Use of Benzimidazoles as Protonating Agents and their Application to the Syntheses of Natural Products

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Contents

1. Preface

Reduced propionates and deoxypropionates are the fundamental backbones of several important natural products. Because every carbon in a propionate is a potential candidate for a chiral center, it is imperative to control both the relative and the absolute stereochemistry. Several methods for the synthesis of deoxypropionates and reduced propionates have already been reported. However, with the ever increasing volume of complexity of natural products and their structures, new methods for synthesis are required.

The title of this dissertation is the use of benzimidazoles as protonating agents and their application to the total synthesis of natural products.

In the first chapter, a general introduction into reduced propionates and deoxypropionates has been provided. Commonly used protocols for the synthesis of the same are also discussed.

In the second chapter, Birch reductions with various protonating agents are discussed. The change in diastereomeric ratio with the change in chiral auxiliaries has also been examined. Its application to the synthesis of the sex pheromone of *Macrocentrus grandii* was then discussed.

In the third chapter, an isomerization reaction is examined along with its result with the change observed with varying chiral auxiliaries. A formal synthesis of seragamide A is also discussed.

In the fourth chapter, a total synthesis of PF1163B has been achieved. PF1163B is a cyclodepsipeptide that has potent antibiotic activities. Its complex structure and useful bioactivity makes it a desired target molecule.

In the fifth chapter, a synthetic study on spongidepsin is discussed. Spongidepsin is also a cyclodepsipeptide with a potent anti-tumor activity.

In the sixth chapter, a conclusion to the thesis is provided.

In the seventh chapter, all experimental details including spectroscopic data of all compounds have been provided.

2. Abbreviations

AIBN: Azobisisobutyronitrile

BOPCl: Bis (2-oxo -3-oxazolidinyl)phosphinic chloride

CSA: Camphorsulfonic acid

DCC: *N,N'*-Dicyclohexylcarbodiimide

DCM: Dichloromethane

DIBAL: Diisobutylaluminium hydride

DIPEA: Diisopropylethylamine

DMAP: Dimethylaminopyridine

DMF: *N,N*- Dimethylformamide

EDCI: *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide

LAH: Lithium Aluminium hydride

NaHMDS: Sodium Hexamethyldisilylamide

p-TsOH : *p*-Toluenesulfonic acid

TBS: *tert*-butyldimethylsilyl

TBTH: Tributyltinhydride

TEA: Triethylamine

TFA: Trifluoroacetic acid

THF: Tetrahydrofuran

Chapter 1: Introduction

1.1 General introduction to reduced propionates and deoxypropionates

Reduced propionates and deoxypropionates are ubiquitous and constitute the skeletal backbone of several important natural products. The complex natural products containing a reduced propionate or a deoxypropionate may range from secondary metabolites to simple lactones derived from insects, fungi or algae.[1] While polyketides impart to living organisms a chemical defense, their exact role, however, remains unsolved.[2] Structurally, deoxypropionates and reduced propionates have the following skeletal structure (**Fig 1**).

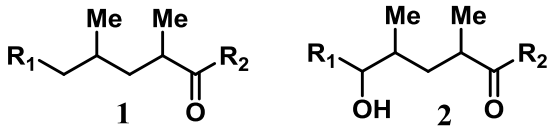


Fig 1. Skeletal structures of deoxypropionates (1) and reduced propionates (2)

Modifications to the structural motifs of the propionates can lead to further complex and diverse structures. It is perhaps then not a surprise that propionates, along with their structural modifications, are used in medicinal chemistry. Pthiocerol dimycoserosate A (PDIM A, **3, Fig. 2**)[3-6] is able to induce an immune response from the host and can increase the cell wall strength of bacteria.[3]

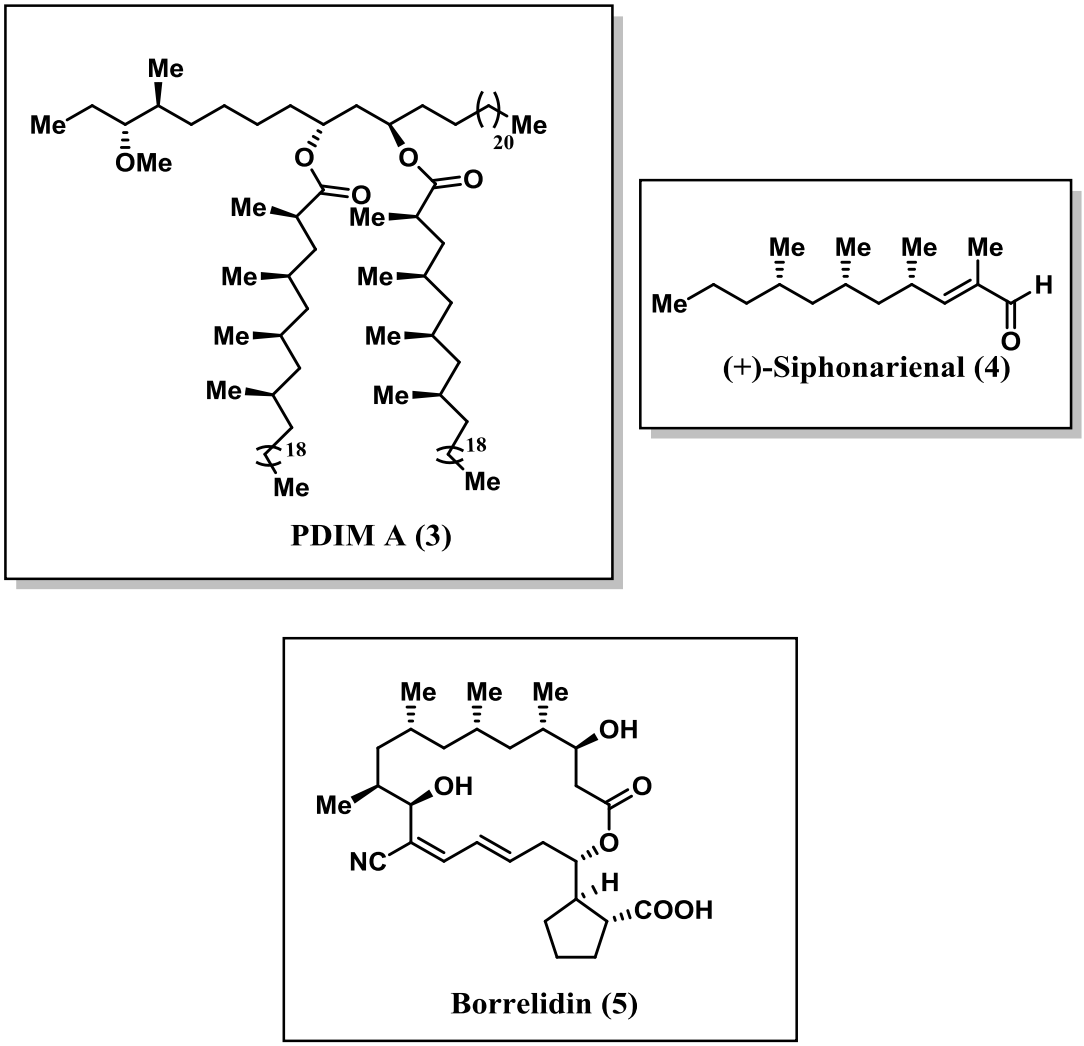


Fig 2. Structures of PDIM A (3) and (+)-Siphonarienal (4) and Borrelidin (5)

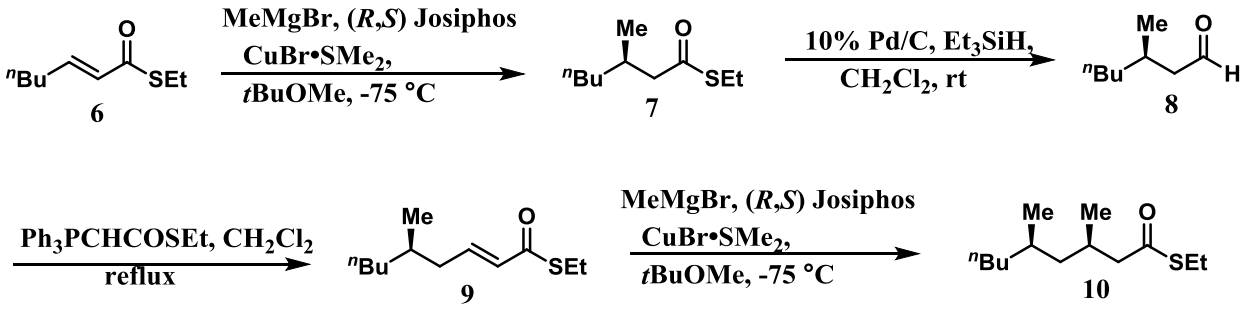
(+)-Siphonarienal (**4, Fig 2**) is another example of a deoxypropionate that was isolated from the gastropod mollusks of the genus *Siphonaria* found in the Mediterranean and Atlantic oceans and shows antimicrobial activity. [7,8] Borrelidin (**5, Fig 2**) is an unwonted example of a polyketide that exhibits cytotoxicity comprising both a *trans* and a *cis* double bond geometry – confirmed by both total synthesis[9-11] and X-ray diffraction studies.[12] The geometry of the double bonds have garnered much attention from the scientific community as normally, during the biosynthesis, *trans* double

bonds are generated from *syn* dehydration of alcohols[13,14], while *cis* geometry results from the action of external enzymes.[15-17]

As our efficiency to fight bacteria is in a downward spiral because of the emergence of antibiotic resistant bacteria, the need of the hour is the isolation, characterization and synthesis of new antibiotics to combat the second generation of drug-resistant pathogens.[18] For this purpose, the generation of a new class of polyketides in modern medicine is required.[19] Aromatic polyketides or polypropionates have also recently carved out a niche for themselves for being both anticancer agents such as doxorubicin or antibiotics tetracyclines. [20]

1.2 Iterative methodology for the synthesis of polyketides

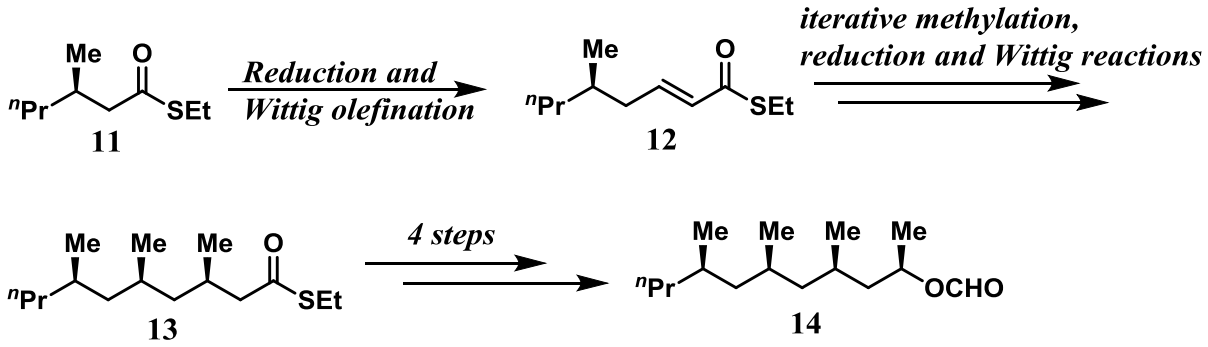
Since the absolute stereochemistry of the reduced propionate and the polyketides are of primary importance, several synthetic chemists have found various methods for the synthesis of one stereochemistry of a chiral carbon over the other. A very common approach to the synthesis of polyketides is an iterative method. [21,22] In 2005, Minnard *et al.* reported an iterative route to obtain enantiomerically pure deoxypropionate subunits (**Scheme 1.1**) and applied the said method for the synthesis of the polyketide lardolure (**14, Scheme 1.2**).[23]



Scheme 1.1: Iterative method of conjugate addition to α,β-unsaturated thioesters

As shown in **Scheme 1.1**, a conjugate addition to α,β-unsaturated thioesters required the use of a chiral ligand such as (*R*)-1-[(S_P)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine. Compound **6** is

an α,β-unsaturated thioester which under the conjugate addition reaction with the aforesaid chiral catalyst provided the new chiral center in *R*-configuration to give reduced **7**. Reduction of the thioester in the presence of palladium catalyst and a Wittig olefination regenerated the α,β-unsaturated thioester **9**. An iterative conjugate addition reaction along the same procedure provided the two *syn*-methyl groups. On optimizing this reaction, Minnard *et al.* set about the total synthesis of (-)-lardolure (**14**) using the same protocol.



Scheme 1.2: Total synthesis of lardulore (14)

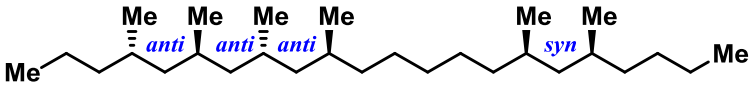
From an enantiomerically pure **11**, reduction with palladium and a Wittig olefination furnished the α,β-unsaturated thioester **12** (**Scheme 1.2**). Iterative reactions including conjugate addition reaction, palladium catalyzed reduction and Wittig olefination provided **13** which was converted to lardolure (**14**) in four further steps. Hence, iterative methods have found their importance in the total synthesis of natural products.

However, iterative methods have certain drawbacks. The routes are generally longer and thus require more time for the synthesis of important natural products.

1.3 Transition metal catalyzed methodology for the synthesis of polyketides

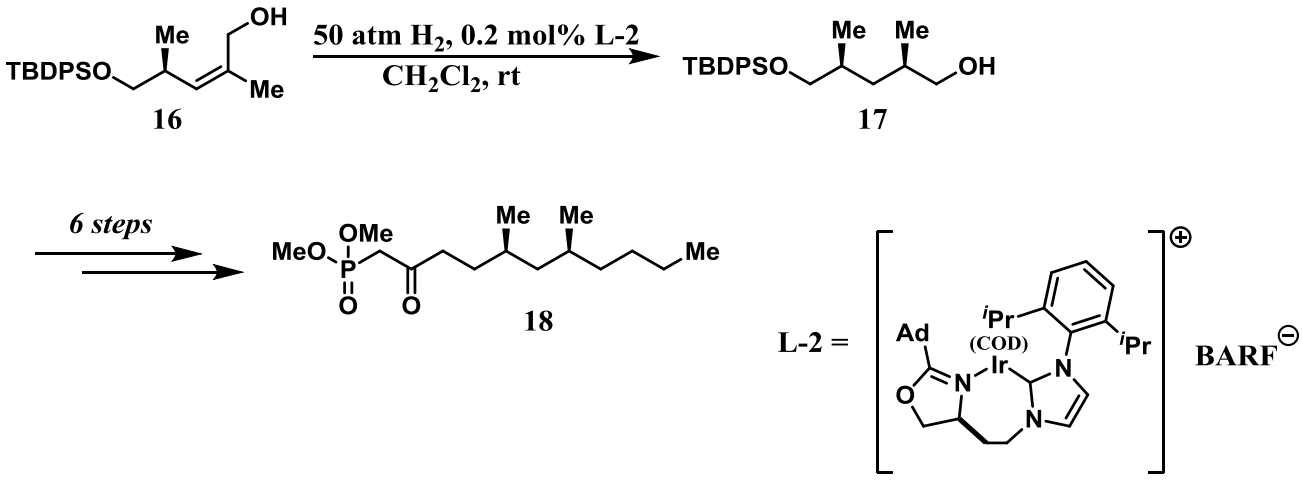
As an alternative to the iterative route, another commonly used pathway for the synthesis of reduced propionates is via one-pot transition metal catalysis.[24-28]

In 2007, Burgess *et al.* designed the synthesis of (*S,R,R,S,R,S*)-4,6,8,10,16,18-hexamethyldocosane (**15**), a hydrocarbon isolated from female Australian melolonthine beetles.[29]



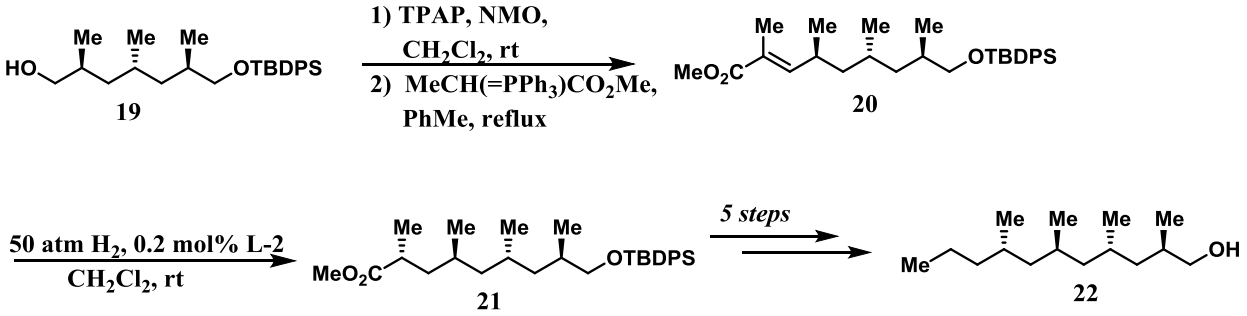
(*S,R,R,S,R,S*)-4,6,8,10,16,18-hexamethyldocosane (15)

The synthesis of the deoxypropionate (**15**) involved the usage of iridium catalyzed hydrogenation reactions to provide the chiral centers stereoselectively (**Scheme 1.3**). Stereoselective hydrogenation of the *Z*-allylic alcohol **16** in the presence of iridium catalyst provided the reduced **17** in a diastereomeric ratio of 34:1. Compound **17** was then converted to the eastern fragment **18** in 6 steps.



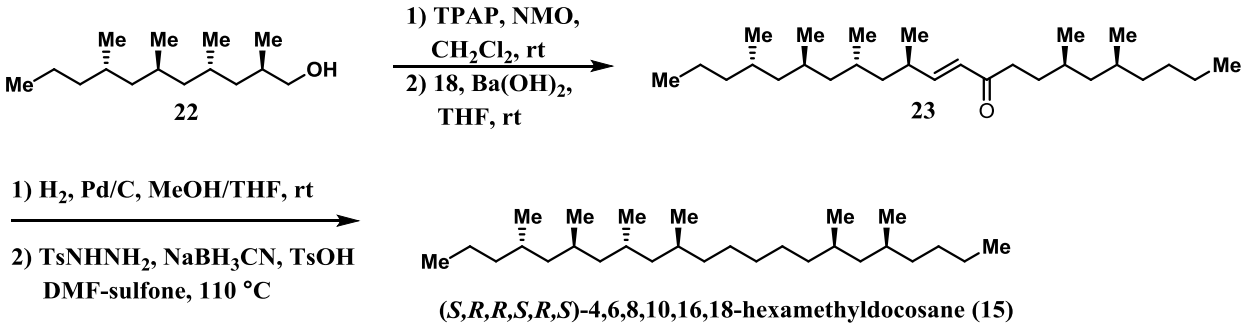
Scheme 1.3: Synthesis of eastern fragment 18

The western fragment of (*S,R,R,S,R,S*)-4,6,8,10,16,18-hexamethyldocosane was synthesized similarly using the asymmetric hydrogenation reaction as the crucial step (**Scheme 1.4**). The alcohol **19** was first converted into the α,β-unsaturated ester **20** following which the unsaturation was reduced under hydrogen using iridium catalyst to provide the reduced ester **21** in high diastereoselectivity. In 5 more steps, the western segment of (*S,R,R,S,R,S*)-4,6,8,10,16,18-hexamethyldocosane **22** was synthesized.



Scheme 1.4: Synthesis of western fragment 22

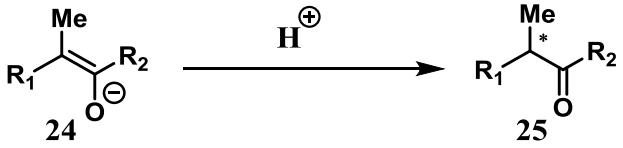
Fusion of the western and the eastern fragment was carried out under Horner-Wadsworth-Emmons conditions (**Scheme 1.5**).[30] The olefin was reduced in the presence of palladium followed by a modified Wolff-Kischner reduction[31,32] to remove the ketone provided the hydrocarbon **15**.



Scheme 1.5: Completion of synthesis of deoxypolyketide 15

1.4 Enolate protonation methodology for the synthesis of polyketides

In **Scheme 1.6**, a pictorial representation of the protonation of enolates has been provided. As the enolate is provided a proton by a protonating agent, there is the formation of a chiral carbon. If somehow, certain factors such as temperature, substrate scope, size of the protonating agent or the acidity of the proton provided can be controlled, the protonation face can be predicted. Protonation of enolates is thus a very important tool for the synthesis of polyketides.

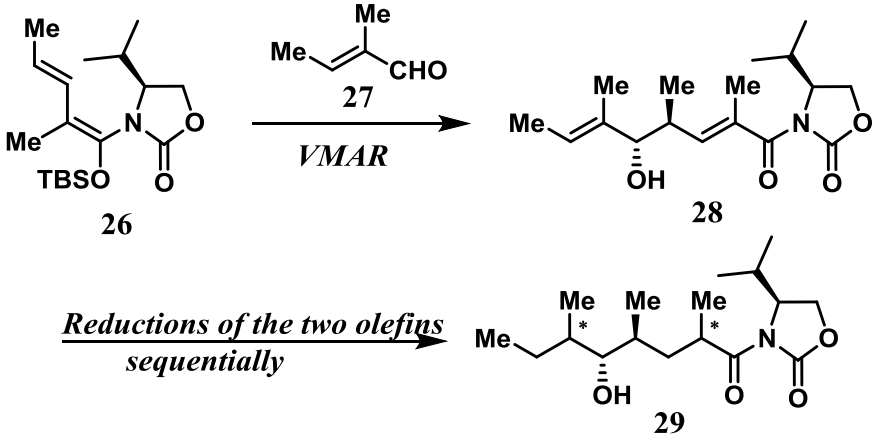


Scheme 1.6: Protonation of enolates

In 2013, in an attempt to further the studies of the synthesis of reduced propionates and find faster transformation routes for the synthesis of the same, Hosokawa *et al.* realized that Birch reductions on α,β-unsaturated imides proceed in stereoselective manner via a chiral enolate.[33]

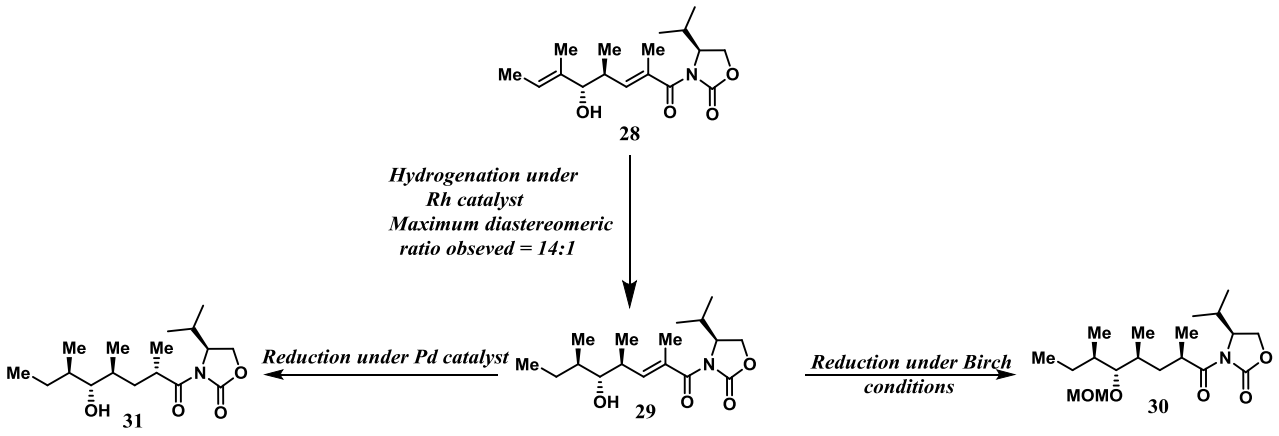
It was reported that after a vinylogous Mukaiyama aldol reaction (VMAR) of the vinylketene silyl *N,O*-acetal **26** and tiglic aldehyde **27**, the adduct would then have the potential to be reduced sequentially and stereoselectively into a reduced propionate with desired stereochemistry (**Scheme 1.7**). This

versatile protocol and its application have found several usages in the synthesis of numerous natural products since then.[34-39]



Scheme 1.7: Synthesis of reduced propionate by Hosokawa *et al.*

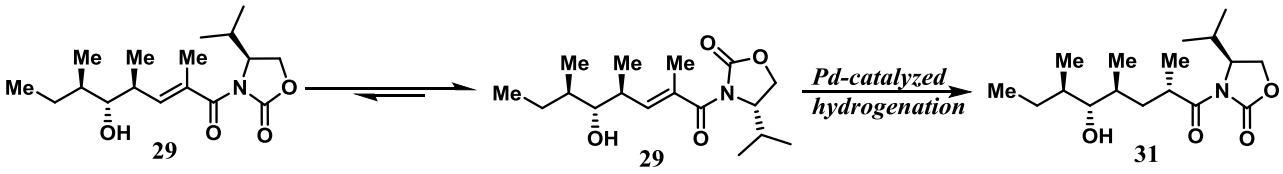
While the unconjugated olefin in **28** was hydrogenated in the presence rhodium or platinum catalysts, the α,β-unsaturated imide was found to be reduced stereoselectively under the Birch reduction conditions where a metal such as sodium or lithium was dissolved in liquid ammonia (**Scheme 1.8**). If palladium was used to reduce the α,β-unsaturated imide, the stereochemistry obtained would be the reverse of the one achieved under the Birch conditions.



Scheme 1.8: Synthesis of reduced propionate under different conditions

The change in the absolute stereochemistry of the newly generated C-2 position going from the palladium reaction to the Birch reduction was

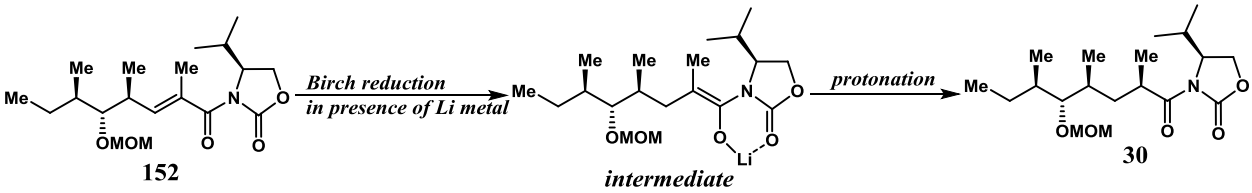
merited to the different intermediates in the two reactions. In the palladium reaction, due to the dipole-dipole interactions of the two carbonyl groups, the oxazolidinone ring flips in order to reduce the dipolar repulsion (**Scheme 1.9**).



Scheme 1.9: Mechanism for Pd-catalyzed reduction

The flipping of the oxazolidinone thus prohibits the hydrogenation of the substrate **29** from the bottom face, thereby leading to the formation of compound **31**, with the newly formed asymmetric carbon bearing *S*-configuration (**Scheme 1.9**).

The Birch reduction reaction, however, differs greatly from the Pd-catalyzed hydrogenation. The intermediate of the Birch reaction is chelated, such that free rotation of the oxazolidinone is restricted (**Scheme 1.10**). The protonation occurs only from the bottom face as the top face is hindered by the chiral auxiliary thereby providing **30** with the newly generated asymmetric carbon bearing *R*-configuration.

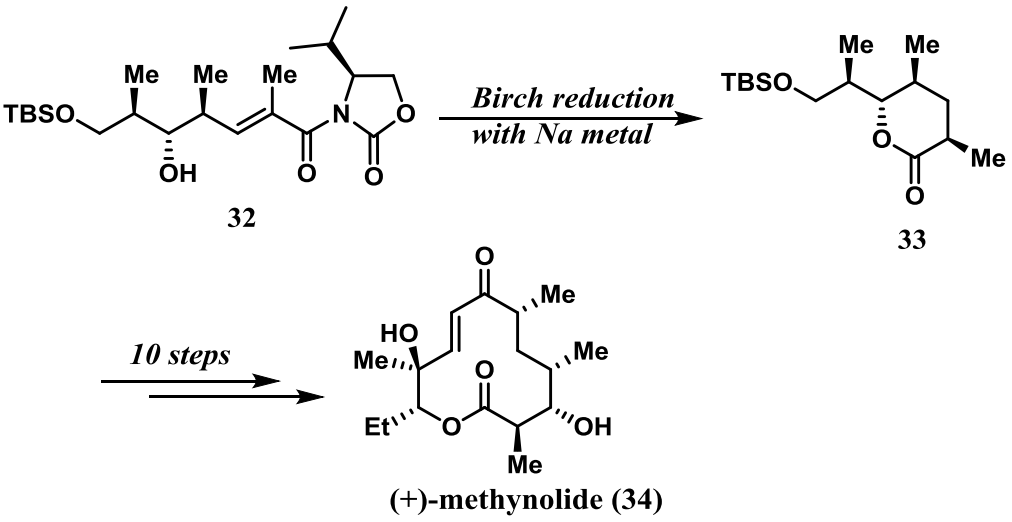


Scheme 1.10: Birch reduction of α,β-unsaturated imide

Thus, interestingly, the configuration of the C-2 position could be altered by either using the Pd catalyzed hydrogenation or the Birch reaction.

This methodology soon found an application in the total synthesis of (+)-methynolide **(34)**, an aglycon of the 12-membered antibiotic methymycin by

Kobayashi *et al.* (**Scheme 1.11**). In their synthesis of the macrocycle, one of the key approaches used was the Birch reduction of aldol adduct **32** to furnish the lactone **33** as a single isomer.[40] The lactone was then further transformed to the macrocyclic methynolide in 10 steps.



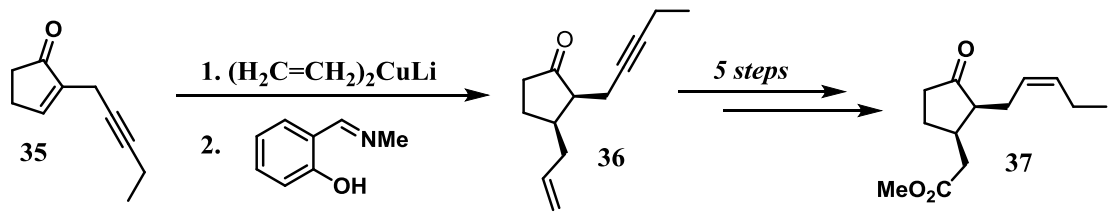
Scheme 1.11: Total synthesis of (+)-methynolide

Thus reduction of α,β-unsaturated imides under hydrogen atmosphere with Pd-catalyst or under the Birch reduction provided efficient and versatile methods for the synthesis of polyketides and deoxypropionates.

1.5 Proton source methodology to quench enolates

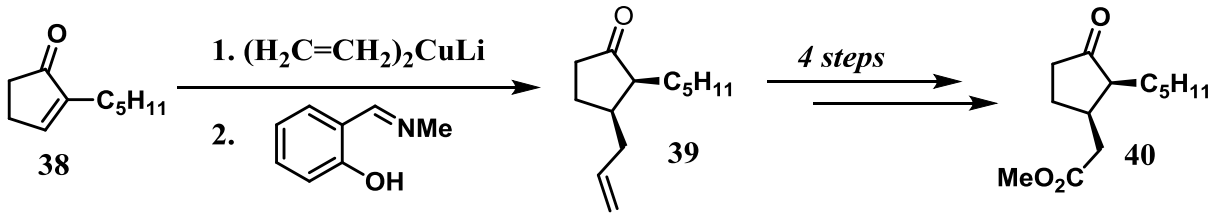
The choice of proton source used to quench enolates also plays an important role in the stereochemistry of the asymmetric carbon that is generated.

In 2001, during the synthesis of methyl jasmonite **37**, a conjugate addition and protonation sequence was attempted (**Scheme 1.12**). It was observed that when enone **35** was subjected to a 1,4-addition reaction with lithium diallylcuprate, followed by protonation of the enolate with 2-(methyliminomethyl)phenol, a *cis:trans* ratio of 85:15 was realized.[41]



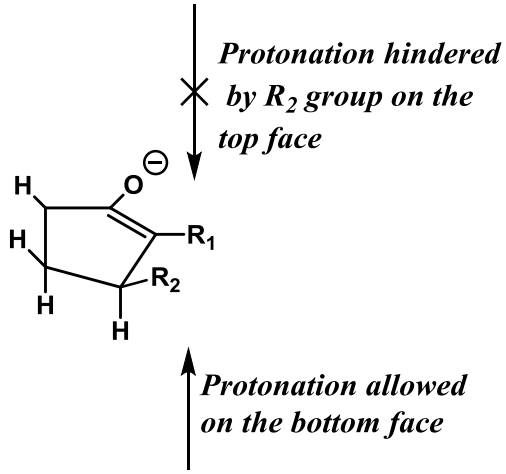
Scheme 1.12: Synthesis of methyl jasmonite

Conversely, in the synthesis of methyl dihydrojasmonite (**40**) diastereomeric ratios were surprisingly better (**Scheme 1.13**). When the enone **38** was subjected to a 1,4-addition reaction with lithium diallylcuprate and the enolate quenched by 2-(methyliminomethyl)phenol, the diastereomeric ratio observed was 94:6 of **39**. However, other proton sources such as ethyl salicylate or *tert*-butyl salicylate provided only 83:17 and 55:45 ratio of *cis:trans* isomers respectively.



Scheme 1.13: Synthesis of methyl dihydrojasmonite

The protonation mechanism is quite simple for the two cases of jasmonites (**Scheme 1.14**). After addition of the cuprate to the enone, the intermediate is somewhat planar. The allyl group blocks off the top face for protonation thereby allowing only the bottom face for the proton source.



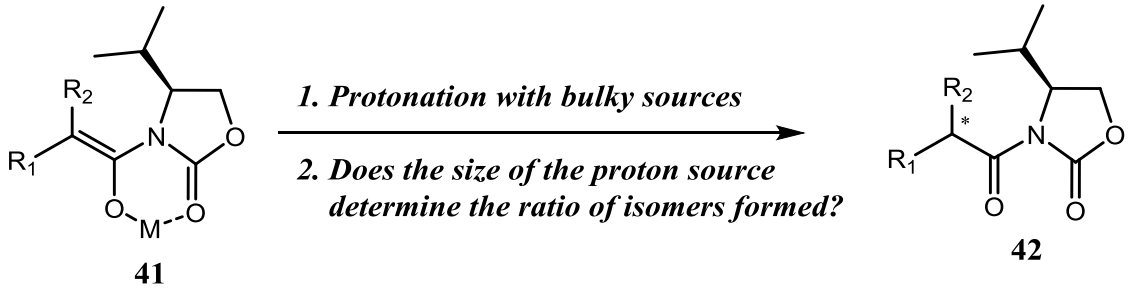
Scheme 1.14: Transition state of protonation for jasmonite compounds

Hence, specific proton sources can stereoselectively quench enolates and can influence the stereochemistry of the newly generated chiral center.

1.6 Motivation behind this dissertation

As mentioned earlier, protonation of enolates is an important methodology for the synthesis of reduced propionates and polyketides. It is interesting to study the change in the ratio of isomers formed from the protonation of enolates and correlate it to the increase in size of the proton source. There is no prior literature studying the effects of bulky proton sources to quench chiral enolates.

It is of primary importance to first screen myriad proton sources that can be used to quench enolates (**Scheme 1.15**). Chiral enolates that are generated in Birch reduction conditions can be used as intermediates for protonation with a variety of proton sources of different sizes and the ratio of epimers can be studied which will then provide evidence for the "size to ratio" correlation.



Scheme 1.15: Protonation study

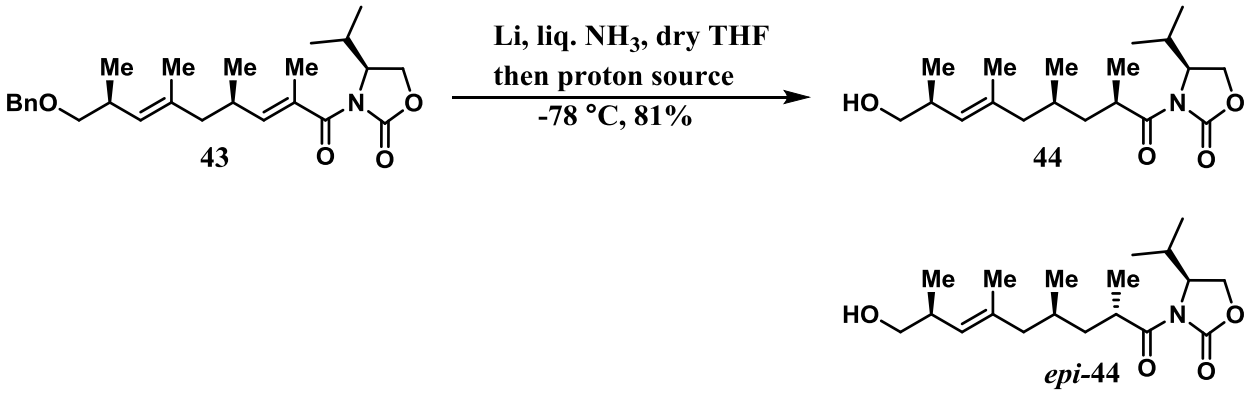
With the protonation of enolates in mind, an isomerization reaction of an α,β-unsaturated imide to the β,γ-unsaturated imide could be accomplished. The β,γ-unsaturated imide can be used as an important intermediate for the synthesis of γ-lactones, a common structural backbone of several important depsipeptides.

Overall, this dissertation presents studies on the protonation of chiral enolates with bulky proton sources. This thesis aims to provide a newer and easier approach to the synthesis of reduced propionates and deoxypropionates. It is able to find important correlation between the size of the proton source that are used and the ratio of isomers obtained. The methodology is then applied in the synthesis of different natural products.

Chapter 2: Birch reduction and the synthesis of sex pheromone of *Macrocentrus grandii*

2.1 Introduction

In 2016, during the synthesis of mycocerosic acid, [36] a component of virulent factor of *Mycobacterium tuberculosis*[3], Hosokawa *et al.* found that when hindered substrate **43** was subjected to Birch conditions, **44** and *epi*-**44** were formed (**Scheme 2.1**). The ratio of **44** and *epi*-**44** changed with the change in proton source (Table 1). The best proton source was found to be 2-methylbenzimidazole.



Scheme 2.1: Birch reduction in the synthesis of mycocerosic acid

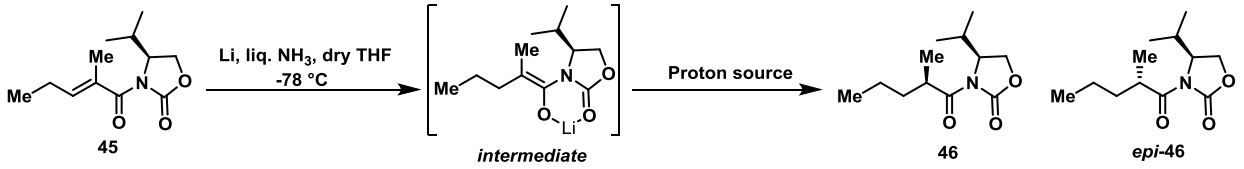
Entry	Proton source	Diastereomeric ratio[a]	Yield (%)
1	ammonium chloride	2:1	72
2	2,6-di-*tert*-butylphenol	2:1	86
3	2-pyridone	4:1	61
4	benzimidazole	12:1	86
5	2-methylbenzimiadzole	>20:1	81

[a] Determined by 400 MHz NMR

Table 1. Protonating agents in the total synthesis of mycocerosic acid

2.2 Optimization of reaction conditions

However, for less hindered substrates such as **45**, 2-methylbenzimidazole only showed moderate selectivity. Therefore, screening for a proton source for the Birch reduction (**Scheme 2.2,** Table 2), it was found that when ammonium chloride (entry 1, Table 2), a very commonly used proton source for Birch reductions, was used to protonate the intermediate, the reaction proceeded with very low stereoselectivity.



Scheme 2.2: Birch reduction on less hindered substrate 45

Entry	Proton source	**46**: *epi*-**46**[a]	Yield (%)
1.	ammonium chloride	1.9:1	59
2.	2,6-di-*tert*-butyl phenol	1.5:1	60
3	2-pyridone	1.5:1	54
4	pthalimide	2.4:1	37
5	benzimidazole	2.6:1	61
6	2-methylbenzimidazole	3.8:1	64
7	2-nonanoylbenzimidazole	4.0:1	44
8	2-cyclohexylbenzimidazole	3.6:1	64
9	2-isobutylbenzimidazole	3.1:1	68
10	2-isopropylbenzimidazole	5.2:1	69
11	2-*tert*-butylbenzimidazole	1.9:1	50
12	2-*n*-butylbenzimidazole	3.4:1	60
13	2-adamantylbenzimidazole	1.5:1	51
14	*N*-(2,6-dimethylphenyl)pivalamide	1.4:1	54
15	*N*-(2,6-diethylphenyl)pivalamide	1.3:1	60

[a] Determined by 400 MHz NMR

Table 2. Protonation for less hindered α,β-unsaturated imide 45

2,6-Di-*tert*-butylphenol (entry 2, Table 2), which is much bulkier in size, afforded slightly better results. 2-Pyridone (entry 3, Table 2), reported by Davies *et al.* as an excellent proton source[42] for isopropyloxazolidinone based chiral auxiliaries, could not change the stereoselectivity.

As a bulky benzimidazole, 2-methylbenzimidazole (entry 6, Table 2) was tried, and **46** and *epi*-**46** in the ratio of 3.8:1 were obtained. Even bulkier 2-isopropylbenzimidazole (entry 10, Table 2) gave good stereoselectivity (5.2:1) with good yield (69%). It was also interesting that 2-nonanoylbenzimidazole (entry 7, Table 2) gave a moderate ratio of the epimers but in poor yield.

On increasing the size of the substituent on the benzimidazole beyond isopropyl to *tert*-butyl (entry 11, Table 2) or adamantyl (entry 13, Table 2) proved detrimental to the reaction. Phenylpivalamides possessing alkyl substituents on the phenyl ring consist of a rather acidic proton (entries 14 and 15, Table 2). However, it would seem as if acidity has less influence than bulkiness.

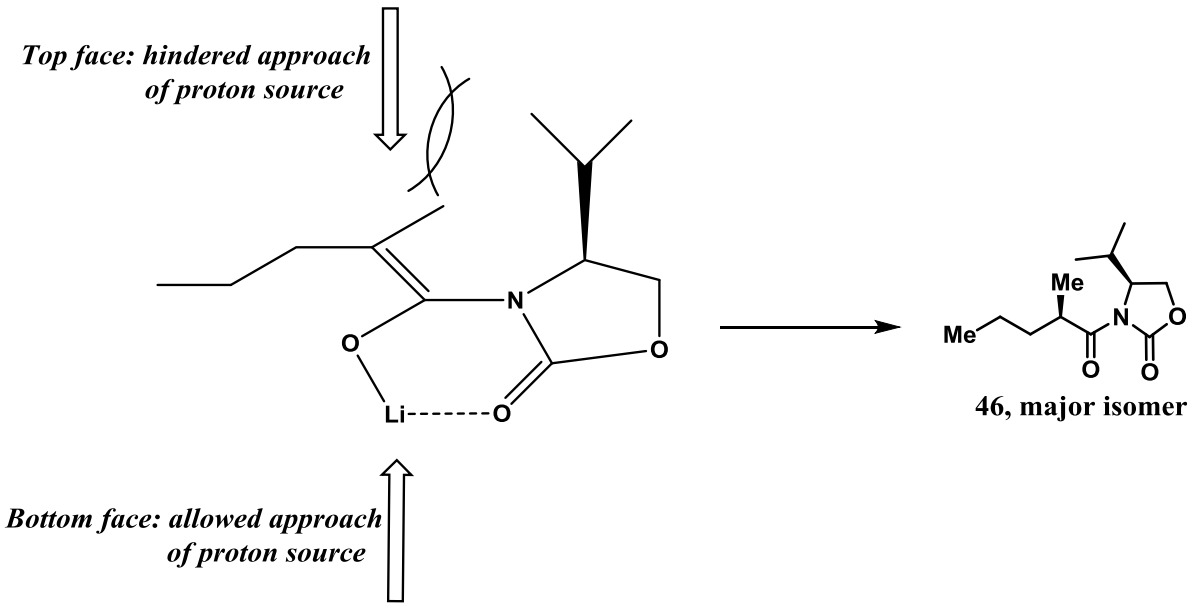
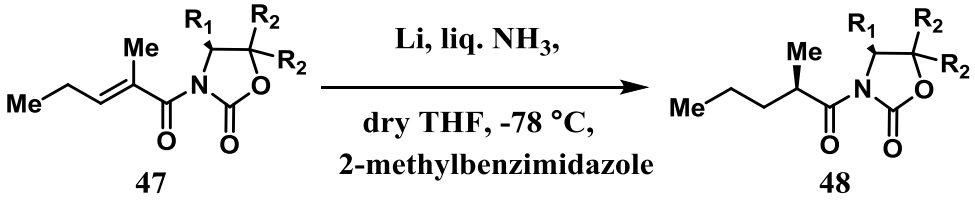


Fig. 3: The approach of proton source

The chelated intermediate[33] (**Fig. 3**) of the Birch reduction is expected to be of planar nature where the proton source approaches the enolate from the bottom face due to the presence of the isopropyl group on the top face. Thus, the ensuing major isomer **46** has a methyl group on the β-face.

On realizing that there is perhaps still scope for improvement, the chiral auxiliaries were changed around in the hope that perhaps other auxiliaries such as 4-cyclohexyl or 5,5-dimethyl derivative of isopropyloxazolidinone may have better effect on the stereoselectivity (**Scheme 2.3**, Table 3). Using the Birch reduction somewhat restricted the choice of chiral auxiliaries that could be used as 4-benzyloxazolidinone or 5,5-diphenyl derivative of oxazolidinone could not be tried.



Scheme 2.3: Changing the oxazolidinone for Birch reductions

Entry	R_1	R_2	Diastereomeric ratio[a]	Yield (%)
1	isopropyl	H	3.8:1	64
2	cyclohexyl	H	3.5:1	48
3	isopropyl	Me	2.1:1	50

[a] Determined by 400 MHz NMR

Table 3. Effects of the Birch reduction on changing chiral auxiliary

As evident from the above table, using 4-cyclohexyloxazolidinone (entry 2, Table 3) leads to a decrease in diastereomeric ratio and yield. The 5,5-dimethyl derivative of oxazolidinone (entry 3, Table 3) exhibited an interesting case. It has been reported that the dimethyl groups have the ability to push the isopropyl moiety over the alkyl chain.[43] However in this study, it seemed not to be the case. The reaction with 5,5-dimethyl derivative of isopropyloxazolidinone yielded lesser diastereomeric ratio and yield than

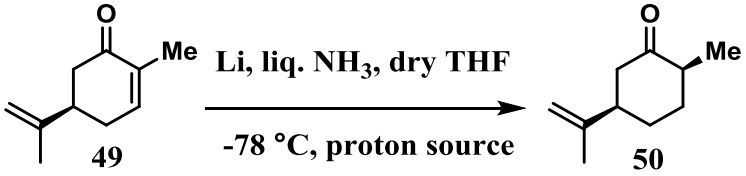
entry 1 itself. The reason for using 2-methylbenzimidazole as the proton source is its commercial availability.

It is to be noticed here, that while **44** was formed in excellent stereoselectivity, it was not so the case with **46**. This is perhaps due to the lack of an extra stereo-controlling γ-methyl group to the enolate that is generated which is present in **43**, but absent in **45**.

Further improvements on the afore-mentioned Birch conditions were tried. The metal atom was at first thought to have some effect on the stereoselectivity, but it was realized that the size and the nature of the metal had no bearing on the ratio of diastereomers as on changing from lithium to sodium, the reaction remained unperturbed.

2.3 Birch reduction on *R*-carvone

Next the Birch reduction followed by the stereoselective protonation on other substrates such as *R*-carvone **49** (**Scheme 2.4,** Table 4) was tried. On protonation, a peculiar trend in the diastereomeric ratio was observed.



Scheme 2.4: Birch on *R*-carvone

Entry	Proton source	Diastereomeric ratio[a]	Yield (%)
1	ammonium chloride[44)]	6:1	62
2	2-methylbenzimidazole	6:1	68
3	2-isopropylbenzimidazole	6:1	68
4	2-*tert*-butylbenzimidazole	6:1	50

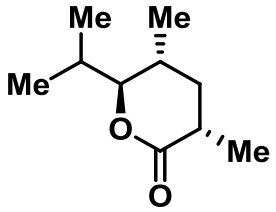
[a] Determined by 400 MHz NMR

Table 4. Protonation of *R*-carvone

The diastereomeric ratio remains the same despite the change in proton source. This result is expected and the reason behind this is two-fold. Firstly, the isopropene group is too far away from the enolate to induce a good stereoselectivity. Secondly, the isopropene moiety assumes an equatorial position. It is therefore understandable that increasing the bulkiness of the proton source has no effect on the ratio of diastereomers.

2.4 Synthesis of pheromone of *Macrocentrus grandii*

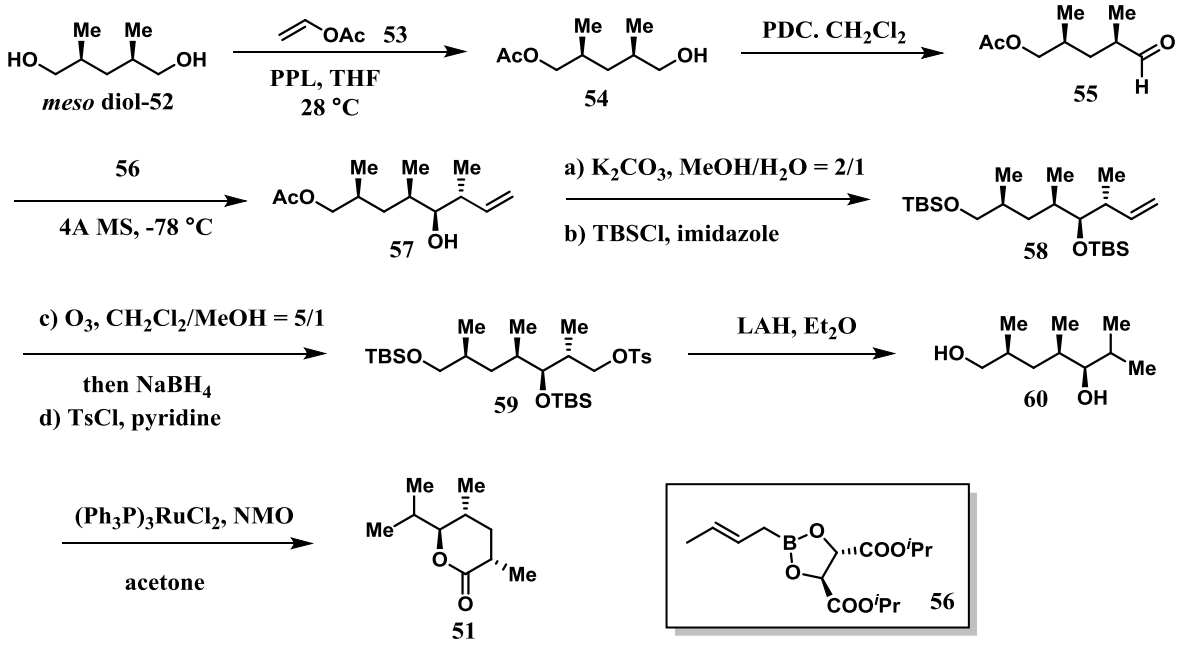
With a clear understanding of Birch reductions with the newly introduced proton source and understanding its limitations, the synthesis of (3*S*, 5*R*, 6*S*)-6-isopropyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one **51**, the sex pheromone of *Macrocentrus grandii* was attempted. The compound is a δ-lactone[45] and controls the population *Ostinia nubilalis*, and hence is able to help in agriculture in an environmentally friendly manner.[46]



(3*S*,5*R*,6*S*)-6-isopropyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one (51)

2.4.1 Previous syntheses of pheromone of *Macrocentrus grandii*

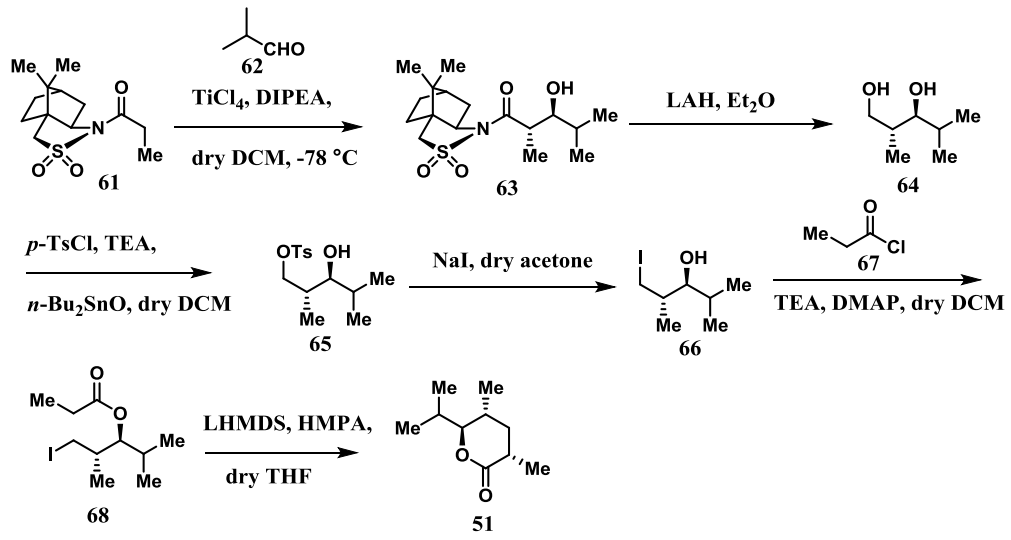
Since its isolation in 1993,[45] the pheromone **51** has been synthesized by a few groups. One of the first ever synthesis of **51** was performed via an enzymatic reaction on the *meso* diol **52** to provide **54** which on oxidation furnished the terminal aldehyde **55** (**Scheme 2.5**).[47]



Scheme 2.5: Enzymatic synthesis of (3*S*,5*R*,6*S*)-6-isopropyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one

The nucleophilic reaction with (*E*)-crotyl-(*S*,*S*)-boronate (**56**) gave the alkene **57**. After ozonolysis of the TBS protected **58**, borohydride reduction and tosylation provided the tosylate **59** which was reduced with LAH to furnish **60**. Oxidative lactonisation with ruthenium provided the target molecule **51**. Thus **51** was synthesized in 9 steps from the diol **52**.[47]

A more recent synthesis[48] involves the use of Oppolzer's chiral auxiliary and the target molecule was synthesized in 6 steps from the chiral synthon **61** (**Scheme 2.6**).

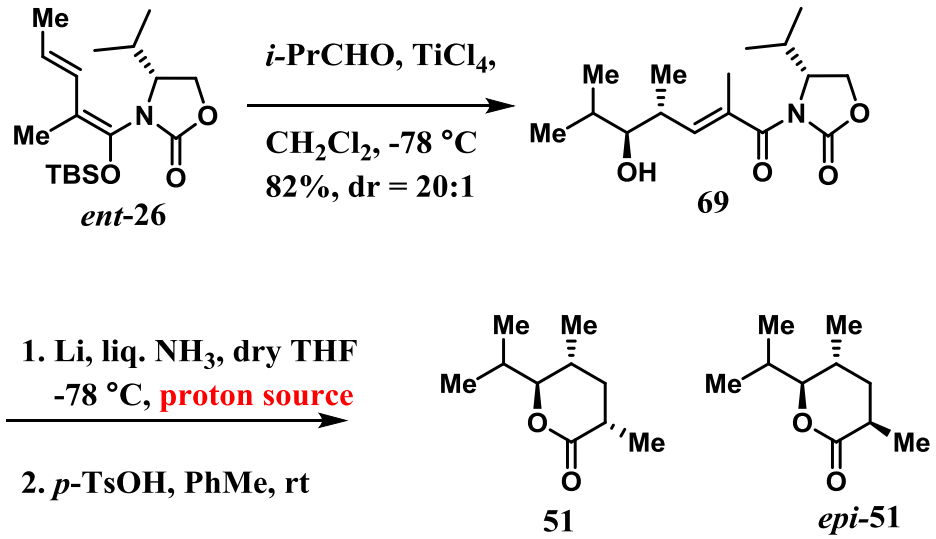


Scheme 2.6: Oppolzer's chiral auxiliary synthesis of (3*S*,5*R*,6*S*)-6-isopropyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one

The chiral synthon **61** was subjected to an asymmetric aldol reaction with isobutyraldehyde to furnish **63** at a diastereomeric excess of 84%. Reductive cleavage with LAH followed by tosylation provided **65**. Iodination and further propionylation with propionyl chloride gave the ester **68**. Cyclisation of ester **68** provided the target lactone **51**.

2.4.2 Optimization of reaction conditions for the synthesis of pheromone of *Macrocentrus grandii*

The development of a shorter synthesis of **51** in just 3 steps was achieved (**Scheme 2.7**). The first step of the synthesis was a vinylogous Mukaiyama aldol reaction with isobutyraldehyde and *ent*-**26** to furnish the aldol adduct **69** in 82% yield in >20:1 diastereomeric ratio. The screening of the proton source for the Birch reaction was then carried out (Table 5). With NH_4Cl (entry 1, Table 5), a 10:1 ratio of **51** and *epi*-**51** was formed. 2-Methylbenzimidazole (entry 3, Table 5) furnished **51** in 14:1 ratio of diastereomers but 2-isopropylbenzimidazole provided **51** as a single isomer in 70% yield (entry 4, Table 5).



Scheme 2.7: Synthesis of (3*S*,5*R*,6*S*)-6-isopropyl-3, 5-dimethyltetrahydro-2*H*-pyran-2-one

Entry	Proton source	Diastereomeric ratio [a] (**51**:*epi*-**51**)	Yield (%)
1	ammonium chloride	10:1	72
2	2,6-di-*tert*-butylphenol	11.4:1	52
3	2-methylbenzimidazole	14:1	74
4	2-isopropylbenzimidazole	>20:1	70

[a] Determined by 400 MHz NMR

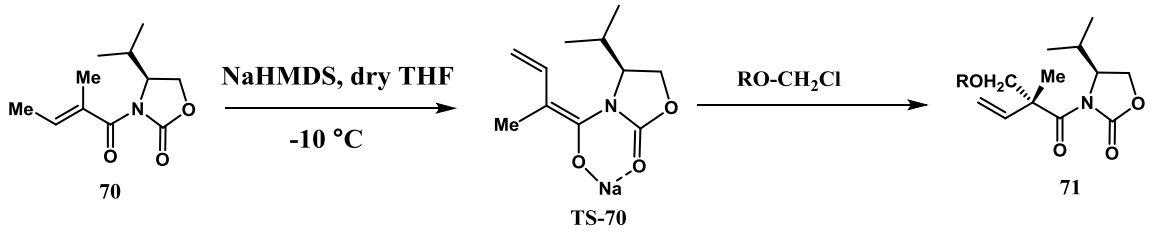
Table 5. Protonation of 69 to furnish lactone 51

Hence, the synthesis of (3*S*,5*R*,6*S*)-6-isopropyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one **51** was achieved in 3 steps by using a vinylogous Mukaiyama aldol reaction, a stereoselective protonation with 2-isopropylbenzimidazole and lactonization. The spectroscopic data of **51** are in accordance with those of the reported literature.[48]

Chapter 3. Isomerization reaction and the formal synthesis of seragamide A and its congeners

3.1 Introduction

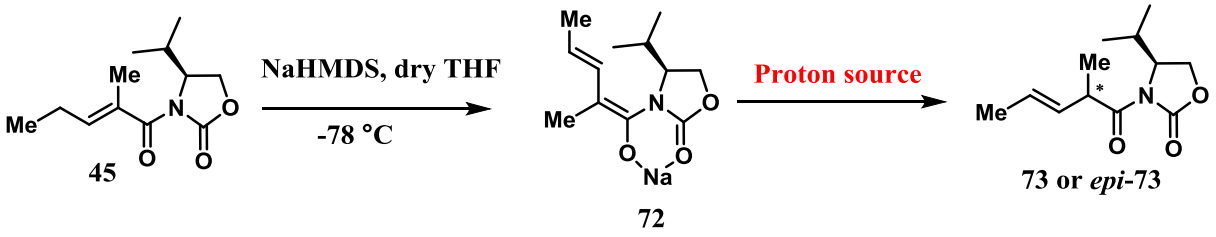
During the synthesis of madindoline A, Hosokawa *et al*. reported that when **70** was treated with NaHMDS and then alkylated with chloroalkyl ethers, there was an alkylation reaction that proceeded smoothly to furnish a quaternary carbon in a good stereoselectivity (**Scheme 3.1**).[49] The reaction was believed to proceed via the enolate **TS-70** and the isopropyl auxiliary, would cover the top face to achieve a stereoselective alkylation. The enolate is chelated and hence rotation around the C-N bond is restricted.



Scheme 3.1: Reported alkylation reaction

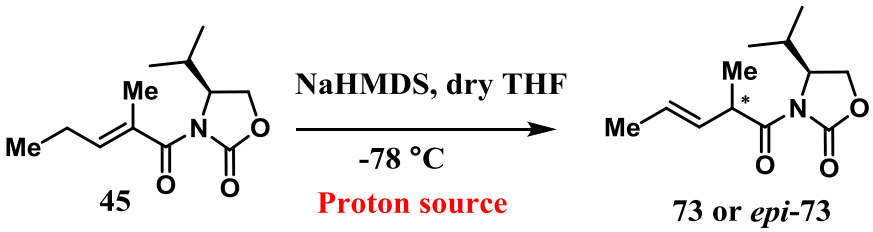
3.2 Optimization of reaction conditions

The isomerization reaction converting an α,β-unsaturated imide into a β,γ-unsaturated imide required a protonation of the dienolate instead of an alkylation (**Scheme 3.2**). The product formed then, could be an important starting point for a variety of complex natural products. Therefore, the reaction conditions were optimized for the protonation reaction (Table 6).



Scheme 3.2: Expected transition state and product of isomerisation reaction

Acetic acid is the most commonly used source of proton for quenching the dienolate reactions. However, it provided **73** or *epi*-**73** with 1.1:1 diastereomeric ratio at 90% yield (entry 1, Table 6). 2-Isopropylbenzimidazole, which worked the best under Birch conditions, gave a good ratio of 15:1 but moderate yield of 67% (entry 4, Table 6). 2,6-Di-*tert*-butylphenol only provided the diastereomers in a 4.5:1 ratio (entry 2, Table 6). 2-*tert*-Butylbenzimidazole furnished the epimers in a 8:1 ratio at only 50% yield (entry 5, Table 6). The best proton source was found to be 2-methylbenzimidazole which provided the β,γ-unsaturated imide in a 20:1 ratio of diastereomers at 85% yield (entry 3, Table 6).



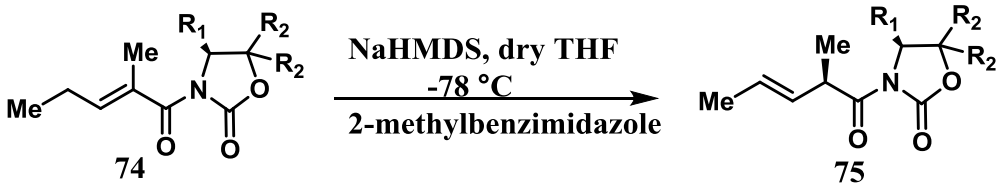
Scheme 3.3: Isomerisation reaction

Entry	Proton source	Diastereomeric ratio[a]	Yield (%)
1	acetic acid	1.1:1	90
2	2,6-di-*tert*-butylphenol	4.5:1	88
3	**2-methylbenzimidazole**	**20:1**	**85**
4	2-isopropylbenzimidazole	15:1	67
5	2-*tert*-butylbenzimidazole	8:1	50

[a] Determined by 400 MHz NMR

Table 6. Optimization of isomerization reaction

Upon changing the oxazolidinone moiety, interesting results were obtained (**Scheme 3.4,** Table 7). 4-Benzyloxazolidinone, 4-cyclohexyloxazolidinone and 5,5-dimethyl derivative of isopropyloxazolidinone were used for trials.



Scheme 3.4: Changing the structure of oxazolidinone

Entry	R_1	R_2	Diastereomeric ratio[a]	Yield (%)
1	isopropyl	H	20:1	85
2	isopropyl	Me	12:1	80
3	cyclohexyl	H	15:1	82
4	Benzyl	H	12:1	88

[a] Determined by 400 MHz NMR

Table 7. Effects of protonation reaction on changing chiral auxiliary

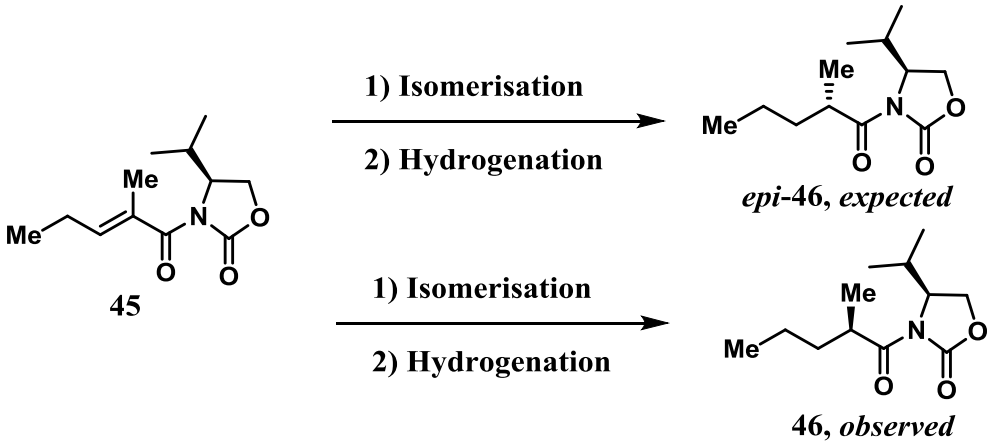
From the above table it is evident that using 4-isopropyloxazolidinone served the best results (entry 1, Table 7). 5,5-Dimethyl derivative of isopropyloxazolidinone (entry 2, Table 7) provided **75** at a 12:1 ratio of diastereomers. It would seem that the dimethyl derivative is detrimental both for the Birch and isomerization reactions.

4-Cyclohexyloxazolidinone (entry 3, Table 7) provided the β,γ-unsaturated imide with 15:1 ratio of isomers and 4-benzyloxazolidinone (entry 4, Table 7) furnished **75** with 12:1 ratio at 88% yield.

3.3 Proof of absolute stereochemistry

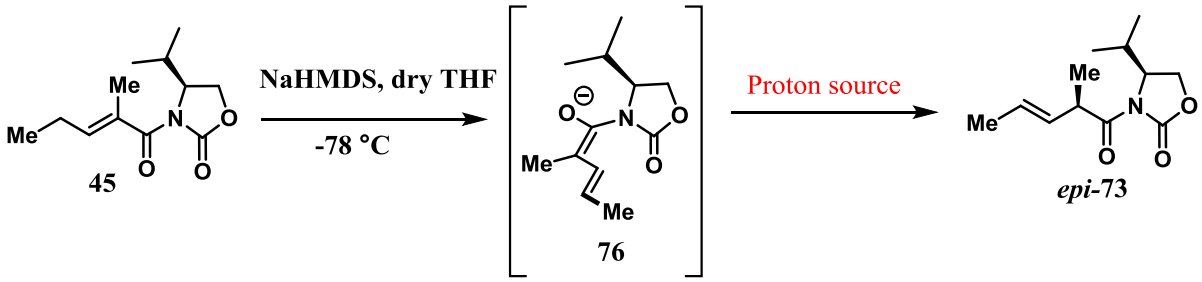
To prove the absolute stereochemistry of **73** or *epi*-**73**, the olefin was hydrogenated to give *epi*-**46** (**Scheme 3.3**). However, surprisingly, from the ^{1}H NMR it was ascertained that the hydrogenation of **73** led to the formation

of **46** only (**Scheme 3.5**). It was then realized that the structure of **73** needed revision along with the intermediate.



Scheme 3.5: Hydrogenation reactions to prove stereochemistry

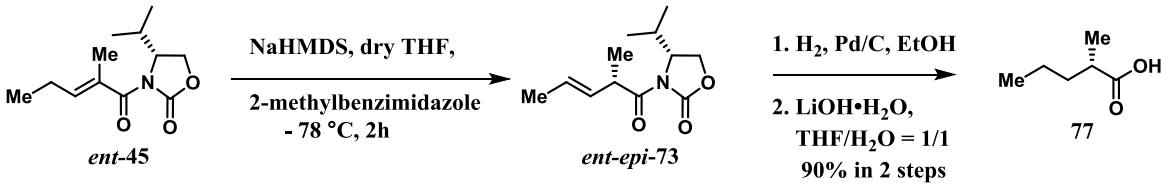
The reaction perhaps goes through the intermediate **76** where the oxazolidinone ring is perpendicular to the dienolate (**Scheme 3.6**). Thus the protonation is allowed only on the bottom face allowing the newly formed methyl group to assume the β-face as depicted below.



Scheme 3.6: Plausible transition state of isomerisation reaction

Although this transition state is uncommon, there is some preceding literature[50] for the formation of unchelated intermediate such as **76**.

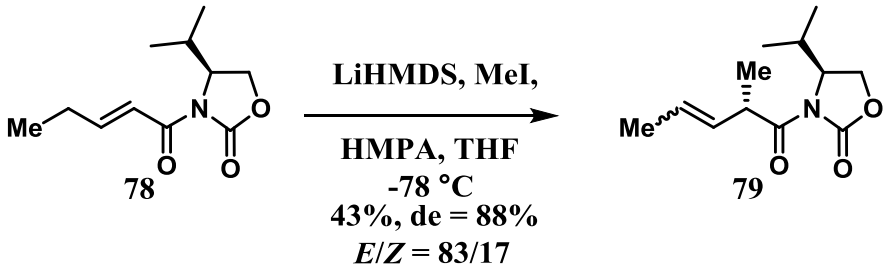
Further, compound *ent*-**45** was isomerized to give *ent*-*epi*-**73** which was hydrogenated and hydrolyzed to give the acid **77** in 90% yield (**Scheme 3.7**). The spectroscopic data of the acid **77** is in accordance with those of the literature[51].



Scheme 3.7: Proof of absolute stereochemistry

3.4: Some previous methods for the synthesis of β,γ-unsaturated imides

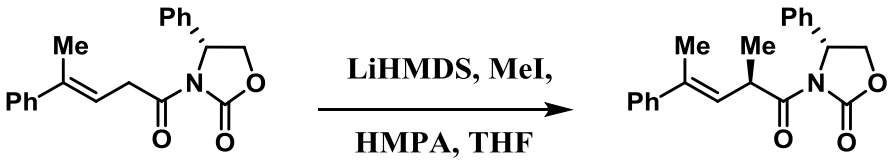
It is noteworthy that while Evans' alkylation could be an alternate route for the stereoselective synthesis of *epi*-**73**, it has proven to be significantly difficult (**Scheme 3.8**). In 1998, in a study of alkylation of chiral dienolates, Nakai *et al.* exhibited that methylation of (*S,E*)-4-isopropyl-3-(pent-2-enoyl) oxazolidin-2-one provided 43% of **79** at 88% de. [52]



Scheme 3.8: Alkylation of (*S,E*)-4-isopropyl-3-(pent-2-enoyl)oxazolidin-2-one

However, the isomerization method thus serves to provide the β,γ-unsaturated imide in higher yields and better stereoselectivity.

In 2007, a study on the synthesis of γ-butyrolactones[53] showed poor stereoselectivity (diastereomeric ratio = 60:40) when (*S,E*)-4-isopropyl-3-(4-phenylpent-3-enoyl)oxazolidin-2-one was methylated (**Scheme 3.9**).



Scheme 3.9: Alkylation reaction

Thus, an isomerization reaction converting an α,β-unsaturated imide into a β,γ-unsaturated imide was achieved with 2-methylbenzimidazole as the proton source. The reaction was then applied to the formal synthesis of seragamide A and its congeners.

3.5 Formal synthesis of seragamide A and its congeners

With the isomerization reaction optimized, a formal synthesis of seragamide A and its congeners was attempted. Seragamide A (**82**), jasplakinolide (**83**), and geodiamolide A (**84**) are cyclodepsipeptides with potent cytotoxic activity.[54,55]

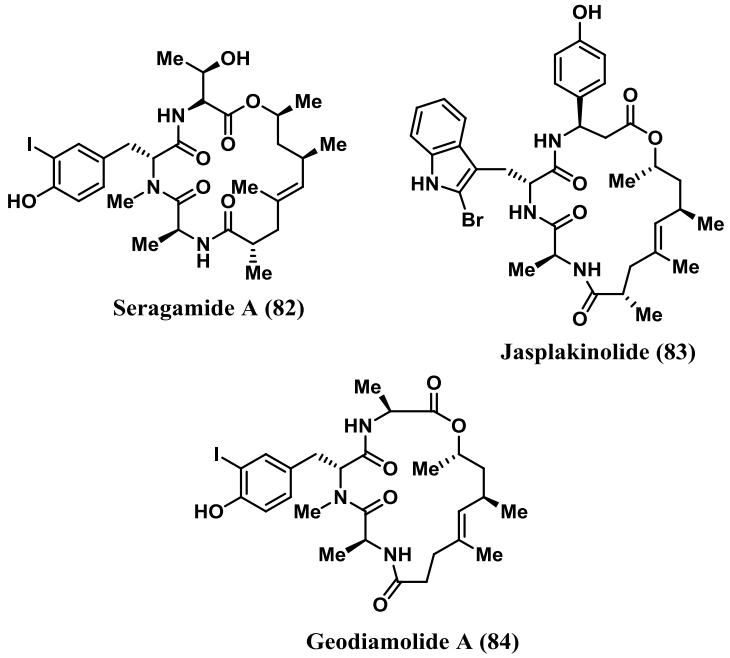
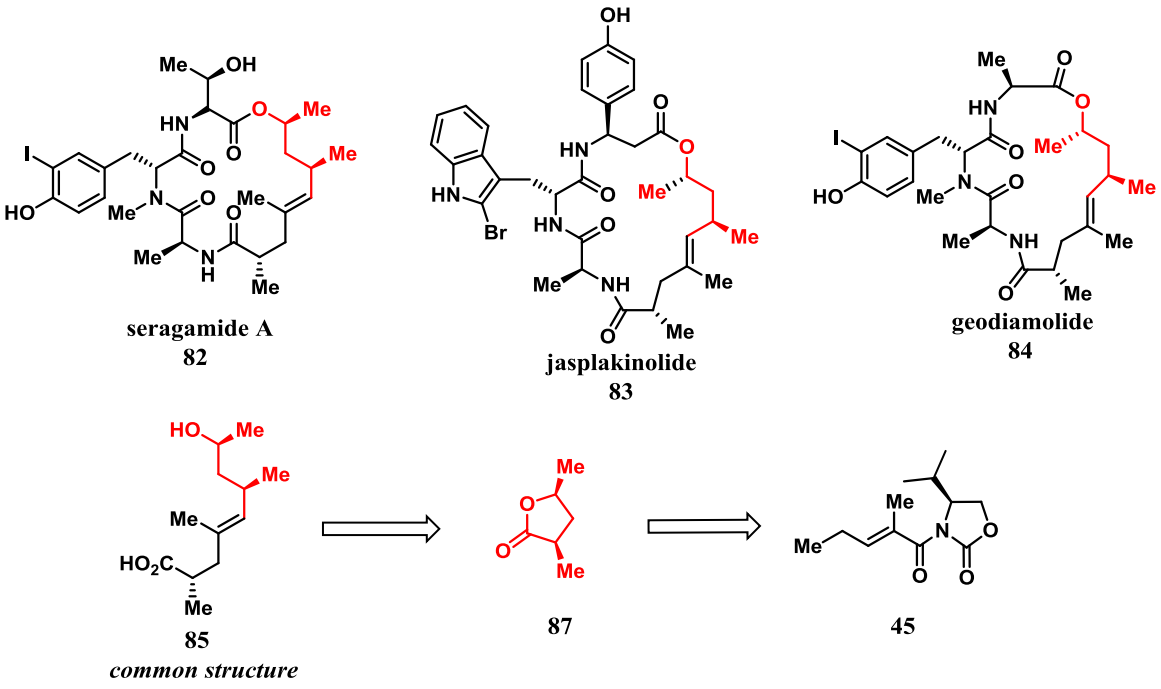


Fig 4. Structures of seragamide A, jasplakinolide and geodiamolide A

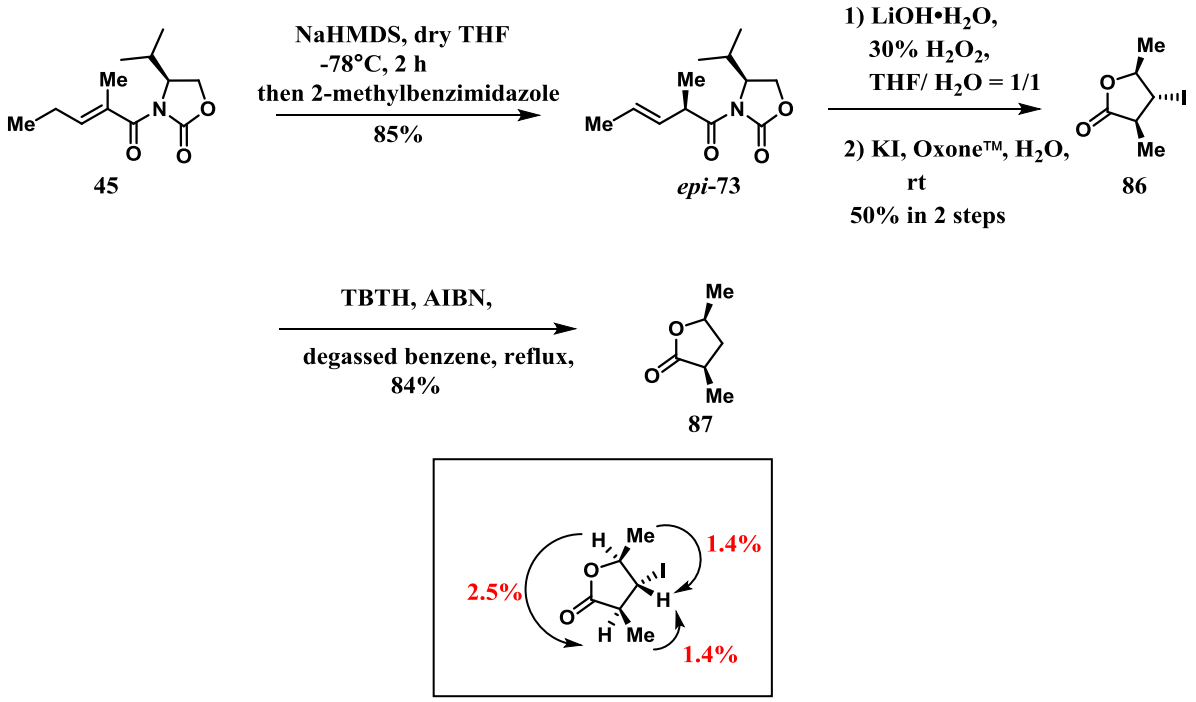
On closer inspection of these molecules, there appeared a common structure **85** (**Scheme 3.10**). Retrosynthesis of the common structure surfaced a key intermediate, the lactone **87**. The lactone could be synthesized from **45**. Synthesis of the common structure **85** from the lactone **87** has already been reported.[56]



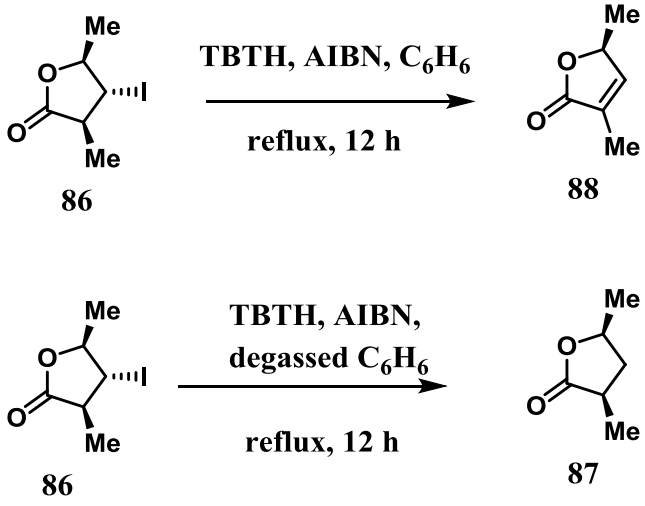
Scheme 3.10: Retrosynthesis of common structure 85

The forward synthesis was then embarked upon (**Scheme 3.11**). An isomerization reaction was carried out to provide 85% of *epi*-**73**. Hydrolysis followed by iodolactonisation furnished the iodolactone **86** as a single isomer. To understand the stereochemistry of **86**, an nOe experiment was carried out. The two methyl groups interacted identically to the proton on C-3. Also, the two protons on the bottom face interacted at 2.5%, thereby conclusively proving the structure to be as described in **Scheme 3.11**. Removal of the iodine group in the presence of *n*-Bu_3SnH/AIBN and degassed benzene under reflux conditions furnished the crucial lactone **87** in 84% yield.[53]

One of the disadvantages of the deiodination reaction seemed to be an unwanted E_1cb reaction which often led to **88** (**Scheme 3.12**). The problem was avoided by degassing benzene before use.

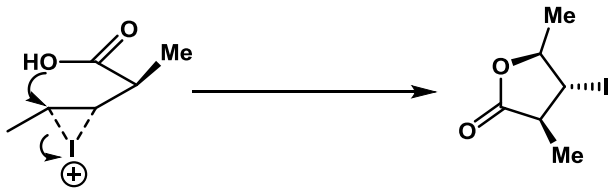


Scheme 3.11: Completion of formal synthesis of seragamide A and NOE of iodolactone 87



Scheme 3.12: Deiodination under benzene and degassed benzene

The iodolactonisation is also an important step which provided the iodolactone as a single isomer. The mechanism is perhaps the following. The iodine attaches itself to the bottom face of the olefin due to the steric hindrance of the methyl on the top face. The carboxylate then attacks from the β-face to provide the iodolactone as a single isomer **86** (**Scheme 3.13**).



89 **86**

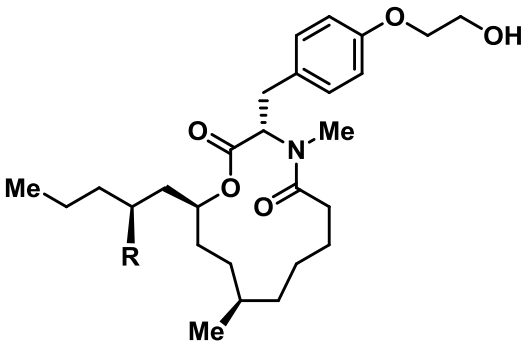
Scheme 3.13: Plausible mechanistic and stereochemical pathway of iodolactonisation

Thus, the formal synthesis of seragamide A and its congeners was completed. The key transformations included an isomerization reaction of the α,β-unsaturated imide to the β,γ-unsaturated imide and a stereoselective iodolactonisation and deiodination.

Chapter 4: Total Synthesis of PF1163B

4.1 Introduction

PF1163A (**90**) and PF1163B (**91**) are cyclodepsipeptides that were isolated from the fermentation broth of *Pencillium sp*.[57] The structure elucidation was done by Nose *et al*. and the first total synthesis was achieved by Tatsuta *et al.* in 14 steps by a contiguous Wittig reaction, hydrogenation and protection sequence.[58]

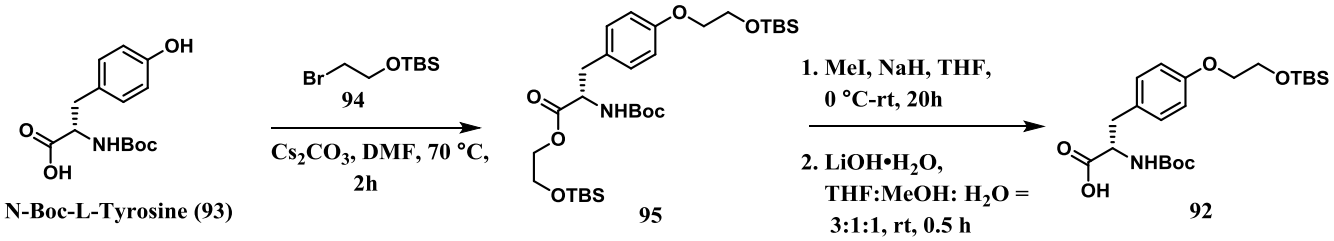


R= OH, PF1163A (90)
R= H, PF1163B (91)

PF1163B (**91**) is a potent inhibitor of ergosterol biosynthesis and shows an IC_{50} value of 34 ng/ml.[59] Because of its complex structure and potent bioactivity, PF1163B (**91**) has been an attractive target for total synthesis.

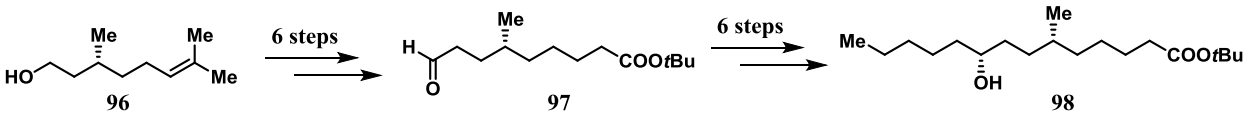
4.2 Previous synthetic studies on PF1163B

As mentioned earlier, Tatsuta *et al.* achieved the first total synthesis of PF1163B. The amino acid fragment was obtained from *N*-Boc-L-tyrosine **93** by alkylation, followed by methylation and finally hydrolysis (**Scheme 4.1**).



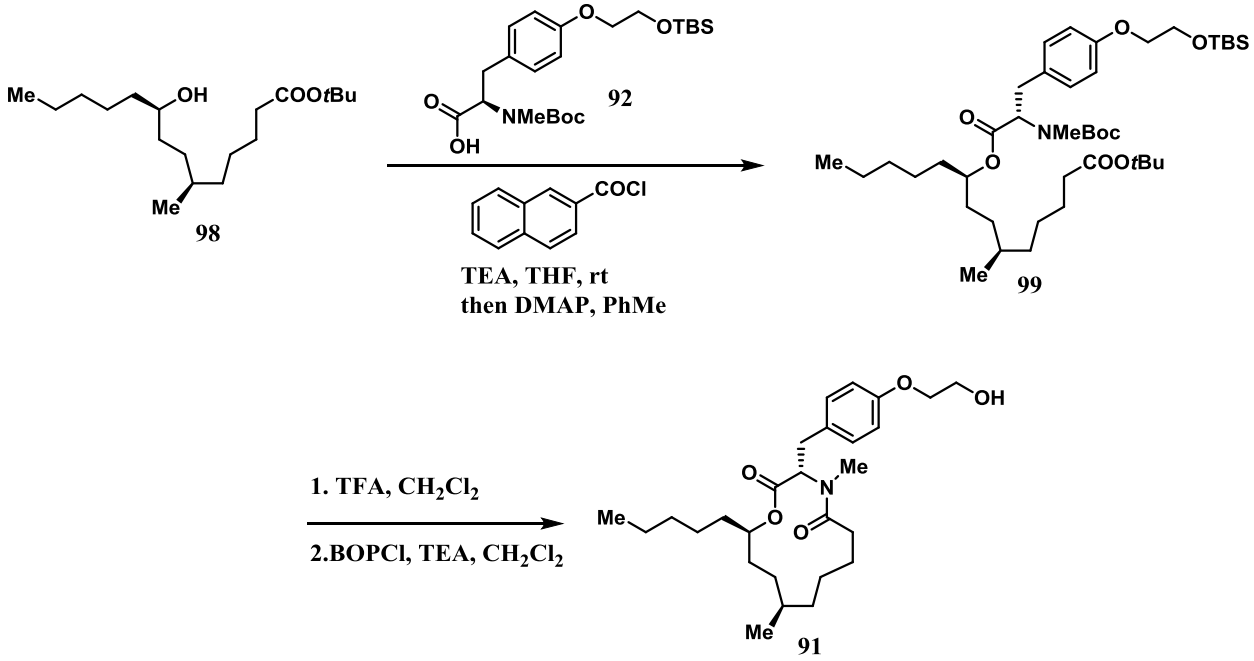
Scheme 4.1: Synthesis of acid 92

The non-peptide segment **98** was made from (*R*)-citronellol **96** in 12 steps by an iterative Wittig olefination and hydrogenation methods (**Scheme 4.2**).



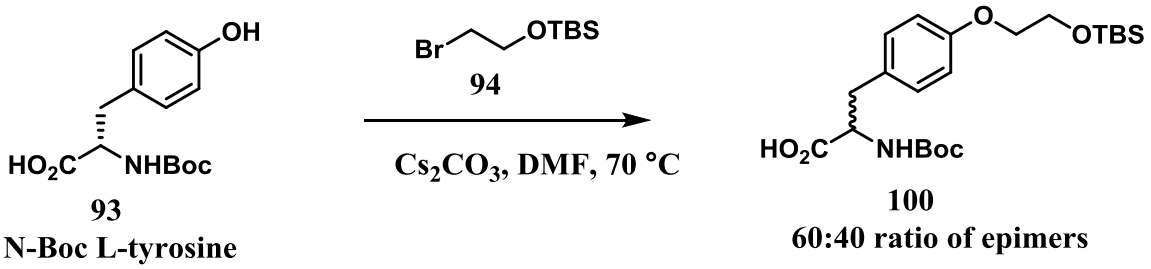
Scheme 4.2: Synthesis of non-peptide fragment 98

Coupling of the two fragments **98** and **92**, by Yamaguchi esterification followed by removal of the Boc and COO*t*Bu groups and then cyclisation afforded PF1163B (**91**) (**Scheme 4.3**).



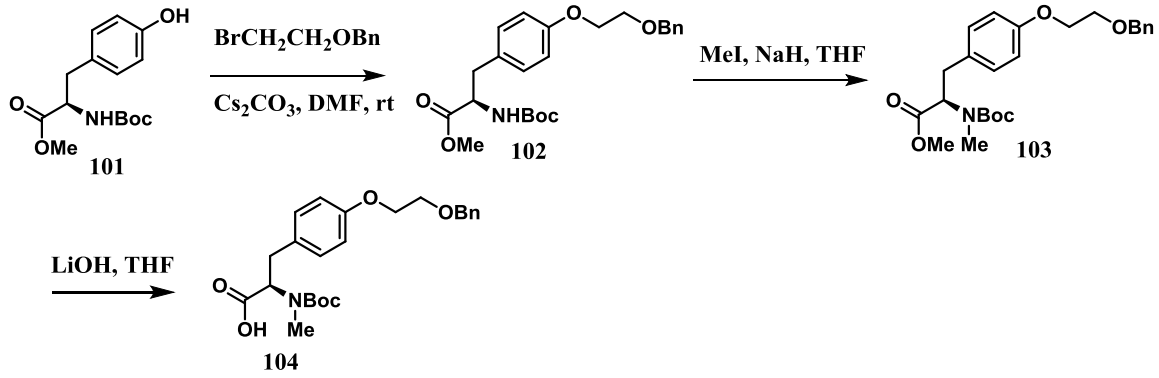
Scheme 4.3: Esterification and completion of synthesis of PF1163B

In 2003, during a study on conformational analysis of PF1163B, Bouzza *et al.* found that the previously reported synthesis of the amino acid fragment **92** led to 60:40 ratio of epimers after the first alkylation reaction at 70 °C (**Scheme 4.4**). However, the same reaction at room temperature led to minimal racemization (97:3). Also, the methylation reaction seemed difficult to drive to completion as the silyl protecting group got removed. So, to avoid these difficulties, the authors designed an improved synthesis starting from *N*-Boc-L-tyrosine methyl ester **101** (**Scheme 4.5**).[60]



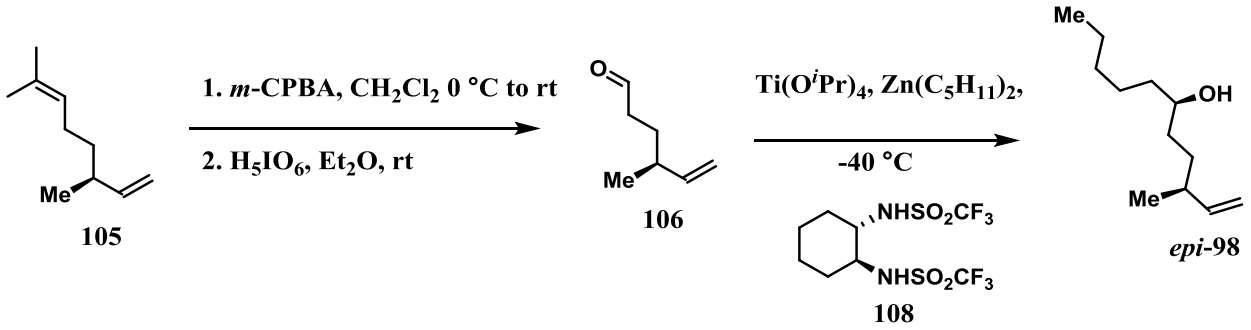
Scheme 4.4: Epimerisation of tyrosine

The authors treated *N*-Boc-L-tyrosine methyl ester **101** with 2-bromo-*O*-benzyl-ethanol in presence of Cs_2CO_3 to afford **102** (**Scheme 4.5**). Methylation followed by hydrolysis provided the amino acid fragment **104**.



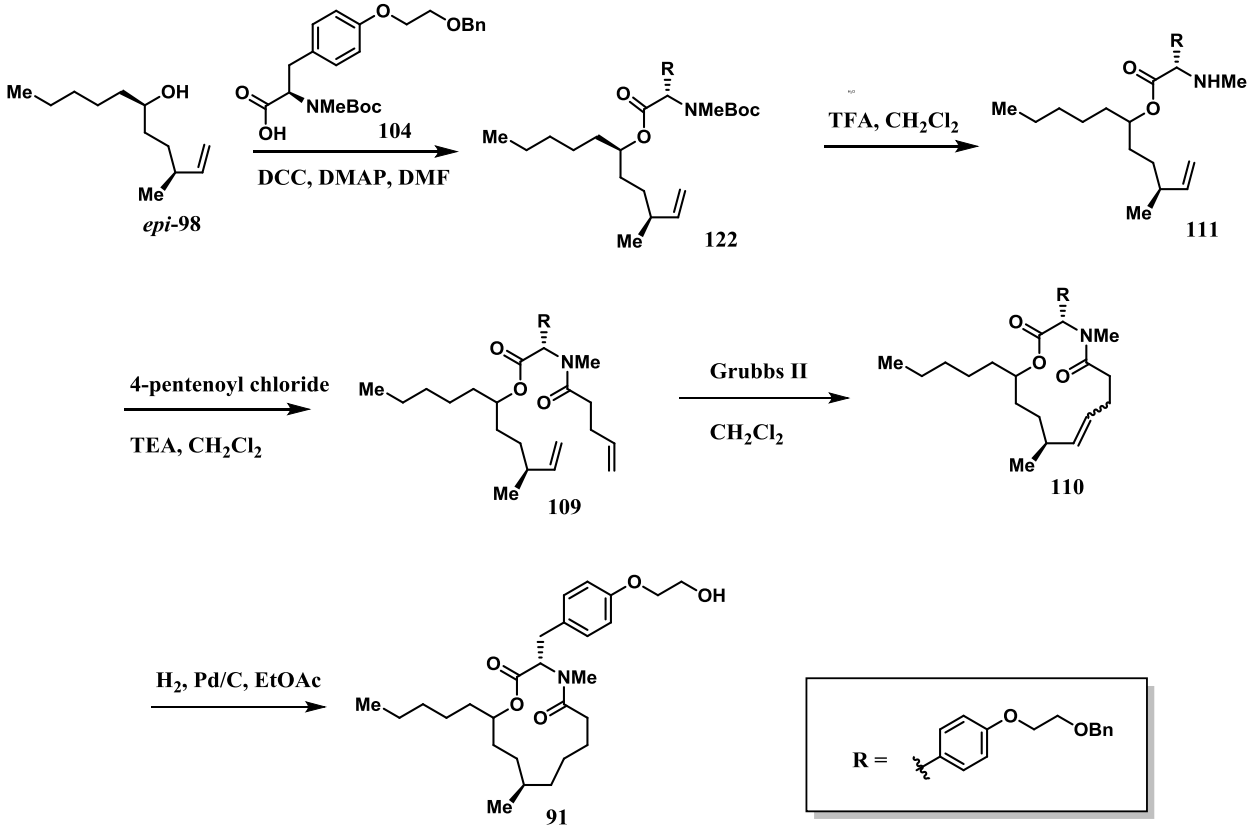
Scheme 4.5: New scheme for the amino acid fragment 104

In the synthesis of the non-peptide moiety, *epi*-**98** was made from (*S*)-citronellene **105** in three steps (**Scheme 4.6**). The aldehyde **106** was synthesized by the cleavage of the epoxide with periodic acid. Further treatment of the aldehyde by the Kobayashi and Knochel method with dipentylzinc furnished the alcohol *epi*-**98**.



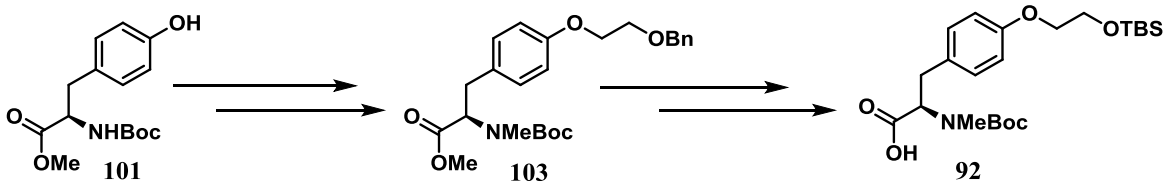
Scheme 4.6: Synthesis of non-peptide fragment *epi*-98

The acid fragment **104** and the alcohol *epi*-**98** were fused with DCC and DMAP (**Scheme 4.7**). The Boc group was removed and the resulting free amine was condensed with 4-pentenoyl chloride to give **109**. A ring closing metathesis reaction in the presence of Grubbs II catalyst served the protected alkene **110** which was then hydrogenated to provide PF1163B (**91**).



Scheme 4.7: Completion of total synthesis of PF1163B by Bouzza *et al.*

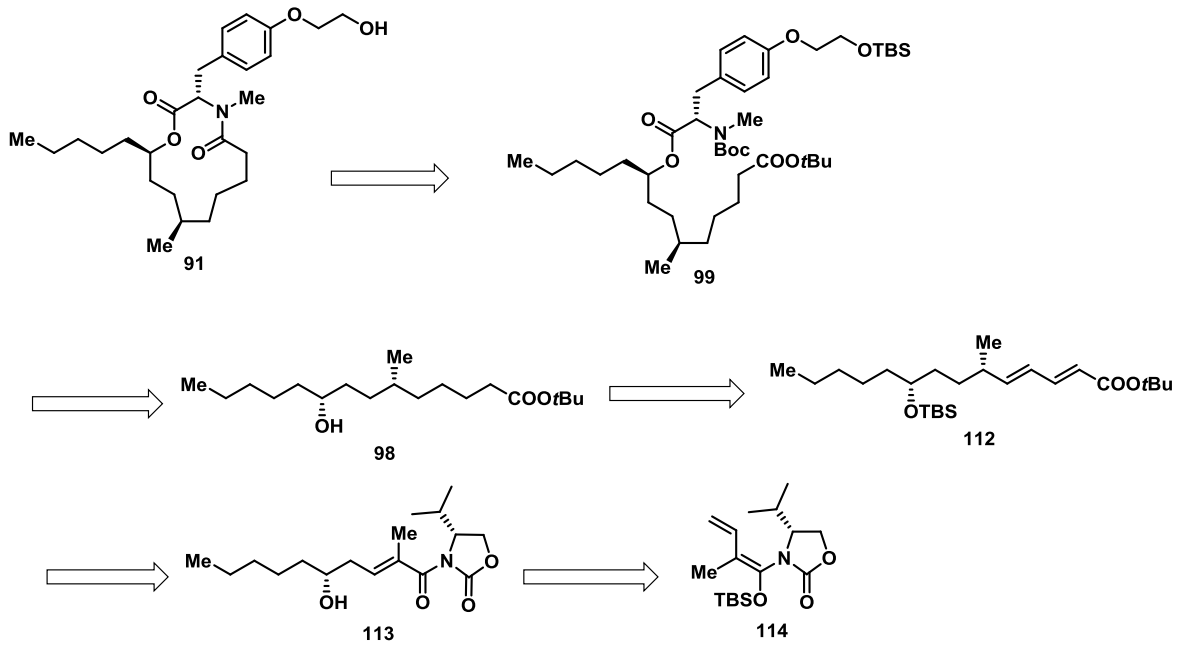
For the studies in this thesis, the total synthesis of PF1163B was achieved in 10 steps. On the retrosynthesis of the target molecule, it was required to synthesize the amino acid fragment **92** without the reported epimerization. The best way to synthesize **92** without the epimerization was to bring about the TBS protection at a later stage in the presence of a weak base such as imidazole, at room temperature or lower (**Scheme 4.8**).



Scheme 4.8: Synthetic plan for acid fragment 92

4.3 Retrosynthesis of PF1163B

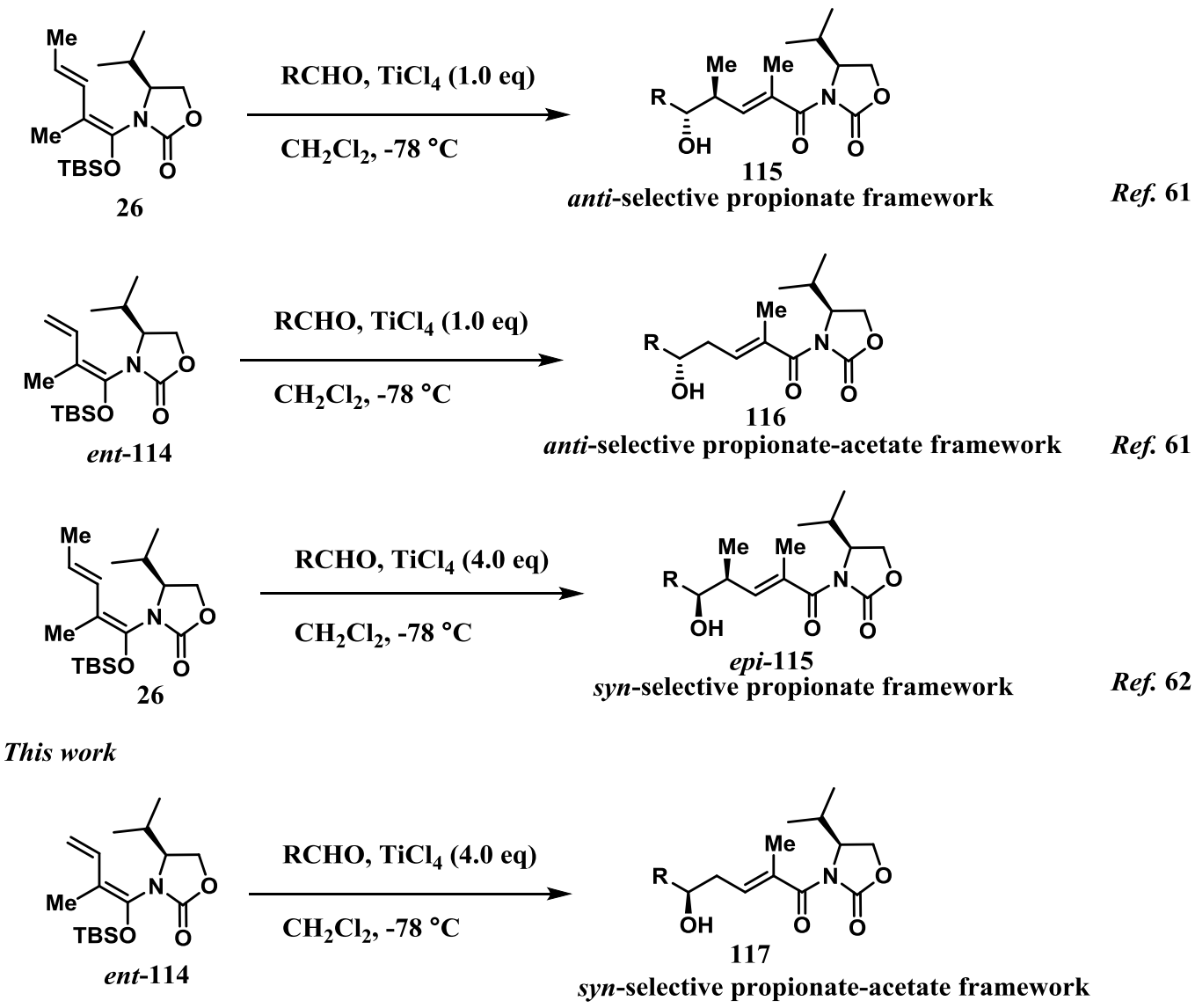
The non-peptide moiety **98** would be synthesized stereoselectively using a vinylogous Mukaiyama aldol reaction and a stereoselective protonation using 2-isopropylbenzimidazole (**Scheme 4.9**). Fusion of alcohol **98** with the acid **92** to give the ester **99** and consequent deprotection and cyclization should lead to the formation of PF1163B (**91**).



Scheme 4.9: Retrosynthetic approach towards PF1163B

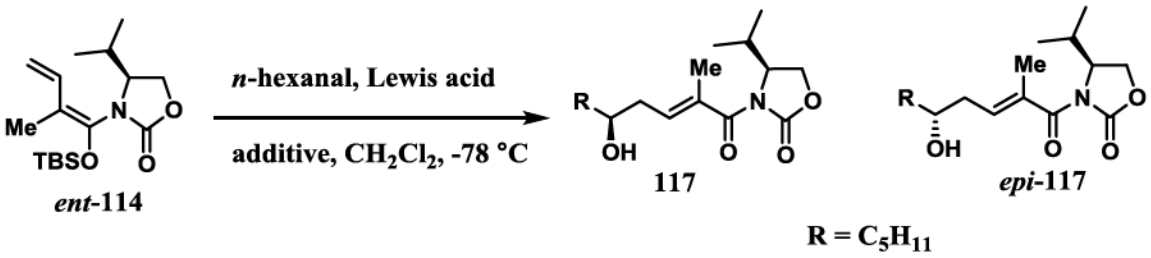
4.4 Optimization of *syn*-VMAR

The vinylogous Mukaiyama aldol reaction (VMAR) is a well-reported and widely used reaction to synthesize propionates and acetates and propionate-acetate frameworks (**Scheme 4.10**). *Anti*-selective VMARs to give propionates and acetate-propionate structures[61] are reported along with *syn*-selective VMAR to provide propionates.[62] However, the need to establish a protocol to obtain the *syn*-selective acetate-propionate fragment is imminent.



Scheme 4.10: Vinylogous Mukaiyama aldol reactions

To study this type of VMAR, vinylketene silyl *N,O*-acetal *ent*-**114** was used along with *n*-hexanal and optimized with different Lewis acids to afford **117** (**Scheme 4.11**). The results are tabulated below (Table 8).



Scheme 4.11: Optimisation of *syn*-VMAR

Entry	Eq. of *ent*-**114**	Lewis acid (eq.)	Eq. of *n*-hexanal	Additive	Diastereomeric ratio [a] (**117**: *epi*-**117**)	Yield (%)
1	1.0	$TiCl_4$ (4.0)	2.0	-	4.1:1	54
2	1.5	$TiCl_4$ (4.0)	1.0	-	4:1	5
3	1.0	$TiCl_4$ (4.0)	3.0	-	4:1	25
4	1.0	$SnCl_4$ (1.0)	1.5	-	1:20	70
5	1.0	$SnCl_4$ (4.0)	1.5	-	2:1	40
6	1.0	$BF_3 \cdot OEt_2$ (4.0)	1.5	-	1:2	32
7	1.0	$TiCl_4$ (4.0)	1.5	MS 4Å	1.2:1	61
8	1.0	$TiCl_4$ (4.0)	1.5	LiI	2:1	40
9	1.0	$SnCl_4$ (4.0)	1.5	$Cu(OTf)_2$	1.5:1	44

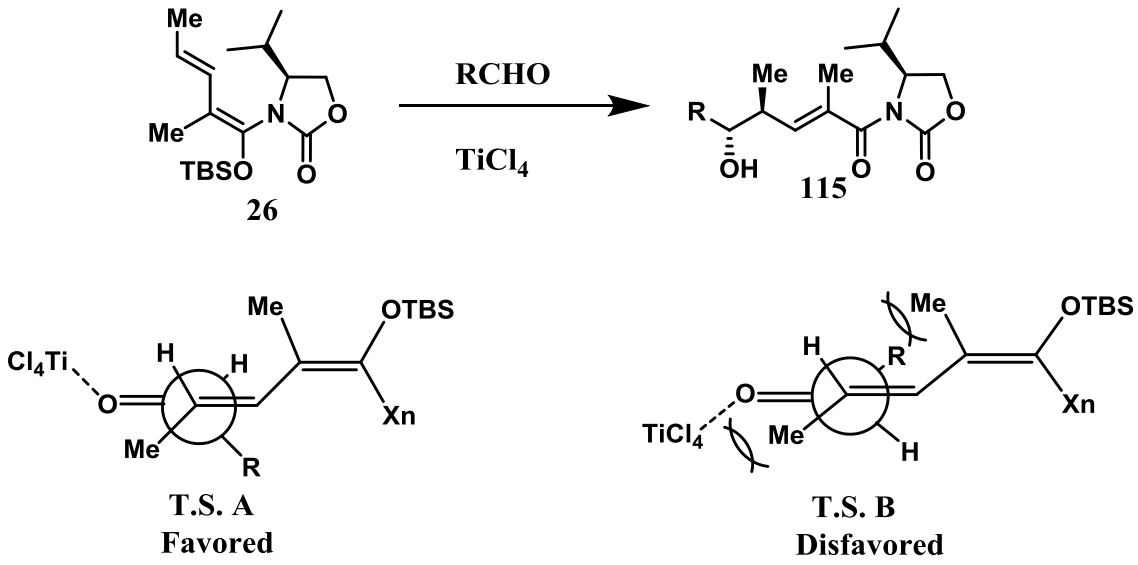
[a] Determined by 400 MHz NMR

Table 8. Optimisation of *syn*-VMAR reactions

As evidenced by the table, the reaction appears to work best with 4 equivalents of $TiCl_4$ without the use of any additive (entry 1, Table 8). The

reaction was also dependent on the equivalents of *ent*-**114** and the aldehyde (entries 2 and 3). Best results were achieved on using solutions of freshly distilled aldehyde and the Lewis acid. $SnCl_4$, so commonly used in VMARs for the synthesis of acetate type moieties, did not function well in this case (entries 4, 5 and 9). The use of any additives seemed to be detrimental to the reaction conditions (entries 7, 8 and 9).

The reaction mechanism of *syn*-selective VMAR is not well understood,[66] while the *anti*-selective VMAR appears to be easier to comprehend (**Scheme 4.12**). In the *anti*-selective case, the reaction proceeds through a favored **T.S. A**, while the **T.S. B** is disfavored due to steric repulsion between the R group of the aldehyde and the inner methyl group of the diene as well as between $TiCl_4$ and the terminal methyl group.[41]



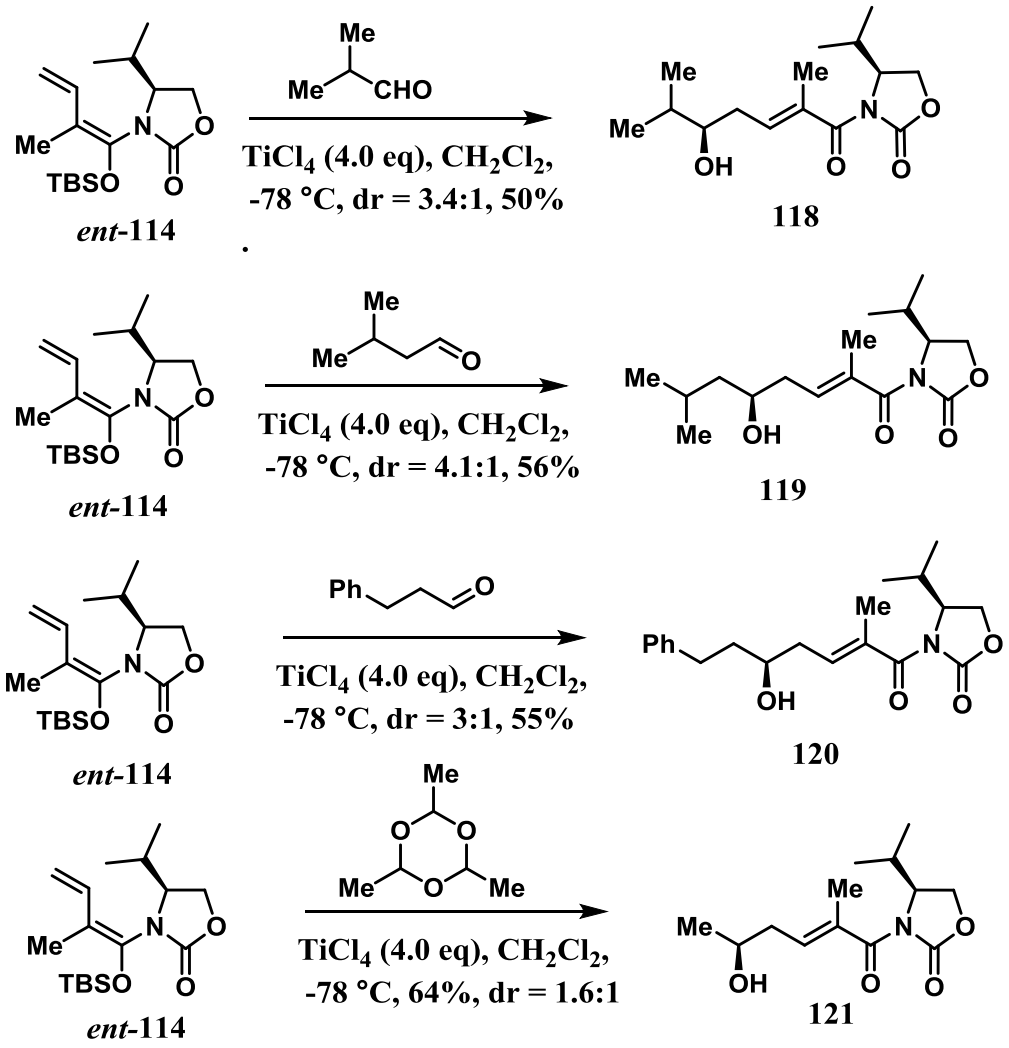
Scheme 4.12: Transition states for *anti*-selective VMARs

In the *syn*-selective VMAR, however, the blue colour of the solution is different from the *anti*-selective VMAR which is red, thereby suggesting that the transition states are different.[66] One argument for the moderate diastereomeric ratio is that in the case of *syn*-selective acetate-propionate type VMARs on *ent*-**114**, which does not possess a terminal methyl group (present in **26** and **T.S. B**) the aldehyde is free to move around and can take

up different positions at the time of reaction, thereby providing a moderate mixture of diastereomers.

This, however, cannot be the entire reason as the *anti*-selective VMAR proceeds with *ent*-**114** in high diastereomeric ratio and yields.

Having found the best conditions for the acetate-propionate type VMARs, the reaction was attempted on other aldehydes (**Scheme 4.13**).

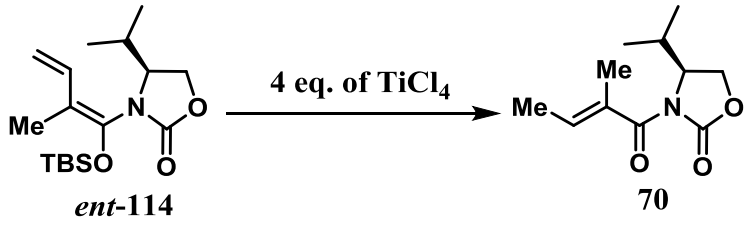


Scheme 4.13: *Syn*-VMAR with other aldehydes

Isobutyraldehyde underwent the *syn*-VMAR smoothly to provide **118** in 3.4:1 ratio at 50% yield while isovaleraldehyde provided its corresponding

syn adduct **119** in a diastereomeric ratio of 4.1:1 at 56% yield (**Scheme 4.13**). Phenylpropanal also worked well to give the alcohol **120** at a ratio of 3:1 in 55% yield. However, attempts to recreate the reaction with paraldehyde, the trimer of acetaldehyde, proved unsatisfactory as the ratio of isomers plunged to 1.6:1. The reaction with paraldehyde is too fast to control, evidenced by the much higher yields, and hence the diastereoselectivity is compromised.

As noted above, the *syn*-VMAR gives moderate yields using silyldienol ether *ent*-**114**. The major side reaction is the protonation of the silyl ether *ent*-**114** to give the α,β-unsaturated imide **70** in the presence of higher equivalents of $TiCl_4$ (**Scheme 4.14**). Any attempt to minimize the formation of the by-product by the use of MS 4Å was thwarted by the decrease in diastereomeric ratio (entry 7, Table 8).



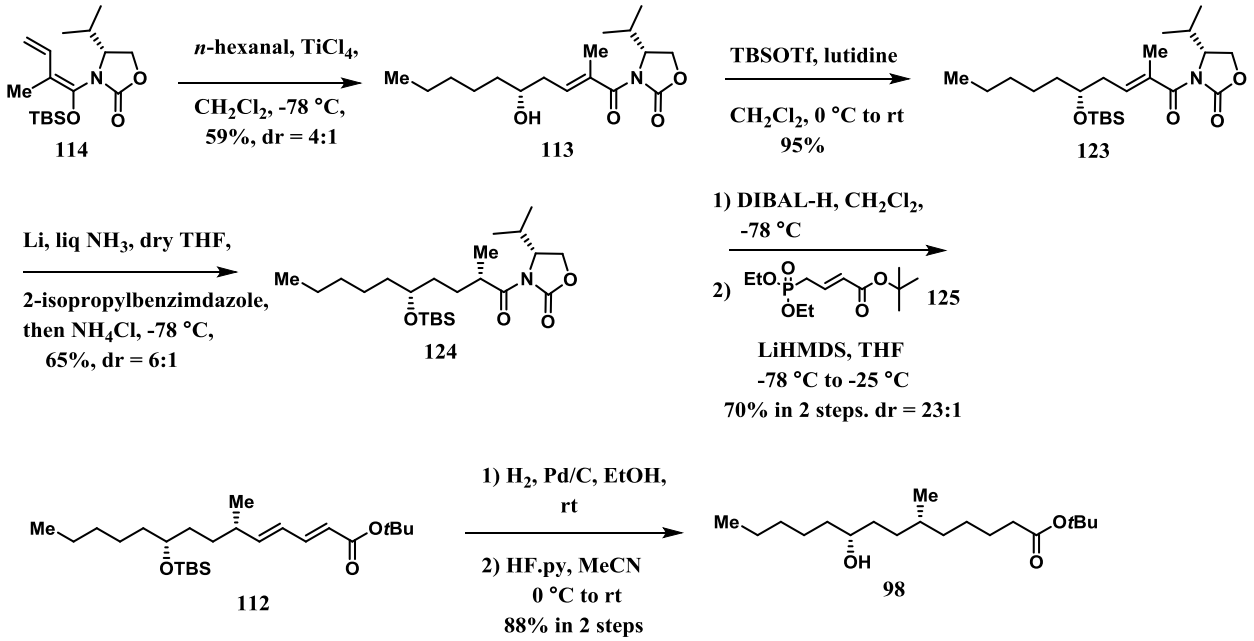
ent-114 70

Scheme 4.14: Formation of major by-product 70

When vinylketene silyl *N,O*-acetal *ent*-**114** was treated with unsaturated aldehydes such as benzaldehyde, *p*-bromobenzaldehyde and crotonaldehyde, the rate of protonation of *ent*-**114** to give **70** seemed faster than the rate of the VMAR. Thus, the reaction failed to give *syn*-adducts with unsaturated aldehydes. Instead, quantitative amount of **70** can be recovered from the reaction mixture.

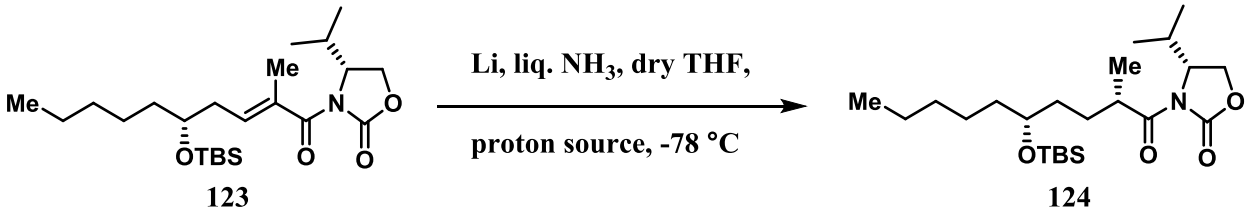
Having optimized the *syn*-VMAR reaction conditions, the total synthesis of PF1163B was embarked upon (**Scheme 4.15**).

4.5 Synthesis of non-peptide fragment **98**



Scheme 4.15. Synthesis of non-peptide fragment 98

The *syn*-VMAR on **114** gave the aldol adduct **113** at a 4:1 ratio of inseparable diastereomers which were protected with TBS and the isomers separated to isolate **123** (**Scheme 4.15**). The Birch reduction on **123** was standardized with the use of different proton sources (Table 9). Ammonium chloride failed to give any diastereoselectivity (entry 1, Table 9), while 2-methylbenzimidazole gave only moderate selectivity (entry 2, Table 9). 2-isopropylbenzimidazole furnished the epimers in a 6:1 ratio (entry 3, Table 9), but on increasing the size of the substituent on benzimidazole beyond isopropyl, to *tert*-butyl, provided only a 2:1 ratio of diastereomers with reduced yield (entry 4, Table 9).



Scheme 4.16: Optimisation of Birch conditions on 123

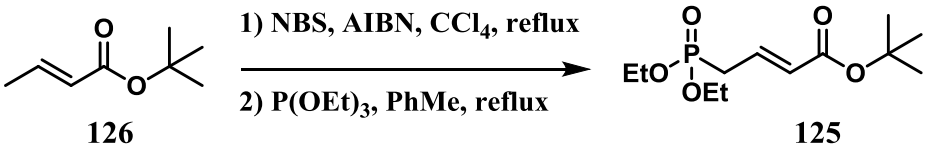
Entry	Proton source	Diastereomeric ratio[a]	Yield (%)
1	ammonium chloride	1.1:1	41
2	2-methylbenzimidazole	4.4:1	64
3	2-isopropylbenzimidazole	6:1	65
4	2-*tert*-butylbenzimidazole	2:1	57

[a] Ratio of isolated products

Table 9. Protonation in the Birch reduction of 123

DIBAl-H reduction of **124** and concomitant Horner-Wadsworth-Emmons reaction on the resulting aldehyde yielded the α,β,γ,δ-unsaturated ester **112** in 70% in 2 steps at 23:1 ratio of diastereomers (**Scheme 4.15**). The diene was hydrogenated, and the TBS group removed to furnish the alcohol **98**. The spectroscopic data of the alcohol **98** is in accordance with those of reported literature.[58]

The phosphonate **125** was prepared easily from commercially available *tert*-butyl crotonate **126** by allylic bromination with NBS and AIBN in CCl_4 followed by an Arbuzov reaction (**Scheme 4.17**).



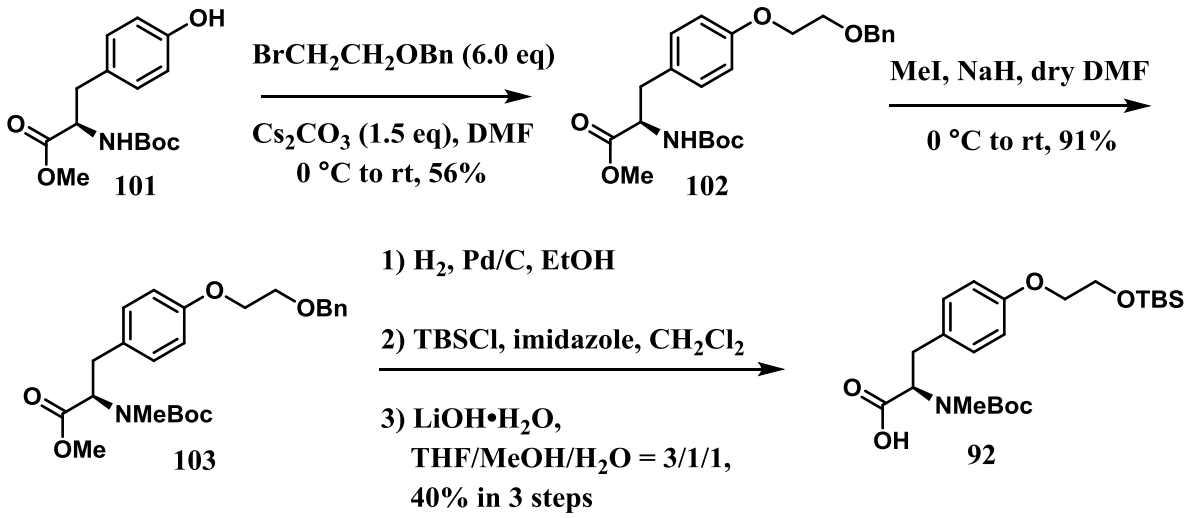
126 125

Scheme 4.17: Synthesis of phosphonate 125

It is noteworthy that the Horner-Wadsworth-Emmons reaction often led to substantial epimerization of the α-carbon and would depend on the temperature. When the ylide was generated at 0 °C, and the aldehyde was added at the same temperature the ratio of the diastereomers was realized to be 4:1. Generation of the ylide and addition of the aldehyde at -78 °C, led to a 20:1 ratio of diasteromers but low yield (25%). A balance seemed to be found when the ylide was generated at -78 °C, then allowed to stir at -25 °C. After returning the reaction to lower temperature (-78 °C), the aldehyde was introduced and the resulting mixture was again stirred at -25 °C. This led to the least amount of epimerization of the C-2 position (dr = 23:1) and the α,β,γ,δ-unsaturated ester **112** was obtained in 70% yield from imide **124**.

4.6 Synthesis of acid fragment **92**

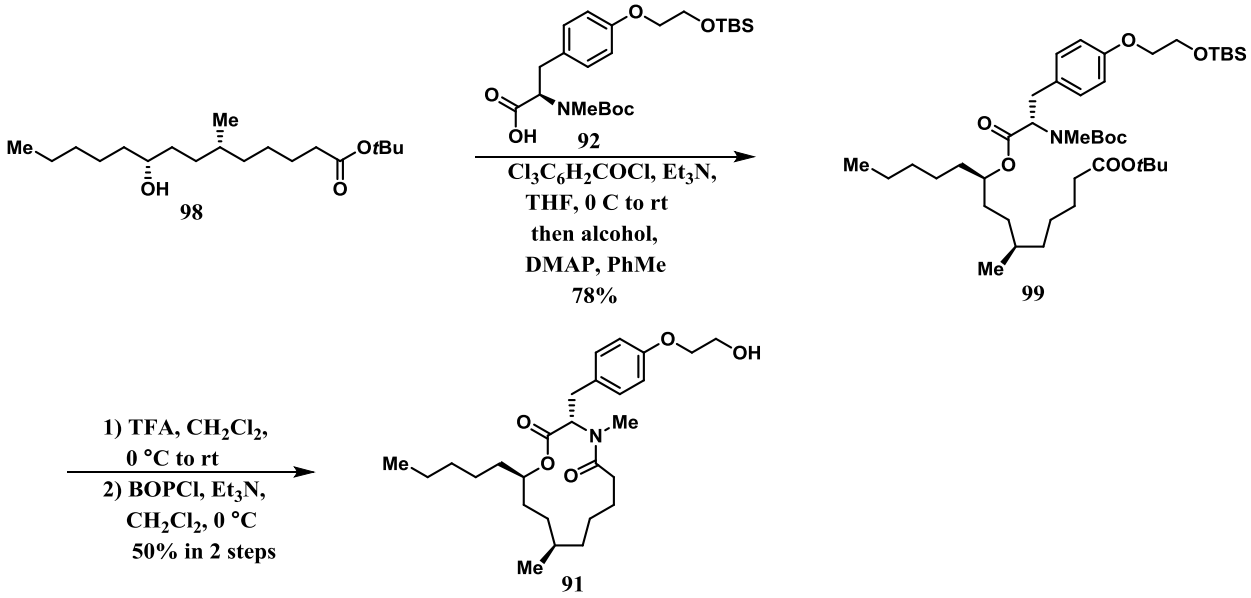
With the alcohol **98** in hand, the amino acid fragment **92** was synthesized (**Scheme 4.18**). As stated earlier, in order to circumvent the epimerization, alkylation of *N*-Boc-L-tyrosine methyl ester **101** with 2-bromo-*O*-benzyl-ethanol was carried out to give **102** in 56% yield. *N*-Methylation under reported conditions seemed difficult to drive to completion and the best conditions were the use of dry DMF to furnish **103** in 91% yield. Hydrogenation to remove the benzyl group, followed by TBS protection in CH_2Cl_2 and hydrolysis provided the amino acid fragment **92** in 40% in 3 steps.



Scheme 4.18: Synthesis of amino acid fragment 92

4.7 Completion of total synthesis of PF1163B

The acid **92** and the alcohol **98** were coupled using Yamaguchi esterification to give **99** in 78% yield (**Scheme 4.19**). Removal of Boc and *tert*-butyl ester with TFA was followed by an intramolecular amidation with BOPCl and TEA in CH_2Cl_2 to provide PF1163B (**91**) in 50% yield over 2 steps.



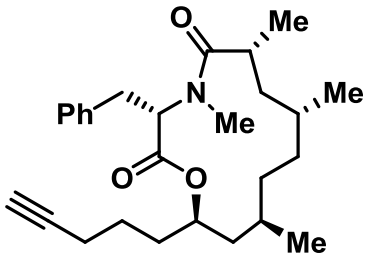
Scheme 4.19: Completion of total synthesis of PF1163B

Thus, PF1163B was synthesized successfully in 10 steps from the dienolate **114**. The major transformations included a stereoselective vinylogous Mukaiyama aldol reaction and a stereoselective Birch reduction with 2-isopropylbenzimidazole as the proton source. Synthesis of the amino acid fragment was also achieved with minimum racemization. Successful fusion of the non-peptide fragment **98** and the amino acid derivative **53** led to the formation of the ester **99**. A BOPCl mediated lactamization afforded the target molecule PF1163B (**91**).

Chapter 5. Synthetic studies on Spongidepsin

5.1 Introduction

Spongidepsin (**127, Fig. 4**) is a macrolide isolated from the Vanatu islands, Australia by Riccio *et al*.[63] It shows cytotoxic and anti-proliferative activities against J774.A1, WEHI-164 and HEK-293 cancer cell lines.[63] Spongidepsin is a 13-membered cyclodepsipeptide comprising 5 stereogenic carbons. [63] The absolute configuration of 4 chiral carbons was determined by spectroscopic analysis, while the *N*-methylphenylalanine moiety with L configuration was assigned by spectroscopic studies and degradation.[63] The unique structure and bioactivity make spongidepsin an attractive target for total synthesis.



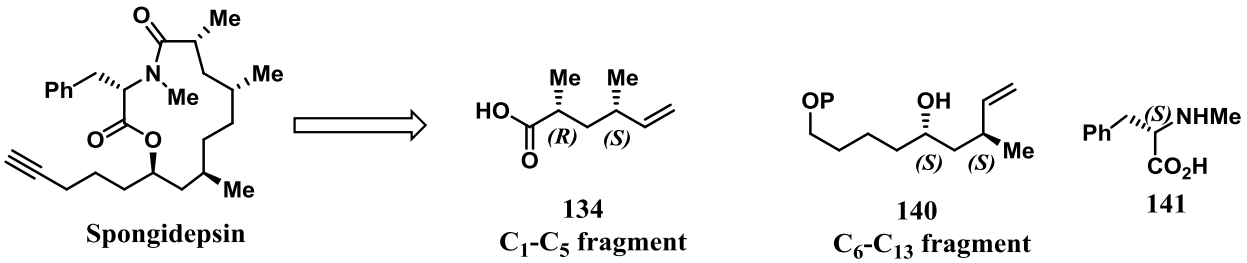
127

Fig. 4: Structure of spongidepsin (127)

5.2 First total synthesis of spongidepsin by Cossy *et al.*

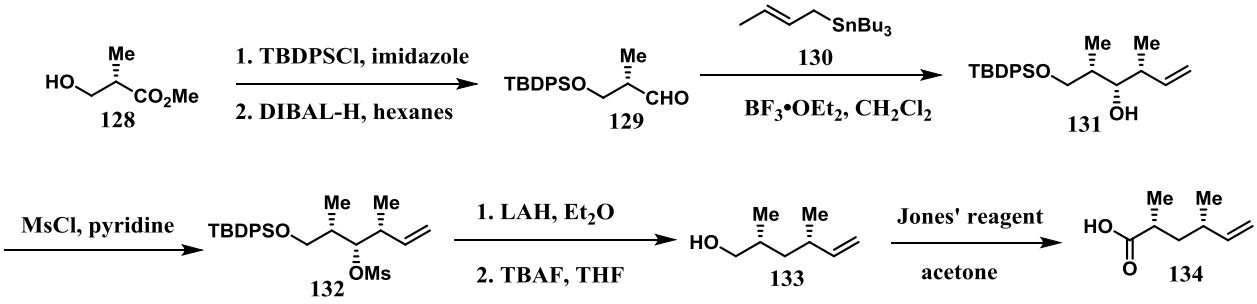
Spongidepsin was first isolated in 2001.[63] Since then, several groups have synthesized the target molecule and many others have achieved formal syntheses.[64-66] One of the first total synthesis of spongidepsin was reported in 2006 by Cossy *et al*.[67] They achieved the synthesis in 14 steps with an overall yield of 13%.

The retrosynthetic analysis applied by the Cossy group has been closely followed by several other groups since (**Scheme 5.1**).



Scheme 5.1: Retrosynthesis of spongidepsin used by Cossy *et al.*

The C_1-C_5 fragment was synthesized using commercially available Roche ester (**Scheme 5.2**).

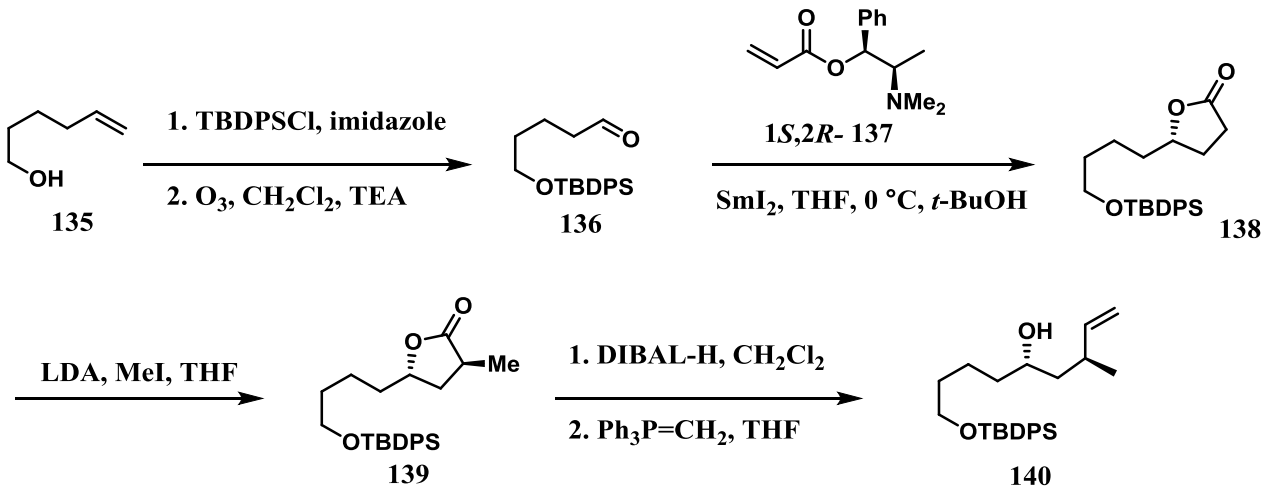


Scheme 5.2: Synthesis of C_1-C_5 fragment

Silyl protection of Roche ester **128** followed by DIBAL reduction gave the aldehyde **129**. Crotylation with but-2-enyl-(tri-*n*-butyl)stannane **130** produced the *syn-syn* adduct **131**.[68] Removal of the hydroxyl group by mesylation and hydride reduction followed by TBAF reaction provided the primary alcohol **133**. Oxidation of the primary alcohol to carboxylic acid **134** was done by Jones' reagent in acetone.

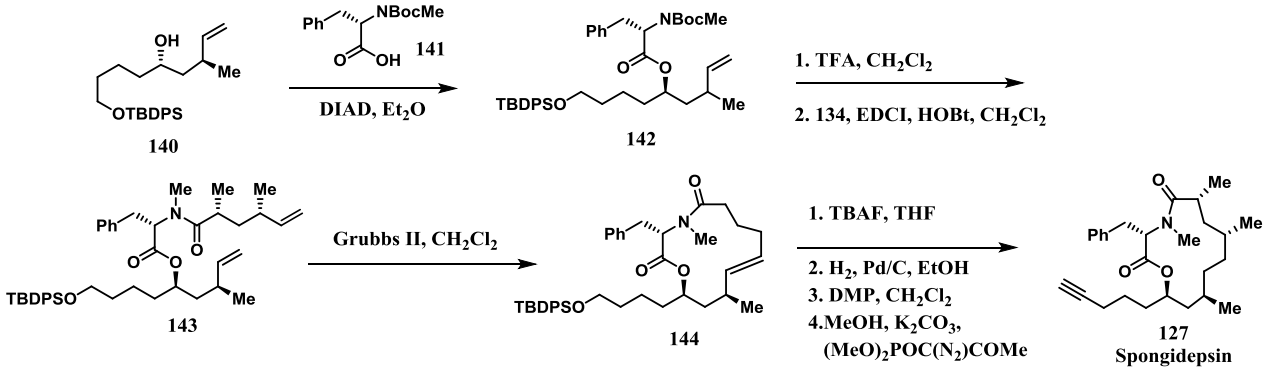
The C_6-C_{13} fragment involved the protection of 5-hexenol with a silyl group and the ozonolysis of the olefin to give the aldehyde **136** (**Scheme 5.3**). A crucial reaction then was the transformation of the aldehyde **136** to **138** using a stereoselective conjugate addition reaction of a ketyl radical to an optically active α,β-unsaturated ester **137** mediated by samarium diiodide which then underwent intramolecular cyclisation to give the lactone **138**.[69] Methylation of the lactone provided **139** in a diastereomeric ratio of 5.7:1. DIBAL

reduction of the lactone to give the lactol was followed by Wittig reaction to furnish the terminal alkene **140**.



Scheme 5.3: Synthesis of C_6-C_{13} fragment

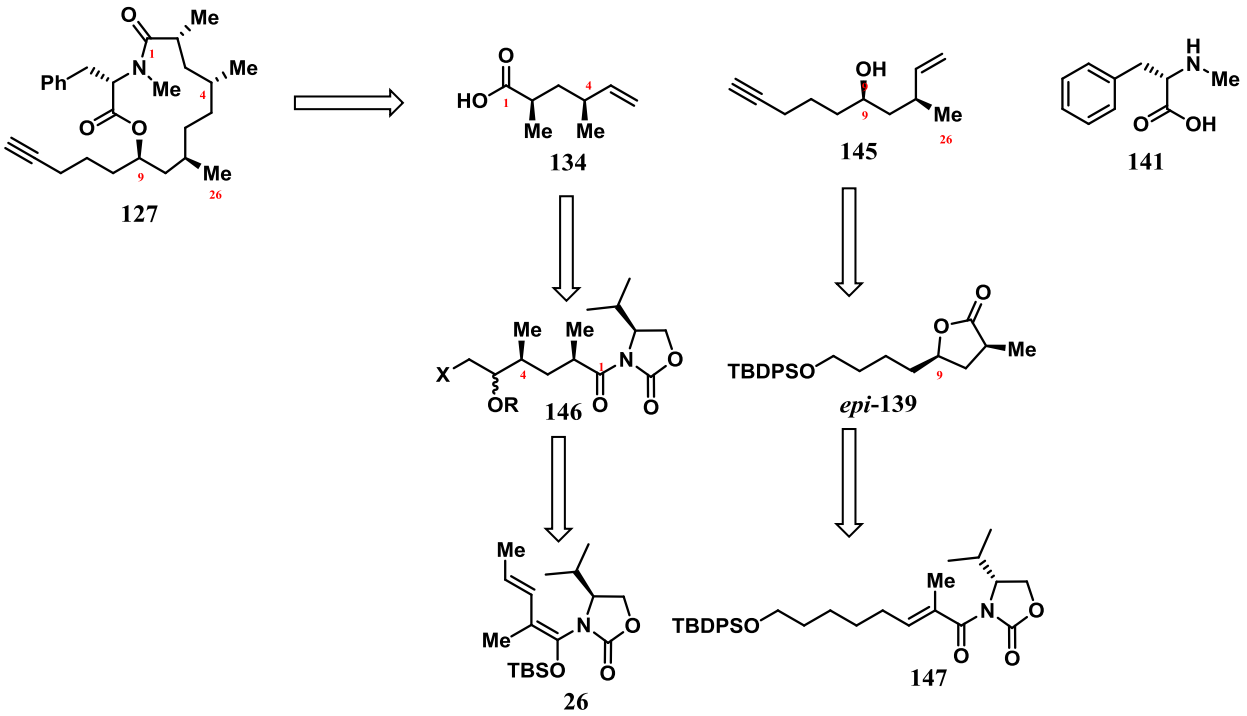
The synthesis was completed with the Mitsunobu reaction of alcohol **140** with the carboxylic acid **141** to give **142** (**Scheme 5.4**). Removal of the Boc group and condensation with **134** in the presence of EDCI gave **143**. Ring closing metathesis with Grubbs-II catalyst provided **144** which was subsequently transformed to spongidepsin (**127**) in 4 steps.



Scheme 5.4: Completion of total synthesis of spongidepsin

5.3 Retrosynthesis of spongidepsin

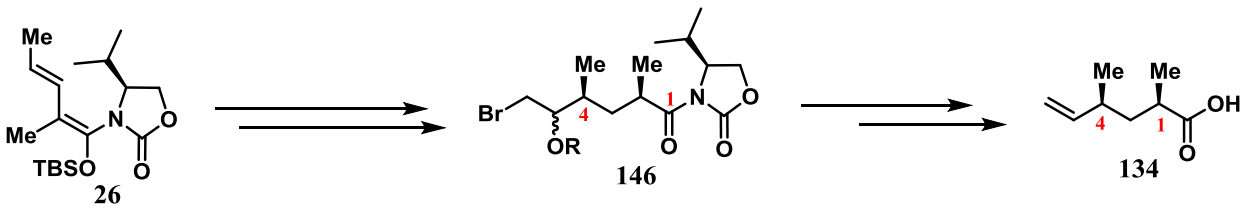
This dissertation focuses on the concise synthesis of segments **134** and **145** (**Scheme 5.5**).



Scheme 5.5: Retrosynthetic approach to Spongidepsin

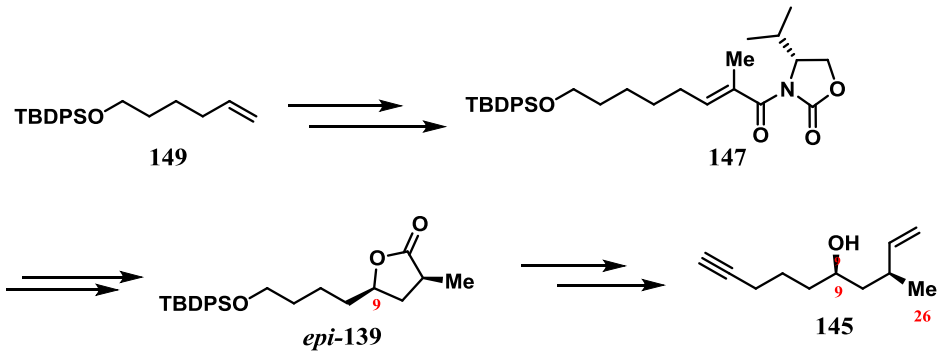
5.4 Synthesis of acid fragment **134**

It was realized that **134** could be synthesized from the imide **146** by a Birch reduction followed by a metal reduction and hydrolysis (**Scheme 5.6**).



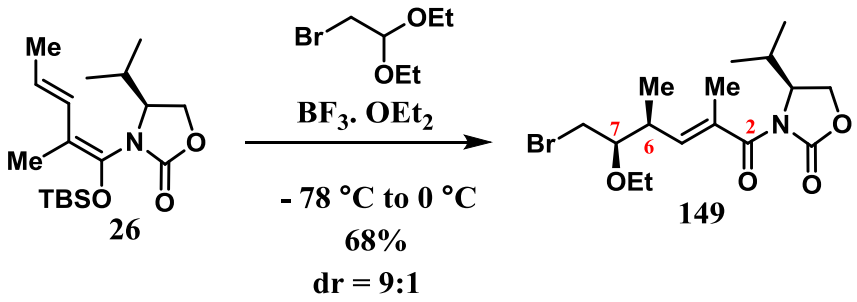
Scheme 5.6: Synthetic plan for acid 134

The alcohol **145** could be achieved from the lactone *epi*-**139**, which in turn might be derived from the imide **147** by an analogous method to that of formal synthesis of seragamide A (**Scheme 5.7**).



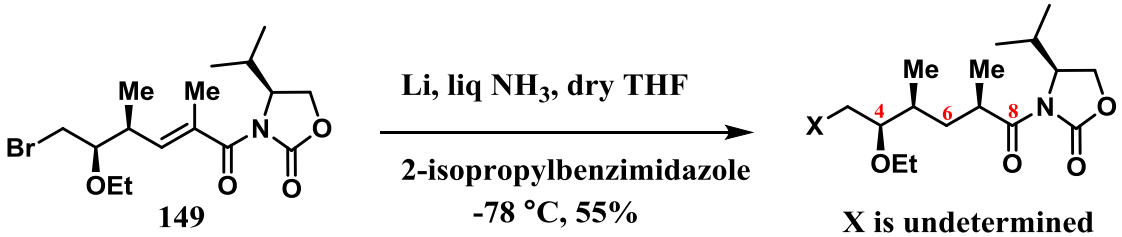
Scheme 5.7: Synthetic plan towards 145

Thus, the synthesis of the acid fragment **134** was embarked upon (**Scheme 5.8**). Vinylketene silyl *N,O*-acetal **26** was treated with commercially available bromoacetaldehyde diethyl acetal in presence of BF_3•OEt_2.[70] The reaction was temperature sensitive and did not proceed at -78 °C. However, raising it to room temperature led to the formation of four diastereomers. The best condition was found to be the addition of the Lewis acid to the acetal at -78 °C and then after the addition of the vinylketene silyl *N,O*-acetal **26**, raising of the temperature to 0 °C. The reaction took 10 hours to complete to furnish **149** as a mixture of 2 diastereomers in 9:1 ratio at 68% yield. It was determined that the 2 diastereomers were brought about by the change in stereochemistry of the ether linkage at C-7 and not by isomerism at C-6 position.



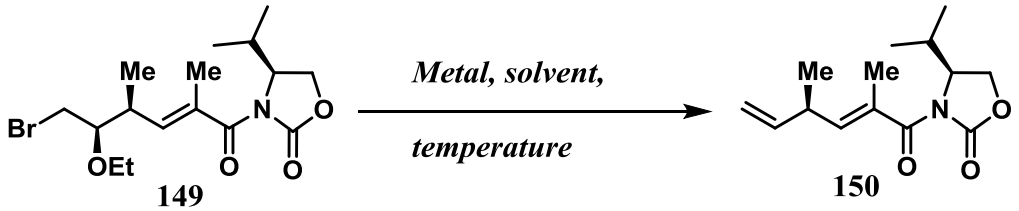
Scheme 5.8: *Syn*-VMAR with acetal

The stereoselective protonation of **149** proved to be challenging. On addition of lithium to **149**, a dark blue solution appeared which was then quenched with 2-isopropylbenzimidazole (**Scheme 5.9**). This led to a single spot on the TLC, which on purification and analysis remained undetermined. The reaction showed no improvement on using a high equivalent of sodium either.



Scheme 5.9: Birch reduction on 149

While an sp^3-sp^3 coupling is difficult to perform, especially at such low temperatures, there is a possibility that it may be case in the Birch reduction. Removal of the bromine moiety and the ether linkage by a reductive elimination before the stereoselective Birch reduction would be better to synthesize **134**. Thus, reductive eliminations were carried out under different conditions (**Scheme 5.10**, Table 10).



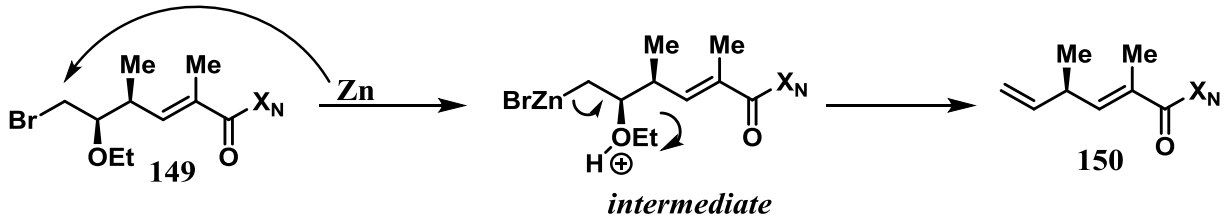
Scheme 5.10: Trials for reductive elimination

Entry	Metal	Solvent	Additive	Temperature	Notes
1	Mg	dry Et_2O	1,2-dibromoethane	50 °C	No reaction, **149** unconsumed.
2	Mg	dry THF	Iodine	50 °C	No reaction, **149** unconsumed
3	Zn powder	EtOH	-	reflux	No reaction, **149** unconsumed
4	Zn dust	EtOH	-	reflux	No reaction, **149** unconsumed
5	Zn dust	EtOH	NH_4Cl	78 °C	Multiple spots on TLC
6	Zn dust	EtOH	NH_4Cl	50 °C	**150** formed in 88%

Table 10. Trials for reductive elimination

When compound **149** was treated with Mg in either diethyl ether or THF, the reaction failed to progress with additives such as 1,2-dibromoethane or iodine **(**entries 1 and 2, Table 10**)**. The reductive cleavage of α-bromoethers is reported in cyclic systems such as carbohydrates in the presence of zinc and refluxing ethanol, but the trials using zinc powder failed to produce **150** (entry 3, Table 10). It was then thought that using a smaller particle size of zinc may propel the reaction forward. Disappointingly however, the reaction did not seem to proceed in zinc dust either in refluxing ethanol (entry 4, Table 10). NH_4Cl is sometimes used as an additive in the presence of Zn dust to cleave cyclic iodoethers.[71] When NH_4Cl (10 eq.) was used along with Zn dust (15 eq.) in EtOH at 78 °C, the starting material disappeared on the TLC (entry 5, Table 10). However, it was ensued by multiple spots and it was impossible to separate. Lowering the temperature to 50 °C resulted in the

complete consumption of **149** to furnish **150** in 88% yield (entry 6, Table 10). The plausible mechanism for the elimination is shown below (**Scheme 5.11**).

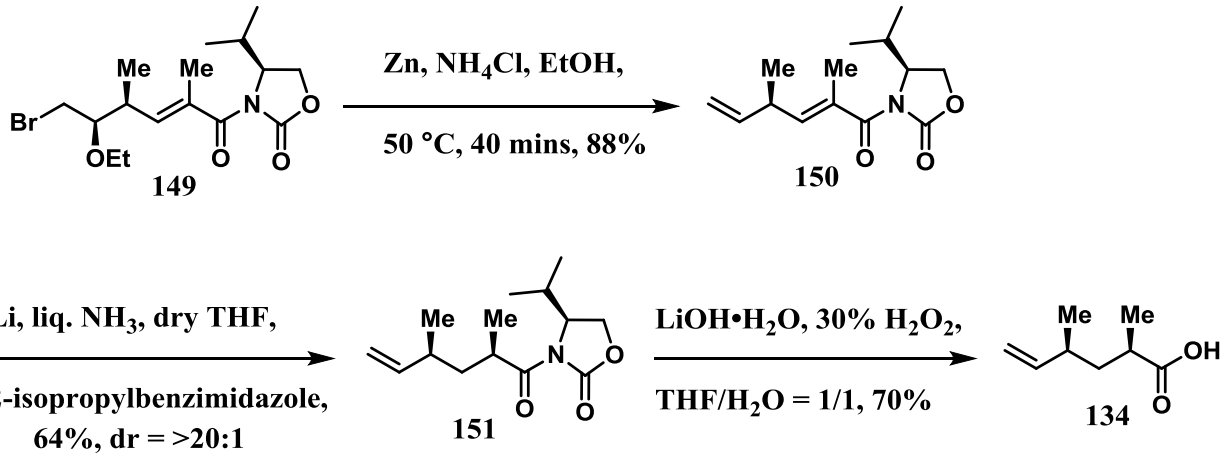


Scheme 5.11: Mechanism of reductive elimination

The zinc inserts itself between the carbon-bromine bond by donating two electrons. Subsequent protonation of the ether by NH_4Cl, and elimination results in the formation of **150**.

It was noteworthy that the reaction seemed to work very fast under Zn dust (15 equivalents) and NH_4Cl (10 equivalents), finishing in 40 minutes. Despite being a heterogeneous mixture in ethanol, the reaction was sensitive to the equivalents of zinc and ammonium chloride used. For example, when 5 equivalents and 3 equivalents of zinc and ammonium chloride were used respectively, the reaction did not finish as some starting material remained even after 15 hours at 50 °C.

Stereoselective protonation of compound **150** under Birch conditions provided **151** in 64% yield at a diastereomeric ratio of >20:1 with 2-isopropylbenzimidazole (**Scheme 5.12**). Removal of the oxazolidinone ring with $LiOH•H_2O$ and 30% H_2O_2 provided the required acid **134** in 70% yield.

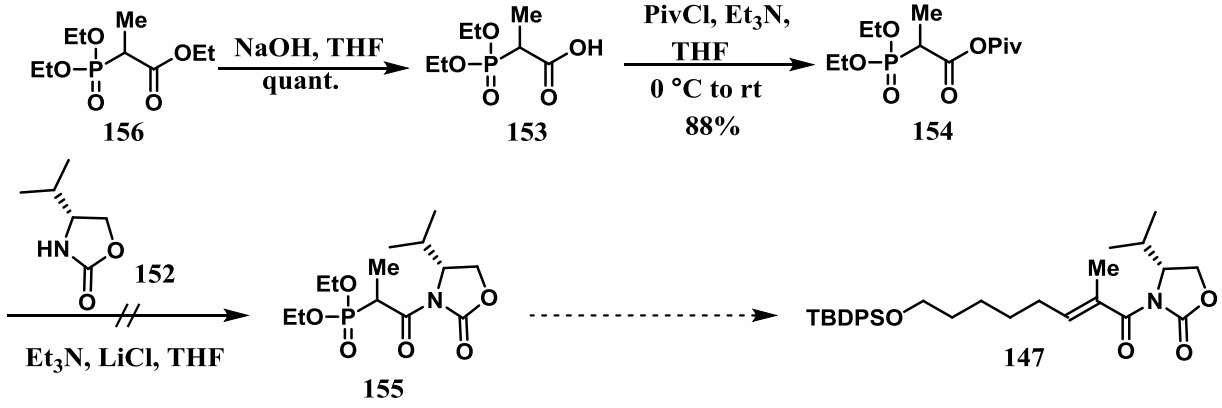


Scheme 5.12: Synthesis of carboxylic acid 134

Thus, the acid fragment **134** was synthesized in 4 steps from **26**.

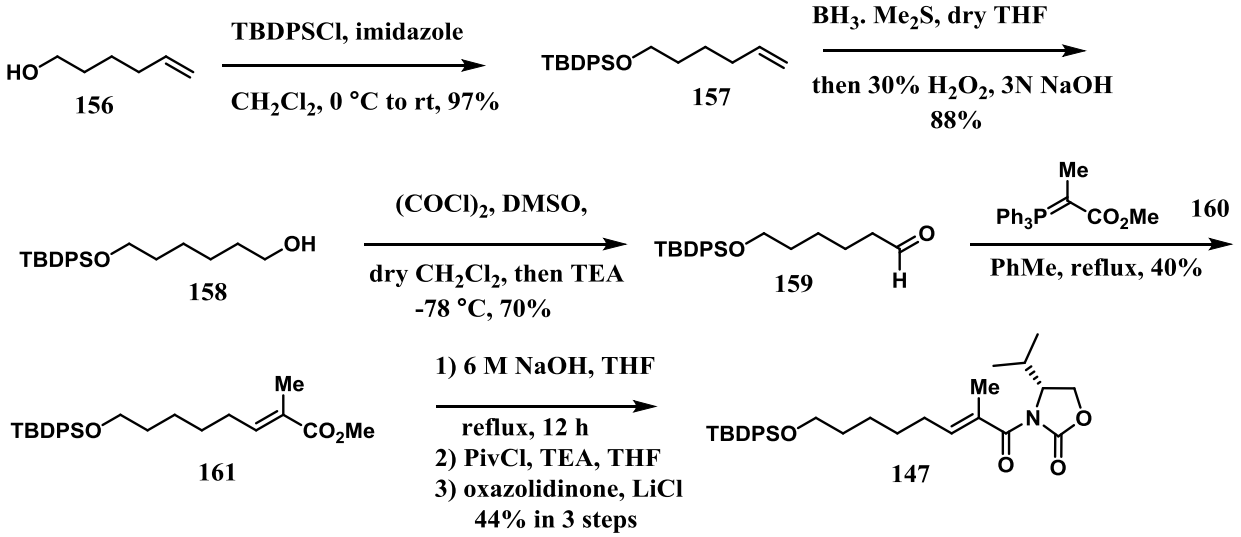
5.5 Synthetic studies on lactone *epi*-**139**

For the synthesis of the lactone *epi*-**139**, it was considered at first to synthesize the imide **147** via the phosphonate **155** by the condensation of oxazolidinone **152** with a phosphonic acid **153** (**Scheme 5.13**). However, efforts to synthesize the pivalate **154** were thwarted as it refused to react with the oxazolidinone **152** to furnish **155**.



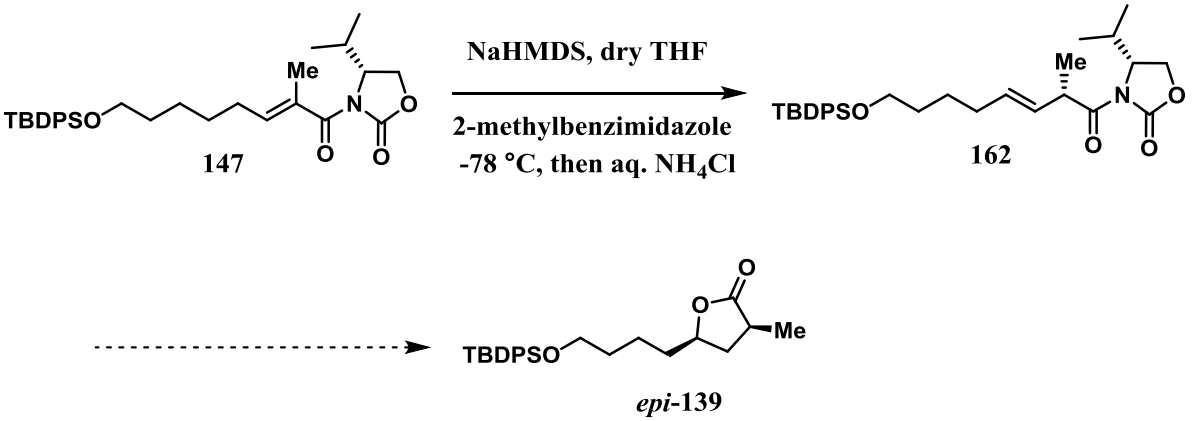
Scheme 5.13: Attempt to synthesize 155

The synthetic plan was then changed (**Scheme 5.14**). It was decided to first do the Horner-Wadsworth-Emmons reaction to give **161** followed by hydrolysis. The α,β-unsaturated acid could then be converted to the imide **147**.



Scheme 5.14: Synthesis of intermediate compound 147

The isomerization of the olefin proceeded smoothly to afford 70% of **162** in a >20:1 ratio (**Scheme 5.15**). The β,γ-unsaturated imide **162** would be converted to the known lactone *epi*-**139**.



Scheme 5.15: Attempt at synthesis of lactone *epi*-139

Chapter 6: Conclusion

In conclusion, this thesis describes the synthesis of reduced propionates using 2-isopropyl and 2-methylbenzimidazoles as bulky proton sources.

In Chapter 1, a general introduction on the syntheses of reduced propionates and deoxypropionates has been provided.

In Chapter 2, synthesis of deoxypropionates using the Birch reduction with 2-isopropylbenzimidazole as the proton source has been disclosed. The reaction was then used for a facile synthesis of the sex pheromone of *Macrocentrus grandii* which is a natural enemy of the European corn borer *Ostrinia nubilialis*.

In Chapter 3, an isomerization reaction has been developed where an α,β-unsaturated imide was isomerized to the β,γ-unsaturated imide stereoselectively using 2-methylbenzimidazole. The isomerization reaction was then used to develop a formal synthesis of seragamide A and its congeners.

In Chapter 4, a total synthesis of PF1163B has been achieved. PF1163B inhibits ergosterol biosynthesis and has an IC_{50} value of 34 ng/mL. For the purpose of the total synthesis, a *syn*-selective VMAR reaction was developed. The reaction, along with the stereoselective protonation with 2-isopropylbenzimidazole under Birch conditions provided the total synthesis of PF1163B in 10 steps.

In Chapter 5, a synthetic study on spongidepsin has been discussed. Spongidepsin has shown IC_{50} values for various cancer cell lines such as J774.A1, WEHI-164, HEK-293. Synthesis of C1-C6 segment has been achieved in four steps. The stereogenic center at the C4 position and the terminal olefin were synthesized by a vinylogous Mukaiyama aldol reaction followed by Zn-mediated reductive elimination of the bromo and ether groups. The Birch reduction with 2-isopropylbenzimidazole provided the

stereogenic center at C2 position. These procedures gave a concise synthesis of chiral 2,4- dimethyl-5-hexenoic acid.

The reactions and the synthetic routes developed in this thesis may find usage elsewhere for the development of variety of synthetically challenging natural products and for the synthesis of polyketides and polypropionates.

Chapter 7: Experimental Procedures

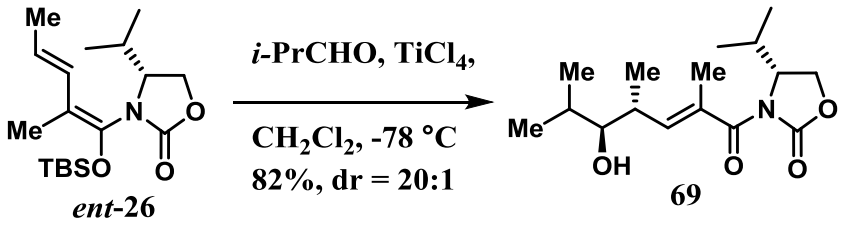
General methods:

^{1}H NMR spectra were recorded at 400 MHz using JEOL ECS 400 instrument. Coupling constants (*J*) have been reported in Hz. ^{13}C NMR spectra were recorded at 100 MHz JEOL ECS instrument. Chemical shifts (δ) are mentioned in parts per million (ppm) and referenced to the residual solvent peak. Melting points (mp) have been determined by using Yanako MP-S3 instrument. FT-IR spectra were collected using JEOL JIR-WINSPEC 50. HRMS and MS were measured using JEOL JMS-SX102A and JEOL JMS-GCMateII. Optical rotations were obtained with JASCO P-2200. All reactions were monitored by analytical thin layer chromatography which was performed on 0.25 mm E. Merck silica gel plates ($60F_{254}$) using UV light as the visualizing agent, an ethanol solution of *p*-anisaldehyde and an aqueous solution of potassium permanganate and heat as the developing agent. Flash and column chromatography were performed using Kanto Kagaku Ltd. Silica gel (60N neutral, particle size 0.040-0.063 mm) and Fuji Silysia Chemical Ltd. Silica gel (BW-820MH, particle size 6nm) respectively.

Materials:

Unless otherwise noted, all reactions were carried out under argon atmosphere with freshly distilled dry solvents. Dichloromethane was distilled from phosphorous pentoxide. DMF was distilled under reduced pressure with molecular sieves. THF was distilled from lithium aluminium hydride.

(i) Synthesis of SexPheromone of Macrocentrus Grandii



Compound 69

To a solution of *i*-PrCHO (0.27 mL, 2.95 mmol) in dichloromethane (3.7 mL) was added $TiCl_4$ (0.16 mL, 1.47 mmoles) and *ent*-**26** (500 mg, 1.47 mmol) as a solution in dichloromethane (15 mL) at -78 °C. After stirring for 28 hours, the reaction was quenched with pyridine (0.5 mL, 5.88 mmol). Then, a saturated aq. Rochelle salt (10 mL) and $NaHCO_3$ (10 mL) were added. The reaction was then allowed to attain room temperature and stirred vigorously until the white slurry was completely dissolved. The resulting solution was then extracted with ethyl acetate (5 ml × 3). The combined organic layer was concentrated and purified by silica gel chromatography (*n*- hexane: EtOAc = 3:1) to yield **69** (360 mg, 1.21 mmoles, 82%) as a light yellow oil.

R_f value: 0.36 (*n*-hexane: EtOAc = 3:1)

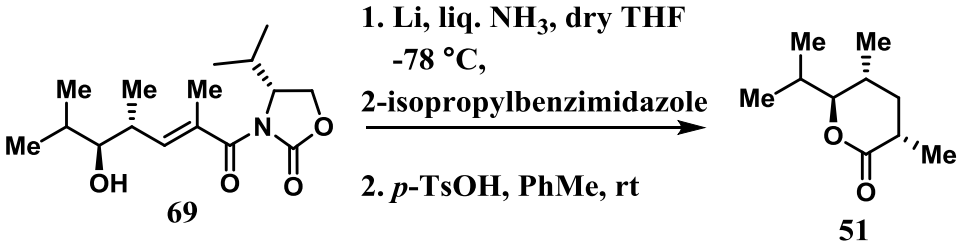
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.82 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.56 (ddd, *J* = 9.0, 5.5, 4.0 Hz, 1H), 4.34 (dd, *J* = 9.0, 9.0 Hz, 1H), 4.18 (dd, *J* = 9.0, 5.5, 1H), 3.18 (ddd, *J* = 8.0, 3.5, 3.0, 1H), 2.95 (OH, d, *J* = 3.0 Hz), 2.71 (ddq, *J* = 10.5, 8.0, 7.0 Hz, 1H), 2.35 (qqd, *J* = 7.0, 7.0, 4.0 Hz, 1H), 1.95 (d, *J* = 1.5, 3H), 1.86 (qqd, *J* = 7.0, 7.0, 3.5 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 7.0, 3H), 0.94 (d, *J* = 7.0, 3H), 0.93 (d, *J* = 7.0 Hz, 3 H), 0.92 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.7, 154.5, 142.4, 131.0, 79.1, 63.4, 58.1, 37.4, 29.1, 28.4, 20.6, 17.9, 15.8, 15.2, 14.7, 13.9

$[\alpha]_D^{25}$ = - 15.9 (*c* 1.02, $CHCl_3$)

IR (KBr): 3532, 2963, 2932, 2876, 1765, 1691, 1390, 1366, 1301, 1208, 997, 776 cm^{-1}

HRMS (ESI): *m/z* $[M+Na]^+$calcd for $C_{16}H_{27}O_4NNa$: 320.1830; found: 320.1832



Compound 51

To a solution of the alcohol **69** (40 mg, 0.134 mmoles) in dry THF (1.6 mL) at -78 °C was added liq. NH_3 and lithium (2.80 mg, 0.402 mmoles). The resulting dark blue solution was allowed to stir for 6 minutes at that temperature and a solution of 2-isopropylbenzimidazole (107.3 mg, 0.67 mmoles) in dry THF (3.0 mL) was cannulated to the above mixture followed by the addition of NH_4Cl (50.2 mg, 0.938 mmoles). The mixture was then allowed to warm to room temperature to remove NH_3, concentrated and extracted with EtOAc three times (2.0 mL × 3). The combined organic layer was then concentrated and used in the next reaction without further purification.

The crude mixture was dissolved in PhMe (1.6 mL) and TsOH• H_2O was added. The resulting mixture was stirred at room temperature for 6 hours and quenched with aq. $NaHCO_3$ (1.0 mL). The organic layer was extracted three times with EtOAc (1.5 mL × 3), dried over Na_2SO_4, concentrated and

purified by silica gel chromatography (*n*-hexane: EtOAc = 7:1) to furnish the lactone **51** (17.2 mg, 0.101 mmoles) as a colourless liquid in 70% yield in 2 steps.

R_f value: 0.67 (*n*-hexane: EtOAc = 3:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.48 (dqd, *J* = 13.0, 7.0, 6.0 Hz, 1H), 1.99-1.81 (m, 3H), 1.40-1.29 (m, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 90.9, 37.7, 36.3, 31.2, 29.4, 19.9, 17.3, 14.2

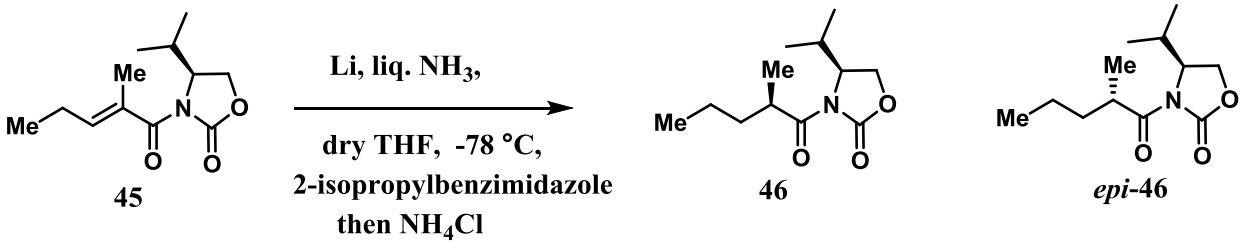
$[\alpha]_D^{25}$ = - 32.1 (*c* 1.08, $CHCl_3$)

IR (KBr): 2966, 2935, 2877, 1727, 1462, 1380, 1261, 1216, 1192, 1121, 996, 795 cm^{-1}

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{10}H_{18}O_2Na$: 193.1199; found 193.1201.

.

(ii) Formal Synthesis of seragamide A



Compound 46

To a solution of compound **45** (30.0 mg, 0.133 mmoles) in dry THF (1.2 mL) and liq. NH_3 at -78 °C, was added lithium (2.8 mg, 0.4 mmoles) in small pieces. The dark blue solution was stirred at the same temperature for 5 minutes. Then, a colourless solution of 2-isopropylbenzimidazole (106.6 mg, 0.67 mmoles) in dry THF (1.5 mL) was added followed by NH_4Cl (42.7 mg, 0.80 mmoles). The reaction was allowed to stir at room temperature thereafter to allow the complete evaporation of liq. NH_3. The reaction was then concentrated, diluted with H_2O (1.0 mL), and the aqueous layer extracted three times with EtOAc (1.5 mL x 3). The combined organic layer was then dried over Na_2SO_4, concentrated and purified by silica gel chromatography to give **46** (17.6 mg, 0.077 mmoles, 69%) as a colourless oil and *epi*-**46** (3.4 mg, 0.014 mmoles, 13%)

R_f value: 0.39 (*n*-hexane: EtOAc= 4:1)

Compound 46:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.46 (ddd, J = 8.9, 3.9, 3.5 Hz), 4.26 (dd, J = 8.9, 8.1 Hz), 4.19 (dd, J = 8.9, 3.0 Hz, 1H), 3.84-3.73 (m, 1H), 2.34 (dqd, J = 7.0, 7.0, 4.0 Hz, 1H), 1.79-1.64 (m, 1H), 1.45-1.29 (m, 3H), 1.13 (d, J = 6.5 Hz, 3H), 0.92 (t, J = 7.0 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.3, 153.7, 63.0, 58.4, 37.2, 36.2, 28.4, 20.2, 17.9, 16.4, 14.6, 14.0.

$[\alpha]_D^{29}$ = + 64.0 (*c* 1.70, $CHCl_3$)

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{12}H_{21}O_3NNa$: 250.1414; found: 250.1415

IR (ATR): 2961, 1773, 1696, 1384, 1199, 990, 757 cm^{-1}

Compound *epi*-46

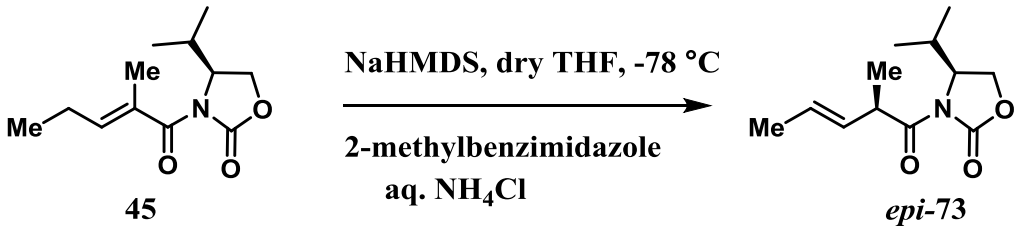
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 4.44 (ddd, *J* = 9.0, 3.9, 3.1 Hz, 1H), 4.25 (dd, *J* = 9.1, 8.1 Hz, 1H), 4.19 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.79-3.69 (m, 1H), 2.34 (qdd, *J* = 7.0, 7.0, 4.0 Hz, 1H), 1.74-1.64 (m, 1H), 1.40-1.25 (m, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.3, 153.7, 63.1, 58.4, 37.4, 35.2, 28.4, 20.4, 17.9, 17.8, 14.6, 14.1

$[\alpha]_D^{28}$ = + 93.3 (*c* 1.85, $CHCl_3$)

IR (ATR): 2961, 1773, 1696, 1384, 1198, 990, 774 cm^{-1}

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{12}H_{21}O_3NNa$: 250.1414; found: 250.1411.



Compound *epi*-73

To a solution of compound **45** (20 mg, 0.088 mmoles) in dry THF (0.80 ml) at -78 °C, was added a freshly prepared solution of NaHMDS 1.0 M in THF (97.6 µL, 0.098 mmoles) and stirred at the same temperature for 2 hours. A solution of 2-methylbenzimidazole (34.9 mg, 0.264 mmoles) in dry THF (0.50 mL) was then added. The reaction mixture was allowed to warm to room temperature and aq. NH_4Cl (1.0 mL) was added and the mixture extracted three times with EtOAc (2.0 mL × 3). The combined organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel chromatography several times (Toluene: EtOAc = 98:2) to give compound *epi*-**73** (16.9 mg, 0.075 mmoles, 85%) as a colourless oil.

R_f value: 0.30 (*n*-hexane: EtOAc= 4:1)

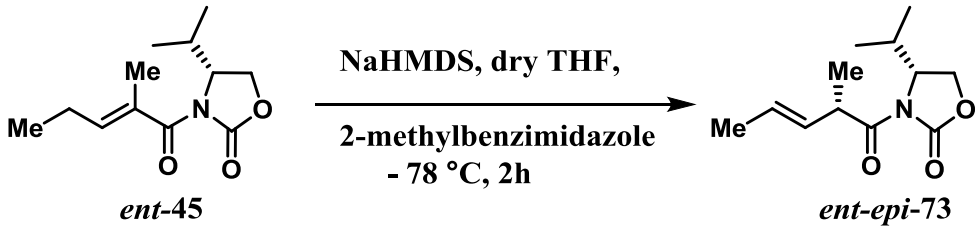
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.69 (dq, *J* = 15.1, 6.5 Hz, 1H), 5.56 (ddq, *J* = 15.1, 7.0, 1.5 Hz, 1H), 4.51-4.42 (m, 2H), 4.26 (dd, *J* = 9.0, 8.5 Hz, 1H), 4.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.32 (qqd, *J* = 7.0, 7.0, 4.0 Hz), 1.67 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 7.0 Hz), 0.84 (d, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 153.6, 129.9, 127.8, 63.0, 58.2, 40.4, 28.2, 17.9, 17.9, 16.8, 14.5

$[\alpha]_D^{28}$ = + 30.7 (*c* 1.41, $CHCl_3$)

IR (ATR): 2966, 1772, 1697, 1365, 1299, 1199, 968, 772 cm^{-1}

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{12}H_{19}O_3NNa$: 248.1257; found: 248.1256.



ent-45 *ent-epi*-73

Compound *ent-epi*-73

To a solution of compound *ent*-**45** (25 mg, 0.111 mmoles) in dry THF (1.0ml) at -78 °C, was added a freshly prepared solution of NaHMDS 1.0 M in THF (122.0 µL, 0.122 mmoles) and stirred at the same temperature for 2 hours. A solution of 2-methylbenzimidazole (44.0 mg, 0.333 mmoles) in dry THF (0.80 mL) was then added. The reaction mixture was allowed to warm to room temperature and an aq. NH_4Cl (1.5 mL) was added and the mixture extracted three times with EtOAc (2.0 mL × 3). The combined organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel chromatography several times (Toluene: EtOAc = 98:2) to give compound *ent-epi*-**73** (21.2 mg, 0.094 mmoles, 86%) as a colourless oil.

R_f value: 0.30 (*n*-hexane: EtOAc= 4:1)

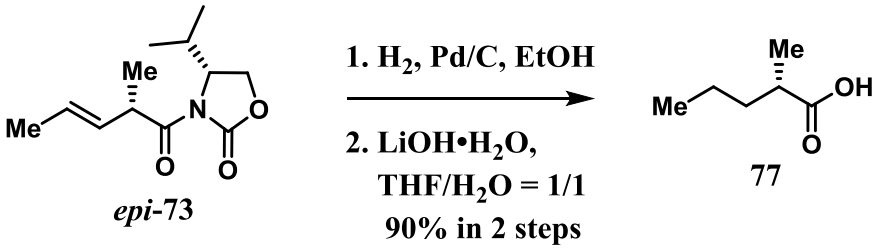
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.69 (dq, *J* = 15.1, 6.5 Hz, 1H), 5.56 (ddq, *J* = 15.1, 7.0, 1.5 Hz, 1H), 4.51-4.42 (m, 2H), 4.26 (dd, *J* = 9.0, 8.5 Hz, 1H), 4.19 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.32 (qqd, *J* = 7.0, 7.0, 4.0 Hz), 1.67 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.89 (d, *J* = 7.0 Hz), 0.84 (d, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 153.6, 129.9, 127.8, 63.0, 58.2, 40.4, 28.2, 17.9, 17.9, 16.8, 14.5

$[\alpha]_D^{28}$ = - 28.0 (*c* 1.30, $CHCl_3$)

IR (ATR): 2966, 1772, 1697, 1365, 1299, 1199, 968, 772 cm^{-1}

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{12}H_{19}O_3NNa$: 248.1257; found: 248.1257.



epi-73 77

Compound 77

To a solution of *ent-epi*-**73** (50 mg, 0.220 mmoles) in EtOH (2 mL) was added 10% Pd/C (5 mg, 10 mol%) and stirred at room temperature for 3 hours under hydrogen atmosphere. The reaction was then filtered through a cake of celite, and the filtrate was concentrated to give *ent*-**46** as a colourless oil. Without further purification, crude *ent*-**46** was dissolved in THF/H_2O (2 mL, 1:1 v/v) and LiOH•H_2O (27.7 mg, 0.660 mmoles) and 30% H_2O_2 (0.15 mL, 0.660 mmoles) were added and the reaction was stirred at room temperature for 4 hours. The reaction was then quenched with 2 M HCl till pH 3. The organic layer was extracted three times with EtOAc (3 × 2.0 mL), dried over Na_2SO_4, concentrated and purified by silica gel chromatography to yield **77** (23.0 mg, 0.198 mmoles, 90%) as a colourless oil. The spectroscopic data of **77** are in accordance with the literature value.[1]

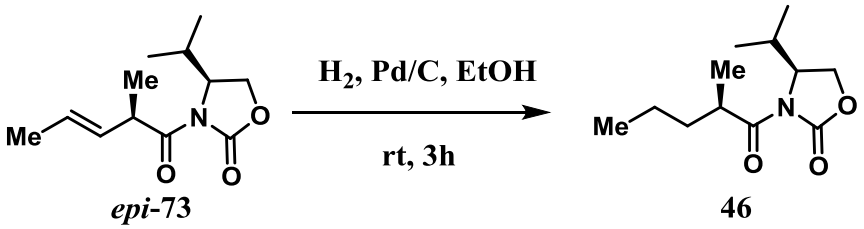
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.54-2.44 (m, 1H), 1.72-1.63 (m, 1H), 1.47-1.31 (m, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 183.4, 39.1, 35.6, 20.3, 16.8, 13.9

$[\alpha]_D^{26}$ = + 17.4 (*c* 1.45, $CHCl_3$)

IR (ATR): 2961, 1702, 1244, 933 cm^{-1}

HRMS (ESI) : *m/z* $[M-H]^+$ calcd for $C_{10}H_{18}O_2$: 115.0765; found 115.0767



epi-73 46

Compound 46

To a solution of compound *epi*-**73** (30.0 mg, 0.133 mmoles) in EtOH (1.2 mL) was added Pd/C (2.8 mg, 10 mol%) and stirred at room temperature for 3 hours. The reaction mixture was then filtered, concentrated and purified by silica gel chromatography to give **46** (30.1 mg, 0.077 mmoles, 99%) as a colourless oil.

R_f value: 0.39 (*n*-hexane: EtOAc= 4:1)

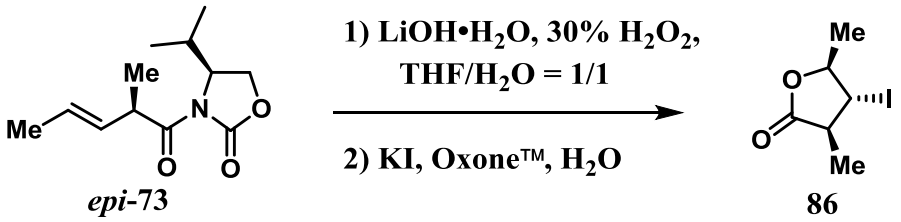
^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.46 (ddd, *J* = 8.9, 3.9, 3.5 Hz), 4.26 (dd, *J* = 8.9, 8.1 Hz), 4.19 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.84-3.73 (m, 1H), 2.34 (dqd, *J* = 7.0, 7.0, 4.0 Hz, 1H), 1.79-1.64 (m, 1H), 1.45-1.29 (m, 3H), 1.13 (d, *J* = 6.5 Hz, 3H), 0.92 (t, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.3, 153.7, 63.0, 58.4, 37.2, 36.2, 28.4, 20.2, 17.9, 16.4, 14.6, 14.0.

$[\alpha]_D^{29}$ = + 64.0 (*c* 1.70, $CHCl_3$)

HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{12}H_{21}O_3NNa$: 250.1414; found: 250.1415

IR (ATR): 2961, 1773, 1696, 1384, 1199, 990, 757 cm^{-1}



epi-73 **86**

Compound 86

To a solution of compound *epi*-**73** (30 mg, 0.133 mmoles) in THF/H_2O (1.2 mL 1:1 v/v) was added LiOH•H_2O (11.2 mg, 0.266 mmoles) and 30% H_2O_2 (27.9 μL, 0.266 mmoles). The reaction was allowed to stir at room temperature for 2 hours. The reaction was then extracted twice with EtOAc (2.0 mL × 2) and the combined aqueous layer was treated with 1 M HCl until pH 3. The resulting solution was then again extracted with $CHCl_3$ and the combined organic layer was dried over Na_2SO_4, and concentrated in vacuo. The resulting acid was used in the next reaction without further purification.

To the crude acid in H_2O (1.2 mL) was added Oxone™ (163.5 mg, 0.532 mmoles) and KI (44.2 mg, 0.266 mmoles). The mixture was then stirred at room temperature for 2 hours. The reaction was quenched with aq. $Na_2S_2O_3$ (2.0 mL) and extracted with EtOAc twice (4.0 mL × 2). The combined organic layer was then dried over Na_2SO_4, concentrated in vacuo and purified by silica gel chromatography (*n*-hexane: EtOAc = 10:1) to give the iodolactone **86** (16.0 mg, 0.066 mmoles, 50% in 2 steps) as a colourless liquid.

R_f value: 0.67 (*n*-hexane: EtOAc = 4:1)

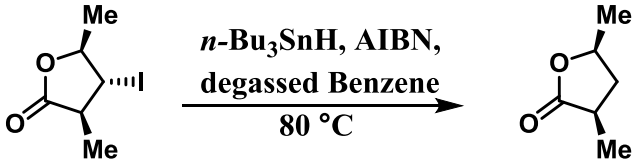
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.63 (dq, *J* = 10.0, 6.5 Hz, 1H), 3.56 (dd, *J* = 12.0, 10.0 Hz, 1H), 2.81 (dq, *J* = 12.0, 7.0 Hz, 1H), 1.50 (d, *J* = 6.5 Hz, 3H), 1.33 (d, *J* = 7.0 Hz, 3H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.2, 82.2, 47.0, 26.7, 17.4, 12.4

$[\alpha]_D^{29}$ = - 23.6 (*c* 1.32, $CHCl_3$)

IR (ATR): 2973, 1762, 1382, 1338, 1170, 1036, 950, 896, 746 cm^{-1}

HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_6H_9O_2INa$: 262.9539; found: 262.9540



86 **87**

Compound 87

To a solution of the iodolactone **86** (40 mg, 0.166 mmoles) in degassed benzene (1.60 mL) was added TBTH (49.2 µL, 0.183 mmoles) and AIBN (5.5 mg, 0.032 mmoles). The mixture was then heated at 80 °C for 12 hours. The solution was then cooled, concentrated and purified by silica gel chromatography (*n*-hexane: EtOAc = 5:1) to give the lactone **87** (15.4 mg, 0.135 mmoles, 82%) as a colourless oil.

R_f value: 0.36 (*n*-hexane: EtOAc = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.47 (dqd, *J* = 10.5, 6.5, 5.9 Hz, 1H), 2.68 (ddq, *J* = 12.0, 8.5, 7.0 Hz, 1H), 2.51 (ddd, *J* = 12.9, 8.5, 5.1 Hz, 1H), 1.54-1.44 (m, 1H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.27 (d, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.6, 74.9, 39.1, 36.4, 20.9, 15.1

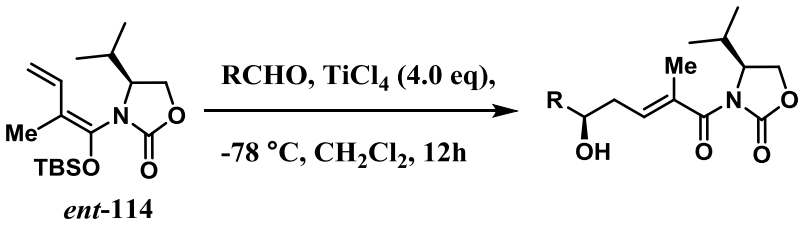
$[\alpha]_D^{30}$ = - 4.2 (*c* 0.21, $CHCl_3$)

IR (KBr) : 2922, 2357, 2341, 1770, 1759, 1375, 1246, 1056 cm^{-1}

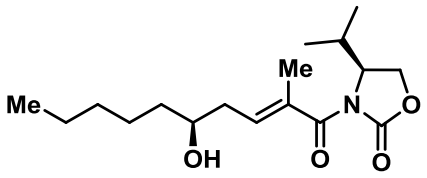
HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_6H_{10}O_2Na$: 137.0573; found 137.0573.

(iii) Total Synthesis of PF1163B

General Procedure for *syn*-VMAR



To a solution of the appropriate aldehyde (0.614 mmoles) and *ent*-**114** (0.307 mmoles) in CH_2Cl_2 (2.0 mL) at -78 °C was added $TiCl_4$ (1.228 mmoles) at one time. The resulting deep blue solution was stirred for 12 hours and quenched with pyridine (4.912 mmoles). An aq. solution of $NaHCO_3$ (2.0 mL) was then added and the resulting mixture was raised to room temperature. The mixture was filtered through celite and the filtrate was extracted three times with $CHCl_3$ (3 × 2.0 mL). The combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography to provide *syn*-VMAR adduct as an inseparable mixture of diastereomers.



Compound *ent*-113

Yield: 50.7 mg, 0.163 mmoles, 53%, dr = 4.1:1.

^{1}H NMR (400 MHz, $CDCl_3$): 6.06-5.97 (1H, m), 4.52 (1H, ddd, *J* = 9.1, 5.0, 5.0 Hz), 4.33 (1H, dd, *J* = 9.1, 8.9 Hz), 4.21 (1H, dd, *J* = 9.1, 5.0 Hz), 3.77-

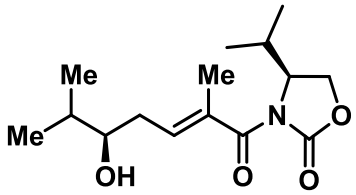
3.68 (1H, m), 2.45-2.23 (3H, m), 1.95 (3H, s), 1.87-1.23 (15H, m), 0.96-0.85 (9H, m)

^{13}C NMR (100 MHz, $CDCl_3$): 171.5, 154.3, 135.3, 133.0, 70.6, 63.4, 58.1, 36.8, 36.7, 31.8, 28.3, 25.6, 22.6, 17.8, 15.1, 14.1, 13.7

$[\alpha]_D^{27}$ = +` 43.7 (*c* 1.10, $CHCl_3$)

IR (ATR): 3369, 2958, 2930, 1770, 1686, 1298, 1204, 754 cm^{-1}

HRMS-ESI: *m/z* [M + Na]$^+$calcd for $C_{17}H_{29}O_4NNa$: 334.1989; found 334.1988.



Compound 118

Yield: 43.6 mg, 0.152 mmoles, 50%, dr = 3.4:1.

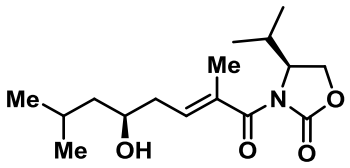
^{1}H NMR (400 MHz, $CDCl_3$): 6.07-5.99 (1H, m), 4.52 (1H, ddd, *J* = 9.0, 5.0, 5.0 Hz), 4.32 (1H, dd, *J* = 9.0, 8.5 Hz), 4.20 (1H, dd, *J* = 9.0, 5.0 Hz), 3.50-3.41 (1H, m), 2.58 (1H, brd, *J* = 3.9 Hz), 2.44-2.25 (3H, m), 1.95 (3H, d, *J* = 1.0 Hz), 1.79-1.67 (1H, m), 0.98 (3H, d, *J* = 7.0 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 0.93 (3H, d, *J* = 7.0 Hz), 0.91 (3H, d, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): 171.6, 154.0, 134.6, 133.4, 75.8, 63.5, 58.3, 33.5, 33.1, 28.6, 18.7, 18.1, 17.8, 14.9, 13.9

$[\alpha]_D^{26}$ = + 71.4 (*c* 1.22, $CHCl_3$)

IR (KBr): 3530, 2962, 2875, 1774, 1686, 1365, 1294, 1209, 1053, 774, 754 cm^{-1}

HRMS-ESI: *m/z* [M + Na]$^{+}$calcd for $C_{15}H_{25}O_4NNa$: 306.1676; found 306.1671.



Compound 119

Yield: 51.2 mg, 0.172 mmoles, 56%, dr = 4.2:1.

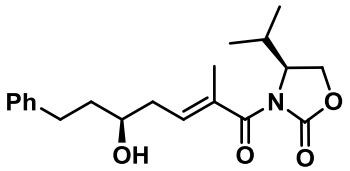
^{1}H NMR (400 MHz, $CDCl_3$): 6.07-5.98 (1H, m), 4.52 (1H, ddd, *J* = 9.1, 5.0, 5.0 Hz), 4.32 (1H, dd, *J* = 9.1, 8.9 Hz), 4.21 (1H, dd, *J* = 9.1, 5.0 Hz), 3.86-3.76 (1H, m), 2.61-2.58(0.8 H, m), 2.45-2.22 (3H, m), 1.96 (3H, d, *J* = 1.0 Hz), 1.88-1.76 (1H, m), 1.54-1.46 (1H, m), 1.30-1.21 (1H, m), 0.95-0.89 (12H, m)

^{13}C NMR (100 MHz, $CDCl_3$): 171.6, 154.0, 133.6, 133.6, 69.1, 63.5, 58.3, 46.1, 36.7, 28.3, 24.7, 23.3, 22.1, 17.9, 14.9, 14.0.

$[\alpha]_D^{17}$ = + 7.2 (*c* 1.02, $CHCl_3$)

IR (KBr): 3507, 2955, 2870, 1789, 1689, 1367, 1298, 1217, 777, 753 cm^{-1}

HRMS-ESI: *m/z* [M + H]$^{+}$calcd for $C_{16}H_{28}O_4N$: 298.2013; found 298.2008.



Compound 120

Yield: 57.3 mg, 0.165 mmoles, 54%, dr = 3:1.

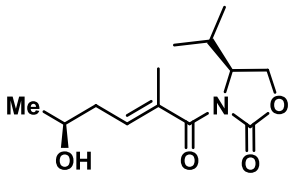
^{1}HNMR (400 MHz, $CDCl_3$): 7.31-7.17 (5H, m), 6.03-5.94 (1H, m), 4.52 (1H, ddd, *J* = 9.0, 4.9, 4.9 Hz), 4.33 (1H, dd, *J* = 9.1, 9.0 Hz), 4.21 (1H, dd, *J* = 9.0, 4.9 Hz), 2.90-2.80 (1H, m), 2.79-2.65 (2H, m), 2.47-2.30 (3H, m), 1.95 (3H, d, *J* = 1.1 Hz), 1.94-1.76 (3H, m), 0.93 (3H, d, *J* = 7.0 Hz), 0.91 (3H, d, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): 171.5, 154.1, 142.1, 134.8, 133.9, 133.1, 128.5, 128.3, 125.7, 70.2, 63.5, 58.2, 38.6, 36.2, 32.1, 28.2, 17.8, 14.9, 14.0

$[\alpha]_D^{17}$ = + 8.7 (*c* 0.96, $CHCl_3$)

IR (ATR): 3522, 2964, 1771, 1681, 1296, 1204, 747, 699 cm^{-1}

HRMS-ESI: *m/z* $[M + H]^+$calcd for $C_{20}H_{28}O_4N$: 346.2013; found 346.2008



Compound 121

Yield: 50.2 mg, 0.197 mmoles, 64%, dr = 1.6:1.

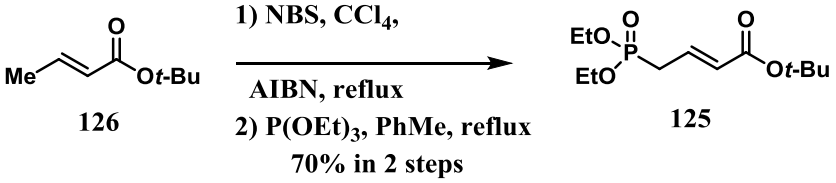
^{1}H NMR (400 MHz, $CDCl_3$): 6.06-5.98 (1H, m), 4.59-4.49 (1H, m), 4.34 (1H (minor isomer), dd, *J* = 9.5, 9.0 Hz), 4.33 (1H (major isomer), dd, *J* = 9.5, 9.0 Hz), 4.23-4.16 (1H, m), 3.99-3.88 (1H, m), 2.81 (brs, 0.36H), 2.61 (0.57H, brs), 2.45-2.24 (3H, m), 1.97-1.93 (3H, m), 1.26 (3H (minor isomer), d, *J* = 7.0 Hz), 1.26 (3H (major isomer), d, *J* = 6.5 Hz) 0.93 (3H, d, *J* = 7.0 Hz), 0.92 (3H (minor isomer), d, *J* = 7.0 Hz), 0.91 (3H (major isomer), d, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): 171.5, 154.2, 154.0, 134.9, 133.5, 133.4, 133.0, 67.1, 66.7, 63.4, 63.4, 58.2, 58.1, 38.3, 37.8, 28.3, 28.2, 22.7, 22.6, 17.8, 15.0, 14.9, 13.9, 13.7

$[\alpha]_D^{17} = +5.8$ (*c* 1.26, $CHCl_3$)

IR (ATR): 3516, 2966, 1771, 1678, 1294, 1202, 752, 729 cm^{-1}

HRMS-ESI: *m/z* $[M + H]^+$calcd for $C_{13}H_{22}O_4N$: 256.1543; found 256.1540.



Compound 125

To a solution of **126** (500.0 mg, 3.516 mmoles) in CCl_4 (20.0 mL), NBS (688.4 mg, 3.868 mmoles) and AIBN (57.7, 0.352 mmoles) was added and the resulting mixture was refluxed for 8 hours. The solution was then filtered, concentrated and the residue taken up in PhMe (20.0 mL) and $P(OEt)_3$ (0.63 mL, 3.70 mmoles) was added. The resulting solution was then refluxed for 26 hours and concentrated. The residue was purified by silica gel chromatography (*n*-hexane: EtOAc = 1/2) to afford **125** (685.0 mg, 2.461 mmoles, 70% in 2 steps) as a colourless oil.

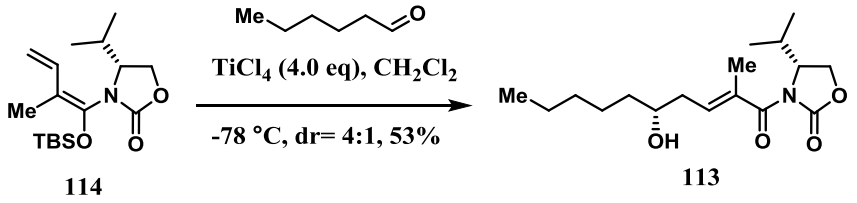
R_f value: 0.76 (100% EtOAc)

^1H NMR (400 MHz, $CDCl_3$) δ = 6.75 (1H, ddd, *J* = 15.5, 6.9, 6.9 Hz), 5.92-5.83 (1H, m), 4.18-4.03 (4H, m), 2.70 (2H, ddd, *J* = 23.0, 8.0, 1.0 Hz), 1.47 (9H, s), 1.33 (3H, t, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.0, 164.9, 136.0, 135.9, 127.7, 127.6, 80.6, 62.3, 62.2, 31.1, 29.7, 28.1, 16.4, 16.3

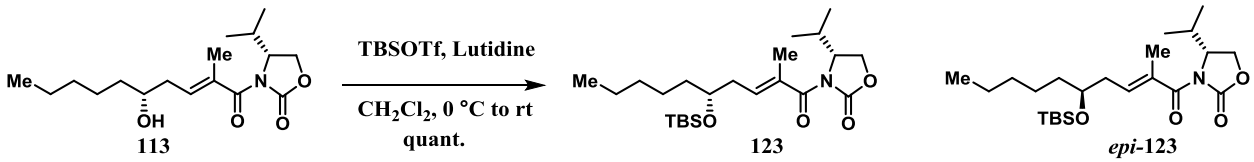
HRMS-ESI: *m/z* $[M + Na]^+$calcd for $C_{12}H_{23}O_5NaP$: 301.1175; found 301.1174

IR (ATR): 2980, 1710, 1652, 1250, 1162, 1019, 961, 843, 731 cm^{-1}



Compound 113

To a solution of *n*-hexanal (75.3 µL, 0.614 mmoles) and **114** (100.0 mg, 0.307 mmoles) in CH_2Cl_2 (2.0 mL) at -78 °C was added $TiCl_4$ (134.6 µL, 1.228 mmoles) at one time. The resulting deep blue solution was stirred for 12 hours and quenched with pyridine (0.40 mL, 4.912 mmoles). An aq. solution of $NaHCO_3$ (2.0 mL) was then added and the reaction was raised to room temperature. The mixture was filtered through celite and the filtrate extracted three times with $CHCl_3$ (3 × 2.0 mL). The combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography to provide **113** (50.7 mg, 0.162 mmoles, 54%) as an inseparable mixture of diastereomers.



Compound 123 and *epi*-123

To a solution of the compound **113** (104.0 mg, 0.333 mmoles) in CH_2Cl_2 (4.0 mL) at 0 °C, was added 2, 6-lutidine (77.1 µL, 0.666 mmoles) and TBSOTf (0.115 mL, 0.500 mmoles) and stirred at room temperature for 20 minutes. After the complete consumption of starting material, the reaction was

quenched with aq. $NaHCO_3$ (3.0 mL). The aqueous layer was extracted twice with CH_2Cl_2 (4.0 mL × 2) and the combined organic layer was concentrated and purified by silica gel column chromatography several times (PhMe: Et_2O = 99:1 to 96:4) to furnish compound **123** (113.0 mg, 0.265 mmoles) and *epi*-**123** (28.8 mg, 0.067 mmoles) in quantitative yield.

R_f value = 0.38 (*n*-hexane: EtOAc = 4:1)

Major isomer (compound **123**):

^{1}H NMR (400 MHz, $CDCl_3$): 6.17 (1H, ddq, *J* = 7.1, 7.1, 1.1 Hz), 4.52 (1H, ddd, *J* = 9.1, 6.0, 5.0 Hz), 4.31 (1H, dd, *J* = 9.1, 8.9 Hz), 4.16 (1H, dd, *J* = 9.1, 5.0 Hz), 3.82-3.74 (1H, m), 2.41-2.29 (3H, m), 1.90 (3H, s), 1.48-1.19 (10H, m), 0.94- 0.85 (18H, m), 0.04 (6H, s)

^{13}C NMR (100 MHz, $CDCl_3$) =.171.8, 153.6, 136.4, 131.7, 71.3, 63.3, 58.2, 37.2, 36.3, 31.9, 28.2, 25.8, 25.0, 22.6, 17.9, 15.0, 14.0, 13.8, -4.5, -4.6

$[\alpha]_D^{24}$ = - 31.9 (*c* 1.05, $CHCl_3$)

HRMS-ESI: *m/z* $[M + Na]^+$calcd for $C_{23}H_{43}O_4NNaSi$: 448.2854; found 448.2856

IR (ATR): 2928, 1785, 1682, 1295, 1202, 1055, 834, 773 cm^{-1}

Minor isomer (compound *epi*-**123**):

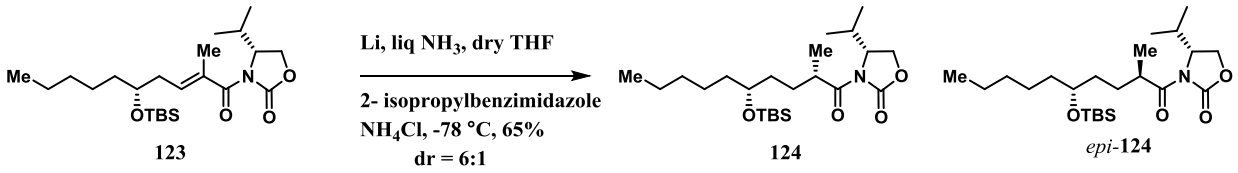
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (1H, ddq, *J* = 7.0, 7.0, 1.5 Hz), 4.51 (1H, ddd, *J* = 9.5, 5.9, 4.5 Hz), 4.30 (1H, dd, *J* = 9.0, 8.9 Hz), 4.17 (1H, dd, *J* = 8.9, 5.1 Hz), 3.81-3.74 (1H, m), 2.40-2.31 (3H, m), 1.91 (3H, d, *J* = 1.5 Hz), 1.50-1.20 (10H, m), 0.92 (3H, d, *J* = 7.0 Hz), 0.89 (3H, d, *J* = 6.9 Hz), 0.87 (9H, s), 0.04 (3H, s), 0.04 (3H, s).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 171.8, 153.5, 136.1, 132.0, 71.3, 63.4, 58.3, 36.3, 31.9, 28.2, 25.8, 25.7, 25.0, 22.6, 17.9, 15.0, 14.0, 13.9, -4.5, -4.6.

$[\alpha]_D^{24}$ = - 39.7 (*c* 1.17, $CHCl_3$)

HRMS-ESI: *m/z* $[M + Na]^+$calcd for $C_{23}H_{43}O_4NNaSi$: 448.2854; found 448.2854

IR (ATR): 2928, 1785, 1682, 1295, 1202, 1055, 834, 773 cm^{-1}



Compound 124 and *epi*-124

To a solution of compound **123** (40.0 mg, 0.093 mmoles) in dry THF (1.6 mL) and liq NH_3 at -78 °C, was added lithium (2.6 mg, 0.372 mmoles) in small portions. After stirring the resulting deep blue solution for about 10 minutes, a solution of 2-isopropylbenzimidazole (74.5 mg, 0.465 mmoles) in dry THF (2.5 mL) was added which was followed by the addition of NH_4Cl (34.8 mg, 0.651 mmoles). The reaction was allowed to warm to room temperature to remove NH_3. The reaction mixture was then concentrated, and the aqueous layer was extracted three times with EtOAc (3.0 mL × 3). The combined organic layer was evaporated and the residue was purified by silica gel column chromatography (*n*-hexane: EtOAc: 100:0 to 94:6) to yield compound **124** (26.1 mg, 0.061 mmoles, 65%) and *epi*-**124** (4.3 mg, 0.010 mmoles, 10.3%) as colourless oils.

Major isomer **124**:

R_f value = 0.23 (*n*-hexane: EtOAc = 10:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.46 (1H, ddd, *J* = 8.5, 3.9, 3.0 Hz), 4.26 (1H, dd, *J* = 9.0, 8.5 Hz), 4.19 (1H, dd, *J* = 9.0, 3.0 Hz), 3.78-3.68 (1H, m), 3.65-3.58 (1H, m), 2.34 (1H, qqd, *J* = 7.0, 7.0, 4.0 Hz), 1.76-1.65 (1H, m),

1.54- 1.18 (13H, m), 1.14 (3H, d, *J* = 7.0 Hz), 0.93-0.85 (18H, m), 0.02 (6H, s)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 153.7, 72.2, 63.0, 58.4, 37.5, 37.2, 32.0, 30.0, 28.4, 25.9, 24.9, 22.6, 18.1, 18.0, 16.4, 14.7, 14.0. -4.7, -4.5

$[\alpha]_D^{23}$ = - 29.2 (*c* 1.17, MeOH)

HRMS-ESI**:** *m/z* [M + Na]$^+$calcd for $C_{23}H_{45}O_4NNaSi$: 450.3010; found 450.3009

IR (ATR): 2929, 1780, 1701, 1385, 1201, 1058, 833, 772 cm^{-1}

Minor isomer epi-**124***:*

R_f value = 0.38 (*n*-hexane: EtOAc = 10:1)

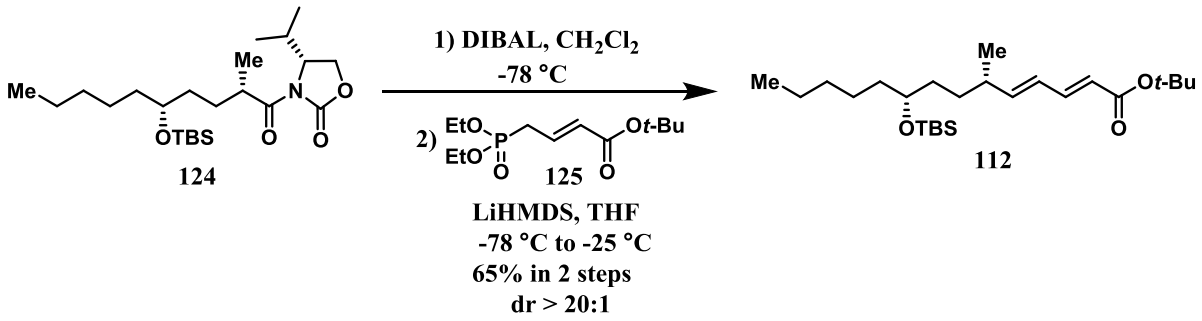
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.45 (1H, ddd, *J* = 8.0, 4.1, 3.0 Hz), 4.25 (1H, dd, *J* = 9.0, 8.0 Hz), 4.20 (1H, dd, *J* = 9.0, 3.0 Hz), 3.74-3.58 (2H, m), 2.35 (1H, qqd, *J* = 7.0, 7.0, 4.0 Hz), 1.82-1.71 (1H, m), 1.49-1.23 (12H, m), 1.21 (3H, d, *J* = 7.0 Hz), 0.92-0.85 (18H, m), 0.03 (6H, s)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 153.6, 72.0, 63.1, 58.4, 37.8, 36.7, 34.4, 32.0, 28.4, 25.9, 25.0, 22.6, 18.1, 17.9, 14.6, 14.1, -4.5, -4.5

$[\alpha]_D^{24}$ = - 60.4 (*c* 1.06, MeOH)

HRMS-ESI**:** *m/z* [M + Na]$^+$calcd for $C_{23}H_{45}O_4NNaSi$: 450.3010; found 450.3007

IR (ATR): 2929, 1780, 1701, 1385, 1201, 1058, 833, 772 cm^{-1}



Compound 112

To a solution of compound **124** (230.2 mg, 0.538 mmoles) in CH_2Cl_2 (4.6 mL) at -78 °C was added diisobutylaluminium hydride (DIBAL) in 1.0 M in hexanes (1.35 mL, 1.345 mmoles). The reaction was stirred for 30 minutes and then MeOH (87.1 μL, 2.152 mmoles) was added and the reaction was allowed to warm to room temperature. To the resulting mixture, aq. Rochelle salt (4.0 mL) was added and vigorously stirred until the white precipitate dissolved. The aqueous layer was then extracted with CH_2Cl_2 three times (3 × 3.0 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated. The resulting aldehyde was used without further purification.

To a solution of the phosphonate **125** (389.3 mg, 1.399 mmoles) in THF (6.0 mL), was added LiHMDS (1.0 M in THF, 1.24 mL, 0.1.237 mmoles) at -78 °C. The reaction was then stirred at -25 °C for 30 minutes. A solution of the crude aldehyde in THF (3.0 mL) was then added to the mixture at -78 °C, following which the reaction temperature was again raised to -25 °C and stirred for 6 hours. The reaction was then quenched with aq. NH_4Cl (5.0 mL), raised to room temperature, and the aqueous layer was extracted three times with EtOAc (3 × 1.0 mL). The combined organic layer was dried over Na_2SO_4, concentrated, and the residue was then purified by silica gel column chromatography (*n*-hexane: PhMe = 95:5 to 80:20) to give the compound **112** (147.9 mg, 0.348 mmoles, 65% in 2 steps) as a colourless oil.

R_f value = 0.43 (*n*-hexane: PhMe = 1:1)

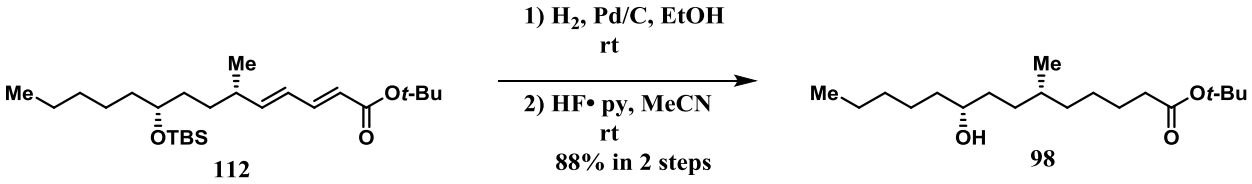
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (1H, dd, *J* = 15.1, 11.0 Hz), 6.10 (1H, dd, *J* = 15.1, 11..0 Hz), 5.95 (1H, dd, *J* = 15.1, 8.0 Hz), 3.63-3.56 (1H, m), 2.25-2.14 (1H, m), 1.48 (9H, s), 1.41-1.20 (14H, m), 1.01 (3H, d, *J* = 7.0 Hz), 0.88 (9H, s), 0.03 (3H,s), 0.02 (3H, s)

^{13}C NMR (100MHz, $CDCl_3$): δ = 166.7, 149.5, 144.1, 126.7, 121.3, 80.0, 72.3, 37.3, 37.0, 34.6, 32.1, 32.0, 30.3, 30.0, 29.7, 28.2, 25.9, 25.0, 22.6, 20.1, 18.1, 14.1, -4.4

$[\alpha]_D^{23}$ = + 39.7 (*c* 1.15, MeOH)

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{25}H_{48}O_3NaSi$: 447.3265; found 447.3264

IR (KBr): 2956, 1710, 1137, 773 cm^{-1}



Compound 98

A solution of compound **112** (89.0 mg, 0.209 mmoles) in EtOH (3.2 mL) and 10% Pd/C (12.0 mg) was stirred under hydrogen atmosphere at room temperature for 3 hours. The mixture was then filtered through a pad of celite, and the filtrate was concentrated and the resulting residue was used without further purification.

The residue was taken up in MeCN (3.0 mL) and HF•py was added dropwise at 0 °C. The reaction mixture was stirred at room temperature. When the starting material disappeared on TLC, the reaction was diluted with EtOAc (8.0 mL) and poured into an aqueous solution of $NaHCO_3$ slowly at 0 °C. The aqueous layer was then extracted three times with EtOAc (3 × 1.2 mL)

and the combined organic layer was dried over Na_2SO_4 and concentrated. The residue was then purified by silica gel chromatography (*n*-hexane: EtOAc = 8:1) to furnish the alcohol **98** (58.1 mg, 0.184 mmoles, 88% in 2 steps) as a colourless oil.

R_f value = 0.21 (*n*-hexane: EtOAc = 4:1)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61-3.51 (1H, m), 2.20 (2H, t, *J* = 7.6 Hz), 1.61-1.08 (20H, m), 1.44 (9H, s), 0.89 (3H, t, *J* = 7.0 Hz), 0.86 (3H, d, *J* = 6.8 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 79.9, 72.3, 37.5, 36.6, 35.6, 34.8, 32.7, 32.6, 31.9, 28.1, 26.5, 25.3, 22.6, 19.5, 14.1

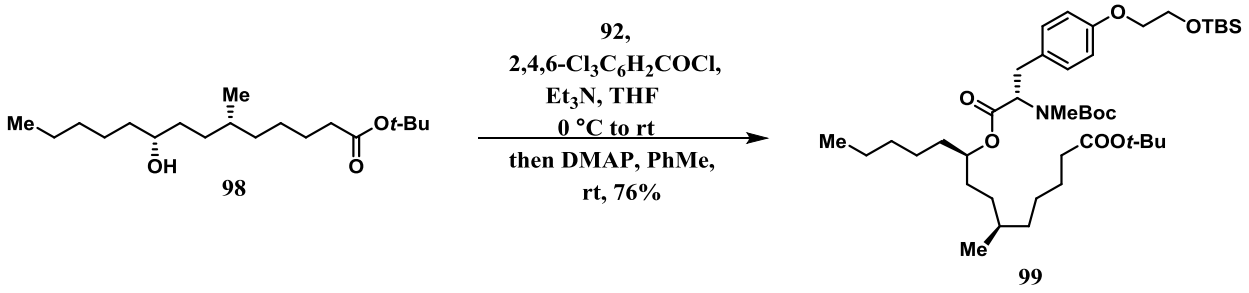
$[\alpha]_D^{26}$ = + 1.0 (*c* 1.03, MeOH)

HRMS-ESI: *m/z* [M + Na]+ calcd for $C_{19}H_{38}O_3Na$: 337.2713; found 337.2712

IR (ATR): 3358, 2928, 1731, 1151, 755 cm^{-1}

Comparison of chemical shifts of ^{1}H NMR spectra of alcohol **98** between Tatsuta's group and our data in $CDCl_3$:

Literature data[38]	Our compound (alcohol **98**)
3.56 (1 H)	3.61-3.51 (1 H)
2.21 (1 H)	2.20 (1 H)
1.44 (9 H)	1.44 (9 H)
1.61-1.08 (20 H)	1.61-1.09 (20 H)
0.90 (3H)	0.89 (3H)
0.86 (3H)	0.86 (3H)



Compound 99

To a solution of **92** (76.7 mg, 0.169 mmoles) and 2,4,6-trichlorobenzoyl chloride (54.7 μL, 0.350 mmoles) in THF (3.0 mL) at 0 °C, was added Et_3N (117.2 μL, 0.059 mmoles) and stirred for two hours at room temperature. The solvent was then evaporated and the residue was taken up in PhMe (2.0 mL). A solution of the alcohol **98** (44.3 mg, 0.140 mmoles) in PhMe (2.0 mL + 0.5 mL wash) and DMAP (68.4 mg, 0.56 mmoles) was then added and the resulting mixture was stirred at room temperature. After 6 hours, an aqueous solution of $NaHCO_3$ was added at 0 °C and the aqueous layer was extracted three times with EtOAc (2.0 mL × 3). The combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography (PhMe: EtOAc = 10:1) to furnish the ester **99** (139.0 mg, 0.185 mmoles, 76%) as a light yellow oil.

R_f value = 0.56 (PhMe: EtOAc = 8:1)

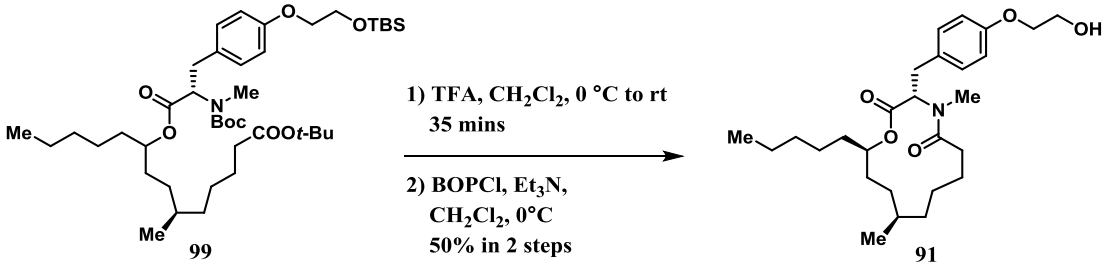
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14-7.05 (2H, m), 6.85-6.78 (2H, m), 4.95-4.82 (1H, m), 4.75-4.67 (0.5H, m), 4.01-3.93 (3.5H, m), 3.28-3.16 (1H, m), 2.95-2.85 (1H, m), 2.76 and 2.70 (3H, s), 2.20 (3H, t, *J* = 7.6 Hz) 1.44 (9H, s), 1.39-1.20 (m, 18H), 0.92-0.81 (m, 12H), 0.09 (s, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) : δ = 173.3, 171.2, 171.0, 157.7, 157.5, 155.2, 129.8, 129.8, 129.6, 129.5, 114.5, 114.4, 80.0, 79.9, 79.7, 75.9, 75.6, 69.3, 69.2, 62.0, 60.8, 59.4, 36.5, 35.6, 34.4, 34.3, 34.1, 33.8, 32.6, 32.4, 32.3, 31.6, 31.5, 30.3, 29.7, 28.3, 28.2, 28.1, 26.5, 25.9, 25.4, 22.5, 19.4, 14.0, -5.2

$[\alpha]_D^{25}$= - 25.8 (*c* 1.01, MeOH)

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{42}H_{75}O_8NNaSi$: 772.5154; found 772.5148

IR (KBr): 2924, 2853, 1733, 1701, 1458, 1250, 1219, 1146, 773 cm^{-1}



Compound 91

To a solution of compound **99** (85.9 mg, 0.114 mmoles) in CH_2Cl_2 (4.0 mL) at 0 °C was added 98% TFA (1.0 mL) and stirred for 35 minutes at room temperature and then concentrated. The residue was then taken up in CH_2Cl_2 (64.0 mL) and cooled to 0 °C. Et_3N (0.19 mL, 1.368 mmoles) was added dropwise which was followed by the addition of BOP-Cl (174.1 mg, 0.684 mmoles). The reaction was allowed to stir at 0 °C for 48 hours after which it was concentrated and aq. $NaHCO_3$ (2.0 mL) was added. The aqueous layer was extracted three times with $CHCl_3$ (4.0 mL × 2) and the combined organic layer was concentrated, dried over Na_2SO_4 and purified by silica gel chromatography (*n*-hexane: EtOAc = 5:1) to give PF1163B **91** (27.0 mg, 0.058 mmoles) as a mixture of rotational isomers.[40]

R_f value = 0.48 (*n*-hexane: EtOAc = 1:1)

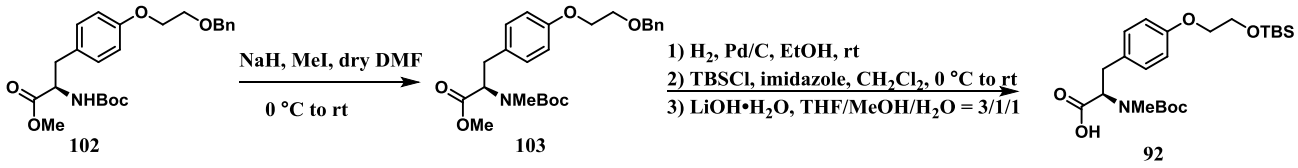
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21-7.05 (2H, m), 6.88-6.79 (2H, m), 5.84-5.75 (0.6H, m), 4.94-4.78 (1H, m(*s-trans*)), 4.60-4.54 (0.27H, m(*s-cis*)), 4.09-4.01 (2H, m), 3.99-3.91 (2H, m), 3.60-3.14(4H, m), 3.04-2.90 (3H, m), 2.84-2.61 (2H, m), 2.47-1.96 (4H, m), 1.54-1.03 (16H, m), 0.92-0.79 (6H, m)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 171.1, 170.2, 157.2, 130.2, 129.7, 129.1, 114.9, 114.4, 75.3, 69.1, 69.0, 61.5, 55.4, 35.1, 35.0, 34.0, 33.7, 33.6, 33.5, 31.7, 31.6, 29.4, 29.3, 28.7, 26.5, 25.0, 20.5, 14.0

$[\alpha]_D^{23}$ = - 109.6 (*c* 0.49, MeOH)

IR (KBr): 3400, 2950, 2929, 1731, 1632, 1512, 1248, 1220, 1078, 772 cm^{-1}

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{27}H_{43}O_5NNa$: 484.3033; found 484.3033.



Synthesis of acid fragment 92

To a solution of ester **102** (46 mg, 0.107 mmoles) in dry DMF (2.0 mL), was added MeI (20.0 μL, 0.321 mmoles) and NaH (5.0 mg, 0.107 mmoles) at 0 °C. The reaction was then allowed to attain room temperature and stirred for 6 h until the TLC showed completion of the reaction. The mixture was diluted with H_2O (5.0 mL) and EtOAc (1.0 mL) and the aqueous layer was then extracted three times. The combined organic part was dried over Na_2SO_4 and concentrated. The residue was used for the next reaction without purification.

The residue (47.0 mg) from methylation reaction was taken up in EtOH (1.6 mL) and 10% Pd/C (5.0 mg, 10 mol %) was added and the reaction was stirred at room temperature under hydrogen atmosphere for 10 h. The mixture was then filtered through celite, and concentrated to give the crude free alcohol. The alcohol was used in the next reaction without further purification.

The crude alcohol (39.0 mg) was dissolved in CH_2Cl_2 (1.4 mL) and TBSCl (18.3 mg, 0.121 mmoles) was added followed by the addition of imidazole (16.0 mg, 2.0 mmoles). The reaction was stirred at room temperature for 1 h and upon the completion of reaction, was quenched with aq. NH_4Cl (1.0 mL). The organic layer was then separated and the organic layer was extracted three times with $CHCl_3$ (3 × 2.0 mL). The combined organic extract was dried over Na_2SO_4 and concentrated. The TBS protected alcohol was used in the next reaction without purification.

The crude TBS protected alcohol (37.0 mg) was dissolved in THF (1.5 mL), H_2O (0.5 mL) and MeOH (0.5 mL). LiOH•H_2O (15.0 mg, 0.237 mmoles) was added and the mixture was stirred for 3h at room temperature. The volatiles were then removed by concentration. 6 M HCl was added to the residue till pH 3. The aqueous layer was then extracted three times with EtOAc (3 × 1.0 mL). The combined organic extract was concentrated and purified by silica gel chromatography (n- hexane: EtOAc = 1:3 to 1:5) to furnish the carboxylic acid **92** as a light yellow wax (32.0 mg, 0.070 mmoles). The spectroscopic data are in accordance with those of the reported literature.[22]

^{1}H NMR (400 MHz, $CDCl_3$): 7.15-7.04 (2H, m), 6.87-6.79 (2H, m), 4.82-4.70 (0.5H, m), 4.59-4.49 (0.5H, m), 4.03-3.92 (4H, m), 3.30-3.18 (1H, m), 3.10-2.90 (1H, m), 2.74 (3H), 2.68 (3H, s), 1.40 (9H, s) 1.34 (9H, s), 0.91 (9H, s), 0.10 (6H, s)

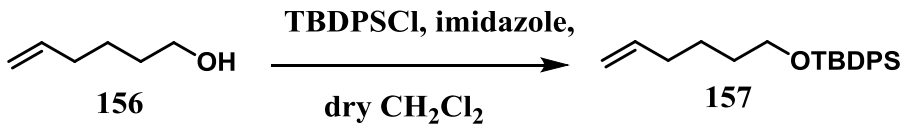
^{13}C NMR (100 MHz, $CDCl_3$): 176.0, 175.6, 157.8, 157.7, 156.4, 155.1, 129.9, 114.7, 114.5, 80.6, 69.3, 62.0, 61.6, 61.4, 34.4, 33.8, 33.0, 30.3, 29.7, 28.2, 28.2, 19.2, 18.4, 14.1, -5.2

$[\alpha]_D^{28}$ = -34.5 (*c* 1.36, MeOH)

IR (KBr): 2930, 2857, 1698, 1513, 1251, 1143, 836, 777 cm^{-1}

HRMS-ESI : *m/z* $[M + Na]^+$ calcd for $C_{23}H_{39}O_6NNaSi$: 476.2439; found 476.2435.

(iv) Synthetic Studies on Spongidepsin



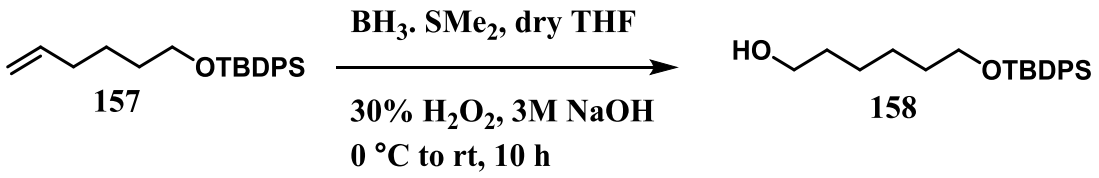
Compound 157

To a solution of **156** (0.656 g, 6.548 mmoles) in dry CH_2Cl_2 (20.0 mL), was added TBDPSCl (1.50 g, 5.457 mmoles) and imidazole (0.743g, 10.915 mmoles) at 0 C to rt. The reaction was allowed to stir for 3 hours and then quenched with aq. NH_4Cl (15.0 mL). The organic layer was extracted with $CHCl_3$ three times (3 × 20.0 mL) and the combined organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (n-hexane: EtOAc = 10:1) to give **157** (1.66 g, 6.039 mmoles) as a colourless oil in 90% yield.

^1H NMR (400 MHz, $CDCl_3$): 7.70-7.65 (4H, m), 7.46-7.35 (6H, m), 5.86-5.74(1H, m), 5.03-4.91 (2H, m), 3.70-3.64 (2H, m), 2.09-2.0 (2H, m), 1.64-1.55 (2H, m), 1.52-1.42 (2H, m), 1.06 (9H, s)

^{13}C NMR (100 MHz, $CDCl_3$):138.9, 135.6, 134.1, 129.5, 127.6, 114.3, 63.7, 33.5, 32.0, 26.8, 25.1, 19.2

HRMS-ESI: *m/z* $[M + H]^+$ calcd for $C_{22}H_{31}OSi$: 339.2139; found 339.2133.



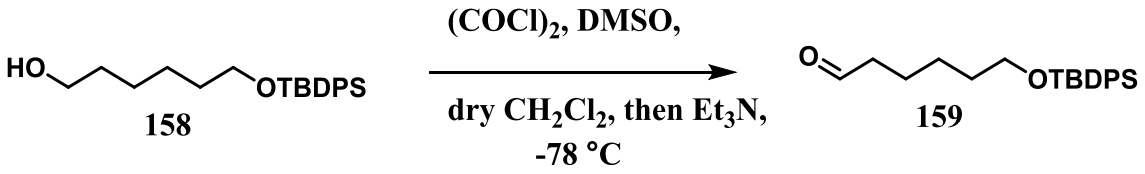
Compound 158

To a solution of **157** (301.0 mg, 0.892 mmoles) in dry THF was added $BH_3.SMe_2$ (0.17 mL, 1.784 mmoles) at 0 °C. The solution was then warmed to room temperature and stirred for 6 h following which 30% H_2O_2 (2.0 mL) and 3 M NaOH (3.0 mL) was added at 0 °C and stirred for an additional 4 h. The reaction was then diluted with H_2O (10.0 mL) and EtOAc (15.0 mL) and the aqueous layer was extracted with EtOAc three times (3 × 15 mL). The combined organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel chromatography (*n*-hexane: EtOAc = 3:1) to give **158** (244.3 mg, 0.685 mmoles) a colourless oil in 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$): 7.69-7.64 (4H, m), 7.45-7.35 (6H, m), 3.69-3.59 (4H, m), 1.43-1.30 (4H, m), 1.05 (9H, s)

^{13}C NMR (100 MHz, $CDCl_3$): 135.6, 134.1, 129.5, 127.6, 63.8, 63.0, 32.7, 32.5, 26.8, 25.6, 25.4, 19.2

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{32}O_2NaSi$: 379.2064; found 379.2059.



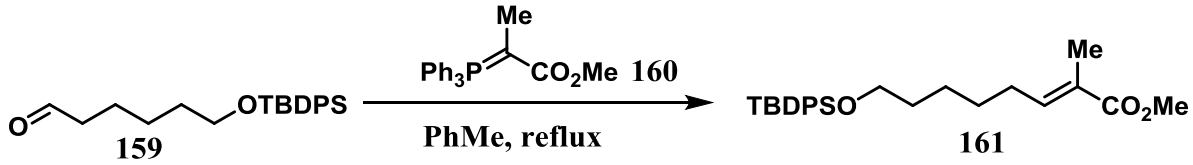
Compound 159

To a solution of oxalyl chloride (70.1 µL, 0.817 mmoles) in dry CH_2Cl_2 (2.0 mL) at -78 °C was added DMSO (116.1 µL, 1.634 mmoles). The mixture was stirred for 30 minutes and a solution of the alcohol **158** (291.5 mg, 0.817 mmoles) in dry CH_2Cl_2 (2.0 mL) was added. After stirring the reaction for 3 h at -78 C, Et_3N (0.57 mL, 4.085 mmoles) was slowly added and the mixture was stirred for an additional 10 minutes following which it was raised to room temperature. H_2O (2.0 mL) was then added and the aqueous layer extracted three times with $CHCl_3$ (3 × 5 mL). The combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography to give the aldehyde **159** (210.1 mg, 0.592 mmoles) as a colourless oil in 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$): 9.74 (1H, t, J = 2.0 Hz), 7.70-7.65 (4H, m), 7.46-7.36 (6H, m), 3.68 (2H, t, J = 7.0 Hz), 2.44-2.38 (2H, m), 1.67-1.55 (4H, m), 1.47-1.37 (2H, m), 1.07 (9H, s)

^{13}C NMR (100 MHz, $CDCl_3$): 202.7, 135.5, 133.9, 129.5, 127.6, 63.5, 43.8, 32.2, 26.8, 25.4, 21.8, 19.2

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{30}O_2NaSi$: 377.1907; found 377.1901.



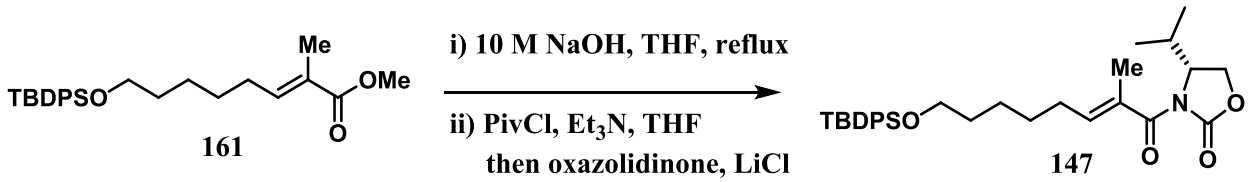
Compound 161

To a solution of **159** (158.6 mg, 0.447 mmoles) in PhMe (3.0 mL) was added PPh_3=CH(Me)CO_2Me (311.7 mg, 0.894 mmoles) and refluxed for 3 h. The reaction was then cooled to room temperature and quenched with aq. NH_4Cl (1.0 mL). The aqueous layer was extracted twice with EtOAc (2 × 2.0 mL) and the combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography to give **161** (76.0 mg, 0.179 mmoles) as a colourless oil in 40% yield.

^{1}H NMR (400 MHz, $CDCl_3$): 7.68-7.64 (4H, m), 7.45-7.34 (6H, m), 6.75 (1H, ddq, *J* = 6.9, 6.9, 1.1 Hz), 3.73 (3H, s), 3.65 (2H, t, *J* = 6.9 Hz), 1.82 (3H, d, *J* = 1.1Hz), 1.47-1.34 (4H, m), 1.04 (9H, s)

^{13}C NMR (100 MHz, $CDCl_3$): 168.7, 142.6, 135.5, 134.0, 129.5, 127.6, 63.7, 51.6, 32.3, 28.6, 28.3, 26.8, 25.5, 19.2, 12.4

HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{26}H_{36}O_3NaSi$: 447.2326; found 447.2321.



Compound 98

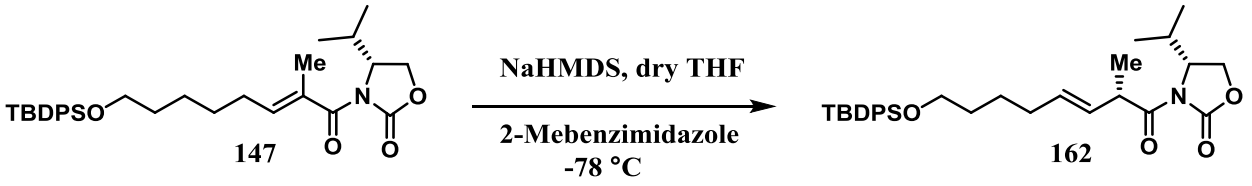
To a solution of **161** (100.0 mg, 0.235 mmoles) in THF (5.0 mL) was added 10 M NaOH. The resulting mixture was then refluxed for 10 h after which it

was cooled and allowed to attain room temperature. The reaction was then cooled to 0 °C and neutralized with 2 N HCl until pH 3. The aqueous layer was then extracted three times with EtOAc (3 × 10 mL) and the combined organic layer was dried over Na_2SO_4 and concentrated to give the crude carboxylic acid. The acid was used in the next reaction without further purification.

The crude acid (94.0 mg) was dissolved in THF (5.0 mL) and cooled to 0 C. Et_3N (86.2 μL, 0.618 mmoles) and PivCl (32.6 μL, 0.265 mmoles) were added sequentially at that temperature. After stirring for 2 hours at room temperature, oxazolidinone (32.5 mg, 0.252 mmoles) and LiCl (15.5 mg, 0.366 mmoles) was added. The reaction was then stirred for 12 hours and then concentrated. The residue was dissolved in EtOAc (5.0 mL) and extracted with H_2O (3.0 mL). The combined organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel chromatography to give **147** (71.6 mg, 0.137 mmoles) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.69-7.64 (4H, m), 7.45-7.34 (6H, m), 6.08 (1H, ddq, *J* = 7.0, 7.0, 1.0 Hz), 4.51 (ddd, *J* = 9.0, 5.5, 4.5 Hz), 4.30 (1H, dd, *J* = 9.1, 9.0 Hz), 4.17 (1H, dd, *J* = 9.1, 4.5 Hz), 3.65 (1H, dd, *J* = 6.9, 6.5 Hz), 2.36 (1H, qqd, *J* = 7.0, 7.0, 4.0 Hz), 2.20-2.11 (2H, m), 1.89 (3H, d, *J* = 1.0 Hz), 1.44-1.38 (4H, m), 1.04 (9H, s), 0.92 (3H, d, *J* = 7.0 Hz), 0.90 (3H,d, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): 175.7, 156.6, 135.5, 134.0, 129.5, 127.6, 66.3, 63.7, 58.2, 54.7, 51.6, 40.4, 36.1, 32.3, 28.6, 28.3, 26.8, 25.5, 21.6, 20.2, 19.2, 17.9, 17.9, 14.5, 12.4

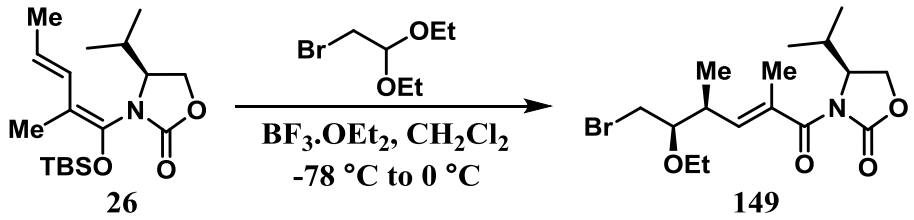


Compound 162

To a solution of **147** (25.0 mg, 0.048 mmoles) in dry THF at -78 C, was added NaHMDS (1.0 M in THF, 81.4 μL, 0.081 mmoles) dropwise. The reaction was allowed to stir at the same temperature for 2 hours. A solution of 2-methylbenzimidazole (19.0 mg, 0.144 mmoles) in dry THF (2.0 mL) was then cannulated and the reaction mixture was raised to room temperature. Aq. NH_4Cl (2.0 mL) was added then and the aqueous layer was extracted with EtOAc three times (3 × 4.0 mL). The combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography to give **162** (17.4 mg, 0.033 mmoles) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 7.68-7.63 (4H, m), 7.45-7.34 (6H, m), 5.70-5.61 (1H, m), 5.56-5.48 (1H, m), 4.52-4.43 (2H, m), 4.25 (1H, dd, *J* = 9.0, 8.9 Hz), 4.18 (1H, dd, *J* = 9.0, 4.5 Hz), 3.63 (1H, dd, *J* = 6.9, 6.5 Hz), 2.30 (1H, qqd, *J* = 7.0, 7.0, 4.0 Hz), 2.03-1.95 (2H, m), 1.46-1.38 (3H, m), 1.22 (3H, d, *J* = 6.9 Hz), 1.04 (9H, s), 0.88 (3H, d, *J* = 7.0 Hz), 0.81 (3H, d, *J* = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): 175.7, 156.6, 135.5, 134.0, 129.5, 127.6, 66.3, 63.7, 58.2, 54.7, 51.6, 40.4, 36.1, 32.3, 28.6, 28.3, 26.8, 25.5, 21.6, 20.2, 19.2, 17.9, 17.9, 14.5, 12.4

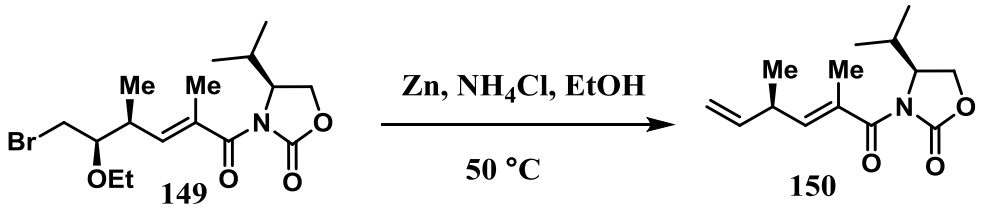


Compound 149

To a solution of bromodiethyl acetal (0.24 mL, 1.545 mmoles) in CH_2Cl_2 (2.0 mL) at -78 °C, was added $BF_3.OEt_2$ (0.18 mL, 1.472 mmoles) at -78 °C. The solution was stirred for 15 mintues at the same temperature after which a solution of **26** (500 mg, 1.472 mmoles) in CH_2Cl_2 (2.0 mL) was cannulated. The temperature was then raised to 0 °C and the reaction was stirred for an additional 12 hours. Pyridine (0.47 mL, 5.888 mmoles) was then added and the reaction was warmed to room temperature after which aq. $NaHCO_3$ (3.0 mL) was added. The aqueous layer was extracted with $CHCl_3$ three times (3 × 4 mL) and the combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography to give **149** (376.8 mg, 1.001 mmoles) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): 5.76 (1H, dd, *J* = 9.0, 1.0 Hz), 4.52 (1H, ddd, *J* = 9.0, 5.5, 4.5 Hz), 4.32 (1H, dd, *J* = 9.0, 8.9 Hz), 4.17 (1H, dd, *J* = 9.0, 5.5 Hz), 3.74 (1H, dq, *J* = 9.0, 7.0 Hz), 3.60 (2H, dd, *J* = 2.5, 2.0 Hz), 3.46 (1H, dq, *J* = 9.0, 7.0 Hz), 2.95-2.84 (1H, m), 2.35 (1H, qqd, *J* = 7.0, 7.0, 4.0 Hz), 1.97 (3H, d, *J* = 1.0 Hz), 1.08 (3H, d, *J* = 7.0 Hz), 0.91 (6H, dd, *J* = 7.1, 7.0 Hz)

^{13}C NMR ($CDCl_3$, 100 MHz): 171.6, 153.6, 139.8, 131.2, 81.1, 66.1, 63.4, 58.1, 36.5, 34.4, 28.2, 17.8, 15.3, 15.3, 15.0, 13.9

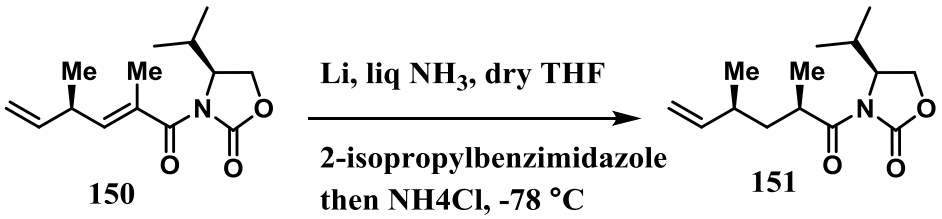


Compound 150

To a solution of **149** (52.0 mg, 0.138 mmoles) in EtOH (2.0 mL) was added Zn dust (135.5 mg, 2.07 mmoles) and NH_4Cl (73.9 mg, 1.38 mmoles) and stirred vigorously at 50 °C for 1 h. After TLC showed complete consumption of starting material, the reaction mixture was cooled to room temperature and filtered through a cotton plug. The filtrate was concentrated and purified by silica gel chromatography to give **150** (29.4 mg, 0.117 mmoles) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): 5.86 (1H, dq, *J* = 8.0, 1.0 Hz), 5.78 (1H. ddd. *J* = 16.0, 10.5, 6.5 Hz), 5.14-5.07 (1H, m), 5.04-4.99 (1H, m), 4.50 (1H, ddd, *J* = 9.0, 5.5, 4.5 Hz), 4.32 (1H, dd, *J* = 9.0, 8.9 Hz), 4.18 (1H, dd, *J* = 9.0, 5.5 Hz), 3.25-3.16 (1H, m), 2.37 (1H, qqd, *J* = 7.0, 7.0, 4.0 Hz), 1.93 (3H, d, *J* = 1.0 Hz), 1.13 (3H, d, *J* = 7.0 Hz), 0.91 (6H, dd, *J* = 7.1, 7.0 Hz)

^{13}C NMR ($CDCl_3$, 100 MHz): 171.8, 153.5, 141.3, 140.3, 130.3, 113.9, 63.3, 58.2, 36.4, 28.1, 19.5, 17.8, 14.9, 13.7

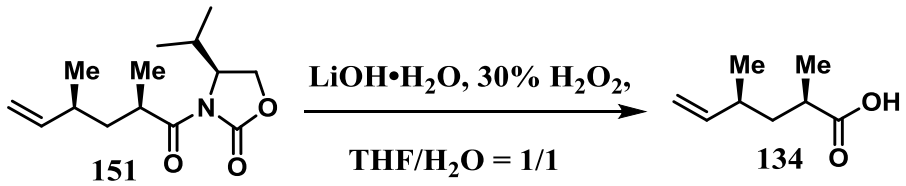


Compound 151

To a solution of **150** (19.3 mg, 0.076 mmoles) in dry THF (1.0 mL) and liq. NH_3 (4.0 mL) at -78 °C, was added lithium in small pieces (1.6 mg, 0.228 mmoles). The dark blue solution was stirred at the same temperature for 6 minutes after which a solution of 2-isopropylbenzimidazole (60.9 mg, 0.38 mmoles) in dry THF (2.5 mL) was cannulated into the reaction mixture. NH_4Cl was then added (28.7 mg, 0.532 mmoles) and the mixture was allowed to attain room temperature to evaporate NH_3. After about 2 hours, the reaction mixture was concentrated and diluted with EtOAc (3.0 mL) and H_2O (1.5 mL). The aqueous layer was extracted three times with EtOAc (3 × 3.0 mL). The combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography to give **151** (12.4 mg, 0.048 mmoles) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): 5.70 (1H, ddd, *J* = 17.5, 10.1, 8.0 Hz), 5.03-4.91 (2H, m), 4.44 (1H, ddd, *J* = 9.0, 4.5, 4.0 Hz), 4.25 (1H, dd, *J* = 9.0, 8.5 Hz), 4.19 (1H, dd, *J* = 9.0, 3.1 Hz), 3.85-3.75 (1H, m), 2.35 (1H, qqd, J = 7.0, 7.0, 4.0 Hz), 2.26-2.16 (1H, m), 1.88-1.79 (1H, m), 1.37-1.30 (1H, m), 1.12 (3H, d, *J* = 6.9 Hz), 1.01 (3H, d, *J* = 7.0 Hz), 0.91 (3H, d, *J* = 7.1 Hz), 0.87 (3H, d, *J* = 7.0 Hz)

^{13}C NMR ($CDCl_3$, 100 MHz): 177.4, 153.6, 143.6, 113.3, 63.0, 58.4, 40.3, 36.2, 35.8, 28.3, 20.8, 18.0, 16.8, 14.6



Compound 134

To a solution of **151** (10.0 mg, 0.039 mmoles) in THF/H_2O (4.0 mL, 1:1 ratio) at room temperature was added LiOH•H_2O (5.0 mg, 0.117 mmoles) and 30% H_2O_2 (8.8 μL, 0.039 mmoles). The reaction was stirred for 3 hours at room temperature and then 2 N HCl was added till pH 3. The aqueous layer was then extracted with EtOAc three times (3 × 4.0 mL). The combined organic layer was dried over Na_2SO_4, concnentrated and purified over silica gel chromatography to give the acid **134** (3.90 mg, 0.027 mmoles) as a colorless wax.

^{1}H NMR ($CDCl_3$, 400 MHz): 5.68-5.57 (1H, m), 5.03-4.93 (2H, m), 2.55-2.48 (1H, m), 2.24-2.18(1H, m), 1.79-1.70 (1H, m), 1.40-1.36 (1H, m), 1.18 (3H, d, J = 7.0 Hz), 1.12 (3H, d, J = 7.0 Hz)

^{13}C NMR ($CDCl_3$, 100 MHz): 183.0, 143.6, 113.9, 40.2, 37.6, 36.1, 20.9, 16.9

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Finally, I dedicate my doctoral dissertation to my father, Mr. Kajal Sengupta, without whose love, encouragement, unwavering faith and undying spirit, I would not have made it this far in my life.

4. Achievements for this dissertation

Publications:

- 2-Isopropylbenzimidazole and 2-methylbenzimidazole as bulky proton sources: Stereoselective protonation and γ- and δ-lactones. Aakash Sengupta and Seijiro Hosokawa, *Tetrahedron Letters*, **2019,** *60*, 411-414.

- Total Synthesis of PF1163B. Aakash Sengupta and Seijiro Hosokawa, *Synlett, in press*. DOI: 10.1055/s-0037-1610694.

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