ABSTRACT

The thesis entitled **"Formal Total Synthesis of Mandelalide A and Synthetic Studies of Tianchimycin A and Madeirolide A"** consists of three chapters.

CHAPTER-I: Describes the formal total synthesis of Mandelalide A.

CHAPTER-II: Describes the stereoselective synthesis of fully functionalized acyclic core Tianchimycin A.

CHAPTER-III: Describes the synthetic studies of Madeirolide A: Synthesis of C1-C11 fragment.

CHAPTER-I

Formal Total Synthesis of Mandelalide A

Marine natural products have a huge potential to become drugs and they have already provided many important drugs in clinical use for cancer therapy. In 2012 McPhail and co-workers isolated a new class of unusual glycosylated polyketide macrolides, called Mandelalides A-D (Figure 1), via bioassay guided fractionation of the cytotoxic extracts of a new Lissoclinum species from Algoa Bay, South Africa. The absolute structures were proposed by extensive NMR, mass spectral and GC studies. Biological evaluation of Mandelalides A and B revealed remarkably potent cytotoxic activity against cancer cell lines in human lung cancer cells (NCI-H460, IC_{50}= 12 nM, 29 nM respectively) and mouse neuroblastoma (Neuro-2A, IC_{50}= 44 nM, 84 nM respectively).

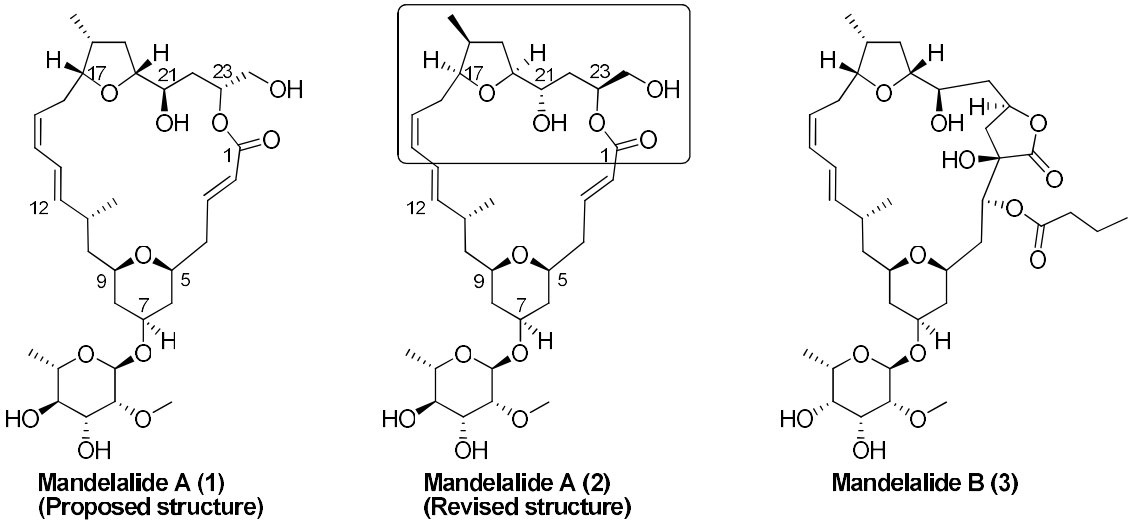
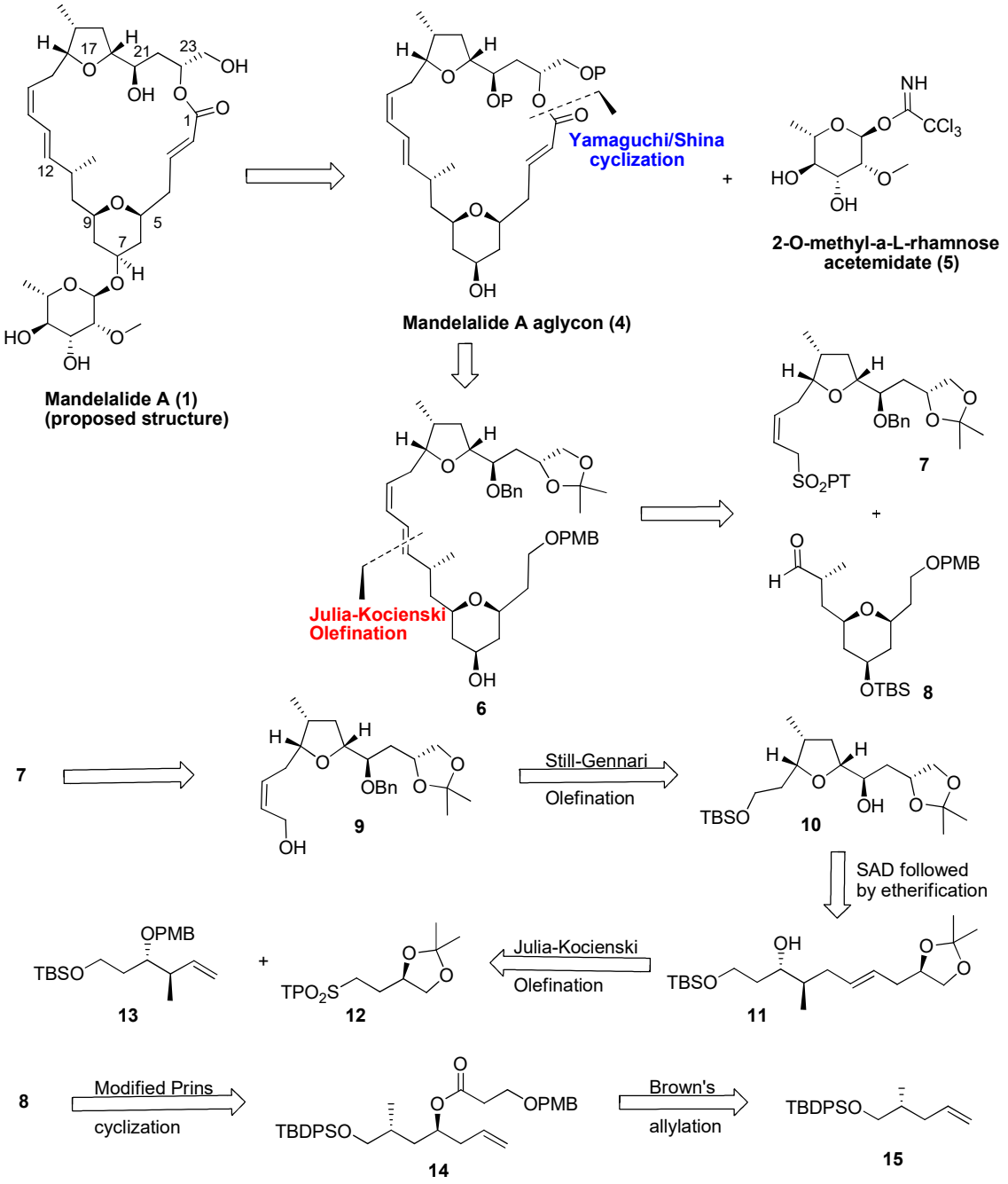


Figure 1

Architecturally, Mandelalide A is a 24-membered macrolide containing three olefinic bonds, two of which were in unusual *E,Z*-configured diene. The macrocycle is decorated with 12 chiral centres, a trisubstituted THF unit and trisubstituted THP moiety glycosylated with an unusual L-rhamnose derived pyranoside. The inimitable structural features and promising biological activities together with natural scarcity rendered Mandelalide A, a fascinating synthetic target for synthetic organic chemists to attempt its total synthesis. In 2014 Frustner et al. reported the first total synthesis of proposed structure of Mandelalide A (**1**) and they disclosed the incorrect structural assignment of the original molecule. Shortly thereafter synthesis of proposed aglycone of Mandelalide A was reported from our group. Immediately Tao et al. reported the total synthesis and stereochemical reassignment of Mandelalide A and postulated that the correct structure of Mandelalide A was a diastereomer of **1** for which the whole tetrahydrofuran moiety had been inverted. High biological significance and formidable composition of structure attracted our attention for its total synthesis after its immediate isolation. In this chapter the details of our synthetic study of Mandelalide A has been described.

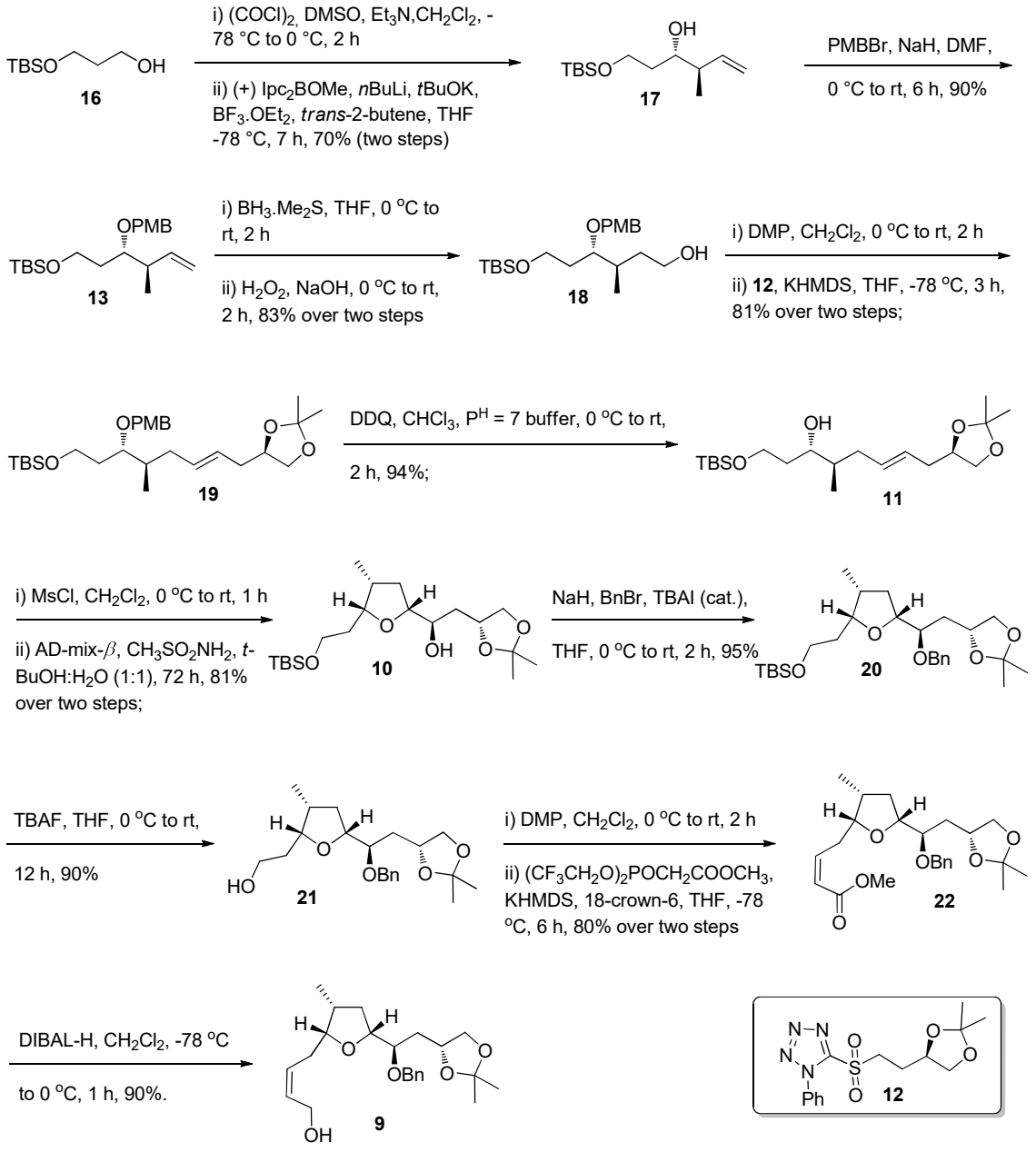
From the inspection of the proposed structure of Mandelalide A, we envisioned that a late-stage glycosylation of the macrocycle **4** with L-rahmnose derived acetamide using regular protocols would construct the proposed structure of the natural product in its protected form (Scheme 1). Disconnection of macrocycle **4** led to the two key building blocks **7** and **8** with similar complexity, required for its construction using Julia-Kocienski olefination followed by Yamaguchi/Shina macrolactonization. We realized that sulfone **7** would be derived from alcohol **9** via Mitsunobu reaction followed by oxidation with ammonium heptamolybdate and H_2O_2. Alcohol **9** could be accessed from **10** via protecting group manipulation followed by Still-Gennari olefination. Furan compound **10** could be acquired from olefin **11** by means of Sharpless asymmetric dihydroxylation with concomitant Williamson type etherification. Compound **11** could be synthesized via coupling of **12** and **13** by means of Julia-Kocienski olefination. Compound **8** with a pyran unit was expected to be synthesized from ester **14** by utilizing segment coupling Prins cyclization, developed by Rychnovsky and co-workers. The ester **14** was expected to be prepared from alkene **15** by Brown's allylation followed by acylation with $PMBOCH_2CH_2COOH$.



Scheme 1. Retrosynthetic analysis

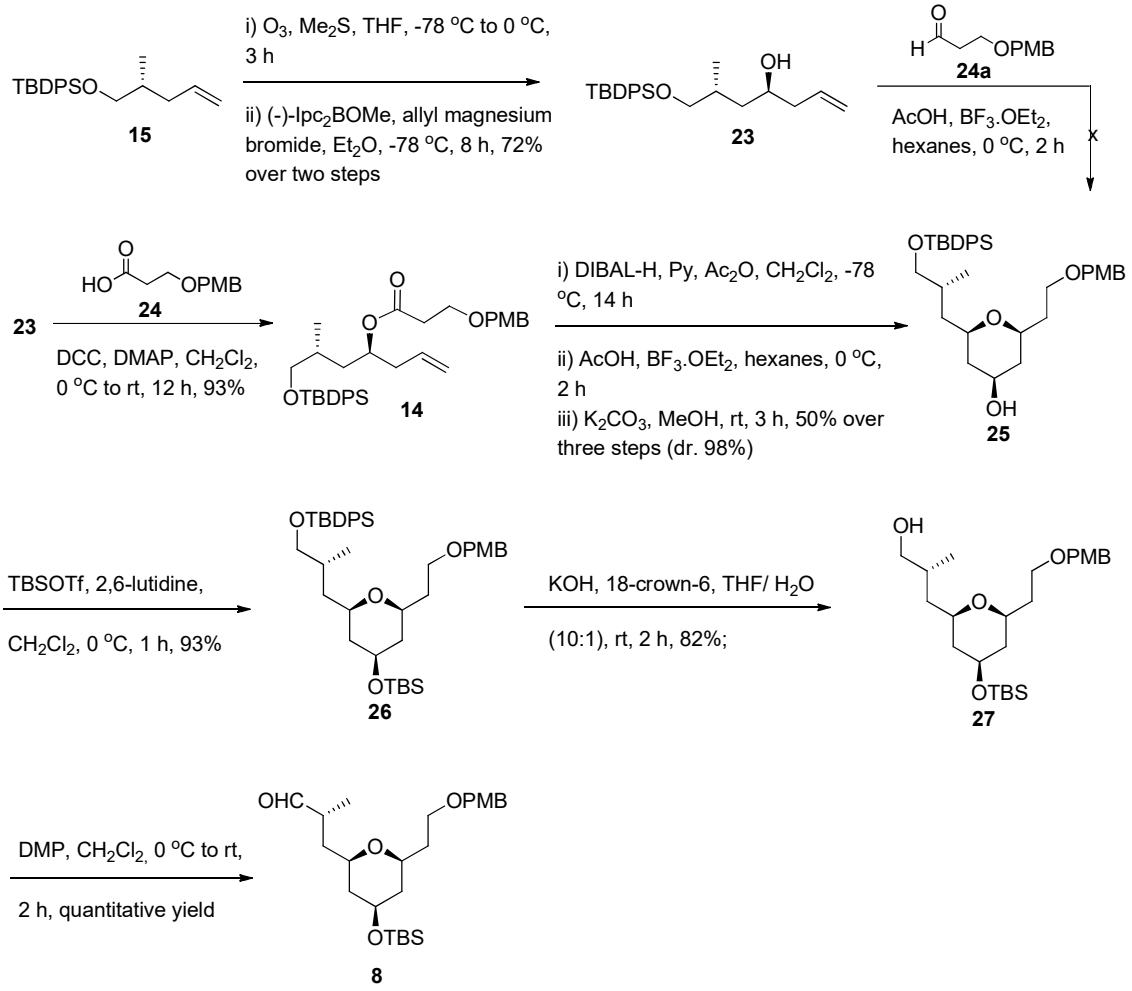
Thus according to our retrosynthetic perspective, for the preparation of sulfone **7**, the synthesis started from **16** (Scheme 2), which on Swern oxidation followed by Brown's crotylation with (+)-Ipc_2BOMe, *trans*-2-butene and $BF_3{\cdot}OEt_2$ afforded **17** in 70% yield over two steps. Protection of secondary hydroxyl group as a PMB ether gave olefin **13**. Hydroboration of the olefin **13**, furnished alcohol **18** which, on Dess-Martin periodinane oxidation, followed by modified Julia-olefination with the known sulfone **12** afforded the chromatographically pure *E*-olefin **19** in 81% yield (two steps). Cleavage of the PMB ether

with buffered DDQ afforded the alcohol **11** in 94% yield. The secondary alcohol **11** was converted to its mesylate by MsCl and Et_3N, which upon Sharpless asymmetric dihydroxylation with AD-mix-β afforded diol, which underwent *in situ* Williamson-type etherification to provide exclusively THF alcohol **10** with excellent diastereoselectivity (79% yield, two steps). The rigorous five membered-ring selectivity in Williamson-type etherification can be explained in terms of extended Baldwin rules where the 5-*exo-tet* cycli zation is favoured over the 6-*exo-tet* cyclization. Alcohol **10** upon benzylation, followed by



Scheme 2

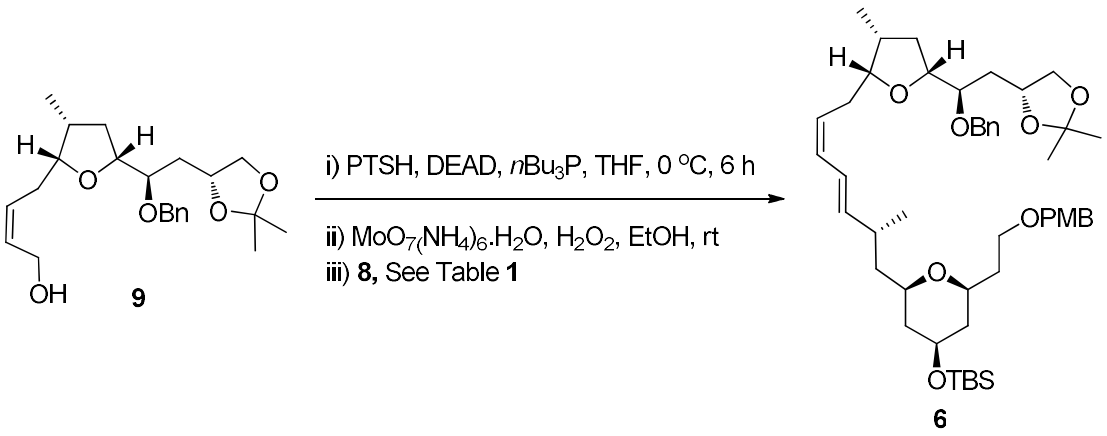
desilylation of the primary TBS with HF-Py furnished primary alcohol **21** in 80% yield over two steps. Dess-Martin periodinane oxidation of primary alcohol **21** afforded aldehyde, which was subjected to Still-Gennari olefination to access the highly *Z*–selective *α,β*-unsaturated ester **22** (*E*:*Z* = 96:4) in 80% yield (over two steps). Reduction of the ester group of **22** with DIBAL-H gave *Z*-allylic alcohol fragment **9** in 90 % yield.



Scheme 3

The synthesis of pyran segment commenced from the known compound **15** (Scheme 3). Ozonolysis of **15** furnished an aldehyde, which was subjected to Brown's asymmetric allylation with (–)-Ipc$_2$BOMe and allyl magnesium bromide at –78 °C to give alcohol **23** in 72% yield (*dr* > 20:1). Prins cyclization between aldehyde **24a** and the homoallylic alcohol **23** was unsuccessful to produce the desired product **25**. Therefore we planned to synthesize the tetrahydropyran unit via segment coupling Prins cyclization. Accordingly, acylation of **23** with acid **24** under DCC-DMAP conditions provided compound **14** in 93% yield. Careful reduction of compound **14** followed by acetyl protection of the resulting lactol gave *α*-

acetoxy ether, which on segment coupling Prins cyclization with $BF_3 \cdot OEt_2$ and acetic acid in hexanes at 0 ºC followed by the C4-OAc deprotection of the resulting pyran ring afforded desired pyran alcohol **25** in 50% yield (three steps). TBS protection of the secondary alcohol of **25** with TBSOTf followed by selective deprotection of TBDPS under basic conditions furnished primary alcohol **27** in 77% yield over two steps. Alcohol **27** was oxidized with Dess-Martin periodinane to give an aldehyde in quantitative yield.



Scheme 4

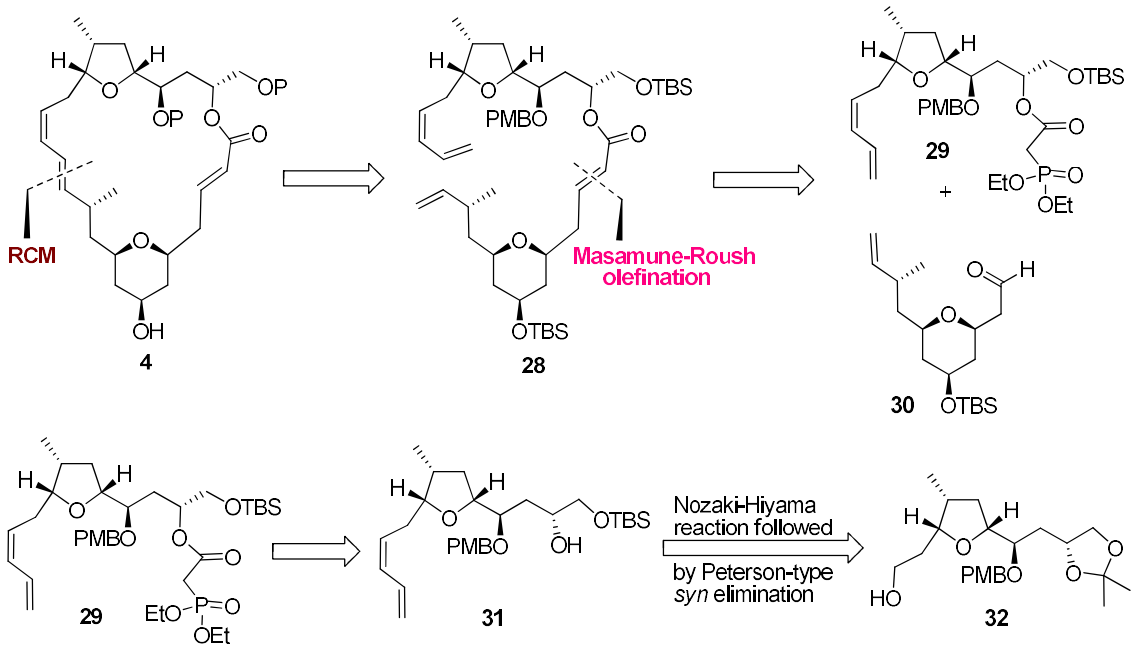
After synthesizing these two key building blocks, we focused our attention to stitching of these units via Julia-Kocienski olefination to accomplish the crucial coupled product **6** (Scheme 4). Accordingly compound **9** was converted to sulfone under Mitsunobu conditions followed by oxidation and then subjected to Julia-Kocienski olefination with aldehyde **8**, under assorted conditions as shown in **Table 1**, which were preceded abortive to furnish precursor for macrocyclization.

Table 1:

Entry	Conditions	Temperature	Time	yield
1	KHMDS, THF	- 78 ºC	2.5 h	0%
2	*n*-BuLi, THF	- 78 ºC	1.5 h	0%
3	*t*-BuLi, THF	- 78 ºC	1.5 h	0%

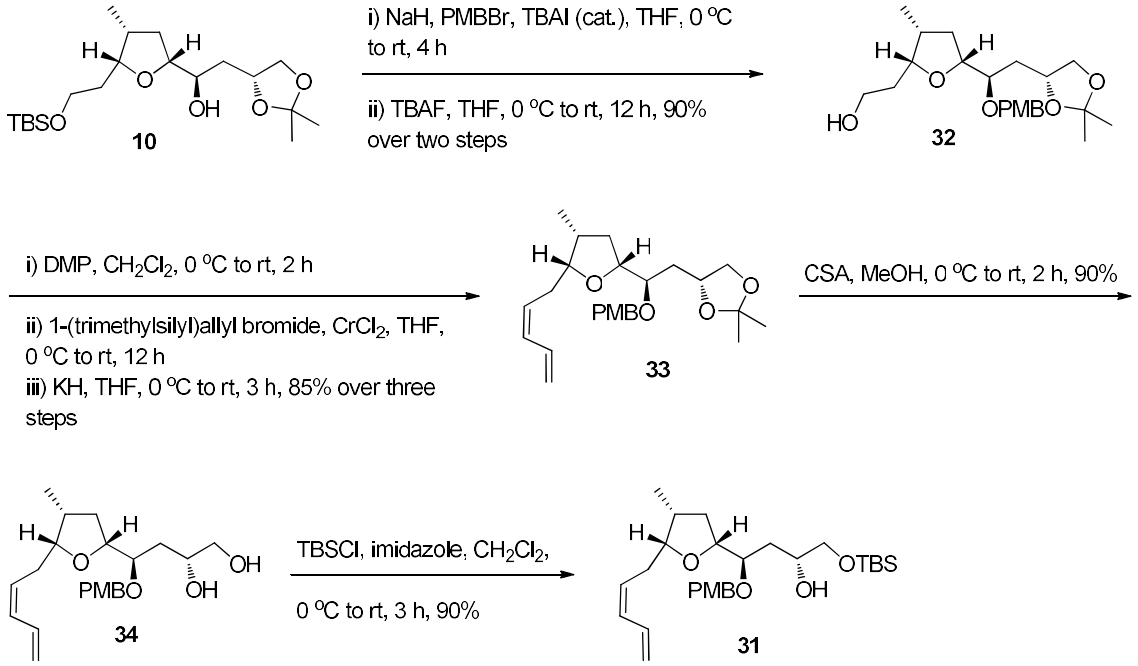
The failure of Julia-Kocienski olefination forced us do devise an alternate strategy. We intended that the pre installation of the α,β-unsaturated double bond at C2-C3 position

followed by late stage ring closing metathesis protocol might provide the desired macrocycle **4.** As depicted in Scheme 5, Masamune-Roush olefination between **29** and **30** would give **28** that could be cyclized via ring-closing metathesis reaction. The phosphonate **29** would be obtained from **31**, which in turn could be obtained from **32** via oxidation followed by Nozaki-Hiyama reaction and Peterson-type *syn* elimination.



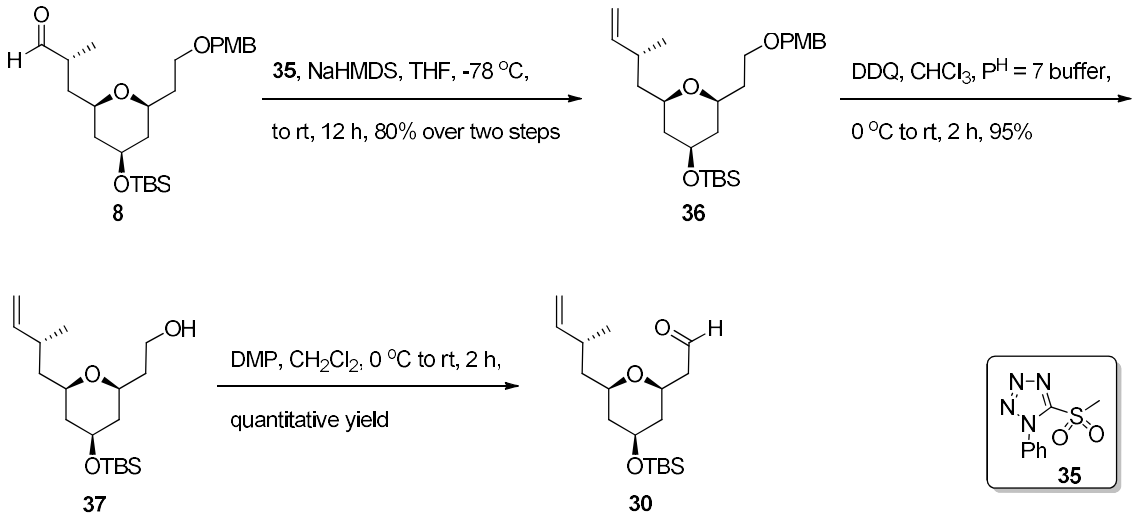
Scheme 5

Accordingly, we started our synthesis from compound **10** (Scheme 5). PMB-protection of the secondary alcohol of **10** as its PMB ether followed by TBS deprotection with TBAF in THF furnished primary alcohol **32** in 90% yield over two steps. Oxidation of **32** with DMP furnished an aldehyde, which was subjected to Nozaki-Hiyama reaction with allyl chromium reagent generated in situ from allyl TMS bromide and chromium (II) chloride followed by Peterson–type *syn* elimination to furnish the required (*Z*)-diene compound **33** in 85% yield. Acetonide deprotection and chemoselective protection of primary alcohol as its TBS ether provided **31** in 90% yield.



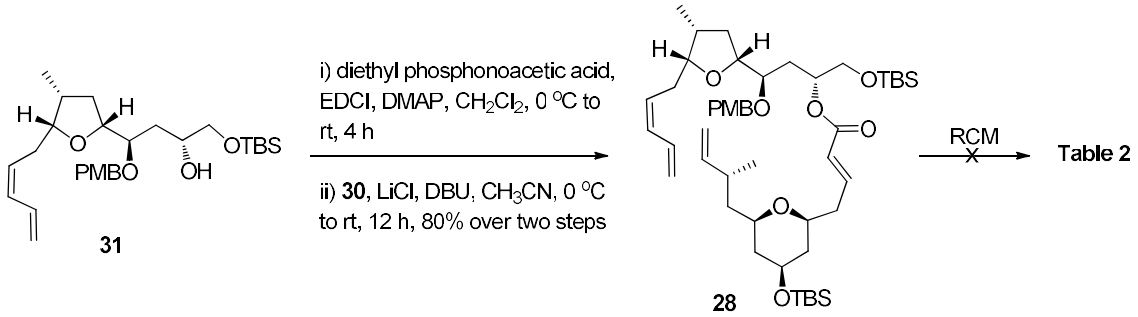
Scheme 6

The synthesis of the aldehyde **30** is depicted in Scheme 7. Olefination of aldehyde **8** via modified Julia reaction with known sulfone **35** gave olefin compound **36** in 80% yield over two steps. Deprotection of PMB group afforded a primary alcohol **37** in 95% yield, which on oxidation with DMP gave aldehyde **30** in quantitative yield.



Scheme 7

With the two key fragments in hand, we focused our attention on the stereocontrolled union of these fragments (Scheme 8) to reach the desired macrocycle. To this end **31** was acylated with diethyl phosphonoacetic acid to give a phosphonate intermediate which underwent Masamune-Roush olefination smoothly with the aldehyde **30** and furnished ring-closing metathesis precursor **28** in 80% yield. Now the stage was set for the crucial macrocyclization, but miserably the ring losing metathesis reaction under variety of conditions, as shown in **Table 2** was failed to provide the desired cyclized product.

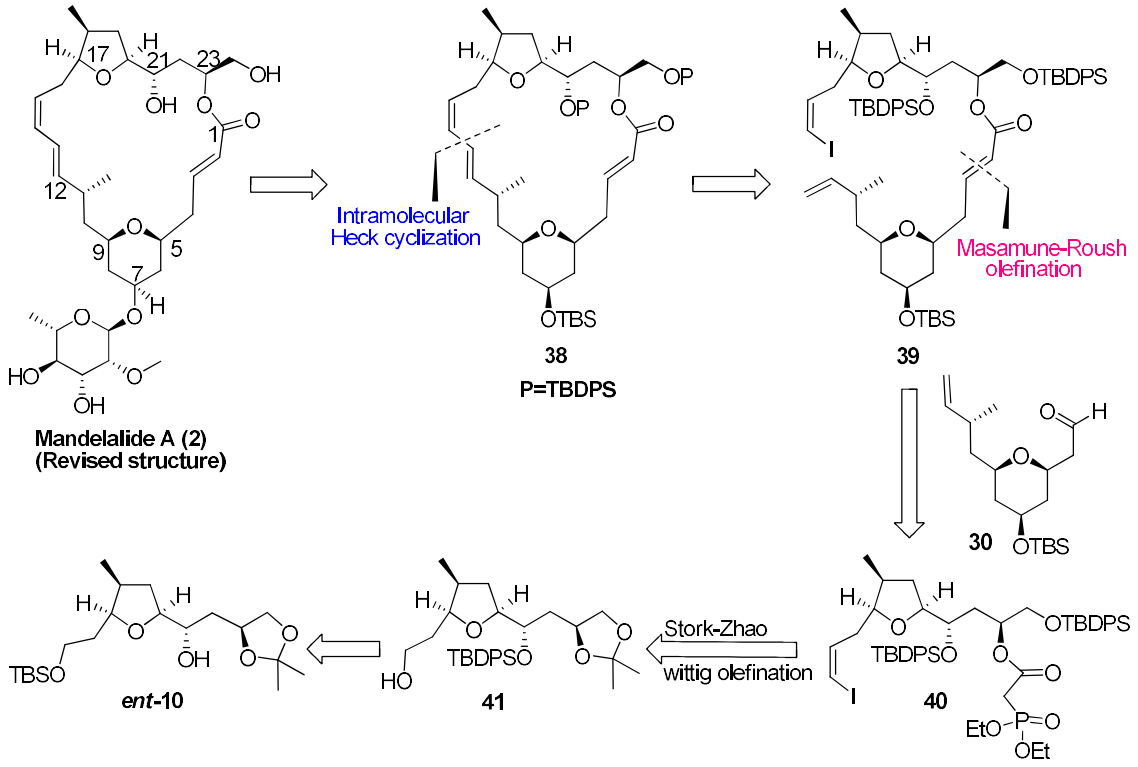


Scheme 8

Table 2:

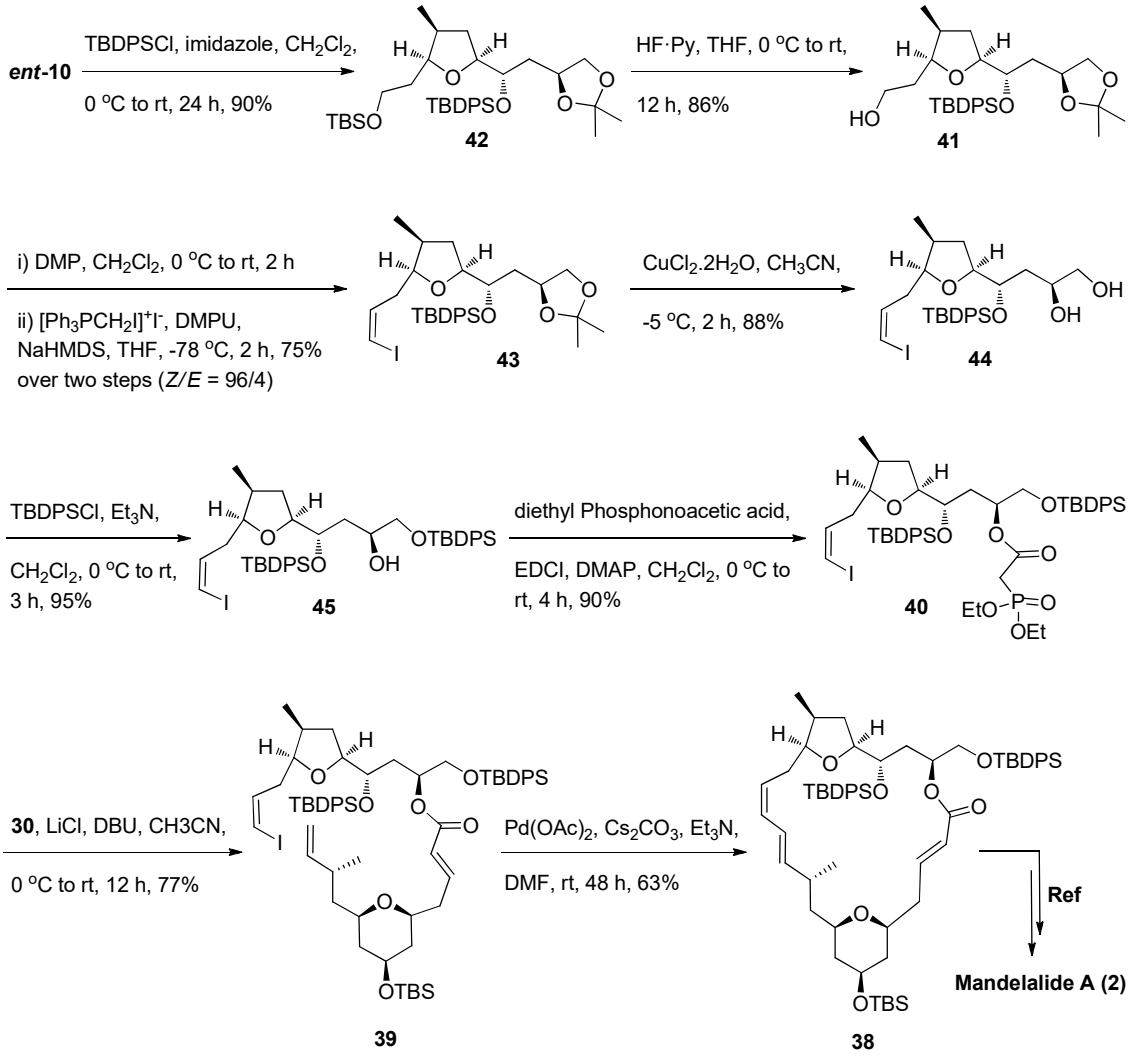
Entry	Catalyst (mol%)	Conditions	Yield
1	Grubbs I (10%)	CH_2Cl_2, 12 h, rt	0%
2	Grubbs II (10%)	Toluene, 12 h, rt	0%
3	Hoveyda-Grubbs catalyst (10%)	Toluene, 12 h, rt	0%

At this stage the structure of Mandelalide A was revised to **2**. Therefore we planned to synthesize the actual natural product via Masamune-Roush olefination followed by intramolecular Heck cyclization. Thus retrosynthetically Mandelalide A could be synthesized from aglycone **38** via the selective deprotection of TBS at C7-OH followed by glycosidation. Fully protected aglycone **38** could be obtained from compound **39** via intramolecular Heck cyclization, which in turn could be obtained from **30** and **40** via Masamune-Roush olefination. Finally compound **40** would be obtained from *ent*-**10** via compound **41**.



Scheme 9

Thus our synthesis started with the *ent*-**10**, which was synthesized from *ent*-**17** following the same sort of reactions as described in scheme 2. TBDPS protection of the secondary alcohol of *ent*-**10** gave compound **42** in 90% yield, which on treatment with HF·Py in THF at 0 ^{o}C furnished primary alcohol **41** in 86% yield. Oxidation of the primary alcohol **41** was carried out with DMP to give an aldehyde, which on reaction with the ylide generated from $[Ph_3PCH_2I]^+I^-$ with NaHMDS gave *Z*-vinyl iodide **43** in 75% yield (*Z*/*E* = 96/4) over two steps. Acetonide deprotection with $CuCl_2.2H_2O$ at –5 ^{o}C gave diol **44** in 88% yield. Selectively primary alcohol was protected as TBDPS ether to give secondary alcohol 4**5** that on acylation with diethyl phosphonoacetic acid under EDCI/DMP conditions afforded the phosphonate **40** in 90% yield. Now the coupling reaction between aldehyde **30** and phosphonate **40** was accomplished by Masamune-Roush olefination in presence of DBU and LiCl delivered compound **39** in 77% yield, which on intramolecular Heck cyclization afforded known compound **38** (63%) which can be converted to Mandelalide A in three steps according to the literature procedure, thus completed the formal total synthesis of the target molecule.



Scheme 10

In summary, a formal total synthesis of Mandelalide A (**2**) has been achieved in 31 total steps (17 longest linear sequence from compound **16**) with 6.83% overall yield by utilizing intramolecular Heck cyclization as a key step. The other key reactions utilized in the synthesis are Julia-Kocienski olefination, asymmetric dihydroxylation followed by in situ cycloetherification and Masamune-Roush olefination reactions. The Julia-Kocienski olefination and the ring closing metathesis approaches were also investigated for the union of the building blocks and stereoselective formation of macrocycle **4** and found unsuccessful as a means to construct the proposed structure of Mandelalide A.

CHAPTER II

Stereoselective Synthesis of Fully Functionalized Acyclic Core of Tianchimycin A

Secondary metabolites produced by actenomycete are an important source of biologically active compounds with novel structures and wide ranging properties. Many of these secondary metabolites are 14 and 16-membered macrolides. Tianchimycin A (**1**) is one such a 16-membered macrolide, isolated from the rare actinomycete *Saccharothrix xinjiangensis* NRRL B-24321 (Figure.1), of Tianchi lake, China in 2013 by Deng and co-workers. Structures of Tianchimycins A-B were determined based on detailed NMR and MS spectroscopy. Architecturally Tianchimycin A is quite interesting. It is a macrocyclic lactone has six stereogenic centers and three olefinic moieties. Out of three double bonds, two are part of 1,4 –butadiene system and the third one is a part of *α,β*-unsaturated lactone moiety. Initial biological studies revealed that they do not have antibacterial activity. However modification of the structure might provide good antibacterial lead. With this intention we initiated a programme for the synthesis of Tianchimycin A to unveil the full biological potential. This chapter describes the stereoselective synthesis of fully functionalized acyclic core of Tianchimycin A.

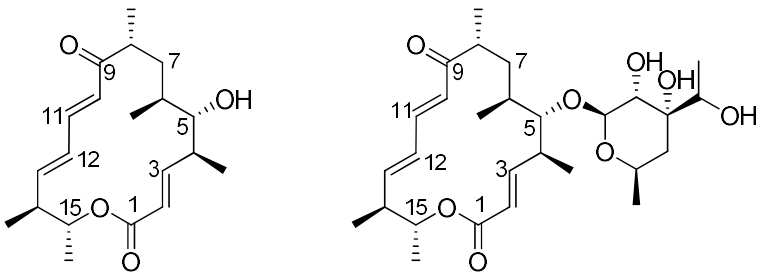
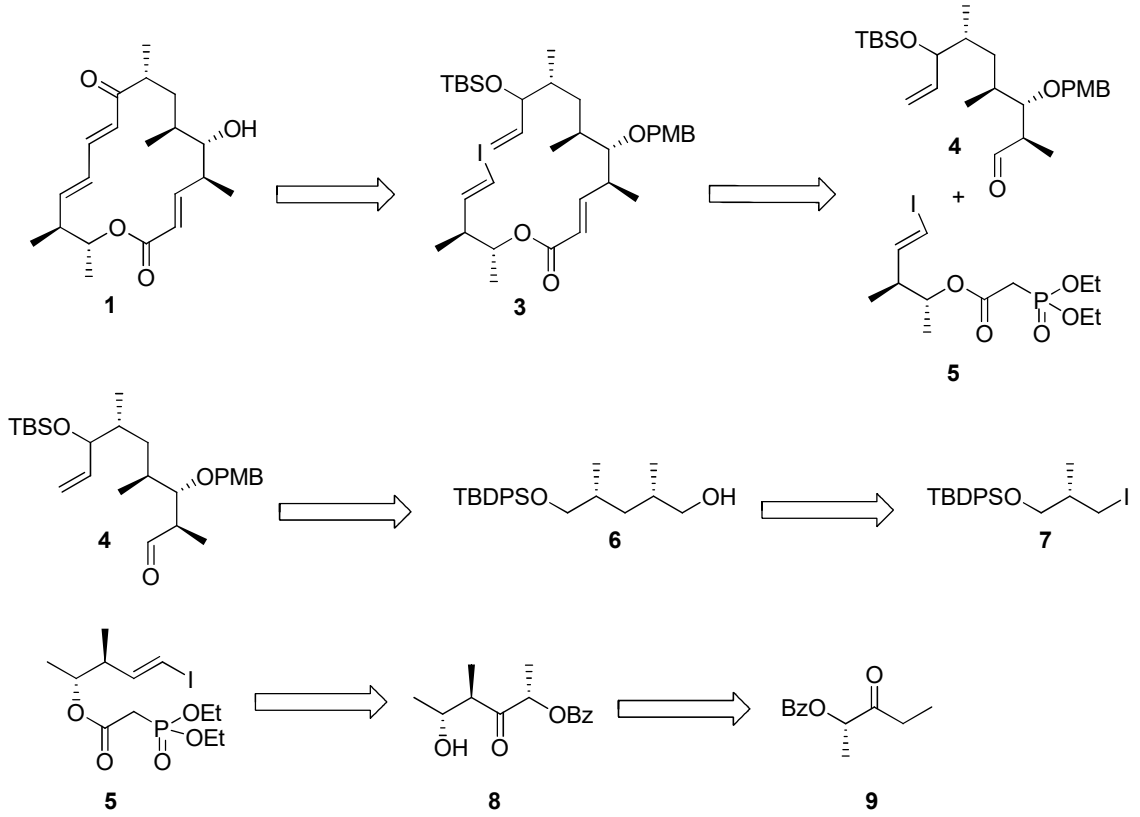


Figure 1

Retrosynthetically (Scheme 1), we envisaged that macrocycle of target molecule could be accessed via intramolecular Heck cyclization, while the cyclization precursor **3** could be obtained from aldehyde **4** and ketophosphonate **5** via Masamune-Roush olefination. The aldehyde **4** would be acquired from the known iodo compound **7** by means of Myers asymmetric alkylation followed by Crimmins aldol reaction and the ketophosphonate **5** might

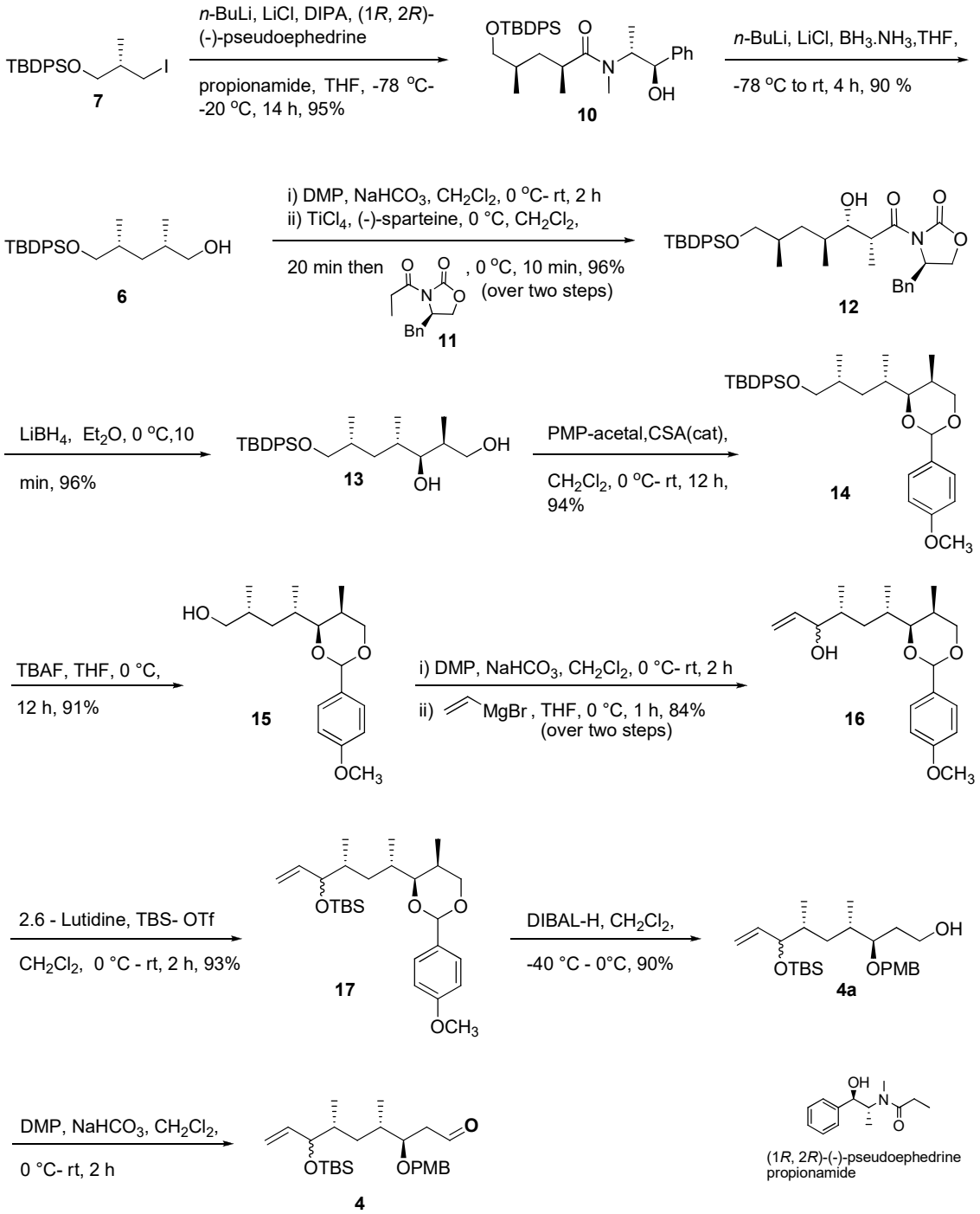
be synthesized from known compound **9** using Paterson's *anti* aldol reaction followed by Takai olefination.



Scheme 1. Retrosynthetic analysis

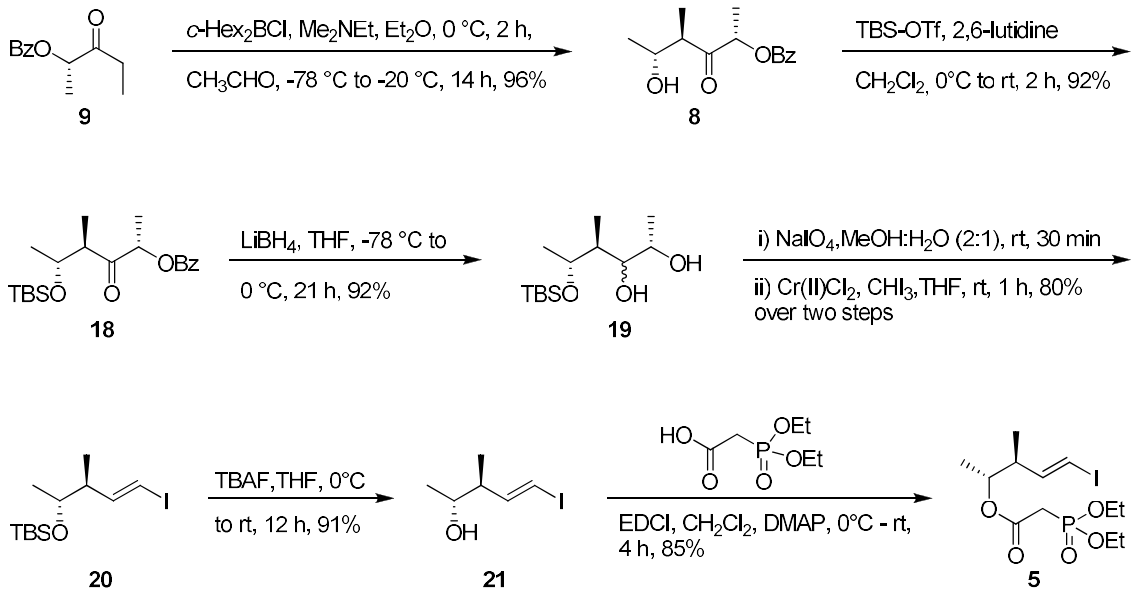
Thus our synthesis commenced with the diastereoselective alkylation of the known iodide **7** with Mayer's pseudoephedrine derived auxiliary to yield amide **10** as a single diastereomer in 95% yield. Reduction of **10** with $BH_3.NH_3$ gave primary alcohol **6** in 90% yield. Compound **6** on oxidation under Dess-Martin Periodinane conditions provided an aldehyde, to which addition of (*Z*)-enolate, generated from **11**, using Crimmins's protocol afforded **12** with excellent diastereoselectivity (98:2 dr), which were separated by standard silica gel column chromatography to obtain the required single isomer **12** in 96% yield. Reductive removal of the chiral auxiliary with $LiBH_4$ in ether furnished the 1,3-diol compound **13**, which on protection as PMP-acetal followed by TBDPS deprotection with TBAF gave a primary alcohol **15**. Oxidation of **15** with DMP gave an aldehyde which on reaction with vinylmganesium bromide yielded diastereomerically mixture of alcohols **16**, which on TBS protection with TBSOTf in presence of 2,6-lutidine gave globally protected

compound **17**. At this stage the *p*-methoxybenzylidine acetal of **17** was opened regioselectively with DIBAL-H to give a primary alcohol **4a**, which was oxidized with DMP to give required aldehyde **4** in 90% yield.



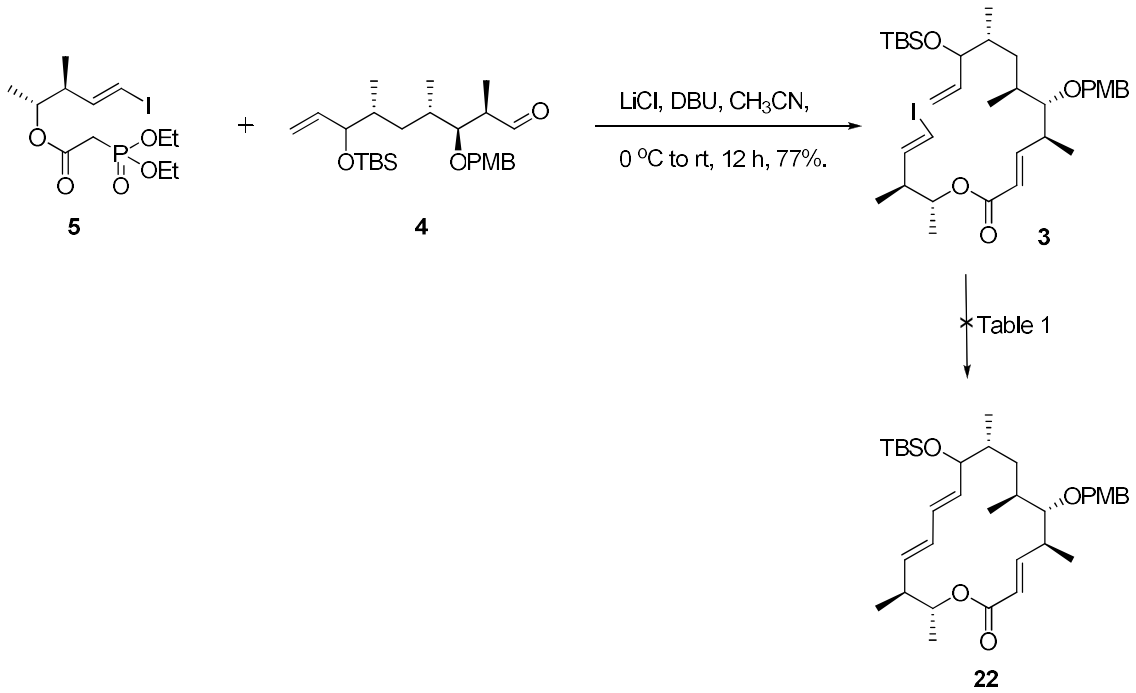
Scheme 2

Synthesis of phosphonate fragment **5** commenced from known keto compound **9** (Scheme 3), which on reaction with acetaldehyde under Paterson's *anti*-aldol conditions using dicyclohexylborane chloride afforded *β*-keto alcohol **8**, in 96% yield with excellent diastereoselectivity which was protected as its TBS ether to give compound **18** in 92% yield. Reduction of the keto as well as benzoate group in **18** with $LiBH_4$ afforded diastereomerically mixture of diols **19** in 92% yield. Oxidative cleavage of the diol with $NaIO_4$ furnished an aldehyde, which on Takai olefination gave vinyl iodide **20** (*E*:*Z* ratio 19:1) in 80% yield over two steps. TBS deprotection from compound **20** furnished a secondary alcohol, which on acylation with diethyl phosphonoacetic acid under EDCI/DMAP conditions afforded the phosphonate **5** in 85% yield.



Scheme 3

Having both the fragments in our hand, the Horner-Wadsworth-Emmons reaction under Masamune-Roush conditions was carried out between aldehyde **4** and the phosphonate **5** in presence of DBU and LiCl in acetonitrile to give key acyclic precursor **3** (Scheme 4) for intramolecular Heck-cyclization. At this stage the crucial intramolecular Heck-cyclization under assorted conditions (Table 1) was not successful leaving the total synthesis still elusive.



Scheme 4

Table 1:

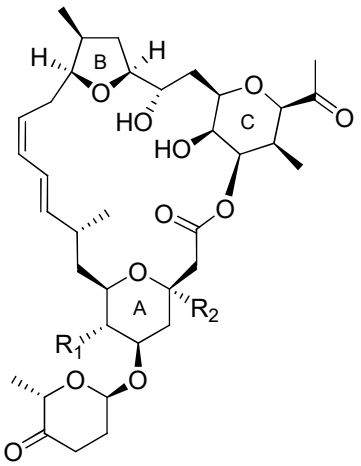
Sl. No	Catalyst	Conditions	Yield (%)
1	$Pd(OAc)_2$	Cs_2CO_3, Et_3N, DMF, rt, 48 h	Decomposition
2	$PdCl_2(MeCN)_2$	Et_3N, HCOOH, MeCN, rt, 1 h	Decomposition
3	$Pd(OAc)_2$	K_2CO_3, DMF, 80 ^oC, 24 h	Decomposition
4	$Pd(OAc)_2$	K_2CO_3, Bu_4NCl, DMF, 60 ^oC, 1 h	Decomposition

In conclusion, we have achieved the fully functionalized acyclic core of Tianchimycin A by employing Mayer's asymmetric alkylation, Crimmins's aldol reaction, Paterson's aldol reaction, Takai olefination and Masamune-Roush olefination as key steps.

CHAPTER III

Synthetic Studies of Madeirolide A: Synthesis of C1-C11 Fragment

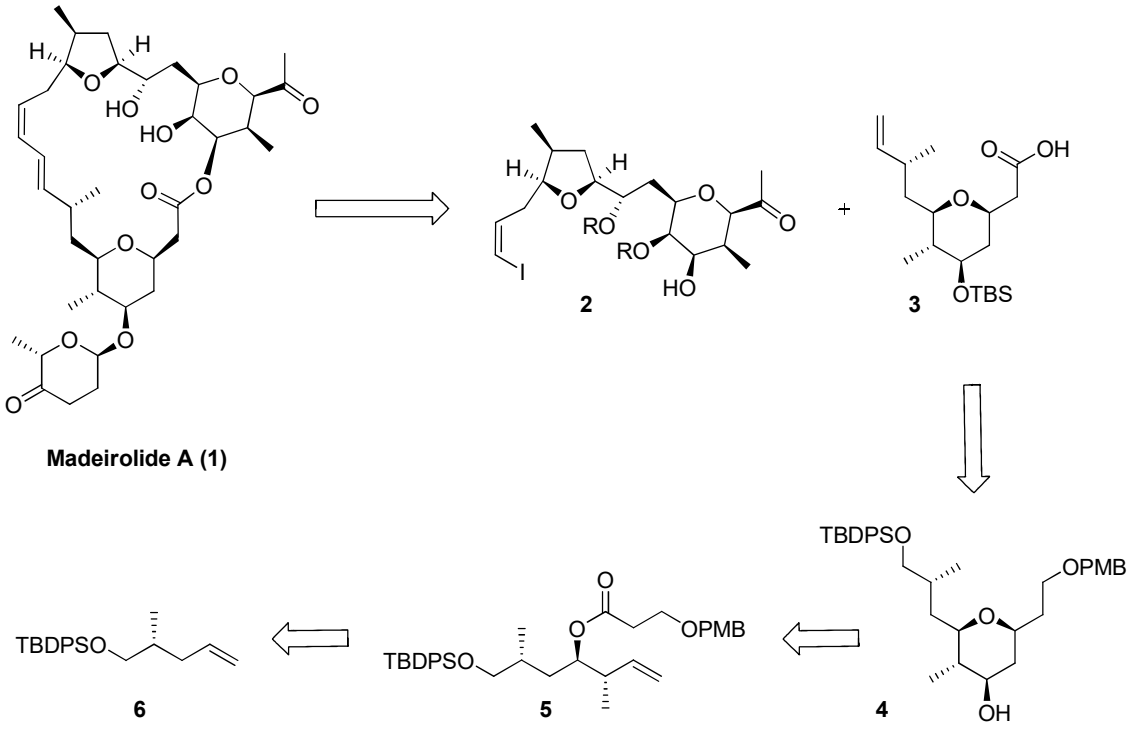
Marine sponges from the order Lithistida have afforded structurally diverse compounds with a variety of biological activities. A notable collection of marine natural products from these sponges are Madeirolides A-B (Figure 1), which were recently disclosed by Wright and Winder from the deep sea off the coast of Madeira, Portugal. Their structures were determined by detailed NMR spectroscopic analysis, and their stereochemical assignment was further validated using Goodman's DP4 computational NMR method. Madeirolide A (**1**) and B (**2**) were shown to be potent inhibitors of the fungal pathogen Candida albicans with fungicidal MIC values of 12.5 and 25 μg/mL respectively. However, the scarcity of isolates from the sponge source (Leiodermatium sp.) has thus far hampered detailed evaluation of their antiproliferative properties. Given the established biological profile of Madeirolides, coupled with its unique structural features have attracted the attention from synthetic and pharmacological communities. As part of our constant interest in developing new strategies for the synthesis of marine natural products, we embarked on the total synthesis of Madeirolides that could enable full-scale biological evaluations. This chapter describes the synthesis of C1-C11 fragment of Madeirolide A, which contains a substituted tetrahydropyran derivative.



Madeirolide A (R_1=Me, R_2=H) (**1**)
Madeirolide B (R_1=H, R_2=OH) (**2**)

Figure 1

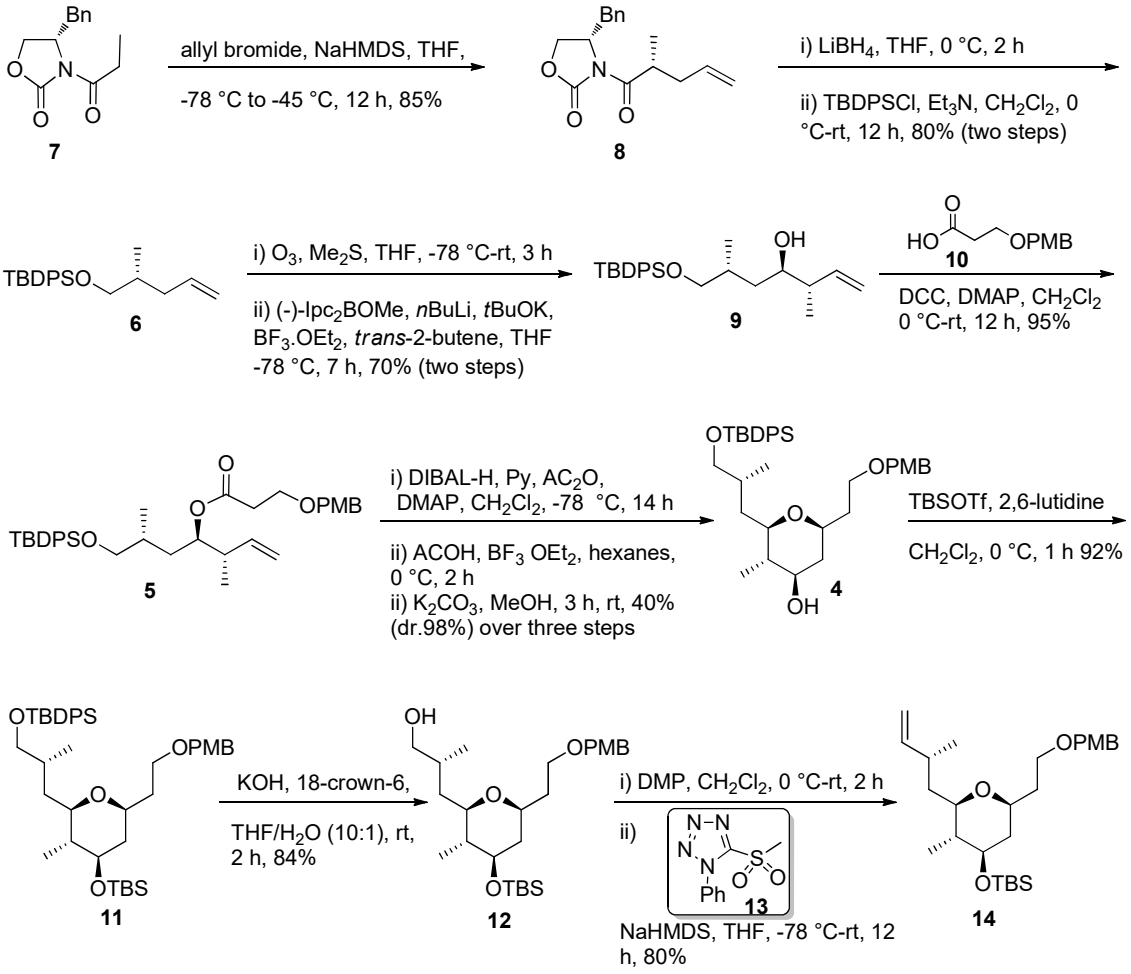
Retrosynthetically (Scheme 1), we envisaged that macrocycle of target molecule could be accessed via intramolecular Heck cyclization, while the cyclization precursor could be obtained from furan iodo compound **2** and pyran acid **3** via Yamaguchi/Shiina macrolactonization. The tetrahydropyran acid fragment **3** could be obtained from the alcohol **4** which in turn could be acquired from ester **5** by utilizing segment coupling Prins cyclization, developed by Rychnovsky and co-workers. The ester **5** was expected to be prepared from alkene **6** by Brown's crotylation followed by acylation with $PMBOCH_2CH_2COOH$.



Scheme 1. Retrosynthetic analysis

The synthesis of pyran segment commenced from the known compound **7** (Scheme 3). Alkylation of **7** with allyl bromide and NaHMDS at –78 °C to –45 °C furnished compound **8** in 85% yield. Removal of chiral auxiliary from compound **8** using $LiBH_4$ in THF at 0 °C provided primary alcohol (volatile) which on protection with TBDPSCl and Et_3N 0 °C resulted in the compound **6** in 80% yield (two steps). Ozonolysis of **6** furnished an aldehyde, which was subjected to Brown's crotylation with *n*-BuLi, (–)-Ipc_2BOMe and *trans*-2-butene at –78 °C to give alcohol **9** in 70% yield (*dr* > 20:1). Acylation of **9** with acid **10** under DCC-DMAP conditions provided compound **5** in 95% yield. Careful reduction of compound **5** followed by acetyl protection of the resulting lactol gave α-acetoxy ether, which

on segment coupling Prins cyclization with $BF_3{\cdot}OEt_2$ and acetic acid in hexanes at 0 ºC followed by the C4-OAc deprotection of the resulting pyran ring afforded desired pyran alcohol **4** in 40% yield (three steps). This, upon TBS protection with TBSOTf followed by selective deprotection of TBDPS under basic conditions furnished primary alcohol **12** in 77% yield over two steps. Alcohol 1**2** was oxidized with Dess-Martin periodinane to give an aldehyde which was subjected to Julia-Kocienski olefination with known sulfone **13**, to give olefin **14** in 80% yield.



Scheme 2

In conclusion we have developed a concise approach for the stereoselective synthesis of the fully functionalized C1-C11 fragment of Madeirolide A in 13 total steps from compound **7** with 11.2% overall yield. The key reactions used in this synthesis are Brown's crotylation, Prins cyclization and Julia olefination. The strategy developed here is flexible and can be used for the completion of the synthesis of the natural product.