



**NANYANG
TECHNOLOGICAL
UNIVERSITY**

**PART I : SYNTHESIS OF SEX PHEROMONE OF THE
PINE SAWFLY, *MACRODIPRION NEMORALIS***
**PART II : SYNTHETIC STUDIES TOWARDS THE TOTAL
SYNTHESIS OF IRIOMOTEOLIDE-1A**

CHIN YEN JIN
SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES
2011

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SYNTHESIS OF IRIOMOTEOLIDE-1A**

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A thesis submitted to the Nanyang Technological University
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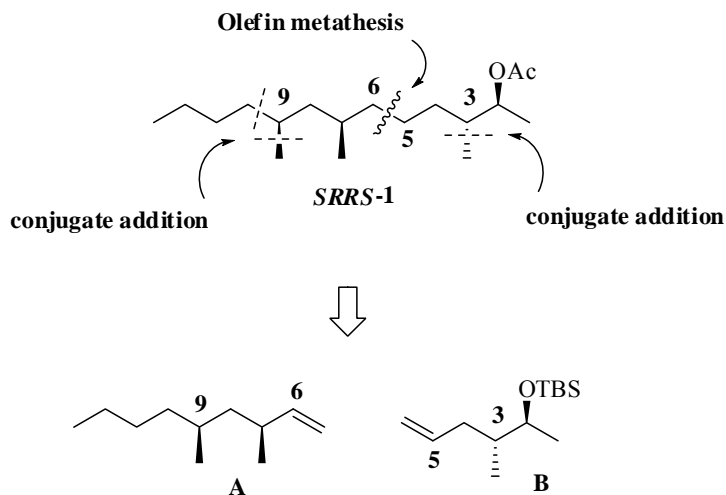
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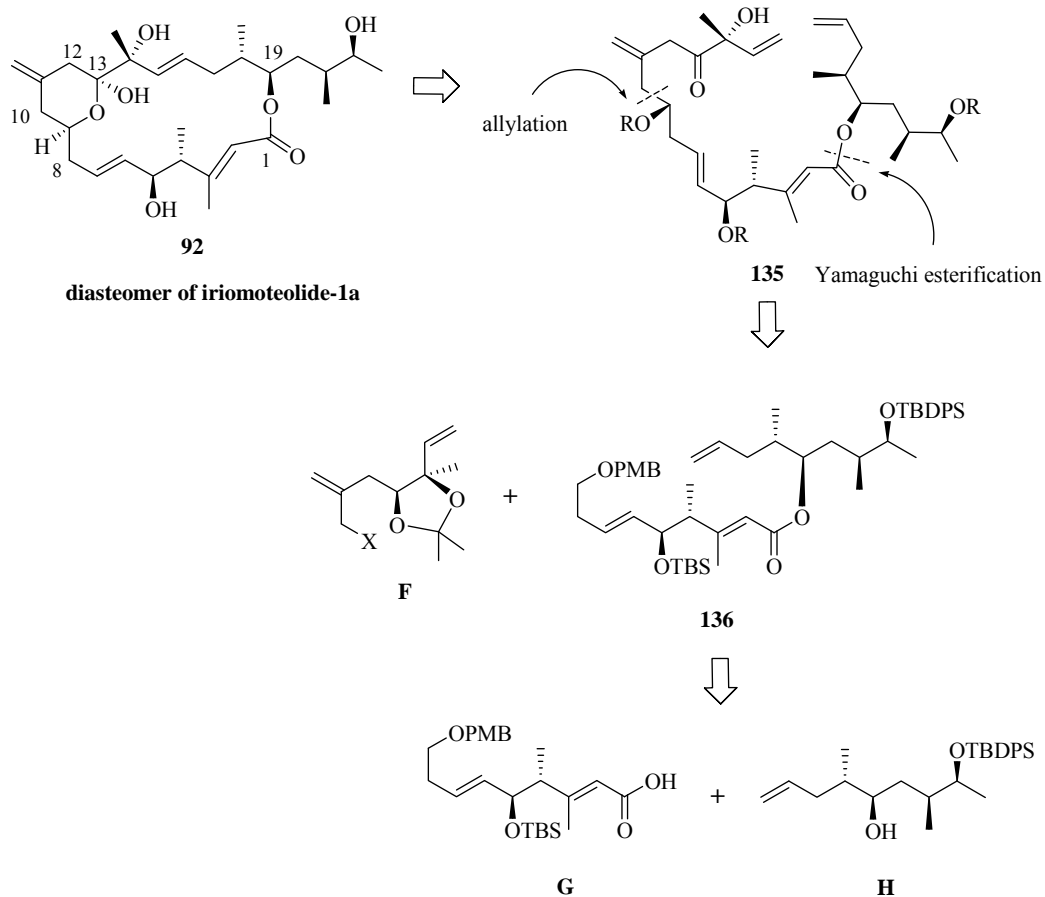
SUMMARY

Conjugate addition of Grignard reagents to α,β -unsaturated esters is one of the most convergent strategies for the construction of C–C bonds. Our group has previously developed a highly efficient CuI-Tol-BINAP-catalyzed asymmetric conjugate using Grignard reagents. The absolute stereochemistry of the newly introduced alkyl group can easily be controlled by using the enantiomer of the ligand. Therefore, one of the highlights in this thesis is to demonstrate the versatility of our group's asymmetric conjugate addition for synthesis of natural products.

In the first part of this thesis, an elegant display of the CuI-Tol-BINAP-catalyzed asymmetric conjugate addition is established in the total synthesis of sex pheromone of the pine sawfly, *Macrodiprion Nemoralis* (*SRRS-1*). The key features of our strategy are: (I) one-pot DIBAL-H reduction–Wittig olefination, (II) olefin cross metathesis of fragment **A** and fragment **B**, and (III) a CuI-Tol-BINAP-catalyzed asymmetric conjugate addition using Grignard reagents in good yields and excellent stereoselectivities.



In the final part of this thesis, the key fragment of a diastereomer of iriomoteolide-1a (**136**) was synthesized via a convergent synthetic strategy that featured the use of our group's asymmetric conjugate addition and Paterson aldol. The synthesis also demonstrated a successful intermolecular Yamaguchi esterification between two elaborate molecular fragments. As excellent enantio- and distereo-control was achieved during the synthesis, a single isomer was isolated towards the end of the synthesis.



INDEX OF ABBREVIATIONS

δ	chemical shift
Δ	reflux
$^{\circ}\text{C}$	degree centigrade
ABq	AB quartet
Ac	acetyl
acac	acetoacetate
AcCl	acetyl chloride
ACCN	<i>azo-bis-cyclohexylcarbonitrile</i>
AcOH	acetic acid
Ac ₂ O	acetic anhydride
AIBN	<i>azo-bis-isobutyronitrile</i>
AllylBr	allylbromide
aq.	aqueous
9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
B:	Lewis base
Bn	benzyl
BOC	tert-butoxycarbonyl
br s	broad singlet
BuLi	butyl lithium
Bz	benzoyl
Cacl _d	calculated
Cat.	catalytic
Cbz	benzyloxycarbonyl
CDCl ₃	deuterated chloroform
COSY	correlated spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
CH ₂ Cl ₂	dichloromethane
CHCl ₃	chloroform

cm ⁻¹	inverse centimeter
Cy	cyclohexane; cyclohexanyl
d	doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylidene acetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
dd	doublets of doublet
ddd	doublets of doublets of doublet
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DIPBr	B-bromodiisopinocampheylborane
DMAP	4-(<i>N,N</i> -dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dq	doublets of quartet
dt	doublets of triplet
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
<i>ee</i>	enantiomeric excess
EI	electron impact ionization
equiv.	equivalent
ESI	electrospray ionization
Et	ethyl
ether	diethyl ether
Et ₃ N	triethylamine
EtOAc	ethyl acetate
EtOH	ethanol
FTIR	Fourier transform infrared spectroscopy
g	gram
h	hour
H	hydrogen

hept	heptet
Hex	hexane
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HMQC	heteronuclear multiple quantum correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
IC	Inhibitory concentration
IR	infrared
Ipc	isopinocampheyl
<i>i</i> -Pr	isopropyl
<i>J</i>	coupling constants
kg	kilogram
KHMDS	potassium bis(trimethylsilyl)amide
L.A.	Lewis acid
LDA	lithium diisopropylamide
M	concentration (mol/dm ⁻³)
M ⁺	parent ion peak (mass spectrum)
m	multiplet
<i>m</i> -CPBA	<i>meta</i> -chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MEM	2-methoxyethoxy methyl
MeOH	methanol
mg	milligram
MHz	Megahertz
min	minute
mmol	millimoles
mol	moles
MS	mass spectrum
Ms	methanesulfonyl
N	concentration (normality)

NaHMDS	Sodium hexamethyl disilazide
NBS	<i>N</i> -bromosuccinimide
<i>n</i> -Bu	<i>n</i> -butyl
nmr	nuclear magnetic resonance
NMP	<i>N</i> -methyl-2-pyrrolidone
NOESY	nuclear Overhauser enhancement spectroscopy
N.R.	no reaction
obs.	observed
OTf	trifluoromethanesulfonate
PBr ₃	phosphorus tribromide
PCC	pyridinium chlorochromate
Pd / C	palladium on carbon
Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
Ph	phenyl
PhH	benzene
PhMe	toluene
PMB	<i>p</i> -methoxybenzyl
PMBz	<i>p</i> -methoxybenzoyl
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million
PPTS	pyridinium <i>p</i> -toluenesulfonate
Py	pyridine
PYBOX	bis(oxazoliny)pyridine
q	quartet
qd	quartets on doublet
quint.	quintet
rt.	room temperature
RBF	round bottom flask
R _f	retention factor
(<i>R</i>)-Tol-BINAP	(<i>R</i>)-(+)-2,2'-Bis(di- <i>p</i> -tolylphosphino)-1,1'-binaphthyl
s	singlet
sat'd	saturated
<i>s</i> -Bu	<i>sec</i> -Butyl
(<i>S</i>)-Tol-BINAP	(<i>S</i>)-(+)-2,2'-Bis(di- <i>p</i> -tolylphosphino)-1,1'-binaphthyl

t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenyl silyl
<i>t</i> -BOC	<i>tert</i> -butoxycarbonyl
TBS	<i>tert</i> -butyldimethyl silyl
<i>t</i> -Bu	<i>tert</i> -butyl
td	triplets of doublet
tdd	triplets of doublets of doublet
TES	triethylsilyl
TFA	trifluoroacetic acid
TfOH	triflate acid
Tf ₂ O	Triflate anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropyl silyl
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
Ts	<i>p</i> -toluenesulfonyl
T.S.	transition state
vol	volume

PART I

**SYNTHESIS OF SEX PHEROMONE OF
THE PINE SAWFLY, *MACRODIPRION
NEMORALIS***

CHAPTER 1

Introduction

1.1 BACKGROUND

1.1.1 Structural and Biological Aspects of Sex Pheromone of the Pine Sawfly, *Macrodiprion nemoralis*

In 1999, Hedenström¹ and co-worker have identified the sex pheromone in the females of *Macrodiprion nemoralis* as (2*S*,3*R*,7*R*,9*S*)-3,7,9-trimethyl-2-tridecyl acetate (*SRRS-1*) (Figure 1.1). It has an overall chain length consisting of 13 carbons, with methyl branching on carbons 3, 7 and 9.

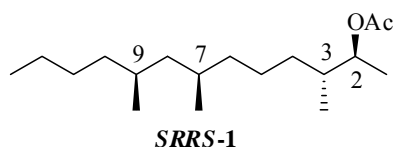


Figure 1.1 Sex pheromone in females of *Macrodiprion nemoralis*

The Diprionidae are a small family of conifer-feeding sawflies with about 128 species worldwide.² *Macrodiprion nemoralis* is one of the largest diprionid species in Europe. In addition, they are commonly known as pine sawflies because they are severe pests on pine trees.³ Hence, population of the sawflies needs to be controlled. Control measures can be applied through sex pheromones by using mass trapping. In this respect, Hedenström *et al.* have reported that a synthetic mixture of 3,7,9-trimethyl-2-tridecyl acetate isomers was capable of strongly attracting the males of *Macrodiprion nemoralis*.^{1,4}

¹ Wassgren, A.-B.; Bergström, G.; Sierpinski, A.; Anderbrant, O.; Högberg, H.-E.; Hedenström, E. *Naturwissenschaften* **2000**, *87*, 24.

² Bergström, G. *Pure Appl. Chem.*, **2007**, *79*, 2305.

³ (a) Smith, D. R. In *Sawfly Life History Adaptations to Woody Plants*; Wagner, M. R.; Raffa, K. F., Eds.; Academic: San Diego, 1993; pp3-32. (b) Anderbrant, O. In *Sawfly Life History Adaptations to Woody Plants*; Wagner, M. R.; Raffa, K. F., Eds.; Academic: San Diego, 1993; pp 119-154.

⁴ See some examples: (a) Hertz, A.; Heitland, W.; Anderbrant, O.; Edlund, H.; Hedenström, E. *Agricultural and Forest Entomology*, **2000**, *2*, 123. (b) Lyytikäinen-Saarenmaa, P.; Anderbrant, O.; Löfqvist, J.; Hedenström, E.; Högberg, H.-E. *For. Ecol. Manage.*, **1999**, *124*, 113. (c) Bergström, G.;

1.2 REPORTED SYNTHETIC STUDIES

1.2.1 Reported Syntheses of Sex Pheromone of the Pine Sawfly, *Macrodiprion nemoralis*

Due to the potent biological activity, the stereoisomers of 3,7,9-trimethyl-2-tridecyl acetate (**1**) have attracted interest as targets for total synthesis. There have been two total syntheses reported so far, namely, the one due to Hedenström *et al.* and the working of Högberg *et al.*^{5,6}

The first stereoselective synthesis of the sixteen stereoisomers of 3,7,9-trimethyl-2-tridecyl acetate (**1**) by Karlsson and Hedenström⁵ in year 1999, was based on two principal modules: optically pure stereoisomers of 2,4-dimethyloctan-1-ol (**3**) and *cis*-3,4-dimethyl- γ -butyrolactone (**4**, Figure 1.2). The authors employed the ring opening of either (2*S*,3*S*)- or (2*R*,3*R*)-3,4-dimethyl- γ -butyrolactone (**4**) using a pure isomer of 1-lithio-2,4-dimethyloctane, followed by Huang-Minlon reduction of the resulting keto alcohol to construct the natural product.

Wassgren, A.-B.; Anderbrant, O.; Fägerhag, J.; Edlund, H.; Hedenström, E.; Högberg, H.-E.; Geri, C.; Auger, M. A.; Varama, M.; Hansson, B. S.; Löfqvist, J. *Experientia*, **1995**, *51*, 370.

⁵ Karlsson, S.; Hedenström, E. *Acta. Chem. Scand.* **1999**, *53*, 620.

⁶ Karlsson, S.; Högberg, H.-E. *Synthesis*, **2000**, 1863.

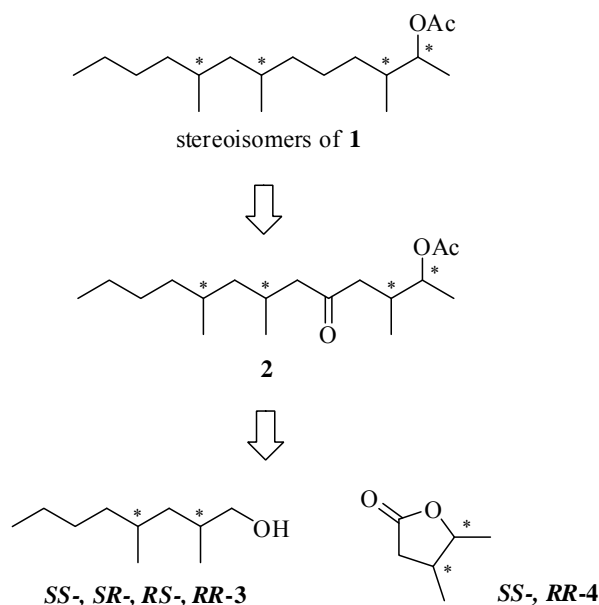
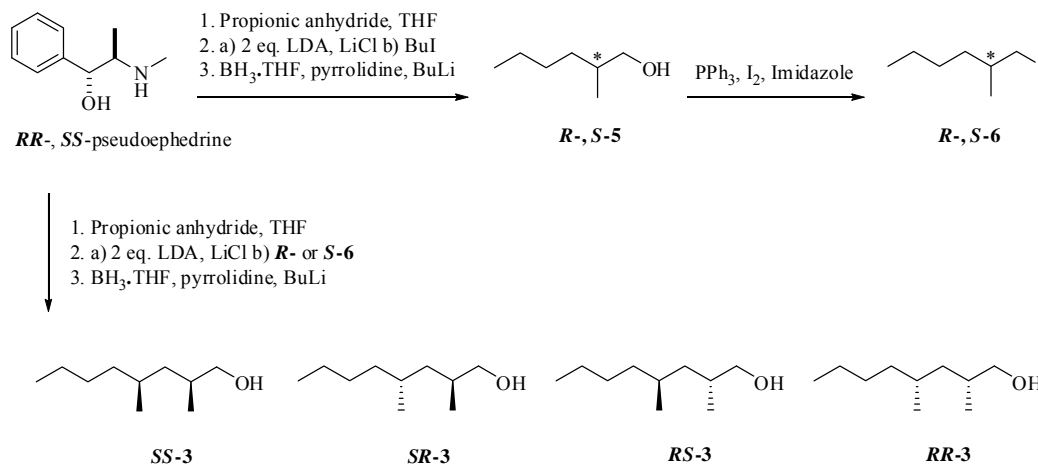


Figure 1.2 Retrosynthetic analysis of sixteen stereoisomers of **1** by Hedenström

Syntheses of the four individual stereoisomers of 2,4-dimethyloctan-1-ol (**3**) began with acylation of the appropriate enantiomer of pseudoephedrine with propionic anhydride to furnish the corresponding amide.^{7,8} The amide was treated with LDA to give the (*Z*)-enolate, followed by alkylation with 1-iodobutane and subsequently subjected to reductive hydrolysis with lithium-borane pyrrolidine complex to provide (*R*)- or (*S*)-2-methylhexane-1-ol (*R*- or *S*-**5**) respectively. The *R*- or *S*-**5** was then transformed into the corresponding iodoalkanes *R*- or *S*-**6**. One of the iodoalkanes *R*- or *S*-**6** was reacted with the (*Z*)-enolate prepared from the enantiomer of pseudoephedrine. The resulting *anti* and *syn* products were reduced by lithium-borane pyrrolidine complex to deliver four individual stereoisomers of alcohol **3** (Scheme 1.1).

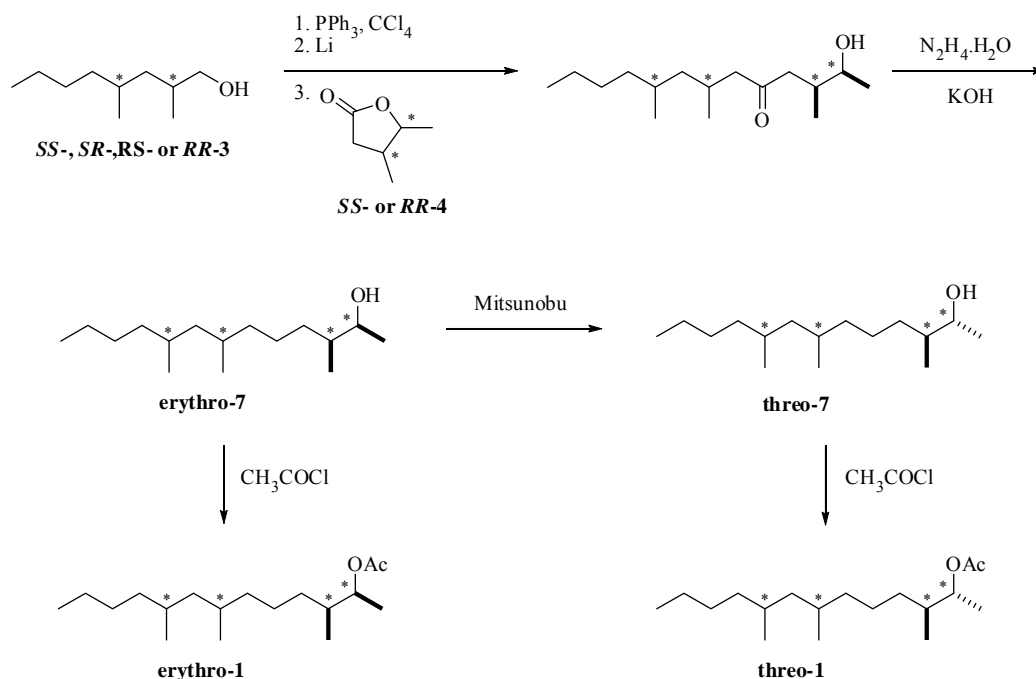
⁷ Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361.

⁸ Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.



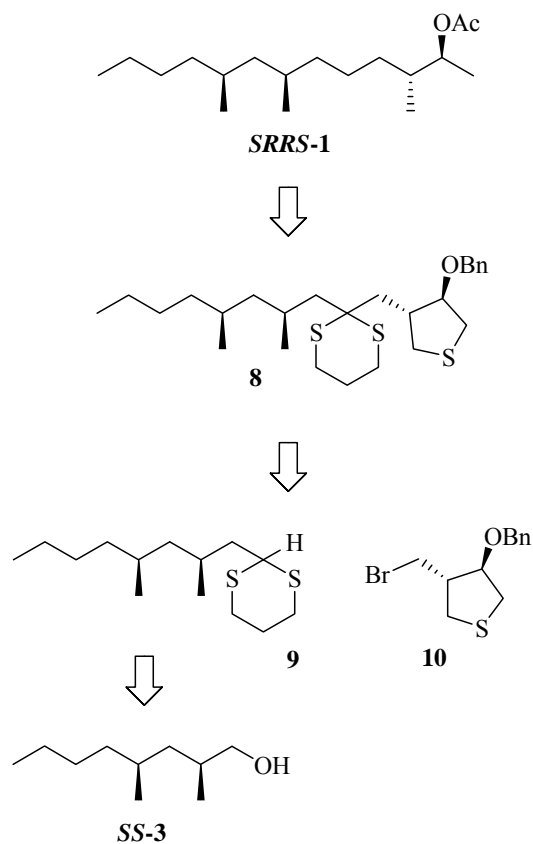
Scheme 1.1 Synthesis of four stereoisomers of 2,4-dimethyloctan-1-ol **3**

The alcohols **3** were further converted into the alkyllithiums and reacted with the preferred enantiomer of *cis*-3,4-dimethyl- γ -butyrolactone (**4**). Huang-Minlon reduction of the resulting keto alcohols proceeded smoothly to provide eight *erythro* isomers (*erythro-7*) individually. The approach to the eight *threo*-isomers (*threo-7*) involved the Mitsunobu inversion at C-2 position of the corresponding *erythro*-isomers (*erythro-7*). Acylation of the sixteen individual *erythro-7* and *threo-7* isomers provided the final sixteen stereoisomers of 3,7,9-trimethyl-2-tridecyl acetate (**1**) (Scheme 1.2).



Scheme 1.2 Synthesis of all sixteen stereoisomers of 3,7,9-trimethyl-2-tridecyl acetate (**1**)

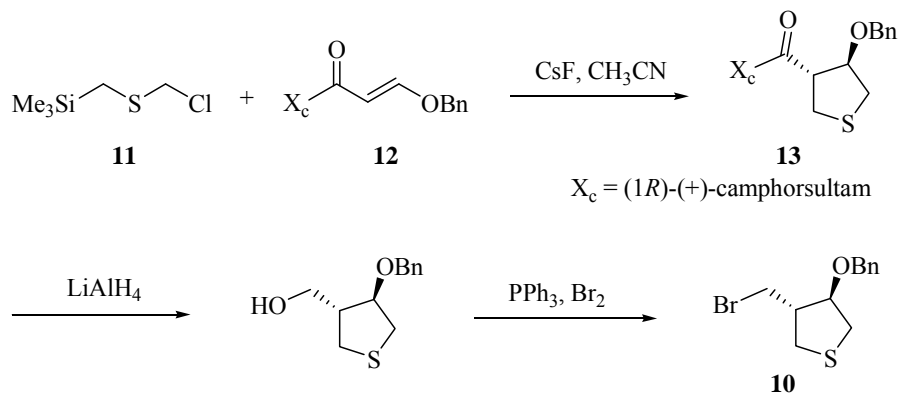
The second total synthesis by Karlsson and Högberg was published a year later.⁶ The target was divided into 2 modules, the tetrahydrothiophene building block **10** and the same module **3** which was also employed by Hedenström (Scheme 1.3). This is a more direct approach to give the *threo*-isomers without applying the Mitsunobu reaction.



Scheme 1.3 Högberg's retrosynthetic analysis of *SRRS-1*

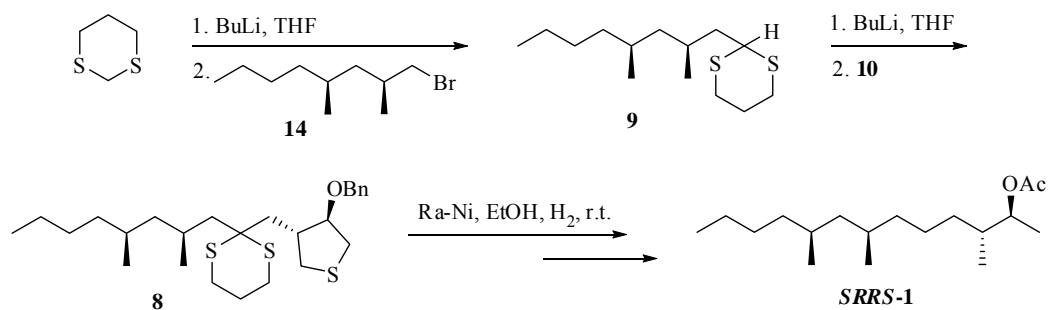
The key enantiopure building block **10** was envisioned to arise from a diastereoselective asymmetric 1,3-dipolar cycloaddition between thioether **11** and the enantiopure camphorsultam amide **12**, which provided **13** smoothly in good yield with high diastereoselectivity.⁹ Finally, the synthesis of building block **10** was completed by reductive removal of the camphorsultam using LiAlH_4 and conversion of the alcohol group into a bromide (Scheme 1.4).

⁹ Karlsson, S.; Högberg, H.-E. *Org. Lett.* **1999**, *1*, 1667.



Scheme 1.4 Synthesis of enantiopure tetrahydrothiophene building block **10**

The alkylation between bromide **14** and the deprotonated dithiane gave **9** in excellent yield.¹⁰ Subsequent alkylation, Raney-Ni reduction under mild condition and acylation yielded the desired product (Scheme 1.5)



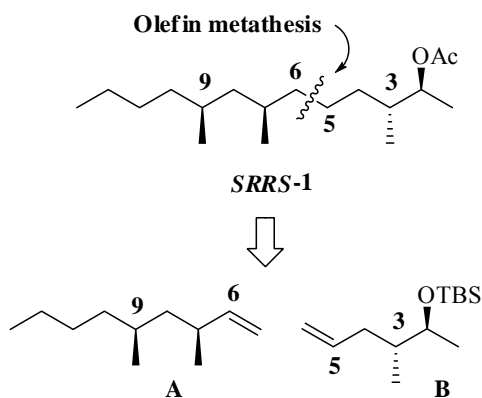
Scheme 1.5 Synthesis of the sex pheromone of *Macrodiprion nemoralis*

¹⁰ Seebach, D.; Willert, I.; Beck, A. K.; Gröbel, B.-T. *Helv. Chim. Acta* **1978**, *61*, 2510.

1.3 RETROSYNTHETIC ANALYSIS

The principal challenge in the synthesis of the sex pheromone of *Macrodiprion nemoralis* is how to stereoselectively introducing the C3, C7 and C9 methyl groups into the molecule. We felt that the challenge could be efficiently addressed by employing the highly efficient CuI-Tol-BINAP-catalyzed asymmetric conjugate addition of Grignard reagents to α,β -unsaturated esters previously developed in our group.¹¹ Herein, we report the enantioselective synthesis of the sex pheromone of *Macrodiprion nemoralis* (*SRRS-1*). However, the final product contains 10% amount of inseparable impurities.

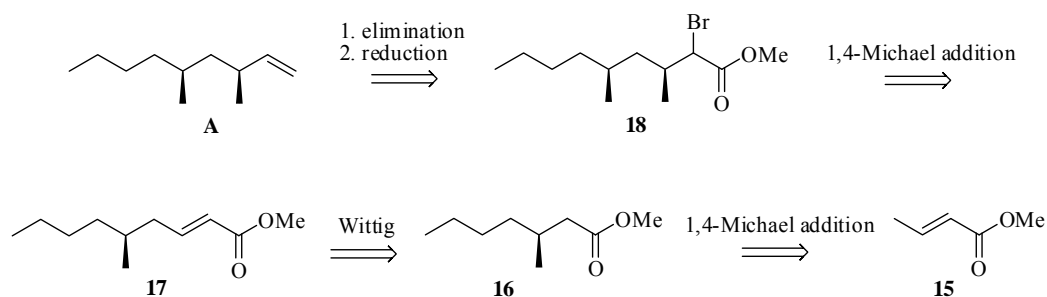
To maximize synthetic convergency, *SRRS-1* was divided into two modules (Scheme 1.6) via disconnection at C5-C6 bond, affording fragment **A** and fragment **B**. An olefin metathesis step could be performed to join these terminal olefins together. Reductive hydrogenation followed by acylation would complete the total synthesis.



Scheme 1.6 Our retrosynthetic analysis of *SRRS-1*

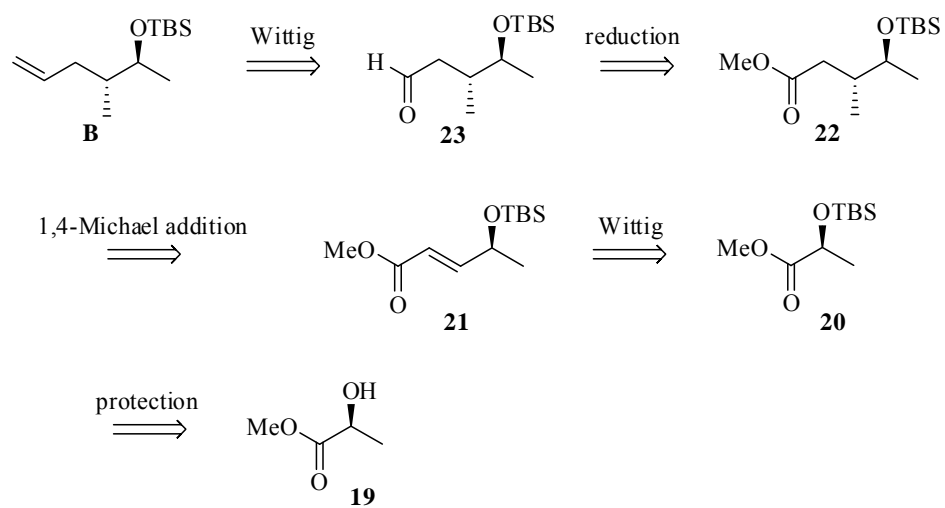
¹¹ (a) Wang, S. Y.; Ji, S. J.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 276. (b) Wang, S. Y.; Lum, T. K.; Loh, T. P. *Adv. Synth. Catal.* **2008**, *350*, 673. (c) Lum, T. K.; Wang, S. Y.; Loh, T. P. *Org. Lett.* **2008**, *10*, 761.

The key building block **A** has a *syn*-1,3-dimethyl array with a vinyl group at the terminal. It can be seen to arise from the reduction of ester **18** to alcohol followed by elimination to give the terminal olefin. The *syn*-deoxypropionate unit **18** can be constructed from the asymmetric conjugate addition adduct **17**. Ester **17** can subsequently be obtained from ester **16** via a one-pot DIBAL-H reduction-Wittig olefination. The first stereogenic methyl center in ester **16** can be introduced from olefin **15** by an asymmetric conjugate addition (Scheme 1.7).



Scheme 1.7 Retrosynthetic analysis of fragment **A**

Fragment **B** is a terminal olefin and can be synthesized from aldehyde **23** by Wittig olefination. The desired aldehyde **23** can be readily obtained from methyl Grignard addition to ester **21** followed by DIBAL-H reduction of the conjugate addition product **22**. Subsequently, the olefin **21** can be made from ester **20** via a one-pot DIBAL-H reduction-Wittig olefination. The synthesis of fragment **B** commences with the TBS-protection of precursor **19**, which is cheap and commercially available (Scheme 1.8).

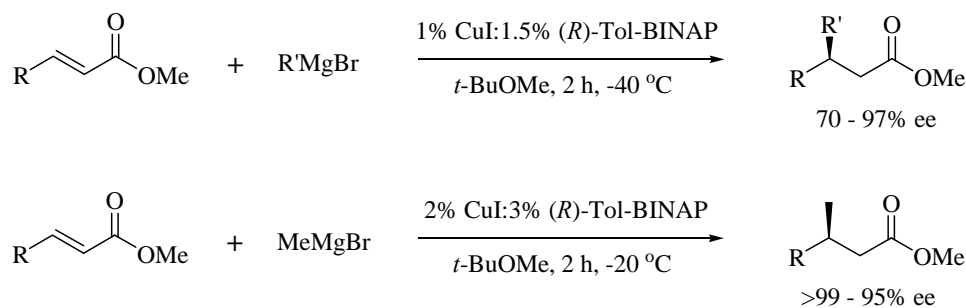
**Scheme 1.8** Retrosynthetic analysis of fragment **B**

CHAPTER 2

***Synthesis of Sex Pheromone of the Pine Sawfly,
Macrodiprion Nemoralis***

2.1 SYNTHESIS OF FRAGMENT A

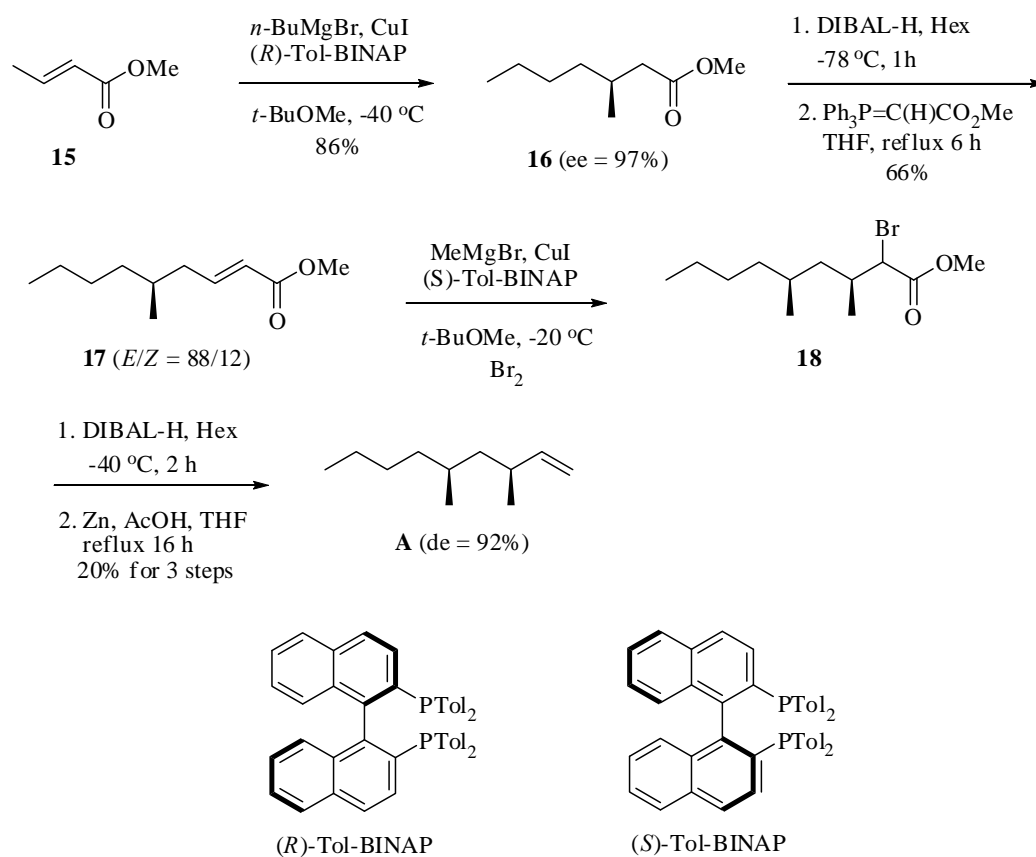
One of the highlights in this total synthesis was to demonstrate the versatility of our group's CuI-Tol-BINAP catalyzed conjugate addition of Grignard reagents on natural product synthesis (Scheme 2.1). Conjugate addition of Grignard reagents to α,β -unsaturated esters is one of the most convenient synthetic methods for the construction of C–C bonds. In addition, not only are α,β -unsaturated esters easier to handle and commercially available, a larger scope of useful chemical transformations can also be applied. Moreover, the reactions require only mild conditions and simple procedures. The absolute stereochemistry of the product can easily be controlled by using the enantiomer of the ligand or by using the geometrical isomer of the starting material. Herein, this methodology was utilized in our total synthesis.



Scheme 2.1 Asymmetric conjugate addition of Grignard reagents to α,β -unsaturated ester

The preparation of key building block **A** started from the commercially available methyl *trans*-2-butenate (**15**). The first stereogenic center in ester **16** was introduced by butyl Grignard using the (*R*)-enantiomer of Tol-BINAP via asymmetric conjugate addition to give methyl ester **16** in 97% *ee* and 86% yield (Scheme 2.2). A one-pot DIBAL-H reduction followed by Wittig olefination provided the *trans*-enoate isomer **17** in 66% yield (*E/Z* = 88:12). The second asymmetric conjugate addition was performed with the (*S*)-enantiomer of Tol-BINAP under the same catalytic conditions

to afford the *syn*-deoxypropionate unit **18**. Neat bromine was used as an enolate-trapping reagent in the quenching step of the conjugate addition. This bromomethyl ester **18** was used in the next step without purification and reduced to the alcohol by DIBAL-H. Without further purification, the alcohol was added zinc dust and glacial acetic acid¹² to furnish the terminal olefin **A** in 20% yield over three steps from the *trans*-enoate **17** and 92% *de*.¹³ Assuming an analogous reaction mechanism, *syn*-stereochemistry was assigned based on enantiomeric Tol-BINAP ligands selected in each methyl addition leading to the deoxypropionate units **A**.



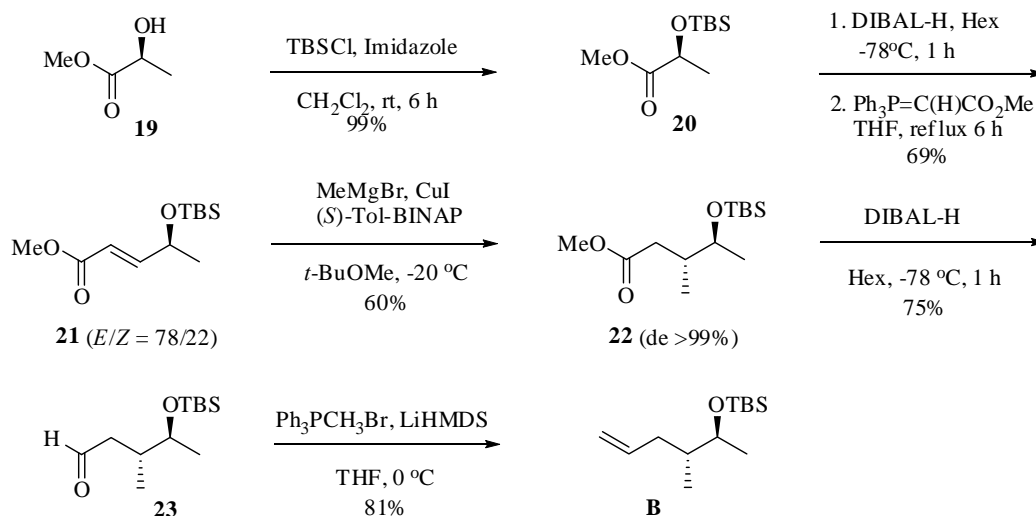
Scheme 2.2 Synthesis of fragment **A**

¹² Fukuyama, T.; Chen, X. *J. Am. Chem. Soc.* **1994**, *116*, 3125.

¹³ Diastereoselectivity was determined in ¹³C NMR spectra by comparing an average of carbon signal with respective diastereomeric mixtures of the deoxypropionate units.

2.2 SYNTHESIS OF FRAGMENT B

The synthesis of fragment **B** commenced with the protection of (–)-methyl-L-lactate (**19**) by *tert*-butyldimethylchlorosilane (Scheme 2.3). The protection proceeded smoothly and gave ester **20** in quantitative yield. One-pot DIBAL-H reduction–Wittig olefination afforded the *trans*-enoate **21** in 69% yield (*E/Z* = 78/22). Subsequently, a methyl moiety was stereoselectively introduced into olefin **21** using (*S*)-Tol-BINAP via asymmetric conjugate addition to provide methyl ester **22** in 60% yield with >99% *de*. Moreover, the reaction could be carried on a large scale (15 mmol). DIBAL-H reduction to aldehyde **23** followed by Wittig olefination¹⁴ furnished the desired fragment **B**.



Scheme 2.3 Synthesis of fragment **B**

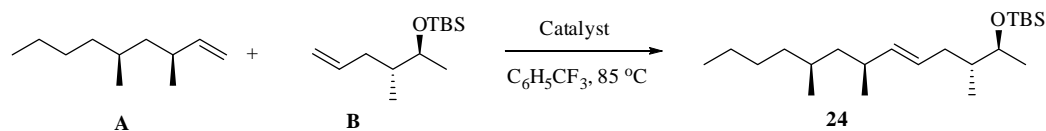
¹⁴ (a) Lebel, H.; Guay, D.; Paquet, V.; Huard, K. *Org. Lett.*, **2004**, *6*, 3047. (b) Satyanarayana, M.; Rzuczek, S. G.; Lavoie, E. J.; Pilch, D. S.; Liu, A.; Liu, L. F.; Rice, J. E. *Bioorg. Med. Chem. Lett.* **2008**, *8*, 3802.

2.3 COUPLING OF FRAGMENT A AND B

With the fragment **A** and **B** in hand, we then carried out intermolecular olefin cross metathesis. Olefin cross-metathesis has gained widespread application in organic synthesis since the development of ruthenium-carbene complexes.¹⁵ However, this method is plagued by several limitations, for example self-coupling, poor reactivity, low yield, polymerization and unpredictable reaction scope. Nevertheless, it is still worthwhile to incorporate metathesis into the synthesis plan because of its elegance in using a mild reaction condition and few number of steps.

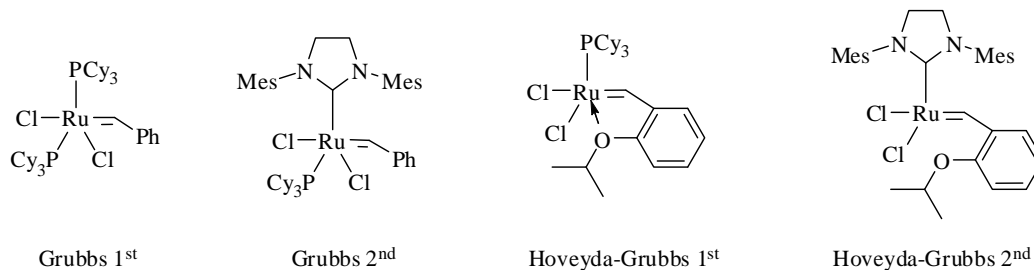
All the catalyst failed to give any cross metathesis product **24** except for the second generation Hoveyda-Grubbs catalyst (Table 2.1, entry 4). Nonetheless, 31% of fragment **B** was recovered in the reaction. Attempts to obtain the product **24** in clean forms proved futile because there were significant amounts of self-coupled and polymerized side products. Therefore, the residue was taken directly to the next step.

¹⁵ (a) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Cossy, J.; Bouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *634*, 216. (c) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Busmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (d) Chatterjee, A. K.; Sander, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939. (e) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.

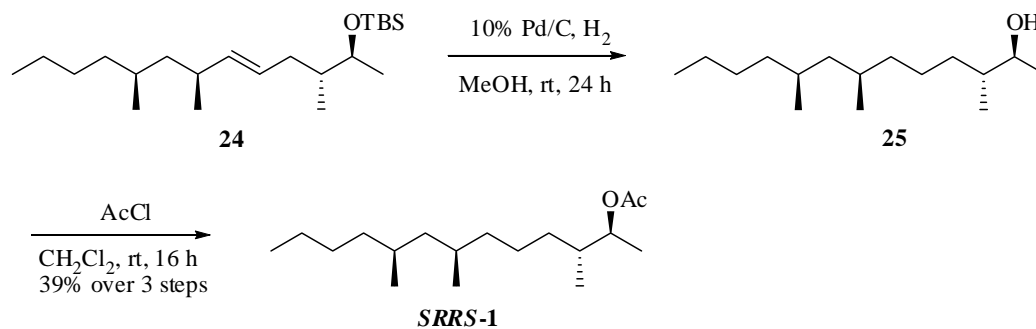
Table 2.1 Cross metathesis with fragment **A** and **B**

Entry	Catalyst	Yield (%)
1	Grubbs 1 st	N.R.
2	Grubbs 2 nd	N.R.
3	Hoveyda-Grubbs 1 st	N.R.
4	Hoveyda-Grubbs 2 nd	To be confirmed in the last step ^b (31% recovered precursor B)

^a All the reactions were carried out in oven dried glassware with 1 equiv of **A** and 1 equiv of **B** with 12 mol % catalyst loading. (Trifluoromethyl)benzene was degassed with argon. The catalyst was added in one portion and the reaction was stirred continuously for 12 h. ^bThe reaction was monitored using TLC and quenched when all of **A** has reacted.



Reductive hydrogenation followed by acylation completed the synthesis of *SRRS-1* in 39% yield over three steps (Scheme 2.4). However, the nmr spectrum of the product indicated the presence of other impurities which interfered with the nmr signals of the desired product. The product contained 10% of inseparable impurities.

**Scheme 2.4** Synthesis of *SRRS-1*

2.4 CONCLUSION

In conclusion, *SRRS-1* was synthesized via a convergent synthetic strategy that features the use of highly efficient CuI-Tol-BINAP-catalyzed asymmetric conjugate additions of Grignard reagents, which was previously developed in our group. Excellent enantio and diastereo-control were achieved during the additions. The synthesis also demonstrated an efficient as well as practical procedure for one pot DIBAL-H reduction-Wittig olefination and a successful intermolecular olefin cross-metathesis.

CHAPTER 3

Experimental Section

3.1 GENERAL INFORMATION

Experiments involving moisture and/or sensitive compounds were performed under a positive pressure of nitrogen in flame-dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a dessicator or via double-tipped cannular needles. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents/compounds was removed by the addition of the stated amount of anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of an oil pump (~30 mmHg, 23-50 °C) and subsequent purging with nitrogen.

All experiments were monitored by analytical thin layer chromatography (refer to section under “Chromatography”). Solvents were removed *in vacuo* under ~30 mmHg and heated with a water bath at 23 °C using Büchi rotary evaporator cooled with circulating ethylene glycol / water mixture (1:1) at -5 °C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego¹⁰. Solvents such as hexane, ethyl acetate, dichloromethane and water were freshly distilled prior to use. Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of

¹⁰ Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture *in vacuo* followed by subsequent purging with nitrogen.

Triethylamine, toluene and dimethyl sulfoxide were distilled over calcium hydride and stored over molecular sieves to maintain dryness. DMF was distilled over Linde type 4Å molecular sieve prior to usage. 1*N* and 6*N* hydrochloric acid was diluted from concentrated 37% solution using deionised water. 3*M* and 6*M* sodium hydroxide solution was prepared from sodium hydroxide pearls. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, sodium carbonate and sodium sulphate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography was performed using Merck 60 F₂₅₄ pre-coated silica gel plates (0.25 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate followed by heating on a hot plate.

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 mm) with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. The solute was loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump.

Instruments & Equipments

Infrared Spectroscopy

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions. Solid samples were analyzed as a KBr pressed-disk.

Optical Rotation

Optical rotations were measured in CHCl_3 on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with 10.0 mm cell (c given in g/100 mL). Absolute configurations of the products were determined by comparison with known compounds. Concentration is denoted as c and was calculated as grams per milliliters (g / 100 mL) whereas the solvent was indicated in parentheses (c , solvent).

Mass Spectroscopy

Mass Spectrometry (EI) spectra were recorded on a Thermo Finnigan Polaris Q GCMS. Mass Spectrometry (ESI and APCI) spectra were recorded on a Thermo Finnigan LCQ Deca XP Max. High Resolution Mass Spectrometry (EI, ESI, FAB) spectra were recorded on a Thermo Finnigan MAT 95 XP. MS and High Resolution Mass Spectrometry were reported in units of mass of charge ratio (m/z).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Avance 300, 400 and 500 NMR spectrometers.

Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.260, singlet) as the internal standard. Multiplicities were given as: s (singlet); d (doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (*n*) for given resonance is indicated by *n*H. Coupling constants are reported as a *J* value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from SiMe_4 (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.03, triplet). The proportion of diastereomers and geometric isomers was determined from the integration of ^1H NMR and ^{13}C NMR spectra.

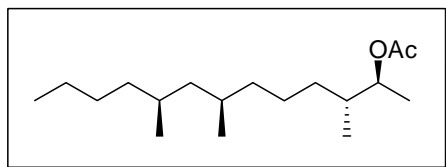
Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 8.0 software.

3.2 SUPPORTING INFORMATION

Experimental Procedures and Characterization Data of Products

(2*S*,3*R*,7*R*,9*S*)-3,7,9-trimethyltridecan-2-yl acetate (**1**)



To a solution of **A** (0.154 g, 1.00 mmol) and **B** (0.228 g, 1.00 mmol) in (trifluoromethyl)benzene (60 mL) was added the 2nd generation Hoveyda-Grubbs catalyst (75 mg, 0.12 mmol) and the mixture was heated at 85 °C for 12 h under N₂. The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was passed to a short silica plug using 100% Hexane and used for the next step without further purification. The intermediate was dissolved in MeOH (5 mL) and 10% Pd/C (0.05 g, 0.05 mmol) was added. The reaction mixture was stirred under hydrogen atmosphere (1 atm) at r.t. for 24 h. The mixture was filtered over celite and concentrated under reduce pressure. The intermediate was stirred overnight in CH₂Cl₂ (15 mL) with acetyl chloride (0.314 g, 4.00 mmol) at r.t. The reaction mixture was concentrated under reduced pressure and purified by flash column chromatography (Hexane/Et₂O 30: 1) to afford the desired product as colourless oil (65.9 mg, 39% yield, with 31% recovered starting material - (3*S*,5*S*)-3,5-dimethylnon-1-ene **A**), contains 10% trace amount of non-separable impurities.

R_f value (hexane/Et₂O 15: 1): 0.34

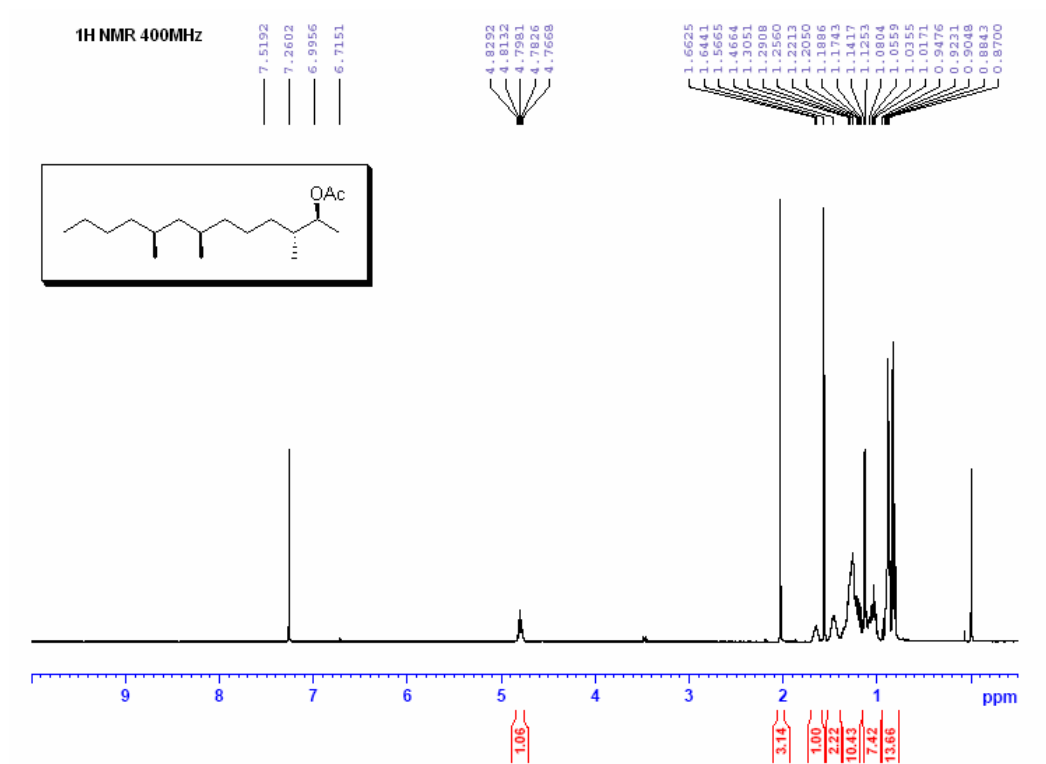
[α]_D²⁰ = +11.2 (*c* = 1.13, CHCl₃).

^1H NMR (400 MHz, CDCl_3): δ 4.83-4.77 (m, 1H), 2.02 (s, 3H), 1.66-1.64 (m, 1H), 1.46 (m, 2H), 1.31-1.01 (m, 17H), 0.93-0.80 (m, 12H).

^{13}C NMR (75 MHz, CDCl_3): δ 170.7, 74.4, 45.2, 37.2, 37.0, 36.6, 32.9, 30.0, 30.0, 29.2, 24.3, 23.0, 21.4, 20.3, 20.2, 15.9, 14.5, 14.1.

FTIR (NaCl, neat): ν 2959, 2928, 2872, 2858, 1738, 1246 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{18}\text{H}_{37}\text{O}_2$ (M+1) 285.2785, found 285.2794.



diethyl ether (60 mL x 3) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (Hexane/Et₂O 99: 1) to afford the desired product as colourless oil (4.08 g, 86% yield, 97% *ee*).

R_f-value (hexane/Et₂O 8: 1): 0.45

$[\alpha]_D^{25} = -3.4$ ($c = 1.2$, CHCl₃), lit. for (*S*)-enantiomer: $[\alpha]_D^{20} = -3.9$ ($c = 1.5$, CHCl₃)¹¹

¹H NMR (300 MHz, CDCl₃): δ 3.67 (s, 3H), 2.31 (dd, $J = 6.0, 14.6$ Hz, 1H), 2.11 (dd, $J = 8.1, 14.6$ Hz, 1H), 1.97-1.93 (m, 1H), 1.29-1.17 (m, 6H), 0.92-0.87 (m, 6H).

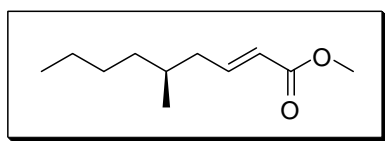
¹³C NMR (100 MHz, CDCl₃): δ 173.8, 51.3, 41.6, 36.5, 30.3, 29.1, 22.7, 19.7, 14.0.

FTIR (NaCl, neat): ν 1738 cm⁻¹.

HRMS (EI) calcd. for C₉H₁₈O₂ 158.1307, found [M]⁺ 158.1304.

The enantiomeric excess determined by chiral GC analysis, employing a Chiraldex G-TA column (30 m x 0.25 mm), 60 °C, retention times (min): t₁ = 33.01 (minor), t₂ = 34.93 (major).

(*S,E*)-methyl 5-methylnon-2-enoate (**17**)



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, (*S*)-methyl 3-methylheptanoate **16** (0.158 g, 1.00 mmol) was dissolved in hexane (1.0 mL) and cooled to -78 °C. DIBAL-H (pre-cooled to -78 °C, 1.1 mL, 1.0 M in heptane, 1.1 mmol) was added carefully over at least 2 portions. After stirring for another 1 h, MeOH (pre-cooled to -78 °C, 0.096 g, 3.3 mmol) was added carefully over 2 portions and stirred for a further half an hour until a white suspension was observed. The ylide

¹¹ Wang, S. Y.; Lum, T. K.; Loh, T. P. *Adv. Synth. Catal.* **2008**, 350, 673.

MeO₂CCH=PPh₃ (0.669 g, 2.00 mmol) was added in one portion followed by THF (5.0 mL) and the reaction mixture was allowed to warm slowly to room temperature over 30 minutes. The reaction mixture was stirred for another 30 minutes and refluxed for an additional 6 h. After that, the reaction mixture was cooled to room temperature and diluted with Et₂O (5 mL) and saturated potassium sodium tartrate (5 mL). The mixture was stirred until a clear biphasic separation was observed. The aqueous layer was extracted with Et₂O (10 mL x 3). The combined organic extracts were washed with saturated NaHCO₃ (15 mL x 2), brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/EtOAc 100: 1) to afford the desired *trans*-product as colorless oil (0.122 g, 66% yield; 75% total yield for the mixture of *E/Z* isomers, *E/Z* = 88: 12).

R_f value (hexane/Et₂O 10: 1): 0.34

[α]_D²⁰ = -1.28 (*c* = 1.09, CHCl₃).

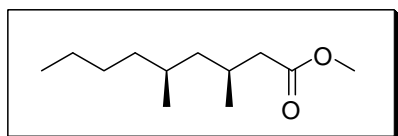
¹H NMR (300 MHz, CDCl₃): δ 7.00-6.90 (m, 1H), 5.81 (dt, *J* = 1.4, 15.6 Hz, 1H), 3.72 (s, 3H), 2.25-2.16 (m, 1H), 2.08-1.98 (m, 1H), 1.57 (m, 1H), 1.31-1.26 (m, 6H), 0.90-0.88 (m, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 167.0, 148.6, 121.8, 51.3, 39.7, 36.3, 32.5, 29.2, 22.8, 19.5, 14.0.

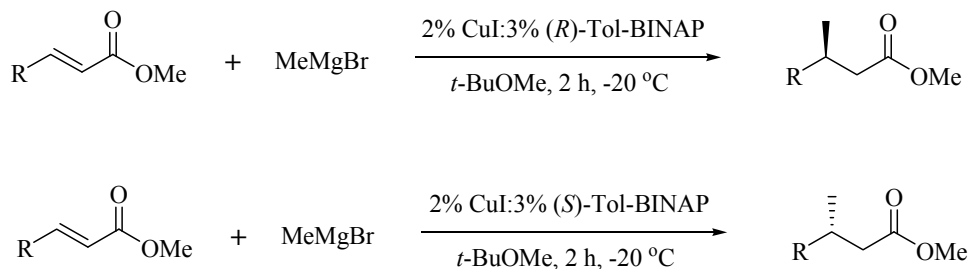
FTIR (NaCl, neat): ν 2957, 2926, 2872, 2859, 1728, 1655, 1321, 1269, 1173 cm⁻¹.

HRMS (ESI) calcd. for C₁₁H₂₁O₂ (*M*+1) 185.1542, found 185.1538.

(3*S*,5*S*)-methyl 3,5-dimethylnonanoate (18')



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, (S)-Tol-BINAP (0.020 g, 0.03 mmol) and CuI (0.004 g, 0.02 mmol) were stirred in CH₂Cl₂ (2 mL) for 20 minutes, concentrated *in vacuo* and then stirred in *t*-BuOMe (4 mL) till a bright yellow suspension was observed. The mixture was then cooled to -20 °C and MeMgBr (0.83 mL, 3.0 M solution in Et₂O, 2.50 mmol) was added carefully into the reaction mixture. After stirring for 15 minutes, a pre-cooled solution of **17** (0.184 g, 1.00 mmol) in *t*-BuOMe (1.2 mL) was added dropwise over 1 h via syringe pump. After stirring at -20 °C for another one and an half hour, the reaction mixture was quenched with MeOH (1 mL), and 1 M NH₄Cl solution (4 mL). The aqueous layer was extracted with Et₂O (15 mL x 3) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/Et₂O 90: 1) to afford the desired product as colourless oil (0.136 g, 68% yield; 92% *de*). The distereoselectivity was determined in ¹³C NMR using an average of two well resolved carbon signals and compared to a diastereomeric mixture of methyl 3,5-dimethylnonanoate. Assuming an analogous reaction mechanism, the *syn*-stereochemistry was assigned based on the enantiomeric Tol-BINAP ligand selected in 1,4-Michael addition of methylmagnesium bromide to an α,β -unsaturated ester.



R_f-value (hexane/Et₂O 8: 1): 0.48

$[\alpha]_D^{20} = -2.97$ ($c = 1.8$, CHCl₃).

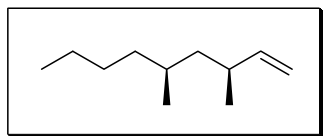
^1H NMR (400 MHz, CDCl_3): δ 3.66 (s, 3H), 2.32-2.28 (m, 1H), 2.06-2.03 (m, 2H), 1.57-1.42 (m, 1H), 1.29-1.19 (m, 6H), 1.07-1.02 (m, 2H), 0.93-0.85 (m, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 173.6, 51.2, 44.6, 41.4, 36.3, 29.9, 29.0, 27.8, 22.9, 20.3, 20.0, 14.0.

FTIR (NaCl, neat): ν 2957, 2928, 2872, 1742, 1173 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{25}\text{O}_2$ (M+1) 201.1855, found 201.1852.

(3*S*,5*S*)-3,5-dimethylnon-1-ene (A)



In a round bottom flask equipped with septum and stirring bar, (*S*)-Tol-BINAP (0.061, 0.09 mmol) and CuI (0.011g, 0.06 mmol) were stirred in CH_2Cl_2 (5 mL) for 20 minutes, concentrated *in vacuo* and then stirred in *t*-BuOMe (12 mL) till a bright yellow suspension was observed. Then, the mixture was cooled to $-20\text{ }^\circ\text{C}$ and MeMgBr (3 mL, Aldrich 3.0 M solution in Et_2O , 9.00 mmol) was added carefully into the reaction mixture. After stirring for 15 minutes, a solution of (*S,E*)-methyl 5-methylnon-2-enoate **17** (0.552 g, 3.00 mmol) in *t*-BuOMe (3.6 mL) was added dropwise over 2h via syringe pump. After stirring at $-20\text{ }^\circ\text{C}$ for another 1 h, the reaction mixture was cooled to $-78\text{ }^\circ\text{C}$ and bromine (0.44 mL, 9.00 mmol) was added slowly. The reaction mixture was allowed to warm to $-40\text{ }^\circ\text{C}$. MeOH (1 mL) was added followed by saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with diethyl ether (20 mL x 2) and the combined organic extracts were washed with saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (20 mL x 2), dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The crude intermediate was passed through a short silica plug using 20: 1 Hexane/Diethyl Ether and used for the next

step without purification. The intermediate was dissolved in CH_2Cl_2 (6 mL), cooled to $-78\text{ }^\circ\text{C}$ and DIBAL-H (6 mL, Aldrich 1.0 M solution in Heptane) was added. The reaction mixture was allowed to warm to $-40\text{ }^\circ\text{C}$ and stirred for another 2 h. After that, saturated NH_4Cl solution (3 mL), Et_2O (10 mL) and 6N HCl (6 mL) were added. The mixture was stirred vigorously at room temperature till a clear biphasic separation was observed. The aqueous layer was extracted with Et_2O (10 mL x 2), and the combined organic extracts were washed with saturated NaHCO_3 solution (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was passed through a short silica plug using 4: 1 Hexane/Diethyl Ether, and used for the next step without further purification. The intermediate was dissolved in THF (4 mL). Subsequently, Zn dust (1.30g) and glacial acetic acid (2.4 mL) were added. The mixture was refluxed overnight, cooled after the reaction completed, filtered over celite and diluted with Et_2O (20mL). The combined organic extracts were washed with 1N NaOH (20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (Hexane 100%) to afford the desired product as colourless oil (30.8 mg, 20% yield, 92% *de*), contains a trace amount of non-separable impurities. Distereoselectivity of this product was assigned on the basis of enantiomeric Tol-BINAP ligands selected in the methyl addition leading to (3*S*,5*S*)-methyl 3,5-dimethylnonanoate **18'**.

R_f -value (hexane 100%): 0.71

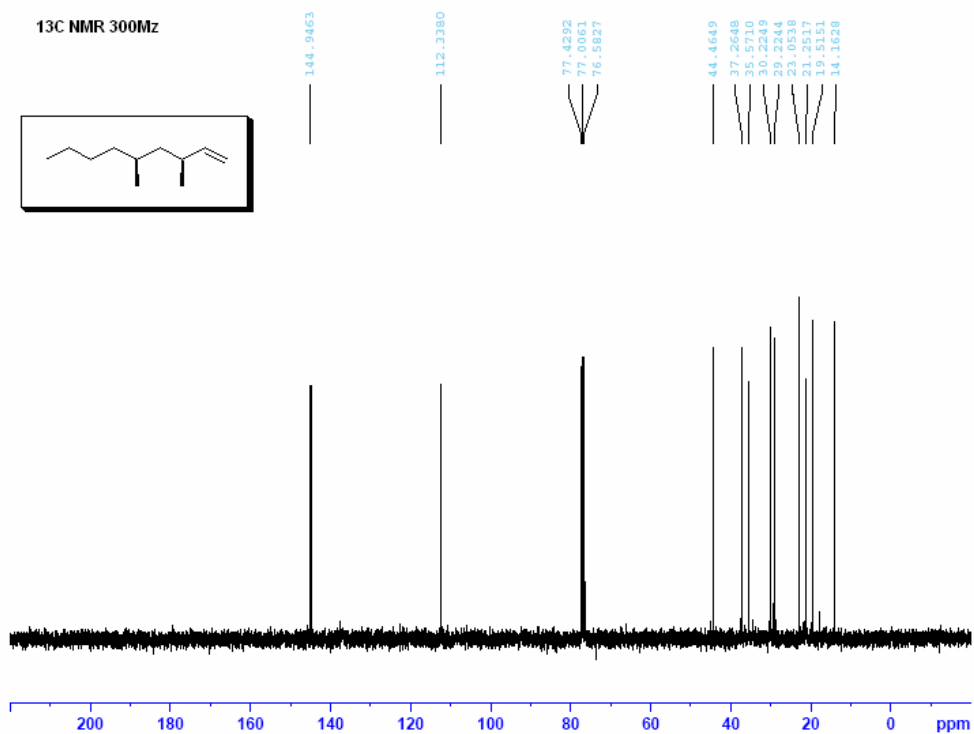
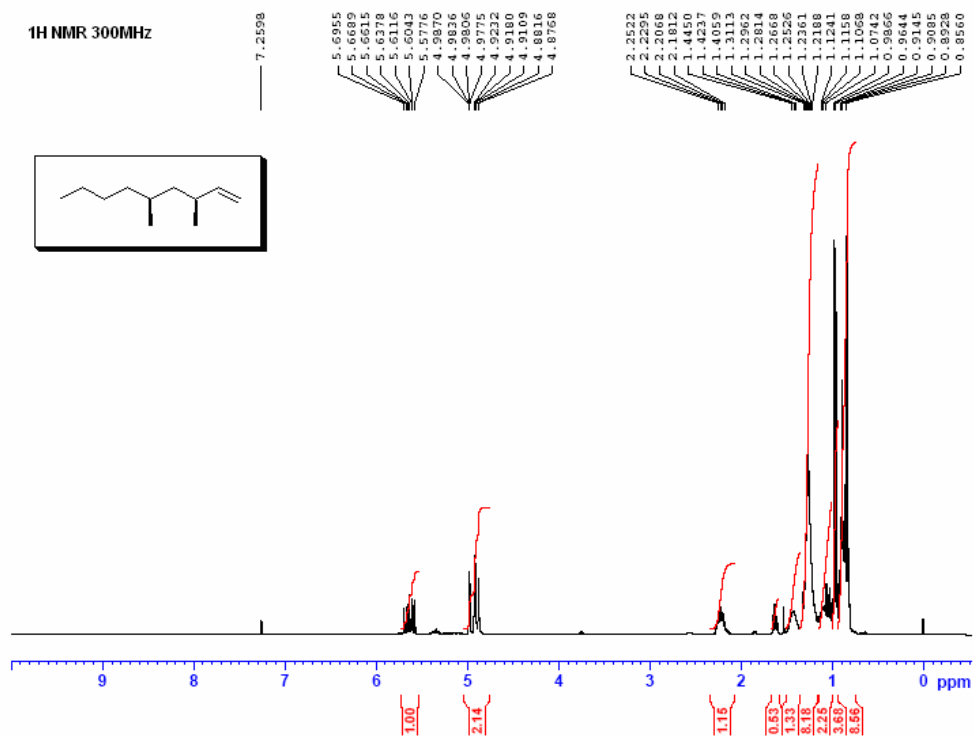
$[\alpha]_D^{20} = +14.0$ ($c = 0.83$, CHCl_3).

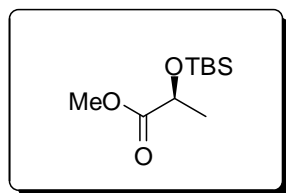
^1H NMR (300 MHz, CDCl_3): δ 5.70-5.58 (m, 1H), 4.99-4.88 (m, 2H), 2.25-2.18 (m, 1H), 1.42 (m, 1H), 1.31-1.22 (m, 6H), 0.99-0.96 (m, 2H), 0.91-0.83 (m, 6H).

^{13}C NMR (75 MHz, CDCl_3): δ 144.9, 112.3, 44.5, 37.3, 35.6, 30.2, 29.2, 23.1, 21.3, 19.5, 14.1.

FTIR (NaCl, neat): ν 2959, 2926, 2872, 2860, 1641, 1458, 1377 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{11}\text{H}_{23}$ (M+1) 155.1800, found 155.1803.



(S)-methyl 2-(*tert*-butyldimethylsilyloxy)propanoate (20)

To a round bottom flask equipped with a rubber septum and a magnetic stirrer bar was added imidazole (0.136 g, 2.00 mmol) and CH₂Cl₂ (2 mL). Then (–)-methyl-L-lactate (**19**) (0.104 g, 1.00 mmol) was added dropwise and the reaction mixture was cooled to 0 °C. *Tert*-butylchlorodimethylsilane (0.226 g, 1.50 mmol) was added slowly and the resulting reaction mixture was stirred overnight at room temperature. The mixture was diluted with CH₂Cl₂ (10 mL), H₂O (10 mL) and extracted with CH₂Cl₂ (20 mL x 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/EtOAc 50: 1) to afford the desired product as pale yellow oil (0.216 g, 99% yield).

R_f value (hexane/EtOAc 9: 1): 0.55.

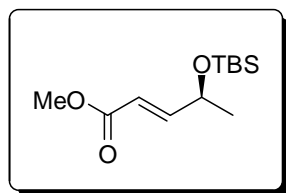
[α]_D²⁰ = -29 (*c* = 1.0, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ 4.32 (q, *J* = 6.7 Hz, 1H), 3.70 (s, 3H), 1.38 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 174.5 (C), 68.4 (CH), 51.7 (CH₃), 25.6 (CH₃), 21.3 (CH₃), 18.3 (C), -5.0 (CH₃), -5.3 (CH₃).

FTIR (NaCl, neat): ν 2953, 1759, 1740, 1373, 1362, 1148 cm⁻¹.

HRMS (ESI) calcd. for C₁₀H₂₃O₃Si (M+1) 219.1416, found 219.1419.

(*S,E*)-methyl 4-(*tert*-butyldimethylsilyloxy)pent-2-enoate (21)

In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, the ester **20** (0.218 g, 1.00 mmol) was dissolved in hexane (1.0 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. DIBAL-H (pre-cooled to $-78\text{ }^{\circ}\text{C}$, 1.1 mL, 1.0 M in heptane, 1.1 mmol) was added carefully over at least 2 portions. After stirring for another 1 h, MeOH (pre-cooled to $-78\text{ }^{\circ}\text{C}$, 0.096 g, 3.3 mmol) was added carefully over 2 portions and stirred for a further half an hour until a white suspension was observed. The ylide $\text{MeO}_2\text{CCH}=\text{PPh}_3$ (0.669 g, 2.00 mmol) was added in one portion followed by THF (5.0 mL) and the reaction mixture was allowed to warm slowly to room temperature over 30 minutes. The reaction mixture was stirred for another 30 minutes and refluxed for an additional 6 h. After that, the reaction mixture was cooled to room temperature and diluted with Et_2O (5 mL) and saturated potassium sodium tartrate (5 mL). The mixture was stirred until a clear biphasic separation was observed. The aqueous layer was extracted with Et_2O (10 mL x 3). The combined organic extracts were washed with saturated NaHCO_3 (15 mL x 2), brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/ EtOAc 100: 1) to afford the desired *trans*-product as colorless oil (0.169 g, 69% yield; 88% total yield for the mixture of *E/Z* isomers, *E/Z* = 78: 22).

R_f value (hexane/ EtOAc 10: 1): 0.54.

$[\alpha]_D^{20} = +1.0$ ($c = 1.0$, CHCl_3).

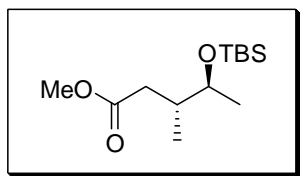
^1H NMR (400 MHz, CDCl_3): δ 6.93 (dd, $J = 4, 15.5$ Hz, 1H), 5.99 (dd, $J = 1.4, 15.2$ Hz, 1H), 4.46-4.43 (m, 1H), 3.72 (s, 3H), 1.25 (d, $J = 6.6$ Hz, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 167.2 (C), 152.2 (CH), 118.5 (CH), 67.6 (CH), 51.5 (CH₃), 25.8 (CH₃), 23.5 (CH₃), 18.2 (C), -4.9 (CH₃).

FTIR (NaCl, neat): ν 2930, 1715, 1659, 1368, 1152, 837, 775 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{24}\text{O}_3\text{SiNa}$ (M+Na) 267.1392, found 267.1394.

(3*R*,4*S*)-methyl 4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate (22)



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, (*S*)-Tol-BINAP (0.020 g, 0.03 mmol) and CuI (0.004 g, 0.02 mmol) were stirred in CH_2Cl_2 (2 mL) for 20 minutes, concentrated *in vacuo* and then stirred in *t*-BuOMe (4 mL) till a bright yellow suspension was observed. The mixture was then cooled to -20 °C and MeMgBr (0.83 mL, 3.0 M solution in Et_2O , 2.50 mmol) was added carefully into the reaction mixture. After stirring for 15 minutes, a pre-cooled solution of **21** (0.244 g, 1.00 mmol) in *t*-BuOMe (1.2 mL) was added dropwise over 1 h via syringe pump. After stirring at -20 °C for another one and an half hour, the reaction mixture was quenched with MeOH (1 mL), and 1 M NH_4Cl solution (4 mL). The aqueous layer was extracted with Et_2O (15 mL x 3) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/ Et_2O 90: 1) to afford the desired product as colourless oil (0.156 g, 60% yield; >99% *de*). The distereoselectivity

was determined in ^{13}C NMR using an average of two well-resolved carbon signals and compared to a diastereomeric mixture (*anti*: *syn* 95: 5) of methyl 4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate. Assuming an analogous reaction mechanism, the *anti*-stereochemistry was assigned based on the enantiomeric Tol-BINAP ligand selected in 1,4-Michael addition of methylmagnesium bromide to an α,β -unsaturated ester.

R_f value (hexane/Et₂O 2: 1): 0.55.

$[\alpha]_D^{20} = +24.5$ ($c = 1.13$, CHCl₃).

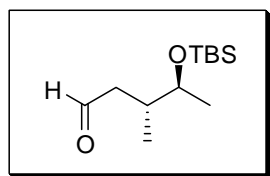
^1H NMR (400 MHz, CDCl₃): δ 3.68 (s, 3H), 3.66-3.62 (m, 1H), 2.51 (dd, $J = 4.4, 14.9$ Hz, 1H), 2.06 (dd, $J = 9.4, 14.9$ Hz, 1H), 2.02-1.92 (m, 1H), 1.09 (d, $J = 6.2$ Hz, 3H), 0.91 (d, $J = 6.6$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (100 MHz, CDCl₃): δ 174.1, 71.5, 51.3, 37.7, 36.8, 25.8 (3C), 20.6, 18.0, 16.2, -4.3, -4.9.

FTIR (NaCl, neat): ν 2957, 2930, 1740, 1252 cm^{-1} .

HRMS (ESI) calcd. for C₁₃H₂₉O₃Si (M+1) 261.1886, found 261.1886.

(3*R*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanal (23)



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, **22** (0.260 g, 1.00 mmol) was dissolved in hexane (4 mL) and cooled to -78°C . DIBAL-H (pre-cooled to -78°C , 1.1 mL, Aldrich 1.0 M in heptane, 1.10 mmol) was added carefully over at least 2 portions. After stirring for another 1 h, MeOH (pre-cooled to -78°C , 0.106 g, 3.30 mmol) was added carefully over 2 portions and stirred for a

further 15 minutes till a white suspension was observed. The reaction mixture was then added saturated potassium sodium tartrate solution (5 mL), diluted with Et₂O (5 mL) and warmed to room temperature. The mixture was stirred until a clear biphasic separation was observed. The aqueous layer was extracted with Et₂O (10 mL x 3). The combined organic extracts were washed with saturated NaHCO₃ (15 mL x 2), brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (Hexane/Et₂O 20: 1) to afford the desired product as pale yellow oil (0.173 g, 75% yield).

R_f value (hexane/Et₂O 8: 1): 0.36.

[α]_D²⁰ = +26.6 (*c* = 1.09, CHCl₃).

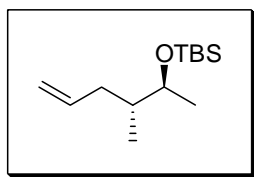
¹H NMR (300 MHz, CDCl₃): δ 9.77 (m, 1H), 3.68-3.60 (m, 1H), 2.25-2.16 (m, 1H), 2.21 (ddd, *J* = 2.7, 8.1, 16.2 Hz, 1H), 2.10-2.01 (m, 1H), 1.12 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 203.1, 72.0, 46.7, 36.0, 25.8 (3C), 21.2, 18.0, 16.9, -4.3, -4.8.

FTIR (NaCl, neat): ν 2957, 2930, 1726, 1709 cm⁻¹.

HRMS (ESI) calcd. for C₁₂H₂₇O₂Si (M+1) 231.1780, found 231.1778.

***Tert*-butyldimethyl((2*S*,3*R*)-3-methylhex-5-en-2-yloxy)silane (B)**



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, methyltriphenylphosphonium bromide (1.15g, 3.20 mmol) was stirred in anhydrous THF (5 mL) for 1 minutes, concentrated *in vacuo* and stirred in anhydrous THF (10

mL) at 0 °C for 10 minutes. Lithium bis(trimethylsilyl)amide (2.88 mL, 1.0 M in THF, 2.88 mmol) was added dropwise and stirred for 1 h at 0 °C. Then, a solution of **23** (0.370g, 1.60 mmol) in THF (5 mL) was added slowly. The mixture was stirred for 2 h at 0 °C. The reaction mixture was diluted with NH₄Cl (10 mL) and extracted with diethyl ether (10 mL x 3). The combined organic layers were washed with water, brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (100% hexane) to give the desired product as colourless oil (0.296 g, 81% yield).

R_f value (hexane 100%): 0.49

[α]_D²⁰ = +12.4 (*c* = 1.12, CHCl₃).

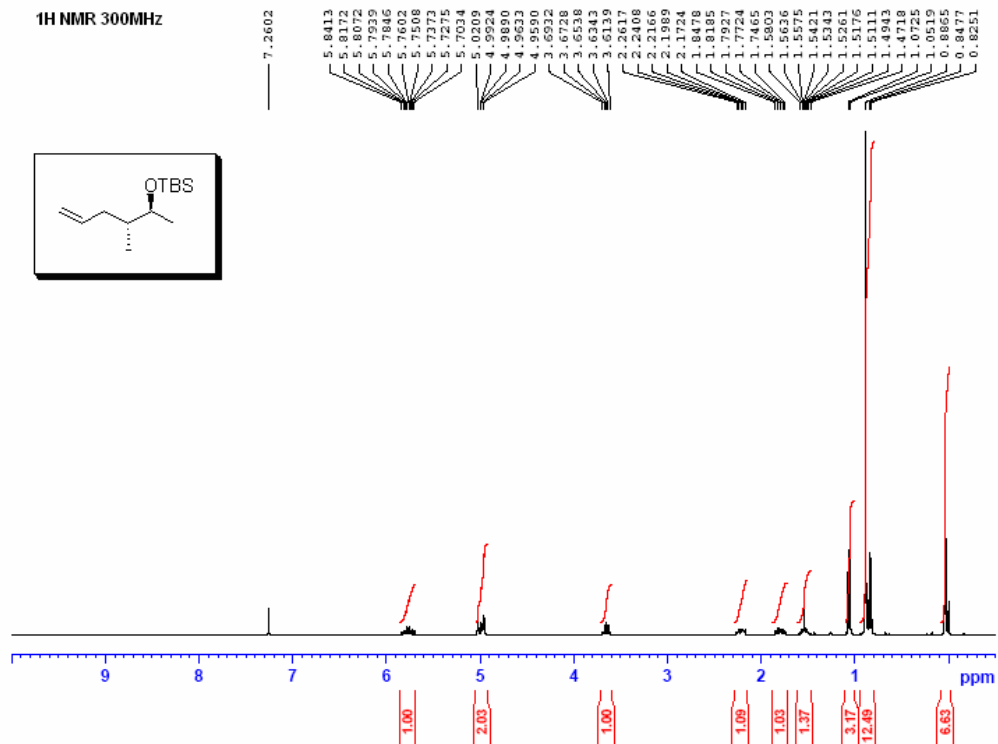
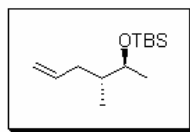
¹H NMR (300 MHz, CDCl₃): δ 5.84-5.81 (m, 1H), 5.02-4.96 (m, 2H), 3.69-3.61 (m, 1H), 2.26-2.17 (m, 1H), 1.85-1.75 (m, 1H), 1.58-1.47 (m, 1H), 1.06 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 138.0, 115.4, 71.7, 40.3, 37.2, 25.9 (3C), 19.8, 18.1, 14.7, -4.3, -4.8.

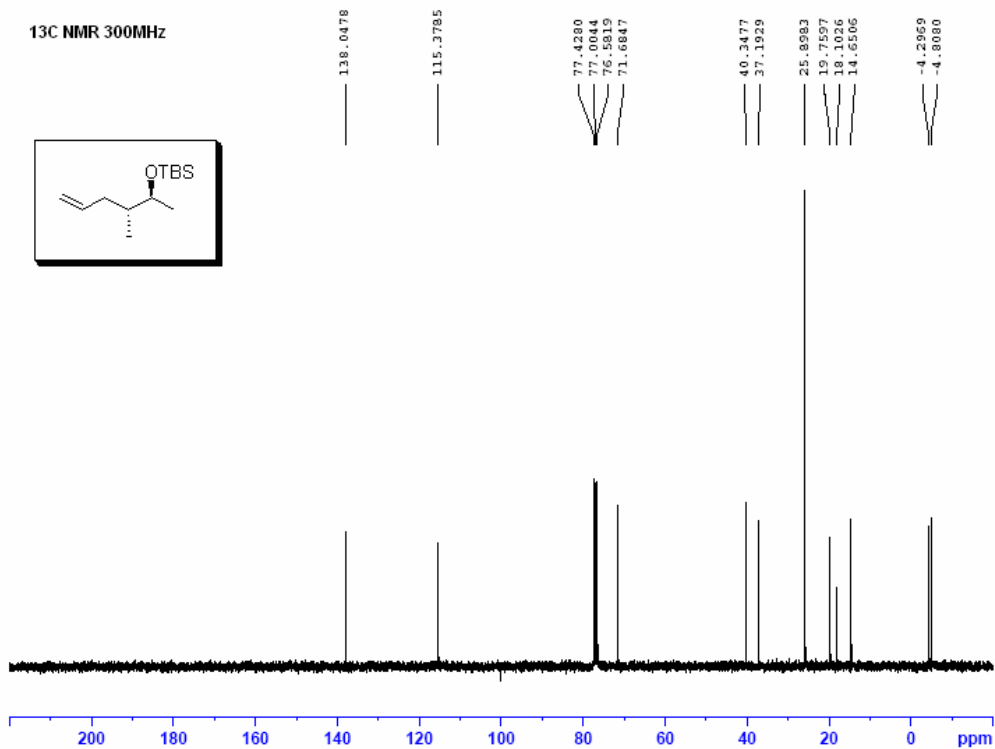
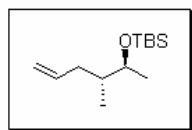
FTIR (NaCl, neat): ν 2957, 2857, 1641, 1252 cm⁻¹.

HRMS (ESI) calcd. for C₁₃H₂₉OSi (M+1) 229.1988, found 229.1986.

¹H NMR 300MHz



¹³C NMR 300MHz



PART II

SYNTHESIS STUDIES TOWARDS THE TOTAL SYNTHESIS OF IRIOMOTEOLIDE-1A

CHAPTER 1

Introduction

1.1 BACKGROUND

In 2007, a series of macrolides named iriomoteolides have been isolated by Tsuda's group from the Iriomote Island of Japan.¹⁷ They are iriomoteolide-1a (**26**), -1b and -1c. These macrolides belong to the class of amphidinolides obtained from *Amphidinium* sp.^{18,19} Among them, iriomoteolide-1a (**26**) has been shown to exhibit potent cytotoxic activity against human B lymphocyte DG-75 cells with an IC₅₀ of 2 ng/mL. Moreover, it displayed remarkably potent cytotoxicity against Epstein-Barr virus (EBV)-infected human B lymphocyte Raji cells with an IC₅₀ of 3 ng/mL.¹⁸ Despite its potent activity, the biological mechanism of action of iriomoteolide-1a is currently unknown.

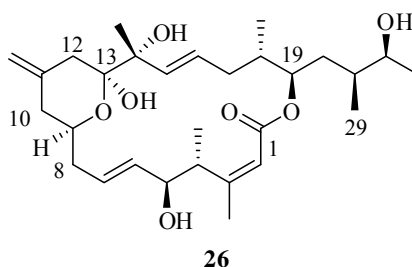


Figure 1.1 Proposed structure of Iriomoteolide-1a (**26**)

Tsuda's group proposed the structure of iriomoteolide-1a (**26**) to be a 20-membered carbon skeleton with nine stereogenic centers which two of them are quaternary centers. The macrolide contains a tetrahydropyran ring, an exomethylene unit, three endogenous double bonds, four hydroxyl groups and five methyl groups.

¹⁷ The investigation of the *Amphidinium* strain HYA024 led to isolation of iriomoteolide-1a (**26**), -1b and -1c. (a) Isolation and structural elucidation of iriomoteolide-1a (**26**): Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Kobayashi, J.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A.; Kitaya, Y.; Omasa, K. *J. Org. Chem.* **2007**, *72*, 4467. (b) Isolation and structural elucidation of iriomoteolide-1b and 1c: Tsuda, M.; Oguchi, K.; Iwamoto, R.; Okamoto, Y.; Fukushi, E.; Kawabata, J.; Ozawa, T.; Masuda, A. *J. Nat. Prod.* **2007**, *70*, 1661.

¹⁸ (a) Review see: Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77. (b) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451.

¹⁹ For some selected synthesis of amphidinolides, see: (a) Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960. (b) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 8091. (c) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W.-M. *Org. Lett.* **2007**, *9*, 2585.

The tetrahydropyran ring is a cyclic hemiketal core, of which contained an exomethylene branch and a tertiary chiral center that is vicinal to the hemiketal ring. The structural of this natural product was elucidated primarily by 2-D NMR analysis.

Due to its challenging molecular structure and interesting biological activities, it has been a popular target of total synthesis and total syntheses of the proposed structure and the diastereomers of the molecule have been disclosed recently.

1.2 REPORTED SYNTHETIC STUDIES

There are several laboratories completed the synthesis of different fragments. The first asymmetric synthesis of the C1-C12 fragment **29** by Yang's group²⁰ has been achieved via sequential application of two catalytic, asymmetric, vinylogous aldol reactions. In Yang's retrosynthetic analysis, they planned to synthesize the cyclic hemiketal core at the late-stage by an intramolecular nucleophilic cyclization of an allymetal species derived from ally chloride **27**.²¹ The intermediate **27** is then constructed from two principal modules: C19-C23 unit **28** and C1-C12 unit **29** (Figure 1.2). A sequential of intermolecular and intramolecular esterifications of the two modules is designed to give the macrocycle **27**.

²⁰ Fang, Li.; Xue, H.; Yang, J. *Org. Lett.* **2008**, *10*, 4645.

²¹ (a) Heumann, L. V.; Keck, G. E. *Org. Lett.* **2007**, *9*, 1951. (b) Smith, A. B.; Razler, T. M.; Meis, R. M.; Pettit, G. R. *Org. Lett.* **2006**, *8*, 797.

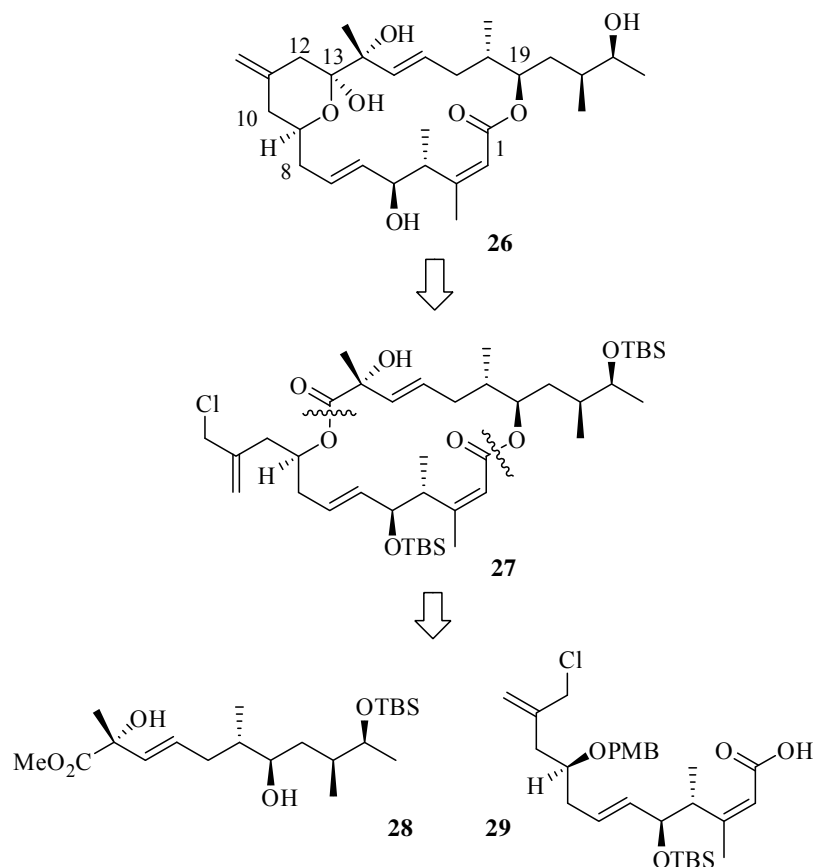
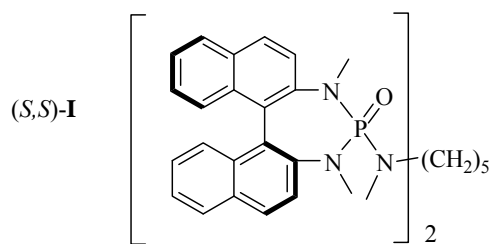
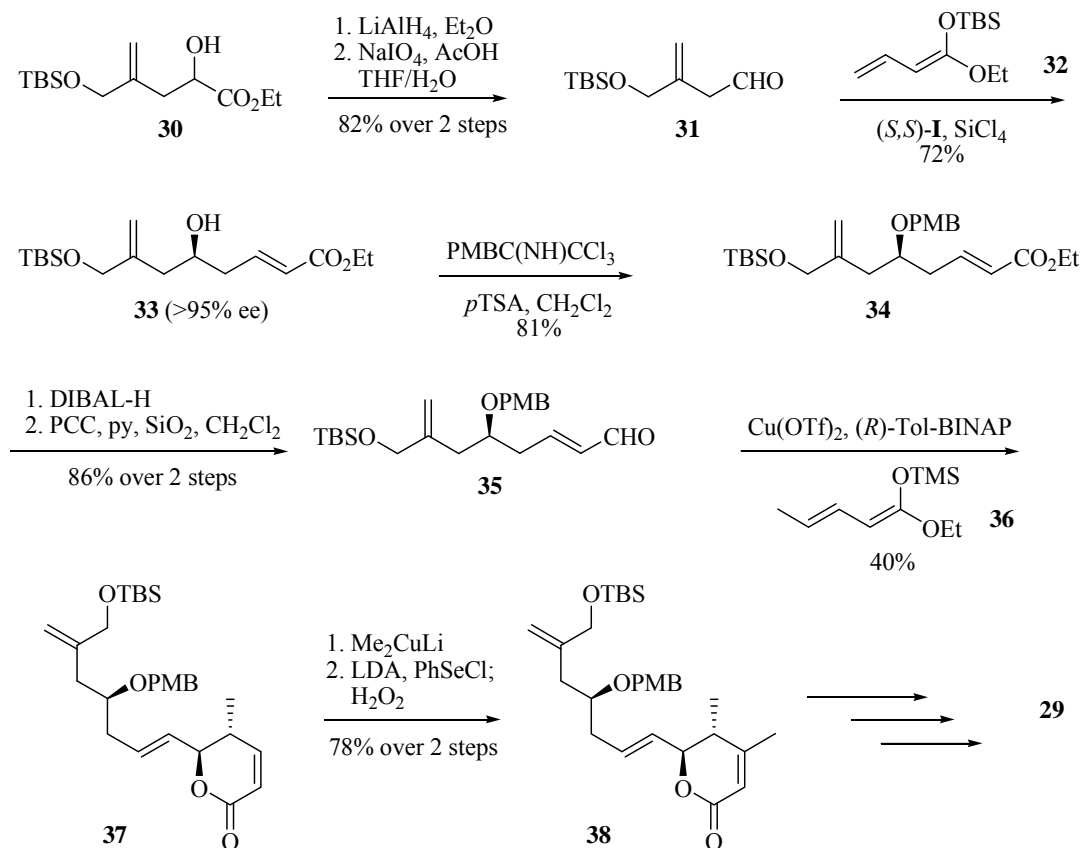


Figure 1.2 Retrosynthetic analysis of iriomoteolide-1a by Yang.

The synthesis of the C1-C12 fragment **29** began with LiAlH₄ reduction of **30** followed by oxidative cleavage of the diol with NaIO₄ to provide aldehyde **31**. The first vinylogous aldol addition of aldehyde **31** to the dienolate **32** could be accomplished with (*S,S*)-bisphosphoramidate **I** as the chiral ligand to obtain secondary alcohol **33** smoothly in good yield with excellent enantioselectivity.²² Consequently, the alcohol **33** was protected and the resulting protected **34** was transformed to aldehyde **35** by DIBAL-H reduction and PCC oxidation. The substrate **35** further undergoes vinylogous aldol coupling with ethyl silyl dienolate **36** to afford α,β -

²² (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560. (b) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774. (c) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800.

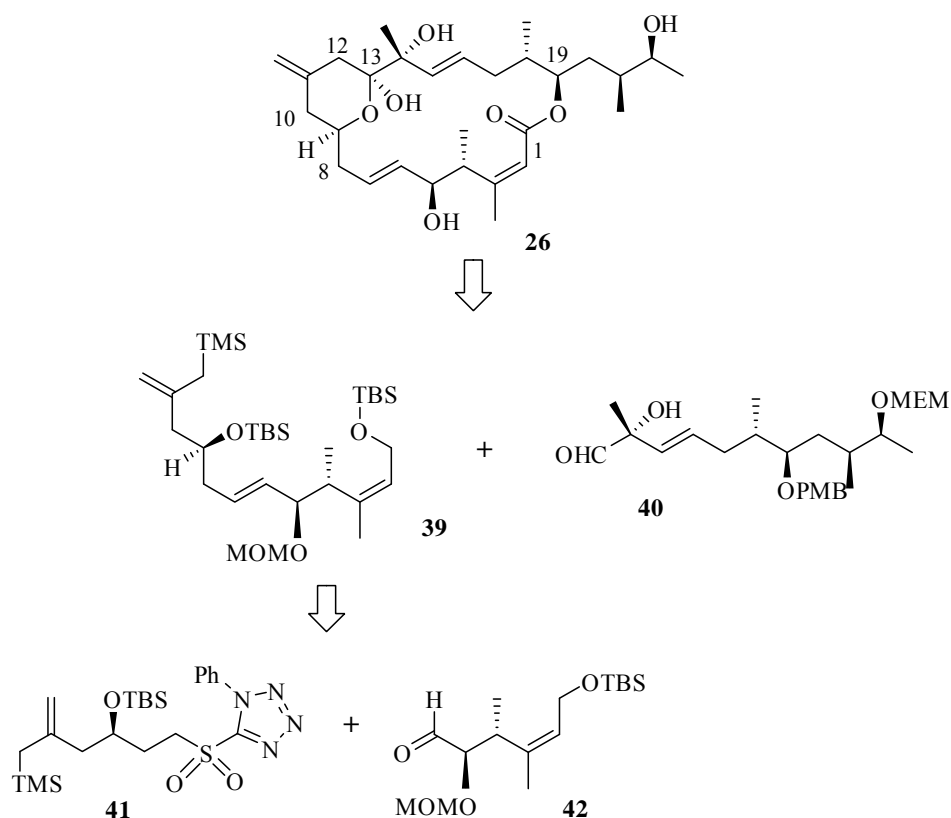
unsaturated- δ -lactone **37**.²³ The methyl group in **38** was then introduced by 1,4-addition with Me_2CuLi and dehydrogenation mediated by PhSeCl . Finally, conversion of TBS group to chloride group followed by a sequence of basic hydrolysis and TBS protection to allow the preparation of **29** (Scheme 1.1).



Scheme 1.1 Synthesis of C1-C12 fragment

²³ (a) Bazán-Tejeda, E.; Bluet, G.; Broustal, G.; Campagne, J.-M. *Chem. Eur. J.* **2006**, *12*, 8358. (b) Bazán-Tejeda, E.; Campagne, J.-M. *Org. Lett.* **2001**, *3*, 3807.

Ghosh's group demonstrated the second synthesis of C1-C12 fragment.²⁴ The target was also divided into two modules with very similar building blocks employed by Yang (Scheme 1.2). The assembly of building blocks **39** and **40** was designed to arise from Sakurai reaction²⁵ and macrolactonization between the C₁-carboxylic acid and C₁₉-hydroxyl group. The key steps involved an enzymatic kinetic resolution of a β -hydroxy amide, a Pd-catalyzed cross-coupling and a Julia-Kocienski olefination between sulfone **41** and aldehyde **42**.



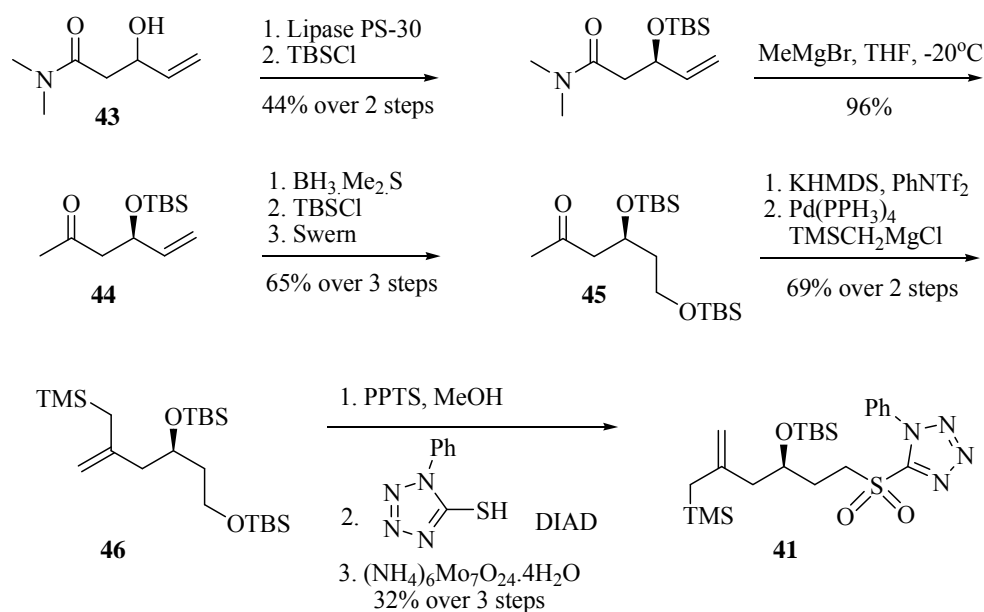
Scheme 1.2 Retrosynthetic analysis of iriomoteolide-1a by Ghosh.

The synthesis of sulfone **41** commenced with an enzymatic kinetic resolution of a β -hydroxy amide **43** followed by protection of alcohol and subsequently methyl Grignard addition to furnish methyl ketone **44**. Addition of borane dimethylsulfide complex to ketone **44** provided a diol. The primary hydroxyl group in diol was then

²⁴ Ghosh, A. K.; Yuan, H. *Tetrahedron Lett.* **2009**, *50*, 1416.

²⁵ Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295.

selectively protected where as the secondary hydroxyl group was oxidized to ketone via Swern oxidation to furnish ketone **45**. Treatment of the ketone **45** with KHMDS and phenyl triflimide gave the corresponding vinyl triflate. A Pd-catalyzed cross coupling between the triflate and trimethylsilylmethylmagnesium chloride afford the desired allyl silane **46**. Deprotection of the primary silyl ether followed by Mitsunobu reaction gave the sulfone **41** (Scheme 1.3).

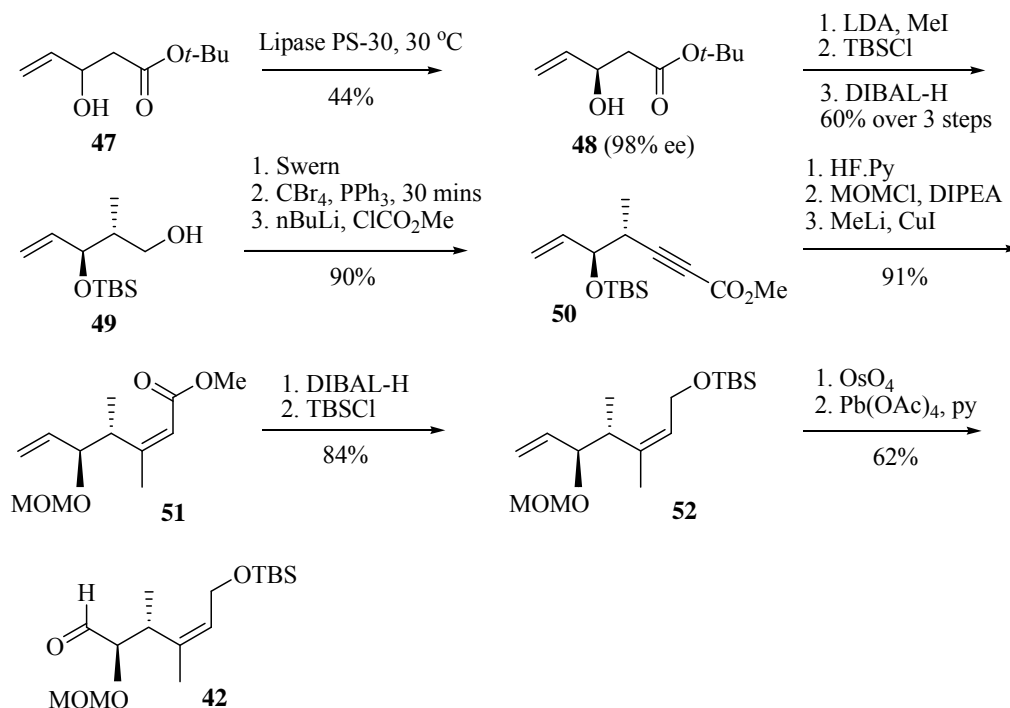


Scheme 1.3 Synthesis of sulfone **41**

The synthesis of aldehyde **42** began with an enzymatic kinetic resolution of a racemic alcohol **47** through lipase PS-30 to offer alcohol **48**. The primary alcohol **49** in turn could be obtained by introduction of methyl group through methyl iodide²⁶ followed by a sequence protection of the secondary hydroxyl group and DIBAL-reduction. Swern oxidation of **49** and Corey-Fuchs' homologation gave alkynyl ester **50**. The substrate **50** further went through conversion of the protecting group and methyl addition to provide alkene **51**. Another ester reduction, alcohol protection by

²⁶ (a) Seebach, D.; Aebi, J.; Wasmuth, D. *Organic Synthesis*; John Wiley and Sons: New York, 1990. Collect. Vol. III. Pp 153-159. (b) Hermann, J. L.; Schlessinger, R. A. *Tetrahedron Lett.* **1973**, *14*, 2429.

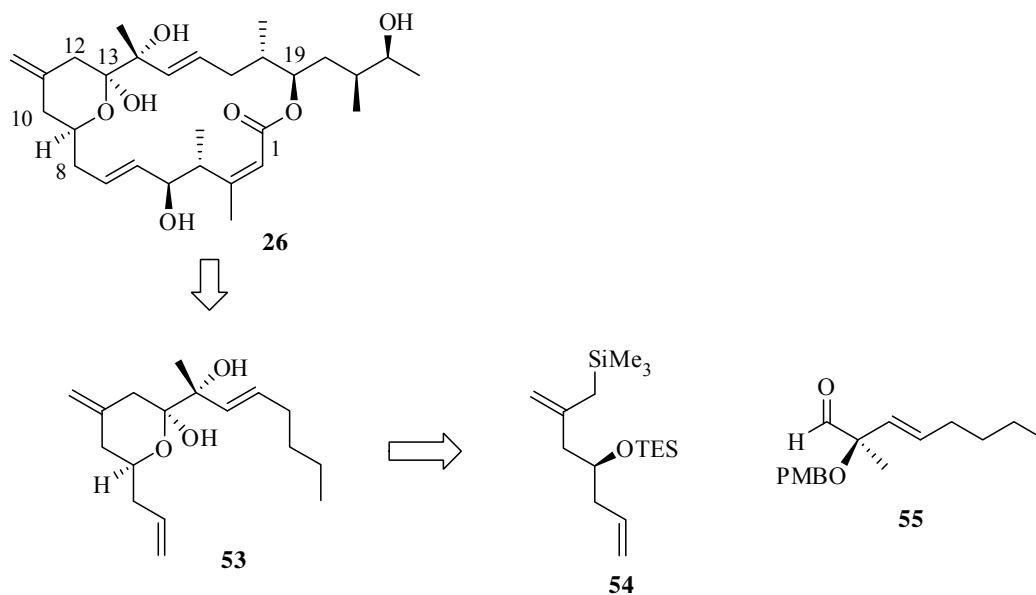
tert-butyldimethylsilyl chloride and oxidative cleavage of the terminal olefin were performed by to yield the aldehyde **42** (Scheme 1.4). With the sulfone **41** and aldehyde **42** in hand, Julia-Kocienski olefination was carried out to complete the C1-C12 module **39**.



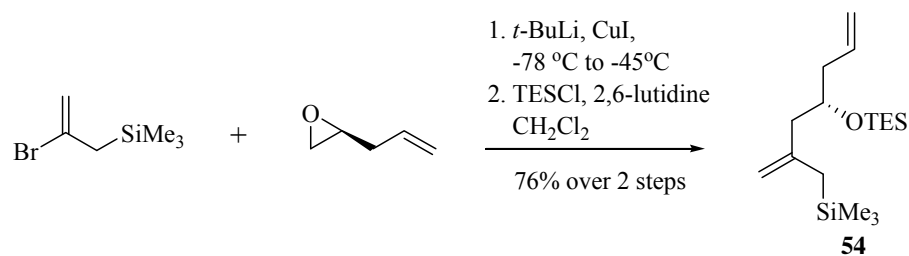
Scheme 1.4 Synthesis of aldehyde **42**

On a separate account, Horne²⁷ *et al.* reported a relatively short synthesis of the cyclic hemiketal core **53** of iriomoteolide-1a which involving a Sakurai reaction of allylsilane **54** and aldehyde **55** that bears a chiral α -tertiary center (Scheme 1.5). The preparation of allylsilane **54** was shown in Scheme 1.6.

²⁷ Xie, J.; Horne, D. A. *Tetrahedron Lett.* **2009**, *50*, 4485.



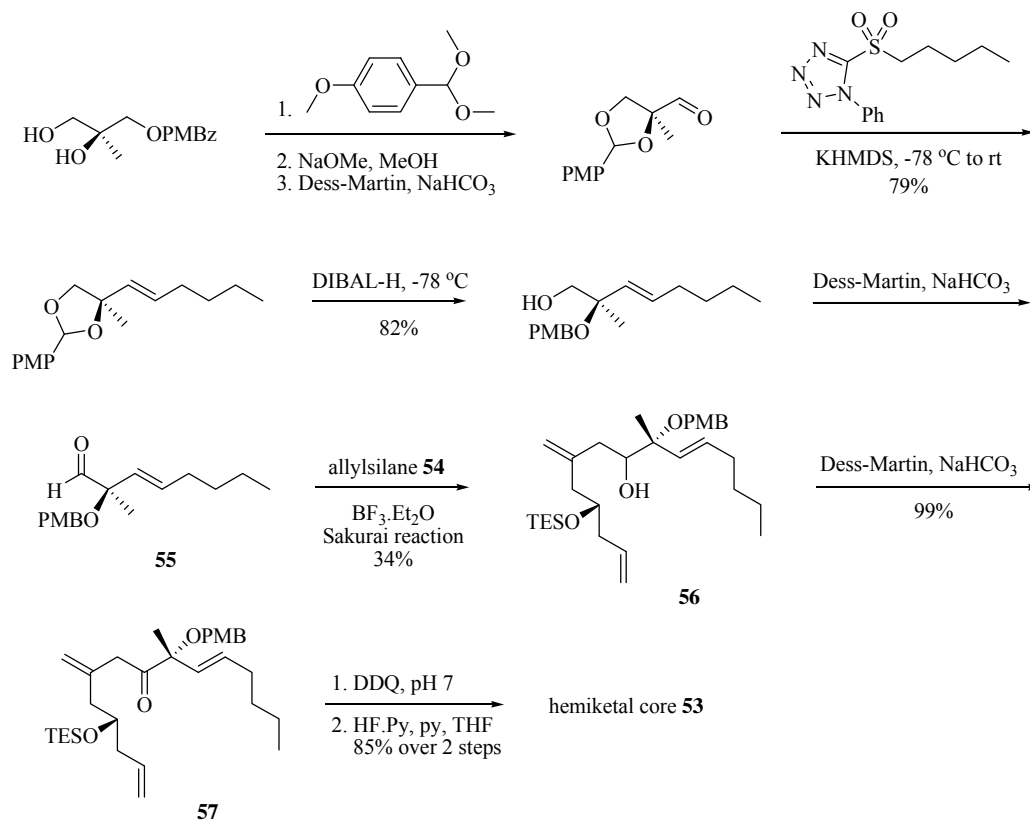
Scheme 1.5 Retrosynthetic analysis of core structure **53**



Scheme 1.6 Synthesis of allylsilane **54**

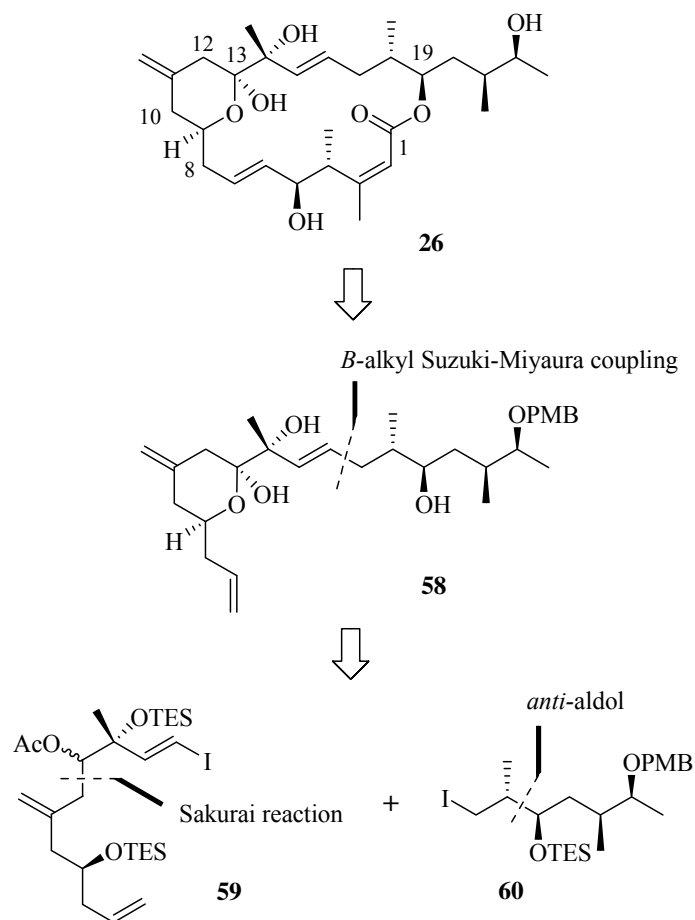
The Sakurai reaction²⁸ between allyltrimethylsilane **54** and aldehyde **55** was the key step and utilized to prepare an α,β -unsaturated alcohol **56**. Subsequent Dess-Martin periodinane oxidation of the resulting alcohol **56**, PMB ether removal by DDQ and TES deprotection by HF.Py led to concomitant cyclization to afford the desired six-membered ring hemiketal core **53** as a single isomer (Scheme 1.7).

²⁸ Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295.

Scheme 1.7 Synthesis of the hemiketal core **53**

Horne *et al.*²⁹ also developed an asymmetric synthesis of the C7-C23 fragment **58**. The fragment **58** can be further dissected into smaller units **59** and **60**, which can be assembled by a *B*-alkyl Suzuki-Miyaura cross-coupling reaction as they key step (Scheme 1.8).

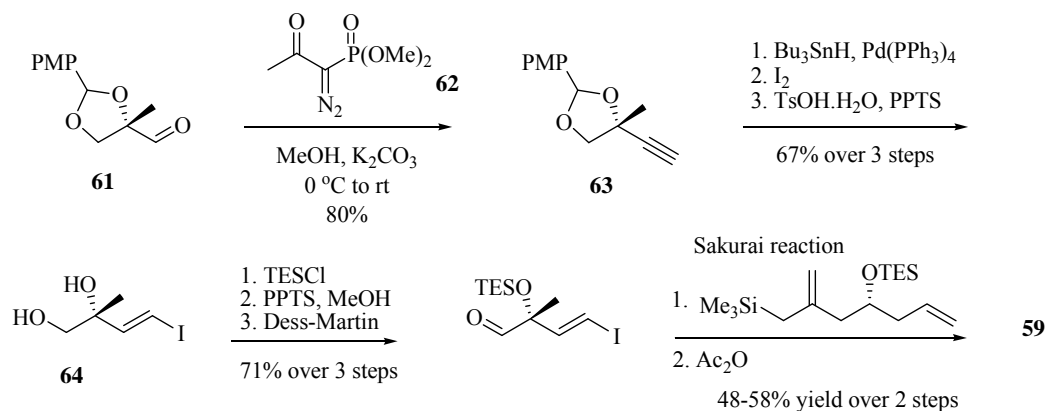
²⁹ Xie, J.; Ma, Y.; Horne, D. A. *Org. Lett.* **2009**, *11*, 5082.



Scheme 1.8 Retrosynthetic analysis of iriomoteolide-1a

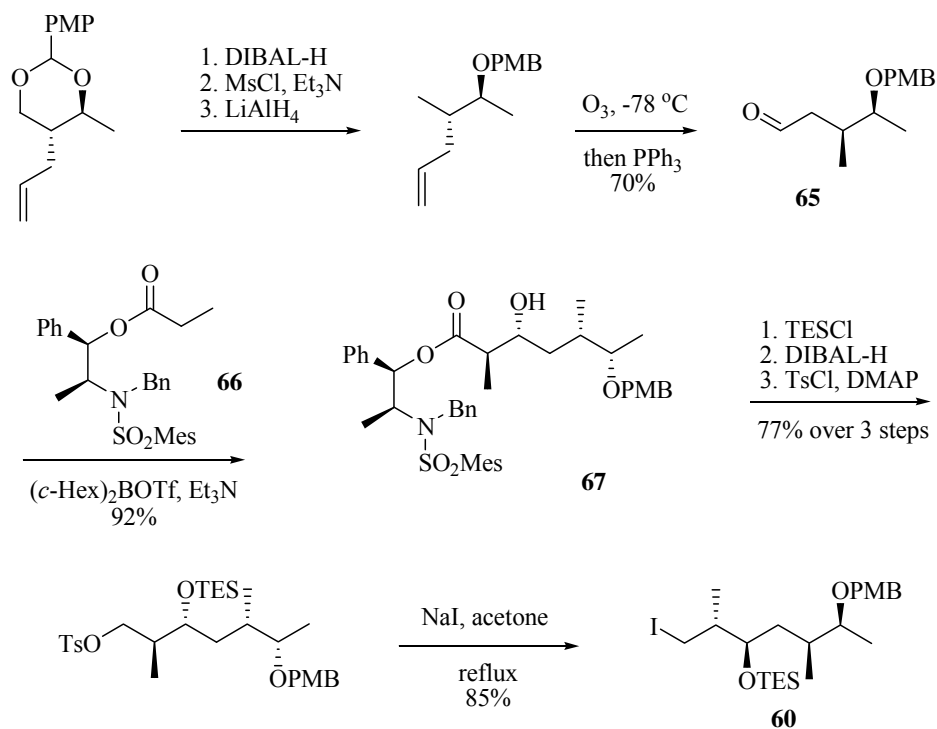
The synthesis of key building block **59** started from homologation of **61** with Bestmann-Ohira reagent **62**.³⁰ Hydrogenation followed by iodination and removal of acetal group afforded *E*-vinyl iodide **64**. Subsequent TES protection on both hydroxyl groups, selective deprotection on primary TES group, Dess-Martin oxidation and further transformations yielded the unit **59** (Scheme 1.9).

³⁰ (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.



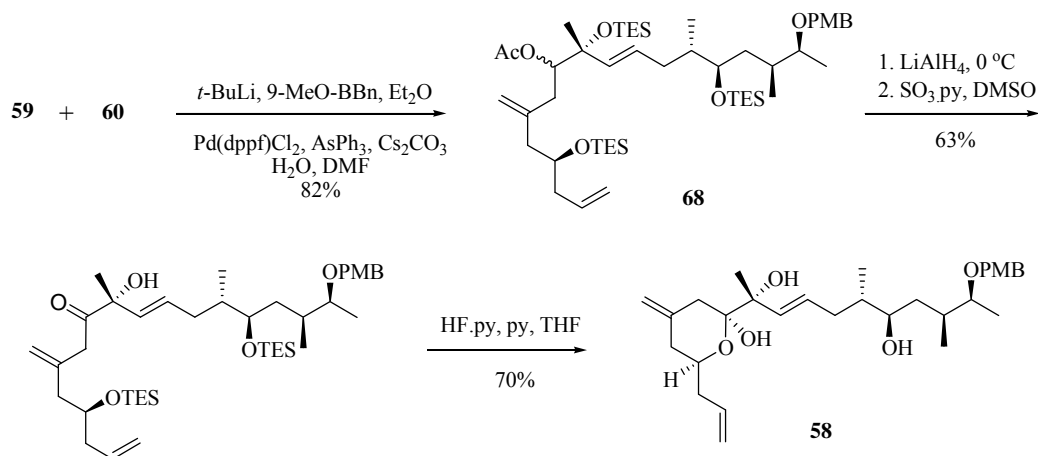
Scheme 1.9 Synthesis of unit 59

The key unit **60** was described to arise from aldol addition of chiral auxiliary **66** to aldehyde **65** that produced *anti*-aldol **67** product smoothly in excellent yield with good diastereoselectivity. Finally, the synthesis of unit **60** was completed by conversion of the ester group into an iodide (Scheme 1.10).



Scheme 1.10 Synthesis of unit 60

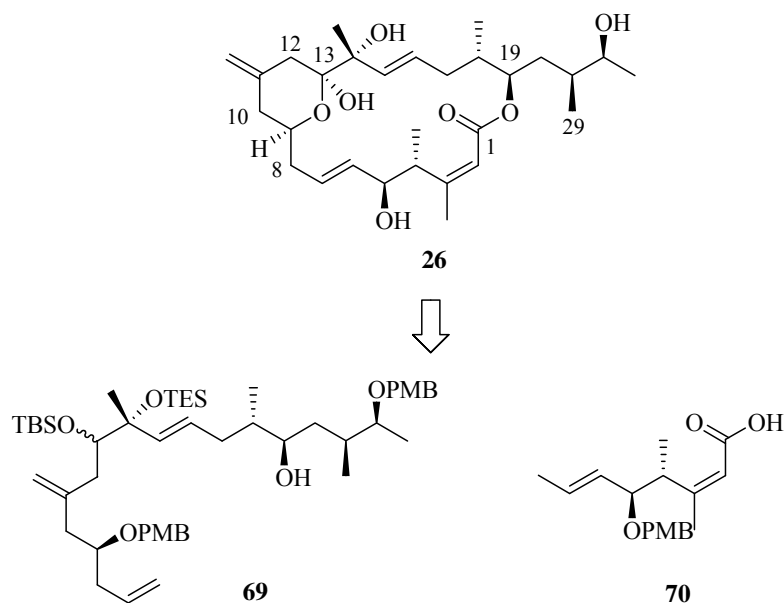
Vinyl iodide **59** and alkyl iodide **60** underwent Suzuki-Miyaura cross coupling smoothly to afford precursor **68** in excellent yield. Further LiAlH₄ cleavage of the acetate group and oxidation of the alcohol functionality provided the β,α -unsaturated ketone. At last, TES protection led to concomitant cyclization and formed C7-C23 fragment **58**.



Scheme 1.11 Synthesis of C7-C23 fragment **58** of iriomoteolide-1a

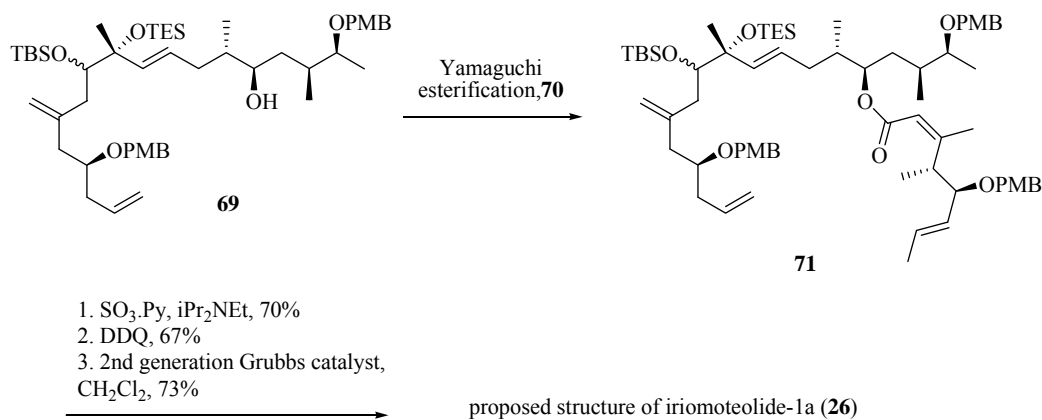
Very recently, Horne and coworker have been the first group to report the total synthesis of the proposed structure of iriomoteolide-1a (Scheme 1.12).³¹ However, he did not agree on the original structural assignment of the natural product. He observed that ¹H and ¹³C NMR spectral data of the synthetic iriomoteolide-1a did not match with the reported for the natural product. In addition, he examined the anticancer activity for his synthetic molecule in two different cell lines (Raji and A431) and no significant cytotoxicity was found at 10 μM concentration. From his studies, it is likely that the C(2)–C(3) double bond configuration of natural product is *E* instead of the originally proposed *Z*.

³¹ Xie, J.; Ma, Y.; Horne, D. A. *Chem. Commun.*, **2010**, 46, 4770.



Scheme 1.12 Retrosynthetic analysis of iriomoteolide-1a

The first total synthesis of the proposed structure of iriomoteolide-1a (**26**) has been completed via a Yamaguchi esterification, PMB deprotection with concomitant hemiketal cyclization, followed by ring closing Grubbs metathesis (Scheme 1.13).



Scheme 1.13 First total synthesis of **26**

1.3 RETROSYNTHETIC ANALYSIS

The principal challenge in the synthesis of iriomoteolide-1a (**26**) is the stereocontrolled installation of the stereogenic centers. We felt that the challenge could be efficiently addressed by employing asymmetric Michael addition of Grignard reagents¹¹, asymmetric crotylation³², boron-mediated Aldol protocol³³ and metal-mediated asymmetric allylation³⁴ in the control of the absolute stereochemistry of the stereogenic centers.

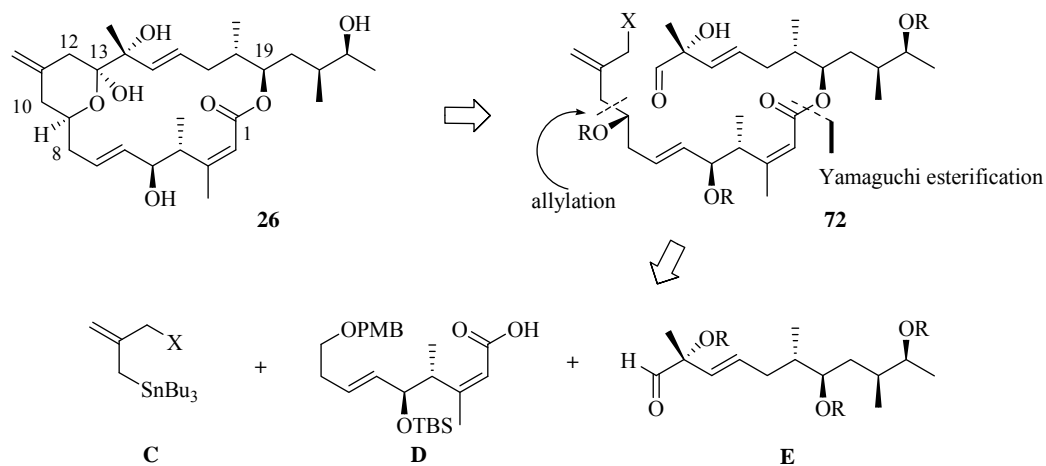
To maximize synthetic convergency, the ether functionality at C-13 of iriomoteolide-1a (**26**) was disconnected to afford the intermediate **72** (Scheme 1.14). Following the dissection of macrolactone **72**, C9-C10 bond and the ester linkage at C-19 can be cleaved to liberate into three main fragments - the alkene **C**, the carboxylic acid **D** and the aldehyde **E**. In the forward synthesis, these connections require a metal-mediated allylation from the alkene **C** and the aldehyde generated species derived from the fragment **D**. Yamaguchi esterification with the aldehyde **E** would prepare the intermediate **72** followed by an intramolecular allylation to close up the

³² For reviews, see (a) Brown H. C.; Ramachandran, P. V. *J. Organomet.Chem.* **1995**, *500*, 1. (b) Brown H. C.; Ramachandran, P. V. *Pure Appl.Chem.* **1994**, *66*, 201. (c) Hoffmann, R. W. *Pure Appl.Chem.* **1988**, *60*, 123. For other asymmetric crotylation, see (d) Roush, W. R.; Palkowitz, A. D.; Palmer, M. J. *J. Org. Chem.* **1987**, *109*, 953. (e) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (f) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

³³ (a) Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893. (b) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821. (c) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499. (d) Kim, B. M.; Williams, S. F.; Masamune, S. *Comprehensive Organic Synthesis* (eds. Trost, B. M. & Fleming, I.) 301-320 (Pergamon Press, Oxford, United Kingdom, 1991). (e) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121.

³⁴ (a) Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 6209. (b) Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 4573. (c) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743. (d) Teo, Y.-C.; Tan, K.-T.; Loh, T.-P. *Chem. Commun.* **2005**, *10*, 1318. (e) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 7435. (f) Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Chem. Commun.* **2005**, *33*, 4217. (g) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (h) Lu, J.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, *18*, 2345. (i) Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, *8*, 1010. (f) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692. (g) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (h) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (i) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001.

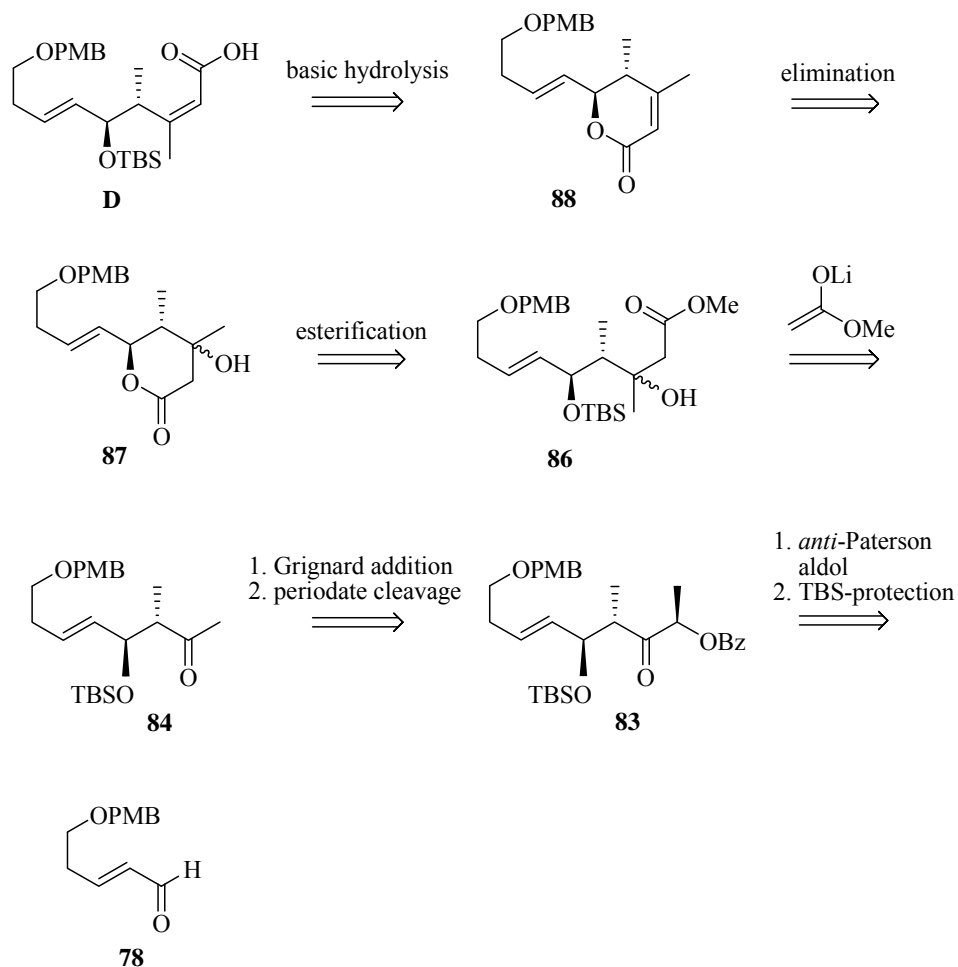
ring. We envisaged that oxidation of the alcohol at C-13 to ketone and hemiketal cyclization will complete the synthesis of the molecule. However, we predicted that the closure of the ring by allylation might succumb to considerable level of difficulty due to the reactivity of the C-14 that bears a chiral α -tertiary center.



Scheme 1.14 Our retrosynthetic analysis of iriomoteolide-1a

1.3.1 Retrosynthesis of Fragment D

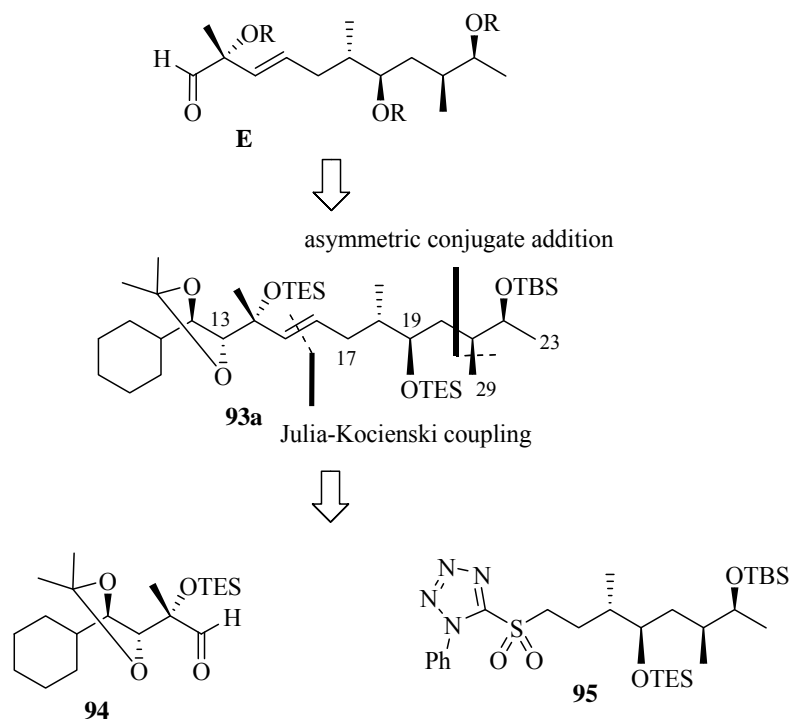
The fragment **D** is a carboxylic acid containing two protected hydroxyl groups and two endogenous double bonds. It can be seen to arise from ring opening of a six-membered ring lactone **88**. Lactone **88** can subsequently be obtained from the intramolecular esterification of β -quaternary alcohol **86** followed by elimination. The addition of lithium 1-methoxyethenolate to ketone **84** would give us the desired alcohol **86**. Grignard addition and oxidative cleavage would prepare the ketone **84** from intermediate **83**. The intermediate **83** in turn can be synthesized from the precursor **78** through *anti*-Paterson aldol reaction and TBS-protection (Scheme 1.15).



Scheme 1.15 Retrosynthetic analysis of fragment **D**

1.3.2 Retrosynthesis of Fragment E

The key building block **E** is an aldehyde containing a α -tertiary center, an endogenous double bond and three protected hydroxyl groups. Disconnection of the olefinic position of **93a** will result in two subunits **94** and **95** (Scheme 1.16). The key steps involve stereoselective introduction of the C-29 methyl by our group's highly efficient CuI-Tol-BINAP-catalyzed asymmetric conjugate addition,^{35,36,37} asymmetric crotylation and Julia-Kocienski olefination.



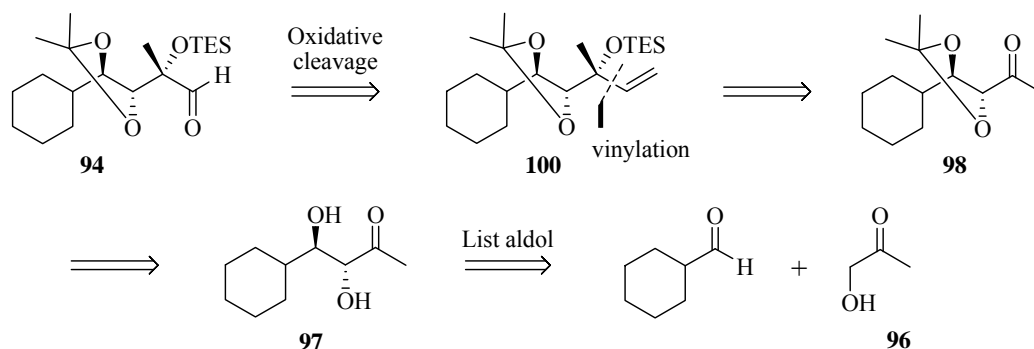
Scheme 1.16 Retrosynthetic analysis of fragment **E**

³⁵ (a) Wang, S. Y.; Ji, S. J.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 276. (b) Wang, S. Y.; Lum, T. K.; Ji, S. J.; Loh, T. P. *Adv. Synth. Catal.* **2008**, *350*, 673. (c) Lum, T. K.; Wang, S. Y.; Loh, T. P. *Org. Lett.* **2008**, *10*, 761. (d) Bates, R. W.; Sridhar, S. *J. Org. Chem.* **2008**, *73*, 8104.

³⁶ For asymmetric addition of Grignard reagents to α,β -unsaturated thioesters, see: Macia Ruiz, B.; Geurts, K.; Fernandez-Ibanez, M. A.; Horst, B.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2007**, *9*, 5123.

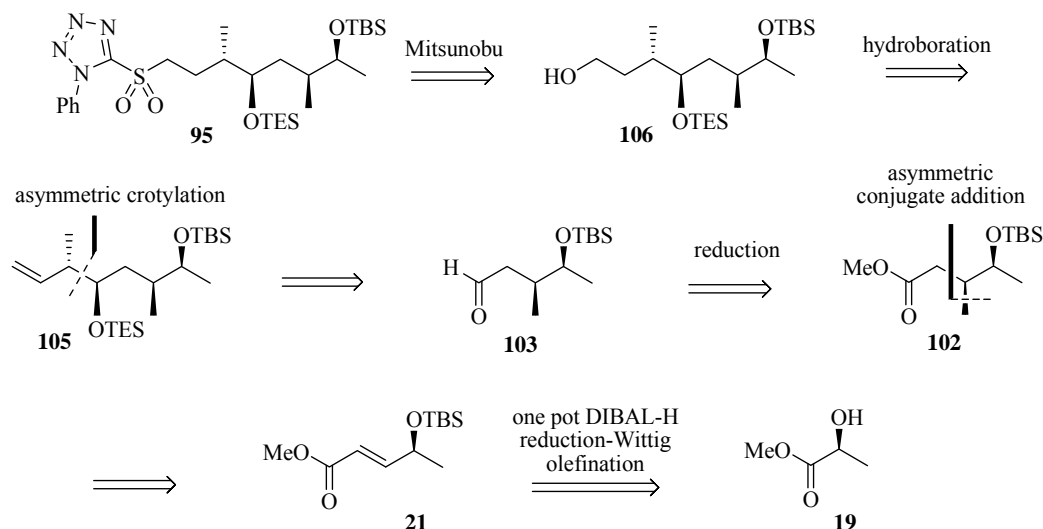
³⁷ For asymmetric addition of Grignard reagents to sulfones, see: Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2008**, *10*, 4219.

The subunit **94** can be prepared from olefin **100** via oxidative cleavage. Olefin **100** in turn can be synthesized from vinyl Grignard addition to ketone **98**, which is raised from the List aldol adduct **97** between cyclohexanecarbaldehyde and hydroxyacetone **96** (Scheme 1.17).

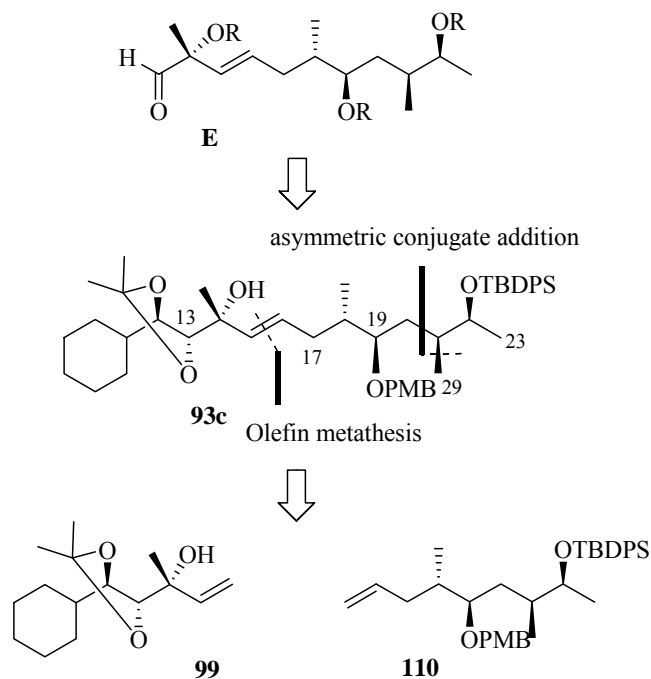


Scheme 1.17 Retrosynthetic analysis of subunit **94**

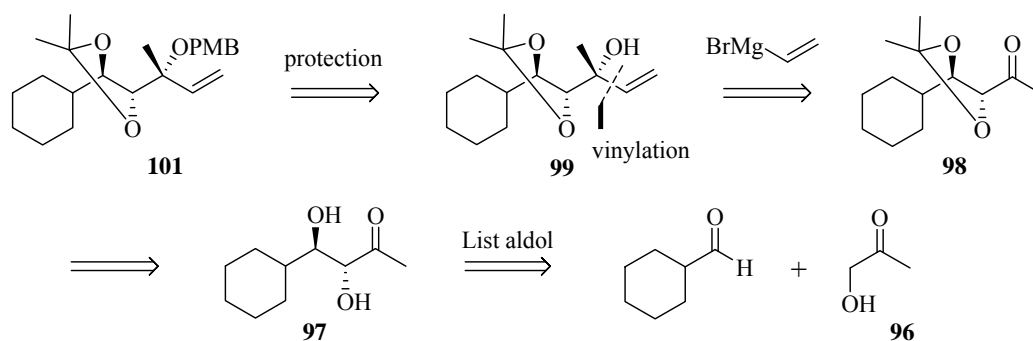
In addition, sulfone **95** can be achieved from alcohol **106** by Mitsunobu reaction. This can be easily afforded using hydroboration on the respective terminal olefin **105**. The reaction of asymmetric crotylation on aldehyde **103** will give homoallylic alcohol **105**. In order to prepare ester **102**, we can also develop the asymmetric conjugate addition to α,β -unsaturated ester **21**, which can be synthesized from commercially available starting materials **19** via one pot DIBAL-H reduction–Wittig olefination (Scheme 1.18).

Scheme 1.18 Retrosynthetic analysis of subunit **95**

A more convergent strategy has also been proposed to synthesize fragment **E** (Scheme 1.19). It can be obtained from intermediate **93c**. This intermediate in turn, can be constructed from alkene **99** and alkene **110** via intermolecular olefin cross-metathesis reaction with *E*-alkene geometry at C15–C16. The strategy employs our group's asymmetric conjugate addition and Paterson aldol.

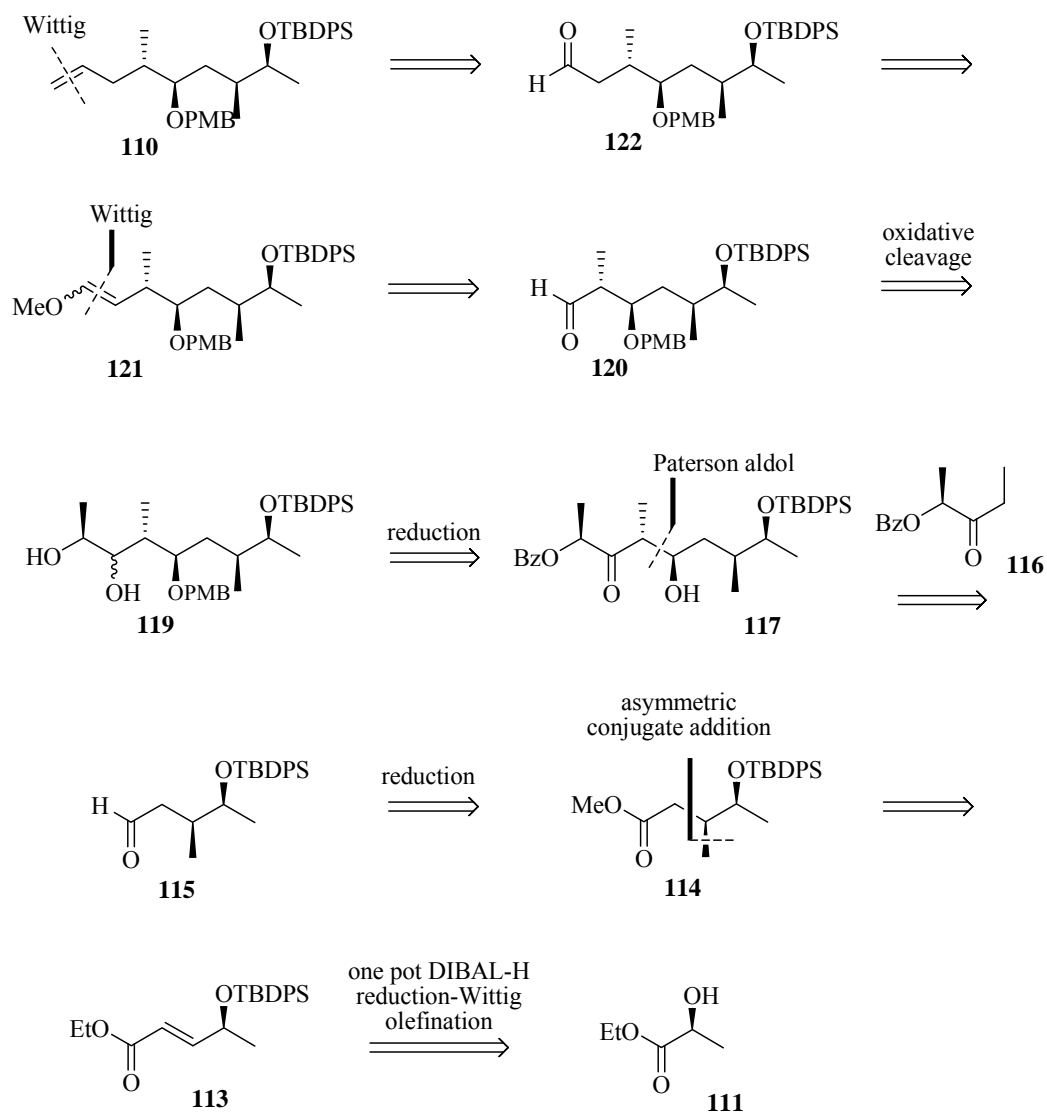
Scheme 1.19 Alternative retrosynthetic analysis of fragment **E**

Similarly, we adopt the same strategy shown in Scheme 1.17 to obtain the subunit **99** (Scheme 1.20).



Scheme 1.20 Retrosynthetic analysis of subunit **99**

Besides, the subunit **110** can be constructed from aldehyde **120** via two applications of Wittig homologation. Aldehyde **120** in turn can be synthesized from the Paterson aldol adduct **117** between aldehyde **115** and ethyl ketone **116** followed by reduction. DIBAL-H reduction of ester **114** will furnish aldehyde **115**. We proposed that a newly generated methyl group in ester **114** can be achieved by a direct asymmetric conjugate addition to α,β -unsaturated ester **113**, which can be synthesized from commercially available starting materials **111** via one pot DIBAL-H reduction-Wittig olefination (Scheme 1.21).



Scheme 1.21 Retrosynthetic analysis of subunit 110

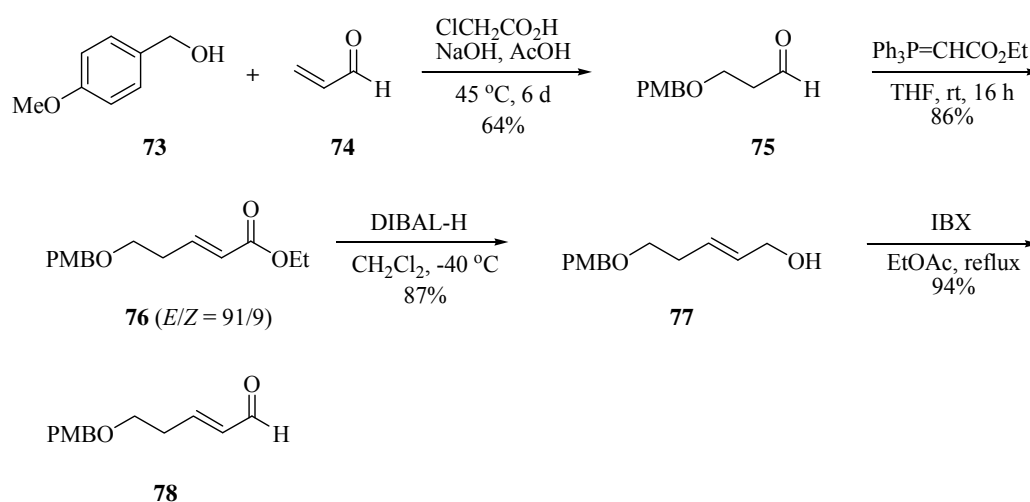
CHAPTER 2

Synthesis of Fragment D

2.1 SYNTHESIS OF ISOMER OF FRAGMENT D, 89

2.1.1 Synthesis of Subunit 78

The synthetic procedure for the alcohol **78** starting from (4-methoxyphenyl)methanol (**73**) and acrylaldehyde (**74**) through slight modification of published procedures is described in Scheme 2.1.³⁷ 4-Methoxyphenyl)methanol (**73**) was first reacted with acrylaldehyde (**74**) for six days to yield the aldehyde **75** in 64% yield. Next, the Wittig reaction of **75** with the stabilized ylide from $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$ gave the *trans*-enoate **76** in 86% yield (*E/Z* = 91/9). The ester **76** was then reduced by DIBAL-H treatment to give the free alcohol **77** in 87% yield. Finally, the *trans* alcohol **77** was oxidized to the aldehyde **78** with IBX as the oxidizing reagent.

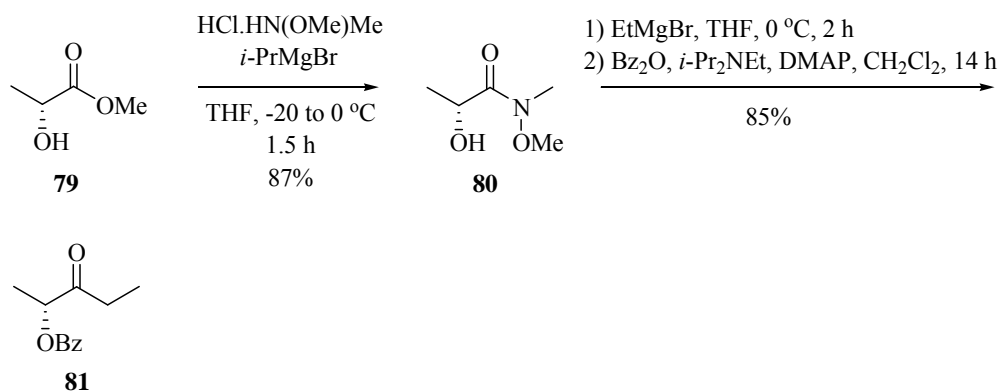


Scheme 2.1 Synthesis of subunit **78**

³⁷(a) Herb, C.; Maier, M. E. *J. Org. Chem.* **2003**, *68*, 8129. (b) Cordero, F. M.; Pisaneschi, F.; Gensini, M.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2002**, 1941. (c) Pearson, W. H.; Lian, W. *Angew. Chem. Int. Ed.* **1998**, *37*, 1724. (d) Bartels, B.; Hunter, R. *J. Org. Chem.* **1993**, *58*, 6756. (e) Furuyama, M.; Shimizu, I. *Tetrahedron: Asymmetry* **1998**, *9*, 1351.

2.1.2 Synthesis of Subunit **81**

Exposure of methyl (*R*)-(+)-lactate (**79**) to *N,O*-dimethylhydroxylamine hydrochloride in the presence of *i*-PrMgBr afforded the Weinreb amide **80** in 87% yield.³⁸ The amide **80** was then added to ethyl Grignard followed by benzoylation of the resulting volatile α -hydroxy ketone with benzoic anhydride to provide (*R*)-**81** (Scheme 2.2).³⁹



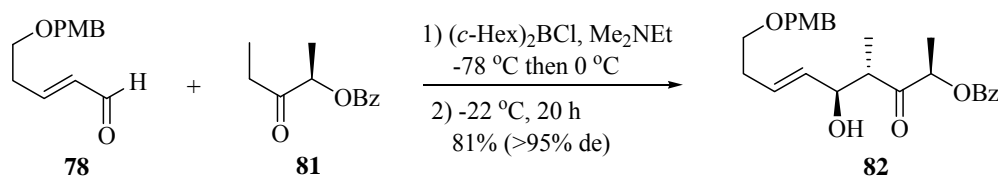
Scheme 2.2 Synthesis of subunit **81**

³⁸ Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

³⁹ The literature method used ethyl (*S*)-(-)-lactate as the starting material: Williams, M. J.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

2.1.3 Synthesis of Subunit **88**

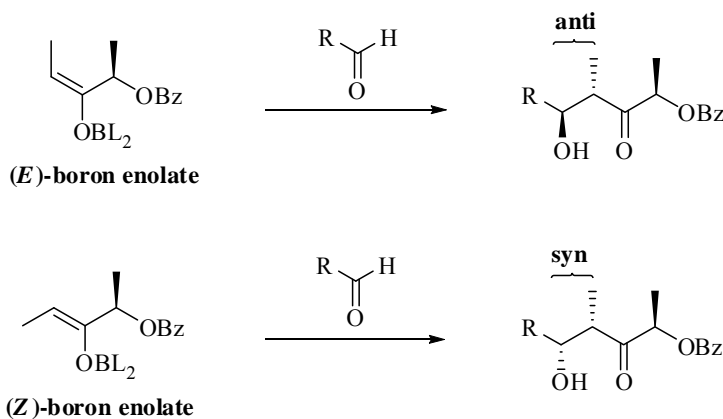
With the aldehyde **78** and the ketone **81** in hand, we then carried out the Paterson aldol reaction using Brown's dicyclohexylboron chloride (*c*-Hex₂BCl). The Paterson aldol reaction proceeded smoothly to produce the desired *anti*-Paterson adduct **82** with 81% yield and high level of diastereoselectivity (>95% de).^{18, 40}



Scheme 2.3 Synthesis of subunit **82** using *anti*-Paterson aldol as the key step

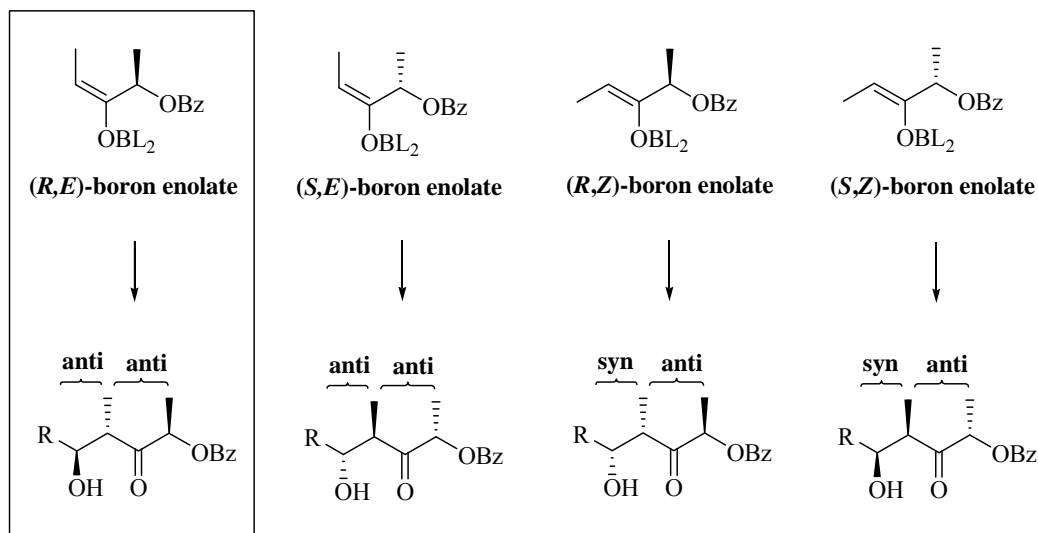
The directed aldol reaction of boron enolates and aldehydes has often been employed in stereoselective organic synthesis and the syntheses of natural products, particularly those of propionate origin, owing in large part to the high levels of chemo-, regio-, diastereo- and enantioselectivity can be achieved. The boron enolate's geometry is able to resolve the relative stereochemistry of the aldol adduct with high fidelity. The (*Z*)-boron enolates generally afford syn aldol products, where as the (*E*)-boron enolates give anti aldol products (Scheme 2.4). In our case, we sought to achieve selective enolisation of **81** to generate the corresponding (*E*)-boron enolate by using Brown's dicyclohexylboron chloride (*c*-Hex₂BCl) as a mild Lewis acid with a sterically undemanding. Consequently, we would get the *anti*-aldol adduct.

⁴⁰ (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, 35, 9083. (b) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, 51, 1. (c) Brown, H. C.; Dhar, R. K.; Ganesan, K. Singaram, B. *J. Org. Chem.* **1992**, 57, 499.



Scheme 2.4 Transfer of boron enolate geometry to aldol product relative stereochemistry

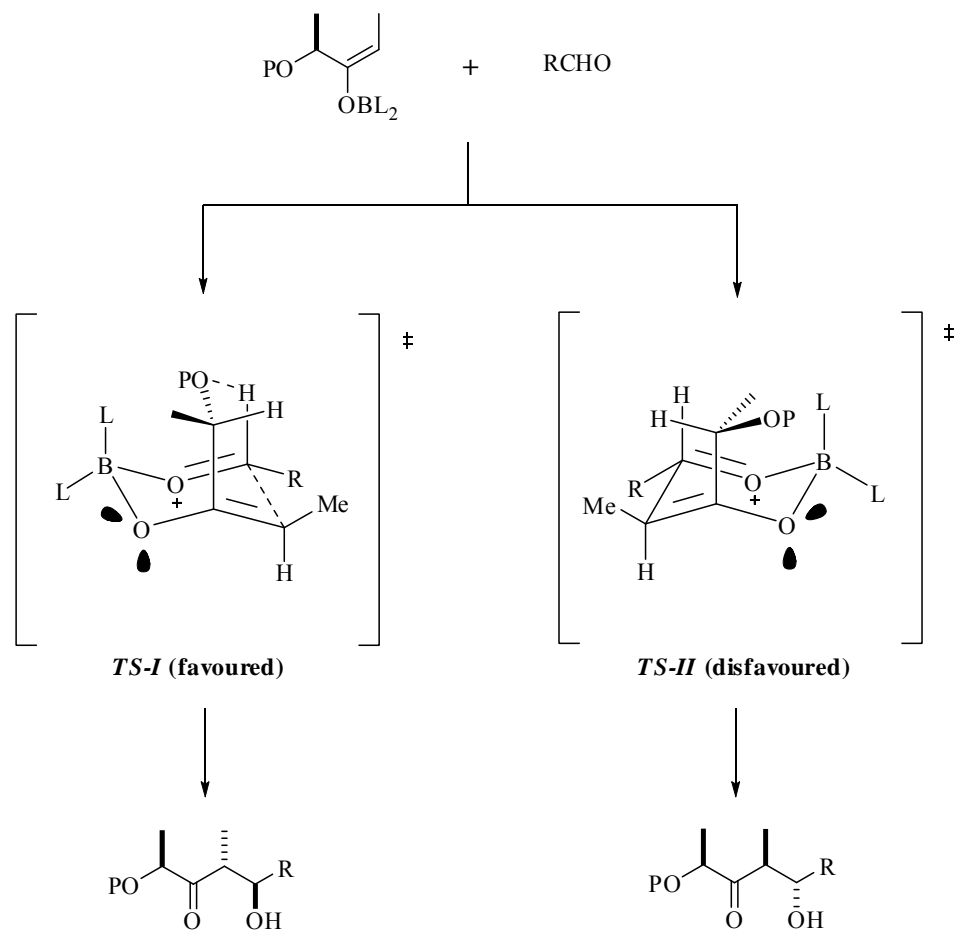
High level of absolute control in the creation of the two new stereogenic centers can be achieved by using chiral aldehyde and/or ketone substrates or with chiral ligands on boron (Scheme 2.5). The use of two or more chiral components in these aldol reactions can result in exceptionally high levels of stereoselectivity. In our synthetic route, we used enantiomeric ketone (*R*)-**81**. The choice of α -alkoxy substituent in ketone **81** is critical in determining the level of induction as, usually the use of benzylic(OBn, OBz), acetonide gave the highest selectivity where was the use of silicon protecting groups often give rise to little or no selectivity. We were able to obtain the desired isomer **82** in good yield and excellent selectivity by using (*R,E*)-boron enolate.



Scheme 2.5 Absolute control of the new stereogenic centers by chiral boron enolate

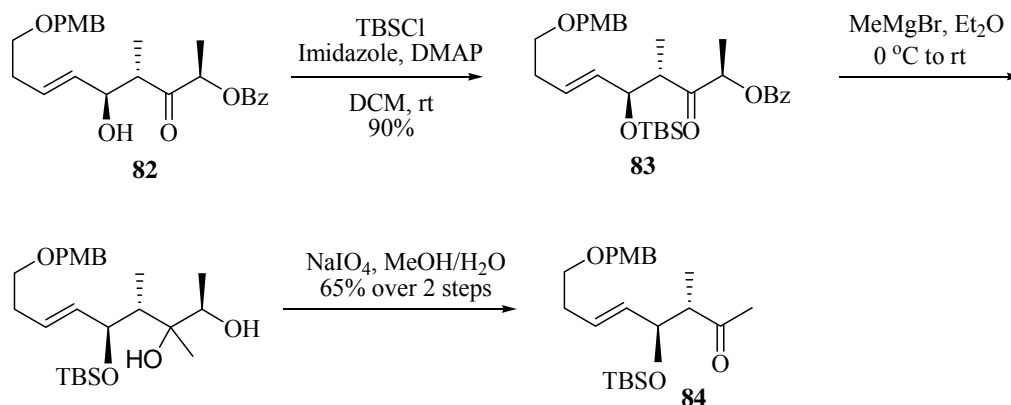
The origin of remote asymmetric induction in the boron mediated-aldol reactions of **81** can be traced to the relative steric and electronic contributions of the substituents (H, Me, OBz) at the enolate stereocentre in the chair transition state.⁴¹ For (*R,E*)-boron enolate, there are two possible transition states, *TS-I* and *TS-II* (Scheme 2.6). In *TS-I*, the benzoate group is directed inwards in the chair arrangement and forms a stabilizing H-bond between the benzoate oxygen and the aldehyde proton, by minimizing steric interactions between the α -methyl group and axial-position ligand on boron. In *TS-II*, the benzoate is directed outwards. The *syn*- adduct is disfavoured due to a destabilizing lone-pair repulsion between the benzoate and enolate oxygen and significant steric interactions between the the α -methyl group and the axial-position ligand on boron.

⁴¹ Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471. (b) Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron: Asymmetry* **1995**, *6*, 2613.

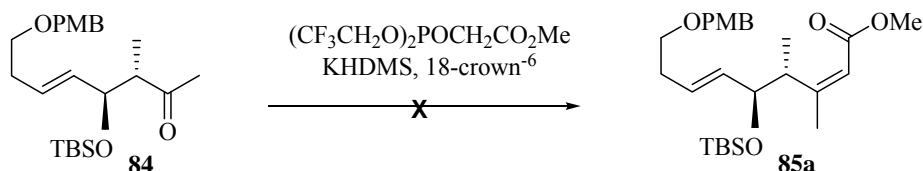


Scheme 2.6 Two possible chair transition states for aldol reaction

The newly formed hydroxyl group in **82** was protected by TBSCl in the presence of imidazole. After TBS protection, ketone **84** was then generated by the tandem reactions of MeMgBr with **83** and periodate cleavage. The calculated yield was 65% (Scheme 2.7).

Scheme 2.7 Synthesis of subunit **84**

Our initial strategy was to synthesize the precursor of fragment **D 85a** by the Still-Gennari modified Horner-Wadsworth-Emmons olefination. In Still modification, *Z*-alkene with excellent stereoselectivity can be achieved when using unstabilized phosphonate together with strongly dissociating conditions (KHDMS and 18-crown-6 in THF).⁴² Unfortunately, we failed to obtain the desired *cis*-enoate **85a** even we used phosphonates with strong electron-withdrawing groups – trifluoroethyl (Scheme 2.8).⁴³ The unreactive and sterically hindered ketone **84** could be the main limitation for the reaction.

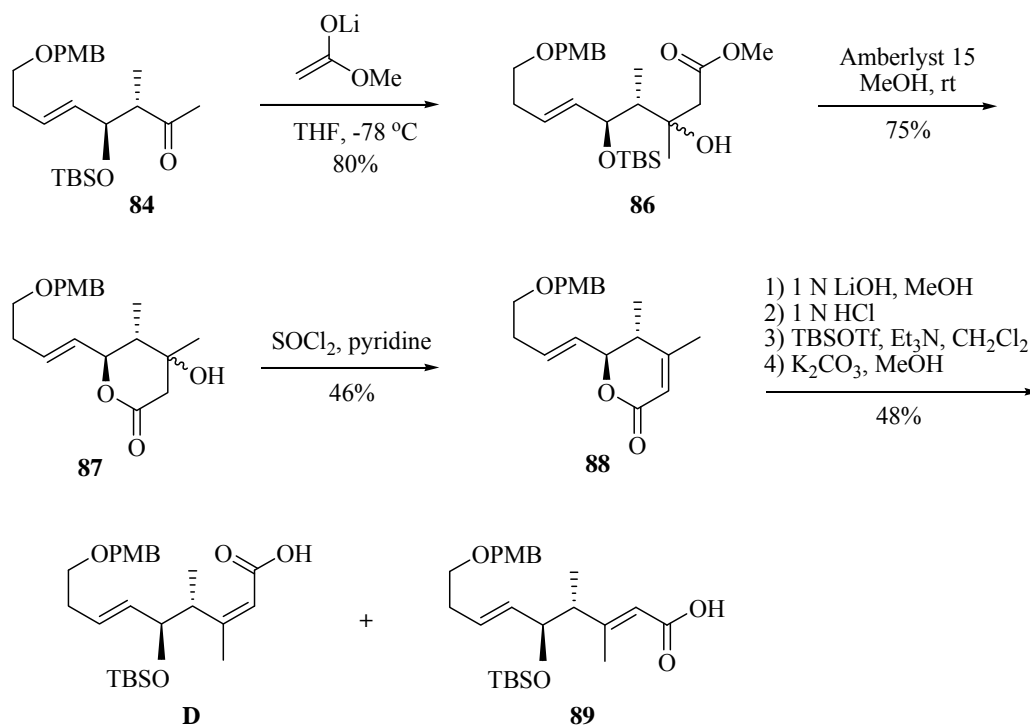
Scheme 2.8 Failed attempt to synthesis of **85a**

The failure in preparing the key intermediate **85a** by Still-Gennari modified Horner-Wadsworth-Emmons olefination strategy prompted us to search for a new synthetic route to effect the construction of the fragment **D**. The new alternative strategy was outlined in Scheme 2.9.

⁴² Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 24, 4405.

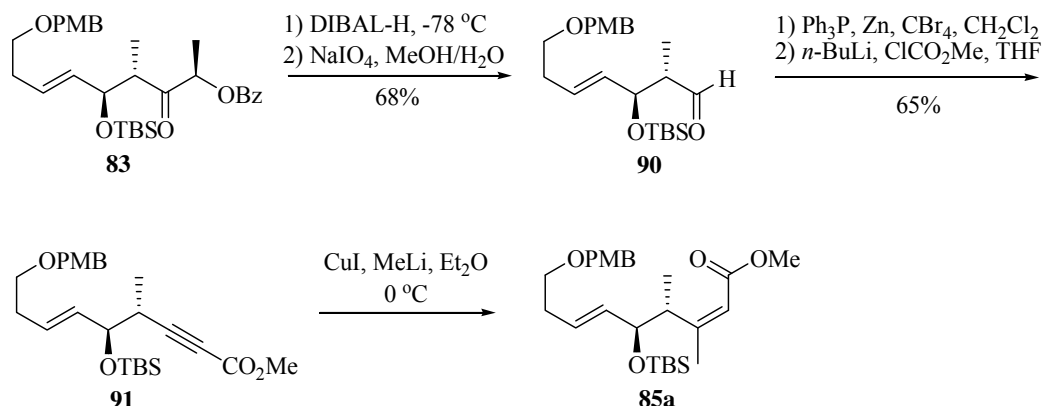
⁴³ Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Organic Syntheses*, **1998**, 9, 88. (b) Patois, C.; Savignac, P.; About-Jaudet, E.; Collignon, N. *Organic Syntheses*, **1996**, 73, 152.

Ketone **84** was treated with lithium 1-methoxyethenolate and converted to β -quaternary alcohol **86**. The alcohol **86** was isolated as diastereomeric mixtures in 80% yield. Reaction of **86** with Amberlyst 15 in methanol afforded lactonization product **87**. After the elimination of C3 hydroxyl group by thionyl chloride in the presence of pyridine, the α,β -unsaturated lactone **88** was observed as the only diastereomer but in moderate yield - 46%. The lactone **88** was then subjected to basic hydrolysis mediated by a strong base such as LiOH in aqueous solution. Subsequently, the hydroxyl group on C5 was selectively protected with TBS group by exposing to TBSOTf in dichloromethane. Unfortunately, the *trans* α,β -unsaturated carboxylic acid **89** instead of *cis* α,β -unsaturated carboxylic acid **D** was obtained as the major isomer.

Scheme 2.9 Synthesis of **89**

2.2 SYNTHESIS OF FRAGMENT D

These early unsuccessful in the formation of the fragment **D** by both Wittig and lactonization strategies lead us to explore a new method to obtain the fragment **D** via Corey-Funhs reaction and alkyne reduction (Scheme 2.10). The synthesis of key intermediate **85a** started with DIBAL reduction of the ketone **83**, followed by periodate cleavage of the diol to afford aldehyde **90** in 68% yield over two steps. Subsequent Corey-Fuchs reaction⁴⁴ in which the anion was trapped with methyl chloroformate established the acetylenic compound **91** in 65% yield over two steps. 1,4-addition of Gilman's reagent to ester **91** furnished the desired *Z*-alkenoic ester **85a**.⁴⁵

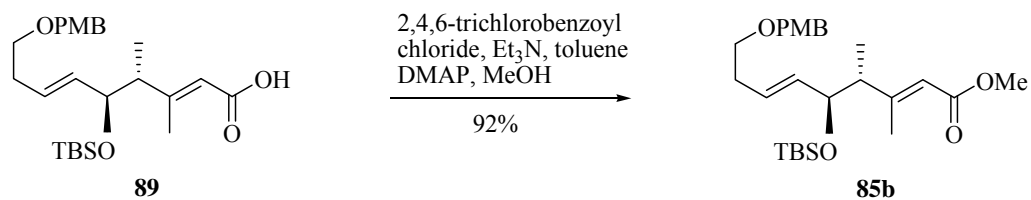


Scheme 2.10 Synthesis of precursor of fragment **D**, **85a**

E-alkenoic ester **85b** was also synthesized in order to make a comparison with the *Z*-alkenoic ester **85a** (Scheme 2.11).

⁴⁴ Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.

⁴⁵ (a) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630. (b) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851. (c) Temmen, O.; Zoller, T.; Uguen, D. *Tetrahedron Lett.* **2002**, *43*, 3181. (d) Caussanel, F.; Wang, K.; Ramachandran, S. A.; Deslongchamps, P. *J. Org. Chem.* **2006**, *71*, 7370.



Scheme 2.11 Synthesis of *E*-alkenoic ester **85b**

Resonances of protons from the methyl group at C3 position in ¹H NMR spectral data of the *Z*-alkenoic ester **85a** and *E*-alkenoic ester **85b** were compared with the reported iriomoteolide-1a. The protons resonate at 1.82 ppm for the *Z*-alkenoic ester **85a**, whereas the protons resonate at 2.13 ppm for the *E*-alkenoic ester **85b** compared to 2.12 ppm for the natural compound **26**, respectively (Figure 2.1 and Figure 2.2).

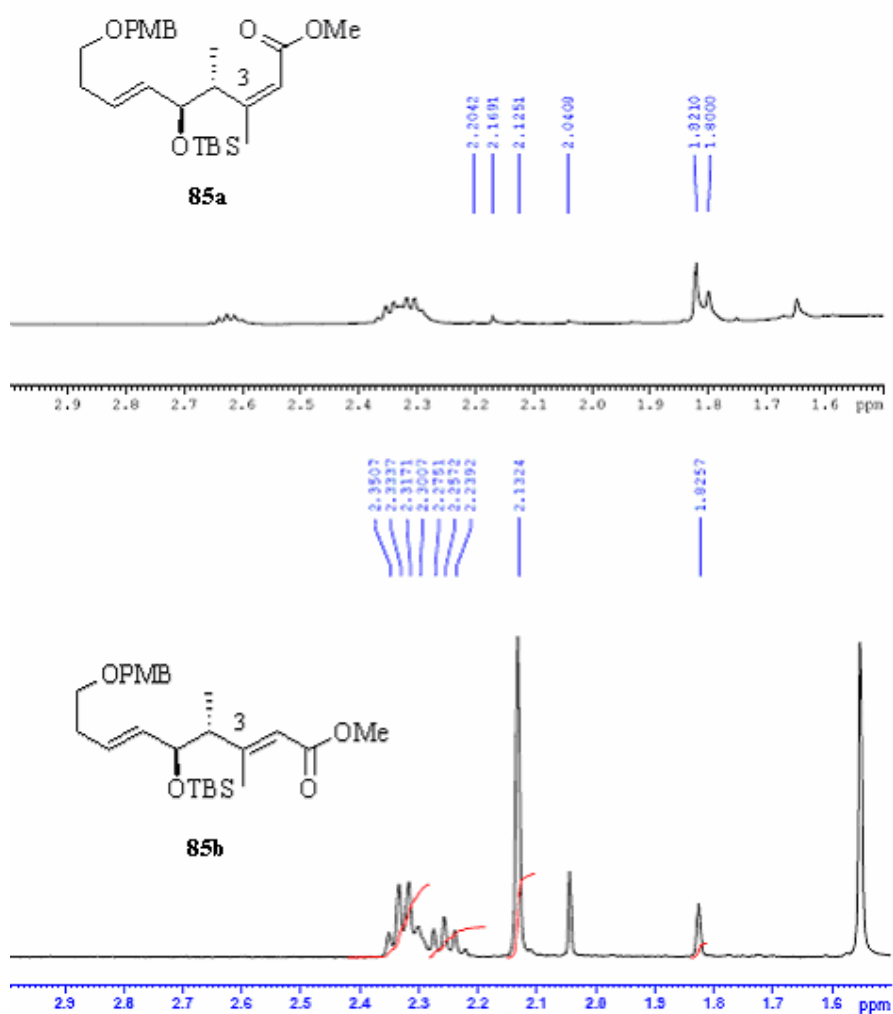


Figure 2.1 Comparison ¹H NMR spectra of 85a and 85b

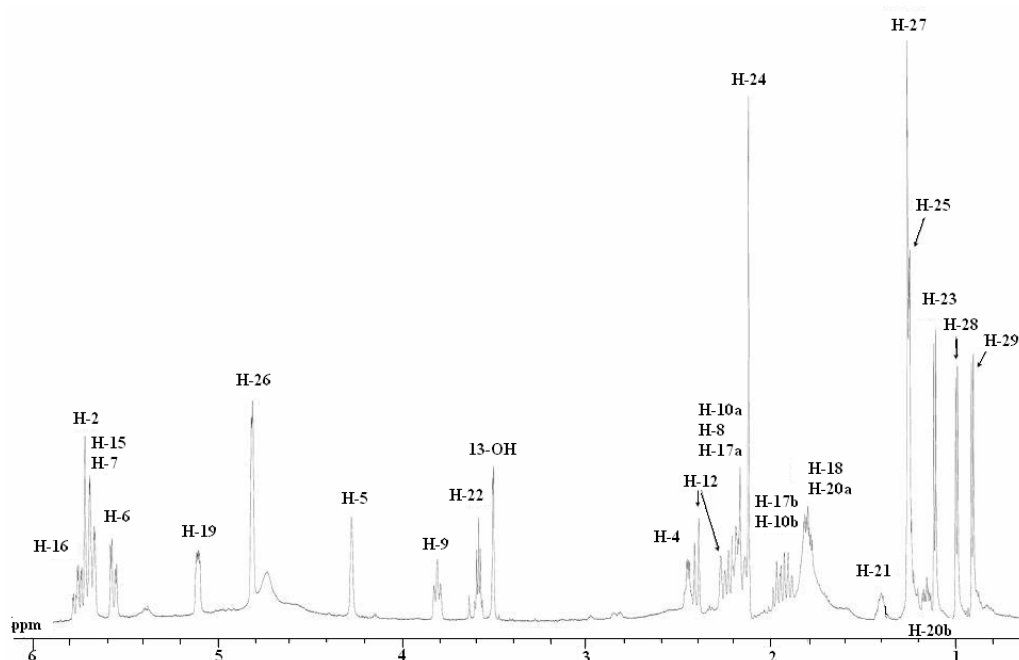
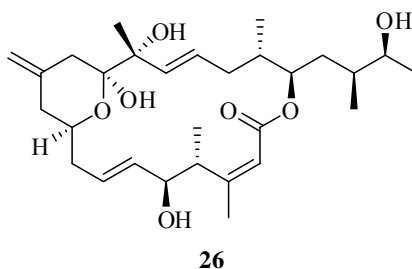


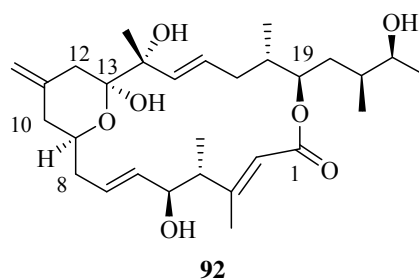
Figure 2.2 ^1H NMR spectrum of natural product, irimoteolide-1a

The significant difference in NMR spectral data between the *Z*-alkenoic ester **91a** and the reported irimoteolide-1a brings into question the original structural assignment of the natural product. It is likely that the C2–C3 double bond configuration of natural product is *trans* instead of *cis* (Scheme 2.13).



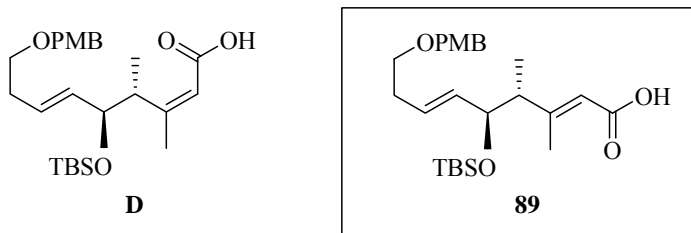
reported structure of irimoteolide-1a

Scheme 2.12 The proposed structure of irimoteolide-1a by Tsuda's group from the *Amphidinium* sp. strain HYA024



Scheme 2.13 The diastereomer of iriomoteolide-1a

The key building block - *trans* α,β -unsaturated carboxylic acid **89** instead of *cis* α,β -unsaturated carboxylic acid **D** will be used in the assembly of diastereomer of iriomoteolide-1a (**92**, Scheme 2.14).



Scheme 2.14 The key intermediate **89**

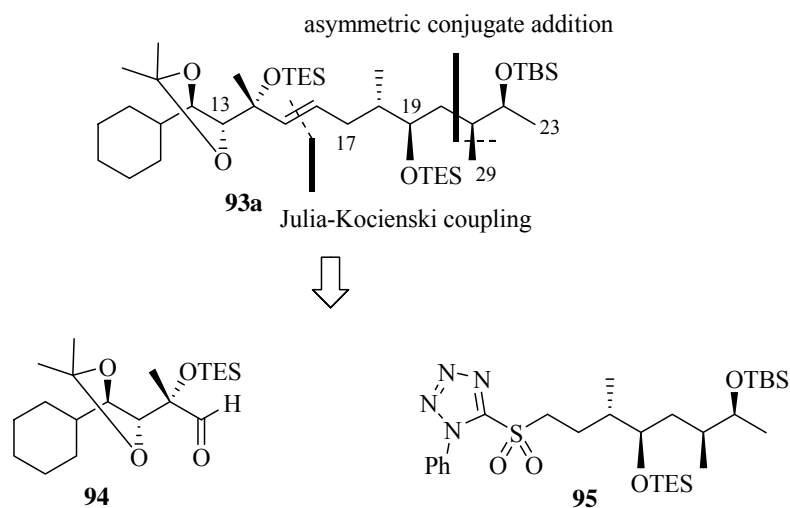
CHAPTER 3

Synthesis of Fragment E

Having successfully synthesized the key intermediate **89**, we turned our attention to the construction of the fragment **E**. One of the highlights in this synthesis was to demonstrate the versatility of asymmetric conjugate addition using CuI-Tol-BINAP on natural product synthesis.

3.1 THE JULIA-KOCIENSKI COUPLING STRATEGY

A quick glance reveals the presence of a carbon-carbon double bond with *E*-configuration in fragment **E**, serves as a potential site for Julia-Kocienski olefination. Upon closer examination, the precursor of fragment **E**, **93a** can be obtained from aldehyde **94** and sulfone **95** (Scheme 3.1).



Scheme 3.1 The Julia-Kocienski olefination strategy between precursors **94** and **95**

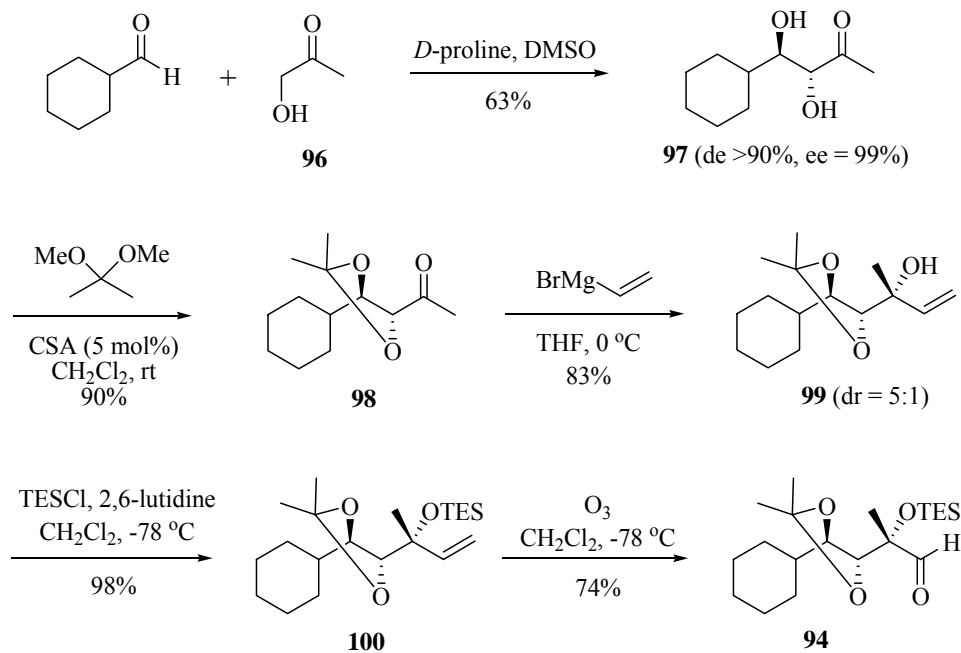
3.1.1 Synthesis of Subunit **94**

Our synthesis of the aldehyde **94** commences with cyclohexanecarbaldehyde and hydroacetone (**96**, Scheme 3.2). We applied the direct asymmetric List aldol reaction catalyzed by D-proline to provide the desired *anti*-diol **97** in 63% yield, with a dr >20: 1 and ee >99%.⁴⁶ The latter was subjected to isopropylidene protection by 2,2-dimethoxypropane to generate isopropylidene **98** in 90% yield.⁴⁷ The Grignard derived from vinyl bromide was added to intermediate **98** leading eventually to tertiary alcohol **99** (dr = 5: 1). The diastereomeric purity of the unprotected alcohol **99** was determined by ¹H NMR analysis. It was easy to isolate the favored desired diastereomer **99** by flash column chromatography on silica gel. Subsequently, protection of **99** with triethylsilyl chloride under basic condition generated the olefin **100**.⁴⁸ Ozonolysis of the protected alkene **100** upon treatment with ozone and triphenylphosphine reduction gave good yield of the desired aldehyde **94** (Table 3.1, entry 1). The reaction was rapid and completed within ten minutes.

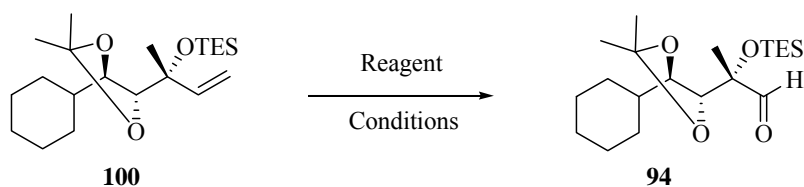
⁴⁶ The diastereoselectivity and enantioselectivity were determined by comparison with the NMR spectroscopic and HPLC analytical results of diastereomers obtained from this paper: Nots, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

⁴⁷ Nicolaou, K. C.; Li, H.-M.; Nold, A. L.; Pappo, D.; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356.

⁴⁸ (a) Askin, D.; Angst, D.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622. (b) Franck, X.; Figadere, B.; Cavé, A. *Tetrahedron Lett.* **1995**, *36*, 711. (c) Seebach, D.; Chow, H. F.; Jackson, R. F. W.; Sutter, M. A.; Thaisrivongs, S.; Zimmermann, J. *Liebigs Ann. Chem.* **1986**, 1281. (d) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 4785.

Scheme 3.2 Synthesis of subunit **94**

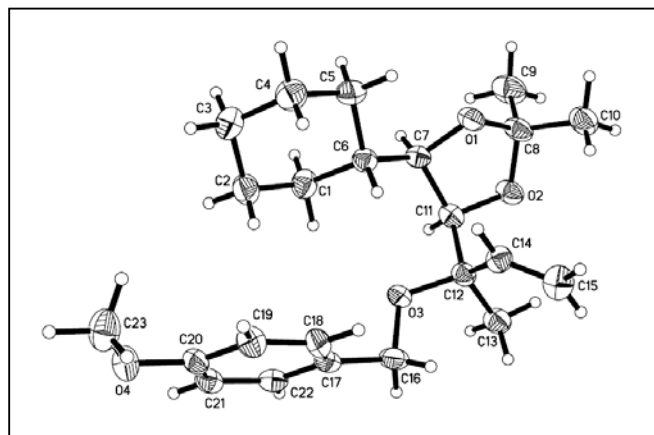
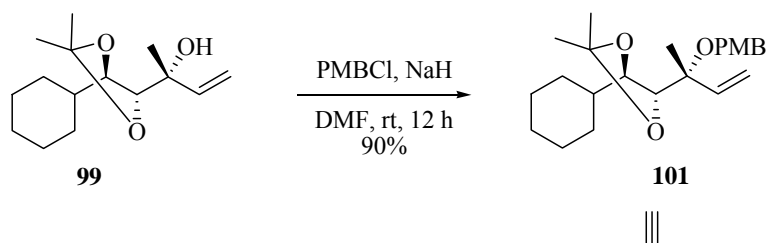
Several attempts to improve the yield of ozonolysis of alkene **100** with other reducing agents like dimethyl sulfide (Table 3.1, entry 2 and 3) and zinc (Table 3.1, entry 4) were not met with failure. Moreover, the use of dimethyl sulfide as reducing agent proved to be a problem at the purification stage of the aldehyde **94**. Albeit after flash chromatography, the aldehyde was often contaminated with some other side products.

Table 3.1 Oxidative cleavage of terminal double bond with various reagents.

Entry	Reagent	Condition	Yield (%) ^a
1	O ₃ , PPh ₃ (1 equiv), CH ₂ Cl ₂	-78 °C to rt	74
2	O ₃ , Me ₂ S (5 equiv), CH ₂ Cl ₂	-78 °C to rt	51
3	O ₃ , Me ₂ S (10 equiv), CH ₂ Cl ₂	-78 °C to rt	53
4	O ₃ , Zn (3 equiv), CH ₂ Cl ₂	-78 °C to rt	54

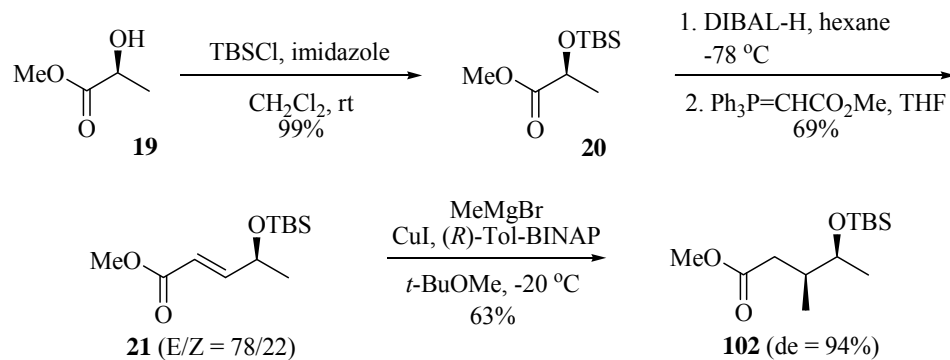
^a The reaction was monitored using TLC to ensure most of the starting material has reacted prior to addition of the reducing agents.

The stereochemistries were further confirmed by X-ray structural analysis of PMB ether protected **101** (Figure 3.1).

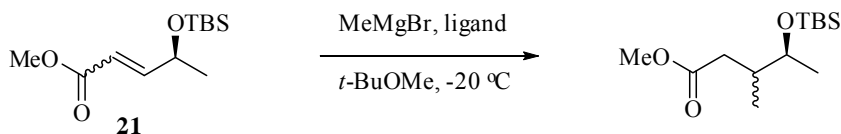
**Figure 3.1** Stereochemical Determination of **99**

3.1.2 Synthesis of Subunit **95**

(-)-Methyl-L-lactate (**19**) was protected with *tert*-butyldimethylsilyl chloride under basic condition followed by a one-pot DIBAL-H reduction–Wittig olefination protocol afforded the *trans*-enoate **21** (*E/Z* = 78/22) in 63% yield (Scheme 3.3). Then, the C29 methyl moiety was stereoselectively introduced into the unsaturated ester **21** using (*R*)-Tol-BINAP by asymmetric conjugate addition, to produce the *syn*-adduct **102** in 94% *de* (Table 3.2, entry 3).⁴⁹ The introduction of methyl group to the *trans*-enoate **21** without the presence of Tol-BINAP ligand was attempted to yield the *anti*-adduct with moderate yield and excellent diastereoselectivity (Table 3.2, entry 1). It might due to the steric effect of *tert*-butyldimethylsilyl group. Fortunately, with the enantiomeric of Tol-BINAP ligands, we can easily control the stereoselectivity of the C29 methyl moiety.

Scheme 3.3 Synthesis of intermediate **102**

⁴⁹ Diastereoselectivity was determined by ¹³C NMR by comparing an average of carbon signals with respective diastereomeric mixtures of the acyclic carbon chain. The stereochemistry was assigned on the basis of enantiomeric Tol-BINAP ligands.

Table 3.2 1,4-Michael Addition of MeMgBr to **21**^a

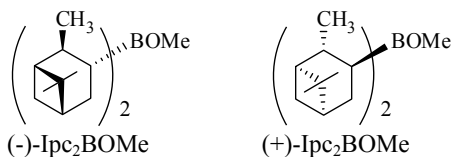
Entry	Ester	catalyst	Yield (%)	<i>anti:syn</i> ^b
1	<i>trans</i> - 21	10 mol % CuI	64	95:5
2	<i>trans</i> - 21	2 mol % CuI + 3 mol % (<i>S</i>)-Tol-BINAP	60	>99:1
3	<i>trans</i> - 21	2 mol % CuI + 3 mol % (<i>R</i>)-Tol-BINAP	63	3:97
4	<i>cis</i> - 21	10 mol % CuI	0	

^a All reactions were performed with **21** (0.5 mmol) and MeMgBr (2.5 mmol, 3M in diethyl ether) in *t*-BuOMe (1 mL) at -20 °C. ^b Determined by crude ¹³C NMR.

Our synthesis of sulfone **95** was continued in Scheme 3.4. DIBAL-reduction followed by asymmetric Brown crotylation⁵⁰ of aldehyde **103** using (–)-Ipc₂BOMe (deprived from (+)-pinene)⁵¹ furnished the *anti*- γ -homoallylic alcohol **104**, with 77% yield and satisfactory diastereomeric ratio of 84% *de* (Scheme 3.4). Asymmetric crotylation⁵² is a widely used method to introduce a γ -homoallylic fragment to an aldehyde. Crotylation of aldehydes proceeded through a chair-like transition state has been discussed by Brown *et al.* In the chair-like transition state, the R group of the

⁵⁰ (a) Brown, H. C.; Randad, R. S. *Tetrahedron* **1990**, *46*, 4157. (b) Brown, H. C.; Racherla, U. S.; Khanna, V. V. *J. Org. Chem.* **1992**, *57*, 6608. (c) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (d) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.

⁵¹



⁵² For reviews, see (a) Brown H. C.; Ramachandran, P. V. *J. Organomet.Chem.* **1995**, *500*, 1. (b) Brown H. C.; Ramachandran, P. V. *Pure Appl.Chem.* **1994**, *66*, 201. (c) Hoffmann, R. W. *Pure Appl.Chem.* **1988**, *60*, 123. For other asymmetric crotylation, see (d) Roush, W. R.; Palkowitz, A. D.; Palmer, M. J. *J. Org. Chem.* **1987**, *109*, 953. (e) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (f) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

aldehyde occupies an equatorial position to minimize the steric interactions between the axial Ipc ligand and the R group. Chair transition state will produce syn adducts from (*Z*)-crotylborane and anti adducts from (*E*)-crotylborane (Figure 3.2).

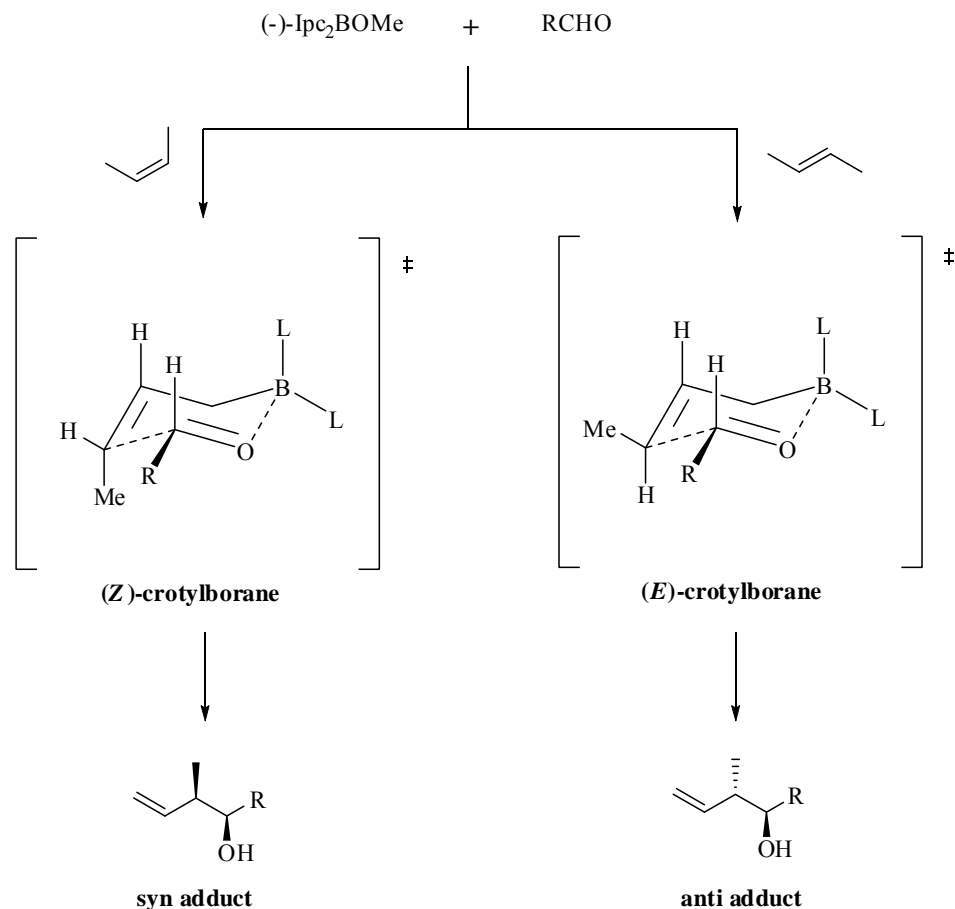


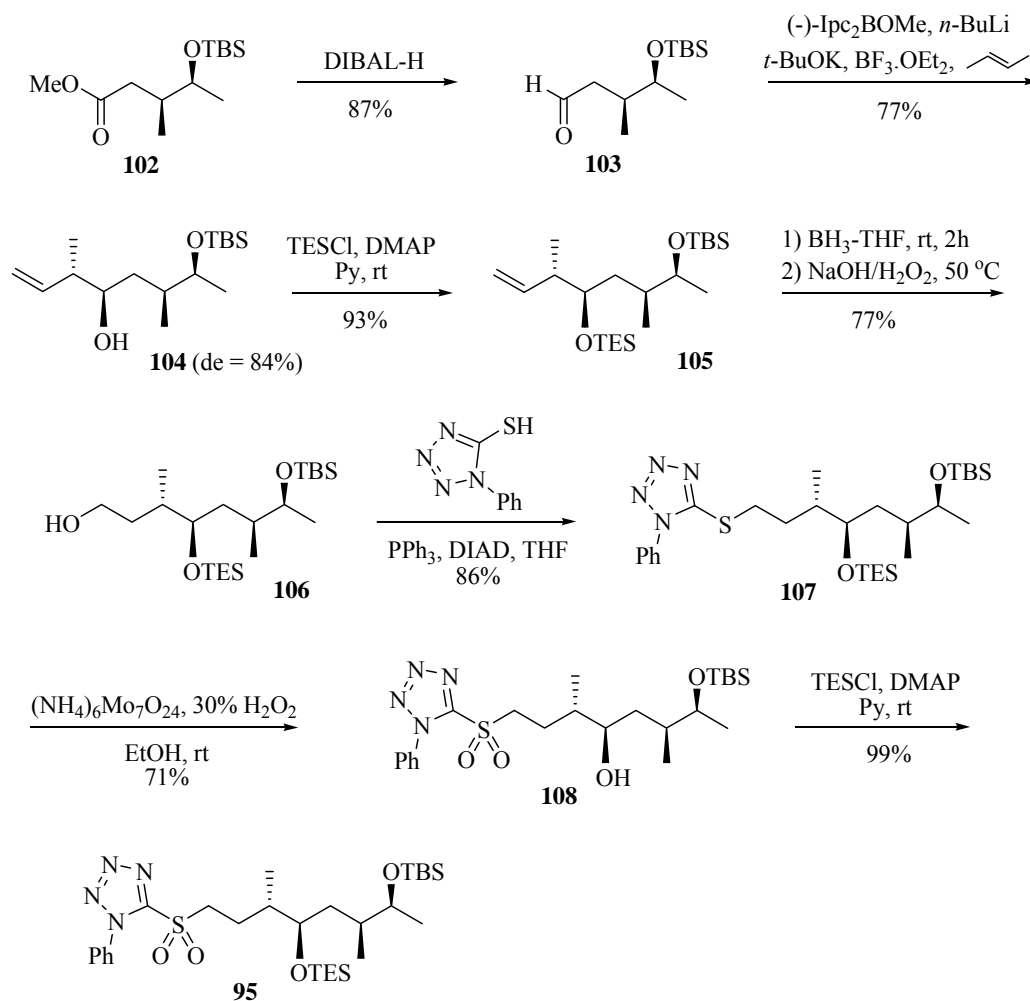
Figure 3.2 Crotylation of aldehydes proceeds through a chair-like transition state

Continuing with the synthesis of sulfone **95**, the secondary hydroxyl group in **104** was protected as the triethylsilyl ether under basic condition (Scheme 3.4). Following oxidation of the terminal olefin in **105** employing hydrogen peroxide as the oxidizing agent,⁵³ the resulting primary alcohol **106** was subjected to Mitsunobu protocol,⁵⁴ affording the desired aryl sulfide **107** in good yield. Finally, completion of

⁵³ Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.

⁵⁴ Paquette, L. A.; Chang, S. K. *Org. Lett.* **2005**, *7*, 3111.

the requisite sulfone **95** was achieved by oxidation using ammonium molybdate and hydrogen peroxide.¹⁸

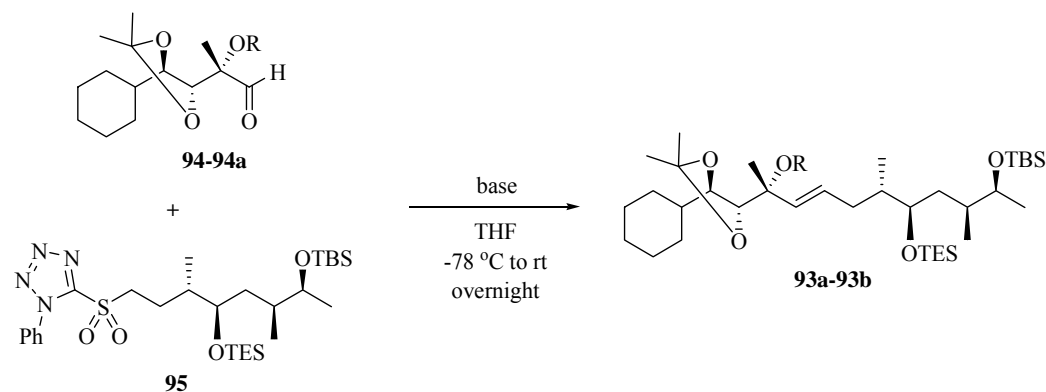


Scheme 3.4 Synthesis of subunit **95**

3.1.3 Coupling to Subunit **94** and **95**

With aldehyde **94** and sulfone **95** in hand, we then carried out Julia–Kocienski olefination⁵⁵ (Table 3.3). The use of KHMDS (in toluene) provided **93a** in only 29% isolated yield with low regioselectivity. Interestingly, when KHMDS (in THF) was used, the desired product was isolated as a single isomer, albeit in low yield (27%, Table 3.3, entry 2). In addition, replacement of the TES ether protecting group with a PMB ether proved detrimental (Table 3.3, entry 3), suggesting steric effect from the adjacent tertiary protected hydroxyl group in operation.

Table 3.3 Julia–Kocienski Olefination

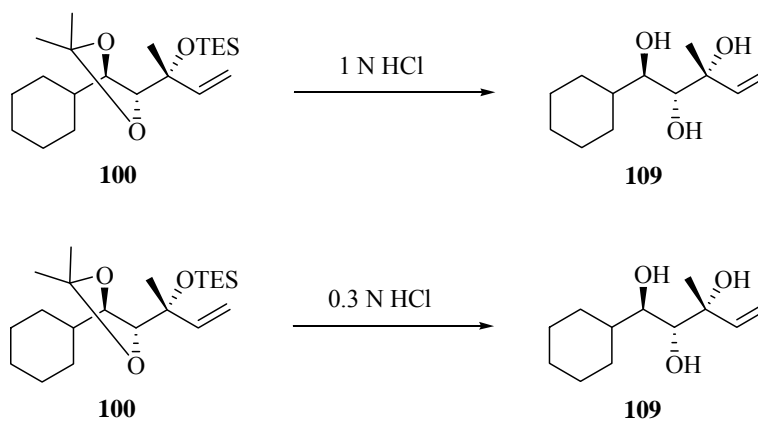


entry	R	Base (soln)	Product (yield, %)	<i>E:Z</i> ^a
1	TES	KHMDS (in toluene)	93a (29)	60:40
2	TES	KHMDS (in THF)	93a (27)	>99:1
3	PMB	KHMDS (in toluene)	93b (trace)	

^a The *E/Z* ratios were determined by ¹H NMR analysis of the crude product mixtures.

⁵⁵ Esteban, J.; Costa, A. M.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 4843.

After we had successfully synthesized the key building block **93a**, we now turned our concentration on the deprotection of isopropylidene in order to prepare an aldehyde functional group. The deprotection of isopropylidene was investigated by the treatment of **100** with 1 N HCl and 0.3 N HCl. Albeit in the low concentration of acidic condition (0.3 N HCl), the TES group was deprotected unexpectedly to form a triol compound (Scheme 3.5). Further oxidative cleavage of **109** is foreseen to lose us one stereogenic center and a carbon. In order to prepare the fragment **E**, we have to explore for a different protecting group.



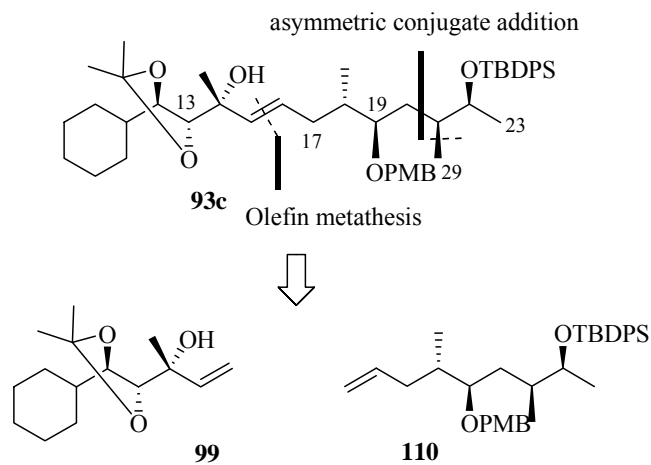
Scheme 3.5

In summary, we have developed an asymmetric synthesis of the C13-C23 fragment **90a** of iriomoteolide-1a.⁵⁶

⁵⁶ Chin, Y.-J.; Wang, S.-Y.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 3674.

3.2 THE OLEFIN METATHESIS STRATEGY

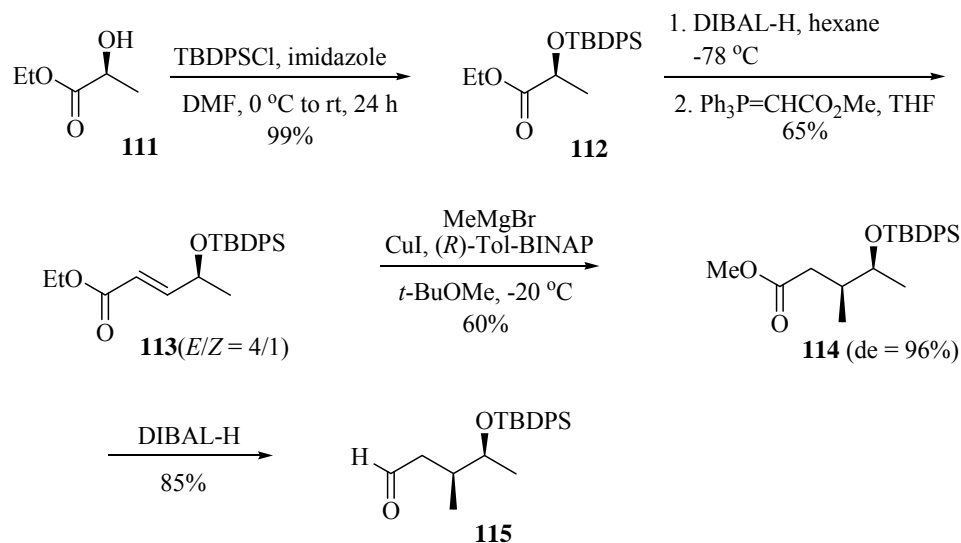
Due to the poor yield of the Julia-Kocienski reaction, we changed our strategy by obtaining the fragment **E** via olefin metathesis between olefins **99** and **110**, with *E*-alkene at C15-C16 (Scheme 3.6).



Scheme 3.6 The olefin metathesis strategy between precursors **99** and **110**

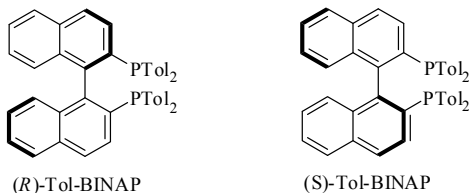
3.2.1 Synthesis of Subunit **110**

For the synthesis of the subunit **110**, (*S*)-ethyl lactate (**111**) was protected with *tert*-butyldiphenylsilyl chloride under basic condition followed by a one-pot DIBAL-H reduction and Wittig olefination afforded the desired conjugated ester **113** (*E/Z* = 4:1) in 65% yield (Scheme 3.7). We then applied the asymmetric conjugate addition with MeMgBr to **113** in the presence of 2 mol% CuI and 3 mol% (*R*)-Tol-BINAP⁵⁷ to provide the β -methyl ester **114** in 60% isolated yield with more than 98:2 diastereoselectivity.⁵⁸ Subsequently, DIBAL-H reduction of ester **114** furnished the corresponding aldehyde **115** in 85% yield.



Scheme 3.7 Synthetic of **115** using asymmetric conjugate addition of MeMgBr as the key step

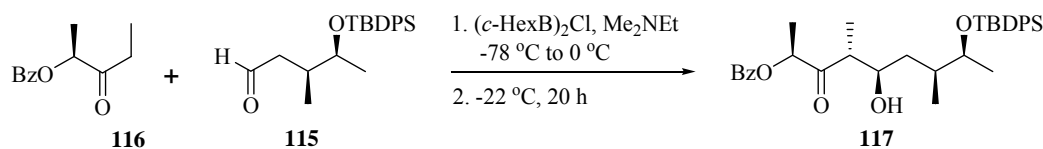
⁵⁷ The ligands are shown below:



⁵⁸ Diastereoselectivity was determined by ¹³C NMR by comparing an average of carbon signals with respective diastereomeric mixtures of the acyclic carbon chain. The stereochemistry was assigned on the basis of enantiomeric Tol-BINAP ligands.

In the next step, the isolated aldehyde **115** was subjected to Paterson aldol reaction to form the corresponding alcohol **117**.⁵⁹ In the attempts to improve the yields, we screened various ratios of precursors and reagents used and found that excess amount of aldehyde **115** over ketone **116** was the most desirable, yielding 85% of the aldol product with >95% de (Table 3.4, entry 4). (*S*)-**116** was prepared from (*S*)-(+)-lactate in a way analogous to the preparation of **81** in the previous chapter (Scheme 2.2).

Table 3.4 Synthesis of alcohol **117**



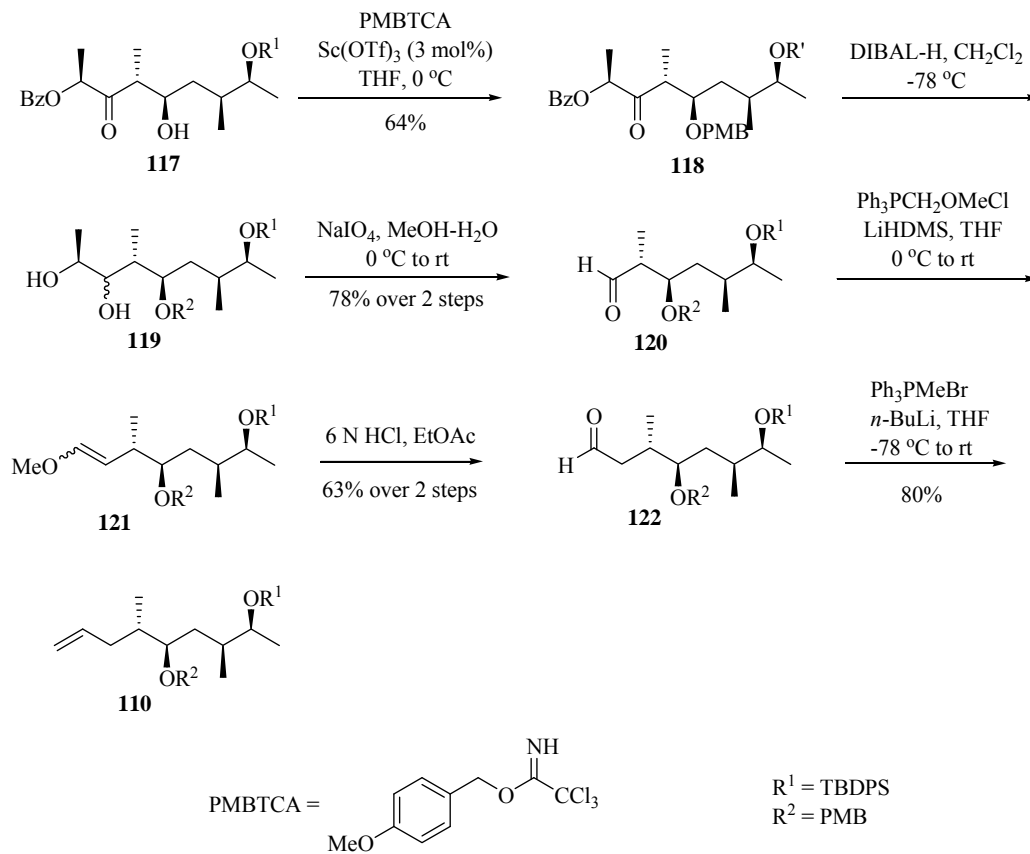
Entry	115/116/Me ₂ NEt/(<i>c</i> -Hex) ₂ BCl	Yield (%) ^a
1	1.0:1.0:2.0:2.0	40
2	1.0:1.0:1.5:1.5	40
3	1.0:1.5:2.0:2.0	45
4	1.3:1.0:1.5:1.5	85 (>95%) ^b

^a Isolated yields. ^b The percentage de was determined on the crude product by NMR spectroscopy.

PMB protection of aldol product **117** catalyzed by 3 mol% Sc(OTf)₃ yielded the desired compound **118** in 64% (Scheme 3.8). Subsequently, aldehyde **120** was generated through DIBAL-H reduction and oxidative cleavage in 78% yield over two steps. The aldehyde **120** was then subjected to Wittig homologation using methoxymethylenetriphenylphosphorane by employing LiHMDS as the base to give

⁵⁹ (a) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, 35, 9083. (b) Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639. (c) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, 51, 1.

methyl ether **121**. Treatment of the latter with 6 N HCl to obtain the aldehyde **122** in 63% yield over two steps. Furthermore, another Wittig homologation of aldehyde **122** gave the desired olefin **110** smoothly in 80% yield.

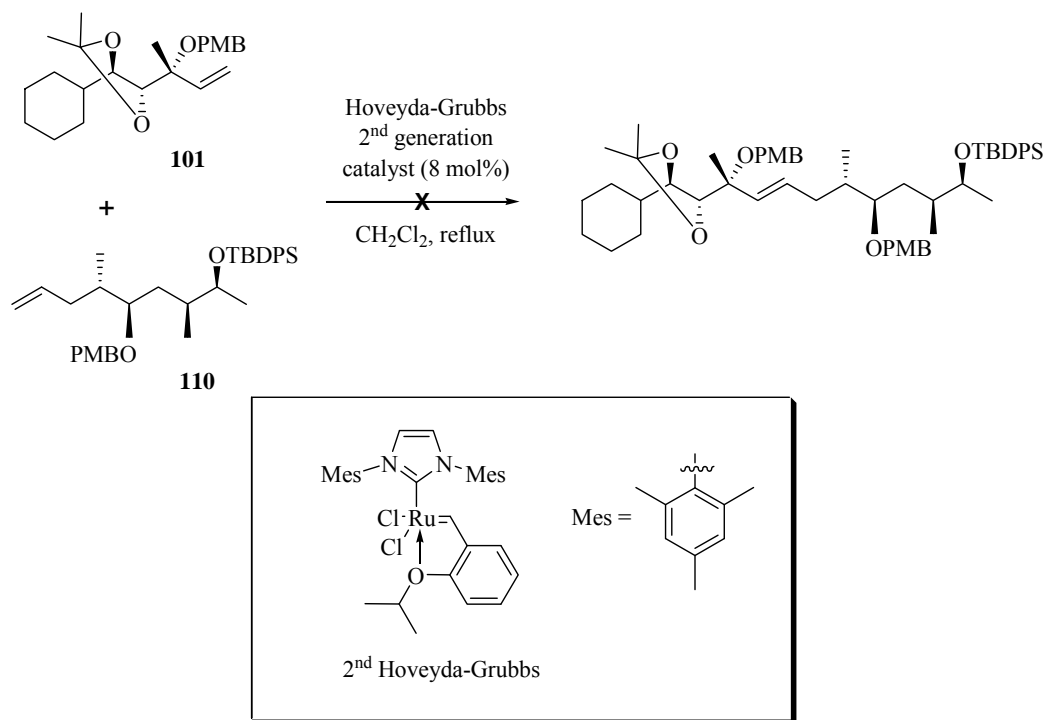


Scheme 3.8 Synthesis of subunit **110**

3.2.2 Coupling to Subunit **99** and **110**

With the two individual subunits in hand, we began coupling of the modules for the synthesis of fragment **E** via an intermolecular cross-metathesis (Scheme 3.10). Since the development of ruthenium-carbene complexes¹⁵, intermolecular olefin metathesis has exhibited tremendous applicability on total synthesis of complex molecules. It is true for larger molecular fragments, there may have several limitations such as poor reactivity, steric hindrance, self-coupling and polymerization. Nevertheless, this coupling is still a worthy attempt because of its ease of use and its elegance in using lesser number of steps to obtain the desired product.

Our initial strategy was to couple subunit **101** with subunit **110**. However, no desired product was obtained. We rationalized that it was probably due to the steric bulk of the PMB group which prevented the two subunits from coupling together (Scheme 3.9).



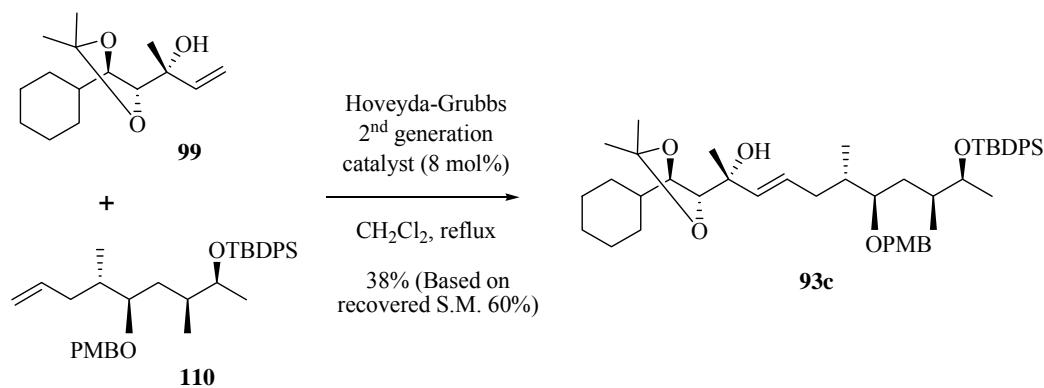
Scheme 3.9 Unsuccessful attempt with intermolecular cross-metathesis

The most selective cross metathesis involves the coupling of a more reactive type I olefin with a less reactive type II olefin.⁶⁰ In order to do a coupling successfully, we decided to employ the unprotected tertiary allylic alcohol **99** (type II olefin: tertiary allylic alcohol) and the more reactive olefin **110** (type I olefin: terminal alkene). The Hoveyda-Grubbs second generation catalyst was used in the reaction.⁶¹ Fortunately, the desired cross metathesis product **93c** was formed in 60% yield (based on recovered starting material) with excellent stereoselectivity (>95% *E*-isomer) when **110** was subjected to cross metathesis with 2.0 equivalents of the unprotected tertiary allylic alcohol **99** under identical conditions (Scheme 3.10).⁶²

⁶⁰ Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

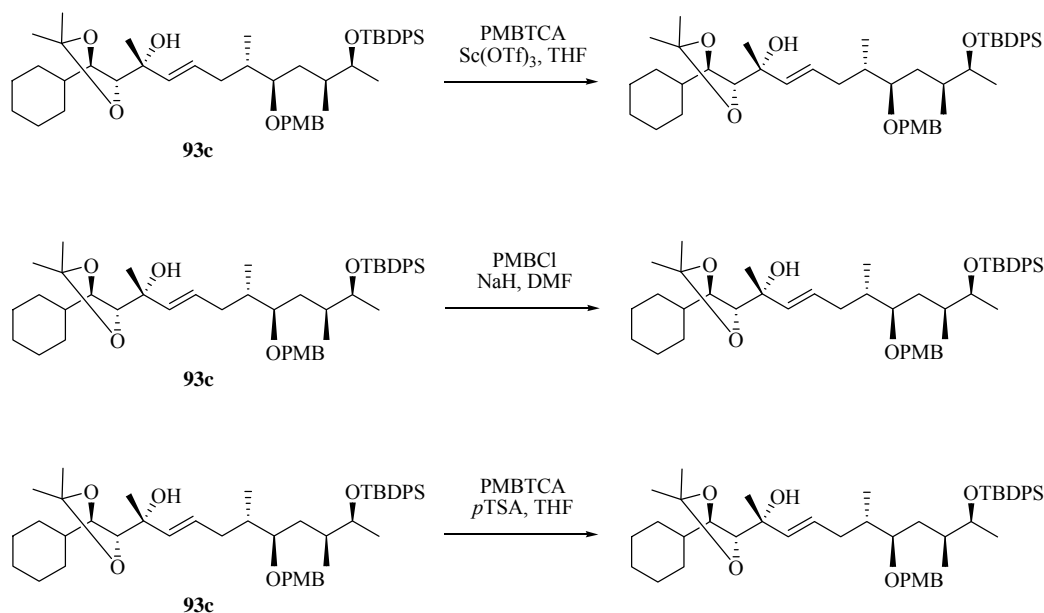
⁶¹ (a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
(b) Hoveyda, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123.

⁶² For an example of cross metathesis reactions between olefins bearing a quaternary carbon atom and an α -olefin in the total synthesis of a natural product, see: Kanada, R. M.; Itoh, D.; Nagai, M.; Niijima, J.; Asai, N.; Mizui, Y.; Abe, S.; Kotake, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 4350.



Scheme 3.10 Synthesis of **93c** via cross metathesis with subunits **99** and **110**

In order to perform a removal of isopropylidene protecting group and oxidative cleavage to prepare fragment **E**, the tertiary alcohol group of **93c** has to be protected initially. Unfortunately, we failed to protect the tertiary alcohol (Scheme 3.11).



Scheme 3.11 Failed trials to protect tertiary alcohol

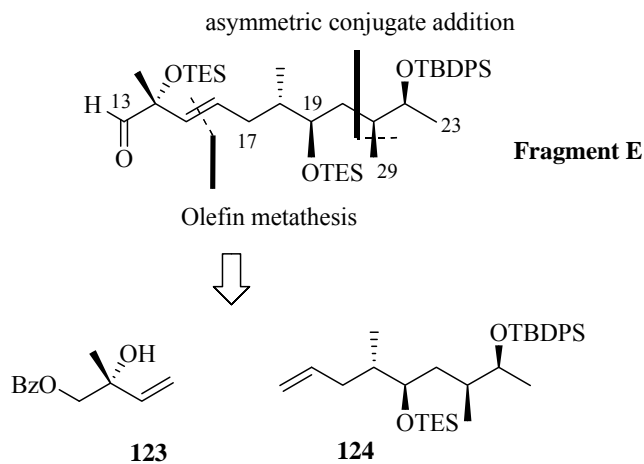
We could not proceed to deprotection of isopropylidene group and oxidative cleavage with free alcohol group at the adjacent position. The failure to obtain fragment **E** with an aldehyde group on the left side of the fragment did not discourage us to search for a new approach.

In summary, we have developed an asymmetric synthesis of the C13-C23 fragment **93c** of iriomoteolide-1a.⁶³

⁶³ Invited paper: Wang, S.-Y.; Chin, Y.-J.; Loh, T.-P. *Synthesis* **2009**, *21*, 3557.

3.3 SYNTHESIS OF FRAGMENT E

In order to avoid the problem of preparation aldehyde group again, the synthetic challenge is now reduced to construct the fragment **E** from the key intermediate **123** and **124** (Scheme 3.12). The key intermediate **123** is expected to be converted readily to the corresponding aldehyde after Bz deprotection and reduction.



Scheme 3.12 The new strategy to prepare fragment **E** between precursors **123** and **124**

3.3.1 Synthesis of Subunit **123**

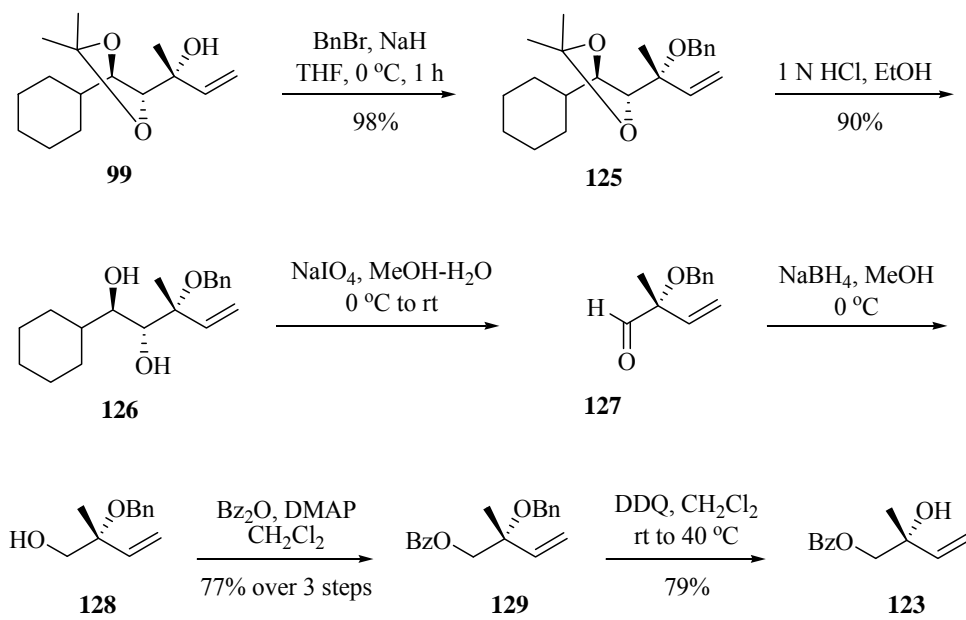
We initially applied benzyl protection protocol on **99** by using sodium bis(trimethylsilyl)amide and benzylbromide in THF.⁶⁴ However, the reaction after 24 hours at room temperature only yielded 41% of the desired benzylether **125**. The reaction was repeated with less sterically demanding sodium hydride at 0 °C for one hour, and complete conversion of **99** to **125** was observed with 98% yield (Scheme 3.13).⁶⁵ Nonetheless, longer prolonged reaction under same condition can result in lower yield and formation of side products.

Isopropylidene deprotection was achieved under acidic condition followed by periodate cleavage of diol **126** to afford aldehyde **127**. Aldehyde **127** was subsequently reduced to primary alcohol **128** by sodium borohydride as the reducing agent. Next, the primary alcohol was reacted with benzoic anhydride in the presence of *N*-ethyl diisopropylamine and dichloromethane to give di-protected alcohol **129** in 77% yield over three steps.⁶⁶ The desired key intermediate **123** was obtained upon treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to eliminate benzyl protecting group.

⁶⁴ (a) Oishi, T.; Suzuki, M.; Watanabe, K.; Murata, M. *Tetrahedron Lett.* **2006**, *47*, 3975. (b) Kang, E. J.; Cho, E. J. Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.*, **2004**, *126*, 2680.

⁶⁵ Gelin, M.; Ferrières, Plusquellec, D. *Eur. J. Org. Chem.* **2000**, 1423.

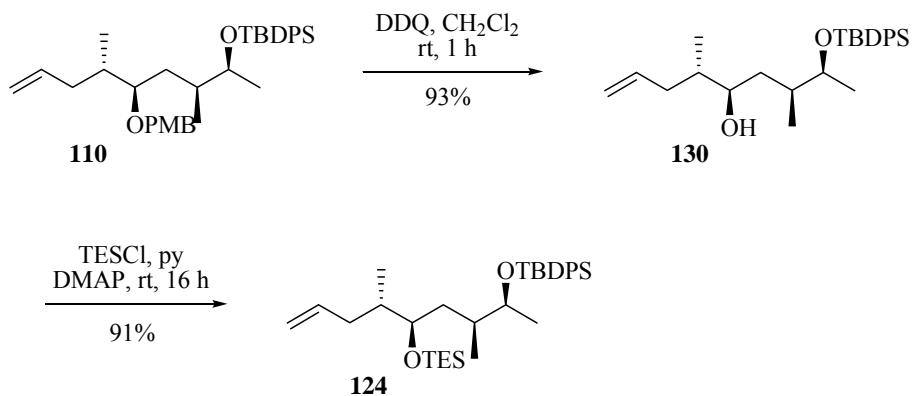
⁶⁶ Zhang, H.-X.; Reddy, M. S.; Phoenix, S.; Deslongchamps, P. *Angew. Chem. Int. Ed.* **2008**, *120*, 1292.



Scheme 3.13 Synthesis of subunit 123

3.3.2 Synthesis of Subunit **124**

The key building block **124** was synthesized via PMB deprotection followed by protection of **130** with triethylsilyl chloride under basic condition. Both of the reactions preceeded smoothly.

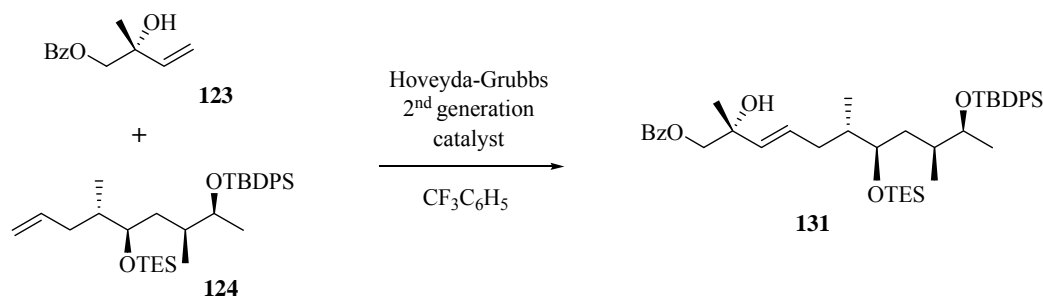


Scheme 3.14 Synthesis of subunit **124**

3.3.3 Coupling to Subunit **123** and **124**

The unprotected alcohol **123** and alkene **124** were subjected to olefin metathesis under various conditions (Table 3.5). It was found that Hoveyda-Grubbs 2nd generation catalyst under seal tube condition for 8 hours failed to give any desired product **131**. However, when the reaction was refluxed with the same catalyst for 8 hours, the product **131** was afforded in 33% with some self-coupled products. In the effort to increase the yield of the reaction, the reaction time was shortened to 5 hours and the catalyst loading was increased to 20 mol%. Surprisingly, the yield of **131** was able to be increased to 65% with lesser self-coupled products. In addition, the reaction was incomplete if the reaction time was less than 4 h.

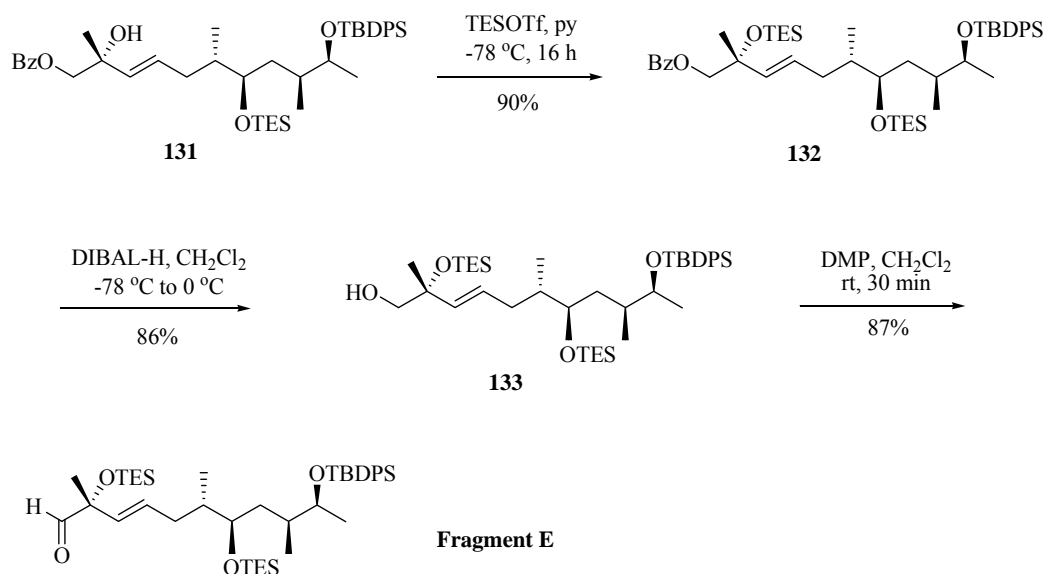
Table 3.5 Olefin metathesis of **123** and **124**



Entry	Catalyst loading (mol %)	Condition	Yield (%) ^a
1	10	Seal tube, 8h	-
2	10	Reflux, 8h	33
3	20	Reflux, 5 h	65

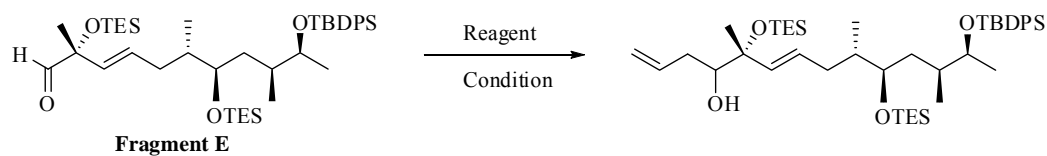
^a All reactions were carried out with 1.2 equiv of **123** and 1 equiv of **124**. (Trifluoromethyl)benzene was degassed with nitrogen. The reaction was quenched when all of **123** has reacted.

The resulting tertiary alcohol **131** was protected as a triethylsilyl ether **132**. The stage was now set to introduce the fragment **E** which required unveiling the primary benzoyl ether protecting group in **132** to reveal the aldehyde group at fragment **E** as described previously, via a selective deprotection of **132** to **133** and Dess-Martin oxidation of **133** by DMP reagent (Scheme 3.15).



Scheme 3.15 Synthesis of fragment **E**

The major uncertainty in our strategy towards natural product iriomoteolide-1a lies in the crucial allylation coupling step of fragment **C** and fragment **E**. Given the reactivity of C-14 in fragment **E** bears a chiral α -tertiary center. We decided to do a model study on the indium-mediated allylation of fragment **E**. However, attempts to realize this strategy were futile. The unexpected results shown in Table 3.6 could be due to the steric constraint caused by the adjacent quaternary carbon.

Table 3.6 Model study on indium-mediated allylation of fragment **E**.

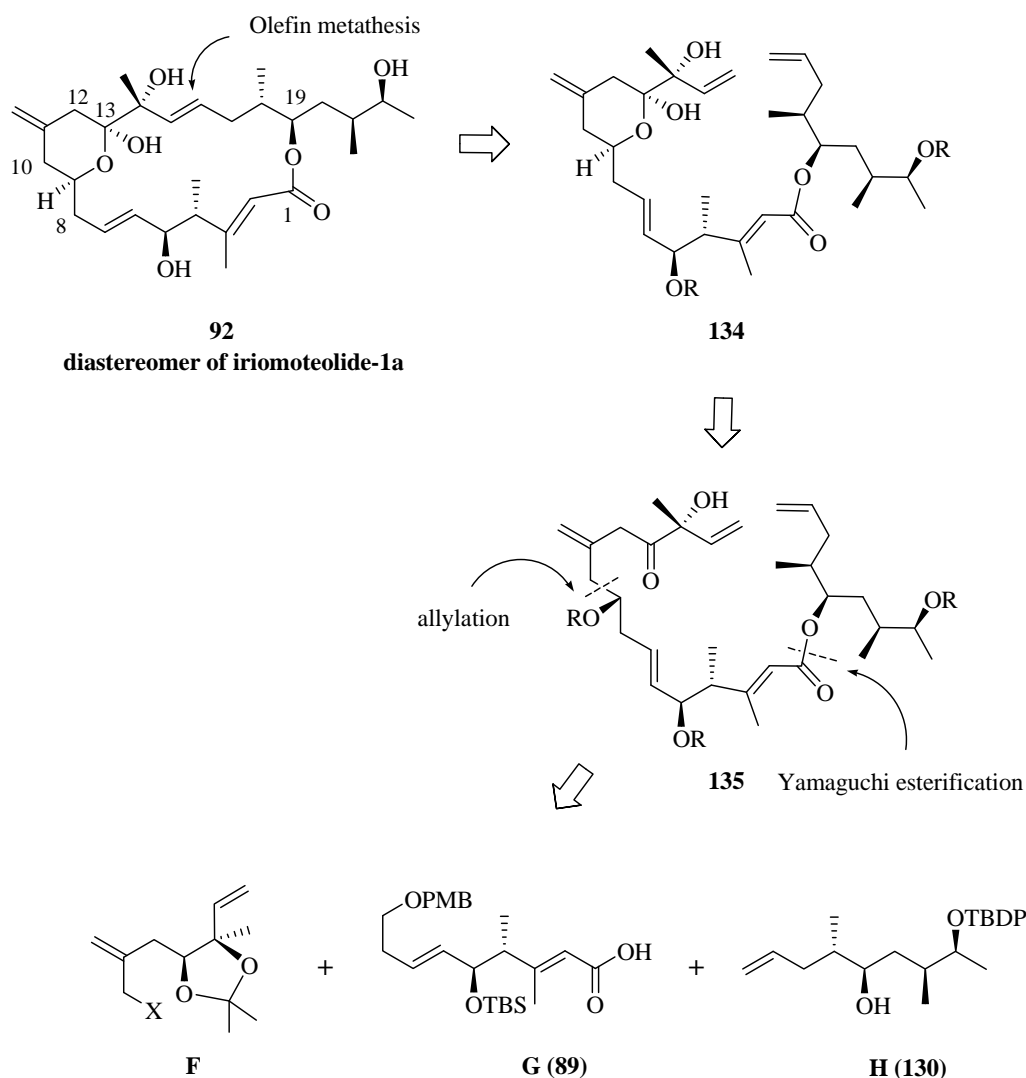
Entry	Reagent	Condition	Yield (%)
1	In (1 equiv), AllylBr (1.5 equiv), DMF	rt	N.R.
2	In (1 equiv), AllylBr (1.5 equiv), H ₂ O	rt	N.R.
3	In (1 equiv), AllylCl (1.5 equiv), H ₂ O	rt	N.R.
4	In (1 equiv), AllylI (1.5 equiv), H ₂ O	rt	N.R.
5	InCl ₃ (0.2 equiv), AllylBr (1.5 equiv), THF	rt	N.R.
6	InCl ₃ (0.2 equiv), Pd(PPh ₃) ₄ , AllylBr (1.5 equiv), THF	rt	N.R.
7	In/InCl ₃ (1 equiv), AllylBr (1.5 equiv), H ₂ O	rt	N.R.
8	In/In(OTf) ₃ (1 equiv), AllylBr (1.5 equiv), THF	rt	N.R.
9	InCl ₃ (20mol%), Bu ₃ SnAllyl (2.0 equiv.), 4 Å mol. Sieve / CH ₂ Cl ₂	rt	N.R.

In summary, we have successfully synthesized the fragment **E**. However, having encounter problem in the indium-mediated allylation of fragment **E** during initial exploration, we have decided to change our synthetic strategy in order to prevent the difficulty of joining the fragments towards the completion of the molecule. The new synthetic strategy was designed and discussed in the following chapter.

CHAPTER 4

New Synthetic Strategy

In the previous chapter, we emphasized on the original structural assignment of the natural product, iriomoteolide-1a (**26**). Based on the chemical shift of the methyl at C(3) in the natural product, it is likely that the C(2)–C(3) double bond configuration of natural product is trans instead of cis. Therefore, a new synthetic route was proposed to assemble 23-membered macrolactone **92**, the revision structure of iriomoteolide-1a (Scheme 4.1). The new route was to adopt olefin metathesis to close up the ring.

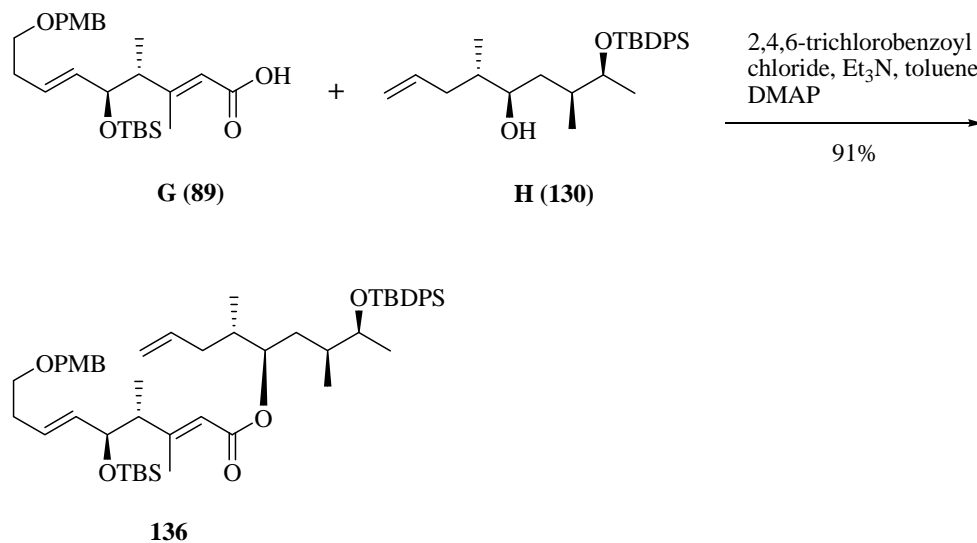


Scheme 4.1 Our new retrosynthetic analysis of a diastereomer of iriomoteolide-1a, **92**

Following the dissection of macrolactone **134**, the ester linkage at C-1 and C(9)–C(10) can be disconnected to liberate the fragment **F**, the carboxylic acid **89** (fragment **G**) and the terminal alkene **130** (fragment **H**). In the forward synthesis, these disconnections require a Yamaguchi esterification and allylation reaction. We have demonstrated the syntheses of the fragment **G** and the fragment **H** in the previous chapter.

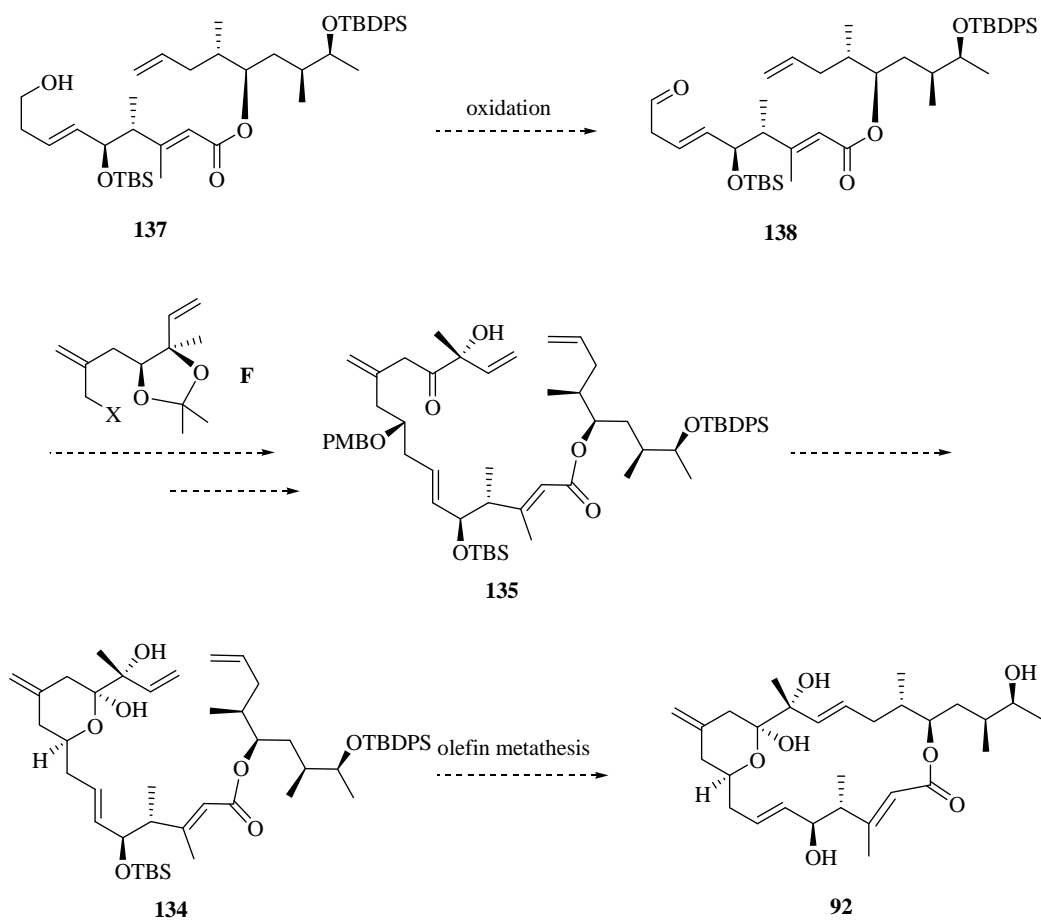
4.1 COUPLING OF **89** AND FRAGMENT **G**

The two main key buildings were associated via Yamaguchi esterification to afford intermediate **136** in 91% yield (Scheme 4.2).



Scheme 4.2 Coupling of fragment **G** and fragment **H**

The elaboration of the diastereomer of iriomoteolide-1a (**92**) is ongoing in our laboratory (Scheme 4.3).



Scheme 4.3 Future work

4.2 CONCLUSION

In conclusion, main fragment of revised structure of iriomoteolide-1a (**92**) was synthesized via a convergent strategy that features the use of our group's asymmetric conjugate addition and Paterson aldol. As excellent enantio- and diastereo-control were achieved during the synthesis, including isolation of desired isomer via column chromatography, a single isomer of **136** was isolated towards the end of the synthesis. Future work for revised structure of iriomoteolide-1a (**92**) will include the application of a metal-mediated allylation of aldehyde **138** using allylic metal generated species from fragment **F** to obtain intermediate **135**. We envisioned that the removal of the benzyl ether protecting group will facilitate the formation of hemiketal ring. With the two double bonds in **134**, an intramolecular olefin metathesis can be performed. Final deprotection of the TBDPS and TBS protected alcohols can be carried out with TBAF and HCl respectively to afford the final natural product.

When I almost finished preparing this thesis, Ye's group has successfully constructed the fully functionalized macrocyclic core of the molecule⁶⁷. Ghosh's group has also reported on the total synthesis of the proposed structure of iriomoteolide-1a (**26**)⁶⁸. On the other hand, Yang *et al* has successfully completed the synthesis of three diastereomers of iriomoteolide-1a (Figure 4.1).⁶⁹ However, the spectra of all these three diastereomers were inconsistent from those spectra of the natural product. The results show that the structure of iriomoteolide-1a requires careful re-evaluation.

⁶⁷ Li, S.; Chen, Z.; Xu, Z.-S.; Ye, T. *Chem. Commun.* **2010**, 46, 4773.

⁶⁸ Ghosh, A. K.; Yuan, H. *Org. Lett.* **2010**, 12, 3120.

⁶⁹ Fang, L.; Yang, J.; Yang, F. *Org. Lett.* **2010**, 12, 3124.

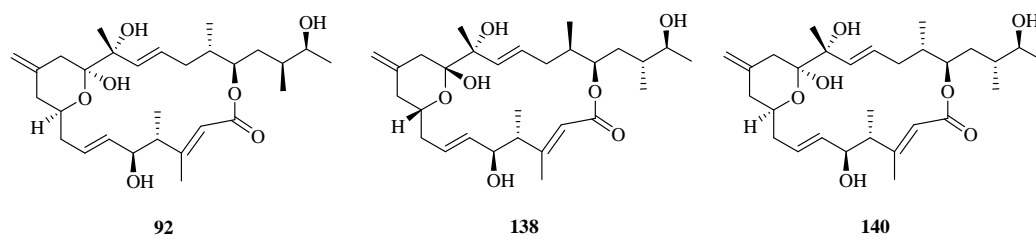


Figure 4.1 Diastereomers of **92**, **138** and **140** were synthesized by Yang *et al*

CHAPTER 5

Experimental Section

5.1 GENERAL INFORMATION

Experiments involving moisture and/or sensitive compounds were performed under a positive pressure of nitrogen in flame-dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a dessicator or via double-tipped cannular needles. Reaction mixtures were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents/compounds was removed by the addition of the stated amount of anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of an oil pump (~30 mmHg, 23-50 °C) and subsequent purging with nitrogen.

All experiments were monitored by analytical thin layer chromatography (refer to section under “Chromatography”). Solvents were removed *in vacuo* under ~30 mmHg and heated with a water bath at 23 °C using Büchi rotary evaporator cooled with circulating ethylene glycol / water mixture (1:1) at -5 °C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego⁷⁰. Solvents such as hexane, ethyl acetate, dichloromethane and water were freshly distilled prior to use. Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled over calcium hydride under nitrogen atmosphere. Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of

⁷⁰ Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture *in vacuo* followed by subsequent purging with nitrogen.

Triethylamine, toluene and dimethyl sulfoxide were distilled over calcium hydride and stored over molecular sieves to maintain dryness. DMF was distilled over Linde type 4Å molecular sieve prior to usage. 1*N* and 6*N* hydrochloric acid was diluted from concentrated 37% solution using deionised water. 3*M* and 6*M* sodium hydroxide solution was prepared from sodium hydroxide pearls. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, sodium carbonate and sodium sulphate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography was performed using Merck 60 F₂₅₄ pre-coated silica gel plates (0.25 mm thickness). Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate followed by heating on a hot plate.

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 mm) with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. The solute was loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump.

Instruments & Equipments

Infrared Spectroscopy

Infrared spectra were recorded on a Bio-Rad FTS 165 FTIR spectrometer. The oil samples were examined under neat conditions. Solid samples were analyzed as a KBr pressed-disk.

Optical Rotation

Optical rotations were measured in CHCl_3 on a *Schmidt + Haensch* polarimeter (Polartronic MH8) with 10.0 mm cell (c given in g/100 mL). Absolute configurations of the products were determined by comparison with known compounds. Concentration is denoted as c and was calculated as grams per milliliters (g / 100 mL) whereas the solvent was indicated in parentheses (c , solvent).

Mass Spectroscopy

Mass Spectrometry (EI) spectra were recorded on a Thermo Finnigan Polaris Q GCMS. Mass Spectrometry (ESI and APCI) spectra were recorded on a Thermo Finnigan LCQ Deca XP Max. High Resolution Mass Spectrometry (EI, ESI, FAB) spectra were recorded on a Thermo Finnigan MAT 95 XP. MS and High Resolution Mass Spectrometry were reported in units of mass of charge ratio (m/z).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a Bruker Avance 300, 400 and 500 NMR spectrometers.

Chemical shifts for ^1H NMR spectra are reported as δ in units of parts per million (ppm) downfield from TMS (δ 0.0) and relative to the signal of chloroform-*d* (δ 7.260, singlet) as the internal standard. Multiplicities were given as: s (singlet); d

(doublet); t (triplet); q (quartet); dd (doublets of doublet); ddd (doublets of doublets of doublet); dddd (doublets of doublets of doublets of doublet); dt (doublets of triplet); or m (multiplets). The number of protons (n) for given resonance is indicated by nH . Coupling constants are reported as a J value in Hz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) are reported as δ in units of parts per million (ppm) downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform- d (δ 77.03, triplet). The proportion of diastereomers and geometric isomers was determined from the integration of 1H NMR and ^{13}C NMR spectra.

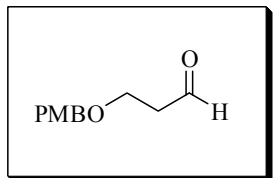
Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 8.0 software.

5.2 SUPPORTING INFORMATION

Experimental Procedures and Characterization Data of Products

3-[(4-methoxybenzyl)oxy]propanal (**75**)



A solution of *p*-methoxybenzyl alcohol (18.0 mL, 20.0 g, 0.14 mol), monochloroacetic acid (0.82 g, 8.69 mmol) and NaOH (0.35 g, 8.69 mmol) in H₂O (1.8 mL) was added dropwise to acrolein (12.0 mL, 10.2 g, 0.18 mol) over 5 min with stirring. Subsequently, acetic acid (3.64 mL, 3.83 g, 63.7 mmol) was added and the solution was maintained at 40 °C for 6 days. After that, the solution was cooled to room temperature and the reaction mixture was diluted with CH₂Cl₂ (500 mL) and washed with H₂O (3 x 150 mL). The organic layer was dried over MgSO₄, filtered and evaporated. Purification of the residue by flash chromatography gave 17.4 g (64%) of the aldehyde **75** as brown oil.

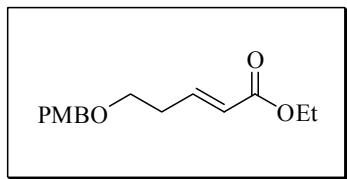
R_f value (hexane/EtOAc 4: 1): 0.18.

¹H NMR (400 MHz, CDCl₃): δ 9.77 (s, 1H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 3.77 (t, *J* = 6.1 Hz, 2H), 2.66 (t, *J* = 6.1 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 43.8, 55.2, 63.4, 72.8, 113.7, 129.3, 129.8, 159.2, 201.2.

FTIR (NaCl, neat): ν 1724, 1615, 1512, 1245 cm⁻¹.

HRMS (ESI) calcd. for C₁₁H₁₄O₃ (M+1) 195.1014, found 195.1021.

(E)-ethyl 5-(4-methoxybenzyloxy)pent-2-enoate (76)

In a round-bottomed flask equipped with a stirring bar, aldehyde **75** (17.4 g, 89.6 mmol) was dissolved in THF (100 mL) at room temperature. Methyl (triphenylphosphoranylidene) acetate (33.4 g, 100.0 mmol) was added in one portion and the reaction mixture was allowed to react at room temperature for 16 h. After the starting material reacted completely (monitored by TLC plate), the mixture was then carefully diluted with EtOAc (100 mL) and sat. aq potassium sodium tartrate (200 mL), and stirred vigorously at r.t. till a clear biphasic separation was observed. The aqueous layer was extracted with EtOAc (2 × 200 mL) and the combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The Ph_3PO was removed by filtering through a short silica plug using hexanes. The filtrate was concentrated and purified by flash chromatography (hexanes to 100: 1 hexanes–EtOAc) to afford the ester **76** as a colorless oil (20.35 g, 86% yield; *E/Z* = 91: 9).

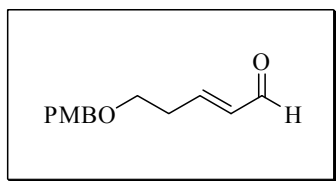
R_f value (hexane/EtOAc 4: 1): 0.32.

^1H NMR (400 MHz, CDCl_3): δ 7.27 (d, J = 8.7 Hz, 2H), 7.04–6.93 (m, 1H), 6.90 (d, J = 8.6 Hz, 2H), 5.90 (d, J = 15.7 Hz, 1H), 4.47 (s, 2H), 4.20 (q, J = 7.12 Hz, 2H), 3.82 (s, 3H), 3.57 (t, J = 6.5 Hz, 2H), 2.54–2.49 (m, 2H), 1.30 (t, J = 7.14 Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.5 (C), 159.2 (C), 145.7 (CH), 130.1 (C), 129.3 (CH), 122.9 (CH), 113.8 (CH), 72.7 (CH_2), 68.0 (CH_2), 60.2 (CH_2), 55.3 (CH_3), 32.6 (CH_2), 14.3 (CH_3).

FTIR (NaCl, neat): ν 1717, 1655, 1612, 1514 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{21}\text{O}_4\text{S}$ ($\text{M}+1$) 265.1437, found 265.1440.

(E)-5-(4-methoxybenzyloxy)pent-2-enal (78)

In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, **76** (0.264 g, 1.00 mmol) was dissolved in hexane (4 mL) and cooled to $-40\text{ }^{\circ}\text{C}$. DIBAL-H (3.0 mL, Aldrich 1.0 M in heptane, 3.00 mmol) was added carefully over 2 portions. After stirring for another 2 h, MeOH (pre-cooled to $-78\text{ }^{\circ}\text{C}$, 0.106 g, 3.30 mmol) was added carefully over 2 portions and stirred for a further 15 minutes till a white suspension was observed. The reaction mixture was then added saturated potassium sodium tartrate solution (5 mL), diluted with Et₂O (5 mL) and warmed to room temperature. The mixture was stirred until a clear biphasic separation was observed. The aqueous layer was extracted with Et₂O (10 mL x 3). The combined organic extracts were washed with saturated NaHCO₃ (15 mL x 2), brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified through a short silica gel column (Hexane/Et₂O 20: 1) to afford the desired product as pale yellow oil (0.193 g, 87% yield). The alcohol **77** was dissolved in EtOAc (5 mL) and 2-iodoxybenzoic acid (0.56 g, 2.00 mmol) was added to the solution at room temperature. The reaction was reflux for 2 h before cooling to $0\text{ }^{\circ}\text{C}$ and quenched with water (5 mL). The aqueous mixture was extracted with ethyl acetate (3 x 5 mL) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Hexane/EtOAc 9: 1) to afford the aldehyde **78** as colourless oil (0.180 g, 94% yield).

R_f value (hexane/EtOAc 48: 1): 0.20.

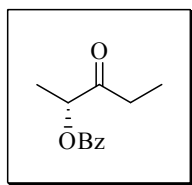
^1H NMR (400 MHz, CDCl_3): δ 9.50 (d, $J = 7.9$ Hz, 1H), 7.25 (d, $J = 8.5$ Hz, 2H), 6.88 (d, $J = 8.4$ Hz, 2H), 6.87–6.85 (m, 1H), 6.17 (dd, $J = 7.9, 15.6$ Hz, 1H), 4.46 (s, 2H), 3.80 (s, 3H), 3.60 (t, $J = 6.22$ Hz, 2H), 2.64–2.59 (m, 2H).

^{13}C NMR (100 MHz, CDCl_3): δ 194.1 (C), 159.3 (C), 155.4 (CH), 134.1 (CH), 129.9 (C), 129.4 (CH), 113.9 (CH), 72.8 (CH_2), 67.6 (CH_2), 55.3 (CH_3), 33.1 (CH_2).

FTIR (NaCl, neat): ν 1690, 1636, 1612, 1514 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{10}\text{O}_3$ ($\text{M}+1$) 221.1189, found 221.1178.

(*R*)-3-oxopentan-2-yl benzoate (**81**)



To a cooled (-20 °C) mixture of methyl D-(+)-lactate (**79**; 7.04 g, 67.6 mmol) and $\text{MeON}(\text{Me})\text{H}\cdot\text{HCl}$ (16.4 g, 168 mmol) in THF (200 mL) was added a 2 M solution of *i*-PrMgCl in THF (168 mL) dropwise over 30 min. The reaction mixture was stirred at -20 °C for 30 min and at 0 °C for a further 30 min before sat. aq NH_4Cl (500 mL) was added. The mixture was extracted with Et_2O (4×150 mL), followed by CH_2Cl_2 (4×150 mL). The combined organic extracts were dried (MgSO_4), concentrated in vacuo, and the residue was purified by column chromatography (hexane/ EtOAc 1: 1) to give the intermediate Weinreb amide (7.83 g, 87% yield) as a colorless oil. To a cooled (0 °C) solution of this amide (2.0 g, 15.0 mmol) in THF (30 mL) was added a 3 M solution of EtMgBr in Et_2O (16 mL) and the reaction mixture was allowed to warm to r.t. After 1 h, saturated aqueous NH_4Cl (80 mL) was added and the mixture was extracted with Et_2O (40 mL), followed by CH_2Cl_2 (2×40 mL). The combined organic

extracts were dried (MgSO_4) and concentrated. Then, CH_2Cl_2 (100 mL) was added. To this solution was added Bz_2O (5.11 g, 22.6 mmol), DMAP (0.20 g, 1.64 mmol), and $i\text{-Pr}_2\text{NEt}$ (5.0 mL, 28.6 mmol). After stirring for 14 h, excess Bz_2O was removed by the addition of ethylenediamine (1.0 g, 16.6 mmol). H_2O (80 mL) was added, the mixture extracted with Et_2O (4×40 mL). The combined organic extracts were dried (MgSO_4), and concentrated to an oil. The residue was purified by column chromatography (hexane/ EtOAc 5: 1) to afford (*R*)-**81** as a colorless oil (2.63g, 85% yield).

R_f value (hexane/ EtOAc 4: 1): 0.53.

$[\alpha]_D^{20} = -25.3$ ($c = 0.9$, CHCl_3)

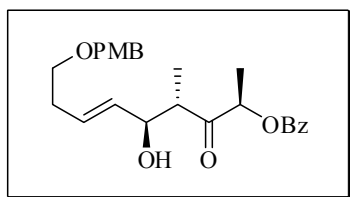
^1H NMR (300 MHz, CDCl_3): δ 8.05–8.07 (m, 2 H), 7.41–7.59 (m, 3 H), 5.33 (q, $J = 7.2$ Hz, 2 H), 2.46–2.68 (m, 2 H), 1.51 (d, $J = 7.0$ Hz, 2 H), 1.07 (t, $J = 7.2$ Hz, 3 H).

^{13}C NMR (75.4 MHz, CDCl_3): δ 208.4, 165.8, 133.3, 129.7, 129.4, 128.4, 75.0, 31.4, 16.4, 7.1.

FTIR (KBr, neat): ν 3062, 2981, 2939, 1720 (C=O), 1716 (C=O), 1452, 1269, 1109, 1026, 711 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_3$ ($M + 1$) 207.1025, found 207.1021.

(2*R*,4*S*,5*S*,*E*)-5-hydroxy-9-(4-methoxybenzyloxy)-4-methyl-3-oxonon-6-en-2-yl benzoate (82**)**



To a stirred solution ($-78\text{ }^{\circ}\text{C}$) of **81** (2.06 g, 10.0 mmol) in Et₂O (40 mL) was added chlorodicyclohexylborane (15.0 mL, 1 M in hexane, 15.0 mmol) and Me₂NEt (1.5 mL, 15 mmol). The mixture was warmed to $0\text{ }^{\circ}\text{C}$, stirred for 2 h, and then recooled to $-78\text{ }^{\circ}\text{C}$. A solution of aldehyde **78** (2.86 g, 13.0 mmol) in Et₂O (10 mL) was added dropwise over 2 min. After 2 h, the reaction mixture was kept in the freezer ($-24\text{ }^{\circ}\text{C}$) for 20 h. The mixture was warmed to $0\text{ }^{\circ}\text{C}$ and quenched by dropwise addition of MeOH (30 mL), pH 7 phosphate buffer (30 mL), and 35% H₂O₂ (30 mL), and stirred for 1 h at r.t. H₂O (100 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et₂O ($3 \times 80\text{ mL}$). The combined organic layers were washed with brine (60 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by column chromatography (from hexane/EtOAc 50: 1 to 20: 1) to afford alcohol **82** as a white solid (3.45 g, 81% yield).

R_f value (hexane/EtOAc 4: 1): 0.20.

$[\alpha]_{\text{D}}^{20} = -19.9$ ($c = 0.99$, CHCl₃).

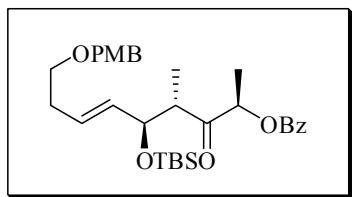
¹H NMR (500 MHz, CDCl₃): δ 8.08 (d, $J = 7.3\text{ Hz}$, 2H), 7.59 (t, $J = 7.45\text{ Hz}$, 1H), 7.47–7.44 (m, 2H), 7.23 (d, $J = 9.5\text{ Hz}$, 2H), 6.87 (d, $J = 8.6\text{ Hz}$, 2H), 5.76–5.70 (m, 1 H), 5.50 (dd, $J = 7.6\text{ Hz}$, 15.4 Hz, 1H), 5.43 (q, $J = 7.1\text{ Hz}$, 1H), 4.43 (s, 2H), 4.24–4.21 (m, 1 H), 3.80 (s, 3H), 3.48 (t, $J = 6.7\text{ Hz}$, 2H), 2.92–2.86 (m, 1 H), 2.37–2.33 (m, 2H), 1.59 (bs), 1.55 (d, $J = 7.1\text{ Hz}$, 3 H), 1.17 (d, $J = 7.15\text{ Hz}$, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ 211.7, 165.8, 135.9, 135.9, 135.7, 134.4, 133.8, 133.2, 129.7, 129.6, 129.5, 129.5, 128.4, 127.6, 127.4, 74.7, 72.2, 72.0, 48.8, 37.4, 36.4, 27.0, 19.2, 18.8, 16.8, 15.6, 14.4.

FTIR (NaCl, neat): ν 1721, 1611, 1514, 1450 cm⁻¹.

HRMS (ESI) calcd. for C₂₅H₃₀O₆Na (M + Na) 449.1940, found 449.1940.

(2*R*,4*S*,5*S*,*E*)-(tert-butyltrimethylsilyloxy)-9-(4-methoxybenzyloxy)-4-methyl-3-oxonon-6-en-2-yl benzoate (83)



To a round bottom flask equipped with a rubber septum and a magnetic stirrer bar was added imidazole (0.136 g, 2.00 mmol), DMAP (0.024 g, 0.20 mmol) and CH₂Cl₂ (2 mL). Then alcohol **82** (0.426 g, 1.00 mmol) was added dropwise and the reaction mixture was cooled to 0 °C. *Tert*-butylchlorodimethylsilane (0.226 g, 1.50 mmol) was added slowly and the resulting reaction mixture was stirred overnight at room temperature. The mixture was diluted with CH₂Cl₂ (10 mL), H₂O (10 mL) and extracted with CH₂Cl₂ (20 mL x 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/EtOAc 50: 1) to afford the desired product as pale yellow oil (0.487 g, 90% yield).

R_f value (hexane/EtOAc 9: 1): 0.50.

[α]_D²⁰ = +0.97 (*c* = 1.2, CHCl₃).

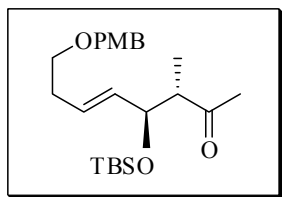
¹H NMR (400 MHz, CDCl₃): δ 8.08 (d, *J* = 8.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.50–7.43 (m, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.65–5.57 (m, 1H), 5.44–5.33 (m, 2H), 4.42 (s, 2H), 4.27–4.22 (m, 1H), 3.80 (s, 3H), 3.47 (t, *J* = 6.7 Hz, 2H), 2.90–2.83 (m, 1H), 2.36–2.31 (m, 2H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.81 (s, 9H), 0.08 (s, 3H), -0.03 (s, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 209.3, 165.7, 159.1, 133.2, 133.0, 130.3, 130.0, 129.8, 129.7, 129.3, 128.4, 113.7, 76.3, 75.3, 72.6, 69.3, 55.2, 48.8, 32.6, 25.8, 18.0, 15.1, 14.3, -3.6, -4.2.

FTIR (NaCl, neat): ν 1721, 1638, 1616, 1514 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{44}\text{O}_6\text{SiNa}$ ($M + \text{Na}$) 563.2803, found 563.2805.

**(3*S*,4*S*,*E*)-4-(*tert*-butyldimethylsilyloxy)-8-(4-methoxybenzyloxy)-3-methyloct-5-
2-one (**84**)**



The ketone **83** (1.08 g, 2.00 mmol) in Et_2O (10 mL) was cooled at 0 °C and methylmagnesium bromide (3.4 mL, Aldrich 3.0 M in Et_2O , 10.0 mmol) was slowly added into the solution. The reaction mixture was stirred at room temperature for 5 h. Then, saturated aqueous NH_4Cl (10 mL) was added carefully with vigorous stirring, the layers were separated, and the aqueous phase was extracted thoroughly with Et_2O (3×10 mL). Subsequently, the combined organic layers were washed with brine (20 mL), dried (MgSO_4), filtered, and concentrated to give a crude mixture of diol. The mixture was passed through a column of silica gel. The diol was used for subsequent reaction without further purification.

To a stirred solution (0 °C) of the diol in MeOH (16 mL) and H_2O (16 mL) was added NaIO_4 (2.16 g, 10.2 mmol) in small portions. After complete addition, the mixture was stirred for 2 h. H_2O (80 mL) was added and the mixture was extracted with Et_2O (4×80 mL). The combined organic layers were washed with brine (80 mL), dried (MgSO_4), filtered, and concentrated in vacuo. The residues was purified by flash column chromatography (hexane/ EtOAc 30:1) to afford ketone **84** as a colorless oil (0.539 g, 65% yield over two steps).

R_f value (hexane/EtOAc 4: 1): 0.43.

$[\alpha]_D^{20} = -6.7$ ($c = 1.05$, CHCl_3).

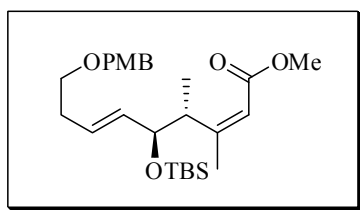
^1H NMR (300 MHz, CDCl_3): δ 7.25 (d, $J = 9.0$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.66–5.56 (m, 1H), 5.36 (dd, $J = 7.9, 15.5$ Hz, 1H), 4.43 (s, 2H), 4.16–4.10 (m, 1H), 3.80 (s, 3H), 3.47 (t, $J = 6.7$ Hz, 2H), 2.68–2.58 (m, 1H), 2.37–2.30 (m, 2H), 2.17 (s, 3H), 0.90 (d, $J = 7.0$ Hz, 3H), 0.83 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 212.2 (C), 159.2 (C), 133.0 (CH), 130.5 (C), 129.7 (CH), 129.3 (CH), 113.8 (CH), 76.9 (CH), 72.6 (CH_2), 69.4 (CH_2), 55.3 (CH_3), 53.0 (CH), 32.7 (CH_2), 31.0 (CH_3), 25.8 (CH_3), 18.0 (C), 13.2 (CH_3), -3.9 (CH_3), -5.1 (CH_3).

FTIR (NaCl, neat): ν 3062, 2960, 2931, 2856, 1722 (C=O), 1514, 1247 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{38}\text{O}_4\text{Si}$ ($M + 1$) 407.2616, found 407.2618.

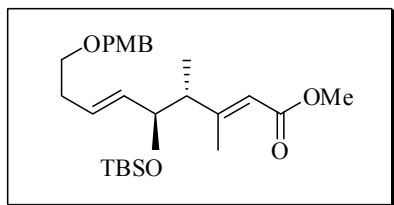
(2Z,4R,5S,6E)-methyl 5-(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-3,4-dimethylnona-2,6-dienoate (85a)



To a stirred suspension of CuI (57 mg, 0.30 mmol) in Et_2O (1 mL) was added MeLi (0.27 mL, 2.2 M in Hexane, 0.60 mmol) at 0 °C. The solution was stirred for 15 min at 0 °C. After that, the solution was cooled to -50 °C and alkyne **91** (44.7 mg, 0.1 mmol) in Et_2O (1 mL) was added into the solution. The reaction was stirred for another 1.5 h and quenched with AcOH (33 μL) and saturated NH_4Cl . The mixture

was extracted with Et₂O (3 x 10 mL), dried over MgSO₄ and concentrated in vacuo. The residue was passed through a short silica gel column.

(2*E*,4*R*,5*S*,6*E*)-methyl 5-(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-3,4-dimethylnona-2,6-dienoate (85b**)**



To a stirred solution of acid **89** (45 mg, 0.10 mmol) in toluene (2 mL) was added Et₃N (40 mg, 0.40 mmol) and 2,4,6-trichlorobenzoylchloride (61 mg, 0.25 mmol) at room temperature. The reaction was stirred at rt for 2.5 h. After that, MeOH (10 mg, 0.31 mmol) and DMAP (24 mg, 0.20 mmol) in toluene (4 mL) were added immediately into the mixture. The reaction was stirred overnight. The mixture was quenched with saturated NaHCO₃, diluted with Et₂O and extracted with Et₂O (3 x 10 mL). The organic layers were washed with water, brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/Et₂O 50:1) to afford ester **85b** as colorless oil (42 mg, 92% yield).

R_f value (hexane/Et₂O 8: 1): 0.22.

[α]_D²⁰ = -0.52 (*c* = 0.81, CHCl₃).

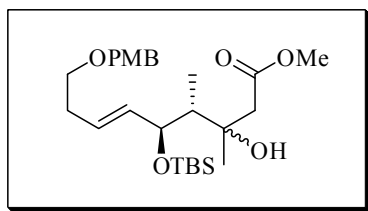
¹H NMR (400 MHz, CDCl₃): δ 7.25 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.68 (s, 1H), 5.61–5.54 (m, 1H), 5.37 (dd, *J* = 7.6, 15.6 Hz, 1H), 4.43 (s, 2H), 3.99–3.97 (m, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 3.47 (t, *J* = 6.8 Hz, 2H), 2.35–2.30 (m, 2H), 2.28–2.24 (m, 1H), 2.13 (s, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.83 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 167.3 (C), 162.3 (C), 159.2 (C), 133.5 (CH), 130.5 (C), 129.3 (CH), 128.9 (CH), 116.5 (CH), 113.8 (CH), 76.5 (CH), 72.6 (CH_2), 69.6 (CH_2), 55.3 (CH_3), 50.7 (CH_3), 50.6 (CH), 32.7 (CH_2), 25.8 (CH_3), 18.1 (C), 16.9 (CH_3), 15.2 (CH_3), -3.9 (CH_3), -5.1 (CH_3).

FTIR (NaCl, neat): ν 2855, 1717, 1645, 1514, 1248 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{42}\text{O}_5\text{Si}$ ($M + 1$) 463.2888, found 463.2880.

(4*S*,5*S*,*E*)-methyl 5-(*tert*-butyldimethylsilyloxy)-3-hydroxy-9-(4-methoxybenzyloxy)-3,4-dimethylnon-6-enoate (86**)**



n-BuLi (15.4 mL, Aldrich 1.6 M in Hexane, 24.6 mmol) was added dropwise into a solution of diisopropylamine (3.5 mL, 26.8 mmol) in THF (75 mL) at 0 °C under nitrogen atmosphere. After stirring for 1 h at 0 °C, the mixture was cooled to -78 °C and a solution of methyl acetate (2.22 mL, 2.04 g, 27.6 mmol) in THF (19 mL) was added into the mixture over 1 h. The reaction was stirred for 1 h at -78 °C. Subsequently, a solution of **84** (1.00 g, 2.46 mmol) in THF (19 mL) was added slowly overnight at -78 °C. The reaction was stirred at -78 °C for additional 3 h. Saturated aqueous NH_4Cl was then added to the reaction mixture to quench the reaction. Then, the mixture was extracted ethyl acetate (3 x 75 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated under reduce pressure to afford the crude product. The residue was purified by flash column chromatography (Hexane/EtOAc 40:1) to obtain the alcohol **86** as light yellow oil (0.946 g, 80% yield).

R_f value (hexane/EtOAc 4: 1): 0.18.

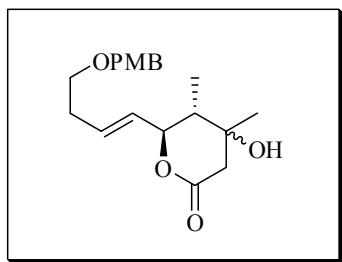
^1H NMR (400 MHz, CDCl_3): δ 7.26 (d, $J = 8.4$ Hz, 2H), 6.89 (d, $J = 8.5$ Hz, 2H), 5.60 (dt, $J = 6.7, 15.5$ Hz, 1H), 5.43 (dd, $J = 8.4, 15.5$ Hz, 1H), 4.45 (s, 2H), 4.12 (m, 1H), 3.90 (s, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.51 (t, $J = 6.6$ Hz, 2H), 2.52–2.41 (m, 2H), 2.39–2.34 (m, 2H), 1.30 (s, 3H), 0.93–0.89 (m, 12H), 0.14–0.05 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 171.9, 159.2, 134.2, 130.3, 129.9, 124.5, 113.8, 79.0, 74.6, 72.6, 69.1, 55.3, 51.5, 45.9, 45.6, 32.6, 25.8, 22.7, 18.0, 13.4, -3.1, -4.6.

FTIR (NaCl, neat): ν 3456, 2930, 1732, 1612, 1514 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{26}\text{H}_{45}\text{O}_6\text{Si}$ ($M + 1$) 481.2979, found 481.2985.

(5*S*,6*S*)-4-hydroxy-6-((*E*)-4-(4-methoxybenzyloxy)but-1-enyl)-4,5-dimethyltetrahydro-2*H*-pyran-2-one (87)



To a solution of **86** (0.481 g, 2.46 mmol) in MeOH (10 mL) was added Amberlyst 15 (1.0 g, 2.46 mmol). The reaction was stirred at room temperature for overnight. Then, Amberlyst 15 was filtered off by gravity filtration and washed with MeOH. The filtrate was dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (Hexane/EtOAc 10:1) to afford lactone **87** as colourless oil (0.617 g, 75% yield).

R_f value (hexane/EtOAc 1: 1): 0.23.

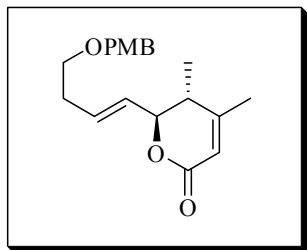
^1H NMR (500 MHz, CDCl_3): δ 7.25 (d, $J = 10.9$ Hz, 2H), 6.87 (d, $J = 10.5$ Hz, 2H), 5.84–5.79 (m, 1H), 5.49 (dd, $J = 10.6, 15.0$ Hz, 1H), 4.67–4.63 (m, 0.65H), 4.43 (s, 2H), 4.26–4.22 (m, 0.35H), 3.80 (s, 3H), 2.75 (d, $J = 21.1$ Hz, 0.35H), 2.68 (d, $J = 22.0$ Hz, 0.65H), 2.54 (d, $J = 21.4$ Hz, 0.3H), 2.49 (d, $J = 22.0$ Hz, 0.7H), 2.40–2.36 (m, 2H), 1.81–1.78 (m, 0.35H), 1.73 (bs, OH), 1.63–1.59 (m, 0.75H), 1.29 (s, 3H), 0.94 (d, $J = 5.0$ Hz, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 169.2, 159.1, 133.5, 130.3, 129.3, 129.0, 113.8, 84.3, 83.4, 72.6, 69.7, 68.9, 55.3, 45.1, 32.6, 27.6, 9.8.

FTIR (NaCl, neat): ν 3433, 2971, 1718, 1612, 1513, 1247 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{27}\text{O}_5$ ($M + 1$) 335.1865, found 335.1858.

(5*R*,6*S*)-6-((*E*)-4-(4-methoxybenzyloxy)but-1-enyl)-4,5-dimethyl-5,6-dihydro-2*H*-pyran-2-one (88)



To a round bottom flask equipped with a rubber septum and a magnetic stirrer bar was added **87** (0.537 g, 1.61 mmol) and pyridine (2.68 mL). The solution was cooled to 0 °C and SOCl_2 (0.58 mL, 8.0 mmol) was added dropwise over 5 min to the solution. The reaction was then stirred at 0 °C and monitored by TLC plate. When the reaction completed, pyridine was evaporated off under reduced pressure. The mixture was diluted with diethyl ether (20 mL), H_2O (10 mL) and extracted with diethyl ether (10 mL x 3). The combined organic extracts were dried over anhydrous sodium sulfate,

filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/Et₂O 50: 1) to afford the desired product as colourless oil (0.234 g, 46% yield).

R_f value (hexane/EtOAc 1: 1): 0.48.

[α]_D²⁰ = -34.9 (*c* = 1.06, CHCl₃).

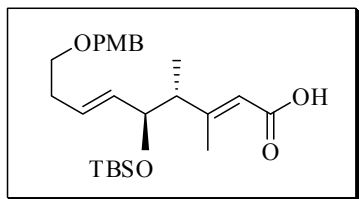
¹H NMR (400 MHz, CDCl₃): δ 7.25 (d, *J* = 10.9 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.87–5.78 (m, 2H), 5.60 (dd, *J* = 7.4, 15.4 Hz, 1H), 4.56–4.52 (m, 1H), 4.48 (s, 2H), 3.80 (s, 3H), 3.48 (t, *J* = 6.5 Hz, 2H), 2.38–2.29 (m, 3H), 1.94 (s, 3H), 1.16 (d, *J* = 7.2 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 163.3, 160.2, 158.9, 133.5, 130.5, 129.1, 127.9, 116.5, 113.2, 83.4, 72.6, 69.5, 55.6, 38.2, 33.1, 22.0, 16.9.

FTIR (NaCl, neat): ν 2857, 1715, 1612, 1514, 1248 cm⁻¹.

HRMS (ESI) calcd. for C₁₉H₂₄O₄Na (*M* + 23) 339.1567, found 339.1572.

(2*E*,4*R*,5*S*,6*E*)-5-(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-3,4-dimethylnona-2,6-dienoic acid (89**)**



To a stirred solution of **88** (0.347 g, 1.10 mmol) in MeOH (23.5 mL) was added 1 N lithium hydroxide (11.0 mL, 11.0 mmol). The reaction was stirred at room temperature overnight. After that, the reaction was quenched with 1 N HCl. 1 N HCl was added dropwise until the pH of the mixture became 5.0. Subsequently, the mixture was extracted with EtOAc (3 x 20 mL). The combined organic extracts were

washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was used in the following reactions without further purification.

To a solution of the crude intermediate in dichloromethane (50 mL) was added TBSOTf (0.97 mL, 5.50 mmol) and Et₃N (1.05 mL, 7.50 mmol) at -78 °C. The reaction was warmed to room temperature and stirred for 5 h. Consequently, MeOH (5.0 mL) was added into the mixture followed by K₂CO₃ (0.30 g, 2.20 mmol). The reaction was allowed to proceed for another 10 min prior to quenching with water (50 mL). The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash chromatography (hexane/Et₂O 8: 1) to afford the desired product as colourless oil (0.237 g, 48% yield over 4 steps). Trans α,β -unsaturated carboxylic acid **89** instead of cis α,β -unsaturated carboxylic acid **D** was obtained as the major isomer.

R_f value (hexane/EtOAc 4: 1): 0.21.

$[\alpha]_D^{20} = +23.6$ ($c = 0.72$, CHCl₃).

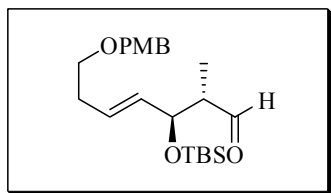
¹H NMR (400 MHz, CDCl₃): δ 7.25 (d, $J = 7.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.71 (s, 1H), 5.62–5.54 (m, 1H), 5.37 (dd, $J = 7.7, 15.2$ Hz, 1H), 4.43 (s, 2H), 3.99–3.96 (m, 1H), 3.80 (s, 3H), 3.47 (t, $J = 6.7$ Hz, 2H), 2.36–2.25 (m, 3H), 2.14 (s, 3H), 0.96 (d, $J = 7.2$ Hz, 3H) 0.83 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 172.0, 165.1, 159.1, 133.4, 130.3, 129.3, 129.0, 116.4, 113.7, 76.6, 72.5, 69.4, 55.2, 50.8, 32.6, 25.7, 18.0, 17.1, 15.2, -3.9, -5.2.

FTIR (NaCl, neat): ν 2930, 2856, 1691, 1659, 1494, 1249 cm⁻¹.

HRMS (ESI) calcd. for C₂₅H₄₁O₅Si (M + 1) 449.2705, found 449.2723.

(2*S*,3*S*,*E*)-(tert-butyltrimethylsilyloxy)-7-(4-methoxybenzyloxy)-2-methylhept-4-enal (90**)**



The ester **83** (0.54 g, 1.0 mmol) was dissolved in CH₂Cl₂ (5 mL) and cooled to -78 °C. DIBAL-H (Aldrich 1 M solution in heptane, 3.0 mL, 3.0 mmol), pre-cooled to -78 °C was added dropwise. After stirring for another 1 h, the reaction was quenched with saturated aqueous potassium sodium tartrate (25 mL), warmed to r.t., and stirred vigorously till a clear biphasic separation was observed. The aqueous layer was then extracted with CH₂Cl₂ (3 × 15 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 5: 1) to afford the intermediate diol as a colorless oil.

To a stirred solution (0 °C) of the diol in MeOH (8 mL) and H₂O (8 mL) was added NaIO₄ (1.08 g, 5.1 mmol) in small portions. After complete addition, the mixture was stirred for 2 h. H₂O (40 mL) was added and the mixture was extracted with Et₂O (4 × 40 mL). The combined organic layers were washed with brine (40 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residues was purified by flash column chromatography (hexane/EtOAc 20:1) to afford aldehyde **90** as a colorless oil (0.267 g, 68% yield over two steps).

R_f value (hexane/EtOAc 4: 1): 0.47.

$[\alpha]_D^{20} = +10.2$ ($c = 1.19$, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 9.73 (s, 1H), 7.23 (d, $J = 9.0$ Hz, 2 H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.70–5.62 (m, 1H), 5.48 (dd, $J = 7.2, 15.4$ Hz, 1H), 4.43 (s, 2H), 4.23–4.21

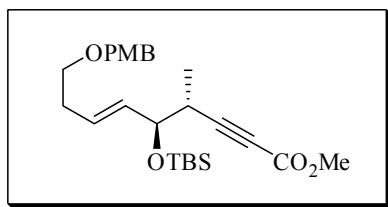
(m, 1H), 3.80 (s, 3H), 3.48 (t, $J = 6.6$ Hz, 2H), 2.46–2.40 (m, 1H), 2.37–2.32 (m, 2H), 0.99 (d, $J = 7.0$ Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 204.8, 159.1, 132.6, 130.4, 129.6, 129.2, 113.7, 75.3, 72.6, 69.4, 55.3, 52.6, 32.6, 25.7, 18.1, 10.7, -3.9, -5.0.

FTIR (KBr, neat): ν 3420, 2930, 2855, 1726 (C=O), 1612, 1514, 1247, 1096 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{37}\text{O}_4\text{Si}$ ($M + 1$) 393.2467, found 393.2461.

(4*R*,5*S*,*E*)-methyl 5-((*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-4-methylnon-6-en-2-ynoate (91)



To a stirred solution of CBr_4 (93 mg, 0.28 mmol) in dichloromethane (0.3 mL) was added Ph_3P (147 mg, 0.56 mmol) in dichloromethane (0.3 mL) solution at 0 °C. The mixture was stirred for 10 min at room temperature and cooled to 0 °C again. Aldehyde **90** (55 mg, 0.14 mmol) in dichloromethane (0.3 mL) was added into the mixture. After 2 h, the reaction was quenched with saturated NaHCO_3 and extracted with dichloromethane (3 x 10 mL), washed with brine, dried over MgSO_4 and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (hexane/EtOAc 100:1 to 50: 1) to afford dibromoalkene. Dibromoalkene was used in the following reaction without further spectroscopic analyzing.

To a stirred solution of dibromoalkene in THF (1 mL) was added *n*-BuLi (0.19 mL, Aldrich 1.6 M in Hexane, 0.31 mmol) at -78 °C. After the reaction was stirred for 30

min, the reaction was treated with methyl chloroformate (26 mg, 0.28 mmol) and warmed to room temperature. The reaction was allowed to stir for another 2.5 h. After that, the mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (hexane/ Et_2O 40: 1) to afford **91** as colourless oil (41 mg, 65% over 2 steps).

R_f value (hexane/ Et_2O 8: 1): 0.28.

$[\alpha]_D^{20} = -5.5$ ($c = 1.12$, CHCl_3).

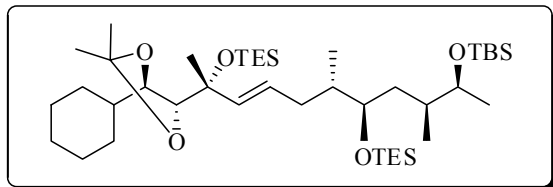
^1H NMR 300 MHz, CDCl_3): δ 7.25 (d, $J = 6.9$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.72–5.63 (m, 1H), 5.51 (dd, $J = 6.6, 15.5$ Hz, 1H), 4.43 (s, 2H), 4.16–4.04 (m, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.48 (t, $J = 6.7$ Hz, 2H), 2.68–2.59 (m, 1H), 2.41–2.32 (m, 2H), 1.11 (d, $J = 7.1$ Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3): δ 159.1 (C), 154.3 (C), 131.6 (CH), 130.5 (C), 129.7 (CH), 129.3 (CH), 113.7 (CH), 91.6 (C), 75.3 (CH), 74.0 (C), 72.6 (CH_2), 69.5 (CH_2), 55.3 (CH_3), 52.5 (CH_3), 33.8 (CH_2), 32.7 (CH), 25.8 (CH_3), 18.1 (C), 15.0 (CH_3), -4.3 (CH_3), -5.0 (CH_3).

FTIR (KBr, neat): ν 2963, 2858, 2237, 1715, 1612, 1514, 1251 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{39}\text{O}_5\text{Si}$ ($M + 1$) 447.2562, found 447.2567.

(5R,9S,10R,12S,13S,E)-5-((4R,5R)-5-cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3,3-diethyl-5,9,12,13,15,15,16,16-octamethyl-10-(triethylsilyloxy)-4,14-dioxa-3,15-disilaheptadec-6-ene (93a)



To a stirred solution of sulfone **95** (31.1 mg, 0.05 mmol) in anhydrous THF (1 mL) at $-78\text{ }^{\circ}\text{C}$ was added dropwise a solution of KHMDS (0.1 mL, 15% in toluene, 0.06 mmol) in THF over 5 minutes. The blue solution was stirred for 30 minutes during which time the solution became green. A solution of aldehyde **94** (27.8 mg, 0.075 mmol) in THF (0.5 mL) was added dropwise over 5 minutes and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. The cooling bath was removed and the mixture was stirred at ambient temperature overnight. The solution has changed from dark brown to light yellow. After a night, water was added and continued stirring for 1 h. The reaction was quenched with brine (10 mL) and extracted with Et_2O (10 mL x 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/ Et_2O 100: 1) to afford the desired *trans*-product as colorless oil (11.0 mg, 29% yield; 48% total yield for the mixture of *E/Z* isomers, 60: 40).

R_f value (hexane/ Et_2O 14: 1): 0.52.

$[\alpha]_{\text{D}}^{20} = -14$ ($c = 1.0$, CHCl_3).

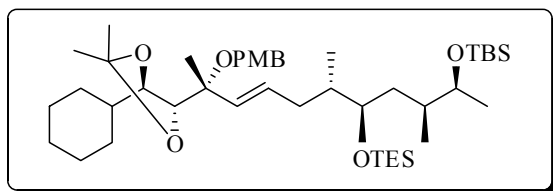
^1H NMR (300 MHz, CDCl_3): δ 5.73 (d, $J = 15.6$ Hz, 1H), 5.58-5.48 (m, 1H), 3.85-3.80 (m, 2H), 3.72-3.68 (m, 2H), 2.10-1.58 (m, 10H), 1.47-1.44 (m, 2H), 1.38 (s, 6H), 1.29 (s, 3H), 1.19-1.17 (m, 4H), 1.08 (d, 2H), 0.99-0.85 (m, 33H), 0.65-0.58 (m, 12H), 0.04 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 134.9 (CH), 128.3 (CH), 106.3 (C), 83.9 (CH), 83.2 (CH), 77.0 (C), 75.1 (CH), 71.2 (CH), 38.2 (CH), 37.3 (CH_2), 36.2 (CH_2), 35.6 (CH), 34.5 (CH), 31.6 (CH_2), 30.2 (CH_2), 27.3 (CH_3), 26.9 (CH_2), 26.6 (CH_2), 25.9 (CH_2), 25.8 (CH_3), 25.1 (CH_3), 20.8 (CH_3), 18.1 (C), 15.4 (CH_3), 15.0 (CH_3), 7.2 (CH_2), 7.0 (CH_3), 6.8 (CH_2), 5.3 (CH_3), -4.0 (CH_3), -4.8 (CH_3).

FTIR (NaCl, neat): ν 2955, 1377, 1254, 1065, 1005, 835, 743 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{42}\text{H}_{87}\text{O}_5\text{Si}_3$ (M+1) 755.5861, found 755.5818.

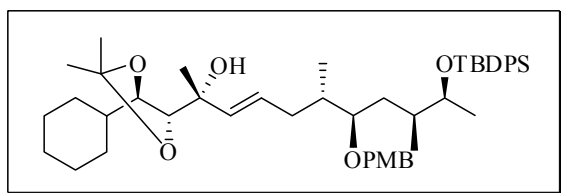
(5*S*,6*S*,8*R*)-8-((2*S*,6*R*,*E*)-6-((4*R*,5*R*)-5-cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(4-methoxybenzyloxy)hept-4-en-2-yl)-10,10-diethyl-2,2,3,3,5,6-hexamethyl-4,9-dioxo-3,10-disiladodecane (93b)



To a stirred solution of sulfone **94** (31.1 mg, 0.05 mmol) in anhydrous THF (1 mL) at -78 $^{\circ}\text{C}$ was added dropwise a solution of KHMDS (0.1 mL, 15% in toluene, 0.06 mmol) in THF over 5 minutes. The blue solution was stirred for 30 minutes during which time the solution became green. A solution of aldehyde **93a** (28.2 mg, 0.075 mmol) in THF (0.5 mL) was added dropwise over 5 minutes and the mixture was stirred at -78 $^{\circ}\text{C}$ for 1 h. The cooling bath was removed and the mixture was stirred at ambient temperature overnight. The solution has changed from dark brown to light yellow. After a night, water was added and stirring was continued for 1 h. The reaction was quenched with brine (10 mL) and extracted with Et_2O (10 mL x 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and

concentrated *in vacuo*. From the ^1H NMR analysis, the desired product was in trace amount.

(2*R*,6*S*,7*R*,9*S*,10*S*,*E*)-10-(*tert*-Butyldiphenylsilyloxy)-2-[(4*R*,5*R*)-5-cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl]-7-(4-methoxybenzyloxy)-6,9-dimethylundec-3-en-2-ol (93c)



To a solution of **110** (11.2 mg, 19.8 mmol) and allylic alcohol **99** (10.0 mg, 39.6 mmol) in CH_2Cl_2 (1.0 mL) was added the 2nd generation Hoveyda–Grubbs catalyst (1.0 mg, 1.6 mmol) and the mixture was heated at reflux for 12 h under N_2 . The mixture was cooled to r.t. and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc, 100: 1 to 20: 1) to afford **93c** as colorless oil (5.8 mg, 38% yield).

R_f value (hexane/EtOAc 4: 1): 0.53.

$[\alpha]_{\text{D}}^{20} = -16.0$ ($c = 0.5$, CHCl_3).

^1H NMR (400 MHz, CDCl_3): δ 7.73–7.86 (m, 4 H), 7.41–7.54 (m, 6 H), 7.10 (d, $J = 8.4$ Hz, 2 H), 7.01 (d, $J = 8.4$ Hz, 2 H), 5.53–5.71 (m, 2 H), 4.30 (d, $J = 10.4$ Hz, 1 H), 4.12 (d, $J = 11.2$ Hz, 1 H), 3.90–3.95 (m, 1 H), 3.84–3.87 (m, 1 H), 3.75–3.76 (m, 4 H), 3.26–3.33 (m, 1 H), 2.11–2.33 (m, 2 H), 1.64–1.98 (m, 4 H), 1.48 (s, 3 H), 1.11–1.41 (m, 15 H), 0.99 (s, 9 H), 0.79–0.97 (m, 9 H).

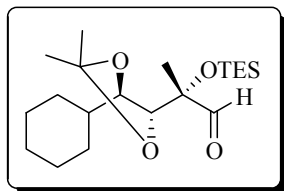
^{13}C NMR (100 MHz, CDCl_3): δ 159.0, 136.0, 135.9, 135.3, 135.0, 134.3, 131.1, 129.6, 129.5, 129.4, 129.3, 128.8, 127.5, 127.3, 113.6, 106.6, 83.2, 82.2, 81.8, 74.0, 72.3,

70.9, 55.2, 37.4, 36.4, 35.9, 35.4, 32.7, 31.6, 30.2, 29.7, 27.1, 26.7, 26.4, 25.8, 25.6, 25.5, 25.0, 19.9, 19.4, 15.6, 14.8.

FTIR (KBr, neat): ν 3581, 3070, 2958, 2922, 2852, 1612, 1454, 1379, 1249, 1161, 1035 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{48}\text{H}_{71}\text{O}_6\text{Si}$ ($M + 1$) 771.5020, found 771.5011.

(S)-2-(((4R,5R)-5-cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(triethylsilyloxy)propanal (94)



Alkene **100** (0.369 g, 1.00 mmol) and CH_2Cl_2 (2 mL) were added to a round bottom flask equipped with a magnetic stirrer bar and cooled to $-78\text{ }^\circ\text{C}$. The reaction mixture was purged with O_2 for a few minutes followed by supplying of O_3 . The completion of the reaction was indicated by color changing of the solution (from colorless to blue). After the completion of the reaction, the supply of O_3 was stopped. The reaction mixture was purged with O_2 for a few minutes and quenched with PPh_3 (0.289 g, 1.10 mmol). The reaction was cooled to room temperature and stirred vigorously for 10 min. CH_2Cl_2 was evaporated *in vacuo* and the resulting residue was purified by flash column chromatography (hexane/ Et_2O 80: 1) to afford the desired product as colorless oil (0.274 g, 74% yield).

R_f value (hexane/ Et_2O 8: 1): 0.45.

$[\alpha]_D^{20} = -42$ ($c = 1.06$, CHCl_3).

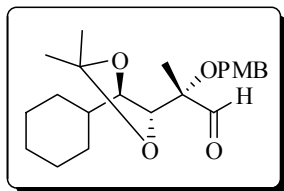
^1H NMR (400 MHz, CDCl_3): δ 9.80 (s, 1H), 4.00 (d, $J = 5.2$ Hz, 1H), 3.87-3.83 (m, 1H), 2.00-1.92 (m, 3H), 1.70-1.66 (m, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H), 1.25-1.15 (m, 3H), 0.96 (t, $J = 7.9$ Hz, 9H), 0.98-0.94 (m, 2H), 0.62 (q, $J = 7.7$ Hz, 6H).

^{13}C NMR (75 MHz, CDCl_3): δ 202.3 (C), 107.2 (C), 83.2 (CH), 82.9 (CH), 81.7 (C), 36.3 (CH), 31.3 (CH_2), 30.2 (CH_2), 26.5 (CH_2), 25.5 (CH_2), 25.4 (CH_2), 25.0 (CH_3), 21.8 (CH_3), 6.9 (CH_2), 6.4 (CH_3).

FTIR (NaCl, neat): ν 2930, 1736, 1381, 1217, 1049, 745 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{39}\text{O}_4\text{Si}$ ($\text{M}+1$) 371.2618, found 371.2603.

(S)-2-((4R,5R)-5-cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(4-methoxybenzyloxy)propanal (94a)



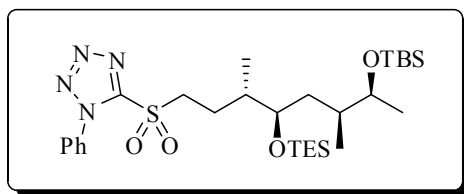
Alkene **80** (0.375 g, 1.00 mmol) and CH_2Cl_2 (2 mL) were added to a round bottom flask equipped with a magnetic stirrer bar and cooled to -78 $^\circ\text{C}$. The reaction mixture was purged with O_2 for a few minutes followed by supplying of O_3 . The completion of the reaction was indicated by color changing of the solution (from colorless to blue). After the completion of the reaction, the supply of O_3 was stopped. The reaction mixture was purged with O_2 for a few minutes and quenched with PPh_3 (0.289 g, 1.10 mmol). The reaction was cooled to room temperature and stirred vigorously for 10 min. CH_2Cl_2 was evaporated *in vacuo* and the resulting residue was

purified by flash column chromatography (hexane/Et₂O 40: 1) to afford the desired product as colorless oil (0.290 g, 77% yield).

R_f value (hexane/Et₂O 4: 1): 0.34.

¹H NMR (400 MHz, CDCl₃): δ 9.92 (s, 1H), 7.00 (m, 2H), 6.87 (d, *J* = 8.2 Hz, 2H), 4.44 (d, *J* = 10.4 Hz, 1H), 4.32 (d, *J* = 10.3 Hz, 1H), 4.07 (d, *J* = 4.88 Hz, 1H), 3.90-3.86 (m, 1H), 3.86 (s, 3H), 2.08-0.84 (m, 20H).

5-((3*S*,4*R*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-3,6-dimethyl-4-(triethylsilyloxy)octylsulfonyl)-1-phenyl-1*H*-tetrazole (95)



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, sulfone **108** (0.496 g, 1.00 mmol) was dissolved in 2 mL of dry pyridine. DMAP (0.012 g, 0.10 mmol) and TESC1 (0.301 g, 2.00 mmol) were added to the reaction mixture and stirred at room temperature. After stirring for 12 h, the reaction was diluted with Et₂O and washed with brine. The organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/Et₂O 10: 1) to afford the desired product as colorless oil (0.605 g, 99% yield).

R_f value (hexane/Et₂O 2: 1): 0.55.

[α]_D²⁰ = -7.0 (*c* = 0.9, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.71-7.68 (m, 2H), 7.62-7.59 (m, 3H), 3.97-3.89 (m, 1H), 3.71-3.64 (m, 3H), 1.99-1.96 (m, 1H), 1.88-1.86 (m, 1H), 1.78-1.77 (m, 1H),

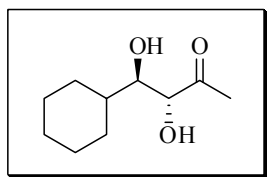
1.64-1.57 (m, 1H), 1.39-1.36 (m, 1H), 1.31-1.25 (m, 1H), 1.07 (d, $J = 5.6$ Hz, 3H), 1.02 (d, $J = 7.5$ Hz, 3H), 0.95 (t, $J = 7.9$ Hz, 9H), 0.86 (s, 9H), 0.85 (d, $J = 7.5$ Hz, 3H), 0.58 (q, $J = 7.9$ Hz, 6H), 0.03 (s, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 153.4 (C), 133.1 (C), 131.3 (CH), 129.6 (CH), 125.0 (CH), 74.5 (CH), 71.6 (CH), 54.4 (CH_2), 37.6 (CH_2), 37.1 (CH), 35.1 (CH_2), 25.8 (CH_3), 22.5 (CH), 20.7 (CH_3), 18.0 (C), 16.2 (CH_3), 14.3 (CH_3), 6.9 (CH_2), 5.1 (CH_3), -4.2 (CH_3), -4.9 (CH_3).

FTIR (NaCl, neat): ν 2957, 1595, 1499, 1339, 1153, 837, 762 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{55}\text{N}_4\text{O}_4\text{SSi}_2$ (M+1) 611.3483, found 611.3475.

(3*R*,4*R*)-4-Cyclohexyl-3,4-dihydroxybutan-2-one (97)



To a mixture of DMSO (80.0 mL) and hydroxyacetone (**96**: 20 mL) was added the cyclohexanecarbaldehyde (10.0 mmol) followed by D-proline (0.35 g, 30 mol%), and the resulting homogeneous reaction mixture was stirred at r.t. for 60 h. Then, half saturated aqueous NH_4Cl (60 mL) and EtOAc (60 mL) were added with vigorous stirring, the layers were separated, and the aqueous phase was extracted thoroughly with EtOAc (3×60 mL). Then, the combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried (MgSO_4) and filtered. The solution was concentrated and the residue was purified by flash column chromatography (hexane/EtOAc from 5: 1, 4: 1, 2: 1, 1: 1) to afford the *anti*-diol **78** as a white powder (1.17 g, 63% yield). The enantioselectivity excess of **78** was determined by HPLC analysis (chiral Daicel

Chiralpak AS, hexanes-*i*-PrOH, 85:15, flow rate 1.0 mL/min, $\lambda = 285$ nm): $t_R = 7.70$ min).

R_f value (hexane/EtOAc 1: 1): 0.50.

$[\alpha]_D^{20} = -81.6$ ($c = 1.0$, CHCl_3). {Lit. $[\alpha]_D +83$ ($c = 1.0$, CHCl_3), for (3*S*,4*S*)-4-cyclohexyl-3,4-dihydroxybutan-2-one}⁷¹

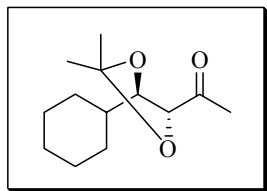
¹H NMR (300 MHz, CDCl_3): δ 4.23 (d, $J = 5.4$ Hz, 2 H), 3.51–3.54 (m, 2 H), 2.31 (s, 4 H), 1.53–1.93 (m, 6 H), 1.04–1.29 (m, 5 H).

¹³C NMR (75.4 MHz, CDCl_3): δ 209.8, 78.3, 77.6, 39.8, 29.7, 27.7, 27.4, 26.2, 26.1, 25.8.

FTIR (KBr, neat): ν 3381, 2920, 2850, 1697 (C=O), 1421, 1359, 1076, 1039, 983 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{10}\text{H}_{19}\text{O}_3$ ($M + 1$) 187.1329, found 187.1334.

1-[(4*R*,5*R*)-5-Cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl]ethanone (98)



To a mixture of **97** (1.860 g, 10.0 mmol), 2,2-dimethoxypropane (10.408 g, 100.0 mmol) and CH_2Cl_2 (20 mL) was added CSA (0.116 g, 0.05 mmol), and the reaction mixture was stirred at r.t. for overnight. Then, half saturated aqueous NaHCO_3 (30 mL) and CH_2Cl_2 (20 mL) added with vigorous stirring, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). Then, the combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried (MgSO_4) and filtered. The solution was concentrated and the residue was purified by flash column

⁷¹ (a) Notz, W.; List, B. *J. Am. Chem. Soc.* **2000**, *122*, 7386.

chromatography (hexane/EtOAc 100: 1) to afford **98** as pale yellow oil (2.042 g, 90% yield).

R_f value (hexane/EtOAc 4: 1): 0.692.

$[\alpha]_D^{20} = +0.87$ ($c = 1.2$, CHCl_3).

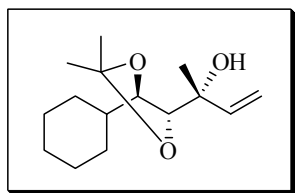
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 4.32 (d, $J = 7.6$ Hz, 1 H), 4.02 (dd, $J = 8.8, 7.6$, Hz, 1 H), 2.26 (s, 3 H), 1.63–1.87 (m, 5 H), 1.60 (s, 3 H), 1.34 (s, 3 H), 0.92–1.25 (m, 6 H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 209.7, 109.4, 82.8, 82.6, 37.6, 29.7, 29.3, 28.4, 26.6, 26.2, 25.4, 24.8.

FTIR (KBr, neat): ν 2927, 2854, 1708 (C=O), 1450, 1355, 1060 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{23}\text{O}_3$ ($M + 1$) 227.1650, found 227.1647.

(R)-2-[(4R,5R)-5-Cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl]but-3-en-2-ol (99)



Freshly prepared vinylmagnesium bromide [prepared from Mg (0.72 g) and 1 M vinyl bromide in THF (30 mL)] was cooled to 0 °C. The ketone **98** (2.26 g, 10.0 mmol) in THF (50 mL) was added dropwise and the resulting reaction mixture was stirred at 0 °C for overnight. Then, saturated aqueous NH_4Cl (50 mL) was added carefully with vigorous stirring, the layers were separated, and the aqueous phase was extracted thoroughly with Et_2O (3×50 mL). Then, the combined organic layers were washed with brine (80 mL), dried (MgSO_4), filtered, and concentrated to give a mixture of **99** and **99'**. The mixture was purified by flash column chromatography (hexane/EtOAc

starting from 250: 1 to 20: 1) to afford (*R,R,R*)-**99** (1.78 g, 70% yield) and (*R,R,S*)-**99'** (0.35 g, 14% yield).

R_f value (hexane/EtOAc 4: 1): 0.60.

$[\alpha]_D^{20} = -29.1$ ($c = 1.0$, CHCl_3).

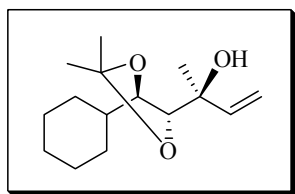
$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.05 (dd, $J = 23.2, 14.4$ Hz, 1 H), 5.34 (dd, $J = 23.2, 2.0$ Hz, 1 H), 5.16 (dd, $J = 14.4, 2.0$ Hz, 1 H), 3.95 (d, $J = 2.0$ Hz, 1 H), 3.87 (dd, $J = 12.0, 8.0$ Hz, 1 H), 2.23 (s, 1 H), 1.66–2.04 (m, 5 H), 1.50 (s, 3 H), 1.34 (s, 3 H), 1.33 (s, 3 H), 1.23–1.28 (m, 6 H).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 142.5, 113.3, 106.7, 82.7, 82.4, 74.7, 36.3, 31.7, 30.3, 28.7, 26.4, 25.7, 25.5, 25.4, 25.0.

FTIR (KBr, neat): ν 3425, 2989, 2927, 2852, 1651, 1381, 1255, 1033, 758 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{27}\text{O}_3$ ($M + 1$) 255.1958, found 255.1960.

(*S*)-2-[(4*R*,5*R*)-5-Cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl]but-3-en-2-ol (99'**)**



R_f value (hexane/EtOAc 4: 1): 0.63.

$[\alpha]_D^{20} = -42.2$ ($c = 1.5$, CHCl_3).

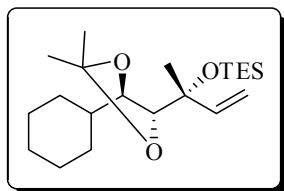
$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 6.01 (dd, $J = 17.1, 10.8$ Hz, 1 H), 5.40 (dd, $J = 17.4, 1.8$ Hz, 1 H), 5.34 (dd, $J = 10.5, 1.5$ Hz, 1 H), 3.90 (d, $J = 5.4$ Hz, 1 H), 3.80–3.85 (m, 1 H), 2.56 (s, 1 H), 1.61–2.07 (m, 5 H), 1.37 (s, 3 H), 1.32 (s, 6 H), 1.20–1.31 (m, 6 H).

^{13}C NMR (75.4 MHz, CDCl_3): δ 142.7, 112.7, 106.8, 82.7, 81.9, 75.5, 36.0, 31.4, 30.2, 27.0, 26.8, 26.3, 25.6, 25.2, 24.8.

FTIR (KBr, neat): ν 3552, 2893, 2926, 2852, 1614, 1450, 1045 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{15}\text{H}_{27}\text{O}_3$ ($M + 1$) 255.1958, found 255.1960.

((R)-2-((4R,5R)-5-cyclohexyl-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-yloxy)triethylsilane (100)



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, alcohol **99** (0.254 g, 1.00 mmol) was dissolved in CH_2Cl_2 (2 mL). Then 2,6-lutidine (0.34 mL, 3.00 mmol) followed by TESOTf (0.32 mL, 1.50 mmol) was added to the reaction mixture at -78 °C. After stirring at -78 °C for 1h, the reaction mixture was quenched with water and the biphasic reaction mixture was extracted with diethyl ether (10 mL x 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/ Et_2O 10: 1) to afford the desired product as colorless oil (0.361 g, 98% yield).

R_f value (hexane/ Et_2O 8: 1): 0.65.

$[\alpha]_{\text{D}}^{20} = -17$ ($c = 1.0$, CHCl_3).

^1H NMR (300 MHz, CDCl_3): δ 6.16 (dd, $J = 10.8, 17.4$ Hz, 1H), 5.23 (dd, $J = 1.7, 17.4$ Hz, 1H), 5.10 (dd, $J = 1.7, 10.8$ Hz, 1H), 3.89-3.79 (m, 2H), 2.11-1.89 (m, 3H),

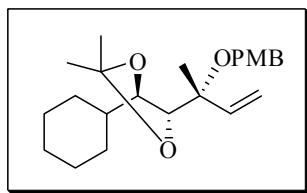
1.66-1.63 (m, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H), 1.22-1.17 (m, 3H), 0.96 (t, $J = 7.9$ Hz, 9H), 0.98-0.93 (m, 2H), 0.62 (q, $J = 7.9$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 142.0 (CH), 113.2 (CH_2), 106.4 (C), 83.6 (CH), 83.3 (CH), 77.4 (C), 35.5 (CH), 31.6 (CH_2), 30.3 (CH_2), 26.9 (CH_2), 26.9 (CH_2), 26.6 (CH_2), 25.7 (CH_3), 25.7 (CH_3), 25.1 (CH_3), 7.2 (CH_2), 6.8 (CH_3).

FTIR (NaCl, neat): ν 2922, 1639, 1379, 1368, 1215, 1249, 872, 743 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{41}\text{O}_3\text{Si}$ (M+1) 369.2825, found 369.2813.

(4*R*,5*R*)-4-Cyclohexyl-5-[(*R*)-2-(4-methoxybenzyloxy)but-3-en-2-yl]-2,2-dimethyl-1,3-dioxolane (101)



To a mixture of DMF (10.0 mL) and **99** (1.27 g, 5.0 mmol) was added NaH (0.36 g, 60%; 9.0 mmol) carefully at 0 °C and the mixture was stirred at the same temperature for 1 h. PMBCl was added dropwise by a syringe and the mixture was slowly warmed to r.t. and stirred for 20 h. Then, saturated aqueous NH_4Cl (50 mL) was added carefully with vigorous stirring, the layers were separated and the aqueous layer was extracted thoroughly with EtOAc (3 \times 50 mL). Then, the combined organic layers were washed with H_2O (80 mL), brine (80 mL), dried (MgSO_4) filtered and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc, 50: 1 to 20: 1) to afford **101** as a pale yellow powder (1.64 g, 88% yield).

R_f value (hexane/EtOAc 4: 1): 0.70.

$[\alpha]_D^{20} = +7.5$ ($c = 1.1$, CHCl_3).

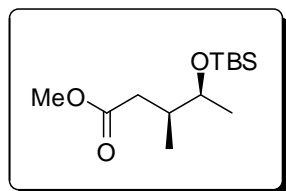
^1H NMR (400 MHz, CDCl_3): δ 7.22 (d, $J = 8.4$ Hz, 1 H), 6.84 (d, $J = 8.4$ Hz, 1 H), 6.19 (dd, $J = 17.6, 5.2$ Hz, 1 H), 5.35 (ddd, $J = 24.0, 10.8, 1.2$ Hz, 1 H), 4.28 (s, 2 H), 3.99 (d, $J = 5.6$ Hz, 1 H), 3.80–3.82 (m, 4 H), 1.48–2.06 (m, 5 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 0.77–1.37 (m, 9 H).

^{13}C NMR (100 MHz, CDCl_3): δ 158.9, 139.5, 131.4, 129.4, 117.8, 113.6, 106.6, 83.2, 82.6, 80.1, 64.3, 55.3, 36.3, 31.4, 30.5, 26.9, 26.5, 25.8, 25.2, 25.1, 20.1.

FTIR (KBr, neat): ν 3007, 2927, 2852, 1612, 1857, 1369, 1053, 767 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{23}\text{H}_{35}\text{O}_4$ ($M + 1$) 375.2519, found 375.2535.

(3*S*,4*S*)-methyl 4-(*tert*-butyldimethylsilyloxy)-3-methylpentanoate (102)



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, (*R*)-Tol-BINAP (0.020 g, 0.03 mmol) and CuI (0.004 g, 0.02 mmol) were stirred in CH_2Cl_2 (2 mL) for 20 minutes, concentrated in *vacuo* and then stirred in *t*-BuOMe (4 mL) till a bright yellow suspension was observed. The mixture was then cooled to -20 °C and MeMgBr (0.83 mL, 3.0 M solution in Et_2O , 2.50 mmol) was added carefully into the reaction mixture. After stirring for 15 minutes, a pre-cooled solution of ester **21** (0.244 g, 1.00 mmol) in *t*-BuOMe (1.2 mL) was added dropwise over 1 h via syringe pump. After stirring at -20 °C for another one and an half hour, the reaction mixture was quenched with MeOH (1 mL), and 1 M NH_4Cl solution (4 mL). The aqueous layer was extracted with Et_2O (15 mL x 3) and the combined

organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/Et₂O 90: 1) to afford the desired product as pale yellow oil (0.164 g, 63% yield; 94% *de*).

R_f value (hexane/Et₂O 8: 1): 0.27.

[α]_D²⁰ = +12 (*c* = 0.65, CHCl₃).

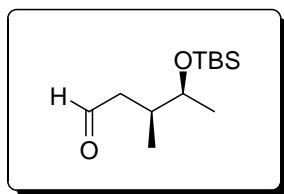
¹H NMR (300 MHz, CDCl₃): δ 3.79-3.76 (m, 1H), 3.66 (s, 3H), 2.48 (dd, *J* = 4.7, 14.5 Hz, 1H), 2.13-2.00 (m, 2H), 1.06 (d, *J* = 6.3 Hz, 3H), 0.88 (d, *J* = 4.9 Hz, 3H) 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ 174.2 (C), 70.6 (CH), 51.4 (CH₃), 37.3 (CH), 37.2 (CH₂), 25.8 (CH₃), 20.0 (CH₃), 18.1 (C), 14.3 (CH₃), -4.3 (CH₃), -5.0 (CH₃).

FTIR (NaCl, neat): ν 2930, 1742, 1381, 1252, 1038 cm⁻¹.

HRMS (ESI) calcd. for C₁₃H₂₉O₃Si (M+1) 261.1886, found 261.1886.

(3*S*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-3-methylpentanal (103**)**



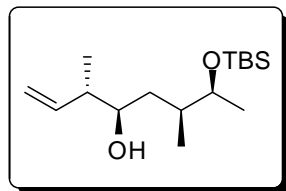
In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, the ester **102** (0.260 g, 1.00 mmol) was dissolved in hexane (4 mL) and cooled to -78 °C. DIBAL-H (pre-cooled to -78°C, 1.1 mL, 1.0 M in heptane, 1.10 mmol) was added carefully over at least 2 portions. After stirring for another 1 h, MeOH (pre-cooled to -78 °C, 0.106 g, 3.30 mmol) was added carefully over 2 portions and stirred for a further 15 minutes till a white suspension was observed. The reaction mixture was then added saturated potassium sodium tartrate solution (5 mL), diluted with Et₂O (5

mL) and warmed to room temperature. The mixture was stirred until a clear biphasic separation was observed. The aqueous layer was extracted with Et₂O (10 mL x 3). The combined organic extracts were washed with saturated NaHCO₃ (15 mL x 2), brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/Et₂O 20: 1) to afford the desired product as pale yellow oil (0.200 g, 87% yield).

R_f value (hexane/Et₂O 8: 1): 0.36.

¹H NMR (400 MHz, CDCl₃): δ 9.76 (m, 1H), 3.80-3.77 (m, 1H), 2.61-2.53 (m, 1H), 2.22-2.17 (m, 2H), 1.06 (d, *J* = 6.3 Hz, 3H), 0.9 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

(3*S*,4*S*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-3,6-dimethyloct-1-en-4-ol (104)



To a round bottom flask equipped with a rubber septum and a magnetic stirrer bar was added KO^tBu (1.5 mL, 1.0 M in THF, 1.50 mmol), dry THF (8 mL) and was allowed to cool to -78 °C. *Trans*-2-butene (0.168 g, 3.00 mmol) was condensed from a gas lecture bottle into the mixture at -78 °C. *n*-Butyllithium (0.94 mL, 1.6 M in hexane, 1.50 mmol) was then added dropwise. After complete addition of *n*-butyllithium, the mixture was stirred at -45 °C for 15 minutes. The resulting orange solution was re-cooled back to -78 °C, and to it was added a solution of (-)-methoxydiisopinocampheylborane (0.949 g, 3.00 mmol) in THF (3 mL). The solution became colorless. The reaction mixture was allowed to stir at -78 °C for 30 minutes

followed by addition of boron trifluoride etherate (1.47 mL, 11.0 mmol). After that, a solution of aldehyde **103** in THF (1 mL) was added via a syringe pump over a period of 30 minutes. The mixture was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 3 h and then treated with 3 N NaOH solution (3 mL, 9 mmol) and 3 mL of 30% H_2O_2 and the content was stirred for 15 minutes at room temperature. The aqueous layer was extracted with Et_2O (15 mL x 3). The combined organic extracts were washed with brine (20 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/ Et_2O 40: 1) to afford the desired product as pale yellow oil (0.221 g, 77% yield; 84% *de*).

R_f value (hexane/ Et_2O 8: 1): 0.23.

$[\alpha]_{\text{D}}^{20} = +7.0$ ($c = 1.0$, CHCl_3).

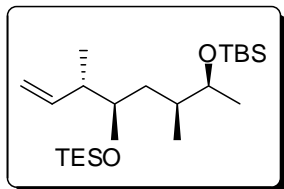
^1H NMR (400 MHz, CDCl_3): δ 5.86-5.77 (m, 1H), 5.10-5.06 (m, 2H), 3.82-3.80 (m, 1H), 3.59-3.56 (m, 1H), 2.23-2.18 (m, 1H), 2.14 (d, $J = 4.9$ Hz, 1H), 1.81-1.78 (m, 1H), 1.67-1.61 (m, 1H), 1.25-1.20 (m, 1H), 1.08 (d, $J = 6.2$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.88 (s, 9H), 0.87 (d, $J = 4.8$ Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 140.5 (CH), 115.6 (CH_2), 73.0 (CH), 71.4 (CH), 43.8 (CH), 37.1 (CH_2), 36.5 (CH), 25.9 (CH_3), 19.2 (CH_3), 18.1 (C), 16.7 (CH_3), 16.4 (CH_3), -4.3 (CH_3), -4.8 (CH_3).

FTIR (NaCl, neat): ν 3381, 2959, 1639, 1377, 1043, 835, 773 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{35}\text{O}_2\text{Si}$ ($\text{M}+1$) 287.2406, found 287.2401.

(5*S*,6*S*,8*R*)-8-((*S*)-but-3-en-2-yl)-10,10-diethyl-2,2,3,3,5,6-hexamethyl-4,9-dioxaspiro[3.10]disiladodecane (105)



To a round bottom flask equipped with a rubber septum and a magnetic stirrer bar was added alcohol **104** (0.287 g, 1.00 mmol), dry pyridine (2 mL) and DMAP (0.024 g, 0.20 mmol). TESCO (0.301 g, 2.00 mmol) was then added and the reaction mixture was allowed to stir for 12 h at room temperature. After stirring for 12 h, the reaction mixture was added saturated NH₄Cl solution (10 mL) and diluted with CH₂Cl₂ (10 mL). The mixture was stirred until a clear biphasic separation was observed. Subsequently, the aqueous layer was extracted with CH₂Cl₂ (10 mL x 3). The combined organic extracts were washed with brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/Et₂O 100: 1) to afford the desired product as colorless oil (0.373 g, 93% yield).

R_f value (hexane): 0.25.

[α]_D²⁰ = +4.0 (*c* = 1.0, CHCl₃).

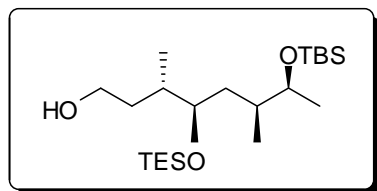
¹H NMR (300 MHz, CDCl₃): δ 5.89-5.77 (m, 1H), 5.03-4.98 (m, 2H), 3.72-3.65 (m, 2H), 2.35-2.30 (m, 1H), 1.60-1.55 (m, 1H), 1.48-1.45 (m, 1H), 1.10-1.20 (m, 1H), 1.08 (d, *J* = 6.2 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.90 (s, 9H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.62 (q, *J* = 7.9 Hz, 6H), 0.05 (s, 3H), 0.04 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 140.4 (CH), 114.6 (CH₂), 74.3 (CH), 71.4 (CH), 42.7 (CH), 37.5 (CH₂), 36.9 (CH), 25.9 (CH₃), 21.0 (CH₃), 18.1 (C), 16.3 (CH₃), 14.6 (CH₃), 7.0 (CH₃), 5.3 (CH₂), -4.1 (CH₃), -4.8 (CH₃).

FTIR (NaCl, neat): ν 3073, 2957, 1640, 1379, 1037, 835 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{48}\text{O}_2\text{Si}_2\text{Na}$ ($\text{M}+\text{Na}$) 423.3091, found 423.3148.

(3*S*,4*R*,6*S*,7*S*)-7-(*tert*-butyldimethylsilyloxy)-3,6-dimethyl-4-(triethylsilyloxy)octan-1-ol (106)



To a round bottom flask equipped with a rubber septum and a magnetic stirrer bar was added alkene **105** (1.202 g, 3.00 mmol). The flask was cooled to 0 °C and hydroboration was initiated by dropwise addition of $\text{BH}_3\text{-THF}$ (1.0 mL, 1.0 M in THF, 1.00 mmol) for 15 minutes. The mixture was stirred at room temperature for 2 h. After stirring for 2 h, the organoborane was dissolved in 5 mL of THF. A solution of 3 N NaOH (1.0 mL, 3.00 mmol) was added followed by the slow addition 1 mL of 30% of hydrogen peroxide aqueous solution. The reaction mixture was heated to 50 °C for 1 h to ensure completion of the oxidation. The mixture was saturated with potassium carbonate. The two phases were separated and extracted with Et_2O (10 mL x 3). The combined organic extracts were washed with brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/ Et_2O 8: 1) to afford the desired product as colorless oil (0.967 g, 77% yield).

R_f value (hexane/ Et_2O 2: 1): 0.18.

$[\alpha]_D^{20} = -5.0$ ($c = 1.0$, CHCl_3).

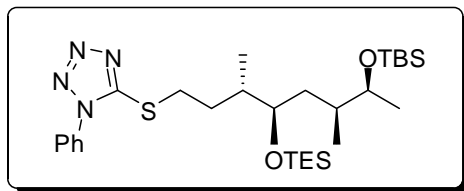
^1H NMR (400 MHz, CDCl_3): δ 3.71-3.64 (m, 3H), 3.53 (m, 1H), 3.06 (m, 1H), 1.76-1.70 (m, 2H), 1.55-1.48 (m, 1H), 1.38 (m, 1H), 1.29-1.25 (m, 2H), 1.07 (d, $J = 6.2$ Hz, 3H), 0.96 (d, 3H), 0.96 (t, $J = 8.1$ Hz, 9H), 0.88 (s, 9H), 0.84 (d, $J = 6.7$ Hz, 3H), 0.62 (q, $J = 7.9$ Hz, 6H), 0.03 (s, 3H), 0.02 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 74.8 (CH), 71.8 (CH), 59.0 (CH_2), 37.2 (CH_2), 37.1 (CH), 33.4 (CH), 32.7 (CH_2), 25.6 (CH_3), 20.5 (CH_3), 18.1 (C), 16.3 (CH_3), 14.3 (CH_3), 6.9 (CH_3), 5.1 (CH_2), -4.2 (CH_3), -4.8 (CH_3).

FTIR (NaCl, neat): ν 3347, 2957, 1379, 1063 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{51}\text{O}_3\text{Si}_2$ (M+1) 419.3377, 419.3369.

5-((3S,4R,6S,7S)-(tert-butyl)dimethylsilyloxy)-3,6-dimethyl-4-(triethylsilyloxy)octylthio)-1-phenyl-1H-tetrazole (107)



In a round bottom flask equipped with a rubber septum and a magnetic stirrer bar, triphenylphosphine (0.393 g, 1.50 mmol) and alcohol **106** (0.419 g, 1.00 mmol) were dissolved in THF (5 mL). DIAD (0.364 g, 1.80 mmol) was next added over 2 minutes at 0 °C resulting in yellow suspension. Subsequently, a solution of 1-phenyl-1H-tetrazole-5-thiol in THF (1 mL) was added over 5 minutes and the reaction mixture was warmed to room temperature. After stirring for 3 h, the reaction was quenched with brine (10 mL) and extracted with Et_2O (10 mL x 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*.

The resulting residue was purified by flash chromatography (hexane/Et₂O 20: 1) to afford the desired product as colorless oil (0.498 g, 86% yield).

R_f value (hexane/Et₂O 8: 1): 0.21.

[α]_D²⁰ = -14 (*c* = 1.1, CHCl₃).

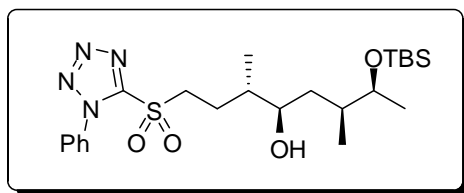
¹H NMR (500 MHz, CDCl₃): δ 7.57-7.55 (m, 5H), 3.68-3.64 (m, 2H), 3.58-3.52 (m, 1H), 3.34-3.30 (m, 1H), 1.88-1.83 (m, 1H), 1.71-1.65 (m, 2H), 1.58-1.55 (m, 1H), 1.41-1.40 (m, 1H), 1.21-1.17 (m, 1H), 1.03 (d, *J* = 6.2 Hz, 3H), 0.99 (d, *J* = 0.66 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.85 (s, 9H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.58 (q, *J* = 7.9 Hz, 6H), 0.02 (s, 3H), -0.02 (s, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 154.4 (C), 133.4 (C), 130.0 (CH), 129.7 (CH), 123.8 (CH), 74.7 (CH), 71.4 (CH), 37.2 (CH), 36.6 (CH₂), 36.4 (CH), 31.9 (CH₂), 29.9 (CH₂), 25.9 (CH₃), 20.5 (CH₃), 18.0 (C), 15.7 (CH₃), 14.7 (CH₃), 7.0 (CH₂), 5.2 (CH₃), -4.1 (CH₃), -4.8 (CH₃).

FTIR (NaCl, neat): ν 2955, 1599, 1500, 1383, 1084, 837, 760 cm⁻¹.

HRMS (ESI) calcd. for C₂₉H₅₅N₄O₂SSi₂ (M+1) 579.3584, found 579.3567.

(3S,4R,6S,7S)-7-(tert-butyldimethylsilyloxy)-3,6-dimethyl-1-(1-phenyl-1H-tetrazol-5-ylsulfonyl)octan-4-ol (108)



In a round bottom flask equipped with rubber a septum and a magnetic stirrer bar, thiol **107** (0.579 g, 1.00 mmol) was dissolved in EtOH (4 mL). A solution of hexaammonium heptamolybdate tetrahydrate (0.024 g, 0.10 mmol) in 2 mL of 30%

hydrogen peroxide was added to the reaction mixture at room temperature and stirred overnight. The reaction was diluted with EtOAc, washed with water and brine. The organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/Et₂O 2: 1) to afford the desired product as yellow oil (0.353 g, 71% yield).

R_f value (hexane/EtOAc 2: 1): 0.30.

[α]_D²⁰ = +4.0 (*c* = 1.0, CHCl₃).

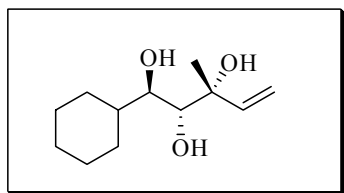
¹H NMR (400 MHz, CDCl₃): δ 7.70-7.68 (m, 2H), 7.63-7.59 (m, 3H), 3.87-3.81 (m, 3H), 3.60-3.55 (m, 1H), 3.14 (d, *J* = 5.4 Hz, 1H), 2.23-2.17 (m, 1H), 1.95-1.86 (m, 2H), 1.70-1.56 (m, 2H), 1.40-1.30 (m, 1H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 5.8 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 153.5 (C), 133.1 (C), 131.4 (CH), 129.7 (CH), 125.1 (CH), 73.1 (CH), 72.5 (CH), 54.7 (CH₂), 37.7 (CH), 36.9 (CH₂), 35.8 (CH), 25.7 (CH₃), 25.3 (CH₂), 18.3 (CH₃), 18.1 (C), 17.7 (CH₃), 16.1 (CH₃), -4.3 (CH₃), -4.8 (CH₃).

FTIR (NaCl, neat): ν 3418, 2957, 1595, 1499, 1339, 1152, 835, 773 cm⁻¹.

HRMS (ESI) calcd. for C₂₃H₄₁N₄O₄SSi (M+1) 496.2618, found 497.2618.

(1*R*,2*R*,3*R*)-1-cyclohexyl-3-methylpent-4-ene-1,2,3-triol (109)



To a stirred solution of **100** (18 mg, 0.05 mmol) in ethanol (1 mL) was added 0.3 N HCl (2 mL). After the reaction was complete, the reaction was diluted with water (10

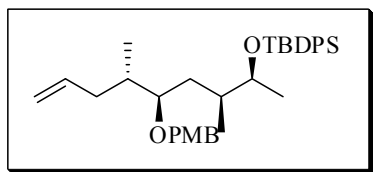
mL) and EtOAc (10 mL). The mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine, dried over MgSO₄, concentrated under reduced pressure. The residue was purified by flash column chromatography.

¹H NMR (400 MHz, MeOD): δ 6.09 (dd, J = 10.9, 17.4 Hz, 1H), 5.35 (dd, J = 2.0, 17.4 Hz, 1H), 5.15 (dd, J = 1.9, 10.9 Hz, 1H), 3.42 (d, J = 10.8 Hz, 1H), 3.34-3.31 (m, 1H), 1.78–1.77 (m, 2H), 1.68–1.66 (m, 3H), 1.44–1.22 (m, 9H).

¹³C NMR (100 MHz, MeOD): δ 140.7, 112.1, 76.8, 76.5, 73.6, 53.4, 39.1, 30.0, 26.6, 26.1, 25.5, 24.4.

HRMS (ESI) calcd. for C₁₂H₂₃O₃ ($M + 1$) 215.1638, found 215.1647.

***tert*-Butyl[(2*S*,3*S*,5*R*,6*S*)-5-(4-methoxybenzyloxy)-3,6-dimethylnon-8-en-2-yloxy]diphenylsilane (**110**)**



Methyltriphenylphosphonium bromide (0.715 g, 2.0 mmol) was dissolved in anhydrous THF (8 mL), and to this solution, cooled to -78 °C, was slowly added *n*-BuLi (1.2 mL of a 1.6 M solution in hexane). After 1 h at -78 °C, aldehyde **122** (0.546 g, 1.0 mmol) in anhydrous THF (5 mL) was added. The mixture was slowly warmed to r.t. H₂O (20 mL) was added and the two phases were separated. The aqueous layer was extracted with Et₂O (3 x 20 mL). The organic layers were collected, and dried (Na₂SO₄), filtered concentrated in vacuo. The crude product was purified by silica gel chromatography (hexane/EtOAc 100:1) to afford **110** as pale yellow oil (80% yield).

R_f value (hexane/EtOAc 4: 1): 0.75.

$[\alpha]_D^{20} = -1.9$ ($c = 1.0$, CHCl_3).

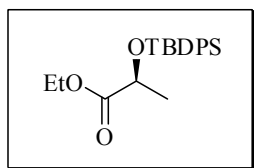
^1H NMR (500 MHz, CDCl_3): δ 7.66–7.69 (m, 4 H), 7.31–7.42 (m, 6 H), 7.18 (d, $J = 8.4$ Hz, 2 H), 6.82 (d, $J = 8.4$ Hz, 2 H), 5.72–5.80 (m, 1 H), 4.98–5.01 (m, 2 H), 4.40 (d, $J = 13.9$ Hz, 1 H), 4.26 (d, $J = 13.9$ Hz, 1 H), 3.75–3.81 (m, 4 H), 3.24–3.26 (m, 1 H), 2.05–2.22 (m, 3 H), 1.71–1.83 (m, 3 H), 1.25–1.32 (m, 2 H), 1.05 (s, 9 H), 0.84–1.02 (m, 9 H).

^{13}C NMR (125 MHz, CDCl_3): δ 159.0, 137.9, 135.0, 134.3, 131.2, 129.5, 129.4, 115.5, 113.8, 81.5, 72.4, 72.3, 77.8, 55.2, 38.5, 37.4, 36.8, 35.4, 32.4, 30.3, 27.0, 19.8, 19.3, 17.2, 15.7, 14.7.

FTIR (KBr, neat): ν 3070, 2960, 2929, 2856, 1514, 1427, 1247, 1111 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{35}\text{H}_{48}\text{O}_3\text{Si} + \text{Na}$ ($\text{M} + \text{Na}$) 567.3270, found 567.3260.

Ethyl (*S*)-2-(*tert*-Butyldiphenylsilyloxy)propanoate (**112**)



To a solution of ethyl (*S*)-(+)-lactate (**111**; 10.40 g, 100.0 mmol) in DMF (200 mL) was added imidazole (10.20 g, 150 mmol), followed by the addition of TBDPSCI (14.5 g, 96.1 mmol) in one portion at 0 °C. The reaction mixture was warmed to r.t. and stirred for 24 h. After cooling to 0 °C, the mixture was poured into aq 0.5 N HCl (50 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were successively washed with H_2O (150 mL) and brine (80 mL), and dried (MgSO_4). The solvent was removed under reduced pressure to give 35.60 g (quant) of crude

silyl ether **112** as a colorless liquid. The material was used in the next step after purification through a pad of silica gel (hexane/EtOAc 10: 1).

R_f value (hexane/EtOAc 4: 1): 0.75.

$[\alpha]_D^{20} = -47.6$ ($c = 1.3$, CHCl_3).

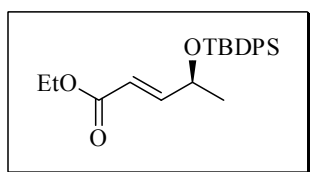
^1H NMR (500 MHz, CDCl_3): δ 7.66–7.67 (m, 4H), 7.35–7.43 (m, 6H), 4.25 (q, $J = 6.5$ Hz, 1H), 4.02 (dq, $J = 7.5, 1.5$ Hz, 2H), 1.37 (d, $J = 6.5$ Hz, 2H), 1.15 (d, $J = 7.5$ Hz, 2H), 1.10 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3): δ 173.8, 135.9, 135.7, 133.6, 133.2, 129.7, 127.6, 127.5, 69.0, 60.6, 26.8, 21.2, 19.2, 14.0.

FTIR (KBr, neat): ν 3070, 2980, 2958, 2893, 2858, 1753 (C=O), 1427, 1136, 1111, 702 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{21}\text{H}_{29}\text{O}_3\text{Si}$ (M+1) 379.1705, found 379.1716.

Methyl (*S,E*)-4-(*tert*-Butyldiphenylsilyloxy)pent-2-enoate (**113**)



In a round-bottomed flask equipped with a stirring bar, ester **112** (19.11 g, 50.0 mmol) was dissolved in hexanes (50 mL) and cooled to -78 °C. DIBAL-H (Aldrich 1 M solution in heptane, 52.5 mL, 52.5 mmol), pre-cooled to -78 °C, was added carefully over several portions. After stirring for another 1.0 h, MeOH (6.5 mL), pre-cooled to -78 °C, was added carefully in one portion and stirred for a further 0.5 h till a white suspension was observed. Methyl (triphenylphosphoranylidene) acetate (25.0 g, 75.0 mmol) was added in one portion, followed by THF (50 mL) and the reaction mixture

was allowed to warm to r.t. and then allowed to reflux for an additional 6 h. The mixture was then cooled to r.t., carefully diluted with EtOAc (100 mL) and sat. aq potassium sodium tartrate (200 mL), and stirred vigorously at r.t. till a clear biphasic separation was observed. The aqueous layer was extracted with EtOAc (2×200 mL) and the combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. The Ph_3PO was removed by filtering through a short silica plug using hexanes. The filtrate was concentrated and purified by flash chromatography (hexanes to 200: 1 hexanes–EtOAc) to afford the desired *E*-enoate **113** as a colorless oil (12.42 g, 65% yield; 81% total yield for the mixture of *E/Z*-isomers, 80: 20).

R_f value (hexane/EtOAc 4: 1): 0.72.

$[\alpha]_D^{20} = -41.8$ ($c = 0.9$, CHCl_3).

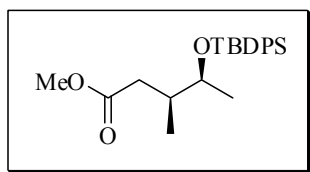
^1H NMR (500 MHz, CDCl_3): δ 7.64–7.71 (m, 4 H), 7.36–7.45 (m, 6H), 6.93 (dd, $J = 15.5, 4.4$ Hz, 1H), 6.93 (dd, $J = 15.5, 1.5$ Hz, 1H), 4.45–4.51 (m, 6H), 1.14 (d, $J = 10.5$ Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3): δ 167.2, 151.8, 135.8, 135.7, 134.0, 133.3, 129.8, 127.6, 127.6, 118.6, 68.6, 51.5, 27.0, 23.3, 19.2.

FTIR (KBr, neat): ν 3070, 2954, 2927, 1703 (C=O), 1427, 1112, 700 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{28}\text{O}_3\text{SiNa}$ ($\text{M}+\text{Na}$) 391.1705, found 391.1729.

Methyl (3*S*,4*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methylpentanoate (**114**)



In a round-bottomed flask equipped with a septum and a stirring bar, (*R*)-Tol-BINAP (0.408 g, 0.6 mmol) and CuI (0.076 g, 0.4 mmol) were stirred in CH₂Cl₂ (10 mL) for 20 min, concentrated in vacuo, and then stirred in *t*-BuOMe (80 mL) till a bright yellow suspension was observed. The mixture was then cooled to -20 °C and MeMgBr (20.0 mL, Aldrich 3.0 M solution in Et₂O, 60.0 mmol) was added carefully. After stirring for 15 min, a solution of *E*-**113** (7.37 g, 20 mmol) in *t*-BuOMe (24 mL) was added dropwise over 10 h via a syringe pump. After stirring at -20 °C for an additional 1 h, the mixture was quenched with MeOH (30 mL) and sat. aq NH₄Cl (100 mL). The aqueous layer was extracted with Et₂O (3 × 100 mL) and the combined organic extracts were dried (Na₂SO₄), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography (hexane/EtOAc 100: 1) to afford the desired product **114** as a colorless oil (4.61 g, 60% yield).

R_f value (hexane/EtOAc 4: 1): 0.73.

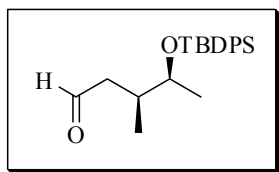
[α]_D²⁰ = -8.4 (*c* = 1.2, CHCl₃).

¹H NMR (500 MHz, CDCl₃): δ 7.66–7.82 (m, 4 H), 7.36–7.44 (m, 6H), 7.79–3.82 (m, 1H), 3.65 (s, 3H), 2.61–2.65 (m, 1H), 2.04–2.16 (m, 2H), 1.07 (s, 9H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 174.1, 135.9, 134.7, 133.9, 129.6, 129.4, 127.6, 127.4, 72.0, 51.4, 51.4, 37.1, 36.8, 27.0, 19.3, 19.1, 14.9.

FTIR (KBr, neat): ν 3070, 2960, 2929, 1737 (C=O), 1280, 1109, 702 cm⁻¹.

HRMS (ESI) calcd. for C₂₃H₃₃O₃Si (*M* + 1) 385.2199, found 385.2206.

(3*S*,4*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methylpentanal (115)

In a round-bottomed flask equipped with a stirring bar, the ester **114** (3.84 g, 10.0 mmol) was dissolved in hexanes (10 mL) and cooled to -78 °C. DIBAL-H (Aldrich 1 M solution in heptane, 11.0 mL, 11.0 mmol), precooled to -78 °C, was added carefully. After stirring for another 1.0 h, the reaction was quenched with sat. aq potassium sodium tartrate (50 mL), warmed to r.t., and stirred vigorously till a clear biphasic separation was observed. The aqueous layer was extracted with EtOAc (2×200 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (hexanes to hexane/EtOAc 50: 1) to afford the desired **115** as a colorless oil (3.00 g, 85% yield).

R_f value (hexane/EtOAc 4: 1): 0.70.

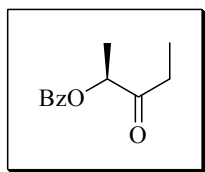
$[\alpha]_{\text{D}}^{20} = -10.5$ ($c = 0.8$, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ 9.73 (s, 1 H), 7.68–7.70 (m, 4 H), 7.38–7.45 (m, 6 H), 3.84–3.86 (m, 1 H), 2.65–2.67 (m, 1 H), 2.18–2.25 (m, 2 H), 1.08 (s, 9 H), 0.97 (d, $J = 6.5$ Hz, 3 H), 0.87 (d, $J = 6.5$ Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ 202.8, 135.9, 135.8, 134.4, 133.8, 129.7, 129.6, 127.6, 127.4, 72.1, 46.2, 34.9, 27.0, 19.2, 18.4, 15.6.

FTIR (KBr, neat): ν 3070, 2959, 2929, 2891, 2858, 1722 (C=O), 1110, 702 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{31}\text{O}_2\text{Si}$ ($M + 1$) 355.2093, found 355.2092.

(S)-3-Oxopentan-2-yl Benzoate (116)

To a cooled ($-20\text{ }^{\circ}\text{C}$) mixture of ethyl (*S*)-lactate (**111**; 8.0 g, 67.6 mmol) and MeON(Me)H·HCl (16.4 g, 168 mmol) in THF (200 mL) was added a 2 M solution of *i*-PrMgCl in Et₂O (168 mL) dropwise over 30 min. The reaction mixture was stirred at $-20\text{ }^{\circ}\text{C}$ for 30 min and at $0\text{ }^{\circ}\text{C}$ for a further 30 min before sat. aq NH₄Cl (500 mL) was added. The mixture was extracted with Et₂O ($4 \times 150\text{ mL}$), followed by CH₂Cl₂ ($4 \times 150\text{ mL}$). The combined organic extracts were dried (MgSO₄), concentrated in vacuo, and the residue was purified by column chromatography (hexane/EtOAc 1: 1) to give the intermediate Weinreb amide (7.19 g, 80% yield) as a colorless oil. To a cooled ($0\text{ }^{\circ}\text{C}$) solution of this amide (2.0 g, 15.0 mmol) in THF (30 mL) was added a 3 M solution of EtMgBr in Et₂O (16 mL) and the reaction mixture was allowed to warm to r.t. After 1 h, saturated aqueous NH₄Cl (80 mL) was added and the mixture was extracted with Et₂O (40 mL), followed by CH₂Cl₂ ($2 \times 40\text{ mL}$). The combined organic extracts were dried (MgSO₄) and concentrated. Then, CH₂Cl₂ (100 mL) was added. To this solution was added Bz₂O (5.11 g, 22.6 mmol), DMAP (0.20 g, 1.64 mmol), and *i*-Pr₂NEt (5.0 mL, 28.6 mmol). After stirring for 14 h, excess Bz₂O was removed by the addition of ethylenediamine (1.0 g, 16.6 mmol). H₂O (80 mL) was added, the mixture extracted with Et₂O ($4 \times 40\text{ mL}$). The combined organic extracts were dried (MgSO₄), and concentrated to an oil. The residue was purified by column chromatography (hexane/EtOAc 5: 1) to afford (*S*)-**116** as a colorless oil (2.17g, 70% yield).

R_f value (hexane/EtOAc 4: 1): 0.52.

$[\alpha]_D^{20} = +24.4$ ($c = 0.6$, CHCl_3). {Lit. $[\alpha]_D^{20} = +25.1$ ($c = 4.6$, CHCl_3)}⁷²

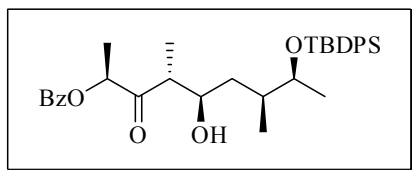
¹H NMR (300 MHz, CDCl_3): δ 8.05–8.07 (m, 2 H), 7.41–7.59 (m, 3 H), 5.33 (q, $J = 7.2$ Hz, 2 H), 2.46–2.68 (m, 2 H), 1.51 (d, $J = 7.0$ Hz, 2 H), 1.07 (t, $J = 7.2$ Hz, 3 H).

¹³C NMR (75.4 MHz, CDCl_3): δ 208.4, 165.8, 133.3, 129.7, 129.4, 128.4, 75.0, 31.4, 16.4, 7.1.

FTIR (KBr, neat): ν 3062, 2981, 2939, 1720 (C=O), 1716 (C=O), 1452, 1269, 1109, 1026, 711 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_3$ ($M + 1$) 207.1013, found 207.1021.

(2*S*,4*R*,5*R*,7*S*,8*S*)-8-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-4,7-dimethyl-3-oxononan-2-yl Benzoate (117**)**



To a stirred solution (-78 °C) of **116** (2.06 g, 10.0 mmol) in Et_2O (40 mL) was added chlorodicyclohexylborane (15.0 mL, 1 M in hexane, 15.0 mmol) and Me_2NEt (1.5 mL, 15 mmol). The mixture was warmed to 0 °C, stirred for 2 h, and then recooled to -78 °C. A solution of aldehyde **115** (4.60 g, 13.0 mmol) in Et_2O (10 mL) was added dropwise over 2 min. After 2 h, the reaction mixture was kept in the freezer (-24 °C) for 20 h. The mixture was warmed to 0 °C and quenched by dropwise addition of MeOH (30 mL), pH 7 phosphate buffer (30 mL), and 35% H_2O_2 (30 mL), and stirred for 1 h at r.t. H_2O (100 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (3×80 mL). The combined organic layers

⁷² Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639.

were washed with brine (60 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The residue was purified by column chromatography (from hexane/EtOAc 50: 1 to 20: 1) to afford alcohol **117** as a colorless solid (4.76 g, 85% yield).

R_f value (hexane/EtOAc 4: 1): 0.48.

[α]_D²⁰ = +9.6 (*c* = 0.9, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 8.11 (d, *J* = 7.6 Hz, 2 H), 7.37–7.69 (m, 13 H), 5.42 (q, *J* = 6.8 Hz, 1 H), 3.82–3.89 (m, 2 H), 2.80 (s, 1 H), 2.76–2.78 (m, 1 H), 1.73–1.95 (m, 2 H), 1.56 (d, *J* = 7.2 Hz, 3 H), 1.24–1.30 (m, 1 H), 1.23 (d, *J* = 7.2 Hz, 3 H), 1.07 (s, 9 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H).

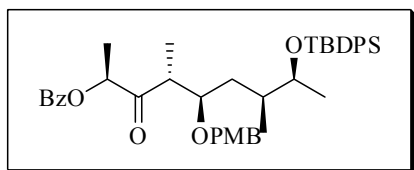
¹³C NMR (75.4 MHz, CDCl₃): δ 211.7, 165.8, 135.9, 135.9, 135.7, 134.4, 133.8, 133.2, 129.7, 129.6, 129.5, 129.5, 128.4, 127.6, 127.4, 74.7, 72.2, 72.0, 48.8, 37.4, 36.4, 27.0, 19.2, 18.8, 16.8, 15.6, 14.4.

FTIR (KBr, neat): ν 3522, 3047, 2962, 2931, 2893, 2856, 1722 (C=O), 1714 (C=O), 1379, 1267, 1111, 702 cm⁻¹.

HRMS (ESI) calcd. for C₃₄H₄₅O₅Si (M + 1) 561.3036, found 561.3011.

(2*S*,4*R*,5*R*,7*S*,8*S*)-8-(*tert*-Butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-

4,7-dimethyl-3-oxononan-2-yl Benzoate (118**)**



Sc(OTf)₃ (30.0 mg, 0.06 mmol, 0.06 equiv) was added to a stirred solution of freshly azeotroped alcohol **117** (0.560, 1.0 mmol, 1.0 equiv) and PMBTCA (0.423g, 1.5 mmol, 1.5 equiv) in THF (20 mL) at 0 °C. After stirring for 12 h, the reaction was

quenched by the addition of aqueous NaHCO₃ (20 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc gradient elution from 50: 1 to 20: 1) to afford PMB ether **118** as a pale yellow oil (0.435 g, 64% yield).

R_f value (hexane/EtOAc 4: 1): 0.62.

[α]_D²⁰ = +15 (*c* = 0.7, CHCl₃).

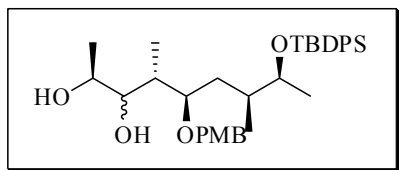
¹H NMR (400 MHz, CDCl₃): δ 8.09 (d, *J* = 7.6 Hz, 2 H), 7.67–7.69 (m, 4 H), 7.56–7.60 (m, 1 H), 7.35–7.48 (m, 8 H), 7.16 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 5.38 (q, *J* = 6.8 Hz, 3 H), 4.21 (d, *J* = 10.8 Hz, 1 H), 4.18 (d, *J* = 10.8 Hz, 1 H), 3.79–3.81 (m, 1 H), 3.77 (s, 3 H), 3.66–3.71 (m, 1 H), 2.99–3.07 (m, 1 H), 1.94 (dt, *J* = 14.4, 4.8 Hz, 1 H), 1.64–1.70 (m, 1 H), 1.44 (d, *J* = 7.2 Hz, 3 H), 1.24–1.33 (m, 2 H), 1.11 (d, *J* = 7.2 Hz, 3 H), 1.05 (s, 9 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ 209.6, 165.7, 159.0, 135.9, 135.8, 134.8, 134.1, 133.2, 130.5, 129.8, 129.4, 129.3, 128.4, 127.6, 127.4, 113.7, 113.5, 79.7, 74.9, 72.4, 72.3, 55.1, 48.3, 36.7, 35.1, 27.0, 19.7, 19.3, 15.8, 15.2, 13.7.

FTIR (KBr, neat): ν 3068, 2962, 2931, 2893, 2858, 1722 (C=O), 1714 (C=O), 1265, 1111, 702 cm⁻¹.

HRMS (ESI) calcd. for C₄₂H₅₂O₆Si+Na (M + Na) 703.3431, found 703.3442.

**(2*S*,4*S*,5*R*,7*S*,8*S*)-8-(*tert*-Butyldiphenylsilyloxy)-5-(4-methoxybenzyloxy)-
4,7-dimethylnonane-2,3-diol (**119**)**



The ester **118** (1.36 g, 2.0 mmol) was dissolved in CH₂Cl₂ (5 mL) and cooled to –78 °C. DIBAL-H (Aldrich 1 M solution in heptane, 6.0 mL, 6.0 mmol), pre-cooled to –78 °C was added dropwise. After stirring for another 1 h, the reaction was quenched with saturated aqueous potassium sodium tartrate (50 mL), warmed to r.t., and stirred vigorously till a clear biphasic separation was observed. The aqueous layer was then extracted with CH₂Cl₂ (3 × 15 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 5: 1) to afford the desired diol **119** as a colorless oil (0.98 g).

R_f value (hexane/EtOAc 4: 1): 0.13 and 0.14.

[α]_D²⁰ = -7.7 (*c* = 1.2, CHCl₃).

¹H NMR (400 MHz, CDCl₃): δ 7.36–7.68 (m, 10 H), 7.29 (d, *J* = 8.4 Hz, 0.68 H), 7.16 (d, *J* = 8.4 Hz, 1.32 H), 6.85 (d, *J* = 8.4 Hz, 0.68 H), 6.81 (d, *J* = 8.4 Hz, 1.32 H), 4.68–4.70 (m, 2 H), 4.27–4.44 (m, 2 H), 3.55–3.58 (m, 1 H), 2.72 (s, 0.33 H), 2.48 (s, 0.67 H), 2.23 (s, 0.67 H), 2.20 (s, 0.33 H), 1.53–1.90 (m, 4 H), 1.11 (d, *J* = 7.0 Hz, 2 H), 1.06 (4) (s, 3 H), 1.05 (7) (s, 6 H), 1.04 (d, *J* = 7.0 Hz, 1 H), 0.97 (d, *J* = 7.0 Hz, 2 H), 0.90–0.93 (m, 5 H), 0.81 (d, *J* = 7.2 Hz, 2 H).

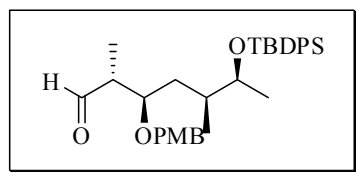
¹³C NMR (100 MHz, CDCl₃): δ 159.3, 159.1, 136.0, 135.9, 134.7, 134.6, 130.4, 130.1, 129.5, 129.4, 128.5, 127.6, 127.5, 127.4, 127.0, 113.8, 113.7, 83.4, 80.2, 76.2, 75.1,

72.6, 72.3, 72.2, 71.0, 68.9, 68.0, 65.3, 55.2 (5), 55.2 (2), 38.6, 37.0, 36.4, 34.6, 33.2, 27.0, 21.0, 20.0, 19.4, 19.3, 18.4, 15.8, 15.5, 14.5, 13.5, 12.0, 11.4.

FTIR (KBr, neat): ν 3417, 3072, 2962, 2989, 1651, 1643, 1247, 1109, 665 cm^{-1} .

HRMS (EI) calcd. for $\text{C}_{35}\text{H}_{51}\text{O}_5\text{Si}$ (M) 579.3506, found 579.3521.

(2*R*,3*R*,5*S*,6*S*)-6-(*tert*-Butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy)-2,5-dimethylheptanal (120)



To a stirred solution (0 °C) of the diol **119** (0.98 g, 1.7 mmol) in MeOH (16 mL) and H_2O (16 mL) was added NaIO_4 (2.16 g, 10.2 mmol) in small portions. After complete addition, the mixture was stirred for 2 h. H_2O (80 mL) was added and the mixture was extracted with Et_2O (4 \times 80 mL). The combined organic layers were washed with brine (80 mL), dried (MgSO_4), filtered, and concentrated in vacuo. The residues was purified by flash column chromatography (hexane/ EtOAc 20:1) to afford aldehyde **120** as a colorless oil (0.83 g, 78% yield over two steps).

R_f value (hexane/ EtOAc 4: 1): 0.58.

$[\alpha]_{\text{D}}^{20} = -26.6$ ($c = 1.3$, CHCl_3).

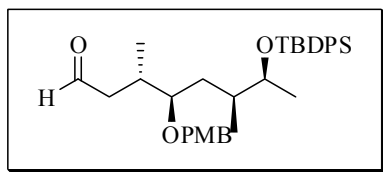
^1H NMR (500 MHz, CDCl_3): δ 9.73 (d, $J = 2.0$ Hz, 2 H), 7.69–7.40 (m, 4 H), 7.37–7.43 (m, 6 H), 7.24 (d, $J = 10.5$ Hz, 2 H), 7.88 (d, $J = 10.5$ Hz, 2 H), 4.49 (d, $J = 13.5$ Hz, 1 H), 4.40 (d, $J = 14.0$ Hz, 1 H), 3.74–3.86 (m, 4 H), 3.64–3.66 (m, 1 H), 2.64–2.686 (m, 1 H), 1.45–1.76 (m, 3 H), 1.28 (m, 3 H), 1.07 (s, 9 H), 0.98 (d, $J = 8.0$ Hz, 3 H), 0.84 (d, $J = 8.5$ Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ 204.7, 159.2, 135.9, 135.8, 1334.9, 134.3, 130.3, 129.5, 129.4, 129.3, 127.5, 113.8, 79.5, 72.8, 71.2, 55.2, 49.3, 40.3, 29.1, 27.0, 26.6, 19.3, 19.2, 15.0, 10.2.

FTIR (KBr, neat): ν 3062, 2960, 2931, 2856, 1722 (C=O), 1514, 1247, 1037, 740 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{45}\text{O}_4\text{Si}$ ($M + 1$) 533.3087, found 533.3092.

(3*S*,4*R*,6*S*,7*S*)-7-(*tert*-Butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)-3,6-dimethyloctanal (122**)**



Methoxymethyltriphenylphosphonium chloride (0.771 g, 2.25 mmol) was dissolved in anhydrous THF (8 mL) and cooled to 0 °C. The solution was slowly added $\text{LiN}(\text{SiMe}_3)_2$ (2.1 mL of a 1 M solution in THF). After stirring 1 h at 0 °C, aldehyde **120** (0.532 g, 1.0 mmol) in anhydrous THF (5 mL) was added. After stirring the mixture overnight at r.t., H_2O (10 mL) was added and the two phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL), and the combined organic layers were collected, dried (MgSO_4), filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexane/ EtOAc 100:1) to give the methyl ether **91**. The product was then dissolved in EtOAc (4 mL) followed by a solution of aqueous 6 N HCl (2 mL). The mixture was stirred at r.t. until the disappearance of **121** as monitored by TLC and then saturated aqueous NaHCO_3 (10 mL) was added. The organic phase was separated, and the aqueous layer was extracted several times with EtOAc (3×20 mL). The combined organic layers were

collected and dried (Na_2SO_4), filtered and evaporated to give crude aldehyde **122**. The residue was purified by flash column chromatography (hexane/EtOAc 100: 1) to afford aldehyde **122** as a colorless oil (63% yield over two steps).

R_f value (hexane/EtOAc 4: 1): 0.59.

$[\alpha]_D^{20} = -16.7$ ($c = 0.5$, CHCl_3).

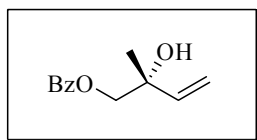
^1H NMR (500 MHz, CDCl_3): δ 9.64 (s, 1 H), 7.64–7.67 (m, 4 H), 7.35–7.43 (m, 6 H), 7.16 (d, $J = 8.5$ Hz, 2 H), 6.83 (d, $J = 8.5$ Hz, 2 H), 4.32 (d, $J = 11.0$ Hz, 1 H), 4.28 (d, $J = 11.0$ Hz, 1 H), 3.76–3.80 (m, 4 H), 3.15–3.18 (m, 1 H), 2.17–2.36 (m, 3 H), 1.66–1.71 (m, 1 H), 1.32–1.40 (m, 2 H), 0.95 (s, 9 H), 0.941 (d, $J = 6.5$ Hz, 3 H), 0.940 (d, $J = 6.5$ Hz, 3 H), 0.89 (d, $J = 7.0$ Hz, 3 H).

^{13}C NMR (125 MHz, CDCl_3): δ 202.4, 159.0, 135.9, 135.8, 134.7, 134.2, 130.6, 129.6, 129.4, 129.3, 127.5, 127.3, 113.6, 80.9, 72.11, 71.0, 55.2, 46.6, 36.7, 33.1, 31.1, 27.0, 19.7, 19.3, 16.5, 15.3.

FTIR (KBr, neat): ν 2958, 2929, 2856, 1722 (C=O), 1247 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{34}\text{H}_{46}\text{O}_4\text{Si} + \text{Na}$ ($M + \text{Na}$) 569.3063, found 569.3083.

(*R*)-2-hydroxy-2-methylbut-3-enyl benzoate (**123**)



To a stirred solution of **129** (1.02 g, 3.47 mmol) in dichloromethane (65 mL) and pH 7.0 buffer (7 mL) was added DDQ (3.16 g, 13.9 mmol) at room temperature. After stirring for 4 h at 40 °C, the reaction mixture was allowed to cool to room temperature. Saturated NaHCO_3 (55 mL) was added and stirred rigorously for 2 h and the mixture was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were

washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (hexane/EtOAc 5:1 to afford the desired product **123** as colourless oil (0.57 g, 79% yield).

$[\alpha]_D^{20} = +17.5$ ($c = 1.0$, CHCl_3).

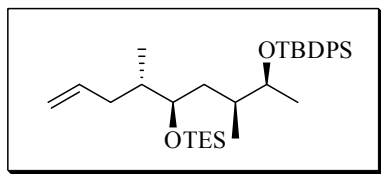
^1H NMR (300 MHz, CDCl_3): δ 8.05-8.02 (m, 2H), 7.59-7.54 (m, 1H), 7.46–7.41 (m, 2H), 5.99 (dd, $J = 10.8, 17.1$ Hz, 1H), 5.40 (dd, $J = 0.8, 17.2$ Hz, 1H), 5.19 (dd, $J = 0.6, 10.8$ Hz, 1H), 4.31 (d, $J = 11.1$ Hz, 1H), 4.24 (d, $J = 11.1$ Hz, 1H), 2.31 (s, 1H), 1.39 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 166.5 (C), 141.3 (CH), 133.2 (CH), 129.8 (C), 129.6 (CH), 128.4 (CH), 114.2 (CH_2), 72.6 (CH_2), 71.1 (CH), 24.6 (CH_3).

FTIR (NaCl, neat): ν 3435, 1713, 1694, 1601, 1452, 1275, 1115, 1026, 928, 710 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{15}\text{O}_3$ ($M + 1$) 207.1021, found 207.1021.

(5*S*,6*S*,8*R*)-10,10-diethyl-2,2,5,6-tetramethyl-8-((*S*)-pent-4-en-2-yl)-3,3-diphenyl-4,9-dioxo-3,10-disiladodecane (124)



To a round bottom flask equipped with a rubber septum and a magnetic stirrer bar was added alcohol **130** (0.424 g, 1.00 mmol), dry pyridine (2 mL) and DMAP (0.024 g, 0.20 mmol). TESCOI (0.301 g, 2.00 mmol) was then added and the reaction mixture was allowed to stir for 12 h at room temperature. After stirring for 12 h, the reaction mixture was added saturated NH_4Cl solution (10 mL) and diluted with CH_2Cl_2 (10

mL). The mixture was stirred until a clear biphasic separation was observed. Subsequently, the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were washed with brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/ Et_2O 100: 1) to afford the desired product as colorless oil (0.485 g, 90% yield).

R_f value (hexane/ EtOAc 4: 1): 0.72.

$[\alpha]_D^{20} = -17.5$ ($c = 0.79$, CHCl_3).

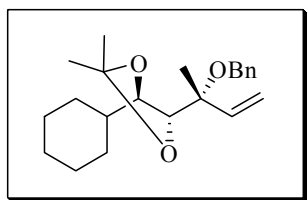
^1H NMR (400 MHz, CDCl_3): δ 7.73–7.62 (m, 4H), 7.43–7.35 (m, 6H), 5.80–5.68 (m, 1H), 5.02–4.96 (m, 2H), 3.81–3.59 (m, 2H), 2.10–1.96 (m, 1H), 1.85–1.71 (m, 3H), 1.29–1.18 (m, 2H), 1.07 (s, 9H), 0.90–0.84 (m, 18H), 0.60–0.84 (m, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 138.2, 136.0, 136.0, 135.1, 134.3, 129.5, 129.3, 127.5, 127.4, 115.2.

FTIR (NaCl, neat): ν 2959, 1639, 1589, 1458, 1427 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{55}\text{O}_2\text{Si}$ ($M + 1$) 511.3980, found 511.3971.

(4*R*,5*R*)-4-((*R*)-2-(benzyloxy)but-3-en-2-yl)-5-cyclohexyl-2,2-dimethyl-1,3-dioxolane (125)



To a stirred solution of **96** (3.59 g, 14.1 mmol) in THF (30 mL) was carefully added sodium hydride (0.68 g, 60% dispersion in mineral oil, 28.2 mmol) at 0 °C. After stirring for 1 h at room temperature, benzyl bromide (2.54 mL, 21.2 mmol) was added

and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residual crude product was purified by flash column chromatography (hexane/EtOAc 50: 1) to afford the desired product **125** as white solid (4.76 g, 98% yield).

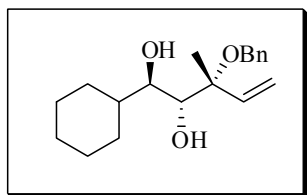
$[\alpha]_{\text{D}}^{20} = -0.5$ ($c = 0.61$, CHCl_3).

^1H NMR (300 MHz, CDCl_3): δ 7.31-7.24 (m, 5H), 6.19 (dd, $J = 11.0, 17.6$ Hz, 1H), 5.39 (dd, $J = 1.3, 11.0$ Hz, 1H), 5.32 (dd, $J = 1.3, 17.6$ Hz, 1H), 4.35 (s, 2H), 4.00 (d, $J = 5.7$ Hz, 1H), 3.83 (dd, $J = 5.6, 9.8$ Hz, 1H), 2.07-1.51 (m, 6H), 1.44 (s, 3H), 1.42 (s, 3H), 1.30 (s, 3H), 1.18-0.74 (m, 5H).

^{13}C NMR (75 MHz, CDCl_3): δ 139.3 (CH), 128.1 (CH), 127.9 (CH), 127.1 (C), 117.9 (CH₂), 106.6 (CH), 83.2 (CH), 82.6 (CH), 64.7 (C), 36.3 (CH), 31.4 (CH₂), 30.4 (CH₂), 26.9 (CH₃), 26.5 (CH₃), 25.8 (CH₂), 25.2 (CH₂), 25.0 (CH₂), 20.0 (CH₃).

HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{33}\text{O}_3$ ($\text{M}+1$) 345.2430, found 345.2414.

(1R,2R,3R)-3-(benzyloxy)-1-cyclohexyl-3-methylpent-4-ene-1,2-diol (126)



1 N HCl solution (25 mL) was added to **125** (1.72 g, 5.0 mmol) in ethanol (20 mL), and the reaction was allowed to stir at room temperature overnight. The reaction mixture was quenched with water (10 mL) and ethanol was then removed under reduced pressure. The remaining aqueous layer was extracted with ethyl acetate (3 x

10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (hexane/EtOAc 5: 1) to afford the desired product **126** as white solid (1.37 g, 90% yield).

$$[\alpha]_{\text{D}}^{20} = -23.1 \text{ (} c = 1.11, \text{CHCl}_3 \text{)}$$

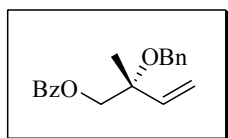
^1H NMR (300 MHz, CDCl_3): δ 7.36-7.25 (m, 5H), 6.09 (dd, $J = 11.1, 17.7$ Hz, 1H), 5.49 (dd, $J = 0.9, 11.1$ Hz, 1H), 5.39 (dd, $J = 0.9, 17.7$ Hz, 1H), 4.70 (s, OH), 4.44 (s, 2H), 3.58-3.47 (m, 2H), 3.35 (s, 1H), 1.88-1.58 (m, 6H), 1.53 (s, 3H), 1.47-1.11 (m, 5H);

^{13}C NMR (75 MHz, CDCl_3): δ 139.1 (CH), 128.5 (CH), 127.7 (CH), 127.6 (C), 119.3 (CH_2), 82.7 (CH), 75.2 (C), 65.1 (CH_2), 59.7 (CH), 39.4 (CH), 30.2 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 24.8 (CH_2), 18.3 (CH_3).

FTIR (NaCl, neat): 3410, 2928, 2855, 1643, 1452, 1215, 1049, 754, 665 cm^{-1}

HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{29}\text{O}_3$ (M+1) 305.2117, found 305.2116.

(R)-2-(benzyloxy)-2-methylbut-3-enyl benzoate (129)



To a stirred solution of **126** (1.37 g, 4.50 mmol) in MeOH (25 mL) and H_2O (25 mL) was carefully added NaIO_4 (8.66 g, 40.5 mmol) at 0 $^\circ\text{C}$. After stirring for 3 h at room temperature, the reaction mixture was quenched with water (20 mL) and stirred rigorously for 5 min. MeOH was selectively removed and the remaining aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts

were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

NaBH₄ (0.19 g, 5.00 mmol) was added slowly to the intermediate aldehyde **127** in MeOH (5 mL) 0 °C and the reaction was stirred for 2 h at room temperature. The reaction mixture was then quenched with water (2 mL) and acetone (2 mL). MeOH was selectively removed and the remaining aqueous layer was extracted with diethyl ether (3 x 5 mL). The combine organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The intermediate was used in the following reaction without further purification.

Benzoic anhydride (1.53 g, 6.80 mmol) was added to a stirred solution of the intermediate alcohol **128**, DMAP (56 mg, 0.46 mmol) and *N*-ethyl diisopropylamine (1.59 mL, 9.00 mmol) in dichloromethane (25 mL) uner N₂ atmosphere at room temperature. The reaction mixture was stirred overnight and then concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (hexane/EtOAc 20: 1) to afford the desired product **129** as colourless oil (1.02 g, 77% yield over 3 steps).

$$[\alpha]_D^{20} = -0.3 \text{ (} c = 1.07, \text{CHCl}_3 \text{)}$$

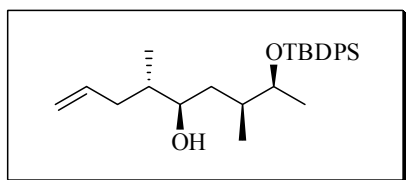
¹H NMR (300 MHz, CDCl₃): δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.43 (dd, *J* = 7.8, 15.2 Hz, 2H), 7.38-7.19 (m, 5H), 5.98 (dd, *J* = 11.1, 17.7 Hz, 1H), 5.38 (d, *J* = 17.7 Hz, 1H), 5.37 (dd, *J* = 1.2, 11.1 Hz, 1H), 4.51 (s, 2H), 4.39 (s, 2H), 1.49 (s, 3H)

¹³C NMR (75 MHz, CDCl₃): δ 166.3 (C), 139.5 (CH), 139.2 (C), 133.0 (CH) 130.1 (C), 129.6 (CH), 128.4 (CH), 128.3 (CH), 127.2 (CH), 117.1 (CH₂), 69.3 (C), 64.9 (CH₂), 20.4 (CH₃).

FTIR (NaCl, neat): 3030, 2984, 2938, 1722, 1600, 1452, 1273, 1113, 1026, 932, 712 cm^{-1}

HRMS (ESI) calcd. for $\text{C}_{19}\text{H}_{21}\text{O}_3$ (M+1) 297.1491, found 297.1503.

(4*S*,5*R*,7*S*,8*S*)-8-(*tert*-butyldiphenylsilyloxy)-4,7-dimethylnon-1-en-5-ol (130**)**



To a stirred solution of **110** (0.545 mg, 1.00 mmol) in dichloromethane (20 mL) and pH 7.0 buffer (1.75 mL) was added DDQ (0.909 g, 4.00 mmol) at room temperature. After stirring for 1 h at 40 °C, the reaction mixture was allowed to cool to room temperature. Saturated NaHCO_3 (15 mL) was added and stirred rigorously for 2 h and the mixture was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (hexane/EtOAc 5:1 to afford the desired product **130** as colourless oil (0.395 g, 93% yield).

R_f value (hexane/EtOAc 4: 1): 0.53.

$[\alpha]_D^{20} = -3.4$ ($c = 0.89$, CHCl_3).

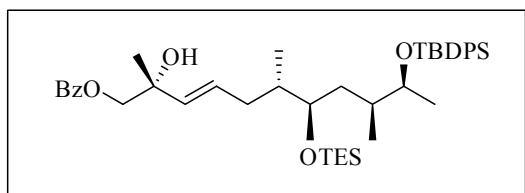
^1H NMR (400 MHz, CDCl_3): δ 7.67 (d, $J = 7.4$ Hz, 4H), 7.45–7.35 (m, 6H), 5.85–5.75 (m, 1H), 5.04–4.99 (m, 2H), 3.86–3.81 (m, 1H), 3.60–3.57 (m, 1H), 2.33–2.30 (m, 1H), 1.96–1.70 (m, 3H), 1.31–1.25 (m, 2H), 1.06 (s, 9H), 0.92 (d, $J = 6.3$ Hz, 3H), 0.88 (d, $J = 6.9$ Hz, 3H), 0.85 (d, $J = 7.0$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 137.7, 136.0, 135.9, 134.5, 133.8, 129.7, 129.6, 127.6, 127.5, 115.8, 73.7, 73.2, 38.8, 36.8, 36.4, 36.4, 27.1, 19.2, 18.2, 17.6, 15.5.

FTIR (NaCl, neat): ν 3398, 3072, 2962, 2932, 1428, 1109 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{41}\text{O}_2\text{Si}$ ($M + 1$) 425.2877, found 425.2876.

(2*R*,6*S*,7*R*,9*S*,10*S*,*E*)-10-(*tert*-butyldiphenylsilyloxy)-2-hydroxy-2,6,9-trimethyl-7-(triethylsilyloxy)undec-3-enyl benzoate (131**)**



To a solution of **124** (53.8 mg, 0.10 mmol, 1.0 equiv) and allylic alcohol **123** (24.7 mg, 0.12 mmol, 1.2 equiv) in $\text{CF}_3\text{C}_6\text{H}_5$ (5.2 mL) was added the 2nd generation Hoveyda–Grubbs catalyst (12.7 mg, 0.02 mmol) and the mixture was heated at reflux (85 °C) for 5 h under N_2 . The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane/EtOAc, 100: 1 to 20: 1) to afford **131** as colorless oil (47 mg, 65% yield).

R_f value (hexane/EtOAc 4: 1): 0.35.

$[\alpha]_{\text{D}}^{20} = -16.2$ ($c = 0.6$, CHCl_3).

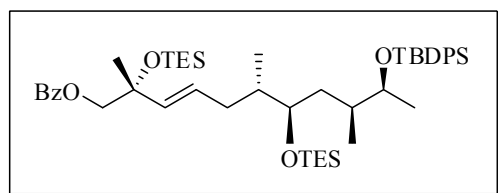
^1H NMR (400 MHz, CDCl_3): δ 8.05 (d, $J = 7.68$, 2H), 7.68–7.66 (m, 4H), 7.58–7.55 (m, 1H), 7.45–7.33 (m, 8H), 5.74–5.67 (m, 1H), 5.51 (d, $J = 15.6$ Hz), 4.27 (d, $J = 10.8$ Hz, 1H), 4.21 (d, $J = 11.2$ Hz, 1H), 3.79–3.77 (m, 1H), 3.57–3.56 (m, 1H), 2.10–2.07 (m, 2H), 1.79–1.69 (m, 2H), 1.52 (m, 2H), 1.39 (s, 3H), 1.04 (s, 9H), 0.96–0.88 (m, 15H), 0.81 (d, $J = 6.8$ Hz, 3H), 0.52 (q, $J = 7.9$ Hz, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 166.5 (C), 135.9 (CH), 135.9 (CH), 135.0 (C), 134.3 (C), 134.0 (CH), 133.1 (CH), 130.0 (CH), 130.0 (C), 129.6 (CH), 129.5 (CH), 129.4 (CH), 128.4 (CH), 127.5 (CH), 127.3 (CH), 74.9 (C), 72.5 (CH_2), 72.1 (CH), 71.6 (CH), 37.9 (CH), 37.1 (CH_2), 35.7 (CH_2), 34.0 (CH), 29.7 (CH_3), 27.1 (CH_3), 25.1 (CH_3), 19.8 (C), 19.4 (CH_3), 15.3 (CH_3), 7.0 (CH_3), 5.2 (CH_2).

FTIR (NaCl, neat): ν 3420, 2959, 1717, 1636, 1456, 1379, 1271 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{43}\text{H}_{64}\text{O}_5\text{Si}_2\text{Na}$ ($M + 23$) 739.4186, found 739.4190.

(2R,6S,7R,9S,10S,E)-10-(tert-butyl-diphenylsilyloxy)-2,6,9-trimethyl-2,7-bis(triethylsilyloxy)undec-3-enylbenzoate (132)



To a round bottom flask equipped with a rubber septum and a magnetic stirrer bar was added alcohol **131** (143 mg, 0.20 mmol) and dry pyridine (1 mL). The mixture was then cooled to -78 $^{\circ}\text{C}$. TESOTf (274 mg, 1.00 mmol) was then added and the reaction mixture was allowed to stir for 16 h at -78 $^{\circ}\text{C}$. After stirring for 16 h, the reaction mixture was added saturated NH_4Cl solution (10 mL) and diluted with CH_2Cl_2 (10 mL). The mixture was stirred until a clear biphasic separation was observed. Subsequently, the aqueous layer was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were washed with brine (15 mL x 1) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography (hexane/ Et_2O 100: 1) to afford the desired product as colorless oil (149 mg g, 90% yield).

R_f value (hexane/EtOAc 4: 1): 0.70.

$[\alpha]_D^{20} = -21.1$ ($c = 0.86$, CHCl_3).

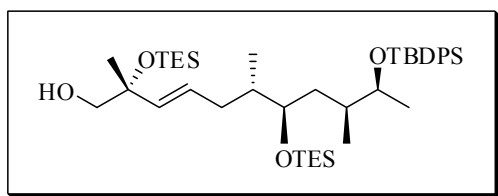
^1H NMR (400 MHz, CDCl_3): δ 8.04 (d, $J = 7.3$ Hz, 2H), 7.68–7.52 (m, 4H), 7.43–7.42 (m, 1H), 7.41–7.33 (m, 8H), 5.67–5.51 (m, 2H), 4.16–4.15 (m, 2H), 3.79–3.76 (m, 1H), 3.68–3.55 (m, 1H), 2.06–2.03 (m, 1H), 1.76–1.67 (m, 2H), 1.56–1.52 (m, 1H), 1.41 (s, 3H), 1.25–1.04 (m, 2H), 1.03 (s, 9H), 0.95–0.77 (m, 27H), 0.62–0.54 (m, 12H).

^{13}C NMR (100 MHz, CDCl_3): δ 136.0, 136.0, 135.9, 135.1, 132.8, 129.7, 129.6, 129.5, 129.4, 128.3, 127.5, 127.4, 127.3, 75.0, 73.9, 72.4, 72.0, 38.3, 37.2, 35.7, 34.4, 27.1, 25.0, 20.1, 19.4, 15.2, 15.1, 7.0, 6.6, 5.2.

FTIR (NaCl, neat): ν 2957, 1724, 1630, 1458, 1271 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{49}\text{H}_{78}\text{O}_5\text{Si}_3\text{Na}$ ($M + 23$) 853.5067, found 853.5055.

(2R,6S,7R,9S,10S,E)-10-(tert-butyl-diphenylsilyloxy)-2,6,9-trimethyl-2,7-bis(triethylsilyloxy)undec-3-en-1-ol (133)

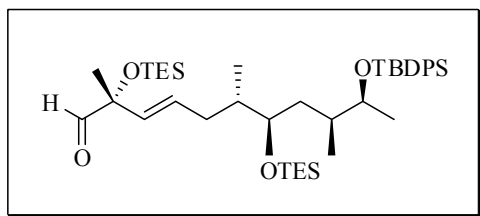


The ester **132** (125 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to -78 °C. DIBAL-H (Aldrich 1 M solution in heptane, 0.45 mL, 0.45 mmol), pre-cooled to -78 °C was added dropwise. After stirring for another 1 h, the reaction was quenched with saturated aqueous potassium sodium tartrate (15 mL), warmed to r.t., and stirred vigorously till a clear biphasic separation was observed. The aqueous layer was then extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were

dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (hexane/EtOAc 10: 1) to afford the desired alcohol **133** as colorless oil (93 mg, 86% yield). The alcohol was used in the following reaction without further spectroscopic analyzing.

R_f value (hexane/EtOAc 4: 1): 0.52.

(2*R*,6*S*,7*R*,9*S*,10*S*,*E*)-10-(*tert*-butyldiphenylsilyloxy)-2,6,9-trimethyl-2,7-bis(triethylsilyloxy)undec-3-enal (E**)**



To a solution of alcohol **133** (90 mg, 0.123 mmol) in dichloromethane (3 mL) was added Dess-Martin periodinane (78 mg, 0.185 mmol, 1.5 equiv.) at 0 °C. The reaction was allowed to proceed for 0.5 hour at room temperature before quenching with a pre-formed mixture of saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (5 mL) and saturated NaHCO_3 solution (5 mL). Upon turning to a colourless solution, the aqueous layer was extracted with diethyl ether (3×10 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL) and dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography (Hexane/EtOAc 12: 1) and the aldehyde **E** was obtained as colourless oil (78 mg, 87% yield).

R_f value (hexane/EtOAc 4: 1): 0.53.

$[\alpha]_D^{20} = +3.86$ ($c = 1.0$, CHCl_3).

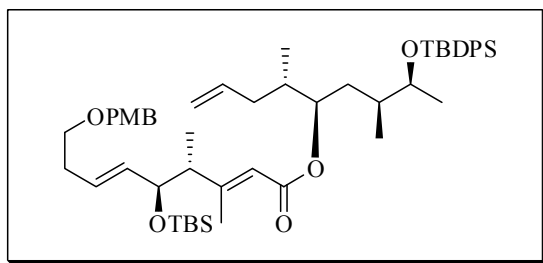
^1H NMR (400 MHz, CDCl_3): δ 9.35 (s, 1H), 7.71–7.69 (m, 4H), 7.44–7.28 (m, 6H), 5.82–5.70 (m, 1H), 5.32–5.26 (m, 1H), 3.81–3.80 (m, 1H), 3.61–3.59 (m, 1H), 2.30–1.96 (m, 4H), 1.42–1.28 (m, 5H), 1.07 (s, 9H), 1.00–0.91 (m, 27H), 0.65–0.55 (m, 12H).

^{13}C NMR (100 MHz, CDCl_3): δ 200.6, 136.0, 135.9, 133.2, 130.8, 129.5, 129.5, 129.4, 127.5, 127.5, 127.3, 80.2, 74.9, 72.5, 53.4, 35.5, 34.2, 29.7, 27.1, 23.4, 18.9, 18.4, 15.6, 15.3, 7.0, 6.6, 5.3, 1.0.

FTIR (NaCl, neat): ν 2957, 1732, 1628, 1460, 1427 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{42}\text{H}_{73}\text{O}_4\text{Si}_3$ ($M + 1$) 725.4707, found 725.4710.

(2E,4R,5S,6E)-((4S,5R,7S,8S)-8-(*tert*-butyldiphenylsilyloxy)-4,7-dimethylnon-1-en-5-yl) 5-(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-3,4-dimethylnona-2,6-dienoate (136)



To a stirred solution of acid **89** (82.0 mg, 0.184 mmol) in toluene (5.5 mL) was added Et_3N (93.3 mg, 0.92 mmol) and 2, 4, 6-trichlorobenzoylchloride (47.7 mg, 0.195 mmol) at room temperature. After 2 h at room temperature, a solution of alcohol **130** (78.1 mg, 0.184 mmol) and DMAP (60 mg, 0.50 mmol) in toluene (3.0 mL). After 12 h at room temperature, the mixture was quenched with saturated NaHCO_3 and diluted with Et_2O , the organic layer was washed with H_2O , brine, dried over MgSO_4 and concentrated under reduced pressure. The resulting residue was purified by flash

column chromatography (hexane/EtOAc 20: 1) to afford **136** as colourless oil (143 mg, 91% yield).

R_f value (hexane/EtOAc 4: 1): 0.69.

$[\alpha]_D^{20} = -11.1$ ($c = 0.81$, CHCl_3).

^1H NMR (300 MHz, CDCl_3): δ 7.67 (dd, $J = 1.7, 6.2$ Hz, 4H), 7.42–7.34 (m, 6H), 7.25 (d, $J = 6.9$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.70–5.67 (m, 2H), 5.65–5.03 (m, 1H), 5.38 (dd, 1H), 5.00–4.96 (m, 2H), 4.90–4.31 (m, 1H), 4.43 (s, 2H), 3.95–3.93 (m, 1H), 3.88–3.81 (m, 1H), 3.80 (s, 3H), 3.47 (t, $J = 6.75$ Hz, 2H), 2.36–2.32 (m, 3H), 2.25–2.21 (m, 2H), 2.11 (s, 3H), 1.92–1.68 (m, 4H), 1.54–1.49 (m, 1H), 1.06 (s, 9H), 0.93 (d, $J = 3.0$ Hz, 3H), 0.91 (d, $J = 2.1$ Hz, 3H), 0.87 (d, $J = 6.9$ Hz, 3H), 0.84 (d, $J = 6.9$ Hz, 3H), 0.81 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (75 MHz, CDCl_3): δ 166.6, 161.7, 159.1, 137.3, 135.9, 135.9, 135.0, 134.2, 133.7, 130.5, 129.5, 129.4, 129.3, 129.0, 127.5, 127.3, 117.3, 115.8, 113.7, 76.6, 75.7, 72.6, 72.2, 69.5, 55.2, 50.6, 37.6, 36.3, 36.2, 32.6, 29.4, 27.1, 25.8, 19.5, 19.3, 18.0, 16.6, 15.5, 15.2, 1.00, -3.8, -5.1.

FTIR (NaCl, neat): ν 2960, 2931, 1732, 1623, 1514, 1470, 1249 cm^{-1} .

HRMS (ESI) calcd. for $\text{C}_{52}\text{H}_{79}\text{O}_6\text{Si}_2$ ($M + 1$) 855.5428, found 855.5415.

Appendix

LIST OF PUBLICATIONS**International Refereed Papers:**

1. Chin Yen Jin, Wang Shun Yi, Loh Teck Peng, *Org. Lett.* **2009**, *11*, 3674.
Synthesis of Iriomoteolide-1a C13-C23 Fragment via Asymmetric Conjugate Addition and Julia-Kocienski Coupling Reaction.
2. Wang Shun Yi, Chin Yen Jin, Loh Teck Peng, *Synthesis*, **2009**, 3557 (invited paper).
Synthesis of C13-C23 Fragment of Iriomoteolide-1a.
3. Wang Shun Yi, Song Ping, Chin Yen Jin, Loh Teck Peng. *Submitted for Publication.*
A General Strategy for the Introduction Stereogenic Centers Bearing Methyl Group: Total Synthesis of Phytophthora Mating Hormone α 1.

Conference papers:

4. Chin Yen Jin, Loh Teck Peng. **A Forefront Study of Chemical Functionalization in Living Cell: Stereoselective Indium-Mediated Allylation Reaction in Aqueous Media.** Abstracts of Papers, PERCH-CIC Congress V, Pattaya, Thailand, 6 – 9 May 2007.

5. Chin Yen Jin, Loh Teck Peng. **A Forefront Study of Chemical Functionalization in Living Cell: Small Peptide-Catalyzed Direct Asymmetric Aldol Reaction**. Abstracts of Papers, International Symposium on Catalysis and Fine Chemical 2007, Singapore, 16 – 21 December 2007.
6. Chin Yen Jin, Loh Teck Peng. **A Forefront Study of Chemical Functionalization in Living Cell: Small Peptide-Catalyzed Direct Asymmetric Aldol Reaction**. Abstracts of Papers, NTU-Waseda Joint Symposium in Chemical and Lifesciences, Singapore, 22 March 2008.
7. Chin Yen Jin, Wang Shun Yi, Loh Teck Peng. **Synthesis of Iriomoteolide-1a C13-C23 Fragment via Asymmetric Conjugate Addition and Julia-Kocienski Coupling Reaction**. Abstracts of Papers, NTU-Kyushu University Joint Symposium, Singapore, 28 January 2010.
8. Chin Yen Jin, Wang Shun Yi, Loh Teck Peng. **Synthesis of Iriomoteolide-1a C13-C23 Fragment via Asymmetric Conjugate Addition and Julia-Kocienski Coupling Reaction**. Abstracts of Papers, 239th American Chemical Society National Meeting & Exposition, San Francisco, California, United State, 21 – 25 March 2010.
9. Chin Yen Jin, Wang Shun Yi, Loh Teck Peng. **Synthesis of Iriomoteolide-1a C13-C23 Fragment via Asymmetric Conjugate Addition and Julia-Kocienski Coupling Reaction**. Abstracts of Papers, 6th Asian-European

Symposium on Metal Mediated Efficient Reactions, Singapore, 7 – 9 June
2010.