Synthesis of Desepoxyisotedanolide–

A Proposed Biosynthetic Precursor of

the Marine Polyketide Tedanolide

and

Application of Kiyooka Aldol Reaction to generate

Tertiary Alcohols Stereoselectively

Von Der Naturwissenschaftlichen Fakultät

der Gottfried Wilhelm Leibniz Universität Hannover

zur Erlangung des Grades

Doktor der Naturwissenschaften

Dr. rer. nat.

genehmigte Dissertation von

M.Sc. Arun Naini

geboren am 04.06.1983

in Bhongir, India

2015

Referent: Prof. Dr. Markus Kalesse

Korreferent: Prof. Dr. Andreas Kirschning

Date of Defense: November 6, 2014

Die vorliegende wurde im Zeitraum von August 2010 bis Juni 2014 unter der Leitung von Herrn Prof. Dr. Markus Kalesse am Institut für Organische Chemie der Gottfried Wilhelm Leibniz Universität Hannover angefertigt.

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbständig verfasst und die benutzten Hilfsmittel und Quellen sowie Kooperationspartner vollständig angegeben habe.

Diese Dissertation wurde weder zuvor veröffentlicht oder als Masterarbeit, Diplomarbeit oder andere Prüfungsleistung verwendet, noch an einer anderen Fakultät eingereicht. Teilergebnisse wurden an den im Publikationsverzeichnis angegebenen stellen veröffentlicht.

Arun Naini,

Hannover,

July 23, 2014

‘‘Imagination is more important than knowledge’’

Albert Einstein

(1879-1955)

SYNTHESIS OF DESEPOXYISOTEDANOLIDE

A Proposed Biosynthetic Precursor of the Marine Polyketide Tedanolide

and Application of Kiyooka Aldol Reaction to generate

Tertiary Alcohols Stereoselectively

Abstract

By

Arun Naini

Keywords: tedanolide, isotedanolide, natural product, total synthesis, polyketides, macrolactone, isomerization, Kiyooka aldol.

Tedanolides are biologically active polyketides, isolated from various marine sponges at different locations. The isolation of these toxic metabolites first came into light in the year 1984 with the isolaton of tedanolide by Schmitz *et al*. from a marine sponge *Tedania ignis*. Until now several other molecules (13-deoxytedanolide, tedanolide C, candidaspongiolides) belonging to this family have been isolated. The radioactive labeled studies performed by Fusetani *et al*. on the derivative of tedanolide, confirmed that this polyketide binds to the 60S ribosomal unit. The tedanolides represent the first known macrolides binding to the eukaryotic proteins. The structural characteristics of the tedanolides are a 18-membered macrolactone and an epoxide on the side chain. The structural complexity of the tedanolides has attracted the attention of several groups, few groups have been successful in accomplishing the total synthesis of tedanolide. Tedanolides represent a rare class of compounds comprising a primary lactone linkage, which makes it very interesting point from the biosynthetic prospective of polyketides. Based on the biosynthetic principle of polyketides, this unique 18-membered primary lactone could arise from a skeletal rearrangement. In order to substantiate this hypothetical rearrangement, the synthesis of a 18-membered secondary lactone desepoxyisotedanolide was initiated. This work consists of the total synthesis of desepoxyisotedanolide followed by the biological studies concerning the activity and the efforts towards isomerization of the secondary lactone to the primary lactone. Additionally few truncated analogues of tedanolide C(10-23) fragment are synthesized to perform biological tests and obtain structure activity relationship of tedanolides. In another part of this work, the Kiyooka aldol reaction was used in our group in the synthesis of tedanolide C. To make this protocol a more general approach for the construction of complex molecules consisting tertiary alcohol, this method was tested with various types of aldehydes and proven to be successful.

Kurzfassung

Arun Naini

Synthese von Isotedanolid

Eine vorgeschlagene Vorstufe in der Biosynthese des marinen Polyketids Tedanolid und Anwendung der Kiyooka Aldolreaktion, stereoselektiv tertiäre Alkohole zu erzeugen

Schlagworte: Tedanolid, Isotedanolid, Naturstoffe, Totalsynthese, Polyketid, Makrolacton, Isomerisierung, Kiyooka Aldol.

Tedanolide sind biologisch aktive Polyketide, die aus verschiedenen marinen Schwämmen an unterschiedlichen Orten isoliert wurden. Die Isolierung dieser toxischen Metaboliten kam im Jahr 1984 in den wissenschaftlichen Fokus mit der Isolierung von Tedanolid durch Schmitz *et al.* aus dem Meeresschwamm *Tedania ignis*. Bis jetzt sind mehrere weitere Mitglieder (13-Deoxytedanolid, Tedanolid C, Candidaspongiolide) dieser Familie isoliert worden. Durch Studien von Fusetani *et al.* an radioaktiv markierten Derivaten der Tedanolide ist bestätigt, dass dieses Polyketid an die ribosomale 60S-Einheit bindet. Die Tedanolide stellen die ersten bekannten Makrolide dar, die an diese eukaryotischen Proteine binden. Strukturell betrachtet handelt es sich bei den Tedanoliden um 18-gliedrige Makrolactone mit einem Epoxid in der Seitenkette. Die strukturelle Komplexität der Tedanolide hat die Aufmerksamkeit mehrerer Gruppen auf sich gezogen, von denen einige die Totalsynthese von Tedanolid erfolgreich abgeschlossen haben. Aus biosynthetischer Sicht stellen die Tedanolide mit ihrer seltenen primären Lactonbindung eine interessante Klasse von Verbindungen dar. Basierend auf dem Prinzip der Biosynthese könnte dieses einzigartige 18-gliedrige primäre Lacton durch eine Umlagerung generiert werden. Um diese hypothetische Umlagerung zu untermauern, wurde die Synthese des 18-gliedrigen sekundären Lactons Desepoxyisotedanolid geplant. Diese Arbeit beinhaltet die Totalsynthese von Desepoxyisotedanolid sowie die biologischen Studien über dessen Aktivität und die Bemühungen, das sekundäre zum primären Lacton zu isomerisieren. Zusätzlich ist das C(10-23)-Fragment von Tedanolid synthetisiert worden, um biologische Tests durchführen und Struktur-Aktivitäts-Beziehungen der Tedanolide bestimmen zu können. In einem weiteren Teil dieser Arbeit wird die Kiyooka Aldolreaktion, die in unserer Gruppe für die Synthese von Tedanolid C verwendet wird, etabliert und an verschiedenen Arten von Aldehyden getestet, um einen allgemeineren Ansatz für den Aufbau komplexer Moleküle, die aus tertiären Alkoholen bestehen, zu entwickeln.

ACKNOWLEDGEMENTS

I would like to thank my advisor Professor Markus Kalesse for giving me this opportunity to work under his guidance for my Ph.D. I am very thankful for the support and encouragement he provided since the very beginning of my work in his group. I really enjoyed working under him and gained a lot of knowledge from his expertise.

I would like to acknowledge Professors Andreas Kirschning and Carla Vogt for accepting my request to be a part of thesis committee.

I would like also thank Professor Richard Taylor for welcoming me to USA to work in his group at University of Notre Dame as a knowledge process in the tedanolide project. It gave me an opportunity to interact with his group. His ideas and inputs in our project during the stay helped me, I thoroughly enjoyed the time in his group. A special thanks to Ian Harrier, for helping me during my days in Rich Taylor group.

I am also very grateful to the members of Kalesse group, especially Bukurije Govori for being my lab mate and for her constant inputs on and off chemistry. Graduate studies wouldn't have been easy without your help. Michael Richter and Lynette Smyth for mentoring me in my early days at the lab. All the current group members Thomas, Magalie, Lisa, Hi Hua, Geritt, Bettina, Jun, Daniel and past group members who were always eager to help me. I would like to thank a lot to Paloma for sparing her valuable time to proof read my thesis. I would like to thank our Braunschweig, Kirschning and Tanja group members for offering help during purification of compounds using HPLC.

I would like to thank our support staff Monika Rettstadt, Dagmar Koertje, Joerg Fohrer, Gerald Draeger and Roswitha Reichel for carrying out my NMR and Mass experiments.

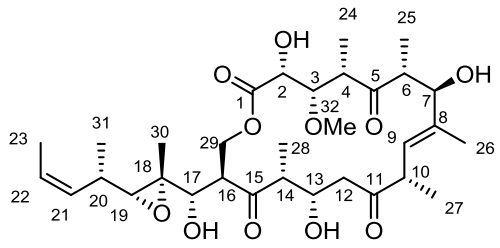
I would like to thank Kristina Struckmeier and Monika Griese for helping with the organizational work.

I would like to thank also Dr. Ulhas Bhatt and Dr. Krishna Reddy Yalamareddy for their constant support in last 10 years for my professional and academic progress. I would like to show my gratitude towards my mentors and lecturers from my school till the college times for continuous enritchening of my knowledge. I am thankful to my friends all over world from east to west; Shailaja, Malla reddy, Kishore and Poorna for giving me strength all the time.

Finally I would like to thank my parents (Laxman Naini and Krishna Veni Naini) for being so patient, understanding and encouraging me and for their eternal love towards me. Especially my brother Shravan for standing by me in every situation, on whom i depend so much. Nikhita, my life partner for everything you bring into my life, for all the time we spent and for all the joy we had. Life wouldn't be so easy without you all.

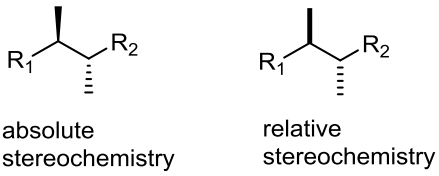
General Comments

The numbering of the atoms in the tedanolides is given beginning from the carboxylic group of macrolactone and followed it with the central framework. The eight methyl groups are separately given numbers. The numbering pattern is not in accordance with the IUPAC rules.



tedanolide (**6**)

In the diagrams and the schemes, the structures for absolute stereochemistry are represented with wedges whereas the relative stereochemistry is shown with bars.



absolute stereochemistry

relative stereochemistry

Table of contents

0. Abbreviations:

°C	degrees Celcius
^{13}C NMR	carbon- 13 nuclear magnetic resonance spectroscopy
^{1}H NMR	hydrogen- 1 nuclear magnetic resonance spectroscopy
Å	angstrom
A	adenine
A site	aminoacyl site
AA	amino acid
abs.	absolute
Ac	acetyl
ACN	acetonitrile
AcOH	acetic acid
AD	asymmetric dihydroxylation
aq.	aqueous
Ar	aromatic
Bn	benzyl
BORSM	based on recovered starting material
Bu	butyl
n-BuLi	*n*-butyl lithium
c	concentration
ca.	approximately
cm^{-1}	reciprocal centimeter
Cp	cyclopentyl
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexane
d	doublet
DCM	dichloromethane
DDQ	2,3-dichloro-4.5-dicyano-1.4-benzoquninone
DH	dehydratase
de	diastereomeric excess
DIBAL-H	diisobutyl aluminium hydride
DIPEA	diisopropyl ethyl amine
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	dimethylsulfoxide
DNA	desoxyribonucleic acid
E	entgegen, opposite
E site	exit site
ED_{50}	effective dosage 50%
ee	enantiomeric excess
eIF2	eukaryotic initiation factor 2
eIF4A	eukaryotic initiation factor 4A
eq	equivalent

ESI	electrospray ionisation
ER	enoyl reductase
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethylacetate
Fig	Figure
FT-IR	Fourier transform infrared spectroscopy
g	gram
G	guanine
h	hour
HMDS	hexamethyldisilazide
HMPT	hexamethylphosphorustriamide
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons-Olefination
Hz	hertz
IBX	*o*-iodoxybenzoic acid
IC_{50}	inhibitory concentration 50%
^{i}-Pr	isopropyl
Ipc	isopinocampheyl
J	coupling constant
KR	ketoreductase
L	litre
LDA	lithium diisoproyl amide
$LiAlH_4$	Lithium aluminium hydride
Lut	lutidine
LiHMDS	Lithium bis(trimethylsilyl)amide
m	multiplet
M	molar
M^+	molecular ion
m/z	mass-to-charge ratio
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minute
$MgSO_4$	magnesium sulfate
mL	millilitre
MT	methyl transferase
mmol	millimole
MMTr	monomethoxytritylchloride
MS	Mass spectrometry
MTBE	*tert*-Butylmethyl ether
mRNA	messenger ribonucleic acid
NaCl	sodium chloride
$NaHCO_3$	sodium bicarbonate
$NaSO_4$	sodium sulfate
ng	nanogram
NH_4Cl	Ammonium chloride
nM	nanomole

NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholine-*N*-oxide
NOE	nuclear Overhauser effect
pet ether	petroleum ether
P site	peptide site
pg	picogram
Ph	phenyl
Piv	pivolyl
PMB	*para*-methoxy benzyl
PMP	*para*-methoxy phenyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfate
Pr	propyl
Py	pyridine
RNA	ribonucleic acid
rRNA	ribosomal ribonucleic acid
rt	room temperature
s	singlet
SAR	structure-activity relationship
sat	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SNi'	intramolecular nucleophilic substitution
t	triplet
Tf	triflate
TBAF	tetra-*n*-butylammoniumfluoride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilylchloride
TBSOTf	*tert*-Butyldimethylsilyltriflate
TE	thioesterase
TES	triethylsilyl
TESCl	triethlsilylchloride
TESOTf	triethlsilyltriflate
TEMPO	2,2,6,6-tetramethylpiperidin-1-oxyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMNO	trimethylamine-N-oxide
TMS	trimethylsilyl
TMSCl	trimethylsilylchloride
TMSOTf	trimethylsilyltriflate
TPAP	tetrapropylammoniumperruthenate
tRNA	transfer ribonucleic acid
Ts	*p*-toluylsulfonyl
U	uridine
UV	ultraviolet
Xc	chiral auxiliary
Z	Zusammen
δ	chemical shift in parts per million
µL	microlitre
µM	micromolar

1. Introduction:

1.1. Natural Products in Treatment of Cancer:

In 2008, approximately 12.7 million cancers were diagnosed (excluding non-melanoma skin cancers and other non-invasive cancers) and in 2010 nearly 7.98 million people died. Cancer accounts for approximately 13% of all deaths. This makes invasive cancer the leading cause of death in developed world and the second most in developing countries.[1] Cancer figures among the leading cause of death worldwide, accounting for 8.2 million deaths in 2012. Lung, liver, stomach, colorectal and breast cancer are the most common cancer deaths every year. It is expected that annual cancer cases will rise from 14 million in 2012 to 22 million within the next two decades.[2]

Natural products are the most important anti-cancer agents and accommodate three quarters of the anti-tumor compounds used as medicine. Out of 140 anti-cancer agents approved since 1940, over 60% can be accommodated as natural products. Of the 126 small molecules among them, 67% are natural in origin. In order to fight against cancer effectively new lead chemotherapeutic agents are necessary, thus increasing the survival rate and minimizing side effect of chemotherapies.[3]

Compounds with anti-tumor activity belong to several structural classes such as anthracyclines, enediynes, indalocarbazoles, isoprenoids, polyketide macrolides, non-ribosomal peptides including glycopeptides and others. Most of the polyketides are produced from the bacteria or fungi. They include a number of anti-tumor drugs (e.g. Taxol), which is made by both plants and fungi. Halogenated anti-tumor candidates include salinosporamide A and rebeccamycin.

The anti-tumor compounds act by several mechanisms such as including apoptosis (programmed cell death) through DNA cleavage mediated by topoisomerase I or II inhibition, mitochondrial permeabilisation, inhibition of key enzymes involved in signal transduction (e.g. proteases), or cellular metabolism, and by inhibiting tumor-induced angiogenesis (recruitment of new blood vessels).

Most of the important compounds used for the chemotherapy of tumors are microbially produced antibiotics or derivatives. Some of the microbial anti-tumor drugs are depicted below (Table 1.1).

Group	Examples
Aromatic polyketides (anthracyclines)	Daunorubicin, doxorubicin (adriamycin), epirubicin, pirirubicin, idarubicin, valrubicin, amrubicin.
Glycopeptides	Bleomycin, phleomycin
Non-ribosomal peptides	Actinomycin D (dactinomycin)
Anthracenones	Mithramycin, streptozotecin, pentostatin
Quinones	Mitosanes mitomycin C
Polyketides	Enediynes calicheamycin
Indolcarbazoles	Glycosides rebbecamycin
Polyketides	Macrolide lactones epothilones, ixebepilones
Nucleosides	2''-deoxycoformycin (pentastatin)
Halogenated compounds	Salinosporamide A

Table 1.1: *Some of the microbial anti-tumor compounds.*

Plants have been another useful source for the anti-tumor agents. Since 1961 nine plant derived compounds have been approved as anti-cancer drugs in the USA. Vinblastine (velban), vincristine (oncovin), etoposide, teniposide, taxol (paclitaxel), navelbine (vinorelbine), taxotere (docetaxel), camptothecin (camptosar, campto), topotecan (hycamtin) and irinotecan are some of the plant derived approved anti-tumor compounds. Although the ocean represents the center of biological diversity, prospecting the marine sources for the biotechnological use in drug discovery is a relatively recent activity. Marine sponges produce numerous bioactive compounds with pharmaceutical properties. Cyatrbine (Cyto star), pederin, theopederins, annamides, trabectedin (yondelis), aplidine, ectienascidin 743 (ET743) are few among the marine products with anti-tumor activity. Sixty eight percent of the pharmaceutically useful marine natural products employed are for cancer and the rest of them for anti-inflammatory, pain, asthma and Alzheimer's disease.

Most often the isolation process of the pharmacologically active substances from the natural resources results in very little quantities. Here comes the necessity of the total synthesis of the natural product through an effective synthetic strategy to produce them in substantial quantities in order to produce a scarce, but biologically intriguing, natural product for further extensive biological investigations and/or medicinal applications. A natural substance of some potential application can be synthesized in the laboratory, or the chemical plant. Natural product synthesis will be a more cost-effective process than the one entailing its extraction from nature, its use becomes economically more feasible and desirable. It provides the scope to tweak the structure of a natural product for the purposes of enhancing its potency or improving its selectivity and physical and chemical properties. Such endeavours often lead to superior pharmacological properties than those possessed by the natural products themselves in terms of efficacy and safety giving an insight into the structure activity relationship. And, as surprising as this may sound these days, the chemical synthesis of a natural product still provides the absolute proof of the assigned structure, for the recent literature abounds with revisions of structures of natural products whose originally isolated minute quantities complicated their characterization.[4,5]

1.2. Sponges (Porifera):

Sponges are sessile aquatic animals of the phylum Porifera. Sponges are similar to the other animals having multicellular, heterotopic, lack cell walls and produce sperm cells. Approximately 5000-10000 known species of sponges are known, which are available in the marine environment ranging from tidal zones to depths exceeding 8,800 meters.[6,7]

Sponges as primitive filter-feeders, produce a high frequency of bioactive components for their chemical defences against environmental stress factors. Highest concentrations of toxic or antioxidant sponge metabolites are found in inhabitants such as coral reefs. Sponges produce high level of cytotoxic chemicals by the emission of mucus in order to create a clear zone around it and push back other marine species. Secondary metabolites can protect the sponge from the predation, which is especially important for physically unprotected sessile organisms like sponges. Sponges and their microscopic endosymbionts are now being researched as possible sources of medicines for treating a wide range of diseases.

Demosponges constitute about 90% of all known sponges, including all fresh water ones, and have the widest range of habitats. Fossils of all types have been found in rocks dated from 580 million years ago. In addition, Archaeocyathids, whose fossils are common in rocks from 530 to 490 million years ago, are also regarded as sponges.

A sponge's body is hollow and is held in shape by the mesohyl, a jelly like substance made mainly of collagen and reinforced by a dense network of fibers also made of collagen. The inner surface is covered with choancocytes, cells with cylindrical or conical collars surrounding one flagellum per choanocyte. The wave-like motion of the whip-like flagella drives water through the sponge's body. All sponges have Ostia, channels leading to the interior through the mesohyl, and in most sponges these are controlled by tube-like procytes that form closable inlet valves. Pinacocytes, plate-like cells, form a single layered external skin over all other parts of the mesohyl that are not covered by chanocytes, and the pinacocytes also digest food particles that are too large to enter the Ostia, while those at the base of the animal are responsible for anchoring it.

Most sponges work rather like chimneys; they take in water at the bottom and eject it from the osculum at the top. The simplest body structure in sponges is a tube or vase shape known as ''asconoid''. Sponges can have structures can be varying from simple asconoid (pinacocytes) to syconoid (chancocytes) and leuconoid (water flow) types. A simple asconoid sponge seldom exceeds 1mm (0.039 inch) in diameter, whereas a leuconid sponge grows to over 1 m (3.3 feet). All fresh water and most shallow-water marine sponges have leuconid bodies. The fact the growth in any direction increases the number of chancocyte chambers enabling them to take a wider range of forms. The body structure is characterized by a stalk-like spongocel surrounded by a single layer of chanocytes (Figure 1.1).

Sponges are traditionally classified into three different types, calcareous sponges (Calcarea), glass sponges (Hexactinellida) and demosponges (Demospongia). Much later a new class homoscleromorpha was identified as a different class from demospongiae.

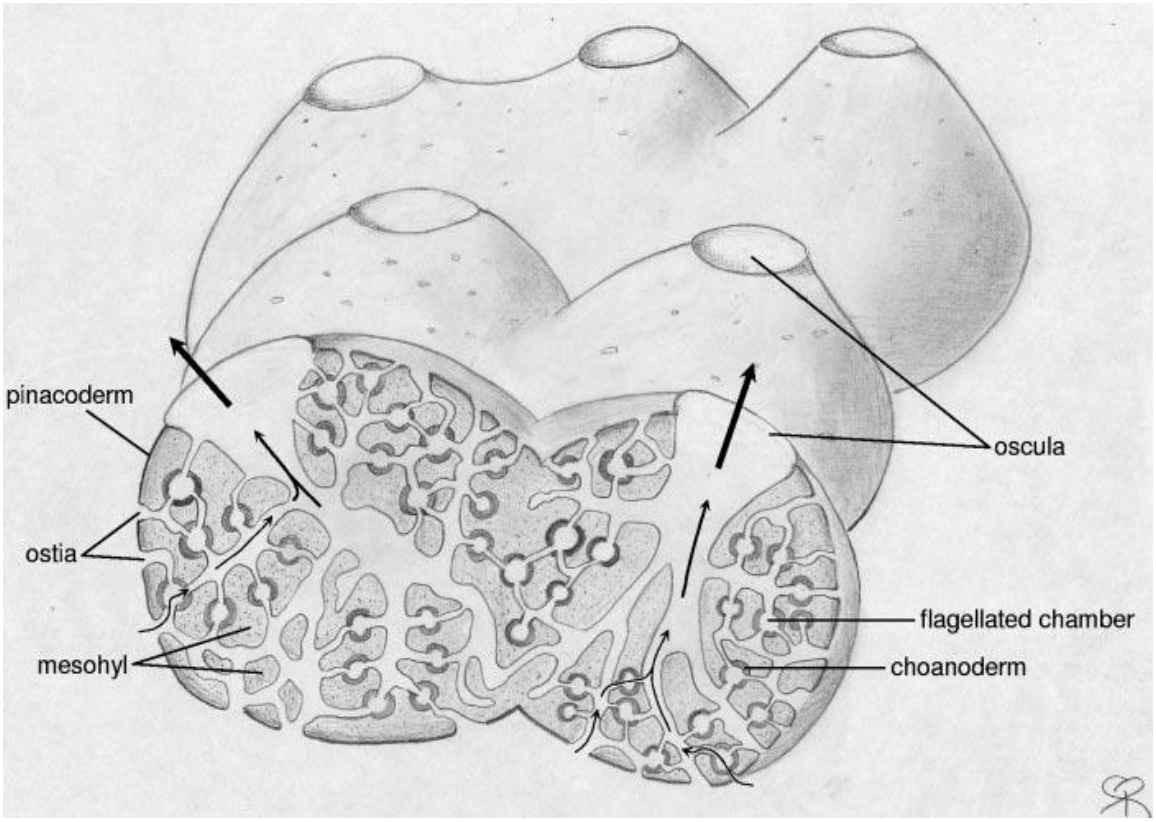


***Fig. 1.1**: Schematic representation of a sponge. Arrows indicate the direction of water flow through the sponge.*

Marine sponges have been ranked at the top with respect to the discovery of bioactive compounds with potential pharmaceutical applications. More than 15,000 marine products have been isolated and tested in the last 20 years until 2012. In 2011 the total number of natural products was 1152. The new natural chemical components from the phylum *Porifera* (sponges) has increased slightly from previous years to 269 compounds. The chemical diversity of sponge natural products is remarkable, including unusual nucleosides, bioactive terpenes, sterol, cyclic peptides, alkaloids, fatty acids, peroxides and amino acid derivatives.

In the last few years several candidates from marine sponges were undergoing preclinical and clinical trials (I, II, III) for anti-cancer activity. Among them are Hemiasterlins A & B, modified halochondrin B, KRN-70000, alipikinidine, fascaphysins, isohomohalichondrin B, halochondrin B, and laulimide/fijianolide, 5-methoxyamphimedine and variolin.[6] The first successful sponge-derived pharmaceutical drugs were the nucleosides spongothymidine and spongouridine which were isolated from *Tectitethya crypta* (Figure 1.2). A derivative of these nucleosides, Ara-C is documented as the first marine derived anticancer agent that is recently used for the treatment of leukemia. Renieramycin M is another natural compound derived from marine sponge with promising anti-cancer activity. Renieramycins belong to the family of the tetrahydroiso-quinoline isolated from the marine sponges belonging to genera Reniera. Monanchocidin (*Monanchora pulchra*), smenospongine

(*Smenospongina*), spongistatin 1 (*Spongia*) and Heteronemin (*Hytrios sp*.) are few other compounds, which exhibited anti-tumor activity.

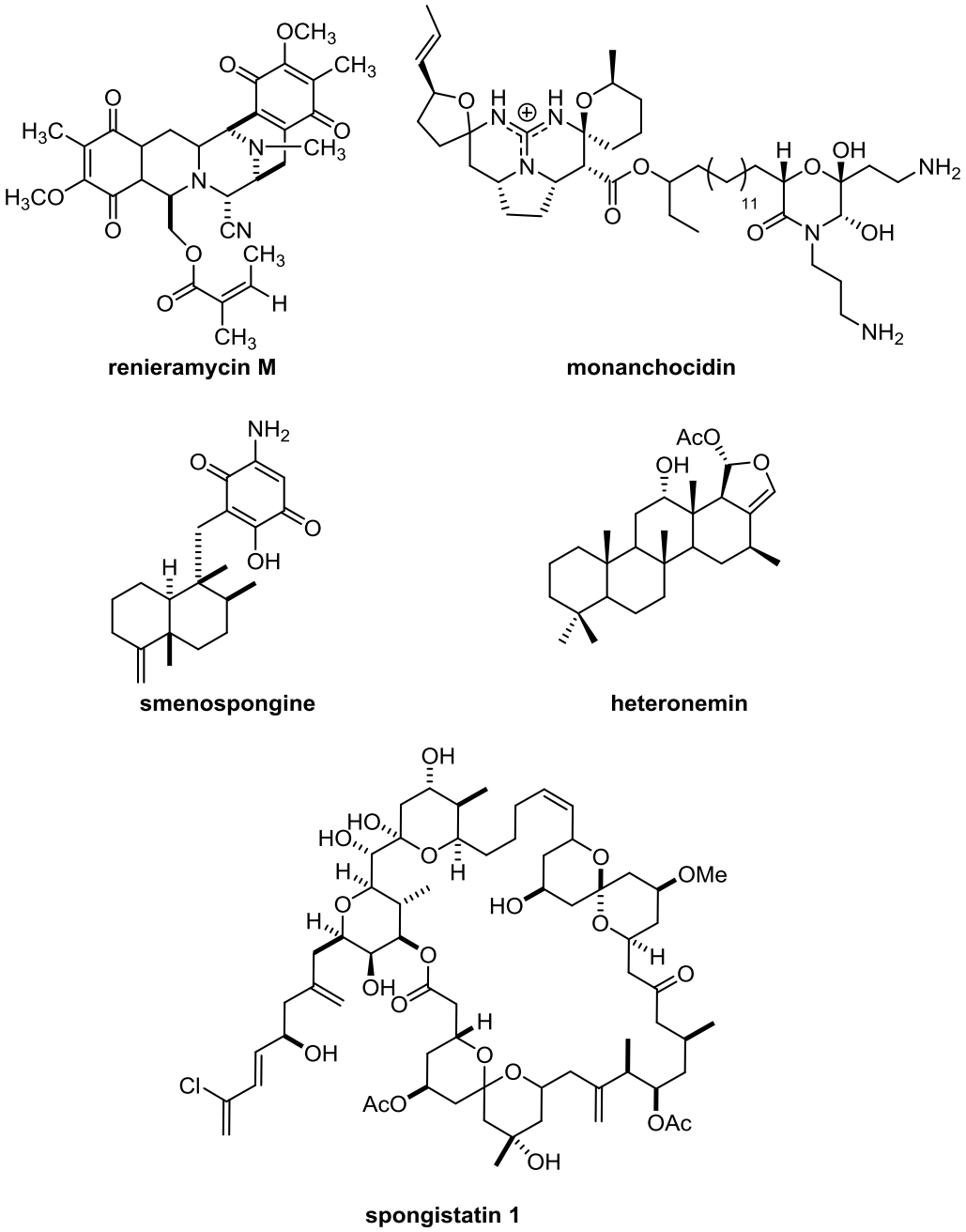


Fig. 1.2: *Natural products obtained from marine sponges.*

1.3. Bermuda Fire Sponge *Tedania Ignis* and its Metabolites:

The fire sponge *tedania ignis* is found abundantly in its endemic locations in the West Indies, Puerto Rico, Bermuda, and southern Florida and other areas (Figure 1.3). The exterior of the fire sponge varies from vermilion to orange. It is brighter red when exposed to sun, the red color is supposedly due to carotenoid pigment. With age, the color of sponge fades to orange-brown and in alcohol preservatives after months become off-white.[8]

The marine sponge is popularly known as fire sponge, as the handling of sponges caused an itching sensation which lasted for several days, it reputedly causes varying degrees of dermatitis upon contact. The reason for the dermatitis is not clear whether by sponge metabolites or due to mechanical irritation by sponge spicules.

***Fig. 1.3**: Fire sponge Tedania ignis growing in a turtle grass bed in Beliz; a cross section of Tedania ignis from Florida.*[9]

But the more interesting part is that these sponge extracts showed cytotoxicity *in vivo* tumor inhibition.[10] In the course of a bioassay-guided search by Schmitz *et al*. for the tumor-inhibitory principles, a number of inactive or mildly cytotoxic components were found. After using different isolation and extraction techniques, initially two pure solids were isolated as epiloliolide (**1**) and the other was asitane-3β, 16α-diol (**2**) (Figure 1.4). Compound **1** and **2** were found to be slightly cytotoxic to a cell culture of human carcinoma of the nasopharynx with an effective dosis 50 (ED_{50}) value of 21 μl/mL. In the course of fractionation, a different class of compounds, diketopiperazines **3**-**5** were also isolated.[11]

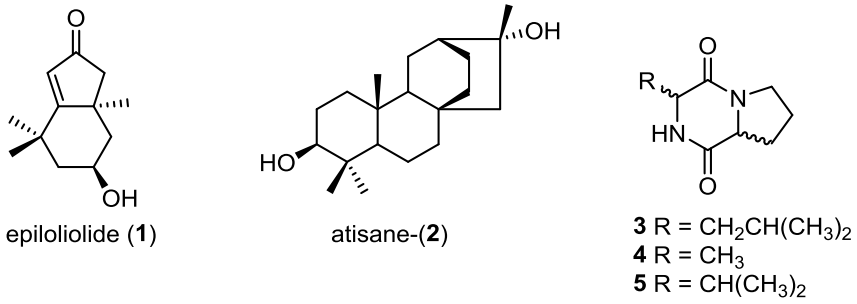


***Fig. 1.4**: Secondary metabolites from Tedania Ignis.*

Later in 1984, Schmitz *et al.* group reported an isolation of a potent cytotoxic macrolide named tedanolide **6** from the sponge *Tedania Ignis* (Figure 1.5). Around 20 kg of the dry sponge yielded 2 mg (app.) of white crystals of tedanolide. The structure of tedanolide (**6**) was determined by X-ray diffraction and NMR studies. Tedanolide is a 18-membered lactone differing from other macrolides at the site of lactonisation, which was found to be highly cytotoxic exhibiting an ED_{50} value of 2.5×10^{-4} μg in human carcinoma of the nasopharynx and 1.6×10^{-5} μg in vitro lymphocytic leukemia.[12] Cell-flow cytofluorometry analysis revealed that tedanolide causes accumulation of the cells in the S-phase at concentrations as low as 0.01 μg/mL.

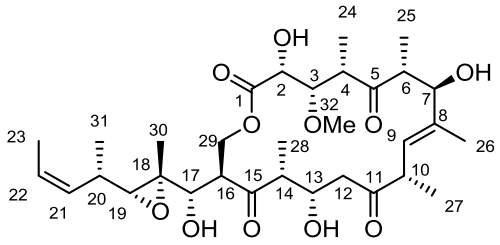


***Fig. 1.5**: Structure of tedanolide (**6**).*

1.4. Family of Tedanolides:

The highly cyclotoxic substance tedanolide (**6**) was first isolated from the marine sponge *Tedania Ignis* (a.k.a firesponge) and characterized by Schmitz *et al.* in 1984.[12] Tedanolide represent the most structurally complex, biological potent polyketide within this group of marine derived inhibitors of protein synthesis. In addition to their potent biological activity, the tedanolide represent interesting structures consisting a rare primary lactone linkage with 18-membered lactone, C(18-19) epoxide and constituting several labile aldol subunits (Figure 1.6). According to the biosynthesis of polyketides,[13-15] tedanolide is made of mixed acetate-propionate biogenesis (acetate units at C-1,2 and -11,12). It differs from other macrolides in that site of lactonization is not the near the end of carbon skeleton.[16]

Continuous search for cytotoxic metabolites from marine invertebrates, In the year 1991, Fusetani *et al.* discovered a new member of natural product 13-deoxytedanolide (**7**) from the the Japanese sponge *Mycaleadhaerens* (purple scallop sponge) belonging to the family of tedanolides (Figure 1.6).[17] Along with this four other active compounds were isolated, out of which compound **7** and a brominated isocoumarin named hiburipyranone are new. 13-Deoxytedanolide (**7**) showed remarkable cytotoxicity against P388 murine leukemia cells with inhibition concentration (IC_{50}) values of 94 pg/mL and 0.19 μg/mL respectively. Structurally, natural product **7** is very much similar to the parent compound tedanolide (**6**) just lacking at the C(13)-hydroxyl group.

As a part of natural products screening program for new anticancer lead compounds, in the year 2005 Ireland *et al.* isolated a new entity in the family of tedanolides, named tedanolide C (**8**) from the extract of the marine sponge *Ircina sp*. (a.k.a stinky sponge) collected in Milne Bay, Papua New Guinea (Figure 1.6).[18] Tedanolide C (**8**) exhibited potent cytotoxicity against haematocrit (HCT-116)

cells *in vitro* with an IC_{50} values of 57 ng/mL and arrested cell lines in S-phase. Tedanolide C (**8**) has the same eighteen membered primary lactone ring, C(18-19) epoxide as tedanolide (**6**) and 13-deoxytedanolide (**7**), but consisted a rather complex oxygenation and methylation patterns. The structure was solved by interpreting NMR and MS data, and the relative stereochemistry was determined from a combination of homo- and heteronuclear coupling constants in conjunction with molecular modelling.

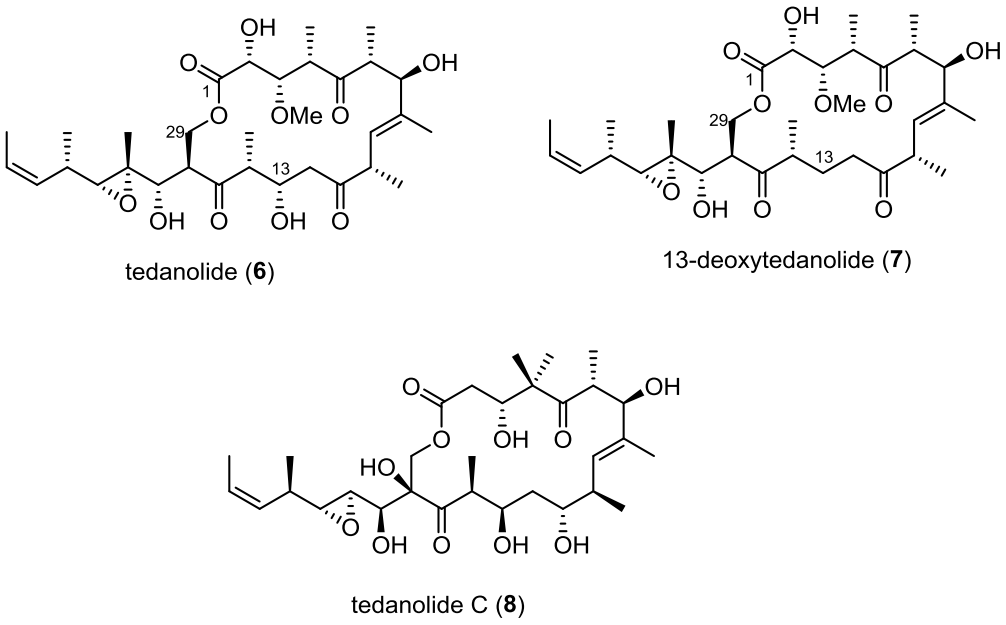
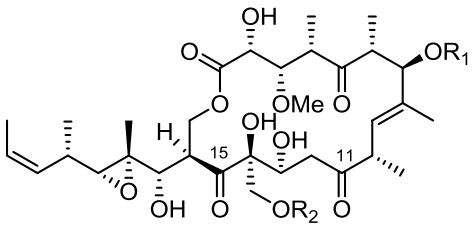


***Fig. 1.6**: Structures of tedanolide (**6**), 13-deoxytedanolide (**7**) and tedanolide C (**8**).*

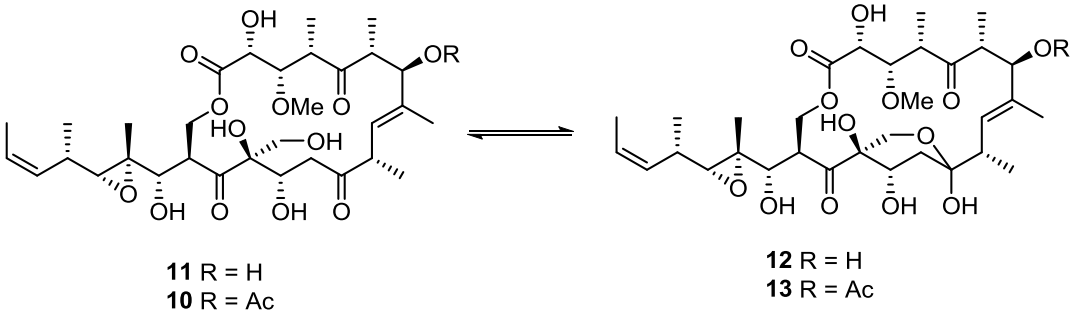
The latest additions in the family of tedanolides are candidaspongiolides **9**-**13** (Figure 1.7). Isolation of candidaspongiolides (**9**) and (**10**) was first reported in 2007 by Mc. Kee *et al.* from the sponge of the genus *Candidaspongia* (Great Barrier Reef, Australia).[19] The candidaspongiolides mixture was potentially toxic, exhibiting a mean panel 50 % growth inhibition (GI_{50}) value of 14 ng/mL in the National Cancer Institute's 60-cell line *in vitro* antitumor screen, protein synthesis inhibition, and apoptosis induction. Continued investigation of the sponge species extracts led to the isolation of three new analogues, precandidaspongiolide A (**11**), precandidaspongioldie B (**12**) and candidaspongiolide B **13** along with candidaspongiolide A (**10**) and tedanolide (**6**).[19] Candidaspongiolide A (**10**) and B (**11**) were isolated as an equilibrium mixture (A:B = 1.7:1) whereas precandidaspongiolide A (**11**) and B (**12**) were isolated as an equilibrium mixture (A:B = 4.5:1). Precandidaspngiolides A and B showed excellent selectivity against melanoma cell lines in the NCI 60-cell-line screen. The LC_{50} values for **11**/**12** against melanoma cell lines were significantly lower than other tumour cell lines. Structurally candidaspongiolides are related to tedanolide (**6**) with modifications on the carbon chain at C11-C15. Interestingly, the myriaporones isolated from a bryozoan are structurally related to the southern hemisphere of tedanolides, have also been isolated

as an equilibrium mixture.[21] The general structure of the candidaspongiolides was determined by analyses of various 2D NMR and MS data sets. The acyl ester components were identified by GC-MS analysis of the derived fatty acid methyl esters.



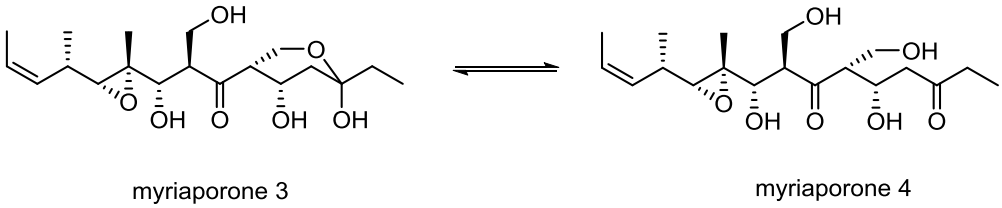
candidaspongiolides

9 R_1 = Ac, R_2 = $COC_{13\text{-}17}H_{27\text{-}33}$
10 R_1 = Ac, R_2 = H



11 R = H
10 R = Ac

12 R = H
13 R = Ac



myriaporone 3

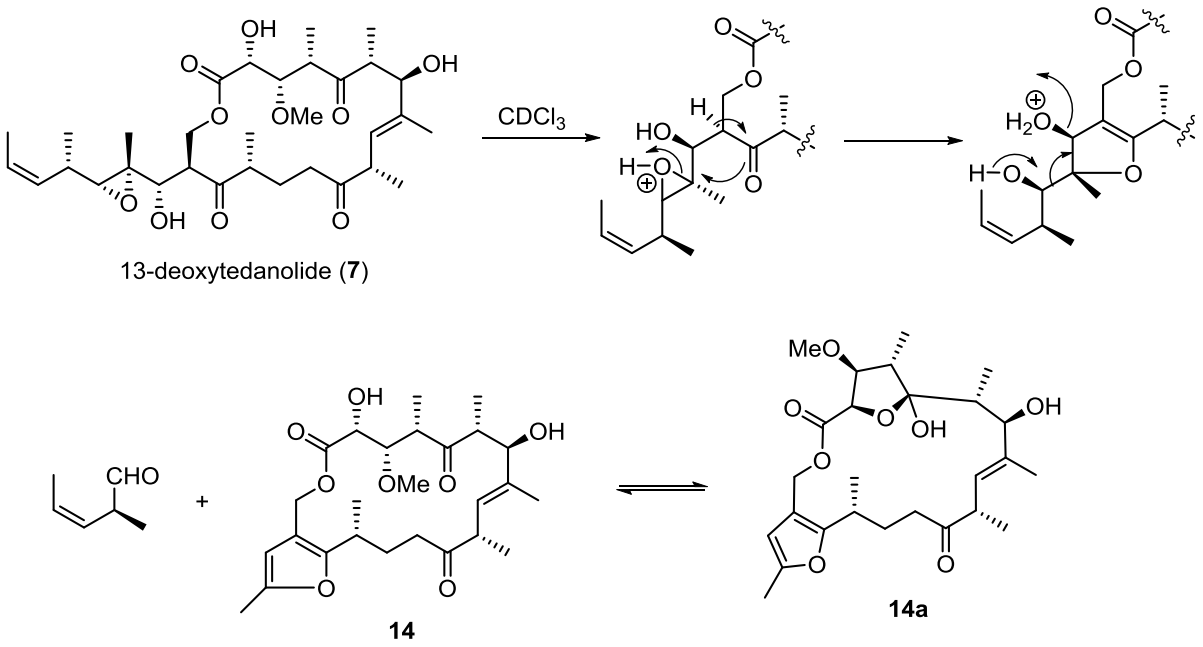
myriaporone 4

***Fig. 1.7**: Structures of candidaspongiolides **9**-**13**.*

1.5. Structure Activity Relationship Studies on 13-Deoxytedanolide (7):

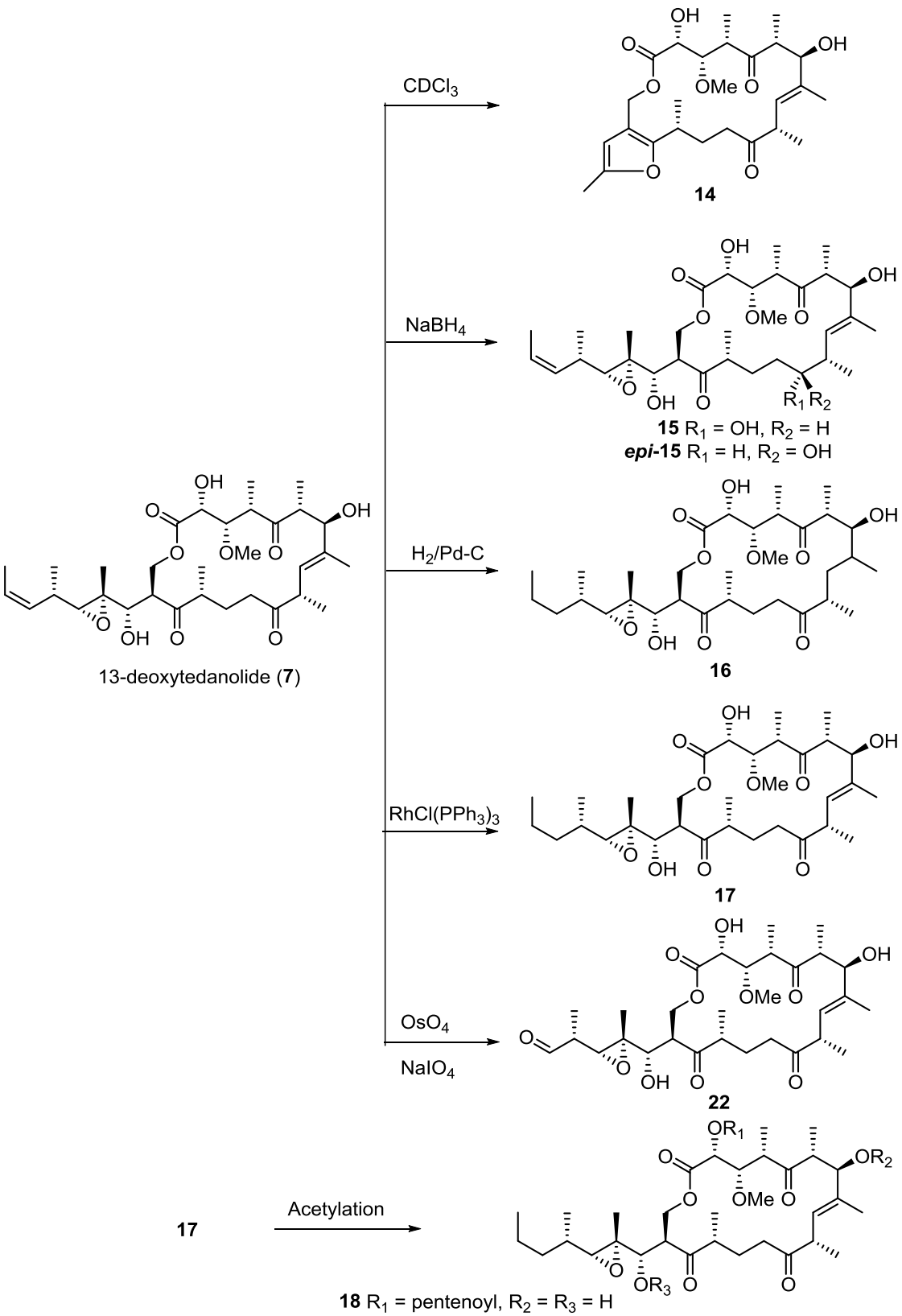
The isolation of 13-deoxytedanolide (**7**) from sponge *Mycaleadhaerens* provided the natural product in substantial amounts (105 mg), whereas tedanolide (**6**) was obtained in a very less amount (2 mg). In an attempt to obtain not only more active and less toxic derivatives but also structure activity relationships (SARs) of tedanolide cyclotoxins, Fusetani *et al.* modified some functional groups as an epoxide, hydroxyls, ketones and olefins of 13-deoxytedanolide (**7**).[22] A total of ten derivatives has been prepared and evaluated for cytotoxicity against P388 leukemia cells as well as for inhibitory effects on polypeptide elongation in yeast cell lysate. This information provided some important information for SARs.

When 13-deoxytedanolide (**7**) was exposed to $CDCl_3$, a considerable amount of less polar compound **14** was observed, confirmed by NMR studies (Scheme 1.1). This product could be generated by acid-catalysed fragmentation and also it's noteworthy that compound **14** was present as a mixture of the ketone **14** and hemiacetal **14a** forms in a ratio of 3:2.



***Scheme 1.1**: Proposed mechanism for the formation of furan **14** from 13-deoxytedanolide (**7**).*

Upon treatment of 13-deoxytedanolide (**7**) with $NaBH_4$, the 11-keto group was selectively reduced to obtain a pair of diastereomers (**15** and **epi**-**15**), catalytic hydrogenation of **7** over Pd-C afforded the tetrahydroderivative **16**, hydrogenation over $RhCl(PPh_3)_3$ yielded **17** in which only the Δ^{21}-olefin was reduced (Scheme 1.2). The three free hydroxyl groups in **7** are tried to acetylated using 4-pentenyl chloride and acetic anhydride to provide **18**-**21**. Oxidation with $OsO_4/NaIO_4$ cleaved the less hindered Δ^{21}-olefin afforded aldehyde **22**.



***Scheme 1.2**: Derivatives of 13-deoxytedanolide (**7**) for SAR studies.*

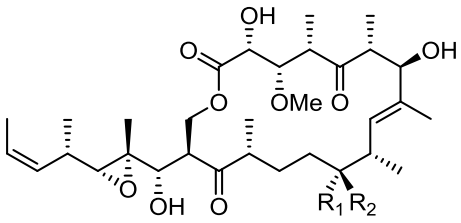
With the derivatives **14**-**22** obtained from the chemical transformations from 13-deoxytedanolide (**7**), the cytotoxicity and inhibitory activity against polypeptide elongation (Table 1.2). The IC_{50} values of their cytotoxicity against P-388 murine leukemia cells ranged from 14 pg/mL to higher than 5 μg/mL, while those of their polypeptide elongation inhibition from 0.15 μM to higher than 100 μM. Furan compound **14** lost both the activities, suggesting the importance of both or either of the C-15 keto group and/or the side chain. Compound **15** retained the activity similar to deoxytedanolide (**7**), this implies that oxygen atom at C(11) in keto form or hydroxyl form will act as hydrogen acceptor. ***epi*-15** has significant decrease in the activity emphasising the strict requirement for spatial alignment of the oxygen atom at C(11). The contribution of Δ^8-olefin functionality to the activity was demonstrated by the significantly reduced activity of **16**, while Δ^{21}-olefin functionality is less important as judged by the fully retained activities of **17**. The northern hemisphere and the Δ^8-olefin may play a role for stabilizing the conformation of the southern hemisphere in the active form. Two hydroxyl groups in the northern hemisphere may not be incorporated in the pharmacophore, which was indicated by the decreased but still potent activity of mono-acylated derivatives **18** and **19**. Dipentenoate **20** showed only weak or no activity. These bulky modifications may generate synergetic effect, to avoid its binding to the ribosome. The oxygen atom at C(17) may also contribute to the potent activity, which was revealed by the loss of polypeptide elongation inhibition of the derivative **21**. Although **21** showed potent cytotoxicity, retention of activity in acetates are frequently explained by hydrolysis of endogenous esterases. The significance of the hydrophobhic terminus was substantiated by reduced activity of **22**, in which terminal aldehyde group was hydrated. The cytotoxicity and polypeptide elongation inhibition of these derivatives disclosed the structural features important for the potent cytotoxicity (Table 1.2).

Compounds	Cytotoxicity	Polypeptide elongation inhibition
	IC_{50} (ng/mL)	IC_{50} (μM)
7	0.064	0.15
14	>5000	>100
15	0.014	0.15
***epi*-15**	92	0.80
16	49	1.5
17	0.2	0.4
18	20	0.75
19	9.2	0.65
20	500	>50
21	8	>50
22	>5000	15.0

Table 1.2. *Biological activity of 13-deoxytedanolide (**7**) and its derivatives.*

1.6. 60S Ribosomal Subunit – Target of 13-Deoxytedanolide (7):

Since the discovery of tedanolides, inspite of their remarkable activity the modes of action remained unknown until 2005, for the first time Fusetani *et al.* had conducted studies on 13-deoxytedanolide (**7**) and elucidated.[23] In this study, a search was performed on the target molecule of 13-deoxytedanolide (**7**) by using radiolabeled analogues **23** and ***epi*-23** (Figure 1.8). From the budding yeast *Saccharomyces cerevisiae* cell lysate, 60S large ribosomal subunit was identified as the target of 13-deoxytedanolide (**7**), and showed that compound **7** strongly inhibited polypeptide synthesis. Furthermore, 13-deoxytedanolide (**7**) was shown to share an unknown binding site on the 60S large ribosomal subunit with pederin.[24]



23 R_1 = H, R_2 = OH
***epi*-23** R_1 = OH, R_2 = H

***Fig. 1.8**: Chemical structures of **r**adiolabeled ligands from 13-deoxytedanolide (**7**).*

Two radiolabeled analogues [11-^{3}H]-(11*S*)-deoxydihydrotedanolide **23** and *epi*-**23** were synthesized by treatment with [^{3}H]-$NaBH_4$. Compounds **7** and **23** inhibited growth of *S.cervisiae* while **24** showed weaker growth inhibition. To identify the 13-deoxytedanolide (**7**) binding protein, the cell lysate of *S.cervisiae* was incubated with radio-labeled 13-deoxydihydrotedanolides and tested whether the radioactivity was detected in the fraction trapped on the glass filter. Binding activity of these compounds correlated well with their anti-yeast activities, suggesting the presence of specific macromolecular target in the yeast. Although many protein synthesis inhibitory natural products are known to bind to the prokaryotic large subunit and inhibit the peptide elongation, 13-deoxytedanolide (**7**) is the first macrolide that binds to the eukaryotic ribosome. Macrolide antibiotics, for example erythromycin and carbomycin, inhibit protein synthesis by binding to the 50S large subunit of prokaryotic ribosomes, but do not bind to the eukaryotic ribosomes. This difference may be due to the size of rings; 12- to 16- membered rings in prokaryotic antibiotics versus 18-membered rings in tedanolides.

The radioligands **23** also bound to the purified salt washed 80S ribosome. Moreover, the radioligand **23** bound to the 60S subunit with high affinity, but didn't bind to the 40S subunit. The 60S subunit had only a high affinity binding site, although 13-deoxytedanolide showed a high-affinity binding and a low-affinity binding to the 80S ribosomal complex. The presence of the high-affinity binding suggested that a covalent bond formed between the ribosome and the macrolide.

The strong binding of 13-deoxytedanolide (**7**) to the 60S subunit of the ribosome suggests that **7** inhibits protein synthesis. By examining the effects of **7**, **23**, **epi-23** on poly(U)-directed poly(Phe) synthesis in the yeast S30 fraction. Compounds **7** and **23** inhibited the reaction at the IC_{50} value of

0.15 μM. In contrast compounds **7** and **23** couldn't inhibit the polypeptide synthesis in the cell lysate prepared from *Escherichiacoli*.

Competitive binding assays were carried out using ribosomal antibiotics, namely, peptidyltransferase inhibitors, puromycin and anisomycin, which share a neighbouring binding site around the peptidyltransferase center, did not prevent the binding of the radioligand **23** to the ribosome. The traditional translocation inhibitor, pederin (Figure 1.9) was found to perturb the binding of the radioligand to the 60S ribosomal subunit. While cycloheximide, another translocation inhibitor did not inhibit it. Theopederin A and onnamide A, which are closely related to pederin[24] (isolated from sponge *Paederusfuscipes*) also competed with 13-deoxytedanolide (**7**) for binding, thus indicating that the potent cyclotoxins of the pederin class share the binding site on the 60S large subunit common to 13-deoxytedanolide (**7**). It is also expected that compound **7** will be an important tool for elucidating structure and function of eukaryotic ribosomes.

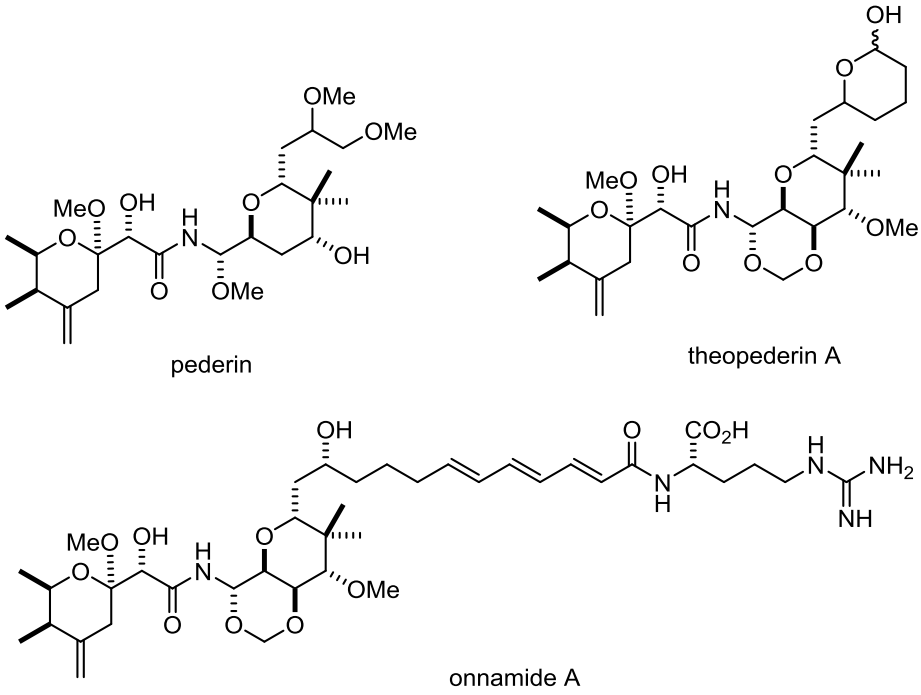


***Fig. 1.9**: Chemical structures of pederin, theopederin A and onnamide A.*

Crystal structures of the 50S ribosomal subunit from *Haloarculamarismortui* complexed with the antibiotic 13-deoxytedanolide (**7**) have been reported by Moore and co-workers in 2007.[25] 13-Deoxytedanolide (**7**) binds to the E-site of the 50S subunit and thus appears to inhibit protein synthesis by competing with deacylated tRNAs for E site binding (Figure 1.10). The specificity of 13-deoxytedanolide for eukaryotic ribosomes is explained by its extensive interactions with protein L44e, which is an E site component of archeal and eukaryotic ribosomes, but not of the eubacterial ribosomes. In addition, protein L28, which is unique to the eubacterial E site, overlaps the site occupied by 13-deoxytedanolide, precluding its binding to eubacterial ribosomes. Homology modeling of the 70S ribosomal subunit of *Thermus thermophilus* with 13-deoxytedanolide showed overlapping

of the 28L protein (gray) and the drug (yellow) (Figure 1.10). This explains the selectivity for eukaryotes and presumably archaea.

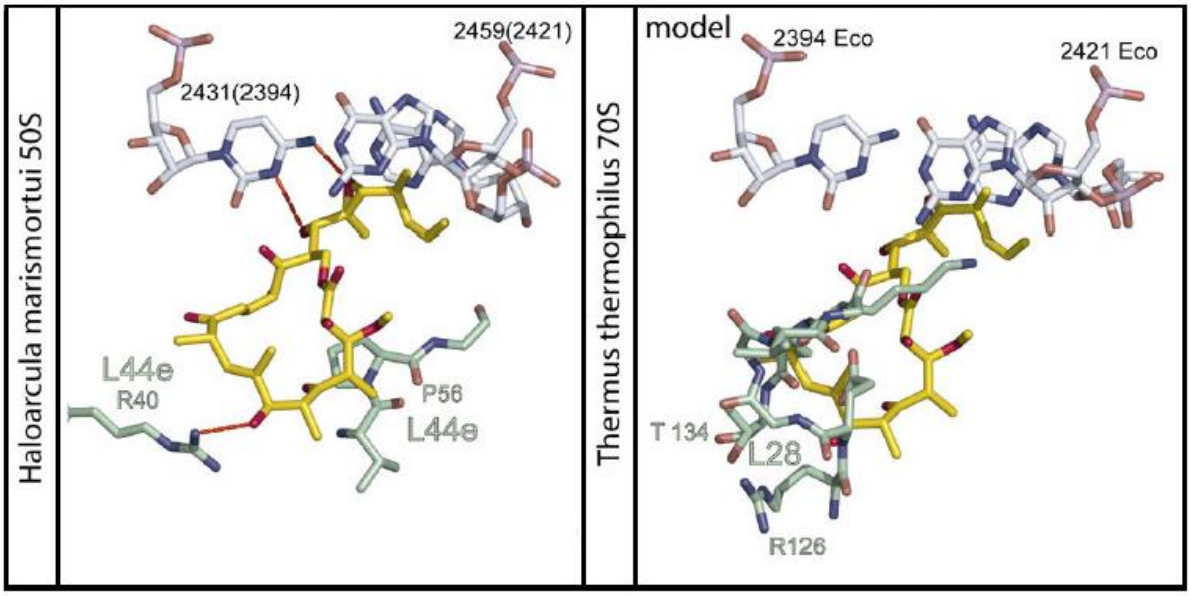


***Fig. 1.10**: Homology modelling studies of 50S and 70S subunit with 13-deoxytedanolide (yellow) (**7**).*

1.7. Myriaporones – Structural Similarity to C10-23 Fragment of Tedanolide:

In the year 1995, Reinhart and co-workers isolated four novel polyketide-derived metabolites, myriaporones **24**-**27** from the Mediterranean bryozoan *Myriaporatruncate* (Figure 1.11).[21, 26-27] Bryozoans are a group of primitive colonial animals widely distributed throughout the worlds marine and fresh water environments. Among those metabolites isolated from marine bryozoans, bryostatins are the most exciting and promising compounds which exhibit pronounced cytotoxicity.

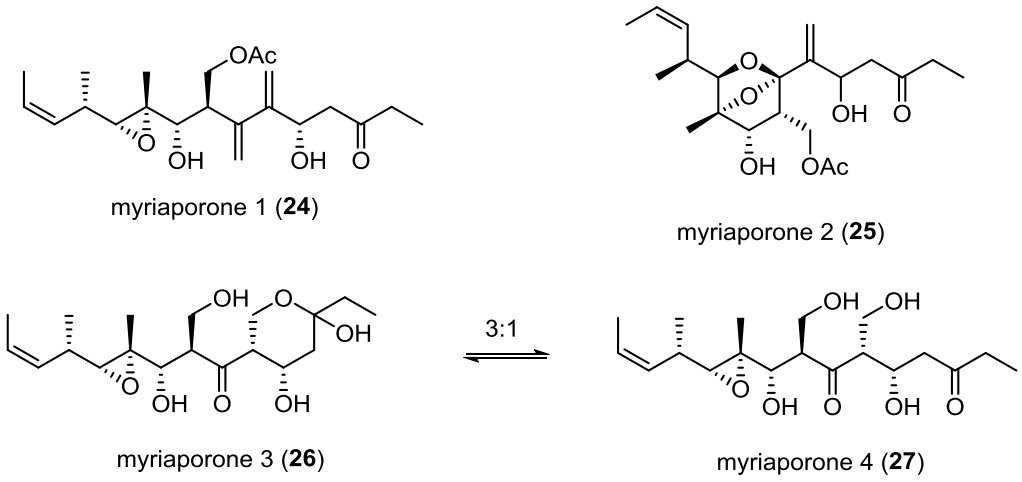


***Fig. 1.11**. Structures of myriaporones **24**-**27**.*

The structures and stereochemistry have been assigned from the analysis of spectroscopic data. The inseparable equilibrium mixture of myriapornes 3 (**26**) and 4 (**27**) showed 88% inhibition of L210 murine leukemia cells at 0.2 μg/mL (IC_{50} value of 100 ng/mL). Additionally, cytofluorometry experiments showed that myriaporone 3/4 caused S-phase arrest. Myriaporone 2 (**25**) showed 70% inhibition against L210 murine leukemia cells at 5 μg/mL. Myriaporone 2 arises from the epoxide opening of by the C(7)-carbonyl in myriaporone 1 (**24**).

The myriaporones are structurally nearly identical to the C10-23 portion of tedanolide (**6**). The C(16)-alcohol is reminiscent of the candidaspongiolides. The myriaporones would then share the same mode of action as tedanolide and their simple structure renders them more attractive as drug candidates. Recent studies established that like tedanolide, myriaporone 3/4 is a potent protein synthesis inhibitor selective for eukaryotes.[28] In order to provide enough material to facilitate these studies, research groups of Taylor and Cuevas were successful in achieving the total synthesis of myriaporones.[29,30]

Tedanolide (**6**) and 13-deoxytedanolide (**7**) are the most studied members of the tedanolide family, they virtually exhibit the same biological activity. The only structural difference is the presence of an alcohol at the C(13) position, which corresponds to C5 position for the myriaporones. Few analogues were designed by Myriam Roy from Taylor group in order to study the structure activity relationships of myriaporones (Figure 1.12).[31] C(16)-deoxymyriaporone 4 (**28**), C(5)-deoxymyriaporone 3/4 (**29**) and C(5,16)-dideoxymyriaporone (**30**) are the analogues lacking the hydroxyl groups as similar to the

difference in **6** and **7** (Figure 1.12).Analogues lacking the *Z*-double bond in myriaporones and to probe the role of equilibrium, C(16)-hydroxyl ether was masked as methyl ether.

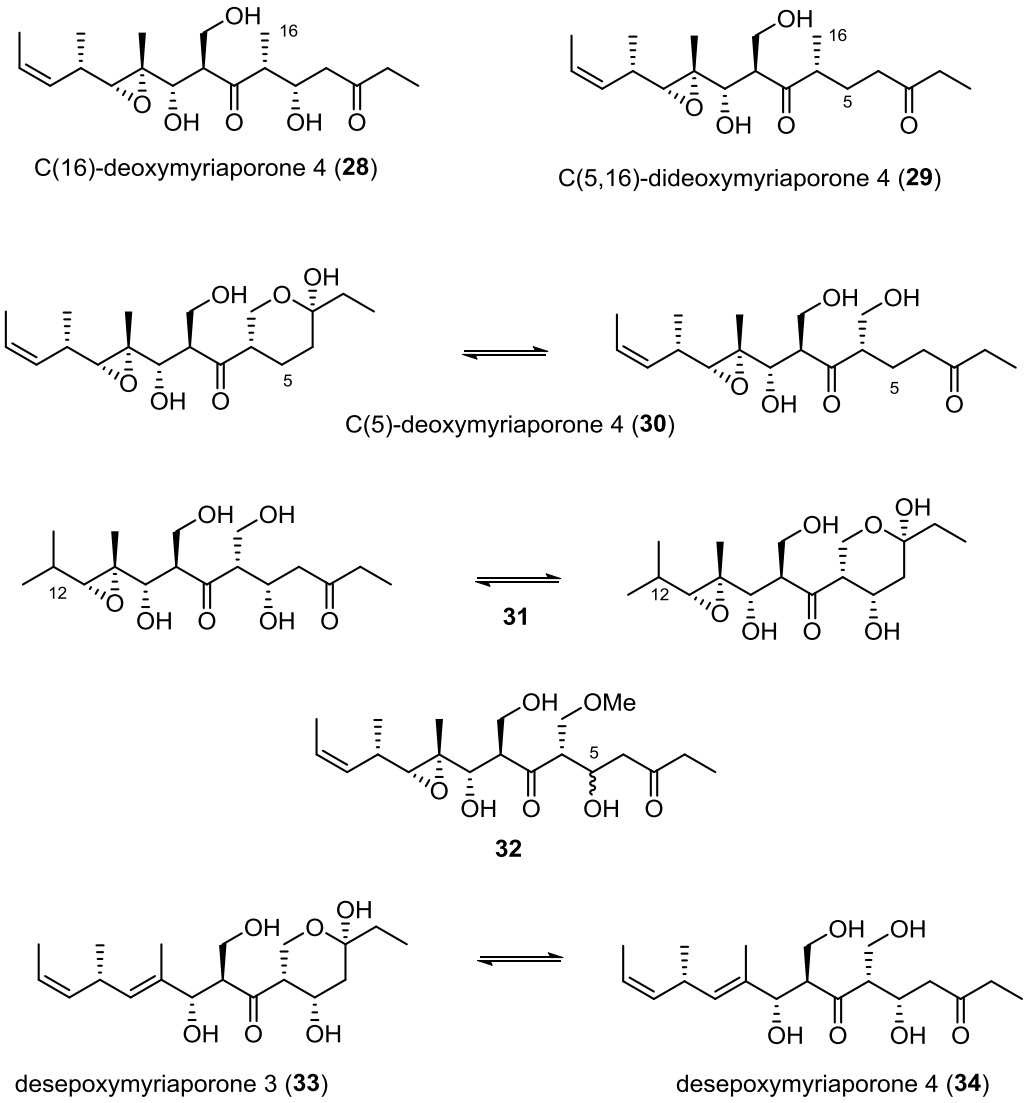


***Fig. 1.12**: Structures of derivatives of myriaporones **28**-**34**.*

Preliminary biological results performed with HTC-116 and MF-7 exhibited significant loss of activity. Thus far, simplification made to myriaporone 3/4 failed to retain the biological activity (Figure 1.13). It was identified that C(10,11) epoxide, C(13,14) *Z*-olefin, alcohol at C(5) and its stereochemistry, C(16) alcohol in the open form and the oxidation state at C(3) in the close form are proven to be essential for the activity.

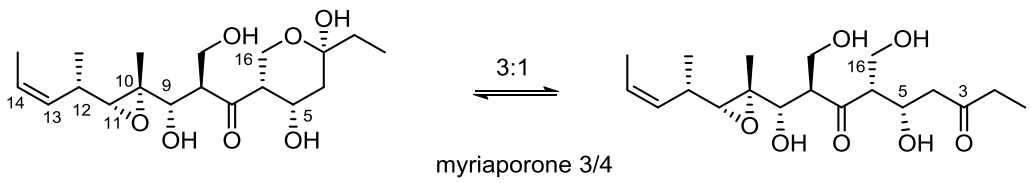


***Fig. 1.13**: Myriaporones 3/4 **26**&**27**.*

1.8. Gephyronic acid – Pharmacophoric Link between two Classes of Natural Products:

An antibiotic compound gephyronic acid (**35**) was isolated from the culture broth of the myxobacterium *Archangiumgephyra*strain Ar 3895 in 1995 by Höfle and Reichenbach.[32] It is an aliphatic acid and tends to form hemiacetal (Figure 1.14). Both forms inhibited growth of yeasts and molds (MIC 1 ~ 25μg/mL) and had a cytostatic effect on mammalian cell cultures (IC_{50} 10 ~ 60 ng/mL). Gephyronic acid (**35**) is a specific inhibitor of eukaryotic protein synthesis showing an IC_{50} value of 1~2 × 10^{-7}mol/L in an *in vitro* translation assay.

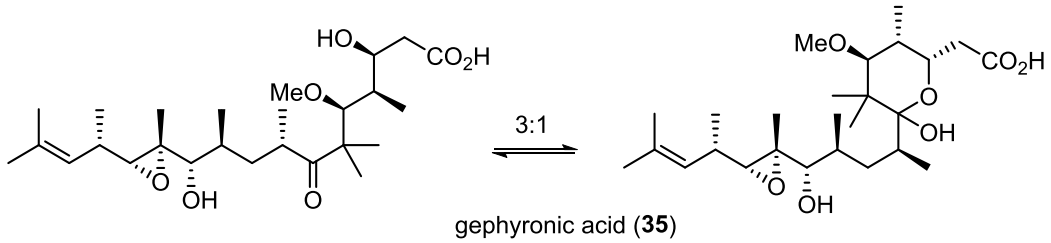


***Fig. 1.14**. Structure of gephyronic acid (**35**).*

A combination of high-field NMR analysis of the natural products resulted in a revision of the structure of gephyronic acid (**35**), including a full assignment of the relative and absolute stereochemistry was finally confirmed by total synthesis from Taylor group.[33,34]

The structurally related polyketide natural products tedanolide (**6**), myriaporone 3/4 (**27**) and gephyronic acid (**35**) are promising bioactive compounds that have been found to be potent and selective eukaryotic protein synthesis inhibitors. Although the the mode of action of gephryronic acid (**35**) is not known.

Recently, polyketide **35** was discussed as a pharmacophoric link to tedanoliode (**6**) and 13-deoxytedanolide (**7**) on its proposed relative configuration.[35] There is a significant structural similarities between the C8-C17 region of gephyronic acid, the C15-C15 region of myriaporones, and the C13-23 region of the tedanolides (Figure 1.15). Moreover, the closed form of gephyronic acid appears to map quite well to the pyran region of the pederin class of polyketides. Thus, combined with their common selective eukaryotic protein synthesis inhibitor activity, gephyronic acid (**35**) may represent a potential pharmacophoric link between structurally distinct classes of biologically active compounds.

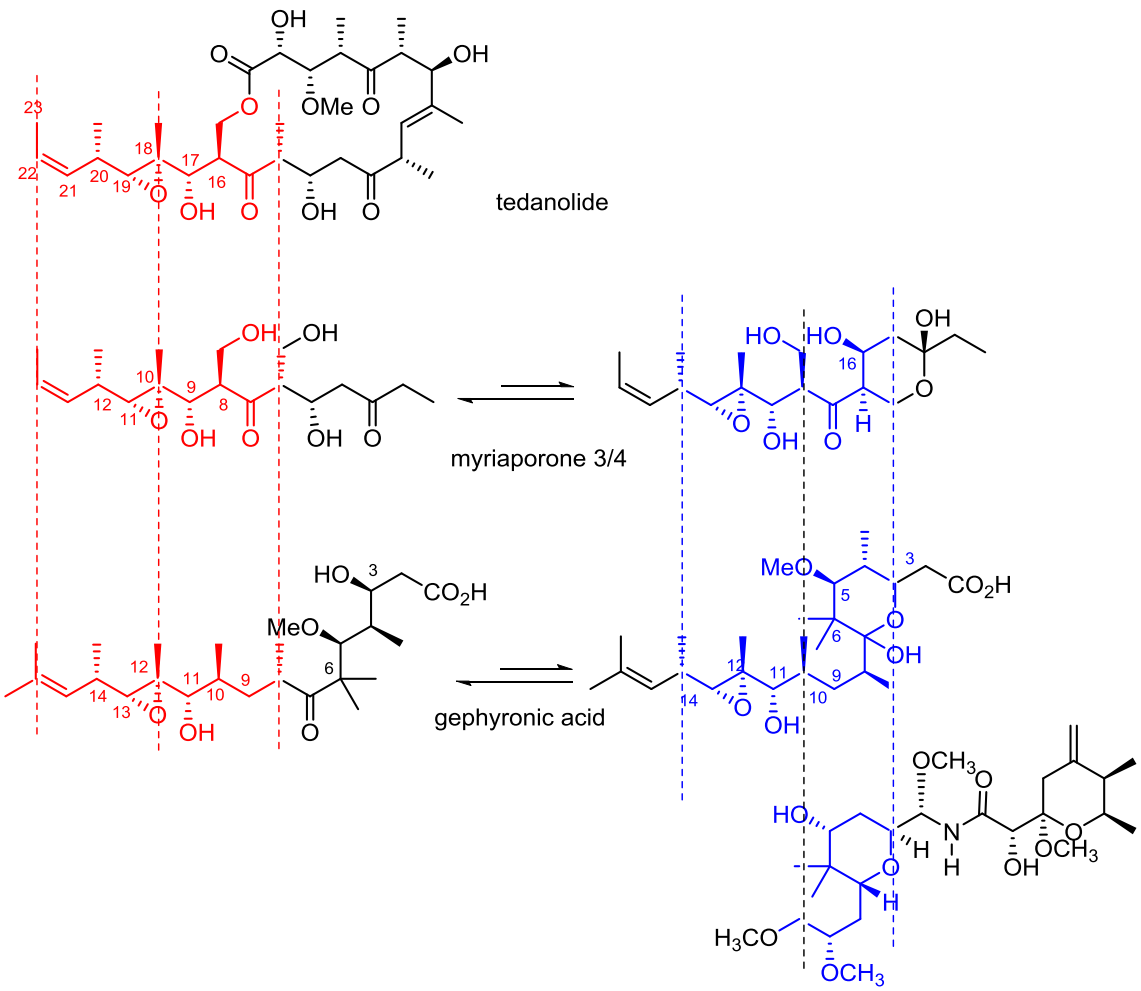
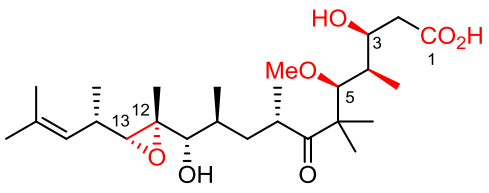


Fig. 1.15: *Structural relationships between eukaryotic protein synthesis inhibitors.*

Although the biological target of gephyronic acid (**35**) was known, the specific target remains unidentified. Various diastereomers of gephyronic acid were made in order to elucidate the structure activity relationships. These studies have provided the evidence for the epoxide C(12-13) in the western part of the molecule as well as the C3-C5 stereotriad and the C1-moeity in the eastern part to be the pharmacophoric subunits for the observed cytotoxicity (Figure 1.16).[31]



gephyronic acid (**35**)

Fig. 1.16: *Phamracophoric subunits of gephyronic acid (**35**).*

1.9. Polyketide Biosynthesis:

The remarkable structural and functional diversity in polyketides biosynthetically arises from combinatorial utilization and template-directed elongation of only a few simple building blocks. Malonyl-CoA and methylmalonyl-CoA comprise the great bulk of monomer units incorporated during chain elongation (Figure 1.17). The chain starter units can be the thioesters of monoacyl groups as acetyl-, propionyl-, and benzyl-CoAs, or structural variants, such as malonamyl-CoA or methoxymalonyl-CoA.[13] There are three types of polyketide synthases (PKS) type I PKS (large and highly modular proteins), type II PKS (aggregates of mono-functional proteins) and type III PKS (which don't use ACP domains). Type I PKS can be iterative (repetition of the same module in a cyclic fashion) or modular (contains a sequence of separate modules and don't repeat domains).

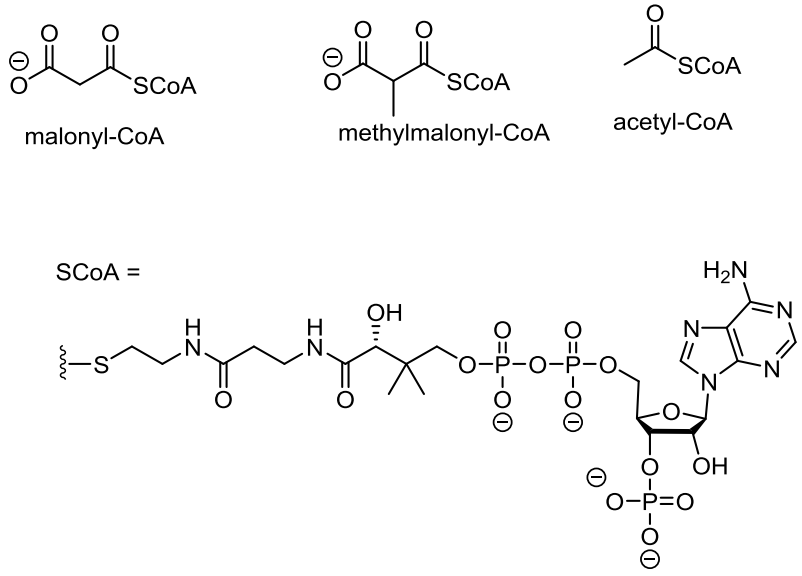


Fig. 1.17: *Structures of common acyl-CoA thioesters used for chain intitiation and elongation of PKSs.*

Several transformations are catalysed in the different modules. An example of best know polyketide, erythromycin will be discussed. To clarify the synthetic implication of the domain organisation, the PKS version is shown in the Figure 1.18. The structural genes responsible for the biosynthesis of first macrolide intermediate 6-deoxyerythronolide B (6-dEB) are three enormous open reading frames (ORFs), *eryAI*, *eryAII* and *eryAIII* coding for three gigantic multienzyme polypeptides, 6-deoxyerythronolide B synthase (DEBS) 1, 2 and 3 respectively. The circles depict the domains and the linker regions are omitted. Each of the DEBS proteins contains two modules, each module contains the three domains require to catalyse one cycle of chain extension [ketosynthase (KS), acyltransferase (AT) and acyl carrier protein (ACP)] as well as variable set of domains [ketoreductase (KR), dehdratase (DH) and enoyl reductase (ER)]. Starting from ketosynthase and finishing with ACP is taken to be a modular unit. DEBS 1 is fronted by a loading didomain (AT and ACP) which accepts the started unit propionate from the propionyl-CoA, while DEBS 3 terminates with the thioesterase (TE) activity which is thought to catalyse the off-loading of the fully formed heptaketide intermediate **37** and cyclise to give 6-dEB **36**.

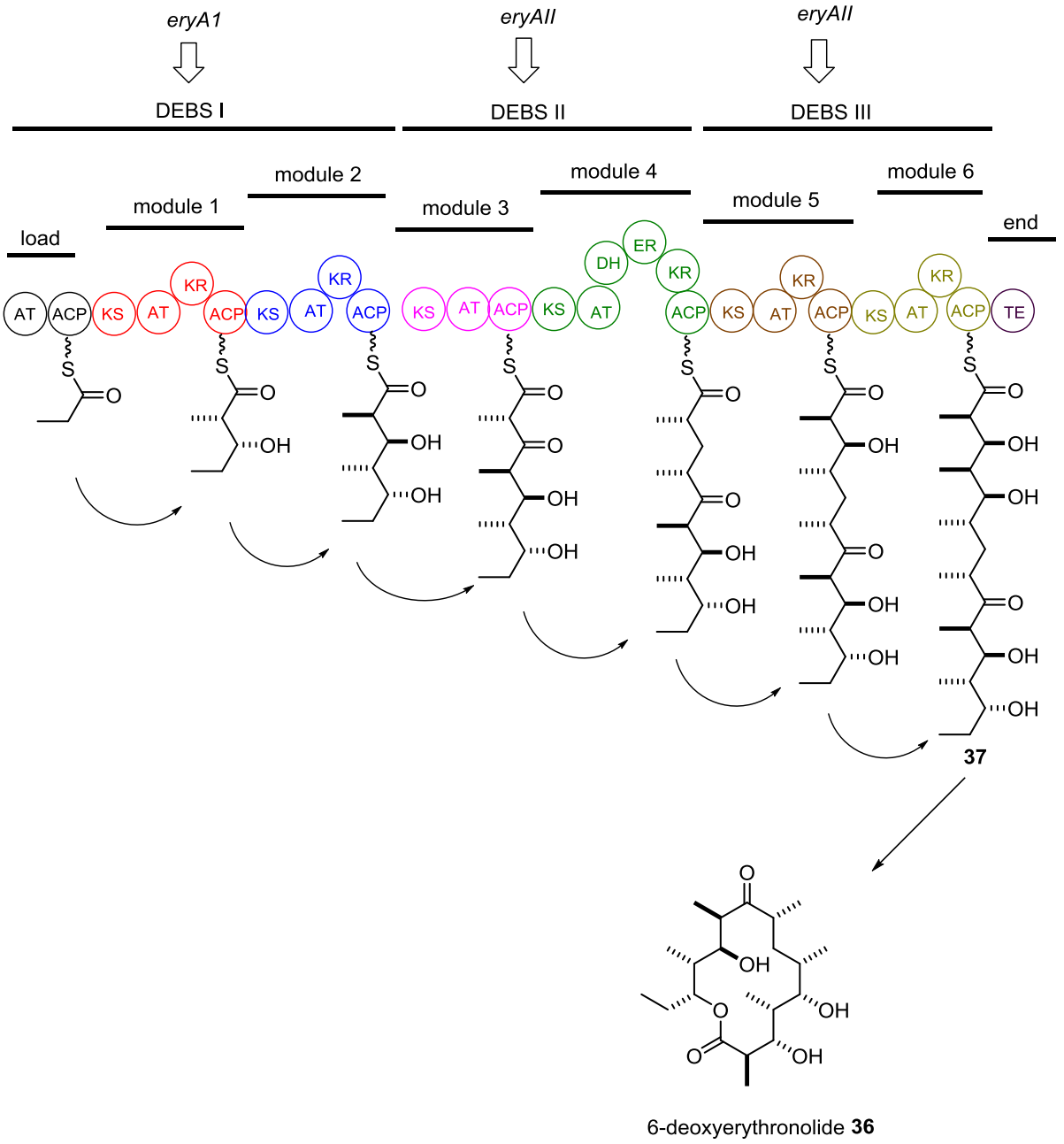


Fig. 1.18: *Domain organization of the erythromycin polyketide synthase.*[13]

The post PKS process involves the conversion of the 6-deoxyerythronolide (**36**) to erythromycins A-D. This direct PKS product **37** then usually is cyclised and becomes the substrate for the enzymes that perform the post-PKS modifications. Among these modifications are methylations (performed by methyl transferases MT) and oxidations (epoxidation or alcohol insertions by cytochrome P450 oxidase). In the case of erythromycins, C-6 erythronolide hydroxylase selectively introduces the hydroxyl group at C(6) position, TDP-mycarose glycosyltransferase attaches the L-mycarose at C(3) position and the amino sugar D-desosamine is then added to C(5) hydroxyl group with the aid of TDP-desosamine glycosyltransferase gives rise to erthyromycin D. Eyrythromycin D later will be converted

to other erythromycins with the help of enzymes C-12 hydroxylase and *O*-methyl transferase (Figure 1.19).

Another example is the case of epothilone,[36] the C(12-13) epoxide is installed by a cytochrome P450 epoxidase found in epoK.

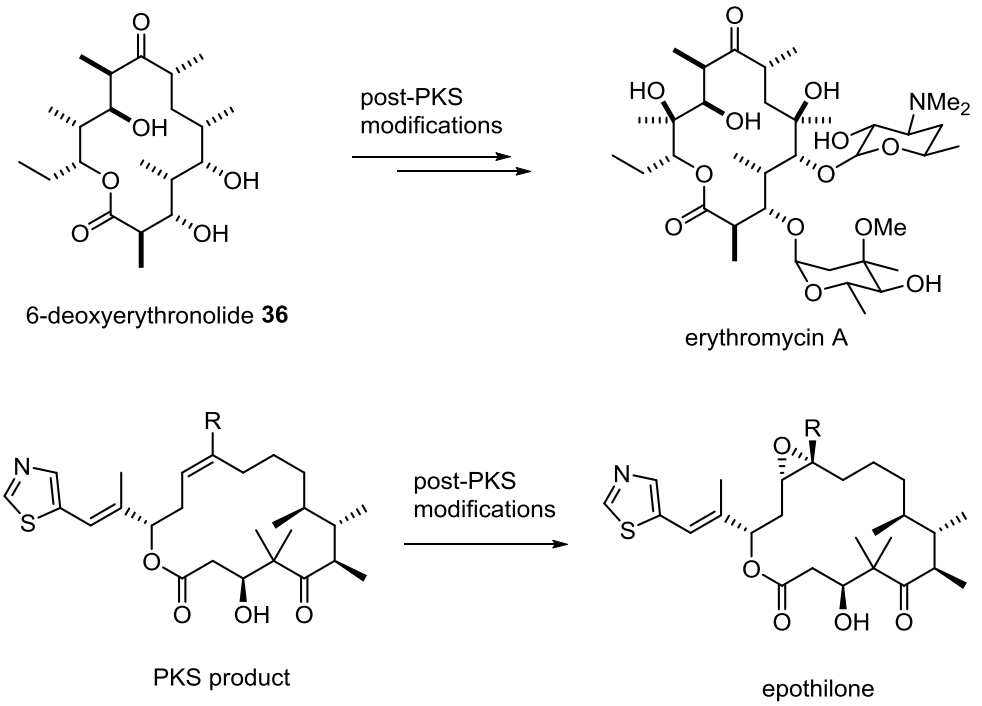


Fig. 1.19: *Post-PKS modifications in polyketide biosynthesis*

It is evident from the above stated examples that the post-PKS modifications are common in the synthesis of polyketides, there could be chance that the biosynthesis of the tedanolides would also include a direct PKS product, which would then undergo post-PKS modifications to give rise to the rare class of compounds with primary lactone linkage macrolides.

2. Objective:

From the biosynthetic prospective of polyketides, macrolides with primary lactone linkage are rare in the nature. Tedanolides are one of the rare class of polyketides consisting this salient feature. From the proposed biosynthesis of tedanolide (**6**), it was envisioned that isotedanolide (**38**), a secondary lactone could be the synthetic precursor (Figure 2.1). In an effort to prove this proposal desepoxyisotedanolide (**40**) was chosen as our synthetic target. The main objective of my Ph.D. dissertation is to synthesize desepoxyisotedanolide (**40**).

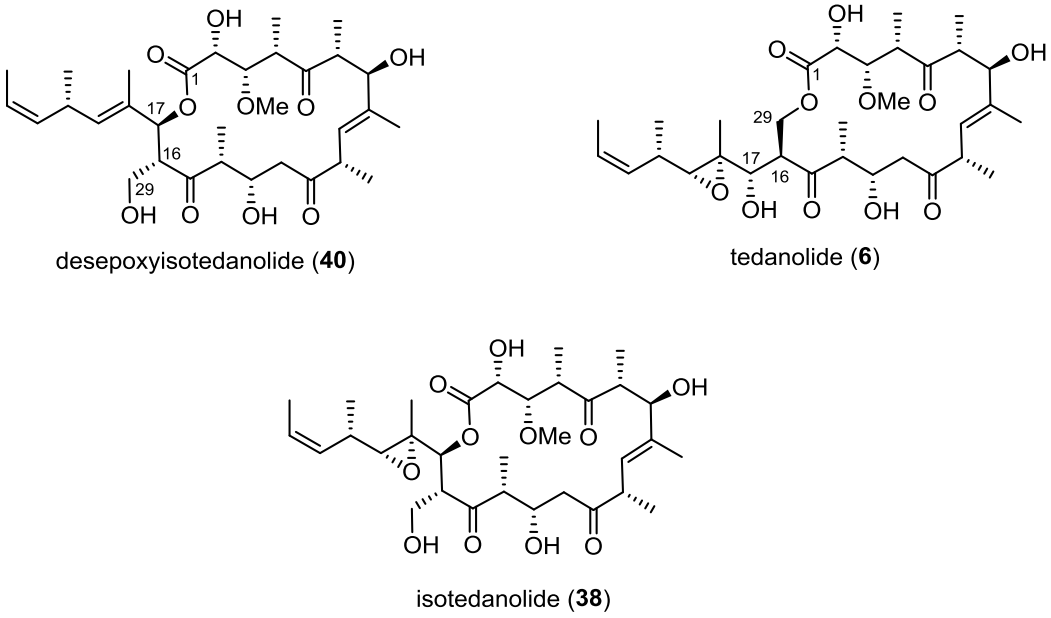
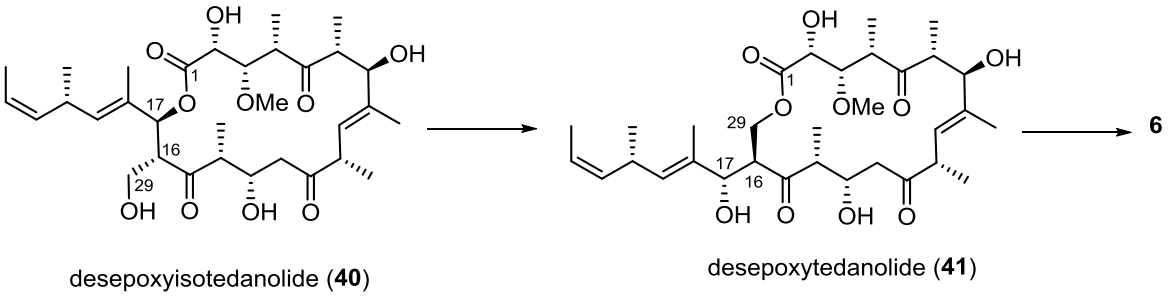


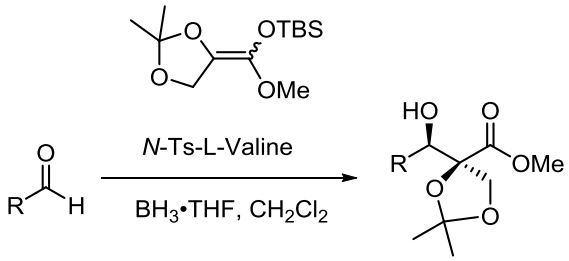
Fig. 2.1: *Desepoxytedanolide (**40**) as a biosynthetic precursor of tedanolide (**6**).*

Additionally, we planned to investigate the isomerisation of desepoxytedanolide (**40**) to the desepoxytedanolide (**41**) in a chemical environment (Scheme 2.1). This will substantiate the proposed biosynthesis of the tedanolide (**6**) and also the biological tests of this derivative **40** could provide more insights into the structure activity relationships of tedanolides.



Scheme 2.1: *Isomerisation of desepoxyisotedanolide (**40**).*

In second part of my thesis, the scope of applying Kiyooka aldol reaction to a variety of aldehydes to generate tertiary alcohols in a stereoselective manner will be explored (Scheme 2.2).



Scheme 2.2: *Kiyooka aldol reaction*

3. Previous work:

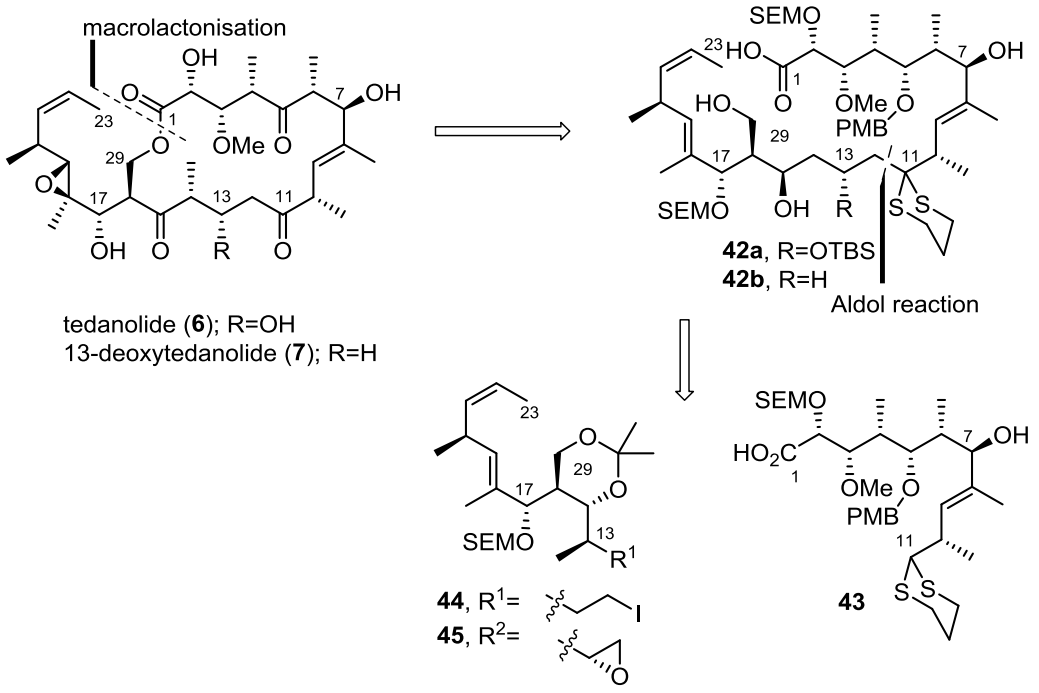
Due to the challenging structural complexity along with promising biological activity of tedanolides, several groups had initiated the synthetic studies resulting in a variety of fragment synthesis and total synthesis of tedanolide (**6**) and 13-deoxytedanolide (**7**).[37-45, 67, 79] No total synthesis had been reported till date for the comparitively more complex molecules tedanolide C (**8**) and candidaspongiolides (**9**-**13**). In this chapter the synthetic work concerning the total synthesis of natural products (**6**&**7**) will be discussed.

3.1. Smith's Approach:

(A unified approach to tedanolide (**6**) and 13-deoxytedanolide (**7**)).
Smith and co-workers were the first to accomplish the total synthesis of the 13- deoxytedanolide (**7**) in 2003[37] and followed it up later with the total synthesis of tedanolide (**6**) in 2007[38] using the unified approach from a common intermediate (Scheme 3.1).

Inspired from the total synthesis of rapamycin,[39] the Smith group used dithiane linchpin **43** as the common advanced intermediate for the synthesis of both tedanolides **6** and **7**.

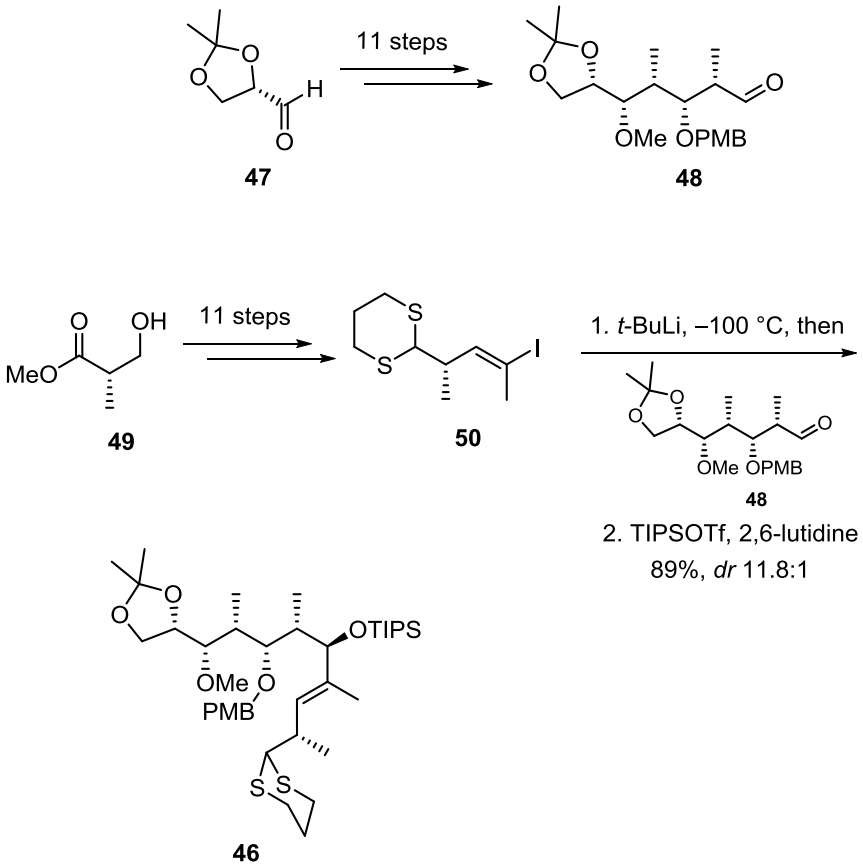
The retrosynthetic part is depicted below in the *Scheme 3.1*. Epoxidation of the double bond C(18-19) was performed at the later stage, disconnection at the macrolactone linkage unfolded the linear fragment **42a**/**42b**. Further disconnection at C(11-12) linkage gave rise to a common fragment, dithiane **43**, and an epoxide fragment **45** employed in the synthesis of tedanolide, whereas an alkyl halide **44** in the case of 13-deoxytedanolide (**7**).



Scheme 3.1*: Retrosynthetic approach towards tedanolide and 13-deoxytedanolide by Smith et al.*

3.1.1. Construction of the Dithiane Fragment 46:

Aldehyde **48** was foreseen as an ideal substrate for further conversions towards the synthesis of dithiane **46** (Scheme 3.2). This polypropionate motif was obtained by a series of aldol condensations beginning from (*S*)-glyceraldehyde acetonide **47** as the starting point in 11 steps. Aldehyde **48** was treated with the lithiated species of vinyl iodide **50** to obtain the essential carbon framework for the dithiane **43**. Iodide **50** was obtained in 11 steps from the commercially available (*S*)-Roche ester **49**. The dithiane **46** was achieved in a linear sequence of 13 steps starting from glyceraldehyde acetonide **47** with an overall yield of 23%.[40]

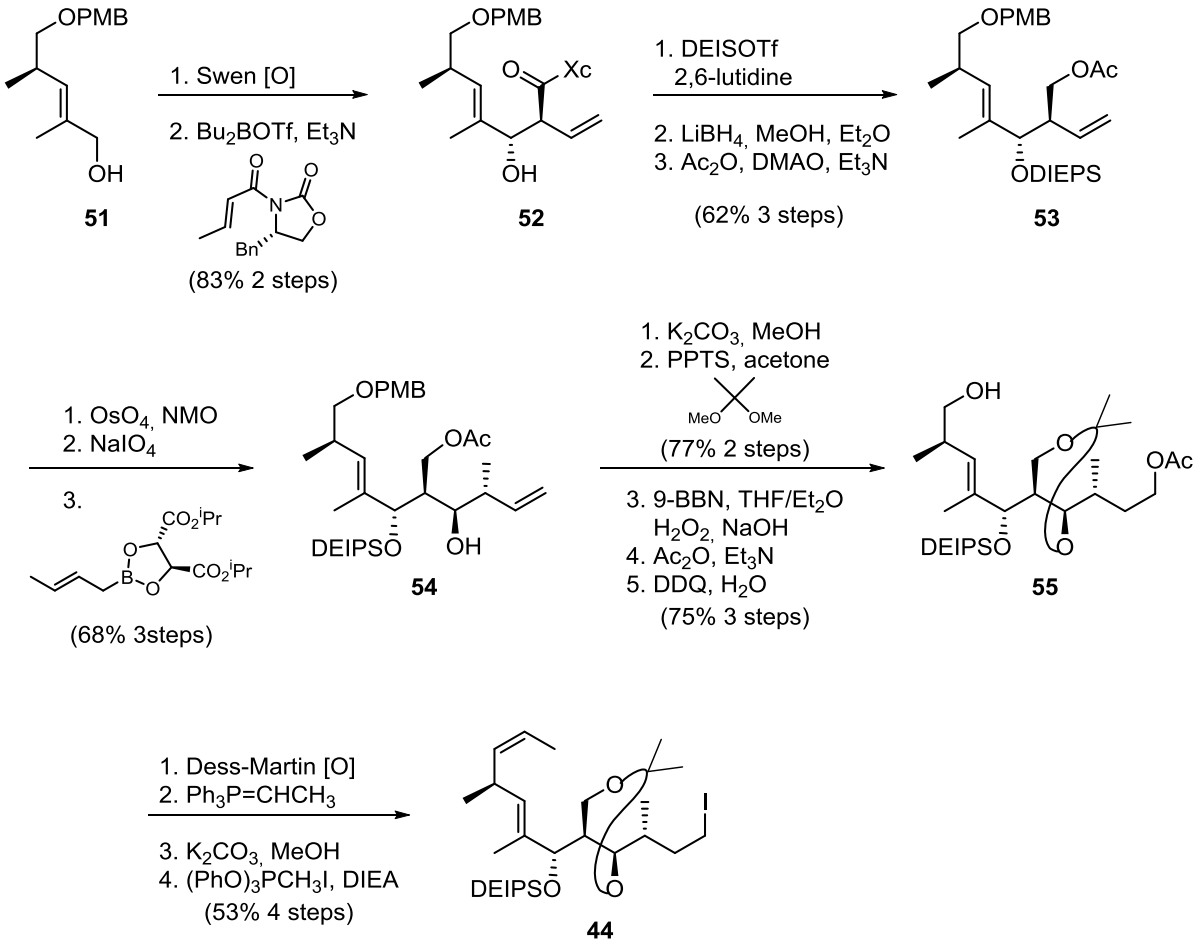


***Scheme 3.2**: Synthesis of dithiane **46**.*

3.1.2 Construction of Iodide Fragment 44:

Synthesis of the fragment **44** began with the known alcohol **51**,[41] Conversion to acetate **53**, using standard transformations proceeded in an overall high yield (51% over 5 steps). Ozonolysis of terminal olefin followed by Roush crotylation[42] afforded compound **54**, subsequent hydroboration of the terminal olefin to the corresponding primary alcohol, followed by removal of the PMB group gave compound **55**. Oxidation of the deprotected hydroxyl group to the aldehyde and immediate Witting olefination led to the desired *Z*-Olefin in very good selectivity (20:1). Finally, deprotection of the

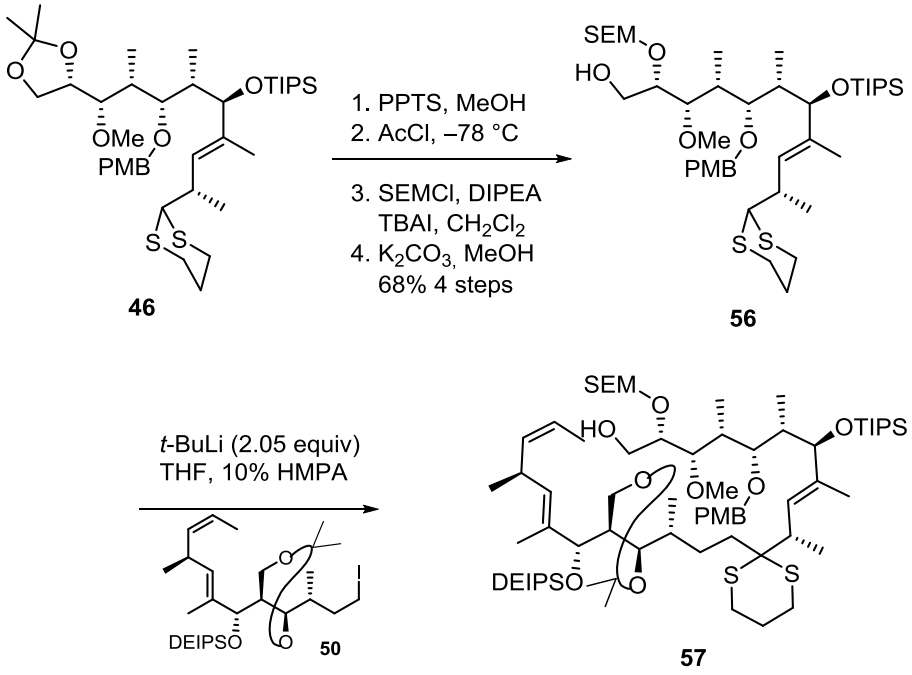
acetyl group and conversion of the primary hydroxyl group to the alkyl iodide using methyltriphenoxyphosphonium iodide gave the iodide **44** (Scheme 3.3).



***Scheme 3.3**: Synthesis of alkyl iodide **44**.*

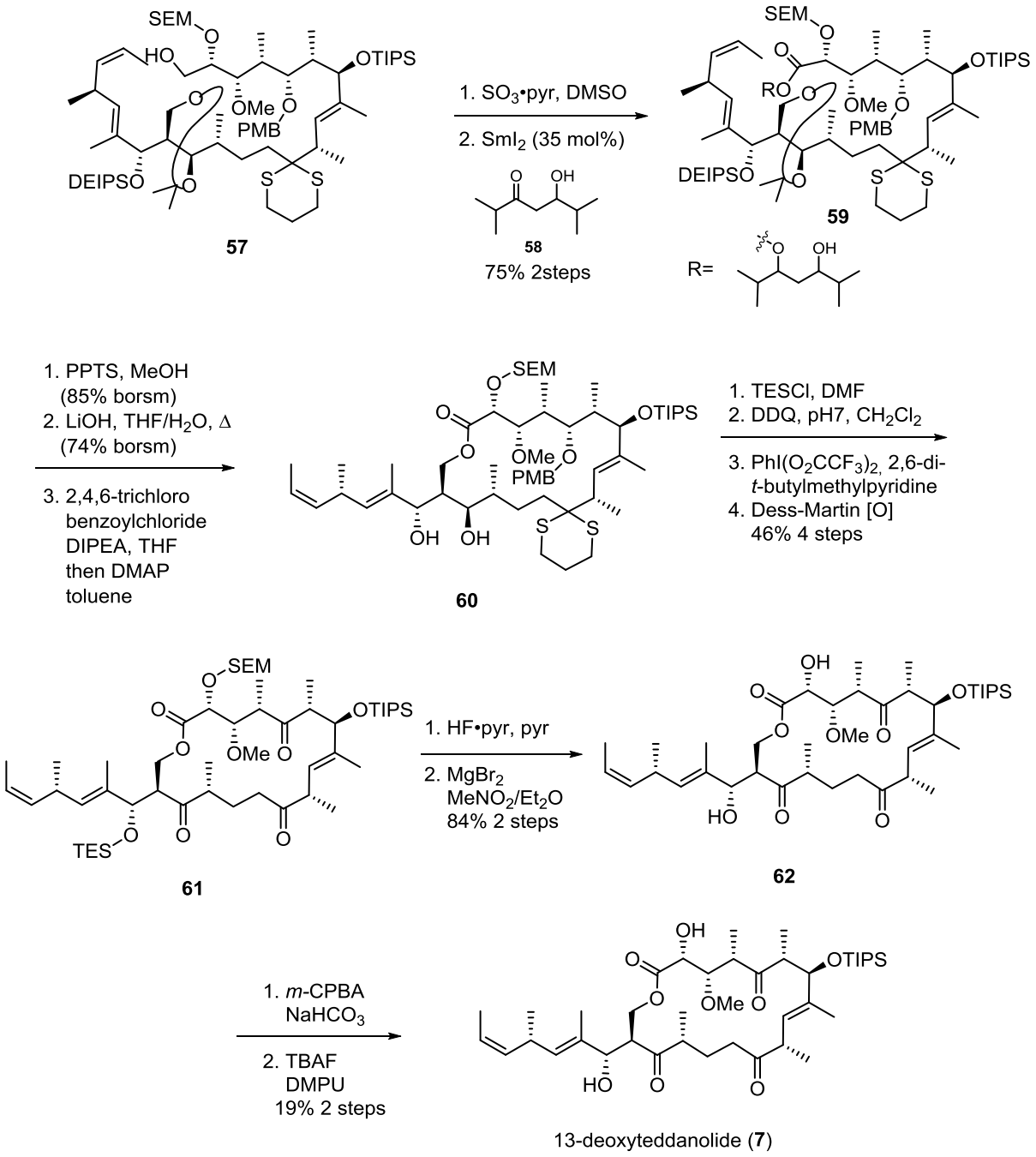
3.1.3. Synthesis of 13-Deoxytedanolide (7):

Construction of SEM ether **56** from dithiane **46** was achieved over a sequence of 4 steps (Scheme 3.4). Lithiated dianion of **56** was treated with iodide **44** to afford compound **57** in 75 % yield, providing the complete carbon framework necessary for the construction of 13-deoxytedanolide (**7**).



***Scheme 3.4**: Synthesis of compound **57**.*

Intermediate **57** was then conveniently converted to the corresponding aldehyde using Parikh-Doering conditions,[43] followed by treatment with SmI_2 in the presence of β-hydroxy ketone **58** to afford a diastereomeric mixture of ester **59**, therefore effectively achieving oxidation at C(1) *via* an Evans-Tischenko reduction (Scheme 3.5).[44] Removal of the acetonide group using standard conditions also led to the loss of the diethylisoproplysilyl (DEIPS) group and hydrolysis at elevated temperature provided the free carboxylic acid necessary for the macrolactonisation, which was achieved using Yamaguchi conditions[45] to provide macrolactone **60**. Selective protection of the less sterically hindered allylic hydroxyl group was achieved with TESCl in DMF, subsequent removal of the PMB ether and the dithiane allowed for Dess-Martin oxidation of the resulting hydroxyl group to afford triketone **61**. Removal of the TES ether and SEM ethers[46] in the presence of TIPS group was achieved selectively in high yields and upon treatment of compound **62** with *m*-CPBA in the presence of $NaHCO_3$[47] the desired epoxide was obtained with excellent stereoselectivtiy (>15:1) and an yield of 48%. Finally removal of the TIPS group using TBAF and aq. DMPU led to 13-deoxytedanolide (**7**).

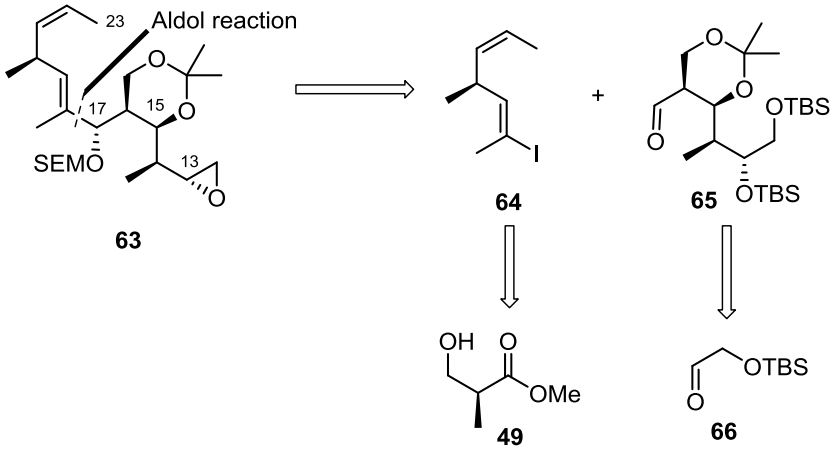


***Scheme 3.5**: Synthesis of 13-deoxytedanolide (**7**).*

3.1.4. Synthesis of Tedanolide (6) by Smith *et al.*:

3.1.5. Construction of the Epoxide 63:

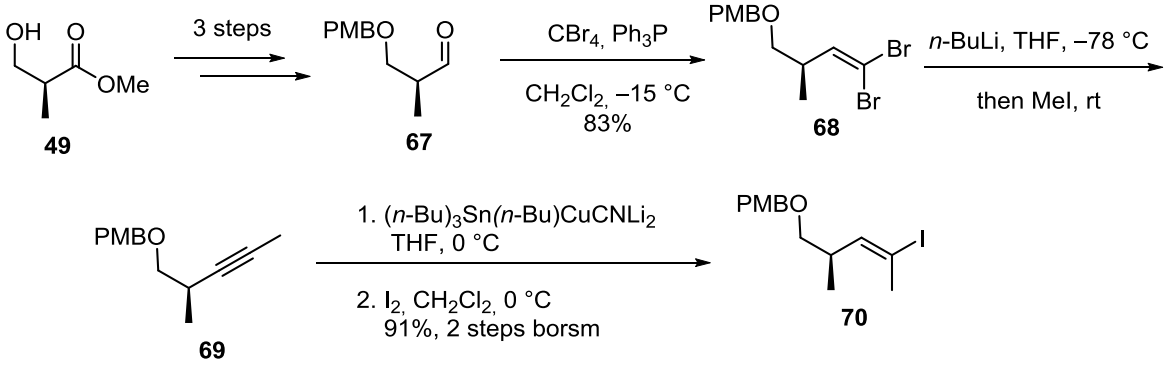
Due to the lengthy first generation sequence leading to epoxide fragment **45** resulted in synthetic inefficiency. For the synthesis of tedanolide (**6**), Smith group developed a second generation strategy employing the alternative β-stereoisomer of C(15) compared to 13-deoxytedanolide (**7**). This would be of no consequence since the C(15) hydroxyl would eventually be oxidized to ketone in the final product **6** (Scheme 3.6). Recognition of the allylic alcohol system at C(17) in compound **63** prompted the construction of this structural array in a stereo selective manner. It was envisioned that disconnection at the C(17-18) bond would result in vinyliodide **64** and aldehyde **65**.



***Scheme 3.6**: Retrosynthetic approach of epoxide **63**.*

3.1.6. Construction of the Vinyliodide fragment 64:

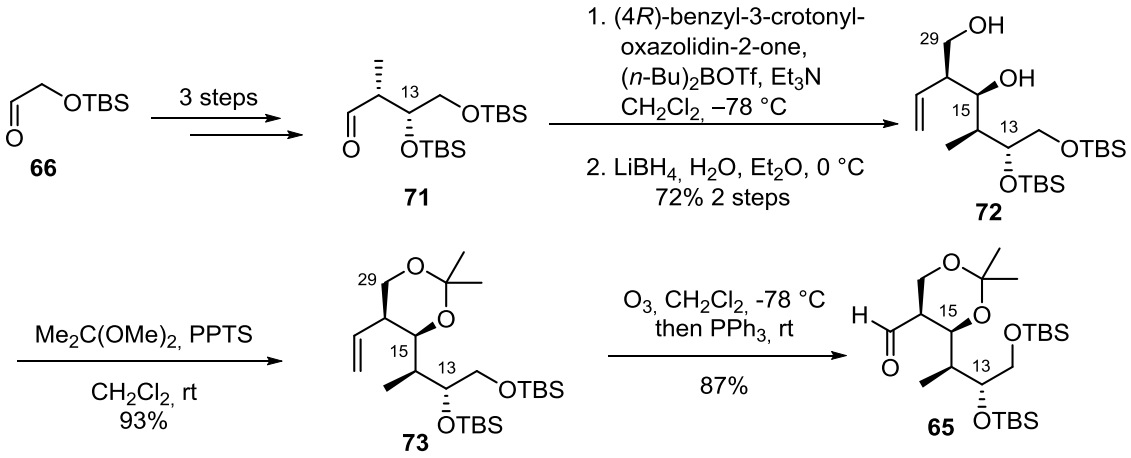
Literature known Roche aldehyde **67** was converted to alkyne **69** *via* Corey-Fuchs protocol[48] in a yield of 83% (Scheme 3.7). In order to obtain the vinyl iodide moiety, stannylcupration of alkyne **69** employing conditions of Pancrazi and coworkers,[49] followed by iodination afforded the desired (*E*)-trisubstitutedvinyliodide **70** as a single isomer. Thus fragment **70** was obtained in four steps with an overall yield of 69% from aldehyde **67**.



***Scheme 3.7**: Synthesis of vinyliodide **70**.*

3.1.7. Construction of the Aldehyde Fragment 65:

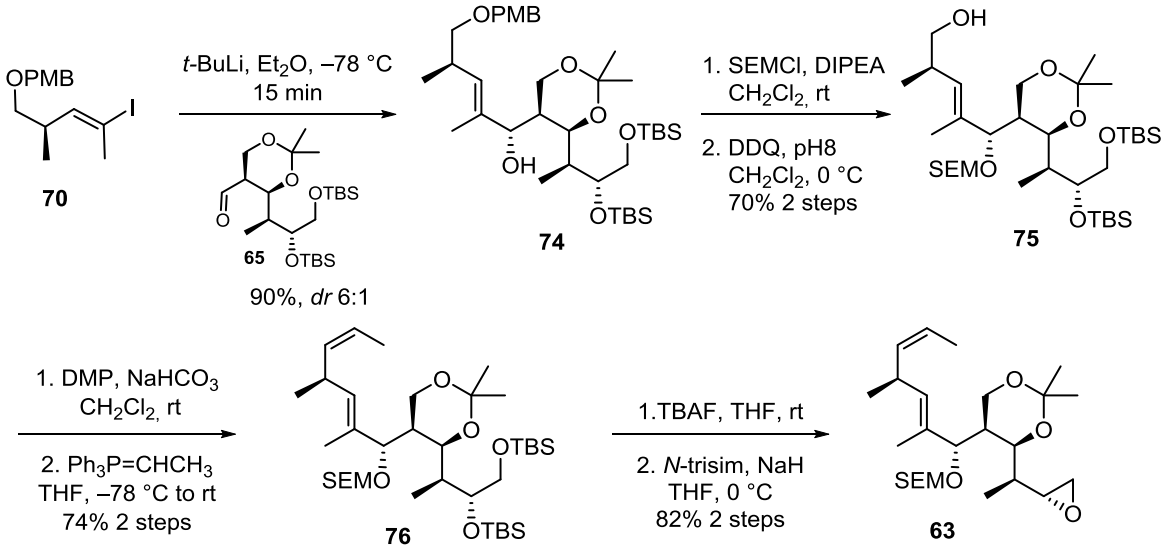
Syn-aldol condensation employing the Evans' crotonateimide[50] of the literature known aldehyde **71**[51] followed by reductive cleavage of the oxazolidinone furinished the homoallylic diol **72**, establishing the C(15) and C(16) stereogenic centers with excellent stereoselectivity (Scheme 3.8). The resulting C(15) and C(29) hydroxyl groups were protected as a cyclic ketal **73**. Ozonolysis of the terminal olefin in compound **73** provided the desired aldehyde **65**.



***Scheme 3.8**: Synthesis of aldehyde **65**.*

3.1.8. Construction of the C(12-23) Fragment 63:

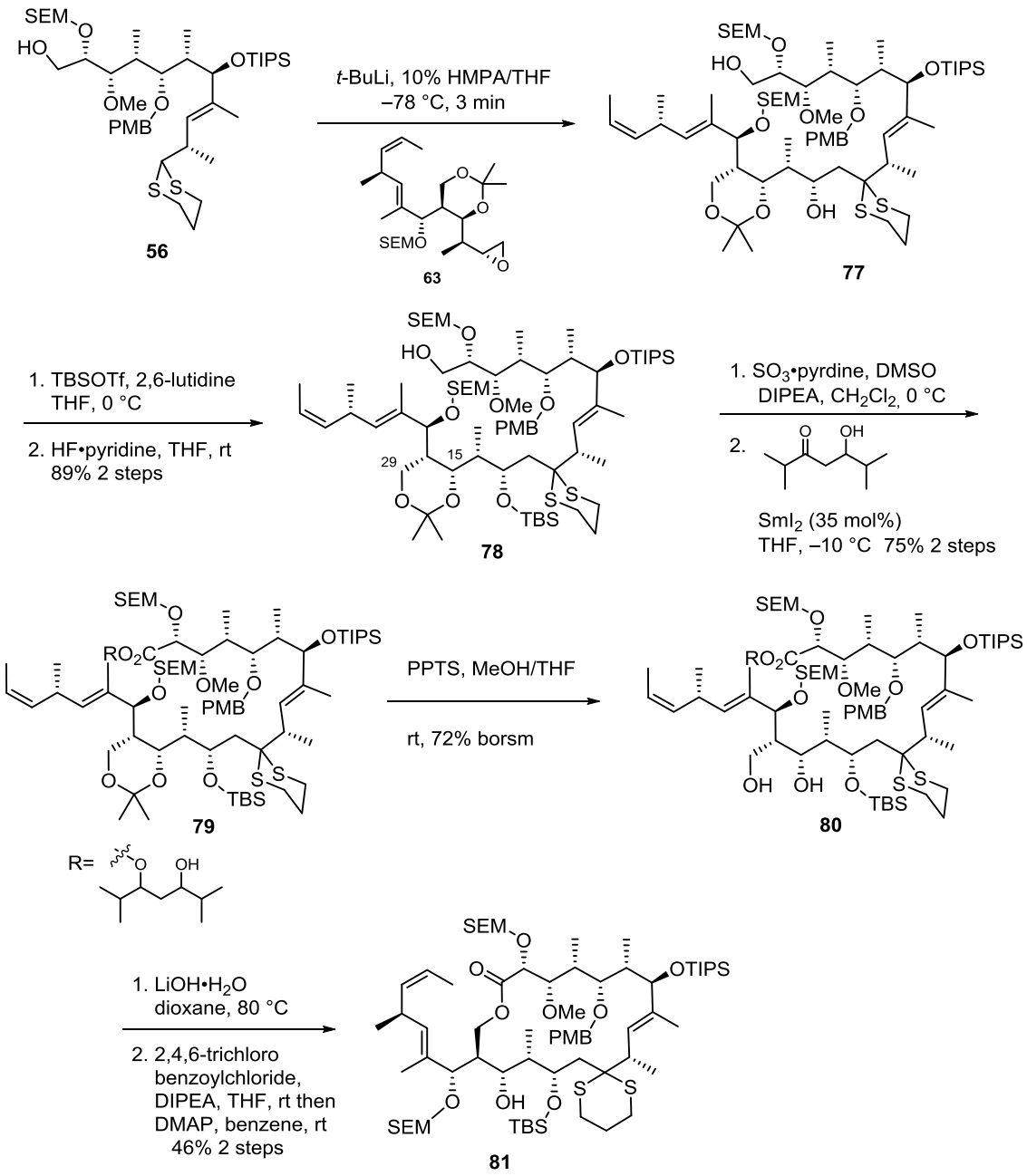
The coupling reaction between vinyliodide **70** and aldehyde **65** was achieved by metal-halogen exchange of vinyliodide **70** with *t*-BuLi in Et_2O, followed by addition of aldehyde **65** to furnish the desired adduct **74** as the major diastereomer (6:1) and a combined yield of 90%. The newly generated C(17) hydroxyl group in compound **74** was protected as SEM ether and the PMB group was oxidatively removed to afford the primary hydroxyl compound **75**. The required (*Z*)-olefin was installed by oxidation of primary hydroxyl to aldehyde followed by Wittig ethylidenation to yield compound **76**. Removal of the TBS groups and inturn conversion of the resulting hydroxyl groups to the desired epoxide was achieved by the Fraser-Reid[12] protocol affording the epoxide (C12-13) fragment **63** (Scheme 3.9).



***Scheme 3.9**: Synthesis of epoxide **63**.*

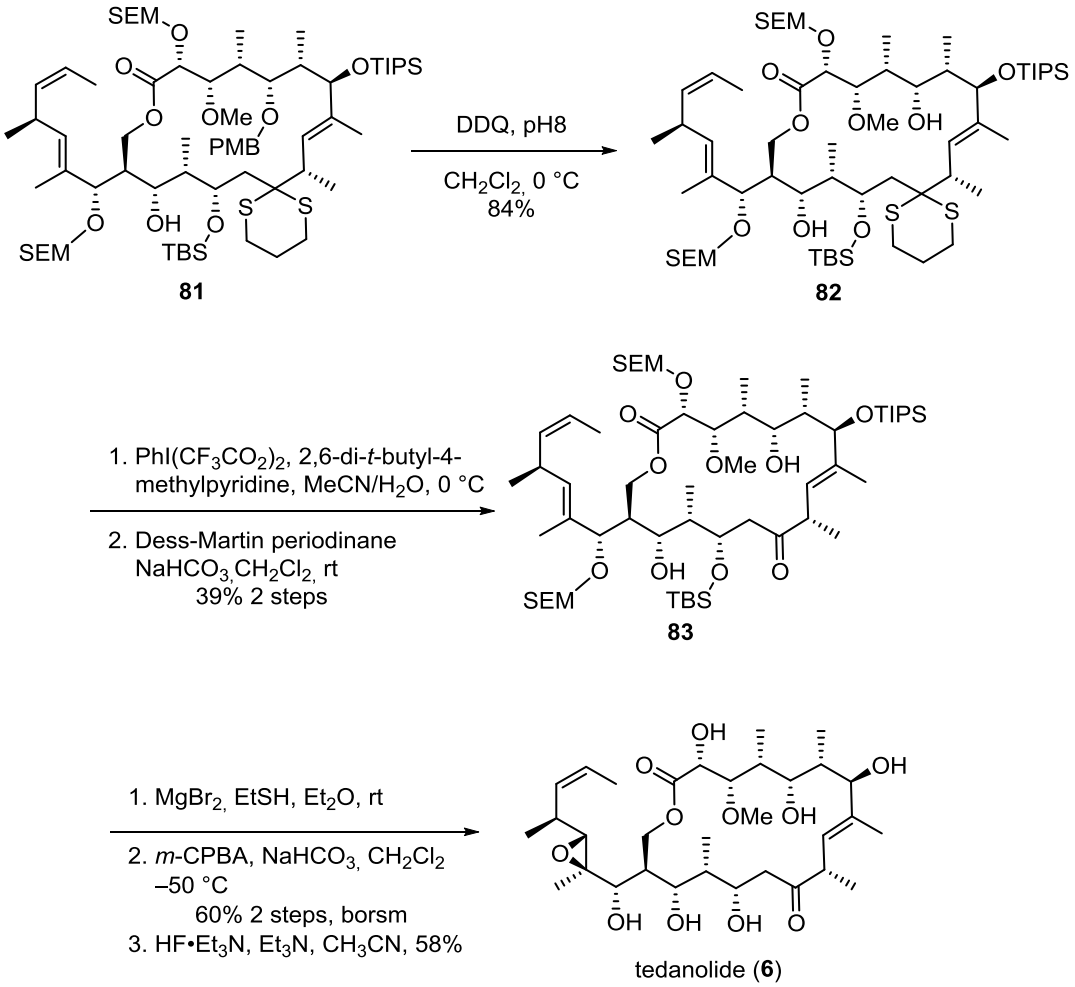
3.1.9. Coupling of Epoxide 63 and Dithiane 56:

In order to assemble the complete carbon framework for the tedanolide (**6**), epoxide **63** was added to the lithiated species of dithiane **56** using Williams' protocol[53] (*t*-BuLi in a 10%HMPA/THF solution) to furnish diol **77** (Scheme 3.10). Diol **77** was subsequently protected with TBSOTf and the primary TBS group was selectively removed using HF-pyridne to afford hydroxy compound **78**, conversion of the primary hydroxyl group to the ester **78** was achieved in similar fashion to deoxytedanolide (**7**), acid catalyzed methanolysis of the C(15,29) acetonide in **79** furnished diol **80** and saponification using LiOH in dioxane/H_2O at reflux provided the carboxylic acid, which was allowed for macrocyclisation employing the Yamaguchi protocol[45] to afford the desired primary macrolactone **81**.



***Scheme 3.10**: Synthesis of compound **81**.*

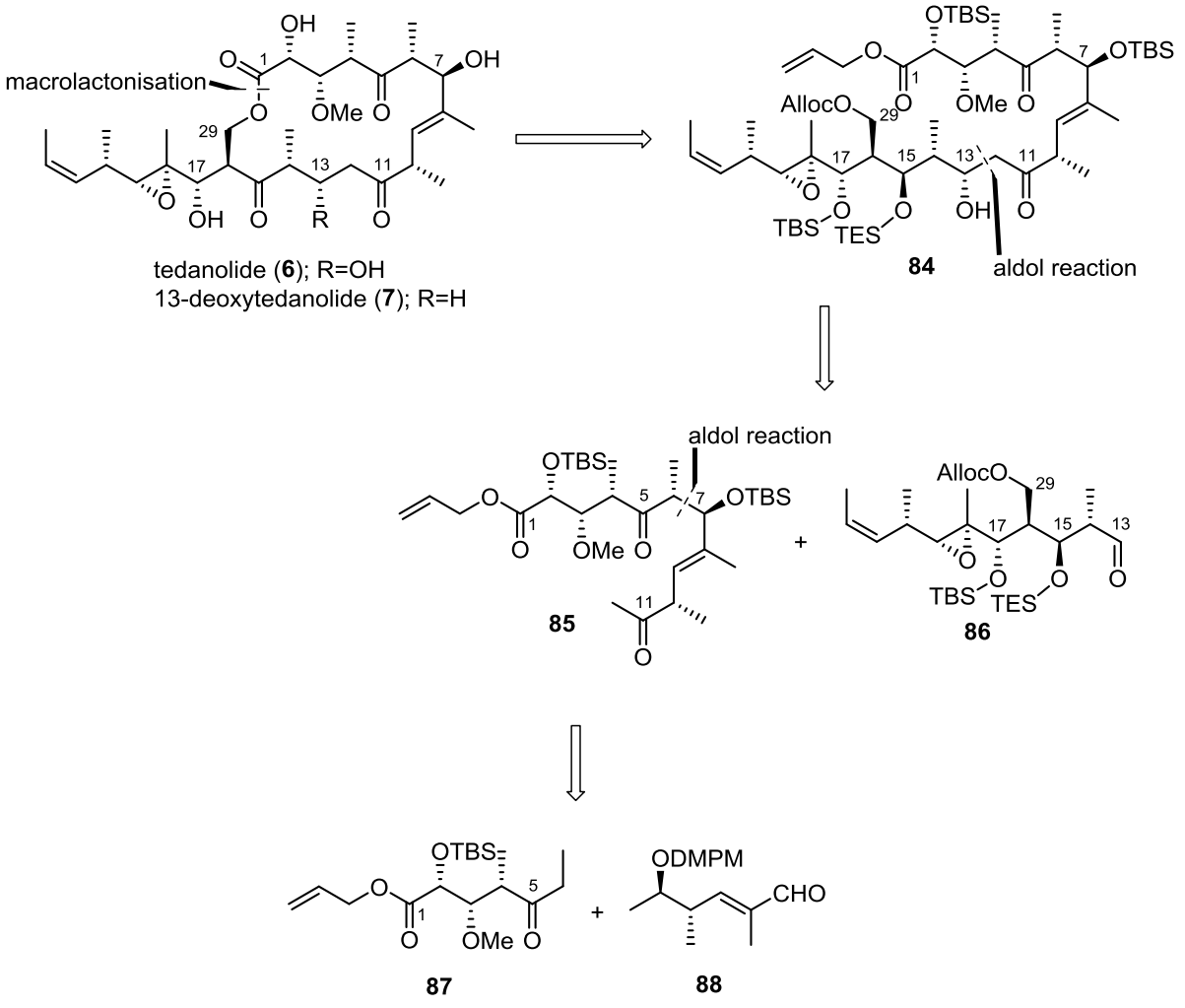
In the final steps, the PMB group was removed oxidatively using DDQ to produce diol **82**, followed by dithiane cleavage with $PhI(CF_3CO_2)_2$ employing Stork protocol[54] and the Dess-Marin oxidation[55] of two hydroxyl groups furnish triketone **83** (Scheme 3.11). SEM deprotection was carried out selectively in the presence of TIPS and TBS groups using the conditions employed by Kim ($MgBr_2$, EtSH).[56] Hydroxyl-directed epoxidation using *m*-CPBA buffered with $NaHCO_3$ furnished the desired epoxide, Global deprotection was achieved using the Et_3N•3HF and Et_3N as described by Roush[57] completed the total synthesis of tedanolide (**1**).



***Scheme 3.11**: Synthesis of tedanolide (**6**).*

3.2. Roush's Approach:

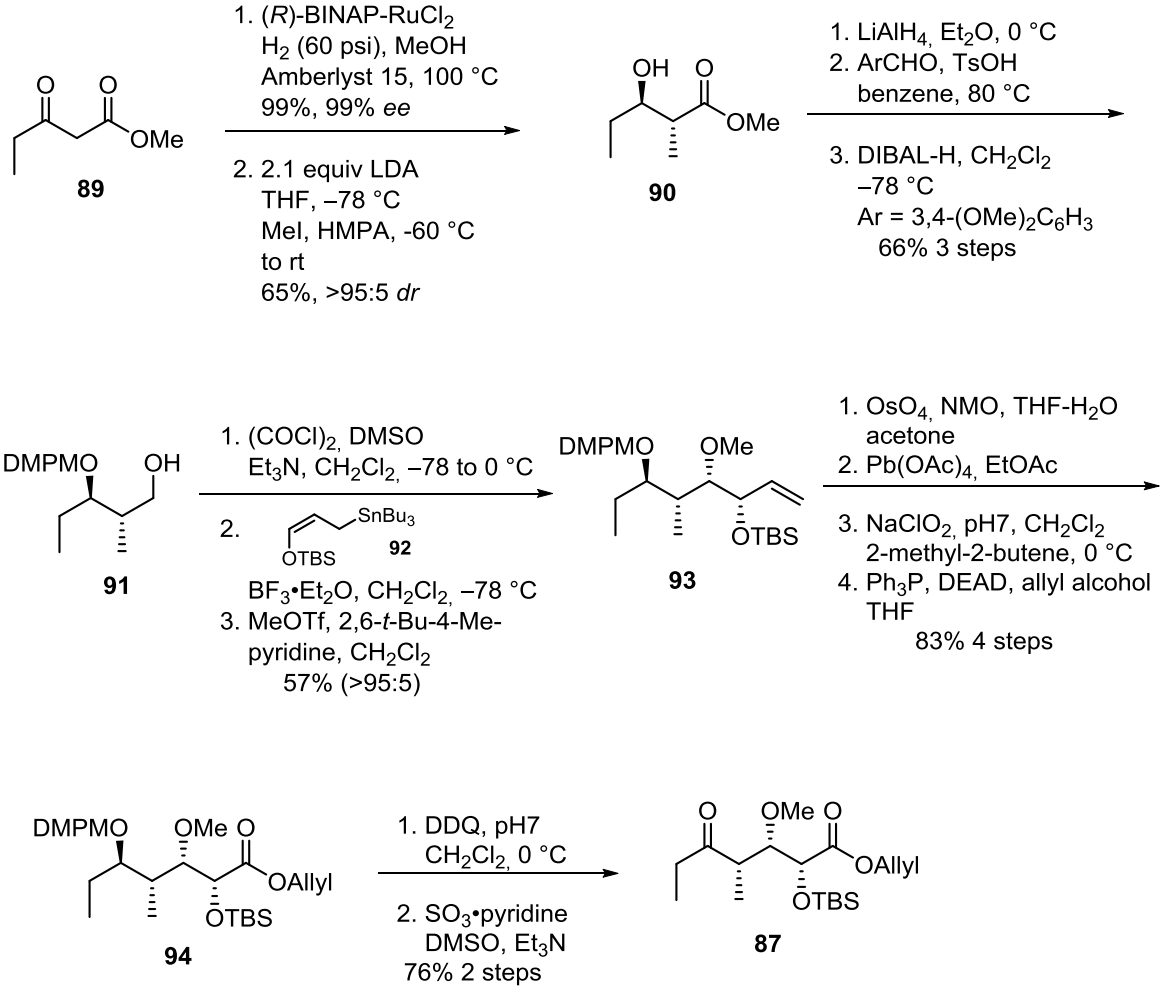
In planning the synthetic approach to tedanolide (**6**) and deoxytedanolide (**7**), the Roush group envisioned compound **84** as a common intermediate to synthesize both macrolides (Scheme 3.12).[58] Compound **84** would be assembled from the convergent aldol coupling of methyl ketone **85** and aldehyde **86**. (*R*)-configuration was chosen for the C(15)-position of **86** due to the earlier studies demonstrating that the lithium enolates of methyl ketone **85** add to 2,3-*anti* aldehydes with greater Felkin selectivity compared to 2,3-*syn* aldehydes. Keeping in mind the fact that C(15) hydroxyl would eventually oxidized to a ketone. Both the C(1)-acid and C(29)-hydroxyl groups would be masked with an allyl group to allow for simultaneous deprotection preceding macrolactonisation. Deoxygenation of C(13)-hydroxyl group was planned on adduct **84** in order to achieve deoxytedanolide (**7**). A convergent route would assemble the C(1)-C(12) ketone **85** *via* the aldol reaction of ethyl ketone **87** and aldehyde **88**.



***Scheme 3.12**: Retrosynthetic approach towards tedanolide and 13-deoxytedanolide by Roush et al.*

3.2.1. Synthesis of Ethyl Ketone 87:

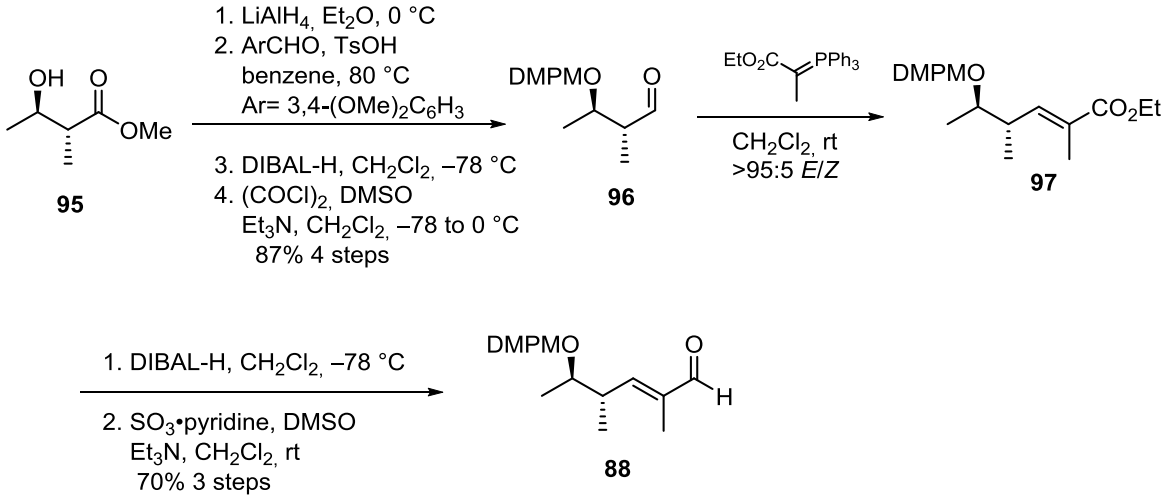
The synthesis began with assymetric hydrogenation of β-ketoester **89**,[59] followed by alkylation of the β-hydroxyester under Fråter conditions[60] to give 2,3-*anti* ester **90** (Scheme 3.13). Reduction of the ester followed by protection of 1,3-diol with 3,4-dimethoxybenzylidene acetal and regioselective reductive acetal opening using DIBAL-H afforded compound **91**. The primary alcohol was oxidized using Swern protocol[61] and the resulting aldehyde was treated with γ-silyloxyallylstannane **92** and BF_3•Et_2O to afford the corresponding 3,4-*syn*-4,5-*syn*-homoallylic alcohol. Methylation of the alcohol (MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine) gave compound **93**. Oxidation of the terminal olefin to aldehyde followed by oxidation[62] provided the C(1)- carboxylic acid, which was converted to allylester **94** under Mitsunobu conditons.[63] DDQ-mediated benzyl ether cleavage followed by the Parikh-Doering oxidation[43] of the resulting alcohol afforded the ethyl ketone **87**.



***Scheme 3.13**: Synthesis of ethyl ketone **87**.*

3.2.2. Synthesis of Aldehyde 88:

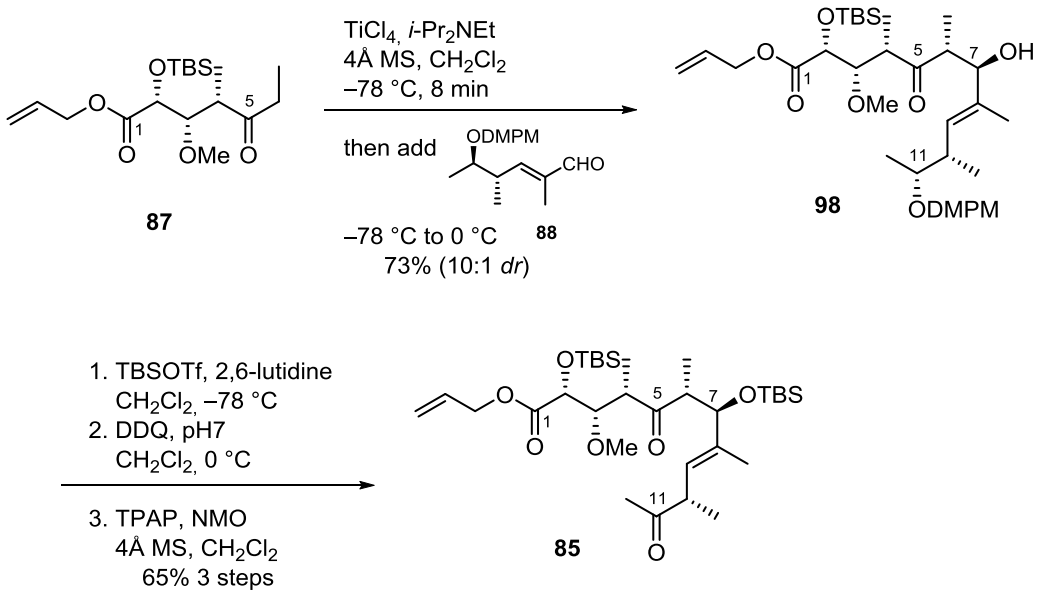
Aldehyde **88** was synthesized from readily available *anti*-β-hydroxy-α-methylbutyrate **95**, which was converted to aldehyde **96** *via* ester reduction, dimethoxybenzylideneacetal formation, regioselectiveacetal reductive opening, and Swern oxidation of the resulting primary alcohol. Wittig olefination of **96** with stabilized ylide $Ph_3P{=}C(Me)CO_2Et$ provided α,β-unsaturated ester **97** (Scheme 3.14). Reduction of ester **97** to allylic alcohol followed by Parikh-Doering oxidation[43] furnished the aldehyde **88**.



***Scheme 3.14**: Synthesis of aldehyde **88**.*

3.2.3. Completion of Synthesis of C(1-12) Ketone 85:

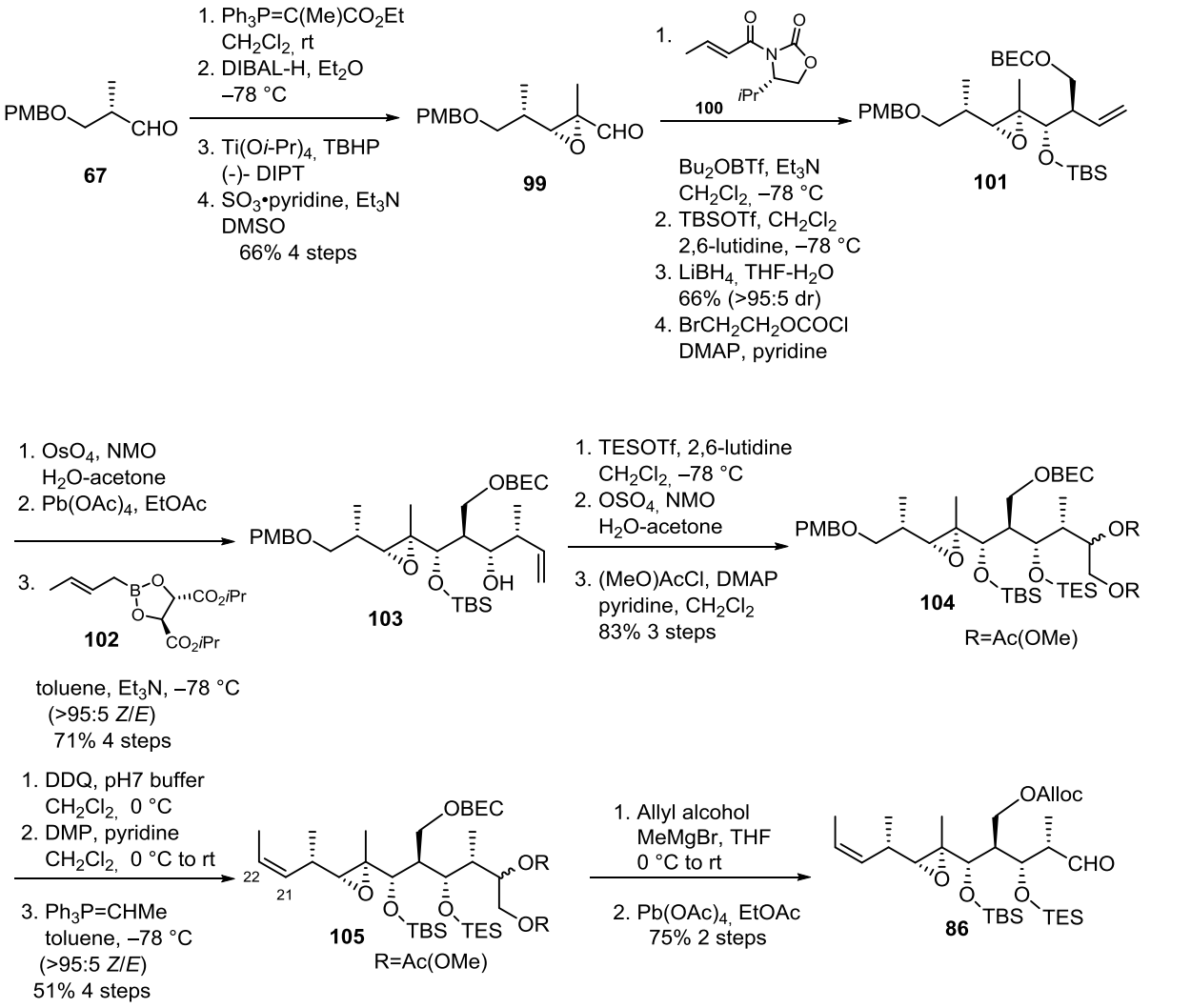
The stereoselective aldol coupling of ethyl ketone **87** and aldehyde **88** was achieved by using $TiCl_4$ and *i*-Pr_2NEt with a good diastereoselectivity and moderate yield by immediate treatment of the titanium enolate of **87** with aldehyde **88** (Scheme 3.15). The free hydroxyl group in compound **98** was protected as TBS ether and DDQ cleavage of dimethoxybenzyl ether followed by TPAP oxidation[64] provided ketone **85**.



***Scheme 3.15**: Synthesis of ketone **85**.*

3.2.4. Synthesis of C(13-23) Aldehyde 86:

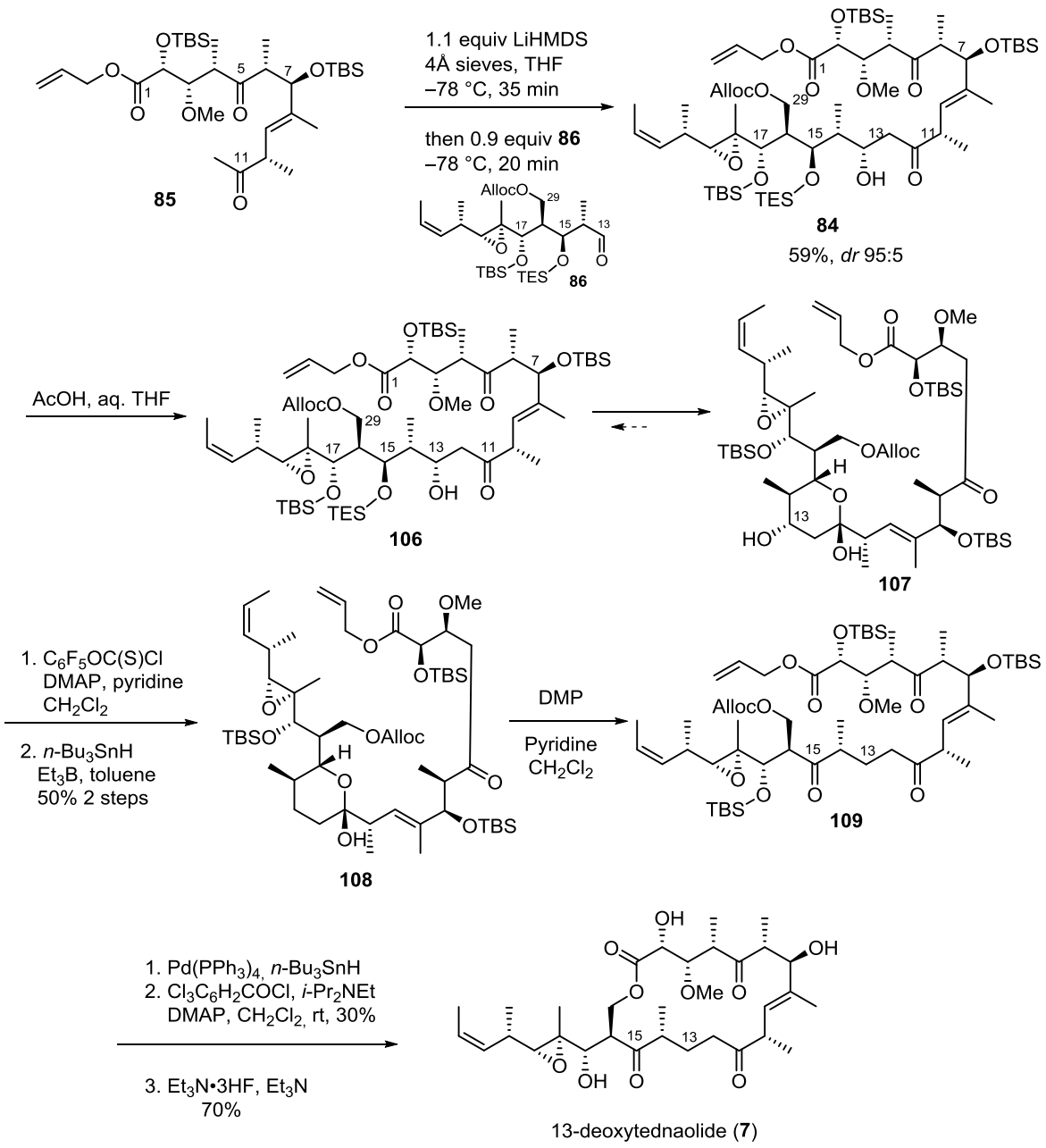
Wittig olefination of literature known aldehyde **67**[65] with stabilized ylide $Ph_3P{=}C(Me)CO_2Et$ furnished the corresponding α,β-unsaturated ester, reduction to the alcohol using DIBAL-H and subsequent Sharpless epoxidation[66] of the allylic alcohol followed by Parikh-Doering oxidation afforded the epoxyaldehyde **101** (Scheme 3.16). Evans aldol reaction of **101** with chiral crotonate imide **102**,[50] followed by silylation of the newly formed alcohol and reduction of the acyl oxazolidinone provided an alcohol functionality which was protected with 2-bromoethylcarbonate (BEC) to provide compound **103**. Oxidative cleavage of the terminal olefin in **103** furnished an aldehyde, which was converted to **105** *via* asymmetric crotylboration with (*S*,*S*)-**104**.[42] The newly generated alcohol in **105** was masked as TES ether and dihydroxylation of the terminal olefin followed by protection of diols as two α-methoxy-acetate esters provided **106**. The C(21)-C(22) (*Z*)-olefin was installed upon oxidative cleavage of PMB ether using DDQ, followed by oxidation of the primary alcohol and Wittig olefination of the resulting aldehyde. Treatment of **107** with allyl alcohol and MeMgBr, transesterified the BEC group to an Alloc group and also cleaved both the α-methoxyacetate groups. The resulting diol was converted to aldehyde **87** using $Pb(OAc)_4$.



***Scheme 3.16**: Synthesis of aldehyde **86**.*

3.2.5. Synthesis of 13-Deoxytedanolide (7) by Roush *et al.*:

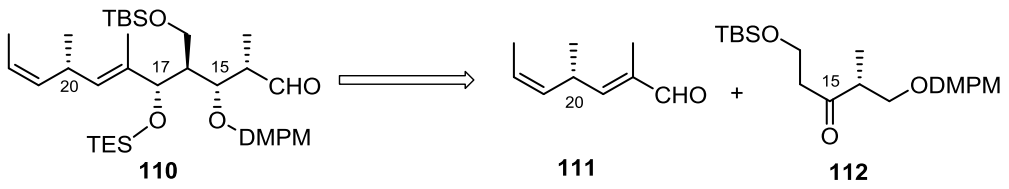
The aldol reaction between ketone **85** and aldehyde **86** using LiHMDS provided **84** as a single diastereomer in moderate yield (Scheme 3.17). Upon cleavage of the C(15) TES ether, the secondary alcohol spontaneously cyclized onto the C(11) carbonyl to form a hemiketal **107**, which proved to be unreactive towards oxidants (DMP, TPAP/NMO, SO_3•pyrdine, PDC). Deoxygenation at C(13) in compound **107** was performed using pentafluorophenylthiocarbonate and subsequent treatment with triethylborane and tributyltinhydride afforded **108**. Dess-Martin periodinane oxidation on this mixture provided triketone **109**. Cleavage of the allyl ester and allyl carbonate was achieved by treatment with $Pd(PPh_3)_4$ and tributyltinhydride in a single step, Yonemitsu-modified Yamaguchi lactonization[45] followed by removal of the TBS groups furnished 13-deoxytedanolide (**7**).



***Scheme 3.17**: Synthesis of 13-deoxytedanolide (**7**) by Roush et al.*

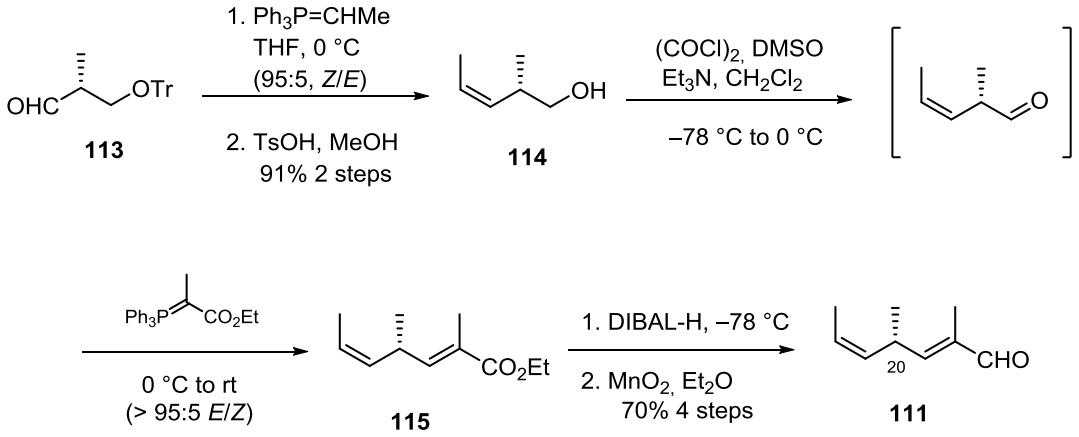
3.2.6. Synthesis of Tedanolide (6) by Roush *et al.*:

For the synthesis of tedanolide (**6**), aldehyde **110** was targeted as a coupling partner for ketone **85** which maintained the (*S*)-configuration at C(15)-position but lacked the epoxide (Scheme 3.18). A late stage C(17)-hydroxyl directed epoxidation of the C(18-19) olefin was envisioned similar to the Kalesse[67] and Smith[38] syntheses of tedanolide. Appropriate protecting groups were chosen in order to facilitate macrolactonisation.



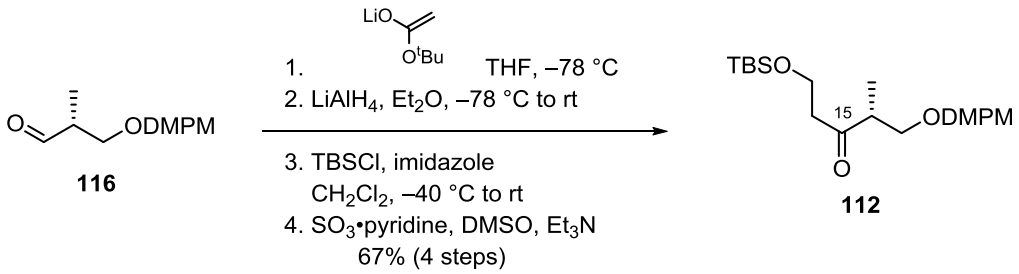
***Scheme 3.18**: Retrosynthesis of aldehyde fragment **110**.*

The C(13-23) framework of aldehyde **110** was achieved *via* the *anti*-aldol reaction of aldehyde **111** and ketone **112** using conditions developed by Paterson,[68] which presented similarities to the work done in the synthesis of tedanolide by the Kalesse group.[67a] Both aldehyde **111** and ketone **112** can be synthesized from the commercially available Roche ester (Scheme 3.19). Formation of aldehyde **111** started from the trityl protected aldehyde **113**. Wittig olefination followed by cleavage of trityl group using mild acidic conditions provided alcohol **114**. Swern oxidation of alcohol **114** to the aldehyde followed by Wittig olefination with the stabilized ylide $Ph_3P{=}C(Me)CO_2Et$ gave the α,β-unsaturated ester **115**. Reduction of ester **115** and subsequent oxidation with MnO_2 provided aldehyde **111**.



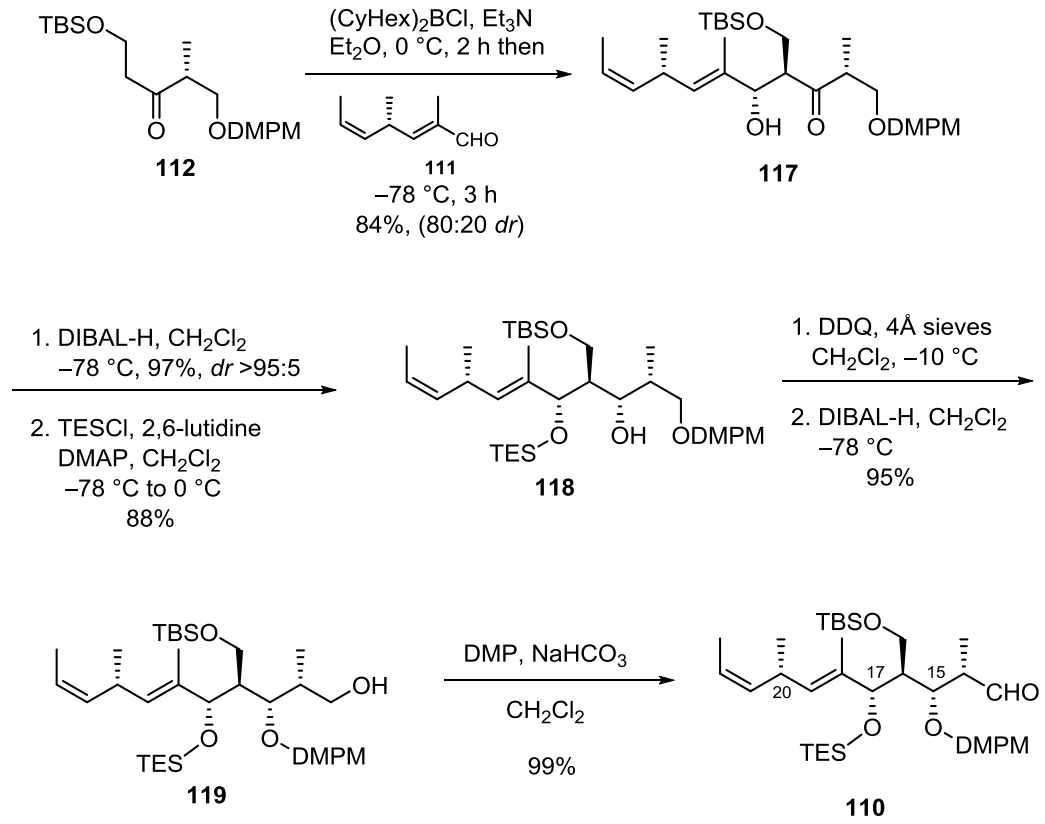
***Scheme 3.19**: Synthesis of aldehyde **111**.*

Ketone **112** was prepared from the DMPM-protected aldehyde **116** (Scheme 3.20). Addition of the lithium enolate of *tert*-butyl acetate to aldehyde **116** resulted in a β-hydroxy ester, which underwent reduction to a 1,3-diol. Selective silylation of primary hydroxyl group and oxidation of the secondary alcohol furnished ketone **112**.



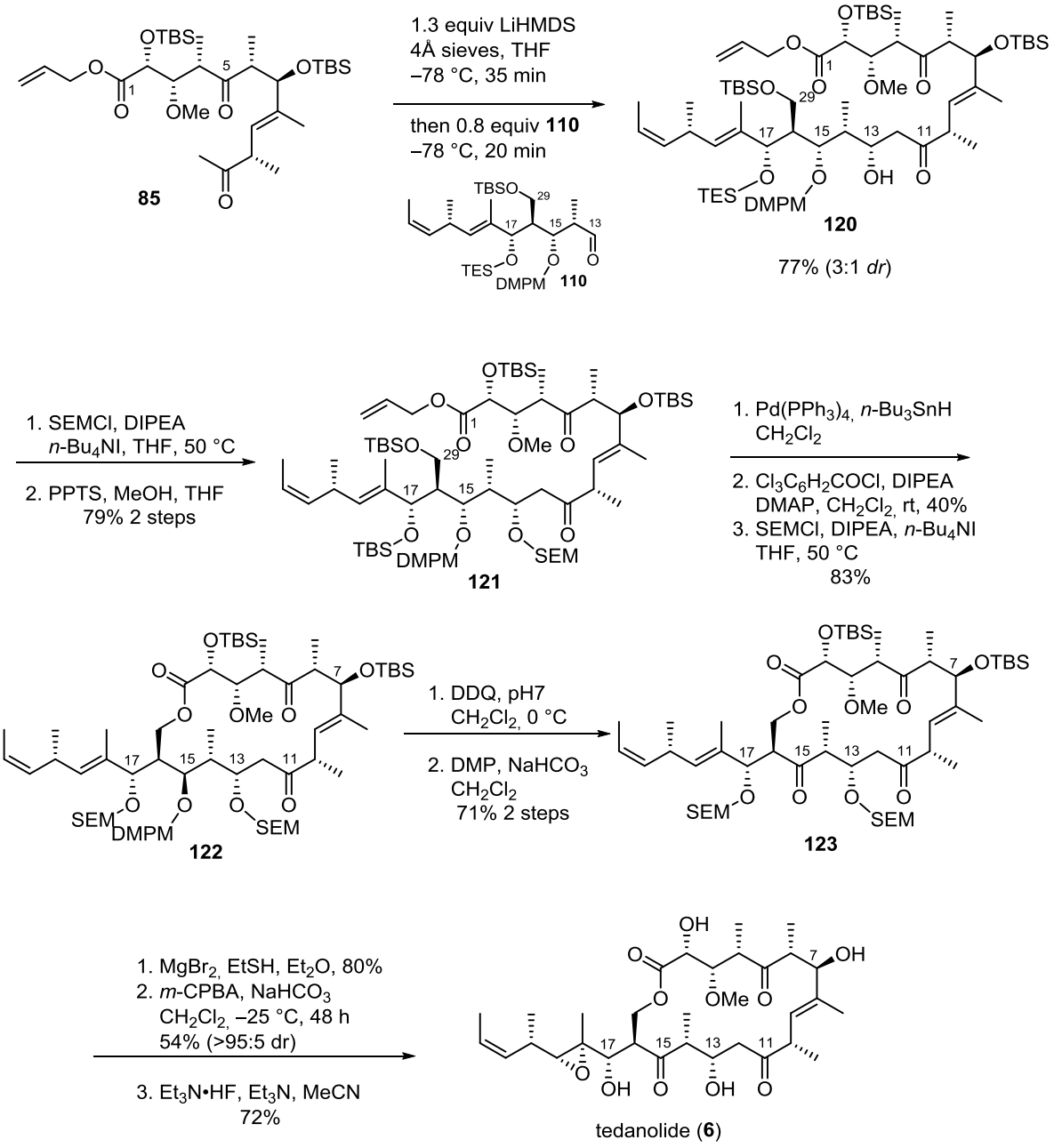
***Scheme 3.20**: Synthesis of ketone **112**.*

Ketone **112** and aldehyde **111** were coupled by Paterson's aldol conditions[68] leading to aldol product **117** as the major diastereomer in a ratio of 80:20 (Scheme 3.21). Redcution of β-hydroxy ketone **117** to the *syn*-1,3-diol with DIBAL-H and selective silylation of the allylic alcohol gave TES ether **118**. The dimethoxy benzyl ether of compound **118** was transferred on to the secondary alcohol *via* benzylideneacetal formation followed by regioselctive acetal reductive opening with DIBAL-H. The resulting primary alcohol in **119** was oxidized using Dess-Martin Periodinane to furnish aldehyde **110**.



Scheme 3.21**: Synthesis of aldehyde **110.

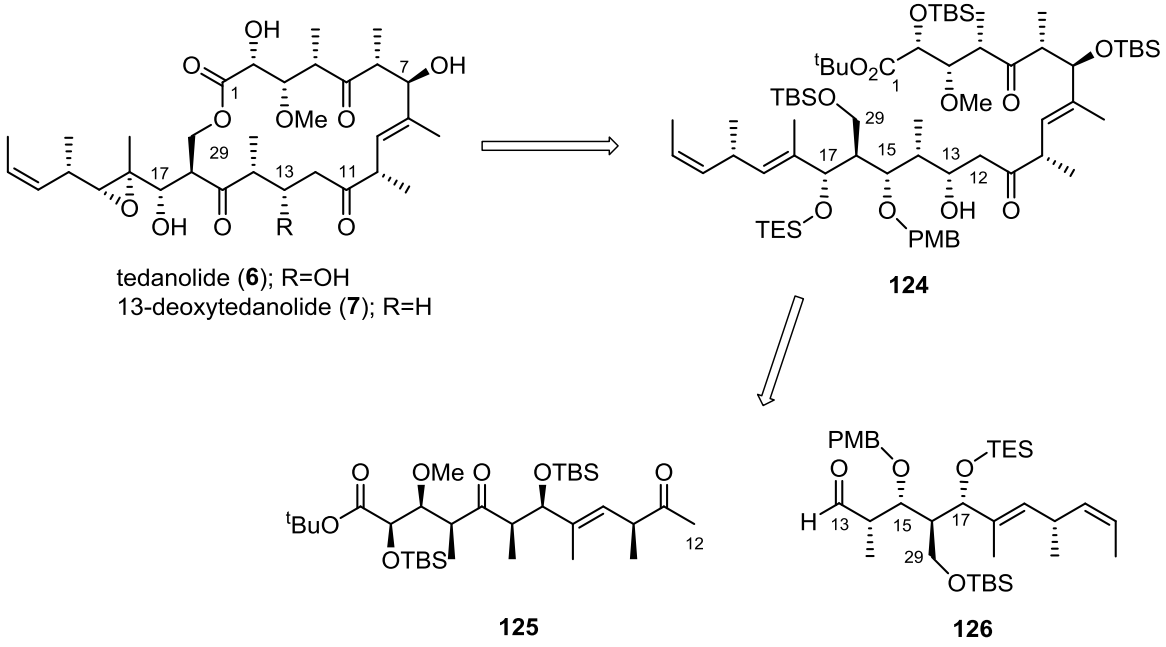
Addition of the lithium enolate of ketone **85** to aldehyde **110** provided the Felkin adduct **120** in 77% yield with 3:1 diastereomeric selectivity (Scheme 3.22). Protection of the newly formed C(13)-alcohol using SEMCl and DIPEA at 50 °C provided the SEM ether in quantitative yield. Under mild acidic conditions (PPTS/MeOH), the primary TBS group along with the C(17)-TES ether was cleaved to provide diol **121**. Finally, the liberation of carboxylic acid functionality allowed for macrolactonisation to take place under the Yonemitsu modification of the Yamaguchi protocol.[45] The cyclisation was completely selective at the primary alcohol, and the free hydroxyl group at C(17) position was protected as SEM ether to obtain macrolactone **122**. Treatment of **122** with DDQ liberated the C(15)-alcohol which was subsequently oxidized using Dess-Martin periodinane to afford the triketone **123**. Removal of the two SEM groups was achieved using $MgBr_2$ and ethane thiol in Et_2O,[56] followed by directed epoxidation of the C(18-19) double bond with *m*-CPBA[41b] to afford a single epoxide diastereomer. Finally the TBS groups are removed using Et_3N buffered HF•Et_3N[69] to provide tedanolide (**6**).



***Scheme 3.22**: Synthesis of tedanolide (**6**) by Roush et al.*

3.3. Loh's Contribution towards Fragment Synthesis of Tedanolide (6):

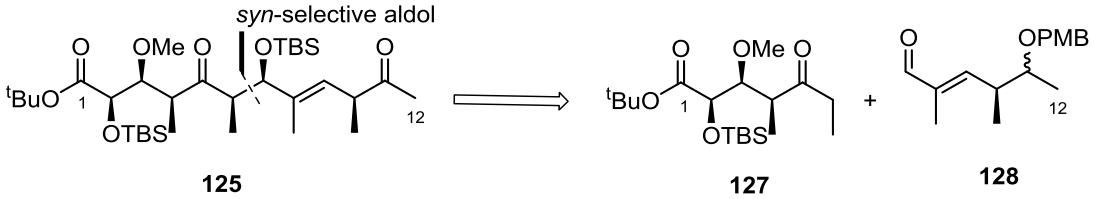
Loh's group contributed valuable inputs towards the synthesis of tedanolide (**6**).[41b, 70] Although the total synthesis of tedanolide (**6**) couldn't be accomplished, the initial inputs on synthesis of individual fragments provided a very detailed information for other groups who were working on tedanolide at that point of time.[57-58, 67] Loh and co-workers envisioned the synthesis of the carbon skeletal framework of tedanolide (**6**) through the aldol reaction between two key fragments, diketoester **125** C(1-12) and aldehyde **126** C(13-23) (Scheme 3.23).



***Scheme 3.23**: Loh's retrosynthetic approach of tedanolide (**6**).*

3.3.1. Synthesis of Diketoester Fragment C(1-12) 125:

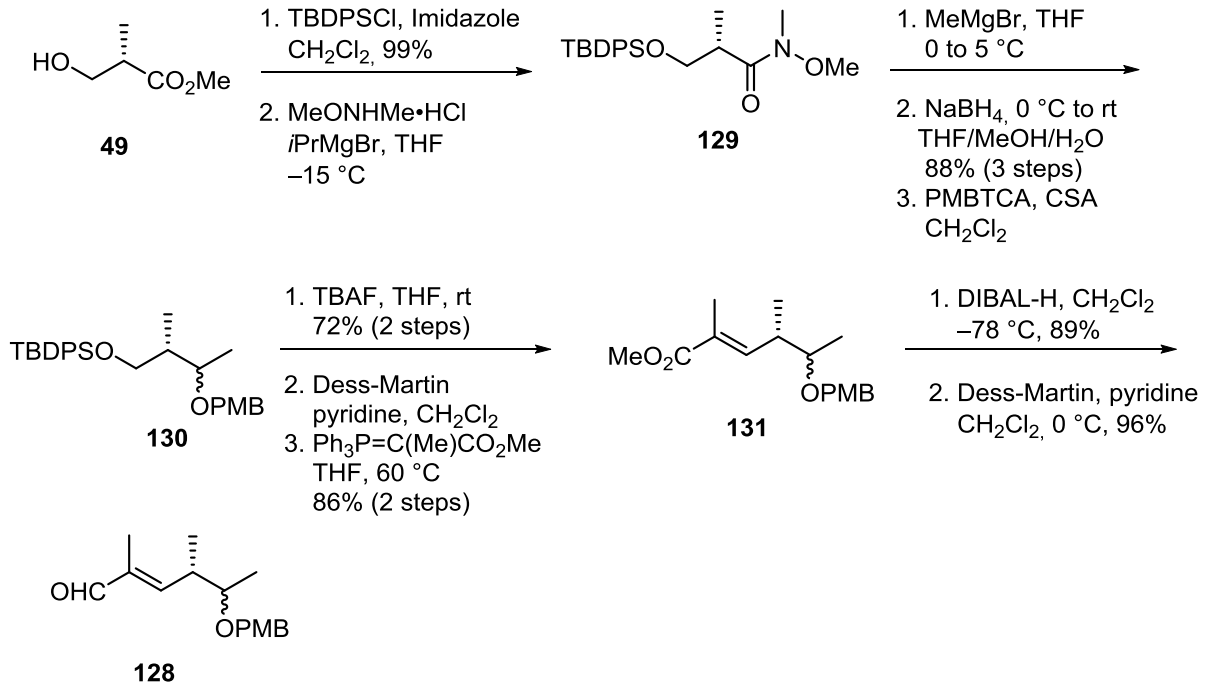
The first key fragment diketoester **125**, would be derived from the *syn*-selective boron-mediated aldol coupling of fragments ketoester **127** and α,β-unstaruated aldehyde **128** (Scheme 3.24).[70a]



***Scheme 3.24**: Syn-selective aldol coupling.*

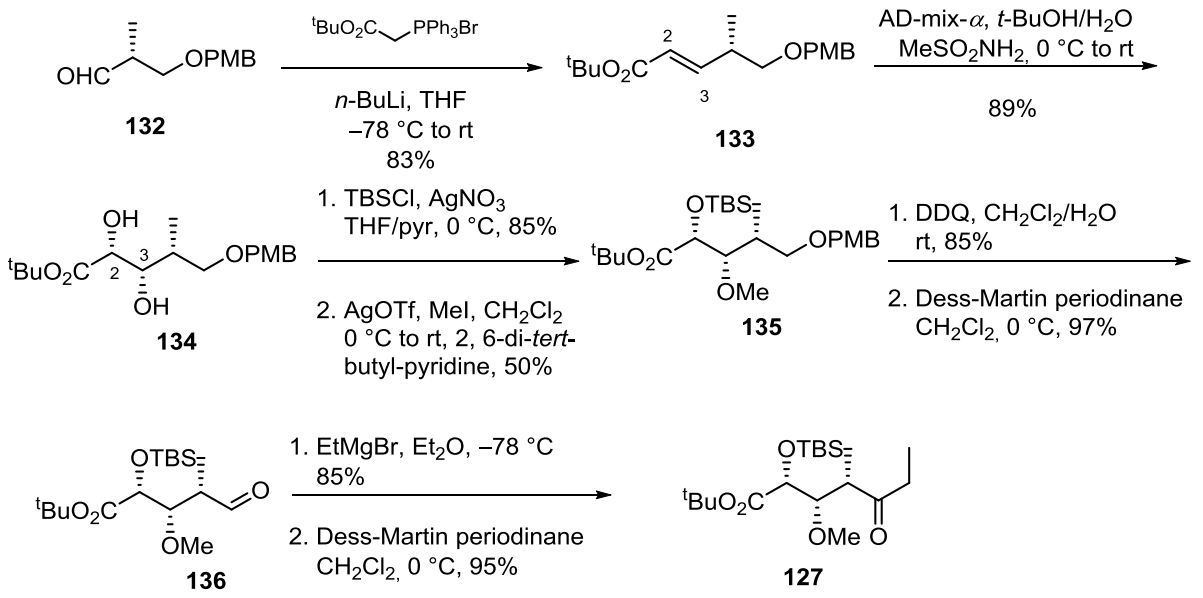
The synthesis of aldehyde **128** began from the Roche ester **49** (Scheme 3.25), protection of primary alcohol with TBDPS group, followed by conversion to Weinreb amide to afford compound **129**. Treatment of Weinreb amide **129** with methylmagnesium bromide yielded the corresponding methyl

ketone, further reduced to a mixture of diastereomeric alcohols and then protected as PMB ether **130**. Liberation of the primary alcohol followed by Dess-Martin periodinane oxidation to the corresponding aldehyde and treatment with stablisied Wittig ylide $Ph_3P{=}CCH_3CO_2Et$ afforded α,β-unstaruated ester **131** with a (*E*:*Z*, 94:6) diasteromeric ratio in favour of desired product. Reduction of the ester **131** to the corresponding allylic alcohol followed by oxidation to the desired aldehyde **128** was achieved using Dess-Martin periodinane.



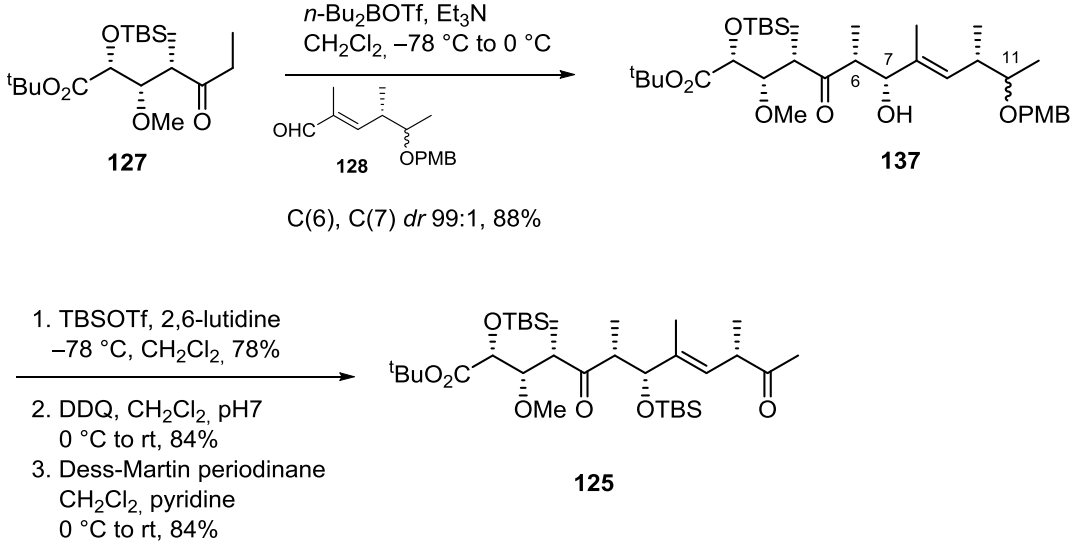
***Scheme 3.25**: Synthesis of aldehyde **128**.*

Once the synthesis of aldehyde **128** was achieved, efforts focused on the preparation of the keto-ester, aldol coupling partner **127**. Synthesis of ethyl ketone **127** started with Wittig reaction of literature known Roche aldehyde **132** with stabilized Wittig ylide t-$BuO_2CCH{=}PPh_3$. Sharpless asymmetric dihydroxylation[66] using AD-mix-α incorporated the C(2) and C(3) hydroxyl groups in a diastereomeric ratio of 6:1 in favour of the desired compound **134**. C(2) and C(3)-hydroxyl groups were then protected as TBS and methyl ethers respectively. The PMB group in compound **135** was removed using aqueous DDQ, followed by oxidation using Dess-Martin periodinane provided aldehyde **136**. Grignard reaction of aldehyde **136** with ethylmagnesium bromide at –78 °C provided a diastereomeric mixture of alcohols which are subsequently oxidized to the corresponding ketone to yield the desired ethylketone aldol coupling partner **127** (Scheme 3.26).



***Scheme 3.26**: Synthesis of ethylketone **127**.*

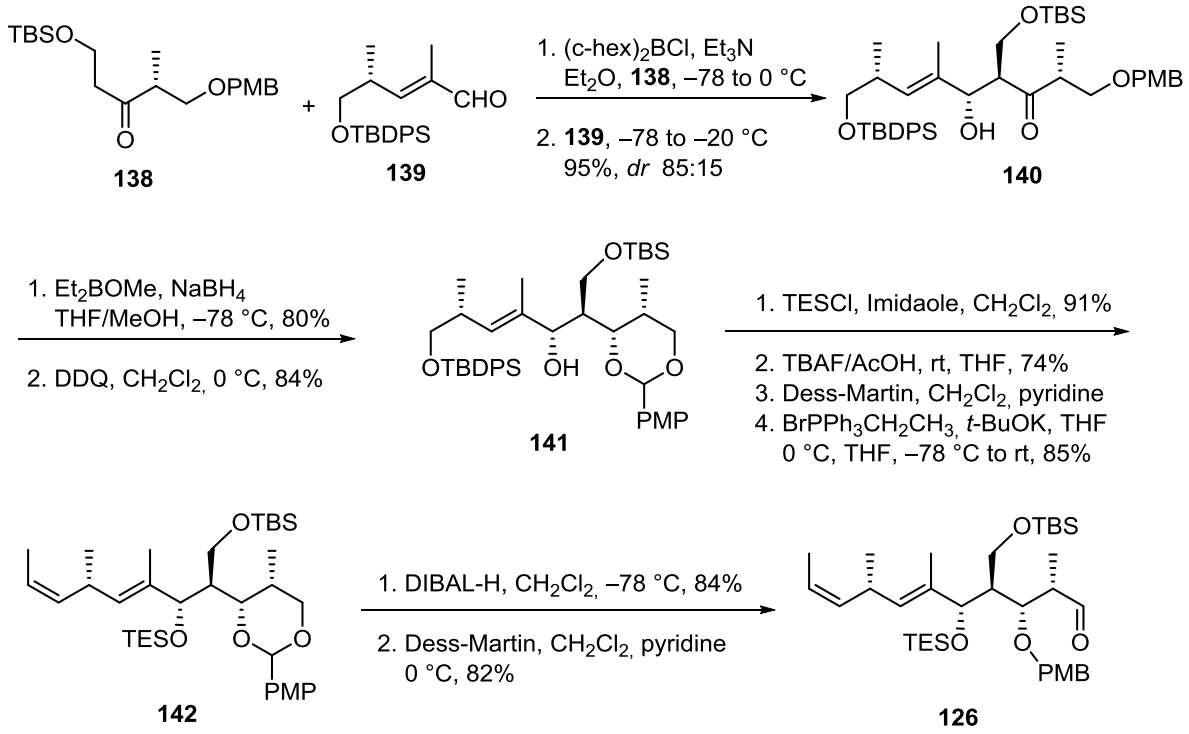
In order to complete the fragment synthesis enal **128** was treated with ethyketone **127** in a *syn*-selective boron-mediated aldol reaction to give compound **137** with good stereoselectivity (94:6). The newly generated hydroxyl group was protected as TBS ether and deprotection of the PMB group followed by Dess-Martin periodinane oxidation provided the C(1-12) diketoester fragment **125** (Scheme 3.27).



***Scheme 3.27**: Synthesis of diketoester **125**.*

3.3.2. Synthesis of Aldehyde Fragment C(13-23) 126:

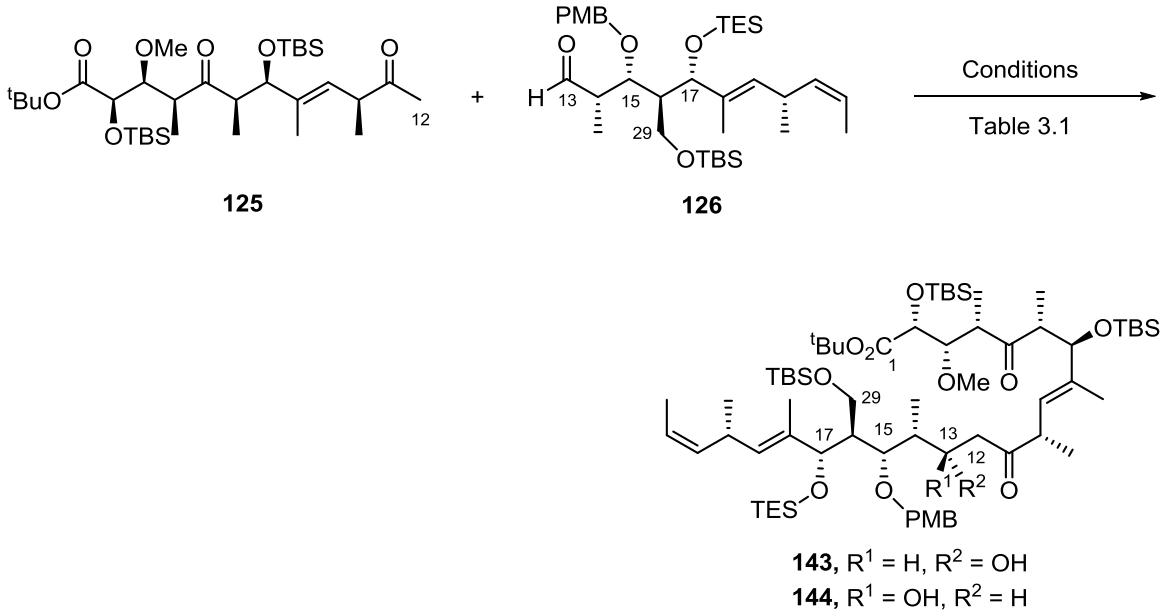
The synthesis of the second key fragment aldehyde **126**,[70b] was based upon two advanced intermediates, ketone **138**[70b] and aldehyde **139**[68c] (Scheme 3.28). These two fragments were reacted in a boron-mediated aldol reaction using Paterson's conditions[68] to afford a mixture of diastereomers (85:15) in favour of desired product **140**. The C(16)-ketone group was selectively reduced to a *syn*-diol as a mixture of diastereomers (>20:1) using $Et_2BOMe/NaBH_4$ and converted to *p*-methoxybenzylidene acetal **141** using DDQ. Installation of the *Z*-double bond at C(21-22) was achieved by removal of TBDPS group followed by Dess-Martin periodinane oxidation and Wittig olefination of the resulting aldehyde with stabilised Wittig ylide $Ph_3P{=}CCH_3$ to afford *Z,E*-diene **142** as the major product (*dr* >10:1). Selective reductive acetal opening using DIBAL-H followed by Dess-Martin oxidation yielded the desired aldehyde **126**.



***Scheme 3.28**: Synthesis of aldehyde **126**.*

Having both the key fragments diketoester **125** and aldehyde **128** in hand, the crucial aldol reaction required to effect the generation of the desired C(13) center of the tedanolide skeleton was performed[70b] (Scheme 3.29). Various aldol reagents were tested to achieve higher selectivity of the newly formed C(13)-carbinol center (Table 3.1). The lithium and sodium enolates of methyl ketone **125**, gave moderate stereoselectivities favouring the desired diastereomer **143**. Addition of HMPA further decreased the diastereoselectivity. Reaction with dibutylboron and 9-BBN enolates of methyl ketone **125** provided similar results as lithium enolate, while dicyclohexylboron enolate gave a slight improvement in diastereoselectivity in favour of desired isomer **143**. Enolization employing (+)-Ipc_2BCl afforded better selectivities in moderate yields. An aldol reaction with $TiCl_4$ gave a mixture of

aldol products. In addition, the ester **125** and aldehyde **126** were recovered with satisfactory yields without any epimerisation.



***Scheme 3.29**: Aldol coupling of fragments **125** and **126**.*

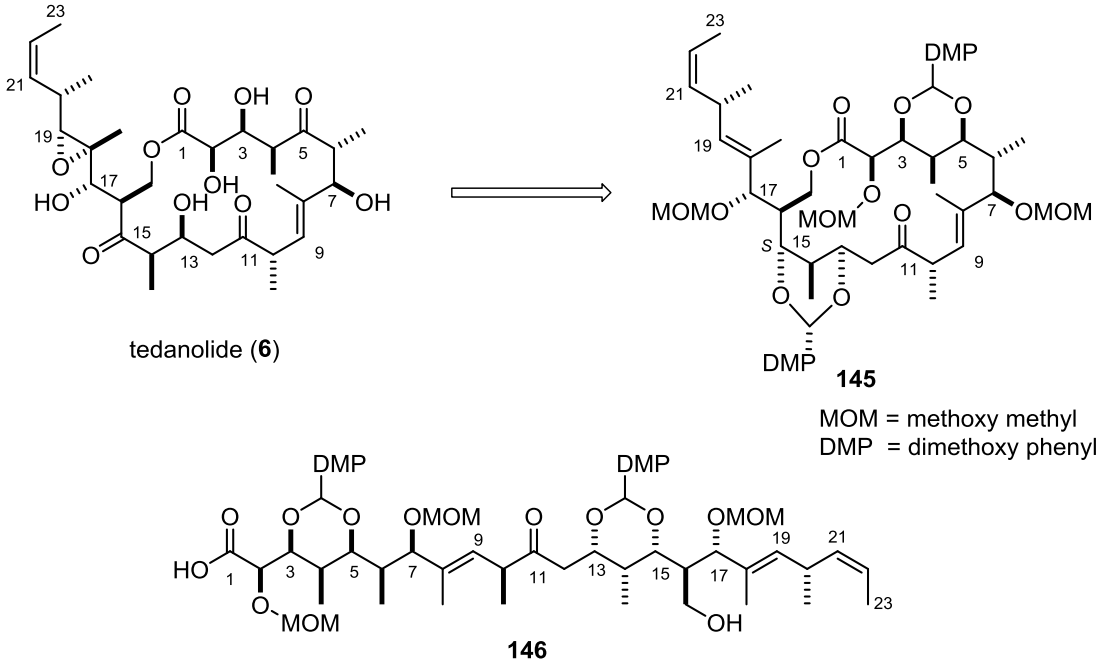
Entry	Conditions	Yield[a] (%)	**143**:**144**[b]	Recovered (%) **125**	**126**
1	LiHMDS, −78 °C, THF	26	68:32	66	59
2	NaHMDS, −78 °C, THF	30	64:36	57	43
3	LiHMDS, 9% HMPA, −78 °C, THF	27	53:47	54	29
4	*n*-Bu_2BOTf, Et_3N, −78 °C, CH_2Cl_2	24	66:34	79	53
5	(*c*-hex)$_2BCl$, Et_3N, Et_2O, 0 °C, 1h then **126**, −78 to −20 °C	47	74:26	59	1
6	9-BBNOTf, Et_3N, Et_2O, −78 to −20°C	52	60:40	14	6
7	(−)-Ipc$_2BCl$, Et_3N, Et_2O, 0 °C, 1h then **126**, −78 to −20 °C	19	15:85	62	56
8	(+)-Ipc$_2BCl$, Et_3N, Et_2O, 0 °C, 1h then **126**, −78 to −20 °C	34	83:17	37	17
9	$TiCl_4$, *i*-Pr_2EtN, CH_2Cl_2, −78 °C	24	41:59	46	0

[a] ***Table 3.1**: Aldol reaction of keto ester **125** and aldehyde **126**.*
Combined isolated yields of **143**and **144** after silica gel chromatography.
[b]Ratio was deteremined from ^{1}H NMR of the purified diastereomers in a mixture

In conclusion, the Loh group developed convergent routes to synthesize both ketoester **125** and aldehyde **126**, and demonstrated their synthetic viability for an aldol coupling. Having accomplished the construction of the C(1-23) carbon backbone of the tedanolide, they failed to finish the total synthesis of the tedanolide (**6**).

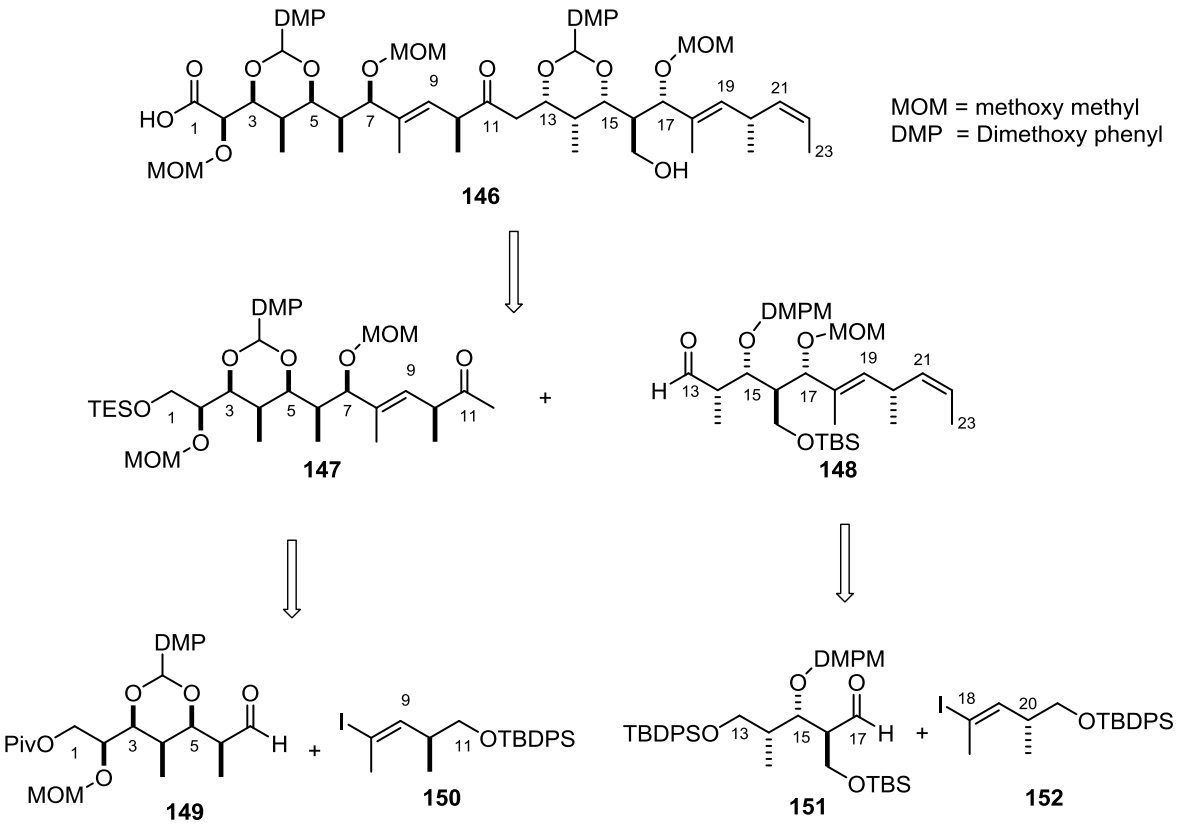
3.4. Yonemitsu's Approach towards the Synthesis of Tedanolide (6):

As a result of extensive studies based on the conformational analysis by molecular mechanics (MM) caluculations of the macrolactone in tedanolide (**6**), the Yonemitsu group designed a seco-acid derivative suitable for effective macrolactonization. Key notes suggested that the aldol structures in compound **6** are not all arranged antiperiplanar in order to avoid decomposition or dehydration; the two pairs of carbonyl groups (C1-C11, C5-C15) are situated opposite to each other, to maintain stability of the 18-membered lactone; In order to maintain the conformational stability in the acyclic intermediates all the aldol groups were to be replaced by the protected diol functionality, and then be oxidised back to the ketones after the formation of the 18-membered macrolactone. Taking all these aspects into consideration, Yonemitsu *et al*. proposed two structures **145** and **146** as promising intermediary lactone and the corresponding seco-acid which would eventually lead to the synthesis of tedanolide (**6**) (Scheme 3.30).[71]



Scheme 3.30*: Resulting structures of conformational studies on tedanoldie (**6**) by Yonemitsu et al.*

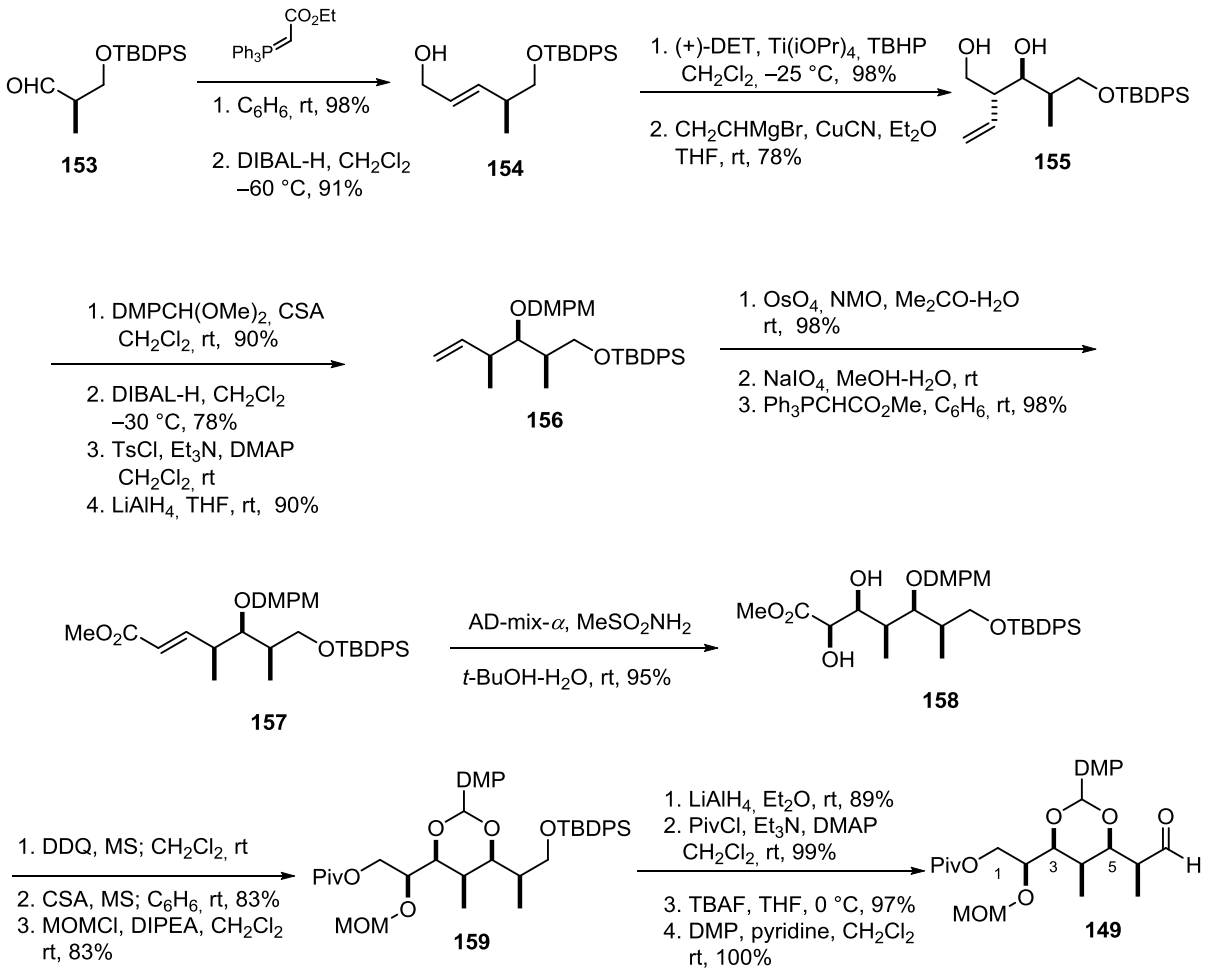
Retrosynthetically, compound **146** would be synthesized by coupling between fragments C(1-12) **147** and C(13-23) **148**. Inturn, these could be obtained from precursors C(1-7) **149**, C(8-11) **150**, C(13-17) **151** and C(18-21) **152**, derived from (*R*) and (*S*)-Roche esters (Scheme 3.31).[72]



***Scheme 3.31**: Retrosynthetic approach towards tedanolide (**6**).*

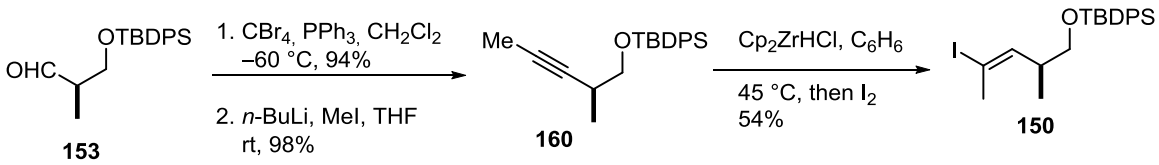
3.4.1. Synthesis of C(1-12) Fragment Methylketone 147:

With the established retrosynthetic pathway the following task involved the synthesis of methylketone **147**, which was based upon the coupling of two fragments vinyliodide **150** and aldehyde **149**, both obtained from the common starting material Roche aldehyde **153** (Scheme 3.32). Wittig reaction of aldehyde **153** with a stabilised ylide, followed by reduction provided allyl alcohol **154**. Subsequent Sharpless asymmetric epoxidation[73] followed by regioselective ring opening with vinylcopper reagent afforded 1,3-diol **155**. Several functional group manipulations lead to compound **156**, which underwent dihydroxylation of the terminal double bond, followed by periodate cleavage and homologation of the resulting aldehyde to afford unsaturated species **157**. The α,β-unsaturated ester **157** was subjected to Sharpless asymmetric dihydroxylation[66] using AD-mix-α to afford diol **158** in excellent yield and diastereoselectivity (>99 % *de*). Treatment of diol **158** with DDQ under anhydrous condition followed by C(2)-hydroxyl protection with methoxymethyl chloride provided compound **159**, which underwent reduction of the ester and protection of the resulting primary hydroxyl group with pivaloyl chloride followed by TBS group removal and subsequent oxidation to aldehyde using Dess-Martin perdiodinane gave compound **149** quantitatively.



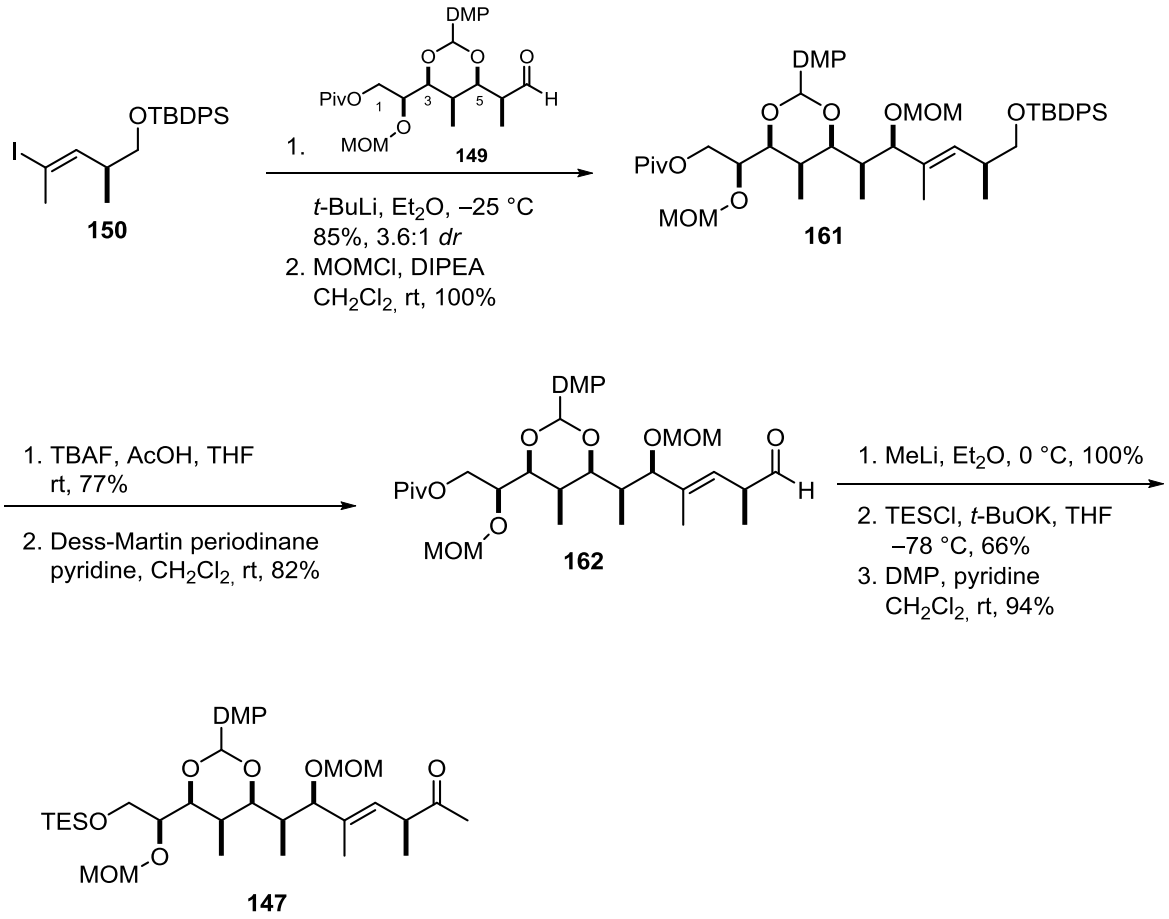
***Scheme 3.32**: Synthesis of aldehyde **149**.*

The synthesis of aldol coupling partner iodoalkene **150** was achieved by hydrozirconation[74] of alkyne **160** using the Schwartz reagent (Scheme 3.33). Alkyne **160** in turn was prepared from Roche aldehyde **153** *via* dibromoalkene following the Corey-Fuchs protocol.[48]



***Scheme 3.33**: Synthesis of iodoalkene **150**.*

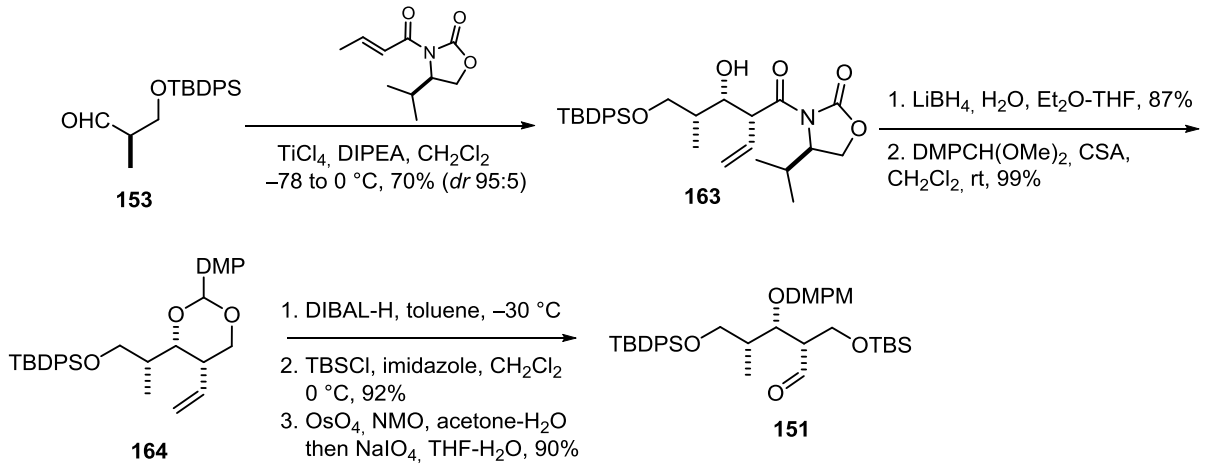
The lithiated species of iodoalkene **150** was then allowed to react with aldehyde **149** to obtain the expected Felkin adduct **161** and its isomer in a ratio of 3.6:1 (Scheme 3.34). The newly generated C(7)-hydroxyl was protected as methoxymethyl (MOM) ether, to which TBDPS group cleavage and oxidation of the resulting primary alcohol resulted in aldehyde **162**. Aldehyde **162** was treated with methyllithium in order to introduce the C(12) methyl group, and the protection of the C(1)-hydroxyl group followed by the oxidation of the C(11)-secondary alcohol afforded methyl ketone **147**.



***Scheme 3.34**: Synthesis of methylketone **147**.*

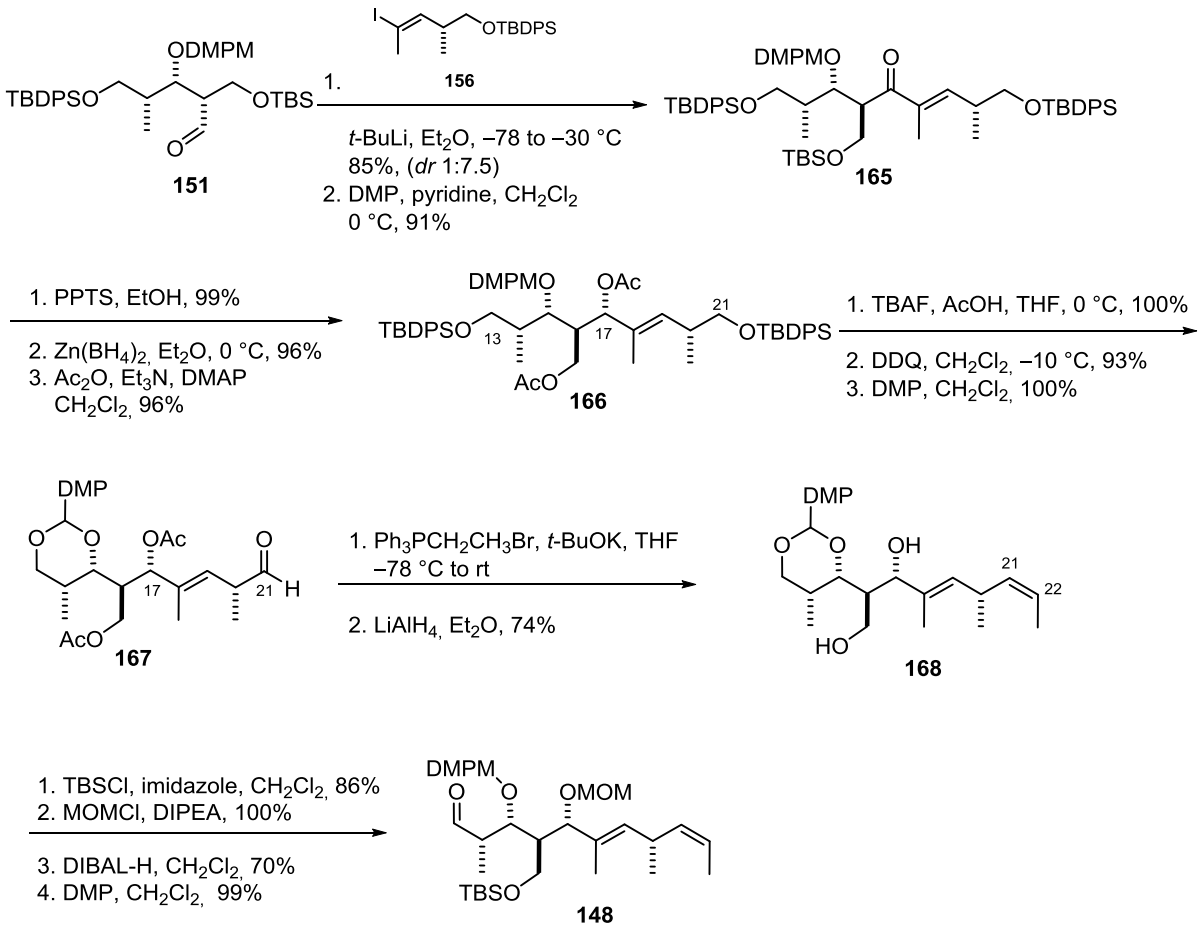
3.4.2. Synthesis of C(13-23) Fragment Aldehyde 148:

Aldehyde **148** was obtained from coupling of two fragments aldehyde **151** and Iodoalkene **152**. Iodoalkene **152** was synthesized in similar fashion to alkene **150** using the enantiomer of Roche aldehyde **153**. Although aldehyde **151** was synthesized by two different routes, both utilizing the Roche aldehyde **153** as starting point, the second route proved to be more efficient with and is depicted below (Scheme 3.35). Evans' asymmetric aldol reaction[50] on aldehyde **153** gave the product **163** in very good selectivites (*dr* = 95:5), Evans' auxiliary was removed by using standard conditions and the resulting 1,3-diol was protected as dimethoxyphenyl acetal to afford compound **164**. Selective reductive acetal opening using DIBAL-H followed by protection of the primary hydroxyl group and treatment of the terminal double bond with OsO_4 and $NaIO_4$ provided aldehyde **151**.



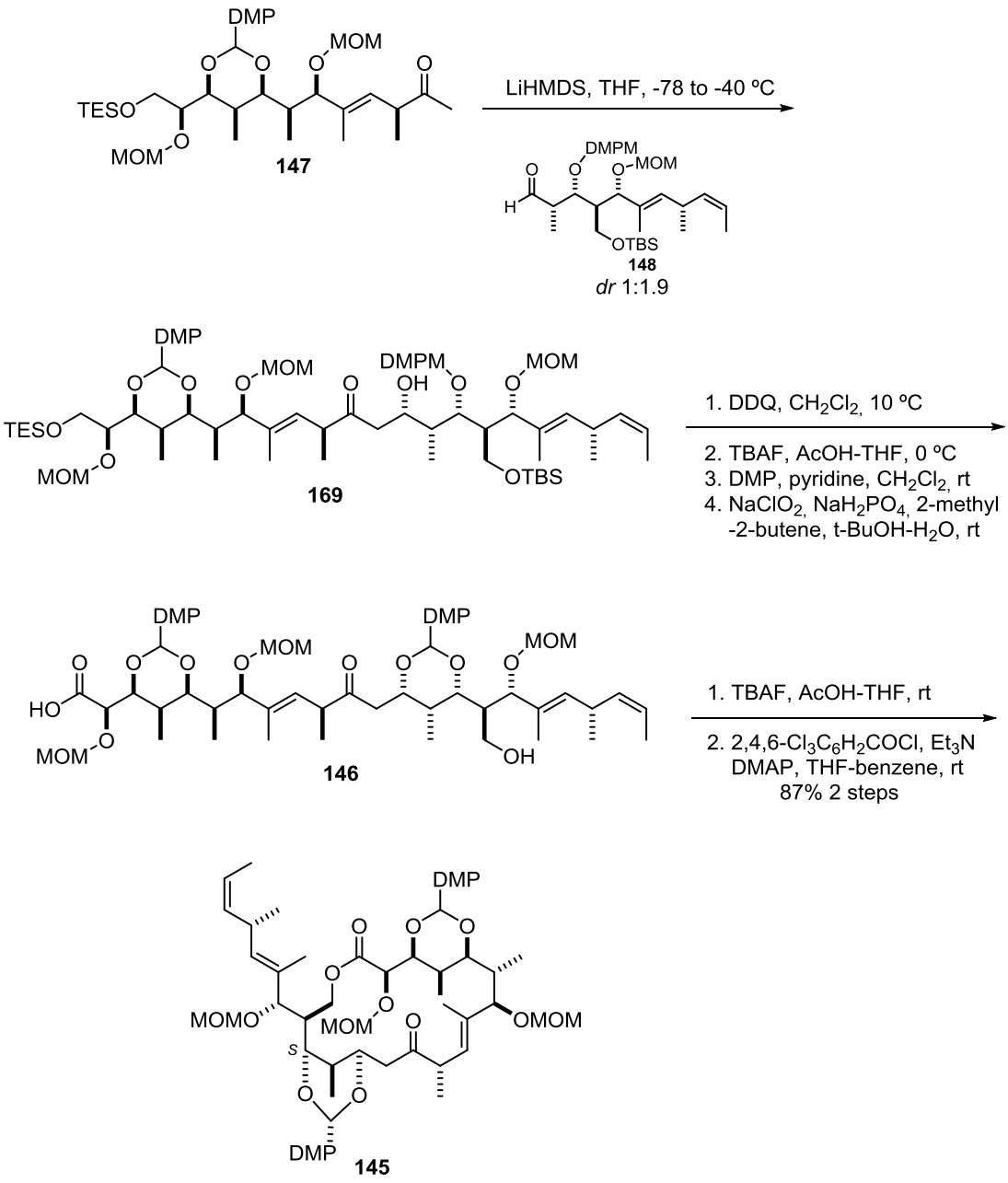
***Scheme 3.35**: Synthesis of aldehyde **151**.*

Aldehyde **151** was then treated with the lithiated species of the iodoalkene **152** resulting in poor diasteroselectivity (1:7.5) in favor of the undesired product (Scheme 3.36). The newly generated hydroxyl group was oxidized to ketone **165**. Removal of the TBS group followed by stereoselective reduction of the ketone provided the desired alcohol C(17/α) and then both hydroxyl groups are protected as diacetate **166**. Installation of the double bond at C(21-22) was achieved by selective protection of the C(13)-alcohol as DMPM acetal followed by the oxidation of the C(21)-alcohol to the corresponding aldehyde, which was treated with a ylide prepared from ethyltriphenylphosphonium bromide to afford the *Z*-olefin **168** with 15:1 selectivity. Reductive acetal opening and oxidation of the primary alcohol provided aldehyde **148**.



***Scheme 3.36**: Synthesis of aldehyde **148**.*

The aldol condensation between the lithium enolate of ketone **147** and aldehyde **148** resulted in a poor diastereoselectivity (1:1.9) in favour of Felkin product **169** (Scheme 3.37). Removal of TES group afforded the corresponding primary alcohol, which is further converted to the carboxylic acid **146** under standard conditions. TBS group removal followed by macrolactonisation using Yamaguchi conditions[45] afforded the macrolactone **145**. On the whole, Yonemitsu and co-workers established a convergent route for individual fragment synthesis, successfully obtained the macrolactone **145**, but the total synthesis of tedanoldie (**6**) was not accomplished.

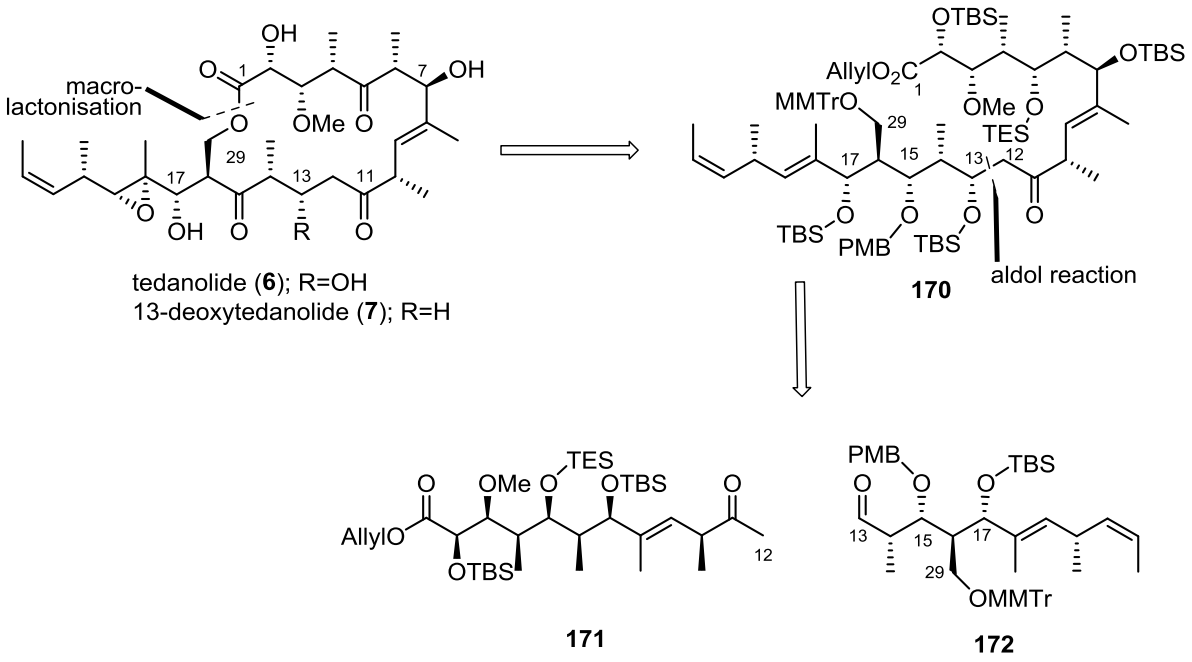


***Scheme 3.37**: Synthesis of macrolactone **145**.*

3.5. Kalesse's Approach:

The total synthesis of tedanolide (**6**) was first accomplished in our group in the year 2006,[67b] In the process of synthesizing the tedanolide (**6**), a late stage C(17)-hydroxyl directed epoxidation at C(18,19) was planned in order to circumvent the problems that are reported by Roush *et al.* during the total synthesis of deoxytedanolide (**7**).[58] Macrolactone cleavage would give rise to compound **170** (Scheme 3.38), which was envisioned as the substrate constituting the complete carbon framework necessary for the target molecule (**6**), in which C(29)- hydroxyl bearing MMTr group and allyl ester on C(1) can be selectively liberated to undergo macrolactonisation.

The retrosynthetic analysis (Scheme 3.38) dissected compound **170** such that the aldol reaction between C(12) and C(13) serves as a juncture between the key intermediates **171** and **172**. (*S*)-configuration was chosen for the C(15)-hydroxyl group and C(1)-carboxylic acid was masked as allyl ester.



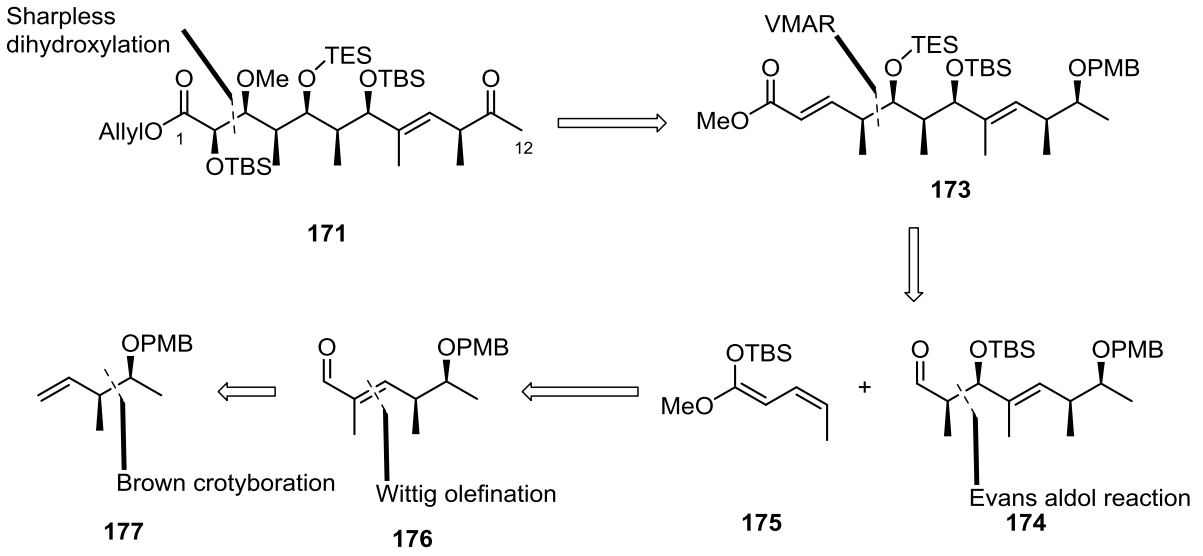
***Scheme 3.38**: Retrosynthetic approach towards tedanolide (**6**) by Kalesse et al..*

3.5.1. Synthesis of Methyl Ketone C(1-12) 171:

The synthesis of the ketone fragment C(1-12) **171** was carried out in our group by J. Hassfeld and U. Eggert.[75-76] Throughout these studies, the scope of aldol coupling of methyl ketone **171** with the 2,3-*syn* model aldehydes was explored and various conditions for macrolactonisation towards the 18-membered ring. The synthesis involved the vinylogous Mukaiyama aldol reaction (VMAR) as the key step, in which four-carbon chain with three contiguous stereo centers, was introduced with high enantiomeric and diastereomeric selectivities.

The retrosynthetic approach of the ketone fragment **171** is depicted below in the Scheme 3.39. Compound **171** could be achieved from the dihydroxylation of the unsaturated ester **173**. The

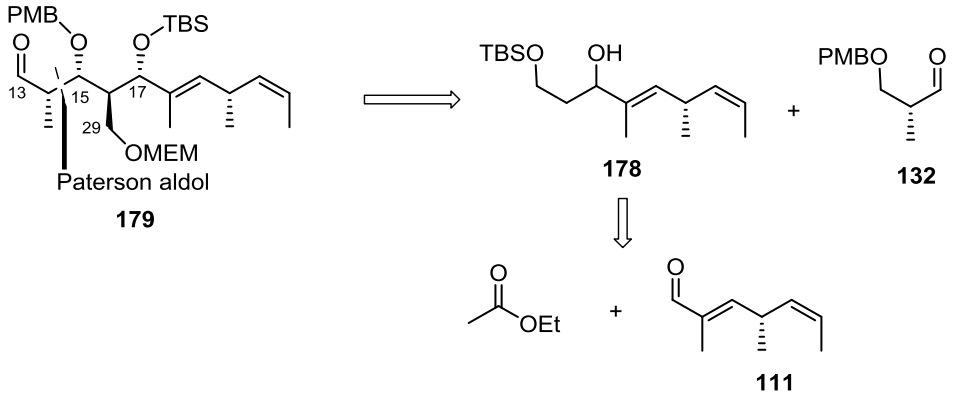
hydroxyl groups at C(2) and C(3) position are introduced using Sharpless asymmetric dihydroxylation,[30,37] obtaining the desired stereochemistry. Ester **177** could be achieved from a vinylogous Mukaiyama aldol reaction of the aldehyde **174**. The vinylogous Mukaiyama aldol reaction on aldehyde **174** using the ketene acetal **175** could provide the α,β-unsaturated ester **173**, bearing the complete carbon framework for the fragment. Aldehyde **174** could be obtained from a *syn*-selective Evans aldol reaction[50] of aldehyde **176**, which in turn could be obtained from the crotylboration of the acetaldehyde using the Brown protocol.[77]



***Scheme 3.39**: Retrosynthesis of methyl ketone **171**.*

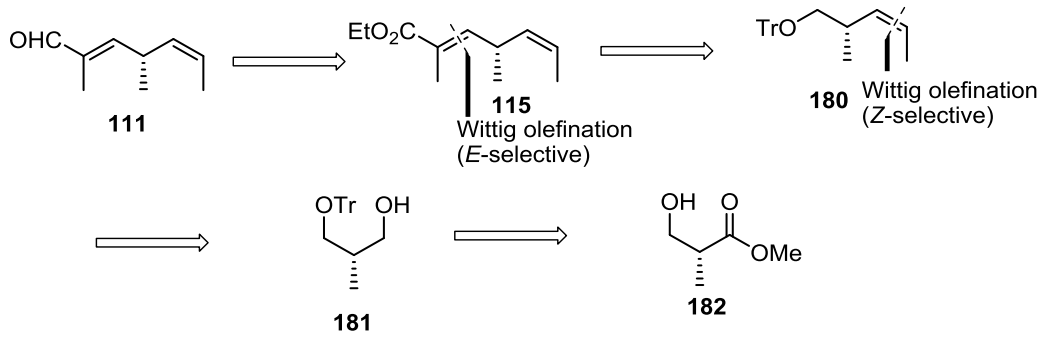
3.5.2. Synthesis of Aldehyde C(13-23) 179:

The synthesis of aldehyde fragment **179** was reported by G. Erhlich, J. Hassfeld and U. Eggert (Scheme 3.40).[78] Two separate synthesis of the aldehyde fragment were developed. In the first approach, *anti*-selective aldol reaction was planned at the C(15-16) bond between the intermediates **178** and **132**. Hydroxy compound **178** was in turn built by an aldol reaction between ethyl acetate and aldehyde **111**.



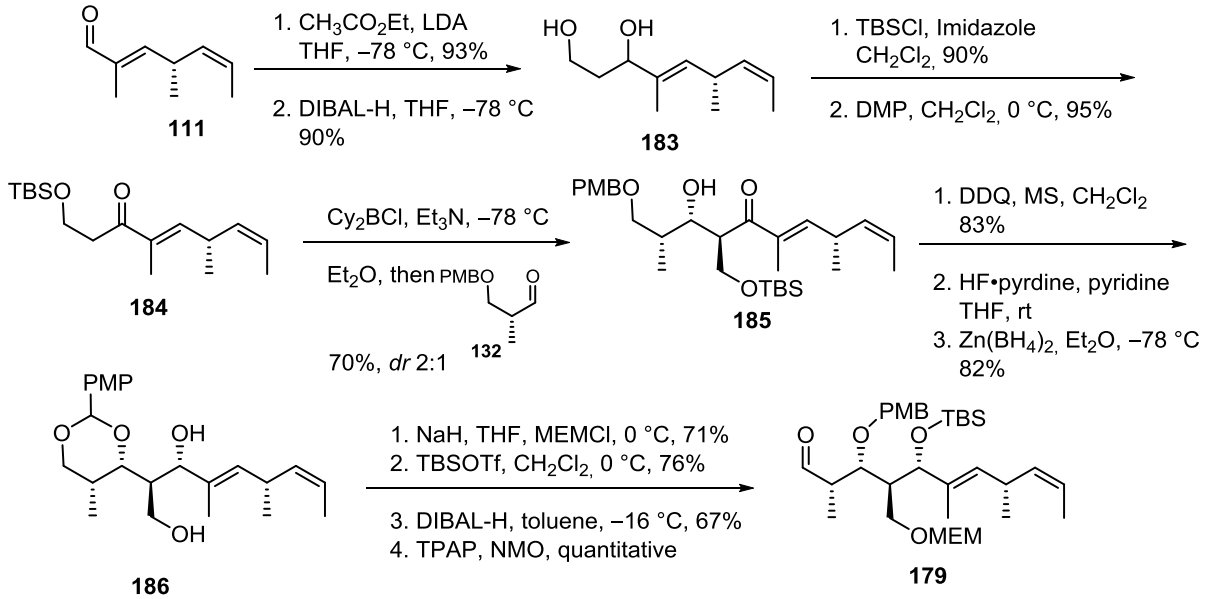
***Scheme 3.40**: First generation approach of aldehyde **179**.*

Aldehyde **111** could be obtained from the ester **115**, which inturn could be obtained from *E*-Wittig olefination of the aldehyde generated from compound **180**. The *Z*-olefin olefin **180** could be obtained from the aldehyde generated from the alcohol **181**, which is obtained from the commercially available Roche ester **182** (Scheme 3.41).



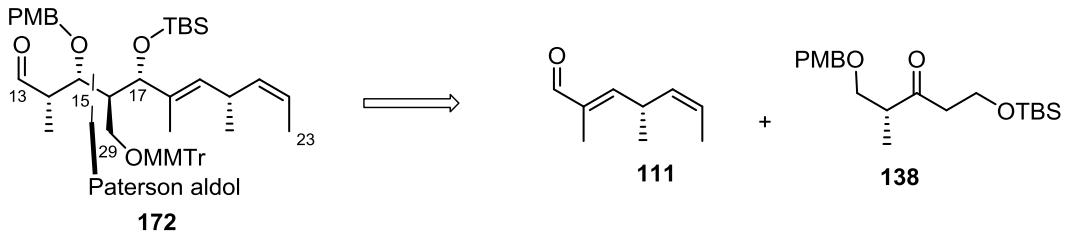
***Scheme 3.41**: Retro synthetic approach of aldehyde **111**.*

The first generation synthesis of the aldehyde **179**, commenced with the treatment of aldehyde **111** was treated with the lithiated species of ethyl acetate, followed by DIBAL-H reduction, TBS-protection of the primary group and oxidation of the secondary alcohol to provide compound **184** (Scheme 5.5). *Anti*-selective aldol reaction with PMB-aldehyde **132** gave the desired Felkin-product **185** in 2:1 diastereomeric ratio. Subsequently, the PMB group was oxidized to PMP acetal using DDQ, and the TBS group was removed using HF-pyridine. Chelation controlled reduction of the ketone in the presence of $Zn(BH_4)_2$ provided allyl alcohol **186** with the desired stereochemistry. To finalise the synthesis, protection of the primary and allyl alcohol functionalities, followed by reductive acetal opening and oxidation furnished the aldehyde **179**.



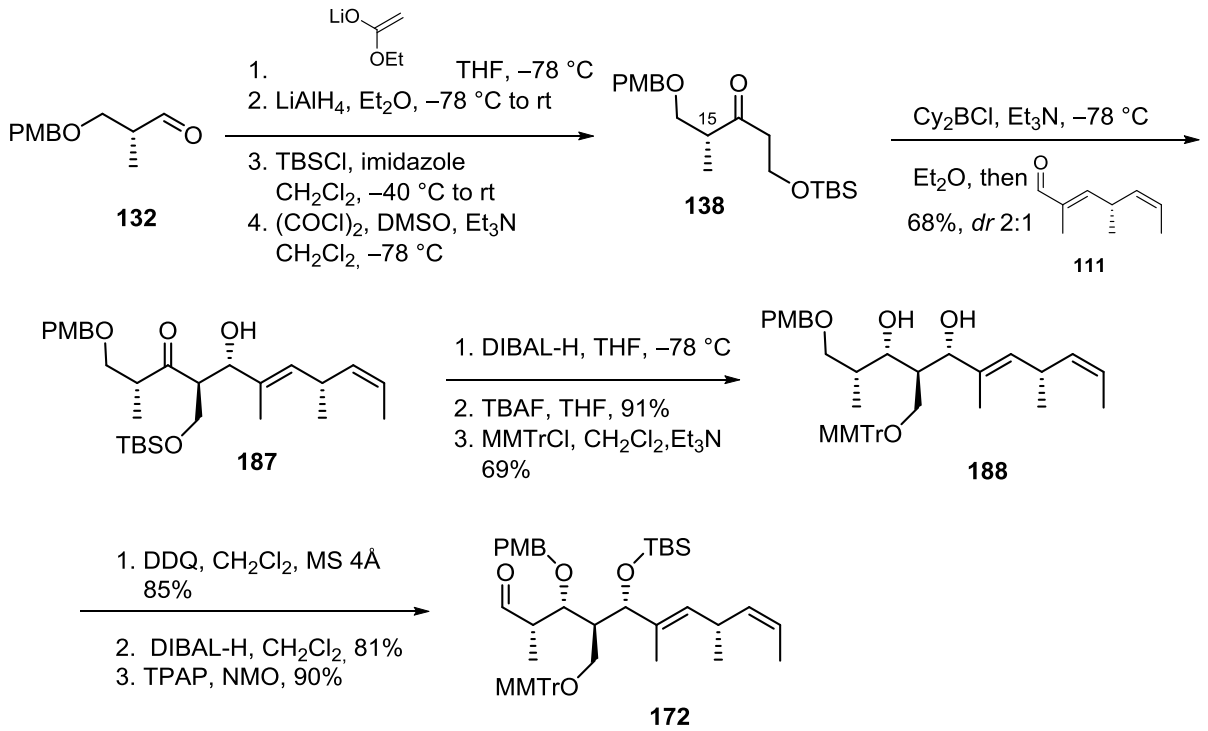
***Scheme 3.42**: First generation synthesis of aldehyde **179**.*

The first generation synthesis of C13-23 aldehyde presented above had its drawbacks, due to the relatively long number of linear steps and occasional uncontrolled migration of protecting groups. This led to development of second generation synthesis of aldehyde **172**, using a more convergent *anti*-selective aldol coupling between C(16) and C(17) (Scheme 3.43). Ketone **138** was planned as the coupling partner for the aldol reaction.



***Scheme 3.43**: Second generation approach of aldehyde **172**.*

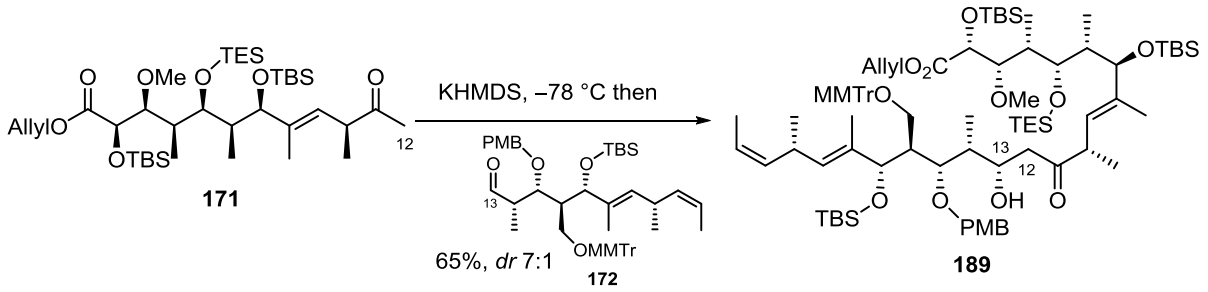
Ketone **138** was prepared in 4 steps from the PMB Roche aldehyde **132**, addition of lithium enolate of ethyl acetate to aldehyde **132** resulted in a β-hydroxy ester that was reduced to a 1,3-diol (Scheme 3.44). Subsequently selective silylation of primary hydroxyl group and oxidation of the secondary alcohol furnished the ketone **138**. Paterson aldol reaction of ketone **138** with aldehyde **111** gave the desired diastereomer **187** in 2:1 ratio. The ketone functionality in **187** stereoselectively reduced with DIBAL-H to the alcohol in high selectivity. Following functional group exchange, the allylic alcohol was selectively protected as TBS ether and the PMB group was transferred on to the secondary hydroxyl *via* a sequence of benzylideneacetal formation followed by regioselctive acetal reductive opening with DIBAL-H. The resulting primary alcohol was oxidized to aldehyde **172** using TPAP/NMO.



***Scheme 3.44**: Synthesis of aldehyde **172**.*

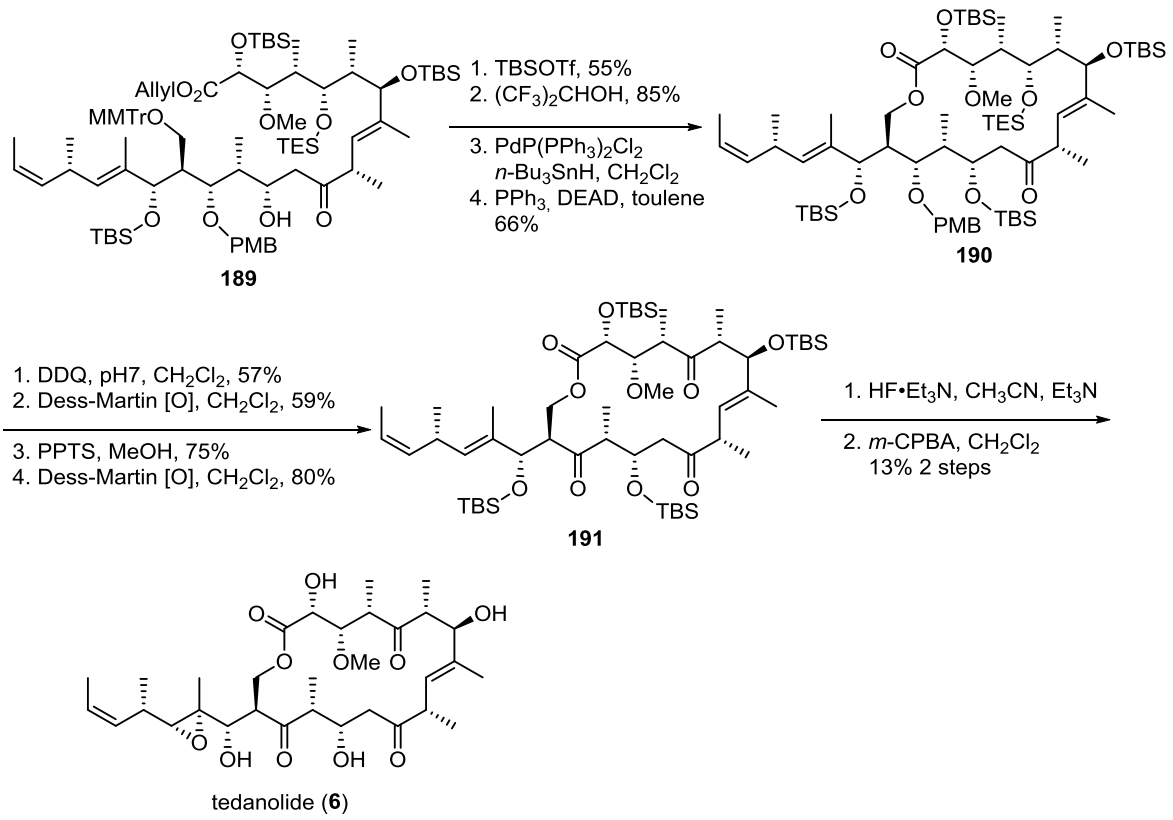
3.5.3. Synthesis of Tedanolide by Kalesse *et al.*(6):

Having established the routes for both fragments, the focus turned towards the completion of tedanolide (**6**). The crucial aldol coupling between the ketone **171** and aldehyde **172** was optimized after careful screening of different bases. KHMDS proved to be the most suitable base for the enolisation of the methyl ketone functionality and thereby achieved the highest diasteroselectivity in favour of Felkin product **189** (*dr* 7:1) (Scheme 3.45).



***Scheme 3.45**: Aldol coupling of ketone **171** and aldehyde **172**.*

The resulting C(13)-hydroxyl group was protected as TBS ether in order to avoid any lactonisation at this position (Scheme 3.46). The moderate yield observed for this protection was attributed firstly, to considerable amount of retro-aldol reaction and the secondly to the cleavage of the MMTr group under these reaction conditions. Finally the MMTr group was removed using a mild acid hexafluoroisopropanol. Palladium-catalyzed allyl ester saponification followed by macrolactonisation under Mitsunobu conditions[63] led to the desired macrolactone **198**. The C(5) and C(15) hydroxyl groups are liberated and oxidized to their respective ketones. The global deprotection was achieved by following the protocol utilized by Roush in the total synthesis of deoxytedanolide[57] (Et_3N•HF in Et_3N). The final epoxidation of the C(18-19) double bond was achieved using excess of *m*-CPBA and $NaHCO_3$ at low temperatures to furnish tedanolide (**6**).



***Scheme 3.46**: Synthesis of tedanolide (**6**).*

In conclusion, the total synthesis of tedanolides achieved by several groups were discussed in detail additionally valuable contributions from Yonemitsu and Loh groups for individual fragment synthesis have been highlighted. A few other research groups[79] had tried to synthesize to make this class of natural product however, they were not successful in accomplishing the total synthesis of tedanolides.

4. Synthetic Part:

4.1. Synthesis of Isotedanolide:

The tedanolide family of natural products is a rare example of macrolactones formed by primary linkage (Figure 4.1). The biosynthesis of these polyketides is elusive and is thought that the presence of the primary hydroxyl group in the tedanolide could arise from the post polyketide synthases (PKS) modifications.[80]

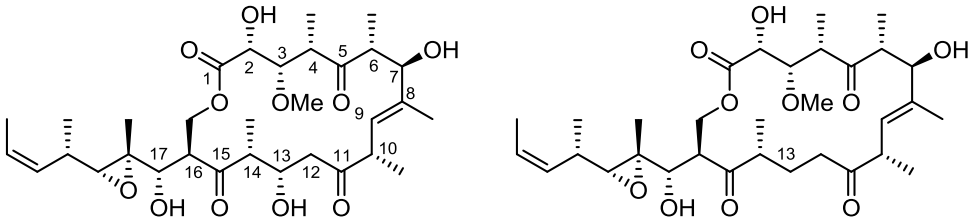
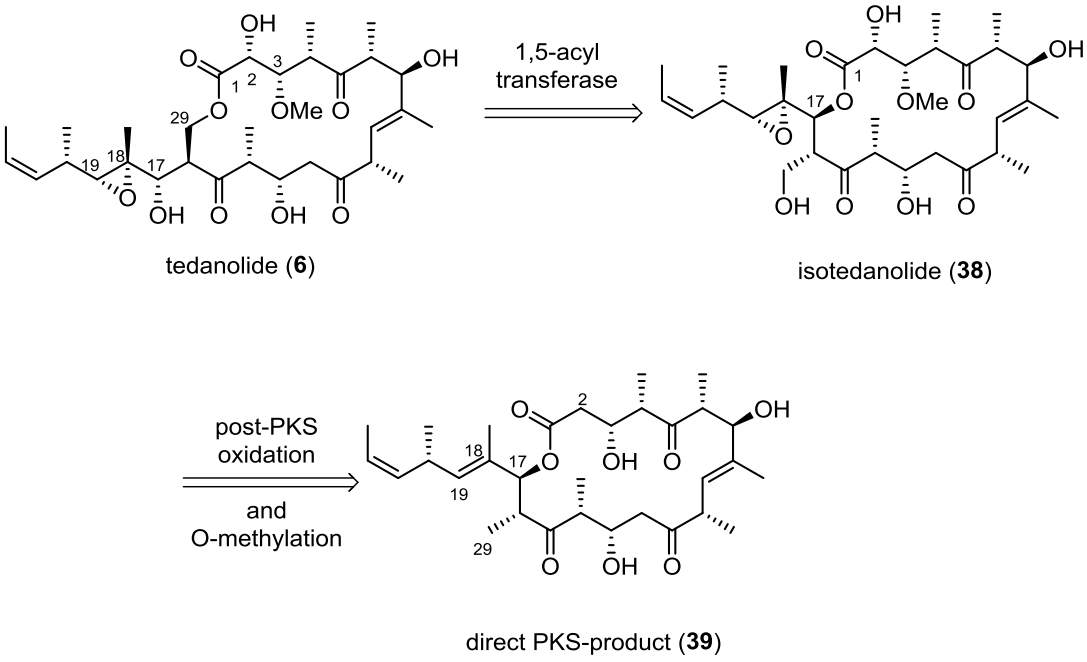


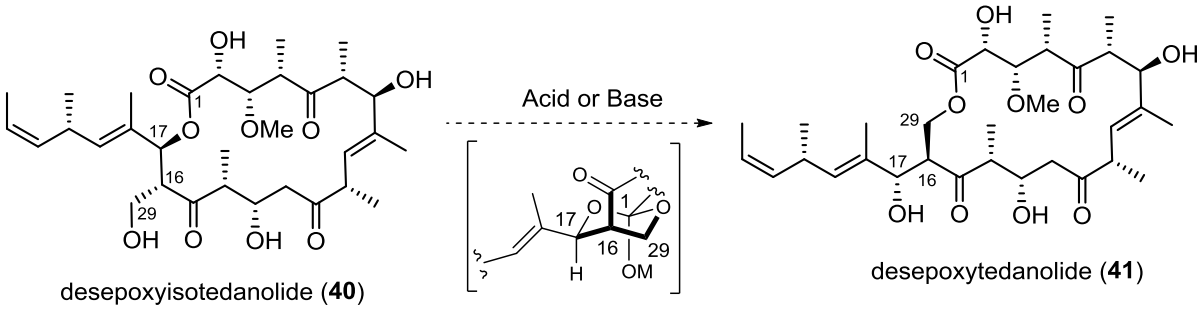
***Fig. 4.1**: Structures of tedanolides **6** and **7**.*

Due to the belief that the oxygenation at C(29) along with the C(2)-hydroxyl occur as post-PKS modifications, it is thought that the C(18-19) epoxide and the C(3) methyl ether may also arise from this process, the direct product of PKS biosynthesis is likely to be the 18-membered lactone (**39**) (Scheme 4.1). This species (**39**) would then act as a substrate for cytochrome of P450 oxidase, and a methyl transferase, which would then produce isotedanolide (**38**).[35]



***Scheme 4.1**: Proposed biosynthesis of tedanolide (**6**).*

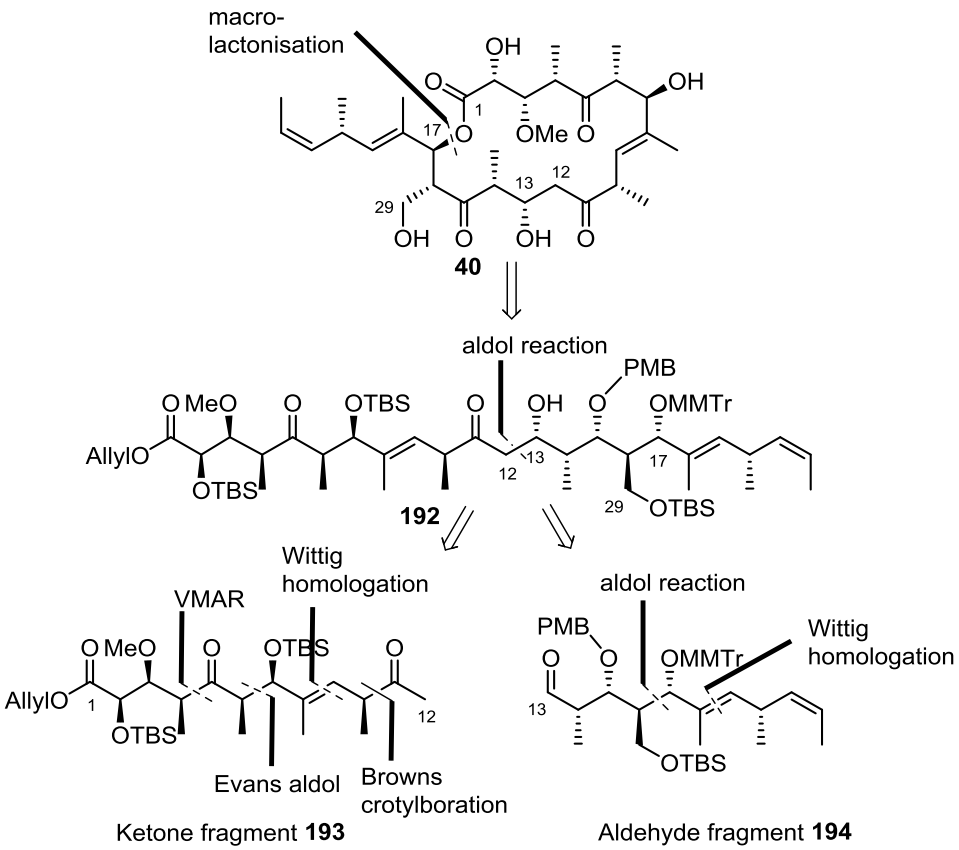
The synthesis of desepoxyisotedanolide (**40**) was initiated in order to probe the proposed biosynthesis of tedanolide.[35] The synthesis of desepoxyisotedanolide (**40**) followed by the isomerisation under chemical conditions to desepoxytedanolide (**41**) was the objective of this project (Scheme 4.2). Based on the literature precedence and the research carried out by several work groups, the synthesis of desepoxyisotedanolide (**40**) was designed.



***Scheme 4.2**: Isomerisation of desepoxyisotedanolide (**40**).*

4.1.1. Retrosynthesis of Desepoxyisotedanolide (40):

The synthetic route was designed similar to that of the total synthesis of tedanolide (**6**), followed earlier in our group.[67] Cleavage of macrolatone would provide the linear fragment **192** consisting of the complete carbon frame work for desepoxyisotedanolide (**40**) (Scheme 4.3). The linear fragment **192** could be built upon the base-induced substrate controlled-aldol reaction of ketone **193** and aldehyde **194**. Selective liberation of the C(17)-allyl hydroxyl group, keeping the C(29)-hydroxyl group protected and cyclisation to the eighteen-membered secondary lactone would furnish the desired secondary macrolactone. A series of oxidations will provide us desepoxyisotedanolide (**40**).



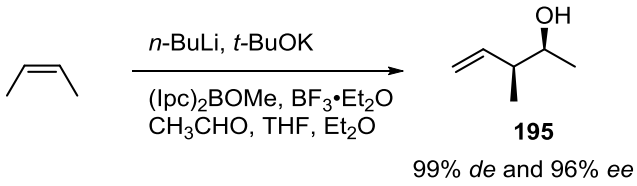
***Scheme 4.3**: Retrosynthetic approach towards desepoxyisotedanolide (**40**).*

Appropriate selection of the protecting groups for the hydroxyl group was the major challenge throughout the synthesis of desepoxyisotedanolide (**40**). An advanced stage intermediate with minimal protecting groups for the ketone part was required in order to avoid problems at later stages. Ketone **193**, earlier reported in our group,[81] containing a ketone at the C(6) position was chosen as a possible coupling partner for the key aldol condensation. It was envisioned that an alternative protecting group strategy was required at the C(17)-hydroxyl group of aldehyde **194** coupling partner, which would allow for deprotection under milder conditions. From our earlier experiences during the synthesis of tedanolide (**6**),[67] monomethoxytrityl group (MMTr) was selectively removed in the presence of TBS group under mild acidic conditions. Keeping this in mind, initially

aldehyde **194**, bearing the MMTr group at the C(17)-hydroxyl and TBS group at the C(29)-primary hydroxyl while retaining the C(15)-hydroxyl as PMB ether, was envisioned as an aldol coupling partner to the ketone **193** in an aldol reaction.

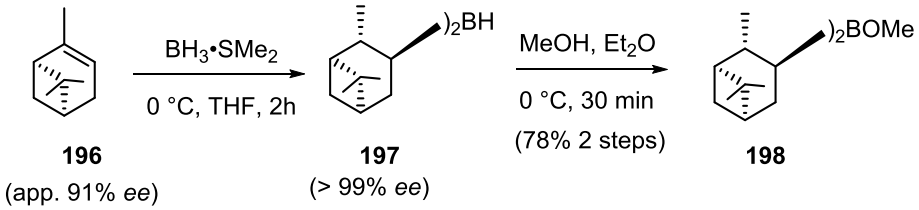
4.1.2. Synthesis of Keto C(1-12) Fragment 193:

The synthesis of methyl ketone **193** began with Brown's crotylboration[77] of commercially available acetaldehyde to afford homoallylic alcohol **195** (Scheme 4.4). The reaction proceeded in good yieldresulting in high diastereo- and enantioselectivity.



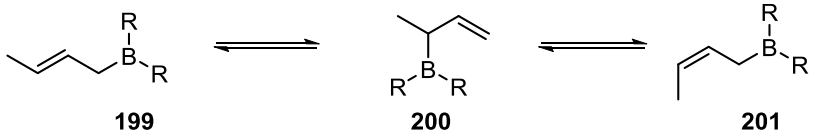
***Scheme 4.4**: Crotylboration of acetaldehyde.*

The synthesis of $(Ipc)_2BOMe$ was achieved from commercially available α-pinene **196**, which readily undergoes hydroboration at 0 °C to form diisopinocampheyldiborane **12** (Scheme 4.5). The best conditions to form optically pure Ipc_2BH involved the use of relatively stable boranemethylsufide and 15% excess α-pinene, in order to reduce the dissociation of diisopinocampheyldiborane. Methanolysis of Ipc_2BH **197**, at 0 °C produced the methoxy-isopinocampheylborane **198**.



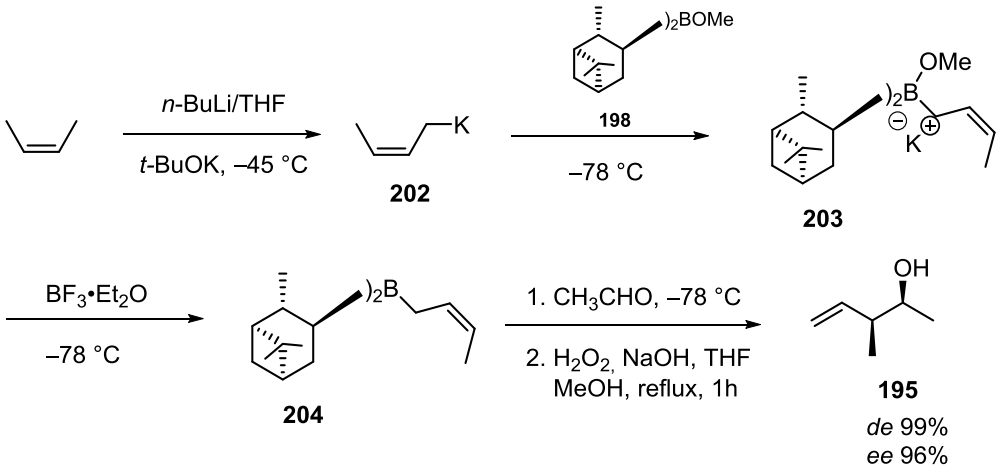
***Scheme 4.5**: Synthesis of methoxy-isopinocampheylborane **198**.*

The reaction of allyllic organometallic reagents with aldehydes affords the corresponding homoallyl alcohols. This transformation generates two new stereo centers and potentially four stereoisomeric products. The crotyl-borane derivatives generally exist as an interconvertible mixture of isomers which adds to the aldehyde to afford a mixture of regioisomers. The fast equilibration of pure (*E*)- and (*Z*)-crotylboron derivatives **199** and **201** *via* a simple borotropic rearrangement involves the 1-methylallyl compound **200** as an intermediate (Scheme 4.7).



***Scheme 4.6**: Equilibration of crotylboranes.*

The rate of isomerization of these intermediates varies greatly with the nature of the other boron substituents. In addition, allyldialkylboranes react readily at −78 °C and the optical purity achieved is considerably greater at low reaction temperatures. Synthetic access to the (*Z*)-crotyldiisopinocampheylborane **203** was achieved using Schlosser'sprocedure (Scheme 4.7).[82] Conversion of (*Z*)-butene to (*Z*)-crotylpotassium **202** was delivered by using a mixture of *n*-butylithium and potassium *tert*-butoxide in THF at −45 °C, followed by treatment with borane-methoxydiisopinocampheylborane **198** at −78 °C. This afforded complex **203**, which was exposed to boron trifluoride etherate to generate trialkylborane **204**, which upon treatment with the acetaldehyde, yielded the *erythro*-3-methyl-4-pent-2-ol **195** in 99% diastereoselectivity and 96% enantioselectivity.



***Scheme 4.7**: Synthesis of compound **195**.*

It is believed that the asymmetriccrotylboration proceeds *via* an intital complexation of the carbonyl oxygen with boron, followed by a transfer of the crotyl group from boron to the carbonyl carbon by a mechanism involving a six-membered transition state (Figure 4.2). In the allyllboration of the aldehydes, depending on the nature of the α-pinene [(+) or (-)], it was proposed that one of two possible six-membered transistion states (**205** or **206**) predominates, determined by the geometry of the asymmetric isopinocampheyl group, and therefore deciding the absolute configuration of the alcohol products.

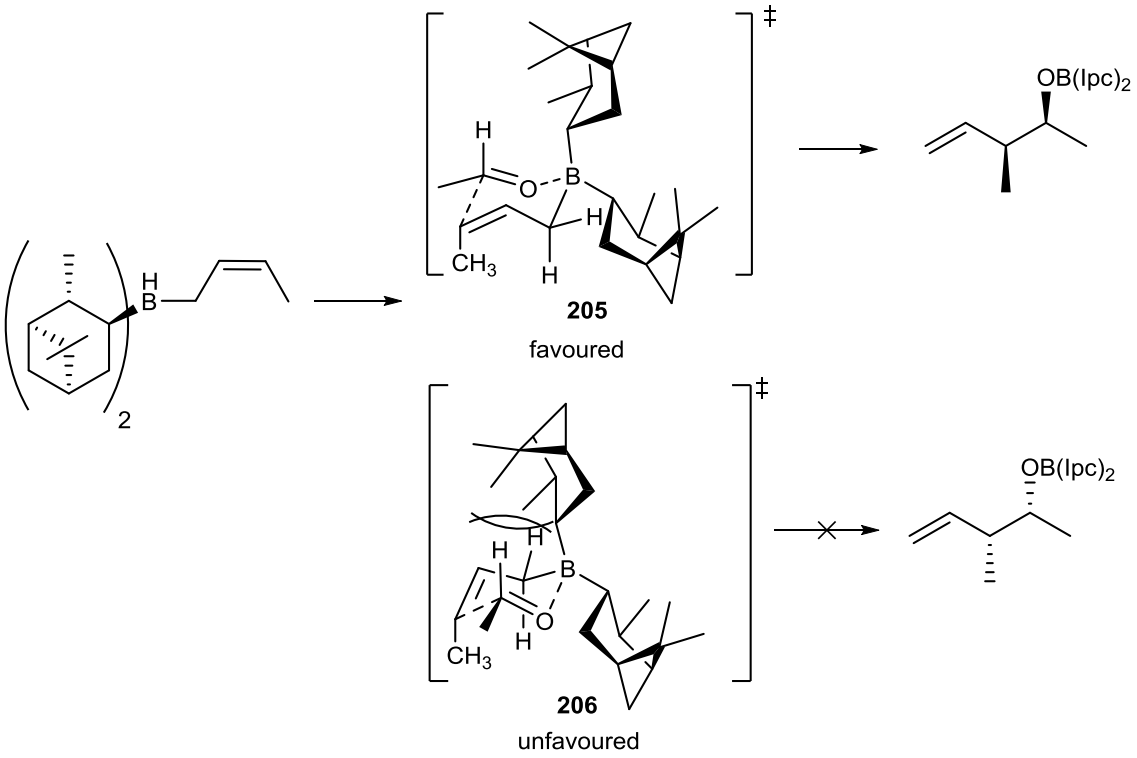
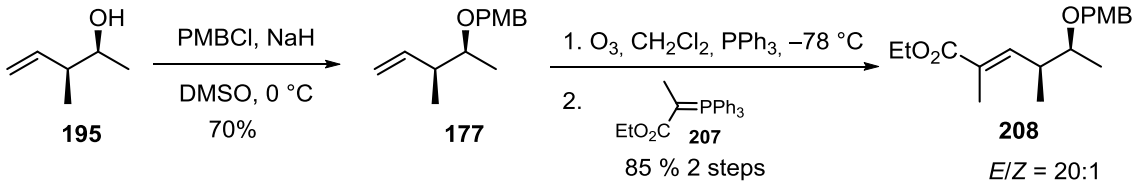


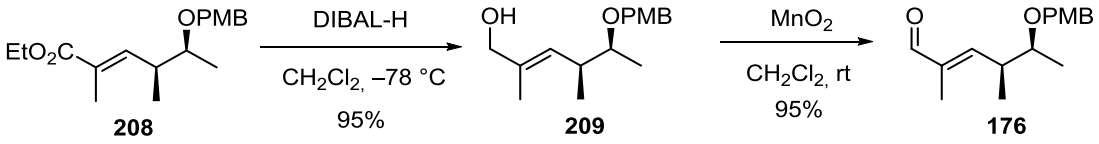
***Fig. 4.2**: Transition states for crotylboration.*

The homoallylic alcohol **195** was protected as PMB ether, followed by ozonolysis of the terminal olefin **177** to the aldehyde, which was treated *insitu* with stabilized Wittig ylide $PPh_3{=}CH_3CO_2Et$ to yield thecorresponding *E*-α,β-unsaturated ester **208** in good yield and selectivity (Scheme 4.8).



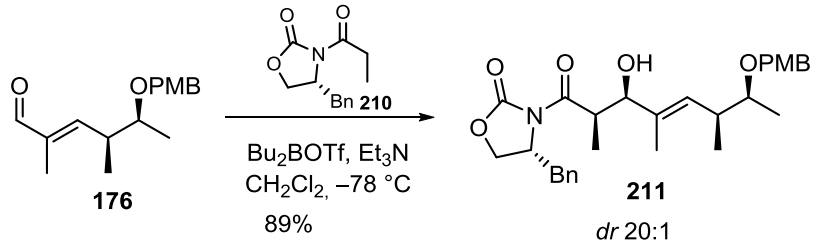
***Scheme 4.8**: Synthesis of α,β-unsaturated ester **208**.*

Ester **208** was reduced to the allyl alcohol **209** using DIBAL-H and the oxidation of the allylic alcohol was conveniently carried out in the presence of manganesedioxide at room temperature, to afford aldehyde **176** (Scheme 4.9).



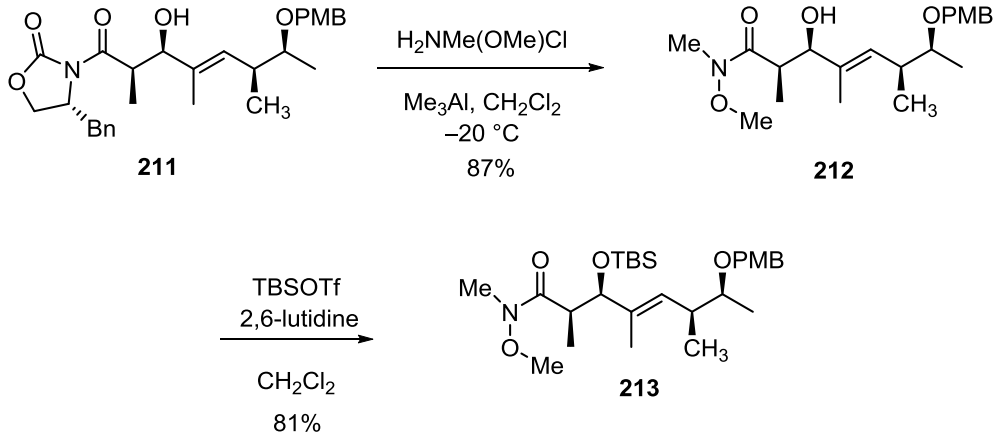
***Scheme 4.9**: Synthesis of α,β-unsaturated aldehyde **176**.*

In a *syn*-selective Evans' aldol reaction,[50] aldehyde **176** was converted to aldol adduct **211** in very good yield and high diastereoselectivity (>20:1) (Scheme 4.10).



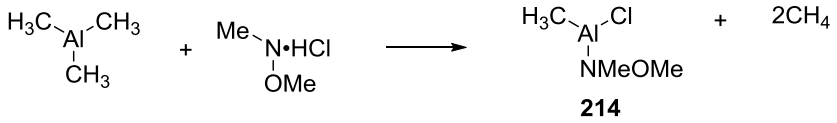
***Scheme 4.10**: Synthesis of aldoladduct **211**.*

The aldol adduct **211** was then treated with *N,O*-dimethyl hydroxylamine in the presence of Lewis acid trimethylaluminium to cleave the chiral auxiliary and afford amide **212** (Scheme 4.11). The free hydroxyl group was protected as TBS-ether under standard conditions to afford amide **213**.



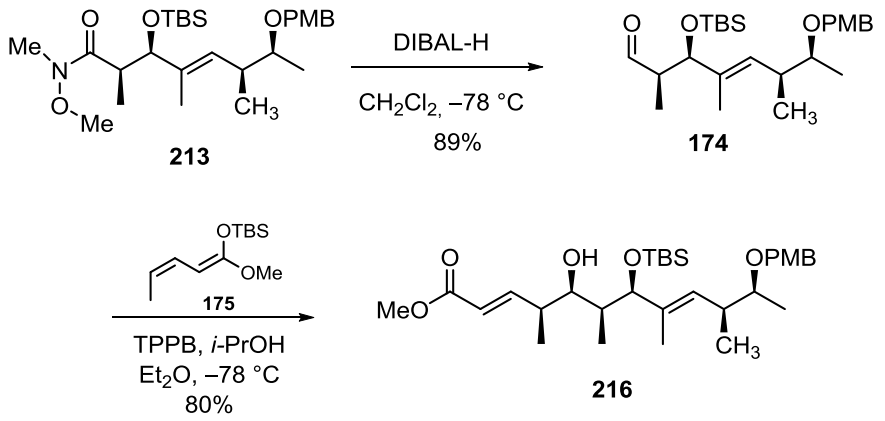
***Scheme 4.11**: Synthesis of amide **213**.*

The addition of trimethylaluminium to the amine hydrochloride generates an active aluminium intermediate **214**,[83] which upon reacting with aldol adduct **211** affords amide **212** (Scheme 4.12).



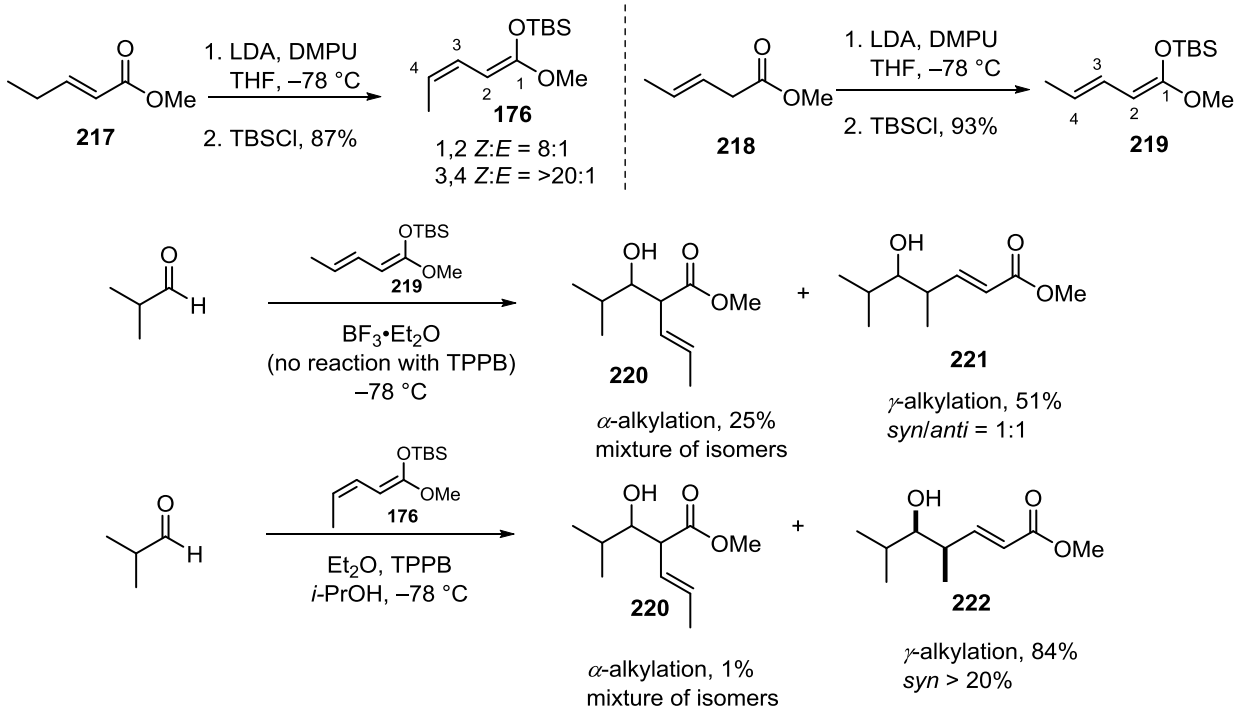
***Scheme 4.12**: Transamination using lewis acid species **214**.*

Amide **213** was reduced selectively to aldehyde **174** using DIBAL-H at −78 °C, and then immediately used in the vinylogous Mukaiyama aldol reaction (VMAR) to afford the α,β-unsaturated ester **215** (Scheme 4.13).



***Scheme 4.13**: Synthesis of ester **216**.*

Aldehyde **174** was added to a solution of trispentafluorophenylborane (TPPB) in diethylether at −78 °C, followed by the addition of a mixture of isopropanol and ketene acetal **175** over a period of two hours at the same temperature.The reaction proceeded in 80% yield of the *syn*-aldol product **216** (*dr* > 20:1). The (*Z*)-3,4-double bond geometry in ketene acetal **175** plays an important role in determining the regio- and stereo-selectivity of the reaction (Scheme 4.14). A detailed description of the vinylogous Mukaiyama aldol reaction with these ketene acetals was done in our group by Jorma Hassfeld.[76, 84] When the *E*- and *Z*-ketene acetals were subjected to VMAR conditions with TPPB and isobutyraldehyde (Scheme 4.14), interestingly the *E*-configured ketene acetal **219** resulted in low yields and poor regioselectivity, favouring the undesired α-alklyated product **220** in substantial amounts. In contrast, the *Z*-ketene acetal **175** delivered in high yields and exclusively γ-akylated product **222**.



***Scheme 4.14**: VMAR reactions using E- and Z-ketene acetals.*

In the open-chain transition state it can be seen that for the *E*-ketene acetal **219**, one substituent is always on the same side of the R group of the aldehyde and that the α-position is accessible to alkylation (Figure 4.3). In the transition state involving the *Z*-ketene acetal **176**, both substituents on the double bond are directed away from the R group of the aldehyde. At the same time, the *Z*-configuration prevents α-alkylation by increased steric hindrance through the adjacent methyl group.

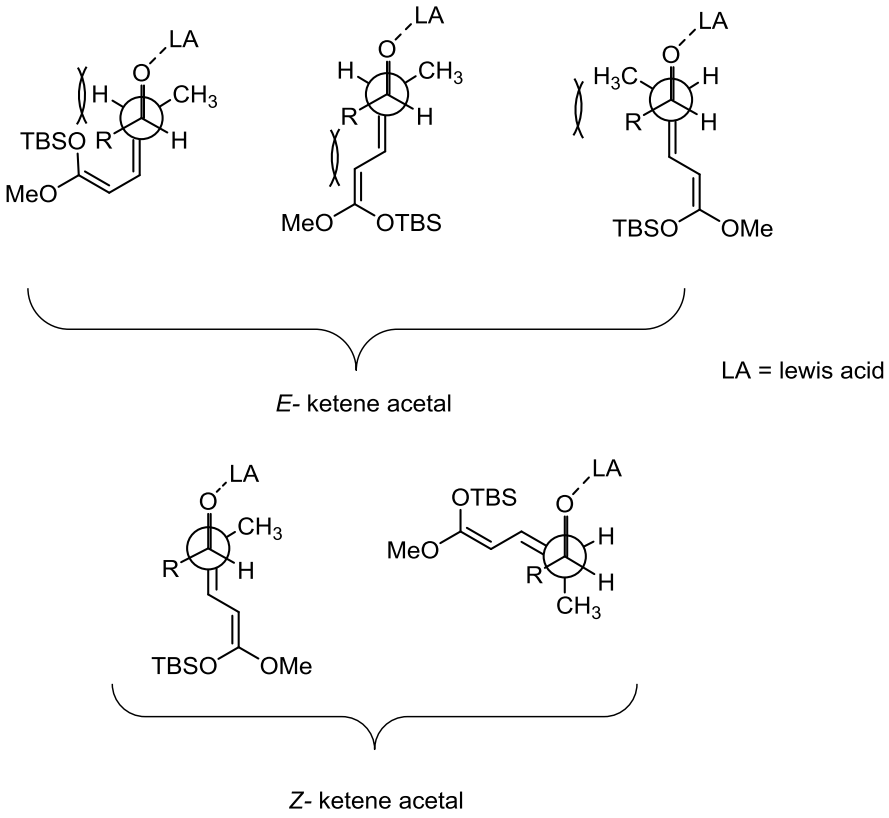
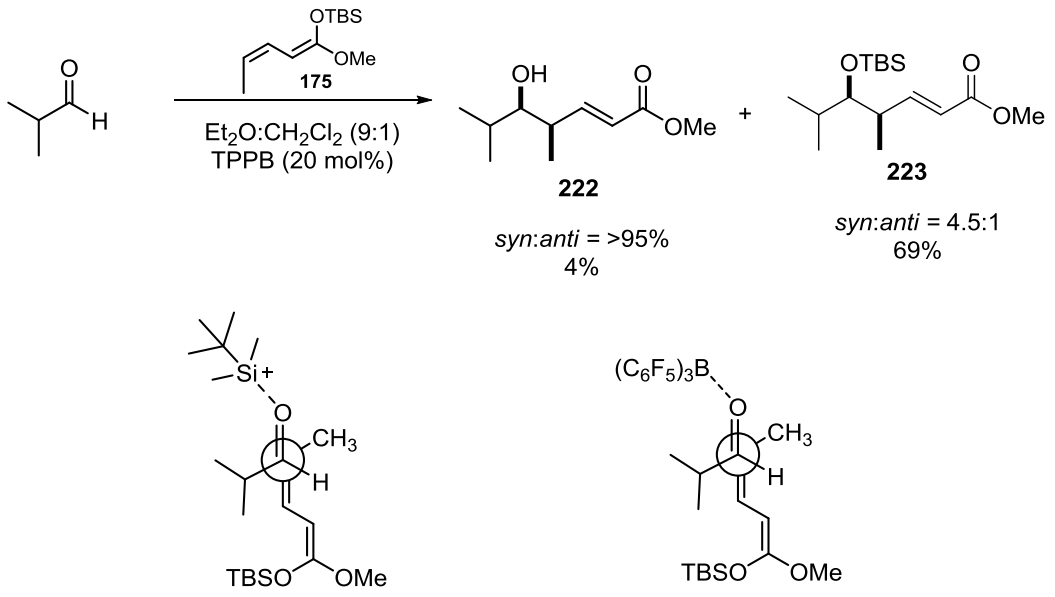


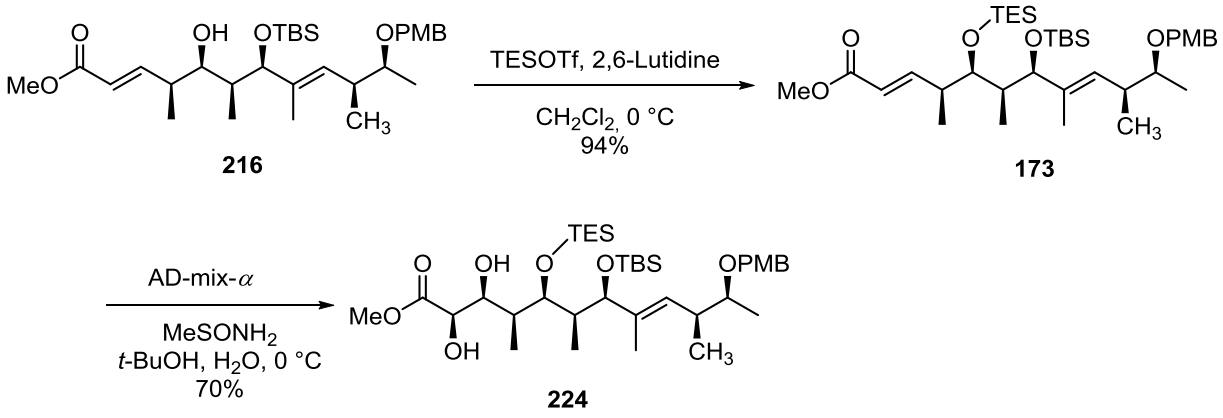
***Fig. 4.3**: Proposed transition states for the VMAR reaction.*

The yield and selectivity of the reaction also depends on the Lewis acid tris(pentaphenylborane) (TPPB) (Scheme 4.15).The bulkiness of the phenyl groupsresults in increased steric hindrance leading to higher diastereoselectivity. It was noted that either the monohydrate or the etherate of TPPB were suitableLewis acidsin this reaction. However, neat TPPB lead to decomposition. Isopropanol was added to the reaction as the scavenger to trap the reactive ''R_3Si'' species. When the reaction was carried out in the absence of isopropanol, two *syn*-aldol products are observed, one with newly formed unprotected hydroxyl **222** and the other as TBS protected **223** with a decrease in diastereoselectivity to 4.5:1.



***Scheme 4.15**: Silyl species competing as a Lewis acid.*

The newly formed hydroxyl group in the α,β-unsaturated ester **216** was protected as triethylsilyl ether and then subjected to Sharpless asymmetric dihydroxylation[66] to afford diol **224** (Scheme 4.16).



***Scheme 4.16**: Synthesis of diol **224**.*

The dihydroxylation reaction proceeded in good yield with high diasteroselectivity in the ratio of 20:1 in favor of the desired product **224**. This presented a mismatched case of AD-mix-α, giving rise to the product, the transition states are depicted below (Figure 4.4).[72, 85] In the case of olefinic compounds with chiral centers, diastereoselective face-selectivity of OsO_4 is governed by the conformation of the olefins. Two favorable conformations of compound **173**, (**A** and **B**) are predictable, **A** is the conformation controlled by the 1,3-allylic strain, whereas in the **B**-conformation, a large group is situated in the antiperiplanar position to the double bond. Face selectivity of α,β-unsaturated esters by AD-mix has been well studied,[66, 86] and the reaction on the *re-si* face can be achieved with AD-mix-

α, but not AD-mix-β. Our case is a mismatched one, where the result clearly shows that the conformation of **173** changed from B to A during the reaction with AD-mix-α.

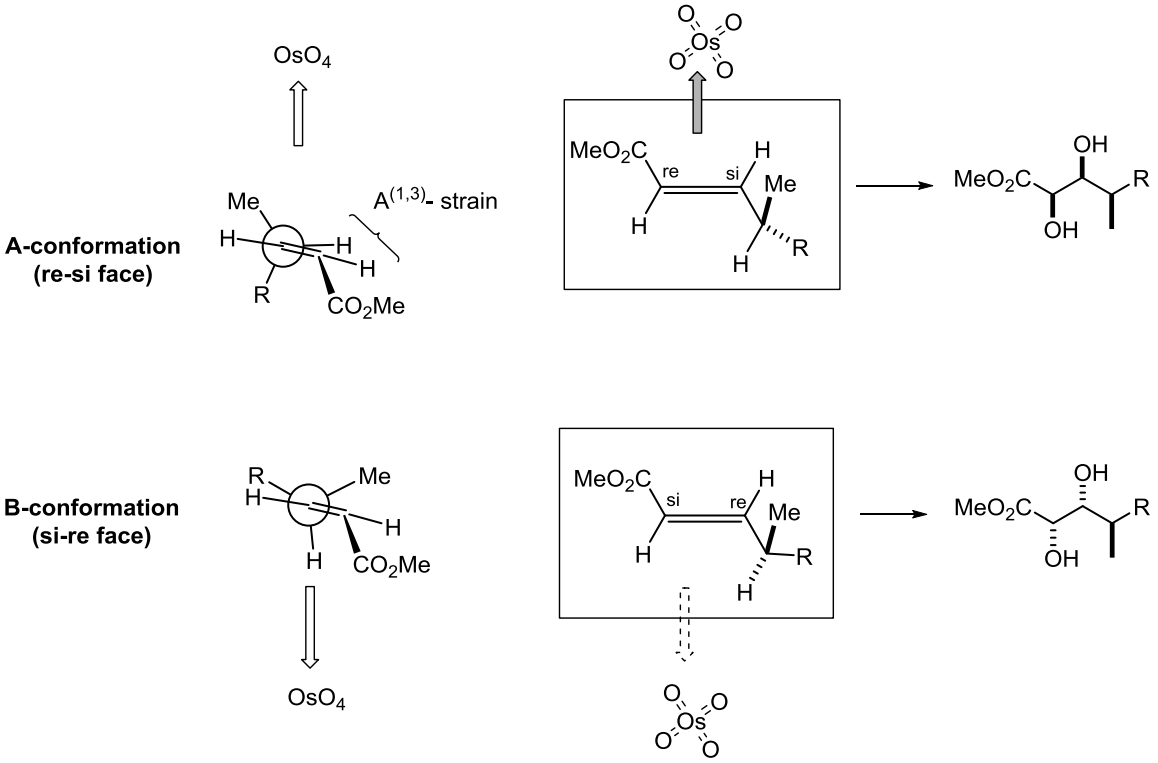
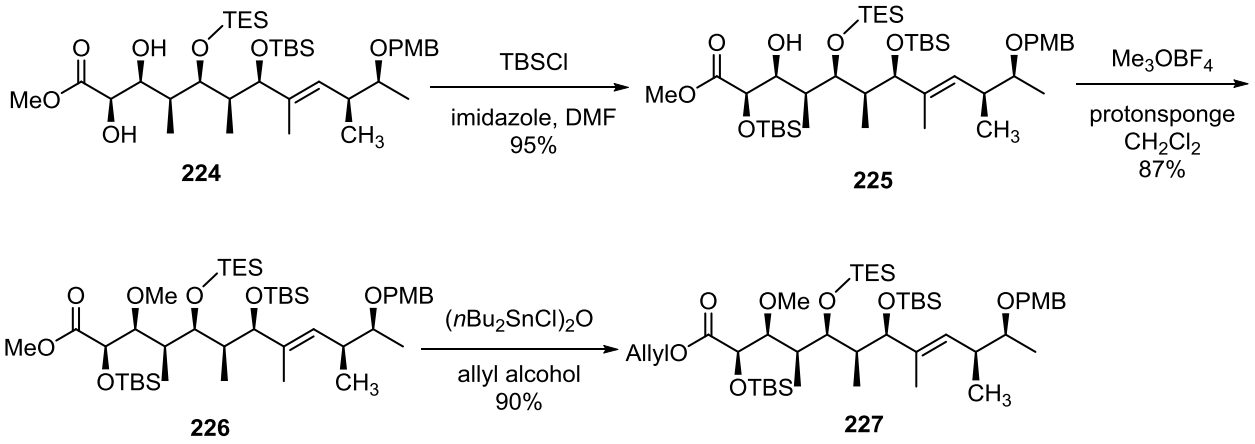


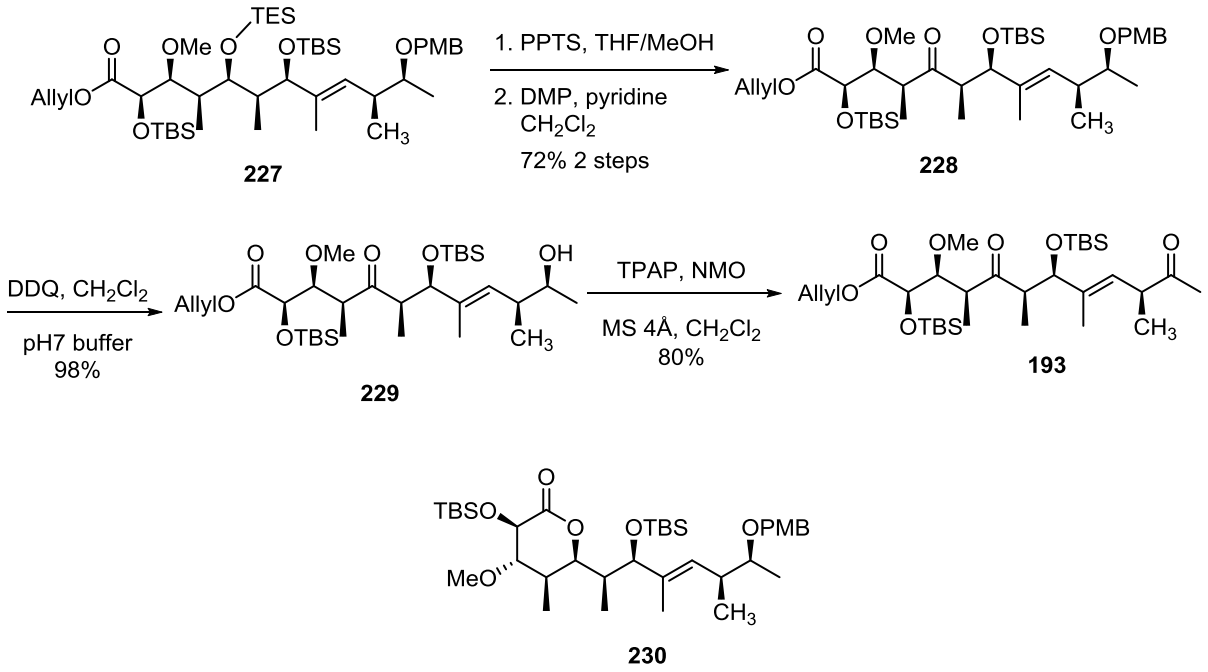
***Fig. 4.4**: Transition states for dihydroxylation.*

The C(2)-hydroxyl group in diol **224** was selectively protected as TBS-ether using TBSCl/imidazole in dimethylformamide and the C(3)-hydroxyl was subsequently protected as methyl ether using Meerwein salt in the presence of proton sponge (Scheme 4.17).[87] In order to avoid a potentially problematic late stage hydrolysis of the methyl ester functionality , methyl ester **226** was treated with dibutylstannanechloride oxide[88] at 160 °C in allyl alcohol for 4 days to provide allylester **227**.



***Scheme 4.17**: Synthesis of allylester **227**.*

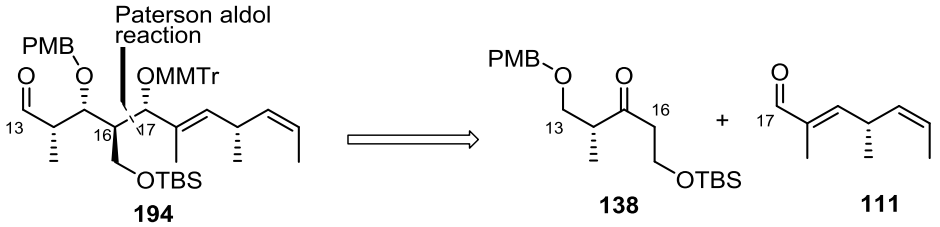
The C(6)-TES ether wasremoved under mildlyacidic conditions using PPTS in a mixture of methanol and THF (Scheme 4.18). The free hydroxyl group was immediately oxidised to the corresponding ketone using Dess-Martin periodinane/pyridine in CH_2Cl_2 in order to avoid the formation of six-membered lactone **230**. Finally, the PMB group was removed using DDQ and the secondary hydroxyl group was oxidised with TPAP/NMO to afford ketone **193**.[89]



***Scheme 4.18**: Synthesis of ketone **193**.*

4.1.3. Synthesis of Aldehyde Fragment C(13-23) 194:

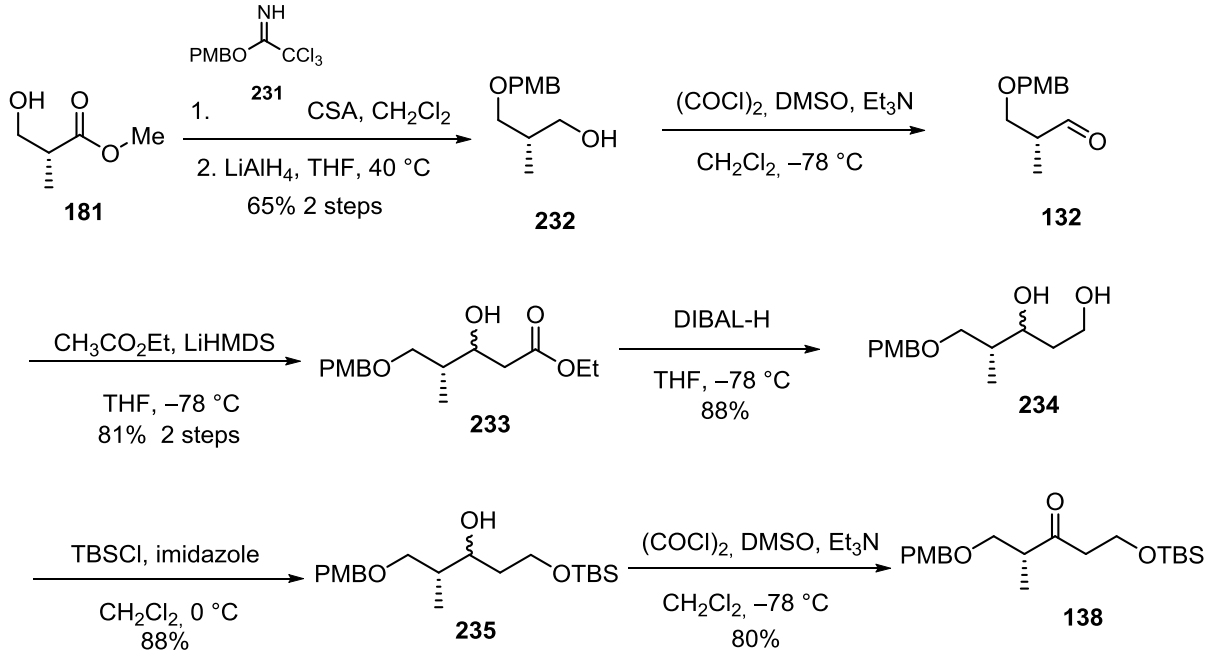
The aldehyde fragment would be built upon coupling of the two keto fragments, ketone **48** and α,β-unsaturated aldehyde **49** (Scheme 4.19). *Anti*-selective Paterson aldol reaction was planned in order to achieve the desired stereochemistry at C(16,17). Both these fragments would be quickly accessed from commercially available Roche ester **181**, following the research work carried out by Gunnar Ehrlich in our group.[90]



***Scheme 4.19**: Retrosynthesis of aldehyde **194**.*

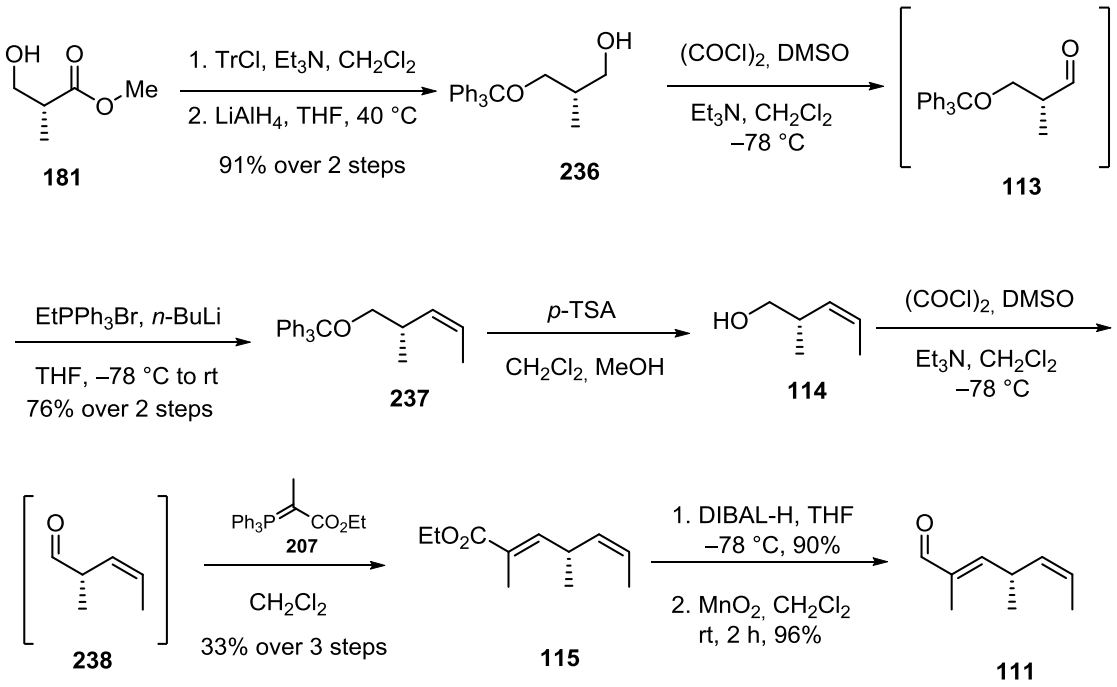
Synthesis of ketone **138** began with the PMB-protection of the primary hydroxyl functionality in Roche ester **181**, followed by reduction of the ester group to primary alcohol **232** (Scheme 4.20). Employing the Swern protocol,[61] the primary hydroxyl group was oxidised to aldehyde **132**, which was

immediately used in an aldol reaction with the lithiated species of ethylacetate to provide a diastereomeric mixture of alcohol **233**. The ester group was reduced using DIBAL-H to diol **234**, then selective protection of the primary hydroxyl group as TBS-ether followed by oxidation of the secondary hydroxyl group provided ketone **138**.



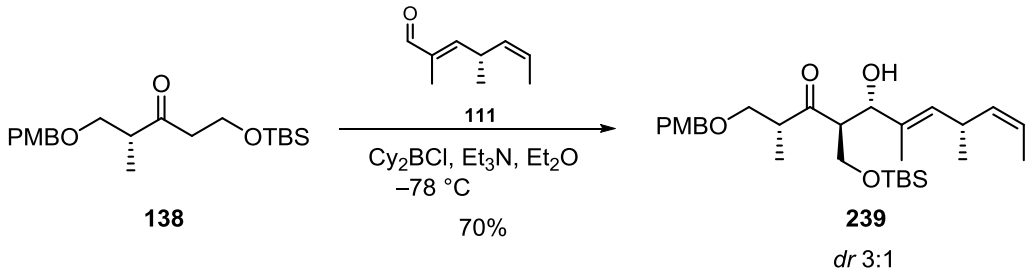
***Scheme 4.20**: Synthesis of ketone **138**.*

The synthesis of aldehyde **111** began from the commercially available Roche ester **181** (Scheme 4.21). Protection of the hydroxyl group with acid labile trityl group, followed by reduction of the ester afforded alcohol **236**. The installation of the *Z*-double bond was achieved by employing the Swern oxidation of alcohol **236** to provide aldehyde **113**, which was immediately used in the Wittig reaction. Ethyltriphenylphosphonium bromide was initially treated with *n*-BuLi to generate the ylide, followed by treatment with aldehyde **113** to afford the *Z*-olefin **237** in good diastereoselectivity (9:1). Removal of the trityl group was done under mild acid conditions involving PPTS in a mixture of methanol/dichloromethane and the resulting volatile alcohol **114** was distilled and subjected to Swern protocol to yield aldehyde **238**, which proved to be highly epimerisable[91] at room temperature when allowed to stand for prolonged time. Aldehyde **238** was immediately treated with stabilised ylide **207** even before quenching the Swern oxidation reaction at −78 °C. The Wittig reaction produced α,β–unsaturated ester **115** with high diastereoselectivity (95:5). Ester **58** was reduced to alyllic alcohol using DIBAL-H and converted to aldehyde **111** using MnO_2.



***Scheme 4.21**: Synthesis of aldehyde **111**.*

The reaction between ketone **138** and aldehyde **111** was performed employing the Paterson conditions,[68] which involved the initial addition of ketone **138** to a mixture of triethylamine and the Lewis acid chloroddicyclohexylborane at −78 °C to form an enolate, which was allowed to stand for 16 h at 2 °C in order to obtain the *E*-enolate, resulting in the desired *anti*-selectivity (3:1) in product **239** (Scheme 4.22). The diastereomers were easlily separated using column chromatography.



***Scheme 4.22**: Paterson aldol reaction of ketone **138**.*

The stereo-differentiation operating in these *anti*-aldol reactions is remarkable and can be traced to the relative steric and electronic properties of the substituents-H, Me and CH_2OPMB at the adjacent stereocenter. A chair-like transition state TS-1 was proposed, responsible for the high level of aldehyde π–face selectivity (Figure 4.5). This minimises the (1,3)-allylic strain with the *E*-enolalkoxy group and has the methyl group pointing outwards and the PMB-methyl group directed in towards the aldehyde. This preference for TS-1 (*si*-face attack) over TS-2 (*re*-face attack) is considered to have an electronic origin, possibly with TS-2 destabilised by lone-pair repulsion[22] between the oxygen atoms.

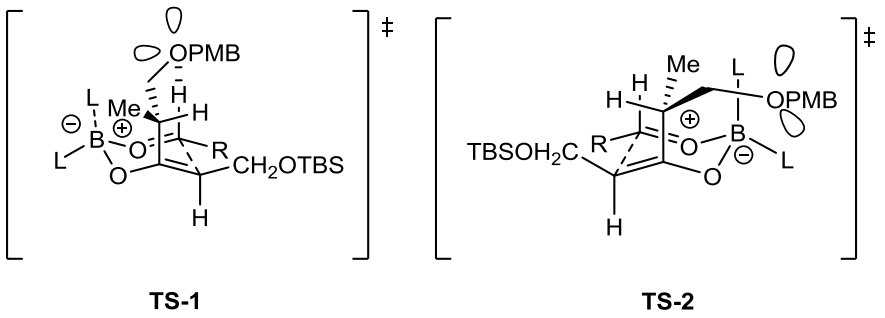
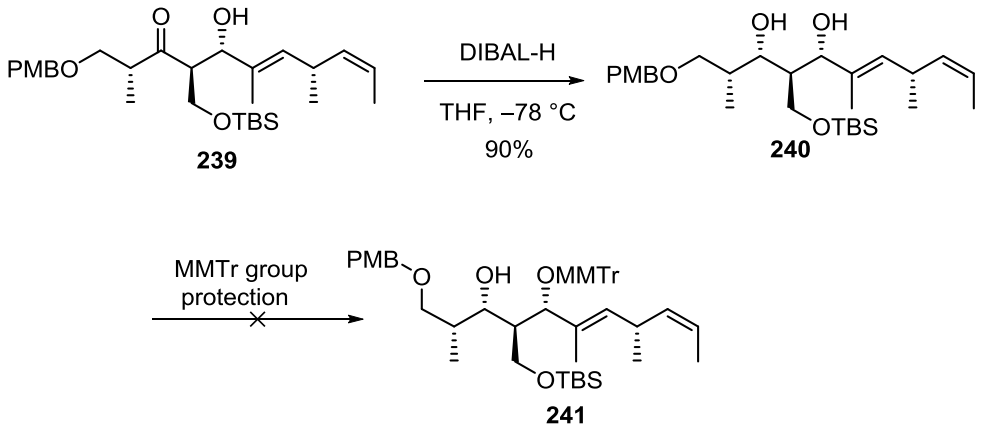


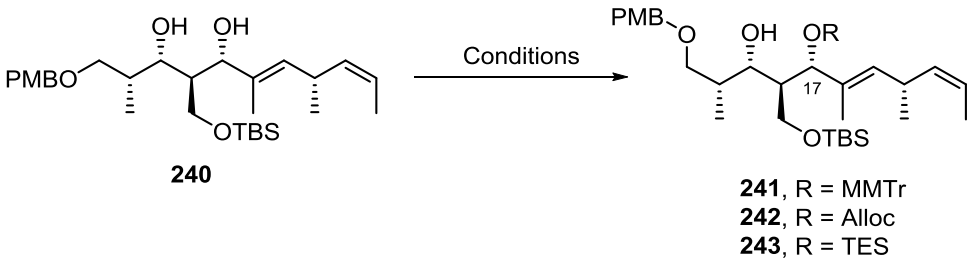
***Fig. 4.5**: Proposed transition states for Paterson aldol reaction.*

The major aldol product **239** was immediately subjected to reduction using DIBAL-H, since the appearance of the retro-aldol products were observed upon long standing of compound **239** (Scheme 4.23). The stereoselective reduction to diol **240** proceeded in high yield and high diastereoselectivity (*dr* 98:2). According to our synthetic plan a very mild protecting group, which can be cleaved in presence of all other protecting groups must be installed at the C(17)-allylic hydroxyl group. The initial plan involved thepresence of monomethoxytrityl group (MMTr) at this position, but unfortunately this protection was unsuccessful.



***Scheme 4.23**: Synthesis of compound **241**.*

As the monomethoxytrityl group protection failed (Table 4.1, entries 1-4), installation of alloc group on the C(17) hydroxyl functionality was attempted, so that both the C(1)-allyl ester and the alloc group could be removed in a single step. Unfortunately, the alloc group protection was not successful (Table 4.1, entries 5-8). In addition, it was also considered that the presence of this alloc ether could increase the chances of elimination at this position at a later stage of the synthesis. The search then switched back to silyl protecting groups. During the synthesis of the southern fragment of tedanolide (**6**), the Roush group installed the TES group at this C(17)-hydroxyl group.[57] It is known from literature that the TES group can be cleaved under mild acidic conditions in the presence of TBS group. Keeping this in mind, the C(17)-hydroxyl group was selectively protected by treatment with triethylsilyl chloride at −78 °C (Table 4.1, entry 9).



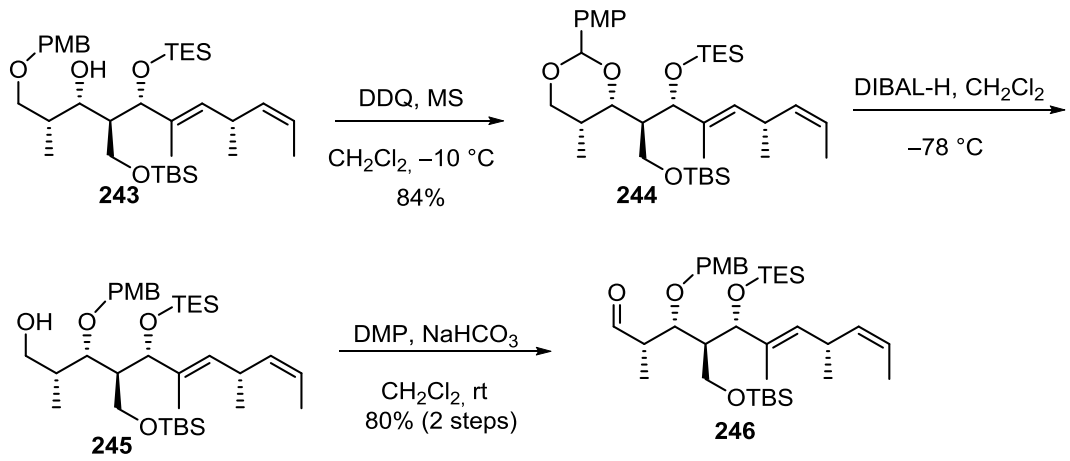
240

241, R = MMTr
242, R = Alloc
243, R = TES

Entry	Substrate	Conditions	Comments
1	**240**	MMTrCl (1.5 eq), Et_3N (3.0 eq), CH_2Cl_2, rt, 16 h	No product **241** observed, starting material retained no further progress with excess of MMTrCl and Et_3N.
2	**240**	MMTrCl (1.5 eq), Et_3N (3.0 eq), DMAP (0.3 eq), CH_2Cl_2, rt, 16 h	Only starting material observed.
3	**240**	MMTrCl (1.3 eq), pyridine/CH_2Cl_2, rt, 16 h	Only starting material observed.
4	**240**	MMTrCl (2.5 eq), imidazole (4.0 eq), CH_2Cl_2, rt, 16 h	Only starting material observed.
5	**240**	AllocCl (1.5 eq), Et_3N (2.0 eq), CH_2Cl_2, rt, 16 h	Only starting material observed.
6	**240**	AllocCl (1.5 eq), pyridine (2.0 eq), CH_2Cl_2, rt, 16 h	Product **242** (25%) isolated but lot of starting material retained.
7	**240**	AllocCl (3.0 eq), imidazole (4.0 eq), CH_2Cl_2, rt, 16 h	Only starting material observed.
8	**240**	AllocCl (5.5 eq), pyridine (6.5 eq), CH_2Cl_2, rt, 16 h	Product **242** (30%) isolated but lot of starting material retained.
9	**240**	TESCl, 2,6-lutidine, DMAP, CH_2Cl_2, −78 °C, 3 h	Product **243** obtained, 80% yield, selective monoprotection at C(17)-position

Table 4.1: *Protection of C(17)-hydoxyl group with various protecting groups.*

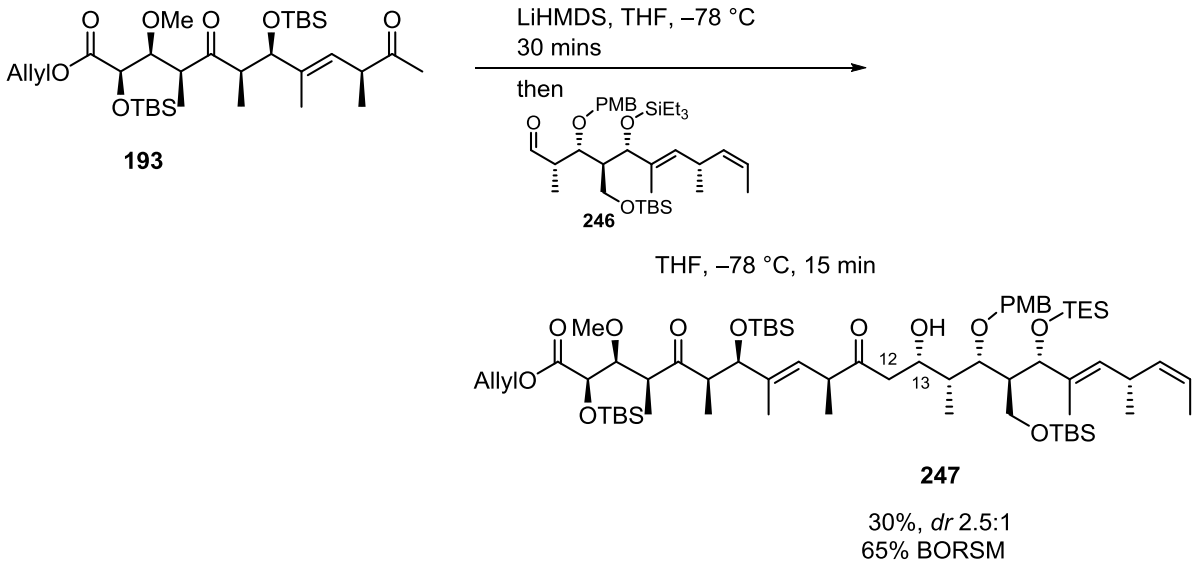
Compound **243** was converted to the PMP acetal **244** using DDQ under anhydrous conditions, followed by reductive acetal opening from the less hindered side using DIBAL-H provided the the primary alcohol **245** (Scheme 4.24). Dess Martin oxidation[55] of the alcohol provided the corresponding aldehyde **246**.



***Scheme 4.24**: Synthesis of aldehyde **246**.*

4.1.4. Coupling of the Fragments 193 and 246:

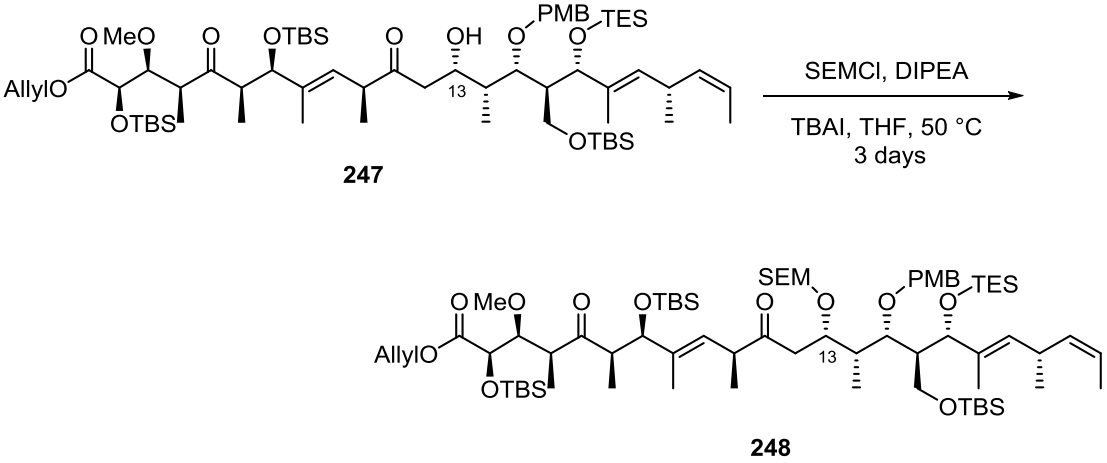
Aldol reaction between the fragments was done using the conditions provided by the Roush group,[57, 58] as both the ketone and aldehyde fragments used by the Roush group are similar to the fragments which are used in this synthesis of tedanolide (**6**). Ketone **193** was treated with lithium hexamethyldisilazane at −78 °C, allowed to enolisation for 30 mins, aldehyde **246** was slowly added drop wise to the reaction mixture and the reaction was quenched after 15 minutes (Scheme 4.25).



***Scheme 4.25**: Synthesis of compound **247**.*

Initial purifications using column chromatography separated the aldol products **247** (*dr* 2.5:1), unreacted ketone **193** and the aldehyde **246** were recovered without any epimerization. The purification of the diastereomersfrom the aldol reaction using normal chromatography was not successful, they are purified with the aid of HPLC on a normal phase column employing EtOAc and heptane as eluent.

The newly formed stereocenter C(13)-hydroxyl group in compound **247** was initially tried to protect as TBS-ether, so that all the TBS ethers can be cleaved in a single step together at the later stage, but the protection was not successful at room temperature, and at higher temperatures silyl group migration was reported by the Roush group.[58] After looking at the different protecting groups we needed a protecting group which should survive the TES groupdeprotection conditions and at the same time the protecting group should be able to remove in presence of primary TBS group. SEM group provided the right combination under these circumstances, as Roush *et al*. used the SEM group at the C(13)-position.[58] So, the C(13)-hydroxyl group was protected as SEM ether using SEM chloride and Hünig's base in tetrahydrofuran (Scheme 4.26).



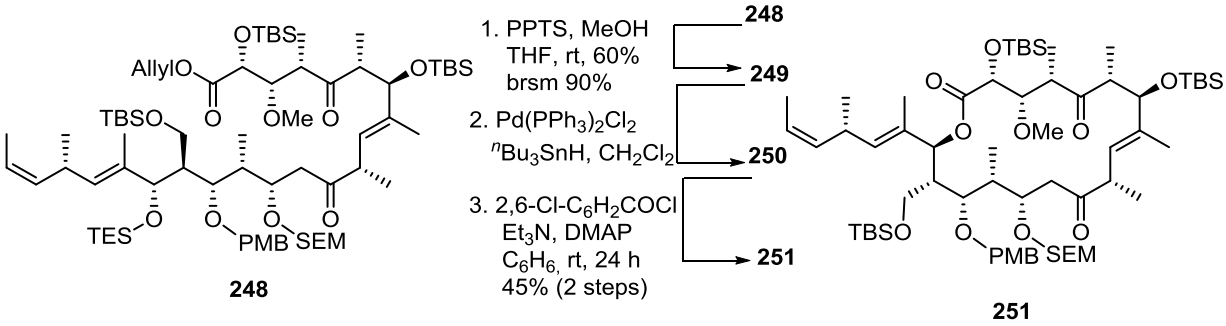
***Scheme 4.26**: Synthesis of compound **248**.*

No	Conditions on substrate 247	Yield	Comments
1	TBSOTf, 2,6-lutidine, CH_2Cl_2, 16 h, 0 ˚C to rt	--	No Reaction, SM recovered
2	TBSOTf, 2,6-lutidine, CH_2Cl_2, 16 h, 0 ˚C to 50 °C	--	No Reaction, SM recovered
3	TMSOTf, 2,6-lutidine, CH_2Cl_2, 16 h , 0 ˚C to rt	--	No Reaction, SM recovered
4	SEMCl, DIPEA, TBAI, THF, 72 h, 0 ˚C to 50 °C	90%	--

***Table 4.2**: Trial with different protecting groups on compound **248**.*

The stage was set to do the macrolactonisation, the C(17)-TES group was tried to remove using PPTS in a solution of methanol and THF at room temperature, After two hours it was observed only the TES group was removed selectively in presence of primary TBS group. Extended reaction times lead to the deprotection of the primary TBS group as well, so the reaction was quenched at this point and the starting material was recovered. C(1)-carboxylic acid was liberated using the literature known procedure with $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ and tributyltinhydride in dichloromethane (Scheme 4.27).[92] The reaction proceeded very smoothly and the crude acid was passed through a silica gel bed, initially eluted with hexanes to get rid of tin impurities and then elution with ethyl acetate gave the semi-crude acid, which was used immediately in the reaction for the macrloactonisation. After screening a

few macrolatonisation conditions (Shiina,[93] Evans Mukaiyama,[94] and Yamaguchi-Yonemitsu) the best yields were obtained by using the modified procedure of Yamaguchi protocol[45] in dry benzene.



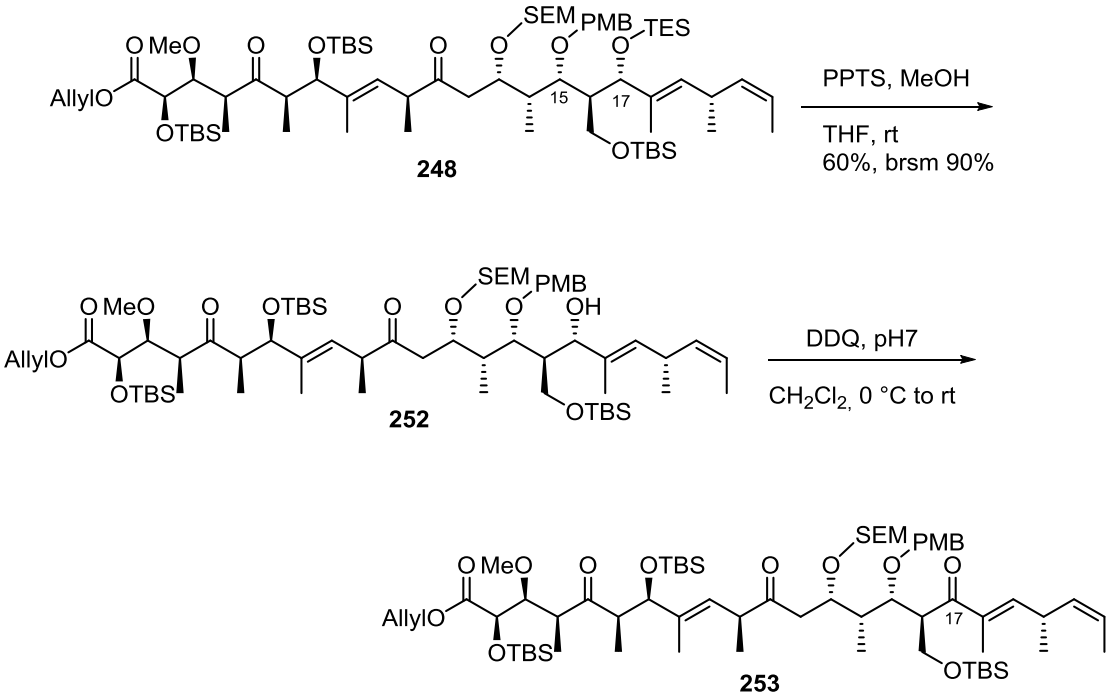
Scheme 4.27 *Synthesis of compound* ***251****.*

No.	Conditions	Yield	Comments
1	2-methyl-6-nitrobenzoicanhydride, DMAP, toluene, THF, 24 h, rt.	--	SM decomposed, No desired product observed.
2	2-bromo-1-methyl pyridine, Et_3N, CH_2Cl_2, 24 h, rt.	--	SM decomposed, No desired product observed.
3	2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, CH_2Cl_2, rt, 52 h.	18 %	No trace of acid, no other major spots.
4	2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, toluene, 110 °C, 16 h.	10 %	TLC showed several spots.
5	2,4,6-trichlorobenzoyl chloride, DIPEA, DMAP, toluene, 110 °C, 5 h.	10 %	TLC showed several spots.
6	2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, benzene, rt.	45 %	DMAP was added after 1h of the anhydride formation.

Table 4.3*: Trial with different conditons for macrolactonisation on compound* ***250****.*

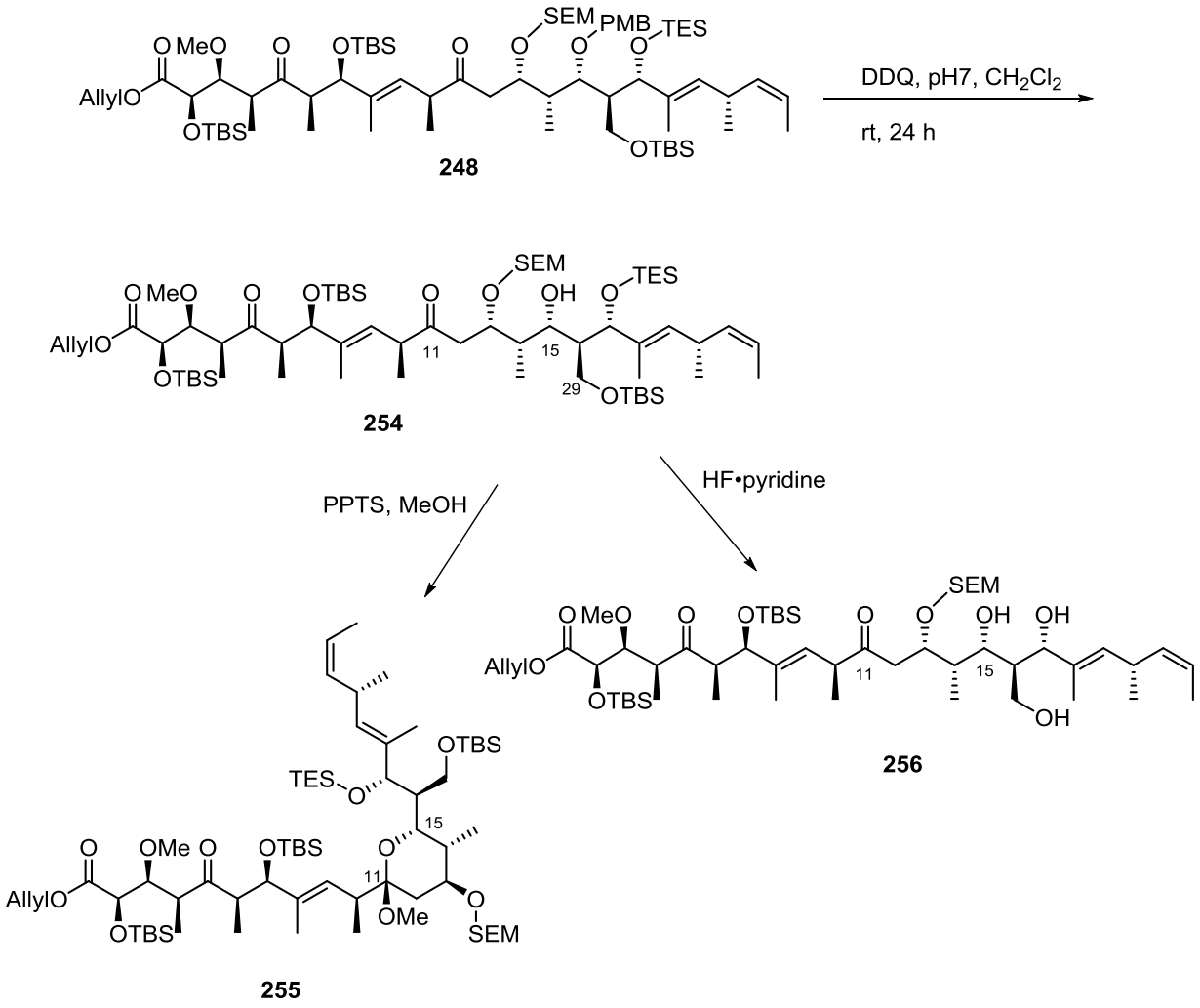
4.1.5. Removal of the PMB group at C(15)-Position before Macrolactonisation:

Trials were made to liberate the C(15)-hydroxyl group prior to macrolactonisation in order to see the competition of the C(15) and C(17)-hydroxyl groups participation in the macrolactonisation. Intially compound **248** was treated with PPTS for the TES group deprotection, which went smoothly to afford alcohol **252** (Scheme 4.28). When compound **252** was tried to react with DDQ to remove PMB group on the C(15)-hydroxyl group, C(17)-hydroxyl group was oxidized to the respective ketone **253**. Other method using ceric ammonium nitrate was unsuccessful resulting in retention of starting material. Hydrogenation and strong Lewis acid conditons cannot be employed on the substrate **252** due to the presence of double bonds and silyl protecting groups (TBS and SEM).



***Scheme 4.28**: Deprotection of PMB group prior to macrolactonisation.*

In an effort to remove the C(15)-PMB group prior to the C(17)-TES group, compound **248** treated with DDQ and the reaction was sluggish, it went for completion at room temperature over a period of 24 h to yield alcohol **254**. The task of removing the TES group was performed using mild acidic conditions (PPTS, MeOH/THF), resulted in a messy reaction indicating the presence of lactol **255** (Scheme 4.29). Basic conditions (HF•pyridine) employed to deprotect the TES ether, it was observed that both the C(29) and C(17)-silyl ethers are deprotected within short period of time giving rise to triol **256**.

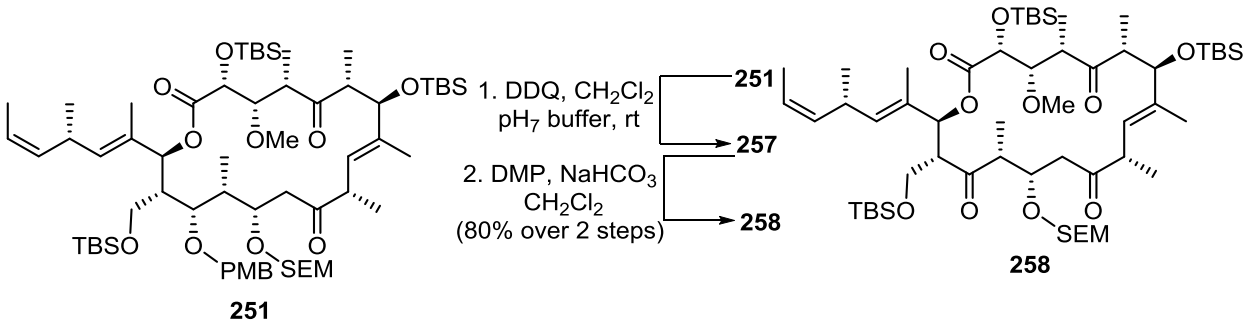


Scheme 4.29: *Deprotection of PMB group prior to macrolactonisation.*

It has proved to be highly challenging and unsuccessful to deprotect the C(17)-TES group selectively when the C(15)-hydroxyl group was unmasked. With these results the focus was shifted back to original route to do macrolactonisation in first place and then the removal of PMB group.

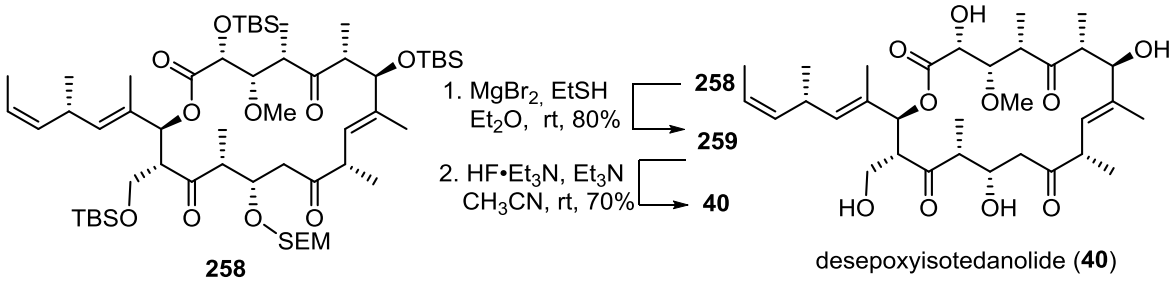
4.1.6. End Game:

The next steps towards completion of the total synthesis of desepoxyisotedanolide (**40**) began with removal of the PMB group in compound **251**. It was carried out using 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone in a mixture of dichloromethane and pH7 buffer (Scheme 4.30). The reaction proceeded smoothly to completion and the resulting alcohol is oxidized to ketone **258** using Dess-Martin periodinane[55] and sodium bicarbonate.



***Scheme 4.30**: Synthesis of triketone **258**.*

Cleavage of the SEM ether at the C(13)-hydroxyl in compound **258** was performed using a mild Lewis acid ($MgBr_2$) and excess of ethane thiol (Scheme 4.31).[56] Global deprotection of the TBS group was achieved using the conditions earlier used in the synthesis of tedanolide (**6**)[57] ($HF{\bullet}Et_3N$, Et_3N in CH_3CN). The reaction proceeded to completion over a period of 3 days to provide desepoxyisotedanolide (**40**).



***Scheme 4.31**: Synthesis of desepoxyisotedanolide (**40**).*

During the purification of desepoxyisotedanolide (**40**), compound **40a** was observed as a minor product (Figure 4.6). From the ^{13}C NMR, only three peaks were observed for carbonyl compounds, which indicates the lack of carbonly group C(5), a new peak was observed at δ108.2, which is clearly indicating the presence of 5-membered lactol. After a detailed 2D NMR studies (COSY and HMBC), C(5)-carbon has clearly HMBC contacts with H-4, H-6, H-7 and methyl groups at C4 and C6.

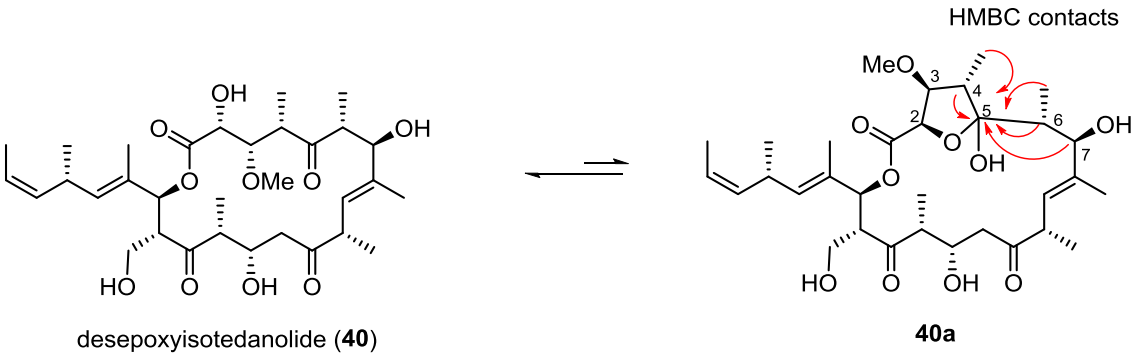
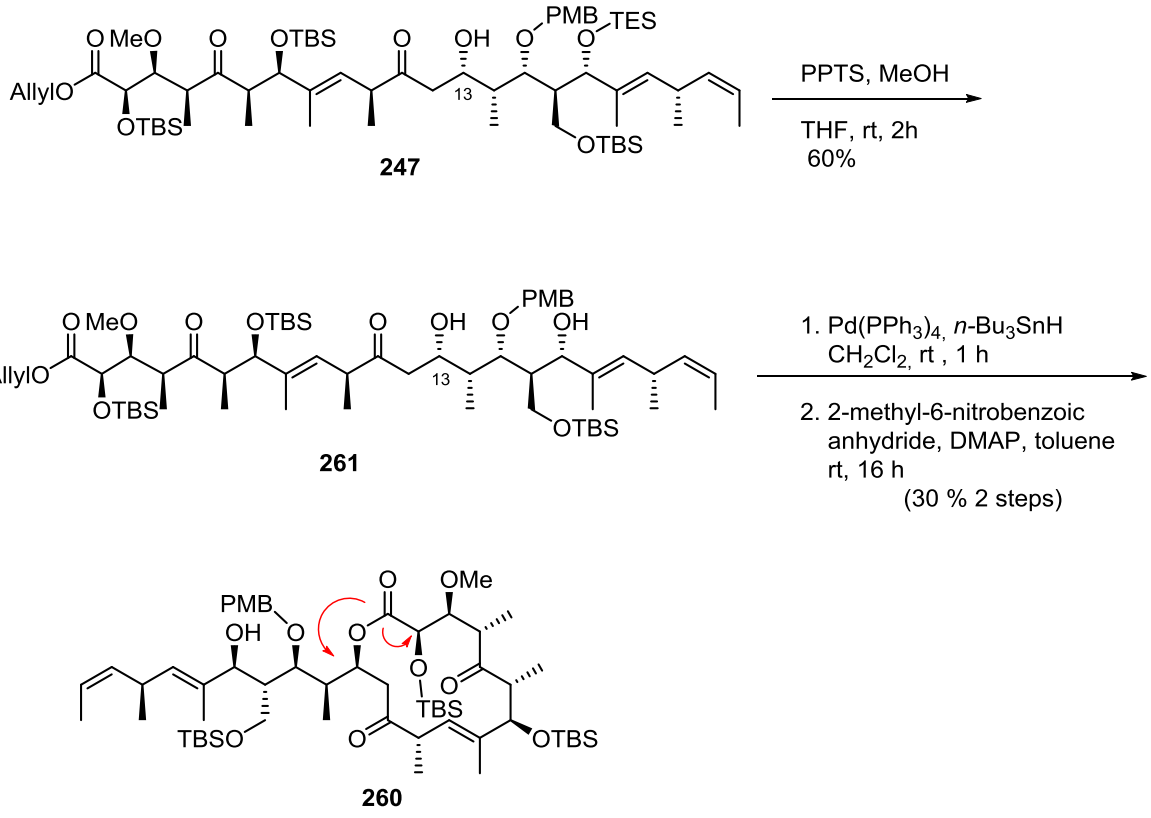


***Fig 4.6**: Isomers of desepoxyisotedanolide **40**, **40a**.*

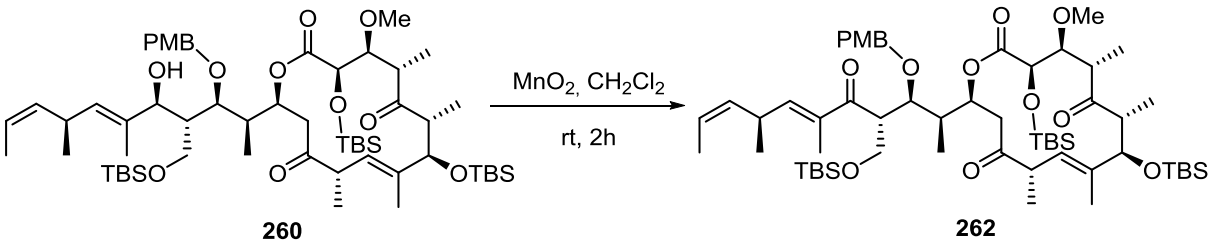
4.1.7. Formation of the 14-Membered Macrolactone 260:

Compound **247** was treated with mild acid PPTS in MeOH and THF to deprotectC(17)-TES ether, When the linear fragment **261** was tried to lactonise to form the 18-membered lactone, it was envisioned that the C(17)-allylic hydroxyl group could be more reactive to form the macrolactone. Initially Yamaguchi lactonisation[45] conditions were used, unfortunately no product was observed. Shiinaprotocol[94] with 2-methyl-6-nitrobenzoic acid anhydride produced the lactonised product **80** (Scheme 4.32). After a detailed two-dimensional NMR studies, the structure was confirmed as a 14-membered lactone **260**. The lactone C(1)-carbonyl group has clearly indicated the HMBC contacts with H-13 proton along with H-2 and H-3 protons. This clearly suggested that the C(13)-hydroxyl group is very active than the C(17)-hydroxyl group in the macrolactonisation. This indicated that the C(13)-hydroxyl group should be masked with a protecting group in order to avoid the fromation of undesired macrolactone **260**.



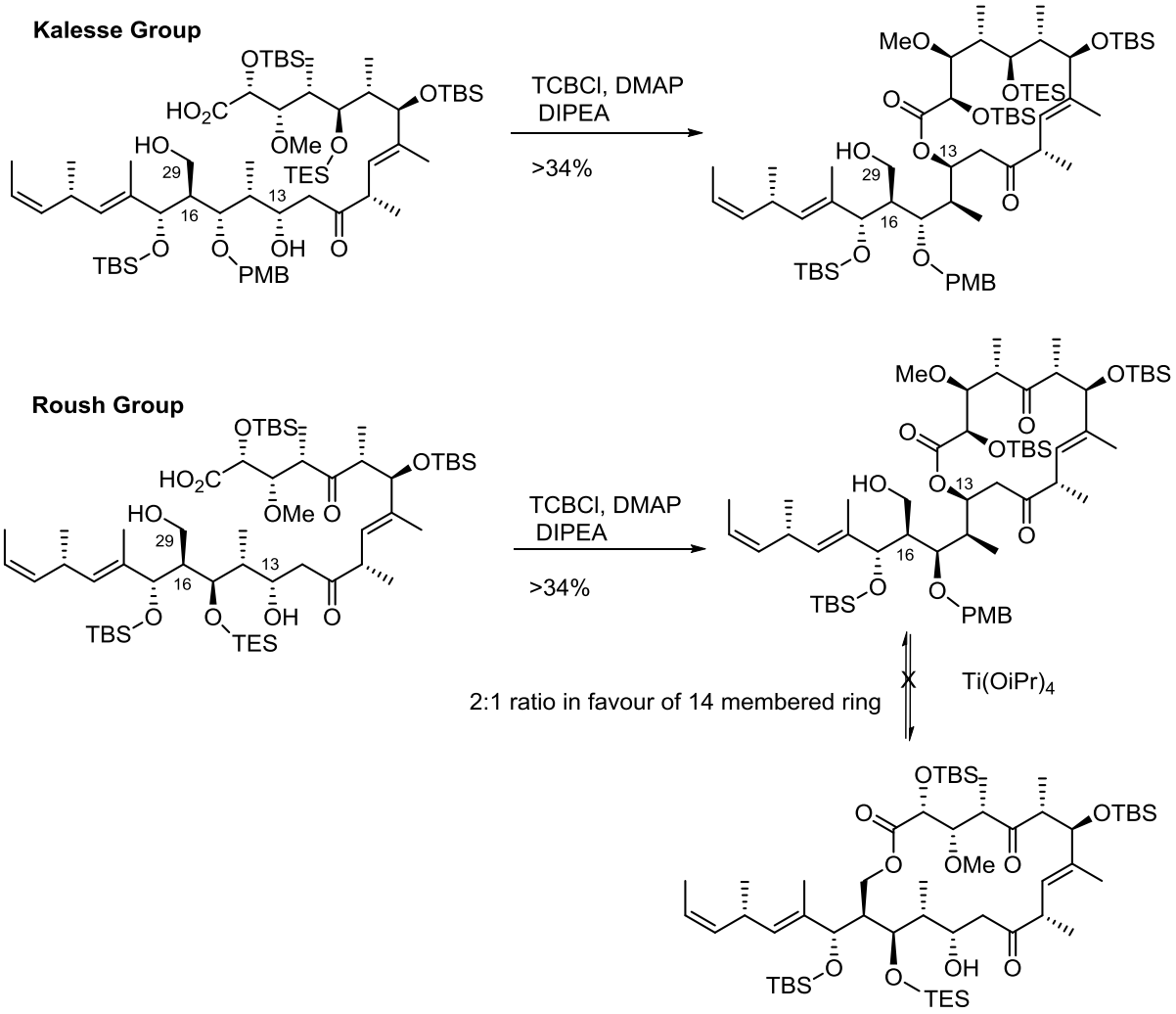
***Scheme 4.32**: Synthesis of macrolactone **260**.*

This structure was further confirmed by a chemical transformation, converting C(17)-allylic alcohol in compound **260** to the ketone using MnO_2, which can only selectively oxidise the allylic and benzylic alcohols. When compound **260** was treated with MnO_2, it was clearly observed by Mass spectrometry that product **262** has formed (Scheme 4.33).



***Scheme 4.33**: Oxidation of macrolactone **260**.*

The formation of the 14-membered lactone was also observed earlier in the synthesis of tedanolide (**6**) by Kalesse and Roush groups (Scheme 4.34). The C(29)-hydroxyl group was expected to be much more reactive , so the macrolactonisation reaction was carried out in the presence of free C(13)-hydroxyl group by the Kalesse group,[67a] Only 14-membered lactone was observed instead of the 18-membered lactone. When Roush group had similar results,[57, 58] efforts were made to transesterify the 14-membered lactone to the desired 18-membered lactone, but even in the presence of strong Lewis acid like $Ti(O^iPr)_4$ 14-membered lactone couldn't be isomerized.



***Scheme 4.34**: Earlier results for the 14-membered macrolactone.*

In conclusion, it is again confirmed that 14-membered lactone is more favoured in compared to 18-membered lactone in macrolactonisation. It is essential to block the C(14)-hydroxyl group in order to achieve the tedanolides. It is also noteworthy, that this 14-membered macrolactone could be a potential biosynthetic intermediate in the process of tedanolide. Efforts were made in our group earlier by Nina Diaz[91] to synthesize this 14-membered macrolide, unfortunately it was not successful and the synthesis of the macrolide couldn't be accomplished.

4.2. Biological activity of Desepoxyisotedanolide (40) in comparision to Tedanolide (6):

The biological studies on desepoxyisotedanolide (**40**) were performed at the Helmholtz Centre for Infection Research (HZI) at Braunschweig. Biological tests were performed on mouse fibroplasts (L-929), cervical carcinoma (KB-3-1) and rat kangaroo kidney cells (PtK2); and the IC_{50} and IC_{90} values have been obtained.

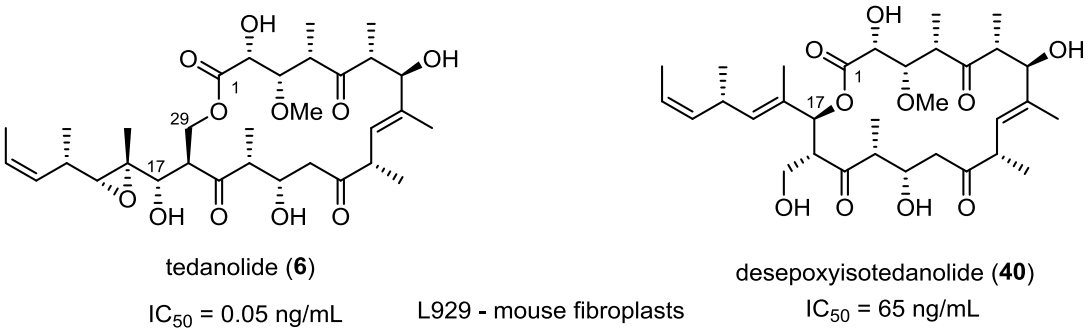


***Figure 4.7**: IC_{50} values against L929 mouse fibroplasts of tedanolide and desepoxyisotedanolide.*

The biological data have revealed that the desepoxyisotedanolide (**40**) is one fold less active than natural product tedanolide (**6**) but still exhibiting potent cytotoxicity. Fusetani *et al.* had reported that 13-deoxytedanolide (**7**) inhibits peptide elongation by binding to the 60S large subunit of the *S. cerevisiae* ribosome. Moore *et al.* in their experiments of binding 13-deoxytedanolide (**7**) to the *Haloarcula marismortui zu* 50S subunit provided the structural explanations for the relative activities of tedanolide. The decrease in the biological activity of desepoxytedanolide (**40**) could be attributed to the lack of groups that normally do hydrogen bonding the C(18-19) epoxide as well as C(17)-hydroxyl group. Additionally, affinity to the ribosome may be further decreased by the alterations in confirmation, as explained by Moore *et al.* in the case of derivatives of 13-deoxytedanolide.

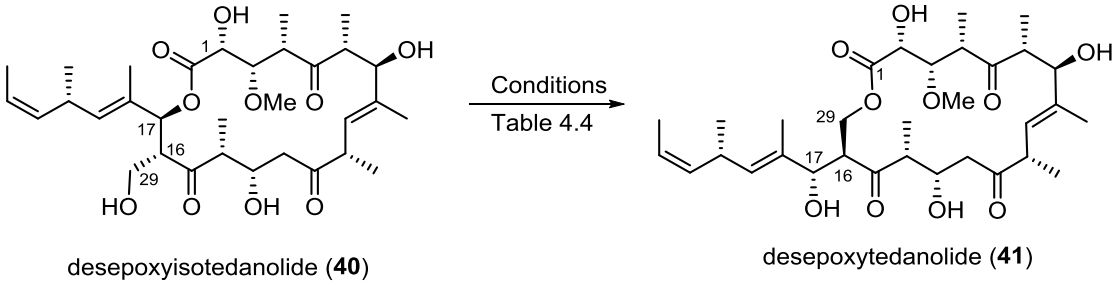
Biological activites of desepoxytedanolide (**40**) in comparison with tedanolide (**6**) against different cell lines are shown below in the Table 4.4.

Cell lines	Tedanolide (**6**)	Desepoxytedanolide (**41**)	Desepoxyisotedanolide (**40**)
L929 Mouse connective tissue	0.05	0.5	65
PtK2 Potoroo kidney	n.d	n.d	600
KB-3-1 Cervix carcinoma	0.2	n.d	25

***Table 4.4**: Biological activity of tedanolides in differernt cell lines.*
n.d = not determined

4.3. Transesterification Experiments:

Having been accomplished the total synthesis of the desepoxyisotedanolide (**40**), our focus was shifted to see the possibility of transesterification to desepoxytedanolide (**41**) (Scheme 4.35). Few attempts were made to explore this transformation under mild acidic and basic conditions (Table 4.4).



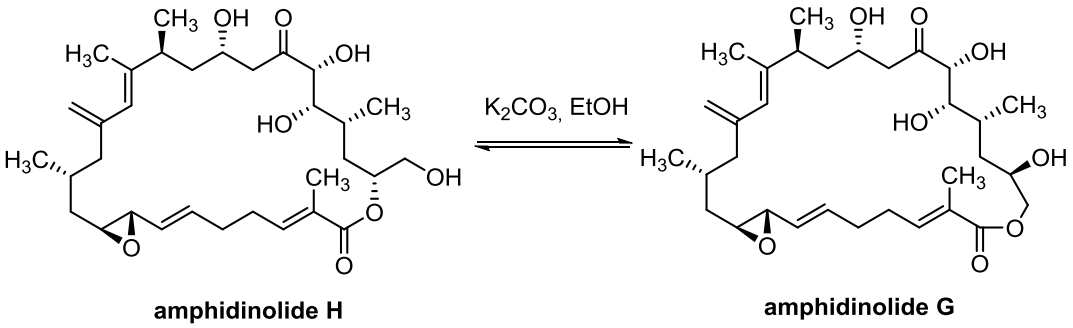
***Scheme 4.35**: Trials to isomerise of desepoxytedanolide (**40**).*

A mild Lewis acid, bis(n-butyldichlorotin)oxide was initially tried at room temperature and at 80 °C, there was no progress in reaction. In a refluxing solution of toluene, led to decomposition (Table 4.5). Mild basic conditions (DMAP, Et_3N, K_2CO_3) in ($CDCl_3$, $CHCl_3$ and DMF) haven't produced any progress in reaction. Neutral conditions (DMAP•HCl in $CHCl_3$, refluxing $CHCl_3$) also failed to isomerize.

No.	Conditions	Yield	Comments
1	(^{n}Bu$_2$SnClO)$_2$, toluene, rt	--	No reaction
2	(^{n}Bu$_2$SnClO)$_2$, toluene, 80 °C	--	No reaction
3	(^{n}Bu$_2$SnClO)$_2$, toluene, reflux	--	Decomposed
4	Et_3N, DMAP, $CDCl_3$, rt	--	No reaction
5	K_2CO_3, $CDCl_3$, rt	--	No reaction
6	DMAP•HCl, $CHCl_3$, rt	--	No reaction
7	$CHCl_3$, reflux	--	No reaction
8	K_2CO_3, DMF, rt	--	No reaction
9	K_2CO_3, EtOH, rt	--	No reaction

***Table 4.5:** Trials to isomerize desepoxyisotedanolide to desepoxytedanolide.*

In 2000, two new members of amphidionolides were isolated, amphidinolide G and H (Scheme 4.36).[95] These two natural products are isomers at the macrolactone linkage and interestingly found to be interconvertible in the presence of K_2CO_3 in ethanol at 4 °C.



***Scheme 4.36**: Transesterification of amphidinolides H and G.*

No success has been achieved even employing these conditions in the case of desepoxyisotednaolide (**40**). Unfortunaley, efforts to isomerisation were unsuccessful, it could be possible that this transesterfication may require a special biological environment to convert to desepoxytedanolide (**41**).

4.4. Synthesis of Simplified Tedanolide Analogues: Connecting Tedanolide to Myriaporones and Gephyronic acid:

The myriaporones were first reported in 1994 by Rinehart *et al*. Extractions from the bryozoan *Myriaporatruncata* in the west Mediterranean Sea led to four novel structures myriaporones 1-4 (**24**-**27**) (Figure 4.7).[26, 27] Out of which, myriaporone 3 and its inseparable hemiacetal isomer myriaporone 4, exhibited an IC_{50} value of 100 ng/mL in L-1210 murine leukemia cells. Initial structure elucidation was done using spectroscopic analysis and later confirmed by total synthesis in Taylor group[29] and Cuevas group[30] independently.

A similar natural product gephyronic acid **35** isolated from the myxobacterium *Archangiumgephyra* at HZI braunschweig by Höfle, Reichenbach and co-workers in 1995.[32] Initial biological studies revealed selective inhibition of the eukaryotic protein synthesis. It exhibits an IC_{50} value of 10 ng/mL against cervix carcinoma and human myelogenous leukemia (K-562) cell lines. Structural similarities between myriaporone, gephyronic acid and the C10-C23 region of tedanolide having similar mode of action[35] prompted us to prepare the simplified analogues along the lines of our synthesis of the southern hemisphere of tedanolides.[96]

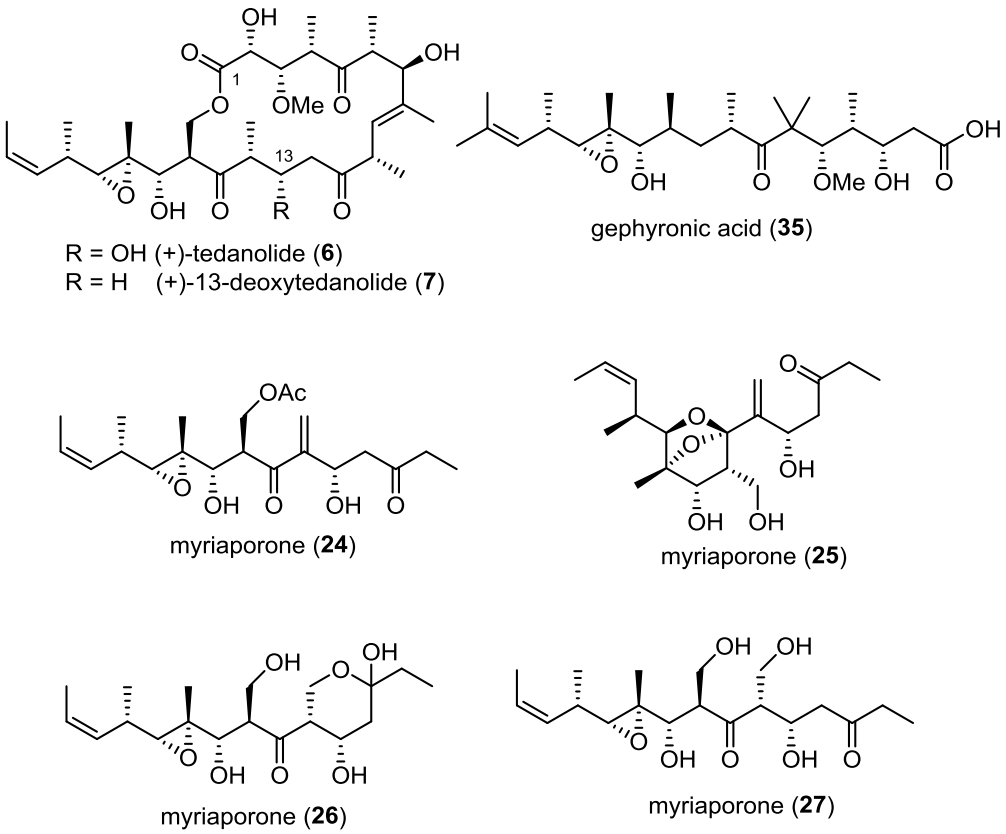
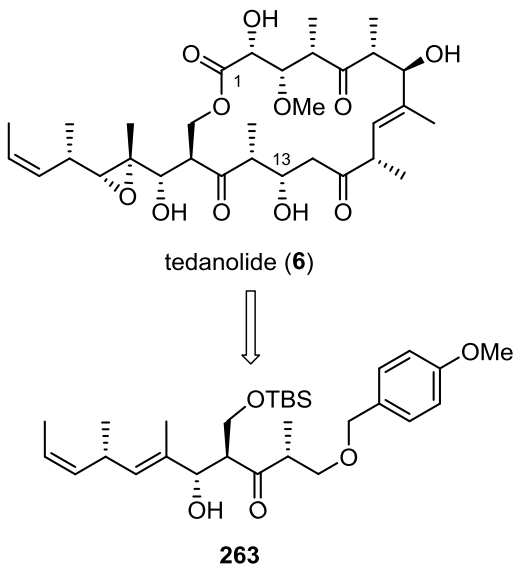


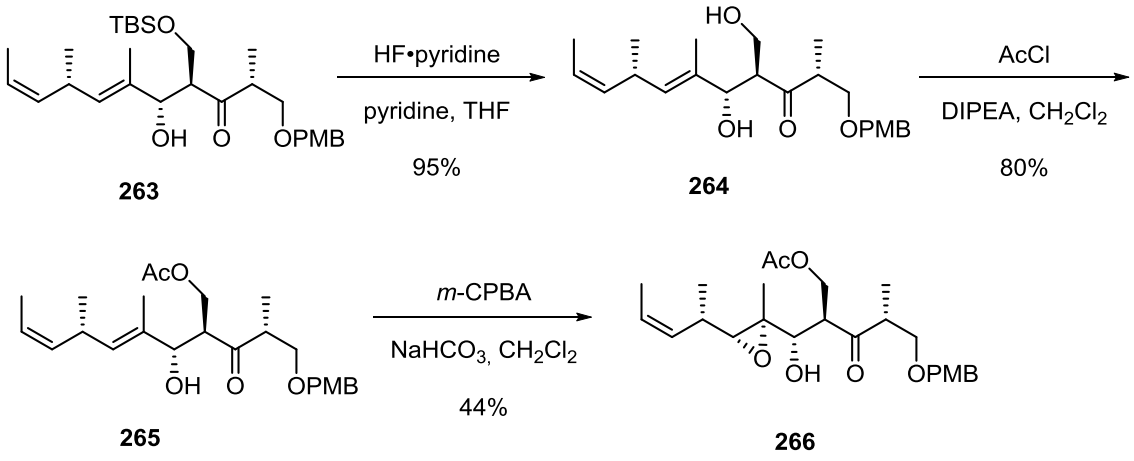
***Fig. 4.7**: Tedanoldes and myriaporones.*

Intermediate **263** was the crucial intermediate served as a building block during the synthesis of tedanolide (**6**) (Scheme 4.37). This intermediate was chosen as a starting point for the simplified analogues.



Scheme 4.37: *Southern fragment of tedanolide as precursor for simplified tedanolide analogue.*

Acetate group was incorporated at the primary hydroxyl group as a substitute for the macrolactone linkage, *p*-methoxybenzyl (PMB) could participate in hydrophobic interactions comparable to the eastern fragment of tedanolide. Additionally the importance of the epoxide on these simplified analogues was explored. These compounds were obtained from the intermediate **263** (Scheme 4.38), TBS group removal followed by selective protection of the primary hydroxyl group as acetate **265**. Epoxide **266** was obtained using Henbest oxidation using *m*-CPBA/$NaHCO_3$.



Scheme 4.38*: Synthesis of simplified tedanolide analogues.*

These simplified tedanolide analogues were investigated for biological activities in mammalian cell lines, the test results revealed that these biologically active compounds are approximately one order of magnitude less than desirable for promising drug candidates (Figure 4.8). The data indicated that incorporation of the acetyl groups, has a more pronounced effect on the biological activity of these derivatives, while epoxidation has only little contribution. These results will potentially provide access to a new target and provides a promising starting point for further optimization.

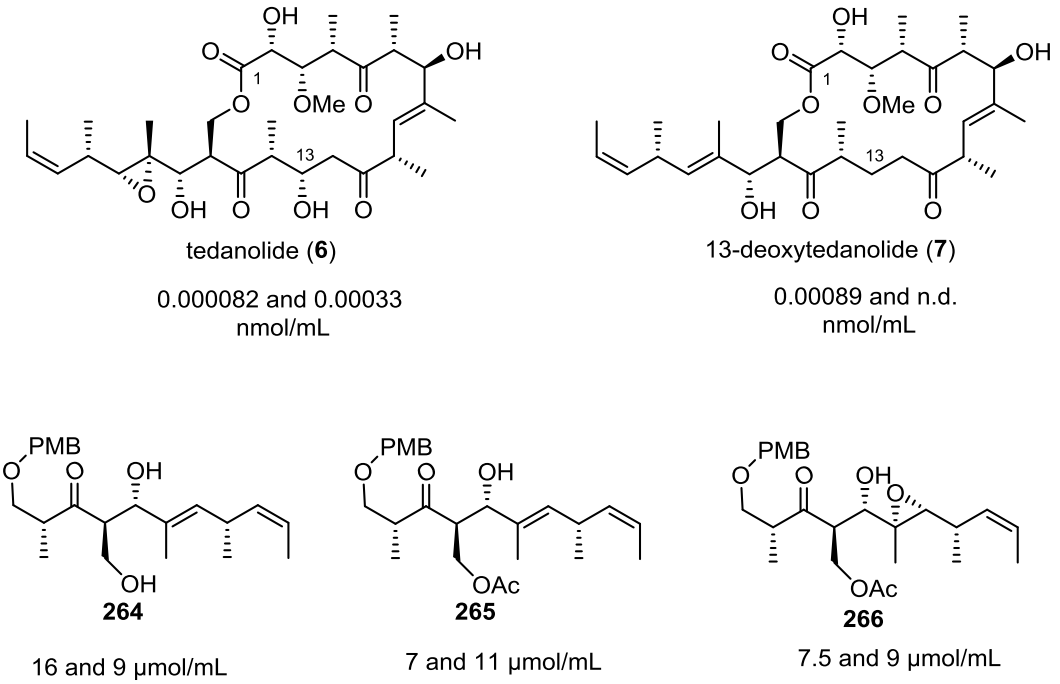
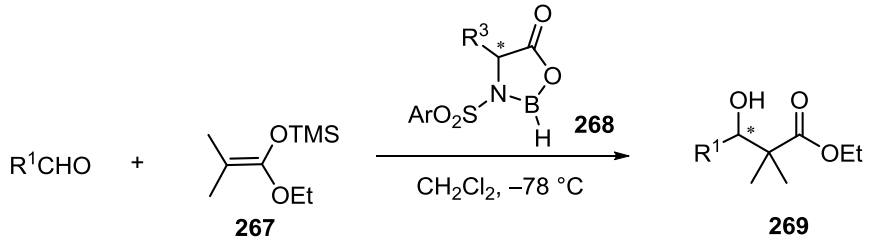


***Fig. 4.8**: IC_{50} values of an MTT assay with L-929 mouse fibroblasts and KB-3-1 cervix carcinoma cell line respectively.*

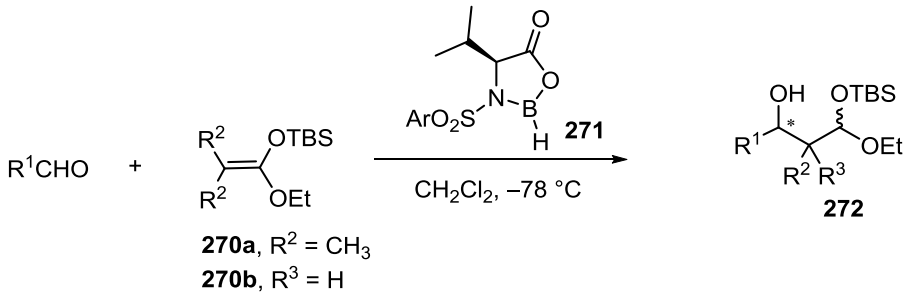
4.5. Kiyooka Aldol Reaction: A Methodology for the Generation of the Chiral Quaternary Center

Chiral lewis acid mediated reactions have been recognized as useful tools for the stereo-selective formation of the C-C bonds. Aldol reaction of the silyl ketene acetals with aldehydes are literature known,[97] Kiyooka and co-workers had reported the chiral boranes **268** promoted reactions of silyl ketene acetals **267** with aldehydes (Scheme 4.39).[98] These reactions yielded different products depending on the type of the silyl group used in the ketene acetals with high enantioselectivity.



***Scheme 4.39**: Kiyooka aldol reaction using the chiral borane as chiral lewis acid*

The chiral borane reagents **271** were prepared by treating the sulfonamides obtained from the corresponding amino-acids and sulfuryl chlorides with an equimolar amount of BH_3•THF complex.[99] Changing the triaalkylsilyl group of the silyl ketene acetal from trimethylsilyl (TMS) to tert-butyldimethylsilyl (TBS) group has a dramatic effect on the reaction course (Scheme 4.40). Condensation of the the TBS ketene acetal with aldehyde in presence of the chiral borane gave surprisingly the diastereomeric β–hydroxyacetal **272**.



***Scheme 4.40**: Kiyooka aldol reaction using the TBS ketene acetal*

This acetal **272** would rise apparently from the reduction of an intermediate ester by hydride transfer from the promoter **271**. High enantioselectivities were observed for ketene acetals **270a** compared to **270b**. A mechanism which accounts for the formation of the compounds **272** is shown below (Figure 4.9). It features a cyclic transition state **273**, coordination of the boron atom of the borane with the oxygen atom of the carbonyl group would lower the energy of the activation for the nucleophilic attack and concurrently facilitate desilylation. The stability of **274** would be enhanced if the trialkylsily group were TBS rather than TMS. Reduction of the ester group of the transient complex **274** by intramolecular hydride transfer from the borane and retransfer of the TBS group would form the acetal complex **275**.

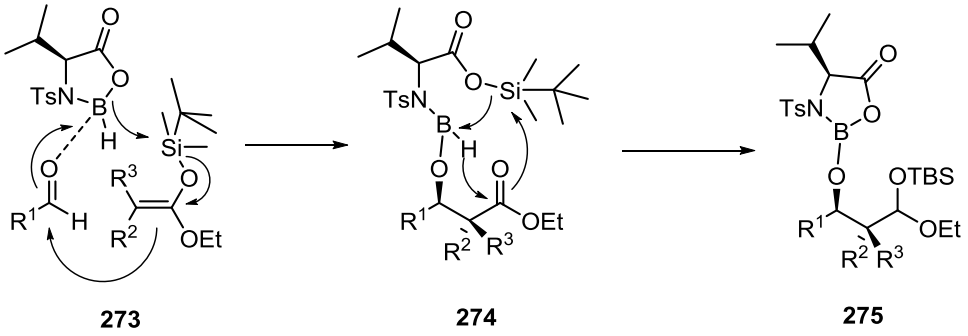
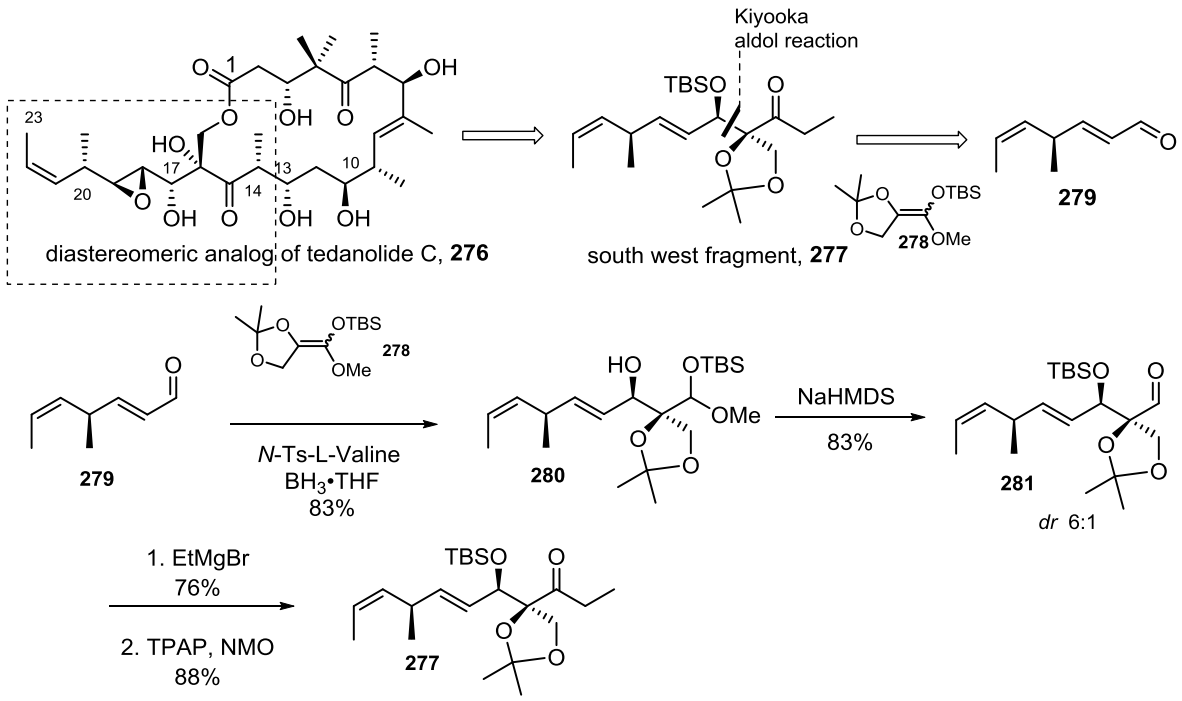


***Fig. 4.9**: Proposed mechanism for the Kiyooka aldol reaction with TBS ketene acetal.*

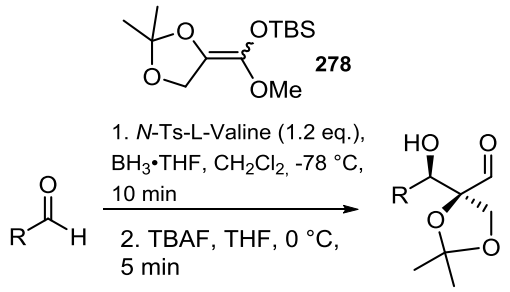
Since the advent of the Kiyooka aldol reaction, lot of work has been done in creating stereoselecitve quaternary centers using this methodology. One of the noteworthy work was done by Hayashi and co-workers, a tetrasubstituted ketene acetal was used for the pivotal step in the synthesis of azaspirene.[100] However in this case, $MgBr_2 \bullet Et_2O$ proved to the best lewis acid in order to get better yields and enantioselectivity. Our experience with the Kiyooka aldol reaction as the ideal transformation to establish a secondary alcohol next to a quaternary center was based on the synthesis of a simplified disorazole analog.[101]

In the synthesis of the diastereomeric analogue of the tedanolide C **276**, to generate one additional stereocenter at C-17 in the southwest fragment **277**, a Kiyooka aldol reaction between aldehyde **279** and ketene acetal **278** was performed (Scheme 4.41).[102]



***Scheme 4.41**: Kiyooka aldol reaction in the synthesis of diastereomeric analogue of tedanolide C.*

To make this methodology a more general protocol for the generation of a variety of tertiary alcohols, few aldehydes we reacted under these reaction conditions to check the enantioselectivity and diastereoselectivity of the products. Benzaldehyde, cinnamaldehyde and valeraldehyde are allowed to react under these conditions and it was observed that the diastereomeric ratio ranges from 6:1 to 10:1 and the enantiomeric ratio was higher than 10:1 (Scheme 4.42).[103]



entry	Starting material	Product	yield (%)	dr	er
1	**282**, R = Phenyl	**285**	83	6:1	>10:1
2	**283**, R = Cinnamyl	**286**	80	10:1	>10:1
3	**284**, R = Valeryl	**287**	40	10:1	>10:1

***Scheme 4.42**: Kiyooka protocol using different aldehydes.*

The diastereoselectivity of the quaternary center could be explained from the proposed transition states **T1** and **T2** (Figure 4.10). In transition state 1 (**T1**), the alkyl chain (R) is having less *syn* pentane interactions compared to transition state (**T2**).

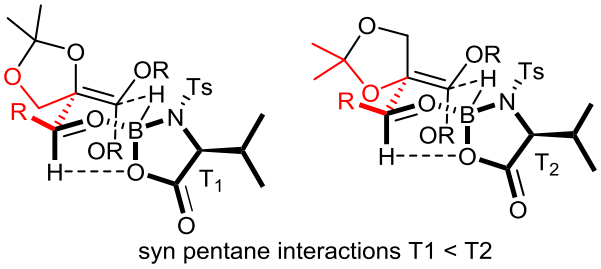


***Fig. 4.10**: Proposed transition states for the Kiyooka aldol reaction.*

5. Conclusion and Outlook:

5.1. Conclusion:

In the first part of my thesis, the total synthesis of despeoxyisotedanolie (**40**) was described (Scheme 5.1). Interestingly desepoxyisotedanolide (**40**) was also found out to be biologically active but not at the same concentration of desepoxytedanolide (**41**) and tedanolide (**6**) (Figure 5.1). With these results, it is evident that the presence of epoxide is contributing to higher biological activity. It could be also important to have this special feature of having primary lactone linkage for this superior activity of tedanolides.

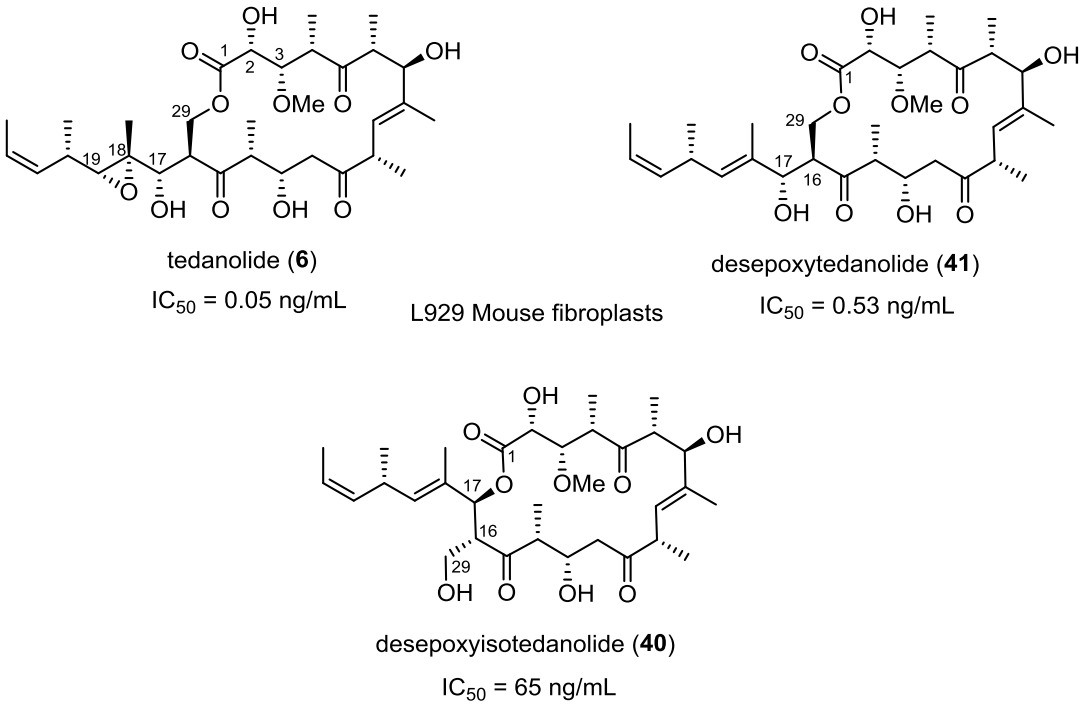
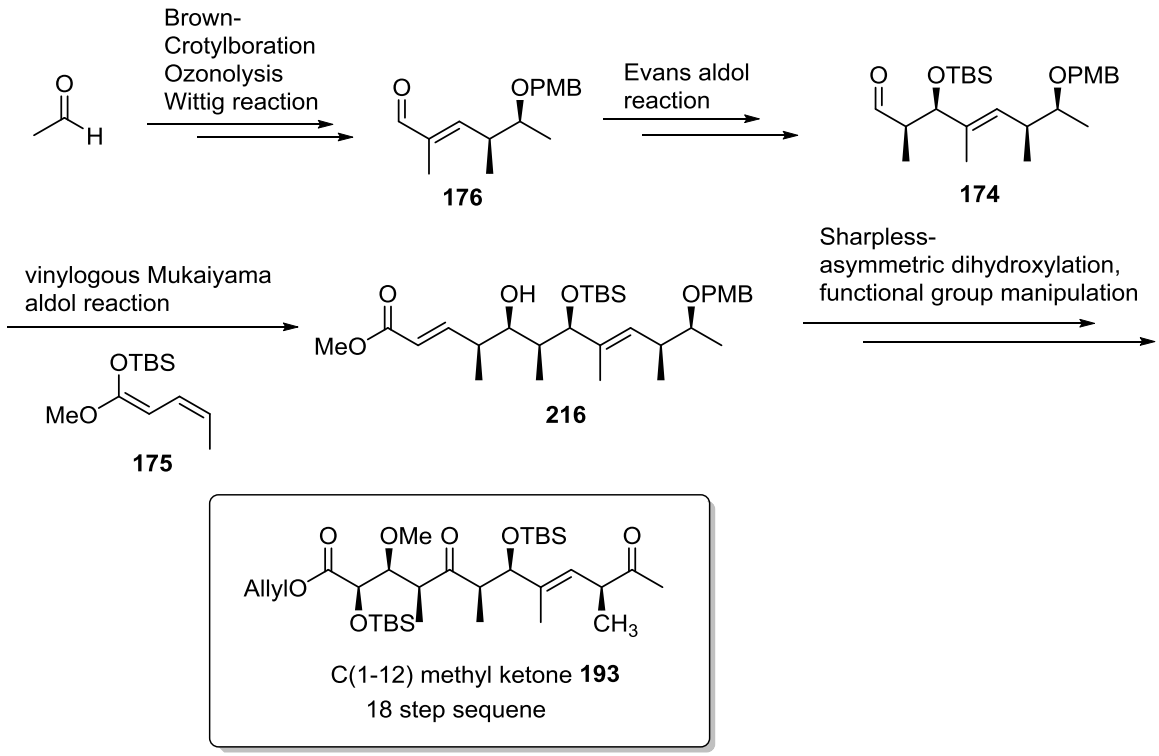


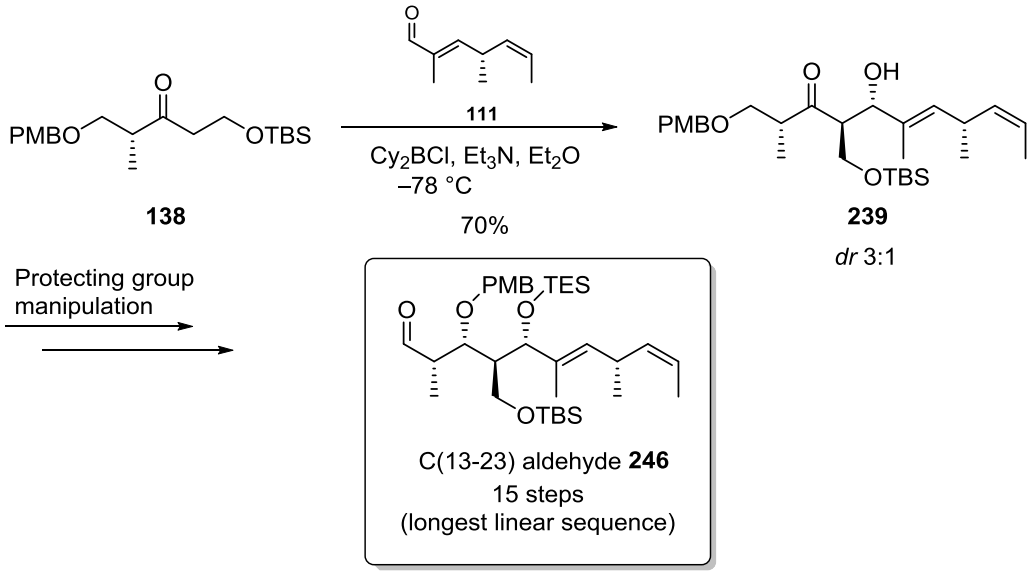
***Fig 5.1**: Biological activity of desepoxyisotedanolide (**40**) in comparision to tedanolide (**6**).*

The synthesis of desepoxyisotedanolide (**40**) was carried out in a similar fashion to synthesis of tedanolide (**6**). The synthesis of methyl ketone **193** (northern hemisphere) was achieved starting from Brown- crotylboration of acetaldehyde following a sequence of 18 steps. The synthesis involved a Evans syn aldol reaction, vinylogous Mukaiyama aldol reaction and a Sharpless asymmetric dihydroxylation as key steps. The vinylogous Mukaiyama aldol reaction proved to be the most economical step with generating 4 carbon atoms with great stereocontrol for the 4,5 all *syn*-product (Scheme 5.1).



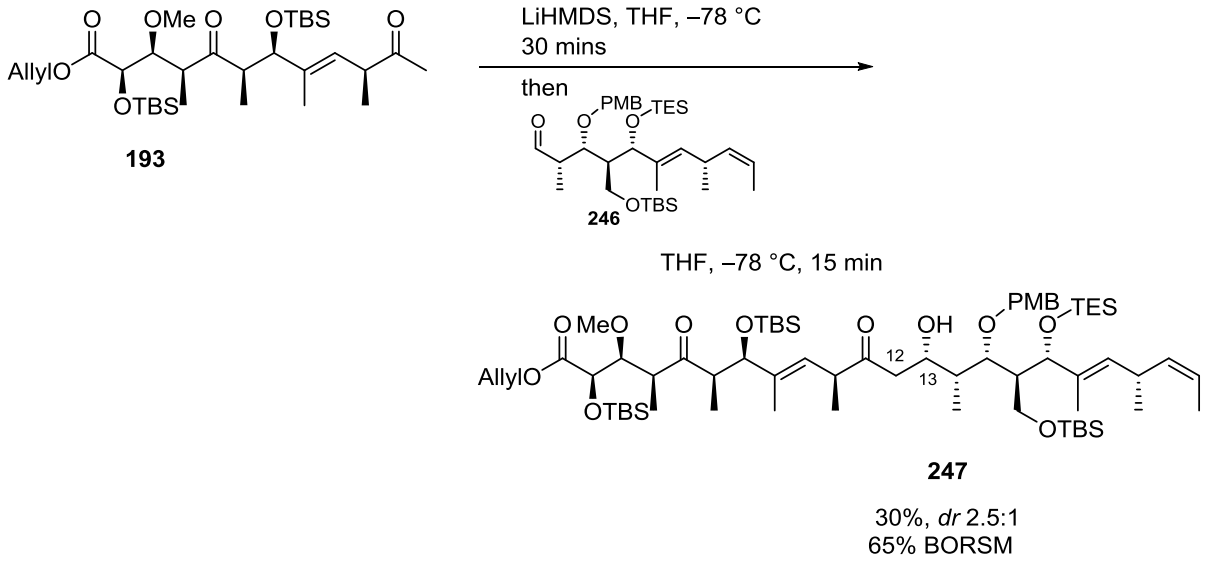
***Scheme 5.1**: Synthesis of methyl ketone **193**.*

The synthesis of aldehyde C(13-23) fragment **246** involved a key reaction of *anti*-selective Paterson aldol reaction between ketone **138** and aldehyde **111** (Scheme 5.2).



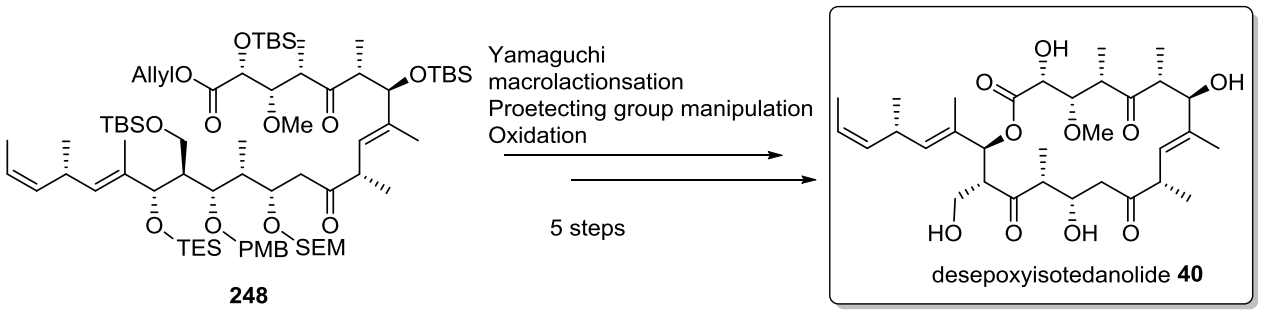
***Scheme 5.2**: Synthesis of aldehyde **246**.*

Both the fragments **193** and **246** are coupled by a substrate controlled aldol reaction to provide the total carbon frame work C(1-23) for desepoxytedanolide (**40**) (Scheme 5.3).



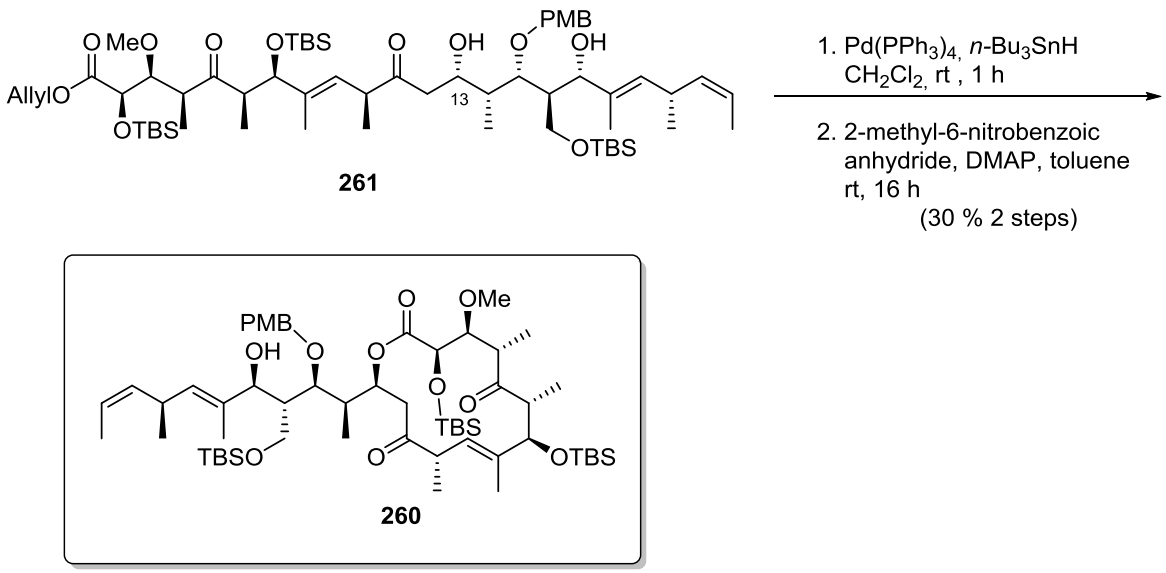
***Scheme 5.3**: Aldol coupling of ketone **193** and aldehyde **246**.*

Compound **247** was converted to desepoxyisotedanolide (**40**) in a sequence involving Yamaguchi macrolactonisation, followed by oxidation of C(15)–hydroxyl group and global deprotection of the silyl groups (Scheme 5.4).



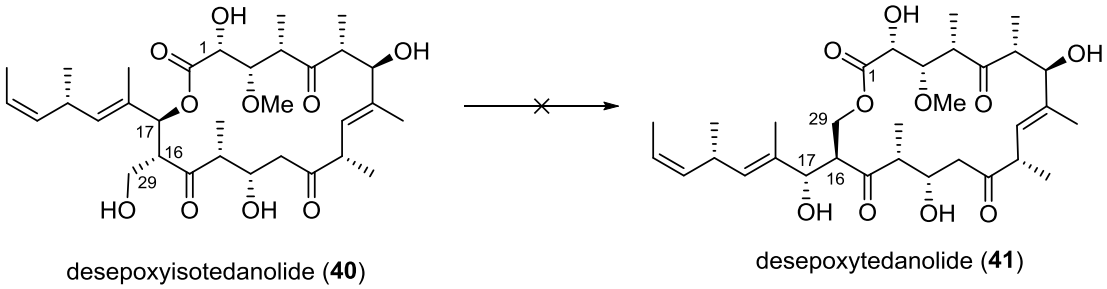
***Scheme 5.4**: Synthesis of desepoxyisotedanolide (**40**).*

During the course of synthesis of desepoxyisotedanolide (**40**) a 14-membered lactone **260** was exclusively formed when the C(14)-hydroxyl group along with C(17)-hydroxyl group were allowed to participate in macrolactonisation under the Shiina protocol (Scheme 5.5).



***Scheme 5.5**: Formation of 14-membered lactone **260**.*

Trials were made to see the isomerization of the desepoxyisotedanolide (**40**) to desepoxytedanolide (**41**) using very mild conditions; unfortunately it was not successful (Scheme 5.6).



***Scheme 5.6**: Transesterification of desepoxyisotedanolide (**40**).*

Few truncated analogues of the C(13-23) aldehyde fragment of tedanolides were made in order to evaluate their biological activity (Figure 5.2). These analogues were found to be active but two fold less compared to the tedanolides.

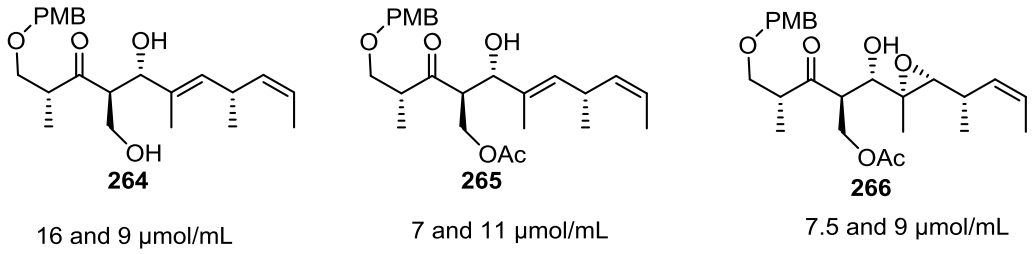
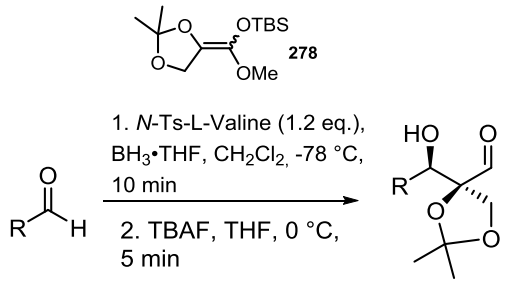


***Fig 5.2**: Simplified analogues of tedanolides.*

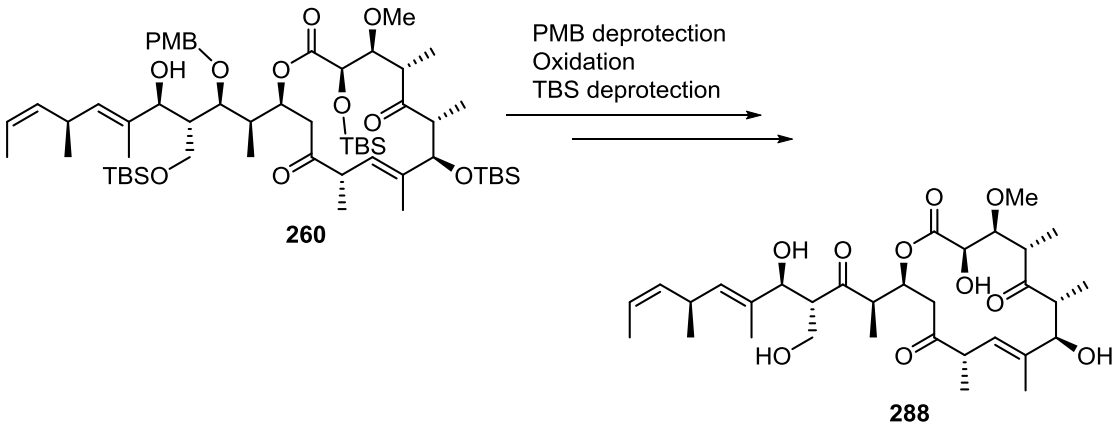
In another part of this thesis, the Kiyooka aldol reaction was used as a protocol to generate tertiary alcohols in a stereo selective manner. This method was tested on a variety of aldehydes and proven to be successful (Scheme 5.7).



***Scheme 5.7**: Kiyooka aldol reaction.*

5.2. Outlook:

From biosynthetical aspect, the synthesis of the 14-membered lactone **288** could be a precursor for tedanolides. Removal of PMB group followed by oxidation at C(15) position and finally global deprotection of all silyl groups using different conditions could provide the macrolactone **288** (Scheme 5.8). This could provide the access to investigate the spontaneous isomerization of the lactones.



***Scheme 5.8**: Synthesis towards lactone **288**.*

6. Experimentals

6.1. Equipment and Devices:

^{1}H-NMR spectra are measured on "Bruker WP-200 SY", "Bruker AM-400" and "Bruker AM-500" spectrometers. As the inner standard a rest signal of a deuterated solvent.[1] As a solvent deuterochloroform ($CDCl_3$), DMSO-d_6 (CD_3SOCD_3), deuterobenzene (C_6D_6) and deuteromethanol (CD_3OD) were used. The chemical shifts are given in ppm on the δ-scale. The coupling constants are measured in hertz (Hz). The multiplets are labeled as: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, sxt = sextet, sep = septet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, br = bright, o = overlapping.

^{13}C-NMR spectra are measured on "Bruker AM-400" at 100 MHz. As a solvent deuterochloroform ($CDCl_3$), DMSO-d_6 (CD_3SOCD_3) and deuteromethanol (CD_3OD) were used.

Mass Spectra (MS-ESI) are presented as a *m/z*-ratio, the signal intensity is given in % compared to the intensity of the most intensive pick.

Optical rotation [α] was measured on a "Perkin-Elmer 341" polarimeter for light with λ = 589 nm, l = 1 dm, *c* is additionally given.

Bulb-to-bulb distillation was done on a „Büchi GKR 50" device.

Flash Chromatographic purification was done on „J.T. Baker Silica gel" (40-60 µm, Pours 60Å) under a slight pressure.

Analytical Thin Layer Chromatography (TLC) was done on 5 x 7,5 cm "Merk 60 F_{254}" aluminium plates covered with a silica gel layer (0,2 mm) and the spots were visualized with UV lamp (254 nm), additionally "Vanillin", "Cer", or "Permanganate" were used to stain the TLC's. Eluent is usually given.

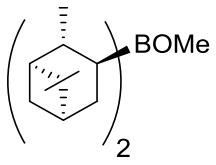
High Performance Liquid Chromatography (HPLC) For non-polar compounds was done on a normal phase column (NP 250/21, Nucleosil 100-7) using Ethyl acetate and Heptane as eluent.

For polar compounds, reverse phase was used to carried out purification on column (Nucleodur C18 ISIS, 5 μm) using acetonitrile and water as eluent.

Solvents and Reagents Reactions were performed under nitrogen/argon atmosphere. Solvents used in the reactions were purified by standard procedures. Tetrahydrofuran was refluxed over sodium/benzophenone and distilled; dichloromethane was refluxed over calcium hydride and distilled. Solvents used for column chromatography are distilled. Reagents and anhydrous solvents (DMSO, DMF, CH_3CN, Diethyl ether) were purchased commercially and use without any purification.

6.2. Preparation of Reagents

(+)-Methoxydiisopinocampheylborane **198**[104]

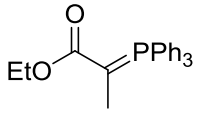


$C_{21}H_{37}BO$
Mol Wt: 316,34

To a solution of (–)-α-pinene (20.0 g, 146.78 mmol, 98%ee) in THF (19 mL) was added borane dimethylsufide complex (6.10 mL, 60.77 mmol). The temperature was maintained below 20-25 °C using ice bath during the addition. Stirring was continued for further 15 min after the completion of addition, ice bath was removed, stirring was stopped and left overnight at room temperature. White solids precipitated out of the solution, THF layer was syringed out under nitrogen. White crystalline solids are washed with dry pentane (2 × 15 mL) and dried under vacuum. Diisopinocampheylborane was obtained as white crystalline solid (13.76 g, 79%). This solid is stable for a month under inert atmosphere at 0 °C.

To the obtained solids was added dry Et_2O (50 mL) and cooled to 0 °C. Pre-cooled methanol (2.30 mL, 56.71 mmol) was added slowly dropwise over a period of 20 min. This reaction is highly exothermic with the evolution of hydrogen. Stirring was continued for further 15 min to obtain a clear solution, solvent removed under vacuum without exposing to air for complete dryness. (+)-Methoxydiisopinocampheylborane (14.64 g) was obtained as white solid quantitatively, which was used in next step without any characterization.

(1-ethoxycarbonylethylidene)triphenylphosphorane **207**[105]



$C_{23}H_{23}O_2P$
Mol Wt: 362,41

To a solution of ethyl-2-bromopropionate (10.0 g, 55.24 mmol) in toluene (20 mL) was added triphenylphosphine (14.48 g, 55.24 mmol). Reaction mixture was heated at 70 °C for a period of 16 h. White solids precipitated out, reaction mixture cooled to 50 °C and distilled water (100 mL) was added, stirred until the solids are completely dissolved. Phases are separated, aqueous layer extracted with MTBE (2 × 30 mL). Aqueous layer then cooled and NaOH was added, initially light yellow solids precipitated out and then turned into yellow fluorescent solids. These solids are filtered out, washed with distilled water (2 × 50 mL), dried under vacuum. Wittig ylide (15.20 g, 52%) was obtained as yellow solid.

Melting point: 158 °C.

bis(*n*-Butyldichlorotin)oxide[88]

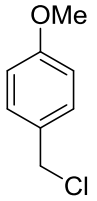
Cl(*n*-Bu)SnOSn(*n*-Bu)Cl

$C_8H_{18}Cl_2OSn_2$
Mol Wt: 438,55

Dibutyltin dichloride (2.00g, 6.58 mmol) was dissolved in ethanol (15 mL) and an equivalent amount of pyridine (0.64 g, 0.66 mL, 8.09 mmol) in ethanol (6 mL) was added. Addition of few drops of water (~1 mL) resulted in a white precipate, the reaction mixture was refluxed for 10 min and a clear solution obtained. Upon cooling to room temperature bis(*n*-butyldichlorotin)oxide (1.00 g) crystallized as white solid.

Melting point: 105-107 °C.

p-Methoxybenzylchloride[106]

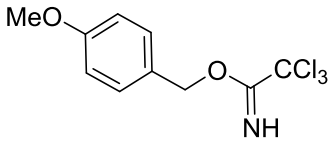


C_8H_9ClO
Mol Wt: 156,61

To a solution of *p*-methoxybenzylalcohol (12.0 mL, 96.40 mmol) in CH_2Cl_2 (300 mL), was added a mixture of thionylchloride (8.76 mL, 120.05 mmol) and benzotriazole (14.35 g, 120.05 mmol) in CH_2Cl_2 (50 mL) dropwise slowly at 0 °C. Reaction mixture stirred for further 10 minutes, the precipitated solids are filtered off and washed with CH_2Cl_2 (2 × 20 mL). The filtrate was concentrated in *vacuo* to yield *p*-methoxybenzylchloride (15.0 g) in quantitative. This product was directly used in the next reaction without further purification.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.30 (d, H_{ar}, 2H, *J* = 7.0 Hz), 6.75 (d, H_{ar}, 2H, *J* = 7.0 Hz), 4.35 (s, CH_2Cl, 2H), 3.65 (s, $ArOCH_3$, 3H).

p-Methoxybenzyltrichloroacetimidate **231**[107]

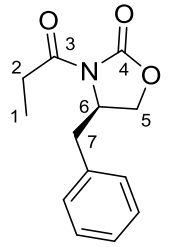


$C_{10}H_{10}Cl_3NO_2$
Mol Wt: 282,55

To the sodium hydride (0.68 g, 16.92 mmol, 60% dispersion in oil) in Et_2O (46 mL) was added *p*-methoxybenzylalcohol (23.58 g, 170.70 mmol) in Et_2O (46 mL) dropwise and stirred for 1 h at room temperature. Reaction mixture cooled to 0 °C, trichloroacetonitrile (24.48 g, 170.70 mmol) in Et_2O (46 mL) was added over a period of 10 minutes. Subsequently reaction mixture warmed to room temperature and stirred for 30 minutes. Reaction mixture was quenched with methanol (0.6 mL) and the solvent was removed in *vacuo*, again methanol (0.6 mL) and hexane (100 mL) was added successively, then filtered over Celite and the filtrate was concentrated in *vacuo* to obtain *p*-methoxybenzyltrichloroacetimidate (41.0 g, 95%) as yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ8.40 (brs, NH, 1H), 7.41 (m, H_{ar}, 2H), 6.95 (m, H_{ar}, 2H), 3.86 (s, CH_3, 3H).

(*R*)-(−)-Benzyl-3-propionyl-2-oxazolidinone (Evans Auxiliary) **210**[108]



$C_{13}H_{15}NO_3$
Mol Wt: 233,27

To an ice-cold methanol (76 mL) was added acetyl chloride (12.54 mL, 174.74 mmol) over a period of 10 min. *D*-Phenylalanine (10.0 g, 60.53 mmol) was added to the reaction, which initially produced a cloudy solution and became clear solution in 10 min. Reaction left stirring for 16 h at room temperature, solvents were removed in *vacuo* to obtain white solids. To the obtained solids in distilled water (300 mL), $NaHCO_3$ (25.0 g, 297.6 mmol) was added slowly portion wise and then ethylchloroformate (6.84 mL, 71.58 mmol) was added dropwise at room temperature and stirred for 4 h. Reaction mixture was extracted with ethyl acetate (2 × 350 mL), combined organic layers are dried over Na_2SO_4, filtered and concentrated in *vacuo* under reduced pressure.

The obtained product was taken in a mixture of ethanol/THF (2:1, 150 mL), to this was added calcium chloride (11.50 g, 103.64 mmol) and sodium borohydride (8.30 g, 219.4 mmol) successively in portions. Apparatus was fixed with condenser and stirred for 16 h at room temperature. Reaction mixture was slowly poured into aq. citric acid (200 mL, 1*M*), stirred for 20 min and extracted with EtOAc (3 × 125 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained residue passed through short silica gel column using pet ether: EtOAc (2:1), the fractions containing compound are concentrated in *vacuo* and the product stored at −25 °C to crystallize for 16 h.

To the obtained solid was added potassium carbonate (10.0 g, 72.35 mmol) and toluene (15 mL) and the resulting mixture was stirred on rotavap at 90 °C (50 mbar) for 4 h. A mixture of ethanol/water (1:1, 75 mL) was added, the organic phase was separated, aqueous layer was extracted with EtOAc and combined organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. Obtained residue was kept at −25 °C to crystallize for 16 h. 8.20 g of the oxazolidine was obtained.

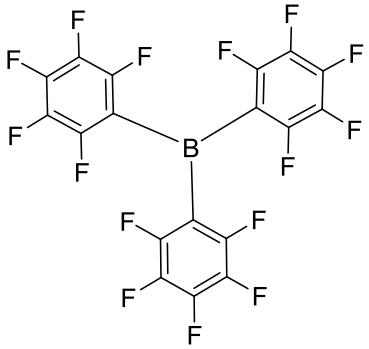
To the above obtained oxazolidine (8.20 g, 46.20 mmol) in THF (150 mL) was added *n*-BuLi (18.5 mL, 46.25 mmol, 2.5*M* in hexanes) at −78 °C slowly dropwise. Freshly distilled propionyl chloride (4.30 mL, 46.20 mmol) was added dropwise to the reaction mixture slowly, after the completion of addition, stirring was continued for another 30 minutes at −78 °C. Reaction mixture was quenched with saturated aq. NH_4Cl (30 mL), the solvent was removed in vacuo and extracted with CH_2Cl_2 (3 × 50 mL), the combined organic layers are washed with aq. NaOH (30 mL, 1*M*) and saturated aq. NaCl (30 mL),

dried over Na_2SO_4, filtered and concentrated in *vacuo*. Obtained residue was cooled at −25 °C to crystallize to obtain (*R*)-(−)-benzyl-3-propionyl-2-oxazolidinone as white solid.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.22-7.42 (m, H_{ar}, 5H), 4.64-4.76 (m, H-6, 1H), 4.17-4.30 (m, H-5, 2H), 3.35 (dd, H-2, ^3J = 13.3 Hz, ^3J = 3.3 Hz, 1H), 2.88-3.08 (m, H-7, 2H), 2.79 (q, H-2, ^3J = 13.4 Hz, ^3J = 9.6 Hz, 1H), 1.25 (t, H-1, ^3J = 7.3 Hz, 3H).

$[\alpha]^{23}_D$ = − 63.0 (*c* 0.99, $CHCl_3$)

Tris(pentafluorophenyl)borane (TPPB)[110]

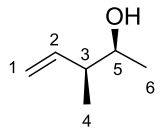


$C_{18}BF_{15}$
Mol Wt: 511,98

To the magnesium turnings (2.50 g) in Et_2O (174 mL) was added slowly dropwise pentafluorobromobenzene (12.98 mL, 25.72 g, 100 mmol) until the reaction mixture becomes turbid, once the turbidity was observed addition was stopped and reaction mixture was cooled to 0 °C. The remaining amount of pentafluorobromobenzene was added slowly dropwise so that the reaction mixture shouldn't boil. In another flask borontrifluoride etherate was taken in toluene (70 mL) and cooled to 0 °C. The Grignard generated was slowly added using syringe to the borontrifluoride etherate in toluene at 0 °C and then warmed to room temperature. Around 100 mL of solvent was removed under reduced pressure. Reaction mixture was heated at 100 °C for 1 h and then concentrated under reduced pressure for complete dryness. The obtained brown residue was filtered using schlenk filter apparatus under nitrogen atmosphere using hexane (200 mL) and Et_2O (200 mL). The filtrate was kept for crystallization at −25 °C for 16 h. The filtrate was concentrated under vacuum, tried to purify by Kugel-Rohr distillation (100 °C/1 m bar).

6.3. Ketone Fragment C(1-12):

6.3.1 Homoallyl alcohol **195**



195

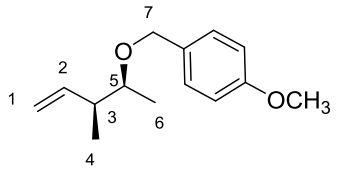
$C_6H_{12}O$
Mol Wt: 100,16

To a stirred suspension (−78 °C) of potassium-*tert*-butoxide (9.79 g, 87.26 mmol, dried at 60 °C/0.3 mbar overnight) in THF (56 mL) was added *cis*-butene (14.0 mL, 155.83 mmol) via double-tipped needle. *n*-BuLi (34.0 mL, 2.5*M* in hexanes, 87.26 mmol) was added over 10 min. After the complete addition, the reaction mixture was warmed to −25 °C for 30 min and recooled to −78 °C. A solution of (+)-Methoxydiisopinocampheylborane (35.0 g, 110.64 mmol) in Et_2O (74 mL) was added slowly. After the resulting solution was stirred for 30 min, Borontrifluoride etherate (14.0 mL, 110.64 mmol) was added slowly dropwise, followed by drop wise addition of acetaldehyde (7.04 mL, 124.66 mmol) in Et_2O (8 mL). After 3 h, the reaction was quenched with aq. NaOH (95 mL, 2*M*) and 30% aq. H_2O_2 (27 mL), warmed to room temperature and then heated to reflux for 1 h. The organic layer was separated and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were washed with distilled water (150 mL) and brine (150 mL), dried over $MgSO_4$ and filtered. After evaporation of a major amount of solvent in *vacuo* (500 mbar, 40 °C water bath), the residual liquid was carefully fractionated to give alcohol **195** (9.00 g, crude) (bp 50-72 °C/90 mbar). This contains residual THF and pinenol.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.63-5.73 (m, H-2, 1H), 4.99-5.03 (m, H-1, 1H), 4.96-4.99 (m, H-1', 1H), 3.58 (dd, *J* = 15.6, 10.1 Hz, H-5, 1H), 2.08-2.21 (m, H-3, 1H), 1.28-1.39 (bs, -OH, 1H), 1.05 (d, *J* = 6.4 Hz, H-4, 3H), 0.93 (d, *J* = 6.9 Hz, H-6, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 140.6, 115.7, 70.9, 44.9, 20.0, 14.8.

6.3.2 PMB-ether **177**



177

$C_{14}H_{20}O_2$
Mol Wt: 220,31

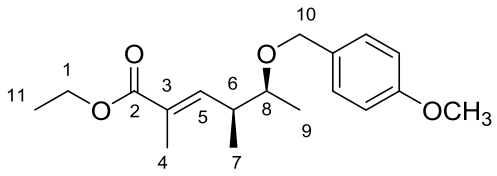
Sodium hydride (5.54 g, 60% in mineral oil, 116.87 mmol) was washed with pentane (2 × 35 mL), DMSO (140 mL) was added and the suspension was stirred at room temperature for 1 h. Crude alcohol **195** from the above step in THF (20 mL) was added over 10 min. The yellowish mixture was cooled to 0 °C and *p*-methoxybenzylchloride (11.31 mL, 86.1 mmol) was added slowly. The mixture was warmed to room temperature and stirred for 16 h. Brine (300 mL) was added and the mixture was extracted with MTBE (4 × 100 mL). The combined organic layers are dried over $MgSO_4$ and evaporated in *vacuo*. Silica gel chromatography (pet ether-EtOAc, 5:1) afforded PMB ether **177** (13.0 g, 60% over two steps) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.88 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.75-5.93 (m, H-2, 1H), 5.04-5.09 (m, H-1, 1H), 5.01-5.04 (m, H-1', 1H), 4.53 (d, *J* = 11.4 Hz, H-7, 1H), 4.42 (d, *J* = 11.4 Hz, H-7', 1H), 3.81 (s, Ar-OCH_3, 3H), 3.36 (p, *J* = 6.2 Hz, H-5, 1H), 2.31-2.47 (m, H-3, 1H), 1.13 (d, *J* = 6.2 Hz, H-4, 3H), 1.05 (d, *J* = 6.8 Hz, H-6, 3H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ 159.1, 140.9, 131.3, 129.2, 114.5, 113.8, 78.2, 70.4, 55.4, 43.1, 16.8, 16.0.

HRMS (ESI) calculated for $C_{14}H_{20}O_2Na$ ([*M*+Na]+): 243.1361, found 243.1331.

6.3.3 α,β-Unsaturated ester **208**



208

$C_{18}H_{26}O_4$
Mol Wt: 306,40

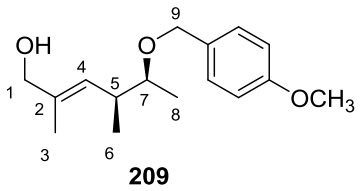
A stream of ozone in oxygen (50 L/h) was passed through a solution containing olefin **177** (13.0 g, 59.0 mmol) and sudan red III (cat.) in CH_2Cl_2 (110 mL) at −78 °C. Ozone gas was bubbled until the color of the solution turned from red to gray. Excess of Ozone was purged with oxygen and then with argon, triphenylphosphine (23.21 g, 88.50 mmol) was added and the stirring was continued at −78 °C for 1 h. and warmed to room temperature. (1-ethoxycarbonylethylidene)triphenylphosphorane **207** (64.19 g, 177.0 mmol) was added. After 16 h, the solvents were removed in *vacuo*. The residue was filtered through a short pad of silica using (pet ether-EtOAc, 2:1) and the solvent was evaporated. Silica gel chromatography (pet ether-EtOAc, 15:1) afforded ester **208** (9.20 g, 56%) of ester as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.62 (dd, *J* = 10.3, 1.4 Hz, H-5, 1H), 4.54 (d, *J* = 11.3 Hz, H-10, 1H), 4.38 (d, *J* = 11.3 Hz, H-10', 1H), 4.19 (q, *J* = 7.1 Hz, H-1, 1H), 3.80 (s, Ar-OCH_3, 3H), 3.37 (p, *J* = 6.2 Hz, H-8, 1H), 2.64 (dp, *J* = 10.3, 6.8 Hz, H-6, 1H), 1.85 (d, *J* = 1.4 Hz, H-4, 3H), 1.30 (t, *J* = 7.1 Hz, H-11, 3H), 1.14 (d, *J* = 6.2 Hz, H-7, 3H), 1.06 (d, *J* = 6.7 Hz, H-9, 3H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ168.4, 159.2, 144.2, 130.9, 129.4, 127.7, 113.9, 78.0, 70.8, 60.6, 55.4, 39.6, 17.4, 16.2, 14.4, 12.8.

HRMS (ESI) calculated for $C_{18}H_{26}O_4Na$ ([*M*+Na]+): 329.1729, found 329.1731
$[\alpha]^{23}_D$ = + 7.8 (*c* 1.2, $CHCl_3$)

6.3.4 Allyl alcohol **209**



209

$C_{16}H_{24}O_3$
Mol Wt: 264,37

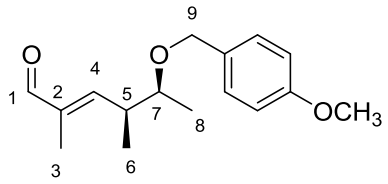
To a stirred solution (−78 °C) of ester **208** (9.30 g, 30.35 mmol) in CH_2Cl_2 (200 mL) was added DIBAL-H (91 mL, 1*M* in CH_2Cl_2, 91.05 mmol) dropwise. After 1 h of stirring, MTBE (220 mL) was added rapidly and the mixture was warmed to room temperature. Dropwise addition of distilled water (9 mL) led to the formation of a colorless gel. Upon addition of aq. NaOH (18 mL, 2*N*) and additional distilled water (9 mL), a white solid precipitated. The resulting suspension was then dried over $MgSO_4$, filtered and evaporated in *vacuo*. Silica gel chromatography (pet ether-EtOAc, 4:1) afforded the desired alcohol **209** (7.90 g, 95%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.6 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.6 Hz, H_{Ar}, 2H), 5.25 (dd, *J* = 9.8, 1.0 Hz, H-4,1H), 4.53 (d, *J* = 11.3 Hz, H-9, 1H), 4.37 (d, *J* = 11.3 Hz, H-9', 1H), 3.96 (s, H-1, 2H), 3.79 (s, Ar-OCH_3, 3H), 3.29 (p, *J* = 6.3 Hz, H-7, 1H), 2.55 (dp, *J* = 9.8, 6.8 Hz, H-5, 1H), 1.71 (bs, -OH, 1H), 1.67 (d, *J* = 0.9 Hz, H-3, 3H), 1.13 (d, *J* = 6.2 Hz, H-6, 3H), 1.00 (d, *J* = 6.7 Hz, H-8, 3H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ 159.1, 134.9, 131.1, 129.3, 128.6, 113.8, 78.8, 70.6, 68.9, 55.4, 38.2, 17.2, 14.2.

HRMS (ESI) calculated for $C_{16}H_{24}O_3Na$ ([*M*+Na]+): 287.1623, found 287.1620
$[\alpha]^{23}_D$ = + 10.4 (*c* 1.9, $CHCl_3$).

6.3.5 α,β-Unsaturated aldehyde **176**



176

$C_{16}H_{22}O_3$
Mol Wt: 262,35

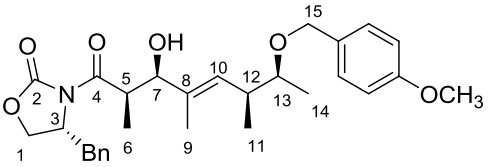
Activated MnO_2 (71.5 g, 417.0 mmol) was suspended in CH_2Cl_2 (250 mL). Alcohol **209** (5.30 g, 20.80 mmol) in CH_2Cl_2 (30 mL) was added at room temperature and stirred for 1 h. The mixture was filtered through a pad of Celite, washed with CH_2Cl_2 (250 mL) and the filtrate evaporated under *vacuo* to afford pure aldehyde **176** (5.00 g, 95%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.38 (s, H-1, 1H), 7.25 (d, *J* = 7.7 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.6 Hz, H_{Ar}, 2H), 6.37 (dd, *J* = 10.1, 1.1 Hz, H-4, 1H), 4.56 (d, *J* = 11.3 Hz, H-9, 1H), 4.37 (d, *J* = 11.3 Hz, H-9', 1H), 3.80 (s, Ar-OCH_3, 3H), 3.45 (p, *J* = 6.2 Hz, H-7, 1H), 2.84 (dp, *J* = 10.1, 6.7 Hz, H-5, 1H), 1.76 (d, *J* = 1.1 Hz, H-3, 3H), 1.17 (d, *J* = 6.2 Hz, H-6, 3H), 1.10 (d, *J* = 6.8 Hz, H-8, 3H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ 195.6, 159.3, 156.6, 139.0, 130.7, 129.4, 113.9, 77.3, 70.7, 55.4, 39.6, 17.1, 15.7, 9.6.

HRMS (ESI) calculated for $C_{16}H_{22}O_3Na$ ([*M*+Na]+): 285.1467, found 285.1466
$[\alpha]^{23}_D$ = + 22.0 (*c* 0.9, $CHCl_3$).

6.3.6 Evans' aldol **211**



211

$C_{29}H_{37}NO_6$
Mol Wt: 495,62

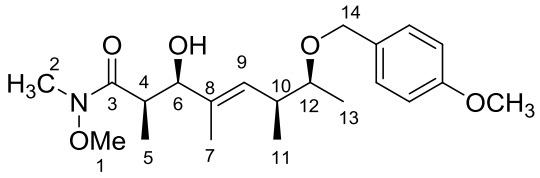
To a stirred solution (−78 °C) of (*R*)-(−)-benzyl-3-propionyl-2-oxazolidinone **210** (1.65 g, 7.06 mmol) in CH_2Cl_2 (20 mL) was added di(*n*-butyl)boryl(trifluoromethane)sulfonate (8.43 mL, 1*M* in CH_2Cl_2, 8.44 mmol) and triethylamine (1.29 mL, 9.19 mmol). The mixture was warmed to 0 °C, stirred for 1 h and then cooled to −78 °C again. A solution of aldehyde **176** (1.80 g, 6.86 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. After 20 min, the reaction was warmed to 0 °C and stirred for 1 h. The reaction was quenched by dropwise addition of pH7 phosphate buffer (7.5 mL), methanol (22.5 mL) and a mixture of methanol and 30% aq. H_2O_2 (2:1, 22.5 mL) and stirred for 1 h. Distilled water (20 ml) was added, the organic layer was separated and the aqueous layer was extracted with MTBE (4 × 20 mL). The combined organic layers are washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated in *vacuo*. Silica gel chromatography (pet ether-EtOAc, 4:1) afforded aldol **211** (3.00 g, 89%) as a colorless gel.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.36 (m, H_{Ar}, 3H), 7.25 (d, *J* = 8.5 Hz, H_{Ar}, 2H), 7.20 (d, *J* = 6.9 Hz, H_{Ar}, 2H), 6.86 (d, *J* = 8.6 Hz, H_{Ar}, 2H), 5.39 (d, *J* = 10.0 Hz, H-10, 1H), 4.61-4.72 (m, H-3, 1H), 4.51 (d, *J* = 11.3 Hz, H-15, 1H), 4.37 (d, *J* = 10.4 Hz, H-15', 1H), 4.29-4.36 (m, H-7, 1H), 4.14 (d, *J* = 5.2 Hz, H-1, 1H), 4.00 (qd, *J* = 6.9, 4.3 Hz, H-13, 1H), 3.80 (s, Ar-OCH_3, 1H), 3.28-3.35 (m, $BnCH_2$, 1H), 3.25 (dd, *J* = 13.2, 3.1 Hz, H-5, 1H), 2.78 (dd, *J* = 13.4, 9.5 Hz, $BnCH_2$, 1H), 2.51-2.62 (m, H-12, 1H), 1.64 (s, H-9, 3H), 1.58 (bs, -OH, 1H), 1.19 (d, *J* = 7.0 Hz, H-6, 3H), 1.11 (d, *J* = 6.2 Hz, H-14, 3H), 1.01 (d, *J* = 6.7 Hz, H-11, 3H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ 176.9, 159.2, 153.1, 135.3, 133.6, 131.2, 129.6, 129.4, 129.1, 127.5, 79.1, 75.8, 70.7, 66.2, 55.4, 40.7, 38.4, 37.9, 17.6, 17.3, 13.7, 11.1.

HRMS (ESI) calculated for $C_{29}H_{37}NO_6Na$ ([*M*+Na]+): 518.2516, found 518.2516
$[\alpha]^{23}_D$ = − 28.2 (*c* 1.2, $CHCl_3$).

6.3.7 Weinreb amide **212**



212

$C_{21}H_{33}NO_5$
Mol Wt: 379,50

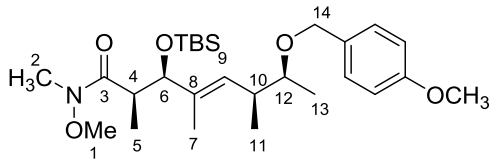
To a stirred suspension (0 °C) of *N*,*O*-dimethylhydroxylamine hydrochloride (0.62 g, 6.34 mmol) in CH_2Cl_2 (10 mL) was added trimethylaluminium (3.17 mL, 2*M* in heptane, 6.34 mmol) over 5 min. The mixture was warmed to room temperature and stirred for 1 h. After 1 h, the clear solution was cooled to −20 °C and compound **211** (1.50 g, 3.02 mmol) in CH_2Cl_2 (5 mL) was added dropwise for 5 min. The reaction was allowed to warm to room temperature over a period of 5 h and was stirred 16 h at rt. The mixture was transferred via syringe to a second flask containing a vigorously stirred solution of tartaric acid (20 mL, 1*M*) at 0 °C. After 1.5 h, distilled water (30 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers are washed with brine (30 mL), dried over $MgSO_4$, filtered and evaporated in *vacuo*. The crude product purified by silica gel column chromatography (pet ether-ethyl acetate, 3:1) afforded compound **212** (1.00 g, 87%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.40 (d, *J* = 10.0 Hz, H-9, 1H), 4.53 (d, *J* = 11.2 Hz, H-14, 1H), 4.36 (d, *J* = 11.2 Hz, H-14', 1H), 4.25 (d, *J* = 2.9 Hz, H-6, 1H), 3.79 (s, Ar-OCH_3, 3H), 3.70 (s, H-1, 3H), 3.68-3.71 (m, H-12, 1H), 3.26 (dd, *J* = 7.9, 6.2 Hz, H-4, 1H), 3.18 (s, H-2, 3H), 3.07 (bs, -OH, 1H), 2.39-2.61 (m, H-10, 1H), 1.61 (s, H-7, 3H), 1.12 (d, *J* = 6.1 Hz, H-5, 3H), 1.09 (d, *J* = 7.1 Hz, H-13, 3H), 1.02 (d, *J* = 6.6 Hz, H-11, 3H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ 177.8, 159.1, 132.8, 131.3, 129.7, 129.4, 113.8, 79.2, 75.6, 70.8, 61.7, 55.4, 39.0, 17.7, 13.9, 10.7.

HRMS (ESI) calculated for $C_{21}H_{33}NO_5Na$ ([*M*+Na]+): 402.2256, found 402.2259
$[\alpha]^{23}_D$ = + 3.18 (*c* 2.2, $CHCl_3$).

6.3.8 TBS-Weinreb amide **213**



213

$C_{27}H_{47}NO_5Si$
Mol Wt: 493,76

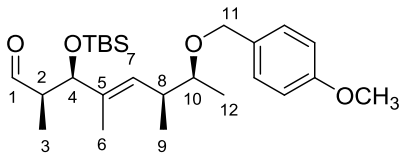
To a stirred solution (0 °C) of amide **212** (5.30 g, 13.96 mmol) in CH_2Cl_2 (68 mL) was slowly added 2,6-Lutidine (2.76 mL) and *tert*-Butyldimethylsilyltrifluoromethane sulfonate (4.20 mL). The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with methanol (2 mL), diluted with CH_2Cl_2 (240 mL) and successively washed with saturated aq. $NaHCO_3$ (60 mL), aq. $NaHSO_3$ (3 × 60 mL) and brine (60 mL), dried over $MgSO_4$ and evaporated in *vacuo*. The crude product was purified by silica gel column chromatography (pet ether- EtOAc, 5:1) to afford compound **213** (5.60 g, 81%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28 (m, d, *J* = 8.5 Hz, H_{Ar}, 2H), 6.86 (d, *J* = 8.5 Hz, H_{Ar}, 1H), 5.09 (d, *J* = 10.0 Hz, H-9, 1H), 4.50 (d, *J* = 11.1 Hz, H-14, 1H), 4.33 (d, *J* = 11.1 Hz, H-14', 1H), 4.14 (d, *J* = 9.4 Hz, H-6, 1H), 3.80 (s, Ar-OCH_3, 3H), 3.62 (s, H-1, 3H), 3.15 (dd, *J* = 7.9, 6.3 Hz, H-4&H-12, 2H), 3.06 (s, H-2, 3H), 2.41 (dd, *J* = 15.7, 8.9 Hz, H-10, 1H), 1.60 (s, H-8, 3H), 1.18 (d, *J* = 6.7 Hz, H-5, 3H), 1.02 (d, *J* = 6.1 Hz, H-13, 3H), 0.98 (d, *J* = 6.6 Hz,H-11, 3H), 0.88 (s, $Si(CH_3)_3$, 9H), 0.05 (s, $SiCH_3$, 1H), -0.02 (s, $SiCH_3$, 1H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ 175.7, 159.1, 135.1, 131.3, 129.4, 113.8, 80.7, 79.4, 70.8, 61.6, 55.4, 40.0, 39.2, 31.8, 25.9, 18.3, 17.6, 17.3, 15.4, 11.3, -4.3, -4.8.

HRMS (ESI) calculated for $C_{27}H_{47}NO_5SiNa$ ([*M*+Na]+): 516.3121, found 516.3122
$[\alpha]^{23}_D$ = + 11.6 (*c* 2.5, $CHCl_3$).

6.3.9 Aldehyde **174**



174

$C_{25}H_{42}O_4Si$
Mol Wt: 434,69

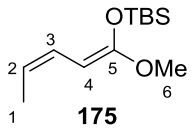
To a stirred solution (−78 °C) of amide **213** (0.82 g, 1.66 mmol) in THF (8 mL) was added DIBAL-H (4.16 mL, 1*M* in CH_2Cl_2, 4.16 mmol) over 20 min. Upon complete addition, the reaction was stirred for further 15 min. Excess DIBAL-H was quenched by the addition of acetone (0.3 mL). The reaction mixture was transferred via syringe to a second flask containing a vigorously stirred mixture of (23 °C) of aq. tartaric acid (16 mL, 1*M*) and pet ether (15 mL) stirred for 1 h. The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 25 mL). The combined organic layers are washed with brine (25 mL), dried over $MgSO_4$, filtered and evaporated in *vacuo*. Silica gel chromatography (pet ether-EtOAc, 5:1) afforded aldehyde **174** (0.64 g, 89%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.64 (d, *J* = 2.1 Hz, H-1, 1H), 7.26 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.22 (d, *J* = 10.0 Hz, H-7, 1H), 4.52 (d, *J* = 11.2 Hz, H-11, 1H), 4.33 (d, *J* = 11.2 Hz, H-11', 1H), 4.21 (d, *J* = 6.7 Hz, H-4, 1H), 3.80 (s, Ar-OCH_3, 3H), 3.14 – 3.31 (m, H-10, 1H), 2.52 – 2.62 (m, H-2, 1H), 2.43 – 2.52 (m, H-8, 1H)1.60 (d, *J* = 1.3 Hz, H-6, 3H), 1.09 (d, *J* = 6.2 Hz, H-12, 3H), 1.04 (d, *J* = 6.8 Hz, H-9, 3H), 1.00 (d, *J* = 6.7 Hz, H-3, 3H), 0.88 (s, $Si(CH_3)_3$, 9H), 0.04 (s, $SiCH_3$, 3H), -0.01 (s, $SiCH_3$, 3H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ 204.5, 159.1, 135.0, 131.2, 130.9, 129.3, 113.8, 78.8, 78.5, 70.6, 55.4, 51.2, 38.7, 25.9, 18.3, 17.5, 16.9, 12.5, 9.7, -4.3, -5.0.

HRMS (ESI) calculated for $C_{25}H_{42}O_4SiNa$ ([*M*+Na]+): 457.2750, found 457.2747
$[\alpha]^{23}_D$ = + 14.88 (*c* 1.8, $CHCl_3$).

6.3.10 Ketene acetal **175**



175

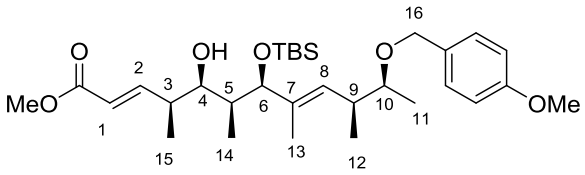
$C_{12}H_{24}O_2Si$
Mol Wt. 228,41

To a solution of diisopropylamine (7.0 mL, 49.3 mmol) in THF (30 mL) was added *n*-BuLi (2.5*M* in hexanes, 19.75 mL, 49.0 mmol) at 0 °C over a period of 10 minutes. The resulting solution was cooled to −78 °C, with an interval of 15 minutes each DMPU (8.00 mL, 66.0 mmol), methyl-(*E*)-pent-2-enoate (5.00 g, 43.0 mmol) and TBSCl (8.10 g, 53.7 mmol) are added successively. After the completion of addition reaction mixture warmed to room temperature and stirred for additional 90 min. sat. aq. $NaHCO_3$ solution (50 mL) was added, the phases are separated, aqueous phase extracted with MTBE (3 × 50 mL). Combined organic layers are washed with water (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated on *vacuo*. Crude compound was purified using distillation (90-100 °C/0.7 mbar) to afford ketene acetal **175** (8.0 g, 82%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.17 (td, *J* = 10.8, 1.7 Hz, H-3, 1H), 5.10 (dqd, *J* = 10.8, 6.9, 1.0 Hz, H-2, 1H), 4.54 (dd, *J* = 10.7, 0.9 Hz, H-4, 1H), 3.60 (s, H-6 3H), 1.67 (dd, *J* = 6.9, 1.7 Hz, H-1, 3H), 0.95 (s, $SiC(CH_3)_3$, 9H), 0.17 (s, $SiCH_3$, 7H).

^{13}C -NMR (100 MHz, $CDCl_3$): δ 158.6, 124.4, 116.6, 75.4, 54.9, 25.8, 18.3, -4.1, 13.3.

6.3.11 VMAR aldol product **216**



216

$C_{31}H_{52}O_6Si$
Mol Wt: 548,84

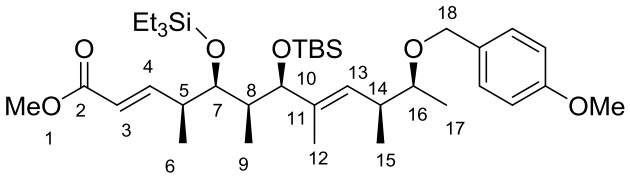
To a stirred solution (–78 °C) of tris(pentafluorophenyl)borane (1.50 g, 2.93 mmol) in Et_2O (35 mL), aldehyde **15** (1.10 g, 2.53 mmol) in Et_2O (8 mL) was added. Ketene acetal **175** (1.27 g, 5.56 mmol) and *i*-PrOH (0.21 mL, 2.77 mmol) were diluted with Et_2O (8 mL) and added via syringe pump over 2 h. The mixture was allowed to warm to −50 °C over 30 min and was then evaporated in *vacuo* at room temperature. Silica gel chromatography (pet ether-EtOAc, 4:1) afforded ester **216** (1.10 g, 80%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.3 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.71 (dd, *J* = 15.7, 9.3 Hz, H-2, 1H), 5.82 (dd, *J* = 15.7, 0.6 Hz, H-1, 1H), 5.23 (d, *J* = 9.9 Hz, H-8, 1H), 4.51 (d, *J* = 11.5 Hz, H-16, 1H), 4.36 (d, *J* = 11.5 Hz, H-16', 1H), 3.90 (d, *J* = 7.7 Hz, H-6, 1H), 3.80 (s, -OMe, 3H), 3.73 (s, Ar-OCH_3, 1H), 3.31-3.36 (m, H-10, 1H), 3.29 (d, *J* = 6.0 Hz, H-4, 1H), 2.62 (dt, *J* = 9.9, 6.7 Hz, H-9, 1H), 2.32-2.51 (m, H-3, 1H), 2.03 (d, *J* = 4.7 Hz, -OH, 1H), 1.57-1.66 (m, H-5, 1H), 1.55 (d, *J* = 1.2 Hz, H-13, 3H), 1.12 (d, *J* = 6.2 Hz, H-11, 3H), 1.00 (d, *J* = 6.6 Hz, H-5, 3H), 0.97 (d, *J* = 6.8 Hz, H-12, 3H), 0.88 (d, *J* = 2.2 Hz, H-14, 3H), 0.88 (s, $Si(CH_3)_3$, 9H), 0.05 (s, $SiCH_3$, 1H), -0.03 (s, $SiCH_3$, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.1, 159.2, 150.9, 136.3, 131.1, 129.8, 129.2, 121.0, 113.9, 82.5, 78.6, 75.3, 70.5, 55.4, 51.6, 41.1, 39.9, 37.8, 26.0, 18.3, 17.2, 16.7, 16.6, 12.10, 8.2, -4.2, -4.9.

HRMS (ESI) calculated for $C_{31}H_{52}O_6SiNa$ ([*M*+Na]+): 571.3431, found 571.3433
$[\alpha]^{23}_D$ = + 8.0 (*c* 0.7, $CHCl_3$).

6.3.12 TES-ether **173**



173

$C_{37}H_{66}O_6Si_2$
Mol Wt: 663,0990

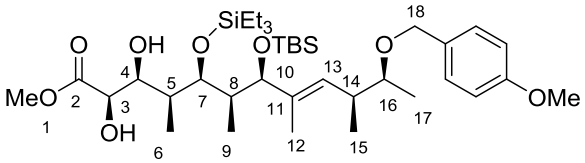
To a stirred solution (0 °C) of ester **216** (580 mg, 1.056 mmol) in CH_2Cl_2 (11 mL) was added 2,6-lutidine (0.32 mL, 2.754 mmol) and TESOTf (0.406 mL, 1.796 mmol) dropwise. After 15 min, the reaction was quenched by the addition of sat. aq. $NaHCO_3$ (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers dried over $MgSO_4$, filtered and evaporated in *vacuo*. Silica gel chromatography (pet ether-EtOAc, 15:1) afforded the ester **173** (660 mg, 0.303 mmol, 94%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.0 Hz, H_{Ar}, 2H), 6.94 (dd, *J* = 15.8, 7.6 Hz, H-4, 1H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.76 (dd, *J* = 15.8, 1.3 Hz, H-3, 1H), 5.16 (d, *J* = 9.8 Hz, H-13, 1H), 4.54 (d, *J* = 11.2 Hz, H-18, 1H), 4.37 (d, *J* = 11.2 Hz, H-18', 1H), 3.80 (s, H-1, 3H), 3.76 (d, *J* = 8.8 Hz, H- 10, 1H), 3.73 (s, $ArOCH_3$, 3H), 3.54 (dd, *J* = 5.7, 2.5 Hz, H-7, 1H), 3.25 (dq, *J* = 12.3, 6.1 Hz, H-16, 1H), 2.50 – 2.65 (m, H-14, 1H), 2.36 – 2.51 (m, H-5, 1H), 1.62 – 1.76 (m, H-8, 1H), 1.52 (d, *J* = 1.1 Hz, H-12, 3H), 1.17 (d, *J* = 6.1 Hz, H-17, 3H), 1.02 (d, *J* = 6.7 Hz, H-15, 3H), 0.91 – 0.99 (m, 12H), 0.88 – 0.83 (m, 12H), 0.60 (q, *J* = 7.9 Hz, 6H), 0.01 (s, $SiCH_3$, 3H), -0.05 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.2, 159.1, 152.4, 136.9, 131.3, 131.2, 129.2, 120.2, 113.8, 80.7, 78.9, 75.0, 70.6, 55.4, 51.5, 42.4, 39.4, 39.0, 26.0, 18.4, 17.6, 17.1, 15.2, 12.0, 11.0, 7.2, 5.8, -4.1, -4.8.

HRMS (ESI) calculated for $C_{37}H_{66}O_6Si_2Na$ ([*M*+Na]+): 685.4296, found 685.4294
$[\alpha]^{23}_D$ = + 7.58 (*c* 1.1, $CHCl_3$).

6.3.13 Diol **224**



224

$C_{37}H_{68}O_8Si_2$
Mol Wt: 697,1130

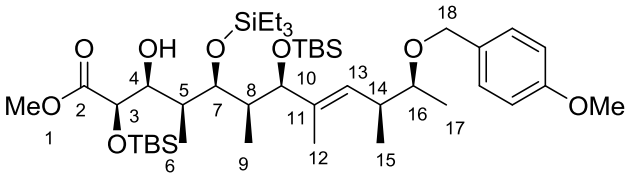
To a stirred solution of AD-mix-α (3.05 g) in *t*-BuOH-H_2O (1:1, 20 mL) was added methanesulfonamide (160 mg, 1.719 mmol) at room temperature. The suspension was cooled to 0 °C and methyl ester **173**(1.10 g, 1.6589 mmol) was added in *t*-BuOH (5 mL). After 5 days, the reaction was quenched by the addition of $Na_2S_2O_3$ (1.67 g), warmed to room temperature and stirred for 1 h. H_2O (20 mL) was added, and the mixture was extracted with EtOAc (4 × 25 mL), dried over $MgSO_4$, filtered and evaporated in *vacuo*. Silica gel chromatography (pet ether- EtOAc, 3:1) afforded diol **224** (0.75 g, 70%) as a mixture of diastereomers (d.r. 24:1).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28 (d, , *J* = 8.7 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.17 (d, *J* = 9.8 Hz, H-13, 1H), 4.51 (d, *J* = 11.8 Hz, H-18, 1H), 4.40 (d, *J* = 11.7 Hz, H-18', 1H), 4.26 (dd, *J* = 5.5, 3.0 Hz, H-3, 1H), 3.80 (s, $ArOCH_3$, 3H), 3.78 (s, H-1, 3H), 3.74 (d, *J* = 9.2 Hz, H-4, 1H), 3.61 (dd, *J* = 5.2, 2.0 Hz, H-10, 1H), 3.29 (p, *J* = 6.2 Hz, H-7, 1H), 3.14 (d, *J* = 5.5 Hz, H-16, 1H), 2.53-2.70 (m, H-14/-OH, 2H), 1.72-1.84 (m, H-8/H-5, 2H), 1.58 (d, *J* = 1.0 Hz, H-12, 1H), 1.12 (d, *J* = 6.2 Hz, H-17, 1H), 0.94-0.98 (m, 18H), 0.88 (s, $Si(CH_3)_3$, 9H), 0.63 (q, *J* = 7.8 Hz, 6H), 0.03 (s, $SiCH_3$, 1H), -0.04 (s, $SiCH_3$, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.3, 159.2, 137.6, 130.9, 130.5, 129.3, 113.9, 81.3, 78.6, 73.5, 73.2, 72.2, 70.4, 55.4, 52.7, 42.5, 39.6, 37.9, 26.0, 18.4, 17.2, 16.6, 11.8, 11.3, 10.7, 7.3, 5.8, -4.1, -4.8.

HRMS (ESI) calculated for $C_{31}H_{52}O_8SiNa$ ([*M*+Na]+): 719.4350, found 719.4146
$[\alpha]^{23}_D$ = − 12.88 (*c* 1.8, $CHCl_3$).

6.3.14 Monohydroxy ester **225**



225

$C_{43}H_{82}O_8Si_3$
Mol Wt: 811,3760

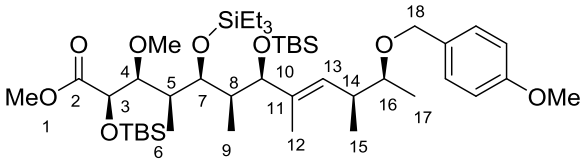
To a stirred solution (0 °C) of diol **224** (750 mg, 1.070 mmol) in DMF (20 mL) was added imidazole (437 mg, 6.420 mmol) and TBSCl (567 mg, 3.765 mmol). After 16 h, the reaction was quenched by the addition of sat. aq NH_4Cl (20 mL) and the mixture was extracted with pet ether- EtOAc (5:1, 4 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated in *vacuo*. Silica gel chromatography (pet ether- EtOAc, 8:1) afforded the desired ester **225** (830 mg, 95%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (d, *J* = 7.0 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.12 (dd, *J* = 9.7, 0.9 Hz, H-13, 1H), 4.54 (d, *J* = 11.5 Hz, H-18, 1H), 4.39 (d, *J* = 11.5 Hz, H-18', 1H), 4.07 (d, *J* = 6.8 Hz, H-3, 1H), 3.79-3.82 (m, H-10, 1H), 3.80 (s, $ArOCH_3$,3H), 3.74 (d, *J* = 7.5 Hz, H-4, 1H), 3.71 (s, H-1, 3H), 3.54 (d, *J* = 7.5 Hz, H-7, 1H), 3.23 (dq, *J* = 12.3, 6.1 Hz, H-16, 1H), 2.54-2.63 (m, H-14, 1H), 2.53 (d, *J* = 4.5 Hz, H-5, 1H), 1.86 (dq, *J* = 13.6, 6.7 Hz, H-8, 1H), 1.58 (d, *J* = 1.1 Hz, H-12, 3H), 1.15 (d, *J* = 6.2 Hz,H-17, 3H), 1.00 (d, *J* = 6.7 Hz, H-15, 4H), 0.95 (m, 12H), 0.88-0.92 (m, 12H), 0.80-0.87 (m, 9H), 0.59 (dt, *J* = 8.4, 4.7 Hz, 6H), 0.07 (s, $SiCH_3$, 3H), 0.06 (s, $SiCH_3$, 3H), 0.02 (s, $SiCH_3$, 3H), -0.04 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.5, 159.1, 137.5, 131.3, 131.2, 129.2, 113.8, 81.6, 78.8, 75.9, 74.1, 71.7, 70.5, 55.4, 52.0, 40.2, 38.7, 26.0, 25.9, 18.4, 18.4, 17.5, 17.2, 11.6, 10.4, 10.4, 7.3, 6.1, -4.1, -4.8, -4.9, -5.1.

HRMS (ESI) calculated for $C_{43}H_{82}O_8Si_3Na$ ([*M*+Na]+): 833.5215, found 833.5204
$[\alpha]^{23}_D$ = + 2.2 (*c* 0.85, $CHCl_3$).

6.3.15 Methyl ester **226**



226

$C_{44}H_{84}O_8Si_3$
Mol Wt: 825,4030

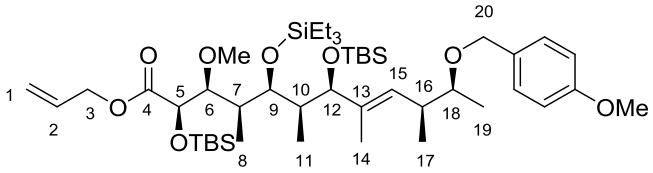
To a stirred solution of trimethyloxonium tetrafluoroborate (1.53 g, 10.89 mmol) in CH_2Cl_2 (21 mL) was added proton sponge (2.32 g, 10.83 mmol). The mixture was cooled to 0 °C and a solution of TBS-ether **225** (560 mg, 0.690 mmol) in CH_2Cl_2 (5 mL) was added slowly. The reaction was protected from light and stirred for 24 h. The mixture was diluted with CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ (3 × 30 mL), dried over $MgSO_4$, filtered and evaporated in *vacuo*. The residue was filtered through a short pad of silica gel with EtOAc and evaporated. Silica gel chromatography (petether-MTBE, 14:1) afforded ester **226** (495 mg, 87%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.18 (dd, *J* = 9.6, 0.9 Hz, H-13, 1H), 4.53 (d, *J* = 11.2 Hz, H-18, 1H), 4.35 (d, *J* = 11.2 Hz, H-18', 1H), 4.28 (d, *J* = 6.6 Hz, H-3, 1H), 3.80 (s, $ArOCH_3$, 3H), 3.79 (d, *J* = 9.0 Hz, H-10, 3H), 3.71 (s, H-1, 3H), 3.46 (d, *J* = 8.7 Hz, H-4, 1H), 3.41 (s, OMe, 1H), 3.34 (dd, *J* = 6.6, 0.8 Hz, H-7, 1H), 3.22 (dq, *J* = 12.2, 6.1 Hz, H-16, 1H), 2.42-2.57 (m, H-14, 1H), 1.83 (dq, *J* = 13.4, 6.6 Hz, H-5, 1H), 1.62-1.68 (m, H-8, 1H), 1.60 (d, *J* = 1.0 Hz, H-12, 3H), 1.16 (d, *J* = 6.1 Hz, H-17, 3H), 1.04 (d, *J* = 6.6 Hz, H-15, 3H), 0.95 (t, *J* = 7.9 Hz, $SiCH_2CH_3$, 9H), 0.90 (s, $SiC(CH_3)_3$, 9H), 0.80-0.89 (m, 15H), 0.61 (qd, *J* = 7.9, 2.9 Hz, $SiCH_2$, 6H), 0.07 (d, *J* = 3.1 Hz, $SiCH_3$, 6H), 0.03 (s, $SiCH_3$, 3H), -0.03 (s, $SiCH_3$, 3H), -0.03 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.6, 159.1, 136.9, 131.9, 131.2, 129.2, 113.8, 82.6, 81.3, 78.8, 75.4, 74.4, 70.6, 60.5, 55.4, 51.8, 39.5, 39.3, 39.0, 26.0, 25.9, 18.4, 18.3, 17.9, 16.9, 11.7, 11.3, 10.1, 7.4, 6.3, -4.1, -4.8, -5.0, -5.0.

HRMS (ESI) calculated for $C_{44}H_{84}O_8Si_3Na$ ([*M*+Na]+): 847.5368, found 847.5368
$[\alpha]^{23}_D$ = +4.64 (*c* 2.5, $CHCl_3$).

6.3.16 Allyl ester **227**



227

$C_{46}H_{86}O_8Si_3$
Mol Wt: 851,4410

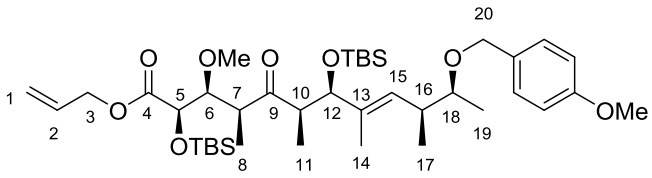
A mixture of methyl ester **226** (220 mg, 0.266 mmol), bis[(dibutyl)chlorotin] oxide (72 mg, 0.13 mmol) and allyl alcohol (5 mL) was heated to 160 °C in a sealed tube under argon for 4 days. The excess allyl alcohol was evaporated and the residue was dissolved in MTBE and filtered through Celite. The solvent was concentrated in *vacuo*, and the crude product was purified by silica gel chromatography (pet ether- MTBE, 15:1) afforded ester **227** (200 mg, 90%) as a colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.92 (ddt, *J* = 16.4, 10.3, 6.0 Hz, H-2, 1H), 5.36 (dq, *J* = 17.2, 1.4 Hz, H-1, 1H), 5.26 (ddd, *J* = 10.4, 2.4, 1.1 Hz, H-1', 1H), 5.18 (dd, *J* = 9.6, 0.9 Hz, H-15, 1H), 4.56-4.66 (m, H-3, 2H), 4.54 (d, *J* = 11.2 Hz, H-20, 1H), 4.35 (d, *J* = 11.2 Hz, H-20', 1H), 4.28 (d, *J* = 6.7 Hz, H-5, 1H), 3.80 (s, $ArOCH_3$, 3H), 3.76-3.80 (m, H-12, 1H), 3.46 (d, *J* = 8.9 Hz, H-6, 1H), 3.41 (s, OMe, 3H), 3.31-3.37 (m, H-9, 1H), 3.23 (dq, *J* = 12.2, 6.1 Hz, H-18, 1H), 2.42-2.57 (m, H-16, 1H), 1.75-1.87 (m, H-7, 1H), 1.65 (dt, *J* = 14.8, 7.6 Hz, H-10, 1H), 1.60 (s, H-12, 3H), 1.16 (d, *J* = 6.1 Hz, H-19, 3H), 1.04 (d, *J* = 6.6 Hz, H-17, 1H), 0.95 (t, *J* = 7.9 Hz, $SiCH_2CH_3$, 9H), 0.90 (s, $SiC(CH_3)_3$, 9H), 0.87 (s, $SiC(CH_3)_3$, 9H), 0.85 (d, *J* = 6.9 Hz, H-8/H-11, 6H), 0.67 – 0.55 (m, $SiCH_2$, 6H), 0.07 (d, *J* = 3.7 Hz, $SiCH_3$, 6H), 0.03 (s, $SiCH_3$, 3H), -0.03 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.8, 159.1, 136.9, 131.9, 131.7, 131.3, 129.2, 119.4, 113.8, 82.7, 81.3, 78.8, 75.7, 74.3, 70.7, 65.7, 60.7, 55.4, 39.5, 39.4, 39.1, 26.0, 25.9, 18.4, 18.0, 16.9, 11.8, 11.4, 10.1, 7.4, 6.3, -4.1, -4.8, -4.9, -5.0.

HRMS (ESI) calculated for $C_{46}H_{86}O_8Si_3Na$ ([*M*+Na]+): 873.5528, found 873.5528
$[\alpha]^{23}_D$ = – 2.0 (*c* 1.0, $CHCl_3$).

6.3.17 Keto ester **228**



228
$C_{40}H_{70}O_8Si_2$
Mol Wt: 735,16

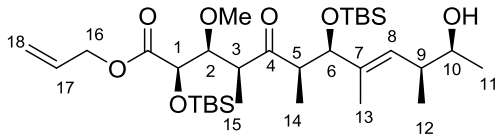
A solution of TES-ether **227** (160 mg, 0.190 mmol) and PPTS (88.4 mg, 0.351 mmol) in THF (1.16 mL) and MeOH (4.68 mL) was stirred at rt for 8 h. The solution was diluted with MTBE (100 mL), washed with H_2O (10 mL), sat. aq. $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in *vacuo*. Without any further purification, the crude product was dissolved in CH_2Cl_2 (1.5 mL). The solution was cooled to 0 °C and pre-dried pyridine (73.3 μL) and a solution of DMP in CH_2Cl_2 (15% w/w, 0.73 mL) was added dropwise. Resulting yellow solution was stirred for additional 30 min. Concentrated in *vacuo* at rt and was directly subjected to column chromatography (pet ether: EtOAc, 20: 1 → 12:1) to afford ketone **25** (100 mg, 72%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.92 (ddt, *J* = 16.4, 10.4, 6.0 Hz, H-2, 1H), 5.35 (dq, *J* = 17.2, 1.4 Hz, H-1, 1H), 5.29-5.22 (m, H-1', 1H), 5.15 (d, *J* = 10.0 Hz, H- 15, 1H), 4.72-4.55 (m, H-3, 2H), 4.52 (d, *J* = 11.2 Hz, H-20, 1H), 4.34 (d, *J* = 11.2 Hz, H-20', 1H), 4.20 (d, *J* = 5.4 Hz, H-5, 1H), 4.16 (d, *J* = 7.9 Hz, H-12, 1H), 3.95 (dd, *J* = 5.4, 2.7 Hz, H-7, 1H), 3.80 (s, $ArOCH_3$, 3H), 3.38 (s, OMe, 3H), 3.17 (dt, *J* = 12.2, 6.1 Hz, H-18, 1H), 2.98 (dq, *J* = 13.9, 6.9 Hz, H-16, 1H), 2.65 (qd, *J* = 7.2, 2.7 Hz, H-7, 1H), 2.29-2.42 (m, H-10, 1H), 1.56 (d, *J* = 1.1 Hz, H-14, 3H), 1.21 (d, *J* = 7.3 Hz, H-19, 3H), 1.14 (d, *J* = 6.9 Hz, H-17, 3H), 1.04 (d, *J* = 6.1 Hz, H-8, 3H), 0.98 (d, *J* = 6.6 Hz, H-11, 3H), 0.91 (s, $SiC(CH_3)_3$, 9H), 0.87 (s, $SiC(CH_3)_3$, 9H), 0.08 (s, $SiCH_3$, 1H), 0.05 (s, $SiCH_3$, 1H), 0.03 (s, $SiCH_3$, 1H), -0.03 (s, $SiCH_3$, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 213.9, 171.4, 159.1, 134.7, 131.8, 131.8, 131.2, 129.3, 119.3, 113.8, 80.1, 79.8, 79.0, 75.5, 70.8, 65.7, 60.3, 55.4, 48.4, 47.8, 39.1, 26.0, 25.9, 18.5, 18.3, 18.0, 16.8, 14.6, 12.0, 10.8, -4.3, -4.8, -4.9, -5.1.

HRMS (ESI) calculated for $C_{40}H_{70}O_8Si_2Na$ ([*M*+Na]+): 757.4507, found 757.4506
$[\alpha]^{23}_D$ = + 9.33 (*c* 0.9, $CHCl_3$).

6.3.18 Alcohol **229**

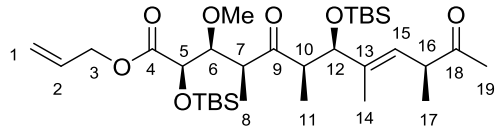


229

$C_{32}H_{62}O_7Si_2$
Mol Wt: 615,01

To a solution of PMB ether **228** (85 mg, 0.115 mmol) in CH_2Cl_2 (1 mL) was added pH7 phosphate buffer (38.3 μl) and DDQ (32.8 mg, 0.144 mmol) at 0 °C. Stirred for additional 30 min, the mixture was diluted with MTBE (80 mL) and washed with sat. aq. $NaHCO_3$ (4 × 15 mL) and brine (25 mL). Organic layer dried over Na_2SO_4, filtered and concentrated in *vacuo*. Crude product purified by column chromatography (pet ether: EtOAc, 12:1 → 5:1) to afford alcohol **229** (70 mg, 98%) as a colorless oil. Crude product was used in next step without any characterization.

6.3.19 Methyl ketone **193**



193

$C_{32}H_{60}O_7Si_2$
Mol Wt: 613,00

A suspension of alcohol **229** (70 mg, 0.113 mmol), NMO (40 mg, 0.314 mmol) and 4 A° molecular sieves (35 mg) in CH_2Cl_2 (1 mL) was stirred at 0 °C for 30 min. TPAP (0.38 mg) was added and warmed to rt, stirred for additional 15 min. Concentrated in *vacuo* and purified by column chromatography (pet ether: EtOAc, 12:1) to afford diketone **193** (56 mg, 80%) as a colorless oil.

^{1}H-NMR (400 MHz, C_6D_6): δ 5.74 (ddt, *J* = 16.3, 10.4, 5.9 Hz, H-2, 1H), 5.37 (d, *J* = 9.7 Hz, H-15, 1H), 5.15 (ddd, *J* = 17.2, 3.0, 1.5 Hz, H-1, 1H), 4.98 (dd, *J* = 10.4, 1.3 Hz, H-1', 1H), 4.43-4.55 (m, H-3/H-5, 3H), 4.41 (d, *J* = 7.4 Hz, H-12, 1H), 4.16 (dd, *J* = 5.7, 3.6 Hz, H-6, 1H), 3.43 (s, OMe, 3H), 3.10 (dq, *J* = 9.6, 6.9 Hz, H-16, 1H), 2.99 (p, *J* = 7.0 Hz, H-10, 1H), 2.90 (qd, *J* = 7.2, 3.6 Hz, H-7, 1H), 1.91 (s, H-19, 3H), 1.60 (d, *J* = 1.2 Hz, H-14, 3H), 1.30 (d, *J* = 7.2 Hz, H-8, 4H), 1.24 (d, *J* = 7.0 Hz, H-11, 3H), 1.03 (s, $SiC(CH_3)_3$, 9H), 1.01 (d, *J* = 6.9 Hz, H-17, 3H), 0.97 (s, $SiC(CH_3)_3$, 9H), 0.21 (s, $SiCH_3$, 3H), 0.16 (s, $SiCH_3$, 3H), 0.10 (s, $SiCH_3$, 3H), 0.00 (s, $SiCH_3$, 3H).

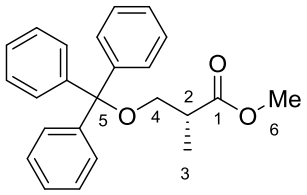
^{13}C-NMR (100 MHz, $CDCl_3$): δ 212.6, 207.2, 171.4, 138.3, 132.2, 118.7, 81.2, 79.2, 75.5, 65.5, 60.3, 49.1, 47.5, 46.9, 27.5, 26.1, 18.7, 18.4, 16.4, 14.0, 12.3, 11.3, -4.3, -4.6, -4.8, -4.8.

HRMS (ESI) calculated for $C_{32}H_{60}O_7Si_2Na$ ([*M*+Na]+): 635.3775, found 635.3772

$[\alpha]^{23}_D$ = + 48.3 (*c* 0.8, $CHCl_3$).

6.4. Aldehyde Fragment C(17-23):

6.4.1 Ester **288**



288
$C_{24}H_{24}O_3$
Mol Wt: 360,45

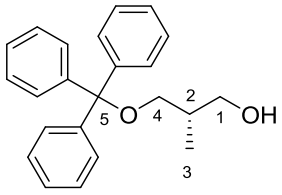
To the Roche ester **181** (8.00 g, 67.72 mmol) in CH_2Cl_2 (130 mL) was added trityl chloride (22.22 g, 101.58 mmol) at room temperature. Triethylamine (15.14 mL, 108.35 mmol) was added dropwise slowly to the reaction mixture, after the addition reaction mixture turned yellow color and the solids precipitated out. Stirring was continued for 16 h at room temperature. Sat. aq. $NaHCO_3$ (130 mL) was added and then stirred for 15 min. Organic layer separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated to yield compound **288** (27.0 g, quantitative) as yellow solid. The crude compound was used directly in the next step without further purification.

^{1}H-NMR (100 MHz, $CDCl_3$): δ 7.46 – 7.56 (m, H_{Ar}, 6H), 7.33-7.42 (m, H_{Ar}, 6H), 7.24-7.35 (m, H_{Ar}, 3H), 3.76 (s, H-6, 3H), 3.39 (dd, *J* = 8.7, 7.0 Hz, H-4, 1H), 3.27 (dd, *J* = 8.7, 5.8 Hz, H-4', 1H), 2.74-2.89 (m, H-2, 1H), 1.22 (d, *J* = 7.1 Hz, H-3, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 175.5, 147.0, 144.0, 128.7, 128.0, 127.9, 127.8, 127.3, 127.0, 86.4, 65.4, 51.7, 40.5, 14.1.

HRMS (ESI) calculated for $C_{21}H_{24}O_3Na$ ([*M*+Na]+): 383.1623, found 383.1621
$[\alpha]^{23}_D$ = − 15.4 (*c* 1.2, $CHCl_3$).

6.4.2 Alcohol **236**



236
$C_{23}H_{24}O_2$
Mol Wt: 332,44

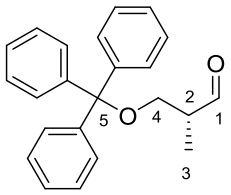
To the $LiAlH_4$ (2.10 g, 55.33 mmol) in THF (50 mL) was added the crude ester **288** (27.0 g, 74.90 mmol) in THF (150 mL) dropwise at room temperature. After the completion of addition, reaction mixture was heated to 40 °C and stirred for 1 h. $LiAlH_4$ (0.74 g, 19.55 mmol) was added in portions to the reaction over a period of 1 h. Stirred for additional 2 h at 40 °C. Reaction mixture cooled to room temperature and quenched carefully with dropwise addition of sat. aq. Na_2SO_4 solution. A thick gel obtained which was diluted with EtOAc (100 mL), filtered over Celite bed and washed with EtOAc (2 × 50 mL). The combined filtrates are concentrated on *vacuo* and the crude compound was purified by silica gel column chromatography (pet ether- ethyl acetate, 4:1) to afford alcohol **236** (20.5 g, 91% over two steps) as white solid.

^{1}H-NMR (100 MHz, $CDCl_3$): δ 7.45-7.53 (m, H_{Ar}, 6H), 7.32-7.42 (m, H_{Ar}, 6H), 7.23-7.32 (m, H_{Ar}, 3H), 3.57-3.74 (m, H-1, 2H), 3.28 (dd, *J* = 9.1, 4.6 Hz, H-4, 1H), 3.09 (dd, *J* = 9.1, 7.7 Hz, H-4', 1H), 2.39 (t, *J* = 5.4 Hz, -OH, 1H), 1.99-2.08 (m, H-2, 1H), 0.91 (d, *J* = 7.0 Hz, H-3, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.0, 128.7, 128.0, 127.2, 87.05, 67.9, 67.6, 36.1, 13.9.

HRMS (ESI) calculated for $C_{23}H_{24}O_2Na$ ([*M*+Na]+): 355.1674, found 355.1673
$[\alpha]^{23}_D$ = − 26.65 (*c* 0.99, $CHCl_3$).

6.4.3 Aldehyde **113**



113
$C_{23}H_{22}O_2$
Mol Wt: 330,43

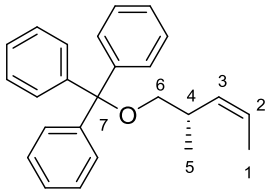
To a solution of Oxalyl chloride (4.28 mL, 45.0 mmol) in CH_2Cl_2 (90 mL) was added dimethyl sulfoxide (4.28 mL, 60.16 mmol) slowly dropwise at −78 °C and stirred for 30 minutes. Alcohol **236** (10.0 g, 30.08 mmol) in CH_2Cl_2 (36 mL) was added dropwise to the reaction mixture at −78 °C and stirred for 1 h. Triethylamine (21.0 mL, 150.40 mmol) was added drop wise to the reaction and warmed to room temperature which resulted in the precipitation of solids. Distilled water (100 mL) was added and stirred for 15 min. Organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 × 30 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound was passed through a pad of silica using EtOAc and the fractions are concentrated to yield the aldehyde **113** (9.30 g, 91%). This compound was used directly in the next step without any characterization.

^{1}H-NMR (100 MHz, $CDCl_3$): δ 9.68 (d, *J* = 1.7 Hz, H-1, 1H), 7.39-7.43 (m, H_{Ar}, 6H), 7.21-7.33 (m, H_{Ar}, 9H), 3.37 (dd, *J* = 9.2, 5.2 Hz, H-4, 1H), 3.33 (dd, *J* = 9.3, 6.5 Hz, H-4', 1H), 2.56-2.65 (m, H-2, 1H), 1.12 (d, *J* = 7.1 Hz, H-3, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 204.3, 143.8, 128.8, 128.0, 127.2, 63.8, 47.2, 11.0.

HRMS (ESI) calculated for $C_{23}H_{22}O_2Na$ ([*M*+Na]+): 353.1517, found 353.1516

6.4.4 Olefin **237**



237
$C_{25}H_{26}O$
Mol Wt: 342,48

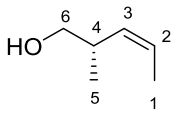
Ethyltriphenylphosphonium bromide (16.52 g, 44.54 mmol) in THF (50 mL) was cooled to −78 °C. To this was added *n*-BuLi (16.70 mL, 2.5*M* in hexanes, 41.76 mmol) slowly drop wise, the solution turned into orange color, after the compete addition cooling bath was removed and stirred for 30 minutes at room temperature. Reaction mixture turned into dark red color and the majority of the solids went into solution. Reaction mixture was again cooled back to −78 °C and the aldehyde **30** (9.20 g, 27.84 mmol) in THF (50 mL) was added quickly drop wise. Cool bath was removed and the reaction stirred at room temperature for 3 h. Distilled water (70 mL) was added to the reaction mixture carefully and stirred for 10 min, organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound purified by silica gel column chromatography (pet ether- EtOAc, 10:1) to afford olefin **237** (7.20 g, 76% over two steps) as a colorless gel.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.50 (dt, *J* = 8.3, 1.8 Hz, H_{Ar}, 6H), 7.31-7.40 (m, H_{Ar}, 6H), 7.21-7.29 (m, H_{Ar}, 3H), 5.45-5.55 (m, H-3, 1H), 5.19-5.29 (m, H-2, 1H), 3.03 (ddd, *J* = 11.6, 8.6, 6.3 Hz, H-6, 1H), 2.93 (ddd, *J* = 11.3, 8.6, 7.0 Hz, H-6', 1H), 2.78-2.90 (m, H-4, 1H), 1.69 (dd, *J* = 6.8, 1.8 Hz, H-1, 3H), 1.05 (d, *J* = 6.6 Hz, H-5, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 144.6, 134.0, 128.9, 127.8, 126.9, 124.1, 86.3, 68.3, 32.5, 18.1, 13.3.

$[\alpha]^{23}_D$ = + 31.63 (*c* 0.99, $CHCl_3$)

6.4.5 Homoallyl alcohol **114**



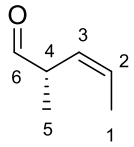
114
$C_6H_{12}O$
Mol Wt: 100,16

To the Olefin **237** (8.50 g, 24.8 mmol) in a mixture of methanol- CH_2Cl_2 (54 mL, 1:2) was added *p*-toluenesulfonicacid monohydrate (0.4 g) and stirred for 16 h at room temperature. Sat. aq. $NaHCO_3$ (50 mL) was added and stirred for 5 min, organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). Combined organic layers are dried over Na_2SO_4, filtered and the solvent was distilled using vigourex column at atmospheric pressure, subsequently the remaining residue was purified by vacuum distillation at 100 °C at 10 m bar. The alcohol **114** was collected using liquid nitrogen cooling bath as colorless liquid (1.60 g, 64%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.40-5.58 (m, H-3, 1H), 5.08 (ddd, *J* = 11.1, 9.5, 1.8 Hz, H-2, 1H), 3.34 (ddd, *J* = 12.1, 7.8, 4.6 Hz, H-6, 1H), 3.28 (dd, *J* = 10.4, 7.6 Hz, H-6', 1H), 2.55-2.68 (m, H-5/OH, 2H), 1.57 (dd, *J* = 6.9, 1.8 Hz, H-1, 3H), 0.87 (d, *J* = 6.7 Hz, H-5, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 133.1, 125.5, 67.4, 34.2, 16.8, 13.0.

6.4.6 Aldehyde **238**

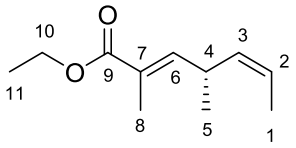


238
$C_6H_{10}O$
Mol Wt: 98,14

To a solution of Oxalyl chloride (2.28 mL, 23.96 mmol) in CH_2Cl_2 (25 mL) was added DMSO (2.26 mL, 31.94 mmol) slowly dropwise at −78 °C and stirred for 30 minutes. Alcohol **237** (1.60 g, 15.97 mmol) in CH_2Cl_2 (20 mL) was added dropwise to the reaction mixture at −78 °C and stirred for 1 h. Triethylamine (11.10 mL, 79.85 mmol) was added drop wise to the reaction and warmed to room temperature which resulted in the precipitation of solids. Distilled water (50 mL) was added and stirred for 10 min. Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 ×

30 mL). Combined organic layers are dried over Na_2SO_4, filtered, taken to next step without concentrating the solvent.

6.4.7 Ester **115**



115
$C_{11}H_{18}O_2$
Mol Wt: 182,26

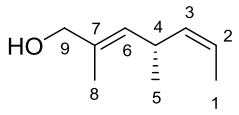
To the aldehyde **238** in dichloromethane from the above step was added Wittig ylide **207** (17.40 g, 48.0 mmol) and stirred for 16 h at room temperature. Solvents removed on vacuo, the residue was passed through a pad of silica using (pet ether- EtOAc, 1:1). Crude compound purified by silica gel column chromatography (pet ether-EtOAc, 15:1) to afford olefin **115** (1.50 g, 33% over three steps) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.58 (dd, *J* = 9.6, 1.4 Hz, H-6, 1H), 5.35-5.51 (m, H-3, 1H), 5.26 (ddd, *J* = 10.7, 9.0, 1.7 Hz, H-2, 1H), 4.16 (q, *J* = 7.1 Hz, H-10, 3H), 3.39-3.58 (m, H-4, 1H), 1.86 (d, *J* = 1.4 Hz, H-8, 3H), 1.63 (dd, *J* = 6.8, 1.7 Hz, H-1, 4H), 1.28 (t, *J* = 7.1 Hz, H-11, 6H), 1.06 (d, *J* = 6.8 Hz, H-5, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 168.6, 145.8, 133.3, 125.9, 123.7, 60.6, 31.6, 20.7, 14.4, 13.1, 12.5.

HRMS (ESI) calculated for $C_{11}H_{18}O_2$ ([*M*]+): 182.1307, found 182.1309
$[\alpha]^{23}_D$ = + 131.63 (*c* 0.99, $CHCl_3$)

6.4.8 Allyl alcohol **289**



289
$C_9H_{16}O$
Mol Wt: 140,23

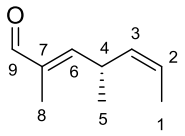
To a stirred solution (−78 °C) of ester **115** (1.10 g, 6.03 mmol) in THF (37 mL) was added DIBAL-H (18.72 mL, 1*M* in CH_2Cl_2, 18.72 mmol) drop wise. Warmed to room temperature and stirred for 90 min. MTBE (40 mL) was added rapidly, dropwise addition of distilled water (2.8 mL) led to the formation of a colorless gel. Upon addition of aq. NaOH (2.8 mL, 4*M*) and additional distilled water (5.2 mL), a white solid precipitated. The resulting suspension was then dried over $MgSO_4$ then filtered and evaporated in *vacuo*. Silica gel chromatography (pet ether-EtOAc, 4:1) afforded the desired alcohol **289** (0.76 g, 90%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.29-5.42 (m, H-2, 1H), 5.20-5.29 (m, H-3/6, 2H), 3.95 (s, 2H), 3.32-3.45 (m, H-4, 1H), 1.68 (d, *J* = 1.4 Hz, H-8, 3H), 1.63 (dd, *J* = 6.7, 1.6 Hz, H-1, 3H), 0.99 (d, *J* = 6.8 Hz, H-5, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 135.4, 133.2, 131.0, 122.2, 69.1, 30.7, 21.7, 14.0, 13.2.

HRMS (ESI) calculated for $C_9H_{16}O$ ([*M*]+): 140.1201, found 140.1201
$[\alpha]^{23}_D$ = + 73.16 (*c* 1.06, $CHCl_3$).

6.4.9 Aldehyde **111**



111
$C_9H_{14}O$
Mol Wt: 138,21

Activated MnO_2 (9.43 g, 108 mmol) was suspended in Et_2O (25 mL) Alcohol **289** (0.76 g, 5.42 mmol) in Et_2O (5 mL) was added at room temperature and stirred for 1 h. The mixture was filtered through a pad of celite, washed with Et_2O (25 mL) and the filtrate evaporated under *vacuo* (50 m bar, 25 °C) to afford aldehyde **37** (0.72 g, 96%) as colorless liquid.

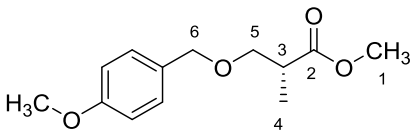
^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.34 (d, *J* = 1.1 Hz, H-9, 1H), 6.22-6.34 (m, H-7, 1H), 5.39-5.52 (m, H-2, 1H), 5.19-5.35 (m, H-3, 1H), 3.54-3.73 (m, H-4, 1H), 1.75 (t, *J* = 1.2 Hz, H-8, 3H), 1.57-1.69 (m, H-1, 3H), 1.11 (dd, *J* = 6.8, 1.0 Hz, H-5, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 195.5, 157.8, 137.0, 132.2, 124.6, 31.7, 20.4, 13.0, 9.2.

HRMS (ESI) calculated for $C_9H_{14}O$ ([*M*]+): 137.0966, found 137.0957
$[\alpha]^{23}_D$ = + 120.35 (*c* 1.2, $CHCl_3$)

6.5 PMB-Ketone Fragment C(13-16):

6.5.1 Ester **290**



290

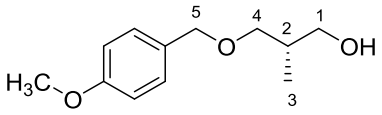
$C_{13}H_{18}O_4$

Mol Wt: 238,28

To the Roche ester **181** (10.0 g, 84.65 mmol) in CH_2Cl_2 (200 mL) was added *p*-methoxybenzyltrichloroacetimiditate (25.65 g, 101.58 mmol) and CSA (0.50 g) at room temperature and stirred for 16 h. Methanol (30 mL) was added and stirred for 1 h, sat. aq. $NaHCO_3$ (30 mL) was added and then the organic layer was separated. Aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). Combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound purified by silica gel column chromatography using (pet ether-EtOAC, 10:1), afforded ester **290** (20.3 g) as a yellow oil.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.22-7.34 (m, H_{ar}, 2H), 6.86-6.99 (m, H_{ar}, 2H), 4.50 (d, H-6, ^2J = 1.8 Hz, 2H), 3.85 (s, H-7, $ArOCH_3$, 3H), 3.73 (s, H-1, 3H), 3.68 (dd, H-5, ^2J = 9.1 Hz, ^3J = 7.3 Hz, 1H), 3.50 (dd, H-5, ^2J = 9.2 Hz, ^3J = 5.9 Hz, 1H), 2.71-2.90 (m, H-3, 1H), 1.21 (d, H-4, ^3J = 7.1 Hz, 3H).

6.5.2 Alcohol **232**



232
$C_{12}H_{18}O_3$
Mol Wt: 210,27

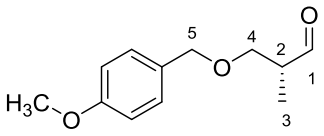
To the $LiAlH_4$ (2.50 g, 66.82 mmol) in THF (150 mL) was added the ester **290** (21.3 g, 89.35 mmol) in THF (70 mL) dropwise at room temperature. After the completion of addition, reaction mixture was heated to 40 °C and stirred for 1 h. $LiAlH_4$ (0.84 g, 22.45 mmol) was added in portions to the reaction over a period of 1 h. Stirring continued for further 2 h at 40 °C, reaction mixture cooled to room temperature and quenched carefully with drop wise addition of sat. aq. Na_2SO_4 solution. A thick gel obtained which was diluted with EtOAc (100 mL), filtered over Celite bed and washed with EtOAc (2 × 50 mL). The combined filtrates are concentrated on *vacuo* and the crude compound was purified by silica gel column chromatography (pet ether-EtOAc, 4:1) to afford compound **232** (11.5 g, 65% over two steps) as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 4.43 (s, H-5, 2H), 3.79 (s, $ArOCH_3$, 3H), 3.53-3.61 (m, H-1, 1H), 3.49 (dd, *J* = 9.1, 4.8 Hz, H-4, 1H), 3.38 (dd, *J* = 9.1, 7.9 Hz, H-1', 1H), 2.83 (s, -OH, 1H), 1.96-2.09 (m, H-2, 1H), 0.86 (d, *J* = 7.0 Hz, H-3, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.3, 130.2, 129.3, 113.9, 75.0, 73.0, 67.6, 55.3, 35.6, 13.6.

HRMS (ESI) calculated for $C_{12}H_{18}O_3Na$ ([*M*+Na]+): 233.1154, found 233.1154
$[\alpha]^{23}_D$ = − 8.28 (*c* 0.98, $CHCl_3$).

6.5.3 Aldehyde **132**

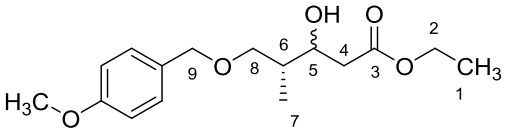


132

$C_{12}H_{16}O_3$
Mol Wt: 208,26

To a solution of oxalyl chloride (1.36 mL, 14.26 mmol) in CH_2Cl_2 (30 mL) was added DMSO (1.35 mL, 19.02 mmol) slowly drop wise at −78 °C and stirred for 30 minutes. Alcohol **232** (2.00 g, 9.51 mmol) in CH_2Cl_2 (20 mL) was added drop wise to the reaction mixture at −78 °C and stirred for 1 h. Triethylamine (6.64 mL, 47.55 mmol) was added drop wise to the reaction and warmed to room temperature which resulted in the precipitation of solids. Distilled water (40 mL) was added and stirred for 10 min. Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated in vacuo, crude compound was passed through a pad of silica using EtOAc and the fractions are concentrated to yield the aldehyde **132** (1.90 g, 95%). This compound was used directly in the next step without any characterization.

6.5.4 α-Hydroxy ester **233**



233

$C_{16}H_{24}O_5$
Mol Wt: 296,36

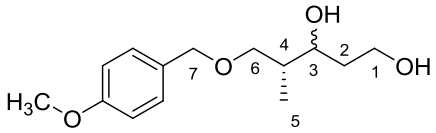
To EtOAc (1.80 mL, 18.24 mmol) in THF (42 mL) was added lithium hexamethyldisilylazide (18.42 mL, 1*M* in THF/ethylbenzene, 18. 24 mmol) dropwise at −78 °C. Stirred for 40 min at this temp and aldehyde **132** (1.90 g, 9.12 mmol) in THF (10 mL) was added dropwise and stirred for 20 min. Sat. aq. NH_4Cl (20 mL) was added and warmed to room temperature, distilled water (20 mL) was added and the organic layer separated, aqueous layer extracted with EtOAc (3 × 10 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated on *vacuo*, crude compound was purified by silica gel column chromatography (pet ether-EtOAc, 4:1) to afford compound **233** (2.20 g, 81%) as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19-7.26 (m, H_{Ar}, 2H), 6.80-6.90 (m, H_{Ar}, 2H), 4.42 (s, H-9, 1H), 4.09-4.23 (m, H-2/H-5, 3H), 3.80 (s, $ArOCH_3$, 3H), 3.30-3.40 (m, H-8, 2H), 2.33-2.62 (m, H-4, 1H), 1.82-1.98 (m, H-6, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, H-7, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.9, 172.8, 159.3, 159.2, 130.2, 130.1, 129.3, 129.3, 113.8, 73.4, 73.3, 73.0, 73.0, 71.8, 69.9, 60.6, 55.3, 39.7, 39.1, 38.4, 38.0, 14.2, 13.7, 11.3.

HRMS (ESI) calculated for $C_{16}H_{24}O_5Na$ ([*M*+Na]+): 319.1521, found 319.1520

6.5.5 Diol **234**



234

$C_{14}H_{22}O_4$

Mol Wt: 254,33

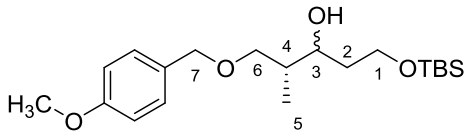
To a stirred solution (−78 °C) of ester **233** (2.10 g, 7.08 mmol) in CH_2Cl_2 (200 mL) was added DIBAL-H (22.0 mL, 1*M* in CH_2Cl_2, 22.0 mmol) dropwise. Warmed to room temperature and stirred for 90 min. MTBE (40 mL) was added rapidly, drop wise addition of distilled water (2 mL) led to the formation of a colorless gel. Upon addition of aq. NaOH (2 mL, 4*N*) and additional distilled water (4.0 mL), a white solid precipitated. The resulting suspension was then dried over $MgSO_4$ then filtered and evaporated in *vacuo*. Silica gel chromatography (pet ether-EtOAc, 1:1) afforded the diol **234** (1.60 g, 88%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.10-7.23 (m, H_{Ar}, 2H), 6.77 (d, *J* = 8.3 Hz, H_{Ar}, 2H), 4.33 (d, *J* = 5.0 Hz, H-7, 2H), 3.62-3.75 (m, $ArOCH_3$/H-3/H-1, 6H), 3.46 (dt, *J* = 28.9, 2.8 Hz, H-6, 1H), 3.27-3.39 (m, H-6', 1H), 1.72-1.95 (m, H-4, 1H), 1.71-1.36 (m, H-2, 2H), 0.78 (dd, *J* = 26.4, 7.0 Hz, H-5, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.4, 130.0, 129.7, 129.5, 129.4, 127.0, 114.0, 114.0, 113.9, 77.4, 75.2, 74.9, 74.2, 73.9, 73.3, 73.2, 62.2, 61.8, 61.5, 55.4, 40.6, 38.6, 38.4, 36.1, 35.1, 13.7, 11.5.

HRMS (ESI) calculated for $C1_4H_{22}O_4Na$ ([*M*+Na]+): 277.1416, found 277.1418

6.5.6 Alcohol **235**



235

$C_{20}H_{36}O_4Si$
Mol Wt: 368,59

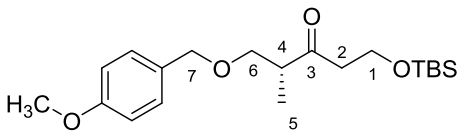
To the diol **234** (1.50 g, 5.89 mmol) in CH_2Cl_2 (30 mL) was added imidazole (0.60 g, 8.83 mmol) and TBSCl (0.97 g, 6.48 mmol) at 0 °C. White solids precipitated out, reaction stirred for 15 min. Distilled water (30 mL) was added, organic layer separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated in *vacuo*, crude compound was purified by silica gel column chromatography (pet ether-EtOAc, 5:1) to afford compound **235** (1.80 g, 88%) as yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.3 Hz, H_{Ar}, 2H), 6.87 (d, *J* = 8.6 Hz, H_{Ar}, 2H), 3.76-3.96 (m, H-3/H-1, 3H), 3.79 (s, $ArOCH_3$, 3H), 3.37-3.57 (m, H-6, 2H), 1.79-1.92 (m, H-4, 1H), 1.51-1.77 (m, H-2, 2H), 0.93 (dd, *J* = 7.0, 3.7 Hz, H-5, 2H), 0.90 (s, $SiC(CH_3)_3$, 9H), 0.07 (s, $SiCH_3$, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.3, 159.25, 130.6, 130.5, 129.31, 129.3, 113.9, 74.3, 73.7, 73.03, 73.01, 72.7, 62.5, 62.2, 55.4, 39.0, 38.8, 36.5, 36.3, 26.0, 18.3, 13.9, 11.5, -5.32, -5.31.

HRMS (ESI) calculated for $C_{20}H_{36}O_4SiNa$ ([*M*+Na]+): 391.2281, found 391.2282

6.5.7 Ketone **138**



138
$C_{20}H_{34}O_4Si$
Mol Wt: 366,57

To a solution of oxalyl chloride (0.69 mL, 7.35 mmol) in CH_2Cl_2 (15 mL) was added DMSO (0.69 mL, 9.76 mmol) slowly dropwise at −78 °C and stirred for 30 minutes. Alcohol **235** (1.80 g, 4.83 mmol) in CH_2Cl_2 (20 mL) was added drop wise to the reaction mixture at −78 °C and stirred for 1 h. Triethylamine (3.41 mL, 24.41 mmol) was added drop wise to the reaction and warmed to room temperature which resulted in the precipitation of solids. Distilled water (30 mL) was added and stirred for 15 min. Organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). Combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*, crude compound was crude compound was purified by silica gel column chromatography (pet ether- EtOAc, 6:1) to afford compound **138** (1.44 g, 80%) as yellow oil.

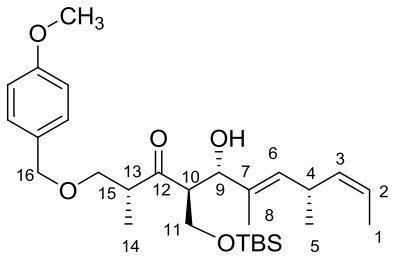
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.13 (d, *J* = 8.6 Hz, H_{Ar}, 2H), 6.77 (d, *J* = 8.6 Hz, H_{Ar}, 1H), 4.32 (d, *J* = 3.9 Hz, H-7, 2H), 3.79 (td, *J* = 6.4, 2.5 Hz, H-1, 2H), 3.70 (s, $ArOCH_3$, 3H), 3.51 (dd, *J* = 9.1, 7.5 Hz, H-6, 1H), 3.34 (dd, *J* = 9.2, 5.7 Hz, H-6', 1H), 2.78 (td, *J* = 7.2, 5.8 Hz, H-4, 1H), 2.60 (td, *J* = 6.4, 3.7 Hz, H-2, 1H), 0.98 (d, *J* = 7.1 Hz, H-5, 3H), 0.78 (s, $SiC(CH_3)_3$, 9H), -0.05 (s, $SiCH_3$, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 211.8, 159.3, 130.3, 129.3, 128.4, 113.8, 73.0, 71.8, 58.7, 55.4, 47.1, 44.9, 26.0, 18.3, 13.2, -5.3.

HRMS (ESI) calculated for $C_{20}H_{34}O_4SiNa$ ([*M*+Na]+): 389.2124, found 389.2126
$[\alpha]^{23}_D$ = − 3.94 (*c* 1.15, $CHCl_3$)

6.6 Aldehyde C(13-23)

6.6.1 Paterson aldol product **239**



239
$C_{29}H_{48}O_5Si$
Mol Wt: 504,78

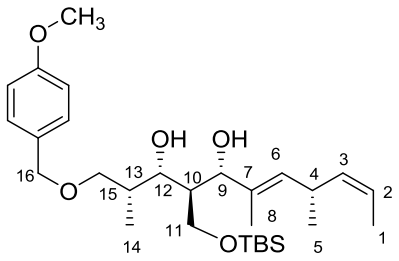
To a solution of dicyclohexylboron monochloride (1*M* in Et_2O, 2.74 mL, 2.74 mmol) in Et_2O (5.6 mL) at −78 °C was added triethylamine (0.43 mL, 3.03 mmol) over a period of 15 min and stirred for another 20 min at this temperature. Ketone **138** (690 mg, 1.88 mmol) in Et_2O (3 mL) was added dropwise over a period of 15 min at −78 °C and stirred for another 30 minutes at this temperature, Warmed to 0 °C and stored at this temperature for 16 h. Aldehyde **111** (200 mg, 1.44 mmol) was added dropwise over a period of 15 minutes at −78 °C and stirred for another 30 minutes. Quenched with methanol (2 mL) and H_2O (2 mL) and warmed to room temperature, organic layer separated and the aqueous layer was extracted with MTBE (4 x 5 mL). Organic layers are dried over Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound was purified by column chromatography (pet ether: EtOAc, 4:1) to obtain aldol product **239** (690 mg, 70%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.7 Hz, H_{Ar}, 1H), 6.86 (d, *J* = 8.7 Hz, H_{Ar}, 1H), 5.32 (dqd, *J* = 9.2, 6.7, 0.7 Hz, H-3, 1H), 5.24 (dd, *J* = 6.1, 2.9 Hz, H-6, 1H), 5.15-5.22 (m, H-2, 1H), 4.44 (d, *J* = 11.7 Hz, H-16, 1H), 4.40 (d, *J* = 11.7 Hz, H-16', 1H), 4.20 (dd, *J* = 7.9, 4.7 Hz, H-9, 1H), 3.80 (s, $ArOCH_3$, 3H), 3.70 (dd, *J* = 6.1, 2.9 Hz, H-15, 1H), 3.67 (dd, *J* = 6.1, 4.0 Hz, H-11, 1H), 3.53 (dd, *J* = 10.1, 5.1 Hz, H-11', 1H), 3.36-3.42 (m, H-4, 1H), 3.35 (dd, *J* = 7.5, 4.8 Hz, H-15', 1H), 3.04-3.17 (m, H-10/OH, 2H), 3.00 (d, *J* = 4.9 Hz, H-13, 1H), 1.66 (d, *J* = 1.3 Hz, H-8, 3H), 1.63 (dd, *J* = 6.7, 1.7 Hz, H-1, 3H), 1.08 (d, *J* = 7.0 Hz, H-5, 3H), 1.00 (d, *J* = 6.7 Hz, H-4, 3H), 0.84 (s, $Si(CH_3)_3$, 9H), -0.02 (s, $SiCH_3$, 3H), -0.03 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 215.9, 159.4, 134.9, 132.9, 132.8, 129.9, 129.5, 121.9, 113.9, 75.9, 73.0, 71.6, 62.6, 57.3, 55.4, 46.7, 30.5, 25.9, 21.4, 18.3, 13.5, 13.1, 11.7, -5.4, -5.5.

HRMS (ESI) calculated for $C_{29}H_{48}O_5NaSi$ ([*M*+Na]+): 527.3169, found 527.3172
$[\alpha]^{23}_D$ = + 21.17 (*c* =1.7 in $CHCl_3$).

6.6.2 Diol **240**



240
$C_{29}H_{50}O_5Si$
Mol Wt: 506,80

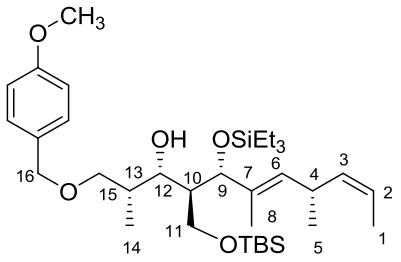
To the compound **239** (50 mg, 0.09 mmol) in THF (2.5 mL) was added DIBAL-H dropwise at −78 °C, stirred for another 2 h. Sat. aq. sodium potassium tartarate (1.5 mL) was added dropwise, warmed to room temperature slowly, extracted with MTBE (3 x 4 mL), dried over Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound purified by silica gel column chromatography (pet ether: EtOAc, 5:1) to obtain diol **240** (45 mg, 90%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.6 Hz, H_{Ar}, 1H), 6.88 (d, *J* = 8.7 Hz, H_{Ar}, 1H), 5.30 (dt, *J* = 13.5, 5.4 Hz, H-3/6, 2H), 5.20 (ddd, *J* = 10.8, 9.3, 1.6 Hz, H-2, 1H), 4.47 (d, *J* = 11.6 Hz, H-16, 1H), 4.42 (d, *J* = 11.6 Hz, H-16', 1H), 4.29 (d, *J* = 9.6 Hz, H-9/OH, 2H), 4.23 (dd, *J* = 8.2, 1.9 Hz, H-12, 1H), 3.81 (s, $ArOCH_3$, 3H), 3.74 (bs, OH, 1H), 3.58 (dd, *J* = 9.0, 4.1 Hz, H-11, 1H), 3.51-3.56 (m, H-11', 1H), 3.48 (dd, *J* = 10.4, 3.2 Hz, H-15, 1H), 3.40 (d, *J* = 8.9 Hz, H-15', 1H), 3.35-3.39 (m, H-4, 1H), 2.02-2.13 (m, H-13, 1H), 1.72-1.81 (m, H-10, 1H), 1.62-1.71 (m, H-1/6, 6H), 1.03 (d, *J* = 1.5 Hz, H-5, 3H), 1.01 (d, *J* = 1.2 Hz, H-14, 3H), 0.84 (s, $Si(CH_3)_3$, 9H), -0.04 (s, $SiCH_3$, 3H), -0.04 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.4, 135.4, 134.2, 133.4, 130.2, 129.3, 121.6, 113.9, 80.0, 76.6, 75.8, 73.3, 62.0, 55.4, 44.7, 35.5, 30.6, 25.9, 21.5, 18.2, 13.1, 11.3, 10.7, -5.4, -5.7.

HRMS (ESI) calculated for $C_{29}H_{50}O_5NaSi$ ([*M*+Na]+): 529.3325, found 529.3326
$[\alpha]^{23}_D$ = + 19.5 (*c* =0.8 in $CHCl_3$).

6.6.3 TES-ether **243**



243
$C_{35}H_{64}O_5Si_2$
Mol Wt: 621,0620

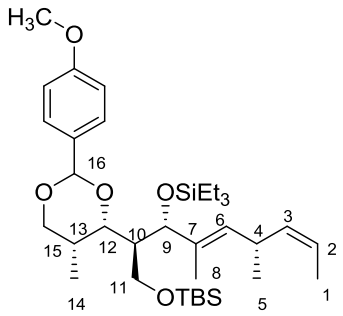
To diol **240** (200 mg, 0.394 mmol) in CH_2Cl_2 (2 mL), was added 2,6-lutidine (136 μL, 1.168 mmol), DMAP (4.8 mg) and TESCl (81 μL, 0.478 mmol) at −78 °C, stirred for 2 h at this temp and additionally 1 h at 0 °C. Quenched with sat. aq. $NaHCO_3$ (20 mL), diluted with Et_2O (20 mL) and warmed to room temperature, stirred for 5 min, organic layer separated, aqueous layer extracted with Et_2O (2 × 10 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound purified by silica gel column chromatography (pet ether-EtOAc, 12:1) to afford compound **243** (190 mg, 80%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.6 Hz, H_{Ar}, 1H), 6.85 (d, *J* = 8.7 Hz, H_{Ar},1H), 5.33 (ddt, *J* = 12.8, 10.8, 6.4 Hz, H-6, 1H), 5.17-5.25 (m, H-2/3, 2H), 4.47-4.42 (m, H-16/16'/9, 3H), 4.23 (s, -OH, 1H), 4.03 (d, *J* = 8.3 Hz, H-12, 1H), 3.80 (s, $ArOCH_3$, 3H), 3.54-3.57 (m, H-15, 1H), 3.51-3.53 (m, H-11, 1H), 3.38-3.45 (m, H-15, 1H), 3.35-3.38 (m, H-4, 1H), 3.32 (dd, *J* = 10.3, 2.7 Hz, H-11, 1H), 2.05-2.19 (m, H-13, 1H), 1.58-1.68 (m, H-10/1/8, 7H), 1.02 (d, *J* = 6.7 Hz, H-5, 3H), 0.95 (t, *J* = 7.9 Hz, $SiCH_2CH_3$, 9H), 0.93 (d, *J* = 1.8 Hz, H-14, 3H), 0.86 (s, $Si(CH_3)_3$, 9H), 0.56 – 0. 96 (m, SiCH2, 6H), -0.03 (s, $SiCH_3$, 3H), -0.02 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 158.9, 134.9, 134.0, 133.3, 129.0, 122.1, 113.7, 81.4, 74.3, 72.6, 72.0, 60.5, 55.4, 45.6, 35.4, 30.5, 25.9, 21.0, 18.1, 13.1, 11.3, 10.5, 6.9, 4.9, -5.4, -5.6.

HRMS (ESI) calculated for $C_{35}H_{64}O_5NaSi_2$ ([*M*+Na]+): 643.4190, found 643.4187
$[\alpha]^{23}_D$ = + 15.0 (*c* =1.9 in $CHCl_3$).

6.6.4 PMP acetal **244**



244

$C_{35}H_{62}O_5Si_2$
Mol Wt: 619,0460

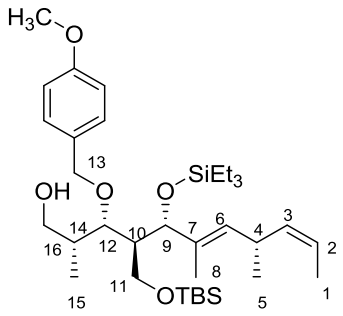
Molecular sieves 4Å (160 mg, powdered and dried) was added to a solution of compound **243** (56 mg, 0.090 mmol) in CH_2Cl_2 (3.5 mL), stirred for 30 min at room temperature. Cooled to −5 °C, DDQ (30.6 mg) was added in one portion, stirred for 45 min at this temp and quenched with sat. aq. $NaHCO_3$ (50 mL), diluted with Et_2O (50 mL) and warmed to room temperature, aqueous layer separated, organic layer was washed with sat. aq. $NaHCO_3$ until the organic layer was colorless. Dried over Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound purified by silica gel column chromatography (pet ether: EtOAc, 20:1) to afford compound **244** (46 mg, 84%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, H_{Ar}, 1H), 6.89 (d, *J* = 8.8 Hz, H_{Ar}, 1H), 5.32-5.40 (m, H-3, 1H), 5.31 (s, H-16, 1H), 5.18 (ddd, *J* = 10.6, 6.2, 1.6 Hz, H-2, 1H), 5.11 (d, *J* = 9.2 Hz, H-6, 1H), 4.50 (d, *J* = 4.4 Hz, H-9, 1H), 3.90-4.03 (m, H-12/15/11, 3H), 3.82 (s, $ArOCH_3$, 1H), 3.68 (dd, *J* = 10.3, 1.9 Hz, H-15', 1H), 3.49 (dd, *J* = 10.1, 6.7 Hz, H-11', 1H), 3.28-3.39 (m, H-4, 1H), 2.06 (ddt, *J* = 8.2, 6.4, 4.1 Hz, H-10, 1H), 1.77 (dt, *J* = 8.6, 5.9 Hz, H-13, 1H), 1.65 (dd, *J* = 6.8, 1.7 Hz, H-1, 3H), 1.57 (d, *J* = 1.2 Hz, H-8, 3H), 1.24 (d, *J* = 6.8 Hz, H-14, 3H), 0.92 (t, *J* = 7.9 Hz, $SiCH_2CH_3$, 9H), 0.91 (d, *J* = 1.6 Hz, H-5, 3H), 0.88 (s, $SI(CH_3)_3$, 9H), 0.54 (dt, *J* = 7.9, 6.0 Hz, $SiCH_2$, 6H), 0.04 (d, *J* = 1.5 Hz, $SiCH_3$, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.8, 135.8, 133.0, 132.1, 131.5, 127.5, 121.8, 80.6, 74.5, 74.4, 59.7, 55.4, 49.5, 31.2, 30.4, 26.1, 21.2, 18.3, 13.3, 12.8, 12.3, 7.0, 4.9, -5.4,-5.4.

HRMS (ESI) calculated for $C_{35}H_{62}O_5NaSi_2$ ([*M*+Na]+): 641.4034, found 641.4030
$[\alpha]^{23}_D$ = + 23.29 (*c* =0.85 in $CHCl_3$).

6.6.5 Alcohol **245**



245

$C_{35}H_{64}O_5Si_2$

Mol Wt: 621,0620

DIBAL-H (1 mL, 1*M* in CH_2Cl_2) was added dropwise to a solution of benzylidene acetal **244** (160 mg, 0.258) in CH_2Cl_2 (5.5mL) at −78 °C. The reaction mixture was stirred for 3 h at this temperature and quenched with EtOAc (1.2 mL), warmed to room temperature. Diluted with Rochelle's salt (60 mL) and MTBE (60 mL) and the biphasic mixture was stirred for 1 h. Organic layer separated and the aqueous layer extracted with MTBE (2 × 15 mL). Combined organic layers are dried over Na_2SO_4, filtered and concentrated under *vacuo*. Crude compound purified by silica gel column chromatography (pet ether: EtOAc, 10:1) to afford alcohol **245** (120 mg, 75%) as a colorless oil.

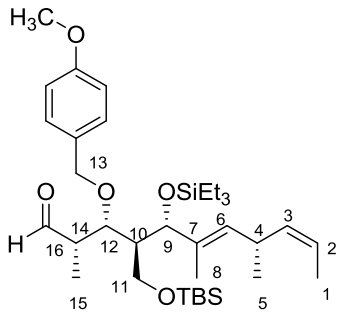
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.7 Hz, H_{Ar}, 1H), 6.87 (d, *J* = 8.7 Hz, H_{Ar}, 1H), 5.28-5.39 (m, H-2, 1H), 5.16-5.23 (m, H-6, 1H), 5.12-5.16 (m, H-3, 1H), 4.56 (d, *J* = 11.2 Hz, H-13, 1H), 4.48 (d, *J* = 11.3 Hz, H-13', 1H), 4.30 (d, *J* = 8.0 Hz, H-9, 1H), 3.81 (d, *J* = 1.2 Hz, $ArOCH_3$, 3H), 3.71 (dd, *J* = 7.2, 2.0 Hz, H-12, 1H), 3.58 (dt, *J* = 10.8, 3.7 Hz, H-11, 1H), 3.37-3.48 (m, H-11'/H-4, , 1H), 3.35 (d, *J* = 7.1 Hz, H-16, 1H), 3.05 (bs,-OH, H), 2.17-2.31 (m, H-10/H-14, 2H), 1.64 (dd, *J* = 6.7, 1.7 Hz, H-1, 3H), 1.62 (d, *J* = 1.1 Hz, H-8, 3H), 1.00 (d, *J* = 6.7 Hz, H-5, 3H), 0.98 (d, *J* = 6.9 Hz, H-15, 3H), 0.92 (t, *J* = 6.2 Hz, $SiCH_2CH_3$, 9H), 0.89 (s, $(SiCH_3)_3$, 9H), 0.01 (s, $SiCH_3$, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 159.0, 135.0, 134.0, 132.0, 131.7, 128.9, 121.8, 113.7, 80.6, 76.9, 73.7, 66.9, 61.0, 55.4, 46.1, 39.5, 30.5, 26.1, 21.1, 18.3, 15.3, 13.2, 11.9, 7.0, 5.0, -5.2.

HRMS (ESI) calculated for $C_{35}H_{64}O_5Si_2Na$ ([*M*+Na]+): 643.4190, found 643.4191

$[\alpha]^{23}_D$ = + 21.2 (*c* =1.0 in $CHCl_3$).

6.6.6 Aldehyde **246**



246

$C_{35}H_{62}O_5Si_2$
Mol Wt: 619,0460

To the alcohol **245** (26 mg, 0.0418 mmol) in CH_2Cl_2 (1 mL) was added $NaHCO_3$ (10.7 mg, 0.128 mmol) and DMP (27 mg, 0.0643 mmol) at rt. Reaction mixture was stirred for 1 h at room temperature. Diluted with Et_2O (15 mL) and sat. aq. $NaHCO_3$ (1.5 mL), washed with sat. aq. $Na_2S_2O_3$ (3 × 5 mL). Organic layer dried over Na_2SO_4, filtered and concentrated in vacuo. Crude compound purified by silica gel column chromatography (pet ether: EtOAc, 10:1) to afford aldehyde **246** (24 mg, 98%) as a colorless oil.

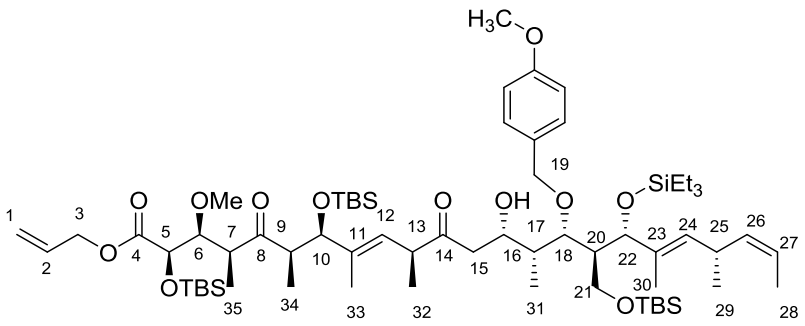
^{1}H-NMR (400 MHz, C_6D_6): δ 9.74 (d, *J* = 0.9 Hz, H-16, 1H), 7.26 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.81 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.22-5.48 (m, H-2/3/5, 3H), 4.58 (d, *J* = 5.5 Hz, H-9, 1H), 4.49 (d, *J* = 11.2 Hz, H-13, 1H), 4.43 (d, *J* = 11.1 Hz, H-13', 1H), 4.33 (t, *J* = 4.3 Hz, H-12, 1H), 3.86 (dd, *J* = 10.0, 6.8 Hz, H-11, 1H), 3.79 (dd, *J* = 10.1, 6.1 Hz, H-11', 1H), 3.35-3.48 (m, H-4, 1H), 3.29 (s, $ArOCH_3$, 3H), 3.17-3.26 (m, H-14, 1H), 2.31 (td, *J* = 10.6, 6.1 Hz, H-10, 1H), 1.64 (d, *J* = 1.2 Hz, H-8, 3H), 1.59 (dd, *J* = 6.4, 1.3 Hz, H-1, 3H), 1.00-1.05 (m, H-5/$SiCH_2CH_3$, 12H), 1.00 (s, ($SiCH_3$)3, 9H), 0.67 (dt, *J* = 8.4, 4.1 Hz, $SiCH_2$, 6H), 0.11 (d, *J* = 2.8 Hz, $SiCH_3$, 6H).

^{13}C-NMR (100 MHz, C_6D_6): δ 203.3, 159.8, 135.5, 133.9, 131.7, 131.1, 122.1, 114.1, 75.8, 75.6, 72.6, 60.5, 54.8, 50.2, 48.3, 30.8, 26.2, 21.4, 18.4, 13.2, 13.1, 10.0, 7.3, 5.3, -5.0, -5.1.

HRMS (ESI) calculated for $C_{35}H_{62}O_5Si_2Na$ ([*M*+Na]+): 641.4034, found 641.4031
$[\alpha]^{23}_D$ = + 16.0 (*c* =1.1 in $CHCl_3$).

6.7. Coupling of Fragments

6.7.1 Aldol product **247**



247

$C_{67}H_{122}O_{12}Si_4$
Mol Wt: 1232,0410

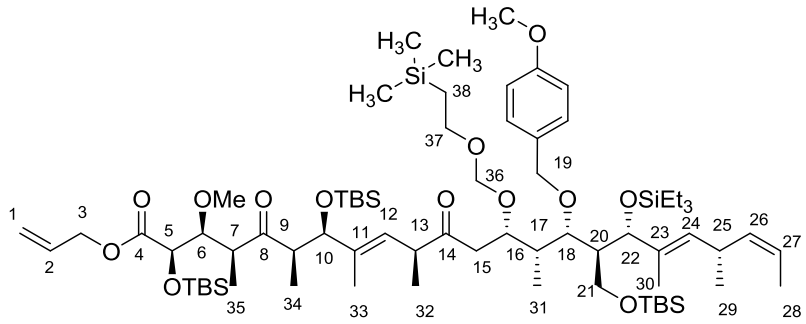
To the ketone **193** (0.143 g, 0.233 mmol) in THF (2 mL) at –78 °C was added LiHMDS (0.3 mL, 1*M* in THF, 0.298 mmol) dropwise over 5 min and the reaction mixture was stirred at –78 °C for 30 min. A solution of aldehyde **246** (0.130 g, 0.209 mmol) in pre-cooled THF (1.5 mL) to –78 °C was added dropwise over 5 min and the reaction mixture was stirred at –78 °C for 20 min. The cold mixture was quenched with pH7 buffer (2 mL) and warmed to room temperature, extracted with MTBE (50 mL), the aqueous layer was extracted with MTBE (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford 0.330 g of colorless oil. Column chromatography on 25 g silica gel (gradient elution with 5–10% EtOAc-hexanes) provided 0.210 g (77%) of aldol adducts with 2.5:1 Felkin selectivity and ketone as colorless oil. Felkin aldol **247** was separated as colorless oil (84 mg, 30%) after preparative HPLC (elution with 7% EtOAc-heptanes, detection via UV absorption at 220 nm). Both the starting materials Ketone (55 mg) and Aldehyde (40 mg) are recovered purely without epimerisation.

^{1}H-NMR (400 MHz, C_6D_6): δ 7.38 (d, *J* = 8.5 Hz, H_{Ar}, 1H), 6.85 (d, *J* = 8.5 Hz, H_{Ar}, 1H), 5.77 (dq, *J* = 10.6, 5.8 Hz, H-2, 1H), 5.59 (d, *J* = 9.7 Hz, H-12, 1H), 5.27-5.45 (m, H-24/26/27, 3H), 5.18 (dd, *J* = 17.2, 1.3 Hz, H-1, 1H), 5.00 (d, *J* = 10.4 Hz, H-1', 1H), 4.59-4.78 (m, H-19/19'/22, 3H), 4.45-4.60 (m, H-18/3/12/12'/5, 5H), 4.21 (dd, *J* = 6.1, 1.8 Hz, H-16, 1H), 4.17 (dd, *J* = 5.6, 4.5 Hz, H-6, 1H), 3.65-3.73 (m, H-21/21', 2H), 3.56 (bs, -OH, 1H), 3.39-3.48 (m, H-25/$ArOCH_3$, 4H), 3.28-3.37 (m, H-13/OCH_3, 4H), 3.02-3.11 (m, H-7, 1H), 2.95-3.02 (m, H-9, 1H), 2.88-2.95 (m, H-17, 1H), 2.44-2.59 (m, H-15/15'/20, 3H), 1.72 (s, H-30, 3H), 1.66 (s, H-33, 3H), 1.60 (d, *J* = 5.4 Hz, H-28, 1H), 1.25-1.35 (m, H-31/35/34, 9H), 1.18 (d, *J* = 6.8 Hz, H-32, 3H), 0.94-1.13 (m, H-29/$SiCH_2CH_3$, $(SiCH_3)_3$, 36H), 0.75 (q, *J* = 8.0 Hz, $SiCH_2$, 6H), 0.06-0.21 (m, $SiCH_3$, 18H).

^{13}C-NMR (100 MHz, C_6D_6): δ 212.0, 210.3, 171.2, 159.5, 138.0, 135.2, 134.4, 132.0, 131.7, 131.5, 129.4, 127.1, 121.6, 118.4, 113.8, 81.4, 80.2, 78.0, 76.9, 75.0, 73.3, 69.6, 65.3, 61.5, 59.9, 54.5, 49.1, 46.5, 46.3, 46.2, 45.7, 41.1, 30.6, 26.0, 25.9, 25.9, 21.0, 18.4, 18.3, 18.2, 16.3, 12.9, 12.9, 12.8 , 12.3, 11.3, 10.3, 7.1, 5.2, -4.4, -4.9, -5.0, -5.0, -5.3, -5.4.

HRMS (ESI) calculated for $C_{67}H_{122}O_{12}Si_4Na$ ([*M*+Na]+): 1253.7911, found 1253.7910
[α]$^{23}_D$ = + 55.9 (*c* =1.0 in $CHCl_3$).

6.7.2 SEM-ether **248**



248

$C_{73}H_{136}O_{13}Si_5$
Mol Wt: 1362,3030

To the Alcohol **247** (0.080 g, 0.0324 mmol) in 3 mL of THF at 0 °C was added DIPEA (0.225 mL, 1.296 mmol) and SEMCl (0.116 mL, 0.6493 mmol) dropwise and the reaction mixture was stirred at 0 °C for 30min. Tetrabutylammonium iodide (0.013 mg, 0.0356 mmol) was added in one portion and heated at 50 °C for 3 days in a sealed tube in the absence of light. Reaction mixture was cooled to room temperature and diluted with MTBE (30 mL) washed with sat. aq. $NaHCO_3$ solution (15 ml), aqueous layer was extracted with MTBE (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude compound purified by column chromatography on silica gel (gradient elution with 3–10% EtOAc-pet ether) provided Compound **248** (78 mg, 90%) as colorless oil.

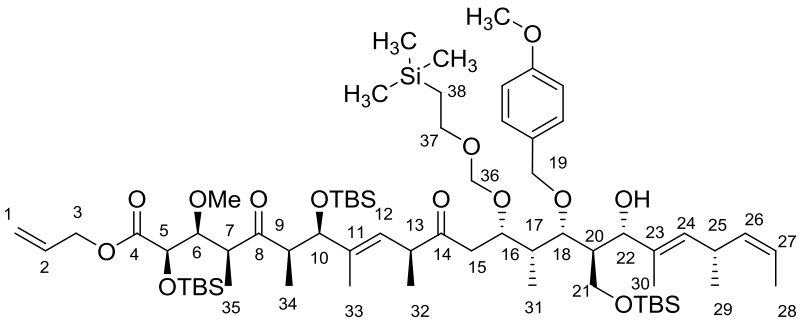
^{1}H-NMR (400 MHz, C_6D_6): δ 7.45 (d, *J* = 8.5 Hz, H_{Ar}, 1H), 6.89 (d, *J* = 8.5 Hz, $H_{Ar,}$ 1H), 5.72-5.90 (m, H-2, 1H), 5.68 (d, *J* = 9.7 Hz, H-12, 1H), 5.30-5.48 (m, H-24/26/27, 3H), 5.18 (dd, *J* = 17.2, 1.3 Hz, H-1, 1H), 5.10 (d, *J* = 6.5 Hz, H-36, 1H), 5.01 (dd, *J* = 12.7, 3.6 Hz, H-36'/1', 2H), 4.78 (d, *J* = 10.8 Hz, H-19/19', 1H), 4.41-4.65 (m, H-5/10/18/22/3/3', 6H), 4.17 (d, *J* = 6.5 Hz, H-16, 1H), 4.13 (dd, *J* = 5.7, 4.4 Hz, H-6, 1H), 3.92-4.02 (m, H-37, 1H), 3.70-3.78 (m, H-21/21', 2H), 3.60-3.70 (m, H-37', 1H), 3.39-3.53 (m, $ArOCH_3$/13/25, 5H), 3.34 (s, OCH_3, 1H), 3.05-3.16 (m, H-15, 1H), 2.94-3.04(m, H-7, 1H), 2.83-2.90(m, H-9, 1H), 2.76-2.82 (m, H-15'/17, 2H), 2.47 (q, *J* = 7.1 Hz, H-20, 1H), 1.83 (s, H-30, 3H), 1.70 (s, H-33, 3H), 1.62 (d, *J* = 5.5 Hz, H-28, 3H), 1.38 (d, *J* = 7.0 Hz, H-31, 3H), 1.25-1.32 (m,H-35/34/32, 12H), 1.07-1.14 (m, H-29/$SiCH_2CH_3$, 12H), 1.00-1.05 (m, H-38/$(SiCH_3)_3$, 29H), 0.76 (q, *J* = 7.9 Hz, H-$SiCH_2$, 6H), 0.20 (s, $SiCH_3$, 3H), 0.16 (m, $SiCH_3$, 12H), 0.12 (s, $SiCH_3$, 3H), 0.08 (s, $SiCH_3$, 9H), -0.02 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ 212.1, 208.5, 171.3, 159.6, 138.1, 135.6, 135.3, 132.3, 132.2, 131.9, 129.4, 127.4, 121.8, 118.7, 114.1, 95.3, 92.0, 88.3, 81.8, 78.6, 78.0, 77.3, 75.9, 75.1, 74.2, 65.8, 65.6,

62.2, 60.2, 54.8, 49.2, 47.2, 46.8, 46.3, 44.4, 40.8, 30.9, 26.4, 26.3, 26.1, 21.4, 18.7, 18.7, 18.5, 18.5, 18.3, 16.8, 13.4, 13.2, 12.7, 12.6, 11.8, 11.6, 7.5, 5.5, -1.1, -1.2, -4.0, -4.6, -4.7, -4.8, -4.9, -5.0.

HRMS (ESI) calculated for $C_{73}H_{136}O_{13}Si_5Na$ ([*M*+Na]+): 1383.8725, found 1383.8723
[α]$^{23}_{D}$ = + 40.6 (*c* =1.0 in $CHCl_3$).

6.7.3 Allyl alcohol **249**



249

$C_{67}H_{122}O_{13}Si_4$
Mol Wt: 1248,04

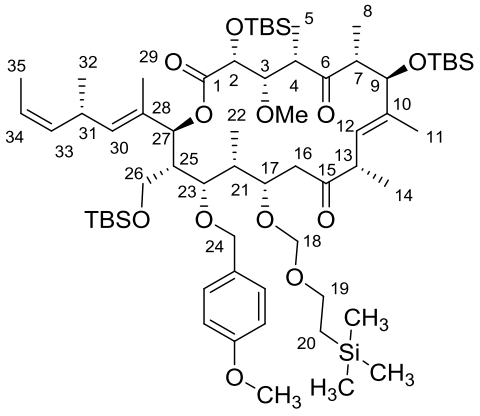
To the SEM product **248** (0.040 g, 0.0293 mmol) in methanol (2.3 mL) and THF (0.5 mL) was added PPTS (0.0133 mg, 0.0528 mmol) in one portion and stirred at room temperature for a period of 2 h, reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (10 ml) and extracted with MTBE (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude compound purified by column chromatography on silica gel (gradient elution with 5–10% EtOAc-pet ether) provided Compound **249** (25 mg, 70%) as colorless oil. Unreacted starting material **248** (5 mg) was recovered back.

^{1}H-NMR (400 MHz, C_6D_6): δ 7.45 (d, *J* = 8.5 Hz, H_{Ar}, 1H), 6.84 (d, *J* = 8.6 Hz, , H_{Ar}, 1H), 5.78 (dq, *J* = 10.5, 5.9 Hz, H-2, 1H), 5.61 (d, *J* = 9.6 Hz, H-12, 1H), 5.52 (d, *J* = 8.6 Hz, H-24, 1H), 5.34-5.46 (m, H-26/27, 2H), 5.18 (dd, *J* = 17.2, 1.4 Hz, H-1, 1H), 5.01 (d, *J* = 10.4 Hz, H-1', 1H), 4.92-4.96 (m, H-36/19/19', 1H), 4.75 (d, *J* = 10.8 Hz, H-36', 1H), 4.62 (d, *J* = 9.0 Hz, H-22, 1H), 4.43-4.60 (m, H-3/3'/5/10/16, 5H), 4.31 (t, *J* = 4.3 Hz, H-18, 1H), 4.13 (dd, *J* = 5.8, 4.2 Hz, H-6, 1H), 3.78-3.91 (m, H-37, 1H), 3.62-3.78 (m, H-21/21'/37'/OH, 4H), 3.53 (dd, *J* = 15.2, 8.1 Hz, H-25, 1H), 3.45 (s, $ArOCH_3$, 3H), 3.36-3.42 (m, H-13, 1H), 3.32 (s, OCH_3, 3H), 2.90-3.11 (m,H-15/7/9, 3H), 2.87 (dd, *J* = 17.3, 4.7 Hz, H-16', 1H), 2.41-2.52 (m, H-17, 1H), 2.33 (dd, *J* = 8.8, 4.3 Hz, H-20, 1H), 1.93 (s, H-30, 3H), 1.67 (s, H-33, 3H), 1.62 (d, *J* = 5.0 Hz, H-28, 3H), 1.24-1.36 (m, H-31/34/35, 9H), 1.20 (d, *J* = 6.8 Hz, H-32, 3H), 1.11 (d, *J* = 6.7 Hz, H-29, 3H), 1.06-1.10 (m, H-38, 2H), 0.99-1.06 (m, $SiC(CH_3)_3$, 27H), 0.04-0.22 (m, $SiCH_3$, 27H).

^{13}C-NMR (100 MHz, C_6D_6): δ 212.29 (s), 209.1, 171.4, 159.8, 138.2, 135.9, 135.0, 132.4, 132.2, 131.3, 129.5, 128.3, 128.2, 127.9, 127.6, 127.4, 121.7, 118.8, 114.3, 95.4, 81.7, 80.2, 78.4, 77.1, 76.0, 75.2, 74.1, 65.9, 65.6, 62.7, 60.3, 54.8, 49.2, 47.3, 46.9, 43.9, 42.3, 30.9, 26.4, 26.2, 26.1, 21.8, 18.7, 18.6, 18.5, 18.5, 16.8, 13.1, 13.1, 13.1, 11.9, 11.5, 11.1, -1.2, -4.0, -4.6, -4.7, -4.7, -5.1, -5.1.

HRMS (ESI) calculated for $C_{67}H_{122}O_{13}Si_4Na$ ([*M*+Na]+): 1269.7860, found 1269.7864
[α]$^{23}_D$ = + 58.6 (*c* =1.0 in $CHCl_3$).

6.7.4 Macrolactone **251**



251

$C_{64}H_{116}O_{12}Si_4$
Mol Wt: 1189,96

a) Allyester cleavage:

To the allylester **249** (48 mg, 0.038 mmol) in CH_2Cl_2 (6 ml) was added $Pd(PPh_3)_4$ (8.7 mg, 0.0076 mmol) followed by tributyltinhydride (41 μl, 0.152 mmol) dropwise at room temperature. The solution turned into dark brown color in 5 min, reaction stirred for 1 h. The reaction mixture was diluted with MTBE (50 mL) and washed with a mixture of sat. aq. NH_4Cl solution and $NaHSO_4$ solution (1*M*, 50 mL). The aqueous layer was back-extracted with MTBE (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography on 5 g silica gel (gradient elution with 100% hexanes to 100% EtOAc) removed the excess tributylstannane and provided 0.050 g of semipure carboxylic acid that was used in the subsequent macrolactonization without further purification.

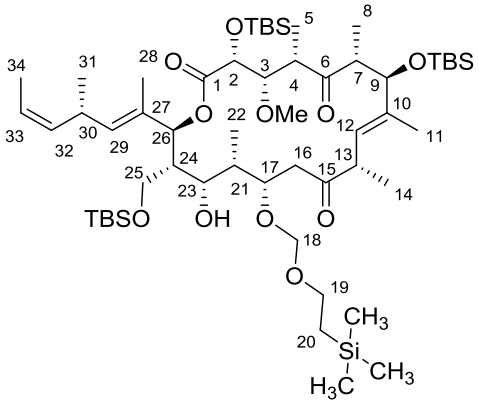
b) Yamaguchi macrolactonisation:

To the crude carboxylic acid (0.050 g) obtained above in dry benzene (22 mL) was added TEA (81.6 µl, 0.584 mmol) and stirred for 30 min at room temperature. 2,4,6-Trichlorobenzoylchloride (28.8 µl, 0.177 mmol) was added dropwise and stirred for 1 h. DMAP (5.3 mg, 0.043 mmol) was added in one portion and the resulting yellow colored solution was stirred for 16 h at room temperature. The reaction mixture was diluted with MTBE (40 mL) and washed with sat. aq. $NaHCO_3$ solution (30 mL). The aqueous layer was back-extracted with MTBE (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography on 8 g silica gel (5% EtOAc-hexanes) gave the desired macrolactone **251** (23 mg, 51%) as yellow oil.

NMR couldn't be interpreted due to conformational instabilities.

HRMS (ESI) calculated for $C_{64}H_{116}O_{12}Si_4Na$ ([*M*+Na]+): 1211.7442, found 1211.7443
$[\alpha]^{23}_D$ = + 2.0 (*c* =1.1 in $CHCl_3$).

6.7.5 Alcohol **257**



257

$C_{56}H_{108}O_{11}Si_4$
Mol Wt: 1069,81

To the macrolactone **251** (23 mg, 0.019 mmol) in CH_2Cl_2 (6 mL) was added pH7 buffer (0.6 mL). Cooled to 0 °C and DDQ (9.5 mg, 0.042 mmol) was added at once and the reaction was stirred for a period of 90 min. The reaction mixture was quenched into a solution of Et_2O (50 mL) and aq. sat. $NaHCO_3$ solution (20 mL), organic layer was separated and washed with aq. sat. $NaHCO_3$ solution (3 × 10 mL), and the organic layer was dried over $MgSO_4$, filtered, and concentrated. Column chromatography on 8 g silica gel (5% EtOAc-pet ether) gave the desired compound **257** (16 mg, 80%) with little traces of *p*-methoxy benzaldehyde as yellow oil.

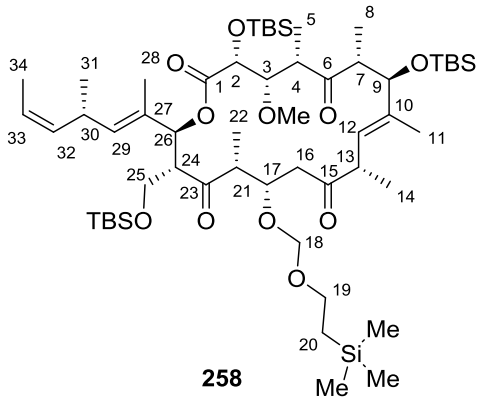
^{1}H-NMR (400 MHz, C_6D_6): δ 5.58 (d, *J* = 9.1 Hz, H-12, 1H), 5.29-5.49 (m, H-26/33/32, 3H), 5.24 (d, *J* = 10.2 Hz, H-29, 1H), 4.80-4.89 (m, H-18/18', 2H), 4.70-4.78 (m, H-17, 1H), 4.34-4.43 (m, H-2/9, 2H), 4.26 (dd, *J* = 6.0, 3.2 Hz, H-3, 1H), 4.17 (d, *J* = 7.3 Hz, H-23, 1H), 3.67-3.87 (m, H-19/19'/25, 3H), 3.58-

3.65 (m, H-25', 1H), 3.51 (s, OCH_3, 3H), 3.36-3.49 (m, H-13/7, 2H), 3.18-3.36 (m, H-21/30, 2H), 2.98 (dd, *J* = 7.4, 3.0 Hz, H-4, 1H), 2.71-2.89 (m,H-16/16', 2H), 2.61-2.72 (m, H-24, 1H), 2.33 (bs, -OH, 1H), 1.73-1.81 (m, H-11/28, 6H), 1.47-1.63 (m, H-5/34, 6H), 1.30 (d, *J* = 6.8 Hz, H-8, 3H), 1.10-1.19 (m, H-14/22/31, 9H), 1.03-1.09 (m, $SiC(CH_3)_3$/H-20, 11H), 0.98 (s, $SiC(CH_3)_3$, 9H), 0.88 (s, $SiC(CH_3)_3$, 9H), 0.24 (s, $SiCH_3$, 3H), 0.18 (s, $SiCH_3$, 3H), 0.11 (m, $Si(CH_3)_3$/$SiCH_3$, 12H), -0.10-0.04 (m, $SiCH_3$, 9H).

^{13}C-NMR (100 MHz, C_6D_6): δ 214.1, 207.8, 169.9, 138.6, 136.2, 135.1, 129.6, 128.8, 122.1, 81.1, 78.3, 76.7, 73.9, 65.9, 65.8, 61.3, 47.4, 42.1, 30.9, 30.5, 30.2, 26.2, 26.1, 25.9, 21.2, 18.6, 18.5, 18.4, 18.2, 15.6, 15.0, 13.1, 12.1, 11.5, 11.2, -1.1, -4.2, -4.3, -4.7, -4.8, -5.5, -5.6.

HRMS (ESI) calculated for $C_{56}H_{108}O_{11}Si_4Na$ ([*M*+Na]+): 1091.6866, found 1091.6869
$[\alpha]^{23}_D$ = + 39.2 (*c* =1.5 in $CHCl_3$).

6.7.6 Triketone **258**



258

$C_{56}H_{106}O_{11}Si_4$
Mol Wt. 1067,79

To the alcohol **257** (14 mg, 0.013 mmol) in CH_2Cl_2 (4 mL) was added $NaHCO_3$ (32.9 mg, 0.392 mmol) and Dess Martin Periodinane (55 mg, 0.131 mmol) at room temperature, the resulting cloudy solution was stirred for 1 h. The reaction mixture was diluted with aq. sat. $NaHCO_3$ solution (5 mL), aq. sat. $Na_2S_2O_3$ solution (10 mL), and Et_2O (10 mL), and stirred at room temperature for 10 min. The biphasic mixture was diluted with Et_2O (30 mL) and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 5 mL), combined organic layers are dried over $MgSO_4$, filtered, and concentrated to afford awhite film. Column chromatography on 5 g silica gel (elution with 5% EtOAc-hexanes) afforded triketone **258** (13 mg, quantitative) as a colorless oil.

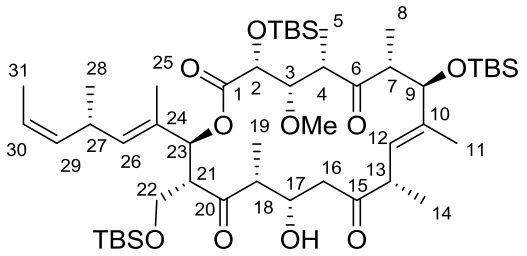
^{1}H-NMR (400 MHz, C_6D_6): δ 5.58 (d, *J* = 1.86 Hz, H-26, 1H), 5.56 (d, *J* = 1.36 Hz, H-12, 1H), 5.32-5.43 (m, H-33, 1H), 5.22-5.31 (m, H-29/32, 2H), 4.96 (dt, *J* = 7.3, 3.2 Hz, H-17, 1H), 4.92 (d, *J* = 6.8 Hz, H-18, 1H), 4.85 (d, *J* = 6.8 Hz, H-18', 1H), 4.39 (d, *J* = 9.7 Hz, H-9, 1H), 4.30 (d, *J* = 6.5 Hz, H-2, 1H), 4.01 (dd, *J*

= 6.4, 3.9 Hz, H-3, 1H), 3.88 (dt, *J* = 9.7, 8.8 Hz, H-19/21, 2H), 3.78 (dt, *J* = 16.7, 8.4 Hz, H-21', 1H), 3.48-3.60 (m, H.19'/20, 2H), 3.45 (s, -OCH_3, 3H), 3.14-3.43 (m, H-7/13/16/21/30, 5H), 2.85 (d, *J* = 4.3 Hz, H-16', 1H), 2.73-2.81 (m, H-4, 1H), 1.83 (d, *J* = 1.1 Hz, H-28, 3H), 1.72 (d, *J* = 0.9 Hz, H-11, 3H), 1.56 (dd, *J* = 6.6, 1.5 Hz, H-34, 3H), 1.52 (d, *J* = 7.2 Hz, H-5, 3H), 1.31 (dd, *J* = 6.9, 3.6 Hz, H-8/22, 6H), 1.11 (dd, *J* = 6.7, 3.1 Hz, H-14/31/20, 8H), 1.05 (s, $SiC(CH_3)_3$, 9H), 0.98 (s, $SiC(CH_3)_3$, 9H), 0.92 (s, $SiC(CH_3)_3$, 9H, 0.22 (s, $SiCH_3$, 3H), 0.15 (s, $SiCH_3$, 3H), 0.10 (s, $SiCH_3$, 3H), 0.08 (s, $Si(CH_3)_3$, 9H), 0.07 (s, $SiCH_3$, 3H), 0.03 (s, $SiCH_3$, 3H), 0.02 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ 214.7, 211.8, 208.1, 169.7, 138.9, 137.3, 134.9, 129.1, 125.9, 122.4, 94.1, 83.3, 80.8, 78.8, 75.9, 73.2, 65.7, 62.1, 61.6, 56.7, 48.8, 47.9, 47.4, 42.8, 31.0, 30.5, 26.2, 26.1, 21.1, 18.7, 18.5, 18.4, 14.8, 13.1, 11.7, 11.2, -1.1, -4.2, -4.3, -4.6, -4.8, -5.2, -5.3

HRMS (ESI) calculated for $C_{56}H_{106}O_{11}Si_4Na$ ([*M*+Na]+): 1089.6710, found 1089.6709
$[\alpha]^{23}_D$ = + 41.8 (*c* =1.3 in $CHCl_3$).

6.7.7 Alcohol **259**



259

$C_{50}H_{92}O_{10}Si_3$
Mol Wt: 937,53

To the sem alcohol **258** (13 mg, 0.012 mmol) in Et_2O (5 mL) was added $MgBr_2$ (44.8 mg, 0.244 mmol) and ethanethiol (0.39 mL, 1.217 mmol) at room temperature, the flask was closed tightly and the resulting solution was stirred at room temperature for 24 h. Reaction mixture was diluted with EtOAc (20 mL) and washed with sat. aq. $NaHCO_3$ solution (10 mL), organic layer was separated and aqueous layer extracted EtOAc (3 × 5 mL), Combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography on 8 g silica gel (5% EtOAc-hexanes) gave the desired compound **259** (9 mg, 80%).

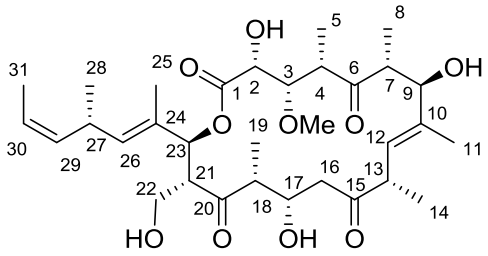
^{1}H-NMR (400 MHz, C_6D_6): δ 5.49 (d, *J* = 9.2 Hz, H-26, 1H), 5.30-5.41 (m, H-23/30, 2H), 5.23-5.28 (m, H-29, 1H), 5.18 (m, H-17, 1H), 5.17 (m, H-11, 1H), 4.33 (d, *J* = 3.1 Hz, H-2, 1H), 4.21 (d, *J* = 9.5 Hz, H-9,

1H), 4.17 (t, *J* = 2.9 Hz, H-3, 1H), 4.07 (t, *J* = 10.0 Hz, H-22, 1H), 3.83-3.93 (m, H-21, 1H), 3.61 (dd, *J* = 9.7, 4.2 Hz, H-22', 1H), 3.44 (s, -OCH_3, 3H), 3.31-3.40 (m, H-27, 1H), 3.16-3.26 (m, H-18, 1H), 3.00-3.11 (m, H-7/14/OH, 3H), 2.85 (dd, *J* = 18.3, 7.1 Hz, H-16, 1H), 2.75 (d, *J* = 5.8 Hz, H-16', 1H), 2.66-2.72 (m, H-4, 1H), 1.72 (d, *J* = 0.7 Hz, H-25, 3H), 1.69 (d, *J* = 0.9 Hz, H-11, 3H), 1.51-1.56 (m, H-19/31, 6H), 1.39 (d, *J* = 7.4 Hz, H-5, 3H), 1.24 (d, *J* = 6.8 Hz, H-8, 3H), 1.01-1.09 (m, $SiC(CH_3)_3$/H-28, 12H), 0.97 (s, $SiC(CH_3)_3$, 9H), 0.88-0.92 (m, $SiC(CH_3)_3$/H-14, 12H), 0.27 (s, $SiCH_3$, 3H), 0.15 (s, $SiCH_3$, 3H), 0.08 (s, $SiCH_3$, 3H), 0.05 (s, $SiCH_3$, 4H), 0.04 (s, $SiCH_3$, 3H), -0.02 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ 213.0, 212.8, 209.3, 169.5, 138.6. 134.8, 128.4, 127.9, 122.0, 81.2, 79.6, 78.8, 75.9, 66.3, 36.1, 59.6, 53.3, 50.9, 50.5, 48.6, 47.8, 42.7, 30.7, 25.9, 25.8, 25.7, 20.9, 18.5, 18.4, 18.2, 15.6, 15.5, 12.9, 11.3, 10.9, 8.9, -4.4, -4.5, -5.1.

HRMS (ESI) calculated for $C_{56}H_{92}O_{10}Si_3Na$ ([*M*+Na]+): 959.5896, found 959.5889
$[\alpha]^{23}_D$ = + 17.2 (*c* =0.8 in $CHCl_3$).

6.7.8 Desepoxyisotedanolide **40**



40

$C_{32}H_{50}O_{10}$
Mol Wt. 594,74

To the TBS ether **259** (8 mg, 0.008 mmol) in CH_3CN (1.5 mL) at 0 °C was added triethylamine (0.8 mL) and HF•Et_3N (0.93 mL) dropwise. The resulting reaction mixture was stirred at room temperature over a period of 3 days. Cooled to 0 °C, reaction mixture was slowly quenched with sat. aq. $NaHCO_3$ solution until the effervescence subsides. Extracted with EtOAc (4 × 5 mL), combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography on 3 g silica gel (3% MeOH-CH_2Cl_2) gave the desired compound **40** (3 mg, 60%).

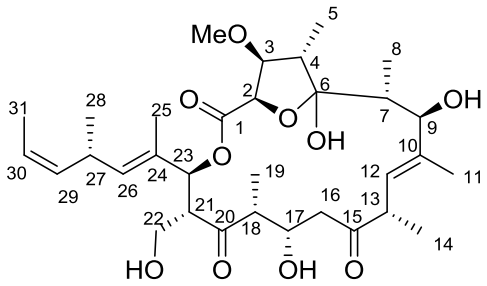
^{1}H-NMR (500 MHz, C_6D_6): δ 5.48 (d, *J* = 8.2 Hz, H-26, 1H), 5.45 (d, *J* = 9.2 Hz, H-23, 1H), 5.30-5.36 (m, H-30, 1H), 5.25-5.28 (m, H-12, 1H), 5.17 (ddd, *J* = 10.8, 9.1, 1.7 Hz, H-29, 1H), 4.76 (tt, *J* = 6.8, 3.6 Hz, H-15, 1H), 3.90-3.97 (m, H-9, 1H), 3.86 (dd, *J* = 10.7, 1.1 Hz, H-2, 1H), 3.82 (dd, *J* = 6.6, 1.0 Hz, H-3, 1H), 3.61-3.68 (m, H-21, 1H), 3.53-3.61 (m, H-22, 1H), 3.24-3.32 (m, -OCH_3/H-27/13/22', 6H), 3.20 (d, *J* = 4.0 Hz, -OH, 1H), 2.91 (qd, *J* = 6.9, 2.9 Hz, H-18, 1H), 2.74-2.84 (m, H-16/16'/7/-OH, 4H), 2.68-2.74 (m,

H-4, 1H), 1.59 (d, *J* = 1.1 Hz, H-25, 3H), 1.54 (d, *J* = 1.2 Hz, H-H-11, 3H), 1.49 (dd, *J* = 6.8, 1.7 Hz, H-31, 3H), 1.35 (d, *J* = 7.0 Hz, H-19, 3H), 1.16 (d, *J* = 6.8 Hz, H-8, 3H), 1.11 (d, *J* = 7.3 Hz, H-5, 3H), 0.99 (d, *J* = 6.7 Hz, H-28, 3H), 0.91 (d, *J* = 7.0 Hz, H-14, 3H).

^{13}C-NMR (125 MHz, C_6D_6): δ 213.8, 213.5, 211.3, 171.3, 138.6, 136.8, 134.8, 131.5, 128.9, 122.5, 81.3, 80.6, 79.8, 72.5, 68.0, 61.9, 60.4, 53.4, 51.2, 50.0, 48.8, 47.0, 43.6, 30.9, 21.1, 16.9, 15.2, 13.0, 12.6, 11.2, 10.9, 10.5.

HRMS (ESI) calculated for $C_{32}H_{50}O_{10}Na$ ([*M*+Na]+): 617.3302, found 617.3304
$[\alpha]^{23}_D$ = + 25.7 (*c* =0.07 in $CHCl_3$).

Minor product 40a



40a

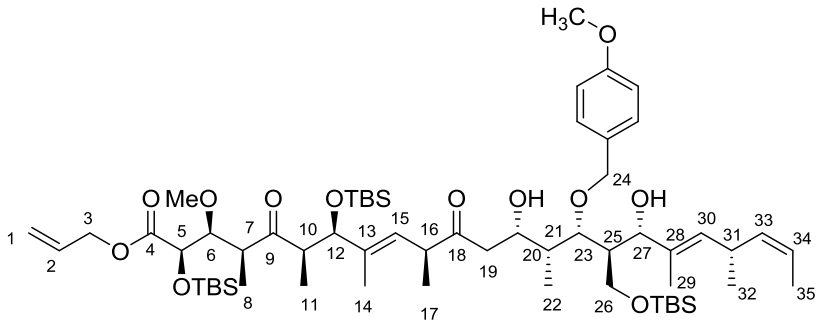
^{1}H-NMR (500 MHz, C_6D_6): δ 5.51 (d, *J* = 8.1 Hz, H-23, 1H), 5.42 (d, *J* = 9.1 Hz, H-26, 1H), 5.28-5.37 (m, H-30, 1H), 5.21-5.29 (m, H-29, 1H), 5.15 (bs, -OH, 1H), 4.75-4.91 (m, H-2/9/12/17, 4H), 3.84–3.91 (m, H-3, 1H), 3.55 (dd, *J* = 10.9, 7.0 Hz, H-22, 1H), 3.26-3.42 (m, H-22'/27, 2H), 3.18 (s, -OCH_3, 3H), 3.06-3.23 (m, H-21, 1H), 3.04 (dd, *J* = 10.6, 6.5 Hz, H-13, 1H), 2.93-3.01 (m, H-16, 1H), 2.88 (ddd, *J* = 20.4, 9.4, 4.9 Hz, H-16', 1H), 242-2.52 (m, H-18, 1H), 2.32-2.39 (m, H-7, 1H), 2.18-2.28 (m, H-4/OH, 2H), 1.58 (d, *J* = 1.1 Hz, H-25, 3H), 1.50 (dd, *J* = 6.6, 1.5 Hz, H-31, 3H), 1.48 (s, H-11, 3H), 1.27 (d, *J* = 6.6 Hz, H-5, 3H), 1.15 (d, *J* = 6.9 Hz, H-19, 3H), 1.13 (d, *J* = 6.6 Hz, H-14, 3H), 1.00 (d, *J* = 6.8 Hz, H-28, 3H), 0.82 (d, *J* = 7.1 Hz, H-8, 3H).

^{13}C-NMR (125 MHz, C_6D_6): δ 211.3, 209.6, 168.6, 138.7, 136.7, 135.2, 128.8, 124.1, 122.2, 108.2, 89.5, 80.4, 78.1, 74.2, 66.9, 62.9, 59.8, 53.7, 52.9, 47.6, 47.3, 46.7, 42.1, 30.9, 21.2, 14.9, 14.4, 14.2, 13.6, 13.0, 12.2, 9.1.

HRMS (ESI) calculated for $C_{32}H_{50}O_{10}Na$ ([*M*+Na]+): 617.3302, found 617.3304
$[\alpha]^{23}_D$ = − 16.0 (*c* =0.03 in $CHCl_3$).

6.8. 14-Membered Macrolactone:

6.8.1 Diol **261**



261

$C_{61}H_{108}O_{12}Si_3$
Mol Wt: 1117,78

To the TES ether **247** (10 mg, 0.008 mmol) in a mixture of MeOH (0.5 mL) and THF (0.1 mL) was added PPTS (3.6 mg, 0.014 mmol) in one protion and stirred at room temperature for a period of 2 h. Reaction mixture was quenched with sat. aq. $NaHCO_3$ solution (5 ml) and extracted with MTBE (2 × 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude compound purified by column chromatography on silica gel (gradient elution with 15% EtOAc-pet ether) provided compound **261** (7 mg, 76%) as colorless oil.

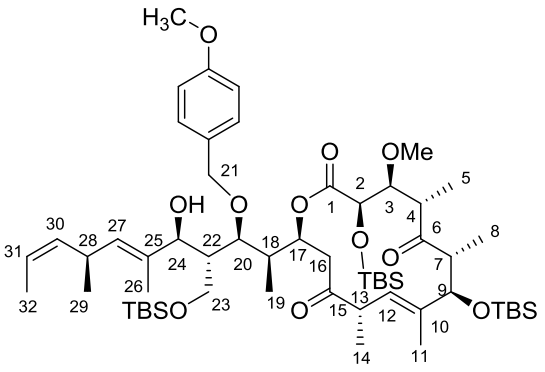
^{1}H-NMR (400 MHz, C_6D_6): δ 7.37 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 6.80 (d, *J* = 8.7 Hz, H_{Ar}, 2H), 5.77 (ddt, *J* = 16.3, 10.4, 5.9 Hz, H-2, 1H), 5.53 (d, *J* = 9.8 Hz, H-15, 1H), 5.44 (d, *J* = 9.0 Hz, H-30, 1H), 5.30 – 5.41 (m, H-33/34, 2H), 5.18 (dd, *J* = 17.2, 1.5 Hz, H-1, 1H), 5.00 (dd, *J* = 10.4, 1.4 Hz, H-1', 1H), 4.77 (d, *J* = 10.7 Hz, H-24, 1H), 4.69 (d, *J* = 10.8 Hz, H-24', 1H), 4.62 (d, *J* = 8.6 Hz, H-27, 1H), 4.51-4.57 (m, H-5/23, 1H), 4.48-4.52 (m, H-3/OH, 1H), 4.46 (d, *J* = 6.7 Hz, H-12, 1H), 4.23 (dd, *J* = 5.6, 3.8 Hz, H-20, 1H), 4.17 (dd, *J* = 5.9, 4.1 Hz, H-6, 1H), 3.74 (bs, OH, 1H), 3.57 (d, *J* = 4.8 Hz, H-26, 2H), 3.47 (s, OCH_3, 3H), 3.44-3.52 (m, H-31, 1H), 3.30 (s, $ArOCH_3$, 3H), 3.22-3.30 (m, H-16, 1H), 2.97-3.04 (m, H-7/10, 2H), 2.86 (dd, *J* = 17.1, 9.0 Hz, H-19, 1H), 2.51 (dd, *J* = 17.1, 3.5 Hz, H-19', 1H), 2.40 (dd, *J* = 9.1, 4.0 Hz, H-25, 1H), 2.21-2.29 (m, H-21, 1H), 1.86 (d, *J* = 1.1 Hz, H-29, 3H), 1.65 (d, *J* = 0.6 Hz, H-11, 3H), 1.59 (d, *J* = 5.1 Hz, H-35, 3H), 1.24 – 1.33 (m, H-8/11/22, 9H), 1.13 (d, *J* = 6.9 Hz, H-17, 1H), 1.08 (d, *J* = 6.8 Hz, H-32, 1H), 0.99 – 1.05 (m, $SiC(CH_3)_3$, 18H), 0.20 (s, $SiCH_3$, 3H), 0.16 (s, $SiCH_3$, 3H), 0.13 (s, $SiCH_3$, 3H), 0.12 (s, $SiCH_3$, 6H), 0.06 (s, $SiCH_3$, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ 217.5, 211.0, 171.5, 159.9, 138.3, 135.8, 134.6, 132.7, 132.2, 131.0, 129.9, 121.7, 118.8, 114.3, 81.9, 81.5, 78.9, 77.3, 75.3, 74.0, 68.7, 65.6, 60.3, 54.8, 49.3, 46.8, 46.1, 45.6, 42.4, 30.8, 26.3, 26.2, 26.1, 16.5, 13.1, 12.7, 11.7, 11.5, 9.9, -4.2, -4.6, -4.7, -5.1, -5.2.

HRMS (ESI) calculated for $C_{61}H_{108}O_{12}Si_3Na$ ([*M*+Na]+): 1139.7046, found 1139.7045

$[\alpha]^{23}_D$ = + 45.1 (*c* =0.7 in $CHCl_3$).

6.8.2 Macrolactone **260**



260

$C_{58}H_{102}O_{11}Si_3$
Mol Wt. 1059,70

a) Allyester cleavage:

To the diol **261** (7 mg, 0.006 mmol) in CH_2Cl_2 (2 ml) was added $Pd(PPh_3)_2Cl_2$ (1 mg, 0.001 mmol) followed by tributyltinhydride (7 μl, 0.025 mmol) dropwise at room temperature. The solution turned into dark brown color in 5 min, reaction stirred for 1 h. The reaction mixture was diluted with MTBE (20 mL) and washed with a mixture of sat. aq. NH_4Cl solution and $NaHSO_4$ solution (1*M*, 20 mL). The aqueous layer was back-extracted with MTBE (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography on 5 g silica gel (gradient elution with 100% pet ether to 100% EtOAc) removed the excess tributylstannane and provided 0.015 g of semi-pure carboxylic acid, which is used in the subsequent macrolactonization without further purification.

b) Shiiina macrolactonisation:

The crude carboxylic acid (0.015 g) obtained above was dissolved in dry toluene (1 mL) and dry THF (0.5 mL) and added to a mixture of DMAP (6.5 mg, 0.063 mmol) and 2-methyl-6-nitrobenzoic anhydride (6 mg, 0.018 mmol) in toluene (3 mL) and THF (4 mL) at room temperature. The resulting solution was stirred for 32 h at room temperature. The reaction mixture was diluted with MTBE (10 mL) and washed with sat. aq. $NaHCO_3$ solution (10 mL). The aqueous layer was back-extracted with MTBE (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography on 8 g silica gel (15% EtOAc-hexanes) gave the macrolactone **260** (3 mg, 45%) as colorless oil.

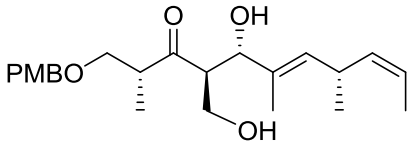
^{1}H-NMR (500 MHz, C_6D_6): δ 7.41 (d, *J* = 8.6 Hz, H_{Ar}, 2H), 6.78 (d, *J* = 8.6 Hz, H_{Ar}, 2H), 5.87 (dd, *J* = 8.0, 6.7 Hz, H-17, 1H), 5.50 (dd, *J* = 19.0, 8.8 Hz, H-27, 1H), 5.34-5.44 (m, H-30/31, 2H), 5.05 (d, *J* = 9.9 Hz, H-12, 1H), 4.82 (d, *J* = 10.6 Hz, H-21, 1H), 4.58 (d, *J* = 10.7 Hz, H-21', 1H), 4.49 (d, *J* = 9.4 Hz, H-24, 1H), 4.38 (d, *J* = 9.3 Hz, H-2, 1H), 4.33 (dd, *J* = 9.2, 1.1 Hz, H-3, 1H), 4.26 (d, *J* = 10.0 Hz, H-9, 1H), 4.00 (dd, *J* = 5.4, 2.3 Hz, H-20, 1H), 3.61 (s, OCH_3, 3H), 3.47-3.57 (m, H-23/28, 2H), 3.43 (dd, *J* = 10.3, 3.5 Hz, H-23', 1H), 3.28 (s, $ArOCH_3$, 3H), 3.21-3.29 (m, H-13, 1H), 3.06-3.17 (m, H-7, 1H), 2.92 (dd, *J* = 19.2, 8.3 Hz, H-16, 1H), 2.78 (dd, *J* = 19.1, 1.6 Hz, H-16', 1H), 2.41 (q, *J* = 7.4 Hz, H-4, 1H), 2.28-2.36 (m, H-18, 1H), 2.10 (dt, *J* = 9.3, 4.7 Hz, H-22, 1H), 1.83 (d, *J* = 0.7 Hz, H-26, 3H), 1.79 (d, *J* = 0.9 Hz, H-11, 3H), 1.61 (d, *J* = 5.1 Hz, H-32, 3H), 1.36 (d, *J* = 7.5 Hz, H-5, 3H), 1.23 (d, *J* = 7.0 Hz, H-19, 3H), 1.21 (d, *J* = 6.6 Hz, H-8, 3H), 1.11 (d, *J* = 6.7 Hz, H-27, 1H), 1.09 (s, $SiC(CH_3)_3$, 9H), 1.06 (d, *J* = 6.6 Hz, H-14, 3H), 0.99 (s, $SiC(CH_3)_3$, 9H), 0.96 (s, $SiC(CH_3)_3$, 9H), 0.45 (s, $SiCH_3$, 3H), 0.27 (s, $SiCH_3$, 3H), 0.22 (s, $SiCH_3$, 3H), 0.11 (s, $SiCH_3$, 3H), 0.09 (s, $SiCH_3$, 3H), 0.07 (s, $SiCH_3$, 3H), -0.03 (s, $SiCH_3$, 3H).

^{13}C-NMR (125 MHz, C_6D_6): δ 212.1, 205.4, 171.0, 160.1, 138.7, 135.8, 134.6, 133.0, 130.1, 130.0, 121.9, 114.5, 80.7, 79.4, 78.6, 77.5, 74.8, 74.2, 71.9, 54.8, 50.6, 47.3, 47.2, 45.5, 42.0, 26.3, 26.2, 26.1, 26.0, 18.7, 18.5, 18.4, 16.2, 15.4, 13.1, 11.7, 11.2, 9.8, -4.5, -4.6, -4.9, -5.2.

HRMS (ESI) calculated for $C_{58}H_{102}O_{11}Si_3Na$ ([*M*+Na]+): 1081.6628, found 1081.6628
$[\alpha]^{23}_D$ = + 45.4 (*c* =0.95 in $CHCl_3$).

6.9. Simplified Tedanolide Analogs:

6.9.1 Diol **264**



264

$C_{23}H_{34}O_5$
Mol Wt. 390,52

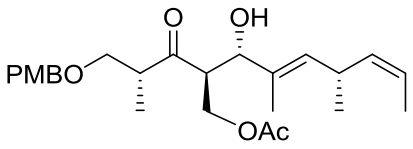
To the ketone **44** (78 mg, 0.15 mmol) in THF (8 mL) was added pyridine (8.1 mL) at 0 °C, HF-pyridine (5.26 mL) was added carefully dropwise to the reaction mixture, warmed to room temperature and stirred for 4 h. Reaction mixture was slowly added to sat. aq. $NaHCO_3$, organic layer separated and the aqueous layer was extracted with EtOAc (3 x 15 mL), combined organic layers are dried over Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound purified by silica gel column chromatography (pet ether: EtOAc, 3:1) to afford compound **53** (58 mg, 95%) as colorless liquid.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.37-5.31 (m, 1H), 5.30 (d, *J* = 7.6 Hz, 1H), 5.22-5.14 (m, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.26 (d, *J* = 8.5 Hz, 1H), 3.79 (s, 3H), 3.65 (dt, *J* = 9.3, 7.9 Hz, 2H), 3.59 (dd, *J* = 11.6, 4.3 Hz, 1H), 3.49 (dd, *J* = 8.7, 4.5 Hz, 1H), 3.42-3.32 (m, 1H), 3.19-3.09 (m, 2H), 2.55 (br s, 2H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.62 (dd, *J* = 6.8, 1.7 Hz, 3H), 1.01 (d, *J* = 3.3 Hz, 3H), 1.00 (d, *J* = 3.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 218.0, 159.6, 134.8, 133.9, 132.8, 129.6, 129.3, 122.3, 114.0, 76.8, 73.4, 62.5, 57.9, 55.4, 47.7, 30.6, 21.4, 13.1, 12.9, 11.5.

HRMS (ESI) calculated for $C_{23}H_{34}O_5Na$ ([*M*+Na]+): 413.5028, found 413.1573.
$[\alpha]^{23}_D$ = + 11.0 (*c* = 1.5 in $CHCl_3$).

6.9.2 Acetate **265**



265

$C_{25}H_{36}O_6$
Mol Wt. 432,56

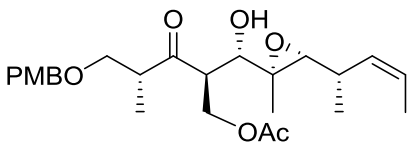
To the diol **264** (57 mg, 0.14 mmol) in CH_2Cl_2 (7 mL) at −78 °C was added DIPEA (46 μL, 0.26 mmol) and acetyl chloride (12.2 μL, 0.17 mmol). Stirred for 1 h, again DIPEA (46 μL, 0.26 mmol) and acetyl chloride (12.2 μL, 0.17 mmol) were added and stirred for 5 h at −78 °C, and then at −50 °C for 16 h. Water (10 mL) and sat. aq. $NaHCO_3$ (10 ml) was added, warmed to room temperature, organic layer separated, aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). Combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound purified by silica gel column chromatography on silica gel (pet ether: EtOAc, 3:1) to obtain compound **265** (45 mg, 80%) as colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.36 (ddd, *J* = 10.7, 6.8, 0.9 Hz, 1H), 5.30 (d, *J* = 9.0 Hz, 1H), 5.21 (ddq, *J* = 10.8, 9.2, 1.7 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.22 (d, *J* = 8.5 Hz, 1H), 4.03 (dd, *J* = 11.3, 5.4 Hz, 1H), 3.82 (s, 3H), 3.67 (d, *J* = 9.1, 7.8 Hz, 1H), 3.42 (dd, *J* = 9.1, 5.5 Hz, 1H), 3.36-3.39 (m, 1H), 3.29-3.31 (m, 1H), 2.99-3.11 (m, 1H), 1.94 (s, 3H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.65 (dd, *J* = 6.8, 1.7 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 214.3, 170.6, 159.4, 134.6, 134.1, 132.5, 129.9, 129.4, 122.5, 114.0, 76.8, 73.1, 62.9, 55.4, 53.6, 47.1, 30.5, 21.3, 20.8, 13.2, 13.1, 11.5.

HRMS (ESI) calculated for $C_{25}H_{36}O_6Na$ ([*M*+Na]+): 455.5395, found 455.3230.
$[\alpha]^{23}_D$ = + 13.2 (*c* = 1.0 in $CHCl_3$).

6.9.3 Epoxide **266**



266

$C_{25}H_{36}O_7$
Mol Wt. 448,56

To the allyl alcohol **265** (14 mg, 0.03 mmol) in CH_2Cl_2 (0.6 mL) was added $NaHCO_3$ (9.5 mg) and *m*-CPBA (5.6 mg, 0.03 mmol) at −78 °C, stirred for 1 h at this temp and warmed to −40 °C and stirred for 16 h at this temperature. Sat. aq. $NaHCO_3$ (2 mL) and CH_2Cl_2 (3 mL) were added and warmed to room temperature, organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL), combined organic layers are dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. Crude compound purified by silica gel column chromatography (pet ether: EtOAc, 6:1) to afford compound **266** (6.5 mg, 44%) as colorless liquid.

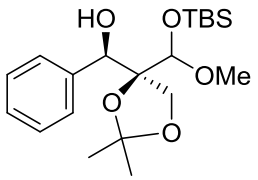
^{1}H-NMR (400 MHz, C_6D_6): δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.60 (m, 1H), 5.21-5.31 (m, 1H), 4.48 (dd, *J* = 11.0, 4.9 Hz, 1H), 4.38 (s, 2H), 4.33 (dd, *J* = 10.9, 8.8 Hz, 1H), 3.77 (dd, *J* = 9.1,7.4 Hz, 1H), 3.58 (dd, *J* = 8.8, 4.6 Hz, 1H), 3.45-3.51 (m, 1H), 3.40 (s, 3H), 3.23-3.13 (m, 1H), 2.62-2.66 (m, 1H), 2.61 (s, 1H), 2.42-2.52 (m, 1H), 1.69 (s, 3H), 1.54 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.41 (s, 3H), 1.28 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (100 MHz, C_6D_6): δ 212.5, 169.9, 159.8, 130.8, 130.5, 129.5, 124.9, 114.1, 76.5, 73.1, 71.9, 66.4, 62.9, 62.3, 54.7, 52.8, 48.4, 31.6, 20.3, 18.7, 13.3, 13.3, 13.2, 12.0.

HRMS (ESI) calculated for $C_{26}H_{36}O_7Na$ ([*M*+Na]+): 471.5389, found 471.2265.
$[\alpha]^{23}_D$ = + 4.5 (*c* = 0.35 in MeOH).

6.10. Kiyooka Aldol Methodology Analogs:

6.10.1 β-Hydroxy acetal **291**



291

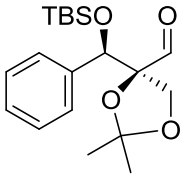
$C_{20}H_{34}O_5Si$

Mol Wt: 382.57

To a suspension of *N*-Ts-L-valine (67 mg, 0.25 mmol, 1.1 eq.) in CH_2Cl_2 (2.1 mL) was added BH_3•THF complex (0.22 mL, 1*M* in THF, 1.0 eq.) dropwise at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and 1 h at rt. Afterwards, the clear solution was cooled to −78 °C and benzaldehyde (23 mg, 0.21 mmol, 1.0 eq.) in CH_2Cl_2 (1.3 mL) was added followed by the subsequent addition of silyl ketene acetal **278** (80 mg, 0.29 mmol, 1.3 eq.) in CH_2Cl_2 (1.3 mL). The mixture was stirred for 10 min at −78 °C, quenched with phosphate buffer pH7 and the resulting biphasic mixture slowly warmed to rt. The two layers were separated, the organic phase was diluted with MTBE, washed with aq. sat. $NaHCO_3$ solution and brine and dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford β-hydroxy acetal **291** (68 mg, 0.18 mmol, 83%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.46 (m, 2H), 7.25-7.35 (m, 3H), 4.68 (d, *J* = 7.6 Hz, 1H), 5.13 (d, *J* = 3.0 Hz, 0.5H), 4.96 (d, *J* = 5.0 Hz, 0.5H), 4.02 (s, 1H), 3.90 (s, 1H), 3.53 (s, 1.5H), 3.40 (s, 1.5H), 1.18-1.23 (m, 3H), 1.02-0.96 (m, 3H), 0.92-0.96 (m, 9H), 0.11-0.18 (m, 6H).

6.10.2 Aldehyde **285**



285

$C_{19}H_{30}O_4Si$
Mol Wt: 350,53

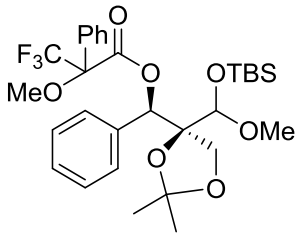
To a solution of β-hydroxy acetal **291** (10 mg, 0.026 mmol, 1.0 eq.) in THF (0.8 mL) was added NaHMDS (36.5 μL, 1*M* in THF, 1.0 eq.) at −78 °C. The resulting mixture was stirred for 5 min at −78 °C, warmed to 0 °C, stirred for 1 h and quenched with sat. aq. NH_4Cl solution. The biphasic solution was diluted with MTB ether and the two layers were separated. The aqueous phase was washed with MTB ether and dried over Na_2SO_4. After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford aldehyde **285** (6.0 mg, 0.017 mmol, 66%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 7.29-7.33 (m, 5H), 4.82(s, 1H), 4.27 (d, *J* = 9.12 Hz, 1H), 3.88 (dd, *J* = 8.0, 1.5 Hz, 1H), 1.35 (s, 3H), 1.15 (s, 3H), 0.86 (s, 9H), 0.00 (s, 3H), -0.24 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 203.4, 128.3, 127.9, 119.6, 111.6, 89.5, 77.3, 67.8, 26.6, 25.8, 25.7, -4.5, -5.3.

HRMS (ESI) calculated for $C_{19}H_{30}O_4SiNa$ ([*M*+Na]$^+$): 373.1811, found: 373.1448.
$[\alpha]^{23}_D$ = − 41.2 (*c* = 0.5, $CHCl_3$).

6.10.3 Ester **292**



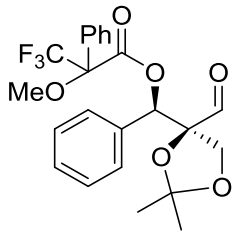
292

$C_{30}H_{41}F_3O_7Si$
Mol Wt: 598.72

To a solution of β-hydroxy acetal **291** (10 mg, 0.026 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) was added TEA (29.6 μL, 0.21 mmol, 8.0 eq.), DMAP (4.5 mg, 0.036 mmol, 1.4 eq.) and *R*-Moscher's chloride (20 μl, 0.10 mmol, 4.0 eq,) at room temperature. The resulting mixture was stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ solution and dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford compound **292** (12 mg, 0.02 mmol, 77%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41-7.45 (m, 2H), 7.32-7.39 (m, 5H), 7.29-7.31 (m, 3H), 6.26 (s, 0.5H), 6.12 (s, 0.5H), 4.66 (s, 0.5H), 4.62 (s, 0.5H), 4.06-4.15 (m, 1H), 3.91-4.01 (m, 1H), 3.48-3.52 (m, 3H), 3.27 (s, 3H), 1.35 (s, 3H), 0.94 (s, 9H), 0.81 (s, 3H), 0.12 (s, 3H), 0.00 (s, 3H).

6.10.4 Aldehyde **293**



293

$C_{23}H_{23}F_3O_6$
Mol Wt: 452.42

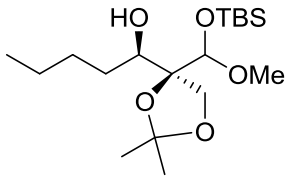
To a solution of compound **292** (5 mg, 0.008 mmol, 1.0 eq.) in THF (1.0 mL) was added TBAF (11.7 μL, 1*M* in THF, 1.4 eq.) at 0 °C. The resulting mixture was stirred for 45 min at 0 °C. The reaction mixture was washed with H_2O (2 mL) and the aqueous layer was extracted with MTBE (2 × 3 mL). Combined organic layers are dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 4:1) to afford compound **293** (3.3 mg, 0.007 mmol, 89%) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 7.37-7.44 (m, 10H), 6.12 (s, 1H), 4.21 (d, *J* = 9.6 Hz, 1H), 3.79 (dd, *J* = 9.2 Hz, 0.8 Hz, 1H), 3.48 (d, *J* = 1.3 Hz, 1H), 1.38 (s, 3H), 1.06 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.5, 165.5, 133.5, 131.8, 129.9, 129.7, 129.0, 128.5, 127.6, 112.9, 88.1, 78.1, 68.2, 66.0, 55.7, 29.8, 26.7, 25.5.

HRMS (ESI) calculated for $C_{23}H_{23}F_3O_6Na$ ([*M*+Na]$^+$): 475.1344, found: 475.1197.
[α]$^{23}_D$ = − 11.51 (*c* = 0.33, $CHCl_3$).

6.10.5 β-Hydroxy acetal **294**



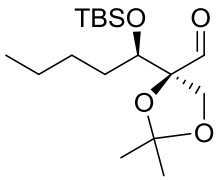
294

$C_{18}H_{38}O_5Si$
Mol Wt: 362.57

To a suspension of *N*-Ts-L-valine (67 mg, 0.25 mmol, 1.1 eq.) in CH_2Cl_2 (2.1 mL) was added BH_3•THF complex (0.22 mL, 1*M* in THF, 1.0 eq.) dropwise at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and 1 h at rt. Afterwards, the clear solution was cooled to −78 °C and valeraldehyde (19.4 mg, 0.22 mmol, 1.0 eq.) in CH_2Cl_2 (1.3 mL) was added followed by the subsequent addition of silyl ketene acetal **278** (80 mg, 0.29 mmol, 1.3 eq.) in CH_2Cl_2 (1.3 mL). The mixture was stirred for 1 h at −78 °C, quenched with phosphate buffer pH7 and the resulting biphasic mixture slowly warmed to rt. The two layers were separated, the organic phase was diluted with MTB ether, washed with sat. aq. $NaHCO_3$ solution and brine and dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford β-hydroxy acetal **294** (36 mg, 0.10 mmol, 40%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.75 (s, 1H), 3.97 (d, *J* = 10.1 Hz, 1H), 3.93 (d, *J* = 10.1 Hz, 1H), 3.47 (s, 3H), 3.39 (d, *J* = 12.2 Hz, 1H), 1.43 (s, 6H), 1.25-1.39 (m, 8H), 0.91 (s, 9H), 0.16 (s, 6H), 0.13 (s, 3H).

6.10.6 Aldehyde **287**



287

$C_{17}H_{34}O_4Si$
Mol Wt: 330.53

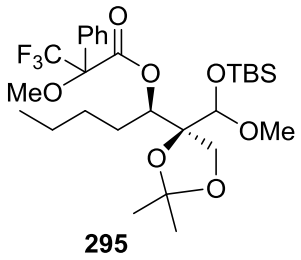
To a solution of β-hydroxy acetal **294** (10 mg, 0.027 mmol, 1.0 eq.) in THF (0.7 mL) was added NaHMDS (27.5 μL, 1M in THF, 1.0 eq.) at −78 °C. The resulting mixture was stirred for 5 min at -78 °C, warmed to 0 °C, stirred for 1 h and quenched with sat. aq. NH_4Cl solution. The biphasic solution was diluted with MTB ether and the two layers were separated. The aqueous phase was washed with MTBE and dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford aldehyde **287** (8.0 mg, 0.024 mmol, 87%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 4.28 (d, *J* = 8.4 Hz, 1H), 3.91 (d, *J* = 10.9 Hz, 1H), 3.85 (dd, *J* = 4.36, 2.1 Hz, 1H), 1.63-1.70 (m, 1H), 1.43-1.51 (m, 2H), 1.40 (d, *J* = 14.3 Hz, 6H), 1.25-1.36 (m, 5H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 201.9, 111.4, 89.3, 75.4, 68.4, 33.4, 28.0, 26.6, 26.5, 25.9, 23.0, 18.3, 14.1, -3.9, -4.3.

HRMS (EI) calculated for $C_{17}H_{34}O_4SiNa$ ([*M*+Na]$^+$): 353.2124, found: 353.1957.
$[\alpha]^{23}_D$ = + 11.62 (*c* = 0.8, $CHCl_3$).

6.10.7 Ester **295**



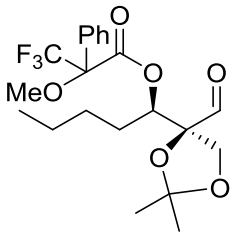
295

$C_{28}H_{45}F_3O_7Si$
Mol Wt: 578.73

To a solution of β-hydroxy acetal **294** (10 mg, 0.027 mmol, 1.0 eq.) in CH_2Cl_2 (1.1 mL) was added TEA (31.0 µL, 0.22 mmol, 8.0 eq.), DMAP (4.7 mg, 0.038 mmol, 1.4 eq.) and *R*-Moscher's chloride (21 µl, 0.11 mmol, 4.0 eq.) at room temperature. The resulting mixture was stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ solution and dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford compound **295** (10 mg, 0.017 mmol, 63%) as a colourless oil.

^{1}H-NMR (400 MHz, C_6D_6) δ 7.59-7.69 (m, 2H), 7.37-7.42 (m, 3H), 5.57 (dd, *J* = 9.1, 1.7 Hz, 1H), 4.68 (s, 1H), 4.07 (d, *J* = 9.0 Hz, 1H), 3.81 (d, *J* = 9.0 Hz, 1H), 3.58 (s, 3H), 3.33 (s, 3H), 1.35 (s, 6H), 1.28-1.32 (m, 9H), 0.91 (s, 9H), 0.1 (s, 6H).

6.10.8 Aldehyde **296**



296

$C_{21}H_{27}F_3O_6$
Mol Wt: 432.43

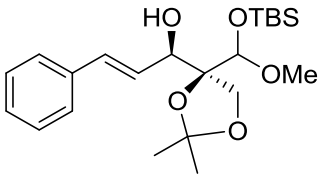
To a solution of compound **295** (4 mg, 0.007 mmol, 1.0 eq.) in THF (0.8 mL) was added TBAF (9.7 μL, 1*M* in THF, 1.4 eq.) at 0 °C. The resulting mixture was stirred for 45 min at 0 °C. The reaction mixture was washed with H_2O (2 mL) and the aqueous layer was extracted with MTBE (2 × 3 mL). Combined organic layers are dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 4:1) to afford compound **296** (2.8 mg, 0.006 mmol, 94%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.58 (s, 2H), 7.52-7.58 (m, 2H), 7.39-7.43 (m, 3H), 5.34 (dd, *J* = 9.6, 3.0 Hz, 1H), 4.08 (d, *J* = 10.2 Hz, 1H), 3.82 (d, *J* = 10.2 Hz, 1H), 3.54 (s, 3H), 1.73-1.82 (m, 1H), 1.56-1.66 (m, 1H), 1.37 (s, 6H), 1.24-1.33 (m, 4H), 0.83-0.90 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 200.5, 166.1, 131.7, 129.9, 128.6, 127.5, 112.4, 87.5, 76.7, 67.7, 66.0, 55.6, 29.8, 27.8, 26.4, 25.9, 22.4, 15.4, 13.9.

HRMS (ESI) calculated for $C_{21}H_{27}F_3O_6Na$ ([*M*+Na]$^+$): 455.1657, found: 455.1428.
$[\alpha]^{23}_D$ = −6.07 (*c* = 0.28, $CHCl_3$).

6.10.9 β-Hydroxy acetal **297**



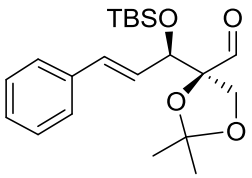
297

$C_{22}H_{36}O_5Si$
Mol Wt: 408.60

To a suspension of *N*-Ts-L-valine (67 mg, 0.25 mmol, 1.1 eq.) in CH_2Cl_2 (2.1 mL) was added BH_3•THF complex (0.22 mL, 1*M* in THF, 1.0 eq.) dropwise at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and 1 h at rt. Afterwards, the clear solution was cooled to −78 °C and *trans*-cinnamaldehyde (29.9 mg, 0.22 mmol, 1.0 eq.) in CH_2Cl_2 (1.3 mL) was added followed by the subsequent addition of silyl ketene acetal **278** (80 mg, 0.29 mmol, 1.3 eq.) in CH_2Cl_2 (1.3 mL). The mixture was stirred for 10 min at −78 °C, quenched with phosphate buffer pH7 and the resulting biphasic mixture slowly warmed to rt. The two layers were separated, the organic phase was diluted with MTBE, washed with sat. aq. $NaHCO_3$ solution and brine and dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford β-hydroxy acetal **297** (75 mg, 0.18 mmol, 80%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40-7.45 (m, 2H), 7.20-7.35 (m, 3H), 6.66-6.77 (m, 1H), 6.38-6.49 (m, 1H), 4.81-4.84 (m, 1H), 4.54-4.68 (m, 1H), 3.94-4.16 (m, 3H), 3.46-3.58 (m, 3H), 1.47 (d, *J* = 2.06 Hz, 6H), 0.90-0.97 (m, 9H), 0.14-0.22 (m, 6H).

6.10.10 Aldehyde **286**



286

$C_{21}H_{32}O_4Si$
Mol Wt: 376.56

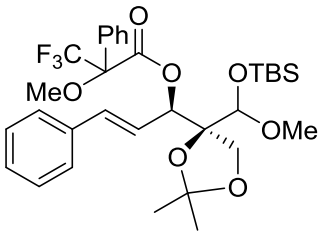
To a solution of β-hydroxy acetal **297** (10 mg, 0.024 mmol, 1.0 eq.) in THF (0.8 mL) was added NaHMDS (36.5 μL, 1*M* in THF, 1.0 eq.) at −78 °C. The resulting mixture was stirred for 5 min at −78 °C, warmed to 0 °C, stirred for 1 h and quenched with sat. aq. NH_4Cl solution. The biphasic solution was diluted with MTBE and the two layers were separated. The aqueous phase was washed with MTBE and dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford aldehyde **286** (6.0 mg, 0.016 mmol, 65%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.82 (s, 1 H), 7.40-7.24 (m, 5H), 6.57 (d, *J* = 16.5 Hz, 1 H), 6.25 (dd, *J* = 8.7, 7.2 Hz, 1 H), 4.46 (dd, *J* = 7.6, 1.2 Hz, 1 H), 4.87 (d, *J* = 8.7 Hz, 1 H), 3.88 (dd, *J* = 8.8, 0.6 Hz, 1 H), 1.43 (d, *J* = 8.4 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.04 (s, 3 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 203.5, 136.2, 133.3, 128.8, 128.7, 128.2, 126.9, 126.8, 119.7, 111.8, 89.5, 76.1, 68.0, 29.8, 26.7, 26.3, 25.9, -3.7, -4.8.

HRMS (ESI) calculated for $C_{21}H_{32}O_4SiNa$ ([*M*+Na]$^+$): 399.1968, found: 399.1631
$[\alpha]^{23}_D$ = −31.83 (*c* = 0.6, $CHCl_3$).

6.10.11 Ester **298**



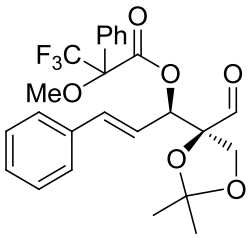
298

$C_{32}H_{43}F_3O_7Si$
Mol Wt: 624.76

To a solution of β-hydroxy acetal **297** (10 mg, 0.024 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) was added TEA (27.2 µL, 0.19 mmol, 8.0 eq.), DMAP (4.2 mg, 0.034 mmol, 1.4 eq.) and *R*-Moscher's chloride (18.5 µl, 0.10 mmol, 4.0 eq,) at room temperature. The resulting mixture was stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ solution and dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 10:1) to afford compound **298** (11 mg, 0.017 mmol, 72%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50-7.59 (m, 2H), 7.23-7.42 (m, 8H), 6.72 (d, *J* = 16.3 Hz, 1H), 6.20-6.34 (m, 1H), 5.92 (dd, *J* = 8.1, 0.8 Hz, 1H), 5.81 (dd, *J* = 8.4, 0.9 Hz, 1H), 4.71 (s, 0.5H), 4.61 (s, 0.5H), 4.07-4.17 (m, 1H), 3.77-3.89 (m, 1H), 3.56 (s, 3H), 3.35 (s, 1.5H), 3.31 (s, 1.5H), 1.32-1.44 (m, 6H), 0.89-0.95 (m, 9H), 0.07-0.14 (m, 6H).

6.10.12 Aldehyde **299**



$C_{25}H_{25}F_3O_6$
Mol Wt: 478.4576

To a solution of compound **298** (5 mg, 0.008 mmol, 1.0 eq.) in THF (1.0 mL) was added TBAF (11.7 µL, 1*M* in THF, 1.4 eq.) at 0 °C. The resulting mixture was stirred for 45 min at 0 °C. The reaction mixture was washed with H_2O (2 mL) and the aqueous layer was extracted with MTBE (2 × 3 mL). Combined organic layers are dried (Na_2SO_4). After removal of the solvents *in vacuo* the residue was purified by silica gel column chromatography (petroleum ether/EtOAc 4:1) to afford compound **299** (3.3 mg, 0.0068 mmol, 86%) as a colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.28-7.55 (m, 10H), 6.82 (d, *J* = 15.8 Hz, 1H), 6.23 (dd, *J* = 8.2, 7.2 Hz, 1H), 5.82 (dd, *J* = 8.4, 0.6 Hz, 1H), 4.19 (d, *J* = 9.3 Hz, 1H), 3.87 (dd, *J* = 9.2, 0.5 Hz, 1H), 3.51 (s, 3H), 1.42 (d, *J* = 2.2 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ 201.9, 165.4, 138.5, 135.2, 131.8, 129.7, 129.0, 128.8, 128.5, 127.3, 127.0, 119.5, 112.7, 87.7, 68.0, 55.9, 29.7, 26.4, 25.7.

HRMS (ESI) calculated for $C_{25}H_{25}F_3O_6Na$ ([*M*+Na]$^+$): 501.1501, found: 501.1398.
$[\alpha]^{23}_D$ = − 11.51 (*c* = 0.3, $CHCl_3$).

7. References

1. *World Cancer Report 2014*. World Health Organization. **2014**. pp. Chapter 1.1.
2. www.who.int.
3. Demain, A. L.; Vaishnav, P. *Micro. Biotech.* **2011**, 4(6), 687-699.
4. Nicolaou, K. C. *Proc. Nat. Acad. Sci*. **2004**, 101, 11928.
5. Tatsuta, K.; Hosokawa, S. *Chem. Rev*. **2005**, 105, 4707.
6. Pedicaris, S.; Vlachogianni, T.; Valavanidis, A. *Nat. Prod. Chem. Res.* **2013**, 1(3), 1-8.
7. Laport, M. S.; Santos. O. C. S.; Muricy. G. *Curr. Pharm. Biotech*. **2009**, 10(1), 86-105.
8. Yaffee, H. S.; Stargardter. F. *Arch. Dermatol*. **1963**, 87, 601.
9. *Tedania ignis*, copyright by Smithsonian institution.
10. Schmitz, F. J. ; Gopichand, Y.; Michaud, D. P.; Prasad, R.S .; Remaley, S. *Pure & appl. Chem.* **1981**, 53, 853.
11. Schmitz, F. J.; Vanderah, D. J.; Hollenbeak, K. H.; Enwall, C. E. L.; Yalamanchili, G. *J. Org. Chem.* **1983**, 48, 3941.
12. Schmitz, F. J.; Gunasekara, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, 106, 7251.
13. Staunton. J.; Wilkinson. B. *Topics in Current Chemistry*, Vol. 195; Springer Verlag, **1998**, 49.
14. Staunton, J.; Weissman, K. J. *Nat. Prod. Rep.* **2001**, 18, 380-416.
15. Fischbach, M. A.; Walsh, C. T. *Chem. Rev.* **2006**, 106, 3468-3496.
16. Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem. Int. Ed.* **1977**, 16, 585-607.
17. Fusetani, N.; Suguwara, T.; Matsunaga, S.; Hirota, H. J. *J. Org. Chem.* **1991**, 56, 4971.
18. Chevallier, C.; Bugni, T. S.; Feng. X.; Harper, M. K.; Orendt, A. M.; Ireland, C. M. *J. Org. Chem.* **2006**, 71, 2510.
19. Meragelman, T. L.; Willis, R. H.; Woldemichael, G. M.; Heaton, A.; Murphy, P. T.; Snader, K. M.; Newman, D. J.; van Soest, R.; Boyd, M. R.; Boyd, M. R.; Cardellina, J. H.; McKee, T. C. *J. Nat. Prod.* **2007**, 70, 1133.
20. Whitson, E. L.; Pluchino, K. M.; Hall, M. D.; McMahon, J. B.; McKee, T. C. *Org. Lett.* **2011**, 13(13), 3518-3521.
21. Rinehart, K. L.; Cheng, J, F.; Lee, J. S. ''Cytotoxic metabolites from Myriapora truncata'' 5514708, 19960507, 1996.
22. Nishimura, S.; Matsunaga, S.; Yoshida, S.; Nakao, Y.; Hirota. H.; Fusetani, N. *Bioorg. Med. Chem.* **2005**, 13, 455.

23. Nishimura, S.; Matsunaga, S.; Yoshida, S.; Nakao, Y.; Hirota. H.; Fusetani, N. *Bioorg. Med. Chem.* **2005**, 13, 449.
24. Pavan, M.; Bo, G. *Physiologia Comparata et Oecologia* **1953**, 3, 307-12.
25. Schroeder, S. J.; Blaha. G.; Tirado-Rives, J.; Steitz, Th. A.; Moore. P. B. *J. Mol. Biol.* **2007**, 367, 1471.
26. Rinehart, K. L.; Tachibana. K. *J. Nat. prod.* **1995**, 58, 344.
27. Cheng, J. F.; Lee, J. S.; Sakai, R.; Jares-Erijiman, E. A., Silva, M. V.; Rinehart, K. L. *J. Nat. Prod.* **2007**, 70, 32.
28. Muthukumar. Y.; Roy. M.; Raja. A.; Taylor. R. E.; Sasse. F. *ChemBioChem.* **2013**, 14, 260-64.
29. Fleming, K. N.; Taylor, R. E. *Angew. Chem. Int. Ed.* **2004**, 43, 1728-30.
30. Perez, M.; del Polzo. C.; Reyes. F.; Rodriguez. A.; Francesch. A.; Echavarren. A. M.; Cuevas. C. *Angew. Chem. Int. Ed.* **2004**, 43, 1724-27.
31. Roy. M. Dissertation, University of Notre Dame, Indiana, **2008**.
32. Sasse. F.; Steinmetz H.; Hoefle. G.; Reichenbach, H. *J. Antibiot.* **1995**, 48, 21.
33. Anderl. T.; Nicolas. L.; Muenkemer. J.; Baro. A.; Sasse. F.; Steinmetz. H.; Jansen. R.; Hoefle. G.; Taylor, R. E.; Laschat. S. *Angew. Chem. Int. Ed.* **2011**, 50, 942-945.
34. Anderl. T.; Nicolas. L.; Muenkemer. J.; Muthukumar. Y.; Baro. A.; Frey. W.; Sasse. F.; Taylor, R. E.; Laschat. S. *Eur. J. Org. Chem.* **2011**, 7294-307.
35. Taylor, R. E. *Nat. Prod. Rep.* **2008**, 25, 854-61.
36. Tang. L.; Shah. S.; Chung. L.; Carney. J.; Katz. L.; Khosla. C.; Julien. B. ‘‘Cloning and heterologus expression of the epothilone gene cluster’’ *Science* (*Washington, D. C.*) **2000**, 287, 640-42.
37. a) Smith III., A. B.; Adams, C. M.; Barbosa, S. A. L.; Degnan, A. P. *J. Am. Chem. Soc.* **2003**, 125, 350; b) Smith III., A. B.; Adams, C. M.; Barbosa, S. A. L.; Degnan, A. P. *Proc. Nat. Acad. Sci.* **2004**, 101, 12042.
38. Smith III., A. B.; Lee. D. *J. Am. Chem. Soc.* **2007**, 129, 10957-62
39. a) Smith III., A. B.; Condon, S. M.; McCauley, J. A.; Leazer, J. L, Jr.; Leahy, J. W.; Maleckza, R. R. J, Jr. *J. Am. Chem. Soc.* **1997**, 119, 947-962. b) Smith III., A. B.; Condon, S. M.; McCauley, J. A.; Leazer, J. L, Jr.; Leahy, J. W.; Maleckza, R. R. J, Jr. *J. Am. Chem. Soc.* **1997**, 119, 962-973. c) Smith III., A. B.; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, 31, 35-46.
40. Smith III., A. B.; Lodsie. S. A.; Org. Lett. **1998**, 1(8), 1249-52.
41. a) Matsushima, T.; Nakajima, N.; Zheng, B. Z.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, 48, 8505. b) Loh, T. P.; Feng. L. C. *Tet. Lett.* **2001**, 42, 3223.
42. Roush, W. R.; Palkowitz, A. D.; Ando. K. *J. Am. Chem. Soc.* **1990**, 112, 6348.

43. Parikh, J. P.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, 89, 5505.
44. Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, 112, 6447.
45. a) Innaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Japan.* **1979**, 52, 1989. b) Review: Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, 106, 911.
46. Vakalopoulos. A.; Hoffmann, H. M. R. *Org. Lett.* **2000**, 2, 1447.
47. Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, 32, 703.
48. Corey, E. J.; Fuchs, P. L. *Tet. Lett.* **1972**, 13, 3769.
49. Betzer, J. F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, 62, 7768.
50. a) Evans, D. A.; Sjogren, E. B.; Bartoli, J.; Dow, R. L. *Tet. Lett.* **1986**, 27, 4957. b) Evans, D. A.; Bartoli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, 103, 2127. c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, 103, 3099.
51. Ramachandran, P. V.; Prabhudas, B.; Pratihar. D.; Chandra. J. S.; Reddy, M. V. R. *Tet. Lett.* **2003**, 44, 3745.
52. Hicks, D. R.; Fraser-Reid. B. *Synthesis.* **1974**, 203.
53. Williams, D. R.; Sit, S. Y. *J. Am. Chem. Soc.* **1984**, 106, 2949.
54. Stork, G.; Zhao, K. *Tet. Lett.* **1989**, 30, 287.
55. a) Dess. D. B.; Martin, J. C. *J. Org. Chem.* **1983**, 45, 4155. b) Dess. D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, 113, 7277.
56. Kim, S.; Kee, I. S.; Park, Y. H. *Synlett.* **1991**, 183.
57. Julian, L. D.; Newcom. J. S.; Roush. W. R. *J. Am. Chem. Soc.* **2005**, 127, 6186.
58. Dunetz, J. R.; Julian. L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2008**, 130, 16407.
59. a) Taber, D. F.; Silverberg, L. J. *Tet. Lett.* **1991**, 32, 4227. b) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, 40, 40.
60. Fráter, G.; Müller, U.; Günther, W. *Tetrahedron.* **1984**, 40, 1269.
61. Mancuso, A. J.; Swern, D. *Synthesis.* **1981**, 165.
62. a) Lindgren, B. O.; Nilsson, T. *Acta. Chem. Scand.* **1973**, 27, 388. b) Kraus, G. A. Taschner, M. J. *J. org. Chem.* **1980**, 45, 1175.
63. Mitsnobu, O. *Synthesis.* **1981**, 1.
64. a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc. Chem. Comm.* **1987**, 1625. b) Ley, S. V.; Norman. J.; Griffith, W. P.; Mardsen, S. P. *Synthesis.* **1994**, 639.
65. Harried, S. S.; Lee, C. P.; Yang. G.; Lee, T. I. H.; Myles, D. C. *J. Org. Chem*, **2003**, 68, 6646.
66. a) Review: Katsuki, T.; Martin, V. S. *Org. React.* **1996**, 48, 1. b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.;

Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, 57, 2768. c) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 94, 2483.

67. a) Ehrlich, G.; Hassfeld, J.; Eggert, U,; Kalesse, M. Chem. Eur. J. 2008, 14, 2232. b) Ehrlich, G.; Hassfeld, J.; Eggert, U.; Kalesse, M. *J. Am. Chem. Soc.* **2006**, 128, 14038.
68. Paterson, I.; Goodman, J. M.; Tsaka, M. *Tet. Lett.* **1989**, 30, 7121. b) Vulpetti, A.; Bennardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron*. **1993**, 49, 685. c) Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, 58, 4182.
69. a) Giudicelli, M. B.; Picq. D.; Veyron, B. *Tet. Lett.* **1990**, 31, 6527. b) Mcclinton, M. A. *Aldrichimica Acta.* **1995**, 28, 31.
70. a) Loh, T. P.; Feng, L. C.; *Tet. Lett.* **2001**, 42, 6001. b) Loh, T. P.; Wong, C. M.; *Tet. Lett.* **2006**, 47, 4485.
71. Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tet. Lett.* **1996**, 37(3), 385.
72. a) Matsushima, T.; Mori, M.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J. I.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, 47(3), 308. b) Zheng, B. Z.; Maeda, H.; Mori, M.; Kusaka, S. I.; Matsushima, T.; Nakajima, N.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, 47(9), 1288.
73. Katsuki. T.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1980**, 102, 5974-76.
74. a) Schwartz, J.; Labinger, J. A. *Angew. Chem.* **1976**, 88, 402. b) Hart. D.; Blachbun, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, 97, 679. c) Wipf, P.; Jahn, H. *Tetrahedron.* **1996**, 52, 12853.
75. Hassfeld, J.; Eggert, U.; Kalesse, M.; *Synthesis.* **2005**, 7, 1183.
76. Hassfeld, J. Dissertation, Universität Hannover, **2005**.
77. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, 108, 5919.
78. Elhrich, G.; Kalesse, M. *Synlett*, **2005**, 4, 655.
79. a) Hirai, A.; Matsui, A.; Komatsu, K.; Tanino, K.; Miyashita. M. *Chem. Comm.* **2002**, 1970. b) Iwata, Y.; Tanino, K.; Miyashita, M. *Org. Lett.* **2005**, 7, 2341. c) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, 64, 663. d) Jung, M. E.; Marquez, R. *Tetrahedron. Lett.* **1999**, 40, 3129. e) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, 2, 1669. f) Jung, M. E.; Lee, C. P. *Tetrahedron. Lett.* **2000**, 41, 9719. g) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, 3, 333. h) Jung, H.; Yoo, M. E. *Org. Lett.* **2007**, 9, 3543. i) Jung, M. E.; Zhange, T. *Org. Lett.* **2008**, 10, 137. j) Nyavanandi, V. K.; Nanduri, S.; Dev, R. V.; Naidu, A.; Iqbal, J. *Tetrahedron. Lett.* **2006**, 47, 6667. k) Nyavanandi, V. K.; Nadipalli, P.; Naduri, S.; Naidu, A.; Iqbal, J. *Tetrahedron. Lett.* **2007**, 48, 6905.

80. Frank, B.; Wenzel, S. C.; Bode, H. C.; Scharfe, M.; Blöcker, H.; Müller, R. *J. Mol. Biol.* **2007**, 374, 24.
81. Diaz, N.; Zhu, M.; Ehrlich, G.; Eggert, U.; Muthukumar, Y.; Sasse. F.; Kalesse, M. *Chem. Eur. J.* **2012**, 18, 4946.
82. a) Rauchschwalbe, G.; Schlosser, M. *Helv. Chim. Acta.* **1975**, 58, 1094. b) Rauchschwalbe, G.; Schlosser, M. *J. Am. Chem. Soc.* **1978**, 100, 3258.
83. Sidler, D. R.; Lovelace, T. C.; McNamara, J. M.; Reider, P. J. *J. Org. Chem.* **1994**, 59(6), 1231.
84. Hassfeld, J.; Christmann, M.; Kalesse, M. *Org. Lett.* **2001**, 3(22), 3561.
85. Matsushima, T.; Mori, M.; Maeda, H.; Nakajima, N.; Uenishi, J. I.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, 46, 1335.
86. Masamune, S.; Choy, W.; Peterson, J. S.; Sita, L. *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 1-30.
87. Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, 117, 3461.
88. Okawara, R.; Wada, M. *J. Organometal. Chem.* **1963**, 1, 81.
89. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis.* **1994**, 639.
90. Ehrlich, G. Dissertation, Universität Hannover, **2007**.
91. Diaz, N. Dissertation, Universität Hannover, **2007**.
92. De la Torre, B. G.; Terres, J. L.; Bardaji. E.; Clapés, P.; Xaus, N.; Jorba, X.; Calvet. S.; Alberico. F.; Valencia, G. *J. Chem. Soc., Chem. Commun.* **1990**, 965.
93. Mukaiyama, T.; Usui, M.; Shimada, E. *Chem. Lett.* **1975**, 1045.
94. Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron. Lett.* **2002**, 43, 7535.
95. Kobayashi, J.; Shimbo, K.; Sato, M.; Tsuda, M. *Org. Lett.* **2000**, 2, 2805.
96. Diaz, N.; Naini, A.; Muthukumar, Y.; Sasse, F.; Kalesse, M. *ChemMedChem.* **2012**, 7, 771.
97. a) Reetz, M. T.; Kyung, S, -H.; Bolm, C.; Zierke, T. *Chem. Ind.* **1985**, 824. b) Kobayashi, S.; Sano, T.; Mukaiyama, T. *Chem. Lett.* **1989**, 1319. c) Takasu, M.; Yamamoto, H. *Synlett.* **1990**, 194. d) Sartor, D.; Saffrich, J.; Helmchen, G. *Ibid.* **1990**, 197.
98. Kiyooka, S, -I.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, 56(7), 2276.
99. Kiyooka, S, -I.; Nakano, M.; Shiota, F.; Fujiyama, R. *J. Org. Chem.* **1989**, 54, 5409.
100. Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osaida, H. *J. Am. Chem. Soc.* **2002**, 124, 12078.
101. Schäckel, R.; Hinkelmann, B.; Sasse, F.; Kalesse, M. *Angew. Chem. Int. Ed.* **2010**, 49, 1619.
102. Bülow, L. Dissertation, Universität Hannover, **2007**.
103. Bülow, L.; Naini, A.; Fohrer, J.; Kalesse, M. *Org. Lett.* **2011**, 13(22), 6038.
104. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, 105, 2092.

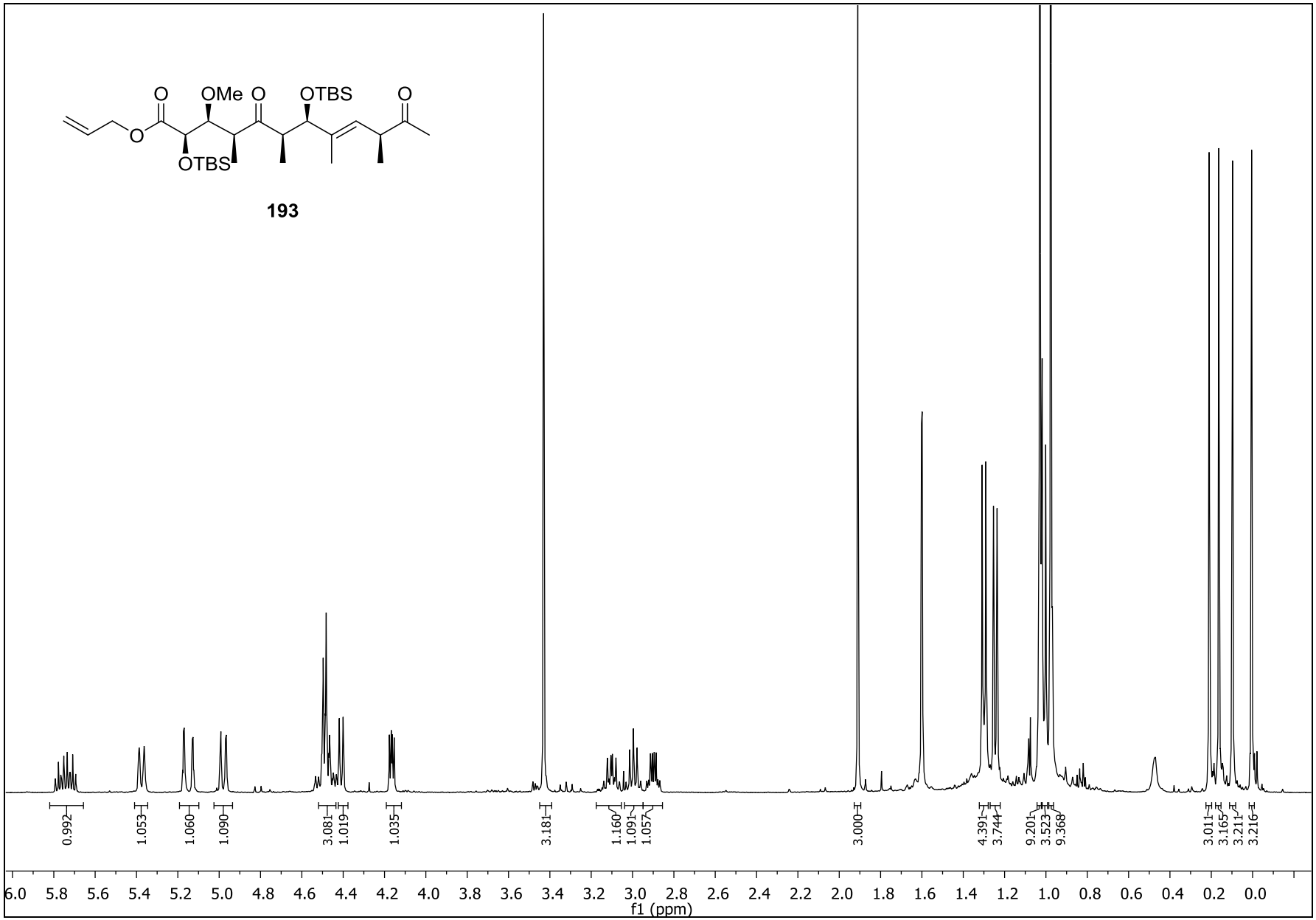
105. Bestmann, H. –J.; Hartung, H. *Chem. Ber.* **1966**, 99, 1198.

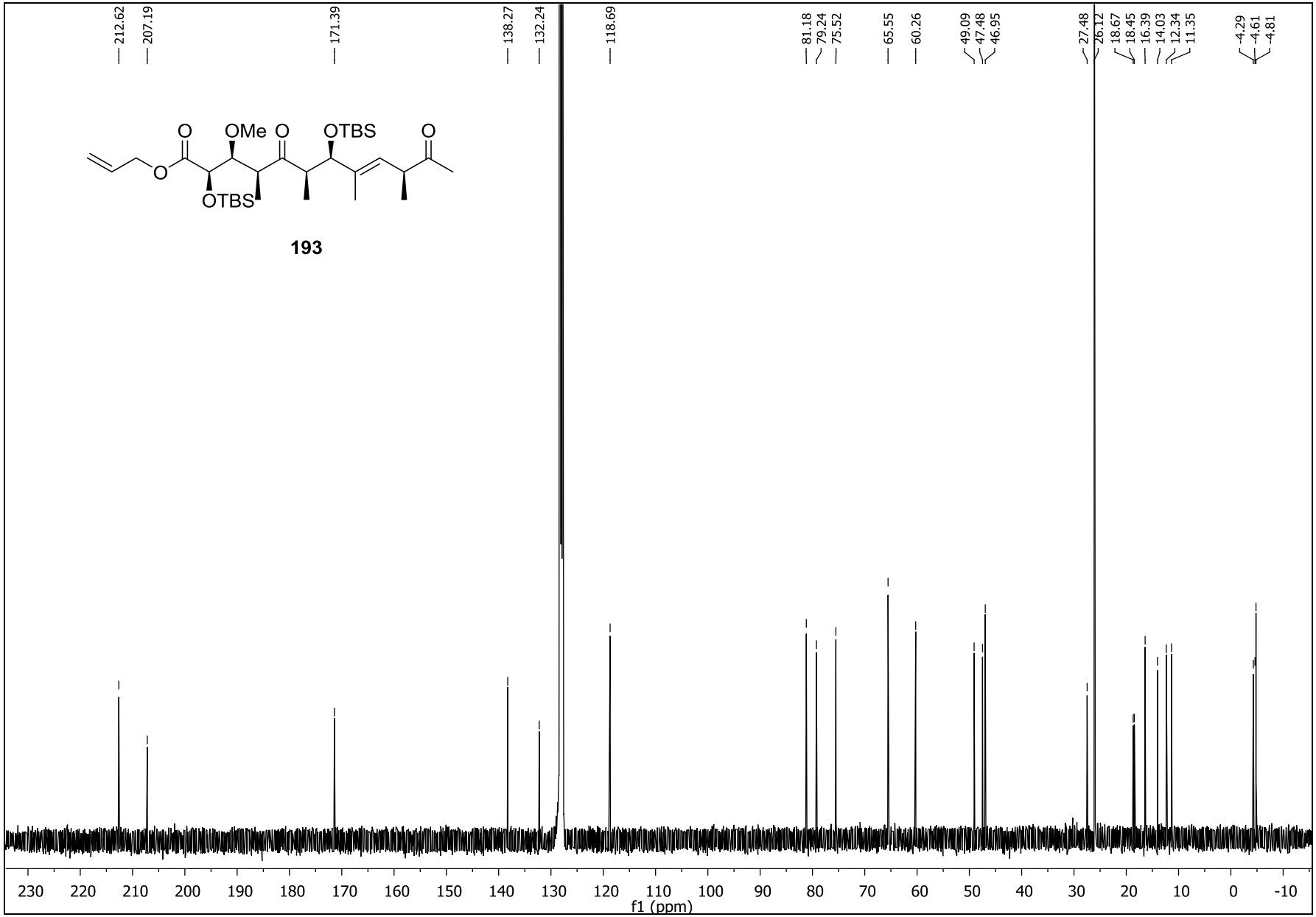
106. Chaudhuri, S. S.; Akamanchi, K. G. *Synlett.* **1999**, 11, 1763.

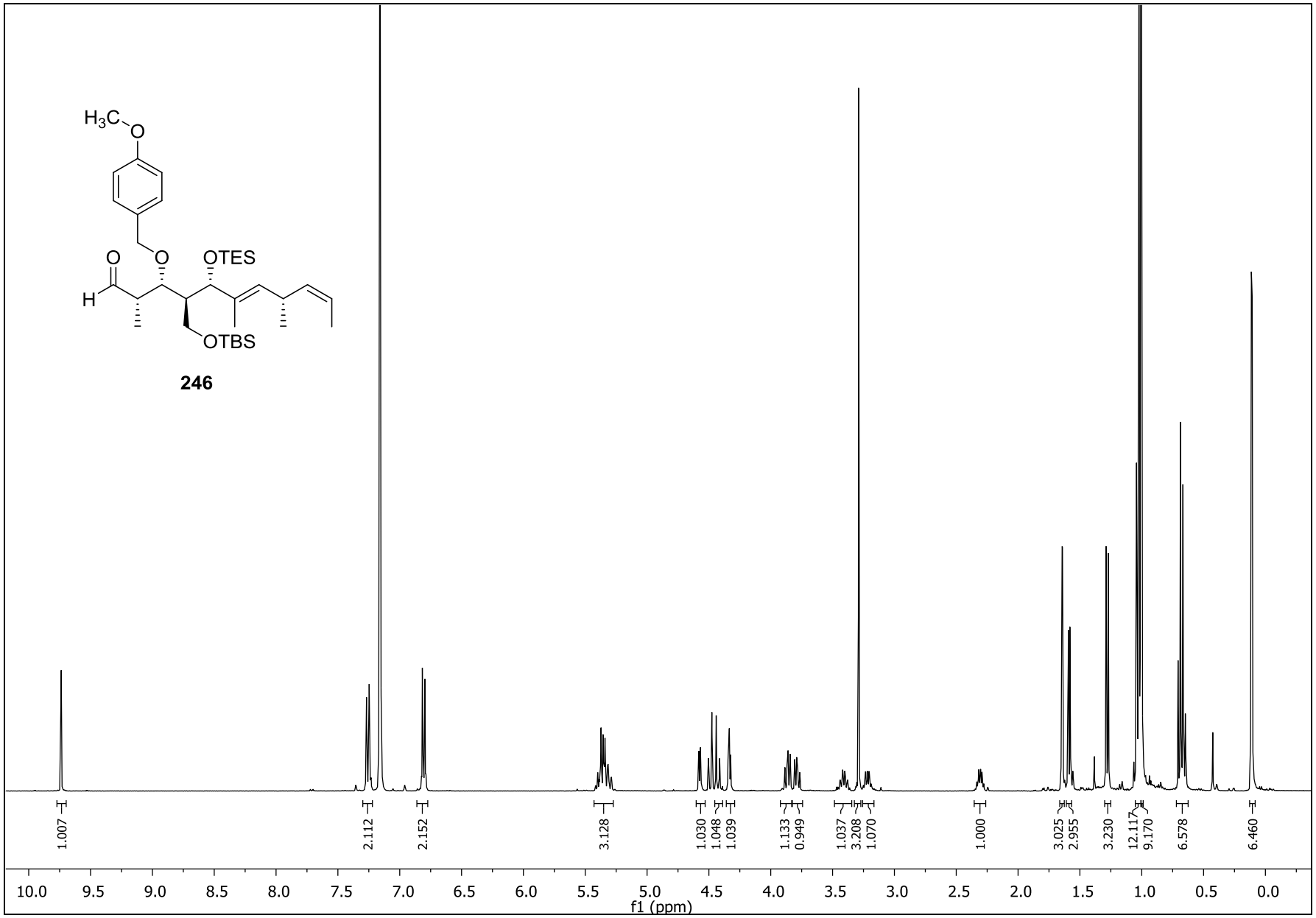
107. Walkup, R. D.; kahl, J. D.; Kane, R. R. *J. Org. Chem.* **1998**, 63, 9113.

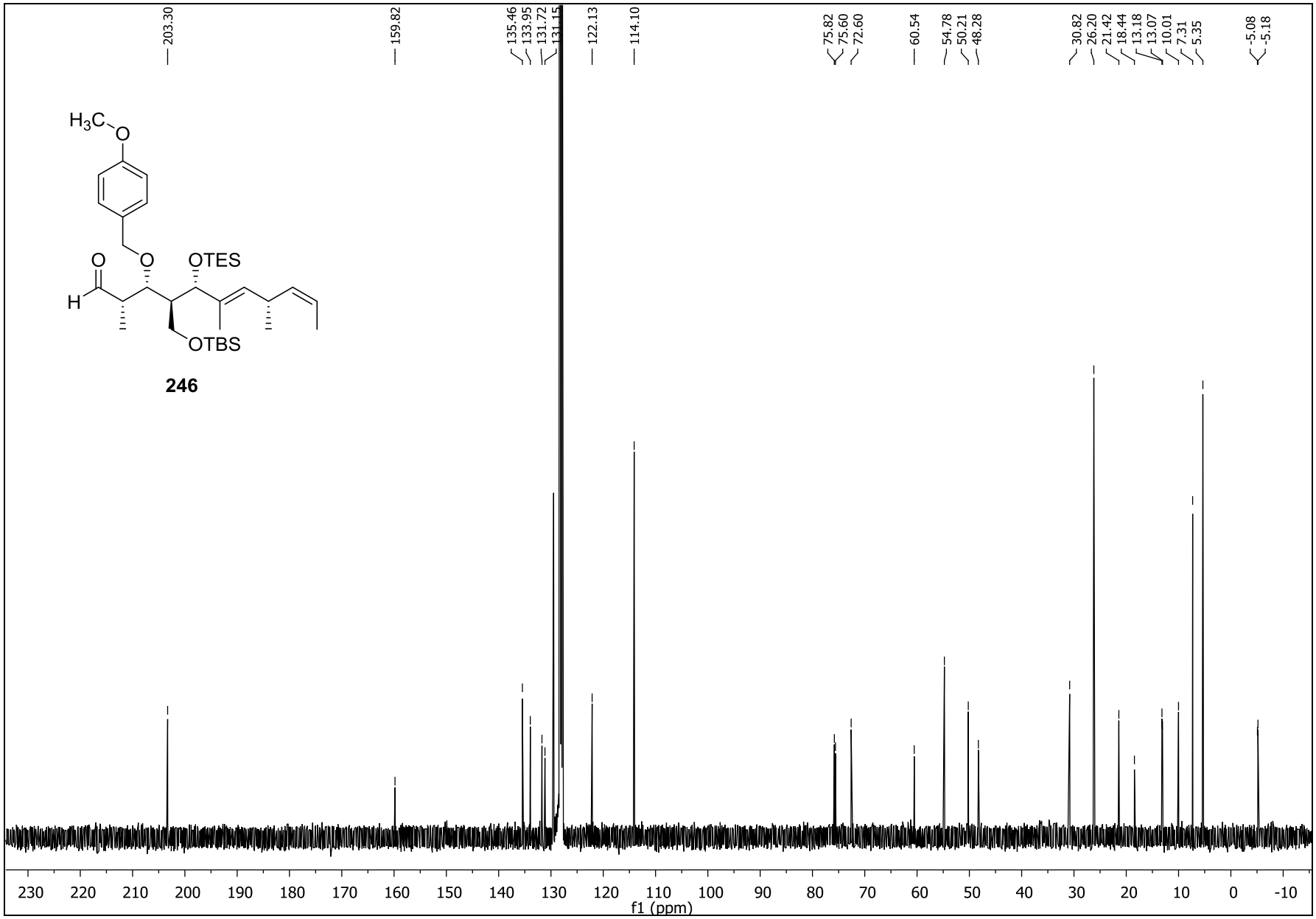
108. a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, 106, 6757. b) Merlo, A. A.; Fernandes, M. S. *Synth. Comm.* **2003**, 33, 1167.

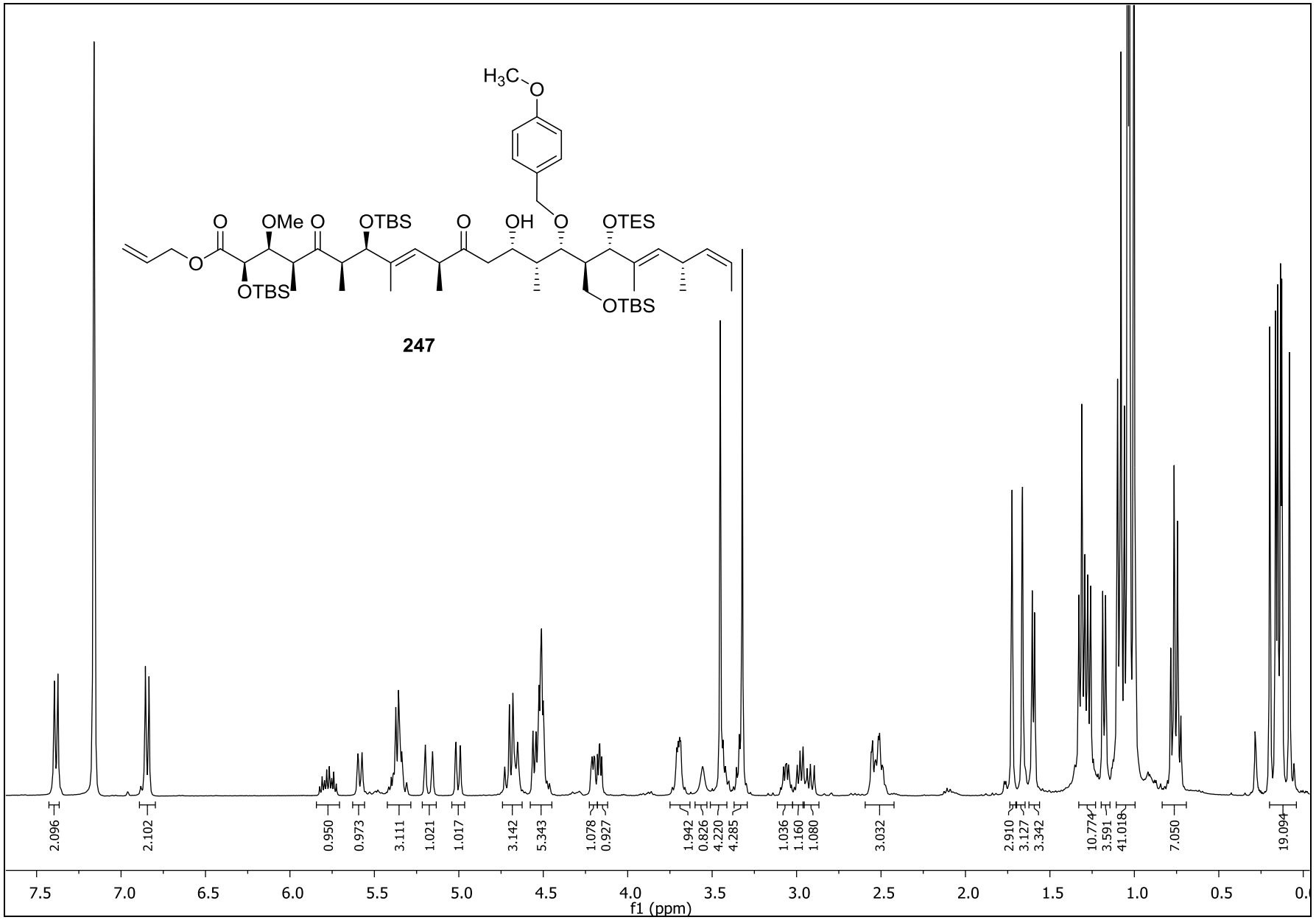
109. Massey, A. G.; Park, A. *J. Organomet. Chem.* **1964**, 2, 245.

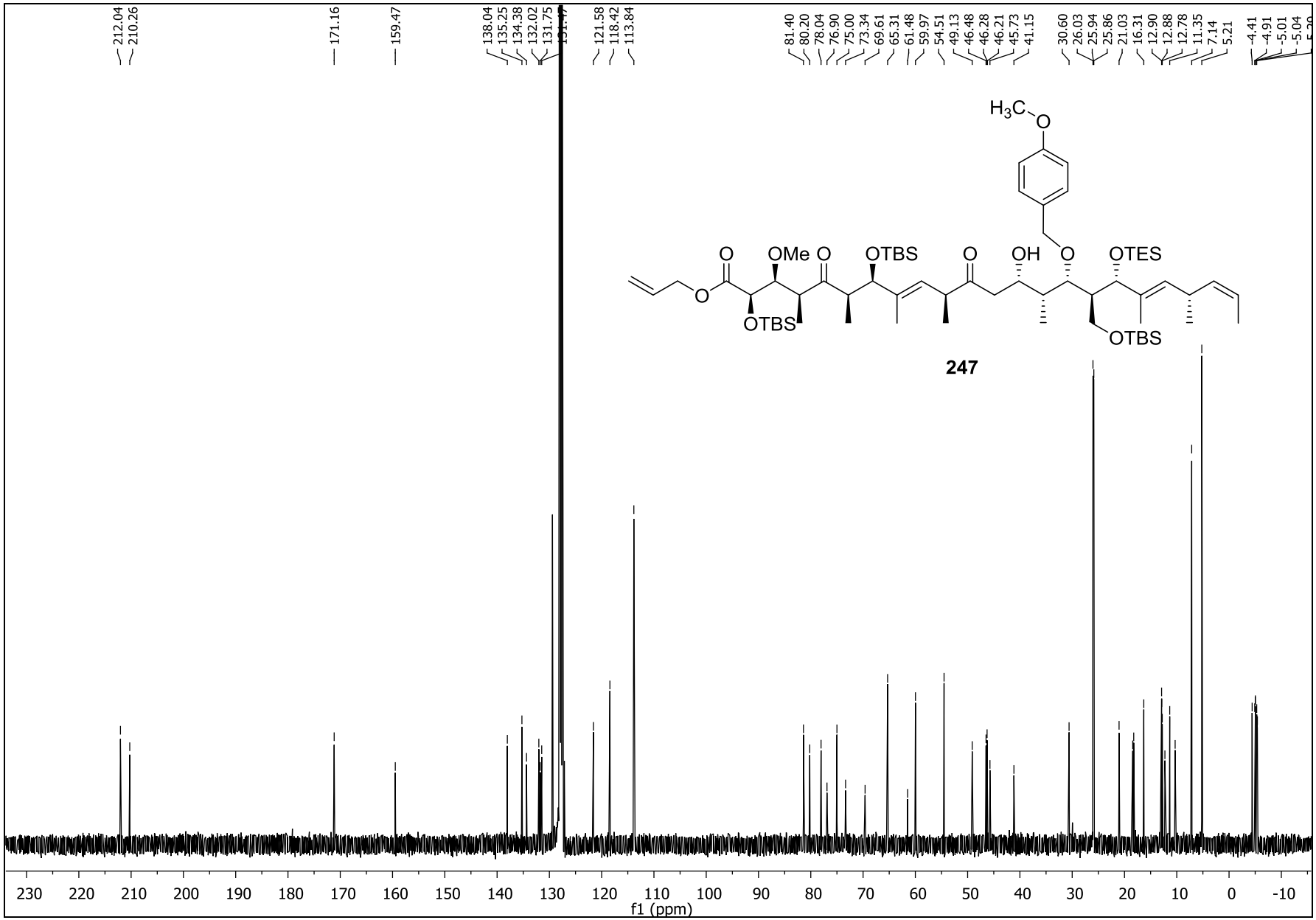

O
OMe
O
OTBS
O
O
OTBS
193
0.992
1.053
1.060
1.090
3.081
1.019
1.035
3.181
1.160
1.091
1.057
3.000
4.391
3.744
9.201
3.523
9.368
3.011
3.165
3.211
3.216
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0
f1 (ppm)

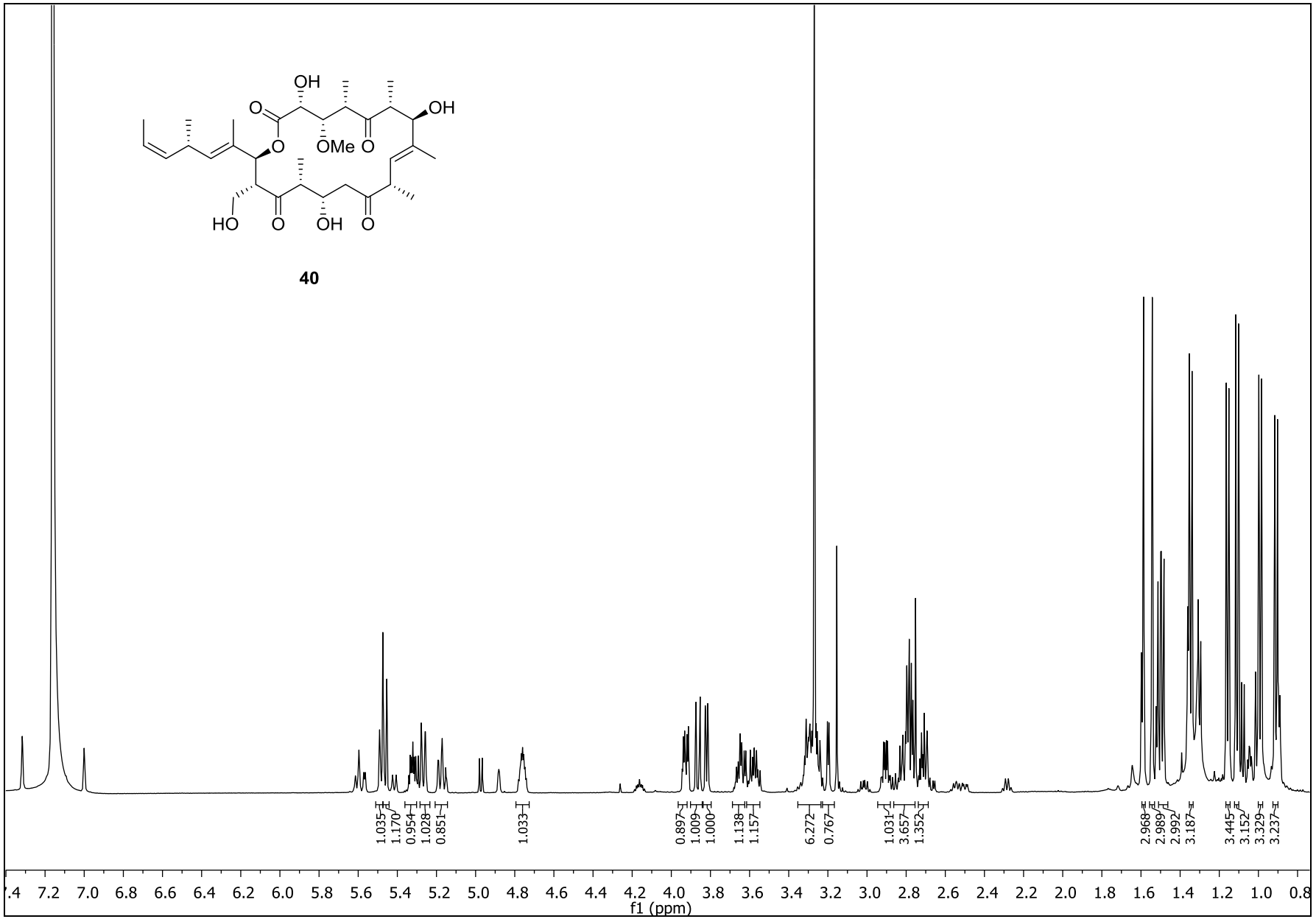

212.62
207.19
171.39
138.27
132.24
118.69
81.18
79.24
75.52
65.55
60.26
49.09
47.48
46.95
27.48
26.12
18.67
18.45
16.39
14.03
12.34
11.35
-4.29
-4.61
-4.81
O
OMe
O
OTBS
O
O
OTBS
193
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

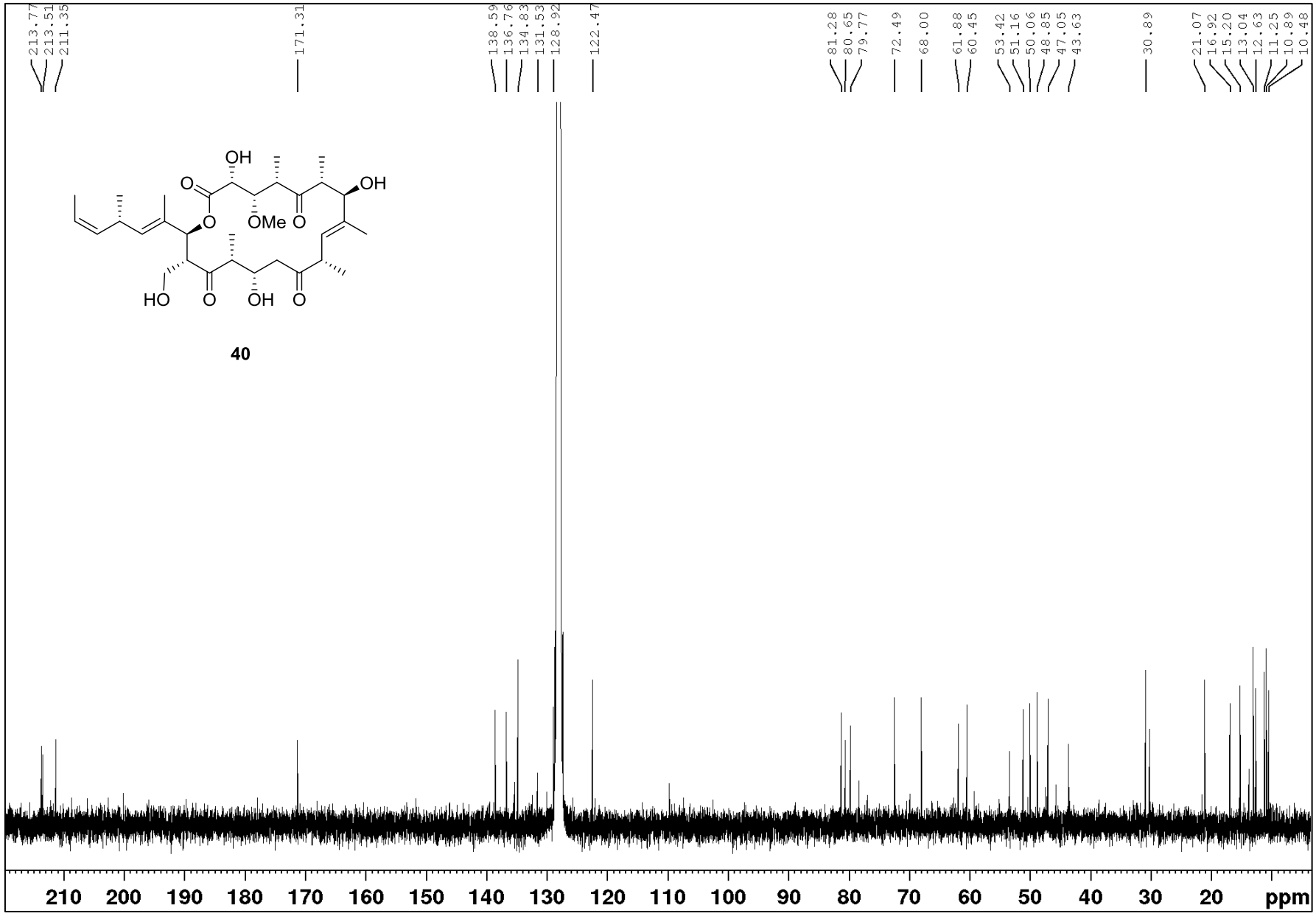

H3C
O
O
O
OTES
H
OTBS
246
1.007
2.112
2.152
3.128
1.030
1.048
1.039
1.133
0.949
1.037
3.208
1.070
1.000
3.025
2.955
3.230
12.117
9.170
6.578
6.460
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


203.30
159.82
135.46
133.95
131.72
131.15
122.13
114.10
75.82
75.60
72.60
60.54
54.78
50.21
48.28
30.82
26.20
21.42
18.44
13.18
13.07
10.01
7.31
5.35
-5.08
-5.18
H3C
O
O
O
OTES
H
OTBS
246
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

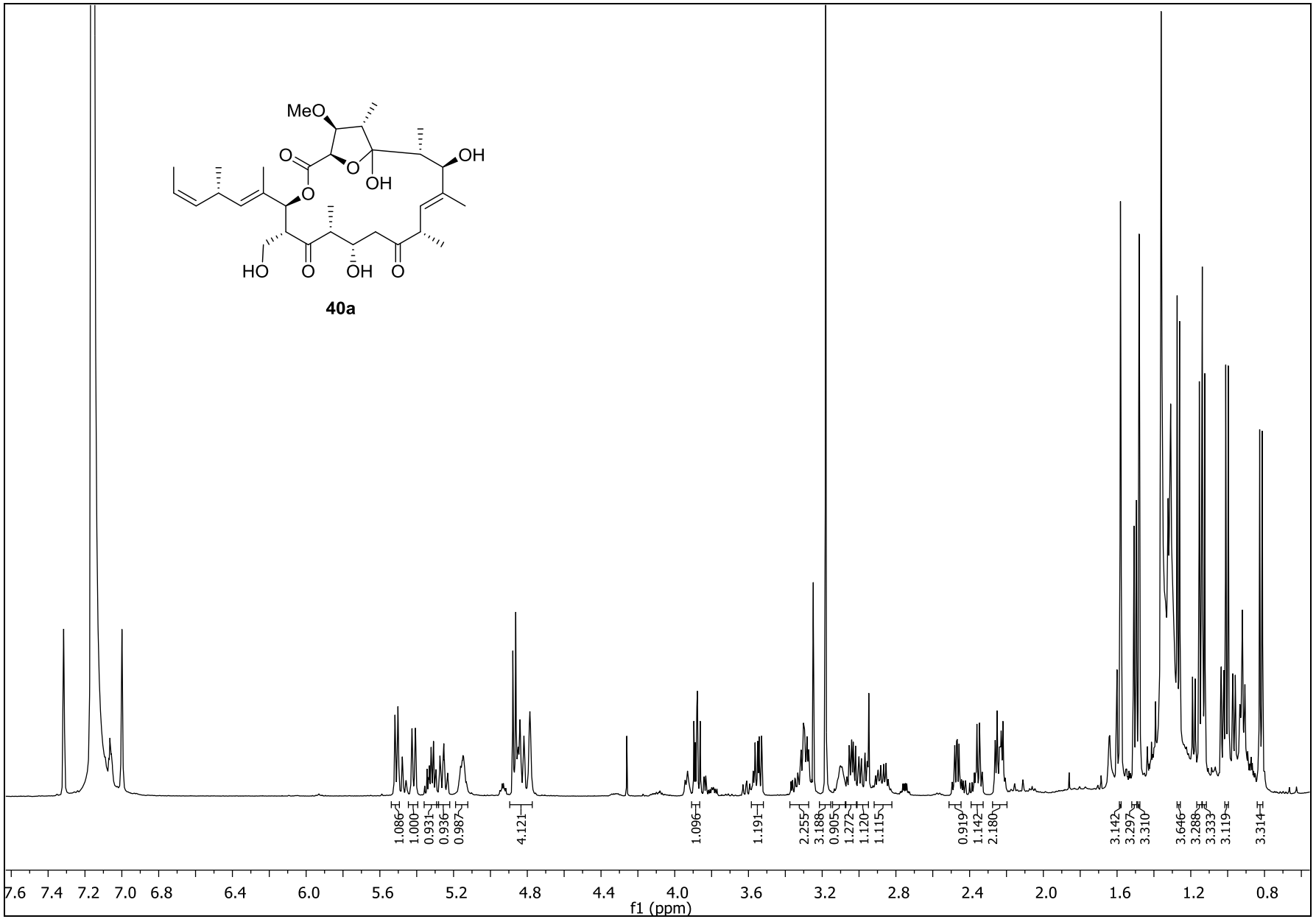

H3C
O
O
OMe
O
OTBS
O
OH
O
OTES
O
OTBS
OTBS
247
2.096
2.102
0.950
0.973
3.111
1.021
1.017
3.142
5.343
1.078
0.927
1.942
0.826
4.220
4.285
1.036
1.160
1.080
3.032
2.910
3.127
3.342
10.774
3.591
41.018
7.050
19.094
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

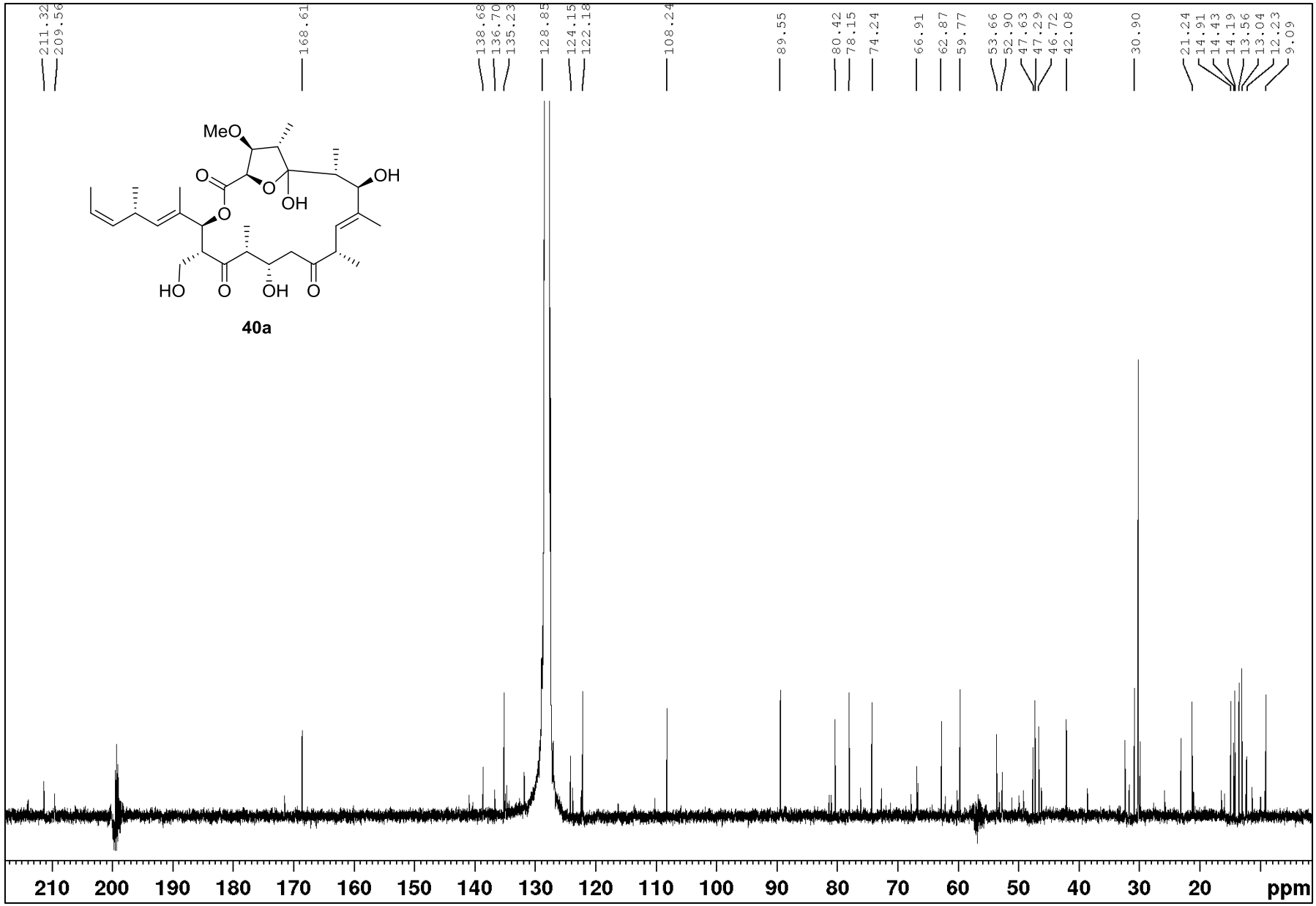

212.04
210.26
171.16
159.47
138.04
135.25
134.38
132.02
131.75
121.58
118.42
113.84
81.40
80.20
78.04
76.90
75.00
73.34
69.61
65.31
61.48
59.97
54.51
49.13
46.48
46.28
46.21
45.73
41.15
30.60
26.03
25.94
25.86
21.03
16.31
12.90
12.88
12.78
11.35
7.14
5.21
-4.41
-4.91
-5.01
-5.04
H3C
O
OMe
OTBS
OH
OTES
247
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
O
OH
O
OMe O
HO
O
OH
O
40
1.035
1.170
0.954
1.028
0.851
1.033
0.897
1.009
1.000
1.138
1.157
6.272
0.767
1.031
3.657
1.352
2.968
2.989
2.992
3.187
3.445
3.152
3.329
3.237
f1 (ppm)


213.77
213.51
211.35
171.31
138.59
136.76
134.83
131.53
128.92
122.47
81.28
80.65
79.77
72.49
68.00
61.88
60.45
53.42
51.16
50.06
48.85
47.05
43.63
30.89
21.07
16.92
15.20
13.04
12.63
11.25
10.89
10.48
OH
O
OH
O
OMe
O
HO
O
OH
O
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

40


MeO
O
O
OH
OH
O
HO
O
OH
O
40a
1.086
1.000
0.931
0.936
0.987
4.121
1.096
1.191
2.255
3.188
0.905
1.272
1.120
1.115
0.919
1.142
2.180
3.142
3.297
3.310
3.646
3.288
3.333
3.119
3.314
7.6 7.4 7.2 7.0 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8
f1 (ppm)


211.32
209.56
168.61
138.68
136.70
135.23
128.85
124.15
122.18
108.24
89.55
80.42
78.15
74.24
66.91
62.87
59.77
53.66
52.90
47.63
47.29
46.72
42.08
30.90
21.24
14.91
14.43
14.19
13.56
13.04
12.23
9.09
MeO
O
O
OH
OH
O
HO
O
OH
O
40a
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

Curriculum Vitae

Personal Data

Name:	Arun Naini
Date of Birth:	June 4, 1983
Place of Birth:	Bhongir, India
Family Status:	Married
Nationality:	India
Email:	arun.naini26@gmail.com

Academic Qualifications

08/2010-06/2014	**Doctoral studies** at Leibniz Universität, Institute ofOrganic Chemistry, Hannover, Germany. Prof. Dr. **Markus Kalesse**, Theme: Total synthesis of Isotedanolide.
08/2011 – 11/2011	**Independent Researcher** at University of Notre Dame, Notre Dame, Indiana, USA. Prof. Dr. **Richard Taylor**, Theme: Studies on Myriaporones and Tedanolides.
07/2003– 05/2005	**Master of Science** (Organic Chemistry, Drug design) MNR PG College, Osmania University, Hyderabad, India.
07/2000– 05/2003	**Bachelor of Science** (Chemistry, Maths and Physics) AV College, Osmania University, Hyderabad, India.
07/1998– 05/2000	**Class XII** (Intermediate), (Chemistry, Maths and Physics), Sir CRR College, Board of Intermediate, Andhra Pradesh, India.

Industrial Experience

10/2005 – 06/ 2010	Research Scientist-II, **Albany Molecular Research Inc.**, Hyderabad Research Center, Hyderabad, India.

Publications

1. Nina Diaz, Arun Naini, Yazh Muthukumar, Florenz Sasse, Markus Kalesse.

   ‘‘Synthesis of simplified tedanolide analogues-connecting tedanolide to myriaporone and gephyronic acid”

   ChemMedChem. 2012 , 7 (5), 771-5.

2. Leila Bülow, Arun Naini, Jörg Fohrer, Markus Kalesse.

   ‘‘A Kiyooka aldol approach for the synthesis of the C(14)-C(23) segment of the diastereomeric analog of tedanolide C”

   Org. Lett. 2011, 13(22), 6038-41.

Conferences and Workshops

- Poster Presentation at *Challenges in Organic chemistry and Chemical Biology ISACS7 Conference* 2012, Edinburgh, **Scotland**.

- Attended symposium on the occasion of 125 years of Angewandte Chemie, March 2013, Berlin, **Germany**.

- Attended the training school in Molecular modeling in April 2013 at Espoo, **Finland**.
  Basics in **Molecular modelling** of small molecules using maestro software and to analyze the conformations.