SYNTHETIC STUDIES TOWARD AMPHIDINOLIDE W AND HELICONOLS A-C

BY

BHASKAR CHATERJEE

RESEARCH GUIDE

(DR. M. K. GURJAR)

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE-411008

AUGUST 2008

Synthetic Studies Toward Amphidinolide W and Heliconols A-C

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

TO

University of Kalyani

BY

BHASKAR CHATTERJEE

DIVISION OF ORGANIC CHEMISTRY

NATIONAL CHEMICAL LABORATORY

PUNE-411008

AUGUST 2008

DEDICATED

TO MY BELOVED

PARENTS

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, Division of Organic Chemistry, National Chemical Laboratory, Pune - 411 008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

Pune-411008 **(Bhaskar Chatterjee)**

August 2008 **Candidate**

NATIONAL CHEMICAL LABORATORY

Dr. Homi Bhabha Road, PUNE - 411 008 (INDIA)

Dr. M. K. Gurjar

Head & Deputy Director

Division of Organic Chemistry: Technology

Telephone and Fax: + 91-20-25902627

+ 91-20-25902629

E-mail: mukund.gurjar@emcure.in

Website: http://www.ncl-india.org

CERTIFICATE

The research work presented in thesis entitled "**Synthetic Studies Toward Amphidinolide W and Heliconols A-C**" has been carried out under my supervision and is a bonafide work of **Mr. Bhaskar Chatterjee**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-411008

October 2006

(Dr. M. K. Gurjar)

Research Guide

ACKNOWLEDGEMENTS

*It gives me great pleasure to express my deep sense gratitude to my research guide **Dr. M. K. Gurjar**, Division of Organic Chemistry, NCL, Pune for his encouragement and constant support throughout my Ph.D. life. Working with him was a great pleasure and learning experience.*

I would like to thank specially Dr. D. K. Mohapatra for his all time help. The help of Mr. I. Shivakumar, Dr. R. A. Joshi, Dr. R. R. Joshi, Dr. C. V. Ramana, Dr. M. N. Deshmukh, Dr. Hotha Srinivas, Dr. S. P. Chavan, Dr. Muthukrishnan, Dr. A. Murugan and Dr. U. R. Kalkote is also gratefully acknowledged.

I gratefully acknowledge the training and support extended by my senior colleagues Dr. Arindam, Dr. Nagaprasad, Dr. Srinivas, Dr. Ykaborom, Dr. Sankar, Dr. Siddhartha, Dr. Mahesh, Sukhen da, Manjusha, Tushar, Bhagwat, Ramdas and Bhargav during the entire tenure of my Ph.d work. I would also like to thank all my fellow labmates; Pradip, Sahoo, Kullu, Gorakh, Anuj, Sabita, Seetaram, Rahamanda, Ritadi, Ramesh, Raghupati, Sumanth, Kiran, Nageshwar, Soumitra, Indu, Susheel, Abhijit, Srinivas, Sharad, Ganesh, Rosy, Debu, Alam, Rambabu, Ankush, Anand, Mangesh, Sunil, Giri, Rahul for their cooperation and friendly attitude. Above all, I would really like to thank Chinmoy, Mukulda, Dhanada and Smritidi who have created a wonderful and soothing atmosphere during the entire period of my Ph.d life in lab as well as in hostel.

I also sincerely acknowledge the help received from the NMR, mass and microanalysis groups particularly Dr. Rajmohan and all the NMR staff for their all time help and nice cooperation. My sincere thanks to Mrs. C. Raphel, Mrs. P. Kulkarni and all other office staff for their cooperative and friendly nature.

I wholeheartedly thank all my friends in NCL and in Hostel, particularly the Bengali group for their cheerful company, which made my stay in NCL a memorable one. My special thanks to Dr. S. K. Chattopadhyay, Dr. S. P. Das and all other teachers who taught me the basics of chemistry and have laid the platform for me to reach this height and indeed to University of Kalyani for helping me attain this degree. I also owe my sincere thanks to Dr. Ganesh Pandey, Head, Division of Organic Chemistry, National Chemical Laboratory, who have provided me sufficient support to fulfill my research work.

It is impossible to express my deep sense of gratitude for my parents and all my relatives in mere words. My parents are my biggest strength and whatever I am and whatever I will be in the future is because of their commitments and selfless sacrifices to my ambitions.

Finally I thank Director, National Chemical Laboratory, Pune for providing infrastructural facilities to complete my work successfully. I am also thankful to UGC, New Delhi for the financial assistance in the form of fellowship.

Bhaskar Chatterjee

ABBREVIATIONS

ACOH	Acetic acid
Ac_2O	Acetic anhydride
Bn	Benzyl
BnBr	Benzyl bromide
$BH_3.SMe_2$	Boron dimethyl sulfide complex
BH_3.THF	Boron tetrahydrofuran complex
$(COCl)_2$	Oxalyl chloride
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIAD	Diisopropylazodicarboxylate
DIPEA	Diisopropylethyl amine
DMF	*N*,*N*'-Dimethyl formamide
DMAP	*N*,*N*'-Dimethylamino pyridine
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
EtOAc	Ethyl acetate
EtOH	Ethanol
Et_3N	Triethyl amine
Et	Ethyl
Im	Imidazole
MeI	Methyl iodide
MeOH	Methanol
MsCl	Methanesulfonyl chloride
MEM	Methoxyethoxymethyl
Me	Methyl
NMO	*N*-Methylmorpholine-*N*-oxide
Pd/C	Palladium on carbon
Ph	Phenyl
Py	Pyridine

PDC	Pyridiniumdichromate
RCM	Ring closing metathesis
TBDMSCl	*tert*-Butyldimethylchlorosilane
TBDPSCl	*tert*-Butyldiphenylchlorosilane
p-TSA	*para*-Toluenesulfonic acid
TBAF	Tetra-n-butylammonium fluoride
TBAI	Tetra-n-butylammonium iodide
TPP	Triphenylphosphine
THF	Tetrahydrofuran
TsCl	*p*-Toluenesulfonyl chloride

GENERAL REMARKS

❋ ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, and DRX-500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.

❋ ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, and DRX-125 MHz spectrometer

❋ EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.

❋ The X-Ray Crystal data were collected on *Bruker SMART APEX* CCD diffractometer using Mo K_{α} radiation with fine focus tube with 50 kV and 30 mA.

❋ Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm^{-1}.

❋ Optical rotations were measured with a JASCO DIP 370 digital polarimeter.

❋ Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.

❋ All reactions are monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I_2 and anisaldehyde in ethanol as development reagents.

❋ All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen or argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

❋ All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.

❋ Silica gel (60–120) used for column chromatography was purchased from ACME

Chemical Company, Mumbai, India.

CONTENTS

ABSTRACT

ABSTRACT

The thesis entitled **"Synthetic Studies Toward Amphidinolide W and Heliconols A-C"** consists of two chapters. The first chapter is further divided into two sections: Section I describes the synthetic studies toward proposed amphidinolide W. Section II outlines the synthetic studies toward the macrolactone core of revised Amphidinolide W. Chapter II deals with the synthetic studies toward Heliconols A-C. Each section/chapter is subdivided into the following parts: Introduction, Present Work, Experimental, Spectroscopic data and References.

Chapter-1

Section 1: *Synthetic studies toward proposed Amphidinolide W*

Amphidinolides are a group of structurally unique macrolides, isolated from marine dinoflagellates of the genus amphidinium, which are symbionts of okinawan marine acoel flatworms *Amphiscolops spp*. This family of macrolides has significant antitumor properties. Owing to their intriguing medicinal properties and limited natural resource, synthetic studies toward this family of macrolides have provoked much interest. In the realm of 12-membered macrolides, amphidinolide W has been isolated from the marine dinoflagellate *Amphidinium* sp. by Kobayashi *et al.* in 2002. It is structurally distinguishable, since it is the only macrolide in the family which lacks an exomethylene unit. Amphidinolide W shows potent cytotoxicity against murine lymphoma L1210 cells *in vitro* with an IC_{50} value of 3.9 μg/mL. Its interesting structural features and promising biological activity invoked our interest in its total synthesis. The structure of naturally isolated amphidinolide W has been proposed as **1**, but a stereochemical revision has been made to structure **2** (Figure 1) based on total synthesis by Ghosh *et.al*.

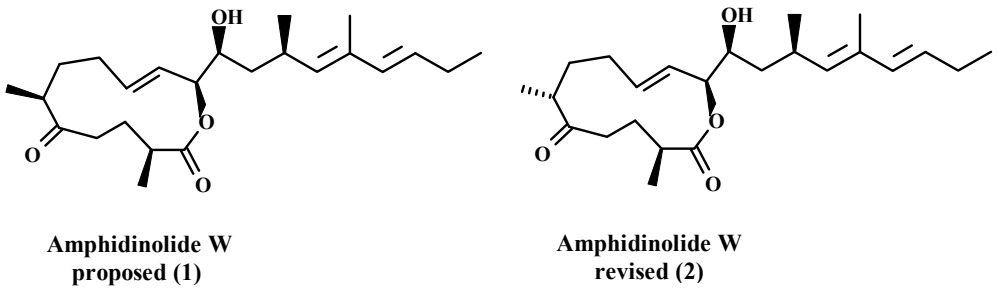
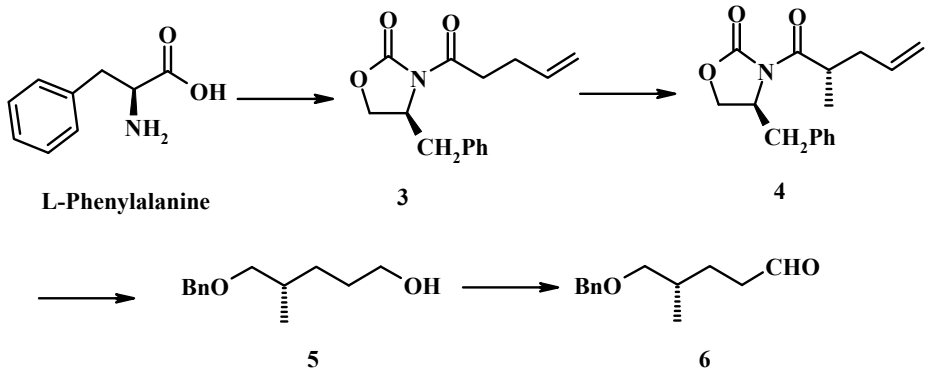


Figure 1: Structure of proposed (**1**) and revised (**2**) amphidinolide W

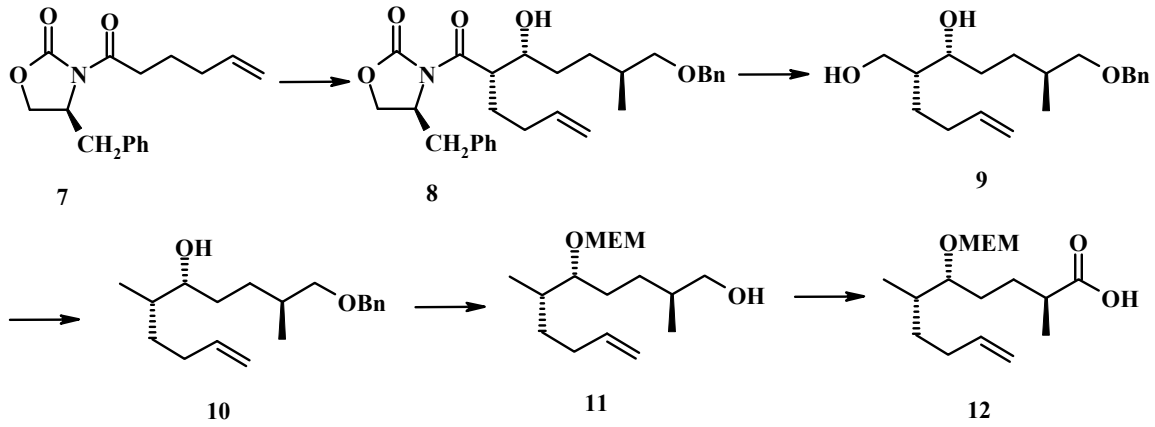
The first section of this chapter describes the synthetic endeavors toward the macrolactone core of proposed amphidinolide W based on a ring closing metathesis approach. We initiated our study with the oxazolidinone derivative **3**, obtained from L-phenyl alanine in three known steps. Methylation using Evans' asymmetric alkylation protocol provided **4** with excellent diastereoselectivity. Subsequent reductive removal of the (4*S*)-benzyl oxazolidinone, benzylation followed by hydroboration gave alcohol **5** which was oxidized with Dess-Martin periodinane (DMP) to form the aldehyde **6** (Scheme 1).



Scheme 1

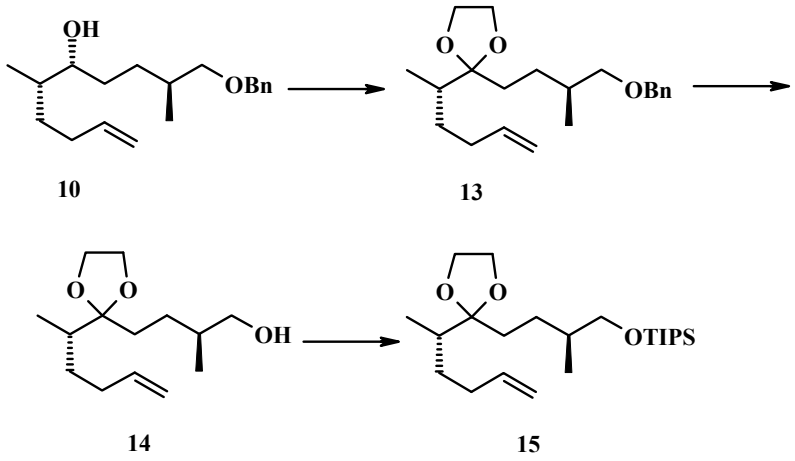
The aldehyde was carried forward for the Evans' aldol reaction with (4*S*)-benzyl oxazolidinone **7** using Bu_2BOTf and DIPEA under Evans' *syn* aldol conditions, resulting product **8** in good yield and diastereoselectivity. The predicted isomer could be

rationalized from literature precedence. Moving ahead with our synthesis, the aldol product was reductively cleaved with sodium borohydride to yield the diol **9**. The primary hydroxyl of diol **9** was selectively tosylated and reduced with lithium aluminium hydride (LAH) to furnish the deoxy compound **10** where the remaining secondary one was protected as its MEM ether which on debenzylation under Birch reduction conditions with Li in liquid ammonia (liq. NH_3) produced **11**. Alcohol **11** was oxidized with PDC in DMF to the corresponding acid **12**, as one of the coupling partners for the pivotal esterification reaction (Scheme 2).



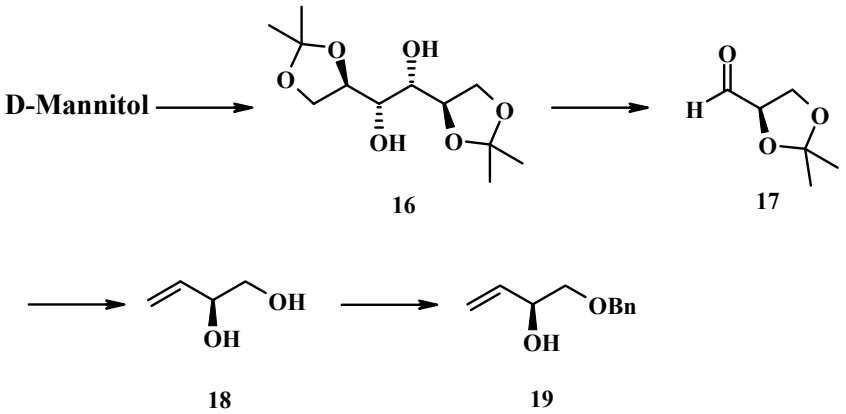
Scheme 2

The intermediate **10** was then carried forward to investigate the configuration of the newly generated methyl centers during the aldol reaction. For this endeavor the deoxy compound **10** was oxidized with IBX to afford the ketone, which was protected as its dioxalane derivative (**13**). Compound **13** was debenzylated and the resulting primary hydroxyl group of **14** was protected as its TIPS ether to furnish the silyl protected compound **15**, whose spectral and analytical data were in complete agreement with the reported values, hence unambiguously confirming the stereochemistry of the methyl centers (Scheme 3).



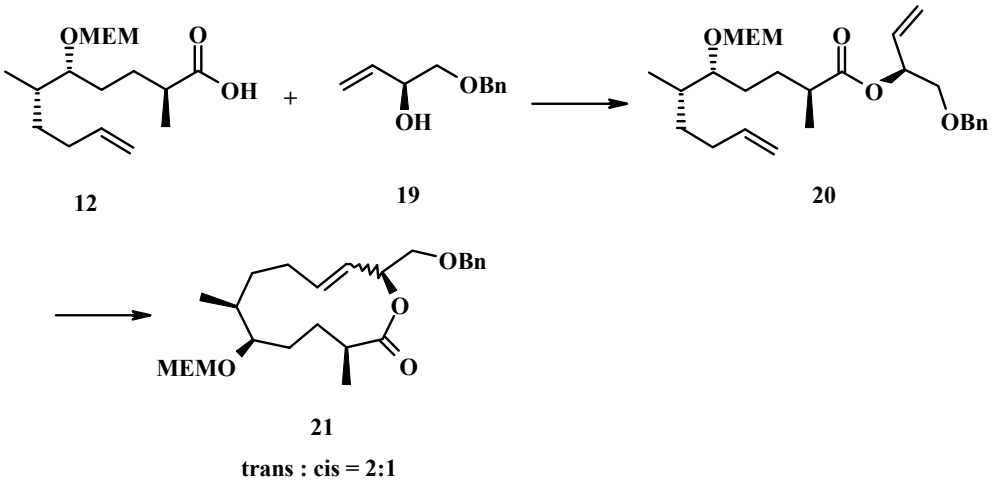
Scheme 3

Our next endeavor was to synthesize the alcohol **19** starting from D-Mannitol as its chiral precursor. Thus D-mannitol was converted to its diisopropylidene derivative (**16**) according to a literature procedure. $NaIO_4$ mediated chopping of **16** gave the aldehyde **17** which was followed up for a one carbon Wittig homologation with subsequent acetonide deprotection under acidic conditions to yield diol **18**. This was selectively benzylated to afford the alcohol **19** which was the other coupling partner for the esterification reaction (Scheme 4).



Scheme 4

Now, the stage was set to couple the acid **12** and the alcohol moieties **19**. Yamaguchi esterification did the needful to furnish the ester as a mixtre of diastereomer, in good yield with a negligible epimerization at the C2 centre. However, flash chromatographic separation of the resulted mixture of diastereomers was possible thus rendering diastereopure **20**. The two alkenyl side arms in **20** were now in suitable position for effecting the ring closing metathesis (RCM) reaction. Thus subjecting **20** to Grubbs 2nd generation catalyst in degassed benzene under refluxing conditions furnished the RCM product **21** as a 2:1 mixture of *trans* and *cis* isomers which was confirmed by ^{1}H and ^{13}C NMR data. Further purification to separate the intractable mixture of two isomers could not be effected by any means (Scheme 5)



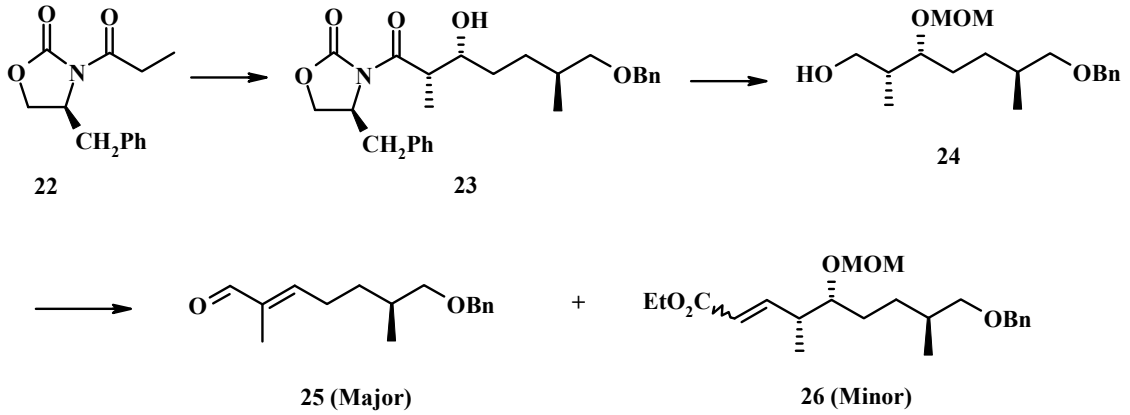
Scheme 5

In conclusion we have developed an efficient stereoselective approach to the macrolactone core of proposed amphidinolide W utilizing the Evans′ approach and the RCM reactions as the key steps. During the execution of this synthetic strategic for the proposed amphidinolide W, the indispensable separation of the mixture of *trans* and *cis* isomers in the RCM reaction with no success and the total synthesis by Ghosh *et al*. along with the revision of the correct structure for amphidinolide W prompted us to find an alternative route to the pivotal lactone core.

Section 2: *Synthetic studies toward the macrolactone core of revised Amphidinolide W*

As part of our ongoing research, the need to hunt for new efficient synthetic strategies is always on demand. For this we were very keen to accomplish a new and more efficient route towards the lactone core of Amphidinolide W. However considering the revision of the structure (confirmed by Ghosh and coworkers) we decided to target the synthesis of the macrolactone of revised Amphidinolide W as our new goal.

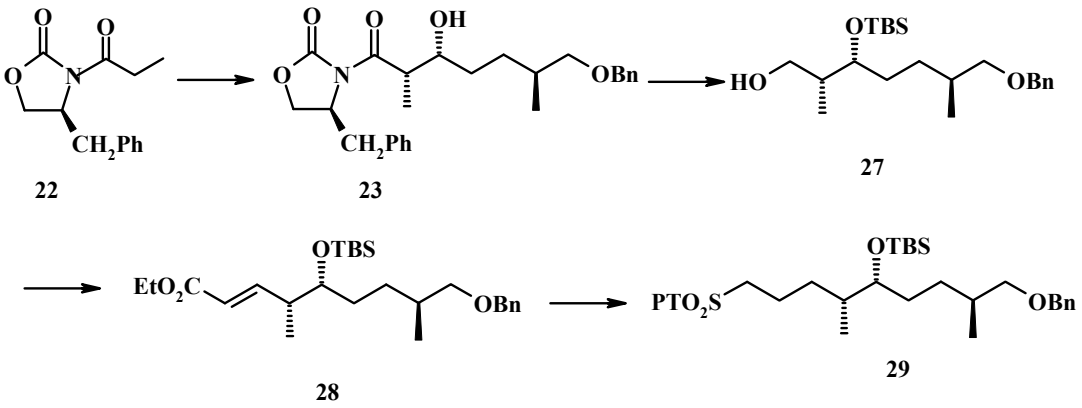
The approach to the aldehyde **6** was akin to our previously mentioned route. On employing the Evans' aldol reaction with the imide **22**, a highly stereoselective aldol product **23** was obtained with excellent yield. MOM ether protection of **23** was followed up with concomitant removal of oxazolidinone to yield **24**. Compound **24** on subsequent oxidation and a two carbon elongation via Wittig olefination afforded unexpectedly an elimination product **25** (Scheme 6) as the major product along with a minor amount of the Wittig product **26**.



Scheme 6

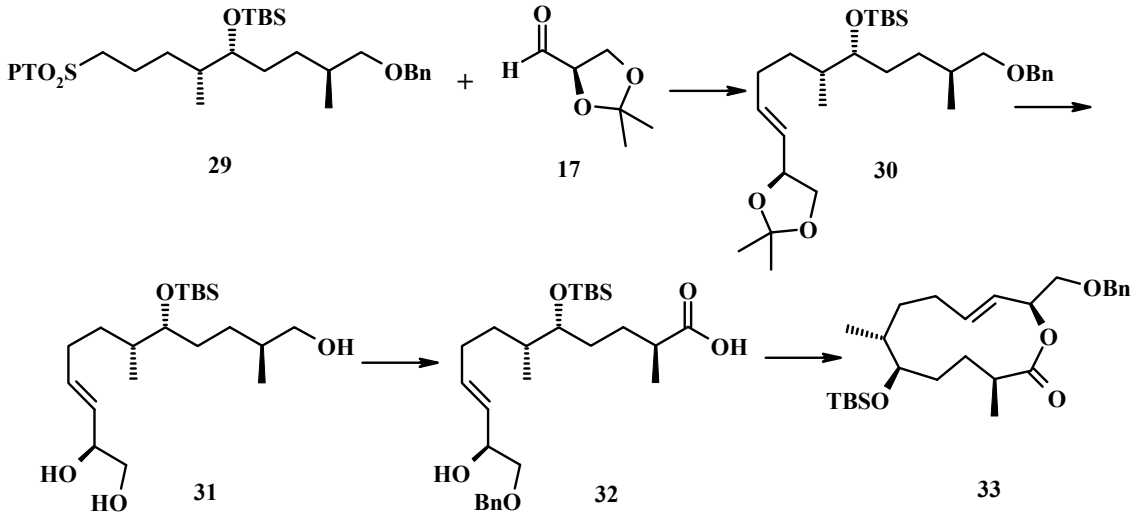
As such the protecting group strategy was manupulated slightly. Instead of MOM ether, the more bulky TBDMS protection of the aldol isomer **23** was followed by reductive removal of oxazolidinone to give **27** in good yield. The primary alcohol in **27** was oxidized and carried forward for a two carbon Wittig homologation to provide **28** exclusively with high *E*-selectivity. The absolute stereochemistry of the newly generated

stereocenters was established at this stage from modified Mosher experiments and NOESY correlation studies. Our next endeavor was to reduce the double bond in a chemoselective fashion and it was effected using $NiCl_2/NaBH_4$ which on further reduction with LAH provided the primary alcohol. Transformation of this resulted alcohol to the sulfone intermediate **29** was carried out in a two stage process. At first the alcohol was converted to the sulfide employing a mitsunobu protocol with 1-phenyl-1*H*-tetrazole-5-thiol. The latter on oxidation using ammonium molybdate tetrahydrate and H_2O_2 mixture afforded the sulfone **29** in good yield (Scheme 7).



Scheme 7

The glyceraldehyde (**17**), to be used for the Julia reaction was achieved in two steps from D-mannitol via a reported procedure which was mentioned earlier. Having obtained the required coupling partners, their engagement was carried out according to the Julia-Kocienski protocol employing KHMDS as a choice of base to deliver the coupled product **30** in good yields and with excellent *E*-selectivity. The acetonide group was selectively cleaved and followed by debenzylation using Birch reduction conditions to yield **31**. The latter was selectively benzylated and a two step oxidation process furnished the seco acid **32**. Our final and main objective was to carry out the lactonisation of the seco acid **32**, which was successfully achieved utilizing the Trost lactonisation protocol with absence of epimerition at C2 thus affording lactone **33** in high selectivity as shown in scheme 8.



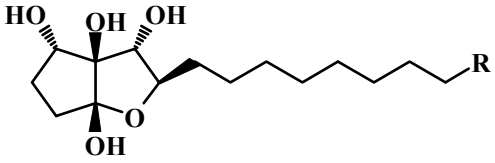
Scheme 8

In conclusion, we have fruitfully established a new and efficient strategy including the successful selective installation of the *trans* olefinic double bond and in addition, the lactone core was achieved in a highly stereoselective manner involving the modified Julia olefination and the epimerization free Trost lactonisation as key steps.

Chapter 2: *Synthetic studies toward Heliconols A-C*

In 2006, Gloer and co-workers reported the isolation, structure elucidation, and biological activity of three new compounds, Heliconols A-C (**1-3**) (Figure 1); all containing an unusual reduced furanocyclopentane unit, obtained from the fresh water aquatic fungus *Helicodendron giganteum* Glen-Bott (Helotiaceae) and collected from a sample of submerged wood in Alaska. Heliconols A-C (**1-3**) were tested against *Candida albicans* (ATCC 14053), *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (ATCC 6051), *Escherichia coli* (ATCC 25922), *Aspergillus flarus* (NRRL 6541), and *Fusarium verticillioides* (NRRL 25457). Heliconol A (**1**) was found to inhibit the growth of F. verticilloides and exhibit profound activity against *C. albicans*, *S. aureus* and *B. subtilis*. It showed also to be more biologically active compared to heliconol B (**2**) and C (**3**). The relative and absolute stereochemistry of heliconol A (**1**) was *prima facie* established by

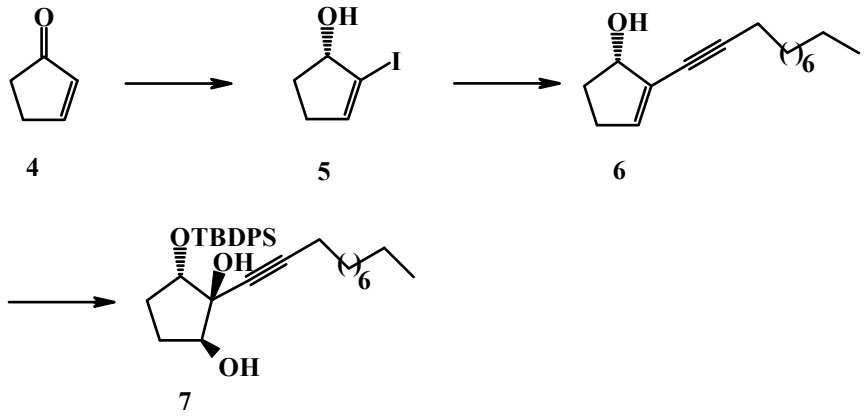
NOESY and single-crystal X-ray crystallographic analysis of its dibromobenzoate derivative.



Heliconol A(1): R = Me
B(2): R = CH_2OH
C(3): R = CO_2H

Figure 1

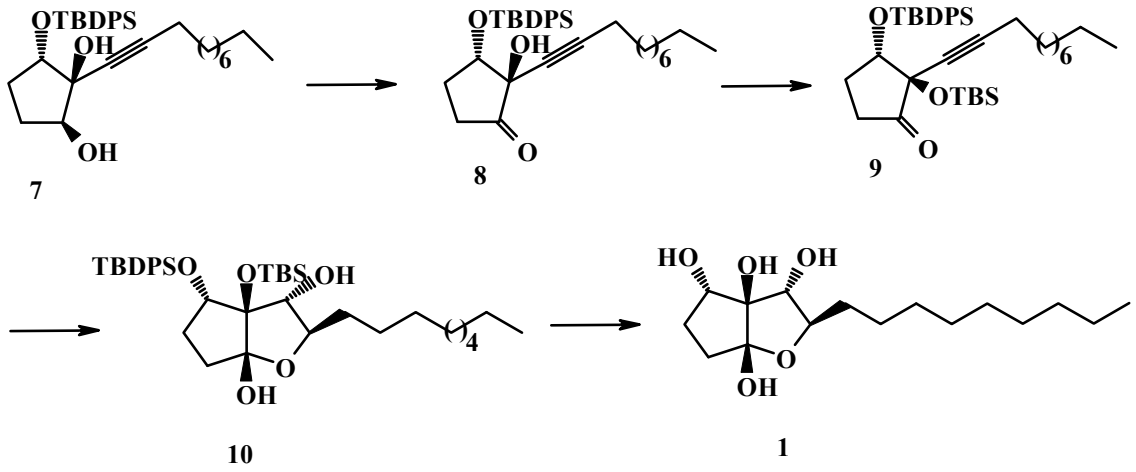
We were mainly interested to develop a vergenic synthetic strategy which would allow the synthesis of all the heliconol derivatives. For this target, we started off with the commercially available 2-cyclopentenone **4** as our starting material which was converted to 2-iodo-2-cyclopentenone by a known literature method. Corey-Bakshi-Shibata (CBS) reduction of the ketone established the newly generated stereocenter of **5** perfectly. Confirmation was achieved through spectral, HPLC analysis and from its optical rotation values. Sonogashira coupling with 1-undecyne proceeded with excellent yields to provide **6**. The free hydroxyl was protected as its TBDPS ether, which was dihydroxylated in a highly stereofacial manner to afford the diol **7** (Scheme 1).



Scheme 1

The diol **7** was smoothly oxidized to the hydroxyl ketone derivative (**8**), which was protected as its TBS ether **9**. Partial reduction of the alkyne followed by

dihydroxylation and in situ cyclisation afforded the bicyclic compound **10**. Finally global deprotection with TBAF furnished Heliconol A (**1**), which was confirmed with all its spectral data. In a similar manner following the same synthetic protocol the other Heliconol derivatives B (**2**) and C (**3**) can be synthesized by simply modifying the alkyne side chain moiety (Scheme 2).



Scheme 2

In conclusion, we have developed a very simple and efficient route for synthesis of heliconol A and its derivatives in a highly stereospecific manner.

CHAPTER - I

.....

.....

SYNTHETIC STUDIES TOWARD AMPHIDINOLIDE W

INTRODUCTION

INTRODUCTION

Cancer is and will become an increasingly important factor in the global burden of disease in the decades to come. Cancer is the Latin word for crab, used by ancients, due to its crab like tenacity of a malignant tumor and sometimes seems to show in grasping the tissue, it invades. The term Cancer is used generically for more than 100 different diseases (such as breast, prostate, stomach, colon, lung, mouth etc.), including malignant tumor of different sites. Common to all forms is the failure of the mechanism that regulates normal cell growth, proliferation and cell death. The estimated number in new cases is expected to rise to 15 million by 2010. Among them, the majority lived in the developing world. In contrast the cancer in developed countries is the second most common cause of death, while epidemiological evidence points to the emergence of a similar trend of developing countries. So the world still conjures up deep fears of silent killer that creeps up on us without warning.

The diseases arise principally as a consequence of exposure of individuals to carcinogenic inhale, eat, drink and their work place or environment. With the existing knowledge it is possible to prevent at least one third of 10 million cancer cases that occur annually through out the world. Our goal is to reduced the morbidity and morality from cancer and improve the quality of life of cancer patients and their families everywhere in the world where the cancer burden is high or there are arising trends of cancer risk factors.

Nature has been a relevant resource for the discovery of anticancer entities. Today, more than 60 % of the anticancer drugs commercially available are of natural origin;[1] naturally derived antiproliferative drugs such as doxorubicin, daunomicin, bleomycin, mytomicin C, vincristine and vinblastine play an important role in curative cancer chemotherapy in a number of solid tumors and haematological malignancies. These available results clearly anticipated the potential of the marine ecosystem in cancer chemotherapy. In this context, it is important to consider that the major antiinfective, anticancer, analgesics and immunosuppressive compounds are of natural origin. The first living organisms appeared in the sea more than 3500 million years ago[2,3] and

evolutionary development has equipped many marine organisms with the appropriate mechanisms to survive in a hostile milieu in terms of extreme temperatures, changes in salinity and pressure, as well as overcoming the effects of mutation, bacteria and viral pathogens. Marine organisms have developed exquisitely complex biological mechanisms showing cross phylum activity with terrestrial organisms.

Technical barriers have created a setback in extensive marine folk medicine in the western world. Chinese pharmacopoeia recommends seaweed-based recipes for a number of disorders such as pain, abscesses, menstrual difficulties and cancer.[4] Marine based chamanic medicine includes representative examples of antiinfective entities.[4] During the last 25 years natural products derived from marine organisms have been the focus of many investigations.[5] Representative examples of marine derived therapeutics include Manoalide, a non steroidal sesterpenoid, a novel marine compound that might be considered as a prototype with therapeutic potential as anti-inflammatory and analgesic. Manoalide is the first inhibitor of phospholipase A2 and is being explored in a number of disorders.[6] Discodermolide, a novel polyhydroxylated lactone with potent immunosuppressive activity shows, *in vivo*, 100-1000 times more potent than cyclosporine-A and also harbours cytotoxic activity.[7]

Several other marine organisms isolated from tropical and subtropical seas such as halichondrin B from sponges; didemnin B, aplidine, and ecteinascidin 743 from ascidans; bryostatin 1 from bryozoan; and dolastatin 10 and kahalalide F from sea hare have attracted the natural product and pharmaceutical chemists.

Other than these therapeutic, a number of marine based macrolides with varying macrolactone sizes have been isolated from different sources which have shown potent cytotoxicity against cancer cell lines. Novel macrolide compounds lasonolide A (**1**)[8] and lasonolide B (**2**)[9], isolated from a marine sponge and other isomers of these compounds serve as useful antitumor agents and as biochemical tools. Other examples of highly potent, cytotoxic macrolides include the salicylihalamides A (**3**) and B (**4**)[10] which were isolated from the sponge *Halicona* sp. This new class of macrolides incorporates a salicylic acid core together with a 12-membered lactone ring and an enamide side chain (Figure 1).

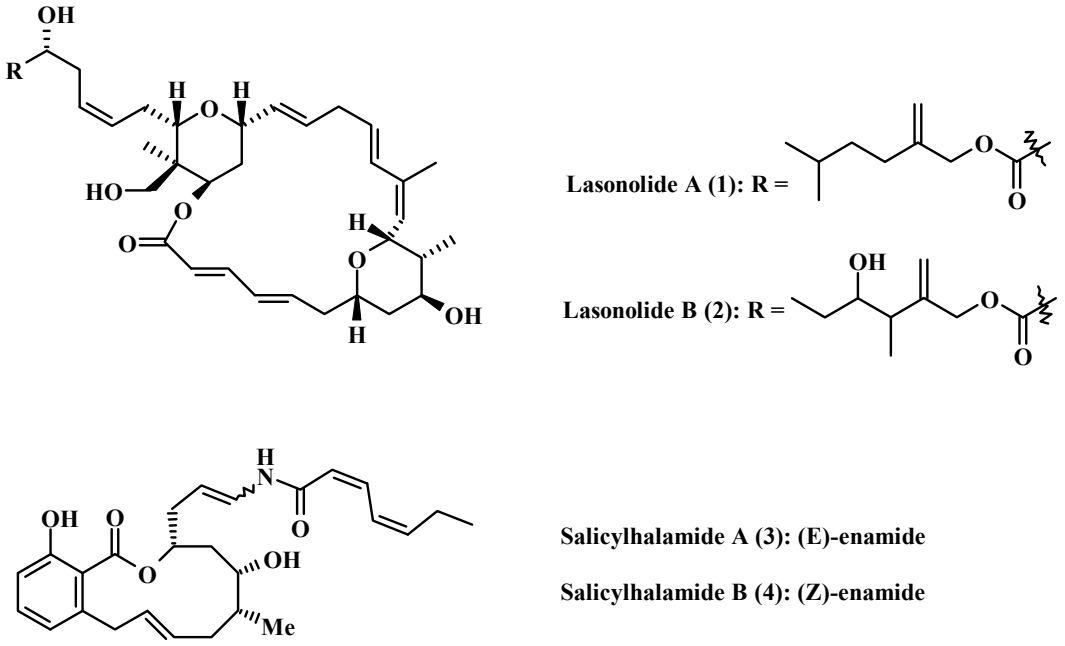
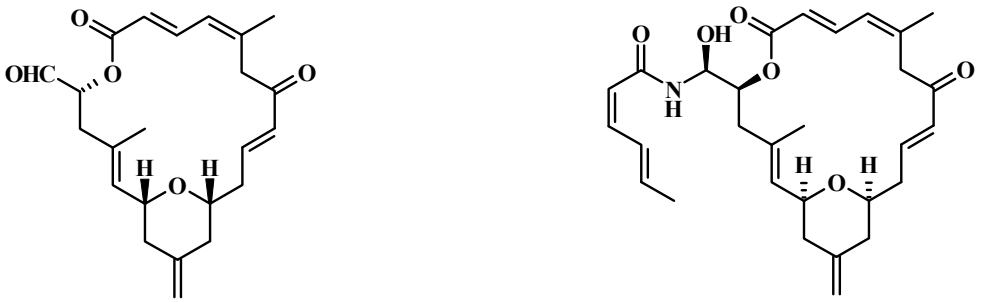


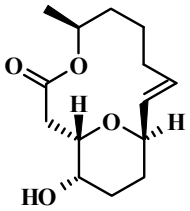
Figure 1

A few other cytotoxic macrolides includes the dactylolide (**5**)[11] and zampanolide (**6**)[12], isolated from the vanuata sponge *dactylospongia* sp.; Aspergilide A (**7**), B (**8**) and C (**9**), isolated from *aspergillus ostianus* strain 01F313[13] and showed cytotoxic activity against mouse lymphocytic leukemia cells (L1210) (Figure 2). Haterumalides and biscelides, isolated from okinawan marine animals representing 14-membered macrolides witnessed strong cytotoxicity against human cancer cell lines. Apart from these there exists a wide range of other macrolide families which are known to exhibit sufficient cytotoxic behaviour.

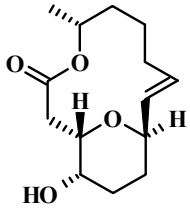


(+)Dactylolide (5)

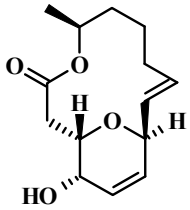
(-)Zampanolide (6)



Aspergilide A (7)



Aspergilide B (8)



Aspergilide C (9)

Figure 2

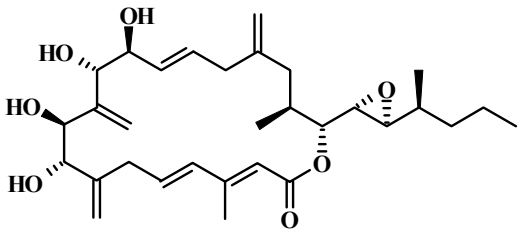
Marine microorganisms such as bacteria, cyanobacteria, dinoflagellates etc. have attracted many natural product chemists as the real producers of marine toxins such as fish and algal poisons and bioactive substances isolated from marine invertebrates such as sponges, tunicates and so on. Among marine microorganisms, dinoflagellates have been important sources of marine toxins and have been investigated world wide by natural product chemists. There have been continued investigations on chemically interesting and biologically significant secondary metabolites from symbiotic marine dinoflagellates *Amphidinium* sp. which were separated from inside cells of Okinawan marine flatworms. These marine dinoflagellates are the source of a series of cytotoxic macrolides, designated ***amphidinolides*** and long chain polyketides of the marine origin.

Amphidinolides: a brief review

The Amphidinolides are a family of cytotoxic macrolides having significant antitumor properties. They were found to exhibit potent cytotoxic activity (70-90% inhibition at 3 μg/mL) against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells. In total, 34 cytotoxic Amphidinolide species have been isolated so far; A-H, J-S, T1, U-Y, G2, G3, H2-H5 and T2-T5, some of whose total synthesis have also been reported. In addition, a linear short polyketide, amphidinin A, and eight long chain polyketides, colopsinols A-E and luteophanols A-C have been isolated from this species.[14-16] Mentioned underneath is a short account of some of the amphidinolide species with regard to their isolation, biological activity and synthetic endeavours.

Amphidinolide A

Amphidinolide A (**10**) is a 20-membered macrolide possessing a dienoate chromophore, three *exo*-methylenes, two 1,2-diols, three branched methyls and an epoxide and exhibits cytotoxicity against L1210 cells (IC_{50} 2.0 μg/ml) and KB cells (IC_{50} 5.7 μg/mL)[17]. The gross structure of **10** (Figure 3) was initially predicted on the basis of NOESY experiments and ^{1}H-^{1}H coupling constants. Synthetic studies for this macrolide has been approached by three different groups; a) Pattenden *et al.*[18] b) Maleczka *et al.*[19] and c) Trost *et al*.[20] all succeeding in its total synthesis, though none of their synthetic compounds could match the spectroscopic data with the natural ones hence causing reinvestigation of the original structure.



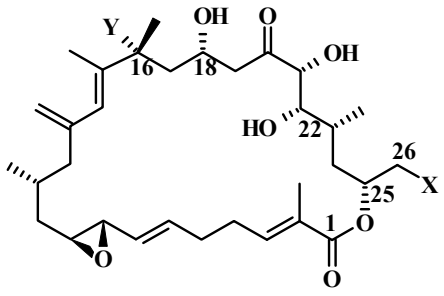
Amphidinolide A (10)

Figure 3

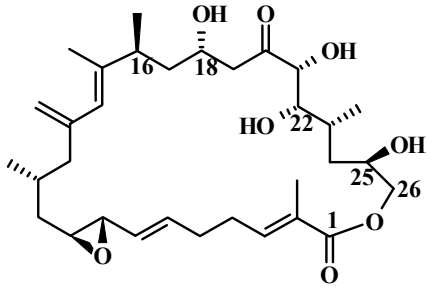
Amphidinolide B and H- type macrolides

Amphidinolide B (**11**) is a 26-membered macrolide with an allyl epoxide and an *S-cis* diene moiety, and shows potent cytotoxicity (IC_{50} 0.00014 and 0.0042 μg/mL) against L1210 and KB cells respectively.[21,22] Three new amphidinolide B congeners were isolated by Shimizu and coworkers as B1, B2 and B3.[23] Amphidinolide B1 was shown to be identical to amphidinolide B by comparison of its spectral and rotation values while amphidinolides B2 and B3 were found to be C18 and C22 epimers of **11** respectively.[23]

Amphidinolides G (**12**) and H (**13**) are similar type macrolides having a 27- and 26-membered lactone ring respectively and are regiomers at the C-26 and C-25 position. Amphidinolide H differs from amphidinolide B in the position of a hydroxyl group at C-16 and C-26 position respectively[24] and exhibits antitumor activity against murine leukemia P338 mice (T/C: 140% at a dose of 0.2 mg/kg). Both amphidinolides G and H are known to have the same absolute configuration (Figure 4). Other related macrolides in this group constitute amphidinolide L, a 26-membered macrolide with a tetrahydropyran moiety,[25] amphidinolide D, H2-H5, and two amphidinolide G congeners G2 and G3.[26] Several synthetic approaches to amphidinolide B and H have been carried out by different groups; one by Kobayashi *et al*.[27,28], Pattenden *et al*.[29] and Nishiyama *et al*.[30]



Amphidinolide B: X = H, Y = OH(11)
Amphidinolide H: X = OH, Y = H(13)



Amphidinolide G (12)

Figure 4

Amphidinolide C, F and U

Amphidinolides C[31] (**14**) and F (**15**) are 25-membered macrolides having two tetrahydrofuran rings and vicinally located one-carbon branches. Amphidinolide C exhibited potent cytotoxicity against tumor cells. Amphidinolide F[32] is a congener of amphidinolide C with a shorter side chain by a C_6 unit than that of **14**. Amphidinolide U[33] (**16**) is a novel 20 membered macrolide possessing a tetrahydrofuran ring, two *exo*-methylenes, three branched methyls, two ketones, two hydroxyl groups, and a C_{10} linear side chain. The gross structure of amphidinolide U is very much closely related to amphidinolide C which suggests that it may be biogenetically related to amphidinolide C (Figure 5).

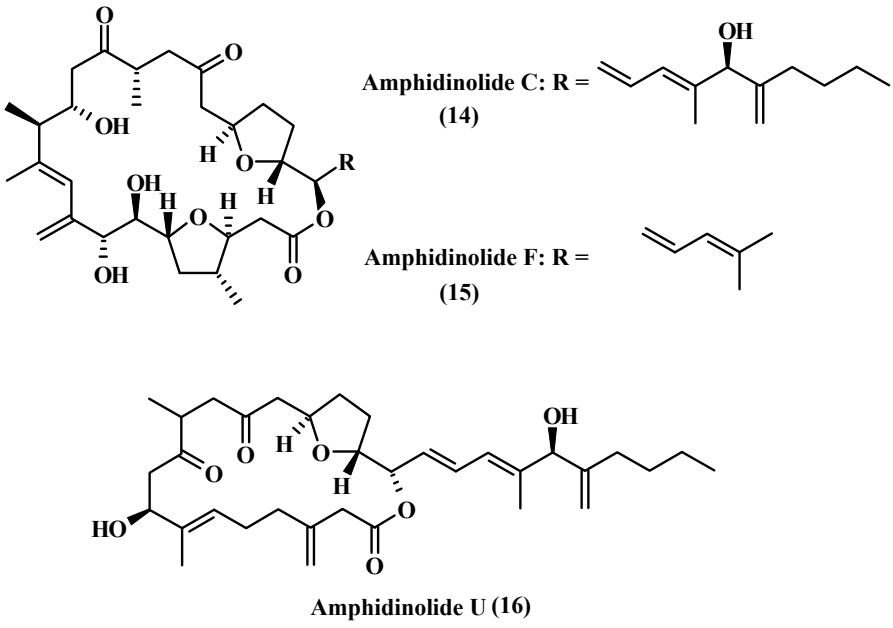


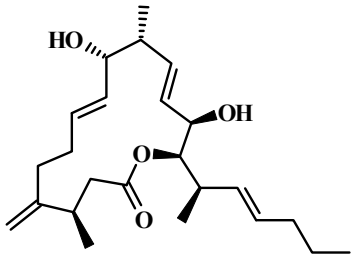
Figure 5

Amphidinolide C exhibits potent cytotoxicity against L1210 and KB cells *in vitro* with IC_{50} values of 0.0058 and 0.0046 μg/mL respectively. On the other hand amphidinolides F and U showed only weak toxicity against L1210 cells (IC_{50}: 1.5 and 12.0 μg/mL) and KB cells (IC_{50}: 3.2 and 20.0 μg/mL) respectively. Roush *et al.*[34] have

developed a synthetic approach towards amphidinolide F. Certain other routes to the fragments of amphidinolide C and U were established by other groups.[35]

Amphidinolide J-type macrolides

Amphidinolide J[36] (**17**) is a 15-membered macrolide with two hydroxyl groups and four C_1 branches, two of which are adjacent to each other. A complete total synthesis of amphidinolide J was reported by Williams and Kissel.[37] Amphidinolides R and S are minor congeners of amphidinolide J,[38] amphidinolide R being only a regioisomer of **17** having a 14-membered macrolactone while amphidinolide S was concluded to be a 9-dehydro form of **17** by spectroscopic data (Figure 6).

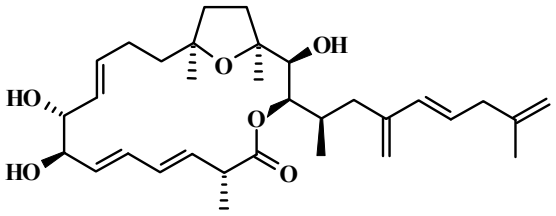


Amphidinolide J (17)

Figure 6

Amphidinolide E

Amphidinolide E[39] (**18**) is a 19-membered macrolide possessing a tetrahydrofuran ring, four C_1 branches, and three hydroxyl groups and exhibits cytotoxicity against L1210 cells (IC_{50}: 2.0 μg/mL) (Figure 7). A number of synthetic approaches including two total syntheses have been reported for this macrolide. Lee and coworkers[40] have carried out a well versed synthesis of the molecule. Other synthetic studies were accomplished by Roush *et al*. [41], Gurjar *et al*. [42] , Marshal *et al*. [43]

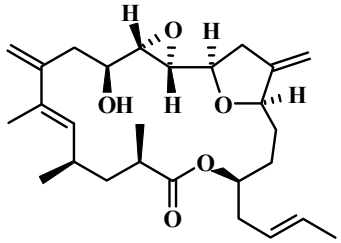


Amphidinolide E(18)

Figure 7

Amphidinolide K

Amphidinolide K,[44] (**19**) a 19-membered macrolide containing a tetrahydrofuran ring, an epoxide, and a S-*trans* diene moiety was structurally elucidated from 2D NMR data. Williams and Meyer[45] have achieved through a total synthesis of its originally proposed structure, based on the sign of its optical rotation, a structural revision and concluded the structure of amphidinolide K to be **19** (Figure 8).



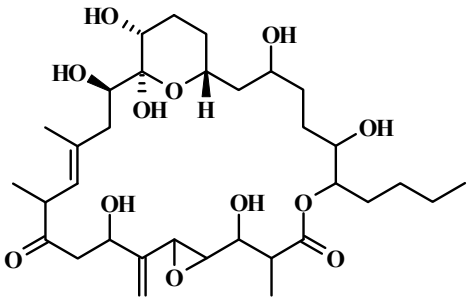
Amphidinolide K(19)

Figure 8

Amphidinolides M and N

Amphidinolide M[46] has a 29-membered macrolactone ring with two tetrahydrofuran units, an epoxide, two diene moieties and two vicinally located methyl or *exo*-methylene groups. The stereochemistry of amphidinolide M is undetermined and it is known to exhibit cytotoxic behaviour against L1210 (IC_{50}:1.1 μg/mL) and KB cells (IC_{50} :0.44 μg/mL). The structure of amphidinolide N[47] (**20**) was interpreted to consist of a 26-membered macrolide containing a 6-membered hemiacetal ring, an epoxide, a keto

carbonyl, four C1 branches and seven hydroxyl groups. Although it's relative stereochemistry was predicted its absolute configuration still remains unclear. This compound shows high cytoxicity against L1210 and KB cells (IC_{50}: 0.00005 and 0.00006 μg/mL), respectively (Figure 9).

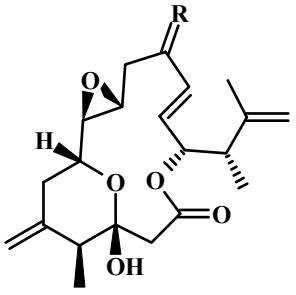


Amphidinolide N (20)

Figure 9

Amphidinolide O-Q and V

Amphidinolides O (**21**) and P (**22**) are 15-membered macrolides possessing a tetrahydropyran ring, an epoxide and two vicinally located methyl or *exo*-methylene groups.[48] The only structural difference between amphidinolide O and P is at the C-11 position, a ketone for **21** and an exo-methylene for **22** which is very rare in natural product analogs (Figure 10). Williams *et al*. have successfully achieved a stereocontrolled synthesis of amphidinolide P.[49] Amphidinolide Q[50] and V[51] are respectively 12 and 14-membered macrolides. Both show cytotoxic behaviour against L1210 (IC_{50}: 6.4 and 3.2 μg/mL) and KB cells (IC_{50}: > 10 and 7 μg/mL), respectively.

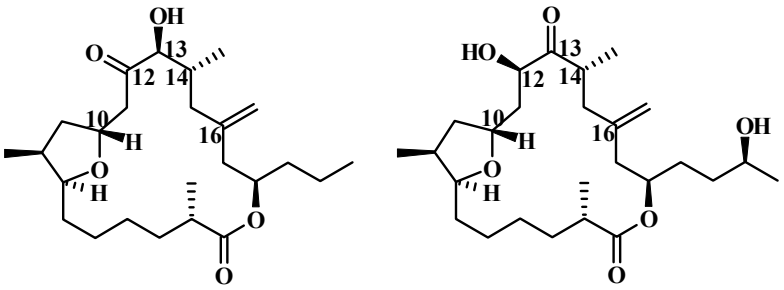


Amphidinolide O: R = O (21)
Amphidinolide P: R = CH_2 (22)

Figure 10

Amphidinolides T-type macrolides:

Amphidinolide T1[52] (**23**) is a 19-membered macrolide possessing a tetrahydrofuran ring, one *exo*-methylene, three branched methyls, one ketone and one hydroxyl group. The structure was elucidated by modified Mosher experiments and confirmed by single crystal X-ray analysis. Amphidinolide T2 [53] (**24**) is a congener of T1 with one carbon elongation at C-21 while amphidinolides T3, T4, T5 are 12-dihydro-13-dehydro isomers of **23** respectively.[53] A number of groups have achieved the total synthesis of these group of macrolide compounds; recently Furstner and coworkers achieved the total synthesis of amphidinolide T4[54] and Ghosh *et al*. have successfully accomplished the total synthesis of amphidinolide T1.[55] Besides these, many synthetic approaches towards amphidinolide T1-T5 were reported by several other groups.[56] Amphidinolides T1-T5 exhibit modest cytotoxic behaviour against L1210 cells *in vitro* with IC_{50} values of 18, 10, 7, 0, 11 and 12 μg/mL rrespectively (Figure 11).



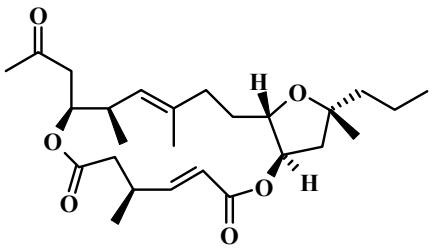
Amphidinolide T1 (23) **Amphidinolide T2 (24)**

Figure 11

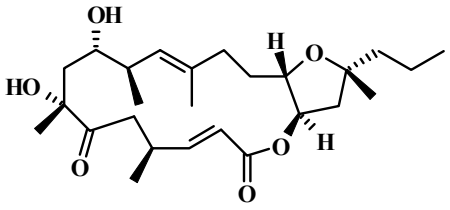
Amphidinolide X and Y:

Amphidinolide X (**25**) is a cytotoxic 16-membered macrodiolide,[57] which consists of a polyketide-derived diacid and diol units from natural sources. More recently, a 17-membered macrolide amphidinolide Y[58] (**26**) was isolated from the same species and it was elucidated to exist as a 9:1 equilibrium mixture of 6-keto and 6(9)-hemiacetal forms on the basis of 2D NMR data. The 6-keto forms of amphidinolide Y possess a tetrahydrofuran ring, five branched methyls, a ketone and two hydroxyl groups. Both

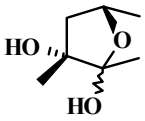
amphidinolides X and Y show cytotoxicity against L1210 cells (IC_{50}: 0.6 and 0.8 μg/mL) and KB cells (IC_{50}: 7.5 and 8.0 μg/mL) respectively (Figure 12). Synthetic studies towards these macrolides were demonstrated by Furstner group [59] and Dai group.[60]



Amphidinolide X(25)



6-keto form



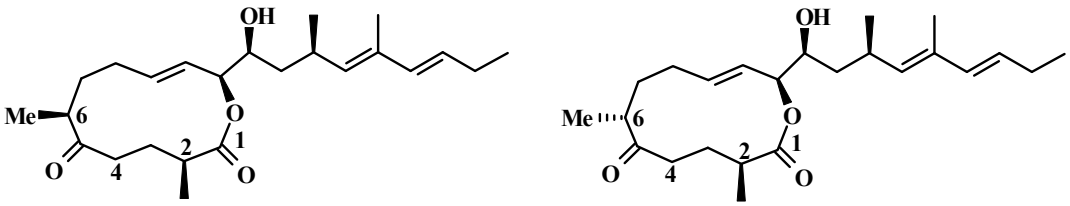
6(9)-hemiacetal form

Amphidinolide Y (26)

Figure 12

Amphidinolide W:

Amphidinolide W (**27**), a cytotoxic 12-membered macrolide was isolated from dinoflagellate *Amphidinium* sp.[61] Its gross structure was assigned on the basis of spectroscopic data, *J*-based configuration analysis and a modified Mosher method. Amphidinolide W is the first macrolide without an exo-methylene unit among all the isolated amphidinolides so far. It exhibits potent cytotoxicity against murine lymphoma L1210 cells *in vitro* with an IC_{50} value of 3.9 μg/mL. A stereoconvergent synthesis by Ghosh *et al*.[62] revised the originally proposed structure of **27** to **28** (a stereochemical inversion at C-6) (Figure 13).



Amphidinolide W proposed

(27)

Amphidinolide W revised

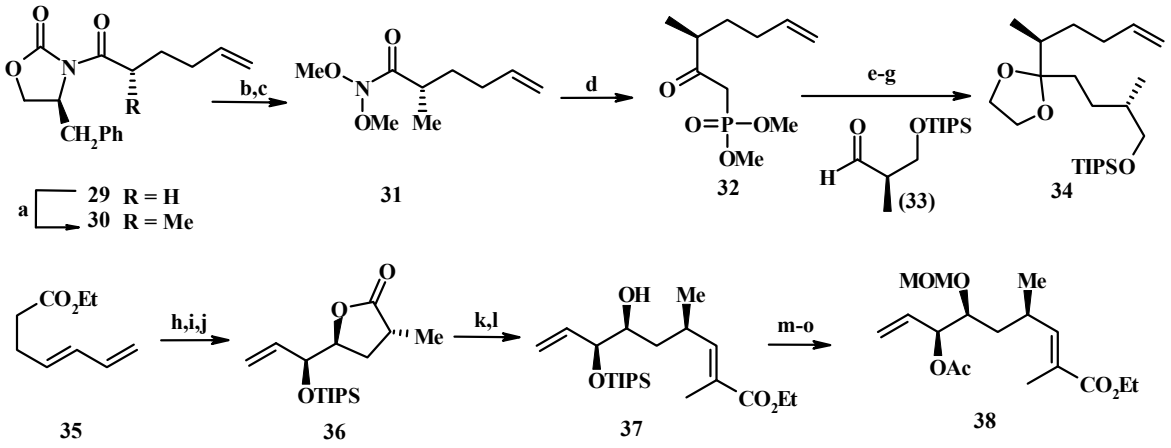
(28)

Figure 13

Past work related to the synthesis of Amphidinolide W:

Ghosh and coworkers[62] have reported the first total synthesis of Amphidinolide W. Their synthetic strategy was based on a cross metathesis approach for the installation of the C9-C10 olefin followed by lactonisation by Yamaguchi procedure. Through chemical correlations involving ^{1}H and ^{13}C NMR they revised the originally proposed structure for amphidinolide W, a stereochemical inversion at C-6.

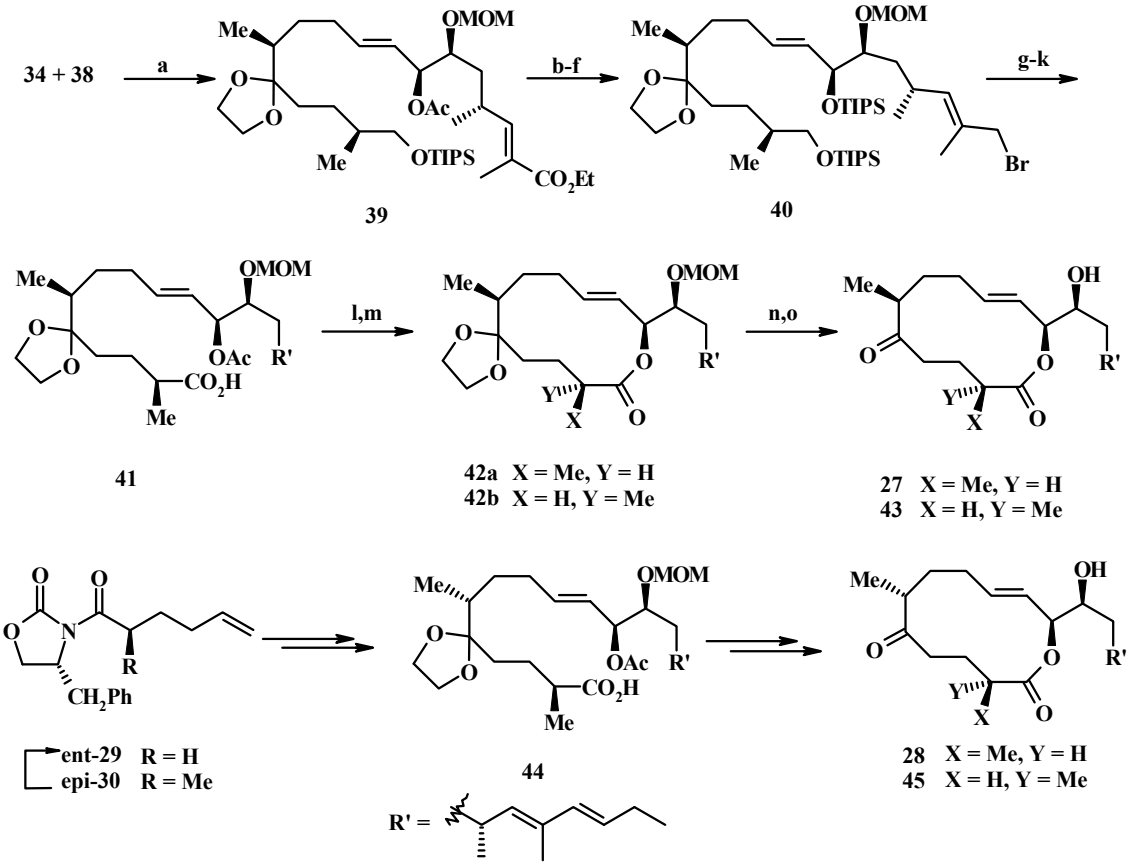
Their synthesis commenced with the methylation of oxazolidinone **29** to provide **30** diastereoselectively (ratio 15:1). Basic hydrolysis of **30** with subsequent amidation afforded Weinreb amide **31** which was converted to the β-ketophosphonate **32** followed by Horner-Emmons reaction with aldehyde **33** to the corresponding enone; the latter on selective reduction and dioxalane protection afforded **34**. The other fragment **38** was synthesized starting with the asymmetric dihydroxylation of diene **35** to furnish the hydroxy lactone which on TIPS protection, stereoselective alkylation followed by DIBAL reduction and subsequent Wittig olefination provided *E*-olefin **37** and then a series of protecting group manipulations afforded fragment **38** (Scheme 1).



Scheme 1

Reagents and Conditions: a) NaHMDS, MeI, –78 °C; b) LiOOH, aqueous THF, 0 °C; c) MeONHMe.HCl, *N*-methylpiperidine, ^{i}BuOCOCl, –15 °C; d) ^{n}BuLi, $MePO(OMe)_2$, –78 °C; e) $Ba(OH)_2$, (**33**), THF/H_2O; f) Red-Al, CuBr, –20 °C; g) *p*-TSA, $HOCH_2$-CH_2OH, $(EtO)_3CH$, 55 °C; h) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 0 °C; i) TIPSOTf, 2,6-lutidine; j) LDA, MeI, –78 °C; k) DIBAL-H, CH_2Cl_2, –78 °C; l) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, 45 °C; m) MOMCl, *i*-Pr_2NEt ; n) TBAF, THF; o) Ac_2O, Et_3N, DMAP.

Cross metathesis of the above two fragments **34** and **38** produced **39** which on sequential DIBAL reduction, selective protection, deprotection and treatment with CBr_4 resulted bromide **40**. Formation of phosphonium salt with subsequent Wittig olefination with propionaldehyde exclusively formed the *E*-olefin. Removal of the TIPS groups followed by diacetate protection, then selective primary acetate removal and oxidation furnished the acid **41**. Macrolactonisation under Yamaguchi conditions provided the macrolactone (**42a**) and its C-2 epimer **(42b)**. Final removal of both the protecting groups furnished natural amphidinolide W (**27**) and its diastereomer **43**, though discrepancies in its ^{1}H and ^{13}C spectrum were observed in the synthetic compound. After thorough investigation they elected to invert the C-6 stereochemistry via a complete synthesis starting from *ent*-**29** and following the same synthetic protocol. Macrolactonisation again provided a 1:1 mixture of diastereomers but spectral agreement with the reported values established the correct structure to be **28** (structural revision of **27**) (Scheme 2).



Scheme 2

Reagents and Conditions : a) $(H_2IMeS)(PCy_3)(Cl)_2Ru$=CHPh (5 mol%), CH_2Cl_2, 45 ^oC; b) DIBAL-H, –78 ^oC; c) PivCl, Py; d) TIPSOTf, 2,6-lutidine; e) DIBAL-H, –78 ^oC; f) CBr_4, PPh_3, 0 ^oC; g) PBu_3, CH_3CN; then ^{t}BuOK, CH_3CH_2CHO, PhH/THF, 0 ^oC; h) TBAF, THF; i) Ac_2O, Et_3N, DMAP; j) lipase PS-30, pH 7.4; k) PDC, DMF; l) K_2CO_3, MeOH; m) $^i Pr_2NEt$, 2,4,6-trichlorobenzoyl chloride, DMAP, PhH, 80 ^oC; n) PPTS, acetone/H_2O, 40 ^oC; o) $BF_3.Et_2O$, Me_2S, –20 ^oC.

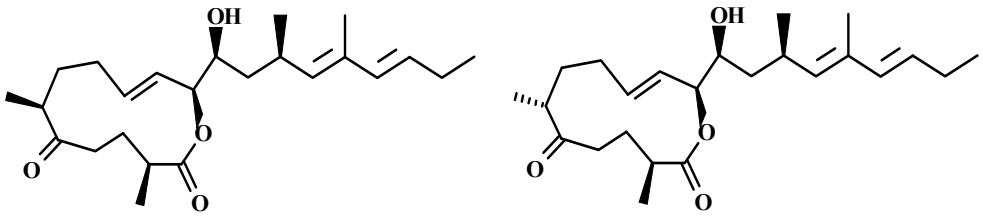
SECTION - I

SYNTHETIC STUDIES TOWARD PROPOSED AMPHIDINOLIDE W

PRESENT WORK

PRESENT WORK

Amphidinolides constitute a group of structurally unique macrolides isolated from marine dinoflagellates of the genus amphidinium, which are symbionts of okinawan marine acoel flatworms *Amphiscolops* spp.[63] Owing to their profound biological activity (mainly antitumor properties) and scarce abundance, these family of macrolides set a great challenge to synthetic organic chemists.[64] Amphidinolide W, a 12-membered macrolide was isolated by Kobayashi[61] in 2002 from marine dinoflagellate Amphidinium sp. The gross structure of Amphidinolide W was elucidated mainly on the basis of spectroscopic studies including analysis of its MTPA esters and its degradation products. Amphidinolide W shows potent cytotoxicity against murine lymphoma L1210 cells in vitro with an IC_{50} value of 3.9 μg/mL and is structurally unique, being the first and only member in the family which lacks an exomethylene unit.[61] This macrolide is characterized by its 12-membered lactone ring and a C-9 side chain consisting of five stereogenic centers in the molecule. Amphidinolide W was naturally isolated having the structure **1**, but a stereochemical revision has been made to structure **2** (Figure 1) based on a total synthesis by Ghosh *et al*.[62] Interesting structural features coupled with the significant biological activities prompted us to undertake its total synthesis.



Amphidinolide W proposed (1)

Amphidinolide W revised (2)

Figure 1: Structure of proposed (**1**) and revised (**2**) amphidinolide W.

The first section of this chapter describes the synthetic endeavors toward the macrolactone core of proposed amphidinolide W based on a ring closing metathesis (RCM) approach.

Retrosynthetic analysis:

A close inspection of the macrolide suggests that the molecule could be disconnected at the $\Delta^{9,10}$ *E*-olefin which could be joined by a ring closing metathesis (RCM) reaction. A further disconnection at the ester stage **3** creates two fragments **4** and **5**. We were initially concerned to test the feasibility of the RCM reaction; as a result a simple alcohol (**11**) was affixed in place of **5** for the job, with the view to extrapolate the side chain later on in our synthesis. Thus fragment **4** could be retraced back to **6**, which can be obtained from the aldol product **7** between aldehyde (**9**) and oxazolidinone derivative (**8**). The aldehyde (**9**) could be derived from the oxazolidinone derivative (**10**) using Evans' asymmetric alkylation as key step. The starting material for the oxazolidinone (**10**) was L-phenylalanine as the cheap and commercially available chiral source (Figure 2).

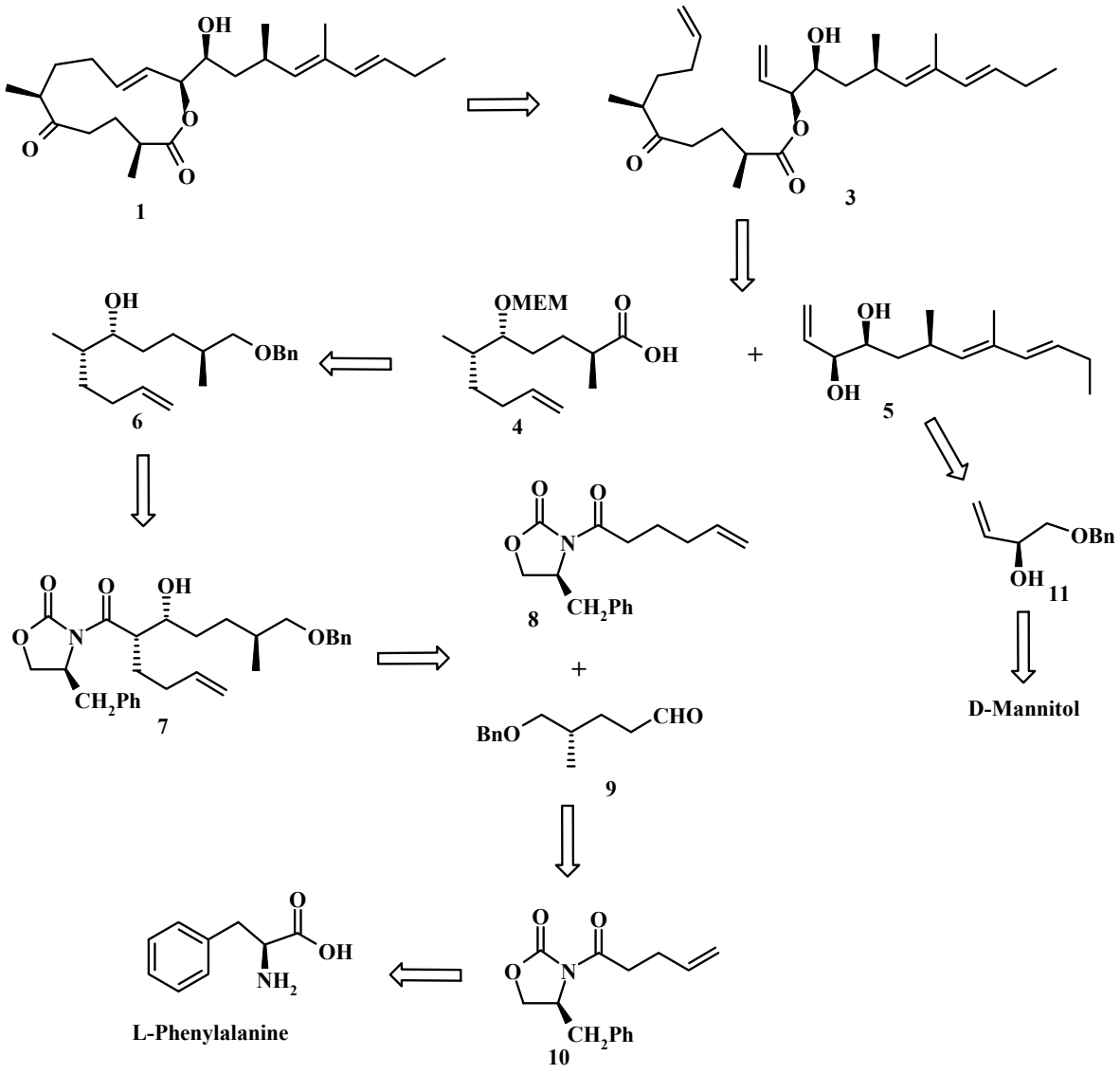
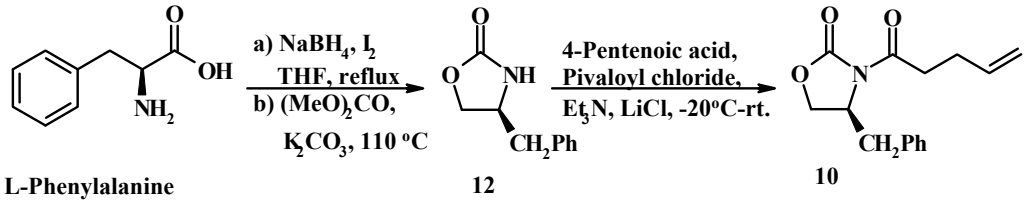


Figure 2: Retrosynthetic analysis of the macrolactone core of amphidinolide W.

Synthetic approach:

We began our synthesis from easily available L-phenylalanine. Accordingly, L-phenylalanine was reduced to L-phenylalanilol with sodium borohydride and iodine in THF[65] and then protected as its cyclic carbamate **12** using K_2CO_3 and dimethyl carbonate at 110 ^oC. *N*-acylation of the carbamate using 4-pentenoic acid, pivaloyl chloride, lithium chloride and Et_3N furnished the chiral imide **10**.[66] The presence of lithium chloride was

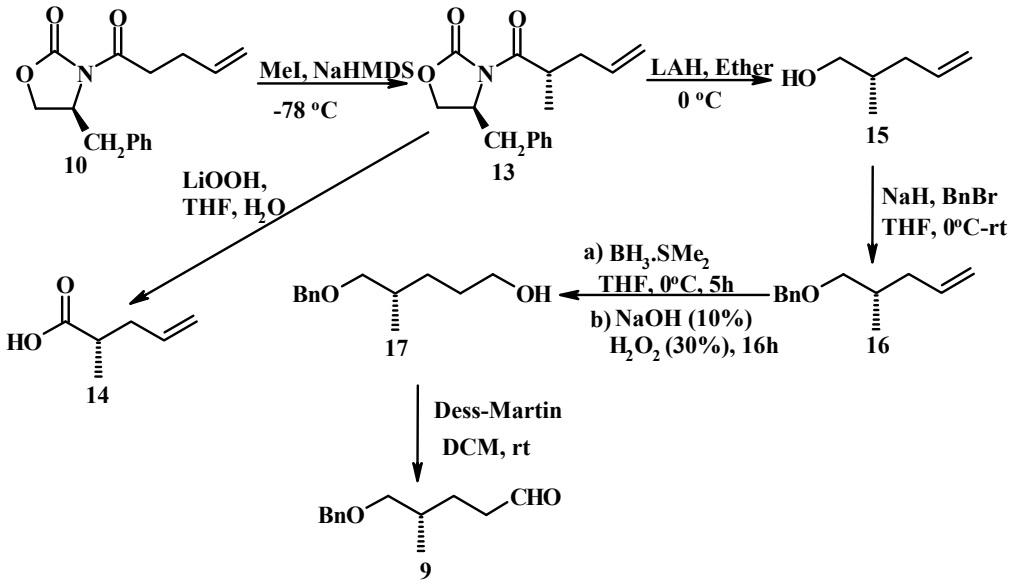
essential for acylation, possibly due to the chelating ability of the lithium ion, which results in activation of the acid anhydride. The ^{1}H and ^{13}C NMR spectrum of **10** were in complete agreement with assigned structure (Scheme 1). For instance the olefinic protons were found resonating at δ 4.99-5.14 (2H) and 5.87 (1H) ppm as multiplets, also there was clean indication of aromatic protons due to the benzyl group.



Scheme 1

The oxazolidinone derivative (**10**) was subjected to lewis acid mediated Evans' alkylation[67] with methyl iodide to afford the methylated derivative (**13)** in 85% yield. The diastereomeric purity (19:1) was assessed on the basis of ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum, a clean doublet at δ 1.23 due to the methyl protons together with the olefinic protons resonating at δ 5.0-5.11 (2H) as a multiplet and 5.78 (1H) ppm as a multiplet accounts for the assigned structure of **13**. Evans and co-workers have previously demonstrated the stereochemical outcome of such a diastereoselective alkylation process.[67] Further evidence could be ascertained by hydrolyzing the oxazolidinone to the acid **14** and comparing the data with the reported values[68] of its optical rotation; literature $[\alpha]_D^{25}$ = +10.1 ($CHCl_3$), observed $[\alpha]_D^{25}$ = +9.5 (*c* 1.0, $CHCl_3$). The oxazolidinone in **13** was smoothly cleaved with lithium aluminium hydride in Et_2O[69] to furnish the alcohol **15** which could not be purified owing to its volatile nature. As such the crude residue was benzylated to afford the benzylated derivative (**16**) in 86% yield, over two steps, after chromatographic purification. The ^{1}H spectra of **16** displayed signals due to benzylic protons at δ 4.48 ppm as a singlet and the aromatic protons in the range 7.23-7.31 ppm as a multiplet, with the remaining protons resonating as usual; ^{13}C spectra was also indicative of the existing carbons in **16**. Next, hydroboration of the benzyl derivative (**16**) was carried out using $BH_3.SMe_2$ to afford the primary alcohol **17** in good

yield.[69] The absence of olefinic protons in the NMR spectrum with 2-protons appearing at δ 3.56 as a triplet due to the -CH_2OH group is a confirmation for the above mentioned compound. On exposure of **17** to Dess-Martin periodinane[70,71] in CH_2Cl_2 provided the desired aldehyde **9** (Scheme 2) which was set for the Evans aldol reaction. The aldehyde **9** was substantiated from its ^1H NMR data which displayed a triplet at δ 9.74 due to the aldehydic proton with the other protons resonating in their respective values.



Scheme 2

A short account on Evans' asymmetric aldol reaction

The directed aldol reaction[72] allows the construction of new carbon-carbon bonds in a regio-, diastereo- and enantioselective manner. The kinetically controlled boron-mediated aldol reaction is particularly powerful for the efficient synthesis of β-hydroxyl carbonyl compounds.[73] Compared to other metal enolates the boron-oxygen bond in boron enolates is relatively short which, on addition to aldehydes, leads to tight cyclic transition states and highly stereoselective carbon-carbon bond formation. Chiral auxiliaries attached to the boron enolate are frequently employed to control the relative and absolute stereochemistry of the aldol products.

Over the last decade, the stereochemical attributes of the asymmetric aldol reaction have been improved through the introduction of architecturally refined enolate metal centers and is one of the most important and general methods for asymmetric carbon-carbon bond formation. The utility of asymmetric aldol reactions has been amply demonstrated through a multitude of synthetic applications.[74] The development of chiral enolates which participate in the highly stereoregulated aldol condensations has been a challenging undertaking.[75] The control of reaction diastereoselection (E1 + E2 vs T1 + T2) and enantioselection (E1 vs E2 or T1 vs T2) must be addressed in conjunction with this problem (Figure 3).

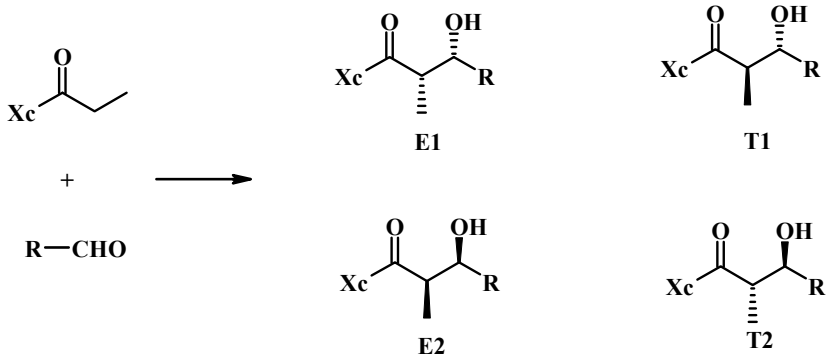


Figure 3

In this aspect the Evans' aldol reaction has served as a promising tool for the diastereo as well as enantioselective generation of chiral centers. Dibutylboron enolates of N-acyl oxazolidinones, which serve as chiral auxiliaries, pioneered by Evans are the most commonly utilized enolates and are highly effective for the formation of Evans syn aldol products. Normally boron-mediated aldol reactions usually proceed through a highly ordered cyclic transition state proposed by Zimmerman and Traxler[76] where other factors have an influence on the selectivity. Thus, (E)-boron enolates usually favour the formation of Evans anti aldol products, whereas (Z)-boron enolates afford the syn aldol products.[77] The transition states for the enolate formation are depicted below (Figure 4).

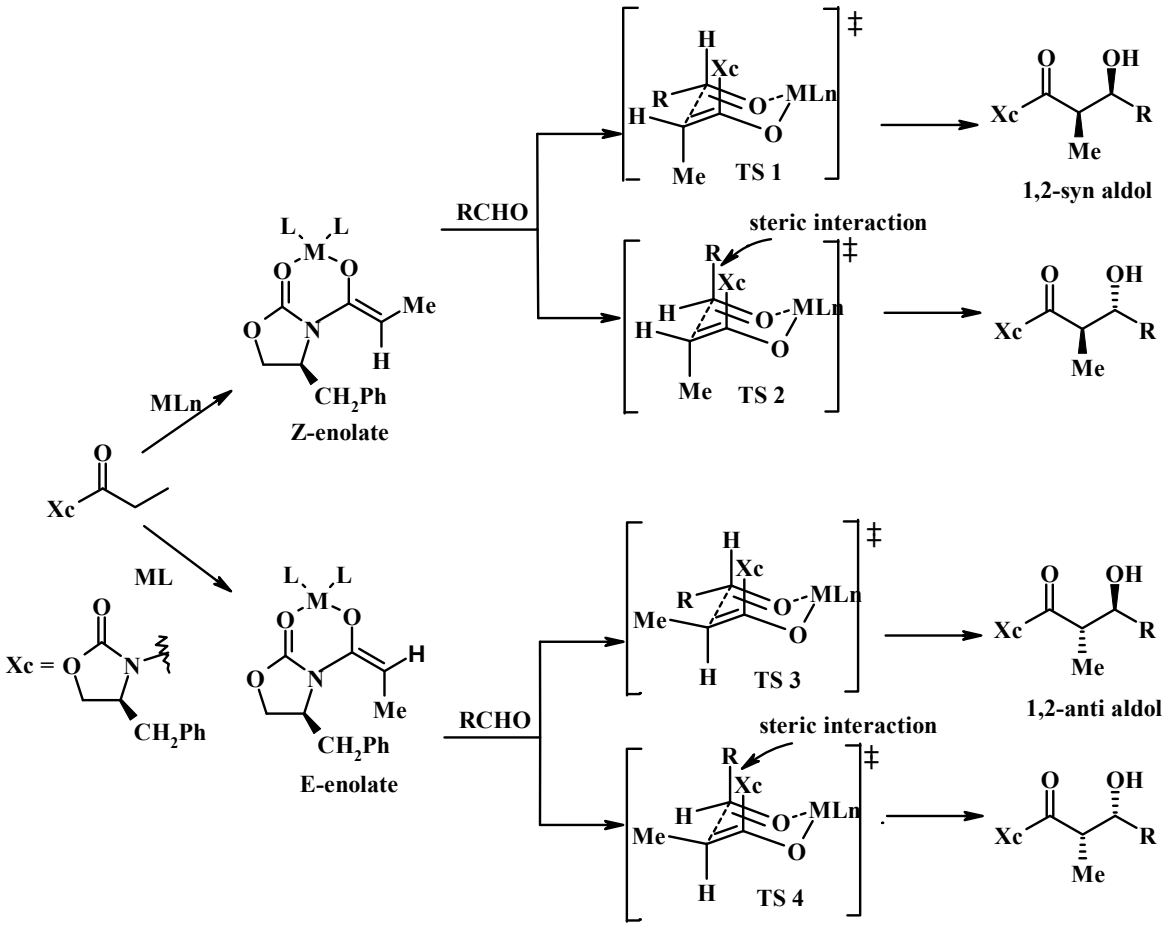


Figure 4

*The (Z)-boron enolate is usually prepared by enolization of the parent imide (**18**) with a boron triflate reagent such as dibutylboron triflate accompanied with a hindered tertiary amine base such as diisopropylethyl amine in dichloromethane as solvent. This method normally gives (Z)-enol borinate (**19**) which results in the formation of syn aldol products of the type **20** in high diastereoselectivity. On the contrary (E)-enol borinates can be obtained by treating with sterically hindered boron compounds having a poor leaving group (dicyclohexylboron chloride) in conjunction with a small amine base (triethylamine), leading to the formation of exclusive anti aldol products.[78,79] The observed selectivity for the (Z)-boron enolates is accounted for by coordination of the aldehyde to the boron enolate leading to the transition state (**TS 5**) in which the dipoles of the enolate oxygen and carbonyl group of the auxiliary are opposed (Figure 5).[80] The*

facial bias of these enolates overrides any inherent π-facial selectivity of chiral aldehydes in all cases except for a few circumstances.

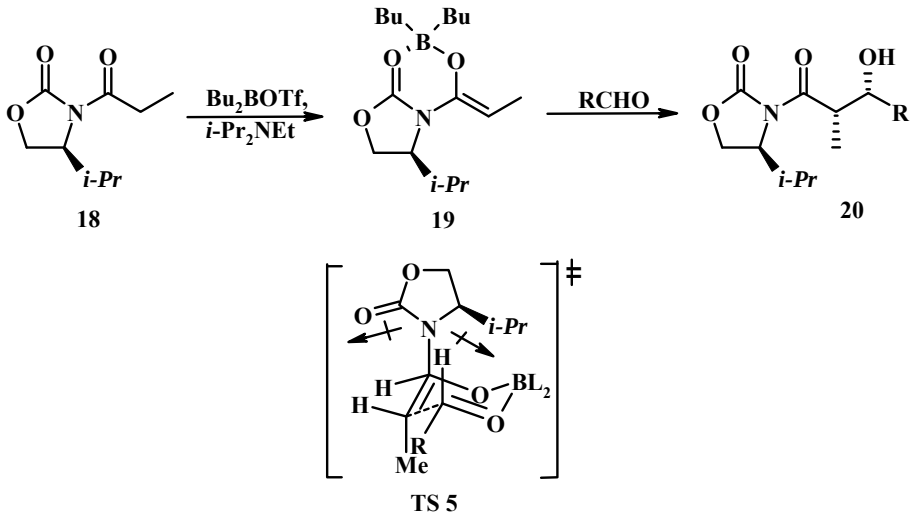
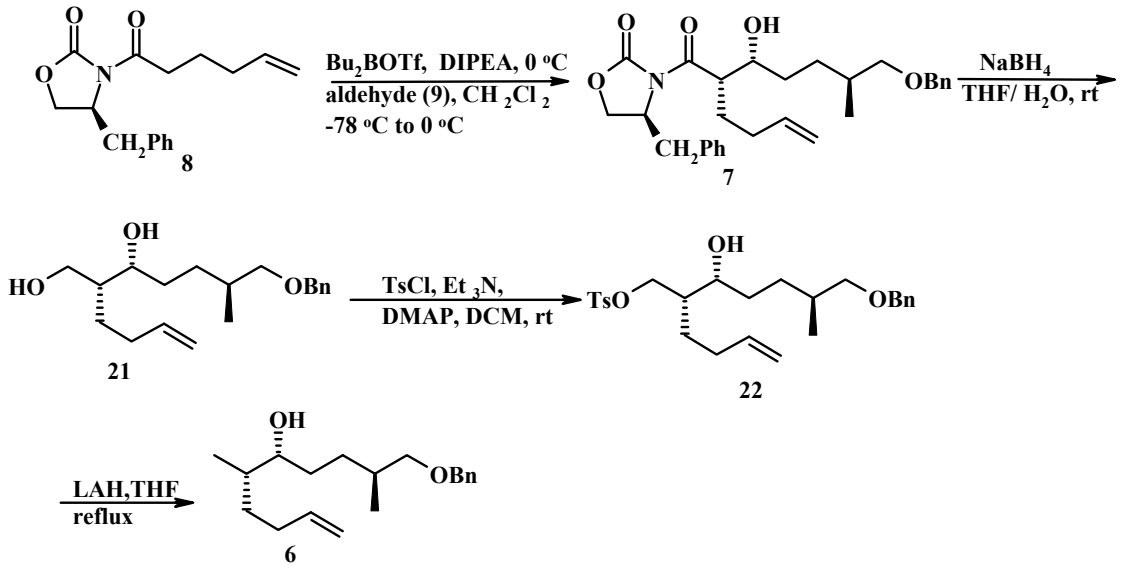


Figure 5

Our next concern was the Evans' aldol reaction[81] between the oxazolidinone derivative (**8**) and the aldehyde **9**. On subjecting the two components to Evans' *syn* aldol conditions using Bu_2BOTf, *i*-Pr_2EtN in CH_2Cl_2 at −78 ^oC, a highly diastereoselective *syn* aldol product **7** was obtained in 72% yield. The stereoselectivity of **7** was assumed on the basis of lit. precedence.[81] Further confirmation about the absolute configuration was established later on. The product was fully characterized by its spectral, mass and elemental analysis data. The ^1H NMR spectrum of **7** showed characteristic peaks at δ 0.95 ppm due to the methyl protons (J = 6.6 Hz), the secondary hydroxyl group appeared as a multiplet at δ 3.81. In addition ^{13}C and DEPT spectrum revealed the presence of nine methylene groups present in the structure of **7**. Moreover mass spectral analysis depicted a base peak at 502.297 $(M + Na)^+$ which provides satisfactory explanation with regard to our assigned structure. Addionally, elemental analysis data gave further assistance to our presumed structure. Our next objective, the nondestructive removal of the oxazolidinone was efficiently carried out using sodium borohydride in a THF, water mixture (3:1) to furnish the diol **21**.[82] In ^1H NMR spectrum there was clean absence of benzylic peaks (-

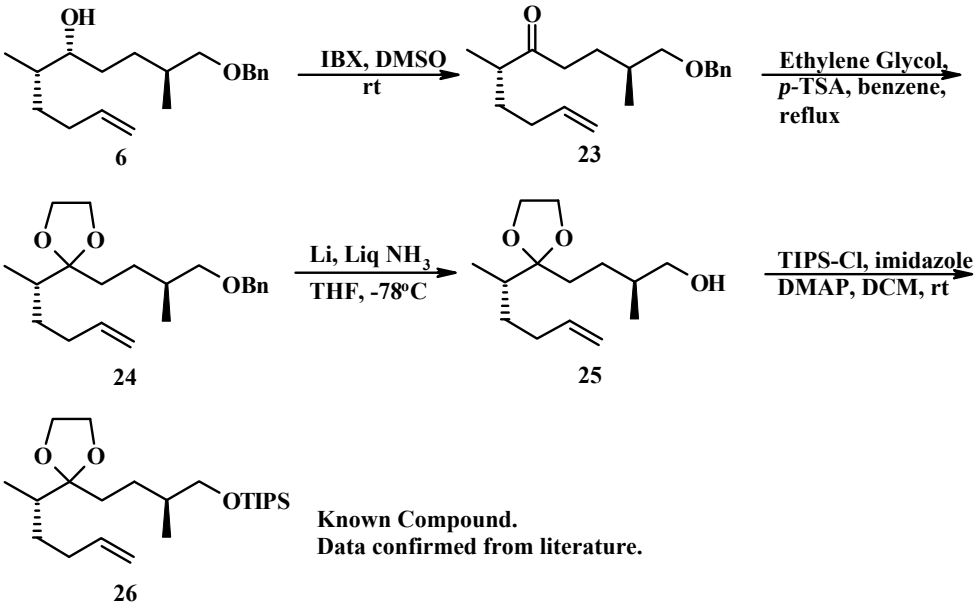
CH_2Ph) at δ 2.66 ppm, thus confirming the removal of oxazolidinone ring. Selective tosylation[83] of **21** to give the primary tosyl derivative (**22**) with concomitant reductive removal of *O*-tosyl group using lithium aluminium hydride afforded the deoxy derivative (**6**) in excellent yields. The disappearance of a sharp singlet at δ 2.45 due to the mono tosyl group along with the appearance of two methyl groups resonating at δ 0.89 and 0.95 ppm in the ^{1}H NMR spectrum as doublets justifies the structure of **6**; all other peaks were in accord with the assigned structure (Scheme 3). Mass spectra and elemental analysis gave further evidence for the assigned structure.



Scheme 3

At this stage it was necessary to confirm the stereochemistry of the newly generated methyl centers. For this endeavor the deoxy compound **6** made previously was subjected to IBX oxidation[84] to give ketone **23** in 90% yield. The presence of a peak at δ 214.4 in the ^{13}C NMR spectrum agrees with the formation of the oxidation product. The carbonyl group was protected as its ketal derivative (**24**) using ethylene glycol and *p*-TSA in refluxing benzene.[85] In the ^{1}H NMR spectrum a new signal at δ 3.91 as a singlet accounting four proton attributed to the ketal product, all other protons resonated in accord with the assigned structure. ^{13}C NMR spectrum also indicated two new methylene carbon signals at δ 65.1 and 65.2 ppm and a quarternary carbon at 113.95 ppm which

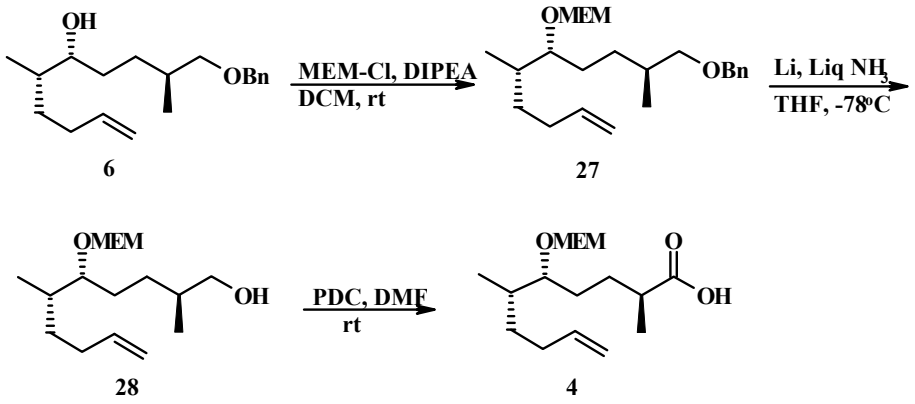
corresponds to the ketal group, also the disappearance of the keto carbonyl peak at 214.4 ppm was relevant in the ^{13}C spectrum. The product was further confirmed from its mass and elemental analysis datas. Debenzylation of **24** was carried out under Birch reduction conditions[86] to give the free alcohol **25** in good yield. The signals due to the benzylic and aromatic protons were completely departed from the ^{1}H NMR spectrum thus accounting for the debenzylated product **25**. Finally TIPS protection of **25** furnished the known compound **26** in 89% yield whose ^{1}H, ^{13}C and optical rotation {literature $[\alpha]_D^{25} = -10.0$ (*c* 2.5, $CHCl_3$), observed $[\alpha]_D^{25} = -7.27$ (*c* 0.6, $CHCl_3$) }values were in complete agreement with the reported ones.[62] The mass spectrum depicted a base peak at 421.359 $(M + Na)^+$ which accounts for the TIPS protected compound, additional confirmatory proof was obtained from its elemental analysis data. This unambiguously confirms the assigned stereochemistry of the new chiral centers (Scheme 4).



Scheme 4

Our next underlying task was to make the acid **4** required for the esterification reaction. For this endeavor, the free hydroxyl group of compound **6** was protected as its MEM ether **27** under standard protection conditions using MEM-Cl, *i*-Pr_2NEt in CH_2Cl_2 at room temperature.[87] The structure of **27** was corroborated from its ^{1}H NMR spectrum

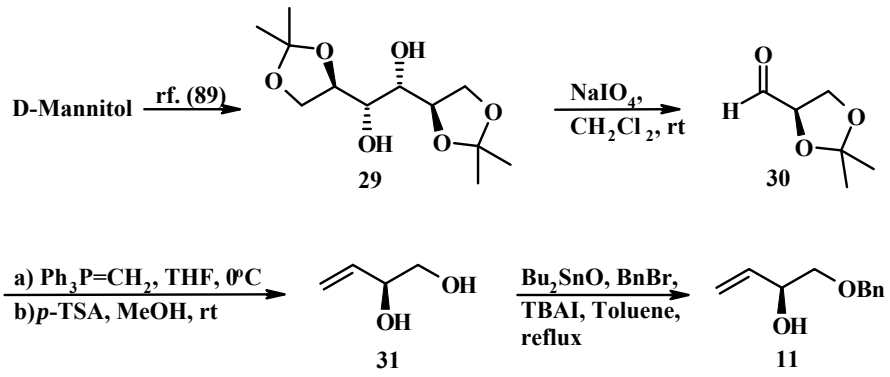
which displays signals at δ 3.38 as a singlet and at 4.72 ppm as ABq (J = 7.1 Hz) signifying the incorporation of the MEM group; all other protons resonated accordingly. Debenzylation of **27** using Li in liq. Ammonia following Birch reduction conditions[86] offered the debenzylated compound **28** in 83% yield. The ^{1}H and ^{13}C NMR spectra fully supported the structure. For instance, the absence of benzylic and aromatic protons in the ^{1}H NMR spectrum were conspicuous. The mass spectrum depicted a base peak at 311.189 $(M + Na)^{+}$ along with the elemental analysis datas, thus accounting for the structure of **28**. The primary hydroxyl group in **28** was then oxidized with PDC in DMF[88] to give the acid counterpart **4** in 77% yield, as one of the partners for the forthcoming esterification reaction. The formation of the acid moiety was proved from its IR spectra which showed an absorption peak at 1710 cm^{-1}; further rationalisation was achieved from its ^{1}H NMR spectrum which depicted a multiplet at δ 2.47 (1H) for C-2 adjacent to the carboxylic acid group, the corresponding methyl group was also deshielded to 1.20 ppm as a doublet. ^{13}C spectrum also supported the formation of the acid by depicting a peak at 182.5 ppm which was attributed to the carboxylic acid group. Moreover mass spectral data showing a base peak at 325.267 $(M + Na)^{+}$ also gives strong evidence for the assigned structure (Scheme 5).



Scheme 5

The other esterification counterpart, alcohol **11**, was synthesized from commercially available D-mannitol. Its cost effectiveness, easy accessibility and atom economy in due course of reactions have made it an useful starting material in total

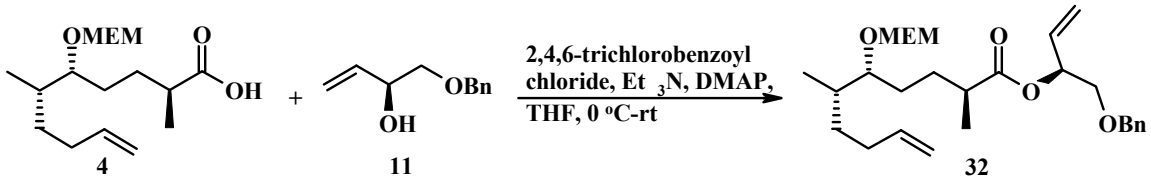
synthesis. Thus isopropylidenation of D-mannitol, following a known literature procedure [89] gave compound **29** which on oxidative cleavage with sodium metaperiodate provided aldehyde **30** in good yields. Subsequent one carbon Wittig homologation was followed up by concomitant acetonide deprotection under mild acidic conditions to give the diol derivative (**31**). The latter on dibutyltin oxide mediated selective benzylation furnished the allylic alcohol **11**.[90] The product was fully characterized from its ^{1}H and ^{13}C NMR spectra; comparison of the optical rotation value with the reported ones[91] [literature $[\alpha]_D^{25} = -5.9$ (*c* 0.5, $CHCl_3$), observed $[\alpha]_D^{25} = -4.4$ (*c* 0.7, $CHCl_3$)] completely justifies the structure without any ambiguity (Scheme 6).



Scheme 6

Having the two coupling partners in hand our next endeavor was to carry out the esterification reaction. Among the various conditions tested, Yamaguchi esterification[92] provided the best results other than the DCC, DMAP or EDCI, DMAP conditions. Thus subjecting acid **4** and alcohol **11** to Yamaguchi esterification conditions, it offered ester **32** in 75% yield. Although a slight epimerization at the C-2 center was observed [(9:1), judged by ^{1}H and ^{13}C NMR], the major isomer was cleanly separated by flash chromatography. Spectral and analytical data unambiguously confirmed the assigned structure. The ^{1}H NMR spectrum revealed signals due to benzylic protons at δ 4.55 (ABq), six olefinic protons in the range 4.90-5.92 ppm and aromatic protons appearing as a multiplet in the range 7.31-7.33 ppm. In addition ^{13}C NMR displayed a signal at δ 175.5 which was attributed to the ester carbonyl group. Further insight into the confirmatory

task was achieved from mass spectral data which displayed a characteristic peak at 485.381 $(M + Na)^+$ and its IR absorption value for ester functionality at 1724 cm^{-1} (Scheme 7).



Scheme 7

Before proceeding for the final macrocyclisation using RCM we would like to discuss a short account on ring closing metathesis reaction and its application towards the synthesis of natural products.

Ring closing metathesis reaction: A brief overview

Since the beginning of organic synthesis, carbon-carbon bond forming reactions have been profound targets for synthetic organic chemists. The Grignard[93], Diels-Alder[94] and the Wittig reactions[95] are the three most promising such reactions which have played decisive roles in shaping the science of chemical synthesis. Apart from these two other interesting reactions emerged as important tools for C-C bond formation; the Pd catalysed carbon-carbon bond forming reactions and the metathesis reactions.[96] Alkene metathesis in its various guises has influenced and shaped the landscape of synthetic organic chemistry more than any other single process over the last 15 years.[97]

Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes.[98] The discovery of efficient catalysts has made this reaction an important base for the construction of complex carbon frameworks. Of particular significance this type metathesis involves no additional reagents beyond a catalytic amount of metal carbene complexes and the only by-product in this reaction mixture, in most cases is a volatile olefine, ethylene. Olefin metathesis can be classified into three closely related type of

reactions; A) Ring opening metathesis polymerization (ROMP), B) Ring closing metathesis and C) acyclic cross metathesis which when carried out on diolefins results in polymers (ADMET) (Figure 6).

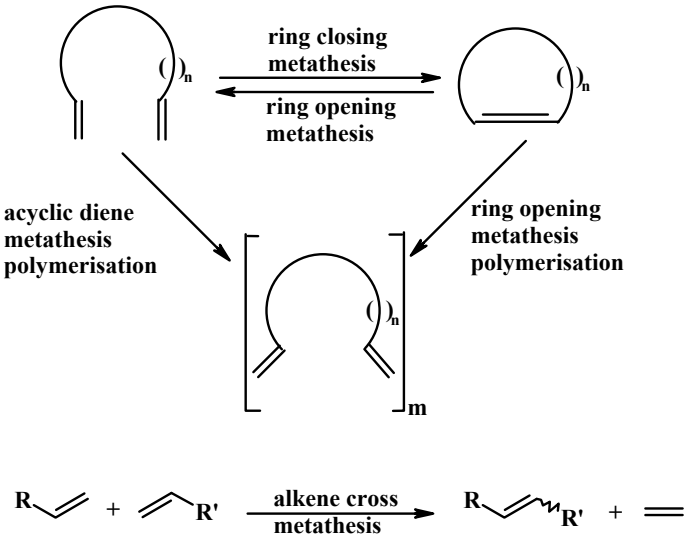


Figure 6: *Most commonly employed olefin metathesis reactions in organic synthesis.*

*Initially olefin metathesis was mostly related to ROMP; ring opening metathesis polymerization is a thermodynamically favoured for strained ring systems such as 3-, 4-, 8-, and larger membered rings. Recently ring closing olefin metathesis (RCM) has received a great deal of attention for the synthesis of medium or large sized rings from acyclic diene precursors. This intensive study is primarily due to the development of well developed metathesis catalysts which have high functional group tolerance and are reactive towards a diverse range of substrates. Several catalyst systems which have triggered the success of olefin metathesis reactions and display high reactivity have been developed. Of these the well defined molybdenum catalyst (**33**) introduced by Schrock[99] and the ruthenium carbene complexes (**34**)[100] and (**35**)[101] are noteworthy. Catalyst **33** displays superb metathesis activity with a wide variety of alkene substrates, particularly for sterically crowded systems.[102] The only drawback in this catalyst is its pronounced sensitivity to air and moisture and lesser functional group tolerance. On the contrary the Grubbs' catalysts (**34**) and (**35**) are more air stable and have more functional group*

tolerance with activity levels comparable to ***33.*** *Besides these there are also some other modified ruthenium and tungsten catalysts which have proved well in metathesis reactions (Figure 7).*

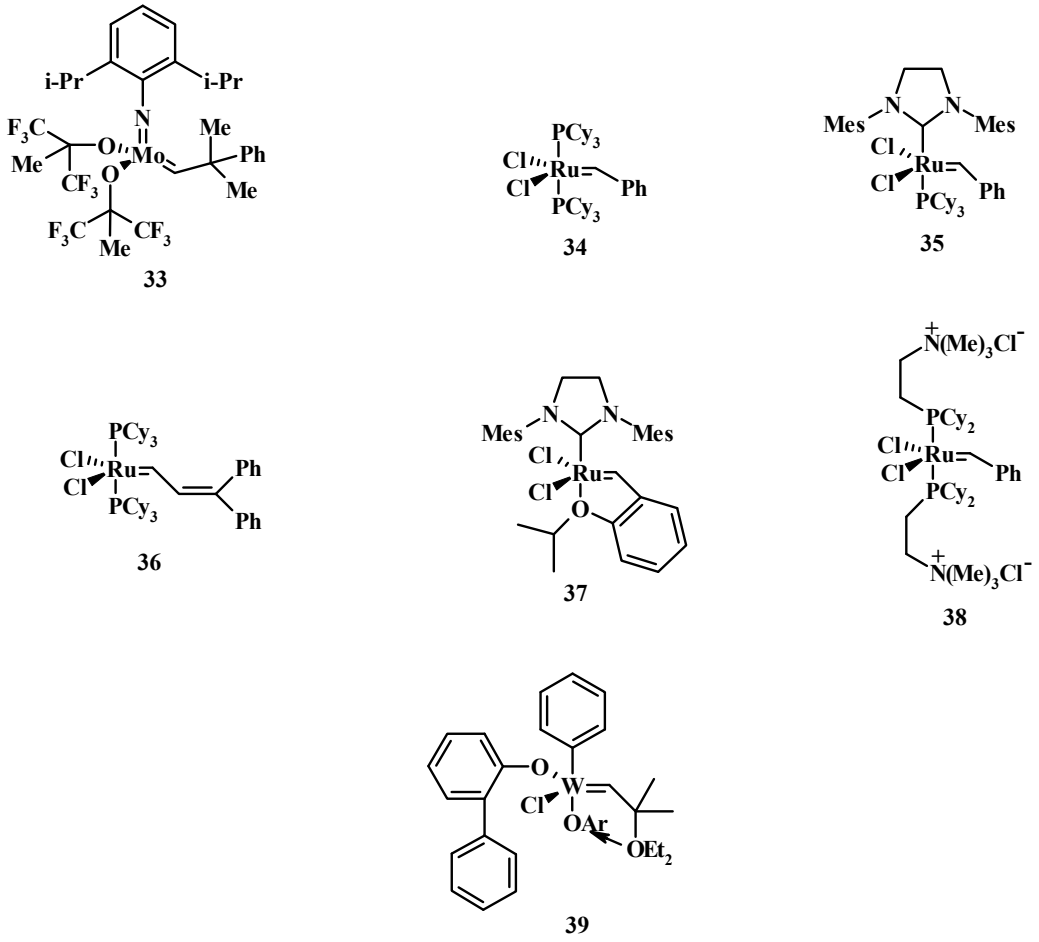


Figure 7: *Tungsten, molybdenum and ruthenium based catalysts for Olefin metathesis.*

The generally accepted mechanism of olefin metathesis (Chauvin mechanism) consists of a sequence of formal [2 + 2] cycloadditions/cycloreversions involving alkenes, metal carbenes, and metallocyclobutane intermediates.[103] *The initial [2 + 2] cycloaddition occurs intermolecularly between the catalyst and one of the olefins of the diene* ***40*** *to give a metal alkylidene (****43****) in the substrate with the release of a ethylene molecule. The second cycloaddition takes place in an intramolecular fashion, forming the metallocyclobutane (****44****) which undergoes ring opening to provide our requisite cyclised*

*product (**41**) and regenerates the metal carbene (**45**) which again enters into the catalytic cycle. Since the intermediates can move the equilibrium of the reaction in either way, so it is necessary to shift the equilibrium in the forward direction. The release of volatile ethylene gas entropically favours the forward process thus accumulating the cycloadduct (**41**) in the reaction mixture (Figure 8).*

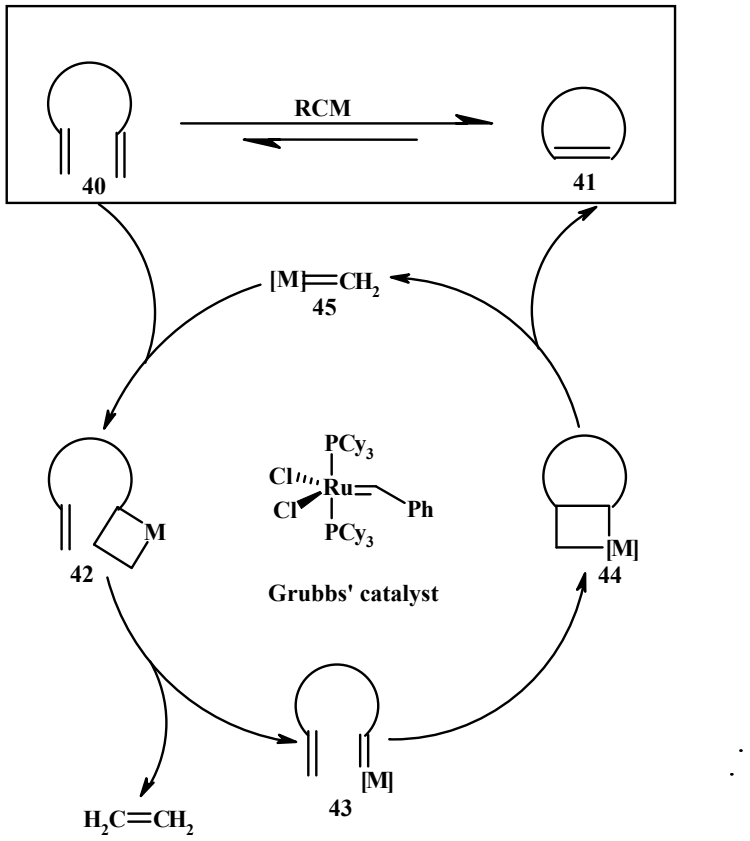


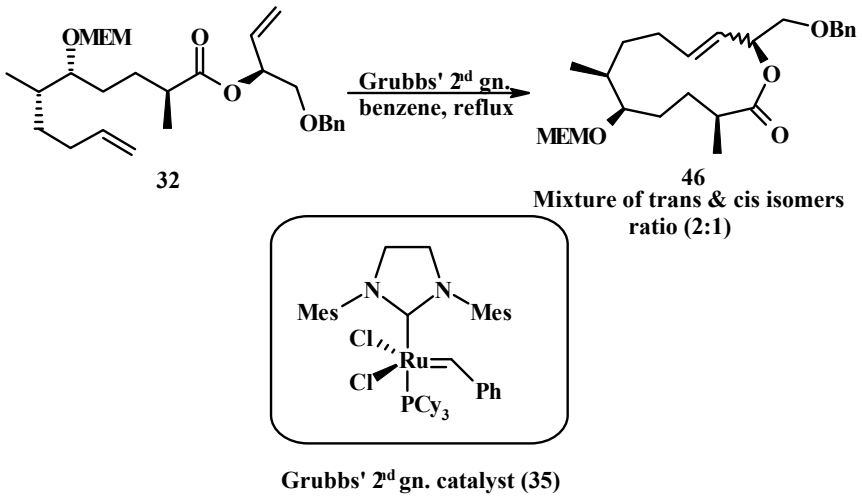
Figure 8: *Mechanism of ring closing metathesis*

Macrocyclisation using RCM:

Ring closing metathesis (RCM) has thus emerged as a potentially useful tool for the formation of rings of various sizes. One of its important aspects is the synthesis of highly flexible large rings (≥ 9) systems in which conformational predisposition of starting material must be considered for favourable cyclisation. However, it has been demonstrated that macrocyclisation metathesis is highly efficient not only with substrates having suitable restrictions but also with substrates devoid of any rigorous

conformational constraints by modification of the reaction conditions. Therefore, RCM is being recognized as one of the most straightforward and reliable methods for formation of large ring systems and comparably favourable to all current synthetic alternatives.

Now that the precursor for the RCM reaction has been staged, we moved forward for the macrocyclisation. Using Grubbs' 2nd generation catalyst in refluxing benzene the desired lactone **46** was obtained only in modest yield and with an inseparable 2:1 mixture of *trans* and *cis* isomers (Scheme 8). Noteworthy was that, no RCM product was obtained with Grubbs' 1st generation catalyst under any condition. The inseparable mixture of isomers was fully characterized through its ^{1}H, ^{13}C, mass and elemental analysis data. For instance in the ^{1}H NMR spectrum the methyl groups were observed at δ 0.90 and at 0.96 ppm as a doublet due to 1H an 2H protons and also at δ 1.10 and at 1.16 ppm as a doublet due to 1H and 2H protons respectively. The 2:1 mixture ratio was cleanly observed in its ^{1}H and ^{13}C NMR spectrum. Mass spectral analysis which accounts for the base peak at 457.265 $(M + Na)^{+}$ provided further support in favour of our assigned structure. However, our many attempts to purify the mixture in order to obtain pure *trans* and *cis* isomers could not be sorted out by any means, such as flash chromatography, HPLC.



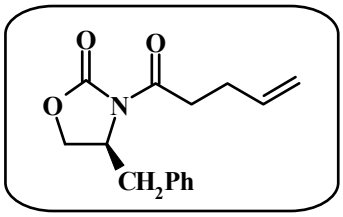
Scheme 8

In conclusion, we have developed a simple and efficient stereoselective approach to the macrolactone core of Amphidinolide W featuring asymmetric Evans alkylation and aldol reactions for successful generation of chiral centres. Surprisingly RCM reaction landed up with a mixture of isomers, without giving much fruitful results. Further studies to ascertain the reasons for these abnormalities and to provide a much more efficient route to its total synthesis is discussed in Section II of this Chapter.

EXPERIMENTAL

EXPERIMENTAL

(*S*)-4-benzyl-3-pent-4-enoyloxazolidin-2-one (10)

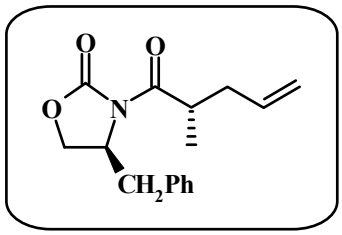


To a solution of 4-pentenoic acid (20.0 g, 200.0 mmol) in THF (200 mL) at –20 ^{o}C were sequentially added Et_3N (112.0 mL, 800.0 mmol) and Pivaloyl chloride (24.6 mL, 200.0 mmol). After stirring the resulting white slurry at the same temperature for 2 h, oxazolidinone (35.4 g, 200 mmol) and LiCl (8.5 g, 200.0 mmol) were added simultaneously and the reaction mixture was then warmed to room temperature and stirred for 4 h. After completion of the reaction, THF was removed in vaccum and the residue was partitioned between ethyl acetate (200 mL) and H_2O (50 mL). The organic layer was washed with $NaHCO_3$ (2 × 50 mL) and brine, dried over Na_2SO_4 and concentrated to give a residue which was chromatographed on silica gel column using EtOAc/light petroleum (1:19) to provide **10** (41.4 g, 80%) as a clear liquid.

Mol.Formula	$C_{15}H_{17}NO_3$
Optical Rotation $[\alpha]_D^{25}$	+40.82 (*c* 1.2, $CHCl_3$)
^{1}H NMR($CDCl_3$, 200 MHz)	δ 2.44 (q, 2 H, *J* = 7.0 Hz), 2.72 (dd, 1 H, *J* = 9.7, 13.3 Hz), 2.97-3.08 (m, 2 H), 3.30 (dd, 1 H, *J* = 3.2, 13.3 Hz), 4.14-4.17 (m, 2 H), 4.64 (m, 1 H), 4.99-5.14 (m, 2 H), 5.87 (m, 1 H), 7.17-7.31 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 75MHz)	δ 28.3, 34.9, 38.1, 55.2, 66.2, 115.8, 127.4, 129.0, 129.4, 135.4, 136.7, 153.3, 172.4 ppm.
ESI MS(m/z)	282.226 $(M + Na)^+$

Elemental Analysis	**Calcd:** C, 69.49; H, 6.61; N, 5.40
	Found: C, 69.34; H, 6.48; N, 5.52

(*S*)-4-benzyl-3-((*S*)-2-methylpent-4-enoyl)oxazolidin-2-one (13)

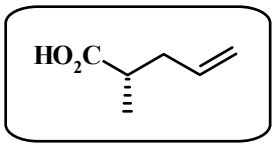


A solution of **10** (5.0 g, 19.3 mmol) in THF (50 mL) was cooled to −78 ^{o}C and NaHMDS (29.0 mL, 29.0 mmol, 1 M in THF) was added dropwise and stirred for 1 h, followed by dropwise addition of methyl iodide (4.8 mL, 77.2 mmol), maintaining the temperature at −78 ^{o}C. After stirring for 1 h the reaction was quenched with saturated NH_4Cl (20 mL) and the two layers were separated. The aqueous layer was extracted twice with EtOAc (2 × 50 mL), the combined organic layers were dried over Na_2SO_4 and concentrated to afford a residue which was purified by flash silica gel chromatography using EtOAc/light petroleum (1:19) yielding **13** (4.5 g, 85%) as a colorless liquid.

Mol.Formula	$C_{16}H_{19}NO_3$
Optical Rotation $[\alpha]_D^{25}$	+77.20 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2931, 1781, 1697, 1650, 1496, 1454, 1110, 750
^{1}H NMR($CDCl_3$, 200 MHz)	δ 1.23 (d, 3 H, *J* = 6.9 Hz), 2.18 (m, 1 H), 2.47 (m, 1 H), 2.75 (dd, 1 H, *J* = 9.6, 13.4 Hz), 3.27 (dd, 1 H, *J* = 3.3, 13.4 Hz), 3.82 (m, 1 H), 4.15-4.18 (m, 2 H), 4.65 (m, 1 H), 5.0-5.11 (m, 2 H), 5.78 (m, 1 H), 7.13-7.37 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 17.0, 37.4, 37.6, 37.9, 55.3, 65.9, 117.0, 127.3, 128.9, 129.4, 135.3, 135.5, 152.9, 176.3 ppm.

ESI MS(m/z)	296.192 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 70.30; H, 7.01; N, 5.13
	Found: C, 70.12; H, 6.86; N, 5.02.

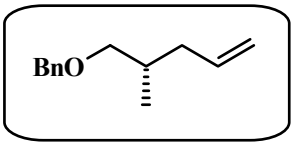
(*S*)-2-methylpent-4-enoic acid (14)



To a solution of the imide **13** (0.5 g, 1.8 mmol) in THF/H_2O (1:1) (10 mL) at 0 ^oC was added 30 % H_2O_2 solution (0.82 mL, 7.2 mmol) followed by $LiOH.H_2O$ (0.15 g, 3.6 mmol) and stirring was continued for 1 h. After completion of the reaction (monitored by TLC), THF was removed in vaccum and the residue was diluted with EtOAc (10 mL) and acidified with 1N HCL to pH ~1. The aqueous layer was extracted with EtOAc (3 × 15 mL), the combined organic layer was dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/light petroleum, 3:7) provided acid **14** (0.192 g, 92%) as a clear liquid.

Mol.Formula	$C_6H_{10}O_2$
Optical Rotation $[\alpha]_D^{25}$	+9.5 (*c* 1.0, $CHCl_3$)
^{1}H NMR($CDCl_3$, 500 MHz)	δ 1.21 (d, 3 H, *J* = 6.9 Hz), 2.19 (m, 1 H), 2.46 (m, 1 H), 2.56 (sextet, 1 H, *J* = 6.9 Hz), 5.06-5.11 (m, 2 H), 5.78 (m, 1 H) ppm.
^{13}C NMR($CDCl_3$, 125 MHz)	δ 16.3, 37.5, 39.2, 117.2, 135.1, 182.8 ppm.
ESI MS(m/z)	137.112 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 63.14; H, 8.83
	Found: C, 62.98; H, 8.96

(*S*)-((2-methylpent-4-enyloxy)methylbenzene (16)



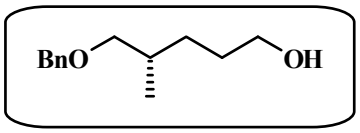
To a solution of LAH (2.5 g, 66.0 mmol) in ether (40 mL) was added compound **13** (12.0 g, 43.9 mmol) in ether (80 mL) dropwise at 0 ^{o}C. After stirring for 1 h the reaction mixture was quenched by the addition of a saturated solution of Na_2SO_4 then filtered, the residue was washed with ether, dried over Na_2SO_4 and concentrated to obtain a residue which was directly benzylated without further purification.

To the above residue was added THF (150 mL) and cooled to 0 ^{o}C. NaH (2.1 g, 87.9 mmol) was added in small portions and stirring was continued for 30 min. Then BnBr (7.9 mL, 65.9 mmol) followed by a catalytic amount of TBAI was added and the reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched with ice cold water, diluted with EtOAc, the layers were separated out and the aqueous layer was extracted twice with EtOAc (2 × 50 mL), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford a residue which was chromatographed on silica gel eluting with EtOAc/light petroleum (1:19) to provide **16** (7.2 g, 86% over two steps) as a clear liquid.

Mol.Formula	$C_{13}H_{18}O$
IR ($CHCl_3$) cm^{-1}	2927, 1648, 1385, 1044, 836
^{1}H NMR($CDCl_3$, 500 MHz)	δ 0.93 (d, 3 H, *J* = 6.5 Hz), 1.83-1.94 (m, 2 H), 2.22 (m, 1 H), 3.26 (dd, 1 H, *J* = 6.3, 8.9 Hz), , 3.31 (dd, 1 H, *J* = 6.3, 8.9 Hz), 4.48 (s, 2 H), 4.97-5.01 (m, 2 H), 5.76 (m, 1 H), 7.23-7.31 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50 MHz)	δ 16.9, 33.5, 38.1, 73.0, 75.2, 116.0, 127.4, 127.5, 128.3, 136.9, 138.8 ppm.
ESI MS(m/z)	213.168 $(M + Na)^+$

Elemental Analysis	**Calcd:** C, 82.06; H, 9.53
	Found: C, 81.84; H, 9.29.

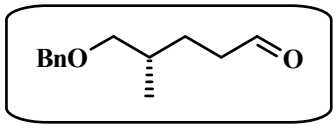
(*S*)-5-benzyloxy-4-methylpentan-1-ol (17)



To a solution of compound **16** (7.0 g, 36.8 mmol) in THF (40 mL) at 0 ^{o}C was added $BH_3.SMe_2$ (4.6 mL, 47.9 mmol) dropwise and stirred for 5 h, then slowly quenched by the simultaneous addition of 10% NaOH solution (20 mL) and 30% H_2O_2 solution (7 mL). It was then stirred at rt for 16 h, then extracted with EtOAc (3 × 30 mL), dried over Na_2SO_4, concentrated under reduced pressure and purified by silica gel column chromatography eluting with EtOAc/light petroleum (1:4) to give **17** (6.75 g, 88%) as a clear oil.

Mol.Formula	$C_{13}H_{20}O_2$
IR ($CHCl_3$) cm^{-1}	3370, 2928, 1610, 1210, 748
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.93 (d, 3 H, *J* = 6.8 Hz), 1.16 (m, 1 H), 1.49-1.59 (m, 3 H), 1.78 (m, 1 H), 2.07 (brs, 1 H), 3.27 (dd, 2 H, *J* = 2.4, 6.4 Hz), 3.56 (t, 2 H, *J* = 6.5 Hz), 4.47 (s, 2 H), 7.28-7.32 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 17.1, 29.7, 30.0, 33.2, 62.8, 73.0, 75.7, 127.5, 128.3, 138.5 ppm.
ESI MS(m/z)	231.125 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 74.96; H, 9.68
	Found: C, 74.89; H, 9.45

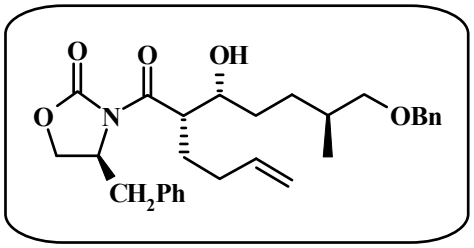
(*S*)-5-benzyloxy-4-methylpentanal (9)



A solution of the alcohol **17** (6.5 g, 31.3 mmol) in CH_2Cl_2 (35 mL), was treated with Dess-Martin periodinane (19.9 g, 46.9 mmol) at room temperature and stirred for 1 h. The reaction mixture was diluted with H_2O (15 mL) and CH_2Cl_2 (15 mL) and filtered. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layers were washed with $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated. The crude residue was purified by silica gel chromatography (EtOAc/light petroleum, 1:9) to afford aldehyde (**9**) (6.1 g, 94.3%) as a colourless liquid.

Mol.Formula	$C_{13}H_{18}O_2$
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.94 (d, 3 H, *J* = 6.5 Hz), 1.43-1.59 (m, 2 H), 1.72-1.90 (m, 2 H), 2.44 (m, 1 H), 3.29 (d, 2 H, *J* = 6.1 Hz), 4.47 (s, 2 H), 7.31 (m, 5 H), 9.74 (t, 1 H, *J* = 1.74 Hz) ppm.

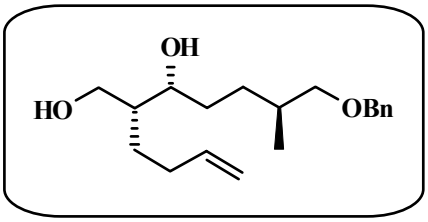
(*S*)-4-benzyl-3-((2*S*,3*R*,6*S*)-7-(benzyloxy)-2-(but-3-enyl)-3-hydroxy-6-methylheptanoyl)oxazolidin-2-one (7)



To an ice-cooled stirred solution of the imide **8** (2.0 g, 7.3 mmol) in CH_2Cl_2 (15 mL) dibutylboron triflate (8.1 mL, 1M in CH_2Cl_2, 8.1 mmol) was added dropwise such that the internal temperature was maintained at 0 ^oC. After 10 min *i*-Pr_2NEt (1.6 mL, 8.8 mmol) was added and stirring was continued for another 30 min at the same temperature. The reaction mixture was then cooled to –78 ^oC and the aldehyde (**9**) (1.5 g, 7.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise and allowed to stir for next 1 h; then warmed to 0 ^oC and stirred for another 1 h, and then quenched slowly with an aqueous solution of pH 7.0 phosphate buffer (8.1 mL), MeOH (16.2 mL) and then with a mixture of 30 % H_2O_2 and MeOH (1:2), (24.3 mL). After stirring at rt for 1 h, the reaction mixture was diluted with CH_2Cl_2 (20 mL), the layers were separated out and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by flash silica gel chromatography (EtOAc/light petroleum, 1:6) to furnish aldol product **7** (2.52 g, 72%) as a thick viscous liquid.

Mol.Formula	$C_{29}H_{37}NO_5$
Optical Rotation $[\alpha]_D^{25}$	+28.89 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3498, 2930, 1780, 1692, 1645, 1478, 1386, 1028, 699
^1H NMR($CDCl_3$, 200 MHz)	δ 0.95 (d, 3 H, *J* = 6.6 Hz), 1.14 (m, 1 H), 1.5-1.74 (m, 5 H), 1.97 (m, 1 H), 2.06-2.16 (m, 2 H), 2.66 (dd, 1 H, *J* = 10.2, 13.1 Hz), 3.20-3.40 (m, 3 H), 3.81 (m, 1 H), 4.09-4.16 (m, 3 H), 4.48 (s, 2 H), 4.68 (m, 1 H), 4.95-5.08 (m, 2 H), 5.78 (m, 1 H), 7.23-7.33 (m, 10 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 17.3, 26.1, 30.1, 31.2, 31.8, 33.4, 38.0, 47.3, 55.6, 65.9, 72.96, 75.6, 76.4, 115.5, 127.4, 127.5, 128.3, 128.98, 129.3, 135.3, 137.8, 138.7, 153.5, 175.6 ppm.
ESI MS(m/z)	502.297 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 72.62; H, 7.78; N, 2.93 **Found:** C, 72.45; H, 7.65; N, 2.89.

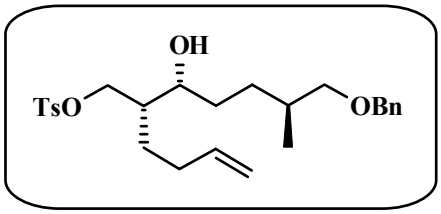
(2*R*, 3*R*, 6*S*)-7-(benzyloxy)-2-(but-3-enyl)-6-methylheptane-1,3-diol (21)



To a solution of the aldol product **7** (5.6 g, 11.7 mmol) in THF/H_2O (3:1), (30 mL), was added $NaBH_4$ (1.8 g, 46.8 mmol) at room temperature. After stirring overnight, it was quenched with a saturated solution of NH_4Cl (15 mL) and diluted with ethyl acetate; the layers were separated and the aqueous layer was extracted twice with EtOAc (2 × 20 mL), the combined organic layers were dried over Na_2SO_4 and concentrated to afford a residue which was chromatographed on silica gel column using EtOAc/light petroleum (1:3) as eluent to provide diol **21** (3.1 g, 87%) as a colourless viscous liquid.

Mol.Formula	$C_{19}H_{30}O_3$
Optical Rotation $[\alpha]_D^{25}$	+7.52 (*c* 0.9, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3368, 2928, 1648, 1452, 1252, 1115, 835, 697
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.95 (d, 3 H, *J* = 6.6 Hz), 1.13 (m, 1 H), 1.36-1.55 (m, 4 H), 1.58-1.83 (m, 3H), 1.98-2.19 (m, 2H), 2.72 (brs, 2 H), 3.29 (dd, 2 H, *J* = 1.5, 6.2 Hz), 3.66-3.83 (m, 3H), 4.48 (s, 2H), 4.93-5.05 (m, 2H), 5.78 (m, 1H), 7.28-7.34 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 17.3, 24.0, 30.3, 30.7, 31.7, 33.5, 43.2, 64.2, 73.0, 75.3, 75.7, 114.8, 126.8, 127.4, 127.5, 128.2, 138.4 ppm.
ESI MS(m/z)	329.265 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 74.47; H, 9.87
	Found: C, 74.25; H, 9.72

(2*R*,3*R*,6*S*)-7-(benzyloxy)-2-(but-3-enyl)-3-hydroxy-6-methylheptyl-4-methylbenzenesulfonate (22)

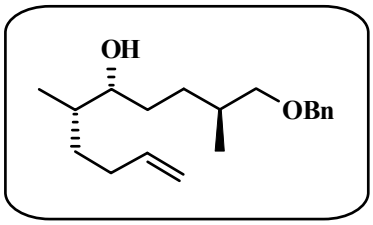


To a stirred solution of **21** (2.7 g, 8.8 mmol) in CH_2Cl_2 (40 mL) at 0 ^oC, were sequentially added Et_3N (2.5 mL, 17.7 mmol), *p*-toluenesulfonyl chloride (2.52 g, 13.2 mmol), and DMAP (catalytic amount). The reaction mixture was stirred at room temperature for 20 h (completion of the reaction was monitored by TLC), then quenched with ice, diluted with CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous layer was extracted twice with CH_2Cl_2 (2 × 25 mL), washed with brine, then dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (EtOAc/light petroleum, 1:5) to afford the mono tosyl derivative (**22**) (3.6 g, 89%) as a clear liquid.

Mol.Formula	$C_{26}H_{36}O_5S$
Optical Rotation $[\alpha]_D^{25}$	-10.1 (*c* 1.0, $CHCl_3$)
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.92 (d, 3 H, *J* = 6.7 Hz), 1.32-1.75 (m, 8 H), 1.89-2.07 (m, 2 H), 2.45 (s, 3 H), 3.27 (dd, 2 H, *J* = 1.4, 6.2 Hz), 3.67 (m, 1 H), 4.0 (dd, 1 H, *J* = 4.8, 9.9 Hz), 4.09 (dd, 1 H, *J* = 7.2, 9.9 Hz), 4.48 (s, 2 H), 4.90-4.99 (m, 2H), 5.68 (m, 1 H), 7.29-7.36 (m, 7 H), 7.78 (d, 2 H, *J* = 8.3 Hz) ppm.
^{13}C NMR($CDCl_3$,75 MHz)	δ 17.3, 21.6, 24.4, 30.3, 31.5, 33.5, 42.5, 70.5, 71.3, 73.0, 75.6, 115.2, 127.4, 127.5, 127.9, 128.3, 129.8, 133.3, 137.9, 138.7, 144.6 ppm.
ESI MS(m/z)	483.307 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 67.79; H, 7.88

Found: C, 67.62; H, 7.63

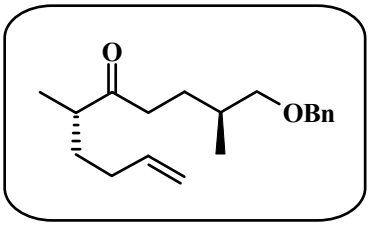
(2*S*,5*R*,6*S*)-1-(benzyloxy)-2,6-dimethyldec-9-en-5-ol (6)



LAH (0.41 g, 10.8 mmol) was added to a stirred solution of the mono tosyl derivative (**22**) (3.3 g, 7.2 mmol) in THF (30 mL) at room temperature and refluxed for 3h. The reaction was quenched with a saturated solution of Na_2SO_4, and then filtered through a pad of celite, washed with EtOAc, the organic layer was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel column (EtOAc/light petroleum, 1:6), to yield **6** (1.9 g 91.5%) as a colourless liquid.

Mol.Formula	$C_{19}H_{30}O_2$
Optical Rotation $[\alpha]_D^{25}$	+4.96 (*c* 1.5, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3374, 2930, 1650, 1461, 1215, 836
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.89 (d, 3 H, *J* = 6.8 Hz), 0.95 (d, 3 H, *J* = 6.7 Hz), 1.07-1.40 (m, 7 H), 1.69-2.18 (m, 3 H), 3.24-3.42 (m, 3 H), 4.48 (s, 2 H), 4.91-5.05 (m, 2 H), 5.78 (m, 1 H), 7.27-7.33 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 75 MHz)	δ 15.4, 17.5, 30.3, 31.0, 31.1, 31.5, 33.7, 38.3, 73.1, 75.8, 76.3, 114.5, 127.4, 127.5, 128.3, 138.8, 139.9 ppm.
ESI MS(m/z)	313.286 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 78.57; H, 10.41
	Found: C, 78.45; H, 10.23

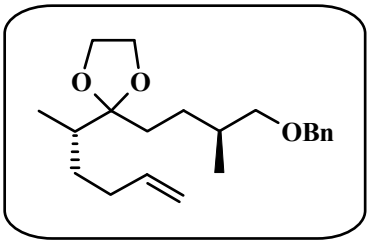
(2*S*,6*S*)-1-(benzyloxy)-2,6-dimethyldec-9-en-5-one (23)



To a solution of the deoxy compound **6** (0.15 g, 0.52 mmol) in DMSO (4 mL), was added IBX (0.29 g, 1.0 mmol). After stirring for 2 h, the reaction mixture was diluted with water (15 mL), filtered and the filtrate was extracted with Et_2O (3 × 15 mL). The organic layer was washed with $NaHCO_3$ solution, brine, dried (over Na_2SO_4) and concentrated. The crude product was purified on silica gel column eluting with EtOAc and light petroleum (1:19) to provide ketone **23** (0.134 g, 90%) as a colorless oil.

Mol.Formula	$C_{19}H_{28}O_2$
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.93 (d, 3 H, *J* = 6.6 Hz), 1.06 (d, 3 H, *J* = 7.0 Hz), 1.25-1.46 (m, 3 H), 1.70-1.78 (m, 2 H), 1.95-2.07 (m, 2 H), 2.43-2.58 (m, 3 H), 3.29 (d, 2 H, *J* = 6.0 Hz), 4.48 (s, 2 H), 4.93-5.04 (m, 2 H), 5.75 (m, 1 H), 7.29-7.33 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 16.4, 17.1, 27.7, 31.4, 32.0, 33.1, 38.9, 45.5, 73.1, 75.6, 115.1, 127.5, 127.6, 128.3, 138.1, 138.7, 214.4 ppm.
ESI MS(m/z)	311.281 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 79.12; H, 9.78
	Found: C, 78.97; H, 9.66

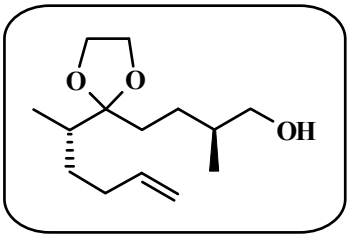
2-((*S*)-4-(benzyloxy)-3-methylbutyl)-2-((*S*)-hex-5-en-2-yl)-1,3-dioxalane (24)



A solution of compound **23** (0.1 g, 0.35 mmol), ethylene glycol (0.4 mL, 6.9 mmol) and *p*-TSA (catalytic amount) in dry benzene (20 mL) was heated under reflux for 4 h using a Dean-Stark apparatus. Upon completion of the reaction (monitored by TLC), it was washed with 5 % $NaHCO_3$ solution, water, brine and dried (over Na_2SO_4). The organic layer was then concentrated to a residue, which on silica gel column purification (EtOAc/light petroleum, 1:19) afforded **24** (0.085 g, 74%) as a colourless liquid.

Mol.Formula	$C_{21}H_{32}O_3$
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.91 (d, 3 H, *J* = 6.9 Hz), 0.94 (d, 3 H, *J* = 6.7 Hz), 1.15 (m, 1 H), 1.43 (m, 1 H), 1.57-1.77 (m, 6 H), 1.99 (m, 1 H), 2.16 (m, 1 H), 3.23 (dd, 1 H, *J* = 6.6, 9.1 Hz), 3.32 (dd, 1 H, *J* = 6.0, 9.1 Hz), 3.91 (s, 4 H), 4.49 (s, 2 H), 4.90-5.05 (m, 2 H), 5.79 (m, 1 H), 7.24-7.34 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 14.1, 17.4, 27.0, 30.4, 31.3, 32.0, 33.8, 39.1, 65.1, 65.2, 73.0, 75.9, 113.95, 114.4, 127.4, 127.5, 128.3, 138.9, 138.99 ppm.
ESI MS(m/z)	355.317 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 75.86; H, 9.70
	Found: C, 75.69; H, 9.64

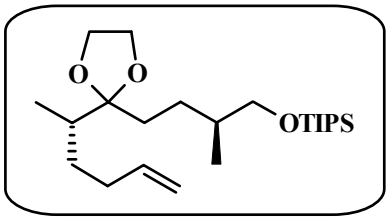
(*S*)-4-(2-((*S*)-hex-5-en-2-yl)-1,3-dioxolan-2-yl)-2-methylbutan-1-ol (25)



To a pre-condensed stirred solution of ammonia (10 mL) at –78 ^{o}C was added small pieces of lithium until deep blue colour persisted, after 30 min compound **24** (0.060 g, 0.18 mmol) in THF (5 mL) was added dropwise. The solution was stirred for 1 h at this temperature, and then quenched with solid NH_4Cl, until the blue colour disappeared. Ammonia was allowed to evaporate completely and the residue was diluted with H_2O (5 mL) extracted with EtOAc (3 × 10 mL). The combined extracts were dried over Na_2SO_4, concentrated and purified on silica gel column using EtOAc/light petroleum (1:6) to produce **25** (0.032 g, 73.2%) as a colourless liquid.

Mol.Formula	$C_{14}H_{26}O_3$
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.92 (d, 6 H, *J* = 6.8 Hz), 1.15 (m, 1 H), 1.43 (m, 1 H), 1.58-1.64 (m, 4 H), 1.68-1.76 (m, 2 H), 2.00 (m, 1 H), 2.18 (m, 1 H), 3.47 (dd, 2 H, *J* = 3.5, 6.0 Hz), 3.93 (s, 4 H), 4.92-5.06 (m, 2 H), 5.79 (m, 1 H) ppm.
ESI MS(m/z)	265.2358 $(M + Na)^+$

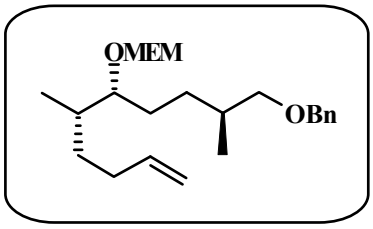
((*S*)-4-(2-((*S*)-hex-5-en-2-yl)-1,3-dioxolan-2-yl)-2-methylbutoxy)triisopropylsilane (26)



Imidazole (0.014 g, 0.2 mmol) was added to a solution of **25** (0.025 g, 0.1 mmol) in CH_2Cl_2 (3 mL) at 0 ^oC followed by TIPS-Cl (0.03 mL, 0.15 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. It was diluted with water (5 mL) and extracted with CH_2Cl_2 (2 × 10 mL), washed with brine, dried over Na_2SO_4 and concentrated to give a residue which was purified by flash silica gel column chromatography (EtOAc/light petroleum, 1:19), to furnish the TIPS protected compound **26** (0.036 g, 89%) as colourless liquid.

Mol.Formula	$C_{23}H_{46}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	–7.27 (*c* 0.6, $CHCl_3$)
^{1}H NMR($CDCl_3$, 500 MHz)	δ 0.90 (d, 3 H, *J* = 6.5 Hz), 0.92 (d, 3 H, *J* = 7.0 Hz), 1.06 (m, 21 H), 1.11-1.19 (m, 2 H), 1.45-1.55 (m, 2 H), 1.62-1.75 (m, 4 H), 1.97 (m, 1 H), 2.17 (m, 1 H), 3.47 (dd, 1 H, *J* = 6.4, 9.6 Hz), 3.52 (dd, 1 H, *J* = 5.8, 9.6 Hz), 3.90-3.93 (m, 4 H), 4.94 (d, 1 H, *J* = 10.3 Hz), 5.01 (d, 1 H, *J* = 17.1 Hz), 5.80 (m, 1 H) ppm.
^{13}C NMR($CDCl_3$, 125 MHz)	δ 11.8, 13.7, 16.6, 17.8, 26.4, 30.1, 31.3, 31.7, 36.1, 38.9, 64.9, 65.0, 68.4, 113.8, 114.1, 138.8 ppm.
ESI MS(m/z)	421.359 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.29; H, 11.63
	Found: C, 69.07; H, 11.48

(8*R*,11*S*)-8-((*S*)-hex-5-en-2-yl)-11-methyl-14-phenyl-2,5,7,13-tetraoxotetradecane (27)

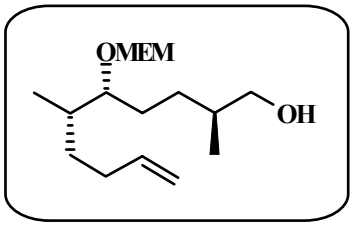


To a solution of the deoxy compound **6** (1.75 g, 6.04 mmol) in CH_2Cl_2 (12 mL), *i*-Pr_2NEt (2.1 mL, 12.1 mmol) was added. It was then cooled to 0 ^oC and MEM-Cl (1.0 mL, 9.1 mmol) was added dropwise. The reaction mixture was then warmed to room temperature and stirred overnight. After completion (monitored by TLC), it was quenched with ice and diluted with H_2O (10 mL), extracted with CH_2Cl_2 (2 × 15 mL), the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated to a give a residue, which on silica gel column chromatography (EtOAc/light petroleum, 1:9) furnished MEM protected compound **27** (1.78 g, 78%) as a colourless liquid.

Mol.Formula	$C_{23}H_{38}O_4$
Optical Rotation $[\alpha]_D^{25}$	-6.55 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2928, 1647, 1454, 1060, 773, 697
^{1}H NMR($CDCl_3$, 300 MHz)	δ 0.88 (d, 3 H, *J* = 6.9 Hz), 0.95 (d, 3 H, *J* = 6.7 Hz), 1.11-1.27 (m, 3 H), 1.43-1.48 (m, 2 H), 1.52-1.63 (m, 2 H), 1.72-1.78 (m, 2 H), 1.98 (m, 1 H), 3.25 (dd, 1 H, *J* = 6.6, 8.8 Hz), 3.33 (dd, 1 H, *J* = 5.9, 8.8 Hz), 3.38 (s, 3 H), 3.42 (m, 1 H), 3.50-3.53 (m, 2 H), 3.68-3.73 (m, 2 H), 4.49 (s, 2 H), 4.72 (ABq, 2 H, *J* = 7.1 Hz), 4.94 (d, 1 H, *J* = 10.4 Hz), 5.0 (d, 1 H, *J* = 17.0 Hz), 5.8 (m, 1 H), 7.28-7.33 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 75 MHz)	δ 14.7, 17.5, 27.5, 29.9, 31.7, 31.9, 33.8, 35.4, 59.0, 67.2, 71.9, 73.1, 75.8, 82.2, 94.9, 114.5, 127.4, 127.5,

	128.3, 138.9 ppm.
ESI MS(m/z)	401.375 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 72.98; H, 10.12
	Found: C, 72.79; H, 9.98

(2*S*,5*R*,6*S*)-5-((2-methoxyethoxy)methoxy)-2,6-dimethyldec-9-en-1-ol (28)

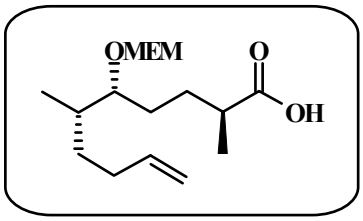


To a vigorously stirred solution of ammonia (15 mL) at –78 °C was added small pieces of lithium (0.19 g, 26.5 mmol). A deep blue colour appeared within 5 min, after 30 min compound **27** (1.0 g, 2.6 mmol) in THF (10 mL) was added dropwise. The solution was stirred for 1 h, and then quenched with solid NH_4Cl, until the blue colour disappeared. Ammonia was allowed to evaporate completely and the residue was diluted with H_2O (15 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were dried over Na_2SO_4, concentrated and purified on silica gel column using EtOAc/light petroleum (2:3) to produce **28** (0.63 g, 82.7%) as a colourless liquid.

Mol.Formula	$C_{16}H_{32}O_4$
Optical Rotation $[\alpha]_D^{25}$	+15.29 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3375, 2929, 1646, 1459, 1254, 1075, 757, 698
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.88 (d, 3 H, *J* = 7.0 Hz), 0.92 (d, 3 H, *J* = 7.0 Hz) 1.04-1.21 (m, 2 H), 1.38-1.61 (m, 5 H), 1.76 (m, 1 H), 1.92-2.18 (m, 2 H), 2.43 (brs, 1 H), 3.39 (s, 3 H), 3.43-3.46 (m, 3 H), 3.54-3.58 (m, 2 H), 3.68-3.85 (m, 2 H), 4.74 (ABq, 2 H, *J* = 7.1 Hz), 4.92-5.06 (m, 2 H), 5.80

	(m, 1 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 14.3, 16.6, 27.2, 29.2, 31.5, 31.6, 35.2, 35.8, 58.9, 67.0, 67.7, 71.7, 82.4, 94.8, 114.3, 138.7 ppm.
ESI MS(m/z)	311.189 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 66.63; H, 11.18
	Found: C, 66.82; H, 11.02

(2*S*,5*R*,6*S*)-5-((2-methoxyethoxy)methoxy)-2,6-dimethyldec-9-enoic acid (4)

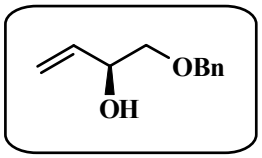


To a solution of debenzylated compound **28** (0.5 g, 1.74 mmol) in DMF (8 mL), PDC (3.3 g, 8.7 mmol) was added and stirred at room temperature overnight. The reaction mixture was diluted with H_2O (25 mL) and extracted with ether (3 ×25 mL). The combined extracts were dried over Na_2SO_4 and concentrated to a residue. Silica gel column purification using EtOAc and light petroleum (1:1) as eluent provided the acid **4** (0.4 g, 77%) as a colourless liquid.

Mol.Formula	$C_{16}H_{30}O_5$
Optical Rotation $[\alpha]_D^{25}$	+23.20 (*c* 0.8, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2928, 1710, 1645, 1462, 1382, 1070, 837
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.87 (d, 3 H, *J* = 6.8 Hz), 1.20 (d, 3 H, *J* = 7.0 Hz), 1.42-1.52 (m, 4 H), 1.65-2.21 (m, 5 H), 2.47 (m, 1 H), 3.39 (s, 3 H), 3.44 (m, 1 H), 3.52-3.57 (m, 2 H), 3.68-3.78 (m, 2 H), 4.73 (ABq, 2 H, *J* = 7.2 Hz), 4.91-5.05 (m, 2 H), 5.78 (m, 1 H) ppm.

^{13}C NMR($CDCl_3$, 50MHz)	δ 14.4, 17.1, 27.4, 29.6, 31.6, 31.9, 35.2, 39.3, 59.0, 67.2, 71.8, 81.5, 94.8, 114.6, 138.8, 182.5 ppm.
ESI MS(m/z)	325.267 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 63.55; H, 10.00
	Found: C, 63.34; H, 9.83

(*S*)-1-(benzyloxy)but-3-en-2-ol (11)

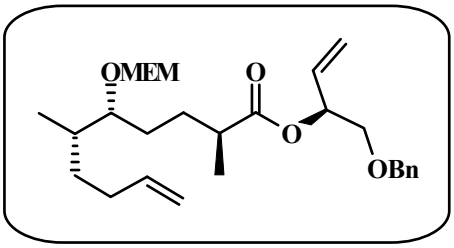


A solution of the diol **31** (1.0 g, 11.4 mmol) prepared from D-mannitol[89] was treated with dibutyltin oxide (4.2 g, 17.0 mmol) in toluene (35 mL) and refluxed for 4 h using a Dean-Stark apparatus. It was cooled and benzyl bromide (2.0 mL, 17.0 mmol) and TBAI (catalytic) were added and again refluxed for 2 h. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with 10 % $NaHCO_3$ solution (2 × 20 mL), water, brine, dried (over Na_2SO_4) and then concentrated. The residue was purified on silica gel column chromatography using EtOAc and light petroleum (1:6) to provide **11** (1.7 g, 84%) as a light yellow colored liquid.

Mol.Formula	$C_{11}H_{14}O_2$
Optical Rotation $[\alpha]_D^{25}$	-4.4 (*c* 0.7, $CHCl_3$)
^{1}H NMR($CDCl_3$, 200 MHz)	δ 2.42 (brs, 1 H), 3.36 (dd, 1 H, *J* = 7.9, 9.6 Hz), 3.54 (dd, 1 H, *J* = 3.5, 9.6 Hz), 4.34 (m, 1 H), 4.57 (s, 2 H), 5.19 (d, 1 H, *J* = 10.5 Hz), 5.36 (d, 1 H, *J* = 17.3 Hz), 5.83 (m, 1 H), 7.30-7.35 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	71.4, 73.3, 74.0, 116.3, 126.8, 127.7, 128.4, 136.6, 137.7 ppm.

ESI MS(m/z)	201.1542 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 74.13; H, 7.92
	Found: C, 74.35; H, 7.76

(2*S*,5*R*,6*S*)-((*S*)-1-(benzyloxy)but-3-en-2-yl)-5-((2-methoxyethoxy)methoxy)-2,6-dimethyldec-9-enoate (32)

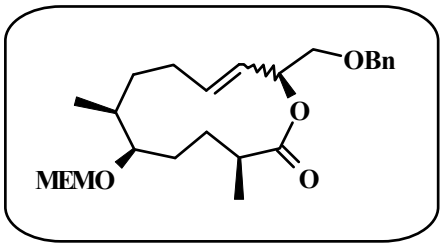


2,4,6-trichlorobenzoyl chloride (0.22 mL, 1.4 mmol) was added to a stirred solution of acid **4** (0.28 g, 0.93 mmol) and *i*-Pr_2NEt (0.33 mL, 1.86 mmol) in THF (10 mL), at 0 ^oC. After 1 h the alcohol **11** (0.182 g, 1.02 mmol) and DMAP (0.17 g, 1.4 mmol) in THF (5 mL) were added and the reaction mixture was warmed to room temperature and stirred for 6 h. The reaction mixture was quenched with saturated $NaHCO_3$ solution (10 mL) and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash silica gel chromatography (EtOAc/light petroleum, 1:9) yielded **32** (0.32 g, 75%) and its C-2 epimer as a 9:1 separable mixture.

Mol.Formula	$C_{27}H_{42}O_6$
Optical Rotation $[\alpha]_D^{25}$	+13.19 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2930, 1724, 1650, 1382, 1255, 1026, 773, 621
^1H NMR($CDCl_3$, 200 MHz)	δ 0.83 (d, 3 H, *J* = 6.8 Hz), 1.18 (d, 3 H, *J* = 7.0 Hz), 1.38-1.48 (m, 4 H), 1.65-1.83 (m, 3 H), 1.96-2.14 (m, 2 H), 2.49 (m, 1 H), 3.38 (s, 3 H), 3.41 (m, 1 H), 3.50-3.57 (m, 4 H), 3.67-3.73 (m, 2 H), 4.55 (ABq, 2 H, *J* =

	12.0 Hz), 4.70 (ABq, 2 H, *J* = 7.1 Hz), 4.90-5.04 (m, 2 H), 5.20-5.37 (m, 2 H), 5.50 (m, 1 H), 5.70-5.92 (m, 2 H), 7.31-7.33 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 14.3, 17.3, 27.3, 29.7, 31.6, 31.8, 35.1, 39.6, 58.9, 67.1, 71.3, 71.7, 72.6, 73.0, 81.3, 94.6, 114.4, 117.8, 127.5, 127.6, 128.3, 133.5, 137.9, 138.7, 175.5 ppm.
ESI MS(m/z)	485.381 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 70.10; H, 9.15
	Found: C, 70.25; H, 9.02

(3*S*,6*R*,7*S*,12*S*)-12-(benzyloxymethyl)-6-(2-mehtoxyethoxy)methoxy-3,7-dimethyloxacyclododec-10-en-2-one (46)



A solution of ester **32** (0.17 g, 0.37 mmol) and Grubbs' second generation catalyst **35** (0.032 g, 0.037 mmol) in dry benzene (70 mL) was degassed under an argon atmosphere and refluxed for 24 h. After completion of the reaction (monitored by TLC), the solvent was evaporated and the residue was chromatographed on flash silica gel column using EtOAc and light petroleum (1:24) to yield **46** (0.072 g, 45%) as an inseparable mixture of *trans* and *cis* (2:1) isomers as a colourless liquid.

Trans: cis = 2:1

Mol.Formula $C_{25}H_{38}O_6$

IR ($CHCl_3$) cm^{-1}	2927, 1723, 1601, 1370, 1116, 1028
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.90 (d, 1 H, *J* = 6.6 Hz), 0.96 (d, 2 H, *J* = 6.6 Hz), 1.10 (d, 1 H, *J* = 7.1 Hz), 1.16 (d, 2 H, *J* = 7.1 Hz), 1.58-1.72 (m, 5 H), 2.08-2.14 (m, 3 H), 2.33 (m, 1 H), 2.66 (m, 1 H), 3.38 (s, 3 H), 3.47-3.61 (m, 5 H), 3.65-3.72 (m, 2 H), 4.55 (m, 2 H), 4.65-4.75 (m, 2 H), 5.10 (m, 1 H), 5.31-5.65 (m, 2 H), 7.31 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 125 MHz)	δ 14.0, 15.2, 18.3, 22.8, 26.2, 28.7, 30.3, 31.9, 34.7, 35.1, 36.6, 36.9, 39.9, 59.1, 67.1, 67.3, 71.5, 71.6, 71.8, 72.4, 73.1, 81.7, 94.3, 126.1, 126.6, 127.6, 127.7, 128.4, 129.6, 130.8, 132.4, 138.08, 138.1, 175.4, 175.6 ppm.
ESI MS(m/z)	457.265 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.10; H, 8.81
	Found: C, 68.93; H, 8.66

SECTION - II

.....

.....

SYNTHETIC STUDIES TOWARD THE MACROLACTONE CORE OF REVISED AMPHIDINOLIDE W

PRESENT WORK

PRESENT WORK

The lack of diastereoselectivity and suitable tools in the separation of *cis* and *trans* isomers observed in the RCM approach to form the 12-membered lactone core of amphidinolide W prompted us to peep deeply into other possible routes to its synthesis. Our objective was aimed at developing a new protocol which not only would render the macrolactone stereoselectively but its application would be exploitable to other related analogues as well. Keeping this in mind and also considering the revision of the structure we decided to target the synthesis of the macrolactone of revised amphidinolide W as our new goal.

We opted to exploit the Julia Kocienski olefination for the formation of the $\Delta^{9,10}$ *E*-alkene stereoselectively and modulate the lactone formation in such a manner so as to control the versatile epimerization at C-2. Discarding the pros and cons that may result in our synthesis we took the initiative to synthesize the lactone core **47** first with the objective to study the stereochemical course of reactions leading to the macrocycle and suitably exploiting it afterwards to its total synthesis. Retrosynthetically we thus disconnect the lactone **47** into two fragments **48** and **49** to be coupled by a modified Julia olefination reaction followed by lactonisation. The precursor to the sulfone intermediate i.e. the aldol product **50** could be obtained by a similar stereoselective Evans' aldol reaction between the aldehyde **9** and imide **51**. The preparation of the aldehyde **9** was akin to our previously mentioned protocol from oxazolidinone derivative (**10)**. The chiral imide auxiliary **51** was synthesized from L-phenylalanine following literature procedure. The corresponding aldehyde **49** could be obtained from D-mannitol (Figure 9).

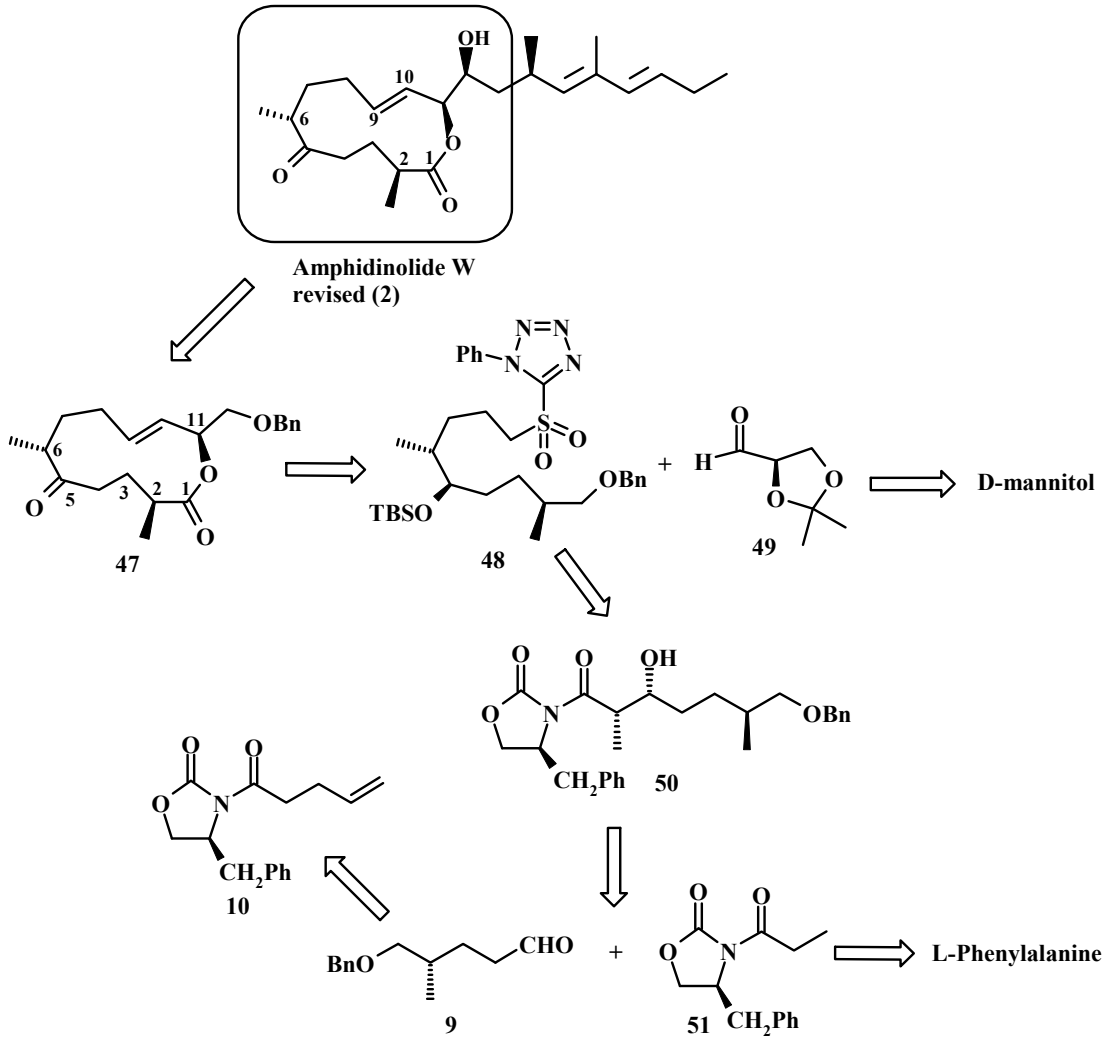
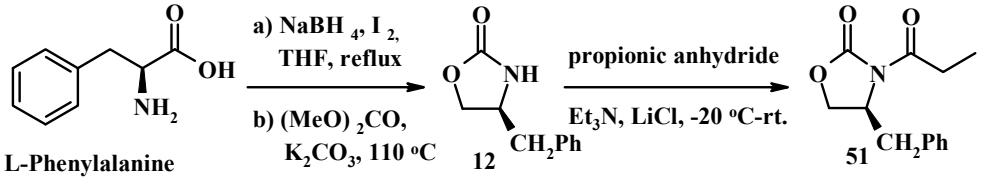


Figure 9: Retrosynthetic disconnection of lactone core of revised Amphidinolide W

Synthetic approach:

Accordingly L-phenylalanine, our chiral precursor was reduced to L-phenylalanilol with sodium borohydride and iodine in THF.[65] Conversion of the latter to the carbamate **12** using K_2CO_3 and dimethyl carbonate at 110 ^oC, followed by *N*-acylation using propionic anhydride, lithium chloride and Et_3N furnished the chiral imide (**51**) (Scheme 9).[66] The imide auxiliary **51** was confirmed from its ^1H and ^{13}C NMR data. In the ^1H NMR spectrum, the methyl and methylene protons resonated at δ 1.21 as a triplet and 2.95 ppm as a multiplet respectively, while the benzylic protons were observed

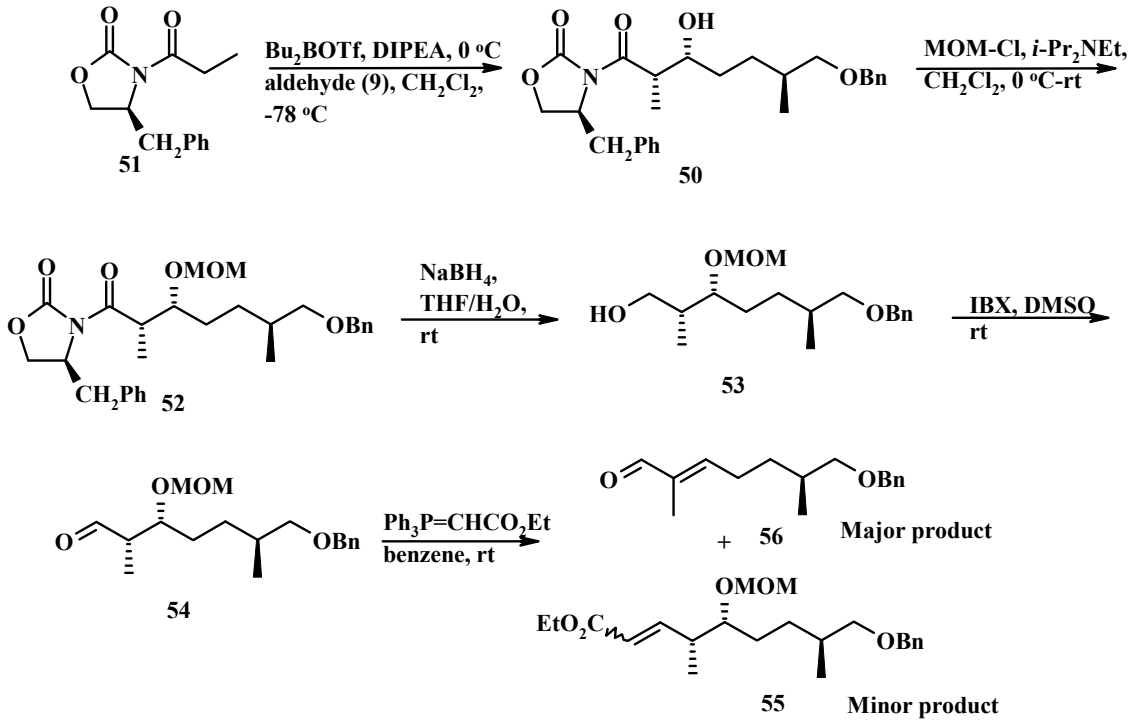
at δ values 2.76 and 3.30 ppm respectively as a doublet of doublet. ^{13}C NMR spectra also indicated the presence of the corresponding carbons.



Scheme 9

The imide **51** was reacted with aldehyde **9,** obtained from oxazolidinone **10** in a similar manner (as shown on Section I) following the Evans' *syn* aldol conditions[81] to generate the *syn* isomer **50** with high diastereoselectivity in 75% yield. The initial *syn* selectivity was assigned on the basis of lit. precedence.[81] Spectral study justified the initial assignment of the structure of **50**. The ^{1}H NMR spectra reveals the appearance of two methyl doublets at δ 0.95 and 1.25 ppm respectively. Furthermore the secondary hydroxyl group resonated at δ 3.91 ppm as a multiplet, rest of the peaks resonated in their expected δ values. In addition, the appearance of a base peak at 462.1612 $(M + Na)^{+}$ provided supporting evidence in favour of our assigned structure. Elemental analysis data further rationalized our compound. The absolute configuration of the new stereogenic centers were established later in our synthesis. Next, the secondary hydroxyl group in **50** was protected as its MOM ether **52** with MOM-Cl and *i*-Pr_2EtN at room temperature[104] in 91% yield with subsequent removal of the oxazolidinone ring was effected with sodium borohydride in THF/H_2O mixture[105] to afford the mixture of products; alcohol **53** and oxazolidinone, which were separated through flash column chromatography and confirmed by NMR spectroscopy. The shifting of the methyl groups in the upfield region in the ^{1}H NMR spectrum at δ 0.75 and 0.88 ppm as doublets and the appearance of two singlets at δ 3.33 and 4.58 ppm confirms the presence of MOM group. Moreover ^{13}C and DEPT spectra displayed peaks at δ 55.9 and 96.7 ppm which were attributed to the -OCH_3 and -OCH_2O- of the MOM group. Elaboration of **53** to the α,β-unsaturated ester **55** followed a two step sequence. The alcohol **53** was at first oxidized to aldehyde **54** with IBX in dimethylsulfoxide. Subsequent Wittig olefination of the aldehyde resulted in an

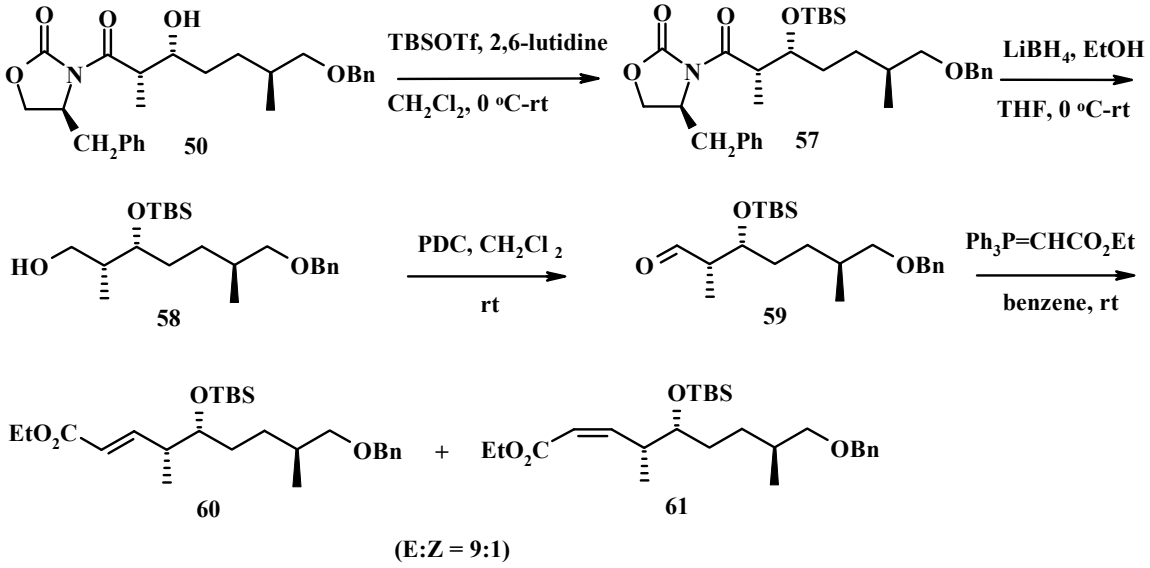
unexpected elimination product **56** as the major product apart from forming a minor quantity of the desired Wittig product **55** (Scheme 10). The Wittig eliminated product **56** was confirmed from its ^{1}H and mass spectral data. The appearance of an aldehydic proton at δ 9.38 ppm as a singlet and an olefinic proton resonating at 6.48 ppm as a triplet proved the formation of the unsaturated aldehyde **56**. Moreover mass spectral analysis depicted a peak at 269.215 attributed to $(M + Na)^+$ hence rationalizing the formation of **56**. The reason behind the eliminated product **56** during Wittig olefination reaction is due to the acidic nature of α-proton with respect to the aldehyde and lack of hindrance imparted by the *β*-substituted MOM group.



Scheme 10

Keeping the above reason in mind, we got to change our protecting group from MOM to the more bulkier TBDMS using TBSOTf and 2,6-lutidine in CH_2Cl_2[106] and similarly followed the reaction sequence as above. The silyl protected aldol compound **57** was supportive from its spectral data; the ^{1}H NMR spectra revealing three singlets at δ –0.02, 0.02 and 0.87 ppm integrating for two methyl and one *tert*-butyl functionality of

the TBS group respectively. Mass and elemental analysis data substantiated the formation of the TBS-protected compound. The oxazolidinone was efficiently removed using $LiBH_4$ in EtOH/THF mixture giving alcohol **58** in 83% yield. Carrying out the oxidation with PDC proved much more beneficial at this stage. Thus, alcohol **58** was oxidized to the aldehyde **59** with concomitant Wittig homologation to result the *α,β*-unsaturated ester **60** and **61** as a mixture of *trans* and *cis* isomers respectively (**60**:**61** = 9:1, *E:Z*) in good yield. The *E/Z* ratio was established from ^1H and ^{13}C NMR spectroscopy. Purification by flash chromatography provided the required *trans* compound **60** in pure form in 79% yield. Clarification for the requisite compound was obtained from its spectral, mass and elemental analysis datas. The ^1H NMR spectrum of **60** displayed peaks due to olefinic protons at δ 5.78 (1 H, *J* = 1.3, 15.8 Hz) and 6.99 ppm (1 H, *J* = 7.3, 15.8 Hz) as a doublet of doublet respectively; in addition ^{13}C spectra showed signals at δ 120.7, 152.1 and 166.6 which were attributed to the olefinic and ester carbonyl respectively (Scheme 11).



Scheme 11

Before moving further ahead, we decided to establish the absolute configurations of the newly generated stereogenic centers in **50**. For this endeavor we need to confirm the stereochemistry of the C5 stereocenter present in **60** first by converting to its

Mosher's ester derivative. Further confirmation of the adjacent methyl center could be achieved by converting **58** to its 1,3-acetonide derivative and studying the NOESY relationship between the adjacent protons.

A short account on modified Mosher's ester method: Determination of absolute stereochemistry

One of the major aspects of natural product and synthetic chemistry is to establish the absolute stereochemistry of the respective chiral centers. Numerous methods are available including some physical methods such as exciton chirality method and X-ray crystallography which can fulfill the needs to some extent but they too have got some limitations. Besides these, there are also some other chemical methods which have been useful for determination of stereochemistry of molecules.[107] *The phenomenon of nonequivalence of internal and external diastereotopic groups in NMR spectra has played a judicious role in determination of absolute stereochemistry. Among these the Mosher's method*[108] *using 2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) esters has been most frequently used. Mosher proposed* [108] *that, in solution, the carbonyl proton and ester carbonyl and trifluoromethyl groups of the MTPA moiety lie in the same plane (Figure 10).*

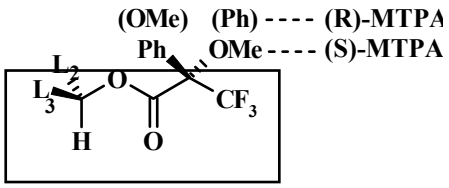


Figure 10

When the MTPA is in the hypothesized conformation, Mosher pointed out that the ^{1}*H NMR signal of* L_2 *of the (R)-MTPA ester will appear upfield relative to that of the (S)-MTPA ester due to the diamagnetic effect of the benzene ring. The lack of reliability in the NMR experiments for the correct assignment of protons prompted the use of modified*

techniques using ^{19}F NMR or lanthanide shift reagents.[109] Thus the modified Mosher ester method (^{1}H) is one of the simple and most efficient ways of determining the absolute configuration of secondary alcohols in a molecule. The basic concept of the modified Mosher's ester method is the same as Mosher proposed.[110] The idealized conformation is shown in Figure 11. The plane with the hypothesized conformation of the MTPA group is referred to as the MTPA plane with the idealized conformation.

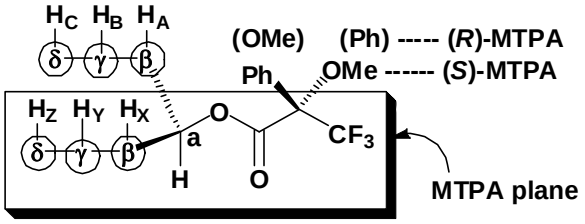


Figure 11: **MTPA plane of an MTPA ester is shown. $H_{A,B,C,.....}$ and $H_{X,Y,Z,....}$ are on the right and left sides of the plane respectively.**

Owing to the diamagnetic effect of the benzene ring, the $H_{A,B,C...}$ NMR signals of (R)-MTPA ester should appear upfield to those of the (S)-MTPA ester. The reverse hold true $H_{X,Y,Z...}$ protons. Thus illustrating in a model as shown in Figure 12, when $\Delta\delta = (\delta_S - \delta_R) \times 1000$ protons on the right side of the MTPA plane must have positive values ($\Delta\delta > 0$) and the protons on the left side of the MTPA plane must have negative values ($\Delta\delta < 0$).

Hence, the modified Mosher's method can be extended as follows:

a) *Assignment of as many proton signals as possible with respect to each of the (R)- and (S)- MTPA esters.*
b) *Calculating the $\Delta\delta$ values for the protons.*
c) *Putting the protons with the positive $\Delta\delta$ values on the right side and those with negative $\Delta\delta$ values on the left side of the model (Figure 12).*
d) *Constructing a molecular model of the compound in question and confirming that all the assigned protons with positive and negative $\Delta\delta$ values are actually found on right and on the left sides of the MTPA plane respectively. The absolute value of $\Delta\delta$ must be proportional to the distance from the MTPA moiety.*

When these conditions are satisfied model A will determine the absolute stereochemistry of the compound.

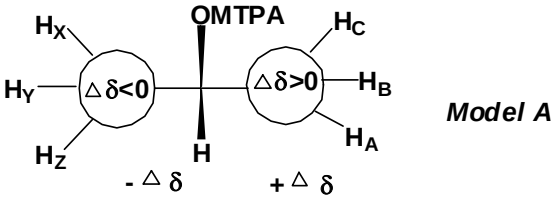
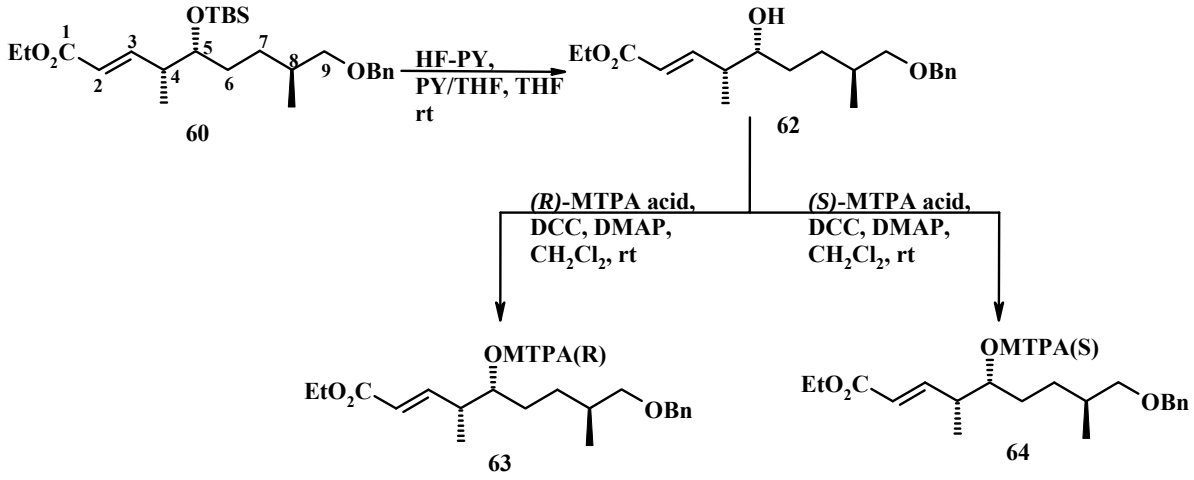


Figure 12: **A projection of MTPA ester is as shown in *Figure 11***

In order to assign the stereochemistry of C5 stereocenter in **60**, the TBDMS group was removed by the treatment of **60** with HF-Py in Py/THF solution leading to **62**.[111] Subsequent treatment of **62** with (*R*)- and (*S*)- MTPA acid respectively using DCC as coupling reagent and DMAP as catalyst in anhydrous CH_2Cl_2 at room temperature afforded the (*R*)- MTPA ester derivative (**63**) and (*S*)- MTPA ester (**64**) respectively (Scheme 12). The $\Delta\delta = (\delta_S - \delta_R) \times 1000$ values were calculated for as many protons as possible from the ^{1}H NMR spectrum of **63** and **64** (Table 1). Then constructing a molecular model of the compound in question and assigning the $\Delta\delta = (\delta_S - \delta_R) \times 1000$ values uniformly as shown in Figure 13, the absolute stereochemistry of C5-OH was determined to be (*R*)-configuration.



Scheme 12

Table 1

Protons	H-3	H-2	H-10	H-11	H-9	H-4	H-13	H-14
δ_S	6.69	5.63	4.40	4.10	3.17	2.56	0.93	0.83
δ_R	6.81	5.75	4.38	4.12	3.11	2.61	0.99	0.80
$\Delta\delta$	−120	−120	+20	−20	+60	−50	−60	+30

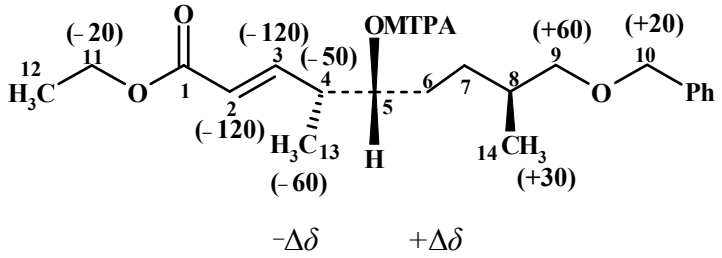
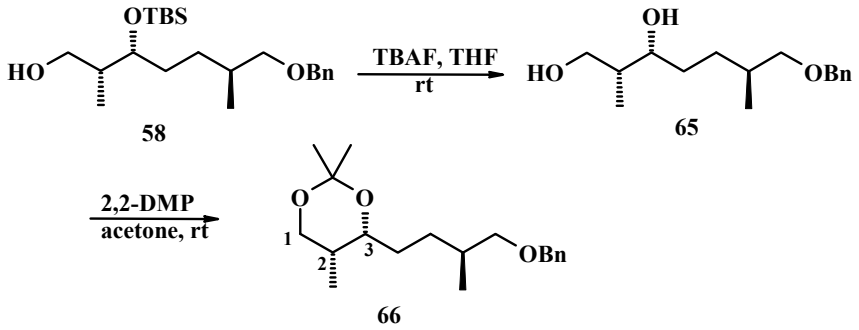
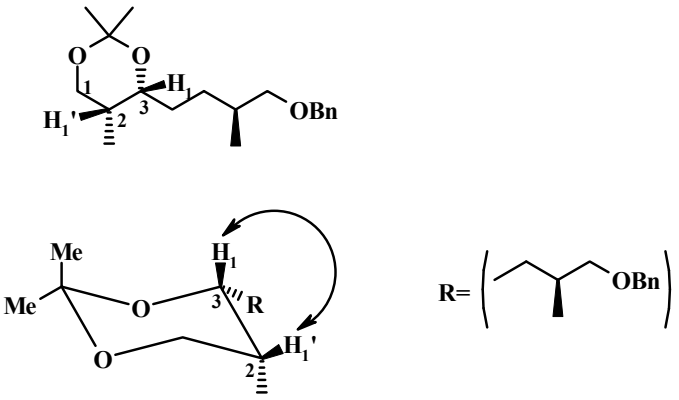


Figure 13

After determining the absolute stereochemistry of the C5-OH center, we proceed to determine the configuration of the adjacent methyl group at in **50**. Thus, compound **58** was deprotected with TBAF in THF[112] to provide the diol **65** which was protected as its isopropylidene derivative (**66**) (Scheme 13). The concerned NOESY correlations between the C2 and C3 protons established their *syn*-relationship, from where we confirmed the stereochemistry of the methyl group to be (*R*)-configuration (Figure 14).



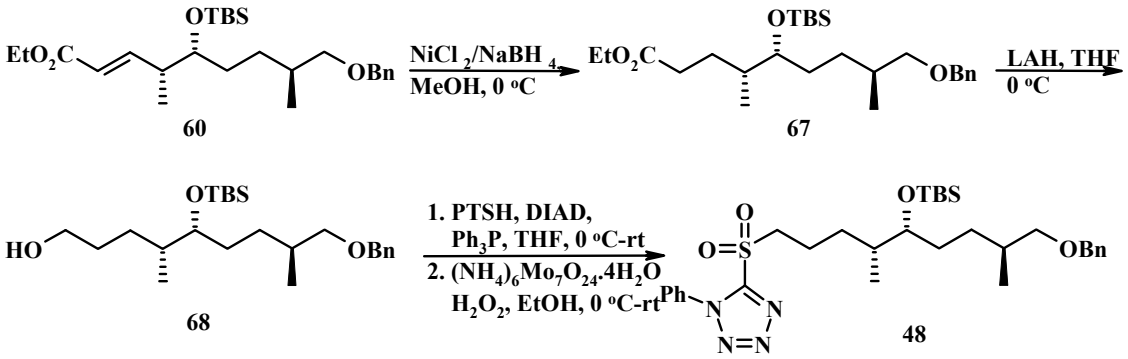
Scheme 13



***NOE* interactions between H_1 and H_1' protons in 66**

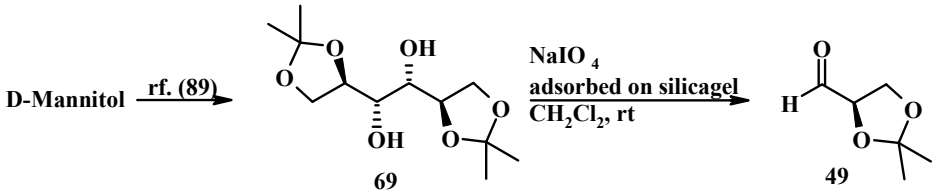
Figure 14

Having established the stereochemistry of all the newly generated chiral centers we proceeded with the *trans*-Wittig isomer **60** for the upcoming tasks. Chemoselective reduction of the double bond in **60** with $NiCl_2/NaBH_4$ in MeOH at 0 ^oC[113] followed by reduction with lithium aluminium hydride in THF provided the alcohol **68** in 89% yield. The absence of peaks due to olefin and ethoxy carbonyl in the ^1H and ^{13}C NMR spectrum revealed the formation of **68**. All other peaks were in accord with the assigned structure. Transformation to the sulfone intermediate, the precursor to the Julia reaction was accomplished in a two-step procedure. Mitsunobu conversion[114] of primary hydroxy to the sulfide derivative with 1-Phenyl-1*H*-tetrazole-5-thiol in THF, followed by oxidation with ammonium molybdate tetrahydrate and H_2O_2 mixture in ethanol furnished the sulfone **48**[115] in 81% yield in two steps, as one of the coupling partners for the forthcoming Julia-Kocienski reaction. The sulfone was fully characterized from its ^1H, ^{13}C, mass and elemental analysis (Scheme 14). In the ^1H NMR spectrum additional peaks were observed in the aromatic region at δ 7.59-7.71 (5H) as a multiplet, which was attributed to the phenyl tetrazole moiety; further evidence in the form of mass and elemental analysis data substantiated the structure of sulfone **48**.



Scheme 14

The other partner necessary for engagement in the Julia-Kocienski olefination was obtained from D-mannitol following reported literature precedence.[89] Thus isopropylidenation of commercially available D-mannitol to its diacetonide derivative (**69**) followed by oxidative cleavage using $NaIO_4$ adsorbed on silica gel, in CH_2Cl_2 yielded 2,3-O-isopropylidene-(*R*)-gyceraldehyde (**49**) (Scheme 15). The spectral values for **49** were in complete agreement with the reported ones.



Scheme 15

A brief introduction on Julia-Kocienski olefination: A versatile C-C bond forming reaction

Connective olefination reactions capable of linking together advanced fragments en route to alkene containing biologically active natural products are highly valued synthetic methods. The great complexity of natural products now tackled by total synthesis [116] demands that olefination methods employed in such endeavors must not only

be highly regio- and stereoselective, but also compatible with the requisite functional fragments. A variety of approaches to olefin synthesis have been developed to satisfy the stringent needs, however no single method is yet available to solve the problem. In connection to these there are the venerable Wittig reaction,[117] the Horner-Wittig,[118] Horner-Wadsworth-Emmons (HWE),[119] Peterson,[120] Johnson,[121] and the Julia olefination[122] which have found profound use in organic synthesis.

The classical Julia olefination (also known as the Julia-Lythgoe olefination)[123] was disclosed by Mark Julia and coworkers nearly thirty years ago outlining a connective olefination procedure which utilized the reductive elimination of β-acyloxysulfones as an alkene forming step.[122] The reaction is generally highly stereoselective for the formation of trans alkene although the trans selectivity increases with increasing chain branching about the newly formed double bond (Figure 15).

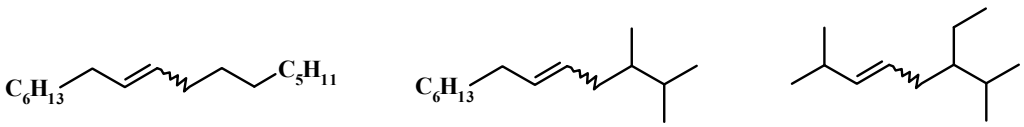
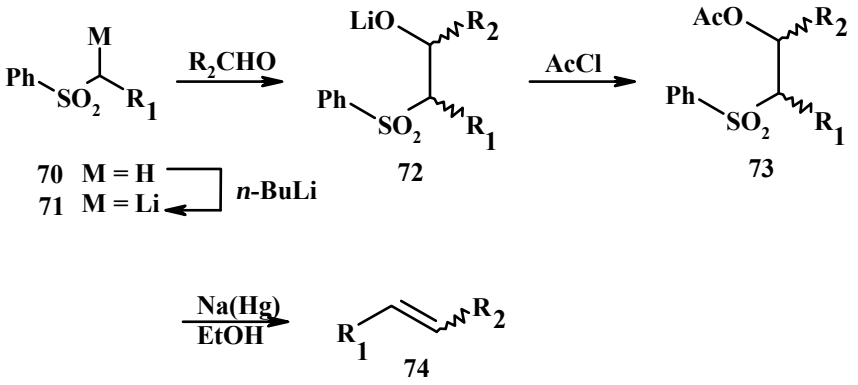


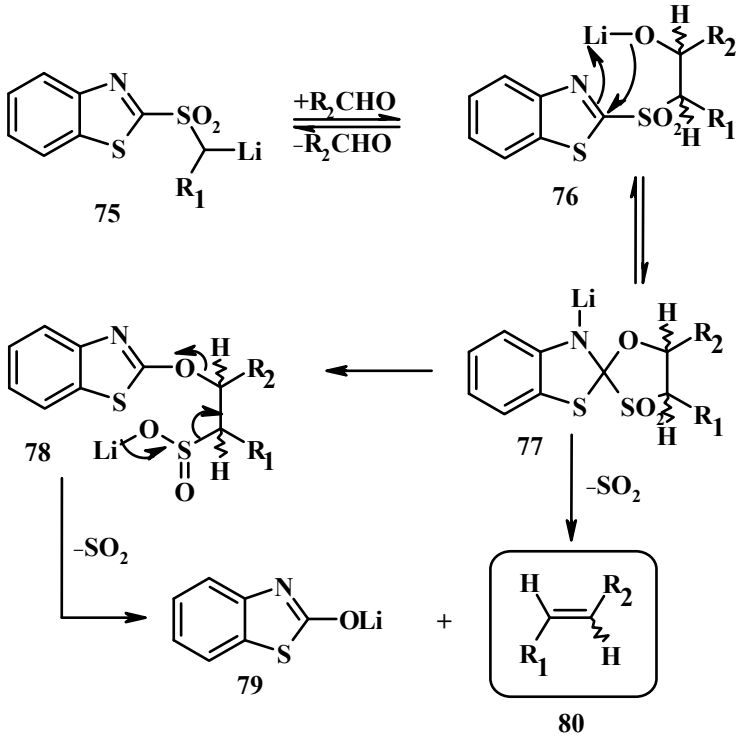
Figure 15: *Effect of chain branching on the stereochemical outcome of Julia olefination*

*But this reaction is relatively cumbersome and typically requires four distinct synthetic operations a) metallation of the phenylsulfone (**70**), b) addition of metallate (**71**) to an aldehyde, c) acylation of the resulting β-alkoxysulfone (**72**) and d) finally reductive elimination of β-acyloxysulfone (**73**) to afford alkene products (**74**) as shown in Scheme 16.*



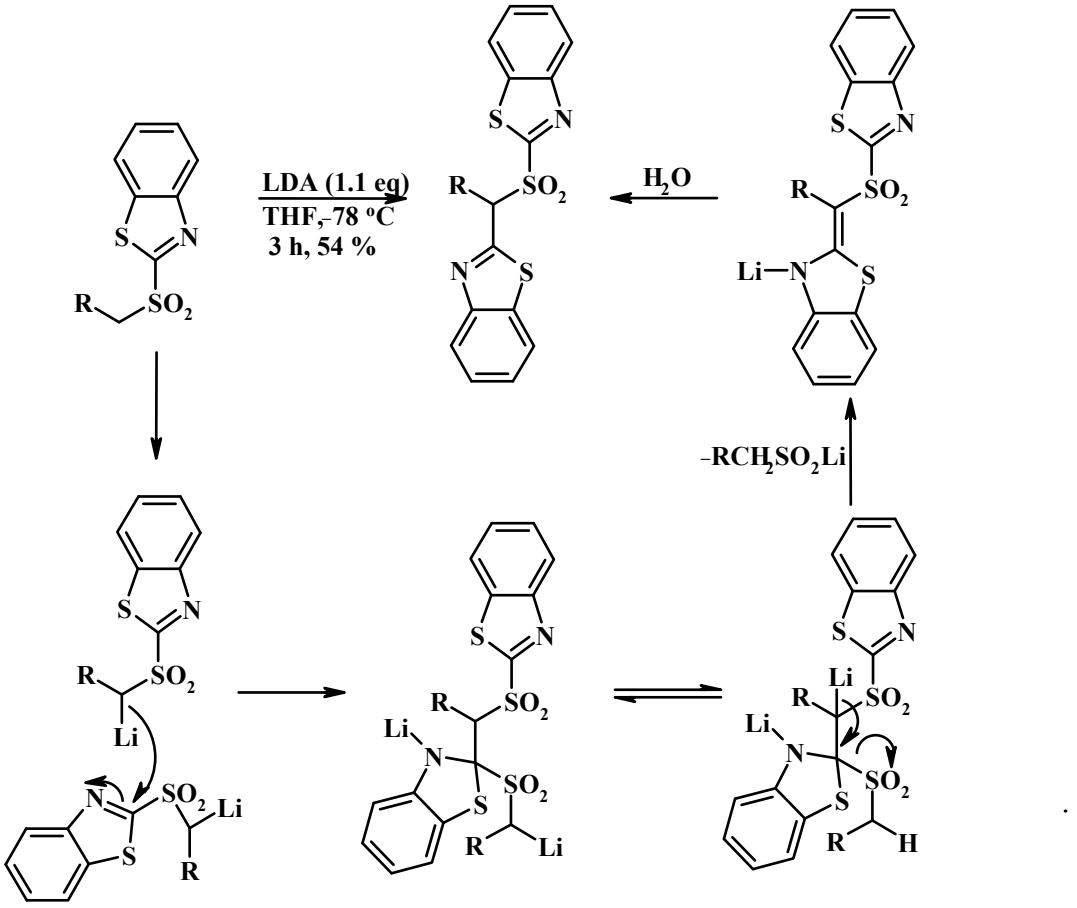
Scheme 16: *The classical Julia olefination*

To overcome this cumbersome process Sylvestre Juia and coworkers introduced the modified one pot Julia olefination employing the use of metallated heteroaryl, typically benzothiazol-2ylsulfones (BT-sulfone) as a replacement of the phenylsulfones.[124] *The mechanism of addition of the metallated BT-sulfone (**75**) to the aldehyde proceeds in an analogous fashion to the classical Julia olefination, however the adduct β-alkoxysulfones (**76**) are unstable and undergoes a facile Smiles rearrangement*[125] *via a spirocyclic intermediate (**77**) with the expulsion of sulfur dioxide and the lithium benzothiazolone (**79**) with the concomitant formation of the olefin (**80**) (Scheme 17).*



Scheme 17: *The modified Julia olefination*

Detailed study has revealed that this process has got some limitations : a) high stereoselectivities are only obtained in certain cases; e.g. In the formation of conjugated dienes; and it varies with the substrate and reaction conditions and b) some of the lithiated benzothiazolyl sulfones are unstable and undergo self condensation even at low temperature (Scheme 18).



Scheme 18: *Mechanism of self condensation of the BT-sulfone*

This is inimical to the olefination process and henceforth necessitated the use of "Barbier-type" reaction conditions i.e. the addition of the base to a mixture of sulfone and aldehyde whereupon in situ lithiation and addition to the sulfone takes place faster than self condensation. Unfortunately, this protocol may not be compatible for complex aldehyde substrates. The limitations encountered in the BT-sulfones created a further

investigation into the matter. Kocienski and coworkers in 1998 introduced the 1-Phenyl-1H-tetrazole-5yl sulfones (PT-sulfones)[126] (Figure 16) and provide a useful alternative to the BT-sulfone in many aspects.

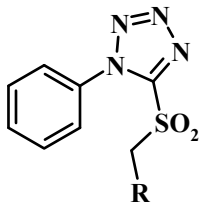
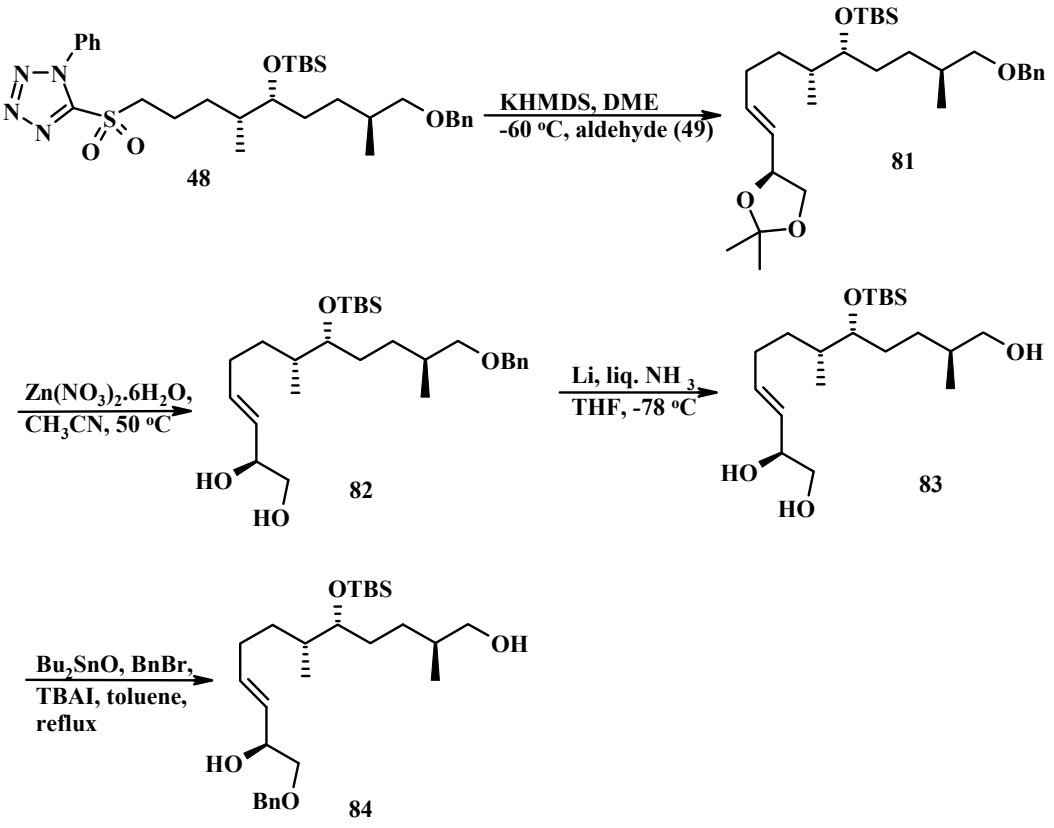


Figure 16: *PT-sulfone*

For instance, the PT- variant of the Julia olefination provides access to high trans- selectivity in the absence of biasing electronic or steric factors. The selectivity is susceptible to change in the base counterion which demonstrates an increase in the E:Z ratio as we move from Li-Na-K and is not markedly affected with chain branching. In addition the PT-sulfones are less prone to self condensation unlike their BT-counterparts. The polarity and coordination ability of the solvent has a marked effect on the reaction sequence, the optimum conditions for enhanced trans selectivity were observed with KHMDS as base in DME as solvent as the most effective ones.

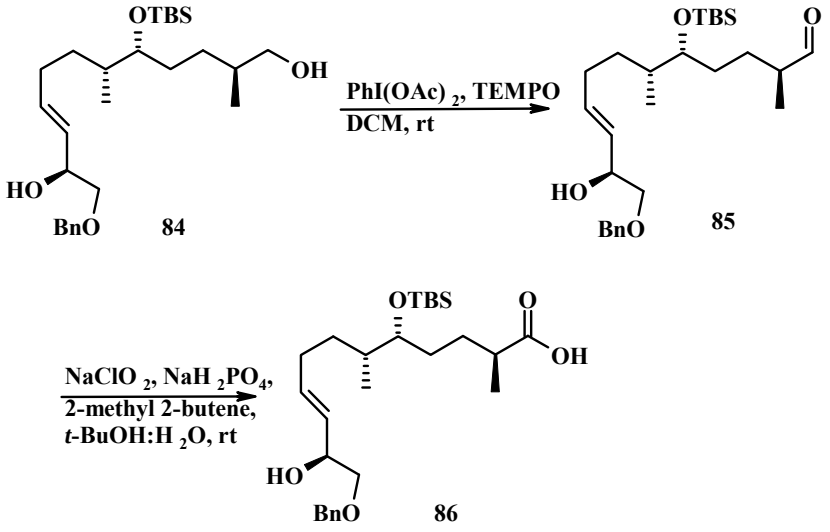
Our next underlying task was to execute the Julia-Kocienski olefination.[126,127] After investigating a variety of conditions for the proposed reaction, we obtained the best results using KHMDS as a choice of base at –60 ^{o}C which offered the olefin compound **81** in 82% yield with excellent selectivity for the *trans*-isomer. The spectral data of the product was entirely compatible with our presumed structure. The ^{1}H NMR spectrum displayed clear splitting at δ 5.41 (1H, J = 8.0, 15.3 Hz) as a doublet of doublet and at 5.76 ppm (1H, J = 6.8, 15.3 Hz) as a doublet of triplet showing a large coupling constant, which cleanly justified the formation of the *trans*-olefin. Moreover ^{13}C spectral analysis also supported the structure. Additional clarification was achieved from mass and elemental analysis. The ESI-MS spectrum depicted a base peak at 527.4708 attributed to $(M + Na)^{+}$. Having successfully accomplished the desired olefin stereochemistry, we

moved ahead to proceed through our synthesis. As such, the isopropylidene group in **81** was selectively cleaved under mild lewis acid conditions,[128] which afforded the diol compound **82** in 74% yield. Birch reduction of the latter with Li in liq. NH_3 smoothly proceeded to give triol **83**. The peaks due to benzylic and aromatic protons were absent in the ^1H and ^{13}C NMR spectrum of **83**. A base peak in the mass spectrum at 397.353 attributed to $(M + Na)^+$ substantiated the triol compound **83**. In addition, elemental analysis data provided supporting evidence for the above compound. Bu_2SnO mediated selective protection[90] of the 1,2-diol led to mono benzylated compound **84** in 84% yield. Additional peaks were observed due to the aromatic and benzylic protons at δ 7.29-7.35 (5H) and at 4.56 ppm (2H) as a multiplet and singlet respectively, in the ^1H NMR spectrum. ^{13}C NMR also witnessed the formation of the mono benzylated compound (Scheme 19).



Scheme 19

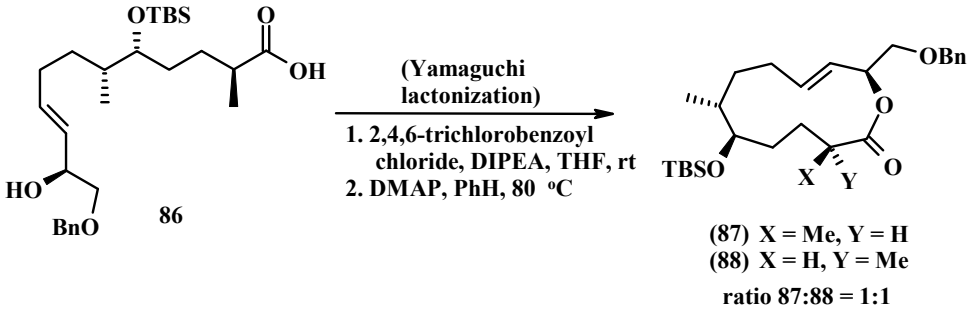
We next carried out the selective oxidation of the primary hydroxyl group in **84**. We envisaged the oxidation process in a two step protocol. At first the diol **84** was selectively oxidized to the hydroxy aldehyde **85** with BAIB and TEMPO in CH_2Cl_2 at room temperature,[129] which on further oxidation with $NaClO_2$ and NaH_2PO_4 furnished the seco acid **86** in excellent yield.[130] The oxidation process went smoothly without giving any over oxidation products for the secondary allylic hydroxyl group. The spectral and analytical data entirely supported the synthesized compound. The presence of a peak at 1708 cm^{-1} in the IR spectrum indicated the presence of the carboxylic acid group. In the ^1H NMR spectrum the methyl group adjacent to the carboxylic acid was found to be deshielded to δ 1.17 ppm as a doublet; rest of the spectrum was compatible with our assigned structure. ^{13}C spectra also revealed a peak at δ 181.6 ppm due to the carboxylic acid moiety (Scheme 20). Mass spectral analysis showed a peak at 501.342 attributed to $(M + Na)^+$ thereby justifying the formation of seco acid **86**. Elemental analysis data were also compatible with the assigned structure.



Scheme 20

Setting the stage for the key lactonization, we took the initiative to work out the Yamaguchi lactonization condition.[92a,62] Thus subjecting **86** to Yamaguchi's lactonization protocol with 2,4,6-trichlorobenzoyl chloride, DIPEA and DMAP, a 1:1 ratio of

compounds **87** and **88** were obtained in combined 55% yield possibly due to epimerization at the C-2 center during base catalysed lactonization. The rationalization for stereochemistry was obtained from the corresponding ^{1}H and ^{13}C NMR spectra. Both the spectra witnessed the formation of diastereomeric mixture of products. For instance, the methyl groups adjacent to the ester were shown to be a mixture of two doublets merging at the center at δ 1.18 and 1.20 respectively. The compounds **87** and **88** could not be separated even on flash column chromatography (Scheme 21).



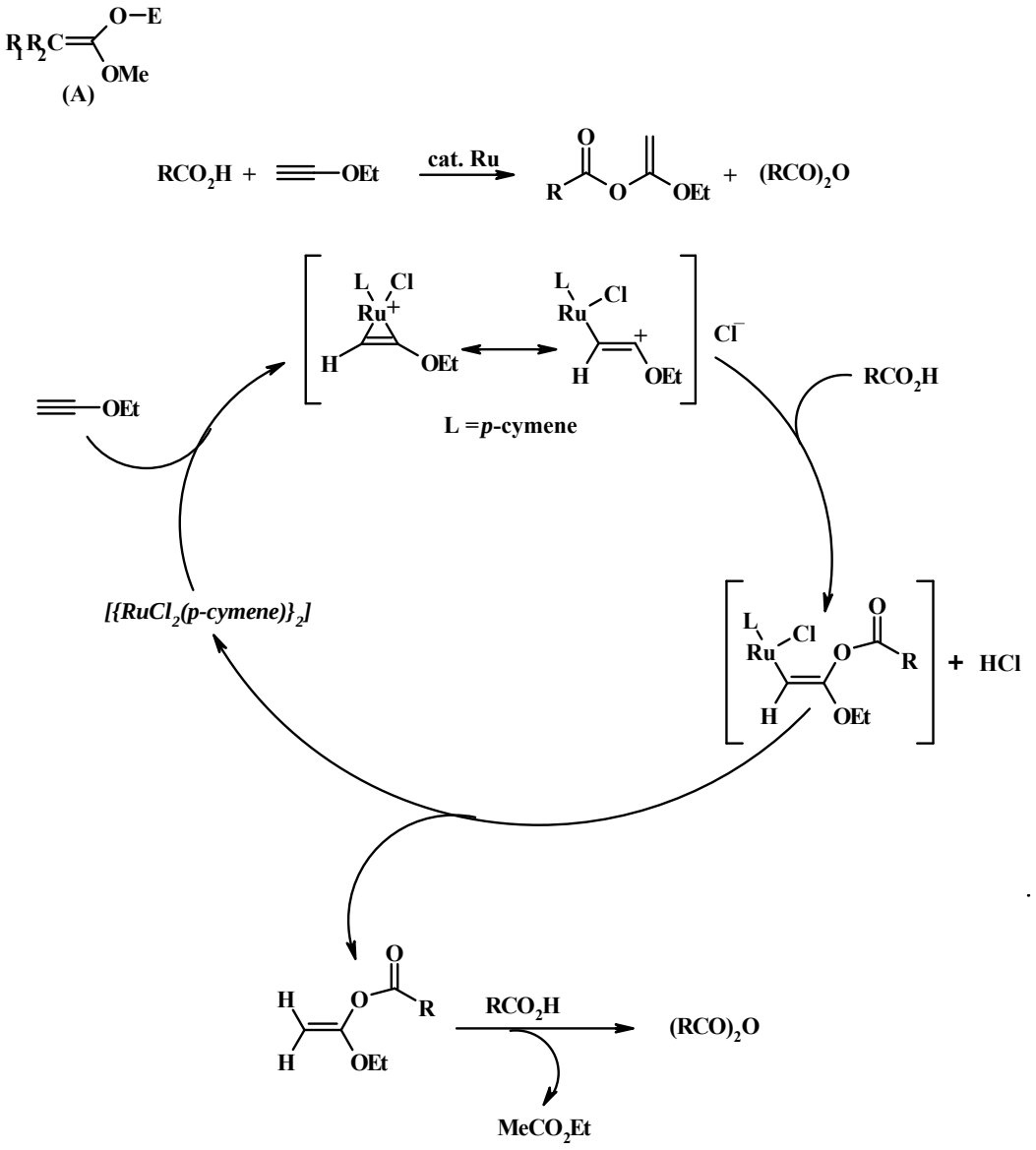
Scheme 21

This intricate nature of the substrate to lactonization due to the intrinsic lability at the C-2 center prompted us to investigate other possible routes to its synthesis. We made an attempt to study the Trost lactonization protocol as a venture to the lactone core.

Trost lactonization: A short note

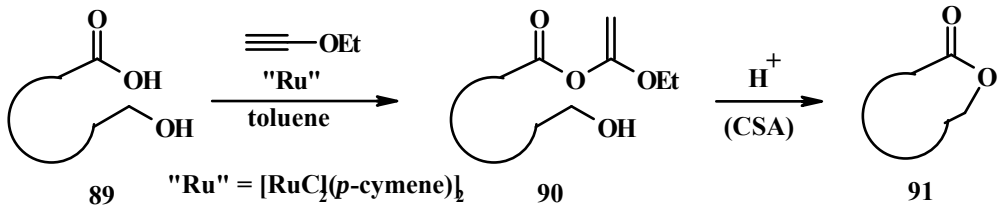
Natural product synthesis necessitates the use of mild reagents under neutral or nearly neutral conditions with easy isolation of products to avoid unwanted complications arising due to multifunctional groups. The introduction of ketene acetal derivatives (A) as reagents for acylation, silylation, carbonylation etc. have been on the rising demand. In connection with this study it is known that 1-alkoxyvinyl esters are efficient reagents for acylation[131,132] of amines or alcohols under almost neutral conditions. These reagents have prepared by mercury (II) catalysed addition of carboxylic acid to the alkoxyacetylene.[132] A limitation arises due to the toxic effect of

mercury salts which have strongly restricted the usage of these reagents. Kita [133] saw this as an opportunity to activate the carboxylic acid as ethoxyvinyl ester by using ruthenium complexes. In any event the ethoxyvinyl esters perform admirably in intermolecular esterification reactions under acid catalysed conditions. The mechanism of formation of 1-ethoxyvinyl esters is shown below (Scheme 22).



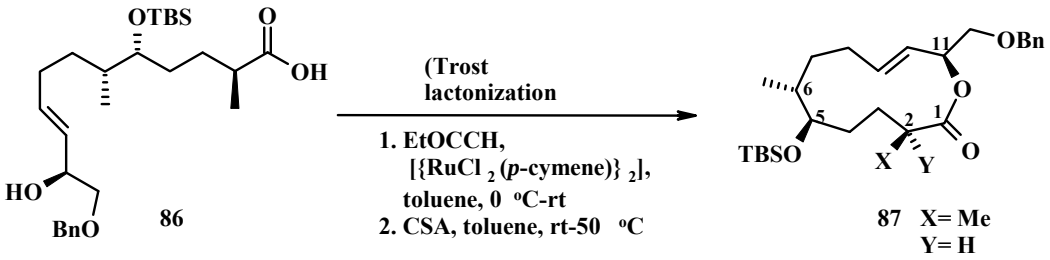
Scheme 22: Catalytic mechanism for the formation of 1-ethoxyvinyl esters

With the advent of modern isolation techniques, numerous large-ring lactones that possess interesting biological activity have been isolated. Numerous methods have been developed which can form such lactones under conditions capable of withstanding a variety of functional groups.[134] *Among these are the Mukaiyama cyclisation, Yamaguchi lactonisation, cyclising using activating agents like carbodiimides (DCC) which have established their position as important lactone forming reagents.*[135] *A possible drawback in these cyclisations is the use of stoichiometric amount of base and refluxing conditions, that may result in undesired side reactions in case of base sensitive substrates. To overcome the limitation encountered in these highly basic conditions, Trost and Chisholm attempted an intramolecular cyclisation of hydroxy acids under mild acidic conditions according to the protocol established by Kita.*[133,136] *In the Trost lactonisation,*[137] *the vinylic ester (**90**) is formed through a ruthenium catalysed reaction of the carboxylic acid group in the hydroxy acid (**89**) with commercially available ethoxyacetylene (Scheme 23). The vinylic ester can be isolated by chromatographic purification and lactonised under mild acidic conditions (CSA 10%) to afford the lactone (**91**). This methodology has been applied in the synthesis of several large ring lactones and thus provides a fruitful alternative to base labile hydroxy acid derivatives.*



Scheme 23: Lactone formation via Trost vinylic esters

Interestingly when lactonization was performed according the condition of Kita *et al*. (Trost lactonization)[136,137] we obtained the desired macrolactone **87** as a sole isomer in 42% yield, thus solving the possible drawback faced in the Yamaguchi lactonization (Scheme 24).



Scheme 24

The characterization of lactone **87** was thoroughly accomplished from its ^{1}H, ^{13}C, mass and elemental analysis data. The downfield shift of the (C-11) proton in the ^{1}H NMR spectrum in the range (δ 5.44-5.53) along with the olefinic proton was indicative of the formation of lactone. Furthermore, IR absorption at 1722 cm^{-1} along with the ^{13}C spectra revealing a peak at δ 175.4 ppm due to the ester carbonyl group confirmed the structure of **87**. Mass and elemental analysis data provided additional evidence to the lactone formation. NOESY interactions between the H_A and H_B protons in **87** gave full support in favour of the desired isomer (Figure 17).

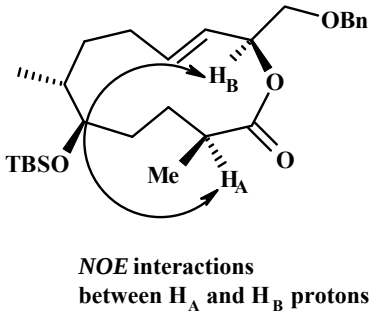


Figure 17: NOESY interactions in compound **87**

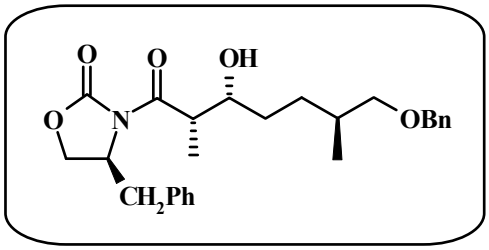
Finally deprotection of TBS and oxidation of the corresponding hydroxyl group will provide lactone **47**. Elaboration of this present intermediate **87** to lactone **47** and towards the total synthesis of amphidinolide W is currently in progress in our laboratory.

In conclusion we have developed a highly efficient synthetic route to the macrolactone core of revised Amphidinolide W. The synthesis features highly stereo and regeoselective incorporation of chiral centers utilizing Evans' asymmetric alkylation, aldol reactions and the execution of a highly stereoselective Julia-Kocienski olefination for the construction of the $\Delta^{9,10}$ *E*-alkene. Selective oxidation processes using BAIB and TEMPO are well versed in the synthesis. Of particular note is the final lactonization using Kita's procedure which selectively produced only the desired isomer thus forestalling the difficulty encountered in the Yamaguchi lactonization. The approach is thus feasible, simple and hopefully can be applied to other related bioactive macrolactone analogues.

EXPERIMENTAL

EXPERIMENTAL

(*S*)-4-benzyl-3-((2*S*,3*R*,6*S*)-7-(benzyloxy)-3-hydroxy-2,6-dimethylheptanoyl)oxazolidin-2-one (50)

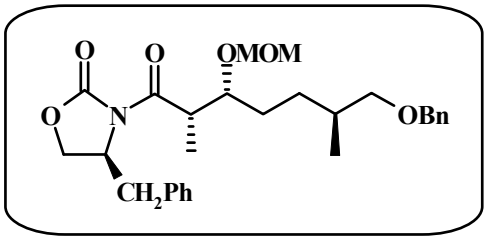


To a solution of the oxazolidinone **51** (3.0 g, 12.9 mmol) in CH_2Cl_2 (20 mL) cooled to 0 ^oC, dibutylboron triflate (14.2 mL, 1M in CH_2Cl_2, 14.2 mmol) was added dropwise followed by *i*-Pr_2NEt (2.7 mL, 15.5 mmol). It was stirred for 30 min, the reaction mixture was then cooled to –78 ^oC and the aldehyde **9** (2.7 g, 12.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise. Stirring was continued for 1 h at –78 ^oC and then warmed to 0 ^oC and stirred for another 1 h, then quenched slowly with an aqueous solution of pH 7.0 phosphate buffer (15 mL), MeOH (30 mL) and then with a mixture of 30 % H_2O_2 and MeOH (1:2), (45 mL). After stirring at rt for 1 h, the reaction mixture was diluted with CH_2Cl_2 (25 mL), the layers were separated out and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue thus obtained was purified by flash silica gel chromatography (EtOAC/light petroleum, 1:5) to furnish aldol product **50** (4.2 g, 75%) as a thick viscous liquid.

Mol.Formula	$C_{26}H_{33}NO_5$
Optical Rotation $[\alpha]_D^{25}$	+42.04 (*c* 1.9, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3506, 2931, 2860, 1781, 1697, 1454, 1210, 1015, 749

^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.95 (d, 3 H, *J* = 6.6 Hz), 1.25 (d, 3 H, *J* = 7.1 Hz), 1.48-1.59 (m, 4 H), 1.79 (m, 1 H), 2.76 (dd, 1 H, *J* = 9.5, 13.2 Hz), 2.90 (brs, 1 H), 3.21-3.34 (m, 3 H), 3.74 (dq, 1 H, *J* = 2.5, 7.1 Hz), 3.91 (m, 1 H), 4.13-4.21 (m, 2 H), 4.48 (s, 2 H), 4.67 (m, 1 H), 7.22-7.33 (m, 10 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 10.3, 17.1, 29.8, 31.1, 33.3, 37.5, 41.9, 54.9, 65.9, 71.6, 72.7, 75.5, 127.2, 127.3, 127.4, 128.1, 128.7, 129.2, 134.9, 138.5, 152.7, 177.1 ppm.
ESI MS(m/z)	462.1612 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 71.05; H, 7.57; N, 3.19
	Found: C, 70.95; H, 7.39; N, 3.08

(*S*)-4-benzyl-3-((2*S*,3*R*,6*S*)-7-(benzyloxy)-3-(methoxymethoxy)-2,6-dimethylheptanoyl)oxazolidin-2-one (52)

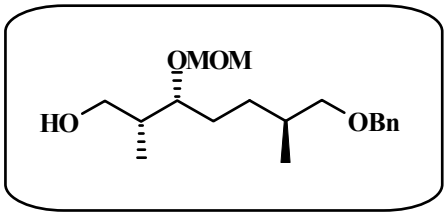


To a solution of aldol product **50** (1.0 g, 2.3 mL) in CH_2Cl_2 (10 mL), *i*-Pr_2NEt (1.6 mL, 9.1 mmol) and MOM-Cl (0.35 mL, 4.5 mmol) were added simultaneously at 0 ^oC. The reaction mixture was stirred overnight at room temperature, then quenched with ice and water, and extracted with CH_2Cl_2 (2 × 10 mL). The combined extracts were dried (over Na_2SO_4), concentrated and purified on silica gel column using EtOAc and light petroleum (1:9) to give **52** (0.99 g, 91%) as a clear liquid.

Mol.Formula	$C_{28}H_{37}NO_6$

Optical Rotation $[\alpha]_D^{25}$	+58.3 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2928, 1780, 1699, 1454, 1381, 1209, 1098, 1031, 750
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.95 (d, 3 H, *J* = 6.6 Hz), 1.23 (d, 3 H, *J* = 7.1 Hz), 1.50-1.80 (m, 5 H), 2.75 (dd, 1 H, *J* = 9.8, 13.3 Hz), 3.26-3.34 (m, 6 H), 3.79 (m, 1 H), 3.96 (m, 1 H), 4.12 (d, 2 H, *J* = 4.6 Hz), 4.48 (s, 2 H), 4.52-4.63 (m, 3 H), 7.21-7.32 (m, 10 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 11.4, 17.2, 29.4, 29.7, 30.1, 33.6, 37.7, 41.4, 55.95, 65.98, 72.9, 75.6, 79.3, 96.4, 127.3, 127.4, 127.5, 128.3, 128.9, 129.4, 135.4, 138.7, 153.1, 174.8 ppm.
ESI MS(m/z)	506.241 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.54; H, 7.71; N, 2.90
	Found: C, 69.42; H, 7.59; N, 2.76

(2*R*,3*R*,6*S*)-7-(benzyloxy)-3-(methoxymethoxy)-2,6-dimethylheptan-1-ol (53)

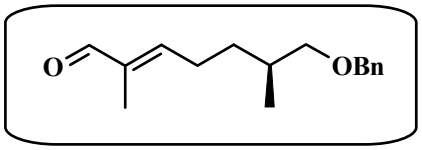


A solution of compound **52** (0.8 g, 1.7 mmol) in THF/H_2O (3:1), (8 mL) was treated with $NaBH_4$ (0.252 g, 6.63 mmol) at room temperature. It was stirred for 6 h, then quenched with a saturated solution of NH_4Cl (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, concentrated and the residue was purified on silica gel column using EtOAc/light petroleum (1:5) to afford **53** (0.44 g, 86%) as a colourless liquid.

Mol.Formula	$C_{18}H_{30}O_4$

Optical Rotation $[\alpha]_D^{25}$	–28.3 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3437, 2926, 1736, 1496, 1454, 1208, 1147, 1098, 918, 698.
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.75 (d, 3 H, *J* = 7.0 Hz), 0.88 (d, 3 H, *J* = 6.7 Hz), 1.35-1.56 (m, 4 H), 1.69-1.86 (m, 2 H), 2.39 (brs, 1 H), 3.21 (dd, 2 H, *J* = 2.4, 6.3 Hz), 3.33 (s, 3 H), 3.41-3.64 (m, 3 H), 4.42 (s, 2 H), 4.58 (s, 2 H), 7.23-7.27 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 10.6, 17.1, 28.8, 29.95, 33.6, 37.8, 55.9, 65.2, 72.99, 75.7, 79.9, 96.7, 127.45, 127.5, 128.3, 138.7 ppm.
ESI MS(m/z)	333.2985 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.64; H, 9.74
	Found: C, 69.54; H, 9.63.

(*S*,*E*)-7-(benzyloxy)-2,6-dimethylhept-2-enal (56)



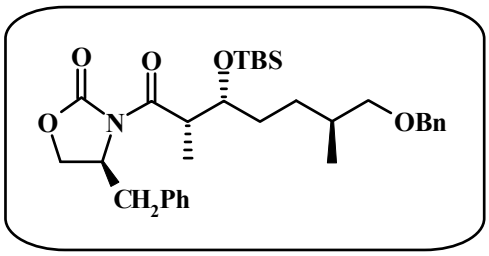
The alcohol **53** (0.35 g, 1.1 mmol) was dissolved in DMSO (4 mL) and IBX (0.38 g, 1.4 mmol) was added at room temperature. It was stirred overnight, then quenched with H_2O and filtered off. The filtrate was extracted with ether (2 × 15 mL), then dried over Na_2SO_4 and concentrated. The residue was column purified on silica gel (EtOAc/light petroleum, 1:9) to produce aldehyde **54** (0.32 g, 93%) as a colourless liquid.

To a solution of the aldehyde **54** (0.32 g, 1.04 mmol) in dry benzene (8 mL), (carbethoxymethylene)triphenyl phosphorane (0.72g, 2.08 mmol) was added at room temperature. It was stirred overnight, then concentrated and the residue was purified by

flash silica gel column chromatography (EtOAc/light petroleum, 1:49) to afford the eliminated product **56** (0.18 g, 70%) as a colourless liquid.

Mol.Formula	$C_{16}H_{22}O_2$
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.97 (d, 3 H, J = 6.7 Hz), 1.36 (m, 1 H), 1.65(m, 1 H), 1.73 (s, 3 H), 1.82 (m, 1 H), 2.30-2.42 (m, 2 H), 3.32 (d, 2 H, *J* = 6.1 Hz), 4.51 (s, 2 H), 6.48 (t, 1 H, *J* = 7.3 Hz), 7.30-7.35 (m, 5 H), 9.38 (s, 1 H) ppm.
ESI MS(m/z)	269.215 $(M + Na)^+$

(*S*)-4-benzyl-3-((2*S*,3*R*,6*S*)-7-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptanoyl)oxazolidin-2-one (57)

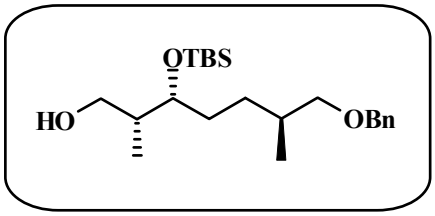


To a stirred solution of the aldol product **50** (5.0 g, 11.4 mmol) in CH_2Cl_2 (20 mL), 2,6-lutidine (2.6 mL, 22.7 mmol) was added followed by TBS-OTf (3.9 mL, 17.0 mmol) at 0 ^oC. The reaction mixture was stirred for 30 min, then quenched with ice, diluted with water (5 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with 1N HCL (2 × 15 mL), brine and dried over Na_2SO_4. It was concentrated to a residue which was purified on silica gel column using EtOAc and light petroleum (1:19) as eluent to provide **57** (5.95 g, 95%) as a colorless viscous liquid.

Mol.Formula	$C_{32}H_{47}NO_5Si$
Optical Rotation $[\alpha]_D^{25}$	+28.36 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2929, 1783, 1704, 1454, 1382, 1209, 1104, 837

^{1}H NMR($CDCl_3$, 200 MHz)	δ –0.02 (s, 3 H), 0.02, (s, 3 H), 0.87 (s, 9 H), 0.93 (d, 3 H, *J* = 6.4 Hz), 1.20 (d, 3 H, *J* = 7.0 Hz), 1.45-1.75 (m, 5 H), 2.75 (dd, 1 H, *J* = 9.6, 13.3 Hz), 3.23-3.30 (m, 3 H), 3.84 (m, 1 H), 4.01-4.14 (m, 3 H), 4.47 (s, 2 H), 4.55 (m, 1 H), 7.22-7.33 (m, 10 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ –4.9, –4.2, 11.5, 17.1, 17.98, 25.6, 25.8, 28.6, 32.7, 33.7, 37.5, 42.6, 55.7, 65.9, 72.9, 75.8, 127.25, 127.3, 127.5, 128.2, 128.9, 129.4, 135.4, 138.7, 152.98, 175.2 ppm.
ESI MS(m/z)	576.3968 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.40; H, 8.55; N, 2.53
	Found: C, 69.26; H, 8.38; N, 2.42

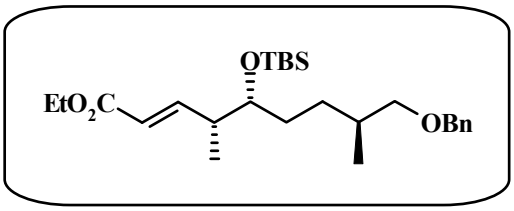
(2*R*,3*R*,6*S*)-7-(benzyloxy)-3-(*tert*-butyldimethylsilyloxy)-2,6-dimethylheptan-1-ol (58)



LiCl (1.7 g, 40.4 mmol) and $NaBH_4$ (1.53 g, 40.4 mmol) were taken in a mixture of absolute ethanol (25 mL) and THF (8 mL) and vigorously stirred for 1 h at room temperature. A solution of **57** (5.6 g, 10.1 mmol) in THF (30 mL) was then added dropwise and the mixture was then stirred for 6 h at room temperature. The solid was then filtered off and the filtrate was neutralized to pH 7 by dropwise addition of saturated NH_4Cl. The solvent was then removed and the residue was partitioned between EtOAc and H_2O. The organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to a residue. Purification by silica gel column chromatography using EtOAc/light petroleum (1:6) afforded **58** (3.2 g, 83.2%) as a colourless liquid.

Mol.Formula	$C_{22}H_{40}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	-1.95 (*c* 0.8, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3430, 2955, 2929, 1471, 1361, 1253, 1096, 836, 774
^{1}H NMR($CDCl_3$, 400 MHz)	δ 0.07 (s, 3 H), 0.09 (s, 3 H), 0.81 (d, 3 H, *J* = 7.0 Hz), 0.89 (s, 9 H), 0.95 (d, 3 H, *J* = 6.7 Hz), 1.05 (m, 1 H), 1.45-1.55 (m, 3 H), 1.75 (m, 1 H), 1.92 (m, 1 H), 2.38 (brs, 1 H) 3.26 (dd, 1 H, *J* = 6.4, 8.9 Hz), 3.32 (dd, 1 H, *J* = 6.3, 8.9 Hz), 3.51 (dd, 1 H, *J* = 5.2, 10.6 Hz), 3.67 (dd, 1 H, *J* = 8.4, 10.6 Hz), 3.75 (m, 1 H), 4.50 (s, 2 H), 7.29-7.34 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 100 MHz)	δ -4.5, -4.3, 11.6, 17.1, 17.96, 25.8, 29.9, 30.2, 33.6, 39.4, 66.0, 73.0, 75.7, 75.8, 127.4, 127.5, 128.3, 138.7 ppm.
ESI MS(m/z)	403.2501 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.42; H, 10.59
	Found: C, 69.24; H, 10.38.

(4*R*,5*R*,8*S*,*E*)-ethyl-9-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnon-2-enoate (60)

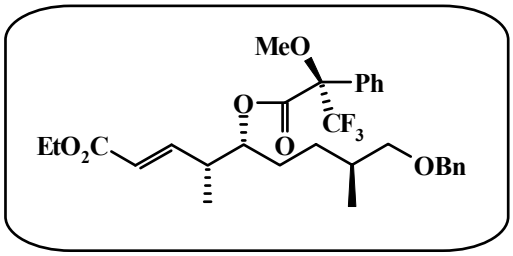


The alcohol **58** (3.0 g, 7.9 mmol) was dissolved in CH_2Cl_2 (25 mL) and PDC (5.9 g, 15.7 mmol) was added at room temperature. It was stirred overnight and then filtered off. The filtrate was concentrated to a residue, which was column purified on silica gel (EtOAc/light petroleum, 1:9) to produce aldehyde **59** (2.4 g, 81%) as a colourless liquid.

A solution of aldehyde **59** (2.4 g, 6.3 mmol) and (carbethoxymethylene)triphenyl phosphorane (4.4 g, 12.7 mmol) in dry benzene (20 mL) were stirred at room temperature for 24 h. The reaction was monitored by TLC and after completion, the solvent was removed in vaccum and the residue was purified by flash silica gel column chromatography eluting with EtOAc and light petroleum (1:24) to afford pure Wittig *E*-isomer **60** (2.2 g, 78.6%) along with the other *Z*- isomer **61** in a 9:1 ratio, as a colourless liquid.

Mol.Formula	$C_{26}H_{44}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	+20.76 (*c* 0.9, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2956, 2930, 2857, 1721, 1652, 1462, 1366, 1257, 1180, 1098, 836, 774
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.03 (s, 6 H), 0.88 (s, 9 H), 0.92 (d, 3 H, *J* = 6.7 Hz), 1.01 (d, 3 H, *J* = 6.9 Hz), 1.28 (t, 3 H, *J* = 7.1 Hz), 1.39-1.78 (m, 5 H), 2.45 (m, 1 H), 3.23 (dd, 1 H, *J* = 6.3, 9.0 Hz), 3.30 (dd, 1 H, *J* = 6.3, 9.0 Hz), 3.59 (m, 1 H), 4.18 (q, 2 H, *J* = 7.1 Hz), 4.48 (s, 2 H), 5.78 (dd, 1 H, *J* = 1.3, 15.8 Hz), 6.99 (dd, 1 H, *J* = 7.3, 15.8 Hz), 7.28-7.33 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ ‒4.5, ‒4.2, 13.7, 14.3, 17.2, 18.1, 25.9, 29.2, 31.5, 33.6, 41.3, 60.1, 72.99, 75.3, 75.7, 120.7, 127.4, 127.5, 128.3, 138.7, 152.1, 166.6 ppm.
ESI MS(m/z)	471.248 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.59; H, 9.88
	Found: C, 69.44; H, 9.69.

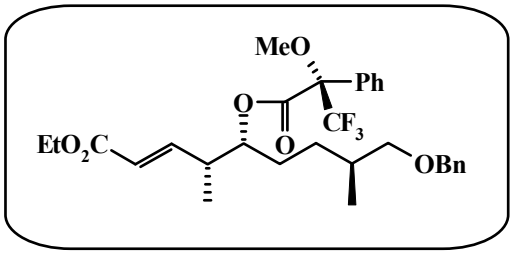
(4*R*,5*R*,8*S*,*E*)-ethyl-9-(benzyloxy)-4,8-dimethyl-5-((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)non-2-enoate (64) [(*S*)-MTPA ester]



The *S*-MTPA acid (0.011 g, 0.045 mmol), alcohol **62** (0.010 g, 0.03 mmol), DCC (0.012 g, 0.06 mmol) and DMAP (0.002 g, 0.015 mmol) were taken in CH_2Cl_2 (2 mL) and stirred for 12 h at room temperature. The reaction mixture was filtered, concentrated and purified by flash silica gel column using EtOAc and light petroleum (1:19) to yield **64** (0.013 g, 76%) as a colourless liquid.

Mol.Formula	$C_{30}H_{37}F_3O_6$
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.83 (d, 3 H, *J* = 6.7 Hz), 0.93 (d, 3 H, *J* = 6.9 Hz), 1.20 (t, 3 H, *J* = 7.1 Hz), 1.34-1.49 (m, 2 H), 1.59-1.73 (m, 3 H), 2.56 (m, 1 H), 3.17 (d, 2 H, *J* = 6.2 Hz), 3.44 (s, 3 H), 4.10 (q, 2 H, *J* = 7.1 Hz), 4.40 (s, 2 H), 5.03 (dt, 1 H, *J* = 4.8, 7.8 Hz), 5.63 (dd, 1 H, *J* = 1.3, 15.8 Hz), 6.69 (dd, 1 H, *J* = 7.5, 15.8 Hz), 7.19-7.31 (m, 8 H), 7.44-7.48 (m, 2 H) ppm.

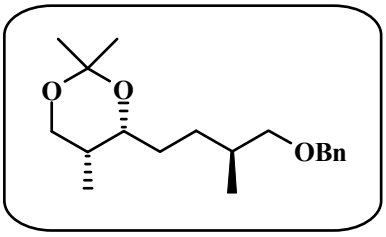
(4*R*,5*R*,8*S*,*E*)-ethyl-9-(benzyloxy)-4,8-dimethyl-5-((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)non-2-enoate (63) [(*R*)-MTPA ester]



The corresponding *R*-MTPA acid (0.011 g, 0.045 mmol), alcohol **62** (0.010 g, 0.03 mmol), DCC (0.012 g, 0.06 mmol) and DMAP (0.002 g, 0.015 mmol) were taken in CH_2Cl_2 (2 mL) and stirred for 12 h at room temperature. The reaction mixture was filtered, concentrated and purified by flash silica gel column using EtOAc and light petroleum (1:19) to yield **63** (0.012 g, 73%) as a colourless liquid.

Mol.Formula	$C_{30}H_{37}F_3O_6$
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.80 (d, 3 H, *J* = 6.7 Hz), 0.99 (d, 3 H, *J* = 6.9 Hz), 1.22 (t, 3 H, *J* = 7.1 Hz), 1.49-1.62 (m, 5 H), 2.61 (m, 1 H), 3.09 (dd 1 H, *J* = 6.2, 9.3 Hz), 3.13 (dd, 1 H, *J* = 6.3, 9.3 Hz), 3.44 (s, 3 H), 4.12 (q, 2 H, *J* = 7.1 Hz), 4.38 (s, 2 H), 5.02 (dt, 1 H, *J* = 4.9, 7.7 Hz), 5.75 (dd, 1 H, *J* = 1.3, 15.8 Hz), 6.81 (dd, 1 H, *J* = 7.3, 15.8 Hz), 7.19-7.31 (m, 8 H), 7.42-7.46 (m, 2 H) ppm.

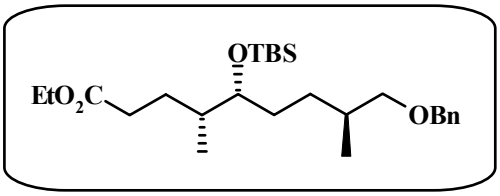
(4*R*,5*R*)-4-((*S*)-4-(benzyloxy)-3-methylbutyl)-2,2,5-trimethyl-1,3-dioxane (66)



A solution of diol **65** (0.1 g, 0.4 mmol) was treated with 2,2-dimethoxy propane (0.07 mL, 0.6 mmol) and *p*-TSA (catalytic) in acetone (5 mL). The solution was stirred overnight at room temperature, then quenched with a saturated solution of $NaHCO_3$, extracted with ethyl acetate (2 × 15 mL), dried over Na_2SO_4 and concentrated. The crude residue was purified on silica gel column (EtOAc/light petroleum, 1:19) to provide the acetonide protected compound **66** (0.085 g, 74%) as a clear liquid.

Mol.Formula	$C_{19}H_{30}O_3$
^{1}H NMR($CDCl_3$, 400 MHz)	δ 0.95 (d, 3 H, *J* = 6.7 Hz), 1.05 (d, 3 H, *J* = 7.0 Hz), 1.13 (m, 1 H), 1.29-1.34 (m, 2 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.47-1.54 (m, 2 H), 1,78 (m, 1 H), 3.26 (dd, 1 H, *J* = 6.6, 8.9 Hz), 3.32 (dd, 1 H, *J* = 6.4, 8.9 Hz), 3.58 (d, 1 H, *J* = 11.6 Hz), 3.87 (dt, 1 H, *J* = 2.3, 6.7 Hz), 4.07 (d, 1 H, *J* = 11.6 Hz), 4.49 (s, 2 H), 7.28-7.33 (m, 5 H) ppm.

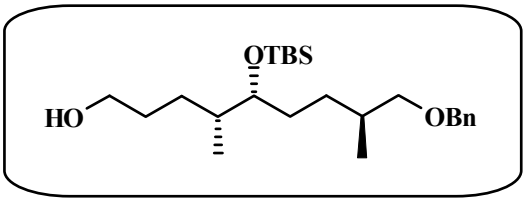
(4*R*,5*R*,8*S*,)-ethyl-9-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnonanoate (67)



The *E*- Wittig isomer **60** (1.95 g, 4.34 mmol) was dissolved in MeOH (15 mL) and $NiCl_2.6H_2O$ (0.26 g, 1.1 mmol) was added in one portion. The reaction mixture was then cooled to 0 ^oC and $NaBH_4$ (0.66 g, 17.4 mmol) was added in small portions to avoid a vigorous reaction. Stirring was continued at 0 ^oC for 30 min then diluted with CH_2Cl_2 (10 mL) and quenched with saturated NH_4Cl (15 mL), the layers were separated out and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified on silica gel column (EtOAc/light petroleum, 1:19) to yield **67** (1.93 g, 98%) as a colourless liquid.

Mol.Formula	$C_{26}H_{46}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	+4.16 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3019, 2930, 1726, 1462, 1215, 755, 669
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.02 (s, 6 H), 0.82 (d, 3 H, *J* = 6.6 Hz), 0.87 (s, 9 H), 0.92 (d, 3 H, *J* = 6.8 Hz), 1.04 (m, 1 H), 1.24 (t, 3 H, *J* = 7.1 Hz), 1.32-1.50 (m, 5 H), 1.69-1.83 (m, 2 H), 2.18-2.38 (m, 2 H), 3.18-3.33 (m, 2 H), 3.49 (m, 1 H), 4.10 (q, 2 H, *J* = 7.1 Hz), 4.48 (s, 2 H), 7.28-7.33 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ -4.4, -4.1, 13.8, 14.3, 17.2, 18.2, 25.96, 28.2, 29.8, 30.9, 32.7, 33.7, 37.0, 60.1, 72.99, 75.7, 75.8, 127.4, 127.5, 128.3, 138.7, 173.8 ppm.
ESI MS(m/z)	473.4261 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.28; H, 10.29 **Found:** C, 69.13; H, 10.09.

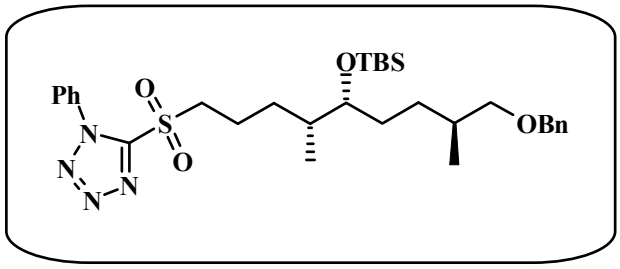
(4*R*,5*R*,8*S*,)-9-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnonan-1-ol (68)



LAH (0.23 g, 6.0 mmol) was added to a stirred solution of **67** (1.8 g, 4.0 mmol) in THF (25 mL) at 0 ^{o}C. After 1 h the reaction was quenched with a saturated solution of Na_2SO_4 and filtered. The residue was washed with EtOAc (3 × 25 mL) and the filtrate was dried (over Na_2SO_4) and concentrated. The crude residue was purified on silica gel column using EtOAc/light petroleum (1:4) to provide **68** (1.45 g, 89%) as a colourless oil.

Mol.Formula	$C_{24}H_{44}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	+4.32 (*c* 1.3, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3379, 3019, 2930, 1604, 1215, 1075, 757, 668
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.02 (s, 6 H), 0.82 (d, 3 H, *J* = 6.7 Hz), 0.87 (s, 9 H), 0.92 (d, 3 H, *J* = 6.8 Hz), 1.04-1.44 (m, 7 H), 1.58-1.74 (m, 3 H), 3.24 (dd, 1 H, *J* = 6.5, 9.0 Hz), 3.30 (dd, 1 H, *J* = 6.2, 9.0 Hz), 3.48 (m, 1 H), 3.61 (t, 2 H, *J* = 6.6 Hz), 4.49 (s, 2 H), 7.28-7.34 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ ‑4.5, ‑4.2, 14.3, 17.2, 18.1, 25.9, 28.5, 29.8, 30.7, 30.95, 33.7, 37.4, 63.3, 72.97, 75.9, 127.4, 127.5, 128.3, 138.7 ppm.
ESI MS(m/z)	431.3634 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 70.53; H, 10.85
	Found: C, 70.37; H, 10.66.

5-((4*R*,5*R*,8*S*,)-9-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4,8-dimethylnonylsulfonyl)-1-phenyl-1*H*-tetrazole (48)



DIAD (1.0 mL, 5.1 mmol) was added to a solution of **68** (1.3 g, 3.2 mmol), Triphenylphosphine (1.5 g, 5.7 mmol) and 1-Phenyl-1*H*-tetrazole-5-thiol (1.14 g, 6.4 mmol) in THF (20 mL) at 0 ^{o}C. After stirring for 1 h the reaction was quenched with brine and the aqueous layer was extracted with EtOAc (2 × 20 mL), dried (over Na_2SO_4) and concentrated. Purification by flash silica gel column chromatography (EtOAc/light petroleum, 1:19) yielded sulfide (1.6 g, 89%) as a clear oil.

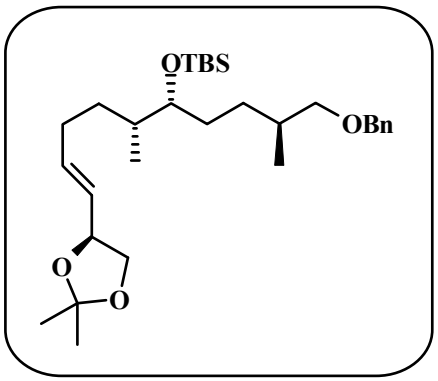
The above intermediate sulfide (1.6 g, 2.8 mmol) was dissolved in EtOH (20 mL) and cooled to 0 ^{o}C. In a separate flask were mixed 30 % H_2O_2 (3.2 mL, 28.0 mmol) and ammonium molybdate tetrahydrate (0.348 g, 0.28 mmol), producing a bright yellow solution that was added by syringe to the reaction flask. The reaction was stirred overnight and then quenched by the addition of water (10 mL), and extracted with EtOAc (2 × 20 mL). The organic layers were dried over Na_2SO_4 and concentrated to afford a residue which was purified on flash silica gel column eluting with EtOAc/light petroleum, (1:19) to furnish sulfone **48** (1.55 g, 92%) as a colourless liquid.

.

Mol.Formula	$C_{31}H_{48}N_4O_4SSi$
Optical Rotation $[\alpha]_D^{25}$	+1.53 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2929, 1596, 1497, 1344, 1152, 1045, 836, 761
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.02 (s, 6 H), 0.82-0.86 (m, 12 H), 0.92 (d, 3 H, *J* = 6.9 Hz), 1.03 (m, 1 H), 1.25-1.48 (m, 6 H), 1.63-1.76

	(m, 2 H), 1.95 (m, 1 H), 3.19-3.32 (m, 2 H), 3.49 (m, 1 H), 3.68 (t, 2 H, *J* = 7.8 Hz), 4.48 (s, 2 H), 7.30 (m, 5 H), 7.59-7.71 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ ⁻4.4, ⁻4.1, 13.9, 17.2, 18.1, 20.4, 25.9, 29.9, 30.7, 31.3, 33.7, 37.2, 56.2, 72.99, 75.5, 75.8, 125.0, 127.4, 127.5, 128.3, 129.7, 131.3, 133.1, 138.7, 153.5 ppm.
ESI MS(m/z)	623.3904 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 61.96; H, 8.05; N, 9.32
	Found: C, 61.82; H, 7.97; N, 9.16

((2*S*,5*R*,6*R*,*E*)-1-(benzyloxy)-10-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,6-dimethyldec-9-en-5-yloxy)(*tert*-butyl)dimethylsilane (81)

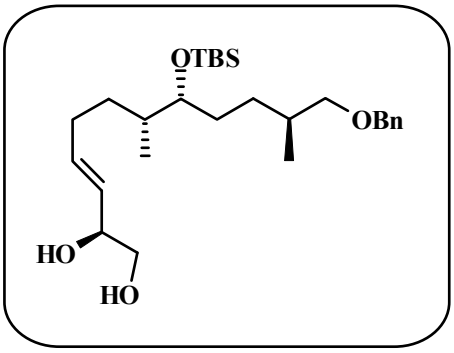


To a solution of the sulfone **48** (0.5 g, 0.83 mmol) in 1,2-dimethoxy ethane (20 mL) at ⁻60 ^oC, was added KHMDS (2.5 mL, 0.5M in toluene, 1.25 mmol) drop wise. The yellow coloured solution was stirred for 30 min and then aldehyde **49** (0.22 g, 1.7 mmol) in DME (6 mL) was introduced slowly via a syringe and stirred at ⁻60 ^oC for 2 h. The reaction was warmed to 0 ^oC and then quenched with a saturated solution of NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to a residue. Purification on flash silica gel column using EtOAc/light

petroleum, (1:49) as eluent, afforded Julia product **81** (0.344 g, 82%) as a colourless liquid.

Mol.Formula	$C_{30}H_{52}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	+17.9 (*c* 2.2, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2929, 1591, 1455, 1379,1252, 1061, 836, 773, 697
^{1}H NMR($CDCl_3$, 400 MHz)	δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.79 (d, 3 H, *J* = 6.7 Hz), 0.86 (s, 9 H), 0.92 (d, 3 H, *J* = 6.8 Hz), 1.00 (m, 1 H), 1.16 (m, 1 H), 1.37 (s, 3 H), 1.41 (s, 3 H), 1.43-1.52 (m, 4 H), 1.71 (m, 1 H), 1.93-2.01 (m, 2 H), 2.08 (m, 1 H), 3.23 (dd, 1 H, *J* = 6.6, 9.0 Hz), 3.30 (dd, 1 H, *J* = 6.2, 9.0 Hz), 3.48 (m, 1 H), 3.53 (t, 1 H, *J* = 8.0 Hz), 4.04 (dd, 1 H, *J* = 6.1, 8.0 Hz), 4.45 (m, 1 H), 4.49 (s, 2 H), 5.41 (dd, 1 H, *J* = 8.0, 15.3 Hz), 5.76 (dt, 1 H, *J* = 6.8, 15.3 Hz), 7.32-7.37 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 100 MHz)	δ -4.5, -4.2, 14.1, 17.2, 18.1, 25.9, 26.7, 29.9, 30.3, 30.7, 31.8, 33.7, 37.1, 69.5, 72.97, 75.8, 75.9, 77.4, 108.97, 127.0, 127.4, 127.5, 128.3, 136.3, 138.8 ppm.
ESI MS(m/z)	527.4708 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 71.38; H, 10.38
	Found: C, 71.14; H, 10.22.

(2*S*,7*R*,8*R*,11*S*,*E*)-12-(benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-7,11-dimethyldodec-3-ene-1,2-diol (82)

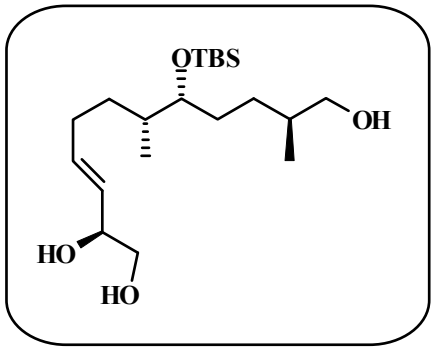


A solution of **81** (0.65 g, 1.3 mmol) in acetonitrile (20 mL) was treated with $Zn(NO_3)_2.6H_2O$ (7.6 g, 25.8 mmol) and heated to 50 ^oC. After 6 h (TLC showing complete disappearance of starting material), the reaction was quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The organic layer was dried (over Na_2SO_4), concentrated and purified on silica gel column (EtOAc/light petroleum, 3:7) giving **82** (0.44 g, 74%) as a colourless liquid.

Mol.Formula	$C_{27}H_{48}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	+11.2 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3369, 2928, 1602, 1454, 1384, 1252, 1114, 835, 772
^{1}H NMR($CDCl_3$, 500 MHz)	δ 0.00 (s, 3 H), 0.01 (s, 3 H), 0.80 (d, 3 H, *J* = 6.6 Hz), 0.86 (s, 9 H), 0.92 (d, 3 H, *J* = 6.8 Hz), 1.01 (m, 1 H), 1.15 (m, 1 H), 1.33 (m, 1 H), 1.45-1.52 (m, 4 H), 1.70 (m, 1 H), 1.98 (m, 1 H), 2.08 (m, 1 H), 3.22-3.31 (m, 2 H), 3.44-3.48 (m, 2 H), 3.60 (m, 1 H), 4.17 (m, 1 H), 4.49 (s, 2 H), 5.43 (dd, 1 H, *J* = 6.6, 15.5 Hz), 5.74 (dt, 1 H, *J* = 6.7, 15.5 Hz), 7.28-7.33 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 125 MHz)	δ -4.4, -4.1, 14.1, 17.1, 18.2, 25.95, 29.8, 30.4, 30.8, 31.99, 33.6, 36.8, 66.6, 73.0, 73.2, 75.7, 76.0, 127.4, 127.5, 128.3, 128.4, 134.5, 138.8 ppm.

ESI MS(m/z)	487.428 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.78; H, 10.41
	Found: C, 69.61; H, 10.22

(2*S*,7*R*,8*R*,11*S*,*E*)-8-(*tert*-butyldimethylsilyloxy)-7,11-dimethyldodec-3-ene-1,2,12-triol (83)

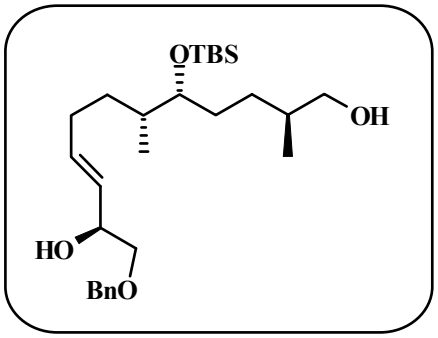


To a vigorously stirred solution of ammonia (10 mL) at –78 ^oC was added small pieces of lithium (0.047 g, 6.7 mmol). A deep blue colour appeared within 5 min, after 30 min compound **82** (0.31 g, 0.67 mmol) in THF (10 mL) was added dropwise. The solution was stirred for 1 h at this temperature, and then quenched with solid NH_4Cl, until the blue colour disappeared. Ammonia was allowed to evaporate completely and the residue was diluted with H_2O (10 mL) extracted with EtOAc (2 × 20 mL). The combined extracts were dried over Na_2SO_4, concentrated and purified on silica gel column using EtOAc/light petroleum (3:1) as eluent to produce **83** (0.195 g, 78%) as a colourless liquid.

Mol.Formula	$C_{20}H_{42}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	+3.83 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3370, 2928, 1619, 1461, 1383, 1252, 1039, 835, 772

^{1}H NMR($CDCl_3$, 400 MHz)	δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.80 (d, 3 H, *J* = 6.7 Hz), 0.87 (s, 9 H), 0.89 (d, 3 H, *J* = 6.8 Hz), 0.99 (m, 1 H), 1.16 (m, 1 H), 1.36 (m, 1 H), 1.44-1.55 (m, 5 H), 1.98-2.11 (m, 2 H), 2.20 (brs, 3 H), 3.42-3.50 (m, 4 H), 3.62 (m, 1 H), 4.18 (m, 1 H), 5.44 (dd, 1 H, *J* = 6.7, 15.5 Hz), 5.73 (dt, 1 H, *J* = 6.9, 15.5 Hz) ppm.
^{13}C NMR($CDCl_3$, 100 MHz)	δ ⁻4.5, ⁻4.1, 13.9, 16.4, 18.1, 25.9, 28.9, 30.1, 30.9, 31.98, 35.8, 35.9, 66.5, 68.4, 73.1, 75.2, 128.6, 134.3 ppm.
ESI MS(m/z)	397.353 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 64.12; H, 11.30
	Found: C, 64.34; H, 11.15

(2*S*,5*R*,6*R*,11*S*,*E*)-12-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-2,6-dimethyldodec-9-ene-1,11-diol (84)

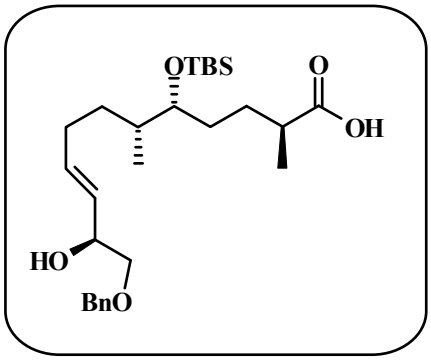


A solution of triol **83** (0.16 g, 0.43 mmol), Bu_2SnO (0.16 g, 0.64 mmol) in toluene (20 mL) was refluxed for 4 h using a Dean-Stark apparatus. It was cooled and benzyl bromide (0.08 mL, 0.64 mmol) followed by TBAI (catalytic) were added and again refluxed for 2 h. After completion (monitored by TLC), the reaction was diluted with CH_2Cl_2 (15 mL) and washed with 10 % $NaHCO_3$ solution, water, brine, dried (over Na_2SO_4) and then concentrated. Purification of the residue by silica gel column

chromatography using EtOAc and light petroleum (3:7) provided **84** (0.166 g, 84%) as a clear liquid.

Mol.Formula	$C_{27}H_{48}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	+10.76 (*c* 1.3, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3392, 2928, 1619, 1384, 1252, 1045, 835, 772
^{1}H NMR($CDCl_3$, 400 MHz)	δ 0.01 (s, 3 H), 0.02 (s, 3 H), 0.80 (d, 3 H, *J* = 6.7 Hz), 0.87 (s, 9 H), 0.89 (d, 3 H, *J* = 6.8 Hz), 1.00 (m, 1 H), 1.16 (m, 1 H), 1.32-1.45 (m, 3 H), 1.48-1.55 (m, 3 H), 1.98-2.07 (m, 2 H), 3.33-3.44 (m, 3 H), 3.48-3.50 (m, 2 H), 4.29 (m, 1 H), 4.56 (s, 2 H), 5.42 (dd, 1 H, *J* = 6.6, 15.5 Hz), 5.74 (dt, 1 H, *J* = 6.9, 15.5 Hz), 7.29-7.35 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 100 MHz)	δ ‑4.5, ‑4.2, 14.0, 16.5, 18.1, 25.9, 29.1, 30.3, 30.8, 31.9, 35.9, 36.5, 68.3, 71.4, 73.3, 74.4, 75.5, 127.8, 127.9, 128.1, 128.5, 134.1, 137.9 ppm.
ESI MS(m/z)	487.433 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.78; H, 10.41
	Found: C, 69.57; H, 10.24

(2*S*,5*R*,6*R*,11*S*,*E*)-12-(benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-11-hydroxy-2,6-dimethyldodec-9-enoic acid (86)



$PhI(OAc)_2$ (0.115 g, 0.36 mmol) was added to a solution of diol **84** (0.11 g, 0.24 mmol) and TEMPO (0.004 g, 0.024 mmol) in CH_2Cl_2 (3 mL). The reaction was stirred for 3 h at room temperature, then quenched with 10 % solution of $Na_2S_2O_3$ (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with aqueous $NaHCO_3$ solution, water and dried over Na_2SO_4. Concentration and purification by silica gel column chromatography (EtOAc and light petroleum, 1:4) afforded aldehyde **85** (0.1 g, 92%) as a clear oil.

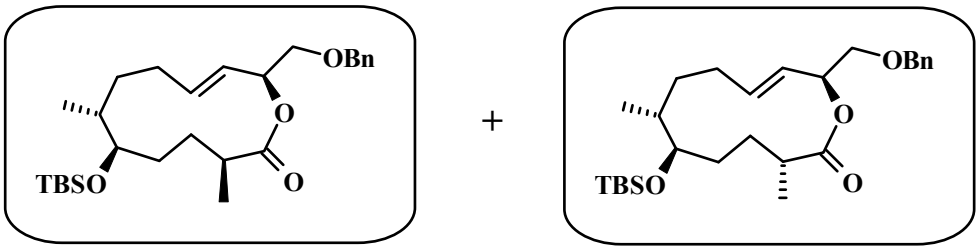
$NaClO_2$ (0.078 g, 0.87 mmol) was added to a solution of aldehyde **85** (0.1 g, 0.22 mmol), 2-methyl-2-butene (0.023 mL, 0.22 mmol) and NaH_2PO_4 (0.1 g, 0.87 mmol) in *t*-butanol and water (3:1), (4 mL) at 0 ^oC. After stirring for 3 h, the reaction was diluted with water (5 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (over Na_2SO_4), concentrated and purified by flash silica gel chromatography using EtOAc and light petroleum, (2:3) as eluent, to furnish the seco acid **86** (0.09 g, 87%) as a colourless liquid.

Mol.Formula	$C_{27}H_{46}O_5Si$
Optical Rotation $[\alpha]_D^{25}$	+20.0 (*c* 1.1, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3393, 2928, 1708, 1619, 1462, 1384, 1252, 1070, 835, 773
^1H NMR($CDCl_3$, 400 MHz)	δ 0.00 (s, 3 H), 0.02 (s, 3 H), 0.80 (d, 3 H, *J* = 6.7 Hz), 0.86 (s, 9 H), 1.17 (d, 3 H, *J* = 7.1 Hz), 1.37-1.46 (m, 4 H), 1.49-1.54 (m, 2 H), 1.69 (m, 1 H), 1.93-2.10 (m, 2 H), 2.42 (m, 1 H), 3.37 (m, 1 H), 3.48-3.51 (m, 2 H), 4.29 (m, 1 H), 4.56 (s, 2 H), 5.42 (dd, 1 H, *J* = 6.7, 15.5 Hz), 5.74 (dt, 1 H, *J* = 6.7, 15.5 Hz), 7.31-7.35 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 100 MHz)	δ -4.4, -4.3, 14.4, 16.9, 18.1, 22.7, 25.9, 30.3, 30.8, 31.7, 37.0, 39.3, 71.4, 73.3, 74.3, 75.3, 127.8, 127.9, 127.96, 128.5, 134.1, 137.9, 181.6 ppm.
ESI MS(m/z)	501.342 $(M + Na)^+$

Elemental Analysis **Calcd:** C, 67.74; H, 9.68

Found: C, 67.56; H, 9.53.

Yamaguchi lactonisation (87) and (88)



87 **88**

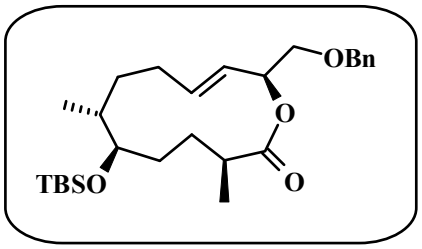
To a solution of the seco acid **86** (0.032 g, 0.07 mmol) in THF (5 mL) were added *i*-Pr_2NEt (0.5 mL, 2.7 mmol) and 2,4,6-trichlorobenzoyl chloride (0.21 mL, 1.33 mmol). The reaction was stirred overnight at room temperature and then it was diluted with benzene (15 mL) and added slowly to a solution of DMAP (0.4 g, 3.33 mmol) in benzene (70 mL) at 80 ^oC by syringe pump over a period of 10 h. The mixture was stirred for another 1 h and then quenched by the addition of saturated $NaHCO_3$ solution, extracted with EtOAc (2 × 20 mL), dried over Na_2SO_4 and concentrated. It was purified on flash silica gel column eluting with EtOAc/light petroleum (1:49) yielding inseparable mixture of products **87** and **88** (1:1) (0.017 g, 55% combined yield) as a colourless liquid.

Mol.Formula $C_{27}H_{44}O_4Si$

^{1}H NMR($CDCl_3$, 400 MHz) δ 0.01 (s, 6 H), 0.84 (d, 3 H, *J* = 6.7 Hz), 0.87 (s, 9 H), 1.18 (d, 2 H, *J* = 6.9 Hz), 1.20 (d, 2 H, *J* = 6.8 Hz) 1.38-1.53 (m, 7 H), 1.77 (m, 1 H), 2.14 (m, 1 H), 2.28 (m, 1 H), 3.28 (m, 1 H), 3.53 (m, 1 H), 3.59 (m, 1 H), 4.58 (ABq, 2 H, *J* = 12.3 Hz), 5.44-5.55 (m, 2 H), 5.91 (ddd, 1 H, *J* = 6.2, 9.4, 15.3 Hz), 7.30-7.36 (m, 5 H) ppm.

^{13}C NMR($CDCl_3$, 100 MHz)	δ -4.9, -4.4, 17.5, 17.9, 18.2, 20.1, 20.9, 25.9, 28.3, 29.7, 30.1, 30.3, 33.2, 33.99, 41.6, 46.4, 51.7, 70.6, 72.4, 73.1, 73.95, 127.4, 127.55, 127.6, 128.2, 128.4, 138.1, 138.3, 175.5 ppm.
ESI MS(m/z)	483.2418 $(M + Na)^+$

(3*S*,6*R*,7*R*,12*S*,*E*)-12-(benzyloxymethyl)-6-(*tert*-butyldimethylsilyloxy)-3,7-dimethyloxacyclododec-10-en-2-one (87)



Ethoxyacetylene (0.03 mL, 40% in hexane, 0.14 mmol) was added to a solution of the seco acid **86** (0.045 g, 0.094 mmol) and [{$RuCl_2$(*p*-cymene)}$_2$] (1.2 mg, 0.0018 mmol) in toluene (8 mL) at 0 ^oC. The resulting mixture was warmed to room temperature and stirred for another 30 min. The dark red solution was then filtered through a pad of silica gel, and the silica gel was washed with dry Et_2O (60 mL) under a nitrogen atmosphere. The filtrate was concentrated under reduced pressure. The crude ethoxyvinyl ester was dissolved in toluene (5 mL) and added to a solution of CSA (2.2 mg, 0.0094 mmol) in toluene (20 mL) and heated to 50 ^oC for 2 h. The mixture was then filtered through a pad of silica gel and concentrated to afford a residue. Purification by flash silica gel chromatography eluting with EtOAc and light petroleum, (1:49) afforded the lactone **87** (0.018 g, 42%) as a colourless liquid.

Mol.Formula	$C_{27}H_{44}O_4Si$
Optical Rotation $[\alpha]_D^{25}$	+29.0 (*c* 0.6, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2929, 1722, 1598, 1384, 1255, 1115, 1026, 772, 618

^{1}H NMR($CDCl_3$, 500 MHz)	δ 0.01 (s, 6 H), 0.85 (d, 3 H, *J* = 6.7 Hz), 0.87 (s, 9 H), 1.18 (d, 3 H, *J* = 6.9 Hz), 1.36-1.42 (m, 2 H), 1.49-1.57 (m, 5 H), 1.75 (m, 1 H), 2.14 (m, 1 H), 2.26 (m, 1 H), 3.28 (m, 1 H), 3.57 (dd, 1 H, *J* = 4.4, 10.8 Hz), 3.61 (dd, 1 H, *J* = 6.7, 10.8 Hz), 4.58 (ABq, 2 H, *J* = 12.4 Hz), 5.44-5.53 (m, 2 H), 5.91 (ddd, 1 H, *J* = 6.2, 9.4, 15.5 Hz), 7.28-7.35 (m, 5 H) ppm.
^{13}C NMR($CDCl_3$, 125 MHz)	δ ‑4.9, ‑4.4, 17.5, 17.8, 18.2, 25.95, 28.4, 30.2, 30.4, 33.3, 34.1, 41.7, 70.7, 72.4, 73.2, 74.0, 127.5, 127.56, 127.6, 128.4, 138.2, 138.3, 175.4 ppm.
ESI MS(m/z)	483.243 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 70.39; H, 9.63
	Found: C, 70.24; H, 9.45

REFERENCES

REFERENCES

1. Craigg, G. M.; Newman, D. J.; Weiss, R. B. *Semin*. *Oncol*. **1997**, *24*, 156-163.
2. Macdougall, J. D. *A short history of Planet Earth*; John Wiley Eds.: New York, **1996**; p. 5.
3. Argulis, L.; Schwart, K. *Five Kingdoms, an illustrated guide to the phyla of life on Earth*; W. H. Freeman & Company: New York, **1982**; pp. 16-17.
4. Ruggieri, G. D. *Science* **1976**, *194*, 491-496.
5. Haefner, B. *Drug Discov. Today* **2003**, *8*, 536-534.
6. Sorriente, A. *Current Med. Chemistry* **1999**, *6*, 415-431.
7. Longley, R.; Cardigan, D.; Harmody, D.; Gunasereka, M.; Gunasereka, S. *Transplantation* **1991**, *52*, 650-661.
8. Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O. *J. Am. Chem. Soc.* **1994**, *116*, 6015-6016.
9. Horton, P. A.; Koehn, F. E.; Longley, R. E.; McConnell, O.; Pomponi, S. A. US Patent Serial Number 5,684,036, 1997.
10. Erickson, K. L.; Beutler, J. A.; Cardellina II, J. H.; Boyd, M. R. *J. Org. Chem*. **1997**, *62*, 8188.
11. Cutignano, A.; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. *Eur. J. Org. Chem.* **2001**, 775.
12. Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 5535.
13. Kito, K.; Ookura, R.; Yoshida, S.; Namikoshi, M.; Ooi, T.; Kusumi, T. *Org. Lett*. **2008**, *10*, 225-228.
14. Kobayashi, J.; Ishibashi, M. *Chem. Rev*. **1993**, *93*, 1753-1769.
15. Kobayashi, J.; Tsuda, M.; Shimbo, K.; Kubota, T. *Pure Appl. Chem*. **2003**, *75*, 337-342.
16. Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep*. **2004**, *21*, 77-93.
17. Kobayashi, J.; Ishibashi, M.; Nakamura, H.; Ohizumi,Y.; Yamasu, T.; Sasaki, T.; Hirata, Y. *Tetrahedron Lett*. **1986**, *27*, 5755.
18. Lam, H. W.; Pattenden, G. *Angew. Chem. Int. Ed*. **2002**, *41*, 508.

19. Maleczka, R. E. Jr.; Terrell, L. R.; Geng, F.; Ward, J. S. III; *Org. Lett*. **2002**, *4*, 2841.
20. Trost, B. M.; Chisholm, J. D.; Wrobleski, S. T.; Jung, M. *J. Am. Chem. Soc*. **2002**, *124*, 12421.
21. Ishibashi, M.; Ohizumi, Y.; Hamashima, M.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. *J. Chem. Soc. Chem. Commun*. **1987**, 1127.
22. Ishibashi, M.; Ohizumi, Y.; Yamasu, T.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J.; Ohta, T.; Nozoe, S. *J. Nat. Prod*. **1989**, *52*, 1036.
23. Bauer, I.; Maranda, L.; Shimuzu, Y.; Peterson, R. W.; Cornell, L.; *J. Am. Chem. Soc*. **1994**, *116*, 2657.
24. Ishibashi, M.; Yamasu, T.; Shigemori, H.; Hirota, H.; Sasaki, T.; Kobayashi, J. *J. Org. Chem*. **1991**, *56*, 5221.
25. Kobayashi, J.; Tsuda, M.; Sasaki, T. *J. Org. Chem*. **1994**, *59*, 3734.
26. Kobayashi, J.; Tsuda, M.; Simbo, K.; Sato, K. *J. Org. Chem*. **2002**, *67*, 6585.
27. Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 4583.
28. Ishiyama, H.; Takemura, T.; Tsuda, M.; Kobayashi, J. *J. Chem. Soc. Perkin Trans 1* **1999**, 1163.
29. Cid, M. B.; Pattenden, G. *Tetrahedron Lett*. **2000**, *41*, 7373.
30. Ohi, K.; Shima, K.; Hamada, K.; Nishiyama, S. *Symposium Papers of the 41st Symposium on The Chemistry of Natural Products, in Nagoya* **1999**, pp. 31-36.
31. Ishibashi, M.; Ohizumi, Y.; Walchli, M. R.; Nakamura, H.; Hirata, Y.; Sasaki, T.; Kobayashi, J. J. Am. Chem. Soc. **1988**, *110*, 490.
32. Ishibashi, M.; Yamasu, T.; Shigemori, H.; Hirota, H.; Sasaki, T.; Kobayashi, J.; Tsuda, M. *J. Antibiot*. **1991**, *44*, 1259.
33. Tsuda, M.; Endo, T.; Kobayashi, J. *Tetrahedron* **1999**, *55*, 14565.
34. Shotwell, J. B.; Roush, W. R. *Org. Lett*. **2004**, *6*, 3865.
35. Mohapatra, D. K.; Rahaman, H.; Chorghade, M. S.; Gurjar, M. K. *Synlett* **2007**, 567.
36. Kobayashi, J.; Sato, M.; Ishibashi, M. *J. Org. Chem*. **1993**, *58*, 2645.
37. Williams, D. R.; KIssel, W. S. *J. Am. Chem. Soc*. **1998**, *120*, 11198.

38. Ishibashi, M.; Takahashi, M.; Kobayashi, J. *Tetrahedron* **1997**, *53*, 7827.
39. Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M.; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem*. **1990**, *55*, 3421.
40. Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem. Int. Ed*. **2006**, *45*, 8019.
41. Va, P.; Roush, W. R. *J. Am. Chem. Soc*. **2006**, *128*, 15960.
42. Gurjar, M. K.; Mohapatra, S.; Phalgune, U. D.; Puranik, V. G.; Mohapatra, D. K. *Tetrahedron Lett*. **2004**, *45*, 7899.
43. Marshall, J. A.; Schaaf, G.; Nolting, A. *Org. Lett*. **2005**, *7*, 5331.
44. Kobayashi, J.; Sato, M.; Ishibashi, M. *J. Org. Chem*. **1993**, *58*, 6928.
45. Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc*. **2001**, *123*, 765.
46. Kobayashi, J.; Yamaguchi, N.; Ishibashi, M. *J. Org. Chem*. **1994**, *59*, 4698.
47. Kobayashi, J.; Yamaguchi, N.; Ishibashi, M.; Sasaki, T. *J. Chem. Soc. Chem. Commun*. **1994**, 1445.
48. Ishibashi, M.; Takahashi, M.; Kobayashi, J. *J. Org. Chem*. **1995**, *60*, 6062.
49. Williams, D. R.; Meyer, K. G.; Mi, L. *Org. Lett*. **2000**, *2*, 945.
50. Ishibashi, M.; Takahashi, M.; Kobayashi, J. *Tetrahedron Lett*. **1996**, *37*, 1449.
51. Kubota, T.; Tsuda, M.; Kobayashi, J. *Tetrahedron Lett*. **2000**, *41*, 713.
52. Tsuda, M.; Endo, T.; Kobayashi, J. *J. Org. Chem*. **2000**, *65*, 1349.
53. Tsuda, M.; Endo, T.; Kobayashi, J.; Kubota, T. *J. Org. Chem*. **2001**, *66*, 134.
54. Furstner, A.; Aissa, C.; Riveiros, R.; Ragot, J. *Angew. Chem. Int. Ed*. **2002**, *41*, 4763.
55. Ghosh, A. K.; Liu, C. *J. Am. Chem. Soc*. **2003**, *125*, 2374.
56. a) Abbineni, C.; Sasmal, P. K.; Mukkanti, K.; Iqbal, J. *Tetrahedron Lett*. **2007**, *48*, 4259; b) Furstner, A.; Aissa, C.; Riveiros, R.; Ragot, J. *J. Am. Chem. Soc*. **2003**, *125*, 15512; c) Deng, L. S.; Huang, X. P.; Zhao, G. *J. Org. Chem*. **2006**, *71*, 4625.
57. Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Katsumata, K.; Horiguchi, T.; Kobayashi, J. *J. Org. Chem*. **2003**, *68*, 5339.
58. Tsuda, M.; Izui, N.; Shimbo, K.; Sato, M.; Fukushi, E.; Kawabata, J.; Kobayashi, J. *J. Org. Chem*. **2003**, *68*, 9109.

59. a) Lepage, O.; Kattnig, E.; Furstner, A. *J. Am. Chem. Soc*. **2004**, *126*, 25970; b) Lepage, O.; Kattnig, E.; Furstner, A. *J. Am. Chem. Soc*. **2006**, *128*, 9194.
60. Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W. M. *Org. Lett*. **2007**, *9*, 2585.
61. Shimbo, K.; Tsuda, M.; Izui, N.; Kobayashi, J.; *J. Org. Chem*. **2002**, *67*, 1020.
62. a) Ghosh, A. K.; Gong, G. *J. Am. Chem. Soc*. **2004**, *126*, 3704; b) Ghosh, A. K.; Gong, G. *J. Org. Chem*. **2006**, *71*, 1085.
63. Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem*. **2001**, *66*, 134.
64. For recent synthesis of amphidinolides: a) Marshall, J. A.; Schaff, G.; Nolting, A. *Org. Lett.* **2005**, *7*, 5331; b) Jin, J.; Chen, Y.; Wu, J.; Dai, W. *Org. Lett.* **2007**, *9*, 2585; c) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem. Int. Ed.* **2006**, *45*, 8019; d) Lepage, O.; Kattnig, E.; Furstner, A. *J. Am. Chem. Soc*. **2004**, *126*, 15970; e) Va, P.; Roush, W. R.; *Org. Lett.* **2007**, *9*, 307; f) Mandal, A. K.; Schneekloth, J. S. Jr.; Kuramochi, K.; Crews, C. M. *Org. Lett.* **2006**, *8*, 427.
65. McKennon, M. J.; Meyers, A. I. *J. Org. Chem*. **1993**, *58*, 3568.
66. Ho, G-J.; Mathre, D. J.; *J. Org. Chem*. **1995**, *60*, 2271.
67. Evans, D. A.; Ennis, M. D.; Mathre, D. J.; *J. Am. Chem. Soc*. **1982**, *104*, 1737.
68. a) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett*. **1987**, *28*, 6141; b) Rama Rao, A. V.; Gurjar, M. K.; Nallaganchu, B. R.; Bhandari, A. *Tetrahedron Lett*. **1993**, *34*, 7081.
69. Crimmins, M. T.; O'Mahony, R. *J. Org. Chem*. **1989**, *54*, 1157.
70. Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155.
71. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.
72. a) Franklin, A. S.; Paterson, I.; *Cont. Org. Synthesis* **1994**, *1*, 317; b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem*. **1982**, *13*, 1; c) Mukaiyama, T.; Kobayashi, S.; *Org. React*. **1994**, *46*, 1; d) Benardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron Asymmetry* **1995**, *6*, 2613.
73. a) Mukaiyama, T.; Inomata, K.; Muraki, M. *J. Am. Chem. Soc*. **1973**, *95*, 967; b) Evans, D. A.; Vogel, E.; Nelson, J. V.; *J. Am. Chem. Soc*. **1979**, *101*, 6120; c) Evans, D. A.; Nelson, J. V.; Vogel, J. V.; Taber, T. R.; *J. Am. Chem. Soc*. **1981**, *103*, 3099.

74. a) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917; b) Ager, D. J.; Prakash, I.; Schaad, D. R.; *Aldrichimica Acta* **1997**, *30*, 3; c) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835.
75. a) Heathcock, C. H.; White, C. T. *J. Am. Chem. Soc*. **1979**, *101*, 7076; b) Masamune, S.; Ali, Sk. A.; Snitman, D. L.; Garvey, D. S. *Angew. Chem. Int. Ed. Engl*. **1980**, *19*, 557; c) Evans, D. A.; Taber, T. R. *Tetrahedron Lett*. **1980**, 4675.
76. Zimmermann, H. E.; Traxler, M. D. *J. Am. Chem. Soc*. **1957**, *79*, 1920.
77. a) Fenzyl, W.; Koster, R.; *Liebigs Ann. Chem*. **1975**, 1322; b) Fenzyl, W.; Koster, R.; Zimmerman, H. -J. *Liebigs Ann. Chem*. **1975**, 2201.
78. a) Brown, H. C.; Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc*. **1989**, *111*, 3441; b) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem*. **1993**, *58*, 147; c) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem*. **1992**, *57*, 499; d) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem*. **1992**, *57*, 2716; e) Brown, H. C.; Ganesan, K.; Dhar, R. K. *J. Org. Chem*. **1992**, *57*, 3767; f) Ganesan, K.; Brown, H. C. *J. Org. Chem*. **1993**, *58*, 7162.
79. a) Goodman, J. M.; Paterson, I. *Tetrahedron Lett*. **1992**, *33*, 7223; b) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc*. **1990**, *112*, 4976.
80. Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem*. **1981**, *53*, 1109.
81. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127.
82. Bauer, M.; Maier, M. E. *Org. Lett*. **2002**, *4*, 2205.
83. Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem*. **1990**, *55*, 6260.
84. Frigerio, M.; Santagostino, M. *Tetrahedron Lett*. **1994**, *35*, 8019.
85. a) Taber, D. F.; Jiang, Q.; Chen, B.; Zhang, W.; Campbell, C. L. *J. Org. Chem*. **2002**, *67*, 4821; b) Jiang, X.; Covey, D. F. *J. Org. Chem*. **2002**, *67*, 4893.
86. Crich, D.; Dudkin, V.; *J. Am. Chem. Soc*. **2002**, *124*, 2263.
87. Corey, E. J.; Gras, J-L.; Ulrich, P. *Tetrahedron Lett*. **1976**, 809.
88. Corey, E. J.; Schmidt, G. *Tetrahedron Lett*. **1979**, 399.

89. Kierstead, R. W.; Faraone, A.; Mennona, F.; Mullin, J.; Guthrie, R. W.; Crowley, H.; Simko, B.; Blaber, L. C. *J. Med. Chem*. **1983**, *26*, 1561.
90. a) Boons, G-J.; Castle, G. H.; Clase, J. A.; Grice, P.; Ley, S. V. *Synlett* **1993**, 913; b) Veyrieres, A. *J. Chem. Soc. Perkin Trans 1* **1981**, 1626; c) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
91. Rama Rao, A. V.; Bose, D. S.; Gurjar, M. K.; Ravindranathan, T. *Tetrahedron* **1989**, *45*, 7031.
92. a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn*. **1979**, *52*, 1989; b) Paterson, I.; Chen, D. Y-K.; Acena, J. L.; Franklin, A. S. *Org. Lett*. **2000**, *2*, 1513.
93. Richey, H. G. *Grignard Reagents: New Developments*, Wiley, Chichester, **2000**, p. 418.
94. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed*. **2002**, *41*, 1668.
95. Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin, A. *Liebigs Ann./Recl*. **1997**, 1283.
96. For a comprehensive treatise of Metathesis reactions and applications, see: *Handbook of Metathesis, Vols. 1, 2, 3*, Grubbs', R. H., Wiley-VCH, Weinheim, 2003, p. 1234.
97. For reviews on alkene-metathesis reactions, see: a) Nicalaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed*. **2005**, *44*, 4490; b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117; c) Furstner, A. *Angew. Chem. Int. Ed*. **2000**, *39*, 3012; d) Grubbs', R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
98. a) Grubbs', R. H.; Pine, S. H. in *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I.; Paquette, L. A.; Eds.; Permagon: New York, 1991, Vol. 5, Chapter 9.3; b) Schrock, R. R. in The Strem Chemiker, Vol. XIV, 1992, No. 1, p.1-6; c) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*, Academic Press, San Deigo, 1997.
99. Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc*. **1990**, *112*, 3875.

100. Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem. Int. Ed*. **1995**, *34*, 2039.
101. a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett*. **1999**, *40*, 2247; b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953.
102. Schrock, R. R.; Hovedya, A. H. *Angew. Chem. Int. Ed*. **2003**, *42*, 4592.
103. Lynn, D. M.; Mohr, B.; Grubbs, R. H. *J. Am. Chem. Soc*. **1998**, *120*, 1627.
104. Savall, B. M.; Blanchard, N.; Roush, W. R.; *Org. Lett*. **2003**, *5*, 377.
105. Crimmins, M. T.; Choy, A. L. *J. Org. Chem*. **1997**, *62*, 7548.
106. Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H.; *Tetrahedron Lett*. **1981**, *22*, 3455.
107. Fiud, J. C.; Horeau, A.; Kagan, H. B. In *Stereochemistry*; Kagan, H. B.; Ed.; George Thieme Publishers: Stuggart, 1977; Vol. 3.
108. a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc*. **1973**, *95*, 512; b) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem*. **1973**, *38*, 2143.
109. a) Yamaguchi, S.; Yasuhara, F.; Kabuta, K.; *Tetrahedron* **1976**, *32*, 1363; b) Yamaguchi, S.; Yasuhara, F. *Tetrahedron Lett*. **1977**, 89.
110. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*. **1991**, *113*, 4092.
111. Nicolaou, K. C.; Ray. M.; Finlay, V.; Ninkovic, S.; Sarabia, F. *Tetrahedron* **1998**, *54*, 7127.
112. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc*. **1972**, *94*, 6190.
113. Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A.; *J. Am. Chem. Soc*. **1979**, *101*, 6420.
114. Mitsunobu, O. *Synthesis* **1981**, 1.
115. a) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R.; *J. Org. Chem*. **1963**, *28*, 1140; b) Smiith, A. B. III; Wan, Z. *Org. Lett*. **1999**, *1*, 1491.
116. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem. Int. Ed*. **2000**, *39*, 44.
117. Wittig, G.; Geissler, G. *Liebigs Ann. Chem*. **1953**, *580*, 44.
118. Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber*. **1958**, *91*, 61.
119. Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc*. **1961**, *83*, 1733.

120. Peterson, D. J. *J. Org. Chem*. **1968**, *33*, 780.
121. Johnson, C. R.; Shanklin, J. R.; Kirchhoff, R. A. *J. Am. Chem. Soc*. **1973**, *95*, 6462.
122. Julia, M.; Paris, J-M. *Tetrahedron Lett*. **1973**, 4833.
123. Kocienski, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc. Perkin Trans 1* **1978**, 829.
124. Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett*. **1991**, *32* 1175.
125. Truce, W. E.; Kreider, E. M.; Brand, W. W. *Org. React*. **1970**, *18*, 99.
126. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A.; *Synlett* **1998**, 26.
127. Blakemore, P. R.; *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563.
128. Takeuchi, T.; Kuramochi, K.; Kobayashi, S.; Sugawara, F.; *Org. Lett*. **2006**, *8*, 5307.
129. Mico, A. D.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem*. **1997**, *62*, 6974.
130. Sasaki, M.; Inoue, M.; Tachibana, K.; *J. Org. Chem*. **1994**, *59*, 715.
131. a) Kita, Y.; Akai, S.; Ajimura, N.; Yoshigi, M.; Tsugoshi, T.; Yasuda, H.; Tamura, Y. *J. Org. Chem*. **1986**, *51*, 4150; b) Kita, Y.; Akai, S.; Yamamoto, M.; Taniguchi, M.; Tamura, Y. *Synthesis* **1989**, 334.
132. Wasserman, H. H.; Wharton, P. S. *J. Am. Chem. Soc*. **1960**, *82*, 661.
133. Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *Synlett* **1993**, 273.
134. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem*. **1996**, *61*, 4560.
135. Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev*. **2006**, *106*, 911.
136. Kita, Y.; Maeda, H.; Omori, K.; Okuno, T.; Tamura, Y. *J. Chem. Soc. Perkin Trans. 1* **1993**, 2999.
137. Trost, B. M.; Chisholm, J. D. *Org. Lett*. **2002**, *4*, 3743.

CHAPTER - II

SYNTHETIC STUDIES TOWARD HELICONOLS A-C

INTRODUCTION

INTRODUCTION

Antibiotics

The term "antibiotics" materialized from the Greek word anti ("against") and bios ("life"). Antibiotics are referred to those drugs, which are used to treat bacterial infections either by destroying bacteria called "bactericidal", or by preventing their reproduction known as "bacteriostatic". Antibiotics, first discovered by Alexander Fleming in 1928, from *Penicilium notatum* was widely used in the Second World War.[1] Since that time, antibiotics have been critical in the fight against many diseases and infection.[2] Their discovery was one of the leading causes for the dramatic rise of average life expectancy in the 20th century and their significance to public health would be impossible to overstate.

Up to date, more than 100 antibiotics are available out of which almost 90% are made from living organisms such as bacteria, rest are produced synthetically, either in whole or in part. Antibiotics are the most commonly used drugs. For example, more than 30% hospitalized patients are treated with one or more courses of antibiotic therapy. However, antibiotics have also been misused by the physicians, e.g. usage of antibiotics in viral respiratory tract infection. Some of the recently used antibiotics are ciprofloxacin, as urinary tract infection, bacterial prostatitis, community-acquired pneumonia, bacterial diarrhea, mycoplasmal infections, and gonorrhea; amoxycilin, as wide range of infections; penicillin used for streptococcal infections, syphilis and lyme disease; aminoglycosides (neomycin, amikacin, gentamycin) for infections caused by Gram-negative bacteria, such as *Escherichia coli*; geldanamycin, as antitumor antibiotics; cefoxitin, as gastrointestinal upset and diarrhea, nausea, allergic reactions; tetracyclines as acne rikettsial infections; Tinidazole, binds to the β subunit of "RNA polymerase" to inhibit transcription of mostly "Gram-positive" and "mycobacteria".

Antibiotics classification

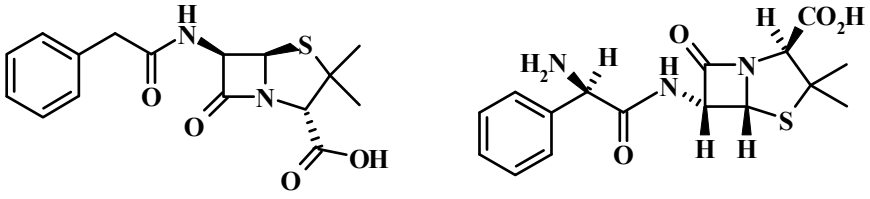
Although antibiotics can be classified under several schemes, based on bacterial spectrum (broad, narrow) or route of administration (injectable, oral, topical) or type of

activity (bactericidal, bacteriostatic), the most useful is based on their chemical structure. The first line of discovery was the isolation of microbial metabolites from Nature, was initiated by Fleming's discovery of a penicillin producing fungus and was closely followed by a systematic search of antibacterial producing microorganisms by pioneers such as Dubos and Waksman. This strategy produced many of the famous classes of antibiotics. These include the cephalosporin and penicillin branches of the β-lactams, the aromatic polyketides of the tetracycline class, the aminoglycosides represented by streptomycin, the polyketide macrolactones exemplified by eryhthromycin, and the glycopeptides of the vancomycin and teicoplanin family. Further search has led to the discovery of sulfa drugs (such as sulfamethoxazole), the dihydrofolate reductase inhibitors, fluoroquinolones and most recently introduced, the oxazolidinones. Antibiotics within a structural class generally have similar pattern of effectiveness, toxicity and allergic potential.

Most of the commonly used types of antibiotics are: penicillin, fluoroquinolone, cephalosporin, macrolide and tetracycline. While each class is composed of multiple drugs, each drug is unique in some way.

Penicillins

The penicillins are the oldest class of antibiotics and have a common chemical structure which they share with the cephalosporins. These are generally bactericidal; inhibit formation of cell wall. There are different types of penicillins: such as penicillin G (**1**), penicillanase-resistant penicillins and ampicillin (**2**) (Figure 1).

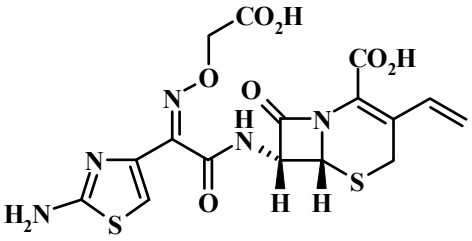


Penicillin G (1) **Ampicillin (2)**

Figure 1

Cephalosporins

Cephalosporin[3] is a bactericidal antibiotics having same mechanism of action like penicillin. The most diverse classes of antibiotics are classified into groups according to their generations depending on their antimicrobial properties. Each generation has a broader spectrum of activity than the previous one (e.g. Cefixime (**3**), a third generation cephalosporin, which has expanded Gram-negative activity) (Figure 2).

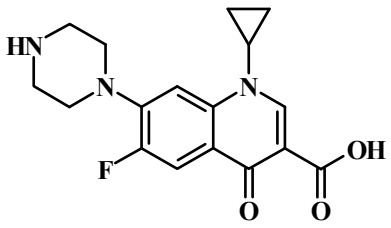


Cefixime (3)

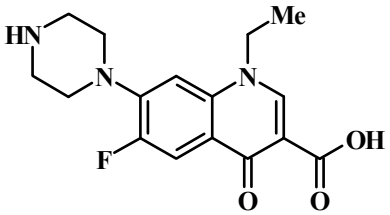
Figure 2

Fluoroquinones

These are synthetic antibiotics that belong to the family called quinolones antibiotics. Their generic name often contains the root "floxacin". The newer fluoroquinolones are far better absorbed than the parent quinolones and are used as broad-spectrum bactericidal drugs which can be consumed intravenous as well as orally. Commonly used fluoroquinolones include the ciprofloxacin (**4**), levofloxacin, lomefloxacin, norfloxacin (**5**), sparfloxacin, clinafloxacin, gatifloxacin, olafloxacin and trovafloxacin (Figure 3). These drugs are well tolerated and relatively safe.



Ciprofloxacin (4)

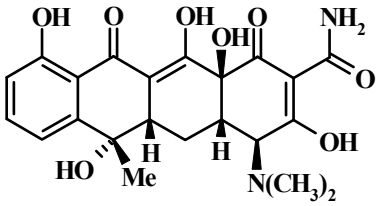


Norfloxacin (5)

Figure 3

Tetracyclines

Tetracyclines,[4] derived from a species of streptomyces bacteria got their name from their chemical structure that contains four rings. These bacteriostatic antibiotics are effective against a wide variety of microorganisms, including rikettsia and amebic parasites. Tetracyclines are used in the treatment of infections of the respiratory tract, sinuses, middle ear, urinary tract, skin and intestine. They are also used to treat Gonorrhea. The most commonly used tetracycline antibiotics are: tetracycline (**6**), doxycycline, minocycline and oxytetracycline (Figure 4). These drugs are nephrotoxic. Tetracyclines can cause skin photosensitivity, which increases the risk of sunburn under exposure to UV light.



Tetracycline (6)

Figure 4

Macrolides

Another type of antibiotics are the macrolide antibiotics[5] possessing macrocyclic lactone, and derived from streptomyces. These are bacteriostatic, binding with bacterial ribosomes to inhibit protein synthesis. Erythromycin,[6] the prototype of this class, has a spectrum and use similar to penicillin. Macrolide antibiotics are used to treat respiratory tract infections (such as pharyngitis, sinusitis and bronchitis), genital, gastrointestinal tract and skin infections. The most commonly prescribed macrolide antibiotics are: erythromycin (**7**), clarithromycin, azithromycin (**8**), roxithromycin (**9**) and troleandomycin (Figure 5).

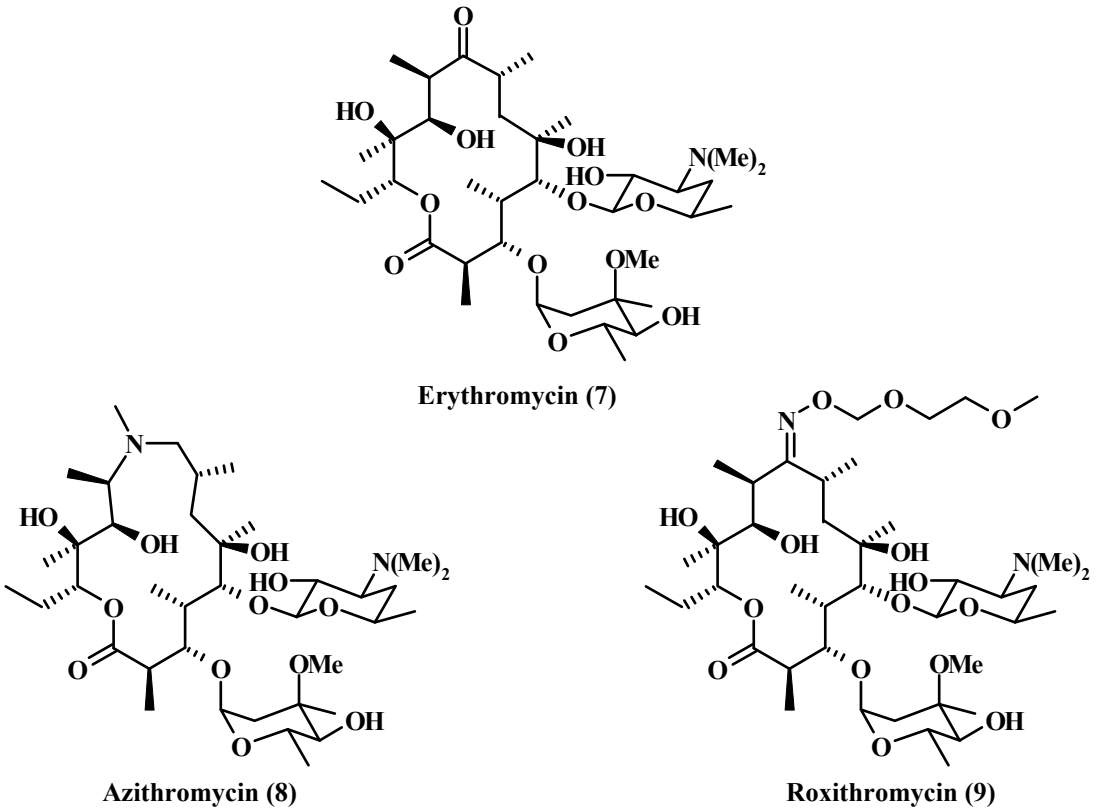
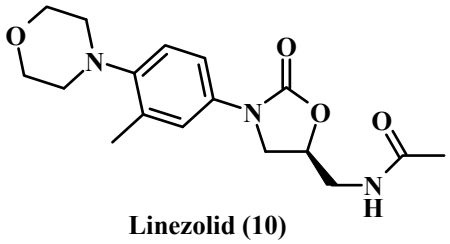


Figure 5

Some of the important antibiotics used frequently are discussed here:

Linezolid

Linezolid, the first oxazolidinone class of synthetic antibiotics, used for the treatment of infections caused by multi-resistant bacteria including streptococcus and methicillin-resistant staphylococcus aureus (MRSA)[7] and is generally used for treatment of serious bacterial infections where older antibiotics have failed due to antibiotic resistance. In cases of skin infections or nosocomial pneumonia where methicillin or penicillin resistance is found are indicators for linezolid use. Linezolid (**10**) is effective against Gram-positive bacteria, notably *Enterococcus faecium*, *Staphylococcus aureus*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* and does not have any effect on Gram-negative bacteria. This antibiotic has been used to treat tuberculosis (Figure 6).[8]

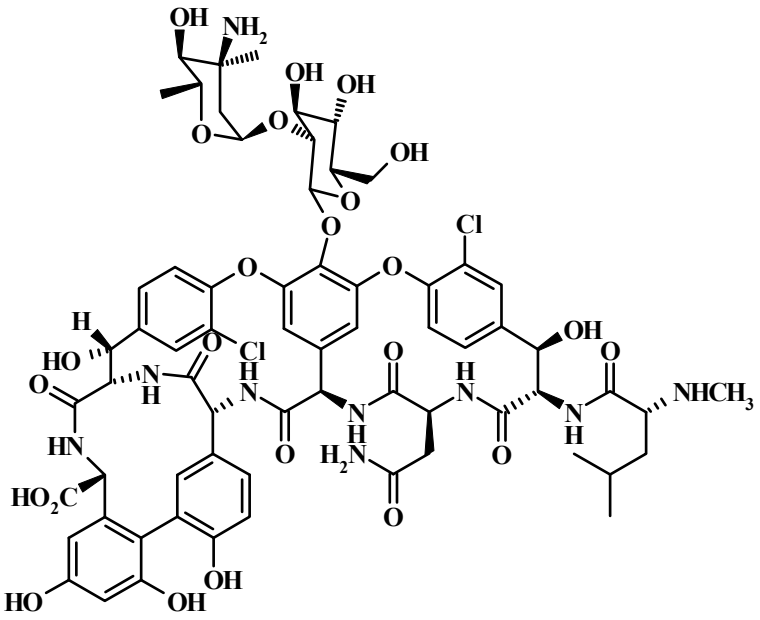


Linezolid (10)

Figure 6

Vancomycin

Vancomycin (**11**) is a natural glycopeptide antibiotic used in the treatment of infections caused by Gram-positive bacteria.[9] It is traditionally being referred to as the drug of "last resort" used only after treatment with other antibiotics had failed, although the emergence of vancomycin-resistant organisms implies that it is increasingly being replaced from its role by linezolid and the carbapenems (Figure 7).

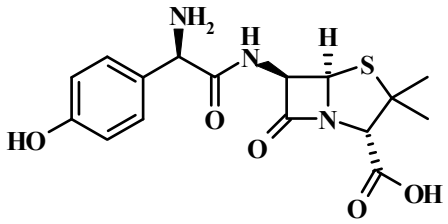


Vancomycin (11)

Figure 7

Amoxicillin

Amoxicillin (**12**) is a moderate spectrum, bacteriolytic, β-lactam antibiotic used to treat bacterial infections caused by susceptible microorganisms. It is more preferred for regular use than other β-lactam antibiotics since it is better absorbed and hence can be orally administered. Amoxicillin is susceptible to degradation by β-lactamase-producing bacteria, and so may be given with clavulanic acid to decrease its susceptibility (Figure 8).

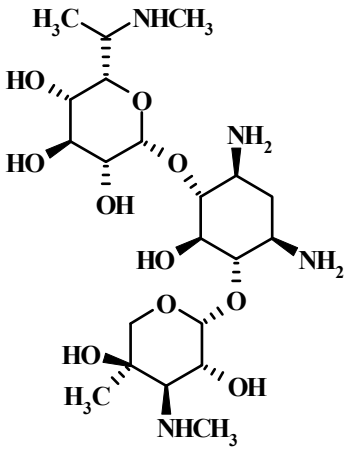


Amoxicillin (12)

Figure 8

Gentamicin

Gentamicin (**13**) is an aminoglycoside antibiotic and can be used for the treatment of many types of bacterial infections, particularly Gram-negative infection.[10] However, gentamicin is not used for *Neisseria gonorrhea*, *Neisseria meningitides* or *Legionella pneumophila* infections. It is synthesized by *Micromonospora*, a genus of Gram-positive widely present in the environment (water and soil). It is administered intravenously, intramuscularly or topically to treat infections. *E. coli* has some resistance to gentamicin despite being Gram-negative. Gentamicin is one of the few heat stable antibiotics which remains active even after autoclaving, thus rendering it particularly useful for certain microbiological growth (Figure 9).



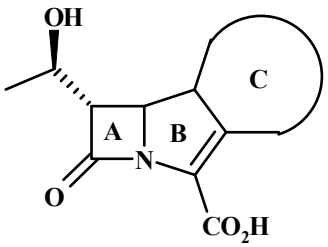
Gentamicin (13)

Figure 9

Side Effects: The most common side effects associated with these antibiotics are diarrhea, nausea, vomiting and upset stomach, abdominal pain, headache, confusion and dizziness.

Apart from the above mentioned antibacterial drugs, several other new classes of antibacterial agents have emerged as promising candidates for antimicrobial therapy which are being continuously probed through their total synthesis and biological tests. A few interesting antibacterial compounds, isolated recently are illustrated below:

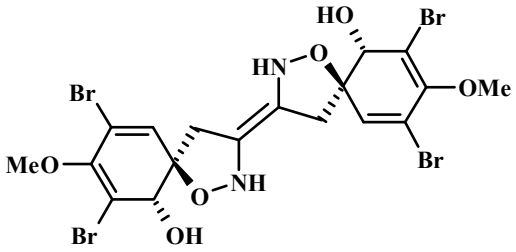
Trinems (Figure 10), are a class of β-lactam antibiotics discovered by Biondi and coworkers[11] as promising substances for treating bacterial infections. Trinems (**14**) are potent antibacterial agents with a broad spectrum of activity against Gram positive and Gram negative bacteria and are stable to most β-lactamases and human hydrolytic enzyme dehydropeptidase (DHP I).



Trinems (14)

Figure 10

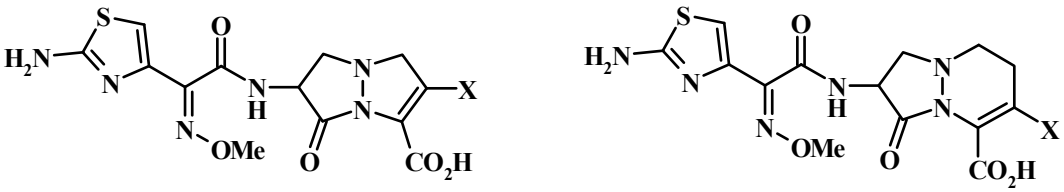
Zamamistatin (**15**) is a novel bromotyrosine derivative and exhibited significant antibacterial activity against *Rhodospirillum salexigens*, which has adhering properties (Figure 11).[12]



Zamamistatin (15)

Figure 11

Several bicyclic pyrazolidinones **16** and **17** have been strongly investigated in laboratories through their total synthesis and biological testing as compounds of antibacterial agents, some of which have been known to show profound antibacterial activity (Figure 12).[13]



16 17

X = -CO$_2$Me/-COMe

Pyrazolidinones

Figure 12

Thus, continuing with our existing research it has been observed that bacterial resistance is combating with the discovery of new drugs, the former being increasingly moving ahead. Hence, future research on antimicrobial therapy may focus on the development of new techniques or some other alternatives to overcome these bacterial resistances to antibiotics.

Antifungal drugs [14]

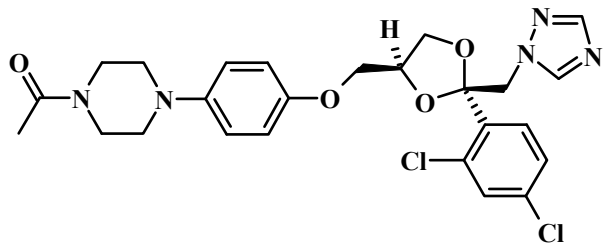
A fungus is one celled form of life. Unlike, a plant which prepares its own food or an animal which eats other plants or animals, a fungus survives by invading and living off other living things. Since, fungi thrive in moist and dark places so fungal infections are especially likely to be found in the mouth, armpits, groin and genital areas. Almost 90% of fungal skin infections are caused by 'dermatophytes' which are parasitic fungi affecting the skin, hair or nails. Among the most common fungal infections include the athlete's foot, jock itch, candidiasis (also called thrust or yeast infection) and ringworm, which is not caused by a worm, but by a fungus. Topical antifungal drugs used relieve the symptoms of fungal infections, such as burning, itching and cracked skin along with the elimination of fungus. However, in cases where external application of creams or ointments is ineffective or those that occur within the body need to be treated with systemic antifungal drugs. These drugs are used, for example, to treat a type of fungal infection called candidiasis, which can occur in the throat, in the vagina, or in other parts

of the body. They may be also used to treat fungal infections such as histoplasmosis, blastomycosis and aspergillosis which can affect the lungs and other organs.

The commonly available antifungal drugs are fluconazole (Diflucan), itraconazole (Sporanox), ketoconazole (Nizoral) and miconazole. These drugs are available in orally as well as in injectable forms. Topical antifungal drugs which are used externally are available in the form of creams, ointments, liquids, powders, aerosol sprays and vaginal suppositories. The commonly used topical antifungal drugs include ciclopirox, clotrimazole, econazole, miconazole, nystatin, oxiconazole, terconazole and tolnaftate. Some of the common antifungal drugs are discussed below:

Ketoconazole

Ketoconazole (**18**) is a synthetic antifungal drug used to prevent and treat skin and fungal infections, especially in immunocompromised patients such as those with AIDS. It is sold under the branded name, Nizoral, as an anti-dandruff shampoo. Ketoconazole is very lipophilic, which leads to accumulation in fatty tissues. Comparatively, fluconazole and itraconazole are more effective triazole compounds and have replaced ketoconazole for internal use. Ketoconazole is best absorbed at highly acidic levels, so antacids or other causes of decreased stomach acid levels will lower the drug consumption when taken orally (Figure 13).

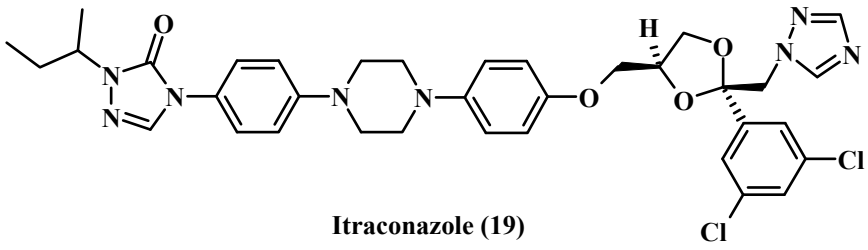


Ketoconazole (18)

Figure 13

Itraconazole

It is a triazole antifungal agent that is prescribed to patients with fungal infections. The drug may be consumed orally or intravenously. Though itraconazole (**19**) is a well tolerated drug but not as compared fluconazole or voriconazole and it has a wide range of adverse effects. Elevated alanine aminotransferase levels are found in 4% of people taking itraconazole which develops a small but real risk of developing congestive heart failure. The cyclodextrin that is used for the syrup can cause diarrhea. Other possible side effects include: nausea, vomiting, abdominal pain, fatigue, loss of appetite, yellow skin (jaundice), yellow eyes, itching, dark urine and pale stool dock (Figure 14).

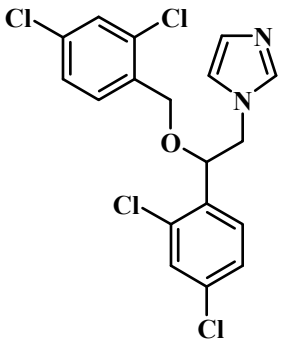


Itraconazole (19)

Figure 14

Miconazole

Miconazole (**20**) is an imidazole antifungal agent which is applied topically to the skin or mucus membranes to cure fungal infections. Unlike nystatin, some miconazole is absorbed by the intestinal tract when used orally which may lead to drug interactions. Of note may be interactions with anticoagulants, phenytoin, terbinafine and some newer atypical antipsychotics, cyclosporine and some statins used to treat hypercholesterolemia (Figure 15).

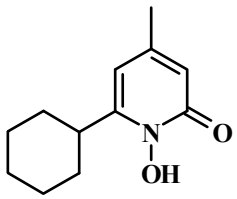


Miconazole (20)

Figure 15

Ciclopirox olamine

This is a synthetic antifungal agent for topical dermatologic use. It acts by inhibiting the membrane transfer system by interrupting the Na^+, K^+, ATPase. Ciclopirox olamine (**21**) is currently being investigated as an alternative to ketoconazole for seborrhoeic dermatitis as it suppresses growth of the yeast *Malassezia furfur* (Figure 16).

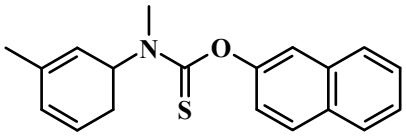


Ciclopirox olamine (21)

Figure 16

Tolnaftate

Tolnaftate (**22**) is a synthetic over-the-counter anti fungal agent. This is available as a cream, powder, spray or liquid aerosol and is used to treat jock itch, athlete's foot and ringworm (Figure 17).

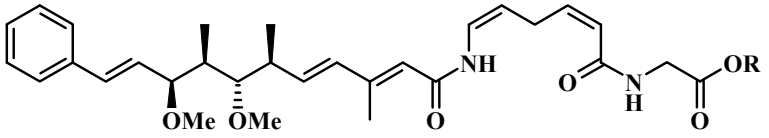


Tolnaftate (22)

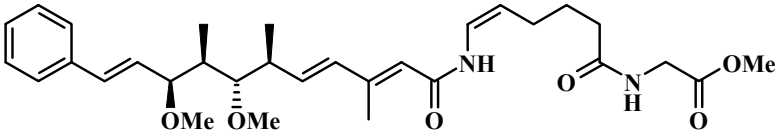
Figure 17

Systemic antifungal drugs may cause serious and possibly life threatening liver damage. Patients should have their liver function tests done, recommended by a physician, prior to the use of such drugs. More serious effects, though not common, but may occur. So, for a detailed study to minimize the toxic effect related with these drugs, several new antifungal compounds have been isolated from natural resources and synthesized in the laboratory for screening purposes. A few of these are:

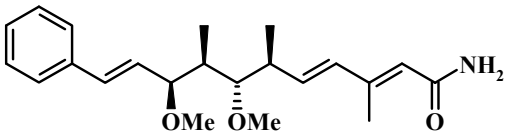
Crocacins A-D (**23-26**), isolated from myxobacterial strains of *chondromyces crocatus* and *chondromyces pediculatus* (Figure 18).[15] A total synthesis of (+)-crocacin C has been reported by Chakraborty *et al*.[16]



Crocacin A (R = Me) (23)
Crocacin B (R = H) (24)



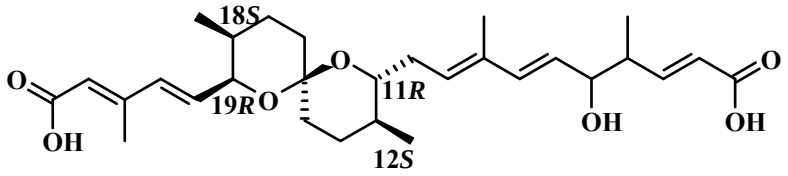
Crocacin D (26)



Crocacin C (25)

Figure 18

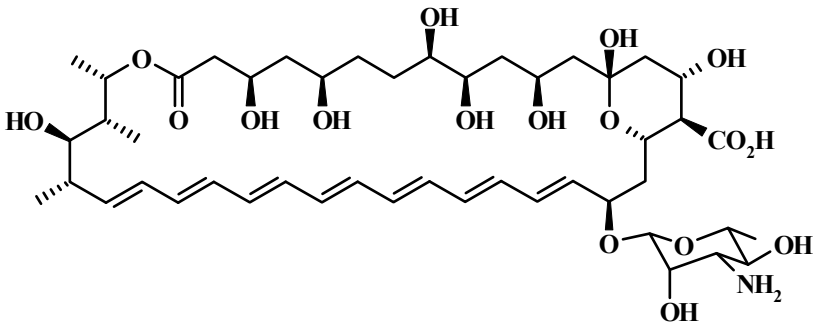
Spirofungin A (**27**) and B (**28**), isolated from the *Streptomyces violaceusniger* Tu 4113 a new polyletide type antibiotics (Figure 19)[17] show antifungal activity especially against yeasts. Synthetic studies towards spirofungin were carried out by Kiyota and coworkers.[18]



Spirofungin A (27)
B (28) (18*R*, 19*S*)

Figure 19

Amphotericin B (**29**) is a macrolide heptaene antibiotic which is widely used to combat severe systemic fungal infections.[19] But its severe toxicity to mammalian cells has resulted in the derivatization of amphotericin into many analogous compounds (Figure 20).[20]



Amphotericin B (29)

Figure 20

Karatungiols A (**30**) and B (**31**) are two novel antimicrobial polyol compounds, isolated from symbiotic marine dinoflagellate *Amphidinium* sp. (Figure 21).[21]

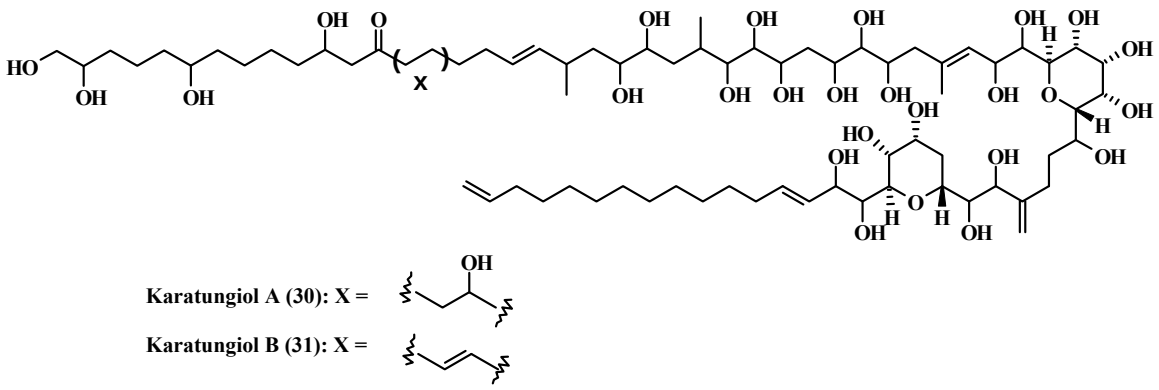
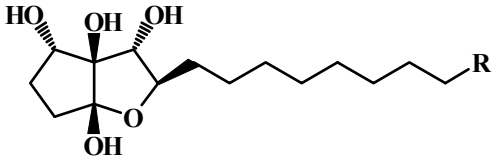


Figure 21

However, injudicious and prolonged use of antibiotics has resulted in the emergence of antibiotic as well as antifungal-resistant pathogens, thereby causing a major threat to global public health.[22] This inevitable consequence is demanding for a renewed effort to develop antibacterial agents that would be active against pathogenic bacteria which withstand to current antibiotics. For this a detailed investigation is on the forefront with the view to develop new antibacterial compounds.

In order to fight against these resistant organisms and decrease the toxicity as well as other side effects, it is now time to find and synthesize more new compounds from which we are also not in exception. In our lab we were interested in a group of metabolites of the fresh water aquatic fungus[23] *Helicodendron giganteum* Glen-Bott (Helotiaceae). Heliconols A-C (**32-34**), a member of the so called helicosporous fungi[24] are newly isolated from the genus *Helicodendron,* by Gloer *et al.*[25] , an intriguing group of aquatic fungal genera that are widespread, but rarely studied. These fungi display a unique mode of adaptation in aquatic environments. They develop only mycelia underwater but sporulate when exposed above the surface, forming conidia that entrap air. The trapped air causes them to float, thereby aiding spore dispersal. To date, this has been the first report from any Helicodendron species. Heliconols A-C are three new polyketide derived hemiketals which contain an unusual reduced furano-cyclopentane ring system which is very rare among natural products and only two preceding reports among fungal metabolites are available.[26] Heliconols A-C were tested against *Candida albicans* (ATCC 14053), *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (ATCC

6051), *Escherichia coli* (ATCC 25922), *Aspergillus flarus* (NRRL 6541), and *Fusarium verticillioides* (NRRL 25457) (Figure 22). Heliconol A (**32**) was found to inhibit the growth of *F. verticilloides* and exhibit profound activity against *C. albicans*, *S. aureus* and *B. subtilis*. On the contrary Heliconols B (**33**) and C (**34**) were found to exhibit lesser activity compared to Heliconol A (**32**). The relative configurations of Heliconol A-C were proposed on the basis of the relevant correlations due to the hydroxyl and the adjacent protons in the NOESY spectrum. The absolute stereochemistry of Heliconol A was *prima facie* established by single-crystal X-ray crystallographic analysis of its dibromobenzoate derivative.[25]



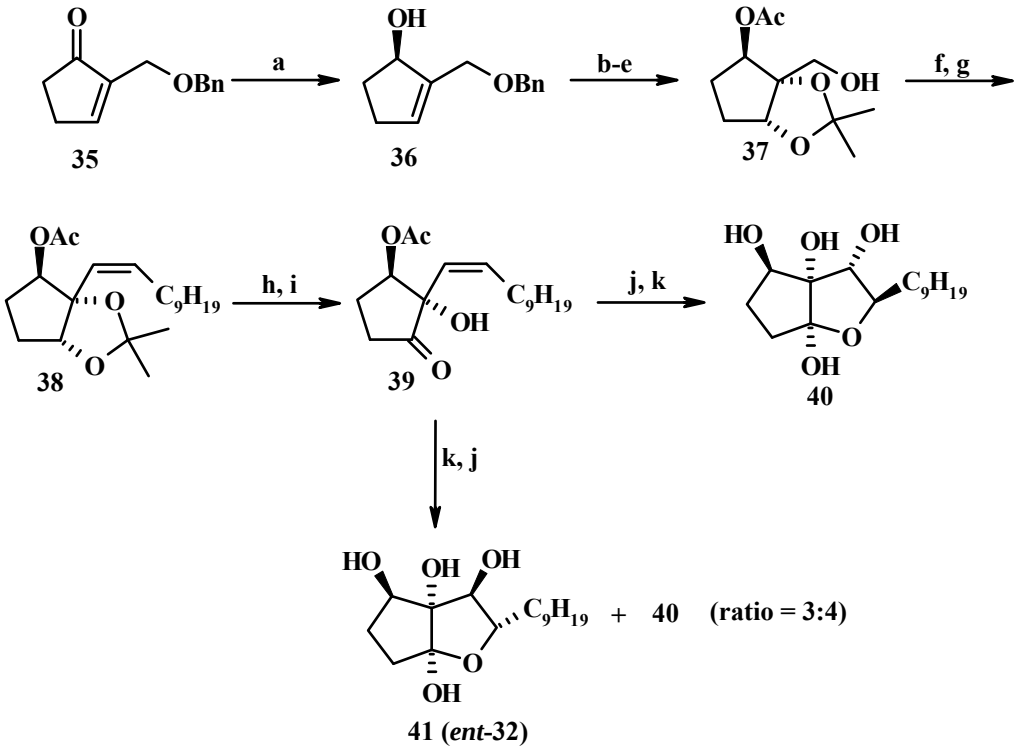
Heliconol A -C
A(32). R = Me
B(33). R = CH_2OH
C(34). R = CO_2H

Figure 22

Past work related to the synthesis of Heliconol A-C

A facile total synthesis of (−)-Heliconol A (*ent*-Heliconol A) has been reported by She and coworkers.[27] They devised a strategy starting from **35** which could be readily obtained from commercially available cyclopentenone. Thus they reduced **35** with (*S*)-*n*Bu-CBS which afforded the alcohol **36** in 87% *ee*. Protection of **36** as its acetate followed by dihydroxylation with OsO_4 generated an easily separable diastereomeric mixture of diols which on subsequent protection as its isopropylidene derivative with concomitant cleavage of the benzyl ether provided **37**. Oxidation under Swern conditions furnished the aldehyde which was staged for the Wittig olefination with the ylide derived from *n*-decatriphenylphosphonium bromide leading to the formation of **38** as a single (*Z*)-isomer in 65% yield. Deprotection of the acetonide to the diol, and finally Swern

oxidation furnished the ketone **39**. Dihydroxylation of this ketone **39** with OsO_4 gave a single isomer, which upon basic hydrolysis produced **40** whose data completely disagreed with the reported ones of the natural product **32**. Using *NOE* correlations they verified the structure of **40**. On the other hand, changing the sequence of osmylation and hydrolysis furnished a 3:4 mixture of **41** which was assigned as *ent*-**32** {confirmed by its optical rotation value} and **40** (Scheme 1).



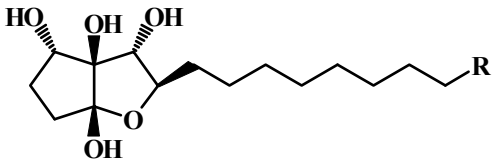
Scheme 1

Reagents and conditions: a) (*S*)-*n*Bu-CBS, BMS, THF, $^{-}10$ ^{o}C; b) Ac_2O, pyridine, DMAP, rt; c) OsO_4, NMO, THF/H_2O, rt; d) 2,2-DMP, CH_2Cl_2, *p*-TSA, rt; e) 5% Pd/C, EtOH, H_2; f) Swern oxidation; g) *n*-BuLi, $C_{10}H_{21}PPH_3^{+}Br^{-}$, THF; h) 80% AcOH, rt; i) Swern oxidation; j) OsO_4, NMO, THF/H_2O, rt; k) K_2CO_3, MeOH, rt.

PRESENT WORK

PRESENT WORK

Nature has stocked the seas with a seemingly limitless range of diverse and often highly complex secondary metabolites, which exhibit one or more of a variety of biological properties including cytotoxicity, neurotoxicity, antiviral and antifungal. Investigation is on the forefront with the continuous isolation and synthesis of new bioactive molecules. In the course of this ongoing research, a new fresh water aquatic fungi,[23] *Helicodendron giganteum* Glen-Bott (Helotiaceae) was isolated from a sample of submerged wood in Alaska. The genus *Helicodendron* is a member of the so called helicosporous fungi[24], an intriguing group of specialized aeroaquatic fungal genera that are widespread, but rarely studied. These fungi display a unique mode of adaptation in aquatic environments. From these extracts, three new polyketide-derived hemiketals were isolated; Heliconols [A-C, (**1-3**)] by Gloer and coworkers[25] each of which contains an unusual reduced furanocyclopentane ring system (Figure 1). The structures of these metabolites were assigned by the analysis of 1D and 2D NMR data.



Heliconol A -C
A(1). R = Me
B(2). R = CH_2OH
C(3). R = CO_2H

Figure 1

Elucidation of structure

A detailed study of the NMR spectra and comparison with their molecular formula suggests that these molecules are bicyclic in nature. The structure of heliconol A was further amplified from its ^1H NMR spectrum and HMBC correlations. The relative

configurations of heliconol A-C (**1-3**) were proposed on the basis of the relevant correlations due to the hydroxyl and the adjacent protons in the NOE spectrum. The absolute stereochemistry of heliconol A was *prima facie* established by single-crystal X-ray crystallographic analysis of its dibromobenzoate derivative. The structural difference among the heliconol derivatives lies only in the side chain functionality, all three having the same bicyclic core (Figure 1). All heliconol derivatives A-C (**1-3**) were tested against *Candida albicans* (ATCC 14053), *Staphylococcus aureus* (ATCC 29213), *Bacillus subtilis* (ATCC 6051), *Escherichia coli* (ATCC 25922), *Aspergillus flarus* (NRRL 6541), and *Fusarium verticillioides* (NRRL 25457). Out of these heliconol A (**1**) was found to be more active compared to heliconol B (**2**) and C (**3**) and it inhibits the growth of *F. verticilloides* and exhibit profound activity against *C. albicans*, *S. aureus* and *B. subtilis*. In addition, the structures of heliconols A-C (**1-3**) contain an unusual reduced furanocyclopentane ring system which is very rare among natural products. Fascinated by the intriguing structural features accompanied by potent biological activity we decided to embark on its total synthesis.

Retrosynthetic analysis

To probe into the retrosynthetic study of heliconols A-C, we envisaged at devising a suitable and general strategy meant to construct heliconol A (**1**) along with other analogs of this species, heliconol B (**2**) and C (**3**), by simple tuning of the side chain functionality. Our retrosynthetic analysis (Figure 2) reveals that the furan ring in heliconol A (**1**) could be synthesized by highly face selective dihydroxylation of **4** in which the *cis*-double bond should be accessible by controlled alkyne reduction of **5** which in turn could be obtained *via* an intrinsic neighbouring group participated face selective dihydroxylation of **6**. A stereospecific reduction, imparted by Corey-Bakshi-Shibata (CBS) reagent, of the carbonyl group present in 2-iodo-2-cyclopentenone derivative derived from 2-cyclopentenone (**7**) as our commercially available starting material followed by well known “Sonogashira cross coupling” reaction of the resulted 2-iodo-2-cyclopentenol derivative with commercially available 1-undecyne conferred the pivotal enyne derivative **6**.

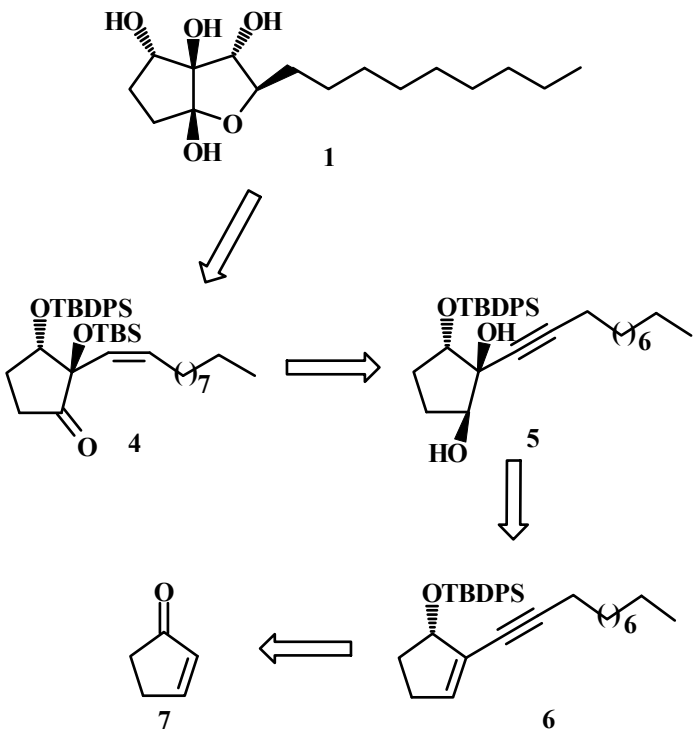


Figure 2: Retrosynthetic analysis of Heliconol A (**1**)

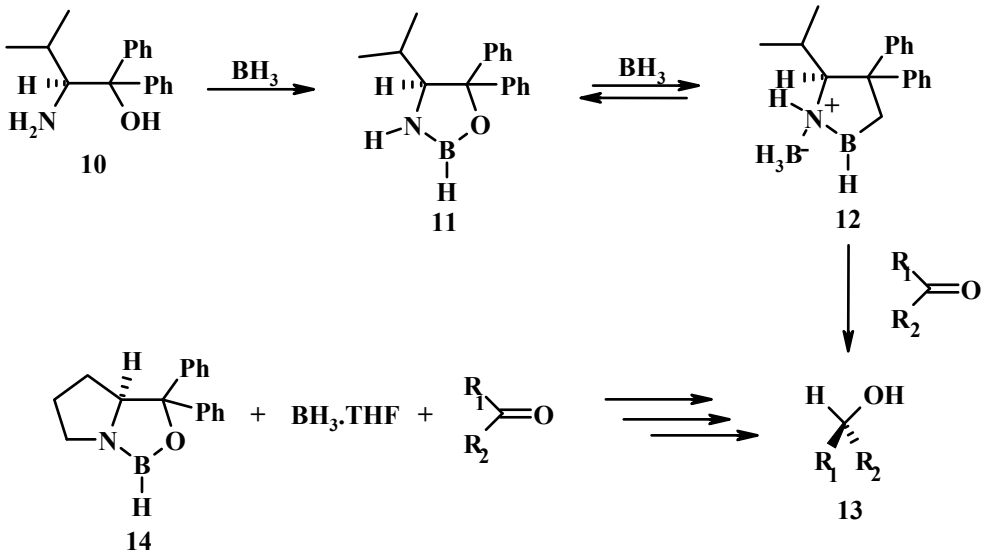
Synthetic approach

The synthesis began with the commercially available cyclopentenone **7** which was converted to its 2-iodo-2-cyclopentenone derivative (**8**) following a literature procedure.[28] The compound was fully characterized from the ^{1}H, ^{13}C NMR and melting point data of its reported specimen. A stereoselective reduction of the carbonyl group by Corey-Bakshi-Shibata (CBS) reagent provided neat access to the hydroxyl derivative (**9**) in a highly enantioselective manner. Excellent enantioselectivities, easy recoverability of the chiral catalyst precursor, nearly quantitative yields and short reaction times contribute to the outstanding utility of the CBS protocol.[29]

A Short Introduction to the Corey-Bakshi-Shibata (CBS) reagent: enantioselective reduction of ketones

In recent years there has been a flood of papers describing research on the enantioselective reduction of ketones using various reagents made from chiral diols or amino alcohols and a boron or aluminium hydride. Although a number of systems have been described which provide useful enantioselectivities but the scope and and mode of reduction is still at the primitive level and needs to be proved and expanded. Among the most interesting reported results are that by Itsuno and his group which employs mixture of borane (2-3 equiv in THF) and a chiral vicinal amino alcohol (1 equiv) such as (S)-2-amino-3-methyl-1,1-diphenylbutan-1-ol.[30]

*Extensive studies have found out that a fast reaction occurs between amino alcohol (**10**) and borane in THF which results in the formation of oxazaborolidine (**11**) with the release of hydrogen gas. Removal of the excess borane and solvent affords colourless crystals after sublimation. A mixture of oxazaborolidine (**11**) and BH_3.THF in THF causes reduction of the ketone in very short time. To check for optimization of the conditions, the reactions were tested with varying amounts of the oxazaborolidine. It was observed that a catalytic amount of **11**, either 0.1 or 0.025 equiv gives good enantioselectivities upto 94.7 % ee. This marks the beginning of a new chiral reducing agent known as the Corey-Bakshi-Shibata reagent. The protocol was utilized for the formation of other chiral oxazaborolidine catalysts. An even better catalyst for the reduction of ketones is the oxazaborolidine (**14**), which can be readily prepared form (S)-(–)-2-(diphenylhydroxymethyl)pyrrolidine((S)-diphenyl-prolinol) by heating at reflux with 3 equiv of BH_3.THF in THF under a Ar-BH_3 atmosphere. The optimum conditions for these reduction processes include 0.6 equiv of borane, 0.05 equiv of oxazaborolidine (**14**) as catalyst in THF at room temperature. The reactions are fast with good to excellent enantioselectivities and the diphenylprolinol ligand can be recovered easily by simple workup which makes this process highly applicable for industrial application (Scheme 1).*



Scheme 1

*A possible drawback of oxazaborolidine (**14**) is its air and moisture sensitivity which limits its usage in organic synthesis. To overcome this problem a new catalyst, the B-methylated oxazaborolidine (**15**) has been prepared. Reaction of (S)-(–)2-(diphenylhydroxymethyl)pyrrolidine and methylboronic acid (1.1 equiv) in toluene at rt for 1.5 h in the presence of 4 A molecular sieves or in refluxing toluene for 3 h using a Dean-Stark trap for complete removal of water results in the formation of colorless solid (**15**) upon removal of solvent. This catalyst is remarkably more stable and serves with appreciably higher or same enantioselectivity as compared to **14** (Figure 3)*

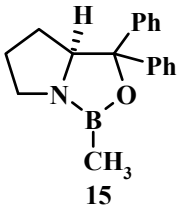
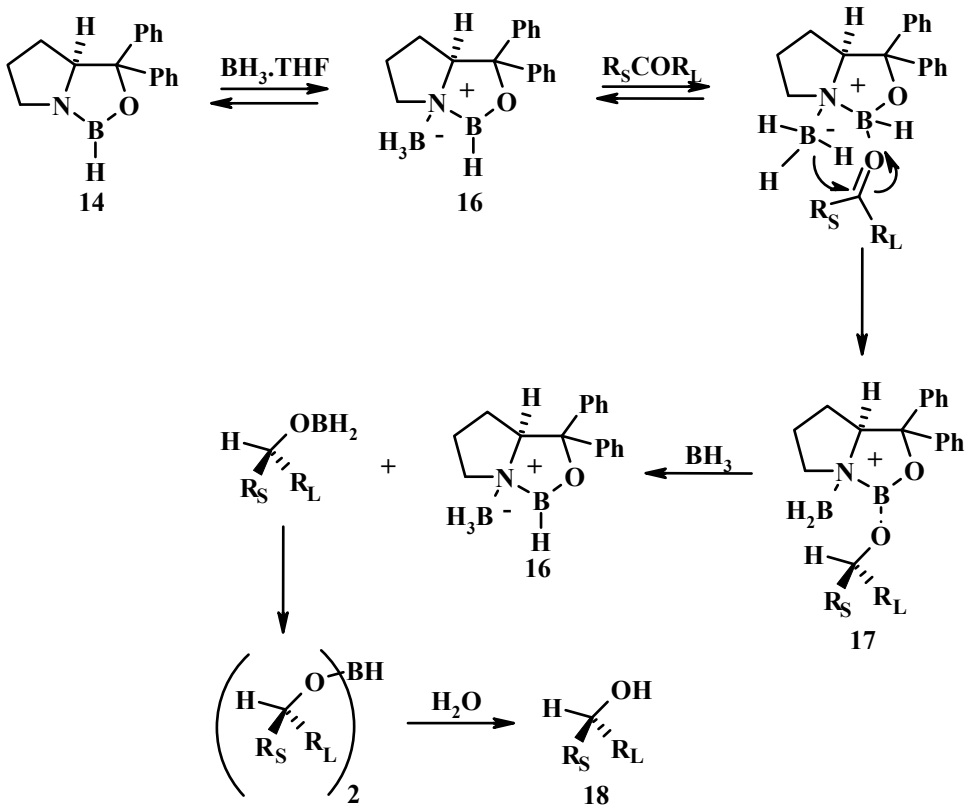


Figure 3

*The mechanism of the reduction is represented in Scheme 2. It clearly indicates that BH_3.THF initially coordinates to the N of the oxazaborolidine (**14**) to form a*

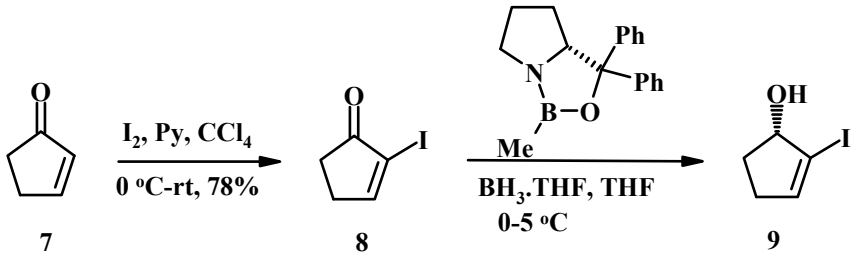
*complex (**16**). As soon as the carbonyl compound is added the other electrophilic boron coordinates to the ketonic oxygen (anti to the larger carbonyl appendage) with concomitant hydride transfer from the NBH_3^- unit to the carbonyl group via a six-membered cyclic transition state as shown in Scheme 2. The intermediate complex **17** then adds up one more molecule of BH_3 to release the complex **16** and the chiral alcohol (**18**).*



Scheme 2

Thus when compound **8** was treated with a catalytic amount of (*R*)-2-methyl-CBS-oxazaborolidine[29] and BH_3.THF (0.6 eq) in THF at 0-5 ^oC, a highly stereoselective allylic alcohol **9** was obtained. The gross structure could be assessed primarily from its proton and ^{13}C NMR values. The peaks due to the olefinic proton resonating at δ 6.28 as a triplet and due to the –CHOH proton at 4.70 ppm as a multiplet in the ^1H NMR were clean indication of the reduced compound. The enantiomeric purity of **9** was determined

by HPLC analysis which was found out to be 92 % ee (crude). Further enhancement of the enantiomeric purity to 96% ee was achieved by re-crystallization from ether-pentane mixture which afforded **9** as colourless crystals (Scheme 3).

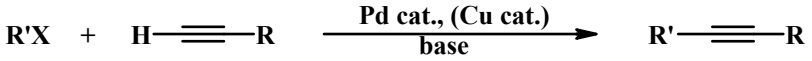


Scheme 3

In order to introduce the alkyne functionality at C-2 position of **9,** we relied upon the Sonogashira cross coupling reaction which is one of the most prominent tools for alkene-alkyne cross coupling in synthetic organic chemistry.[31]

The Sonogashira coupling reaction: A Booming methodology in synthetic organic chemistry.

The array of transition metal catalysed cross-coupling reactions can easily be considered nowadays cornerstones in the field of organic synthesis. Among these, the Palladium-catalysed cross coupling reactions have emerged as the most powerful devices for construction of multi component frameworks in synthetic organic chemistry.[32] The sp^2-sp coupling reaction between the aryl or alkenyl halides or triflates and terminal alkynes to prepare arylalkynes or conjugated enynes, which are synthetic precursors to many natural products, have gained sufficient importance. The reason being that these conjugated en-yne products can be functionalized to a variety of other carbon frameworks which serve as backbone to much natural product synthesis. So far, the Palladium catalyzed sp^2-sp cross coupling reaction with or without the presence of copper catalysts has become the most important method to prepare such en-yne analogs (Scheme 4).[33]



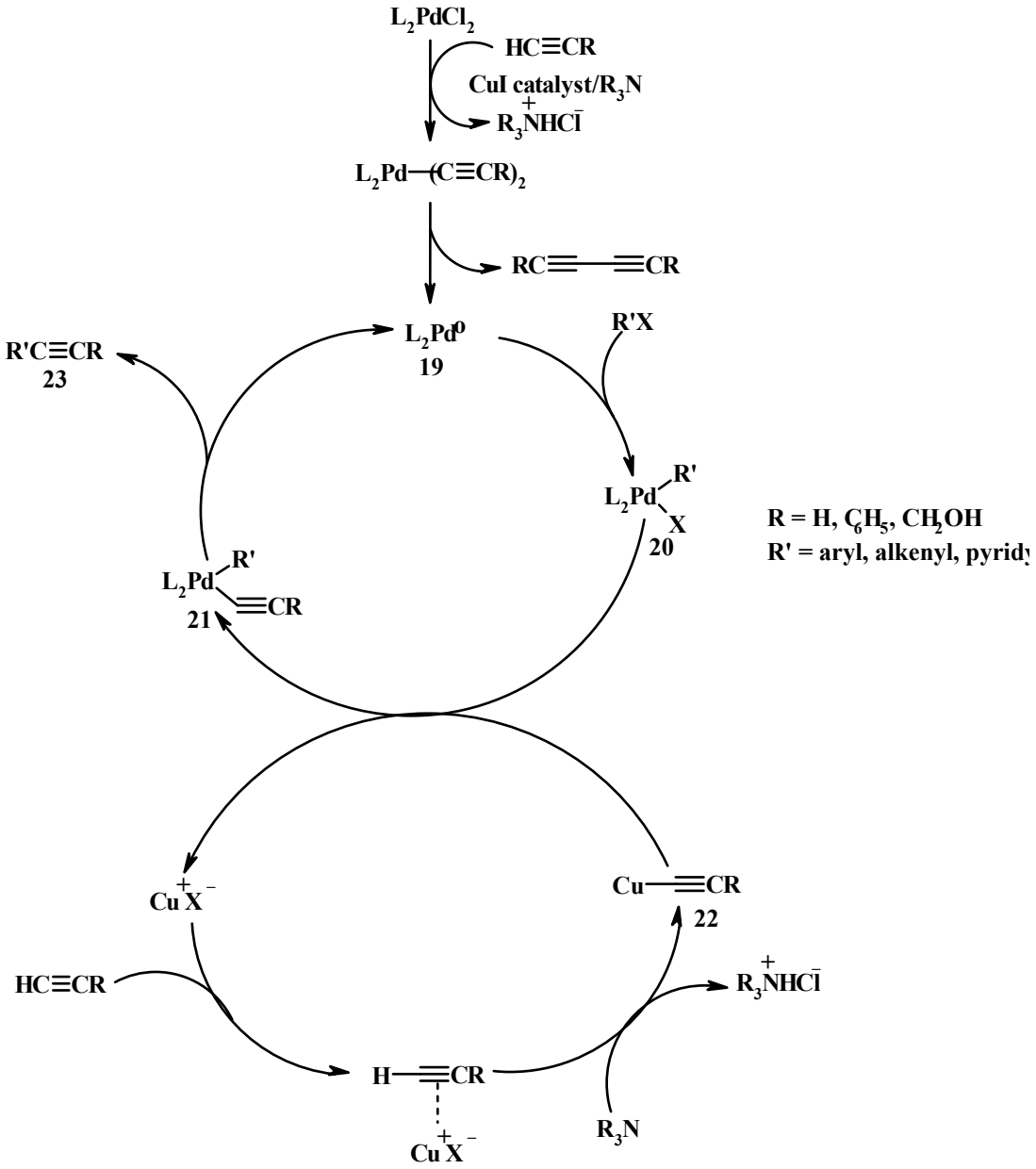
R' = aryl, heteroaryl, vinyl
R = aryl, heteroaryl, alkenyl, alkyl, SiR_3
X = I, Br, Cl, OTf

Scheme 4

The synthesis of the enyne derivatives dates back to the known coupling reaction between copper acetylides and phenyl or vinyl halides (the so called Stephens-Castro reaction),[34] but its scope was limited owing to the violent reaction conditions and the difficulties prevailing in preparation of the copper acetylides. Two other earlier studies were also reported by Heck[35] and Cassar[36] in 1975. Both procedures involve a similar substitution pattern but with different catalyst reagents. A drawback in the above two mentioned cases are the high temperature (up to 100 ^oC) required for the alkynylation process. Sonogashira and Hagihara reported that addition of a catalytic amount of Cu (I) species such as iodide generally accelerates the reaction, thus performing the alkynylation at room temperature.[31] This reaction is commonly referred to as the Sonogashira coupling reaction. Although the Sonogashira coupling reaction exemplifies the sp^2-sp coupling to form an enyne, but this reaction can be extended to the primary and secondary alkyl halides[37] resulting in a sp^3-sp coupling, although the scope and feasibility of this reaction is not much explored. A crucial drawback of the Sonogashira coupling reaction is that the copper catalysts involved in this reaction has a few shortcomings. Apart from being an environmentally unfriendly and difficult to recover co reagent, the generation of copper acetylides in situ often promotes the homocoupling products of the terminal alkyne (Glasser coupling)[38] along with the main reaction product. This is especially a problematic issue when the alkyne involved in the reaction is expensive or is difficult to prepare. Though alternative procedures have been developed such as carrying out the reaction in a reductive atmosphere such as hydrogen, to diminish the homocoupling[39] or slow addition of the alkyne, significant efforts have been

carried out to develop procedures in the absence of these copper salts. One of the most important features that need to be addressed with regard to these coupling reactions is the applicability of the reaction to different substrates. Thus the general reactivity order of the sp^2 species is vinyl iodide≥ vinyl triflate > vinyl bromide > vinyl chloride > aryl iodide > aryl triflate > aryl bromide >> aryl chloride; therefore, the Sonogashira coupling usually runs smoothly when the more expensive and unstable aryl or vinyl iodides are used. Moreover, if the organic halide is activated, that is, electron poor, the situation is even more favourable. Thus, deactivated aryl bromides are difficult starting materials for coupling reactions, whereas the cheapest aryl chlorides, if not strongly activated, represent a real challenge for any cross coupling reaction.[40]

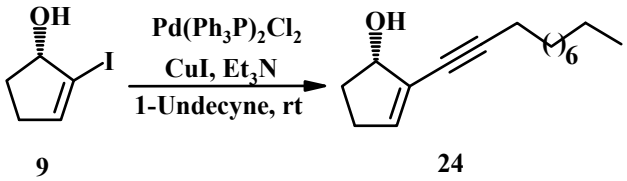
*The mechanism of the Sonogashira coupling reaction is outlined in Scheme 5. Although the detailed mechanism needs some clarification but it is generally accepted that a 14-electron Pd^0L_2 (**19**) is formed by reduction of different Pd (II) complexes with electron donors such as phosphines, amines and ethers used as ligands and solvents via σ-complexation-dehydropalladation-reductive elimination sequence*[32a] *to afford the Pd^0 species and some amount of diacetylene byproduct. The Pd^0 species then oxidatively adds to the aryl or vinyl halide, the addition being facilitated if X = I or OTf and if the electron density about the C-X bond is reduced by the presence of electron withdrawing groups. This is followed by alkynylation of the adduct (**20**) to give **21** which subsequently reductively eliminates the en-yne (**23**) together with the regeneration of the Pd^0 catalyst. The role of Cu (I) cocatalyst is not clearly understood but it is assumed, though not proven, that an in situ formation of copper acetylide (**22**) takes place, whose indirect evidence has recently been found.*[41]



Scheme 5

On subjecting **9** to $(Ph_3P)_2PdCl_2$-CuI catalysed system in Et_3N with 1-undecyne afforded the allylic alcohol **24** with excellent yields.[31] The compound was thoroughly investigated from its ^1H and ^{13}C NMR data. For instance the ^1H NMR spectrum of **24** showed a new resonance arising due to the methyl protons of the appended side chain on C2 at δ 0.88 ppm as a triplet. The other protons resonated in their expected values. In

addition ^{13}C NMR spectrum also displayed signals due to alkyne carbons at δ 75.7 and 93.2 ppm together with 128.7 and 137.8 ppm due to the olefinic carbons. Moreover mass spectral analysis depicted a base peak at 257.28 $(M + Na)^+$ along with the elemental analysis data accounts for the confirmation of the coupled product **24** (Scheme 6).

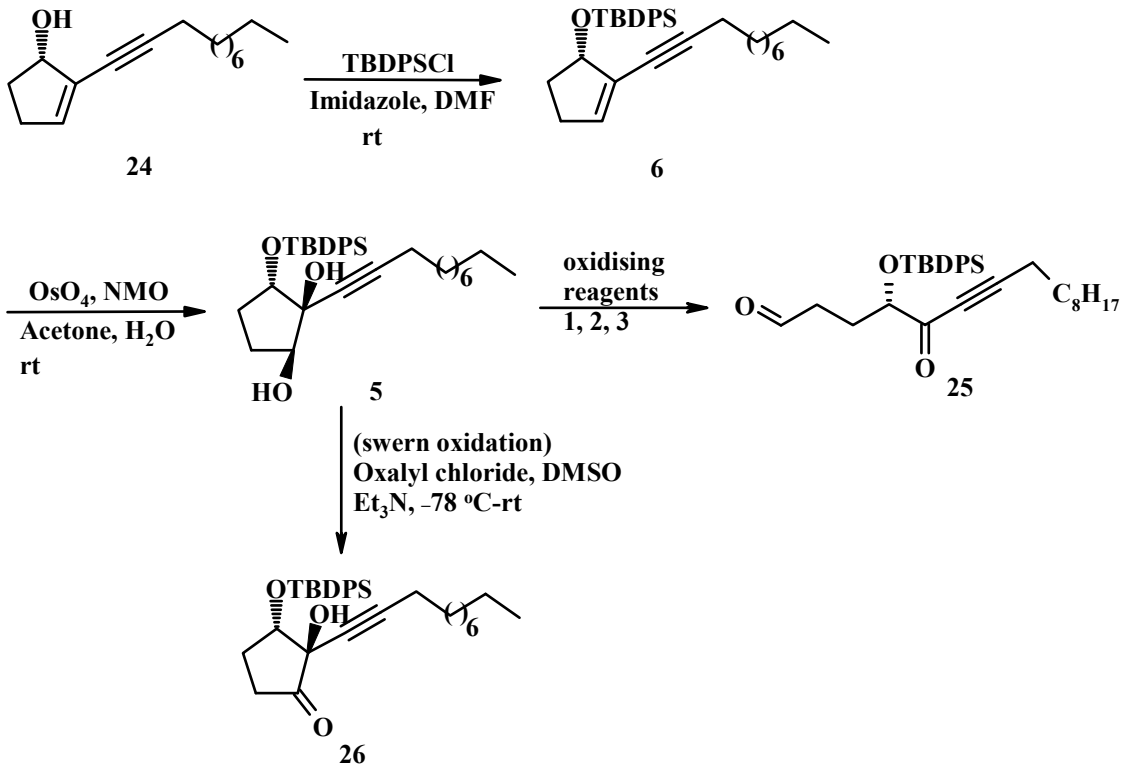


9 **24**

Scheme 6

Compound **24** was protected as its TBDPS ether **6** using TBDPSCl in CH_2Cl_2 in 98% yield. The additional peaks at the aromatic region in the ^1H and ^{13}C NMR spectrum witnessed the formation of **6**. Our next endeavor was to dihydroxylate the olefin in a highly stereofacial manner. The predisposed bulky TBDPS functionality provided sufficiently hindrance on the α-face in such a way that osmylation of **6** proceeded entirely from the opposite side i.e, from less hindered face.[42] The diol **5** was characterized from its spectral, mass and elemental analysis. The absence of peaks in the olefinic region in the ^1H and ^{13}C NMR spectrum supported the structure. Further evidence could be ascertained from its mass spectrum which displayed a $(M + Na)^+$ peak at 529.587. To oxidize the secondary hydroxyl group of the diol **5** was the set up for a real challenge. We initially tried the oxidation with IBX in DMSO but the reaction failed to give any desired product. Instead, a ring opened product **25** was obtained which resulted due to an oxidative cleavage of the cyclopentane diol moiety. Rationalization of the by-product was achieved by a thorough analysis of its ^1H NMR spectrum which depicted a triplet at δ 9.64 due to the aldehyde proton (Scheme 7). After observing similar results with PDC and Dess-Martin periodinane, we thoroughly investigated the pros and cons in various oxidation processes (Table 1). Gratifyingly Swern oxidation[43,44] produced our desired ketone **26** in 80% yield. The absence of aldehyde proton in the NMR spectrum and the appearance of a peak at δ 210.3 ppm due to the keto group, in the ^{13}C spectrum justified the assigned structure; all other peaks resonated accordingly. Further support of evidence

was deduced from its mass spectral analysis which displayed a base peak at 527.58 $(M + Na)^+$ and its IR absorption peak at 1758 cm^{-1}.



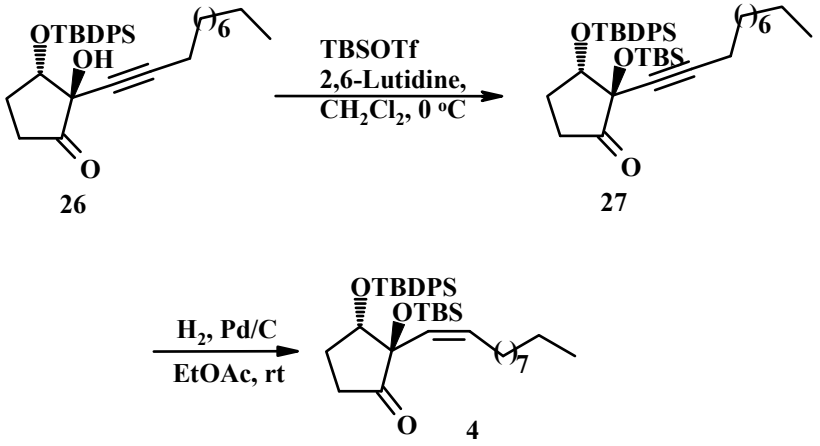
Scheme 7

Table 1:

Entry	Oxidizing reagents	Product
1.	IBX, DMSO, 92%	**25**
2.	PDC, CH_2Cl_2, 85%	**25**
3.	Dess-Martin periodinane, CH_2Cl_2, 95%	**25**
4.	Swern oxidation, 80%	**26**

Having successfully overcoming the vital oxidation step, we focused on the alkyne moiety to reduce it in a *cis* selective manner in order to obtain the required olefin, which would readily be in position to furnish our required bicyclic hemiketal. Forecasting the need for facial dihydroxylation we envisioned to install a tertiary hydroxyl protecting

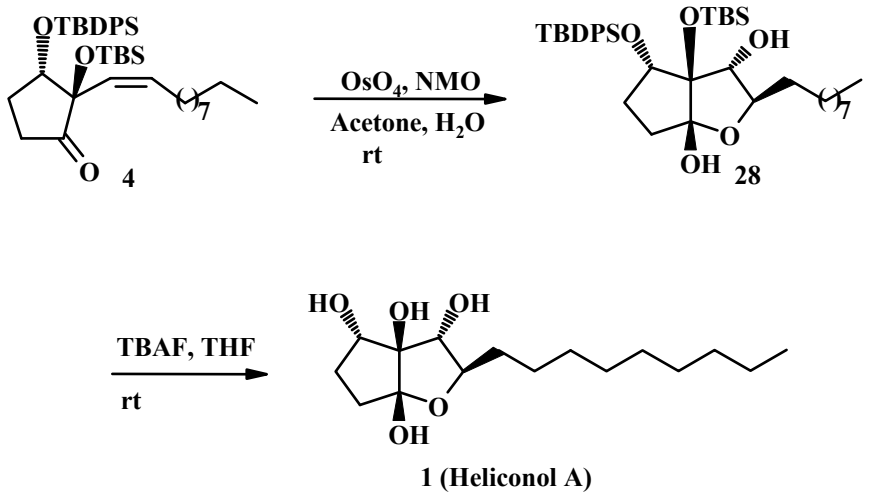
group, say as a *tert*-butyl-dimethylsilyl ether,[45] thus providing a bulky group on the *β*-face of cyclopentane: enough conformational freedom was thereby allowed to secure the desired stereocenter during second osmylation. The *tert*-hydroxyl group in ketone **26** was hence protected using TBSOTf and 2,6-lutidine in CH_2Cl_2 at 0 ^oC to provide the TBS protected compound **27** in 72% yield. The characteristic signals due to the TBS group were observed in the ^1H NMR spectrum of **27**. Compound **27** was then treated with Lindlar catalyst[46] for partial hydrogenation in a *cis*-selective manner which proved unfruitful as it provided the *Z*-olefin **4** in only 10% yield (by ^1H NMR analysis). Extensive optimization was conducted to effect conversion to *Z*-olefin by treatment with Pd/C in ethyl acetate under hydrogen atmosphere in 95% yield. The olefin product **4** was clarified from the characteristic signals in the ^1H NMR spectrum due to the olefinic protons at δ 5.74 ppm as a double of triplet (J = 5.8, 12.0 Hz) and at 5.82 ppm as a doublet (J = 12.0 Hz). Rests of the protons resonated in their respective δ values (Scheme 8). ^{13}C NMR spectrum, elemental analysis data and mass spectral data at 643.44 attributed as $(M + Na)^+$ also supported the formation of the olefin.



Scheme 8

Having set the stage for the crucial dihydroxylation, we treated olefin **4** with OsO_4 and NMO in acetone/water mixture at ambient temperature to afford the dihydroxylated compound followed by *in situ* cyclised product **28** as the sole product with requisite stereocenters in 84% yield, just as we had expected. This justifies the initial disposition of

TBS group at the tertiary position. The spectral, mass and elemental data were compatible with the assigned structure. The disappearance of the olefinic protons in the ^{1}H NMR spectrum and the ^{13}C signal for keto functionality was indicative of the cyclised or hemiketal derivative (**28**). In the ^{13}C and dept NMR spectrum there were clear signals due to ten methylene groups, also the hemiketal carbon showed a peak at δ 109.4 in the ^{13}C NMR spectrum, thus accounting for the structure of **28**. The ESI mass spectral data displayed a characteristic peak at 677.15 attributed to $(M + Na)^{+}$ which substantiated the formation of the cyclized product instead of dihydroxylated compound as intermediate. Elemental analysis data were also compatible with the assigned structure. Finally global deprotection of **28** using TBAF in THF furnished the target natural product heliconol A (**1**) in 96% yield. The ^{1}H and ^{13}C NMR spectra in DMSO-d_6 of synthetic heliconol A (**1**) were concordant to that of natural product.[25] The optical rotation value of synthetic Heliconol A ($[\alpha]_D^{25}$ +19.6 (*c* 0.9, acetone)) also compares agreeably to that of natural Heliconol A (lit. $[\alpha]_D^{25}$ +21.0 (*c* 1.6, acetone)) which unambiguously confirms the absolute configuration (1*R*,4*S*,5*S*,6*R*,7*R*)- of heliconol A (**1**) (Scheme 9).



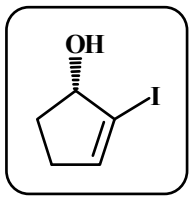
Scheme 9

In conclusion we have developed a highly stereospecific strategy to the total synthesis of heliconol A employing stereoselective reduction of ketone, face selective dihydroxylation, Sonogashira cross coupling reaction and a *cis*-selective reduction as the key features involved. The synthesis presents a flexible outlook towards the synthesis of other analogs of heliconol derivatives as well as related natural products.

EXPERIMENTAL

EXPERIMENTAL

(*S*)-2-iodocyclopent-2-enol (9)

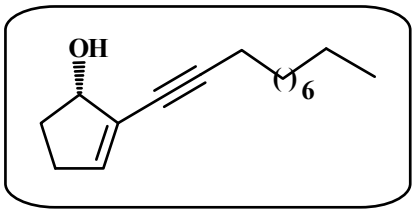


To a solution of (*R*)-2-methyl-CBS-oxazaborolidine (0.61 g, 2.19 mmol) in THF (15 mL) at 0 ^{o}C were added sequentially solutions of **8** (4.55 g, 21.9 mmol) in THF (20 mL) and BH_3.THF (13.13 mL, 13.13 mmol, 1.0 M in THF) dropwise. The reaction mixture was then stirred at 5 ^{o}C for 30 min, then quenched by the addition of aqueous buffer (pH 7, 10 mL), followed by 30% H_2O_2 (5 mL). After stirring for 30 min, ethyl acetate (30 mL) was added; the layers were separated out and the organic layer was washed successively with 1N HCL (10 mL), H_2O (10 mL), saturated $NaHCO_3$ solution (10 mL) and brine (10 mL); then dried over Na_2SO_4, concentrated in vacuo to leave a residue which on silica gel column chromatography (EtOAc/light petroleum, 1:19) yielded **9** (3.9 g, 85%) as a white solid. Recrystallisation from ether-pentane afforded **9** as colorless crystals, mp 61.2-61.6 ^{o}C; the enantiomeric purity was determined to be 96% [HPLC, Column: Kromacil 5-CelluCoat (250 × 4.6mm, 5 u); Eluent: IPA: PE 01:99; Flow Rate: 0.5 ml/min].

Mol.Formula	C_5H_7IO
Optical Rotation $[\alpha]_D^{25}$	–25.5 (*c* 1.0, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3583, 2851,1604, 1215, 756.
^{1}H NMR($CDCl_3$, 200 MHz)	δ 1.89 (m, 1 H), 2.26-2.38 (m, 2 H), 2.50 (m, 1 H), 4.70 (m, 1 H), 6.28 (t, *J* = 2.41 Hz, 1 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 31.4, 32.8, 82.2, 100.4, 142.5 ppm.
ESI MS(m/z)	227.15 $(M + NH_4)^+$

Elemental Analysis	**Calcd:** C, 28.60; H, 3.36
	Found: C, 28.48; H, 3.20

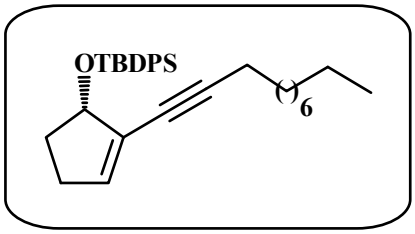
(*S*)-2-(undec-1-ynyl)cyclopent-2-enol (24)



To a solution of **9** (0.9 g, 4.3 mmol) in Et_3N (15 mL), were simultaneously added $Pd(Ph_3P)_2Cl_2$ (0.3 g, 0.43 mmol) and CuI (0.163 g, 0.86 mmol) at room temperature and the reaction flask was degassed with argon. 1-Undecyne (0.98 g, 6.43 mmol) in Et_3N (10 mL) was then added dropwise and the reaction mixture was again degassed with argon. After stirring for 1 h, the reaction mixture was filtered; filtrate was concentrated and residue was purified by silica gel column chromatography (EtOAc/light petroleum, 1:19) to give **24** as a colorless liquid (0.93 g, 95%).

Mol.Formula	$C_{16}H_{26}O$
Optical Rotation $[\alpha]_D^{25}$	$^{-}$23.0 (*c* 1.4, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3492, 2223,1669, 1557, 1214, 1051, 861
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.88 (t, *J* = 6.5 Hz, 3 H), 1.27 (m, 10 H), 1.52-1.59 (m, 3 H), 1.68-1.86 (m, 2 H), 2.25-2.39 (m, 4H), 2.51 (m, 1 H), 4.74 (m, 1 H), 6.08 (t, *J* = 2.5 Hz, 1 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 14.0, 19.5, 22.6, 28.7, 28.9, 29.1, 29.2, 29.4, 30.5, 31.8, 32.6, 75.7, 78.9, 93.2, 128.7, 137.8 ppm.
ESI MS(m/z)	257.28 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 81.99; H, 11.18;
	Found: C, 81.83; H, 10.96

(*S*)-*tert*-butyldiphenyl(2-(undec-1-ynyl)cyclopent-2-enyloxy)silane (6)



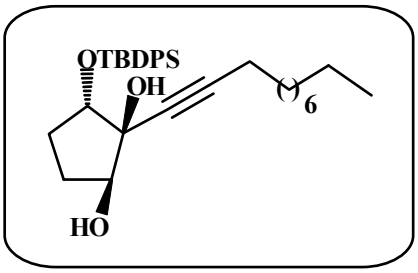
Imidazole (0.44 g, 6.4 mmol) was added to a solution of **24** (0.75 g, 3.2 mmol) in DMF (10 mL) at room temperature. The reaction flask was cooled to 0 ^{o}C and then TBDPSCl (1.3 mL, 4.8 mmol) was added dropwise. The reaction was stirred overnight at room temperature. After completion of the reaction, (monitored by TLC), it was quenched with water (30 mL) and extracted with ether (2 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to give a residue, which was purified on silica gel column chromatography eluting with EtOAc/light petroleum (1:19) to provide **6** as a colorless liquid (1.49 g, 98%).

Mol.Formula	$C_{32}H_{44}OSi$
Optical Rotation $[\alpha]_D^{25}$	-45.6 (*c* 1.9, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2856, 2211, 1716, 1464, 1217, 757.
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.88 (t, *J* = 6.5 Hz, 3 H), 1.09 (s, 9 H), 1.26 (m, 11 H), 1.40-1.49 (m, 3 H), 1.68 (m, 1 H), 1.86 (m, 1 H), 2.08-2.41 (m, 4 H), 4.81 (t, *J* = 6.3 Hz, 1 H), 6.03 (t, *J* = 2.6 Hz, 1 H), 7.31-7.40 (m, 6 H), 7.68-7.80 (m, 4 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 14.2, 19.3, 19.6, 22.7, 27.0, 28.8, 29.1, 29.3, 29.4, 29.5, 30.3, 31.9, 33.9, 76.9, 80.1, 93.0, 127.3, 127.5, 129.1, 129.4, 129.5, 134.1, 134.7, 136.0, 136.2, 137.6 ppm.
ESI MS(m/z)	495.17 $(M + Na)^+$

Elemental Analysis **Calcd:** C, 81.29; H, 9.38

Found: C, 81.25; H, 9.32

(1*S*,2*S*,5*S*)-5-(*tert*-butyldiphenylsilyloxy)-1-(undec-1-ynyl)cyclopentane-1,2-diol (5)

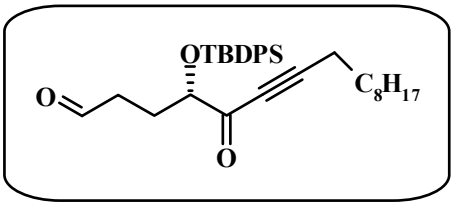


OsO_4 (0.4 mL, 0.008 mmol, 0.02 M in toluene) was added to a solution of **6** (1.2 g, 2.54 mmol) and NMO (1.2 mL, 5.0 mmol, 50% aqueous solution) in acetone/water (4:1, 20 mL) at room temperature. The mixture was stirred overnight and then quenched with a saturated solution of sodium sulfite (10 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo to leave a residue, which on silica gel column purification (EtOAc/light petroleum, 1:6) furnished **5** as a colorless liquid (1.15 g, 90%).

Mol.Formula	$C_{32}H_{46}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	−9.2 (*c* 1.5, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3484, 2401, 1600, 1427, 1215, 929, 758
^{1}H NMR($CDCl_3$, 400 MHz)	δ 0.89 (t, *J* = 6.8 Hz, 3 H), 1.10 (s, 9 H), 1.28 (m, 9 H), 1.37-1.40 (m, 2 H), 1.47-1.54 (m, 4 H), 1.82-1.91 (m, 2 H), 2.08 (m, 1 H), 2.23 (t, *J* = 7.2 Hz, 2 H), 4.23 (dd, *J* = 4.9, 7.0 Hz, 2 H), 7.36-7.43 (m, 6 H), 7.68 (dd, *J* = 1.3, 7.9 Hz, 2 H), 7.77 (dd, *J* = 1.4, 7.9 Hz, 2 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ 14.2, 19.0, 19.3, 22.7, 26.9, 27.0, 27.8, 28.7, 29.0, 29.2, 29.3, 29.5, 31.9, 77.6, 78.5, 79.3, 79.8, 87.5,

	127.56, 129.6, 133.8, 134.3, 135.8, 136.0 ppm.
ESI MS(m/z)	529.587 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 75.84; H, 9.15
	Found: C, 75.71; H, 9.26

Ring opened product (25)

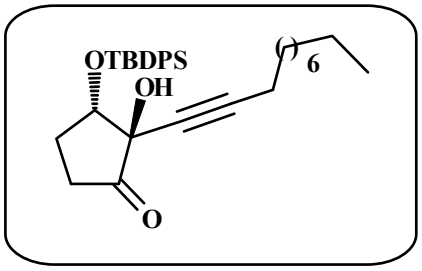


To a solution of diol **5** (0.12 g, 0.24 mmol), in DMSO (3 mL), was added IBX (0.134 g, 0.48 mmol) at room temperature. The reaction was stirred for 2 h, then quenched with water (10 mL) and extracted with ether (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford a residue which was purified on silica gel column eluting with ethyl acetate/light petroleum, (1:19) to furnish the compound **25** (0.11 g, 92%) as a colourless oil.

Similar results were obtained with Dess-Martin Periodinane and PDC oxidation.

Mol.Formula	$C_{32}H_{44}O_3Si$
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.88 (t, *J* = 6.7 Hz, 3 H), 1.11 (s, 9 H), 1.26 (m, 11 H), 1.53 (m, 3 H), 1.95-2.06 (m, 2 H), 2.31 (t, *J* = 7.0 Hz, 2 H), 2.37-2.57 (m, 2 H), 4.25 (t, *J* = 5.5 Hz, 1 H), 7.35-7.42 (m, 6 H), 7.61-7.66 (m, 4 H), 9.64 (t, *J* = 1.2 Hz, 1 H) ppm.

(2*R*,3*S*)-3-(*tert*-butyldiphenylsilyloxy)-2-hydroxy-2-(undec-1-ynyl)cyclopentanone (26)



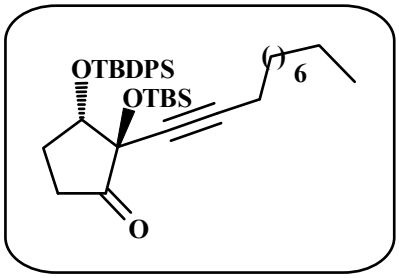
To a solution of oxalyl chloride (0.96 mL, 1.9 mmol, 2M in CH_2Cl_2) in dry CH_2Cl_2 (10 mL) at –78 ^oC was added a solution of dry DMSO (0.3 mL, 3.85 mmol) in CH_2Cl_2 (2 mL). After stirring for 30 min at that temperature diol **5** (0.65 g, 1.3 mmol) in CH_2Cl_2 (5 mL) was added dropwise. Stirring was continued for 24 h after which Et_3N (0.8 mL, 5.8 mmol) was added slowly and stirred for 30 min before warming it to room temperature. The reaction mixture was then diluted with water (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography (EtOAc/light petroleum, 1:9) afforded ketone **26** (0.52 g, 80%) as a colorless oil.

Mol.Formula	$C_{32}H_{44}O_3Si$
Optical Rotation $[\alpha]_D^{25}$	–2.0 (*c* 1.3, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3458, 2409, 1758, 1471, 757
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.87 (t, *J* = 6.5 Hz, 3 H), 1.10 (s, 9 H), 1.25 (m, 10 H), 1.47-1.58 (m, 2 H), 1.83-2.11 (m, 5 H), 2.27 (t, *J* = 7.03 Hz, 2 H), 2.55 (m, 1 H), 4.10 (dd, *J* = 6.9, 8.73 Hz, 1 H), 7.33-7.44 (m, 6 H), 7.69-7.79 (m, 4 H) ppm.
^{13}C NMR($CDCl_3$, 100MHz)	δ 14.1, 19.0, 19.4, 22.6, 26.5, 26.8, 28.5, 28.9, 29.1, 29.3, 29.5, 31.9, 32.6, 74.2, 78.1, 78.3, 91.5, 127.6, 127.63, 129.8, 133.1, 134.0, 135.8, 136.0, 210.3 ppm.
ESI MS(m/z)	527.58 $(M + Na)^+$

Elemental Analysis **Calcd:** C, 76.14; H, 8.79

Found: C, 75.98; H, 8.84

(2*R*,3S)-2-(*tert*-butyldimethylsilyloxy)-3-(*tert*-butyldiphenylsilyloxy)-2-(undec-1-ynyl)cyclopentanone (27)

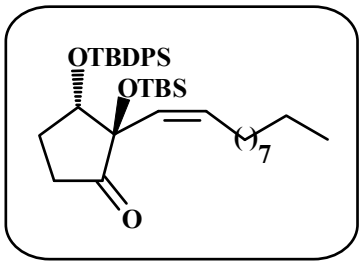


To a solution of Ketone **26** (0.38 g, 0.76 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC, was added 2,6-lutidine (0.2 mL, 1.53 mmol) followed by TBSOTf (0.3 mL, 1.14 mmol). The reaction was stirred for 30 min, and then quenched with water (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined layers were dried over Na_2SO_4, concentrated and purified on silica gel column chromatography (EtOAc/light petroleum, 1:19) to yield **27** as a colorless liquid (0.34 g, 72%).

Mol.Formula	$C_{38}H_{58}O_3Si_2$
Optical Rotation $[\alpha]_D^{25}$	+6.6 (*c* 1.5, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2930, 2401, 1760, 1428, 1215
^1H NMR($CDCl_3$, 200 MHz)	δ 0.07 (s, 3 H), 0.10 (s, 3 H), 0.73 (s, 9 H), 0.77 (t, *J* = 5.0 Hz, 3 H), 0.96 (s, 9 H), 1.15 (m, 10 H), 1.34-1.44 (m, 3 H), 1.57-1.67 (m, 2 H), 1.88-2.32 (m, 5 H), 4.04 (t, *J* = 5.5 Hz, 1 H), 7.21-7.33 (m, 6 H), 7.59-7.65 (m, 4 H) ppm.

^{13}C NMR($CDCl_3$, 100MHz)	δ -3.1, -2.8, 14.2, 18.2, 19.1, 19.4, 22.7, 25.8, 26.8, 26.9, 28.4, 29.1, 29.2, 29.3, 29.5, 29.7, 31.9, 75.7, 77.3, 78.9, 91.7, 127.6, 127.7, 129.7, 129.8, 133.4, 134.4, 135.9, 136.0, 209.3 ppm.
ESI MS(m/z)	636.57 $(M + NH_4)^+$
Elemental Analysis	**Calcd:** C, 73.73; H, 9.44
	Found: C, 73.48; H, 9.32

(2*R*,3*S*,*Z*)-2-(*tert*-butyldimethylsilyloxy)-3-(*tert*-butyldiphenylsilyloxy)-2-(undec-1-enyl)cyclopentanone (4)

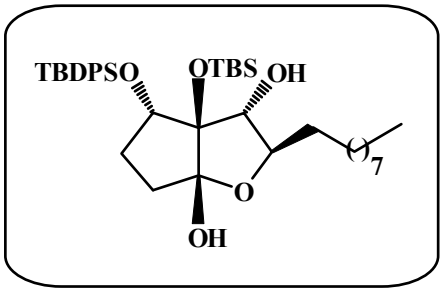


Compound **27** (0.21 g, 0.34 mmol) was hydrogenated in ethyl acetate (7 mL) with 10% Pd/C (50 mg) at atmospheric pressure. After stirring for 1 h, (completion of reaction was monitored by TLC), the reaction mixture was filtered over a pad of Celite, concentrated and purified on silica gel column chromatography eluting with EtOAc/light petroleum (1:19) yielding olefin **4** as a colorless liquid (0.2 g, 95%).

Mol.Formula	$C_{38}H_{60}O_3Si_2$
Optical Rotation $[\alpha]_D^{25}$	+2.4 (*c* 0.9, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	2925,1758, 1635, 1451, 1086

^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.12 (s, 3 H), 0.21 (s, 3 H), 0.95 (s, 9 H), 1.01 (t, *J* = 6.0 Hz, 3 H), 1.16 (s, 9 H), 1.38 (m, 13 H), 1.81-1.96 (m, 2 H), 2.08-2.24 (m, 3 H), 2.29-2.54 (m, 2 H), 4.32 (t, *J* = 5.7 Hz, 1 H), 5.74 (dt, *J* = 5.8, 12.0 Hz, 1 H), 5.82 (d, *J* = 12.0 Hz, 1 H), 7.49-7.56 (m, 6 H), 7.75-7.84 (m, 4 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ −3.4, −2.6, 14.1, 18.4, 19.3, 22.7, 25.9, 26.8, 26.9, 27.1, 29.2, 29.3, 29.45, 29.5, 29.6, 31.9, 32.9, 79.5, 82.8, 125.1, 127.5, 129.7, 133.1, 134.4, 135.8, 135.96, 136.0, 215.2 ppm.
ESI MS(m/z)	643.44 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 73.49; H, 9.74
	Found: C, 73.26; H, 9.45

(2*R*,3*R*,3a*R*,4*S*,6a*R*)-3a-(*tert*-butyldimethylsilyloxy)-4-(*tert*-butyldiphenylsilyloxy)-2-nonyl-hexahydro-2H-cyclopenta[b]furan-3,6a-diol (28)

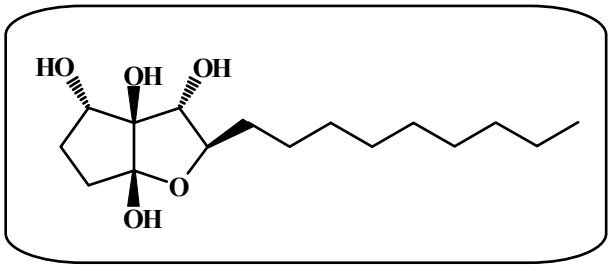


To a solution of **4** (0.12 g, 0.2 mmol) and NMO (0.1 mL, 0.4 mmol, 50% aqueous solution) in acetone/water (4:1, 5 mL) was added OsO_4 (1 mL, 0.02 mmol, 0.02 M in toluene). The reaction mixture was stirred for 96 h, (completion being monitored by TLC), then quenched with a saturated solution of sodium sulfite (5 mL). Ethyl acetate (10 mL) was added and the layers were separated out. The aqueous layer was extracted with ethyl acetate (3 × 20 mL), the combined organic layers were dried over Na_2SO_4,

concentrated in vacuo and the residue was purified by flash silica gel column chromatography (EtOAc/light petroleum, 1:19) to afford **28** as a colorless liquid (0.11 g, 84%).

Mol.Formula	$C_{38}H_{62}O_5Si_2$
Optical Rotation $[\alpha]_D^{25}$	+5.0 (*c* 1.2, $CHCl_3$)
IR ($CHCl_3$) cm^{-1}	3494, 2929, 1662, 1590, 1428, 1113, 970
^{1}H NMR($CDCl_3$, 200 MHz)	δ 0.08 (s, 3 H), 0.13 (s, 3 H), 0.83 (s, 9 H), 0.87 (t, *J* = 5.9 Hz, 3 H), 1.09 (s, 9 H), 1.26 (m, 15 H), 1.56-1.73 (m, 4 H), 1.89 (m, 1 H), 3.09 (brs, 1 H), 3.88 (dd, *J* = 5.96, 12.8 Hz, 1 H), 4.03 (t, *J* = 5.8 Hz, 1 H), 4.31 (m, 1 H), 4.92 (d, *J* = 5.8 Hz, 1 H), 7.33-7.45 (m, 6 H), 7.66-7.81 (m, 4 H) ppm.
^{13}C NMR($CDCl_3$, 50MHz)	δ −3.2, −2.9, 14.1, 17.7, 19.0, 22.7, 25.7, 26.2, 27.0, 29.3, 29.5, 30.2, 31.9, 34.7, 35.1, 84.0, 84.5, 84.7, 85.7, 109.4, 127.8, 127.83, 130.1, 130.2, 131.7, 133.1, 135.9, 135.91 ppm.
ESI MS(m/z)	677.15 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 69.67; H, 9.54
	Found: C, 69.73; H, 9.41

(+)-Heliconol A (1)



Heliconol A (1)

To a solution of **28** (0.082 g, 0.13 mmol) in THF (2 mL) at 0 ^{o}C, TBAF (0.3 mL, 0.3 mmol, 1 M in THF) was added and the reaction mixture was stirred for 30 min at room temperature. After completion (monitored by TLC), the reaction was quenched with a saturated solution of NH_4Cl (1 mL) and diluted with ethyl acetate (2 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and purified by flash silica gel chromatography eluting with ethyl acetate/light petroleum (7:3) to afford **1** (Heliconol A) as a colourless liquid (0.036 g, 96%).

Mol.Formula	$C_{16}H_{30}O_5$
Optical Rotation $[\alpha]_D^{25}$	+19.6 (*c* 0.9, Acetone)
IR ($CHCl_3$) cm^{-1}	3369, 2925, 2854, 1653, 1464, 1309, 1016
^{1}H NMR(DMSO-d_6,400 MHz)	δ 0.84 (t, *J* = 7.0 Hz, 3 H), 1.23 (m, 13 H), 1.34-1.41 (m, 2 H), 1.49-1.59 (m, 3 H), 1.77-1.87 (m, 2 H), 3.56 (dt, *J* = 4.4, 7.5 Hz, 1 H), 3.72 (t, *J* = 7.2 Hz, 1 H), 4.04 (m, 1 H), 4.59 (s, 1 H), 5.51 (d, *J* = 4.0 Hz, 1 H), 5.58 (d, *J* = 6.7 Hz, 1 H), 5.85 (s, 1 H) ppm.
^{13}CNMR(DMSO-d_6, 100MHz)	δ 14.0, 22.2, 25.4, 28.8, 29.0, 29.1, 29.2, 30.6, 31.4, 34.1, 35.1, 80.1, 81.5, 83.3, 84.0, 108.6 ppm.
ESI MS(m/z)	325.16 $(M + Na)^+$
Elemental Analysis	**Calcd:** C, 63.55; H, 10.00
	Found: C, 63.46; H, 9.86

REFERENCES

REFERENCES

1. Fleming A. (**1946**). Chemotherapy: yesterday, today and tomorrow. In (Hunter PA, Darby GK, Russell NJ. eds) Fifty Years of Antimicrobials: Past Perspectives and Future Trends. 53rd Symposium of the Society for General Microbiology. pg. 1-18. Cambridge University Press.
2. Pelczar, M.J., Chan, E.C.S. and Krieg, N.R. (**1999**) "Host-Parasite Interaction; Nonspecific Host Resistance", In: Microbiology Conceptsand Applications, 6th ed., McGraw-Hill Inc., New York, U.S.A. pp. 478-479.
3. Podolsky, M. Lawrence (**1998**) *Cures Out of Chaos: How Unexpected Discoveries Led to Breakthroughs in Medicine and Health*, Harwood Academic Publishers.
4. Klajn, Rafal, *Chemistry and chemical biology of tetracyclines*, retrieved 20 June **2007**.
5. Macrolide Antibiotics: Chemistry, Biology, and Practice, 2nd Edition, Ed. Satoshi Omura, **2002**, Academic Press.
6. Woodward, R. B., *et al*. *J. Am.* Chem. *Soc***. 1981,** *103,* 3215.
7. Burkhardt, O.; Pletz, M W.; Mertgen C. P.; Welte, T. (**2007**). *Recent Patents Anti-Infect Drug Disc* 2 (2): 123–30.
8. Von der Lippea, B.; Sandvenb, P.; Brubakk, O. *J. Infect.* **2006,** *52* (2): 92–6.
9. Moellering, R.C. Jr. *Clin Infect Dis* **2006,** *42*, S3–S4.
10. Sundin, D.P.; Sandoval, R.; Molitoris, B.A *J. Am. Soc. Nephrol.* **2001,** *12,* 114-123.
11. Biondi, S. *Trienems: synthesis and antibacterial activity of a new generation of antibacterial β-lactams, Spec. Publ. R. Soc. Chem.* **1997**, Vol. *198* (Anti-infectives), pp 86-100.
12. Takada, N.; Watanabe, R.; Suenaga, K.; Yamada, K.; Ueda, K.; Kita, M.; Uemura, D. *Tetrahedron Lett*. **2001**, *42*, 5265.
13. Ternansky, R. J.; Draheim, S. E. *Tetrahedron Lett*. **1988**, *29*, 6569.
14. Dismukes, W. E. *Clinical Infectious Diseases* **2000**, *30*, 653.

15. a) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Hofle, G. *Eur. J. Org. Chem*. **1999**, 1085; b) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenback, H. *J. Antibiotic*. **1998**, *51*, 1075.
16. Chakraborty, T. K.; Jayaprakash, S. *Tetrahedron Lett*. **2001**, *42*, 497.
17. Holtzel, A.; Kempter, C.; Metzger, J. W.; Jung, G.; Groth, I.; Fritz, T.; Fiedler, H. –P. *J. Antibiotic*. **1989**, 699.
18. Shimizu, Y.; Kiyota, H.; Oritani, T. *Tetrahedron Lett*. **2000**, *41*, 3141.
19. Sarosi, G. A. *Postgrad. Med*. **1990**, *88*, 151.
20. Driver, M. J.; MacLachlan, W. S.; MacPherson, D. T.; Readshaw, S. A.; *J. Chem. Soc. Chem. Commun*. **1990**, 636.
21. Washida, K.; Koyama, T.; Yamada, K.; Kita, M.; Uemura, D. *Tetrahedron Lett*. **2006**, *47*, 2521.
22. a) Gross, L. J. *Science* **1994**, *265*, 590; b) Page, M. G. *Science* **1994**, *265*, 589; c) Powers, J. H. *Curr. Opin. Infect. Dis*. **2003**, *16*, 547.
23. Reatugui, R. F.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *J. Nat. Prod*. **2005**, *68*, 701.
24. Fisher, P. *J. Mycol. Res*. **2005**, *109*, 519 and references therein.
25. Mudur, S. V.; Swenson, D. C.; Gloer, J. B.; Campbell, J.; Shearer, C. A. *Org. Lett*. **2006**, *8*, 3191.
26. Che, Y.; Araujo, A. R.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod*. **2005**, *68,* 435.
27. Quan, W.; Yu, B.; Zhang, J.; Liang, Q.; She, X.; Pan, X. *Tetrahedron*, **2007**, *63*, 9991.
28. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 917-918.
29. a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551-5553. b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925-7926. c) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763-784. d) Corey, E. J.; Helal, C. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012.

30. a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Chem. Commun*. **1983**, 469. b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem*. **1984**, *49*, 555.
31. a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467; b) Chinchilla, R.; Najera, C. *Chem. Rev*. **2007**, *107*, 874.
32. a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; de Meijere, A.; Eds.; Wiley: New York, 2002; b) *Cross Coupling Reactions*; Miyuara, N.; Ed.; Springer: Berlin, 2000.
33. a) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; de Meigere, A.; Eds.; Wiley-Interscience: New York, 2002; p 493. b) Sonogashira, K. *J. Organomet. Chem*. **2002**, *653*, 46.
34. Stephans, R. D.; Castro, C. E. *J. Org. Chem*. **1963**, *28*, 3313.
35. Dieck, H. A.; Heck, F. R. *J. Organomet. Chem*. **1975**, *93*, 259.
36. Cassar, L. *J. Organomet. Chem*. **1975**, *93*, 253.
37. a) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642; b) Altenhoff, G.; Wurtz, S.; Glorius, F. *Tetrahedron Lett*. **2006**, *47*, 2925.
38. Kotora, M.; Takahashi, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.; de Meijere, A.; Eds.; Wiley-Interscience: New York, 2002, p 973.
39. Elangovan, A.; Wang, Y.-H.; Ho, T. -I. *Org. Lett*. **2003**, *5*, 1841.
40. Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed*. **2002**, *41*, 4176.
41. Bertus, P.; Fecourt, F.; Bauder, C.; Pale, P. *New. J. Chem*. **2004**, *28*, 12.
42. a) Smith, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855; b) Knapp, S.; Yu, Y. *Org. Lett*. **2007**, *9*, 1359.
43. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
44. For reviews on Swern oxidation: a) Tidwell, T. T. *Synthesis* **1990**, 857; b) Tidwell, T. T. *Org. React*. **1990**, 39, 297.
45. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc*. **1972**, *94*, 6190.
46. Lindlar, H.; Dubuis, R. *Organic Syntheses*; Wiley: New York, **1973**, Collect. Vol. V, 880.