STUDIES TOWARDS THE SYNTHESIS OF BIO-ACTIVE LACTONES: HALICHONDRIN B, SYNARGENTOLIDE A, (5*R*,7*S*), (5*S*,7*R*)-KURZILACTONES AND (+)-ANAMARINE

A THESIS

SUBMITTED TO UNIVERSITY OF HYDERABAD

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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MARCH 2012

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CERTIFICATE

This is to certify that the research work incorporated in this thesis entitled *"Studies towards the Synthesis of bio-active lactones: Halichondrin B, Synargentolide A, (5R,7S), (5S,7R)-Kurzilactones, and (+)-Anamarine"* has been carried out under my supervision and is a bonafide work of **Mr. CHINTAM NAGENDRA REDDY**. This work is original and has not been submitted in part or full, for any degree or diploma to this or any other university.

Place: Hyderabad

Date:

Dr. J. S. YADAV

(Supervisor)

DECLARATION

I hereby declare that the research work embodied in this thesis is the result of investigations carried out by me at Indian Institute of Chemical Technology, Hyderabad, under the supervision of **Dr. J. S. YADAV**, Director, Indian Institute of Chemical Technology, CSIR, Hyderabad-500 007, India. This work is original and has not been submitted, in part or full, for any degree or diploma to this or any other university.

Place: Hyderabad

Date: (**CHINTAM NAGENDRA REDDY)**

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ACKNOWLEDGEMENTS

It gives me an immense pleasure and pride to express my sincere gratitude and respect for my teacher and guide ***Bhatnagar Laureate, Dr. J. S. Yadav,*** *FNA, , FNASc, FTWAS Director, Indian Institute of Chemical Technology, Hyderabad for his expert and inspiring guidance. I proclaim my indebtedness to him for his constant encouragement along with the useful suggestions and constructive criticisms during the entire tenure of this work. I consider myself fortunate to be associated with him who gave a decisive turn and a significant boost to my career.*

It is pleasant duty to express my sincere thanks to ***Dr. G. Sabitha*** *for her encouragement and pragmatic suggestions throughout my research work. I am delightedly fortunate to associate with her.*

I record my deep sense of gratitude to ***Dr. S.Chandrasekhar****, Head, Natural Products Chemistry Division, for his constant encouragement and ardent interest shown during the progress of work. I am grateful to thanks to* ***Dr. J. S. Yadav****, as a director of IICT for providing the infrastructure and necessary facilities.*

I take this opportunity to thank ***Dr. A.C. Kunwar, Dr. Jagadeesh, Dr. A.V.Sharma and T. Prabhakar*** *for providing analytical support. I am also thankful to* ***Dr. G.V.M. Sharma, Dr. J. Madhusudhana Rao, Dr. B.V.Rao, Dr. B. V. Subba Rdddy, Dr. S.Raghavan, Dr. D. K, Mohapatra, Dr. H.M. Meshram, Dr. Saibal Das, Dr. P.Srihari and Dr. K.Venkatram Reddy*** *for their support and helpful discussions during this period.*

I express my special thanks to the University of Hyderabad. . I would like to express my great sense of gratitude to ***prof. D. Basavaiah*** *dean School of Chemistry, University of Hyderabad.*

I express my deep heartfelt of thanks to all my senior colleagues, Dr. M. Rajkumar, Dr. M. Shashi kumar Reddy, Dr. Maruthi Krishna Prakash, Dr. R. Swapna, Dr. N. M. K. Reddy, Dr. K. Bhaskar Reddy, Dr. K. Sudhakar, Dr. Nargis, Dr. P. Gopal, Dr. V. Bhaskar Reddy and Dr. M. Bhikshapathi for their valuable suggestions and encouragement during the course of this work.

It gives me an immense pleasure to put on record my sincere thanks and acknowledgement for their help and support, of my labmates Mr. R. Srinivas, Mr. K. Yadagiri, Dr. V. Bhaskar, Mr. Ch. Srinivas Reddy, Mrs. Padmaja, Mr. Nagendra Prasad, Mr. Sukanth Kishore Das, Mr. Sambit Naik, Mr. D. Vasudeva Reddy, Mr. A. Senkara Rao, Mr. G. Chandra Sekhar, Mr. T. Ram Mohan Reddy, Mr. K. Shankaraiah, Mr. A. Yagundhar Reddy, Mr. A. Raju, Mr. Ch. Gurumurthy, Mr. A. Maheswar Reddy, Mr. A. Praveen reddy, Miss. G. Mounika, Mr. Tirupathi Reddy, Mr. Ravi, Mr. Murali, Mr. Ranjith, Mr. Surendar Singh, Mr. A. Sandeep reddy, Mrs. Swetha and lab boy T. Prem Kumar for their constant support throughout my work.

My heartfelt thanks to my friends Mr. P. Janardan Reddy, Mr. P. Balasubramanyam, Mr. A. Venkat Reddy, Mr. N. V. Subba Reddy, Mr. Chenna Reddy, Mr. salva Reddy, Mr. Haragopal, Mr.

G. Viswanatha Reddy, Mr. Subba Reddy, Mr. Seshadri, Mr. Maheswar Reddy, Mr. S. Nagendra, Mr. G. Madhusudhan Reddy, Mr. Ganganna, Mr. Narashimha, Mr. Bala Murali Krishna, Mr. Narasimha Chary, Mr. Vikram Reddy, Mr. Phaneendra Reddy and friends from NPL, FCL, Catalysis, Floro Organics division, Nanotechnology division and Discovery laboratories for their co-operation.

I wish to express my sincere thanks to my beloved teachers ***Dr. Siva Reddy***, ***Dr. Y. Lingappa***, ***Dr. Krishan Reddy***, ***Dr. B. V. Ramana***, ***Dr. G.Gangi Reddy***, ***Dr Rajkumar and Dr.Chennakeshava reddy*** *who guided me to a career in chemistry during my graduation and post-graduation days.*

My special thanks to Krishna Rao, Dr. K. V. Reddy, Madhuri, Murali, Srilatha and pavani for having helped me in many ways.

My feelings are beyond the words for their affection, patience, unfailing support and endless optimism of my brother C. Srinivasa Reddy and my sister C. Ramanamma.

I extend my deep love to my parents Sri. C. Jayarami Reddy and Smt. C. Someswaramma, who were behind me and guided me in every aspect towards success all through my life.

I take this opportunity to record my appreciation to spectroscopic and analytical division of IICT.

*Financial assistance from the Council of Scientific and Industrial Research (**CSIR**), New Delhi in the form of fellowship is gratefully acknowledged.*

Finally, I thank the ***Director, IICT****, for allowing me to submit this work in the form of a thesis.*

Chintam Nagendra Reddy

GENERAL REMARKS

- Boiling points and melting points are uncorrected. Melting points were recorded on Buchi R-535 apparatus.
- Infrared spectra were recorded on Perkin-Elmer infrared-683 spectrophotometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}.
- Mass measurements were carried out on CEC-21-110B double focusing mass spectrometer operating at 70 eV using direct inlet systems and are given in mass units (m/z).
- Proton magnetic resonance spectra were recorded on Varian Gemini-200, Avance 300 Varian Unity-400 and Varian FT-80A. Most of the samples were made in CCl_4/chloroform-d (1:1) using tetramethylsilane (Me_4Si) as the internal standard and are given in the δ scale. The standard abbreviations s, d, t, q, m, dd, dt, br s, refer to singlet, doublet, triplet, quartet, multiplet, double doublet, doublet triplet, broad singlet respectively.
- The optical rotations were measure on JASCO DIP-360 Digital polarimeter.
- All reactions involving air-sensitive compounds were conducted in oven-dried glassware at 90-110 ^oC for 6-12 h. Solutions were transferred with syringes or cannulas (double-ended needles) *via* nitrogen pressure.
- Analytical thin-layer chromatography (TLC) was performed on precoated silica gel-60 F_{254} (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapour or UV light or by spraying sulphuric-β-naphthol or phosphomolybdic acid-sulphuric acid or sulphuric acid-anisaldehyde and heating the plates at 120 ^oC.
- All the reactions were monitored by employing TLC techniques using appropriate solvent systems for development. Anhydrous DMF, THF, diethyl ether, hexane and toluene were obtained from an Innovative Technologies solvent purification system. *n*-Pentane, petroleum-ether (boiling range 35 ^oC to 60 ^oC) were distilled over P_2O_5 and stored over pressed sodium wire; dry ether, dry benzene and dry THF were made by distilling them from sodium-benzophenone ketyl. All chlorinated solvents, pyridine, DMF and TEA were distilled over CaH_2

and stored over 4 A^o molecular sieves. Acetone was distilled over potassium permanganate and potassium carbonate.

- All solvent extracts were concentrated at reduced pressure on Buchi-RE-121 rotary evaporator below 50 ^oC. Yields reported are isolated yields of material judged homogenous by TLC and PMR spectroscopy.
- All solvents used for silica gel column chromatography were distilled prior to use. Silica gel used was either 60-120 or 100-200 mesh.

ABBREVIATIONS

Ac	:	Acetyl
Ac_2O	:	Acetic anhydride
AcOH	:	Acetic acid
aq	:	Aqueous
atm	:	Atmosphere
Bn	:	Benzyl
n-BuLi	:	*n*-butyl lithium
^{t}Bu	:	*tert*-butyl
c	:	Concentration
CCl_4	:	Carbon tetrachloride
$CeCl_3$	:	Cerium Chloride
m-CPBA	:	*meta*-Chloroperbenzoic acid
CuCN	:	Copper cyanide
cm	:	Centimetre
DCM	:	Dichloromethane
L(+)-DIPT	:	L(+)- Diisopropyltartarate
DMAP	:	4-(dimethylamino)pyridine
DMF	:	*N*,*N*-dimethylformamide
DMP	:	2,2-dimethoxypropane
DMSO	:	Dimethyl sulphoxide
EI-MS	:	Electron impact mass spectrometry
ESI-MS	:	Electrospray ionization mass spectrometry
Et	:	Ethyl
EtMgBr	:	Ethyl magnesium bromide
EtOAc	:	Ethyl acetate
Fig	:	Figure
g	:	gram
h	:	hour (s)
HMPA	:	Hexamethyl phosphoramide
HRMS	:	High Resolution Mass Spectrometry
Hz	:	Hertz
IR	:	Infrared

IBX	:	Iodoxy benzoic acid
J	:	Coupling costant
$^{i}Pr_2EtN$	:	Diisopropyl ethyl amine (Hunig's base)
$LIALH_4$	:	Lithium aluminium hydride
LC-MS	:	Liquid chromatography mass spectrometry
Li	:	Lithium
$LiNH_2$	:	Lithiumamide
Liq	:	Liquid
MeI	:	Methyl iodide
mL	:	millilitre
mp	:	melting point
MOM	:	Methoxymethyl
MOMCl	:	Methoxymethylchloride
MsCl	:	Methanesulphonylchloride
MHz	:	Megahertz
NMR	:	Nuclear magnetic resonance
nOe	:	nuclear Overhauser enhancement
PMB	:	*p*-methoxybenzyl
PMBBr	:	*p*-methoxybenzylbromide
PMR	:	Proton magnetic resonance
PPTS	:	Pyridiniumparatolunesulphonate
^{i}Pr	:	*iso*-propyl
PTSA	:	*para*-toluenesulphonic acid
Py	:	Pyridine
R_f	:	Retardation factor
rt	:	room temperature
TBAF	:	tetrabutylammonium fluoride
TBS	:	*tert*-butyldimethylsilyl
TBHP	:	*tert*-butyl hydroperoxide
TEA	:	Triethylamine
THF	:	Tetrahydrofuran
THP	:	Tetrahydropyran
$Ti(O_iPr)_4$	:	Titanium isopropoxide
TLC	:	Thin layer chromatography

TosMIC	:	Tosyl methyl isocyanide
TPP	:	Triphenylphosphine
Ts	:	Tosyl (*p*-toluenesulphonyl)
Zn	:	Zinc
[α]	:	Optical rotation

Synopsis

SYNOPSIS

The thesis entitled **"Studies towards the synthesis of bio-active lactones: Halichondrin B, Synargentolide A, (5*R*,7*S*), (5*S*,7*R*)-Kurzilactones, and (+)-Anamarine"** is divided into three chapters.

CHAPTER I: Synthesis of the C38-C54 segment of Halichondrin B.

SECTION A: This section deals with the introduction and previous synthetic approaches to Halichondrin B and C38-C54 spiroketal segment of Halichondrin B.

SECTION B: This section comprises present work on the synthesis of the C38-C54 spiroketal segment of Halichondrin B.

CHAPTER II: This chapter deals with the introduction, earlier synthetic approaches and present work of Synargentolide A.

CHAPTER III: Total synthesis of Kurzilactone, epi-Kurzilactone and (+)-Anamarine.

SECTION A: This section describes the introduction, earlier synthetic approaches, present work of (5*R*,7*S*)-Kurzilactone and its enantiomer.

SECTION B: This section comprises introduction, earlier synthetic approaches and present work of (+)-Anamarine.

CHAPTER I: Synthesis of the C38-C54 segment of Halichondrin B.

Section A: This section deals with the introduction, previous synthetic approaches to C38-C54 spiroketal segment of Halichondrin B.

The halichondrins are a family of polyether macrolides that were isolated from the marine sponge *Halichondria okadai* kadota[1,2] in very minute quantities. Among them, halichondrin B (**1**) (Figure 1) was isolated in 1986 by Hirata *et.al* and found to exhibit potent in vitro IC_{50} value of 0.3 nM against L1210 leukemia and remarkable in vivo activities against various human solid tumor xenographs, including LOX melanoma, KM20L colon, FEMX melanoma, and OVCAR-3 ovarian tumors.[3]

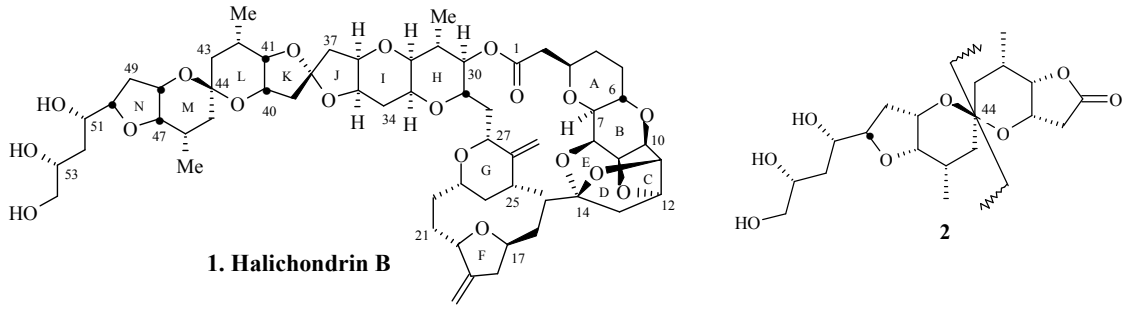


Figure 1

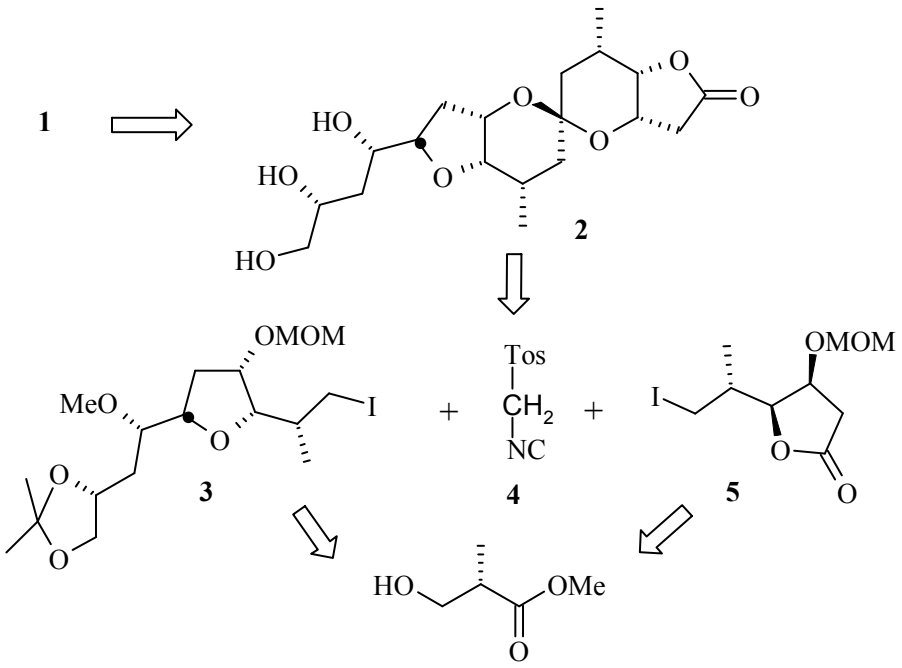
Halichondrin B **1** was highly prioritized for development as a novel anticancer therapeutic by the United States National Cancer Institute in 1991. Kishi's team had set themselves an enormous challenge with halichondrin B. A few years later, however, organic chemist Yoshito Kishi of Harvard University in Cambridge, Massachusetts, eyed the halichondrin B **1** structure and decided to take a crack at it. To date, one total synthesis of halichondrin B **1** has been reported.[4] Several fragment syntheses have been reported.[5]

Due to its biological relevance in cancer therapeutic development, its preclinical stage A, and structural challenge, halichondrin B has generated a great deal of interest

within synthetic community. An Expeditious Synthesis of the C(38)-C(54) Halichondrin B (**1**) subunit was first time reported by Steven D. Burke *et.al*.[5a,b]

CHAPTER I: Section B: This section describes the synthesis of the C38-C54 segment of halichondrin B comprising KLM and N rings with a C44 spiroketal including 10 chiral centers using double alkylation TosMIC strategy.

Retrosynthetically (Scheme 1), spiroketal C38-C54 fragment **2** was envisaged to be obtained by alkylation of TosMIC (tosyl methyl isocyanide) **4** with the use of iodo compounds **3** and **5**, which are in turn prepared from (*S*)-Roche ester **6**.



Scheme 1. Retrosynthetic analysis for C38-C54 segment of halichondrin B

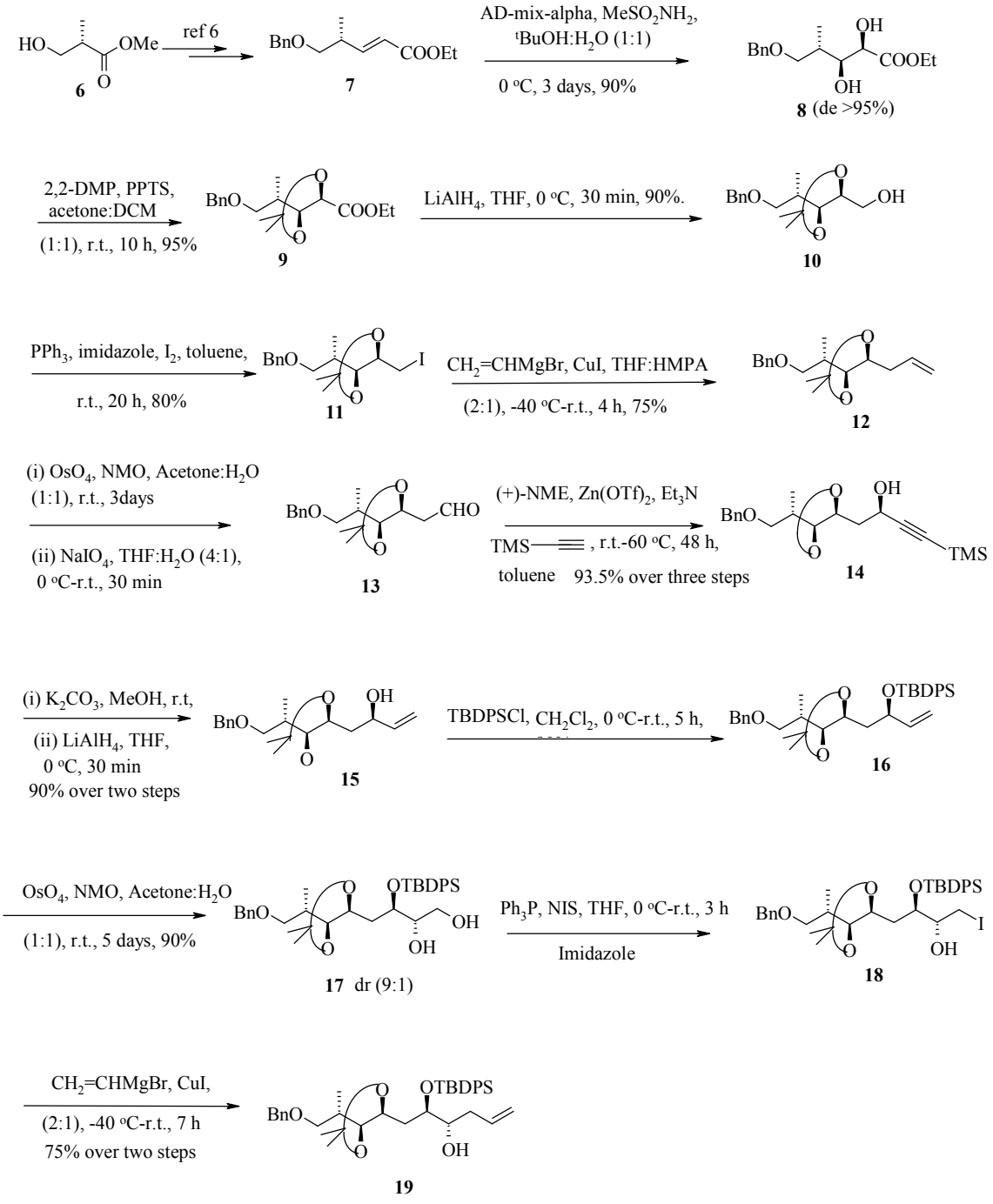
We chose to adopt a convergent strategy, disconnecting the carbon backbone at C(44-45) iodo compound and C(43-44) TosMIC compound thus dividing the target into two key subunits **3** and **31.**

Synthetic strategy for spiroketal C38-C54 fragment (2):

Synthesis of (*R*)-4-((*S*)-2-((2*S*,4*S*,5*S*),-5-((*R*)-1-iodopropan-2-yl)-4yl-(methoxymethoxy)-tetrahydrofuran-2-yl)-2-methoxyethyl)-2,2-dimethyl-1,3-dioxalane (3):

The synthesis of functionalized tetrahydrofuran fragment **3** was started from commercially available methyl (*S*)-(-)-3-hydroxy-2-methylpropionate **6**. The sequential of reactions involved in the synthesis of the key intermediate **19** was shown in Scheme 2.

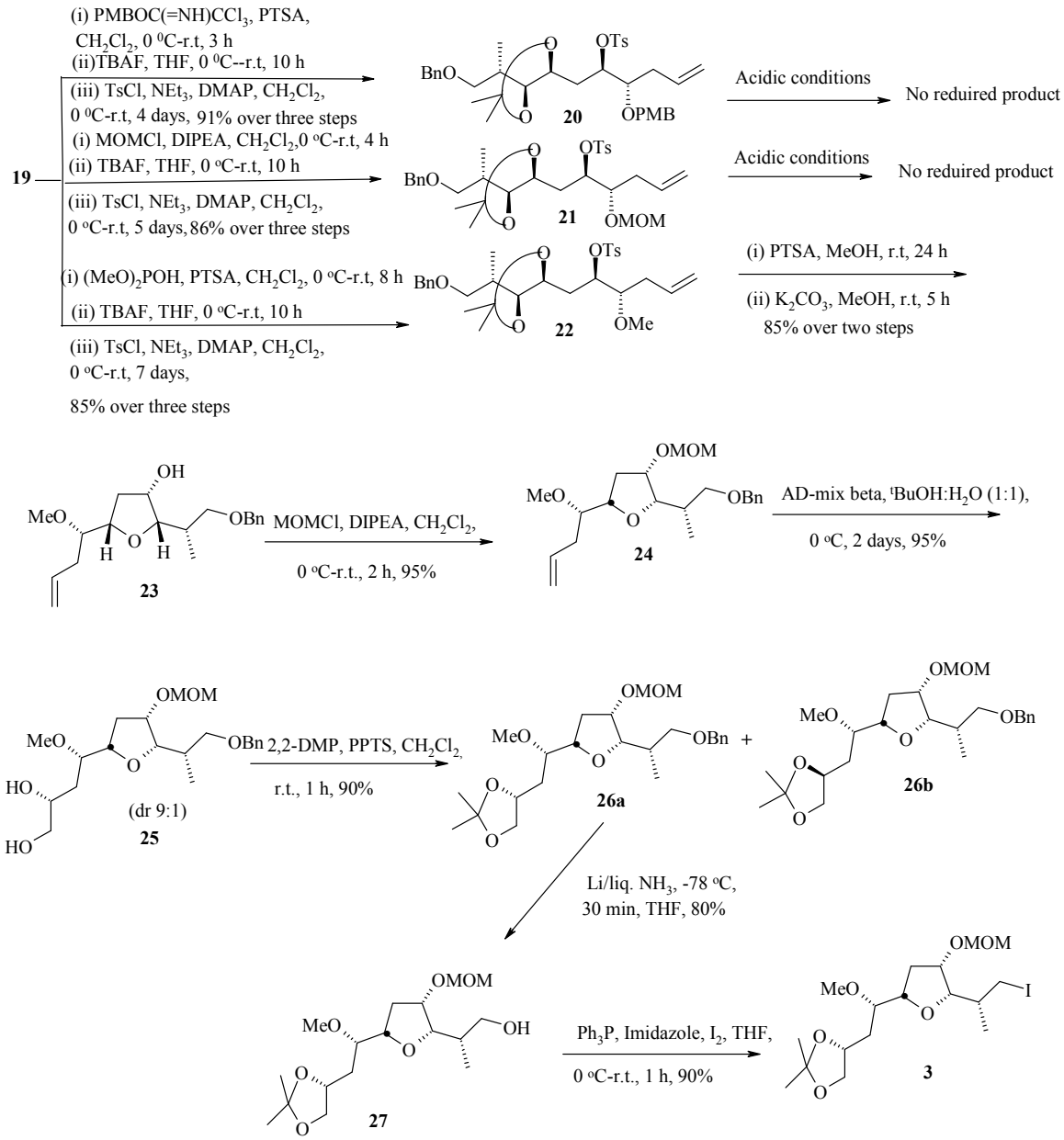
(*R,E*)-Ethyl 5-(benzyloxy)-4-methyl-2-enoate **7** (synthesized from Roche ester **6** in three steps)[6] was subjected to Sharpless asymmetric dihydroxylation with AD-mix-α, in ^{t}BuOH/H_2O (1:1) to provide diol **8** (90% yield with >95% de),[7] which was masked as its acetonoide **9** using 2,2-dimethoxy propane and catalytic PPTS in 95% yield (Scheme 2). Ester group in compound **9** was reduced using LAH to furnish alcohol **10** in 90% yield. Iodination of the resulting alcohol **10** gave iodo compound **11**, followed by coupling with vinylmagnesium bromide in the presence of CuI[8] afforded terminal alkene **12** in 75% yield. Dihydroxylation of **12** followed by $NaIO_4$ treatment gave aldehyde **13**, which without further purification was used for the next step. The zinc-mediated asymmetric addition of TMS acetylene to aldehyde **13** under Carreira's conditions[9] gave the propargylic alcohol **14** in good yield and with high diastereoselectivity (de >96%). Deprotection of TMS group using K_2CO_3 in methanol, followed by LAH reduction gave secondary allylic alcohol **15** in 90% yield over two steps. The secondary hydroxyl group in **15** was protected as TBDPS ether **16**. Dihydroxylation of terminal alkene **16** using OsO_4, NMO in acetone:H_2O (1:1) furnished diol **17** in 90% yield with high diastereoselectivity (9:1 dr).[10]



Scheme 2. Synthesis of intermediate **19**

The primary alcohol was selectively converted into iodo compound **18** by using TPP and *N*-iodosuccinamide in THF, which without purification was subjected to coupling

reaction[8] with vinylmagnesium bromide in the presence of CuI to afford homoallyl alcohol **19** in 75% yield over two steps.

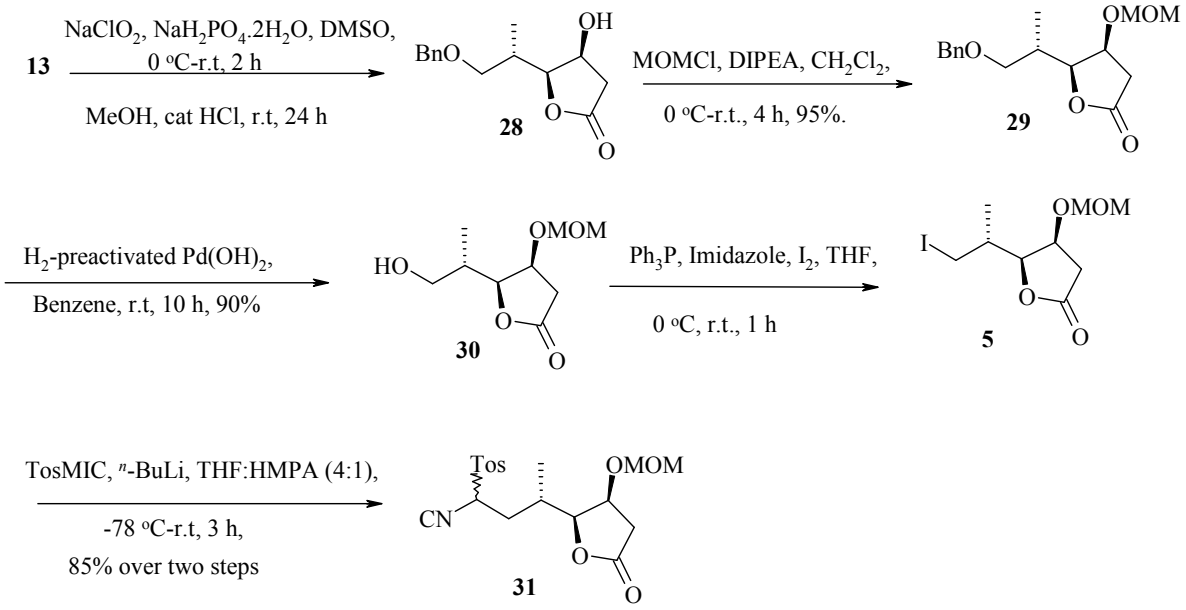


Scheme 3. Synthesis of iodo compound **3**

Our next task was to convert compound **19** in to functionalized 2,5-*syn* tetrahydrofuran **23** (Scheme 3). Accordingly, the secondary hydroxyl group in compound **19** was protected as PMB and MOM ether, followed by removal of TBDPS group and converted them into tosylates **20** and **21**. Acetonide deprotection in **20** and **21** could not be achieved under PPTS/MeOH conditions, instead, starting materials recovered back. The tosyl compounds **20** and **21** under several acidic conditions such as PTSA/MeOH, 3NHCl/MeOH, 60% CH_3COOH/MeOH, CAN/MeOH, $CeCl_3.7H_2O$/MeOH gave mixtures of compounds and could not be identified. However, change of protecting group into methyl ether **22**[11] gratifyingly, furnished the desired compound **23**. Thus compound **19** was converted into *O*-methyl compound by methylation using dimethyl phosphite, in the presence of PTSA followed by the removal of TBDPS group to furnish alcohol, which was subsequently tosylated to give **22** in 85% yield over three steps (Scheme 3). Next, acetonide in compound **22** was deprotected under acidic conditionsusing PTSA in MeOH followed by intramolecular backside displacement in the presence of K_2CO_3/MeOH to give 2,5-*syn* tetrahydrofuran **23**[12] in 85% yield over two steps. The free hydroxyl group in compound **23** was protected as MOM ether **24**. Next, an asymmetric dihydroxylation of **24** using AD-mix-β in ^{t}BuOH/H_2O (1:1) at 0 ^{o}C gave the diol **25** in 95% yield with 9:1 diastereomeric ratio.[13]

The 1,2-diol function in compound **25** was protected as its acetonide by 2,2-dimethoxy propane in the presence of PPTS and the resulting acetonides **26a** and **26b** were easily separable by column chromatography. Debenzylation of compound **26a** by using Li in liquid NH_3 gave primary alcohol **27**, which on exposure to TPP, iodine, and imidazole in THF afforded yellow colored compound **3** in 90% yield.

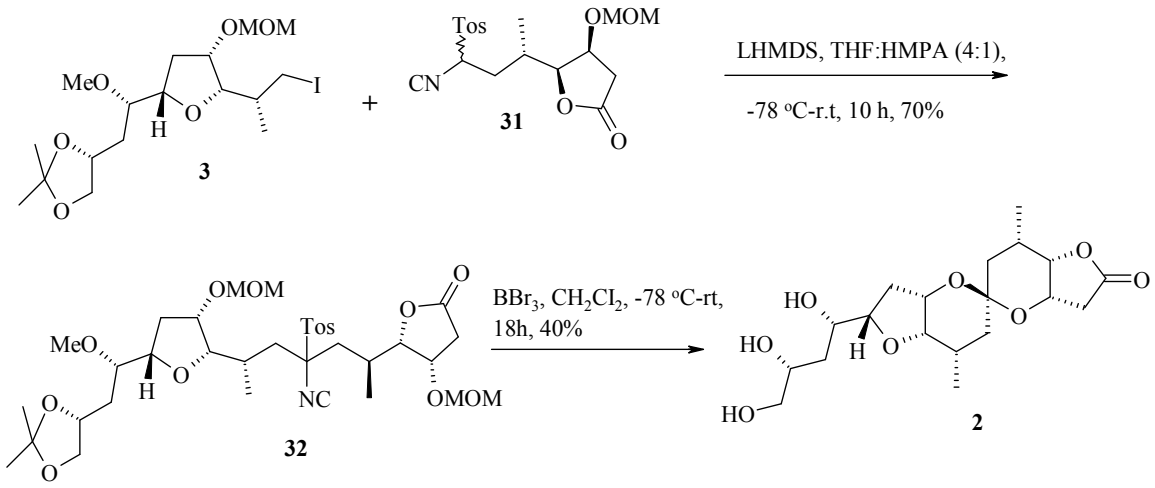
(4*S*,5*S*)-5-((*S*)-4-isocyano-4-tosylbutan-2-yl)-4-(methoxymethoxy)-dihydrofuran-2(*3H*)-one (31):



Scheme 4. Lactone fragment **31**

For the preparation of other alkylated fragment **31**, aldehyde **13** (As shown in Scheme 2) was chosen as starting material. Thus, oxidation of aldehyde **13** using sodium chlorite in DMSO under buffer conditions provided the corresponding carboxylic acid, followed by deprotection of acetonide as well as cyclization occured in one-pot by using catalytic concentrated HCl in methanol to furnish 5-membered lactone **28**[14] (Scheme 4). The resulting secondary hydroxyl group in **28** was protected as its MOM ether by using MOM-Cl and DIPEA to furnish **29**. Removal of the benzyl group by $Pd(OH)_2/H_2$ in benzene followed by treatment with iodine and TPP yielded iodo compound **5**. The crude alkyl iodid **5** on treatment with TosMIC **4** (tosyl methyl isocyanide) in the presence of *n*-BuLi in a mixture of THF:HMPA (4:1) afforded **31**[15] in 85% yield over two steps.

Synthesis of the C38-C54 segment (2) of halichondrin B



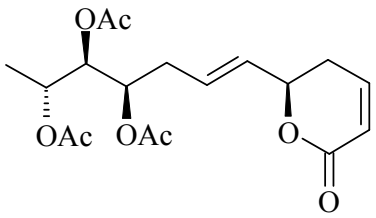
Scheme 5. Synthesis of the C38-C54 segment (**2**) of halichondrin B

Further alkylation of the anion generated from **31** using LHMDS in THF:HMPA (4:1) with iodo compound **3** gave di alkylated product **32**[15] (70%), which on treatment with BBr_3 in CH_2Cl_2[16] afforded our target spiroketal **2** comprising KLM and N rings containing ten chiral centers. The spectral and analytical data of the synthetic fragment **2** were in good agreement with the reported data of Burke *et al*[5a] approach, which completes the synthesis of C38-C54 segment of halichondrin B.

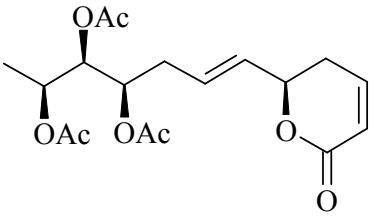
CHAPTER II: This chapter deals with the introduction, earlier synthetic approaches and present work of Synargentolide A.

Natural products containing α,β-unsaturated δ-lactone moiety exhibits various pharmacological properties such as cytotoxic, antitumor, antibacterial, antileukemic and antifungal activities. Synargentolide A **2** of this group was isolated in 1998 by Collett and co-workers from *Syncolostemon argenteus*[17] from the Ongoya forest in the Kwazulu-Natal midlands of South Africa. The basic structure of α-pyrone is that an α,β-unsaturated

δ-lactone connected to polyoxygenated chain. This type of moieties show interesting biological activities along with having many other relevant pharmacological properties.[18] The structure of synargentolide A was proposed to be **2** by Davies-Coleman and Rivett[17] on the basis of spectroscopic findings (^{1}H NMR, ^{13}C NMR, IR, HREI, HMQC and NOE findings) Mosher ester analysis, and acetonide formations. Alberto Marco *et al*.[19] synthesized the published structure of synargentolide A **2** and found that the spectroscopic data of the synthetic product did not match with those reported for the natural product and therefore stated that the proposed structure for the synargentolide A **2** differs from the actual one.



1. Revised structure of synargentolide A

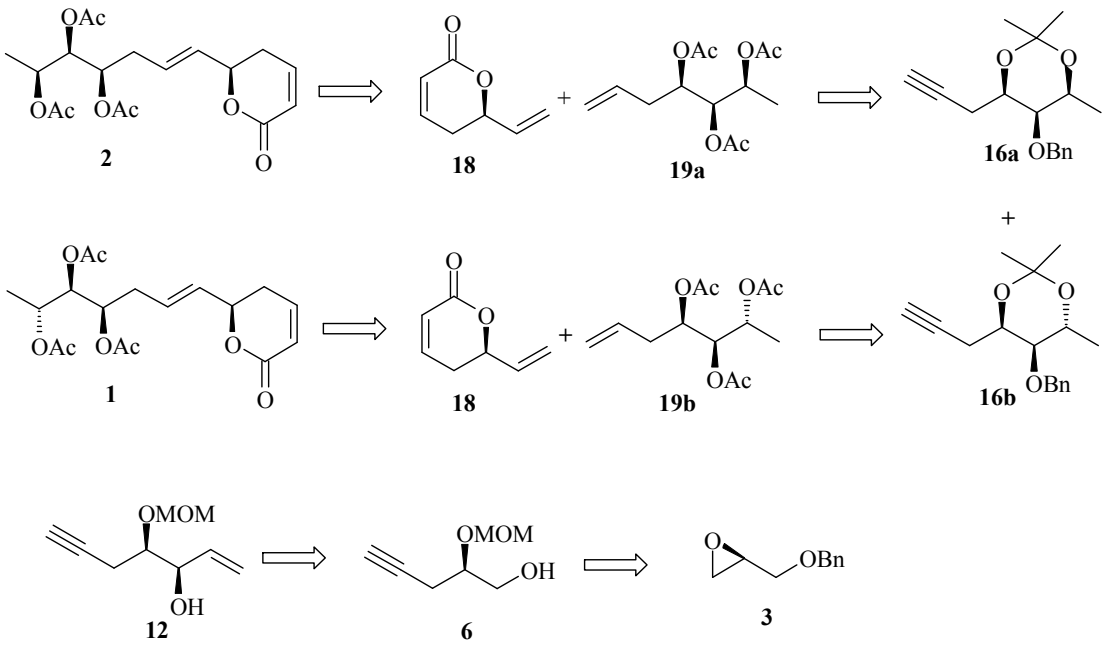


2. Published structure of synargentolide A

Figure 1

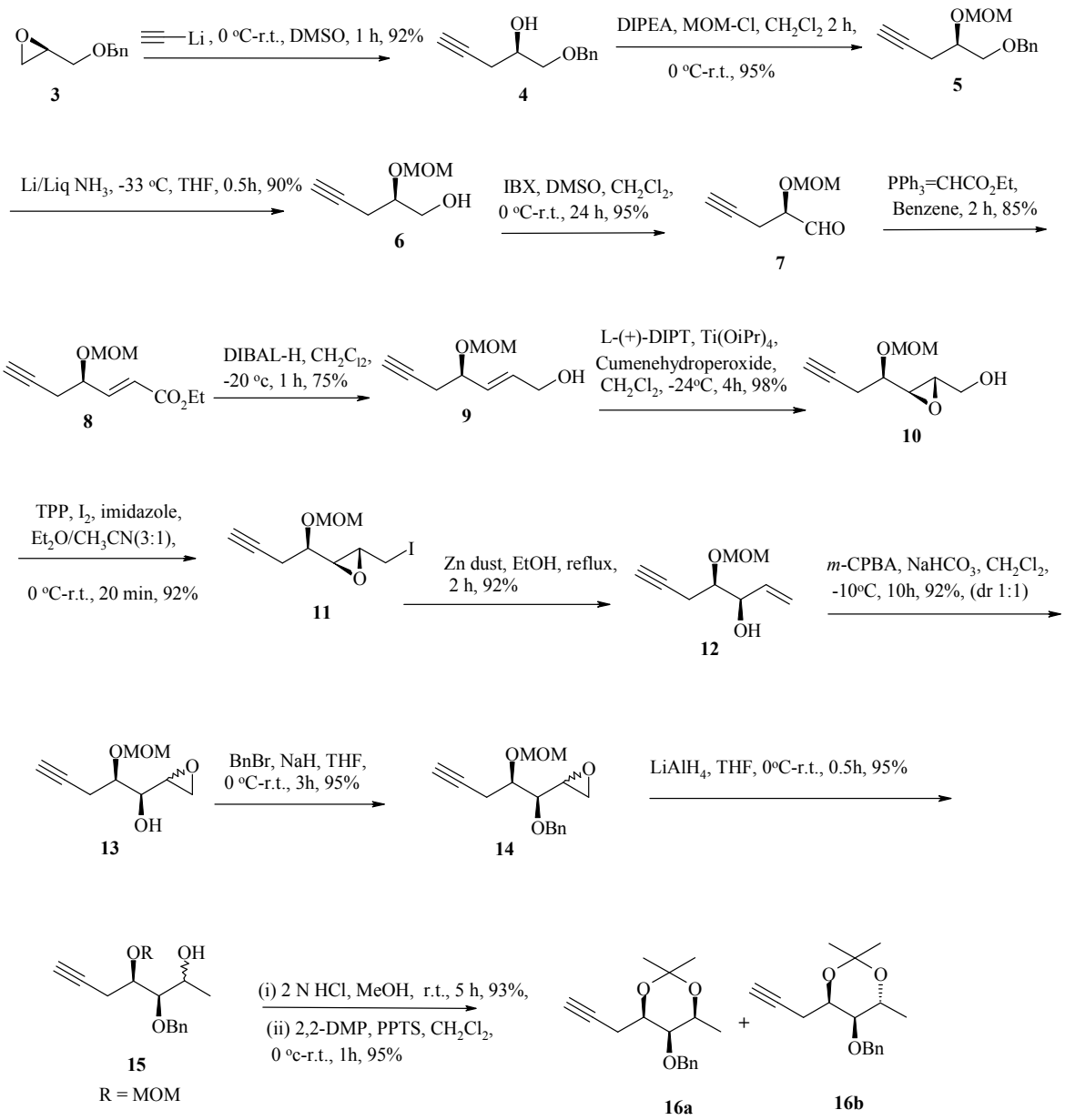
The retrosynthesis is outlined in Scheme 1 Which showed The target molecule **2** (published structure)[17] and **1** (revised structure) could be prepared independently by cross-metathesis reaction of **19a** and **19b** with vinyl lactone **18**. The substrates **19a** and **19b** inturn could be obtained from the commercially available (*R*)-benzyl glycidyl ether **3** by sequential reactions such as epoxide opening, Sharpless asymmetric epoxidation, epoxide opening and formation of epoxide and its reductive opening.

The synthesis began with the commercially available (*R*)-benzyl glycidyl ether **3** (Scheme 2).



Scheme 1. Retrosynthetic analysis for the published and revised structures of synargentolide A

Accordingly the ring opening of epoxide **3** with lithium acetylide ethylene diamine complex provided chiral homopropargyl alcohol **4** in 92% yield. The secondary hydroxyl group in compound **4** was protected as its MOM ether **5** using MOMCl and Hunig's base and the subsequent removal of benzyl group furnished alcohol **6**. Oxidation of **6** using IBX in DMSO/DCM gave the corresponding aldehyde **7**, which was subjected to Wittig reaction with the stable ylide to afford α,β-unsaturated ester **8**.

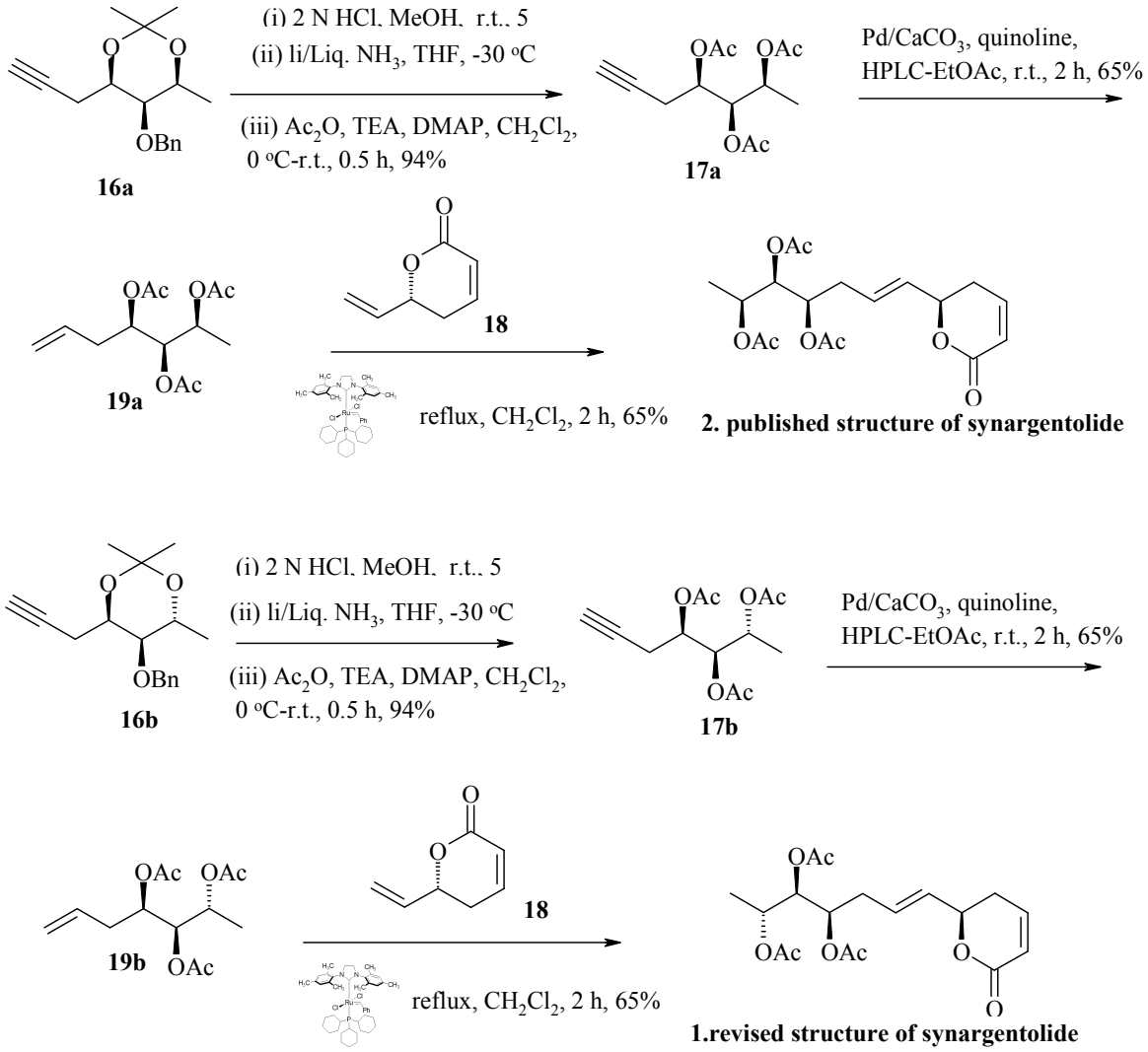


Scheme 2

After reduction of **8** to allylic alcohol **9** (75%) using DIBAL-H, Sharpless asymmetric epoxidation delivered epoxy alcohol **10** in 98% yield as a single diastereomer, which was elaborated to allylic alcohol **12** by an iodination/reductive ring opening sequence.

Epoxidation of the terminal double bond in **12** using *m*-CPBA provided an inseparable mixture of epoxy alcohol **13** in a ratio of 1:1 (92% combined yield). After protection of the secondary hydroxyl group as benzyl ether, the resulting compound **14** was treated with LAH to give an alcohol again as an inseparable mixture (**15**). The MOM group was deprotected in compound **15** and a subsequent 1,3-diol functionalized compound was protected as its acetonide by 2,2-dimethoxypropane in the presence of PPTS and the resulting acetonides **16a** and **16b** were easily separable by flash chromatography. In order to confirm the relative configuration of 1,3-acetonides **16a** and **16b**, ^{13}C NMR chemical shifts were studied. The two methyl groups in the acetonide part in **16a** resonated at 19.0 and 29.6 ppm indicating that the two hydroxyl groups are in a 1,3-syn orientation and further substantiated by the appearance of the quaternary carbon in the down-field region (98.8 ppm).[20] In contrast, for the acetonide derivative **16b** signals were found at 24.8 and 23.8 ppm and quaternary carbon at 100.7 ppm, which were characteristic for the methyl groups in the acetonide part of 1,3-anti diol.[20]

To determine the correct absolute configuration of natural synargentolide A, both isomers of synargentolide A **1** and **2** were synthesized by the following steps from **16a** and **16b** as shown in Scheme 3. Removal of benzyl and acetonide groups, followed by acetylation of the three hydroxy groups was performed to provide **17a** in 94% yield (Scheme 3). The terminal triple bond was reduced partially to double bond under Lindlar's conditions to afford **19a**. Finally, the cross-metathesis reaction between **19a** and vinyl lactone **18**[21] was smoothly performed using Grubbs' second generation catalyst to give the published structure of synargentolide A **2** (Fig. 1). This did not turn out to be identical with the natural product but matched with the synthesized product.[19]



Scheme 3

In a similar fashion, synthesis of **1** was commenced from **16b** (Scheme 3) independently repeating the steps as in the case of **2** and the target molecule **1** was obtained in good yield. The spectral properties (Fig. 2) and optical rotation of the synthetic compound **1** were found to be identical with those published for the natural synargentolide A **2** $[\alpha]_D^{25}$: +36.5 (c 1, $CHCl_3$), lit.[17] $[\alpha]_D^{27}$: +40 (c 1.1, $CHCl_3$). Therefore, the structure of natural product stands revised to be of **1**.

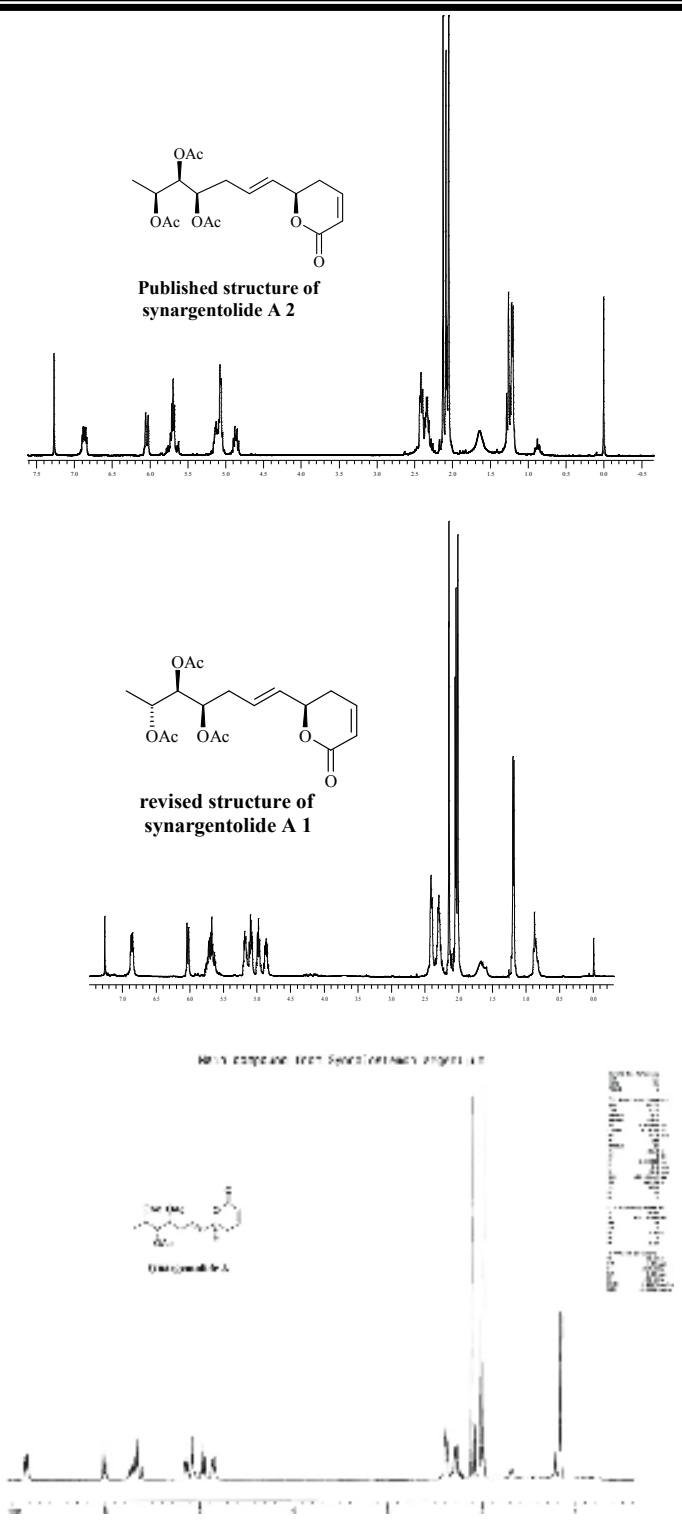
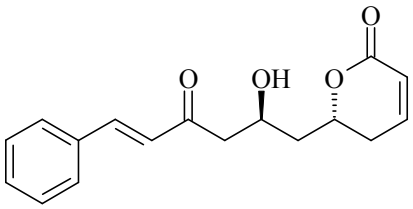


Figure 2. Comparison of the δ 0.0-7.0 range of the ^{1}H-NMR spectra of the synthetic lactones (Alberto Marco *et al*)[19] and **1** (synargentolide A **1** prepared by us) with that of natural synargentolide A (Davies-Coleman and Rivett *et al*).

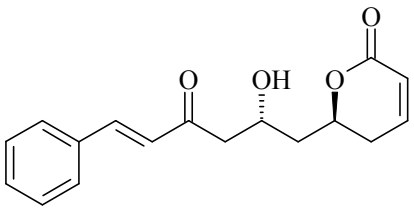
Chapter III: Total synthesis of Kurzilactone, epi-Kurzilactone and (+)-Anamarine.

Section A: This section describes the introduction, earlier synthetic approaches, present work of (5*R*,7*S*)-Kurzilactone and its enantiomer.

The α,β-unsaturated δ-lactone core unit (or 5,6-dihydro-2-(2*H*)-pyranone moiety) is present in various natural products.[22,23] These compounds display[24] important biological activities some exhibit antitumoral activity, while others are tumor promoting. Moreover, it has been shown that the unsaturated moiety plays an essential role in the biological activity, due to its potentiality to act as a Michael acceptor in the presence of protein functional groups. (5*R*,7*S*) Kurzilactone **1**[25] is one such lactone isolated from the leaves of *Cryptocarya kurzii*, a plant that is indigenous to MalaysiaKurzilactone exhibits a marked cytotoxicity against the KB human carcinoma cell line (IC_{50} = 1 mg mL^{-1}). Initially, the stereogenic centers bearing hydroxy groups in the side chain were assigned a *syn*-relationship through an NMR experiment, but a corrected *anti*-relationship with a (5*R*,7*S*) configuration of the C(5) and C(7) stereogenic centers was later assigned on the basis of a total synthesis[26]



1. (5*R*,7*S*)-Kurzilactone

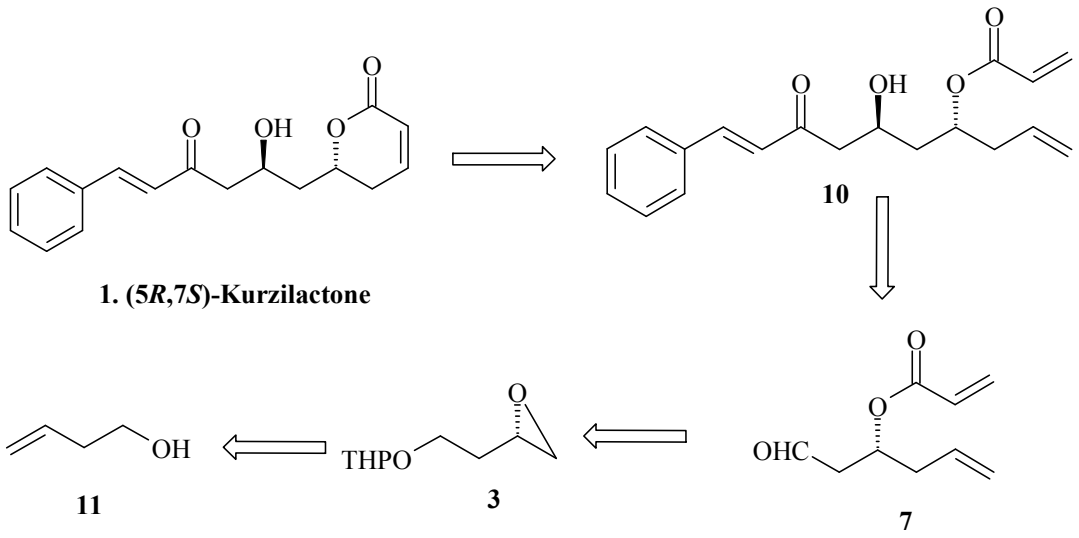


2. (5*S*,7*R*)-Kurzilactone

Figure 1

Retrosynthetic analysis revealed that the target compound **1** could be obtained from **10** by olefin ring closing metathesis using Grubbs' catalyst 1st generation. The compound **10**, inturn could be obtained from aldehyde compound **7** by Mukaiyama aldol

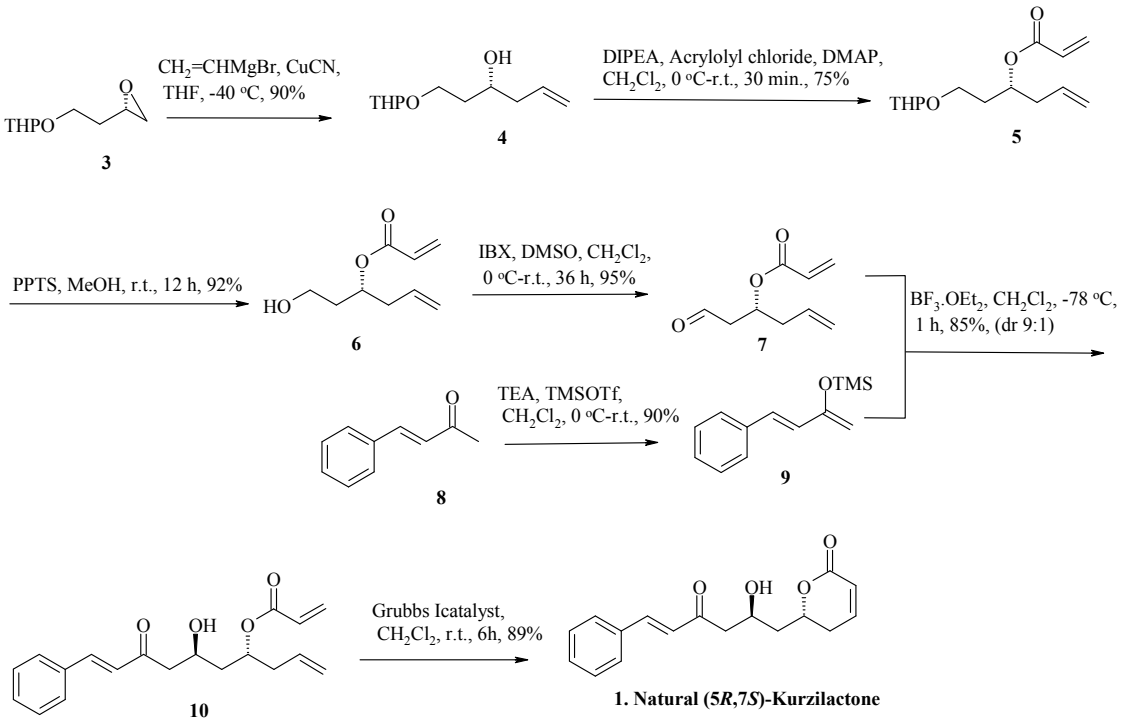
reaction. The aldehyde compound **7** prepared from chiral epoxide **3.** Preparation of chiral chiral epoxide **3** was achieved from commercially available homoallylic alcohol **11** (Scheme 1).



Scheme 1. Retrosynthetic analysis for the (5*R*,7*S*)-Kurzilactone

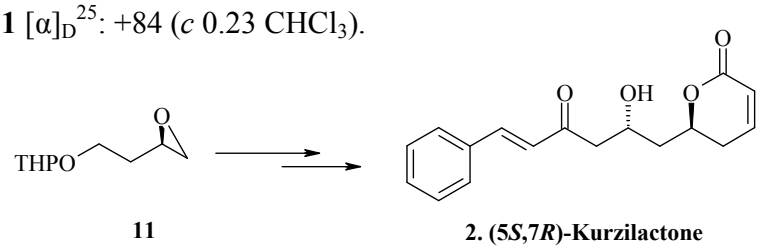
We began our synthesis of (5*R*,7*S*)-Kurzilactone **1** (Scheme 2) by treating the known epoxide[27] **3** with vinylmagnesium bromide in the presence of copper(I) cyanide in tetrahydrofuran at –40 °C to give the homoallylic alcohol **4** in a good yield. Alcohol **4** was esterified with acryloyl chloride in the presence of *N*,*N*-diisopropylethylamine and a catalytic amount of 4-(dimethylamino) pyridine to give the acryloyl ester **5** in 75% yield. Removal of the tetrahydropyranyl group, followed by oxidation of the resulting alcohol **6** with 2-iodobenzoic acid (IBX), gave the aldehyde **7**. The boron trifluoride diethyl etherate complex mediated Mukaiyama aldol reaction[28] of the aldehyde **7** with the trimethyl-silyl enol ether **9** derived from (3*E*)-4-phenylbut-3-en-2-one (**8**) gave the aldol adduct **10** in 92% yield with good diastereoselectivity (90:10 *anti*:*syn*). Subsequent ring-closing metathesis of the ester in the presence of Grubbs' first-generation catalyst in

dichloromethane at room temperature for six hours gave the natural (5*R*,7*S*)-Kurzilactone **1** in 89% yield. The optical rotation of the synthetic product (5*R*,7*S*)-Kurzilactone **1** $[\alpha]_D^{25}$: +80 (*c* 0.2, $CHCl_3$) matched the reported value.[26]



Scheme 2

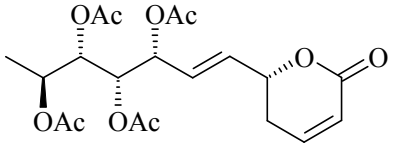
The (5*S*,7*R*)-Kurzilactone **2** is enantiomer of natural (5*R*,7*S*)-Kurzilactone **1**[29] which was synthesized in an identical manner, but starting from the known epoxide.[27](**11**) (Scheme 3). The optical rotation {$[\alpha]_D^{25}$: –80 (*c* 0.15 $CHCl_3$)} of the synthetic product (5*S*,7*R*)-Kurzilactone **2** was found to be opposite to that reported for natural (5*R*,7*S*)-Kurzilactone **1** $[\alpha]_D^{25}$: +84 (*c* 0.23 $CHCl_3$).



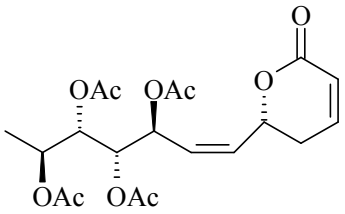
Scheme 3

Section B: This section describes the introduction, earlier synthetic approaches and present of (+)-anamarine via cross-metathesis protocol**.**

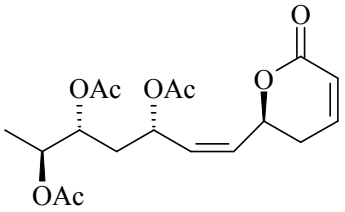
(+)-Anamarine (**1**)[30] is a member of the polyoxygenated 5,6-dihydro-2*H*-pyran-2-one (α,β-unsaturated δ-lactone)-containing natural products family isolated from the flowers and leaves of a Peruvian Hyptis (Figure 1). Other members of the α,β-unsaturated δ -lactone family are spicigerolide **2**,[31] hyptolide **3**[32] and synrotolide diacetate **4**[33] isolated from the Hyptis and Syncolostemon and related genera of the family Lamiaceae. These lactones have been found to exhibit antibacterial, antifungal, as well as cytotoxicity against human tumor cells.[34]



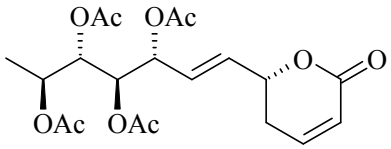
1. (+)-anamarine



2. (-)- Spicigerolide



3. Hyptolide

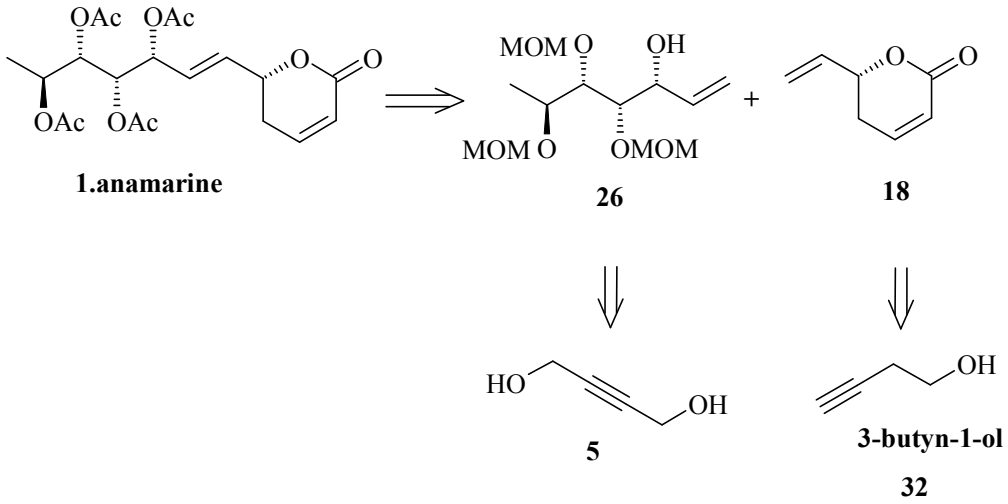


4. (-)-Synrotolide diacetate

Figure 1

In addition, 6-substituted-α,β-unsaturated-δ-lactones have been reported to inhibit HIV protease,[35] induce apoptosis,[36,37] and have proven to be anti-leukemic,[38] along with having many other relevant pharmacological properties.[18] Thus, these lactones have attracted the attention of synthetic chemists.

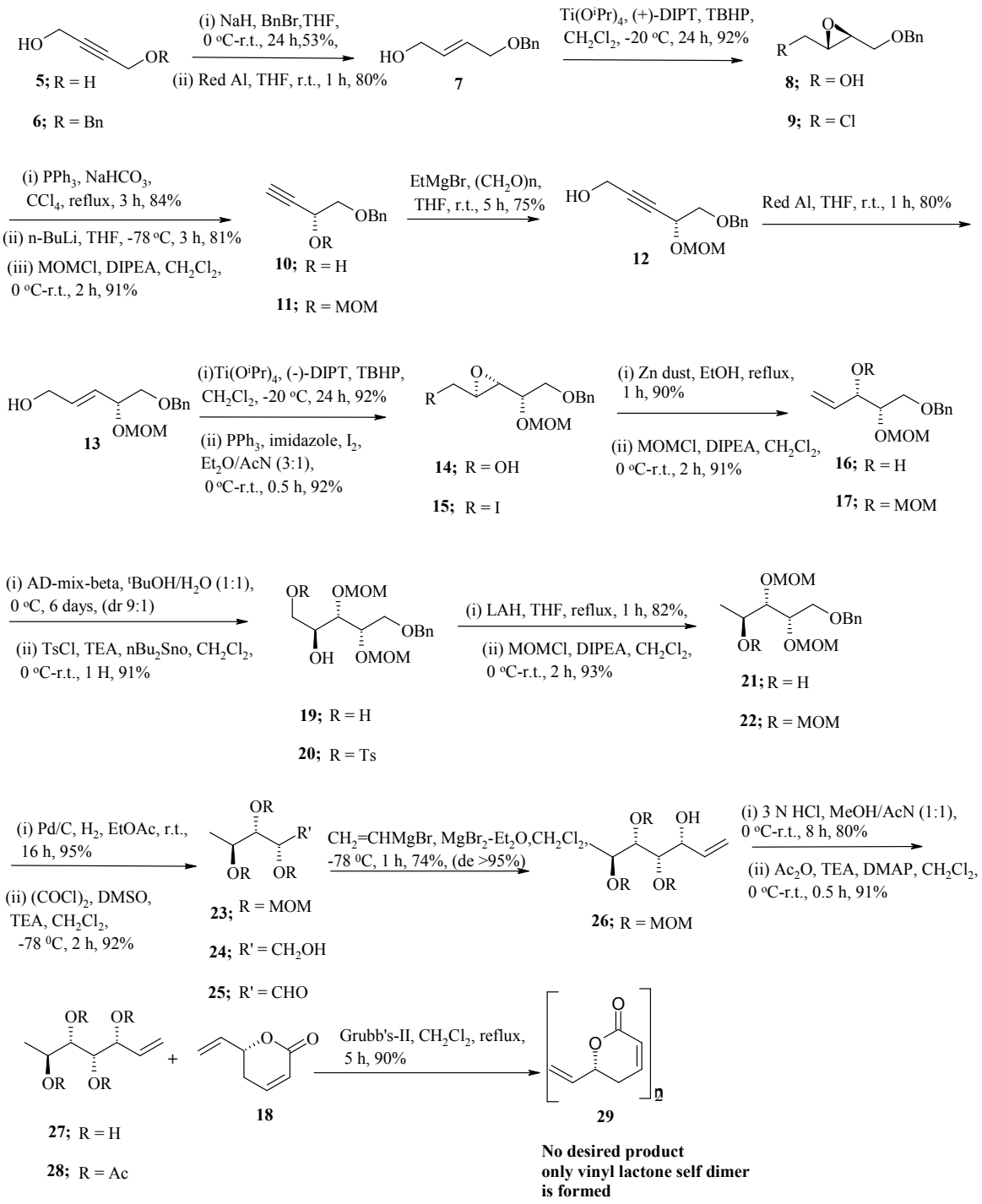
Retrosynthetic analysis reveals that the target compound **1** (Scheme 1) can be obtained by cross-metathesis reaction of olefin **26** and vinyl lactone **18**. The substrate **26** in turn could be made from the commercially available 2-butyn-1,4-diol **5** by sequential reactions. While, the vinyl lactone **18**[21] is accessible from 3-butyn-1-ol **32**.



Scheme 1. Retrosynthetic analysis for (+)- Anamarine.

Accordingly, the synthesis of **1** starts with the readily available 2-butyn-1,4-diol **5** (Scheme 2) that was subjected to selective monobenzylation to afford the propargyl alcohol **6**. Partial reduction of the triple bond using LAH gave low yields of product along with an unknown by-product. However, using Red-Al in THF, the problem was solved and the required allylic alcohol **7** was obtained in a very good yield (80%). The alcohol **7** was subjected to Sharpless asymmetric epoxidation [(+)-DIPT/Ti(O^iPr)$_4$/TBHP/ −20 ^oC, 24 h, 92%] to afford epoxy alcohol **8**, which was converted into propargylic alcohol **10** by a two-step process; first by converting to chloro epoxy compound **9** which on elimination using ^{n}BuLi afforded the propargylic alcohol **10** (81% yield over two steps). The hydroxyl group in **10** was protected as its MOM ether

(MOMCl/DIPEA/CH_2Cl_2/0 ^oC to rt, 2 h, 91%) to afford **11**. The MOM ether **11** was treated with Grignard reagent prepared from ethyl bromide and magnesium followed by quenching with para formaldehyde in dry THF to afford **12** in 75% yield. In order to get the *trans*-allyl alcohol, compound **12** was treated with Red-Al in THF at rt, which reduced the alkyne to the desired *trans*-olefin **13** in 80% yield. In the next step, olefin **13** was subjected to Sharpless asymmetric epoxidation using (−)-DIPT, $Ti(O^iPr)_4$, and TBHP to furnish the desired epoxy alcohol **14**, which was converted into the corresponding epoxy iodide **15** in 92% yield. Compound **15** on refluxing in ethanol in the presence of Zn dust eliminated to afford allylic alcohol **16** and the resulting alcohol was protected as MOM ether **17**. Asymmetric dihydroxylation[39] of **17** using AD-mix-β in $^tBuOH/H_2O$ (1:1) at 0 ^oC gave the diol **19** in 90% yield (dr 9:1). Selective conversion of the primary hydroxyl group of **19** into a tosylate was carried out using tosyl chloride in the presence of TEA and nBu_2SnO in CH_2Cl_2 to give **20** in 91% yield, which was reduced to the methyl compound by using $LiAlH_4$ in THF in 82% yield. The secondary alcohol was protected as its MOM ether **22** and the benzyl group was removed using Pd/C, H_2 in EtOAc to afford the primary alcohol **23**, which was converted into the corresponding aldehyde **25** under Swern oxidation conditions. To create a fourth stereogenic center with the required stereochemistry, a chelating controlled vinyl Grignard reaction[40] was performed. Thus, adding a solution of vinylmagnesium bromide in THF to the complex formed between **25** and 1 eq of magnesium bromide etherate in CH_2Cl_2, provided the chelation-controlled product **26** in excellent yield and with high (>95%)

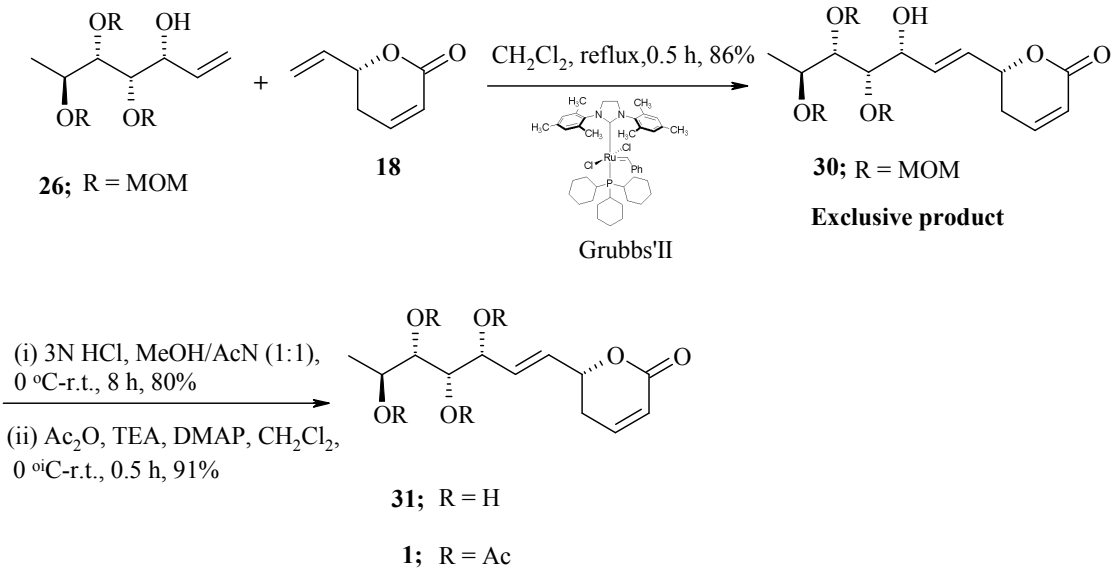


Scheme 2

diastereofacial selectivity. The three MOM groups were removed and subsequently protected as acetates to give tetraacetate derivative **28**, which was expected to give

directly the target molecule **1** when subjected to cross-metathesis reaction with vinyl lactone **18** using Grubbs' II generation catalyst. But, this reaction failed to give the desired target **1**, instead it gave exclusively the dimer of vinyl lactone **29** (Scheme 2).

However, the tri MOM derivative **26** underwent CM reaction smoothly with vinyl lactone **18** using Grubbs' II generation catalyst to yield the desired lactone dimer **30** (86%) exclusively (Scheme 2).



Scheme 3

Subsequent removal of MOM groups in **30** using 3 N HCl in MeOH/CH_3CN (1:1), at 0 ^oC afforded tetrahydroxy derivative **31**. Acetylation of **31** with acetic anhydride in the presence of TEA and DMAP furnished the target lactone, anamarine **1** in 91% yield. The spectral data of the synthetic compound matched with the literature values.[41]

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CHAPTER I

Section A

Introduction, previous synthetic approaches to C38-C54 spiroketal segment of Halichondrin B

INTRODUCTION:

The term macrolide was introduced in 1957 by Woodward to denote the class of substances produced by *Streptomyces* species containing a macrocyclic lactone ring. The macrolide class is large and structurally diverse. Macrolides are produced by the fermentation of microorganisms and/or are found in marine invertebrates, such as sponges, bryozoa, or marine cyanobacteria, and in dinoflagellate species belonging to the genera *Amphidinium*, *Gambierdiscus*, *Prymnesium,* and *Protoceratium*. The polyether and macrolide antibiotics have been the focus of a great deal of attention since the 1950's, when the first of these metabolites were isolated. Around 80 polyethers[1] and 100 macrolides[2] have now been characterized. The polyether antibiotics, as a class, effect antibacterial activity[3] by complexing to the alkali-metal cations within cells. As a result, the transmembranal ionic flux that is necessary to sustain the integrity of the bacterial cells is disrupted. The macrolides,[4] on the other hand, bind selectively to bacterial ribosomes and disrupt the biosynthesis of proteins ***de novo*** within the cell. Despite their quite distinct modes of action and apparent structural diversity, the polyether and macrolide antibiotics are related in that they are all products of Actinomycetes ; their aglycon moieties have a polyketide origin, being constructed from C_2 (acetate), C_3 (propionate), and C_4 (butyrate) subunits. These two broad structural groups arise by the differential elaboration of pre-assembled polyoxygenated fatty-acid derivatives. The polyethers are longchain polyfunctional carboxylic acids, possessing characteristic tetrahydrofuran and tetrahydropyran ring systems, whereas the macrolides are elaborated twelve-, fourteen-, and sixteen membered macrocyclic lactone ring systems. The mechanistic similarities of construction of the aglycon and the structural correlations which exist between the aglycons of these antibiotics strengthen the hypothesis that the macrolides and polyethers share a common evolutionary origin.

Among several macrolides, most of them are polymethylated, polyhydroxy(methoxy)lated, or polyether compounds, whilst a few embed contiguous isoxazole units. In general, such compounds exhibit potent biological activities. Polymethylated and polyhydroxy(methoxy)lated marine macrolides comprise antitumoral compounds such as amphidinolide **A**[5a] and C[5b] isolated from cultures of the symbiotic dinoflagellate *Amphidinium* sp. and misakinolide **A** isolated from the marine sponge

Theonella sp.,[5c] antifungal compounds such as swinholide **A** isolated from the marine sponge *Theonella swinhoei*,[5d] and ichtyotoxic compounds such as latrunculin **A** and **B** isolated from the sponge *Latrunculia magnijica*.[5e] Polyether macrolides are represented by antifungal compounds such as goniodomin **A** isolated from the blooming dinoflagellate *Goniodoma pseudogoniaulax*,[6a] by diarrhetic toxins such as pectenotoxin isolated from the marine scallop *Patinopecten yessoensis* but produced by the dinoflagellate *Dinophysis fortii*,[6b] and by antitumoral compounds such as bryostatin 1 isolated from the bryozoan *Bugulu neritinu*.[6c] Isoxazole-bearing macrolides are represented by halichondramide, an antifungal compound isolated from both the sponge *Hulichondriu* sp.[7a] and the nudibranch *Hexabranchus sanguineus*,[7b] by ulapualide **A** and B, antitumoral compounds isolated from eggs of the nudibranch *Hexabranchus sanguineus*,[7c] and, finally, by the structurally related kabiramide C isolated from eggs of an unidentified nudibranch.[7d]

Some of the marine animal and terrestrial plant anticancer constituents are discussed below.

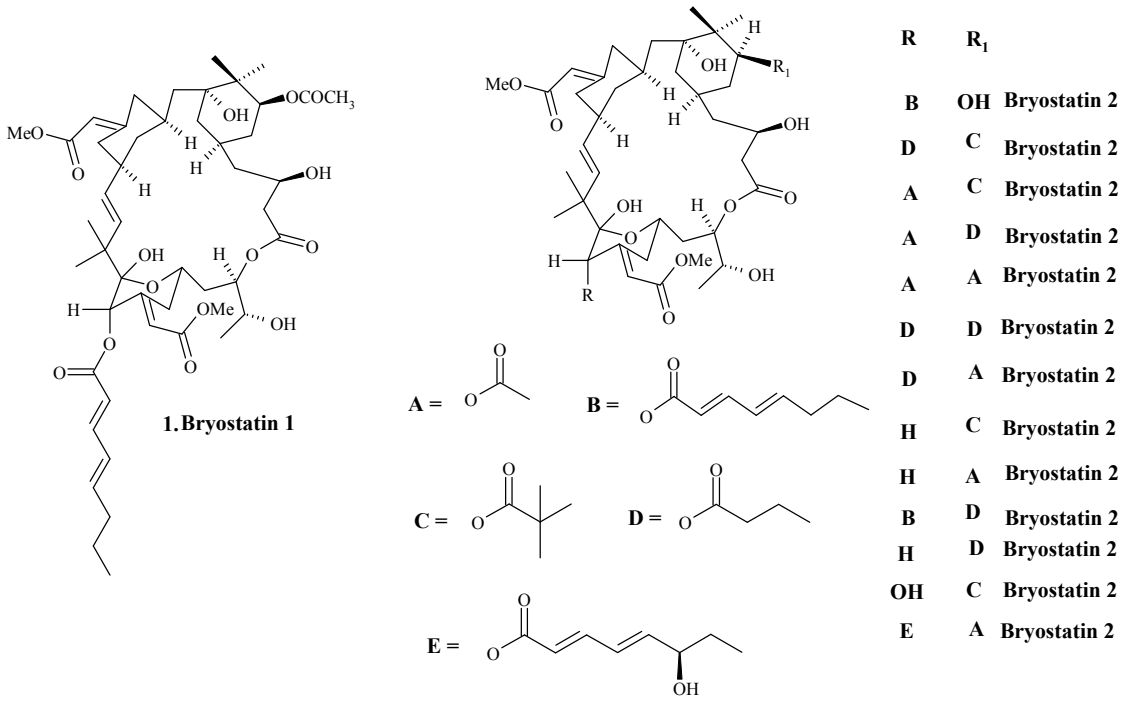
Bryostatins:

Discovery [8] of the bryostatin series of marine Bryozoa constituents represents an especially important advance for the future and bryostatin 1 **(1)** has been undergoing a very successful series of human Phase I clinical trials for over two years.[9-11] The considerable therapeutic potential of bryostatin 1 **(1)** is based in part on its ability to influence protein kinase C which mediates one arm of a major signal transduction pathway involving lipophilic secondary messengers.

bryostatin 1 **(1)** has been found to cause differentiation of B-chronic lymphocytic leukemia in an unprecedented fashion,[12] and be capable of converting leukemia cells ***in vitro*** to those typical of hairy cell leukemia which is curable.[13] Successful extension of these experiments to the clinic may result in the first really curative technique for human chronic lymphocytic leukemia. The potential for treating chronic myelogenous leukemia patients is also very promising.[14,15] Bryostatin 1 **(1)** was found capable of inducing macrophage-like differentiation in maturing CML cells.[15] Most importantly, bryostatin l was dramatically effective against cells taken from patients in the CML blast phase. Against a line of acute lymphoblastic leukemia, bryostatin 1 **(1)** was found capable of

inducing further differentiation along the B-cell lineage.[16,17] Interestingly, bryostatin 1 has been found to potentiate ARA-C apoptosis or programmed cell death, and this combination looks very promising for clinical evaluation.[18,19,20,21] Another facet of the activity of bryostatin 1 against lymphomas involves its ability to convert a high-grade lymphoma cell line 20 an intermediate grade, again offering clinical potential.[22]

Another nice advance that will eventually be tested in the clinic involves its use in adoptive immunotherapy.[23] With an intradermal murine tumor model, the adoptive transfer of bryostatin 1-stimulated DLN cells induced regression of established liver and pulmonary metastases resulting in curative responses.[23] In other murine experiments, bryostatin 1 has proved to be dramatically (1 pg/mouse) effective against lethal whole body irradiation producing a *70%* survival rate that increased to about *80%* using coadministered GM-CSF.[24]



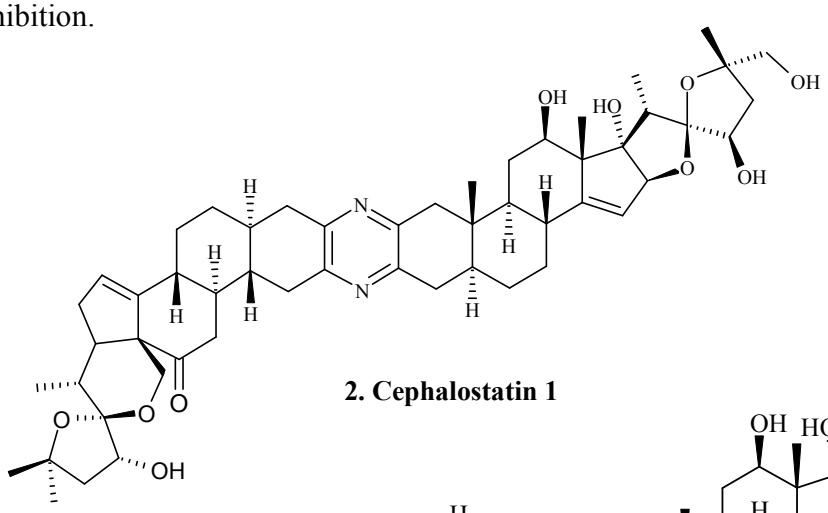
R	R_1	
B	OH	Bryostatin 2
D	C	Bryostatin 2
A	C	Bryostatin 2
A	D	Bryostatin 2
A	A	Bryostatin 2
D	D	Bryostatin 2
D	A	Bryostatin 2
H	C	Bryostatin 2
H	A	Bryostatin 2
B	D	Bryostatin 2
H	D	Bryostatin 2
OH	C	Bryostatin 2
E	A	Bryostatin 2

Figure 1

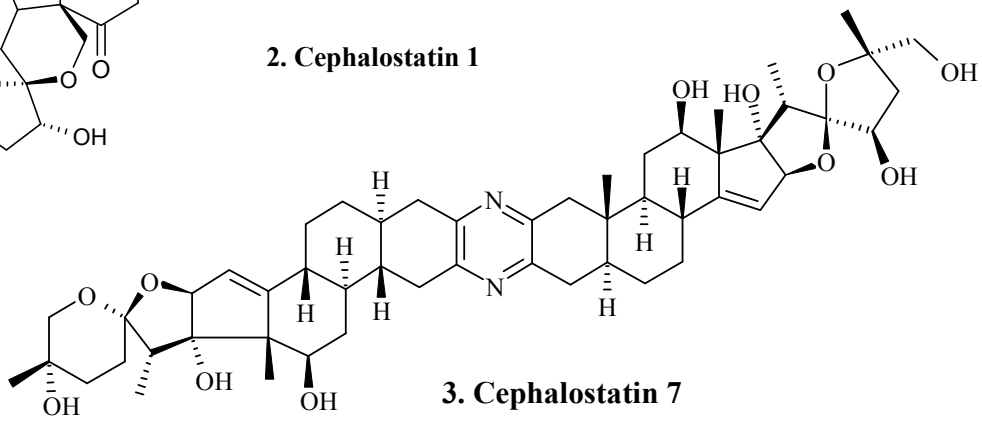
Cephalostatins:

Cephalostatins as constituents of the African marine worm ***Cephalodiscus gilchristi.*** Cephalostatin 7 **(3)**, especially, displayed remarkable potency with TGI values

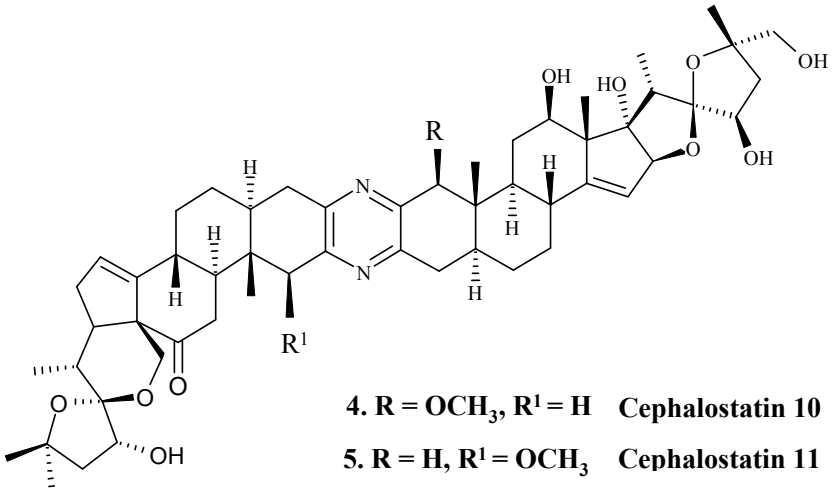
to pg/ml against a number of human cancer cell lines such as those derived from non-small cell lung cancer, small cell lung cancer, renal, brain and leukemias.[25] The structural determinations of cephalostatins 1 **(2)** and 7 **(3)**, cephalostatins 10 **(4)** and 11 **(5)**, cephalostatins 12[26] **(6)** and 13 **(7)**, cephalostatins 14 **(8)** and 15[27] **(9)** were difficult but the extraordinary and selective effects against various human cancer cell lines in the NCI panel have been very rewarding. Presently, several of the newer cephalostatins appear to compete quite favorably with cephalostatins 1 **(2)** and 7 **(3)** in terms of cancer cell growth inhibition.



2. Cephalostatin 1

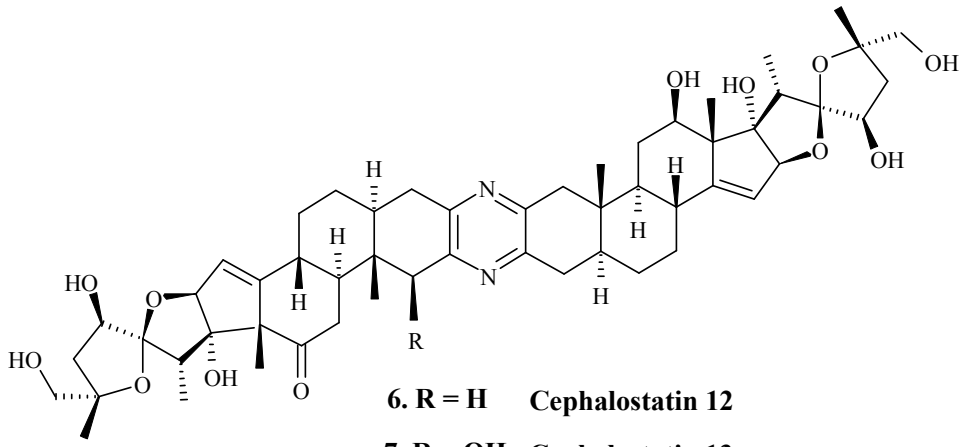


3. Cephalostatin 7



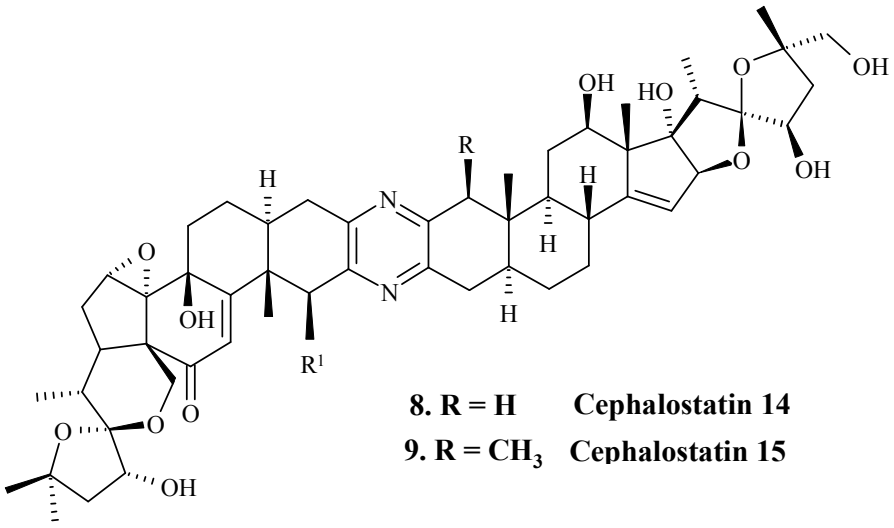
4. R = OCH_3, R^1 = H Cephalostatin 10

5. R = H, R^1 = OCH_3 Cephalostatin 11



6. R = H Cephalostatin 12

7. R = OH Cephalostatin 13



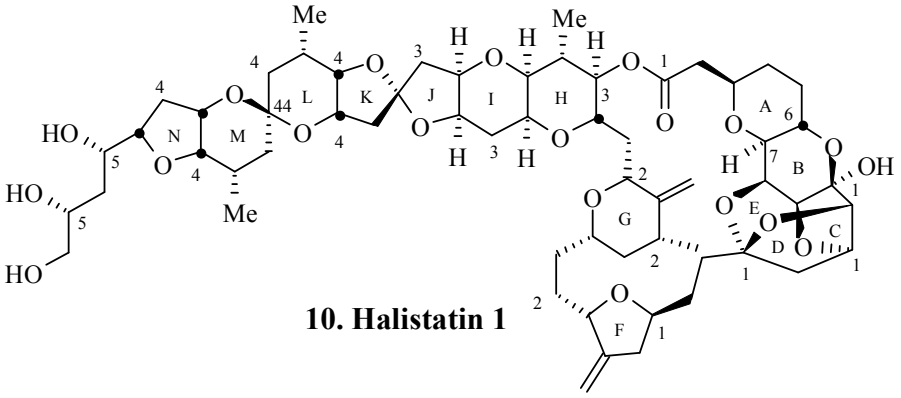
8. R = H Cephalostatin 14

9. R = CH_3 Cephalostatin 15

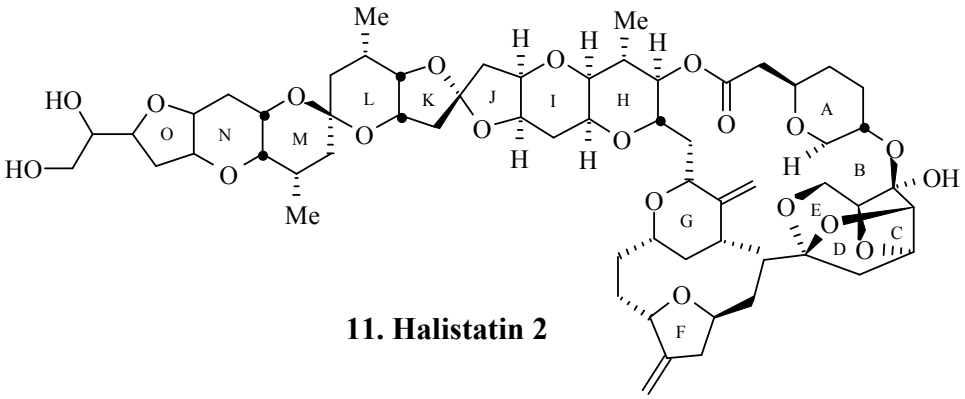
Figure 2

Halistatins

Halistatin 1[28] **(10)** and the related halistatin 2[29] **(11)** were found to be exceptionally potent antineoplastic constituents of two different marine sponges located in The Republic of Comoros. Against the NCI human cancer cell line panel, the negative $logl_{10}$ GI50 values range to over nine and represent an excellent selection of human cancer types. Briefly stated, the halistatins offer considerable promise for improving future human cancer treatment.



10. Halistatin 1

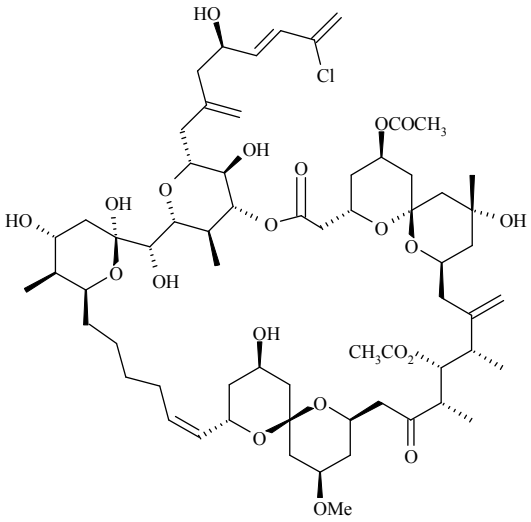


11. Halistatin 2

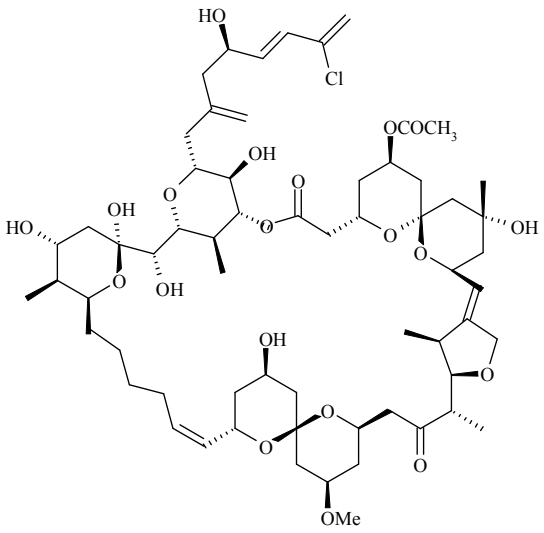
Figure 3

Spongistatins:

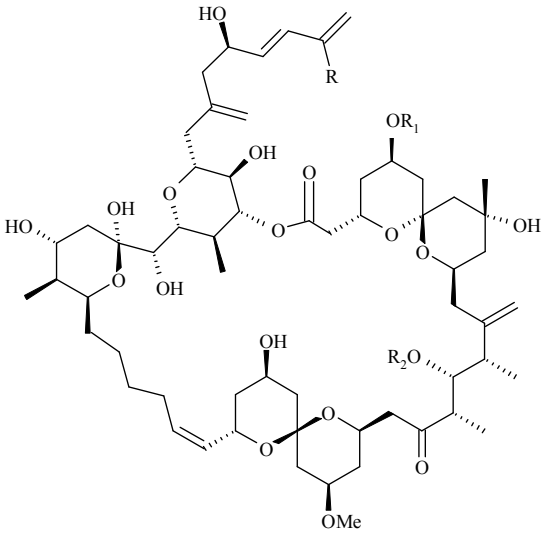
Spongistatin 1[30] **(12)** discovered in a ***Spongia sp.*** Spongistatin 1 plays a very important role in clinical features. Spongistatins were extracted from the bright red marine sponge ***Spirastrella spinispirulifera*** collected off the south coast of Africa. Spongistatins 1 **(12)** and 5 **(13)** are closely correlated to the important class of microtubule-interactive antimitotics. Among the major objectives for continued research with the spongistatins will be completing an X-ray crystal structure determination to establish the stereochemistry at each asymmetric center and the absolute configuration.



12. Spongistatin 1



13. Spongistatin 5



R = H, R_1 = R_2 = $COCH_3$ **Spongistatin 2**

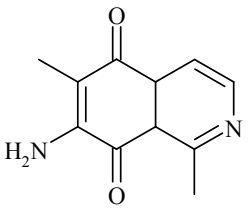
R = Cl, R_1 = H, R_2 = $COCH_3$ **Spongistatin 3**

R = Cl, R_1 = $COCH_3$, R_2 = H **Spongistatin 4**

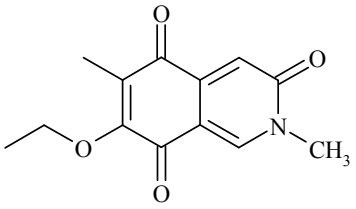
Figure 4

Cribrostatins:

Cribrostatins 1 and 2 **(14**, **15)** were isolated from a blue sponge located in the Republic of Maldives.[31] Cribrostatin 1 **(14)** has shown very selective activity against all of the nine human melanoma cell lines comprising the NCI panel.



14. Cribrostatin 1

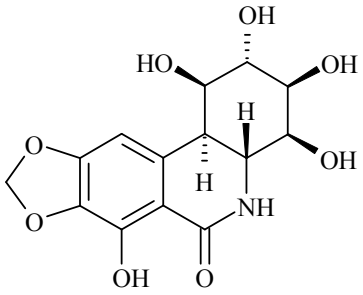


15. Cribrostatin 2

Figure 5

Pancratistatin:

pancratistatin **16** was found to be the first substance to cure Japanese encephalitis in an experimental animal.[32] Other research has been focused on devising an efficient total synthesis of pancratistatin **16**.

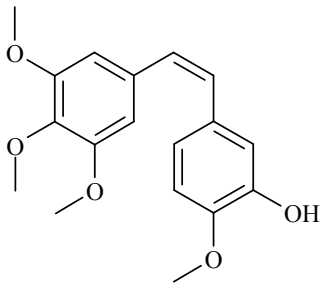


16. Pancratistatin

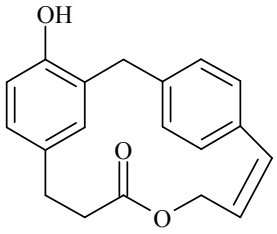
Figure 6

Combretastatin:

Among the many isolation, synthetic and antineoplastic evaluations have been pursuing to advance the combretastatin A-4 **(17)** lead has been successful synthesis of a water soluble pro-drug and the isolation and structure determination of combretastatin D-2 **(18)**. [33] The surprisingly strong and selective activity of combretastatin A-4 **(17)** against unusually difficult human cancer cell types continues to be very impressive.[34]



17. Combretastatin A-4



18. Combretastatin D-2

Figure 7

Halichondrins:

Continuing search for physiologically active substances from marine sources, recently found eight antitumor compounds[35] from Halichondria okadai Kadota. Prior studies by Scheuer and Tsukitani[36] resulted in the identification of okadaic acid as a cytotoxic constituent of this animal. However, the same animal focused on the fact that sponge extracts exhibited remarkable in vivo antitumor activity.[37] Bioassay against B−16 melanoma cells guided the isolation of extremely bioactive compounds which were named halichondrins. Halichondria okadai Kadota was collected on the coast of Aburatsubo in the Miura Peninsula which is to the south of Tokyo. This black colored animal is living in the mediolittoral zone. The marine sponges live in unique association[38] with a larger amount of symbionts such as bacteria than that of their cells.

ISOLATION AND PURIFICATION OF HALICHONDRINS

The isolation and purification of halichondrins was shown in Figure 8. Frozen specimens were crushed in a blender with MeOH. After standing for a period of three days, the solid residue was removed by filtration. The resulting brownish filtrate was concentrated carefully under reduced pressure at low temperature. The remaining aqueous solution was extracted with *n*-butanol saturated enough with water. The combined organic layers were concentrated under reduced pressure. Thus obtained extracts were dissolved with 70% aqueous MeOH, and then the solution was washed with three portions of *n*-hexane. The MeOH layer was concentrated under reduced pressure to

give an oily material which was charged on TSK G30005 polystyrene gel column[39] well washed with ethanol and then water.

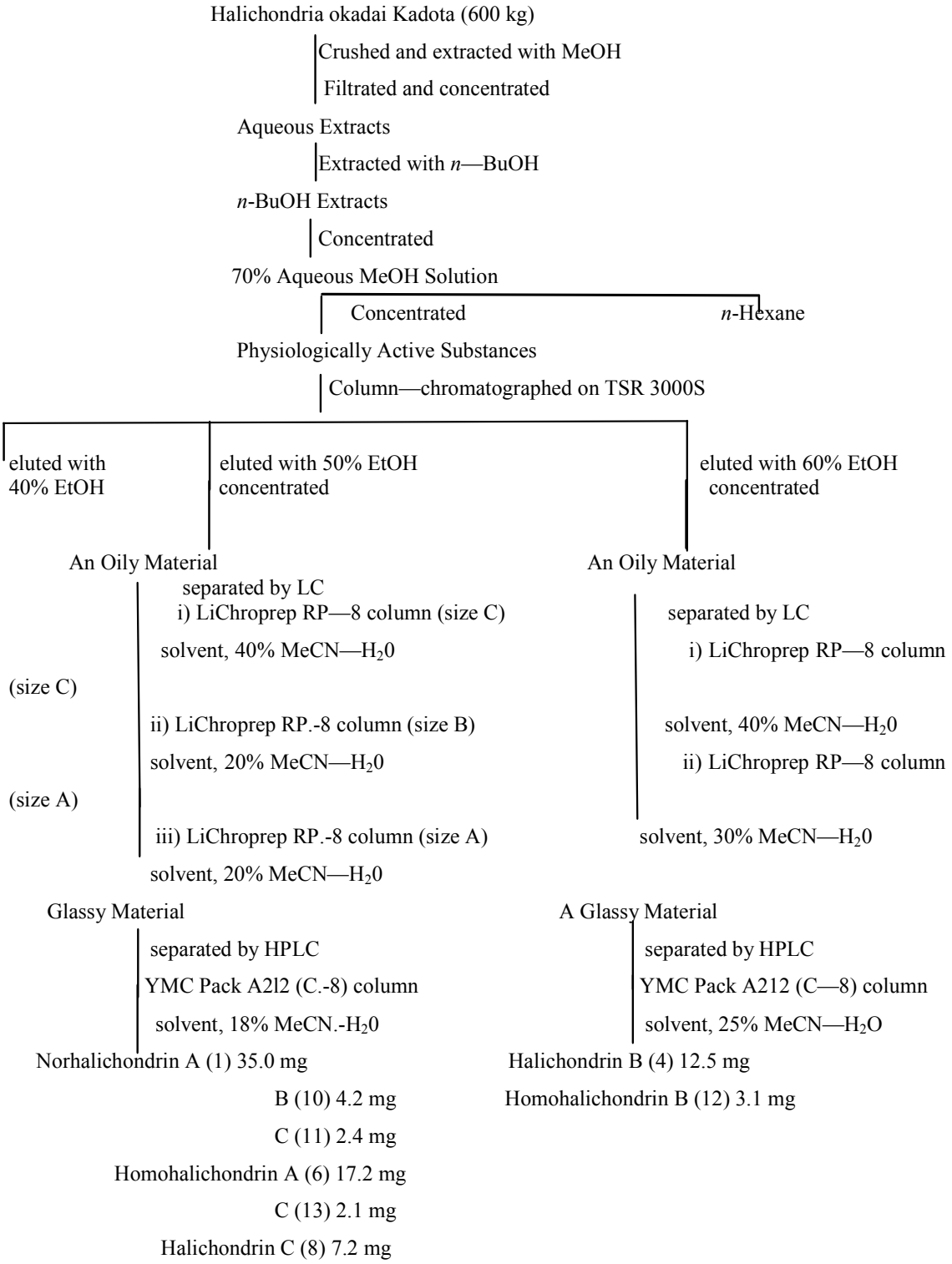


Figure 8: Scheme for the isolation and purification of a series of halichondrins.

The bioactive fractions against B-16 melanoma cells in vitro were eluted with 50% ethanol and then 60% ethanol. Each fraction was further separated by the use of LiChroprep RP−8 column and YMC Pack A2l2 (C−8) column. The repeated purification was done and finally, eight active compounds against B-l6 melanoma cells were obtained. The major component of this series was norhalichondrin A which was given in 5 X 10^{-6}% yield.

PHYSIOLOGICAL ACTIVITIES:

Halichondrins are antitumor polyether macrolides isolated from a marine sponge[40] and these new compounds were compared by cytotoxicity against B-l6 melanoma in vitro as summarized in Table 1. Although data of homohalichondrin C, and norhalichondrins B and C are not shown, the corresponding activities are inferior to that of halichondrin B. Bioactivity of halichondrin B is about 50 times that of norhalichondrin A whereas the acute toxicity of norhalichondrin A (LD_{50}, approximately 50 hg/kg for mice) is the highest among those. Antitumor activity of halichondrin B was investigated by the use of in vivo system. Tables 2, 3 and 4 show results against B-l6 melanoma, and P-388, L-1210 leukemia, respectively. Dose of halichondrin B for mice in low concentration resulted in the high T/C% and also dose by intravenous injection was effective. Homohalichondrin B is also bioactive comparably with halichondrin B in this in vivo system. Further studies on activities of halichondrin B and homohalichondrin B are currently under way.

TABLE 1: Cytotoxicity of halichondrins against B−l6 melanoma cells

Sample	IC_{50}[a] (ng/mL)
Halichondrin B	0.093
Norhalichondrin A	5.2
Homohalichondrin A	0.26
Halichondrin C	0.35
Homohalichondrin B	0.1

TABLE 2: Antitumor activity against B-16 melanoma in vivo

Sample	volume (μg/kg)	Dose for mice	M.S.T.[a] (day)	T/C[b]
Halichondrin B	0	day 1-9 i. p.	16	——
	2.5		32.5	203
	5.0		39	244
	0	day 1, 3, 5, 7, 9 i. p.	19	——
	5.0		37.5	197
	10.0		39.5	208
	0	day 1, 5, 9 i. p.	18	——
	10.0		36.5	203
	20.0		39.5	219
	0	day 1, 4, 7, 10 i. v.	17.5	——
	10.0		27.5	157

TABLE 3: Antitumor activity against P-388 leukemia in vivo

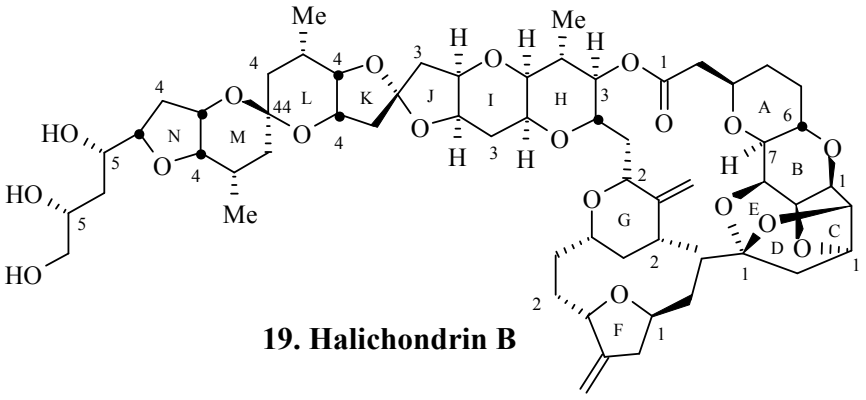
Sample	volume (μg/kg)	Dose for mice	M.S.T.[a] (day)	T/C (%)
Halichondrin B	0	day 1-9 i. p.	11	——
	1.25		15	136
	2.50		16.5	150
	5.00		26	236
	10.0	day 1, 3, 5, 7, 9 i. p.	35.5	323

TABLE 4: Antitumor activity against L—1210 leukemia in vivo

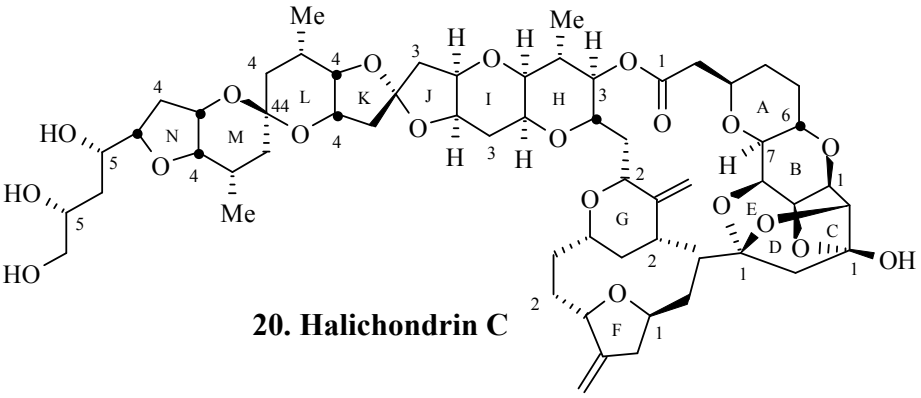
Sample	volume (μg/kg)	Dose for mice	M.S.T.[a] (day)	T/C (%)
Halichondrin B	0	day 1-5, 7-12 i. p.	7	——
	30		10	143
	50		14.5	207
	70		14	200
	0	day 1, 3, 5, 7, 9, 11 i. p.	8	——
	50		11	138
	100		30<	375<

STRUCTURE OF HALICHONDRINS:

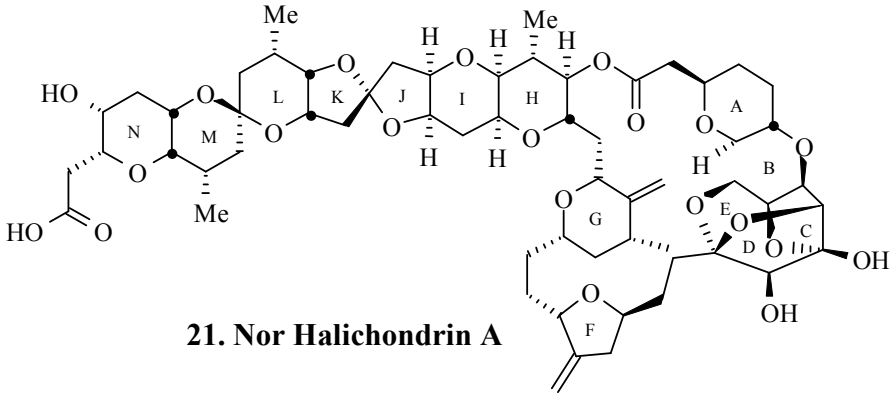
The molecular formulae and molecular weights of this series were summarized in Table 5. These compounds were not labile in basic media whereas acid solution caused obvious decomposition. The structural elucidation of norhalichondrin A **21** is the major component of this series. The structure of norhalichondrin A **21** has been unambiguously determined by X−ray crystallographic analysis. The optical rotation of norhalichondrin A **21** is $[\alpha]_D^{25} = -47.8^o$ (c = 1.13). Norhalichondrins B **22** and C **23** are carboxylic acids because the Rf values on the HPTLCNH_2 plates are zero with 10% MeOH−C$HC1_3$ as solvent. Halichondrins B **19** and C **20** were obtained as a crystalline form: Halichondrin B **19**, m.p. 164−166°C; halichondrin C **20**, m.p. 169−172°C. The optical rotations of halichondrin B **19** and halichondrin C **20** are $[\alpha]_D^{25} = -58.9^o$ (c = 0.94) and $[\alpha]_D^{25} = -41.6^o$ (c = 0.49), respectively. The molecular formula of halichondrin B **19** is $C_{60}H_{86}0_{19}$. However, X−ray crystallographic studies of a crystal of halichondrin B **19** unfortunately failed because of its relatively large molecular weight, 1110, and then the absence of any heavy atoms such as bromine or iodine atoms. The optical rotation of homohalichondrin A **24** is $[\alpha]_D^{25} = -97.1^o$ (c = 1.23). The terminal moiety (−O−CH−CHOH−CH_2OH) of homohalichondrins B **25** and C **26** corresponds to homohalichondrin A **24**. On the other hand, the tricyclo parts of homohalichondrins B and C are consistent with those of halichondrins B **(19)** and C **(20)**, respectively.



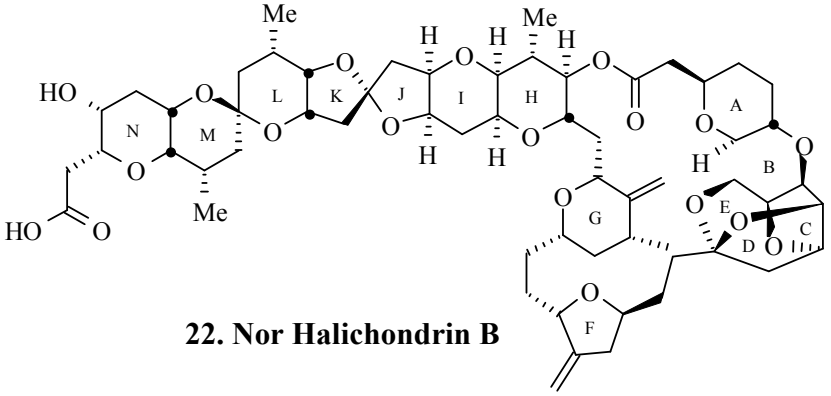
19. Halichondrin B



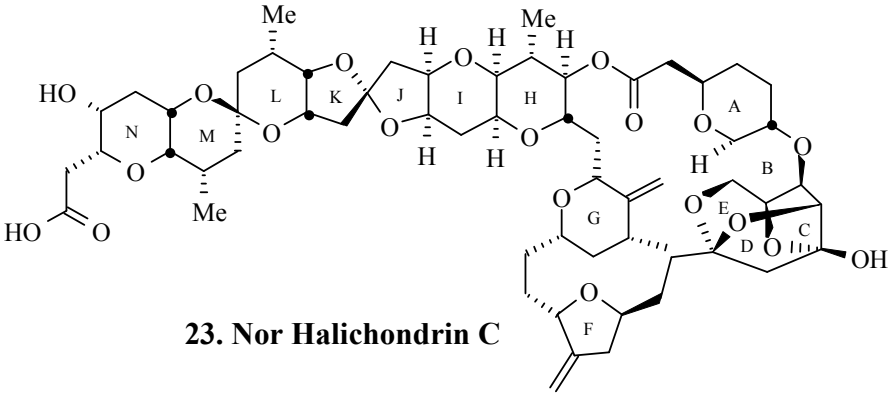
20. Halichondrin C



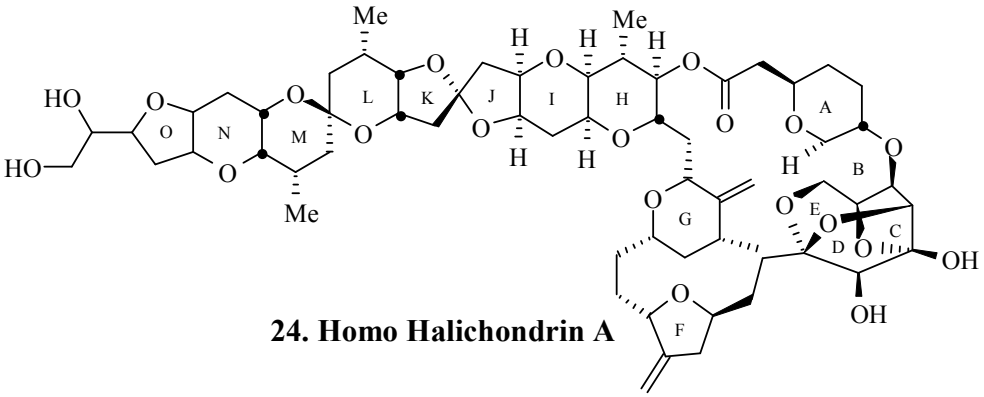
21. Nor Halichondrin A



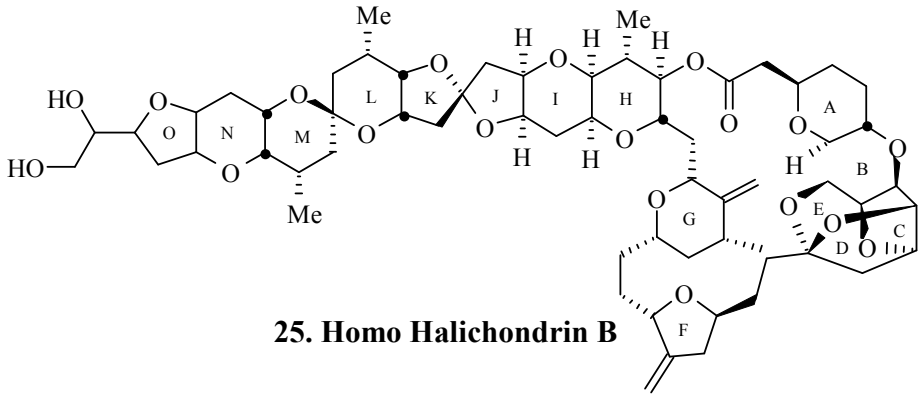
22. Nor Halichondrin B



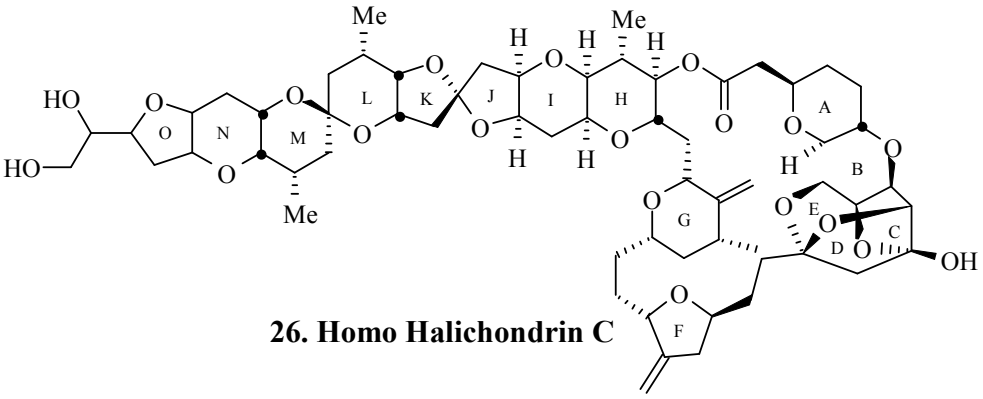
23. Nor Halichondrin C



24. Homo Halichondrin A



25. Homo Halichondrin B



26. Homo Halichondrin C

Figure 9

STRUCTURE-ACTIVITY RELATIONSHIP:

Both of halichondrin B **(19)** and homohalichondrin B **(25)** shows comparable activity, but that of norhalichondrin A **(21)** is very weak. It is to be desired that the terminal moiety is halichondrin-type or homohalichondrin-type. Alternatively, the desirable structure of the 2,6,9-trioxatricyclo[3.3.2.$0^{3,7}$decane system is B-type. By the

way, the length of a molecule of halichondrins, 30-35 A (Figure 9), corresponds to half of the lipid bilayer of biomembrane.

TABLE 5: Molecular formula and molecular weight of halichondrins

	Molecular formula	Molecular weight
Nor halichondrin A	$C_{59}H_{82}O_{21}$	1126
Halichondrin B	$C_{60}H_{86}O_{19}$	1110
Homohalichondrin A	$C_{61}H_{86}O_{21}$	1154
Homo halichondrin C	$C_{61}H_{86}O_{20}$	1138
Nor halichondrin B	$C_{59}H_{82}O_{19}$	1094
Nor halichondrin C	$C_{59}H_{82}O_{20}$	1110
Homohalichondrin B	$C_{61}H_{86}O_{19}$	1122
Halichondrin B	$C_{60}H_{86}O_{20}$	1126

This may be associated with the following facts. Structural variations of this series depend on 'head and tail' of a long molecule, which are assigned to the tricyclo system and the terminal moiety. It is very important for antitumor activity that the tricyclo ring is relatively lipophilic and then the terminal moiety contains two or three hydroxyls but not a carboxylate.

The structure of norhalichondrin A **21** was unambiguously determined by X-ray analysis. Based on spectral analysis, halichondrin B was assigned to proposed structure **19**, including its stereochemistry. Other halichondrins were also structurally identified. Interestingly, a variation of the structures exists in only "head and tail" of the molecule. The important features of these molecules are as follows: (1) a long-straight carbon chain such as palytoxin[41] and brevetoxin;[42] (2) a novel 2,6,9-trioxatricyclo[3.3.2.$0^{3,7}$]decane system, the first example naturally found as far as we know; (3) a polyether macrolide such as pectenotoxins[43]; (4) two spirosystems, involving a l,6-dioxaspiro[4.4jnonane system; (5) two boat-shaped pyranose rings; (6) two cis-fused pyranose rings. Subsequently, our interests concentrated on the biological origins of these molecules as well as tedanolide[44]. However, it is known that okadaic acid[36] is also isolated from a dinoflagellate such as Prorocentrum lima.[45] Therefore, it is proposed that halichondrins

may be produced by symbiotic bacteria such as blue-green algae. It should be conceivable by culture of these marine micro-organisms to elucidate the biosynthetic pathway of halichondrins, which involves a general concept in biosynthesis of long-straight carbon chains such as palytoxin.

Halichondrin B (19):

Halichondrin B **19** is a naturally occurring compound originally isolated from the marine sponge *Halichondria okadai* Kadota by Hirata and Uemura in 1986. Halichondrin B (Figure 9) is the most potent component of a class of polyether macrolides isolated in exceedingly low yields ($1.8x10^{-8}$ to $4.0x10^{-5}$%) from a variety of sponge genera.[40] With a tubuline-based mechanism of action as an antimitotic agent, halichondrin B displays an in vitro IC_{50} value of 0.3 nM against L1210 leukemia and remarkable in vivo activities against various human solid tumors xenographs, including LOX melanoma, KM20L colon, FEMX melanoma, and OVCAR-3 ovarian tumors[46] Halichondrin B shows exquisite anticancer activity against murine cancer cells both in culture and in *in vivo* studies. Halichondrin B **19** was highly prioritized for development as a novel anticancer therapeutic by the United States National Cancer Institute and, in 1991, was the original test case for identification of mechanism of action (in this case, tubulin-targeted mitotic inhibitor) by NCI's now famous but then-brand-new "60-cell line screen"[47] The complete chemical synthesis of halichondrin B **19**, a large (MW = 1,110) polyether macrolide, was achieved by Yoshito Kishi and colleagues at Harvard University in 1992,[48] an achievement that ultimately enabled the discovery and development of the structurally simplified and pharmaceutically optimized analog eribulin (E7389, ER-086526, NSC-707389).[49,50] Eribulin **27** was approved by the U.S. Food and Drug Administration on November 15, 2010, to treat patients with metastatic breast cancer who have received at least two prior chemotherapy regimens for late-stage disease, including both anthracycline- and taxane-based chemotherapies.[51]

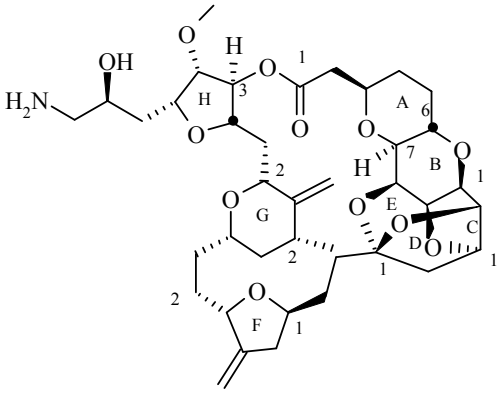
Eribulin **27** is a synthetic compound that mimics part of the structure of halichondrin B **19**, a molecule found in the sea sponge *Halichondria okadai*, which has potent tumour-fighting activity shortly after its discovery in 1986 as shown in Figure 10.

But it is present in very low concentrations, making it difficult to isolate. A few years later, however, organic chemist Yoshito Kishi of Harvard University in Cambridge, Massachusetts, eyed the halichondrin B **19** structure and decided to take a crack at it.

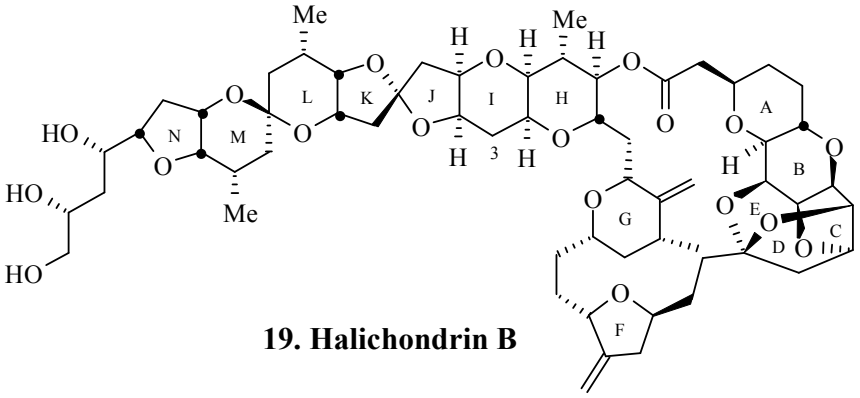
Figure 10: The drug eribulin **27** was inspired by a compound from the sea sponge *Halichondria okadai*.

Kishi's team had set themselves an enormous challenge with halichondrin B. Halichondrin B **19** has a staggering 32 stereocentres, meaning that there are 2^{32} − more than 4 billion possible forms, or isomers, of the molecule. "It's just ridiculous," says Robert Salomon, an organic chemist at Case Western Reserve University in Cleveland, Ohio, whose lab spent four years unsuccessfully trying to synthesize the compound in the early 1990s. Nevertheless, Kishi's team succeeded. By the time he published a method for synthesizing the compound in 1992 (T. D. Aicher *et al*. *J. Am. Chem. Soc.* **114,** 3162–3164; 1992), researchers at the Natural Products Branch of the US National Cancer Institute (NCI) in Frederick, Maryland, had discovered that halichondrin B fights cancer cells by inhibiting a protein component of the cytoskeleton — the internal latticework of rods and filaments that gives a cell its shape. That protein, called tubulin, is needed to support the rapid growth of cancer cells and is the target of several other cancer chemotherapies, including Taxol (paclitaxel).

To date, one total synthesis of halichondrin B **19**[48] and several fragment syntheses have been reported.[52]



27. Eribulin



19. Halichondrin B

Figure 11

Total synthesis of Halichondrin B (19):

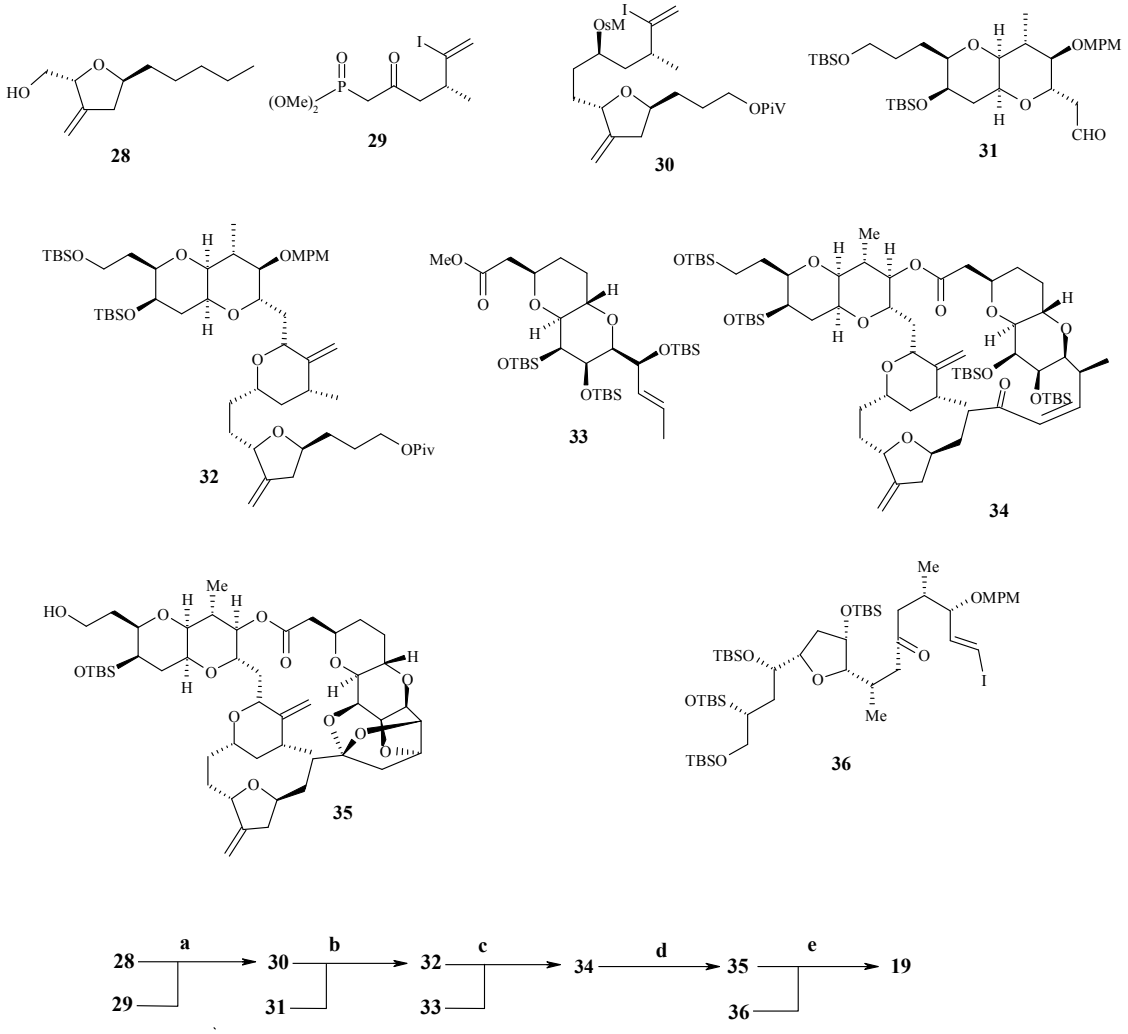
Yashito Kishi *et.al* approach:[48]

This approach describes the total synthesis of halichondrin B **19** in a convergent fashion. Horner-Emmons reaction, Dess-Martin oxidation, Yamaguchi lactonisation and Mitsunobu reactions are used as key steps.

Scheme 1 shows outline synthesis of halichondrin B **(19)**. Coupling of **28** and **29** was accomplished by Horner-Emmons reaction, followed by conjugate reduction. During this process, isomerisation of double-bond from the C19 exocyclic to the C19-C20 endocyclic position was observed. This transformation was accomplished via the preparation of the aldehyde from the primary alcohol **28**[53] by Dess-Martin oxidation.[54] Conjugate reduction of the resulting enone by Stryker reagent,[55] without double-bond

isomerisation. Reduction of saturated ketone with $NaBH_4$ to produce 1:1 mixture of two diastereoisomers. These two diastereomers transformed into corresponding mesylates which were used for the next step.

Coupling of segment **30** with segment **31**[56] was accomplished by the Ni(II)/Cr(II)-mediated reaction[57] to afford primary alcohol and subsequent base-induced cyclisation to furnish the desired tetrahydropyran **32** in 55% yield. The Ni(II)/Cr(II)- mediated coupling of the C14 aldehyde obtained from **32** and **33** followed by Dess-Martin oxidation afforded tras-enone.



Scheme 1: Total synthesis of halichondrin B **19**

Reagents and conditions: (a) (1) 28/Dess-Martin reagent, CH_2Cl_2, r.t.; (2) 4 (1.5 equiv), NaH, THF, 0 ^oC; (3) Stryker reagent, C_6H_6, r.t.; (4) $NaBH_4$, MeOH, 0 ^oC; (5) Polar

alcohol, Ms_2O, Et_3N, 0 ^oC, (b) (1) 30+31, $NiCl_2$-$CrCl_2$, DMF-THF, r.t; (2) KH, DME, 80 ^oC; (c) (1) 32, LAH, Et_2O, 0 ^oC; (2) Dess-Martin reagent, CH_2Cl_2, r.t.; (3) Aldehyde+33, $NiCl_2$-$CrCl_2$, DMF, r.t; (4) Dess-Martin reagent, CH_2Cl_2, r.t.; (5) DDQ, CH_2Cl_2, ^{t}BuOH, r.t.; (6) LiOH, H_2O-THF (3:1), r.t.; (7) Yamaguchi lactonization (d) (1) TBAF,THF, r.t.; (2) PPTS, CH_2Cl_2, r.t.; (3) p-O_2NPhCOCl, Pyridine, CH_2Cl_2, r.t.; (4) TBSOTf, ET_3N, CH_2Cl_2, r.t.; (5) K_2CO_3, MeOH, r.t.; (e) (1) 10/ Dess-Martin reagent, CH_2Cl_2, r.t.; (2) Aldehyde+36, $NiCl_2$-$CrCl_2$, DMF, r.t; (3) Dess-Martin reagent, CH_2Cl_2, r.t.; (4) TBAF,DMF, r.t.; (5) DDQ, CH_2Cl_2, ^{t}BuOH, r.t.; (6) CSA, CH_2Cl_2, r.t.

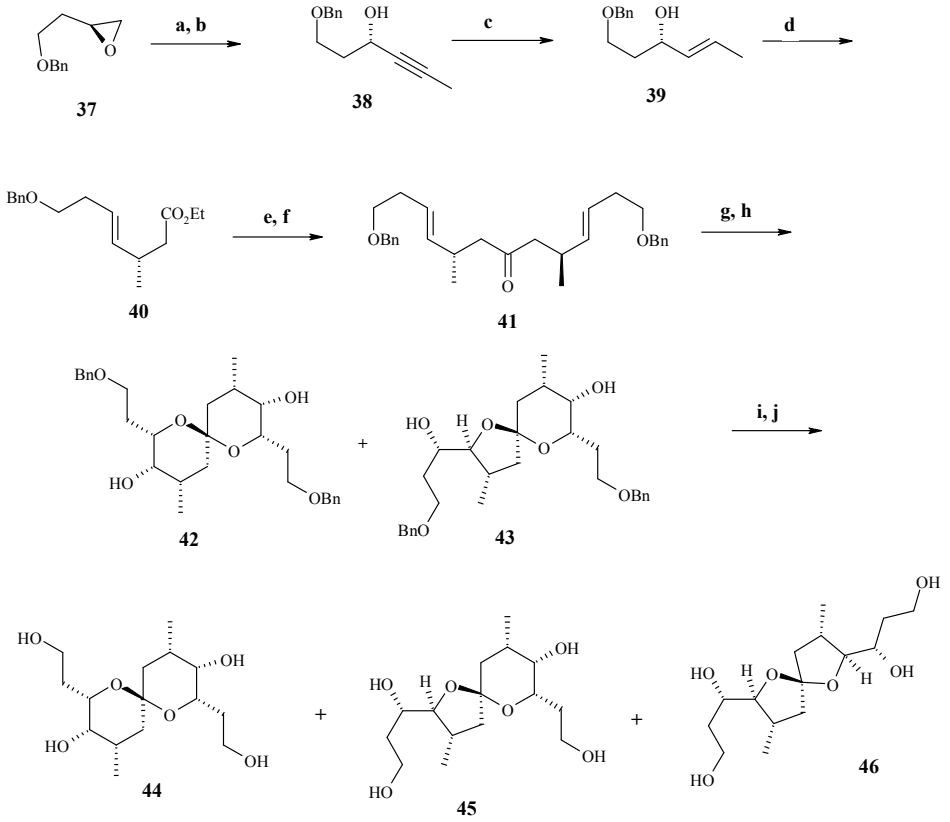
After removal of C30 MPM group, hydrolysis of C1 methyl ester and Yamaguchi lactonisation gave lactone enone **34** in 63% yield. A parallel Micheal reaction and subsequent ketalisation of the C1-C21 segment afforded polycyclic product **35**. Coupling of aldehyde which was derived from **35** with **36**, was effected by Ni(II)/Cr(II)-mediated reaction and after Dess-Martin oxidation to afford trans enone in 60% yield. The enone was successfully transformed into the halichondrin B **19** in three steps.

An Expeditious Synthesis of the C(38)-C(54) Halichondrin B (19) Subunit:
Steven D. Burke *et.al* approach:[58]

This approach describes the synthesis of the C(38)-C(54) Halichondrin B **19** subunit in a linear fashion. Efficient construction of the K, L, M, and N rings, including 10 asymmetric centers, was accomplished by exploiting the local *C*2-symmetry about the C(44)-spiroketal carbon. In this synthesis, synthetic strategy involves Claisen rearrangement conditions, Claisen self-condensation and Sharpless's asymmetric dihydroxylation.

The known (*S*)-epoxide **37**, commercially available from (*S*)-malic acid,[59] which was opened with the ethylenediamine complex of lithium acetylide (Scheme 1).[60] Isomerization of the crude terminal alkyne with KO*t*-Bu afforded the thermodynamically favored internal alkyne **38,** subsequently reduction with LAH in THF afforded in the *E*-allylic alcohol **39** as a single geometrical isomer.[61] Allylic alcohol **39** was subjected to Johnson ortho ester Claisen rearrangement conditions[62] to provide the ethyl ester **40**.

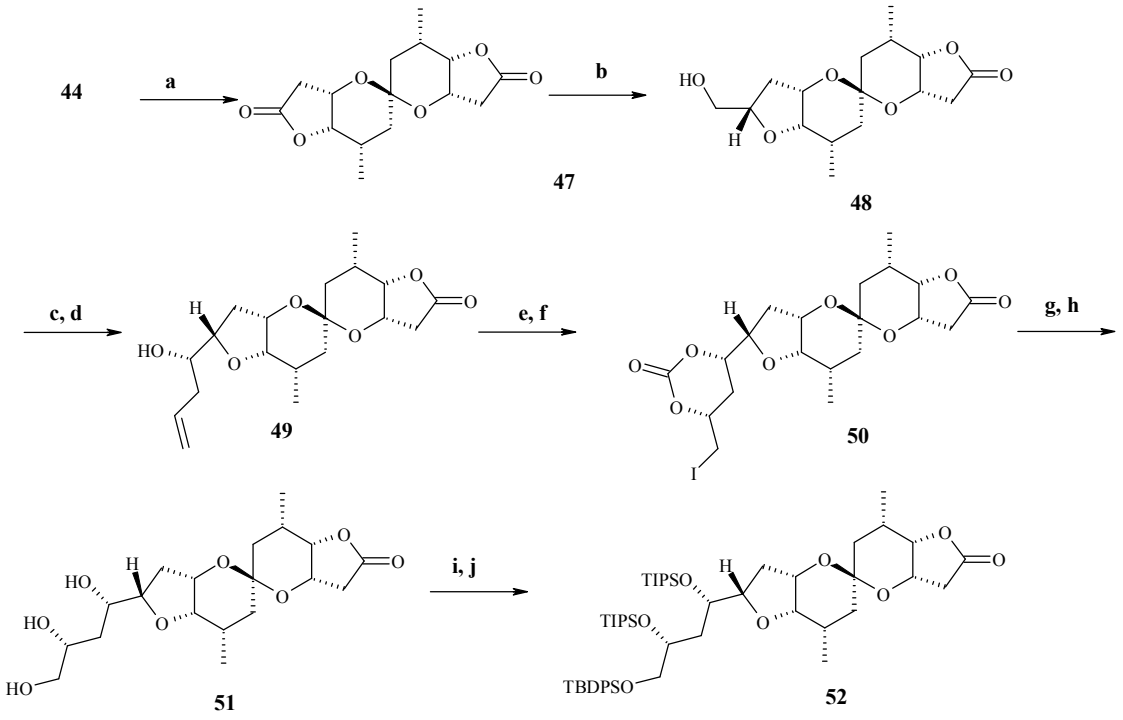
Claisen self-condensation of **40** (Scheme 2) with LHMDS and TMEDA to the ester in THF over 4.5 h at 0 °C, gave the β-keto ester in good yield. Decarboalkoxylation under Krapcho conditions[63] cleanly provided the *C*2-symmetric ketone **41** as a a viscous oil (96%). Asymmetric dihydroxylation with Sharpless's AD-mix-α at 0 °C afforded the *C*2-symmetric tetraol, as virtually a single diastereomer, thus setting the C(40), C(41), C(47), and C(48) stereocenters in one step. Acid catalyzed spiroketalization[64] of the tetraol with camphorsulfonic acid in PhH/MeOH (1:1) yielded the thermodynamic ratio (1.1:1.0) of the *C*2-symmetric 1,7-dioxaspiro[5.5]undecane **42**, and the isomeric, undesired 1,6-dioxaspiro[4.5]decane **43** as a separable mixture of isomers. Operationally, the mixture of ketals **42** and **43** was debenzylated via hydrogenolysis and then equilibrated with catalytic trifluoroacetic acid in refluxing methanol to the more favorable thermodynamic mixture of desired **44**, plus **45** and **46** (5:2:1). After separation, ketals **45** and **46** were recycled to **44** by reexposure to the equilibrating conditions.



Scheme 2

Reagents and conditions: (a) $LiCCH.H_2NCH_2NH_2$, DMSO, 15 ^oC-r.t.; (b) KO^tBu, DMSO, 15 ^oC, 85% two steps; (c) LAH, THF, 96%; (d) $CH_3CH_2CO_2H$, 140 ^oC, 96%; (e) LHMDS, TMEDA, THF, 0 ^oC, 84%; (f) LiCl, DMSO, H_2O, 190 ^oC, 96%; (g) AD-mix-α, 0 ^oC, $^tBuOH/H_2O$ (1:1); (h) CSA, MeOH/PhH (1:1), 92% two steps; (i) H_2 gas, $Pd(OH)_2/C$, EtOH, 100% (j) TFA, MeOH, 98%.

Selective oxidation of the primary alcohol groups in tetrol **44** (Scheme 2) with tetrapropylammonium perruthenate (VII) (TPAP)[65] afforded the *C*2-symmetric bislactone **47** as a white crystalline solid, and its absolute stereochemistry was secured by X-ray crystal structure determination. Partial conversion of **47** to **48** was executed by lactone olefination[66] to the vinyl ether with tebbe reagent, followed by hydroboration/oxidation[67] with 9-BBN/aq $NaBO_3$. Oxidation of primary alcohol **48** with the Dess-Martin periodinane[68] provided the corresponding aldehyde, which was taken crude into a chelation-controlled allylation[69] with $TiCl_4$ and allyltributylstannane[70] at -78 °C to provided the homoallylic alcohol **49** as a single isomer.



Scheme 3

Reagents and conditions: (a) TPAP, NMO, 4-A^o sieves, $^tBuOH/CH_3CN$, r.t., 75%; (b) Tebbe reagent ($Cp_2TiCH_2.AlMe_2Cl$), pyridine, $PhCH_3$/THF, -78 ^oC-r.t., 9-BBN,

$NaBO_3.4H_2O$, H_2O, 41%; (c) Dess-Martin, CH_2Cl_2, r.t.; (d) $TiCl_4$, (Allyl)$SnBu_3$, CH_2Cl_2, -78 ^oC, 96%; (e) $(BOC)_2O$, DMAP, pyridine, CH_2Cl_2, r.t., 91%; (f) IBr, $PhCH_3$, -80 ^oC, 96%; (g) 0.5 M LiOH, DME, 60-70 ^oC, (h) CSA, PhH, reflux, 94%; (i) TBDPSCl, DMAP, CH_2Cl_2, pyridine, r.t., 90%; (j) TIPSOTf, pyridine, DMAP, r.t., 99%.

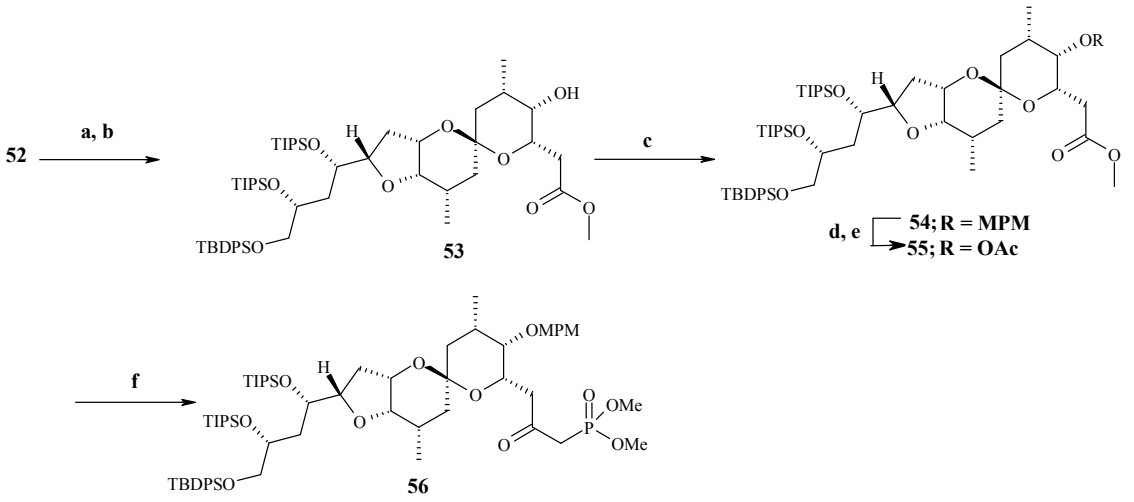
Alternatively, homoallylic alcohol **49** was converted to the corresponding BOC carbonate with excess $(BOC)_2O$ and DMAP. Treatment of the BOC carbonate with iodine monobromide at -80 °C afforded the iodo carbonate **50** in excellent yield (96%) and diastereoselectivity (>18:1).[71] Compound **51** was obtained from **50** by LiOH treatment in DME. The primary alcohol in **51** was selectively protected as a TBDPS ether, and the two secondary alcohols were then protected with TIPSOTf to afford the desired C(38)-C(54) segment **52**, suitable for subunit coupling.

Halichondrin B: synthesis of C (37)−C (54) Subunit

The revised approcch of Burke at al describes synthetic plan for construction of the L, M, N rings of β-ketophosphonate **56,** including 10 chiral centers was based upon the exploitation of local C_2 symmetry about the C(44)-spiroketal carbon, with late-stage symmetry breaking by sequential extension at C(38)-C(50).

Steven D. Burke *et.al* revised approach:[72]

The γ-lactone **52** was saponified with LiOH in aqueous THF followed by esterification with $TMSCHN_2$ at room temperature to afford **53** in 95% yield. However, treatment of hydroxyl ester **53** with excess of the MPM-trichloro-acetimidate and $BF_3.OEt_2$ at −78 ^oC in ether gave **54** in good yield. Some portion of MPM protected compound **54** was deprotected by hydrolysis with $Pd(OH)_2/H_2$ and converted into the corresponding acetate **55**. ^1H NMR Analysis of compound **26** clearly indicates the structure accomplished to the **52** is [5,5]-spiroketal arrangement. Finally protected methyl ester **54** was exposed to several equivalents of lithiomethyl dimethylphosphonate at −78 ^oC, to afford the desired β-ketophosphonate **56** in 54% yield.



Scheme 4

Reagents and conditions: (a) 1.0 M LiOH(aq), ^{t}BuOH/THF, r.t.; (b) $TMSCHN_2$, MeOH/PhH (2:7), r.t., 95% two steps; (c) $MPMOC(NH)CCl_3$, $BF_3.OEt_2$, Et_2O, -78 ^{o}C, 88%; (d) H_2 gas, $Pd(OH)_2/C$, EtOH, 100%; (e) Ac_2O, CH_2Cl_2, DMAP, 99%; (f) $LiCH_2P(O)(OMe)_2$, THF, -78 ^{o}C, 54%.

CHAPTER I

Section B

Present work on the synthesis of the C38-C54 spiroketal segment of Halichondrin B

The work of this chapter was published in

Tetrahedron Letters 2012 *(Just Accepted)*

PRESENT WORK

Organic synthesis has a long history that can be traced back to ancient times although at first it was not recognized as such because it was practiced randomly and strictly heuristically. The practice and advancement of the field of organic synthesis requires and cultivates some of the most sophisticated virtues and talents of human nature, knowledge, creativity, and geometric and artistic perception. The centrality of the field of organic synthesis to chemistry in particular and to the other sciences lies in general not only in its capacity to deliver substances for further studies and usage, but more significantly in its capacity to create new entities.

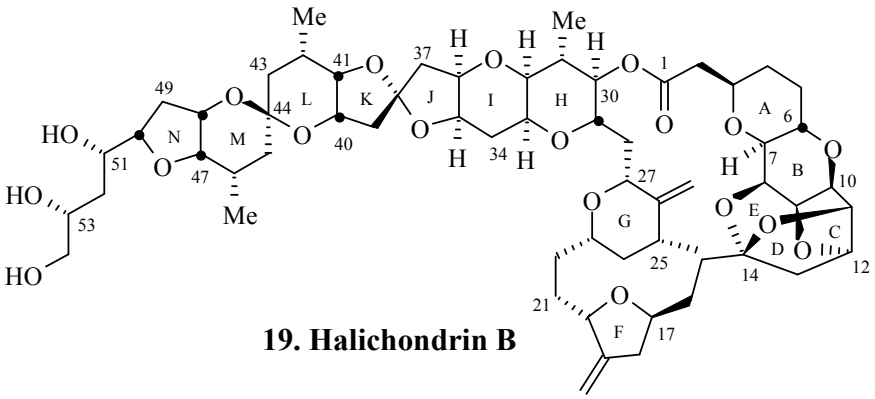
Ever since synthetic organic chemists realized their ability to assemble molecules from the elements and other simple starting materials, natural products served to fascinate and challenge them. The chemical synthesis of nature's molecules without the aid of enzymes often presents formidable challenges to human ingenuity and skill. The structures of natural products in an almost infinite range of complexity and stability therefore often present distinct synthetic problems that require strategies and tactics for their solution. It is this, almost unlimited variation in structures and the constant discovery of new molecular constructs that keeps the field of natural product syntheses so attractive and vibrant. The dazzling biological properties exhibited by many natural products and the attendant opportunities these molecules offer for probing biological questions also serve as major attractions in this field of investigations.

During several investigations of the biological potential of the New Zealand marine biota, attention was drawn to a bright yellow sponge *Lissodendoryx* sp. (family Myxillidae, order Poecilosclerida) collected by dredging from deep water (>100 m) off the Kaikoura Peninsula in 1983. Extracts from this sponge were strongly inhibitory against the murine leukemia cell line P388, a DNA virus (*Herpes simplex* Type I), and an RNA virus (*Polio* vaccine virus). Initial studies on the sponge in 1985 established that the active components were stable, and furthermore, crude extracts of this sponge offered significant extensions of life-span in an *in vivo* murine P388 model (T/C ~250%). One strongly bioactive compound, obtained in the initial studies, gave data very reminiscent of those published for the halichondrin series of compounds, although differences were noted which suggested that a new halichondrin had been obtained.

Data generated in the new National Cancer Institute drug evaluation program, which is based on inhibition of cell growth in 60 human tumor cell lines, were used to compare new compounds with agents of known mechanism of action in terms of their differential cytotoxicity. Two marine natural products, halichondrin B (**19**) and homohalichondrin B (**25**), appeared repeatedly when the data base was probed with known antimitotic agents. Both compounds were highly cytotoxic (IC_{50} values for L1210 murine leukemia cells of 0.3 and 1 nM, respectively), with accumulation of cells arrested in mitosis at toxic concentrations, that both inhibited the polymerization of purified tubulin, and that both inhibited microtubule assembly dependent on microtubule-associated proteins. Limited amounts of homohalichondrin B (**25**), the less active agent, were available, so only halichondrin B (**19**) was studied in detail. Halichondrin B (**19**) did not interfere with colchicine binding to tubulin, buitt was a noncompetitive inhibitor of the binding of vinblastine to tubulin (apparent *Ki, 5.0* p ~). Halichondrin B (**19**) was therefore compared with other agents which interfere with the binding of vinca alkaloids to tubulin (vinblastine, maytansine, dolastatin 10, phomopsin A, rhizoxin) in terms of its effects on tubulin polymerization, inhibition of GTP hydrolysis, inhibition of nucleotide exchange, and stabilization of tubulin, as well as the quantitative assessment of its effects on vinca alkaloid binding and inhibition of cell growth. Since halichondrin B (**19**) was originally isolated from the same organism as the phosphatase inhibitor okadaic acid, and since it is about 50-fold more effective than okadaic acid as an inhibitor of L1210 cell growth, perturbations of cellular microtubules observed following treatment with okadaic acid should be interpreted cautiously.

Halichondrin B (**19**) is an architecturally unique polyether macrolide that exhibits cancer cell growth inhibition profiles most highly correlated to those produced by structurally unrelated, tubulin-binding standard agents such as vincristine and taxol. However, medicinal applications are hampered because (**19**) is not readily available from its natural sources. Although its structural complexity makes synthesis a redoubtable challenge, its extremely high potency encourages consideration of total synthesis as a practical source of supply.

The structural complexity, interesting biological activity and the scarcity of this compound have stimulated studies towards the total synthesis of Halichondrin B.



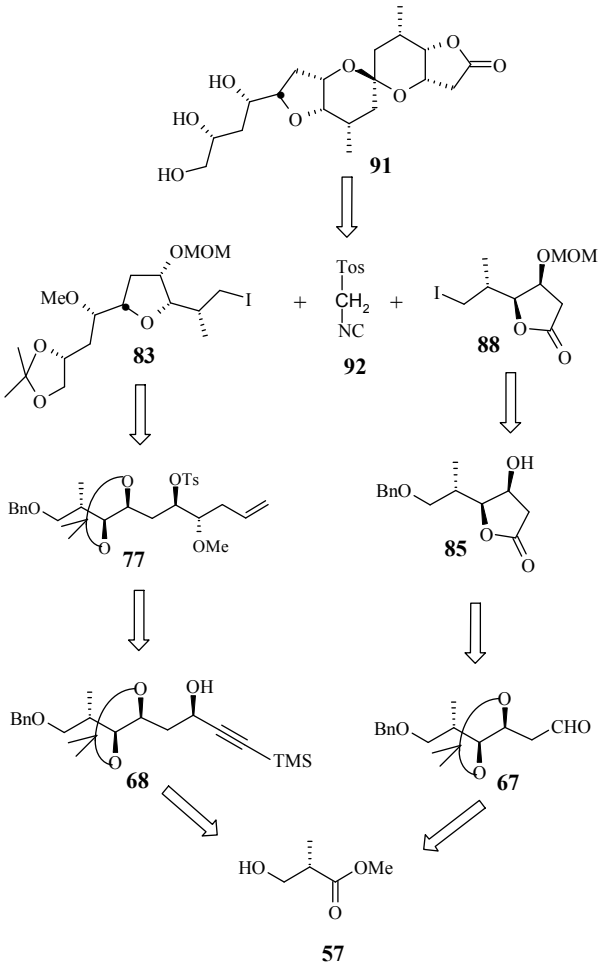
19. Halichondrin B

Figure 11

We herein report an expeditious synthesis of the C(38)-C(54) spiroketal fragment (**91**) of halichondrin B subunit *via* Carreira's addition, Sharpless asymmetric dihydroxylation, double alkylation of TosMIC strategy and double vinyl coupling reactions.

Retrosynthetic strategy for spiroketal C38-C54 fragment (91) of halichondrin B:

Retrosynthetic analysis revealed that the target spiroketal C38-C54 fragment **91** of halichondrin B could be obtained from **83** and **88** by alkylation of TosMIC (tosyl methyl isocyanide) **92**. The compound **83**, inturn could be obtained from **77**, prepared *via* Carreira's addition**.** The compound **68** could be obtained from (methyl (*S*)-(-)-3-hydroxy-2-methylpropionate **57** by Sharpless asymmetric dihydroxylation. In the same manner compound **88** also obtained from (methyl (*S*)-(-)-3-hydroxy-2-methylpropionate **57** (Scheme 5).



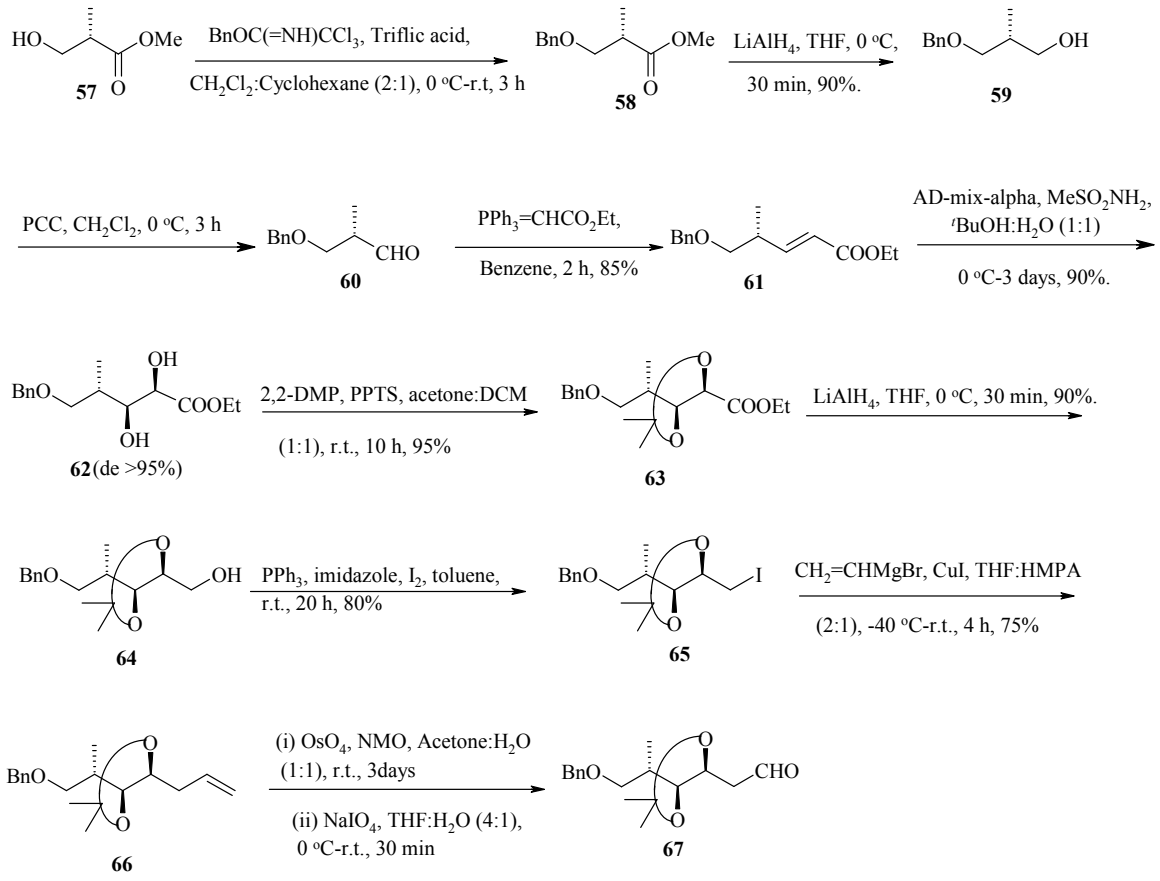
Scheme 5: Retrosynthetic analysis for **91**

Synthesis of (*R*)-4-((*S*)-2-((2*S*,4*S*,5*S*),-5-((*R*)-1-iodopropan-2-yl)-4yl-(methoxymethoxy)-tetrahydrofuran-2-yl)-2-methoxyethyl)-2,2-dimethyl-1,3-dioxalane (83):

The synthesis of functionalized tetrahydrofuran fragment **83** was started from commercially available methyl (*S*)-(-)-3-hydroxy-2-methylpropionate **57**. The sequence of reactions involved in the synthesis of the key intermediate aldehyde **67** was shown in Scheme 6.

Acid catalyzed benzylation of **57**, in the presence of *O*-benzyltrichloroacetamidate and catalytic amount of triflic acid in a mixture of cyclohexane and CH_2Cl_2 (2:1) at 0 ^oC afforded the benzyl ether **58**[73] in 87% yield. Appearance of signals in the aromatic region and signal at δ 4.7 as a singlet corresponding to the benzylic protons in the ^1H NMR spectrum of the compound **58** confirmed the conversion. Treatment of **58** with $LiAlH_4$ in

THF at 0 ^{o}C gave the alcohol **59** (90% yield). Disappearance of ester methyl signals, appearance of a broad singlet at δ 2.39 integrating for one proton due to free hydroxyl group in ^{1}H NMR spectrum supported the structure of **59**.



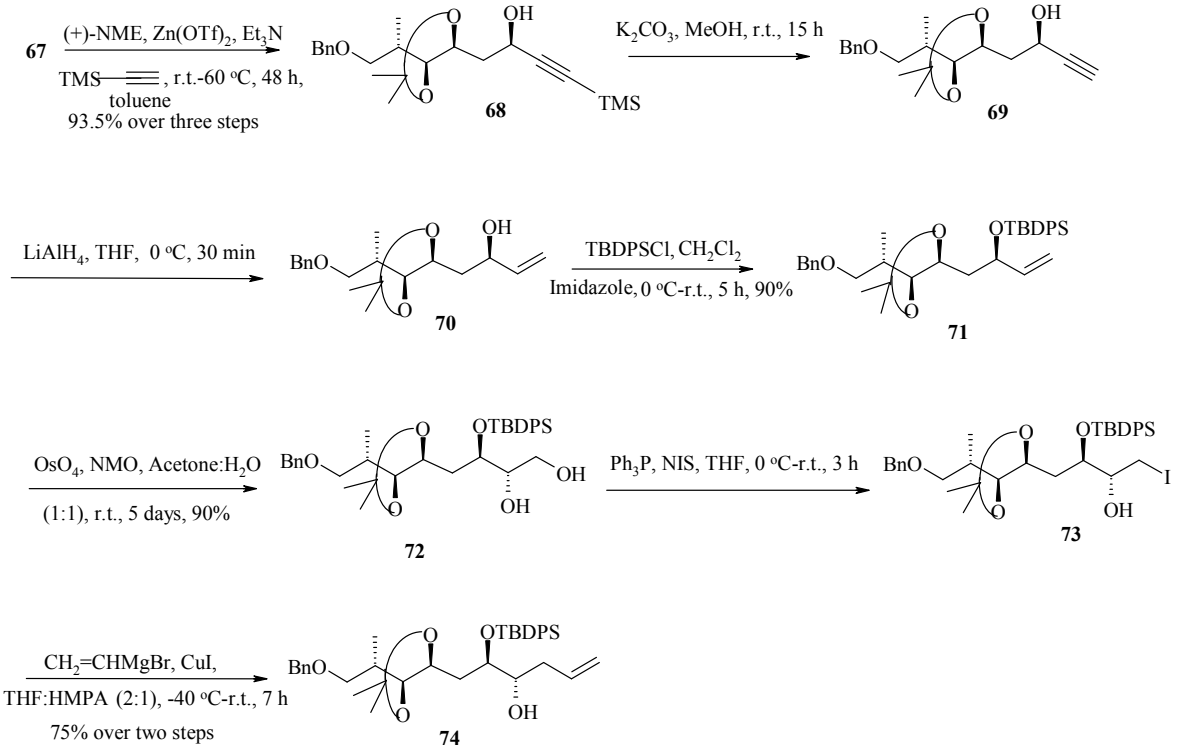
Scheme 6: Synthesis of the key intermediate aldehyde **67**

A strong absorption in IR spectrum at 3411 cm^{-1} further supported the structure of **59**. PCC oxidation of alcohol **59** in CH_2Cl_2 at 0 ^{o}C afforded the aldehyde **60** in 92% yield. The structure of the compound **60** was established from its spectral data. The aldehyde proton appeared as a singlet at δ 9.76. Signals of remaining protons remained unchanged. The aldehyde **60** was used for the next reaction immediately. Aldehyde **60** was subjected to Wittig olefination using stabilized ylide ($Ph_3P{=}CHCO_2Et$) in benzene to furnish α,β-unsaturated ester **61** in 85% overall yield (Scheme **6**). The newly introduced protons corresponding to α,β-unsaturated ester group in ^{1}H NMR of **61** resonated at δ 6.90 (dd, J = 6.79, 15.86 Hz, 1H), 5.81 (dd, J = 1.51, 15.86 Hz, 1H), and disappearence

of CHO signal at 9.76 conforming the product as a ester. The coupling constant at 15.8 Hz indicate the formation of α,β-unsaturated ester group as *E*-geometry. In the IR spectrum a characteristic strong absorption at 1717 cm^{-1} for α,β-unsaturated ester functional group has observed. The structure of **61** was further confirmed by mass spectrum, which showed a molecular ion peak at *m/z* 271 $[M+Na]^+$. Asymmetric dihydroxylation[74] of **61** using AD-mix-α and methane sulphonamide in $^tBuOH/H_2O$ (1:1) at 0 ^oC gave the diol **62** in 90% yield with 9:1 diastereomeric ratio, confirmed by chiral HPLC analysis. The compound **62** was confirmed by spectral data. In PMR sprctrum disappearance of olefinic protons indicates formation of 1,2 diol compound **62**. In IR spectrum showed strong absorption at 3449 cm^{-1} for the hydroxyl function. Further it was characterized by ESI-MS data which showed a value of *m/z* 305 for the $[M+Na]^+$.

The internal 1,2-diol **62** was then reacted with 2,2-dimethoxypropane and catalytic amount of PPTS in 1:1 mixture of CH_2Cl_2 and Me_2CO to give acetonide **63** in 95% yield (Scheme 6). The ^1H NMR spectrum of **63** confirmed by appearance of two singlets for two methyl groups of acetonide at δ 1.41 and δ 1.40. It was also characterized by ESI-MS data, which showed $[M+K]^+$ peak at *m/z* 361. Disappearence of strong absorption at 3456 cm^{-1} in IR spectrum further confirmed the product formation. The ester **63** was subjected to reduction using LAH in dry THF at 0 ^oC to afford primary alcohol **64** in 90% yield. The formation of compound **64** was confirmed by its characteristic spectral data. In PMR spectrum the signals corresponding to the OCH_2CH_3 were disappeared. IR spectrum showed strong absorption at 3448 cm^{-1} for the hydroxyl function. The formation of the product was further supported by its $[M +K]^+$ peak observed at *m/z* 319 in ESIMS. Compound **64** on exposure to TPP, I_2, and imidazole at room temperature gave the corresponding iodide **65** in 20 h. Displacement of hydroxyl group attached to - CH2- signals which appeared in **64** towards upfields and presence of other required signals in ^1H NMR spectrum characterized the compound **65**. It was further supported by ESI-MS, which showed $[M+Na]^+$ peak at *m/z* 413 (Scheme 6). Displacement of iodo group in compound **65** with vinylmagnesium bromide in the presence of CuI[75] afforded terminal alkene **66** in 75% yield. Compound **66** was confirmed from ^1H NMR, IR and ESI-MS spectral data. ^1H NMR spectrum of the compound **66** exhibited two multiplets due to olefinic protons at δ 5.93-5.74 and δ 5.11-

5.00 integrating one and two protons respectively **66** (Scheme 6). In addition, IR Spectrum showed olifinic absorbtion at 2925 cm^{-1} and ESIMS showed $[M+Na]^+$ signal at *m/z* 313, further conformed the structure **66** (Scheme 3). Dihydroxylation of **66** in presence of 0.02 molar OsO_4 and 1.2 equivalent of NMO in presence of 1:1 ratio of Me_2CO and H_2O at room temperature to afforded 1,2-diol, which was subjected to next reaction without further purification. $NaIO_4$ chapping of 1,2 diol compound in 4:1 ratio of THF and H_2O gave aldehyde **67**, which without further purification was used for the next step.

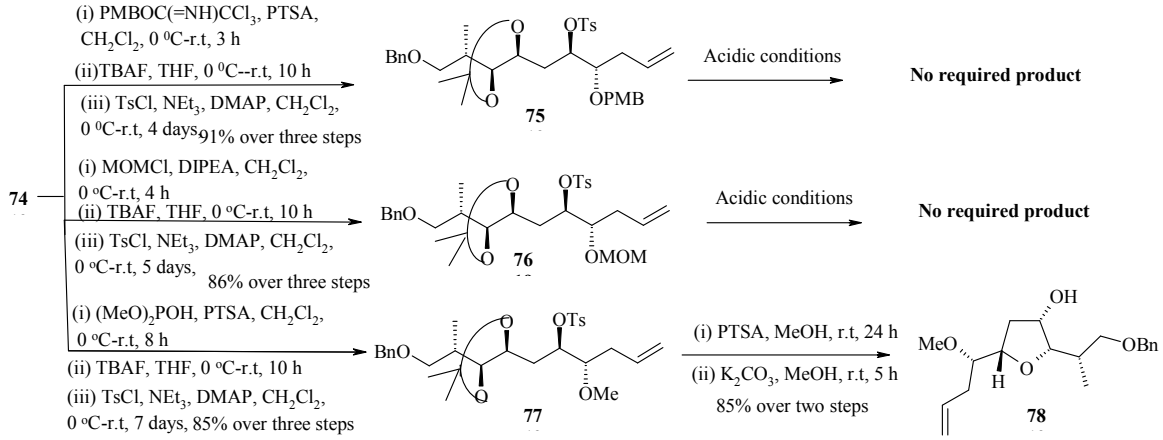


Scheme 7

The zinc-mediated asymmetric alkynylation of TMS acetylene with aldehyde **67** under Carreira's conditions[76] ((+)-NME, Zinc triflate, TMS-acetylene and TEA) to afford the propargylic alcohol **68** in good yield and with high diastereoselectivity (de >96%). Compound **68** was confirmed from ^1H NMR spectrum wherein the protons of TMS group resonated at δ 0.17 as a sharp singlet and a mutilet at δ 4.55-4.44 for three protons including a benzyl group. The other protons resonated at their respective chemical shifts.

A proton due to the aldehyde group disappeared. In IR spectrum showed strong absorption at 3449 cm^{-1} for the hydroxyl function. The formation of the product was further supported by its $[M + Na]^+$ peak observed at *m/z* 413 in ESIMS. The TMS group in compound **68** was deprotected under methanolic K_2CO_3 conditions. The structure of compound **69** was characterized from its ^1H NMR, IR and mass spectral properties. The ^1H NMR spectrum of compound **69** clearly showed a disappearance of TMS group protons at δ 0.17, and appearance of acetylinic group protons at δ 2.41as a doublet. In IR spectrum an absorbance at 3416 cm^{-1} for the hydroxyl functional group was observed, and in mass spectrum appearance of a molecular ion peat at *m/z* 341 $[M+Na]^+$ further confirmed the product. In order to get the secondary allyl alcohol, compound **69** was treated with 1.5 eq of lithium alumunium hydride[9] in anhydrous THF at 0 ^oC, which reduced the alkyne to the desired terminal olefin **70** in 80% yield. The PMR spectrum showed a multiplet at δ 5.85-5.68 due to one olefinic proton, at δ 5.37 (td, *J* = 1.6, 10.3 Hz) and δ δ 5.22 (td, *J* = 1.5, 11.0 Hz) integrating two protons respectively. In the IR spectrum a characteristic C=C stretch at 1644 cm^{-1}, a C-H deformation stretch at 920 cm^{-1} for the C-H protons and hydroxyl absorption at 3449 cm^{-1} was observed. The structure of the olefin **70** was further confirmed by the mass spectrum, which showed a molecular ion peak at *m/z* 343 $[M+Na]^+$. The secondary hydroxy group in compound **70** was protected as its silyl ether **71** by treatment with 1 eq of *tert*-butyldiphenylsilyl chloride and 2 eq of imidazole in dry dichloromethane at 0 ^oC. In ^1H NMR δ 7.71-7.55 multiplet for five protons, δ 7.42-7.18 multiplet for five protons and appearance of singlet at δ 1.06 for nine protons indicates the presence of *tert*.butyldiphyenylsilyl protection. While the remaining protons resonated at their respective chemical shifts. Further the formation of the product was supported by ESIMS which showed $[M+Na]^+$ peaks at m/z 581. Next, compound **71** was subjected to catalysed OsO_4 dihydroxylation in presence of 1 eq of OsO_4 and 1.2 eq of NMO at room temperature to give 1,2-diol compound in 90% yield with high diastereoselectivity confirmed by chiral HPLC.[77] In PMR spectrum the structure of 1,2-diol **72** was confirmed by the absence of olefinic group protons. The other protons resonated at their respective chemical shift positions. IR spectrum showed a strong absorption band at 3449 cm^{-1} for -OH stretching frequency and ESIMS showed $[M+Na]^+$ signal at *m/z* 593, further confirmed the structure **72** (Scheme 7). The primary

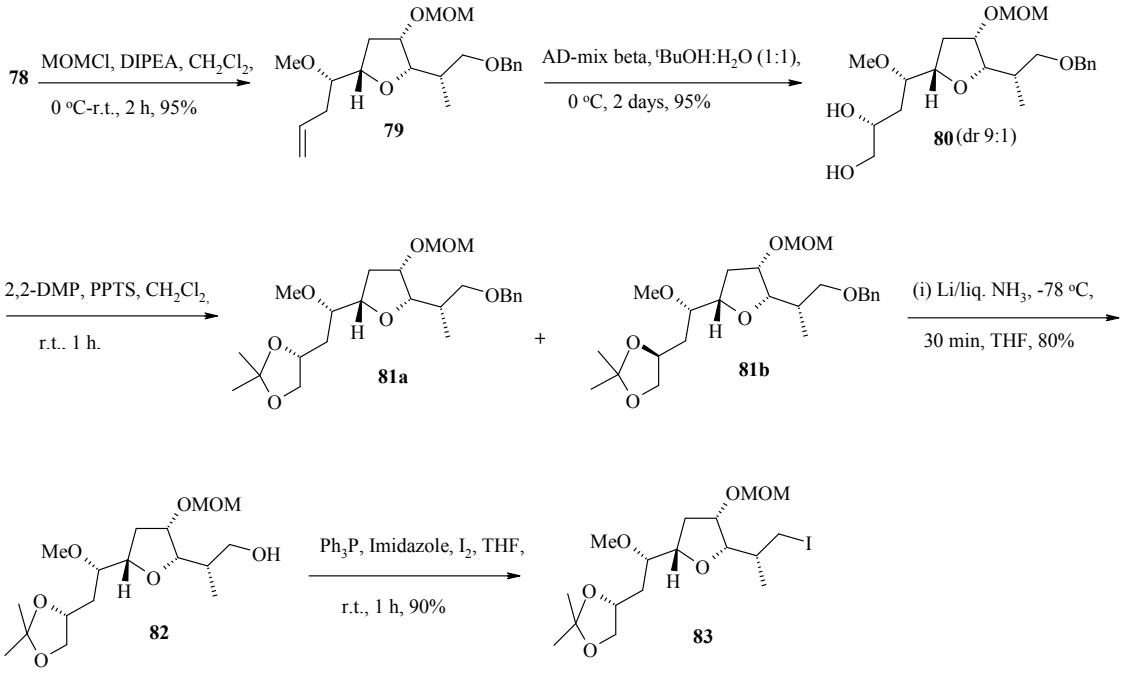
alcoholic function in compound **72** was selectively converted into monoiodo compound **73** by using TPP and *N*-iodosuccinamide in THF, which without purification was subjected to coupling reaction using vinyl magnesium bromide in the presence of CuI[74] to afford homoallyl alcohol **74** in 75% yield over two steps ^{1}H NMR spectrum of the compound **74** exhibited two multiplets due to olefinic protons at δ 5.77-5.58 and δ 5.96-4.90 integrating one and two protons respectively. Oxygen attached C-H signals were integrated for six protons confirmed that the elimination of iodo group anticipated line. In addition, IR spectrum showed hydroxyl absorbtion at 3459 cm^{-1} and ESIMS showed $[M+Na]^+$ signal at *m/z* 625, further confirmed the structure **74** (Scheme 7).



Scheme 8

Our next task was to convert compound **74** into functionalized 2,5-*syn* tetrahydrofuran **78** (Scheme 8). Accordingly, the secondary hydroxyl group in compound **74** was protected as PMB ether with PMB imidate in CH_2Cl_2 under PTSA conditions, followed by removal of TBDPS group with TBAF in THF and converted into its tosylate compound **75** in presence of tosyl chloride, DMAP and triethyl amine. The tosylated compound **75** was characterized by its PMR spectrum, which showed signals at δ 7.82 (d, *J* = 8.1 Hz, 2H, ArH), 7.49 (d, *J* = 7.50 Hz, 2H, ArH) and 2.55 (s, 3H, Ar-C**H$_3$**) corresponding to tosyl group. IR spectrum showed a strong absorption at 1046 cm^{-1} corresponding to S=O stretching clearly indicating the presence of tosyl group. Further it was characterized by ESI-MS data which showed a value of *m/z* 585 for the $[M+Na]^+$.

Acetonide deprotection in compound **75** could not be achieved under PPTS/MeOH conditions, instead, starting materials recovered back. The tosyl compounds **75** under several acidic conditions such as PTSA/MeOH, 3NHCl/MeOH, 60% CH_3COOH/MeOH, CAN/MeOH, $CeCl_3.7H_2O$/MeOH gave mixtures of compounds and could not be identified. In the same manner the secondary hydroxyl group in compound **74** was protected as MOM ether using 1.2 eq of MOMCl and 2 eq of DIPEA, followed by removal of TBDPS group with TBAF in THF and converted into its tosylate compound **76** in presence of tosyl chloride, DMAP and triethyl amine. The tosylated compound **76** was characterized by its PMR spectrum, which showed signals at δ 7.80 (d, J = 8.2 Hz, 2H, ArH), 7.49-7.02 (m, 7H, ArH), and 2.51 (s, 3H, Ar-C**H$_3$**) corresponding to tosyl group. IR spectrum showed a strong absorption at 1040 cm^{-1} corresponding to S=O stretching clearly indicating the presence of tosyl group. Further it was characterized by ESI-MS data which showed a value of *m/z* 661 for the $[M+Na]^+$. Acetonide deprotection in **76** could not be achieved under PPTS/MeOH conditions, instead, starting materials recovered back. The tosyl compounds **76** under several acidic conditions such as PTSA/MeOH, 3NHCl/MeOH, 60% CH_3COOH/MeOH, CAN/MeOH, $CeCl_3.7H_2O$/MeOH gave mixtures of compounds and could not be identified. However, change of protecting group into methyl ether **77**[78] gratifyingly, furnished the desired compound **78**. Thus, compound **74** was converted into *O*-methyl compound by methylation using dimethyl phosphite, in the presence of PTSA followed by the removal of TBDPS group to furnish alcohol, which was subsequently tosylated to give **77** in 85% yield over three steps (Scheme 8). Next, acetonide in compound **77** was deprotected under acidic conditions using PTSA in MeOH followed by intramolecular backside displacement in the presence of K_2CO_3/MeOH to give 2,5-*syn* tetrahydrofuran **78**[79] in 85% yield over two steps. The structure of **78** was confirmed by its PMR spectrum, which shows disappearance of two doublets at δ 7.77 and 7.33 and disappearance δ 2.55 (s, 3H, Ar-C**H$_3$**) corresponding to tosyl group, which earlier appeared in **77** and remaining all protons were resonated at their respective chemical shifts. The ESIMS mass spectrum data, which showed $[M+Na]^+$ peak at *m/z* 343 further confirmed the product **78**. In the IR spectrum a strong absorption band corresponds to OH group appeared at 3452 cm^{-1} further confirmed the product **78**.

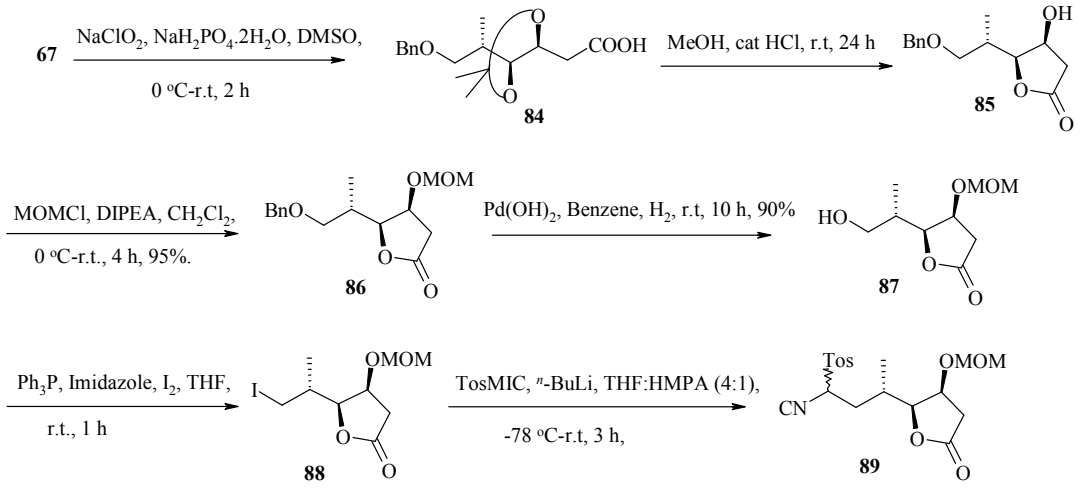


Scheme 9

Protection of secondary hydroxy group in **78** as MOM ether afforded **79** using *i*Pr_2NEt and MOMCl in CH_2Cl_2. Compound **79** was characterized by appearance its PMR spectrum signals at δ 4.68 (dd, *J* = 6.5, 24.7 Hz, 2H) and 3.34 (s, 3H, CH_2-O-C**H**$_3$). Further it was characterized by ESI-MS data which showed a value of *m/z* 387 for the $[M+Na]^+$. Asymmetric dihydroxylation[47] of **79** using AD-mix-β in ^{t}BuOH/H_2O (1:1) at 0 ^{o}C gave the diol **80** in 95% yield with 9:1 diastereomeric ratio, which was confirmed by chiral HPLC.[80] The compound **80** was confirmed by spectral data. In PMR sprctrum disappearance of olefinic protons indicates formation of diol compound **80**. IR spectrum showed strong absorption at 3444 cm^{-1} for the hydroxyl function. Further it was characterized by ESI-MS data which showed a value of *m/z* 421 for the $[M+Na]^+$. The diol compound **80** was then reacted with 2,2-dimethoxypropane and catalytic amount of PPTS in 9:1 mixture of CH_2Cl_2 to give acetonides **81a** and **81b** (9:1) as a seperable diastereomers in 93% yield (Scheme 9). The ^{1}H NMR spectrum of **81a** showed two sets of singlets at δ 1.36 and 1.31 for two methyl groups, it was also characterized by ESI-MS data, which showed $[M+Na]^+$ peak at *m/z* 461. In IR spectrum disappearance of strong

absorption at 3444 cm^{-1} due to hydroxyl group confirmed the conversion of diol into corresponding 1,2 terminal acetonide protection. Substrate **81a** on treatment with lithium in liquid NH_3 underwent debenzylation to produce primary alcohol **82**. In ^1H NMR spectrum of **82**, disappearance of peaks due to benzyl group in aromatic region was observed. IR spectrum showed a strong absorption at 3461 cm^{-1} due to hydroxyl group confirmed the conversion. ESI- MS signal at *m/z*: 371 $[M+Na]^+$ further confirmed the transformation (Scheme 9). Compound **82** on exposure to TPP, I_2, and imidazole at room temperature gave the corresponding iodide **83** in 1 h. In the ^1H NMR spectrum of **83**, it showed the disappearance of substituted methoxy group protons and the appearance of iodo attached CH_2 protons at δ 3.67-3.42 (m, 2H) and in IR spectrum disappearance of strong absorption at 3461 cm^{-1} due to hydroxyl group further confirmed the conversion of primary alcohol into corresponding iodo compound.

(4*S*,5*S*)-5-((*S*)-4-isocyano-4-tosylbutan-2-yl)-4-(methoxymethoxy)-dihydrofuran-2(*3H*)-one (89):



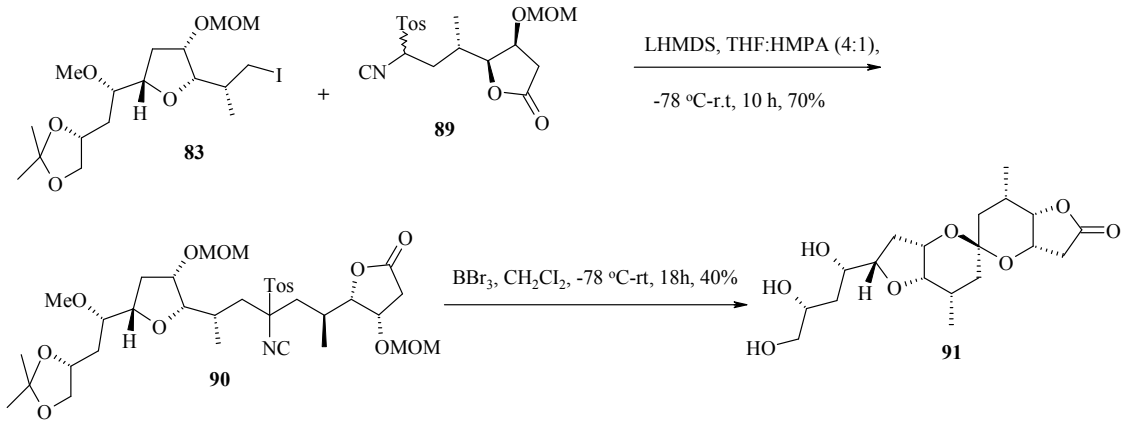
Scheme 10: Lactone fragment **89**

The aldehyde **67** was oxidized to the acid **84** with $NaClO_2$ in the presence of $NaH_2PO_4.2H_2O$ (buffer conditions) in DMSO with 78% yield. The crude acid compound **84** was directly used for the next step. In acid compound **84** Deprotection of acetonide as well as cyclization occured in one-pot by using catalytic concentrated HCl in methanol to furnish 5-membered lactone **85**[81] (Scheme 10). The structure of the compound **85** was

established from its spectral data. In the ^{1}H NMR spectrum of **85**, a proton resonated at δ 4.36 as a doublet of doublet (J = 4.5, 6.0 Hz) due to lactone center and disappearance of two sets of singlets corresponding acetonide group was observed. The molecular ion peak at *m/z* 273 $[M+Na]^+$ in its ESIMS spectrum and strong absorption band at 1765 cm^{-1} for ester carbonyl group in the IR spectrum confirms the structure. The secondary hydroxyl group of compound **85** was protected as its methoxy methyl ethers **86** using 2 eq of hunig's base and 1.5 eq of MOMCl in CH_2Cl_2 afforded the MOM ether compound **86** in 95% yield. The structure of ether **86** was characterized from its ^{1}H NMR, IR and mass spectral properties. The MOM ether **86** exposed to $Pd(OH)_2$ and H_2 gas to give primary alcoholic compound **87** in 90% yield. Compound **87** was characterized by disappearance of PMR spectrum signals in aromatic region. Further it was characterized by a strong absorption at 3426 cm^{-1} and ESI-MS data which showed a value of *m/z* 277 for the $[M+Na]^+$ (Scheme 10). Compound **87** on exposure to TPP, I_2, and imidazole at room temperature gave the corresponding iodide **88** in 1 h., which was directly used for the next step. The crude alkyl iodide **88** on treatment with TosMIC **92** (tosyl methyl isocyanide) in the presence of *n*-BuLi in a mixture of THF:HMPA (4:1) afforded **89**[82] in 85% yield over two steps. The TosMIC compound **89** was characterized by its PMR spectrum, which showed signals at δ 7.86 (d, J = 8.3 Hz, 2H, ArH), 7.43 (d, J = 7.5 Hz, 2H, ArH), and 2.51 (s, 3H, Ar-C**H$_3$**) corresponding to tosyl group and δ 4.51 (dd, J = 3.0, 12.0 Hz, 1H) for TosMIC attached center proton. IR spectrum showed a strong absorption at 1085 cm^{-1} corresponding to S=O stretching clearly indicating the presence of tosyl group. The structure of the TosMIC compound **89** was further confirmed by the mass spectrum, which showed a molecular ion peak at *m/z* 404 $[M+Na]^+$.

Now, the stage was set to prepare C38-C54 segment (**91**) of halichondrin B by coupling of fragments **83** and **89** with LHMDS through the formation of intermediate compound **90.** In order to get compound **90**, compounds **83** and **89** were coupled in presence of LHMDS (THF:HMPA 4:1) with 70% yield. The di alkylated product **90**[82] was subjected to spiroketalisation with 1.0 molar solution of BBr_3 in CH_2Cl_2 to afford C38-C54 segment (**91**)[83] of halichondrin B in 40% yield.

Synthesis of the C38-C54 segment (91) of halichondrin B

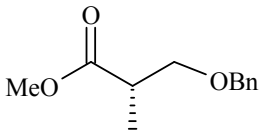


Scheme 11: Synthesis of the C38-C54 segment **(91**) of halichondrin B

The spectral and analytical data of the synthetic fragment **91** were in good agreement with the reported data of Brurke *et al* approach.[73] The PMR spectrum of compound **91** revealed the absence of TosMIC group and other protons resonated at their respective chemical shift positions. In ^{13}C NMR spectrum appearance of quaternary carbon at δ 97.1 which is characteristic peak for the spiroketal function confirmed the conversion. In IR it was characterized by a strong absorption at 3432 cm^{-1} due to hydroxyl group and molecular ion peak at *m/z* 409.1833 $[M+Na]^+$, in its HR-ESI-MS spectrum further confirmed the spiroketal fragment **91** formation (Scheme 11).

EXPERIMENTAL SECTION

(*S*)-methyl 3-(benzyloxy) 2-methylpropanoate (58):



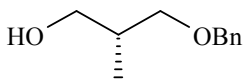
Trifluoromethanesulfonic acid (1.4 mL, 9.33 mmol) was added to a solution of commercially available methyl (*S*)-(-)-3-hydroxy-2-methyl propionate **57** (11 g, 93.2 mmol) and *O*-benzyltrichloroacetimidate (34.8 mL, 138 mmol) in a mixture of cyclohexane and methylene chloride (2:1) (100 mL) cooled to 0 ^{o}C. After stirring at the same temperature for 3 h, the mixture was diluted with ether (100 mL) and washed successively with water (80 mL), 0.1N HCl (40 mL), saturated $NaHCO_3$ (2x1000 mL) and brine (100 mL). The organic layers were dried (Na_2SO_4), filtered, and concentrated in *vacuo*. The residue was diluted with hexane. The white precipitate formed was removed by filtration and washed with hexane. The combined filtrates were concentrated in *vacuo*. The residue was purified by column chromatography (1:9, EtOAc/hexane) to afford **58** (13.5 g, 64.9 mmol, 70%) as a colorless oil.

$[\alpha]_D^{25}$: +16.0 (*c* 3.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38-7.21 (m, 5H), 4.47 (s, 2H), 3.65 (s, 3H), 3.59 (dd, 1H, *J* = 10, 3 Hz), 3.44 (dd, 1H, *J* = 10 Hz, 3 Hz), 2.72 (m, 1H), 1.15 (d, 3H, *J* = 5.2 Hz).

IR (Neat): 3076, 2924, 2872, 1738, 1187, 1012, 813 cm^{-1}.

(*R*)-3-(benzyloxy) 2-methylpropan-1-ol (59):



A solution of methyl (2*R*)-3-benzyloxy-2-methyl propionate **58** (13.0g, 62.5 mmol) in THF (100 mL) was added drop wise to a suspension of lithium aluminium hydride (3.0 g, 78.9 mmol) in THF (100 mL) under ice cooling. After stirring the reaction mixture at room temperature for 30 min, water (8 mL), 15% NaOH solution (9 mL) and

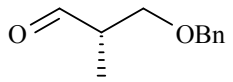
water (8 mL) were successively added and the mixture was stirred for 10 min. The resulting suspension was filtered through a pad of Celite and the precipitate was washed with EtOAc. The combined filtrates were dried (Na_2SO_4) and concentrated in *vacuo*. The residue was purified by column chromatography (3:7, EtOAc/hexane) to afford compound **59** (11.0 g, 61.1 mmol, 95%) as a colorless oil.

$[\alpha]_D^{25}$: +13.0 (c 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.21 (m, 5H), 4.49 (s, 2H,), 3.58 (d, 2H, *J* = 6.1 Hz), 3.51 (t, 1H, *J* = 4.4 Hz), 3.39 (t, 1H, *J* = 8.1 Hz), 2.39 (br s, 1H), 2.04 (m, 1H), 0.89 (d, 3H, *J* = 7.4 Hz).

IR (Neat) : 3337, 3123, 2928, 2868, 1234, 747 cm^{-1}.

(S)- 3-(benzyloxy) 2-methylpropanal (60):



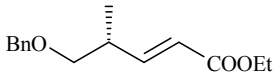
Pyridinium chlorochromate (PCC) (26.2 g, 121 mmol) and Celite (8 g) were added to a solution of alcohol **59** (10.9 g, 60.5 mmol) in CH_2Cl_2 (300 mL). After stirring the reaction mixture at 25 ºC for 3 h, isopropanol (20 mL) was added and the solvent was removed under reduced pressure. The residue was filtered through Celite pad with Et_2O and the organic layer was washed with dil.HCl, water, brine and dried (Na_2SO_4). Removal of solvent afforded a gummy material, which was purified by silica gel column chromatography (2:8, EtOAc/hexane) to afford the aldehyde **60** (9.63 g, 54.1 mmol, 90%) as an oil.

$[\alpha]_D^{27}$: +28.1 (c 2.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.70 (s, 1H), 7.35-7.25 (m, 5H,), 4.50 (s, 2H), 3.68 – 3.58 (m, 2H), 2.69–2.57 (m, 1H), 1.32 (d, 3H, *J* = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.7, 137.8, 128.3, 127.6, 127.4, 73.1, 70.0, 46.6, 10.6.

(*R*,*E*)-ethyl 5-(benzyloxy)-4-methyl-2-enoate (61):



To a solution of **60** (9.5 g, 13.4 mmol) in anhydrous benzene (150 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (22 g, 63.4 mmol). The mixture was maintained at 80 °C for 2 h, and then the solvents were removed *in vacuo*. The residue was purified by silica gel column chromatography (1.5:8.5, EtOAc/hexane) to afford **61** (13.1 g, 52.8 mmol, 98%) as a colorless oil

$[\alpha]_D^{27}$: +12.4 (c = 1, $CHCl_3$).

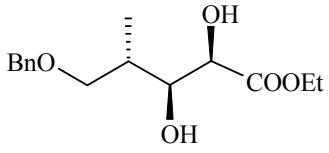
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.27 (m, 5H, Ar-H), 6.90 (dd, *J* = 6.7, 15.8 Hz,1H), 5.81 (dd, *J* = 1.5, 15.8 Hz,1H), 4.49 (s, 2H, CH_2-OAr), 4.17 (q, *J* = 7.5, Hz, 2H, CH_2), 3.43-3.30 (m, 2H), 2.69-2.55 (m, 2H), 1.30 (t, *J* = 7.55 Hz ,3H, CH_3), 1.10 (d, *J* = 6.7 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 151.0, 138.0, 128.2, 127.48, 127.4, 120.8, 73.7, 72.9, 60.1, 36.6, 15.9, 14.1.

IR (neat): 2975, 2858, 1717, 1452, 1268, 1183, 1097, 983 cm^{-1}.

ESIMS: 271 $[M+Na]^+$.

(2*R*,3*S*,4*S*)-ethyl 5-(benzyloxy)-2,3-dihydroxy-4-methylpentanoate (62):



Admix-α (73.38 g) and methane sulphonamide (4.97 g, 42.61 mmol) were added to the compound **61** (13 g, 52.41 mmol) in 262.09 mL of ^{t}BuOH and 262.09 mL of water at 0 ^{o}C. The reaction mixture was stirred at the same temperature for 3 days. After 3 days the reaction mixture was quenched by the addition of saturated solution of Na_2SO_3 (45 mL) and KOH (40 mL). After 10 minutes, the reaction was warmed to room temperature

and stirred for additional 30 min. The reaction contents were transferred to a separatory funnel with EtOAc, the phases were separated aqueous layer further extracted with EtOAc (4 X 250 mL). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuo and the residue was purified by column chromatography (5:5, EtOAc/hexane) to afford the diol compound **62** (13.03 g, 14.16 mmol, 90%) as a viscous liquid with >95% diastereoselectivity determined by chiral HPLC.

$[\alpha]_D^{25}$: +10.2 (*c* = 0.9, $CHCl_3$).

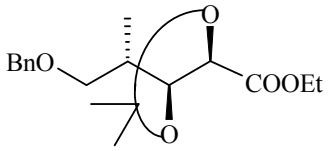
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35-7.22 (m, 5H), 4.52 (s, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 4.11 (t, *J* = 6.9 Hz,1H), 3.77 (br s, 2H, OH), 3.63 (dd, *J* = 4.1, 9.0 Hz, 1H), 3.55-3.44 (m, 2H), 2.23-2.05 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.4, 137.4, 128.3, 127.7, 127.5, 76.9, 74.8, 73.3, 71.6, 61.6, 35.2, 14.0, 13.5.

IR (neat): 3449, 2973, 2932, 1736, 1454, 1214, 1095, 860 cm^{-1}.

ESIMS: *m/z* 305 $[M+Na]^+$.

(4*R*,5*S*)-ethyl 5-((*S*)-1-(benzlyoxy)pyropan-2-yl)-2,2-dimethyl-1,3-dioxolane-4-caboxylate (63):

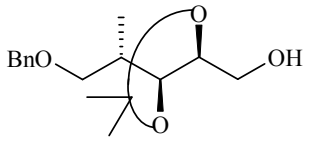


2,2-Dimethoxypropane (7.34 mL, 70.24 mmol) and catalytic PPTS (1.2 g, 4.78 mmol) were added successively to a solution of diol **62** (13.25 g, 47.0 mmol) in a mixture of CH_2Cl_2:Me_2CO (1:1) (150 mL). The solution was stirred for 10 h at room temperature and then quenched with solid $NaHCO_3$. The crude compound was concentrated in vacuo and purified by column chromatography (2:8, EtOAc/hexane) to afford the acetonide product **63** (14.36 g, 44.59 mmol, 95%) as a coloress liquid.

$[\alpha]_D^{25}$ –8.9 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.35-7.18 (m, 5H), 4.46 (s, 2H), 4.32-4.06 (m, 4H), 3.55 (dd, *J* = 5.2, 9.0 Hz, 1H), 3.42-3.32 (m, 1H), 2.17-2.03 (m, 1H), 1.41(s, 3H), 1.40 (s, 3H), 1.27 (t, *J* = 6.90 Hz, 3H), 1.02 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 171.2, 138.2, 128.1, 127.2, 127.1, 110.4, 80.6, 76.8, 72.8, 71.6, 61.0, 36.4, 26.8, 25.4, 13.8, 13.2.
IR (neat):	2985, 2934, 1746, 1455, 1261, 1101, 860 cm^{-1}.
ESIMS:	*m/z* 361 $[M+K]^+$.

((4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (64):



To a stirred suspension of $LiAlH_4$ (2.53 g, 66.57 mmol) in anhydrous THF (20 mL) at 0 ^oC was added dropwise, a solution of compound **63** (14.31 g, 44.44 mmol) in anhydrous THF (60 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1/2 h. It was then cooled to 0 ^oC, diluted with ether and quenched with drop wise addition of saturated aqueous Na_2SO_4 (20 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (4:6, EtOAc/hexane) to afford the compound **64** (11.19 g, 39.96 mmol, 90%) as a viscous liquid.

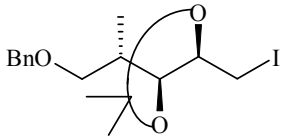
$[\alpha]_D^{25}$	–9.0 (*c* = 0.75, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz):	δ 7.34-7.23 (m, 5H), 4.48 (s, 2H), 3.98-3.90 (m, 1H), 3.84-3.68 (m, 2H), 3.61-3.50 (m, 2H), 3.38 (q, *J* = 8.8 Hz, 1H), 2.06-1.96 (m, 1H), 1.37 (s, 3H), 1.36 (s, 3H), 0.99 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.2, 128.3, 128.2, 127.4, 108.3, 79.4, 78.3, 72.9, 72.0, 63.2, 36.7, 27.0, 27.0 13.4.

IR (neat): 3448, 2983, 2931, 1454, 1214, 1058, 902 cm^{-1}.

ESIMS: *m/z* 319 $[M+K]^+$.

(4*S*,5*R*)-4-((*S*)-1-(benzyloxy)propan-2-yl)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxalane (65):



To a stirred solution of alcohol **64** (11.14 g, 39.78 mmol) in 35 mL of toluene at 0 °C was added triphenylphosphine (15.63 g, 59.65 mmol), imidazole (6.76 g, 99.41 mmol), and iodine (10.49 g, 79.54 mmol). After 20 h the reaction was quenched with saturated solution of $Na_2S_2O_3$, aqueous layer was exctracted with EtOAc (2 x 40 mL) and dried over anhydrous Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel column chromatography (2:8, EtOAc/hexane) to afford iodo compound **65** (12.40 g, 31.79 mmol, 80%) as a yellow liquid.

$[\alpha]_D^{25}$: –16.0 (*c* = 0.7, $CHCl_3$).

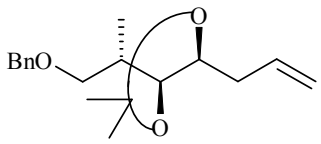
^{1}H NMR ($CDCl_3$, 300 MHz): δ ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.23 (m, 5H), 4.48 (s, 2H), 3.90-3.81 (m, , 1H), 3.70 (t, *J* = 6.6 Hz, 1H), 3.55 (dd, *J* = 5.0, 9.0 Hz, 1H), 3.41-3.28 (m, 2H), 3.25-3.16 (m, 1H), 2.08-1.92 (m, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.2, 128.3, 127.5, 127.5, 108.8, 82.9, 77.8, 73.1, 71.7, 36.4, 27.5, 27.4, 13.9, 7.8.

IR (neat): 2975, 2925, 1455, 1239, 1100, 885 cm^{-1}.

ESIMS: *m/z* 413 $[M+Na]^+$.

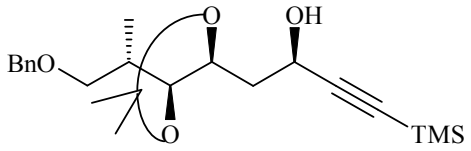
(4*S*,5*S*)-4-allyl-5-((S)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolane (66):



Vinylmagnesium bromide (31.66 mL, 31.66 mmol, 1.0 M in THF) was added to CuI (0.2 g) at –40 ^{o}C followed by precooled iodide **65** (12.35 g, 31.66 mmol) in THF-HMPA (2:1, 30 ml). Then the mixture was allowed to warm to r.t. After 4 h reaction at r.t., the reaction was quenched by adding saturated solution of NH_4Cl at 0 ^{o}C, the solid was removed by filtration, and the organic layer was washed with brine. After drying over Na_2SO_4, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (3:7, EtOAc/hexane) to give **66** (6.88 g, 23.72 mmol, 75%) as a colorless liquid.

$[\alpha]_D^{25}$:	–28.1 (*c* = 0.9, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz):	δ 7.34-7.22 (m, 5H), 5.93-5.74 (m, 1H), 5.11-5.00 (m, 2H), 4.48 (s, 2H), 3.90 (td, *J* = 3.7, 7.5 Hz, 1H), 3.62-3.53 (m, 1H), 3.48-3.14 (m, 2H), 2.42-2.19 (m, 2H), 2.0-1.88 (m, 1H), 1.35 (s, 3H), 1.32 (s, 3H), 1.0 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 138.4, 134.3, 128.2, 127.4, 127.4, 117.1, 107.9, 81.8, 78.2, 72.9, 72.1, 38.2, 36.6, 27.2, 27.1, 14.2.
IR (neat):	2981, 2929, 1454, 1243, 1097, 1055, 912 cm^{-1}.
ESIMS:	*m/z* 313 $[M+Na]^+$.

(*R*)-1-((4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-2,2-dimetyl-1,3-dioxalan-4yl)-4-(trimethylsilyl)but-3-yn-2-ol (68):



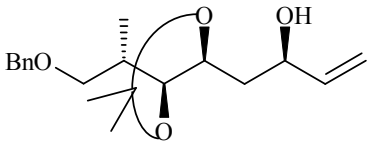
NMO (4.13 g, 35.29 mmol) and the alkene **66** (6.83 g, 23.55 mmol) were dissolved in 1:1 ratio of Me_2CO:H_2O (50 mL). A 0.02 M solution of OsO_4 in toluene (2 mL) was added, and the reaction mixture was stirred for 3 days at r.t., then cooled in ice bath. The reaction was quenched by addition of sat. Solution of Na_2SO_3 (25 mL). Most of

the acetone removed by rotary evaporation, and the aqueous mixture was extracted with EtOAc (3 x 60mL). The combined organic extracts were concentrated under reduced pressure, and the crude diol was used for the next step without further purification. $NaIO_4$ (7.29 g, 34.22 mmol) was added to the crude diol (7.40 g, 22.83 mmol) in 4:1 ratio of THF:H_2O (50 mL) at room temperature. The reaction was completed within 1/2 h. After filtration two layers were separated, the aqueous layer was extracted with EtOAc (2 X 50 mL) and dried over Na_2SO_4 and concentrated to give crude aldehyde **67** which was directly used for the next step without further purification.

To a solution of zinc triflate (6.83 g, 18.81 mmol) and (1*R*,2*S*)-*N*-(+)-methylephedrine (3.97 g, 20.5 mmol) in toluene (1 mL) was added Et_3N (2.85 mL, 28.21 mmol) through a septum. The resulting slurry was stirred for 2 h and then trimethylsilyl acetylene (3 ml, 33.33 mmol) was added. After 30 min a solution of aldehyde **67** (5 g, 17.12 mmol) in toluene (15 mL) was added via a cannula. The reaction mixture was then heated to 60 °C. After 48 h the reaction mixture was concentrated in vacuo and purified by flash chromatography (3:7, EtOAc/hexane) to afford propargylic alcohol **68** as a yellow color liquid (5.66 g, 14.51 mmol, 93.5% yield over three steps) with >96% diastereoselectivity.

$[\alpha]_D^{25}$:	–8.7 (*c* = 0.55, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz):	δ 7.35-7.25 (m, 5H), 4.55-4.44 (m, 3H), 4.05-3.91 (m, 1H), 3.80-3.64 (m, 1H), 3.54 (q, *J* = 9.0 Hz, 1H), 3.38 (d, *J* = 6.0 Hz, 1H), 2.71(br s, 1H, OH), 2.01-1.86 (m, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.17 (s, 9H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 138.1, 128.2, 127.5, 127.5, 108.5, 105.9, 89.2, 82.2, 81.7, 73.07, 72.0, 61.6, 41.2, 35.2, 27.0, 26.9, 12.0, –0.20.
IR (neat):	3445, 2925, 2858, 1454, 1249, 1058, 845, 762 cm^{-1}.
ESIMS:	*m/z* 413 $[M+Na]^+$.

(*R*)-1-((4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3en-2-ol (70):



K_2CO_3 (4 g, 29.0 mmol) was added to the TMS-acetylene compound **68** (5.61 g, 14.38 mmol) in methanol (20 mL) at room temperature. The resulting mixture was stirred for further 5 h, after which the reaction was quenched by addition of phosphate buffer (pH 7). The combined organic phases were dried over Na_2SO_4, filtered, concentrated in vacuo and directly used for the next step without purification.

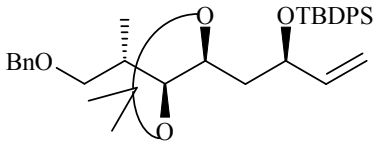
To a stirred suspension of $LiAlH_4$ (0.58 g, 15.26 mmol) in anhydrous THF (15 mL) at 0 ^oC was added dropwise, a solution of propargyl alcohol (4.06 g, 12.76 mmol) in anhydrous THF (50 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1/2 h. It was then cooled to 0 ^oC, diluted with ether and quenched with drop wise addition of saturated aqueous Na_2SO_4 (10 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (3.5:6.5, EtOAc/hexane) to afford the compound **70** (3.67 g, 11.46 mmol, 90% yield over two steps) as a viscous liquid.

$[\alpha]_D^{25}$: –15.2 (*c* = 1.6, $CHCl_3$).

^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.22 (m, 5H), 5.85-5.68 (m, 1H), 5.37 (td, *J* = 1.5, 10.3 Hz, 1H), 5.22 (td, *J* = 1.6, 11.0 Hz, 1H), 4.46 (s, 2H), 4.35-4.19 (m, 1H), 4.11-3.91 (m, 1H), 3.71 (q, *J* = 8.3 Hz, 1H), 3.58 (td, *J* = 1.5, 9.0 Hz, 1H), 3.37 (d, *J* = 6.0 Hz, 1H), 2.03-1.83 (m, 1H), 1.80-1.53 (m, 2H), 1.38 (s, 3H), 1.36 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz):	δ 140.0, 138.2, 128.2, 127.5, 127.5, 114.5, 108.4, 82.9, 82.2, 78.1, 73.0, 71.9, 41.0, 36.2, 27.1, 27.0, 14.0.
IR (neat):	3449, 2926, 2860, 1453, 1215, 1096, 920 cm^{-1}.
ESIMS:	*m/z* 343 $[M+Na]^+$.

((*R*)-1-((4S,5S)-5-((S-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-yloxy)(*tert*-butyl)diphenylsilane (71):



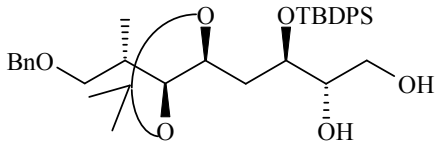
Imidazole (1.53 g, 22.5 mmol), and TBDPSCl (3.71 ml, 13.54 mmol) were added to a stirred solution of compound **70** (3.62 g, 11.31 mmol) in CH_2Cl_2 (25 mL) at 0 °C. Stirring was continued for 5 h and then the mixture was diluted with CH_2Cl_2 (20 mL). Evaporation of the solvent under reduced pressure followed by column chromatography (1:9, EtOAc/hexane) afforded the silyl ether **71** (5.67 g, 10.16 mmol, 90%) as a colorless liquid.

$[\alpha]_D^{25}$:	–26.9 (*c* = 2.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.71-7.55 (m, 5H), 7.42-7.18 (m, 10H), 5.86-5.64 (m, 1H) 5.08-4.94 (m, 2H), 4.44 (s, 2H), 4.42-4.31 (m, 1H), 3.68 (td, *J* = 2.8, 9.1 Hz, 1H), 3.56-3.36 (m, 2H), 3.34-3.24 (m, 1H), 1.91-1.76 (m, 1H), 1.71-1.55 (m, 2H), 1.22 (s, 3H), 1.20 (s, 3H), 1.06 (s, 9H), 0.91 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 139.8, 135.9, 135.8, 129.4, 129.4, 128.2, 128.2, 127.5, 127.4, 127.2, 115.22, 107.9, 82.4, 81.6, 75.4, 73.0, 72.5, 41.9, 35.0, 27.1, 27.1, 26.9 (3 x C), 19.2, 11.9.

IR(neat): 2933, 2894, 2858, 1461, 1246, 1105, 1061, 923 cm^{-1}.

ESIMS: *m/z* 581 $[M+Na]^+$.

(2*S*,3*R*)-4-((4S,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3,dioxalan-4-yl)-3-(*tert*-butyldiphenylsilyloxy)butane-1,2-diol (72):



NMO (1.53 g, 13.07 mmol) and the terminal alkene **71** (5.62 g, 10.07 mmol) were dissolved in 1:1 ratio of Me_2CO:H_2O (40 mL). A 0.02 M solution of OsO_4 in toluene (1.5 mL) was added, and the reaction mixture was stirred for 5 days at room temperature, then cooled in ice bath. The reaction was quenched by addition of saturated solution of Na_2SO_3 (15mL). Most of the acetone removed by rotary evaporation, and the aqueous layer was extracted with EtOAc (3 X 60 mL). The combined extracts were concentrated under reduced pressure, and the residue was purified by column chromatography (8:2, EtOAc/hexane) to give the corresponding diol **72** (5.36 g, 9.05 mmol, 90%) as a viscous liquid with high diastereoselectivity (9:1) determined by chiral HPLC.

$[\alpha]_D^{27}$: –14.0 (*c* = 1.5, $CHCl_3$).

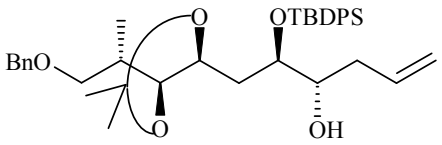
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.72-7.60 (m, 5H), 7.46-7.22 (m, 10H), 4.45 (s, 2H), 4.21-3.85 (m, 3H), 3.65 (t, *J* = 10.5 Hz, 2H), 3.58-3.53 (m, 1H), 3.48-3.40 (m, 1H), 3.36-3.16 (m, 1H), 2.02-1.79 (m, 1H), 1.76-1.44 (m, 2H), 1.32 (s, 3H), 1.26 (s, 3H), 1.06 (s, 9H), 0.89 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 135.8, 132.7, 129.8, 128.2, 127.7, 127.6, 127.6, 127.4, 108.3, 83.1, 80.7, 73.7, 73.0, 71.7, 71.2, 63.6, 35.5, 33.2, 26.9 (5 x C), 19.3, 14.7;

IR(neat): 3449, 2930, 2858, 1460, 1247, 1103, 927 cm^{-1}.

ESIMS: *m/z* 615 $[M+Na]^+$.

(2*R*,3*S*)-1-((4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(*tert*-butyldiphenylsilyloxy)hex-5-en-3-ol (74):



To a stirred solution of diol **72** (5.31 g, 8.96 mmol) in 25 mL of THF at 0 °C was added triphenylphosphine (4.7 g, 17.93 mmol) and *N*-iodosuccinamide (4.0 g, 17.77 mmol). After 3 h the reaction was quenched with saturated solution of $Na_2S_2O_3$ and the aqueous layer was extracted with EtOAc (3 X 40 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo and the crude unstable mono iodo compound **73** was directly used for the next step.

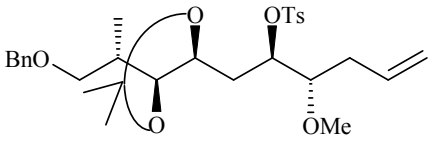
Vinylmagnesium bromide (28.77 mL, 28.77 mmol, 1.0 M in THF) was added to CuI (0.1 g) at -40 ^oC followed by precooled iodide **73** (5.05 g, 7.19 mmol) in THF-HMPA (2:1, 15 ml). Then the mixture was allowed to warm to r.t. After 7 h reaction at rt., the reaction was quenched by adding saturated solution of NH_4Cl, the solid was removed by filtration, and the organic layer was washed with brine. After drying over Na_2SO_4, the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (4:6, EtOAc/hexane) to give **74** (3.0 g, 5mmol, 75% yield over two steps) as colorless oil.

$[\alpha]_D^{25}$: –28.0 (*c* = 1.95, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.61 (m, 5H), 7.42-7.31 (m, 5H), 7.29-7.21 (m, 5H), 5.77-5.58 (m, 1H), 4.96-4.90 (m, 2H),4.43 (s, 2H), 4.02-3.86 (m, 1H), 3.85-3.76 (m, 1H), 3.65-3.54 (m, 1H), 3.45 (q, *J* = 8.9 Hz, 1H), 3.36-3.23 (m, 2H), 3.13 (br s, 1H, OH), 2.30-1.89 (m, 2H), 1.88-1.69 (m, 2H), 1.52-1.43 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 1.02 (s, 9H), 0.82 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz):	135.9, 135.4, 129.7, 129.7, 128.3, 128.2, 128.0, 127.6, 127.5, 127.4, 116.5, 108.1, 82.7, 80.9, 74.4, 73.2, 72.8, 71.8, 36.9, 33.6, 29.7, 27.1 (5 x C), 19.5, 14.8.
IR (neat):	3459, 2927, 2857, 1460, 1247, 1104, 909 cm^{-1}.
ESIMS:	*m/z* 625 $[M+Na]^+$.

(2*R*,3*S*)-1-((4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-2,2-dimethyl-1,3-dioxalan-4-yl)-3-methoxyhex-5-en-2yl 4-methylbenzenesulfonate (77):



Catalytic amount of PTSA (0.2 g, 1.16 mmol) was added to the stirred solution of compound **74** (2.45 g, 4.06 mmol) and $(OMe)_2POH$ (0.56 mL, 6.10 mmol) at 0 ^oC in 20 mL of CH_2Cl_2. The reaction mixture was stirred for 8 h at the same temperature and then quenched with solid $NaHCO_3$. Most of CH_2Cl_2 was removed by rotary evaporation. The unstable crude *O*-methyl compound directly used for the next step without further purification.

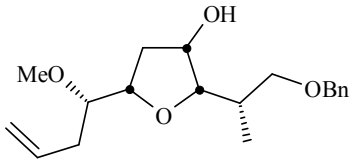
A 1M solution of TBAF in THF (6.1 mL) was added to a solution of *O*-methyl compound (1.88 g, 3.04 mmol) in dry THF (15 mL) at 0 ^oC. The mixture was stirred at r.t., for 10 h. After completion of the reaction, the mixture was diluted with EtOAc (35 mL). The combined organic layers were washed with sat. NaCl, and the mixture was extracted with ethyl acetate (3 X 20 mL). The organic extracts were washed with brine and dried over Na_2SO_4. The evaporation of the solvent under reduced pressure and the crude secondary alcoholic compound directly used for the next step.

Et_3N (0.72 ml, 7.12 mmol) and catalytic amount of DMAP were added to a secondary alcoholic solution (0.98 g, 2.6 mmol) in dry CH_2Cl_2 (20 mL) at 0 ^oC. After 15 min, tosyl chloride was (0.54 g, 2.83 mmol) added to the reaction mixture at the same temperature. The reaction mixture was stirred at room temperature for 7 days, after which it was diluted with water and extracted with CH_2Cl_2 (2 X 15 mL). The organic layer was

washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (3:7, EtOAc/hexane) to afford the compound **77** (1.25 g, 2.35 mmol, 85% yield over three steps) as a light yellow colored liquid.

$[\alpha]_D^{25}$:	–16.8 (*c* = 1.25, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 500 MHz):	δ 7.77 (d, *J* = 8.30 Hz ,2H), 7.33-7.22 (m, 7H), 5.68-5.51 (m, 1H), 5.09-4.93 (m, 2H), 4.79-4.61 (m, 1H), 4.48 (ABq, *J* = 8.3, 11.3 Hz, 2H), 4.03-3.81 (m, 1H), 3.62-3.43 (m, 2H), 3.42-3.27 (m, 2H), 3.25 (s, 3H), 2.44 (s, 3H), 2.29 (ddd, *J* = 7.5, 8.3, 12.8 Hz, 1H), 2.02-1.80 (m, 2H), 1.75-1.60 (m, 2H), 1.33 (s, 3H), 1.31 (s, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 144.3, 138.2, 134.2, 132.5, 129.4, 129.4, 128.1, 128.1, 127.7, 127.7, 127.3, 118.3, 107.9, 83.1, 82.0, 81.0, 78.4, 74.9, 72.8, 57.5, 36.3, 34.9, 30.7, 27.2, 26.8, 21.4, 14.1.
IR (neat):	3031, 2973, 2928, 1735, 1454, 1237, 1097, 912 cm^{-1}.
ESIMS:	*m/z* 555 $[M+Na]^+$.

(2*S*,3S,5*S*)-2-((*S*)-1-benzyloxy)propan-2yl)-5-((*S*)-1-methoxybut-3enyl)-tetrahydrofuran-3-ol (78):

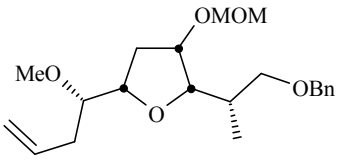


Catalytic amount of PTSA (0.1 g, 0.58 mmol) was added to a stirred solution of compound **77** (1.2 g, 2.25 mmol) in MeOH (15 mL) under N_2 at room temperature. Then the reaction mixture was stirred at same temperature for 24 h. The mixture was quenched with solid $NaHCO_3$ and the solvent was removed under reduced pressure and the crude

diol was used for the next step without further purification. Solid K_2CO_3 (0.7 g, 5.0 mmol) was added to the crude diol in 15 mL of methanol at room temperature. The reaction mixture was stirred for about 5 h. Evaporation of methanol under reduced pressure, followed by purification using column chromatography (3:7, EtOAc/hexane) afforded *syn*-tetrahydrofuran compound **78** (0.61 g, 2.0 mmol, 85% yield over two steps) as a colorless liquid.

$[\alpha]_D^{25}$:	–29.0 (*c* = 1.15, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.36-7.27 (m, 5H), 5.87-5.77 (m, 1H), 5.15-5.00 (m, 2H), 4.50 (s, 2H), 4.26-4.18 (m, 1H), 3.93 (ddd, *J* = 2.9, 3.9, 6.9 Hz, 1H), 3.79 (t, *J* = 3.9 Hz, 1H), 3.65-3.53 (m, 2H), 3.43-3.33 (m, 1H), 3.32 (s, 3H), 3.02 (br s, 1H, OH), 2.39 (t, *J* = 6.9 Hz, 1H), 2.34-2.21 (m, 1H), 2.12-1.87 (m, 3H), 1.01 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	138.4, 135.0, 128.1, 127.4, 127.3, 116.4, 84.5, 81.9, 78.1, 74.1, 73.1, 73.0, 56.8, 38.7, 36.1, 33.5, 14.5.
IR(neat):	3452, 2924, 1453, 1194, 1089, 914 cm^{-1}.
ESIMS:	*m/z* 343 $[M+Na]^+$.

(2*S*,3S,5*S*)-2-((*S*)-1-benzyloxy)propan-2yl)-5-((*S*)-1-methoxybut-3enyl)-3-(methoxymethoxy)-tetrahydrofuran (79):

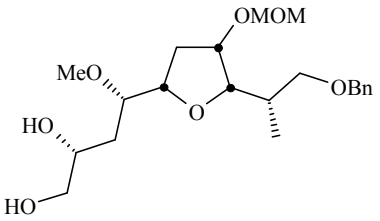


To a solution of hydroxyl compound **78** (0.56 g, 1.75 mmol) in anhydrous DCM (20 mL) at 0 ^oC under nitrogen, was added $^iPr_2NEt$ (0.6 mL, 4.65 mmol) drop wise and after 5 min MOMCl (0.2 mL, 2.5 mmol) was added drop wise. After stirring 2 h at room temperature, the reaction mixture was diluted with water, saturated aqueous NH_4Cl and brine solution then dried over anhydrous Na_2SO_4. The residue was purified on silica gel

column chromatography (2:8, EtOAc/hexane) to afford the pure **79** as a clear colorless liquid (0.6 g, 1.64 mmol, 95%).

$[\alpha]_D^{27}$:	–16.6 (*c* = 1.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 200 MHz):	δ 7.31-7.23 (m, 5H), 5.84-5.70 (m, 1H), 5.10-4.94 (m, 2H), 4.68 (dd, *J* = 6.5, 24.7 Hz, 2H), 4.45 (s, 2H), 4.30-4.13 (m, 1H), 3.89-3.76 (m, 1H), 3.69 (t, *J* = 4.3 Hz , 1H), 3.53 (ddd, *J* = 4.3, 6.5, 8.7 Hz, 1H), 3.45-3.35 (m, 2H), 3.34 (s, 3H), 3.23 (s, 3H), 2.32 (t, *J* = 6.5 Hz, 1H), 2.28-2.17 (m, 1H), 2.13-1.88 (m, 2H), 1.80-1.52 (m, 1H), 1.03 (d, *J* = 6.5 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 138.4, 134.4, 128.1, 127.4, 127.2, 116.3, 97.6, 84.5, 82.4, 81.2, 78.1, 72.9, 71.7, 56.7, 55.9, 38.8, 35.8, 33.4, 15.2.
IR(neat):	2930, 1453, 1274, 1150, 1032, 919 cm^{-1}.
ESIMS:	*m/z* 387 $[M+Na]^+$.

((2*R*,4S)-4-((2*S*,4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2yl)-4-(methoxymethoxy)-tetrahydrofuran-2-yl)-4-metthoxybutane-1,2-diol (80):

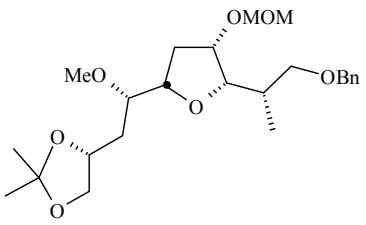


Admix-β (2.11 g) was added to the compound **79** (0.55 g, 1.51 mmol) in 7.5 mL of ^{t}BuOH and 7.5 mL of water at 0 ^{o}C. The reaction mixture was stirred at the same temperature for 2 days and then quenched by the addition of saturated solution of Na_2SO_3 (7 mL). After 10 min., the reaction was warmed to room temperature and stirred for additional 30 min. The reaction contents were transfered to a separatory funnel with 25 mL of EtOAc. The phases were separated and aqueous layer further extracted with

EtOAc (3 X 15 mL). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuo and the residue was purified by silica-gel column chromatography (8:2, EtOAc/hexane) to afford diol **80** (0.57 g, 1.43 mmol, 95%) as a viscous liquid with diastereoselectivity (9:1) determined by chiral HPLC.

$[\alpha]_D^{25}$:	–4.1 (*c* = 0.9, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz):	δ 7.34-7.23 (m, 5H), 4.77 (dd, *J* = 6.6, 32.6 Hz, 2H), 4.45 (s, 2H), 4.38-3.96 (m, 2H), 3.95-3.74 (m, 3H), 3.58 (ddd, *J* = 1.7, 3.0, 10.3 Hz, 1H), 3.48 (q, *J* = 9.8 Hz, 1H), 3.38 (s, 3H), 3.35-3.27 (m, 2H), 3.25 (s, 3H), 2.22-1.96 (m, 1H), 1.92-1.48 (m, 4H), 1.04 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 136.7, 126.4, 125.7, 125.6, 95.8, 80.8, 79.9, 78.3, 75.3, 74.8, 72.6, 71.9, 67.4, 55.0, 54.0, 34.1, 31.6, 30.9, 13.4.
IR(neat):	3444, 2928, 1457, 1217, 1091, 1032, 918 cm^{-1}.
ESIMS:	*m/z* 421 $[M+Na]^+$.

(*R*)-4-((*S*)-2-((2*S*,4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-4-methoxymethoxy-tetrahydrofuran-2-yl)-2-methoxyethyl)-2,2-dimethyl-1,3-dioxolane (81a):



2,2-Dimethoxypropane (0.2 mL, 2 mmol) and catalytic PPTS (0.1 g, 0.39 mmol) were added successively to a solution of diol **80** (0.52 g, 1.30 mmol) in CH_2Cl_2 (10 mL). The solution was stirred for 1 h at room temperature and then quenched with solid $NaHCO_3$. The crude compound was concentrated in vacuo and purified by column

chromatography (3:7, EtOAc/hexane) to separate two diastereomers in 9:1 ratio and the acetonide product **81a** (0.45 g, 1.0 mmol, 90%) as a colorless liquid.

$[\alpha]_D^{25}$: –7.6 (c = 1.15, $CHCl_3$).

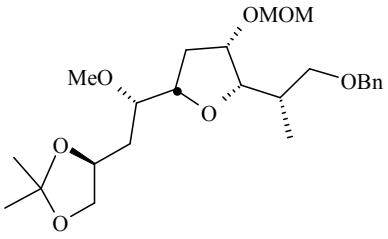
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.25 (m, 5H), 4.69 (dd, J = 4.5, 30.5 Hz, 2H), 4.44 (s, 2H), 4.26 (ddd, J = 3.4, 5.7, 12.5 Hz, 1H), 4.19-4.08 (m, 1H), 4.05-3.96 (m, 2H), 3.83-3.70 (m, 1H), 3.61-3.44 (m, 3H), 3.35 (s, 3H), 3.30-3.26 (m, 1H), 3.24 (s, 3H), 2.14-1.97 (m, 1H), 1.95-1.58 (m, 4H), 1.36 (s, 3H), 1.31 (s, 3H), 1.04 (d, J = 7.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 128.2, 127.6, 127.4, 108.5, 97.6, 85.5, 82.5, 80.0, 78.7, 73.7, 73.0, 71.8, 69.2, 56.8, 55.90, 35.8, 33.4, 32.7, 26.3, 26.1, 15.2.

IR(neat): 2981, 2928, 1456, 1211, 1091, 1034, 918 cm^{-1}.

ESIMS: m/z 461 $[M+Na]^+$.

(S)-4-((S)-2-((2S,4S,5S)-5-((S)-1-(benzyloxy)propan-2-yl)-4-methoxymethoxy-tetrahydrofuran-2-yl)-2-methoxyethyl)-2,2-dimethyl-1,3-dioxolane (81b):



$[\alpha]_D^{25}$: +5.3 (c = 0.95, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.18 (m, 5H), 4.71 (dd, J = 5.2, 49.8 Hz, 2H), 4.46 (s, 2H), 4.27-4.07 (m, 2H), 4.01 (q, J = 13.5 Hz, 2H), 3.76 (td, J = 4.5, 8.3 Hz, 1H), 3.62-3.40 (m, 4H), 3.35 (s, 3H),

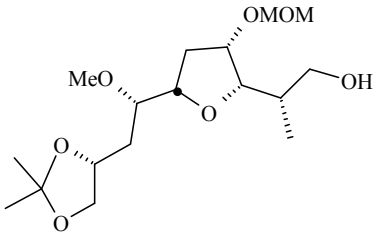
3.33 (s, 3H), 2.16-1.97 (m, 1H), 1.96-1.52 (m, 4H), 1.34 (s, 3H), 1.30 (s, 3H), 0.91 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.6, 126.4, 125.6, 125.7, 106.7, 97.6, 83.6, 80.8, 79.8, 78.2, 75.3, 72.6, 71.9, 71.2, 55.0, 54.0, 35.8, 34.0, 31.6, 25.1, 24.0, 13.4.

IR(neat): 2982, 2931, 1454, 1213, 1092, 1035, 918 cm^{-1}.

ESIMS: *m/z* 461 $[M+Na]^+$.

(*S*)-2-((2*S*,3*S*,5*S*)-5-((*S*)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4yl)-1-methoxymethoxy)-3-(methoxymethoxy)-tetrahydrofuran-2yl)propan-1-ol (82):



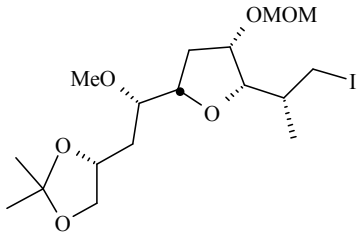
To a solution of lithium (32 mg, 4.57 mmol) in liquid NH_3 (6 ml) was added compound **81a** (0.4 g, 0.91 mmol) in dry THF (10 ml) at -78 ^oC. The mixture was stirred for 30 min and quenched with solid NH_4Cl (1.36 g). Ammonia was allowed to evaporate and the residual mixture was taken in EtOAc (15 ml) and washed with water, brine and dried (Na_2SO_4). Removal of the solvent and purification by column chromatography (6:4, EtOAc/hexane) afforded pure alcohol **82** (0.25 g, 0.72 mmol, 80%) as a colorless liquid.

$[\alpha]_D^{25}$: –20.1 (*c* = 0.95, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.81 (dd, *J* = 5.9, 29.6 Hz, 2H), 4.28-4.21 (m, 1H), 4.15 (td, *J* = 6.9, 20.7 Hz, 1H) 4.08-3.99 (m , 2H), 3.90-3.64 (m, 1H), 3.61-3.52 (m, 2H), 3.50 (q, *J* = 5.9, 7.9 Hz, 2H), 3.41 (s, 3H), 3.32 (s, 3H), 2.15-2.04 (m, 1H), 1.95-1.57 (m, 4H), 1.37 (s, 3H), 1.32 (s, 3H), 1.06 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz):	δ 108.5, 97.5, 84.9, 83.3, 81.4, 78.7, 73.5, 69.7, 69.0, 56.6, 55.8, 37.4, 36.5, 33.0, 26.6, 25.5, 15.1.
IR(neat):	3461, 2929, 1458, 1374, 1231, 1034, 918 cm^{-1}.
ESIMS:	*m/z* 371 $[M+Na]^+$.

(*R*)-4-((*S*)-2-((2*S*,4*S*,5*S*),-5-((*R*)-1-iodopropan-2-yl)-4yl-(methoxymethoxy)-tetrahydrofuran-2-yl)-2-methoxyethyl)-2,2-dimethyl-1,3-dioxalane (83):



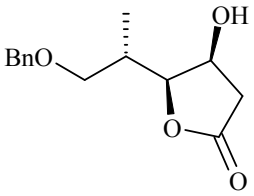
To a stirred solution of alcohol **82** (0.2 g, 0.57 mmol) in 15 mL of THF at 0 °C was added triphenylphosphine (0.22 g, 0.84 mmol), imidazole (0.86 g, 12.70 mmol), and iodine (0.22 g, 1.72 mmol). After 1 h the reaction was quenched with saturated solution of $Na_2S_2O_3$. Aqueous layer was exctracted with EtOAc (2 X 8 mL) and dried over anhydrous Na_2SO_4, concentrated in vacuo. The residue was purified by silica gel column chromatography (3:7, EtOAc/hexane) to afford iodo compound **83** (0.23 g, 0.5 mmol, 90%) as a yellow liquid.

$[\alpha]_D^{25}$:	–10.6 (*c* = 1.15, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz):	δ δ 4.73 (dd, *J* = 6.4, 20.2 Hz, 2H), 4.24-3.96 (m, 4H), 3.87-3.73 (m, 1H), 3.67-3.42 (m, 2H), 3.39 (s, 3H), 3.33 (s, 3H), 3.30 (d, *J* = 3.9 Hz, 1H), 3.19-3.08 (m, 1H), 2.06 (ddd, *J* = 5.4, 6.6, 13.0 Hz, 1H), 1.97-1.47 (m, 4H), 1.37 (s, 3H), 1.32 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 108.3, 97.4, 84.8, 83.2, 81.4, 79.9, 73.5, 69.1, 55.5, 55.9, 38.6, 32.5, 29.4, 26.7, 25.2, 15.4, 10.0.

IR(neat): 2930, 1455, 1372, 1211, 1034, 919 cm^{-1}.

(4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-4-hydroxy-dihydrofuran-2(*3H*)-one (85):



A solution of 79% $NaClO_2$ (0.61 g, 6.74 mmol) in 4.0 mL of water was added drop wise to a stirred solution of the above crude aldehyde **67** (1.0 g, 3.42 mmol) in 1 mL of DMSO and $NaH_2PO_4.2H_2O$ (1.06 g, 6.79 mmol) in 4.0 mL of water over 5 min at room temperature. The mixture was left 2 h at room temperature, and then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted with EtOAc (3 X 20 mL) and washed with brine, dried over Na_2SO_4, and concentrated to give the acid, which was used as such for the next step without purification. The above crude acid was dissolved in methanol (15 mL), and 3N HCl (0.3 mL) was added to it. The reaction mixture was stirred at room temperature overnight and then quenched with solid $NaHCO_3$ and filtered, and the filtrate was concentrated in vacuo and the residue was purified by column chromatography (6:4, EtOAc/hexane) to give 5 memberd lactone **85** (0.4 g, 1.6 mmol, 70% yield over two steps) as a white solid.

M.p: 85-89 ^{o}C

$[\alpha]_D^{25}$: +3.4 (*c* = 0.95, $CHCl_3$).

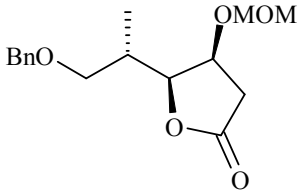
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.26 (m, 5H), 4.51 (s, 2H), 4.36 (dd, *J* = 4.5, 6.0 Hz, 1H), 3.71-3.65 (m, 1H), 3.55 (d, *J* = 5.2 Hz, 2H), 3.32 (br s, 1H, OH)2.72 (dd, *J* = 6.0, 17.3 Hz, 1H), 2.47-2.31 (m, 2H), 1.11 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.0, 137.4, 128.4, 127.8, 127.4, 85.8, 73.4, 71.0, 68.3, 39.3, 32.9, 13.9.

IR(neat): 2929, 1765, 1453, 1077, 1021, 901 cm^{-1}.

ESIMS: *m/z* 273 $[M+Na]^+$.

(4*S*,5*S*)-5-((*S*)-1-(benzyloxy)propan-2-yl)-4-(methoxymethoxy)-dihydrofuran-2(*3H*)-one (86):



To a solution of hydroxy compound **85** (0.35 g, 1.40 mmol) in anhydrous DCM (20 mL) at 0 ^oC under nitrogen, was added $^iPr_2NEt$ (0.47 mL, 3.64 mmol) drop wise and after 5 min MOMCl (0.13 mL, 1.61 mmol) was added drop wise. After stirring 4 h at room temperature, the reaction mixture was diluted with water, saturated aqueous NH_4Cl and brine solution then dried over anhydrous Na_2SO_4. The residue was purified on silica gel column chromatography (5:5, EtOAc/hexane) to afford pure **86** as a clear colorless liquid (0.38 g, 1.29 mmol, 95%).

$[\alpha]_D^{25}$: –1.7 (*c* = 0.95, $CHCl_3$).

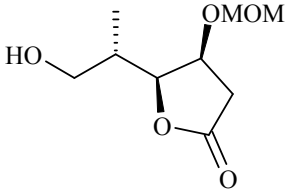
^1H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.24 (m, 5H), 4.65 (dd, *J* = 7.4, 22.2 Hz, 2H), 4.51 (s, 2H), 4.33 (dd, *J* = 3.7, 7.4 Hz, 1H), 3.68-3.54 (m, 3H), 3.39 (s, 3H), 2.75-2.62 (m, 3H), 1.05 (d, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.1, 138.5, 128.2, 127.7, 127.4, 95.8, 84.64 73.7, 73.2, 71.8, 56.2, 37.2, 32.8, 12.6.

IR(neat): 2936, 1780, 1453, 1209, 1100, 1024 cm^{-1}.

ESIMS: *m/z* 317 $[M+Na]^+$.

(4*S*,5*S*)-5-((*S*)-1-hydroxypropan-2-yl)-4-(methoxymethoxy)-dihydrofuran-2(*3H*)-one (87):



50 mL two-neck round-bottomed flask was charged with $Pd(OH)_2/C$. C_6H_6 (8 mL) was added and then H_2-gas was passed via a balloon for 30 min (for the activation of the catalyst). A solution of OBn compound **86** (0.33 g, 1.12 mmol) in C_6H_6 (10 mL) was added to the activated catalyst at room temperature. The reaction mixture was stirred for another 10 h. After completion of the reaction, the benzene was removed by rotary vacuo and purified by column chromatography (6.5,:3.5, EtOAc/hexane) to give alcohol compound **87** (0.2 g, 0.98 mmol, 90%) as a viscous liquid.

$[\alpha]_D^{25}$: +2.1 (c = 0.95, $CHCl_3$).

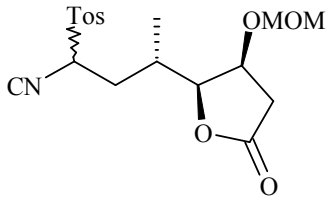
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.68 (dd, J = 6.9, 17.7 Hz, 2H), 4.40 (dd, J = 3.9, 7.9 Hz, 1H), 4.29 (dd, J = 2.9, 9.8 Hz, 1H), 3.83-3.73 (m, 2H), 3.41 (s, 3H), 2.78-2.64 (m, 2H), 2.40-2.30 (m, 1H), 1.71 (br s, 1H, OH), 1.01 (d, J = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.1, 138.5, 128.2, 127.7, 127.4, 95.8, 84.64 73.7, 73.2, 71.8, 56.2, 37.2, 32.8, 12.6.

IR(neat): 3426, 1769, 1302, 1212, 1154, 1025 cm^{-1}.

ESIMS: *m/z* 227 $[M+Na]^+$.

(4*S*,5*S*)-5-((*S*)-4-isocyano-4-tosylbutan-2-yl)-4-(methoxymethoxy)-dihydrofuran-2(*3H*)-one (89):



To a stirred solution of alcohol **87** (0.15 g, 0.73 mmol) in 13 mL of THF at 0 °C was added triphenylphosphine (0.23 g, 0.87 mmol), imidazole (0.12 g, 1.76 mmol), and iodine (0.29 g, 2.21 mmol). After 1 h the reaction was quenched with saturated solution of $Na_2S_2O_3$, aqueous layer was exctracted with EtOAc (2 X 10 mL) and dried over anhydrous Na_2SO_4, concentrated in vacuo and the crude unstable iodo compound **88** directly used for the next step. To TosMIC (0.24 g, 1.23 mmol) in THF (10 mL) at –78

°C was added *n*-BuLi (0.5 mL, 0.8 mmol, 1.6 M in hexane) and stirred for 30 min. HMPA (1.0 mL) was added and continued the stirring for an additional 15 min before adding a solution of iodo compound **88** (0.2 g, 0.63 mmol) in THF (8 mL) *via* a cannula. The reaction was allowed to warm up to room temperature for 3 h and quenched with saturated aq NH_4Cl solution. THF was removed under vacuo and water (8 mL) added to it. The aqueous layer was extracted with ethyl acetate (3 X 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuo. Purification through silica gel column chromatography (4:6, EtOAc/hexane) gave **89** (0.2 g, 0.52 mmol, 85% yield over two steps) as a yellow viscous liquid.

$[\alpha]_D^{25}$: +1.0 (*c* = 0.95, $CHCl_3$).

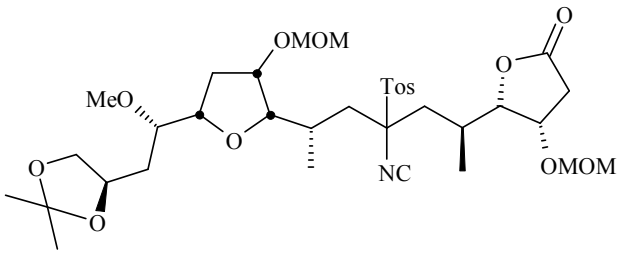
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 2H), 4.82 (dd, *J* = 6.4, 22.4 Hz, 2H), 4.51 (dd, *J* = 3.0, 12.0 Hz, 1H), 4.31 (dd, *J* = 4.5, 6.0 Hz, 1H), 3.72 (q, *J* = 12.2 Hz, 1H), 3.50 (s, 3H), 2.75 (dd, *J* = 6.0 Hz, 17.3 Hz, 1H), 2.51 (s, 3H), 2.48-2.15 (m, 2H), 2.10-1.82 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.3, 165.0, 146.5, 130.0, 129.9, 129.7, 95.9, 83.1, 78.2, 69.5, 55.6, 38.2, 32.5, 30.7, 21.6, 15.7.

IR(neat): 2980, 2930, 1728, 1690, 1454, 1217, 1085 cm^{-1}.

ESIMS: *m/z* 404 $[M+Na]^+$.

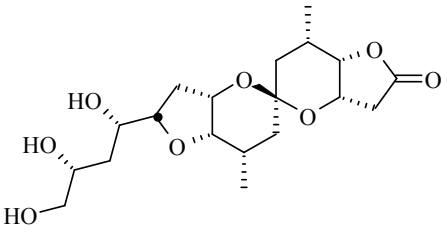
(4*S*,5*S*)-5-((2S,6*S*)-6-((2*S*,3*S*,5*S*)-5-((*S*)-2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-methoxyethyl-3-(methoxymethoxy)-tetrahydrofuran-2-yl)-4-isocyano-4-tosylhepta-2-yl-4-(methoxymethoxy)-dihydrofuran-2(*3H*)-one (90):



To **89** (0.15 g, 0.4 mmol) in THF (10 mL) at –78 °C was added LHMDS (0.78 mL, 0.78 mmol, 1.0 M in hexane) and stirred for 30 min. HMPA (2 mL) was added and continued the stirring for an additional 15 minutes before iodo compound **83** (0.19 g, 0.41 mmol) in THF (5.0 mL) was added *via* a cannula. The reaction was allowed to warm up to room temperature for 10 h and quenched with saturated aq. NH_4Cl solution. THF was removed under vacuo and water (5 mL) added to it. The aqueous layer was extracted with ethyl acetate (3 X 13 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuo. Purification through a column chromatography (3.5:6.5, EtOAc/hexane) gave **90** (0.19 g, 0.26 mmol, 70%) as a colorless oil.

$[\alpha]_D^{25}$:	–40.6 (*c* = 0.95, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 400 MHz):	δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 2H), 4.83 (dd, *J* = 6.5, 32.7 Hz, 2H), 4.75 (dd, *J* = 6.0, 25.0 Hz, 2H), 4.25 (dt, *J* = 3.2, 10.8 Hz, 1H), 4.09-3.90 (m, 3H), 3.86-3.79 (m, 2H), 3.65-3.60 (m, 2H), 3.49 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 3.19 (t, *J* = 2.5 Hz, 1H), 2.91-2.79 (m, 2H), 2.75 (dd, *J* = 6.5, 18.2 Hz, 2H), 2.51 (s, 3H), 2.21-1.70 (m, 6H), 1.68-1.55 (m, 2H), 1.39 (s, 3H), 1.32 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 176.3, 164.9, 146.4, 130.1, 129.9, 129.8, 108.3, 95.8, 95.5, 83.5, 83.0, 80.6, 79.5, 78.1, 76.8, 72.1, 71.0, 68.9, 57.8, 56.03, 55.4, 37.5, 35.1, 34.1, 32.5, 31.1, 30.6, 29.8, 26.8, 26.7, 21.6, 17.2, 15.6.
IR(neat):	2980, 2930, 2133, 1778, 1640, 1333, 1152, 1094, 917 cm^{-1}.
ESIMS:	*m/z* 730 $[M+NH_4]^+$.

Spiro ketal (91):



To a solution of **90** (0.14 g, 0.2 mmol) in CH_2Cl_2 (8 mL) was added 1M solution of BBr_3 in DCM (1.56 mL, 1.56 mmol) at −78 ^oC. The reaction mixture was stirred at same temperature for about 18 h. The reaction mixture was allowed to warm to room temperature and it was quenched with saturated solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (7 X 7 mL), washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuo. The residue was purified by column chromatography (7:3, Acetone/hexane) to afford spiroketal **91** (30 mg, 0.07 mmol, 40%) as a colorless viscous oil.

$[\alpha]_D^{25}$: –83.1 (*c* = 0.5, EtOAc).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.06 (dt, *J* = 3.1, 10.1 Hz, 1H), 3.85-3.77 (m, 1H), 3.65 (dt, *J* = 3.4, 9.5 Hz, 1H), 3.48 (dd, *J* = 3.8, 10.7 Hz, 1H), 3.40-3.27 (m, 4H), 3.06 (t, *J* = 2.2 Hz, 1H), 2.23 (A of ABX, J_{AB} =16.5 Hz, J_{AX} = 0.2 Hz, 1H), 2.09-1.81 (m, 3H), 1.93 (B of ABX, J_{AB} = 16.5 Hz, J_{BX} = 4.1 Hz, 1H), 1.62 (ddd, *J* = 5.0, 9.6, 14.1 Hz, 1H), 1.53-1.04 (m, 6H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.46 (br s, 3H, OH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.1, 97.1, 80.5, 80.4, 79.5, 72.8, 72.0, 71.9, 69.4, 66.3, 38.5, 36.5 36.3, 36.1, 32.5, 25.5, 25.4, 17.6, 17.3.

IR(neat): 3432, 2926, 2872, 1782, 1194, 1013, 972 cm^{-1}.

HRMS (ESI): Calcd for $C_{19}H_{30}O_8Na$ $[M+Na]^+$: 409.1835; found: 409.1833.

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CHAPTER II

Introduction, earlier synthetic approaches and present work of Synargentolide A

The work of this chapter was published in

Tetrahedron Letters **2009**, *50*, 6298-6302.

1INTRODUCTION

Naturally isolated α-pyrone derivatives exhibit various important biological activities. Among these compounds, 6-substituted-5,6-dihydro-2*H*-pyran-2-one[1] (α,β-unsaturated-δ-lactone, Figure 1) subunit has been found in many biologically promising natural products. The pyrone unit is broadly distributed in all parts of plant (Annonaceae, Lamiaceae, Lauraceae and Piperaceae families) including fruits, stems, root and leaves. Various kinds of substitutions have been found at the C-6 position of the ring such as polyacetoxy, polyhydroxy alkane and combination of both or even simple alkane.

Naturally isolated 6-substituted- α,β-unsaturated-δ-lactones gained great attention of researcher due to their wide range of biological properties,[2] such as they inhibit HIV protease,[3] induce apoptosis,[4,5] and have proven to be anti-leukemic,[6] along with having many other relevant pharmacological properties.[7] Synargentolide A (**14**),[8] spicegerolide (**8**),[9] hyptolide (**9**),[10] synrotolide diacetate (**7**),[11] and anamarine (**6**)[12] isolated from Syncolostemon and Hyptis species are examples of α,β-unsaturated δ-lactones. Biological activity of these types of molecules and their structural complexities is much attracted and great challenge to synthesize them in efficient and optically pure form. Some of the synthethetic methodologies for dihydropyrones are given below.

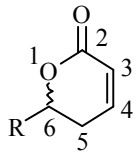


Figure 1: 5,6-dihydropyran-2-one

SYNTHETIC METHODOLOGIES FOR DIHYDROPYRANONES

Many different synthetic methods for the creation of 5,6-dihydropyran-2-one rings have been reported. These are divided into four groups as follows:

1. Lactonization of substituted *δ*-hydroxy acid derivatives (Figure 2).[13]
2. Oxidation of substituted dihydropyran derivatives (Figure 3).[14]
3. Ring-closing metathesis (Figure 4).[15]
4. Miscellaneous methods (Figure 5 & 6).

1. Lactonization of δ-hydroxyl acid derivatives: Any reaction which can generate δ-hydroxyl acid or its derivative, later in cyclization gave lactone. Depend upon the substrate elimination,

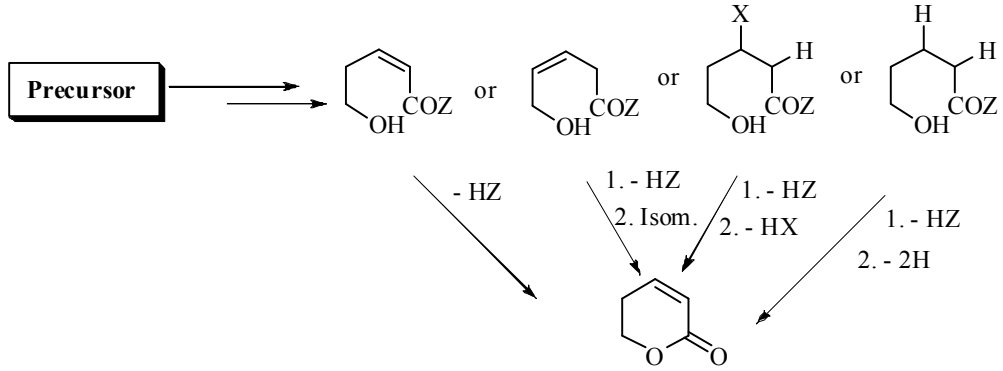


Figure 2: Formation of 5,6-dihydropyran-2-ones *via* lactonization of a *δ*-hydroxy acid derivative.

dehydrogenation, double bond migration followed by lactonization reactions are used to produce lactone ring.

2. Oxidation of substituted dihydropyrone derivatives: 2-Hydroxy-5,6-dihydro-2H-pyran which can be generated by various methods transformed into target compound by photochemical oxidation with singlet oxygen, different methods present in the literature.

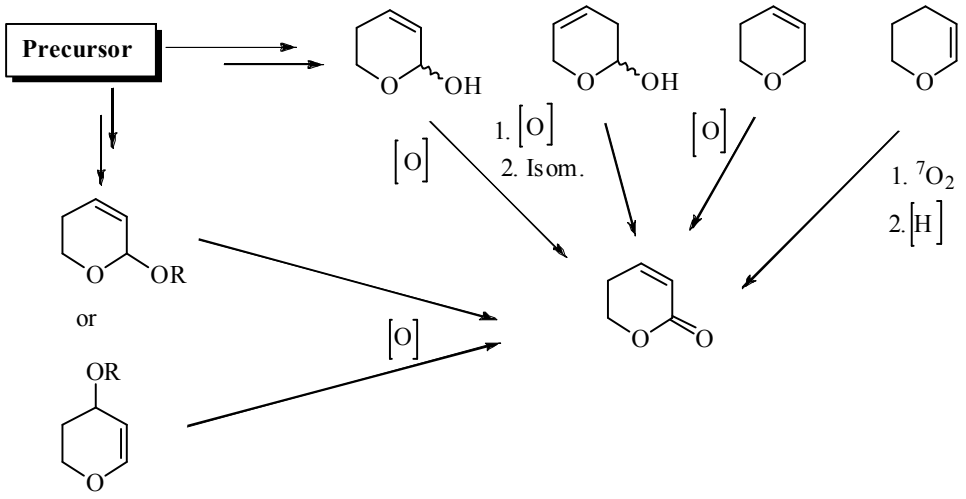


Figure 3: Formation of 5,6-dihydropyran-2-ones *via* oxidation of dihydropyran intermediates

3. Ring closing metathesis: Except very strained substrates transition metal catalyzed

RCM reaction useful in the preparation of 5,6-dihydropyron-2-ones. In this reaction directly heterocyclic systems are produced.

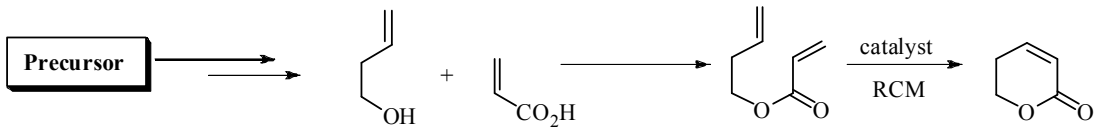


Figure 4: Formation of 5,6-dihydropyran-2-ones *via* ring-closing metathesis.

4. Miscellanious methods: Intramolecular Horner-Wadsworth-Emmons olefinations,[16] Baeyer-Villiger reactions,[17] metal-mediated/catalyzed cyclocarbonylations,[18] halo and selenolactonizations,[19] cycloadditions,[20]and intramolecular aldolization[21] reactions are used to prepare the dihydropyranones.

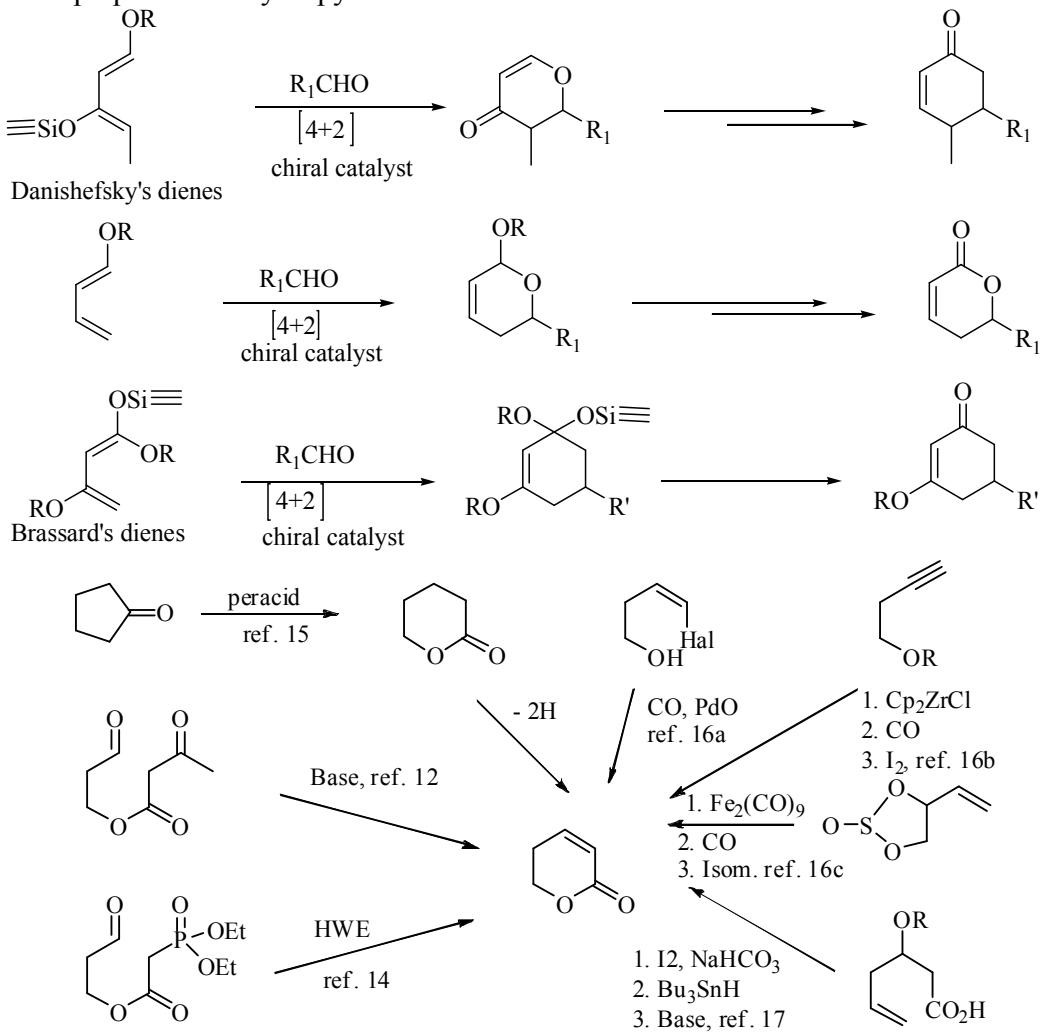


Figure 5: Further methods for the preparation of 5,6-dihydropyran-2-ones.

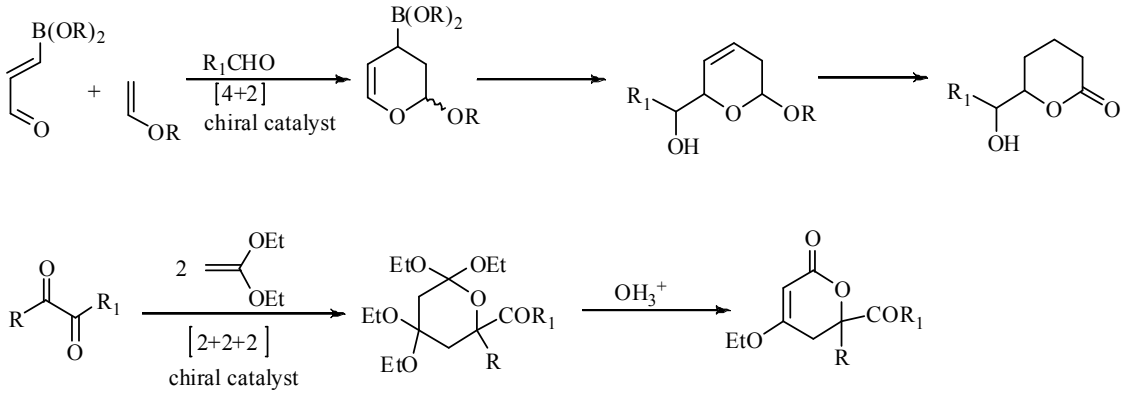


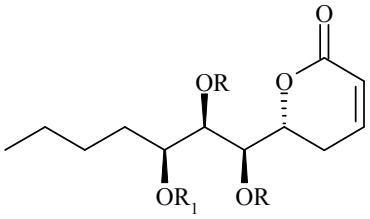
Figure 6: Generation of chiral 5,6-dihydropyran-2-ones *via* asymmetric cycloadditions

ISOLATION, PURIFICATION AND CHARACTERIZATION:

Isolation and purification of the natural product present in the mixture of other compounds depends on the structure, stability and quantity of the compound. Plant materials such as leaves, stem bark, roots or whole plant are typically extracted by maceration with methanol or ethanol at room temperature. Isolations are performed by partitioning the initial extract with hexane, chloroform or dichloromethane and ethyl acetate, followed by repeated silica gel chromatography using flash columns, preparative TLC, chromatotrography separations and filtering on gel columns. On talc layers, compounds may be detected by UV light (254 nm) and spraying with anisaldehyde–sulphuric acid, phosphomolybdic acid or Kedde's reagent. After the purification of the compound structure elucidation, biological activity tested by different analytical and biological methods. The isolation and biological profile of some of these natural products is described below.

(+)-Boronolide (1)

(+)-Boronolide **1** was isolated from *Tetradenia fruticosa* and *Tetradenia barbera*,[22] which are used as local folk medicine in southern Africa. (+)-Deacetylboronolide (**2**) and (+)-acetylboronolide (**3**) were obtained from *Tetradenia riparia*.[23] These are used as a tribal medicine in central Africa. Medicinal properties of boronolides have been exploited for long time in crude form. Zulu used roots of these plants as an emetic, and an infusion of leaves have been reported to be effective against malaria.[24]



1 R = R_1 =Ac (+) Boronolide

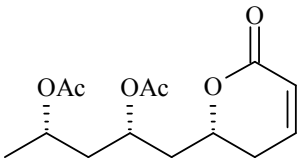
2 R = R_1 = H (+) Deacetyl boronolide

3 R = H, R_1 = Ac (+)-acetyl boronolide

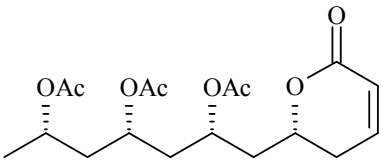
Figure 7

Cryptocarya diacetate (4)

Cryptocarya diacetate **4**[25] and Cryptocarya triacetate **5**[26] were isolated from the bark of *Cryptocarya latifolia*.[27] These compounds exhibit significant cytotoxic activity.



4. Cryptocarya diacetate

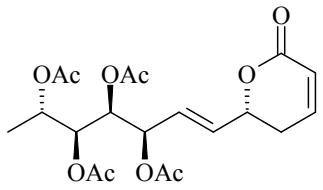


5. Cryptocarya triacetate

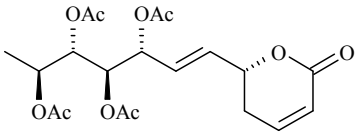
Figure 8

Anamarine and related tetraacetoxy lactones

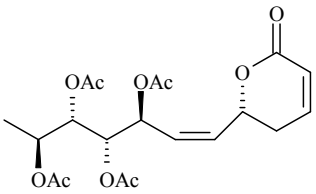
α,β-unsaturated-δ-lactones (+)-anamarine **6**,[12] (−)-synrotolide diacetate **7**,[11] (−)-spicigerolide **8**[9] have been isolated from *Hyptis s*pecies and other botanically related genera. These compounds contain polyoxygenated chain connected with an α,β-unsaturated six membered lactone. They show various types of pharmacological properties, such as cytotoxicity against human tumour cells, antimicrobial and antifungal activity. (−)-Spicigerolide exhibits cytotoxicity with ED_{50}=1.5 μg/mL in human nasopharyngeal carcinoma (KB) assay system. Other structurally similar lactones (-)-synrotolide and (+)-anamarine from *Hyptis* and taxonomically related species have been found to be antimicrobial.[28]



6. (+)-Anamarine



7. (-)-Synrotolide diacetate

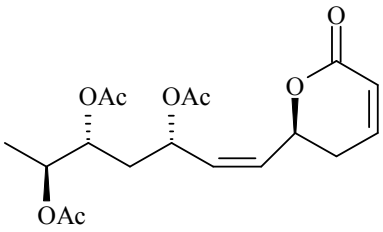


8. (-)- Spicigerolide

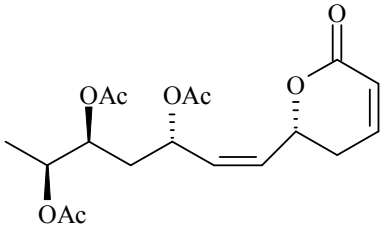
Figure 9

Hyptolide and related lactone

(+)-Hyptolide **9** and Synparvolide B **10** are polyoxygenated α,β-unsaturated-δ-lactones. (+)-Hyptolide **9** was isolated from *Hyptis pectinata*[29] species and synparvolide B **10** from the leaves of *Syncolostemon parviflorus.*[30] These compounds display potent biological activities including anti-inflammatory properties.



9. Hyptolide



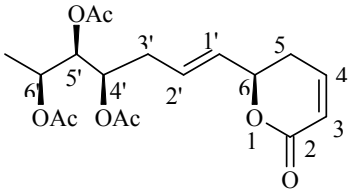
10. Synparvolide B

Figure 10

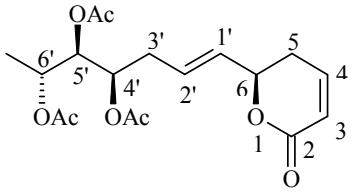
Stereoisomers of Synargentolide A

Synargentolide A **11** an α,β-unsaturated-δ-lactone has been isolated from the species of *Syncolostemon argenteus*[8] found in Ongoya forest midland of South Africa. The relative configuration of synargentolide A has been established based on spectral chiroptical and chemical evidence and the structure was proposed to be **12**. Later, it was realized that the NMR data of synthetic product did not match with the data of natural product and they were different. Hence, the proposed structure of **12** was revised to be **11** by synthesizing several isomers of natural product and synthesis of their spectroscopic data. α,β-Unsaturated-δ-lactone ring containing molecules are known to exhibit various pharmacological activities towards cytotoxic, anti-inflammatory, anti-viral and anti tumor properties. Due to their large range of biological properties, these compounds are very

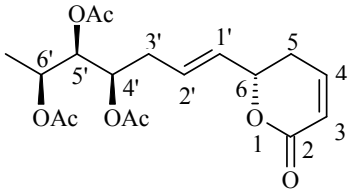
attractive to chemists to synthesize by simple and efficient method. Although synargentolide A has not been examined for its biological activity so far, several such lactones offer a wide range of applications. Therefore, it is prompted us to take-up the synthesis of Synargentolide A.



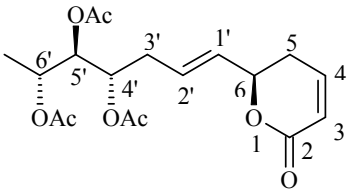
12. Published structure of synargentolide A



11. Revised structure of synargentolide A



13. Epimer of synargentolide A



14. Diastereomer of synargentolide A

Figure 11

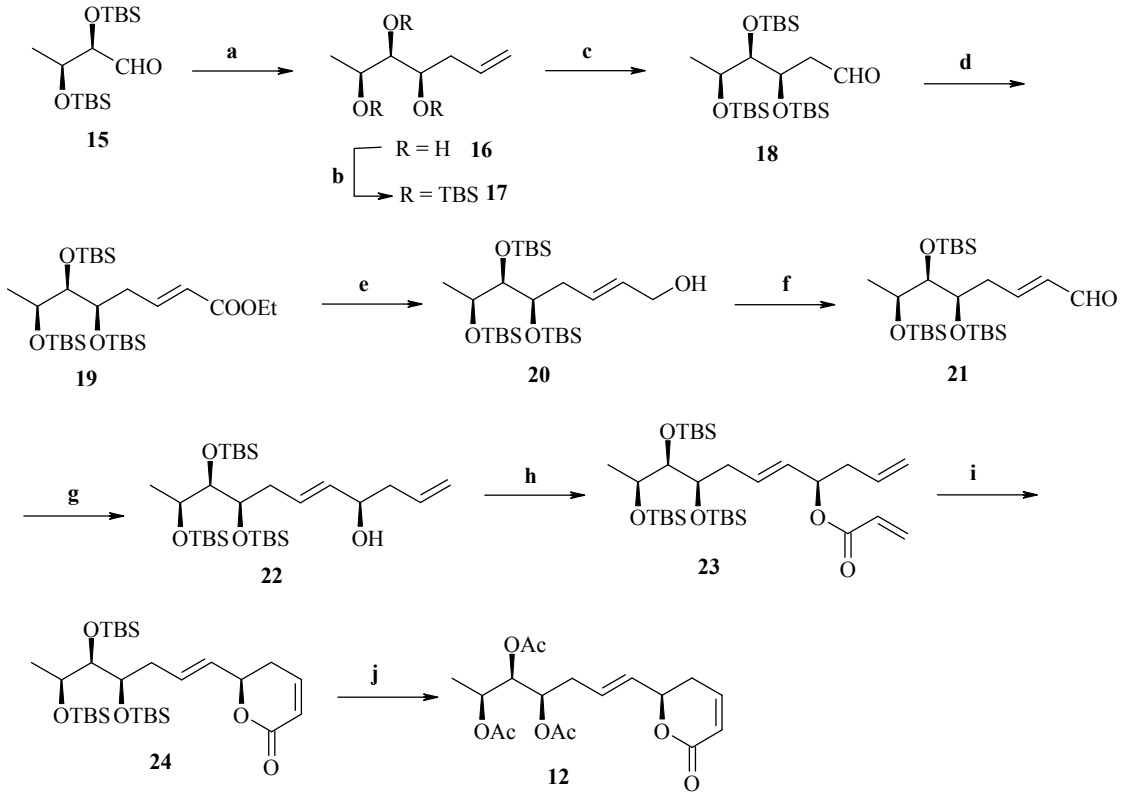
PREVIOUS SYNTHETIC APPROACHES

Alberto Marco *et al*. approach:

Alberto Marco *et al*.[31] first time reported the stereoselective synthesis of the published structure **12** for synargentolide A and isomer **13**.

The synthesis of **12** started from chiral aldehyde **15** which was prepared by reported method[32] and this aldehyde **15** was subjected to allylation by using allyl-$BIpc_2$ complex in Et_2O to produce homoallylic alcohol **16**. The secondary alcohol was protected with TBDMSOTf by using 2,6-lutidine to obtain olefinic TBDMS ether **17**. The compound **17** was subjected to ozonolysis to obtain aldehyde **18** and subsequently converted to ester **19** by using C_2 Wittig reagent. This ester **19** was reduced to alcohol **20** using DIBAL-H and the resulting alcohol **20** was converted into aldehyde **21** using

MnO_2. The aldehyde was subjected to allylation by using allyl-$BIpc_2$ complex in Et_2O to produce corresponding homoallylic alcohol **22** with diastereomeric ratio (9:1). The homoallylic alcohol was esterified with acryloyl chloride in the presence of DIPEA and DMAP to obtain acryloyl ester **23** which underwent ring-closing metathesis (RCM) using the Grubbs' first generation catalyst to produce the corresponding α,β-unsaturated-δ-lactone **24**. Finally, compound **24** was treated with PPTS in MeOH followed by acetylation with acetic anhydride in Et_3N and DMAP to produce the proposed synargentolide A **12** (Scheme 1).



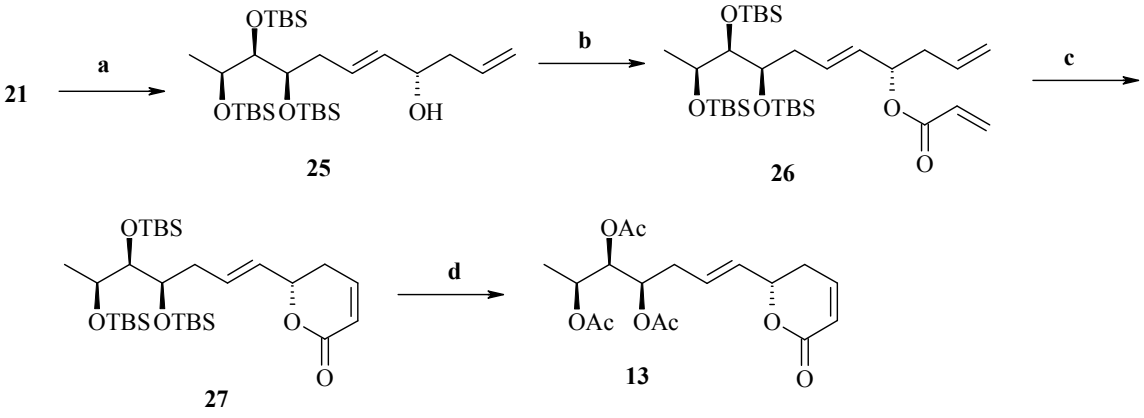
Scheme 1

Reagents and conditions: (a) allyl-$BIpc_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C, 1 h (single diastereoisomer, 58% overall yield after the ozonolysis–allylation sequence); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 1 h 92%; (c) O_3, −78 °C, then PPh_3, RT, 2 h; (d) $(EtO)_2POCH_2COOEt$, LiCl, DIPEA, MeCN, RT, 3 h (65% overall yield after the ozonolysis–olefination sequence); (e) DIBAL, 0 °C, 1 h,

75%; (f) MnO_2, CH_2Cl_2, reflux, 2 h; (g) allyl-$BIpc_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C, 1 h (9:1 mixture of diastereoisomers, 60% overall yield after the oxidation-allylation sequence); (h) acryloyl chloride, DIPEA, CH_2Cl_2, 2 h (69% of the epimer mixture); (i) 10% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, reflux, 3 h (78% of the epimer mixture); (j) (i) PPTS, aq. MeOH, reflux, 2 d; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 1 h ((60% overall yield of the 9:1 epimer mixture after the two steps).

Since, the spectral data of the synthetic product **12** did not match with those reported for the natural product. Therefore, they have synthesized the epi-synargentolide A **13**.

Further aldehyde **21** was subjected to Brown's allylation by using allyl-$BIpc_2$ complex in Et_2O to produce corresponding homoallylic alcohol **25** with diastereomeric ratio (9:1). The homoallylic alcohol was esterified with acryloyl chloride in the presence of DIPEA and DMAP to obtain acryloyl ester **26** which underwent ring-closing metathesis (RCM) using the Grubbs' first generation catalyst to produce corresponding α,β-unsaturated-δ-lactone **27**. Finally compound **27** was treated with PPTS in MeOH followed by acetylation with acetic anhydride in presence of Et_3N and DMAP to produce epi-synargentolide A **13** (Scheme 2). They also found that the spectral data of the synthetic epi-synargentolide **13** did not match with those reported for the proposed structure of the natural product.



Scheme 2

Reagents and conditions: (a) allyl-$BIpc_2$ [from (−)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C, 1 h (9:1 mixture of diastereoisomers, 60% overall yield after the

oxidation-allylation sequence); (b) acryloyl chloride, DIPEA, CH_2Cl_2, 2 h (69% of the epimer mixture); (c) 10% $PhCH=RuCl_2(PCy_3)_2$, CH_2Cl_2, reflux, 3 h (78% of the epimer mixture); (d) (i) PPTS, aq. MeOH, reflux, 2 d; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 1 h ((60% overall yield of the 9:1 epimer mixture after the two steps).

During their course of synthesis, they could not identify the original structure of synargentolide A **11**, instead they have synthesized published structure **12** and isomer **13**.

This was proved by the relative comparison of ^{1}H NMR copies (figure 11) and ^{13}C NMR spectroscopic data (Table 1) of synthetic synargentolides **13** and **11** with natural synargentolide A **12** as given below.

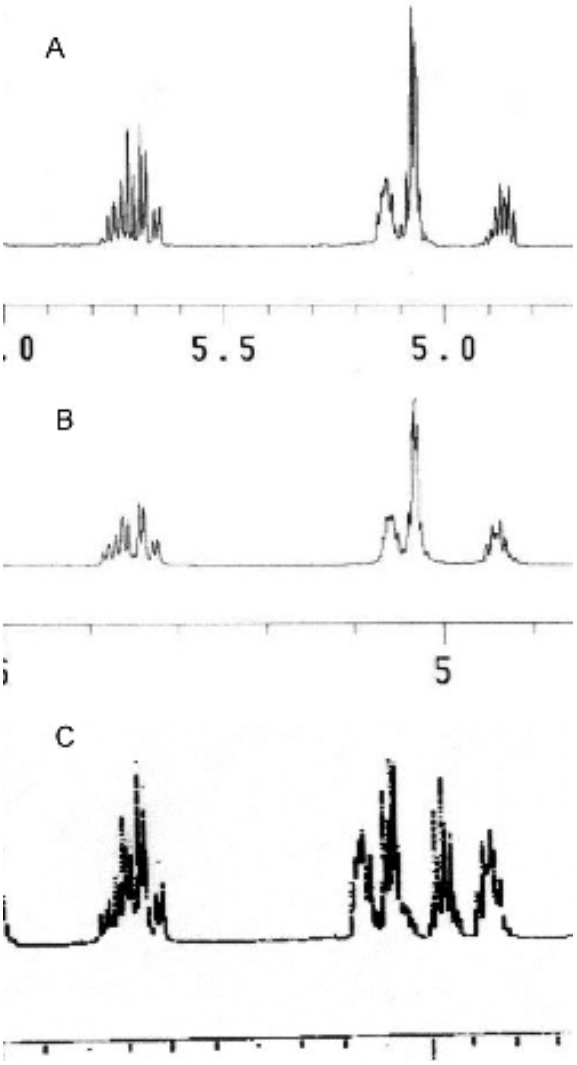


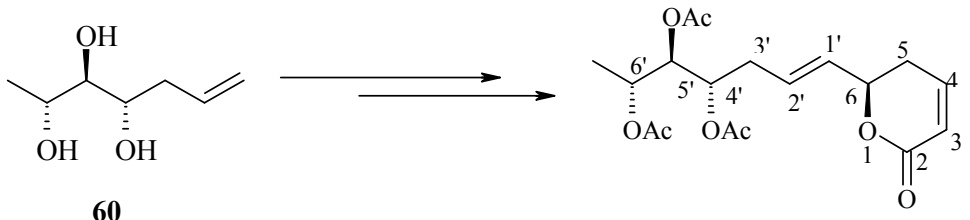
Figure **12:** Comparison of the δ 6.00-4.70 range of the ^{1}H-NMR spectra of the synthetic lactones **12** (A) and **13** (B) with that of natural syngentolide A (C).

Table 1. ^{13}C-NMR data of synthetic lactones **12** and **13** and of natural synargentolide A **11**			
	Compound		
Carbon	14	11	Synargentolide A 13
C-2	163.8	163.8	163.8
C-3	121.9	121.9	121.6
C-4	144.5	144.4	144.5
C-5	29.8	29.4	29.4
C-6	77.7	77.2	77.2
C-1’	131.4	131.0	130.9
C-2’	128.6	128.1	128.3
C-3’	34.2	34.0	34.0
C-4’	70.7	70.5	69.7
C-5’	74.4	74.3	73.8
C-6’	69.0	68.7	67.4
C-7’	16.6	16.5	16.0
OAc (C=O)	170.3,170.2 (x2)	170.1 (x2), 170.0	170.2, 170.1, 170.0
OAc (Me)	21.2, 21.0, 20.8	21.0, 20.8, 20.6	21.0, 20.9, 20.8

It turns out, therefore, that the structures **13** and **12** published for the natural lactone synargentolide A **11** were not correct. The authors established the relative configuration of the C-4′/C-5′/C-6′ carbon chain of synargentolide A **11** by NMR examination of the two acetonides formed between the hydroxyl pairs at C-4′/C-5′ (1,3-dioxolane) and C-4′/C-6′ (1,3-dioxane).[8] The five-membered acetonide was found to be *trans* on the basis of 2D- NOE correlations, whereas the six-membered acetonide was found to be *cis* on the basis of the ^{13}C- NMR chemical shifts of the methyl signals. Furthermore, the absolute configurations at C-6 and C-6′ were determined by CD measurements and NMR studies of the Mosher esters, respectively.

Assuming the correctness of the authors’ stereochemical conclusions, it appears that the proposed structure differs from the actual one in more than mere configurational aspects.The assignment of a *syn, syn*-relative configuration within the C-4′/C-5′/C-6′ chain seems well founded on the basis of the presented data.[8] However, and in order to definitively exclude the possibility of a mis-assignment in this fragment, they have synthesized lactone **14**, which shows the *anti, anti* arrangement within the aforementioned carbon chain. The known *ribo*-1,2,3-triol **60** was the starting material, and the synthetic strategy was identical to that depicted in Scheme 1. This provided lactone **14** as a colorless oil (contaminated with about 10% of its C-6 epimer): ^{1}H- NMR

(500 MHz) δ 6.85 (ddd, *J* = 9.8, 5, 3.5 Hz, 1H), 6.02 (dt, *J* = 9.8, 1 Hz, 1H), 5.74 (dt, *J* = 15.5, 7 Hz, 1H), 5.65 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.13 (dd, *J* = 5.5, 4.5 Hz, 1H), 5.08 (m, 2H), 4.87 (dt, *J* = 10, 5.5 Hz, 1H), 2.50-2.30 (m, 4H), 2.10 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 170.0, 169.9, 169.8, 163.8 (C), 144.5, 130.7, 129.0, 121.6, 77.6, 73.3, 70.6, 68.6 (CH), 33.3, 29.5 (CH_2), 21.1, 20.9, 20.8, 15.2 (CH_3). Lactone **14** therefore also proved different from the natural product. Note the diagnostic ^{13}C chemical shift value of the terminal methyl group at about 15 ppm. Lactones **12**, **13**, and synargentolide A **11** show this signal above 16 ppm. This supports the conclusion that synargentolide A **11** does not have an *anti, anti* relative configuration in its side chain as has lactone **14**.



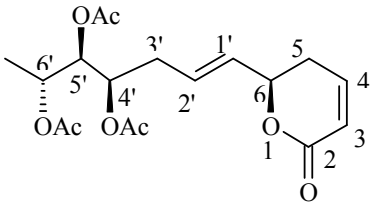
60 **14. Diastereomer of synargentolide**

PRESENT WORK

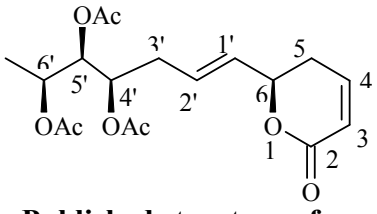
Polyhydroxylated δ-lactones are common structural motifs found ubiquitously in natural products displaying a variety of biological profiles. Synargentolide A is such a lactone isolated from the acetone extract of the dried aerial parts of *Syncolostemon argenteus* of the Southern African genus *Syncolostemon*, a plant from the Ongoya forest in the Kwazulu-Natal midlands of South Africa.[8] The structure of synargentolide A was proposed to be **12** by Davies-Coleman and Rivett[8] on the basis of spectroscopic findings (^{1}H NMR, ^{13}C NMR, IR, HREI, HMQC and NOE findings) Mosher ester analysis, and acetonide formations. The molecular formula of **12**, the major compound, was established as $C_{I8}H_{2}40_{8}$ by HREI mass spectrometry and its IR spectrum is consistent with the presence of an α,β-unsaturated δ-lactone (ν_{max} 1735 cm^{-1}) and a trans-disubstituted double bond (ν_{max} 940 cm^{-1}). Although ^{13}C NMR spectroscopy only accounted for 17 of the 18 carbon atoms, it was clear from an HMQC experiment that an oxymethine carbon signal was concealed beneath the $CDCI_3$ solvent peak. From the chemical shifts of the ^{13}C signals, it was apparent that **12** contained four carbonyl carbons (δ 163.8, 170.0, 170.1 and 170.2), arising from three acetate moieties and the carbonyl carbon of the 5,6-dihydro-α-pyrone ring, and four vinylic carbons (δ 121.6, 128.3. 130.9 and 144.5) from an endocyclic and an exocyclic double bond. These data were supported by the ^{1}H NMR spectrum which revealed signals for the α-and β-protons of the α-pyrone ring (δ 6.01 and 6.84), two further vinylic protons (δ 5.64 and 5.71) four oxymethine protons (δ 4.86, 4.96, 5.08 and 5.15) and three acetate methyl singlets (δ l.99, 2.02 and 2.12). All seven degrees of unsaturation implied by the molecular formula are thus accounted for. The *E*-configuration of the exocyclic double bond in **12**, suggested from the IR data, was established using spin-decoupling NMR experiments. Irradiation of the 3'-methylene protons reduced the signal for H-2' from a double triplet, which overlapped with the H-l' resonance, to a doublet with $J_{1',2'}$ = 15.7 Hz, indicative of a *trans*-disubstituted double bond (J = 9-11 Hz for a *cis*-olefin.[8] Alberto Marco et al.[31] synthesized the published structure of synargentolide A **12** and found that the spectroscopic data of the synthetic product did not match with those reported for the natural product and therefore stated that the proposed structure for the synargentolide A **12** differs from the actual one.

As a part of our current interest in naturally occurring, pharmacologically active δ-lactones, we became interested in the synthesis of synargentolide A and to determine the absolute configuration of the natural product.

A convergent synthesis of **11** and **12** has been developed using lithium acetylide epoxide opening, Sharpless asymmetric epoxidation, Lindlars partial hydrogenation, and Cross-metathesis as key reactions.



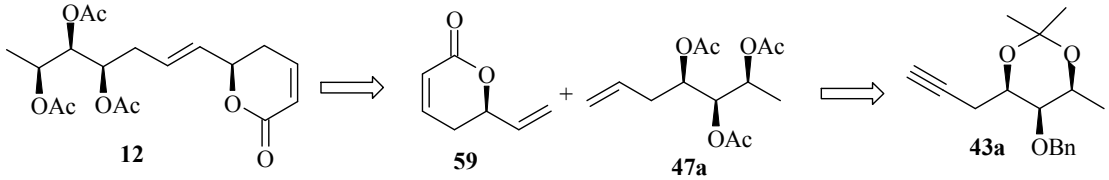
revised structure of synargentolide A 11

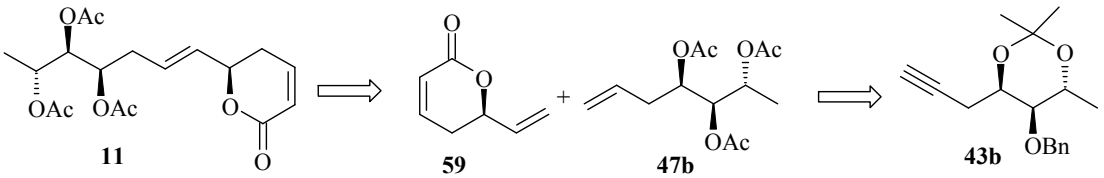


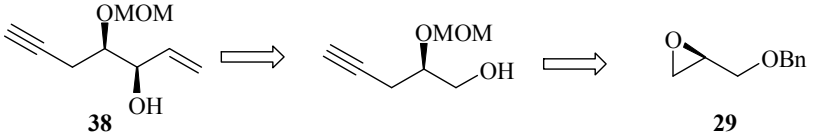
Published structure of synargentolide A 12

Figure 13

The retrosynthesis is outlined in Scheme 3 showing the target molecules **12** (published structure)[8] and **11** (revised structure) could be prepared independently by cross-metathesis reaction of **47a** and **47b** with vinyl lactone **59**. The substrates **47a** and





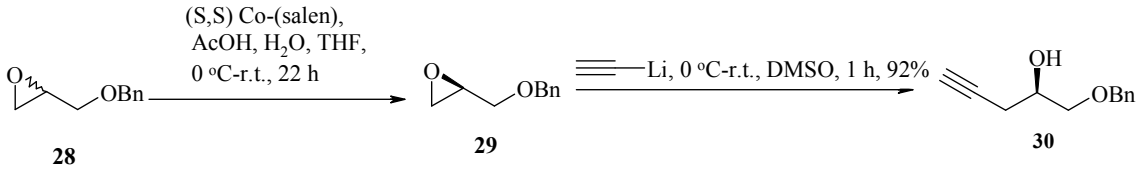


Scheme 3: Retrosynthetic analysis for the published and revised structures of synargentolide A.

47b inturn could be obtained from commercially available (*R*)-benzyl glycidyl ether **29** by sequence reactions such as epoxide opening, Sharpless asymmetric epoxidation, epoxide opening and formation of epoxide and its reductive opening.

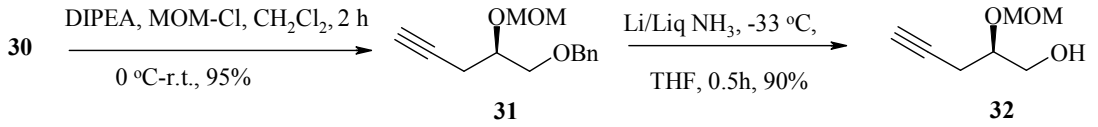
Synthesis:

The synthesis commenced from *R*-(-)-benzyl glycidyl ether **29**. Jacobsen resolution[33] of **28** using (*S*,*S*)-(salen)Co(II) precatalyst,[34] AcOH and H_2O (0.51 eq) for 22 h resulted in (*R*)-benzyl glycidyl ether (Scheme 4). Regioselective opening of epoxide **29** with lithium acetylide in the presence of DMSO solvent to gave homopropargyl alcohol **30**. ^{1}H NMR spectrum of the compound **30** exhibited a triplet due acetylenic proton at δ 1.93 with 2.6 Hz coupling constant. Oxygen attached C-H signals were integrated for five protons confirmed that the regioselection was in anticipated line. In addition, IR Spectrum showed hydroxyl absorbtion at 3434 cm^{-1} and ESI-MS showed $[M+Na]^+$ signal at *m/z* 213, further confirmed the structure **30** (Scheme 4).



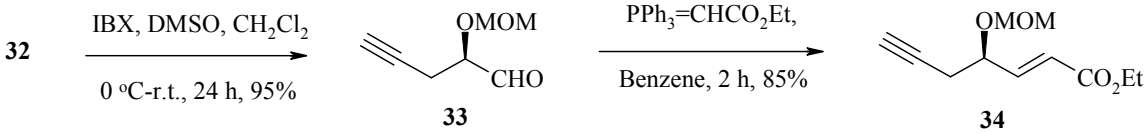
Scheme 4

Methoxy methyl (MOM) ether protection of **30** carried out with 2 eq of MOMCl in the presence of *i*Pr_2NEt in CH_2Cl_2 to produce **31**. ^{1}H NMR spectrum of MOM ether **31** exhibited a singlet at δ 4.69 integrating for two protons and again a singlet at δ 3.36 integrating for three protons and presence of other required peaks confirmed the structure of **31**. ESI-MS signal at *m/z*: 257 $[M+Na]^+$ further confirmed the transformation. Substrate **31** on treatment with lithium in liquid NH_3 underwent debenzylation to produce alcohol **32**. In ^{1}H NMR spectrum of **32,** disappearance of peaks due to benzyl group in aromatic region was observed. IR spectrum showed a strong absorption at 3437 cm^{-1} due to hydroxyl group confirmed the conversion. ESI- MS signal at *m/z*: 167 $[M+Na]^+$ further confirmed the transformation (Scheme 5).



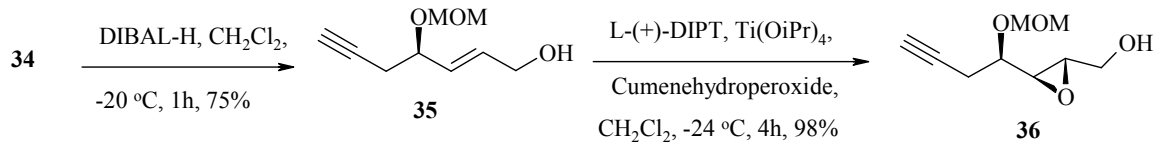
Scheme 5

The compound **32** on oxidation with IBX in DMSO and CH_2Cl_2 solution afforded unstable crude aldehyde **33** which, was directly used for the next reaction immediately. Aldehyde **33** was subjected to Wittig olefination using stabilized ylide ($Ph_3P{=}CHCO_2Et$) in benzene to furnish α,β-unsaturated ester **34** in 85% overall yield (Scheme 6). The newly introduced protons corresponding to α,β-unsaturated ester group in ^{1}H NMR of **34** resonated at δ 6.84 (dd, J = 6.4, 15.8 Hz, 1H), 6.03 (d, J = 15.8 Hz, 1H) conforming the product as an ester. The coupling constant at 15.8 Hz indicate the formation of α,β-unsaturated ester group with *E* geometry. In the IR spectrum a characteristic strong absorption at 1717 cm^{-1} for α,β-unsaturated ester functional group has observed. The structure of **34** was further confirmed by the mass spectrum, which showed a molecular ion peak at *m/z* 235 $[M+Na]^+$.



Scheme 6

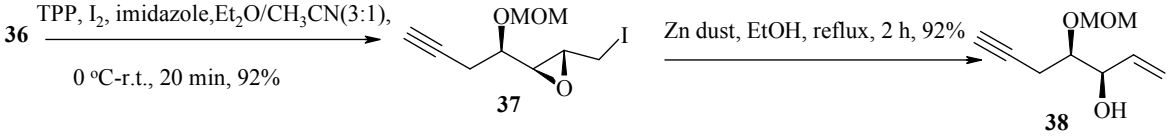
The α,β-unsaturated ester **34** was reduced to allylic alcohol using DIBAL-H in dry CH_2Cl_2 and subjected to Sharpless asymmetric epoxidation[35] using (+)-DIPT, Ti(O^{i}Pr)$_4$ and cumene hydroperoxide to furnish the desired (*S,S*)-epoxide **36** in 98% yield. The epoxy alcohol **36** had its PMR, IR & mass spectra consisting with its structure. The two-epoxy protons in the PMR spectrum resonated as multiplets at δ 3.12-3.06, while the IR spectrum showed absorptions at 3442 cm^{-1} for the hydroxyl function and at 1153 cm^{-1} for the epoxy linkage.



Scheme 7

The structure of the epoxy alcohol **36** was further confirmed by the molecular ion peak at *m/z* 209 $[M+Na]^+$ in mass spectrum (Scheme 7).

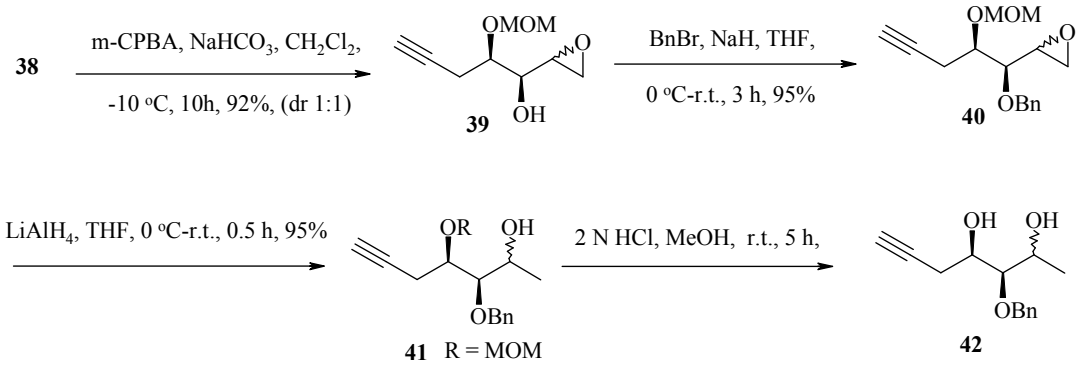
Compound **36** on exposure to TPP, I_2, and imidazole at room temperature gave the corresponding iodide **37** in 20 min. The unstable crude epoxy iodo compound was directly used for the next step. The epoxy iodo compound **37** was converted into a secondary allylic alcohol **38** in 92% yield by refluxing with activated Zinc in dry ethanol (Scheme 8). The compound **38** was confirmed by spectral data. The olefinic protons were resonated as multiplet at δ 5.85-5.57, two doublets at δ 5.41 (d, 1H, J = 16.4 Hz) and δ 5.02 (d, 1H, J = 10.5 Hz) in PMR spectrum. The IR spectrum showed a strong and broad hydroxyl absorption band at 3446 cm^{-1}. Compound **38** gave molecular ion peak at *m/z* 193 $[M+Na]^+$ in the ESI mass spectrum.



Scheme 8

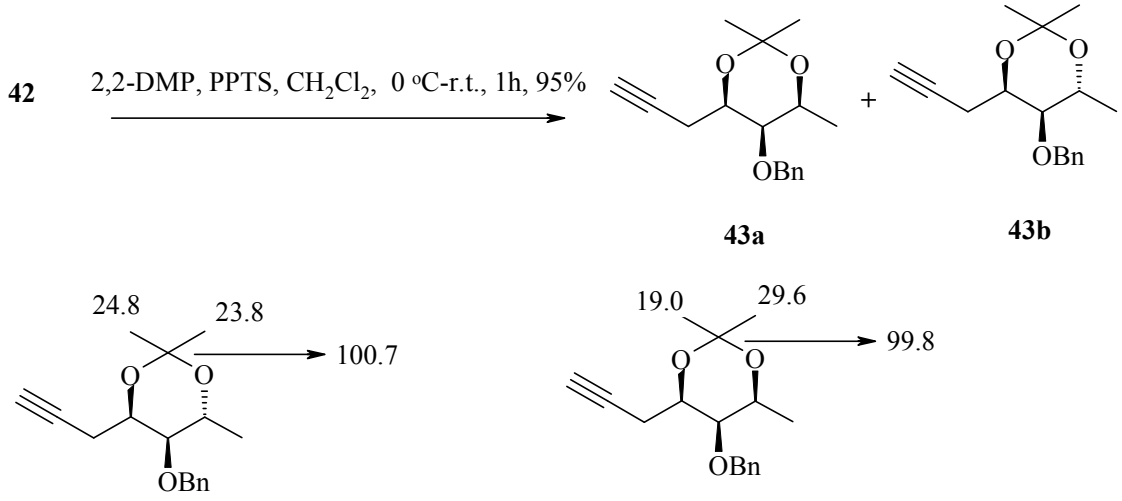
The terminal epoxide **39** was prepared by using *m*-CPBA and solid $NaHCO_3$ in anhydrous CH_2Cl_2 at 25 ^oC in 92% yield with 1:1 diastereomeric ratio. The structure of compound **39** was confirmed by ^1H NMR spectrum. Disappearance of three olefinic protons and appearance of three protons as a multiplet at δ 2.82-2.59 in PMR spectrum due to terminal epoxide was observed. The other protons resonated at their expected chemical shifts. The secondary hydroxy group of compound **39** was protected as its benzyl ether using NaH and BnBr in anhydrous THF at 0 ^oC **40** in 95% yield (Scheme 9). The structure of **40** was confirmed by its ^1H NMR spectrum, which showed a multiplet at δ 4.48-4.54 for two benzylic protons, two MOM-CH_2 group protons and a multiplet in the region at δ 7.40–δ 7.20 for five aromatic protons. It was also characterized by its ESI-MS data, which showed $[M+Na]^+$ peak at *m/z* 299 (Scheme 9). Reductive opening of the terminal epoxide **40** with LAH in THF gave alcoholic compound **41** in 95% yield (Scheme 9), which showed two doublets for one methyl resonating at δ 1.12 and multiplet at δ 4.88-4.54 for benzylic protons and MOM metheledine group. The aromatic protons appeared as two doublets while the other protons appeared as multiplets. The

resulting PMR spectroscopic signals showed that compound **41** has 1:1 ratio of non-seperable diastereomers. The compound **41** was also characterized by its ESI-MS data, which showed $[M+Na]^+$ peak at *m/z* 301 and IR spectrum revealed the hydroxyl absorption at 3455 cm^{-1}. Deprotection of MOM group using 2 N HCl in MeOH afforded diol **42** in 93% yield. Formation of the 1,3 diol **42** was confirmed by its spectral data. ^1H NMR spectrum showed the disappearance of peaks at δ 4.75 (d, *J* = 6.7 Hz, 1H), 4.64 (d, *J* = 6.7 Hz, 1H) and 3.37 (s, 3H) due to MOM group and the IR spectrum showed absorption at 3411cm^{-1} for the hydroxyl groups.



Scheme 9

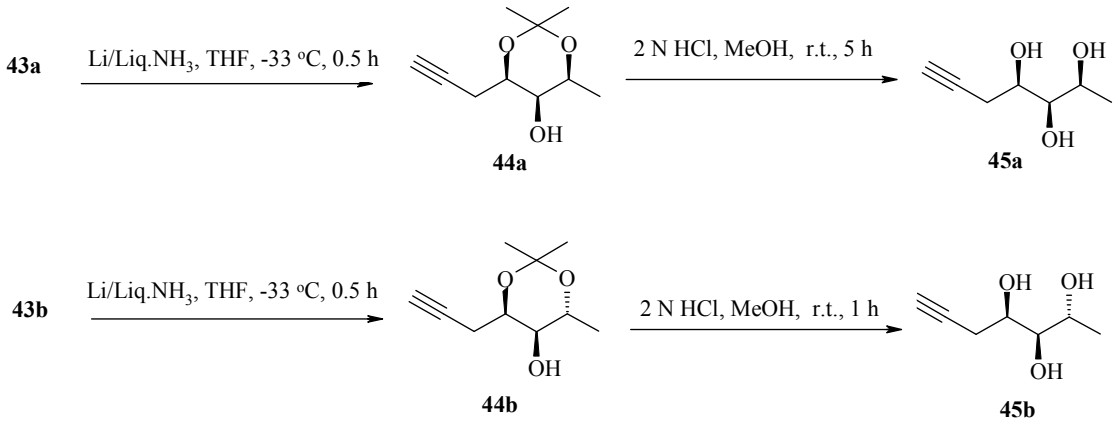
The relative stereochemistry of 1,3-diol system in **42** was determined by using Rychnovsky's acetonide method.[36] Thus treatment of diol **42** with 2,2-DMP, PPTS in CH_2Cl_2 produced *syn* and *anti*-acetonides (**43a & 43b**) were in 95% yield.



Scheme 10

The *anti* relationship of two hydroxyl groups in **43b** was confirmed by the appearance of the methyl carbons resonance at δ 24.8, 23.8 ppm and the acetal carbon at δ 100.7 ppm in its ^{13}C NMR spectroscopy.The *syn* relationship of two hydroxyl groups in **43a** was confirmed by the appearance of the methyl carbons resonance at δ 19.0, 29.6 ppm and the acetal carbon at δ 98.8 ppm in its ^{13}C NMR spectroscopy.

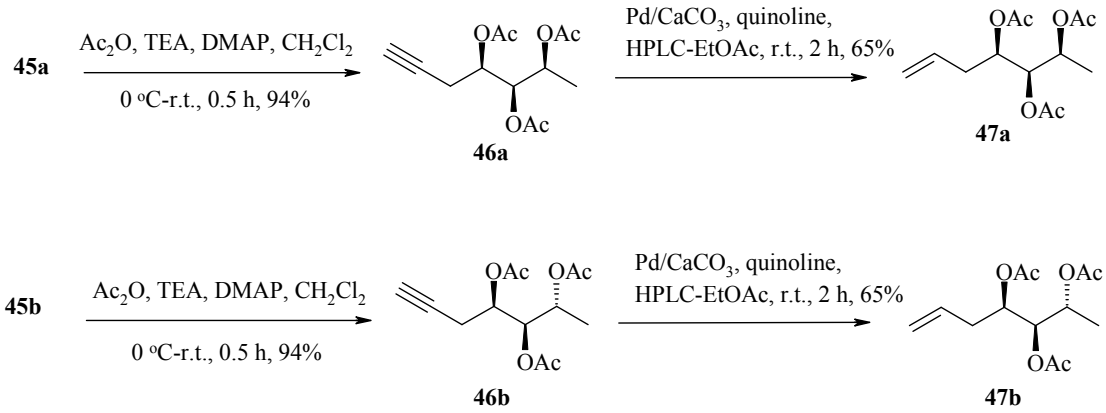
The debenzylation of compound **43a** by using Li/liq:NH_3, afforded compound **44a** in 91% yield. The structure assigned to **44a** was supported by its ^1H NMR spectrum, which revealed that five aromatic protons were disappeared in the region δ 7.36-7.17 and ABq peak at δ 4.61. IR spectrum showed a strong absorption at 3475 cm^{-1} corresponding to hydroxyl group and ESI-MS signal at *m/z*: 207 $[M+Na]^+$ further confirmed the product **44a** (Scheme 11). The conformation of compound **44b** obtained from **43b** is same as compound **44a** which obtained from **43a**. Deprotection of acetonide groups in **44a** and **44b** using 2 N HCl in MeOH afforded triol **45a** and **45b** in 93% yield. The crude triols of two compounds were used for the next step.



Scheme 11

The triol **45a** was protected as its triacetate **46a** with acetic anhydride and triethylamine 0 ^oC-rt, 0.5 h, 94% yield (Scheme 12). The ^1H NMR spectrum of **46a** indicated the presence of three OAc at δ 2.10, 2.08 and 2.02 ppm as singlet. The IR spectrum showed a strong absorption band at 169.0, 169.7 and 169.6 cm^{-1} due to presence of acetate protection. The mass spectrum supported the structure that revealed a peak at *m/z* 293 $[M + Na]^+$ in ESIMS. The triol **45b** was protected as its triacetate **46b** with acetic anhydride, DMAP and TEA at 0 ^oC-rt, 2 h in 94% yield (Scheme 12). The ^1H NMR

spectrum of **46b** indicated the presence of three OAc at δ 2.11, 2.08 and 2.02 ppm as singlet. The IR spectrum showed a strong absorption band at 170.0, 169.9 and 169.8 cm^{-1} due to presence of acetate protection. The triple bond compound **46a** was partially reduced to terminal double bond **47a** using Lindlar's catalyst. $Pd/CaCO_3$, poisoned with quinoline in ethylacetate for 2 h, 65% (Scheme 12).[37] The ^1H NMR spectrum of **47a** δ 5.66 (m, 1H) and 5.14-5.06 (m, 2H) indicate complete conversion of **46a** into the **47a**. While the remaining protons resonating at their respective chemical shifts. The mass spectrum supported the structure **47a** that revealed a peak at *m/z* 295 $[M + Na]^+$ in ESIMS. The triple bond compound **46b** was partially reduced to terminal double bond **47b** using Lindlar's catalyst. $Pd/CaCO_3$, poisoned with quinoline in ethylacetate for 2 h, 65% (Scheme 12).[37] The ^1H NMR spectrum of **47b** δ 5.69 (m, 1H) and 5.16 (dt, *J*=7.0, 3.1 Hz, 2H) indicate complete conversion of **46b** into the **47b**. While the remaining protons resonating at their respective chemical shifts.

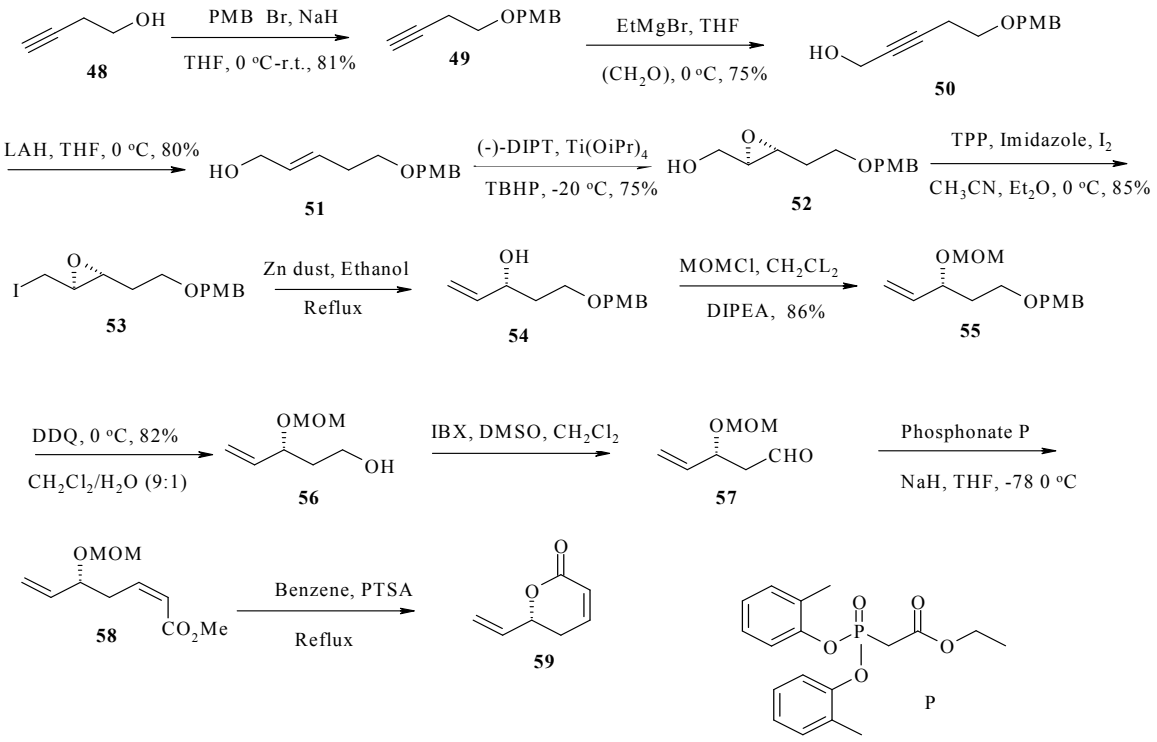


Scheme 12

The synthesis of the key intermediate vinyl lactone **59** is based on a sequence of reactions starting form commercially available 3-butyn-1-ol **48** (scheme 13). Compound **48** was protected as its *p*-methoxybenzylether using PMBBr and NaH in dry THF at room temperature to afford the compound **49** in 81% yield.[38] The newly introduced protons corresponding to PMB group in ^1H NMR of **49** resonated at δ 3.78 as singlet for methoxy group, δ 4.45 as doublet for two protons and two doublets at, δ 7.21 and δ 6.82 for aromatic protons confirming the product. The ether was treated with the Grignard reagent prepared from ethyl bromide and magnesium followed by quenching with para

formaldehyde in dry THF to afford compound **50** in 75% yield. The structure of ether **50** was characterized from its PMR, IR and mass spectral properties. The PMR spectrum of compound **50** clearly showed a broad singlet at δ 4.44 for hydroxymethyl protons. In IR spectrum an absorbance at 3415 cm^{-1} for the hydroxyl functional group and in mass spectrum appearance of a molecular ion peat at m/z 243 $[M+ Na]^+$ further confirmed the product.

In order to get the *trans*-allyl alcohol, compound **50** was treated with 1.5 eq of lithium alumunium hydride[39] in dry THF at room temperature resulted the *trans* olefin **51** in 80% yield. Both IR and PMR spectral data confirmed the presence of *trans* olefin. The PMR spectrum showed a multiplet at δ 5.67-5.61 for the olefinic protons. In the IR spectrum a characteristic C=C stretch at 1609 cm^{-1}, a C-H deformation stretch at 971 cm^{-1} for the *trans* C-H protons and hydroxyl absorption at 3449 cm^{-1} has observed. The structure of the olefin **51** was further confirmed by the mass spectrum, which showed a molecular ion peak at *m/z* 245 $[M + Na]^+$.



Scheme 13

In the next step, olefin **51** was subjected to Sharpless asymmetric epoxidation[35] using (–)-DIPT, $Ti(O^iPr)_4$ and TBHP to furnish the desired (*R,R*)-epoxide **52** in 75% yield (Scheme 13). The epoxy alcohol **52** had its PMR, IR & mass spectra consisting with its structure. The two-epoxy protons in the PMR spectrum resonated as multiplets at δ 3.07-2.98 and δ 2.98-2.86, while the IR spectrum showed absorptions at 3424 cm^{-1} for the hydroxyl function and at 1175 cm^{-1} for the epoxy linkage. The structure of the epoxy alcohol **52** was further confirmed by the molecular ion peak at *m/z* 239 $[M + H]^+$ in mass spectrum. In the next step, the epoxy alcohol **52** was converted to the corresponding iodo compound **53** in 85% yield using PPh_3, imidazole, I_2 in dry ethyl ether and dry acetonitrile (3:1).[40]

Formation of compound **53** was confirmed by its PMR, IR and mass spectral properties. In PMR spectrum iodo methylene protons resonated at δ 3.01-2.96 as a multiplet compared to alcohol and two-epoxy protons resonated as multiplets at δ 3.25-3.19 and δ 2.92-2.89. The Mass spectrum revealed a molecular ion peak at *m/z* 349 $[M + H]^+$. The compound **53** was converted into a secondary allylic alcohol **54** in 85% yield[41] by refluxing with activated Zinc in dry ethanol. The compound **54** was confirmed by spectral data. The olefinic protons were resonated as multiplet at δ 5.83-5.57, two doublets at 5.21 (d, 1H, J = 17.3 Hz) and 5.07 (d, 1H, J = 10.5 Hz) in PMR spectrum. The IR spectrum showed a strong and broad hydroxyl absorption band at 3443 cm^{-1}. Compound **54** gave molecular ion peak at *m/z* 245 $[M + Na]^+$ in the ESI mass spectrum.

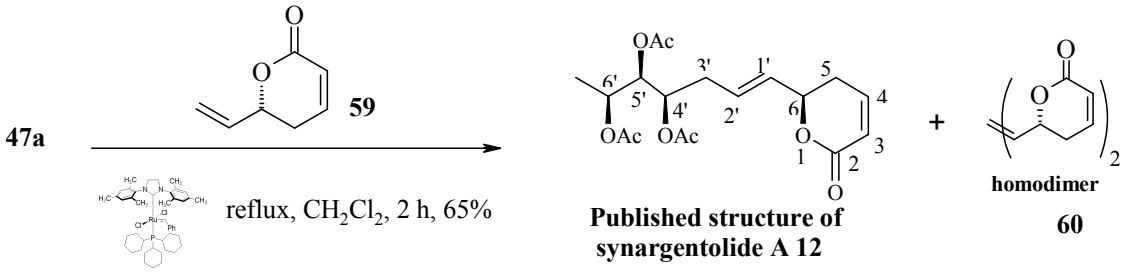
The secondary hydroxyl group of compound **54** was protected as its methoxy methyl ether **55** using 3 eq of hunig's base and 2 eq of MOMCl in 86% yield.[42] The formation of compound **55** was established from its PMR, IR, and mass spectral data. The PMR spectrum showed two doublets at δ 4.63 (d, J = 6.2 Hz) and δ 4.47 (d, J = 6.2 Hz) for methylene protons of $–OCH_2O$ group and the other singlet at δ 3.31 for the methoxy group. The mass spectrum showed molecular ion peak at *m/z* 267 (M^+ + H) further confirmed the product. The deprotection of *p*-methoxybenzyl group of compound **55** with DDQ[43] in DCM:H_2O (9:1) afforded the alcohol **56** in 82% yield. Formation of the alcohol **56** was confirmed by its spectral data. PMR spectrum showed the disappearance of peaks due to *p*-methoxy benzyl group and the IR spectrum showed absorption at 3422 cm^{-1} for the hydroxyl group. The alcohol compound **56** was oxidized to aldehyde **57** using IBX[44]

in 72% yield. The structure of the compound **57** was established from its spectral data. The aldehyde proton appeared as a singlet at δ 9.76. Signals of remaining protons remained unchanged. The IR spectrum of **57** showed an absorption band at 1721 cm^{-1} for the aldehyde group.

The compound **57** was then subjected to Still's modification of Horner-Wadsworth-Emmons[45] reaction using NaH and phosphonate (P) in dry THF at –78 ^{o}C to afford the *cis* α,β-unsaturated ester **58** as a major isomer in 85% yield along with the traces of *trans* isomer, that could be separated by column chromatography. The formation of compound **58** was evident from its PMR spectrum. In the PMR spectrum, olefin protons resonated as multiplet at δ 6.31-6.26 and doublet at δ 5.81 (d, 1H, J = 10.7 Hz) confirming the *cis* geometry of the olefin and ethyl protons of ester appeared as a quartet at δ 4.14 (J = 6.8 Hz) and triplet at δ 1.29 (J = 6.8 Hz). The other proton signals remained unchanged. The IR spectrum showed a strong absorption band at 1648 cm^{-1} for the C=C stretching and at 1720 cm^{-1} for the α,β-unsaturated carbonyl group. The mass spectrum showed a molecular ion peak at *m/z* value 237 $[M + Na]^{+}$ further confirming the product **58**. Next the attention was directed towards the cyclization of ester **58** to get the lactone **59**. The compound **58** when refluxed overnight in benzene using catalytic amount of PTSA resulted in the formation of lactone **59** in 85% yield. The structure of the compound **59** was established from its ^{13}C and PMR spectral data. The C_2 and C_3 olefinic protons resonated as a multiplet at δ 6.83 and doublet of doublet at 6.02 (J = 2.5, 11.1 Hz) respectively. The C_4 methylene protons resonated at δ 2.49-2.39 as a multiplet. The C_5 proton appeared at δ 4.95-4-85 as a multiplet and remaining olefin protons appeared as multiplet at δ 5.93 and two doublets at δ 5.40 (J = 17.1 Hz), 5.28 (J = 11.1 Hz). The structure was further confirmed by its mass and IR spectral studies. The IR spectrum showed absorption at 1720 cm^{-1} for the α,β-unsaturated-δ-lactone. The structure of the compound **59** was further confirmed by its mass spectrum showing molecular ion peak at *m/z* 125 (M^{+} + H).

To determine the correct absolute configuration of natural synargentolide A, both isomers of synargentolide A **12** and **11** were synthesized. Thus, the cross-metathesis (CM) of the vinyl lactone **59** and compound **47a** using Grubbs' 2nd generation catalyst in

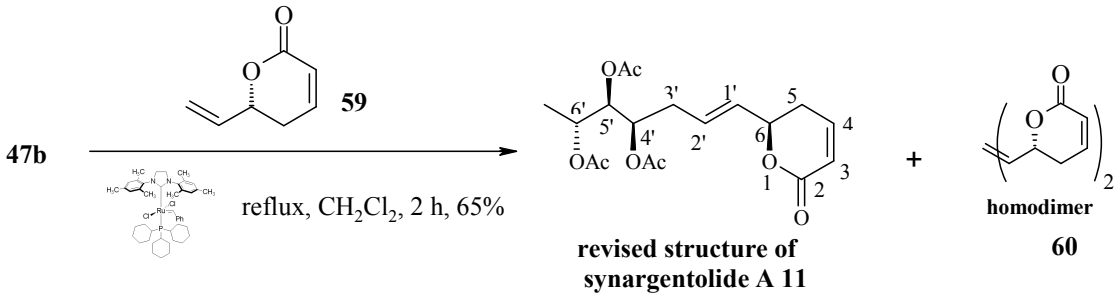
CH_2Cl_2 at 50 °C yielded synargentolide A **12** in 65% yield (Scheme 14). The formation of synargentolide A **12** was confirmed by IR, ^1H, ^{13}C NMR and ESIMS spectra. The IR spectrum showed absorption band at 1740, 1376 cm^{-1} designated to α,β-unsaturated carbonyl and acetate group. In the ^1H NMR spectrum (Fig. 14) formation of product **12** was confirmed by disappearence of terminal double bond proton signals at olefinic region and appearance of proton signals at δ 6.86 (ddd, *J* = 8.4, 4.9, 1.1 Hz, 1H), 6.04 (dt, *J* = 9.8, 1.8 Hz, 1H), 5.75–5.65 (m, 2H), 5.12 (m, 1H, CH), 5.06 (m, 2H), 4.85 (dt, *J* = 8.8, 6.2 Hz, 1H, CH) indicating the formation of cross coupled product. The ^{13}C NMR spectrum (Table 1) showed olefin carbons resonated at δ 170.3, 170.2, 170.1, 163.8, 144.5, 131.4, 128.6, 121.8, 77.7, 74.4, 70.7, 69.0, 34.2, 29.8, 21.2, 21.0, 20.8, 16.6;. HR-ESI-MS signal at *m/z*: 391.1355 $[M+Na]^+$ further confirmed the published structure of synargentolide A **12** (Scheme 14). The spectral data of the synthetic product **12** did not match with the data of the natural product.



Scheme 14

Similarly, the olefin cross-metathesis reaction between compound **47b** and **59** using Grubbs' generation II catalyst following above procedure gave synargentolide A **11** in 65% yield (Scheme 15). The compound synargentolide A **11** was confirmed by IR, ^1H, ^{13}C NMR and ESIMS spectra. The ^1H NMR spectrum (Fig. 14) of this compound resonated at δ 6.84 (ddd, *J* = 8.8, 4.0, 2.4 Hz, 1H), 6.02 (dt, *J* = 10.4, 2.4 Hz, 1H), 5.75–5.63 (m, 2H), 5.15 (m, 1H), 5.08 (dt, *J* = 7.2, 4.0 Hz, 1H, CH), 4.96 (m, 1H, CH), 4.86 (m, 1H, CH) along with all other required resonated protons confirmed the product. The IR spectrum showed absorption band at 1738, 1374 cm^{-1} designate to α,β-unsaturated carbonyl and acetate group. In ^{13}C NMR spectrum (Table 1), the values at δ 170.2, 170.1, 170.0, 163.8, 144.5, 130.9, 128.3, 121.5, 77.2, 73.7, 69.6, 69.6, 34.0, 29.5, 21.0, 20.8, 20.7, 16.0. also supported the below structure **11**. HR-ESI-MS signal at *m/z*:

391.1359 $[M+Na]^+$ further confirmed the structure of synargentolide A **11** (Scheme 15). The spectral properties and optical rotation of synthetic synargentolide **11** to be identical with those published for the natural synargentolide.



Scheme 15

In conclusion, we have performed a stereoselective synthesis of the natural synargentolide A and shown it to be **11**. Synargentolide A is therefore 6*R*[4*R*,5R,6*R*-triacetyloxy-1*E*-heptenyl]-5,6-dihydro- *2H*-pyran-2-one.

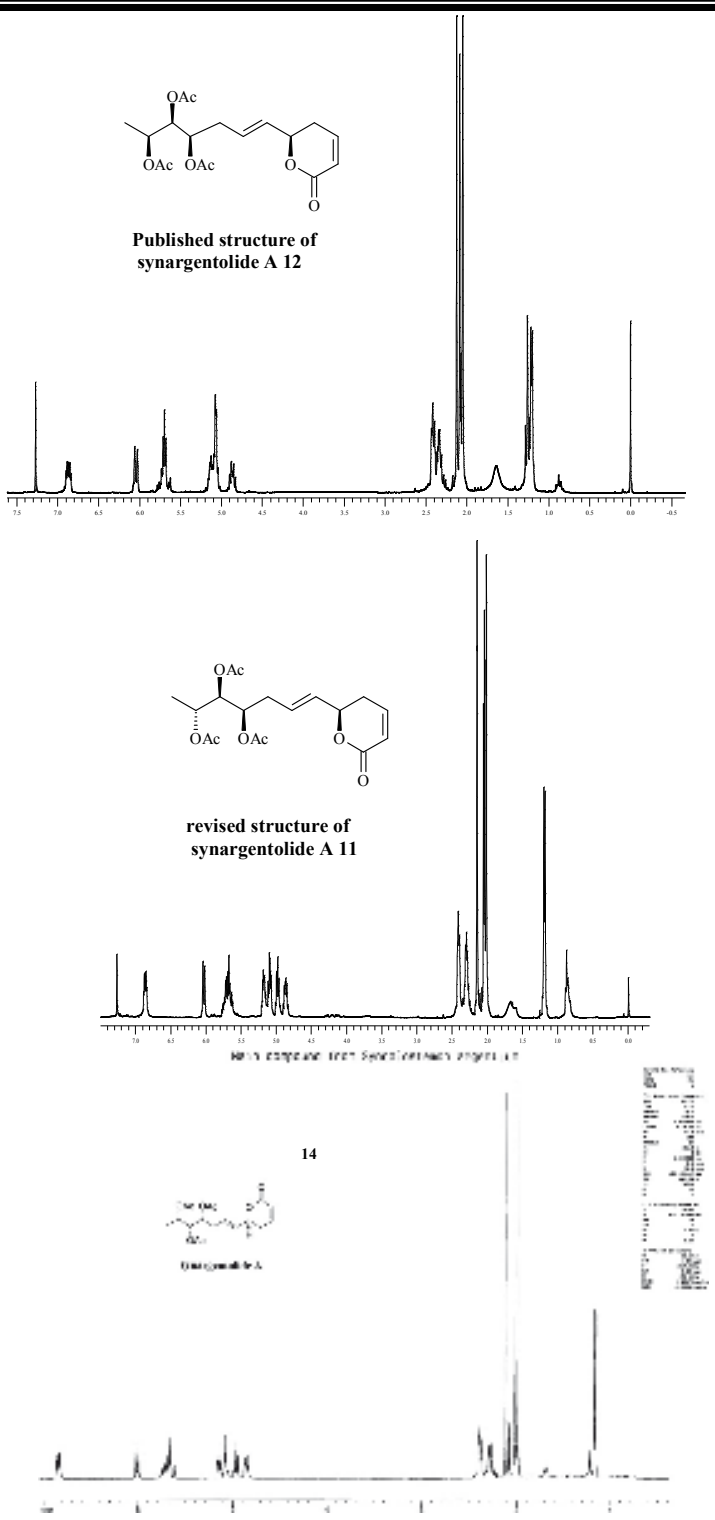
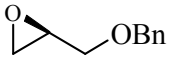


Figure 14: Comparison of the δ 0.0-7.0 range of the ^{1}H-NMR spectra of the synthetic lactones **12** (Alberto Marco *et al*) and **11** (Sabitha group *et al*) with that of natural syngentolide A (Davies-Coleman and Rivett *et al*).

EXPERIMENTAL SECTION

(2*R*)-2-[(benzyloxy)methyl]oxirane (29):



To the (*S,S*)-(salen)Co(II) precatalyst (0.28 g, 0.46 mmol, 0.5 mol.%) in a flask was charged sequentially with (±)-benzyl glycidyl ether **28** (15.5 g, 94.51 mmol) and AcOH (0.11 mL, 1.83 mmol, 0.02 eq). After the reaction mixture turned from a red suspension to a dark brown solution, the flask was cooled to 0 ^{o}C and THF (1 mL) followed by H_2O (0.93 mL, 51.66 mmol, 0.55 eq) were added. The reaction mixture was allowed to warm to room temperature over 2 h and stirred for an additional 20 h. Distillation of the reaction mixture under *vacuo* (75 ^{o}C, 11 mmHg) gave unreacted (*R*)-benzyl glycidyl ether **29** (7.05 g, 45.5% yield) as a colorless oil (EtOAc /hexane, 3:7).

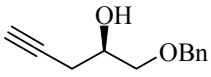
$[\alpha]_D^{27}$: –5.2 (*c* = 2.0, CHCl3).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35–7.28 (m, 5H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 3.76 (dd, *J* = 11.2, 2.8 Hz, 1H), 3.42 (dd, *J* = 11.2, 5.8 Hz, 1H), 3.18 (m, 1H), 2.78 (dd, *J* = 4.5, 4.2 Hz, 1H), 2.60 (dd, *J* = 4.5, 2.5 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 140.0, 128.5, 127.8, 73.3, 70.9, 50.9, 44.3.

ESIMS: *m/z* 165 $[M+H]^+$.

(2*R*)-1-(benzyloxy)-4-pentyn-2-ol (30):



Lithium acetylide-EDA complex (5.89 g, 64.02 mmol) was added to a solution of epoxide **29** (7 g, 42.6 mmol) in dry DMSO (30 mL), and the mixture was stirred overnight at room temperature. After quenching with ice, 0.5 M H_2SO_4 was used to neutralize the basic solution to pH 7. The solution was extracted with diethyl ether (3 x

70 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by column chromatography (EtOAc /hexane, 4:6) afforded **30** (7.4 g, 92%) as a colorless liquid.

$[\alpha]_D^{27}$: –10.6 (c = 1, $CHCl_3$).

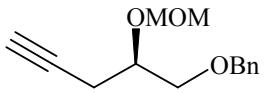
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.22 (m, 5H, Ar-H), 4.55 (s, 2H, CH_2-OAr), 3.97-3.85 (m, 1H), 3.58 (dd, *J* = 4.0, 9.2 Hz, 1H), 3.47 (dd, *J* = 6.4, 9.4 Hz , 1H), 2.45-2.34 (m, 2H), 1.93 (t, *J* = 2.6 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 128.3, 127.7, 127.6, 80.2, 73.3, 72.6, 70.4, 68.6, 23.3.

IR(neat): 3434, 3062, 2914, 2864, 1453, 1112 cm^{-1}.

ESIMS: *m/z* 213 $[M+Na]^+$.

1-([(2*R*)-2-(methoxymethoxy)-4-pentynyl]oxymethyl)benzene (31):



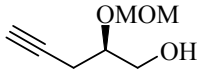
To alcohol **30** (7.35 g, 38.6 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 ^oC were added diisopropyl ethylamine (13.3 g, 103.1 mmol) and catalytic MOMCl (4.67 g, 58.0 mmol) successively. The mixture was stirred for 2 h at room temperature, quenched by adding water (20 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 (2 g) and concentrated under vacuum to remove the solvent and the crude residue was purified by column chromatography (EtOAc/ hexane, 7:3) to afford the MOM ether **31** (8.55 g, 95% yield) as colorless oil.

$[\alpha]_D^{27}$: –8.0 (c = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34-7.21 (m, 5H, Ar-H), 4.69 (s, 2H), 4.54 (s, 2H, CH_2-OAr), 3.91-3.81 (m, 1H), 3.57 (d, *J* = 5.2 Hz, 2H), 3.36 (s, 3H), 2.58-2.40 (m, 2H), 1.89 (t, *J* = 2.2 Hz, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz):	δ 137.9, 128.2, 128.1, 127.5, 95.8, 80.5, 74.1, 73.2, 71.4, 69.9, 55.4, 21.8.
IR(neat):	3030, 2893, 1151, 1103, 1035 cm^{-1}.
ESI-MS:	*m/z* 257 $[M+Na]^+$.

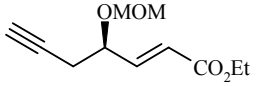
(2*R*)-2-(methoxymethoxy)-4-pentyn-1-ol (32):



Lithium metal (1.3 g, 185.7 mmol) was added to a stirred solution of freshly distilled ammonia (30 mL) and compound **31** (8.5 g, 36.32 mmol) in anhydrous THF (50 mL) in a 250 mL two neck round bottom flask fitted with a cold finger condenser at –33 ^oC. The reaction mixture was then stirred for another 30 min at –33 ^oC and quenched by the addition of solid ammonium chloride (5 g) and the ammonia was then allowed to evaporate. The residue left was partitioned between water (5 mL) and ether (10 mL) and the aqueous phase was extracted with ether. The combined organic layers were washed with water (2 mL), brine (2 mL), dried over anhydrous Na_2SO_4 (3 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 6:4) to afford the pure **32** (4.68 g, 90% yield) as a clear colorless liquid.

$\alpha]_D^{27}$:	–71.6 (c = 1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 4.72 (m, 2H, CH_2), 3.77-3.68 (m, 2H, CH_2), 3.59 (m, 1H, CH), 3.41 (s, 3H, CH_3), 2.43 (m, 2H, CH_2), 1.93 (m, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 96.5, 80.6, 78.1, 70.2, 64.3, 55.6, 36.2, 21.6.
IR (neat):	3437, 3293, 2932, 1640, 1363, 1105 cm^{-1}.
ESIMS:	*m/z* 167 $[M+Na]^+$.

Ethyl (*E*,4*R*)-4-(methoxymethoxy)-2-hepten-6-ynoate (34):



To an ice-cooled solution of 2-iodoxybenzoic acid (19.31 g, 71.51 mmol) in anhydrous DMSO (20 mL, 270.02 mmol) was added a solution of alcohol **32** (4.68 g, 32.5 mmol) in anhydrous CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 24 h and then filtered through a Celite pad and washed with Et_2O (15 mL). The combined organic filtrates were washed with H_2O (2 x 20 mL) and brine (5 mL), dried over anhydrous Na_2SO_4 (2 g), and concentrated *in vacuo*. The unstable crude aldehyde **33** was used for further reaction.

To a solution of **33** (4.68 g, 32.5 mmol) in anhydrous benzene (70 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (23.21 g, 66.88 mmol). The mixture was maintained at 80 °C for 2 h, and then the solvents were removed *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 2.5:7.5) to afforded **34** (6.0 g, 85%) as a colorless oil.

$[\alpha]_D^{27}$: +29.0 (c = 1, $CHCl_3$).

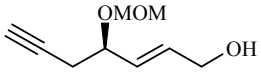
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.84 (dd, *J* = 6.4, 15.8 Hz, 1H), 6.03 (d, *J* = 15.8 Hz, 1H), 4.63 (ABq, *J* =3.5, 10.0 Hz, 2H), 4.37-4.29 (m, 1H), 4.19 (q, *J* = 7.5, 14.3 Hz, 2H), 3.38 (s, 3H), 2.59-2.39 (m, 2H), 1.97 (t, *J* = 2.9 Hz, 1H), 1.31 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7, 145.3, 122.8, 94.6, 79.3, 73.1, 70.6, 60.3, 55.4, 24.9, 13.9.

IR (neat): 2926, 2860, 1717, 1459, 1123, 1031 cm^{-1}.

ESIMS: 235 $[M+Na]^+$.

(*R*,*E*)-4-(methoxymethoxy)hept-2-en-yn-1-ol (35):

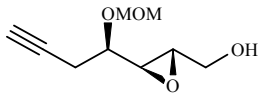


To a stirred solution of ester **34** (5.9 g, 28.83 mmol) in anhydrous CH_2Cl_2 (70 mL) was added DIBAL-H (32.74 mL, 1.7 M, 55.66 mmol in hexane) dropwise over a period of 5 min at -78 ^oC under N_2 atmosphere. After stirring for 1 h at room temperature

anhydrous MeOH (3 mL) was added at 0 ^{o}C, and the mixture was allowed to warm to room temperature saturated aqueous solution of sodium potassium tartarate (30 mL) was added, and the resulting mixture was stirred vigorously until the two layers were separated. The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with H_2O, brine solution and dried over anhydrous Na_2SO_4 (2 g). Removal of solvent *in vacuo* and purification by silica gel column chromatography using (EtOAc/hexane, 4:6) to afford the alcohol **35** (3.5 g, 75% yield) as a liquid.

$[\alpha]_D^{27}$:	+9.0 (c = 1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ δ 4.61(dd, *J* = 6.7, 34.7 Hz, 2H), 4.24-4.10 (m, 3H), 3.37 (s, 3H), 2.55-2.34 (m, 2H), 1.93 (t, *J* = 3.0 Hz, 1H), 1.70 (bds, 1H, OH).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 133.3, 128.6, 93.5, 80.4, 74.0, 70.0, 62.0, 55.2, 25.4.
IR (neat):	3423, 3293, 2937, 1417, 1150, 1036 cm^{-1}.
ESIMS:	*m/z* 193 $[M+Na]^+$.

(2*S*,3*R*)-3-[(1*R*)-1-(methoxymethoxy)-3-butynyl]oxiran-2-ylmethanol (36):

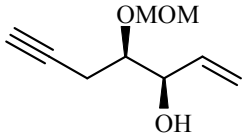


In a 500 mL two neck round bottomed flask, 20 mL of anhydrous CH_2Cl_2 was added to 4 ^{o}A powdered activated molecular sieves and suspension mixture was cooled to –20 ^{o}C, Ti(O*i*Pr)$_4$ (1.13 mL, 4 mmol) and L-(+)-DIPT (0.68 g, 3.3 mmol) in anhydrous CH_2Cl_2 (15 mL) were added subsequently with stirring and the resulting mixture was stirred for 30 min at –24 ^{o}C, compound **35** (3.4 g, 20 mmol) in anhydrous CH_2Cl_2 (10 mL) was then added and the resulting mixture was stirred for another 30 min at –24 ^{o}C followed by addition of cumenehydroperoxide (3.64 mL, 24 mmol) and the resulting mixture was stirred at the same temperature for 4 h. It was then warmed to 0 ^{o}C, quenched with 3 mL of water and stirred for 1 h at room temperature. After that 30%

aqueous NaOH solution saturated with NaCl (3 mL) was added and the reaction mixture was stirred vigorously for another 30 min at room temperature. The resulting mixture was then filtered through Celite rinsing with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography (EtOAc/hexane, 5:5) to afford **36** (3.64 g, 98%) as a viscous liquid.

$[\alpha]_D^{25}$:	+ 2.0 (*c* = 1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 4.71(dd, *J* = 6.7, 37.7 Hz, 2H), 3.91(dd, *J* = 2.2, 12.8 Hz, 1H), 3.67-3.48 (m, 2H), 3.38 (s, 3H), 3.12-3.06 (m, 2H), 2.60-2.40 (m, 2H), 1.97 (t, *J* = 3.0 Hz, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 95.5, 79.5, 75.1, 70.6, 60.9, 56.9, 56.1, 55.6, 22.3.
IR (neat):	3442, 3284, 2928, 1445, 1153, 1102 cm^{-1}.
ESIMS:	*m/z* 209 $[M+Na]^+$.

(3*R*,4*R*)-4-(methoxymethoxy)-1-hepten-6-yn-3-ol (38):



To a stirred solution of **36** (3.54 g, 19.0 mmol) in mixture of 27 mL of anhydrous ether and 9 mL of anhydrous CH_3CN was added TPP (7.47 g, 28.51 mmol), imidazole (2.58 g, 38 mmol) and iodine (3 g, 23 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 20 min. Solids were filtered and washed with ether. The filtrate was extracted with ether, washed with 10% aqueous $Na_2S_2O_3$ solution, water, brine solution and dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and the unstable crude iodo compound **37** was used for further reaction.

A solution of compound **37** (5.17 g, 17.46 mmol) in ethanol (50 mL) was added to zinc dust (17.8 g, 261.76 mmol) in 250 mL round bottom flask. The reaction mixture was stirred at reflux for 2 h and then Et_2O (10 mL) and NH_4Cl (3 g) were added to the

reaction mixture at 0 ^{o}C, allowed to stir at room temperature for 1 h and filtered through bukner funnel-flask setup and the filtrate was concentrated under reduced pressure. Column chromatography (EtOAc/hexane, 3:7) afforded pure product **38** (2.76 g, 92% yield) as a colorless liquid.

$[\alpha]_D^{25}$: –10.0 (*c* = 1, $CHCl_3$).

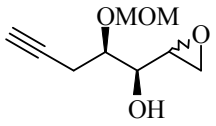
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.83-5.37(m, 1H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.23 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 6.5 Hz, 1H), 4.70 (d, *J* = 7.3 Hz, 1H), 4.22 (m, 1H, CH), 3.57 (m, 1H, CH), 3.41(s, 3H, CH3), 2.62–2.35 (m, 2H, CH2), 1.94 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.7, 117.2, 96.7, 80.3, 79.3, 73.4, 70.2, 55.8, 21.2.

IR (neat): 3446, 3295, 2897, 1040 cm^{-1}.

ESIMS: *m/z* 193 $[M+Na]^+$.

(1*R*,2*R*)-2-(methoxymethoxy)-1-(2-oxiranyl)-4-pentyn-1-ol (39):

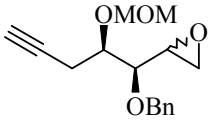


To a suspension of $NaHCO_3$ (4 g, 47.61 mmol) in CH_2Cl_2 (20 mL) was added terminal alkene **38** (2.7 g, 15.88 mmol) in CH_2Cl_2 (30 mL) under nitrogen atmosphere. Crystalline *m*-CPBA (4.1 g, 23.76 mmol) was added in portions to the reaction mixture and stirred at ambient temperature for 10 h. The reaction mixture was diluted with CH_2Cl_2. The CH_2Cl_2 layer was washed with a solution of sodium metabisulfite followed by 5% $NaHCO_3$ solution and water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ((EtOAc/hexane, 5:5) to afford the recemic terminal epoxide **39** (2.76 g, 90%) as a color less liquid confirmed by chiral HPLC analysis.

$[\alpha]_D^{25}$: –19.0 (*c* = 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 300 MHz):	δ 4.82-4.68 (m, 2H), 3.86-3.76(m, 1H), 3.60 (bds, 1H, OH), 3.42 (s, 3H), 3.10-2.96 (m, 1H), 2.82-2.59 (m, 3H), 2.56-2.44 (m, 2H), 1.98-1.92 (m, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 96.4, 80.2, 77.1, 77.5, 71.0, 55.8, 52.4, 44.9, 20.9.
IR (neat):	3446, 3285, 2924, 1150, 1035 cm^{-1}.
ESIMS:	*m/z* 209 $[M+Na]^+$.

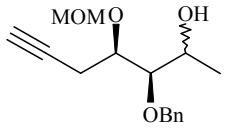
2-[(1*R*,2*R*)-1-(benzyloxy)-2-(methoxymethoxy)-4-pentynyl]oxirane (40):



To a stirred suspension of NaH (0.85 g, 35.41 mmol) in anhydrous THF (20 mL) under nitrogen atmosphere was added alcohol **39** (2.66 g, 14.3 mmol) in anhydrous THF (10 mL) dropwise at 0 ºC. The reaction mixture was allowed to warm to 25 ºC and stirred for 30 min. It was then cooled to 25 ºC and benzyl bromide (1.7 mL, 10 mmol) was added dropwise, stirred for 3 h and cooled to 0 ^oC then quenched with ice, extracted with ether (3 x 25 mL). The combined extracts were washed with brine, dried over Na_2SO_4 (1 g) and purified by column chromatography (EtOAc/hexane, 4:6) to afford **40** (3.8 g, 95%), a non separable diastereomeric mixture as a colorless oil.

$[\alpha]_D^{25}$:	–45.8 (*c* = 1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.40-7.20 (m, 5H, Ar-H), 4.88-4.54 (m, 4H), 3.94-3.78 (m, 1H), 3.36 (s, 3H), 3.26-3.07 (m, 1H), 2.80-2.43 (m, 5H), 1.91-1.84 (m, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 137.8, 128.7, 128.1, 128.0, 127.5, 96.3, 80.4, 77.7, 76.5, 72.5, 70.2, 55.8, 52.7, 46.1, 20.6.
IR (neat):	2995, 2894, 1454, 1100, 1040 cm^{-1}.
ESIMS:	*m/z* 299 $[M+Na]^+$.

(3*R*,4*R*)-3-(benzyloxy)-4-(methoxymethoxy)-6-heptyn-2-ol (41):



To a stirred suspension of $LiAlH_4$ (0.5 g, 13.51 mmol) in anhydrous THF (20 mL) at 0 ºC was added dropwise a solution of terminal epoxide **40** (3 g, 10.86 mmol) in anhydrous THF (30 mL). The reaction mixture was allowed to warm to 25 ºC and stirred for 30 min. Reaction mixture was then cooled to 0 ºC and quenched with dropwise addition of saturated aqueous Na_2SO_4 (10 mL). The precipitate formed was filtered and washed with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 (2 g) and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (7:3, EtOAc/hexane) to afford **41** (2.86 g, 95%), a non seperable diastereomeric mixture as a viscous liquid.

$[\alpha]_D^{25}$: – 37.7 (*c* = 1, $CHCl_3$).

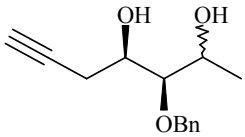
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.23 (m, 5H, Ar-H), 4.88-4.54 (m, 4H), 4.13-3.85 (m, 2H), 3.48-3.39 (m, 1H), 3.37 (s, 3H), 2.70-2.45 (m, 2H), 1.50 (s, 1H), 1.22 (d, *J* = 6.7 Hz, d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.9, 128.4, 128.3, 128.0, 127.8, 96.6, 82.8, 76.3, 75.4, 70.3, 67.06, 55.8, 21.8, 19.6.

IR (neat): 3455, 2931, 1453, 1149, 1098, 1036 cm^{-1}.

ESIMS: *m/z* 301 $[M+Na]^+$.

3*R*,4*R*)-3-(benzyloxy)-6-heptyne-2,4-diol (42):



To a stirred solution of compound **41** (2.76 g, 10 mmol) in a MeOH (15 mL) was added catalytic amount of 3N HCl under N_2, then the mixture was stirred at room temperature for 5 h. The mixture was quenched with solid $NaHCO_3$ (0.3 g) and filtered,

the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/ hexane, 6:4) to afford compound **42** (2.1 g, 93% yield) a non separable diastereomeric mixture as a viscous liquid.

$[\alpha]_D^{25}$: – 30.4 (*c* = 1, $CHCl_3$).

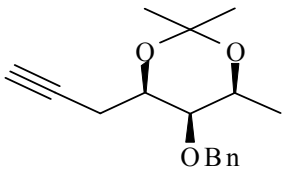
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.35-7.23 (m, 5H, Ar-H), 4.80-4.61 (m, 2H), 3.79 (m, 2H), 3.43 (dd, *J* = 1.5, 4.5 Hz , 1H), 2.73-2.40 (m, 2H), 2.2 (t, *J* = 6.0 Hz, 1H), 1.56 (brd s, 1H, OH), 1.23 (d, *J* = 6.7 Hz, d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.7, 128.5, 128.4, 128.0, 81.2, 75.9, 73.4, 71.0, 70.8, 68.7, 19.9.

IR (neat): 3411, 3295, 2922, 1453, 1060 cm^{-1}.

ESIMS: *m/z* 257 $[M+Na]^+$.

(4*S*,5*S*,6*R*)-5-(benzyloxy)-2,2,4-trimethyl-6-(2-propynyl)-1,3-dioxane (43a):



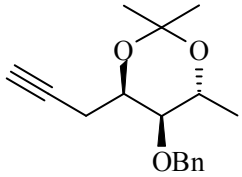
2,2-Dimethoxypropane (1.72 mL, 16.53 mmol) and PPTS (cat) were added successively to a solution of diol **42** (2 g, 8.54 mmol) in a mixture of CH_2Cl_2: Et_2O (9:1) (20 mL). The solution was stirred for 1 h at room temperature and then quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with ether (3 x 20 mL). The organic layers were washed with brine, dried over Na_2SO_4 (1 g) and concentrated. The crude compound was purified on column chromatography (EtOAc/hexane, 7:3) to afford the pure acetonide **43a** (2.2 g, 95%) as a viscous liquid.

$[\alpha]_D^{25}$: –42.0 (*c* = 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42-7.21 (m, 5H, ArH), 4.72 (ABq, *J* = 11.3 Hz, 2H, C**H$_2$**-OAr), 3.97 (m, 2H), 3.29 (m, 1H, CH), 2.68 (dd, *J* = 2.6, 16.4 Hz, 0.5H), 2.65 (dd, *J* = 2.4, 10.0 Hz, 0.5H),

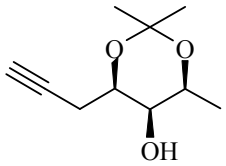
	1.98 (m, acetylinic CH), 1.43 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.18 (d, *J* = 6.4 Hz, 3H, CH_3).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 138.2, 128.2, 128.1, 127.6, 98.8, 80.6, 75.0, 72.8, 71.6, 70.6, 68.5, 29.6, 29.3, 19.0, 17.7.
IR (neat):	2985, 1455, 1378, 1229, 1091 cm^{-1}.
ESIMS:	*m/z* 297 $[M+Na]^+$.

(4*R*,5*S*,6*R*)-5-(benzyloxy)-2,2,4-trimethyl-6-(2-propynyl)-1,3-dioxane (43b):



$[\alpha]_D^{25}$:	–19.5 (*c* = 1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 500 MHz):	δ 7.34-7.23 (m, 5H, ArH), 4.61 (ABq, *J* = 11.7 Hz, 2H, C**H$_2$**-OAr), 4.0, (m, 1H, CH), 3.74 (m, 1H, CH), 3.40 (m, 1H, CH), 2.62 (dd, *J* = 2.9, 16.5 Hz, 0.5H), 2.60 (dd, *J* = 2.9, 16.5 Hz, 0.5H), 2.42 (dd, *J* = 2.9, 16.5 Hz, 0.5H), 2.41 (dd, *J* = 2.9, 16.5 Hz, 0.5H), 1.92 (m, acetylinic CH), 1.35 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.19 (d, *J* = 6.8 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 138.0, 128.3, 127.9, 127.7, 100.7, 82.1, 81.0, 74.1, 69.7 (2xC), 69.1, 24.8, 23.8, 20.0, 19.4.
IR (neat):	2990, 1455, 1377, 1202, 1083 cm^{-1}.
ESIMS:	*m/z* 297 $[M+Na]^+$.

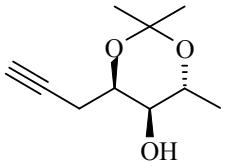
(4*S*,5*S*,6*R*)-2,2,4-trimethyl-6-(2-propynyl)-1,3-dioxan-5-ol (44a):



Lithium metal (0.12 g, 17.14 mmol) was added to a stirred solution of freshly distilled ammonia (10 mL) and compound **43a** (1 g, 3.64 mmol) in anhydrous THF (20 mL) in a 250 mL two neck round bottom flask fitted with a cold finger condenser at –33 ^{o}C. The reaction mixture was then stirred for another 30 min at –33 ^{o}C and quenched by the addition of solid ammonium chloride (2 g) and the ammonia was then allowed to evaporate. The residue left was partitioned between water (3 mL) and ether (10 mL) and the aqueous phase was extracted with ether. The combined organic layers were washed with water (2 mL), brine (2 mL), dried over anhydrous Na_2SO_4 (1 g) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/ hexane, 4:6) to afford the pure compound **44a** (0.6 g, 91% yield) as a clear colorless liquid.

$[\alpha]_D^{25}$:	+40.0 (*c* = 1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 4.17-3.93 (m, 2H), 3.36 (d, *J* = 11.5 Hz, 1H), 2.67-2.54 (m, 1H), 2.44-2.34 (m, 1H), 2.0 (t, *J* = 2.6 Hz, 1H), 1.62 (bds, 1H, OH) 1.47 (s, 3H), 1.42 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 101.1, 80.8, 71.8, 70.1, 69.8, 66.3, 29.7, 21.3, 19.1, 17.4.
IR (neat):	3475, 1377, 1202, 1083 cm^{-1}.
ESIMS:	*m/z* 207 $[M+Na]^+$.

(4*R*,5*S*,6*R*)-2,2,4-trimethyl-6-(2-propynyl)-1,3-dioxan-5-ol (44b):



$[\alpha]_D^{25}$:	+25.5 (*c* = 1, $CHCl_3$).

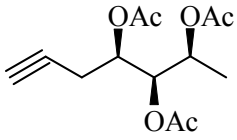
^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.20-3.94 (m, 2H), 3.36 (d, *J* = 10.2 Hz, 1H), 2.67-2.40 (m, 2H), 1.98 (t, *J* = 2.5 Hz, 1H), 1.60 (s, 3H), 1.50 (s, 3H), 1.20 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 99.5, 81.3, 71.0, 70.5, 69.6, 66.9, 28.9, 24.3, 20.1, 19.5.

IR (neat): 3477, 1378, 1201, 1085 cm^{-1}.

ESIMS: *m/z* 207 $[M+Na]^+$.

(1*R*,2*R*)-2-(acetyloxy)-1-[(1*S*)-1-(acetyloxy)ethyl]-4-pentynyl acetate (46a):



To a stirred solution of compound **44a** (055 g, 3 mmol) in a MeOH (10 mL) and was added 2N HCl (cat.) under N2, then the mixture was stirred at room temperature for 1 h. The mixture was quenched with solid $NaHCO_3$ (0.2 g) and filtered, the solvent was removed under reduced pressure and the crude triol **45a** was directly used for the next step without further purification.

Anhydrous Et_3N (1.35 g, 13.36 mmol), Ac_2O (1 mL, 9.8 mmol), and DMAP (10 mg) were added to a solution of triol **45a** (0.35 g, 2.43 mmol) in anhydrous CH_2Cl_2 (20 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (ethyl acetate/hexane, 2:8) to afford **46a** (0.56 g, 94%) as a colorless liquid.

$[\alpha]_D^{25}$: +30.0 (*c* = 1, $CHCl_3$).

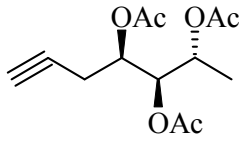
^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.22 (dd, *J* = 6.7, 14.0 Hz, 1H), 5.12-5.02 (m, 2H), 2.58-2.40 (m, 2H), 2.10 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.0 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.0, 169.7, 169.6, 78.0, 73.0, 71.0, 68.4, 67.3, 29.6, 21.0, 20.9, 20.7, 17.0.

IR (neat): 3280, 2925, 1740, 1365, 1210 cm^{-1}.

ESIMS: *m/z* 293 $[M+Na]^+$.

(1*R*,2*R*)-2-(acetyloxy)-1-[(1*S*)-1-(acetyloxy)ethyl]-4-pentynyl acetate (46b):



$[\alpha]_D^{25}$: +22.5 (*c* = 1, $CHCl_3$).

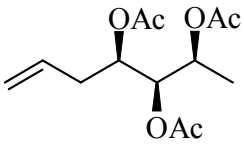
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.24 (t, *J* = 5.2 Hz, 1H), 5.14-5.01 (m, 2H), 2.56-2.39 (m, 2H), 2.11 (s,3H), 2.08 (s,3H), 2.02 (s, 3H), 1.23 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.0, 169.9, 169.8, 78.1, 73.2, 70.9, 68.5, 67.0, 29.2, 21.0, 21.0, 20.6, 16.2.

IR (neat): 3285, 2926, 1742, 1370, 1216 cm^{-1}.

ESIMS: *m/z* 293 $[M+Na]^+$.

(1*R*,2*R*)-2-(acetyloxy)-1-[(1*S*)-1-(acetyloxy)ethyl]-4-pentenyl acetate (47a):



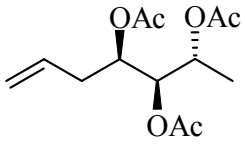
To solution of compound **46a** (0.46 g, 0.17 mmol) in EtOAc (10 mL), 1 drop of quinoline and Lindlar's catalyst ($Pd/BaSO_4$) were added and stirred at room temperature under H_2 atm for 2 h. After completion of the reaction, the reaction mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified on silica gel column chromatography (ethyl acetate/hexane, 2:8) to afford the compound **47a** (0.43 g, 94%) as colorless liquid.

$[\alpha]_D^{25}$: +1.5 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.66 (m, 1H), 5.30-4.93 (m, 5H), 2.35-2.14 (m, 2H), 2.06 (s, 3H, CH_3), 2.01 (s, 3H,

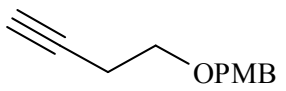
	CH_3), 1.99 (s, 3H, CH_3), 1.15 (d, J = 6.0 Hz, 3H, CH_3).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 170.1, 170.0, 169.9, 132.0, 118.8, 74.2, 70.2, 68.7, 35.3, 121.0, 20.8, 20.6, 16.3.
IR(neat):	3422, 2946, 2889, 1644, 1603, 1422, 1151, 1742, 1370, 1216 cm^{-1}.
EIMS:	*m/z* 295 $[M+Na]^+$.

(1*R*,2*R*)-2-(acetyloxy)-1-[(1*R*)-1-(acetyloxy)ethyl]-4-pentenyl acetate (47b):



$[\alpha]_D^{25}$:	+22.5 (c = 1, $CHCl_3$).
^1H NMR ($CDCl_3$, 200 MHz):	δ 5.69 (m, 1H), 5.16 (dt, J = 7.0, 3.1 Hz, 1H, CH), 5.11-5.03 (m, 3H), 4.94 (m, 1H, CH), 2.24 (m, 2H, CH_2), 2.13 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.0 (s, 3H, CH_3), 1.18 (d, J = 6.2 Hz, 3H, CH_3).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 169.9.169.8, 169.7, 132.2, 118.4, 73.7, 69.7, 67.2, 35.4, 20.8, 20.6, 20.5, 15.9.
IR(neat):	1744, 1372, 1222 cm^{-1}.
EIMS:	*m/z* 295 $[M+Na]^+$.

1-((but-3-ynyloxy)methyl)-4-methoxybenzene (49):



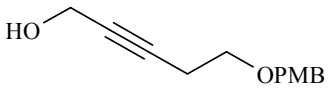
To a stirred suspension of freshly activated NaH (13.12 g, 320 mmol) in dry THF (150 mL) under N_2 atmosphere was added **48** (19.2 g, 274.27 mmol) in dry THF (50 mL) in a dropwise manner at 0 ^oC. After stirring for 30 min at 0 ^oC, PMB-Br (66.14 g, 329

mmol) was added dropwise. The reaction mixture was stirred for 6 h at 0 ^{o}C, and quenched with saturated KBr solution. The layers were separated and aq. layer was extracted with ethyl acetate (2 X 100 mL). The combined organic layers were washed with water, brine solution and then dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford **49** (42.4 g, 81% yield) as viscous liquid.

^{1}H NMR ($CDCl_3$, 200MHz): δ 7.21 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 4.45 (s, 2H), 3.78 (s, 3H), 3.52 (t, *J* = 7.5 Hz, 2H), 2.44 (dt, *J* = 2.5, 7.5 Hz, 2H), 1.87 (t, *J* = 2.5 Hz, 1H).

IR (neat): 2930, 2860, 1612, 1512, 1247, 1097, 1034, 820 cm^{-1}.

5-(4-methoxybenzyloxy)pent-2-yn-1-ol (50):



Freshly prepared EtMgBr (prepared *in situ* from 10.43 g (435.58 mmol of Mg) and 33.6 mL (310.06 mmol) of ethyl bromide in 60 mL of dry THF) was added dropwise to stirred solution of alkyne **49** (42 g, 218 mmol) in dry THF (200 mL) at 0 ^{o}C. After completion addition, reaction mixture was stirred for 1 h at room temperature and para-formaldehyde (38 g) was added. The resulting mixture was stirred further for 3 h at room temperature and then quenched with saturated aqueous NH_4Cl solution. The organic layer was separated and aqueous layer was extracted with ethyl acetate (2 X 100 mL). The combined organic layers were washed with water, brine solution and dried over anhydrous Na_2SO_4. Concentration under reduced pressure and purification by silica gel column chromatography (EtOAc/pet-ether, 2:8) afforded alcohol **50** (40.8 g, 85%) as a viscous liquid.

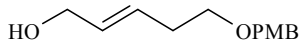
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.21 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 4.44 (s, 2H), 4.17 (t, *J* = 2.2 Hz,

2H), 3.79 (s, 3H), 3.51 (t, J = 6.7 Hz, 2H), 2.51-2.44 (m, 2H).

IR (neat): 3415, 2932, 2866, 1616, 1513, 1248, 1020, 1094, 822 cm^{-1}.

ESIMS: *m/z* 243 $[M+Na]^+$.

(*E*)-5-(4-methoxybenzyloxy)pent-2-en-1-ol (51):



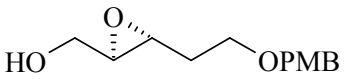
To a stirred suspension of $LiAlH_4$ (10.36 g, 272.83 mmol) in dry THF (40 mL) at 0 ^oC was added dropwise a solution of alkyne **50** (40.5 g, 182.4 mmol) in dry THF (150 mL) under nitrogen. The reaction mixture was allowed to warm to room temperature and then refluxed for 4 h. It was then cooled to 0 ^oC, diluted with ether and quenched by dropwise addition of saturated aqueous Na_2SO_4 (30 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate several times. The combined organic layers were dried over anhydrous Na_2SO_4. Solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (EtOAc/pet-ether, 2:8) to afford allyl alcohol **51** (32.51 g, 80%) as a clear liquid.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.12 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 5.67-5.61 (m, 2H), 4.39 (s, 2H), 4.02-3.98 (m, 2H), 3.78 (s, 3H), 3.44 (t, J = 6.4 Hz, 2H), 2.37-2.24 (m, 2H), 1.98 (br s, OH).

IR (neat): 3449, 2935, 2835, 2855, 1736, 1609, 1512, 1246, 1032, 971 cm^{-1}.

ESIMS: *m/z* 245 $[M+Na]^+$.

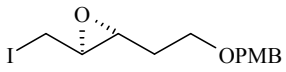
((2*R*,3*R*)-3-(2-(4-methoxybenzyloxy)ethyl)oxiran-2-yl)methanol (52):



100 ml dry CH_2Cl_2 was added to 4 ^oA powdered, activated molecular sieves (2 g) and the suspension mixture was cooled to –20 ^oC. (-) DIPT (5.76 g, 28.8 mmol) and Ti ($O^iPr)_4$ (8.12 mL, 28.8 mmol) were added subsequently with stirring and the resulting mixture was stirred for 30 min at –20 ^oC. Allyl alcohol **51** (40.1 g, 143.48 mmol) in dry CH_2Cl_2 (100 mL) was added and the resulting mixture was stirred for another 30 minutes at –20 ^oC, cumenehydroperoxide (32 mL, 215.78 mmol) was added and the resulting mixture was stirred at the same temperature for 6 h. After completion of the reaction, (monitored by TLC) it was warmed to 0 ^oC, quenched with 10 mL water and stirred for 1 h at 0 ^oC. 30% aqueous NaOH solution saturated with NaCl (10 mL) was then added and the resulting mixture was stirred vigorously for another 30 min at 0 ^oC. The resulting mixture was vacuum filtered through Celite and the filter cake was washed well with CH_2Cl_2. The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (2 X 100 mL), the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure and purified by silica gel (EtOAc/pet-ether, 4:6) chromatography gave the epoxide **52** (24.0 g, 70 %), as a viscous liquid.

$[\alpha]_D^{25}$:	+ 24.1 (*c* = 1, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.19 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.41 (s, 2H), 3.78 (s, 3H), 3.62-3.47 (m, 4H), 3.07-2.98 (m, 1H), 2.98-2.86 (m, 1H), 1.92-1.72 (m, 2H) .
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 159.1, 130.1, 129.1, 113.7, 72.6, 66.4, 61.6, 56.4, 55.1, 53.6, 31.9.
IR (neat):	3424, 2926, 2863, 1611, 1513, 1247, 1175, 1093, 1031, 819 cm^{-1}.
ESIMS:	239 $[M+H]^+$.

(2*S*, 3*R*)-2-(iodomethyl)-3-2-[(4-methoxybenzyl)oxy]ethyloxirane (53):



To a stirred solution of **52** (21.6 g, 90.36 mmol) in a mixture of 90 mL of anhydrous ether and 10 mL of anhydrous CH_3CN was added TPP (299 g, 108.28 mmol), imidazole (12 g, 176.44 mmol) and iodine (36 g, 121.10 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 20 min. After completion of reaction quenching with 10% aqueous $Na_2S_2O_3$ solution and extracted with ether dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford **53** as a colorless liquid (25.52 g, 81%).

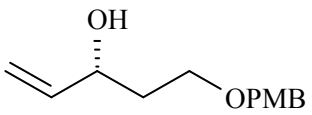
$[\alpha]_D^{25}$: – 16.2 (*c* = 1, $CHCl_3$).

^1H NMR ($CDCl_3$, 200 MHz): δ 7.21 (d, *J* = 8.7 Hz, 2H), 6.20 (d, *J* = 8.7 Hz, 2H), 4.42 (d, *J* = 3.9 Hz, 2H), 3.79 (s, 3H), 3.55-3.51 (m, 2H), 3.25-3.19 (m, 1H), 3.01-2.96 (m, 1H), 2.92-2.89 (m, 2H), 1.88-1.74 (m, 2H).

IR (neat): 2930, 2859, 1611, 1512, 1247, 1174, 1096, 1033, 819 cm^{-1}.

EIMS: *m/z* 349 $[M+H]^+$.

(3*R*)-5-[(4-methoxybenzyl)oxy]-1-penten-3-ol (54):



A stirred suspension of **53** (25 g, 71.04 mmol) and zinc (48 g, 705.88 mmol) in anhydrous EtOH (30 mL) was refluxed for 30 min. The reaction mixture was filtered on *Celite* pad and concentrated under reduced pressure, crude product was purified by column chromatography (EtOAc/pet-ether, 3:7) to furnish **54** (13.6 g, 85%)

$[\alpha]_D^{25}$: – 9.3 (*c* = 1, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz): δ 7.19 (d, *J* = 7.8 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.83-5.75 (m, 1H), 5.21 (d, *J* = 17.3 Hz, 1H), 5.07 (d, *J* = 10.5 Hz, 1H), 4.45 (s, 2H), 3.79 (s, 3H), 3.42 (dd, *J* = 2.9,

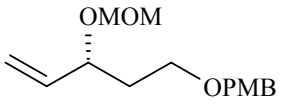
8.7 Hz, 2H), 3.29 (dd, *J* = 6.8, 8.7 Hz, 1H), 2.25 (br s, 1H), 2.22 (t, *J* = 6.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 155.1, 140.4, 129.9, 129.2, 114.2, 113.7, 72.8, 71.7, 67.9, 55.1, 36.2.

IR (neat): 3443, 2934, 2861, 1612, 1512, 1246, 1092, 819 cm^{-1}.

ESIMS: *m/z* 245 $[M+Na]^+$.

1-methoxy-4-([(3*R*)-3-(methoxymethoxy)-4-pentenyl]oxymethyl)benzene (55):



To a stirred solution of compound **54** (13.2 g, 59.44 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 ^oC under N_2, $^iPr_2NEt$ (20.44 mL, 158.44 mmol) was added followed by drop wise addition of MOMCl (5.72 mL, 71.04 mmol). After stirring for 2 h at room temperature, the reaction mixture was diluted with water, saturated aqueous NH_4Cl, brine solution and then dried over anhydrous Na_2SO_4. The residue was concentrated under vacuo and purified by silica gel column chromatography (EtOAc/pet-ether, 1:9) to afford the pure compound **55** (13.4 g, 88%) as a clear colorless liquid.

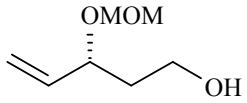
$[\alpha]_D^{25}$: + 44.8 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.20 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 5.69-5.62 (m, 1H), 5.16 (dd, *J* = 10.4, 18.7 Hz, 2H), 4.63 (d, *J* = 6.2 Hz, 1H), 4.47 (d, *J* = 6.2 Hz, 1H), 4.39 (s, 2H), 3.78 (s, 3H), 3.78-3.77 (m, 1H), 3.55-3.51 (m, 1H), 3.48-3.43 (m, 1H), 3.31 (s, 3H), 1.88-1.81 (m, 1H), 1.79-1.72 (m, 1H).

IR (neat): 2946, 1612, 1513, 1463, 1247, 1095, 1034, 994, 923, 820 cm^{-1}.

ESIMS: *m/z* 267 $[M+H]^+$.

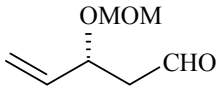
(3*R*)-3-(methoxymethoxy)-4-penten-1-ol (56):



To a stirred solution of compound **55** (13.2 g, 49.6 mmol) in CH_2Cl_2 (27 mL) and water (3 mL) was added DDQ (13.48 g, 59.36 mmol) at r.t. The reaction mixture was stirred for 2.5 h at room temperature before being quenched by the addition of 10 mL of saturated aqueous $NaHCO_3$. The layers were separated and aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (EtOAc/pet-ether, 2:8) to give the compound **56** (6.12 g, 85%) as a pure yellow oil.

$[\alpha]_D^{25}$:	+ 54.2 (*c* = 1, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 5.76 (m, 1H), 5.23 (dd, *J* = 9.1, 14.3 Hz, 2H), 4.76 (d, *J* = 6.1 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 1H), 4.28-4.19 (m, 1H), 3.83-3.67 (m, 2H), 3.38 (s, 3H), 2.02 (br s,1H), 1.83-1.73 (m, 2H).
IR(neat):	3422, 2946, 2889, 1644, 1603, 1422, 1151, 1031, 925 cm^{-1}.
EIMS:	*m/z* 169 $[M+Na]^+$.

(*R*)-3-(methoxymethoxy)pent-4-enal (57):



To an ice-cooled solution of iodoxybenzoic acid (21.12 g, 78.2 mmol) in DMSO (20 mL) was added a solution of alcohol **56** (5.72 g, 39.16 mmol) in dry CH_2Cl_2 (20 mL). After stirring for 2 h at room temperature, the reaction mixture was filtered through a Celite pad and washed with ether. The combined organic layers were washed with water, brine solution and dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude

product was purified by column chromatography on silica gel (EtOAc/pet-ether, 1:9) to give an aldehyde **57** (5.04 g, 90%) as a viscous liquid.

$[\alpha]_D^{25}$: + 12.4 (*c* = 1, $CHCl_3$).

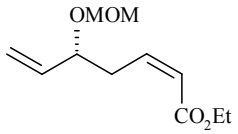
^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.76 (t, *J* = 2.9 Hz, 1H), 5.77-5.71 (m, 1H), 5.28 (dd, *J* = 10.7, 29.2 Hz, 2H), 4.59 (ABq, *J* = 6.8 Hz, 2H), 4.58-4.53 (m, 1H), 3.33 (s, 3H), 2.71-2.05 (m, 1H), 2.55-2.49 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.4, 136.3, 118.0, 93.7, 72.0, 72.0, 55.4, 48.7.

IR(neat): 2927, 1721, 1638, 1421, 1217, 1030 cm^{-1}.

EIMS: *m/z* 167 $[M+Na]^+$.

(*R*,*Z*)-ethyl 5-(methoxymethoxy)hepta-2,6-dienoate (58):



A solution of bis-2,2,2-(trifluoromethyl) (ethoxy carbonyl methyl) phosphonate (8.48 g, 26.52 mmol) in THF (10 mL) was added to a stirred solution of NaH (1.2 g, 30 mmol) in THF (35 mL) at 0 ^oC under N_2 slowly. The mixture was stirred at 0 °C for 30 min. Then the mixture was cooled to -78 °C and the above aldehyde **57** in THF (10 mL, plus 5 mL X 2 of rinse) was added drop wise over 10 minutes. The resulting mixture was stirred at -78 °C for 30 min. Then the mixture was quenched with sat. NH_4Cl (4 mL) and the product was extracted into EtOAc (3 X 30 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure (water bath temperature should not exceed more than 30 °C) and the crude product was purified by using silica gel column chromatography to afford (*Z)*-olefin ester **58** (4.56 g 70%) as a colourless liquid.

$[\alpha]_D^{25}$: + 56.1 (*c* = 0.5, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.31-6.26 (m, 1H), 5.81 (d, *J* = 10.7 Hz, 2H), 5.74-5.67 (m, 1H), 5.21 (dd, *J* = 9.8, 18.6 Hz, 2H), 4.65 (d, *J* = 6.8 Hz, 1H), 4.51

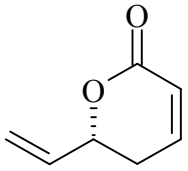
(d, J = 6.8 Hz, 1H), 4.14 (q, J = 6.8 Hz, 2H), 4.14-1.10 (m, 1H), 3.34 (s, 3H), 2.93 (t, J = 6.8 Hz, 3H), 1.29 (t, J = 6.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.2, 145.3, 137.4, 121.2, 117.4, 93.8, 76.3, 59.8, 55.4, 34.6, 14.2.

IR(neat): 1612, 1720, 1384, 1248, 1033, 817 cm^{-1}

ESIMS: *m/z* 237 $[M+Na]^+$.

(*R*)-6-vinyl-5,6-dihydro-2H-pyran-2-one (59):



To a stirred solution of compound **58** (4 g, 32.25 mmol) in dry benzene (30 mL) was added catalytic amount of PTSA under nitrogen atmosphere. The reaction mixture was refluxed for 1 h. The aqueous layer was extracted twice with EtOAc, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (EtOAc/pet-ether, 5:5) to give the lactone **59** (2.24 g, 90%) as a liquid.

$[\alpha]_D^{25}$: + 82.1 (c = 1, $CHCl_3$).

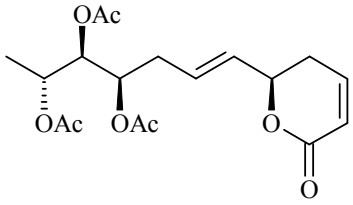
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.83 (m, 1H), 6.02 (dd, J = 2.5, 11.1 Hz, 1H), 5.93 (m, 1H), 5.40 (d, J = 17.1 Hz, 1H), 5.28 (d, J = 11.1 Hz, 1H), 4.95-4.85 (m, 1H), 2.49-2.39 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.8, 144.4, 134.7, 121.4, 117.8, 77.7, 29.2.

IR(neat): 2922, 1720, 1638, 1384, 1249, 1032, 763 cm^{-1}

EIMS: *m/z* 125 $[M+Na]^+$.

(2*R*,3*R*,4*R*,*E*)-7-((*R*)-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)hept-6-ene-2,3,4-triyltriacetate (11):



Grubbs' second generation catalyst (50 mg, 0.056 mmol, 10 mol%) was dissolved in 5 mL of CH_2Cl_2 and was added dropwise to a solution of the compound **59** (0.2 g, 0.73 mmol) and compound **47b** (0.4 g, 3.22 mmol) in 5 mL of CH_2Cl_2 at 0 ^oC. After completion of addition, reaction mixture was allowed to stir for 2 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/hexane, 6:4) to afford the pure product **11** (0.15 g, 65% yield) as a colorless oil.

$[\alpha]_D^{25}$: +33.5 (*c* = 1, $CHCl_3$).

^1H NMR ($CDCl_3$, 300 MHz): δ 6.84 (ddd, *J* = 8.8, 4.0, 2.4 Hz, 1H), 6.02 (dt, *J* = 10.4, 2.4 Hz, 1H), 5.75-5.63 (m, 2H), 5.15 (m, 1H), 5.08 (dt, *J* = 7.2, 4.0 Hz, 1H, CH), 4.96 (m, 1H, CH), 4.86 (m, H, CH), 2.39 (m, 2H, CH2), 2.28 (m, 2H, CH2), 2.12 (s, 3H, CH3), 2.04 (s, 3H, CH3), 2.0 (s, 3H, CH3), 1.18 (d, *J* = 6.4 Hz, 3H, CH3).

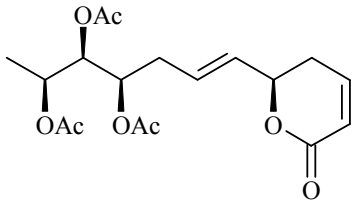
^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.2, 170.1, 170.0, 163.8, 144.5, 130.9, 128.3, 121.5, 77.2, 73.7, 69.6, 67.4, 34.0, 29.5, 21.0, 20.8, 20.7, 16.0.

IR(neat): 1738, 1374, 1221, 1024 cm-1.

ESIMS: *m/z* 391 $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{18}H_{24}O_8Na$ $[M+Na]^+$: 391.1368; Found: 391.1359.

(2*S*,3*R*,4*R*,*E*)-7-((*R*)-6-oxo-3,6-dihydro-*2H*-pyran-2-yl)hept-6-ene-2,3,4-triyltriacetate (12):



Grubbs' second generation catalyst (50 mg, 0.056 mmol, 10 mol%) was dissolved in 5 mL of CH_2Cl_2 and was added dropwise to a solution of the compound **59** (0.2 g, 0.73 mmol) and compound **47a** (0.4 g, 3.22 mmol) in 5 mL of CH_2Cl_2 at 0 ^oC. After completion of addition, reaction mixture was allowed to stir for 2 h. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/hexane, 6:4) to afford the pure product **12** (0.15 g, 65% yield) as a colorless oil.

$[\alpha]_D^{27}$: +12.5 (*c* = 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.86 (ddd, *J* = 8.4, 4.9, 1.1 Hz, 1H), 6.04 (dt, *J* = 9.8, 1.8 Hz, 1H), 5.75–5.65 (m, 2H), 5.12 (m, 1H, CH), 5.06 (m, 2H), 4.85 (dt, *J* = 8.8, 6.2 Hz, 1H, CH), 2.45– 2.30 (m, 4H), 2.12 (s, 3H, CH3), 2.08 (s, 3H, CH3), 2.04 (s, 3H, CH3), 1.20 (d, *J* = 5.8 Hz, 3H, CH3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.3, 170.2, 170.1, 163.8, 144.5, 131.4, 128.6, 121.8, 77.7, 74.4, 70.7, 69.0, 34.2, 29.8, 21.2, 21.0, 20.8, 16.6.

IR(neat): 1740, 1376, 1225, 1027 cm^{-1}.

ESIMS: *m/z* 391 $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{18}H_{24}O_8Na$ $[M+Na]^+$: 391.1368; Found: 391.1355.

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CHAPTER III

Section A

Introduction, earlier synthetic approaches, present work of (5R,7S)-Kurzilactone and its enantiomer

The work of this chapter was published in

Synthesis **2009,** 3301-3304

INTRODUCTION:

The chemistry of natural products attracts a very lively interest. New substances, more or less complicated, useful natural products are constantly discovered and their properties investigated. In the course of investigation of complicated substances, the investigator is sooner or later is confronted by the problem of synthesis or the preparation of the substance by chemical method. There can be various motives; perhaps the chemists want to check the correctness of the structure that has been isolated through the synthesis of that molecule. If the substance is of practical importance, one may hope that the synthetic compound will be less expensive or more easily accessible than the natural product. It can also be desirable to modify some details in the structure of the molecule. An antibiotic substance of medicinal importance is often first isolated from a microorganism, perhaps a mould or a germ. There ought to exist a number of related compounds with similar effects. They may be more or less potent. Some may have undesirable secondary effects. It is by no means, or even probable, that the compound produced by the microorganism most likely as a weapon in the struggle for existence is the very best from the medicinal point of view. If it is possible to synthesize the compound, it will also be possible to modify the details of the structure and to find the most effective remedies.

Unlike many one-time discoveries or inventions, the endeavor of total synthesis[1] is in a constant state of effervescence and flux. It has been on the move and center stage throughout the twentieth century and continues to provide fertile ground for new discoveries and inventions. The harvest of chemical synthesis touches upon our everyday lives in myriad ways, medicines, high-tech materials for computers, communication and transportation equipment, nutritional products, vitamins, plastics, clothing and tools for biology and physics.

The synthesis of a molecule is however, a very difficult task. Every group, every atom must be placed in its proper positions and this should be taken in its most literal sense. It is sometimes said that organic synthesis is at the same time an exact science and a fine art.

The practice of total synthesis is being enriched constantly by new tools such as new reagents and catalysts as well as analytical instrumentation for the rapid purification and characterization of compounds.

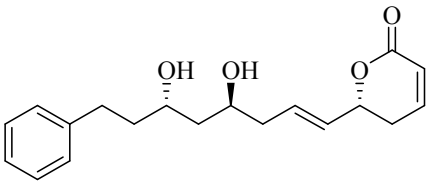
Thus the original goal of total synthesis is to confirm structure of a natural product and exploration and discovery of new chemistry along the pathway to the target molecule.

5,6-Dihydropyrones:

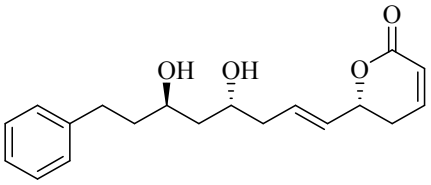
Lactone rings are a structural feature of many natural products. Amongst the naturally occurring lactones, which all display a wide range of pharmacological activities, those bearing a 5,6-dihydropyranones moiety are relatively common in various types of natural sources. Because of their manifold biological properties, those compounds are marked interest not only from a chemical, but also from a pharmacological perspective. As a matter of fact, dihydropyranones of both natural and unnatural origin have been found to be cytotoxic. In addition, they exhibit HIV protease, induce apoptosis and have even proven to be antileukemic, along with having many other relevant pharmacological properties. Some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor. Over the past two decades, an increasing number of α-pyrones have been isolated from a variety of sources. Some of important biologically active pyrones have been described in the following few pages.

Strictifolione:

Strictifolione is such lactone which was isolated from *Cryptocaria Strictifolia* and has shown to display antifungal activity.[3]



Strictifolione 1



Diasteriomer of Strictifolione 2[2]

Figure 1

(6*R*)-6-[(4*R*,6*R*)-4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2*H*-pyran-2-one & (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one:

(6*R*)-6-[(4*R*,6*R*)-4,6-Dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-*2H*-pyran-2-one **3** is also one such natural product,[4] isolated from *Ravensara crassifolia* by Hostetmann et al. along with a structurally similar compound (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-*2H*-pyran-2-one **4**,[5] which were both shown to possess antifungal activity (Figure 2).

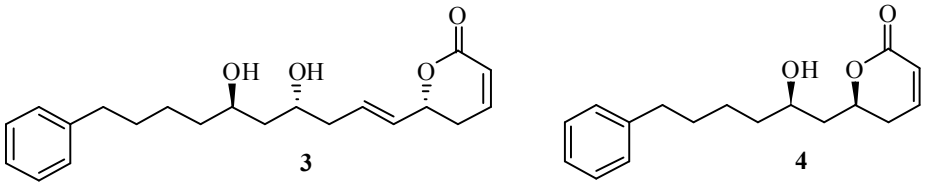
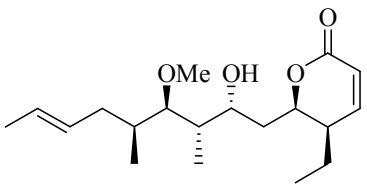


Figure 2

Pironetin:

Pironetin[6] or PA-48153C[7] is an unsaturated δ-lactone derivative, was isolated independently by two research groups from *Streptomyces sp.* NK10958 and from the fermentation broths of *Streptomyces prunicolor* PA-48153, respectively. This very interesting compound possesses plant growth regulatory and immunosuppressive activities. Recently, the biological effects of pironetin and its derivatives on cell cycle progression and antitumor activities were reported.[8] More importantly, the mode of action of pironetin is different from those established for the immunosuppressants cyclosporine A (CsA) and FK506 that inhibit T cell activation.[9] Pironetin showed suppressive effects on the responses of T and B lymphocytes to mitogens.

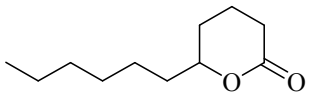


Pironetin 5

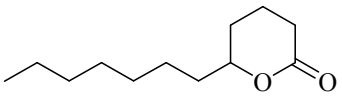
Figure 3

Decalactones:[10]

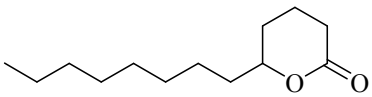
To evaluate promotive effects of hyperthermia on antitumor activity of new delta-alkyllactones of low molecular weight (184–254 Da), chemically synthesized, which are different from natural macrocyclic lactones of high molecular weight (348–439 Da), such as camptothecin and sultriecin. Delta-hexadecalactone (DH16:0) and delta-tetradecalactone (DTe14:0) displayed cytostatic activity (at 100 μM survival level: 20.7%, 66.1%; at 50 μM - 41.2%, 82.4%, respectively). Their activity was more marked at 42 °C (at 100 μM 10.6%, 27.6%; at 50 μM 30.6, 37.5 %, ibid). The other DALs, delta-undecalactone (DU11:0), delta-dodecalactone (DD12:0), and delta-tridecanolactone (DTr13:0) were almost ineffective. Delta-hexadecanolactone (DH16:0) exhibited the most cytostatic effect that was significantly enhanced by hyperthermia. It allows to consider as a potent antitumor agent, especially in combination with hyperthermia.



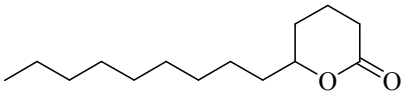
Delta-undecalactone 6



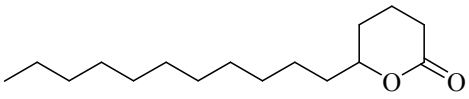
Delta-dodecalactone 7



Delta-tridecalactone 8



Delta-tetradecalactone 9

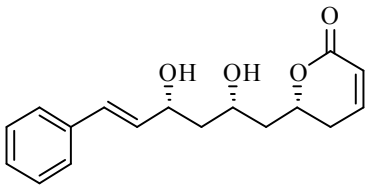


Delta-hexadecalactone 10

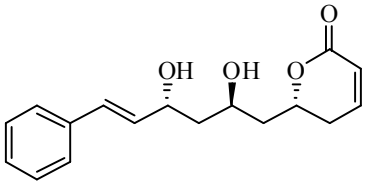
Figure 4

Cryptomoscatones:[11]

Cryptomoscatone-D1 and D2 were isolated for the first time from the bark of *Cryptocarya moschata.* The Cryptocarya species have been used as traditional medicines in South Africa for their anti-inflammatory and other activities.



Cryptomoscatone D1, 11

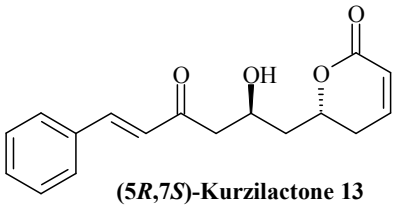


Cryptomoscatone D2, 12

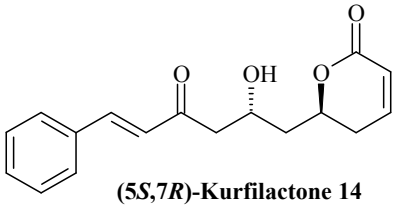
Figure 5

Kurzilactone:

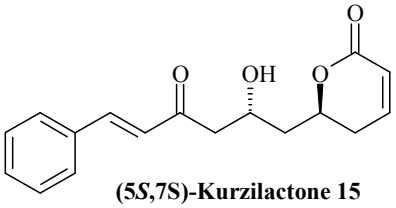
Kurzilactone is a new Kawa-type lactone [12] isolated from leaves of Cryptocarya species (Lauraceae) such as *Cryptocarya kurzii* is a plant that is indigenous to Malaysia. Ethylacetate extraction of *Cryptocarya kurzii* showed a significant cytotoxicity against the KB human carcinoma cell line (IC_{50}=1μg/mL) .[12a] Initially, the stereogenic centers bearing hydroxy groups in the side chain of **13** were assigned a *syn*-relationship through an NMR experiment, but a corrected *anti*-relationship with a (5*R*,7*S*) configuration of the C(5) and C(7) stereogenic centers was later assigned on the basis of a total synthesis.[13] No synthesis has been reported for its enantiomer, (5*S*,7*R*)-**14**. The structural uniqueness of kurzilactone, coupled with its interesting bioactivity and our interest on the synthesis of 6-substituted α,β-unsaturated δ-lactones, prompted us to explore the synthesis of (5*R*,7*S*) Kurzilactone **13** and its enantiomer (5*S*,7*R*) kurzilactone**14**. Our strategy involves the stereoselective establishment of the C-7 stereogenic center in **13** aand **14** by means of a Mukaiyama aldol reaction.



(5*R*,7*S*)-Kurzilactone 13



(5*S*,7*R*)-Kurfilactone 14



(5*S*,7S)-Kurzilactone 15

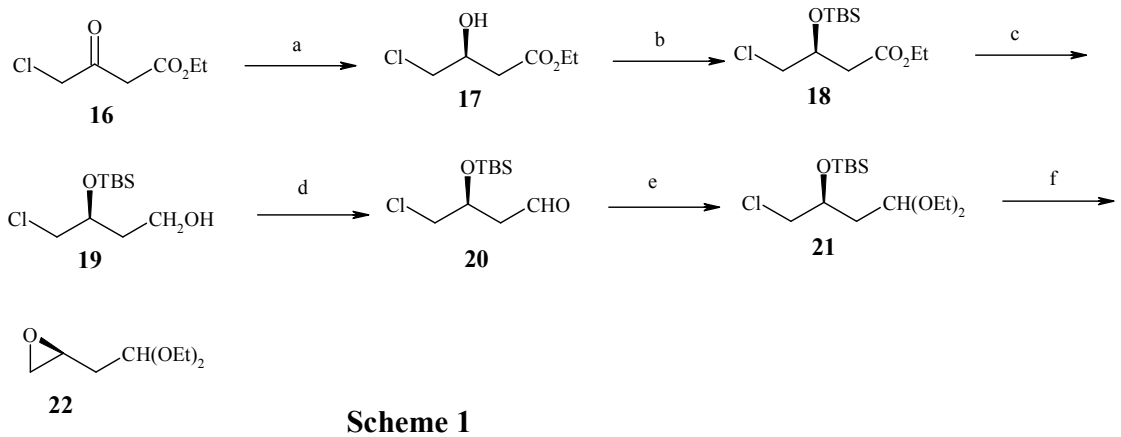
Figure 6

Earlier synthetic approach of Kurzilactone:

Biao Jiang approach:[13]

According to this approach Chiral epoxy aldehyde synthon equilant **22** prapared from ethyl (*S*)-4-chloro-3-hydroxy butanoate **17**, which was obtained from commercial -4-chloro acetoacetate **16**,[13] by hydrogenation over catalytic ruthenium optically active phase complex. The chlorohydrin **17** was protected as the *tert*-butyldimethylsilyl ether **18** which was reduced with $LiAlH_4$ at 0°C and oxidized the resulting alcohol **19** under Swern conditions to give aldehyde **20** in 92% yield. The aldehyde compound **20** was converted into **21** by treatment with $HC(OEt)_3$ with Amberlyst-15 catalyst[14] followed by removal of TBS group with TBAF to give the desired **22** as shown in Scheme 1 which was used for the next step.

In order to coupling of epoxide **22** with the thioacetal compound **24**, commercially available *trans*-cinnamaldehyde **23** was transformed into the thioacetal **24** with $HS(CH_2)_3SH$ and CAN[15] as a catalyst in $CHCl_3$. The epoxide **22** was coupled with the acyl anion equivalent **24**, prepared by metallation at −78°C with ^{n}BuLi in the presence of $BF_3{\cdot}Et_2O$ at −78°C to obtain **25** in 58% yield. After masking the resulting hydroxyl group with TBSCl, the diethyl acetal **26** was treated with

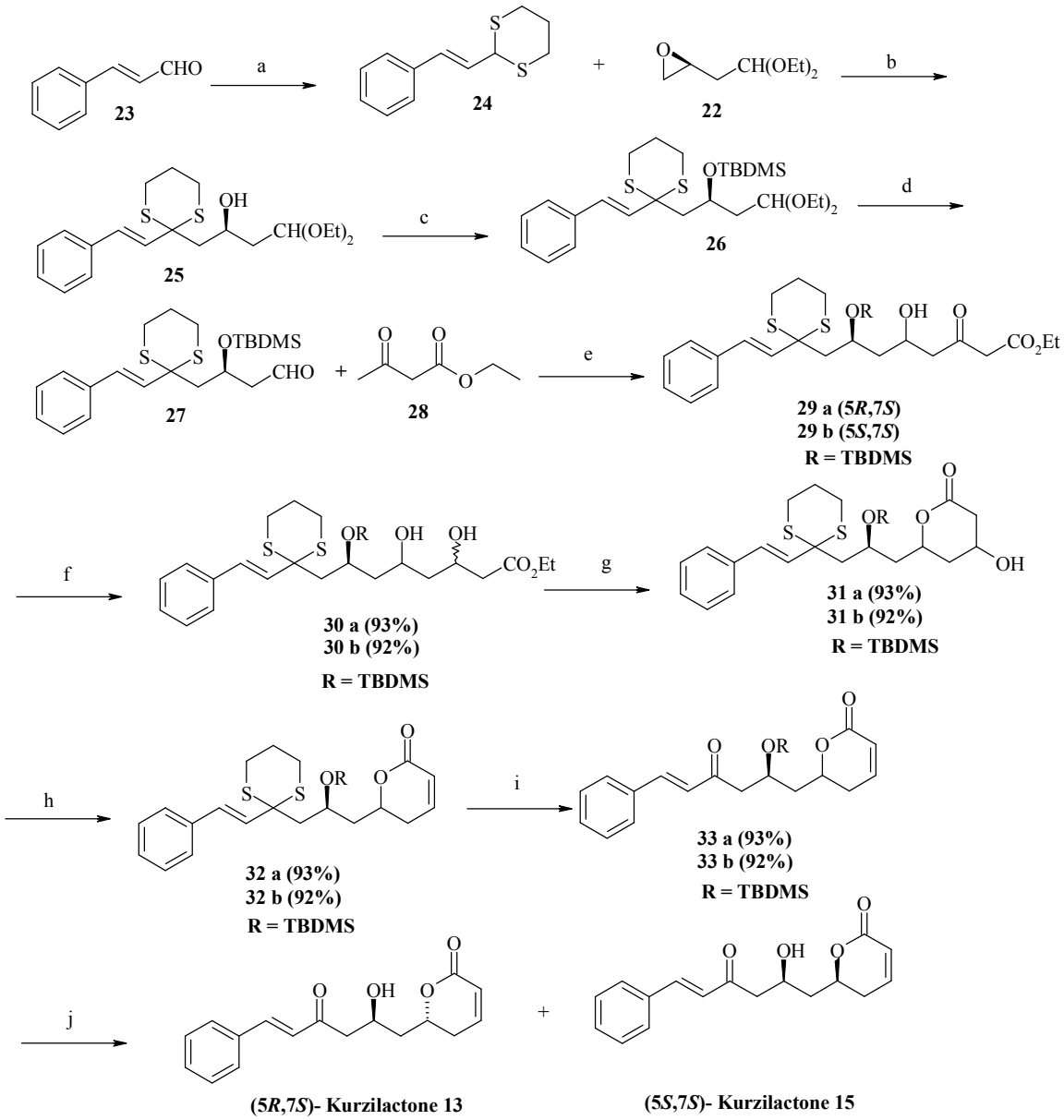


Scheme 1

Reagents and conditions: (a) H_2, $Ru(OAc)_2$[(R)-BINAL], EtOH, 40 kg/cm^2 , 100 ^{o}C, 1.5 h, 94%; (b) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 24 h, 98%; (c) $LiAlH_4$, Et_2O, 0 ^{o}C, 2

h, 91%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60 °C, 92%; (e) $HC(OEt)_3$, amberlyst-15, CH_2Cl_2, r.t., 48 h, 74%; (f) $^nBu_4NF$, 24h, 60%.

CF_3CO_2H in $CHCl_3$ to afford aldehyde **27** in 95% yield. Coupling of aldehyde **27** with the dianion of ethyl acetoacetate **28** to give 5,7-*cis*-dihydroxy ketone **29a** along with its *trans* isomer **29b** in 2:1 ratio. Reduction of compound **29** with $NaBH_4$ to afford hydroxyl ester **30a** and **30b**, which was cyclised by treatment with catalytic PTSA to form δ lactone **31a** and **31b**.[16]



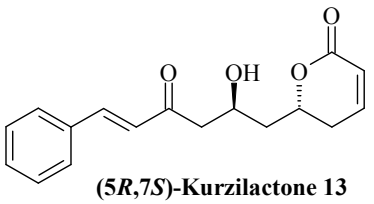
Scheme 2

Reagents and conditions: (a) $HS(CH_2)_3SH$, CAN, $CHCl_3$, 0 ^oC, 70%; (b) ^nBuLi, BF_3. Et_2O, THF, − 78 ^oC, 58%; (c) TBDMSCl, Imidazole, CH_2Cl_2, 81%; (d) 50% CF_3COOH, $CHCl_3$, 0 ^oC, 2 h, 95%; (e) NaH, THF, ^nBuLi, −50 ^oC to −10 ^oC, 76%; (f) $NaBH_4$, THF, −40 ^oC, 90%; (g) PTSA, , CH_2Cl_2, r.t., 93% (h) MsCl, TEA, , CH_2Cl_2, 0 ^oC, 91%; (i) $HgClO_4$, $CaCO_3$, THF:H_2O (5:1), 75%; (j) aqueous HF, CH_3CN, 58%.

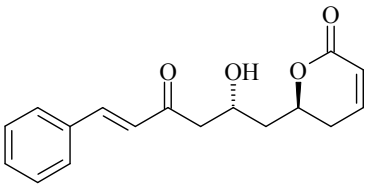
Elimination of OH group in **31a** and **31b** was effected via mesylate displacement[17] to afforded **32a** and **32b**, which on thioketal cleavage with $HgClO_4/CaCO_3$ in THF/H_2O[18] followed by the removal of TBS group[19] with HF to obtained (5*S*,7*S*)-kurzilactone **15** and (5*R*,7*S*)-kurzilactone **13** respectively.

PRESENT WORK:

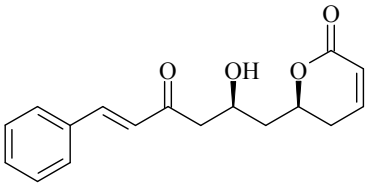
The α,β-unsaturated δ-lactone core unit (or 5,6-dihydro-2-(2*H*)-pyranone moiety) is present in various natural products.[20,21] These compounds display[22] important biological activities some exhibit antitumoral activity, while others are tumor promoting. Moreover, it has been shown that the unsaturated moiety plays an essential role in the biological activity, due to its potentiality to act as a Michael acceptor in the presence of protein functional groups. Kurzilactone exhibits a marked cytotoxicity against the KB human carcinoma cell line (IC_{50} = 1 mg mL^{-1}). Initially, the stereogenic centers bearing hydroxy groups in the side chain were assigned a *syn*-relationship through an NMR experiment, but a corrected *anti*-relationship with a (5*R*,7*S*) configuration of the C(5) and C(7) stereogenic centers was later assigned on the basis of a total synthesis.[23]



(5*R*,7*S*)-Kurzilactone 13



(5*S*,7*R*)-Kurzilactone 14

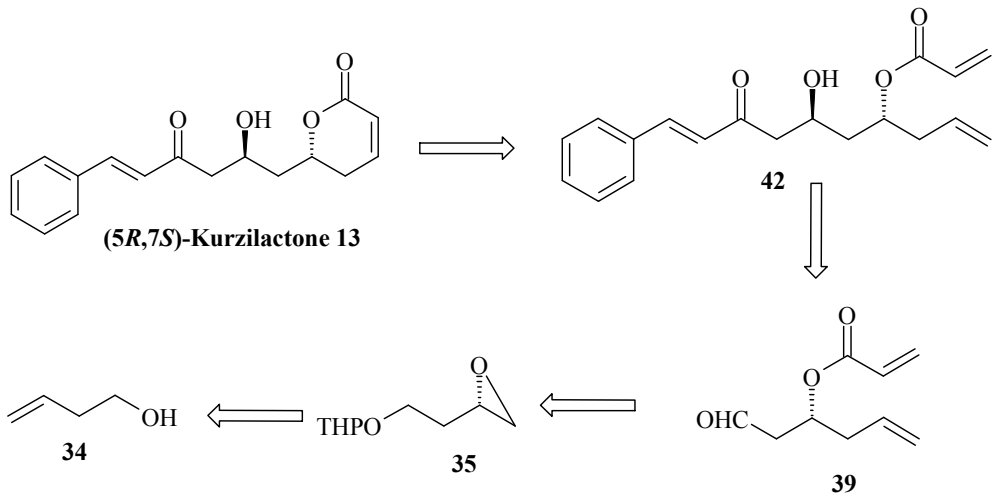


(5*S*,7*S*)-Kurzilactone 15

Figure 7

Three possible stereoisomers of kurzilactone, **13, 14** and **15** were shown in Figure 7. The structural uniqueness of kurzilactone, coupled with its interesting bioactivity and our interest on the synthesis of 6-substituted α,β-unsaturated δ-lactones,[24] prompted us to explore the synthesis of (5*R*,7*S*)-**13** and its enantiomer (5*S*,7*R*)-**14**. Our strategy involves the stereoselective establishment of the C-7 stereogenic center by means of a Mukaiyama aldol reaction.[25] Jacobsen resolution and ring closing metathesis are other key steps used.

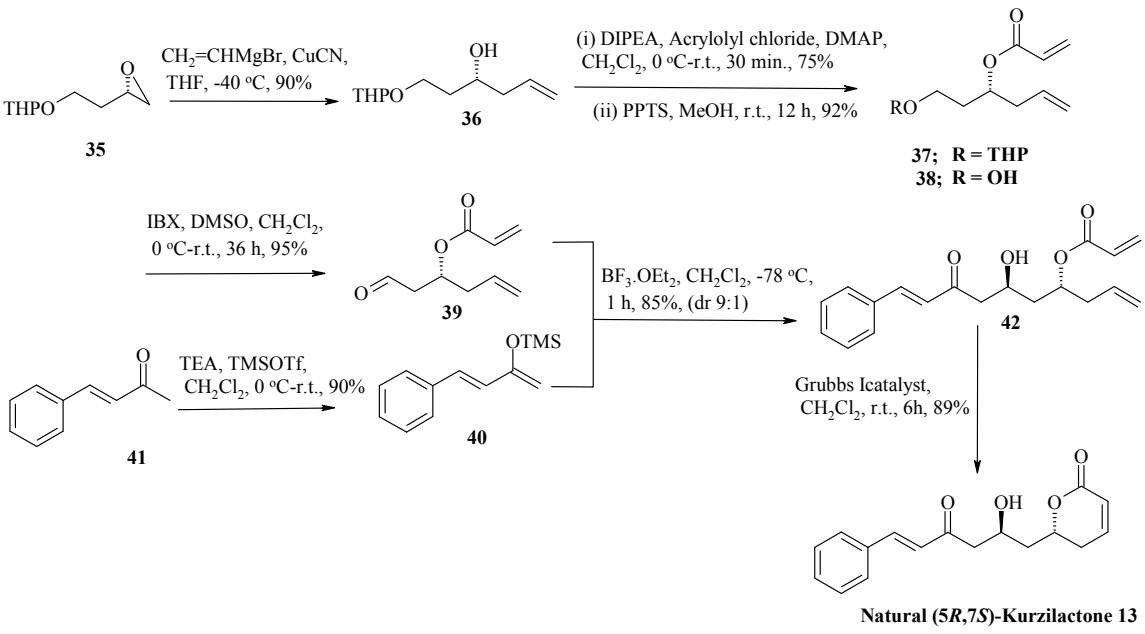
Synthesis of (5*R*,7*S*)-Kurzilactone 13:



Scheme 3: Retrosynthesis for (5*R*,7*S*)-Kurzilactone **13**

Retrosynthetic analysis revealed that the target compound **13** could be obtained from **42** by olefin ring closing metathesis using Grubbs' catalyst 1st generation. The compound **42**, inturn could be obtained from aldehyde compound **39** by Mukaiyama aldol reaction.[25] The aldehyde **39** prepared from chiral epoxide **35.** Preparation of chiral chiral epoxide **35** was achieved from commercially available homoallylic alcohol **34** (Scheme 3).

Accordingly, the synthesis of (5*R*,7*S*)-Kurzilactone **13** was started from commercially available 3-buten-1-ol **34**. Compound **34** protected as its THP ether with an equimolar quantity of 3,4-dihydro-2*H*-pyran (DHP) and a catalytic amount of PTSA in anhydrous CH_2Cl_2 to which was subjected to epoxidation using anhydrous *m*-CPBA and sodium bicarbonate in anhydrous CH_2Cl_2 followed by quenching with saturated Na_2SO_3 to afford recemic epoxide in 96% yield. The recemic epoxide was subjected to hydrolytic kinetic resolution (HKR)[27] using chiral Jacobsen's salen obalt(III)[28] acetate catalyst [(*S,S*)-(-)-*N,N'*-bis-3,5-di *tert*butylic salicylidene)-1,2-cyclohexanediamino-cobalt(III) acetate] to afford enantiorich (>96% ee) epoxide **35** in 47% yield.



Scheme 4

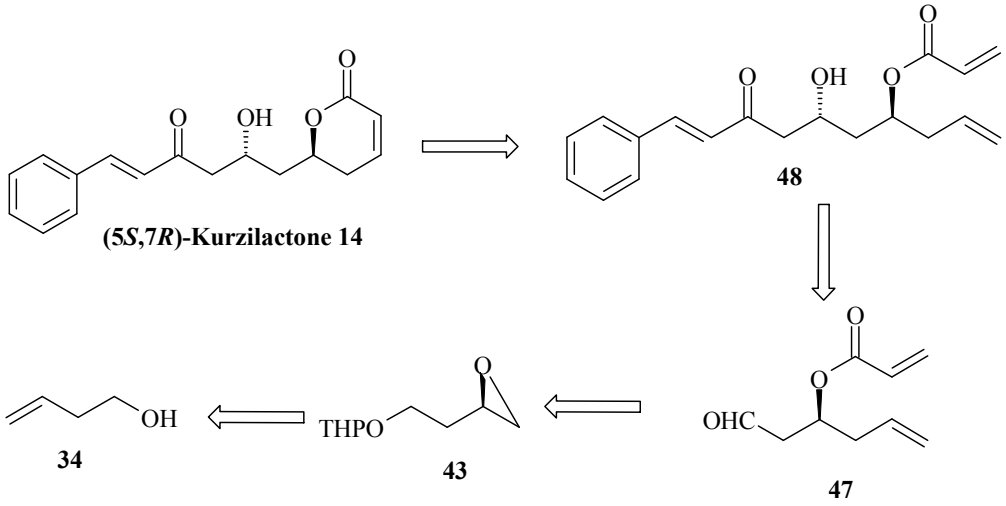
Regioselective opening of epoxide **35** with vinylmagnesium bromide (formed by addition of vinyl bromide to Mg in THF) in the presence of CuCN gave homoallylic alcohol **36**. ^{1}H NMR spectrum of the compound **36** exhibited two multiplets due to olefinic protons at δ 5.91-5.61 and δ 5.18-5.06 integrating one and two protons respectively. Oxygen attached C-H signals were integrated for five protons confirmed that the regioselection was in anticipated line. In addition, IR Spectrum showed hydroxyl absorbtion at 3444 cm^{-1} and ESIMS showed $[M+Na]^+$ signal at *m/z* 223, further confirmed the structure **36** (Scheme 4). The homoallyl alcohol was converted to its acryloyl ester **37** by using acryloyl chloride, DIPEA in dry CH_2Cl_2 at 0 ^{o}C to furnish the compound **37** in 85% yield. The structure of the compound **37** was established from its IR and mass data. In the IR spectrum, an absorbance at 1724 cm^{-1} for the ester functional group and ESI-MS data which showed a value of *m/z* 277 for the $[M+Na]^+$ further confirmed the product **37**.

Deprotection of THP in compound **37** carried out by using PPTS in MeOH to afford **38**. Compound **38** was characterized by disappearance of singlet peak at 4.61 ppm corresponding to THP group in ^{1}H NMR spectrum, and a strong absorption at 3430 cm^{-1}

in IR spectrum, HR-ESI-MS signal at *m/z*: 193.0849 $[M+Na]^+$ further confirmed the transformation (Scheme 4). The alcohol compound **38** was oxidized to aldehyde **39** using IBX in 72% yield (Scheme 4). The structure of the compound **39** was established from its spectral data. The aldehyde proton appeared as a singlet at δ 9.75. Signals of remaining protons remained unchanged. The IR spectrum of **39** showed an absorption band at 1722 cm^{-1} for the aldehyde group.

The boron trifluoride diethyl etherate complex mediated Mukaiyama aldol reaction[25] of the aldehyde **39** with the trimethylsilyl enol ether **40** derived from (3*E*)-4-phenylbut-3-en-2- one (**41**) gave the aldol adduct **42** in 92% yield with good diastereoselectivity (90:10 *anti*:*syn*). The structure assigned to **42** was supported by its ^1H NMR spectrum, which revealed six aromatic protons including one olfine proton resonating at δ 7.60-7.48 and 7.42-7.33 as two multiplets, one proton at C7 chiral center resonating at δ 4.16 as a multiplet, free OH proton resonating at δ 3.41 as a broad siglet and two protons which are adjacent to α,β-unsaturated keto group resonating at δ 2.99-2.66 multiplet along with other required signals. IR spectrum showed a strong absorption at 3489 cm^{-1} corresponding to hydroxyl group, 1718 cm^{-1} for the α,β-unsaturated carbonyl group and 1646 cm^{-1} for the α,β-unsaturated ester group. HR-ESI-MS signal at *m/z*: 337.1415 $[M+Na]^+$ further confirmed the product **42** formation via Mukaiyama aldol reaction (Scheme 4). In order to get the six membered lactone, the compound **42** was subjected to ring closing metathesis (RCM)[28] reaction using the first-generation Grubbs' catalyst to afford target compound **13** in 73% yield. The PMR spectrum of compound **13** revealed the absence of ester group, and the appearance of α,β-unsaturated lactone protons at δ 6.96-6.87 as a multiplet and at δ 6.00 as a dd (J = 2.0, 10.0 Hz). The molecular ion peak at *m/z* 309.1094 $[M+Na]^+$, in its HR-ESI-MS spectrum and a strong absorption bands at 3447, 1712 and 1051 cm^{-1} in the IR spectrum also confirms the structure of compound **13** (Scheme 4).

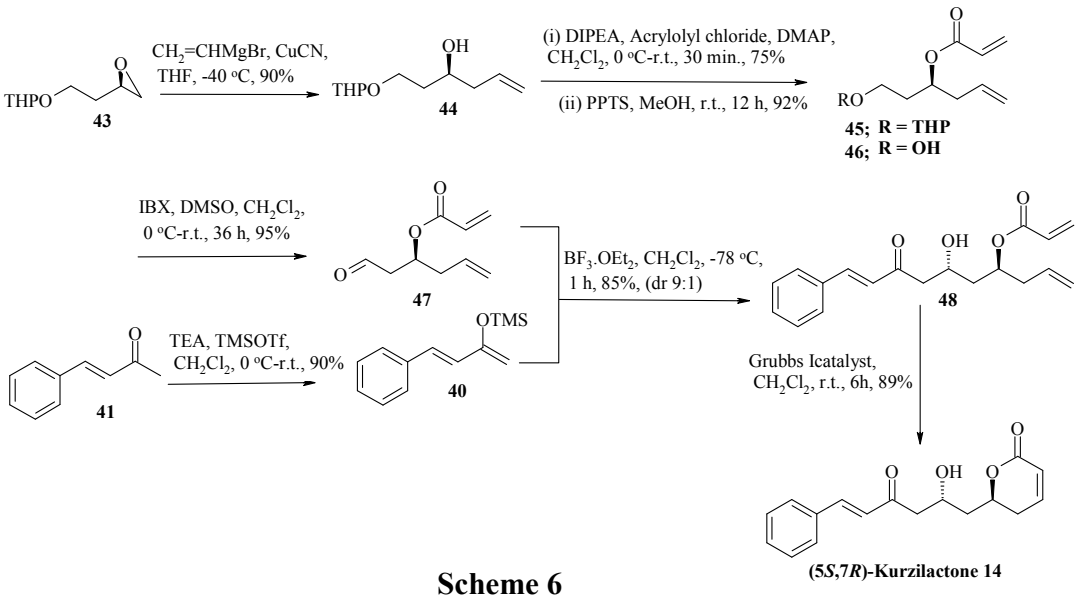
Synthesis of (5*S*,7*R*)-Kurzilactone 14:



Scheme 5: Retrosynthesis for (5*S*,7*R*)-Kurzilactone **14**

Retrosynthetic analysis revealed that the target compound **14** could be obtained from **48** by olefin ring closing metathesis using Grubbs' catalyst 1st generation. The compound **48**, inturn could be obtained from aldehyde compound **47** by Mukaiyama aldol reaction.[25] The aldehyde **47** prepared from chiral epoxide **43**. Preparation of chiral epoxide **43** was achieved from commercially available homoallylic alcohol **34** (Scheme 5).

Accordingly, the synthesis of (5*S*,7*R*)-Kurzilactone **14** was started from commercially available 3-buten-1-ol **34**. Compound **34** protected as its THP ether with an equimolar quantity of 3,4-dihydro-2*H*-pyran (DHP) and a catalytic amount of PTSA in anhydrous CH_2Cl_2 to which was subjected to epoxidation using anhydrous *m*-CPBA and sodium bicarbonate in anhydrous CH_2Cl_2 followed by quenching with saturated Na_2SO_3 to afford recemic epoxide in 96% yield. The recemic epoxide was subjected to hydrolytic kinetic resolution (HKR)[27] using chiral Jacobsen's salen obalt(III)[28] acetate catalyst [(*S,S*)-(-)-*N,N'*-bis-3,5-di *tert*butylic salicylidene)-1,2-cyclohexanediamino-cobalt(III) acetate] to afford enantiorich (>96% ee) epoxide **43** in 47% yield.



Scheme 6

Regioselective opening of epoxide **43** with vinylmagnesium bromide (formed by addition of vinyl bromide to Mg in THF) in the presence of CuCN gave homoallylic alcohol **44**. ^{1}H NMR spectrum of the compound **44** exhibited two multiplets due to olefinic protons at δ 5.91-5.61 and δ 5.18-5.06 integrating one and two protons respectively. Oxygen attached C-H signals were integrated for five protons confirmed that the regioselection was in anticipated line. In addition, IR Spectrum showed hydroxyl absorbtion at 3444 cm^{-1} and ESI-MS showed $[M+Na]^+$ signal at *m/z* 223, further confirmed the structure **44** (Scheme 6). The homoallyl alcohol was converted to its acryloyl ester **45** by using acryloyl chloride, DIPEA in dry CH_2Cl_2 at 0 ^{o}C to furnish the compound **45** in 85% yield. The structure of the compound **45** was established from its IR and mass data. In the IR spectrum, an absorbance at 1724 cm^{-1} for the ester functional group and ESI-MS data which showed a value of *m/z* 277 for the $[M+Na]^+$ further confirmed the product **45**.

Deprotection of THP of **45** carried out by using PPTS in MeOH to afford **46**. Compound **46** was characterized by disappearance of singlet peak at 4.61 ppm corresponding to THP group in ^{1}H NMR spectrum, and a strong absorption at 3427 cm^{-1} in IR spectrum, HR-ESI-MS signal at *m/z*: 193.0849 $[M+Na]^+$ further confirmed the transformation (Scheme 6). The alcohol compound **46** was oxidized to aldehyde **47** using

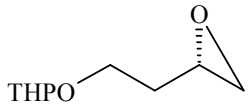
IBX in 72% yield (Scheme 6). The structure of the compound **47** was established from its spectral data. The aldehyde proton appeared as a singlet at δ 9.75. Signals of remaining protons remained unchanged. The IR spectrum of **47** showed an absorption band at 1722 cm^{-1} for the aldehyde group.

The boron trifluoride diethyl etherate complex mediated Mukaiyama aldol reaction[25] of the aldehyde **47** with the trimethylsilyl enol ether **40** derived from (3*E*)-4-phenylbut-3-en-2- one **41** gave the aldol adduct **48** in 92% yield with good diastereoselectivity (90:10 *anti*:*syn*). The structure assigned to **48** was supported by its ^1H NMR spectrum, which revealed 6 aromatic protons including one olfine proton resonating at δ 7.60-7.48 and 7.42-7.33 as two multiplets, one proton at C7 chiral center resonating at δ 4.16 as a multiplet, free OH proton resonating at δ 3.41 as a broad siglet and two protons which are adjusant to α,β-unsaturated keto group resonating at δ 2.99-2.66 multiplet along with other required signals. IR spectrum showed a strong absorption at 3478 cm^{-1} corresponding to hydroxyl group, 1717 cm^{-1} for the α,β-unsaturated carbonyl group and 1646 cm^{-1} for the α,β-unsaturated ester group. HR-ESI-MS signal at *m/z*: 337.1415 $[M+Na]^+$ further confirmed the product **48** formation via Mukaiyama aldol reaction (Scheme 6). In order to get the six membered lactone, the compound **48** was subjected to ring closing metathesis (RCM)[28] reaction using the first-generation Grubbs' catalyst to afford target compound **14** in 73% yield. The PMR spectrum of compound **14** revealed the absence of ester group, and the appearance of α,β-unsaturated lactone protons at δ 6.96-6.87 as a multiplet and at δ 6.00 as a dd (J = 2.0, 10.0 Hz). The ESIMS shows the peak at *m/z* 309 $[M+Na]^+$ and a strong absorption bands at 3445, 1717 and 1052 cm^{-1} in the IR spectrum also confirms the structure of compound **14** (Scheme 6).

In conclusion, we have achieved a short and convergent synthesis of both natural (5*R*,7*S*)-Kurzilactone **13** and its enantiomer (5*S*,7*R*)-Kurzilactone **14**. The highlight of the total synthesis is in the use of the Mukaiyama aldol reaction, which gives the requisite C(7) stereochemistry directly.

EXPERIMENTAL SECTION

2-(2-((*S*)-oxiran-2-yl)ethoxy)tetrahydro-2*H*-pyran (35):



To the (*S,S*)-(salen)Co(II) precatalyst (47 mg, 0.07 mmol, 0.5 mo.%) in a flask was charged sequentially with (±)-epoxide (2.66 g, 15.46 mmol) and AcOH (0.018 mL, 0.3 mmol, 0.02 eq). After the reaction mixture turned from a red suspension to a dark brown solution, the flask was cooled to 0 ^{o}C and THF (0.14 mL) followed by H_2O (0.15 mL, 8.33 mmol, 0.55 eq) were added. The reaction mixture was allowed to warm to room temperature over 2 h and stirred for an additional 20 h. The reaction mixture was directly purified by column chromatography (EtOAc/hexane, 2:8) to furnish **35** (1.25 g, 47%).

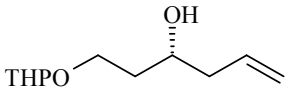
$[\alpha]_D^{25}$: –3.1 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.59 (t, *J* = 3.0 Hz, 1H), 3.91-3.77 (m, 2H), 3.55-3.42 (m, 2H), 3.05-2.97 (m, 1H), 2.74 (t, *J* = 4.5 Hz, 1H), 2.51-2.45 (m, 1H), 1.92-1.45 (m, 8H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.7, 64.0, 61.9, 50.0, 46.8, 32.6, 30.5, 25.1, 19.4.

ESIMS: *m/z* 199 $[M+Na]^+$.

(3*R*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)-5-hexen-3-ol (36):



$Br(CH_2)_2Br$ (2 drops) and freshly prepared H_2C=CHBr (1.0 mL, 13.95 mmol) were added sequentially in a drop wise manner to Mg turnings (0.33 g, 13.95 mmol) in anhyd THF (25 mL) at r.t. The mixture was stirred for 0.5 h and then CuCN (10 mg) was added. The mixture was cooled to –78 °C then a solution of epoxide **35** (1.20 g, 6.97 mmol) in THF (6 mL) was added, and the mixture warmed to –40 °C and stirred for 4 h. The reaction was quenched with sat. aq NH_4Cl (30 mL) and the mixture was extracted

with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4; 1 g), and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 3:7) to give **36** as a yellow liquid (1.25 g, 90%).

$[\alpha]_D^{25}$: –3.1 (*c* = 1.0, $CHCl_3$).

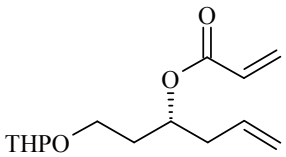
^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.86 (m, 1 H), 5.18–5.06 (m, 2 H), 4.61 (m, 1 H, CH), 4.06–3.78 (m, 3 H), 3.69–3.47 (m, 2 H, CH_2), 3.10 (br s, 1 H, OH), 2.27 (t, *J* = 6.9 Hz, 2 H, CH_2), 1.89–1.45 (m, 8 H, 4 x CH_2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.9, 117.3, 98.9, 70.0, 65.9, 62.3, 41.8, 35.7, 30.5, 25.2, 19.4.

IR (neat): 3444, 2941, 1439, 1127, 1030 cm^{-1}.

ESIMS: *m/z* 223 $[M+Na]^+$.

(3*R*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)hex-5-en-3-yl Acrylate (37):



Acryloyl chloride (0.34 g, 3.75 mmol) was added drop wise under N_2 to a soln of alcohol **36** (0.75 g, 3.75 mmol), DIPEA (0.70 mL, 5.62 mmol), and DMAP (0.05 mmol) in anhyd CH_2Cl_2 (10 mL). The mixture was stirred at r.t. for 30 min until the reaction was complete (TLC). The mixture was then poured into brine and extracted with CH_2Cl_2 (2 x 20 mL). The organic phases were washed with 1 M aq HCl (5 mL) and brine (8 mL), dried (Na2SO4; 1 g), and evaporated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, 1:9) to give **37** as a liquid (0.71 g, 75%).

$[\alpha]_D^{25}$: –15.3 (*c* = 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.39 (td, *J* = 1.1, 17.1 Hz, 1H), 6.17–6.04 (m, 1H), 5.86–5.70 (m, 2H), 5.17 (m, 1H, CH), 5.14–5.04 (m, 2H), 4.56 (td, *J* = 3.5,

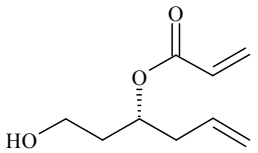
15.4 Hz, 1H, CH), 3.89–3.73 (m, 2H, CH_2), 3.54–3.34 (m, 2H, CH_2), 2.49–2.32 (m, 2H, CH_2), 1.97– 1.44 (m, 8H, 4 x CH_2).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.6, 133.2, 130.4, 128.6, 117.8, 98.7, 70.9, 63.6, 61.9, 38.7, 33.5, 30.5, 25.3, 19.3.

IR (neat): 2944, 1724, 1406, 1195, 1037 cm^{-1}.

ESIMS: *m/z* 277 $[M+Na]^+$.

(3*R*)-1-Hydroxyhex-5-en-3-yl Acrylate (38):



A catalytic amount of PPTS was added to a stirred solution of ester **37** (0.61 g, 2.4 mmol) in MeOH (20 mL) under N_2, and the mixture was stirred for 12 h at r.t. The reaction was quenched with solid $NaHCO_3$ (1 g), and the mixture was filtered. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 7:3) to give compound **38** as a pale yellow liquid (0.37 g, 92%).

$[\alpha]_D^{25}$: –17.0 (*c* = 1.0, $CHCl_3$).

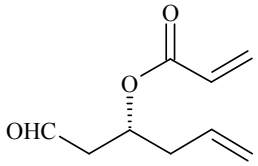
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.42 (dd, *J* = 1.5, 17.3 Hz, 1H), 6.16–6.05 (m, 1H), 5.88–5.68 (m, 2H), 5.20–5.08 (m, 2 H), 5.06 (m, 1H), 3.67–3.45 (m, 2H), 2.47 (br s, 1H, OH), 2.39 (m, 2H),1.94–1.82 (m, 1H), 1.75–1.63 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 133.1, 131.0, 128.2, 117.8, 70.7, 58.2, 38.7, 36.6.

IR (neat): 3427, 1721, 1407, 1295, 1197, 1052 cm^{-1}.

ESIMS: *m/z* 193 $[M+Na]^+$.

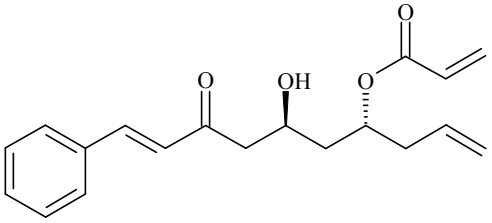
(3*R*)-1-Oxohex-5-en-3-yl Acrylate (39):



A soln of alcohol **38** (0.3 g, 1.76 mmol) in anhyd CH_2Cl_2 (8 mL) was added to an ice-cooled soln of 2-iodoxybenzoic acid (0.71 g, 1.65 2.64 mmol) in anhyd DMSO (2.0 mL). The mixture was stirred at r.t. for 12 h then filtered through a pad of Celite that was subsequently washed with Et_2O (10 mL). The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4; 1.0 g), and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/hexane, 1:9) to give **39** as a yellow viscous liquid (0.281 g, 95%).

^{1}H NMR ($CDCl_3$, 500 MHz):	δ 9.75 (m, 1H, CHO), 6.39 (dd, *J* = 1.3, 17.3 Hz, 1H), 6.09 (dd *J* = 10.3, 17.1 Hz, 1H), 6.0–5.8 (m, 2H), 5.25–5.12 (m, 3H), 3.22 (d, *J* = 6.9 Hz, 2H, CH_2), 2.83 (t, *J* = 6.4 Hz, 2H, CH_2).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 205.3, 165.9, 130.9, 129.9, 128.1, 119.2, 59.2, 47.9, 40.8.
IR (neat):	1722, 1407, 1191, 985 cm^{-1}.
ESIMS:	*m/z* 186 $[M + NH_4]^+$.

(4*R*,6*S*,9*E*)-6-Hydroxy-8-oxo-10-phenyldeca-1,9-dien-4-yl Acrylate (42):



$BF_3{\cdot}OEt_2$ (0.144 mL, 1.16 mmol) was added dropwise to a soln of the aldehyde **39** (0.15 g, 0.89 mmol) and silyl enol ether **40** (0.25 g, 1.16 mmol) in anhyd CH_2Cl_2 (10 mL) at –78 °C, and the resulting soln was stirred at –78 °C for 1 h. The reaction was quenched by addition of sat. aq $NaHCO_3$ (3 mL), and the mixture was extracted with $CHCl_3$ (2 x 20 mL). The combined organic extracts were dried (Na_2SO_4; 1 g), filtered,

and concentrated. The residue was purified by column chromatography (EtOAc/hexane, 4:6) to give **42** as a yellow viscous liquid (0.257 g, 92%).

$[\alpha]_D^{25}$: –15.0 (*c* = 1.0, $CHCl_3$).

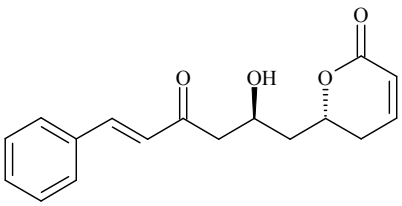
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.60–7.48 (m, 3H), 7.42–7.33 (m, 3H), 6.68 (dd, *J* = 5.2, 16.6 Hz, 1H), 6.40 (ddd, *J* = 1.5, 9.0, 17.3 Hz, 1H), 6.16–6.03 (m, 1H), 5.86–5.68 (m, 2H), 5.27–5.03 (m, 3H), 4.16 (m, 1H), 3.41 (br s, 1H, OH), 2.99–2.66 (m, 2H), 2.52– 2.35 (m, 2H), 1.97–1.66 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.0, 166.0, 143.6, 134.1, 133.2, 131.0, 130.7, 130.6, 128.9, 128.3, 126.2, 118.1, 70.7, 64.6, 46.6, 40.5, 38.9.

IR (neat): 3478, 1717, 1646, 1609, 1576, 1406, 1273, 1198, 1050 cm^{-1}.

ESIMS: *m/z* 337 $[M+Na]^+$.

(6*R*)-6-[(2*S*,5*E*)-2-Hydroxy-4-oxo-6-phenylhex-5-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (13):



Grubbs' first-generation catalyst (0.033 g, 0.0415 mmol) was added to a soln of **42** (0.132 g, 0.415 mmol) in anhyd CH_2Cl_2 (15 ml) at 0 °C, and the mixture was allowed to warm to r.t. over 6 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane, 7:3) to give **13** as a white solid (0.114 g, 95%).

M.p: 74-76 ^oC

$[\alpha]_D^{25}$: +80.0 (*c* = 0.35, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58 (d, *J* = 16 Hz, 1H), 7.54–7.39 (m, 5 H), 6.90 (m, 1H), 6.73 (d, *J* = 16 Hz, 1H), 6.00 (dd *J* = 2, 10 Hz, 1H), 4.77 (m, 1H),

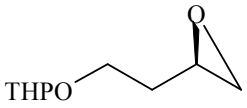
4.50 (m, 1H), 3.52 (br s, 1H, OH), 2.93 (dd, J = 2.8, 17.4 Hz, 1H), 2.81 (dd, J = 8.8, 17.5 Hz, 1H), 2.39 (m, 2H), 1.88 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.4, 164.2, 145.1, 144.0, 134.1, 130.9, 129.0, 128.5, 126.1, 121.5, 75.0, 64.2, 46.9, 41.7, 30.0.

IR (neat): 3447, 1712, 1652, 1606, 1386, 1253, 1178, 1051 cm^{-1}.

HRMS (ESI): Calcd for $C_{17}H_{18}O_4Na$ $[M+Na]^+$: 309.1102; found: 309.1094.

2-(2-((*R*)-oxiran-2-yl)ethoxy)tetrahydro-2*H*-pyran (43):



To the (*R,R*)-(salen)Co(II) precatalyst (47 mg, 0.07 mmol, 0.5 mo.%) in a flask was charged sequentially with (±)-epoxide (2.66 g, 15.46 mmol) and AcOH (0.018 mL, 0.3 mmol, 0.02 eq). After the reaction mixture turned from a red suspension to a dark brown solution, the flask was cooled to 0 ^oC and THF (0.14 mL) followed by H_2O (0.15 mL, 8.33 mmol, 0.55 eq) were added. The reaction mixture was allowed to warm to room temperature over 2 h and stirred for an additional 20 h. The reaction mixture was directly purified by column chromatography (EtOAc/hexane, 2:8) to furnish **43** (1.25 g, 47%).

$[\alpha]_D^{25}$: +3.1 (c = 1.0, $CHCl_3$).

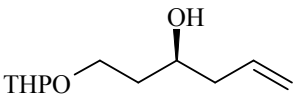
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.59 (t, J = 3.0 Hz, 1H), 3.91-3.77 (m, 2H), 3.55-3.42 (m, 2H), 3.05-2.97 (m, 1H), 2.74 (t, J = 4.5 Hz, 1H), 2.51-2.45 (m, 1H), 1.92-1.45 (m, 8H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 98.7, 64.0, 61.9, 50.0, 46.8, 32.6, 30.5, 25.1, 19.4.

ESIMS: m/z 199 $[M+Na]^+$.

(3*S*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)-5-hexen-3-ol (44):

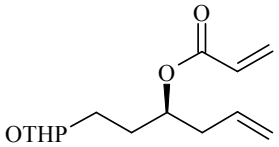
Compound **44** was similarly obtained following the procedure reported for **36** as a liquid from **43** with 90%yield.



$[\alpha]_D^{25}$:	+3.1 (*c* = 1.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 500 MHz):	δ 5.86 (m, 1 H), 5.18–5.06 (m, 2 H), 4.61 (m, 1 H, CH), 4.06–3.78 (m, 3 H), 3.69–3.47 (m, 2 H, CH_2), 3.10 (br s, 1 H, OH), 2.27 (t, *J* = 6.9 Hz, 2 H, CH_2), 1.89–1.45 (m, 8 H, 4 x CH_2).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 134.9, 117.3, 98.9, 70.0, 65.9, 62.3, 41.8, 35.7, 30.5, 25.2, 19.4.
IR (neat):	3444, 2941, 1439, 1127, 1030 cm^{-1}.
ESIMS:	*m/z* 223 $[M+Na]^+$.

(3*S*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)hex-5-en-3-yl Acrylate (45):

Compound **45** was similarly obtained following the procedure reported for **37** as a liquid from **44** with 75% yield.

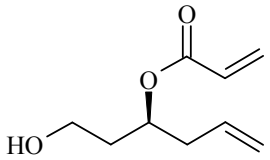


$[\alpha]_D^{25}$:	+15.3 (*c* = 1.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 500 MHz):	δ 6.39 (td, *J* = 1.1, 17.1 Hz, 1 H), 6.17–6.04 (m, 1 H), 5.86–5.70 (m, 2 H), 5.17 (m, 1 H, CH), 5.14–5.04 (m, 2 H), 4.56 (td, *J* = 3.5, 15.4 Hz, 1 H, CH), 3.89–3.73 (m, 2H, CH_2),

	3.54–3.34 (m, 2 H, CH_2), 2.49–2.32 (m, 2 H, CH2), 1.97– 1.44 (m, 8 H, 4 × CH_2).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 165.6, 133.2, 130.4, 128.6, 117.8, 98.7, 70.9, 63.6, 61.9, 38.7, 33.5, 30.5, 25.3, 19.3.
IR (neat):	2944, 1724, 1406, 1195, 1037 cm^{-1}.
ESIMS:	*m/z* 277 $[M+Na]^+$.

(3*S*)-1-Hydroxyhex-5-en-3-yl Acrylate (46):

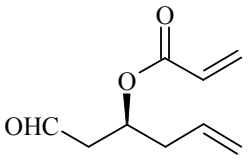
Compound **46** was similarly obtained following the procedure reported for **38** as a liquid from **45** with 92%yield.



$[\alpha]_D^{25}$:	+17.0 (*c* = 0.5, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 500 MHz):	δ 6.42 (dd, *J* = 1.5, 17.3 Hz, 1 H), 6.16–6.05 (m, 1 H), 5.88–5.68 (m, 2 H), 5.20–5.08 (m, 2 H), 5.06 (m, 1 H), 3.67–3.45 (m, 2 H), 2.47 (br s, 1 H, OH), 2.39 (m, 2 H),1.94–1.82 (m, 1 H), 1.75–1.63 (m, 1 H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 166.4, 133.1, 131.0, 128.2, 117.8, 70.7, 58.2, 38.7, 36.6.
IR (neat):	3427, 1721, 1407, 1295, 1197, 1052 cm^{-1}.
ESIMS:	*m/z* 193 $[M+Na]^+$.

(3*S*)-1-Oxohex-5-en-3-yl Acrylate (47):

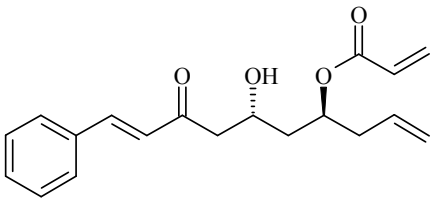
Compound **47** was similarly obtained following the procedure reported for **39** as a liquid from **46** with 95% yield.



^{1}H NMR ($CDCl_3$, 500 MHz):	δ 9.75 (m, 1 H, CHO), 6.39 (dd, *J* = 1.3, 17.3 Hz, 1 H), 6.09 (dd *J* = 10.3, 17.1 Hz, 1 H), 6.0–5.8 (m, 2 H), 5.25–5.12 (m, 3 H), 3.22 (d, *J* = 6.9 Hz, 2 H, CH_2), 2.83 (t, *J* = 6.4 Hz, 2 H, CH_2).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 205.3, 165.9, 130.9, 129.9, 128.1, 119.2, 59.2, 47.9, 40.8.
IR (neat):	1722, 1407, 1191, 985 cm^{-1}.
ESIMS:	*m/z* 186 [M + NH_4+].

(4*S*,6*R*,9*E*)-6-Hydroxy-8-oxo-10-phenyldeca-1,9-dien-4-yl Acrylate (48):

Compound **48** was similarly obtained following the procedure reported for **42** as a liquid from **47** with 85% yield.

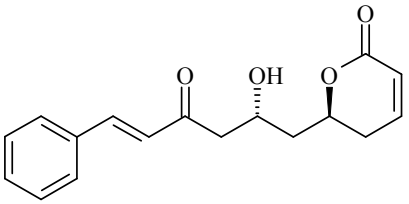


$[\alpha]_D^{25}$:	+15.0 (*c* = 1.0, $CHCl_3$).
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.60–7.48 (m, 3H), 7.42–7.33 (m, 3H), 6.68 (dd, *J* = 5.2, 16.6 Hz, 1H), 6.40 (ddd, *J* = 1.5, 9.0, 17.3 Hz, 1H), 6.16–6.03 (m, 1H), 5.86–5.68 (m, 2H), 5.27–5.03 (m, 3H), 4.16 (m, 1 H), 3.41 (br s, 1 H, OH), 2.99–2.66 (m, 2H), 2.52– 2.35 (m, 2H), 1.97–1.66 (m, 2H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 200.0, 166.0, 143.6, 134.1, 133.2, 131.0, 130.7, 130.6, 128.9, 128.3, 126.2, 118.1, 70.7, 64.6, 46.6, 40.5, 38.9.
IR (neat):	3478, 1717, 1646, 1609, 1576, 1406, 1273, 1198, 1050 cm^{-1}.

ESIMS: *m/z* 337 $[M+Na]^+$.

(6*S*)-6-[(2*R*,5*E*)-2-Hydroxy-4-oxo-6-phenylhex-5-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one (14):

Compound **14** was similarly obtained following the procedure reported for **13** as a liquid from **48** with 89% yield.



M.p: 74-76 ^{0}C.

$[\alpha]_D^{25}$: –78.0 (*c* = 0.35, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58 (d, *J* = 16 Hz, 1H), 7.54–7.39 (m, 5 H), 6.90 (m, 1H), 6.73 (d, *J* = 16 Hz, 1H), 6.00 (dd *J* = 2, 10 Hz, 1H), 4.77 (m, 1H), 4.5 (m, 1H), 3.52 (br s, 1H, OH), 2.93 (dd, *J* = 2.8, 17.4 Hz, 1H), 2.81 (dd, *J* = 8.8, 17.5 Hz, 1 H), 2.39 (m, 2H), 1.88 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.4, 164.2, 145.1, 144.0, 134.1, 130.9, 129.0, 128.5, 126.1, 121.5, 75.0, 64.2, 46.9, 41.7, 30.0.

IR (neat): 3447, 1712, 1652, 1606, 1386, 1253, 1178, 1051 cm^{-1}.

ESIMS: 309 $[M+Na]^+$.

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CHAPTER III

Section B

Introduction, previous synthetic approaches and Present work of (+)-Anamarine

The work of this chapter was published in

Tetrahedron Letters **2010,** *51,* 5736-5739

INTRODUCTION:

A natural product is a chemical compound or substance produced by a living organism, found in nature that usually has a pharmacological or biological activity for use in pharmaceutical drug discovery and drug design.[1] Over the past few years natural products have continued to be of interest on account of their diverse biological properties. Synthesis of biologically important natural products has always fascinated organic chemists. Due to their continuous efforts, tremendous development in the synthesis of complex natural products such as steroids, terpenes, alkaloids, antibiotics etc, have been possible.[2] Natural products including plants, animals and minerals have been basis on treatment of human diseases. History of medicine dates back practically to the existence of human civilization. The current accepted modern medicinal chemistry has gradually developed over the years by scientific and observational efforts of scientists. Natural products chemistry actually began with the work of Serturner, who first isolate morphine from opium. This, inturn, was obtained from opium poppy (*Papaver somniferum*) by process that has been used for over 5000 years.

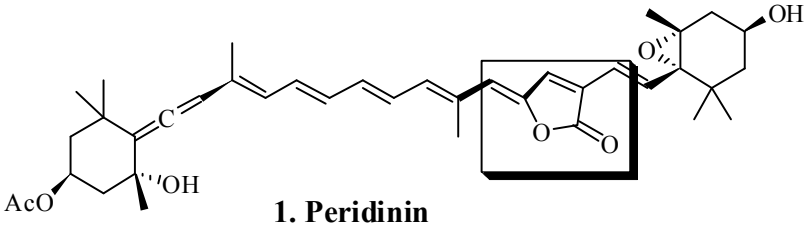
Natural sources and screening of natural products

Natural products may be extracted[3] from tissues of terrestrial plants, marine organisms or microorganism fermentation broths. Natural product extracted from these sources typically contains novel, structurally diverse chemical compounds. Pharmacognosy provides the tools to identify select and process natural products destined for medicinal use. The plant kingdom: plants have always been rich source of lead compounds (morphine, cocaine, digitalis, quinine and muscarine), anticancer agent paclitaxel (Taxol) from the yew tree and the antimalarial agent artemisinin from *Artemisia annua*. The microbial world: After the discovery of pencillin microorganisms became highly popular, leading to an impressive arsenal of antibacterial agents such as cephalosporins, tetracyclins, aminoglycosides and rifamycins. The marine world: Coral, fish, sponges and marine microorganisms have a wealth of biologically potent chemicals with interesting inflammatory, antiviral and anticancer activity. For e.g. Curacin A, discodermalide, bryostatine and cephalostatins. Animal sources: some times animals can be a sourse of lead compounds e.g. Antibiotic peptides from skin of the African clawed frog. Venoms and toxins: obtained from animals, plants, spiders, scorpions and insects

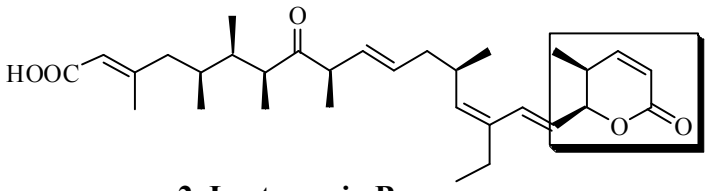
have very specific interactions with a macromolecular target in the body. They have proved important tools in studying receptors, ion channels and enzymes.eg. teprotide a peptide isolated from the venom of the Brazilian viper was used in the development of antihypertensive agents cilazapril and captopril. Natural products research continues to explore a variety of lead structures, which may be used as templates for the development of new drugs.[4] This development has broadly divided the modern synthetic organic chemistry into two inter-related yet independent branches, the "asymmetric synthesis", in which the emphasis is on chiral reagents, and the "chiron approach" in which starting materials are optically active. The evolution of asymmetric synthesis is unpredictable, but the dramatic progress will certainly persist. It appears as if we have entered an era of optically active reagents with astounding inherent prochiral free selectivity. The beauty and power of many of these new reagents lie in their capacity to move us beyond the influence of existing chiral centers in substrates to a very high predictable control of stereoselectivity.

UNSATURATED LACTONES:

Over the past two decades, an increasing number of cyclic esters containing natural products[5] have been isolated from a variety of sources.



1. Peridinin



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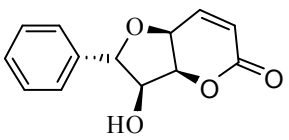
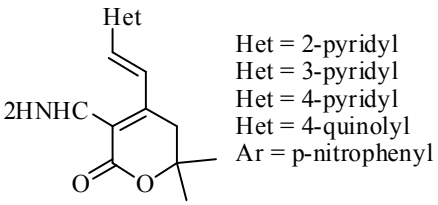


3. Isoaltholactone

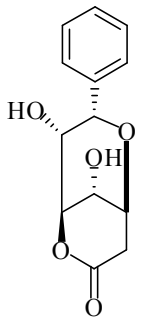


4. Heteroaryl lactones

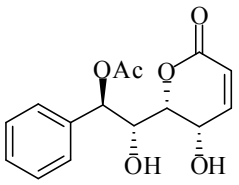
Figure 1

5,6-Dihydropyrones:

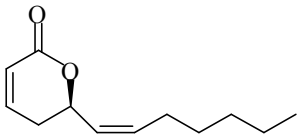
Lactone rings are a structural feature of many natural products. Amongst the naturally occurring lactones, which all display a wide range of pharmacological activities, those bearing a 5,6- dihydropyranones moiety are relatively common in various types of natural sources. Because of their manifold biological properties, those compounds are marked interest not only from a chemical, but also from a pharmacological perspective. As a matter of fact, dihydropyranones of both natural and unnatural origin have been found to be cytotoxic. In addition, they exhibit HIV protease, induce apoptosis and have even proven to be antileukemic, along with having many other relevant pharmacological properties.[6] Some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor.



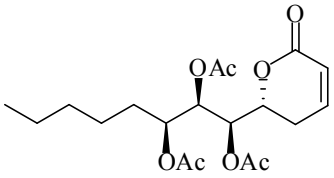
5. Goniopypyrone



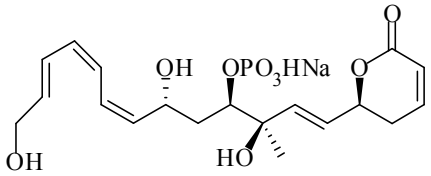
6. 7-acetyl-goniotriol



7. (-)-argentilactone



8. Boronolide



9. Fostriecin

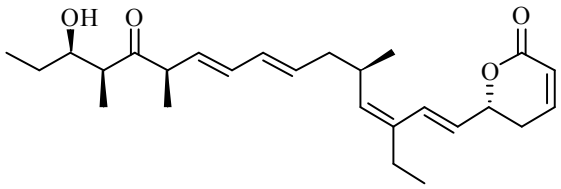
Figure 2. 5,6-Dihydropyran-2-one-containing natural products

Over the past two decades, an increasing number of α-pyrones have been isolated from a variety of sources. Some of important biologically active pyrones are listed in Figure 2. McLaughlin *et. al*. reported the isolation of Goniopypyrone (**5**) and 7-acetyl-goniotriol (**6**) from *Goniothalamus giganteus,* both of these compounds are cytotoxic to human tumor cells.

Argentilactone[11] (**7**) was first isolated in 1977 from the rhizomes of *Aristolochia argenita,* and exhibit both antileishmanial activity and cytotoxic activity against mouse leukemia cells. From *Syncolostemon rotundifolius*, Davies-Coleman and Rivett[12] reported the compound Syntrotolide (**13**). Boronolide (**8**) occurs in the leaves of *Tetradinia barberae,* whose stereochemistry was confirmed by Davies-Coleman and Rivett. Fostriecin (**9**) is under clinical evaluation as an antitumor drug in clinical trials; it inhibits the DNA, RNA and protein synthesis and was shown to block cells in the G2 phase of the cell cycle and to have inhibitiory effects on partially purified type II topoisomerase from *Ehrlich ascites carcinoma*.

(-)-Callystatin A

(-)-Callystatin A (**10**) exhibits remarkable cytotoxicity with an IC50 value of 10 pg/mL against KB cell lines and 20 pg/mL against L1210 cells (Figure 3).[13]

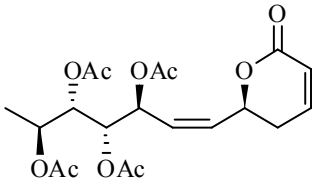


10. (-)- Callylstatin A

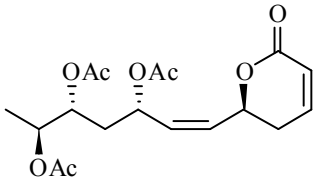
Figure 3

Polyoxygenated lactones

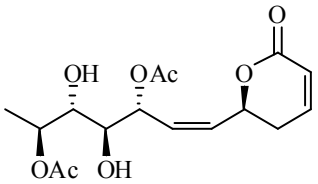
α,β-unsaturated δ-lactones (+)-spicigerolide (**11**),[14] (+)-hyptolide (**12**),[15] (-)-synrotolide (**13**)[16] and synargentolide A (**14**)[17] were isolated from several *Hyptis* species and other botanically related genera (Figure 4). These compounds contain a polyoxygenated chain connected with α,β-unsaturated six membered lactone and have been found to show a wide range of pharmacological properties, such as cytotoxicity against human tumor cells, antimicrobial or antifungal activity etc.



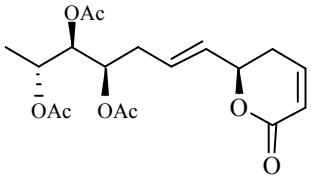
11. Spicigerolide



12. Hyptolide



13. (-)- Synrotolide

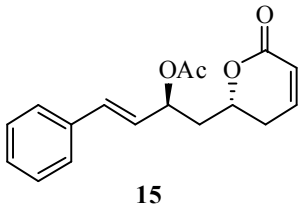


14. synargentolide A

Figure 4

(+)-(6*R*,2′*S*)-Cryptocaryalactone (15)

(+)-(6*R*,2′*S*)-Cryptocaryalactone **15**[18] was isolated from *Cryptocarya bourdilloni* (Figure 5). *Cryptocarya* species have been used as traditional medicine in South Africa for their antiinflammatory and other activities.[19a] The synthesis of (+)-(6*R*,2′*S*)-Cryptocaryalactone **15** and also its epimer **16** was reported.[19b]



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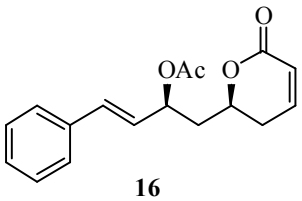

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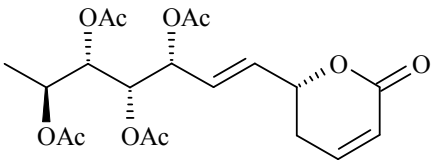
Figure 5

Anamarine and its stereoisomers:

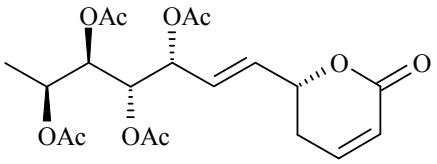
α,β-Unsaturated lactones (+)-Anamrine **17**, C10-epi-anamarine **18** and 5,10-bis-epi-anamarine **19** contains a polyoxygenated chain connected with an α,β-unsaturated six-membered lactone. The (+)-Anamrine **17** was found to exhibit antibacterial, antifungal, as well as cytotoxicity against human tumor cells.[20] In addition, 6-substituted-α,β-unsaturated-δ-lactones have been reported to inhibit HIV protease,[21] induce apoptosis,[22,23] and have proven to be anti-leukemic,[24] along with having many other relevant pharmacological properties.[25] Pharmacological properties of these types make

these compounds interesting synthetic goals. Efforts in this direction[42] were limited for many years to the syntheses of natural (+)-anamarine and its two epimers (**18** and **19**) as shown in Figure 6.

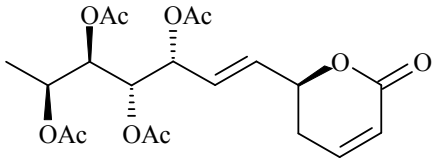
Combustion analysis and mass spectrometry indicated the molecular formula $C_{20}H_{26}O_{10}$ for (+)-anamarine. The spectroscopic evidence suggested a close relationship between olguine and anamarine. So that the same basic skeleton was assumed for both compounds. However, a comparison of the ^{1}H-NMR spectra of the two compounds revealed some differences. Thus, the ^{1}H-NMR spectrum of anamarine showed the presence of four acetoxyl groups, while no signals of oxirane ring protons could be observed. (Olguine contained three acetoxyl groups and two oxirane protons.) In addition, the multiplicity of the signals of the two olefinic protons belonging to an α,β - unsaturated carbonyl function (6.07 and 6.90) suggested the presence of two protons at C-4. (Olguine had one acetoxyl group at C-4 and therefore only one proton at this centre.) Irradiation of the two H-4 protons at 2.46 confirmed their coupling to H-2 and H-3. As in the case of olguine, the ^{1}H-NMR spectrum of anamarine revealed the presence of a set-CH_3 group (1.20, *J*=6 Hz) and two other olefinic protons, whose signals were centred at 5.84 ppm. The signals of the remaining protons appeared between 4.90 and 5.40 ppm, corresponding to the lactonic proton at C-5 and four protons geminal to acetoxyl groups.



17. (+)-anamarine



18. C10-epi-anamarine



19. C5, C10-bis-epi-anamarine

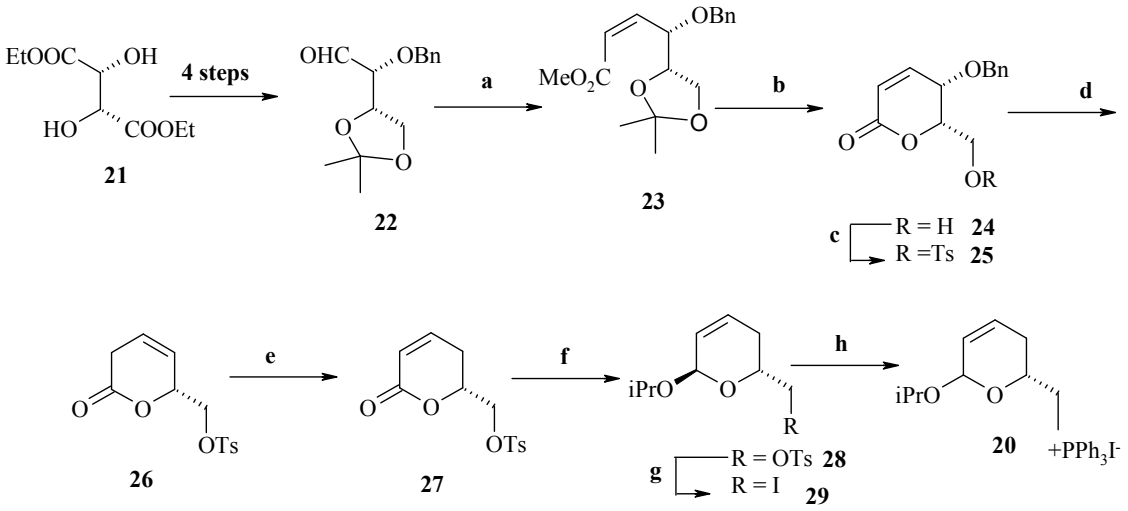
Figure 6

All the spectroscopic data, including the positive Cotton effect observed in the CD curve at 260 nm, were compatible with structure (**17**). However, in order to confirm the location of the double bond at the side chain and to establish the stereochemistry of the four asymmetric centres at this chain, an X-ray analysis was carried out.[26]

FriederW. Lichtenthaler *et al*. approach:[27]

This approach describes a convergent total synthesis of (+)-Anamarine from (*R*, *R*)-tartrate and D-gulonolactone. In this synthesis, synthetic strategy involves reversible β-eliminative ring opening. The construction of the two C6- segments **20** and **30** in enantiomerically pure form, utilizing (*R*,*R*)-tartrate **21** and D-gulonolactone **31**[28] have been reported.

Synthesis of pyranoid six-carbon skeleton: (20)



Scheme 1: Synthesis of pyranoid six-carbon skeleton

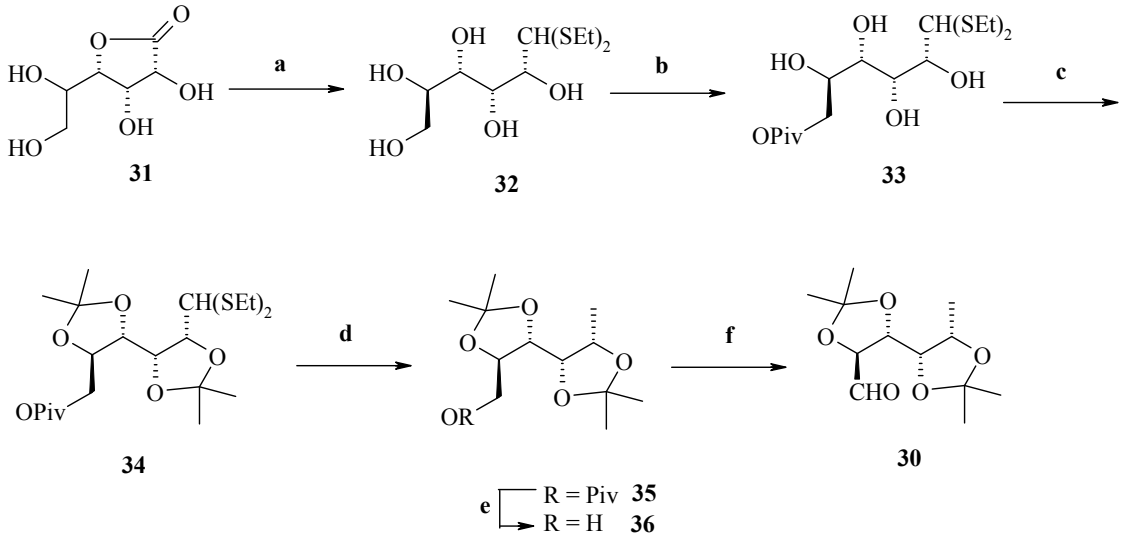
Reagents and conditions: (a) Ph_3P=CHCOOMe, Methanol, 1 h, 25 ^oC, 71%; (b) LiOH, THF/MeOH, (TFA/H_2O 9:1), 79%; (c) TsCl, Pyridine, 15 h, 0 ^oC, 84%; (d) Zn-Hg/HCl, THF, 1 h, 0 ^oC, 91%; (e) DBU, THF, 2 h, 25 ^oC, 95%; (f) DIBAL, THF, −65 ^oC, BF_3/^{i}PrOH, CH_2Cl_2, 6 h, 25 ^oC, 92%; (g) NaI, EtCOMe, 6 h, 80 ^oC, 97%; (h) Ph_3P, fusion, 16 h, 80%.

Preparation of the pyranoid six-carbon half **20** followed by well-established procedures in the first few steps.[29,30] The conversion of diethyl tartrate **21** into the L-

threose derivative **22**, suitably blocked for an ensuing C2-extension to give **23**[30] and subsequent hydrolysis to yield enelactone **24**[30] in an overall yield of 30% for the 6 steps involved. Tosylation of **24** readily afforded the crystalline **25**, which on exposure to zinc amalgam/HCl in ether underwent reductive cleavage of the allylic benzyloxy group with concomitant shift of the double bond into the unconjugated position.[31] The resulting **26** however, on brief treatment with base quantitatively transposed the olefinic double bond into conjugation to afford compound **27** in 84% yield. Iodination of **28** proceeded smoothly to provide syrupy **29**, which on fusion with triphenylphosphane afforded the desired phosphonium salt **20** in crystalline form.

Synthesis of side-chain six-carbon segment: (30)

The side-chain six-carbon segment **30** started from readily accessible progenitor D-gulonolactone **31**. The D-gulonolactone **31** was converted into the diethyl dithioacetal of D-gulose **32**. Selective pivaloylatian of the primary hydroxy group provided **33**, which on subsequent P_20_5-induced acetonation afforded the isopropylidenederivative **34** as syrup.

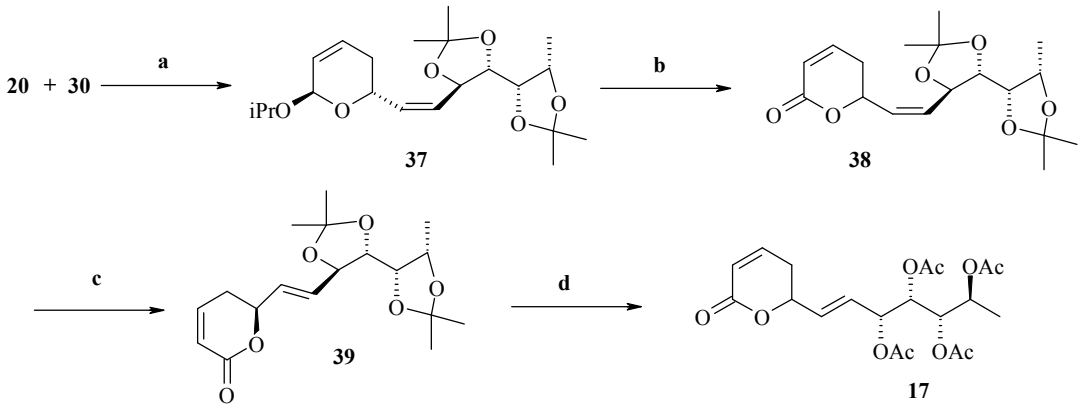


31 **32** **33** **34** **30**

Scheme 2: Synthesis of side-chain six-carbon segment

Reagents and conditions: (a) (i) Me_3SiCl, pyridine, imidazole; (ii) DIBAL, toluene, −65 ^oC; (iii) EtSH, HCl, 0 ^oC, (88% over three steps); (b) Piv Cl, pyridine, −10 ^oC-40 ^oC, 81%; (c) p_2O_5, acetone, 6 h, 25 ^oC, 84%; (d) (Raney-Ni), EtOH, 1 h, reflux; (e) ^{t}BuOK, H_2O, Et_2O, 2 h, 0 ^oC-25 ^oC, 92%; (f) PCC, Al_2O_3, NaOAc, 5 h, 25 ^oC, 75%.

Desulfurization of **34** under Raney-Ni gave **35** which on depivaloylation[32] in presence of ^{t}BuOK afforded **36**, on subsequent PCC oxidation yielded **30** as a liquid. Wittig reaction of two synthons (**20** and **30)** gave compound **37** in 60% yield.



Scheme 3

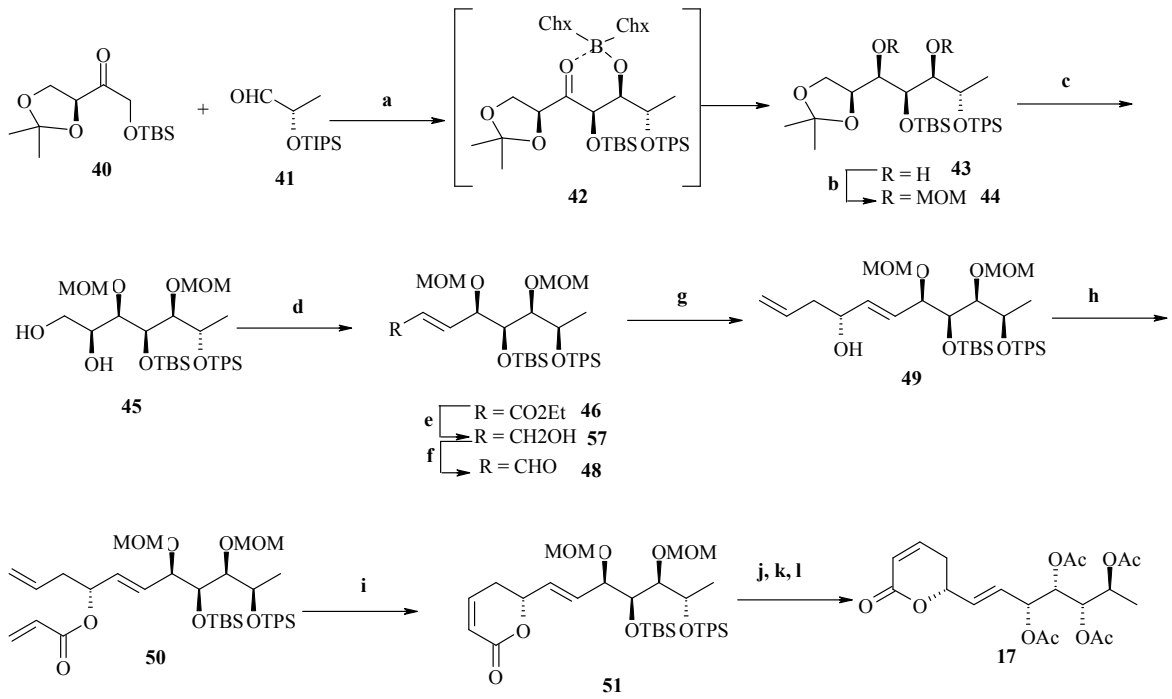
Reagents and conditions: (a) ^{n}BuLi, THF/HMPA (2:1), −78 ^{o}C-r.t., 1 h, 60%; (b) 0.1 N HCl/Me_2CO (1:2), 0 ^{o}C, 15 min, $NaHCO_3$, PCC/Al_2O_3/NaOAc, CH_2Cl_2; (c) Ph_2S_2/hν, Benzene, 5 h, 25 ^{o}C, 73%; (d) TFA, 10 min, Ac_2O, Pyridine.

Compound **37** was subjected to acetal hydrolysis and subsequent PCC oxidation to provide highly crystalline enelactone **38**, which on isomerisation to the E-isomer **39** by irradiation in the presence of diphenyldisuifide. The concluding steps, deacetonation and acetylation of compound **39** proceeded smoothly to give (+)-anamarine **17** as a white solid.[26]

Alberto Marco *et al*. approach:[33]

This approach describe a stereoselective synthesis of the naturally occurring, α,β-unsaturated lactone (+)-anamarine. In this approach, synthetic strategy involves highly stereoselective aldol reaction of a protected erythrulose derivative with a chiral aldehyde. Another relevant step was an asymmetric aldehyde allylation with a chiral allylborane. The lactone ring was made by means of a ring-closing metathesis.

The synthesis of **17** was started from commercially available L-erythrulose. TBS procted L-erythrulose acetal **40** was prepared in two steps.[34] The aldol reaction between the boron enolate of ketone **40** and the (*S*)-lactaldehyde derivative **41** generates with high diastereoselectivity the boron aldolate **42**



Scheme 4

Reagents and conditions: (a) Chx_2BCl, Et_3N, Et_2O, 0 °C, then 5, from −78 °C to 0 °C, 5 h, then $LiBH_4$, −78 °C, 2 h, 75% of 7; (b) MOMCl, DIPEA, 4 days, 72%; (c) PPTS, aq MeOH, r.t., overnight, 70%; (d) $Pb(OAc)_4$, CH_2Cl_2, r.t., 1 h, then $(EtO)_2POCH_2COOEt$, LiCl, DIPEA, MeCN, rt, overnight, 88% overall; (e) DIBAL, hexane–toluene, 0 °C, 4 h, 82%; (f) PCC, celite, CH_2Cl_2, r.t., 1.5 h, 90%; (g) allylBIpc$_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78 °C, 3 h; (h) Acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, rt, 12 h, 81%; (i) Gr I catalyst (10%), CH_2Cl_2, reflux, 3 h, 98%; (j) $BF_3 \cdot Et_2O$, SMe_2, −10 °C, 30 min; (k) aq HF, rt, 7 h; (l) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, rt, overnight (62% overall for the three steps).

which, by means of an oxidative hydrolytic work-up, gives rise to the corresponding aldol adduct (Scheme 4).[35] In the present case, however, aldolate **42** was reduced in situ with $LiBH_4$ to yield the *syn*-1,3-diol **43**.[36] After protection of the hydroxyl groups and hydrolytic cleavage of the acetonide ring,[37] diol **45** was oxidatively cleaved to an intermediate α-alkoxy aldehyde (not depicted) which, without purification, was olefinated by means of a modified Horner–Emmons reaction[38] to conjugated ester **46**. Standard functional group manipulations afforded conjugated aldehyde **48**, which was then

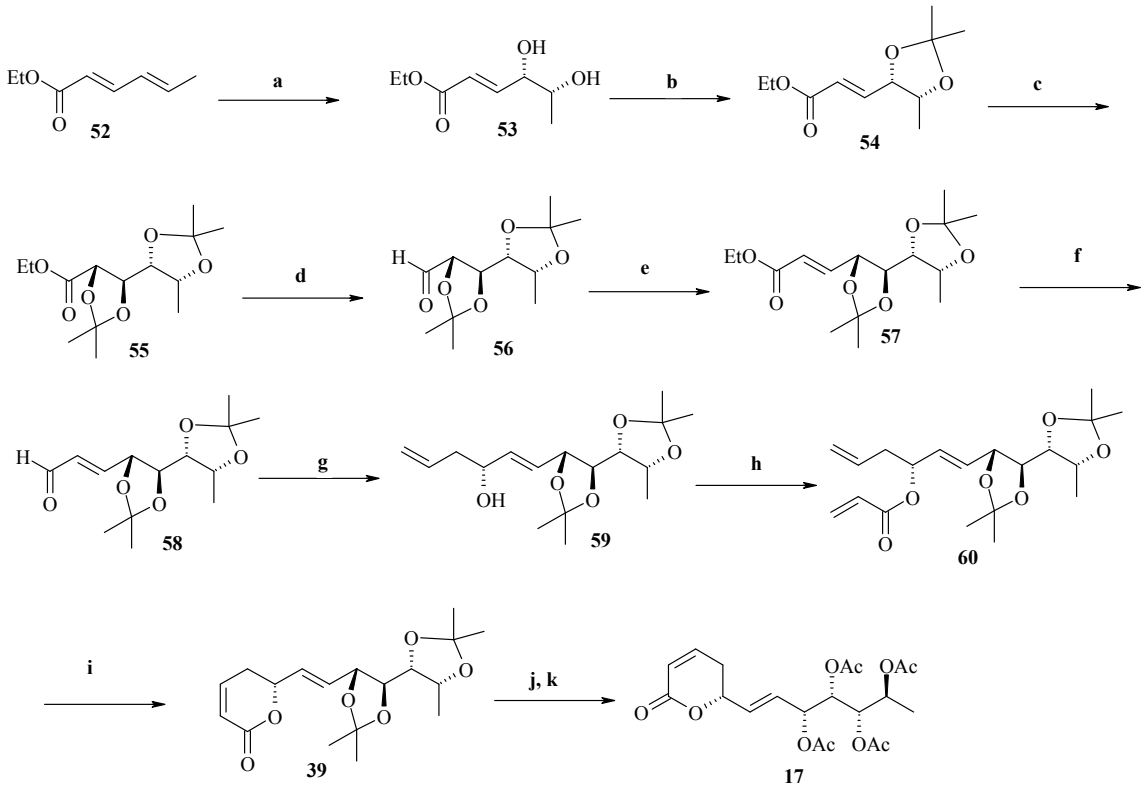
subjected to asymmetric allylation[39] to alcohol **49**. Acylation of the latter with acryloyl chloride,[40] followed by ring-closing metathesis in the presence of the second-generation Grubbs' ruthenium catalyst A,[41] provided conjugated lactone **51**. Finally, cleavage of all protecting groups and peracetylation furnished (+)-anamarine **17** in 62% yield overall for the three steps.

George A. O'Doherty *et al.* approach: [42]

The enantioselective synthesis of anamarine has been achieved in this approach. This route relies on enantio- and regioselective Sharpless dihydroxylation of dienoate ester and a diastereoselective Leighton allylation established the desired C-5 stereochemistry.

In this approach the synthesis was started from commercially available ethyl sarbate **52**. The starting material ethyl sarbate **52** was enantioselectivrly subjected to Sharpless asymmetric dihydroxylation with AD-mix-α, (1 mol % OsO_4, 2 mol % $(DHQ)_2PHAL$, 3 eq of $K_3Fe(CN)_6$, 3 eq of K_2CO_3, and 1 eq of $MeSO_2NH_2$. in $^tBuOH/H_2O$ (1:1) to provide diol **53** with 90% yield with high enantiomeric excess which was masked as its acetonoide **54** using 2,2-dimethoxy propane and catalytic CAN in 95% yield (Scheme 5). Once again, the α,β-unsaturated ester **54** was dihydroxylated in a diastereomerically matched sense,[43] with the AD-mix-β (2 mol % OsO_4, 4 mol % $(DHQD)_2PHAL$, 3 eq of $K3Fe(CN)_6$, 3 eq of K_2CO_3, and 1 eq of $MeSO_2NH_2$). This diastereoselectively matched reaction gave a diol with 9:1 diastereomeric ratio, which was protected as the acetonide **55** (66% yield for two steps). The bis-acetonide **55** was isolated with greater enantiomeric purity (>96% ee) than the initial acetonide **54.**[44] The ester **55** was converted into alcohol using DIBAL-H. Further alcohol was converted into aldehyde **56** under Swern conditions using $(COCl)_2$, DMSO. The corresponding aldehyde **56** subsequently this aldehyde was converted into α,β-unsaturated ester **57** on 2C-Wittig reaction. The ester **57** was converted into aldehyde **58** using DIBAL-H at −78 ^oC in CH_2Cl_2. The aldehyde **58** was subjected to allylation by using Leighton allyl silane reagent to produce the corresponding homoallylic alcohol **59** with 9:1 diastereomeric ratio (Scheme 5). The homoallylic alcohol **59** was coupled with DCC (4 eq) and acrylic acid (4 eq) in CH_2Cl_2, providing triene **60** in 83% yield. The acryloyl ester **60** which

underwent ring-closing metathesis (RCM) using the Grubbs' first generation catalyst to produce corresponding α,β-unsaturated-δ-lactone **39**.



Scheme 5

Reagents and conditions: (a) AD-mix-α, $Me_2SO_2NH_2$, ^tBuOH: H_2O (1:1), 74%; (b) 2,2 DMP, CSA, CH_2Cl_2, 74%; (c) (i) AD-mix-β, $Me_2SO_2NH_2$, tBuOH: H_2O (1:1), −78 ^oC, 80%; (ii) 2,2 DMP, CSA, CH_2Cl_2, 80%; (d) (i) DIBAL-H, anhydrous CH_2Cl_2, −20 ^oC, 1 h, 82%; (ii) $(COCl)_2$, DMSO, CH_2Cl_2, TEA, anhydrous CH_2Cl_2, −78 ^oC, 2 h, 82%; (e) PPh_3=$CHCO_2Et$, Ph–H, rt, 2 h, 81%; (f) DIBAL-H, anhydrous CH_2Cl_2, −20 ^oC, 1 h, 82%; (g) $C_{23}H_{29}SiClBr_2$, CH_2Cl_2, −10 ^oC, 92%; (h) $C_3H_4O_2$, DCC, DMAP, CH_2Cl_2, 78%; (i) $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, reflux, 77%; (j) 10% HCl, THF, 65 ^oC, 10 min, 85%; (k) Ac_2O, Et_3N, cat. DMAP, CH_2Cl_2, 86%.

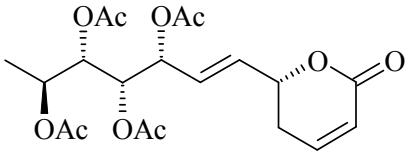
Finally compound **39** was treated with 10% HCl in THF followed by acetylation with acetic anhydride in Et_3N and DMAP to produce (+)-anamarine **17** in 86% yield over two steps.[27] In addition to total synthesis of (+)-anamarine, this approach also describes

the total synthesis of C10-epi-anamarine **18** and 5,10-bis-epi-anamarine **19** by using similar sequence of reactions as in case of synthesis of (+)-anamarine.

PRESENT WORK

5,6-Dihydro-2*H*-pyran-2-one (δ-pyranone) is an ubiquitous structural unit found in a number of bioactive natural products of therapeutic significance. Natural products and analogues possessing this moiety have been shown to exhibit a number of biological activities including anti-cancer activity. Anamarine, a C_{12} compound isolated from the flowers and leaves of an unclassified Peruvian *Hyptis* species was shown to have constitution **17** on the basis of ^{1}H-, ^{13}C-NMR and X-ray crystallographic data, featuring *R*-configuration in the pyranoid ring and L-gluco arrangement in the C_6-side chain. (+)-Anamarine **17** structurally similar to other members of the polyhydroxy δ-pyranone natural products such as spicigerolide **11**, synrotolide 1**3**, synargentolide A 1**4** etc. These compounds have been found to exhibit antibacterial, antifungal, as well as cytotoxicity against human tumor cells. In addition, 6-substituted-α,β-unsaturated-δ-lactones have been reported to inhibit HIV protease, induce apoptosis, and have proven to be anti-leukemic, along with having many other relevant pharmacological properties.[3] So far, and to the best of our knowledge, three syntheses have been reported on the synthesis of this natural product **17**[27,33,42] (Figure 7). These excellent bioactivities have encouraged us to take up the synthesis of (+)-Anamarine **17** via cross-metathesis (CM) protocol in a convergent manner.

In continuation of our research on the synthesis of lactone-containing natural products,[45] we herein disclose our strategy towards the synthesis of (+)-Anamarine **17** following a convergent approach utilizing Sharpless asymmetric epoxidation, Grignard reaction, Sharpless dihydroxylation, Red-Al reduction and cross-metathesis (CM) as key steps.

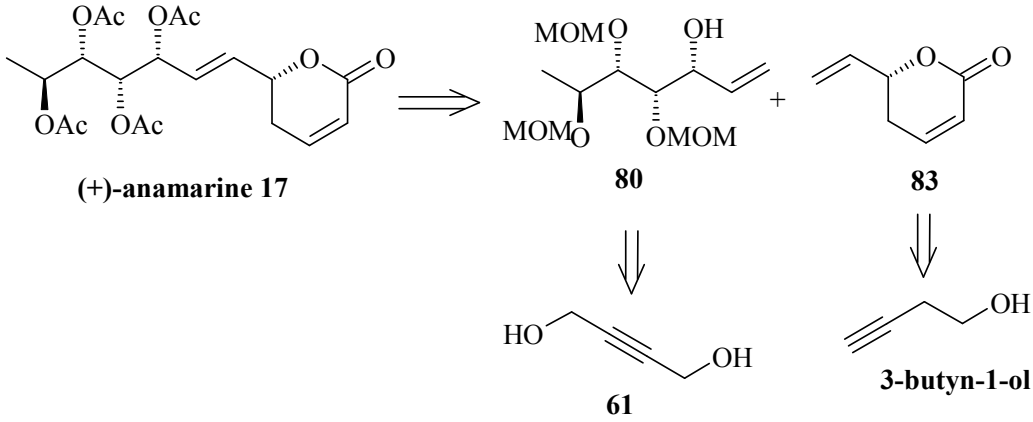


(+)-anamarine 17

Figure 7

Retrosynthetic analysis reveals that the target compound **17** (Scheme 6) can be obtained by CM reaction of olefin **80** and vinyl lactone **83**. The substrate **80** in turn could

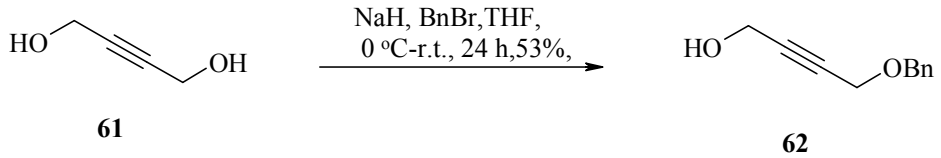
be made from the commercially available 2-butyn-1,4-diol **61** by sequence of reactions, whereas, the vinyl lactone **83**[45o] is accessible from 3-butyn-1-ol.



Scheme 6: Retrosynthetic analysis for (+)-Anamarine.

Synthesis of (3*R*,4*S*,5*S*,6*S*)-4,5,6-tri(methoxymethoxy)-1-hepten-3-ol (80):

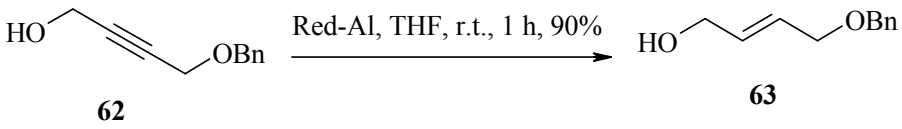
The requisite propargylic alcohol **62** was prepared from commercially available simple 2-butyn-1,4-diol **61**. Accordingly the diol **61** was subjected to monobenzylation with NaH and benzylbromide in presence of 4:1 ratio of dry THF and DMF at 0 ^{o}C temperature (Scheme 7). Compound **62** was confirmed by its strong absorption under uv light while the alcohol was inactive. This was further supported by ^{1}H NMR spectrum wherein the benzyl proton was observed at δ 4.57 as a singlet. Further, the remaining peaks resonated at their respectable places. The mass spectrum supported the structure that revealed a peak at *m/z* 199 $[M + Na]^{+}$ in ESI-MS.



Scheme 7

In order to obtain required geometry, compound **62** was partially hydrogenated under Red-Al in dry THF at 0 ^{o}C to give allyl alcohol **63** in 90% yield (Scheme 8). In ^{1}H

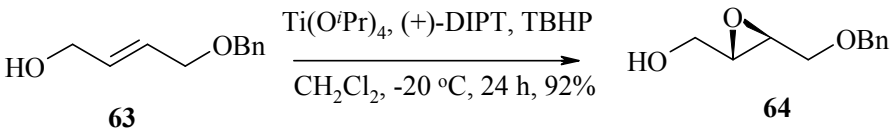
NMR spectrum peaks at δ 5.90-5.71 as multiplet reveals the presence of double bond. This was further confirmed by absorption peaks at 3340, 1662 and 723 cm^{-1} in IR spectrum. The formation of the product **63** was further supported by its $[M + Na]^+$ peak observed at *m/z* 201 in ESI-MS.



62 **63**

Scheme 8

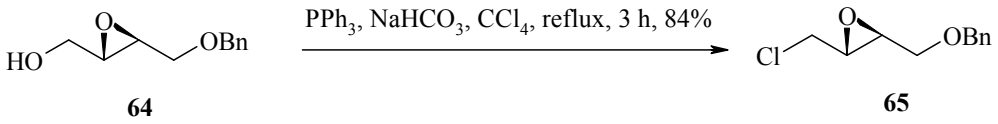
Compound **63** was treated with (+)-DIPT in presence of $Ti(O^iPr)_4$ and tertiary butyl hydro peroxide (TBHP) as oxygen source in CH_2Cl_2 at –20 ^oC to obtain epoxy alcohol **64** in 92% yield (Scheme 9).[46] Compound **64** was confirmed from ^1H NMR spectrum wherein the protons attached to the epoxide ring resonated at δ 3.20-3.14 (m, 1H) and 3.05-3.0 (m, 1H) while the remaining protons resonated at their respective chemical shifts. The protons due to the olefinic group disappeared. IR-spectrum revealed the stretching frequencies at 1453 cm^{-1} and 1102 cm^{-1} as an evidence for the presence of ether linkages. The formation of the product **64** was further supported by its $[M + Na]^+$ peak observed at *m/z* 217 in ESI-MS.



63 **64**

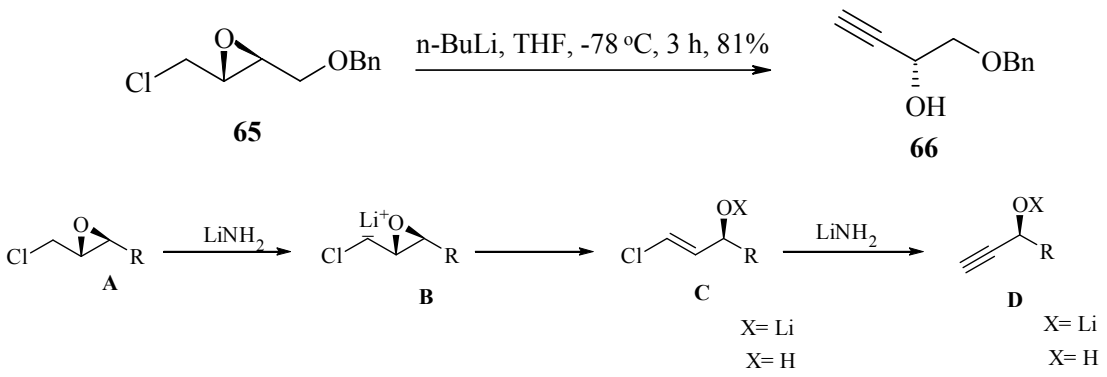
Scheme 9

In the next step, the epoxy alcohol **64** was converted to the corresponding chloride **65** using TPP, dry CCl_4 and $NaHCO_3$ in 84% yield. The mass, IR and ^1H NMR spectral data confirmed its structure. In the ^1H NMR spectrum, epoxy protons resonated at δ 3.13 (td, J = 1.8, 5.4 Hz, 1H), 3.10-3.02 (m, 1H) and methylene protons of chloromethyl group appeared as a multiplet at 3.73-3.43. All other protons resonated at their respective chemical shift values. A molecular ion peak at *m/z* 215 $(M+Na)^+$ further confirmed the structure of product **65**.



Scheme 10

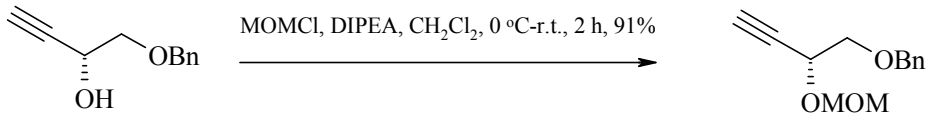
The conversion of epoxy chloride **65** to the corresponding propargyl alcohol **66** in 81% yield was accomplished by treating compound **65** with 3 eq of 2.5 molar ^{n}BuLi in anhydrous THF.[37] The formation of compound **66** was well characterized by ^{1}H NMR, IR and mass spectral studies. The acetylenic proton of alkyne compound **66** appeared at δ 2.46 (*J* = 1.9 Hz) as a doublet. IR spectrum showed absorption peaks at 3408 cm^{-1} and 2115 cm^{-1} for the hydroxyl group and terminal alkyne respectively. Mass spectrum showed a molecular ion peak at *m/z* value 199 $[M + Na]^{+}$ further confirming the product **66** (Scheme 11). A plausible mechanism for the opening of epoxychloride (**A**) to form alkynol is indicated in Scheme 11. Base abstracts a proton from the carbon bearing chlorine group from **A** with concomitant cleavage of epoxide to form the vinyl chloride (**C**). Then compound C further undergoes dehydrohalogenation to result the alkynol (Scheme 11).



Scheme 11

Protection of propargyl secondary hydroxy group of **66** as MOM ether afforded **67** using *i*Pr$_2$NEt and MOMCl in CH_2Cl_2. Compound **67** was characterized by appearance its PMR spectrum signals at δ 4.65 (d, *J* = 6.7 Hz, C**Ha**Hb-O-CH_3, 1H), 4.62 (d, *J* = 1.7 Hz,

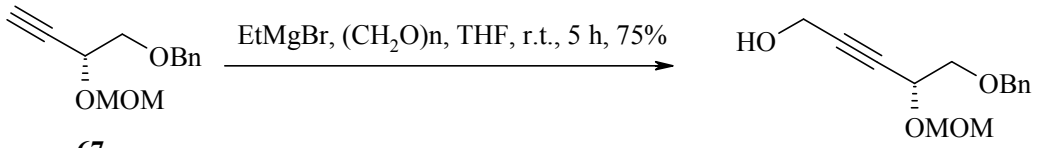
CHa**Hb**-O-CH_3, 1H) and 3.39 (s, 3H, CH_2-O-C**H3**). Further it was characterized by ESI-MS data which showed a value of *m/z* 243 for the [M+Na]+.



66 **67**

Scheme 12

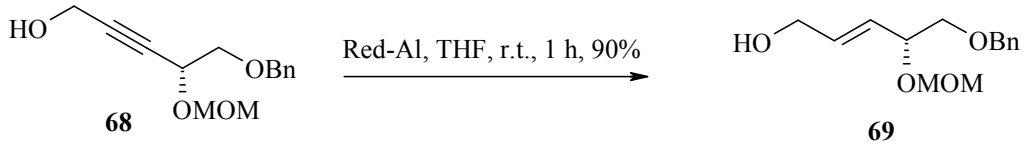
The ether **67** was treated with the Grignard reagent prepared from ethyl bromide & magnesium followed by quenching with paraformaldehyde in anhydrous THF to afford compound **68** in 75% yield (Scheme 13). The structure of ether **68** was characterized from its PMR, IR and mass spectral properties. In PMR spectrum the disappearance of peak at δ 2.41 due to acetylenic proton, clearly indicates formation of compound **68**. In IR spectrum a strong absorption at 3426 cm^{-1} for the hydroxyl functional group and in mass spectrum appearance of a molecular ion peat at *m/z* 273 $[M+Na]^+$ further confirmed the product **68**.



67 **68**

Scheme 13

In order to get the *trans*-allyl alcohol, compound **68** was treated with 1.5 eq. of Red-Al[9] in anhydrous THF at room temperature, which reduced the alkyne to the desired *trans* olefin **69** in 90% yield. Both IR and PMR spectral data confirmed the presence of *trans* olefin. The PMR spectrum showed a multiplet at δ 5.89 (dt, J = 5.2, 16.6 Hz, 1H) and 5.58 (dt, J = 1.5, 9.5 Hz, 1H) for the *trans* olefinic protons.

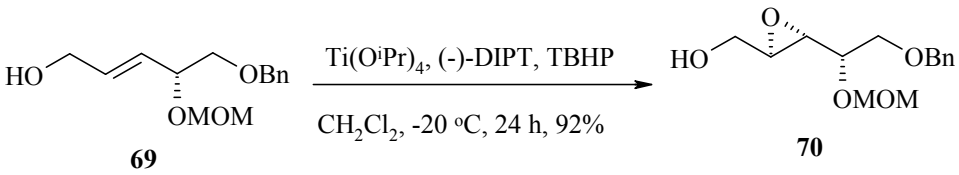


68 **69**

Scheme 14

In the IR spectrum a characteristic C=C stretch at 1644 cm^{-1}, a C-H deformation stretch at 971 cm^{-1} for the *trans* C-H protons and hydroxyl absorption at 3422 cm^{-1} has observed. The structure of the olefin **69** was further confirmed by the mass spectrum, which showed a molecular ion peak at *m/z* 275 $[M+Na]^+$.

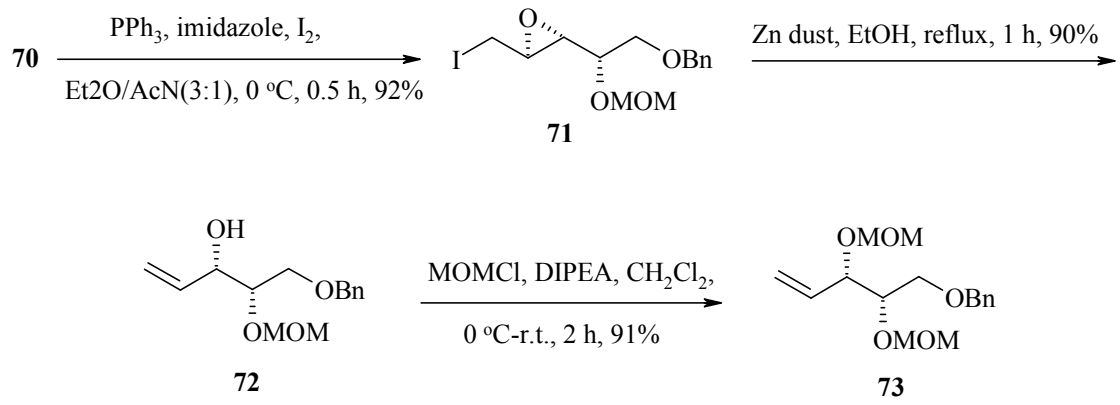
In the next step, olefin **69** was subjected to Sharpless asymmetric epoxidation[46] using (-)-DIPT, Ti(O*i*Pr)$_4$ and cumene hydroperoxide to furnish the desired (*R,S*)-epoxide **70** in 92% yield. The epoxy alcohol **70** had its PMR, IR & mass spectra consisting with its structure. The two-epoxy protons in the PMR spectrum resonated as doublets at δ 3.10 and at δ 3.02, while the IR spectrum showed absorptions at 3444 cm^{-1} for the hydroxyl function and at 1101 cm^{-1} for the epoxy linkage. The structure of the epoxy alcohol **70** was further confirmed by the molecular ion peak at *m/z* 291 $[M+Na]^+$ in mass spectrum.



Scheme 15

Compound **70** on exposure to TPP, I_2, and imidazole at 0 ^oC gave the corresponding iodide **71** in 30 min. which was directly used for the next step. The compound **71** was converted into a secondary allylic alcohol **72** in 90% yield, by refluxing of compound **71** with activated Zinc in dry ethanol (Scheme 16). The compound **72** was confirmed by spectral data. The olefinic protons were resonated as multiplet at δ 5.96-5.82, two doublet of triplets at δ 5.37 (dt, *J* = 1.5, 17.3 Hz, 1H) and 5.07 (d, *J* = 1.3, 10.5 Hz, 1H) in PMR spectrum. The IR spectrum showed a strong and broad hydroxyl absorption band at 3448 cm^{-1}. Compound **72** gave molecular ion peak at m/z 275 $[M+Na]^+$ in the ESI mass spectrum. Protection of secondary allylic hydroxy group of **72** as MOM ether afforded **73** using *i*Pr$_2$NEt and MOMCl in CH_2Cl_2. Compound **73** was characterized by appearance of signals in its PMR spectrum as multiplet at δ 4.83-4.61 for four protons (including previous methelidine protons of MOM group) and 3.33 (s, 3H, CH_2-O-C**H3**).

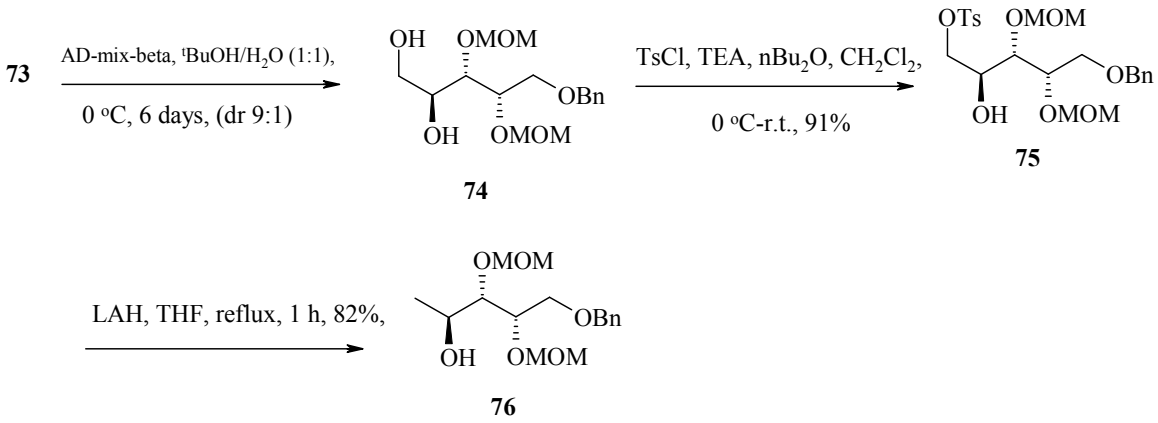
Further it was characterized by ESI-MS data which showed a value of *m/z* 319 for the $[M+Na]^+$.



Scheme 16

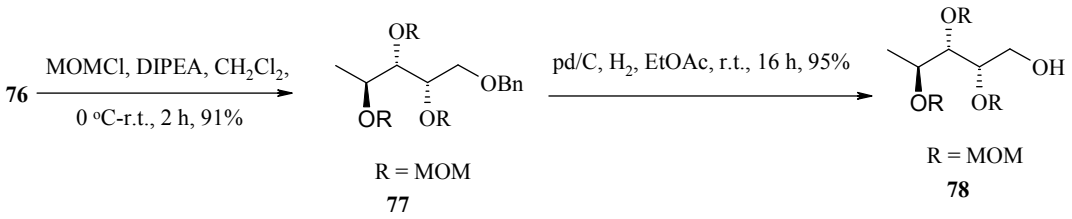
Asymmetric dihydroxylation[47] of **73** using AD-mix-β in ^{t}BuOH/H_2O (1:1) at 0 ^{o}C gave the diol **74** in 90% yield with 9:1 diastereomeric ratio. The compound **74** was confirmed by spectral data. In PMR sprctrum disappearance of olefinic protons indicates the formation of diol compound **74**. IR spectrum shows the strong absorption at 3380 cm^{-1} for the hydroxyl function. Further it was characterized by ESI-MS data which showed a value of *m/z* 353 for the $[M+Na]^+$.

The primary hydroxyl group in **74** was selectively tosylated using tosyl chloride, Et_3N and ^{n}Bu_2O in anhydrous CH_2Cl_2 at 0 ^{o}C to afford compound **75** in 92% yield. Compound **75** was directly used for the next step without further purification. In the next step, in order to remove the tosylate group, compound **75** was refluxed with $LiAlH_4$ in anhydrous THF, to yield compound **76** in 82% yield. The formation of the product **76** was well established with its spectral properties. In the PMR spectrum a new doublet peak at δ 1.24 (J = 6.7 Hz) corresponding to the new methyl group was observed. The peaks related to tosyl group were not observed. The ESI-MS mass spectrum data showed $[M+Na]^+$ peak at *m/z* 337. In the IR spectrum a band corresponds to hydroxyl group appeared at 3454 cm^{-1} further confirmed the product **76**.



Scheme 17

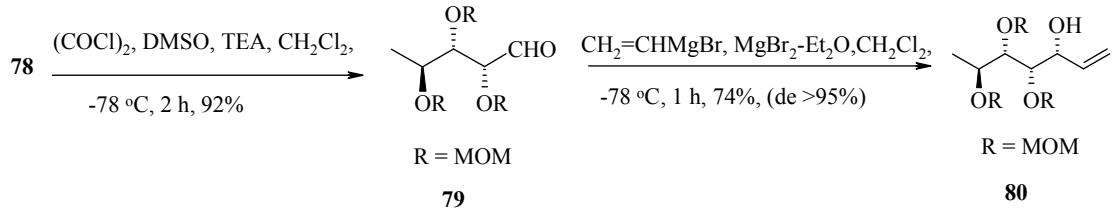
Methoxy methyl (MOM) ether protection of **76** carried out with 2 equivalents of MOMCl in the presence of *i*Pr_2NEt in CH_2Cl_2 to produce **77**. ^{1}H NMR spectrum of MOM ether **77** exhibited a multipet at δ 4.74-4.57 integrating for four protons (2 x CH_2) and again a singlet at δ 3.35 integrating for three protons and presence of other required peaks confirmed the structure of **77**. ESI-MS signal at *m/z*: 381 $[M+Na]^+$ further confirmed the transformation. The tri MOM ether **77** exposed to Pd/C and H_2 gas to gave primary alcoholic compound **78** in 95% yield. Compound **78** was characterized by disappearance of PMR spectrum signals in aromatic region. Further it was characterized by a strong absorption at 3460 cm^{-1} and ESI-MS data which showed a value of *m/z* 291 for the $[M+Na]^+$ (Scheme 18).



Scheme 18

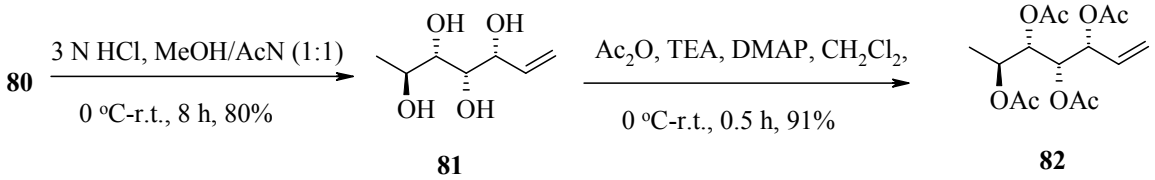
Oxidation of alcohol **78** using Swern oxidation yielded the corresponding aldehyde **79** and subjected to chelation controlled Grignard reaction[48] with vinylmagnesium bromide (formed by addition of vinyl bromide to Mg in THF) in the presence of $MgBr_2$-OEt_2 to afford allylic alcohol **79** with >95% diastereoselectivity. ^{1}H NMR spectrum of the compound **80** exhibited one multiplet at δ 5.97, two doublets of triplets at δ 5.40 and 5.12 due to three olefinic protons respectively. Oxygen attached C-H signals were integrated for

four protons confirmed that the stereoselection was in anticipated line. In addition, IR spectrum showed hydroxyl absorbtion at 3451 cm^{-1} and ESI-MS showed $[M+Na]^+$ signal at *m/z* 317, further confirmed the structure **80** (Scheme 19).



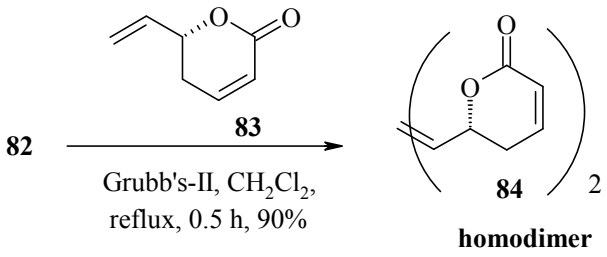
Scheme 19

Deprotection of three MOM groups **80** using 3 N HCl in 1:1 ratio of MeOH/CH_3CN afforded tetrol **81**, which was used for the next step without further purification. The tetrol **82** was protected as its tetraacetate **82** with acetic anhydride and TEA at 0 ^oC-rt, 30 min. in 91% yield (Scheme 20). The NMR spectrum of **82** indicated the presence of four OAc at δ 2.10, 2.09, 2.08 and 2.04 ppm as singlets. The IR spectrum showed a strong absorption band at 1748, 169.0, 169.7 and 169.6 cm^{-1} due to presence of acetate groups. The mass spectrum supported the structure that revealed a peak at *m/z* 353 $[M + Na]^+$ in ESI-MS.



Scheme 20

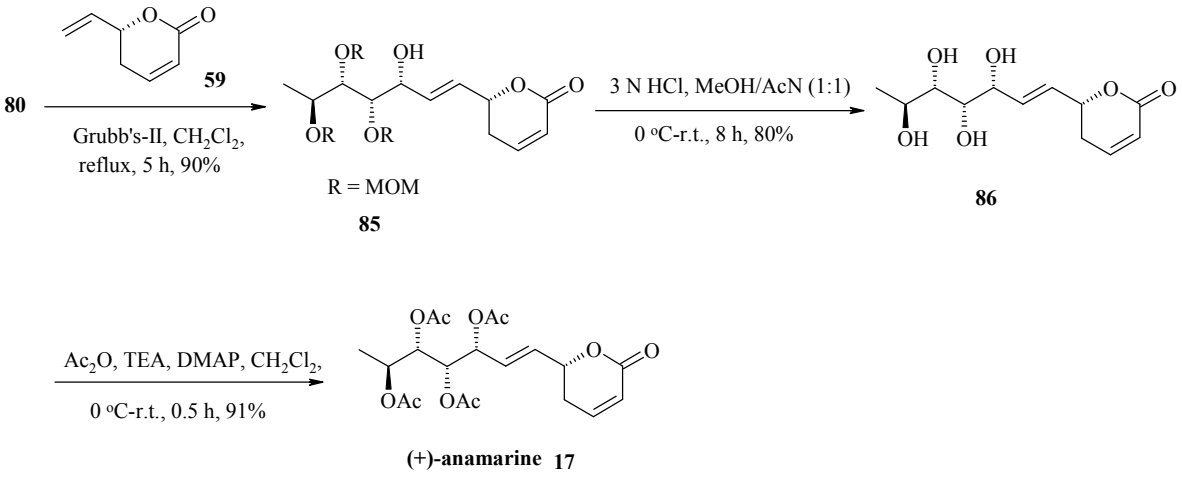
Now, the stage was set to prepare the anamarine **17** by olefin cross-metathesis reaction. However, cross-metathesis reaction[49] between tetraacetate compound **82** and the known vinyl lactone **83** in the presence of Grubbs' 2nd generation or Hoveyda catalyst in CH_2Cl_2 was found to give completely the vinyl lactone homodimerized Product **84** in 90% yield within 15 min (Scheme 21), which was confirmed by its mass spectral data.



Scheme 21

But, the cross-metathesis reaction of tri MOM protected compound **80** with vinyl lactone **83** in the presence of Grubbs' 2nd generation catalyst in CH_2Cl_2 at reflux temperature afforded the desired cross-coupled product **85** exclusively in good yield (Scheme 22). In the ^{1}H NMR spectrum of **85** newly introduced four protons belongs to olefinic region, which was resonated at δ 6.92-6.86 as multiplet for one proton and at δ 6.09-5.94 as multiplet for three protons. In ^{13}C NMR spectrum the ester carbonyl group appeared at δ 163.8 and the IR spectrum showed absorption at 1722 cm^{-1} for ester carbonyl group. The ESI-MS of **85** peak at *m/z* 413 corresponding to $[M+Na]^+$ clearly indicate the product formation.

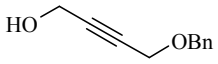
Again deprotection of three MOM groups **85** using 3 N HCl in 1:1 ratio of MeOH/CH_3CN afforded tetrol **86**, which was used for the next step without further purification. The acetylation of compound **86** with acetic anhydride, TEA and DMAP afforded (+)-anamarine **17** as a white solid (Scheme 22). The NMR spectrum of **17** indicated the presence of four OAc at δ 2.11, 2.07, 2.06 and 2.03 ppm as singlets and at δ 1.17 as a doublet for terminal methyl protons. The IR spectrum showed a strong absorption band at 1739 cm^{-1} due to presence of acetate group. HR-ESI-MS signal at *m/z*: 449.1434 $[M+Na]^+$ further confirmed structure of (+)-Anamarine A (Scheme 22).


80
59
Grubb's-II, CH2Cl2,
reflux, 5 h, 90%
OR
OH
OR
OR
R = MOM
85
3 N HCl, MeOH/AcN (1:1)
0 oC-r.t., 8 h, 80%
OH
OH
OH
OH
86
Ac2O, TEA, DMAP, CH2Cl2,
0 oC-r.t., 0.5 h, 91%
OAc
OAc
OAc
OAc
(+)-anamarine 17

Scheme 22

EXPERIMENTAL SECTION

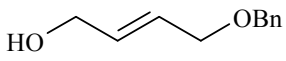
4-(benzyloxy)-2-butyn-1-ol (62):



To a suspension of NaH (7.25 g, 181.25 mmol) in 4:1 ratio of anhydrous THF and DMF (60 mL) at 0 ^{o}C was added diol **61** (13 g, 151.16 mmol) in THF (100 mL) in a dropwise manner. The reaction mixture was stirred at room temperature for 5 h and again the mixture was cooled to 0 ^{o}C. After addition of BnBr (16.15 mL, 94.44 mmol), the reaction was brought to room temperature and stirred for 24 h, cooled to 0 ^{o}C and quenched with saturated NH_4Cl solution (80 mL) carefully. Then EtOAc (200 mL) was added, organic layer was separated, washed with H_2O (3 x 50 mL) and brine solution (40 mL) and dried *in vacuo*. Column chromatography (EtOAc/hexane, 4:6) of the crude product afforded **62** as colorless oil (14.09 g, 53%) along with 20% recovered starting material **61**.

^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.34-7.25 (m, 5H, ArH), 4.57 (s, 2H, C**H$_2$**-OAr), 4.27 (t, *J* = 1.7 Hz, 2H), 4.17 (t, *J* = 1.7 Hz, 2H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 136.9, 128.2, 127.9, 127.7, 84.9, 80.9, 71.4, 57.2, 50.4.
ESIMS:	*m/z* 199 $[M+Na]^+$.

(*E*)-4-(benzyloxy)-2-buten-1-ol (63):



To a stirred suspension of Red-Al (37.28 g, 119.31 mmol) in anhydrous THF (140 mL) at 0 ^{o}C was added dropwise, a solution of compound **62** (14 g, 79.54 mmol) in anhydrous THF (90 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. It was then cooled to 0 ^{o}C, diluted with ether and quenched with

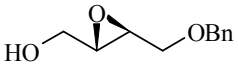
dropwise addition of saturated aqueous Na_2SO_4 (20 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (EtOAc/ hexane, 4.5:5.5) to afford the compound **63** (12.73 g, 90%) as a viscous liquid.

^{1}H NMR ($CDCl_3$, 300 MHz): 7.34-7.20 (m, 5H, ArH), 5.90-5.71 (m, 2H), 4.48 (s, 2H, C**H$_2$**-OAr), 4.07 (d, *J* = 4.5 Hz, 2H), 3.98 (d, *J* = 5.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 135.3, 128.2, 127.9, 127.7, 127.4, 73.2, 69.5, 61.1.

ESIMS: *m/z* 201 $[M+Na]^+$.

(2*R*,3*R*)-3-[(benzyloxy)methyl]oxiran-2-ylmethanol (64):



In a 500 mL two neck round bottomed flask, 40 mL of anhydrous CH_2Cl_2 was added to 4 ^{o}A powdered activated molecular sieves and suspension mixture was cooled to –20 ^{o}C, $Ti(O^iPr)_4$ (4 mL, 14.08 mmol) and L-(+) DIPT (2.43 g, 11.79 mmol) in anhydrous CH_2Cl_2 (15 mL) were added subsequently with stirring and the resulting mixture was stirred for 30 min at –24 ^{o}C. Compound **63** (12.63 g, 71 mmol) in anhydrous CH_2Cl_2 (50 mL) was then added and the resulting mixture was stirred for another 30 min at –24 ^{o}C followed by addition of TBHP (14.19 mL, 71 mmol) and the resulting mixture was stirred at the same temperature for 24 h. It was then warmed to 0 ^{o}C, quenched with 6 mL of after and stirred for 1 h at room temperature. After that 30% aqueous NaOH solution saturated with NaCl (10 mL) was then added and the reaction mixture was stirred vigorously for another 30 min at room temperature. The resulting mixture was then filtered through *Celite* rinsing with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced

pressure and purified by silica gel column chromatography (EtOAc/ hexane, 4:6) to afford **64** (12.65 g, 92%) as a viscous liquid.

$[\alpha]_D^{25}$: –15.5 (*c* 1.0, $CHCl_3$)

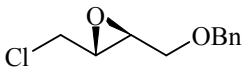
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.22 (m, 5H, ArH), 4.54 (q, *J* = 12.0, 16.6 Hz, 2H, C**H$_2$**-OAr), 3.87 (dd, *J* = 2.2, 12.0 Hz, 1H), 3.70 (dd, *J* = 3.0, 11.3 Hz, 1H), 3.60 (dd, *J* = 4.5, 12.8 Hz,1H), 3.49 (dd, *J* = 5.2, 11.3 Hz,1H), 3.20-3.14 (m, 1H), 3.05-3.0 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 128.3, 127.8, 127.7, 73.2, 69.5, 61.1, 55.8, 54.2.

IR (neat): 3419, 2922, 2864, 1453, 1102, 935 cm^{-1}.

ESIMS: *m/z* 217 $[M+Na]^+$.

(2*S*,3*R*)-2-(benzyloxymethyl)-3-(chloromethyl)oxirane (65):



To a stirred solution of epoxy alcohol **64** (12.55 g, 64.7 mmol) in anhydrous CCl_4 (130 mL), TPP (30 g, 112.35 mmol) and $NaHCO_3$ (5.43 g, 64.64 mmol) were added. The reaction mixture was vigorously refluxed for 3 h and the resulting solid was filtered and washed with ether. Concentration under reduced pressure and purification by silica gel column chromatography afforded **65** (11.51 g, 84%) as a viscous liquid.

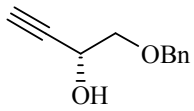
$[\alpha]_D^{25}$: –4.7 (*c* = 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.37-7.22 (m, 5H, ArH), 4.55 (ABq, *J* = 12.0, 15.1 Hz, 2H, C**H$_2$**-OAr), 3.73-3.43(m, 4H), 3.13 (td, *J* = 1.8, 5.4 Hz,1H), 3.10-3.02 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 128.4, 127.7, 127.6, 73.2, 69.0, 57.0, 54.5, 44.1.

IR(neat): 3029, 2861, 1452, 1101, 916 cm^{-1}.

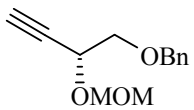
(2*R*)-1-(benzyloxy)-3-butyn-2-ol (66):



^{n}BuLi (64.58 mL, 161.46 mmol) was added to a stirred solutions of compound **65** (11.41 g, 53.82 mmol) in dry 100 mL THF at –78 ^{o}C. The reaction mixture was stirred at same temperature for about 3 h. After 3 h the reaction mixture was allowed to warm to room temperature and quenched by adding saturated solution of NH_4Cl at 0 ^{o}C, the solid was removed by filtration, and the organic layer was washed with brine. Dried over Na_2SO_4 and the solvent was removed in vacuum. The residue was purified with silica gel column chromatography (EtOAc/hexane, 3.5:6.5) to give **66** (7.67 g, 81%) as a colorless liquid.

$[\alpha]_D^{25}$:	–2.5 (*c* 1.0, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 500 MHz):	δ 7.34-7.27 (m, 5H, ArH), 4.62 (ABq, *J* = 12.5, 18.2 Hz, 2H, C**H$_2$**-OAr), 4.57-4.53 (m, 1H), 3.66 (dd, *J* = 2.8, 9.6 Hz, 1H), 3.61-3.56 (m, 1H), 2.46 (d, *J* = 1.9 Hz, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 137.4, 128.4, 127.9, 127.7, 81.6, 73.6, 73.4, 73.3, 61.4.
IR (neat):	3408, 3030, 2921, 2864, 2115, 1452, 1111 cm^{-1}.
ESIMS:	*m/z* 199 $[M+Na]^+$.

1-([(2*R*)-2-(methoxymethoxy)-3-butynyl]oxymethyl)benzene (67):



To alcohol **66** (7.57 g, 43.01 mmol) in anhydrous CH_2Cl_2 (70 mL) at 0 ^{o}C were added diisopropyl ethylamine (14.79 mL, 114.65 mmol), catalytic DMAP and MOMCl (4.15 mL, 581.55 mmol) successively and the mixture was stirred for 2 h at room temperature, quenched by adding water (20 mL) and extracted with CH_2Cl_2 (3 x 40 mL).

The organic extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4 (2 g) and concentrated under vacuum to remove the solvent and the crude residue was purified by column chromatography (EtOAc/hexane, 3:7) to afford the MOM ether **67** (8.6 g, 91% yield) as colourless oil.

$[\alpha]_D^{25}$: –72.2 (c 1.0, $CHCl_3$).

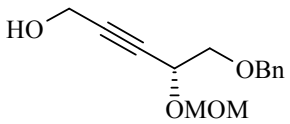
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38-7.4 (m, 5H, ArH), 4.92 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 6.7 Hz, 1H), 4.62 (d, *J* = 1.7 Hz, 1H), 4.59-4.50 (m, 2H, C**H$_2$**-OAr), 3.67 (d, *J* = 5.6 Hz, 2H), 3.39 (s, 3H, CH_3), 2.41(d, *J* = 2.0 Hz,1H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.8, 128.3, 127.6, 127.5, 94.3, 79.8, 74.4, 73.3, 72.2, 64.9, 55.6.

IR(Neat): 2892, 3030, 1452, 1153, 1029 cm^{-1}.

ESIMS: *m/z* 243 $[M+Na]^+$.

(4*R*)-5-(benzyloxy)-4-(methoxymethoxy)-2-pentyn-1-ol (68):

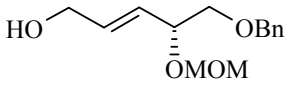


To a suspension of Mg (2.31 g, 96.25 mmol) in anhydrous THF (60 mL) ethyl bromide (7.21 g, 66.14 mmol) was added dropwise under nitrogen atmosphere at 0 ^oC. It is allowed to stir for half an hour at room temperature. To this Grignard reagent, compound **67** (8.5 g, 38.63 mmol) in anhydrous THF (50mL) was added at 0 ^oC. After stirring for 2 h at room temperature, Para formaldehyde (3.5 g) was added to the reaction mixture. The reaction mixture was stirred for another 5 h. The reaction mixture was quenched with saturated NH_4Cl solution and filtered over *Celite* pad. The filtrate was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated to give crude material, which after column chromatography (EtOAc/ hexane, 5:5) provided the pure product **68** (7.2 g, 75%) as a liquid.

$[\alpha]_D^{25}$: –79.6 (c 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz):	δ 7.34-7.27 (m, 5H, ArH), 4.88 (d, *J* = 6.0 Hz, 1H,), 4.61 (d, *J* = 6.7 Hz, 1H), 4.59 (m, 1H), 4.53 (ABq, *J* = 12.5, 18.2 Hz, 2H, C**H$_2$**-OAr), 4.22 (d, *J* = 1.5 Hz, 2H), 3.62 (d, *J* = 5.2 Hz, 2H), 3.37 (s, 3H, CH_3).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 137.6, 128.3, 127.5, 127.4, 94.1, 85.0, 81.1, 73.3, 72.1, 65.1, 55.5, 50.5.
IR(Neat):	3426, 3030, 2929, 1452, 1027 cm^{-1}.
ESIMS:	*m/z* 273 $[M+Na]^+$.

(*E*,4*R*)-5-(benzyloxy)-4-(methoxymethoxy)-2-penten-1-ol (69):

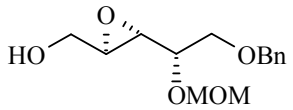


To a stirred suspension of Red-Al (13.31 g, 42.6 mmol) in anhydrous THF (100 mL) at 0 ^oC was added dropwise, a solution of compound **68** (7.1 g, 28.4 mmol) in anhydrous THF (100 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. It was then cooled to 0 ^oC, diluted with ether and quenched with dropwise addition of saturated aqueous Na_2SO_4 (20 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography (EtOAc/ hexane, 5.5:4.5) to afford the compound **69** (6.72 g, 94%) as a viscous liquid.

$[\alpha]_D^{25}$:	–35.8 (*c* 0.65, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.34-7.27 (m, 5H, ArH), 5.89 (dt, *J* = 5.2, 16.6 Hz, 1H), 5.58 (dt, *J* = 1,5, 9.5 Hz, 1H), 4.69 (d, *J* = 6.7 Hz, 1H), 4.58 (d, *J* = 6.7 Hz, 1H), 4.60-4.53 (s, 2H, C**H$_2$**-OAr), 4.25 (ABq, *J* = 6.0, 11.3 Hz, 1H), 4.11 (dd, *J* = 1.5, 5.2 Hz, 1H), 3.55-3.44 (m, 2H), 3.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz):	δ 133.1, 128.3, 128.2, 128.2, 127.7, 127.6, 127.5, 94.0, 75.0, 73.1, 72.7, 62.4, 55.2.
IR(Neat):	3422, 2892, 1451, 1095, 1031 cm^{-1}.
ESIMS:	*m/z* 275 $[M+Na]^+$.

(2*R*,3*S*)-3-[(1*S*)-2-(benzyloxy)-1-(methoxymethoxy)ethyl]oxiran-2-ylmethanol (70):



In a 500 mL two neck round bottomed flask, 70 mL of anhydrous CH_2Cl_2 was added to 4 °A powdered activated molecular sieves and suspension mixture was cooled to –20 °C, Ti(O^{i}Pr)$_4$ (1.5 mL, 5.31 mmol) and L-(+) DIPT (1 g, 4.85 mmol) in anhydrous CH_2Cl_2 (20 mL) were added subsequently with stirring and the resulting mixture was stirred for 30 min at –24 °C. Compound **69** (6.62 g, 26.26 mmol) in anhydrous CH_2Cl_2 (50 mL) was then added and the resulting mixture was stirred for another 30 min at –24 °C followed by addition of TBHP (7.88 mL, 39.40 mmol) and the resulting mixture was stirred at the same temperature for 24 h. It was then warmed to 0 °C, quenched with 4 mL of water and stirred for 1 h at room temperature. After that 30% aqueous NaOH solution saturated with NaCl (10 mL) was then added and the reaction mixture was stirred vigorously for another 30 min at room temperature. The resulting mixture was then filtered through *Celite* rinsing with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purified by silica gel column chromatography (EtOAc/ hexane, 6:4) to afford **70** (6.6 g, 94%) as a viscous liquid.

$[\alpha]_D^{25}$:	+1.0 (*c* 0.8, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 7.36-7.20 (m, 5H, ArH), 4.77 (d, *J* = 6.6 Hz, 1H, CH), 4.67 (d, *J* = 6.4 Hz, 1H, CH), 4.53 (ABq, *J* = 12.0, 14.0 Hz, 2H, C**H$_2$**-OAr), 3.84 (d, *J* = 12.4 Hz, 1H), 3.65-3.51 (m, 4H), 3.36 (s, 3H, CH_3); 3.10 (d, *J* = 2.2

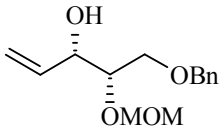
Hz, 1H) 3.02 (d, *J* = 1.32 Hz, 1H), 1.70 (bd s, 1H, OH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.7, 128.3, 127.6, 127.4, 95.7, 75.6, 73.3, 70.0, 61.1, 56.1, 55.5, 55.4.

IR(Neat): 3444, 2897, 1453, 1101, 1031 cm^{-1}.

ESIMS: *m/z* 291 $[M+Na]^+$.

(3*S*,4*S*)-5-(benzyloxy)-4-(methoxymethoxy)-1-penten-3-ol (72):



To a stirred solution of **70** (6.5 g, 24.25 mmol) in mixture of 40 mL of anhydrous ether and 15 mL of anhydrous CH_3CN was added TPP (7.62 g, 29.08 mmol), imidazole (3.3 g, 48.52 mmol) and iodine (4.76 g, 36.33 mmol) at 0 ^oC. The resulting mixture was stirred at room temperature for 30 min. Solids were filtered and washed with ether. The filtrate was extracted with ether, washed with 10% aqueous $Na_2S_2O_3$ solution, water, brine solution and dried over anhydrous Na_2SO_4. The residue was concentrated under reduced pressure and the unstable crude iodo compound **71** was used for further reaction. A solution of compound **71** (8.3 g, 22 mmol) in ethanol (60 mL) was added to zinc dust (18.6 g, 287.0 mmol) in 250 mL round bottom flask. The reaction mixture was stirred at reflux for 1 h and then Et_2O (30 mL) and NH_4Cl (4 g) were added to the reaction mixture at 0 ^oC, allowed to stir at room temperature for 1 h and filtered through bukner funnel-flask setup and the filtrate was concentrated under reduced pressure. Column chromatography (EtOAc/hexane, 3:7) afforded pure product **71** (4.97 g, 90% yield) as a colorless liquid.

$[\alpha]_D^{25}$: +1.4 (*c* 0.9, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42-7.27 (m, 5H, ArH), 5.96-5.82 (m, 1H), 5.37 (dt, *J* = 1.5, 17.3 Hz, 1H), 5.22 (dt, *J* = 1.3, 10.5 Hz, 1H), 4.79-4.71 (m, 2H), 4.54 (ABq, *J* = 11.8, 15.2 Hz, 2H,

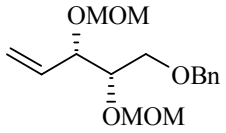
C**H$_2$**-OAr), 4.34-4.26 (m, 1H), 3.74-3.56 (m, 3H), 3.39 (s, 3H), 2.99 (bd s, 1H, OH).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 136.8, 128.3, 127.7, 127.6, 116.7, 96.8, 79.3, 73.4, 72.6, 69.9, 55.7.

IR(Neat): 3448, 2890, 1452, 1103, 1034, 921cm^{-1}.

ESIMS: *m/z* 275 $[M+Na]^+$.

1-([(2*S*,3*S*)-2,3-di(methoxymethoxy)-4-pentenyl]oxymethyl)benzene (73):



To alcohol **72** (4.99 g, 19.44 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 ^oC were added diisopropyl ethylamine (6.68 mL, 51.78 mmol), catalytic DMAP and MOMCl (1.87 mL, 23.22 mmol) successively and the mixture was stirred for 2 h at room temperature, quenched by adding water (10 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 (1 g) and concentrated under vacuum to remove the solvent and the crude residue was purified by column chromatography (EtOAc/ hexane, 2:8) to afford the MOM ether **73** (5.3 g, 92% yield) as colourless oil.

$[\alpha]_D^{25}$: +18.8 (c 1.0, $CHCl_3$)

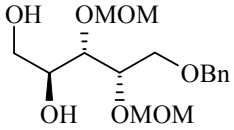
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.25 (m, 5H, ArH), 5.78 (m, 1H), 5.31 (dd, *J* = 2.2, 17.3 Hz, 1H), 5.24 (dd, *J*=3.0, 10.5 Hz,1H), 4.83-4.61 (m, 4H), 4.54 (ABq, *J* = 12.0, 15.1 Hz, 2H, C**H$_2$**-OAr); 4.23 (m, 1H), 3.78 (m, 1H), 3.67-3.48 (m, 2H), 3.36 (s, 3H, CH_3), 3.33 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 134.2, 127.8 127.1, 127.0, 118.1, 96.5, 93.7, 77.7, 76.3,72.9, 69.6, 55.2, 55.1;

IR(Neat): 2891, 1452, 1151, 1033, 919 cm^{-1}.

ESIMS: *m/z* 319 $[M+Na]^+$.

(2*S*,3*S*,4*S*)-5-(benzyloxy)-3,4-di(methoxymethoxy)pentane-1,2-diol (74):



Admix-β (24.59 g) was added to the compound **73** (5.2 g, 17.56 mmol) in 87 mL of ^{t}BuOH and 87 mL of water at 0 ^{o}C. The reaction mixture was stirred at the same temperature for 6 days. After 6 days the reaction mixture was quenched by the addition of saturated solution of Na_2SO_3 (30 mL). After 10 minutes, the reaction was warmed to room temperature and stirred for additional 30 minutes. The reaction contents were transffered to a separatory funnel with 100 mL of EtOAc. The phases were separated, aqueous layer further extracted with EtOAc (3 x 30 mL). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuo. and the residue was purified by silica-gel column chromatography (EtOAc/hexane, 7:3) to afford diol **74** (5.2 g, 90%) as a viscous liquid with diastereoselectivity (9:1) determined by chiral HPLC.

$[\alpha]_D^{25}$: –11.0 (c 1.0, $CHCl_3$).

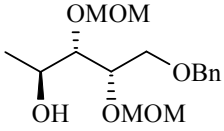
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.21 (m, 5H, ArH), 4.79-4.60 (m, 4H), 4.53 (q, *J* = 12.2, 13.4 Hz, 2H, C**H$_2$**-OAr), 4.03 (t, *J* = 5.4 Hz, 1H), 3.79-3.58 (m, 6H), 3.39 (s, 3H, CH_3); 3.38 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 137.6, 128.3, 127.7, 127.6, 98.4, 97.4, 78.6, 76.4, 73.4, 70.7, 69.4, 63.1, 56.3, 55.9;

IR(Neat): 3380, 2933, 1452, 1153, 1026 cm^{-1}.

ESIMS: *m/z* 353 $[M+Na]^+$.

(2*S*,3*S*,4*S*)-5-(benzyloxy)-3,4-di(methoxymethoxy)pentan-2-ol (76):



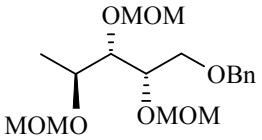
To a stirred solution of diol **74** (5.1 g, 15.45 mmol) in anhydrous Et_3N (4.3 mL, 42.57 mmol) and $SnBu_2O$ (cat) at 0 °C was added *p*-toluenesulfonyl chloride (2.6 g,

13.85 mmol). After the reaction mixture was stirred at 25 °C for 1 h, the reaction was quenched with water (50 mL) and the resultant mixture was then extracted with EtOAc (2 x 50 mL). The extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 (1 g), and concentrated *in vacuo*. The residue was directly used for the next step without purification by column chromatography.

To a stirred suspension of $LiAlH_4$ (1 g, 27.02 mmol) in anhydrous THF (20 mL) at 0 ^oC was added dropwise a solution of compound **75** (6.6 g, 13.63 mmol) in anhydrous THF (30 mL). The reaction mixture was refluxed for 1 h. It was then cooled to 0 ^oC, diluted with ether and quenched with dropwise addition of saturated aqueous Na_2SO_4 (30 mL). The solid material was filtered and washed thoroughly with hot EtOAc (4 x 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 (1 g). The solvent was removed under *vacuo* and the residue was purified by column chromatography (EtOAc/hexane, 4:6) to afford the compound **76** (3.5 g, 82%) as a colorless liquid.

$[\alpha]_D^{25}$:	–0.9 (*c* 0.65, $CHCl_3$)
^1H NMR ($CDCl_3$, 300 MHz):	δ 7.39-7.28 (m, 5H, ArH), 4.83-4.62 (m, 4H), 4.54 (s, 2H, C**H**$_2$-OAr), 4.01-3.94 (m, 1H), 3.93-3.83 (m, 1H), 3.70-3.54 (m, 2H), 3.52-3.44 (m, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 1.62 (br s, 1H, OH), 1.24 (d, *J* = 6.7 Hz, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 137.8, 128.3, 127.7, 127.6, 98.2, 97.2, 83.5, 76.5, 73.4, 69.9, 56.1, 55.9, 19.0.
IR(Neat):	3454, 2952, 1542, 1149, 1028, 915cm^{-1}.
ESIMS:	*m/z* 337 $[M+Na]^+$.

1-[(1*S*,2*S*,3*S*)-4-(benzyloxy)-2,3-di(methoxymethoxy)-1-methylbutyl]oxy-2-propanol (77):



To alcohol **76** (3.4 g, 10.82 mmol) in anhydrous CH_2Cl_2 (30 mL) at 0 ^oC were added diisopropyl ethylamine (3.72 mL, 28.28 mmol), and MOMCl (1.0 mL, 12.42 mmol) successively and the mixture was stirred for 2 h at room temperature, quenched by adding water (10 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 (2 g) and concentrated under vacuum to remove the solvent and the crude residue was purified by column chromatography (EtOAc/ hexane, 3:7) to afford the MOM ether **77** (3.6 g, 93% yield) as colourless oil.

$[\alpha]_D^{25}$: +1.5 (*c* 0.8, $CHCl_3$)

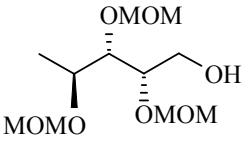
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32-7.27 (m, 5H, ArH), 4.74-4.57 (m, 6H), 4.52 (q, *J* = 12.0, 14.3Hz, 2H, C**H$_2$**-OAr), 3.90-3.74 (m, 3H), 3.63-3.51 (m, 2H, CH_2), 3.37 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 3.33 (s, 3H, CH_3), 1.21 (d, *J* = 6.7 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.0, 128.3, 127.7, 127.6, 97.7, 97.2, 95.1, 79.6, 76.5, 73.3, 73.2, 70.2, 56.0, 55.7, 55.3, 16.3.

IR(Neat): 2934, 2891, 1452, 1150, 917 cm^{-1}.

ESIMS: *m/z* 381 $[M+Na]^+$.

(2*S*,3*S*,4*S*)-4-(2-hydroxypropoxy)-2,3-di(methoxymethoxy)pentan-1-ol (78):

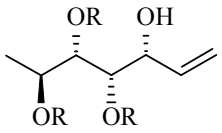


A stirred solution of **77** (3.5 g 9.77 mmol) and 10% Pd/C (75 mg) in anhydrous EtOAc (20 mL), was hydrogenated at 1 atm and at room temperature for 16 h. The reaction mixture was filtered through *Celite* pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 5:5) to give **78** (2.4 g, 95%) as a colorless liquid.

$[\alpha]_D^{25}$: –14.5 (*c* 0.8, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 300 MHz):	δ 4.77-4.61 (m, 6H), 3.94-3.80 (m, 1H), 3.77-3.58 (m, 4H), 3.42 (s, 3H), 3.41 (s, 3H), 3.35 (s, 3H), 1.23 (d, J = 6.0 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 138.0, 128.3, 127.7, 127.6, 97.7, 97.2, 95.1, 79.6, 76.5, 73.3, 73.2, 70.2, 56.0, 55.7, 55.3, 16.3.
IR(Neat):	3460, 2937, 2894, 1130, 1031, 916 cm^{-1}.
ESIMS:	*m/z* 291 $[M+Na]^+$.

(3*R*,4*S*,5*S*,6*S*)-4,5,6-tri(methoxymethoxy)-1-hepten-3-ol (80):



R = MOM

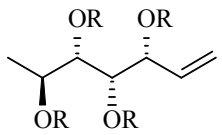
To a stirred solution of oxalyl chloride (1.45 g, 11.41 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C, dry DMSO (2.67 g, 34.23 mmol) was added dropwise. After 30 min, alcohol **78** (2.3 g, 8.58 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 2 h at –78 °C, Et_3N (7.15 g, 70.8 mmol) was added slowly and stirred for 30 min allowing the reaction mixture warm to rt. The reaction mixture was then diluted with water (20 mL) and CH_2Cl_2 (3 X 40 mL). The combined organic layer was washed with water (40 mL), brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the aldehyde **79**, which was directly used for further reaction.

The crude aldehyde **79** (1.57 g, 6 mmol) dissolved in CH_2Cl_2 (30 mL) under argon was added via cannula to a stirred suspension of $MgBr_2$ −Et_2O (3 g, 11.62 mmol) at 0 °C. After stirring for 10 min, the flask was cooled to −78 °C and vinyl magnesium bromide (11.80 mL, 11.80 mmol) purchased from Aldrich as 1.0 M solution in THF) was added slowly at −78 °C and the reaction was stirred further at this temperature for 1 h. The solvent was then removed in vacuo, after which the residue was diluted with CH_2Cl_2 and allowed to warm to 0 °C. Then, the reaction mixture was diluted with saturated aq NH_4Cl and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were

washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Silica gel column chromatography (EtOAc/hexane, 3:7) afforded 1,2 *syn*-isomer **80** (>95% de) as a pale yellow viscous oil.

$[\alpha]_D^{25}$:	–16.1 (*c* 1.0, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 5.97 (m,1H), 5.40 (td, *J* = 1.5,10.5Hz,1H), 5.21 (td, *J* = 1.5, 11 Hz,1H), 4.81-4.64 (m, 6H), 4.34-4.25 (m, 1H), 3.90 (m,1H), 3.74 (m, 1H), 3.63 (ABq *J* = 4.7, 9.6 Hz,1H), 3.44 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 3.38 (s, 3H, CH_3), 1.27 (d, *J* = 6.6 Hz, 3H, CH_3).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 137.4, 116.8, 98.5, 97.6, 95.2, 82.5, 79.8, 72.7, 71.8, 56.1, 56.0, 55.4, 16.4.
IR(Neat):	3451, 2932, 1150, 1029, 918 cm^{-1}.
ESIMS:	*m/z* 317 $[M+Na]^+$.

(1*S*,2*R*)-2-(acetyloxy)-1-[(1*S*,2*S*)-1,2-di(acetyloxy)propyl]-3-butenyl acetate (82):

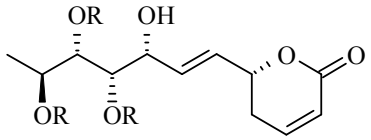


R = Ac

To a stirred solution of compound **80** (0.6 g, 2.04 mmol) in a mixture of MeOH (10 mL) and CH_3CN (10 mL) was added 3 N HCl (cat.) under N_2, then the mixture was stirred at room temperature for 8 h. The mixture was quenched with solid $NaHCO_3$ (0.5 g) and filtered, the solvent was removed under reduced pressure and the crude tetraol **81** was directly used for next step without further purification. Anhydrous Et_3N (1.2 g, 11.80 mmol), Ac_2O (0.75 mL, 7.35 mmol), and DMAP (20 mg) were added to a solution of tetraol **81** (0.24 g, 1.48 mmol) in anhydrous CH_2Cl_2 (10 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (ethyl acetate/hexane, 2:8) to afford **82** (0.43 g, 90%) as a colorless liquid.

$[\alpha]_D^{25}$:	–3.2 (*c* 1.0, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 5.74 (m, 1H,) 5.38-5.32 (m, 2H), 5.30-5.28 (m, 1H), 5.21-5.15 (m, 1H), 5.09 (t, *J* = 5.2 Hz, 1H), 5.01 (t, *J* = .6.0 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 170.0, 169.8, 169.7, 169.5, 131.2, 119.7, 72.6, 72.0, 71.0, 67.4, 20.9, 20.7, 20.6, 20.5, 16.3.
IR(Neat):	2937, 1748, 1373, 1223, 1031 cm^{-1}.
ESIMS:	*m/z* 353 $[M+Na]^+$.

(6*R*)-6-[(*E*,3*R*,4*S*,5*S*,6*S*)-3-hydroxy-4,5,6-tri(methoxymethoxy)-1-heptenyl]-5,6-dihydro-2*H*-2-pyranone (85):



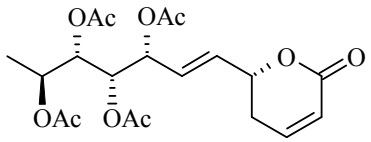
R = MOM

Grubbs' second generation catalyst (90 mg, 0.11 mmol, 10 mol%) was dissolved in 5 mL of CH_2Cl_2 and was added dropwise to a solution of the compound **80** (0.6 g, 2.04 mmol) and vinyl lactone **83** (0.7 g, 5.6 mmol) in 4 mL of CH_2Cl_2 at 0 ^oC. After completion of addition, reaction mixture was allowed to stir for 0.5 h at 70 ^oC. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc/hexane, 7:3) to afford the pure product **85** exclusively (0.56 g, 86% yield) as a colorless liquid.

$[\alpha]_D^{25}$:	+5.2 (*c* 0.8, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 6.89 (m,1H), 6.10-5.93 (m, 3H), 4.98 (m, 1H), 4.82-4.63 (m, 6H), 4.22 (m, 1H), 3.88 (dt, *J* = 5.5, 24.2 Hz, 1H), 3.71 (dt, *J* = 3.7, 30.7 Hz, 1H), 3.64 (m, 1H), 3.43 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 2.48 (m, 2H), 1.28 (d, *J* = 6.5 Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 75 MHz):	δ 163.8, 144.4, 132.6, 128.7, 121.6, 98.3, 97.7, 95.2, 82.3, 79.7, 76.3, 73.5, 72.7, 56.1, 55.9, 55.4, 29.4, 16.4.
IR(Neat):	3444, 2930, 1722, 1246, 1029, 916 cm^{-1}.
ESIMS:	*m/z* 413 $[M+Na]^+$.

(1*S*,2*R*,3*E*)-2-(acetyloxy)-1-[(1*S*,2*S*)-1,2-di(acetyloxy)propyl]-4-[(2*R*)-6-oxo-3,6-dihydro-2*H*-2-pyranyl]-3-butenyl acetate Anamarine (17):



To a stirred solution of compound **85** (0.4 g, 1.02 mmol) in a mixture of MeOH (5 mL) and CH_3CN (5 mL) was added 3 N HCl (cat.) under N_2, and then the mixture was stirred at room temperature for 8 h. The mixture was quenched with solid $NaHCO_3$ (0.2 g) and filtered, the solvent was removed under reduced pressure and the the crude lactone tetraol **86** was directly used for next step without further purification. Anhydrous Et_3N (0.4 g, 4.0 mmol), Ac_2O (0.2 mL, 2 mmol), and DMAP (5 mg) were added to a solution of lactone tetraol **86** (0.1 g, 0.38 mmol) in anhydrous CH_2Cl_2 (10 mL) under nitrogen atmosphere at room temperature. The mixture was stirred at room temperature for 30 min. The solvent was removed under reduced pressure, and the mixture was purified by silica gel column chromatography (ethyl acetate/hexane, 3:7) to afford **17** (0.1 g, 80%) as a white solid.

M.p:	109-111 ^oC
$[\alpha]_D^{25}$:	+17.8 (*c* 0.3, $CHCl_3$)
^{1}H NMR ($CDCl_3$, 300 MHz):	δ 6.88 (ddd, *J* = 3.5, 5.2, 9.9 Hz, 1H), 6.05 (ddd, *J* = 1.7, 1.7, 9.9 Hz, 1H), 5.88-5.74 (m, 2H), 5.36 (dd, *J* = 5.2, 7.2 Hz, 1H), 5.30 (dd, *J* = 3.5, 7.2 Hz, 1H), 5.17 (dd, *J* = 3.5, 7.0 Hz,1H), 4.96 (m, 1H) 4.90 (dq, *J* = 6.4, 6.4 Hz, 1H), 2.45 (m, 2H), 2.11 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.06 (s, 3H, CH_3),

	2.03 (s, 3H, CH_3), 1.17 (d, J = 6.4 Hz, 3H, CH_3).
^{13}C NMR ($CDCl_3$, 75 MHz):	δ 170.0, 169.8, 169.7, 169.5, 163.4, 144.5, 133.0, 125.6, 121.5, 75.9, 71.9, 71.5, 70.4, 67.5, 29.4, 21.0, 20.9, 20.8, 20.7, 15.9.
IR(Neat):	2925, 1739, 1374, 1023, 974 cm-1.
HRMS (ESI):	Calcd for $C_{20}H_{26}O_{10}Na$ $[M+Na]^+$: 449.1423; Found: 449.1434.

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LIST OF PUBLICATIONS

1. Synthesis of the C38-C54 Spiro ketal Segment of Segment of halichondrin B. J. S. Yadav,* **C. Nagendra Reddy**, G. Sabitha. ***Tetrahedron Lett.*** **2012** (*Just accepted*).
2. A Concise and efficient Synthesis of (5*R*,7*S*)-Kurzilactone and Its (5*S*,7*R*)-Enantiomer by the Mukaiyama Aldol Reaction. Gowravaram Sabitha,* Peddabuddi Gopal, **C. Nagendra Reddy**, Jhillu S. Yadav. ***Synthesis*** **2009**, 3301-3304.

3. First stereoselective synthesis of synargentolide A and revision of absolute stereochemistry. Gowravaram Sabitha, * Peddabuddi Gopal, **C. Nagendra Reddy**, J. S. Yadav. ***Tetrahedron Lett.*** **2009**, *50*, 6298-6302.

4. Stereoselective total synthesis of (+)-anamarine via cross-metathesis protocol. Gowravaram Sabitha,* **C. Nagendra Reddy**, Peddabuddi Gopal, J. S. Yadav. ***Tetrahedron Lett.*** **2010**, *51*, 5736-5739.

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6. Stereoselective total synthesis of (+)-strictifolione and (6*R*)-6-[(4*R*,6*R* -4,6-dihydroxy-10-phenyldec-1-enyl]-5,6-dihydro-2H-pyran-2- one by Prins reaction and olefin cross-metathesis. Gowravaram Sabitha,* Narjis Fatima, Peddabuddi Gopal, **C. Nagendra Reddy**, Jhillu S. Yadav. **Tetrahedron*: Asymmetry*** **2009**, *20*, 184-191. **(Top 25 hottest articles)**

7. Stereoselective total synthesis of hyptolide. Gowravaram Sabitha,* Atla Raju, **Chintam Nagendra Reddy**, J. S. Yadav. **2012** (*manuscript under preparation*).