Ti(III)–MEDIATED EPOXIDE OPENING REACTIONS TO CONSTRUCT FIVE–MEMBERED CARBOCYCLES, STUDIES DIRECTED TOWARD THE SYNTHESIS OF RHIZOPODIN AND THE TOTAL SYNTHESIS OF DEOXOCASSINE

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
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BY
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Dedicated To

My Beloved Family Members

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. Tushar Kanti Chakraborty, Director, Central Drug Research Institute, CSIR, Lucknow–226 001, India. Formerly, Director grade scientist & Head, Organic–III division, Indian Institute of Chemical Technology, CSIR, Hyderabad. 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, **MIDDE SREEKANTH**

Date: 30th March, 2011. **(Candidate)**

CERTIFICATE

I hereby certify that the entire work embodied in this thesis has been carried out by **Mr. Midde Sreekanth** under my co–supervision at Indian Institute of Chemical Technology, Hyderabad. I state that no part or full has been submitted elsewhere for any degree or diploma.

Dr. DHEVALAPALLY B. RAMACHARY
(Co–supervisor)

DEAN
SCHOOL OF CHEMISTRY
UNIVERSITY OF HYDERABAD

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Midde Sreekanth

GENERAL REMARKS

1. All reactions were carried out in oven or flame–dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted.
2. Commercially available compounds were used as received unless otherwise indicated.
3. All evaporations were carried out under reduced pressure on Buchi rotary evaporator or Heidolph rotary evaporator below 45 $^{\circ}$C.
4. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck Kiesel gel 60 F254 plates with UV light, iodine, 7% ethanolic phosphomolybdic acid–heat and 2.5% methanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)–heat as developing agents.
5. Acme's silica gel 60–120 mesh or 100–200 mesh was used for flash column chromatography.
6. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
7. IR spectra were recorded as neat liquids using ALPHA FT–IR Spectrometer (Bruker).
8. NMR spectra were recorded using $CDCl_3$ as solvent on UNITY–INOVA–500 MHz Varian, Avance–300 MHz Bruker, UNITY–400 MHz Varian spectrometers using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scale.
9. Multiplicities of ^{1}H NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), ABq (AB quartet), br (broad), m (multiplet, for unresolved lines), br s (broad singlet) etc.
10. ^{13}C NMR spectra were recorded on 100 and 75 MHz spectrometers with complete proton decoupling.
11. Mass spectra were recorded on a Micromass VG Autospec–M and Micromass QuattroLC mass spectrometers. Mass spectra were obtained under electro spray ionisation (ESI).

12. High Resolution Mass Spectra were measured using above mentioned mass spectrometers at 5 or 7K resolution using polyethylene glycol as an internal reference compound.
13. Accurate mass measurement was performed on Q STAR XL Hybrid mass spectrometer (Applied Biosystems, USA).
14. Optical rotations were measured with a digital Horiba–SEPA–300 polarimeter.
15. All solvents and reagents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry or Purification of Laboratory Chemicals (3^{rd} Edition) by Perrin and Armarego.

CONTENTS

ABBREVIATIONS

Ac	:	Acetyl
AIBN	:	Azobisisobutyronitrile
aq.	:	Aqueous
Ar	:	Aryl
Bn	:	Benzyl
Boc	:	*tertiary*– Butyloxycarbonyl
^{n}Bu	:	*normal*–Butyl
^{t}Bu	:	*tertiary* –Butyl
Bz	:	Benzoyl
Calcd	:	Calculated
(*R*)–B–Me–CBS	:	(*R*)–2–Methyl–CBS–oxazaborolidine
Cbz	:	Benzyloxycarbonyl
CNS	:	Central nervous system
Cp	:	Cyclopentadienyl
m–CPBA	:	*meta*–Chloroperbenzoic acid
CSA	:	Camphor–10–sulfonic acid
DAST	:	Diethylaminosulfur trifluoride
DDQ	:	2,3–Dichloro–5,6–dicyanobenzoquinone
DEAD	:	Diethyl azodicarboxylate
DIBAL–H	:	Diisobutylaluminium hydride
DIPEA	:	*N*,*N*–Diisopropylethylamine
DIPT	:	Diisopropyl tartrate
DMAP	:	4–Dimethylaminopyridine
DMF	:	*N*,*N*–Dimethylformamide
DMP	:	Dess–Martin periodinane
DMSO	:	Dimethyl sulfoxide
DNA	:	Deoxyribonucleic acid
DQF–COSY	:	Double quantum filtered correlation spectroscopy
dr	:	Diastereomeric ratio

ESI	:	Electrospray ionization
ESI–MS	:	Electrospray ionization mass spectrometry
ESR	:	Electron spin resonance
Et	:	Ethyl
Et_3N	:	Triethylamine
EtOH	:	Ethyl alcohol
EWG	:	Electron withdrawing group
h	:	Hour
HRMS	:	High resolution mass spectrometry
HSQC	:	Heteronuclear single quantum coherence
Hünig's base	:	*N*,*N*–Diisopropylethylamine
Hz	:	Hertz
IR	:	Infrared
2,6–lutidine	:	2,6–Dimethylpyridine
Me	:	Methyl
min	:	Minute(s)
MeOH	:	Methyl alcohol
Ms	:	Methanesulfonyl (mesyl)
4 Å MS	:	4 Å Molecular sieves
MHz	:	Megahertz
NaHMDS	:	Soduim bis(trimethylsilyl)amide
NMR	:	Nuclear magnetic resonance
nOe	:	Nuclear overhauser effect
NOESY	:	Nuclear overhauser effect spectroscopy
Ph	:	Phenyl
PMB	:	*para*–Methoxybenzyl
PNBA	:	*para*–Nitrobenzoic acid
^{i}Pr	:	*iso*–Propyl
quant.	:	Quantitative
Red–Al	:	Sodium bis(2–methoxyethoxy)aluminium hydride
rt	:	Room temperature

R_f	:	Retardation factor
TBAF	:	Tetra–*n*–butylammonium fluoride
TBAI	:	Tetra–*n*–butylammonium iodide
TBDPSCl	:	*tertiary*–Butyldiphenylsilyl chloride
TBHP	:	*tertiary* –Butylhydroperoxide
TBSCl	:	*tertiary*–Butyldimethylsilyl chloride
TBSOTf	:	*tertiary* –Butyldimethylsilyl trifluoromethanesulfonate
TESOTf	:	Triethylsilyl trifluoromethanesulfonate
THF	:	Tetrahydrofuran
THP	:	Tetrahydropyran
TIPSOTf	:	Triisopropylsilyl trifluoromethanesulfonate
TMS	:	Tetramethylsilane
p–Tol	:	*para*–Tolyl
TPP	:	Triphenylphosphine
Ts	:	*para*–Toluenesulfonyl

SYNOPSIS

CHAPTER–I

CHAPTER–II

CHAPTER–III

LIST OF PUBLICATIONS

1. Ti(III)–mediated opening of 2,3–epoxy alcohols to build five–membered carbocycles with multiple chiral centres

   Midde Sreekanth, Gavinolla Pranitha, Bharatam Jagadeesh and Tushar Kanti Chakraborty*

   Tetrahedron Lett. **2011**, ***52*****,** 1709–1712.

2. Synthetic studies towards potent cytostatic macrolide rhizopodin: stereoselective synthesis of the C16–C28 fragment

   Tushar Kanti Chakraborty,* **Midde Sreekanth** and Kiran Kumar Pulukuri

   Tetrahedron Lett. **2011,** *52*, 59–61.

3. Stereoselective synthesis of 2,3,6–trisubstituted piperidine: application in the synthesis of (+)–deoxocassine

   Tushar Kanti Chakraborty,* **Midde Sreekanth** and Gangarajula Sudhakar

   (Manuscript under preparation)

4. Studies directed towards the synthesis of rhizopodin: stereoselective synthesis of the C1–C15 fragment

   Tushar Kanti Chakraborty,* Kiran Kumar Pulukuri and **Midde Sreekanth**

   Tetrahedron Lett. **2010**, *51*, 6444–6446.

5. Studies directed towards the synthesis of antascomicin A: stereoselective synthesis of the C22–C34 fragment of the molecule

   Tushar Kanti Chakraborty,* Bajjuri Krishna Mohan and **Midde Sreekanth**

   Tetrahedron Lett. **2006**, *47*, 5003–5005.

6. Studies directed towards the total synthesis of lycoperdinosides: stereoselective construction of the C1–C9 and C10–C21 segments of the molecules

   Tushar Kanti Chakraborty,* Rajib Kumar Goswami and **Midde Sreekanth**

   Tetrahedron Lett. **2007**, *48*, 4075–4078.

ABOUT THE AUTHOR

The author, **Mr. Midde Sreekanth*** was born on 16th April, 1984 at Sathupally, Khammam Dist (A.P.), India. He obtained his B. Sc. degree in April, 2003 from Santhinikethan Degree College, Sathupally affiliated to Kakatiya University, Warangal (A.P.), India. Then he moved to University of Hyderabad, Hyderabad for pursuing M. Sc. degree at School of Chemistry and obtained the same in April, 2005. At the end of M.Sc. programme, he worked in the area of Baylis-Hillmann chemistry with Prof. D. Basavaiah as part of course curriculum. After that, he has joined as a junior research fellow with Dr. Tushar Kanti Chakraborty (at present, Dr. Tushar Kanti Chakraborty is the Director of Central Drug Research Institute, CSIR, Lucknow, India.) at Indian Institute of Chemical Technology, Hyderabad in August, 2005 for doctoral research. His main research interests include the total synthesis of natural products. He has been as an external Ph.D. student of School of Chemistry, University of Hyderabad under the co–supervision of Dr. D. B. Ramachary since 2007.

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INTRODUCTION

Stereoselective synthesis based on free readicals is a challenging task and an attractive scenario in the organic chemistry.[1] Radical chemistry got its importance during the development of chain reactions.[2] High degree of functional group tolerance is the key feature of these reactions. Since radicals are usually stable under protic conditions, alcohols or even water can, in principle, be used as solvents in radical chemistry. Consequently, protic functional groups do not need protection. Understanding of the principles of the kinetic and thermodynamic behavior led to the synthetic applications of the radical reactions.[3] The use of chain reactions has resulted in number of very impressive total syntheses of natural products as shown in Scheme 1.[4] The characteristic features of free radicals can be deduced from ESR data.[5] The course of some radical reactions can be understood by theoretical means.[6]

Scheme 1

However, because the crucial intermediates are free radicals, no influence of the ligand sphere of the reagent generating the radical on the selectivity of the reaction is usually observed. These transformations are, therefore, classical examples of substrate controlled reactions. An alternative approach to radical chemistry is constituted by controlling the course of the radical reaction by a suitably designed reagent both during radical generation and the ensuing transformation of the metal–bound radical. This concept of reagent control has been applied with excellent success in organometallic chemistry and in catalysis.[7] So far, successful application of this approach to radical chemistry has been rare.[8] The purpose of this work is to extend these novel emerging concepts in C–C and C–H bond forming reactions. Metal–initiated reactions, leading to transformations of free radicals, will not be treated because no metal bound radicals are obtained like vitamin B_{12}–initiated reactions[9] and cobaloxime chemistry.[10] The recently described living radical polymerizations initiated by well–designed metal complexes[11] are also thought to proceed

via chain reactions of free radicals. The selectivity determining step of allylic oxidations catalyzed by chiral copper complexes is thought to proceed through an organocopper(III) reagent.[12] Even though C–H activation by manganese porphyrins,[13] DNA cleavage by metal complexes, e.g. bleomycin,[14] and DNA foot–printing,[15] the radicals formed there have not been used in C–C bond forming reactions. In principle, reagent control can be exercised at different stages in a radical reaction.

(a) The first step in the series of transformations of a radical reaction is constituted by the generation of the radical from a suitable precursor. The usual selectivities of this generation, e.g. by electron transfer, can be controlled by the electron transfer reagent and its ligand sphere. Clearly, the radical precursor needs to have a functional group that allows for binding of the reagent in close proximity of the newly generated radical prior to its formation.

(b) In the subsequent transformation of the radical, the selectivities of the reaction, e.g., addition to carbon–carbon multiple bonds, should, in principle, also be amenable to reagent control if the metal complex remains bound to the radical.

(c) In the case of a free radical reaction, reagent control is possible if the radical or the radical trap is complexed by a carefully designed reagent. The stereochemical course of the following transformation is thus amenable to reagent control by the metal and its ligand. Metal–initiated radical reactions with suitable radical precursors allow for reagent control in both of the above–mentioned two points, a and b. Although these radical reactions have been applied to demanding synthetic reactions with great success for some time,[16] attempts to influence the usual selectivities by ligand variations have appeared in the literature only recently. The focus will be on the epoxide–containing molecules as radical precursors for reagent control in radical chemistry.

There have been many reports in recent years on the radical mediated opening of epoxides using Ti(III) reagents and its application in the synthesis of many natural products.[17] The reaction reported in 1988[18] was extended later to various 2,3–epoxy alcohols that led to the development of a facile method for the synthesis of chiral allylic alcohols.[19] Interestingly, when the similar reaction was carried out in our laboratory for an extended period of time, a different class of products, namely, chiral 1,3–diols, were obtained from both di– and trisubstituted 2,3–epoxy alcohols.[20] This was successfully

employed to construct the 1,3–diol moieties of many polyketide natural products. The fact that even in this radical–induced epoxide ring–opening reaction of the trisubstituted 2,3–epoxy alcohols excellent diastereoselectivity was observed in the hydrogen abstraction step, resulting in the chiral induction in the 2–position, prompted us to investigate the stereoselection in the quenching of the intermediate radicals with other trapping agents. It was described[27] that during the opening of trisubstituted epoxy alcohols **3** the radical intermediates **3a** could be successfully trapped by using radical quencher to prepare 1,3–diol **4** with chiral quaternary carbon centers in the C2–position stereoselectively, especially 1,3–*syn* diols and in good yields (Scheme 2).

Scheme 2. Synthesis of quaternary chiral centres

A general strategy of the methodology described for 2–methlyl–1,3–diol framework is shown in scheme 3. The advantage of this method is that among the four possible diastereomers **5**–**8** of the 2–methlyl–1,3–diol frame work, stereoselectively **5**–**7** can be synthesized *via* the opening of epoxy alcohols **9**–**12**. Both *syn*– and *anti*–epoxy alcohols, **9** and **10**, respectively, on epoxide ring opening with $Cp_2Ti(III)Cl$ should give *syn,syn*–diol **5** as the major product, whereas the products from epoxy alcohols **11** and **12** depend on the relative sizes of R_1 and R_2. When R_1 is bigger than R_2, the major product is the *anti,syn*–diol **6**. With smaller R_1, the *syn,anti*–product **7** predominates. Unlike the classical S_N2–type hydride opening of epoxides where exclusive diastereoselectivity is observed, this radical mediated reaction was feared to lead to the epimerization of the radical bearing center. However, excellent diastereoselectivity was observed during the hydrogen abstraction process. This was attributed to the possibility of the reaction going *via* six–membered cyclic Ti(IV)–intermediate, where the stereochemistries at C_1 and C_3 and the sizes of the R_1 and R_2 were deciding factors for the observed facial selectivity.

Scheme 3. Radical mediated opening of trisubstituted epoxy alcohol

For the 1,3–*syn*–diol substrates **5** originating from the epoxides **9** and **10**, the cyclic six membered intermediate **I** (Figure 1) takes a chair type conformation where the approach of the hydrogen atom is antiperiplanar to the α–C–O bond which, having the lowest σ^* orbital energy, occupies, in the reactive conformer, a position eclipsing the singly occupied *p*–orbital at the radical center enabling maximum overlap, lowering the energy of the *p*–orbital and consequently minimizing the free
energy of activation for the reaction.

Figure 1. Transition state models for epoxide opening reactions

The 1,3–*anti*–diols (**6** and **7**) resulting from the epoxides **11** and **12**, on the other hand, come from a twist–boat conformation **II** (Figure 1) where the sizes of R_1 and R_2 decide the stereochemical outcome of the reaction. In fact, it is the product stability here, which probably decides the course of the reaction. The C_2–methyl possibly takes a position where it is closer to the smaller one of R_1 and R_2 with two dihedral angles of about 90 and 30 degrees.

Significant applications of this method for the synthetic studies of natural products by Chakraborty *et al*:

Synthesis of highly substituted tetrahydropyrans[21]

The salient feature of this strategy is the facile 6–*exo* S_N2 type ring closure reaction mediated by different hydroxyl groups present in the acyclic precursor **A**. By carefully choosing the requisite nucleophilic oxygen and a suitable leaving group at δ–position, various tetrahydropyran frameworks **13–17** were constructed as shown in scheme 4. For the synthesis of the key building block **A**, chiral centers C_3 and C_4 were subsequently fixed by applying $Cp_2Ti(III)Cl$ radical–mediated epoxide ring opening reaction over the compound **18**.

Scheme 4

Tetrahydropyrans **19** and **21** were synthesized from a common intermediate **20**, produced from **23**, consisting of 2–methyl–1,3–diol moiety which in turn was prepared from either of the *syn*–epoxy alcohol **22** or *anti*–epoxy alcohol **24** *via* a Ti(III) radical–mediated epoxide ring opening reaction (Scheme 5).

Scheme 5

Total synthesis of (+)–conagenin

Total synthesis[22] of low molecular weight immunomodulator (+)–conagenin (**30**) has been accomplished by the application of Ti(III) mediated epoxide opening reaction over the epoxy alcohol **33** as one of the prime steps (Scheme 6).

Scheme 6. Stereoselective total synthesis of (+)–conagenin

Total synthesis of clavosolide A

Scheme 7. Stereoselective total synthesis of clavosolide A

Total synthesis[23] of the C_2–symmetric macrolide clavosolide A (**25**) was relied on the synthesis of the functionalized THP ring **28** which in turn was achieved from the epoxy alcohol **29** that involved a crucial Ti(III) mediated epoxide opening reaction (Scheme 7).

Total synthesis of stevastelin B3

Ti(III) mediated epoxide opening reaction of the 2,3–epoxy alcohol **35** delivered the diol **36** which was further transformed to get stevastelin B3 (Scheme 8).[24]

Scheme 8. Total synthesis of stevastelin B3

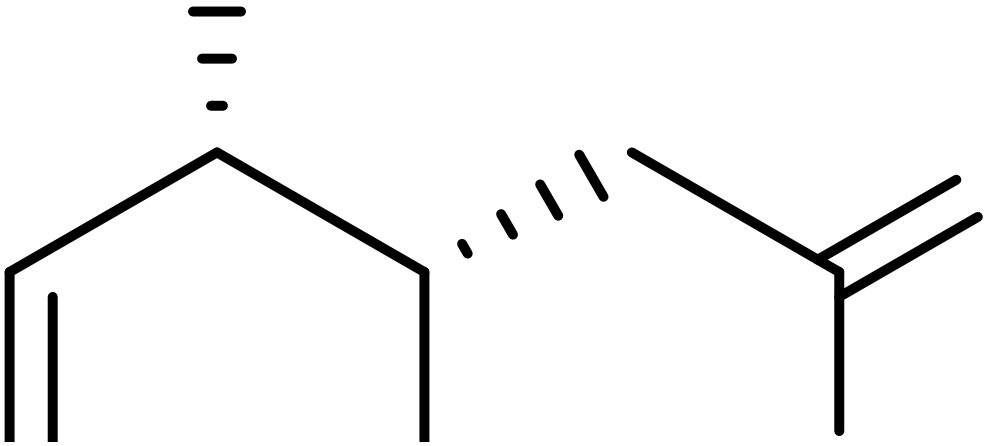
Synthetic studies of penifulvin

Treatment of the epoxy alcohol **41** with Ti(III) radical produced a bicyclic motif **40** which was further manipulated to intermediate **39**. This intermediate can be further transformed to penifulvin D (Scheme 9).[25]

Scheme 9. Synthetic studies of penifulvin D

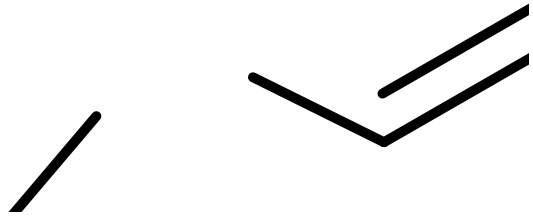
(+)–Sch 642305

Formal total synthesis[26] of (+)–Sch 642305 (**43**) is based on the crucial epoxide opening reaction of the intermediate **46** to get the cyclohexane system **45** and was transformed to the alcohol **44**, an advanced intermediate in the total synthesis of (+)–Sch 642305 (Scheme 10).



Scheme 10. Formal total synthesis of (+)–Sch 642305

Synthesis of oxacycles, azacycles and carbocycles[27]



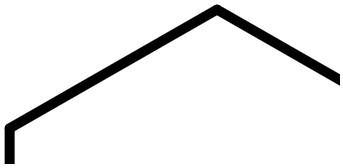
Scheme 11. Synthesis of oxacycles, azacycles, carbocycles

As described earlier, quenching of the generated radical either by external *α,β*–unsaturation or by proton abstraction lead to the chiral 1,3–diols. Further studies in this area lead to various oxacycles, azacycles and 6–membered carbocycles as shown in scheme 11 where the generated intermediate radical was being trapped intramolecularly with suitably placed *α,β*–unsaturation.

Thus conceptually five–membered carbocycles can be synthesized from 2,3–epoxy alcohols **48** (X = CH_2, n = 1) *via* a similar sort of Ti(III) mediated reaction. And our interest is to make the highly functionalized five–membered carbocycles with multiple chiral centres where the carbocyclization has been triggered by a Ti(III) mediated epoxide opening reaction followed by intramolecular trapping of the generated radical with suitably placed unsaturation.

Contemporary radical approaches to functionalized five–membered carbocycles:

Tributyltin hydride is among the most popular reagents[28] to conduct free–radical reactions. It is mild and selective, so carbonyl groups and alcohols do not need to be initially protected. The tributyltin hydride induced intramolecular cyclization reaction of unsaturated ketone[29] moiety present in compound **50** with electronically deficient olefin resulted in the formation of functionalized cyclopentanes **51**, bearing two synthetically useful side arms for further elaboration (Scheme 12).



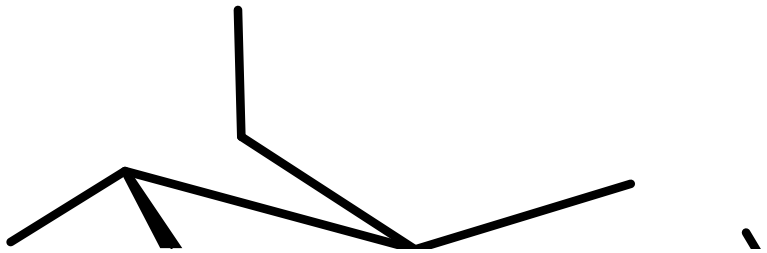
Scheme 12

An efficient synthesis of highly substituted cyclopentane derivatives **54** has been achieved by radical cyclization of modified Baylis–Hillman adducts **53**. Tributyltin hydride–mediated radical step has been performed in benzene in the presence of AIBN, and the products **54** were obtained selectively *via* the 5–*exo*–*trig* mode of cyclization in excellent yields (Scheme 13).[30]

Scheme 13

An enantioselective construction of the cyclopentane moiety of clavulactone **61** from D–glucose **55** has been reported. As a key step, the radical–mediated cyclization of

thioesters has been achieved in high yield with tributyltin/AIBN (Scheme 14).[31] The cyclopentane **60** was obtained from **59** as a mixture of isomers, while starting from derivative **56** with cyclic acetal–protected 1,3–dihydroxyl functionality, the product **57** was isolated predominantly with high selectivity.



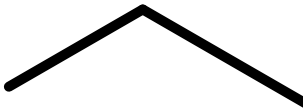
Scheme 14

Phenyl selenides play a prominent role in the development of radical cyclization reaction. A special feature of the group as a source of carbon radicals is that it is able to withstand a very wide range of conditions and can even tolerate the presence of strong bases. The bicyclic products **63–65** have been obtained by a sequential application of two powerful bond–forming processes, ring–closing metathesis and radical cyclization.[32] The radical step (Scheme 15) has been performed under standard conditions with phenyl selenides **62**, and it was established that the PhSe–group served as a very convenient radical source, which could be introduced at an early stage in synthetic routes.

Scheme 15

Samarium diiodide is a powerful single electron transfer agent, which is extensively used for C–C bond formation reactions. A short and concise synthesis of the cyclopentane segment of jatrophane diterpene kansuinine A (**69**) from commercially

available chiral hydroxyester **66** has been reported (Scheme 16).[33] As a key construction method, a SmI_2–mediated cyclization of *δ*–iodoester **67** has been employed, and the fully functionalized cyclopentane framework **68** was obtained with excellent stereocontrol.

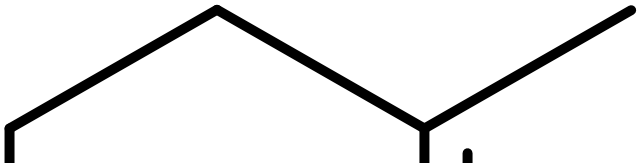


Scheme 16

A series of *cis*–1,3–cyclopentanediols **71–72** has been prepared by samarium diiodide–promoted epoxide ring–opening/ketyl olefin cyclization sequence from *α,β*–epoxy ketones **70** (Scheme 17).[34] It has been shown that the relative stereochemistry could be controlled at three stereocenters in the cyclization product. In all cases, complete selectivity for *cis*–1,3–diols has been achieved, while the diastereoselectivity at the second newly formed stereocenter was found to be substrate dependent.

Scheme 17

The Ti(III)–catalyzed radical cyclizations of epoxypolyprenes have been reported. It has been found that the presence of an *α,β*–unsaturated ester caused a change in the regioselectivity on the closing of the second cycle. Thus, the isomeric 5–*exo*–*trig* cyclization products **74** have been obtained from epoxyalkene **73** in the presence Cp_2TiCl as an easily separable mixture with **75** as the later was quantitatively transformed into a bicyclic derivative during the chromatography separation on silica gel (Scheme 18).[35]



Scheme 18

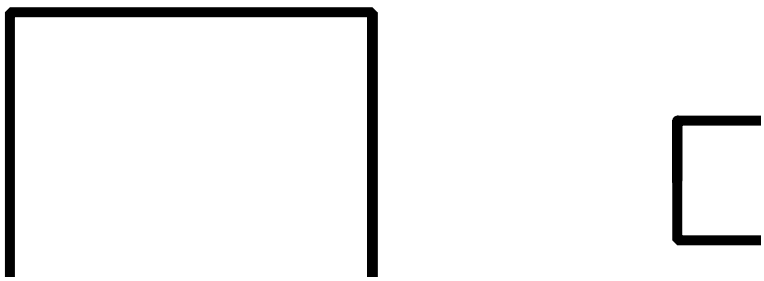
PRESENT WORK

The successful application of Ti(III) mediated epoxide opening reaction for the synthetic studies of several biologically active natural products, various oxacycles, azacycles and carbocycles prompted us to develop a strategy for the synthesis of highly functionalized five membered carbocycles (**76**) which are integral part of several bilogically active natural products (Figure 2).[36]

Figure 2

For the construction of fully functionalized five membered carbocycles (**76**) with mulitiple chiral centres, *via* a Ti(III) mediated epoxide opening reaction, we have envisioned that various 2,3–epoxy alcohols **83A–D** with in–built α,β–unsaturation are the suitable candidates which in turn can be prepared by applying Sharpless' kinetic resolution[37] method on allylic alcohols **84A–D** (Scheme 19). These allylic alcohols could be prepared from aldehydes **85a–b** by the application of successive Wittig olefination[38]

and silyl deprotection reactions. These aldehydes can be obtained from the propargylic alcohols **86a–b** which in turn could be prepared from commercially available 4–pentyn–1–ol **87**. Presence of trisubstituted unsaturation as shown in **83B**,**D** can provide five–membered carbocycles with additional methyl centre at the side arm.



Scheme 19. Retrosynthetic analysis

RESULTS AND DISCUSSION

We have started our synthesis from the readily available 4–pentyn–1–ol **87** which was protected by using the known[39] procedure, as PMB ether (**88**) in 85% yield by reacting with 1 eq of PMBBr and 1 eq of NaH in THF at 0 °C to rt for 12 h (Scheme 20). Successful protection was confirmed by the presence of aromatic signals at δ 7.25–7.17, 6.85–6.79 in the ^{1}H NMR spectrum and a signal at *m/z* 227 in the ESI mass spectrum that corresponds to $[M+Na]^+$. Treatment of the anion, generated[40] from alkyne **88** by reacting with ^{n}BuLi, with acetaldehyde at –78 °C in THF for 10 min produced the propargylic alcohol **86a** in 90% yield. The ^{1}H NMR spectrum showing the doublet signal at δ 1.39 that corresponds to the methyl group derived from acetaldehyde was the prime support for the product formation and the rest of the protons were being observed at their respective chemical shift values. Presence of a signal at *m/z* 271.1300 in the high resolution ESI mass spectrum that corresponds to $[M+Na]^+$ (calcd 271.1310) was also an additional support for the effective nucleophilic addition.

Scheme 20

Careful reduction of the propargylic alcohol **86a** with Red–Al[41] in ether at 0 °C to rt for 4 h afforded the allylic alcohol **89** in 94% yield. Reduction was supported by the appearance of signals corresponding to olefinic protons at δ 5.66–5.44 in the ^{1}H NMR spectrum of compound **89** whilst rest of the protons were being resonated at their respective chemical shift values. Appearance of a signal at *m/z* 273.1464 in the high resolution ESI mass spectrum that corresponds to $[M+Na]^+$ (calcd 273.1466) was also in good agreement with the result obtained. Protection of the hydroxyl group present in **89** was accomplished by reacting with 1.1 eq TBSOTf and 1.5 eq of 2,6–lutidine[42] in CH_2Cl_2 at 0 °C for 10 min to get the silyl ether **90** in 90% yield. Appearance of signals at δ 0.89 and 0.10–0.01 integrating for 9 and 6 protons respectively in the ^{1}H NMR spectrum of compound **90** corresponding to TBS group was in well accordance with the protection of the hydroxyl group and the remaining protons were being resonated at their respective chemical shift values. In addition to this, high resolution ESI mass spectrum of the compound **90** showed a signal at *m/z* 387.2319 corresponding to the $[M+Na]^+$ (calcd 387.2311). Oxidative cleavage of the PMB ether **90** was carried out by reacting with 1.5 eq of DDQ under buffered conditions[43] ($CHCl_3$/buffer, pH = 7, 20:1) to afford the primary alcohol **91** in 71% yield. Disappearance of aromatic, benzylic methylene and methoxy signals corresponding to the –OPMB group in the ^{1}H NMR spectrum and appearance of broad signal at 3344 cm^{-1} in the IR spectrum of the primary alcohol **91** supported the successful deprotection. In addition to this, a signal at *m/z* 267.1764 in the high resolution ESI mass spectrum corresponding to $[M+Na]^+$ (calcd 267.1756) provided the satisfying support for the transformation. Oxidation of the alcohol **91** under Swern conditions[44] by reacting with 1.5 eq of $(COCl)_2$, 3.2 eq of DMSO and 5 eq of Et_3N in CH_2Cl_2 at –78 °C–0 °C for 3 h furnished the aldehyde **85a** which was taken forward to next reaction, after a flash column chromatography, without any further characterization.

Reaction of the aldehyde **85a** with 1.2 eq of stabilized phosphorane[38] Ph_3P=CHCOOEt in CH_2Cl_2 at rt for overnight furnished the *α,β*–unsaturated ester **92** in 93% yield (Scheme 21). Appearance of signals corresponding to COOEt functionality at δ 4.28–4.12, 1.29 in the ^{1}H NMR spectrum of compound **92** was the basic support for the presence of ester. In addition to this, olefinic region was also carrying signals at δ 6.92, 5.79, 5.58–5.41 integrating for 1H, 1H and 2H respectively with rest of the protons being

resonating at their corresponding chemical shift values suggested the success of the reaction. High resolution ESI mass spectrum carrying a signal at *m/z* 335.2021 corresponding to $[M+Na]^+$ (calcd 335.2018) was also in accordance to the successful formation of the product **92**. Desilyaltion[45] of the compound **92** by using 1.4 eq of TBAF (1M in THF) in THF at 0 °C to rt for 6 h furnished the allylic alcohol **84A** in 80% yield. Disappearance of signals corresponding to TBS group and presence of the remaining signals at their respective chemical shift values in the ^{1}H NMR spectrum of the compound **84A** clarified the deprotection. High resolution ESI mass spectrum carrying a signal at *m/z* 221.1145 corresponding to $[M+Na]^+$ (calcd 221.1153) was also in good concurrence with the formation of the allylic alcohol **84A**.

Scheme 21

Compound **93** has been prepared in 86% from the aldehyde **85a** by reacting with 1.2 eq of stabilized phosphorane[38] $Ph_3P=C(CH_3)COOEt$ in CH_2Cl_2 at rt for overnight (Scheme 21). The ^{1}H NMR spectrm consisting of a singlet at δ 1.82 corresponding to the methyl group adjacent to the ester, signals corresponding to COOEt functionality, olefinic signals in the regions δ 6.7 (1H), 5.57–5.44 (2H) collectively supported the successful olefination. In addition to this, a signal at *m/z* 349.2180 corresponding to $[M+Na]^+$ (calcd 349.2174) in the high resolution ESI mass spectrum was helpful in confirming the transformation without any ambiguity. Silyl deprotection of the compound **93** to get compound **84B** was carried out by reacting with 1.4 eq of TBAF[45] (1M in THF) in THF at 0 °C to rt for 6 h. Disappearance of signals corresponding to TBS group and presence of the remaining signals at their respective chemical shift values in the ^{1}H NMR spectrum of

the compound **84B** clarified the deprotection. High resolution ESI mass spectrum carrying a signal at *m/z* 235.1302 corresponding to $[M+Na]^+$ (calcd 235.1310) was also in good concurrence with the formation of the allylic alcohol **84B**.

Sharpless' asymmetric epoxidation

The Sharpless epoxidation reaction is an enantioselective chemical reaction to prepare 2,3–epoxyalcohols from primary and secondary allylic alcohols. The stereochemistry of the resulting epoxide is determined by the diastereomer of the chiral tartrate diester (usually diethyl tartrate or diisopropyl tartrate) employed in the reaction. The oxidizing agent is *tert*–butyl hydroperoxide. Enantioselectivity is achieved by a catalyst formed from titanium tetra(isopropoxide) and diethyl tartrate. The reaction is believed to proceed through catalysis by a dimeric titanium species. The reaction is catalyzed by $Ti(O^iPr)_4$ which binds hydroperoxide, allylic alcohol group and the asymmetric tartrate ligand *via* oxygen atoms (putative transition state depicted in Figure 3, only part of DIPT was shown for clarity).

Figure 3. Mechanism for Sharpless' epoxidation reaction

Now the racemic allylic alcohol **84A** was transformed into desired chiral epoxy alcohol **83A** by using the Sharpless kinetic resolution[37] protocol (Scheme 22). Reaction of the allylic alcohol **84A** with 1 eq of $Ti(O^iPr)_4$, 1.2 eq of L–(+)–DIPT, 2.5 eq of TBHP (4.63M in toluene) in CH_2Cl_2 containing activated 4Å MS (20% *w/w*) at –20 °C for 2–3 h

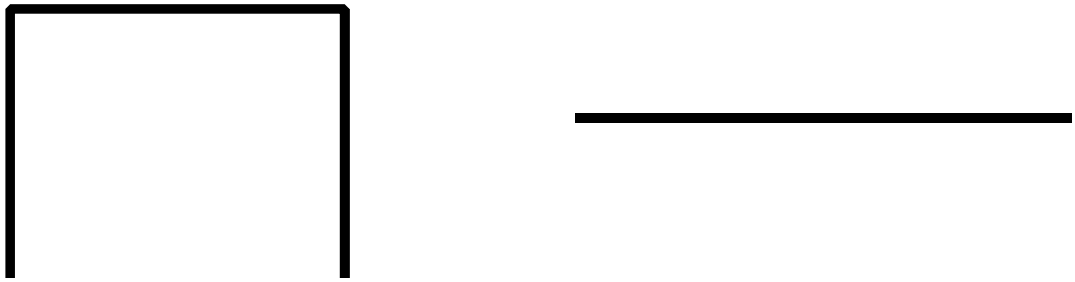
afforded the required 2,3–epoxy alcohol **83A** in 47% yield. Unreacted allylic alcohol **94** was recovered in 45% yield. Disappearance of the olefinic signals in the region δ 5.67–5.48, presence of characteristic epoxide signals at δ 2.96 (m, 1H), 2.17 (m, 1H) and remaining protons being at their respective chemical shift values in the ^{1}H NMR spectrum collectively confirmed the formation of the expected product. A high resolution ESI mass spectrum consisting of a signal at *m/z* 237.1096 corresponding to $[M+Na]^+$ (calcd 237.1102) further justified the success of the reaction.

Scheme 22

In a similar manner, epoxy alcohol **83B** was obtained from the allylic alcohol **84B** in 44% yield where as the unreacted allylic alcohol **95** was recovered in 47% yield (Scheme 22). The ^{1}H NMR spectrum of the compound **83B** was in very good agreement with the expectations and appearance of a signal at *m/z* 251.1269 corresponding to $[M+Na]^+$ (calcd 251.1259) in the high resolution ESI mass spectrum is additional confirmation. To our pleasure, unreacted allylic alcohols **94–95** could be converted back to the precursor allylic alcohols **84A–B** *via* a two step sequence *i.e.* Swern oxidation[44] and Luche reduction[47] conditions.

Reaction of the anion,[40] generated from alkyne **87** by reating with ^{n}BuLi, with benzyloxyacetaldehdye in THF at –78 °C for 10 min afforded the addition product **86b** in 87% yield (Scheme 23). Appearance of a total of 9 protons, in the ^{1}H NMR spectrum of the compound **86b**, in the aromatic region δ 7.36–7.15, 6.84–6.78 was the basic support for the formation of product and the remaining protons were observed at their corresponding chemical shift values. High resolution ESI mass spectrum carrying a signal at *m/z* 377.1741 corresponding to $[M+Na]^{+}$ (calcd 377.1728) was also in good concurrence with the formation of the propargylic alcohol **86b**. Reduction of the triple bond present in **86b** was achieved in 88% yield by allowing it to react with Red–Al[41] in ether at 0 °C to rt for 4 h to get compound **96**. In the ^{1}H NMR spectrum of the compound **96**, olefinic signals were observed at δ 5.72, 5.37, signals of –OPMB and –OBn functionalities were observed and the remaining protons appeared at their appropriate chemical shift values. In addition to this, a signal at *m/z* 379.1901 corresponding to $[M+Na]^{+}$ (calcd 379.1885) in the high resolution ESI mass spectrum was helpful in confirming the transformation without any ambiguity. Reaction of the compound **96** with 1.1 eq of TBSOTf and 1.5 eq of 2,6–lutidine[42] in CH_2Cl_2 at 0 °C for 10 min furnished the silyl ether **97** in 88% yield. Appearance of signals at δ 0.89, 0.06 and 0.04 integrating for 9, 3 and 3 protons respectively in the ^{1}H NMR spectrum of compound **97** corresponding to TBS group is in well agreement with the protection of the hydroxyl group and the remaining protons resonated at their respective chemical shift values. The high resolution ESI mass spectrum of the compound **97** showed a signal at *m/z* 493.2738 corresponding to the $[M+Na]^{+}$ (calcd 493.2750). Reaction of the PMB ether **97** with 1.5 eq of DDQ under buffered conditions[43] ($CHCl_3$/buffer, pH = 7, 20:1) furnished the primary alcohol **98** in 75% yield. Disappearance of signals corresponding to –OPMB group in the ^{1}H NMR spectrum and appearance of broad signal at 3365 cm^{-1} in the IR spectrum of the primary alcohol **98** is the prime support for the oxidative cleavage of the PMB ether functionality. In addition to this, a signal at *m/z* 373.2164 in the high resolution ESI mass spectrum corresponding to $[M+Na]^{+}$ (calcd 373.2174) provided the agreeable support for the successful transformation. Reaction[44] of the alcohol **98** with 1.5 eq of $(COCl)_2$, 3.2 eq of DMSO and 5 eq of Et_3N in CH_2Cl_2 at –78 °C to 0 °C for 3 h furnished the aldehyde **85b** which was

taken forward to next reaction, after a flash column chromatography, without any further characterization.



Scheme 23

Wittig olefination[38] of the aldehyde **85b** was carried out by reacting with 1.2 eq of stabilized phosphorane Ph_3P=CHCOOEt in CH_2Cl_2 at rt for overnight to furnish the *α,β*–unsaturated ester **99** in 75% yield (Scheme 24). Appearance of signals corresponding to COOEt functionality at δ 4.16 and 1.28 in the ^{1}H NMR spectrum of the compound **99** is the basic support for the presence of ester. In addition to this olefinic region carrying signals at δ 6.91, 5.79, 5.66 and 5.48 integrating for 1H each with rest of the protons being at their corresponding chemical shift values supported the olefination. High resolution ESI mass spectrum carrying a signal at *m/z* 441.2420 corresponding to $[M+Na]^+$ (calcd 441.2437) was also in accordance with the successful formation of the product **99**. Desilyaltion of the compound **99** by using 1.4 eq of TBAF[45] (1M in THF) in THF at 0 °C to rt for 6 h furnished the allylic alcohol **84C** in 89% yield. Disappearance of signals corresponding to TBS group and presence of the remaining signals at their respective chemical shift values in the ^{1}H NMR spectrum of the compound **84C** confirmed the deprotection. High resolution ESI mass spectrum carrying a signal at *m/z* 327.1567

corresponding to $[M+Na]^+$ (calcd 327.1572) was also in good concurrence with the formation of the allylic alcohol **84C**.

Scheme 24

Treatment of the aldehyde **85b** with 1.2 eq of stabilized phosphorane[38] $Ph_3P=C(CH_3)COOEt$ in CH_2Cl_2 at rt for overnight furnished the compound **100** in 78% yiled (Scheme 24). The ^1H NMR spectrm consisting of a singlet at δ 1.82 corresponding to the methyl group adjacent to the ester, signals corresponding to COOEt functionality, olefinic signals at δ 6.74 (1H), 5.69 (1H), 5.5 (1H) collectively supported the formation of the product. In addition to this, a signal at *m/z* 455.2580 corresponding to $[M+Na]^+$ (calcd 455.2593) in the high resolution ESI mass spectrum was also in favour of the the transformation. Silyl deprotection[45] of the compound **100** to get compound **84D** was carried out by reacting with 1.4 eq of TBAF (1M in THF) in THF at 0 °C to rt for 6 h. Disappearance of signals corresponding to TBS group and presence of the remaining signals at their respective chemical shift values in the ^1H NMR spectrum of the compound **84D** confirmed the deprotection. High resolution ESI mass spectrum carrying a signal at *m/z* 341.1715 corresponding to $[M+Na]^+$ (calcd 341.1728) was also in agreement with the formation of the allylic alcohol **84D**.

Racemic allylic alcohol **84C** was transformed into desired chiral epoxy alcohol **83C** by using the Sharpless kinetic resolution[37] protocol (Scheme 25). Reaction of the allylic alcohol **84C** with 1 eq of $Ti(O^iPr)_4$, 1.2 eq of *L*–(+)–DIPT, 2.5 eq of TBHP (4.63M in toluene) in CH_2Cl_2 containing activated 4Å MS (20% *w/w*) at –20 °C for 2–3 h afforded the required 2,3–epoxy alcohol **83C** in 45% yield.

Scheme 25

Unreacted allylic alcohol **101** was recovered in 46% yield. Absence of the olefinic signals, appearance of characteristic epoxide signals at δ 2.95 (m, 1H), 2.8 (m, 1H) and remaining protons being at their respective chemical shift values in the ^{1}H NMR spectrum confirmed the successful epoxidation. A high resolution ESI mass spectrum consisting of a signal at *m/z* 343.1511 corresponding to $[M+Na]^+$ (calcd 343.1521) further justified the success of the reaction. In a similar manner, epoxy alcohol **83D** was obtained from the allylic alcohol **84D** in 44% yield where as the unreacted allylic alcohol **102** was recovered in 48% yield (Scheme 25). The ^{1}H NMR spectrum of the compound is in very good agreement with the expectations and appearance of a signal at *m/z* 357.1664 corresponding to $[M+Na]^+$ (calcd 357.1677) in the high resolution ESI mass spectrum was additional confirmation. To our pleasure, unreacted allylic alcohols **101–102** could be converted back to the precursor allylic alcohols **84C–D** *via* a two step sequence *i.e.* Swern oxidation[44] and Luche reduction conditions.[47]

Now the stage was set to carry out the crucial $Cp_2Ti(III)Cl$ radical mediated epoxide ring opening reaction. Reaction of the epoxy alcohols **83A–D** with $Cp_2Ti(III)Cl$

radical which was generated *in situ* by the reaction of 3 eq Cp_2TiCl_2, 3 eq of Zn and 6 eq of fused $ZnCl_2$, produced a radical which underwent smooth intramolecular cyclization with α,β–unsaturation there by forming a new C–C bond and lead to highly functionalized five–membered carbocycles **76A–D** as the major isolable products (Scheme 26).

Scheme 26

The relative stereochemistries of C2, C3 (**76A**–**D**) and C8 (**76B**,**D**) centres were unequivocally assigned by incisive NMR studies[48] such as NOESY and HSQC experiments. These compounds have been analyzed by using 1D–1H decoupling and 2D NMR techniques such as DQF–COSY and NOESY. The conformation of the molecule is fixed by considering the observed coupling constants and nOes.

We have observed a consistency in nOe correlations for all of the products **76A–D**. Strong nOe cross–peaks $C_2H \leftrightarrow C_8H_a$ and H_b, $C_2H \leftrightarrow C_7H$, $C_6H \leftrightarrow C_8H_a$ and $C_1H \leftrightarrow C_7H$ were observed for the compounds **76A–D**. In addition to these observations, strong nOe correlation $C_3H \leftrightarrow C_9H$ was also observed in compounds **76B**,**D** (Figure 4). Interestingly, the fixation of C8 methyl stereo centre was found to be the same in both **76B** and **76D**.

In conclusion we have synthesized highly functionalized five–membered carbocycles with multiple chiral centres by applying $Cp_2Ti(III)Cl$ radical mediated ring opening of 2,3–epoxy alcohols followed by intramolecular trapping of the radical with suitably placed α,β–unsaturation. That three consecutive chiral centres were fixed in a single–step radical mediated reaction is noteworthy. These structural moieties can be manipulated to get the aforementioned natural products.

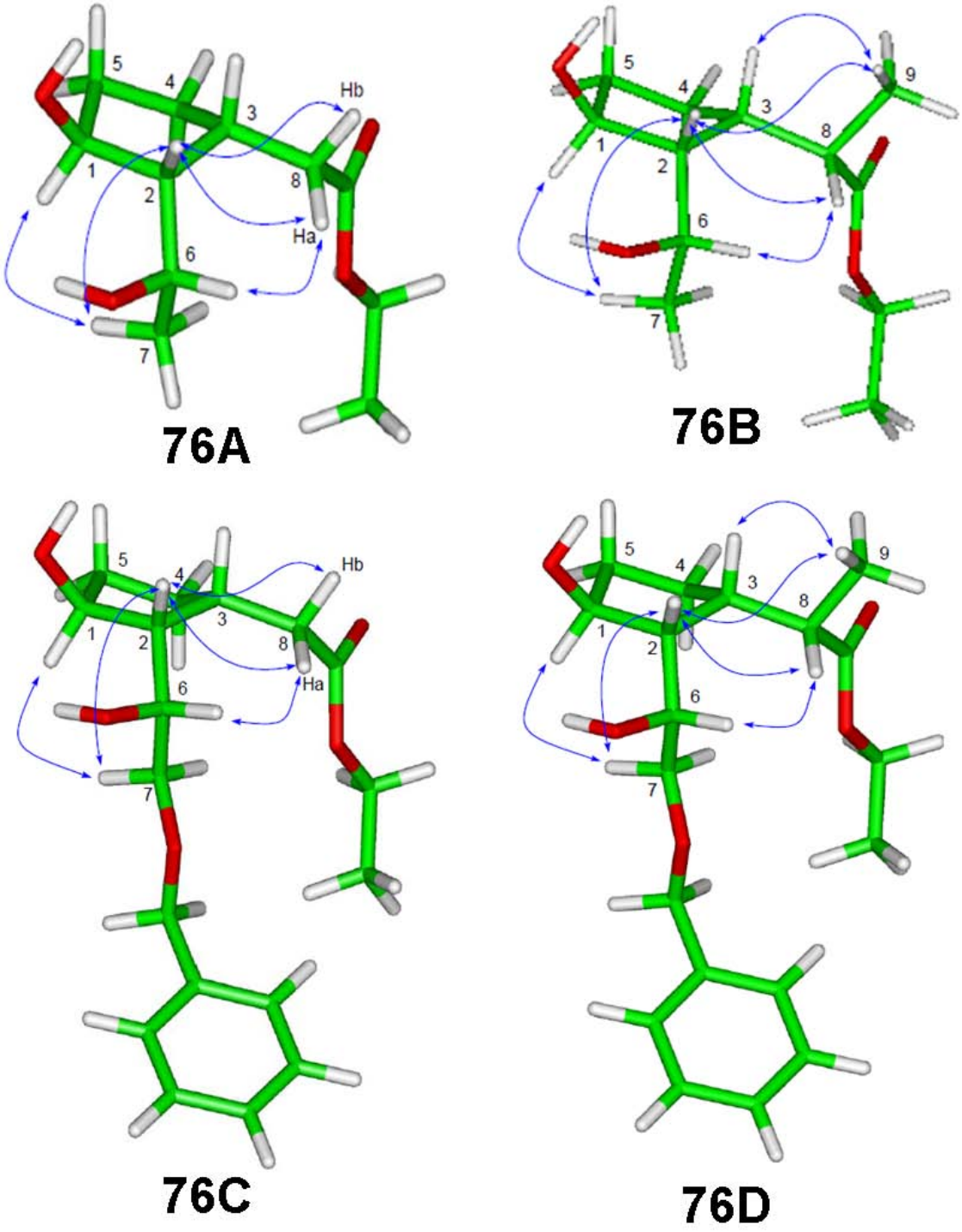
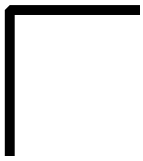


Figure 4

EXPERIMENTAL SECTION

1–Methoxy–4–((pent–4–ynyloxy)methyl)benzene (88)



Neat *p*–methoxybenzylalcohol (22.23 mL, 178.3 mmol) was added dropwise to a solution of PBr_3 (5.69 mL, 58.84 mmol) in Et_2O (300 mL) at 0 °C. After the completion of addition, stirring was continued for 2 h before the mixture was poured over ice. The ether layer was separated, washed with saturated aqueous $NaHCO_3$ (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4), filtered and concentrated at reduced temperature and *in vacuo* to get the PMBBr as light yellow oil. The residue was directly used for the next reaction without allowing for standing.

To a solution of 4–pentyn–1–ol **87** (15 g, 178.3 mmol) in THF (400 mL) was added 1 eq of NaH (60% dispersion in oil, 7.1 g, 178.3 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 1 h after which it was again cooled to 0 °C. To the reaction mixture, a solution of PMBBr in THF (50 mL, 2×) was added and allowed to stir for overnight at room temperature. The reaction mixture was then brought to 0 °C and quenched with saturated aqueous NH_4Cl (50 mL). THF was evaporated under vaccum and the residue was extracted with EtOAc (2×250 mL). The combined organic layers were washed with water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was then purified by column chromatography (Silica gel, 4% EtOAc in petroleum ether as eluant) to furnish the PMB protected alcohol **88** (30.9 g, 85%) as light yellow colored oil.

***R*$_f$:** 0.5 (Silica gel, 10% EtOAc in petroleum ether).

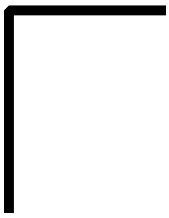
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25–7.17 (m, 2H, Ar*H*), 6.85–6.79 (m, 2H, Ar*H*), 4.41 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 3.78 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.50 (t, *J* = 6 Hz, 2H, PMBOCH_2), 2.32–2.24 (m, 2H, HC≡CCH_2CH_2), 1.88–1.73 (m, 3H, *H*C≡CCH_2CH_2).

ESI–MS: *m/z* (%) 227 (100) $[M+Na]^+$.

Generalized experimental procedure for addition of acetylide over an aldehyde:

A solution of ^{n}BuLi in hexane (1.6M, 1.1 eq) was added dropwise to the magnetically stirred solution of terminal alkyne (1 eq) in THF (3 mL/mmol) at –78 °C under the atmosphere of nitrogen. After 30 min, aldehyde (1.1 eq) was added, stirred for 10 min at –78 °C and then the resulting solution was warmed to room temperature. Reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (2×). The combined organic extracts were washed with water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. Standard column chromatography by using silica gel afforded the propargylic alcohol.

7–(4–Methoxybenzyloxy)hept–3–yn–2–ol (86a)



Column chromatography: Silica gel, 10% EtOAc in petroleum ether eluant.

Yield: 90%, Colorless oil.

***R*$_f$:** 0.5 (Silica gel, 30% EtOAc in petroleum ether).

IR (neat): ν_{max} 3399, 2930, 2855, 1611, 1511, 1244, 1173, 1074, 1032, 818 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, J = 8.1 Hz, 2H, Ar*H*), 6.87 (d, J = 8.1 Hz, 2H, Ar*H*), 4.50–4.40 (m, 3H, *p*–$CH_3OC_6H_4CH_2$, CH_3CH(OH)), 3.79 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.54–3.48 (m, 2H, PMBOCH_2), 2.40–2.26 (m, 3H, $CH_2C{\equiv}C$, CH(O*H*)), 1.77 (p, J = 6.6 Hz, 2H, PMBOCH_2CH_2), 1.39 (d, J = 6.6 Hz, 3H, CH_3CH(OH)).

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.99, 130.36, 129.15, 113.63, 83.59, 82.55, 72.4, 68.23, 58.35, 55.13, 28.59, 24.58, 15.39.

ESI–MS: *m/z* (%) 266 (70) $[M+NH_4]^+$, 271 (65) $[M+Na]^+$.

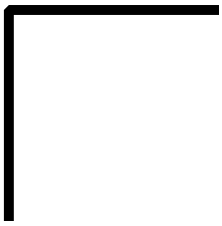
HRMS (ESI): Calcd for $C_{15}H_{20}O_3Na$ $[M+Na]^+$ 271.1310, found 271.1300.

1–(Benzyloxy)–7–(4–methoxybenzyloxy)hept–3–yn–2–ol (86b)

Column chromatography: Silica gel, 20% EtOAc in petroleum ether eluant.

Yield: 87%, Colorless oil.

***R*$_f$:** 0.5 (Silica gel, 40% EtOAc in petroleum ether).



IR (neat): ν_{max} 3406, 2921, 2854, 1609, 1453, 1242, 1071, 1026, 815, 737, 695 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.36–7.15 (m, 7H, Ar*H*), 6.84–6.78 (m, 2H, Ar*H*), 4.62–4.52 (m, 2H, PhC*H*$_2$), 4.46 (m, 1H, C*H*(OH)), 4.39 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 3.78 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.58–3.41 (m, 4H, PMBOC*H*$_2$, BnOC*H*$_2$), 2.34–2.22 (m, 2H, C*H*$_2$C≡C), 1.81–1.7 (m, 2H, PMBOCH$_2$C*H*$_2$), 1.41(br s, 1H, CH(O*H*)).

^{13}C NMR (75 MHz, CDCl$_3$): δ 159.05, 137.63, 130.43, 129.18, 128.4, 127.79, 127.72, 113.68, 85.7, 77.96, 73.27, 72.48, 68.31, 61.73, 55.19, 28.54, 15.52.

ESI–MS: *m/z* (%) 355 (10) $[M+H]^+$, 377 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{22}H_{26}O_4Na$ $[M+Na]^+$ 377.1728, found 377.1741.

Generalized experimental procedure for reduction of a triple bond with Red–Al:

To a stirred solution of the propargylic alcohol (1 eq) in ether (3 mL/mmol), Red–Al (3.46M solution in toluene, 3.3 eq) was added slowly in dropwise manner at 0 °C. The reaction mixture was allowed to come to room temperature and stirred for 4 h. It was recooled to 0 °C, quenched with saturated aqueous potassium sodium tartrate solution, extracted with EtOAc (2×). The combined organic extracts were washed with water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by silica gel column chromatography furnished the allylic alcohol.

(*E*)–7–(4–Methoxybenzyloxy)hept–3–en–2–ol (89)

Column chromatography: Silica gel, 12% EtOAc in petroleum ether eluant.

Yield: 94%, Colorless oil.

***R*$_f$:** 0.4 (Silica gel, 40% EtOAc in petroleum ether).

IR (neat): ν_{max} 3387, 2930, 2851, 1612, 1511, 1245, 1173, 1095, 1033, 968 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 9.1 Hz, 2H, Ar*H*), 6.87 (d, *J* = 8.3 Hz, 2H, Ar*H*), 5.66–5.44 (m, 2H, C*H*=C*H*), 4.41 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.21 (m, 1H, CH_3CH(OH)), 3.78 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.46–3.39 (m, 2H, PMBOCH_2), 2.14–2.02 (m, 2H, CH_2CH=CH), 1.97 (br s, 1H, CH(O*H*)), 1.72–1.61 (m, 2H, PMBOCH_2CH_2), 1.22 (d, *J* = 6 Hz, 3H, CH_3CH(OH)).

^{13}C NMR (75 MHz, $CDCl_3$): δ 158.99, 134.59, 130.51, 129.86, 129.13, 113.63, 72.36, 69.14, 68.56, 55.11, 29.04, 28.57, 23.3.

ESI–MS: *m/z* (%) 273 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{15}H_{22}O_3Na$ $[M+Na]^+$ 273.1466, found 273.1464.

(*E*)–1–(Benzyloxy)–7–(4–methoxybenzyloxy)hept–3–en–2–ol (96)

Column chromatography: Silica gel, 20% EtOAc in petroleum ether eluant.

Yield: 88%, Colorless oil.

***R_f*:** 0.5 (Silica gel, 40% EtOAc in petroleum ether).

IR (neat): ν_{max} 3437, 2931, 2857, 1611, 1511, 1452, 1245, 1098, 1032, 819, 741 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.15 (m, 7H, Ar*H*), 6.85–6.78 (m, 2H, Ar*H*), 5.72 (m, 1H, C*H*=CHCH(OH)), 5.37 (m, 1H, CH=C*H*CH(OH)), 4.54 (s, 2H, PhCH_2), 4.37 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.23 (m, 1H, C*H*(OH)), 3.78 (s, 3H, *p*–C$H_3OC_6H_4CH_2$), 3.46–3.36 (m, 3H, PMBOCH_2, BnOCH*H*), 3.27 (m, 1H, BnOC*H*H), 2.15–2.06 (m, 2H, CH_2CH=CH), 1.71–1.6 (m, 2H, PMBOCH_2CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 137.8, 132.9, 130.53, 129.15, 128.49, 128.35, 127.68, 113.64, 77.2, 74.27, 73.19, 72.39, 71.16, 69.16, 61.72, 51.14, 28.93, 28.83.

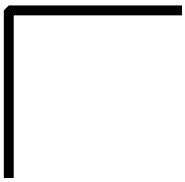
ESI–MS: *m/z* (%) 379 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{22}H_{28}O_4Na$ $[M+Na]^+$ 379.1885, found 379.1901.

Generalized experimental procedure for TBS protection of an allylic alcohol:

To a solution of the allylic alcohol (1 eq) in CH_2Cl_2 (3 mL/mmol), 2,6–lutidine (1.5 eq) followed by TBSOTf (1.1 eq) were added at 0 ºC. After stirring for 10 to 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (2×). The combined organic extracts were washed with saturated aqueous $CuSO_4$, water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residual oil by using silica gel flash column chromatography provided the TBS ether.

(*E*)–*tert*–Butyl(7–(4–methoxybenzyloxy)hept–3–en–2–yloxy)dimethylsilane (90)



Column chromatography: Silica gel, 4% EtOAc in petroleum ether eluant.

Yield: 90%, Colorless oil.

***R*$_f$:** 0.6 (Silica gel, 10% EtOAc in petroleum ether).

IR (neat): ν_{max} 2953, 2928, 2855, 1613, 1512, 1247, 1090, 1039, 834, 775 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.17 (m, 2H, Ar*H*), 6.9–6.78 (m, 2H, Ar*H*), 5.48 (m, 1H, CH_2CH=CH), 4.67 (m, 1H, CH_2CH=C*H*), 4.42 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.23 (m, 1H, C*H*(OTBS)), 3.79 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.47–3.38 (m, 2H, PMBOCH_2), 2.14–2.01 (m, 2H, CH_2CH=CH), 1.73–1.61 (m, 2H, PMBOCH_2CH_2), 1.17 (d, *J* = 6 Hz, 3H, CH_3CH(OTBS)), 0.89 (s, 9H, ^{t}*Bu*–Si), 0.10–0.01 (m, 6H, $(CH_3)_2$Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.08, 135.17, 129.19, 128.24, 127.48, 113.71, 113.58, 72.53, 69.39, 69.29, 64.67, 55.19, 29.33, 28.61, 25.89, 24.62, –4.52, –4.77, –5.22.

ESI–MS: *m/z* (%) 387 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{21}H_{36}O_3NaSi$ $[M+Na]^+$ 387.2311, found 387.2319.

(*E*)–(1–(Benzyloxy)–7–(4–methoxybenzyloxy)hept–3–en–2–yloxy)(*tert*–butyl)dimethylsilane (97)

Column chromatography: Silica gel, 5% EtOAc in petroleum ether eluant.

Yield: 88%, Colorless oil.

***R*$_f$:** 0.5 (Silica gel, 10% EtOAc in petroleum ether).

IR (neat): ν_{max} 2931, 2854, 1512, 1247, 1091, 968, 832, 776 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.34–7.21 (m, 7H, Ar*H*), 6.89–6.83 (m, 2H, Ar*H*), 5.67 (m, 1H, CH_2CH=CH), 5.45 (m, 1H, CH_2CH=C*H*), 4.54 (s, 2H, PhCH_2), 4.41 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.27 (m, 1H, C*H*(OTBS)), 3.78 (s, 3H, *p*–C$H_3OC_6H_4CH_2$), 3.46–3.36 (m, 4H, PMBOCH_2, BnOCH_2), 2.17–2.06 (m, 2H, CH_2CH=CH), 1.73–1.62 (m, 2H, $PMBOCH_2CH_2$), 0.89 (s, 9H, ^{t}*Bu*Si), 0.06 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, CDCl$_3$): δ 159.04, 138.48, 131.0, 130.73, 130.59, 129.17, 128.19, 127.43, 127.34, 113.67, 75.19, 73.17, 72.55, 72.49, 69.31, 55.15, 29.21, 28.75, 25.84, 18.26, –4.56, –4.74.

ESI–MS: *m/z* (%) 488 (100) $[M+NH_4]^+$, 493 (85) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{28}H_{42}O_4NaSi$ $[M+Na]^+$ 493.2750, found 493.2738.

Generalized experimental procedure for oxidative cleavage of PMB ether:

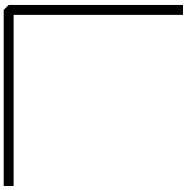
To a stirred solution of PMB ether (1 eq) in $CHCl_3$:buffer (pH = 7, 20:1, 5 mL/mmol), DDQ (1.3 eq) was added at room temperature and then allowed to stir for 10 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with EtOAc (2×). The combined organic extracts were washed with water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. Crude product thus obtained was purified by using silica gel column chromatography.

(*E*)–6–(*tert*–Butyldimethylsilyloxy)hept–4–en–1–ol (91)

Column chromatography: Silica gel, 10% EtOAc in petroleum ether eluant.

Yield: 71%, Colorless oil.

***R*$_f$:** 0.5 (Silica gel, 30% EtOAc in petroleum ether).



IR (neat): ν_{max} 3344, 2954, 2928, 2856, 1362, 1253, 1146, 1057, 997, 967, 774 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ 5.53 (dt, *J* = 14.7, 6.3 Hz, 1H, CH_2CH=CH), 5.46 (dd, *J* = 15.8, 5.3 Hz, 1H, CH_2CH=C*H*), 4.23 (m, 1H, C*H*(OTBS)), 3.66–3.63 (m, 2H, CH_2OH), 2.15–2.06 (m, 2H, CH_2CH=CH), 1.68–1.61 (m, 2H, CH_2CH_2OH), 1.18 (d, *J* = 6.3 Hz, 3H, CH_3CH(OTBS)), 0.89 (s, 9H, ^{t}*Bu*–Si), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, CDCl$_3$): δ 135.28, 128.21, 69.27, 62.28, 32.13, 28.35, 25.89, 24.58, –4.55, –4.76.

ESI–MS: *m/z* (%) 267 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{13}H_{28}O_2NaSi$ $[M+Na]^+$ 267.1756, found 267.1764.

(*E*)–7–(Benzyloxy)–6–(*tert*–butyldimethylsilyloxy)hept–4–en–1–ol (98)

Column chromatography: Silica gel, 12% EtOAc in petroleum ether eluant.

Yield: 75%, Colorless oil.

***R*$_f$:** 0.3 (Silica gel, 30% EtOAc in petroleum ether).

IR (neat): ν_{max} 3365, 2931, 2856, 1462, 1252, 1082, 969, 835, 777 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.35–7.2 (m, 5H, Ar*H*), 5.68 (dt, *J* = 15, 6.8 Hz, 1H, CH_2CH=CH), 5.46 (dd, *J* = 15, 6 Hz, 1H, CH_2CH=C*H*), 4.52 (s, 2H, PhCH_2), 4.25 (m, 1H, C*H*(OTBS)), 3.62 (t, *J* = 6 Hz, 2H, CH_2OH), 3.4–3.29 (m, 2H, BnOCH_2), 2.17–2.07 (m, 2H, CH_2CH=CH), 1.7–1.58 (m, 2H, CH_2CH_2OH), 0.88 (s, 9H, ^{t}*Bu*Si), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.38, 131.06, 130.93, 128.21, 127.5, 127.4, 75.01, 73.19, 72.46, 62.23, 31.99, 28.61, 25.81, –4.58, –4.75.

ESI–MS: *m/z* (%) 373 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{20}H_{34}O_3NaSi$ $[M+Na]^+$ 373.2174, found 373.2164.

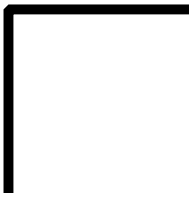
Generalized experimental procedure for Swern oxidation[44] followed by Wittig olefination[38]:

To a solution of $(COCl)_2$ (1.5 eq) in CH_2Cl_2 (8 mL/mmol) at –78 °C, DMSO (3.2 eq) was added slowly in dropwise manner with stirring under nitrogen atmosphere. After 20 min, primary alcohol (1 eq), dissolved in anhdrous CH_2Cl_2, was added into the reaction mixture. After 30 min of stirring at –78 °C, Et_3N (5 eq) was added, stirred for another 30 min at –78 °C and then for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (2×). The combined organic extracts were washed with water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde thus obtained was directly used in the next reaction without any further purification and characterization.

The crude aldehyde was taken in CH_2Cl_2 (3 mL/mmol) and the stabilized ylide ($Ph_3PCHCOOEt$ or $Ph_3P{=}C(CH_3)COOEt$, 1.2 eq) was added to it at room temperature. The reaction was allowed to stir for 12 h at the same temperature under nitrogen atmosphere. Then it was concentrated *in vacuo* and purified by using silica gel column chromatography.

(*2E,6E*)–Ethyl 8–(*tert*–butyldimethylsilyloxy)nona–2,6–dienoate (92)

Column chromatography: Silica gel, 4% EtOAc in petroleum ether eluant.



Yield: 93%, Colorless oil.

***R_f*:** 0.4 (Silica gel, 5% EtOAc in petroleum ether).

IR (neat): ν_{max} 2956, 2928, 2856, 1723, 1656, 1256, 1144, 1083, 1044, 970, 775 cm^{-1}.

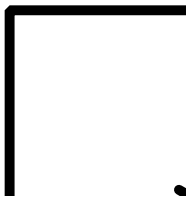
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (dt, *J* = 15.7, 6.6 Hz, 1H, C*H*=CHCOOEt), 5.79 (d, *J* = 15.7 Hz, 1H, CH=C*H*COOEt), 5.58–5.41 (m, 2H, C*H*=C*H*CH(OTBS)), 4.28–4.12 (m, 3H, C*H*(OTBS), COOC$H_2$$CH_3$), 2.34–2.24 (m, 2H, C$H_2$CH=CHCOOEt), 2.23–2.14 (m, 2H, C$H_2$$CH_2$CH=CHCOOEt), 1.29 (t, *J* = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.17 (d, *J* = 6.2 Hz, 3H, CH_3CH(OTBS)), 0.88 (s, 9H, ^{t}*Bu*–Si), 0.04 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.56, 148.33, 135.89, 127.0, 121.66, 69.07, 60.09, 31.88, 30.41, 25.86, 24.56, 14.23, –4.59, –4.8.

ESI–MS: *m/z* (%) 335 (65) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{17}H_{32}O_3NaSi$ $[M+Na]^+$ 335.2018, found 335.2021.

(*2E,6E*)–Ethyl 8–(*tert*–butyldimethylsilyloxy)–2–methylnona–2,6–dienoate (93)



Column chromatography: Silica gel, 3% EtOAc in petroleum ether eluant.

Yield: 86%, Colorless oil.

***R_f*:** 0.5 (Silica gel, 5% EtOAc in petroleum ether).

IR (neat): ν_{max} 2955, 2928, 2856, 1711, 1366, 1254, 1078, 966, 833, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.7 (m, 1H, C*H*=C(CH_3)COOEt), 5.57–5.44 (m, 2H, C*H*=C*H*CH(OTBS)), 4.23 (m, 1H, C*H*(OTBS)), 4.17 (q, *J* = 7.2 Hz, 2H, COOC$H_2$$CH_3$), 2.28–2.21 (m, 2H, C$H_2$CH=C($CH_3$)), 2.19–2.13 (m, 2H, C$H_2$$CH_2$CH=C($CH_3$)), 1.82 (s, 3H, CH=C(C$H_3$)COOEt), 1.3 (t, *J* = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.18 (d, *J* = 6.2 Hz, 3H, CH_3CH(OTBS)), 0.88 (s, 9H, ^{t}*Bu*–Si), 0.04 (s, 3H, CH_3Si), 0.02(s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.05, 141.28, 135.71, 128.03, 127.38, 69.08, 60.29, 30.89, 28.39, 25.83, 24.55, 14.22, 12.36, –4.62, –4.84.

ESI–MS: *m/z* (%) 349 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{21}H_{36}O_3NaSi$ $[M+Na]^+$ 349.2174, found 349.2180.

(*2E,6E*)–Ethyl 9–(benzyloxy)–8–(*tert*–butyldimethylsilyloxy)nona–2,6–dienoate (99)

Column chromatography: Silica gel, 3% EtOAc in petroleum ether eluant.

Yield: 75%, Colorless oil.

***R*$_f$:** 0.5 (Silica gel, 10% EtOAc in petroleum ether).

IR (neat): ν_{max} 2930, 2855, 2363, 1721, 1257, 1090, 972, 836, 777 cm^{-1}.

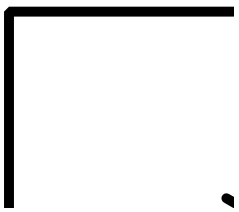
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.2 (m, 5H, Ar*H*), 6.91 (dt, *J* = 15.7, 6.4 Hz, 1H, C*H*=CHCOOEt), 5.79 (d, *J* = 15.7 Hz, 1H, CH=C*H*COOEt), 5.66 (dt, *J* = 15.4, 6.2 Hz, 1H, C*H*=CHCH(OTBS)), 5.48 (dd, *J* = 15.5, 5.7 Hz, 1H, CH=C*H*CH(OTBS)), 4.51 (s, 2H, PhCH_2), 4.25 (m, 1H, C*H*(OTBS)), 4.16 (q, *J* = 6.9 Hz, 2H, COOC$H_2$$CH_3$), 3.37–3.31 (m, 2H, BnOCH_2), 2.34–2.15 (m, 4H, CH_2CH_2CH=CH), 1.28 (t, *J* = 6.9 Hz, 3H, $COOCH_2CH_3$), 0.88 (s, 9H, ^{t}*Bu*Si), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.44, 148.13, 138.39, 131.47, 129.66, 128.18, 127.43, 127.35, 121.7, 75.06, 73.18, 72.29, 60.04, 31.74, 30.51, 25.79, 14.19, –4.66, –4.79.

ESI–MS: *m/z* (%) 436 (85) $[M+NH_4]^+$, 441 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{24}H_{38}O_4NaSi$ $[M+Na]^+$ 441.2437, found 441.2420.

(*2E,6E*)–Ethyl 9–(benzyloxy)–8–(*tert*–butyldimethylsilyloxy)–2–methylnona–2,6–dienoate (100)



Column chromatography: Silica gel, 3% EtOAc in petroleum ether eluant.

Yield: 78%, Colorless oil.

***R*$_f$:** 0.6 (Silica gel, 10% EtOAc in petroleum ether).

IR (neat): ν_{max} 2930, 2855, 1710, 1460, 1363, 1254, 1085, 967, 834, 777 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.22 (m, 5H, Ar*H*), 6.74 (m, 1H, C*H*=C(CH_3)COOEt), 5.69 (dt, *J* = 15.1, 6 Hz, 1H, C*H*=CHCH(OTBS)), 5.5 (dd, *J* = 15.8, 6 Hz, 1H, CH=C*H*CH(OTBS)), 4.55 (s, 2H, PhCH_2), 4.29 (m, 1H, C*H*(OTBS)), 4.17 (q, *J* = 6.8 Hz, 2H, COOC$H_2$$CH_3$), 3.45–3.34 (m, 2H, BnOCH_2), 2.3–2.13 (m, 4H, CH_2CH_2CH=CH), 1.82 (s, 3H, CH=C(CH_3)COOEt), 1.28 (t, *J* = 6.8 Hz, 3H, $COOCH_2CH_3$), 0.89 (s, 9H, ^{t}*Bu*Si), 0.06 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.04, 141.17, 138.42, 131.28, 130.12, 128.19, 128.1, 127.4, 127.36, 75.1, 73.19, 72.36, 60.3, 31.05, 28.3, 25.8, 18.23, 14.22, 12.38, –4.64, –4.78.

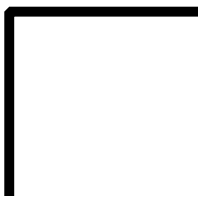
ESI–MS: *m/z* (%) 450 (100) $[M+NH_4]^+$.

HRMS (ESI): Calcd for $C_{25}H_{40}O_4NaSi$ $[M+Na]^+$ 455.2593, found 455.2580.

Generalized experimental procedure for *O*–silyl deprotection:

To a magnetically stirred solution of the silyl ether in THF (3 mL/mmol) at 0 °C was slowly added TBAF (1 M in THF, 1.4 eq), allowed to room temperature and stirred for 6 to 8 h. The reaction mixture was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc (2×). The combined organic extracts were washed with water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by using silica gel column chromatography furnished the allylic alcohol.

(*2E,6E*)–Ethyl 8–hydroxynona–2,6–dienoate (84A)



Column chromatography: Silica gel, 20% EtOAc in petroleum ether eluant.

Yield: 80%, Colorless oil.

***R_f*:** 0.25 (Silica gel, 30% EtOAc in petroleum ether).

IR (neat): ν_{max} 3411, 2975, 2928, 1718, 1653, 1368, 1268, 1195, 1040, 971 cm^{-1}.

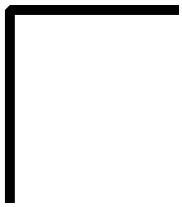
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (dt, *J* = 15.1, 6.4 Hz, 1H, C*H*=CHCOOEt), 5.79 (d, *J* = 15.5 Hz, 1H, CH=C*H*COOEt), 5.67–5.48 (m, 2H, C*H*=C*H*CH(OH)), 4.29–4.10 (m, 3H, C*H*(OH), COOC$H_2$$CH_3$), 2.35–2.25 (m, 2H, C$H_2$CH=CHCOOEt), 2.24–2.15 (m, 2H, C$H_2$$CH_2$CH=CHCOOEt), 1.54 (br s, 1H, CH(O*H*)), 1.29 (t, *J* = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.24 (d, *J* = 6.2 Hz, 3H, CH_3CH(OH)).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.48, 148.11, 135.36, 128.34, 121.5, 68.26, 60.05, 31.53, 30.29, 23.24, 14.06.

ESI–MS: *m/z* (%) 221 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{11}H_{18}O_3Na$ $[M+Na]^+$ 221.1153, found 221.1145.

(*2E,6E*)–Ethyl 8–hydroxy–2–methylnona–2,6–dienoate (84B)



Column chromatography: Silica gel, 18% EtOAc in petroleum ether eluant.

Yield: 85%, Colorless oil.

***R_f*:** 0.3 (Silica gel, 30% EtOAc in petroleum ether).

IR (neat): ν_{max} 3412, 2975, 2928, 1707, 1367, 1268, 1122, 1061, 968, 745 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.7 (m, 1H, C*H*=C(CH_3)COOEt), 5.68–5.48 (m, 2H, C*H*=C*H*), 4.29–4.11 (m, 3H, C*H*(OH), COOC$H_2$$CH_3$), 2.31–2.11 (m, 4H, C$H_2CH_2$CH=CH), 1.82 (s, 3H, CH=C(CH_3)COOEt), 1.59 (br s, 1H, CH(O*H*)), 1.3 (t, *J* = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.24 (d, *J* = 6.4 Hz, 3H, CH_3CH(OH)).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.11, 141.08, 135.14, 129.05, 128.07, 68.51, 60.37, 30.85, 28.17, 23.29, 14.16, 12.32.

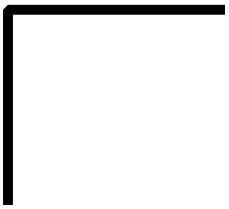
ESI–MS: *m/z* (%) 235 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{12}H_{20}O_3Na$ $[M+Na]^+$ 235.1310, found 235.1302.

(*2E,6E*)–ethyl 9–(benzyloxy)–8–hydroxynona–2,6–dienoate (84C)

Column chromatography: Silica gel, 23% EtOAc in petroleum ether eluant.

Yield: 89%, Colorless oil.



***R*$_f$:** 0.4 (Silica gel, 40% EtOAc in petroleum ether).

IR (neat): ν_{max} 3463, 2921, 2855, 1712. 1652, 1269, 1193, 1097, 1035, 971, 739, 698 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.36–7.21 (m, 5H, Ar*H*), 6.89 (dt, *J* = 15.7, 6.4 Hz, 1H, C*H*=CHCOOEt), 5.82–5.66 (m, 2H, CH=C*H*COOEt, C*H*=CHCH(OH)), 5.44 (dd, *J* = 15.7, 6.2 Hz, 1H, CH=C*H*CH(OH)), 4.53 (s, 2H, PhCH_2), 4.24 (m, 1H, C*H*(OH)), 4.15 (q, *J* = 7.2 Hz, 2H, COOCH_2CH$_3$), 3.44 (m, 1H, BnOC*H*H), 3.29 (m, 1H, BnOCH*H*), 2.53 (br s, 1H, CH(O*H*)), 2.33–2.13 (m, 4H, CH_2CH_2CH=CH), 1.28 (t, *J* = 7.2 Hz, 3H, COOCH$_2$CH_3).

^{13}C NMR (75 MHz, CDCl$_3$): δ 166.53, 148.02, 137.74, 131.59, 129.26, 128.37, 127.73, 127.69, 121.67, 74.17, 73.24, 71.01, 60.13, 31.49, 30.57, 14.17.

ESI–MS: *m/z* (%) 327 (100) [M+Na]$^+$.

HRMS (ESI): Calcd for $C_{18}H_{24}O_4Na$ [M+Na]$^+$ 327.1572, found 327.1567.

(*2E,6E*)–Ethyl 9–(benzyloxy)–8–hydroxy–2–methylnona–2,6–dienoate (84D)

Column chromatography: Silica gel, 25% EtOAc in petroleum ether eluant.

Yield: 88%, Colorless oil.

***R*$_f$:** 0.3 (Silica gel, 10% EtOAc in petroleum ether).

IR (neat): ν_{max} 3462, 2922, 2856, 1703, 1448, 1264, 1099, 968, 738, 698 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.35–7.22 (m, 5H, Ar*H*), 6.68 (m, 1H, C*H*=C(CH$_3$)COOEt), 5.74 (dt, *J* = 15.1, 6 Hz, 1H, C*H*=CHCH(OH)), 5.44 (dd, *J* = 15.8, 6

Hz, 1H, CH=C*H*CH(OH)), 4.54 (s, 2H, PhCH_2), 4.25 (m, 1H, C*H*(OH)), 4.16 (q, *J* = 6.8 Hz, 2H, COOCH_2CH$_3$), 3.45 (m, 1H, BnOC*H*H), 3.29 (m, 1H, BnOCH*H*), 2.3–2.12 (m, 5H, CH_2CH_2CH=CH, CH(O*H*)), 1.8 (s, 3H, CH=C(CH_3)), 1.29 (t, *J* = 6.8 Hz, 3H, COOCH$_2$CH_3).

^{13}C NMR (75 MHz, CDCl$_3$): δ 168.02, 140.92, 137.75, 131.99, 129.07, 128.33, 128.16, 127.69, 127.65, 74.18, 73.2, 71.02, 60.33, 31.07, 28.08, 14.17, 12.33.

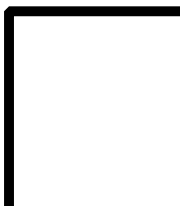
ESI–MS: *m/z* (%) 319 (20) $[M+H]^+$, 336 (100) $[M+NH_4]^+$, 341 (20) $[M+Na]^+$

HRMS (ESI): Calcd for $C_{19}H_{26}O_4Na$ $[M+Na]^+$ 341.1728, found 341.1715.

Generalized experimental procedure for Sharpless' kinetic resolution reaction:

To a solution of activated 4Å MS (20% *w/w*) in CH_2Cl_2 (4 mL/mmol), Ti(O^iPr)$_4$ (1 eq) and L–(+)–DIPT (1.2 eq) were added sequentially at –20 °C under nitrogen atmosphere . After 20 min of stirring, a solution of the allylic alcohol (1 eq) in CH_2Cl_2 was added to the reaction mixture and stirring was continued for 30 min. TBHP (4.63 M in toluene, 2.5 eq) was added and stirred for 2 to 3 h at –20 °C. Then the reaction mixture was quenched with water, warmed up to room temperature, stirred for 10 h and extracted with EtOAc (2×). The combined organic extracts were washed with water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel column chromatography provided the pure epoxy alcohol.

(*E*)–Ethyl 5–((*2S,3S*)–3–((*S*)–1–hydroxyethyl)oxiran–2–yl)pent–2–enoate (83A)



Column chromatography: Silica gel, 25% EtOAc in petroleum ether eluant.

Yield: 47%, Colorless oil.

***R$_f$*:** 0.4 (Silica gel, 50 % EtOAc in petroleum ether).

[α]$_D^{19}$: –5.4 (*c* 4.5, $CHCl_3$).

IR (neat): ν_{max} 3451, 2978, 2929, 1715, 1653, 1368, 1268, 1205, 1173, 1039 cm^{-1}.

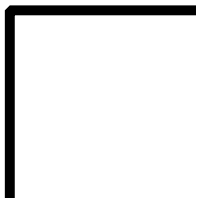
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.92 (dt, *J* = 15.3, 6 Hz, 1H, C*H*=CHCOOEt), 5.82 (d, *J* = 15.3 Hz, 1H, CH=C*H*COOEt), 4.16 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 3.88 (m, 1H, C*H*(OH)), 2.96 (m, 1H, $CH_2CHOCHCH(OH)$), 2.71 (m, 1H, $CH_2CHOCHCH(OH)$), 2.43–2.27 (m, 2H, $CH_2CH=CH$), 2.01 (br s, 1H, CH(O*H*)), 1.76–1.67 (m, 2H, $CH_2CHOCHCH(OH)$), 1.28 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.21 (d, *J* = 7.1 Hz, 3H, $CH_3CH(OH)$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.37, 147.34, 122.0, 64.77, 61.71, 60.2, 54.17, 29.99, 28.51, 18.75, 14.11.

ESI–MS: *m/z* (%) 232 (20) $[M+NH_4]^+$, 237 (90) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{11}H_{18}O_4Na$ $[M+Na]^+$ 237.1102, found 237.1096.

(*E*)–Ethyl 5–((*2S,3S*)–3–((*S*)–1–hydroxyethyl)oxiran–2–yl)–2–methylpent–2–enoate (83B)



Column chromatography: Silica gel, 20% EtOAc in petroleum ether eluant.

Yield: 44%, Colorless oil.

***R_f*:** 0.5 (Silica gel, 50% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: –10.72 (*c* 3.27, $CHCl_3$).

IR (neat): ν_{max} 3452, 2978, 2930, 1706, 1367, 1268, 1196, 1139, 1094, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (m, 1H, C*H*=C(CH_3)COOEt), 4.18 (q, *J* = 7.3 Hz, 2H, $COOCH_2CH_3$), 3.9 (dq, *J* = 13.2, 3.7 Hz, 1H, C*H*(OH)), 2.96 (td, *J* = 11.7, 5.9 Hz, 1H, $CH_2CHOCHCH(OH)$), 2.72 (m, 1H, $CH_2CHOCHCH(OH)$), 2.4–2.27 (m, 2H, $CH_2CH=C(CH_3)$), 1.84 (s, 3H, CH=C(CH_3)), 1.74–1.67 (m, 2H, $CH_2CHOCHCH(OH)$), 1.3 (t, *J* = 7.3 Hz, 3H, $COOCH_2CH_3$), 1.22 (d, *J* = 5.9 Hz, 3H, $CH_3CH(OH)$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.88, 140.19, 128.59, 64.8, 61.76, 60.4, 54.4, 30.5, 24.99, 18.72, 14.11, 12.22.

ESI–MS: *m/z* (%) 229 (20) $[M+H]^+$, 251 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{12}H_{20}O_4Na$ $[M+Na]^+$ 251.1259, found 251.1269.

(*E*)–Ethyl 5–((*2S,3S*)–3–((*S*)–2–(benzyloxy)–1–hydroxyethyl)oxiran–2–yl)pent–2–enoate (83C)

Column chromatography: Silica gel, 25% EtOAc in petroleum ether eluant.

Yield: 45%, Colorless oil.

***R*$_f$:** 0.25 (Silica gel, 30% EtOAc in petroleum ether).

$[\alpha]_D^{19}$: –7.9 (*c* 4.4, $CHCl_3$).

IR (neat): ν_{max} 3430, 2982, 2924, 2866, 1712, 1653, 1451, 1368, 1273, 1206, 1172, 1104, 1036, 894, 745, 701 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 5H, Ar*H*), 6.93 (dt, *J* = 15.1, 6.8 Hz, 1H, C*H*=CHCOOEt), 5.82 (m, 1H, CH=C*H*COOEt), 4.56 (s, 2H, PhCH_2), 4.16 (q, *J* = 7.6 Hz, 2H, COOCH_2CH$_3$), 3.69 (m, 1H, C*H*(OH)), 3.62–3.5 (m, 2H, BnOCH_2), 2.95 (m, 1H, CH$_2$C*H*OCHCH(OH)), 2.8 (m, 1H, CH$_2$CHOC*H*CH(OH)), 2.39–2.29 (m, 2H, CH_2CH=CH), 1.83–1.61 (m, 2H, CH_2CH$_2$CH=CH), 1.29 (t, *J* = 7.6 Hz, 3H, COOCH$_2$CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.37, 147.33, 137.57, 128.36, 127.76, 127.67, 121.95, 73.43, 71.23, 69.24, 60.18, 58.14, 55.23, 30.01, 28.42, 14.14.

ESI–MS: *m/z* (%) 321 (45) $[M+H]^+$, 338 (100) $[M+NH_4]^+$, 343 (20) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{18}H_{24}O_5Na$ $[M+Na]^+$ 343.1521, found 343.1511.

(*E*)–Ethyl 5–((*2S,3S*)–3–((*S*)–2–(benzyloxy)–1–hydroxyethyl)oxiran–2–yl)–2–methylpent–2–enoate (83D)

Column chromatography: Silica gel, 20% EtOAc in petroleum ether eluant.

Yield: 44%, Colorless oil.

***R*$_f$:** 0.3 (Silica gel, 30% EtOAc in petroleum ether).

$[\alpha]_D^{19}$: –7.3 (*c* 3.4, $CHCl_3$).

IR (neat): ν_{max} 3463, 2923, 1704, 1267, 1097, 898, 740 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35–7.24 (m, 5H, Ar*H*), 6.71 (t, *J* = 7.3 Hz, 1H, C*H*=C(CH_3)COOEt), 4.55 (s, 2H, PhCH_2), 4.17 (q, *J* = 7.3 Hz, 2H, COOCH_2CH_3), 3.68 (m, 1H, C*H*(OH)), 3.61–3.5 (m, 2H, BnOCH_2), 2.94 (m, 1H, CH_2C*H*OCHCH(OH)), 2.79 (m, 1H, CH_2CHOC*H*CH(OH)), 2.35–2.26 (m, 2H, CH_2CH=C(CH_3)), 1.83 (s, 3H, CH=C(CH_3)), 1.78–1.61 (m, 2H, CH_2CH_2CH=CH), 1.3 (t, *J* = 7.3 Hz, 3H, $COOCH_2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.95, 140.22, 137.59, 128.66, 128.38, 127.79, 127.68, 73.46, 71.26, 69.38, 60.46, 58.16, 55.54, 30.57, 25.01, 14.19, 12.30.

ESI–MS: *m/z* (%) 335 (40) $[M+H]^+$, 352 (100) $[M+NH_4]^+$, 357 (30) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{19}H_{26}O_5Na$ $[M+Na]^+$ 357.1677, found 357.1664.

Generalized experimental procedure for the transformations 94→84A, 95→84B, 101→84C and 102→84D *via* Swern oxidation and Luche reduction:

Allylic alcohols **94**, **95**, **101**, **102** were oxidised to the corresponding ketones *via* Swern oxidation method[44] as described for the synthesis of **85a–b**.

To a solution of the *α,β*–unsaturated ketone in MeOH at 0 °C was wdded $CeCl_3 \cdot 7H_2O$ (2.2 eq) and stirred for 15 min at the same temperature followed by the portionwise addition of $NaBH_4$ (2.2 eq). Reaction mixture was warmed to room temperature and stirred for additional 1.5 h before it was quenched with saturated aqueous NH_4Cl solution. MeOH was evoparated and the crude residue was then extracted with EtOAc (2×). Combined organic extracts were washed with water, saturated aqueous NaCl,

dried (Na_2SO_4) and concentarted *in vacuo*. Purification by standard silica gel column chromatography afforded the allylic alchols **84A–D**.

Generalized experimental procedure for Ti(III) radical mediated epoxide opening reaction:

Activated Zn powder (6 eq), freshly fused $ZnCl_2$ (3 eq) and Cp_2TiCl_2 (3 eq) were taken in THF (15 mL/mmol) and stirred for 30 min at room temperature. The color of the reaction mixture turned into deep green from deep red. Then it was cooled to –20 °C and 2,3–epoxy alcohol (1 eq) dissolved in THF was added. The reaction mixture was allowed to room temperature, stirred for 16 h before it was quenched with 1N HCl and then extracted with EtOAc (2×). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, saturated aqueous NaCl, dried (Na_2SO_4) and concentrated *in vacuo*. The crude residual oil thus obtained was purified by using standard silica gel column chromatography to get the five–membered carbocycle.

Ethyl 2–((*1R,2R,3S*)–3–hydroxy–2–((*S*)–1–hydroxylethyl)cyclopentyl) acetate (76A)

Column chromatography: Silica gel, 28% EtOAc in petroleum ether eluant.

Yield: 35%, Colorless oil.

***R*$_f$:** 0.3 (Silica gel, 40% EtOAc in petroleum ether).

[α]$_D^{24}$: +28.1 (*c* 1.43, $CHCl_3$).

IR (neat): ν_{max} 3357, 2963, 2924, 1729, 1372, 1298, 1256, 1171, 1115, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.52 (td, *J* = 4.7, 1.5 Hz, 1H, C_1H), 4.14 (q, *J* = 7.2 Hz, 2H, $COOCH_2CH_3$), 3.97 (qd, *J* = 6.5, 4 Hz, 1H, C_6H), 2.61 (m, 1H, C_3H), 2.40 (dd, *J* = 16, 6.5 Hz, 1H, C_8H_b), 2.34 (dd, *J* = 16, 7.3 Hz, 1H, C_8H_a), 2.13 (m, 1H, C_4H_β), 1.8 (m, 1H, C_5H_α), 1.67 (m, 1H, C_5H_β), 1.37 (d, *J* = 6.5 Hz, 3H, C_7H_3), 1.34 (m, 1H, C_4H_a), 1.32 (dt, *J* = 10.3, 4.3 Hz, 1H, C_2H), 1.26 (t, *J* = 7.2 Hz, 3H, $COOCH_2CH_3$)

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 74.7, 66.8, 60.6, 56.1, 38.8, 34.0, 33.4, 29.3, 21.9, 14.2.

ESI–MS: *m/z* (%) 217 (95) $[M+H]^+$, 239 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{11}H_{20}O_4Na$ $[M+Na]^+$ 239.1259, found 239.1265.

(*S*)–Ethyl 2–((*1S,2R,3S*)–3–hydroxy–2–((*S*)–1–hydroxyethyl)cyclopentyl) propanoate (76B)

Column chromatography: Silica gel, 28% EtOAc in petroleum ether eluant.

Yield: 35%, Colorless oil.

***R_f*:** 0.3 (Silica gel, 50% EtOAc in petroleum ether).

$[\alpha]_D^{24}$: +26.3 (*c* 0.95, $CHCl_3$).

IR (neat): ν_{max} 3358, 2969, 2934, 1728, 1452, 1376, 1254, 1180, 1047 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.53 (td, *J* = 4.6, 2.3 Hz, 1H, C_1H), 4.12 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 4.0 (qd, *J* = 6.4, 4 Hz, 1H, C_6H), 2.61 (qd, *J* = 7.1, 4.8 Hz, 1H, C_8H), 2.54 (m, 1H, C_3H), 1.99 (m, 1H, C_4H_β), 1.72 (m, 1H, C_5H_α), 1.64 (m, 1H, C_5H_β), 1.56 (dt, *J* = 8.8, 4.4 Hz, 1H, C_2H), 1.51 (m, 1H, C_4H_α), 1.37 (d, *J* = 6.5 Hz, 3H, C_7H_3), 1.2 (t, *J* = 7.2 Hz, 3H, $COOCH_2CH_3$), 1.17 (d, *J* = 7 Hz, 3H, C_9H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 75.2, 67.5, 60.3, 51.9, 40.9, 40.0, 33.6, 25.7, 22.3, 14.7, 14.3.

ESI–MS: *m/z* (%) 231 (100) $[M+H]^+$, 253 (50) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{12}H_{22}O_4Na$ $[M+Na]^+$ 253.1415, found 253.1427.

Ethyl 2–((1R,2S,3S)–2–((R)–2–(benzyloxy)–1–hydroxyethyl)–3–hydroxycyclo pentyl) acetate (76C)

Column chromatography: Silica gel, 25% EtOAc in petroleum ether eluant.

Yield: 45%, Colorless oil.

***R_f*:** 0.4 (Silica gel, 60% EtOAc in petroleum ether).

$[\alpha]_D^{24}$: +20.7 (*c* 0.41, $CHCl_3$).

IR (neat): ν_{max} 3391, 2926, 1721, 1652, 1256, 1105, 1038, 747 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.20 (m, 5H, Ar*H*), 4.52 (s, 2H, PhCH_2), 4.35 (td, *J* = 5.3, 2.5 Hz, 1H, C_1H), 4.03 (q, *J* = 7.4 Hz, 2H, COOC$H_2$$CH_3$), 3.96 (m, 1H, C_6H), 3.6 (d, *J* = 5 Hz, 2H, C_7H_2), 2.56 (m, 1H, C_3H), 2.35 (dd, *J* = 15.4, 5.4 Hz, 1H, C_8H_b), 2.17 (dd, *J* = 15.4, 8.5 Hz, 1H, C_8H_a), 2.05 (m, 1H, C_4H_β), 1.76 (m, 1H, C_5H_α), 1.58 (m, 1H, C_5H_β), 1.46 (dt, *J* = 9.7, 4.8 Hz, 1H, C_2H), 1.24 (m, 1H, C_4H_α), 1.15 (t, *J* = 7.4 Hz, 3H, $COOCH_2CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 137.7, 128.6, 127.9, 127.8, 74.9, 73.8, 73.6, 70.3, 60.4, 51.6, 38.9, 34.9, 33.6, 29.0, 14.2

ESI–MS: *m/z* (%) 323 (70) $[M+H]^+$, 345 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{18}H_{26}O_5Na$ $[M+Na]^+$ 345.1677, found 345.1669.

(*S*)–Ethyl 2–((*1S,2S,3S*)–2–((*R*)–2–(benzyloxy)–1–hydroxyethyl)–3–hydroxycyclo pentyl) propanoate (76D)

Column chromatography: Silica gel, 22% EtOAc in petroleum ether eluant.

Yield: 55%, Colorless oil.

***R_f*:** 0.5 (Silica gel, 50% EtOAc in petroleum ether).

$[\alpha]_D^{24}$: +28.9 (*c* 0.84, $CHCl_3$).

IR (neat): ν_{max} 3391, 2930, 1720, 1452, 1264, 1176, 1100, 1041, 740, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 5H, Ar*H*), 4.52 (s, 2H, PhCH_2), 4.35 (td, *J* = 5.1, 2.6 Hz, 1H, C_1H), 4.03 (q, *J* = 7.2 Hz, 2H, COOC$H_2$$CH_3$), 4.00 (m, 1H, C_6H), 3.6 (d, *J* = 5.4 Hz, 2H, C_7H_2), 2.56 (qd, *J* = 7.2, 5.1 Hz, 1H, C_8H), 2.44 (m, 1H, C_3H), 1.92

(m, 1H, C_4H_β), 1.69 (m, 1H, C_2H), 1.66 (m, 1H, C_5H_α), 1.58 (m, 1H, C_5H_β), 1.42 (m, 1H, C_4H_α), 1.15 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.1 (d, J = 7.1 Hz, 3H, C_9H_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 137.6, 128.5, 127.9, 127.8, 75.3, 74.0, 73.6, 70.8, 60.2, 48.3, 41.3, 41.0, 33.6, 25.3, 15.5, 14.3.

ESI–MS: *m/z* (%) 337 (100) $[M+H]^+$, 359 (95) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{19}H_{28}O_5Na$ $[M+Na]^+$ 359.1834, found 359.1820.

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INTRODUCTION

The term macrocycle refers to medium and large ring compounds with respectively 8–11 and 12 or more atoms in the ring. Macrocycle structures that have one or more ester linkages are generally referred to as macrolides or macrocyclic ring lactones.[1–4] In some cases, macrocyclic lactams have also been described as macrolides. Originally macrolides denoted a class of antibiotics derived from species of *streptomyces* and containing a highly substituted macrocyclic lactone ring aglycon with few double bonds and one or more sugars, which may be aminosugars, non–nitrogen sugars or both.[5] To our knowledge the largest naturally occurring macrolides are the 60–membered quinolidomycins[6] and the largest constructed macrolide is the 44–memberd swinholide.[7]

The nomenclature of macrolides is anything but straightforward. Trivial names are widely used, especially for naturally occurring macrocyclic lactones. According to IUPAC rules, macrolides as well as other lactones formed from aliphatic acids should be named by adding "olide" as a suffix to the name of the hydrocarbon with the same number of carbon atoms. The numbering starts from the ester carbonyl carbon. The IUPAC rules also give an alternative way of naming lactones based on the rules for naming heterocycles. According to this rule the lactones are named as oxacyclo ketones and the numbering starts from the ring oxygen. The AutoNom[8] naming program uses this latter rule although the "olide'' naming is generally used in the literature. The macrolide structure of this work is sometimes identified by their trivial names.

The chemistry of macrocyclic compounds originated in 1926 when Ruzicka[1,3,9] elucidated the structures of cietone (**1**) and muscone (**2**) as large–ring ketones (Figure 1). Before this, it was believed on the basis of Bayer's strain theory that large–ring compounds would be too unstable to exist because the internal bond angles in large planar rings do not have tetrahedral geometry. In fact large rings are able to adopt nonplanar conformations and they are flexible and almost strain free.[2]

In 1927 Kerchbaum isolated the first macrocyclic lactone, exaltolide (**3**) and ambrettolide (**4**), from *Angelica* root and *Ambrette* seed oil, respectively.[10] The discovery of these vegetable musk oils aroused interest in finding synthetic routes to these and related macrolides owing to commercial importance in the fragrance industry.[2] Even today exaltolide (**3**) is one of the most widely produced macrocyclic musk lactones (Figure 1).

The production was estimated at 200 tons in 1996. The importance of macro–cyclic musks is increasing due to their ready biodegradability.

Figure 1

The interest in macrolides has grown enormously after 1950. The tremendous interest in macrolide chemistry can be understood if one takes a look at the diversity of the structures and physiological effects of macrolides. Natural products containing a macrolactone framework are found in plants, insects, and bacteria and they may be of terrestrial or marine origin. The useful properties of macrolides range from perfumery to biological and medicinal activity. The new findings in the field of antitumor active and other antibiotic macrolides, together with pheromones and plant growth regulators with macrolactone framework, are an inspiration to chemists to study macrolides.

Macrolide antibiotics play therapeutically an important role. They are regarded as among the safest of antibiotics and they have successfully been used to treat infections caused by gram–positive organisms, certain gram–negative and anaerobic bacteria.[11]

The wide variety of macrolide structure in nature can be appreciated just by looking at some examples of different types of macrolides with C_2–symmetry (Figure 2). Some examples of C_2–symmetric macrodiolides are IKD–8344 (**5**),[12] swinholide A (**6**),[7] (–)–disorazole C_1 (**7**),[13] (+)–carpaine (**8**),[14] glucolipsin A (**9**),[15] elaiolide (**11**),[16] and clavosolide A (**12**)[17] while nonactin (**10**)[18] (Figure 2A,B) represent the macrotetralide. Recent findings in the field of macrolides revealed that most of pharmacologically active macrolides have highly substituted structures as can be seen from these examples.

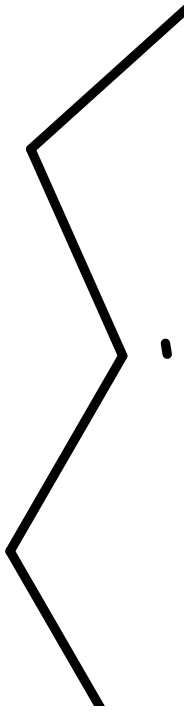


Figure 2A

Figure 2B

Rhizopodin is one such example, which was isolated from the culture broth of the myxobacterium, *Myxococcus stipitatus* in 1993 by Sasse *et al*.[19] Initially it was proposed (Figure 3) that rhizopodin was a 16–membered macrolide (**15**)[19] but later revised as a C_2–

symmetric 38–membered dilactone (**16**) bearing 18 stereogenic centers, two disubstituted oxazole rings, two conjugated diene systems and two enamide side chains by X–ray analysis of its complex with rabbit muscle G–actin and extensive NMR studies (Figure 4).[20–22] It showed potent cytostatic activity against a range of tumor cell lines in the low nanomolar range.[23] This observed cytostatic activity is attributed to its formation of a complex with G–actin where the enamide side chains play a key role. It specifically binds to select sites of G–actin and disrupts the cytoskeleton there by inhibits the actin polymerization.[22]

Figure 3. Proposed structure of rhizopodin (**15**)

Figure 4. Revised structure of rhizopodin (**16**)

Actin is a globular, roughly 42–kDa protein found in all eukaryotic cells (the only known exception being nematode sperm) where it may be present at concentrations of over 100 μM. It is also one of the most highly–conserved proteins, differing by no more than

20% in species as diverse as algae and humans. Actin is the monomeric subunit of two types of filaments in cells: microfilaments, one of the three major components of the cytoskeleton, and thin filaments, part of the contractile apparatus in muscle cells. Thus, actin participates in many important cellular processes including muscle contraction, cell motility, cell division and cytokinesis, vesicle and organelle movement, cell signaling, and the establishment and maintenance of cell junctions and cell shape. Many of these processes are mediated by extensive and intimate interactions of actin with cellular membranes. In vertebrates, three main groups of actin isoforms, alpha, beta, and gamma have been identified. The alpha actins are found in muscle tissues and are a major constituent of the contractile apparatus. The beta and gamma actins co–exist in most cell types as components of the cytoskeleton, and as mediators of internal cell motility. Rhizopodin that has the ability to bind to actin filaments, block polymerization and the elongation of actin. As a result of the inhibition of actin polymerization, there can be change cellular morphology, inhibit cellular processes such as cell division, and even cause cells to undergo apoptosis.

Unlike other macrolides with actin polymerization inhibitory activity like swinholide A (**6**)[7], misakinolide A (**13**)[24] and bistheonellide B (**14**)[25], rhizopodin behaves as a bivalent inhibitor forming a ternary complex with the two actin molecules. Biological studies[26] further revealed that rhizopodin affects the dynamics of actin skeleton of macrophages there by showing significant changes in the phagocyte efficiency for yeast cells. The monomeric rhizopodin macrolide (ball–and–stick model; N blue, C orange, O red) does not provide an optimal explanation of the electron density (blue mesh: $2F_o–F_c$, 1σ) and results in significant difference density ($F_o–F_c$, green, 3σ; red, –3σ). The revised model of rhizopodin provided an optimal fit to the electron density (Figure 5). Rhizopodin and in particular its enamide side chain is remarkably well adapted to the molecular surface of actin (Figure 6). Recognition is primarily achieved through van der Waals interactions of the enamide side chain with the hydrophobic residues in the binding cleft of actin. The only polar interactions involve two water–mediated hydrogen bonds of the terminal carbonyl oxygen of rhizopodin to the backbone nitrogen atoms of Ile136 and Ala172.

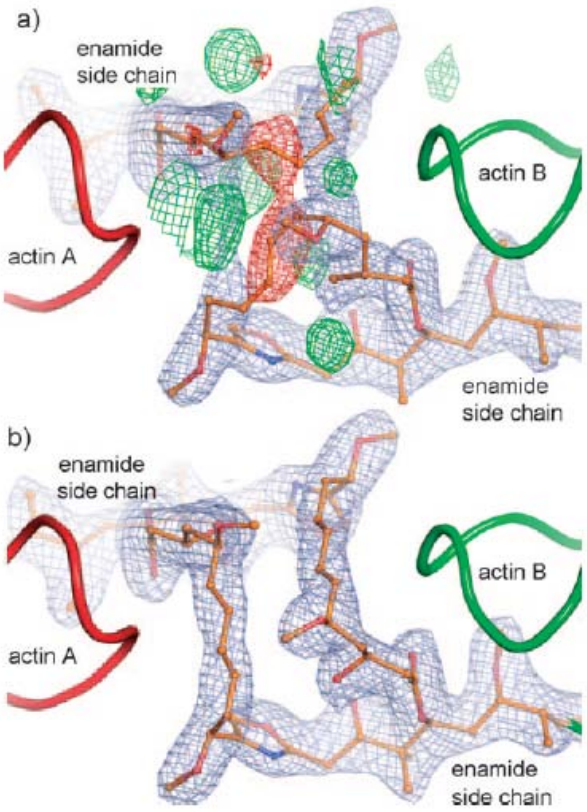


Figure 5. Three–dimensional representation of the rhizopodin/actin complex

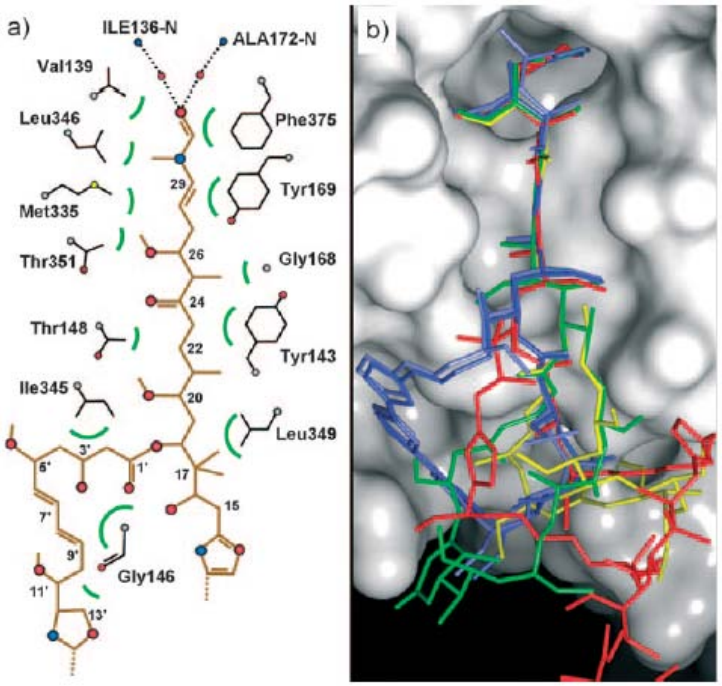


Figure 6. Binding of rhizopodin to G–actin

The conformation of the enamide side chain is similar to that of other macrolides such as kabiramide, reidisphingolid,[23,27] and sphinxolid.[28] The complex of G–actin with bistramide A, a macrolide with a structurally divergent side chain, indicates that physically blocking the 1–3 cleft suffices to prevent actin polymerization.[29] This inference is reinforced by the fact that the macrolide rings of the other inhibitors are structurally distinct, each interacting with a different set of residues on the molecular surface of actin (Figure 6).

Evaluation of the biological properties of monorhizopodin (**33**) and 16–*epi*–monorhizopodin (**34**) in actin polymerization and cytotoxicity assays has been recently reported[32] by Nicolaou and his co–workers. They have presented that monorhizopodin (**33**) exhibited potent inhibitory activity of actin polymerization, *via* its enamide side chain structural motif. And the corresponding 16–*epi*–isomer (**34**) has showed somewhat lower potency, and was comparable to that of latrunculin A. However, neither monorhizopodin (**33**) nor 16–*epi*–monorhizopodin (**34**) exhibited cytotoxicity against MDA–MB–231 breast cancer cells (up to 100 mm concentrations).

Contemporary works

In combination of potent cytostatic activity of rhizopodin to inhibit the actin polymerization with its complex architecture makes it an attractive target in the synthetic organic community.

Tao Ye's approach: Synthesis of C9–C23 fragment

Ye and his co–workers have reported[30] the C9–C23 (C9'–C23') fragment (**18**) of the rhizopodin. They have envisioned that the total synthesis of the molecule could be achieved by macrolactonization/cyclodimerization of the monomer **17** which in turn can be obtained from the C9–C23 fragment (**18**) *via* a Stille coupling or Wittig olefination at the terminal olefinic bond. Fragment **18** was achieved from the intermediate **19** by applying DAST mediated oxazole ring formation and Keck allylation. Compound **19** was obtained from **20** which involved a peptide coupling where as **20** was derived from the compound **21**. Brown's crotyl boration, HWE olefination and Sharpless' epoxidation reactions were

applied on compound **22** to make **21**. Compound **22** was obtained from the commercially available *D*–pantolactone (Scheme 1).

Scheme 1

Chakraborty, T. K.'s approach: Synthesis of C1–C15 fragment

Chakraborty and his co–workers have reported[31] the stereoselctive synthesis of C1–C15 fragment (**25**) of the rhizopodin. They have envisoned that the C_2–symmetric rhizopodin could be synthesized by the macrolactonization/cyclodimerization of the suitably protected monomer **23** which in turn could be achieved *via* a NHK reaction of the key intermediates **24** and **25**. A Stille coupling of the compounds **26** and **27** provided the fragment **25**. Stannane **26** was synthesized by employing Urpi's enantioselective addition of titanium enolates over the dimethyl acetal of cinnamaldehyde **29** and Ohira reaction to make the triple bond. Iodide **27** was obtained from the oxazole **30** which in turn was

prepared from the acid **31** and amine salt **32** by applying peptide coupling, DAST mediated one–pot oxazole formation and Keck allylation reactions (Scheme 2).

Scheme 2

Nicolaou, K. C.'s approach: Total synthesis of monorhizopodin, 16–*epi*–monorhizopodin

Nicolaou and his co–workers have reported[32] the total synthesis of initially proposed monomeric structure of rhizopodin and its 16–epimer. Target molecule has been achieved by the macrolactonization of the seco acid **37** followed by HWE olefination with keto phosphonate **35** which in turn was achieved from aldehyde **36** that involved a Brown's *E*–crotyl boration (Scheme 3).

Scheme 3

Seco acid **37** has been accomplished by the SmI_2 mediated Barbier reaction of the iodo fragment **38** and an aldehyde **39** that was derived from the diol **42** which involved a

Brown's *Z*–crotyl boration. Iodo–ester **38** has been realised *via* Stille coupling of the stannane **41** and the iodide **40**. Application of the Denmark's protocol over the aldehyde **43** and few manipulations brought the iodide **40** into vision. Stannane **41** has been furnished by the application of enantioselective alkynyaltion over the aldehyde **44** followed by few transformations (Scheme 3).

PRESENT WORK

We predicted that the total synthesis of this molecule would not only provide an access to larger quantities for further biological studies, but also help to design and build more potent synthetic analogs. The wealth of biological functions and chemical structure prompted us to initiate a program aimed at the total synthesis of rhizopodin. Rhizopodin is a C_2–symmetric diolide consisting of 18 stereogenic centers, two disubstituted oxazole rings, two conjugated diene systems and two enamide side chains.

Retrosynthetic analysis for rhizopodin (**16**) was illustrated in scheme 4. We have envisaged that total synthesis of rhizopodin can be achieved by macrocyclization or cyclodimerization[33] of suitably protected monomer unit **23** which can be obtained by selective silyl deprotection and ester hydrolysis of compound **45**. Monomer unit **45** would be prepared from Nozaki–Hiyama–Kishi coupling[34a–g] or SmI_2 mediated Barbier reaction[34h] between **46** and **47**. Fragment **46** could be achieved from aldehyde **48** *via* application of 1,3–*anti* diastereofacial Mukaiyama aldol reaction.[35] A Horner–Wadsworth–Emmons olefination[36] reaction between the phosphonate **49** and aldehyde **50** could be a key execution to realize the motif **48**. Keto–phosphonate **49** could be derived from the enantioselective addition of titanium enolate[37] of **51** to dimethyl acetal **52** followed by displacement of the chiral auxiliary. The chiral auxiliary **51** could be prepared from commercially available L–valine **56**, where as dimethyl acetal **52** from 1,3–propanediol **55**. Aldehyde **50** could be realized by the Evans' *syn* aldol[38] reaction between chiral auxiliary **54** and aldehyde **53** followed by few functional group manipulations. The chiral auxiliary **54** could be obtained from D–phenylalanine **57** where as the aldehyde **53** from 1,3–propanediol **55.**

Scheme 4. Retrosynthetic analysis of C16–C28 fragment of rhizopodin

RESULTS AND DISCUSSION

Our synthesis commenced with the mono PMB protection[39] of the commercially available 1,3-propanediol **55** by using 1 eq of PMBBr which was produced by the reaction of 1 eq of PMBOH and 0.33 eq of PBr_3 at 0 °C in Et_2O, 1 eq of NaH (60% dispersion in oil) and 0.01 eq of TBAI at 0 °C–rt for 12 h to get the compound **58** in 80% yield (Scheme 5). Appearance of signals at δ 7.22 (d), 6.85 (d) integrating for 2 protons each corresponding to Ar*H* and a singlet integrating for 3 protons at δ 3.8 corresponding to OMe group in the ^{1}H NMR spectrum of compound **58** confirmed the mono protection. In addition to this, a signal at *m/z* 219 in the ESI–MS spectrum of compound **58** that corresponds to the $[M+Na]^+$ was additional support for the formation of the product. Compound **58** was oxidized to corresponding aldehyde **53** by applying Swern oxidation procedure.[40] Reaction of the alcohol **58** with 1.5 eq of $(COCl)_2$, 3.2 eq of DMSO and 5 eq of Et_3N in CH_2Cl_2 at –78 °C–0 °C for 3 h furnished the aldehyde **53** which was taken forward to next reaction, after a flash column chromatography, without any further characterization.

Scheme 5

For the preparation[41] of the chiral auxiliary **54**, we started with the readily available D–phenylalanine (**57**) which was reduced to the corresponding aminol **59** in 71% yield by using 2.4 eq of $NaBH_4$ and 1 eq of I_2 in THF at 0 °C to reflux conditions for 18 h (Scheme 6). The amino alcohol was protected to get carbamate **60** by using 2 eq of $(EtO)_2CO$ and 0.1 eq of K_2CO_3 at 135 °C. The analytical data of compound **60** were in good agreement with the reported values.[41] *N*–acylation of the oxazolidinone **60** was carried out to get the chiral auxiliary **54** in 95% yield by treating with 1.1 eq of ^{n}BuLi (1.6M in hexane) and 1.3 eq of propanoyl chloride at –78 °C in THF for 1.5 h. Perfect support for the formation of the product was obtained from the ^{1}H NMR spectrum of the compound **54** showing signals

corresponding to propanoyl moiety at δ 3.05–2.82 ($COCH_2CH_3$) and a triplet at δ 1.2 (J = 7.6 Hz, $COCH_2CH_3$). Signal at *m/z* 256 in the ESI–MS spectrum which corresponds to the $[M+Na]^+$ further justified the product.

Scheme 6

Now both the starting materials, aldehyde **53** and chiral auxiliary **54**, were ready for the asymmetric aldol reaction. The asymmetric aldol addition mediated by chiral auxiliaries is one of the most important and general methods for carbon–carbon bond formation.

Figure 7. Mechanism for Evans' *syn* aldol reaction

In particular, the Evans' dialkylboron triflate mediated aldol reaction[38] is a well accepted and useful method for the preparation of *β*–hydroxy acid and their derivatives in high enantiomeric purity. The transition state **I** (Figure 7) has been proposed for the boron enolate (and the titanium enolate) to give the "Evans' *syn* aldol" product. If the chloride ion is lost, the titanium enolate can also proceed through **IIb** in which both the aldehyde and the auxiliary are coordinated to titanium. This minor competitive path–way for the titanium enolates of oxazolidinone provides the "non–Evans' *syn* aldol" as the major product because of the change in π–facial selectivity and the overall diastereoselectivity reduced. The acyloxazolidinethione enolates proceed through the "chelated" transition state **IIc** due to the known higher affinity of sulfur for titanium.

Thus, di-*n*-butylborontriflate mediated Evans' *syn* aldol reaction between chiral oxazolidinone **54** and aldehyde **53** gave the aldol product **61** in 90% yield (Scheme 7). Appearance of signals integrating for a total of 9 protons at the aromatic region *δ* 7.33–6.81 in the ^{1}H NMR spectrum of the product **61** supported the C–C bond formation. Rests of the protons resonated at their respective chemical shift values. High resolution ESI mass spectrum carrying a signal at *m/z* 450.1873 corresponding to $[M+Na]^+$ (calcd 450.1892) was also in accordance to the successful formation of the aldol adduct **61**.

Scheme 7

As the successful fixation of both methyl and hydroxyl centre was over *via* an Evans' aldol reaction, reductive removal[42a] of the chiral auxiliary by using 5 eq of $NaBH_4$ in a 5:1 mixture of THF and water at 0 °C–rt for overnight furnished the dihydroxy compound **62** in 76% yield (Scheme 8). Disappearance of the signals corresponding to the chiral auxiliary moiety in the ^{1}H NMR spectrum of the compound **62** was the proof for the success of the reaction and the remaining protons resonated at their respective chemical shift values. In addition to this, high resolution ESI mass spectrum carrying a signal at *m/z* 277.1404 corresponding to $[M+Na]^+$ (calcd 277.1415) was also in good agreement with the successful formation of the diol **62**. Selective *O*–silylation[42b–c] of the diol **62** was carried

out by using 1.1 eq of TBDPSCl, 2.5 eq of Et_3N and 0.05 eq of DMAP in CH_2Cl_2 at 0 °C–rt for overnight to get the TBDPS ether **63** in 90% yield. Appearance of signals corresponding to both phenyl rings and ^tBu moiety at δ 7.66–7.30 and 1.05 respectively in the ^1H NMR spectrum of compound **63** was in good agreement with the successful mono silylation. High resolution ESI mass spectrum carrying a signal at *m/z* 515.2611 corresponding to $[M+Na]^+$ (calcd 515.2593) was also in concurrence with the formation of the TBDPS ether **63**.

Scheme 8

Reaction of the secondary alcohol **63** with 1.2 eq of NaHMDS and 4.5 eq of MeI in THF[42d] at 0 °C–rt for 4 h furnished the methyl ether **64** in 89% yield (Scheme 8). Appearance of a singlet at δ 3.29 integrating for 3H corresponding to CHOCH_3 was in agreement with the successful methylation whilst rest of the protons resonated at their corresponding chemical shift values. High resolution ESI mass spectrum carrying a signal at *m/z* 529.2746 corresponding to $[M+Na]^+$ (calcd 529.2750) was also in good agreement with the formation of the compound **64**. Desilylation[42e–f] of the compound **64** was carried out by reacting with 1.5 eq of TBAF (1M solution in THF) in THF at 0 °C–rt for 7 h to get the primary alcohol **65** in 78% yield. Disappearance of the signals corresponding to both phenyl rings and ^tBu group of TBDPS moiety supported the successful desilylation. In addition to this, a signal at *m/z* 291.1573 corresponding to $[M+Na]^+$ (calcd 291.1572) in the high resolution ESI mass spectrum was helpful in confirming the transformation without

any ambiguity. Primary alcohol **65** was oxidized to corresponding aldehyde **50** by applying Swern oxidation procedure.[40] Reaction of the primary alcohol **65** with 1.5 eq of $(COCl)_2$, 3.2 eq of DMSO and 5 eq of Et_3N in CH_2Cl_2 at –78 °C–0 °C for 3 h furnished the aldehyde **50** which was taken forward to the next reaction, after a flash column chromatography, without any further characterization.

Scheme 9

Dimethyl acetal **52** was obtained from the 1,3–propanediol **55** in 3 steps by following the reported procedure.[43] Mono benzylation of the diol **55** was achieved by reacting with 1 eq of BnBr, 1.1 eq of NaH (60% dispersion in oil) and 0.05 eq of TBAI at 0 °C–rt for 12 h to get the compound **66** in 90% yield (Scheme 9). Appearance of signals at δ 7.33–7.16 (m), 4.5 (s) integrating for 5 and 2 protons respectively corresponding to the –OBn group in the ^{1}H NMR spectrum of compound **66** confirmed the mono protection. In addition to this, a signal at *m/z* 167 in the ESI–MS spectrum which corresponding to $[M+H]^+$ also supported the formation of the product. Compound **66** was oxidized to the aldehyde **67** by applying Swern oxidation procedure.[40] Reaction of the alcohol **66** with 1.5 eq of $(COCl)_2$, 3.2 eq of DMSO and 5 eq of Et_3N in CH_2Cl_2 at –78 °C–0 °C for 3 h furnished the aldehyde **67** which was taken forward to next reaction, after a flash column chromatography, without any further characterization. Treatment of the aldehyde **67** with 9 eq of trimethyl orthoformate and 1.04 eq of $CeCl_3 \cdot 7H_2O$ in MeOH at rt for overnight provided the dimethyl acetal **52** in 80% yield. Sharp singlet at δ 3.33 integrating for 6 protons in the ^{1}H NMR spectrum of compound **52** corresponding to two methoxy groups was a proof for the acetal formation. Rests of the protons resonated at their corresponding chemical shift values.

Scheme 10

In order to prepare the chiral auxiliary **51**, by known protocol,[44] we started with the readily available L–valine **56**. Treatment of the L–valine with 2.4 eq of $NaBH_4$ and 1 eq of I_2 at 0 °C to refluxing conditions for 18 h in THF furnished the valinol **68** in 65% yield (Scheme 10). Reaction of the valinol **65** with 2.6 eq of CS_2 and 2.7 eq of KOH in EtOH under refluxing conditions for 72 h furnished the thiazolidinethione **69** in 88% yield. The ^{1}H NMR spectrum of the compound **69** was in very good agreement with that of the reported one[44]. A signal at *m/z* 162 corresponding to $[M+H]^+$ in the ESI mass spectrum also confirmed the formation of the product. *N*–acylation of the thiazolidinethione **69** was carried out to get the chiral auxiliary **51** in 80% yield by treating with 1.1 eq of ^{n}BuLi (1.6M in hexane) and 1.3 eq of propanoyl chloride at –78 °C in THF for 1.5 h.

Now the stage was set in order to carry out enantioselective addition of the titanium enolate derived from the chiral auxiliary **51** to the dimethyl acteal **52**. Integration of both enantioselective aldol reaction and alkylation of the aldol adduct was reported[37] by Urpi *et al*, which is relatively advantageous to the conventional synthesis of *α*–alkyl–*β*–alkoxy carbonyl compounds which involves both the steps to be done separately. The aforementioned adducts were obtained in very good stereoselectivities. This transformation involves a Lewis acid–mediated cross–coupling reaction of dimethyl acetals to a chiral 1,3–thiazolidine–2–thione–derived titanium enolate. Wide range of acetals was employed.

It is likely that the reaction proceeds *via* an S_N1–like process. The observed stereochemistry might be ruled by an open transition state which involves the approach of an intermediate oxocarbenium ion to the less hindered face (*Si* face) of a putative chelated

Z–enolate and determines the *R* configuration at the *α*–center (Figure 8). Furthermore, transition states **Ts–A** and **Ts–B** shown in Figure 8 can be invoked in order to explain the stereochemistry of adducts **A** and **B**, assuming that interactions of the substituents of the oxocarbenium ion and the auxiliary must be minimized. Then, the preferential formation of the *anti* adduct can be rationalized through an antiperiplanar arrangement (**Ts–A**) on the basis of stereoelectronic and steric considerations.

Figure 8

Thus, as reported[37] by Urpi *et al*, compound **70** was obtained in 82% yield by the reaction of auxiliary **51** with 1.1 eq of $TiCl_4$, 1.1 eq of DIPEA, 1 eq of dimethyl acetal **52** and 1 eq of $SnCl_4$ in CH_2Cl_2 at –78 °C to –40 °C for 4 h (Scheme 11).

Scheme 11

The ^{1}H NMR spectrum showing the signals corresponding to both auxiliary and acetal motif supported the formation of the adduct. A high resolution ESI mass spectrum

consisting of a signal at *m/z* 418.1477 corresponding to $[M+Na]^+$ (calcd 418.1486) further justified the success of the reaction.

Displacement of the chiral auxiliary[45] present in compound **70** was crucial. Treatment of the carbanion, generated by the reaction of dimethyl methylphosphonate with ^{n}BuLi at –78 °C for 30 min, with the compound **70** at –78 °C for 30 min provided the keto phosphonate **49** in 90% yield (Scheme 12). Disappearance of the signals corresponding to the thiazolidinethione auxiliary motif in the ^{1}H NMR spectrum of the compound **49** was in concurrence with the efficient knock out of the auxiliary moiety. Appearance of the signal corresponding to methylene, flanked between carbonyl group and phosphonate moiety, as a multiplet at δ 3.11–2.92 and two methoxy singlets integrating for 3 protons each at δ 3.76 and 3.73 lent support for the successful introduction of phosphonate functionality while the remaining protons resonated at their respective chemical shift values. High resolution ESI mass spectrum carrying a signal at *m/z* 381.1442 corresponding to $[M+Na]^+$ (calcd 381.1442) was also in excellent agreement with the formation of the product. Keto phosphonate coupling between the compound **49** and the aldehyde **50** was successfully carried out under Paterson conditions[36] (Scheme 12). Horner–Wadswoth–Emmons olefination using $Ba(OH)_2 \cdot 8H_2O$ as base is mild and efficient and to our delight, α,β–unsaturated ketone **71** was obtained in 77% yield. Appearance of signals at aromatic region corresponding to –OBn and –OPMB groups in the ^{1}H NMR spectrum of compound **71** suggested the coupling. A large coupling constant of the order of 15 Hz for the olefinic proton resonating at δ 6.11 confirmed the *E*–geometry of the double bond. Benzylic methylene protons of both –OPMB and –OBn were observed as ABq at δ 4.46 and 4.38 respectively. Rests of the protons resonated at their respective chemical shift values. Signal at *m/z* 521.2891 in the high resolution ESI mass spectrum of the compound **71** corresponding to $[M+Na]^+$ (calcd 521.2879) further justified the formation of the product.

Chemoselective hydrogentaion[46] of the double bond in the presence of other functional groups like –OBn and –OPMB can be achieved simply *via* poisoning of Pd/C by adding nitrogen containing bases or amines like ^{n}BuNH$_2$. Hydrogenation of the α,β–unsaturated ketone **71** under the atmospheric pressure of hydrogen in EtOAc, containing 0.1 eq of ^{n}BuNH$_2$, furnished the saturated ketone **72** in quantitative yield (Scheme 12). Disapperance of olefinic proton signals and the presence of signals corresponding to both –

OBn and –OPMB in the ^{1}H NMR spectrum of the compound **72** supported the successful chemoselective hydrogenation. In addition to this, the high resolution ESI mass spectrum of the copmound **72** carrying a signal at *m/z* 523.3043 corresponding to $[M+Na]^{+}$ (calcd 523.3035) lent support for the efficient transformation.

Scheme 12

To our displeasure and in our hands, several attempts to protect[47] the ketone functionality of the compound **72** as 1,3–dithiane or 1,3–dithiolane or 1,3–dioxane or 1,3–dioxolane were unsuccessful (Scheme 13). These results obliged us to carry out the synthesis by applying a chiral reduction, protection protocol. To our delight, this later route further simplified both spectroscopic analysis and the chemical synthesis, as we have proceeded with diastereomerically pure prodcut.

Scheme 13

Corey–Bakshi–Shibata (CBS) reduction

The CBS reduction[48] of ketones is one of the most important, fundamental and practical reactions for producing non–racemic chiral alcohols, which can be transformed into various functionalities, without racemization, to synthesize industrially important molecules such as pharmaceuticals, agrochemicals and natural products.

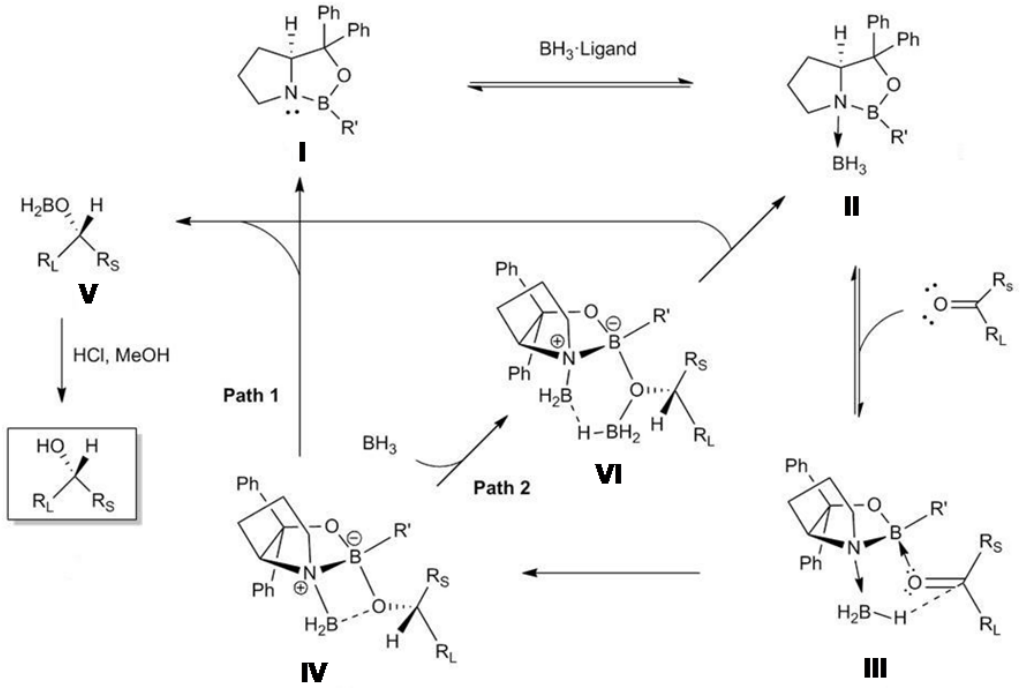


Figure 9

The general mechanistic model which was developed for reduction of ketones with oxazaborolidine catalyst **I** is outlined in Figure 9. The mechanistic model explains 1) the absolute stereochemistry of the reduction, 2) the outstanding enantioselectivity obtained for the reduction, 3) the exceptional rate enhancement of the reduction, and 4) the turnover of the catalyst. The initial step in the pathway is the rapid (and probably reversible) coordination of BH_3 to the Lewis basic nitrogen atom on *α* face of oxazaborolidine **I** to form the *cis*–fused oxazaborolidine·BH_3 complex **II**. Unambiguous support for the initial step comes from the observation by ^{11}B NMR spectroscopy that **I** and BH_3·THF form the 1:1 complex *B*–H–**II** and the fact that crystalline *B*–Me–**II** (**II**, R = Me) can be isolated and structurally defined by single–crystal X–ray diffraction analysis. The coordination of the electrophilic BH_3 to the nitrogen atom of **I** serves to activate BH_3 as a hydride donor and also to increase strongly the Lewis acidity of the endocyclic boron atom. The strongly

Lewis acidic complex **II** then readily binds to the ketonic substrate at the more sterically accessible electron lone pair and *cis* to the vicinal BH_3 group (**III**). This manner of binding minimizes unfavorable steric interactions between the oxazaborolidine and the ketone, and aligns the electronically deficient carbonyl carbon atom and the coordinated BH_3 for stereoelectronically favorable, face–selective hydride transfer *via* a six–membered transition state to form the reduction product **IV**.

Thus, the rate enhancement for the oxazaborolidine–catalyzed reduction is due to the activation of the stoichiometric reducing agent BH_3 by coordination with the Lewis basic nitrogen atom of **I** with simultaneous intensification of the Lewis acidity of the boron atom in the heterocycle for coordination to the ketone. This leads to subsequent enthalpically and entropically favorable faceselective intramolecular hydride transfer. Dissociation of the reduction product from **IV** to regenerate the oxazaborolidine catalyst may occur by two different pathways: 1) reaction of the alkoxide ligand attached to the endocyclic boron atom with the adjacent boron atom of **IV** to regenerate **I** and form the borinate **V** by cycloelimination; or 2) by the addition of BH_3 to **IV** to form a sixmembered BH_3–bridged species **VI**, which decomposes to produce the catalyst–BH_3 complex **II** and borinate **V**. The facile disproportionation of **V** to afford dialkoxyborane $(RO)_2BH$ and BH_3 allows the efficient use of the three hydrogen atoms of the stoichiometric reductant.

Thus, reduction of the ketone **72** by reacting with (*R*)–B–Me–CBS and $BH_3 \cdot SMe_2$ in THF at –40 °C to 0 °C for 15 h furnished the diastereomerically pure alcohol **73** in 88% yield (Scheme 14). Disappearance of the carbonyl carbon signal in the ^{13}C NMR spectrum of compound **73** proved the transformation. In addition to this, presence of a broad signal at 3455 cm^{-1} in the IR spectrum of the compound **73** also suggested the presence of –OH functionality. In the high resolution ESI mass spectrum of compound **73**, a signal at *m/z* 525.3183 corresponding to $[M+Na]^+$ (calcd 525.3192) lent support for the reduction. Reaction of the alcohol **73** with 1.1 eq of TIPSOTf and 1.1 eq of 2,6–lutidine[49] in CH_2Cl_2 at 0 °C–rt for 10 min furnished the TIPS ether **74** in 85% yield. Appearance of a singlet at δ 1.05 integrating for 21 protons in the ^1H NMR spectrum of compound **74** corresponding to TIPS group is in accordance with the protection of the hydroxyl group and the remaining protons were at their respective chemical shift values. Further clarification was

obtained from the high resolution ESI mass spectrum of the compound **74** carrying a signal at *m/z* 681.4506 corresponding to the $[M+Na]^+$ (calcd 681.4526).

Scheme 14

Oxidative cleavage of PMB ether **74** was carried out by reacting with 1.5 eq of DDQ under buffered conditions[50] ($CHCl_3$/buffer, pH = 7, 20:1) to afford the primary alcohol **75** in 64% yield. Disappearance of aromatic, benzylic methylene and methoxy signals corresponding to the –OPMB group in the ^1H NMR spectrum and appearance of broad signal at 3438 cm^{-1} in the IR spectrum of the primary alcohol **75** supported the successful deprotection. In addition to this, a signal at *m/z* 561.3949 in the high resolution ESI mass spectrum corresponding to $[M+Na]^+$ (calcd 561.3951) provided the satisfying support for the transformation. Alcohol **75** was oxidized to the corresponding aldehyde **48** in quantitative yield by reacting with 2 eq of Dess–Martin periodinane[51] in the presence of 2 eq of $NaHCO_3$ in CH_2Cl_2 at 0 °C–rt for 1 h. The aldehyde thus obtained was taken forward to the next reaction, after a flash column chromatography, without any further characterization.

Mukaiyama aldol reaction

The Mukaiyama aldol addition is a type of aldol reaction between silyl enol ether and an aldehyde catalyzed by a Lewis acid (Figure 10). The method works on unbranched aliphatic aldehydes, which are often poor electrophiles for catalytic, asymmetric processes. This may be due to poor electronic and steric differentiation between their enantiofaces.

Figure 10

1,3–Asymmetric Induction Models[35a]. The only well–established strategy for controlling aldehyde face selectivity *via* 1,3– induction involves internal chelation to a *β*–heteroatom substituent.[35b] Preferential formation of the 1,3–*anti* diastereomer is consistent with reaction through transition state as shown in figure 11, which involves nucleophilic attack on the less hindered face of a conformationally locked, internally chelated intermediate. In these systems the chelating metal center (M) must possess a minimum of two open coordination sites to simultaneously complex both carbonyl[35c] and ether oxygens. NMR spectroscopic experiments by Keck have established that the protecting group (P) must also permit effective bidentate complexation of the Lewis acid between the carbonyl and ether oxygen.[35d–f]

Figure 11

It was established that good levels of 1,3–stereoinduction can be achieved in $BF_3 \cdot OEt_2$ promoted Mukaiyama aldol reactions (1 eq of $BF_3 \cdot OEt_2$, CH_2Cl_2, –78 °C),[35g–k] irrespective of the nature of the *β*–alkoxy protecting group (P) or the size of the enolsilane substituent (R). The revised 1,3–asymmetric induction model is derived from several assumptions common to the Felkin–Anh analysis for 1,2–asymmetric induction. It was assumed that torsional effects will dictate that aldehyde transition state conformations adopt a staggered relationship between the newly forming bond and the aldehyde R–substituents. Second, it was assumed that the principal addition product evolves from that reactant–like transition structure wherein the *β*–stereogenic center is oriented *anti*, rather than *gauche*, to the forming bond since this geometry reduces nonbonded interactions between the aldehyde R substituents and the incoming nucleophile. Aldehyde face selectivity is governed by steric and electrostatic effects in the aldehyde that originate from interactions between the *β*–substituents and the carbonyl reaction center. Accordingly, minimization of electrostatic and steric repulsion between these substituents affords the preferred transition structure illustrated in two different perspectives (**A** and **B**) as shown in figure 12.

Figure 12

This model, which leads to the 1,3–*anti* diastereomer, clearly depicts the staggered conformation of the R–substituents with respect to the incoming nucleophile (**A**), and the favored orientation of the *β*–stereocenter relative to the coordinated carbonyl moiety (**B**). The relevant steric and electronic interactions that favor this specific aldehyde rotamer in the transition state may be estimated in the conformational analysis of the constrained BF_3–coordinated aldehydes.

The revised 1,3–asymmetric induction model differs in a key respect from leading predictive theories for acyclic stereocontrol such as the Felkin–Anh[35l–m] and Cram–Reetz models. The relative energies between competing transition states in the latter stereochemical models are primarily based on interactions between the incoming nucleophile and the carbonyl substrate. Although intermolecular nonbonded interactions can clearly play an important role in dictating the facial selectivity of many carbonyl addition processes,[35n–o] it was proposed that 1,3–stereoinduction is governed to a large extent by conformational effects that occur within the aldehyde. This conclusion evolves from the assumption that steric interactions between the nucleophile and carbonyl substrate will essentially be identical during attack on either aldehyde diastereoface for competing transition states that orient the β–stereogenic center of the aldehyde *anti* to the incoming nucleophile.

Thus, as shown in scheme 15, reaction of the aldehyde **48** with 2 eq of silyl enol ether **78**, 1.1 eq of $BF_3 \cdot OEt_2$ in CH_2Cl_2 at –78 °C for 1 h furnished the corresponding aldol adducts **76** and **77** (*dr* ≥8:1) with the required one as the major diastereomer. Both the diastereomers were separated by using standard silica gel column chromatography.

Scheme 15

The success of this reaction was proved by the spectral data. Presence of singlets at δ 3.69, 1.19 and 1.14 integrating for 3 protons each in the ^{1}H NMR spectrum clearly proved the introduction of ester functionality and *gem*–dimethyl moiety into the compound while the rest of the protons resonated at their respective values. Carbonyl carbon was

observed at δ 178.28 in the ^{13}C NMR spectrum of the compound **76**. Appearance of signals at *m/z* 639 and 656 corresponding to $[M+H]^+$ and $[M+NH_4]^+$ respectively in the ESI mass spectrum further supported the formation of the product. In supplement to this, a signal at *m/z* 661.4495 corresponding to $[M+Na]^+$ (calcd 661.4475) in the high resolution ESI mass spectrum also proved the efficient transformation without any ambiguity.

Treatment of the alcohol **76** with 1.3 eq of TESOTf[52] and 1.3 eq of 2,6–lutidine in CH_2Cl_2 at 0 °C–rt for 10 min provided the TES ether **79** in 80% yield (Scheme 16). Apperance of a triplet at δ 0.96 (9H) and a quartet at δ 0.61 (6H), the characteristic signals corresponding to TES group, in the ^1H NMR spectrum of compound **79** suggested the successful protection. In addition to this, a signal at *m/z* 775.5352 in the high resolution ESI mass spectrum corresponding to $[M+Na]^+$ (calcd 775.5340) supplied the agreeable support for the conversion. Reduction of the methyl ester using 2 eq of DIBAL–H[53] in CH_2Cl_2 at –78 °C for 30 min delivered the C16–C28 fragment **46** of the rhizopodin in an overall yield of 13.4% starting from **49** in the longest linear sequence of 10 steps.

Scheme 16

Disappearance of carbonyl signal in the ^{13}C NMR spectrum and methoxy signal corresponding to the ester functionality in the ^1H NMR spectrum of the compound **46** together supported the success of the reduction. Appearance of a broad signal at 3473 cm^{-1}

in the IR spectrum also supported the presence of primary hydroxyl group. Presence of signals at *m/z* 726 and 748 corresponding to $[M+H]^+$ and $[M+Na]^+$ respectively in the ESI mass spectrum further supported the formation of the product. In addition to this, a signal at *m/z* 747.5394 corresponding to $[M+Na]^+$ (calcd 747.5391) in the high resolution ESI mass spectrum also suggested the success of the reaction.

In conclusion we have synthesized the C16–C28 fragment of rhizopodin by using an enatioselective addition of titanium enolate to dimethyl acetal, $^{n}Bu_2BOTf$ mediated Evans' aldol reaction, Horner–Wadsworth–Emmons olefination under Paterson's conditions, Corey–Bakshi–Shibata reduction of ketone and Mukaiyama aldol reactions were applied as key steps.

EXPERIMENTAL SECTION

(*R*)–2–Amino–3–phenylpropan–1–ol (59):

To a solution of $NaBH_4$ (27.46 g, 726.39 mmol) in THF (400 mL) at room temperature, D–phenylalanine **57** (50 g, 302.67 mmol) was added portionwise with stirring under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and a solution of I_2 (76.87 g, 302.67 mmol) in THF (100 mL) was added slowly in dropwise manner over a period of 45 min, resulting in vigorous evolution of H_2 gas. After the addition of I_2 was completed and the gas evolution was ceased, the reaction mixture was heated to reflux for 18 h. Then the reaction mixture was cooled to 0 °C and MeOH (200 mL) was added cautiously until the mixture became clear. After stirring for 0.5 h, solvents were removed in rotary evaporator and the residual colorless solid was dissolved in 20% aqueous KOH solution (600 mL). The solution was stirred for 4 h and extracted with CH_2Cl_2 (3×400 mL). The combined organic layers were washed with water (500 mL), saturted aqueous NaCl (500 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Recrystallization (hot EtOAc followed by petroleum ether, 1:4) afforded the pure compound **59** (32.5 g, 71%) as colorless solid.

***R*$_f$:** 0.45 (Silica gel, 4:1:1 of ^{n}BuOH:AcOH:H_2O).

$[\alpha]_D^{22}$: +24.0 (*c* 1.0, EtOH).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.4–7.1 (m, 5H, Ar*H*), 3.58 (dd, *J* = 11.7, 3.5 Hz, 1H), 3.22 (dd, *J* = 11.7, 7.0 Hz, 1H), 3.04 (m, 1H), 2.75 (dd, *J* = 13.0, 4.8 Hz, 1H), 2.44 (dd, *J* = 13.0, 9.3 Hz, 1H), 2.15–1.95 (br s, 3H, –N*H*$_2$, –O*H*).

(*R*)–4–Benzyloxazolidin–2–one (60):

A mixture of compound **59** (20 g, 132.27 mmol), K_2CO_3 (1.83 g, 13.23 mmol) and $(EtO)_2CO$ (32.05 mL, 264.53 mmol) was carefully heated to 135–140 °C and EtOH was allowed to distil as it was formed. After 6 h, the light brown slurry thus obtained was cooled to room temperature, diluted with CH_2Cl_2 (400 mL), and filtered through a short pad of celite to remove K_2CO_3 and the filter cake was washed with CH_2Cl_2 (200 mL, 3×).

The combined filtrates were washed with water (300 mL), saturated aqueous NaCl (300 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure to afford a pale yellow solid. Recrystallization (hot EtOAc followed by petroleum ether, 1:4) gave the title compound **60** (18.75 g, 80%) as colorless needles.

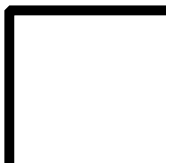
***R*$_f$:** 0.5 (Silica gel, 80% EtOAc in petroleum ether).

M.P.: 85 °C.

[α]$_D^{22}$: –62.4 (*c* 1.0, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.5–7.1 (m, 5H, Ar*H*), 5.58 (br s, 1H, N*H*), 4.6–4.0 (m, 3H, CH_2O, BnC*H*), 2.92 (d, *J* = 9.5 Hz, 2H, PhCH_2).

(*R*)–4–Benzyl–3–propionyloxazolidin–2–one (54):



Oxazolidinone **60** (15 g, 84.65 mmol) was dissolved in THF (250 mL) and cooled to –78 °C. A solution of ^{n}BuLi in hexane (1.6M, 93.1 mL, 93.1 mmol) was added dropwise. After 15 min, propanoyl chloride (9.56 mL, 110.04 mmol) was introduced into the reaction mixture, slowly allowed to room temperature over a period of 30 min and stirred for additional 1 h. The reaction mixture was re–cooled to 0 °C, quenched with saturated aqueous solution of NH_4Cl (20 mL) and extracted with EtOAc (2×250 mL). The combined organic extracts were washed with water (100 mL), saturated aqueous NaCl (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the crude compound by column chromatography (Silica gel, 12–14% EtOAc in petroleum ether) afforded the acylated product **54** (18.76 g, 95%) as colorless solid.

***R*$_f$:** 0.50 (Silica gel, 15% EtOAc in petroleum ether).

M.P.: 74–75 °C.

$[\alpha]_D^{22}$: +122 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.16 (m, 5H, Ar*H*), 4.62 (m, 1H, BnC*H*), 4.21–4.05 (m, 2H, OCH_2CH), 3.31 (m, 1H, PhC*H*H), 3.05–2.82 (m, 2H, COCH_2CH_3), 2.71 (dd, *J* = 9.8 Hz, 1H, PhCH*H*), 1.2 (t, *J* = 7.6 Hz, 3H, $COCH_2CH_3$).

ESI–MS: *m/z* (%) 234 (15) $[M+H]^+$, 256 (100) $[M+Na]^+$.

3–(4–Methoxybenzyloxy)propan–1–ol (58):

Neat *p*–methoxybenzylalcohol (16.39 mL, 131.4 mmol) was added dropwise to a solution of PBr_3 (4.19 mL, 43.36 mmol) in Et_2O (200 mL) at 0 °C. After the completion of addition, stirring was continued for 2 h before the mixture was poured over ice. The ether layer was separated, washed with saturated aqueous $NaHCO_3$ (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4), filtered and concentrated at reduced temperature and *in vacuo* to get the PMBBr as light yellow oil. The residue was directly used for the next reaction without allowing for standing.

To a solution of 1,3–propanediol **55** (10 g, 131.4 mmol) in THF (300 mL) was added sodium hydride (60% dispersion in oil, 5.25 g, 131.4 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 1 h after which it was again cooled to 0 °C. To the reaction mixture, a solution of PMBBr in THF (50 mL, 2×) was added and allowed to stir for overnight at room temperature. The reaction mixture was then brought to 0 °C and quenched with saturated aqueous NH_4Cl (50 mL). THF was evaporated under reduced pressure and extracted with EtOAc (2×250 mL). The combined organic layers were washed with water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was then purified by column chromatography (Silica gel, 10% EtOAc in petroleum ether as eluant) to furnish the mono–PMB protected alcohol **58** (20.63 g, 80%) as light yellow colored oil.

***R_f*:** 0.3 (Silica gel, 30% EtOAc in petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.8 Hz, 2H, Ar*H*), 6.85 (d, *J* = 8.8 Hz, 2H,

Ar*H*), 4.44 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 3.8 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.76 (t, *J* = 4.6 Hz, 2H, CH_2OH), 3.63 (t, *J* = 6.1 Hz, 2H, PMBOCH_2), 1.84 (m, 2H, CH_2CH_2OH).
ESI–MS: *m/z* (%) 219 (100) $[M+Na]^+$.

(*R*)–4–Benzyl–3–((*2R,3S*)–3–hydroxy–5–(4–methoxybenzyloxy)–2–methyl pentanoyl)oxazolidin–2–one (61):

To a solution of $(COCl)_2$ (6.67 mL, 76.44 mmol) in CH_2Cl_2 (400 mL) at –78 °C, DMSO (11.59 mL, 163.06 mmol) was added slowly in dropwise manner with stirring under nitrogen atmosphere. After 20 min, a sloution of mono–PMB protected propanediol **58** (10 g, 50.96 mmol) in CH_2Cl_2 (50 mL, 2×) was added into the reaction mixture *via* cannula. After 30 min of stirring at –78 °C, Et_3N (35.5 mL, 254.79 mmol) was added, stirred for another 30 min at –78 °C and then for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2×250 mL). The combined organic extracts were washed with water (200 mL), saturated aqueous NaCl (200 mL), dried (Na_2SO_4) and concentrated *in vacuo* to get 3–(*p*–methoxybenzyloxy)propanal. The crude aldehyde **53** (9.89 g, quantitative yield, R_f = 0.5, 30% EtOAc in petroleum ether) thus obtained was directly used for the next reaction, after a flash column using silica gel, without any further characterization.

Di–*n*–butylborontriflate (1M in CH_2Cl_2, 61.15 mL, 61.15 mmol) was added to a solution of imide **54** (13.07 g, 56.05 mmol) in CH_2Cl_2 (150 mL) at 0 °C, followed by the dropwise addition of DIPEA (11.54 mL, 66.24 mmol). After stirring at 0 °C for 1 h, the reaction mixture was cooled to –78 °C and a solution of 3–(*p*–methoxybenzyloxy)propanal **53** (9.89 g, 50.96 mmol) in CH_2Cl_2 (30 mL, 2×) was added in dropwise mode. The resulting pale yellow solution was stirred at –78 °C for 1.5 h, then allowed to warm to 0 °C over 30 min and stirred at the same temperature for 30 min. The reaction mixture was then quenched at 0 °C by the addition of phosphate buffer (pH = 7, 70 mL) followed by MeOH (250 mL), resulting in a homogeneous solution. After 5 min, 70 mL of 30% aqueous H_2O_2

in MeOH (100 mL) was added dropwise over a period of 30 min. After having been stirred at 0 °C for 1 h, the reaction mixture was concentrated by rotary evaporation and the resulting residual oil was extracted with EtOAc (2×250 mL). The combined organic extracts were washed with 1M HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), saturated aqueous NaCl (100 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (Silica gel, 15% EtOAc in petroleum ether as eluant) to provide the aldol product **61** (19.59 g, 90%) as colorless liquid.

***R*$_f$:** 0.3 (Silica gel, 30% EtOAc in petroleum ether).

$[\alpha]_D^{28}$: –41.48 (*c* 9.27, $CHCl_3$).

IR (neat): ν_{max} 3504, 2928, 2864, 1774, 1690, 1611, 1511, 1456, 1381, 1297, 1205, 1094, 1027, 970, 821, 750, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.15 (m, 7H, Ar*H*), 6.81 (d, *J* = 8.8 Hz, 2H, Ar*H*), 4.62 (m, 1H), 4.41 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.18–4.06 (m, 3H), 3.79–3.72 (m, 4H), 3.67–3.54 (m, 2H), 3.27 (m, 1H), 3.13 (br s, 1H), 2.71 (m, 1H), 1.81 (m, 1H), 1.69 (m, 1H), 1.25 (d, *J* = 6.8 Hz, 3H, CH_3CH), 1.44 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 176.27, 158.92, 152.79, 134.93, 129.93, 129.18, 129.07, 128.65, 127.09, 113.52, 72.54, 70.08, 67.69, 65.83, 54.91, 42.34, 37.43, 33.54, 11.03.

ESI–MS: *m/z* (%) 428 (65) $[M+H]^+$, 445 (100) $[M+NH_4]^+$, 450 (85) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{24}H_{29}O_6Na$ $[M+Na]^+$ 450.1892, found 450.1873.

(*2S,3S*)–5–(4–Methoxybenzyloxy)–2–methylpentane–1,3–diol (62):

To a solution of the aldol **61** (8 g, 18.73 mmol) in a mixture of THF and water (5:1, 120 mL) was added $NaBH_4$ (3.54 g, 93.64 mmol) in portionwise manner at 0 °C. The reaction mixture was stirred at room temperature for overnight, quenched with 1M HCI (50 mL) at 0 °C and then extracted with EtOAc (2×150 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), saturated aqueous NaCl (100 mL), dried (Na_2SO_4), filtered and concentrated under vacuum. Purification by column chromatography (Silica gel, 40% EtOAc in petroleum ether eluant) afforded the pure 1,3-dihydroxy compound **62** (3.62 g, 76%) as light yellow oil.

***R*$_f$:** 0.5 (Silica gel, EtOAc).

[α]$_D^{27}$: +16.51 (*c* 5.27, $CHCl_3$).

IR (neat): ν_{max} 3393, 2924, 2862, 1611, 1511, 1458, 1411, 1244, 1175, 1086, 1026, 942, 820, 757, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–7.16 (m, 2H, Ar*H*), 6.86–6.79 (m, 2H, Ar*H*), 4.43 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 3.98 (m, 1H, C*H*OH), 3.79 (s, 3H, OCH_3), 3.69 (m, 1H, C*H*HOH), 3.65–3.55 (m, 3H, PMBOCH_2, C*H*HOH), 3.42 (br s, 1H, O*H*), 2.83 (br m, 1H, O*H*), 1.98–1.51 (m, 3H, CH_3CH, $PMBOCH_2CH_2$), 0.89 (d, *J* = 7.6 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 129.82, 129.23, 128.87, 113.74, 73.98, 72.88, 69.17, 66.34, 55.14, 39.41, 32.85, 10.72.

ESI–MS: *m/z* (%) 255 (40) $[M+H]^+$, 277 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{14}H_{22}O_4Na$ $[M+Na]^+$ 277.1415, found 277.1404.

(*2S,3S*)–1–(*tert*–Butyldiphenylsilyloxy)–5–(4–methoxybenzyloxy)–2–methylpentan–3–ol (63):

To a 0 ºC cooled solution of diol **62** (3 g, 11.79 mmol) in CH_2Cl_2 (35 mL) were added Et_3N (4.17 mL, 29.94 mmol), TBDPSCl (3.37 mL, 12.98 mmol) and DMAP (73 mg, 0.59 mmol). After additions were completed, the mixture was allowed to warm to room temperature and stirring was continued for overnight. The reaction mixture was cooled to 0 ºC, quenched with saturated aqueous NH_4Cl (15 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with water (30 mL), saturated aqueous NaCl (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel column chromatography (10% EtOAc in petroleum ether as eluant) yielded the compound **63** (5.23 g, 90%) as pale yellow oil.

***R*$_f$:** 0.4 (Silica gel, 28% EtOAc in petroleum ether).

[α]$_D^{19}$: +1.2 (*c* 3.4, $CHCl_3$).

IR (neat): ν_{max} 3503, 2932, 2859, 1512, 1246, 1103, 1034, 818, 742, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66–7.59 (m, 4H, Ar*H*), 7.42–7.30 (m, 6H, Ar*H*), 7.23–7.16 (m, 2H, Ar*H*), 6.84–6.78 (m, 2H, Ar*H*), 4.42 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 3.95 (dt, *J* = 9.8, 3.0 Hz, 1H, C*H*OH), 3.78 (s, 3H, OCH_3), 3.67–3.53 (m, 4H, PMBOCH_2, TBDPSOCH_2), 2.89 (br s, 1H, O*H*), 1.83–1.56 (m, 3H, CH_3CH, PMBOCH_2CH_2), 1.05 (s, 9H, ^{t}*Bu*Si), 0.90 (d, *J* = 7.6 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.08, 135.56, 135.47, 133.25, 133.12, 127.63, 129.66, 129.18, 113.7, 72.76, 72.02, 68.45, 67.73, 55.14, 40.04, 34.06, 26.80, 19.12, 10.76.

ESI–MS: *m/z* (%) 493 (10) $[M+H]^+$, 515 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{30}H_{40}O_4Na$ $[M+Na]^+$ 515.2593, found 515.2611.

***tert*–Butyl((*2S,3S*)–3–methoxy–5–(4–methoxybenzyloxy)–2–methylpentyloxy) diphenylsilane (64):**

A solution of NaHMDS (1M in THF, 7.31 mL, 7.31 mmol) was added dropwise over 10 min to a stirred solution of the alcohol **63** (3 g, 6.09 mmol) in THF (20 mL) at 0 ºC under nitrogen atmosphere. The resultant solution was stirred at the same temperature for 10 min and then MeI (1.71 mL, 27.4 mmol) was added in dropwise manner. The reaction mixture was stirred at 0 ºC for further 1 h and for 3 h at room temperature. Saturated aqueous NH_4Cl (15 mL) was added at 0 ºC and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with water (30 mL), saturated aqueous NaCl (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by chromatography (Silica gel, 10% EtOAc in petroleum ether as eluant) to get the methyl ether **64** (2.75 g, 89%) as colorless oil.

***R_f*:** 0.6 (Silica gel, 20% EtOAc in petroleum ether).

$[\alpha]_D^{28}$: –4.53 (*c* 2.76, $CHCl_3$).

IR (neat): ν_{max} 3064, 2930, 2858, 1512, 1463, 1246, 1092, 1037, 817, 742, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.61 (m, 2H, Ar*H*), 7.43–7.31 (m, 6H, Ar*H*), 7.24–7.18 (m, 2H, Ar*H*), 6.85–6.79 (m, 2H, Ar*H*), 4.41 (ABq, *J* = 12.1 Hz, 2H, *p*–$CH_3OC_6H_4CH_2$), 3.79 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.67 (m, 1H, C*H*OCH_3), 3.55–3.44 (m, 4H, PMBOCH_2, TBDPSOCH_2), 3.29 (s, 3H, CHOCH_3), 1.86–1.67 (m, 3H, CH_3CH, $PMBOCH_2CH_2$), 1.05 (s, 9H, ^{t}*Bu*Si), 0.85 (d, *J* = 6.8 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.06, 135.57, 133.90, 130.62, 129.52, 129.17, 128.99, 127.58, 127.36, 113.71, 78.38, 72.60, 67.15, 65.72, 58.31, 55.23, 39.16, 31.77, 26.89, 19.27, 11.29.

ESI–MS: *m/z* (%) 507 (20) $[M+H]^+$, 524 (100) $[M+NH_4]^+$, 529 (5) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{31}H_{42}O_4NaSi$ $[M+Na]^+$ 529.2750, found 529.2746.

(*2S,3S*)–3–Methoxy–5–(4–methoxybenzyloxy)–2–methylpentan–1–ol (65):

TBAF (1M in THF, 5.92 mL, 5.92 mmol) was added slowly to a stirred solution of the silyl ether **64** (2 g, 3.95 mmol) in THF (20 mL) at 0 °C. The mixture was stirred at room temperature for 12 h and then quenched with saturated aqueous NH_4Cl (15 mL). THF was removed *in vacuo* and the syrupy residue was extracted with EtOAc (2×50 mL). Combined organic extracts were washed with water (30 mL), saturated aqueous NaCl (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crude product was then purified by chromatography on silica gel (25% EtOAc in petroleum ether as eluant) to get the primary alcohol **65** (826 mg, 78%) as colorless oil.

***R_f*:** 0.4 (Silica gel, 50% EtOAc in petroleum ether).

$[\alpha]_D^{28}$: –12.82 (*c* 2.97, $CHCl_3$).

IR (neat): ν_{max} 3418, 2929, 2872, 1612, 1512, 1461, 1245, 1084, 1032, 820 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23–7.16 (m, 2H, Ar*H*), 6.86–6.79 (m, 2H, Ar*H*), 4.40 (ABq, *J* = 11.3 Hz, 2H, *p*–$CH_3OC_6H_4CH_2$), 3.79 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.61 (m, 1H, C*H*HOH), 3.54–3.39 (m, 4H, PMBOCH_2, CH*H*OH, C*H*OCH_3), 3.35 (s, 3H, CHOCH_3),

2.52 (br s, 1H, O*H*), 2.01 (m, 1H, CH_3CH), 1.84–1.65 (m, 2H, $PMBOCH_2CH_2$), 0.84 (d, *J* = 6.8 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.07, 130.35, 129.21, 113.67, 81.47, 72.57, 66.77, 65.79, 57.82, 55.16, 36.78, 30.22, 11.88.

ESI–MS: *m/z* (%) 269 (45) $[M+H]^+$, 286 (100) $[M+NH_4]^+$, 291 (55) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{15}H_{24}O_4Na$ $[M+Na]^+$ 291.1572, found 291.1573.

3–(Benzyloxy)propan–1–ol (66):

NaH (60% dispersion in oil, 5.78 g, 144.54 mmol) was added slowly to a solution of 1,3–propanediol **55** (10 g, 131.4 mmol) in THF (300 mL) at 0 °C in portiowise manner. BnBr (15.6 mL, 131.4 mmol) and TBAI (2.42 g, 6.57 mmol) were added sequentially and allowed to stir for overnight at room temperature. It was then quenched with saturated aqueous NH_4Cl (50 mL) and THF was evaporated under reduced pressure. The crude residue was then extracted with EtOAc (2×250 mL). The combined organic layers were washed with water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (Silica gel, 15% EtOAc in petroleum ether as eluant) provided the compound **66** (19.65 g, 90%) as clear oil.

***R_f*:** 0.4 (Silica gel, 25% EtOAc in petroleum ether).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.16 (m, 5H, Ar*H*), 4.50 (s, 2H, $PhCH_2$), 3.75 (t, *J* = 5.7 Hz, 2H, $BnOCH_2$), 3.63 (t, *J* = 5.7 Hz, 2H, CH_2OH), 2.17 (br s, 1H, O*H*), 1.84 (m, 2H, CH_2CH_2OH).

ESI–MS: *m/z* (%) 167 (46) $[M+H]^+$.

((3,3–Dimethoxypropoxy)methyl)benzene (52):

To a solution of $(COCl)_2$ (6.29 mL. 72.19 mmol) in CH_2Cl_2 (400 mL) at –78 °C, DMSO (10.95 mL, 154.01 mmol) was added slowly in dropwise manner with stirring under nitrogen atmosphere. After 20 min, mono–benzyl protected propanediol **66** (8 g, 48.13 mmol), dissolved in CH_2Cl_2 (50 mL, 2×) was introduced into the reaction mixture

via cannula. After 30 min of stirring at –78 °C, Et_3N (33.54 mL, 240.65 mmol) was added, stirred for another 30 min at –78 °C and then for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2×250 mL). The combined organic extracts were washed with water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde **67** (7.9 g, quantitative yield, R_f = 0.6, 30% EtOAc in petroleum ether) thus obtained was passed through a short pad of sodium sulphate and used for the next reaction without any further characterization.

To a magnetically stirred solution of the aldehyde **67** (7.9 g, 48.13 mmol) in MeOH (120 mL) at rt were added $HC(OMe)_3$ (47.39 mL, 433.16 mmol) and $CeCl_3 \cdot 7H_2O$ (18.65 g, 50.05 mmol). The reaction mixture was then stirred for overnight, MeOH was evaporated and extracted with EtOAc (2×150 mL). Combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL), water (100 mL), saturated aqueous NaCl (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (Silica gel, 8% EtOAc in petroleum ether as eluant) afforded the dimethyl acetal compound **52** (8.09 g, 80%) as light yellow oil.

***R*$_f$:** 0.7 (Silica gel, 30% EtOAc in petroleum ether).

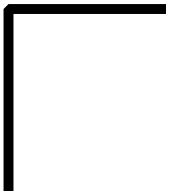
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.14 (m, 5H, Ar*H*), 4.56 (t, *J* = 6 Hz, 1H, C*H*$(OCH_3)_2$), 4.5 (s, 2H, PhC*H*$_2$), 3.55 (t, *J* = 6 Hz, 2H, BnOC*H*$_2$), 3.33 (s, 6H, $(OCH_3)_2$), 1.92 (q, *J* = 6 Hz, 2H, $BnOCH_2CH_2$).

(*S*)–2–Amino–3–methylbutan–1–ol (68):

To a solution of $NaBH_4$ (23.23 g, 614.59 mmol) in THF (400 mL) at room temperature, *L*–valine **56** (30 g, 256.08 mmol) was added portionwise with stirring under nitrogen atmosphere. The reaction mixture was cooled to 0 °C and a solution of I_2 (65.04

g, 256.08 mmol) in THF (100 mL) was added slowly in dropwise manner over a period of 45 min, resulting in vigorous evolution of H_2 gas. After the completion of I_2 addition, the reaction mixture was heated to reflux for 18 h. Then the reaction mixture was cooled to 0 °C and MeOH (150 mL) was added cautiously until the mixture became clear. After stirring for 0.5 h, solvents were removed in rotary evaporator, the residual product was dissolved in 20% aqueous KOH solution (400 mL), stirred for 4 h and extracted with CH_2Cl_2 (3×300 mL). The combined organic layers were washed with water (500 mL), saturted aqueous NaCl (500 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Recrystallization (hot EtOAc followed by petroleum ether, 1:4) gave pure valinol **68** (17.17 g, 65%) as colorless solid.

(*S*)–4–Isopropylthiazolidine–2–thione (69):



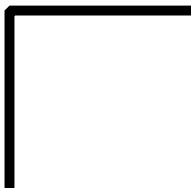
To a magnetically stirred solution of compound **68** (10 g, 96.94 mmol) in EtOH (80 mL) at room temperature were added slowly CS_2 (15.19 mL, 252.04 mmol) and a solution of KOH (14.68 g, 261.73 mmol) in water (50 mL). The resulting reaction mixture was refluxed for 72 h. After cooling to room temperature, ethanol was evaporated under reduced pressure and extracted with CH_2Cl_2 (3×150 mL). The combined organic extracts were washed with 1M HCl (150 mL), water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue thus obtained was purified by silica gel column chromatography (10% EtOAc in petroleum ether as eluant) to get the compound **69** as colorless solid (13.76 g, 88%).

***R*$_f$:** 0.4 (Silica gel, 30% EtOAc in petroleum ether).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (br s, 1H, N*H*), 4.05 (m, 1H, NHC*H*), 3.4 (ddd, *J* = 8.3, 7.5, 3 Hz, 2H, CH_2S), 2.0 (m, 1H, C*H*$(CH_3)_2$), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3), 1.03 (d, *J* = 6.8 Hz, 3H, CH_3).

ESI–MS: *m/z* (%) 162 (100) $[M+H]^+$, 184 (30) $[M+Na]^+$.

(*S*)–1–(4–Isopropyl–2–thioxothiazolidin–3–yl)propan–1–one (51):



(*S*)–4–Isopropylthiazolidine–2–thione **69** (7 g, 43.4 mmol) was dissolved in THF (120 mL), cooled to –78 °C and a solution of ^{n}BuLi in hexane (1.6M, 29.84 mL, 47.74 mmol) was added in dropwise manner. After 15 min, propanoyl chloride (4.9 mL, 56.42 mmol) was added dropwise, slowly allowed to room temperature over a period of 30 min and stirred for additional 1 h. The reaction mixture was recooled to 0 °C, quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (2×150 mL). The combined organic extracts were washed with water (100 mL), saturated aqueous NaCl (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by column chromatography (Silica gel, 2–3% EtOAc in petroleum ether as eluant) produced the compound **51** (7.54 g, 80%) as yellow oil.

***R*$_f$:** 0.5 (Silica gel, 10% EtOAc in petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.12 (m, 1H), 3.48 (m, 1H), 3.32 (m, 1H), 3.10 (m, 1H), 2.99 (d, *J* = 10.7 Hz, 1H), 2.35 (m, 1H, C*H*$(CH_3)_2$), 1.15 (t, *J* = 7.8 Hz, 3H, CH_2CH_3), 1.06 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 0.97 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$).

ESI–MS: *m/z* (%) 240 (100) $[M+Na]^+$.

(*2R,3R*)–5–(Benzyloxy)–1–((*S*)–4–isopropyl–2–thioxothiazolidin–3–yl)–3–methoxy–2–methylpentan–1–one (70):

$TiCl_4$ (2.29 mL, 20.93 mmol) was added dropwise to a solution of auxiliary **51** (4.13 g, 19.02 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The yellow rigid suspension was stirred for 5 min at 0 °C and cooled to –78 °C. After 10 min, a solution of DIPEA (3.64 mL, 20.93

mmol) in CH_2Cl_2 (10 mL) was added. The dark red enolate solution thus obtained was stirred for 2 h at –40 °C, a solution of $SnCl_4$ (2.22 mL, 19.02 mmol) in CH_2Cl_2 (10 mL) followed by dimethyl acetal **52** (4 g, 19.02 mmol), as a solution in CH_2Cl_2 (10 mL), were added in dropwise manner. The resulting mixture was stirred at the same temperature for 2 h, quenched by the addition of saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (2×75 mL). The combined organic extracts were washed with water (50 mL), saturated aqueous NaCl (50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (Silica gel, 3% EtOAc in petroleum ether as eluant) provided the title compound **70** (6.17 g, 82%) as light yellow colored oil.

***R*$_f$:** 0.3 (Silica gel, 7% EtOAc in petroleum ether).

$[\alpha]_D^{28}$: +144.83 (*c* 5.1, $CHCl_3$).

IR (neat): ν_{max} 2961, 2934, 2870, 1693, 1456, 1364, 1312, 1248, 1152, 1085, 1022, 913, 852, 738, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.19 (m, 5H, Ar*H*), 5.24 (m, 1H), 5.03 (m, 1H), 4.53–4.41 (m, 2H), 3.77 (m, 1H), 3.58–3.50 (m, 2H), 3.43 (dd, *J* = 11.3, 9.1 Hz, 1H), 3.29 (s, 3H, OC*H*$_3$), 2.95 (dd, *J* = 11.3, 1.2 Hz, 1H), 2.28 (m, 1H), 1.91 (m, 1H), 1.68 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 202.41, 176.33, 138.29, 128.12, 127.45, 127.28, 79.38, 72.78, 71.62, 66.24, 57.75, 41.83, 30.39, 30.36, 28.99, 18.85, 16.95, 12.92.

ESI–MS: *m/z* (%) 396 (25) $[M+H]^+$, 418 (55) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{20}H_{29}NO_3NaS_2$ $[M+Na]^+$ 418.1486, found 418.1477.

Dimethyl (*3R,4R*)–6–(benzyloxy)–4–methoxy–3–methyl–2–oxohexylphosphonate (49):

^{n}BuLi (1.6M solution in hexane, 11.8 mL, 18.95 mmol) was added to flask with $MeP(O)(OMe)_2$ (2.46 mL, 22.74 mmol) in THF (55 mL) at –78 °C and allowed to stir for 30 min. A solution of compound **70** (3 g, 7.58 mmol) in THF (10 mL, 2×) was added to the reaction flask and allowed to stir for additional 30 min. Then the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) at the same temperature. After warming

to room temperature, the mixture was extracted with EtOAc (2×75 mL). The combined organic extracts were washed with water (50 mL), saturated aqueous NaCl (50 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash column chromatography (Silica gel, 2% MeOH in $CHCl_3$) provided the pure phosphonate **49** (2.45 g, 90%) as colorless oil.

***R*$_f$:** 0.5 (Silica gel, 4% MeOH in $CHCl_3$).

[α]$_D^{28}$: –52.69 (*c* 15.34, $CHCl_3$).

IR (neat): ν_{max} 3482, 2947, 2861, 1709, 1456, 1367, 1247, 1018, 810, 740, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.19 (m, 5H, Ar*H*), 4.53–4.41 (m, 2H, PhC*H*$_2$), 3.76 (s, 3H, P(O)(OC*H*$_3$)(OCH$_3$)), 3.73 (s, 3H, P(O)(OCH$_3$)(OC*H*$_3$)), 3.58–3.48 (m, 3H, BnOC*H*$_2$, C*H*OCH$_3$), 3.26 (s, 3H, CHOC*H*$_3$), 3.11–2.92 (m, 2H, C*H*$_2$P(O)(OCH$_3$)$_2$), 2.30 (br s, 1H, CH$_3$C*H*), 1.86–1.58 (m, 2H, BnOCH$_2$C*H*$_2$), 1.02 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 204.43, 204.36, 137.87, 127.78, 127.01, 79.61, 72.35, 65.54, 57.28, 52.36, 52.28, 52.19, 49.64, 41.95, 40.23, 30.53, 11.24.

ESI–MS: *m/z* (%) 359 (60) $[M+H]^+$, 376 (30) $[M+NH_4]^+$, 381 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{17}H_{27}O_6NaP$ $[M+Na]^+$ 381.1442, found 381.1442.

(*3R,4R,8S,9S,E*)–1–(Benzyloxy)–3,9–dimethoxy–11–(4–methoxybenzyloxy)–4,8–dimethylundec–6–en–5–one (71):

To a solution of $(COCl)_2$ (0.24 mL. 2.79 mmol) in CH_2Cl_2 (15 mL) at –78 °C, DMSO (0.42 mL, 5.96 mmol) was added slowly in dropwise manner with stirring under nitrogen atmosphere. After 20 min, compound **65** (500 mg, 1.86 mmol), dissolved in CH_2Cl_2 (6 mL, 2×) was added *via* cannula into the reaction mixture. After 30 min of stirring at –78 °C, Et_3N (1.29 mL, 9.32 mmol) was added, stirred for another 30 min at –78 °C and then for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2×25 mL). The combined organic extracts were washed with water (20 mL), saturated aqueous NaCl (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde **50** thus obtained, after passing through a short

pad of sodium sulphate, was directly used for the next reaction without any further purification and characterization.

A solution of the ketophosphonate **49** (1.13 g, 3.16 mmol) in THF (12 mL) was stirred in the presence of activated $BaOH_2 \cdot 8H_2O$ (1.06 g, 3.35 mmol) at room temperature for 30 min and then a solution of the aldehyde **50** (496 mg, 1.86 mmol) in mixture of THF and water (40:1, 8 mL) was added. The inhomogeneous mixture was stirred vigorously at room temperature for 30 min, saturated aqueous $NaHCO_3$ (20 mL) and then extracted with EtOAc (2×25 mL). The combined organic extracts were washed with water (20 mL), saturated aqueous NaCl (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by silica gel column chromatography (20% EtOAc
in petroleum ether as eluant) gave the compound **71** as colorless oil (715 mg, 77%).

***R*$_f$:** 0.4 (Silica gel, 20% EtOAc in petroleum ether).

$[\alpha]_D^{24}$: –36.93 (*c* 3.88, $CHCl_3$).

IR (neat): ν_{max} 2931, 2863, 1691, 1614, 1512, 1456, 1366, 1248, 1092, 741 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.15 (m, 7H, Ar*H*), 6.86–6.77 (m, 3H, Ar*H*, COCH=C*H*), 6.11 (d, *J* = 15.6 Hz, 1H, COC*H*=CH), 4.46 (ABq, *J* = 11.7 Hz, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.38 (ABq, *J* = 11.7 Hz, 2H, PhCH_2), 3.78 (s, 3H, *p*–C$H_3OC_6H_4CH_2$), 3.63–3.41 (m, 5H, PMBOCH_2, BnOCH*H*, 2×C*H*OCH$_3$), 3.31 (s, 3H, CHOCH_3), 3.30–3.23 (m, 4H, BnOC*H*H, CHOCH_3), 3.02 (p, *J* = 6.8 Hz, 1H, CH=CHC*H*), 2.56 (m, 1H, COC*H*CH_3), 1.81 (m, 1H, $BnOCH_2$C*H*H), 1.75–1.53 (m, 3H, $PMBOCH_2CH_2$, $BnOCH_2$CH*H*), 1.06 (d, *J* = 6.8 Hz, 3H, CH_3CH), 1.01 (d, *J* = 6.8 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 202.29, 159.04, 148.88, 138.63, 138.36, 130.38, 129.32, 129.17, 128.22, 127.47, 127.40, 113.64, 81.16, 79.53, 72.77, 72.58, 68.46, 66.39, 66.34, 58.02, 55.14, 47.08, 39.45, 31.69, 31.06, 14.41, 12.27.

ESI–MS: *m/z* (%) 499 (20) $[M+H]^+$, 521 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{12}H_{20}O_4Na$ $[M+Na]^+$ 521.2879, found 521.2891.

(*3R,4R,8S,9S*)–1–(Benzyloxy)–3,9–dimethoxy–11–(4–methoxybenzyloxy)–4,8–dimethylundecan–5–one (72):

To a magnetically stirred solution of compound **71** (550 mg, 1.1 mmol) in EtOAc (5 mL) at room temperature were added ^{n}BuNH$_2$ (0.001 mL, 0.11 mmol) and Pd/C (55 mg,

10% *w/w*). Reaction mixture was hydrogenated under atmospheric pressure of H_2 for 15 min, filtered through a short pad of celite using EtOAc (15 mL) and the filter cake was washed with EtOAc (2×5 mL). The combined filtrates were concentrated *in vacuo* and a flash column chromatography (Silica gel, 15–18% EtOAc in petroleum ether as eluant) afforded the compound **72** (552 mg, 100%) as colorless oil.

***R*$_f$:** 0.5 (Silica gel, 30% EtOAc in petroleum ether).

[α]$_D^{25}$: –31.82 (*c* 5.13, $CHCl_3$).

IR (neat): ν_{max} 2930, 2862, 1709, 1609, 1512, 1457, 1366, 1247, 1090, 741 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.17 (m, 7H, Ar*H*), 6.85–6.78 (m, 2H, Ar*H*), 4.46 (ABq, *J* = 12.1 Hz, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.39 (ABq, *J* = 12.8 Hz, 2H, PhCH_2), 3.78 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.6–3.43 (m, 5H, PMBOCH_2, BnOCH*H*, 2×C*H*OCH$_3$), 3.29 (s, 3H, CHOCH_3), 3.24 (s, 3H, CHOCH_3), 3.16 (m, 1H, BnOC*H*H), 2.74 (m, 1H, C*H*CO), 2.56–2.40 (m, 2H, COCH_2), 1.87–1.55 (m, 6H), 1.32 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H, CH_3CH), 0.84 (d, *J* = 6.8 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 213.27, 158.94, 138.25, 130.46, 129.09, 128.18, 127.42, 127.37, 113.56, 81.82, 79.69, 72.78, 72.42, 66.95, 66.11, 57.83, 55.05, 49.46, 40.95, 34.81, 31.66, 30.92, 30.74, 25.68, 14.67, 12.14.

ESI–MS: *m/z* (%) 501 (15) $[M+H]^+$, 518 (30) $[M+NH_4]^+$, 523 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{30}H_{44}O_6Na$ $[M+Na]^+$ 523.3035, found 523.3043.

(*3R,4S,5S,8S,9S*)–1–(Benzyloxy)–3,9–dimethoxy–11–(4–methoxybenzyloxy)–4,8–dimethylundecan–5–ol (73):

To a solution of the ketone **72** (500 mg, 0.99 mmol) in THF (5 mL) at –40 °C were added (*R*)–B–methyl–CBS oxazaborolidine (0.44 mL, 1.49 mmol) in THF (1 mL) and $BH_3{\cdot}Me_2S$ (0.19 mL, 1.99 mmol) in THF (1 mL). The reaction mixture was slowly brought to 0 °C over a period of 15 h and quenched with 10 mL of MeOH. The reaction mixture was stirred 15 min at rt and saturated aqueous NH_4Cl (10 mL) was poured.

Solvents were removed under reduced pressure and extracted with EtOAc (2×20 mL). The combined organic extracts were washed with water (20 mL), saturated aqueous NaCl (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel column chromatography of the residue (18% EtOAc in petroleum ether as eluant) afforded the desired product **73** as colorless oil (442 mg, 88%).

***R_f*:** 0.4 (Silica gel, 30% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: –17.8 (*c* 2.19, $CHCl_3$).

IR (neat): ν_{max} 3455, 2930, 2868, 1512, 1458, 1368, 1248, 1090, 1033, 742 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.15 (m, 7H, Ar*H*), 6.84–6.77 (m, 2H, Ar*H*), 4.48 (ABq, *J* = 12.1 Hz, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.39 (s, 2H, PhCH_2), 3.78 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.58–3.34 (m, 6H, PMBOCH_2, BnOCH_2, 2×C*H*OCH_3), 3.31 (s, 3H, CHOCH_3), 3.30 (s, 3H, CHOCH_3), 3.15(m, 1H, C*H*OH), 2.88 (br s, 1H, OH), 1.94–1.14 (m, 10H), 0.86 (d, *J* = 6.8 Hz, 3H, CH_3CH), 0.78 (d, *J* = 6.9 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.03, 138.21, 131.47, 130.58, 129.21, 1228.32, 127.66, 127.55, 113.67, 82.32, 81.33, 77.2, 74.02, 73.04, 72.53, 67.12, 57.93, 57.17, 55.20, 40.94, 35.53, 32.44, 30.85, 30.68, 27.54, 14.97, 11.66.

ESI–MS: *m/z* (%) 503 (100) $[M+H]^+$, 520 (60) $[M+NH_4]^+$.

HRMS (ESI): Calcd for $C_{12}H_{20}O_4Na$ $[M+Na]^+$ 525.3192, found 525.3183.

((*3R,4R,5S,8S,9S*)–1–(Benzyloxy)–3,9–dimethoxy–11–(4–methoxybenzyloxy)–4,8–dimethylundecan–5–yloxy)triisopropylsilane (74):

To a solution of alcohol **73** (400 mg, 0.79 mmol) in CH_2Cl_2 (3 mL), 2,6–lutidine (0.1 mL, 0.88 mmol) followed by TIPSOTf (0.24 mL, 0.88 mmol) were added at 0 ºC.

After stirring for 10 to 15 min, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with EtOAc (2×15 mL). The combined organic extracts were washed with saturated aqueous $CuSO_4$ (10 mL), water (10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel column chromatography of the residue (8–10% EtOAc in petroleum ether as eluant) afforded the titled product **74** as colorless oil (445 mg, 85%).

***R*$_f$:** 0.6 (Silica gel, 20% EtOAc in petroleum ether).

[α]$_D^{25}$: –13.38 (*c* 1.3, $CHCl_3$).

IR (neat): ν_{max} 2937, 2864, 1512, 1460, 1369, 1247, 1093, 883, 737, 674 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.15 (m, 7H, Ar*H*), 6.84–6.77 (m, 2H, Ar*H*), 4.46 (s, 2H, *p*–$CH_3OC_6H_4CH_2$), 4.38 (s, 2H, $PhCH_2$), 3.94 (m, 1H, C*H*OTIPS), 3.77 (s, 3H, *p*–$CH_3OC_6H_4CH_2$), 3.57–3.14 (m, 4H), 3.30–3.10 (m, 8H), 1.99–1.18 (m, 10H), 1.05 (s, 21H, OTIPS), 0.93–0.78 (m, 6H, 2×CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 159.07, 138.58, 130.62, 129.23, 128.27, 127.61, 127.42, 113.70, 82.36, 79.39, 73.46, 72.94, 72.59, 67.26, 67.04, 57.89, 57.48, 55.24, 41.69, 35.98, 31.39, 31.12, 30.95, 27.95, 18.29, 14.88, 12.94, 10.35.

ESI–MS: *m/z* (%) 659 (5) $[M+H]^+$, 676 (100) $[M+NH_4]^+$.

HRMS (ESI): Calcd for $C_{39}H_{66}O_6NaSi$ $[M+Na]^+$ 681.4526, found 681.4506.

(*3S,4S,7S,8R,9R*)–11–(Benzyloxy)–3,9–dimethoxy–4,8–dimethyl–7–(triisopropyl silyloxy)undecan–1–ol (75):

To a stirred solution of compound **74** (350 mg, 0.53 mmol) in $CHCl_3$:phosphate buffer (pH = 7, 20:1, 5 mL), DDQ (181 mg, 0.79 mmol) was added at room temperature and stirred at the same temperature for 20 min. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ (6 mL), extracted with EtOAc (2×20 mL). The combined organic extracts were washed with water (10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (Silica gel,

18% EtOAc in petroleum ether as eluant) gave pure compound **75** (183 mg, 64%) as clear oil.

***R*$_f$:** 0.4 (Silica gel, 30% EtOAc in petroleum ether).

[α]$_D^{24}$: –19.97 (*c* 3.35, $CHCl_3$).

IR (neat): ν_{max} 3438, 2935, 2865, 1459, 1376, 1087, 882, 736, 673 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.20 (m, 5H, Ar*H*), 4.47 (ABq, *J* = 11.7 Hz, 2H, PhCH_2), 3.95 (m, 1H, C*H*OTIPS), 3.75–3.66 (m, 2H, BnOCH_2), 3.57–3.50 (m, 2H, CH_2OH), 3.34 (s, 3H, CHOCH_3), 3.29–3.19 (m, 5H, 2×C*H*OCH$_3$, CHOCH_3), 1.95–1.86 (m, 2H), 1.76–1.16 (m, 8H), 1.05 (s, 21H, OTIPS), 0.87 (d, *J* = 7.8 Hz, 3H, CH_3CH), 0.83 (d, *J* = 5.9 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.52, 128.22, 127.55, 127.38, 85.54, 79.34, 73.42, 72.90, 66.95, 61.49, 57.39, 57.17, 41.65, 35.04, 31.91, 31.34, 31.09, 27.12, 18.24, 15.47, 12.89, 10.31.

ESI–MS: *m/z* (%) 539 (60) $[M+H]^+$, 556 (100) $[M+NH_4]^+$.

HRMS (ESI): Calcd for $C_{31}H_{58}O_5NaSi$ $[M+Na]^+$ 561.3951, found 561.3949.

(*3S,5S,6S,9S,10R,11R*)–Methyl 13–(benzyloxy)–3–hydroxy–5,11–dimethoxy–2,2,6,10–tetramethyl–9–(triisopropylsilyloxy)tridecanoate (76):

To a stirred solution of compound **75** (130 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) at 0 °C, $NaHCO_3$ (40 mg, 0.48 mmol) was added followed by Dess–Martin periodinane (205 mg, 0.48 mmol) under nitrogen atmosphere. The reaction mixture was allowed to room temperature and stirred for 1 h. Saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) were added. The resultant biphasic mixture was stirred for 15 min and then extracted with EtOAc (2×10 mL). The combined organic phases were washed with water (10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated *in*

vacuo. The aldehyde **48** (R_f = 0.7, quantitative yield, 30% EtOAc in petroleum ether) thus obtained, after passing through a short pad of sodium sulphate, was directly used for the next reaction without any further characterization.

To a stirred solution of the aldehyde **48** (128 mg, 0.24 mmol) and enol silane **78** (0.097 mL, 0.48 mmol) in 3 mL of CH_2Cl_2 was added $BF_3{\cdot}Et_2O$ (0.033 mL, 0.27 mmol) at –78 °C. Reaction mixture was maintained at the same temperature for 1 h, quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with EtOAc (2×10 mL). The combined organic extracts were washed with water (10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a residue, which was subjected to flash column chromatography (Silica gel, 12–14% EtOAc in petroleum ether as eluant) to get alcohol **76** (99 mg, 64%) as colorless oil.

***R*$_f$:** 0.4 (Silica gel, 20% EtOAc in petroleum ether).

$[\alpha]_D^{27}$: –4.07 (*c* 1.97, $CHCl_3$).

IR (neat): ν_{max} 3615, 2937, 2866, 1727, 1516, 1460, 1377, 1254, 1089, 736 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.20 (m, 5H, Ar*H*), 4.47 (s, 2H, PhC*H*$_2$), 3.97 (m, 1H, C*H*OTIPS), 3.78 (m, 1H, C*H*OH), 3.69 (s, 3H, COOC*H*$_3$), 3.58–3.49 (m, 2H, BnOC*H*$_2$), 3.36 (s, 3H, CHOC*H*$_3$), 3.34–3.17 (m, 5H, 2×C*H*OCH$_3$, CHOC*H*$_3$), 2.76 (br s, 1H, O*H*), 2.0–1.81 (m, 2H), 1.79–1.22 (m, 8H), 1.19 (s, 3H, (CH$_3$)C(C*H*$_3$)), 1.14 (s, 3H, (C*H*$_3$)C(CH$_3$)), 1.05 (s, 21H, OTIPS), 0.87 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CH), 0.83 (d, *J* = 7.6 Hz, 3H, C*H*$_3$CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.28, 138.54, 128.28, 127.63, 127.45, 82.55, 79.56, 73.48, 73.39, 72.96, 66.91, 58.12, 57.60, 51.88, 46.91, 42.22, 35.78, 32.21, 31.53, 30.68, 28.0, 22.78, 20.05, 18.28, 15.42, 12.93, 10.35.

ESI–MS: *m/z* (%) 639 (8) $[M+H]^+$, 656 (100) $[M+NH_4]^+$.

HRMS (ESI): Calcd for $C_{36}H_{66}O_7NaSi$ $[M+Na]^+$ 661.4475, found 661.4495.

(*3R,5S,6S,9S,10R,11R*)–Methyl 13–(benzyloxy)–3–hydroxy–5,11–dimethoxy–2,2,6,10–tetramethyl–9–(triisopropylsilyloxy)tridecanoate (77):

***R*$_f$:** 0.4 (Silica gel, 20% EtOAc in petroleum ether).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.17 (m, 5H, Ar*H*), 4.47 (s, 2H, PhC*H*$_2$), 3.93-3.8 (m, 2H, C*H*OTIPS, C*H*OH), 3.62 (s, 3H, COOC*H*$_3$), 3.55–3.48 (m, 2H, BnOC*H*$_2$), 3.31-

3.15 (m, 8H, CHOCH_3, 2×CHOCH$_3$, CHOCH_3), 1.95–1.15 (m, 10H), 1.12 (s, 3H, (CH$_3$)C(CH_3)), 1.06 (s, 3H, (CH_3)C(CH$_3$)), 0.99 (s, 21H, OTIPS), 0.85-0.73 (m, 6H, 2×CH_3CH).

(*3S,5S,6S,9S,10R,11R*)–Methyl 13–(benzyloxy)–5,11–dimethoxy–2,2,6,10–tetramethyl–3–(triethylsilyloxy)–9–(triisopropylsilyloxy)tridecanoate (79):

To a stirred solution of compound **76** (80 mg, 0.125 mmol) in CH_2Cl_2 (3 mL) at 0 °C, 2,6–lutidine (0.019 mL, 0.163 mmol) and TESOTf (0.037 mL, 0.163 mmol) were added sequentially. After 10 min of stirring at same temperature, the reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and extracted with EtOAc (2×10 mL). Combined organic extracts were washed with saturated aqueous $CuSO_4$ (10 mL), water (10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 2–5% EtOAc in petroleum ether as eluant) afforded pure compound **79** (75 mg, 80%) as colorless liquid.

***R*$_f$:** 0.7 (Silica gel, 10% EtOAc in petroleum ether).

[α]$_D^{21}$: –8.7 (*c* 0.57, $CHCl_3$).

IR (neat): ν_{max} 2936, 2870, 1731, 1514, 1460, 1377, 1246, 1096, 818, 736, 675 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.59–7.23 (m, 5H, Ar*H*), 4.42–4.52 (m, 2H, PhCH_2), 4.16 (m, 1H), 3.98 (m, 1H), 3.81 (m, 2H, BnOCH_2), 3.65 (s, 3H, COOCH_3), 3.58 (m, 1H),

3.35–3.13 (m, 7H), 2.18–1.72 (m, 2H), 1.71–1.42 (m, 3H), 1.38–1.2 (m, 8H), 1.14 (s, 3H), 1.05 (s, 21H, OTIPS), 0.96 (t, J = 7.9 Hz, 9H, 3×SiCH$_2$CH_3), 0.91–0.7 (m, 6H), 0.61 (q, J = 7.9 Hz, 6H, 3×SiCH_2CH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ 177.54, 129.5, 129.39, 128.29, 127.62, 81.59, 74.38, 73.58, 72.96, 66.97, 62.05, 57.57, 56.13, 51.52, 48.39, 42.26, 34.47, 33.77, 31.05, 29.68, 27.07, 21.28, 20.32, 18.28, 15.7, 12.96, 10.34, 7.04, 5.71.

ESI–MS: *m/z* (%) 754 (15) $[M+H]^+$, 771 (100) $[M+NH_4]^+$.

HRMS (ESI): Calcd for $C_{42}H_{80}O_7NaSi_2$ $[M+Na]^+$ 775.5340, found 775.5352.

(*3S,5S,6S,9S,10R,11R*)–13–(Benzyloxy)–5,11–dimethoxy–2,2,6,10–tetramethyl–3–((triethylsilyloxy)methyl)–9–(triisopropylsilyloxy)tridecan–1–ol (46):

To a solution of the compound **79** (50 mg, 0.066 mmol) in CH_2Cl_2 (4 mL) at –78 °C, DIBAL–H (1M solution in toluene, 0.13 mL, 0.13 mmol) was added dropwise with stirring under nitrogen atmosphere. After stirring for 30 min at the same temperature, the reaction mixture was quenched by the addition of MeOH (3 mL), stirred for 0.5 h at the same temperature, potassium sodium tartrate (5 mL) was then added, stirred at room temperature for 1 h and extracted with EtOAc (2×15 mL). The combined organic extracts were washed with water (10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (Silica gel, 10% EtOAc in petroleum ether as eluant) provided compound **46** (38 mg, 79%) as clear oil**.**

***R*$_f$:** 0.3 (Silica gel, 10% EtOAc in petroleum ether).

[α]$_D^{24}$: –17.7 (*c* 0.7, $CHCl_3$).

IR (neat): ν_{max} 3473, 2950, 2870, 1461, 1379, 1090, 1009, 734, 674 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.18 (m, 5H), 4.44 (ABq, *J* = 12 Hz, 2H, PhCH_2), 3.96–3.88 (m, 1H), 3.68 (dd, *J* = 7.5, 0.8 Hz, 1H), 3.56–3.41 (m, 3H), 3.29–3.12 (m, 9H), 1.96–1.72 (m, 3H), 1.64–1.05 (m, 7H), 0.99 (s, 21H, OTIPS), 0.96–0.85 (m, 12H), 0.84–0.71 (m, 9H), 0.65–0.52 (m, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.3, 127.6, 127.5, 82.9, 79.6, 77.1, 73.5, 73.0, 70.4, 66.9, 57.6, 56.4, 42.4, 39.5, 34.1 33.3, 31.6, 31.0, 26.7, 22.6, 21.5, 18.3, 15.9, 12.9, 10.3, 7.1, 5.6.

ESI–MS: *m/z* (%) 726 (80) $[M+H]^+$, 748 (25) $[M+Na]^+$.

HRMS (ESI): calcd for $C_{41}H_{80}O_6NaSi_2$ $[M+Na]^+$ 747.5391, found 747.5394.

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INTRODUCTION

Functionalized piperidines are among the most ubiquitous heterocyclic structural frameworks in natural products and synthetic compounds with important pharmacological activities.[1] Hydroxylated piperidine alkaloids are frequently found in living systems. Piperidine alkaloids possessing a 2,3– or 2,3,6–substitution, particularly a hydroxy group at C3 position occur abundantly in nature.[2] 2–Alkyl–3–hydroxypiperidines, 2,6–dialkyl–3–hydroxypiperidines and the corresponding 5–hydroxy–2–piperidinones are structural units found in a number of drugs, and drug candidates.[3]

The hydroxylated piperidines display a wide range of biological activities such as antibiotic, analgesic, anaesthetic, cytotoxic and CNS stimulating properties.[4] The physiological effects stem from their ability to mimic carbohydrate substrates in a variety of enzymatic processes.[5] Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids as important tools in the study of biochemical pathways.[6]

Numerous compounds possessing either 2,6–*cis* or 2,6–*trans* substitution pattern have been discovered, typical representatives of this class of compounds[7] include (+)–spectaline (**1**), (+)–azimic acid (**2**), (+)–carpamic acid (**3**), (+)–deoxocassine (**4**), (–)–prosafrinine (**5**), (–)–cassine (**6**), (–)–deoxocassine (**7**), (+)–prosophylline (**8**), (+)–desoxoprosophylline (**9**), (–)–prosopinine (**10**), (+)–azimine (**11**) and (+)–carpaine (**12**). The latter two structures correspond to C_2–symmetric macrocyclic dilactones containing two molecules of the characteristic 2–methyl–3–piperidinol skeleton with a carboxyl group as a terminal substituent at the C–6 position. They are readily hydrolyzed to (+)–azimic acid (**2**) and (+)–carpamic acid (**3**), which are presumably their biosynthetic precursors (Figure 1). Since their discovery in the 1960s, much effort has been directed to the synthesis[8] of these alkaloids such as cassine (**6**) and other related derivatives like deoxocassine (**7**). With respect to biologically active target molecules there is an increasing interest in the diastereo– and enantioselective synthesis of piperidines.

A number of the 2,6–disubstituted piperidin–3–ols have been found[9] in plants of *Cassia*, *Prosopis*, *Azima*, *Bathiorhamnus* species and from venoms of fire ants *Solenopsis* species. (–)–Cassine was isolated[10] from the leaves and twigs of *Cassia excelsa* and its

structure was established in 1963. It exhibits antimicrobial activity against *Staphylococcus aureus*. Deoxocassine[11] was a simple analogue of natural alkaloid (–)–cassine.

Figure 1

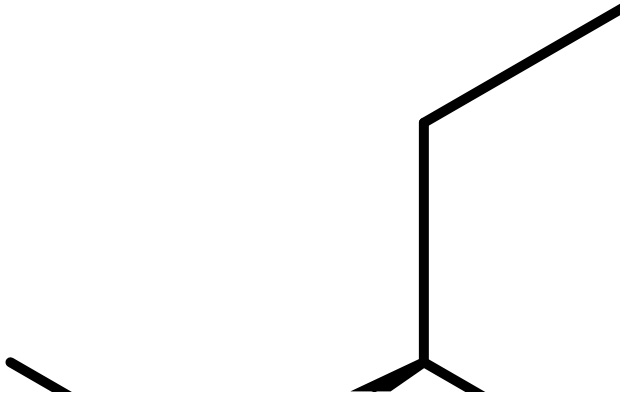
Selectivity, versatility, and flexibility are among the major concern in organic synthesis. Development of multifunctional chiral nonracemic building blocks or synthons has been proven to be a powerful strategy to meet the needs of both the versatility and flexibility.

In the present chapter we describe the synthesis of a 2,3,6–substituted piperidine building block for accomplishing the total synthesis of many of these natural alkaloids and we demonstrate the applicability of our chiral synthon by subsequent total synthesis of (+)–deoxocassine (**4**).

Contemporary approaches to 2,6–disubstituted piperidin–3–ols:

Raghavan, S. *et al* approach:

Raghavan and his co–worker have reported[12] the total synthesis of (–)–deoxocassine (**7**) and (+)–desoxoprosophylline (**9**) where the 2,6–disubstituted piperidin–3–ol moiety was achieved *via* intramolecular amidomercuration of carbamate **13**. The required carbamate **13** was accessed from the corresponding bromo–carbamate **14** which inturn was obtained by the reaction of alkene **15** with NBS. *N–Cbz*–sulfilimine **15** was derived from the corresponding sulfoxide **16** by using the Burgess reagent (Scheme 1).



Scheme 1

Pedrosa, R. *et al* approach:

(+)–Deoxocassine (**4**) and (–)–desoxoprosophylline (**17**) were derived from *δ*–amino–*γ*–hydroxyl carbonyl compound **18** through a stereoselective intramolecular reductive amination reaction. Compound **18** was prepared by elaboration of olefin **19**, which in turn could be easily obtained by nucleophilic addition of 4–butenylmagnesium

bromide (**21**) to homochiral *α*–dibenzylamino aldehyde **20** that was derived from natural *α*–amino acids (Scheme 2).[13]

Scheme 2

Lhommet, G. *et al* approach:

Total synthesis of (–)–deoxocassine (**7**) was reported[14] by Lhommet and his co–workers which involved a diastereoselective reduction of the double bond of the *β*–enamino carbonyl compound **22**. Oxazolidino piperidine **22** was accessed from the triketo compound **23** which in turn was obtained from the allylic alcohol **24** (Scheme 3).

Scheme 3

Sasaki, N. A. *et al* approach:

Sasaki and his co–worker have reported[15] the total synthesis of (+)–deoxoprosopinine (**25**) as depicted in scheme 4. They have demonstrated that base mediated intramolecular cyclization of amine **27** would provide the piperidine **26**. A Julia olefination between aldehyde **28** and sulfone **29** was the key execution to get amine **27**. Aldehyde **28** could be obtained from L–ascorbic acid (**30**) where as the sulfone **29** from D–serine (**31**).

Scheme 4

Padwa, A. *et al* approach:

Padwa and his co–worker have reported[11a] the enantioselective total synthesis of (+)–azimic acid (**2**) and (+)–deoxocassine (**4**) by the application of *aza*–Achmatowicz reaction as the prime step (Scheme 5). Target molecules were achieved by the few chemical modifications of the intermediate ester **32** which was derived from the hemiaminal **33** by applying Luche reduction and Lewis acid mediated alkylation. Oxidative rearrangement of compound **34** in *aza*–Achmatowicz reaction by reacting with *m*–CPBA afforded the compound **33**.

Scheme 5

Kibayashi, C. *et al* approach:

Kibayashi and his co–workers have reported[8m] the total synthesis of C_2–symmetric macrocylic lactones (+)–azimine (**11**) and (+)–carpaine (**12**) by the Yamguchi macrolactonization of suitably protected corresponding monomers (+)–azimic acid (**2**) and (+)–carpamic acid (**3**), respectively (Scheme 6). These monomers were realized by the reductive N–O bond cleavage of compound **35** which in trun was obtained from compound **36**. Intramolecular hetero–Diels–Alder reaction of the *N*–acylnitroso compound **37** provided the compound **36**.

Scheme 6

Lee, H. K. *et al* approach:

Lee and his co–workers have demonstrated[16] the expedient synthesis of 2–piperidone **38**, an advanced intermediate for the synthesis of *prosopis* or *cassia* alkaloids, by applying reductive ring opening of 2–azetidinone **41** to get compound **40**, stereoselective installation of *Z–α,β–*unsaturated ester to get **39** and subsequent lactam formation (Scheme 7), as key steps.

Scheme 7

Cossy, J. *et al* approach:

The construction of the piperidine ring of (–)–prosophylline (**42**) was envisaged to arise by intramolecular nucleophilic displacement of a mesylate by an amine present in compound **44**. The stereogenic centers at C–6 and C–3 were attained through enantioselective allyltitanations of aldehydes where as the stereogenic center at C–2 was from D–glyceraldehyde acetonide **47**. The ketonic side chain was built up by using a cross–metathesis reaction over the substituted piperidine **43** (Scheme 8).[8h]

Scheme 8

Herdeis, C. *et al* approach:

Total synthesis of (+)–desoxoprosophylline (**9**) has been accomplished[17] by the application of rearrangement of traizoline followed by extrusion of nitrogen from the compound **48** which in turn was achieved by tandem Wittig [2+3]–cycloaddition of lactol **50** (Scheme 9). Lactol was accessed from L–gulonolactone (**51**).

Scheme 9

PRESENT WORK

In combination of both the biological significance and necessity of developing versatile approaches to access of these alkaloids, we were interested in making a chiral template that meets the requirement. Our salient feature of the synthesis is the construction of chiral building block **C** and subsequent oxidation followed by Wittig olefination[18] to deliver the intermediate **B** which upon hydrogenation would provide the natural alkaloid **A**. Appropriate choice of starting materials to make compound **C** and Wittig partner at late stage can make clear path to any of the aforementioned alkaloids.

Figure 2

The retrosynthetic analysis of (+)–deoxocassine (**4**) is shown in Scheme 10. We have envisioned that hydrogenation of compound **52** would result in one–pot debenzylation, *N*–Cbz deprotection and saturation of the olefinic bond to get the final

target molecule. Compound **52** could be accessed from alcohol **53** by successive Dess–Martin periodinane oxidation[19] and Wittig olefination. A base mediated intramolecular nucleophilic displacement of a mesylate by amine functionality in compound **54** followed by *N*–protection and silyl deprotection would provide the alcohol **53**.

Scheme 10

Orthogonally protected compound **54** could be realized from the compound **55** which in turn was achieved from the alkynol **56** *via* Mistunobu inversion,[20] hydrogenation and amine protection sequence. Nucleophilic addition[21] of acetylide derived from dimbromo alkene **58**, by applying Corey–Fuchs reaction,[22] over the aldehyde **57** was the key execution to get the compound **56**. Commercially available L–alanine (**59**) would be the precursor for the aldehyde **57** whereas L–ascorbic acid (**30**) for dibromo olefin **58**.

We started our synthesis from readily available L–alanine (**59**) which was perbenzylated[23] by reacting with 3.3 eq of BnBr and 3.5 eq of K_2CO_3 in EtOH at 0 °C–rt for 5 days to get compound **60** in 82% yield (Scheme 11). Appearance of signals at δ 7.4–7.14 integrating for 15 protons corresponding to $-NBn_2$ and COOBn groups and rest of the protons being at their respective chemical shift values in the ^{1}H NMR spectrum of compound **60** suggested the successful perbenzylation. Reduction of the benzyl ester **60** was carried out by treating with 2 eq of $LiAlH_4$ at 0 °C–rt for 4 h in THF to provide the

primary alcohol **61** in 61% yield. Successful reduction was confirmed by the presence of aromatic signals at δ 7.4–7.2 integrating for 10 protons in the ^{1}H NMR spectrum and a signal at *m/z* 256 in the ESI mass spectrum that corresponds to $[M+H]^+$. Compound **61** was oxidized to corresponding aldehyde **57** by applying Swern oxidation procedure.[24] Reaction of the alcohol **61** with 1.5 eq of $(COCl)_2$, 3.2 eq of DMSO and 5 eq of Et_3N in CH_2Cl_2 at –78 °C–0 °C for 3 h furnished the aldehyde **57** in quantitative manner which was taken forward to the next reaction, after a flash column chromatography, without any further characterization.

Scheme 11

Commercially available L–ascorbic acid (**30**) was converted to the diol **65** in a four–step sequence[25] as shown in Scheme 12. Reaction of ascorbic acid (**30**) with acetone in the presence of catalytic amount of acetyl chloride afforded the acetonide **62**. Oxidative cleavage of the acetonide **62** was carried out by reacting with K_2CO_3 and 30% H_2O_2 to afford the acid **63** which was immediately esterified by reacting with $(Me)_2SO_4$ and $NaHCO_3$ to get the compound **64** in 32.4% yield over three steps.

Reduction of the ester **64** with 1.2 eq of $LiAlH_4$ at 0 °C–rt for 1 h in THF afforded the corresponding diol **65** in 40% yield. The ^{1}H NMR spectrum of the diol **65** was in very good agreement with our expected product. Oxidative cleavage[26] of the diol **65** was accomplished by reacting it with 2 eq of $NaIO_4$ in CH_2Cl_2 and in the presence of aqueous $NaHCO_3$ at 0 °C–rt for 1.5 h to furnish the aldehyde **66** which was immediately subjected to a Corey–Fuchs reaction by allowing it to react with 4 eq of TPP and 2 eq of CBr_4 in CH_2Cl_2 at 0 °C–rt for 3 h to get the dibromo olefin **58** in 28% yield over two steps.

Scheme 12

In general, the hydroxyl group of the amino alcohol is installed[27] either by the addition of an organometallic reagent to an amino aldehyde or by the reduction of an amino ketone. Two modes of stereocontrol determine which diastereomer is the major product from the addition of an organometallic reagent to protected amino aldehyde or reduction of protected amino ketones. Chelation control, in which a Lewis acid or metal ion coordinates to the carbonyl oxygen and the amine nitrogen, enforces a *syn*–periplanar relationship between the amine and carbonyl groups and leads to the *anti* diastereomer (A: Chelation control, Figure 3).

Felkin–Anh control, in which a dihedral angle of about 90º between the amine and carbonyl groups maximizes stereoelectronic interactions in the transition state,[28] leads to the *syn* diastereomer (B: Felkin–Anh control, Figure 3). Stereocontrol in the addition or reduction of carbamate, which is ubiquitous protecting groups for amines, protected amino carbonyls would appear to favor chelation control since both the carbonyl oxygen and the carbamate nitrogen are sterically accessible for coordination to a Lewis acid. Thus, chelation stereocontrol in the addition or reduction of carbamate–protected amino carbonyls provides a method for the stereoselective synthesis of *anti* carbamate–protected amino alcohol. To achieve Felkin–Anh control in the addition or reduction of protected

amino carbonyls and thus to produce *syn*–amino alcohols, the amino group must be modified to make it sterically bulky. This would result in a steric preference for a Felkin–Anh transition state (Figure 3) and minimizes chelation involving the amino nitrogen and the carbonyl oxygen.

Figure 3

By taking advantage of this, we could successfully utilize *α*–aminoacids by protecting amine functionality as dibenzyls. The *N*,*N*–dibenzyl protecting group rendered the amine group sufficiently bulky to ensure Felkin–Anh control transition state and can lead to *syn*–amino alcohol.

Treatment of the aldehyde **57** at –78 ºC with the Li–acetylide, prepared *in situ* by reacting compound **58** with 1.9 eq of ^{n}BuLi in THF at –78 °C for 30 min and subsequently at room temperature for an additional 30 min, gave the expected adduct **56** as the major diastereomer in 66.5% yield (Scheme 13).[21] Appearance of signals at *δ* 7.38–7.19 integrating for 10 protons corresponding to –*N*Bn$_2$ group and a singlet at *δ* 1.33 integrating for 6 protons corresponding to acetonide in the ^{1}H NMR spectrum of compound **56** suggested the successful nucleophilic addition. In addition to this, presence of a broad signal at 3442 cm^{-1} in the IR spectrum of the compound **56** also supported the presence of –OH functionality. High resolution ESI mass spectrum carrying a signal at *m/z* 380.2214

corresponding to $[M+H]^+$ (calcd 380.2225) was also in agreement to the successful formation of the compoound **56**.

Compound **56** was subjected to Mitsunobu inversion[20] by using 3.5 eq of DEAD, 3.5 eq of TPP and 4.2 eq of *p*–nitrobenzoic acid in THF at 0 °C–rt for 4 h to get the *p*–nitrobenzoate ester **67** in 73.6% yield (Scheme 13). Appearance of a multiplet at δ 8.35–8.12 integrating for 4 protons corresponding to *p*–nitrobenzoyl moiety and rest of the protons being at their respective chemical shift values in the ^{1}H NMR spectrum of compound **67** confirmed the esterification. Benzoate deprotection of compound **67** was carried out by using 2 eq of K_2CO_3 in MeOH at 0 °C–rt for 45 min to provide the alkynol **68** in 90% yield. Disappearance of a signals corresponding to *p*–nitrobenzoyl moiety and rest of the protons being at their respective chemical shift values in the ^{1}H NMR spectrum of compound **68** confirmed the successful saponification. In addition to this, a broad signal at 3444 cm^{-1} in the IR spectrum of the compound **68** also suggested the presence of –OH functionality. High resolution ESI mass spectrum carrying a signal at *m/z* 380.2214 corresponding to $[M+H]^+$ (calcd 380.2225) was also in accordance to the successful formation of the compoound **68**.

Scheme 13

Hydrogenation of the alkynol **68** in the presence of $Pd(OH)_2/C$ (20% *w/w*) in MeOH provided the amine **69** in quantitative yield which was immediately protected as *N*–Boc carbamate[29] by reacting with 1.1 eq of Boc_2O and 1.1 eq of Et_3N in CH_2Cl_2 at 0 °C–rt for overnight to afford the compound **55** in 81% yield (Scheme 14). This conversion was confirmed by spectral studies. Disappearance of the aromatic signals in the ^{1}H NMR

spectrum of compound **55** confirmed the transformation and the characteristic signals corresponding to BocNH were observed at appropriate chemical shift values. Appearnace of a multiplet integrating for 4 protons at δ 1.82–1.5 corresponding to two methylenes supported the saturation of triple bond. Rests of the protons were also observed at their respective chemical shift values. Carbamate carbonyl signal was observed at δ 155.8 in the ^{13}C NMR spectrum of the compound **55**. Signal at *m/z* 326.1946 in the high resolution ESI mass spectrum of the compound **55** corresponding to $[M+Na]^+$ (calcd 326.1943) further confirmed the formation of the product.

Scheme 14

Reaction of the alcohol **55** with 1.5 eq of BnBr, 1.4 eq of NaH (60% dispersion in oil) and 0.1 eq of TBAI at 0 °C–rt for 3 h in DMF[30] resulted in the formation of the benzyl ether **70** in 88% yield (Scheme 14). Appearance of a signal at δ 7.39–7.25 integrating for 5 protons corresponding to the phenyl group in the ^{1}H NMR spectrum of compound **70** confirmed the protection. The characteristic signals of phenyl ring were observed at appropriate chemical shift values in the ^{13}C NMR spectrum of compound **70**. In addition to this, a signal at *m/z* 416.2399 in the high resolution ESI mass spectrum corresponding to $[M+Na]^+$ (calcd 416.2412) provided the satisfying support for the transformation. Acetonide deprotection[31] of the compound **70** was achieved by allowing it to react with 1.1 eq CSA in MeOH at 0 °C–rt for 4 h to get the diol **71** in 89% yield. Disappearance of the signals corresponding to acetonide in the ^{1}H NMR spectrum of compound **71** and rests of the protons resonating at their corresponding chemical shift values supported the success of the reaction. Appearance of a broad signal at 3343 cm^{-1} in the IR spectrum also showed the presence of hydroxyl groups. In addition to this, a signal at *m/z* 376.2106 in the high

resolution ESI mass spectrum corresponding to $[M+Na]^+$ (calcd 376.2099) supplied further support for the conversion.

Selective *O*–silylation[32] of the diol **71** was carried out by using 1.1 eq of TBSCl, 2 eq of Et_3N and 0.1 eq of DMAP in CH_2Cl_2 at 0 °C–rt for overnight to get the TBS ether **72** in 76% yield (Scheme 15). Appearance of signals at δ 0.91 and 0.08 integrating for 9 and 6 protons respectively in the ^1H NMR spectrum of compound **72** corresponding to TBS group was in accordance with the selective *O*–silylation and the remaining protons resonated at their respective chemical shift values. In addition to this, a signal at *m/z* 468 corresponding to the $[M+H]^+$ in the ESI mass spectrum of the compound **72** was also in very good agreement with the conversion.

Scheme 15

Reaction of the alcohol **72** with 1.5 eq of MsCl, 2 eq of Et_3N and 0.5 eq of DMAP in CH_2Cl_2 at 0 °C–rt for 3 h furnished the corresponding mesylate **54** in 70% yield (Scheme 15). Appearance of a singlet at δ 3.04 in the ^1H NMR spectrum of the compound **54** integrating for 3 protons that corresponds to –OMs group lent support for the mesylation and the rest of the protons were observed at their respective chemical shift values. *N*–Boc deprotection of compound **54** was carried out under mild conditions.[33] Reaction of the carbamate **54** with 1.5 eq of TBSOTf and 2 eq of 2,6–lutidine for 1 h afforded the corresponding *N*–*tert*–butyldimethyl– silyloxycarbonyl intermediate which was immediately cleaved by reacting with 1% citric acid in MeOH (*w/v*) at rt for overnight to get the primary amine **73** in 85% yield. Disappearance of signals corresponding to Boc group and presence of the remaining signals at their respective chemical shift values in the ^1H NMR spectrum of the compound **73** clarified the deprotection. A signal at *m/z* 446 corresponding to $[M+H]^+$ in the ESI mass spectrum of the compound **73** also confirmed the formation of the product.

Refluxing a solution of primary amine **73** in MeOH containing 2 eq of DIPEA for overnight afforded the piperidine **74** in 80% yield (Scheme 16). Disappearance of the signal corresponding to –OMs group in the ^{1}H NMR spectrum of the compound **74** was the prime support for the successful transformation and the rests of the protons were observed at their respective chemical shift values. ESI mass spectrum of compound **74** showed a signal at *m/z* 350 corresponding to $[M+H]^{+}$. A high resolution ESI mass spectrum consisting of a signal at *m/z* 350.2503 corresponding to $[M+H]^{+}$ (calcd 350.2515) further justified the success of the reaction.

Scheme 16

Reaction of the 2°–amine **74** with 2.4 eq of Na_2CO_3 and 1.8 eq of CbzCl afforded the corresponding *N*–Cbz carbamate[34] **75** which was directly subjected to the *O*–silyl deprotection[35] reaction by allowing it to react with 0.1 eq of CSA in a mixture of CH_2Cl_2 and MeOH (3:1) at 0 °C–rt for overnight to get the compound **53** in 57% yield over two steps (Scheme 16). Disappearance of signals corresponding to TBS group and the presence of the characteristic *N*–Cbz signals with remaining protons at their respective chemical shift values in the ^{1}H NMR spectrum of the compound **53** collectively proved the conversion. Carbamate carbonyl carbon was observed at δ 157.3 in the ^{13}C NMR spectrum of the compound **53**. In addition to this, a broad signal at 3440 cm^{-1} in the IR spectrum of the compound **53** also suggested the presence of –OH functionality. High resolution ESI mass spectrum carrying a signal at *m/z* 392.1828 corresponding to $[M+Na]^{+}$ (calcd 392.1837) was also in excellent agreement with the formation of the product. Alcohol **53** was oxidized to the corresponding aldehyde **76** in quantitative yield by reacting with 4 eq of Dess–Martin periodinane[19] in CH_2Cl_2 at 0 °C–rt for 2 h. The aldehyde thus obtained

was taken forward to the next reaction, after a flash column chromatography, without any further characterization.

Treatment of 10 eq of phosphonium salt **77** with 9 eq of ^{n}BuLi at 0 °C for 15 min produced[18] an intermediate ylide which was allowed *in situ* to react with the aldehyde **76** at the same temperature for 1 h to obtain the the compound **52** in 75% yield (Scheme 17). Aliphatic long chain signals were observed at δ 1.41–1.13 and the olefinic signals were observed at δ 5.62 and 5.38 in the ^{1}H NMR spectrum of compound **52**. ESI mass spectrum of compound **52** showed a signal at *m/z* 528 corresponding to $[M+H]^{+}$. High resolution ESI mass spectrum carrying a signal at *m/z* 528.3457 corresponding to $[M+Na]^{+}$ (calcd 528.3453) was also in excellent agreement with the formation of the product. Hydrogenation of the compound **52** in the presence of Pd/C (20% *w/w*) in a mixture of MeOH and HCl (50:1) resulted in one–pot debenzylation as well. Thus the *N*–Cbz deprotection and saturation of the olefinic bond furnished the final target molecule (+)–deoxocassine (**4**) in 80% yield.

Scheme 17

Absence of the aromatic and olefinic signals in the ^{1}H NMR spectrum of compound **4** confirmed the successful one–pot debenzylation, *N*–Cbz deprotection and saturation of the olefinic bond. The ^{1}H NMR and ^{13}C NMR were in very good agreement with that of the reported for the (+)–deoxocassine (**4**).

Our synthetic (+)–deoxocassine (**4**) showed specific rotation $[\alpha]_D^{25}$ = +12.2 (*c* 0.29, $CHCl_3$); lit. value: $[\alpha]_D^{20}$ = +11.8 (*c* 1.0, $CHCl_3$)[13] [whereas $[\alpha]_D^{20}$ = –12.3 (*c* 0.19, $CHCl_3$)[11c] for (–)–deoxocassine (**7**)].

The ESI mass spectrum of compound **4** showed a signal at *m/z* 284 corresponding to $[M+H]^+$ and in addition to this, the high resolution ESI mass spectrum carrying a signal at *m/z* 284.2954 corresponding to $[M+H]^+$ (calcd 284.2953) was also in support for the formation of the product.

Thus, we have demonstarted the synthesis of a versatile chiral synthon **53** and accomplished the total synthesis of (+)–deoxocassine (**4**). We believe that our intermediate will find suitable application in the total synthesis of many other piperidine alkaloids.

EXPERIMENTAL SECTION

(*S*)–Benzyl 2–(dibenzylamino)propanoate (60):

L–Alanine **59** (15 g, 168.54 mmol) and anhydrous K_2CO_3 (81.54 g, 589.9 mmol) were suspended in EtOH (350 mL). The resulting mixture was stirred for few minutes and BnBr (66.05 mL, 556.18 mmol) was added dropwise over 30 min. After stirring for 5 days at room temperature, solids were separated by filtration (EtOAc was used for washing) and volatiles were removed under reduced pressure. The resultant syrupy residue was then extracted with EtOAc (2×250 mL). The combined organic layers were washed with water (150 mL), saturated aqueous $NaHCO_3$ (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentared *in vacuo*. The crude product was then purified by standard column chromatography (Silica gel, 5% EtOAc in petroleum ether) to afford the titled compound **60** as light yellow colored oil (49.6 g, 82%).

***R*$_f$:** 0.6 (Silica gel, 10% EtOAc in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4–7.14 (m, 15H, Ar*H*), 5.21 (d, *J* = 12.1 Hz, 1H, PhC*H*H), 5.13 (d, *J* = 12.4 Hz, 1H, PhCH*H*), 3.82 (d, *J* = 14 Hz, 2H, PhCH_2), 3.62 (d, *J* = 14 Hz, 2H, PhCH_2), 3.55 (q, *J* = 7.0 Hz, 1H, Bn_2NCH), 1.33 (d, *J* = 7.0 Hz, 3H, CH_3CH).

(*S*)–2–(Dibenzylamino)propan–1–ol (61):

To a magnetically stirred solution of benzyl ester **60** (40 g, 111.42 mmol) in THF (300 mL) at 0 °C was added $LiAlH_4$ (8.46 g, 222.84 mmol) in portionwise manner. The reaction mixture was stirred for 4 h at room temperature and cooled to 0 °C before the excess hydride was quenched by dropwise addition of H_2O (12 mL) followed by the addition of 3N NaOH (12 mL) and H_2O (37 mL). After being stirred for overnight, the reaction mixture was filtered through a short pad of celite and the filter cake was washed with EtOAc (2×250 mL). The combined washings and filtrate were washed with water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*.

BnOH was distilled out under high vacuum and the residue was purified by column chromatography (Silica gel, 4% EtOAc in petroleum ether) to get the required alcohol **61** as colorless oil (17.28 g, 61%).

***R*$_f$:** 0.3 (Silica gel, 10% EtOAc in petroleum ether).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4–7.2 (m, 10H, Ar*H*), 3.82 (d, *J* = 13.4 Hz, 2H, PhC*H*$_2$), 3.46 (t, *J* = 10.5 Hz, 1H, C*H*HOH), 3.36 (d, *J* = 13.4 Hz, 2H, PhC*H*$_2$), 3.35 (m, 1H, CH*H*OH), 3.10 (br s, 1H, CH_2O*H*), 2.99 (m, 1H, CH_3C*H*), 0.98 (d, *J* = 6.7 Hz, 3H, C*H*$_3$CH).

ESI–MS: *m/z* (%) 256 (100) $[M+H]^+$.

(*S*)–1–((*S*)–2,2–Dimethyl–1,3–dioxolan–4–yl)ethane–1,2–diol (65):

Acetyl chloride (30 mL, 10% *w/v*) was added to a suspension of L–ascorbic acid **30** (300 g, 1.7 mol) in acetone (1.2 L) and the resultant slurry was stirred for 3 h at room temperature and for 6 h at 0 °C. Reaction mixture was filtered through Büchner funnel. The colorless solid thus obtained was washed with cold acetone and dried under vacuum to afford the acetonide **62** which was subjected to the oxidative cleavage reaction without any further characterization.

To a magnetically stirred solution of the acetonide **62** in water (1.8 L) at 0 °C was added K_2CO_3 (468 g, 3.38 mol) in portionwise manner over a period of 1 h. Resultant reaction mixture was stirred until a clear solution was obtained. To the reaction mixture, at the same temperature, was added 30% H_2O_2 (375 mL) in dropwise manner over a period of 1 h. The resultant reaction mixture was stirred for overnight at room temperature to get the acid **63**.

To the above reaction mixture was added $NaHCO_3$ (600 g, 7.14 mol) and $(Me)_2SO_4$ (600 mL, 6.3 mol) and stirred for 6 h at 40 °C. Then the reaction mixture was filtered and the filtrate was extracted with CH_2Cl_2 (1 L). Combined extracts were washed

with water (300 mL), saturated aqueous NaCl (300 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the ester **64** as colorless oil (105 g, 32.4% over three steps).

To a 0 °C cooled solution of the ester **64** (100 g, 526.3 mmol) in THF (750 mL) was added $LiAlH_4$ (23.97 g, 631.58 mmol) in portionwise manner and the resultant reaction mixture was stirred for 1 h at room temperature and cooled to 0 °C before the excess hydride was quenched by dropwise addition of H_2O (45 mL) followed by the addition of 3N NaOH (45 mL) and H_2O (135 mL). After being stirred for overnight, the reaction mixture was filtered through a short pad of celite and the filter cake was washed with EtOAc (2×250 mL). The combined washings and filtrate were washed with water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentrated under vacuum. The residue thus obtained was purified by column chromatography (Silica gel, 50% EtOAc in petroleum ether) to get the required diol **65** as colorless oil (35 g, 40%).

***R*$_f$:** 0.3 (Silica gel, 80% EtOAc in petroleum ether).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.16 (td, J = 6.6, 4.6 Hz, 1H, OCH_2CH), 4.04 (dd, J = 8.1, 6.6 Hz, 1H, OC*H*HCH), 3.84 (dd, J = 8.2, 6.7 Hz, 1H, OCH*H*CH), 3.70–3.60 (m, 3 H, C*H*OHCH_2OH), 2.88 (br s, 1H, O*H*), 2.72 (br s, 1H, O*H*), 1.43 (s, 3H, CCH_3CH$_3$), 1.36 (s, 3H, CCH$_3$CH_3).

(*R*)–4–(2,2–Dibromovinyl)–2,2–dimethyl–1,3–dioxolane (58):

To a magnetically stirred solution of diol **65** (30 g, 185.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added saturated aqueous $NaHCO_3$ solution (12 mL). After being stirred for 10 min at the same temperature, $NaIO_4$ (79.22 g, 370.4 mmol) was added to the reaction mixture and stirred for 1.5 h at room temperature. Anhydrous Na_2SO_4 (5 g) was added and filtered through a short pad of Na_2SO_4 and the filter cake was washed with CH_2Cl_2 (3×25 mL). Evaporation of the solvent under reduced temperature and at atmospheric pressure afforded the aldehyde **66** (R_f = 0.6, 80% EtOAc in petroleum ether) having volatile nature which was immediately subjected to the next reaction.

To a solution of TPP (194.3 g, 740.76 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added CBr_4 (122.83 g, 370.38 mmol) in portionwise manner and stirred for 30 min at room temperature. The resultant deep brown solution thus obtained was cooled to 0 °C and a solution of the aldehyde **66** in CH_2Cl_2 (20 mL, 2×) was introduced *via* cannula. The reaction mixture was stirred for 2 h at room temperature before it was quenched with slow addition of petroleum ether (15 mL) at 0 °C. Resultant mixture was stirred for additional 1 h at room temperature and filtered through ahort pad of celite and the filter cake was washed with a mixture of petroleum ether and EtOAc (8:2, 200 mL, 2×). Combined filtrate and the washings were concentrated *in vacuo* and purified by flash column chromatography (Silica gel, 10% EtOAc in petroleum ether eluant) to get the dibromo–olefin **58** as light yellow colored oil (15 g, 28% over two steps).

***R*$_f$:** 0.7 (Silica gel, 30% EtOAc in petroleum ether).

(*3R,4S*)–4–(Dibenzylamino)–1–((*R*)–2,2–dimethyl–1,3–dioxolan–4–yl)pent–1–yn–3–ol (56):

To a solution of $(COCl)_2$ (6.87 mL. 78.72 mmol) in CH_2Cl_2 (400 mL) at –78 °C, DMSO (11.94 mL, 167.94 mmol) was added slowly in dropwise manner with stirring under nitrogen atmosphere. After 20 min, alcohol **61** (13.39 g, 52.48 mmol), dissolved in CH_2Cl_2 (50 mL, 2×) was introduced into the reaction mixture *via* cannula. After 30 min of stirring at –78 °C, Et_3N (36.57 mL, 262.4 mmol) was added, stirred for another 30 min at –78 °C and then for 30 min at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2×250 mL). The combined organic extracts were washed with water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde **57** (13.28 g, quantitative yield, R_f = 0.6, 10% EtOAc in petroleum ether) thus obtained was passed through a short pad of Na_2SO_4 and used for the next reaction without any further characterization.

^{n}BuLi (1.6M in hexane, 62.3 mL, 99.66 mmol) was added to a magnetically stirred solution of dibromo olefin **58** (15 g, 52.45 mmol) in THF (100 mL) at –78 °C. Stirring was continued at –78 °C for 30 min and then at room temperature for another 30 min, recooled to –78 °C and a solution of the aldehyde **57** (13.28 g, 52.45 mmol) in THF (20 mL, 2×) was added *via* cannula. After 30 min, the reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (2×200 mL). The combined organic layers were washed with water (150 mL), saturated aqueous NaCl (150 mL), dried (Na_2SO_4) and concentrated in rotary evaporator. The crude residue thus obtained was purified by column chromatography (Silica gel, 14% EtOAc in petroleum ether eluant) to afford the alkynol **56** (13.24 g, 66.5%) as yellow color oil.

***R*$_f$:** 0.5 (Silica gel, 30% EtOAc in petroleum ether).

$[\alpha]_D^{30}$: –31.4 (*c* 2.8, $CHCl_3$).

IR (neat): ν_{max} 3442, 2985, 2930, 2882, 1493, 1452, 1374, 1216, 1151, 1061, 1026, 842, 743, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38–7.19 (m, 10H, Ar*H*), 4.71 (m, 1H, C*H*CH_2), 4.25–4.02 (m, 4H, PhCH_2, CHCH_2), 3.81 (m, 1H, C*H*OH), 3.37 (d, *J* = 13.2 Hz, 2H, PhCH_2), 3.11–2.85 (m, 2H, CH_3C*H*, CHO*H*), 1.33 (s, 6H, acetonide 2×CH_3), 1.21 (d, *J* = 7.3 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.06, 129.03, 128.43, 127.25, 110.15, 85.78, 83.48, 69.7, 65.54, 63.03, 55.82, 54.64, 25.96, 25.88, 9.43.

ESI–MS: *m/z* (%) 380 (100) $[M+H]^+$, 402 (35) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{24}H_{30}NO_3$ $[M+H]^+$ 380.2225, found 380.2214.

(*3S,4S*)–4–(Dibenzylamino)–1–((*R*)–2,2–dimethyl–1,3–dioxolan–4–yl)pent–1–yn–3–yl 4–nitrobenzoate (67):

To a stirred solution of compound **56** (10 g, 26.35 mmol) in THF (5 mL), PPh_3 (24.19 g, 92.23 mmol), *p*–nitrobenzoic acid (18.5 g, 110.67 mmol) were added sequentially at 0 °C under nitrogen atmosphere. After 15 min, DEAD (14.52 mL, 92.23 mmol) was introduced into the reaction mixture, allowed to warm to room temperature and stirred for 4 h. It was then concentrated in *vacuo*. Purification by column chromatography (Silica gel, 8% EtOAc in petroleum ether eluant) gave the compound **67** (10.25 g, 73.6%) as clear oil.

***R_f*:** 0.7 (Silica gel, 30% EtOAc in petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.35–8.12 (m, 4H, Ar*H*), 7.41–7.12 (m, 10H, Ar*H*), 5.79 (d, *J* = 5.9 Hz, 1H, C*H*OCOAr), 4.71 (m, 1H, C*H*CH_2), 4.1 (dd, *J* = 8, 6.6 Hz, 1H, CHC*H*H), 3.92–3.78 (m, 3H, PhCH_2, CHCH*H*), 3.58 (d, *J* = 13.9 Hz, 2H, PhCH_2), 3.3 (p, *J* = 6.6 Hz, 1H, CH_3C*H*), 1.43 (s, 3H, acetonide CH_3), 1.36 (s, 3H, acetonide CH_3), 1.28 (d, *J* = 6.6 Hz, 3H, CH_3CH).

(*3S,4S*)–4–(Dibenzylamino)–1–((*R*)–2,2–dimethyl–1,3–dioxolan–4–yl)pent–1–yn–3–ol (68):

To a solution of the compound **67** (9 g, 17.03 mmol) in MeOH (50 mL) was added K_2CO_3 (4.63 g, 34.06 mmol) at 0 ^oC under nitrogen atmosphere and the reaction mixture was stirred for 45 min at room temperature. Saturated aqueous NH_4Cl solution (15 mL) was added to it and MeOH was evaporated *in vacuo*. Crude residue was extracted with EtOAc (2×150 mL). Combined organic extracts were washed with water (100 mL), saturated aqueous NaCl (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (Silica gel, 14% EtOAc in petroleum ether eluant) afforded the pure propargyl alcohol **68** (5.81 g, 90%) as colorless liquid.

***R_f*:** 0.5 (Silica gel, 30% EtOAc in petroleum ether).

$[\alpha]_D^{27}$: –19.8 (*c* 1.2, $CHCl_3$).

IR (neat): ν_{max} 3444, 2984, 2927, 2855, 1493, 1453, 1375, 1217, 1152, 1062, 1027, 843, 744, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.2 (m, 10H, Ar*H*), 4.71 (m, 1H, C*H*CH_2), 4.25–4.03 (m, 4H, PhC*H*$_2$, CHC*H*$_2$), 3.8 (m, 1H, C*H*OH), 3.38 (d, *J* = 13.2 Hz, 2H, PhC*H*$_2$), 3.11–2.87 (m, 2H, CH_3C*H*, CHO*H*), 1.33 (s, 6H, acetonide 2×C*H*$_3$), 1.21 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.05, 129.05, 128.44, 127.27, 110.17, 85.79, 83.51, 69.72, 65.56, 63.04, 55.84, 54.66, 25.97, 25.89, 9.44.

ESI–MS: *m/z* (%) 380 (100) $[M+H]^+$, 402 (10) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{24}H_{30}NO_3$ $[M+H]^+$ 380.2225, found 380.2214.

***tert*–Butyl(*2S,3S*)–5–((*R*)–2,2–dimethyl–1,3–dioxolan–4–yl)–3–hydroxypentan–2–ylcarbamate (55):**

To a magnetically stirred solution of compound **68** (5 g, 13.18 mmol) in MeOH (50 mL) was added $Pd(OH)_2$/C (1 g, 20% *w/w*) and hydrogenated by using H_2 filled balloons under atmospheric pressure. After completion of reaction, the reaction mixture was filtered through a short pad of celite and the filter cake was washed with MeOH (60 mL, 3×). The combined filtrate and washings were concentrated *in vacuo* and dried under vacuum. The residue was then dissolved in CH_2Cl_2 (50 mL), basified with Et_3N (2 mL, 14.45 mmol) and Boc_2O (3.32 mL, 14.45 mmol) was added. After being stirred at room temperature for overnight, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL) followed by evaporation of MeOH and extracted with EtOAc (2×150 mL). The combined organic extracts were washed with water (50 mL), saturated aqueous NaCl (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (Silica gel, 30% EtOAc in petroleum ether eluant) afforded the compound **55** (3.2 g, 81%) as colorless oil.

***R*$_f$:** 0.5 (Silica gel, 60% EtOAc in petroleum ether).

$[\alpha]_D^{31}$: –15.1 (*c* 0.49, $CHCl_3$).

IR (neat): ν_{max} 3442, 2981, 2933, 1688, 1510, 1454, 1371, 1247, 1168, 1054, 855 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.87 (m, 1H, BocN*H*), 4.19–4.02 (m, 2H, CHCH_2), 3.74–3.58 (m, 2H, C*H*CH_2, C*H*OH), 3.54 (m, 1H, CH_3C*H*), 1.82–1.5 (m, 4H, CH_2CH_2), 1.45 (s, 9H, ^{t}*Bu*), 1.42 (s, 3H, acetonide CH_3), 1.37 (s, 3H, acetonide CH_3), 1.11 (d, J = 6.8 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 109.11, 76.19, 74.37, 69.47, 50.79, 30.76, 30.39, 28.37, 26.84, 25.71, 14.52.

ESI–MS: *m/z* (%) 304 (10) $[M+H]^+$, 326 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{15}H_{29}NO_5Na$ $[M+Na]^+$ 326.1943, found 326.1946.

***tert*–Butyl(*2S,3S*)–3–(benzyloxy)–5–((*R*)–2,2–dimethyl–1,3–dioxolan–4–yl)pentan–2–ylcarbamate (70):**

NaH (461 mg, 60% dispersion in oil, 11.54 mmol) was added in portionwise manner to a stirred solution of compound **55** (2.5 g, 8.24 mmol) in DMF (30 mL) at 0 °C under nitrogen atmosphere. After the completion of addition, the reaction mixture was stirred at 0 °C for 15 min. Then BnBr (1.47 mL, 12.36 mmol) was added slowly followed by the addition of TBAI (304 mg, 0.82 mmol). After stirring for 3 h at room temperature, the reaction mixture was quenched at 0 °C by slow addition of saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2×150 mL). The combined organic layers were washed with water (4×25 mL), saturated aqueous NaCl (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (Silica gel, 18% EtOAc in petroleum ether eluant) afforded the compound **70** (2.72 g, 88%) as colorless solid.

***R_f*:** 0.5 (Silica gel, 30% EtOAc in petroleum ether).

$[\alpha]_D^{31}$: –34.1 (*c* 0.41, $CHCl_3$).

IR (neat): ν_{max} 3442, 2980, 2929, 2869, 1695, 1501, 1453, 1369, 1245, 1166, 1057, 740, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.25 (m, 5H, Ar*H*), 4.73–4.49 (m, 3H, PhCH_2, CHC*H*H), 4.12–3.97 (m, 2H, BnOC*H*, CHCH*H*), 3.83 (br s, 1H, BocN*H*), 3.55–3.41 (m,

2H, C*H*CH_2, CH_3C*H*), 1.82–1.46 (m, 4H, CH_2CH_2), 1.43 (s, 9H, ^tBu), 1.4 (s, 3H, acetonide CH_3), 1.35 (s, 3H, acetonide CH_3), 1.11 (d, J = 6.8 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3, 138.54, 128.39, 127.74, 127.64, 108.81, 81.16, 75.78, 72.3, 69.22, 48.14, 29.72, 28.4, 26.9, 26.73, 25.66, 15.03.

ESI–MS: *m/z* (%) 394 (100) $[M+H]^+$, 411 (10) $[M+NH_4]^+$, 416 (55) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{22}H_{35}NO_5Na$ $[M+Na]^+$ 416.2412, found 416.2399.

***tert*–Butyl(*2S,3S,6R*)–3–(benzyloxy)–6,7–dihydroxyheptan–2–ylcarbamate (71):**

A solution of compound **70** (2 g, 5.09 mmol) in MeOH (20 mL) was treated with CSA (1.3 g, 5.6 mmol) at 0 °C. After being stirred for 4 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL, pH = 8) and extracted with EtOAc (4×75 mL). The combined organic extracts were washed with water (30 mL), saturated aqueous NaCl (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was purified by column chromatography (Silica gel, 60% EtOAc in petroleum ether eluant) to afford the diol **71** (1.6 g, 89%) as colorless solid.

***R_f*:** 0.2 (Silica gel, EtOAc).

$[\alpha]_D^{31}$: –24.79 (*c* 0.71, $CHCl_3$).

IR (neat): ν_{max} 3343, 2975, 2930, 2870, 1688, 1501, 1453, 1366, 1246, 1168, 1060, 740, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H, Ar*H*), 4.67–4.5 (m, 3H, PhCH_2, BnOC*H*), 3.84 (m, 1H, BocN*H*), 3.7–3.54 (m, 2H, C*H*OH, CH_3C*H*), 3.48–3.34 (m, 2H, CH_2OH), 2.65 (br s, 1H, O*H*), 2.16 (br s, 1H, O*H*), 1.83–1.47 (m, 4H, CH_2CH_2), 1.43 (s, 9H, ^tBu), 1.13 (d, J = 6.8 Hz, 3H, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.56, 138.39, 128.38, 127.77, 127.66, 81.18, 79.38, 72.17, 71.89, 66.74, 47.99, 28.84, 28.38, 26.28, 15.22.

ESI–MS: *m/z* (%) 354 (80) $[M+H]^+$, 371 (15) $[M+NH_4]^+$, 376 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{19}H_{31}NO_5Na$ $[M+Na]^+$ 376.2099, found 376.2106.

***tert*–Butyl(*2S,3S,6R*)–3–(benzyloxy)–7–(*tert*–butyldimethylsilyloxy)–6–hydroxy heptan–2–ylcarbamate (72):**

Et_3N (0.79 mL, 5.7 mmol), TBSCl (467 mg, 3.1 mmol) and DMAP (34 mg, 0.28 mmol) were added sequentially to a stirred solution of compound **71** (1 g, 2.83 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After being stirred for overnight at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed water (30 mL), saturated aqueous NaCl (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (Silica gel, 15% EtOAc in petroleum ether eluant) provided the pure compound **72** (1 g, 76 %) as colorless oil.

***R*$_f$:** 0.7 (Silica gel, 60% EtOAc in petroleum ether).

$[\alpha]_D^{31}$: –21.95 (*c* 0.41, $CHCl_3$).

IR (neat): ν_{max} 3445, 2932, 2860, 1695, 1499, 1457, 1365, 1251, 1168, 1062, 839, 777 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.2 (m, 5H, Ar*H*), 4.68–4.43 (m, 3H, PhCH_2, BnOC*H*), 3.81 (br s, 1H, BocN*H*), 3.63–3.5 (m, 2H, CH_2OTBS), 3.48–3.31 (m, 2H, CH_3C*H*, C*H*OH), 1.79 (m, 1H, C*H*HCH_2), 1.42 (s, 9H, ^{t}*Bu* Boc), 1.26 (m, 3H, CH*H*CH_2), 1.12 (d, *J* = 6.6 Hz, 3H, CH_3CH), 0.91 (s, 9H, ^{t}*Bu*Si), 0.08 (s, 6H, (CH_3)$_2$Si).

ESI–MS: *m/z* (%) 468 (100) $[M+H]^+$, 485 (15) $[M+NH_4]^+$, 490 (75) $[M+Na]^+$.

(*6R,9S,10S*)–9–(Benzyloxy)–2,2,3,3,10,14,14–heptamethyl–12–oxo–4,13–dioxa–11–aza–3–silapentadecan–6–yl methanesulfonate (54):

To a magnetically stirred solution of compound **72** (600 mg, 1.28 mmol) in CH_2Cl_2 (8 mL) was added Et_3N (0.36 mL, 2.56 mmol) at 0 °C and stirred for 10 min. Then MsCl (0.15 mL, 1.92 mmol) was added followed by DMAP (78 mg, 0.64 mmol) and the reaction

mixture was stirred at room temperature for 3 h. It was then quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with water (30 mL), saturated aqueous NaCl (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (Silica gel, 15% EtOAc in petroleum ether eluant) afforded pure mesylate **54** (490 mg, 70%) as a light yellow oil.

***R*$_f$:** 0.5 (Silica gel, 30% EtOAc in petroleum ether).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38–7.3 (m, 5H, Ar*H*), 4.72–4.54 (m, 4H, PhC*H*$_2$, BnOC*H*, C*H*OMs), 3.92–3.66 (m, 3H, BocN*H*, TBSOC*H*$_2$), 3.43 (m, 1H, CH_3CH), 3.04 (s, 3H, C*H*$_3$SO$_2$OCH), 1.86–1.52 (m, 4H, C*H*$_2$C*H*$_2$), 1.43 (s, 9H, ^{t}*Bu* Boc), 1.13 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CH), 0.9 (s, 9H, ^{t}*Bu*Si), 0.07 (s, 6H, (C*H*$_3$)$_2$Si).

(*2R,5S,6S*)–6–Amino–5–(benzyloxy)–1–(*tert*–butyldimethylsilyloxy)heptan–2–yl methanesulfonate (73):

To a solution of compound **54** (400 mg, 0.73 mmol) in CH_2Cl_2 (20 mL) at room temperature were added 2,6–lutidine (0.17 mL, 1.46 mmol) and TBSOTf (0.25 mL, 1.1 mmol). The reaction mixture was then stirred at room temperature for 1 h. After evaporation of CH_2Cl_2, a solution of citric acid in MeOH (1% *w/v*, 10 mL) was added and the resultant mixture was stirred at room temperature for overnight. The reaction mixture was quenched with saturated aqeous $NaHCO_3$ (10 mL), MeOH was evaporated and extracted with EtOAc (2×50 mL). The combined organic extracts were washed with water (30 mL), saturated aqueous NaCl (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (Silica gel, 4% MeOH in $CHCl_3$) afforded the primary amine **73** as colorless oil (278 mg, 85%).

***R*$_f$:** 0.3 (Silica gel, 10% MeOH in $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.39–7.19 (m, 5H, Ar*H*), 4.74–4.39 (m, 3H, PhC*H*$_2$O, C*H*OMs), 3.95–3.27 (m, 6H, N*H*$_2$, TBSOC*H*$_2$, CH_3CH, BnOC*H*), 3.0 (s, 3H,

C*H*$_3$SO$_2$OCH), 1.84–1.47 (m, 3H, C*H*HC*H*$_2$), 1.34–1.11 (m, 4H, C*H*$_3$CH, CH*H*CH$_2$), 0.89 (s, 9H, ^{t}*Bu*Si), 0.07 (s, 6H, (C*H*$_3$)$_2$Si).

ESI–MS: *m/z* (%) 446 (70) $[M+H]^+$.

(*2S,3S,6S*)–3–(Benzyloxy)–6–((*tert*–butyldimethylsilyloxy)methyl)–2–methylpiperidine (74):

A solution of amine **73** (240 mg, 0.54 mmol) and DIPEA (0.18 mL, 1.08 mmol) in MeOH (40 mL) was refluxed for overnight. The solvent was evaporated and the residue was purified by flash column chromatography (Silica gel, 1% MeOH in $CHCl_3$) to get the compound **74** as colorless oil (150 mg, 80%).

***R*$_f$:** 0.6 (Silica gel, 10% MeOH in $CHCl_3$).

IR (neat): ν_{max} 3400, 2929, 2858, 1461, 1254, 1097, 840, 776 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ 7.35–7.22 (m, 5H, Ar*H*), 4.55 (ABq, *J* = 11.6 Hz, 2H, PhC*H*$_2$), 3.55 (dd, *J* = 8.9, 3.8 Hz, 1H), 3.39 (dd, *J* = 8.9, 3.8 Hz, 1H), 2.97 (m, 1H), 2.79–2.54 (m, 3H), 2.39–2.14 (m, 3H), 1.61 (m, 1H), 1.44–1.14 (m, 4H), 0.89 (s, 9H, ^{t}*Bu*Si), 0.05 (s, 6H, (C*H*$_3$)$_2$Si).

ESI–MS: *m/z* (%) 350 (100) $[M+H]^+$.

HRMS (ESI): Calcd for $C_{20}H_{36}NO_2Si$ $[M+H]^+$ 350.2515, found 350.2503.

(*2S,3S,6S*)–Benzyl–3–(benzyloxy)–6–(hydroxymethyl)–2–methylpiperidine–1–carboxylate (53):

To a magnetically stirred solution of compound **74** (100 mg, 0.29 mmol) in a mixture of CH_2Cl_2 and H_2O (3:1, 2 mL) were added Na_2CO_3 (74 mg, 0.7 mmol) and CbzCl (0.075 mL, 0.52 mmol). The resulting mixture was stirred at room temperature for

overnight and then extracted with EtOAc (2×10 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude compound **75** (R_f = 0.5, 20% EtOAc in petroleum ether) thus obtained was directly used for the next reaction without any further purification and characterization.

To a solution of compound **75** in a mixture of MeOH (0.5 mL) and CH_2Cl_2 (0.5 mL) was added CSA (6.7 mg, 0.029 mmol) and stirred at room temperature for overnight. Solvents were removed under reduced pressure and extracted with EtOAc (2×10 mL). The combined organic layers were washed with water (5 mL), saturated aqueous NaCl (5 mL), dried (Na_2SO_4) and concentrated in rotary evaporator. The crude residue thus obtained was purified by column chromatography (Silica gel, 60% EtOAc in petroleum ether eluant) to afford the alcohol **53** (60 mg, 57% over two steps) as clear oil.

***R*$_f$:** 0.2 (Silica gel, 50% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: –9.18. (*c* 1.8, $CHCl_3$).

IR (neat): ν_{max} 3440, 2931, 2872, 1684, 1450, 1412, 1353, 1299, 1091, 1062, 740, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.24 (m, 10H, Ar*H*), 5.16 (s, 2H, PhC*H*$_2$OCO), 4.56–4.47 (m, 3H, PhC*H*$_2$, BnOC*H*), 4.37 (m, 1H, C*H*CH_2OH), 3.69–3.6 (m, 2H, C*H*$_2$OH), 3.41 (m, 1H, CH_3C*H*), 2.11 (m, 1H), 1.66 (br s, 1H, CH_2O*H*), 1.79–1.72 (m, 2H), 1.55 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 138.41, 136.75, 128.48, 128.33, 127.91, 127.67, 127.5, 127.4, 74.99, 70.07, 67.24, 65.17, 51.8, 49.73, 19.61, 19.15, 18.24.

ESI–MS: *m/z* (%) 370 (100) $[M+H]^+$, 392 (70) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{22}H_{27}NO_4Na$ $[M+Na]^+$ 392.1837, found 392.1828.

(*2S,3S,6S*)–Benzyl–3–(benzyloxy)–6–((*Z*)–dodec–1–enyl)–2–methylpiperidine–1–carboxylate (52):

To a stirred solution of compound **53** (35 mg, 0.095 mmol) in CH_2Cl_2 (5 mL), was added Dess–Martin periodinane (205 mg, 0.48 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to attain room temperature and stirred for 2 h. Saturated aqueous $Na_2S_2O_3$ (3 mL) followed by $NaHCO_3$ (3 mL) were added and stirred for 15 min. The resultant biphasic mixture was then extracted with EtOAc (2×10 mL). The combined

organic phases were washed with water (10 mL), saturated aqueous NaCl (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The aldehyde **76** (R_f = 0.5, 30% EtOAc in petroleum ether) thus obtained, after passing through a short pad of sodium sulphate, was directly used for the next reaction without any further characterization.

To a magnetically stirred solution of phosphonium salt **77** (472 mg, 0.95 mmol) in THF (3 mL) at 0 °C was added ^{n}BuLi (1.6M in hexane, 0.53 mL, 0.86 mmol) and stirred for 15 min. Then a solution of aldehyde **76** dissolved in THF (2 mL) was introduced into the reaction mixture *via* cannula and stirred for additional 1 h at the same temperature. Reaction mixture was then quenched by the careful addition of saturated aqueous NH_4Cl (3 mL) and extracted with EtOAc (2×5 mL). The combined organic extracts were washed with water (3 mL), saturated aqueous NaCl (3 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by standard column (Silica gel, 7% EtOAc in petroleum ether eluant) chromatography afforded the compound **52** (35 mg, 75%) as colorless oil.

***R*$_f$:** 0.5 (Silica gel, 20% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: +24.6 (*c* 1.19, $CHCl_3$).

IR (neat): ν_{max} 2924, 2854, 1694, 1455, 1410, 1351, 1298, 1074, 736, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 10H, Ar*H*), 5.62 (m, 1H, olefin), 5.38 (m, 1H, olefin), 5.12 (s, 2H, PhCH_2OCO), 5.05 (m, 1H, C*H*CH=CH), 4.62–4.46 (m, 3H, PnCH_2, BnOC*H*), 3.43 (m, 1H, CH_3C*H*N), 2.34–1.44 (m, 4H, BnOCHCH_2CH_2), 1.41–1.13 (m, 21H, (CH_2)$_9$CH_3, CH_3CHN), 0.88 (t, *J* = 6.9 Hz, 3H, $(CH_2)_9CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 155.99, 138.56, 136.99, 131.78, 131.24, 130.37, 129.64, 128.32, 127.73, 127.39, 75.12, 69.96, 66.97, 49.9, 47.65, 31.9, 29.68, 29.62, 29.54, 29.34, 29.17, 27.2, 23.92, 22.68, 20.08, 19.62, 14.12.

ESI–MS: *m/z* (%) 506 (40) $[M+H]^+$, 528 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{33}H_{47}NO_3Na$ $[M+Na]^+$ 528.3453, found 528.3457.

(+)–Deoxocassine (4):

To a solution of compound **52** (20 mg, 0.046 mmol) in a mixture of MeOH and HCl (5 mL, 50:1) was added Pd/C (4 mg, 20% *w/w*). Reaction mixture was hydrogenated under atmospheric pressure of hydrogen. After the completion of the reaction, it was filtered through a short pad of celite and the filter cake was washed with MeOH (15 mL, 3×). Combined filtrates were concentrated under reduced pressure to get the HCl salt of compound **4** which was dissolved in water (5 mL) and basified with liquor ammonia (3 drops) and extracted with EtOAc (3×10 mL). The combined organic layers were washed with water (5 mL), saturated aqueous NaCl (5 mL), dried (Na_2SO_4), concentrated *in vacuo* and purified by column chromatography (Neutral Al_2O_3, 3% MeOH in CH_2Cl_2 eluant) to get the (+)–deoxocassine (**4**) as colorless solid (9 mg, 80%).

***R_f*:** 0.2 (Silica gel, 10% MeOH in $CHCl_3$).

$[\alpha]_D^{25}$: +12.2 (*c* 0.29, $CHCl_3$).

IR (neat): ν_{max} 3258, 3125, 2919, 2850, 1461, 1371, 1263, 1052, 991 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (m, 1H), 3.18 (m, 1H), 2.58–2.43 (m, 2H), 2.03 (m, 1H), 1.8–1.55 (m, 4H), 1.4–1.14 (m, 25H), 0.88 (t, *J* = 6 Hz, 3H, terminal C*H*$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): δ 74.14, 58.56, 56.42, 36.49, 34.03, 31.9, 31.57, 29.77, 29.64, 29.58, 29.34, 26.21, 22.68, 18.91, 14.12.

ESI–MS: *m/z* (%) 284 (100) $[M+H]^+$.

HRMS (ESI): Calcd for $C_{18}H_{38}NO$ $[M+H]^+$ 284.2953, found 284.2954.

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SYNOPSIS

Title of the thesis:	Ti(III)–mediated epoxide opening reactions to construct five–membered carbocycles, studies directed toward the synthesis of rhizopodin and the total synthesis of deoxocassine
Name of the student:	Midde Sreekanth (07CHPH02)
Research supervisor:	Dr. Tushar Kanti Chakraborty
Co–supervisor:	Dr. Dhevalapally B. Ramachary

The thesis entitled **"Ti(III)–mediated epoxide opening reactions to construct five–membered carbocycles, studies directed toward the synthesis of rhizopodin and the total synthesis of deoxocassine"** consists of three chapters.

Chapter–I: Describes the $Cp_2Ti(III)Cl$ radical mediated opening of chiral 2,3–epoxy alcohols to construct five–membered carbocycles with multiple chiral centres.

Chapter–II: Illustrates the stereoselective synthesis of the C16–C28 fragment of C_2–symmetric cytostatic macrolide rhizopodin.

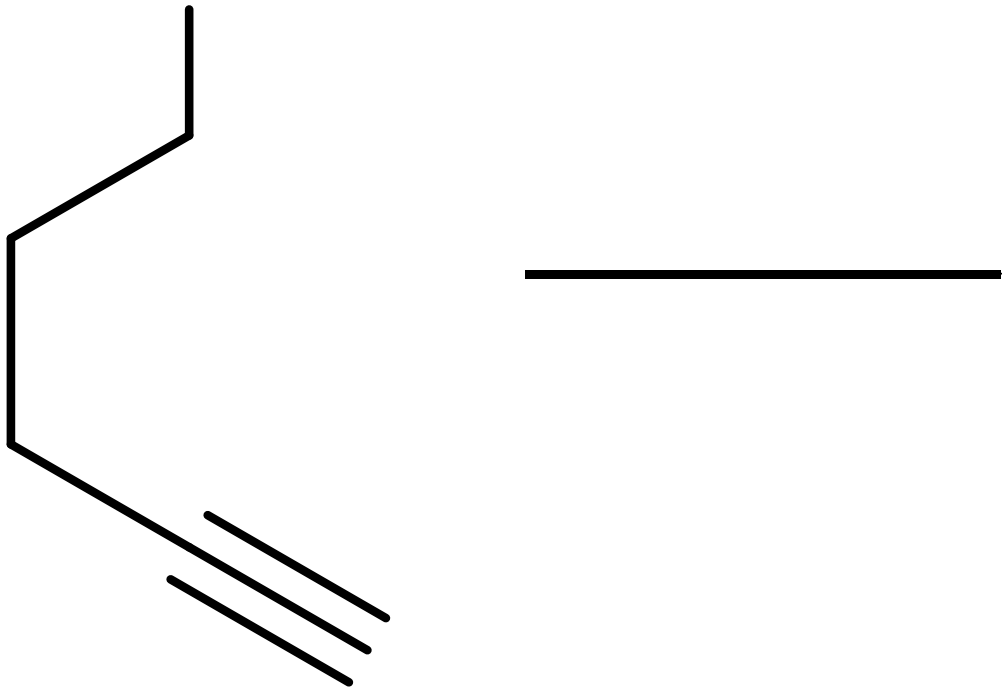
Chapter–III: Deals with the total synthesis of piperidine alkaloid (+)–deoxocassine.

CHAPTER–I

Ti(III)–mediated epoxide opening reactions to construct five–membered carbocycles:

Cyclopentanoid motif is an important and integral part of many biologically active natural products. For the stereoselective preparation of highly functionalized five–membered carbocycles, even though a wide variety of methods were available, still new methods are always of considerable interest. $Cp_2Ti(III)Cl$ mediated reactions play a significant role in organic synthesis. With the inspiring results of Ti(III) radical mediated reactions, found in literature and our laboratory, we were interested to investigate Ti(III)–mediated epoxide opening reactions for the construction of highly functionalized five–membered carbocycles. Ti(III)–mediated epoxide opening followed by intramolecular trapping of the generated radical with suitably placed unsaturation can provide the cyclic products. Thus five–membered carbocycles can be synthesized from 2,3–epoxy alcohols **11A**–**D** *via* a Ti(III)–mediated epoxide opening reaction. Presence of trisubstituted

unsaturation as shown in **11A**–**D** can provide five–membered carbocyles with additional methyl centre at the side arm.

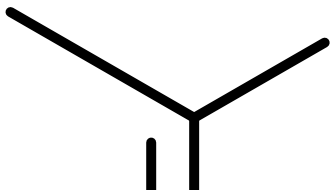


Scheme 1

We started our synthesis from the commercially available pent–4–yn–1–ol (**1**) which was protected as its PMB ether by using PMBBr to get compound **2** in 85% yield

(Scheme 1). Treatment of the acetylide, generated from compound **2** by using ^{n}BuLi, with aldehydes **3a**–**b** resulted in the formation of propargyl alcohols **4a**–**b** in excellent yield. Reaction of compounds **4a–b** with Red–Al produced the allylic alcohols **5a–b** which were protected using TBSOTf to get the TBS ethers **6a–b**. Oxidative cleavage of PMB ether functionality was carried out by employing DDQ under buffered conditions to get the primary alcohols **7a–b** which were oxidized to the corresponding aldehydes **8a–b** under Swern oxidation conditions. Reaction of the aldehydes **8a–b** with stabilized phosphoranes Ph_3P=C(R')COOEt (R' = H, CH_3) produced the α,β–unsaturated esters **9A–D** which were desilylated using TBAF to get the allylic alcohols **10A–D**. Sharpless kinetic resolution (SKR) of the racemic compounds **10A–D** by using L–(+)–DIPT resulted in the formation of 2,3–epoxy alcohols **11A–D** in appropriate yield. To our pleasure, unreacted allylic alcohols **12A–D** could be converted back to the precursor allylic alcohols **10A–D** *via* a two step sequence *i.e.* Swern oxidation and Luche reduction conditions.

Now the stage was set to carry out the crucial Cp_2Ti(III)Cl mediated epoxide ring opening reaction. Reaction of the epoxy alcohols **11A–D** with Cp_2Ti(III)Cl, generated *in situ* by the reaction of Cp_2TiCl_2 with Zn dust and fused $ZnCl_2$, produced a radical which underwent smooth intramolecular cyclization with α,β–unsaturation therein the molecule to form a new C–C bond stereoselectively and led to highly functionalized five–membered carbocycles **13A–D** as the major isolable products (Scheme 2).



Scheme 2

The relative stereochemistries of C2, C3 (**13A–D**) and C8 (**13B**,**D**) centres were unequivocally assigned by incisive NMR studies such as NOESY and HSQC experiments.

These compounds have been analyzed by using 1D–1H decoupling and 2D NMR techniques such as DQF–COSY and NOESY. The conformation of the molecule is fixed by considering the observed coupling constants and nOes.

We have observed a consistency in nOe correlations for all of the products **13A–D**. Strong nOe cross–peaks $C_2H \leftrightarrow C_8H_a$ and H_b, $C_2H \leftrightarrow C_7H$, $C_6H \leftrightarrow C_8H_a$ and $C_1H \leftrightarrow C_7H$ were observed for the compounds **13A–D**. In addition to these observations, strong nOe correlation $C_3H \leftrightarrow C_9H$ was also observed in compounds **13B**,**D** (Figure 1). Interestingly, the fixation of C8 methyl stereo centre was found to be the same in both **13B** and **13D**.

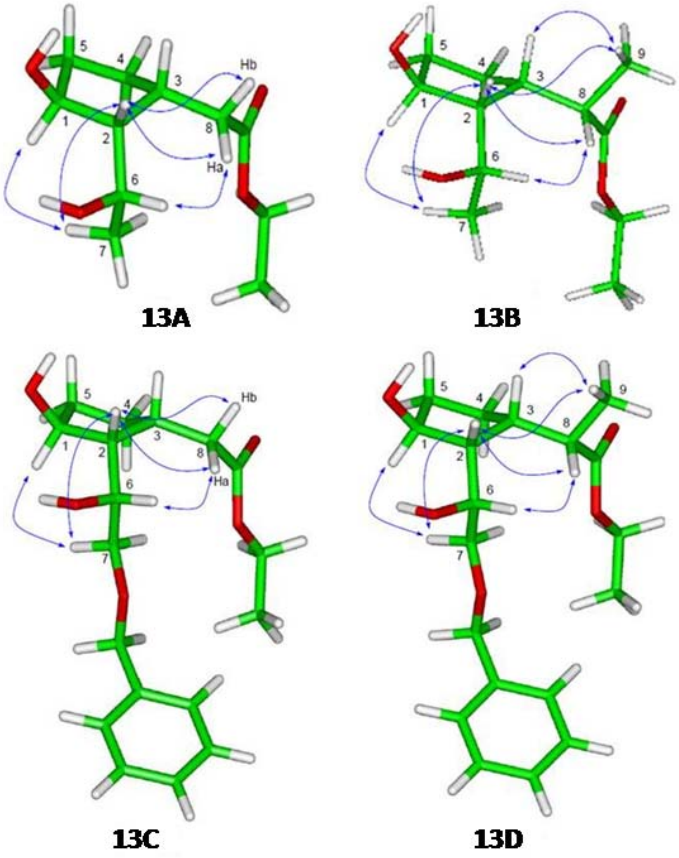


Figure 1

Several biologically active iridoids and other natural prodcuts are having highly substituted cyclopentanoid motif and the products **13A–D** would find suitable applications in natural product synthesis. That three consecutive new chiral centres were

stereoselectively fixed in a single–step radical mediated reaction is noteworthy achievement.

CHAPTER–II

Stereoselective synthesis of the C16–C28 fragment of rhizopodin:

Myxobacteria produce a wide variety of secondary metabolites with interesting biological activities and distinct structures. Rhizopodin (**14**) is one such example, which was isolated from the culture broth of the myxobacterium, *Myxococcus stipitatus* in 1993 by Sasse *et al*. Initially it was proposed that rhizopodin was a 16–membered macrolide but later revised as a C_2–symmetric 38–membered dilactone bearing 18 stereogenic centres, two disubstituted oxazole rings, two conjugated diene systems and two enamide side chains by X–ray analysis of its complex with rabbit muscle G–actin and extensive NMR studies (Figure 2).

Figure 2. Rhizopodin (**14**)

It showed potent cytostatic activity against a range of tumor cell lines in the low nanomolar range. The cytostatic activity was attributed to formation of a ternary complex with two G–actin molecules where the enamide side chains play a key role. It specifically binds to select sites of G–actin and disrupts the cytoskeleton there by inhibiting the actin polymerization. Biological studies further revealed that rhizopodin affects the dynamics of

actin skeleton of macrophages there by showing significant change in the phagocyte efficiency for yeast cells.

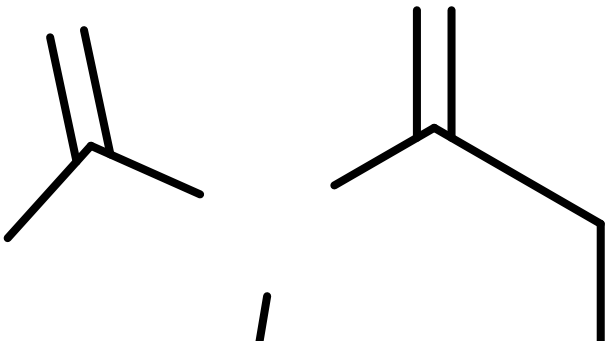
Scheme 3 discloses the retrosynthetic analysis of the rhizopodin (**14**). Inspection of the structure of rhizopodin revealed that it could be synthesized by the macrolactonization/cyclodimeriaztion of suitably protected compound **15** which in turn could be obtained from the two key intermediates **16** and **17**. In the present chapter we describe the synthesis of C16–C28 fragment (**16**) of the molecule.

For the synthesis of the fragment **16**, an enatioselective addition of titanium enolate to dimethyl acetal, $^{n}Bu_2BOTf$ mediated Evans' aldol reaction, Horner–Wadsworth–Emmons olefination under Paterson's conditions, Corey–Bakshi–Shibata (CBS) reduction of ketone and Mukaiyama aldol reactions were applied as key steps.

Scheme 3. Retrosynthetic analysis of rhizopodin (**14**)

Our synthesis commenced with the Evans' aldol reaction of (*R*)–4–benzyl–3–propionyloxazolidin–2–one (**18**) and the aldehyde **19**, prepared by the oxidation of mono–PMB protected 1,3–propanediol, to furnish the compound **20** in 90% yield (Scheme 4). Reductive removal of the chiral auxiliary by using $NaBH_4$ gave a 1,3–dihydroxy

compound **21** in 76% yield. Selective *O*–silylation of the primary hydroxyl group by using TBDPSCl furnished the compound **22** in 90% yield. Etherification of the secondary hydroxyl group by using MeI afforded compound **23** in 89% yield. Desilylation of compound **23** was carried out by using TBAF to obtain the primary alcohol **24** in 78% yield. Oxidation of the alcohol **24** by Swern oxidation method produced the aldehyde **25** in quantitative manner.



Scheme 4

As described by Urpi *et al*, enantioselective addition of titanium enolate of (*S*)–1–(4–isopropyl–2–thioxothiazolidin–3–yl)propan–1–one (**26**) over the dimethyl acetal **27** furnished the compound **28** in 82% yield (Scheme 5).

Scheme 5

Displacement of thiazolidinethione auxiliary of compound **28** by the anion generated from dimethyl methylphosphonate by using ^{n}BuLi resulted in the formation of *β*–keto phosphonate **29** in 90% yield (Scheme 6). Keto phosphonate coupling between

compound **29** and the aldehyde **25** by using $Ba(OH)_2 \cdot 8H_2O$ as a base gave the *α,β*–unsaturated ketone **30** in 77% yield. Chemoselective hydrogenation of compound **30** provided the compound **31** in quantitative yield and the keto functionality was then reduced under standard CBS conditions to get compound **32** in 88% yield. Protection of the secondary hydroxyl group as its TIPS ether by using TIPSOTf resulted in the formation of orthogonally protected compound **33** in 85% yield. Oxidative cleavage of PMB ether with DDQ under buffered conditions gave the primary alcohol **34** in 64% yield.

Scheme 6

Oxidation of the primary alcohol **34** by using Dess–Martin periodinane furnished the *β*–methoxy aldehyde **35** in quantitative yield, which was subjected to a 1,3–*anti* diastereofacial selective Mukaiyama aldol reaction with methyl trimethylsilyl dimethylketene acetal to provide compound **36** as the major diastereomer in 64% yield (*dr* ≥8:1). The hydroxyl group was then protected as TES ether using TESOTf to get compound **37** in 80% yield. Reduction of the methyl ester by using DIBAL–H delivered the C16–C28 fragment (**16**) of the rhizopodin in 79% yield (Scheme 7).

Scheme 7

Thus the stereoselective synthesis of the C16–C28 fragment (**16**) of C_2–symmetric cytostatic macrolide rhizopodin was achieved in an overall yield of 13.4% starting from acetate aldol **28** in a linear sequence of 10 steps and further work to complete the total synthesis of the molecule is now under progress in the laboratory.

CHAPTER–III

Total synthesis of (+)–deoxocassine:

Piperidine alkaloids possessing a 2,3– or 2,3,6–substitution, particularly a hydroxy group at C3 position occur widely in nature. The hydroxylated piperidines display a wide range of biological activities such as antibiotic, anesthetic and CNS stimulating properties. The physiological effects stem from their ability to mimic carbohydrate substrates in a variety of enzymatic processes. Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids as important tools in the study of biochemical pathways.

Numerous compounds possessing variety combination of relative stereochemistries at 2,3,6–positions have been found in the nature. Since their discovery in the 1960s, much effort has been directed both to the synthesis of the 2,3,6–substituted piperidines and

subsequent application to the total synthesis natural alkaloids. (+)–Deoxocassine was a simple analogue of natural alkaloid (–)–cassine.

Figure 3. (+)–Deoxocassine (**38**)

The retrosynthetic analysis of (+)–deoxocassine (**38**) is shown in Scheme 8. We have envisioned that hydrogenation of compound **39** will result in one–pot debenzylation, *N*–Cbz deprotection and saturation of the olefinic bond to get the final target molecule. Compound **39** could be accessed from alcohol **40** by successive Dess–Martin periodinane oxidation and Wittig olefination.

Scheme 8. Retrosynthetic analysis of (+)–deoxocassine (**38**)

A base mediated intramolecular nucleophilic displacement of a mesylate by an amine in compound **41** followed by *N*–protection and silyl deprotection would provide the alcohol **40** (Scheme 8). Orthogonally protected compound **41** could be realized from the compound **42** which in turn was achieved from the alkynol **43** *via* Mistunobu inversion,

hydrogenation and amine protection sequence. Nucleophilic addition of acetylide derived from dimbromo alkene **45** over the aldehyde **44** was the key execution to get the compound **43**. Commercially available L–alanine (**47**) would be the precursor for the aldehyde **44** whereas L–ascorbic acid (**46**) for dibromo–olefin **45**.

We started our synthesis with the readily available L–alanine **47** which was perbenzylated by reacting with BnBr to get ester **48** that was reduced by reacting with $LiAlH_4$ to get alcohol **49** in 50% yield over two steps. Swern oxidation of the alcohol **49** furnished the aldehyde **44** in quantitative yield (Scheme 9).

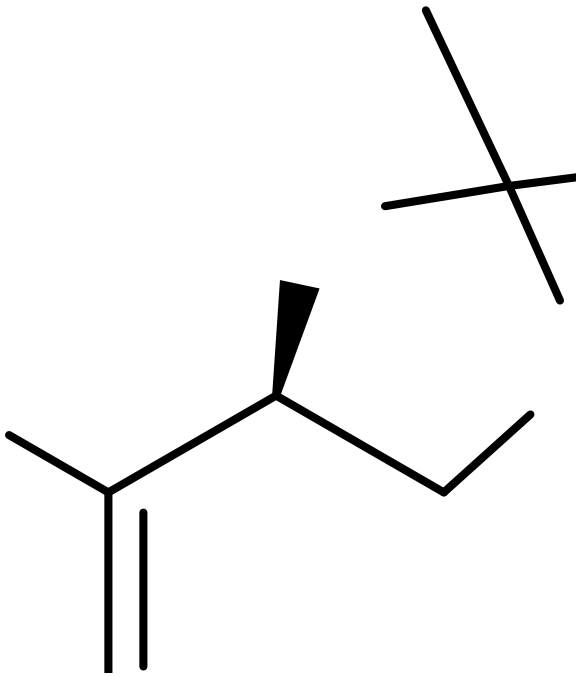
Scheme 9

Commercially available L–ascorbic acid **46** was converted to the diol **50** in a four–step sequence as shown in Scheme 10. Oxidative cleavage of the diol was carried out by reacting it with $NaIO_4$ and treatment of the resultant aldehdye with triphenylphosphine (TPP) and CBr_4 afforded the dibromo–olefin **45** in 28% yield over two steps.

Scheme 10

Treatment of the acetylide, derived from compound **45** by reacting with ^{n}BuLi, with the aldehyde **44** afforded the alkynol **43** as the major diastereomer in 66.5% yield (Scheme 11). Mitsunobu inversion of the hydroxyl group present in compound **43** afforded

the ester **51** which upon saponification provided the alkynol **52** in 66% yield over two steps. Hydrogenation of the compound **52** by using $Pd(OH)_2/C$ furnished the primary amine **53** in quantitative yield which was immediately protected as *N*–Boc carbamate to get compound **42** in 81% yield.



Scheme 11

Treatment of the compound **42** with BnBr furnished the benzyl ether **54** which upon treatment with CSA delivered the diol **55** in 78% yield over two steps (Scheme 11). Selective *O*–silylation of the diol was carried out by reacting with TBSCl to get the compound **56** in 76% yield. Reaction of the alcohol **56** with MsCl furnished the orthogonally protected compound **41** in 70% yield. Boc deprotection of carbamate **41** was carried out under mild conditions by reacting with TBSOTf and 2,6–lutidine followed by 1% citric acid in MeOH to get the primary amine **57** in 85% yield.

Hünig's base mediated intramolecular displacement of mesylate functionality by amine present in compound **57** furnished the piperidine compound **58** in 80% yield (Scheme 12). Protection of the piperidine **58** as *N*–Cbz carbamate was achieved by reacting with CbzCl to get compound **59** and subsequent silyl deprotection afforded the primary alcohol **40** in 57% yield over two steps. Oxidation of the alcohol **40** was carried out by reacting with Dess–Martin periodinane (DMP) to get the corresponding aldehyde **60** in quantitative manner.

Scheme 12

Reaction of the phosphonium salt **61** with ^{n}BuLi produced an ylide which was allowed to react with aldehdye **60** to get the compound **39** in 75% yield (Scheme 13). Hydrogenation of the compound **39** by using Pd/C resulted in one–pot debenzylation, *N*–Cbz deprotection and saturation of the olefinic bond to get the final target molecule (+)–deoxocassine (**38**) in 80% yield.

Scheme 13

The research work described in this thesis has been included in the following publications:

1. Ti(III)–mediated opening of 2,3–epoxy alcohols to build five membered carbocycles with multiple chiral centres

   Midde Sreekanth, Gavinolla Pranitha, Bharatam Jagadeesh and Tushar Kanti Chakraborty*

   Tetrahedron Lett. **2011**, *52*, 1709–1712.
2. Synthetic studies towards potent cytostatic macrolide rhizopodin: stereoselective synthesis of the C16–C28 fragment

   Tushar Kanti Chakraborty,* **Midde Sreekanth** and Kiran Kumar Pulukuri

   Tetrahedron Lett. **2011**, *52*, 59–61.
3. Stereoselective synthesis of 2,3,6–trisubstituted piperidine: application in the synthesis of (+)–deoxocassine

   Tushar Kanti Chakraborty,* **Midde Sreekanth** and Gangarajula Sudhakar

   (Manuscript under preparation)
4. Studies directed towards the synthesis of rhizopodin: stereoselective synthesis of the C1–C15 fragment

   Tushar Kanti Chakraborty,* Kiran Kumar Pulukuri and **Midde Sreekanth**

   Tetrahedron Lett. **2010**, *51*, 6444–6446.