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A new Epothilone-Analogue with high biological activity on MDR cell lines and the ability to pass the blood-brain-barrier

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Abstract

Epothilone and its derivatives, a class of novel natural products, were first isolated by Höfle from a strain of the *Sorangium* genus. Owing to their antifungal and antitumor activities, as well as their microtubule-binding properties, particularly their cytotoxic effects against drug-resistant tumor cell lines, epothilones have garnered significant interest in the fields of chemistry, biology, and medicine. Accordingly, our project aims to develop the synthesis of a new epothilone derivative **170** with superior behavior over known tubulin blinders, while also overcoming resistance issues and improving physical characteristics for crossing the blood-brain barrier.

The retrosynthetic synthesis of the fragment **170** identified three key intermediates fragments **173**, **175** and **176**. Initially, we tested the strategy outlined in Schinzer's method, however, the Reformatsky reaction was found to be incompatible with our system. As an alternative, we applied the approach reported by Schering AG published in 2005 to synthesize key intermediate **176**. Starting from (*D*)-pantolactone, aldehyde **72** was synthesized on a multigram scale. To construct the side chain at C6, aldehyde **72** took part in a Grignard reaction. Notably, the availability of various Grignard reagents offers a wide range of possibilities for modifying biological activity by introducing different functional groups. Consequently, ketone **176** was synthesized using **72** and benzylbromomagnesium followed by an oxidation step. Over the course of the 12-step synthesis, the overall yield for this component exceeded 12%.

The secondary fragment **210**, subsequently oxidized to the corresponding aldehyde **175**, was synthesized from cyclohexanone **204**. Through a four-step process, 6-phenylhept-6-enotic acid **202** was prepared and utilized for the synthesis of acyl chloride **195**. This intermediate was then reacted with oxazolidinone auxiliary **194** to yield amide **193** with 81% yield. The steric hindrance provided by the auxiliary was utilized to control the orientation of new substituents, successfully establishing the chiral center at C8. Following the removal of the oxazolidinone auxiliary, segment **210** was obtained with a total yield of 17%.

Utilizing existing fragment **213**, we tested two methods to incorporate fragment **210** to achieve *E*-alkene configuration at C12-C13. The first method involved a Wittig reaction, in which the thiazole segment **213** was converted into Wittig salts over two steps as the starting materials. Meanwhile, alcohol **210** was protected with a TBS group to yield intermediate **221**, which was subsequently oxidized to form ketone **222**. The Wittig salts were treated with NaHMDS to generate the ylid, and ketone **222** was added to ylid solution at -78 °C for several hours. However, none of the attempted reactions successfully yielded the desired alkene. The second approach employed the Julia-Kocienski olefination. After evaluating a series of precursor alkyl sulfones, which are critical for controlling selectivity, we selected 1-*tert*-butyl-5-mercaptotetrazole **233** as the starting material for the preparation of sulfone **239**. A mixture of 1 equiv. ketone **222**, 1 equiv. sulfone **239** and 1.1 equiv. LiHMDS (1 mol/L

in THF) was stirred at -78 °C for 3 h, resulting in the desired alkene **225b** with a 68% yield. Additionally, stereochemical analysis of the alkene product showed a *Z*/*E* selectivity ratio of 2:98.

In order to synthesis the desired molecule, we attempted a one-pot aldol reaction to couple **225b** with ketone **176**. The intermediate **239** was synthesized from **225b** in two steps. However, the coupling of fragments **239** and **176** proved unsuccessful, despite exploring several strategies, including the aldol reaction, Reformatsky reaction, and Mukaiyama reaction. This unresolved challenge presents a major barrier to completing the total synthesis of the macromolecule, highlighting the necessity for innovative strategies to address this critical limitation.

Zusammenfassung

Epothilon und seine Derivate, eine Klasse neuartiger Naturstoffe, wurden erstmals von Höfle aus einem Stamm der Gattung Sorangium isoliert. Aufgrund ihrer antimykotischen und antitumoralen Aktivitäten sowie ihrer Mikrotubuli-bindenden Eigenschaften, insbesondere ihrer zytotoxischen Wirkung gegen arzneimittelresistente Tumorzelllinien, haben Epothilone großes Interesse in den Bereichen Chemie, Biologie und Medizin geweckt. Dementsprechend zielt unser Projekt darauf ab, die Synthese eines neuen Epothilon-Derivats zu entwickeln, das ein besseres Verhalten als die bekannten Tubulin-Blinder aufweist, während es gleichzeitig Resistenzprobleme überwindet und die physikalischen Eigenschaften für die Überwindung der Blut-Hirn-Schranke verbessert.

Bei der retrosynthetischen Synthese des Fragments **170** wurden drei wichtige Zwischenprodukte identifiziert: die Fragmente **173**, **175** und **176**. Zunächst testeten wir die in der Methode von Schinzer aus dem Jahr 1998 beschriebenen Strategie, jedoch erwies sich die Reformatsky-Reaktion als inkompatibel mit unserem System. Als Alternative wendeten wir den von der Schering AG im Jahr 2005 veröffentlichten Ansatz zur Synthese des Schlüsselintermediats **176** an. Ausgehend von (*D*)-Pantolacton wurden die Aldehyde **72** im Multigramm-Maßstab synthetisiert. Um die Seitenkette an C6 aufzubauen, nahmen die Aldehyde **72** an einer Grignard-Reaktion teil. Die Verfügbarkeit verschiedener Grignard-Reagenzien bietet eine breite Palette von Möglichkeiten zur Veränderung der biologisc hen Aktivität durch Einführung verschiedener funktioneller Gruppen. Folglich wurde das Keton **176** unter Verwendung von **72** und Benzylbrommagnesium synthetisiert, gefolgt von einem Oxidationsschritt. Im Verlauf der 12-stufigen Synthese lag die Gesamtausbeute für diese Komponente bei über 12 %.

Das sekundäre Fragment **210**, das anschließend zu dem entsprechenden Aldehyd **175** oxidiert wurde, wurde aus Cyclohexanon **204** synthetisiert. In einem vierstufigen Prozess wurde die Säure **202** hergestellt und für die Synthese von Acylchlorid **195** verwendet. Dieses Zwischenprodukt wurde dann mit dem Oxazolidinon-Hilfsstoff **194** umgesetzt, um das Amid **193** mit einer Ausbeute von 81 % zu erhalten. Die sterische Hinderung durch das Hilfsmittel wurde genutzt, um die Ausrichtung der neuen Substituenten zu kontrollieren und das chirale Zentrum an C8 erfolgreich zu etablieren. Nach der Entfernung der Oxazolidinon-Hilfsstoffe wurde das Segment **210** mit einer Gesamtausbeute von 17 % erhalten.

Unter Verwendung des vorhandenen Fragments **213** testeten wir zwei Methoden zur Einbindung des Fragments **210**, um eine *E*-Alken-Konfiguration an C12-C13 zu erreichen. Bei der ersten Methode handelte es sich um die Wittig-Reaktion, bei der das Thiazolsegment **213** in zwei Schritten in Wittig-Salze als Ausgangsstoffe umgewandelt wurde. In der Zwischenzeit wurde der Alkohol **210** mit einer TBS-Gruppe geschützt, um das Zwischenprodukt **221** zu erhalten, das anschließend zum

Keton **222** oxidiert wurde. Die Wittig-Salze wurden mit NaHMDS behandelt, um jlide zu erzeugen. Keton **222** wurde der jlid-Lösung bei -78 °C für mehrere Stunden zugesetzt. Keine der versuchten Reaktionen führte jedoch zu dem gewünschten Alken. Der zweite Ansatz war die Julia-Kocienski-Olefinierung. Nach Auswertung einer Reihe von Vorläufer-Alkylsulfonen, die für die Kontrolle der Selektivität entscheidend sind, wählten wir 1-*tert*-Butyl-5-mercaptotetrazol **233** als Ausgangsmaterial für die Herstellung von Sulfon **239**. Ein Gemisch aus 1 Äquivalent Keton **222**, 1 Äquivalent Sulfone **239** und 1,1 Äquivalent LiHMDS (1 mol/L in THF) wurde 3 Stunden lang bei -78 °C gerührt und ergab das gewünschte Alken **225b** mit einer Ausbeute von 68 %. Die stereochemische Analyse des Alkenprodukts ergab ein *Z/E*-Selektivitätsverhältnis von 2:98.

Um das gesamte Molekül zu synthetisieren, versuchten wir eine Ein-Topf-Aldol-Reaktion, um **225b** mit dem Keton **176** zu koppeln. Das Zwischenprodukt **239** wurde aus **225b** in zwei Schritten synthetisiert. Die Kopplung der Fragmente **239** und **176** erwies sich jedoch als erfolglos, obwohl verschiedene Strategien wie die Aldol-Reaktion, die Reformatsky-Reaktion und die Mukaiyama-Reaktion erprobt wurden. Diese ungelöste Aufgabe stellt ein großes Hindernis für die Vollendung der Makromolekülsynthese dar und unterstreicht die Notwendigkeit innovativer Strategien, um diese kritische Einschränkung zu überwinden.

Table of Contents

List of abbreviations

Å	angstrom
Ac	acetyl
BBN	9-borabicyclo (3.3.1) nonane
Bn	benzyl
Bu	butyl
ca.	catalytic
calcd.	calculated
Ce	cesium
Chx2BOTf	dicyclohexylboron triflate
CSA	camphorsulfonic acid
DCC	*N, N'*-dicyclohexylcarbodiimid
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DERA	2-deoxyribose-5-phosphate-aldolase-catalyst
DHP	3,4-dihydropyran
DIBAL-*H*	diisobutylaluminum hydride
DIEA	*N, N*-diisopropylethylamine
DMAc	dimethylacetamide
DMDO	dimethyldioxiran
DMF	N, N-dimethylformamide
4-DMAP	4-dimethylaminophenol
DMPE	1,2-bis(dimethylphosphino)ethane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
ESI	electrospray ionization
Et	ethyl
et al.	Et alia (and others)
FT-IR	Fourier transform infrared
GTP	guanosine triphosphate
h	hour
HWE	Horner-Wadsworth-Emmons Reaktion
HMPA	hexamethylphosphoramide

HPLC	high Performance liquid chromatography
i	iso
IC50	half-inhibitory concentration
4-IBAcid	4-iodobenzoic acid
(-)-IpC2B-allyl	(-)-B-Allyldiisopinocampheyl
IR	infrared
IUPAC	international Union of Pure and Applied Chemistry
KHMDS	potassium bis(trimethylsilyl)amide
KMHDS	potassium bis (trimethylsilyl)amide
LDA	lithium diisopropylamide
LiAlH4	lithium aluminum hydride
LiHMDS	lithium bis(trimethylsilyl)amide
M	molar (concentration of solutions)
MAPs	microtube-associated protein(s)
Me	methyl
MIC	minimun inhibitory concentration
min	minute
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
n	normal (e.g. unbranched alkyl chain)
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
Os	osmium
ox.	oxidation
p	para
Pd	palladium
Ph	phenyl
PhSH	thiophenol
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl

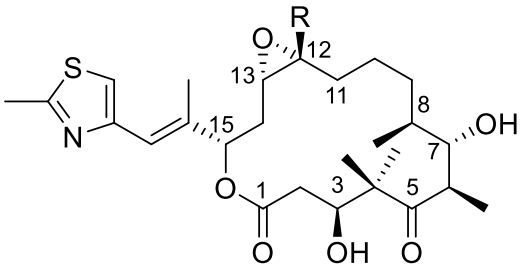
*p*TsOH	*p*-Toluenesulfonic acid
Py	pyridine
RCM	ring-closing metathesis
RT	room temperature
s	secondary
SAR	structure-activity-relationship
sat.	saturated
t, tert-	tertiary
TBAF	tetrabutylammoniumfluorid
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
t-BuOK	potassium *tert*-butoxide
TCBC	2,4,6-trichlorobenzoyl chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMSCN	trimethylsilyl cyanide
TPAP	tetra-*n*-propylammonium perruthenate
TPS	triphenylsilyl chloride
Ts	toluenesulfonyl
UV	ultraviolet

1. Background

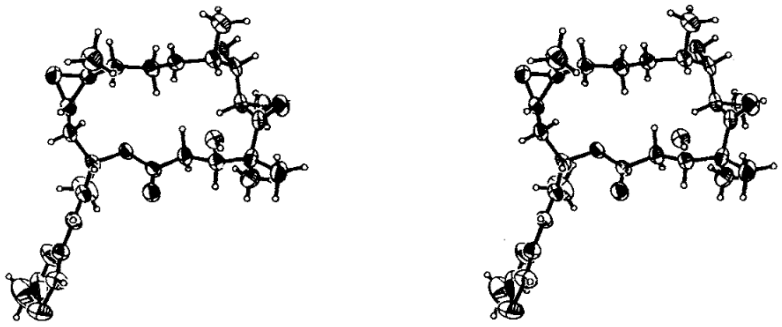
1.1 Discovery of Epothilone

Since the 19th century, when the German apothecary assistant Friedrich Sertürner successfully isolated the analgesic and sleep-inducing compound from opium, which he named morphium, a new era in drug discovery, centered around the poppy plant, was inaugurated.[1] Instead of just applying on an empirical basis with plants, many bioactive natural compounds, especially alkaloids, might be isolated from their natural sources. Then, scientists started the chemical synthesis of natural products with the goal of improving quality and reducing costs. Today, natural products continue to play an essential role in the process of drug development, particularly in the treatment of cancer and infectious diseases. Obviously, after the discovery of drugs derived from microorganisms, it offers greater opportunities. In this context, myxobacteria are a significant source of many novel types of secondary metabolites. In 1937, Imshenetski and Solntseva isolated a new species of cellulose-degrading myxobacteria, called *Sorangium cellulosum*. And a *Sorangium cellulosum* is particularly valuable because 46% of isolated metabolites are coming from that culture broth, which grows on cellulose as carbon source and competes with fungi.[2]

In July 1985 *Sorangium cellulosum*, strain So ce90 was isolated by Hans Reichenbach from a soil sample collected at the banks of the river Zambesi in southern Africa.[3] The discovery of two closely related antifungal compounds, epothilone A and B, resulted of an antifungal screening of Sorangium strains. Finally, Höfle and his co-workers [4] later isolated them. Elemental analysis and physical data helped to confirm the chemical structural formula ($C_{26}H_{39}NO_6S$ for epothilone A and $C_{27}H_{41}NO_6S$ for epothilone B) and 2D NMR correlation was in agreement with the structures as shown in Scheme 1. By the use of X-rays to examine the perfectly crystalline epothilone B, the absolute configurations of all stereogenic centers were determined [5].



R=H, epothilone A, **1**
R=CH_3, epothilone B, **2**



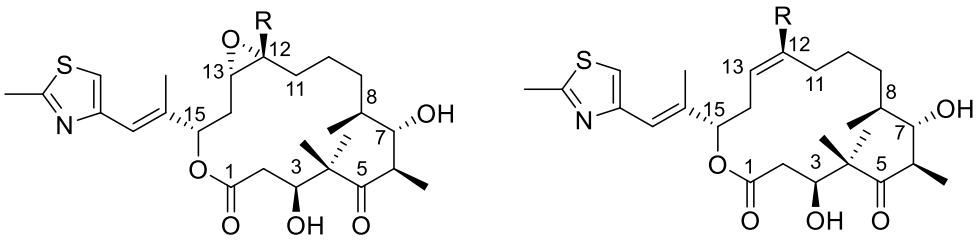
Scheme 1: Stereopresentation of the crystal structure of epothilone B from Höfle.

However, due to the high cytotoxic activity and lack of adequate selectivity for anticancer use, these results are not particularly appealing at the moment. After a long time to try, including testing derivates of functional groups, the epothilone fails to confer superior benefits in comparison to the burgeoning clinical efficacy of paclitaxel [6]. Up until the year 1995, D. M. Bollag's lab published that the epothilones are equivalent and exhibit kinetics similar to paclitaxel inducing tubulin polymerization into microtubules *in vitro* (filtration, light scattering, sedimentation, and electron microscopy), as well as in causing increased microtubule stability and bundling in cultured cells.[7] The most remarkable finding was that epothilone B appeared to be even more active than paclitaxel, which replaced microtubule-bound paclitaxel and likewise caused cell cycle arrest at the G2-M transition with minimal impairment. Immediately, pharmaceutical companies and academia opened a series of studies on this compound. It was also found that compound **2** exhibits superior biological activity compared to compound **1**, competing with paclitaxel for the same microtubule binding site. Furthermore, **2** demonstrated vastly greater therapeutic efficacy at maximally tolerated doses and with reduced toxicity. Because of its effectiveness *in vitro*, **2** has been proposed as a lead molecule for future clinical development among epothilone analogs.[7]

Biosynthesis genes have been shown to be technically useful in production, but despite much research and development, it remains unable to obtain large quantities of epothilone B which has been shown most efficient in combating resistant tumors at that time. [8] Until 1998, with the development of the culture media, processes and isolation techneiques resulting in a technically efficient production process. From 1997 to 1999, the rich supply of epothilones was isolated from fermentation process or as intermediates or via semi-synthesis. These were the main scores to study epothilones and its impressive biological profile.[3]

In August 1998, S. J. Danishefsky’s group published a new 16-membered macrolide, named epothilone D, shown in Scheme 2, which lacked the epoxide functionality, and exhibited far superior therapeutic results *in vivo*.[9] The name "epothilone D" was assigned to this substance at a later date. Compared with epothilone B, epothilone D

has a higher maximum tolerated dose. Meanwhile, this group published the total synthesis of epothilone D in 2002 and modified the structure. [10]

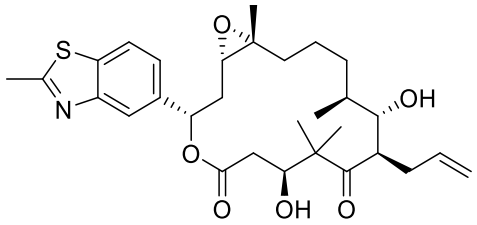


1: R=H, epothilone A
2: R=Me, epothilone B

3: R=H, epothilone C
4: R=Me, epothilone D

Scheme 2: The structures of epothilone A-D.

Since 2000, Schering AG started a MedChem program with epothilones related to modifications synthesizing many analogues using Schinzer's strategy including 6,7-aldol coupling. [11] Rationally, a new analog, ZK-EPO was discovered, which modified epothilone B at carbon C6 (replacing the methyl group with an allyl group) and C15 (replacing the side chain by a benzothiazole). This compound combines high activity and efficacy, a fast and efficient cellular uptake, no recognition by efflux mechanisms, and an improved therapeutic window.



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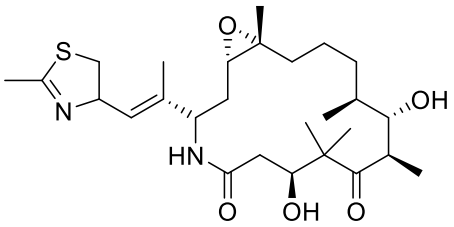
Scheme 3: The structure of epothilone ZK-EPO.

Meanwhile, more research focuses on modifying other selected parts of the structure and functional groups to improve different needs. For example, in order to improve metabolic stability, Bristol-Myers Squibb (BMS) started a large research program and the lactone was replaced by a lactam as a semi-synthesis production, now named ixabepilone.[12] However, the first total synthesis of this new type of lactam was published by D. Schinzer at al.[13] Similar to paclitaxel, ixabepilone was confirmed to block cells in the mitotic phase of the cell division cycle [14] and increased water solubility and plasma stability, but it exhibits one-fold reduction in cytotoxicity.[15]



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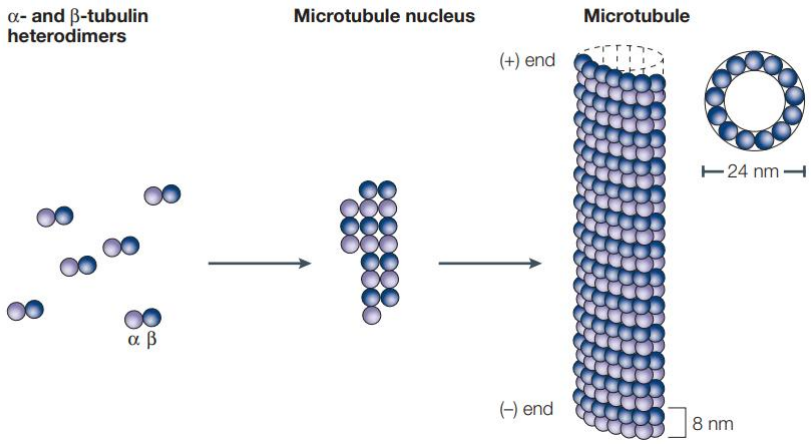
Scheme 4: The structure of ixabepilone.

The analogues of epothilone have amassed a huge family up to this point. The most typical is the 16-membered lactone with a thiazolethylene side chain which is present in natural epothilones.

1.2 Mechanism of Action

Cancer, the world's most lethal illness, claimed approximately 10 million lives in 2020 alone.[16] Preventing, diagnosing, treating, and curing cancer continues to be one of the most pressing health issues facing humanity today. As it grows uncontrollably, the cancer cell has the potential to infect neighboring tissues and cause damage. In 1971, the pacific yew tree discovery of Taxol® (paclitaxel), a complex triterpene used to treat cancer and already on the market, sped up technological and economic progress.[17] Since epothilone A and B have been confirmed that they also kill tumor cells through a similar mechanism, a serious of experiments proved the superiority of epothilone B over paclitaxel later.[18] To optimize the epothilone derivatives, most researchers also talk more about the molecular and cellular biology of tubulin and tubulin binding agents. These results provide more insights into SAR studies to optimize the epothilone core.

Microtubules are long, filamentous protein polymers forming dense parallel arrays like bundles between axons and dendrites in order to the growth and remain of these neurites.[19] In point of fact, microtubules have critical roles in all eukaryotic cells as a part of cytoskeleton, including intracellular transport, secretion, cell motility, and, most crucially, the mitotic process, which is a dynamic process that occurs both *in vitro* and *in vivo*. The dynamic process is a most critical characteristic, which requires microtubules never arrive at a stable state; rather, they are always either in the process of polymerization (growth) or depolymerization (shrinking).[19] Actually, microtubule nucleus is made up from α/β tubulin heterodimers. After that, the end of the microtubule nucleus is prolonged, which results in the formation of a cylinder with 13 protofilaments oriented head-to-tail. (shown in Scheme 5).[20] Several post-translational modifications act on six tubulin and seven -tubulin isotypes to control microtubule function. Microtubule function can also be explained by a number of proteins that connect with microtubules.



Scheme 5: Polymerization of the microtubules.

As is common knowledge, the process of mitosis is always divided into several stages: the first stage, known as prophase, involves the formation of two dipolar spindle-shaped arrays of microtubules; the second stage, known as metaphase, involves the chromosomes being assembled to an equatorial position on the mitotic spindle; and the third stage, known as anaphase, involves the microtubule dynamics changing and the chromosomes being partition to move the new daughter cells. It is clear that microtubules play an important role in prometaphase by assisting chromosomes at kinetochores in attaching to the spindle in a timely and appropriate manner. It would appear that microtubules could be a target for antimitotic medicines based on the fact that chromosomes could be blocked in this state until apoptosis occurred since the depolymerization was reduced resulting in lacking bipolar attachments.[20] As well as, compared with normal cells, cancer cells are more sensitive to drugs due to frequent divition. In most cases, when a significant number of antimitotic drugs that restrict cell proliferation by acting on the polymerization dynamics of the spindle are utilized, there are simple classifications that may be made into two main groups.[21] One is microtubule-destabilizing agents, such as Vinca alkaloids and second are microtubule-stabilizing agents such as paclitaxel and epothilones.

By 1995, paclitaxel is used clinically successful, and now it is widely used to treat breast and ovarian cancer, non-small-cell lung cancer and Kaposi's sarcoma.[20] Paclitaxel binds with β tubulin subunits in a 1:1 stoichiometry, it accesses the *o* inside of the microtubule and binds inside the surface by diffusing through small openings or fluctuations of the microtubule lattice.[22] Then stabilizes the microtubule by markedly reduce the dissociation of α/β tubulin. The most notable is that paclitaxel can also be effective *in vitro*. In the presence of magnesium (Mg^{2+}), guanosine triphosphate (GTP), and microtubule-associated proteins, the assembly of microtubules takes place (MAPs).[23] Based on works of P. B. Schiff's group, more and shorter microtubules proceed to be polymerized when assembly takes place in the presence of paclitaxel.[24] In this experiment, tubulin, at a concentration of 7.7 μM (1 mg/ml total protein),

underwent assembly in standard conditions with and without the addition of 10 µM paclitaxel for a duration of 20 minutes. Subsequent to centrifugation at 120,000g for 30 minutes, the quantification of protein content in both the pellets and supernatants was determined. In the absence of paclitaxel, centrifugation yielded a pellet containing 0.57 mg of protein. Contrastingly, under the influence of 10 µM paclitaxel during tubulin assembly, the resulting pellet contained 0.78 mg of protein. The maximal protein pelleting occurred at a paclitaxel concentration approximately stoichiometrically aligned with the dimer concentration. Nevertheless, subsequent to the seminal discovery by Schiff and Horwitz [25], paclitaxel and its analogs remained the exclusive repertoire of microtubule depolymerization inhibitors documented in the scientific literature for over a decade until the discovery of epothilones.

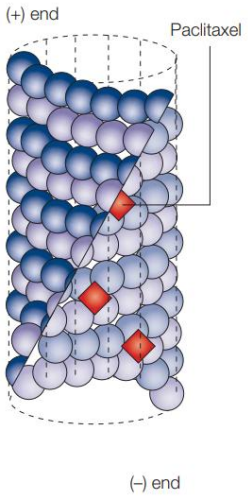


Figure 1: Paclitaxel bind to microtubules.

Although paclitaxel has been found to be efficient against various cancer cells, even though this ability has been also shown *in vitro*, it still was useful despite the side effects and its low water solubility. Then it was discovered that epothilones and its analogs can bind at or near the paclitaxel site on the tubulin subunit and competitively inhibit the binding of paclitaxel, which also results in a mitotic block, and as well as arrest at the G2/M phase of the cell cycle.[26] In addition, it has more potency in cell culture models with inhibitory concentration (IC_{50}) values in the low nanomolar range.[22] This means that epothilones are superior over paclitaxel as a killer of tumor cells. Then experiments demonstrated that epothilone B showed a 2000-5000-fold higher potency than paclitaxel.[23] In addition, epothilones are a poor substrate for P-glycoprotein, a membrane-associated protein that can decrease drug absorption and intracellular concentration, therefore they maintain activity against multidrug-resistance.[27]

Figure 2 illustrates the binding of epothilone B to the microtubule. The backbone structure of the tubule is depicted in light green, with the M loop highlighted in yellow. The M loop plays a crucial role in maintaining microtubule stability. The binding of epothilone B effectively locks the microtubule in a stable yet non-functional state, ultimately leading to cancer cell death.

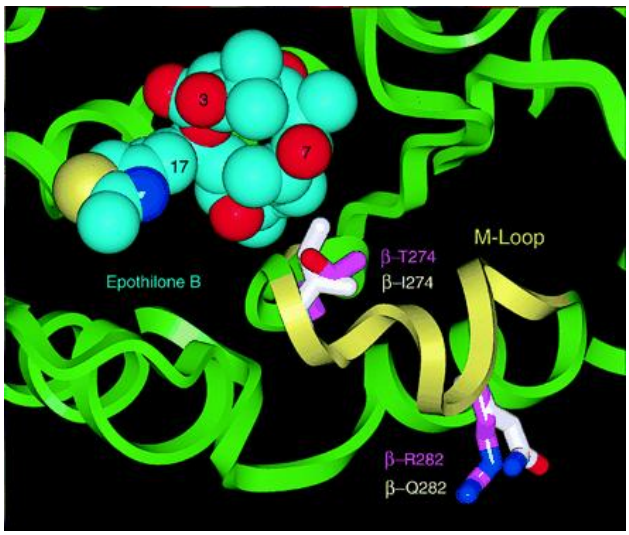


Figure 2 Space-filling model of the Epothilone B conformation[28]

Analysis using computational models suggests that epothilones also can modify the function of microtubules, making them more flexible.[29] Because of the greater flexibility of the macrolactone ring, molecular dynamics simulations have projected that epothilones will be able to pass through the microtubule wall more efficiently than paclitaxel.[30]

The epothilones, on the other hand, seem to have better qualities: they are more water soluble and they are simpler and can be produced by bacterial fermentation. For these reasons, they are effective against numerous cancer cell lines, including those derived from prostate, colon, lung, breast, ovarian bladder, squamous cell, leukemia, and fibroblasts.[31]

1.3 Total Synthesis

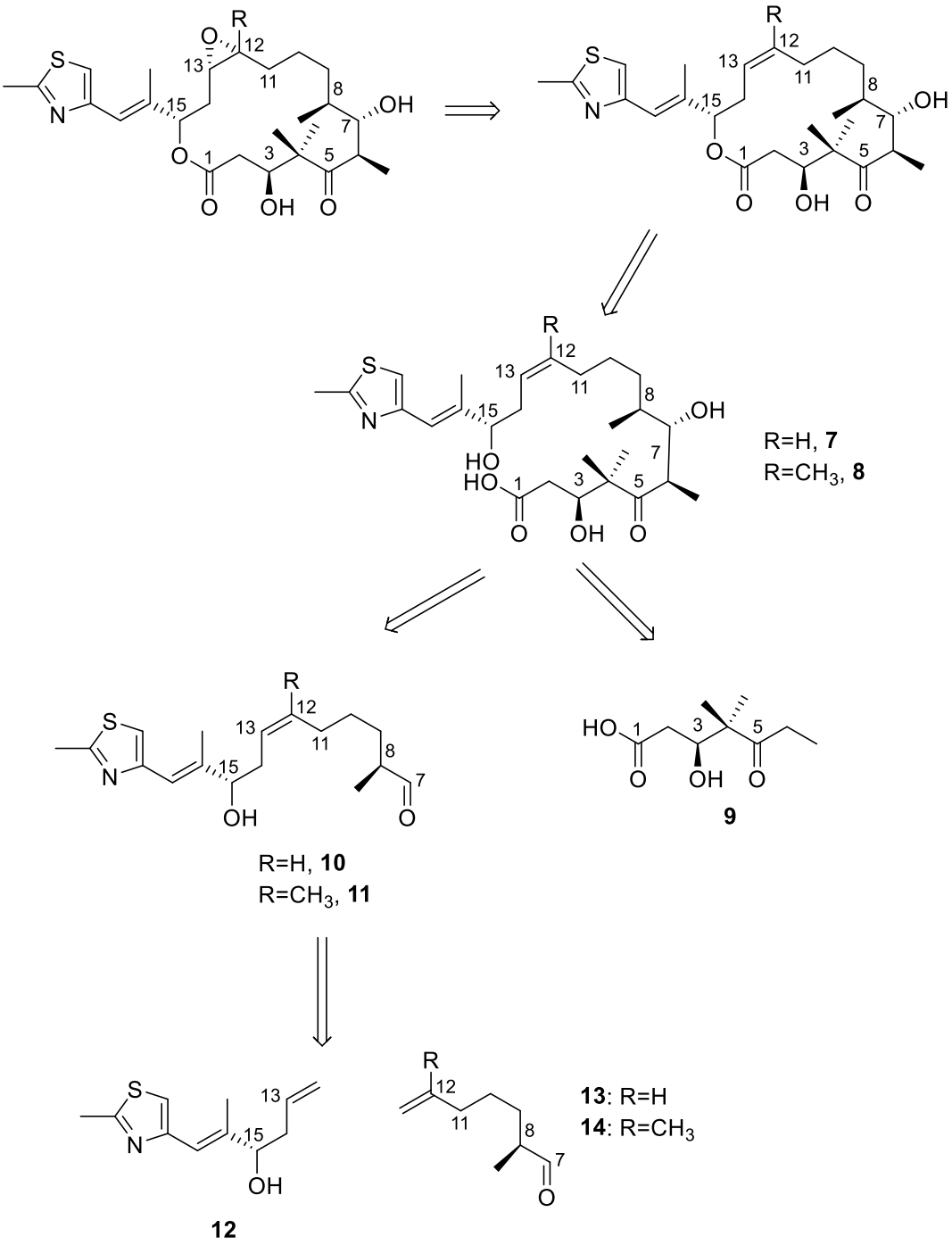
Based on the importance of epothilone B (**2**) in pharmacoloy, more and more groups started efforts to synthesize **2**. The vast majority of biosynthesized epothilones occur as protonated or methylated C12 homologous pairs. Due to their low abundance and overlap with other strong peaks during chromatography, homologues are notoriously difficult to identify. In most cases, the more highly conserved homologues (just B and D, for instance) will be more valuable. Therefore, the chemical approach is likely to be successful in resolving this issue. [20]

1.3.1 Retrosynthesis of Epothilone A/B

In order to accommodate the need for more in-depth research, chemical procedures for synthesizing epothilones and its derivatives have progressed to include functionalization and structural modification. The initial key goals of total synthesis are

epothilones A (**1**) and B (**2**) and their deoxy-analogues C (**3**) and D (**4**). Based on the structure, the majority of the methods used in epothilones synthesis are quite comparable.

The final stage in the standard restrosynthesis analysis is the stereocontrolled epoxidation of the C12–C13 double bond, which yields **3** and **4**. Furthermore, the second-to-last stage offers alternatives. One is macrolactonization, wherein the carbon C15 is broken off to form a seco-acid. The aldol reaction between an aldehyde including the carbon chain C7-C21 and a ketone can produce the seco-acid. When it comes to carbon atoms in the C6-C8 range, the aldol reaction may reliably produce the most favorable configurations. The carbon chain C7-C21 can be divided into thiazole and the olefin, which is coupled by olefin metathesis reaction or other methods. As an alternative, the ring can be closed by olefin metathesis between C12 and C13, which, with the help of a catalyst made of a metal like ruthenium, can produce the necessary isomers. At the same time, the aldol reaction takes place in C6-C8 at first. Similarly, the last step can also occur at C11-C12, which used Pd (0)-catalyzed cross-coupling reaction to substitute alkenes. But it is clear that the three smaller segments are initial products for synthesis of the macrolide.



Scheme 6: Retrosynthesis of the epothilone A and B.

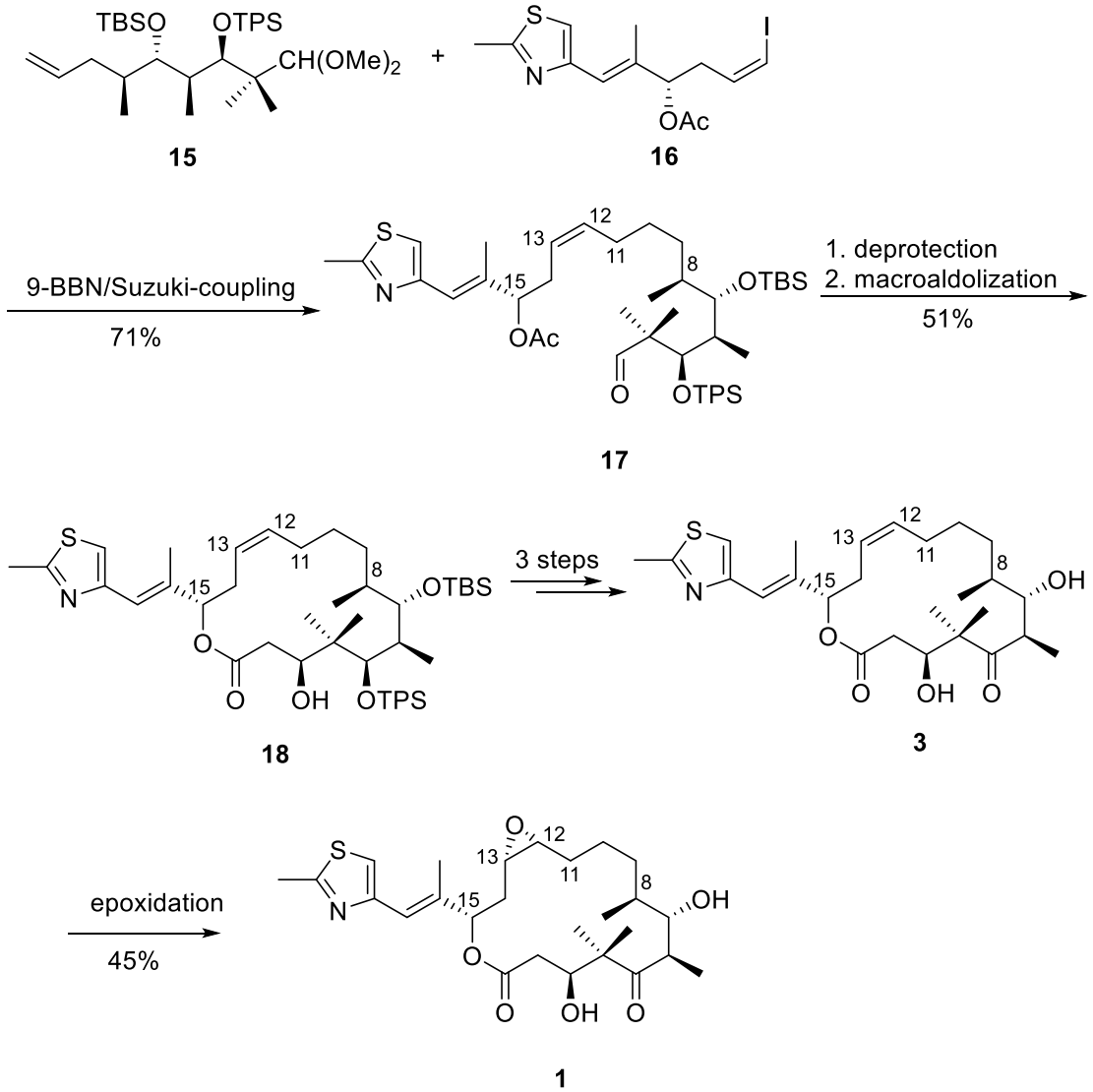
1.3.2 Total synthesis of Epothilones

1.3.2.1 Danishefsky's synthetic methods

Scientists, notably synthetic chemists, have been attracted to the epothilones ever since their isolation and identification, due to their potential role in cancer research and treatment. **1** was initially synthesized by Danishefsky and coworkers in 1996 [32], and subsequent total syntheses were published by Nicolaou *et al*.[33] and Schinzer *et al*.[11]

and their strategies have been reported in due course.

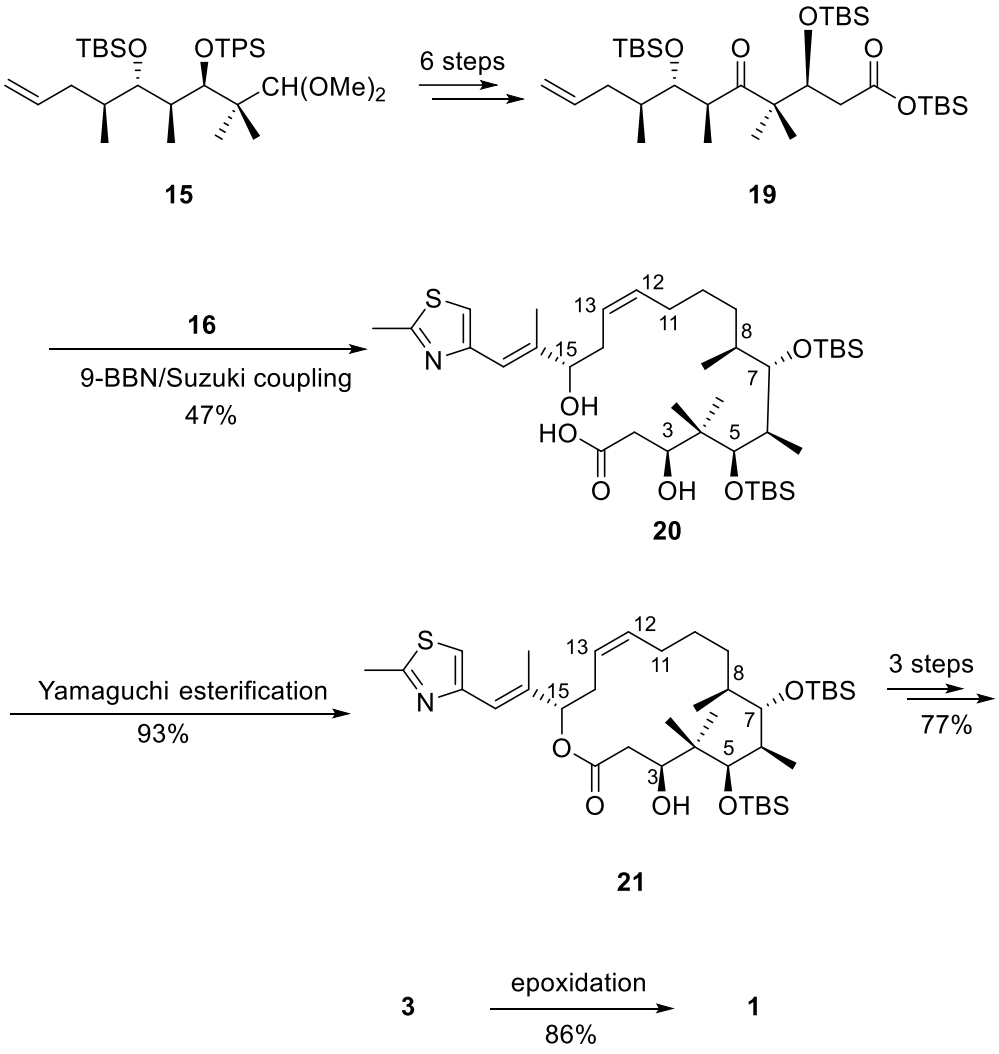
In 1996, Danishefasky and his colleagues published their strategy to the total synthesis of **1**.[32] This approach relies on the retrosynthesis analysis that divides the whole molecule into three unusual segments. Subsequently, the two "halves" were linked through a *B*-alkyl Suziki carbon-carbon bond construction and the ring was closed via an intramolecular aldol reaction. In this context, the methyl group of C1 bound acetoxy group served as the nucleophile for macroaldolization after deprotonation. Moreover, these conditions provided a remarkable stereoselectivity of 6:1 in favor of the diasteromer with (*S*)-alcohol **18**. Then the desoxyepothilone **3** was obtained after 3 steps and (-)-epothilone A **1** was obtained via epoxidation.



Scheme 7: Total synthesis of epothilone A using the macroaldol strategy from Danishefsky.

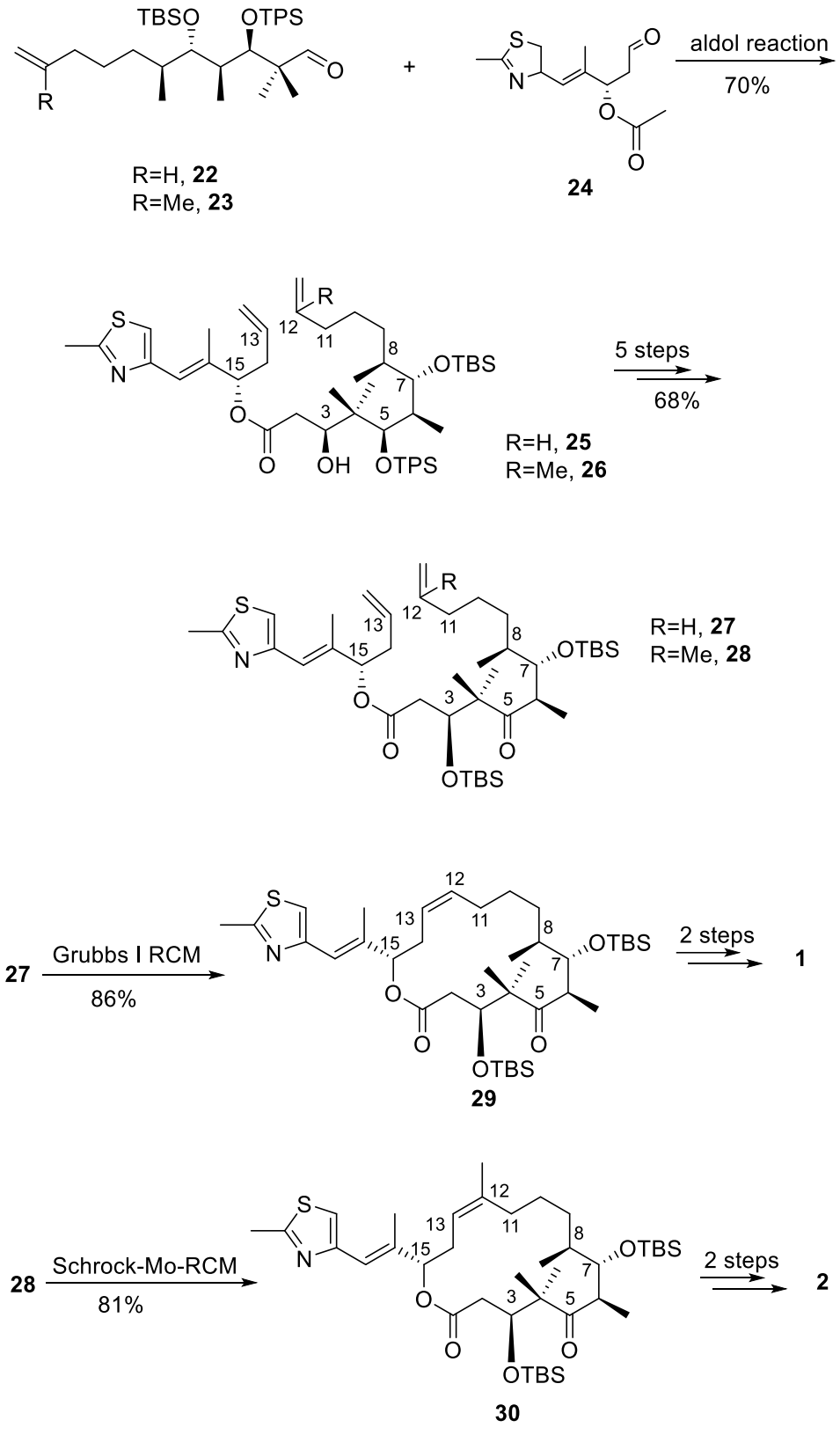
Based on the *B*-alkyl Suzuki pathway, Danishefsky's group also provided another approach to synthesize **3** via Yamaguchi esterification as the ring closing step. [34] They converted compound **15** into compound **19** after 6 steps, which served as the source for

the Suzuki reaction. This intermediate was then reacted with compound **16** via Suzuki coupling to yield compound **20**. And epothilone A **1** was achieved after 5 steps.



Scheme 8: Total synthesis of epothilone A using the Yamaguchi esterification from Danishefsky.

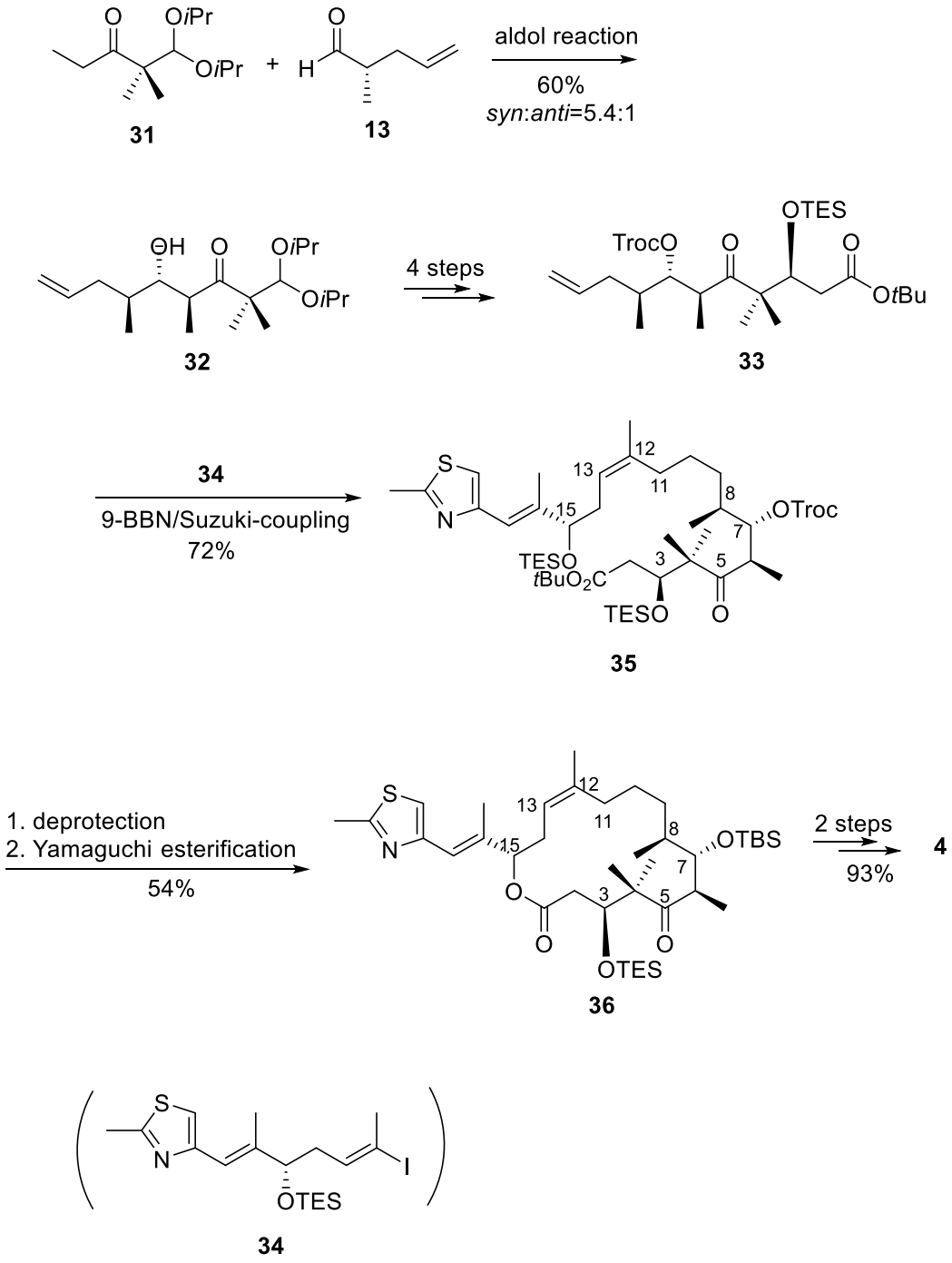
At a similar time, they also published another potential strategy involving ring-closing metathesis (RCM) for the synthesis of epothilone A, which could also be applied to the synthesis of epothilone B.[35] During this process, aldol addition with **22** or **23** and the aldehyde segment **24** resulted in the formation of the intermediate **25** and **26** as a 1:1 diastereomeric mixture at C3. It should be noticed that the configuration of (*3R*) was rectified to (*3S*) via an oxidation-reduction. After further modifications, the intermediates **27** and **28** were obtained. Compound **29** was produced by cyclizing precursor **27** with Grubbs' first-generation ring-closing metathesis (RCM) catalyst, resulting in an *E/Z* isomer mixture with a ratio of 1:1.7, which could be separated and desilylated to give **1**. In contrast, the RCM of intermediate **28** required the treatment with Schrock's catalyst to furnish compound **30** as an *E/Z* mixture at a ratio of 1:1 followed by purification and epoxidation to yield **2**. [36]



Scheme 9: Total synthesis of 1/2 using RCM approch from Danishefsky.

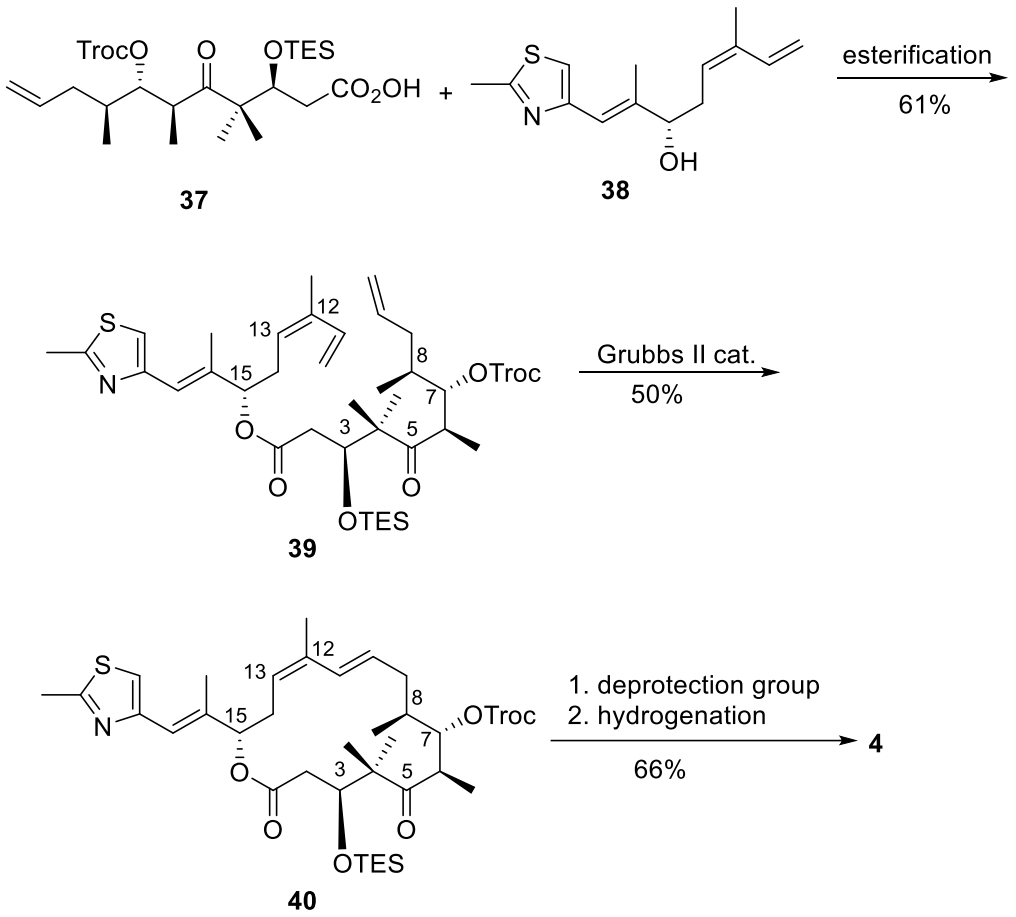
For the synthesis of epothilone B, based on previous works, they also employed the *B*-alkyl Suzuki coupling from **34** and **33** to generate seco-intermediate **35**. Modified with protecting groups followed by Yamaguchi esterification can result in the formation of

36, serving as the source of **4**.[10, 37]



Scheme 10: *B*-alkyl Suzuki approach to synthesis of epothilone D from Danishefsky.

Similarly, another strategy was applied for providing epothilone B via the original RCM approach. Initially, olefin **38** and acid **37** were connected by esterification to form the seco-intermediate **39**, which was then treated with Grubbs II catalyst to give the ring-closed derivative **40**. Due to the impact of double bond at C12-C13, it resulted in lowered yield. After purification, **40** was deprotected and hydrogenation of the C10-C11 bond led to the formation of **4**.[36b]



Scheme 11: Grubbs II catalyzation approach to synthesis of of epothilone D from Danishefsky.

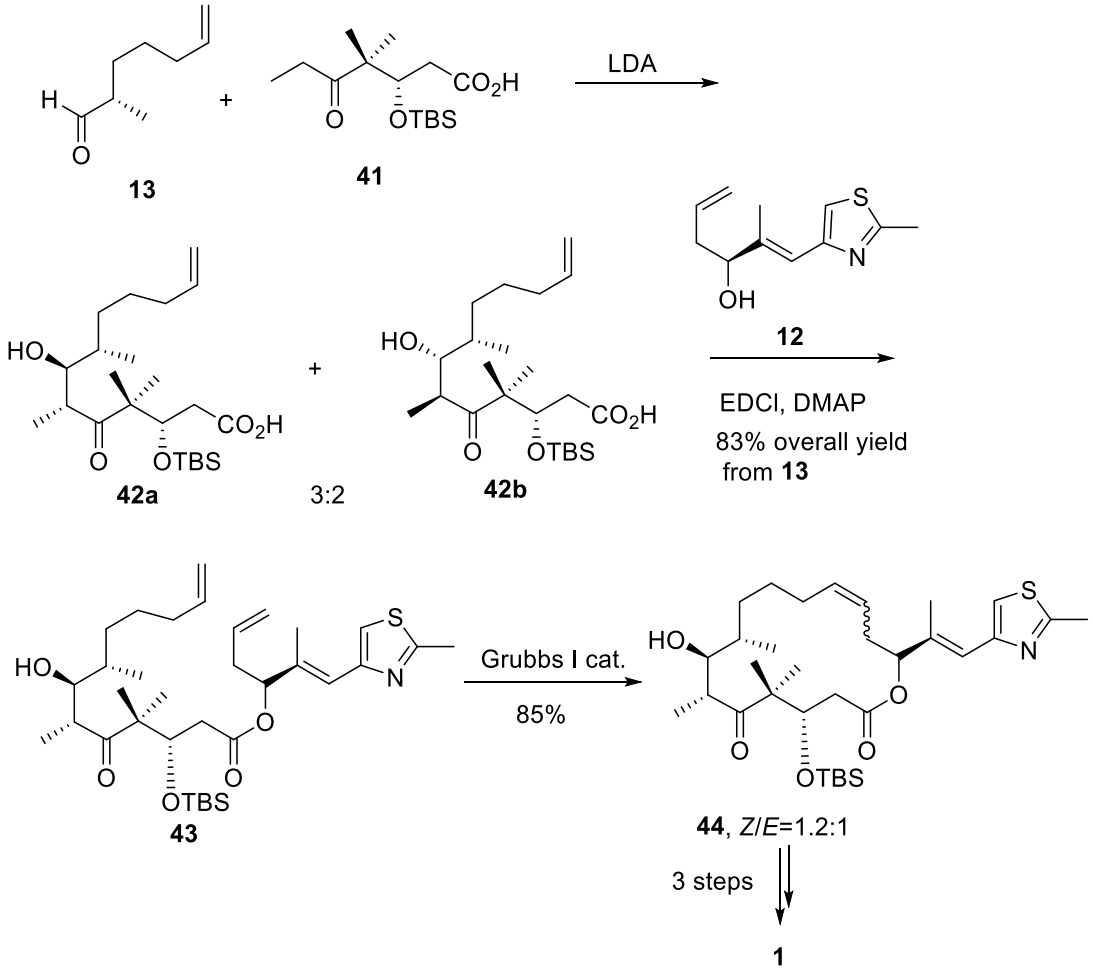
Danishefsky and his associates have significantly advanced the field of study with their extensive research and innovative ideas. While only a few typical strategies have been discussed here, their work offers numerous possibilities for the synthesis of epothilones using organic methods.

1.3.2.2 Nicolaou's synthetic methods

The Nicolaou group was the second group which successfully accomplished the entire synthesis of both **1** and **2**. In the described epothilone A synthesis, their strategy centered on an aldol addition involving a C6 ketone enolate and a C7 aldehyde, also olefin metathesis formed the C12–C13 double bond.

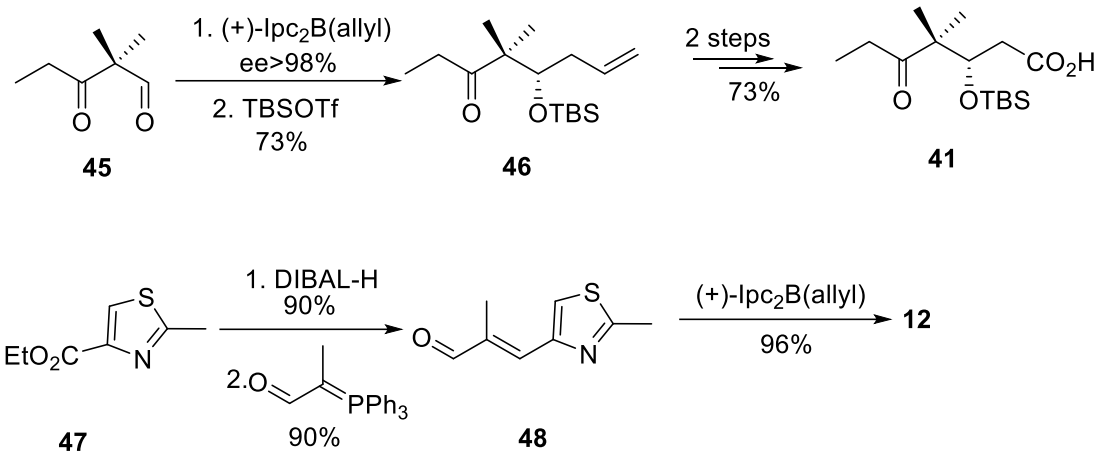
As outlined in Scheme 12, aldehyde **13** was transformed into **42** and its diastereomers in a 3:2 ratio when initially treated with LDA followed by addition of 1.6 equivalents of ketone segment **41**. The desired configuration was favored. DCC and 4-DMAP were used to enable the esterification of the combination with the homoallylic thiazole alcohol **12** and mixture of **42**, yielding a separatable mixture of di-olefine intermediates **43**. This two-step process achieved an overall yield of 83%, with the target isomers

constituting 52% of the product. The double bond can be achieved through RCM with a 1.2:1 mixture of *Z*/*E* isomers in the presence of 10 mol% Grubbs' ruthenium catalyst. Chromatography successfully isolated the *Z*-configuration in its pure form. Compound **3** was obtained after the cleavage of protection group from (*Z*)-**44**. The final step, treating **3** with the epoxidation protocol gave **1** in 55% yield, together with its epoxide isomer in 20% yield. [38]



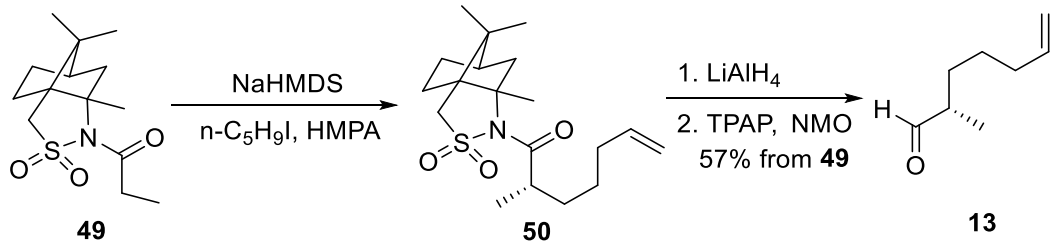
Scheme 12: Grubbs I catalyzation approach to synthesis of 1 from Nicolaou

The group also provided a detailed method to prepare segment **41** including carbon C1-C6.[39] The initial source step is the addition of H. C. Brown's chiral (+)-Ipc_2B (allyl) reagent to aldehyde **45**, affording the desired alkylated product with greater than 98% ee. The new hydroxy group was protected with TBSOTf, followed by an ozonolysis cleavage and oxidation with $NaClO_2$ to afford the carboxylic acid **41**. At the same time, the asymmetric allylboration reaction was also used for the synthesis of the stereogenic centers at carbon C15. The thiazole ester **47** was converted into the corresponding aldehyde by adding DIBAL-H reduction reagent and then treated with ylide through a stereoselective Wittig reaction to provide (*E*)-α, β-unsaturated aldehyde **48** in 88% yield. This can be reacted with the borane to prepare the thiazole segment **12** in 96% yield and more than 97% ee.



Scheme 13: Synthesis of the thiazole segment 12 from Nicolaou.

Aldehyde **13** was obtained by Oppolzer alkylation from chiral sultam derivative **49**. In the presence of HMPA, 5-iodo-1-pentene underwent a diastereoselective addition reaction, where the enolate reacted selectively with the primary alkyl iodide only from the bottom face to afford **50**. Here, the alternative possibility was effectively inhibited through the steric hindrance induced by gem-dimethyl substituents positioned at the apical region of the [2.2.1]-bicyclic ring system. Then the chiral auxiliary was smoothly excised with $LiAlH_4$ followed by oxidation with TPAP/NMO, providing aldehyde **13** in 57% total yield.

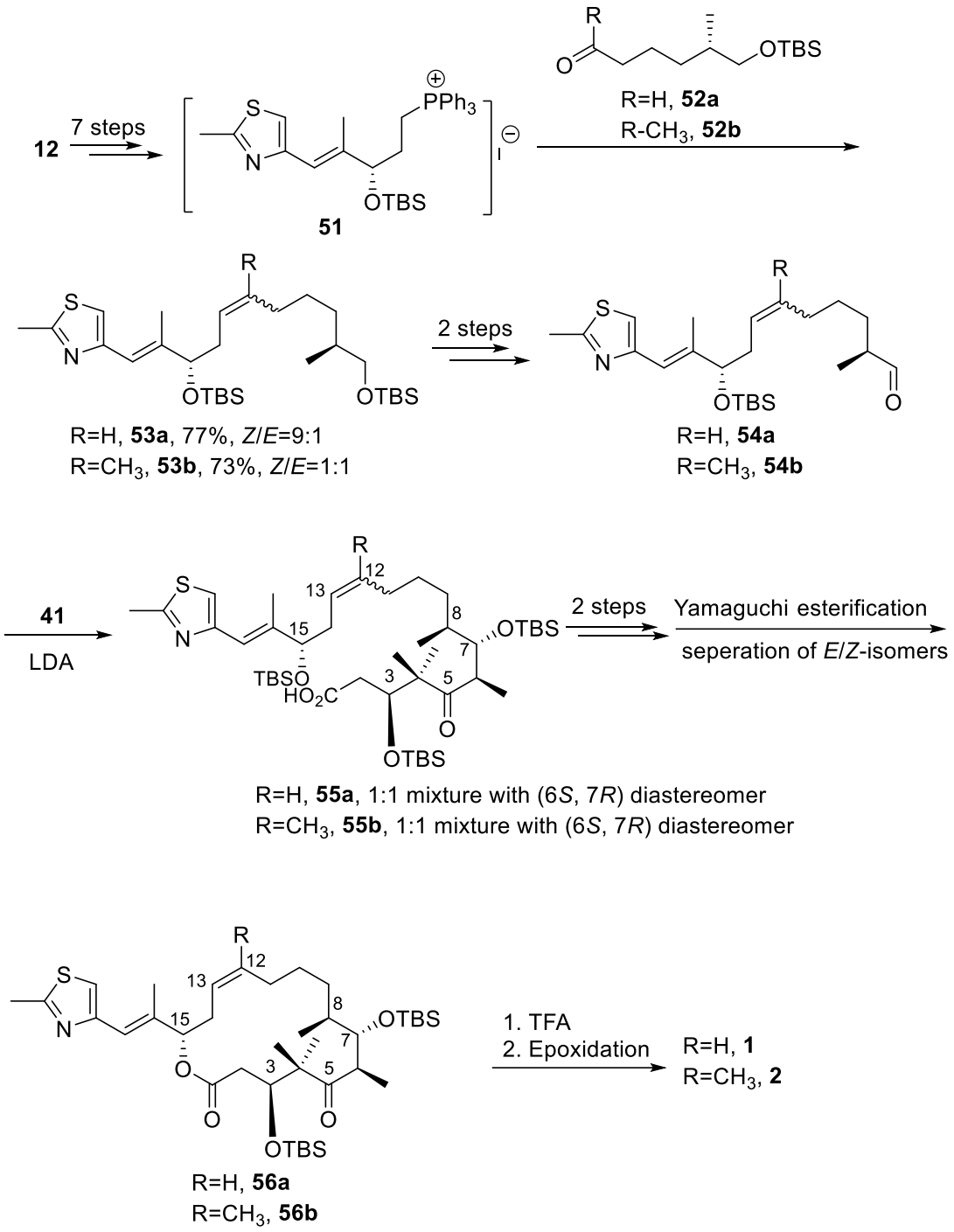


Scheme 14: Synthesis of aldehyde 13 from Nicolaou.

In this synthesis approach, the process begins with a non-stereoselective aldol-type addition involving aldehyde **13** and ketone **41**, yielding a 1.2:1 mixture of *Z/E* isomers. Subsequently, Yamaguchi macrolactonization was employed as an alternative to the RCM method for the synthesis of compound **1**. The Wittig reaction, utilizing phosphonium salt **51** derived from precursor **12** through a seven-step sequence, and compound **52a**, produced a 9:1 *Z/E* mixture of olefins **53a**. [33] The subsequent conversion of **53a** into aldehyde **54a**, followed by aldol addition with keto acid **41**, resulted in a 1:1 diastereomeric mixture of aldol adducts **55a**. These adducts underwent protective group modifications and were subjected to Yamaguchi esterification, yielding intermediates **56a**. The intermediates were then desilylated to form compound **3**, which was epoxidized to afford compound **1**.

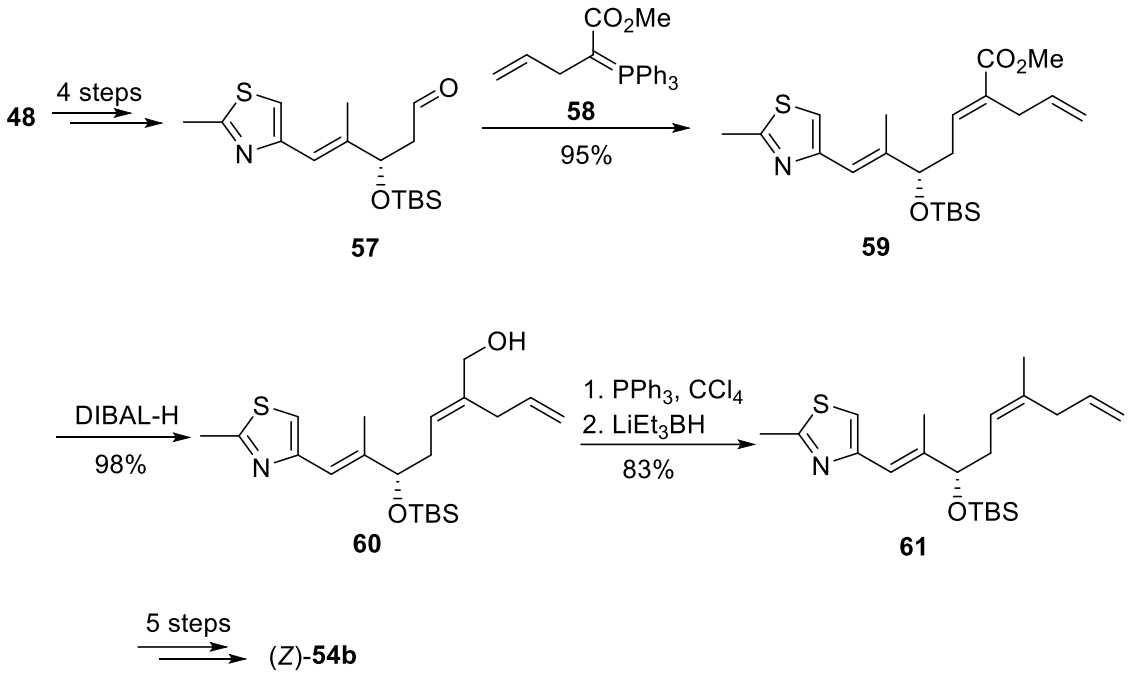
Actually, this method also applied for the synthesis of **2**. The only modification was the unselective Wittig reaction of **52b** with salt **51** to give **53b** as a 1:1 ratio of *Z/E*

isomers.[40]



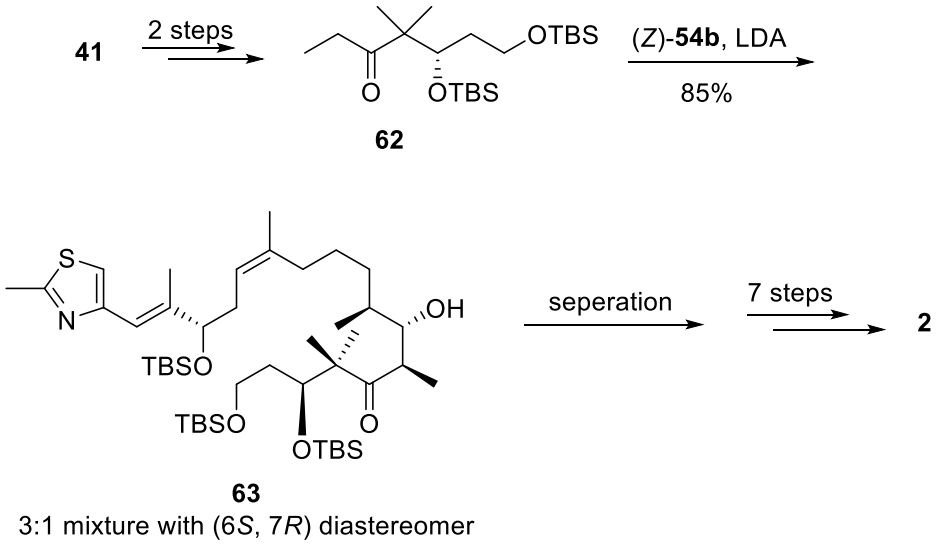
Scheme 15: Yamaguchi esterification approach to synthesis of 1 from Nicolaou

To improve the stereocontrol in the synthesis of the desired olefin, a HWE olefination was envisioned.[40] Initially, an (*E*)-selective olefination of aldehyde **57** with phosphorane **58** gave the pure (*E*)-olefin **59**. The ester was subsequently reduced to alcohol **60**, which was then deoxygenated to generate the (*Z*)-olefin **61**, serving as the precursor for further synthesis targeting (*Z*)-configured olefins.



Scheme 16: Synthesis of (*Z*)-54b from Nicolaou.

The aldehyde (*Z*)-**54b** was subjected to aldol addition with ketone **62** to give a 3:1-diastereomeric mixture of **63** in favor of the desired (6*R*,7*S*)-diastereomer. Removal of the wrong diastereomer followed by 7 steps gave epothilone B (**2**).

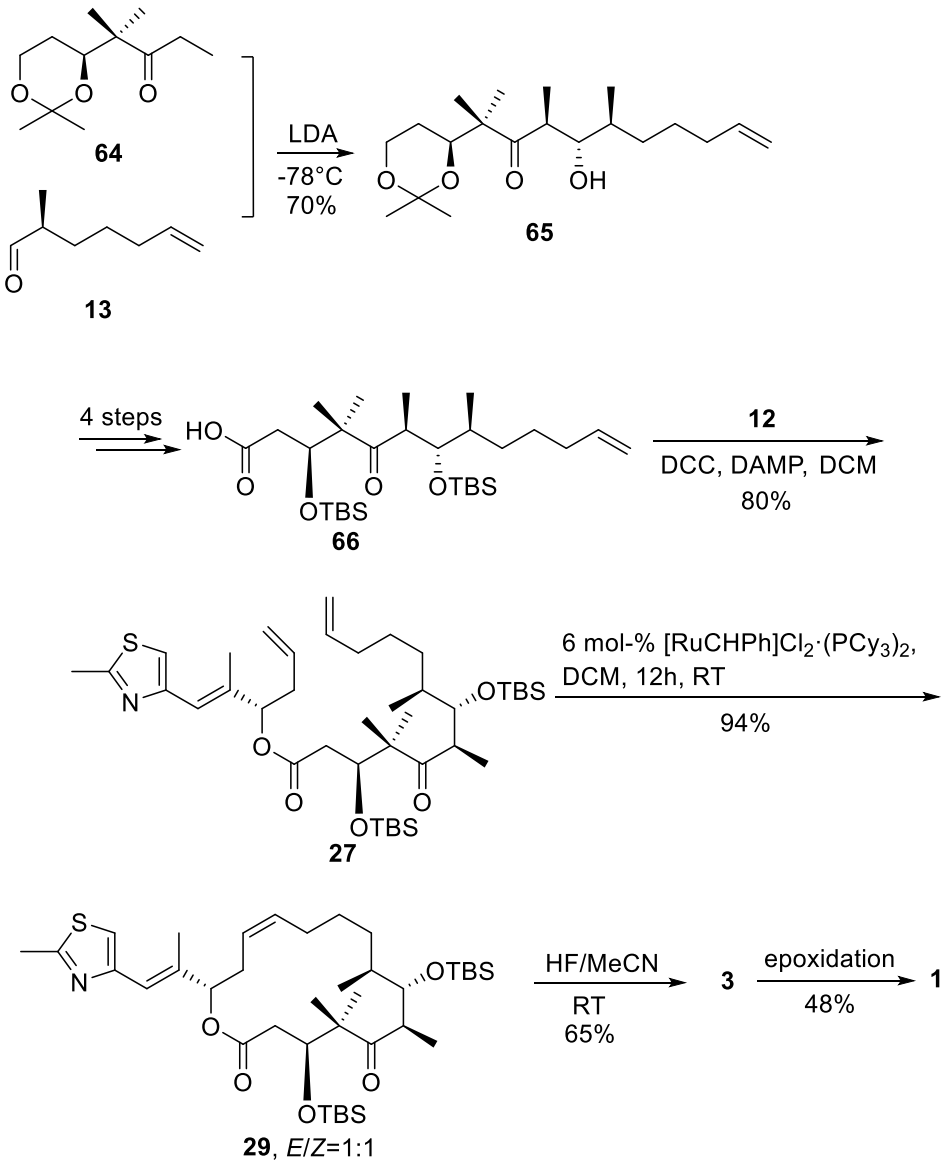


Scheme 17: Total synthesis of the 2 using (*Z*)-54b from Nicolaou.

1.3.2.3 Schinzer's synthetic methods

At the same time, Schinzer's group also published their approach to construct **1** with three key segments.[11] They tested different methods to construct the chiral centers, also providing more possibility to promote the selectivity of alkylation. The first critical reaction, the aldol reaction, which achieved the correct diastereomer with high

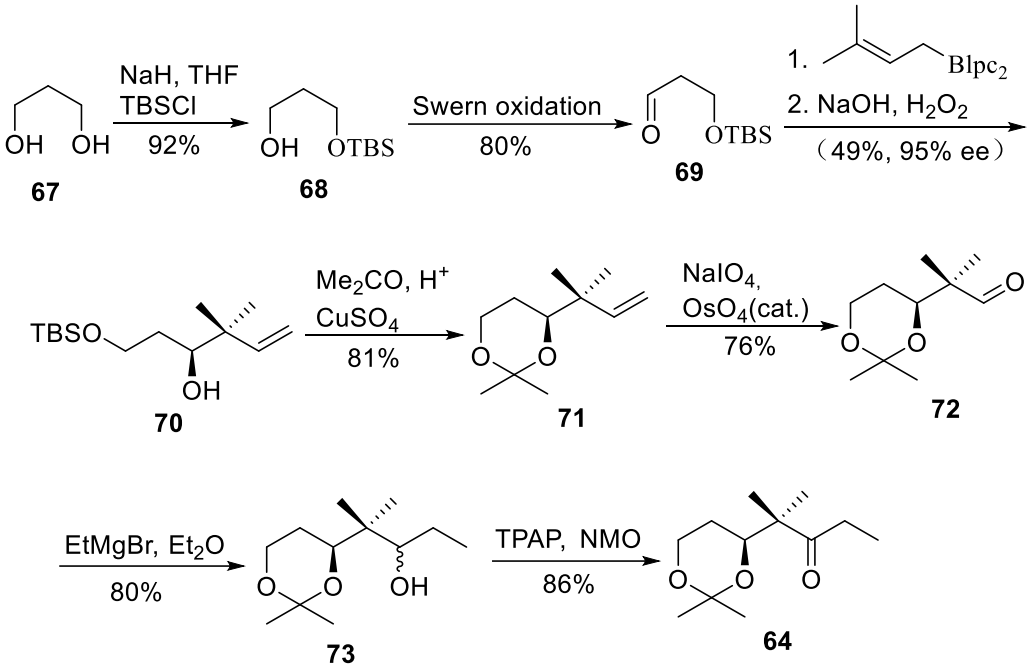
diastereoselectivity, completed the construction of the stereochemical triad C6-C7-C8 by treating gem-dimethyl ketone **64** with LDA at -78 °C followed addition of aldehyde **13**. In this step, only the desired diastereomer was obtained in 70% yield.[41] After necessary adjustment of the triol, the primary alcohol was transformed to the carboxylic acid **66** as the source for esterification. Next, esterification reaction connected the thiazole alcohol **12** to the acid **66** in presence of DCC and DMAP. After stirring at room temperature overnight in the presence of Grubbs I catalyst, RCM provided advanced intermediate **29** in a ratio of 1:1 of *Z/E*- mixture of diastereomers. [41] The pure *Z* olefin was obtained by chromatographic separation. In the final stage, olefin **29** was desilylated with HF/MeCN and DMDO was added at lower temperature to provide a 16:1 ratio of epoxide isomers in favor of **1** as the best results.



Scheme 18: Total synthesis of the 1 from Schinzer.

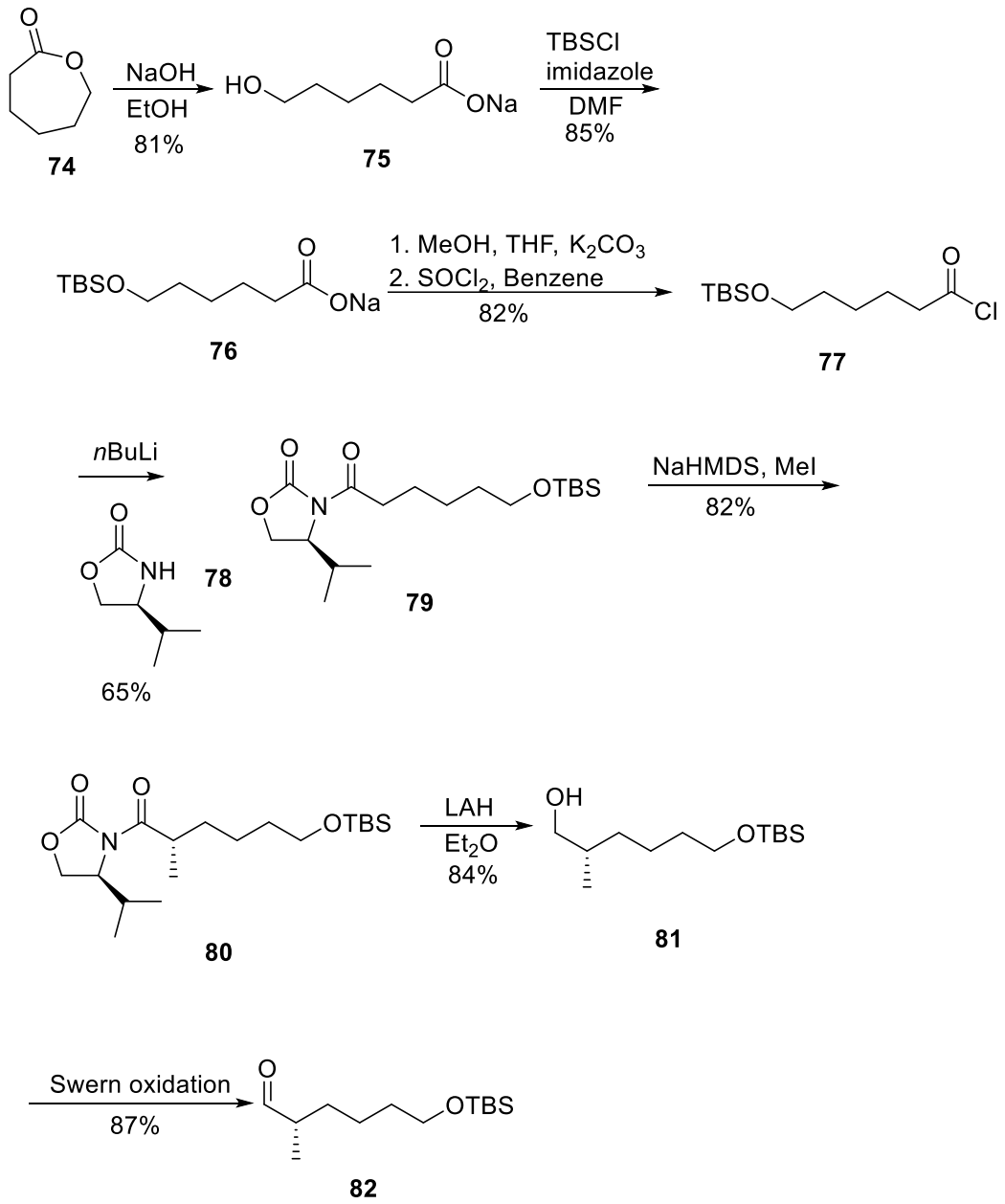
Schinzer's group also provided new methods to synthesize different segments.[42] Ketone **64** was obtained from 1,3-propandiol **67** which contains two hydroxy groups at

carbon C1 and C3. Protecting one of the primary alcohols by monosilylation, and subsequent, oxidation of other alcohol to the aldehyde, provided the starting material for an (-)-IpC_2B-allyl addition resulting in the functionalized homoallylic alcohol **70** with the correct configuration in 95% ee after oxidative workup in solution with sodium hydroxide and hydrogen peroxide. Then deprotection of the TBS group and protection of the diol led to the formation of acetonide **71**, oxidative cleavage of the double bond afforded **72**. Next, **73** was obtained by a Grignard addition reaction to extend the carbon chain. The key segment ketone **64** was generated in high overall yield after oxidizing the secondary alcohol.



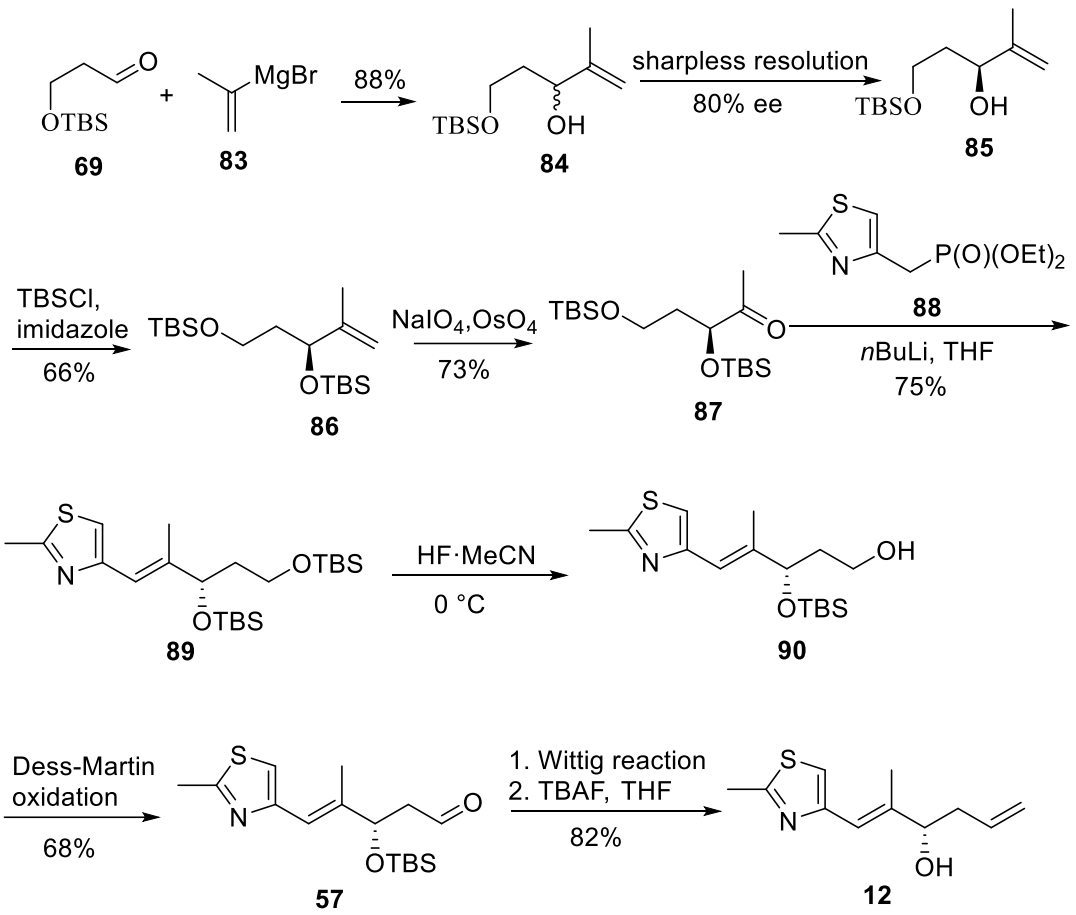
Scheme 19: Synthesis of the segment ketone 64 from Schinzer.

The other key intermediate, aldehyde **82** can be reached from ε-caprolactone (Scheme 20). In order to set the configuration at carbon C8 in the natural product, a diastereoselective methylation strategy was designed using oxazolidinone chemistry.[43] So, opening of the lactone **74**, protection of the resulting alcohol, and transferring the ester **76** to acid-chloride **77** prepared the desired substrate. It reacted with oxazolidinone **78** to generate amide **79**. Considering the hindrance of the β-face of the Evans auxiliaries, the electrophile was attacked from α-face of the preformed enolate of **79**, resulting in the diastereoselective formation of compound **80**. Cleavage of the Evans auxiliary and oxidation of the alcohol provided the segment aldehyde **82**.



Scheme 20: Synthesis of the segment aldehyde 82 from Schinzer.

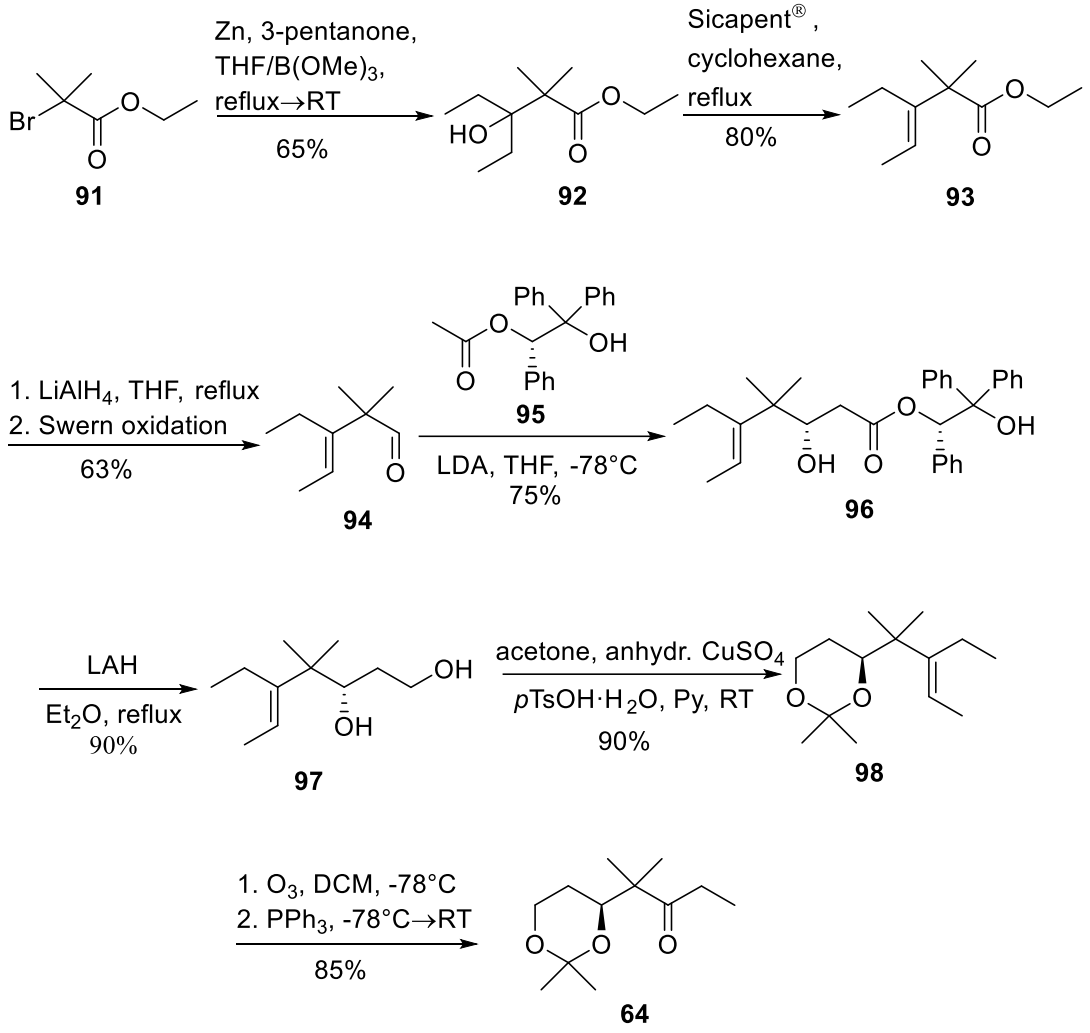
Subunit **12** was derived from **69**, which can be prepared from the same simple starting materials like key intermediate **64**. The addition of propenyl Grignard reagent **83** to starting material **69** yielded the functionalized allylic alcohol **84**. Subsequent Sharpless resolution provided the desired (*S*)-configuration in compound **85** with 80% ee.[44] Following protection of the alcohol, the methyl ketone **87** was generated through oxidation with $NaIO_4$ and OsO_4. The heterocyclic substrate was derived directly from the thiazole derivate **88** via Horner-Emmons reaction that facilitated in the formation of the desired olefin **89**. The primary hydroxyl group in **90** was established by deprotection and final oxidation gave aldehyde **57.** Wittig reaction and deprotection generated the thiazole segment **12.**



Scheme 21: Synthesis of the segment thiazole 12 from Schinzer.

In 1999, the Schinzer group published a new method for the synthesis of **1**.[45] The obvious change is a reported new routing to get the segment ketone **64**. And at the same time, the selectivity of the olefin-metathesis reaction has slightly improved. The yield is 94% with a slightly favored selectivity of the *Z*-isomer (*Z*/*E*=1.7:1).[45]

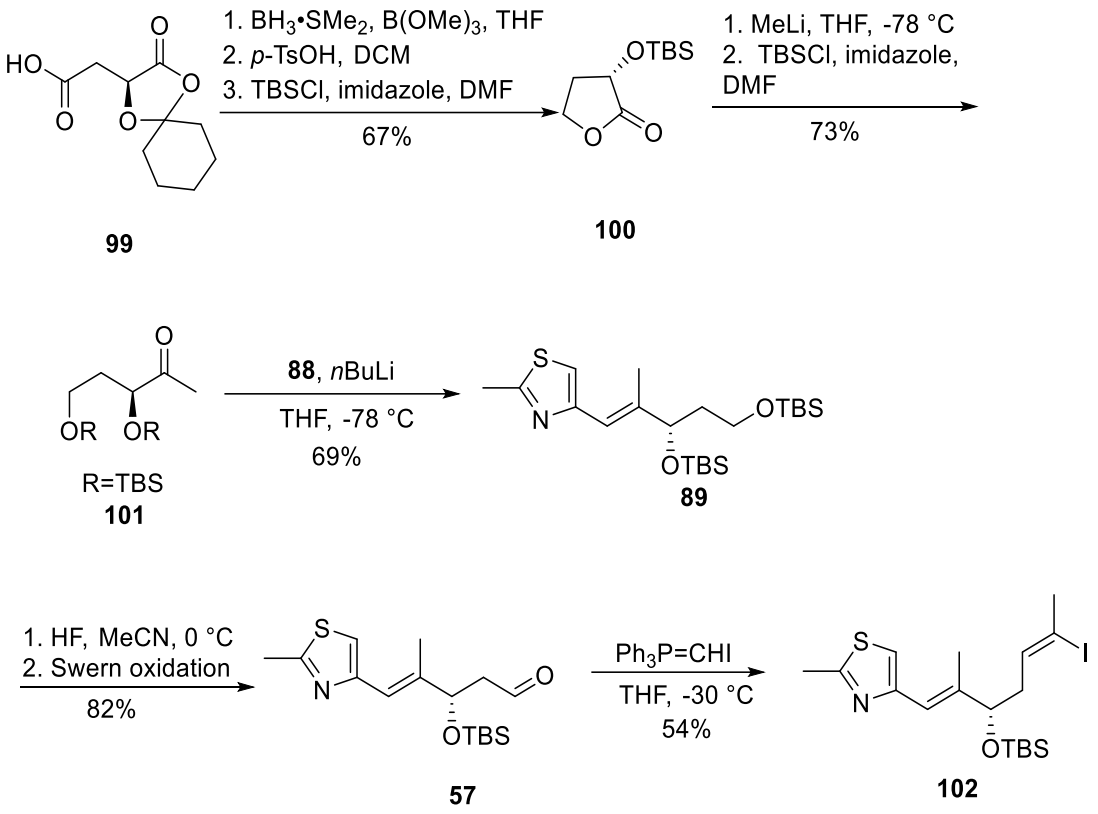
The new method for segment ketone **64** used α-bromo ester **91** as the starting material. It reacted with 3-pentanone by a Reformatsky reaction to provide the hydroxyester **92**. Taking advantage of the symmetrical structure in **92**, the ester afforded *E*-isomer of **93** by dehydration. Then ester **93** was treated with $LiAlH_4$ and Swern oxidation gave aldehyde **94** as starting material for the aldol reaction. It was mentioned earlier that the diastereoselective aldol reaction can achieve the desired stereocenter, so (*S*)-(-)-2-hydroxy-1,2,2-triphenyl acetate **95** was treated with LDA followed by addition of aldehyde **94**. Ester **96** with the desired chiral center was obtained in 96% ee and 75% yield. Reduction of the auxiliary yielded diol **97**, which was subsequently protected as a ketal. Final ozonolysis then afforded the segment ketone **64**.



Scheme 22: New synthesis of the segment ketone 64 from Schinzer.

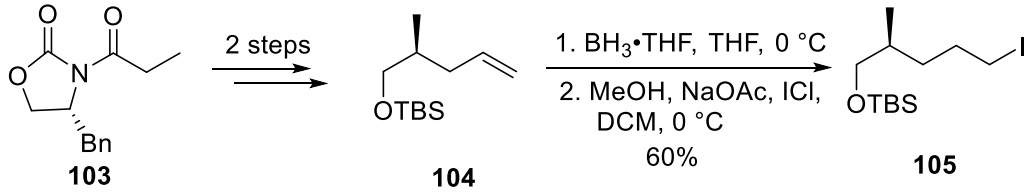
Our group reported a quite identical method to synthesize **2** based on the methodology used to obtain **1**. Thus, both ethyl ketone **64** and a more complex aldehyde were assembled through an aldol reaction.

After finding that the Grubbs catalyst was ineffective for RCM to establish a trisubstituted double bond, a transition metal-mediated coupling process was employed to construct the trisubstituted double bond instead of olefin metathesis. For the synthesis of thiazole fragment, a second-generation sequence was used, starting from (*S*)-malic acid **101** which can be prepared from cyclohexylidene ketal **99**. Selective reduction with BH_3•Me_2S, followed by treatment with an acid catalyst, afforded the well-known lactone **100**. After TBS protection conditions, addition of MeLi to the silyl lactone produced ketone **101**, which served as the starting material for the HWE reaction to obtain compound **89**. In consideration of the chiral center at carbon C15, the alcohol was converted into aldehyde **57** as a source of the Witting reaction, which subsequently led to the formation of vinyl iodide **102** as the only stereoisomer in 54% yield.



Scheme 23: Synthesis of the segment thiazole 102 from Schinzer.

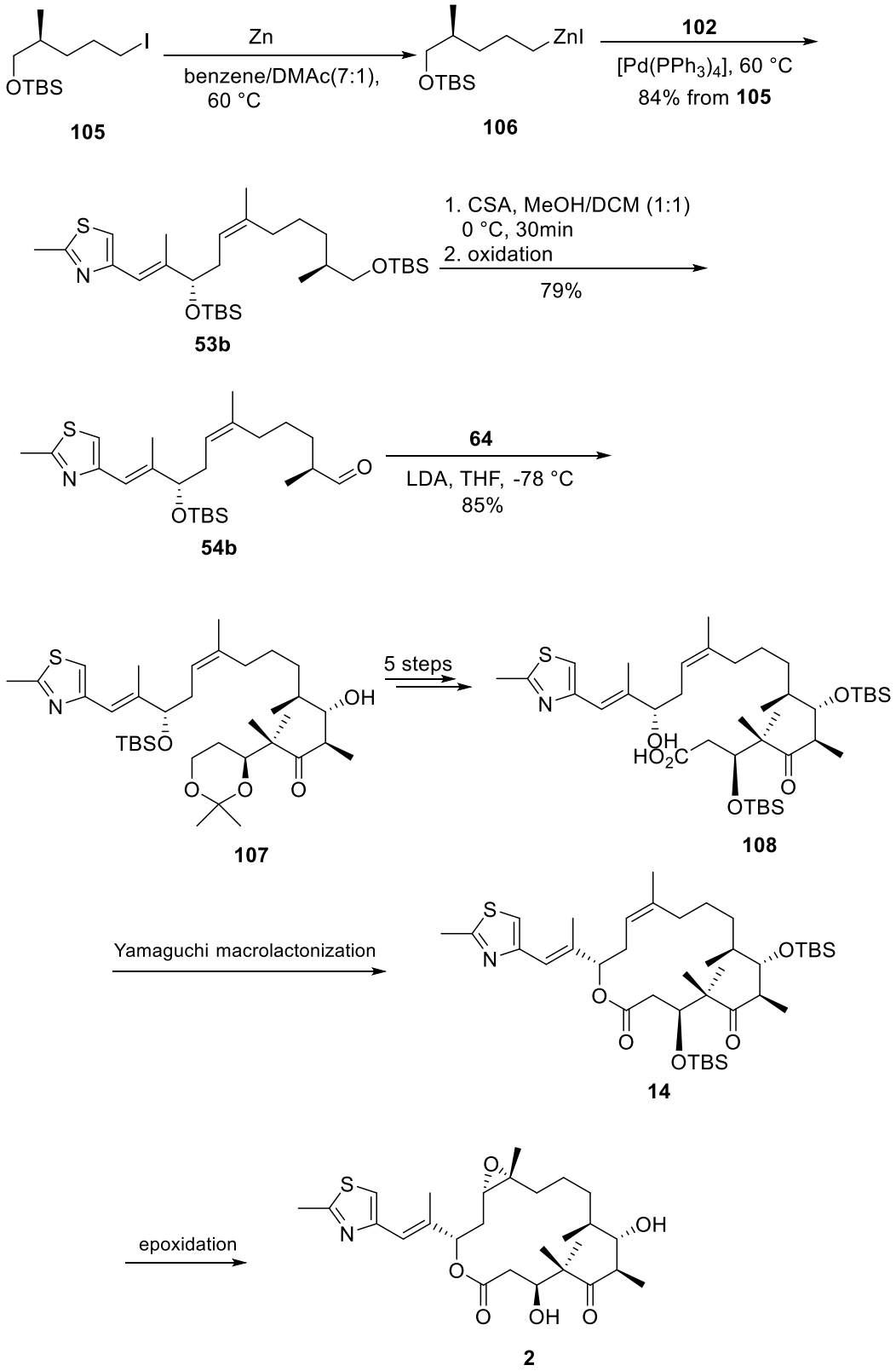
On the other hand, the Evans auxiliary as a stereogenic unit can help to control the stereochemical outcome of the methylation at carbon center C8, followed by the decomposition of the oxazolidinone and protection of the alcohol with TBSCl. The hydroboration/iodination reaction was the last step in the process of obtaining the alkyl iodide **105**. (Shown in Scheme 24).



Scheme 24: Synthesis of the iodide 105 from Schinzer.

The zinc regent of **106** was prepared and an effective palladium-mediated coupling method was chosen for the synthesis of the bis-silyl ether **53b**. Then, CSA in MeOH/DCM was used to achieve selective deprotection of the primary alcohol. Followed by oxidation of the primary alcohol, aldehyde **54b** was produced and used in the aldol process. Ketone **64** was treated with LDA to obtain the desired enolate and then addition of 0.5 equivalents of aldehyde **54b**, provided product **107** in 85% yield, and a ratio of anti-Cram to Cram was determined as 9:1 by HPLC. Adjustment of the protecting groups through cleavage of the ketal group and protection of all hydroxy groups via silylation, followed by further oxidation state modifications, yielded acid

108. This compound served as the precursor for the Yamaguchi macrolactonization, which produced compound **14**. Final epoxidation and deprotection of this intermediate yielded compound **2**.

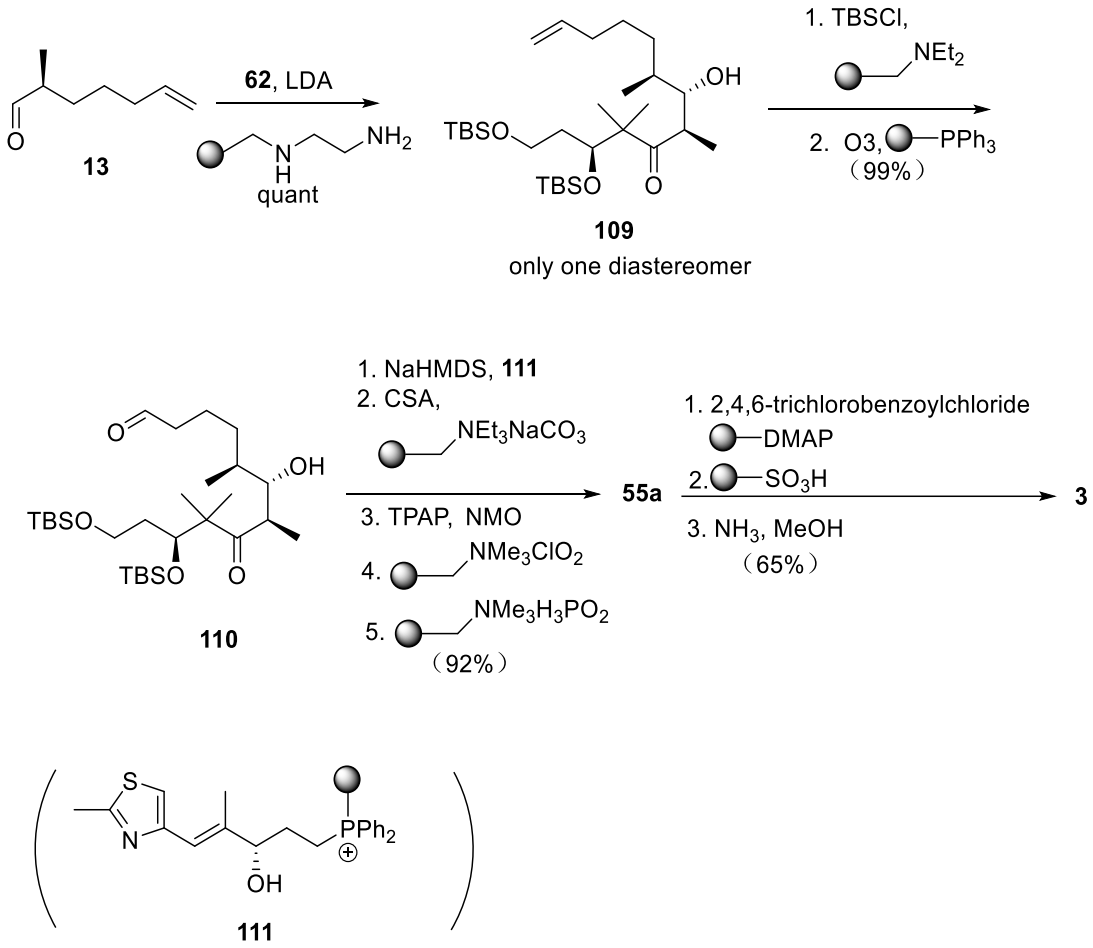


Scheme 25: Total synthesis of 2 from Schinzer.

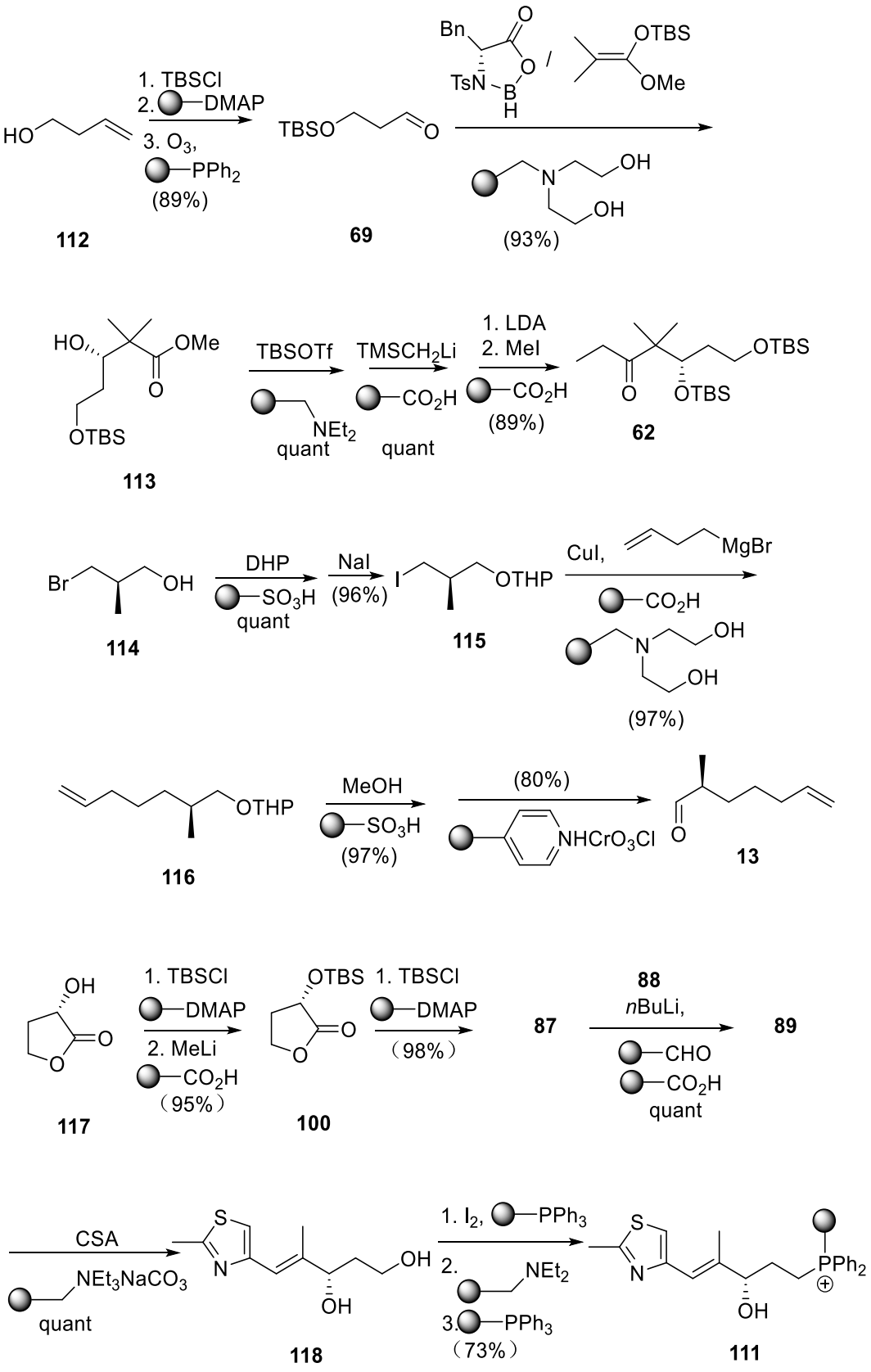
1.3.2.4 Ley's synthetic methods

With the development of the solid-phase synthesis, it could be used to produce with high efficiency and high yield. In 1997, Nicolaou and his colleagues were the first to synthesize epothilone A using this method.[46] Later, the Ley group[47] used immobilized reagents and scavengers to reduce the work up and purification process to obtain epothilone as well as improving large-scale preparations of complex natural products.

Scheme 26 shows the philosophy applied in an approach to synthesize **3**. The key reaction is an aldol addition in which ketone **62** reacted with aldehyde **13** to form **109**, which obtained just one diastereomer with the desired configuration. The (*Z*)-selective Wittig reaction of aldehyde **110** and the ylide generated from the immobilized phosphonium salts **111** formed **55a**. As one can see, the aldol reaction between **62** and **13** and the Wittig reaction between **110** and **111** were achieved near quantitative. Then the synthesis of **3** passed 3 steps and the total yield is over 65% from **13**. This method was also employed for the synthesis of different segments. Scheme 27 describes the detailed process. After several steps, they produced **62** with 74% yield from **112** over 7 steps. On other side, aldehyde **13** was obtained from **114** achieving 90% yield through 5 steps. The Wittig salts **111** was prepared from **117** and passed 8 steps giving 68% yield. The essential acids, bases, and di-phenyl phosphine, which were traditionally employed for catalyzing reactions, mediating the degradation of intermediates, and aiding in the isolation of reaction products, have been innovatively immobilized onto a solid support in a groundbreaking development introduced by Ley. This immobilization represents a significant advancement in the field without necessitating aqueous workup, filtration, or chromatography, rendering the process essentially quantitative across various stages.[48]



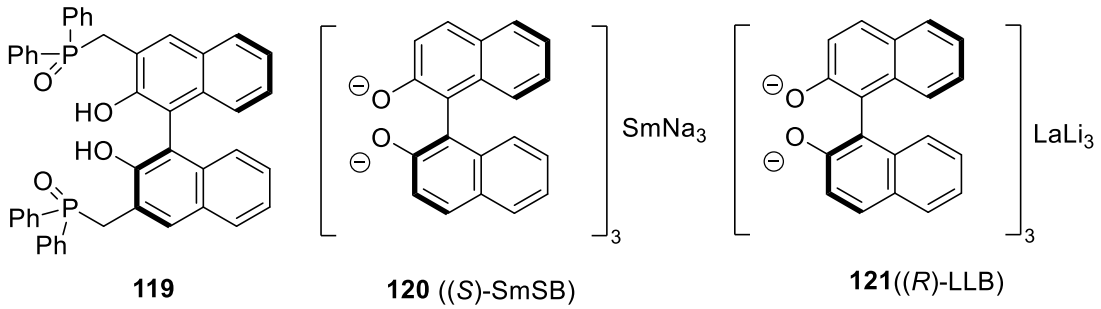
Scheme 26: Synthesis of 3 using solid-phase synthesis method from Ley.



Scheme 27: Synthesis of segments using solid-phase synthesis method from Ley.

1.3.2.5 Shibasaki's synthetic methods

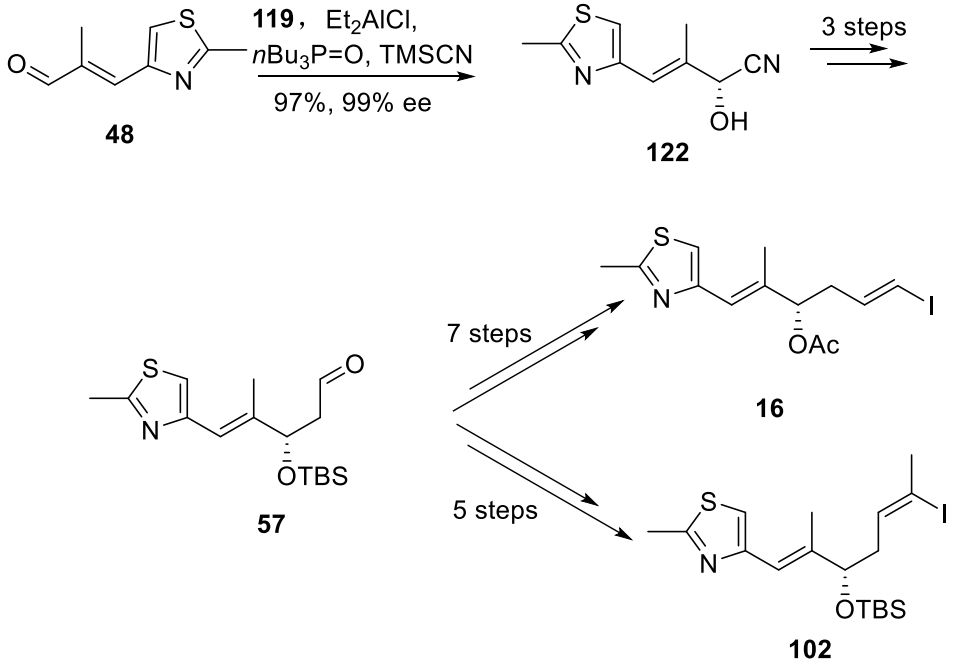
Distinct from other research areas, Shibasaki's group contributed to the development of a variety of chiral multifunctional catalysts (e.g. **119-121**, Figure 4). [49]



119 **120** ((*S*)-SmSB) **121**((*R*)-LLB)

Figure 3: Shibasaki's catalysts

The catalyst **119** helped to control the chiral center at C15 with a high yield and high selectivity from **48** to **122**, which could be the intermediate to produce the vinyl iodide.[50] The preparation of the vinyl iodide **16** was identical to Danishefsky's method, and **102** was also used by Schinzer for the synthesis of epothilone B.

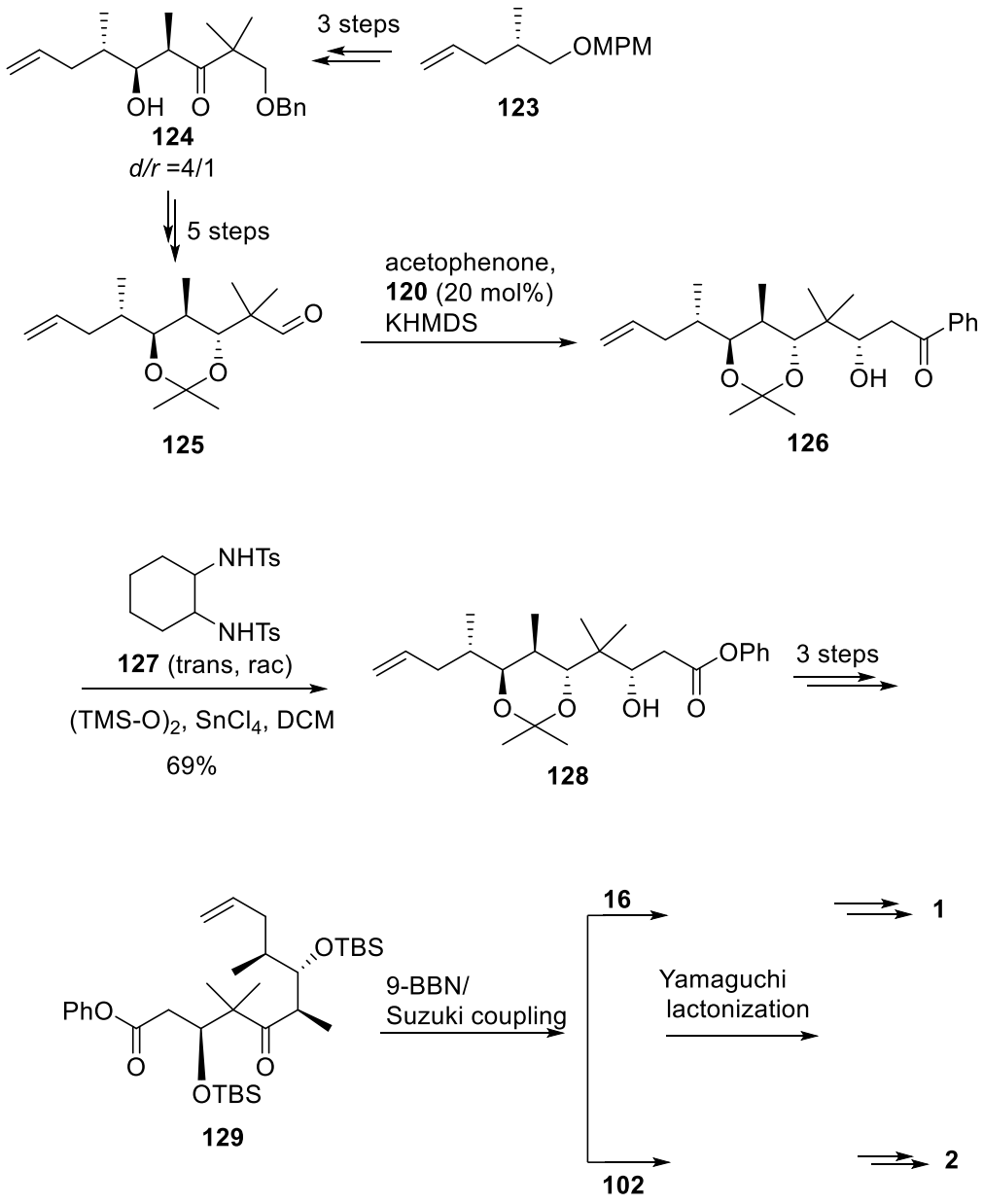


48 **122** **16** **57** **102**

Scheme 28: **Synthesis of thiazole segments using catalyst 118 from Shibasaki**

To complete the total synthesis of epothilones, the other key intermediate **129** was prepared, which was coupled with **16** or **102** via B-alkyl Suzuki reaction. The ring was then closed through Yamaguchi esterification to obtain the total molecule following the Danishefsky/Schinzer precedence. The synthesis of **129** started with **123**, followed by chain elongation of olefin to generated **124**. Compound **124** was converted to aldehyde **125** through 5 steps. The aldehyde **125** then reacted with acetophenone in the presence

of a 20 mol% catalyst of **120** in an aldol reaction, yielding phenyl ketone **126**. This was sunsequently converted to phenyl ester **128** via a novel Baeyer-Villiger oxidation, catalyzed by diamide **127**. After three additional steps, ketone **129** was generated, which acted as the coupling partner for **16** and **102**, leading to the formation of the **1**-precursor and **2**-precursor.

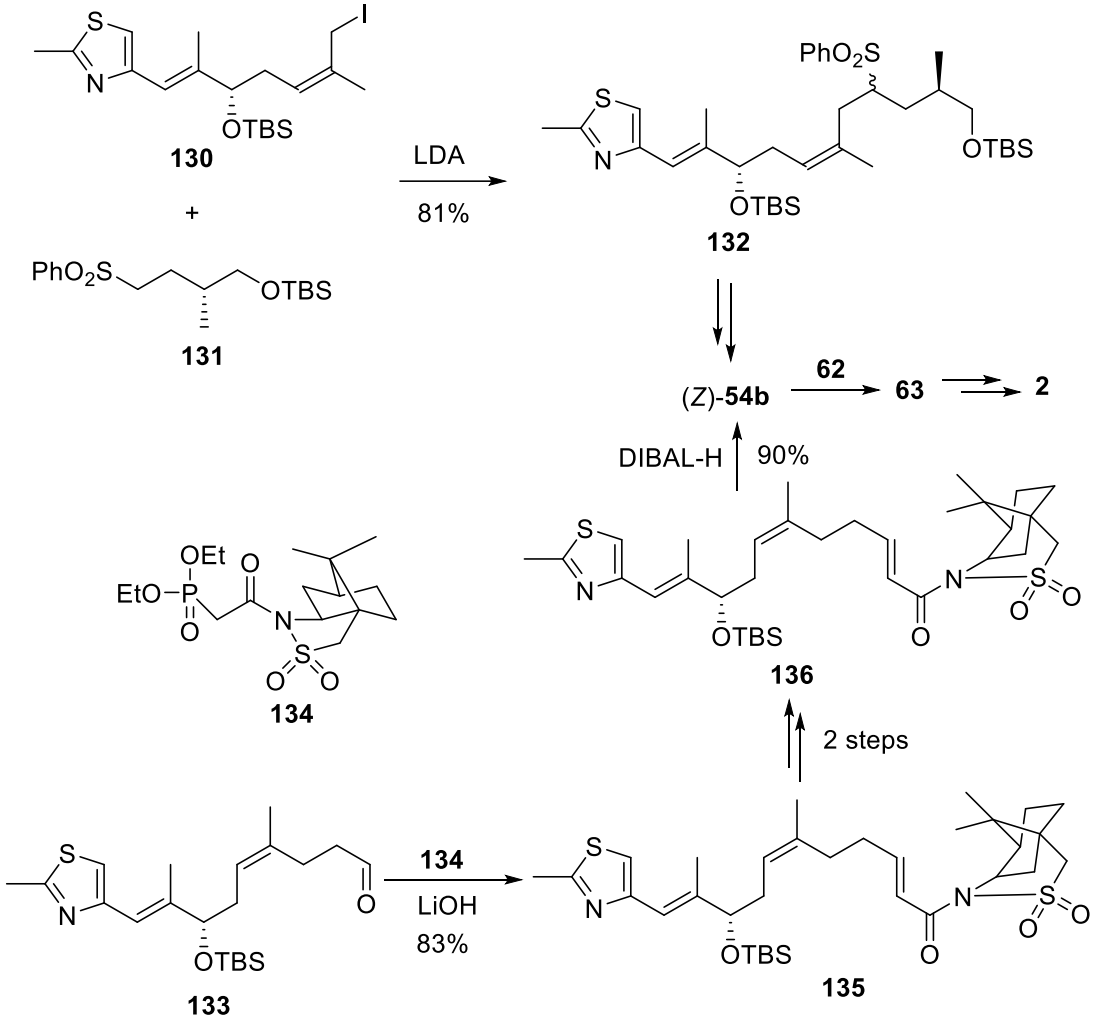


Scheme 29: Synthesis of 1/2 using catalyst 120 from Shibasaki

1.3.2.6 Mulzer's synthetic methods

Mulzer's group [51] has developed two more accessible routes to synthesize compound (*Z*)-**54b**, which has subsequently been employed by Nicolaou in an aldol addition to yield the intermediate **63** derivate of **2**. The first method, alkylation of compound **131** with iodide **130** produced sulfone **132**, which underwent desulfonylation and was

subsequently converted into (*Z*)-**54b**.[52] The stereogenic centers at C15 and C8 have been derived from the chiral carbon pool. In alternative approach, aldehyde **133** was olefinated with *Oppolzer*'s sultam **134** to give **135**. Subsequent transformations of enamid **135** involved hydride addition and diastereoselective methylation, leading to **136**. After removed of the auxiliary, (*Z*)-**54b** was obtained.[53]

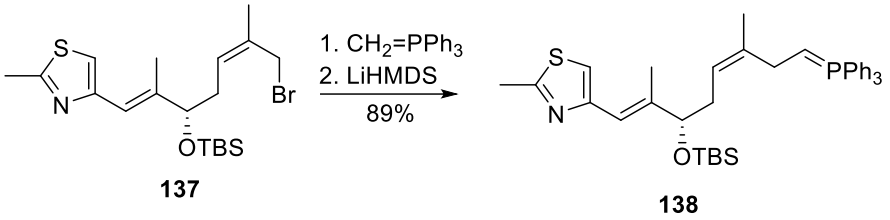


Scheme 30: Two strategies of synthesizing 2 from Mulzer

1.3.2.7 White's synthetic methods

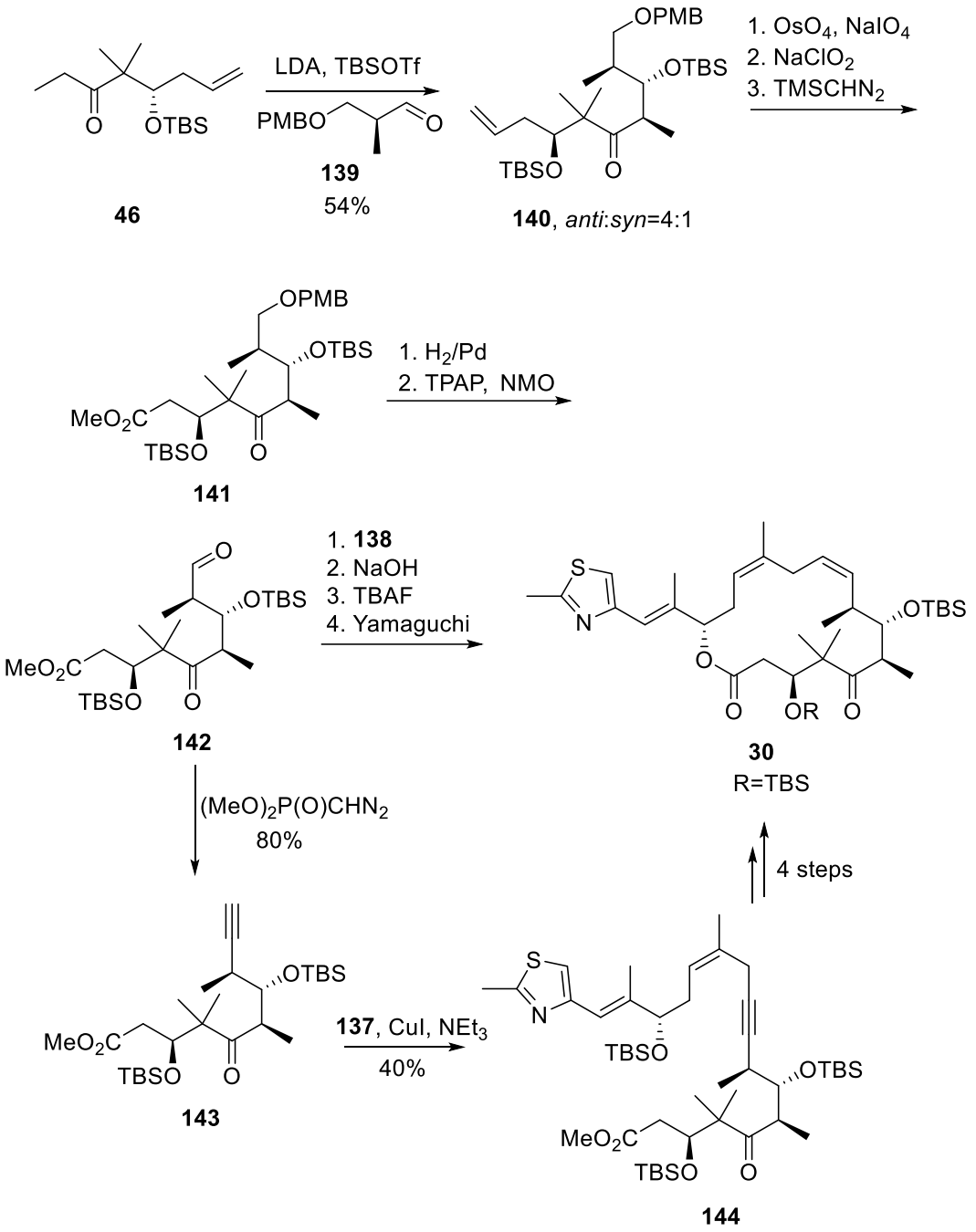
New discoveries were made by White's group [54] in relation to the formation of the (*Z*)-9,10-olefin moiety as well as the Wittig-olefination of phosphorane **138** and aldehyde **142** in the present of base. The chain elongation reaction using an ylide resulted in the formation of the C10 phosphorane **138** from bromide **137**. An aldol addition of ketone **46** and aldehyde **139** shown in Scheme 32 generated **140** with a ratio of *anti*:*syn*=4:1, first reported by Mulzer.[55] Oxidation of the double bond in the precursor compound **140** led to the formation of the carboxylic ester **141**. Subsequent formation of the aldehyde at C9 produced compound **142**, which reacted with **138** to generate the (*Z*)-9,10-olefin. This olefin intermediate subsequently underwent a series of reactions to afford **30**. In a different route also shown in Scheme 32, bromide **137** was used to react

with the alkyne **143** by Sonogashira reaction, which could be obtained quickly and easily from aldehyde **142** by using the Gilbert-Seyferth reagent.[56] With the help of the Lindlar catalyst, the resluting alkyne **144** was hydrogenated to produce the (*Z*)-9,10-olefin. This was then elaborated into **30** with additional 3 steps.



137 **138**

Scheme 31: White's partial synthesis of thiazole segment.



Scheme 32: White's synthesis of 144.

In addition to those described above, many other research groups have successfully synthesized epothilone A and B.

Sinha's group[57] synthesized **1** using his catalyst, AB 38C2, followed both Nicolaou's RCM and Danishefsky's macrolactonization approach. Similar, Panek[58]and Liu *et al*.[59] also followed the macrolactonization strategy to the synthesis of **1**. An alkyne ring-closing metathesis (RCM) strategy were used to synthesize a macrolide intermediate, which was subsequently converted exclusively into the (*Z*)-olefin through Lindlar hydrogenation.

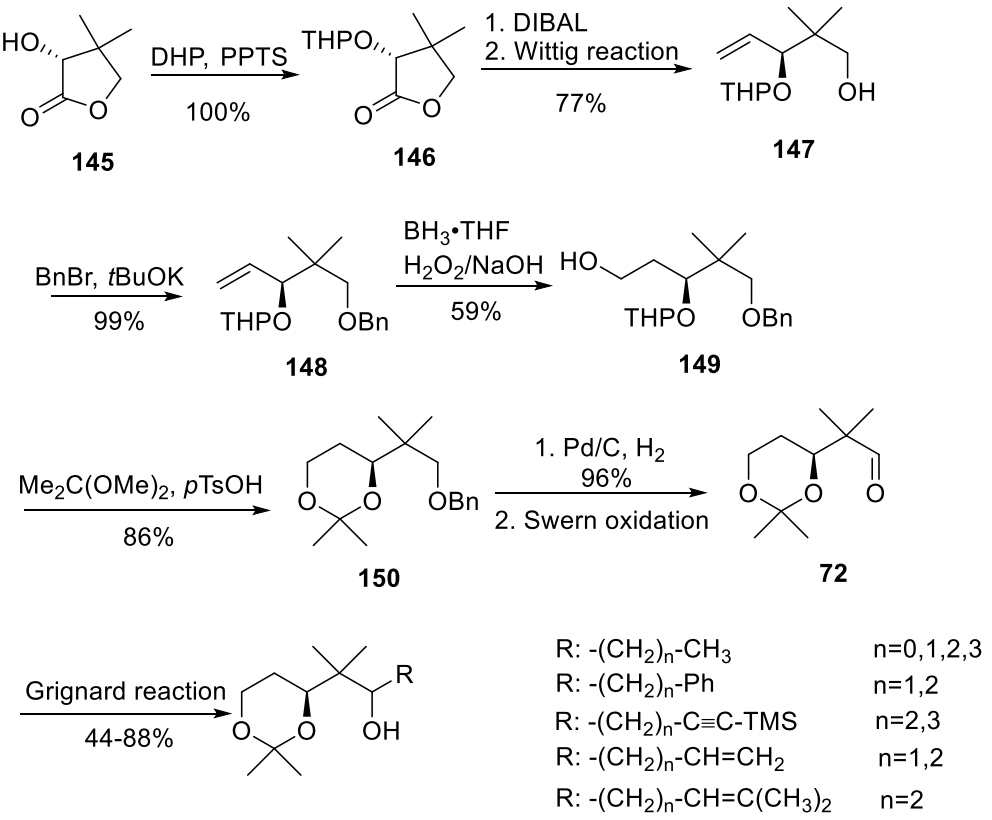
To facilitate the synthesis of epothilone B, numerous scientists have made significant contributions. Grieco's *et al*.[60] approach involves olefin metathesis to synthesize **2**. Carreira's group[61] developed a highly innovative nitile-oxide-olefin cycloaddtion to establish the C12-C15 section which applied to the synthesis of **2** based on Mulzer's methods. Based on White's methods, Ermolenko's *et al*.[62] improved the synthesis of each segment to give White's intermediates and obtained finally epothilone B. Thomas'[63], Taylor's[64] and Avery's[65] approach provide a novel stereoselective approach to (*Z*)-12,13-double bond.

Apart from the synthesis of epothilone A and B, many research groups are dedicated to synthesizing some fragments, or epothilone derivates. They obtained important intermediates or catalysts that are not only applicable to the synthesis of epothilone analogies but also to the synthesis of other complex natural products.

1.3.3 Total Synthesis of the Fully Synthetic Epothilone ZK-EPO

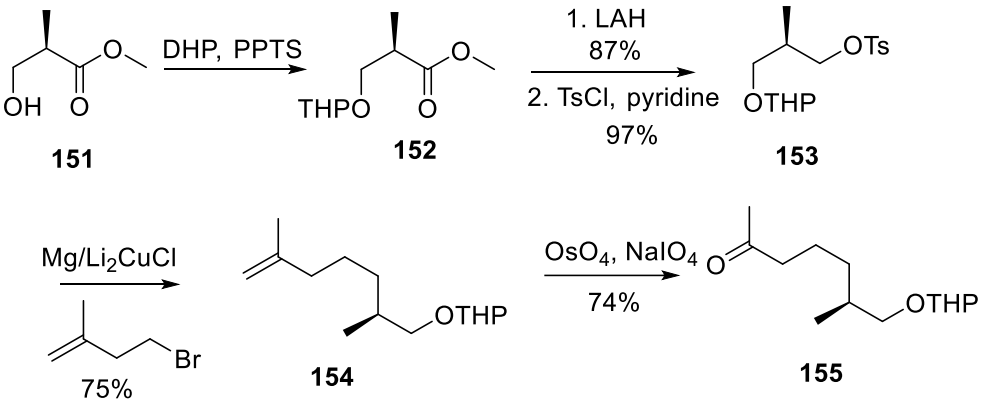
Actually, our target molecule is similar to the fully synthetic epothilone ZK-EPO **5** from the Schering company. It has been developed for large-scale production as part of their contribution to a new anti-cancer drug and has demonstrated highly promising biological data in phase II of various clinical trials.

Especially for ketone **64**, they had published an easy and efficient method that can be used for all of its derivates.[66] Instead of propanediol, the starting material is *D*-(-)-pantolactone **145**, which not only contained the carbon chain from C2 to C5 but also includes the geminal dimethyl group at C4 and the chiral center at C3. This provides more convenience to give fragment **64**, reducing a significant number of labor efforts. First, the starting material was treated with DHP and PPTS, then the lactone **146** was reducted by DIBAL-*H* at -78 °C resulting in conjugated alcohol, which would react with 2 eq. triphenyl phosphonium ylide by Wittig reaction to obtain olefin **147**. Hydroboration-oxidation of the double bond provided **149** followed by protection of the primary alcohol in **148**, then deprotection of hydroxyl group at C3 and protection of the resulting diol as ketal, the stable key intermediate **150** was obtained. Removal of the benzyl group, alcohol was oxidated to aldehyde **72** as the starting material for the Grignard reaction. The introduction of different substituents at carbon 5 is achieved by subsequent Grignard reaction or the addition of the corresponding alkyl-lithium compounds followed by an oxidation of the resulting epimeric alcohols to yield ketones shown in Scheme 33.



Scheme 33: Synthesis of the segment ketone from Schering AG.

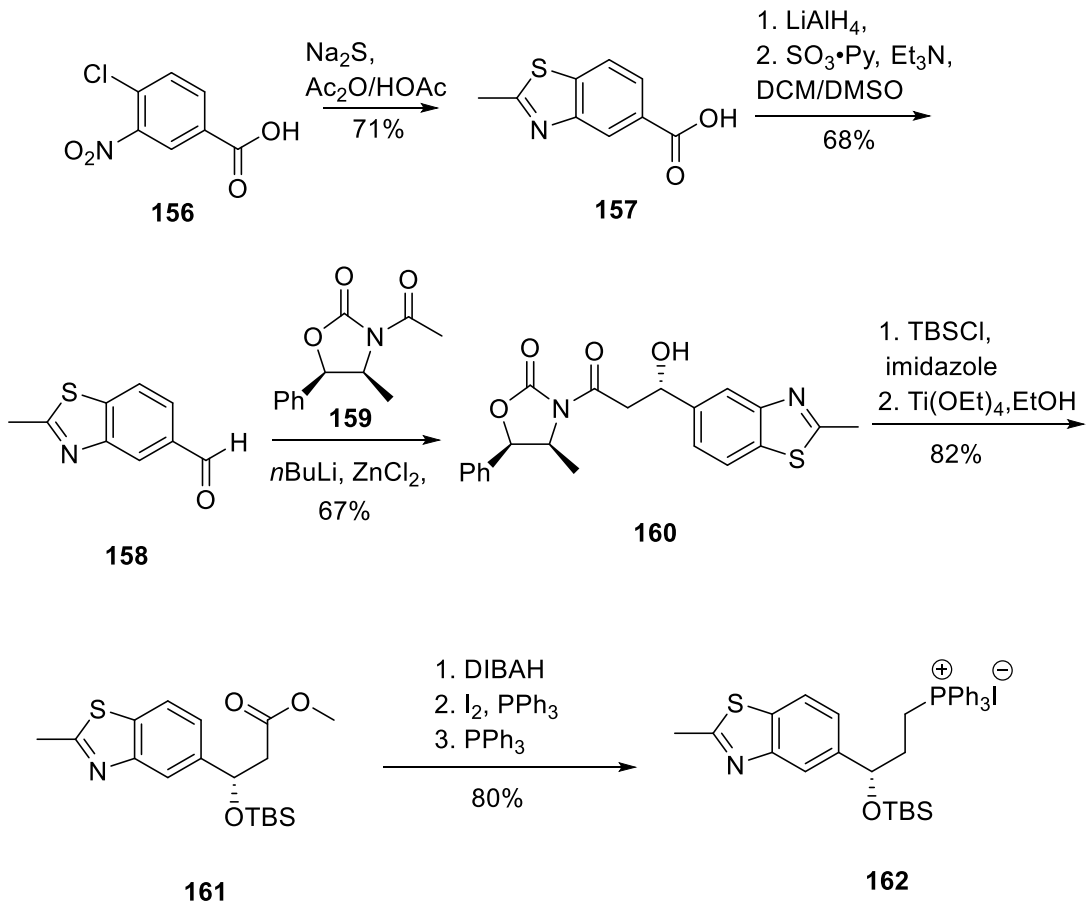
The segment **155** can be built from Roche ester **151** which contains carbons C7-C9 and the chiral center at C8.[67] The primary alcohol was protected with DHP again, then ester **152** was reducted by $LiAlH_4$ and the resulting alcohol was derivatized with TsCl to give tosylate **153**. Then the extension of the carbon chain to C12 was achieved in the presence of 2-methyl-1-butenyl-4-magnesium bromide and a catalytic quantity of Mg/Li_2CuCl_4 via an alkylation. This was followed by oxidation of the double bond leading to the segment ketone **154**.



Scheme 34: Synthesis of the segment 154 from Schering AG.

The synthesis of the thiazole segment began with benzoic acid **156**, by reaction with Na_2S, acetic acid and its anhydride. After aldehyde **158** has been synthesized through a reduction-oxidation sequence, it can be subjected to an Evans aldol addition to form the

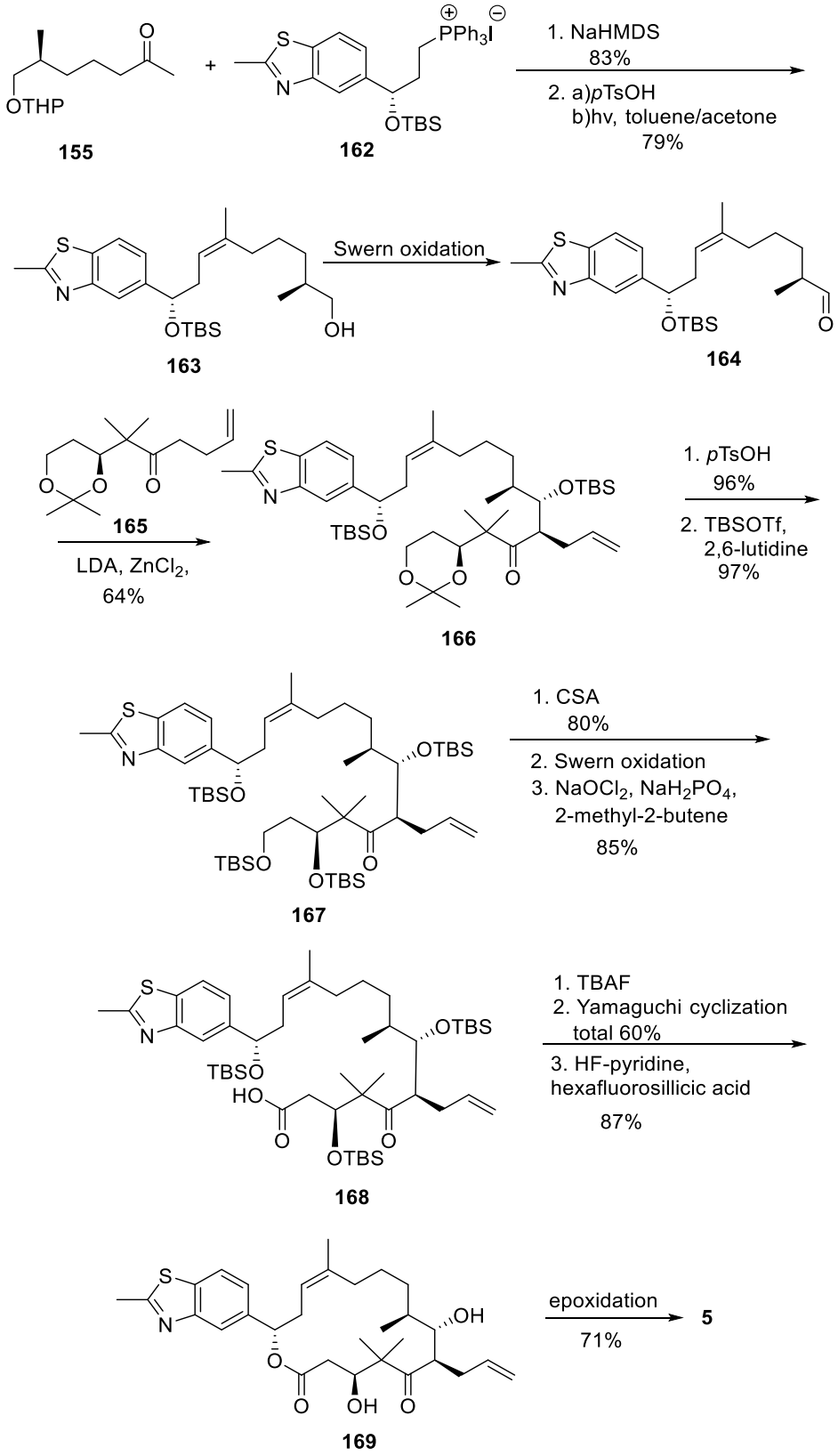
stereogenic centre at C15, and the diastereoisomers can be separated through crystallization. Then, the chiral auxiliary was removed by transesterification after the secondary alcohol had been protected. This was followed by reduction to the corresponding alcohol and subsequent iodination, leading to the phosphonium salt **162**. In total, the yield was 16%.[68]



Scheme 35: Synthesis of thiazole segment from Schering AG.

Wittig reaction between thiazole segment **162** and ketone **155** afforded roughly a 1:1 ratio of *E/Z* isomers of **163**. It is important to note that chromatography can be employed to separate the isomers after the removal of the tetrahydropyranyl ether, yielding pure (*Z*)-**163** and (*E*)-**163**. The (*E*)-**163** can then be irradiated with light of a wavelength greater than 280 nm, resulting in a 6:4 mixture of *E/Z*-**163**, which had to separated again providing a total yield exceeding 43%. Subsequently, Swern oxidation was applied on compound **163**, resulting in aldehyde **164** with an overall yield of 36% originating from compound **162**. An aldol reaction took place directly between **164** and ketone **165** to obtain **166** with high diastereoselectivity (*anti*:*syn*=20:1). And the minor 6,7 diastereoisomer can be separated by chromatography. Release of the diol group followed by persilylation generated tetrasilyl ether **167**. At slightly acidic conditions, the primary silyl ethers are removed, and then carboxylic acid **168** is formed by a two-step oxidation sequence. Thereafter, the protecting group is removed and Yamaguchi

cyclization conditions are applied to the hydroxy acid to produce the 16-membered macrolactone. The addition of hexafluorosilicic acid significantly enhances the cleavage of both silyl ethers to give **169**, improving the yield and reducing the reaction's sensitivity to variations in the quality of different batches of HF•pyridine. High stereoselectivity and a 12% overall yield are obtained by epoxidizing the double bond, resulting in the fully synthetic epothilone **5**.



Scheme 36: Total synthesis of ZK-EPO 5 from Schering AG.

1.4 Structural-Activity Relationships

After more and more epothilones are synthesized or isolated, the vast amount of data on the structural-activity relationships was published. According to this including tubulin polymerization data, Figure 4[23] summarizes the conclusion of this investigation.

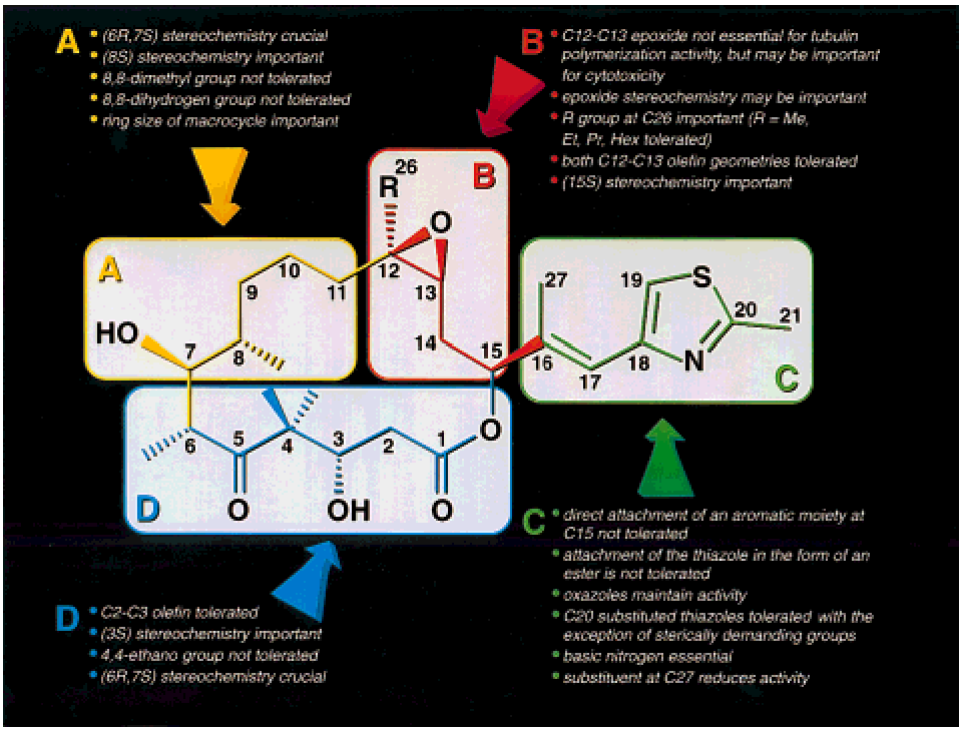


Figure 4: Structure-activity relationship of the epothilones.

Generally, the molecule was divided into four regions. The first region A, which includes carbon C7-C11, contains two chiral centers and one hydroxy group. From the analysis, it is necessary to keep the methyl group at the C8. It retains the bioactivity against leukemia cell lines compared with **1**.[23] Likewise, it is also proved that the (*S*) stereochemistry at C8 increased the ability to induce tubulin polymerization *in vitro*.[69] The carbon chain between C9 and C11 suggests that ring contraction or expansion, through the removal of an existing group or the incorporation of an additional CH_2-group, results in a substantial loss of biological potency.[70]

The region D, contains two chiral centers and one geometry center. Similar to C8, the stereochemistry at C6 and C7 is necessary to keep tubulin induction potential.[69] Interestingly, it should be noticed that the methyl group at C6 can be transferred to other alkyl substituents, even larger groups since the Schering company prepared a series of patents with the biological data.[71] However, the C7-hydroxy group plays a critical role in determining the activity of epothilones, similar to the oxetane oxygen in paclitaxel. It forms a hydrogen bond with specific regions, contributing to the biological activity..[72] Meanwhile, modifications at C3, such as removing the hydrogen group or

altering the conformation of the C2-C3 bond, affect the analogues' stability in an aqueous solution..[73] In addition, the C6-C8 bridged epothilones were evaluated for their biological activity against the human ovarian cancer and prostate cancer cell lines, which also can be effected on the tubulin assembly.[71a] On the other hand, the gemi-dimethyl group at C4 is not necessary but also depends on the change of functional group. Nicolaou's group attempted to convert the dimethyl group to a 3-membered ring resulting in lacking of any tubulin polymerization and antiproliferative activity.[69] The patent from Schering also includes related structures that feature 4-, 5-, and 6-membered rings at C4. The results indicate that these compounds lack biological activity until the ring is replaced by a methyl group. This derivative, in which the methyl group at C4 was replaced, exhibited growth inhibitory activity against the mouse fibroblast cell line L929, similar to that of **1**.[74]

For the region B, several articles have reported modifications to the epothilone macrocyclic framework at the C12-C13 carbon positions. A comparison of compounds 1 and 2 reveals that the presence of a methyl group at C12 enhances bioactivity. Consequently, the role of the C12 substituent has been studied extensively. Substituents larger than a methyl group, such as ethyl, propyl, acetal, cyclohexyl, and cyclopropyl groups, have been tolerated when modified at the C12 position.[70]

Currently, deoxyepothilones with an alkyl group attached to carbon C13, rather than C12, have become more prevalent. According to Sinha's results, when an ethyl group is attached to C13, a slight increase in activity is observed.[75] Meanwhile, the geometry of the C12/C13 double bond in the (*Z*)-configuration is crucial for their biological potential. The (*Z*)-configuration is essential for maintaining the correct three-dimensional conformation of the molecule, which is necessary for its interaction with tubulin and its ability to inhibit cell division. The oxirane ring system serves a crucial role in stabilizing the bioactive three-dimensional conformation of the macrocyclic skeleton, ensuring effective interaction with biological targets. This role is distinct from traditional chemical functions such as serving as a reactive electrophile or a hydrogen bond acceptor.[72] Additionally, when compared to a series of epothilone derivatives developed through Nicolaou's research, the presence of the oxirane ring in these compounds appears to sustain or enhance their biological activity.

Modifications of the heterocyclic side chain are a key aspect of epothilone research, as such modifications may enable the modulation of the physicochemical properties and potentially the pharmacokinetic profiles of these natural products.[72] For the region C, the side chain attached to carbon C15, particularly when featuring a heterocyclic group, is crucial for sustaining biological activity. This heterocycle is critical for promoting microtubule polymerization, a necessary mechanism for the compound's anticancer effects. It should be noticed that the aromatic side chain (such as the thiazole or other heterocyclic moieties at C15) through van der Waals contributes to tubulin binding

interactions with proteins rather than hydrogen bonding involving the heteroaromatic nitrogen atom.[73] Next, it could be confirmed that the nitrogen in the heterocyclic ring is optimally placed in the *ortho*-position to the attachment point of the linker between the heterocycle and the macrocyclic skeleton, as the exchange of the positions of the sulfur and nitrogen atoms would lead to a profound loss in biological activity.[76] But the sulfur could be exchanged to oxygen.[77] Nicolaou and Scarpeli [78] designed a series of pyridines which was considered to replace the original heterocycle. This report established a similar biological activity system and the methyl group substituents attached to pyridine also influenced on the tubulin polymerization. In summary, the nitrogen atom should be located at the *ortho*-position, and the methyl substituent should be located at the 4-position (*para* to the nitrogen), or 5-position (*meta* to the nitrogen) of the pyridine ring.[23, 78-79] Meanwhile, they also compared several different 12,13-cyclopropane analogies with 15*R* or 15*S* stereochemistry and proved that the stereochemistry at C15 is associated with biological activity.[23] Other epothilone analogies with alternative substituents such as bulkier alkyl or aryl substrates at *ortho*-position of the thiazole moiety performed a similar activity. The allylic methyl group attached to C16 can be removed with only a minor change in biological activity.[72] On the other side, the methyl group on carbon C16 can be exchanged to heterocycles instead of bulky groups.[27]

Modifications of the lactone is another trend. The replacement of the lactone oxygen by nitrogen has emerged as one of the most important strategies in epothilone-based anticancer drug discovery, which has led to the development of ixabepilone **6** [80], the lactam analog of **2**. Based on metabolically more stable, it also attached a lot of attention and developed a series of analogues.

Several structural alterations to the epothilone framework, and their combination equivalents, have been studied extensively. Total synthesis has often been used to create these molecules, because in comparison to other approaches, it is a flexible approach that allows broader access to structurally diverse analogs. The research that was done to find analogs of epothilone, together with the *in vitro* biological activity that was effective, gives preclinical biological features of the more promising members of this drug, which led to subsequent drug discovery attempts to find enhanced drug analogs.

1.5 Clinical Studies with Epothilone

In the mentioned, several natural semi- and fully synthetic epothilones have been entered the clinical trial development as anticancer chemotherapic agents.

The manufacturer of ixabepilone, which is a semi-synthetic second-generation analog of the natural product EpoB and now as the most widely clinically developed agent of this class, has sponsored several Phases I–III clinical studies, in which more than 3500

patients have been treated for various tumor types.[81] It was developed by Bristol-Myers Squibb (BMS, New York, NY, USA), marketed in the United States under the name Ixempra®, and approved by the Food and Drug Administration (FDA) in the United States in 2007 for the treatment of metastatic or advanced breast cancer, either as a single agent or together with capecitabine for the treatment of patients with metastatic or locally advanced breast cancers that show resistance to treatment with anthracyclines and taxanes.[82] Founding in early data, Ixabepilone can work on various cancer cells, including colorectal cancer, ovarian carcinoma, breast, as well as to sensitive human pancreatic carcinoma and murine fibrosarcoma. In Phase II studies, ixabepilone was effective against hormone-refractory prostate cancer [83], non-small cell lung cancer [84], renal [85] and pancreatic carcinomas [86]. It should be noted that the effects of these compounds are minimal in the context of gynecological cancers.[87] At present, the combination of ixabepilone with capecitabine has shown the superior efficacy in treatment with triple-negative breast cancer.

Among them, the most attractive to our attention is **5**, Sagopilone, which has demonstrated high activity in human tumor xenograft models of breast, ovarian, prostate, cervical and pancreatic cancer, non-small cell and small-cell lung cancer, glioma and melanoma. In Phase II clinical trials, Sagopilone has shown that is effective with balanced tolerability in patients with recurrent ovarian cancer resistance.[88] But patients with progressive brain metastases from breast cancer[89] or glioblastoma[90] have limited treatment options. A fact is that sagopilone has a good hematological toxicity profile in heavily pre-treated patients with glioblastoma as it could be used with other chemotherapy drugs.[91]

Utidelone, deoxyepothilone B or epothilone D, is a product of Biostar Technologies, Ltd., based in Beijing, China. In both *in vitro* and in vivo testing, UTD1 has shown significant effectiveness against paclitaxel-sensitive cancers. These tumors include multidrug-resistant human colon, leukemia, and breast malignancies. In phase II clinical investigations, the therapy of metastatic breast cancer showed good efficacy and safety, particularly in breast cancer that had been treated with anthracyclines and taxanes in the past. [92] Results of a Phase III trial suggested the use of UTD1 plus capectitabine as a novel therapeutic regimen.[93] In addition, this treatment is not commonly accepted.

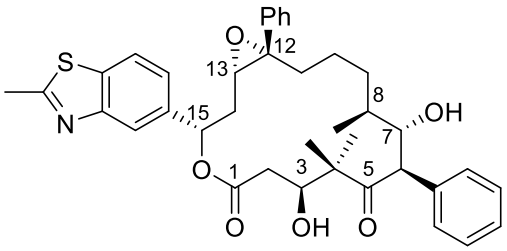
The issues of safety and toxicity provide the biggest challenge for the development of anti-cancer therapeutics. For instance, **6, 4**, or **5** have high occurrences of myelosuppression, alopecia, peripheral neuropathy, hypersensitivity responses, as well as diarrhea and weariness.[81] For example, in Phase I trials of ixabepilone, the most often used epothilone, peripheral neuropathy and fatigue were the most frequently observed adverse effects across all proposed regimens. In Phase II, patients with pretreatment of metastatic breast cancer have been the most likely to develop serious side effects, including leukopenia, sensory peripheral neuropathy, and fatigue.[94]

Due to the development of multidrug resistance (MDR), the chemotherapy that is based on paclitaxel is ineffective in the treatment of several malignancies, including cancer of the prostate, lung, ovary, and breast.[82] This highlights the critical need for the discovery of new anticancer medications. Epothilones have the benefit of retaining their cytotoxic activity even in resistant cell lines that overexpress MDR pathways. They do this by inducing microtubule-stabilizing effects using a mechanism that is analogous to that of taxanes. Ixabepilone and UTD1 are currently being used in clinical trials in combination with traditional anticancer medications. This has the effect of enhancing cancer treatment and making patients' prognoses more favorable. And focusing on synthesis of epothilones and its derivatives, provides the mature synthetic strategies and is applied for large-scale production. Also with the fermentation procedures, the straightforward construction of epothilones has made it possible to produce hundreds of derivatives, some of which have an activity that are orders of magnitude higher than those of **2**, ixabepilone, or even paclitaxel. Because of this, the potential for several of these chemicals to treat cancer is very encouraging. However, additional clinical tests need to be carried out in order to guarantee both their safety and their efficacy.

2. Objectives of the Thesis

Based on compound **5**, a new derivate was designed that has more lipophilic groups at carbon C12 and C6 (see Scheme 37). From the analysis of the structure-activity relationships in chapter 1.4, the majority of C12 analogs synthesized were tolerated.[23] So, we envisioned a new analogue that has a phenyl group attached at C12 keeping the biological activity since potent inhibitors of human cancer cell growth *in vitro*, **3** and **4** are practically equipotent inducers of tubulin polymerization as **1** and **2**, respectively. However, a modest increase in activity occurs when the methyl group at position C13 is replaced with an ethyl group.[72] At the same time, we would employ a phenyl group attached and reserve the stereochemistry at C6, which is necessary to keep tubulin induction potential. All together the new derivate could increase the antitumor activity and decrease the toxicity providing more data for further analysis.

The new derivate **170**, which is a 16 membered macrolactone, also involves an epoxide, two hydroxy groups, 7 stereocenters, a geometrical center, as well as the heterocyclic benzothiazole ring. Since the fundamental structure is similar to **1** and **2**, a lot of known and established methodologies and strategies for sculpting the structural framework could be used. Considering the hydroxy groups, the cis epoxide, and the internal ester, these characteristics provide a wonderful approach for disconnection that could be applied for compositing the framework of the molecule. Though there are numerous possibilities to generate the macrocyclic system, the macrolactonization and aldol reaction have been verified quite effective to achieve this transformation, and then the olefin metathesis approaches can be used for ring-closing.

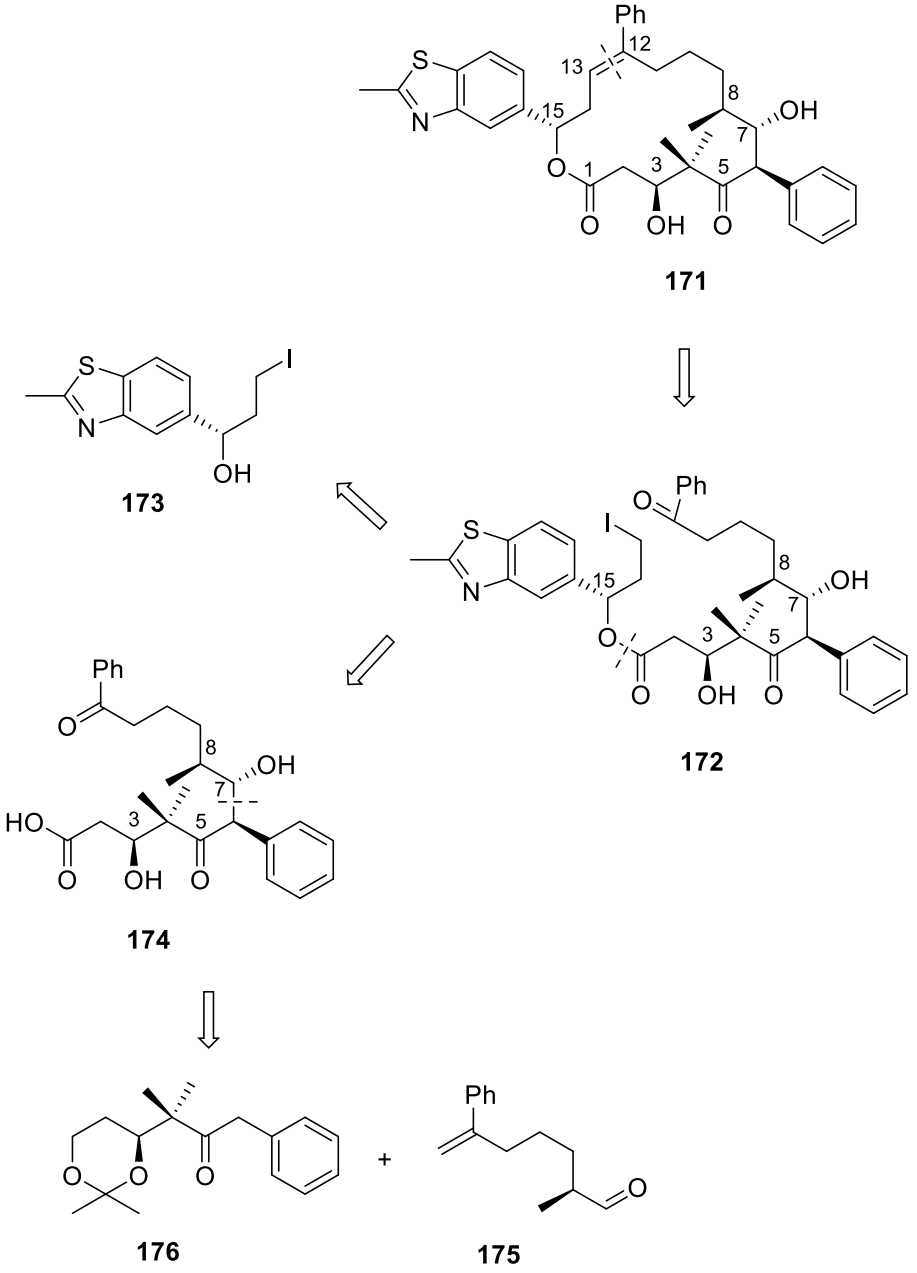


170

Scheme 37: The structure of the new derivate of epothilone.

3 Theoretical Parts

With the structure analysis, the synthetic plan shown in Scheme 38 devoted to the design of a flexible, effective, and eco-friendly method. Regarding the significance of the epothilone analog, we also aimed to search for a new routine that has the ability to easily deliver a new class of epothilones.

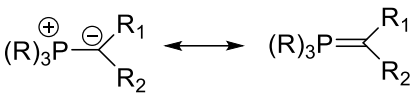


Scheme 38: Retrosynthetic analysis of derivate 5.

In generally, the epoxide could be achieved through an epoxidation reaction using olefin **171**. However, as an important member of the epothilone family, olefin **171** provides a new epothilone derivate with a different thiazole side chain. The incorporation of the

new side chain, benzothiazole, removes the linker between the macrocycle and the heterocycle, thereby increasing antiproliferative activity.[95] In addition, the presence of a phenyl group at carbon C13 serves as an additional lipophilic substituent. The primary challenge consequently involves not only the hindrance caused by the side chain but also the necessity to introduce the desired stereocenter at the side chain. Fortunately, extensive literature and patents provide a variety of potential solutions, with the goal of achieving a *Z*-olefin with high selectivity and chromatographic separation of isomers.

The Wittig reaction is an essential method for producing a favorable olefin. Firstly, the preparation of the ylide from the corresponding alkyl halide serves as the starting material. It should be noted that alkylidene phosphoranes can also be thought of as resonance-stabilized species, indicating that their reactivity is influenced by the substituents R_1 and R_2. The phenyl group, as an electron-withdrawing substituent, reduces the nucleophilicity of the phosphorane and stabilizes the negative charge, marking a significant difference between the two segments. Thus, we produced **172** to be used as the starting material for the Wittig reaction.



Next analysis at the juncture revealed that ester linkage excision and ester bond cleavage produced the corresponding seco-acid **174** and the thiazole segment **173**. This esterification reaction was efficiently carried out using a DCC/NMAP system.

The segment benzothiazole can be derived from a benzoic acid **156** as discussed in Section 1.3.3. For the carboxylic acid building block, the aldol reaction can be achieved in all *syn* fashion, leading to cleavage between carbons C6 and C7, thereby yielding the ketoacid **176** and aldehyde **175**. Additionally, another stereocenter at carbon C8 can be introduced using Evans auxiliary. This asymmetric aldol reaction achieves high diastereoselectivity by the steric hindrance of the chiral auxiliaries.

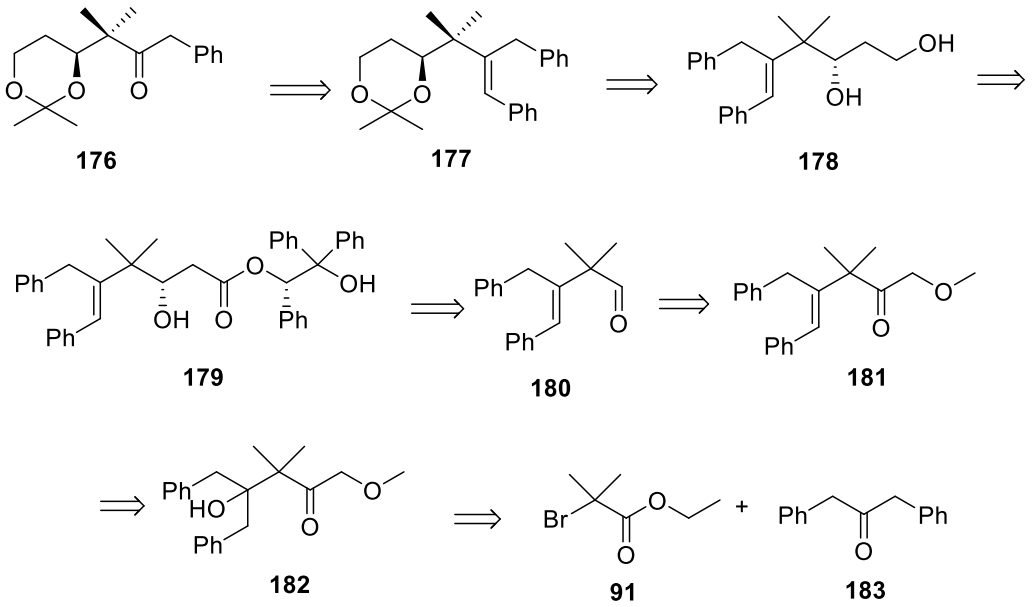
As a result, the total molecule can be divided into these three fragments. This Chapter described in detail the synthesis of each segment and the construction of the final macromolecule.

3.1 Synthesis of the Ketone Segment 176

3.1.1 Attempt synthesis of ketoacid **176** via the Schinzer route

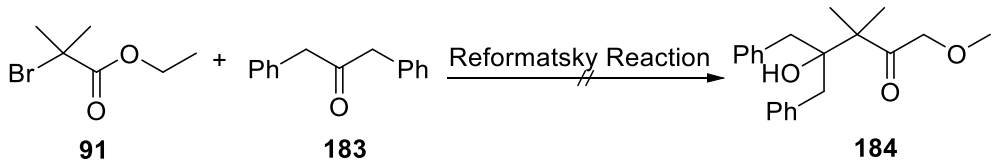
In previous works, the synthesis of the ketone segment followed the approach from Schinzer's strategy proposed in 1999.[45] The ketone **176** derivates from olefin **177** through a sequence of ozonolysis followed by ketal protection. The 1,3-diol **178** could be achieved from ester **179**, wherein the chiral center is synthesized by adding a dianion

to **180**. Here, the dianion was added to the aldehyde via an aldol reaction resulting in the ester with excellent diastereoselectivity and good yield. Subsequently, ester **181** undergoes a reduction reaction with 2 equivalents of LAH followed by Swern oxidation resulting in aldehyde **180**. Meanwhile, in ester **182**, an elimination reaction takes place with P_4O_{10} leading to the formation of **181**. Furthermore, the synthesis of *β*-hydroxyester **182** was planned to start with an α-carbonyl bromide **91** and ketone **183** via Reformatasky reaction.



Scheme 39: The retrosynthetic analysis of ketone segment 176 from Schinzer strategy.

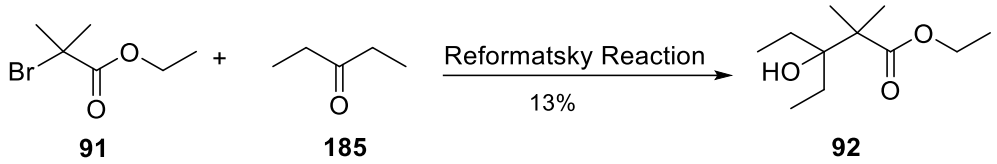
According to the Reformatsky reaction, the zinc metal as activated with 1,2-dibromoethane to afford the zinc enolate, which subsequently interacts with **183**. During this process, a six-membered chair conformation is expected to generate the chelated transition state. Initially, we started with 1.2 equivalents of **91** and 1.2 equivalents of zinc which was treated with $B(OMe)_3$ at 80 °C until the metal was fully consumed then1 equivalent of **183** was added. Even after prolonged reflux followed by work up, only ketone **183** was isolated. However, it indicates that no reaction took place.



Scheme 40: The Reformatsky reaction with 91 and 183

To verify the impact of substituents on the Reformatsky reaction, we replaced the ketone **183** with the simpler ketone **185** and repeated the reaction under unchanged conditions, as shown in Scheme 41. As a result, the Reformatsky reaction product **92** was obtained with a yield of 13%. In this reaction, our focus was primarily on

optimizing the reaction conditions and the zinc activation process. However, the quality of compound 185 was suboptimal, as it was not freshly prepared. As a result, the reaction yield was lower than expected.

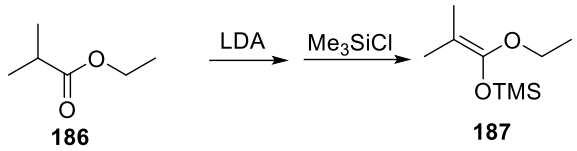


Scheme 41: The Reformatasky reaction for α-carbonyl bromide and ketone.

The meager yield in the initial stage is inadequate to fulfill the requirements of subsequent research. Therefore, further investigative studies are necessary to elucidate the underlying reasons and search for a new potential pathway. A critical issue was the activity of the zinc used. After using $B(OMe)_3$ to remove oxide layer on the metal's surface, 1,2-dibromoethane and diphenyl propanone were subsequently added, followed by the addition of compound **91** with heating to 80 °C. This resulted in significant bubbling and the consumption of solids, indicating that the metal had been successfully inserted into compound **91** to generate zinc enolate. However, after adding the other starting materials, **184** could not be detected even after several hours. We also attempted to use a zinc-copper solution or a zinc halides solution, but neither facilitated the reaction, indicating that the product must be formed through a different pathway. Even under various conditions and using different metals, such as Ti (II) chloride, active Mg, and Mn (II), the outcomes remained unchanged.

In addition to the reaction of the zinc enolates and ketone, another important factor is the formation of the six-membered transition state. Solvents like THF facilitate the formation of the chair structure in *tert*-butyl bromozincacetate. Smaller solvent molecules, such as ether, also increase the possibility of constructing six-membered rings by reducing steric hindrance in this chair structure. Furthermore, it has been demonstrated that more polar solvents, such as dimethyl formamide, significantly enhance activity. Thus, we attempted to use THF, DMF, or Et_2O as solvent. However, no product could be isolated, indicating that the choice of solvent did not influence the reaction's progress. Therefore, the main issue is considered to originate from the substrates.

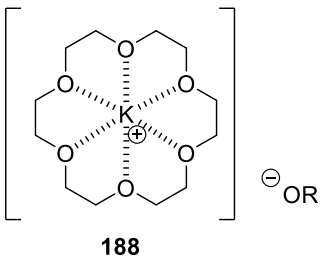
The carbon connected to bromo atom contains a dimethyl group, which may inhibit enolate formation. This hypothesis was validated by first treating ethyl isobutylate **186** with LDA at -78 °C for 30 minutes to produce the desired enolate. The enol silane was then synthesized after adding TMSCl to the mixture, resulting in **187**, which were separated chromatographically, yielding 60%.



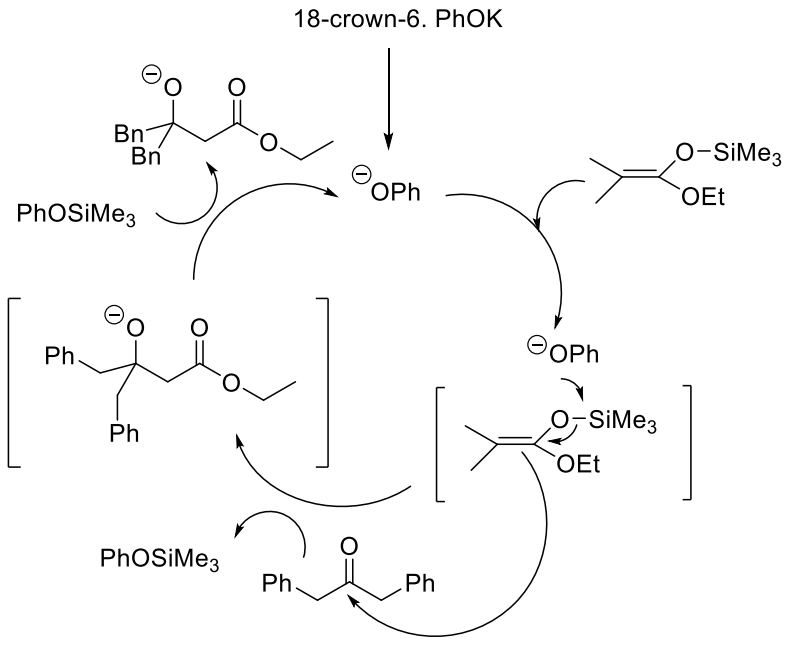
Scheme 42: The synthesis of enolates 187.

This finding demonstrates that enolates are expected to form the correct enolate and that the dimethyl group at the α-position exerts minimal influence. Subsequently, we considered the phenyl group, when attached to a system where resonance donation is not possible (e.g., as a substituent on a saturated carbon), its mesomeric effect may dominate.

Utilizing the trimethylsilyl enol ethers, a novel approach in the presence of potassium alkoxide-crown ether complexes as Lewis base catalyst can be applied to complete the Mukaiyama aldol reaction.[96] At first, potassium phenoxide and 18-crown-6 were dissolved in THF and thus mixed to get KOPh-18-crown-6 as a catalyst **188** (see Scheme 43). The postulated catalyst cycle is shown in Scheme 44. The naked counter anion PhO^- would activate enolates to generate silicate, which can attack the ketone followed generating PhOTMS as a possible catalytic cycle.



Scheme 43: The catalyst of KOPh-18-crown-6.

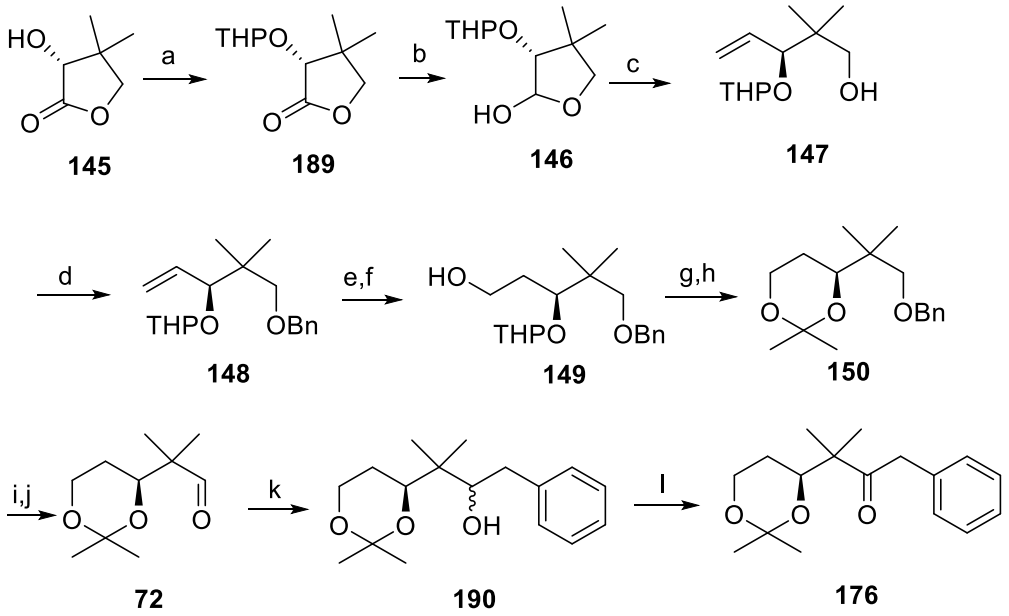


Scheme 44: The predicted mechanism of Mukaiyama reaction with the catalyst.

In this experiment, we explored the reaction of TMS enol ether and ketones at -78 °C in the presence of a preformed crown ether complex. TLC examination revealed that, even after workup, the ketone remined isolated, indicating that this system does not promote the desired reactivity. The absence of condensatio is attributed to the significant influence of the benzyl group on the reactivity of the enolates, as confirmed by TLC analysis.

3.1.2 Synthesis of ketoacid **176** via the Schering AG route

In 2005[97], the Schering company published a novel approach that accumulated a series of derivatives of ketone segments. Another idea, which begins with (D)-pantolactone as a highly convergent method avoiding the asymmetric synthesis of a chiral center. The starting material, which already contains carbon atoms C2–C5 including the geminal dimethyl moiety at C4 and the chiral center at C3, comes from *DL*-pantolactone by a chiral resolution with (*D*)-phenylethylamine. (*D*)-pantolactone serves as a generally chiral building block for the synthesis of chiral molecules. Pantothenic acid is a very common organic chemical with a low price. In industrial production, 2,2-dimethyl-3-hydroxypropionaldehyde is typically obtained from isobutyraldehyde and formaldehyde. The addition of sodium cyanide, followed by hydrolysis, acidification, and lactonization, yields (*D*)-pantolactone. Based on the structure of (*D*)-pantolactone, we focused on opening the ring followed by connecting carbon C1 and extended the side chain on carbon C5.



Scheme 45: The synthesis of ketone 176. a) DHP(1.8 equiv.), catalytic PPTS, DCM, RT, 4 h; b) DIBAL-*H*(1.1 equiv.), Toluene, -78 °C, 5 h; c) Methyltriphenylphosphonium bromide(1.3 equiv.), *t*-BuOK(2.7 equiv.), THF, -60 °C to RT, 24 h, 67%; d) *t*-BuOk(2.1 equiv.), BnBr(1.1 equiv.), THF, RT, overnight, 91%; e) $BH_3 \cdot S(Me)_2$ (3 equiv.), Cyclohexene (5 equiv.), THF, RT, overnight; f) H_2O_2/NaOH, 98%; g) AcOH/THF/H_2O (4:2:1), reflux 3.5 h; h) 2,2-DMP(5.6 equiv.), catalytic (±)-CSA, RT, 16 h, 56%; i) H_2, catalytic Pd/C, EtOH, RT, 2 h, 69%; j) Parikh-Doering oxidation, 84%; k) BnMgBr (1.5 equiv.), Et_2O, -

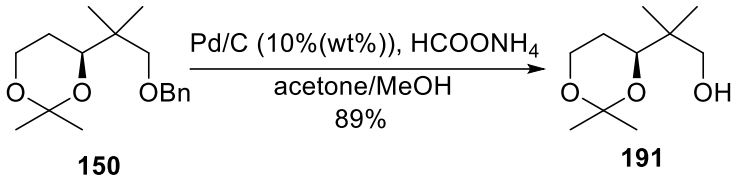
78 °C, 1 h, 64%; l) Parikh-Doering oxidation, 80%.

Firstly, the hydroxyl group at carbon C2 was protected as tetrahydropyrane ether to generate **189**. Then the lactone was treated with DIBAL-*H* at -78 °C to produce lactol **146**. Additionally, the temperature should not exceed -65 °C to prevent the formation of the side product 1,4-diol. Then the combained two steps do not need further purification and the lactol is directly treated with Wittig mix to prolong carbon C1. Two equivalents of base are required: one for ylide preparation, and another for opening the lactol cycle. The lactol was transferred to the aldehyde, which is the electrophile that was attacked. This resulted in a negative charge being placed on oxygen and a positive charge being placed on phophorus. The recombining oxygen then attacks the phosphorus, creating a 4-membered ring via an addition. Finally, the olefin can be obtained by elimination of $Ph_3P{=}O$.

The lactol **146** was treated with 2.7 equivalents of *t*-BuOK and then 1.3 equivalents of methyltriphenylphosphonium bromide were added resulting olefin **147** after 24 h at room temperature achieved in 67% yield. Of interest, the THP-isomer of **147** can be separated very easily via column chromatography with ether/pentane (1:4).

Olefin **148** was treated via a hydroboration-oxidation sequence yielding diol **149**, after protection of the primary alcohol as benzyl ether. As an alternative to BH_3•THF, we employed BH_3•$S(Me)_2$ for anti-Markovnikov hydration since it increases stability and higher solubility while just obtaining compound **149**. Due to its electron-deficient nature, boron functions as a Lewis acid in borane. Borane-ligand complexes, acting as Lewis bases, are efficiently employed in the hydroboration of double bonds. The reaction initiates with borane adding to the alkene, simultaneously breaking and forming bonds. In comparison to BH_3·THF, the stronger S–BH_3 bond in BH_3·SMe_2 reduces the availability of borane, making it more suitable for controlled reactions. This reduced reactivity helps to prevent excessive reaction rates and minimizes the formation of undesired side products. In this step, this enhanced control enabled us to achieve yields of up to 99%. Moreover, **149** could be used directly in the next stage of the synthesis without further purification.

Subsequently, intermediate **149** was converted via the deprotection-protection procedure into compound **150**. The O-THP ester was refluxed under acidic conditions for 3.5 h until it decomposed. In order to provide the ketal protecting group, the intermediate 1,3-diol was treated with 2,2-DMP under catalytic conditions overnight, yield to 56%. Aldehyde **72** was produced as a result of the removal of benzyl ether followed by the Parikh-Doering oxidation. The yield was not as promised, and additional testing indicated that the ketal group was partly deprotected. In this case, we also attempted to use more mild conditions shown in Scheme 46. The O-benzyl derivate was treated with palladium on carbon (0.35 g per 1 mmol benzyl group) and ammonium formate (0.3 g per 1 mmol benzyl group) in methanol.[98] Finally, the yield can reach up to 89%.



Scheme 46: The second method to produce 191

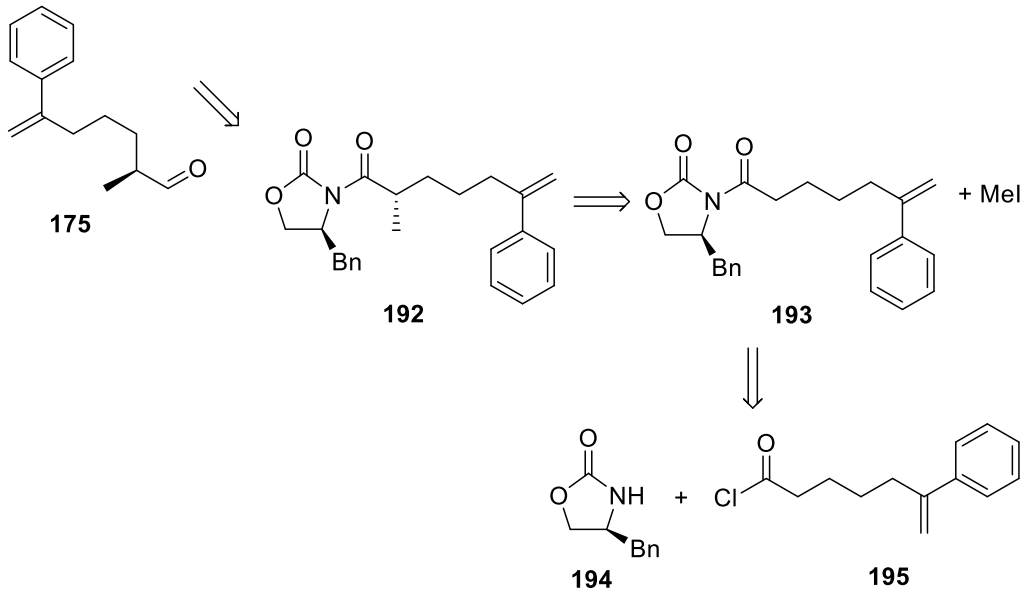
This new strategy has some drawbacks, including a longer reaction time (from 2 h to overnight), the need for extra palladium, which is not environment friendly, and generates higher costs. As a result, this final experiment did not provide a viable solution to the problem.

Here, we had built the carbon chain C1 to C5, and according to the retrosynthesis, the side chain at carbon C5 also needs to be achieved. Following that, the Grignard reaction was utilized in order to connect the needed substituent. This offers a great potential to a variety of epothilone derivatives with potentially intersting biological activity. The benzyl magniusmbromide Grignard reagent reacted with aldehyde **72** at 0 °C for 30 min followed by oxidation of the resulting epimeric alcohols to yield ketone **176**.

After a total of twelve steps, we successfully obtained ketone **176** from (*D*)-pantolactone, and the overall yield was greater than 12%. This approach produced **176** on a large scale, although the routing is quite lengthy. As a whole, the procedure is consistent with the tenets of green chemistry because it involves fewer purifications, milder reaction conditions, and simple commonality available chemicals.

3.2 Synthesis of Aldehyde Segment 175

For the aldehyde fragment **175**, our focus is on synthesizing the chiral center at carbon C8, which is located in the α position of the carbonyl group. We propose to employ a chiral auxiliary to construct this chiral center. Utilizing the steric hindrance provided by the auxiliary to control the orientation of new substituents has been demonstrated with high diastereoselectivity in asymmetric synthesis. The retrosynthetic analysis was shown in Scheme 47. Considering economical starting materials, we employed auxiliary **194**, which reacts with **195** to provide **193**. The electrophiles will attack from the opposite face to the chiral controlling group at C4 position of the oxazolidinone ring, allowing for the creation of the desired chiral center by alkylation with methyl iodide.



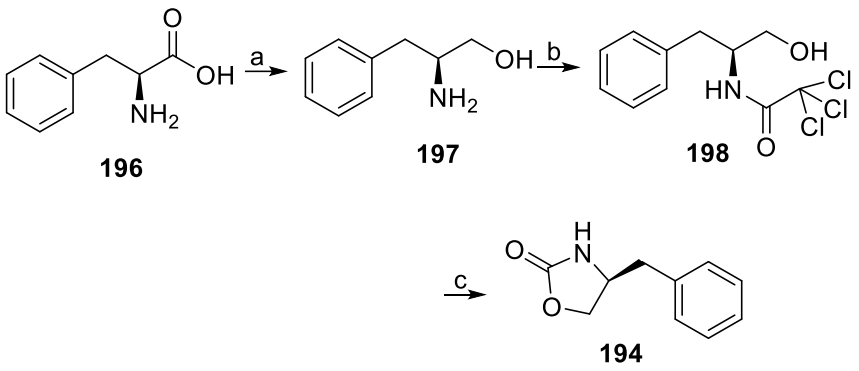
Scheme 47: Retrosynthetic analysis of the aldehyde segment.

3.2.1 Synthesis of oxazolidinone auxiliary **194**

Chiral auxiliaries are incorporated into synthetic routes to control the absolute configuration of stereogenic centers through steric hindrance. Oxazolidinone auxiliaries, provided by David A. Evans [99], are one of the most common compounds that are applied to many stereoselective transformations.

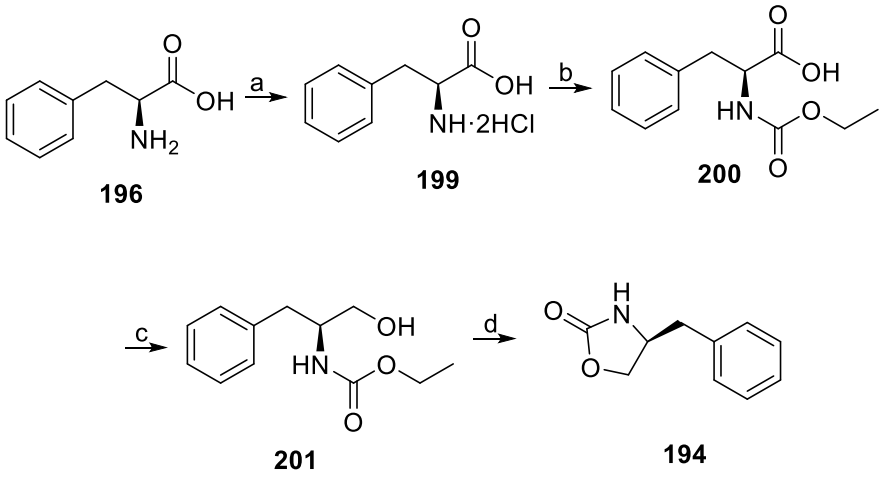
Alternative approaches to the generation of oxazolidinone auxiliaires have been used by T. Fukuyama [100]. In generally, they produced it by several steps involving salt formation, reducing by Grignard reagents to generate primary alcohols, performing a double alkylation and closing the ring. Instead of Grignard reaction to afford an alcohol, we started from *L*-phenylalanine and reaction with $NaBH_4$, followed by the addition of I_2 to increase the activity as an electrophile.[101]. Because the trivalent boron withdraws electrons from nearby carbon, it can act as a nucleophile to attack the carbonyl group, leading to the formation of a tetrehedral alkoxide intermediate. This intermediate, which is unstable, contains an $-O^-$ group and an $-OBH_3$ group. The strong O-B bond facilitates elimination and generate the aldehyde which could not be isolated. The intermediate then rapidly undergoes further reduction, also attarbuting by the trivalent boron. Consequently, more than two equvalents of $NaBH_4$ are needed. The new unstabilized tetrahedral intermediate is ultimately converted to an alcohol by protonation.

Next, followed by Fukuyama's method, **198** was achieved though *N*-alkylation, and **194** was generated after reduction.



Scheme 48: The synthesis of the oxazolidinone auxiliary from Fukuyama. **a) $NaBH_4$ (2.3 equiv.), I_2 (1 equiv.), 0 °C to reflux, 16 h; MeOH until the solution become clear, 2 M NaOH, RT, 8 h, 92%; b) Cl_3CCOCl (1.2 equiv.), pyridine, RT, 12 h, 62%; c) K_2CO_3 (2.3 equiv.), EtOH, reflux, 2 h, 83%.**

In this experimental process, the extensive use of pyridine caused significant challenges during workup. Notably, large quantities of hydrochloric acid were required to remove residual pyridine, resulting in product losses and environmental concerns. To address these issues, we attempted alternative solvents and avioded the production of the side-product HCl. An alternative approach, as shown in Scheme 49, synthesizes **194** using a strategy developed from N. Lewis [102].

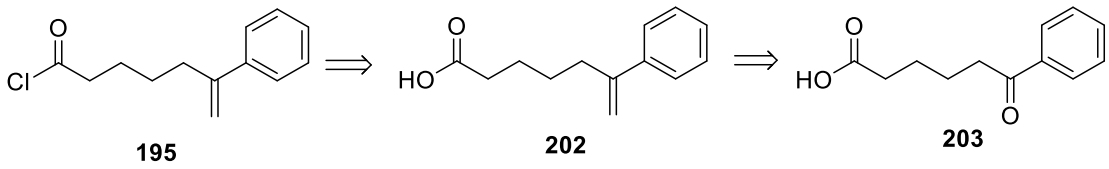


Scheme 49: The synthesis of the oxazolidinone auxiliaries from Lewis. **a) MeOH/HCl, RT→reflux, 4 h, 99%; b) $ClCO_2Et$ (1.1 equiv.), aq. $NaHCO_3$, 2 h, 92%; c) $NaBH_4$ (2 equiv.), $CaCl_2$ (4 equiv.), THF/EtOH, overnight, 92%; d) K_2CO_3 (3.5% mol), PhOH, reflux, 3 h, 82%.**

The new method begins with the same starting materials and, after three steps, yields intermediate **201**, which subsequently undergoes intramolecular cyclization via lactonization to afford compound **194**. In this process, water is formed as the by-product, thus avoiding the generation of corrosive HCl. This approach results in an improved overall yield compared to previous methods.

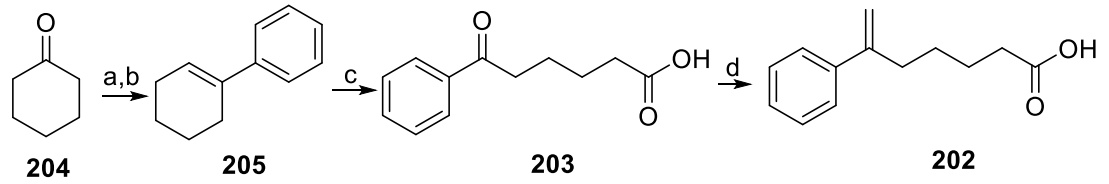
3.2.2 Synthesis of 6-phenylhept-6-enotic acid **195**

The *N*-acylation reaction can be employed to produce **193**, wherein an oxazolidinone auxiliary was treated with *n*Buli for deprotonation followed by the addition of an acid chloride as the acylating agent. When looking for an efficient synthesis route for acyl chloride **195**, the conjugated acid **202** was found to be more convenient. Additionally, the Wittig reaction serves as a key method for introducing a double bond and can be performed with a ketone. Consequently, the retrosynthesis could originate from 6-phenylhept-6-enoic acid **203**.



Scheme 50: Retrosynthetic analysis of 195.

In the 2010s, P. P. Thottumkara [103] reported a novel approach to the synthesis of 6-oxo-phenylheptanoic acid **203**. Advantages of this process include the use of a facile and operationally convenient catalytic procedure instead of ozonolysis or OsO_4 oxidation system. Additionally, this method utilizes cyclohexanone as a starting material, which contains both the basic carbon chain and the carbonyl group.

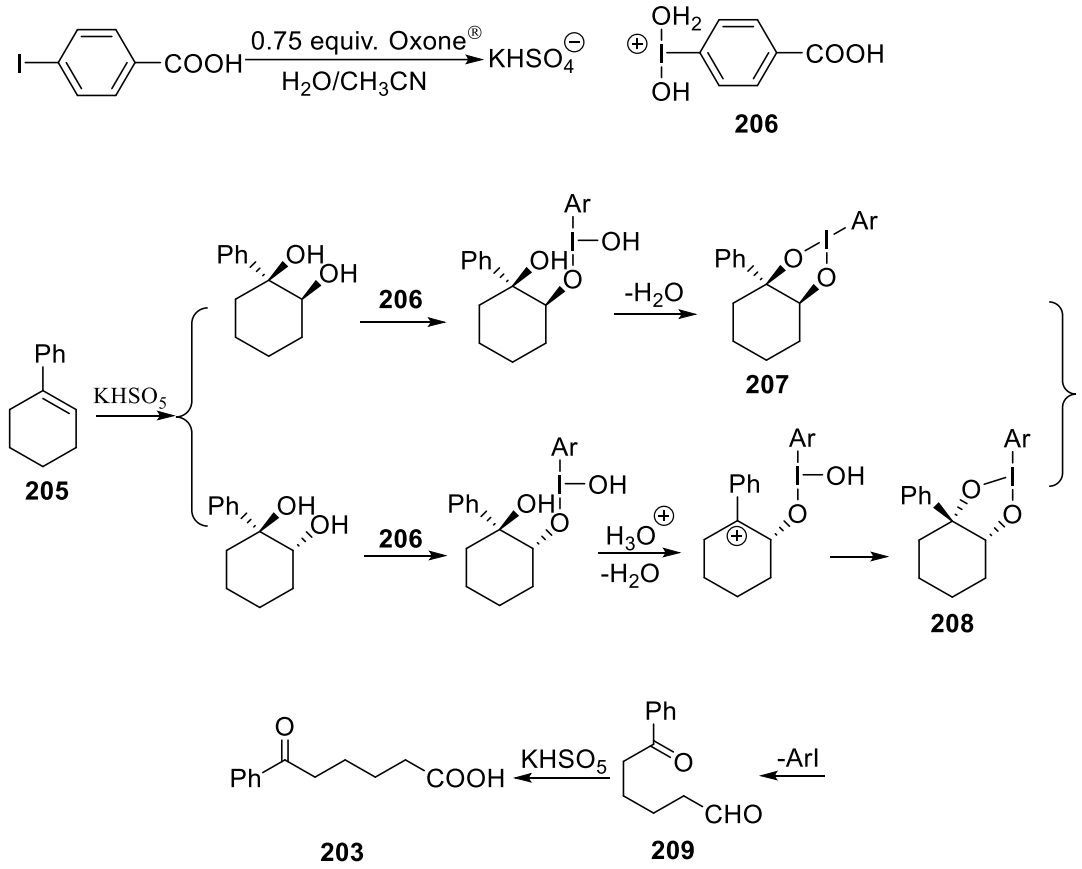


Scheme 51: The synthesis of 6-phenylhept-6-enotic acid. a) PhMgBr, Et_2O, -78 °C, 1 h; b) TFA (1.0 equiv.), CH_3CN, RT, overnight, 63%; c) Oxone® (2.0equiv), catalytic 4-IBAcid (0.05 equiv.), H_2O/CH_3CN (1:1 v/v), 60 °C, 3 h, 100%; d) Methyltriphenylphosphonium Bromide (1.3 equiv.), *t*-BuOK (2.6 equiv.), THF, RT, overnight, 71%.

In accordance with the depicted Scheme 51 shown, the initial step involves the reaction of cyclohexanone **204** with a Grignard reagent, followed by an elimination reaction, yielding cyclohexene **205**. The product of Grignard reaction can be directly treated with acid TFA in CH_3CN overnight without further purification, resulting in the formation of **205** with an overall yield of 63%. Drawing from the study by P. P. Thottumkara, optimal conditions for the cleavage of the alkene to generate the corresponding oxidized product **203** involved treatment with a catalyst, 4-IBAcid (0.05 equivalent) and 2 equivalents of Oxone® in a mixed solvent system of H_2O/CH_3CN (1:1, v/v) at 60 °C for 3 hours, yielding the desired product in a high yield of 99%.

During this stage, the 4-iodobenzoic acid underwent a reaction with the Oxone®, resulting in the formation of iodonium ion **206**. In addition, **205** quickly converted to

cis or *trans*-1,2-diol following treatment with catalyst 4-IBAcid. The intermediates **207** or **208** were obtained. Due to the effect of the phenyl group, the *cis*-diol was cleaved faster than *trans*-diol. Intermediates are also stabilized by the phenyl group. Cleavage of -ArI forms the aldehyde **209**. Finally, the aldehyde is oxidized into an acid by consuming an additional 0.5 equivalent of Oxone®.[104] It is important to note that the products have different outcomes depending on the quantity of Oxone®. Experimental data show that 1.5-2.0 equivalents of Oxone® are necessary for the quantitative conversion of **205** to **203**.



Scheme 52: Proposed Mechanism for Cleavage of Alkenes.

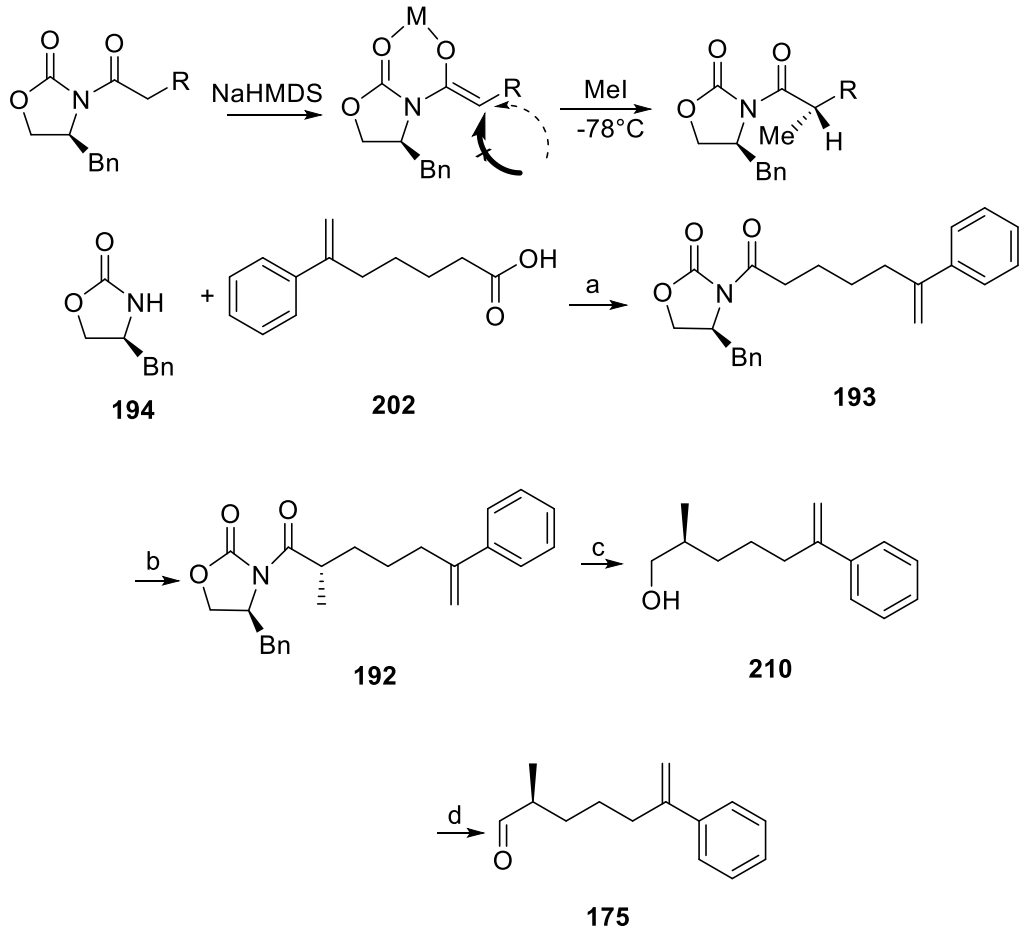
Finally, **202** was synthesized after the keto-acid **203** was treated with ylid via the Wittig reaction. Through these four procedures, a yield of over 60% of **202** could be attained.

3.2.3 Synthesis of segment aldehyde **175**

After successfully preparing oxazolidinone auxiliary **194** and 6-phenylhept-6-enotic acid **202**, our objective was to synthesize intermediate **193** through an *N*-acylation reaction. To achieve this, the oxazolidinone **194**, after deprotonation with *n*BuLi, was treated with acyl chloride derived from acid **202** via acyl substitution. Next, the resulting compound **193** was treated with NaHMDS to form the desired enolate, which was then reacted with methyl iodide to establish the chiral framework. Once the chiral

center is established, the auxiliary can be removed. Additionally, the auxiliary can be recycled for future use.

In the acylation reaction, the acid **202** would react with pivaloyl chloride to provide enoyl chloride **195**, then **195** would be treated with the oxazolidinone which was deprotonated with *n*BuLi to provide the amide **193** in 81% yield as white crystals. At -78 °C, the pale yellow solid **192** undergoes alkylation when reacted with the sodium enolate of **193** in the presence of NaHMDS and methyl iodide. This chemical transformation involves the nucleophilic addition of the sodium enolate, generated *in situ*, to the electrophilic methyl iodide, resulting in the introduction of a methyl substituent yielding the molecular framework **192**. Furthermore, ^{1}H and ^{13}C spectroscopy confirm the diastereoselective formation of the stereogenic center. *N*-Acyl oxazolidinones demonstrate similarities to esters in their ability to form enolates. In this regard, NaHMDS was utilized as the base to facilitate deprotonation, leading to a *E*-enolate. The interaction of the metal counterion with the oxygen atoms of the chelated oxazolidinone moiety introduces a spatial constraint, which orients one side of the resulting enolate configuration away from the substituent *R* of the oxazolidinones. Consequently, this geometric arrangement significantly enhances the accessibility of this enolate face for an electrophilic attack.



Scheme 53: The synthesis of desired aldehyde segment. a) PivCl (1.1 equiv.), Et_3N (1.3 equiv.),

Evans auxiliary (1.7 equiv.), *n*BuLi (1.7 equiv.), THF, -78°C to RT, 4 h, 81%; b) NaHMDS(1.1 equiv.), MeI (5.0 equiv.), THF, -78 °C, 3 h, 61%; c) $NaBH_4$ (4.0 equiv.), THF/H_2O (1:1, v/v), RT, overnight, 92%; d) Parikh-Doering oxidation, 82%.

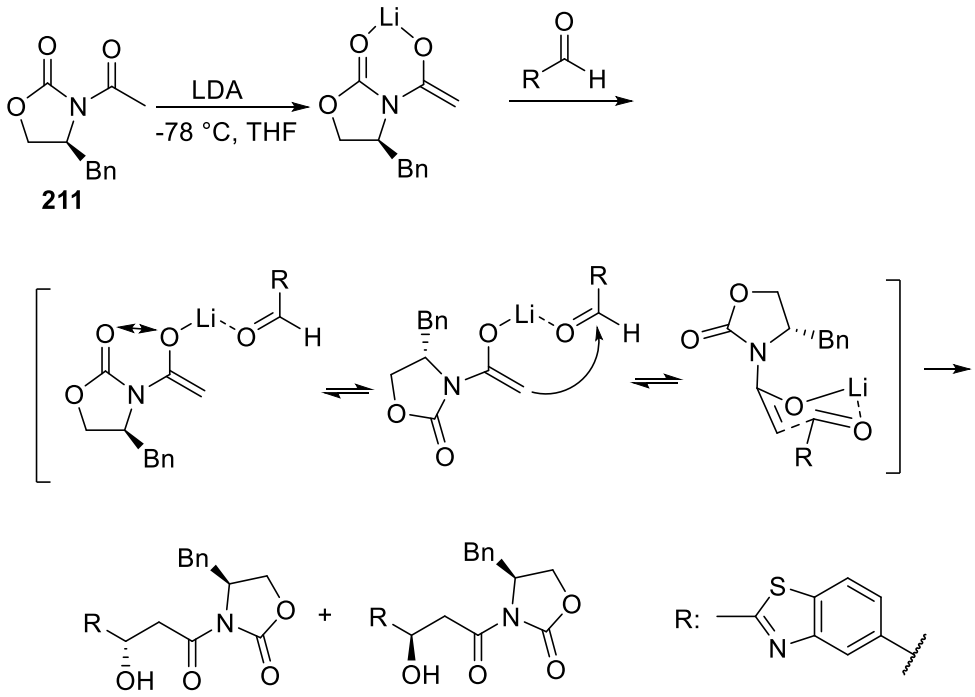
After reducing of the amide with $NaBH_4$ for two hours, the required alcohol **210** was obtained. This process is faster than hydrolysis to cleave auxiliaries. Subsequently, **210** was treated with oxidating agents to yield the aldehyde segment **175**.

3.3 Synthesis of Thiazole Segment

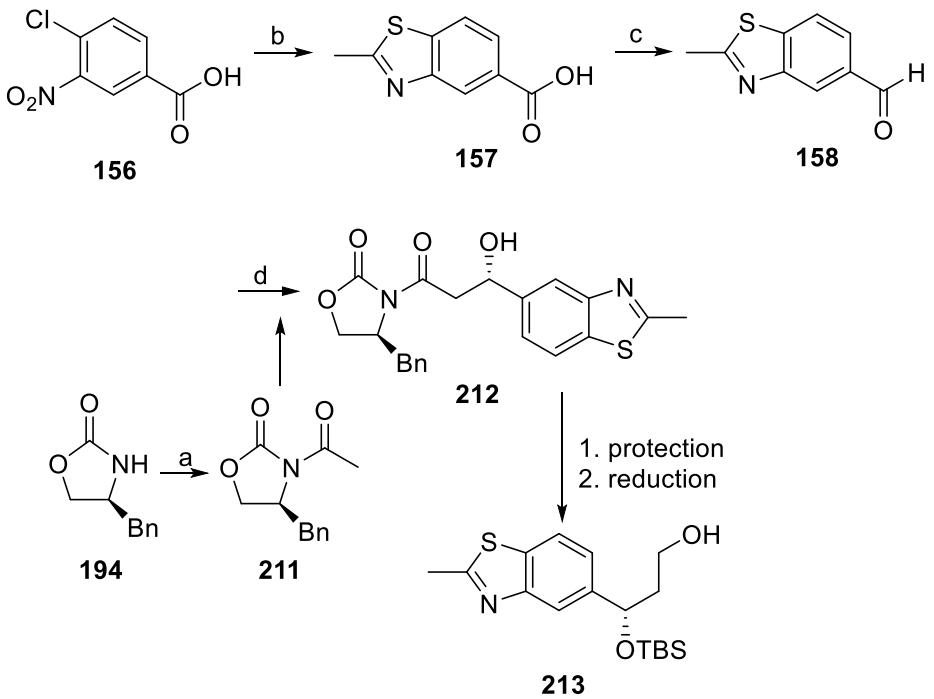
The target molecule contains a thiazole side chain identical to that of compound **5**. Therefore, we adopted the efficient method developed by Schering corporation, which involved recycling the chiral auxiliary to construct such a side chain.[68] This approach builds upon prior research efforts focused on synthesizing the target compound. The synthesis began with benzoic acid **156**, which was treated with sodium sulfide, acetic acid, hydrochloric acid and was refluxed overnight, resulting in the formation of benzothiazole **157**.

The modification of benzothiazole from acid **157** to aldehyde **158** was achieved via a reduction-oxidation reaction. This was followed by an Evans aldol reaction using the resulting products **158** as starting materials to form compound **212,** establishing the stereogenic center at C15. [67] The described reaction involves the utilization of **211** with LDA at -78 °C. LDA deprotonates the oxazolidinone at the α-carbon position relative to the carbonyl group, forming a lithium enolate. The resulting enolate is stabilized by the oxazolidinone ring structure. Subsequently, the enolates react with aldehyde **158**, resulting in the formation of a compound guided by a six-membered transition state.

The stereochemistry of the resulting product is influenced by several factors, including the presence of a 1,3-diaxial interaction, steric hindrance imposed by the asymmetric auxiliary, and the minimization of dipole interactions between the two carbonyl groups. Specifically, an initial dipole-dipole repulsion between oxygen atoms induces a 180° flip in the molecule's conformation, causing the aldehyde to favor attacking the opposite face of the oxazolidinone.[105] This process ultimately leads to the formation of diastereomeric compounds. Meanwhile, the incorporation of zinc chloride significantly reduces the required excess of the chiral auxiliary, yielding an 8:2 ratio of diastereomers. [68] X-ray analysis confirms that the major product possesses the desired configuration. It is worth noting that compound **212** can be isolated through crystallization. Following the protection of alcohol by TBSCl and the removal of oxazolidinone auxiliary, the primary alcohol **213** would be achieved. Fortunately, in our previous experiments conducted in collaboration with Schering, we have retained some of this intermediate, which saves time for our next experiments and reduces the complications associated with product purification.



Scheme 54: Mechanism of Evans aldol reaction.



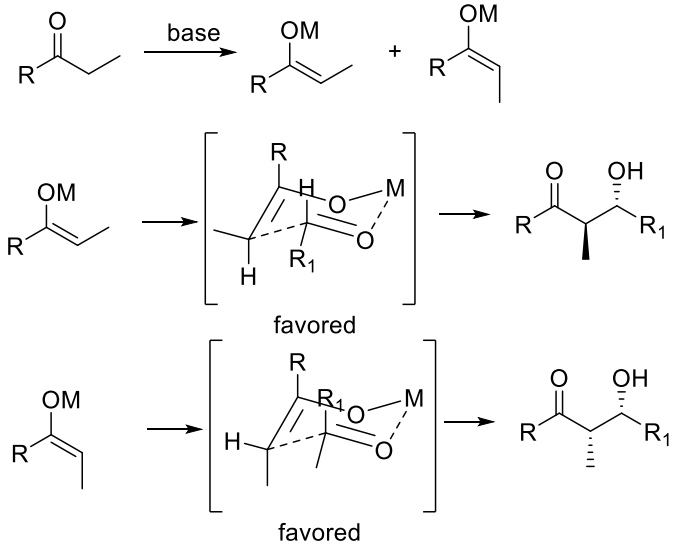
Scheme 55: The synthesis of thiazole segment. **a) EtOCl, *n*BuLi, THF, -78 °C to RT, 4 h, 86%; b) Na_2S, Ac_2O, HOAc, reflux, 62%; c) 1. $LiAlH_4$, THF, RT to reflux; 2. SO_3•pyridine, Et_3N, DCM/DMSO, RT, 59%; d) *n*BuLi, $ZnCl_2$, THF, -78 °C;**

3.4 Attempted Coupling of Ketone 176 with Aldehyde 175

Considering the characteristic features of the two segments **175** and **176**, we proposed

an aldol reaction to couple these pieces. The aldol reaction involves the addition of the enol/enolate of a carbonyl compound to an aldehyde or a ketone, generating the corresponding *β*-hydroxy carbonyl compound. A typical model process divides into two parts. First, the ketone is converted into either an enol or an enolate, depending on the reaction conditions. Subsequently, the enol or enolate undergoes nucleophilic addition to an aldehyde, yielding the aldol product. Among the various enolates employed, lithium, boron, titanium, and silyl enol ethers are the most commonly used. These have represented a major advancement in achieving high levels of regio- and stereoselectivity in aldol reactions.

In order to predict the configuration of products, H. Zimmerman and M. D. Traxler [106] proposed the Zimmerman-Traxler model, in which the aldol reaction has a six-membered chair transition state resulting in different diaseteroisomers. In a classic aldol reaction, the equilibrium formation of a nucleophile is a reversible process under both basic and acidic conditions. Upon the addition of aldehyde, a six-membered chair transition could be generated, followed by the elimination of one mole of water to afford an alkene via condensation. As shown in Scheme 56, the resulting condensation products depends on the stereochemistry of the enolates: *E*-enolates typically form *anti*-products, while *Z*-enolates lead to *syn*-products. In addition, the selectivity of condensation is primarily governed by the preference for placing substituents in equatorial positions within the six-membered transition states, thereby minimizing steric hindrance and maximizing stability.

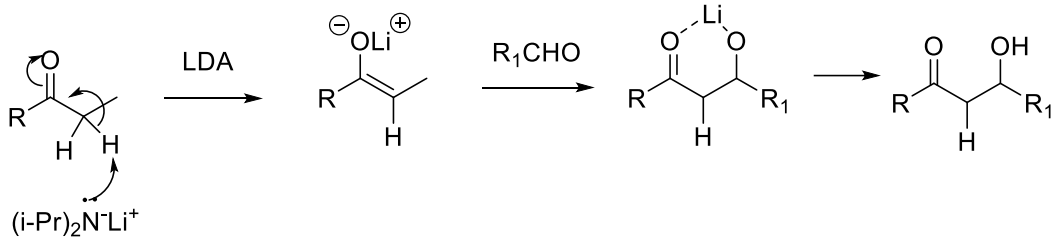


Scheme 56: The stereoselectivity of aldol reaction.

In reality, the products are also influenced by additional factors such as the counterion. Therefore, we aim to identify a suitable method that can be adopted in this project to achieve good selectivity. By considering these factors alongside the Zimmerman-Traxler model, we can refine our approach to optimize the reaction conditions and improve the stereoselectivity of the resulting compounds.

3.4.1 Attempted aldol reaction under strongly basic conditions

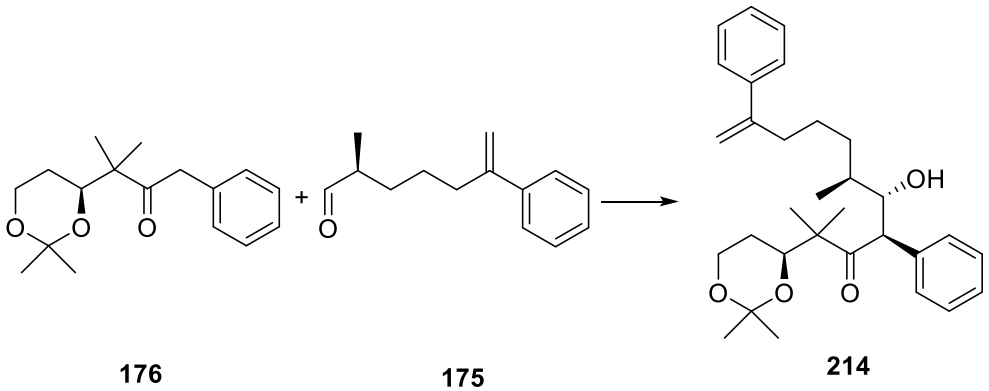
Reviewing classic synthetic methods reveals that most approaches utilize lithium enolates generated from the ketone segment. Then the enolates subsequently react with aldehydes to yield aldol products. LDA or NaHMDS as strong bases is typically used in stoichiometric amounts formed the metal alkoxide of the aldol products. Next, the enolate was directly added to the aldehyde forming six-membered transition states in a one-pot reaction, thereby streamlining the process and avoiding multiple steps.



Scheme 57: The Mechanism of aldol reaction in different conditions.

In this process, LDA was prepared by diisopropylamine and *n*BuLi at 0 °C and then the ketone **176** was added at -78 °C. The stoichiometric amounts of the aldehyde **175** were added dropwise at the same temperature until the metal alkoxide was generated. Monitoring the reaction via TLC reveals the disappearance of the starting material, ketone **176**, while the aldehyde **175** exhibited minimal changes. Regrettably, even with prolonged reaction duration at lower temperatures, the aldol products could only be detected by HPLC and could not be isolated, as confirmed by NMR analysis after the workup process.

As shown in Table 1, multiple parameters and variables were systematically examined in an effort to optimize the reaction conditions and improve the isolation efficiency of the desired aldol products. (Table 1, entry 1 to entry 9)



176 175 214

Table 1: Aldol reaction between ketone 176 and aldehyde 175.

Entry	Conditions	Yield
1	**175** (1equiv.), **176** (1.2 equiv.), LDA (1.2 equiv.), -78 °C, THF	<1%

	3 h-12 h	
2	**175** (1equiv.), **176** (1.2 equiv.), LDA (1.2 equiv.), $ZnCl_2$ (1.2 equiv.) -78 °C, THF 3 h-12 h	<1%
3	**175** (1equiv.), **176** (1 equiv.-4equiv.), LDA(1 equiv.-4 equiv.) -78 °C, THF 3 h	<1%
4	**175** (1equiv.), **176** (1.2 equiv.), LDA (1.2 equiv.) -78 °C-RT, THF 3 h	<1%
5	**175** (1equiv.), **176** (1.2 equiv.), LiHMDS (1.2 equiv.) -78 °C, THF, 3 h	0
6	**175** (1equiv.), **176** (1.2 equiv.), NaHMDS (1.2 equiv.) -78 °C, THF 3 h	0
7	**175** (1equiv.), **176** (1.2 equiv.), KHMDS (1.2 equiv.) -78 °C, THF 3 h	0
8	**175** (1equiv.), **176** (1.2 equiv.), LiHMDS (1.2 equiv.) -78 °C, Et_3N/Toluene 3 h	0
9	**175** (1equiv.), **176** (1 equiv.), NaOH (1.1 equiv.) EtOH/H_2O (1:2), 0 °C overnight	0

In Entries 1 to 4, LDA was emplyed with ketone **176** to generate the enolate, which was then reacted with aldehyde **175** at different conditions. We varioued the reaction temperature and reaction time, only the amount of trace amount of profuct was detected by HPLC. Next efforts to modify the quality of the base and ketone, no significant changes in the yield were observed. Meanwhile, considering the reactivity of carbonyl compounds, we added 1.1 equivalents of $ZnCl_2$, as indicated in entry 2. Zinc chloride coordinates with the oxygen atom of the carbonyl group, enhancing the electrophilic character of the carbon atom and chelates the formed aldol adduct. However, as observed, this method did not yield a significant improvement in our project. Further investigations were conducted to explore alternative counterions and metal enolates that could potentially enhance the yield of the desired products.

In entries 5 to 7, we evaluated other strong bases with similar mechanisms of enolate generation. LiHMDS, NaHMDS, and KHMDS all functioned similarly in forming metal enolates. These bases possess comparable pKa values, which are sufficient to deprotonate the ketone and generate the corresponding enolate. However, differences in the metal–oxygen (M–O) bond strength and coordination environment may influence

the steric hindrance and the ease of enolate cleavage during the aldol addition step. We hypothesize that Na^+ and K^+, due to their larger ionic radii and weaker coordination, may facilitate a greater concentration of free enolate anions in solution compared to Li^+. The experimental procedure involved reacting the metal enolate with aldehyde **175** at the temperature of -78 °C for an extened period. Regardingly, no aldol product was detected.

According to the study by David B. Collum [107], the Et_3N/toluene system efficiently enolizes acyclic ketones and esters, achieving higher *E*/*Z* selectivity. However, the experiments detailed in entry 8 revealed that these attempts did not yield aldol products. Finally, we tested another approach using NaOH as the base, based on the research of P. Singh's [108], which suggested the synthesis of the *β*-hydroxy ketones through the reaction of a ketone with an aldehyde in an ethanol/water(1:2) solvent mixture in the presence of NaOH at 0-2 °C. Following the process outlined in Entry 9, it was found that this system was not applicable to our reaction. After a series of experimental protocols, our investigation revealed that this particular system was not suitable for our intended reaction.

With evaluating various methodologies involved different strong base-mediated approaches, it became evident that none of these techniques were effective under our specific reaction conditions. This observation indicates that factors such as reaction time, temperature, reagent ratios, slovent choice, addition of $ZnCl_2$ as an additive and counterion selection had minimal impact on the outcomes of this aldol reaction. Consequently, we plan to explore other strategies to address the issue.

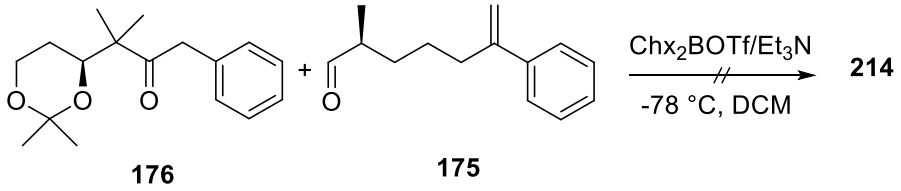
3.4.2 Attempted aldol reaction via Boron-enolates

Boron is often used to form carbon-carbon bonds through borylation reactions due to its significantly shorter bond length compared to metals such as Li, Al and Mg. This shorter bond length enhances the interaction with substrates, leading to a tighter and more organized transition state, which results in greater selectivity in the reaction.

P. V. Ramachandran and his colleagues [109] explored optimal conditions yielding the *anti*-aldol product (>97%) from bulky *tert*-butyl propanoates using dicyclohexylboron triflate (Chx_2BOTf) as a catalyst in the presence of Et_3N. Their study elucidated the influence of the steric properties of the ester moiety, the reagent, and the amine on diastereoselectivity, resulting in the identification of the optimal conditions for achieving high selectivity in the formation of *anti*-aldol products.

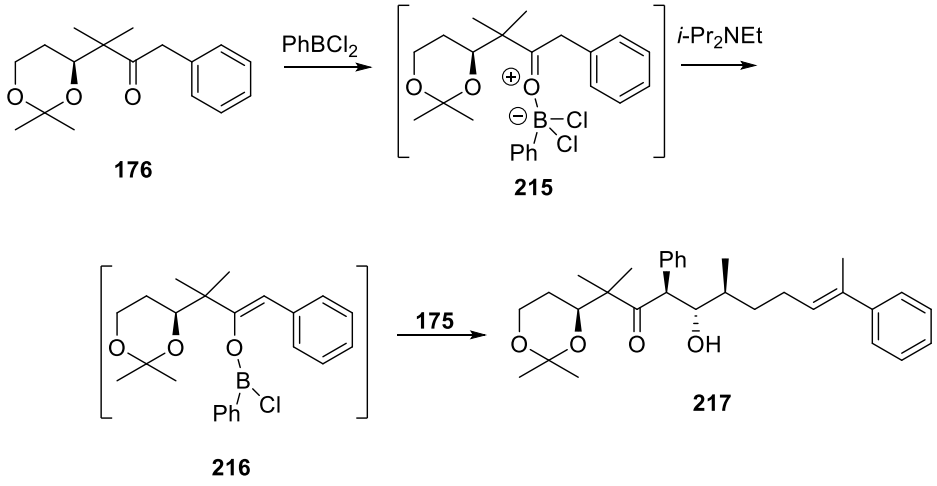
The typical procedure for anti-selectivity in aldol reactions is following: ketone **176** (1 mmol) dissolved in 5 mL DCM was added to the solution of dicyclohexylboron triflate at -78 °C followed by adding triethylamine (2.2 equiv.) dropwise and stirring the mixture for 2 h at -78 °C. In addition, the solution of Chx_2BOTf was prepared from

dicylohexylborane (1.5 equiv.), which reacted with trifluoromethanesulfonic acid (1.69 equiv.) at 0 °C. After completed consumption of the ketone, aldehyde **175** (1.5 equiv.) was added to the enolate solution and stirred for 3 h at the -78 °C. Using TLC to monitor the reaction's progress, it was observed that he aldehyde component exhibited no noticeable changes until the temperature was increased to room temperature and maintained overnight. Upon analyzing the product, it was found that the structure of the ketone had been decomposed or undergone undesired transformation and the aldehyde was isolated. These results suggest that elevated reaction temperatures are unsuitable for this transformation, however, standard reaction conditions were also ineffective in achieving the desired aldol coupling. In addition to temperature sensitivity, the borane enolate used in this reaction is highly moisture-sensitive, even trace amounts of water can hydrolyze the borane complex and render it inactive. It may another factor caused the failure of reaction. the structure of the enolate itself may be a primary reason for the failure of the aldol addition. As previously discussed, the resonance stabilization provided by the phenyl group reduces the nucleophilicity of the enolate, thereby lowering its reactivity toward the aldehyde. Furthermore, the bulky ketone may create steric hindrance, preventing the nucleophile and electrophile from aligning properly. As a result, the six-membered chair-like transition state could not form.



Scheme 58: Attempted synthesis of 214 using Chx_2BOTf.

Next, we found that H. Hamana[110] has developed an alternative method to achieve a cross-aldol reaction under mild conditions using phenyldichloroborane and Hünig's base. In this method, the ketone reacts with lewis acid to form a lewis acid complex, which then reacts with *i*-Pr_2NEt to generate a boron enolate. This boron enolate is then utilized in the acyclic stereoselective aldol reaction.



Scheme 59: The synthesis of 217 from 176 via $PhBCl_2$ and Hunig's base.

In their procedure, a solution of aldehyde, in the presence of base, was added to a mixture of ketone and $PhBCl_2$ in DCM. It is essential to first combine the aldehyde with diisopropylethylamine before adding it to the ketone and borane. The addition of the aldehyde after the base to the ketone and borane mixture resulted in a significant formation of self-condensation products. However, in our study, directly combining the ketone and borane following the addition of the aldehyde and base caused intramolecular rearrangement, resulting in a shift of the double bond. To address this issue, we propose exploring alternative strategies, such as initially incorporating the aldehyde segment and thiazole to mitigate the reactivity of the double bond.

3.4.3 Attempted aldol reaction via Titanium-enolates

Titanium enolates differ from ionic lithium enolates and covalent boron enolates by exhibiting an intermediate character that can accommodate additional ligands. This allows for the formation of a chelated transition state when donor groups are present on either the enolate or the electrophile. This property can be used to enhance the nucleophilicity of the enolate and to improve stereoselectivity in the reaction.

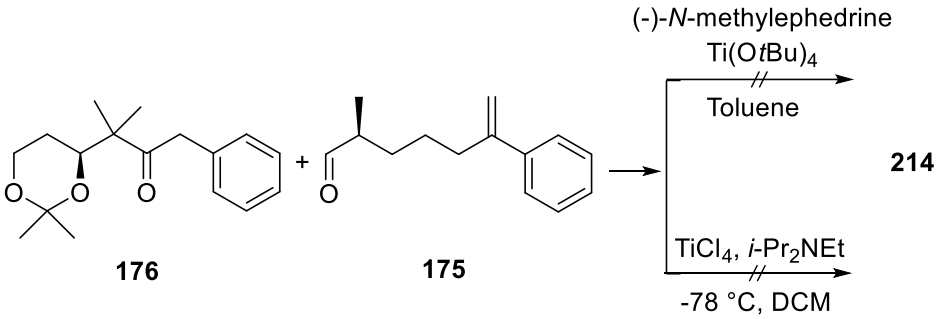
A. Evans [111] investigated a series of aldol products using titanium enolates with various substrates to achieve high yield and selectivity. In our approach, first, chlorotitanium enolate derivatives were prepared by sequentially adding 1.1 equivalents of $TiCl_4$ and 1.2 equivalents of diisopropylethylamine to a solution of the ketone **176** in DCM at -78 °C. After 30 minutes, the condensation process was initiated by the addition of the aldehyde. The quantity of aldehyde was systematically varied, with stoichiometries ranging from 1.2 to 5 equivalents. Unexpectedly, the anticipated aldol product did not form within this range, and instead, unreacted starting materials could be isolated. It suggests a lack of reactivity or a blockade in the reaction pathway under discussed conditions. Considering the possible reasons why no aldol product was formed, we evaluated not only the steric hindrance and potential deactivation of the nucleophile, but also the coordination behavior of the titanium species. Unlike lithium or boron enolates, titanium enolates are known to strongly coordinate with oxygen lone pairs. In our procedure, $TiCl_4$ was first mixed with the ketone, which may have led to excessive coordination at the carbonyl oxygen, thereby inhibiting proper enolate formation or reactivity. This strong coordination may have also interfered with the approach of the electrophile, preventing the desired aldol coupling from occurring. So the order of addition maybe try the $TiCl_4$ with base first, then add the ketone slowly.

Apart from $TiCl_4$, Scholtis [112] reported the synthesis of *anti*-configuration aldol products using titanium(IV) *tert*-butoxide in the presence of an amine. In this process, a mixture of ketone, 1 equivalent of Ti (O*t*$Bu)_4$, 1 equivalent of aldehyde **175**, and 2 equivalents of (-)-*N*-methylephedrine was mixed at room temperature. Compared with $TiCl_4$ to form titanium enolates by direct coordination to carbonyls, this condition form enolates is more milder and more flexible through ligands exhange with ketones and

bases.

However, even though extending the reaction time and stirring overnight at room temperature, only the starting materials could be isolated, indicating that the reactants exhibited minimal reactivity under these conditions.

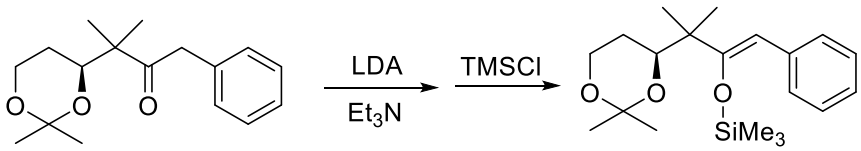
At beginning, we hypothesized that the absence of observable product formation might be due to the system's inability to access the transition state necessary for reaction initiation. Meanwhile, we also considered other potential contributing factors. In this process, Ti(O*t*Bu)$_4$ undergoes ligand exchange with the ketone, and the presence of (–)-*N*-methylephedrine serves not only as a base but also controls enolate formation. We considered that the coordination between (–)-*N*-methylephedrine and Ti(O*t*Bu)$_4$ may be incomplete, resulting in slow enolate generation. Additionally, (–)-*N*-methylephedrine contains multiple potential donor atoms (–OH and –N), which may also coordinate to titanium and potentially hinder enolate formation. Therefore, it may be beneficial to conduct a model reaction to confirm the efficiency of this system. We suggest altering the order of addition such that Ti(O*t*Bu)$_4$ and (–)-*N*-methylephedrine are mixed first, followed by slow addition of the ketone. The aldehyde should be added only after complete enolate formation. Furthermore, to improve reactivity, more coordinating solvents such as Et_2O or THF could be employed, and the reaction temperature optimized between –78 °C and 0 °C. Typically, these reactions are conducted at low temperatures to maintain control over the process.



Scheme 60: Attempted aldol reaction via Titanium-enolates.

3.4.4 Attempted Mukaiyama reaction

To overcome the reduced reactivity caused by the structural influence of the enolate in the one-pot aldol reaction, we prepared the corresponding silyl enol ether to ensure complete enolate formation.



176 218

Scheme 61: The Mechanism of preparation of enolates 218.

Initially, LDA was employed for the deprotonation of the ketone **176**, followed by the addition of TMSCl to stabilize the resultant enolate, achieving a 56% conversion. The detailed process is described in Scheme 61. The successful synthesis of compound **218** confirmed that enolate formation was not the limiting factor in the reaction. Next, we performed a Mukaiyama aldol reaction between the silyl enol ether and the aldehyde **175**.

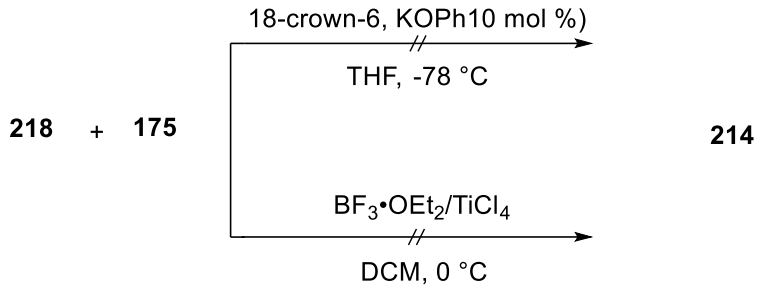
Drawing inspiration from the methodology outlined in Chapter 3.1.1, a combination of 18-crown-6 and KOPh was introduced to catalyze the enolate formation in the presence of aldehyde. In this systerm, the 18-crown-6 structure is of such a size as to allow potassium ions to fit in the cavity. The cation complexing agents lower the degree of aggregation of the enolate and metal cations, resluting in enhancing reacivity. The K^+-18-crown-6-complex was synthesized by mixing 18-crown-6 with KOPh. Then this complex was added to the mixture of **175** and **218** at -78 °C and allowed to react for several hours.

However, the reactants did not exhibit sufficient reactivity under these conditions, as evidenced by the isolation of the aldehyde **218** after workup. We concluded that KOPh is not a suitable Lewis acid and therefore cannot serve as a catalyst in our Mukaiyama aldol reaction. It does not activate the aldehyde toward nucleophilic attack, which is essential for this transformation. Additionally, 18-crown-6 merely enhances the solubility of K^+ in organic solvents and does not contribute to electrophilic activation. Furthermore, KOPh acts as a strong Brønsted base, which may lead to the cleavage of the silyl enol ether, reverting it to the corresponding ketone and thereby inhibiting the desired aldol coupling.

In an effort to explore alternative approaches, we investigated a classical Lewis acid-catalyzed aldol addition. Since silyl enol ethers are not sufficiently nucleophilic to react directly with aldehydes at the carbonyl carbon, we employed equimolar amounts of $BF_3 \cdot OEt_2$ and $TiCl_4$ to activate the aldehyde. The silyl enol ether was then added to the reaction mixture. Unfortunately, this method did not afford the desired aldol product.

Upon analyzing the possible reasons for this failure, we first considered the reactivity of the aldehyde. To prevent side reaction between the Lewis acid and the silyl enol ether, leading to the formation of unreactive Ti–O–Si species, it is advisable to premix the aldehyde with $BF_3 \cdot OEt_2$ or $TiCl_4$ and allow sufficient time for complexation before adding the enol ether **218** slowly.

In addition, TMS-enol ethers are not particularly stable and may decompose under strongly acidic conditions. Therefore, using more stable enol ether derivatives would be advantageous under these conditions. We also considered that the lone pair on the enol oxygen may be delocalized through resonance, reducing its nucleophilicity and thus diminishing its reactivity toward electrophilic carbonyl compounds.



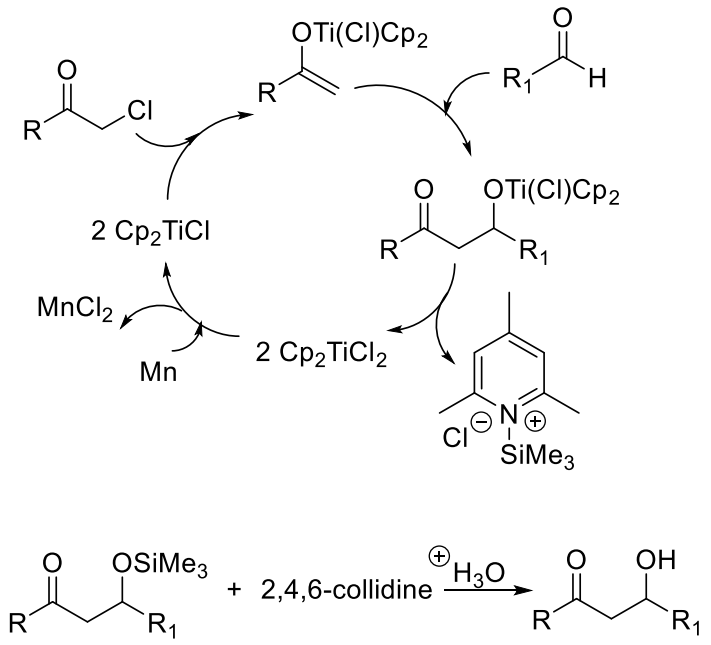
Scheme 62: Attemped synthesis of 214 from enolates 218.

3.4.5 Attempted a modified Reformatsky-type reaction

The Reformatsky reaction also plays an important role to the construction of the carbon-carbon bond between α-halogen ketones and aldehydes. With advancements in metal-catalyzed versions of this process, the classic Reformatsky reaction can also be used to control the synthesis of a stereochemical center. Generally, the Reformatsky reaction involves the coupling of an α-halo ester or ketone, typically an α-bromide, with an aldehyde. However, a key challenge in this methodology lies in the selective introduction of the halogen at the α-position of the ketone, which can be synthetically demanding and may require specific reaction conditions to achieve efficiently. R. Robles and his co-workers [113] introduced a kind of Reformatsky reaction involving Ti-based catalysts, which may offer potential applications within our system.

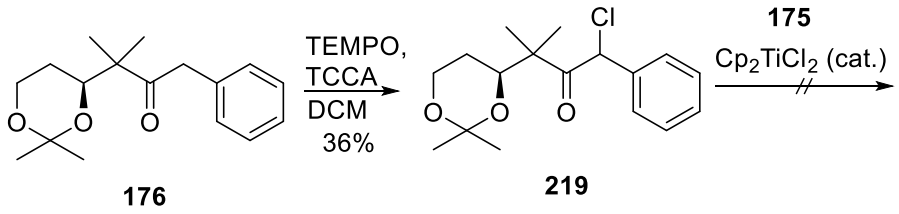
Their approach begins with the conversion of the ketone **176** to an α-chloro ketone **219**, which is then treated with TEMPO and TCCA. This transformation proceeds via a radical mechanism. In this context, TEMPO acts as a radical initiator, facilitating the formation of the reactive intermediate required for the reaction to proceed.

A combination of TMSCl and 2,4,6-collidine is used to prepare the catalyst Cp_2TiCl. As shown in Scheme 63, it is postulated that an α-halo ketone would react with 2 equivalents of Cp_2Ti^{III} Cl, resulting in the formation of a titanium (IV) enolate and releasing 1 equivalent of $Cp_2Ti^{IV}Cl$. This enolate subsequently participated in the reaction with an aldehyde, yielding adducts. It is observed that the TMSCl/collidine is employed as the source for generating titanocene, which is an essential reagent in this process. Following a final acidic treatment, the desired β-hydroxy ketone is expected to be produced. Eventually, it is hypothesized that Mn present within the reaction medium reduces $Cp_2Ti^{IV}Cl$ to Cp_2Ti^{III} Cl, thereby concluding the catalytic cycle.



Scheme 63: The proposed mechanism of Reformatsky reaction.

In our experimental framework, the implemented approach produced α-chloro ketone **219** with a yield of 36%. When this *α*-chloro ketone was subsequently combined with the aldehyde and subjected to an activating catalyst for an extended period at room temperature, an unexpected outcome was observed. Specifically, the *α*-halo ketone underwent decomposition, leading to the isolation of the unreacted aldehyde rather than the intended chemical transformation.



Scheme 64: Attempted synthesis of 214 from α-chloride ketone 219.

Actually, this reaction proceeds via a radical reductive coupling mechanism. Cp_2TiCl reacts with α-chloro ketone to form a carbon-centered radical via single electron transfer. Then adds to aldehyde to generate a new C-C bond. However, the rapid generation of radicals by the Ti species can promote undesired side reactions, reducing the efficiency of productive coupling. Additionally, the α-chloro ketone is sensitive to moisture; even trace amounts of water or nucleophiles present in the solvent can hydrolyze or displace the chloro substituent, leading to decomposition of the α-chloro ketone and further hampering the reaction outcome.

3.5 Coupling of Aldehyde 175 with Thiazole Segment 213

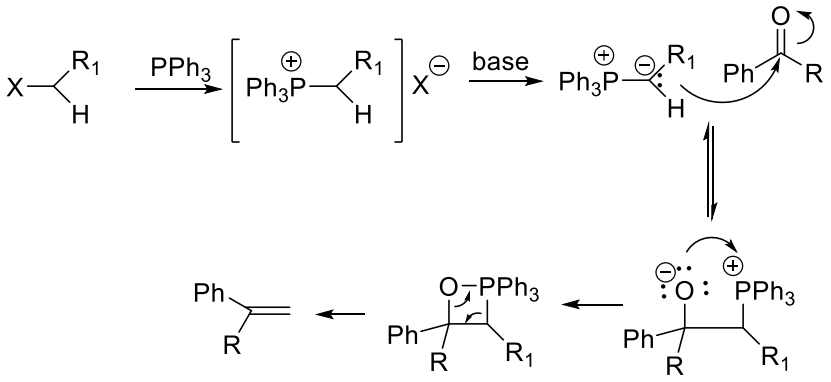
Cross-coupling, olefin metathesis, and Wittig-type olefination reactions are common

methods for preparing trisubstituted alkenes. However, both cross-coupling and olefin metathesis necessitate the prior synthesis of specific metal catalysts and are dependent on the nature of the alkene substrate. Comparatively, the Wittig reaction and the Julia-Kocienski olefination are relatively simple to implement.

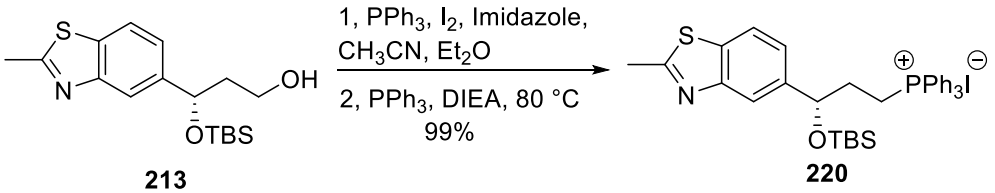
3.5.1 Attempted Wittig reaction

The synthesis of the target molecule necessitates a crucial step involving the coupling of the aldehyde and the thiazole segment. Based on preliminary retrosynthetic analysis, the Wittig reaction was chosen due to its high yield and superior selectivity in forming *Z*-alkenes.

Therefore, we synthesized Wittig salt **220**, derived from the thiazole segment **213** as the starting material. It refers to the introduction of iodine or iodine-containing groups into alcohol molecules to form iodinated derivatives. The primary alcohols in **213** were converted to iodides through a treatment with PPh_3 in acetonitrile and I_2 in the presence of imidazole in ether, resulting in a 78% yield of the iodide. Next, the iodide was reacted with PPh_3 and DIPEA to give the corresponding Witting salt without further purification. These salt was then deprotonated using a strong base, such as *n*BuLi, to generate unstabilized ylide. Notably, the use of unstabilized ylides leads to the formation of Z-alkene products with moderate to high selectivity, driven primarily by kinetic control.



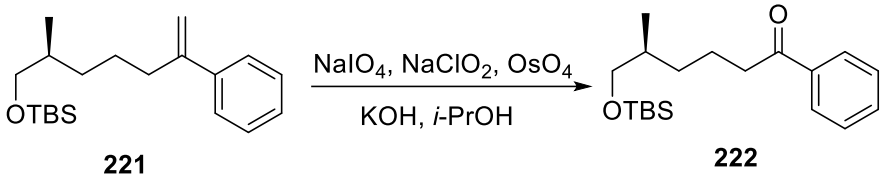
Scheme 65: Mechanism of Wittig reaction.



Scheme 66: The synthesis of 220.

In this process, our objective was to construct a carbon-carbon bond at the C12-C13 position. To achieve this, alcohol **210** was protected with TBSCl to afford **214**. Meanwhile, Wittig olefination was employed to construct a double bond by the reaction

of an aldehyde or ketone with a triphenyl phosphonium ylide. Consequently, oxidative cleavage of the olefin **221** to the ketone was necessary. We utilized the $OsO_4/NaIO_4$ system, as it is a safer method compared with ozonolysis for this transformation. Additionally, the relatively expensive OsO_4 catalyst can be reused by converting it into water-soluble Os(VI) species with KOH/*i*-PrOH. The olefin **221** is mixed with catalytic OsO_4 and 2 equivalents of $NaIO_4$ in THF/water/*t*-butanol at 33 °C for 22 h, achieving **222** in 67% yield. There reaction conditions are relatively mild, reducing the risk of side reactions and degradation of sensitive functional groups in the substrate.

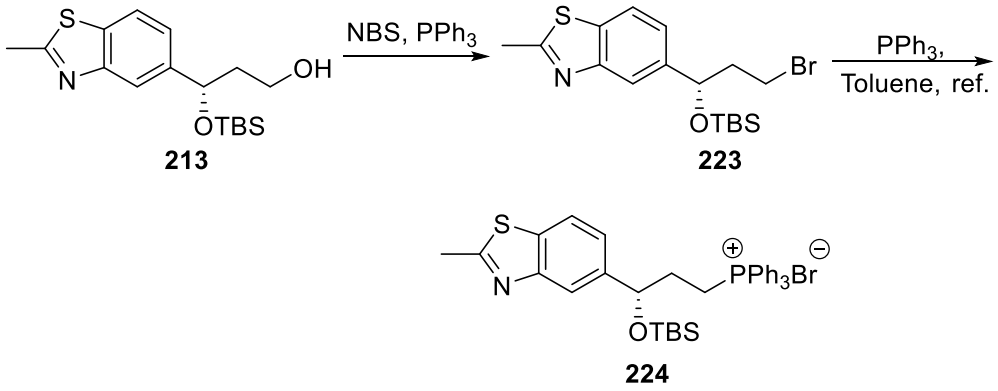


221 **222**

Scheme 67: The synthesis of 222.

According to the mechanism of the Wittig reaction, the salts are deprotonated with NaHMDS and are coupled with ketones to form alkenes, with the *Z*-configuration being the most favorable. We utilized 1.2 equivalents of NaHMDS to deprotonate compound **220** and generate the ylide, subsequently adding ketone **222** at -78 °C and maintaining the reaction for several hours. Even though with these efforts, ketone **222** remained unreacted and was recovered after workup.

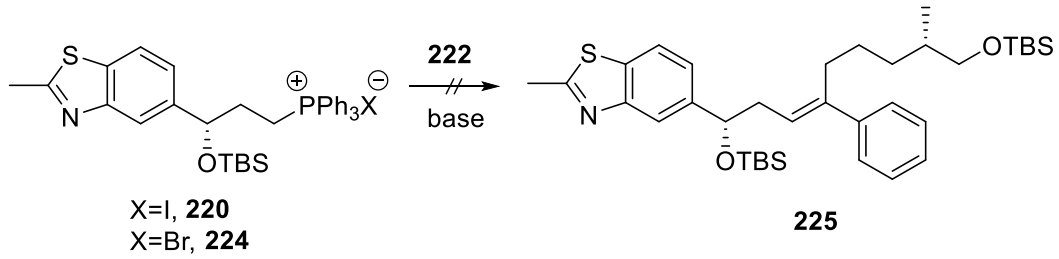
To test the reactivity of this conditions in our systerm, we also attempted to use other halides to generate the different phosphonium salt. As shown in Scheme 68, the new phosphonium salts were obtained from compound **213** through a two-step process involving NBS, achieving a yield exceeding 90%.



213 **223** **224**

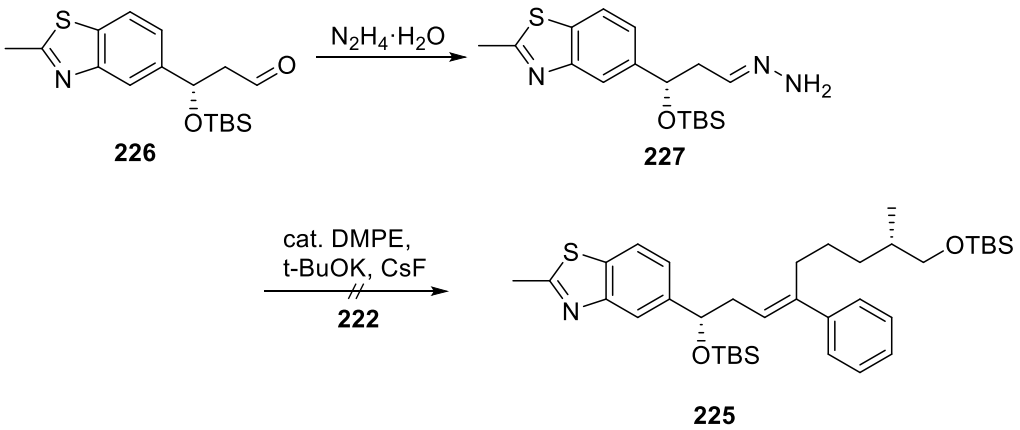
Scheme 68: The synthesis of 224.

The Witting salt **224** wwas treated with NaHMDS and added to the ketone **222,** which was activated by $CeCl_3$. The reaction mixture was then heated to 80 °C, after 5 h stirring; however, the ketone still did not react.



Scheme 69: The reaction of Wittig salts and ketone 222.

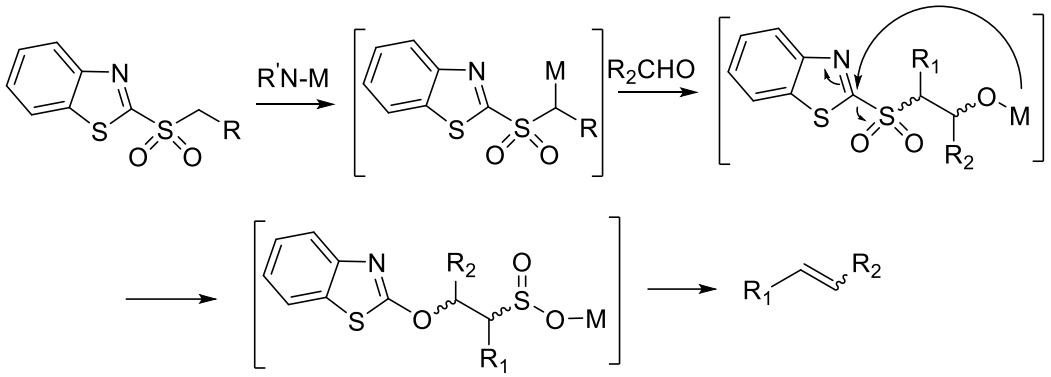
We then explored an alternative approach of the synthesis of **225**, as illustrated in Scheme 70. The starting material **226** was prepared from **213** by oxidation and subsequently reacted with N_2H_2•H_2O to synthesize intermediate **227**. Following this, **227** was treated with (Cymene)ruthenium dichloride as a catalyst, base and CsF. This reaction, facilitated by the presence of a Lewis base, led to the formation of monometallic adducts. The mixture subsequently reacted with reagent **222** at 45 °C to provide alkenes **225**. However, after two days, the initial compounds remained unaltered and were isolated.



Scheme 70: Attempted synthesis of 225 from 226.

3.5.2 Attempted Julia-Kocienski Olefination process

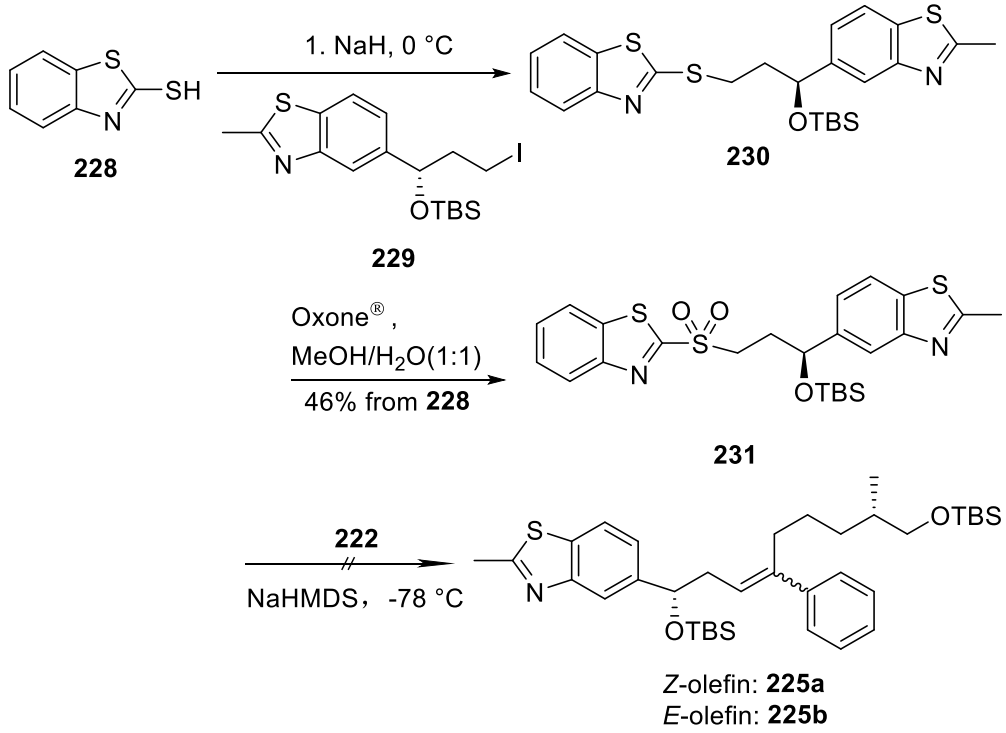
The Julia-Kocienski olefination, as well as one-pot Julia olefination, can be applied to generate a wide variety of alkenes involving the reaction of an α-metalated aryl alkyl sulfone with a carbonyl compound. In this type of reaction, the aryl group, a critical substitution for controlling selectivity, is originated from thiols and is connected with alkenes to form a sulfone. A wide variety of aryl groups are available, including benzothiazol-2-yl (BT), pyrid-2-yl (PYR), 1-phenyl-1*H*-tetrazol-5-yl (PT) and 1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT). Using BT as an illustration, the underlying mechanism is shown in Scheme 71. After deprotonation to form a metallated sulfone nucleophile, the carbonyl electrophile is attacked by the nucleophile, causing a spontaneous Smiles rearrangement. This rearrangement produces alkenes as a result of the elimination of sulfur dioxide.[114]



Scheme 71: Mechanism of Julia-Kocienski olefination reaction.

Apart from factors such as substituents, the sulfone anion, the counterion, solvents, and any added cation-complexing agents, numerous other elements have influenced stereoselectivity of the double bond.[114] We aim to identify an appropriate aryl group that can be introduced under straightforward conditions to achieve high *Z*-selectivity in our attempts.

Firstly, the most commonly used leaving group, BT, was evaluated for our objective, as illustrated in Scheme 72. Sulfide reagent **230** was synthesized by 2-mercapto-benzothiazol **228** with NaH, followed by a subsequent reaction with iodide **229** at room temperature overnight, yielding **230** in 83% yield. Then the sulfide was oxidized with Oxone® to provide the sulfones **231**.



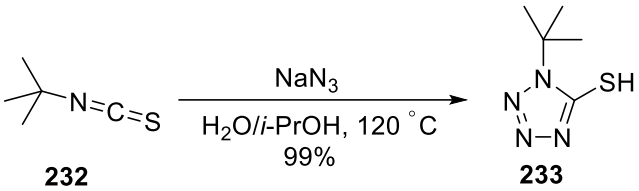
Scheme 72: Attempted synthesis of 225 from 228.

Incorporating a base (LDA or NaHMDS) into sulfonates produces a metallated benzonthiazoyl sulfone, which is expected to react rapidly with ketone **222**. However,

after stirring the mixture at -78 °C for several hours, no reaction of sulfonate with ketone was observed under these conditions.

In terms of activity and stereoselectivity in the formation of alkenes, the Julia-Kocienski olefination offers additional options. Kaori and Daiki [115] proposed a novel pathway to get *Z*-alkenes in high yield. Interestingly, upon following this method, we achieved *E*-alkenes with high selectivity.

In contrast to the other possible leaving groups, such as PT, we opted for 1-*tert*-butyl-1*H*-tetrazol-5-yl alkyl sulfones, which should reat with ketone **222** in the presence of LiHMDS in THF at low temperature to give trisubstituted (*E*)-alkenes in good yields stereoselectively.

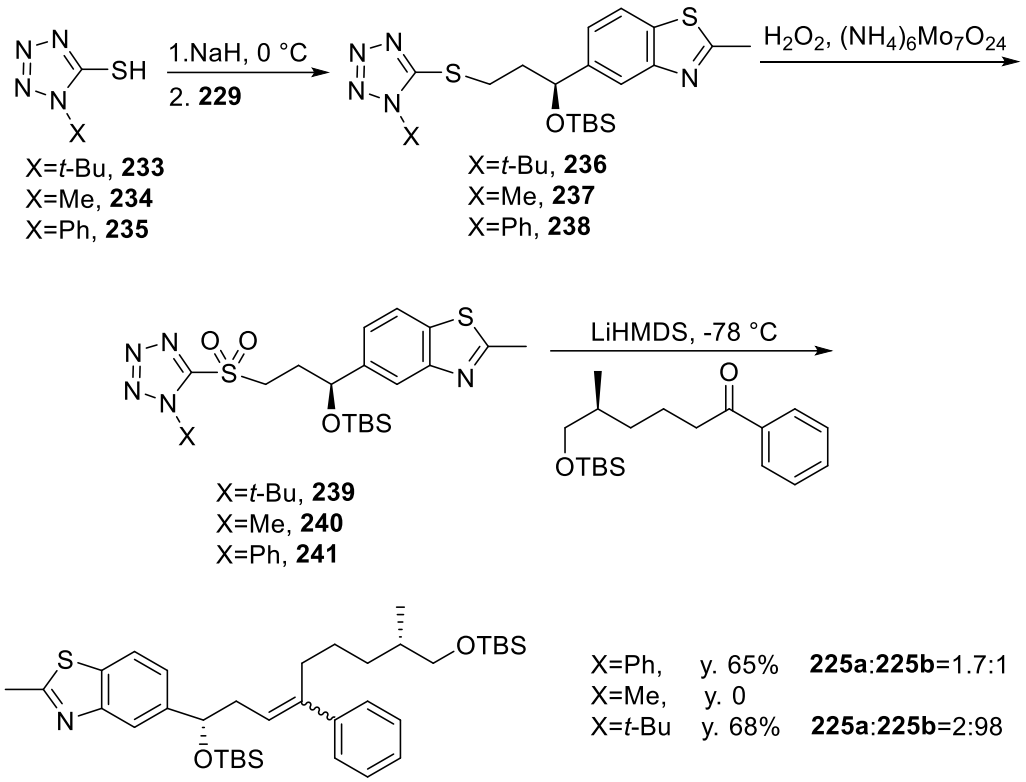


232 **233**

Scheme 73 The synthesis of 233

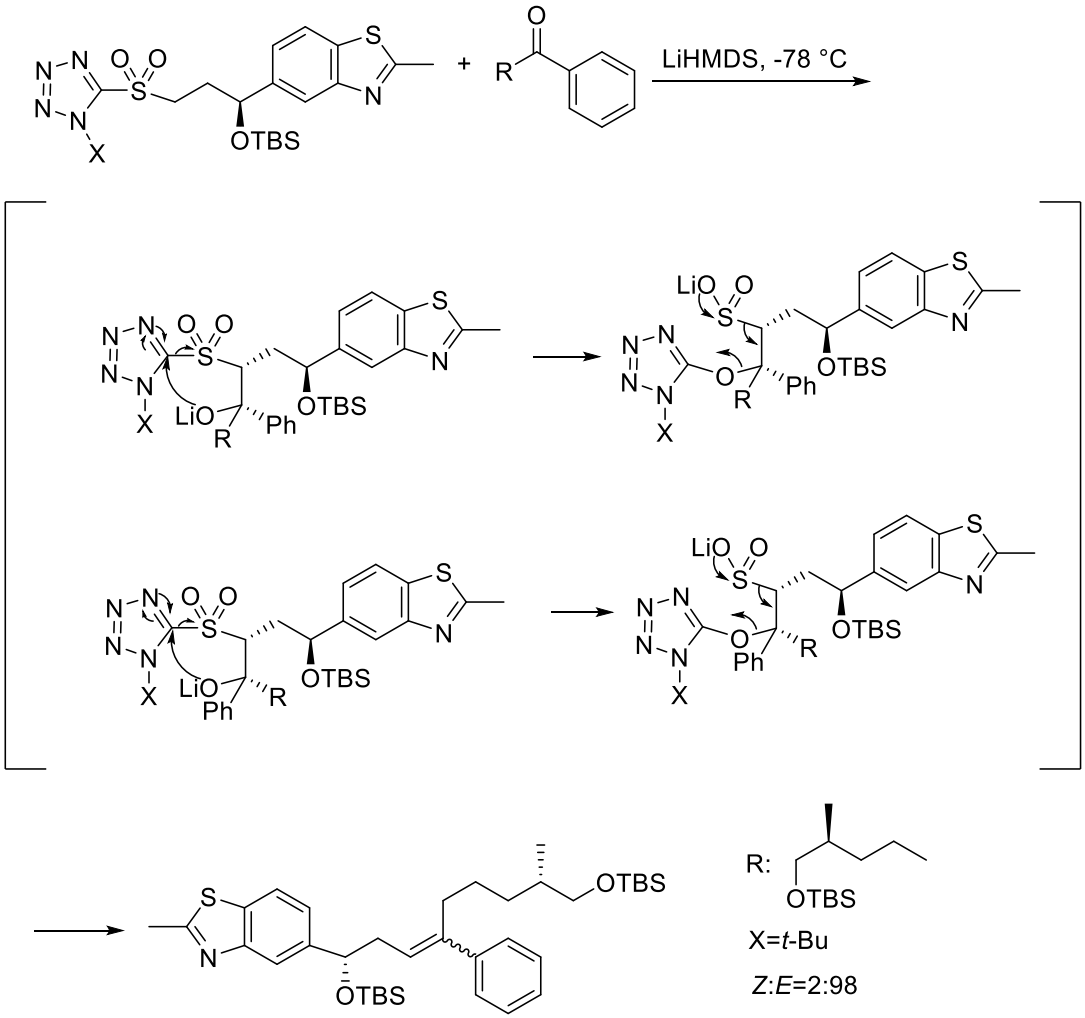
As illustrated in Scheme 73, a solution of NaN_3 in H_2O was treated with a commercially available isothiocyanate solution in *i*-PrOH for 24 hours at 120 °C, directly generating 1-phenyl-5-mercaptottazoles **233** as white crystallasation. To facilitate a comparison of leaving group effects, compounds **234** and **235** were also synthesized. These were then coupled with the iodide **229** to afford sulfides **236**-**238** and subsenquent oxidization using 35% H_2O_2 and ammonium molybdate achieved the sulfones **239**-**241**. To optimize the Julia-Kocienski olefination process, we conducted a detailed comparison using various bases. The results indicated that LiHMDS, rather than NaHMDS or KHMDS, is the most effective for this system.

Simultaneously, we undertook a comparative examination on the reactivity of iodide and bromide in their interactions with 5-mercaptotriazoles to synthesise sulfides. The results of this set of studies clearly showed that bromide ions were less reactive in this situation. This observation aligns with the fundamental scientific principle that iodide ions function as superior leaving groups in S_N^2 reactions. This is attributable to their larger atomic size and lower bond dissociation energy compared to bromide ions.



Scheme 74: The synthesis of 225.

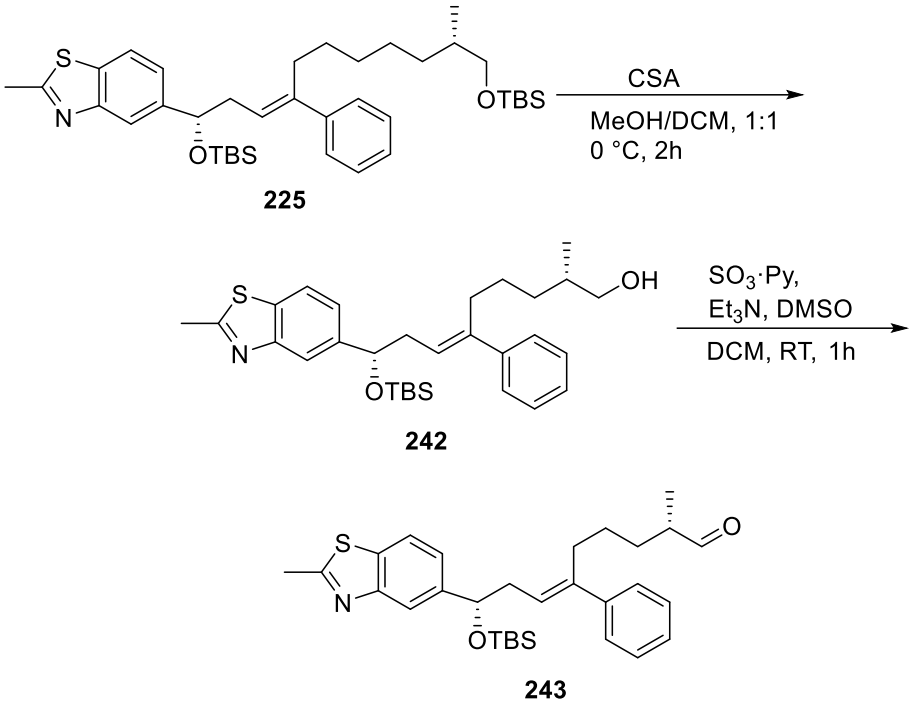
As part of our experimental study, we mixed 1 equiv ketone **222**, 1 equivalent sulfones **241** and 1.1 equivalents LiHMDS (1 mol/L in THF) at -78 °C. The mixture was stirred at this temperature for 3 h to provide the alkene **225** in 68% yield. Moreover, stereochemical analysis of the alkene product showed a *Z*/*E* selectivity ratio of 2:98. This high degree of selectivity suggests that, under the given reaction conditions, the *E*-isomer is formed more frequently than the *Z*-isomer. It should be noted that the *E*-olefin-attributed signals in the NMR spectra were absent when the amount of starting material was less than 500 mg. The predicted intermediates are shown in Scheme 75.



Scheme 75: The proposed mechanism of alkene synthesis via Julia-Kocienski olefination reaction.

As mentioned in section 3.4.2, we attempted the strategic coupling of the segment ketone **176** and aldehyde in the presence of dichlorophenylborane ($PhBCl_2$) and Hünig's base to reach the entired fragment. To mitigate the high reactivity of the terminal double bond due to electron transfer during the reaction, we firstly coupled segment thiazole **213** and ketone **222**. After successfully establishing the desired double bond configuration, we now intend to apply this methodology to couple compounds **225** and **176**. To facilitate this, we initially converted compound **225** into aldehyde **243** through a two-step process, as depicated in Scheme 76.

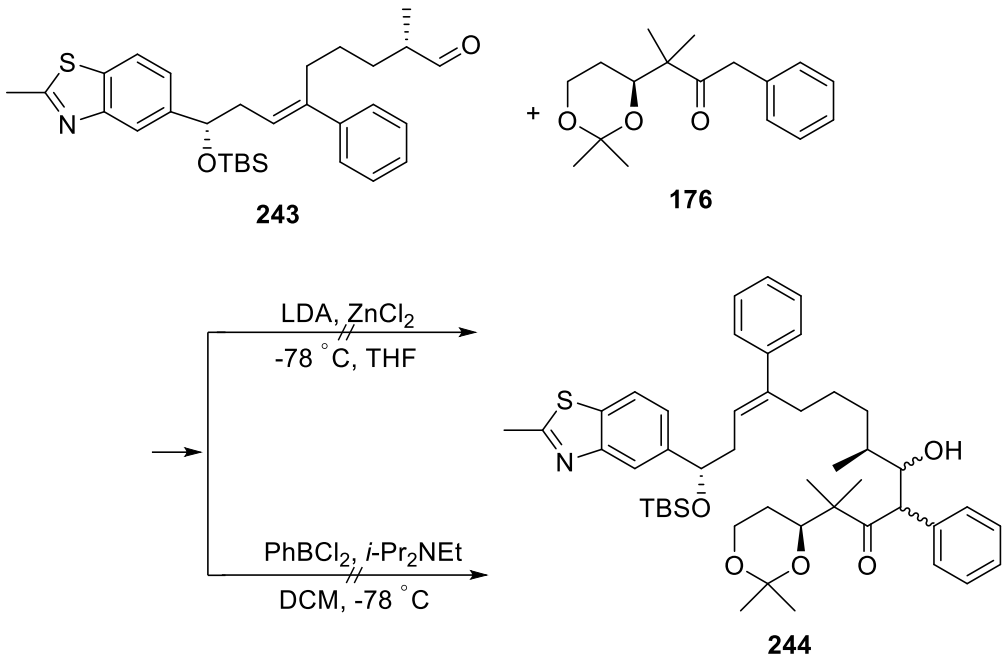
The olefin **225** was subjected to deprotection of the primary TBS-protecting group using mild acidic solution. The starting materials were dissolved in methanol and treated with acid for 2 h at 0 °C, facilitating the removal of the TBS group and isolation of the primary alcohol. This alcohol was then oxidized to the corresponding aldehyde **243**, which was used as the starting material in an aldol reaction.



Scheme 76: The synthesis of 243.

Based on previous work, we conducted experiments to evaluate two aldol reactions, as illustrated in Scheme 77. The first approach involved employing the classic methodology using LDA as a base and adding $ZnCl_2$ to facilitate the reaction. Specifically, ketone **176** was deprotonated by LDA at -78 °C, then the aldehyde **243** and $ZnCl_2$ were added to the reaction mixture. The reaction was maintained at this temperature for several hours to ensure sufficient time for the aldol condensation to occur. Despite following these conditions, TLC analysis revealed no significant changes in the reaction mixture, indicating a lack of product formation or observable progress. Furthermore, HPLC analysis of the reaction solution also failed to detect any product or intermediate, suggesting that the reaction did not proceed under these conditions.

In another aldol reaction, ketone **176**, dissolved in THF and cooled to -78 °C, was firstly reacted with $PhBCl_2$. Subsequently, a mixture of aldehyde and base was added. However, TLC analysis indicated that while the starting materials were consumed, only a limited number of new compounds were produced. NMR spectra of the isolated products revealed that the olefins were decomposed, meaning that the aldol reaction did not proceed as expected. Despite numerous attempts to establish the C6-C7 carbon-carbon bond, the aldol reaction was unsuccessful under these conditions due to interference from the side chain. Actually, we initially followed the method reported by Schinzer in the synthesis of epothilone B, where this transformation was achieved using an aldol reaction with a yield of 68% and high diastereoselectivity favoring the *anti* configuration (*anti:syn* = 10:1).[116] In that case, the side chain was a methyl group. Our results suggest that replacing the methyl group with a phenyl group significantly hinders the aldol coupling.



Scheme 77 Attempted synthesis of 244

Currently, we lack fragment **176** of the target molecule, which has resulted in the aldol reaction exhibiting no reactivity within our system. The intermediate **244** is pivotal, requiring only three additional steps to synthesize the final product, it is imperative to explore alternative methodologies for coupling **243** and **176**. Meanwhile, the reaction proceeded rather sluggishly, and if was not possible to obtain all the necessary analytical data, the relevant information and experimental procedure can be found in Schinzer's publication on the total synthesis of epothilone B. [116]

4 Summary and Outlook

4.1 Summary

In light of the pronounced antifungal and anticancer activities of epothilones, we embarked on a study to develop an effective and versatile method for the synthesis of a new epothilone analog. This decision is strongly supported by the substantial biological efficacy and its potential for advancing therapeutic applications. With the help of retrosynthetic analysis, we systematically deconstructed the 16-membered macrocyclic lactone—comprising a cis-epoxide moiety, seven stereocenters, and two geometric elements—into three distinct segments (**176**, **175** and **213**). These segments were subsequently synthesized.

To synthesis the first segment **176**, we followed the strategy of Schering AG. The process began with (*D*)-pantolactone as the starting material. After performing a reduction and subsequent lactone ring opening, the C2-C5 segment was successfully constructed, featuring the chiral center at C3 and the geminal dimethyl moiety at C4. Next, the C1 carbon was incorporated through a Wittig reaction, while the side chain at C6 was constructed using a Grignard reaction. It is noteworthy that the availability of various Grignard reagents provides a broad range of options for structural modification in order to study the biological activity by introducing different functional groups. Throughout the 12-step synthesis, the overall yield for this component exceeded 12%.

Furthermore, segment **175** was synthesized starting from cyclohexanone **204**, which was reacted with the Grignard reagent phenylmagnesium bromide to produce the corresponding alcohol**,** incorporating carbons C7 through C12. Subsequent elimination of alcohol led to the formation of 1-phenylcyclohexene **205**. Then oxidation and cleavage of the double bond yielded the keto-acid **203**. Following this, a Witting reaction was carried out with the desired keto-acid to produce olefin **202**. In parallel, Evans asymmetric alkylation was utilized to introduce the chiral center at carbon 8. Following the removal of the oxazolidinone auxiliary, segment **210** was obtained with a total yield of 17%. Olefin **210** was then oxidized to yield ketone **222**, followed by protection of the alcohol. Ketone **222** was employed as the reactant for the Julia-Kocienski olefination reaction.

The thiazole group **213** is derived from **156**. Regarding benzothiazole **156**, it was obtained in a one-pot reaction and then treated in a reduction-oxidation reaction sequence to achieve aldehyde **158**, which could be submitted to an Evans aldol addition of 3-acetyl-(4*S*, 5*R*)-4-methyl-5-phenyl-2-oxazolidinone to establish the stereogenic center at C15. Crystallization offered the possibility to an easier separation the diastereoisomers. The auxiliary was then deconstructed through the process of

reduction and produced thiazole segment **213**. It should be mentioned that based on our collaboration with Schering AG, we still had enough starting material, and therefore, did not need to focus on the synthesis thiazole fragment.

Following a number of trials, it was determined that the Julia olefination method is the most effective technique to connect segment **222** and segment **213**. 1-*tert*-Butyl-5-mercaptotetrazole should be used as the appropriate leaving group. To facilitate the Julia-Kocienski olefination reaction, we prepared compound **213**, which was subsequently iodinated to yield iodide **229**. In addition, 5-mercaptotetrazole **232** can be directly generated from a solution of NaN_3 and H_2O with a commercially available isothiocyanate in *i*-PrOH for 24 hours at 120 °C. Compound **233** was then coupled with iodide **229** to generate **236** and subsequently oxidized using 35% H_2O_2 and ammonium molybdate to yield sulfone **239**. Concurrently, olefin **210** was protected as a TBS group to provide **221**. This was followed by oxidations with $NaIO_4$ and catalytic OsO_4 to afford the ketone **222**. The Julia-Kocienski olefination can be effectively voted by treating with LiHMDS, achieving a very high *Z/E* selectivity of 2:98 of olefins **225**, in 68% yield.

For the central coupling, we envisioned a diastereoselective aldol reaction with ketone **176** and the α-chiral aldehyde **243**. However, various attempts with a high variety of conditions failed and no reaction was observed. The presence of the benzyl group diminished the reactivity of the α-carbonyl, preventing the aldol condensation from occurring under these conditions.

4.2 Outlook

Since the Julia-Kocienski olefination can be employed in our project, the synthesis of the entire molecule is almost completed. However, segment **176** could not be integrated with segment **243** in a one-pot aldol reaction or analogous methods. For the future, we propose to search other strategies to address this issue.

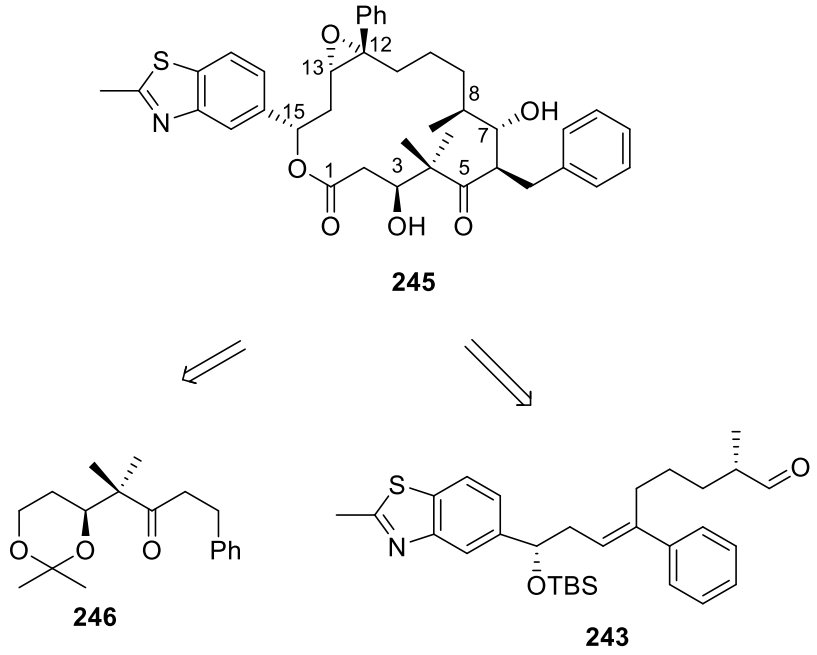
Conversely, with the advancements in computational chemistry, we are poised to further elucidate the mechanism of this reaction step. This involves conducting detailed computational analyses, including quantum chemical calculations and molecular dynamics simulations. These methods will enable us to rigorously evaluate the feasibility of the aldol reaction within this system, optimize reaction conditions, and identify potential reaction pathways. By analyzing the structures and energetics of the intermediates and transition states, we can gain insights into the mechanistic aspects and improve the likelihood of successful reaction outcomes.

In our retrosynthetic analysis, we initially favored the aldol reaction to synthesize the *syn*-aldol product. Alternatively, we plan to explore the use of effective catalysts to enhance the feasibility and efficiency of the reaction. Apart from organocatalysts or

Lewis acids and bases, metal catalysts and enzyme catalysts might also be considered. In particular, enzyme catalysts often offer a valuable alternative, potentially providing high selectivity and yield for the reaction.

Simultaneously, the use of catalysts could also assist in completing the Mukaiyama aldol reaction. We have confirmed that ketone **176** can be converted into the trimethylsilyl enolate **218**, and additional catalysts may further facilitate the aldol condensation, potentially yielding the *syn*-aldol product. This approach offers an alternative strategy for achieving our objective.

On the other side, based on the analysis of the relationship between biological activity and structure presented in section 1.4, we also prefer to synthesize another novel derivative **245**, which extends one carbon on the side chain at C6, as illustrated in Scheme 78. As observed, a range of processes can be applied in a new project. Additionally, this modification is expected to mitigate the influence of the benzyl group in the aldol reaction, providing a viable alternative.

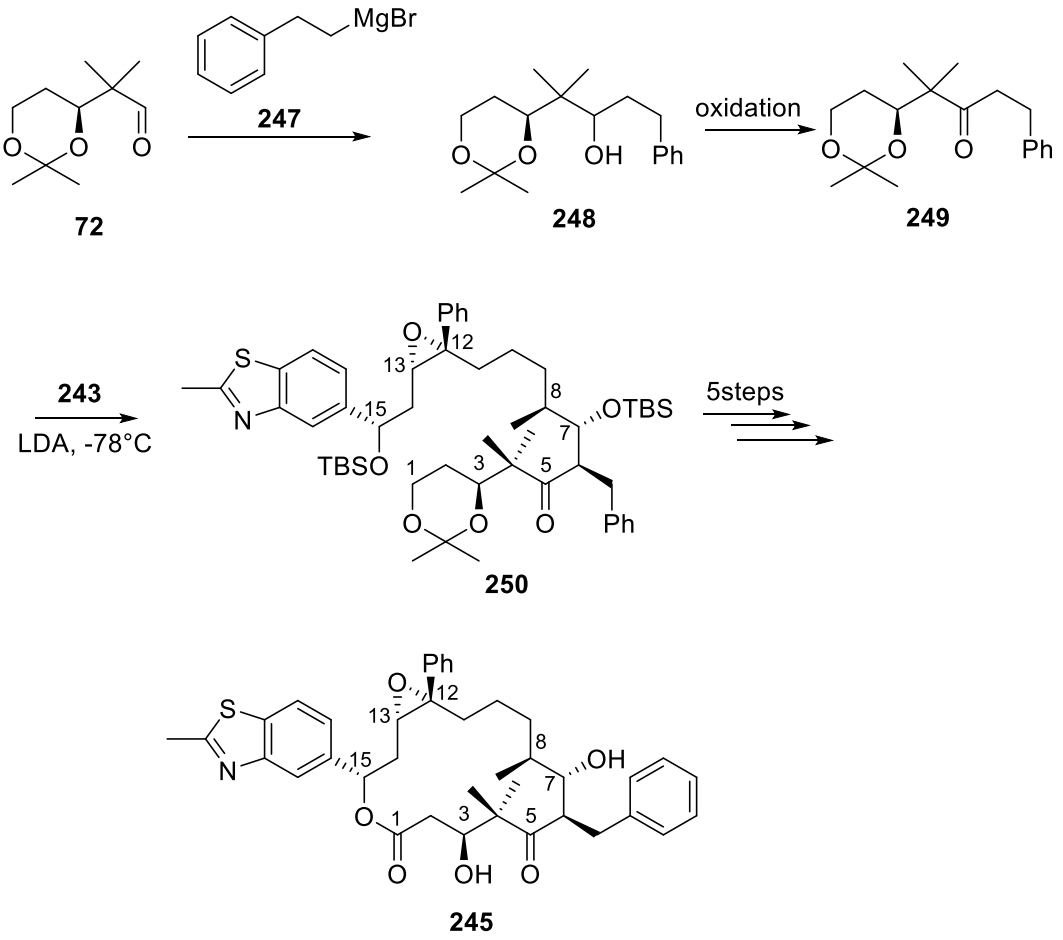


Scheme 78: Retrosynthetic analysis of new derivate epothilone 245.

In chapter 3.1.2, a synthetic approach is detailed that employs a Grignard reagent and subsequent reactions to produce a new derivative. Initially, the Grignard reagent is reacted directly with compound **72**, leading to the formation of a new side chain. This approach offers significant advantages, as the availability of various Grignard reagents provides multiple options for achieving diverse derivatives. In this reaction, compound **72** is coupled with **247** to produce intermediate **248**, which is then subjected to oxidation to afford compound **249**. Next, compound **243** undergoes an aldol reaction with **249**, yielding the desired derivative **250**.

The feasibility of the aldol reaction in this system is attributed to the limited impact of the phenyl group to the α-carbon, enabling direct reactivity of the aldehyde with the

carbon chain through established reactions. Subsequently, **250** is deprotected to remove the ketal at C1-C3. The TBS-protecting group at C15 is also removed. Next, the primary alcohol at C1 is oxidized to the desired acid, and the acyclic framework is closed via macrolactonization. These processes can result in the formation of the overarching molecular structure designed as compound **245** after removing protection groups.



Scheme 79: The strategy of synthesis of 245.

The synthesis of derivates can serve as a compelling validation of the efficacy of our environmentally benign and adaptable synthetic methodology, confirming both the versatility and utility of the established route. Furthermore, this endeavor not only substantiates the feasibility of our synthetic approach but also supplies essential raw materials, thereby facilitating opportunities for further biological investigations.

In addition, the exploration of derivative synthesis has exposed certain limitations within our initial synthetic strategy. Recognizing these constraints will influence future research efforts aimed at optimizing and advancing our synthetic methodologies. This recognition underscores the necessity of exploring and implementing novel approaches and catalytic systems that may enhance efficacy while effectively addressing the identified challenges. Awareness of these limitations necessitates a forward-thinking approach and encourages the pursuit of innovative strategies and catalysts to overcome current obstacles in our synthetic approaches. In this regard, the ongoing evolution of

synthetic methodologies is essential for ensuring the sustainable and successful progression of chemical synthesis

5 Experiments

5.1 Materials and Method

In experiments involving air- and moisture-sensitive substances, stringent protocols were employed to ensure that reactions were conducted in a controlled environment. This protective atmosphere was maintained using flame-dried glassware under a nitrogen atmosphere. A rigorous solvent selection process was followed to guarantee the complete absence of moisture in the experimental setup. Reactions were carried out exclusively in solvents that were both dry and pure. Tetrahydrofuran (THF) and diethyl ether were dried using sodium/benzophenone, while dichloromethane (DCM) was dried with calcium hydride, both in a nitrogen atmosphere, and freshly distilled prior to use. Additionally, other solvents used in the experimental procedures were either dried with molecular sieves or, where feasible, obtained in reagent-grade form, eliminating the need for further purification steps.

Commercially purchased high-quality chemicals were used as received, without any additional purification. Liquid reagents and solutions were introduced either through a septum or via a nitrogen counter-current using commercially available plastic injection syringes. Whenever possible, solid reagents were dissolved in an appropriate solvent before being added through a septum. Alternatively, when solubility permitted, solid reagents were added directly under a nitrogen counter-current. A systematic approach was adopted for handling air-sensitive solids, with all weighing and transfer operations conducted under controlled conditions in an argon atmosphere. This was facilitated by the use of a LABmaster 130 glove box (M. Braun GmbH), which provided a safe and inert environment.

Preparative column chromatography was carried out using Macherey-Nagel Silica Gel 60M (0.040–0.063 mm). If applicable, the column chromatography process was expedited by applying a slight excess pressure, approx. 0.2-0.4 bar. The solvent mixtures used are reported in volume ratios.

Analytical thin-layer chromatography (TLC) was performed using POLYGRAM SIL G/UV254 prefabricated plates with fluorescent indicators from Macherey-Nagel. Separated substances were visualized by UV irradiation at a wavelength of 254 nm or by staining with vanillin or potassium permanganate reagents, followed by heating with a heat gun.

Vanillin reagent: 8.6 g vanillin was dissolved in 200 mL ethanol and 2.5 mL concentrated sulfuric acid was added slowly.

Potassium permanganate reagent: 3 g potassium permanganate and 20 g potassium carbonate were dissolved in 300 mL water and 5 mL 5% sodium hydroxide solution was added.

The nomenclature was done according to the IUPAC rules using the software ChemBioDraw Ultra 21.0.0.

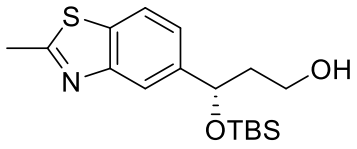
The ^{1}H- and ^{13}C- NMR spectra were measured either on Brucker AVIII 400 MHz or on Brucker AV Neo 600 MHz spectrometer. The used solvent is reported for each spectrum and the chemical shift (δ) are reported in [ppm] from tetramethylsilane, referenced to the solvent resonance resulting from incomplete deuteration ($CDCl_3$: ^{1}H-NMR = 7.26 ppm, ^{13}C-NMR = 77.16 ppm; CD_3OD: ^{1}H-NMR = 3.31 ppm, ^{13}C-NMR = 49 ppm; $(CD_3)_2CO$: ^{1}H-NMR = 2.05 ppm, ^{13}C-NMR = 29.84 ppm, 206.26 ppm). The signal multiplicity is abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, ddt = doublet of doublet of triplet, dt = doublet of triplet, br = broad signal.

The high-resolution mass spectra (HRMS) were measured on Water Xevo G2 TOF spectrometer, using ionization (ESI) technique.

The IR-spectra were measured on Vertex 70V FT-IR spectrometer, using attenuated total reflection (ATR) technique. The position of the absorption bands is given in wavenumbers (ṽ) [cm^{-1}]. The relative intensity of the bands is abbreviated as follows: w = weak, m = medium, s = strong, br = broad signal.

The specific optical rotations were measured on an Anton Paar MCP150 polarimeter at 589 nm and at a concentration (c) in [g/100mL].

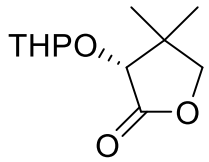
The thiazole segment used in this study was derived from leftover materials produced during a collaborative project with Schering AG. Detailed information regarding its synthesis has been previously published.[67] Prior to its use, the quality of the thiazole segment was verified through ^{1}H-NMR spectra to ensure it met the necessary standards for subsequent experiments.



(*S*)-3-((tert-butyldimethylsilyl) oxy)-3-(2-methylbenzo[d]thiazol-5-yl) propan-1-ol (213)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.41 (dd, *J* = 8.3, 1.6 Hz, 1H), 5.10 (dd, *J* = 6.8, 4.9 Hz, 1H), 3.80 – 3.64 (m, 2H), 2.91 (s, 3H), 1.98 (dtd, *J* = 5.9, 4.9, 2.7 Hz, 2H), 0.91 (s, 9H), 0.07 (s, 3H), -0.14 (s, 3H).

Synthesis of ketone segment:



(3*R*)-4,4-dimethyl-3-((tetrahydro-2*H*-pyran-2-yl) oxy) dihydrofuran-2(3*H*)-one (189)

To a solution of *D*-(-)-pantolactone (10 mmol, 1.3 g) in 10 mL DCM was added 3,4-dihydro-2*H*-pyran (18 mmol, 1.5 g, 1.64 mL) and pyridinium *p*-toluenesulfonate (0.2 mmol, 0.05 g), the mixture was stirred overnight at room temperature. The solution was added to a sat. aq solution of $NaHCO_3$ and extracted with DCM. The organic layers were dried over Na_2SO_4 and concentrated in vacuum to afford lactone (9.9 mmol, 2.14 g) as colorless oil. The crude tetrahydropyranyl isomers were used without purification and the yield can reach max. 100%.

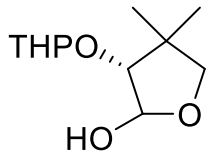
1*H* NMR (less polar tetrahydropyranyl isomer, 400 MHz, $CDCl_3$) δ 5.19 – 5.13 (m, 1H), 4.14 (s, 1H), 4.00 (d, J = 8.9 Hz, 1H), 3.91 (d, J = 8.7 Hz, 1H), 3.86-3.82 (m, 1H), 3.55 (dtd, J = 11.2, 4.4, 1.7 Hz, 1H), 1.85 – 1.68 (m, 3H), 1.65 – 1.49 (m, 3H), 1.21 (s, 3H), 1.13 (s, 3H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 175.76, 97.35, 77.42, 62.35, 40.22, 30.27, 25.48, 23.40, 19.63, 19.05.

^{1}*H* NMR (more polar tetrahydropyranyl isomer, 400 MHz, $CDCl_3$) δ 4.84 (t, *J* = 3.0 Hz, 1H), 4.23 – 4.15 (m, 2H), 3.96 (d, *J* = 8.8 Hz, 1H), 3.88 (dd, *J* = 8.9, 0.7 Hz, 1H), 3.53 (dddd, *J* = 11.3, 4.5, 3.5, 1.6 Hz, 1H), 1.95 – 1.85 (m, 1H), 1.73 (ddd, *J* = 9.4, 4.1, 3.1 Hz, 2H), 1.65 – 1.50 (m, 3H), 1.19 (d, *J* = 1.1 Hz, 3H), 1.09 (s, 3H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 174.99, 98.46, 78.28, 61.65, 40.61, 30.16, 25.33, 23.83, 19.61, 18.28.

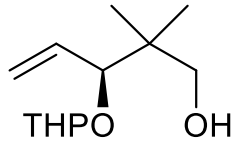
HRMS (ESI) (m/z) $[C_{11}H_{19}O_4]^+ = [M+H]^+$: calcd. 215.1283, found 215.1294.



(3*R*)-4,4-dimethyl-3-((tetrahydro-2*H*-pyran-2-yl) oxy) dihydrofuran-2-ol (146)

To a solution of lactone isomers (4.7 mmol, 1g) in 5 mL toluene was added DABAL-H (5.6 mmol, 1M in hexane) at -78 °C dropwise over 2 h. After stirrering at -78 °C for another 3 h, a mixture of water (3 mL) and *i*-PrOH (1.5 mL) was added slowly to the solution. After removing the cooling bath, the solution was stirred at room temperature until a fine crystalline precipitate formed. The precipitate was removed by the filtration and the filtrate was concentrated in vacuo to yield **146** (0.9 g, 4.14 mmol, 88%) as colorless oil. The product of this step was directly used for next reaction without further purification.

HRMS (ESI) (m/z) $[C_{11}H_{21}O_4]^+ = [M+H]^+$: calcd. 217.1440, found 217.1446.



(3*R*)-2,2-dimethyl-3-((tetrahydro-2*H*-pyran-2-yl) oxy) pent-4-en-1-ol (147)

A mixture of methyltriphenylphosphonium bromide (8.8 mmol, 3.15 g) and potassium *tert*-butoxide (16 mmol, 2 g) was dissolved in 5 mL THF. The solution was stirred at room temperature for 1h. Then a solution of **146** (3.25 mmol, 0.7 g) in THF (2 mL) was added and the mixture stirred at 23 °C overnight. The solvent was removed in vacuum and sat. aqueous $NaHCO_3$ and DCM were added until all solids were dissolved. After separation of the organic layer, the water phase was extracted 2 times with DCM. Then the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography (Pentane/diethyl ether, 4/1) to give the tetrahydropyranyl ether isomers **147** as colorless oil. (3.63 g, 1.85 mmol, 57%).

^{1}*H* NMR (less polar, 600 MHz, $CDCl_3$) δ 5.74 (dddt, J = 18.7, 10.3, 7.4, 1.4 Hz, 1H), 5.25 (dtt, J = 10.4, 2.3, 1.0 Hz, 1H), 5.22 – 5.17 (m, 1H), 4.44 (dq, J = 4.5, 2.1 Hz, 1H), 4.00 (dp, J = 7.5, 1.2 Hz, 1H), 3.94 (dtd, J = 11.5, 3.5, 1.7 Hz, 1H), 3.68 (dd, J = 11.1, 2.5 Hz, 1H), 3.51 – 3.44 (m, 1H), 3.18 (dt, J = 11.1, 1.5 Hz, 1H), 1.83 – 1.76 (m, 3H), 1.56 – 1.45 (m, 3H), 0.93 (dt, J = 8.9, 1.8 Hz, 3H), 0.78 (t, J = 1.5 Hz, 3H).

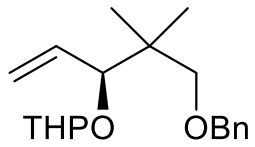
$[\alpha]_D^{20}$ = 79.0° (c=0.3 g/100mL in $CHCl_3$)

^1H NMR (more polar, 600 MHz, $CDCl_3$) δ 5.95 – 5.87 (m, 1H), 5.22 – 5.17 (m, 2H), 4.66 (dt, J = 5.1, 2.5 Hz, 1H), 3.94 (dtd, J = 11.5, 3.5, 1.7 Hz, 1H), 3.91 – 3.87 (m, 1H), 3.84 (dq, J = 8.1, 1.0 Hz, 1H), 3.58 (ddd, J = 10.9, 3.5, 1.3 Hz, 1H), 3.30 (ddd, J = 10.9, 2.7, 1.1 Hz, 1H), 3.18 (dt, J = 11.1, 1.5 Hz, 1H), 1.74 – 1.67 (m, 3H), 1.56 – 1.45 (m, 12H), 0.93 (dt, J = 8.9, 1.8 Hz, 3H), 0.84 (t, J = 1.4 Hz, 3H).

$[\alpha]_D^{20}$ = -86.7° (c=0.22 g/100mL in $CHCl_3$)

^{13}C NMR (151 MHz, $CDCl_3$) δ 136.65, 134.89, 118.71, 116.47, 100.25, 97.89, 80.98, 79.25, 70.32, 64.77, 63.37, 38.77, 30.85, 25.35, 22.74, 21.18, 20.04, 19.00.

HRMS (ESI) (m/z) $[C_{12}H_{23}O_3]^+ = [M+H]^+$: calcd. 215.1467, found 215.1456.



2-((5-(benzyloxy)-4,4-dimethylpent-1-en-3-yl) oxy) tetrahydro-2*H*-pyran (148)

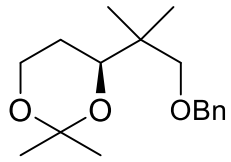
To a solution of potassium *tert*-butoxide (4.2 mmol, 0.47 g) in 3 mL THF was added alcohol **147** (2 mmol, 0.43 g) in 1 mL THF over 1 h. The mixture was stirred for another 1 h, and benzyl bromide (2.2 mmol, 0.26 mL) was added over a period of 20 min. The mixture was stirred at room temperature overnight, sat. NH_4Cl solution and water were added (5 mL) and extracted with EtOAc. The organic layers were concentrated in vacuo and the residue filtered over silica gel with a mixture of pentane-diethyl ether (10:1) to give olefin **148** (0.55 g, 1.82 mmol, 91%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 4H), 7.29 – 7.24 (m, 1H), 5.89(ddd, *J* = 17.3, 10.4, 7.9 Hz, 0.2H), 5.67 (ddd, *J* = 17.2, 10.4, 8.3 Hz, 0.8H), 5.28 – 5.14 (m, 2H), 4.67 (t, *J* = 3.3 Hz, 0.8H), 4.59 (dd, *J* = 4.7, 2.7 Hz, 0.2H), 4.55 – 4.45 (m, 2H), 4.03 (dt, *J* = 8.3, 0.8 Hz, 1H), 3.95 – 3.82 (m, 1H), 3.49 – 3.42 (m, 1H), 3.36 (dd, *J* = 13.7, 8.6 Hz, 1H), 3.26 (d, *J* = 8.6 Hz, 0.8H), 3.13 (d, *J* = 8.6 Hz, 0.2H), 1.80 (dtd, *J* = 14.7, 7.9, 3.7 Hz, 1H), 1.70 – 1.61 (m, 1H), 1.59 – 1.45 (m, 4H), 1.00 (s, 3H), 0.92 (d, *J* =

2.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.09, 134.75, 133.18, 132.95, 130.70, 129.73, 129.69, 129.64, 128.58, 128.56, 128.50, 120.20, 117.23, 100.31, 94.24, 80.25, 70.76, 63.10, 61.84, 38.21, 30.75, 25.74, 22.00, 20.59, 19.25.

HRMS (ESI) (m/z) $[C_{19}H_{28}O_3Na]^+ = [M+Na]^+$: calcd. 327.1936, found 327.1947.



(*S*)-4-(1-(benzyloxy)-2-methylpropan-2-yl)-2,2-dimethyl-1,3-diol (150)

To a solution of BH_3•SMe_2 (6 mmol, 0.57 mL) in dry Et_2O (20 mL) was added cyclohexene (10 mmol, 1 mL) at 0 °C. After the mixture was stirred at that temperature for 30 min, the temperature was increased to room temperature and stirred for another 1h resulting in the formation of a cloudy white suspension. Olefin **148** (2 mmol, 0.6 g) dissolved in 3 mL of Et_2O was added to the mixture once it had been cooled down to 0 °C again. After removal of the cooling bath and stirring overnight, NaOH (3 M, 16 mL) and H_2O_2 (35%, 6.8 mL) were added slowly at 0 °C, and the solution was stirred for another 4 h. Half-sat. aqueous $Na_2S_2O_3$ (60 mL) was added to quench this reaction. The organic phase was separated and the aqueous phase was extracted with Et_2O, then the combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (Pentane/diethyl ether, 5/1) to give the alcohol (1.85 mmol, 0.4 g, 93%) as colorless oil.

The alcohol (1.2 mmol, 0.38 g) was dissolved in 35 ml of a solvent mixture (AcOH/THF/H_2O, 4:2:1). The mixture was heated to 45 °C for 3.5 h, and then the solvents were removed to give (*S*)-5-(benzyloxy)-4,4-dimethylpentane-1,3-diol as colorless oil.

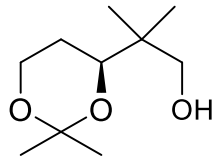
To a solution of diol in DCM (10 mL) were added 2,2-dimethoxypropane (11.2 mmol, 1.4 mL) and (±)-camphor-10-sulfonic acid (0.2 mmol, 0.05 g). The mixture was stirred at room temperature overnight, then poured into sat. $NaHCO_3$ and extracted with DCM. The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography

(pentane/ ether, 10:1) to afford **150** (0.8 mmol, 0.22 g, 63%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 4H), 7.22 – 7.18 (m, 1H), 4.42 (d, J = 1.1 Hz, 2H), 3.86 (td, J = 11.9, 2.9 Hz, 1H), 3.79 – 3.75 (m, 2H), 3.26 (d, J = 8.7 Hz, 1H), 3.08 (d, J = 8.7 Hz, 1H), 1.64 – 1.55 (m, 1H), 1.34 (s, 3H), 1.27 (s, 3H), 1.25 – 1.20 (m, 1H), 0.82 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 139.14, 128.65, 128.37, 127.73, 127.46, 127.44, 98.31, 80.27, 76.54, 73.38, 60.46, 38.09, 31.06, 25.35, 22.82, 20.01, 19.40.

HRMS (ESI) (m/z) $[C_{17}H_{27}O_3]^+ = [M+H]^+$: calcd. 279.1960, found 279.1991.

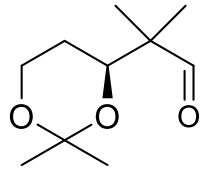


(*S*)-2-(2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpropan-1-ol (191)

To a solution of **150** (2.4 mmol, 0.66 g) in EtOH (10 mL) was added Pd/C (0.09 g, 10%) and stirred under a H_2 atmosphere at 23 °C for 2 h until the starting material has disappeared indicated by TLC. DCM was added, the mixture was filtered through celite to remove the catalyst and the filtrate was concentrated in vacuo to give (*S*)-2-(2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpropan-1-ol **191** (1.59 mmol, 0.3 g, 66%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 – 3.73 (m, 3H), 3.64 (d, *J* = 11.4 Hz, 1H), 3.29 (d, *J* = 11.5 Hz, 1H), 2.93 (s, 3H), 1.66 (tdd, *J* = 8.5, 4.5, 2.3 Hz, 2H), 1.45 (d, *J* = 2.1 Hz, 3H), 1.40 (s, 3H), 0.91 – 0.88 (m, 3H), 0.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 98.77, 80.69, 78.18, 72.57, 72.10, 60.24, 38.28, 31.21, 25.67, 22.53, 21.75, 19.16, 18.39.

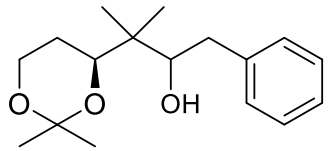


(*S*)-2-(2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpropanal (72)

To a solution of (*S*)-2-(2,2-dimethyl-1,3-dioxan-4-yl)-2-methylpropan-1-ol (2 mmol, 0.38 g) in DCM (5 mL) was added Et_3N (8 mmol, 1.2 mL) and DMSO (1.2 mL). The mixture was cooled to 0 °C, then the required amount of SO_3•pyridine complex (4 mmol, 0.64 g) was added gradually. The solution was stirred at 0 °C for 2 h, purred into sat. NH_4Cl 10 mL and extracted with Et_2O, the organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentan/ diethyl ether, 2:1) to give aldehyde **72** (1.8 mmol, 0.39 g, 90%).

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 3.97 (ddd, *J* = 14.7, 11.9, 2.7 Hz, 2H), 3.88 (dd, *J* = 5.5, 1.9 Hz, 0.6H), 3.85 (dd, *J* = 5.5, 1.9 Hz, 0.4H), 1.68 (dtd, *J* = 12.9, 12.0, 5.5 Hz, 1H), 1.43 (d, *J* = 0.8 Hz, 3H), 1.33 (d, *J* = 0.7 Hz, 3H), 1.28 – 1.24 (m, 1H), 1.02 (s, 3H), 0.87 (s, 3H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 206.32, 98.61, 73.12, 59.94, 49.03, 31.06, 25.43, 22.48, 19.13, 18.81.

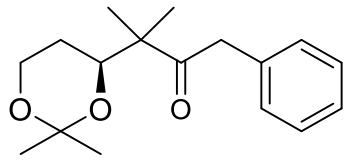


(4*S*)-4-(2-methyl-3(*RS*)-hydroxybut-2-yl)-2,2-dimethyl [1,3] dioxane (190)

To a solution of aldehyde **72** (1.9 mmol, 0.54 g) in dry Et_2O (2 mL) was added a solution of benzylmagnesium bromide (2.85 mmol, 3 mL, 0.9 M in toluene) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. The mixture was poured into sat. NH_4Cl solution and extracted with EtOAc. The organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude alcohols (4*S*)-4-(2-methyl-3(*RS*)hydroxybut-2-yl)-2,2-dimethyl [1,3] dioxane **190**. The data relates to the mixture of isomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.18 (m, 10H), 4.01 – 3.85 (m, 4H), 3.79 (dd, J = 10.4, 2.1 Hz, 1H), 3.74 (dd, J = 10.5, 2.2 Hz, 1H), 3.48 (q, J = 7.0 Hz, 1H), 2.88 (dd, J = 13.4, 2.3 Hz, 1H), 2.81 (dd, J = 13.6, 2.2 Hz, 1H), 2.55 (ddd, J = 16.6, 13.5, 10.5 Hz, 2H), 1.82 (ddtd, J = 29.1, 12.9, 11.9, 5.5 Hz, 2H), 1.58 – 1.49 (m, 2H), 1.47 (d, J = 2.0 Hz, 6H), 1.39 – 1.35 (m, 6H), 1.03 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.88 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.50, 140.23, 130.75, 129.57, 129.47, 129.40, 129.19, 128.90, 128.54, 128.43, 128.26, 126.30, 126.16, 98.87, 98.57, 80.07, 78.18, 60.39, 60.35, 38.57, 38.28, 29.68, 25.60, 25.33, 21.25, 20.53, 19.39, 19.09.



(4*S*)-4-(2-Methyl-3-oxo-4-phenylbut-2-yl)-2,2-dimethyl [1,3] dioxane (176)

To a solution of (4*S*)-4-(2-methyl-3(*RS*)-hydroxybut-2-yl)-2,2-dimethyl [1,3] dioxane **189** in DCM (10 mL) was added Dess–Martin periodinane (1.27 g, 3 mmol) and $NaHCO_3$ (0.5 g, 6 mmol) in portions. The solution was stirred at room temperature overnight, poured into water 10 mL and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane/ diethyl ether, 4:1) to give (4S)-4-(2-Methyl-3-oxo-4-phenylbut-2-yl)-2,2-dimethyl [1,3] dioxane **176** as colorless oil (1.3 mmol, 0.36 g, 83%).

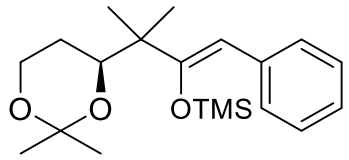
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 – 7.29 (m, 2H), 7.26 – 7.23 (m, 1H), 7.16 – 7.12 (m, 2H), 4.07 (dd, *J* = 11.8, 2.5 Hz, 1H), 3.96 (td, *J* = 11.9, 2.8 Hz, 1H), 3.89 – 3.86 (m, 1H), 3.85 (s, 2H), 1.65 (dtd, *J* = 12.9, 12.0, 5.4 Hz, 1H), 1.44 – 1.42 (m, 3H), 1.38 (d, *J* = 0.8 Hz, 2H), 1.38 – 1.34 (m, 1H), 1.20 (s, 2H), 1.15 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 212.27, 135.13, 129.84, 129.70, 128.76, 128.45, 128.41, 127.10, 126.70, 98.63, 74.53, 60.12, 45.81, 29.95, 29.69, 25.45, 21.68, 21.41, 19.29, 19.17.

HRMS (ESI) (m/z) $[C_{17}H_{25}O_3]^+ = [M+H]^+$: calcd. 277.1804, found 277.1827.

IR (ATR): $\tilde{\nu}$ = 3064 (w), 3031 (w), 2971 (m), 2936 (m), 2866 (m), 1707(s), 1602 (w), 1496 (m), 1454 (m), 1383 (m), 1311 (w), 1253 (w), 1215 (w), 1158 (w), 1114 (s), 1097 (s), 1023 (s), 998 (s), 952 (m), 752 (m), 730 (s), 697 (s).

$[\alpha]_D^{20}$ = 27.222° (c=0.9 g/100mL in $CHCl_3$).



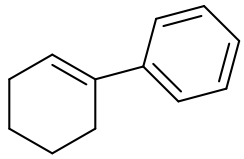
***(S, Z)* -((3-(2,2-dimethyl-1,3-dioxan-4-yl)-3-methyl-1-phenylbut-1-en-2-yl) oxy) trimethylsilane (218)**

Diisopropylamine (0.86 mL, 0.6 g, 6 mmol) was dissolved in dry THF (5 mL). Then *n*BuLi (3 mL, 2 mol/L in hexane, 6 mmol) was added at 0 °C and the mixture was stirred for 0.5 h at 0 °C. **176** (1.4 g, 5 mmol) in dry THF (2 mL) was slowly added to LDA solution at -78 °C. The reaction was stirred at -78 °C for 20 min followed by the addition of TMSCl (0.76 mL, 0.65 g, 6 mmol). The temperature was increased to room temperature and the mixture was stirred overnight. Ice water was employed for quenching the reaction, followed by extraction with pentane. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane/ diethyl ether, 10:1) to give **218** (3.3 mmol, 1.15 g) in 60% yield.

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.24 (m, 6H), 5.68 (s, 1H), 3.96 (ddd, *J* = 11.6, 4.4, 2.7 Hz, 2H), 3.87 (ddd, *J* = 11.6, 5.4, 1.9 Hz, 1H), 1.58 (s, 1H), 1.46 (d, *J* = 0.7 Hz, 3H), 1.39 – 1.37 (m, 3H), 1.30 (s, 1H), 1.14 (s, 3H), 1.09 (s, 3H), -0.03 (s, 9H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 157.37, 137.48, 129.44, 129.18, 128.37, 128.12, 125.85, 125.44, 107.69, 98.58, 73.19, 60.56, 43.68, 30.07, 26.07, 20.22, 19.38, 1.22.

Synthesis of the aldehyde segment,

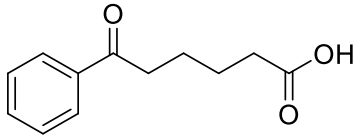


2,3,4,5-tetrahydro-1,1-biphenyl (205)

To a solution of cyclohexanone **204** (100 mmol, 10.4 mL) in Et_2O (400 mL) was added phenyl magnesium bromide dissolved in Et_2O (150 mmol, 50 mL) at -78 °C. After 1 h stirring at -78 °C, the mixture was warmed to room temperature and 1 M HCl was added until the precipitation has disappeared. Then ethyl acetate was added, the organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuo. The residue was 1-phenylcyclohexan-1-ol. Without further purification, the alcohol was directly dissolved in acetonitrile (100 mL), trifluoroacetic acid was added dropwise (100 mmol, 7.4 mL) at 0 °C, and the mixture was stirred overnight. After dilution with ethyl acetate, sat. $NaHCO_3$ was added. The organic layer was separated, washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane/ 0.5% ether) to give 2,3,4,5-tetrahydro-1,1'-biphenyl **205** (63 mmol, 9.97 g, 63%) as colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.26 (ddd, J = 7.8, 6.8, 1.2 Hz, 2H), 7.21 – 7.14 (m, 1H), 6.08 (tt, J = 3.9, 1.7 Hz, 1H), 2.37 (dddd, J = 8.7, 6.2, 2.5, 1.7 Hz, 2H), 2.21 – 2.12 (m, 2H), 1.79 – 1.69 (m, 2H), 1.62 (qd, J = 6.1, 2.7 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.81, 136.69, 128.31, 126.63, 125.05, 124.92, 27.51, 26.01, 23.19, 22.29.



6-oxo-6-phenylhexanoic acid (203)

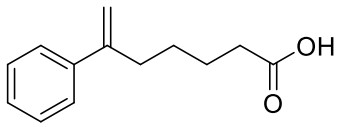
2,3,4,5-tetrahydro-1,1'-biphenyl **205** (1 mmol, 0.16 g), 4-iodobenzoic acid (0.05 mmol, 0.012 g) and Oxone (2 mmol, 0.61 g) were mixed in a solution of water and acetonitrile (20 mL, 1:1/v:v). The mixture was heated to 60 °C for 3 h. After cooling to room temperature, the solution was filtered to remove solids. The combined organic layers

were dried over Na_2SO_4 and concentrated in vacuo. 6-Oxo-6-phenylhexanoic acid **203** was afforded as white solid without purification. (0.97 mmol, 0.2 g, 97%).

^1H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 2H), 7.49 – 7.43 (m, 1H), 7.42 – 7.32 (m, 2H), 7.29 – 7.23 (m, 2H), 2.90 (t, *J* = 7.0 Hz, 2H), 2.31 (t, *J* = 7.2 Hz, 2H), 1.81 – 1.48 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.00, 179.07, 136.97, 133.18, 128.60, 128.15, 38.20, 33.90, 24.41, 23.64.

HRMS (ESI) (m/z) $[C_{12}H_{15}O_3]^+ = [M+H]^+$: calcd. 207.1021, found 207.1021.



6-phenylhept-6-enoic acid (202)

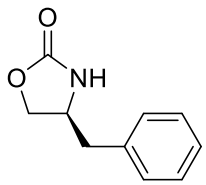
To a suspension of methyltriphenylphosphonium bromide (1.3 mmol, 0.46 g) in THF (5 mL) was added potassium *tert*-butoxide (2.6 mmol, 0.3 g). The mixture was stirred at room temperature for 0.5 h. Then 6-oxo-6-phenylhexanoic acid **203** (1 mmol, 0.21 g) was added and reaction was stirred overnight. The solvent was removed in vacuo. The residue diluted with dichloromethane (3 mL) and aqueous NaOH (1 M, 3 mL). The aqueous layer was separated, washed with dichloromethane and acidified to pH1 with concentrated HCl. Then the aqueous layer was extracted 3 times with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. 6-phenylhept-6-enoic acid **202** was obtained as gentle yellow solid (0.63 mmol, 1.26 g, 62%) after flash chromatography (Hexane/Ethyl acetate 5:1).

^1H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 7.18 (td, *J* = 7.2, 1.3 Hz, 2H), 7.15 – 7.10 (m, 1H), 5.14 (d, *J* = 1.7 Hz, 1H), 4.93 – 4.92 (m, 1H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.23 – 2.17 (m, 2H), 1.58 – 1.49 (m, 2H), 1.37 (ddd, *J* = 15.3, 8.8, 6.7 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 180.26, 180.25, 148.12, 141.22, 128.43, 127.50, 126.24, 112.69, 35.05, 33.98, 27.63, 24.37.

HRMS (ESI) (m/z) $[C_{13}H_{17}O_2]^+ = [M+H]^+$: calcd. 205.1229, found 205.1226.

Synthesis of the oxazolidinone auxiliary:



(*S*)-4-benzyloxazolidin-2-one (194)

Method A: *L*-phenylalanine **196** (91 mmol, 15 g) and sodium borohydride (209 mmol, 6.7 g) were dissolved in THF (300 ml). Then the mixture was cooled to -78 °C and iodine (91 mmol, 22 g) was added gradually. After stirring at that temperature for 15 min, the solution was refluxed for 1 h. Methanol was added to the mixture until it turned clear (ca. 200 mL), and the solvents were removed in vacuum. Next, 2 M NaOH (300 mL) was added and stirred overnight. The slurry was diluted with 350 mL DCM, then the aqueous layer was separated, extracted two times with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated in vacuum. Without additional purification, 12.7 g of white crystalline material **197** was given. Yield 92%.

To a solution of the crude (*S*)-2-amino-3-phenylpropan-1-ol **197** (10 mmol, 1.51 g) in pyridine (15 mL) was added trichloroacetyl chloride (1.3 mL, 11 mmol) at 0 °C. The mixture was gradually warmed to room temperature. After stirring overnight, the reaction was quenched by addition of brine and extracted with DCM. The combined organic extracts were washed with 1 M HCl and water, dried over Na_2SO_4, filtrated and then vacuum-evaporated. The crude product was purified by column chromatography on silica gel (Hexane/Ethyl acetate 4:1) to afford **198** as colorless oil.

To a suspension of **198** (2 g, 7 mmol) in EtOH (50 mL) was added K_2CO_3 (0.48 g, 3.5 mmol), and the mixture was heated at reflux for 2 h. After concentration under reduced pressure, the residue was partitioned between brine and DCM. The aqueous layer was separated and extracted with DCM. The combined organic extracts were dried over Na_2SO_4, filtrated, and evaporated under vacuum. The residue was purified by column chromatography (Hexane/Ethyl acetate 4:1) to afford **194** as pale yellow solid. The total yield is 48% from **196** (44 mmol, 7.74 g).

Method B: *L*-phenylalanine **196** (10 mmol, 1.65 g) was treated with 2 M methanolic

hydrochloric acid (2 M HCl in menthol, 2 mL) and stirred overnight. The solvent then removed in vacuum to give the corresponding methyl ester as hydrochloride salt. The crude amino acid ester **199** was dissolved in water (50 mL) and $NaHCO_3$ (3.8 g, 0.05 mmol) was added portion wise. Ethyl chloroformate (1 mL, 11 mmol) was added dropwise and the solution was vigorously stirred for 4h to give the *N*-ethoxycarbonylamino acid ester **200** as colorless crystalline solid.

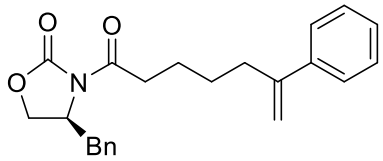
Calcium chloride (2.5 g, 0.02 mol) and $NaBH_4$ (1.7 g, 0.04 mol) were added to a solution of ester **200** (2.4 g, 0.01 mol) in ethanol (20 mL) and THF (10 mL) and the white suspension was stirred overnight. The mixture was then poured into aqueous citric acid (1 M, 40 mL). Extraction with ethyl acetate and washing with brine gave a viscous oil which was filtered through a silica gel plug to give the alcohol **201** as a colorless crystalline solid.

Alcohol **201** (1.7 g, 8 mmol) was dissolved in toluene (10 mL), K_2CO_3 (0.04 g, 0.3 mmol) was added and the mixture was heated under reflux for 3 h. The hot solution was filtrated and allowed to cool, the chiral oxazolidinone **194** was obtained as colorless prisms by filtration. Evaporation of the filtrate and recrystallization of the residue from toluene gave a second crop of crystals. (Total yield 68%)

^1H NMR (600 MHz, $CDCl_3$) δ 7.41 (td, J = 7.4, 1.6 Hz, 2H), 7.37 – 7.32 (m, 1H), 7.28 – 7.23 (m, 2H), 5.95 (dd, J = 51.9, 31.0 Hz, 1H), 4.51 (tdd, J = 8.5, 3.6, 2.0 Hz, 1H), 4.25 – 4.13 (m, 2H), 2.95 (tdd, J = 11.7, 9.8, 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.52, 136.05, 129.12, 129.10, 127.35, 69.71, 53.89, 41.53, 41.51.

HRMS (ESI) (m/z) $[C_{10}H_{12}O_2N]^+ = [M+H]^+$: calcd. 178.0868, found178.0850.



(*S*)-4-benzyl-3-(6-phenylhept-6-enoyl) oxazolidine-2-one (193)

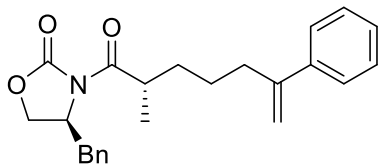
To a solution of 6-phenylhept-6-enoic acid **202** (1 mmol, 0.2 g) in 20 mL THF was added Et_3N (1.3 mmol, 0.18 mL) and PivCl (1.1 mmol, 0.14 mL) at -78 °C. Then the mixture was stirred at that temperature for 15 min, allowed to warm to 23 °C and stirred

for additional 1.5 h. The resulting mixture was added to a solution of (*S*)-4-benzyloxazolidin-2-one **194** (1.7 mmol, 0.35 g) in 5 mL THF which had been treated with *n*BuLi (1.7 mmol, 0.68 mL, 2.5 M in hexane) at -78 °C. After stirring at low temperature for 15 min, the temperature was increased to 23 °C and stirring continued overnight. Sat. aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (Hexane/EtOAc, 5:1) to afford the (*S*)-4-benzyl-3-(6-phenylhept-6-enoyl) oxazolidine-2-one **193** (0.6 mmol, 0.24 g, 61%) as white solid.

^{1}*H* NMR (600 MHz, $CDCl_3$) δ 7.41 (dt, *J* = 8.1, 1.4 Hz, 2H), 7.36 – 7.30 (m, 4H), 7.30 – 7.24 (m, 2H), 7.20 (d, *J* = 7.5 Hz, 2H), 5.28 (d, *J* = 1.6 Hz, 1H), 5.09 (t, *J* = 1.6 Hz, 1H), 4.65 (ddt, *J* = 10.7, 7.1, 3.2 Hz, 1H), 4.24 – 4.09 (m, 2H), 3.27 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.98 (ddd, *J* = 17.0, 8.1, 6.7 Hz, 1H), 2.89 (ddd, *J* = 17.0, 8.1, 6.9 Hz, 1H), 2.73 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.57 (td, *J* = 7.5, 1.3 Hz, 2H), 1.74 (dddd, *J* = 13.8, 8.1, 7.0, 3.1 Hz, 2H), 1.55 (p, *J* = 7.7 Hz, 2H).

^{13}*C* NMR (151 MHz, $CDCl_3$) δ 173.32, 153.57, 148.22, 141.32, 135.44, 129.59, 129.54, 129.08, 129.02, 128.41, 127.47, 126.27, 112.65, 66.29, 55.28, 41.84, 38.04, 35.48, 35.21, 27.67, 23.98.

HRMS (ESI) (m/z) $[C_{23}H_{26}O_3N]^+ = [M+H]^+$: calcd. 364.1913, found 364.1918.



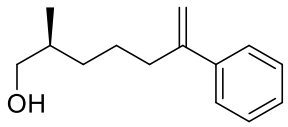
(*S*)-4-benzyl-3-((*S*)-2-methyl-6-phenylhept-6-enoyl) 98xazolidine-2-one (192)

A solution of oxazolidinone **193** (0.6 mmol, 0.24 g) in THF (2 mL) was slowly added to a solution of NaHMDS (0.66 mmol, 2 M in ether, 0.33 mL) at -78 °C. The mixture was stirred for 1 h at that temperature. A further three hours were spend stirring the mixture at -78 °C after addition of methyl iodide (3 mmol, 0.18 mL). The reaction was quenched by addition of saturated NH_4Cl solution, warmed to room temperature and extracted with ethyl acetate. The combined the organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography

(hexane/ethyl acetate 5:1) to obtain the alkylated amide **192** (0.48 mmol, 0.18 g, 80%) as a viscous, colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.11 (m, 10H), 5.21 (d, *J* = 1.6 Hz, 1H), 5.00 (q, *J* = 1.4 Hz, 1H), 4.61 – 4.51 (m, 1H), 4.11 – 4.04 (m, 2H), 3.73 – 3.58 (m, 1H), 3.18 (dt, *J* = 13.5, 4.1 Hz, 1H), 2.73 – 2.64 (m, 1H), 2.53 – 2.40 (m, 2H), 1.83 – 1.65 (m, 1H), 1.47 – 1.33 (m, 4H), 1.14 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 177.20, 153.14, 148.21, 141.27, 135.41, 129.57, 129.55, 129.03, 129.00, 128.38, 127.43, 126.21, 112.60, 66.11, 55.42, 41.67, 37.64, 35.33, 33.01, 25.84, 17.51.



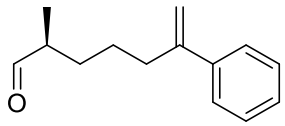
(*S*)-2-methyl-6-phenylhept-6-en-1-ol (210)

A solution of amide **192** (1 mmol, 0.4 g) in a mixture of water and THF (6 mL, 1:1/v:v) was treated at 0 °C with portions of sodium borohydride (4 mmol, 0.15 g) until TLC showed complete conversion of the starting material. The organic layer was separated and dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (pentane/ether 4:1) yielded (*S*)-2-methyl-6-phenylhept-6-en-1-ol **210** (0.92 mmol, 0.19 g, 92% as colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.29 – 7.22 (m, 2H), 7.22 – 7.17 (m, 1H), 5.20 (d, *J* = 1.5 Hz, 1H), 4.99 (q, *J* = 1.4 Hz, 1H), 3.41 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.33 (dd, *J* = 10.5, 6.5 Hz, 1H), 2.52 – 2.35 (m, 2H), 1.54 (dqd, *J* = 8.2, 6.7, 5.2 Hz, 1H), 1.48 – 1.43 (m, 1H), 1.37 (dddd, *J* = 19.7, 11.0, 9.7, 4.9 Hz, 2H), 1.08 (dddd, *J* = 13.0, 8.3, 7.0, 2.5 Hz, 1H), 0.82 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.68, 141.46, 128.39, 127.43, 126.24, 112.39, 68.41, 35.71, 35.68, 32.85, 25.70, 16.68.

$[\alpha]_D^{20}$=-0.696° (c=1.58 g/100mL in $CHCl_3$).

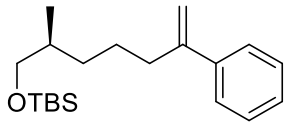


(*S*)-2-methyl-6-phenylhept-6-enal (175)

To a solution of alcohol **210** (1.5 mmol, 0.3 g) in 5 mL DCM were added Et_3N (6.2 mmol, 0.86 mL) and DMSO (0.86 mL). The mixture was cooled to 0 °C, and SO_3•pyridine complex (3 mmol, 0.49 g) was added gradually. The solution was stirred at 0 °C for 2 h, poured into sat. NH_4Cl (10 mL） and extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane/ diethyl ether, 4:1) to give aldehyde **175** (1.2 mmol, 2.48 g, 82%) as colorless oil.

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 9.51 (d, *J* = 1.9 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.29 – 7.23 (m, 2H), 7.23 – 7.18 (m, 1H), 5.21 (d, *J* = 1.4 Hz, 1H), 4.99 (q, *J* = 1.4 Hz, 1H), 2.53 – 2.41 (m, 2H), 2.25 (qd, *J* = 6.9, 1.9 Hz, 1H), 1.77 – 1.60 (m, 1H), 1.48 – 1.28 (m, 3H), 0.99 (d, *J* = 7.0 Hz, 3H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 205.25, 148.08, 141.15, 128.43, 127.53, 126.20, 112.75, 46.23, 35.35, 30.09, 25.55, 13.43.



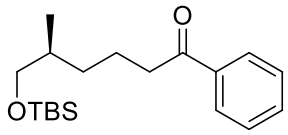
(*S*)-*tert*-butyldimethyl((2-methyl-6-phenylhept-6-en-1-yl) oxy) silane (221)

To a solution of **210** (0.41 g, 2 mmol) in DCM (20 mL) was added TBSCl (0.36 g, 4.8 mmol) and imidazole (0.16 g, 4.8 mmol) portion wise. The mixture was stirred at room temperature overnight. Then the reaction was quenched with water, the aqueous layer was separated, and extracted with DCM. The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography on silica gel (pentane/ diethyl ether, 4:1) to give (*S*)-*tert*-butyldimethyl ((2-methyl-6-phenylhept-6-en-1-yl) oxy) silane **221** (1.68 mmol, 0.53 g, 84%) as colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 2H), 7.31 – 7.19 (m, 3H), 5.22 (d, *J* = 1.6 Hz, 1H), 5.02 (q, *J* = 1.6 Hz, 1H), 3.41 – 3.26 (m, 3H), 2.49 – 2.40 (m, 2H), 1.59 – 1.34 (m, 4H), 1.28 – 1.20 (m, 1H), 1.10 – 1.01 (m, 1H), 0.86 (d, *J* = 0.8 Hz, 9H), 0.82 (dd, *J* = 6.7, 2.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.84, 141.60, 128.67, 128.37, 127.86, 127.38, 126.70, 126.26, 112.23, 68.49, 35.80, 35.74, 33.02, 26.11, 25.86, 25.82, 18.50, 16.86, -5.21, -5.24.

$[\alpha]_D^{20}$ = -1.917° (c=1.2 g/100mL in $CHCl_3$)



(*S*)-6-((tert-butyldimethyl) oxy) -5-methyl-1-phenylhexan-1-one (222)

To a solution of olefin **221** (0.16 g, 0.5 mmol) in THF (2.5 mL), water (0.6 mL) and *t*-butanol (0.16 mL) was added osmium tetroxide (31 µL, 0.005 mmol) and sodium periodate (0.21 g, 1 mmol). The mixture was heated to 33 °C. After 22 h, an extra amount of sodium periodate was added and stirring was continued for additional 3 h. After being poured into ethyl acetate, the organic layer was separated and washed with saturated $Na_2S_2O_3$, water, half-concentrated aq. NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography (pentane/ diethyl ether, 30:1). The ketone **222** (0.36 mmol, 1.15 g) was obtained with a yield of 67% as colorless oil.

^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 6H), 3.41 – 3.30 (m, 2H), 2.96 (dd, *J* = 5.4, 1.1 Hz, 1H), 2.74 (dd, *J* = 5.4, 1.0 Hz, 1H), 1.60 – 1.49 (m, 1H), 1.46 – 1.36 (m, 1H), 1.33 – 1.25 (m, 2H), 1.20 (d, *J* = 7.1 Hz, 1H), 0.88 (d, *J* = 2.7 Hz, 9H), 0.82 (dd, *J* = 6.7, 2.3 Hz, 3H).

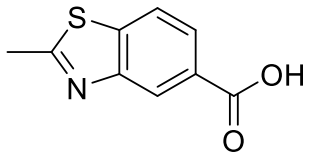
^{13}C NMR (101 MHz, $CDCl_3$) δ 201.16, 140.35, 140.31, 129.18, 128.43, 127.49, 126.14, 126.12, 68.42, 68.35, 35.78, 34.28, 26.10, 22.49, 22.45, 18.49, 16.80, 16.74, -5.23.

HRMS (ESI) (m/z) $[C_{18}H_{32}O_3SiNa]^+ = [M+Na]^+$: calcd. 331.2069, found 331.2067.

IR (ATR): $\tilde{\nu}$ = 3953 (m, frequency multiplication peak), 2895 (m), 2895 (w), 2855 (m), 1687 (m), 1598 (w), 1581 (w), 1463 (w), 1450 (w), 1388 (w), 1252 (m), 1203 (w), 1179 (w), 1146 (w), 1089 (s), 1040 (w), 1005 (w), 973 (w), 834 (s), 774 (m), 752 (m), 731 (w), 690 (m), 666 (m).

$[\alpha]_D^{20}$ = -5.882° (c=0.34 g/100mL in $CHCl_3$)

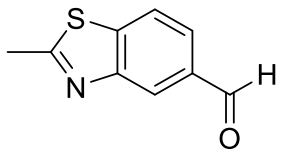
Synthesis of thiazole segment:



2-Methyl-5-benzothiazolcarboxylic acid (157)

3-Nitro-4-chloro-benzoic acid **156** (5 mmol, 1 g) and $Na_2S•H_2O$ (1.95 g, 15 mmol) were dissolved in water (5 mL), and the mixture was heated to 120 °C for 1 h. Then the brown mixture was cooled to 0 °C and Ac_2O (9 mL) was added dropwise, followed by dropwise addition of AcOH (5 mL). The temperature was increased to 23 °C and the mixture was stirred overnight. Then the reaction was distributed between water (10 mL) and EtOAc (20 mL) and stirred for another 30min. The precipitated sulfur was removed by filtration over celite. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. After addition of diisopropyl ether, a first crystalline batch of **157** (24.3 mg, max. 126 mmol, max. 25.4%) was obtained. The residue of the celite filtration was extracted with EtOAc. Solvents were removed and the residue was purified by the column chromatography (hexane/ ethyl acetate, 2:1). The acid **157** (2.6 mmol, 0.5 g) was obtained with a yield of 52% as yellow solid.

HRMS (ESI) (m/z) $[C_9H_8O_2SN]^+ = [M+H]^+$: calcd. 194.0276, found 194.0279, 194.0272.



2-Methylbenzothiazol-5-yl-carbaldehyde (158)

To a suspension of $LiAlH_4$ (0.19 g, 5 mmol) in THF (20 mL) was added the solution of acid **157** (0.19 g, 1 mmol) in THF (20 mL). After gas formation had ceased, the mixture was heated under reflux for 2 hours. After cooling to 23 °C, the mixture was poured into water, diluted with ethyl acetate, filtered through celite and the organic layer was separated. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The crude product was resolved in ethyl acetate, filtered through silica gel and concentrated in vacuo to give 2-Methyl-benzothiazol-5-yl-methanol (0.78 mmol, 0.14 g, 78%) as crude product which is used without purification in the next step.

^{1}*H* NMR (400 MHz, DMSO) δ 7.94 (d, *J* = 8.2 Hz, 1H), 7.84 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.34 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.62 (s, 2H), 2.78 (s, 3H).

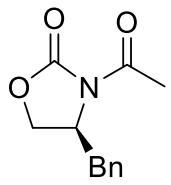
^{13}*C* NMR (101 MHz, DMSO) δ 167.14, 153.19, 140.99, 133.40, 123.62, 121.47, 119.56, 62.76, 19.82.

HRMS (ESI) (m/z) $[C_9H_{10}OSN]^+ = [M+H]^+$: calcd. 180.0483, found 180.0487.

To a solution of 2-Methyl-benzothiazol-5-yl-methanol (0.19 g, 1 mmol) in DCM (3 mL) and DMSO (0.6 mL) was added triethylamine (0.6 mL, 4 mmol). The solution was cooled to 10 °C, SO_3-pyridine (0.32 g, 2 mmol) was added in portions and the mixture stirred for 2 hours at 0 °C. The solution was poured into water and extracted with DCM. The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ ethyl acetate, 2:1). The aldehyde **158** (0.89 mmol, 0.16 g) was obtained as yellow oil with a yield of 89%.

^{1}*H* NMR (600 MHz, DMSO) δ 10.12 (d, *J* = 0.5 Hz, 1H), 8.43 (dd, *J* = 1.6, 0.6 Hz, 1H), 8.26 (dt, *J* = 8.3, 0.6 Hz, 1H), 7.90 (dd, *J* = 8.3, 1.5 Hz, 1H), 2.86 (s, 3H).

^{13}*C* NMR (101 MHz, DMSO) δ 192.82, 169.55, 153.01, 141.76, 134.63, 124.13, 123.92, 122.94, 19.95.



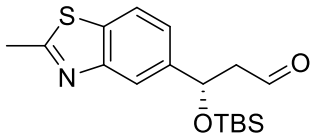
(4*S*,5*R*)- 4-Methyl-5-phenyl-3-acetyl-2-oxazolidinone (211)

A solution of (*S*)-4-benzyloxazolidin-2-one **194** (1.7 mmol, 0.35 g) in THF 5 mL was treated with *n*BuLi (1.7 mmol, 0.68 mL, 2.5 M in hexane) at -78 °C. After stirring at -78 °C, acetyl chloride was added at this temperature. After stirring for 15 min, the temperature was increased to 23 °C and the mixture was stirred overnight. Sat. aqueous $NaHCO_3$ was added. The aqueous layer was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (Hexane/EtOAc, 5:1) to afford **211** (0.33 g, 1.53 mmol, 90%) as yellow solid.

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 3H), 7.17 – 7.13 (m, 2H), 4.61 (ddt, *J* = 9.6, 7.4, 3.3 Hz, 1H), 4.17 – 4.09 (m, 2H), 3.25 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.72 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.50 (s, 3H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 170.42, 153.77, 135.35, 129.55, 129.10, 127.50, 66.23, 55.11, 37.96, 23.95.

HRMS (ESI) (m/z) $[C_{12}H_{14}O_3N]^+ = [M+H]^+$: calcd. 220.0974, found 220.0961.

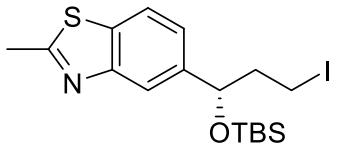


(*S*)-3-((*tert*-butyldimethylsilyl) oxy)-3-(2-methylbenzo[*d*]thiazol-5-yl) propanal (226)

To a solution of **213** (0.68 g, 2 mmol) in DCM (5 mL) and DMSO (1.2 mL) was added triethylamine (1.2 mL, 8 mmol). The solution was cooled to 0 °C, SO_3-pyridine (0.64 g, 4 mmol) was added in portions and the mixture was stirred for 2 hours at 0 °C. The solution was poured into water. The aqueous layer was separated and extracted with DCM. The combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by the column

chromatography (pentane/ ethyl ether, 4:1). The aldehyde **226** (1.72 mmol, 0.58 g) was obtained as colorless oil with a yield of 86%.

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 10.45(s, 1H), 7.97 (d, *J* = 1.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.3, 1.7 Hz, 1H), 5.31 (dd, *J* = 8.3, 4.7 Hz, 1H), 2.87 (s, 3H), 2.85 – 2.81 (m, 1H), 2.70 (d, *J* = 4.7 Hz, 0.6H), 2.67 (d, *J* = 4.8 Hz, 0.4H), 0.87 (s, 9H), 0.07 (s, 3H), -0.14 (s, 3H).

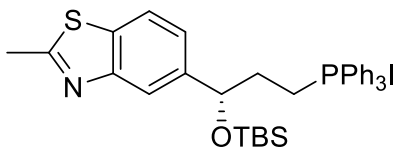


(*S*)-5-(1-((tert-butyldimethylsilyl) oxy)-3-iodopropyl)-2-methylbenzo[*d*]thiazole (229)

Alcohol **213** (1 mmol, 0.34 g) and PPh_3 (1.1 mmol, 0.29 g) were dissolved in CH_3CN (1.3 mL) and Et_2O (5 mL), then the mixture was cooled to 0 °C, I_2 (1.05 mmol, 0.13 g) and imidazole (1.3 mmol, 0.09 g) were added sequentially. Then the temperature was increased to room temperature and the mixture reaction was stirred for another hour. The solvents were removed under vacuum and the residue directly passed through a short silica gel plug with pentane/ ether 4:1 to give iodide **229** (0.78 mmol, 0.35 g, 78%) as colorless oil.

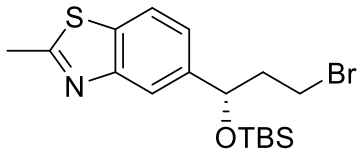
^{1}*H* NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.6 Hz, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.23 (m, 1H), 4.82 (dd, *J* = 7.6, 4.4 Hz, 1H), 3.20 (dt, *J* = 9.6, 7.5 Hz, 1H), 3.07 (ddd, *J* = 9.7, 7.2, 5.6 Hz, 1H), 2.78 (s, 3H), 2.20 (dtd, *J* = 14.5, 7.3, 5.7 Hz, 1H), 2.07 (dtd, *J* = 14.6, 7.6, 4.4 Hz, 1H), 0.83 (s, 9H), 0.03 (s, 3H), -0.22 (s, 3H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 167.83, 153.31, 142.97, 134.57, 123.06, 121.38, 119.73, 74.73, 44.93, 34.25, 25.99, 20.25, 2.85, -4.32, -4.65.



(*S*)-5-(1-((*tert*-butyldimethylsilyl) oxy)-3-(iodotriphenyl-λ^5-phosphaneyl) propyl)-2-methylbenzo[*d*]thiazole (220)

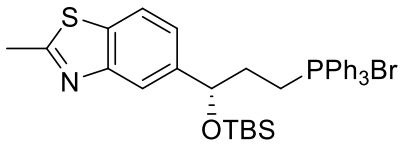
Iodide **229** (0.16 mmol, 70 mg), PPh_3 (0.23 mmol, 0.06 g) and DIEA (1.1 mmol, 0.14 g) were mixed and the mixture was heated in a sealed flask at 90 °C for 12 h. After cooling to room temperature, DIEA was removed by pentane (dry) in vacuum, then the suspenion was dissolved in dry pentane again following waiting for 1min, removed the solvents again in vacuum. The Wittig salt **220** (0.15 mmol, 106.5 g, 95%) was isolated without further purification.



(*S*)-5-(1-((*tert*-butyldimethylsilyl) oxy)-3-bromopropyl)-2-methylbenzo[*d*]thiazole (223)

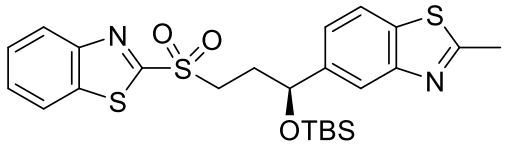
To a solution of alcohol **213** (0.34 g, 1 mmol) in DCM (2 mL) was added PPh_3 (0.39 g, 1.5 mmol) and NBS (0.26 g, 1.5 mmol) in one patch at 0 °C, and the mixture was stirred for 1 h at 0 °C. Then the reaction was quenched with aq. $NaHCO_3$. The aqueous layer was separated and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (pentane/ diethyl ether, 4:1) to afford **223** (0.92 mmol, 0.37 g, 92%) as yellow oil.

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.6 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.33 (dd, *J* = 8.3, 1.7 Hz, 1H), 4.98 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.59 – 3.49 (m, 1H), 3.40 – 3.34 (m, 1H), 2.85 (s, 3H), 2.29 (ddt, *J* = 14.0, 8.1, 5.7 Hz, 1H), 2.12 (dddd, *J* = 14.5, 8.3, 6.4, 4.2 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 3H), -0.16 (s, 3H).



(*S*)-5-(3-(bromotriphenyl-l5-phosphaneyl)-1-((tert-butyldimethylsilyl) oxy) propyl)-2-methylbenzo[*d*]thiazole (224)

Bromide **223** (0.6 g, 0.9 mmol) and PPh_3 (0.23 g, 0.86 mmol) were dissolved in toluene (10 mL) and the mixture was refluxed for 18 h. After cooling to room temperature, the mixture was filtered. The Wittig salt **224** (0.8 mmol, 0.54 g, 91%) was obtained after removal of the solvent without further purification.



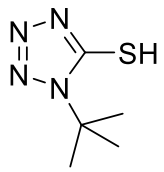
(*S*)-5-(3-(benzo[d]thiazol-2-ylsulfonyl)-1-((*tert*-butyldimethylsilyl) oxy) propyl)-2-methylbenzo[*d*]thiazole (231)

To a solution of 2-mercapto-benzothiazol **228** (0.16 g, 1 mmol) in THF (4 mL) was added NaH (60%, 104 mg, 2.6 mmol) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. Then the Iodide **229** (0.36 g, 0.82 mmol) was added followed by stirring at room temperature overnight. The reaction was quenched with NH_4Cl, and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to provide **230** without further purification.

Product **230** was dissolved in a solvent mixture (5 mL, 1/1=MeOH/H_2O) and Ooxone® (0.74 g 2.4 mmol) was added. The mixture was stirred at room temperature overnight. Then the reaction was diluted with EtOAc and washed with H_2O. The separated water phase was extracted with EtOAc for 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography (pentane/ diethyl ether, 4:1) to provide **231** (0.64 mmol, 0.24 g, 46%) as yellow solid.

^{1}*H* NMR (600 MHz, $CDCl_3$) δ 7.92 (dt, *J* = 1.5, 0.7 Hz, 1H), 7.83 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.40 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 7.35 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.28 (ddd, *J* = 8.0, 7.3, 1.2 Hz, 1H), 5.02 (dd, *J* = 7.4, 4.6 Hz, 1H), 3.41 – 3.32 (m, 2H), 2.84 (s, 3H), 2.31 – 2.17 (m, 2H), 0.92 (s, 9H), 0.09 (s, 3H), -0.12 (s, 3H).

Preparation of mercaptotetrazole 233-235:



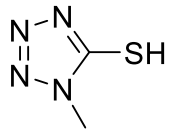
1-*tert*-butyl-5-mercaptotetrazole (233)

To a solution of NaN_3 (0.663 g, 10 mmol) in H_2O (4 mL) was added a solution of *tert*-butyl isothiocyanate (1.15 g, 10 mmol, 1.3 mL) in *i*-PrOH (3.0 mL) at 120 °C using an oil bath and the resulting mixture was refluxed for 24 h. The mixture was treated with conc. HCl (1 mL) at 0 °C and then the separated aqueous layer was extracted twice with EtOAc (10 and 5 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give *tert*-butyl-mercaptotetrazole **233** (10 mmol, 1.6 g, 100%), which was used in the next step without further purification.

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 1.84 (s, 9H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 162.20, 63.54, 27.49.

HRMS (ESI) (m/z) $[C_5H_{10}N_4S]^+ = [M+H]^+$: calcd. 159.0704, found 159.0683.

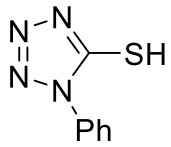


1- methyl-5-mercaptotetrazole (234)

To a solution of NaN_3 (0.663 g, 10 mmol) in H_2O (4 mL) was added a solution of methyl isothiocyanate (0.73 g, 10 mmol) in *i*-PrOH (3.0 mL) at 120 °C using an oil bath and the resulting mixture was refluxed for 24 h. The mixture was treated with conc. HCl (1 mL) at 0 °C and then the separated aqueous layer was extracted twice with EtOAc (10 and 5 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give methyl-mercaptotetrazole **234** (10 mmol, 1.2 g, 100%), which was used in the next step without further purification.

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 1.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.78, 27.60



1-phenyl-5-mercaptotetrazole (235)

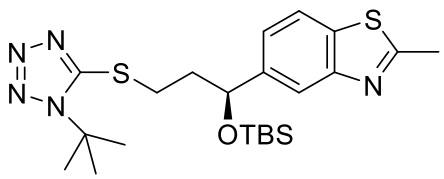
To a solution of NaN_3 (0.663 g, 10 mmol) in H_2O (4 mL) was added a solution of phenyl isothiocyanate (1.35 g, 10 mmol) in *i*-PrOH (3.0 mL) at 120 °C using an oil bath and the resulting mixture was refluxed for 24 h. The mixture was treated with conc. HCl (1 mL) at 0 °C and then the separated aqueous layer was extracted twice with EtOAc (10 and 5 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give phenyl-mercaptotetrazole **235** (10 mmol, 1.8 g, 100%), which was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.90 (m, 1H), 7.58 – 7.50 (m, 2H), 7.42 (dd, J = 8.3, 6.9 Hz, 1H), 7.35 – 7.23 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.87, 134.11, 130.22, 129.89, 129.45, 125.51, 123.89.

HRMS (ESI) (m/z) $[C_7H_7N_4S]^+ = [M+H]^+$: calcd. 179.0391, found 179.0371.

Preparation of sulfide reagents 236-238:



(*S*)-5-(3-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl) thio)-1-((*tert*-butyldimethylsilyl) oxy)

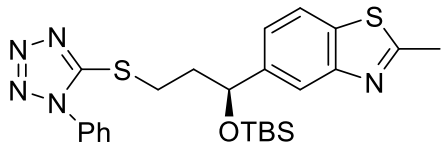
propyl)-2-methylbenzo[d]thiazole (236)

To a solution of mercaptotetrazole **233** (1 mmol, 0.16 g) in THF (2.5 mL) was added 60% NaH (19 mg, 1.1 mmol) at 0 °C. After the mixture was stirred at 0 °C for 10 min, iodide (0.36 g, 0.8 mmol) was added and the resulting mixture was stirred at reflux for 6 h. Then the reaction was quenched with aq. NH_4Cl, and the mixture was extracted twice with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (silica gel; hexane/EtOAc (4:1)) provided the sulfide **236** (0.96 mmol, 0.46 g, 96%).

1*H* NMR (400 MHz, CDCl3) δ 8.10 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 5.02 (dd, J = 7.1, 4.8 Hz, 1H), 3.41 (td, J = 7.2, 2.2 Hz, 2H), 3.06 (s, 3H), 2.27 – 2.14 (m, 2H), 0.91 (s, 9H), 0.08 (s, 3H), -0.15 (s, 3H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 168.16, 155.40, 152.50, 145.09, 131.50, 124.70, 121.82, 117.91, 73.00, 40.05, 29.87, 28.72, 25.83, 17.80, -4.43, -4.85.

IR (ATR): ṽ = 2988 (w), 2952 (w), 2929 (m), 2896 (w), 2956 (m), 1713 (w), 1609 (w), 1554 (w), 1525 (w), 1462 (m), 1419 (m), 1391 (s), 1361 (s), 1313 (w), 1286 (w), 1251 (m), 1223 (m), 1173 (m), 1152 (w), 1132 (w), 1089 (s), 1066 (m), 1025 (w), 1005 (w), 990 (m), 937 (w), 913 (m), 888 (w), 834 (s), 776 (s), 730 (s), 696 (w), 664 (m), 644 (m), 595 (m), 544(w).



(*S*)-5-(1-((*tert*-butyldimethylsilyl) oxy)-3-((1-phenyl-1*H*-tetrazol-5-yl) thio) propyl)-2-methylbenzo[d]thiazole (238)

To a solution of mercaptotetrazole **235** (1 mmol, 0.18 g) in THF (2.5 mL) was added 60% NaH (19 mg, 1.1 mmol) at 0 °C. After the mixture was stirred at 0 °C for 10 min, iodide (0.36 g, 0.8 mmol) was added and the resulting mixture was stirred at RT overnight. The reaction was quenched with aq. NH_4Cl, and the mixture was extracted twice with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$), and

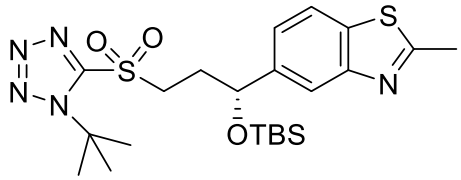
concentrated. Column chromatography (silica gel; hexane/EtOAc (4:1)) provided the sulfide **238** (0.93 mmol, 0.46 g, 93%).

^{1}*H* NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.7 Hz, 1H), 7.82 – 7.76 (m, 1H), 7.55 (d, *J* = 2.8 Hz, 4H), 7.38 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.26 (s, 1H), 5.02 – 4.93 (m, 1H), 3.46 – 3.37 (m, 2H), 2.89 (d, *J* = 3.9 Hz, 3H), 2.28 – 2.20 (m, 2H), 0.90 (d, *J* = 3.1 Hz, 9H), 0.06 (s, 3H), -0.15 (d, *J* = 5.8 Hz, 3H).

^{13}*C* NMR (101 MHz, $CDCl_3$) δ 168.33, 154.25, 143.25, 133.68, 130.12, 129.79, 129.70, 129.02, 123.83, 123.18, 121.20, 119.16, 115.28, 73.25, 39.99, 29.38, 28.71, 25.84, 19.80, -4.47, -4.88.

IR (ATR): ṽ = 3056 (w), 2952 (m), 2927 (m), 2897 (m), 2855 (m), 1710 (w), 1640 (w), 1597 (m), 1572 (w), 1525 (w), 1499 (m), 1461 (m), 1415 (m), 1387 (m), 1361 (w), 1312 (w), 1276 (w), 1249 (m), 1173 (m), 1153 (w), 1086 (s), 1014 (w), 964 (w), 937 (w), 912 (w), 890 (w), 835 (s), 814 (m), 776 (s), 759 (s), 731 (s), 691 (s), 644 (m), 613 (w), 597 (w), 546 (w).

Preparation of sulfone reagents 239-241:



(*R*)-5-(3-((1-(*tert*-butyl)-1*H*-tetrazol-5-yl) sulfonyl)-1-((*tert*-butyldimethylsilyl) oxy) propyl)-2-methylbenzo[*d*]thiazole (239)

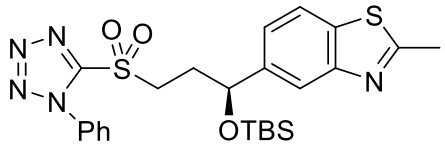
The sulfide **236** (1 mmol, 0.48 g) was treated with $(NH_4)_6Mo_7O_{24}•H_2O$ (134 mg, 0.1 mmol) and 35% H_2O_2 (0.6 mL, 9 mmol) in EtOH (2 mL). After the resulting mixture was stirred at RT for 11 h, aq. Na_2SO_3 was added slowly at 0 ºC and extracted twice with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated. Column chromatography (silica gel, hexane/EtOAc 2:1) provided sulfone **239** (0.67 mmol, 0.34 g, 67%) as colorless needles.

^{1}H NMR (400 MHz, CDCl3) δ 7.97 – 7.88 (m, 1H), 7.80 (dd, J = 8.2, 0.5 Hz, 1H), 7.35 (dd, J = 8.4, 1.7 Hz, 1H), 5.10 (t, J = 5.6 Hz, 1H), 3.98 – 3.87 (m, 1H), 3.80 – 3.71 (m, 1H), 2.86 (s, 3H), 2.39 (ddd, J = 8.3, 7.3, 5.7 Hz, 2H), 1.82 (s, 9H), 0.93 (s, 9H), 0.11 (s, 3H), -0.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.31, 154.01, 141.94, 134.78, 122.80, 121.71, 119.47, 72.45, 65.53, 53.26, 33.33, 29.79, 25.97, 20.21, 18.32, -4.48, -4.88.

HRMS (ESI) (m/z) $[C_{22}H_{36}O_3S_2N_5Si]^+ = [M+H]^+$: calcd.510.2029, found 510.2035.

IR (ATR): ṽ = 2988(w), 2952(m), 2928(m), 2855(m), 2209(w), 2115(w), 1713(w), 1675(w), 1554(w), 1525(w), 1462(w), 1419(w), 1391(s), 1362(s), 1286(w), 1251(m), 1223(m), 1173m), 1132(w), 1089(s), 1024(w), 1005(w), 990(w), 964(w), 937(w), 914(w), 888(w), 835(s), 776(s), 732(s), 696(w), 644(m), 612(w), 595(w), 544(w).



(*S*)-5-(1-((*tert*-butyldimethylsilyl) oxy)-3-((1-phenyl-1*H*-tetrazol-5-yl) sulfonyl) propyl)-2-methylbenzo[d]thiazole (241)

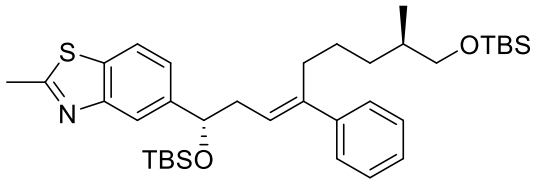
The sulfide **238** (1 mmol, 0.5 g) was treated with $(NH_4)_6Mo_7O_{24}•H_2O$ (134 mg, 0.1 mmol) and 35% H_2O_2 (0.6 mL, 9 mmol) in EtOH (2 mL). After the resulting mixture was stirred at RT for 11 h, aq. Na_2SO_3 was added slowly at 0 ºC and extracted twice with EtOAc. The combined extracts were washed with brine, dried with $MgSO_4$, and concentrated. Column chromatography (silica gel, hexane/EtOAc 2:1) provided sulfone **241** (0.7mmol, 0.38g, 72%) as colorless needles.

^{1}H NMR (400 MHz, CDCl3) δ 7.98 – 7.90 (m, 1H), 7.82 – 7.75 (m, 1H), 7.55 (d, J = 2.8 Hz, 5H), 7.38 (dd, J = 8.2, 1.6 Hz, 1H), 7.26 (s, 1H), 4.97 (d, J = 6.2 Hz, 1H), 3.45 – 3.36 (m, 2H), 2.89 (d, J = 3.9 Hz, 4H), 2.28 – 2.19 (m, 2H), 0.89 (s, 8H), 0.06 (s, 3H), -0.16 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.90, 153.70, 133.32, 131.81, 130.06, 125.52, 125.41, 122.14, 72.33, 67.79, 52.61, 33.18, 29.72, 29.05, 26.19, 26.16, 26.15, 20.08, 18.51, -

4.30, -4.68.

IR (ATR): $\tilde{\nu}$ = 2988 (w), 2952 (m), 2929 (m), 2856 (m), 1729 (w), 154 (w), 1525 (w), 1463 (m), 1424 (w), 1373 (m), 1363 (m), 1335 (m), 1251 (m), 1223 (m), 1211 (w), 1172 (m), 1158 (m), 1123 (w), 1086 (s), 1066 (s), 1024 (w), 1006 (w), 964 (w), 937 (w), 918 (w), 892 (w), 835 (s), 815 (m), 777 (s), 698 (w), 643 (m), 624 (m), 594 (w), 564 (w), 549 (w), 539 (w).



2-methyl-5-((5*S*, 12*R*, *E*)-2,2,3,3,12,15,15,16,16-nonamethyl-8-phenyl-4,14-dioxa-3,15-disilaheptadec-7-en-5-yl) benzo[d]thiazole (225b)

To a solution of sulfone **239** (88 mg, 0.17 mmol) and ketone **222** (61 mg, 0.19 mmol) in 1mL THF were added LiHMDS (0.2 mmol, 0.2 mL, 1 mol/L in THF) at -78 °C and the mixture was stirred at that temperature for 3 h and subsequently was quenched with aq. NH_4Cl and EtOAc. The separated aqueous layer was extracted twice with EtOAc and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (hexane: EtOAc = 5:1) provided **225b** (56.23 mg, 53%, selectivity as *E*-isomers) as yellow oil.

^{1}*H* NMR (600 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.37 (m, 3H), 7.34 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 5.46 (d, *J* = 1.5 Hz, 1H), 4.99 (dd, *J* = 7.4, 4.7 Hz, 1H), 3.47 (dd, *J* = 10.5, 5.8 Hz, 1H), 3.42 – 3.38 (m, 2H), 2.89 (s, 3H), 2.53 – 2.45 (m, 2H), 2.25 – 2.18 (m, 1H), 1.71 (s, 9H), 1.60 (ddt, *J* = 12.5, 6.6, 1.5 Hz, 2H), 1.49 – 1.40 (m, 2H), 1.14 (tdd, *J* = 12.9, 5.0, 2.4 Hz, 1H), 0.91 (s, 9H), 0.89 (s, 3H), 0.88 (s, 3H), 0.07 (s, 3H), -0.14 (s, 3H).

^{13}*C* NMR (151 MHz, $CDCl_3$) δ 168.32, 152.41, 148.53, 141.32, 133.77, 128.24, 127.28, 126.10, 123.23, 121.40, 119.15, 112.25, 73.65, 68.26, 40.06, 35.57, 35.54, 32.70, 29.99, 28.68, 25.85, 25.55, 19.78, 18.17, 16.53, -4.50, -4.54, -4.96.

HRMS (ESI) (m/z) $[C_{36}H_{58}O_2SNSi_2]^+ = [M+Na]^+$: calcd.646.3546, found 646.3549.

IR (ATR): $\tilde{\nu}$ = 3379(w), 3084(w), 3055 (w), 3024(w), 2948(m), 2929(s), 2856(w), 1738(w), 1686(w), 1626(w), 1574(w), 1523(w), 1494(w), 1461(m), 1445(m), 1420(w), 1391(m), 1363(m), 1251(m),1226(w), 1176(w), 1133(w), 1090(s), 1066(m), 1030(s), 1006(w), 965(w), 939(w), 892(m), 836(s), 777(s), 702(s), 661(w), 645(w), 616(w), 595(w)

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