STUDIES TOWARDS THE TOTAL SYNTHESIS OF VIRIDENOMYCIN

MOSA, FATHIA,A.

STUDIES TOWARDS THE TOTAL SYNTHESIS OF VIRIDENOMYCIN

Fathia A. Mosa

A Thesis submitted to the University of Durham for the degree of Doctor of Philosophy

Department of Chemistry

2011

Supervisor: Prof. Andrew Whiting

Abstract

Viridenomycin is a very important antibiotic, which showed strong inhibitory activity against gram-positive bacteria and an active agent against B16 melanoma. In this work we confirmed the asymmetric and stereoselective synthesis of *tert*-butyl(1*R*,3*Z*,5*E*,7*E*,10*RS*)-10-hydroxy-1-phenylundeca-3,5,7-trienylcarbamate as the key building block towards the synthesis of the southern polyene section of viridenomycin. In this synthesis, a series of reactions were carried out, including Heck-Mizoroki couplings, Suzuki-Myuara couplings, deprotection of the silyl ethers, selective oxidation and enol-acetylation. In addition, the full explanation for regeoselectivity of hydroboration with catecholborane on terminal alkynes was introduced. Also, our efficient iododeboroation methodology was applied to the alkenyl hindered boronate ester and led to the terminal (E)-alkenyl isomer which was the only isomer obtained. Therefore, this iododeboronation will be a very important method for practical use to prepare highly stereoselective terminal (*E*)-alkenyl iodide. Moreover, selective cleavage of *tert*-butoxycarbonyl (Boc) for the deprotection of the corresponding triene was studied. In addition, two mild cleavage protecting groups (TFAA, phthalimide) are studied. In conclusion, we have demonstrated an efficient methodology and a flexible approach to the synthesis of conjugated (*Z*,*E*,*E*)-triene core of viridenomycin.

Acknowledgements

It is with a deep sense of gratitude that I am so grateful to my supervisor Prof. Andy Whiting for his close supervision, guidance, advice, courteous supports and helpful comments throughout all stages of this work. Without him the thesis wouldn't have been possible. I also offer my deep thanks and gratitude to Dr. D. Hernault for his valuable assistance in the HPLC measurements. I am highly indebted to the Libyan Government for their financial supported to me. I thank NMR service and Mass Spectrometry Service at Durham University. Finally, my thanks go to Durham University and the Chemistry Department for offering me this opportunity to submit this Ph D thesis.

Fathia A. Mosa

"*If a man does his best, what else is there*?"

General George S. Patton (1885-1945)

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

Ac	Acetyl
AP	Atmospheric pressure
α	Observed optical rotation in degrees
[α]	Specific rotation
br	Broad (IR and NMR)
t-Bu	*tert*-Butyl
Bn	Benzyl
Boc	Di-*tert*-butyl dicarbonate
°C	Degrees Celsius
calcd	Calculated
δ	Chemical shift in parts per million downfield from tetramethylsilane
D	Doublet (spectra)
DCM	Dichloromethane

DEAD	Diethylazodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
dL	Deciliter
DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DMP	Dess Martin periodinane
DMSO	Dimethyl sulfoxide
DOWEX 50 WX8	A strong acid cation resin containing 8% divinylbenzene.
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
Ee	Enantiomeric excess
EI	Electron impact
Eq	Equivalent
ESI	Electrospray ionization
Et	Ethyl
He·La cell	A cell from a strain of human cervical cancer cells that is used in medical and biological research
Hz	Hertz
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High-resolution mass spectrometry
IR	Infrared

IPA	2-Propanol
J	Coupling constant in Hz (NMR)
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LRMS	Low-resolution mass spectrometry
MALDI	Matrix assisted laser desorption/ionization
Me	Methyl
MHz	Megahertz
mol	mole(s)
MNBA	2-Methyl-6-nitrobenzoic anhydride
Ms	Methanesulfonyl (mesyl)
m/z	Mass-to-charge ratio
NMR	Nuclear magnetic reasonance
P	Protecting group
ppm	Parts per million
Q	Quartet (NMR)
R_f	Retention factor (in chromatography)
Rt	Room temperature
S	Singlet (NMR); second(s)
S_N2	Bimolecular nucleophilic substitution
T	Triplet (NMR)

TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
Temp	Temperature
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl; tetramethylsilane
TOF MS	Time-of-flight mass spectrometry
Tol	Tolyl
TPPO	Triphenylphosphine oxide
*t*R	Retention time (in chromatography)
UV	Ultraviolet

CHAPTER I

Introduction

CHAPTER I

ONISOPRENOID POLYNENES NATURAL PRODUCTS: CLASSIFICATION, BIOACTIVITY

1.1. Introduction

Natural products have been attractive to research scientists for many years in different areas, such as drug discovery, industrial applications or synthetic studies. Some of the richest sources of natural products are marine microorganisms such as bacteria, cyanobacteria, dinoflagellates, *etc*. as the real producers of a variety of bioactive substances.[1] "Natural products are both a fundamental source of new chemical diversity and an integral component of today's pharmaceutical compendium."[2] More than 13000 bioactive metabolites have been reported.[3] However, interest in the discovery of natural product drugs has declined, partly due to the diminishing returns from traditional resources such as soil bacteria.[2] The polyenes are defined as "a class of natural products that are known as potent antifungal and antibacterial compounds."[4] Most of the polyene natural products contain a macrolactone ring with several conjugated or unconjugated double bonds. The conjugated double bonds are responsible for the physical and chemical properties of the compounds (photolability, strong ultra violet/visible light absorption and low solubility in water).[5] The polyenes are also known to be "inhibitors of a number of enzymes, such as cholesterol acyltransferase".[4] Moreover, polyenes are an important group of natural metabolites produced by multi-functional enzymes in a process that resembles fatty acid biosynthesis.[6] However, while in the biosynthesis of fatty acids, each step is

followed by further extension of the complete sequence of reactions, including keto-reduction, dehydration and reduction. However, in the synthesis of polyenes and other macrolides, each product may be subject to all, some or none of the above reactions.[7] Recently, polyene antibiotics have been received growing interest because of their strong biological activities.[8] Until now, more than 200 polyenes produced by *Streptomyces* species have been confirmed together with their biological activities.[8]

1.2. Classification of nonisoprenoid polyenes according to chemical structure

The polyene natural products are classified according to the number of conjugated double bonds which they possess because these conjugated double bonds form a chromophore that is responsible for their physical and chemical properties.[5,9] Each of the different groups of polyenes will be considered in the following sections. The effect of the conjugated double bonds on their biological activity has been studied, for example, recent research has reported the effect of fatty acids with more than two conjugated double bonds on tumor cells, demonstrating that "the antitumor effect was superior when the amount of conjugated double bonds in a fatty acids polyene chain was higher."[10] Furthermore, conjugated polyene construction is considered by chemists to be an important structural feature of many insect pheromone components, alarm system of seaweeds and components of the female sex attractant.[11] In this overview, the polyene natural products are divided according to the number of the conjugated double bonds *i.e*. trienes, tetraenes, pentaenes, hexaenes and heptaenes.

i. Trienes.

This group consists of the different types of polyenes which contain three conjugated double bonds. The existence of a triene moiety is important for biological activities in many trienes. Conjugated *trans*-triene polyene systems are found in many insect pheromones, for example, undeca-(1,3*E*,5*E*)-triene **1**, nona-(1,3*E*,5*E*)-triene **2** and octa-(*1*,*3E*,*5E*)-triene **3** are sex-pheromone components of some of the marine brown algae *species*.[11]

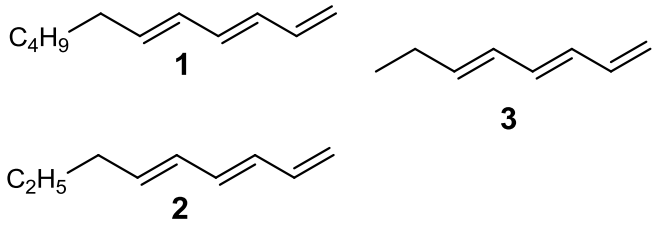
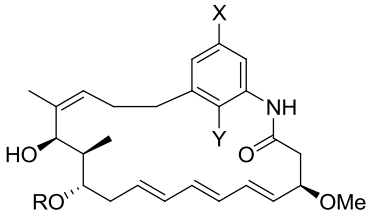


Figure 1.10 Some *trans*-triene polyene systems found in insect pheromones.

The (*E*,*E*,*E*)-triene ansamycin antibiotics are a very important class of the ansamycin family since they have powerful biological activities, such as antibacterial, antifungal and antitumor agents.[12] The (*E*,*E*,*E*)-triene ansamycins are characterized by a 21-membered macrolactane ring with four stereocenters and an (*E*,*E*,*E*)-triene that plays an important role in their biological activities.[13,14,15] The ansamycin compounds include the ansatrienins (or mycotrienins),[14,15] trienomycins,[14] thiazinotrienomycins[14] and cytotrienins.[14,16]



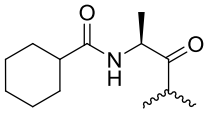
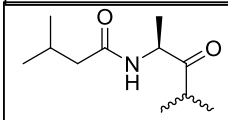
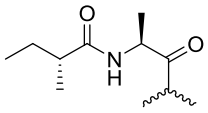
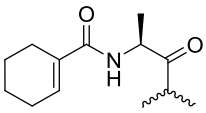
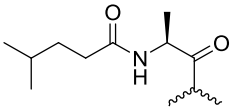
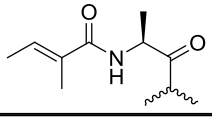
R	X	Y	
	O	O	(+)-Mycotrienin **I 4**
	OH	OH	(+)-Mycotrienin **II 5**
	OH	H	(+)-Trienomycin A **6**
	OH	H	(+)-Trienomycin B **7**
	O	O	(+)-Ansatrienin A_3 **8**
	OH	H	(+)-Trienomycin C **9**
	O	O	(+)-Ansatrienin A_2 **10**
	OH	H	(+)-Trienomycin D **11**
	O	O	(+)-Ansatrienin A_4 **12**
	OH	H	(+)-Trienomycin E **13**
	OH	H	(+)-Trienornycin F **14**
H	O	O	(+)-Mycotrienol **I 15**
H	OH	OH	(+)-Mycotrienol **II 16**
H	OH	H	(+)-Trienomycinol **17**

Figure 1.11 Structures of related ansatrienin antibiotics.

Mycotrienins are a class of compounds that belong to the benzoquinone ansamycins such as naturally-derived mycotrienin I **4** and II **5** (Figure 1.11), isolated from *Streptomyces rishirensis*.[14] They are useful as inhibitors of osteoclastic bone resorption, "marble bone disease,"[17] and they also possess potent antifungal activity.[14] Mycotrienols I and II (Figure 1.11) were produced with mycotrienins I and II by *Streptomyces rishiriensis* T-23.[14]

Another study including 12-triene ansamycin showed that these trienes, such as mycotrienin I **4**, inhibited endoplasmic reticulum stress-induced XBP1 activation.[18,19]

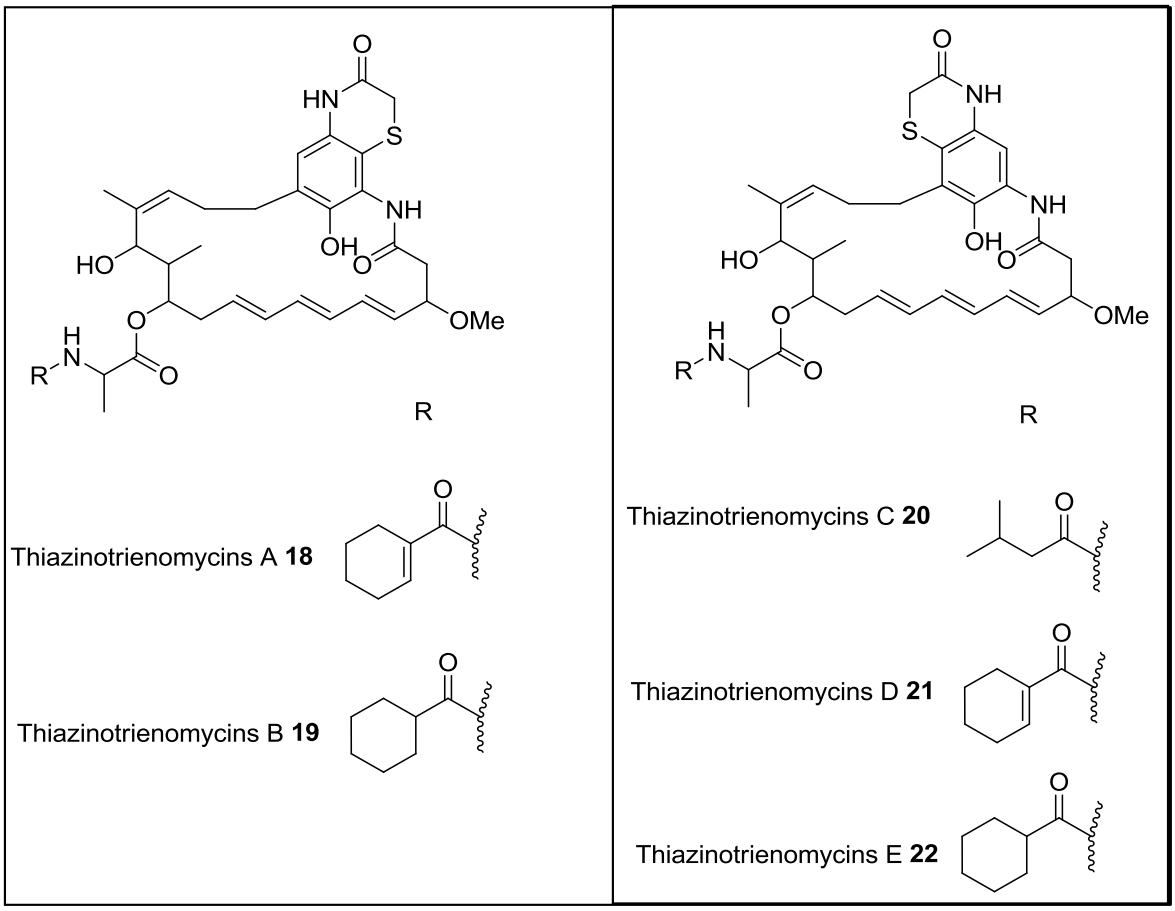


Figure 1.12 Structures of ansatrienin antibiotics (+)-thiazinotrienomycins A-E.

Trienomycins A-F (Figure 1.12) were isolated from many *Streptomyces* sp. These compounds showed strong activity *in vitro* against HeLa S3 cells.[14,20] Ansatrienin antibiotics, (+)-thiazinotrienomycins A-E **18**-**22** (Figure 1.12), isolated from *Streptomyces* sp. MJ672-m3, have important activity *in vitro* against tumor cells from the cervix, stomach

and breast.[21] The mode of action of thiazinotrienomycin is to inhibit membrane transport of thymidine and uridine.[21]

The (*E*,*E*,*E*)-triene cytotrienins A-D **23-26** (Figure 1.13) are found in *Streptomyces* sp. RK95-74.[12] Those ansamycins possess an unusual aminocyclopropane carboxylic acid side-chain and cytotrienins A **23** and B **25** are potent causative agents of apoptosis in human leukemia HL-60 cells.[12] The total synthesis and the biological activity of cytotrienin A **23** has been reported.[16] Moreover, there are (*E*,*E*,*E*)-triene conjugate chromophores in amphidinols (AMs) which are a class of polyhydroxy polyene compounds isolated from various marine dinoflagellates that belong to *Amphidinium* species. These mainly consist of a linear polyene-polyhydroxyl structures and show potent antifungal activity that significantly exceeds that of commercial drugs.[22]

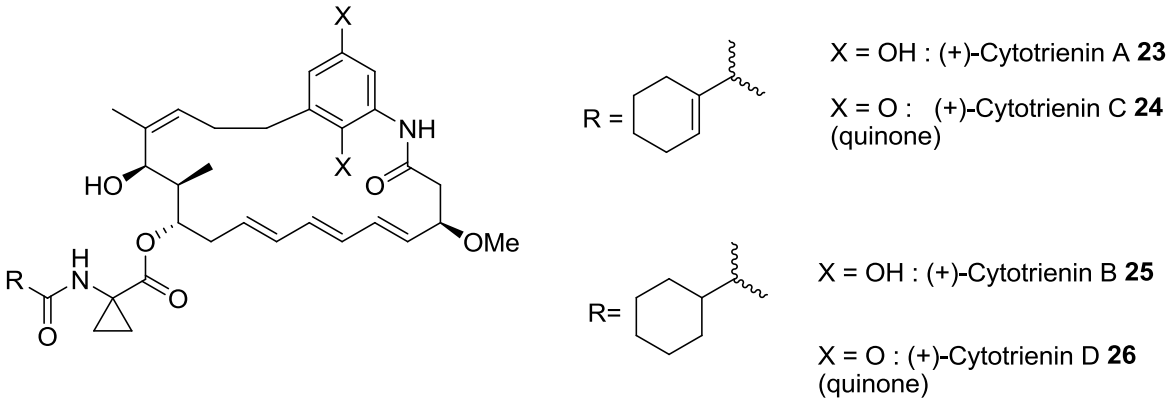
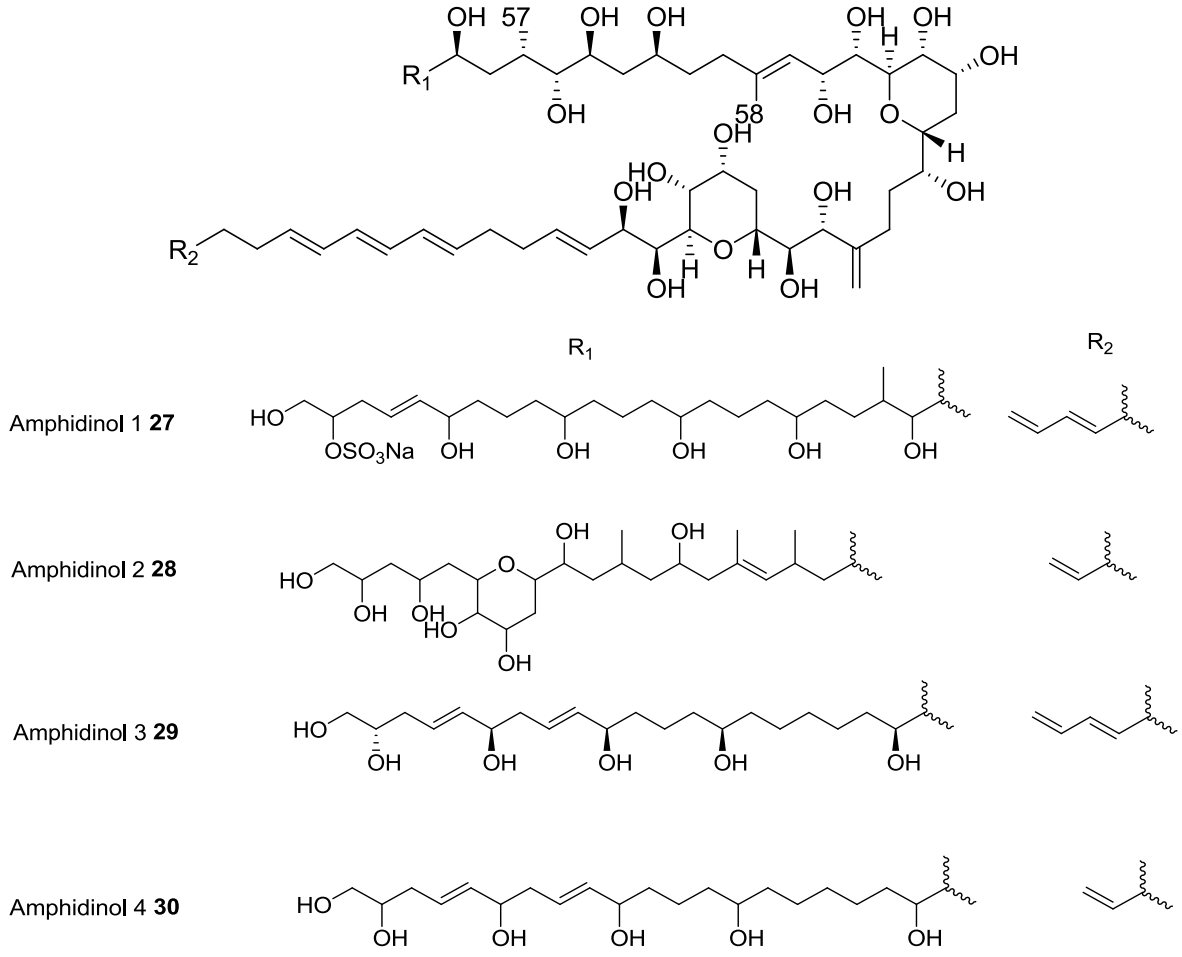


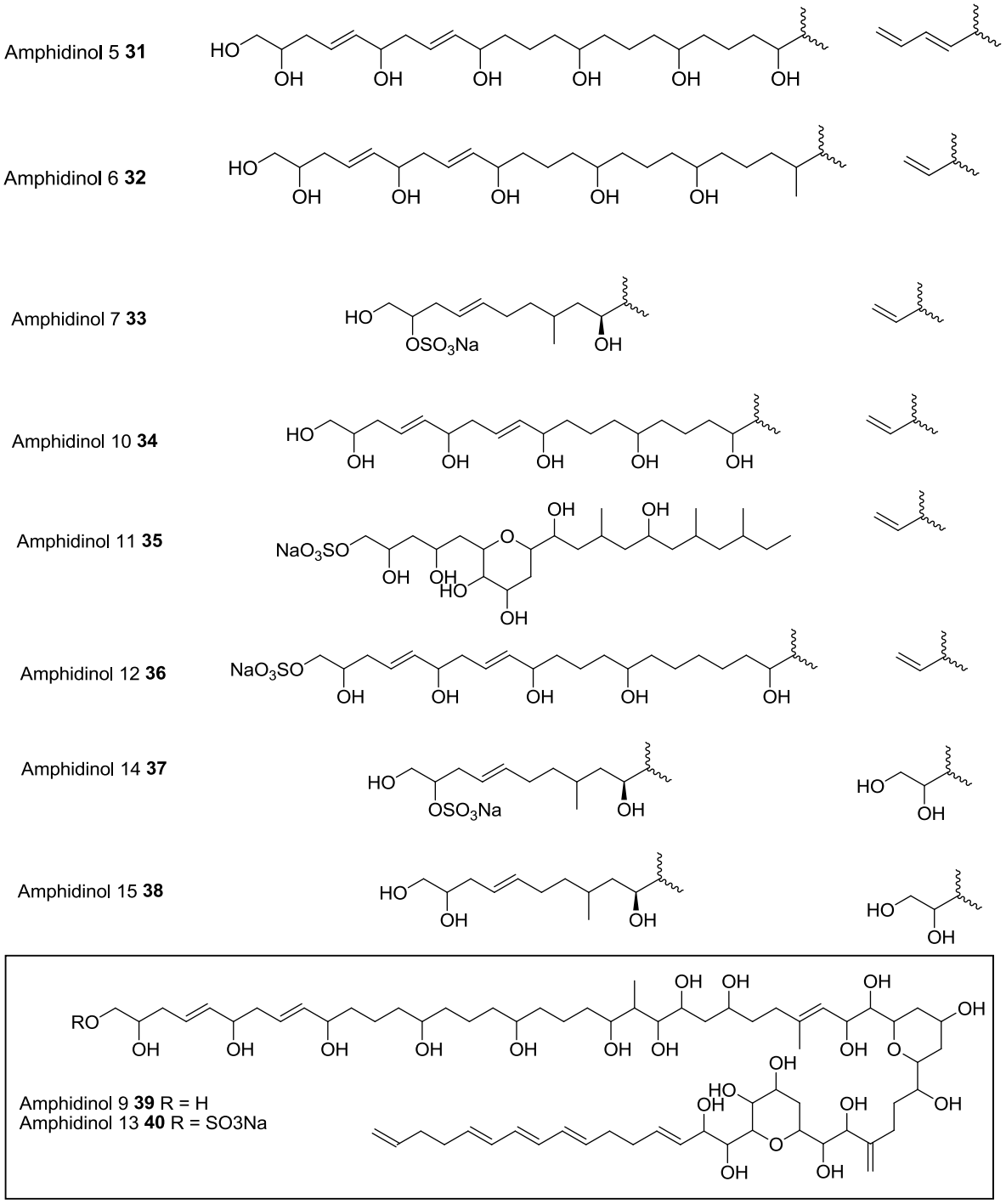
Figure 1.13 Structures of cytotrienins A-D.

Amphidinols (Figure 1.14) show strong membrane-permeabilizing effects in the form of antifungal and hemolytic activity relative to their specific structural characteristics.[21] The

mode of action of these compounds can be explained by forming bio-membrane pores or lesions as a result of penetration of the polyolefin (hydrophobic) moieties of AMs into membrane lipids and the formation of channels lining with polyhydroxyl (hydrophilic) parts.[23] In addition, the bilayer membrane pores cause disruption of electrochemical processes which lead to cell swelling, osmolysis and death.[23,24] Amphidinol 3 **29** has strong antifungal and hemolytic activity.[2]

Figure 1.14 Structures of (*E*,*E*,*E*)-triene amphidinols.

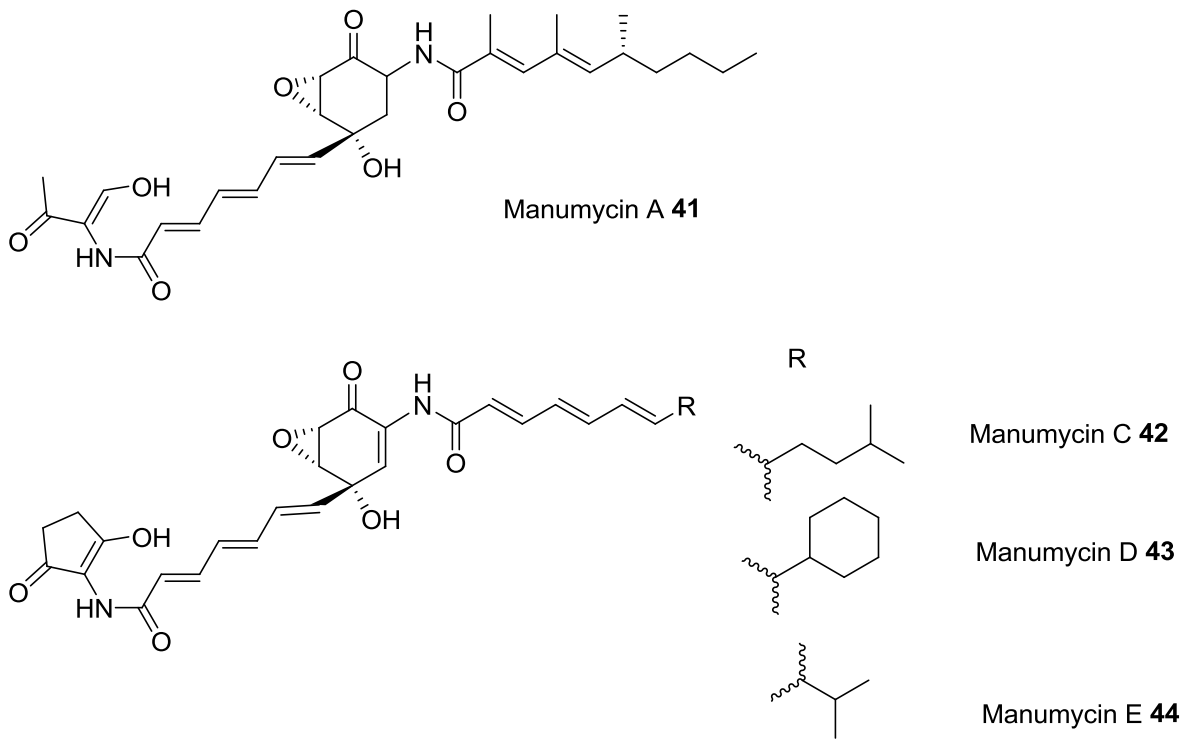


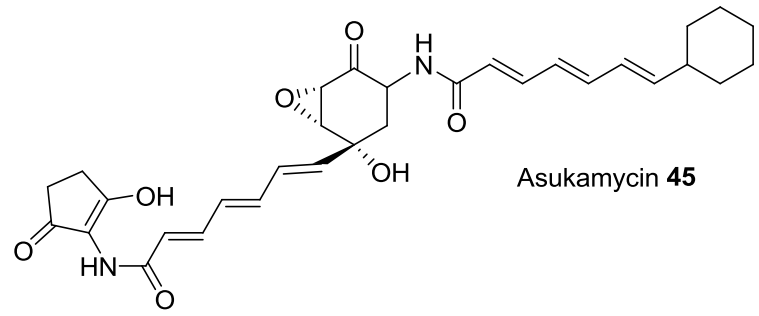


Another important example of conjugated (*E*,*E*,*E*)-triene polyenes are the manumycins (Figure 1.15), which represent a group of compounds with antibiotic, cytotoxic and other

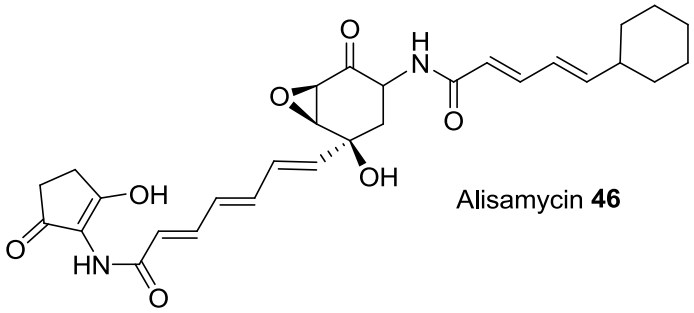
biological features. Manumycins are usually isolated from *Streptomyces* species[26] and manumycin A, C, D, E **41**-**44** are potent and selective inhibitors of farnesyl transferase *in vitro* and *in vivo.*[26] Several manumycins act as inhibitors of interleukin-1 converting enzyme, making them potential lead structures for the development of anticancer and antiinflammatory agents.[27,28,29] Asukamycin **45** is an antifungal agent and a potent inhibitor of rasfarnesyl-protein.[28] It also inhibits the growth of Gram-positive bacteria including *Nocardia asteroids*.[28,30,31,32] Alisamycin **46** has an antibiotic, antitumor and antiparasitic action.[28,33]

Figure 1.15 Structures of some manumycins family.

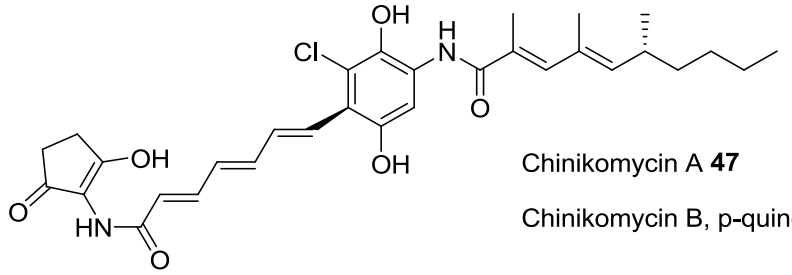




Asukamycin **45**



Alisamycin **46**



Chinikomycin A **47**

Chinikomycin B, p-quinone **48**

Chinikomycins A **47** and B **48** have been isolated recently from a marine-derived *Streptomyces* species.[34] Chinikomycin A **47** revealed selectivity against the spread of cell lines of breast cancer, melanoma and renal cancer.[26,31] Chinikomycin B **48** showed selective activity against tumor cell line breast cancer.[26,31]

The most important of the (*E*,*E*,*E*)-triene polyene macrolide antibiotics is rapamycin (sirolimus, rapamune) **49** and its derivative compounds. Rapamycin **49** is a lipophilic

macrocyclic antibiotic macrolide produced by the soil bacteria *Streptomyces hygroscopicus* and it is widely used as an immunosuppressant and it used in the treatment of cardiovascular, autoimmune and neurodegenerative diseases.[35,36,37] These compounds are currently the most selective kinase inhibitors known and the only inhibitors of mTOR (mammalian target of rapamycin) associated kinase activity.[37,38] Rapamycins bind cyclophilin FKBP12 and this complex binds and inhibits the function of mTOR; a serine–threonine kinase.[37,38] Rapamycin **49** inhibits vascular smooth muscle cell proliferation and migration and inhibits hepatic fibrosis in rats by attenuating multiple profibrogenic pathways.[39,40] Rapamycin also inhibits lymphocyte proliferation, neovascularization and fibrosis.[41]

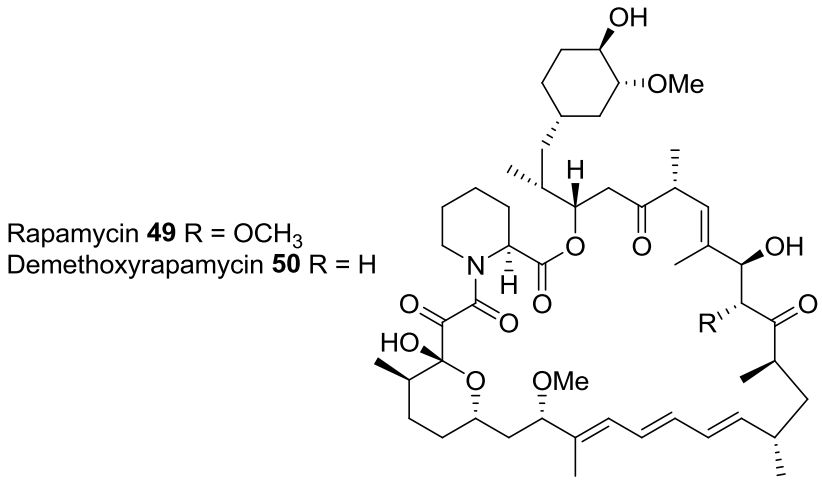


Figure 1.16 Structures of rapamycin **49** and demethoxyrapamycin **50**.

Hong-Nong *et al*. recently reported the isolation of a nonmacrolide polyenic compound, the (*E,E,E*)-triene prorocentin **51**, from marine dinoflagellate, *Prorocentrum lima*.[42] This polyene possesses an all-*trans*-triene moiety and an epoxide, as well as the 6/6/6-*trans*-

fused/spiro-linked tricyclic ether rings. Prorocentin **51** inhibits human colon adenocarcinoma DLD-1 and human malignant melanoma RPMI7951.[42]

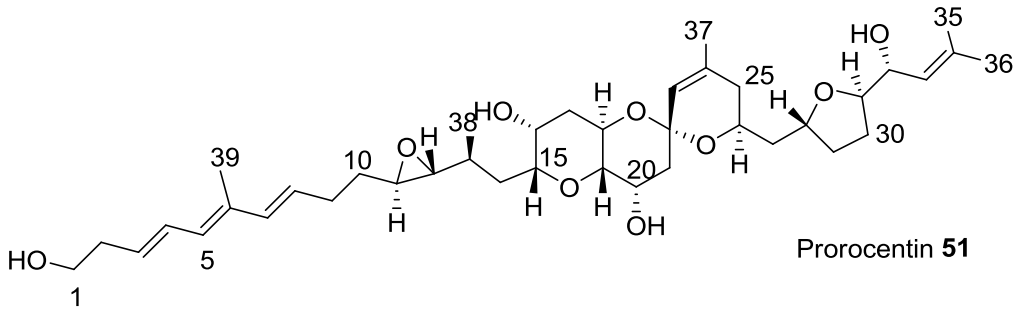


Figure 1.17 Structure of prorocentin **51**.

The (*E,Z,E*)-triene side-chain was characterized in the natural enantiomer of (−)-exiguolide **52** (Figure 1.18) which was isolated from the marine sponge *Geodia exigua*.[43]

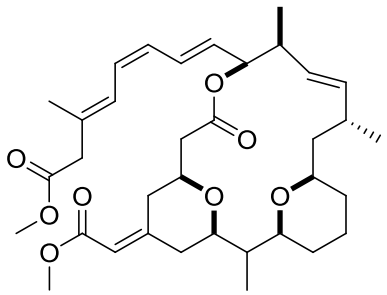


Figure 1.18 Structure of (-)-exiguolide **52**.

A similar conjugated (*Z,Z,E*)-triene was found in phostriecin **53**, sultriecin **54** and cytostatin **55**.[44] These compounds were identified as antitumor antibiotics when isolated from *Streptomyces sp.*[44]

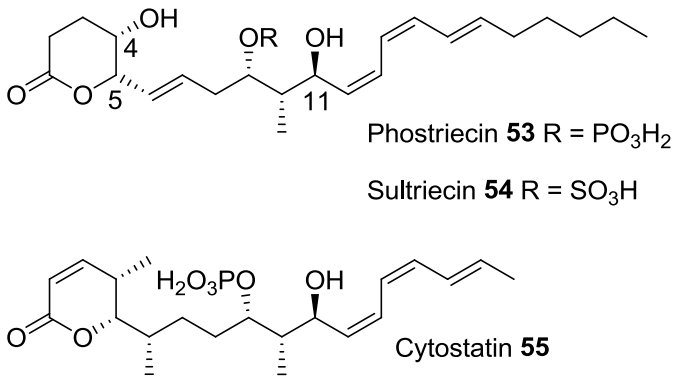


Figure 1.19 Structures of some conjugated (*Z*,*Z*,*E*)-trienes.

The (*E*,*E*,*Z*)-triene side chain was characterized in natural leukotriene metabolites, that can be used to treat asthma and bronchitis. Two of the important leukotrienes are resolvin E1 **56** and leukotriene **57**.[45,46] Furthermore, there are studies on leukotrienes which have confirmed the *cis*,*trans*,*trans*-conjugated triene geometry, and that this was responsible for the biological activity of leukotrienes.[46]

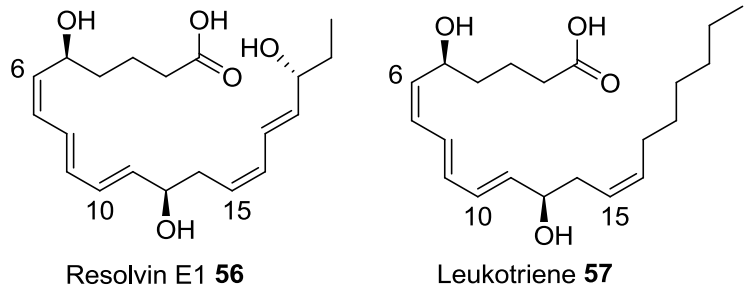


Figure 1.20 Structure of some conjugated (Z,*E*,*E*)-trienes.

ii. Tetraenes

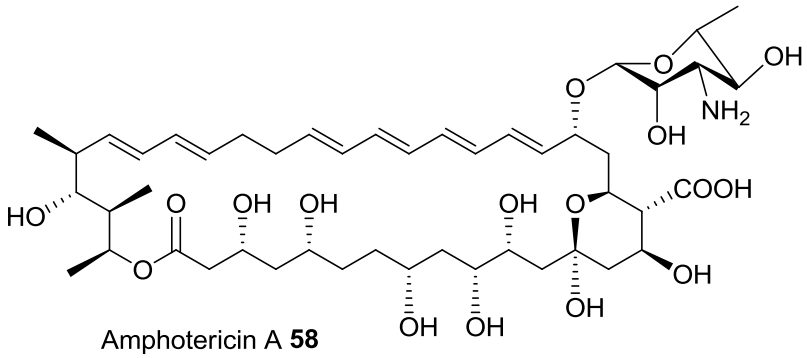
As can be seen from Table 1.10, there are many compounds containing the tetraene moiety and which were isolated from different natural sources with full structural assignment and stereochemistry determined.

Table 1.10 Examples of some important tetraenes (See structures in Figure 1.21).

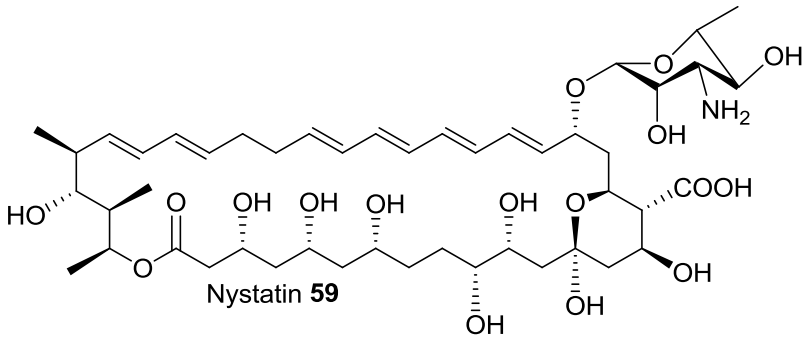
Tetraene Name	Producing Organism	Biological Activity
Amphotericin A **58**	*S. nodosus*	Antifungal activity.[47]
Nystatin **59**	*S. albulus* *S. noursei* *S. nodosus*	It possesses a potent broad-spectrum antifungal action.[48] Antimalarial activity.[49] It inhibits herpes simplex virus I (HSV) and HSV II infections.[50]
Pimaricin **60** (Natamycin)	*S. natalensis* *S. chattanoogensis* *S. gilveosporus*	It used as a natural preservative in food industry.[51] The treatment of fungal keratitis, and cutanous, vaginal and intestinal candidiasis.[52] Antimalarial activity.[49]
AB-400 **61**	*Streptomyces* sp. RGU5.3,	Antifungal activity.[53]
Rimocidin **62**	*S. rimosus* *S. diastaticus*	Antifungal activity.[54]
Rimocidin B **63** and C **64**	*S. diastaticus*	Antifungal activity.[55]
CE-108 A **65**, B **66** and C **67**	*S. diastaticus* var. 108	Antifungal activity.[56]
Lucensomycin (Etruscomycin) **68**	*S. lucensis*	Antifungal activity.[57]
Arenomycin B **69**	*A.tumemacerans.* *Var.griseoarenicolor*	Antifungal activity.[58]
Tetrin A[59] **70** and B[60] **71**	*Streptomyces sp.*	Antifungal activity.[59,60]

Tetrin C **72**	*Streptomyces* sp. GK9244	Antifungal activity against *Mortierella ramannianus*.[61]
Tetramycin A **73** and B **74**	*S. noursei var. jenensis*	Antifungal activity.[62]
Viridenomycin **75**	*S. gannmycicus and S. viridochromogenes*	Antifungal, antibacterial and anti-tumour.[63]
Polifungin **76**	*S. noursei var. polifungini*	Antifungal activity.[64]
Fumigillin **77**	*Aspergillus fumigates*	Amebicidal, anticancer, antiparasitic and antibacterial properties.[65,66] Angiogenesis inhibitor.[66]
Lajollamycin **78**	*Streptomyces nodosus*	Antimicrobial and antitumour activities.[67]
Superstolide A **79**	*Neosiphonia superstes*	Highly cytotoxic against several cancer cell lines.[68]

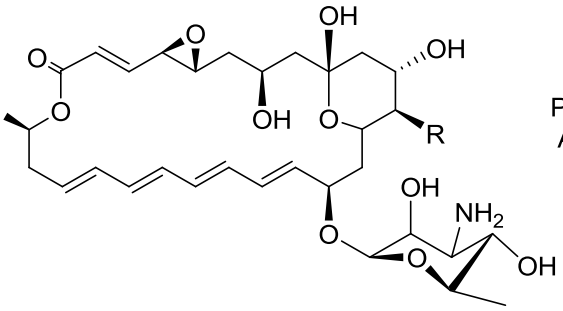
Figure 1.21 Structures of some important tetraenes.



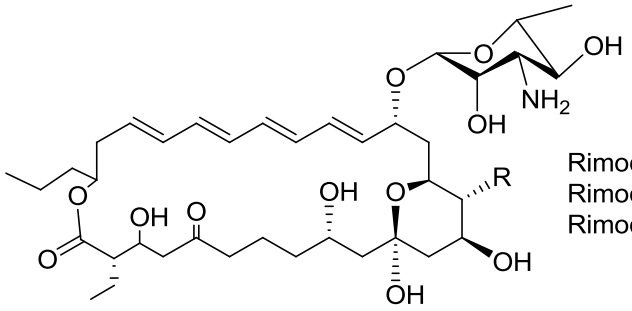
Amphotericin A **58**



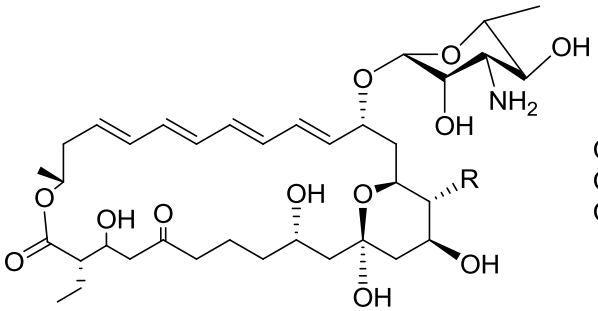
Nystatin **59**



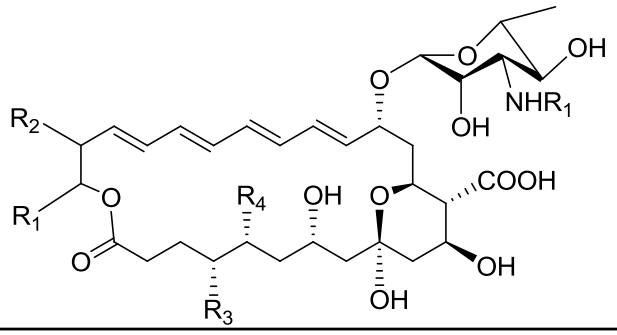
Pimaricin **60** R = COOH
AB-400 **61** R = $CONH_2$



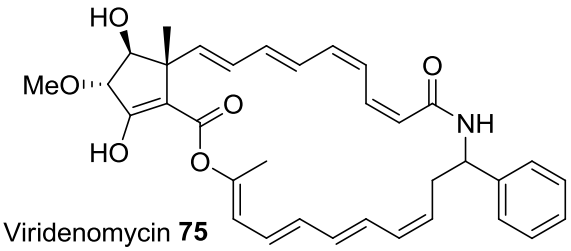
Rimocidin **62** R = COOH
Rimocidin B **63** R = $CONH_2$
Rimocidin C **64** R = CH_3



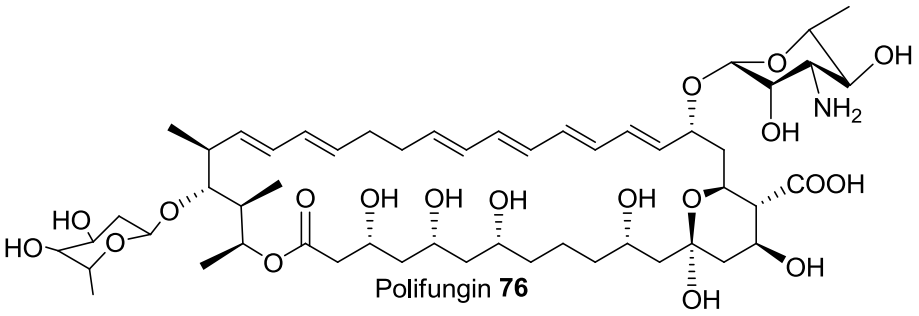
CE-108 **65** R = COOH
CE-108B **66** R = $CONH_2$
CE-108C **67** R = CH_3



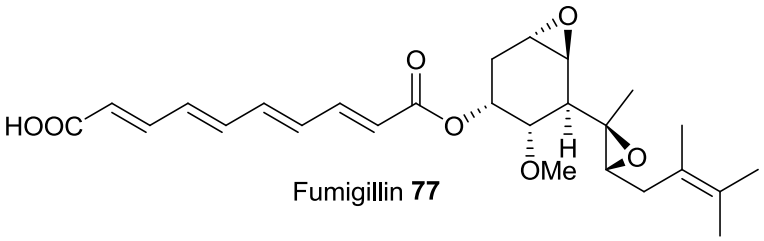
	R_1	R_2	R_3	R_4
Lucensomycin **68**	n-C_4H_9	H	-O-	(epoxy)
Arenomycin B **69**	n-C_4H_9	H	H	OH
Tetrin A **70**	CH_3	CH_3	H	OH
Tetrin B **71**	CH_3	CH_3	OH	OH
Tetrin C **72**	CH_3	CH_3	H	H
Tetramycin A **73**	CH_3	C_2H_5	H	OH
Tetramycin B **74**	CH_3	C_2H_5	OH	OH



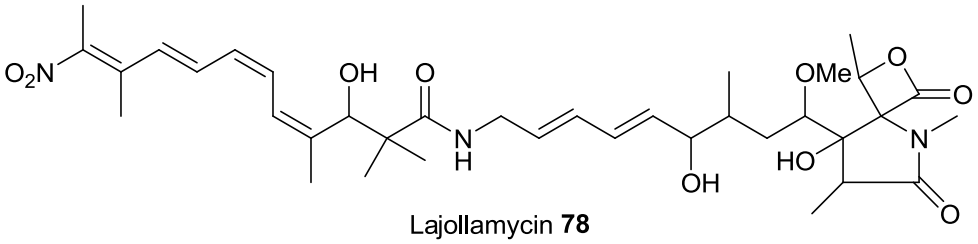
Viridenomycin **75**



Polifungin **76**

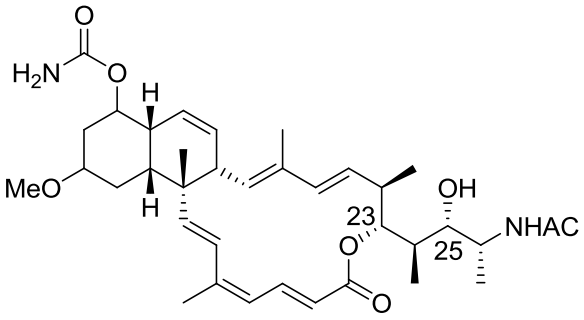


Fumigillin **77**



Lajollamycin **78**

(+)-Superstolide A **79**



iii. Pentaenes

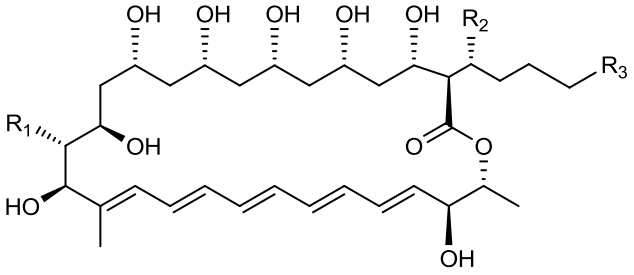
Many polyenes are characterised by the existence of a pentaene chromophore and they are intrinsically fluorescent. Table 1.11 gives examples of some important pentaenes.

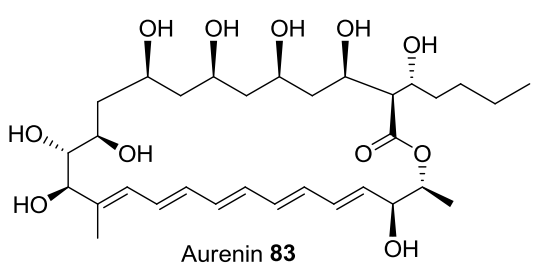
Table 1.11 Examples of some important pentaenes (See structures in Figure 1.22).

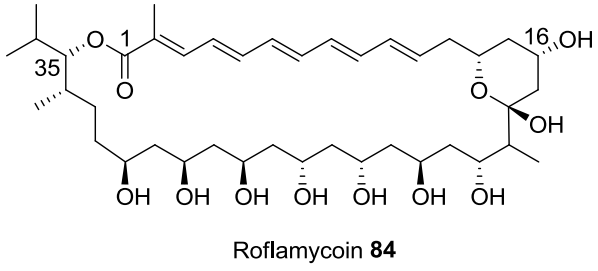
Pentaene name	Producing organism	Biological activity
TPU-0043 (Chainin) **80**	*Streptomyces* sp. TP-A0625. *Chainia minutisclerotica*	Antifungal activity. [69,70, 71]
Filipin III **81**	*S. filipinensis*	Antifungal[72] and antimalarial activity. [49]
Fungichromin **82** (Pentamycin) (Cogomycin) (Lagosin) (Cantricin) (Moldcidin B)	*S. padanus* PMS-702, *S. cellulosae* *S. roseoluteus* *S. fradiae* *S. griseus*	Strong antifungal activity against *R. solani* AG-4 and it is considered as an active ingredient for the control of *Rhizoctonia* damping-off of cabbage.[73]
Aurenin **83**	*Actinomyces aureorectus*	Antifungal activity.[9]
Roflamycoin (Flavomycoin) **84**	*Streptomyces roseoflavus*	Antifungal activity.[74]
RK-397 **85**	*Streptomyces* sp.	Antifungal activity, anticancer activity, inhibits human leukemia cell lines K-562 and HL-60 at 50 and 25 μg/mL, respectively.[75,76,77]
Roxaticin **86**	Streptomycete X-14994	Antifungal activity.[78]
Mycoticin A **87** and B **88**	*Streptomyces* sp.	It exhibits broad antimicrobial activities against filamentous fungi, yeast, and bacteria.[79, 80]
Lienomycin **89**	*Actinomyces diastatochromogenes* var. *lienomycini*	Antifungal activity, antibacterial and antitumor.[81]

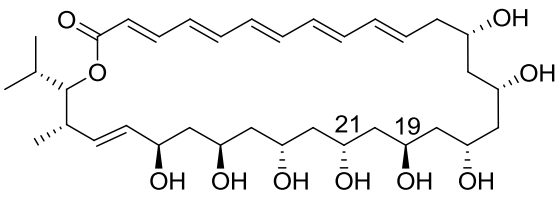
Marinisporolide A **90** and B **91**	*Marinispora sp.*	Antifungal activity against *Candida pathogens*.[3]
Myxalamide D **92** and related compounds (**93** and **94)**.	*Cystobacter fuscus* *Myxococcus xanthus.*	Antifungal activitiy against the Phythopathogenic fungus *Phythopthora capsici*.[82,83,84]
Strevertene A - G **95-101**	*Streptoverticillium sp.* LL-30F848	Antifungal activity against phytopathogenic fungi.[85]
Eurocidin D **102**	*Streptoverticillium sp.*	Antifungal activity against *T. vaginalis*.[85b]
Mirabilin **103**	*Siliquariaspongia mirabilis*	Antitumor.[86]
Mycolactones A **105** and B **106**	*Mycobacterium ulcerans* *Mycobacterium marinum*	Highly potent biological activity.[87]
Spirangiens A **104** and B **105**	*Sorangium cellulosum* (strain So ce90)	Antifungal activity.[88]

Figure 1.22 Chemical structures of some important pentaenes.

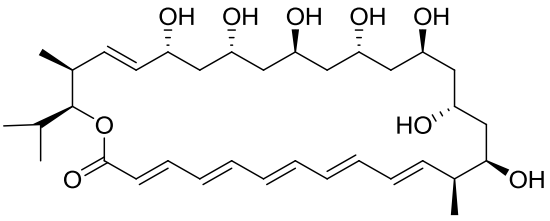




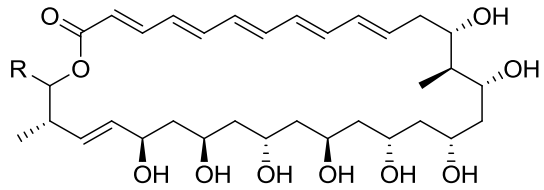




RK-397 **85**

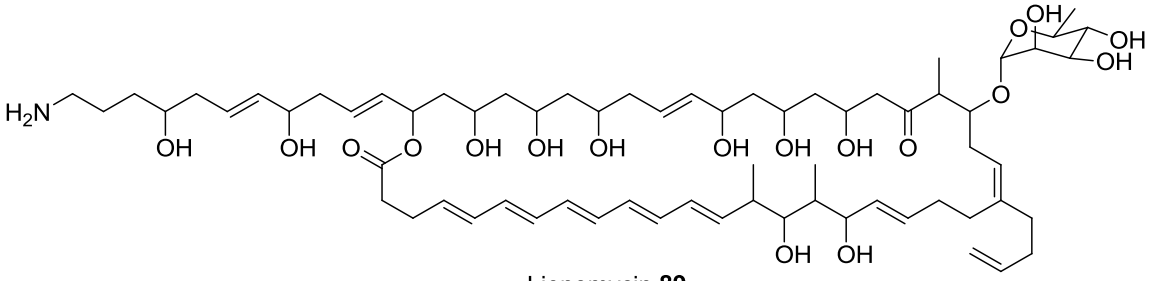


Roxaticin **86**

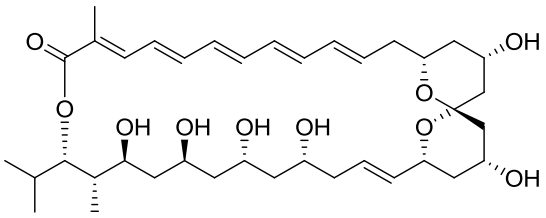


Mycoticin A **87** R = i-Pr

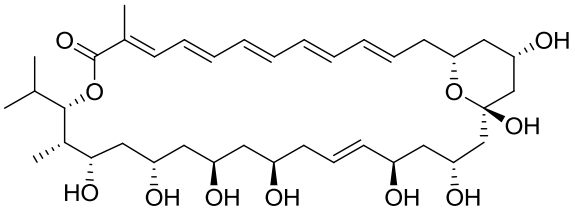
Mycoticin B **88** R = s-Bu



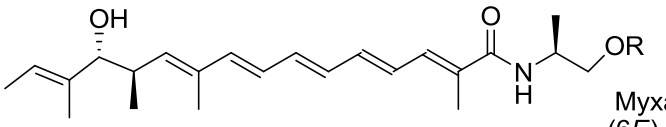
Lienomycin **89**



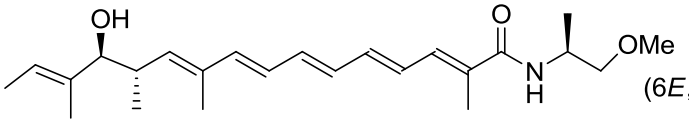
Marinisporolide A **90**



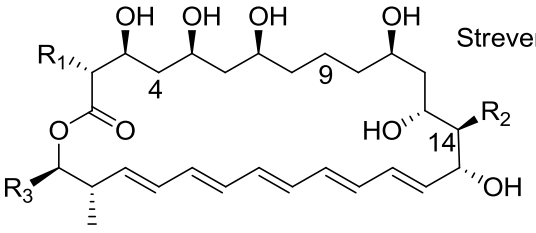
Marinisporolide B **91**



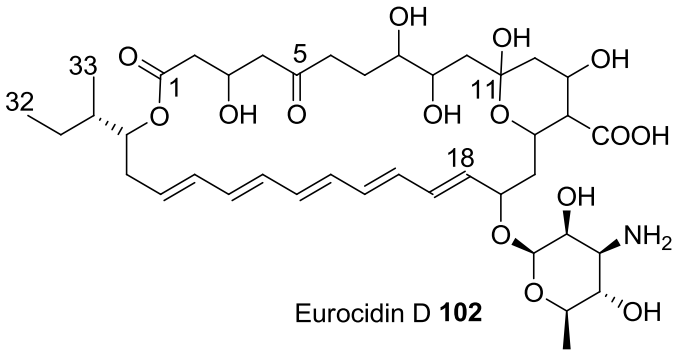
Myxalamide D **92** R = H
(6*E*)-2'-O-Methylmyxalamide D **93** R = OMe



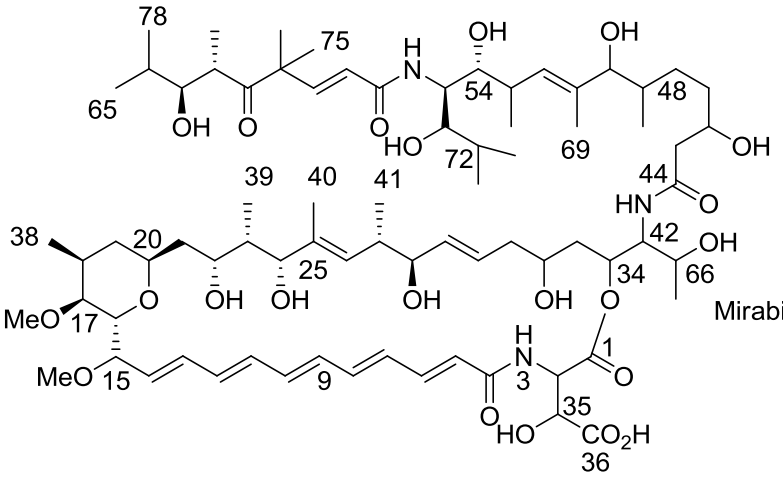
(6*E*,10*Z*)-2'-O-Methylmyxalamide D **94**



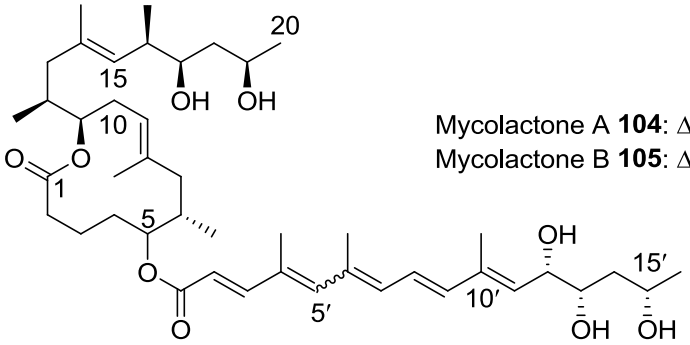
Strevertenes A **95** R_1 = Me, R_2 = CO_2H, R_3 = Me
B **96** R_1 = Et, R_2 = CO_2H, R_3 = Me
C **97** R_1 = Me, R_2 = CO_2H, R_3 = Et
D **98** R_1 = Et, R_2 = CO_2H, R_3 = Et
E **99** R_1 = Me, R_2 = CO_2H, R_3 = *i*-Pr
F **100** R_1 = Et, R_2 = CO_2H, R_3 = *i*-Pr
G **101** R_1 = Me, R_2 = CH_2OH, R_3 = Me



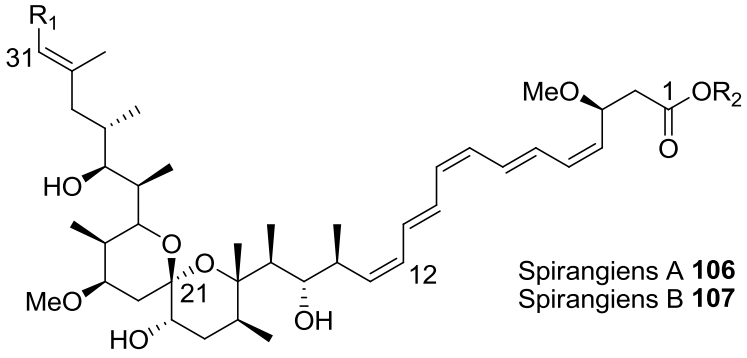
Eurocidin D **102**



Mirabilin **103**



Mycolactone A **104**: $\Delta^{4',5'} = Z$
Mycolactone B **105**: $\Delta^{4',5'} = E$



Spirangiens A **106**
Spirangiens B **107**

iii. Hexaenes

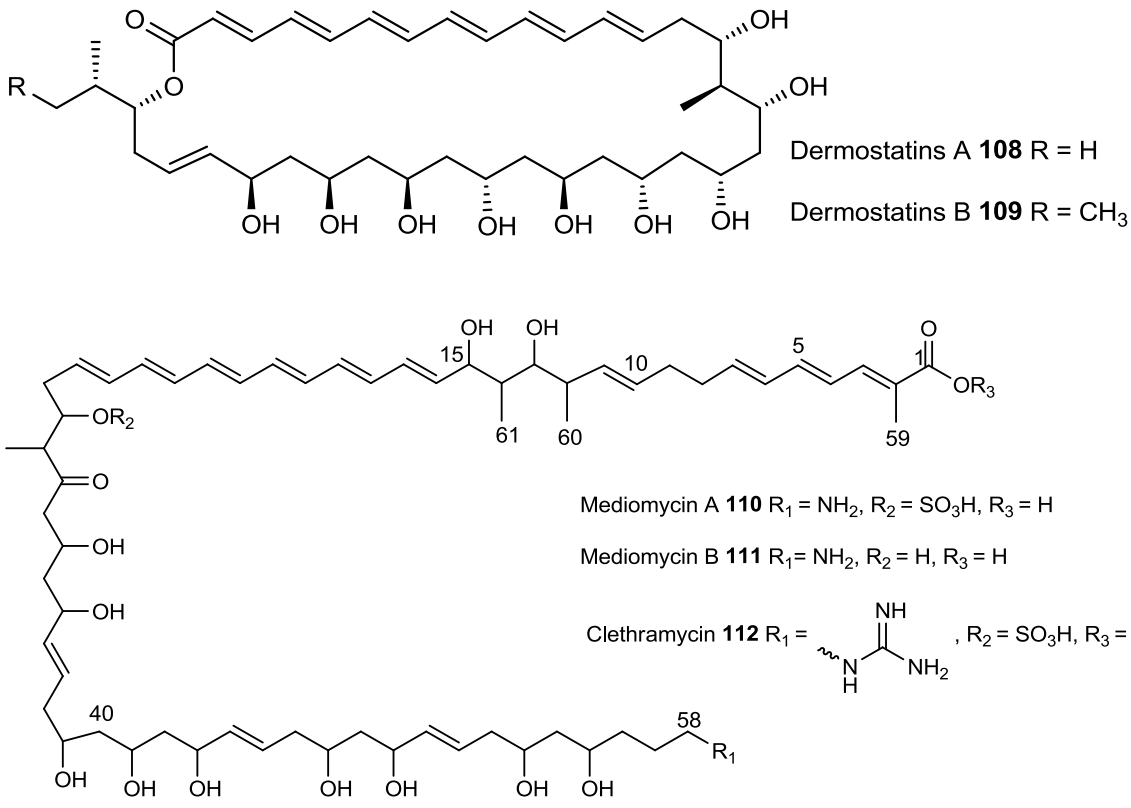
The class of hexaene antibiotics can be divided into two sub-groups on the basis of the hexaene chromophore type:

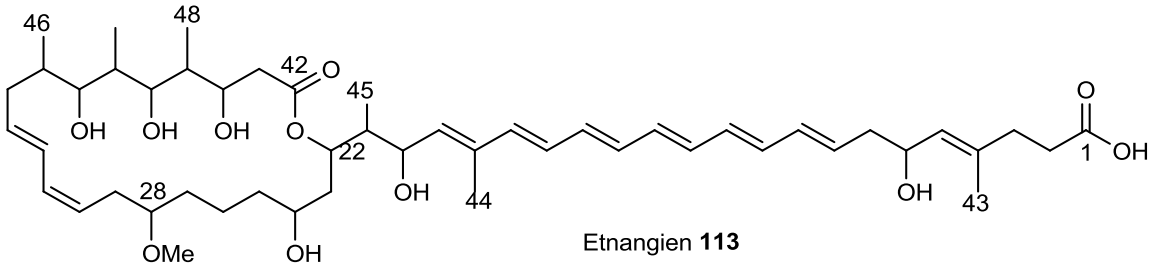
1. Hexaene macrolides, which are often characterized by 20- to 40-membered lactone rings, contain six conjugated carbon-carbon double bonds and often, the lactone ring carries a sugar moiety.[58] Some macrolides contain an aliphatic side-chain, optionally carrying an aromatic substituent. Usually, the macrolide ring carries at least one hydroxyl group.[58] The most effective polyenes in this group are dermostatins A **108** and B **109** that have drawn attention on the basis of their range of biological activities.[89] The dermostatins (Figure 1.12) have a conjugated hexaene-ketone chromophore.
2. Linear hexaene polyene antibiotics, such as mediomycins A **110**, B **111** and clethramycin **112**, were isolated from *Streptomyces mediocidicus* ATCC23936 activity.[90] These compounds demonstrated a broad spectrum of antifungal *in* v*itro* activity.[90] The other hexaenes, such as mediocidin, endomycin, hexaene-80 and hexaene-85, have been reported based on only UV absorption data, for these, neither isolation nor structural elucidation has been conducted. [90]

Table 1.12 Examples of some important hexaenes (See structures in Figure 1.23).

Hexaene name	Producing organism	Biological activity
Dermostatins A **108** and B **109**	*S. virdigreseus* Thirum.	Potent antifungal activity against a number of human pathogens and deep vein mycoses.[89] Anti-proliferative activity against HIV in H9 cells.[89]
Mediomycin A **110** and B **111**	*S. mediocidicus* ATCC23936.	Broad spectrum of antifungal activity.[90]
Clethramycin **112**	*S. mediocidicus ATCC23936.*	Broad spectrum of antifungal activity.[90]
Etnangien **113**	*Sorangium cellulosum.*	Active against range of gram-positive bacteria.[91] Inhibits retroviral RNA and DNA polymerases.[92]

Figure 1.23 Chemical structures of some important hexaenes.





Etnangien **113**

v. Heptaenes

The most important group in the heptaenes are the heptaene macrolide antibiotics which include the antifungal polyene macrolide antibiotic amphotericin B **114** (Fungilin, Fungizone, Abelcet, AmBisome, Fungisome, Amphocil, Amphotec) which has a broad spectrum of antifungal activity in humans.[93] The rod-shaped structure of AmB molecule, with the polar mycosamine head, the hydroxyl groups on the one side of the macrolide ring and the *trans*-hexaenes polyene fragment on the opposite side, makes it possible to interact both with the polar part of the lipid membrane and acyl chains.[93] Table 1.13 gives examples of some important heptaenes.

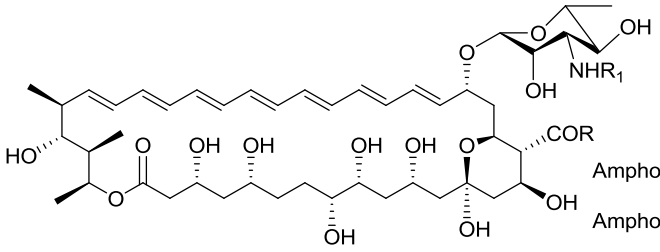
Table 1.13 Examples for some important heptaenes (See structures in Figure 1.24).

Heptaene name	Producing Organism	Biological Activity
Amphotericin B **114** and its derivative compounds **115-117**.	*S. nodosus*	Antifungal activity against deep-seated mycotic infections[93] and intracranial fungal masses.[94] Active agent against visceral leishmaniasis,[95] prion infection,[96] and *Plasmodium falciparum* infection.[97] It also is described for use in treating malaria infections in humans and animals.[49] It inhibits herpes simplex virus I (HSV) and HSV II infections.[58] It inhibits Hepatitis B virus (HBV)

		production.[58] It is used as mouth rinses in oral suspension form to treat severe mucocutaneous candidal infections in the mouth.[98]
Candidin **118**	*S. viridoflavus*	Antifungal activity.[99] It is used for treating a mammalian tumors/cancers.[100]
Mycoheptin **119**	*Streptoverticillium mycoheptinicum*	Antifungal activity against the causal agents of deep-seated and systemic mycoses and yeast-like fungi.[101,102] It is used in the therapy of coccidioidomycosis, histoplasmosis, cryptococcosis, chromodermycosis, blastomycosis, aspergillosis, sporotrichosis and candidiasis.[101,102]
Hamycin **120**	*S. pimprina*	It has antifungal activity against a wide range of pathogenic fungi and has therapeutic efficacy in mice infected with a variety of yeast and yeast-like and flamentous fungi such as *Blastomyces dermatidis, C. albicans, Cryptococcus neoformans, Histoplasma capsulatum*, and *Aspergillus niger*.[103] It is successfully used in the treatment of oral thrush, several other clinical forms of candidiasis in normal as well as diabetic hosts.[103] It is effective in the treatment of various superficial and deep seated mycoses.[103]
Levorin A2 **121** (candicidin D)	*A. levoris* *S. griseus* ATCC 3570	Antifungal activity. It possesses the ability to inhibit the growth of adenoma prostatae.[104,105]
Partricin A **122** and B **123** (Vacidin A)	*S. aureofaciens*	It possesses high antifungal activity (particularly against *Camtida albicans)* and antiprotozoal activity.[106]
67-121 A **124** and B **125**	*Actinoplanes caeruleus*	It is active *in vitro* against yeast and fungi.[107,108]
Perimycin A **126** (synonyms: fungimycin, NC-1968,	*S. coelicolor var. aminophilus*	Antifungal activity. It induces specific permeability changes of the yeast plasma membrane resulting in the loss of potassium ions from the cells ("potassiumleas death").[109]

aminomycin)		
DJ-400 B_1 **127** and B_2 **128**	*S. surinam*	Antifungal activity.[9,110]
FR-008 **129** (Candicidin)	*S. griseus*	Antifungal compound[111] "plays an important role in protecting the fungus gardens of leaf-cutting ants against pathogenic fungi *Escovopsis* sp."[111]
Trichomycin A **130**	*S. hachijoensis*	It used as a potent clinical drug for the treatment of vaginal infections.[112]

Figure 1.24 Chemical structures of some important heptaenes.

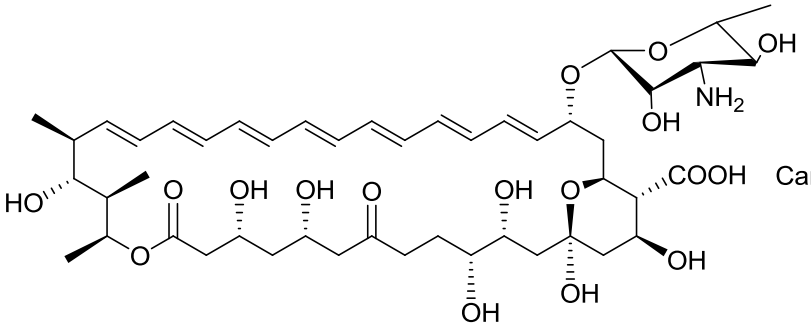


Amphotericin B **114** R = OH, R_1 = H

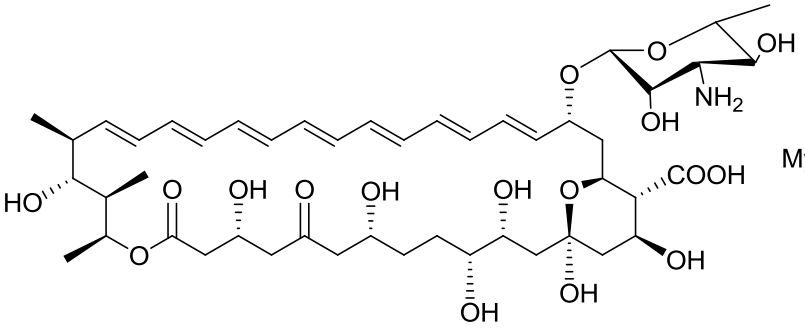
Amphotericin B methyl ester **115** R = OMe, R_1 = H

N-Acetylamphotericin B **116** R= OH, R_1 = COMe

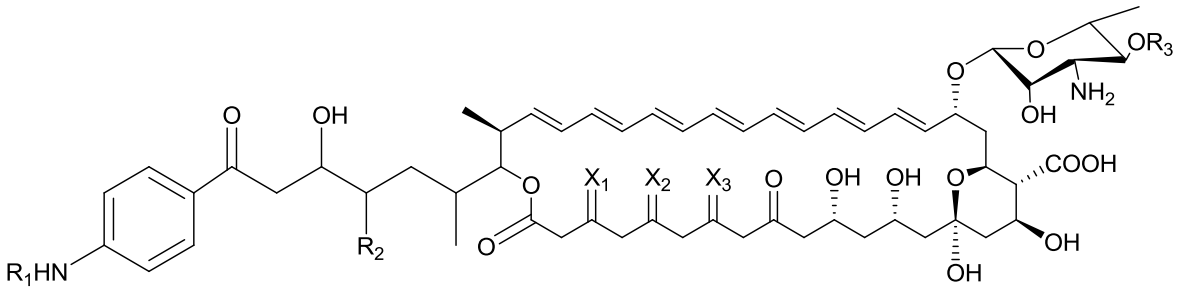
N-Acetylamphotericinmethyl ester **117** R = OMe, R_1 = COMe

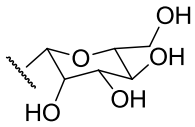


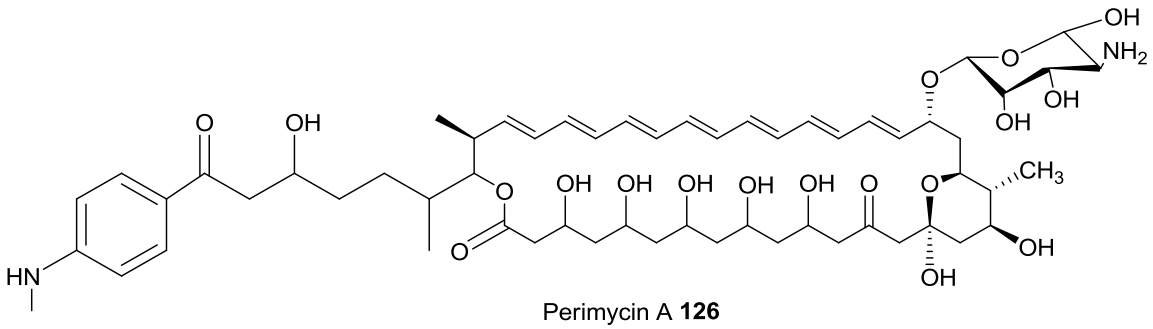
Candidin **118**



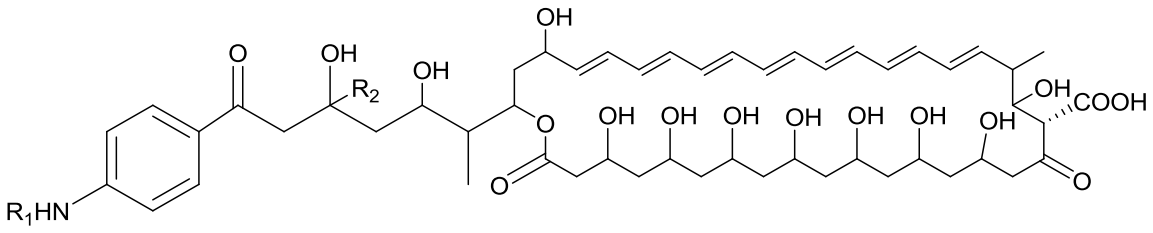
Mycoheptin **119**

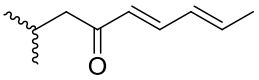


	R_1	R_2	R_3	X_1	X_2	X_3
Hamycin **120**	H	H	H	H,OH	H,OH	H,OH
Levorin A_2 **121**	H	Me	H	=O	H, H	=O
Particin A **122**	Me	H	H	H,OH	=O	H,OH
Particin B **123**	H	H	H	H,OH	=O	H,OH
67-121A **124**	Me	H	H	H,OH	H,OH	H,OH
67-121B **125**	Me	H		H,OH	H,OH	H,OH

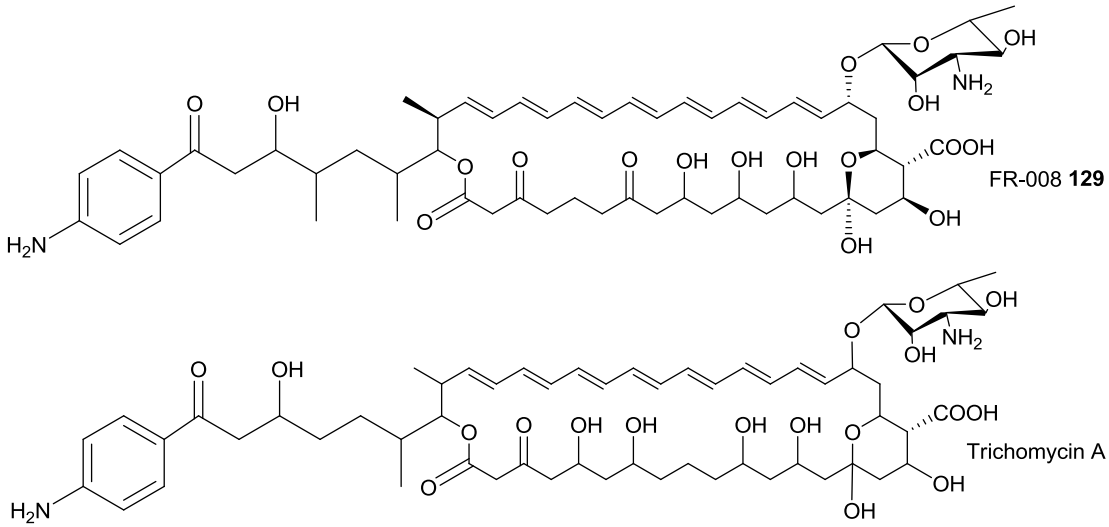


Perimycin A **126**



DJ-4OO B_1 **127** R_1 = Me, R_2 = 

DJ-4OO B_2 **128** $R_1 = R_2$ = H



1.3. Correlation between polyene chemical structure and biological activity

In general, the biological activity of the polyenes increases as the number of conjugated double bonds increases. Hamilton-Miller gave many examples supporting this general rule.[9] Furthermore, when several natural product tetraene macrolides and their derivatives were compared with the heptaene macrolide (amphotericin B) in their biological activities on *Trypanosoma cruzi*, these compounds were less effective, but also less toxic.[113] Kotler-Brajtburg *et al.*[114] attempted to correlate the chemical structures of polyenes and their biological properties and they classified polyenes into two groups according to their ability to cause K^+ leakage and cell death. Group I included trienes, tetraenes (pimaricin **60** and etruscomycin **68**), pentaenes (chainin **80** and filipin **81**) and one hexaene (dermostatin **108**), while group II included the heptaenes (amphotericin B **114**, amphotericin B methyl ester **115**, N-acetylamphotericin B **116**, hamycin **120** and candicidin **129**).[114] Group I antibiotics

caused K^+ leakage and cell death or hemolysis at the same concentrations of added polyene, while group II caused considerable K^+ leakage at low concentrations and cell death or hemolysis at high concentrations.[114] Furthermore, this classification is supported by Akiyama *et al.*,[115] who also classified polyene antibiotics according to their synergistic effect on fungi into two groups: a non-heptaene group (pimaricin **60**, filipin **81** and pentamycin **82**); and a heptaene group (amphotericin B **114**).[115] Moreover, in a study regarding the correlation between the size of the polyene antibiotic chromophore and their biological effects on fungi (*Saccharomyces cerevisiae*), Brajtburg *et al.*[116] found that large polyene antibiotics (amphotericin B **114**, hamycin **120**, candicidin **129** and the semi-synthetic derivatives of these) caused both a reversible inhibition of *Saccharomyces cerevisiae* growth and a killing of the yeast cells, whereas small polyene antibiotics (<7 double bonds in their macrolide rings such as pimaricin **60**, etruscomycin **68**, chainin **80**, filipin **81** and dermostatin **108**) did not induce the reversible inhibition.[116] Recently, in a study on effect polyene macrolides on the vacuole disruption (*S. cerevisiae*), it was found that the heptaenes are more effective than pentaenes and tetraenes.

1.4. Polyene mode of action

The first experiments that shed light on the mode of action of antifungal polyenes were implemented in late 1950.[118] It was shown that these polyene antibiotics interacted with specific lipids in the cell membrane of a sensitive organisms.[118] "All organisms susceptible to polyenes, e.g. yeasts, algae and protozoa, contain sterols in their outer membrane,"[119] whereas bacteria that are not affected by most polyenes do not have sterols in their cell

membrane. In contrast, fungi are sensitive to polyenes because they have sterols in their membrane and it has been suggested that the effect of polyene antibiotics are limited to the fungi that have sterols in the composition of their cell membrane.[118,119] Furthermore, the activity of polyene antibiotics is related to their ability to form micelles with the ergosterol in the cell membranes of fungal cells.[98] As a result of this binding, structural damage and membrane permeabilisation occurs leading to loss of electrolytes and other components such as cytoplasmic proteins;[98] "As a consequence of which the fungal cells die."[98] However, it has been reported that polyene antibiotics have the ability to form pores in the fungal cell membrane completely lacking sterols.[118] "In spite of this, the formed channels are not responsible for their antifungal activity."[118,119] For example, the mechanism of action of amphotericin B is based on interaction with bio-membranes, however, the exact binding properties of antibiotics in lipid membranes is still unclear.[120] There is a full discussion of polyene m**e**chanisms in a review by Ghannoum and Rice.[119]

1.5. Conclusion

The polyenes are classified according to the number of conjugated double bonds to trienes, tetraenes, pentaenes, hexaenes and heptaenes. Many studies have explained that there is a correlation between the size of the polyene antibiotic chromophore and their biological effects, however, their mechanism of action still remains obscure.

CHAPTER II

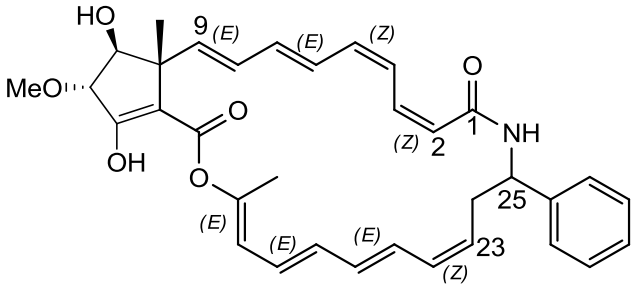
Studies towards the total synthesis of viridenomycin

Chapter II

Studies towards the total synthesis of viridenomycin

2.1. Introduction

Viridenomycin **75** is attracting much attention as a total synthesis target because of its potent biological activities and complex molecular architecture. Viridenomycin **75** (Figure 2.10) was first isolated from the culture broth of *Streptomyces viridochromogenes* strain No. T-24146 in 1975 as a weakly acidic and lipophilic substance, which showed strong inhibitory activity against *Trichomonas vaginalis* and gram-positive bacteria.[121] In 1991, this compound was isolated from the culture broth of *Streptomyces gannmycicus* as an agent for prolongation of the survival periods of mice infected with B16 melanoma and some fungi.[122,123] Structurally, it consists of a fully substituted cyclopentene ring, a phenyl group and 24-membered macrocyclic polyene lactam.[123] The structure of viridenomycin **75** was established except for the absolute configuration and the relative configuration at C-25.[123,124]



75

Figure 2.10 Structure of viridenomycin **75**.

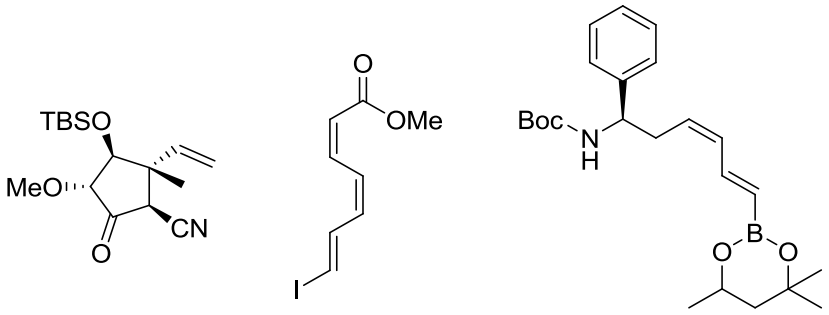
2.2. The aim of the project.

This study is mainly aimed at developing suitable methodology for the synthesis of the southern unit of viridenomycin **75** (C_{16}-C_{23}), as an important step to complete the synthesis of the polyene macrolactam viridenomycin **75**.

2.3. Previous work.

The significant antifungal and antitumor activity of viridenomycin and its uniquely complex structural features have caused it to become a prime synthetic target within the group since 2009. To our knowledge, there are no studies reporting the total synthesis of this interesting antibiotic, however, several groups have reported their attempts,[125] or the synthesis of different parts of the structure,[126] including ourselves.[127,128] Our group has successfully defined a pathway for the convergent construction of the fully substituted cyclopentane unit[127a] **131**, the northern tetraene section [(*Z*,*Z*,*E*-)-trienyl iodide **132**][127b] and the synthesis of (*Z*,*E*)-dienyboronate ester[127c] **133** as an important step towards synthesis of the southern section of viridenomycin.

Figure 2.11 Previous synthesized structures of viridenomycin **75** within the group.



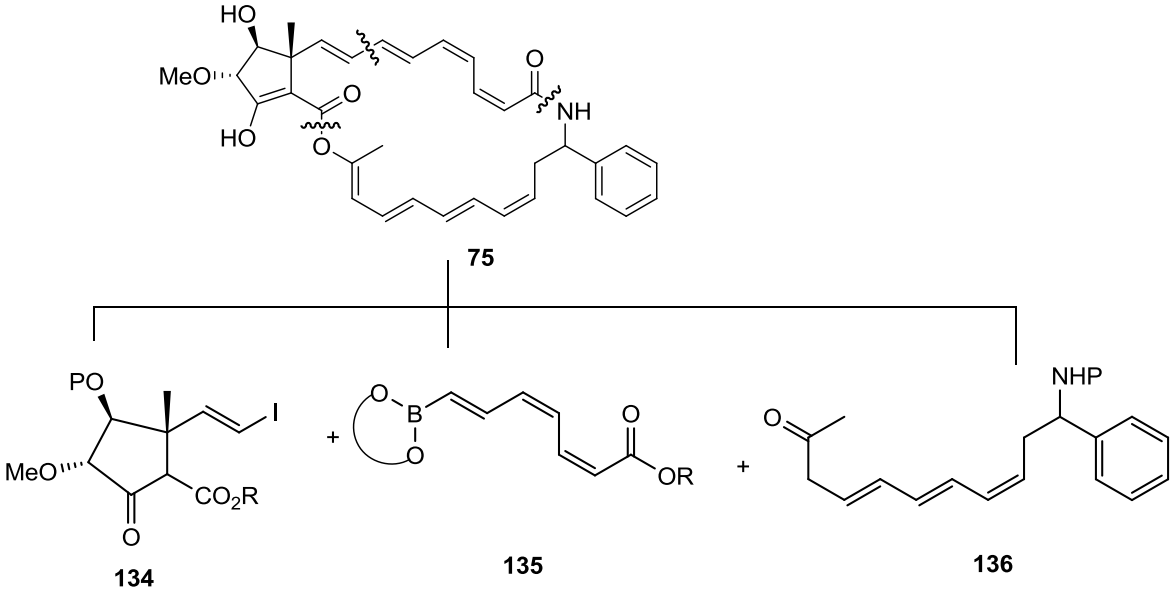
131 **132** **133**

2.4. Our Synthetic Strategies

i. Retrosynthetic Plan

To approach the viridenomycin **75** structure, the molecule was initially divided into three primary fragments, as explained in Scheme 2.10.

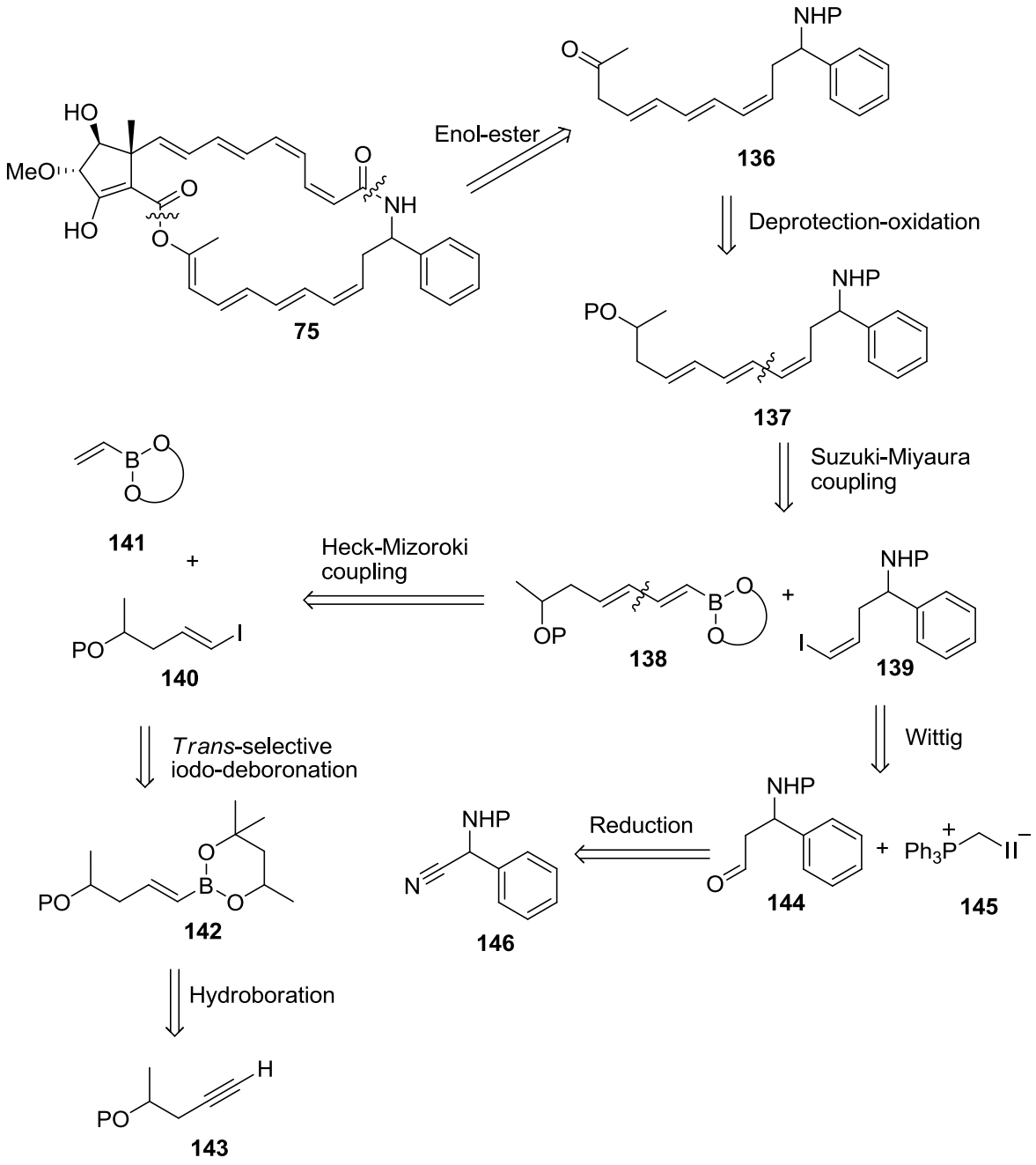
Scheme 2.10 Initial retrosynthetic analysis of viridenomycin **75**



ii. Retrosynthetic strategy to construct of the C_{16}-C_{23} chain (southern hemisphere tetraene of viridenomycin).

The initial retrosynthetic plan for the synthesis of southern hemisphere (C_{16}-C_{23}) is shown in Scheme 2.11. In the retrosynthetic plan, the triene **136** was disconnected at the C_4-C_5 bond, which presents a convenient cleavage point for a convergent coupling of

dialkenylboronate ester **137** and the (*Z*)-alkenyl iodide **138**.



Scheme 2.11 The initial retrosynthetic plan for the synthesis of southern hemisphere **137**

The intermediate **138** can then be retrosynthetically broken into two segments; the (*E*)-alkenyl iodide **140** and a suitable vinylboronate ester **141**. The (*E*)-alkenyl iodide **140** could then be transformed cleanly by a stereoselective iododeboronation of the (*E*)-alkenylboronate ester **142**. Whereas, the (*Z*)-alkenyl iodide **139** could be obtained from the chiral aldehyde **144** and a Wittig reaction using the ylide derived from salt **145**.

iii. Enol-lactonization

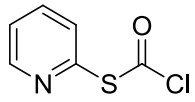
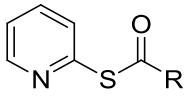
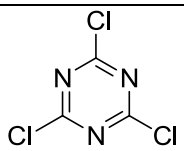
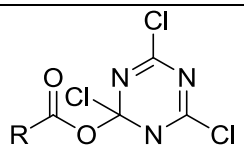
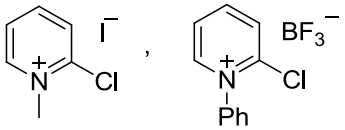
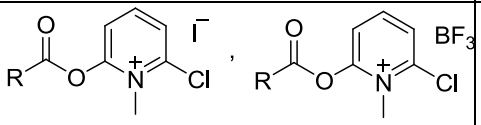
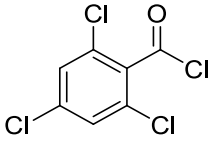
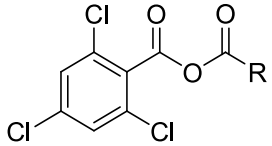
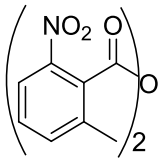
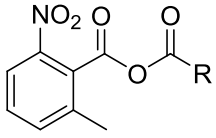
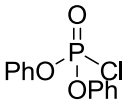
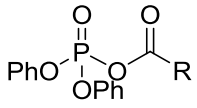
Viridenomycin **75** is characterized by the existence of an enol-lactone moiety, hence, the ketone **136** is required for an enol-lactonization reaction. It was, therefore, necessary to understand the ability of ketone **136** to undergo enolisation, followed by trapping as an activated ester derivative; this is one of the key steps in the retrosynthetic analysis, and hence, towards the total synthesis of viridenomycin **75**. In order to tackle this reaction, it is necessary to survey the known methods for enol-lactonization.

iv. Methods for enol-ester formation

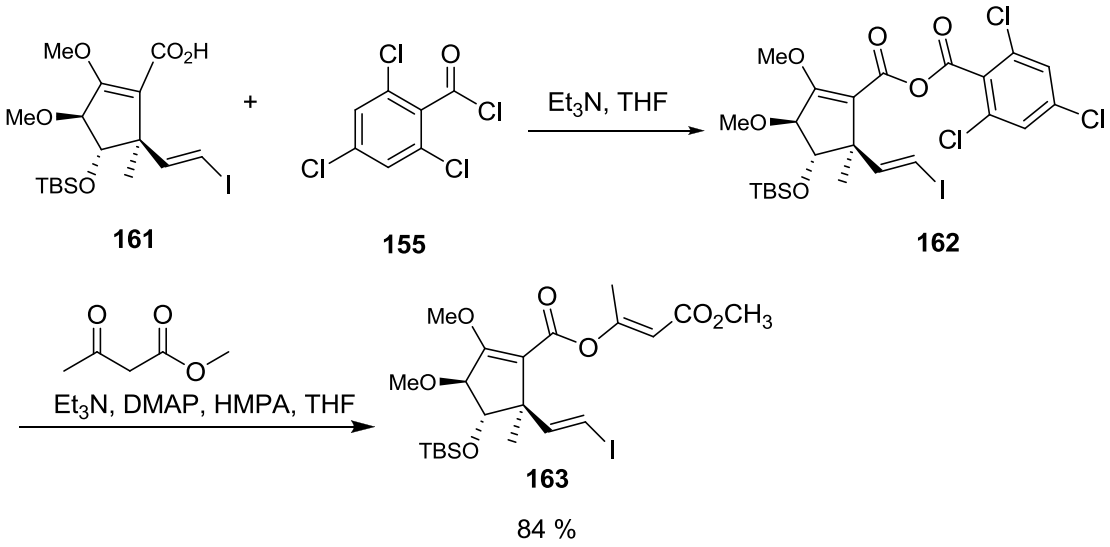
Enol-ester lactonization is usually achieved by the reaction of an enol derivative with an activated carboxylic acid derivative to afford the enol-ester lactone moiety. There are many examples of suitable acylating agents, generally derived from the activation of acids by thioesters,[129] cyanuric chloride **149**,[130] 1-methyl-2-chloropyridinium iodide **151**,[131] 2,4,6-trichlorobenzoyl chloride **155**,[132] 2-methyl-6-nitrobenzoic anhydride (MNBA) **157**,[133] phosphorous reagents[134] or carbodiimides.[135] Mixed anhydrides can also be used to activate the carboxylic acid functions, for example, with trifluoroacetic anhydride (TFAA), acetic anhydride (Ac_2O) and di-*tert*-butyl pyrocarbonate (Boc_2O).[136] Table 1 provides a list of the

activating reagents that can be used for the carboxylic acid moiety the potentially access enol ester systems.

Table 2.10 Examples different acid activating agents for carboxylic acids

Activating reagent for the carboxylic acid	Activated form of the carboxylic acid (RCOOH)	Ref.
 **147**	 **148**	129
 **149**	 **150**	130
 **151** **152**	 **153** **154**	131
 **155**	 **156**	132
 **157**	 **158**	133
 **159**	 **160**	134

There are few examples of the activation of ketones *via* the enol for derive enol esters in the total synthesis of natural products. The most important and relevant example for the formation of an enol ester was introduced by Meyers *et al.*[125a,125b] who modified the Yamaguchi macrolactonization as a part of their studies towards viridenomycin **75** (Scheme 2.12).



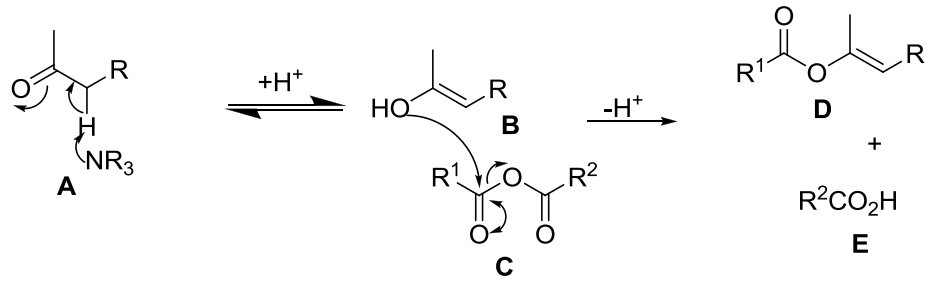
Scheme 2.12 Enol-esterification using Yamaguchi reagent **155**.

Despite of some studies on enol-lactonization, it is clear that it remains a difficult process, and therefore, needs to be refined and improved, or new efficient conditions developed.[137] The mechanism of enol-esterification from a ketone using a base (generally organic base) and an activated form of the acid is shown in Scheme 2.13. The enol-form of ketone **B** is generated in the reaction *in situ* by the organic base followed by addition of a mixed anhydride to obtain the enol-ester **D**.

Hence, the development of new methods for the synthesis of enol-lactone moiety of

viridenomycin **75** may be one of the major are as of study in this project.

Scheme 2.13 The mechanism of enol-esterifiction using an organic base and an activated form of acid.



2.5. Summary

The main aims of this research project towards developing a total synthesis of viridenomycin and building the southern hemisphere polyene, is therefore, 1) the development an efficient route for the southern polyene reaction of viridenomycin **75**; 2) to develop an efficient enol-esterification reaction suitable for use in the total synthesis; 3) examination of suitable *N*-protecting groups for the benzylic amide function suitable *N*-deprotection methods; and 5) the highly stereocontrolled synthesis of the complete southern polyene unit to allow construction of natural product building block **136**.

CHAPTER III

Results and Discussion

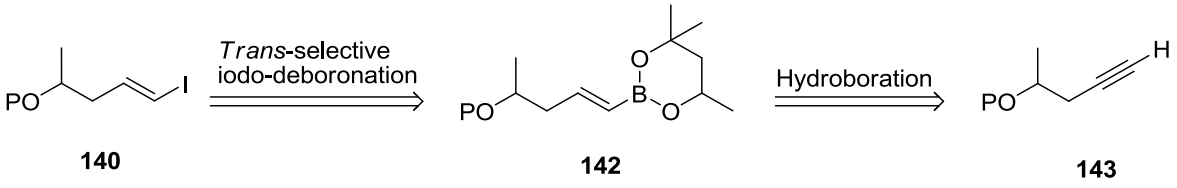
Chapter III

Results and Discussion

3.10. Synthesis of the TBS-protected-homopropargylic alcohol

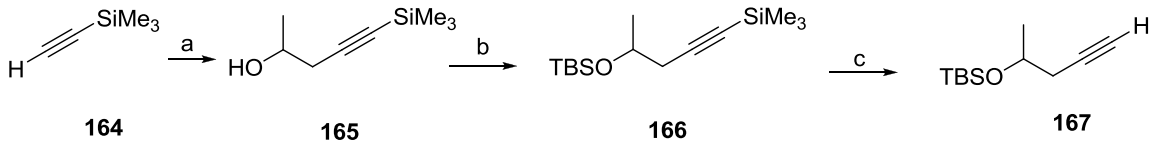
Our synthetic studies started with the synthesis of a protected hydroxyl polyene derivative **143** (See Scheme 2.11) in order to access the corresponding hydroboration product **142** and then *trans*-selective iodo-deboronation to afford *trans*-alkenyl iodide **140** as reshown in Scheme 3.10.

Scheme 3.10 Retrosynthetic plan of *trans*-alkenyl iodide **140**.



140 **142** **143**

This was developed starting from TMS-acetylene **164** (Scheme 3.11). Hence, the deprotonation of the terminally protected alkyne **164** with *n*-BuLi according to the method of Burchat *et al.*[138] was carried out as shown in Scheme 3.11. This was followed by the addition of (±)-propylene oxide, assisted by a Lewis acid ($BF_3.Et_2O$) to give the desired alcohol **165**.[139] The hydroxyl group was protected by silylation with *tert*-butyldimethylsilylchloride (TBSCl) to give the silyl ether **166**. Subsequent removal of the alkyne protecting silyl group with methoxide gave the terminal alkyne **167** (Scheme 3.11).[140]

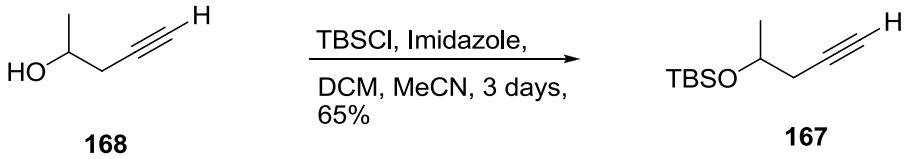


164 **165** **166** **167**

Scheme 3.11 Reagents and conditions: (a) *n*-BuLi (1.05 eq), Et_2O, -75 °C, 30 min, then (±)-propylene oxide (1.0 eq), and further addition of $BF_3 \cdot Et_2O$ (1.0 eq) in 2h, -75 °C, 85%; (b) TBSCl, imidazole, DCM, 20h, 0 °C to rt, 81%; (c) K_2CO_3 (1.1 eq), MeOH, rt, 48h, 89%.

An alternative method to prepare the terminal alkyne **167** (Equation 3.10) was also carried out, employing one step from commercially available (±)-4-pentyn-2-ol **168**, however, this reaction (with the conditions: TBSCl, imidazole, DCM, MeCN, 3 days)[141] was very slow. It was also found that if the reaction was left stirring at rt for more than 48 h, the starting material was not consumed completely by TLC.

Equation 3.10 Synthesis of silyl ether **167**



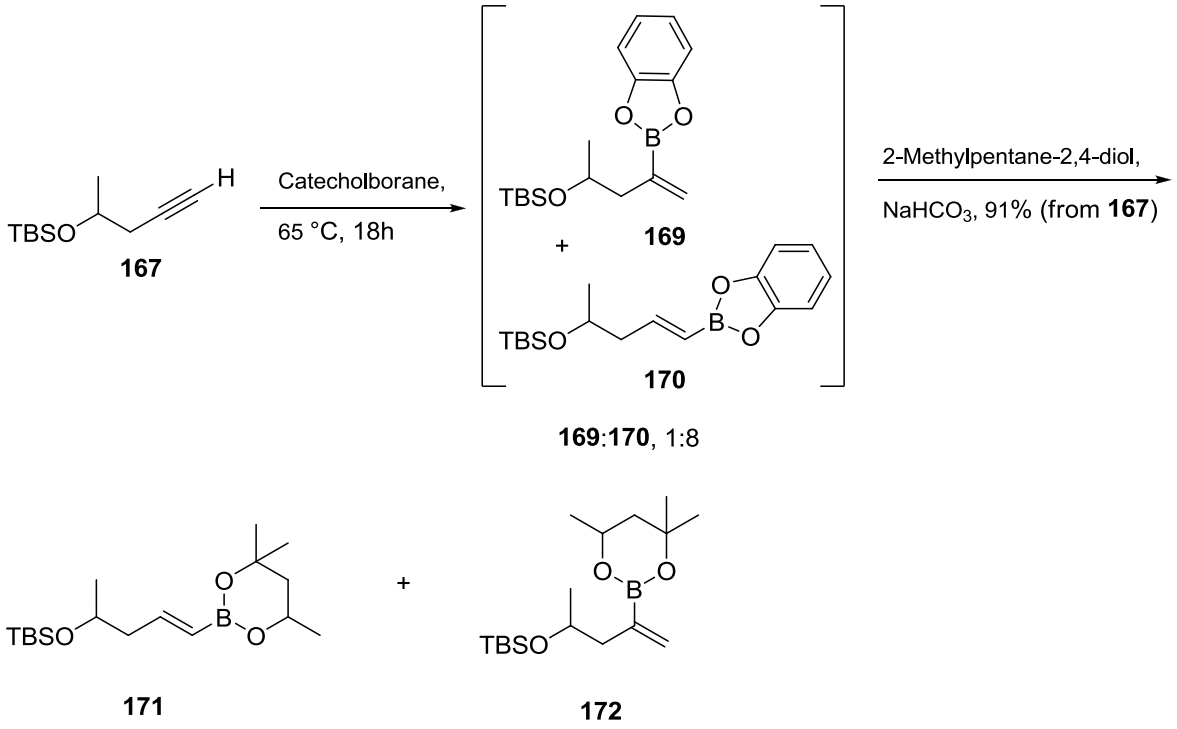
168 **167**

3.11. Stereoselective synthesis of (*E*)-vinylboronic ester 171 via catecholborane mediated hydroboration of alkyne 167

Brown hydroboration of terminal-alkynes with catecholborane usually yields products derived from stereospecific *cis*-addition or *syn*-addition, with the boron-atom regioselectively attached to the least hindered carbon-atom of the triple bond.[142]

However, the hydroboration of alkyne **167** with catecholborane (Scheme 3.12) gave a mixture regioisomeric products **169** and **170**, which followed by treatment with 2-methylpentane-2,4-diol in the presence of base ($NaHCO_3$) gave the desired product **171** as a mixture with **172** (See Figure 3.10).

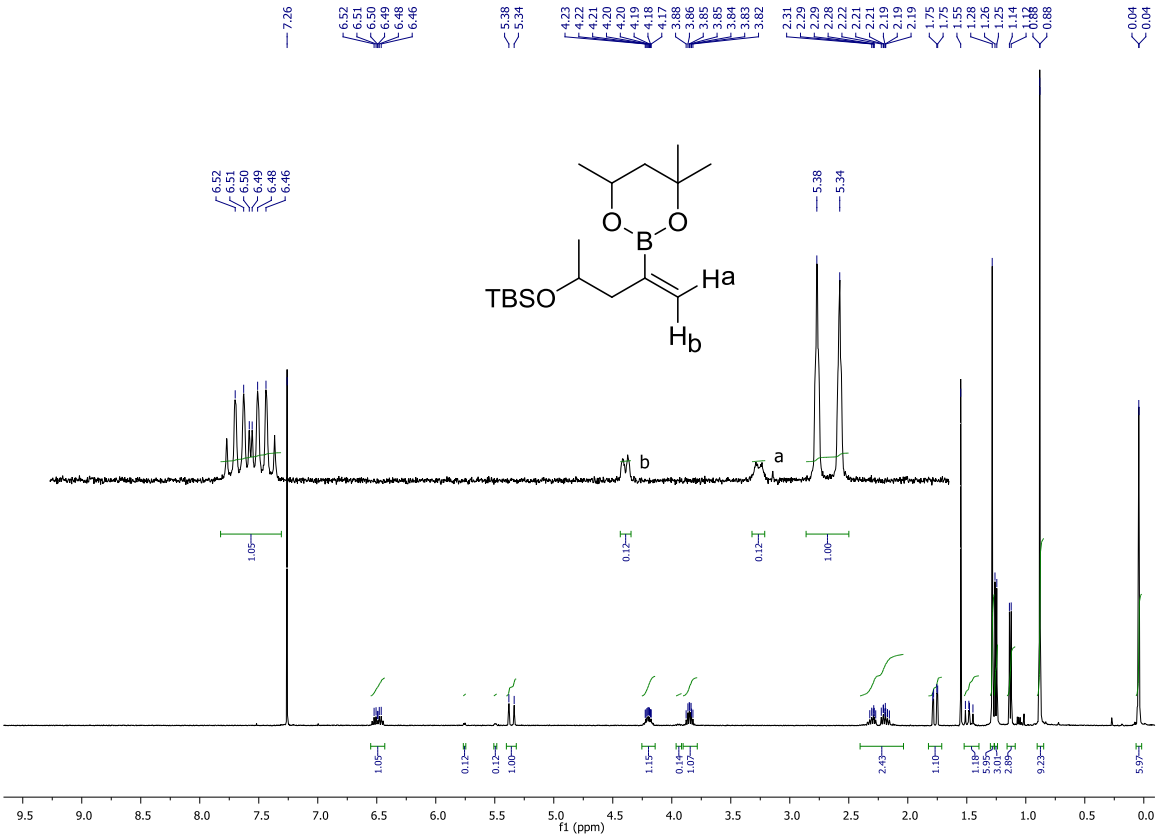
Scheme 3.12 Hydroboration of alkyne **167**



The consumption of alkyne **167** by the hydroboration with catechol was readily observed by ^{1}H-NMR which showed the lack of complete regiocontrol resulting in a 1:8 ratio of adducts **169** and **170**, respectively. After transesterification, the desired product **171** was isolated using silica gel chromatography in good yield (91%) together with the regioisomer **172**. The boronate ester **171** was more stable than boronate ester **170** being more readily purified and handled. Compound **170** decomposes completely even in the nmr tube

presumably due to facile hydrolysis.

Figure 3.10 [1]Hnmr of compound regioselectivity product **172**

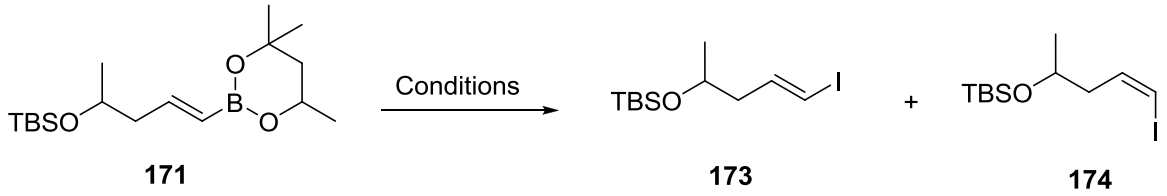


It was concluded that, despite many literature[142] reports that catecholborane gives high regioselectivity to place the boron atom preferentially at the terminal position, we found that the hydroboration with catecholborane proceeded with a lack of regiocontrol and this may be due to the unhindered nature of the triple bond at substrate alkyne **167**. The existence of regioisomer **172** was easily detected by [1]H-nmr as shown in Figure 3.10.

3.12. Iodo-deboronation

Subsequent stereoselective iodo-deboronation of **171** by initial treatment with sodium methoxide before the addition of the ICl should provide the *E*-alkenyl iodide **173** as a major product under conditions previously reported.[127a] Unfortunately, substantial amounts of the (*Z*)-isomer **174** were produced with these conditions (Equation 3.11) as explained in Table 3.10. The second step, which involved the addition of ICl was carried under low temperature conditions (entries 1, 2 and 3) and room temperature condition (entries 4 and 5). However, this did not improve the stereocontrol in the formation of alkenyl iodide **173**.

Equation 3.11 Iodo-deboronation of boronate **171**



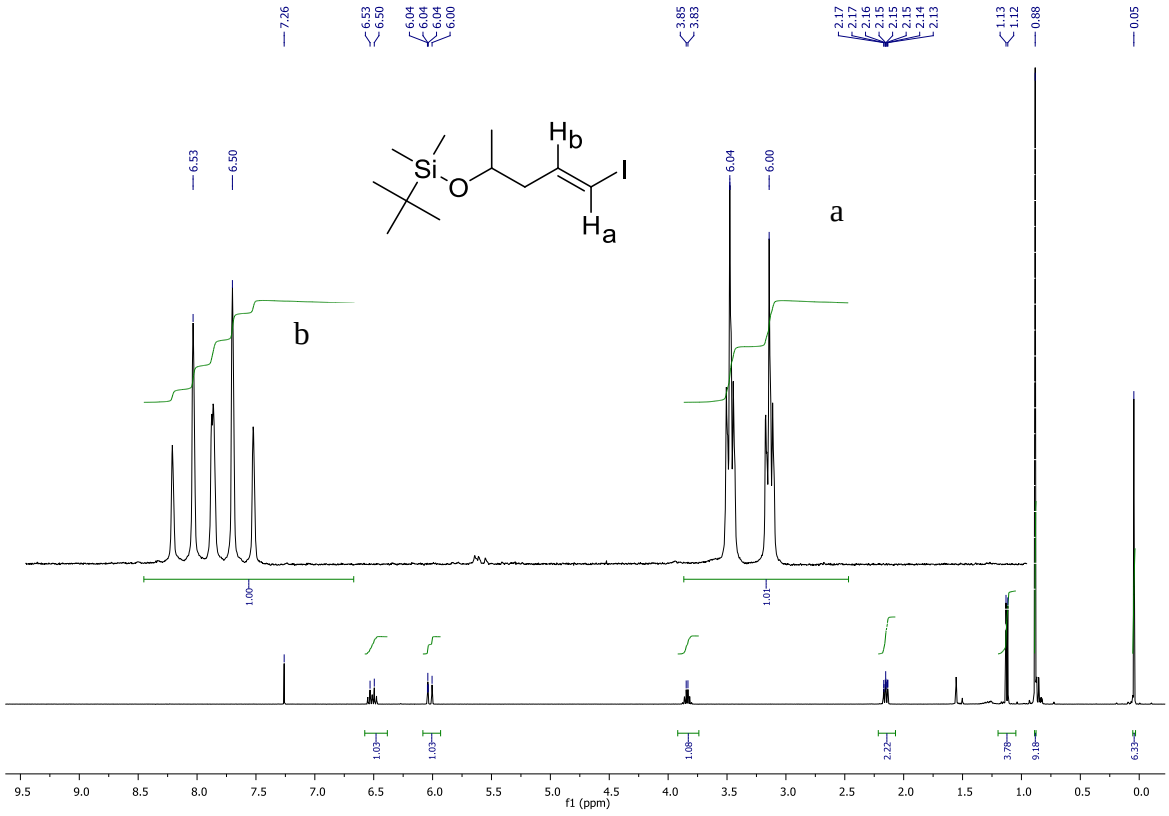
171 **173** **174**

Table 3.10 Iodo-deboronation of boronate **171** under different conditions.

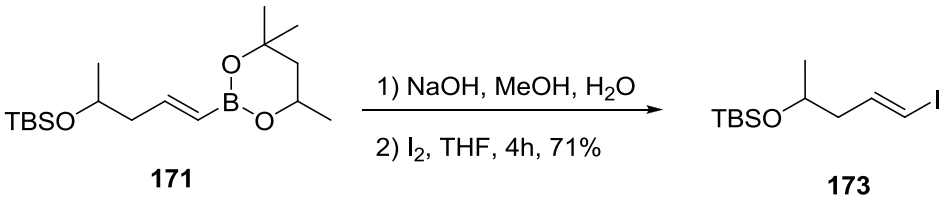
Entry	Substrate (grams)	Conditions	(173:174) or (*E*:*Z*)	Yield
1	2.0	NaOMe (1.2 eq), MeOH, rt, 30 min, then, ICl, THF, -78 ºC, 1h.	6:1	72 %
2	10.0	NaOMe (1.2 eq), MeOH, rt, 30 min, then, ICl, THF, -78 ºC, 2h.	3:1	48 %
3	1.0	NaOMe (1.2 eq), MeOH, rt, 30 min, then, ICl, THF, rt, 30 min, 0 ºC	3:1	59 %
4	1.0	NaOMe (1.2 eq), MeOH, rt, 30 min, then, ICl, THF, rt, 30 min	3:1	68 %
5	1.0	NaOMe (1.2 eq), MeOH, rt, 30 min, then, ICl, THF, rt, 10 min,	2:1	62 %

Therefore, instead of using the highly reactive ICl, the reaction conditions were adjusted by using the less electrophilic diiodine. Hence, subsequent stereoselective iodo-deboronation of boronate **171** by treatment with sodium hydroxide, followed by the addition of the diiodine[143] provided the (*E*)-alkenyl iodide **173**. This iododeboronation method (Equation 3.12) is the first application of this approach on a hindered alkenylboronate ester **171** and provides high stereoselectivity (100%) for the (*E*)-alkenyl iodide **173** as evideneced the ^{1}H NMR spectroscopy, which showed a clear 14.4 Hz *trans*-coupling (Figure 3.11).

Figure 3.11 ^{1}H NMR of the (*E*)-alkenyl iodide **173**.



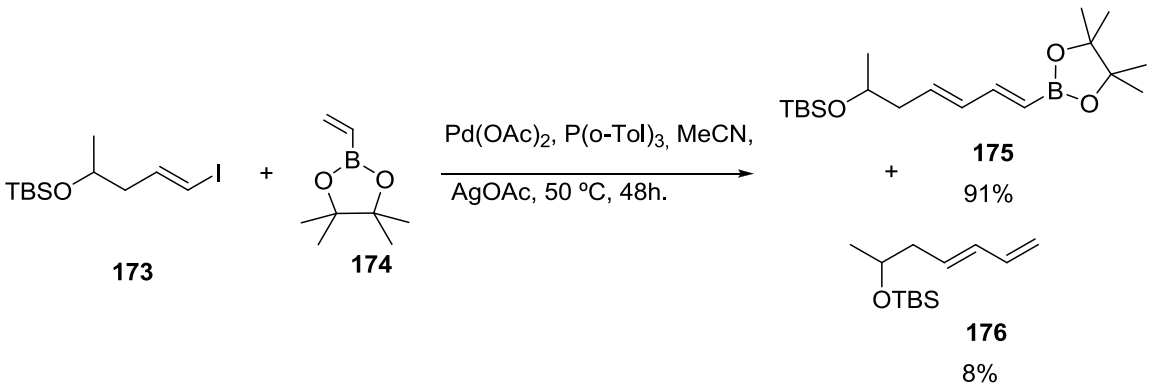
Equation 3.12 Stereoselectivity synthesis of (*E*)-alkenyl iodide **173**



171 **173**

3.13. Heck-Mizoroki couplings

Having prepared *trans*-alkenyliodide **173**, Heck-Mizoroki couplings with the commercially available vinylboronate **174** were attempted under optimized Heck-Mizoroki reaction conditions [silver(I) acetate, catalytic $Pd(OAc)_2$ and tri(*o*-tolyl)phosphine] which provided the dienylboronate **175** in 91% yield and 99% stereocontrol (see Figure 3.12).[127a] Small amounts of the of the Suzuki–Miyaura product **176** were also produced, as shown in Equation 3.13. Both products **175** and **176** are separated by SiO_2 chromatography due to the compound **175** being more polar than **176**.



173 **174** **175** 91% **176** 8%

Equation 3.13 Synthesis of boronate ester **175**

Changing the vinylboronate ester from **174** to **177** under the same optimised Heck-Mizoroki conditions (Equation 3.14),[127a] slightly improved the reaction, thus providing ester **27** in 93% yield and with less Suzuki-Miyaura product. Fortunately, both (*E*,*E*)-

dialkenyl boronate **175** and **178** had excellent *trans*-olefin selectivity (>99%) and the Suzuki-Miyaura by-product **176** was minimal and readily separated by SiO_2 chromatography.

Equation 3.14 Synthesis of boronate ester **178**

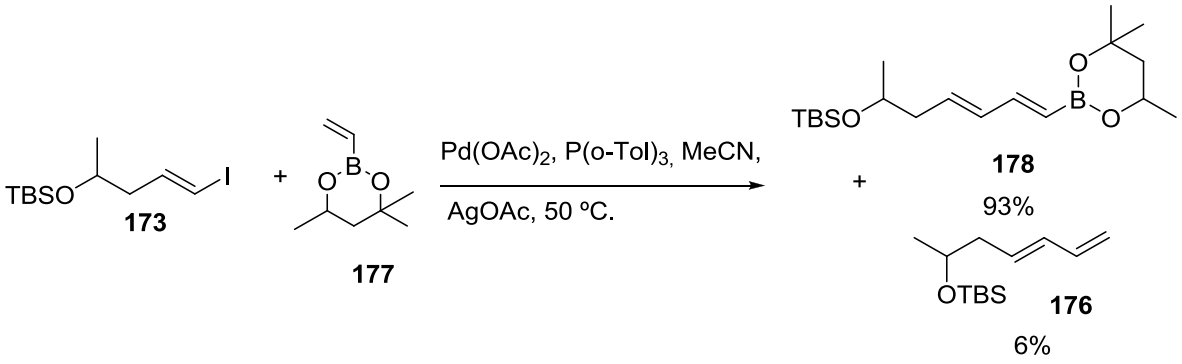
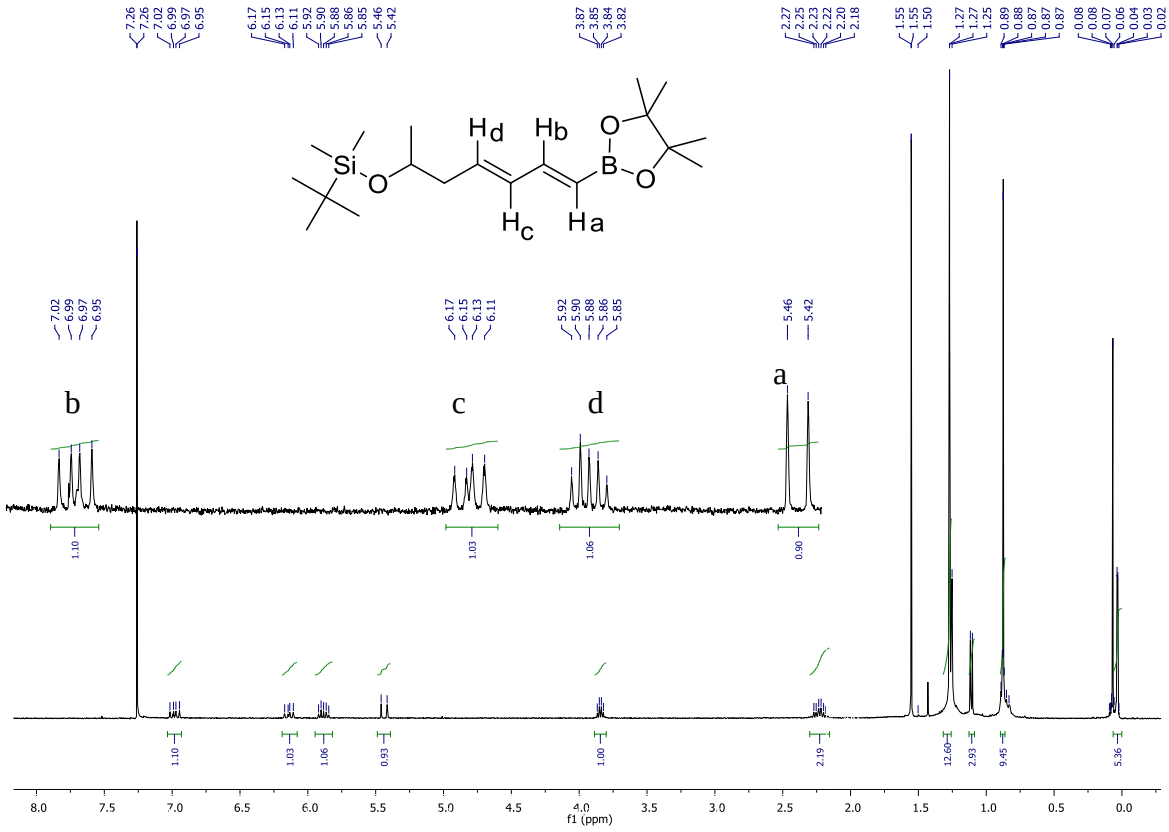
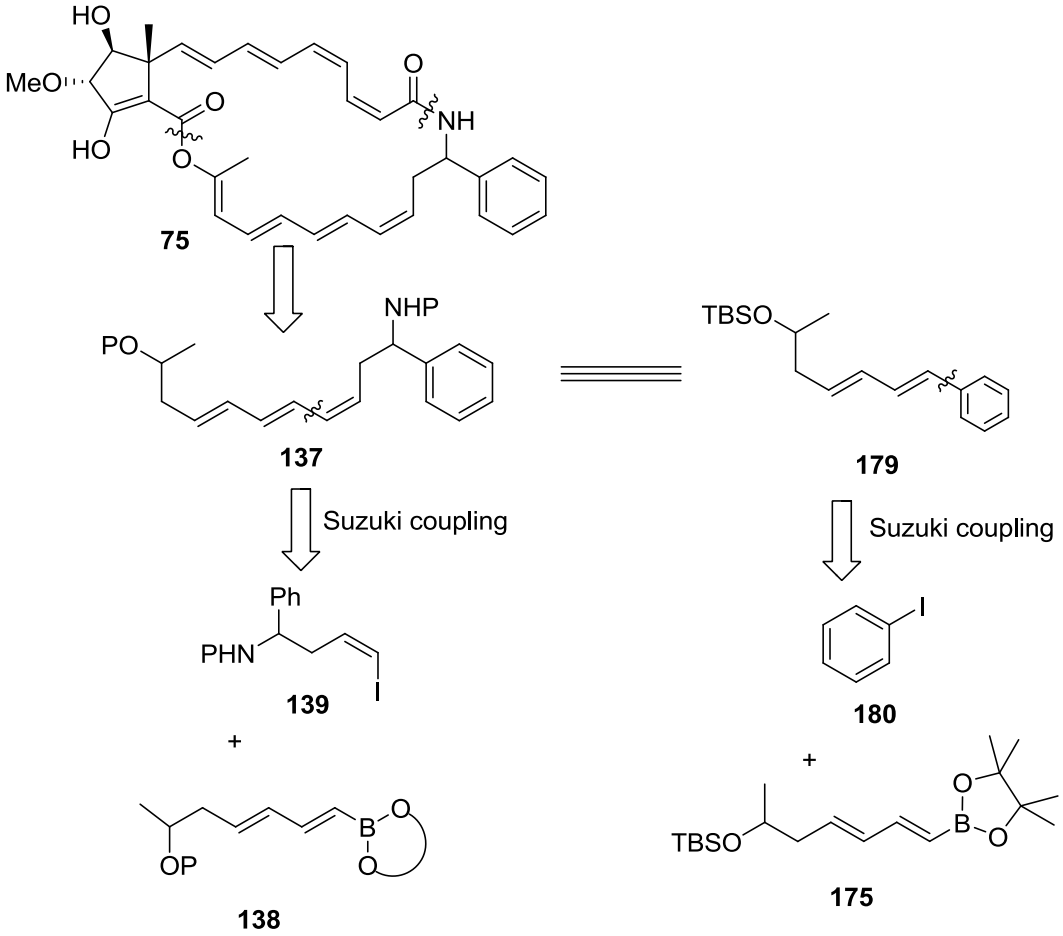


Figure 3.12 ^{1}H NMR of the dienylboronate **175**.



3.14. Model Compound for Southern Polyene of Viridenomycin

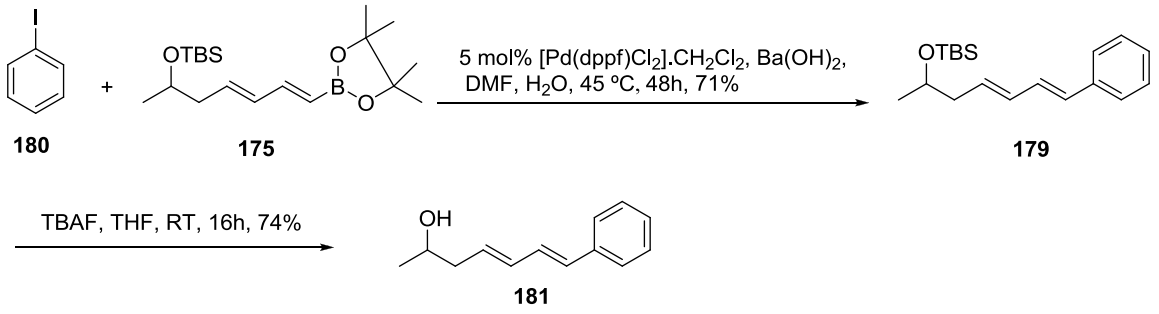
To study the synthesis and reactivity of the southern hemisphere of Viridenomycin, a structure of type **137** was required in order to examine the oxidation and enolization steps. In place of this compound, the model compound **179** was suggested (Scheme 3.13) as a structure which could be lead to develop our understanding of the behaviour of the southern section of viridenomycin **137** in the oxidation and enolization steps.



Scheme 3.13 Model compound **179** for southern part of viridenomycin **137**.

This model compound **179** was prepared from the reaction between commercially available iodobenzene **180** and the dienyl boronate ester **175**, which proceeded without incident in the presence of $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ as catalyst and $Ba(OH)_2$ as base in DMF and H_2O at room temperature, as shown in Scheme 3.13, and the products were purified by SiO_2 chromatography to give the compound **179** in 71% yield.[144] In conclusion, the conjugated (*E,E*)-dienyl aryl system is the preferred product for these Suzuki-Miyaura conditions with excellent *trans*-olefin selectivity.

The cleavage of the TBS-group of ether **179** was conveniently carried out using 1 M tetrabutylammonium fluoride (TBAF) in THF, which gave the corresponding alcohol **181** (Scheme 3.14) in 74% yield as a yellow solid.



Scheme 3.14 Synthesis of the compound **181**

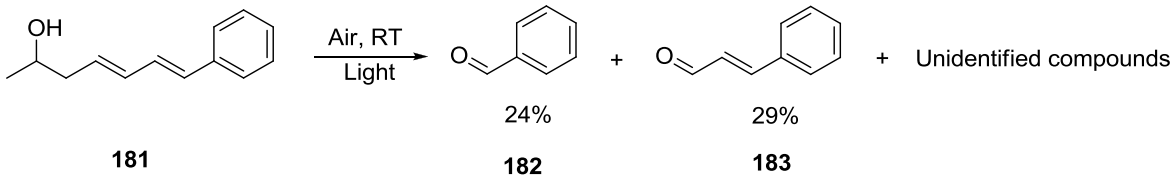
3.14.1. The decomposition of alcohol 181

The alcohol **181** was found to be unstable at room temperature even when stored as a solid, and thus was preferably kept in the fridge under an inert atmosphere because it decomposed at rt in air to give cinnamaldehyde **182**, together with other components (Equation 3.15). Indeed, a solid sample of alcohol **181** after standing at rt in air was transformed into an oily

material. Purification by silica gel chromatography to give both benzaldehyde (24%) and cinmaaldehyde (29%) respectivetly together with other mixed and unidentified fractions.

The main reason is possibly that the photo-autoxidate process is likely to cleavage of the electron-rich olefins which leads to the decomposition of the whole structure. The autoxidation mechanism has been explained before on the basis of the free-radical processes.[145a-d]

Equation 3.15 The decomposition of alcohol **181**.

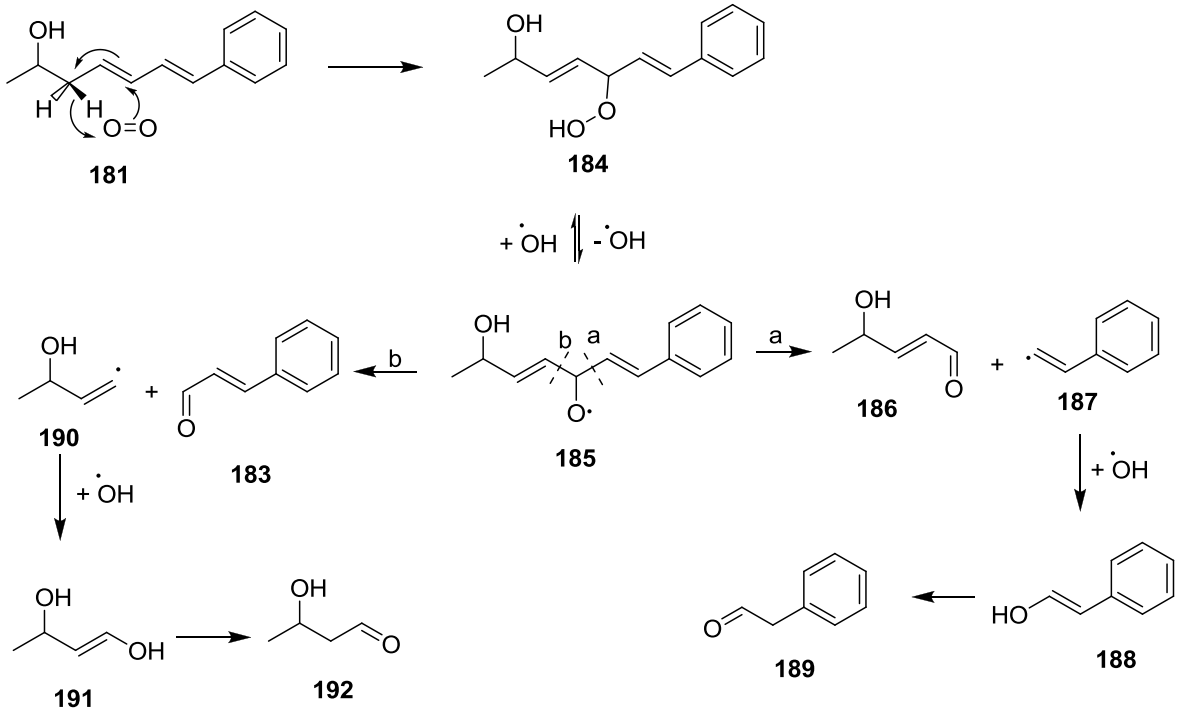


Moreover, the autoxidation of electron-rich substrates under ambient conditions can, in general terms, be characterized by α-oxidation (or allylic) oxidation products.[145b] "With unsaturated fats, susceptibility to autoxidation is dependent on the availability of allylic hydrogens for reactions with peroxy radicals."[145d]

A suggested mechanism for the autooxidation of **181** (Scheme 3.15) is similar to the mechanism of autoxidation of unsaturated fats (linoleate autoxidation).[145d] The first step is hydrogen abstraction on the reactive allylic carbon of compound **181** by the reaction with molecular oxygen, which provides unsaturated hydroperoxide **184**. The next step is the decomposition of an unsaturated hydroperoxide **184** by the homolytic cleavage of the oxygen-oxygen bond to yield an alkoxy **185** and hydroxy radical.[145d] Carbon-carbon cleavages (a) and (b) lead to aldehydes **186** and **183** and olefin radicals **187** and **190**, which

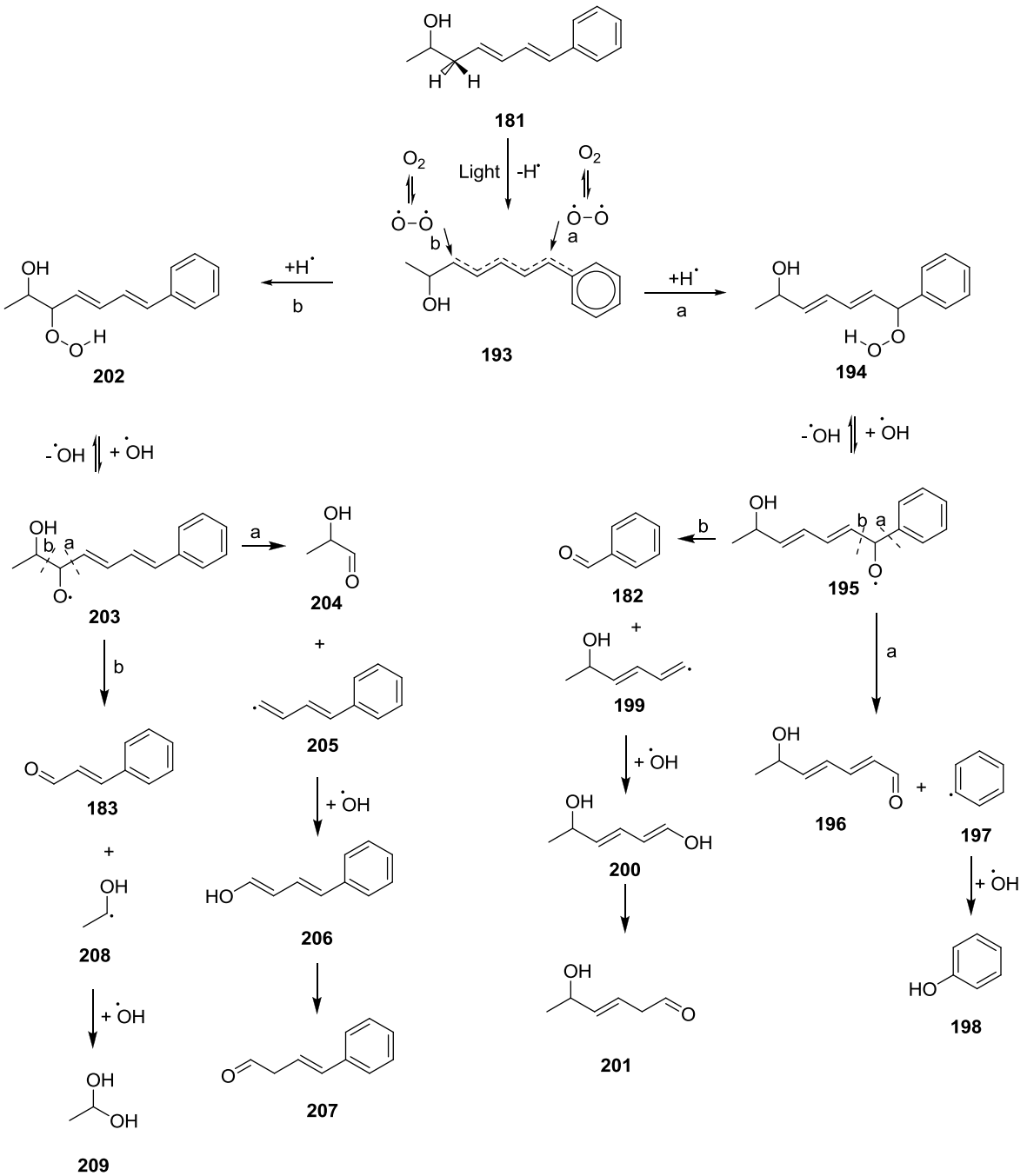
then react with hydroxy radicals to form enols **188** and **191**, and hence tautomerize to the corresponding aldehydes **189** and **192** (Scheme 3.15).

Scheme 3.15 Suggested mechanism for autoxidation of alcohol **181**.



The reaction of molecular oxygen with pentadienyl radical **193** can produce a mixture of unsaturated hydroperoxides **194** and **202**. The most favourited site for the attacking of molecular oxygen is the ends of pentadienyl radical **193** (a and b), as shown in Scheme 3.16. In the following reaction sequence, the first step of the decomposition of the unsaturated hydroperoxides **194** and **202** is the homolytic cleavage of the oxygen-oxygen bond to yield alkoxy radicals **195** and **203** and hydroxy radicals.[145d] Carbon-carbon cleavages (a) and (b) provides aldehydes **196** and **183** and olefin radical **187**, which then

reacts with hydroxy radicals to form 1-enols, which tautomerize to the corresponding aldehydes (Scheme 3.16).

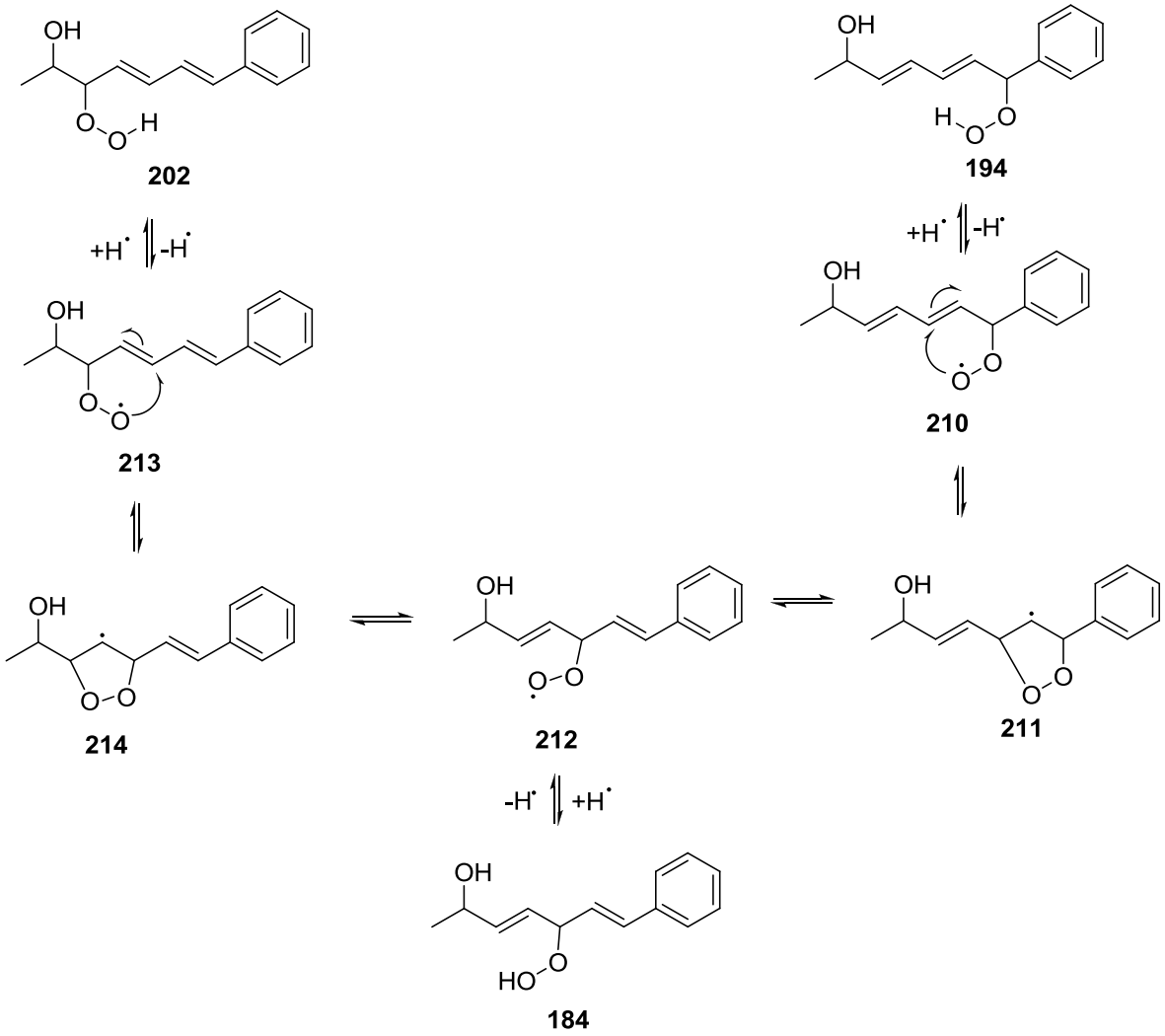


Scheme 3.16 Suggested mechanism for autoxidation of alcohol **181**.

Another suggested mechanism depends on the sensitivity of electron-rich compounds to both air and light (photooxidation). The photosensitized allylic alcohol **181** can be the subject of abstract hydrogen by light to give pentadienyl radical **193** (Scheme 3.16).

In another approach, both unsaturated hydroperoxides **194** and **202** can lose hydrogen to lead to the formation of five-membered epidioxides **211** and **214**.[145d] The five-membered ring in compounds **211** and **214** can then be reopened and gain a hydrogen radical to give unsaturated hydroperoxide **184**, which decomposes as explained in Scheme 3.17.

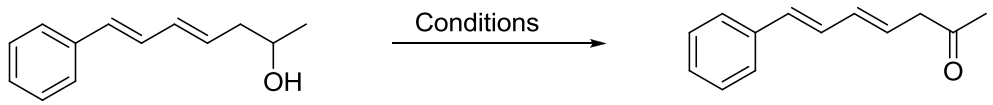
Scheme 3.17 Suggested mechanism for autoxidation of alcohol **181**.



3.14.2. Oxidation of allylic alcohol 181

Unfortunately, attempts to oxidize (Equation 3.16) the alcohol **181** with pyridinium chlorochromate (PCC) as a mild oxidizing agent in the presence of sodium acetate led only to decomposition (Table 3.11, entry 1).[146a] The oxidation of alcohol **181** to the ketone **215** with Dess-Martin periodinane (DMP) without $NaHCO_3$ (entry 2) did not afford the desired product either.[146b] Attempts to oxidize alcohol **181** by activated manganese(IV) oxide and potassium permanganate led to over-oxidation of the substrate (entry 3), which could be due to the effect of a strongly acidic oxidant potassium permanganate.[146c] The Swern oxidation of alcohol **181** to the corresponding ketone **215** using oxalyl chloride and dimethyl sulphoxide (entry 4) provided the desired product, but in low yield (39%) after SiO_2 chromatography.[146d]

Equation 3.16 Attempts conditions to oxidize the alcohol **181** to the ketone **215**.



181 **215**

Table 3.11 Attempts to oxidize the alcohol **181** to the ketone **215**

Entry	Conditions	Result
1	NaOAc (0.08 eq), PCC (2.0 eq), DCM, 2h, rt.	Decomposition
2	DMP (1.1 eq), DCM, 2h, rt.	Decomposition
3	$KMnO_4$ (3.2 eq), MnO_2 (17.3 eq), DCM, 3h, rt.	Decomposition
4	$(COCl)_2$ (2 eq), DMSO (4 eq), DCM, -78 ºC, 10 min, then Et_3N (5 eq), -78 ºC to rt.	39% (keto-enol form)
5	$NaHCO_3$ (3 eq), DMP (2.0 eq), DCM, 2.5 h, rt.	91%
6	$NaHCO_3$ (3 eq), DMP (1.5 eq), t-BuOH (0.8eq), DCM, 4h, rt.	100%

The oxidation with DMP in the presence of sodium carbonate at 0 °C (entry 5) led to the

desired product **215** as a main product in 81 % after SiO_2 chromatography. The sodium carbonate most likely prevents the effect of the by-product acetic acid from causing the decomposition of the product **215**.[146e] The best conditions for this oxidation were, therefore, obtained for the Dess-Martin periodinane, $NaHCO_3$ and *tert*-butanol as a catalyst (entry 6) providing a quanitative yield after isolation by SiO_2 chromatography.[146f] Table 3.11 summarizes the conditions which used to oxidize alcohol **181** to ketone **215**.

3.14.3. Enol-acetylation of ketone 215

In order to investigate both the stereselectivity and regioselectivity of enol-esterification in conjugated beta-ethylene dienes, such as **215**, the reaction conditions were initially examined involving a simple anhydride and pyridine. The aim being to model suitable conditions for the coupling of a ketone of type **136** with model of an activated acid derivative of building block **134**. Hence, enol acetylation of ketone **215** with acetic anhydride in the presence of pyridine at room temperature led to the desired product **216** (65%) as a mixture of (*E*) and (*Z*)-enolacetates in a 4:1 ratio as shown in Figure 3.13 (Equation 3.17). The existence of the regioselectivity product **217** was also indicated clearly by ^1H NMR spectroscopy due to the readily observed CH_2 resonance at δ_H 2.31-2.45 ppm. The regioselectivity of the formation of the enol ester **217** was unexpected since the hydrogens in the α-positions next to the dialkenyl aromatic are usually more acidic than the α-protons at the methyl group, and hence, the thermodynamically contolled enol-esterification conditions were expected to produce **216** with higher selectivity.

Equation 3.17 Enol-acetylation of ketone **215**

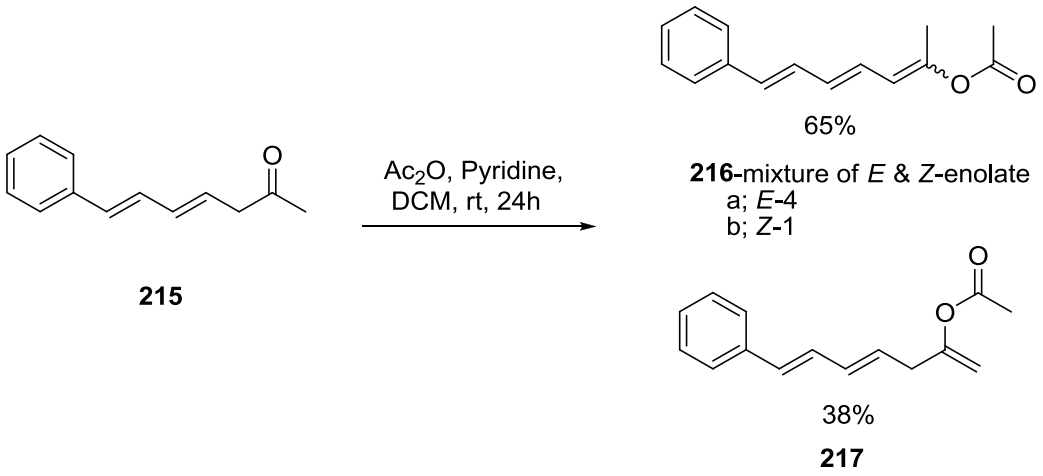
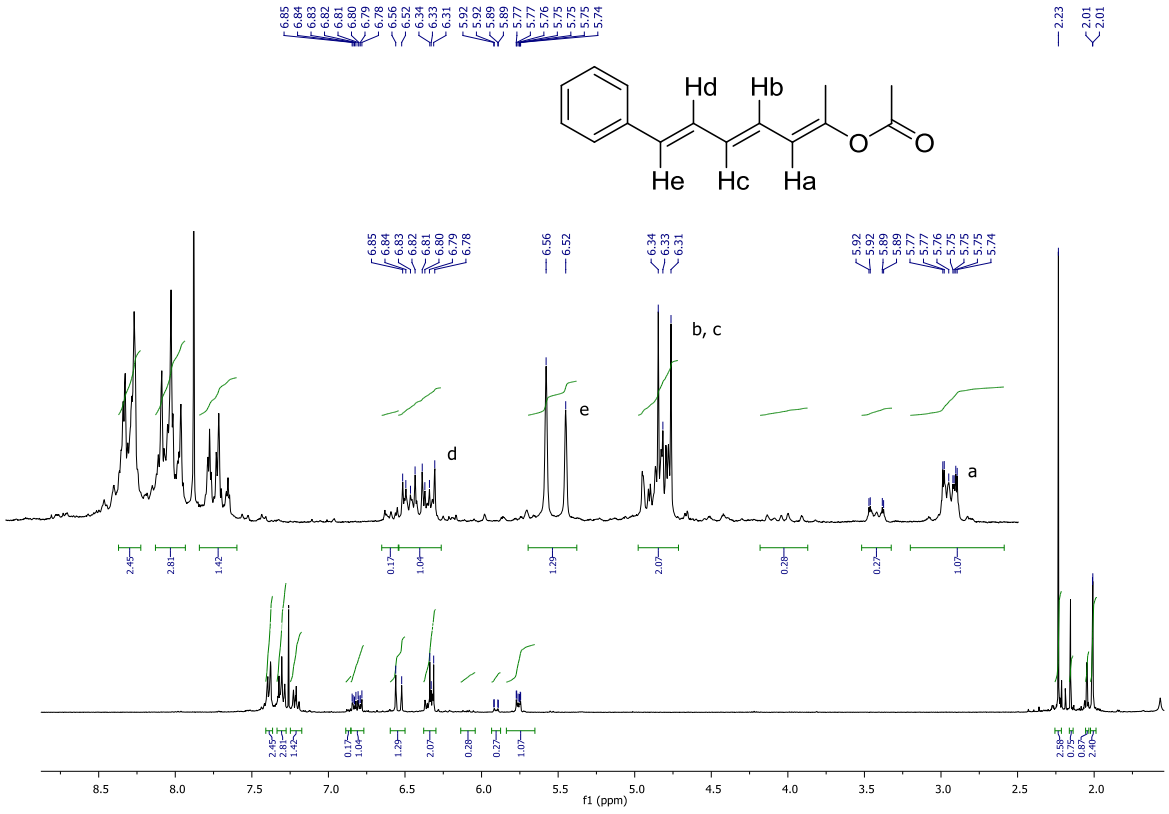


Figure 3.13 [1]Hnmr of compound **216**.



3.14.4. Enol-esterification of ketone 215

As a second, and more advanced, model for the potential coupling acid **134** with ketone **136**, the enol-esterification of model **215** was investigated with phenybutric acid derivatives. Firstly, commercial available 4-phenylbutyric acid **218** was as used to test the reactivity of ketone **215** towards the synthesis of enol ester **220** (Scheme 3.18). Many conditions were used and are summarized in Table 3.12.

Scheme 3.18 Attempts to Synthesis of Enol-ester **220** of Ketone **215**

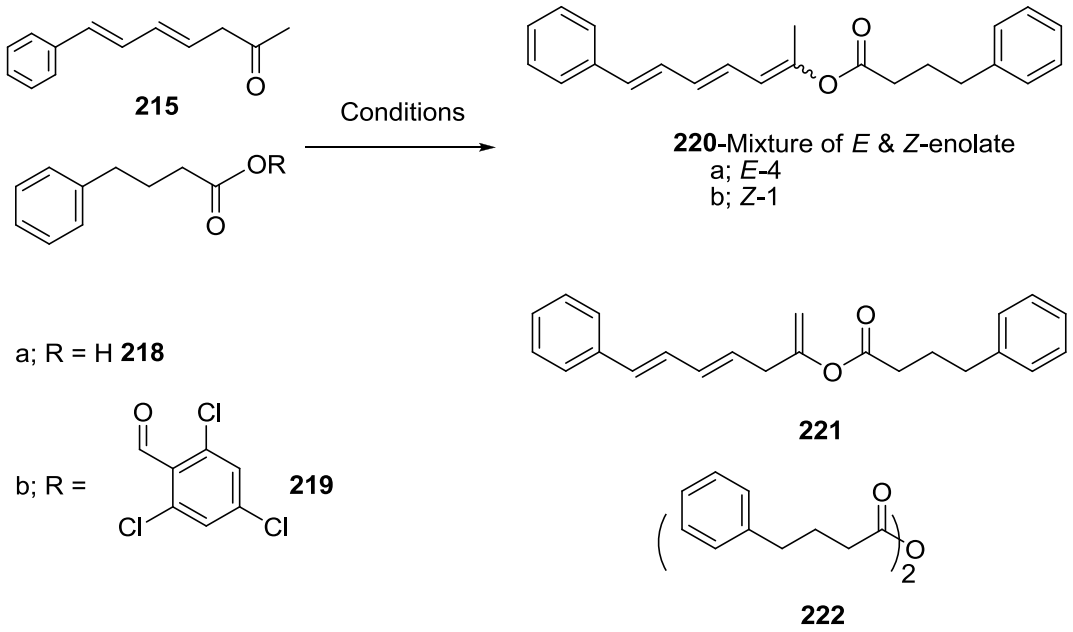


Table 3.12 Attempts to synthesis enol-ester **220** of ketone **215** with different conditions

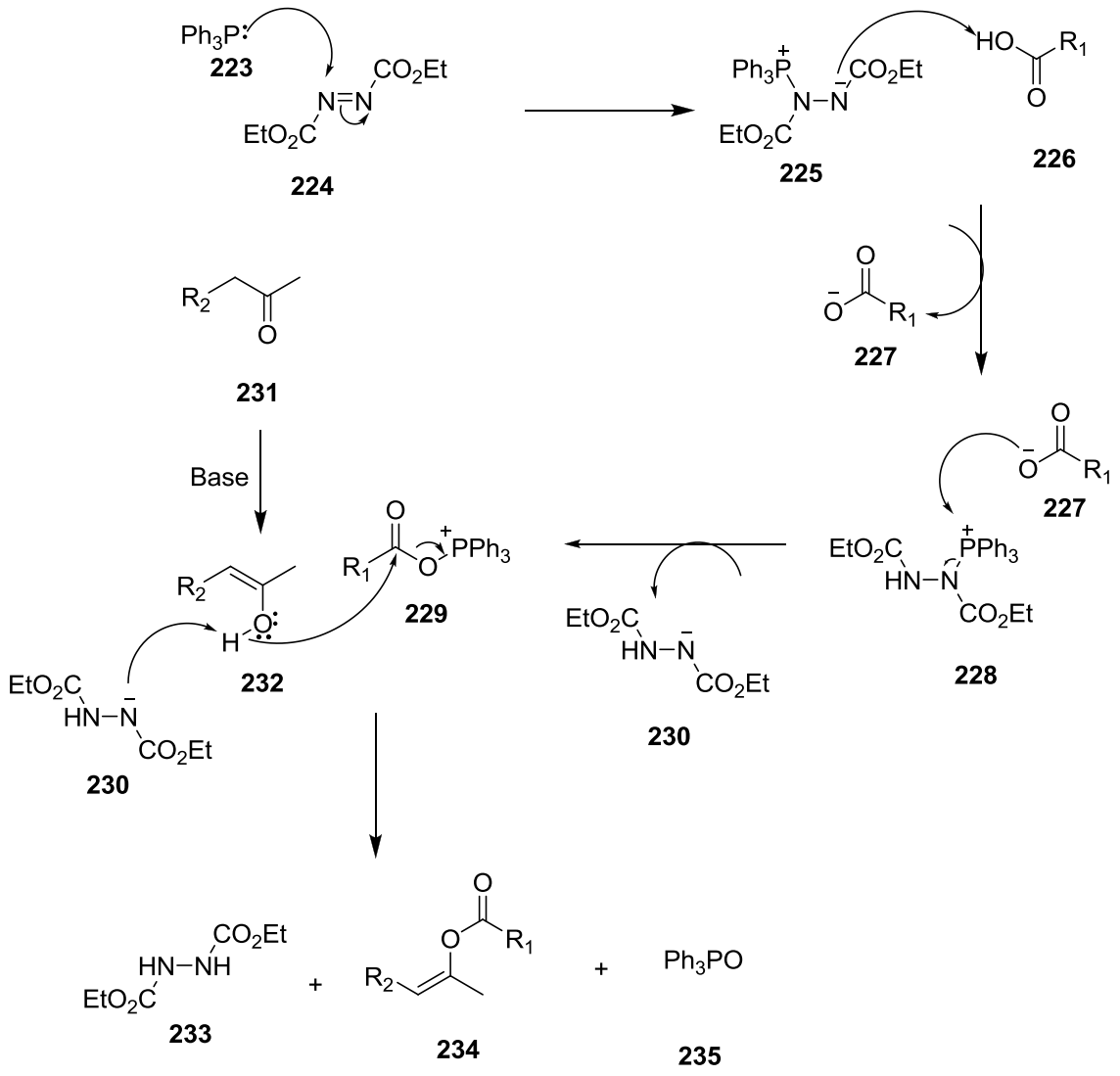
Entry	Conditions	Result
1	**215**, PPh_3 (1.05 eq), DMAP (1.0 eq), DEAD (1.05 eq), **218** (1.1 eq), THF, rt, 22h.	SM
2	**215**, CDI (1.1 eq), THF, **218** (1.1 eq), rt, 3 days.	SM
3	**215,** CDI (1.1 eq), DMAP, THF, **218** (1.1 eq), rt, 23h.	SM
4	**215**, Et_3N (3.0 eq), DMAP (10 mol%), toluene, rt, 3h, then,	SM

	CDI (1.1 eq), **218** (1.1 eq), 48h.	
5	**215**, Et_3N (4.0 eq), DMAP (1.0 eq), toluene rt, 3h, then, TFAA (4.8 eq), **218** (4.8 eq), 2h.	**222** (33 %), **220** (5%)
6	**215**, pyridine (2 eq), DMAP (10 mol%), toluene, 2h, then TFAA (1.1 eq), **218** (1.1 eq), rt, 4h.	**222** (83%)
7	**215**, Et_3N (3.0 eq), DMAP (10 mol%), toluene, rt, 10 min then add mixed anhydride **219** (1.0 eq), 24h.	**222** (24%), **220** (27%)
8	**215**, pyridine (3.0 eq), DMAP (10 mol%), THF, rt, 10 min then add mixed anhydride **219** (1.0 eq), 24h.	**220** (29%), **222** (23%),
9	**215**, Et_3N (3.0 eq), DMAP (10 mol%), HMPA (0.1 eq), toluene, rt, 2h then add mixed anhydride **219** (1.0 eq), 24h.	**220** + **221** (15%), **222** (57%)
10	**215**, Et_3N (3.0 eq), DMAP (10 mol%), toluene, rt, 10 min then add MNBA (1.1 eq) and **218** (1.1 eq), 16h.	**220** + **221** (45%), **222** (28%)
11	**215**, Et_3N (3.0 eq), $ZnCl_2$ (15 mol %), toluene, rt, 10 min then add MNBA (1.1 eq) and **218** (1.1 eq), 24h.	**222** (100%)
12	**215**, Et_3N (3.0 eq), TMSCl (1.05 eq), $ZnCl_2$ (1.0 eq), DCM, rt, 4h, then add mixed anhydride **219** (1.0 eq), 23h.	**222** (85%)

i- Mitsunobu Reaction (Table 3.12, Entry 1)

The Mitsunobu reaction is a condensation-dehyration reaction, in which triphenyphosphine **223** is oxidized to triphenylphosphine oxide **235**, and diethylazodicarboxylate (DEAD) **224** is reduced to hydrazine dicarboxylate **233**.[147a] The synthesis of ester **220** from ketone **215** by the reaction with 4-phenylbutyric acid **218** in the presence of a catalytic amount of dimethylaminopyridine (DMAP) to generate enol system with Mitsunobu reaction conditions (entry 1) did not lead to the desired product **220**.[147a] The suggested mechanism for this type of enol-esterification is explained in Scheme 3.19.

Scheme 3.19 Mechanism of enol-esterification wih DEAD **224** as a reagent

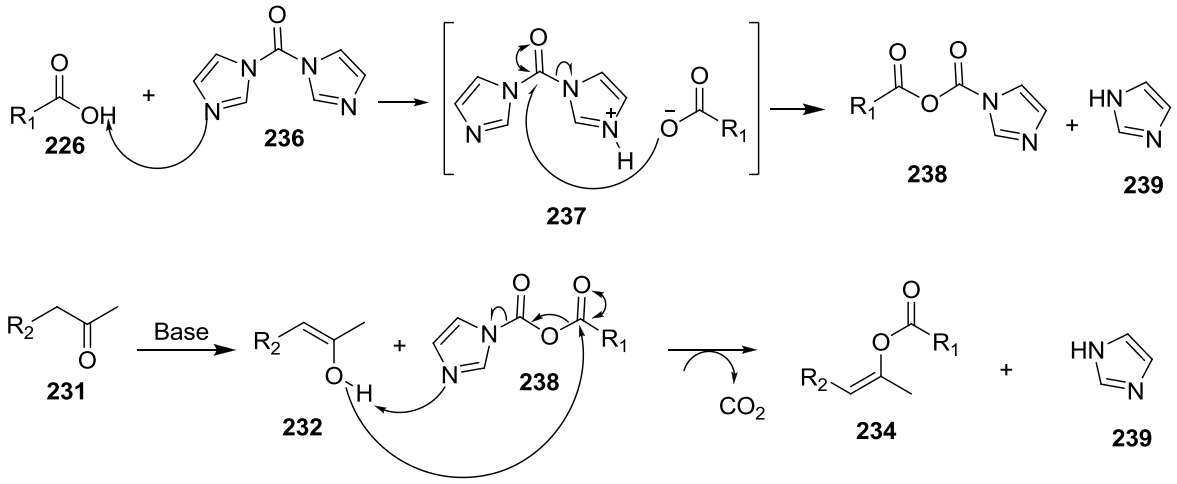


ii- Application of CDI 236 reagent for enol esterification of ketone 215 (Table 3.12, Entries 2-4)

1,1'-Carbonyldiimidazole (CDI) **236** is often used for esterfication reactions.[147b] Unfortunately, attempts to apply CDI conditions (entry 2, 3 and 4) for ketone **215** did not lead to the desired product **220**. The suggested mechanism for this type of enol-

esterification is explained in Scheme 3.20.

Scheme 3.20 Mechanism of enol-esterification with CDI **236** reagent



iii- Application of TFAA reagent for enol esterification of ketone 215 (Table 3.12, Entries 5 and 6)

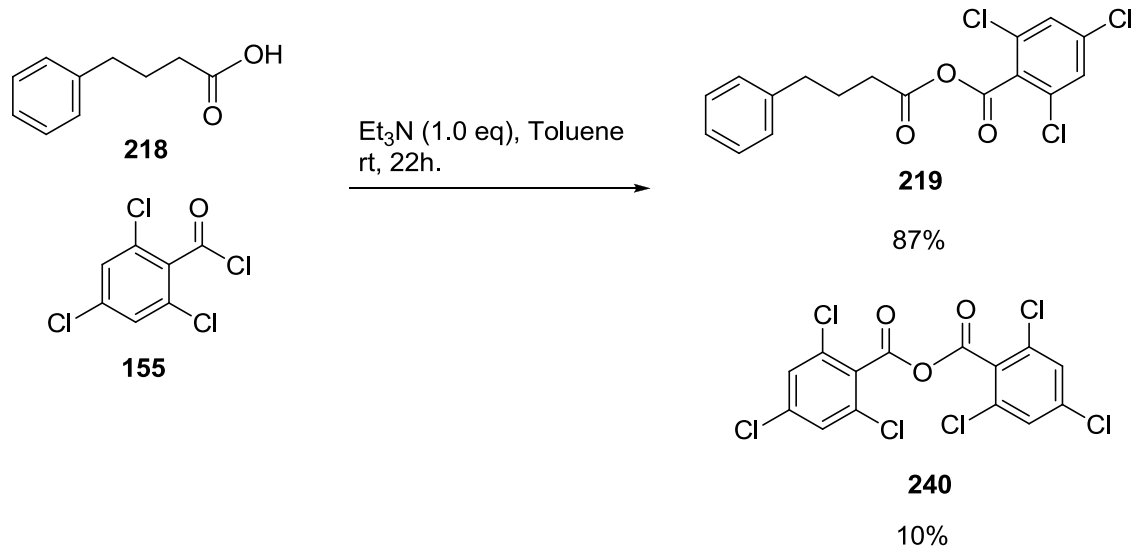
The treatment of 4-phenylbutyric acid **218** with trifluoroacetic anhydride **(**TFAA) should generate mixed anhydride, which added directly to mixture of ketone **215**, triethylamine and DMAP as a catalyst should form the enol ester **220**. Unfortunately these conditions (entry 5) led to the desired product **220** in very low yield (5 %). 4-Phenylbutyric anhydride **222** appeared as a main by-product (entry 6) in 83% in the presence of stoichiometric pyridine.

iv- Application of Yamaguchi reagent 155 for enol esterification of ketone 215 (Table 3.12, Entries 7 - 9)

The enol esterification was performed using the Yamaguchi's strategy[174c] (entry 7). Firstly,

the mixed anhydride **219** was synthesized from the commercial available 4-phenylbutyric acid **218** and 2,4,6-trichlorobenzoyl chloride (Yamaguchi reagent) **155** (Equation 3.18) and then subjected to Yamaguchi's conditions in toluene and THF (entry 7 and 8 respectively), which both afforded the desired product **220** (24%) with the symmetrical anhydride **222**. Using HMPA as the polar solvent and DMAP as catalyst with mixed anhydride **219** (entry 9) led to a loss of regioselectivity, providing a mixture of products **221** and **221** in ratio of 4:1 according to ^{1}H NMR.

Equation 3.18 synthesis of mixed anhydride **219**



v- Application of MNBA reagent 157 for enol esterification of ketone 215 (Table 3.12, Entries 10 - 12)

On other hand, using 2-methyl-6-nitrobenzoic anhydride (MBNA) **157** with triethylamine in the presence of DMAP (entry 10) resulted in the highest increase in the enol ester **221**

formation as a 3:1 mixture with enol ester **220**. Furthermore, using the Lewis acid $ZnCl_2$ as a catalyst under the MNBA conditions (entry 11), this gave the symmetric anhydride **222** as a main product.[147d]

In another method, the trimethysilyl enol ether of ketone **215** was generated (entry 12) and then reacted with mixed anhydride **219**, which give the symmetric anhydride **222** (83%). As mentioned before, this is the by-product 4-phenylbutyric anhydride **219**, which appeared as a main product and resulted in high yield as a competitive by-product in several entries in Table 3.12, which contributed to the low yield of the desired product **220**.

3.14.5. Conclusion:

The conditions that lead to the by-product, the symmetric anhydride **222** for example, with the catalyst $ZnCl_2$, which lead to produce **222** as a major product (entries 6, 11 and 12) need to avoided in order to access enol ester derivatives. Using CDI did not afford any significant amount of the enol ester (entries 2 to 4). The desired product (*E*)-enol ester **220** is the thermodynamic product of enolisation of **215** and the kinetic product is the regio-isomer enol ester **221**, so the conditions, which gave the thermodynamic product **220**, are required (i. e. no catalyst). The ^{1}H NMR of compound **220** as a pure single isomer, which obtained by recrystallization using methanol (Table 3.12, entry 7), is explained in Figure 3.15. Hence the best conditions for the formation of **220** were using the Yamaguchi conditions and there (as entry 7, Table 3.12) gave **220** as a single, pure compound in 13% yield of the recrystallization from methanol.

Figure 3.14 ^{1}H NMR of compound **220** before crystallisation

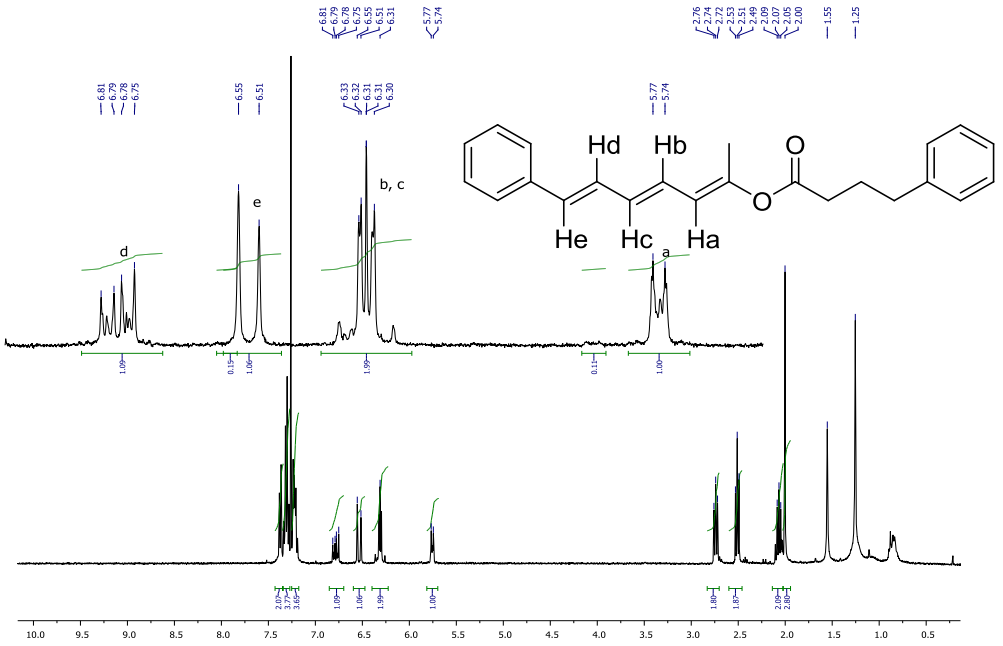
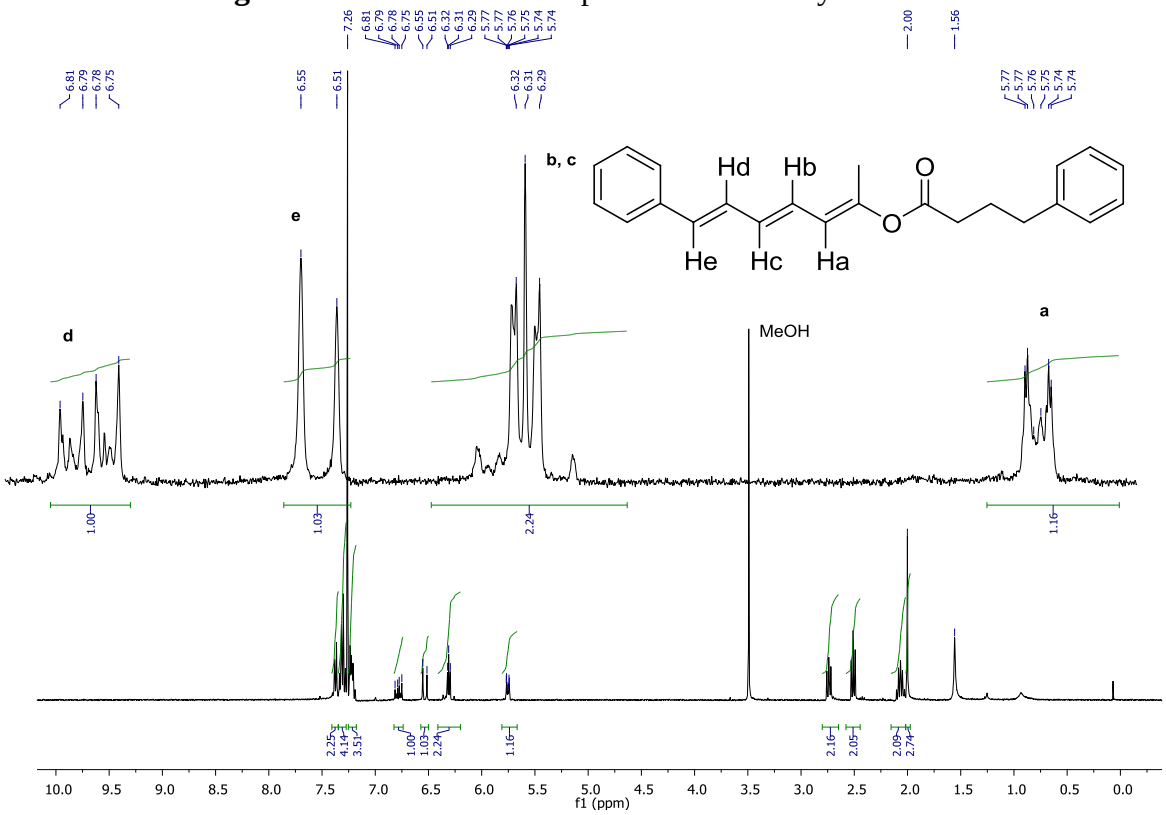


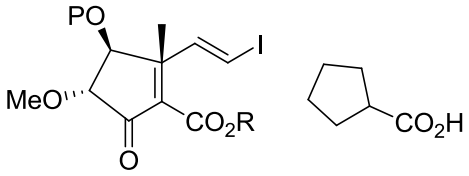
Figure 3.15 ^{1}H NMR of compound **220** after crystallization.



3.14.6. Attempts to synthesis of enol-ester 246 of ketone 215.

As the model of cyclopentene core of viridenomycin (see Scheme 2.10), the commercial available cyclopentane carboxylic acid **241** was used for this purpose and to study its reactivity towards the enol esterification reaction with ketone **215**.

Figure 3.16 Cyclopentane carboxylic acid **241** as a model of viridenomycin core **134**.

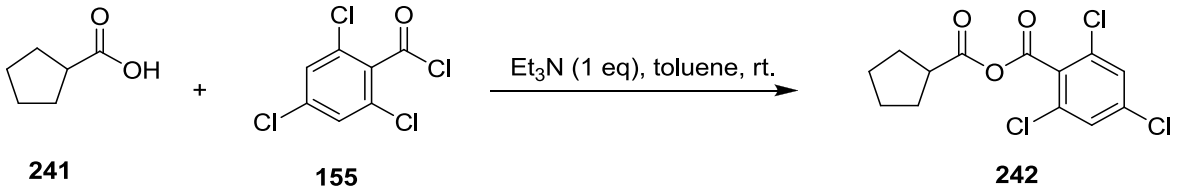


134 **241**

R = H

Using Yamaguchi method, treatment of cyclopentane carboxylic acid **241** with 2,4,6-trichlorobenzoyl chloride **155** generated the mixed anhydride **242** as a stock solution which was used without further purification.

Equation 3.19 Generation of mixed anhydride **242**.



241 **155** **242**

When mixed anhydride **242** was used to react with the commercial available acetophenone **243** as shown in Table 3.13 (Entry 1) and Scheme 3.21, no significant for olefinic protons corresponding to an enol-ester **244** were detected by ^{1}H NMR spectra. The conditions (Table 3.13, Entry 2) also did not led to the enol-ester **244**. It was concluded that despite the simplicity of the structure of enol-ester **244**, there is a difficulty in producing this enol ester,

because of the conjugated aromatic system which neighbouring for the carbonyl group. Moreover, generating carbanion of ketone **243** is difficult and it can react in different ways that led to a mixture for undesirable products. It thus seems that the model ketone **215** is better than the commercially available acetophenone **243** for the enol-esterification reactions.

Scheme 3.21 Attempts to synthesis enol-ester **244** of ketone **243.**

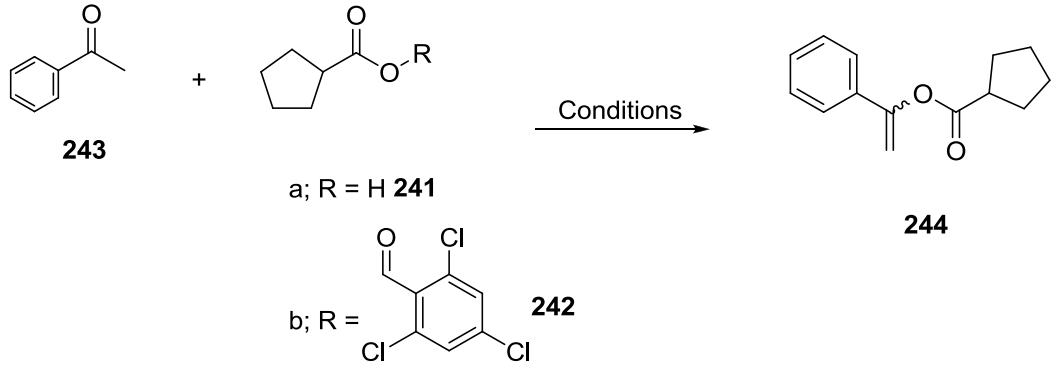


Table 3.13 Attempts to synthesis enol-ester **244** of ketone **243** with different conditions.

Entry	Conditions	Result
1	**243**, pyridine (6.0 eq), DMAP (5 mol%), toluene, rt, mixed anhydride **242** (3 eq), 48h.	No significant to olefinic protons by ^{1}H NMR spectra.
2	**243**, pyridine (6.0 eq), DMAP (5 mol%), MNBA (1.3 eq), THF, rt, 10 min then add **241** (1.3 eq), < 48h.	No reaction.

Therefore, the mixed anhydride **242** was generated as the reagent to react (Scheme 3.22) with ketone **215** under different conditions (Table 3.14, Entries 1-3). The best conditions were obtained from Entry 3 (Table 3.13) with using DMAP as a catalyst, however, the problem was how to isolate the desired enol-ester **246** from the mixture of other enol-esters and the by-products such as the symmetrical and unsymmetrical anhydrides. By using silica

gel chromatography, the desired enol-ester **246** was not isolated. Therefore, working on the enol-esterification reaction using this model **215** perhaps needs further studies and the development of completely new approaches for enol-esterification reacrions.

Scheme 3.22 Attempts to synthesis enol-ester **246** of ketone **215**.

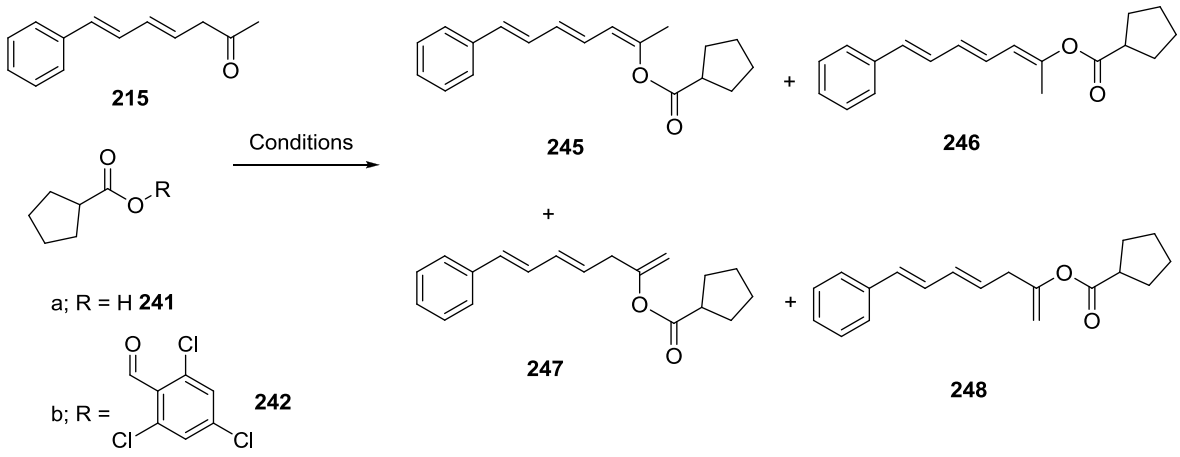


Table 3.14 Attempts to synthesis enol-ester **246** of ketone **215** with different conditions.

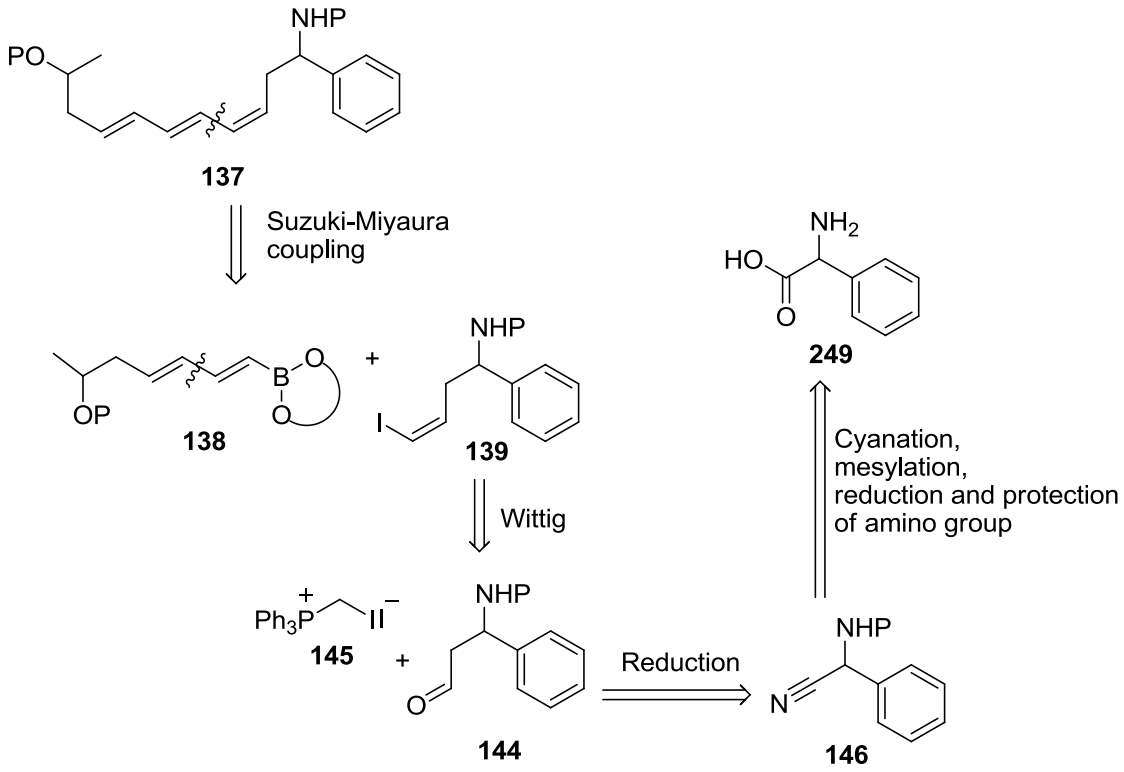
Entry	Conditions	Result
1	**215**, Et_3N (3.0 eq), toluene, rt, 20 min, then add mixed anhydride **242** (2 eq), 3days.	The reaction was very slowly and the staring material was still present in the reaction after 3 days.
2	**215**, Et_3N (3.0 eq), DMAP (10 mol%), THF, rt, 10 min then add **241**(1.1 eq), 24h.	Unidentified mixture of enol esters (16%)
3	**215**, Et_3N (3.0 eq), DMAP (10 mol %), HMPA (0.1 eq), toluene, rt, mixed anhydride **242** (2.0 eq), 24h.	Unidentified mixture of enol esters (60%)

3.15. Enantioselective synthesis conditions of alcohol 250

According to the retrosynthetic plan of the compound **139** (Scheme 3.23), the synthesis began with a one-pot reduction-protection of the amino acid **249** using sodium

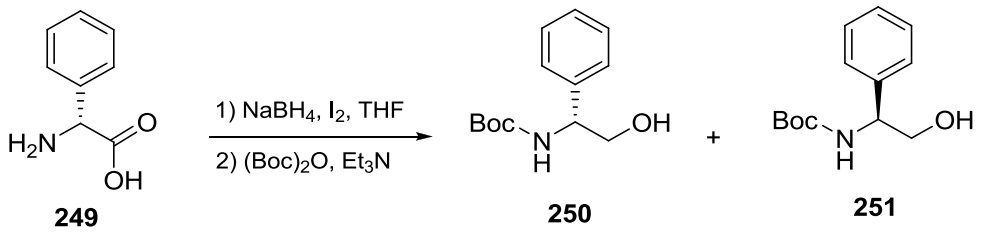
borohydride-iodine then *N*-Boc protection of the amino group with di-*tert*-butyl dicarbonate in the presense of triethyl amine as base.[148] This was an efficient, optimized overall process, and to our knowledge there are only two other reported examples of a one-pot amino acid reduction/*N*-protection sequence.[149] Both employ lithium aluminumhydride (LAH) to achieve the reduction prior to *N*-protection with Boc_2O, affording the *N*-Boc-amino alcohols in 69–83% yield.[149] In all other instances, the amino alcohols, usually obtained *via* LAH, activated borohydride or mixed anhydride reductions, are isolated prior to *N*-protection and often extensive aqueous work-ups are required following the reduction methods cited leading to diminished yields.[149] The protocol[148] employed herein is rapid, efficient and readily scaled up.

Scheme 3.23 The retrosynthetic plan of the compound **139**



During the first phase of this study, our efforts involved attempts to isolate the pure alcohol derivative **250** from starting amino acid (*R*)-phenylglycine **249**. The difficulty, which was faced, was obtaining a high enantiomeric excess of compound **250** using the two-step sequence shown in Equation 3.20. As shown in Table 3.15, several conditions were attempted in order to obtain highly enantiomerically pure product **250**. Consequently, it was found that the best conditions for large scale were from conditions C and small scale conditions D (Table 3.15). In conditions D, the reaction was carried out under mild conditions by using 2.2 eq of $NaBH_4$ and 2.2 eq of I_2, rather than the previous conditions[148] in order to minimize the basicity of the reaction medium. Thus, it was found that there was a strong effect of basicity on the racemization which decreased as the basicity of the solution decreased. Therefore, mild conditions were required to prevent this racemization during the reduction of the amino acid, followed by *N*-protection of amino-group (conditions D) which gave enantiopure compound **250**. On the other hand, adding the Boc-group was attempted under cold conditions (0-5 $^{\circ}$C) in the second step to prevent further racemization (conditions B), which may result from *N*-inversion at the secondary NH center because of the conversion of amino group under cold conditions is slower than under warm conditions.

Equation 3.20 Enantioselective synthesis conditions of alcohol product **250**.



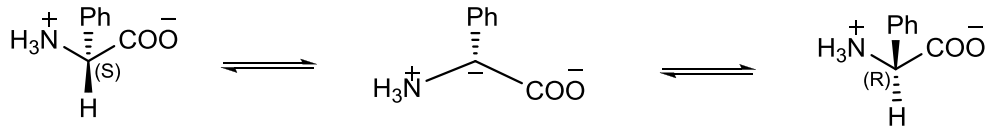
249 **250** **251**

Table 3.15 Determination of enantiomeric excess of compound **250** by HPLC under modification of reaction conditions shown in equation 3.20.

Entry	Reagents and Conditions	% yields	Enantiomeric excess %
A	1) $NaBH_4$ (2.4 eq), I_2 (1.0 eq), normal THF, 18h, reflux; 2) $(Boc)_2O$, Et_3N, 3h, rt.	76	65.7
B	1) $NaBH_4$ (2.4 eq), I_2 (1.0 eq), dry THF; 2) $(Boc)_2O$, Et_3N, 3h, 0-5 °C	88	63.3
C	1) $NaBH_4$ (2.4 eq), I_2 (1.0 eq), THF (fresh distillated), 18h, reflux; 2) $(Boc)_2O$, Et_3N, 3h, rt.	94	≥99.8
D	1) $NaBH_4$ (2.2 eq), I_2 (2.2 eq), dry THF, 18h, reflux; 2) $(Boc)_2O$, Et_3N, 3h, rt.	72	≥99.8

The amino acid racemization (Scheme 3.24) occurs in a basic (or acidic) medium by the formation of the carbanion (enol) intermediate. The base abstracts the α-proton of **252** and this is the rate-limiting step in the reaction. Finally, re-addition of the proton occurs resulting in racemisation.

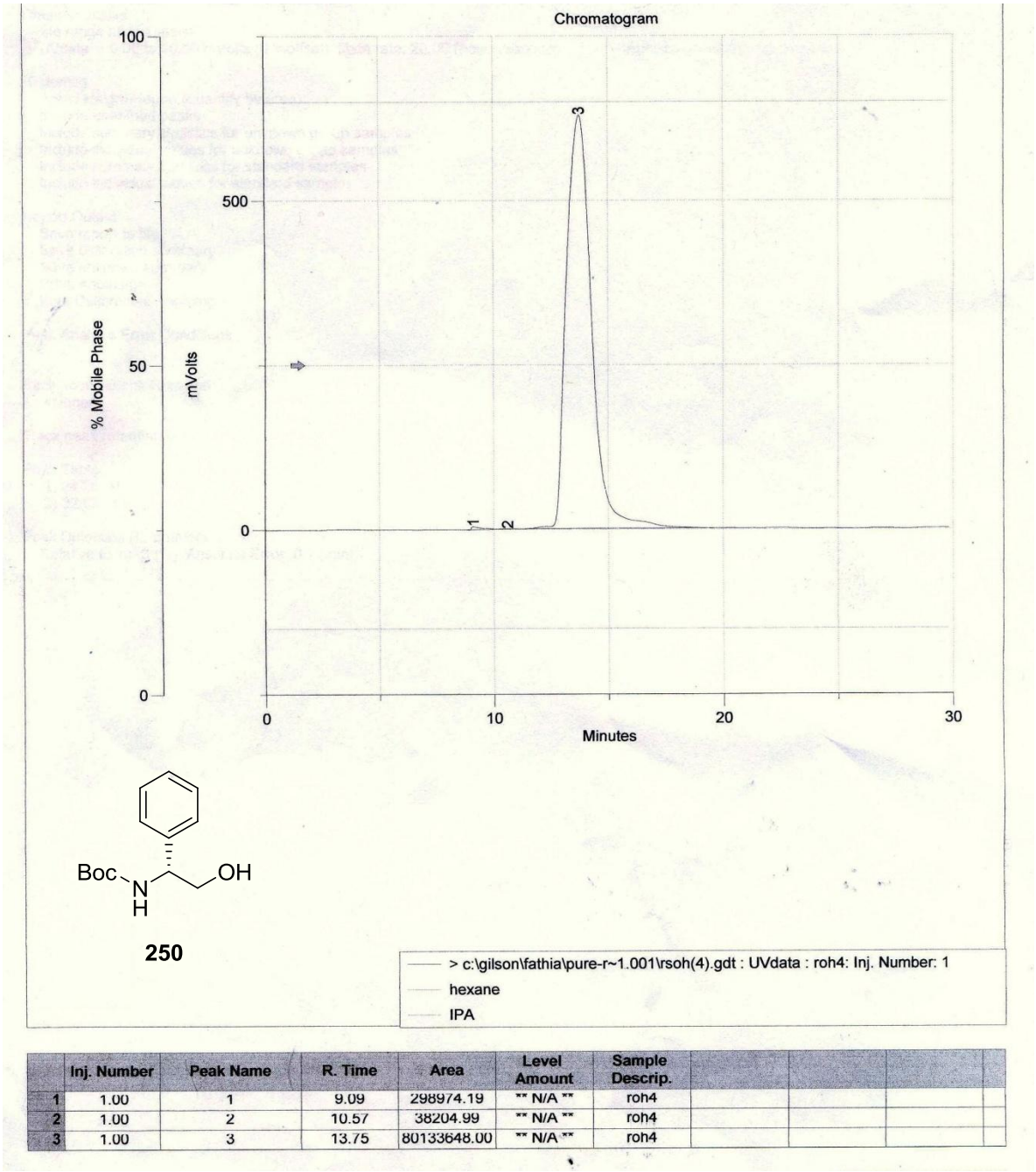
Scheme 3.24 The amino acid racemization in acidic or basic medium.



(S)-Phenylglycine — Planar carbanion — (*R*)-Phenylglycine

252 **253** **249**

Figure 3.17 HPLC chromatogram of compound **249** using Chiralpak OD column, λ = 235nm, hexane : EtOH (90 : 10) and flow rate = 0.5 mL/min

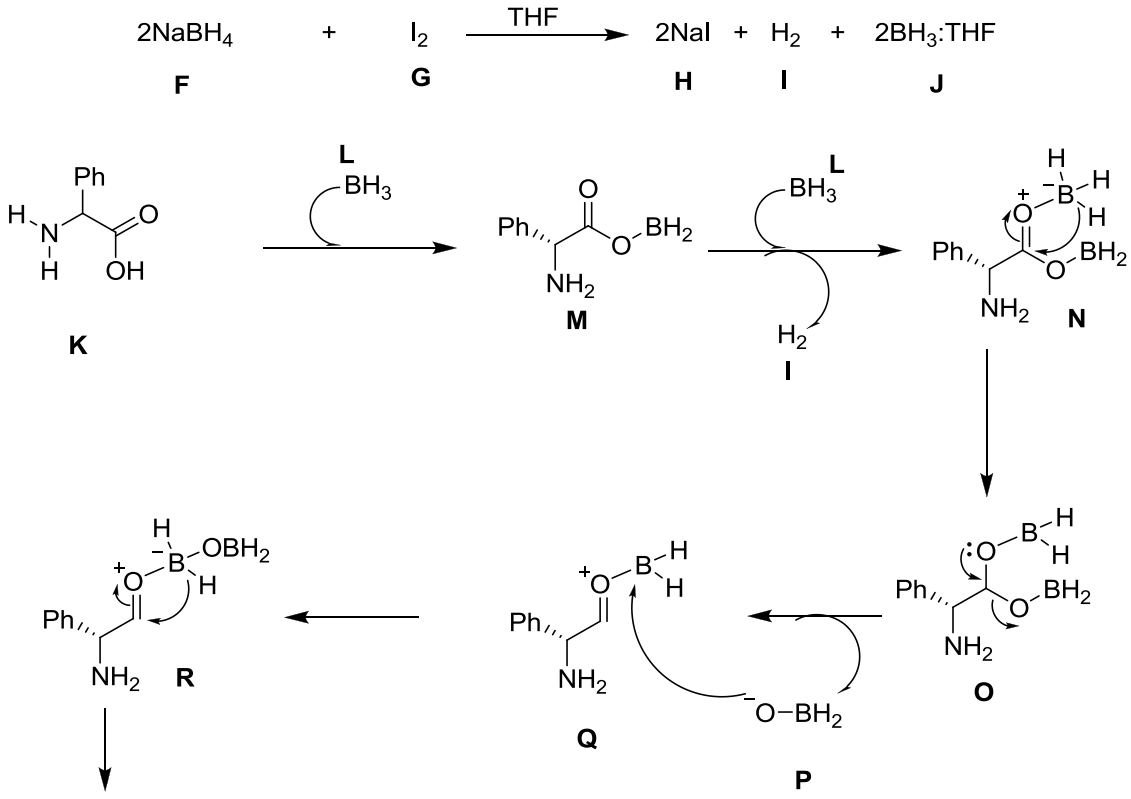


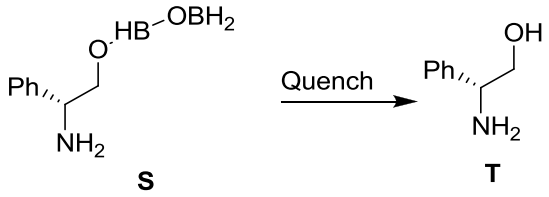
	Inj. Number	Peak Name	R. Time	Area	Level Amount	Sample Descrip.				
1	1.00	1	9.09	298974.19	** N/A **	roh4				
2	1.00	2	10.57	38204.99	** N/A **	roh4				
3	1.00	3	13.75	80133648.00	** N/A **	roh4				

3.15.1. Suggested mechanism of reduction of carboxylic acid by $NaBH_4/I_2$

The mechanistic steps of the reduction involves: first, the iodine reacts with sodium borohydride to give borane, sodium iodide, and hydrogen iodide; Then, hydrogen iodide reacts with further sodium borohydride which leads to more borane formation and sodium iodide plus hydrogen. Thus, it is the borane which reduces the acid to alcohol (Scheme 3.25).[150]

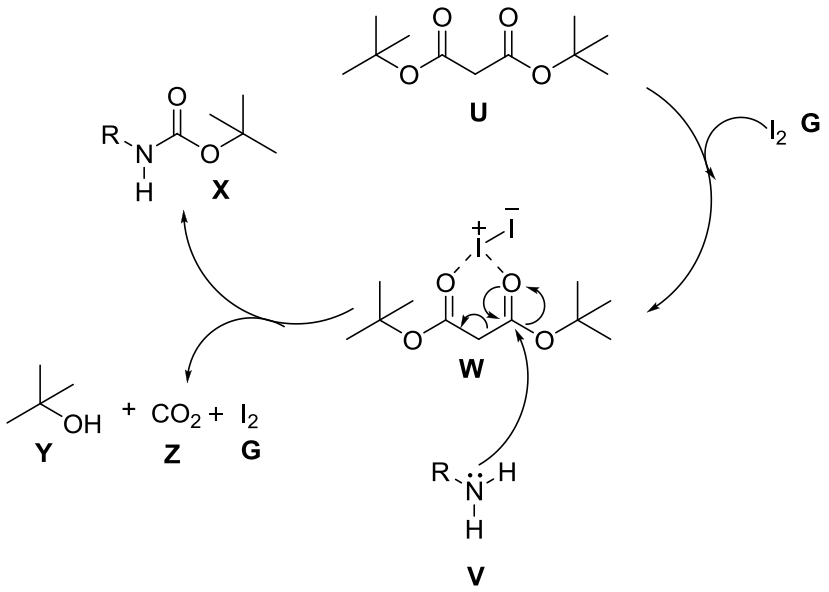
Scheme 3.25 Suggested mechanism of reduction of carboxylic acids using $NaBH_4/I_2$ system





Moreover, the fact that reactive BH_3-THF acts as reducing agent for carboxylic acids is clear, yet the mechanistic explanation of is still ambiguous.[150] Moreover, in the *N*-Boc protection of amino group step (in Equation 3.20), any existence of iodine, which is used in the first step, may assist *N*-Boc protection of the amino group, as reported before and shown in Scheme 3.26.[151] In this mechanism and from ^{1}H NMR and IR studies, coordination of I_2 with $(Boc)_2O$ in the transition state (**W**) was suggested.[151]

Scheme 3.26 The mechanism for iodine-catalyzed *N*-Boc protection of amines.



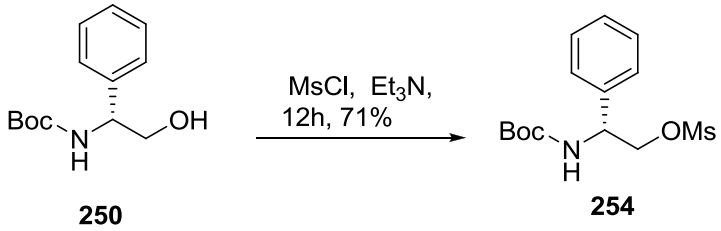
3.15.2. Conclusion

To prevent racemization of phenylglycine to access **250** in the first step of the reaction, it was necessary to understand that the first step was very sensitive to the aqueous conditions (conditions A and B) and that the solvent should be freshly distillated to prevent any racemisation (conditions C and D). Furthermore, it was found that there is an affect of the basicity on the scale up of the reaction; the conditions D were applied on small scale and there was not any racemisiation, whereas the conditions C was applied on large scale and there was not any racemisation.

3.16. Methanesulfonylation (mesylation) of primary alcohol 250

Methanesulfonylation (mesylation) of primary alcohol **250** (Equation 3.21) was considered to be preferred, most preferably using MsCl (methanesulfonyl chloride) and Et_3N because the mesylate group is considered an excellent leaving group in nucleophilic substitution reactions.[148] Hence, mesylte **254** could be isolated readily and scaled up conveniently to give high yields, as shown in Equation 3.21.

Equation 3.21 Mesylation of primary alcohol **249**

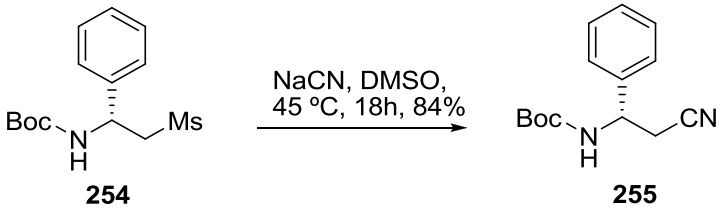


250 **254**

3.17. Cyanation Reaction

The cyanation reaction of mesylte **254** was carried out as shown in Equation 3.22 using a nucleophilic S_N2 displacement of mesylate group by cyanide ion, using sodium cyanide in DMSO to give **255** in 84% yield.[148] Many attempts were used to know the good HPLC separation system for **255** (Table 3.16) to help to determine the accurate enantiomeric excess purity of **255**. The best HPLC separation of two enantiomers was HPLC conditions in entry 5 (Table 3.16).

Equation 3.22 Cyanation reaction



254 **255**

Table 3.16 HPLC conditions using Chiralpak OJ column at λ = 254nm.

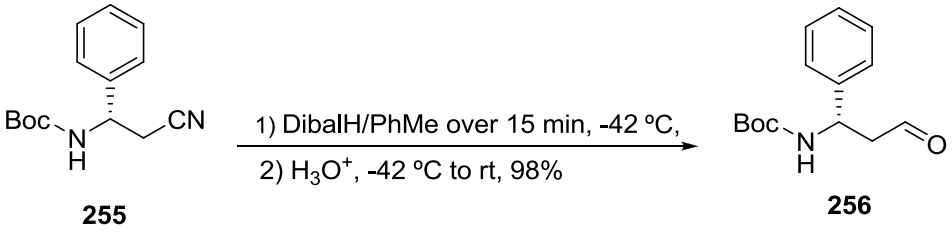
Entry	Hexane : IPA	Flow rate (mL/min)	*t*R of **255**	*t*R of *s*-enantiomer of **255**
1	70 : 30	0.75	19.79	17.10
2	90 : 10	0.75	22.91	18.93
3	90 : 10	1.0	17.34	14.17
4	95 : 05	1.0	32.52	24.59
5	95 : 05	0.75	44.37	32.24

Fortunately, both steps (mesylation and nucleophilic displacement by cyanide) were carried out under conditions that did not cause racemization, as determined using chiral HPLC. In addition, we reported a new system for determining the enantiomeric excess of the cyanide compound **255** by chiral HPLC. This showed an e.e. ≥ 99.8% under conditions: Chiralpak OJ column, hexane:2-propanol (95:5), 0.75 mL/min and λ = 254 nm.

3.18. Reduction of nitrile 255 to aldehyde 256

The reduction of nitrile function of **255** using diisobutylaluminum hydride (Dibal-H) as a relatively mild reducing agent under specially developed conditions (Equation 3.23) gave the aldehyde **256** in 98% yield.[152] This aldehyde **256** was purified using flash SiO_2 column chromatography immediately upon isolation because of its unstability. However, this reaction was amenable to scale up and isolation of good quantities of the aldehyde, which were used soon after purification.

Equation 3.23 Reduction of nitrile **255**



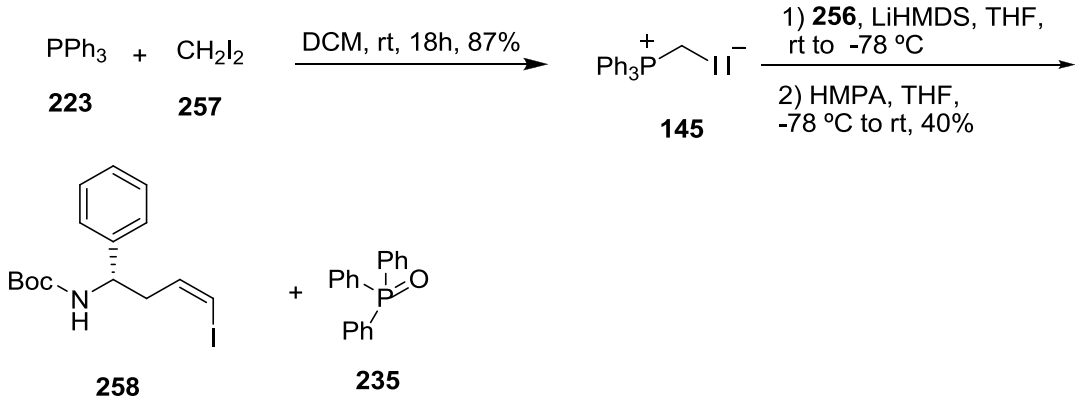
255 **256**

3.19. Wittig Homologation of aldehyde 256

The phosphonium salt **145** was prepared from the reaction of triphenylphosphine **223** with diiodomethane (CH_2I_2) as shown in Scheme 3.27.[153a] To form the Wittig reagent (Ph_3P=CHI), the phosphonium salt **145** was suspended in THF and a strong base (LiHMDS) in the presence of HMPA was added.[153a] Olefination of aldehyde **256** with the Wittig reagent (Ph_3P=CHI, THF; -78 °C) generated the (*Z*)-alkenyl iodide **258**.[153a] Unfortunately, the yield of the desired product, (*Z*)-alkenyl iodide **258** was low (40%). This was due to the problems of removal of the triphenylphosphine oxide (TPPO) **235** is removed by silica gel column chromatography due to the similarity polarity between TPPO

and (*Z*)-alkenyl iodide **258**. However, despite these issues, the desired (*Z*)-alkenyl iodide **258** was isolated in 40% yield (Scheme 3.27) and used in the next step.

Scheme 3.27 Wittig Reaction of Aldehyde **256**

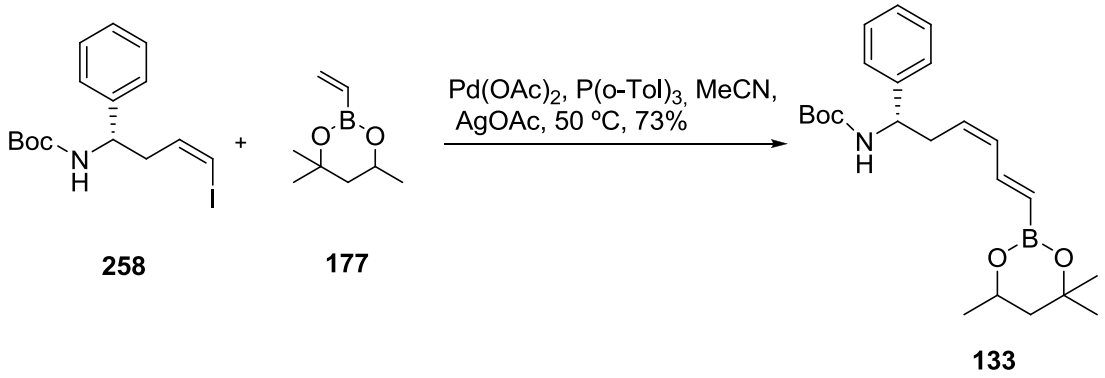


There is an alternative method to minimize the TPPO quantities by complexation method in which the addition of a metal salt to form a complex with the TPPO.[153b] The copper (II) chloride ($CuCl_2$) was used for this purpose but, unfortunately, gave some TPPO by-product and, therefore, column chromatography was the most useful purification technique compared to the complexation method.'[153b]

3.20. Heck-Mizoroki couplings of (*Z*)-alkenyl iodide 258

Heck-Mizoroki couplings were attempted under optimized Heck reaction conditions, by using vinyl boronate **177**, with silver(I) acetate, $Pd(OAc)_2$, tri(*o*-tolyl)phosphine (Equation 3.24).[127a] Fortunately, these conditions led to the desired produce the (1*R*,3*Z*,5*E*)-dienylboronate **133** in an excellent 73% yield after silica gel chromatography. Importantly, there was no sign of any competing Suzuki-Miyaura side-products.

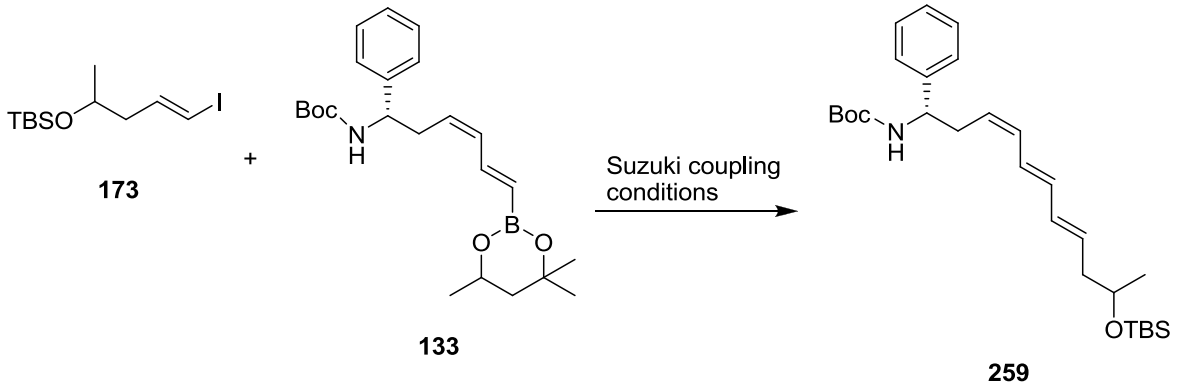
Equation 3.24 Heck reaction



258 **177** **133**

3.21. Rout to synthesize the southern hemisphere of viridenomycin using dialkenylboronate 133

Equation 3.25 Suzuki–Miyaura couplings conditions



173 **133** **259**

Table 3.17 Different Suzuki–Miyaura couplings conditions.

Entry	Conditions (equivalents)	Base (1.2 eq)	Temp.	Solvent	Result
1	**133** (1.2), $Pd(PPh_4)_4$ (0.05), **173**, 48h	*t*-BuOK	67	THF	Traces of **259** in the crude
2	**133** (1.2), $Pd(PPh_4)_4$ (0.1), **173**, 48h	*t*-BuOK	67	THF	Traces of **259** in the crude
3	**133** (1.2), $Pd(dppf)Cl_2.CH_2Cl_2$ (0.15), **173**, 24h.	$Ba(OH)_2$	rt	DMF	Traces of **259** in the crude
4	**133** (1.2), $Pd(PPh_4)_4$ (0.05), **173**, 48h	Ag_2O	67	THF	No reaction
5	**133** (1.2), $Pd(PPh_4)_4$ (0.05), **173**, 48h	Ag_2O	80	DMF	No reaction
6	**133** (1.1), $Pd(OAc)_2$ (0.05), triphenyphosphine (0.1), **173**, 48h	Ag_2O	67	THF	No reaction

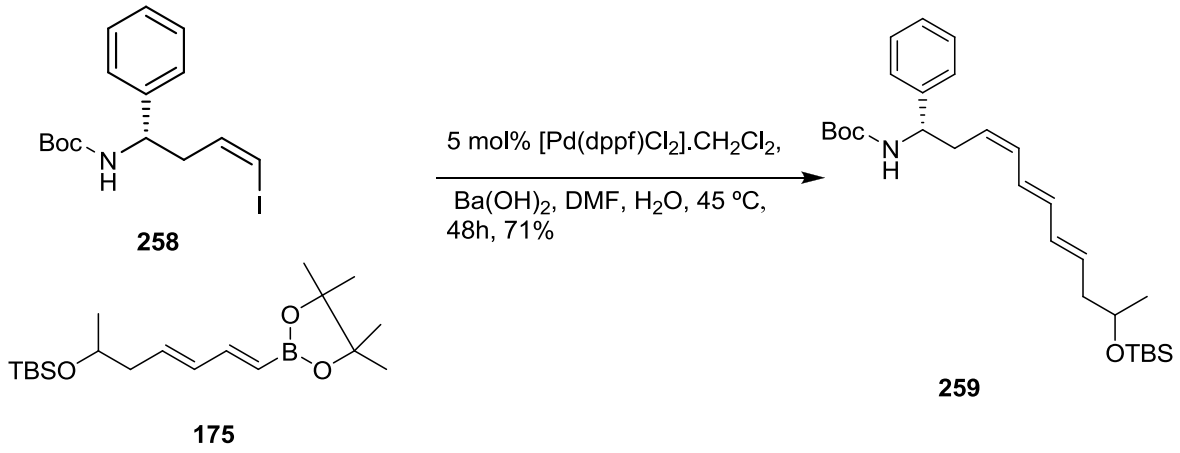
Initial attempts at Suzuki–Miyaura couplings were disappointing, the reaction of (*Z*)-alkenyl iodide **258** and dialkenylboronate **133** did not lead to give triene **259** under a different Suzuki–Miyaura conditions (Table 3.17). Most of these attempts of Suzuki–Miyaura couplings (Table 3.17) were run on small scale (10 mg) of substrate ((*E*)-alkenyl iodide **173**). From ^{1}H NMR spectroscopy, the oily crude product contained only traces of the desired triene **259** (entries 1 and 2). Unfortunately, these used couplings conditions did not give any sign for a good yield of the target triene **259**.

3.21.1. Alternative route to synthesize the southern hemisphere of Viridenomycin using (*Z*)-alkenyl iodide 258

Another route was suggested in order to synthesize the triene core **259** as shown in Equation 3.26. In this route, the dienyl boronate ester **175** was reacted with (*Z*)-alkenyl iodide **258** using a Suzuki–Miyaura coupling.

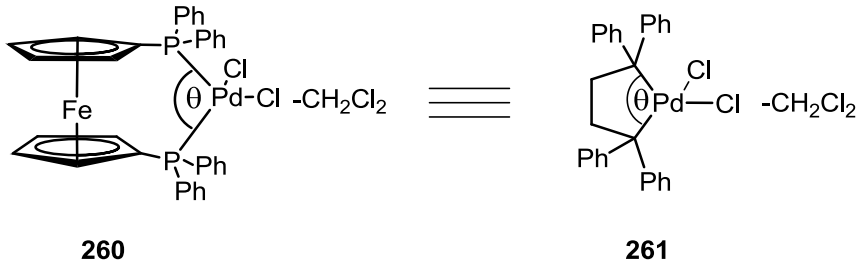
However, Suzuki–Miyaura coupling between (*Z*)-alkenyl iodide **258** and the dialkenylboronate ester **175** under literature conditions[144] proceeded without incident in the presence of $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ and $Ba(OH)_2$ in DMF and H_2O at room temperature as shown in Equation 3.26, affording the triene **259** in 71% yield after silica gel chromatography.

Equation 3.26 Suzuki–Miyaura couplings



Moreover, the catalyst used, $Pd(dppf)Cl_2.CH_2Cl_2$ **260** (Figure 3.18), has been shown to be an extremely active catalyst for the Suzuki reaction of aryl halides in water.[144] The large bite angle (θ), as shown in Figure 3.18, helps favor reductive elimination in the Suzuki reaction mechanism, while the weakly electron-donating bidentate triarylphosphine ligand (dppf) stabilizes the catalytic center due to the rigid and blocked conformation of the ferrocenyl backbone.[154] In addition, a large bite angle of the ligand brings the two organic groups closer, promoting the reductive elimination step.[154]

Figure 3.18 Bite angle (θ) of $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$



Fihri *et al.* (2007) reported many examples of using this catalyst **260** in Suzuki coupling to synthesize many natural products compounds.[154b] For recycling the catalyst **260**, a small amount of PEG-2000 (20% aqueous poly(ethyleneglycol) allows the recycling of the $Pd(dppf)Cl_2$ catalyst for three times without any significant loss of catalytic activity.[154]

3.21.2. Conclusion

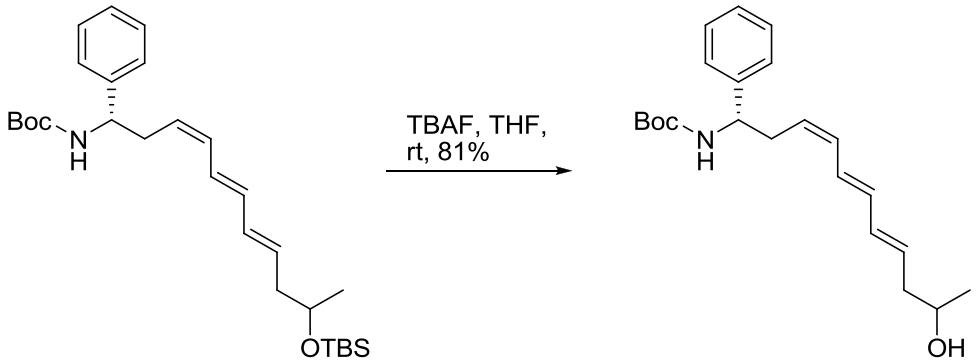
The Suzuki coupling depends on the catalyst, the base, the solvent and temprature; As seen in Table 3.17, the solvents used were THF and DMF. Without adding water, the Suzuki reaction gave no coupled product **259** whereas when water was added to DMF (Equation 3.26) the Suzuki reaction proceeded in good yield. Moreover, the aqueous conditions increases the activity of the base, which will lead to accelerating the proceeding of coupling. In conclusion, it appears that the Suzuki coupling of **258** depends on the nature of the solvent; a more polar solvent leads to a better yields. With these conditions (5 mol% $[Pd(dppf)Cl_2].CH_2Cl_2$, $Ba(OH)_2$, DMF, H_2O, 45 ºC, 48h), we confirm the synthesize of triene **259**.

3.22. Deprotection of TBS-Group of *t*-butyldimethylsilyl ether 259

Deprotection of *t*-butyldimethylsilyl ether **259** using silica supported sodium hydrogen sulfate ($NaHSO_4 \cdot SiO_2$) as a heterogeneous catalyst gave very poor yields of alcohol **262** (10%) under different times and equivalents of the catalyst not like mentioned in the literature as an efficiency method.[155a] However, the cleavage of the TBS-group of ether **259** was conveniently carried out using 1 M tetrabutylammonium fluoride (TBAF) in THF which gave the corresponding allylic alcohol **262** (Equation 3.27) in an excellent 81% after

purification by silica gel chromatography.[155b]

Equation 3.27 Deprotection of *t*-butyldimethylsilyl ether **259**



259 **262**

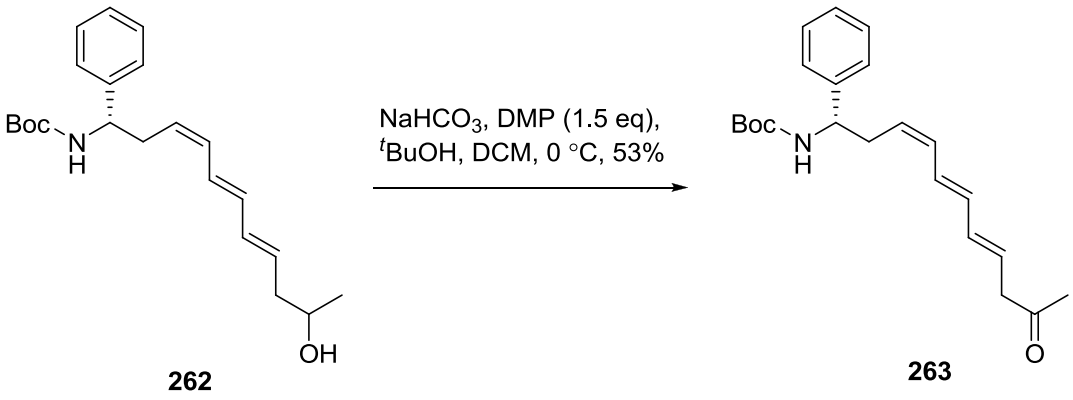
Introducingly, compared to model compound **181**, which underwent facile and rapid autooxidation in air (see Equation 3.15), compound **262** was found to be much more stable. This suggests that the benzene junction of **181** adds to the susceptibility to undergo autooxidation.

3.23. Synthesis of ketone 263

Trying to oxidize the allylic alcohol **262** using Dess–Martin periodinane[146f] (Equation 3.28) led to the allylic ketone **263** but all attempts to purify it on silica gel chromatography or activated alumina led to complete decomposition of the ketone **263**. Hence it was used as a crude compound without any further purification in further experiments. However, compound **263** was isolated in clear (albeit crude) form in an estimated yield of 53%. Compound **263**, according to ^{1}H NMR, was isolated as an 67:11:10 mixture of *ZEE*:*ZEZ*:*ZEEE* alkene isomers (Figure 3.19) and unidefined impurities. Moreover, by the comparision between ^{1}H NMR spectra for both allylic protons (CH_2) for ketones **215** and

263 as shown in Figures 3.19 and 3.20, there are similarities in the chemical shifts and the the *J* couplings (~ 6 Hz).

Equation 3.28 Oxidation of allylic alcohol **262**



262 **263**

Figure 3.19 ^{1}H NMR of compound **263** as a crude sample.

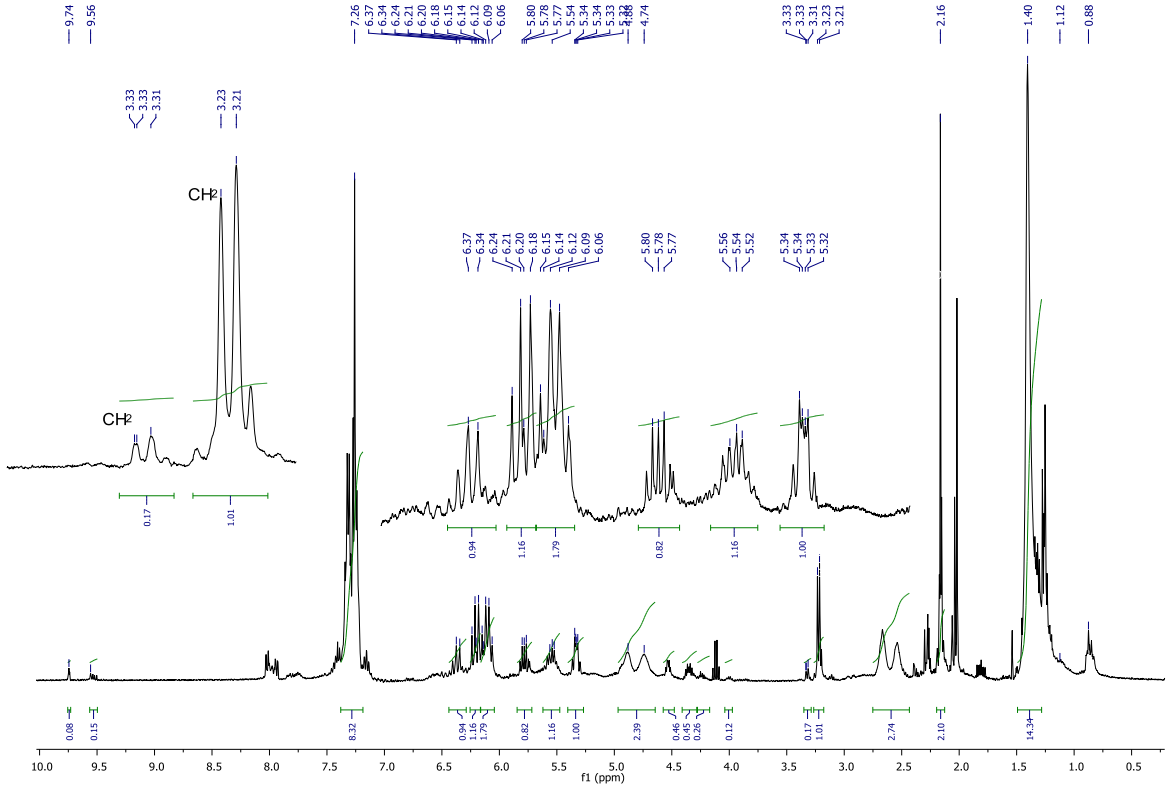
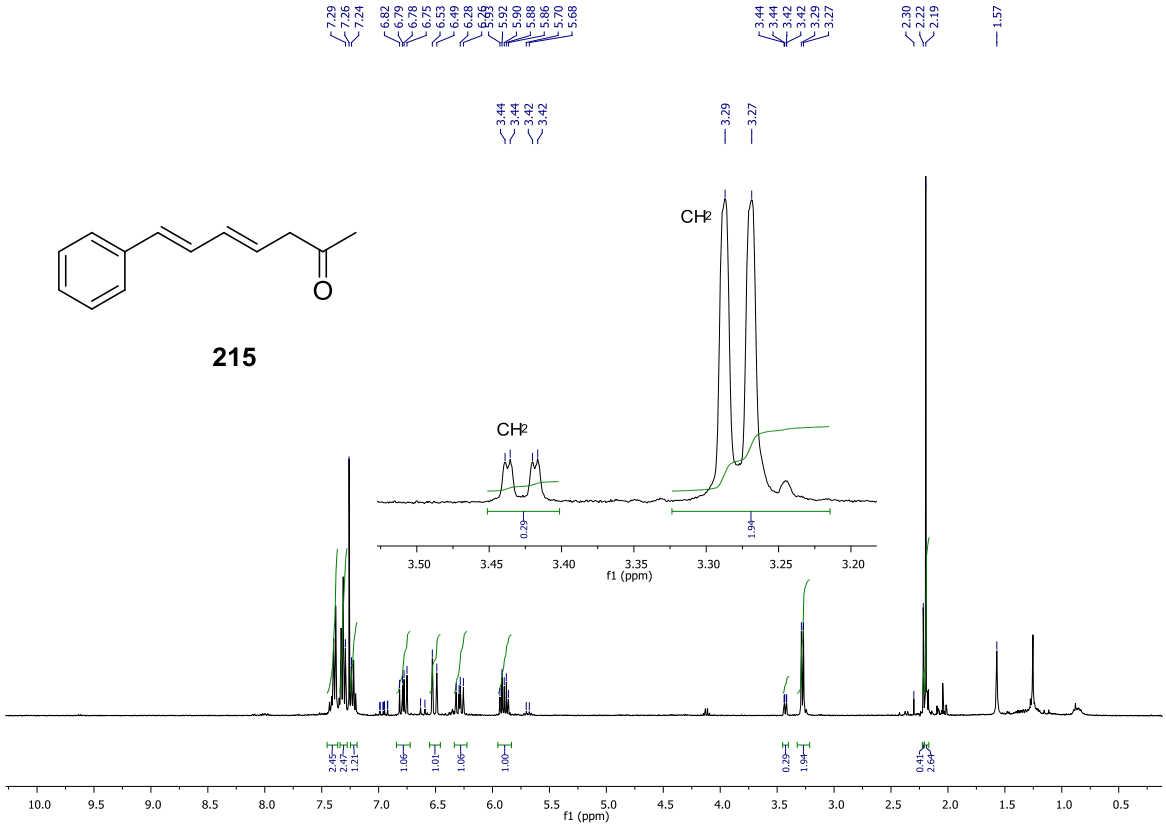


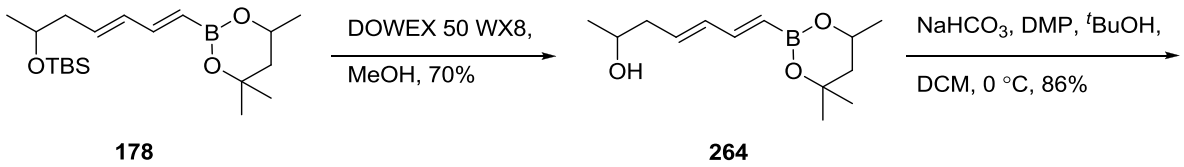
Figure 3.20^{1}H NMR of compound **215**



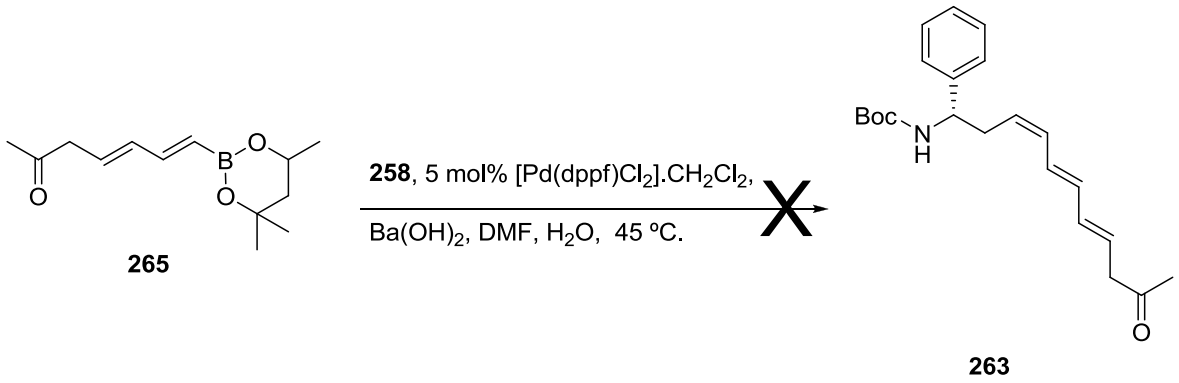
3.23.1. Another route for synthesis of ketone 263.

The last oxidation step (Equation 3.28) led to a further adaption of the strategy to incorporate the ketone moiety required in synthon **137**. To achieve this, a further modification was made to the synthesis route as proposed in Scheme 3.28.

Scheme 3.28 Attempt of preparation of ketone **263** with Suzuki–Miyaura couplings



178 **264**



Hence, after desilylation of the *O*-TBS ether of **178** under mildly acidic methanolic conditions using DOWEX 50 WX8 200 mesh, the resulting secondary alcohol **264** was exposed to Dess–Martin periodinane[146f] oxidation to derive the ketone **265** in a gratifying yield of 86%. However, use of this ketone **265** for coupling with (*Z*)-alkenyl iodide **258** under the previously employed mild Suzuki–Miyaura coupling conditions (Scheme 3.26) did not led to the desired product **263**. The main problem was instability of the allylic triene ketone **265**, which decomposed under the reaction conditions.

Hence, attempts were made to protect ketone **265** as an enol ester to try and access either **267** or **268**, which could then be exposed to the Suzuki-Miyaura coupling conditions. Attempts to do an enol acetylation of ketone **265** with acetic anhydride in the presence of organic base at room temperature (Table 3.18) led to the decomposition of the compound **265**, and the compound **269** as one of the decomposition products especially isolated with entry 3 (Table 3.18). The boronate ester **269** has a crystalline structure (Figures 3.22 and 3.23).

Equation 3.29 Attempts to enol acetylation of ketone **265** with acetic anhydride

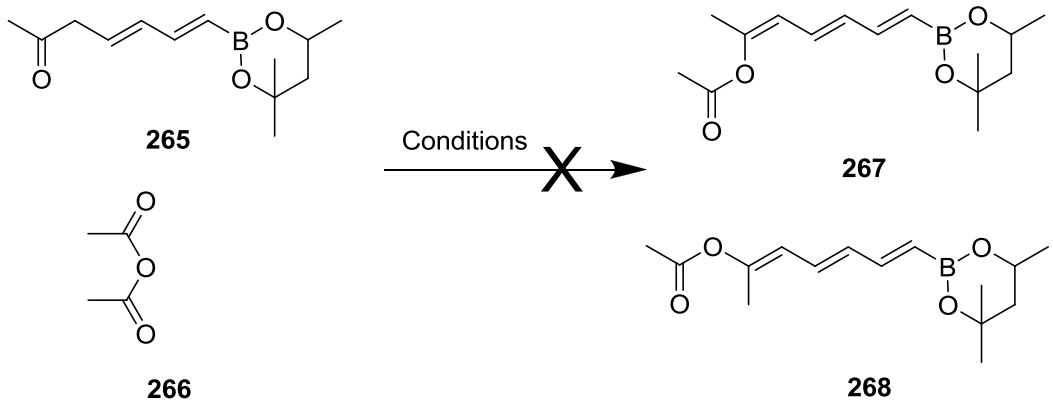


Table 3.18 Attempts to enol acetylation of ketone **265** with acetic anhydride

Entry	Conditions	Result
1	Et_3N (1.05 eq), THF, rt, 48h.	Traces
2	Et_3N (3 eq), DMAP (10 mol%), toluene, rt, 18h.	Traces
3	Pyridine (3 eq), rt, 3 days.	Decomp. **269** (%)

Figure 3.21 Structure of boronate ester **269**

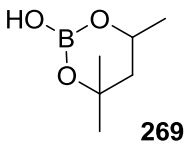


Figure 3.22 Molecular structure of Compound **269** (major conformation). Thermal ellipsoids are drawn at the 50% probability level.

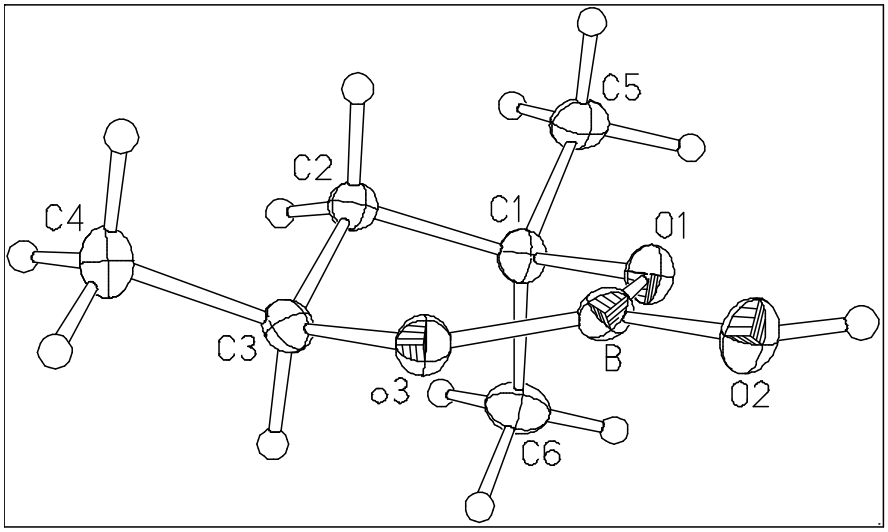
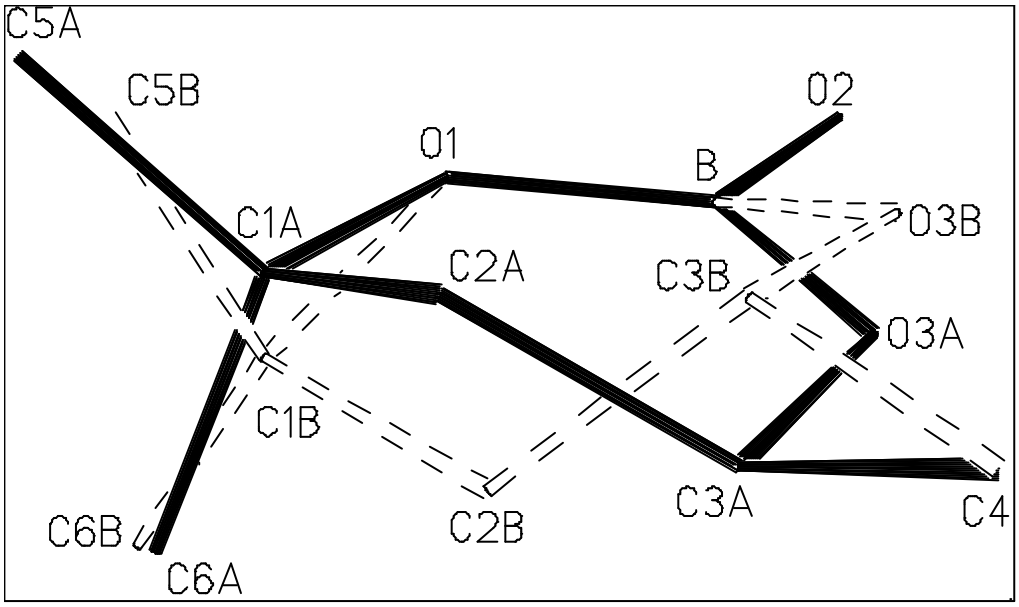


Figure 3.23 Disorder of the molecule **269** (H atoms are omitted)



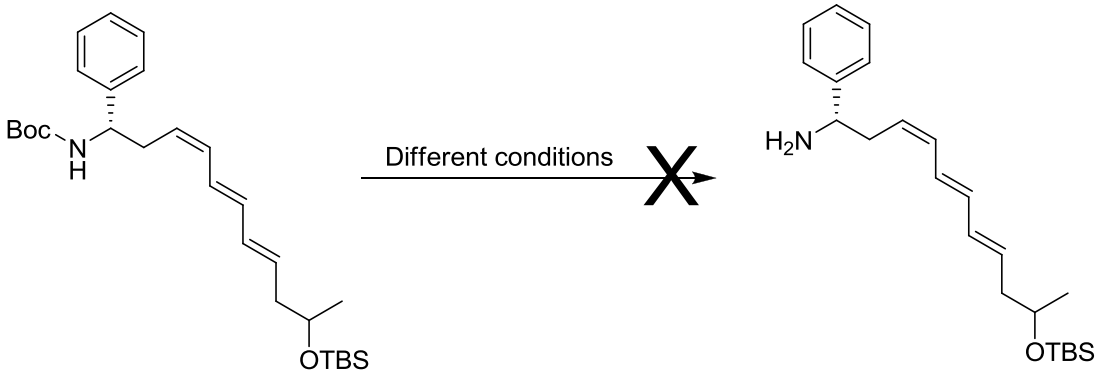
The origin of **269** as a by-product again suggests that facile autooxidation reactions are responsible for the decomposition of ketone **265**. Therefore, either than using ketone **265** as

the key building block for the synthesis of viridenomycin, the precursor alcohol (**262**) and its TBS ether (**259**) were used to developing the further methodologies required.

3.24. Deprotection of *N*-Boc protecting group of 259

The most common protecting group for amines is *t*-butyl carbamate (Boc) group, which is stable to hydrolysis under basic conditions and to many other nucleophilic agents. Selective cleavage of the *N*-Boc group of intermediate **259** was also examined in order to access the corresponding amine salt under acidic conditions (using TFA or HCl) for further elaboration *via* amide formation to the model of the lactam function in viridenomycin. However, since **259** contains both Boc and TBS protecting groups, it proved difficult to achieve deprotection without causing decomposition of compound **259** under a acidic conditions as follows: 1) TFA : DCM (50:50); 2) 4M HCl in dioxane. Simiarly, under basic conditions such as KO^{t}Bu (8 eq), H_2O,THF, reflux, 80 ^oC, 23h decomposition also occured.[156] The main reason for these problems stem from the sensitivity of TBS group and the triene structure under the acidic and basic conditions used.

Equation 3.30 Attempts to cleavage of *N*-Boc of compound **259** under different conditions



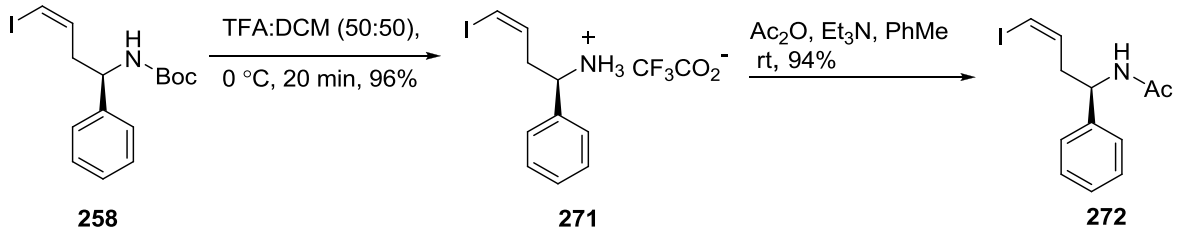
259 **270**

Table 3.19 Attempts to cleavage of Boc under different conditions

Entry	Different conditions	Result
1	TFA : DCM (50:50)	Decomposition
2	4M HCl in dioxane	Decomposition
3	KO^{t}Bu (8 eq), H_2O,THF, reflux, 80 ºC, 23h	Decomposition

Hence, to achieve deprotection of the *N*-Boc group, another substrate, (*Z*)-alkenyl iodide **258** is introduced instead of triene **259** and examined towards acidic deprotection conditions. Fortunately, cleavage of *N*-Boc group was achieved clearly and efficiently using acidic conditions with the reagent TFA in DCM (50:50), which a quantitative yield of the TFA salt in 96% yield over 20 minutes (Scheme 3.29). The formation of **271** was confirmed by synthesis of the corresponding acetamide **272** in 94% yield using Ac_2O/Et_3N (Scheme 3.29).

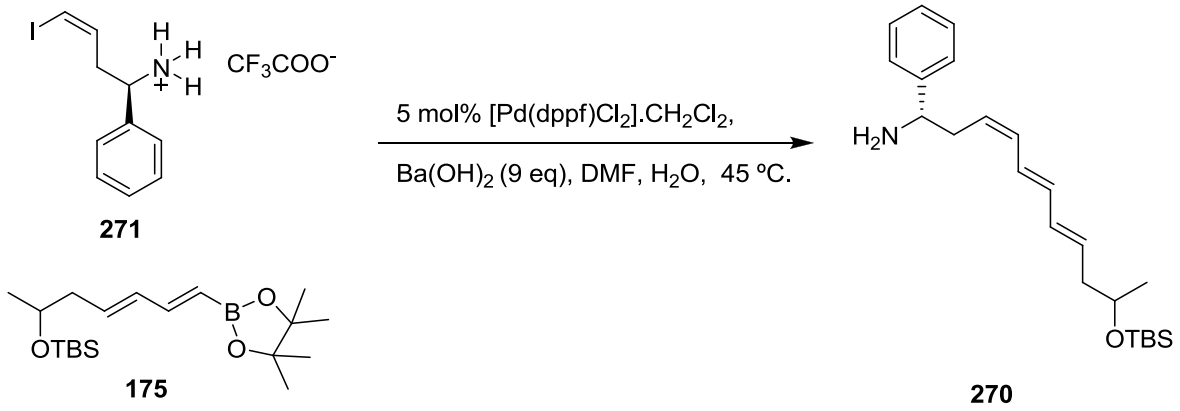
Scheme 3.29 Cleavage of Boc of compound **258** using TFA:DCM (50:50)



258 **271** **272**

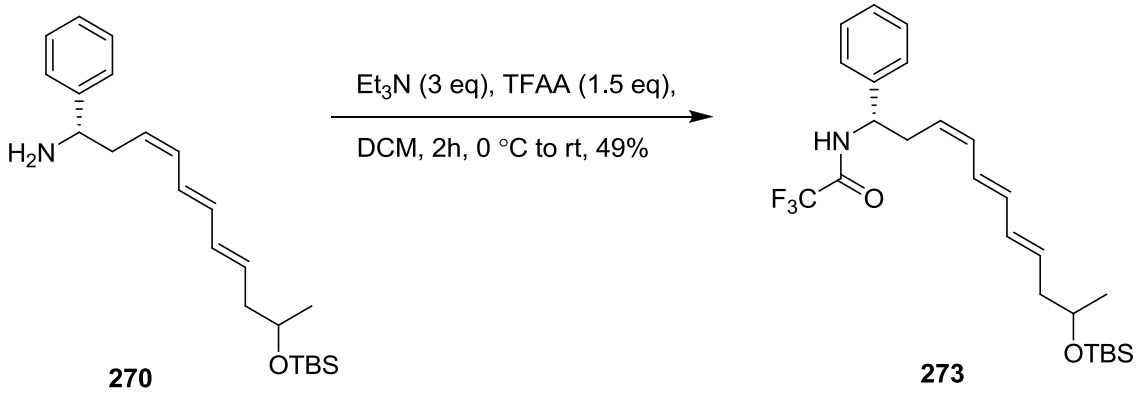
TFA salt **271** was then subjected to Suzuki–Miyaura reaction conditions (Equation 3.31). Fortunately, the free amine **270** (without further purification) is appeared to be the major product by ^{1}H NMR spectra.

Equation 3.31 Suzuki–Miyaura reaction



The compound **273** was prepared in order to examine the purity of the secondry amine **270** in the presence of Et_3N and TFAA as shown in Equation 3.32.

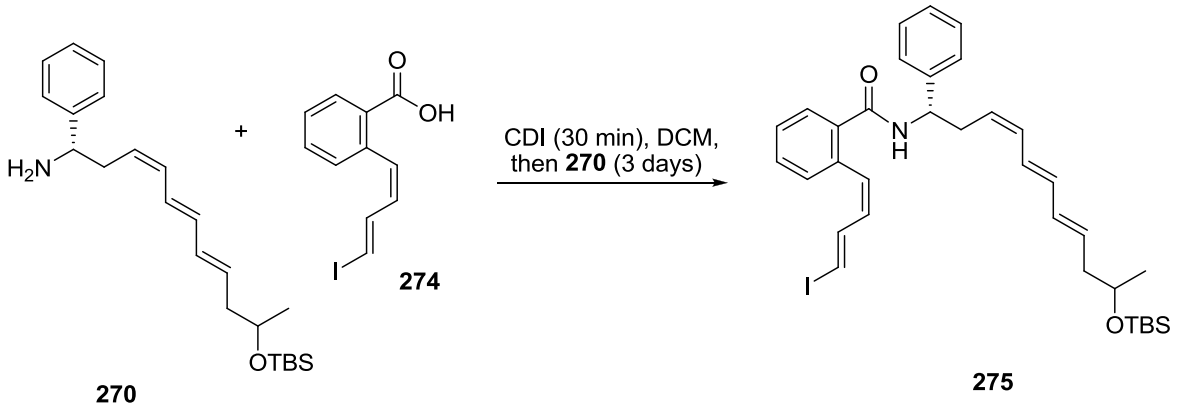
Equation 3.32 Intoducing *N*-trifluoroacetyl group on **273**



1,1'-Carbonyldiimidazole (CDI) **236** is used for activated 2-((1*Z*,3*E*)-4-iodobuta-1,3-dienyl)benzoic acid **274**, and then the secondary amine **270** was added. Unfotunatly, the

product, which isolated after SiO_2 column chromatography purification, gave very broad signal by ^1H NMR. Thus, it can not confirm the structure of the amide **275**.

Equation 3.33 The CDI-mediated amidation of secondry amine **270** with the carboxylic acid **274**



3.25. Introducing new mild cleavage protecting groups instead of Boc.

Due to the issues encountered in deprotecting the *N*-Boc group in synthons such as **259**, alternative *N*-protecting groups were examined that would be readily accessed from TFAA salt **271**. In particular, two protecting groups (TFAA, phthalimide) were suggested for this purpose.

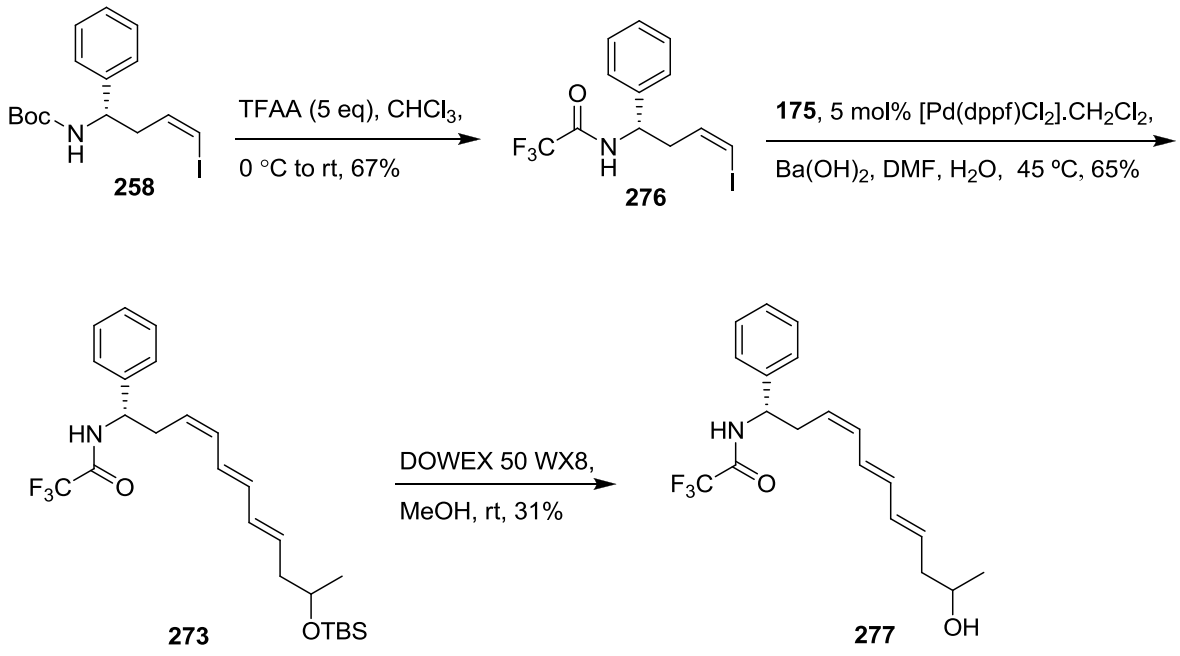
3.25.1. *N*-Trifluoroacetyl protecting group

The *N*-trifluoroacetyl group is easily removed by mild basic conditions and therefore, it is used as a protecting group for amines. In addition, triflouroacetic anhydride (TFAA) is used as a reagent for the cleavage *N*-Boc groups together with the introduction of a *N*-trifluoroacetyl group, *in situ*. Therefore, iodoalkene **258** was exposed to TFAA to give the

(*Z*)-alkenyl iodide trifluoroacetamide **276** in 67% yield (Scheme 3.28).

The gratifying *in situ* conversion of *N*-Boc system **258** was then followed by exposure to Suzuki–Miyaura coupling conditions with dienylboronate ester **175** to give the desired triene **273** in 65% yield. Hence, the triene **273** was isolated in 65% yield after silica gel chromatography. Since the trifluoroacetamide group of **273** would be cleavable under basic conditions, acidic methanolic conditions (DOWEX 50 WX8 200 mesh) were then applied for the deprotection of the TBS ether to derive the secondary alcohol **277**, albeit in only 31% yield (Scheme 3.30). However, the secondary alcohol isolated in pure form.

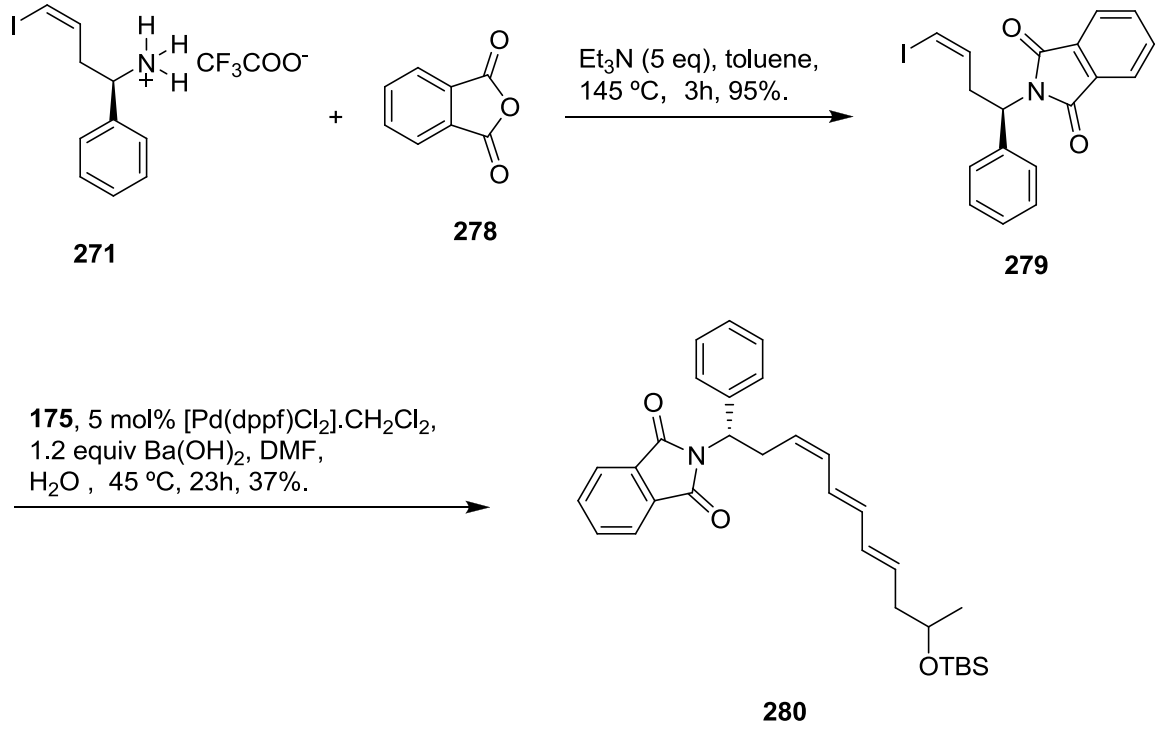
Scheme 3.30 Protection of the secondary amino group with a trifluoroacetamide and synthesis of tricyclic core **277**



3.25.2. *N*-Phthalimide protecting group

The phthalimide amine-protecting group was selected as possible alternative to either the *N*-Boc or *N*-trifluoroacetamide protecting groups because the phthalimide group can be readily cleaved using hydrazine. The disadvantage of *N*-phthaloyl group could be easily that it is opened by other nucleophiles. Nonetheless, the phthalimide **279** was prepared from **271** by the dehydrative condensation of the amine salt and phthalic anhydride **278** in the presence of triethylamine at 145 ˚C (Scheme 3.31) in a good yield (95%).

Scheme 3.31 Protection of the secondary amino group with a phthalimide and synthesis of tricyclic core **280**



271 **278** **279** **280**

The resulting (*Z*)-alkenyl iodide **279** was then reacted with dialkenyl boronate ester **175** under mild Suzuki–Miyaura couplings conditions (Scheme 3.31) to give the desired product **280** in low yield (37%). The easily opening of *N*-phthaloyl group could be the

reason of this low yield.

3.26. Summary and Recommendations

In summary, novel synthetic routes to synthesis southern polyene part **136** of viridenomycin **75** have been investigated. The enantioselective synthesis of the triene core **259** has been achieved. A key aspect of this synthesis was the development of the iododeboronation (Equation 3.12) which, applied for the first time on this type of an alkenyl hindered boronate ester **171**, gave the terminal (*E*)-alkenyl iodide **173**, as one isomer (100%) and no sign of the (*Z*)-isomer **174**. Therefore, this iododeboronation will be a very important method for practical use to prepare highly stereoselective terminal (*E*)-alkenyl iodides. Many reactions were carried out efficiently including, Heck-Mizoroki couplings, Suzuki–Miyaura couplings and a simple and efficient method for the selective cleavage of *tert*-butoxycarbonyl (Boc) was introduced on the suitable substrate **258**. In addition, two alternative protecting groups (TFAA, phthalimide) were studied. Further studies are necessary in order to complete the total synthesis of viridenomycin **75** by incorporating the southern polyene fragments prepared in this thesis.

CHAPTER IV

Experimental Section

CHAPTER IV

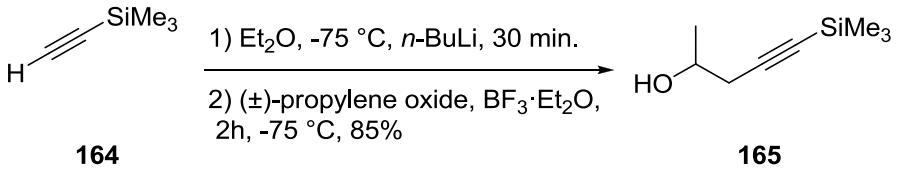
Experimental Section

4.1. General experimental

All ^{1}H NMR were recorded on either Varian Mercury-400, Bruker Avance-400 or Varian-Mercury 500 spectrometers. ^{13}C NMR spectra were recorded on Varian Mercury-400, Varian Mercury-500 and Bruker Avance-400 instruments at frequencies of 100 MHz. ^{11}B NMR were recorded on the Bruker Avance-400 at a frequency of 128 MHz. Chemical shifts are expressed as parts per million downfield from the internal standard TMS except for ^{11}B NMR which is expressed as parts per million downfield shift. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. UV-Vis spectra were recorded on a Unicam UV2 spectrometer. Column chromatography was performed on Davisil Silica gel, 60 meshes. TLC was performed on Polygram SIL G/UV254 plastic backed silica gel plates with visualization achieved using a UV lamp or staining with basic $KMnO_4$. All glassware was oven dried (130 °C) before use and cooled under a positive pressure of argon. Dry solvents were dried by distillation from CaH_2 (DCM, hydrocarbons) or sodium-benzophenone ketyl (THF). The enantiomeric excesses were determined by HPLC using chiral column. All chemicals were purchased from standard chemical suppliers. Specific rotation is expressed in units: 10 degrees $cm^2\ g^{-1}$ and the concentration (c) is expressed in units g dL^{-1}.

4.2. Experimental Section.

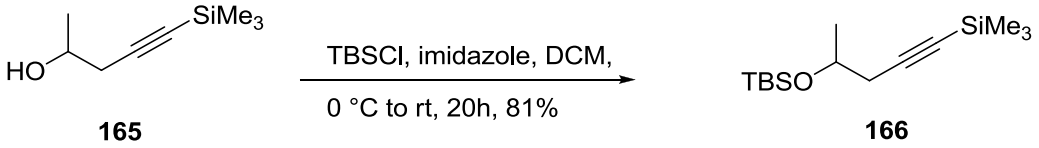
(±)-5-Trimethylsilyl-4-pentyn-2-ol 165



164 **165**

n-BuLi (1.97 M in hexane, 7.3 mL, 14.2 mmol) is added dropwise to trimethylsilyacetylene **164** (2.0 mL, 14.2 mmol) in dry ether (20 mL) at -78 °C. After 30 mins of stirring, (±)-propylene oxide (0.95 mL, 14.0 mmol) is added to the reaction solution and then $BF_3.Et_2O$ (1.70 mL, 14.0 mmol) is added. After 2h of stirring at -75 °C, the reaction poured in a buffer solution (pH = 7.4 + Et_2O + ice). After extraction, the combined organic layers are dried over $MgSO_4$ and concentrated. Purification by silica gel chromatography (EtOAc : hexane, 2 : 8, as eluent) afforded 1.79 g (84%) of alcohol **165**. All spectroscopic and analytical properties were identical to those reported in the literature.[139]

(±)-2-*(tert*-Butyldimethylsiloxy)-5-trimethylsilyl-4-pentyne 166

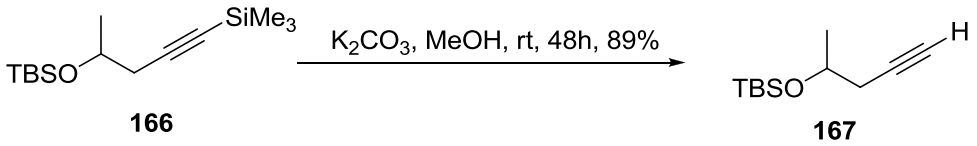


165 **166**

TBSCl (2.89 g, 19.2 mmol, 2 eq) is added portionwise to trimethylsilyl alcohol **165** (1.50 g, 6 mmol, 1 eq) in dry DCM (25 mL) at 0 °C under argon. The reaction is stirred at 0 °C for 30 minutes, and then imidazole (0.82 g, 12.0 mmol, 1.25 eq) was added portionwise. The reaction mixture was stirred 19 hours, poured in a buffer solution (pH = 7.4 + Et_2O + ice). The aqueous layer was extracted with ether (3 x 25 mL) and the combined organic layers

were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified via silica gel column chromatography (diethyl ether : hexane, 5 : 95, as eluent) to give the desired product **166** (2.10 g, 81%). All spectroscopic and analytical properties were identical to those reported in the literature.[157]

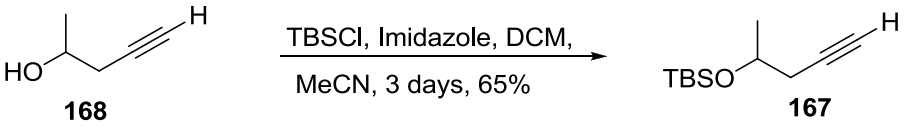
(±)-2-*(tert*-Butyldimethylsiloxy)-4-pentyne 167



166 **167**

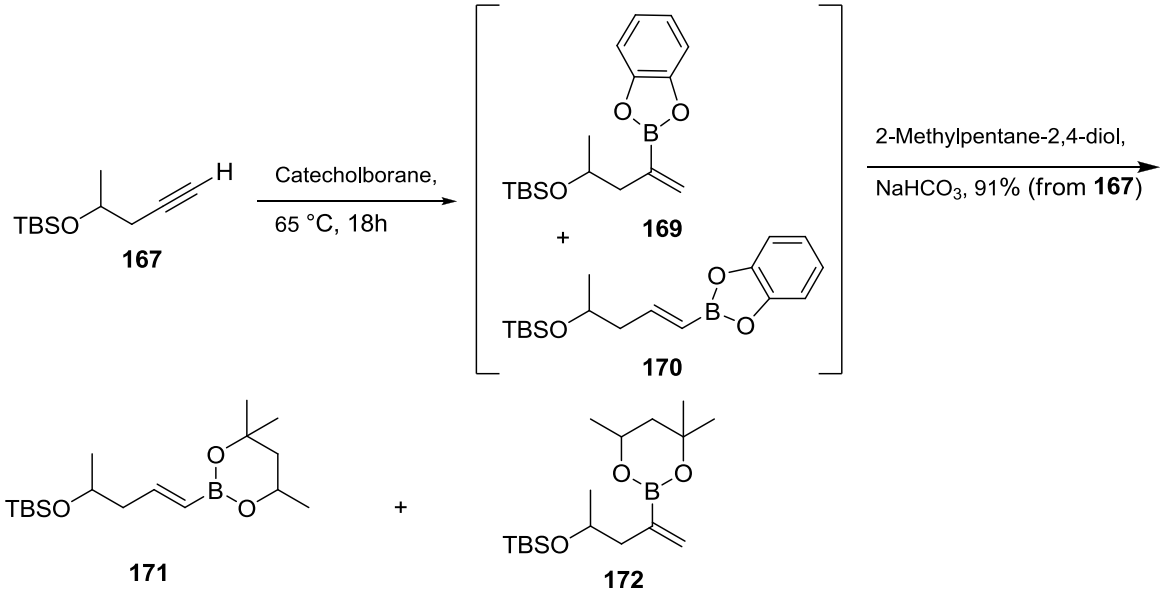
To a solution of disilyl ether **166** (0.50 g, 1.9 mmol) in 4:1 MeOH-Et_2O (20 mL) under argon is added K_2CO_3 (0.281 g, 2.0 mmol) which finely powdered (dried under 0.5 mmHg with the gun with hot air during 1h). After 48h the reaction mixture is partitioned between ether and water and the aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (diethyl ether : petroleum ether, 10 : 90, as eluent) to give 0.32 g (89%) of TBS ether **167** as a colourless oil, R_f 0.83 (hexane : EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): 0.07 (s, 3H, Si*Me*), 0.08 (s, 3H, Si*Me*), 0.89 (9H, s, ^{t}*Bu*Si), 1.23 (3H, d, *J* 6.0, CH*Me*), 1.97 (1H, t, *J* 2.7, C≡C*H*), 2.24 (1H, ddd, *J* 16.5, 7.1, 2.7, CH*H*), 2.35 (1H, ddd, *J* 16.5, 5.6, 2.7, C*H*H) 3.92-3.99 (1H, dp, *J* 7.1, 6.0, C*H*OTBS); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c –4.7 (Si*Me*), –4.6 (Si*Me*), 18.1 (Si*C*Me_3), 23.2 (*Me*CH), 25.8 (*Me*$_3$C), 29.3 (*C*H_2), 67.5 (C≡*C*H), 69.6 (*C*≡CH), 81.9 (H*C*OTBS); Spectroscopic and analytical properties were identical to those reported in the literature.[141]

(±)-2-*(tert*-Butyldimethylsiloxy)-4-pentyne 167



(±)-Pent-4-yn-2-ol **168** (1.0 g, 11.9 mmol) was dissolved in a solution of DCM (10 mL), CH_3CN (10 mL), and TBSCl (1.810 g, 12.0 mmol, 1.01 eq), imidazole (1.21 g, 17.8 mmol, 1.5 eq) and DMAP (0.15 g, 1.2 mmol, 10 mol%) was then added portionwise and left to stir for 3 days. The reaction was diluted with DCM (50 mL), washed with brine (30 mL), water (30 mL) and dried ($MgSO_4$). The organic layer was evaporated, which afforded an oil that was purified by silica gel column chromatography (diethyl ether : petroleum ether, 20 : 80, as eluent) to yield **167** (1.533 g, 65%) as a colorless oil, spectral data mentioned above.

(±) *trans*-2-[4-(*tert*-Butyldimethylsiloxy)-1-pentenyl]-4,4,6-trimethyl-1,3,2-dioxaborolane 171



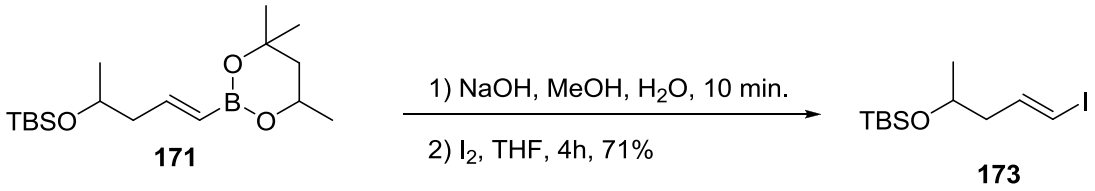
To a stirred terminal alkyne **167** (5.00 g, 25.20 mmol) at 0 °C under argon, catecholborane

(3.00 g, 25.20 mmol) was added dropwise. After that, the reaction mixture heated to 65 °C. After the mixture is stirred until the consumption of starting material by NMR and detected the formation of a mixture of the product **170** : **169** (9:1) as pale yellow oil; which have the following spectral data: ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.14 (6H, s, *Me*$_2$Si), 0.97 (9H, s, *Me*$_3$CSi), 1.25 (3H, d, *J* 6.1 Hz, *Me*CHOSi), 2.38 - 2.47 (2H, m, C*H*$_2$), 4.03 (1H, q, *J* 6.1 Hz, C*H*OSi), 5.82 (1H, dt, *J*, 18.0, 1.4 Hz, =C*H*B), 7.02 – 7.06 (1H, m, -C*H*=), 7.10-7.12 (2H, m, *H*-3′ & *H*-4′), 7.25-7.27 (2H, m, H-2′ & H-5′); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C (100 MHz, $CDCl_3$) -4.7 (*Me*Si), -4.5 (*Me*Si), 18.1 (Me$_3$*C*Si), 23.6 (*Me*CHOSi), 25.8 (*Me*$_3$CSi), 46.5 (*C*H$_2$**)**, 67.9 (*C*HOSi), 112.2 (*C*-3′ & *C*-4′), 121.2 (=*C*HB), 122.4 (*C*-2′ & *C*-5′), 148.3 (*C*-1′ & *C*-6′), 154.3 (CH$_2$*C*H=); Compound **169**: ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.14 (6H, s, *Me*$_2$Si), 0.97 (9H, s, *Me*$_3$CSi), 1.30 (3H, d, *J* 6.1 Hz, *Me*CHOSi), 2.38 - 2.47 (2H, m, C*H*$_2$), 4.14 (1H, q, *J* 6 Hz, C*H*OSi), 5.97 (1H, d, *J*, 3.3 Hz, =CH*H*), 6.32 (1H, d, 3.2 Hz, -C*H*H=), 7.15-7.18 (2H, m, *H*-3′ & *H*-4′), 7.25-7.27 (2H, dd, *J*, 6, 3 Hz, H-2′ & H-5′)

After that (18 hours) the product was cooled to room temperature, and diluted with DCM (50 mL) allowing the addition of 2-methylpentane-2,4-diol (2.98 g, 25.2 mmol) and sat. aq. $NaHCO_3$ (40 mL). After stirring for 2 hours, the reaction is diluted with DCM (50 mL). The organic layer was washed with 1M NaOH (3 x 50 mL) followed by $NaHCO_3$ (50 mL) and water (50 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a yellow crude, which was purified by silica gel column chromatography (EtOAc : petroleum ether, 5 : 95, as eluent) to afford 7.50 g (91%) as a mixture of of the product **171** : **172** (8:1) as pale yellow oil; R_f 0.76 (hexane : EtOAc, 4:1); λ_{max} /cm^{-1} (film) 2970 (w, =C-H), 1461 (s,

C=C), 1451 (s), 1255 (s); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.04 (s, 6H, Si(*Me*$_3$)$_2$), 0.88 (s, 9H, ^{t}*Bu*Si), 1.14 (d, *J* = 6.1 Hz, 3H, CH*Me*$_3$), 1.25 (d, *J* = 6.1 Hz, 3H, BOCCH*Me*$_3$), 1.28 (6H, s, BOC*Me*$_2$), 1.76 (1H, d, *J* 11.6, 2.2 Hz, BOCCHCH*H*), 1.79 (1H, dd, *J* 10.8, 3.0 Hz, BOCCHC*H*H), 2.15-2.34 (2H, m, C*H*$_2$CH=CH), 3.82-3.88 (1H, m, C*H*OBO), 4.15-4.24 (1H, m, C*H*OTBS), 5.37 (1H, d, *J* 17.7 Hz, CH=C*H*B), 6.50 (1H, dq, *J* = 17.7, 6.8 Hz, CH_2C*H*=CHB); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c –5.6 (Si*Me*$_2$), 18.1 (Si*C*(Me)$_3$), 23.2 (*Me*CHOTBS), (*Me*CHOB), 23.7 (*Me*CHOB), 25.7 (SiC*Me*$_3$), 28.9 (*Me*COB), 29.4 (boronate *C*H_2), 30.2 (*Me*COB), 46.1 (*C*H_2CH=), 64.4 (*C*HOTBS), 67.6 (BO*C*Me$_2$), 147.8 (CH_2*C*H=); δ_B (128 MHz, $CDCl_3$) 25.64; LRMS (ES^+): *m*/*z* (rel. int.) 350 ($MHNa^+$, 27%), 349.4 (MNa^+, 72%), 295.3 (MNa^+-H-Me_2, 29%), 277.3 (MNa^+-*t*-Bu-Me, 32%), 235.2 ($MHNa^+$-TBS, 14%), 195.2 (M^+-OTBS, 15%), 141.2 (100%); HRMS (TOF ES^+): Acc. MS calc. for $C_{17}H_{34}{}^{10}BO_3NaSi^+$ $[M-H+Na]^+$, 348.2383; found 348.2396; together with the compound **172**: ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.04 (s, 6H, Si(*Me*$_3$)$_2$), 0.88 (s, 9H, ^{t}*Bu*Si), 1.14 (d, *J* = 6.1 Hz, 3H, CH*Me*$_3$), 1.25 (d, *J* = 6.1 Hz, 3H, BOCCH*Me*$_3$), 1.28 (6H, s, BOC*Me*$_2$), 1.76 (1H, d, *J* 11.6, 2.2 Hz, BOCCHCH*H*), 1.79 (1H, dd, *J* 10.8, 3.0 Hz, BOCCHC*H*H), 2.15-2.34 (2H, m, C*H*$_2$CH=CH), 3.91-3.97 (1H, m, C*H*OTBS), 4.15-4.24 (1H, m, C*H*OBO), 5.50 (1H, d, *J* 4 Hz, CH=C*H*B), 5.76 (1H, d, *J* 4 Hz, CH_2C*H*=CHB).

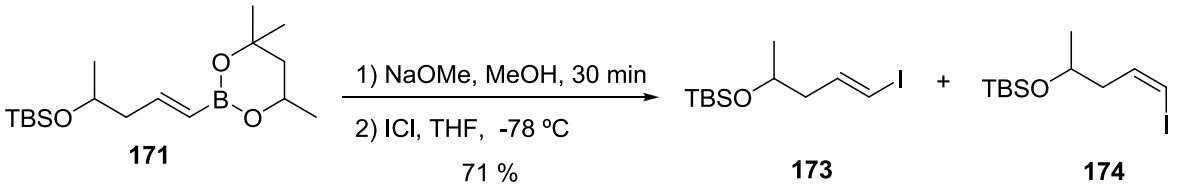
(±)-(*E*)-4-(*t*-Butyldimethylsilyloxy)-1-iodopent-1-ene 173



To a solution of (±)-(*E*)-2-[4-*(tert*-butyldimethylsiloxy)-1-pentenyl]-4,4,6-trimethyl-1,3,2-dioxaborolane **171** (1.00 g, 3.06 mmol) in THF (10 mL) under Ar at room temperature, was added sodium hydroxide (1.84 mL, 9.19 mmol, 5 M in de-ionized water). The reaction mixture left to stir at room temperature for 10 minutes then a solution of iodine (1.55 g, 6.13 mmol) dissolved in THF (5 mL) was added dropwise over ca. 1 minute. The reaction mixture was left to stir at room temperature for 4 h in the absence of light, followed by the quenching with 5% aqueous sodium metabisulfite solution (40 mL). The aqueous layer was extracted with diethyl ether (3 x 25 mL), the combined organic extracts were washed with 5% aqueous sodium metabisulfite solution (40 mL), water (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by silica gel chromatography (petroleum ether as eluent), to give (±)-(*E*)-4-(*tert*-butyldimethylsilyloxy)-1-iodopent-1-ene **173** (0.714 g, 71%) as a light sensitive yellow oil (*E*-isomeric purity > 99%); R_f 0.83 (hexane : EtOAc, 4:1); λ_{max} /cm^{-1} (film): 2928 (w, =C-H), 1472 (w, C=C), 834 (vs), 773 (vs); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.05 (6H, s, *Me*Si), 0.88 (9H, s, *Me*$_3$CSi), 1.12 (3H, d, *J* 6.0 Hz, *Me*CHOSi), 2.13- 2.22 (2H, m, C*H*$_2$), 3.84 (1H, h, *J* 6.1 Hz, C*H*OSi), 6.02 (1H, dt, *J* 14.4, 1.3 Hz, -C*H*=), 6.51 (1H, dt, *J*, 14.4, 7.6 Hz, =C*H*I); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c -4.8 (*Me*Si), -4.5 (*Me*Si), 18.1 (Me$_3$*C*Si), 23.5 (*Me*CHOSi), 25.84 (*Me*$_3$CSi), 46.0 (*C*H$_2$), 67.5 (*C*HOSi), 128.4 (=*C*H), 143.6 (=*C*H); LRMS (ES$^+$): *m*/*z*

(rel. int.) 269.3 (M-^{t}Bu, 100%); LRMS (EI): *m*/*z* (rel. int.) 324.9 (M-H, 21%), 310.9 (M-I, 100%); HRMS (TOF ES$^+$): Acc. MS calc. for $C_{11}H_{22}OSiI^+$ $[M-H]^+$, 325.0485; found 325.0476.

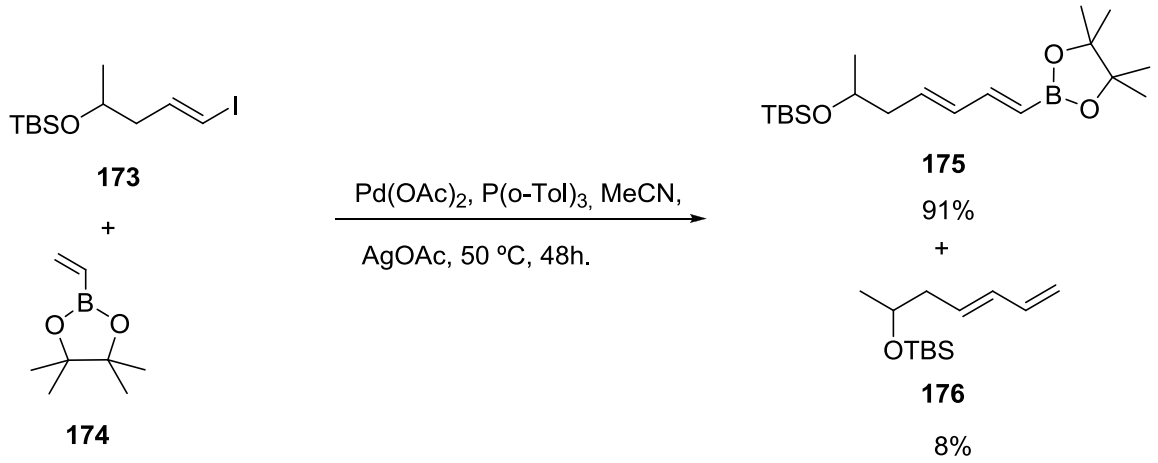
(±)-(*Z*,*E*)-4-(*t*-Butyldimethylsilyloxy)-1-iodopent-1-ene, 173



171 173 174

To a stirred solution of boronate **171** (3.251 g, 10.0 mmol) in dry THF (20 mL) under argon at -78 ºC in the absence of light, was added dropwise NaOMe (23.9 mL of a 0.5 M solution in MeOH, 12.0 mmol). The reaction mixture is stirred at rt for 30 min. After this time, the reaction mixture is cooled to -78 ºC and ICl (23.9 mL of a 1.0 M solution in DCM, 12.0 mmol) was added over 5 min. The reaction is stirred for 30 min. and then, the reaction was allowed to warm to room temperature. After 2 h, the reaction was diluted with Et_2O (50 mL) before washing with 5% aq. $Na_2S_2O_5$ (20 mL, 2x), water (25 mL) and brine (25 mL) before drying ($MgSO_4$) and solvent removal to afford the crude product which purified by silica gel chromatography (petroleum ether, as eluent) provided the compound **173** (2.025 g, 62%) as a light sensitive yellow oil (3:1 *E*:*Z* mixture of isomers which could not be separated), which was identical to that reported previously; together with the compound **174**: ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.04 (6H, s, *Me*$_2$Si), 0.88 (9H, s, *Me*$_3$CSi), 1.15 (3H, d, *J* 6.1, *Me*CHOSi), 2.34-2.37 (2H, m, C*H*$_2$), 3.91 (1H, p, 6, C*H*OSi), 5.84 (1H, q, *J* 7.1, -C*H*I), 6.08 (1H, dt, *J*, 7.1, 1.5, =C*H*).

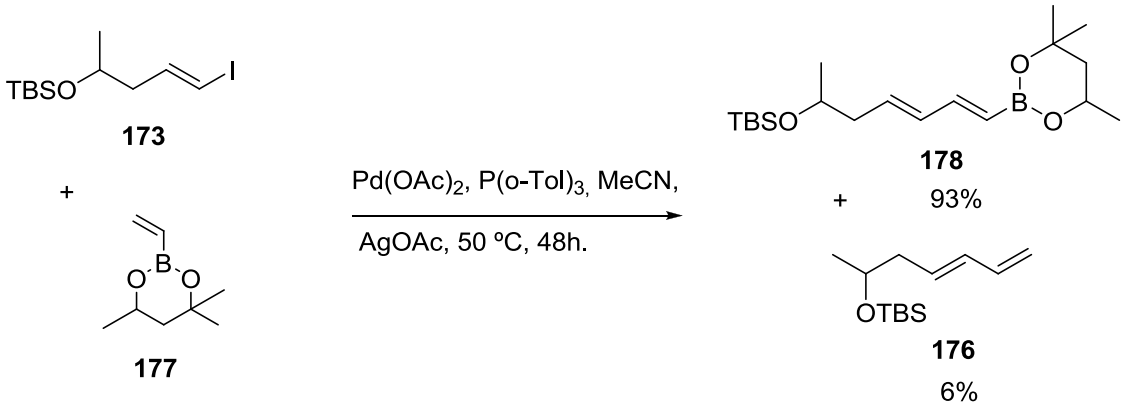
(±) 2-(2*E*, 3*E*)-[6-*(tert*-Butyldimethylsiloxy)-1,3-heptadienyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 175



To a dried Schlenk tube under a positive pressure of argon was added $Pd(OAc)_2$ (120 mg, 0.53 mmol), silver(I) acetate (1.92 g, 11.8 mmol), tri(*o*-tolyl)phosphine (325 mg, 1.0 mmol), and dry MeCN (25 mL). The mixture degassed using the freeze-pump-thaw method (2 x), and vinylboronate pinacol ester **174** (1.97 g, 12.3 mmol) and *(E)*-alkenyl iodide **173** (3.49 g, 10.7 mmol) were added, and then the mixture was degassed using the freeze-pump-thaw method (2 x) and heated to 50 °C with vigorous stirring. After 48 h, the mixture was cooled, diluted with Et_2O (50 mL), passed through Celite, washed with 5% HCl (20 mL), water (20 mL), and brine (20 mL), dried ($MgSO_4$), and evaporated to give crude product as a yellow oil. Purification by SiO_2 chromatography (EtOAc : petroleum ether, 1:19, as eluent) gave the desired product **175** as pale yellow oil (33.4 g, 91%); R_f 0.64 (hexane: EtOAc, 4:1); UV λ_{max}^{EtOH} nm (log ε) 203 (4.032), 244 (4.206), 276 (3.677); λ_{max} /cm^{-1} (film) 2927 (w, C-H), 1604 (s, C=C), 1359 (s), 1255 (s), 1144 (s), 1005 (vs), 833 (vs), 772 (vs); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.03 (3H, s, *Me*Si), 0.04 (3H, s, *Me*Si), 0.87 (9H, s, Me_3CSi), 1.11 (3H, d, *J* 6.1 Hz, *Me*CHOSi), 1.27 (12H, s, Me_2CCMe_2), 2.22 (2H, m, CH_2),

3.84 (1H, q, *J* 6.0 Hz, C*H*OSi), 5.43 (1H, d, *J* 17.7 Hz, =C*H*B), 5.88 (1H, dt, 15.3, 7.5 Hz, =C*H*CH_2), 6.14 (1H, ddd, *J* 15.3, 10.4, 0.8 Hz, CH=C*H*-CH=), 6.98 (1H, dd, *J* 17.7, 10.4 Hz, -C*H*=CHB); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C -4.7 (*Me*Si), -4.5 (*Me*Si), 18.1 (Me_3*C*Si), 23.5 (*Me*CHOSi), 24.8 (*Me*$_3$CSi), 25.8 (*Me*$_2$CC*Me*$_2$), 43.1 (*C*H_2**)**, 68.3 (*C*HOSi), 83.1 (*C*OB), 134.4 (=*C*H), 135.8 (=*C*H), 150.1 (*C*H=CHB); δ_B (128 MHz, $CDCl_3$) 30.56; LRMS (TOF AP$^+$): *m*/*z* (rel. int.) 337.1 (M-Me, 70%), 221.2 (M-OTBS, 100%); HRMS (TOF AP$^+$): Acc. MS calc. for $C_{19}H_{38}{}^{10}BO_3{}^{28}Si^+$ $[M+H]^+$, 352.2720; found 352.2714. Further, purification by SiO_2 chromatography (EtOAc : petroleum ether, 1:19, as eluent) gave also the Suzuki–Miyaura product *tert*-butyl-dimethyl-(1-methyl-hexa-3,5-dienyloxy)-silane **176** as pale yellow oil (200 mg, 8%); R_f 0.78 (hexane : EtOAc, 4 : 1); UV $\lambda_{max}{}^{EtOH}$ nm (log ε) 196 (3.072), 224 (3.656), 252 (3.015), 272 (2.790); λ_{max} /cm^{-1} (film) 2957 (w, C-H), 1500 (s, C=C), 1387 (s), 1301 (s), 1183 (s), 1004 (vs), 830 (vs), 771 (vs); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C) δ_H: 0.03 (3H, s, *Me*Si), 0.04 (3H, s, *Me*Si), 0.88 (9H, s, *Me*$_3$CSi), 1.12 (3H, d, *J* 6.1 Hz, *Me*CHOSi), 2.13-2.26 (2H, m, C*H*$_2$CH=), 3.83 (1H, q, *J* 6.0 Hz, C*H*OTBS), 4.97 (1H, dt, *J* 10.2, 1.7 Hz, =CH*H*), 5.10 (1H, dt, *J* 16.9, 1.7 Hz, =C*H*H), 5.68 (1H, dt, *J* 15.2, 7.5 Hz, CH_2C*H*=), 6.05 (1H, dd, *J* 15.2, 10.2 Hz, C*H*=CH=CHH); 6.31 (1H, dt, *J* 16.9, 10.2 Hz, CH=C*H*=CHH); ^{13}C NMR (101 MHz, $CDCl_3$) δ_c: -4.7 (*Me*Si), -4.5 (*Me*Si), 18.1 (Me_3*C*Si), 23.6 (*Me*CHOSi), 25.9 (*Me*$_3$CSi), 43.0 (*C*H_2), 68.5 (*C*HOTBS), 115.1 (=*C*H_2), 131.8 (=*C*H), 132.9 (=*C*H), 137.2 (CH_2*C*H=); LRMS (EI): *m*/*z* (rel. int.) 211.2 (M-Me, 2%), 169.2 (M-^{t}Bu, 60%), 159.2 (MeCHOTBS-M, 100%).

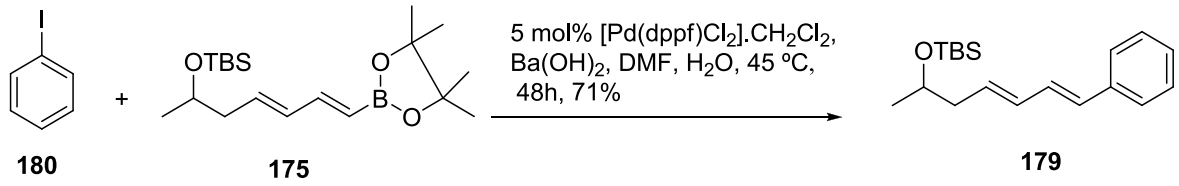
***tert*-Butyldimethyl((4*E*,6*E*)-7-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)hepta-4,6-dien-2-yloxy)silane 178**



To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (0.70 g, 4.17 mmol), $Pd(OAc)_2$ (0.043 g, 0.193 mmol), tri(*o*-tolyl)phosphine (0.12 g, 0.39 mmol), and dry MeCN (20 mL). The mixture degassed using the freeze-pump-thaw method (3 x), and vinylboronate ester **177** (0.66 g, 4.25 mmol) and alkenyl iodide **173** (1.26 g, 3.86 mmol) were added, and then the mixture was degassed using the freeze-pump-thaw method (2 x) and heated to 50 °C with vigorous stirring. After 48h, the mixture was cooled, diluted with Et_2O (50 mL), passed through Celite, washed with 5% HCl (25 mL), water (40 mL), and brine (40 mL), dried ($MgSO_4$), and evaporated to give crude product as a yellow oil. Purification by SiO_2 chromatography (EtOAc : petroleum ether, 1 : 19, as eluent) gave the desired product **178** as pale yellow oil (1.24 g, 93%); R_f 0.69 (hexane : EtOAc, 4 :1); UV λ_{max}^{EtOH} nm (log ε) 244 (4.324), 278 (3.791); λ_{max} /cm^{-1} (film) 2928 (w, C-H), 1500 (w, C=C), 1387 (s), 1301 (s), 1183 (s), 1003 (vs), 831 (vs), 771 (vs); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ_H 0.04 (6H, s, *Me*Si), 0.88 (9H, s, Me_3CSi), 1.11 (3H, d, *J* 6.1, *Me*CHOSi), 1.27 (3H, d, *J* 6.2, BOCH*Me*), 1.30 (6H, d, *J* 1.7 Hz, BOCMe_2), 1.50 (1H, dd, *J* 13.9, 11.8

Hz, BOCCHC*H*H), 1.78 (1H, dd, *J* 13.9, 2.9 Hz, BOCCHCH*H*), 2.13-2.30 (2H, m, CH_2CH=CH), 3.83 (1H, q, *J* 6.1 Hz, C*H*OTBS), 4.17-4.26 (1H, m, C*H*OB), 5.38 (1H, d, *J* 17.5 Hz, CH=C*H*B), 5.82 (1H, dt, *J* 15.2, 7.5 Hz, CH_2C*H*=), 6.11 (1H, ddd, *J* 15.2, 10.4, 0.8 Hz, C*H*=CH=CHB); 6.89 (1H, dd, *J* 17.4, 10.2 Hz, CH=C*H*=CHB); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c -4.7 (*Me*Si), -4.6 (*Me*Si), 18.1 (Me_3*C*Si), 23.1 (*Me*CHOB), 23.4 (*Me*CHOSi), 25.9 (*Me*$_3$CSi), 28.1 (*Me*COB), 31.3 (*Me*COB), 43.1 (*C*H_2CHOTBS), 46.0 (boronate *C*H_2), 64.7 (*C*HOTBS), 68.4 (BO*C*Me_2), 70.6 (Me*C*HOB), 133.7 (=*C*H), 134.0 (=*C*H), 134.7 (=*C*H), 146.5 (CH_2*C*H=); δ_B (128 MHz, $CDCl_3$) 25.85; LRMS (TOF AP$^+$): *m*/*z* (rel. int.) 337.1 (M-Me, 22%), 315.2 (100%), 221.2 (M$^+$-OTBS, 100%), 165 (62%); HRMS (TOF AP$^+$): Acc. MS calc. for $C_{19}H_{38}{}^{10}BO_3{}^{28}Si^+$ $[M+H]^+$, 352.2720; found 352.2717. The compound **176** was isolated by SiO_2 chromatography (EtOAc : petroleum ether, 1 : 19, as eluent) as pale yellow oil (52 mg, 6%); which showed identical spectroscopic properties to those previously reported.

***tert*-Butyldimethyl((4*E*,6*E*)-7-phenylhepta-4,6-dien-2-yloxy)silane 179**

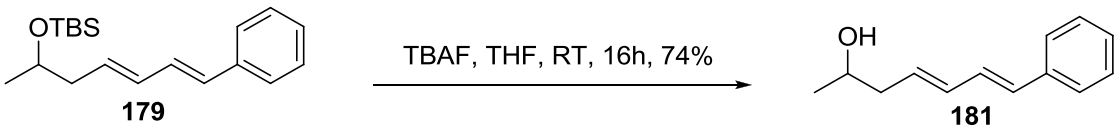


180 **175** **179**

To a dried Schlenk tube under a positive pressure of argon was added iodobenzene **180** (400 mg, 1.96 mmol) and dialkenyl boronate **175** (698 mg, 1.98 mmol) in DMF (20 mL) and H_2O (2 mL). The mixture was degassed using the freeze-pump-thaw method (3 x), and

$Ba(OH)_2$ (403 mg, 2.53 mmol) and $Pd(dppf)Cl_2$ (72 mg, 0.10 mmol) were added, and then the mixture was degassed using the freeze-pump-thaw method (3 x). The mixture was vigorously stirred at room temperature for 48h before it was diluted with EtOAc (50 mL) and passed through Celite, washed with 5% HCl (25 mL), water (25 mL), and brine (25 mL), dried ($MgSO_4$), and evaporated to give crude product as yellow oil. Purification by SiO_2 chromatography (EtOAc : petroleum ether, 5 : 95, as eluent) gave the desired product **179** as yellow oil (396 mg, 71%); R_f 0.78 (hexane : EtOAc, 4:1); UV λ_{max}^{EtOH} nm (log ε) 204 (3.680), 228 (3.621), 272 (3.779), 284 (3.737), 300 (3.627), 316 (3.443), 348 (2.886); ν_{max} /cm^{-1} (film) 2955 (m), 2927 (m), 2855 (m), 1360 (s), 1252 (s), 1080 (s), 987 (vs), 833 (vs), 723 (vs), 690 (s); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.05 (3H, s, *Me*Si), 0.06 (3H, s, *Me*Si), 0.89 (9H, s, Me_3CSi), 1.12 (3H, d, *J* 6.1, *Me*CHOSi), 2.20-2.31 (2H, m, CH_2CHOSi), 3.83-3.91 (1H, m, C*H*OSi), 5.77-5.84 (1H, dt, *J* 15.1, 7.5, =C*H*CH_2), 6.21 (1H, dd, *J* 15.2, 9.8, C*H*=$CHCH_2$), 6.45 (1H, d, *J* 15.7, PhC*H*=CH), 6.75 (1H, dd, *J* 15.7, 10.2, PhCH=C*H*), 7.17-7.22 (1H, m, *H*-4′), 7.28-7.32 (2H, m, *H*-3′ & *H*-5′), 7.37-7.39 (2H, m, *H*-2′ & *H*-6′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c -4.6 (*Me*Si), -4.5 (*Me*Si), 18.1 (Me_3*C*Si), 23.6 (*Me*CHOSi), 25.8 (Me_3CSi), 43.2 (*C*H_2**)**, 68.6 (*C*HOSi), 126.2 (*C*-2′ & *C*-6′), 127.1 (PhCH=*C*H), 128.5 (*C*-3′ & *C*-5′), 129.3 (*C*H=$CHCH_2$),130.4 (Ph*C*H=), 132.1 (=*C*HCH_2), 137.0 (*C*-1′); LRMS (CI): *m*/*z* (rel. int.) 287.1 (M-Me, 2%), 248 (M-^{t}Bu, 8%), 171.1 (M-OTBS, 40%), 159.1 (MeCHOTBS-M, 100%).

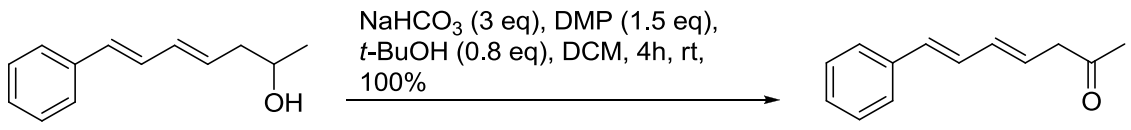
(4*E*,6*E*)-7-Phenylhepta-4,6-dien-2-ol 181



179 **181**

The TBSO-ether compound **179** (390 mg, 1.29 mmol**)** was dissolved in THF (15 mL) and TBAF (2.6 mL, 2.58 mmol, 1M solution in THF) was added drop wise at rt. The result mixture is stirred at rt until the TLC indicated the consumption of starting material. The reaction mixture is diluted with 50 mL EtOAc, washed with 25 mL brine, 25 mL water, dried over $MgSO_4$, concentrated *in vacuo* and the residue was purified by SiO_2 chromatography (EtOAc : petroleum ether, 1:4 as eluent) to give the desired product **181** as yellow solid (180 mg, 74%); R_f 0.18 (hexane: EtOAc, 4:1); Mp 48-50 °C; UV λ_{max}^{EtOH} nm (log ε) 192 (3.624), 200 (3.563), 228 (3.463), 288 (3.492), 332 (3.563); ν_{max} /cm^{-1} (film) 3294 (br, OH), 3019 (m), 2963 (m), 2926 (m), 1595 (m), 1447 (m), 1370 (m), 1119 (m), 1066 (s), 992 (vs), 746 (vs), 690 (vs); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 1.24 (3H, d, *J* 6.2, *Me*CHOH), 2.23-2.38 (2H, m, CH_2CHOH), 3.85-3.93 (1H, m, C*H*OH), 5.82 (1H, dt, *J* 15.1, 7.6, =C*H*CH_2), 6.30 (1H, ddd, *J* 15.1, 10.4, 0.6, C*H*=$CHCH_2$), 6.49 (1H, d, *J* 15.7, PhC*H*=CH), 6.77 (1H, dd, *J* 15.7, 10.4, PhCH=C*H*), 7.17-7.23 (1H, m, *H*-4′), 7.28-7.32 (2H, m, *H*-3′ & *H*-5′), 7.37-7.39 (2H, m, *H*-2′ & *H*-6′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 22.9 (*Me*CHOH), 42.8 (*C*H_2**)**, 67.4 (*C*HOH), 126.2 (*C*-2′ & *C*-6′), 127.4 (PhCH=*C*H), 128.6 (*C*-3′ & *C*-5′), 128.8 (*C*H=$CHCH_2$),130.6 (Ph*C*H=), 131.3 (=*C*HCH_2), 133.8 (*C*-1′); LRMS (CI): *m/z* (rel. int.) 188.2 (M^+, 30%), 171.1 (M-OH, 90%), 129.0 (100%), 91% ($PhCH_2$-M, 56%); HRMS (TOF AP^+): Acc. MS calc. for calcd for $C_{13}H_{15}O^+$ $[M-H]^+$, 187.1123; found 187.1112.

(4*E*,6*E*)-7-Phenylhepta-4,6-dien-2-one 215



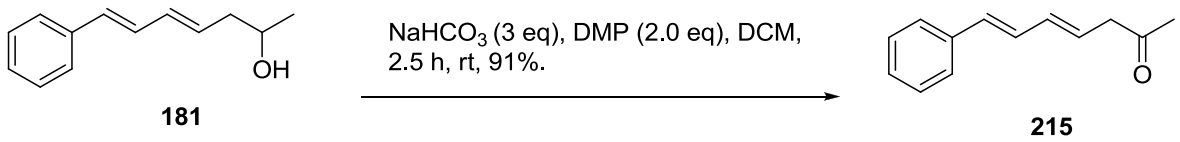
181 **215**

To a solution of **181** (120 mg, 0.64 mmol) in DCM (6 mL) under Ar at 0 °C was added $NaHCO_3$ (214 mg, 2.55 mmol), Dess-Martin periodinane (405 mg, 0.96 mmol) and *tert*-butanol (0.05 mL, 0.51 mmol) The resulting mixture was stirred for 4 h at 0 ºC before a saturated aqueous $Na_2S_2O_3$ solution (5 mL) was added. After being stirred for 10 min, the mixture was extracted with ether (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in DCM, passed through silica-gel, and evaporated to provide the allylic ketone **215** as a mixture of *E*/*Z* and enol 66:10:1 (120 mg, 100%): R_f 0.31 (hexane: EtOAc, 4:1); UV λ_{max}^{EtOH} nm (log ε) 208 (3.516), 268 (3.299), 280 (3.298), 328 (2.729); ν_{max} /cm^{-1} (film) 2358 (m, =C-H),1715 (s, C=O), 1494 and 1447 (m, C=C aromatic), 1356 (m), 1236 (s), 989 (s), 742 (s), 691(vs); ^{1}HNMR (400 MHz, $CDCl_3$): δ_H 2.19 (3H, s, *Me*CO), 3.27 (2H, d, *J* 7.3, C*H*$_2$), 5.89 (1H, dt, *J* 15.2, 7.3, =C*H*CH_2), 6.20- 6.30 (1H, m, C*H*=CHCH_2), 6.50 (1H, d, *J* 15.7, PhC*H*=CH), 6.77 (1H, dd, *J* 15.7, 10.4, PhCH=C*H*), 7.19-7.32 (1H, m, *H*-4′), 7.29-7.32 (2H, m, *H*-3′ & *H*-5′), 7.37-7.39 (2H, m, *H*-2′ & *H*-6′); δ_C (101 MHz, $CDCl_3$) 29.4 (*Me*CO), 47.5 (*C*H_2), 125.7 (*C*-2′ & *C*-6′), 126.3 (*C*-3′ & *C*-5′), 127.5 (PhCH=*C*H), 128.3 (*C*H=CHCH_2),128.5 (Ph*C*H=), 132.27 (=*C*HCH_2), 137.1 (*C*-1′); 206.4 (C=O); LRMS (AP^+): *m/z* (rel. int.) 188.1 (M^+, 15%), 187.1 (M+H, 100%), 170.1 (M-O, 15%), 169.1 (M-OH, 82%); HRMS (TOF AP^+): Acc. MS calc. for calcd for $C_{13}H_{15}O^+$ $[M+H]^+$, 187.1123;

found 187.1120.

For *Z*-isomer of ketone **215**, ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.21 (3H, s, *Me*CO), 3.27 (2H, dd, *J* 7.6 & 1.2, C*H*$_2$), 5.65-5.72 (1H, m, =C*H*CH_2), 6.33- 6.44 (1H, m, C*H*=$CHCH_2$), 6.61 (1H, d, *J* 15.2, PhC*H*=CH), 6.95 (1H, ddd, *J* 15.4, 11.1 & 1.1, PhCH=C*H*), 7.19-7.24 (1H, m, *H*-4′), 7.29-7.32 (2H, m, *H*-3′ & *H*-5′), 7.37-7.39 (2H, m, *H*-2′ & *H*-6′).

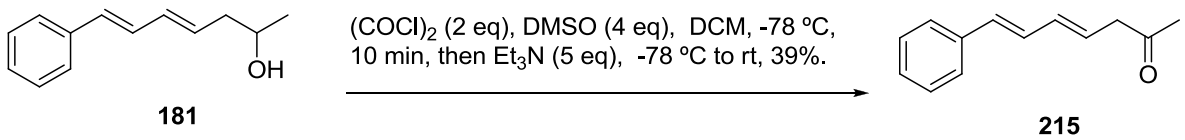
(4*E*,6*E*)-7-Phenylhepta-4,6-dien-2-one 215



181 **215**

To a solution of allylic alcohol **181** (100 mg, 0.53 mmol) in dry DCM (4 mL) under a positive pressure of argon at 0 °C were added $NaHCO_3$ (134 mg, 1.59 mmol, 3 eq) and Dess-Martin periodinane (450 mg, 1.06 mmol, 2 eq). The resulting mixture was stirred for 2.5 h at 0 ºC, then solution of a saturated $Na_2S_2O_3$ (10 mL) was added. After stiring for 10 min, two layers were separted. The aqueous layer was extracted with ether (25 mL x 2). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was dissolved in DCM passed through silica-gel, and evaporated to provide the allylic ketone **215** as a mixture of *E*:*Z* 7:1 (90 mg, 91%), which was identical to that previously reported.

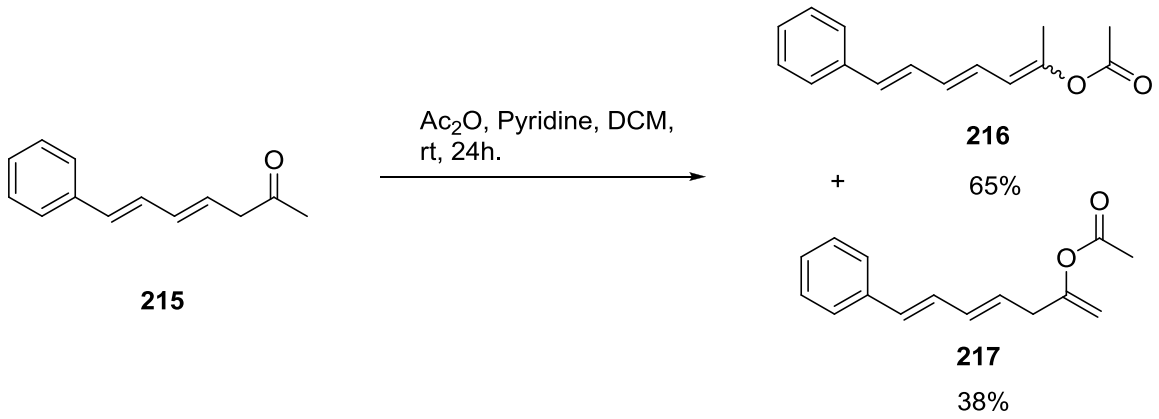
Attempt to synthesis (4*E*,6*E*)-7-Phenylhepta-4,6-dien-2-one 215 by Swern oxidation



181 **215**

To a stirred solution of oxalyl chloride (0.12 mL, 1.36 mmol, 2 eq) in CH_2Cl_2 (2 mL) at –78 °C under argon was added dropwise DMSO (0.19 mL, 2.72 mmol, 4 eq) over 1 min. Following stirring for 10 min, a solution of allylic alcohol **181** (128 mg, 0.68 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 1 min. After stirring for 15 min, triethyl amine (0.47 mL, 3.40 mmol, 5 eq) was added dropwise over 2 min, then following stirring for 5 min, then the reaction mixture left to warm to with stirring for 1h. The consumption of starting was detected by TLC. The reaction was poured in H_2O (50 mL), the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), then the combined organic layers were dried (MgSO4) and evaporated. Purification of the residue by flash SiO_2 column chromatography (EtOAc: petroleum ether, 1:9 as eluent) gave the allylic ketone **215** (50 mg, 39%), which was identical to that previously reported.

(2*Z*,4*E*,6*E*)-7-Phenylhepta-2,4,6-trien-2-yl acetate 216



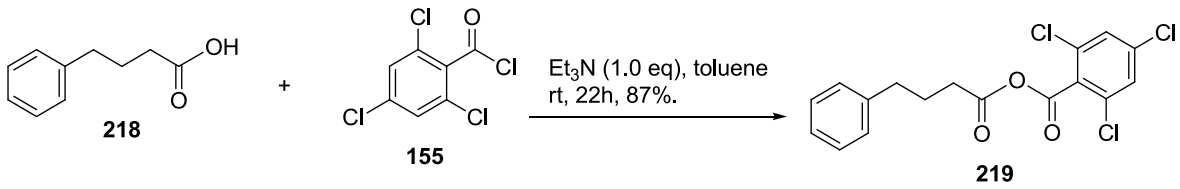
To a solution of substrate **215** (25 mg, 0.13 mmol), in DCM (5 mL) under Ar at room temperature, was added pyridine (0.02 mL, 0.27 mmol) and Ac_2O (0.01 mL, 0.13 mmol). The reaction mixture left to stir at rt for 24 h and the solvent removed. The crude product was subjected to silica gel column chromatography (petroleum ether : EtOAc, 8 : 1, as eluent) to give the desired product **216** as a yellow thick oil (21 mg, 68%) as a mixture of *E* and *Z* enol esters (*EEZ : EEE* = 5 : 1): R_f 0.38 (hexane : EtOAc, 4 : 1); UV λ_{max}^{EtOH} nm (log ε) 200 (3.569), 308 (3.495), 316 (3.480), 336 (3.351); ν_{max} /cm^{-1} (film) 2926 (m, =C-H), 1746 (s, C=O), 1666, 1493 and 1448 (m, C=C), 1371 (s), 1204 (vs), 989 (vs), 747 (vs), 689 (vs); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 2.01 (3H, s, *Me*CH=), 2.23 (3H, s, *Me*CO), 5.74 - 5.77 (1H, m, =C*H*CO_2Me), 6.31 - 6.33 (2H, m, *H*-4 & *H*-5), 6.54 (1H, d, *J* 15.5, PhC*H*=CH), 6.78 - 6.84 (1H, m, PhCH=C*H*), 7.18 - 7.23 (1H, m, *H*-4′), 7.28 - 7.32 (2H, m, *H*-3′ & *H*-5′), 7.37 - 7.39 (2H, m, *H*-2′ & *H*-6′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 19.9 (*C*-1), 20.8 (*Me*CO), 117.5 (*C*-3**)**, 125.6 (*C*-6), 126.3 (*C*-2′ & *C*-6′), 127.4 (C-4′), 128.5 (*C*-3′ & *C*-5′), 132.2 (Ph*C*H=), 132.6 (*C*-4 & *C*-5), 137.3 (*C*-1′), 146.6 (=*C*-O), 168.6 (C=O);

LRMS (TOF AP^+): *m*/*z* (rel. int.) 229 (M+H, 30%), 185 (M-Ac, 40%), 169 (M-AcO, 100%); HRMS (TOF AP^+): Acc. MS calc. for $C_{15}H_{17}O_2^+$ $[M+H]^+$, 229.1229; found 229.1224.

(4*E*,6*E*)-7-Phenylhepta-1,4,6-trien-2-yl acetate 217

Compound **217** was also isolated as a yellow thick oil (11 mg, 38%) as a mixture of *E* and *Z* enol esters (1*E*, 4*E*, 6E : 1*Z*, 4*E*, 6E = 4:1); ^1H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 2.04 (s, 3, *Me*), 2.31 – 2.45 (m, 2H, CH_2), 4.98 (dd, *J* = 12.5, 6.3 Hz, 2H, C=CH_2), 5.85 – 5.64 (m, 1H, =C*H*CH_2), 6.47 (1H, d, *J* = 15.6 Hz, PhC*H*=CH), 6.75 (dd, *J* 15.6, 10.5, 1H, PhCH=C*H*), 7.18 - 7.23 (1H, m, *H*-4′), 7.28 - 7.32 (2H, m, *H*-3′ & *H*-5′), 7.37 - 7.39 (2H, m, *H*-2′ & *H*-6′); LRMS (TOF AP^+): *m*/*z* (rel. int.) 186.1 (M+H-Ac, 100%), 169.1 (M-AcO, 28%); HRMS (TOF AP^+): Acc. MS calc. for $C_{15}H_{17}O_2^+$ $[M+H]^+$, 229.1229; found 229.1219.

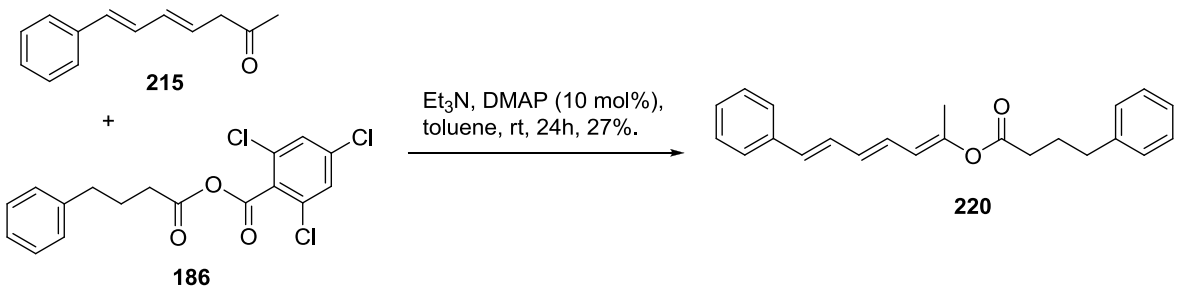
4-Phenylbutyric 2,4,6-trichlorobenzoic anhydride 219



To a solution of 4-phenylbutyric acid **218** (1.87 g, 11.40 mmol) in dry toluene (30 mL) under Ar at room temperature was added 2,4,6-trichlorobenzoyl chloride **155** (2.77 g, 11.40 mmol) and triethylamine (1.59 mL, 11.40 mmol) in toluene (30.0 mL). The resulting solution was stirred at room temperature for 22 h. After that time, the mixture was triturated

with hexane to precipitate triethylamine hydrochloride as white crystals, which is filtered, and the resulting solution concentrated under reduced pressure to give the desired compound **219** as a white solid (3.86 g, 87%); R_f 0.52 (hexane : EtOAc, 4:1); Mp = 58-60 °C; ν_{max} /cm^{-1} (film) 2929 (m, C-H), 1810 (vs, C=O anhydride), 1744 (s), 1575, 1547 &1494 (m, C=C aromatic), 1241 (m), 1076 (vs), 980 (vs), 750 (vs, C-Cl); $C_{17}H_{13}Cl_3O_3$ requires C, 54.94; H, 3.53; found C, 54.04; H, 3.40; ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 1.98 (2H, q, *J* 7.4, $CH_2CH_2CH_2$), 2.44 (2H, t, *J* 7.4, CH_2C=O), 2.68 (2H, t, *J* 7.4, CH_2Ph), 7.16-7.23 (3 H, m, *H*-4′, *H*-2′ & *H*-6′), 7.26-7.32 (2 H, m, *H*-3′ & *H*-5′) and 7.40 (2 H, s, =C*H*Cl); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 25.6 ($CH_2CH_2CH_2$), 34.4 (CH_2C=O), 34.7 (CH_2Ph),126.1 (*C*-4′), 128.3 (2C, =*C*H-CCl), 128.4 (2C, *C*-2′ & *C*-6′), 128.5 (2C, *C*-3′ & *C*-5′), 129.8 (2C, ClC*C*C=O), 133.1 (2C, =*C*Cl, *Ortho* position), 137.6 (=*C*Cl, *Para* position), 140.8 (*C*-1′), 157.5 (ClCC*C*=O);), 169.1 (C-1′-*C*=O); LRMS (EI): *m*/*z* (rel. int.) 207 ($C_7H_3Cl_3O$-M, 100%).

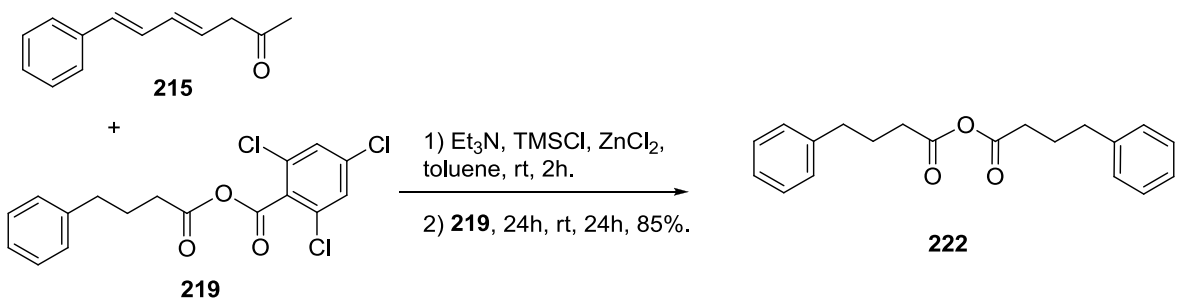
(2*Z*, 4*E*, 6*E*)-7-Phenylhepta-2,4,6-trien-2-yl 4-phenylbutanoate 220



To a solution of ketone **215** (25 mg, 0.13 mmol) in dry toluene (2 mL) under an atmosphere of argon at room temperature, was added Et_3N (0.06 mL, 0.40 mmol) and DMAP (2 mg,

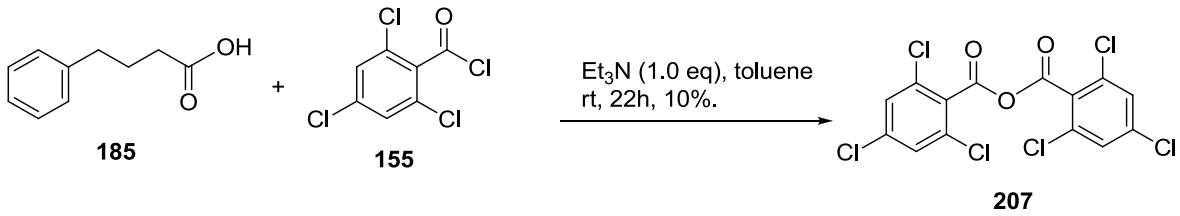
0.01 mmol). The resulting solution was stirred at room temperature for 10 miutes and then the mixed anhydride **6** (50 mg, 0.134 mmol) was added. The reaction is stirred for 24h and the solvent removed. The crude product subjected to SiO_2 column chromatography (hexane : EtOAc, 7:1, as eluent) to give the desired product **220** as a yellow thick oil (12 mg, 27%) as a mixture of *E* and *Z* enolate (*EEZ:EEE* = 8 : 1), which separated by recrystallisation with MeOH to give the enol ester **220** as yellow solid (6 mg, 13%), Mp = 64 – 66 ^{o}C, R_f 0.47 (hexane : EtOAc, 4 : 1); UV λ_{max}^{EtOH} nm (log ε) 208 (3.925), 288 (3.574); ν_{max} /cm^{-1} (film) 2929 (m, C-H), 1720 (s, C=O), 1374 (vs), 1301 (vs), 1164 (s), 838 (s), 668 (s); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 2.00 (3H, s, *Me*CH=), 2.02-2.10 (2H, m, C*H*$_2$), 2.51 (2H, t, *J* 7.4, C*H*$_2$CO), 2.73 (2H, t, *J* 7.3, PhC*H*$_2$), 5.74-5.76 (1H, m, *H*-3), 6.25-6.36 (2H, m, *H*-4 & *H*-5), 6.53 (1H, d, *J* 15.5, PhC*H*=CH), 6.75-6.81 (1H, m, PhCH=C*H*), 7.18-7.24 (4H, m, Ar-*H*), 7.28-7.35 (4H, m, Ar-*H*), 7.36-7.38 (2H, m, Ar-*H*); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 20.1 (*C*-1), 20.8 (*Me*CO), 26.5 (*C*H$_2$CO), 33.5 (*C*H$_2$), 35.0 (Ph*C*H$_2$), 117.4 (*C*-3**)**, 125.6 (*C*-6), 126.1 (*C*-2′ & *C*-6′), 126.3 (*C*-2″ & *C*-6″) 127.4 (*C*-4′, *C*-4″), 128.4 (*C*-3″ & *C*-5″), 128.5 (*C*-3′ & *C*-5′), 132.1 (Ph*C*H=), 132.6 (*C*-4 & *C*-5), 137.3 (*C*-1′ & *C*-1″), 149.6 (=*C*-O), 171.1 (C=O); LRMS (EI): *m*/*z* (rel. int.) 332.2 (M^{+}, 2%), 186.1 (M-Ph(CH$_2$)$_3$CO$_2$, 70%), 91.0 (PhCH$_2$-M, 100%).

4-Phenylbutyric anhydride 222



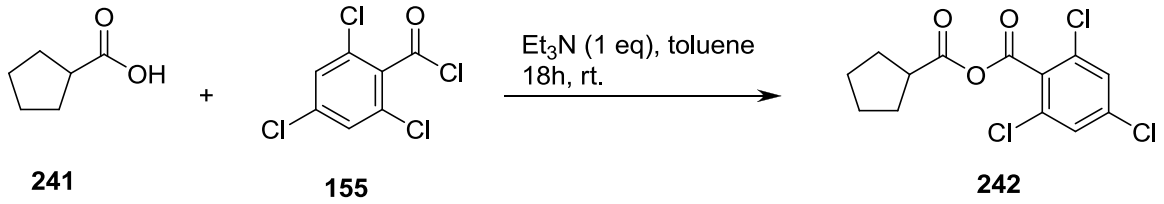
To a solution of ketone **215** (20 mg, 0.11 mmol) in dry toluene (2 mL) under Ar at room temperature, was added Et_3N (0.02 mL, 0.11 mmol), TMSCl (0.01 mL, 0.11 mmol) and $ZnCl_2$ (0.11 mL, 0.11 mmol). The resulting solution was stirred at room temperature for 2h and then the mixed anhydride **219** (40 mg, 0.11 mmol) was added. The reaction is stirred for 24h and the solvent removed. The crude product subjected to SiO_2 column chromatography (EtOAc : petroleum ether, 1 : 9, as eluent) to give the symmetrical anhydride **189** as a white solid (28 mg, 85%): Mp = 34 – 35 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 1.79 (4H, q, *J* 7.6, C*H*$_2$), 2.38 (4H, t, *J* 7.4, C*H*$_2$CO), 2.68 (4H, t, *J* 7.4, PhC*H*$_2$), 7.17-7.21 (6H, m, *H*-2′, *H*-2′′, *H*-4′, *H*-4′′ & *H*-6′, *H*-6′′), 7.26-7.31 (4H, m, *H*-3′, *H*-3′′, *H*-5′, *H*-5′′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 26.2 (*C*H$_2$), 33.0 (*C*H$_2$CO), 34.9 (PhCH$_2$), 126.0 (*C*-4′, *C*-4′′), 128.4 (*C*-2′, *C*-2′′, *C*-6′, & *C*-6′′)128.5 (*C*-3′, *C*-3′′, *C*-5′ & *C*-5′′), 138.9 (*C*-1′ & *C*-1′′), 141.1 (*C*OO); LRMS (AP$^+$): *m*/*z* (rel. int.) 311.2 (MH$^+$, 2%), 164 (MH-C_6H_5-C_3H_6-CO, 15%), 147.1 (M-$C_6H_5(CH_2)_3CO_2$, 100%).

2,4,6-Trichlorobenzoic anhydride 207



To a solution of 4-phenylbutyric acid **185** (1.873 g, 11.41 mmol) in dry toluene (30 mL) under Ar at room temperature was added 2,4,6-trichlorobenzoyl chloride **155** (2.772 g, 11.407 mmol) and triethylamine (1.59 mL, 11.407 mmol) in toluene (30.0 mL). The resulting solution was stirred at room temperature for 22 h. After that time, the mixture was triturated with hexane to precipitate triethylamine hydrochloride as white crystals, which is filtered, and the resulting solution concentrated under reduced pressure and triturated with hexane to give the byproduct compound **207** as a white solid (0.480 g, 10%); R_f 0.38 (hexane : EtOAc, 4 : 1); Mp = 107 – 108 ˚C. ν_{max} /cm^{-1} (film) 3073 (m, =C-H), 1811 (s, C=O anhydride), 1798 (s, C=O anhydride), 1755, 1740, 1572 &1545 (s, C=C aromatic), 1369, 1206 (s), 1079 (s), 983 (vs), 858 (vs), 819(s), 764 (C-Cl); $C_{14}H_4Cl_6O_3$ requires C, 38.84; H, 0.93; found C, 38.84; H, 0.98; δ_H (400 MHz, $CDCl_3$) 7.39 (4 H, s, =C*H*); δ_C (100 MHz, $CDCl_3$) 128.3 (4C, *C*H), 129.8 (2C,=*C*C=O), 133.1 (4C, =*C*Cl, *Ortho* position), 137.6 (2C, =*C*Cl, *Para* position), 157.5 (*C*=O); LRMS (ESI): *m*/*z* (rel. int.) 471 (MK^+, 100%), 223 (M-$C_7H_2Cl_3O_2$, 100%).

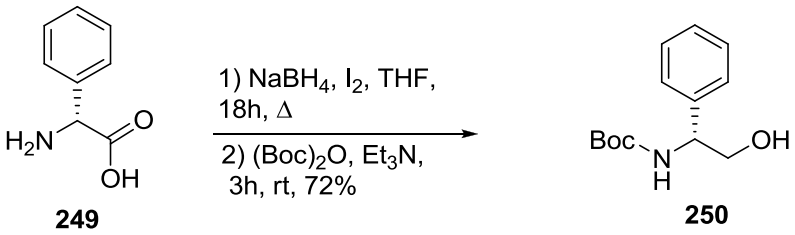
Preparation stock solution of 2,4,6-trichlorobenzoic cyclopentanecarboxylic anhydride 242



241 **155** **242**

To a stirred solution of cyclopentane carboxylic acid **241** (3.20 g, 28.04 mmol) in dry toluene (80 mL) under Ar at rt, was added 4 ˚A molecular sieves (0.80 g), Et_3N (4.30 mL, 30.84) and 2,4,6-trichlorobenzoyl chloride (6.84 g, 28.04 mmol). The reaction mixture was stirred at rt for 18h. The reaction mixture keeped closed under Ar for futher using.

***tert*-Butyl (1*R*)-2-hydroxy-1-phenylethylcarbamate 250**



249 **250**

To a stirring solution of 0.27 g (7.28 mmol, 2.2 eq) of sodium borohydride and dry THF (150 mL) at 0 °C is added 1.84 g (7.28 mmol, 2.2 eq) of iodine in 6 ml of dry THF. The iodine-THF solution was added dropwise to the borohydride-THF suspension. After that, 0.50 g (3.31 mmol, 1eq) of (*R*)-phenylglycine **249** was added to the mixture in one portion. The reaction was heated at reflux for 18 h. After this period, the reaction was cooled to 0 °C and 0.60 ml of methanol was added to the reaction, then diluted with 5 ml of dry THF and 0.48 ml (3.47 mmol, 1.05 eq) of triethylamine was added in one portion. With vigorous stirring 0.73 g (3.34 mmol, 1.01 eq) di-*tert*-butyl dicarbonate is added in one portion. The

reaction was allowed to warm to room temperature further than 48h. The solvents were removed and the resulting white solid was suspended by adding 4 ml of ethyl acetate and 3 ml of water. The white residue was broken down by addition 10% aq. HCl and brine. The aqueous phase is extracted with ethyl acetate (3 x 10 ml) and the combined organic phases were washed with: a) a 1:1 solution of 5% HCl and brine (8 ml); b) a 1:1 solution of saturated $NaHCO_3$ and brine (8 ml); and finally c) water (8 ml). The organic phase was dried over $MgSO_4$. The solvent was removed *in vacuo* to leave 1.10 g of crude product that recrystallized using cyclohexane and DCM system to give the desired product **250** (0.56 g, 72%) as white needles: Mp 136-137°C, lit. value 138-139 °C (from cyclohexane/ DCM);[158] $[\alpha]^{21}_D$ -40.0° (c 1.0, $CHCl_3$), lit. value -41.9° (c 1.0, $CHCl_3$);[158] $C_{13}H_{19}NO_3$ requires C, 65.85; H, 8.03; N, 6.03 found C, 65.80; H, 8.07; N, 5.90; νmax/cm^{-1} (KBr disk) 3233 (broad, -OH), 3061(broad, N-H), 1675 (strong, C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.40 (9H, s, *Me*$_3$CO), 1.90 (1H, broad, exchanges with D_2O, O*H*), 3.86 (2H, d, *J* 4.1, C*H*$_2$OH), 4.85 ((1H, brd, C*H*Ph), 5.32 ((1H, brd, N*H*), 7.26-7.31 (3H, m, *H*-2′, *H*-4′ & *H*-6′), 7.33-7.38 (2H, m, *H*-3′ & *H*-5′); ^{13}C NMR (400 MHz, $CDCl_3$): δ_c 28.3 (*Me*$_3$CO), 37.5 (*C*HPh), 71.2 (*C*H_2), 79.9 (quaternary, Me$_3$*C*O), 126.7, 128.3, 128.9, 137.7 (quaternary, *C*-1′), 155.0 (quaternary, C=O); LRMS (ES^+): *m*/*z* (rel. int.) 238.2 (MH^+, 25%); 223.2 (MH^+-Me, 100%), 182.2 ($MHNa^+$-C_6H_5, 75%);; Enantiomeric excess was determined by HPLC (e.e. ≥ 99.8%) with a Chiralpak OD column (90:10, hexane:ethanol), 0.5 mL/min; λ = 235 nm; *R*-enantiomer tR = 13.85 min, *S*-enantiomer tR = 15.66 min.

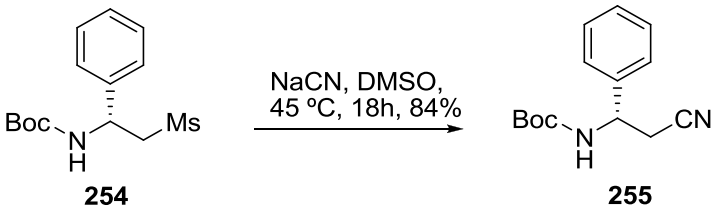
(2*R*)-2-[(*tert*-Butoxycabonyl) amino]-2-phenylethylmethanesulfonate.

250 **254**

To a stirred solution of 0.50 g (2.11 mmol, 1 eq) of *tert*-butyl (1*R*)-2-hydroxy-1-phenylethylcarbamate **250** in dry DCM (10 mL) under argon is added 0.44 mL of freshly distilled triethylamine (3.16 mmol, 1.5 eq) then cooled to 0 C. Then, 0.17 ml (2.2 mmol, 1.05 eq) of methanesulfonyl chloride in 5 mL of dry DCM is added dropwise. The reaction was stirred at <20 °C for 12 h, after this time 4 mL of saturated $NaHCO_3$ was added. After stirring for a further 20 min, the aqueous phase was diluted with DCM (2 x 10 mL) and the combined organic phases washed with saturated sodium chloride solution (2 x 5 mL). After drying the organic phase ($MgSO_4$), the solvents were removed *in vacuo* to yield 0.67 g of an off-white solid that was recrystallised from DCM-hexane to give 0.47 g (71%) of (2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylethyl methanesulfonate **254** as a white solid: m.p.111-113 °C, lit. value 112-114 °C (from cyclohexane/ DCM);[159a] $[\alpha]^{21}_{D}$ -21° (c 1.0, $CHCl_3$), lit. value -21° (c 1.0, $CHCl_3$);[159b] $C_{14}H_{21}NO_5S$ requires C, 53.15; H, 6.75; N, 4.38%; found C, 53.32; H, 6.71; N, 4.44%; ^{1}H NMR (400 MHz, CDCl3) δ_H 1.43 (9H, s, *Me*$_3$CO), 2.87 (3H, s, *Me*SO_3), 4.38-4.49 (2H, m, CHC*H*$_2$), 5.02 (1H, bs, PhC*H*), 5.16 (1H, brs, *exchanges with* D_2O, N*H*), 7.31-7.33 (3H, m, *H*-2′, *H*-4′ & *H*-6′), 7.36-7.40 (2H, m, *H*-3′ & *H*-5′); ^{13}C NMR (400 MHz, $CDCl_3$) δ_c 28.3 (*M*e$_3$CO), 37.4 (*C*HPh), 71.2 (*C*H$_2$), 79.9 (quaternary, Me$_3$*C*O), 126.7, 128.3, 128.9, 137.7 (quaternary, *C*-1′), 155.0 (quaternary,

C=O); ; LRMS (ES^+): *m*/*z* (rel. int.) 301.2 (MH^+-Me, 92%), 260.2 ($MNaH^+$-$MeSO_2$, 100%).

***tert*-Butyl(1*R*)-2-cyano-1-phenylethylcarbamate 255**

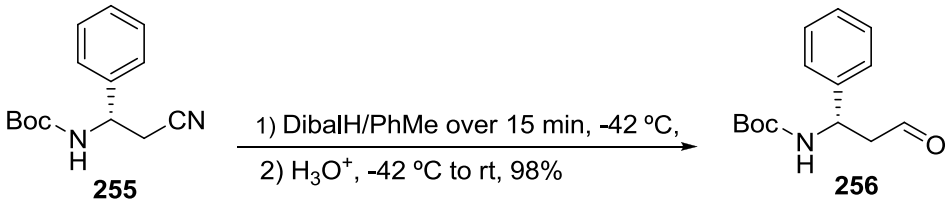


254 **255**

To a 0.45 g (1.43 mmol) of (2*R*)-2-[(*tert*-butoxycarbony)amino]-2-phenylethylmethanesulfonate **254** in anhydrous DMSO (10 ml) under argon, is added 0.28 g (5.50 mmol, 4 eq) NaCN in one portion. The reaction was stirred at 45 °C for 18h. The reaction is then cooled to 0 °C and 10 mL of water added. The DMSO-H_2O phase extracted with diethyl ether (3 X 10 mL). The combined ether Extracts are then washed with saturated NaCl (3 x 25 mL), water (2 x 25 mL) and dried ($MgSO_4$). Removal of the solvent *in vacuo* gives a white solid that is recrystallised from DCM-hexane to yield 0.26 g (84%) of tert-butyl (1*R*)-2-cyano-1-phenylethycarbamate **255** as white crystals. Mp 114 – 115 °C, lit value 110-112 °C;[160] $[\alpha]^{21}_D$ -42.1(c 0.5, EtOH), lit. for *S*-enantiomer $[\alpha]^{21}_D$ +41.6° (c 0.5, EtOH);[160] $C_{14}H_{18}N_2O_2$ requires C, 68.01; H, 7.29; N, 10.94% found C, 68.27; H, 7.37; N, 11.37%; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.45 (9H, s, Me_3CO), 2.89 (1H, dd, *J* 16.4, 6.2, CH*H*CN), 2.99 (1H, dd, *J* 16.4, 6.2, C*H*HCN), 4.99 (2H, bd, *J* 5.7, *exchanges with* D_2O, N*H*, PhC*H*), 7.33-7.37 (3H, m, *H*-2′, *H*-4′ & *H*-6′), 7.39-7.43 (2H, m, *H*-3′ & *H*-5′); ^{13}C NMR (400 MHz, $CDCl_3$): δ_c 26.9 (CH_2), 28.3 (9H, s, Me_3CO), 80.6 (quaternary,), 117.0 (quaternary, *C*N), 126.2, 128.7, 129.2, 139 (quaternary, *C*-1′);); LRMS (CI): *m*/*z* (rel.

int.) 246.6 (M^+, 7%), 206.2 (MH-Me-CN, 57%), 206.2 (M-Me_2-CN, 100%); Enantiomeric excess was determined by HPLC (e.e. ≥99.8%) with a Chiralpak OJ column (95:5 hexane:2-propanol), 0.75 mL/min; λ = 254 nm; *R*-enantiomer tR = 44.37 min, *S*-enantiomer tR = 35.25 min.

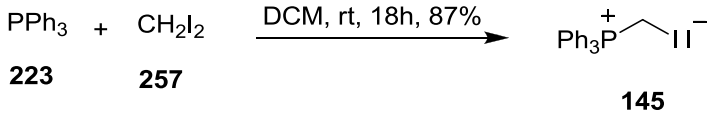
***tert*-Butyl (1*R*)-3-oxo-1-phenylpropylcarbamate 256**



tert-Butyl(1*R*)-2-cyano-1-phenylethylcarbamate **255** (10.20 g, 41.41 mmol) was dissolved in dry ether (150 mL), cooled to -42 °C and stirred under argon. Dibal-H was added (165.65 mL, 1M solution in PhMe, 165.65 mmol) over 15 min. The mixture was stirred for 30 minutes, and methanol (6 mL) followed by saturated NH_4Cl (150 mL). After allowing the mixture to warm to room temperature, the thick gel was quenched by the slow addition of 5% HCl (150 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL), and the organic layer washed with 5% HCl and brine (2 x 25 mL of each), saturated $NaHCO_3$and brine (2 x 25 mL of each), and dried ($MgSO_4$). Evaporation gave *tert*-butyl (1*R*)-3-Oxo-1-phenylpropylcarbamate **256** (10.12 g, 98%) as a yellow solid; Mp 82-85 °C (lit.[152] value 91-93°C); $[\alpha]^{21}_D$ -26.1° (c 0.08, $CHCl_3$), lit. for *S*-enantiomer $[\alpha]^{21}_D$ +27.5° (c 0.08, $CHCl_3$);[161] R_f 0.35 (hexane: EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.37 (9H, s, *Me*$_3$CO), 2.83-2.97 (2H, m, C*H*$_2$CHO), 5.09 (1H, brd, C*H*Ph), 5.15 (1H, brs, NH signal

exchanges with D_2O), 7.21-7.27 (3H, m, *H*-2′, *H*-4′ & *H*-6′), 7.28-7.32 (2H, m, *H*-3′ & *H*-5′), 9.70 (1H, dd, *J* 2.5, 1.6 Hz, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ_c 28.3 (*Me*$_3$CO), 49.9 (*C*H_2CHO), 54.5 (*C*HPh), 126.3 (*C*-2′ & *C*-6′), 127.7 (*C*-4′), 128.1 (*C*-3′ & *C*-5′), 143.8 (*C*-1′, quaternary), 154.9 (Me$_3$*C*=O), 200.0 (*C*HO). Spectroscopic and analytical properties were identical to those reported in the literature.[152]

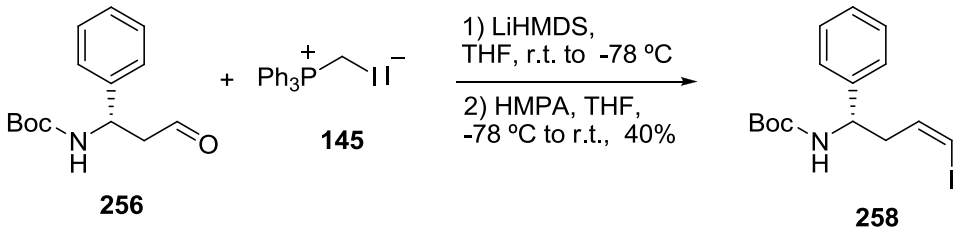
Iodomethyltriphenylphosphonium iodide 145



223 **257** **145**

To a suspension of triphenylphosphine **223** (5.0 g, 19.06 mmol) in dry DCM (50 mL) was added diiodomethane **257** (6.14 mL, 4 eq). The mixture was stirred at rt for 18h, concentrated in *vacuo* and the crystals were collected by filtration. After washing with hexane, and drying in *vacuo* (0.1 mmHg), iodomethyltriphenylphosphonium iodide **145** (8.78 g, 87%) was isolated as a white solid, Mp 226-229°C (dec) (Lit.[162] 230 °C (dec); ^{1}H NMR (400 MHz, DMSO, 20 °C): δ_H 5.13 (2H, d, *J* 8.8, C*H*$_2$), 7.80-7.98 (15H, m, $(C_6H_5)_3$); ^{13}C NMR (101 MHz, DMSO): δ_C 40.4 (*C*H_2), 130.6 (*C*-3′ & *C*-5′), 130.7 (*C*-3′ & *C*-5′), 134.3 (*C*-2′ & *C*-6′), 134.4 (*C*-2′ & *C*-6′), 135.6 (C-4′), 135.7 (C-4′). Spectroscopic and analytical properties were identical to those reported in the literature.[162]

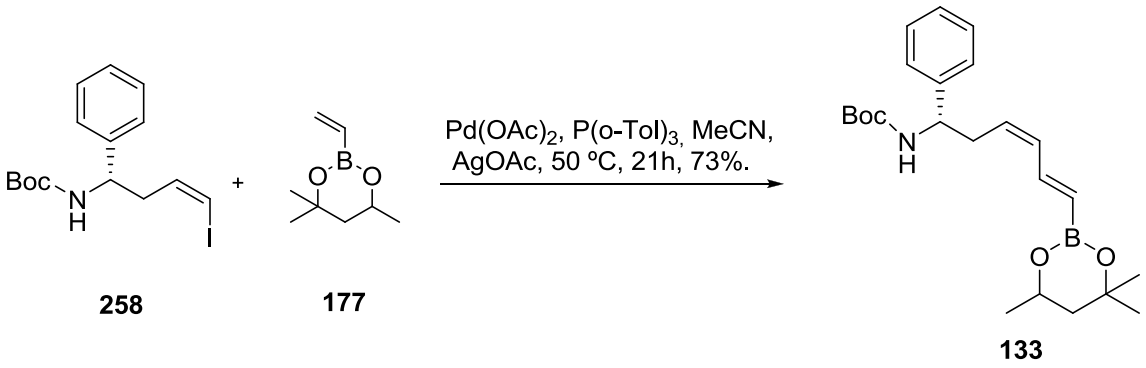
***tert*-Butyl *N*-[(*Z*,1*R*)-4-iodo-1-phenylbut-3-enyl]carbamate 258**



To a suspension of iodomethyltriphenylphosphonium iodide **145** (475 mg, 0.90 mmol) in THF (10 mL) at room temperature was slowly added lithium hexamethyldisilazide (1.0 M solution in THF, 1.79 mL, 1.80 mmol). After stirring for 10 min, the dark red-colored solution was cooled to −78 °C and HMPA (0.57 mL, 3.26 mmol) was added. A solution of aldehyde **256** (203 mg, 0.81 mmol) in THF (5 mL) was added slowly and the mixture was allowed to warm up to room temperature and, after 20 min, the reaction was quenched with sat. NH_4Cl (5 mL) and filtered. The resulting solution was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$) and concentrated in *vacuo*. The residue was purified by SiO_2 chromatography (EtOAc : petroleum ether, 1 : 19, as eluent) to give *tert*-Butyl N-[(*Z*,1*R*)-4-iodo-1-phenylbut-3-enyl]carbamate **258** (122 mg, 40%) as white solid (30:1 *Z*:*E* isomers could not be separated); R_f 0.50 (hexane : EtOAc, 4 : 1); Mp 103-105°C (lit.[127c] value 104-106°C); $[\alpha]^{21}_D$ -25.3° (c 1.2, $CHCl_3$), lit. for *S*-enantiomer $[\alpha]^{21}_D$ +27.9° (c 0.08, $CHCl_3$);[127c] ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.42 (9H, s, *Me*$_3$CO), 2.63 (2H, br, C*H*$_2$CHPh), 4.86 (2H, br, C*H*Ph & N*H*), 6.11 (1H, dd, *J* 13.7, 7.5, =C*H*CH$_2$), 6.33 (1H, d, *J* 7.5, =C*H*I), 7.20 – 7.26 (3H, m, *H*-4′, *H*-2′ & *H*-6′), 7.33 – 7.37 (2 H, m, *H*-3′ & *H*-5′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 28.3 (*Me*$_3$CO), 41.9 (*C*H$_2$), 53.5 (Ph*C*H), 85.2 (C*H*I), 126.3 (*C*-2′ & *C*-6′),

127.5 (*C*-4′), 128.6 (*C*-3′ & *C*-5′), 137.1 (=*C*HCH$_2$), 142.1 (*C*-1′, quaternary), 155.1 (*C*=O); Spectroscopic and analytical properties were identical to those reported in the literature.[127c]

***tert*-Butyl (1*R*, 3*Z*, 5*E*)-1-phenyl-6-(4,4,6-trimethyl-1,3,2-dioxaborinan-2-yl)-3,5-hexadienylcarbamate 133**

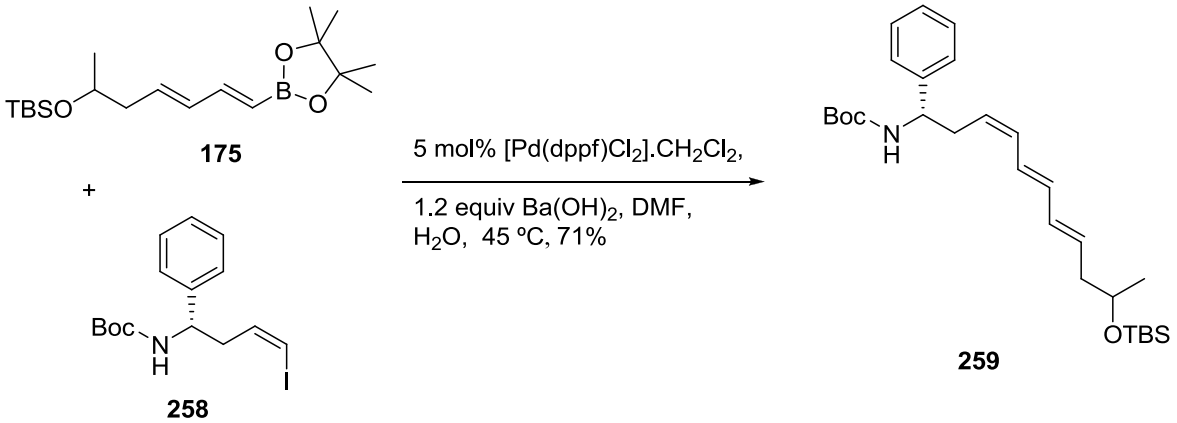


258 **177** **133**

To a dried Schlenk tube under a positive pressure of argon was added silver(I) acetate (48 mg, 0.29 mmol), Pd(OAc)$_2$ (3 mg, 0.01 mmol), tri(*o*-tolyl)phosphine (8 mg, 0.03 mmol), vinylboronate (0.05 mL, 0.0.29 mmol), and a (*Z*)-alkenyl iodide **258** (100 mg, 0.268 mmol) in dry MeCN (5 mL). The mixture was degassed using the freeze-pump-thaw method (3 x), and heated to 50 °C with vigorous stirring. After 21h, the mixture was cooled, diluted with Et$_2$O (25 mL) and passed through Celite, washed with 5% HCl (20 mL), water (20 mL), and brine (20 mL), dried (MgSO$_4$), and evaporated to give crude product as a yellow oil. Purification by SiO$_2$ chromatography (EtOAc : petroleum ether, 1 : 9 as eluent) gave the desired product **133** (78 mg, 73%, 19:1 *ZE*:*EE*) as a thick orange oil; R_f 0.32 (hexane: EtOAc, 4:1); $[\alpha]^{21}_D$ -157.8 (c 9.5, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): δ_H 1.28 (3H, d, *J* 6.3, BOCH*Me*), 1.30 (6H, d, *J* 1.7 Hz, BOC*Me*$_2$), 1.40 (9H, s, *Me*$_3$CO), 1.50 (1H, dd, *J*

13.9, 11.8 Hz, BOCCHC*H*H), 1.79 (1H, dd, *J* 13.9, 2.9 Hz, BOCCHCH*H*), 2.71-2.75 (2H, m, CH_2CH=), 3.82 - 3.88 (1H, m, C*H*OBO), 4.18 - 4.24 (1H, m, C*H*OB), 4.78 (1H, brs, C*H*Ph), 4.85 (1H, brs, NH signal exchanges with D_2O), 5.36-5.44 (1H, m, CH=C*H*B), 5.50 (1H, d, *J* 17.3 Hz, =CH-C*H*=CHB), 6.14 (1H, t, *J* 11.3 Hz, CH_2-C*H*=), 7.13 (1H, dd, *J* 17.4, 11.3 Hz, CH_2-CH=C*H*), 7.22-7.35 (5H, m, C_6H_5); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 23.1 (*Me*CHOB), 28.1 (Me_2COB), 28.3 (Me_3CO), 31.2 (boronate CH_2), 46.0 (CH_2CHPh), 54.4 (*C*HPh), 64.7 (BO*C*HMe), 70.8 (BO*C*Me_2), 77.2 (Me_3CO), 126.2 (*C*-2′ & *C*-6′), 126.4 (=CH), 127.1 (*C*-4′), 128.5 (*C*-3′ & *C*-5′), 128.9 (=*C*H), 133.6 (CH_2CH=), 139.3 (C-1′, quaternary), 155.2 (*C*=O); δ_B (128 MHz, $CDCl_3$) 26.07. Spectroscopic and analytical properties were identical to those reported in the literature.[127c]

***tert*-Butyl(1*R*, 3*Z*, 5*E*, 7*E*)-10- *tert*-Butyldimethylsiloxy-1-phenylundeca-3,5,7-trienylcarbamate 259**

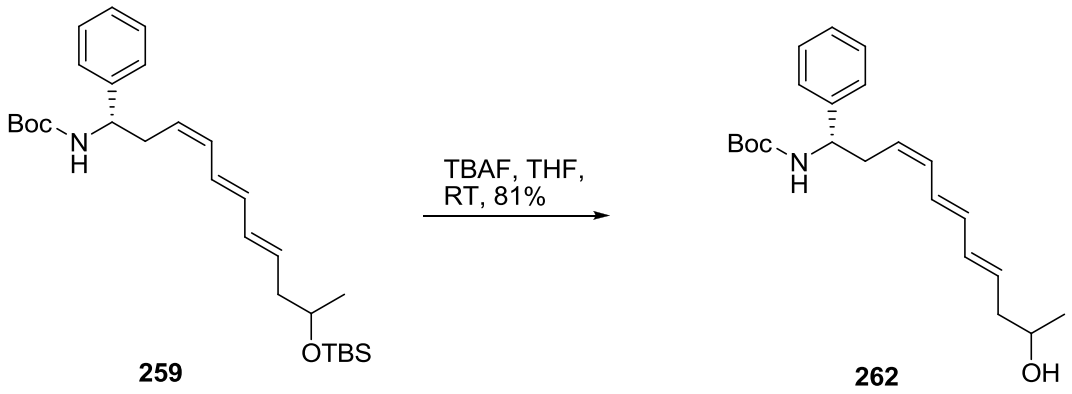


To a dried Schlenk tube under a positive pressure of argon was added (*Z*)-alkenyl iodide **258** (95 mg, 0.25 mmol) and dialkenyl boronate **175** (99 mg, 0.28 mmol) in DMF (4 mL) and H_2O (0.4 mL). The mixture degassed using the freeze-pump-thaw method (3 x), and

$Ba(OH)_2$ (52 mg, 0.31 mmol) and $Pd(dppf)Cl_2.CH_2Cl_2$ (10 mg, 0.01 mmol) were added, and then the mixture was degassed using the freeze-pump-thaw method (3 x). The mixture was vigorously stirred at 45 °C with vigorous stirring for 48h before it was diluted with EtOAc (25 mL) and passed through Celite, washed with 5% HCl (20 mL), water (20 mL), and brine (20 mL), dried ($MgSO_4$), and evaporated to give crude product as a brown oil. Purification by SiO_2 chromatography (EtOAc : petroleum ether, 1 : 9, as eluent) gave the desired product **259** as yellow oil (84 mg, 71%); R_f 0.73 (hexane : EtOAc, 4 : 1); $[\alpha]^{21}_D$ -285.7 (c 1.4, $CHCl_3$); UV λ_{max}^{EtOH} nm (log ε) 204 (4.063), 272 (4.389), 284 (4.309), 304 (3.775), 320 (3.695); λ_{max} /cm^{-1} (film) 2924 (s), 2870 (m), 1700 (s, C=O), 1494 (m), 1363 (s), 1253 (s), 996 (s), 729 (vs); ^{1}H NMR (700 MHz, $CDCl_3$, 20 °C): δ_H 0.04 (6H, s, *Me*Si), 0.88 (9H, s, Me_3CSi), 1.12 (3H, d, *J* 6.1, *Me*CHOSi), 1.41 (9H, s, Me_3CO), 2.16-2.29 (2H, m, CH_2CHOSi), 2.59-2.73 (2H, m, CH_2CHPh), 3.83 (1H, q, *J* 6.1 Hz,C*H*OSi), 4.76 (1H, brd, C*H*Ph), 4.84 (1H, brs, NH signal exchanges with D_2O), 5.28 (1H, dt, *J* 15.0, 7.5, =C*H*CH_2CHOSi), 5.71 (1H, dt, *J* 15.0, 7.5 Hz, =C*H*CH_2CHPh), 6.10 (2H, t, *J* 12.2 Hz, *H*-& *H*-3), 6.19 (1H, dd, *J* 14.4, 11.4 Hz, =C*H*), 6.32 (1H, dd, *J* 14.4, 11.4 Hz, =C*H*), 7.22-7.27 (3H, m, *H*-4′, *H*-2′ & *H*-6′), 7.31-7.35 (2H, m, *H*-3′ & *H*-5′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c -4.7 (*Me*Si), -4.5 (*Me*Si), 18.1 (Me_3*C*Si), 23.5 (*Me*CHOSi), 25.9 (Me_3CSi), 28.3 (Me_3CO), 35.0 (*C*H_2Ph), 43.2 (*C*H_2CHOSi**)**, 68.6 (*C*HOSi), 79.5 (Me_3*C*O), 125.7 (=*C*H), 126.0 (=*C*H), 126.3 (=*C*H), 127.2 (=*C*H), 128.5 (=*C*H), 130.9 (=*C*-), 131.5 (=*C*H), 132.2 (=*C*H), 132.4 (=*C*H), 134.1 (=*C*H), 155.2 (*C*=O); LRMS (ESI): *m*/*z* (rel. int.) 494.4 (MNa^+, 100%); LRMS (AP^+): *m*/*z* (rel. int.) 472.3 (MH^+, 5%), 372.3 (MH_2^+-Boc, 100%); 240.2 (MH^+-Boc-OTBS, 25%); 159.1 (M^+-Boc-OTBS-C_6H_6-H_2, 37%); HRMS (TOF AP^+): Acc.

MS calc. for $C_{28}H_{46}NO_3{}^{28}Si^+$ $[M+H]^+$, 472.3247; found 472.3253.

***tert*-Butyl (1*R*, 3*Z*, 5*E*, 7*E*)-10-hydroxy-1-phenylundeca-3,5,7-trienylcarbamate 262**

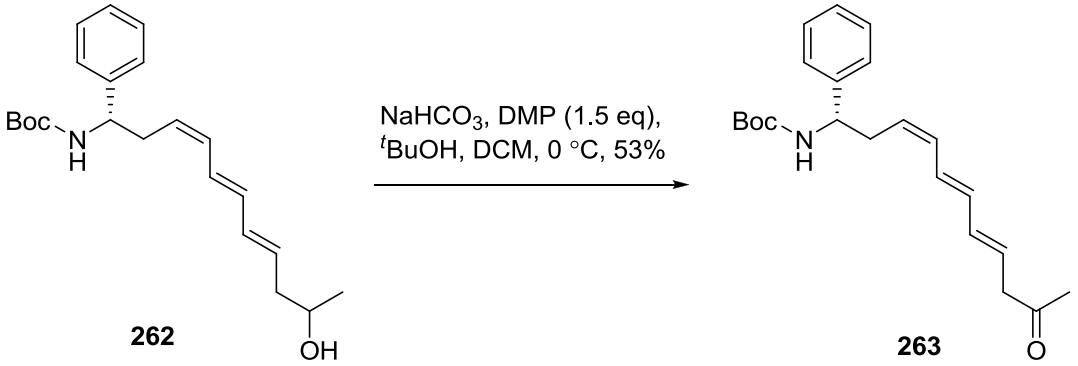


259 **262**

The triene compound **259 (**182 mg, 0.37 mmol**)** is dissolved in THF and TBAF (1.54 mL, 1.54 mmol, 1M solution in THF, 4 eq) was added drop wise at RT. The result mixture is stirred until the consumption of starting material by TLC. The reaction mixture is diluted with EtOAc (25 mL), washed with brine (20 mL), water (20 mL), and dried over $MgSO_4$, concentrated *in vacuo*. Purification of the residue by SiO_2 chromatography (EtOAc : petroleum ether, 1 : 9, as an eluent) gave the allylic alcohol **262** as yellow oil (112 mg, 81%); R_f 0.84 (hexane: EtOAc, 1:1); $[\alpha]^{21}{}_D$ -352.9 (c 1.7, $CHCl_3$); UV $\lambda_{max}{}^{EtOH}$ nm (log ε) 244 (3.581), 272 (3.841), 284 (3.815), 300 (3.667), 316 (3.629), 328 (3.221), 348 (3.071); λ_{max} /cm^{-1} (film) 3386 (br, OH), 2924 (s), 2870 (m), 1685 (vs, C=O), 1507 (m), 1365 (s), 1248 (s), 1166 (vs), 700 (vs); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 1.21 (3H, d, *J* 6.2, *Me*CHOH), 1.41 (9H, s, Me_3CO), 1.52 (1H, brs, OH, exchanges with D_2O), 2.19-2.34 (2H, m, CH_2CHOH), 2.59-2.73 (2H, m, CH_2CHPh), 3.81-3.90 (1H, m, C*H*OH), 4.75 (1H, brs, C*H*Ph), 4.84 (1H, brs, NH signal exchanges with D_2O), 5.31 (1H, dt, *J* 15.1, 7.6, CH_2C*H*=), 5.71 (1H, dt, *J* 14.0, 7.4, =C*H*CH_2CHPh), 6.06-6.23 (3H, m, =C*H*), 6.36 (1H,

dd, *J* 12.3, 7.2, =C*H*), 7.22-7.27 (3H, m, *H*-4′, *H*-2′ & *H*-6′), 7.31-7.34 (2H, m, *H*-3′ & *H*-5′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 22.9 (*Me*CHOH), 28.3 (*Me*$_3$CO), 35.0 (*C*H$_2$CHPh), 42.4 (*C*H$_2$CHOH**)**, 54.5 (*C*HPh), 67.7 (*C*HOH), 77.2 (Me$_3$*C*O), 126.3, 127.2, 128.5, 133.5, 133.6, 188.7 (*C*=O); LRMS (ESI): *m*/*z* (rel. int.) 381.3 ($MHNa^+$, 23%); 380.3 (MNa^+, 100%); 358.0 (MH^+, 4%); HRMS (ES^+): Acc. MS calc. for $C_{22}H_{31}NNaO_3$ $[M+Na]^+$, 380.2202; found 380.2180.

Attempted synthesis of *tert*-butyl(1*R*,3*Z*,5*E*,7*E*)-10-oxo-1-phenylundeca-3,5,7-trienylcarbamate 263

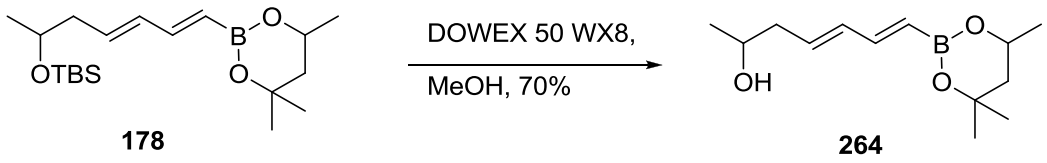


262 **263**

To a solution of **262** (170 mg, 0.48 mmol) in dry DCM (10 mL) under Ar at 0 °C was added $NaHCO_3$ (120 mg, 1.43 mmol, 3 eq) and Dess-Martin periodinane (403 mg, 0.95 mmol, 3 eq). The resulting mixture was stirred for 3 h at 0 ºC before a saturated aqueous $Na_2S_2O_3$ solution (6 mL) was added. After being stirred for 10 min, the mixture was extracted with ether (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was dissolved in DCM, passed through silica-gel, and evaporated to provide the allylic ketone **263** (89 mg, 53%) as a mixture of *ZEE*/*ZEZ*/*ZEEE* (67:11:10); λ_{max} /cm^{-1} (film) λ_{max} /cm^{-1} (film) 2926

(s), 1702 (vs, C=O), 1494 (m), 1366 (s), 1251 (s), 742 (s), 699 (s); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 1.40 (9H, s, Me_3CO), 2.16 (3H, s, *Me*CO), 2.54 (1H, br, C*H*HCHPh), 2.67 (1H, br, CH*H*CHPh), 3.32 (2H, d, *J* 7.4, CH_2CO), 4.74 (1H, brs, C*H*Ph), 4.88 (1H, brs, N*H*), 5.33 (1H, dt, *J* 11.1, 7.9, =C*H*CH_2CO), 5.50-5.58 (1H, m, CH_2C*H*=), 5.78 (1H, dt, *J* 14.6, 7.4, =C*H*CH_2CHPh), 6.02-6.24 (3H, m, =C*H*), 6.30-6.34 (1H, m, =C*H*), 7.22-7.34 (5H, m, C_6H_5).

(4*E*,6*E*)-7-(4,4,6-Trimethyl-1,3,2-dioxaborinan-2-yl)hepta-4,6-dien-2-ol 264

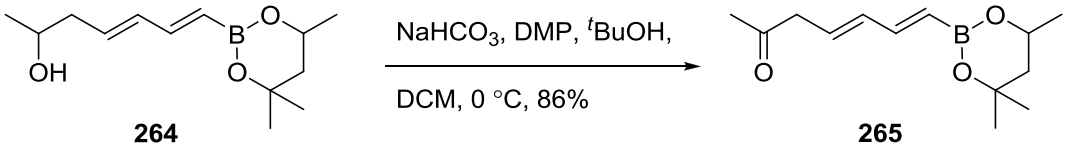


178 **264**

To a solution of substrate **178** (512 mg, 1.45 mmol) in MeOH (40 mL) under Ar at rt, was added DOWEX 50 WX8 200 mesh (400 mg). The reaction left to stir at rt for 18 h. TLC indicated that there is some of substrate so another quantity of DOWEX 50 WX8 200 mesh (983 mg) was added. After 3h of stirring at rt, the TLC indicated consumed of the starting material. The reaction mixture is filtered and evaporated. Purification of the residue by SiO_2 chromatography (EtOAc : petroleum ether, 1 : 3, as eluent) gave the desired product **264** (241 mg, 70%); R_f 0.83 (hexane : EtOAc, 1:1); UV λ_{max}^{EtOH} nm (log ε) 204 (3.697), 244 (3.927), 277 (3.294); λ_{max} /cm^{-1} (film) 3343 (br, OH), 2970 (m), 2929 (w), 1387 (s, C=C), 1302 (vs), 1008 (s); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): δ_H 1.18 (3H, d, *J* 6.1, CH*Me*), 1.26 (3H, d, *J* 6.1, BOCCH*Me*), 1.29 (6H, s, BOC*Me*$_2$), 1.48 (1H, dd, *J* 13.8, 11.6, BOCCHC*H*H), 1.63 (br, OH), 1.77 (1H, d, *J* 13.8, 2.9 Hz, BOCCHCH*H*), 2.18-2.32 (2H, m, CH_2CH=CH), 3.80-3.88 (1H, m, C*H*OH), 4.21 (1 H, dqd, *J* 12.3, 6.2, 2.9, C*H*OBO),

5.42 (1H, d, *J* 17.5, 1H, CH=C*H*B), 5.81 (1H, dt, *J* 15.1, 7.4, CH_2C*H*=), 6.19 (ddd, *J* 15.1, 10.4, 0.8, 1H,C*H*=CH=CHB); 6.91 (dd, *J* 17.5, 10.4, 1H, CH=C*H*=CHB); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 22.8 (*Me*CHOH), 23.1 (*Me*CHOB), 28.1 (Me_2COB), 31.2 (CH_2CH=), 42.6 (CH_2OH), 46.0 (boronate CH_2), 64.7 (*C*HOH), 67.3 (BO*C*Me_2), 70.7 (Me*C*HOB), 132.7 (=*C*H), 135.8 (=*C*H), 146.5 (CH_2*C*H=); δ_B (128 MHz, $CDCl_3$) 25.99; LRMS (TOF AP^+): *m*/*z* (rel. int.) 239.2 (MH^+, 50%), 195.2 (M^+-Me_2CH_2, 100%); HRMS (TOF AP^+): Acc. MS calc. for $C_{13}H_{24}{}^{10}BO_3^+$ $[M+H]^+$, 238.1855; found 238.1842.

(4*E*,6*E*)-7-(4,4,6-Trimethyl-1,3,2-dioxaborinan-2-yl)hepta-4,6-dien-2-one 265

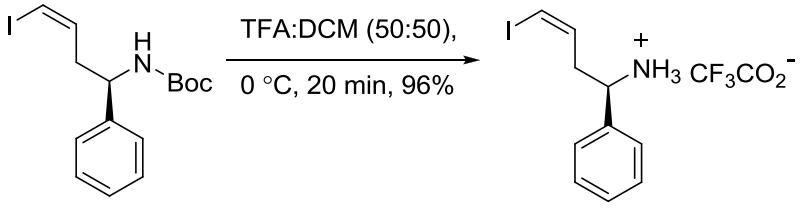


264 **265**

To a solution of substrate **264** (0.44 g, 1.48 mmol) in DCM (40 mL) under Ar at 0 ºC were added $NaHCO_3$ (1.55 g, 2.55 mmol), Dess-Martin periodinane (1.175 g, 2.77 mmol) and *tert*-butanol (0.14 mL, 1.48 mmol). The resulting mixture was stirred for 4 h at 0 ºC. The crude product was filtered, evaporated and subjected to silica gel chromatography (EtOAc : petroleum ether, 1 : 4, as eluent) to give the desired product **265** as yellow oil (0.375 g, 86%); R_f 0.31 (hexane : EtOAc, 1 : 4); UV $\lambda_{max}{}^{EtOH}$ nm (log ε) 200 (3.704), 244 (3.986), 276 (3.327); λ_{max} /cm^{-1} (film) 2973 (m), 1712 (s, C=O), 1372 (vs, C=C), 1304 (vs), 1162 (s); ^{1}H NMR (400 MHz, $CDCl_3$, 20°C): 1.26 (3H, d, *J* 6.1, BOCCH*Me*), 1.29 (6H, s, BOC*Me*$_2$), 1.49 (1H, dd, *J* 13.8, 11.7, BOCCHC*H*H), 1.78 (1H, dd, *J* 13.8, 2.9 Hz, BOCCHCH*H*), 2.14 (3H, s, MeCO), 2.18-2.32 (2H, m, C*H*$_2$CH=CH), 3.20 (2H, d, *J* 7.6,

C*H*$_2$CO), 4.17-4.25 (1H, m, C*H*OBO), 5.45 (1H, d, *J* 17.5, 1H, CH=C*H*B), 5.89 (1H, dt, *J* 15.2, 7.3, CH$_2$C*H*=), 6.17 (ddd, *J* 15.2, 10.4, 0.8, 1H,C*H*=CH=CHB); 6.91 (dd, *J* 17.5, 10.4, 1H, CH=C*H*=CHB); ^{13}C NMR (100 MHz, $CDCl_3$, 20°C): δ_c 23.1 (*Me*CHOB), 28.09 (*Me*$_2$COB), 31.2 (*C*H$_2$CH=), 42.5 (*C*H$_2$OH), 45.9 (boronate *C*H$_2$), 64.6 (*C*HOH), 67.2 (BO*C*Me$_2$), 70.7 (Me*C*HOB), 132.7 (=*C*H), 135.8 (=*C*H), 146.5 (CH$_2$*C*H=); δ_B (128 MHz, $CDCl_3$) 25.99; LRMS (TOF AP$^+$): *m*/*z* (rel. int.) 237.2 (MH$^+$, 100%), 236.2 (M$^+$, 20%); HRMS (TOF AP$^+$): Acc. MS calc. for $C_{13}H_{22}{}^{10}BO_3^+$ [M+H]$^+$, 236.1698; found 236.1673.

Ammonium [(*Z*,1*R*)-4-iodo-1-phenylbut-3-enyl] trifluoroacetate 271

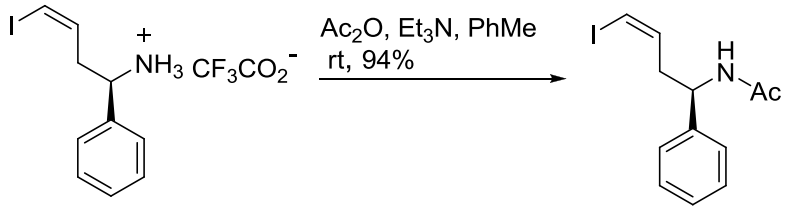


258 **271**

To a solution of substrate **258** (26 mg, 0.07 mmol) in DCM (0.5 mL) at 0 ºC was added TFA (0.5 mL). After 20 min of stirring the reaction mixture at 0 ºC, the TLC indicated the consumption of the substrate. Toluene (5 mL) was added to the reaction mixture and the TFA was removed by evaporation. Another 5 mL of toluene was added and the solvent was trapped on rotary. The brown oily product (25 mg, 96%) was indicated by ^{1}H NMR as the desired ammonium TFA salt **271**; ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 2.71-2.83 (2H, m, C*H*$_2$CHPh), 4.19 (1H, t, *J* 7.6, C*H*Ph), 5.98 (1H, dd, *J* 14.2, 7.0, =C*H*), 6.37 (1H, d, *J* 7.6, =C*H*), 7.14-7.18 (2H, m, Ph), 7.34-7.36 (2H, m, Ph), 8.08-8.57 (3H, brd, N*H*$_3$)); ^{13}C NMR (101 MHz, $CDCl_3$): δ_C (101 MHz, $CDCl_3$) 39.0 (*C*H$_2$Ph), 54.4 (*C*HPh), 87.0 (=*C*HI), 127.0 (*C*-4′), 127.3 (*C*-3′ & *C*-5′), 129.0 (*C*-2′ & *C*-6′), 135.3 (=*C*HCH$_2$), 162.2 (*C*=O); ^{19}F

(376 MHz, $CDCl_3$) δ_F -75.52.

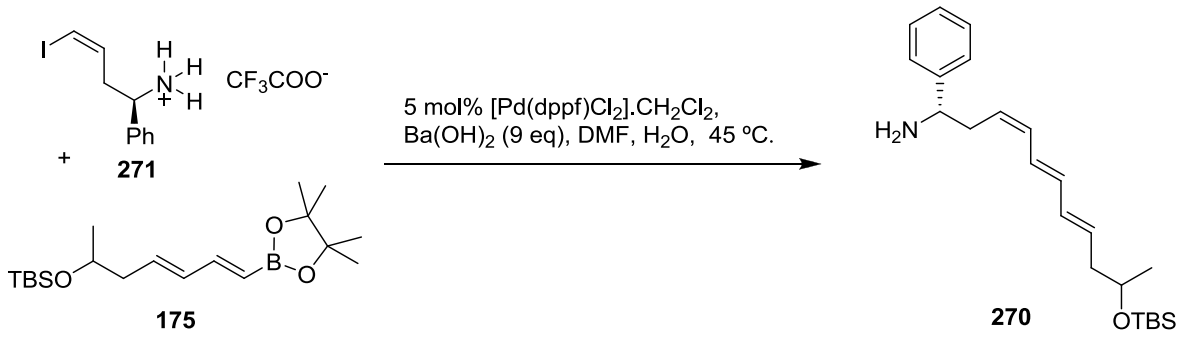
***(1R,3Z)*-*N*-(4-iodo-1-phenylbut-3-enyl)acetamide 272**



271 **272**

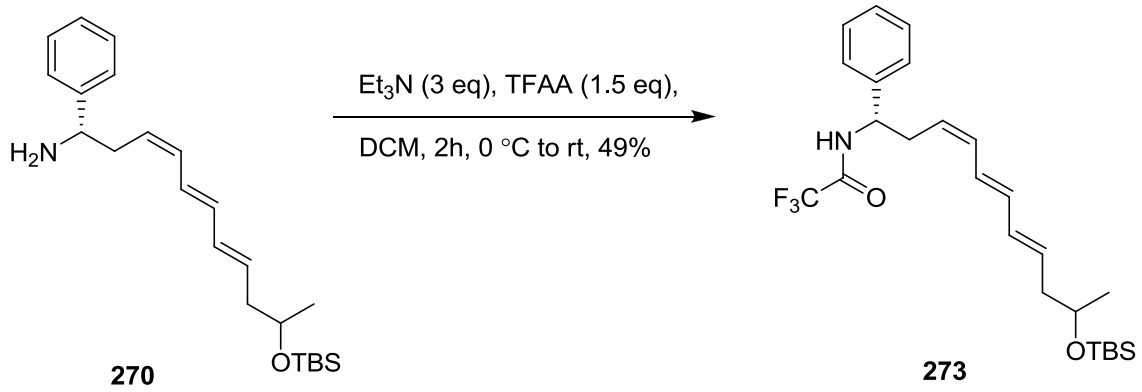
To a stirred solution of TFAA salt **271** (37 mg, 0.10 mmol) in dry toluene (1 mL) was added Et_3N (0.08 mL, 0.57 mmol) and acetic anhydride (0.01 mL, 0.12 mmol). After 24h, the reaction mixture was trapped on rotatory and then on high vacuum to give the crude product which purified by SiO_2 chromatography (EtOAc : petroleum ether, 1 : 3, as eluent) to give the desired product **272** as white solid (36 mg, 94%): Mp = 89 – 90 ^oC; R_f 0.04 (hexane : EtOAc, 4 : 1); $[\alpha]^{21}_D$ -289.8° (c 1.38, $CHCl_3$); λ_{max} /cm^{-1} (film) 3279 (s, NH), 2924 (m), 1643 (s, C=O), 1551 (s), 1493 and 1433 (m, C=C), 751 (s), 696 (vs); ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.95 (3H, s, *Me*), 2.55 – 2.71 (2H, m, CH_2CHPh), 5.16 (1H, dd, *J* 14.7, 8.2, C*H*Ph), 5.91 (1H, d, *J* 7.8, N*H*), 6.11 (1H, dd, *J* 14.2, 6.9, =C*H*), 6.29 (1H, dt, *J* 7.5, 1.3, =C*H*I), 7.20 – 7.26 (3H, m, *H*-4′, *H*-2′ & *H*-6′), 7.27 – 7.34 (2 H, m, *H*-3′ & *H*-5′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 23.3 (*Me*CO), 41.0 (*C*H_2), 52.1 (Ph*C*H), 85.5 (C*H*I), 126.5 (*C*-4′), 128.8 (*C*-2′ & *C*-6′), 127.7 (*C*-3′ & *C*-5′), 137.1 (=*C*HCH_2), 140.9 (*C*-1′, quaternary), 169.7 (*C*=O); LRMS (ES^+): *m*/*z* (rel. int.) 338.1 (MNa^+, 100%), 316.2 (MH^+, 50%); HRMS (TOF ES^+): Acc. MS calc. for $C_{12}H_{15}NOI^+$ $[MHNa]^+$, 316.0198; found 316.0203.

Attemp to synthesis (1*R*,3*Z*,5*E*,7*E*)-10-(*tert*-Butyldimethylsilyloxy)-1-phenylundeca-3,5,7-trien-1-amine 270



To a dried Schlenk tube under argon were added TFAA salt **271** (100 mg, 0.268 mmol), dialkenyl boronate **175** (104 mg, 0.295 mmol) and $Ba(OH)_2$ (505 mg, 2.948 mmol) in DMF (10 mL) and H_2O (1 mL). The mixture was degassed using the freeze-pump-thaw method (3 x), and $Pd(dppf)Cl_2.CH_2Cl_2$ (14 mg, 0.013 mmol) was added. The mixture was again degassed using the freeze-pump-thaw method (3 x) and stirred vigorously at 45 ºC for 48h before being diluted with Et_2O (50 mL), passing through Celite, and washing with brine (40 mL). The aqueous layer was extracted with Et_2O (2 x 25 mL) and the combined organic extracts were washed with brine (3 x 25 mL), dried ($MgSO_4$) and evaporated to give crude product **270** (100 mg); λ_{max} /cm^{-1} (film) 3378 (br), 2955 (m), 2928 (m), 2856 (m), 1605 (m), 11361 (s), 1252 (s), 1144 (s), 833 (vs), 774 (vs); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.03 (6H, s, *Me*$_2$Si), 0.88 (9H, s, *Me*$_3$CSi), 1.12 (3H, d, *J* 6.1, *Me*CHOSi), 2.18-2.27 (2H, m, C*H*$_2$CHOSi), 2.49-2.98 (2H, m, C*H*$_2$CHPh), 3.82 (1H , dd, *J* 12.2, 6.1, C*H*OSi) 3.94 – 4.07 (1H, m, C*H*Ph), 5.34-5.41 (1H, m, =C*H*), 5.69 (1H, dt, *J* 14.7 & 7.5, =C*H*CH$_2$), 5.64-5.73 (1H, m, =C*H*), 6.07-6.25 (3H, m, =C*H*), 6.39 (1H, dd, *J* 14.3, 11.3) 7.39 – 7.18 (5 H, m, C$_6$*H*$_5$).

Trifluoromethyl (1*R*,3*Z*,5*E*,7*E*,10*RS*)-10- *tert*-butyldimethylsiloxy-1-phenylundeca-3,5,7-trienylcarbamate 273

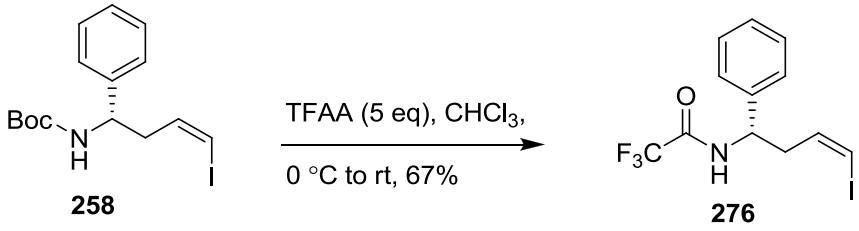


270 **273**

To a stirred solution of substrate **270** (288 mg, 0.775 mmol) in DCM (12 mL) at 0 °C under Ar, was added Et_3N (20.33 mL, 2.325 mmol) and TFAA (0.20 mL, 1.162 mmol). The reaction mixture was stirred for 2h, then the reaction mixture diluted Et_2O (25 mL) and washed water (20 mL). Th e aqoueous layer extracted with Et_2O (2 x 25 mL), dryied ($MgSO_4$) and evaporated to give the crude product which purified by silica gel column chromatography (EtOAc : petroleum ether, 1 : 9, as an eluent) to give the desired product **273** as as yellow oil (261 mg, 65%); R_f 0.71 (hexane : EtOAc, 4:1); $[\alpha]^{21}_D$ -44.4° (c 13.5, $CHCl_3$); UV λ_{max}^{EtOH} nm (log ε) 208 (4.450), 236 (4.186), 276 (3.988); λ_{max} /cm^{-1} (film) 2928 (m), 2856 (m), 1698 (s, C=O), 1163 (vs), 993 (s), 834 (vs), 773 (vs), 699 (vs); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 0.03 (3H, s, *Me*Si), 0.04 (3H, s, *Me*Si), 0.88 (9H, s, *Me*$_3$CSi), 1.13 (3H, d, *J* 6, *Me*CHOSi), 2.17-2.30 (2H, m, C*H*$_2$CHOSi), 1.13 (2H, t, *J* 7, C*H*$_2$CHPh), 3.84 (1H, q, *J* 6, C*H*OSi), 5.10 (1H, dd, *J* 14 & 7, C*H*Ph), 5.23 (1H, ddd, *J* 18, 11 & 7, =C*H*), 5.74 (1H, dt, *J* 15 & 7, =C*H*), 6.07-6.29 (3H, m, =C*H*), 6.33 (1H, dd, *J* 14 & 11, =C*H*), 6.64 (1H, d brd, *J* 7, N*H*), 7.27- 7.33 (3H, m, *H*-2′, *H*-4′ & *H*-6′), 7.35-7.39 (2H, m, *H*-3′ & *H*-5′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c -4.7 (*Me*Si), -4.6 (*Me*Si), 18.1

(Me_3CSi), 23.5 (*Me*CHOSi), 25.8 (Me_3CSi), 33.5 (CH_2Ph), 43.2 (CH_2CHOSi**)**, 68.5 (*C*HOSi), 124.8 (*C*-4′), 126.4 (*C*-2′ & *C*-6′), 128.1 (=*C*H), 128.9 (*C*-3′ & *C*-5′), 132.2 (=*C*H), 132.6 (=*C*H), 133.1 (=*C*H), 134.7 (=*C*H), 135.1 (=*C*H), 139.3 (*C*-1′, quaternary), 155.3 (*C*=O); ^{19}F (376 MHz, $CDCl_3$) δ_F -75; LRMS (TOF AP^+): *m*/*z* (rel. int.) 391.3 (MH^+-C_6H_5, 100%); LRMS (ES^+): *m*/*z* (rel. int.) 321.3 (M-Me-OTBS, 100%); HRMS (TOF ES^-): Acc. MS calc. for $C_{25}H_{35}NO_2SiF_3^+$ $[M-H]^+$, 466.2389, found 466.2321.

(1*R*,3*Z*)-2,2,2-Trifluoro-*N*-(4-iodo-1-phenylbut-3-enyl)acetamide 276

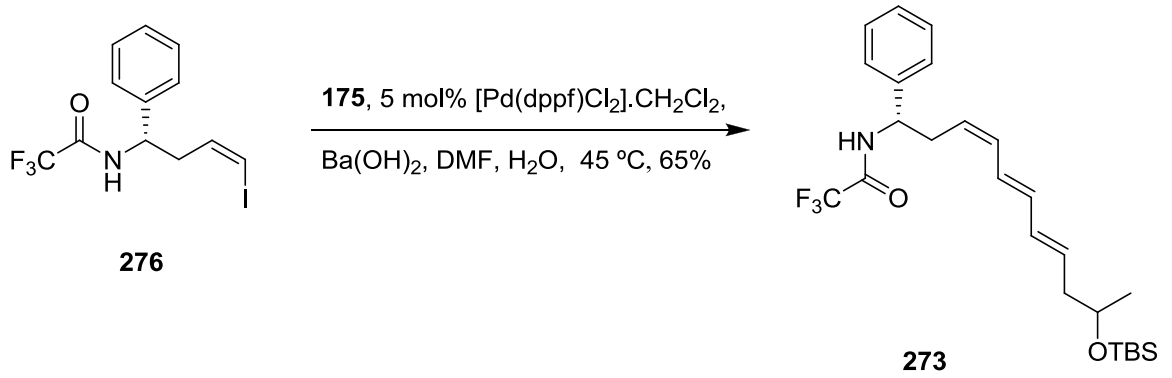


258 **276**

To a stirred solution of substrate **258** (110 mg, 0.30 mmol) in $CHCl_3$ (1 mL) at 0 ºC was added trifluoroacetic anhydride (0.17 mL, 1.18 mmol). The reaction mixture was stirred at room temperature for 3 h, then diluted with toluene (5 mL) and evaporated to give the crude product which purified by silica gel column chromatography (EtOAc : petroleum ether, 1 : 9, as an eluent) to give the desired product **276** (73 mg, 67%) as a white solid: Mp 84 – 86 ˚C; R_f 0.1 (hexane : EtOAc, 19 : 1); $C_{12}H_{11}F_3NIO$ requires C, 39.05; H, 3.00; N, 3.79% found C, 37.62; H, 2.81; N, 3.49%; λ_{max} /cm^{-1} (film) 2924 (m), 1702 (s, C=O), 1644 (s), 1162 (vs), 698 (vs); $[\alpha]^{21}_D$ -18.4 (c 0.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 2.71-2.85 (2H, m, C*H*$_2$CHPh), 5.19 (1H, dd, *J* 8, 7, C*H*Ph), 6.15 (1H, dd, *J* 14, 7, =C*H*), 6.42 (1H, dt, *J* 7 & 1.2, =C*H*I), 5.56-6.59 (1H, brd, N-*H*), 7.30-7.36 (3H, m, *H*-4′, *H*-2′ & *H*-6′), 7.38-7.42 (2H, m, *H*-3′ & *H*-5′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 40.5 (CH_2Ph), 52.8

(*C*HPh), 86.8 (=*C*HI), 126.4 (*C*-4′), 128.5 (*C*-2′ & *C*-6′), 129.1 (*C*-3′ & *C*-5′), 135.2 (=*C*HCH$_2$), 138.9 (*C*-1′, quaternary), 156.7 (*C*=O); ^{19}F (376 MHz, $CDCl_3$): δ_F -75.67; LRMS (ES): *m*/*z* (rel. int.) 292.7 (MH^+-C_6H_5, 100%); LRMS (ES^+): *m*/*z* (rel. int.) 392.1 (MNa^+, 100%); HRMS (TOF AP^+): Acc. MS calc. for $C_9H_{12}NOF_3NaI^+$ $[M+Na]^+$, 391.9735; found 391.9742.

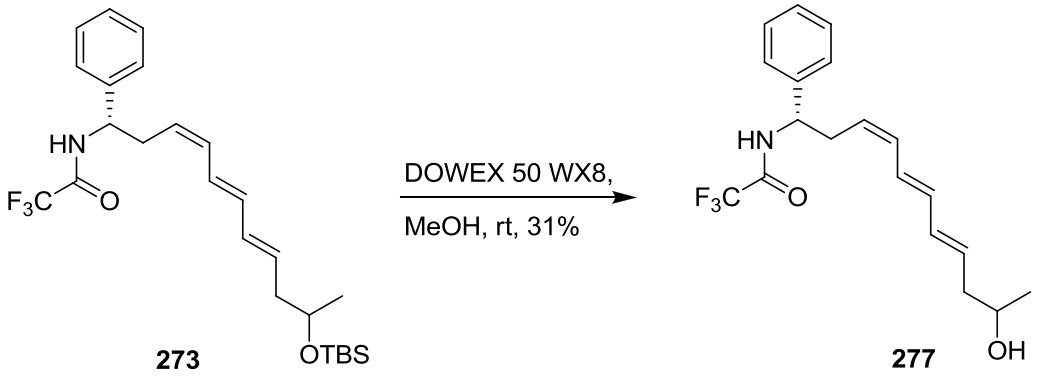
Trifluoromethyl (1*R*,3*Z*,5*E*,7*E*,10*RS*)-10-*tert*-butyldimethylsiloxy-1-phenylundeca-3,5,7-trienylcarbamate 273



To a dried Schlenk tube under Ar was added alkenyl iodide **276** (135 mg, 0.85 mmol), dialkenyl boronate **175** (331 mg, 0.94 mmol), DMF (12 mL), H_2O (1.2 mL), and $Ba(OH)_2$ (175 mg, 1.02 mmol). The mixture was degassed using the freeze-pump-thaw method (3 x) and Pd(dppf) $Cl_2.CH_2Cl_2$ (35 mg, 0.042 mmol) was added. The mixture was again degassed using the freeze-pump-thaw method (3 x), heated at 45 ºC for 18 h before being diluted with Et_2O (20 mL) and passing through Celite. After washing with brine (25 mL), the aqueous layer was extracted with Et_2O (2 x 20 mL). The organic layer was washed with brine (2 x 20 mL), dried ($MgSO_4$) and evaporated to give crude product as brown oil.

Purification by silica gel chromatography (EtOAc : petroleum ether, 1 : 9, as eluent) gave the desired product **273** as a yellow oil (261 mg, 65%); which showed identical spectroscopic properties to those previously reported.

Trifluoromethyl (1*R*,3*Z*, 5*E*,7*E*,10*RS*)-10-hydroxy-1-phenylundeca-3,5,7-trienylcarbamate 277

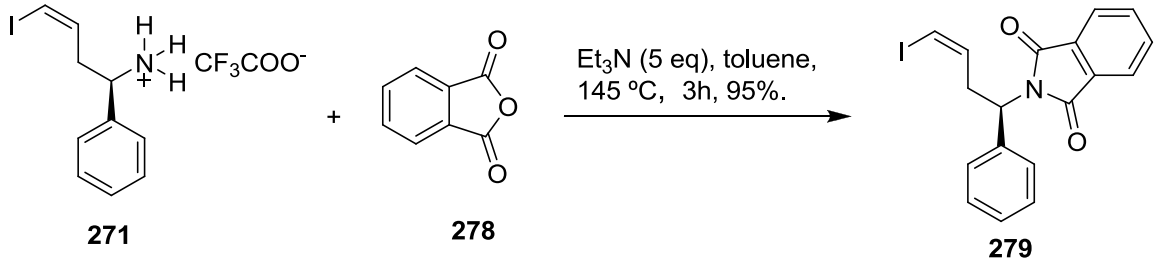


273 **277**

To a solution of **273** (136 mg, 0.384 mmol) in methanol (6 mL) was added DOWEX W8 (136 mg). The reaction mixture left to stir under argon at rt for 42 hours, then diluted with ethyl acetate (25 mL), filtered and evaporated**.** Purification by SiO_2 chromatography (EtOAc : petroleum ether, 2 : 3, as eluent) gave the desired product **277** as yellow oil (38 mg, 31%); R_f 0.71 (hexane : EtOAc, 4 : 1); $[\alpha]^{21}_D$ -500° (c 1.6, $CHCl_3$); UV λ_{max}^{EtOH} nm (log ε) 208 (4.514), 236 (4.231), 272 (4.035), 328 (3.283); λ_{max} /cm^{-1} (film) 3292 (br, OH), 2928 (m), 2856 (m), 1698 (s, C=O), 1163 (vs), 993 (s), 834 (vs), 773 (vs), 699 (vs); δ_H (400 MHz, $CDCl_3$) 1.18-1.12 (3H, m, *Me*CHOH), 2.19-2.31 (2H, m, C*H*$_2$CHOH), 2.68 (1H, t, *J* 7, C*H*HCHPh), 2.79 (1H, q, *J* 7, CH*H*CHPh), 3.84 (1H, q, *J* 6, C*H*OH), 5.10 (1H, dt, *J* 15 & 7, C*H*Ph), 5.26 (1H, ddd, *J* 18, 11 & 3, =C*H*), 5.73 (1H, dt, *J* 14 & 7,

=C*H*), 6.09-6.26 (3H, m, =C*H*), 6.36 (1H, dd, *J* 14 & 2, =C*H*), 6.95 (1H, brd, N*H*), 7.26-7.32 (3H, m, *H*-2′, *H*-4′ & *H*-6′), 7.34-7.38 (2H, m, *H*-3′ & *H*-5′); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 22.7 (*Me*CHOH), 33.5 (*C*H_2Ph), 42.6 (*C*H_2CHOH**)**, 67.4 (*C*HOH), 124.7 (=*C*H), 125.6 (=*C*H), 126.6 (*C*-4′), 126.4 (*C*-2′ & *C*-6′), 128.1 (=*C*H), 128.7 (*C*-3′ & *C*-5′), 132.2 (=*C*H), 132.6 (=*C*-), 133.2 (=*C*H), 134.3 (=*C*H), 134.4 (=*C*H), 139.3 (*C*-1′, quaternary), 156.4 (*C*=O); ^{19}F (376 MHz, $CDCl_3$) δ_F -75.73; LRMS (ES^+): *m*/*z* (rel. int.) 392.5 (MHK^+, 35%), 391.6 (MK^+, 100%); HRMS (TOF AP^+): Acc. MS calc. for $C_{19}H_{21}NO_2F_3^+$ $[M-H]^+$, 352.1524; found 352.1513.

(1*R*, 3*Z*)-2-(4-Iodo-1-phenylbut-3-enyl)isoindoline-1,3-dione 279

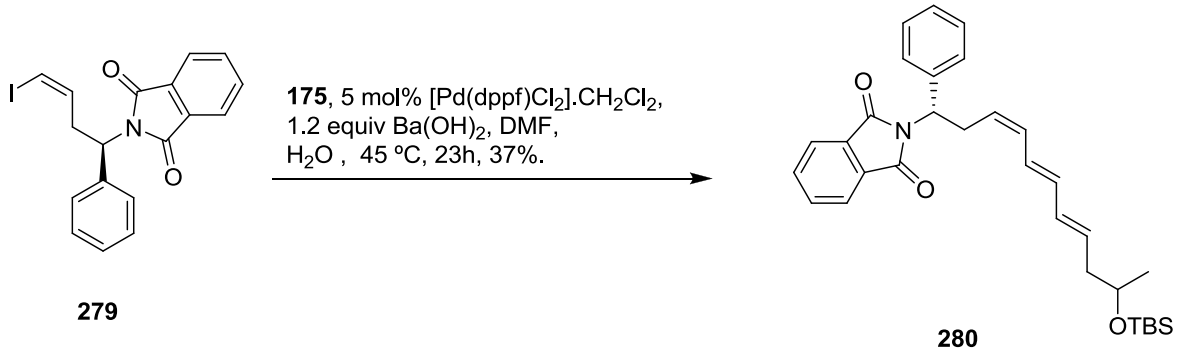


271 **278** **279**

To Boc-alkenyl iodide **258** (226 mg, 0.560 mmol) in DCM (0.9 mL) was added TFA (0.9 mL) at 0˚C. After 20 min of stirring at 0˚C, the TFA salt was trapped with toluene (3 x 5 mL). The TFA salt **278** (320 mg, 0.827 mmol) was then suspended with phthalic anhydride (245 mg, 0.654 mmol) in toluene (14 mL) at rt, treated with triethylamine (0.58 mL, 4.133 mmol) and left to warm to rt, diluted with ethyl acetate (25 mL) and washed with brine (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated. The crude product was purified by SiO_2 column chromatography (EtOAc : petroleum ether, 1 :

4, as eluent) to give the desired product **279** as a thick white oil (231 mg, 95%); $[\alpha]^{21}_{D}$ -48° (c 0.02, $CHCl_3$); λ_{max}/cm^{-1} (film) 2919 (m), 1770 (m), 1706 (vs, C=O), 1384 (s), 1350 (s), 1330 (s), 717 (vs), 696 (s); ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ_H 3.18 (1H , dtd, *J* 14.8, 6.6, 1.5, C*H*CHPh), 3.33 -3.49 (1H, m, C*H*CHPh), 5.51 (1H, dd, *J* 9.7, 6.9, C*H*Ph), 6.18 (1H , dd, *J* 13.9, 6.9, =C*H*), 6.33 (1H , dt, *J* 7.5, 1.3, =C*H*I), 7.27-7.30 (1H, m, *H*-4′), 7.32-7.36 (2H, m, *H*-2′ & *H*-6′), 7.55-7.57 (2H, m, *H*-3′ & *H*-5′), 7.69 (2H, dd, *J* 5.5, 3.0, *H*-2″ & *H*-5″), 7.81 (2H, dd, *J* 5.5, 3.0, *H*-3″ & *H*-4″); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c 36.54 (*C*H_2Ph), 53.23 (*C*HPh), 85.39 (=*C*HI), 128.07 (*C*-4′), 128.09 (*C*-2′ & *C*-6′), 128.58 (*C*-3′ & *C*-5′), 131.75 (*C*-1″, *C*-6″, quaternary), 133.99 (*C*-3″, *C*-4″), 137.11 (=*C*HCH_2), 138.54 (*C*-1′, quaternary), 168.09 (*C*=O); LRMS (EI): *m*/*z* (rel. int.) 276 (M-I, 100%); HRMS (TOF ES$^+$): Acc. MS calc. for $C_{18}H_{15}NO_2I^+$ $[M+H]^+$, 404.0148; found 404.0140.

_N_-Phthalimidyl (1*R*,3*Z*,5*E*,7*E*,10*RS*)-10-*tert*-butyldimethylsiloxy-1-phenylundeca-3,5,7-trienylamine 280



279 **280**

To a dried Schlenk tube under argon were added *Z*-alkenyl iodide **279** (190 mg, 0.47 mmol), dialkenyl boronate **175** (183 mg, 0.52 mmol) and $Ba(OH)_2$ (97 mg, 0.57 mmol) in DMF (8 mL) and H_2O (0.4 mL). The mixture was degassed using the freeze-pump-thaw

method (3 x), and Pd(dppf)Cl_2.CH_2Cl_2 (23 mg, 0.021 mmol) was added. The mixture was again degassed using the freeze-pump-thaw method (3 x) and stirred vigorously at room temperature for 23 h before being diluted with Et_2O (25 mL), passing through Celite, and washing with brine (25 mL). The aqueous layer was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated to give crude product as a yellow oil. Purification by SiO_2 chromatography (EtOAc : petroleum ether, 1 : 9, as eluent) gave the desired product **280** as yellow oil (87 mg, 37%); $[\alpha]^{21}_D$ 177.7° (c 0.07, $CHCl_3$); UV λ_{max}^{EtOH} nm (log ε) 208 (4.535), 232 (4.263), 272 (4.069); λ_{max} /cm^{-1} (film) 2928 (s), 2855 (m), 1710 (s, C=O), 1471 (m), 1385 (m), 1253 (m), 994 (s), 718 (vs); δ_H (400 MHz, $CDCl_3$) 0.05 (3H, s, *Me*Si), 0.06 (3H, s, *Me*Si), 0.90 (9H, s, Me_3CSi), 1.14 (3H, d, *J* 6.1, *Me*CHOSi), 1.41 (9H, s, Me_3CO), 2.17-2.31 (2H, m, CH_2CHOSi), 3.08-3.13 (1H, m, CH*H*CHPh), 3.57-3.61 (1H, m, C*H*HCHPh), 3.82-3.87 (1H, m, C*H*OSi), 5.35 (1H, dd, *J* 18 & 10, C*H*Ph), 5.44 (1H, dd, *J* 10 & 4, =C*H*), 5.64-5.73 (1H, m, =C*H*), 6.03-6.16 (3H, m, =C*H*), 6.44 (1H, dt, *J* 14 & 11, =C*H*), 7.27-7.32 (1H, m, *H*-4′), 7.34-7.38 (2H, m, *H*-2′ & *H*-6′), 7.54-7.57 (2H, m, *H*-3′ & *H*-5′), 7.68 (2H, dd, *J* 5.4 & 2.4, *H*-2″ & *H*-5″), 7.80 (2H, dd, *J* 5.4 & 2.4, *H*-3″ & *H*-4″); ^{13}C NMR (101 MHz, $CDCl_3$): δ_c -4.7 (*Me*Si), -4.5 (*Me*Si), 18.1 (Me_3*C*Si), 23.5 (*Me*CHOSi), 25.7 (Me_3CSi), 29.7 (*C*H_2CHPh), 43.2 (*C*H_2CHOSi), 54.6 (*C*HPh), 68.6 (*C*HOSi), 125.8 (=*C*H), 126.3 (=*C*H), 128.0 (*C*-4′), 128.1 (*C*-2′ & *C*-6′), 128.5 (*C*-3′ & *C*-5′), 131.6 (=*C*H), 131.8 (*C*-1″, *C*-6″, quaternary), 132.1 (=*C*H), 132.4 (=*C*H), 132.5 (=*C*H), 133.8 (*C*-3″, *C*-4″), 134.0 (=*C*HCH_2), 139.1 (*C*-1′, quaternary), 168.2 (*C*=O);); LRMS (ESI): *m*/*z* (rel. int.) 524.3 (MNa^+, 100%).

References:

1. Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77-93.
2. Fenical, William; Jensen, Paul R. *Nat. Chem. Biol.* **2006**, *2*, 666-673.
3. Kwon, H. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Org. Chem.*, **2009**, *74*, 675–684.
4. Pellati, F.; Calo, S.; Benvenuti, S. *J. Chromatogr. A* **2007**, *1149*, 56-65.
5. Seco, E. M.; Cuesta T.; Fotso, S.; Laatsch, H.; Malpartida, F. *Chem. & Bio.* **2005**, *12*, 535-543.
6. Aparicio, J. F.; Mendes, M. V.; Anton, N.; Recio, E.; Martin, J. F. *Curr. Med. Chem.* **2004**, *11*, 1645-1656.
7. Aparicio, J. F. *Chem. & Bio.* **2005**, *12*, 509-510.
8. Cai, P.; Kong, F.; Fink, P.; Ruppen, M. E.; Williamson, R. T.; Keiko, T. *J. Nat. Prod.* **2007**, *70*, 215-219.
9. Hamilton-Miller, J. M. T. *Bacteriol. Rev.* **1973**, *37*, 166-196.
10. Smyk, B.; Amarowicz, R.; Szabelski, M.; Gryczynski, I.; Gryczynski, Z. *Analytica Chimica Acta.* **2009**, *646*, 85-89.
11. Dabdoub, M. J.; Dabdoub, V. B.; Baroni, A. C. M.; Hurtado, G. R.; Barbosa, S. L. *Tetrahedron lett*. **2010**, *51*, 1666-1670.
12. Evano, G.; Schaus, J. V.; Panek, J. S. *Org. Lett*. **2004**, *6*, 525-528.
13. Linzhuan, W.; Aiming, L.; Guizhi, S.; Feng, H.; Qiuping, L.; Yuzhen, W.; Huanzhang, X.; Qunjie, G.; Yiguang, W. *J. Appl. Microbiol.* **2009**, *106*, 755–763.
14. Wrona, I. E.; Agouridas, J.; Panek, J. S. C. R. *Chimie* **2008**, *11*, 1483-1522.

15. Obringer, M.; Barbarotto, M.; Choppin, S.; Colobert, F. *Org. Lett.* **2009**, *11*, 3542–3545.
16. Hayashi, Y.; Shoji, M.; Ishikawa, H.; Yamaguchi, J.; Tamura, T.; Imai, H.; Nishigaya, Y.; Takabe, K.; Kakeya, H.; Osada, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6657–6660.
17. Feuerbach, D.; Waelchli, R.; Fehr, T.; Feyen, J. H. M. *J. Biol.Chem.* **1995**, *270*, 25949.
18. Kawamura, T.; Tashiro, E.; Shindo, K.; Imoto, M. *J. Antibiot.* **2008**, *61***,** 303-311.
19. Kawamura, T.; Tashiro, E.; Shindo, K.; Imoto, M. *J. Antibiot.* **2008**, *61***,** 312-317.
20. Smith, A. B., III; Wood, J. L.; Wong, W.; Gould, A. E.; Rizzo, C. J.; Barbosa, J.; Funayama, S.; Komiyama, K.; Omura, S. *J. Am. Chem. Soc*. **1996**, *118*, 8308-8315.
21. Smith, A. B.; Barbosa, J. *Tetrahedron Lett.* **1998**, *39*, 2891-2894.
22. Meng, Y.; Wagoner, R. M. V.; Misner, M.; Tomas, C.; Wright, J. L. C. *J. Nat. Prod.* **2010**, *73*, 409–415.
23. Morsy, N.; Houdai, T.; Matsuoka, S.; Matsumori, N.; Adachi, S.; Oishi, T.; Murata, M.; Iwashita, T.; Fujita, T. *Bioorg. Med. Chem.* **2006**, *14*, 6548-6554.
24. Morsy, N.; Matsuoka, S.; Houdai, T.; Matsumori, N.; Adachi, S.; Murata, M.; Iwashita, T.; Fujita, T. *Tetrahedron* **2005**, *61*, 8606-8610.
25. Houdai, T.; Matsumori, N.; Murata, M. *Org. Lett.* **2008**, *10*, 4191-4194.
26. Olano, C.; Méndez, C.; Salas, J. *Mar. Drugs.* **2009**, *7*, 210-248.
27. Tanaka, T.; Tsukuda, E.; Uosaki, Y.; Matsuda, Y. *J. Antibiot.* **1996**, *49*, 1085-1090.
28. Sattler, I.; Thiericke, R.; Zeeck, A. *Nat. Prod. Rep.* **1998**, *15*, 221-240.

29. Dixit, D.; Sharma, V.; Ghosh, S.; Koul, N.; Mishra, P. K.; Sen, E. *Free Radic. Biol. Med.* **2009**, *47*, 364–374.

30. Shipley, P. R.; Donnelly, C. C.; Le, C. H.; Bernauer, A. D.; Klegeris, A. *Int. J. Mol. Med.* **2009**, *24*, 711-715.

31. Solanki, R.; Khanna, M.; Lal, R. *Indian J. Microbiol.* **2009**, *48*, 410–431.

32. Hu, Y.; Floss, H. G. *J. Am. Chem. Soc* **2004**, *126*, 3837-3844.

33. Macdonald, G.; Alcaraz, L.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 5433-5436.

34. Li, F; Maskey, R. P.; Qin, S.; Sattler, I.; Fiebig, H. H.; Maier, A.; Zeeck, A.; Laatsch, H. *J. Nat. Prod*. **2005**, *68*, 349-353.

35. Ley, S. V.; Tackett, M. N.; Maddess, M. L.; Anderson, J. C.; Brennan, P. E.; Cappi, M.W.; Heer, J. P.; Helgen, C.; Kori, M.; Kouklovsky, C.; Marsden, S. P.; Norman, J.; Osborn, D. P.; Palomero, M. A.; Pavey, J. B. J.; Pinel, C.; Robinson, L. A.; Schnaubelt, J.; Scott, J. S.; Spilling, C. D.; Watanabe, H.; Wesson, K. E.; Willis, M. C. *Chem. Eur. J*. **2009**, *15*, 2874-2914.

36. Huang, S.; Houghton, P. J. *Drug Resist. Updates* **2002**, *4*, 378-391.

37. Gregory, *M. A.;* Hong, H.; Lill, *R.E.;* Gaisser, *S.;* Petkovic, *H.;* Low, *L.;* Sheehan, *L. S.;* Carletti, *I.;* Ready, *S.J.;* Ward, *M. J.;* Kaja, *A. L;* Weston, *A. J.;* Challis, *I. R.;* Leadlay, *P. F.;* Martin, *C. J.;* Wilkinson, *B.;* Sheridan, R. M. *Org. Biomol. Chem.* **2006**, *4*, 3565-3568.

38. García-Martínez, J.; Moran, J.; Clarke, R.; Gray, A.; Cosulich, S.; Chresta, C.; Alessi, D. *Biochem J.* **2009**, *421*, 29-42.

39. Moss, S. C.; Lightell D. J.; Marx, S. O.; Marks A.R.; Woods T.C. *J. Biol. Chem.* **2010**, *285*, 11991 -11997.

40. Bridle, K. R.; Popa, C.; Morgan, M. L.; Sobbe, A. L.; Clouston, A. D.; Fletcher, L. M.; Crawford, D. H. G. *Liver Transplantation*, **2009**, *15*, 1315-1324.

41. Mejias, M.; Garcia-P. E.; Gallego, J.; Mendez, R. B., Fernandez, M. *J. Hepatol.* **2010**, *52*, 529-539.

42. Lu, Chung-K.; Chou, H.-N.; Lee, C,-K.; Lee, T.-H. *Org. Lett.* **2005**, *7*, 3893-3896.

43. Fuwa, H.; Sasaki, M. *Org. Lett.* **2010**, *12*, 584–587.

44. Burke, C. P.; Haq, N.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 2157–2159.

45. Ogawa, N.; Kobayashi, Y. *Tetrahedron Lett.* **2009**, *50*, 6079-6082.

46. Marcheselli, V. L.; Mukherjee, P. K.; Arita, M.; Hong,S.; Antony,R.; Sheets,K.; Winkler,J. W.; Petasis, N. A.; Serhan,C. N.; Bazan, N. G. *Prostaglandins Leukot. Essent. Fatty Acids.* **2010,** *82*, 27-34.

47. Borgos, S. E. F.; Tsan, P.; Sletta, H.; Ellingsen, T. E.; Lancelin, Jean-Marc; Zotchev, S. B. *J. Med. Chem.* **2006,** *49*, 2431-2436.

48. Samaranayake, Y. H.; Yau, J. Y.; Thein, Z. M.; Jayatilake, J. A. M. S.; Yeung, K. W. S.; Samaranayake, L. P. *Med. Mycol.* **2010**, 1-10.

49. Wiehart, U. I. M.; Rautenbach, M.; Hoppe, H. C. *Biochem. Pharmacol.* **2006**, *71*, 779–790.

50. Mao, H.; Tu, W.; Liu, Y.; Qin, G.; Zheng, J.; Chan, P. L.; Lam, K. T.; Peiris, J. S. M.; Lau, Y. L. *J. Virol.* **2009**, *84*, 4148-4157.

51. Chen, G. Q.; Lu, F. P.; Du, L. X. *J. Agric. Food Chem.* **2008**, *56*, 5057–5061.

52. Bobkowska, B. D.; Konopka, K.; Duzgunes, N. *Arch. Oral Biol.* **2003**, *48*, 805-814.

53. Cañedo, L. M.; Costa, L.; Criado, L. M.; Puentes, F. J. L.; Moreno, M. A. *J. Antibiot.* **2000**, *53*, 623- 626.

54. Smith, A. B.; Pitram, S. M.; Fuertes, M. J.; *Org. Lett*. **2003**, *5*, 2751-2754.

55. Seco, E. M.; Fotso, S.; Laatsch, H.; Malpartida, F. *Chem. & bio.* **2005**, *12*, 1093–1101.

56. Rolon, M.; Seco, E. M.; Vega, C.; Nogal, J. J.; Escario, J. A.; Gomez-Barrio, A.; Malpartida, F. *Int. J. Antimicrob. Agents* **2006**, *28*, 104-109.

57. Radics, L.; Incze, M.; Dornberger, K.; Thrum, H. *Tetrahedron* **1982**, *38*, 183-189.

58. Stankov, G. *PCT Int. Appl*. **1999**, 26pp, US005880101A.

59. Trost, B. A.; Hane, J. T.; Metz, P. *Tetrahedron Lett.* **1986**, *47*, 5695-5698.

60. Ryu, G.; Choi, W. C.; Lee, B. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1429-1434.

61. Ryu, G.; Choi, W. C.; Hwang, S.; Yeo, W. H.; Lee, C. S.; Kim, S. K. *J. Nat. Prod.* **1999**, *62*, 917-919.

62. Radics, L.; Incze, M.; Dornberger, K.; Thrum, H. *Tetrahedron* **1982**, *38*, 183-189.

63. Mulholland, N. P.; Pattenden, G. *Tetrahedron Lett.* **2008**, *64*, 7400-7406.

64. Fjærvik, E.; Zotchev, S. B. *Appl. Microbiol. Biotechnol.* **2005**, *67*, 436-343.

65. Whiting, A.; Thirsk, C. *J. Am. Chem. Soc. Perkin Transactions 1* **2002**, *8*, 999-1023.

66. Yamaguchi, J.; Hayashi, Y. *Chem. Eur. J.* **2010**, *16*, 3884-3901.

67. Hill, R. A. *Annu. Rep. Prog. Chem., Sect. B.* **2006**, *102*, 123-137.

68. Tortosa, M.; Yakeli, N. A.; Roush, W. R. *J. Org. Chem.*, **2008**, *73*, 9657–9667.

69. Igarashi, Y.; In, Y.; Ishida, T.; Fujita, T.; Yamakawa, T.; Onaka, H.; Furumai, T. *J. Antibiot.* **2005**, *58*, 523-525.

70. In, Y.; Ohishi, H.; Miyagawa, H.; Kitamura, K.; Igarashi, Y.; Ishida, T. *Bull. Chem. Soc. Japn*, **2006**, *79*, 126-133.

71. In, Y.; Ohishi, H.; Ishida, T.; Igarashi, Y. *Chem. Commun.* **2003**, *14*, 1692-1693.

72. Lopes, S; Goormaghtigh, E.; Cabral, B. J. Costa; Castanho, M. *J. Am. Chem. Soc***.** **2004**, *126*, 5396-5402.

73. Shih, H. D.; Liu, Y. C.; Hsu, F. L.; Mulabagal, V.; Dodda, R.; Huang, J. W. *J. Agric. Food Chem.* **2003,** *51*, 95–99.

74. Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc.* **1997,** *119*, 2058-2059.

75. Fu, F.; Loh,T. P. *Tetrahedron Lett.* **2009**, *50*, 3530-3533.

76. Burova, S, A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495-2500.

77. Denmark, S.E.; Fujimori, S. *J. Am. Chem. Soc.* **2005**, *127*, 8971-8973.

78. Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10899-10905.

79. Dreher, S. P.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 341–342.

80. Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett*. **1987**, *28*, 6001-6004.

81. Pawlak, J.; Nakanishi, K. *J. Org. Chem.* **1987**, *52*, 2896-2901.

82. Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc*. **2007**, *129*, 3826-3827.

83. Feng, Z.; Qi, J.; Tsuge, T.; Oba, Y.; Sakagami, Y.; Ojika, M. *Biosci. Biotechnol. Biochem.* **2006**, *70*, 699-705.

84. Kundim, B. A.; Itou, Y.; Sakagami, Y.; Fudou, R.; Yamanaka, S.; Ojika, M.; *Tetrahedron* **2004**, *60*, 10217-10221.

85. (a) Bonini, C.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Videtta, V. *Tetrahedron Lett.* **2008**, *49*, 5455–5457. (b) Schlingmann, G.; Milne, L.; Borders, D. B.; Carter, G. T. *Tetrahedron* **1999**, *55*, 5977-5990.

86. Plaza, P.; Baker, H. L.; Bewley, C. A. *J. Nat. Prod.* **2008**, *71*, 473–477.

87. Song, F.; Fidanze, S.; Benowitz, A. B.; Kishi, Y. *Tetrahedron* **2007**, *36*, 5739-5753.

88. Paterson, I.; Findlay, A. D.; Noti, C. *Chem. Commun.* **2008**, 6408-6410.

89. Sinz, C. J.; Rychnovsky, S. D. *Tetrahedron* **2002**, *58*, 6561-6576.

90. Cai, P.; Kong, F.; Fink, P.; Ruppen, M. E.; Thomas W. R.; Keiko, T. *J. Nat. Prod.* **2007**, *70*, 215-219.

91. Irschik, H.; Schummer, D.; Hofle, G.; Reichenbach, H.; Steinmetz, H.; Jansen, R. *J. Nat. Prod.* **2007,** *70*, 1060-1063.

92. Li, P.; Li, J.; Arikan, F.; Ahlbrecht, W.; Dieckmann, M.; Menche, D. *J. Am. Chem. Soc.* **2009**, *131*, 11678–11679.

93. Gagoś, M.; Herec, M.; Arczewska, M.; Czernel, G.; Serra, M. D. Gruszecki, W. I. *Chem. Phys. Lipids* **2008**, *136*, 44-49.

94. Rajshekhar, V. *Neurol. India* **2007**, *55*, 267-273.

95. Sundar, S.; Chakravarty, J.; Agarwal, D.; *Rai*, M.; *Murray*, H. W. *N. Engl. J. Med.* **2010**, *362*, 504-512.

96. Soler, L.; Caffrey, P.; McMahon, H. E. M. *Biochim. Biophys. Acta.* **2008,** *1780,* 1162-1167.

97. Grijalba, Toledo M.; Cheron, M.; Borowski, E.; Bolard, J.; Schreier, S. *Biochim. Biophys. Acta.* **2006**, *1760*, 973-979.

98. Groeschke, J.; Solassol, I.; Bressolle, F.; Pinguet, F. *J. Pharm. Pharmacol.* **2006**, *42*, 362-366.

99. Zotchev S. B. *Curr. Med. Chem.*, **2003**, *10*, 211-223.

100. Solomon, K. R.; PCT Int. Appl., **2003**, 46 pp. WO 2003086418

101. Ékzemplyarov, O. N. *Khim. Farm. Zh.* **1977**, *11*,140–145.

102. Belakhov. V. V.; Shenin, Y. L. *Pharm. Chem. J.* **2007**, *41*, 314-318.

103. Dhuley, J. N. *FEMS Immunol Med Microbiol.* **1999**, *26*, 175-180.

104. Kozhuharova, L.; Gochev, V.; Koleva, L. *World J. Microbiol. Biotechnol.* **2008**, *24*, 1–5.

105. Zieliski, J.; Borowy-B., H.; Golik, J.; Gumieniak, J.; Zimiski, T.; Koodziejczyk, P.; Pawlak, J.; Borowski, E. *Tetrahedron Lett.* **1979**, 20, 1791-1794.

106. Bruzzese, T.; Rimaroli, C.; Bonabello, A.; Ferrari, E.; Signorini, M. *Eur. J. Med. Chem.* **1996**, 31, 965-972.

107. Wright, J. J.; Greeves, D.; Mallams, A. K.; Picker, D. H. *J. Chem. Soc. Chem. Commun.* **1977**, 710-712.

108. Weinstein, M. J.; Wagman, J. H.; Marquez, J. A.; Patel, M.G. *PCT Int. Appl.* **1982,** US Patent 4,359, 462.

109. Koodziejczyk, P.; Zieliski, J.; Pawlak, J.; Golik, J.; Falkowski, L.; Borowski, E. *Tetrahedron Lett.* **1976**, *17*, 3603-3609.

110. Aszalos, A. *Modern Analysis of Antibiotics* **1986**, CRC Press

111. Haeder, S.; Wirth, R.; Herz H.; Spiteller, D. *PNAS* **2009**, *106*, 4742–4746.

112. Komori, T.; Morimoto, Y.; Niwa, M.; Hirata, Y. *Tetrahedron Lett.* **1989**, *30*, 3813-3816.

113. Rolon, M.; Seco, E. M.; Vega, C.; Nogal, J. J.; Escario, J. A.; Gomez-Barrio, A.; Malpartida, F. *Int. J. Antimicrob. Agents* 2006, *28*, 104-109.

114. Kotler-Brajtburg, J.; Medoff, G.; Kobayashi, G. S.; Boggs, D.; Schlessinger, R. C.; Pandey; Rinehalt, K. L. *Antimicrob. Agents Chemother*. **1979**, *15*, 716-722.

115. Akiyama, S.; Tabkui, T.; Kaneko, M.; Komiyama, S.; Kumano, M. *Antimicrob. Agents Chemother*, **1980**, *18*, 226-230.

116. Brajtburg, J.; Medoff, G.; Schlessinger, D.; Kobayashi, G. S.; Kuttin, E. S.; Baum, G. L. *International Congress Series (Human and animal mycology Proceedings)* **1980**, *480*, 273-276.

117. Ogita, A.; Fujita, K.; Usuki, y.**;** Tanaka, T. *Int J Antimicrob Agents* 2010, *35*, 89-92.

118. Hac-Wydro, K.; Dynarowicz-L., P. *Biophys. Chem.* **2006**, *123*, 154-161.

119. Ghannoum, M.; Rice, L. B. *Clin. Microbiol. Rev*. **1999**, *12*, 501-517.

120. Herec, M.; Akhmed I. A.; Kuklin, A.; Gago, M.; Gruszecki, W. I. *Chem. Phys. Lipids* **2007**, *147*, 78-86.

121. Hasegawa, T.; Kamiya, T.; Henmi, T.; Iwasaki, H.; Yamatodani, S. *J. Antibiot.* **1975**, *28*, 167-175.

122. Nakagawa, M.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett*. **1991**, *32*, 659-662.

123. Nakagawa, M.; Toda, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1992**, *45*, 1133-1138.

124. O'Hagan, D. *Nat. Prod. Rep.* **1993**, *10*, 593-624.

125. (a) Kruger, A. W.; Meyers, A. L. *Tetrahedron Lett.* **2001**, *42*, 4301-4304. (b) Waterson, A. G.; Kruger, A. W.; Meyers, A. L. *Tetrahedron Lett.* **2001**, *42*, 4305-4308. (c) Arrington, M. P.; Meyers, A. L. *Chem. Comm.* **1999**, *15*, 1371-1372.

126. (a) Ishihara, J.; Hagihara, K.; Chiba, H.; Ito, K.; Yanagisawa, Y.; Totani, K.; Tadano, K. *Tetrahedron Lett.* **2000**, *41*, 1771-1774. (b) Trost, B. M.; Jiang, C. H. *Org. Lett.* **2003**, *5*, 1563-1565. (c) Mulholland, N. P.; Pattenden, G. *Tetrahedron* **2008**, *64*, 7400-7406. (d) Patenden, G.; Blake. A. J. Constandinos, L. *Tetrahedron Lett*. **2005**, *46*, 1913-1915. (e) Mullholland, N. P.; Pattenden, G. *Tetrahedron Lett.* **2005**, *46*, 937-939.

127. (a) Batsanov, A. S.; Knowles, J. P.; Lightfoot, A. P.; Maw, G.; Thirsk, C. E.; Twiddle, S. J. R.; Whiting, A. *Org. Lett.* **2007**, *9*, 5565-5568. (b) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 2525-2532. (c) Maw, G. N.; Thirsk, C.; Toujas, J. L.; Vaultier, M.; Whiting, A. *Synlett* **2004**, *7*, 1183-1186.

128. (a) Hunt, A. R.; Stewart, S. K.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 3599-3602. (b) Stewart, S. K.; Whiting, A. *J. Organomet. Chem.* **1994**, *482*, 293-300. (c) Lightfoot, A. P.; Maw, G.; Thirsk, C.; Twiddle, S.; Whiting, A. *Tetrahedron Lett.* **2003**, *44*, 7645-7648.

129. (a) Corey, E. J. and Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, 96, 5614-5616. (b) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, 57, 2661-2663. (c) Masamune,

S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, 16, 585-607.

130. (a) Venkataraman, K. and Wagle, D. R. *Tetrahedron Lett.* **1980**, 21, 1893-1896. (b) Venkataraman, K. and Wagle, D. R. *Tetrahedron Lett.* **1979**, 20, 3037-3040.

131. (a) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49-50. (b) Narasaka, K.; Maruyama, K.; Mukaiyama, T. *Chem. Lett*. **1978**, 885-888.

132. (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989-1993. (b) Storer, R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2004**, *10*, 2529-2547. (c) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7-9.

133. (a) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, 43, 7535-7539. (b) Shiina, I.; Oshiumi, H.; Hashizume, M.; Yamai, Y. S.; Ibuka, R. *Tetrahedron Lett.* **2004**, *45*, 543-547. (c) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822-1830.

134. (a) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612-1614. (b) Corey, E. J.; Hua, D. H.; Pan, B. C.; Seitz, S. P. *J. Am. Chem. Soc*. **1982**, *104*, 6818-6820.

135. (a) Litvinenko, L.M. and Kirichenko, A.I. *Dokl. Chem.* **1967**, 763-766. (b) Dokl. Akad. Nauk SSSR Ser. Khim. **1967**,176, 97-100. (c) Steglich, W.; Höfle, G. *Angew. Chem.***1969**, *81*, 1001-1002.

136. White, J. D.; Johnson, A. T. *J. Org. Chem.* **1994**, 59, 3347-3358.

137. Mehta, G.; Bera, M. K.; Chatterjee, S. *Tetrahedron Lett.* **2008**, *49*, 1121-1124.

138. Burchat A.F.; Chong J.M.; Nielsen N. *J. Organomet. Chem.* **1997**, *542*, 281-283.

139. Kobayashi, Y., Asano, M., Yoshida, S., and Takeuchi, A. *Org. Lett.* **2005**, *7*, 1533-1536.

140. Selles P.; Lett R. *Tetrahedron Lett.* **2002** *43*, 4621.

141. Schwartz, B. D.; Hayes, P.Y.; Kitching, W.; De Voss, J. J. *J. Org. Chem*, **2005**, *70*, 3054-3065.

142. (a) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371. (b) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 5249–5255. (c) Lane, C. F.; Kabalka, G. W. *Tetrahedron* **1976**, *32*, 981–990.

143. Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031-6034.

144. Jiang, N.; Ragauskas, A. J. *Tetrahedron Lett.* **2006**, *47*, 197-200.

145. (a) Simic, M. G. *J. Chem. Educ*. **1981**, *58*, 125-131. (b) Correa, P. E.; Hardy, G.; Riley, D. P. *J. Org. Chem.* **1988**, *53*, 1695-1702. (c) Lee J. H. Photooxidation and photosensitized oxidation in linoleic acid, milk, and lard. PhD thesis, **2002**, The Ohio State University, Columbus, OH, USA (d) Frankel E. N. *Prog. Lipid Res.* **1980**, 19, 1-22.

146. (a) Corey, E. J. and Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647 – 2650. (b) Dess, D. B. and Martin J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156. (c) Shaabania, A.; Mirzaeia, P.; Naderia, S.; Leeb, D. G.; *Tetrahedron*, **2004**, *60*, 11415-11420. (d) Mancuso, A. J.; Huang, S.-L.; Swern, D.; *J. Org. Chem.* **1978,** *43*, 2480–2482. (e) Smith, A. B.; Kim, D-S; Xian, M.; *Org. Lett.* **2007**; *9*, 3307 – 3309. (f) Tojo, G. and Fernández, M., *Oxidation of alcohols to aldehydes and ketones: a guide to current common practice*, Published by Birkhäuser, **2005**.

147. (a) Fitzjarralda, V. P.; Pongdee, R.; *Tetrahedron Lett.* **2007**, *48*, 3553–3557. (b) Davies, J. S.; Howe, J.; Breton, M. L.; *J. Chem. Soc., Perkin Trans. 2,* **1995**, 1321-1326. (c) Dhimitruka, I.; SantaLucia, J. Jr.; *Org. Lett.* **2006**, *8*, 47-50. (d) Freifeld, I.; Bose, G.; Eckardt, T.; Langer, P.; *Eur. J. Org. Chem.* **2007**, 351–355.

148. Mosa, F.; Thirsk, C.; Vaultier, M.; Maw, G.; Whiting, A. *Org. Synth.* **2008**, *85*, 219-228.

149. (a) Correa, A.; Denis, J.-N.; Greene, A. E. *Synth. Commun.* **1991**, *21*, 1-9. (b) Cran, G. A.; Gibson, C. L.; Handa, S. *Tetrahedron: Asymm.* **1995**, *6*, 1553-1556.

150. Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623-4628.

151. Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, 71, 8283-8286.

152. Toujas, J. L.; Jost, E.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 713-717.

153. (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173-2174. (b) Isola, A. M.; Holman, N. J.; Tometzki, G. B.; Watts, J. P.; Koser, S. ; Klintz, R.; Munster, P.; **2000** "*Triphenylphosphine oxide complex process*" USPatent 6011181.

154. (a)Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st*, **2004** John Wiley & Sons. (b) Fihri, A.; Meunier, Hierso, J. C. *Coord. Chem. Rev.* **2007**, *251*, 2017-2055.

155. (a) Das, B.; Reddy, K.R.; Thiripathi, P. *Tetrahedron Lett.* **2006**, *47*, 5855-857. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; **1999**, John Wiley & Sons: New York.

156. Tom, N. J.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron*, **2004**, 45, 905-906.

157. Metz, P.; Fleischer, M.; Frohlich, R. *Tetrahedron*, **1995**, *51*, 711-732.

158. Cox, *G. G.;* Harwood; L. M. *Tetrahedron Asymmetry* **1994**, *5*, 1669−1672.

159. (a) Lazer, E. S.; Miao, H-C.; Sorcek, W. R.; Spero, D. M. *J. Med. Chem.* **1994,** *37*, 913-923. (b) O'Brien, P. M.; Sliskovic, D. R.; Blankley, C. J.; Roth, B. D.; Wilson, M. W. *J. Med. Chem.* **1994**, *37*, 1810-1822.

160. Correa, A.; Denis, J. N.; Greene, A. E. *Synth*. *Commun*. **1991**, *21*, 1-9.

161. Rezaei, M.; Harris, T. M.; Rizzo, C. J. *Tetrahedron Lett.* **2003**, *44*, 7513–7516

162. Conway, J. C.; Quayle P.; Regan, A. C.; Urch, C. J. *Tetrahedron* **2005**, *61*, 11910-11923.