MS (70 eV, EI): m/z (%): 324 (1<, $[M]^+$), 306 (26, $[M^+-H_2O]$, 266 (3), 248 (20), 198 (8), 169 (20), 167 (14) , 143 (86), 131 (72), 117 (38), 99 (82), 93 (63), 83 (28).

HRMS (EI): calcd for $C_{21}H_{23}O_4Si$ $[M^+$-*t*-Bu] 380.9601

Found 380.9602

(*E*)-(4*R*,5*S*,3'*S*)-5-(*tert*-butyldimethylsilyloxy)-1,3-dihydroxy-2,2,4-trimethyltrideca-6,10 -dien-3-one (**91**):



91

A solution of acetonide protected diol **89** (0.1660 gr, 0.3784 mmol) in CH_3CN (6.3 ml) was added H_2O (0.903 ml) followed by $CeCl_3.7H_2O$ (0.423 g, 1.1352 mmol) at ambient temperature. The reaction was stirred at reflux temperature for 1.5 hr. After completion as indicated by TLC, the reaction mixture was diluted with Et_2O, quenched with $NaHCO_3$ (saturated aq), and the aqueous layer was re extracted with Et_2O (2X). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (5:1, Pentene:Et_2O) provided 0.1182 gr of diol **91** in 78% yield as clear oil.

General Data: $C_{22}H_{42}O_4Si$, MW: 398.65; DC: R_f = 0.62 (Pentene/Et_2O 1:1), UV (-), vanillin: black.

IR (film) $\tilde{V}$ (cm^{-1}): 3425 (br s), 2958 (m), 2886 (w), 2858 (m), 1680 (s), 1473(w) , 1256 (m), 1103 (m), 987 (w), 836 (s) , 775 (s).

^1H NMR (400 MHz, $CDCl_3$): δ (ppm): 5.83-5.87 (m, 1H, H-10), 5.79-5.66 (dq, 1H, ^3J=9 Hz, ^3J= 2.0 Hz, H-7), 5.47-5.40 (dd, 1H, ^3J = 21.3, ^3J = 5.2, H-6), 5.02-5.31 (m, 2H, H-11), 4.29-4.38 (m, 1H, H-5), 4.10-4.17 (m, 1H, H-3`), 3.82-3.86 (m, 2H, H-1'), 3.39-3.40 (m, 1H, 3'-OH), 3.12-3.20 (dq, $^3J$= 7.1 Hz, $^3J$= 2.6 Hz, 1H, H-4), 2.69 (br s, 1H, 1'-OH), 2.10-2.13 (m, 4H, H-8, H-9), 1.62-1.67 (m, 2H, H-2`), 1.41 (s, 3H, H-1),

1.2 (s, 3H, C2-CH_3), 1.03-1.07 (d, ^3J= 7.0 Hz, 3H, C4-CH_3), 0.91 (s, 1x9H; OSiC$(CH_3)_3$), 0.09, 0.1 (2s, 2x3H; OSi$(CH_3)_2$).

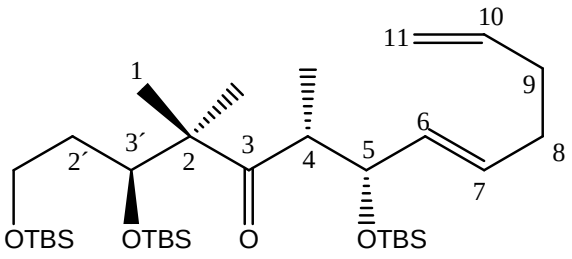
^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 138,115 (d, C-10), 131.590 (d, C-6), 129. 763 (d, C-7), 114.77 (t, C-11), 76.73 (d, C-3`), 74.9 (s,C-5), 62.34 (t, C-1`), 52.34 (s, C-2), 45.5 (d, C-4), 33.31 (t, C-9), 32.50 (t, C-2'), 26.7 (t, C-8), 25.15(q, OSiC(CH_3)$_3$, 23.24 (q, C-1), 21.00 (q, C2-CH_3), 20.05 (q, C2-CH_3), 18.5, 18.4 (s, OSi$C$$(CH_3)_3$), 15.094 (q, C4-$CH_3$), -4.9 , -4.0 (q, OSi$(CH_3)_2$).

MS (70 eV, EI): m/z (%): 397.1 (1<, $[M]^+$), 339.43 [M^+- *t*Bu], 282.20 (5), 265.43 (100) [M^+- OTBS], 248 (20), 167 (14) , 155.43 (22), 143 (86), 105.43 (77), 75(79).

HRMS (EI): calcd for $C_{22}H_{42}O_4Si$: 398.290

Found: 398.302

(*E*)-(4*R*,5*S*,3'*S*)-(1,3,5-Tris-(*tert*-butyldimethylsilyloxy)-2,2,4-trimethyltrideca-6,10-dien-3-one (**92**):



92

2,6-Lutidine (0.336 ml, 2.8 mmol, 8.0 equiv) and TBSOTf (0.344 ml, 1.49 mmol, 4.1 equiv) were slowly added at - 78°C to a solution of alcohol **91** (380 mg, 0.36 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred at -78° C for 30 min and at 0°C for 1 h. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated in

vacuo. Silyl ether **92** (0.2142 g, 90%) was obtained as a colorless oil after purification of the residue by flash chromatography (pentane/Et_2O 20:1).

General Data: $C_{34}H_{70}O4Si_3$, MW: 627.17; DC: R_f = 0.62 (Pentene/Et_2O 1:1), UV (-), vanillin: black.

IR (film) $\tilde{V}$ (cm^{-1}): 2957 (s), 2931 (m), 2886 (w), 2858 (m), 1679 (s), 1473(w), 1257 (s), 1099 (br s), 987 (w), 836 (s), 775 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 5.83-5.87 (m, 1H, H-10), 5.70-5.66 (dt, 1H, ^3J=9 Hz, ^3J= 2.0 Hz, H-7), 5.47-5.40 (dd, 1H, ^3J = 21.3, ^3J = 5.2, H-6), 5.02-5.31 (m, 2H, H-11), 4.29-4.38 (m, 1H, H-5), 4.10-4.17 (m, 1H, H-3`), 3.80-3.85 (m, 2H, H-1'), 3.10-3.219 (dt, $^3J$= 7.1 Hz, $^3J$= 2.6 Hz, 1H, H-4), 2.69 (br s, 1H, 1'-OH), 2.10-2.13 (m, 4H, H-8, H-9), 1.62-1.67 (m, 2H, H-2`), 1.41 (s, 3H, H-1), 1.2 (s, 3H, C2-CH_3), 1.03-1.07 (d, ^3J= 7.0 Hz, 3H, C4-CH_3), 0.89 (s, 2x 9H, C3'-SiC(CH_3)$_3$, C5-SiC(CH_3)$_3$), 0.87, (s, 9H, C1'-SiC(CH_3)$_3$), 0.08, 0.05 (s, 2x3H, C5-OSiC(CH_3)$_2$), 0.05 (s, 2x3H, C3'-OSiC(CH_3)$_2$), 002,0.01 (s, 2x3H, C1'-OSiC(CH_3)$_2$).

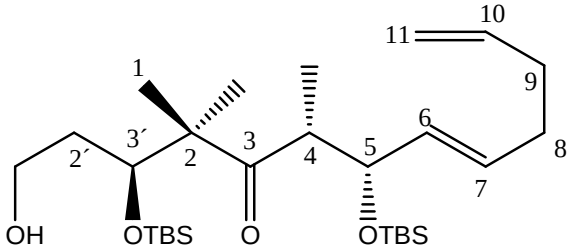
^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 218.25 (s, C-3), 138.115 (d, C-10), 131.590 (d, C-6), 129. 763 (d, C-7), 114.77 (t, C-11), 76.73 (d, C-3`), 74.9 (s,C-5), 61.34 (t, C-1`), 52.34 (s, C-2), 45.5 (d, C-4), 33.31 (t, C-9), 32.50 (t, C-2'), 26.7 (t, C-8), 26.22 (q, C5-OSiC(*C*H_3)$_3$), 26.11 (q, C3`-OSiC(*C*H_3)$_3$), 25.96 (q, C1'-OSiC(*C*H_3)$_3$), 24.52 (q, C2-CH_3), 20.05 (q, C2-CH_3), 18.52 (s, C5-OSi*C*(CH_3)$_3$), 18.34 (s, C3'-OSi*C*(CH_3)$_3$, 18.29 (s, C1-OSi*C*(CH_3)$_3$), 15.094 (q, C4-CH_3), -5.24, -5.27 (q, C1'-OSi(CH_3)$_2$), -3.78, -3.97 (q, C3'-OSi(CH_3)$_2$), -3.66, -3.69 (q, C5-OSi(CH_3)$_2$).

MS (70 eV, EI): m/z (%): 624 (1<, $[M]^+$), 566.03 [M^+- *t*Bu], 546.40 (2) [C1`- $C5^+$], 434.27 (5), 394.27 (20), 304. 23 (100) [C1`- C3'$^+$], 226.18 (71) [C5- $C11^+$], 166 (17), 140 (21), 104 (58), 84.27 (44), 68 (44).

HRMS (EI): calcd for $C_{34}H_{70}O4Si_3$: 624.460

Found: 624.468.

(*E*)-(4*R*,5*S*,3'*S*)-(3,7-Bis-(*tert*-butyldimethylsilyloxy)-1-hydroxy-2,2,4 trimethyltrideca-6,10-dien-3-one (**93**):



93

To a solution of **92** (0.3486 g, 0.556 mmol) in THF (12 ml) was added a stock solution of HF.Py (this stock was prepared by addition of 1.0 ml HF.Py to 2.5 ml pyridine in 5 ml THF) at 0°C. The resulting reaction mixture was warmed to 25°C by removing the ice-bath and allowed to stir at that temperature until starting material was gone. Saturated $NaHCO_3$ solution was added to quench the reaction and two layers were separated. The aqueous layer was extracted with ethyl acetate (50ml x 3). The combined organic extracts were dried over $MgSO_4$, and the solvents were removed under reduced pressure. The crude product obtained was subjected to column chromatography over silica gel with 10:1 pentene:ether as eluent to yield the desired primary alcohol **93** (0.195 g, 70%) as pale yellow oil.

General Data: $C_{28}H_{56}O_4Si_2$, MW: 512.91; DC: R_f = 0.62 (Pentene/Et_2O 1:1), UV (-), vanillin: black.

IR (film) $\tilde{V}$ (cm^{-1}): 3460.47 (s), 2930 (s), 2886 (w), 2858 (m), 1694 (s), 1464(w), 1361.31 (s), 1094 (br s), 988 (w), 836 (s), 775 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 5.71-5.85 (m, 1H, H-10), 5.46-5.22 (dt, 1H, ^{3}J=9 Hz, ^{3}J= 2.0 Hz, H-7), 5.30-5.35 (dd, 1H, ^{3}J = 15.0, ^{3}J = 7.2, H-6), 4.92-5.08 (m, 2H, H-11), 4.10-4.15 (t, ^{3}J= 15.1, 1H, H-5), 4.00-4.05 (m, 1H, H-3`), 3.60-3.68 (m, 2H, H-1'), 3.0-3.09 (dt, $^{3}J$= 7.1 Hz, $^{3}J$= 2.6 Hz, 1H, H-4), 2.01-2.11 (m, 4H, H-8, H-9), 1.83 (s, 1H, OH), 1.59-1.62 (m, 2H, H-2`), 1.19 (s, 3H, H-1), 1.05-1.12 (d, ^{3}J= 7.0 Hz, 3H, C4-CH_3) ,0.98 (s, 3H, C2-CH_3), 0.89 (s, 2x 9H, C3'-$SiC(CH_3)_3$, C5-$SiC(CH_3)_3$), 0.87, (s, 9H, C1'-$SiC(CH_3)_3$), 0.08, 0.05 (s, 2x3H, C5-$OSiC(CH_3)_2$), 0.05 (s, 2x3H, C3'-$OSiC(CH_3)_2$), 002,0.01 (s, 2x3H, C1'-$OSiC(CH_3)_2$).

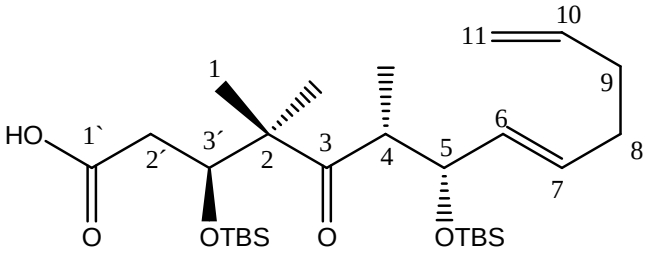
^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 218.73 (s, C-3), 138.28 (d, C-10), 132.19 (d, C-6), 129. 763 (d, C-7), 114.67 (t, C-11), 75.87 (d, C-3`), 72.9 (s,C-5), 60.34 (t, C-1`), 53 (s, C-2), 38.428 (d, C-4), 33.1 (t, C-9), 32.25 (t, C-2'), 31.5 (t, C-8), 28.98 (q, C5-$OSiC(CH_3)_3$), 28.88 (q, C3`-$OSiC(CH_3)_3$), 24.52 (q, C2-CH_3), 21.05 (q, C2-CH_3), 18.52 (s, C5-$OSiC(CH_3)_3$), 18.34 (s, C3'-$OSiC(CH_3)_3$, 15.094 (q, C4-CH_3), -3.78, -3.97 (q, C3'-$OSi(CH_3)_2$), -3.66, -3.69 (q, C5-$OSi(CH_3)_2$).

MS (70 eV, EI): m/z (%): 512.2 (1<, $[M]^+$), 494.3[M^+- H_2O], 341.1 (100), 333.1 (60), 225.1 [C7- $C14^+$], 189 (24), 173 (8), 148 (8), 131 (13).

HRMS (EI): calcd for $C_{28}H_{56}O_4Si_2$: 512.370

Found: 512.3714

(*E*)-(3'*S*,5*R*)-3,5-bis(tert-butyldimethylsilyloxy)-2,2,4-trimethyl-3-oxotrideca-6,10-dienoic acid (**94**):



94

A solution of PDC (1.07 g, 2.60 mmol,11.0 equiv) in DMF (3 ml) was added to a solution of alcohol **93** (123 mg, 0.273 mmol) in DMF (2 ml). The reaction mixture was stirred for 36 h at room temperature, mixed with brine (50 mL), diluted with water, and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (pentane/Et_2O 2:1) to furnish acid **94** (85.3 mg, 69 %) as a viscous, colorless oil.

General Data: $C_{28}H_{54}O_5Si_2$, MW: 526.9; DC: R_f = 0.62 (Pentene/Et_2O 2:1), UV (-), vanillin: black.

IR (film) $\tilde{V}$ (cm^{-1}): 3084 (w), 2930 (s), 2858 (w), 1694 (s), 1472 (m), 1440(s), 1409 (w), 1361.31 (s), 1094 (br s), 938 (w), 836 (s), 775 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 5.71-5.82 (m, 1H, H-10), 5.46-5.22 (dt, 1H, ^3J=9 Hz, ^3J= 2.0 Hz, H-7), 5.30-5.35 (dd, 1H, ^3J = 15.0, ^3J = 7.2, H-6), 4.92-5.08 (m, 2H, H-11), 4.29-4.33(t, ^3J= 15.1, 1H, H-5), 4.09-4.13 (m, 1H, H-3`), 3.01-3.09 (dt, $^3J$= 7.1 Hz, $^3J$= 2.6 Hz, 1H, H-4), 2.46-2.53 (dd, 1H, $^3J$ = 16.0, $^2J$ = 2.2, H-2`), 2.29-2.34 (dd, 1H, ^3J = 16.0, ^2J = 6.6, H-2`) 2.01-2.11 (m, 4H, H-8, H-9), 1.2 (s, 3H, H-1), 1.19-1.22 (d, ^3J= 7.0 Hz, 3H, C4-CH_3) ,1.01 (s, 3H, C2-CH_3), 0.89 (s, 2x 9H, C3'-

$SiC(CH_3)_3$, C5-$SiC(CH_3)_3$), 0.87, (s, 9H, C1'-$SiC(CH_3)_3$), 0.08, 0.05 (s, 2x3H, C5-$OSiC(CH_3)_2$), 0.05 (s, 2x3H, C3'-$OSiC(CH_3)_2$), 002,0.01 (s, 2x3H, C1'-$OSiC(CH_3)_2$).

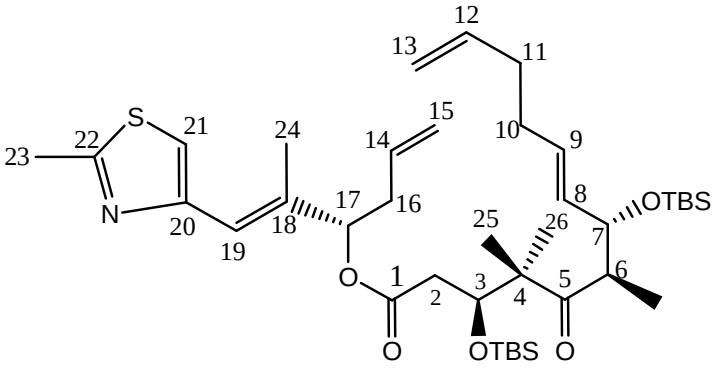
^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 138.01 (d, C-10), 132.12 (d, C-6), 131. 68 (d, C-7), 114.82 (t, C-11), 75.87 (d, C-3`), 73.9 (s,C-5), 53.41 (t, C-1`), 48.49 (s, C-2), 39.693 (d, C-4), 33.1 (t, C-9), 31.5 (t, C-2'), 31.1 (t, C-8), 29.68 (q, C5-$OSiC(CH_3)_3$), 25.91 (q, C3`-$OSiC(CH_3)_3$), 23.52 (q, C2-CH_3), 22.05 (q, C2-CH_3), 18.52 (s, C5-$OSiC(CH_3)_3$), 18.34 (s, C3'-$OSiC(CH_3)_3$, 15.094 (q, C4-CH_3), -3.78, -3.97 (q, C3'-$OSi(CH_3)_2$), -3.66, -3.69 (q, C5-$OSi(CH_3)_2$).

MS (70 eV, EI): m/z (%): 527.1 (1<, $[M+H]^+$), 491.2 (18), 469.2 [M-^{t}Bu], 333.1 (60), 225.1 [C5- $C14^+$], 189 (10), 173 (8), 73 (10).

HRMS (EI): calcd $C_{28}H_{54}O_5Si_2$ for: 526.35

Found: 527.3598 $[M+H]^+$

(3*S*,6*R*,)-((*S*,*E*)-2-methyl-1-(2-methylthiazol-4-yl)hexa-1,5-dien-3-yl)-3,7-bis(tert-butyldimethylsilyloxy)-4,4,6-trimethyl-5-oxotrideca-8,12-dienoate (**95**):



95

A solution of EDCI (40 mg, 0.208 mmol) in 1 ml CH_2Cl_2 was added dropwise to solution of alcohol **41** (40.2 mg, 0.192 mmol), carboxylic acid **94** (84.3 mg, 0.160 mmol) and DMAP (3.91 mg, 0.0302 mmol) in 1 ml CH_2Cl_2 at 0°C for 15 minutes and 4 hr at rt. The reaction mixture was poured to brine. The organic layer were separated, dried over $MgSO_4$ and concentrated under vacuo. The resulting residue was separated by silica gel column (6:1 pentene/ether) to provide 88 mg (76%) of ester **95** as pale yellow oil.

General Data: $C_{39}H_{67}NO_5SSi_2$, MW: 718.19; DC: R_f = 0.47 (Pentene/Et_2O 4:1), UV (+), vanillin: dark blue.

IR (film) $\tilde{V}$ (cm^{-1}): 3081 (w), 2956 (s), 2930 (s), 2894 (s), 2857 (s), 1742 (s), 1698 (s), 1473(s), 1361.31 (m), 1303 (m), 1255 (s), 1117 (m), 1094 (vs), 992 (w), 836 (s), 775 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 6.952 (s, 1H, H-21), 6.498 (s, 1H, H-19), 5.71-5.75 (m, 2H, H 15, H-12), 5.41-5.49 (dt, 1H, ^{3}J=15.0 Hz, ^{3}J= 7.2 Hz, H-9), 5.30-5.35 (dd, 1H, ^{3}J = 9.1, ^{3}J =2.0, H-8), 4.92-5.13 (m, 4H, H-13, H-14), 4.27-4.39(dd, ^{3}J= 6.1, ^{3}J= 3.1, 1H, H-17), 4.112-4.124 (q, ^{3}J= 7.1,1H, H-7), 4.06-4.08 (t, ^{3}J= 8.0, 1H, H-3), 3.04-3.1 (m, 1H, H-6), 2.710 (s, 1H, H-23), 2.41-2.55 (m, 3H, H-2, H-16), 2.23-2.29 (dd, ^{3}J= 16.9, ^{3}J= 6.2,1H, H-16), 1.79-2.09 (m, 7H, H-10, H-11, H-24), 1.25 (s, 3H, H-25), 1.04-107 (d, ^{2}J= 6.38, H6-CH_3) 0.96 (s, 3H, H-26), 0.88, 0.86 (s, 9H, Si*t*Bu), 0.09, 0.03, 0.02, -0.08 (s, 3H, SiCH_3)

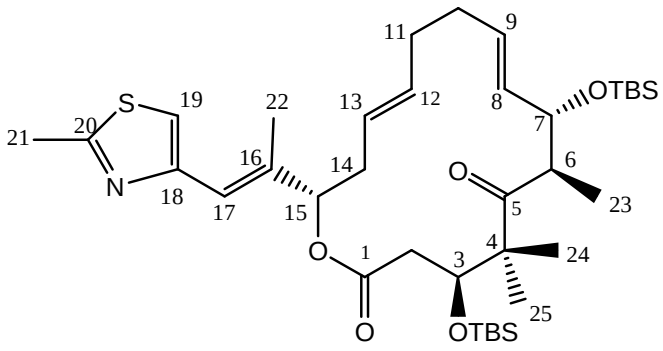
^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 214.3 (s, C-5), 169.75 (s, C-1), 163.5 (s, C-20), 151.91 (s, C-18), 138.1 (d, C-16), 132.32 (d, C-8), 130.95 (d, C-13), 130.18 (d, C-12), 125.87 (d, C-9), 117.88 (d, C-19), 115.82 (d, C-17), 78.81 (d, C-15), 72.56 (d, C-7), 64.8 (d, C-3), 52.54 (s, C-4), 47.60 (d, C-6), 42.13 (t, C-2), 36.1 (t, C-10), 32.1 (t, C-11), 28.68 (t, C-14), 25.91 (q, Si*t*Bu), 24.94 (q, Si*t*Bu), 23.9 (q, C-21), 19.05 (s, Si*C*$(CH_3)_3$), 18.24 (s, Si*C*$(CH_3)_3$, 17.1 (q, C-24), 17.0 (q, C-25), 16.1 (q, C-22), 14.25 (q, C-23) -4.92, -4.9 (q, SiCH_3), -3.66, -3.69 (q, SiCH_3).

MS (70 eV, EI): m/z (%): 717.2 (1<, M^+), 580.2 (4) [TBSO^+= C7-C22], 525.2 (4) [HO^+=C1-C13], 469.1 (41) [HO^+=C7-C22], 399 (100), 225.1 (80), 192.0 (100), 151 (50).

HRMS (EI): calcd $C_{39}H_{67}NO_5Si2S$ for: 717.3

Found: 717.4280

(3*S*,7*R*,9*E*,13*E*,16*S*)-4,8-bis(tert-butyldimethylsilyloxy)-5,5,7-trimethyl-16-((*E*)-1-(2-methylthiazol-4-yl)prop-1-en-2-yl)oxacyclohexadeca-9,13-diene-2,6-dione. (**97**):



97

Grubbs catalyst first generation was added to a solution of diene **95** (74,4 mg, 0.11 mmol) in CH_2Cl_2 (53 mL, 0.002 m), and the reaction mixture was stirred for 16 h at room temperature. The solvent was removed in vacuo and the crude product was purified by flash chromatography (pentane/Et_2O 20:1) to give a mixture of diastereomers **96** and **97** (Z/E 1:4, 50 mg, 68%, colorless viscous oil).

Major isomer characteristic for *trans*-Olefin (**97**):

General Data: $C_{37}H_{63}NO_5SSi_2$, MW: 690.14; DC: R_f = 0.37 (Pentene/Et_2O 4:1), UV (+), vanillin: black.

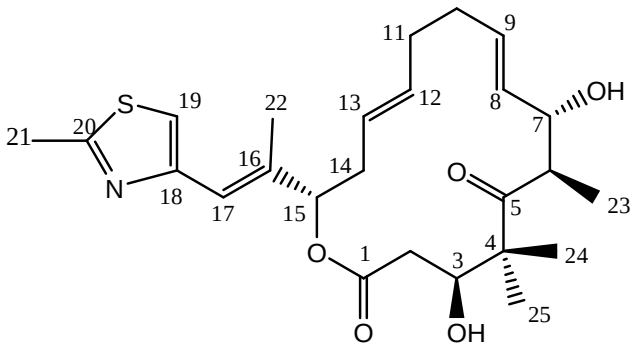
IR (film) $\tilde{V}$ (cm^{-1}): 2956 (s), 2930 (s), 2894 (s), 2857 (s), 1742 (s), 1698 (s), 1473(s), 1348 (m), 1303 (m), 1255 (s), 1361 (m), 1255 (s), 1183 (m), 1097 (vs), 992 (w), 836 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 6.916 (s, 1H, H-19), 6.526 (s, 1H, H-17), 5.48-5.51 (m, 2H, H-8, H-9), 5.41-5.49, 5.24 (dd, 1H, ^{3}J = 15.5, ^{3}J = 7.9, H-12), 5.09-5.12 (dd, 1H, ^{3}J= 10, ^{3}J= 2.8, H-13), 4.34-4.35 (dd, ^{3}J= 6.9, ^{3}J= 2.7, 1H, H-15), 4.11-4.32 (t, ^{3}J= 17.1,1H, H-7), 3.46-3.48 (t, ^{3}J= 11.7, 1H, H-3), 2.93-2.97 (m, 1H, H-6), 2.69 (s, 1H, H-21), 2.45-2.49 (dd, ^{3}J= 16.9, ^{3}J= 7.1,2H, H-2), 2.39-2.43 (dt, ^{3}J= 7.7, ^{3}J= 2.6 ,2H, H-14), 2.1 (s, 4H, H-10, H-11), 1.15-1-16 (dd, ^{3}J= 11, 3H, H-23), 1.13 (s, 3H, H-23), 1.110 (s, 3H, H-25), 0.9, 0.8 (s, 2x 9H, Si*t*Bu), 0.17, 0.09, 0.029, -0.001 (s, 2x3H, $SiCH_3$).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 214.13 (s, C-5), 171.20 (s, C-1), 164.7 (s, C-22), 152.31 (s, C-20), 138.1 (s, C-18), 133.32 (d, C-15), 132.30 (d, C-12), 131.35 (d, C-8), 120.90 (d, C-9), 117.82 (d, C-21), 116.3 (d, C-19), 114.79 (t, C-13, C-14), 78.61 (d, C-17), 74.06 (d, C-3, C-7), 53.08 (s, C-4), 48.99 (d, C-6), 40.30 (t, C-2), 37.5 (t, C-6), 33.1 (t, C-10), 31.1 (t, C-11), 26.68 (q, Si*t*Bu), 25.91 (q, Si*t*Bu), 22.9 (q, C-23), 19.85 (q, C-25),18.52 (s, Si*C*$(CH_3)_3$), 18.34 (s, Si*C*$(CH_3)_3$, 14.59 (q, C-24) -4.93, -4.92 (q, $SiCH_3$), -5.67, -5.89 (q, $SiCH_3$).

LC- MS: m/z (%): 691.4 (10) [$M+H^+$], 558.2 (5), 560.2 (10), 286,2 (15), 287.0 (5).

(4*S*,7*R*,8*S*,9*E*,13*E*,16*S*)-4,8-dihydroxy-5,5,7-trimethyl-16-((*E*)-1-(2-methylthiazol-4-yl)prop-1-en-2-yl)oxacyclohexadeca-9,13-diene-2,6-dione (**98**):



98

To a solution of **97** (20.9 mg, 0.0303 mmol) in CH_3CN (3 mL) was added $(HF)_3.Et_3N$ (1.2 ml, 7.36 mmol) and Et_3N (0.1 ml, 10% v/v) . The mixture was heated in a 45°C oil bath for 20 hrs, after which it was cooled to room temperature and added to EtOAc (40 ml). The mixture was washed with 5% KH_2PO_4 (aq.) (2x30 ml) and the combined aqueous layers extracted with EtOAc (4x20 mL). The combined organic extracts were washed with brine (2X), dried over $MgSO_4$ and concentrated. The residue was purified by flash chromatography (silica gel, Et_2O) to afford **98** (7.1 mg, 50%) as colorless solid.

General Data: $C_{25}H_{35}NO_5S$, MW: 461.61; DC: R_f = 0.37 (Et_2O 4:1), UV (+), vanillin: black.

IR (film) $\tilde{V}$ (cm^{-1}): 3440 (br m), 2930 (s), 2894 (s), 2857 (s), 1742 (s), 1698 (s), 1473(s), 1348 (m), 1303 (m), 1260 (s), 1361 (m), 1255 (s), 1183 (m), 1097 (vs), 992 (w), 836 (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 6.916 (s, 1H, H-19), 6.526 (s, 1H, H-17), 5.6-5.7 (m, 2H, H-9), 5.5-5.6, 5.24 (dd, 1H, ^{3}J = 15.5 Hz, ^{3}J = 7.4 Hz, H-8), 5.43-5.39 (ddd, 1H, ^{3}J= 17.1, 11.4, 6.3 Hz, H-12, H-13), 5.28 -5.32 (d, ^{3}J= 20.1 Hz, 1H, H-15), 5.1 (s, OH), 4.21-4.22 (d, ^{3}J= 4.1 Hz,1H, H-7), 3.10-3.14 (br s, OH), 2.8-2.93 (s, 1H, H-21), 2.55-2.71 (dt, ^{3}J = 15.8, 7.0 Hz, 1H, H-6), 2.38 -2.47 (dd, ^{3}J= 12.6, 6.4 Hz,2H, H-2), 2.10-2.23 (dd, ^{3}J= 12.6, 6.4 , 2H, H-14, H-10), 2.01-2.09 (s, 5H, H-14, H-10), 1.69 (s, 3H, H-23), 1.3 (s, 3H, H-25), 1.110 (s, 3H, H-23).

^{13}C-NMR (100 MHz, $CDCl_3$): δ(ppm): 214.13 (s, C-5), 171.13 (s, C-1), 170.7 (s, C-22), 152.31 (s, C-20), 138.1 (s, C-18), 133.32 (d, C-15), 132.80 (d, C-12), 129.35 (d, C-8), 125.90 (d, C-9), 115.82 (d, C-21), 116.3 (d, C-19), 113.79 (t, C-13, C-14), 78.61 (d, C-17), 74.06 (d, C-3, C-7), 52.08 (s, C-4), 49.9 (d, C-6), 40.30 (t, C-2), 32.5 (t, C-6), 31.1 (t, C-10), 30.1 (t, C-11), 26.9 (q, C-23),21.85 (q, C-25), 14.59 (q, C-24)

MS (70 eV, EI): m/z (%): 461.0 (1<, M^+), 443 (4) [M^+-H_2O], 274 (34), 171 (38), 168.0 (100), 151 (20).

HRMS (EI): calcd $C_{25}H_{35}NO_5S$ for: 461.21

Found: 461.22

Chapter 6

Literature

[1]. C. Berg, *Pharmazeutische Zeitung*, **1997**, *47*, 52-54.

[2]. Information from the Internet Homepages of the American Cancer Society (ACS: http://www.cancer.org) and of the National Cancer Institute (NCI: http://www.nci.nih.gov).

[3]. a) Wani. M.C., Taylor H.L, Wall. M.E., Coggon. P., McPhail. A. T., *J. Am. Chem. Soc.* **1971**, *93*, 2325 - 2327; b) Junod. T., *Life*, **1992**, *15*, 71 – 76. c) Taxane Anticancer Agents : Basic Science and Current Status : Georg. G. I., Chen T.T., Ojima. I., Wyas. D.M., *ACS Symposium Series*, **1995**, 583, 35.

[4]. a) Rowinsky. E.K., Donehower. R.C., New Engl. *J. Med.* **1995**, *332*, 1004 - 1014 ; b) Cortes. J.E., Pazdur. R., *J. Clin. Oncol*. **1995**, **13**, 2643 - 2655.

[5]. Nicolaou. K.C., Dai. W.-M., Guy. R.K., *Angew. Chem.*, **1994**, *33*, 15 - 44.

[6]. Nicolaou. K.C., Guy. R.K., Gunzer. J.L., *MedChem News*, **1997**, *7*, 12 -18.

[7]. Höfle. G., Bedorf. N., Gerth. K., Reichenbach. H. (GBF), DE-B 4138042,1993 [*Chem. Abstr*., **1993**, *120*, 52 841] .

[8]. a) D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J. Liesch, M. Goetz, E. Lazarides, C.M. Woods, *Cancer Res*., **1995**, *55*, 2325-2333; for a recent review on the biology of epothilones, see b) D. M. Bollag, Exp. Opin. *Invest. Drugs*, **1997**, *6*, 867-873.

[9]. S. Borman, Chem. *Eng. News*, **1996**, *74*(52), 24 - 26.

[10]. G. Höfle, N. Bedorf, K. Gerth, H. Reichenbach (GBF), DE-B 4138042,1993 [Chem. Abstr. 1993, 120, 52 841] .

[11]. a) D. M. Bollag, P. A. McQueney, J. Zhu, O. Hensens, L. Koupal, J.Liesch, M. Goetz, E. Lazarides, C. M. Woods, *Cancer Res*. **1995**, *55*,2325 - 2333 ; for a recent review on the biology of epothilones, seeb) D. M. Bollag, Exp. Opin. *Invest. Drugs*, **1997**, *6*, 867 - 873.

[12]. G. Höfle, N. Bedorf, H. Steinmetz, D. Schomburg, K. Gerth, H.Reichenbach, *Angew. Chem*., **1996**, *108*, 1671 - 1673 ; *Angew. Chem. Int. Ed. Engl*., **1996**, *35*, 1567 – 1569.

[13]. S. F. Victory, D. G. Vander Velde, R. K. Jalluri, G. L. Grunewald,G. I. Georg, Bioorg., *Med. Chem. Lett*., **1996**, *6*, 893 - 898.

[14]. R. J. Kowalski, P. Giannakakou, E. Hamel, *J. Biol. Chem*., **1997**, *272*, 2534 - 2541.

[15]. Wang, M. M.; Xia, X. Y.; Kim, Y.; Hwang, D.; Jansen, J. M. et al. *Org. Lett*. **1999**, *1*, 43-46.

[16]. Mulzer, J. *Mon. Chem.* **2000**, *131*, 205-238.

[17]. Ballone, P.; Marchi, M. *J. Phys. Chem. A* **1999**, *103*, 3097-3102.

[18]. Giannakakou, P.; Gussio, R.; Nogales, E.; Downing, K. H.; Zaharevitz, D. et al. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 2904-2909.

[19]. Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S. N.; He, L. F. et al. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 4256-4261.

[20]. Nicolaou, K. C.; Ritzen, A.; Namoto, K. *Chem. Commun.* **2001**, 1523-1535.

[21]. Nicolaou, K. C.; Vourloumis, D.; Li, T. H.; Pastor, J.; Winssinger, N. et al. *Angew. Chem.-Int. Edit.* **1997**, *36*, 2097-2103.

[22]. Taylor, R. E.; Zajicek, J. *J. Org. Chem.* **1999**, *64*, 7224-7228.

[23]. Taylor, R. E.; Chen, Y.; Galvin, G. M.; Pabba, P. K. *Organic and Biomolecular chemistry* **2004**, *2*, 127-132.

[24]. Tang, L.; Qiu, R. G.; Li, Y.; Katz, L. *J. Antibiot.* **2003**, *56*,16-23.

[25]. Njardarson, J. T.; Biswas, K.; Danishefsky, S. J. *Chem. Commun.* **2002**, 2759-2761.

[26]. Probing the ring size of epothilones: Total synthesis of [14]-, [15]-, [17]-, and

[18] epothilones A. Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Finlay, M. R. V.; Boddy, C. N. C. *Angew. Chem.-Int. Edit.* **1998**, *37*, 81-84.104

[27]. Highly concise routes to epothilones: The total synthesis and evaluation of epothilone 490. Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C. et al. *J. Am. Chem. Soc.* **2002**, *124*, 9825-9832.

[28]. Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Chou, T. C.; Dong, H. J. et al. *J. Am. Chem. Soc.* **2003**, *125*, 2899-2901.

[29]. Meng, D. F.; Su, D. S.; Balog, A.; Bertinato, P.; Sorensen, E. J. et al. *J. Am. Chem. Soc.* **1997**, *119*, 2733-2734.

[30]. Nicolaou, K. C.; Sasmal, P. K.; Rassias, G.; Reddy, M. V.; Altmann, K. H. et al. *Angew. Chem.-Int. Edit.* **2003**, *42*, 3515-3520.

[31]. Chemical synthesis and biological evaluation of novel epothilone B and trans-12, 13-cyclopropyl epothilone B analogues. Nicolaou, K. C.; Ritzen, A.; Namoto, K.; Buey, R. M.; Diaz, J. F. et al. *Tetrahedron* **2002**, *58*, 6413-6432.

[32]. Nicolaou, K. C.; Namoto, K.; Ritzen, A.; Ulven, T.; Shoji, M. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9313-9323.

[33]. Nicolaou, K. C.; He, Y.; Roschangar, F.; King, N.P.; Vourloumis, D. et al. *Angew. Chem.-Int. Edit.* **1998**, *37*, 84-87.

[34]. Nicolaou, K. C.; Vallberg, H.; King, N. P.; Roschangar, F.; He, Y. et al. *Chem.-Eur. J.* **1997**, *3*, 1957-1970.

[35]. Regueiro-Ren, A.; Leavitt, K.; Kim, S. H.; Hofle, G.; Kiffe, M. et al. *Org. Lett.* **2002**, *4*, 3815-3818.

[36]. Borzilleri, R. M.; Zheng, X. P.; Schmidt, R. J.; Johnson, J. A.; Kim, S. H. et al. *J. Am. Chem. Soc.* **2000**, *122*, 8890-8897.

[37]. McDaid, H. M.; Mani, S.; Shen, H. J.; Muggia, F.; Sonnichsen, D. et al. *Clin. Cancer Res.* **2002**, *8*, 2035-2043.

[38]. a) Epothilone A: A. Balog, D. Meng, T. Kamencka, P. Bertinato, D.-S. Su, E.J. Sørensen, S. J. Danishefsky, *Angew. Chem.*, **1996**, *108*, 2976-2978; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2801-2803; b) Epothilone B: D.-S. Su,

D. Meng, P. Bertinato, A. Balog, E. J. Sørensen, S. J. Danishefsky, Y. H. Zheng, T.-C. Chou, L. He, S. B. Horwitz, *Angew. Chem.* ,**1997**, *109*, 775-777; *Angew. Chem. Int. Ed. Engl*., **1997**, *36*, 757-759.

[39]. a) Epothilone A: K. C. Nicolaou, Y. He, D. Vourloumis, H. Valberg, Z. Zang, *Angew. Chem*., **1997,** *109*, 170-172; *Angew. Chem. Int. Ed. Engl*., **1997**, *36*, 166-168; b) Epothilone A: K. C. Nicolaou, F. Sarabia., S. Ninkovic, Z. Yang, *Angew. Chem*., **1997**, *109*, 539-540; *Angew*. *Chem. Int. Ed. Engl*., **1997**, *36*, 525-527; c) Epothilone A and B: K. C. Nicolaou, S. Ninkovic, F. Sarabia, D. Vourloumis, Y. He, H. Vallberg, M. R. V. Finlay, Z. Yang, *J. Am. Chem. Soc*,. **1997**, *119*, 7974-7991.

[40] a) D. Schinzer, A. Limberg, A. Bauer, O. M. Böhm, M. Cordes, Angew. Chem. 1997, 109, 543-544*; Angew. Chem. Int. Ed. Engl*., **1997**, *36*, 523-524; b) D. Schinzer, A. Limberg, O. M. Böhm, *Chem. Eur. J*., **1996**, *2*, 1477-1482.

[41] a) L. Wessjohann, *Angew. Chem*., **1997**, *109*, 739-742; *Angew. Chem. Int. Ed. Engl*,. **1997**, *36*, 715-718; b) M. Kalesse, *Eur. Chem. Chron*., **1997**, 7-11; c) M. R. V. Finlay, *Chem. Ind*., **1997**, *24*, 991-996; d) R. E. Taylor, Y. Chen, *Org.Lett*., **2001**, *14*, 2221-2224; e) M. Valluri, R. M. Hindupur, P. Bijoy, G. Labadie, J.-Chul Jung, M. A. Avery, *Org. Lett*., **2001**, *23*, 3607-3609.

[42] D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sørensen, S. J. Danishefsky, Y.-H- Zheng, T.-C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc.*, **1997**, *119*, 10073-10092.

[43] D. Meng, D.-S. Su, A. Balog, P. Bertinato, E. J. Sørensen, S. J. Danishefsky, Y.-H-Zheng, T.-C. Chou, L. He, S. B. Horwitz, *J. Am. Chem. Soc*., **1997**, *119*, 2733-2734.

[44] a) R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. DiMare, M. O`Regan, *J. Am. Chem. Soc.*, **1990**, *112*, 3875-3886; b) A. Balog, C. R. Harris, K: savin, X.-G. Zhang, T.-C. Chou, S. J. Danishefsky, *Angew. Chem. Int. Ed. Engl*,. **1998**, *37*, 2675-2678.

[45] C. R. Harris, S.D Kuduk, K. Savin, A. Balog, S. J. Danishefsky, *Tetrahedron Lett.*,**1999**, *40*, 2263.

[46] C. R. Harris, S.D Kuduk, A. Balog, K. Savin, P. W. Glunz, S. J. Danishefsky, *J.Am. Chem. Soc*., **1999**, *121*, 7050-7062.

[47] K. C. Nicolaou, N. Winssinger, J. Pastor, S. Ninkovic, F. Sarabia, Y.He, D.Vourloumis, Z. Yang, T. Li, P. Giannakakou, E. Hamel, *Nature*, **1997**, *36*, 757-759.

[48] K. C. Nicolaou, Y. He, D. Vourloumis, H. Vallberg, Z. Yang, *Angew. Chem.*, **1996**, *108*, 2554-2556; *Angew. Chem. Int. Ed. Engl*., **1996**, *35*, 2399-2401.

[49] H. C. Brown, K. S. Bhat, R. S. Randad, *J. Org. Chem*., **1989**, *54*, 1570-1576.

[50] P. Schwab, M. B. France, J. W. Ziller, R. H. Grubbs, *Angew. Chem*., **1995**, *107*, 2179-2181; *Angew. Chem. Int. Ed. Engl*., **1995**, *34*, 2039-2041.

[51] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 1989-1993.

[52] D. Enders, J. Tiebes, N. DeKimple, M. Keppens, C. Stevens, G. Smagghe, O. Betz, *J. Org. Chem*., **1993**, *58*, 4881-4884.

[53] D. Schinzer, A. Bauer, J. Schieber, *Synlett,* **1998**, 861-864.

[54] M. Braun, D. Waldmüller, *Synthesis* ,**1989**, 856-858.

[55] D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc*., **1988**, *110*, 2506-2526.

[56]. a). *Organic Synthesis*, Coll.Vol.10, **2004**, 464. b). *Organic Synthesis*, Coll.Vol.77, **2000**, 45. c). Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H., *J. Am. Chem. Soc*., **1995**, *117*, 4413-4414. d). Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H., *J. Org. Chem*., **1996**, *61*, 4560-4567.

[57]. P. Eilbracht, M. Acker, B. Rosenstock, *Chem. Ber*., **1989**, *122*, 151 - 158.

[58]. D. Schinzer, A. Bauer, J. Schieber, *Chem. Eur. J*., **1999**, *9*, 2492- 2500.

[59]. S. Hanessian, A. Tehim, P. Chen, *J. Org. Chem*., **1993**, *58*, 7768 – 7781.

[60]. a) H. P. Buser, B. Pugin, F. Spindler, M. Sutter, *Tetrahedron,* **1991**, *47*, 5709-5716; b) S.-J. Shiuey, J. J. Partridge, M. R. Uskokovic, *J. Org.Chem*. **1988**, *53*, 1040 -1046.

[61]. F. Matsuda, N. Tomiyoshi, M. Yanagiya, T. Matsumoto, *Tetrahedron*, **1990**, 46, 3469 - 3488.

[62]. Crandall, J.K, Mayer, C.F., *J.Org.Chem*. **1970**, *35*, 3049-3053.

[63]. Swift, M.D, Sutherland, A. *Org. Lett*., **2007**, *9*, 5239-5242.

[64]. Limberg, A., *Dissertation*, Technische Universität Braunschweig, **199**8.

[65]. Umezawa, T., Hayashi, T., Sakai, H., Teramoto, H., Yoshikawa, T., Izumida, M., Tamatani, Y. Hirose, T., Ohfune, Y., Shinada, T., *Org. Lett*., **2006**, *8*, 4971-4974.

[66]. Tius, M.A., Hu, H., Kawakami, J. Busch-Peterson, J., *J. Org. Chem*., **1998**, *63*, 5971.

Curriculum **V**itae

Personal Data

Name:	Noviandi Meta Adityawarman
Date of Birth:	19.11.1979
Place of Birth:	Jakarta, Indonesia

School education

1985 – 1991	Elementary School in Jakarta, Indonesia
1991 – 1994	Junior High school in Jakarta, Indonesia
1994 – 1997	High School in Jakarta, Indonesia

University Education and Doctoral Thesis

1997 – 2002	Bachelor of Science at Bogor Agricultural University-Bogor, West Java; Faculty of Chemistry.
2002 – 2003	Master of Science at Otto-Von-Guericke Universität Magdeburg, Germany; Faculty of Process and Systems Engineering. Thesis: "*Experimental and theoretical Investigation of the Chromatographic separation of a ternary mixture using chromatography"* under guidance of Prof. Dr. Andreas Seidel-Morgenstern.
29.10.2003	Master examination and M.Sc. graduation at Otto-Von-Guericke Universität Magdeburg.
2004 – 2005	Research training at Otto-Von-Guericke Universität Magdeburg under guidance Prof. Dr. Dieter Schinzer.
2005 - 2010	Doctoral Thesis with The title: "*Total Synthesis of 8,9-Dehydro-Epothilone C*" under guidance Prof. Dr. Dieter Schinzer.

Poster

Schinzer, Dieter., Adityawarman, Noviandi Meta,.

Total Synthesis of 8,9 – Dehydro Epothilone C., ESF COST High Level Research Conference Hotel Villa del Marre, 5-10 September 2010, Italy.