ASYMMETRIC SYNTHESIS OF BIOACTIVE POLYOLS

By

SUCHETA CHATTERJEE

CHEM 01201004001

BHABHA ATOMIC RESEARCH CENTRE

A thesis submitted to
the

Board of Studies in Chemical Sciences

In partial fulfillment of

requirements for the Degree of

DOCTOR OF PHILOSOPHY

of

HOMI BHABHA NATIONAL INSTITUTE

November 2014

Homi Bhabha National Institute[1]

Recommendations of the Viva Voce Committee

As members of the Viva Voce Committee, we certify that we have read the dissertation prepared by Sucheta Chatterjee entitled " Asymmetric Synthesis Of Bioactive Polyols" and recommend that it may be accepted as fulfilling the thesis requirement for the award of Degree of Doctor of Philosophy.

Chairman – Prof. T. Mukherjee	Tulsi Mukherjee	**Date:** 14.08.15
Guide / Convener – Prof. S. Chattopadhyay		**Date:** 14/8/15
External Examiner-Prof. Ashok K. Prasad		**Date:** 14.08.15
Member 1 – Prof. S. K. Ghosh		**Date:** 14.08.15
Member 2- Prof. S. Banerjee		**Date:** 14/08/15
Member 3 – Prof. A. Chattopadhyay	A Chattopadhyay	**Date:** 14/8/15

Final approval and acceptance of this thesis is contingent upon the candidate's submission of the final copies of the thesis to HBNI.

I/We hereby certify that I/we have read this thesis prepared under my/our direction and recommend that it may be accepted as fulfilling the thesis requirement.

Date: 14/8/2015

Place: Mumbai

<Signature>	**<Signature>**
Co-guide (if applicable)	**Guide**

[1] This page is to be included only for final submission after successful completion of viva voce.

STATEMENT BY AUTHOR

This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at Homi Bhabha National Institute (HBNI) and is deposited in the Library to be made available to borrowers under rules of the HBNI.

Brief quotations from this dissertation are allowable without special permission, provided that accurate acknowledgement of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the Competent Authority of HBNI when in his or her judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

Sucheta Chatterjee

Sucheta Chatterjee

DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

Sucheta Chatterjee

Sucheta Chatterjee

List of Publications arising from the thesis

Journal

1. "A chemoenzymatic asymmetric synthesis of the hydroxy acid segment of schulzeines B and C.", Biswas, S.; Chattopadhyay, S.; Sharma, A., *Tetrahedron: Asymmetry*, **2010**, *21*, 27-32.

2. "First asymmetric synthesis of the oxylipin (6*S*,9*R*,10*S*)-6,9,10-trihydroxyoctadeca-7E-enoic acid.", Chatterjee, S.; Kanojia, S. V.; Chattopadhyay, S.; Sharma, A., *Tetrahedron: Asymmetry* **2011**, *21*, 367-372.

3. "A Chemoenzymatic Synthesis of Hept-6-ene-2,5-diol Stereomers: Application to Asymmetric Synthesis of Decarestrictine L, Pyrenophorol and Stagonolide E.", Sucheta Chatterjee, Sneha Ghadigaonkar, Payel Sur, Anubha Sharma, and Subrata Chattopadhyay, *J. Org. Chem*, **2014**, *79*, 8067-8076.

4. "Chemoenzymatic synthesis of the macrolide antibiotic (-)-A26771B", Sucheta Chatterjee, Anubha Sharma, and Subrata Chattopadhyay, *RSC Adv.*, **2014**, *4*, 42697-42705.

5. "An expeditious synthesis of the macrolide antibiotic (-)-A26771B", Sucheta Chatterjee, Suchandra Chatterjee, Subrata Chattopadhyay, and Anubha Sharma *Tetrahedron: Asymmetry* (commun.)

Sucheta Chatterjee

Sucheta Chatterjee

Dedicated to…….

…….Maa, Baba, Joy

…And to all those who love me and motivate me to dream big…

ACKNOWLEDGEMENTS

I would like to start by thanking my PhD guide, Prof Subrata Chattopadhyay (Head, Bio-Organic Division, BARC) who has been the most influential person in my life since I joined BARC. His continual support, advice, encouragement, criticism and selfless ways in dealing with issues are very inspiring. All these have made me a stronger and better person both professionally and personally. I feel lucky that he gave me a chance to join his research group a few years ago and it has been a privilege working under his guidance since.

Next, I would like to acknowledge the contributions of my immediate superior, Dr. Anubha Sharma in my life and career. Her valuable inputs, extraordinary tenacity, pleasing personality, and never-give-up attitude and faith in me has helped me come a long way, not to forget her indispensable advices in times of crisis.

I would like to express deep gratitude to my doctoral committee chairman, Prof. T. Mukherjee, doctoral committee members Dr. S. K. Ghosh, Dr. A. Chattopadhyay and Dr. Sharmila Banerjee for their valuable time and suggestions which helped me improve the quality of my research work. Thanks are due to Dr. S. K. Nayak, Dr. B. S. Tomar (Dean, Academic, Chemical Sciences, HBNI), Dr. Swapan K. Ghosh for their help and guidance. Dr. Alok Samanta deserves special mention in my life since the early days of BARC Training school. I will treasure his love, guidance and advice all my life.

The cheerful presence and friendship of my labmates and colleagues made those long hours I spent in the lab. cherishable one. These wonderful people are Sunita, Akhil da, Dibakar da, , Seema, Ajish sir, Sneha, Bhaskar da, Neeta mam, Papiya, Sampada, Payel, Trilochan da, Siba, Raghu da, Ankur, Brindavan, Rekha mam, Soumu, Gangababu, Minakshi, Shikha, Prasad da, Siddharth da, Sandeep, Shitaljit, Kshama di, Mrunesh, Manoj, Kavita, Abha mam, Mrityunjay, Saikat, Jitesh sir, Soumya da, Patro sir, Mahesh sir,

Rangarajan. I appreciate the administrative help extended to me time and again by Vasavan ji and Yadav ji.

I gracefully acknowledge the contributions of all the teachers/professors in my school/university who have played an pivotal role in my life. I am fortunate to have a loving friend in Nabanita. Thanks are due to my school buddies Shreya, Koeliya and Annie for giving me those fun and joyous moments and standing by me in times of need. I would like to convey my deepest love and regards to my childhood friend Munia for constantly motivating me to aim higher. I would never forget the concern and affection shown by Mr. and Mrs Arya and Mr and Mrs. Thankarajan. I would like to thank my in-laws who would be really proud of me when I finally complete my doctorate.

Thank you is too small a word for my companion and husband, Agrim whose deep love, support, critical comments, useful and practical tips and fun-loving nature has helped me cope the ups and downs of life and made me stronger. This journey of life wouldn't have been possible without your sacrifices and patience.

And finally I have saved the best for the last. I would like to thank god for being really partial to me and blessing me with truly wonderful parents and brother. I am what I am because of them. Words fail me to express my gratitude towards my maa (Mrs. Kanchan Biswas) and baba (Dr. Subrata Biswas) for their unparalleled and unconditional love, patience, sacrifice, hard-work, effort to instill good moral values in me and giving me a very good life and upbringing. Lastly I want to convey my deepest love and gratitude to my brother, Joy (Sudipto Biswas) for being there for me always. His wisdom, philosophy of life, dynamic outlook and immense faith in me makes me embrace life more positively each day. Thank you all for everything.

……..*Sucheta*

CONTENTS

SYNOPSIS

Preamble

Given the importance of stereochemistry in biological recognition, the significance of asymmetric synthesis has become overwhelming in modern organic synthesis. As a result, development of asymmetric synthesis has become a central theme in contemporary synthetic organic chemistry.[1] Aliphatic polyhydroxy compounds, in particular, the polyhydroxy acids and the corresponding macrolides are of wide natural occurrence, and often show impressive anti-cancer, antiviral, antifungal as well as vaccine adjuvant activities.[2] In view of these, the present work was focused on the development of operationally simple and practical asymmetric methodologies that were used to devise novel syntheses of a few chosen target compounds of this class. These are presented in the thesis in three chapters as detailed below. The bibliography is presented in Chapter IV.

CHAPTER I: INTRODUCTION TO ASYMMETRIC SYNTHESIS AND POLYOLS

This chapter deals with a broad review on asymmetric synthesis. The features covered include (i) genesis and importance of chirality; (ii) different methods of enantiomeric syntheses with special emphasis on asymmetric transformations; (iii) thermodynamics and kinetics of preparing stereomers; and (iv) methods of assessing enantiomeric purities. This is followed by a concise account of biocatalytic organic transformations.[3] In addition a brief summary of the natural polyols with special emphasis on the chosen targets is presented. Finally, the objectives of the present work are enumerated.

CHAPTER II: GLYCERALDEHYDE-BASED ASYMMETRIC SYNTHESES OF SOME TARGET ALIPHATIC POLYOLS

This chapter deals with the syntheses of two chiral aliphatic polyols using (*R*)-2,3-cyclohexylideneglyceraldehyde (**1**), obtained from D-Mannitol as a chiral template. These include (i) the oxylipin **I**, isolated from *D. loretense*, used to reinforce the immune system of

the AIDS patients,[4] and (ii) the C-20 fatty acid segment **II** of schulzeines B and C, which inhibit yeast α-glucosidase and viral neuraminidase.[5]

(i) Total Synthesis of Oxylipin

We have developed a simple and efficient asymmetric synthesis of the acid **I** using a "building-block" approach (**Figure 1.**). The chiral building blocks **A** and **B** were synthesized starting from the aldehyde **1** by addition of two different organometallic reagents to generate the stereogenic centres of **I**. These were coupled via a cross metathesis reaction[6] to install the 7*E*-olefin function of the target oxylipin.

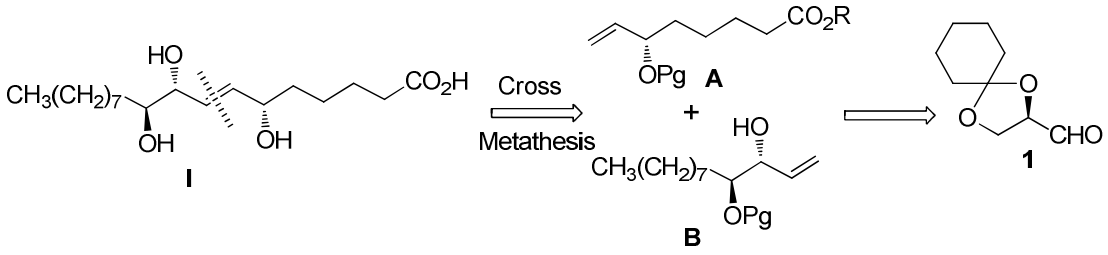
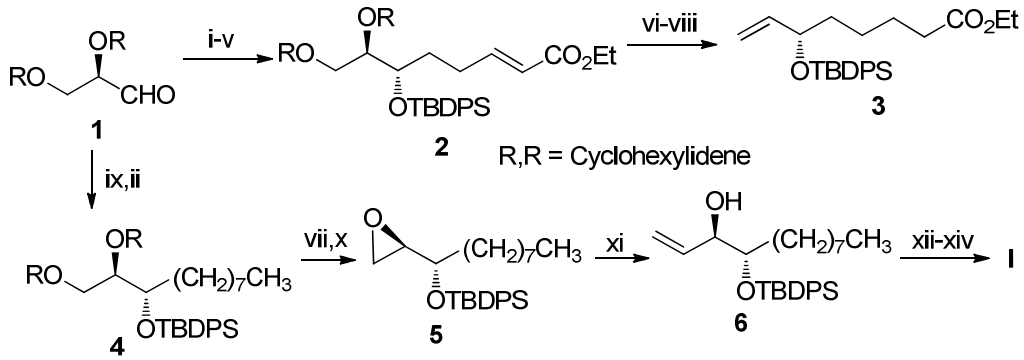


Figure 1.

The synthesis commenced with a highly diastereoselective Ga-mediated allylation of **1** in [bmim][Br][7] furnishing the corresponding *anti*-homoallylic alcohol, which was converted to



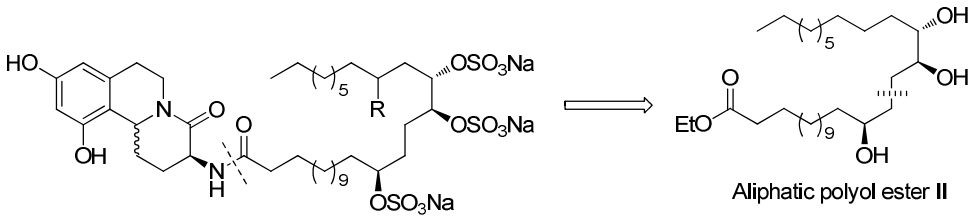
i) Allyl bromide/Ga/[bmim][Br]/25 °C/4 h (86%), (ii) TBDPSCl/imidazole/DMAP/CH_2Cl_2/25 °C/10 h (88% for **2**, 86% for **4**), iii) $BH_3.Me_2S$/ THF/0 °C/3 h; aqueous NaOH/H_2O_2/0 to 25 °C/15 h (93%), (iv) PCC/NaOAc/ CH_2Cl_2/0 °C/3 h (81%), v) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$/0 to 25 °C/18 h (91%), vi) H_2/10% Pd-C/ EtOH /25 °C/22 h (~quant.), (vii) Aqueous 80% TFA/CH_2Cl_2/0 °C/3 h/25 °C/18-24 h (81% for **3**, 84% for **5**), (viii) *p*-TsCl/pyridine/0 to 25 °C/24 h (89%); Zn/DMF/80 °C/4 h (84%), (ix) $CH_3(CH_2)_7Li$/ THF/-78 °C to 25 °C/3 h (86%), (x) *p*-TsCl/pyridine/0 °C/18 h (84%); K_2CO_3/MeOH/25 °C/3 h (90%), xi) Me_3SI/*n*-BuLi/THF/-40 °C/4 h/25 °C/12 h (81%), (xii) **3**/Grubbs' II catalyst/CH_2Cl_2/25 °C /22 h (63% based on **3**), (xiii) Bu_4NF/THF/0 °C/3 h (87%), (xiv) Ethanolic KOH/25 °C/4 h (95%).

Scheme 1.

the ester **2** by protecting the alcohol group as the *tert*-butyldiphenylsilyl (TBDPS) ether, hydroboration-oxidation of the olefin function, subsequent oxidation with pyridinium chlorochromate (PCC) and a base-catalyzed Horner-Emmons reaction with triethyl phosphonoacetate. After catalytic hydrogenation, the product was deacetalized with aqueous trifluoroacetic acid (TFA) to furnish the diol, which on ditosylation with *p*-toluenesulphonyl chloride (*p*-TsCl)/pyridine followed by heating with NaI/Zn-dust afforded the alkene ester **3** (building block **A**). For the synthesis of block **B**, the aldehyde **1** was reacted with $CH_3(CH_2)_7Li$ to furnish the *anti*-C_{11} alcohol almost exclusively (dr = 95:5), which was silylated to give **4**. Its TFA-catalyzed deacetalization, followed by tosylation of the primary carbinol group and subsequent base treatment furnished the epoxide **5**. This on an *n*-BuLi-catalyzed reaction with Me_3SI afforded the allylic alcohol **6**. Finally, a cross-metathesis between the ester **3** and **6** in the presence of Grubbs' II catalyst, followed by a F^--mediated desilylation and alkaline hydrolysis furnished **I (Scheme 1)**.

(ii) Synthesis of the Schulzeines B and C Fatty Acid Chain Segment II

Retrosynthesis of schulzeines B and C suggested the C_{28} fatty acid ester **II** as the target polyol intermediate that on amidation with the required isoquinoline core and a late stage trisulfation would provide the schulzeines. Hence, a convergent synthesis of **II** was



Schulzeine B: R = H, (11b*S*); Schulzeine C: R = H, (11b*R*)

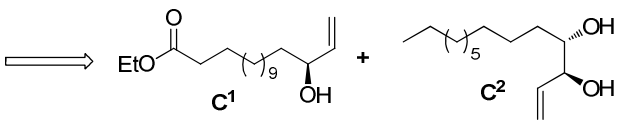
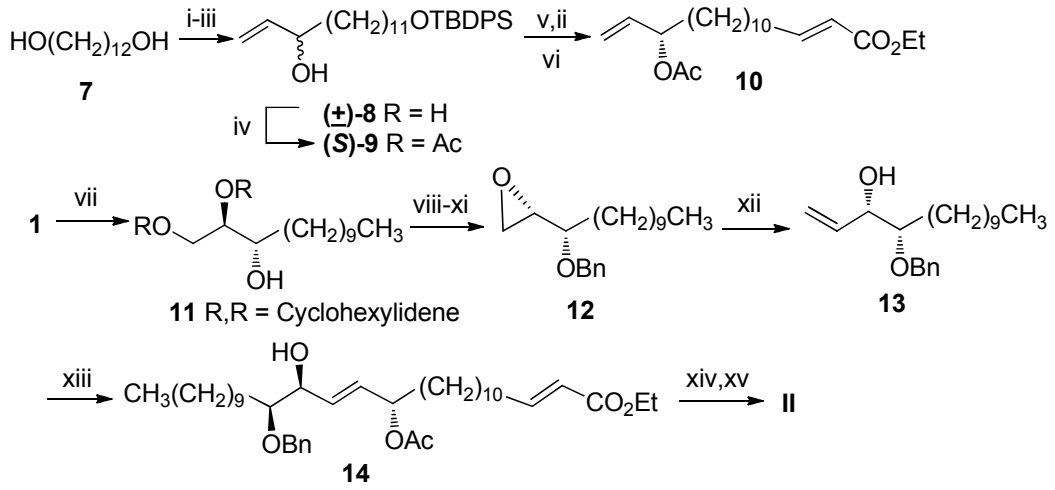


Figure 2.

conceived using a cross metathesis reaction[6] between the building blocks **C**^{1} and **C**^{2} (**Figure 2.**), which were synthesized by a biocatalytic route, and using the aldehyde **1** respectively.

For the synthesis of **II**, the diol **7** was converted to the allylic alcohol **8** by monosilylation followed by a PCC oxidation and reaction with vinylmagnesium bromide. Its Novozym 435® (lipase)-catalyzed *trans*-acetylation with vinyl acetate furnished (*S*)-**9** and (*R*)-**8** in 96% and 91% enantiomeric excesses (ees) respectively at 50% conversion. Desilylation of (*S*)-**9** with Bu_4NF furnished the corresponding primary alcohol, which on PCC oxidation and subsequent Wittig-Horner reaction with triethyl phosphonoacetate afforded the conjugated ester **10** (equivalent to C^{1} synthon). In a separate sequence of reactions, the aldehyde **1** was reacted with $CH_3(CH_2)_9Li$ to furnish the *anti*-triol derivative **11** (dr: = 96:4). This was converted to the epoxide **12** by benzylation, acid-catalyzed deacetalyzation, monosilylation of the resultant diol at the primary carbinol site, mesylation of the other alcohol function, acid-catalyzed



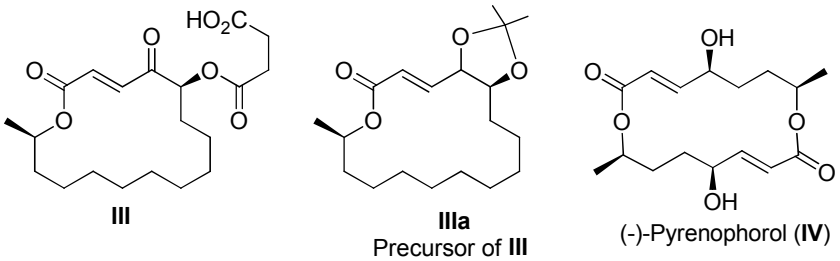
i) TBDPSCl/imidazole/DMAP/CH_2Cl_2/25 ^{o}C/8 h (68%), ii) PCC/NaOAc/CH_2Cl_2/25 ^{o}C/3 h (**8**: 92%; **10**: 88%), iii) CH_2=CHMgBr/THF/25 ^{o}C/6 h (77%), iv) Vinyl acetate/Novozym 435/25 ^{o}C/26 h (50%), v) Bu_4NF/THF/0 to 25 ^{o}C/ 3 h (93%), vi) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$/0 to 25 ^{o}C/18 h (77%), vii) $CH_3(CH_2)_9Li$/THF/-78 ^{o}C/3 h (81%), viii) NaH/THF/BnBr/Bu_4NI/reflux/4 h (93%), ix) Aqueous 2N HCl/25 ^{o}C/6 h (75%), x) TMSCl/ EtOAc/-20 ^{o}C/20 min; MsCl/Et_3N/-20 ^{o}C/30 min; aqueous 2N HCl/25 ^{o}C/1 h (79%), xi) K_2CO_3/MeOH/25 ^{o}C /3 h (84%), xii) Me_3SI/*n*-BuLi/THF/-40 ^{o}C/1 h then -40 to 25 ^{o}C/12 h (80%), xiii) **10**/Grubbs' II catalyst/ CH_2Cl_2/25 ^{o}C/22 h (61% based on **13**), xiv) H_2/10% Pd-C/EtOH/25 ^{o}C (88%), xv) Amberlyst 15®/EtOH/ 25 ^{o}C/18 h (91%).

Scheme 2.

desilylation and base treatment. Its reaction with the sulphorane, generated from Me_3SI afforded the allylic alcohol **13** (equivalent to C^2 synthon). The cross-metathesis reaction between **10** and **13** gave the ester **14**. Its catalytic hydrogenation followed by an acid-catalyzed *trans*-esterification with ethanol furnished **II** (**Scheme 2**).

CHAPTER III: CHEMOENZYMATIC SYNTHESES OF TWO MACROLIDES

Chemoenzymatic approaches, involving the biocatalytic reactions as some of the key steps are viable options in the syntheses of natural products and their congeners.[8] In this chapter, the chemoenzymatic syntheses of (i) the polyketide secondary metabolite, (-)-A26771B (**III**), isolated from the fungus *Penicillium turbatum* with reported moderate activity against the gram-positive bacteria, mycoplasma, and fungi;[9] and (ii) the 16-membered homodimeric macrodiolide, pyrenophorol (**IV**), produced by *Pyrenophora avenae*[10] are described. A number of enantioselective syntheses of **III**, including several formal syntheses targeting **IIIa**, an advanced precursor of **III** have been reported.[11] In the present investigation, a formal (up to **IIIa**) and two total syntheses of **III** were developed using the lipase-catalyzed acylation of secondary carbinol moieties to install the required stereogenic centres as well as to construct the macrolide core. In addition, a shorter synthesis of **III** was developed using a combination of biocatalytic kinetic resolution and a chemical asymmetric allylation as the key steps. The target **IV** was also synthesized by two routes from

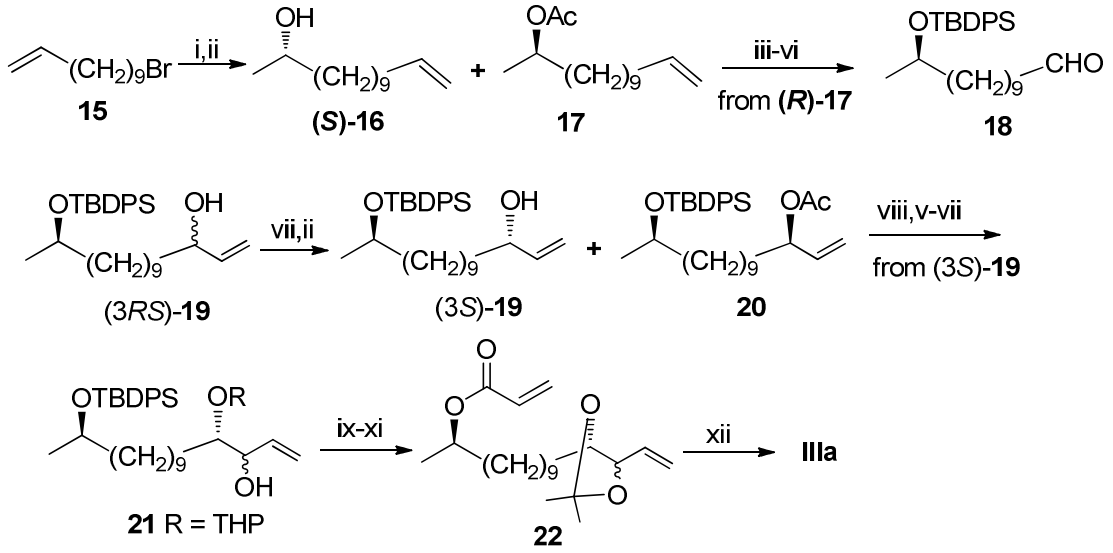


III **IIIa** Precursor of **III** (-)-Pyrenophorol (**IV**)

Figure 3. Chemical structures of the target molecules.

the stereomers of a versatile synthon via a diversity-oriented synthetic (DOS) strategy. The chemical structures of the synthesized compounds are shown in **Figure 3** followed by a brief account of the syntheses.

(i) Synthesis of the Antibiotic (-) A26771B (III). For the synthesis, an effective protocol for accessing the chiral methylcarbinol [MeCH(OH)] unit of **III** was developed by reacting the Grignard reagent of 11-bromo-1-undecene (**15**) with acetaldehyde followed by a Novozym 435®)-catalyzed *trans*-acetylation of the resultant (±)-alcohol **16** to obtain the acetate (*R*)-**17** and (*S*)-**16** in good ees at optimized conversions. Alkaline hydrolysis of (*R*)-**17**, base-catalyzed silylation with *tert*-butyldiphenylsilyl chloride (TBDPSCl) followed by Upjohn



i) Mg/THF/25 ^{o}C/CH_3CHO/3 h (90%), ii) Vinyl acetate/ diisopropyl ether/Novozym 435®/25 ^{o}C/75 min (for **16**)/6 h (for **19**), iii) K_2CO_3/ aqueous MeOH/25 ^{o}C/6 h (~100%), iv) TBDPSCl/imidazole/4-DMAP/ CH_2Cl_2/0 to 25 ^{o}C/7 h (91%), v) OsO_4/NMO /acetone-H_2O (8:1)/*t*-BuOH/25 ^{o}C/10 h (95% and 98% for **18** and **21**), vi) $NaIO_4$/MeCN-H_2O/0 ^{o}C/2 h (91% and 90% for **18** and **21**), vii) CH_2=CHMgBr /THF/-40 ^{o}C/1 h (90% and 87% for **18** and **21**), viii) DHP/PPTS/CH_2Cl_2/25 ^{o}C/4 h (88%), ix) PPTS/MeOH/25 ^{o}C/6 h; 2,2-DMP/PPTS (91%), x) Bu_4NF/THF/0 ^{o}C/4 h (91%), xi) Ethyl acrylate/diisopropyl ether/Novozym 435®/25 ^{o}C/24 h (93%), xii) Grubbs' II catalyst /CH_2Cl_2/reflux/8 h (89%).

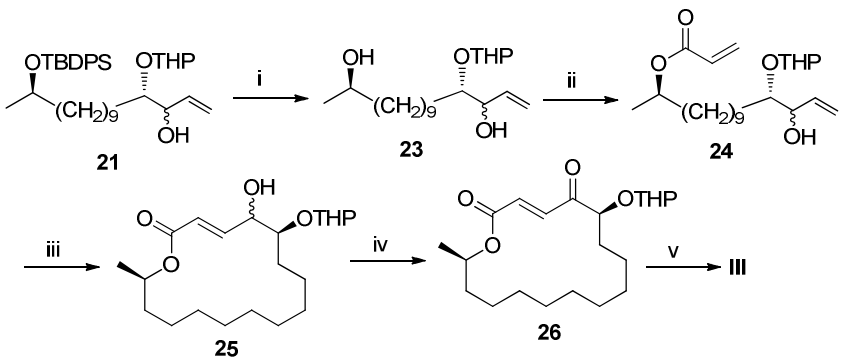
Scheme 3.

dihydroxylation and $NaIO_4$ treatment furnished the aldehyde **18**, which on reaction with vinylmagnesium bromide followed by another Novozym 435®-catalyzed acetylation furnished (3*S*)-**19** (95% ee) and the acetate **20** (98% ee). Tetrahydropyranylation of (3*S*)-**19** with 3,4-dihydropyran (DHP)/pyridinium *p*-toluenesulphonate (PPTS), dihydroxylation of

the alkene, its $NaIO_4$ cleavage, and reaction of the resultant aldehyde with vinylmagnesium bromide furnished **21**. This on acid-catalyzed

depyranylation and reaction with 2,2-dimethoxypropane (2,2-DMP) furnished the corresponding 3,4-acetonide, which was desilylated and subjected to a Novozym 435®-catalyzed acrylation to obtain **22**. Its ring-closing metathesis furnished the desired macrolide **IIIa** (**Scheme 3**).

For the synthesis of **III**, the alcohol **21** was desilylated with Bu_4NF to obtain the diol **23**. Its Novozym 435-catalyzed reaction with ethyl acrylate furnished **24**, which on an RCM reaction furnished the macrolide **25**. This on PCC oxidation followed by acidic depyranylation and a base-catalyzed succinoylation produced the target compound **III** (**Scheme 4**).

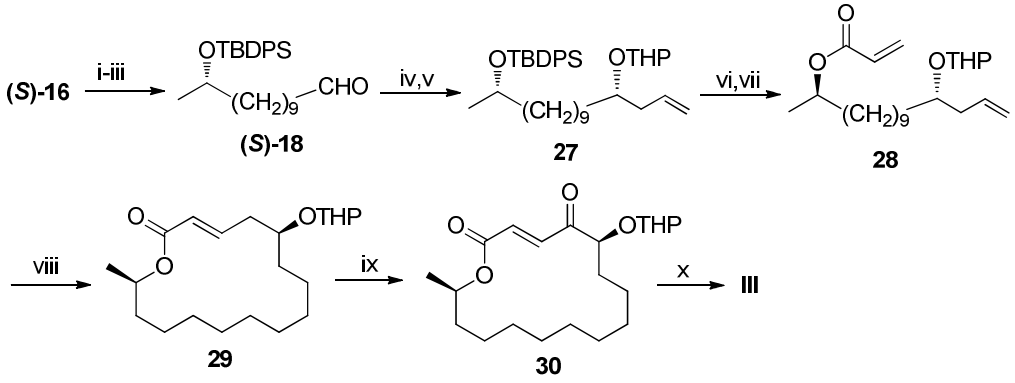


i) Bu_4NF/THF/0 °C/4 h (84%), ii) CH_2=$CHCO_2Et$/Novozym 435/25 °C/72 h (88%), iii) Grubbs' II catalyst/CH_2Cl_2/50 °C/4 h (68%), iv) PCC/NaOAc/CH_2Cl_2/2 h (89%), v) TFA/moist THF/0 °C/3 h; succinic anhydride/DMAP (cat.)/CH_2Cl_2/2 h (74%).

Scheme 4.

Alternate synthesis of III. To reduce the number of synthetic steps and avoid several unnecessary protection/ deprotection steps, an alternate synthesis of **III** was developed (**Scheme 5**). For this, the alcohol (*S*)-**16** (**Scheme 3**) was converted to the aldehyde (*S*)-**18** by silylation and oxidative olefin cleavage as mentioned for the synthesis of **IIIa**. Its asymmetric allylation with allyl$SnBu_3$/$InCl_3$/(*R*)-BINOL[12] furnished an allylic alcohol as a single stereomer, which was converted to the THP ether **27**. After desilylation with Bu_4NF, the

resultant alcohol was esterified with acrylic acid under the Mitsunobu conditions to obtain the acrylate **28**. Its RCM reaction furnished the desired macrolide **29**, which was



i) TBDPSCl/imidazole/4-DMAP/CH_2Cl_2/0 to 25 °C/7 h (91%), ii) OsO_4/NMO/acetone-H_2O (8:1)/*t*-BuOH/25 °C/10 h (97%), iii) $NaIO_4$/MeCN-H_2O/0 °C/2 h (92%), iv) AllylSnBu_3/$InCl_3$/4Å molecular sieve/(*R*)-BINOL/ THF/-78 °C/4 h; 25 °C/8 h (89%), v) DHP/PPTS/CH_2Cl_2/25 °C/4 h (90%), vi) Bu_4NF/THF/0 °C/4 h (91%), vii) Ph_3P/DIAD/CH_2=$CHCO_2H$/THF/12 h (71%), viii) Grubbs' II catalyst/CH_2Cl_2/reflux/8 h (71%), ix) SeO_2/ 1,4-dioxane/reflux/24 h (63%), x) TFA/ moist THF/0 °C/3 h; succinic anhydride/DMAP (catalytic)/CH_2Cl_2/ 2 h (74%).

Scheme 5.

converted the γ-oxo compound **30** via a SeO_2-catalyzed allylic oxidation.[13] This was subsequently converted to **III** as above.

(ii) Diversity-oriented Synthesis (DOS) of Pyrenophorol Enantiomers. Retrosynthesis (**Figure 4**) of natural pyrenophorol (**IV**), a C_2-symmetric molecule with four stereogenic carbinol centres revealed the synthon **D**, amenable from **E** as its immediate precursor.

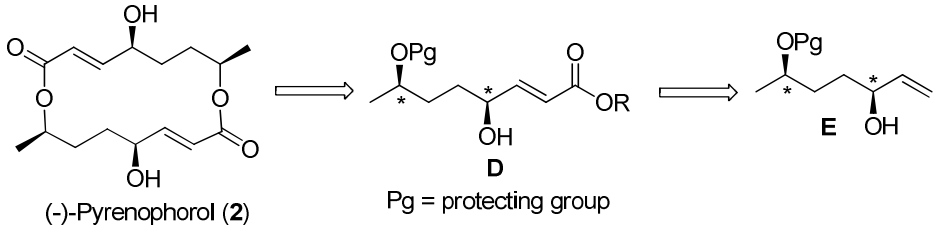
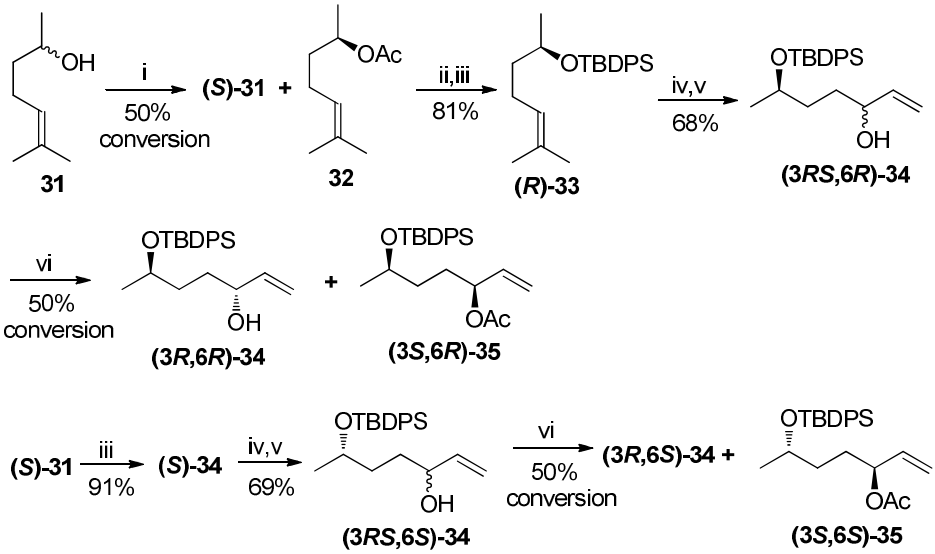


Figure 4. Chemical structure and retrosynthesis of natural pyrenophorol.

Availability of all the stereomers of **E** would provide easy access to various stereomers of **IV** via a DOS strategy. Hence, we synthesized all the four stereomers of an **E** equivalent by a biocatalytic route to use them to synthesize the enantiomers of **IV**.

Synthesis of the DOS intermediate stereomers. The synthesis (**Scheme 6**) commenced by resolution of (±)-sulcatol (**31**) via a Novozym 435®-catalyzed acetylation with vinyl acetate to obtain the (*S*)-**31** and (*R*)-acetate **32** (both >98% ees) at 50% conversion. The acetate **32** on $LiAlH_4$ reduction and reaction with TBDPSCl/imidazole gave (*R*)-**33**. Reductive ozonolysis of (*R*)-**33** followed by reaction with vinylmagnesium bromide furnished (3*RS*,6*R*)-**34**. As above, its Novozym 435®-catalyzed-acetylation afforded (3*R*,6*R*)-**34** and (3*S*,6*R*)-**35** both with >98% ees at 50% conversion. A similar sequence of reactions on (*S*)-**31** furnished (3*R*,6*S*)-**34** and (3*S*,6*S*)-**35** both with >98% ees at 50% conversion

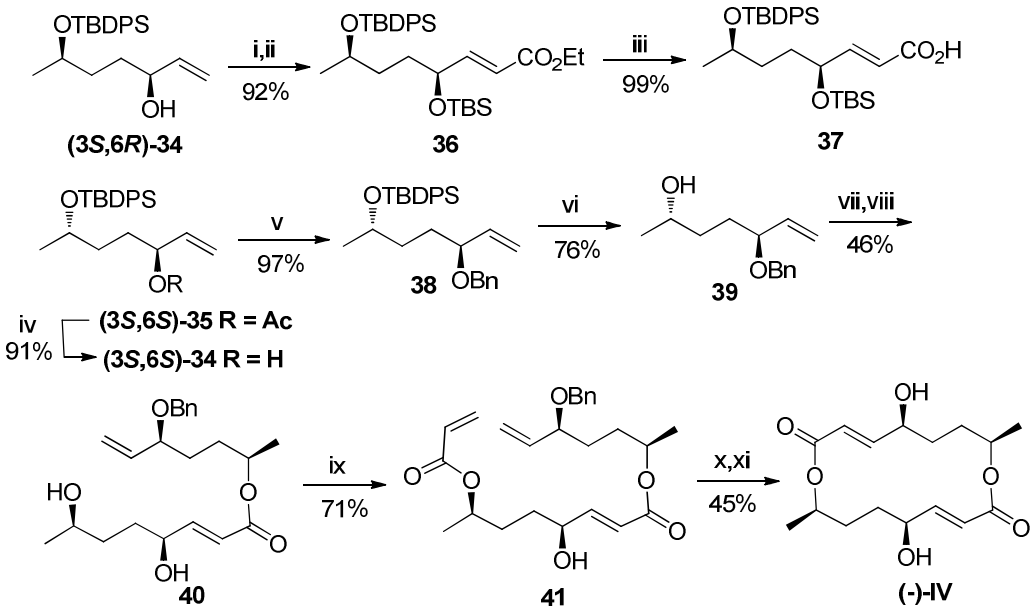


i) Novozym 435/vinyl acetate/hexane/50 min, ii) $LiAlH_4/Et_2O$/2 h, iii) TBDPSCl/ imidazole/DMAP/ CH_2Cl_2/25 °C/7 h (81%), iv) O_3/CH_2Cl_2/-78 °C /1.5 h; Ph_3P/-78 to 25 °C/18 h, v) CH_2=CHMgBr/ THF/-78 °C/3 h, vi) Novozyme 435/vinyl acetate/25 °C/6 h.

Scheme 6.

Synthesis of natural pyrenophorol. For the synthesis, a cross-metathesis of ethyl acrylate and (3*S*,6*R*)-**34**, obtained from the corresponding acetate and silylation with *tert*-butyldimethylsilyl chloride (TBSCl)/ imidazole furnished **36**. Its alkaline hydrolysis gave the acid **37**. Alkaline hydrolysis of the acetate (3*S*,6*S*)-**35** followed by benzylation gave **38**, which was desilylated to obtain the alcohol **39**. Esterification of **37** with the alcohol **39** under Mitsunobu conditions and a global desilylation afforded the diol ester **40**. Its Novozym 435®

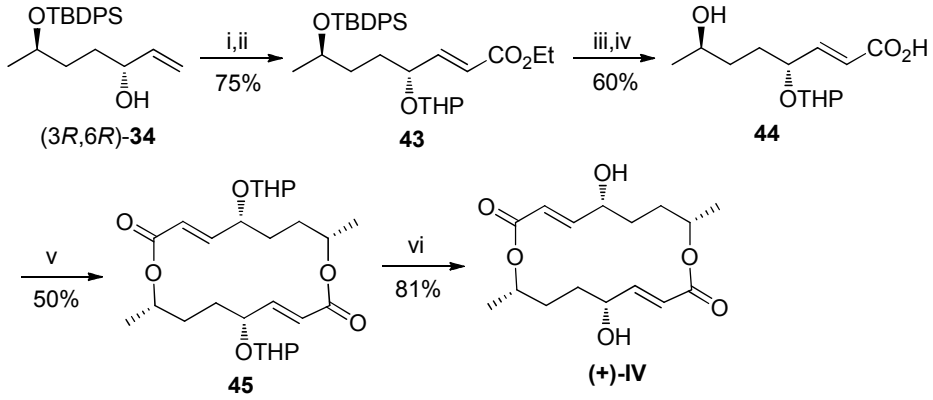
catalyzed acrylation proceeded regioselectively to give **41**. This on an RCM reaction and debenzylation completed the synthesis of (5*S*, 8*R*,13*S*,16*R*)-**IV** (**Scheme 7**).



i) CH_2=$CHCO_2Et$/Hoveyda-Grubbs' II catalyst/CH_2Cl_2/25 °C/3 h, ii) TBSCl/imidazole/DMAP/CH_2Cl_2, iii) Aqueous 20% NaOH/MeOH/25 °C/2 h, iv) K_2CO_3/MeOH/25 °C/6 h, v) NaH/BnBr/Bu_4NI/THF/80 °C/ 4 h, vi) Bu_4NF/THF/0 to 25 °C/8 h, vii) **37**//Ph_3P/DIAD/THF/0 to 25 °C/18 h, viii) Aqueous HF/MeCN/ 25 °C/16 h, ix) CH_2=$CHCO_2Et$/ Novozym 435/diisopropyl ether/30 h, x) Grubbs' II catalyst/CH_2Cl_2/ reflux/72 h, xi) $TiCl_4$/CH_2Cl_2/25 °C/0.5 h.

Scheme 7.

Synthesis of enantiomer of natural pyrenophorol. To demonstrate the versatility of the DOS approach, the synthesis of (+)-**IV** was also accomplished (**Scheme 8**) using the DOS intermediate (3*R*,6*R*)-**34**. Thus, its cross-metathesis with ethyl acrylate in the presence of Hoveyda-Grubbs' II catalyst and subsequent tetrahydropyranylation furnished **43**. After alkaline hydrolysis, the resultant acid was desilylated to obtain the hydroxy acid **44** with proper stereochemistry for dimerization. Accordingly, compound **44** was subjected to Mitsunobu esterification under high dilution to obtain the pyrenophorol derivative **45**, which on depyranylation produced (+)-**IV**.



(3*R*,6*R*)-**34** **43** **44** **45** **(+)-IV**

i) CH_2=$CHCO_2Et$/Hoveyda-Grubbs' II catalyst/CH_2Cl_2/25 ^oC/3 h, ii) DHP/PPTS/CH_2Cl_2/7 h, iii) Aqueous NaOH/MeOH/25 ^oC/0.5 h, iv) Bu_4NF/THF/80 ^oC/2 h, v) Ph_3P/DIAD/THF/0 to 25 ^oC/18 h, vi) PPTS/MeOH/25 ^oC/6 h.

Scheme 8.

References

1 (a) Asymmetric Synthesis; Morrison, J. D., Ed.; Academic Press: NY, **1983**; Vol. 2, Chapter 2; (b) Gawley, R. E.; Aube, J. Principles of Asymmetric Synthesis, 2nd Edition, 2012; Catalytic Asymmetric Synthesis, (Ed. Ojima, I.), John Wiley & Sons, 2013.

2 Turner, W. B.; Aldridge, D. C. in *Fungal Metabolites* II. Academic Press, London, 1983.

3 Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev*. **2005**, *105*, 313–354.

4 Lovera, A.; Bonilla, C.; Hidalgo, J. *Rev. Peru´ Med. Exp. Salud Publica* **2006**, *23*, 177–181.

5 Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; Van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc*. **2004**, *126*, 187–193.

6 (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18–29; (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed*. **2005**, *44*, 4490–4527.

7 Goswami, D.; Chattopadhyay, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1957–1961.

8 (a) Hudlicky, T.; Reed, J. W. *Chem. Soc. Rev*. **2009**, *38*, 3117–3132; (b) Clouthierzab, C. M.; Pelletier, J. N. *Chem. Soc. Rev*. **2012**, *41*, 1585–1605.

9 Michel, K. H.; Demarco, P. V.; Nagarajan, R. *J. Antibiot*. **1977**, *30*, 571–575.

10 Nozoe, S.; Hirai, K.; Tsuda, K.; Ishibashi, K.; Shirasak, M. *Tetrahedron Lett.* **1965**, 4675–4677.

11 (a) Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, *65*, 612–615; (b) Gebauer, J.; Blechert, S. *J. Org. Chem.* **2006**, *71*, 2021–2025 and references cited therein.

12 Teo, Y. -C.; Tan, K. -T.; Loh, T. -P. *Chem. Commun.,* **2005,** 1318–1320.

13 Bestmann, H. J.; Schobert, R. *Angew Chem. Int. Ed. Engl*. **1985**, *24*, 791-792.

LIST OF FIGURES

CHAPTER I

"Introduction to asymmetric synthesis and polyols"

I.1: PREAMBLE

Recent advances in biological and material sciences have led to identification of various target and purpose-specific fine chemicals. Further, extensive research on natural products chemistry especially with an eye to drug development has led to the isolation of myriads of bioactive compounds as well as identification of suitable pharmacophores. These compounds often bear complex structures and possess chirality. Even at the height of maturity, synthetic organic chemistry is facing the challenge to design and develop efficient syntheses for such functionally enriched complex biologically active compounds. Development of facile, atom economic, high yielding and selective synthetic routes appears the only solution to meet the requirements in a sustainable manner. Because most syntheses proceed from simple starting materials to complex targets, ideally the synthesis should aim to reach the target molecule using readily available, inexpensive starting materials via simple, safe and environmentally acceptable protocols. Thus, the design and development of new reactions and reaction sequences that allow for a great increase in target-relevant complexity are clearly essential for progress towards the next level of sophistication in organic synthesis.[1] Given the importance of stereochemistry in bio-recognition, the issue of asymmetric synthesis has become overwhelming in modern organic synthesis. The recognition that stereoisomers of a compound are separate molecular entities with specific properties has made a paradigm shift of the perspectives of organic synthesis.

In addition, introduction of the green chemistry philosophy to develop environmentally-safe chemical processes, and the concept of multi-target rather than target-specific syntheses have become the buzzword of modern organic synthesis. A given synthetic protocol becomes reliable only when it can be employed to achieve a given organic transformation efficiently and cleanly with no undesired conversions occurring under the chosen conditions. Because most syntheses proceed from simple starting materials to

complex targets, there are two general ways of approaching this ideal synthesis (*i. e*., achieving maximum relevant complexity increase while minimizing step count): the use of strategy-level reactions (e.g., the Diels–Alder reaction) that allow in one step for a great increase in target-relevant complexity or the use of multistep processes (*e. g*., polydirectional synthesis, tandem, serial, cascade, domino, and homo- and heterogenerative sequences) that produce similar or greater complexity changes in one operation. This is especially important to obtain "molecules with tailored properties" in the most efficient manner. On the other hand, green chemistry encourages the design of products and processes with minimum or no waste and generation of hazardous substances, and seeks to reduce the negative impact of chemistry on the environment by preventing pollution and wastes. The emphasis is to formulate processes to maximize the yield of the required products without creating wastes rather than only reducing it. From this perspective, syntheses of pure stereomers also contribute to green chemistry. Overall, selectivity has become the keyword of modern organic synthesis as it provides solutions to the above problems, and vigorous effort is being directed to this end.[2] This is generally achieved using metal complexes and/ or biocatalysts that ensures higher degree of selectivity, better efficacy, and thus, fulfills the criteria of ideal organic synthesis.

Thus, the major focus of the present investigation has been on asymmetric synthesis, and some of the key aspects of asymmetric synthesis is presented in the following section. Subsequently the scope and limitation of biocatalysis in organic synthesis is discussed, since this methodology has been extensively used in the present investigation. In tune with this theme, the present investigation was targeted to design asymmetric syntheses of some medicinally important aliphatic polyols, via chemoenzymatic routes or using some sugar-derived renewable natural products. The choice of the target molecules was decided by their potential use in medicinal chemistry, particularly as anti-fungal, anti-inflammatory and

chemo-preventive agents, which are of prime importance of our group. Hence, brief account of asymmetric synthesis and a summary of the natural polyols are presented in the following. This is followed by an overview of the aliphatic polyols and the objectives of the present investigations.

I.2: KEY ASPECTS OF ASYMMETRIC SYNTHESIS

Although asymmetric synthesis is sometimes viewed as a sub-discipline of organic chemistry, in actuality, this topical field transcends any parochial classification and pervades essentially the whole of chemistry.[3] The importance of enantiomerically pure compounds comes from the central role of enantiomer recognition in biological activities. There are many examples of drugs,[4a] agrochemicals[4b] and other chemical compounds where the desired biological property is related to the absolute configuration of the compound in question. Although biological implication of the chirality of a molecule is very well-understood, the differential recognition by the stereomers is also being utilized in designing novel molecular entities for various non-biological applications. Thus, chirality plays a crucial role in deciding various properties of a molecule. A short account of the importance of chirality on biological activities is provided in the following.

***I.2.1 Importance of chirality on bioactivity*.** This aspect is well rationalized by the fact that the biological perception and action of any molecule is primarily guided through its interaction with various proteins such as enzymes, receptors and other biopolymers (polysaccharides, and nucleic acids). All these provide chiral environments that can discriminate the different stereomers of the organic molecules. The recognition events in biology and the action of drugs that intervene in these events almost always involve the molecular recognition of a biologically active molecule by a chiral non-racemic receptor structure. The two enantiomers of a drug molecule cannot be expected to bind equally well to the receptor and so should cause different biological responses. Thus, only one enantiomer of

the drugs is often endowed with the desired biological activity, while the other enantiomer is inactive or possesses a different activity and may cause toxic side effects. For drug delivery, the potency of an active enantiomer compared with a racemic mixture of active and inactive enantiomers is that the dose can be reduced to half. Moreover, the problems that arise with optically impure pharmaceuticals, even when employed at high enantiomeric excess (ee), are no less significant. Enantiomers may also be competitive antagonists. This is the case for (+)- and (-)-isopropylnoradrenaline acting on the α_1-adrenergic receptors in rats.[4c] A further possibility is that the non-beneficial enantiomer may preferentially participate in biotoxication. An example is deprenyl, an antidepressant and anti-Parkinson's disease drug, for which the less active (*S*) isomer is converted into (*S*)-(+)-amphetamine, which causes undesired CNS stimulation.[4d] Another drug, *S*-propanolol is a β-blocker, but the *R*-isomer is a contraceptive. The most dramatic example in this aspect is the well known case of thalidomide. Its (*R*)-enantiomer is sedative and was used for morning sickness of pregnant women. However, the (*S*)-enantiomer was later found to be teratogenic causing wide spread birth defects. This tragedy really emphasized the importance of synthesis of enantiomerically pure compounds. In the series of eight isomers of the pyrethroid deltamethrin, the (*R*,*R*,*S*) isomer is the most powerful insecticide, whereas the (*R*,*S*,*S*) stereoisomer is inactive.[4e] For the food additive, aspartame, the (*S*,*S*)-enantiomer is used as an artificial sweetener, whilst the (*S*,*R*)-isomer tastes bitter and must be avoided in the manufacturing process. Even when the other enantiomers are inert, it may be desirable to synthesize and use the active one in its pure form. The *S*-enantiomer of ibuprofen is a pain reliever, whereas the *R*-form is inactive. Some selective examples highlighting this aspect is shown in **Figure I.2.1.**

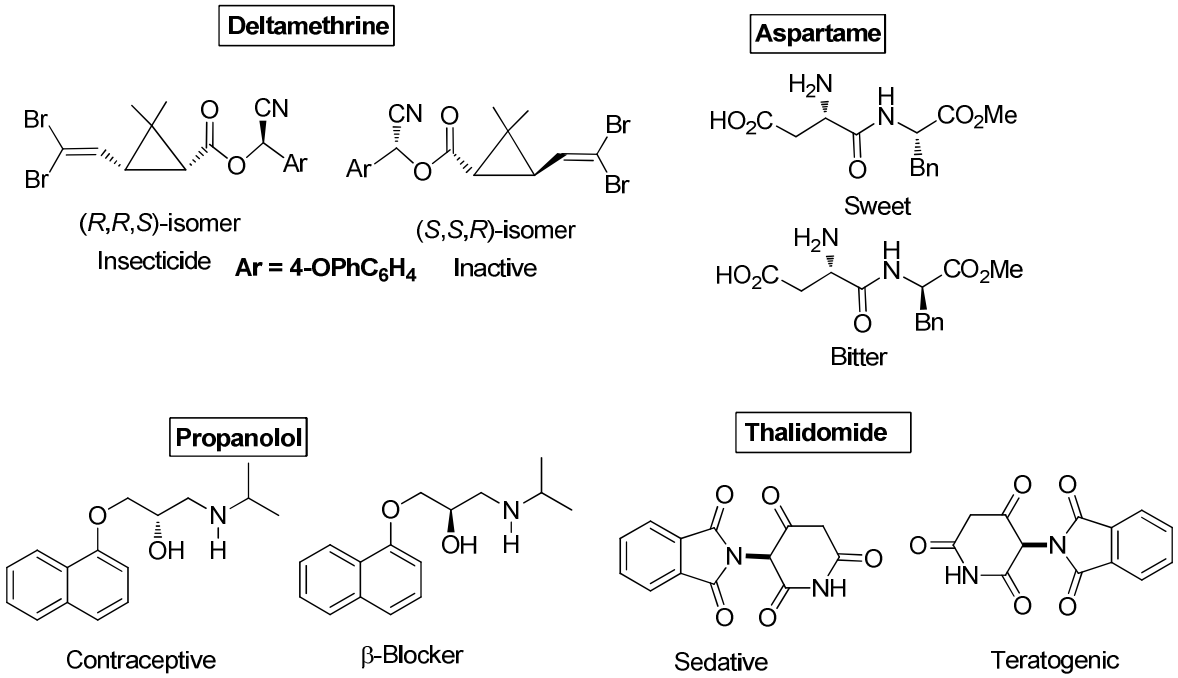


Figure I.2.1. Role of chirality in biological activities.

From the foregoing, the importance of chirality especially on drugs, agrochemicals, perfumeries and food-additives are obvious. In view of this, development of enantiomeric synthesis has assumed great significance. This is especially most important for the pharmaceutical industries, since the enantiomers of chiral drugs are considered as two different compounds. Enantiomeric synthesis of target compounds can be accomplished using different strategies, which are briefly presented below.

I.2.2 Strategies of enantiomeric synthesis. There are several methods to obtain enantiomerically pure materials, which include classical optical resolution via fractional crystallization of diastereomers, chromatographic separation of enantiomers, chiral pool synthesis, enzymatic and microbial routes, and asymmetric synthesis.

Resolution of racemates. This protocol[5a-d] *via* preferential crystallization of diastereomeric salts or covalently bonded diastereomers is the oldest and still one of the most important methods in obtaining enantiomerically pure compounds in the industry. In resolution, by differential crystallization, a racemic material is converted into a separable mixture of

diastereomers, using a stoichiometric amount of an optically pure resolving agent. Some of the commonly used resolving agents are: (i) tartaric acid, for resolution of secondary alcohols and amines; and (ii) alkaloids such as brucine salts or amines such as α-phenylethyl amine, for resolution of acids. Ideally the resolving agent should be available in its enantiomeric forms with high optical purity, and should produce crystalline diastereomeric derivatives. Moreover, this method requires recovery of the starting materials and reagents, and provides 50% of the unwanted isomer, which must be racemized or discarded.

***Chiral pool synthesis*.** This method does not involve formation of any new stereogenic centres. Instead, the stereogenic centres of the target molecules are derived from that present in the starting chiral materials. Nature provides a large repertoire of optically active compounds, the so called chiral pool materials. Amongst these, the enantiomerically pure compounds such as α-amino acids, steroids, carbohydrates, alkaloids and terpenes are important starting materials in enantiomeric syntheses.[6] Some well-known and often-used 'chiral pool' materials are shown in **Figure I.2.2**.

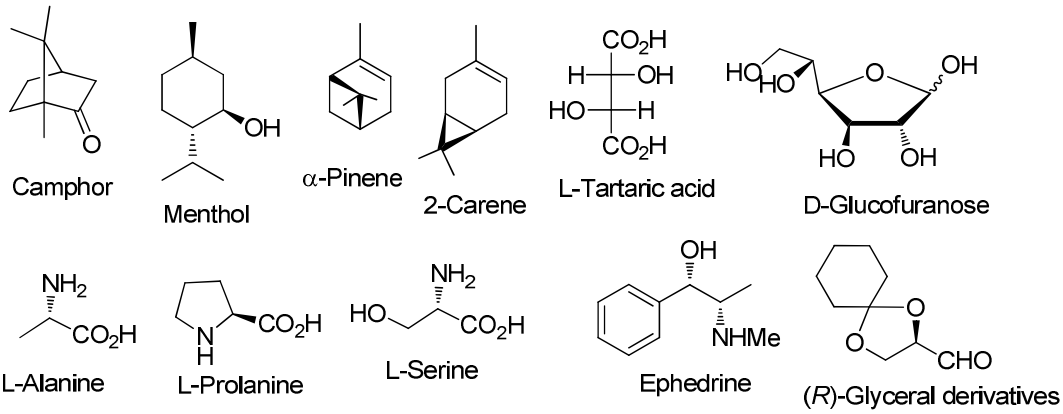


Figure I.2.2. Examples of some natural chiral pool materials.

Well-designed transformations and synthesis starting from these chiral compounds have resulted in a large number of enantiomerically pure compounds. However, this approach is limited by the availability of inexpensive starting materials with the right sense of chirality. Often the natural pool materials are available in one of their enantiomeric forms. For

example, naturally occurring sugars and amino acids possess only the D- and L-configurations respectively. Thus, when the synthesis of a target compound requires the other enantiomer of these starting materials, the synthesis becomes lengthy and inefficient and may even be difficult to accomplish. At times, it may be difficult to find a suitable enantiopure starting material, and other methods may prove more fruitful. Also, utmost care needs to be taken to avoid any racemization during the reaction sequence. In terms of versatility and utility, carbohydrates are the most preferred 'chiral pool' materials, since they contain several stereogenic centres, and often provide suitable steric bias for the subsequent transformations. However, the carbohydrate-based syntheses may require a number of protection and deprotection steps due to the presence of several and similar functionality (secondary hydroxyl groups). Further, many 'chiral pool' materials such as the alkaloids, steroids and triterpenes are not universally useful in asymmetric synthesis because their structures may not match with those of the target compounds.

***Asymmetric reactions*.** An asymmetric reaction is defined as a reaction in which an achiral unit in an ensemble of substrate molecules is converted to stereoisomeric products in unequal amounts.[7] Thus, an asymmetric synthesis is one, which creates new stereogenic centres in a controlled way. The energy profile of such reactions suggests favourable formation of racemates as the transition states $R^{\#}$ and $S^{\#}$ are enantiomeric and therefore, are isoenergic. As a consequence, the rate of formation of the *R*-isomer is equal to that of the *S*-isomer, and the reaction affords a racemic mixture. Thus, for the development of an asymmetric synthesis, the transition states must be diastereomeric so that their potential energies are different. This would ensure that the enantiomeric products are formed at different rates because of the involvement of different activation energies in their generation. As different molecular entities, the transition state diastereomers would be produced in unequal amounts, making the processes enantio- or diastereoselective (or both), and, hence may give rise to

enantiomerically pure products. In other words, the newly generated stereogenic centre should not be the first one in the ensemble. This can be achieved only by using a chiral reagent, substrate, solvent, catalyst or physical forces such as circularly polarized light. Under these conditions, the reactions can be stereo-differentiating to "induce" chirality at the newly formed stereogenic centers. Asymmetric synthesis involves i) selective displacement of an enantiotopic group at the prochiral or chiral centres, and (ii) selective addition of a reagent to an enantiotopic (*Re*/*Si*)-face of a π-bond (**Figure I.2.3.**).[8]

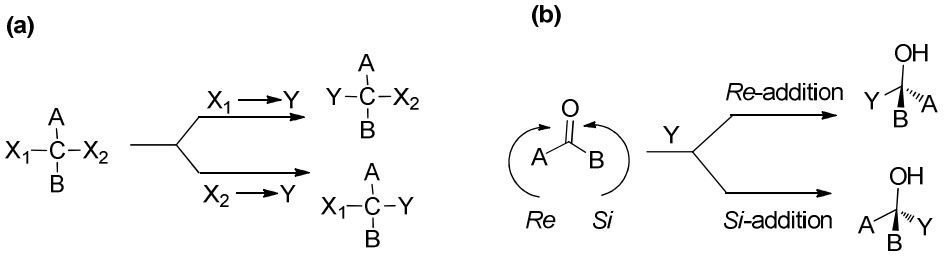


Figure I.2.3. Asymmetric reactions (**a**) enantiotopic substitution, (**b**) face-selective addition.

These are known as topo-, isomer- and face-differentiating reactions. The topo- and isomer-differentiating reactions can induce asymmetry by substitution or by preferential removal/elimination of a *pro-R* or a *pro-S* substituent, all these events being governed by theromodynamic and/ or kinetic factors. Two types of stereo-differentiating reactions can be broadly conceived: (i) when the chirality of the reagent, solvent, or catalyst influences the enantio-differentiation to produce the enantiomers; and (ii) when the chirality of the substrate controls the stereochemical outcome of the reaction to furnish diastereomers. In the first category, the most widely encountered situation is the regent-controlled "asymmetric induction" and some important achievements in this field include, but not limited are the asymmetric catalytic hydrogenation of dehydroamino acids, as described by Knowles *et al.*[9a] Sharpless epoxidation[9b,c] and dihydroxylation,[9d] and the second generation catalytic hydrogenation process developed by Noyori *et al.*[9e]

Catalytic asymmetric synthesis has economic and environmental advantages over stoichiometric asymmetric synthesis for industrial scale production of enantiomerically pure compounds. This can have a high turnover of chirality, and under well-chosen conditions, many chiral molecules can be produced by one catalyst molecule. The aspect of multiplication of chirality is characteristic of both biocatalysts and chemical catalysts. Some commercially important chemical asymmetric reactions that can be readily cited are the synthesis of *L*-menthol by asymmetric isomerization,[9f,g] asymmetric cyclopropanation[9h] and synthesis of *L*-dopa by asymmetric hydrogenation.[9i]

Although metal/metal salt-catalyzed reactions remain the mainstay in asymmetric synthesis, the last few years have witnessed a spectacular advancement in new catalytic methods based on metal-free small organic molecules (organocatalysis).[10a,b] In many cases, these give rise to extremely high enantioselectivities, and offer notable preparative advantages such as (i) the catalysts are available, inexpensive and stable; (ii) usually the reactions can be performed under an aerobic atmosphere with wet solvents; (iii) the organocatalysts can be anchored to a solid support and reused more conveniently than organometallic/bioorganic analogues; and (iv) was promising for high throughput screening and process chemistry. The organocatalytic reactions are more closely related to enzyme- or antibody-catalyzed reactions than to organometallic processes. Hence these are often also known as artificial enzymes or enzyme mimetics.[10c]

One of the most adopted protocol for creating chiral molecules is the addition of nucleophiles to the keto/aldehyde functionality. The resultant alcohols are of wide occurrence in nature, and are also precursors to varied types of other target molecules such as macrolides, spiroketals, amines, heterocylic compounds etc. Different organometallic reagents are primarily chosen as the nucleophiles for such reactions, which can be carried out under reagent-controlled or substrate-controlled conditions, or a combination of both. Several

models have been proposed to explain such a diastereoselectivity for the substrate-controlled reactions. Two of the most preferred models are briefly discussed below.

Cram's model[11]: When a carbonyl group attached to an asymmetric centre (*e. g.*, $RCOCR_LR_MR_S$ in which R_L, R_M and R_S stand for large, medium, and small groups respectively) undergoes nucleophilic addition with organometallic or metal hydride reagents, two diastereomeric products, *erythro* and *threo* result, of which one predominates. The relative configuration of the predominant isomer is often predicted by Cram's empirical models. In the open chain model, the C=O group of the ketone is flanked by the two smaller groups (R_S and R_M) with the large group (R_L) nearly eclipsed with R (**Figure I.2.4a.**). The reaction takes place after coordination of the metallic part of the reagent with the C=O followed by transfer of the alkyl (R') or H to the trigonal carbon from the side of R_S (route a) in preference to that closer to R_M (route b) to give the product **A**. Although no mechanistic rationalization has been claimed, it is reasoned that the complexed C=O group becomes effectively the bulkiest group, and is thus, better placed between R_S and R_M. Although only one enantiomer of the substrate is shown in the model, the rule is equally applicable to the racemic substrate wherein racemic products are obtained.

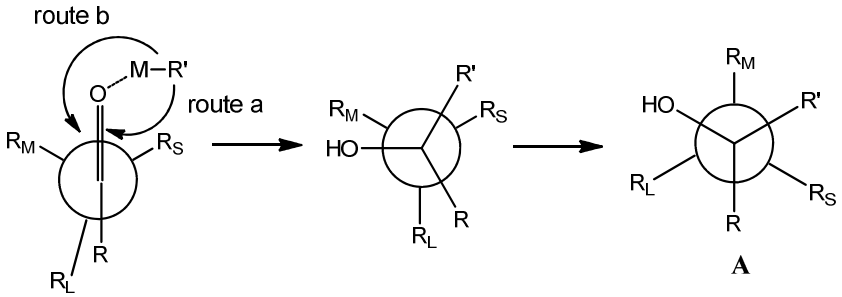


Figure I.2.4a. Cram's open chain model.

If the substrate contains a chelating group such as OH, NH_2 and OMe, α-to carbonyl moiety, the stereochemistry of the product is predicted by Cram's rigid (chelate) *cyclic model* (**Figure I.2.4b.**). In this model, the metallic part of the reagent is doubly coordinated to form a five-

membered ring as in **B**. When the chelating group is $R_{M,}$ the cyclic model predicts the same stereochemistry as the open chain model; but if it is R_S or $R_{L,}$ opposite stereochemistry follows. Asymmetric induction through chelate model is usually high.

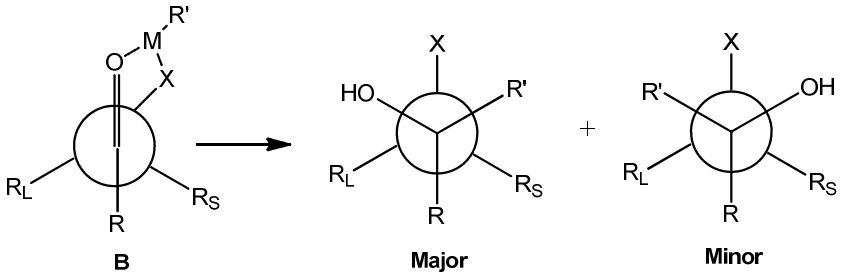


Figure I.2.4b. Cram's cyclic chelate model

If a strongly electronegative group, *e. g*., a halogen atom is present α to the C=O group, a *dipolar* model is suggested to predict the stereochemical outcome of the reaction. The dipoles of the carbonyl bond and the C-X bond oppose each other and so they are placed *anti* as in the model **C** to minimize the dipolar repulsion. The nucleophile adds from the side of R_S giving the major product as shown in **Figure I.2.4c**.

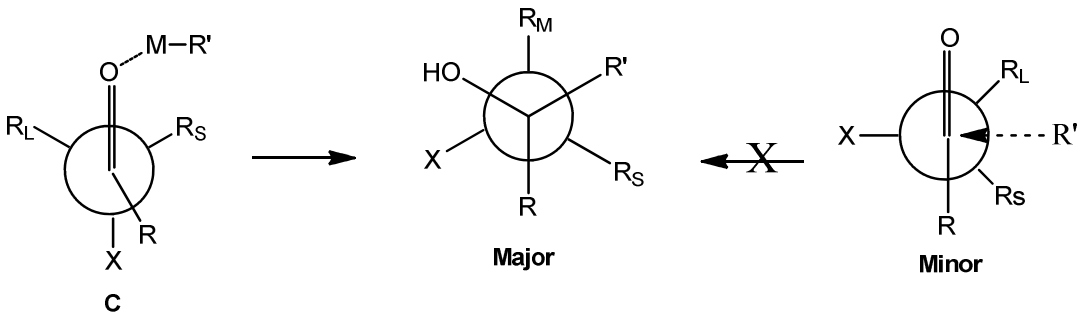


Figure I.2.4c. Cram's dipolar model.

Despite predicting the stereochemical course of the reactions correctly, the Cram's models often fail to give a quantitative assessment of the asymmetric induction in terms of steric interactions. A few alternative models have been proposed to predict the stereochemical outcome of the designated reactions in more quantitative terms. Of these the Felkin-Anh model, discussed below has gained consensus.

Felkin-Anh model[12]: In this model, two reactive conformations **D** and **D'** (**Figure I.2.5.**) have been considered in which either the largest (R_L) or the most electron withdrawing group (which provides the greatest σ*-π* overlap with the carbonyl π* orbital) at C_α is placed at right angle to the C=O double bond. Between the two, the first (conformation **D**) with R_M opposing C=O and R_S gauche to R is usually preferred. The non-bonded interactions, involving R and R_S (rather than R and R_M as in **D'**) are thus minimized. The model predicts the same stereochemistry as Cram's, but provides a more quantitative assessment of the 1,2-asymmetric induction. A third conformation (**D''**) may make some contribution but is generally ignored (unfavorable steric interactions).

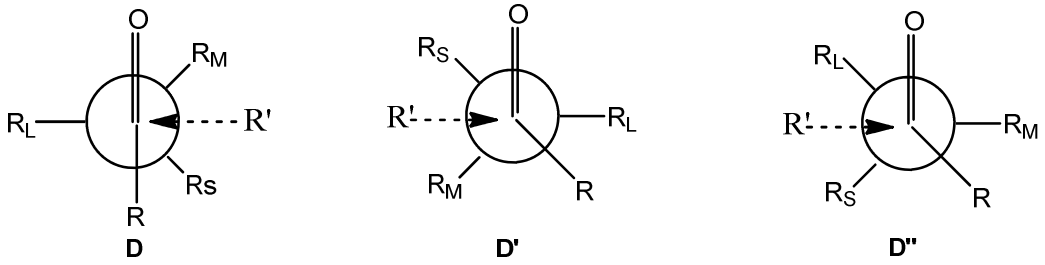


Figure I.2.5. Felkin-Anh model.

***Energy considerations in asymmetric synthesis*.**

The selectivity achieved in the reactions will depend on the differences of the activation energies, ΔΔG*, since they take place under kinetic control. This implies that the most abundant product is that originating *via* the lowest activation energy. Thus, no asymmetric induction is possible without any chiral auxiliary, as the transition states of formation of the enantiomeric products have identical activation energies (**Figure I.2.6a.**) When the products in the asymmetric synthesis are diastereomeric, the selectivity can be dictated also by the difference in kinetic energies (kinetic control, **Figure I.2.6b.**), but when the reaction is reversible, the selectivity (at equilibrium) will depend on the difference between the free energies of the products, ΔG° (thermodynamic control).

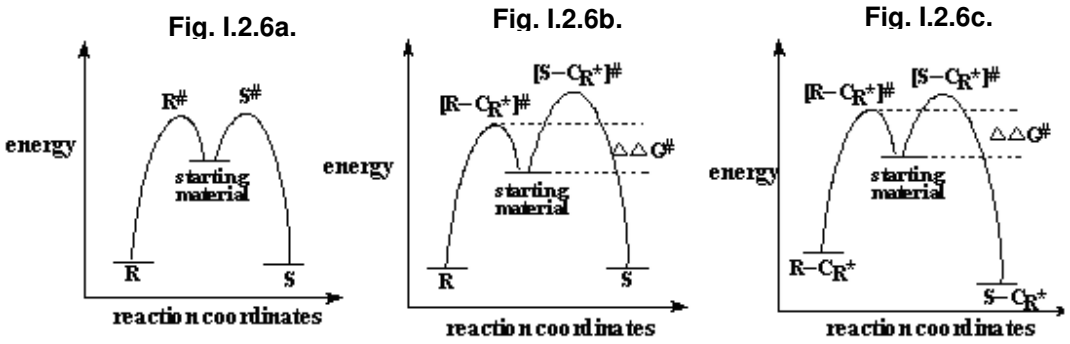


Figure I.2.6a-c. Energetics of asymmetric transformations.

Figure I.2.6c describes a unique situation in which initially, under the conditions of kinetic control, the product of *R*-configuration predominates. By contrast, thermodynamic control leads to the predominant formation of the most stable product (S-C_R*). The ratios of the products depend directly on the magnitude of $\Delta\Delta G^{\#}$ (for kinetic control) or $\Delta G°$ (for thermodynamic control). This would require a $\Delta G°$ or $\Delta G^{\#} \geq 1.0$ kcal/mol for achieving an enantioselectivity of 70% and such an energy difference is usually provided by simple electrostatic interactions.

Thus, the design of an asymmetric reaction must aim at maximization of $\Delta\Delta G^{\#}$ or $\Delta G°$, depending on whether product formation is kinetically or thermodynamically controlled. In spite of all these attributes and even after handling hundreds of asymmetric reactions, very little is known concerning the nature of the transition states of a particular reaction. But, it has become clear that more rigid and organized transition states magnify the effect of the strike interactions, hydrogen bonds, selective solvation *etc*. Considering that the rigidity of the transition state is more pronounced at lower temperatures, asymmetric induction is usually best achieved by carrying out the reactions at lower temperatures.

Eliel[8b] has summarized several conditions for an efficient asymmetric process.

i) It has to be highly selective.

ii) The new centre of chirality must be cleanly separated from the rest of the molecule.

iii) The chiral auxiliary must be recovered without any racemization.

iv) The chiral auxiliary reagent must be easily and inexpensively available.

v) The reaction must proceed in good chemical yield.

vi) The balance between chiral auxiliary/reagent and product with the new chiral centre of chirality is also important. Thus, best chiral auxiliary is an efficient chiral catalyst.

I.2.3 Strategies for determination of enantiomeric purities. Growing interest and improvement in enantioselective syntheses led to an increased demand for accurate, reliable and convenient methods of measuring the enantiomeric composition. Enantiomeric excess (ee), defined as the absolute difference between the mole fraction of each enantiomer is a measurement of purity used for chiral substances. It reflects the degree to which a sample contains one enantiomer in greater amounts than the other. A large number of methods for the determination of ees regardless of the chiral analytes have been developed over the years. As in the asymmetric syntheses, determination of % ees is also based on the fact that while two enantiomers have identical physical properties in an achiral environment, the diastereoisomers have different physical properties to allow their separation using various instrumental techniques such as HPLC, GC and NMR spectroscopy. To this end, formation of the required diastereoisomers can be achieved transiently via a reversible diastereotopic non-covalent interaction between the analyte and a chiral reagent, or by their covalent attachment using their functionalities.

The non-covalent technique relies on different interactions of a chiral molecule with other chiral compounds depending on the enantiomer used. For example, in the HPLC or GC analysis, an analyte solution is passed over a chiral stationary phase so that it has a rapid and reversible diastereotopic interaction with the stationary phase, allowing separation. Despite being quick and accurate (±0.05%), these protocols need expensive chiral columns as well as

both the enantiomers of the analyte, and the chiral stationary phase may only work for limited types of compounds. Nevertheless a wide variety of chiral columns is available and routinely used. Compared to the conventional HPLC, use of the supercritical fluid chromatography in chiral separations offers advantages such as short analysis and equilibration times due to low mobile phase viscosity and superior diffusion characteristics.[13]

The % ees can also be determined using chiral paramagnetic lanthanide complexes that can bind reversibly to certain chiral molecules *via* the metal centre to form two diastereomeric complexes, and may often have different NMR signals. The coordination process is usually faster than the NMR timescale and normally leads to a downfield shift of the resonance. The differences in the resonance signals from each enantiomer are observed, and the relative areas may be utilized to derive % ee, provided sufficient resolution of signals is obtained. However, as the complexes are paramagnetic, line broadening is a major problem in these analyses. Also, the compound is required to possess a Lewis basic lone pair (OH, NH_2, C=O, CO_2H *etc*) and accuracy of the method is only ±2%.

In the alternative approach, the analyte is covalently attached to a second, enantiomerically pure molecule to obtain a mixture of diastereoisomers that can be separated by normal, achiral chromatography, or analyzed from their NMR spectra due to the large separation in the signals of their diastereotopic moieties.[14a] The most popular derivatizing agent for alcohols and amines is α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) or Mosher's acid as the MTPA esters and amides can be analyzed conveniently.[14b] The difference ($\geq$ 0.15 ppm) in the OMe singlets or that (~0.17 ppm) of the ^{19}F atoms between the diastereoisomers in the ^{1}H or ^{19}F NMR spectroscopy can be used to determine the % ees. In addition, the diastereoisomers are often separable by chromatography. The Mosher's derivatives can also be used to determine the absolute configuration of a stereocentre

empirically using the δ differences (Δδ).[14c] Besides, various other derivatizing agents, notably various optically active mandelic acid derivatives are also used for this purpose.[14d]

I.3: BIOCATALYTIC ORGANIC REACTIONS

Myriads of chemical reactions are essential in the cellular systems sustaining life. Nature, the super chemist executes them in an energy-efficient manner and under moderate conditions (temperature, pH, aqueous and hydrophobic environments) using enzymes or the biocatalysts, abundant in the microbial, plant and animal kingdoms. This has triggered hectic activities among the synthetic organic chemists to use biocatalysts for designing atom-economic and selective green organic reactions to obtain the desired products faster in higher yields and with minimum wastes. The knowledge of biocatalysis to humans predates the recorded history for brewing. The use of enzymes and whole cell microorganisms has been important particularly in the food and beverage industries for the production of cheese, wine, beer etc. Over the past 30 years, there is a substantial increase in the application of biocatalysis to produce fine chemicals, especially in the pharmaceutical industry.[15] In 1833, Payen and Persoz investigated the hydrolysis of starch by diastase which was later acknowledged by Berzelius as a biocatalytic reaction in 1835. In 1874, the first company (Christian Hansen's Laboratory) was set up for the marketing of enzyme preparations for cheese making in Copenhagen. In 1894, Emil Fischer described the elegant aspects of enzyme catalysis and also coined the term enzyme specificity. Enzymes as catalysts in synthetic organic chemistry gained importance in the latter half of the 20th century, but suffered from two major limitations *viz*. (i) non-availability of many enzymes in large enough quantities and at affordable cost; and (ii) narrow substrate specificity, often poor stereo- and/or regioselectivity and/or insufficient stability under the operating conditions. However, with the advent of recombinant DNA technology and development of directed evolution,

these problems are adequately addressed. Currently, biocatalysis has become a part of the toolkit of synthetic organic chemists and biotechnologists.[16]

Similar to other catalysts,[17a] biocatalysts increase the speed of a reaction by stabilizing its transition state, without affecting the thermodynamics. However, they offer some unique characteristics such as higher rate enhancement and catalytic turnover number and most importantly excellent selectivity over conventional chemical catalysts. For example, the rate enhancement by biocatalysts can range by a factor of 10^6-10^{12} *vis-à-vis* 10-10^3 by chemical catalysts. Likewise only 0.005-0.05 mol% of biocatalysts are required to achieve the conversion, as opposed to 5-50 mol% of chemical catalysts. Moreover, biocatalyst offer chiral (stereo), positional (regio-), and functional group specific (chemo-) selectivities, all desirable attributes in chemical synthesis as these may minimize the number of protection/deprotection steps as well as side reactions, and assist easier isolation of the desired products with less environmental problems.

Enzymes are more than just highly evolved catalysts[17b] and many of the unique characteristics of these sophisticated systems can be explained in terms of their built-in feedback mechanisms and subtle intra- and intermolecular cooperation. They are proteins and possess three-dimensional architectures containing primarily hydrophobic and a few polar sites. These allow enzymes to effectively surround and enclose their substrates ("induced fit") to catalyze the reactions. Hence, the biocatalytic reactions follow saturation or Michaelis-Menten kinetics involving the reversible formation of an enzyme-substrate (ES) complex. Formation of the ES complex is maximum when the substrate size and the disposition of their groups match well with the enzyme conformation. This factor, classically referred to as “lock and key mechanism” is responsible for the substrate specificity of the enzyme and enantioselectivity of the biocatalytic reactions. Besides, the binding also helps in bringing the reacting substrates closer (“proximity effect”) and weakens some of the existing covalent

bonds in the substrates. These, in turn, reduce the activation energy by stabilizing the transition state of the reactions. Finally, the exclusion of the trapped water molecules brought about by the substrate binding maximizes the increase in entropy and decreases the dielectric constant, thus intensifying the electrostatic effects. It is worth noting that the spherical enzyme architectures behave like soft balls wherein the bound water molecules work as lubricants, stabilize the enzyme conformation and help in "squeezing in" the guest substrates. This helps in accommodating even structurally different substrates than the natural ones, helping their use in organic reactions.

Given that the enzyme secondary and tertiary structures are stabilized by various weak non-covalent forces *viz*. hydrogen bonding, hydrophobic interaction and dipolar/ionic interactions, it is also possible to modulate the enzyme conformation marginally by suitable alteration of the environment. This has given rise to the concept of solvent engineering wherein the stereochemical courses of many enzymatic reactions are tailored by merely using water-immiscible organic solvents.[18] This technique widens the scope of biocatalytic reactions from a variety of considerations. Most of the organic compounds are insoluble in water, and some even degrade, leading to no reaction or side reactions. Although the enzymatic reactions are reversible, the thermodynamic equilibria of the reverse processes are unfavorable in water. For example, in natural aqueous medium the lipases and proteases catalyze hydrolysis of lipids and proteins. But the same enzymes can be used to catalyze syntheses of these biomolecules by esterification and aminolysis in an organic medium. The product recovery in non-aqueous enzymatic reactions are also easier. Moreover, while the bound water molecules are essential to maintain the activity of the enzymes, their denaturation is also induced in aqueous environment. In contrast, the enzymes have very rigid conformations in dry solvents, and the crystalline insoluble enzymes can be recovered without much loss of activity and reused. Hydrophobic solvents are usually superior to

hydrophilic ones as the reaction media because the latter have a greater tendency to strip the tightly bound, essential water from the enzyme and deactivate it. Finally, the organic media can significantly reduce the problem of enzyme inhibition by dissolving the substrates and products.

It is now well-accepted that there is an enzyme-catalyzed reaction equivalent to almost every type of known organic reactions. Based on the type of reactions carried out by them, enzymes are classified into five broad categories *viz*. (i) oxidoreductases: They catalyze oxidation and reduction within the cell; (ii) hydrolases: They catalyze hydrolysis and formation of ester and amide bonds; (iii) transferases: They catalyze the transfer of functional groups such as methyl, hydroxymethyl, formyl, glycosyl, acyl, alkyl, phosphate, and sulfate groups; (iv) lyases: These are responsible for catalyzing addition and elimination reactions; and (v) ligases: They are responsible for the most important cellular processes of creating chemical bonds with nucleotide triphosphates, but have very few industrial applications.

Both isolated enzymes and whole cells can be used as biocatalysts.[19] Compared to the whole cells, isolated enzymes offer several benefits, including simpler reaction apparatus, higher productivity owing to higher catalyst concentration, and simpler product purification. Compared to isolated enzymes, a whole-cell system has an advantage of recycling the cofactors (nonprotein components involved in enzyme catalysis) and is more useful for the cofactor-requiring enzymes such as oxidoreductases, lyases etc. In addition, it can carry out selective synthesis using cheap and abundant raw materials. However, the whole-cell systems require expensive equipment and tedious work-up because of large volumes, and have low productivity. More importantly, uncontrolled metabolic processes may result in undesirable side reactions during cell growth. The accumulation of these undesirable as well as desirable products may be toxic to the cells, and their separation from the rest of the cell culture can be

difficult. Another drawback to whole-cell systems is that the cell membrane may act as a mass transport barrier between the substrates and the enzymes. The whole-cell biocatalysis approach is typically used when a specific biotransformation requires multiple enzymes or when it is difficult to isolate the enzyme. In terms of industrial applications, despite needing expensive cofactors, the oxidoreductases are widely used, and many processes have been developed using the whole cell systems. Of particular interest among hydrolases are amidases, proteases, esterases, and lipases. Amongst these, the lipases hydrolyze triglycerides into fatty acids and glycerol; proteases *viz.* α-chymotrypsin, papain, and subtilisin hydrolyze/form peptide bonds. The oligosaccharides and polysaccharides, vital for cellular recognition and communication processes are industrially synthesized using transferases. Isomerases are rarely used in industrial applications, the notable exception being the use of glucose isomerase for high-fructose corn syrup production.

Biocatalysis can be used for synthesizing enantiopure compounds by (i) kinetic resolution (KR) of a racemic mixture or (ii) asymmetric transformations of a prochiral molecule. The KR protocol relies on the higher reaction rate of a particular enantiomer in its racemic mixture for the specific reaction. The maximum yield in such kinetic resolutions is 50%. In biocatalyzed asymmetric synthesis, a non-chiral unit becomes chiral in such a way that the different possible stereoisomers are formed in different quantities. The oxidoreductases, present in many microorganisms including common baker's yeast are often used for the asymmetric reduction of ketones. On the other hand, the same enzyme can catalyze enantioselective Baeyer–Villiger oxidation of cyclic ketones. The lipases are widely used in esterification/aminolysis of α- or β-substituted acids as well as esterification/*trans*-esterification of secondary alcohols under the KR protocol, and provide good to excellent enantioselectivity. In some studies, lipases have also been found to be promiscuous to carry out reactions akin to those expected. Some examples in this category include: (i) use of

Candida antarctica lipase for Michael addition reactions **18**,[20a] (ii) use of the same *C. antarctica* lipase for Cannizzaro-type reaction of substituted benzaldehydes,[20b] and (iii) Henry reaction of aromatic aldehydes and nitroalkanes by Lipase A from *Aspergillus niger*.[20c]

The characteristics of limited operating regions, substrate or product inhibition, and reactions in aqueous solutions have often been considered as the most serious drawbacks of biocatalysts. Many of these drawbacks, however, turn out to be misconceptions and prejudices. For example, many commercially used enzymes show excellent stability with half-lives of months or even years under process conditions. In addition, many enzymes accept non-natural substrates and convert them into desired products. More importantly, almost all of the biocatalyst characteristics can be tailored with protein engineering and metabolic engineering to meet the desired process conditions. Biocatalysts can constitute a significant portion of the operating budget; however, their cost can be reduced by reusing them when immobilized.

I.4: AN OVERVIEW OF ALIPHATIC POLYOL DERIVATIVES

Natural oxygenated fatty acids include those possessing hydroxy, keto or epoxy functionalities, the hydroxy acids being most common.[21] The epoxy acids are available from some seed oils after long storage. The most widely occurring natural acids in this class are vernolic acid and its positional isomer, coronaric acid. Most of the natural hydroxy acids are optically active and may contain one or more hydroxy group(s) and additional olefin functions. The polyhydroxy acids constitute a distinctive group and are available in the chain length of C_{14} to C_{24}. Many biotic and abiotic sources contribute to the occurrence of these compound in various environmental media.[22] These indicate the requirement for specific development conditions of various microorganisms and their interactions with their habitats, and have attracted attention in soil and biogeochemical research. For instance, several rhizosphere bacteria were identified to release the phosphate solubilizing gluconic and

ketogluconic acids into soil thus improving the P supply for plants.[23a] Mono- and dihydroxy (poly) carboxylic acids, *e. g*., lactic, malic, tartaric, and citric acids, are often components of plant root exudates.[23b] Many lipidic components of plants contain the polyol derivatives and are essential for plant male reproductive development and also protection against pathogens. Mycolic acids, with a 2-alkyl-3-hydroxy carboxylic acid skeleton are high molecular weight (contain up to 80 C-atoms), complex compounds in this category.[23c] Importantly, the macrolides, derived from the polyhydroxy acids are also abundant in nature, especially as marine metabolites.[24]

Regarding their biological activities, the C_{18}-hydroxy acids with diverse oxygenation patterns have been reported to be cytotoxic against P388 mouse leukemic,[24d] and HeLa cells.[25a] A ketohydroxy acid, obtained[25b] from corn also showed encouraging anti-cancer activity, while a dihydroxytetradecatrienoate and its ester, isolated from the fungus *Mycosphaerella rubella* showed selective antibacterial activity against *Sarcina lutea, Bacillus cereus* and *B. subtilis*, but not against *Escherichia coli* and *Saccharomyces cerevisiae*.[26a] Likewise, the antiviral property of some hydroxylated unsaturated fatty acids from the Basidiomycete, *Filoboletus,* have been described.[26b] Pinellic acid is the active principle of the Kampo medicine, Sho-seiryu-to (SST), which is used as an oral adjuvant for nasally administered influenza vaccine.[26c]

I.5: OBJECTIVES OF THE PRESENT WORK

The present work was mainly focused on the development of operationally simple and practically viable asymmetric syntheses of some aliphatic polyols and macrolides. Impressive progress notwithstanding, development of simple, efficient and scalable strategies remains a challenging and important goal in asymmetric organic synthesis.[27] This provided the primary motivation of the present investigations. The diverse pharmacological profiles of many of the chosen class of compounds and their structural complexity provided the additional fillip. In

particular, our group is actively engaged in formulating efficient syntheses of new immunomodulatory, anti-inflammatory, and anti-neoplastic agents.[28] To this end, the mannitol-derived compound, (*R*)-cyclohexylideneglyceraldehyde has been found to be an excellent chiral template for enantiomeric syntheses of a diverse array of natural products and their congeners. The aldehyde is amenable to various diastereoselective transformations using commonly available, inexpensive reagents.[29a-c] In addition, the lipase-catalyzed esterification of secondary alcohols under kinetic control has often been found to proceed with good to excellent enantioselectivity.[29d-j] Hence, with the objective of developing some operationally simple asymmetric syntheses of the target compounds, the two above mentioned asymmetric strategies were judiciously used.

CHAPTER II

"Glyceraldehyde- Based

Asymmetric Syntheses

of Some Target Aliphatic Polyols"

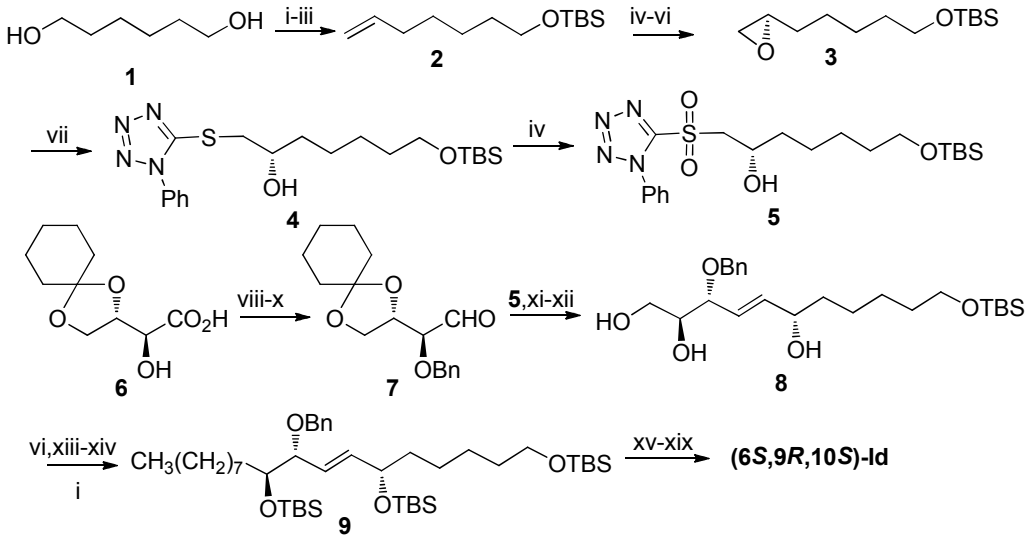
CHAPTER II.1 TOTAL SYNTHESIS OF OXYLIPIN

II.1.1. Introduction

Araceae is one of the dominant tropical families amongst the herbs and vines, and many of the species are used as traditional remedies or food. The plant, *Dracontium loretense* Engl. belonging to this family (subfamily Lasioideae) is widely distributed in the Peruvian Amazon, where it is known as "jergo´n sacha". Various preparations of jergo´n sacha such as dried powder, tincture, alcoholic and aqueous-alcoholic extracts are popular amongst the current Peruvian herbal medicines, and available in pharmacies and stores. The infusion of its corms is considered immune-booster in Peruvian folk medicine. The combination of the extracts of *D. loretense* and *Uncaria tomentosa* is also used by AIDS patients to reinforce the immune system.[30a-c] Very recently, four novel oxylipins **Ia**-**d** (**Figure II.1.1.**) were isolated from the *n*-butanol extract of *D. loretense* corms and their structures were elucidated by extensive NMR and mass spectrometry. The *n*-butanol extract and some of its fractions (10 μg/mL) as well as compound **Id** (10 μM) showed potential immunostimulatory effect as revealed by the ^{3}H-thymidine incorporation assay with human peripheral blood mononuclear cells (PBMCs). However, these were toxic to the cells at a higher concentration. Amongst the constituent oxylipins of *D. loretense*, only compound **Id** exhibited proliferation activity on the OKT3-activated PBMCs, while its C-10 epimer **Ic** was inactive.[31] This emphasized the crucial role of the C-10 stereochemistry for the biological activity. Earlier, our group also found differential immunomodulatory activities of the castanospermine epimers.[32] Amongst the three stereogenic carbinol centres at C-6, C-9 and C-10 of **Id**, the configuration at C-6 was unresolved when the present synthesis of (*6S,9R,10S*)-**Id** was developed.[33a] However, recently Saikia *et al*.[33b] have proposed the (6*R*,9*R*,10*S*)-stereochemistry for natural **Id** on the basis of the optical rotation and ^{1}H NMR *J*-values of their synthetic sample.

II.1.2. Previous Syntheses

Besides our own synthesis, Saikia *et al.*[33b] have also synthesized (*6S,9R,10S*)-**Id**. In addition, a synthesis of (6*R*,9*R*,10*R*)-**Id** has been reported, wherein the 9*R*,10*R*-stereochemisty was installed by Sharpless asymmetric dihydroxylation, while that at C-6 was obtained by a CBS reduction.[33c] For the synthesis of (*6S,9R,10S*)-**Id** (**Scheme II.1.1.**), the diol **1** was converted to the alkenol **2** by monosilylation, PCC oxidation, and Wittig olefination.



(i) TBSCl/imidazole/CH_2Cl_2, (ii) PCC/CH_2Cl_2/mol.sieves, (iii) CH_3PPh_3I/*n*-BuLi/THF/-78 ^oC to room temperature, (iv) *m*-CPBA/CH_2Cl_2/0 ^oC, (v) (*R*,*R*)-(salen)Co(III)OAc/H_2O/0 ^oC, vi) Bu_2SnO/*p*-TsCl/Et_3N/CH_2Cl_2; K_2CO_3/MeOH, (vii) PT-SH/CH_2Cl_2/Mont K-10, (viii) $NaHCO_3$/ $(CH_3O)_2SO_2$/H_2O/40 ^oC, (ix) BnBr/Ag_2O/DMF/0 ^oC, (x) DIBAL-H/Et_2O/-90 ^oC, (xi) KHMDS/THF/-78 ^oC, (xii) TBHP/*tert*-BuOH-H_2O (1:1)/reflux, (xiii) Heptylmagnesium bromide/THF/CuI/-20 ^oC, (xiv) TBSCl/imidazole/CH_2Cl_2, (xv) *p*-TSA/MeOH/0 ^oC, (xvi) Dess-Martin periodinane/$NaHCO_3$/ CH_2Cl_2, (xvii) $NaClO_2$/$NaHPO_4$/Me_2C=CHMe/*tert*-BuOH-H_2O, (xviii) DDQ/CH_2Cl_2-H_2O (10:1), (xix) HCl (cat)/ MeOH/0 ^oC.

Scheme II.1.1.

Its epoxidation with *m*-CPBA and Jacobsen's hydrolytic kinetic resolution gave **3** (obtained from the resolved diol). This on regioselective ring opening with 1-phenyl-1H-tetrazole-5-thiol (PT-SH)/monmorillonite K-10 clay furnished **4**, which was oxidized to the sulfone **5** by *m*-CPBA oxidation. In a parallel sequence of reactions, the vitamin C-derived threonic acid derivative **6** was esterified, benzylated and subjected to DIBAL-H reduction to obtain the aldehyde **7**. A Julia-Kocienski olefination between **5** and **7**, followed by acetonide deprotection under neutral conditions afforded the diol **8**. Its mono-tosylation at the primary

carbinol group and base-treatment furnished the corresponding terminal epoxide, which on reaction with a suitable Grignard reagent followed by silylation gave **9**. Selective deprotection of its -CH_2OTBS group, Dess-Martin periodinane oxidation, Pinnick oxidation and desilylation completed the synthesis.[33b]

II.1.3. Present Work

The primary motivation of the present work stems from our own interest in natural immunomodulatory, anti-ulcer, anti-inflammatory, and anti-neoplastic agents.[28] Especially the reported immunomodulatory activity of **Id** was very attractive because many such agents can boost human health. In view of these, and lack of any synthesis of **Id** prompted us to develop first asymmetric synthesis[4a] of the (6*S*,9*R*,10*S*)-stereomer of the compound **Id**.

In the present work, a convergent strategy towards the synthesis of the C_{18} fatty acid **Id** was conceived using the chiral building blocks, '**A**' and '**B**'. It was envisaged that the building blocks, '**A**' and '**B**' can be constructed by carrying out metal-mediated diastereoselective addition of alkyl/allyl halides to the aldehyde **10**. This would provide the required stereogenic diol/carbinol moieties of the '**A**' and '**B**' units, while the cyclohexylidenedioxy group can be functionalized to provide the terminal alkene functionality. A cross metathesis reaction between the '**A**' and '**B**' units can furnish the entire C_{18}-carboxylic acid framework with the required chiral carbinol moieties at the appropriate location and the desired 7*E*-olefin function of the target oxylipin (**Figure II.1.1.**).

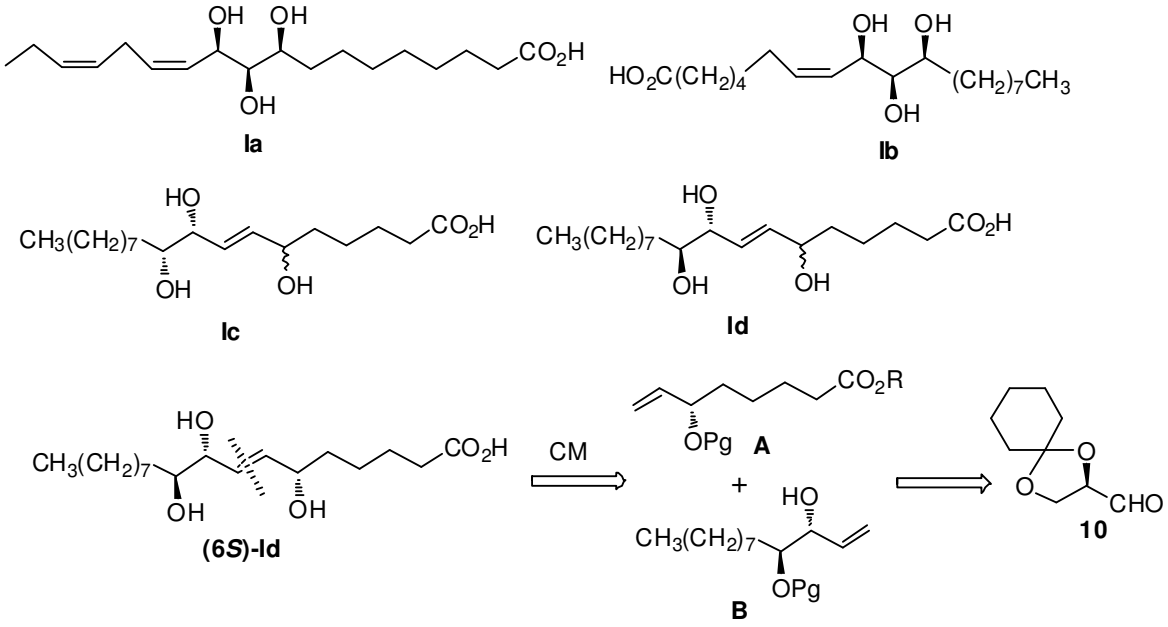


Figure II.1.1. Chemical structures of the oxylipins **Ia-d** and retrosynthesis of **Id**.

The synthesis (**Scheme II.1.2.**) commenced by a diastereoselective allylation of the aldehyde **10**. Earlier using the Luche protocol, the Zn-dust-mediated reaction of allyl bromide with **10** in THF-aqueous NH_4Cl furnished the homoallylic alcohol **11** along with its 3*R*-epimer in 90:10 diasteromeric ratio (dr).[34a] However, we were unable to reproduce the results and obtained **11** with a dr = 69:31. In view of this, we followed a recently reported Ga-mediated allylation protocol in the room temperature ionic liquid, [bmim][Br].[34b] The reaction proceeded with excellent diastereoselectivity (*syn*/*anti* = 5:95) to produce **11** in appreciable yield. The pure *anti*-isomer **11** was easily separated from the trace quantity of the 3*R*-epimer (formed in the reaction) by column chromatography and the relative stereochemistries of its stereogenic centres were confirmed from the ^{1}H NMR multiplets at δ 3.71-3.79 and 3.88-4.01 for the carbinol protons (1:3 ratio). The ^{1}H NMR multiplets of the designated protons appear at δ 3.52-3.58, 3.68-3.76 and 3.93-4.02 in 1:1:2 ratio for the *syn*-isomer.

The alcohol **11** was subjected to silylation with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole and *N*,*N*-dimethylaminopyridine (DMAP) to furnish **12**. Its formation was revealed from the absence of the IR OH stretching band, and appearance of the ^{1}H NMR singlet at δ 1.07 (9H) along with the aromatic multiplets at δ 7.36-7.44 (6H) and δ 7.67-7.76 (4H) for the TBDPS moiety. The alkene function of **12** was regioselectively hydroborated with BH_3-Me_2S (BMS) and the intermediate trialkyl borane oxidized with H_2O_2/NaOH to afford the alcohol **13**. Appearance of the hydroxyl IR band (3433 cm^{-1}) and the ^{1}H NMR triplets (δ 3.39, 2H) for the –CH_2OH group in place of the olefinic resonances confirmed its formation. This on oxidation with pyridinium chlorochromate (PCC) afforded the aldehyde **14**. This was characterized from the IR bands at 2714 (-CHO) and 1729 (-CO) cm^{-1}, and the one-proton ^{1}H NMR triplets at δ 9.14 for the CHO protons. Its base-catalyzed Horner-Emmons reaction with triethyl phosphonoacetate

produced the conjugated ester **15**. The strong IR peak at 1716 cm^{-1} (ester), and the ^{1}H NMR resonances at δ 4.14 (q, $-CO_2CH_2$), the olefinic resonances at δ 5.66 (d) and δ 6.71-6.79 (m) as well as the ^{13}C NMR peak at δ 166.5 revealed its identity. The ^{1}H NMR coupling constant (16.0 Hz) for its olefinic doublets revealed it to be predominantly the *E*-isomer, although this was of no consequence for the synthesis. Catalytic hydrogenation of **15** gave the ester **16** (lack of olefinic NMR resonances), which on treatment with aqueous trifluoroacetic acid (TFA) furnished the diol ester **17**. A strong IR band at 3455 cm^{-1} and a broad ^{1}H NMR signal at δ 2.43 for the OH group in place of the ^{1}H NMR resonances for the cyclohexyl protons confirmed its identity. Reaction of the diol **17** with excess *p*-toluenesulphonyl chloride (*p*-TsCl) in the presence of pyridine furnished the corresponding ditosylate [IR bands at 1370 and 1177 cm^{-1}; ^{1}H NMR six-proton singlet at δ 2.45 (CH_3-Ph)], which on heating with NaI and Zn-dust in DMF afforded the alkene ester **18** cleanly. The olefinic resonances at δ 4.92-5.01 (m, 2H) and δ 5.70-5.80 (m, 1H) in its ^{1}H NMR spectrum were consistent with its structure (^{1}H and ^{13}C NMR spectra shown in **Figures II.1.2.** and **II.1.3.**). Compound **18** is the required **A**-unit equivalent of **Figure II.1.1**.

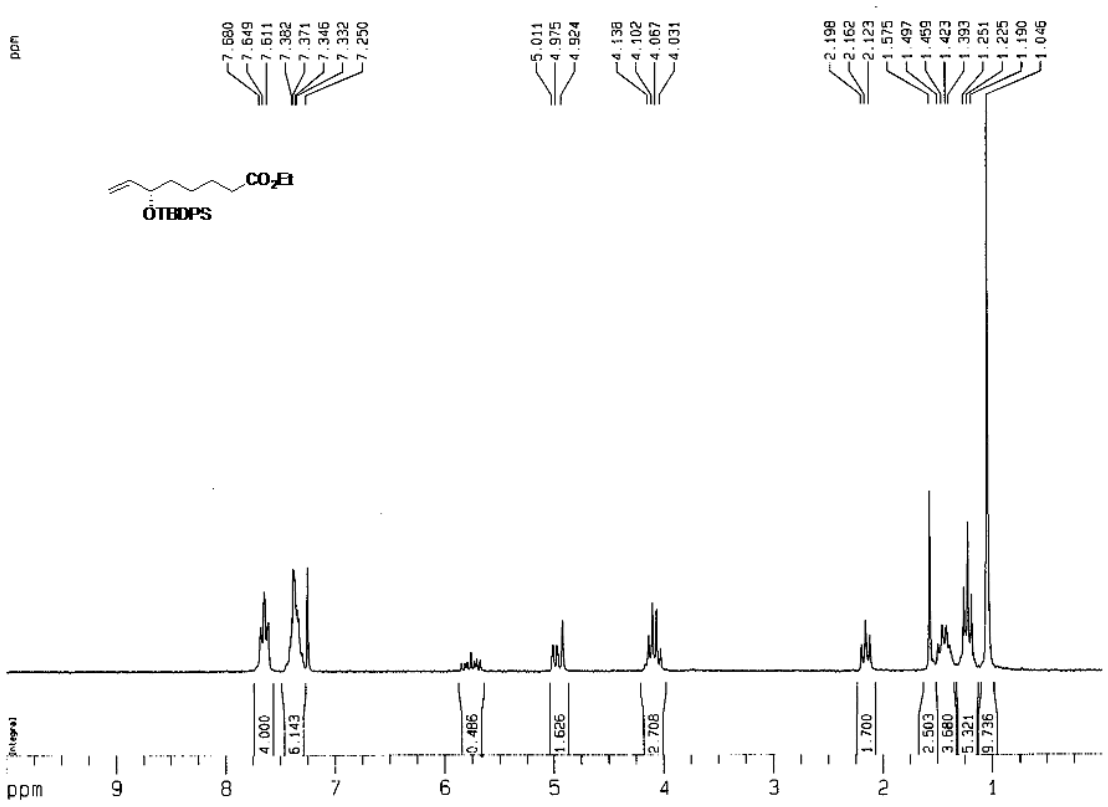


Figure II.1.2. The ^{1}H NMR of **18**.

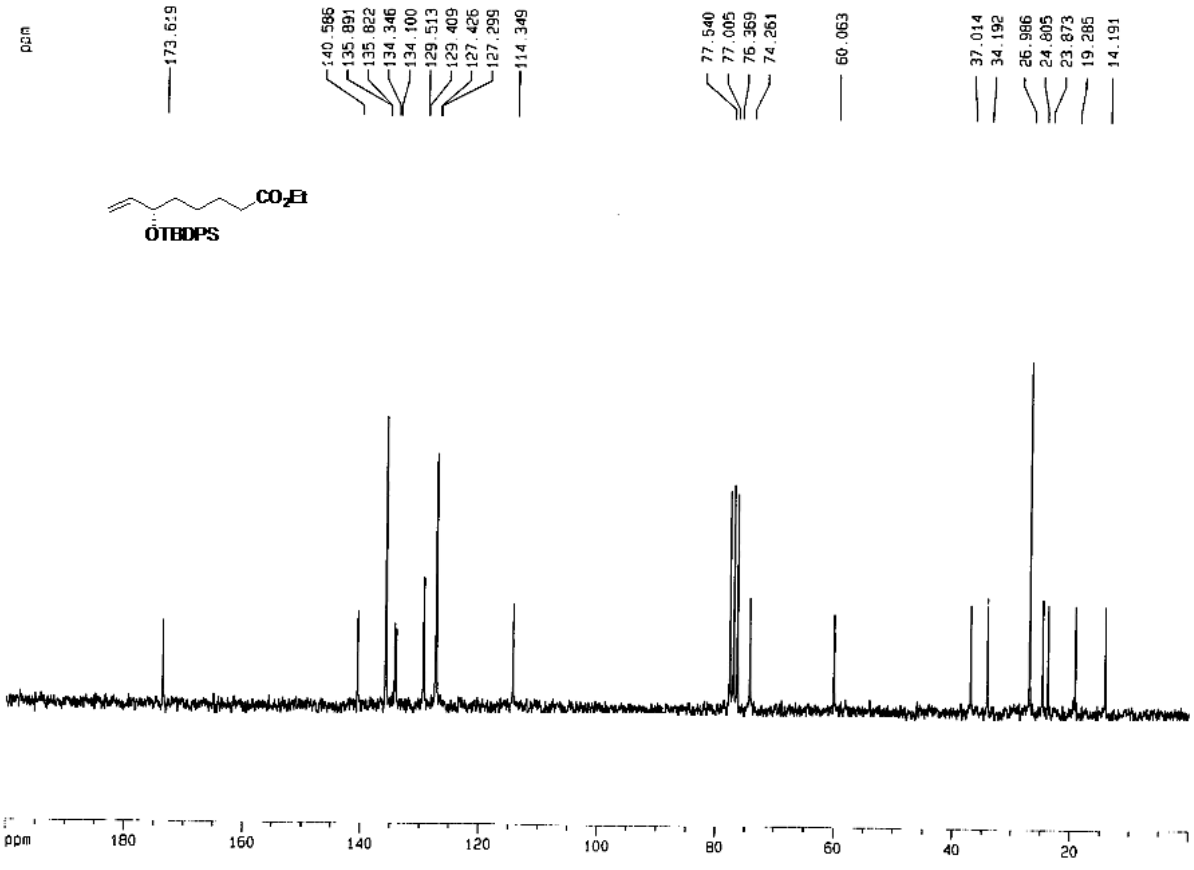


Figure II.1.3. The ^{13}C NMR of **18**.

For the synthesis of the other chiral building block **23** (**B** equivalent), we resorted to addition of alkyl lithium to the aldehyde **10**, as reported by our group.[35] Thus, the aldehyde **10** was reacted with $CH_3(CH_2)_7Li$ to furnish the *anti*-triol derivative **19** almost exclusively (dr = 95:5). When the reaction was carried out with the Grignard reagent $CH_3(CH_2)_7MgBr$, compound **19** was obtained as a 29:71 mixture of the *syn*/*anti* isomers. The *anti*-compound **19**[36] could be easily isolated as a pure enantiomer by column chromatography. The *anti*-stereochemistry of **19** was confirmed from the ^1H NMR resonances of the carbinol protons that appeared at δ 3.70-3.78 (1H) and δ 3.86-3.97 (m, 3H). For the corresponding *syn*-isomer, these appeared as 1:1:2 multiplets at δ 3.46-3.48, δ 3.68-3.72 and δ 3.94-4.02. Silylation of the alcohol **19** with TBDPSCl/DMAP in CH_2Cl_2 produced compound **20** (absence of IR hydroxyl bands and appearance of the NMR resonances for the TBDPS group), which on treatment with aqueous TFA furnished the diol **21** (IR peak at 3398 cm^{-1} and absence of upfield cyclohexyl ^1H NMR resonances and acetal ^{13}C peak at ~ δ 108). A regioselective tosylation of the primary carbinol function of **21** was accomplished uneventfully by reaction with *p*-TsCl/pyridine. Its IR spectrum showed bands at 3528 cm^{-1} (OH) as well as at 1362 and 1177 cm^{-1} (OTs), while the ^1H NMR three-proton singlet at δ 2.45 accounted for the CH_3-Ph group. The resultant monotosylate was converted to the epoxide **22** by treatment with K_2CO_3 in MeOH. This was characterized from the ^1H NMR resonances at δ 2.11-2.16 (m, 1H), δ 2.43-2.48 (m, 1H) and δ 2.86-2.91 (m, 1H) along with the ^{13}C NMR peaks at ~ δ 45.9 and δ 54.1 for the epoxide functionality. Next, the sulphorane, generated by a base (*n*-BuLi)-catalyzed deprotonation of Me_3SI was reacted with the epoxide **22**. The reaction proceeded regioselectively at the C-1 position to afford the allylic alcohol **23** as the **B** unit equivalent. Compound **23** was characterized from its ^1H and ^{13}C NMR spectra (**Figures II.1.4.** and **II.1.5.**). This simple protocol of converting the cyclohexylidenedioxy moiety of **10** into a one-carbon homologated allylic alcohol has tremendous potential in organic synthesis.

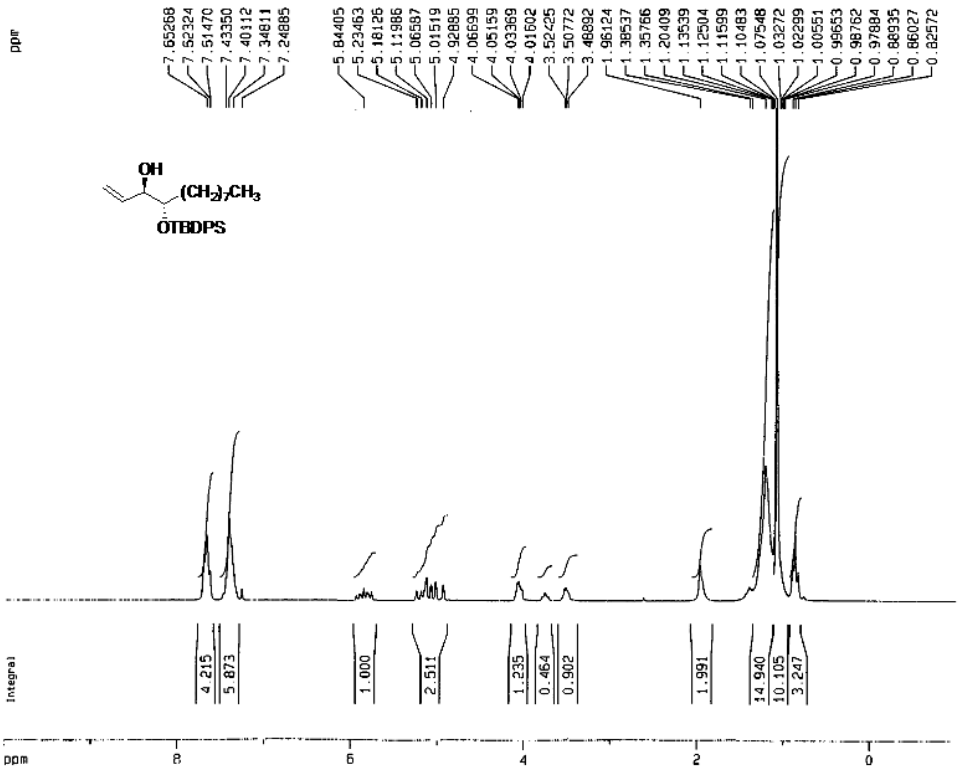


Figure II.1.4. ^{1}H NMR spectrum of **23.**

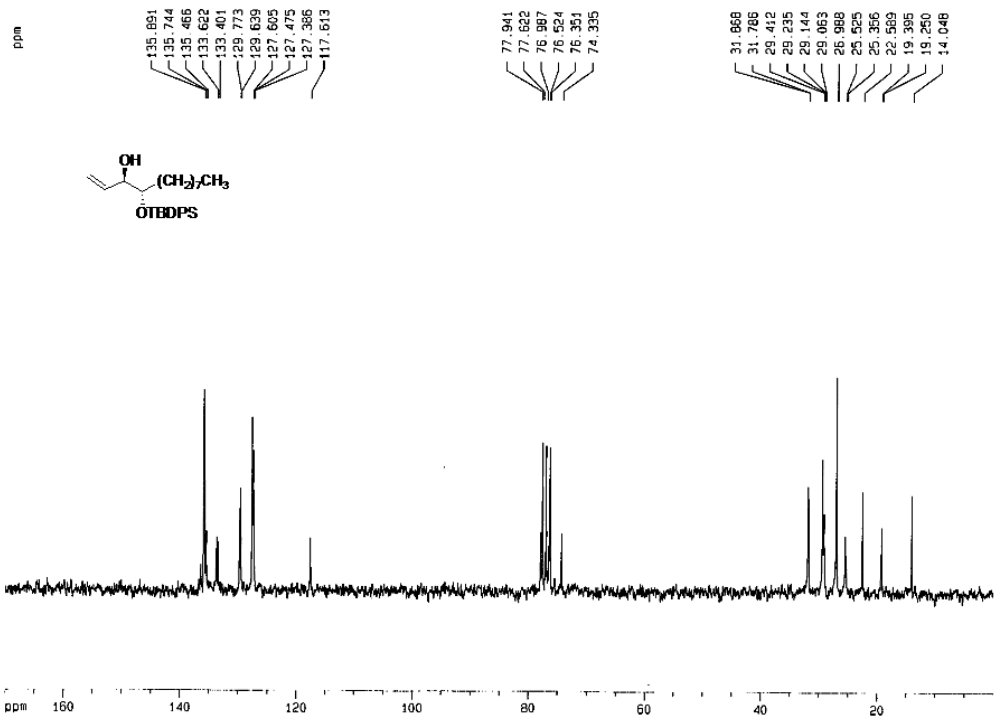


Figure II.1.5. ^{13}C NMR spectrum of **23.**

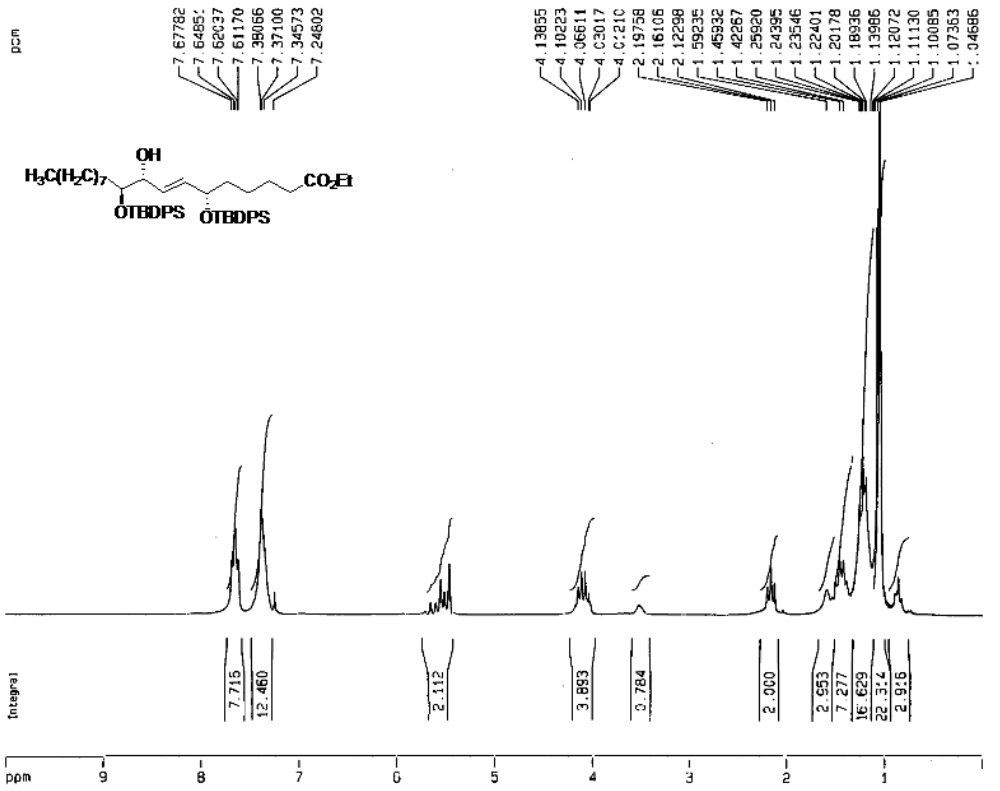


Figure II.1.6. ^{1}H NMR spectrum of **24**.

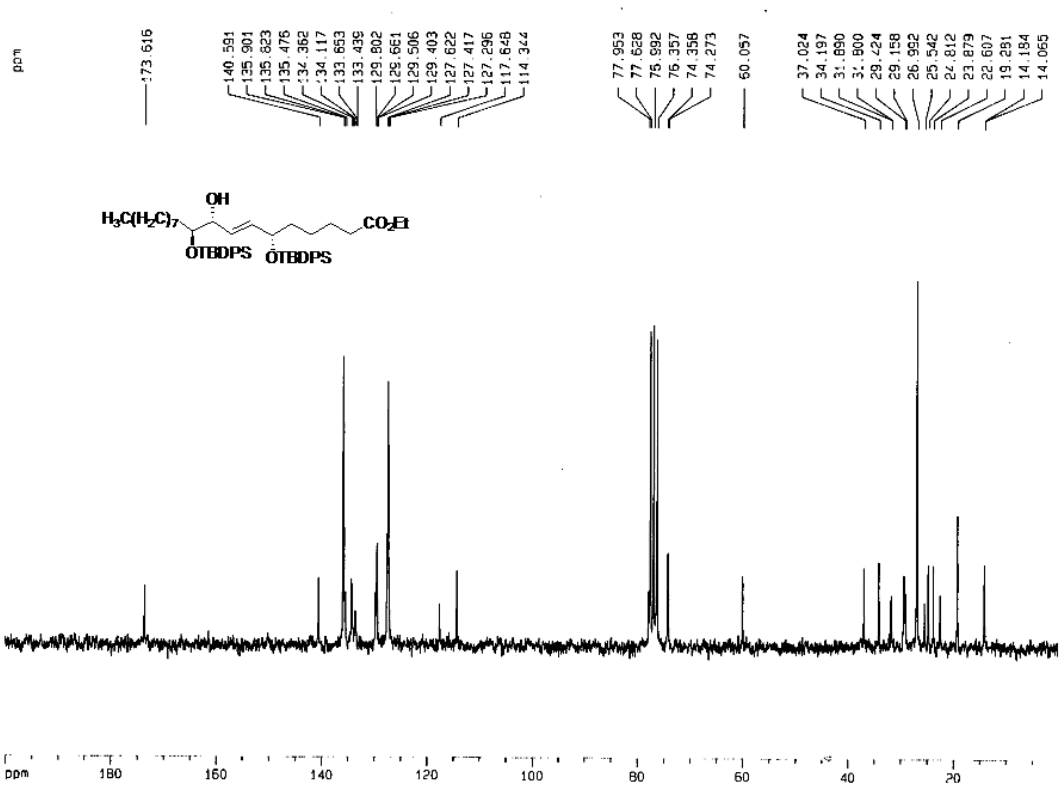
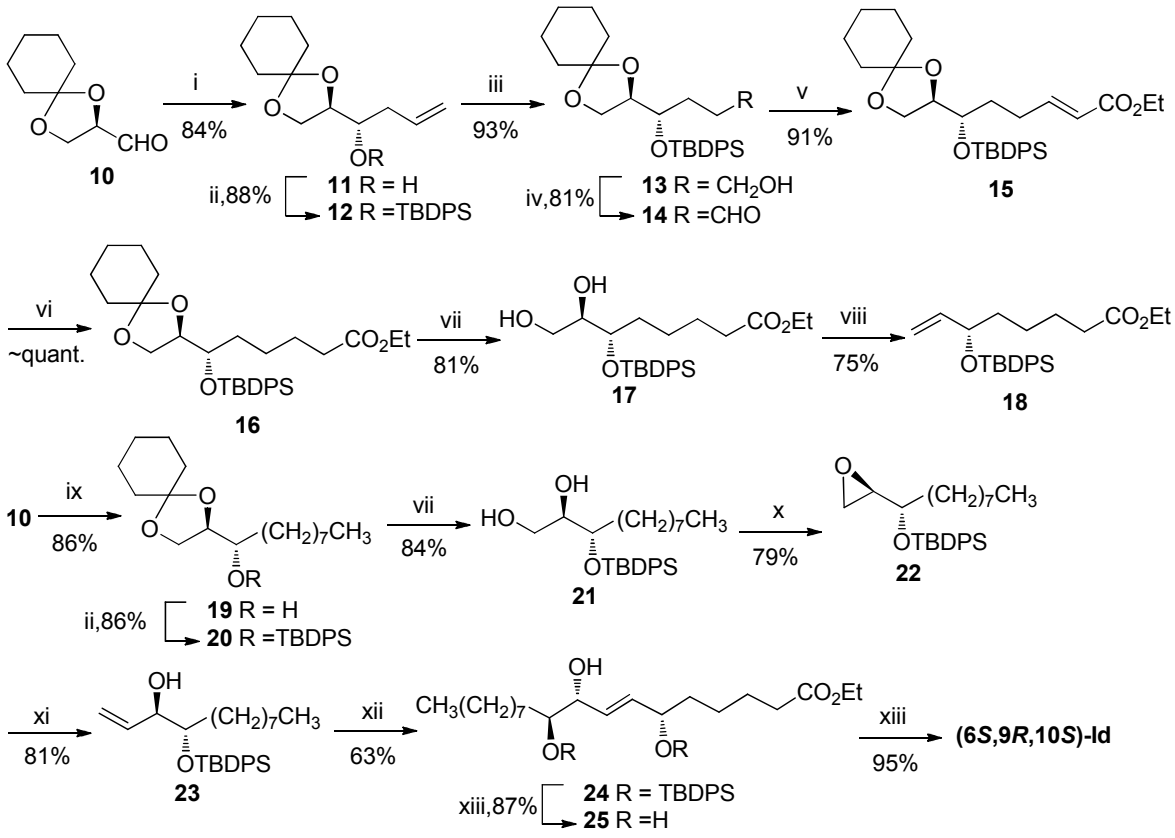


Figure II.1.7. ^{13}C NMR spectrum of **24**.

Besides its IR bands at 3475 cm^{-1} (OH), and at 997 and 925 cm^{-1} (terminal alkene), its ^1H NMR resonances at δ 4.01-4.07 (allylic carbinol) along with the olefinic multiplets at δ 4.93-5.23 (2H) and 5.74-5.95 (1H) confirmed its formation.

The compounds **23** and **18** were subsequently coupled by a cross metathesis reaction. The olefin metathesis reactions, pioneered by Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock have turned out to be promising strategies for the construction of C-C bonds.[37] Different versions of the reaction *viz*. cross metathesis (CM), ring-opening metathesis (ROM), ring-closing metathesis (RCM), ring-opening metathesis polymerization (ROMP), acyclic diene metathesis (ADMET) and ethenolysis have assumed major significance in the chemical industries, as these create fewer undesired by-products and hazardous wastes than alternative organic reactions. Moreover, these entail easy synthesis of new and known molecules to streamline the development and industrial production of pharmaceuticals, plastics and other materials at lower costs. In view of these, the inventors collectively received the 2005 Nobel Prize in Chemistry.[38] Our group has successfully utilized cross metathesis of terminal alkenes to formulate efficient syntheses of three hydroxy fatty acids,[29h,i] while the ring-closing metathesis reaction has been used to construct several macrolides (presented in Chapter III).[39] In the present synthesis, the alcohol **23** was subjected to a cross-metathesis reaction with the ester **18** in the presence of Grubbs' II catalyst to furnish the desired alcohol **24** (63%, based on **18**) along with the unreacted substrates **18** and **23**. The homo-dimerized product of **18** was also obtained in 10-12% yields respectively. We used the alcohol **23** in excess, as its dimerized product was expected to be highly polar, to ensure easy separation from the alcohol **24**. The ^1H NMR olefinic multuplets at δ 5.68-5.72 (2H) in place of the terminal olefinic resonances along with other relevant NMR signals confirmed its structure (^1H and ^{13}C NMR spectra shown in **Figures II.1.6.** and **II.1.7.**). Increasing steric bulk through addition of a hydroxyl protection often reduces the cross-

metathesis reactivity of the alkenols.[37f] Hence we used the unprotected alcohol **23** directly for the metathesis reaction. This also helped to avoid the additional carbinol protection/deprotection steps. Desilylation of the compound **24** with Bu_4NF afforded the ester **25** (IR OH band at 3435 cm^{-1} and absence of the TBDPS NMR resonances), which on alkaline hydrolysis furnished the trihydroxy acid **Id**. It showed IR bands at 3630-3550 and 1729 cm^{-1}, typical of the –COOH functionality.



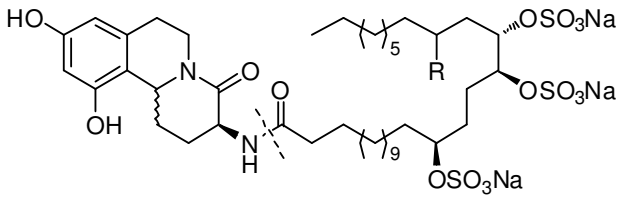
i) Allyl bromide/Ga/[bmim][Br]/4 h, (ii) TBDPSCl/imidazole/DMAP/CH_2Cl_2/25 ^oC/10 h, iii) BMS/THF/ 0^o C/3 h; aqueous NaOH/H_2O_2/0 to 25 ^oC/15 h, (iv) PCC/NaOAc/CH_2Cl_2/0 ^oC/3 h, v) NaH/THF /$(EtO)_2P(O)CH_2CO_2Et$/0 to 25 ^oC/18 h, vi) H_2/10% Pd-C/EtOH/25 ^oC/22 h, (vii) Aqueous 80% TFA/CH_2Cl_2/0 ^oC/3 h/25 ^oC/18-24 h, (viii) *p*-TsCl/pyridine/0 to 25 ^oC/24 h (89%); Zn/NaI/DMF/80 ^oC/4 h, (ix) $CH_3(CH_2)_7Li$/THF/-78 to 25 ^oC/3 h, (x) *p*-TsCl/pyridine/0 ^oC/18 h; K_2CO_3/MeOH/25 ^oC/3 h, xi) Me_3SI/*n*-BuLi/THF/-40 ^oC/4 h/25 ^oC/12 h, (xii) **18**/Grubbs' II/CH_2Cl_2/25 ^oC/22 h, (xii) Bu_4NF/ THF/0 ^oC/3 h, (xiii) Ethanolic KOH/25 ^oC/4 h.

Scheme II.1.2.

II.2. ASYMMETRIC SYNTHESIS OF THE HYDROXY ACID SEGMENT OF SCHULZEINES B and C

II.2.1. Introduction

The tetrahydroisoquinoline alkaloids, schulzeines A-C (**II**-**IV**) were isolated by a bioassay-guided screening of the hydrophilic extract of the marine sponge *Penares schulzei*, and found to inhibit yeast α-glucosidase with IC_{50} values of 48-170 nM and viral neuraminidase with IC_{50} values ~ μM.[40] The chemical structures of schluzeines as well as the relative stereochemistries of their stereogenic centres were elucidated by chemical degradation and extensive 2D-NMR studies. The Mosher method was used to establish their absolute configurations. Schulzeines encompass the 9,11-tetrahydroisoquinoline constellation, comprising of a fused δ-lactam ring (**A**) and a C_{28} sulfated fatty acid side chain (**B**) linked via an amide bond (**Figure II.2.1.**).[41]



II: Schulzeine A: R = Me, (11b*R*); **III** Schulzeine B: R = H, (11b*S*)*;*
IV: Schulzeine C: R = H, (11b*R*)

Figure II.2.1. Chemical structures of schulzeines A-C.

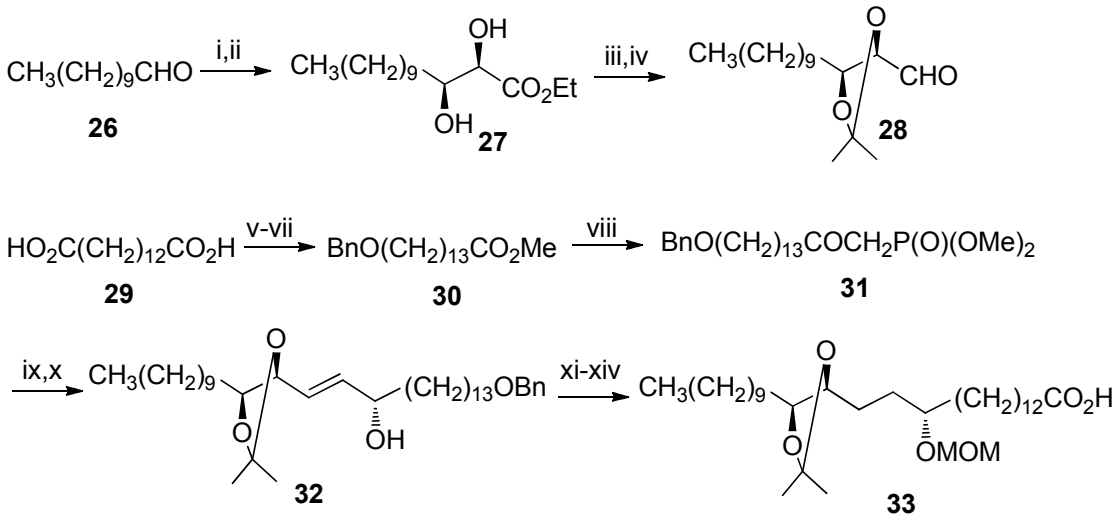
Schulzeines B and C differ in the stereochemistry at the C-11b of the tetrahydroisoquinoline moiety, while schulzeine A possesses an additional C-20 methyl substitution in the fatty acid chain. More recently, the stereochemistry of this stereogenic centre in schulzeine A has been revised.[42] Although the pharmacophore of the schluzeines has not been identified so far, their *O*-sulfated fatty acid segment is structurally related to other glucosidase inhibitors, including penasulfate[43a] and the penarolides.[43b] The glycosidase inhibitors are of importance in drug development because of their profound effect on glycoprotein processing, oligosaccharide metabolism, and cell-cell and cell-virus recognition

processes.[44] In particular, the α-glucosidase inhibitors are potential therapeutics for the treatment of viral diseases, cancer, and diabetes.[45]

II.2.2. Previous Syntheses

The intriguing bioactivity combined with the unique structure of schulzeines aroused a few synthetic efforts towards these targets.[46] Of these, the first synthesis targeted the tetrahydroisoquinoline subunit of schulzeines only,[46a] hence not discussed. The two other routes were similar, both using Sharpless' asymmetric dihydroxylation (ADH) and asymmetric ketone reduction for installing the stereogenic centres.

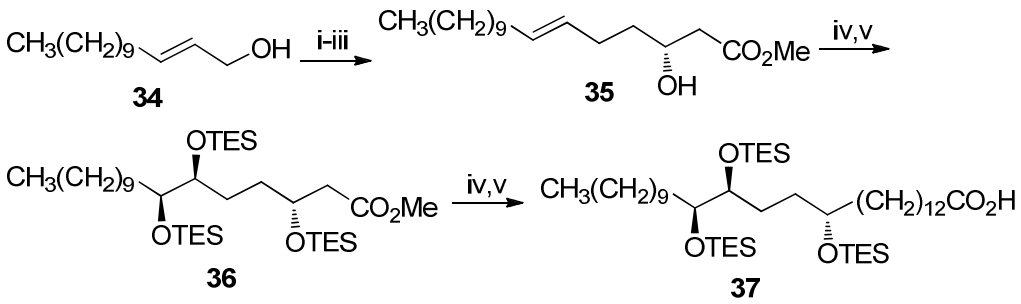
In one of these (**Scheme II.2.1.**),[46b] the aldehyde **26** was two-carbon homologated by Wittig reaction with a suitable phosphorane and subjected to an ADH reaction with the AD-mix-β reagent to obtain **27**. After protecting its diol moiety as an acetonide, the compound was converted to the aldehyde **28** by DIBAL-H reduction of its ester group. In a parallel sequence, the diacid **29** was converted to the ester **30** by borane reduction, benzylation and esterification. This was converted to the phosphonate **31** by an *n*-BuLi-mediated condensation with $MeP(O)(OMe)_2$. A Horner-Emmons reaction between **31** and **28** followed by a BINAL-H mediated asymmetric ketone reduction furnished **32**. Its MOM protection, catalytic hydrogenation, IBX oxidation followed by Pinnick oxidation afforded the schulzeines B and C segment **33**.



i) $Ph_3P{=}CHCO_2Et$/benzene, ii) AD-mix β/*tert*-BuOH-H_2O, iii) 2,2-Dimethoxypropane/PTS, iv) DIBAL-H/CH_2Cl_2, v) $BH_3.Me_2S$/THF, vi) BnCl/KOH/reflux, vii) MeOH/PTS/reflux, viii) $MeP(O)(OMe)_2$/*n*-BuLi/THF/-78 °C, ix) DBU/LiCl/MeCN/**28**, x) (*S*)-BINAL-H/THF/-78 °C, xi) MOMCl/Hünig's base/CH_2Cl_2, xii) H_2/Pd(OH)$_2$-C/EtOAc, xiii) IBX/DMSO, xiv) $NaClO_2$/$NaH_2PO_4.2H_2O$/*tert*-BuOH-H_2O/2-methyl-2-butene.

Scheme II.2.1.

In another synthesis, (**Scheme II.2.2.**),[46c] the alcohol **34** was converted to the corresponding bromide, used for γ-allylation of methyl acetoacetate and the resultant β-ketoester subjected to asymmetric catalytic hydrogenation to furnish **35**. Its ADH reaction with the AD-mix-α reagent and silyl protection of the resultant triol gave the ester **36**. Its DIBAL-H reduction followed by a Wittig reaction with a suitable phosphonium salt and catalytic hydrogenation produced the target schulzeine segment **37**.



i) NBS/PPh_3/CH_2Cl_2, ii) NaH,*n*-BuLi/$MeCOCH_2CO_2Me$/THF/-78 °C, iii)(*R*)-BINAP-$RuBr_2$/H_2/MeOH/80 °C, iv) AD-mix-α/*tert*-BuOH-H_2O, v) TESCl/CH_2Cl_2, vi) DIBAL-H/CH_2Cl_2/-78 °C, vii) $BnO_2C(CH_2)_{10}PPh_3$ /KHMDS,viii) H_2/Pd(OH)$_2$-C/2,6-lutidine/EtOH.

Scheme II.2.2.

II.2.3. Present Work

The primary aim of the present work was to formulate a simple and efficient asymmetric synthesis of the common C_{28}-hydroxyalkyl ester unit **53** of the schulzeines B and C. We chose compound **53** as the target, as it can be easily converted to schulzeines B and C by amidation of the required isoquinoline core and a late stage trisulfation. To this end, an enantio-convergent synthesis of **53** was conceived using a cross metathesis reaction between the building blocks $\mathbf{B^1}$ and $\mathbf{B^2}$ (**Figure II.2.2.**). A similar strategy was also used in the synthesis of **Id**. We envisaged that the required building blocks can be individually synthesized by a biocatalytic route, and using the aldehyde **10** respectively.

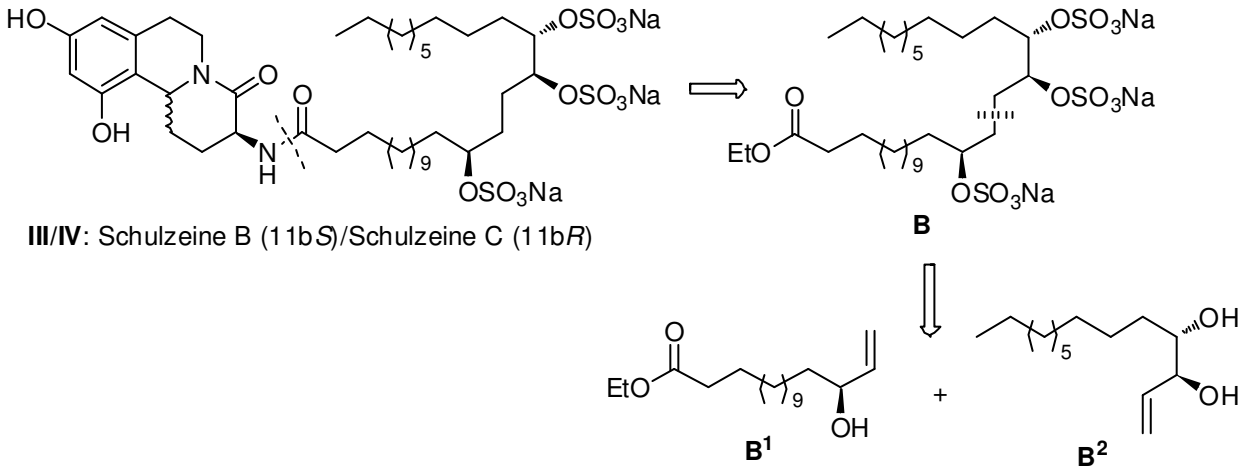
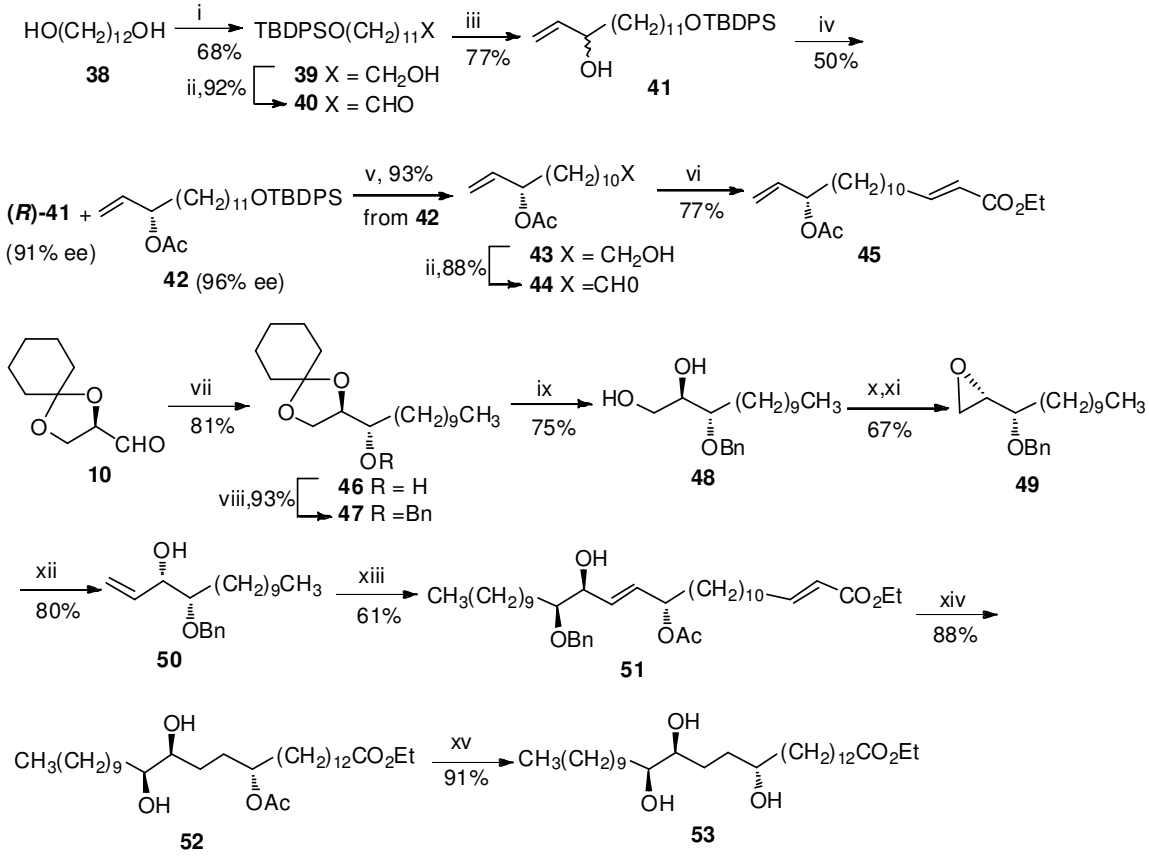


Figure II.2.2. Retrosynthesis of the polyol segment of the schulzeines B and C.

As per the synthetic plan (**Scheme III.2.3.**), the commercially available diol **38** was monosilylated with TBDPSCl/DMAP to furnish compound **39**. Its formation was revealed from the ^{1}H NMR *tert*-butyl singlet at δ 1.04 (9H) along with the aromatic multiplets at δ 7.25-7.41 (6H) and δ 7.64-7.69 (4H) for the TBDPS group. This on PCC oxidation afforded the aldehyde **40** (IR CHO stretching bands at 2712 and 1726 cm^{-1}, ^{1}H NMR triplets at δ 9.75 (J = 1.2 Hz) and ^{13}C peak at δ 203.0). Its reaction with vinylmagnesium bromide afforded the allylic alcohol (±)-**41**, which was characterized from the ^{1}H NMR terminal olefinic signals at δ 5.06-5.26 (2H) and δ 5.78-5.98 (1H).

For its resolution, a lipase-catalyzed *trans*-acetylation appeared promising. We were particularly interested in the lipase preparation, Novozym 435® due to its ability in resolving methylcarbinols,[29g] and allylic alcohols,[29h] as observed from our group. The choice of the inexpensive vinyl acetate as the acyl donor was to ensure irreversibility in the acylation reaction. Also, it assists in easy isolation of the products, since it is volatile. True to our expectation, the alcohol (±)-**41** could be efficiently resolved with Novozym 435®/vinyl acetate to obtain the (*S*)-acetate **42** (96% ee) and (*R*)-**41** (91% ee) at ~50% conversion (5.5 h).



i) TBDPSCl/imidazole/DMAP/CH_2Cl_2/25 °C/8 h (68%), ii) PCC/NaOAc/CH_2Cl_2/25 °C/3 h (**40**: 92%; **44**: 88%), iii) CH_2=CHMgBr/THF/25 °C/6 h (77%), iv) Vinyl acetate/Novozym 435/25 °C/26 h (50%), v) Bu_4NF/ THF/0 to 25 °C/3 h (93%), vi) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$/0 to 25 °C/18 h (77%), vii) $CH_3(CH_2)_9Li$/ THF/-78 °C/3 h (81%), viii) NaH/THF/BnBr/Bu_4NI/4 h (93%), ix) Aqueous 2N HCl/25 °C/6 h (75%), x) TMSCl/EtOAc/-20 °C/20 min; MsCl/Et_3N/-20 °C/30 min; aqueous 2N HCl/25 °C/1 h (79%), xi) K_2CO_3/MeOH/25 °C/3 h (84%), xii) Me_3SI/BuLi/THF/-40 °C/1 h, -40 °C/3 h then 25 °C/12 h (80%), xiii) **45**/Grubbs' II catalyst/CH_2Cl_2/25 °C/22 h (61% based on **50**), xiv) H_2/10% Pd-C/EtOH/25 °C (88%), xv) Amberlyst 15®/EtOH/25 °C/18 h (91%).

Scheme II.2.3.

The IR spectrum of **42** showed an IR peak at 1740 cm^{-1}, and its ^1H NMR and ^{13}C spectra revealed peaks at δ 2.04 (s, 3H) and at δ 170.2 respectively, characteristic of the

acetate functionality. For determining the % ees of the products, a part of the acetate (*S*)-**42** was hydrolyzed with KOH/MeOH to furnish the alcohol (*S*)-**41**. The % ees of the enantiomeric alcohols (*R*)- and (*S*)-**41** were determined from the relative intensities of the methoxyl resonances of the corresponding MTPA esters, prepared using (*R*)-α-methoxytrifluoromethyl phenylacetyl (MTPA) chloride.[14b]

The acetate **42** was desilylated with Bu_4NF to furnish the primary alcohol **43** (absence of NMR peaks for the TBDPS group), which was used for the synthesis of the building block **45** (**B**$^{\mathbf{1}}$ equivalent). For assigning the configuration of **42**, a part of the alcohol **43** was mesylated and subsequently reduced with $LiAlH_4$ to furnish (*S*)-tetradec-1-en-3-ol. Comparison of its optical rotation with the reported value established its configuration.[47] Next, the alcohol **43** was oxidized with PCC to furnish the aldehyde **44** (IR: 2716, 1737 cm^{-1}; ^1H NMR triplets at δ 9.72 and ^{13}C NMR peak at δ 202.1). This on a Wittig-Horner reaction with triethyl phosphonoacetate furnished the conjugated ester **45**. Its IR spectrum showed IR bands at 1739 (ester), 1722 (OAc) and 982 (*E*-alkene) cm^{-1} in place of the CHO bands. Likewise, its ^1H NMR doublets at δ 5.79 with a *J*-value of 15.8 Hz ascertained the *E*-geometry of the incipient olefin function. The ^1H and ^{13}C NMR spectra of **45** are shown in **Figures II.2.3.** and **II.2.4**.

For the other building block **50** (**B**$^{\mathbf{2}}$ equivalent), following our own methodology,[35] the aldehyde **10** was reacted with $CH_3(CH_2)_9Li$ to furnish the *anti*-triol derivative **46** almost exclusively (dr: = 96:4). Use of the corresponding Grignard reagent produced a 22:78 mixture of *syn*/*anti* triol derivative. The stereochemically pure *anti*-compound **46**[48] was easily obtained by column chromatography. Its 2,3-*anti*-stereochemistry was confirmed from the ^1H NMR resonances of the carbinol protons that appeared at δ 3.63 (t, 1H) and δ 3.87-3.97 (m, 3H). For the corresponding *syn*-isomer, these appeared at δ 3.46-3.48, δ 3.68-72 and δ 3.94-4.02 as 1:1:2 multiplets.[48] The reaction of **46** with benzyl bromide (BnBr) and Bu_4NI in the

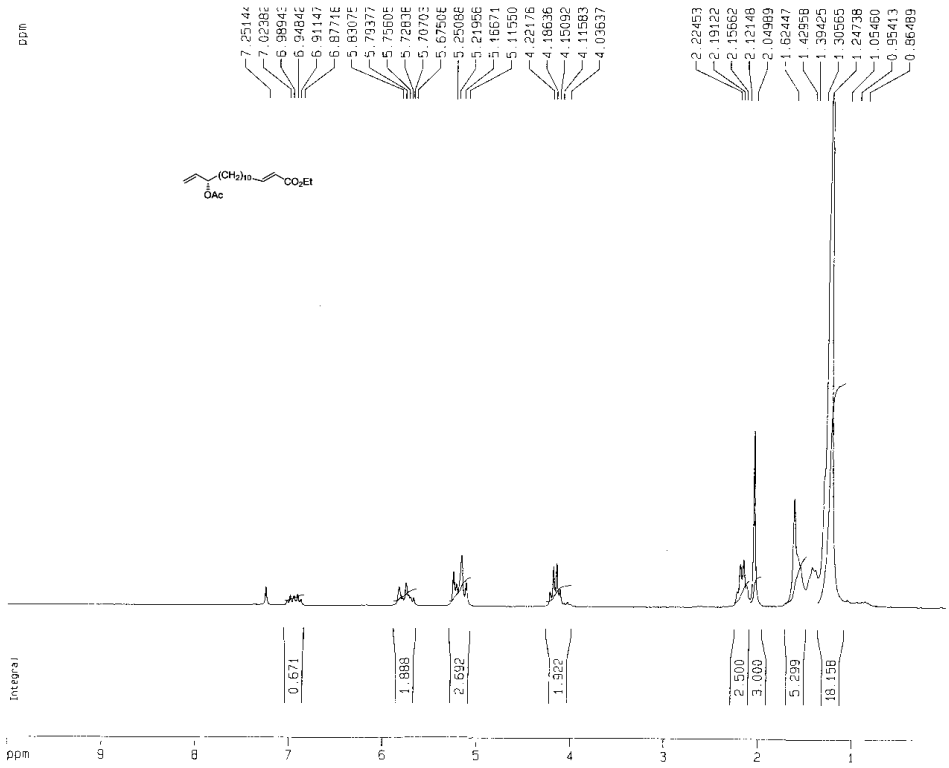


Figure II.2.3. ^{1}H NMR spectrum of **45**.

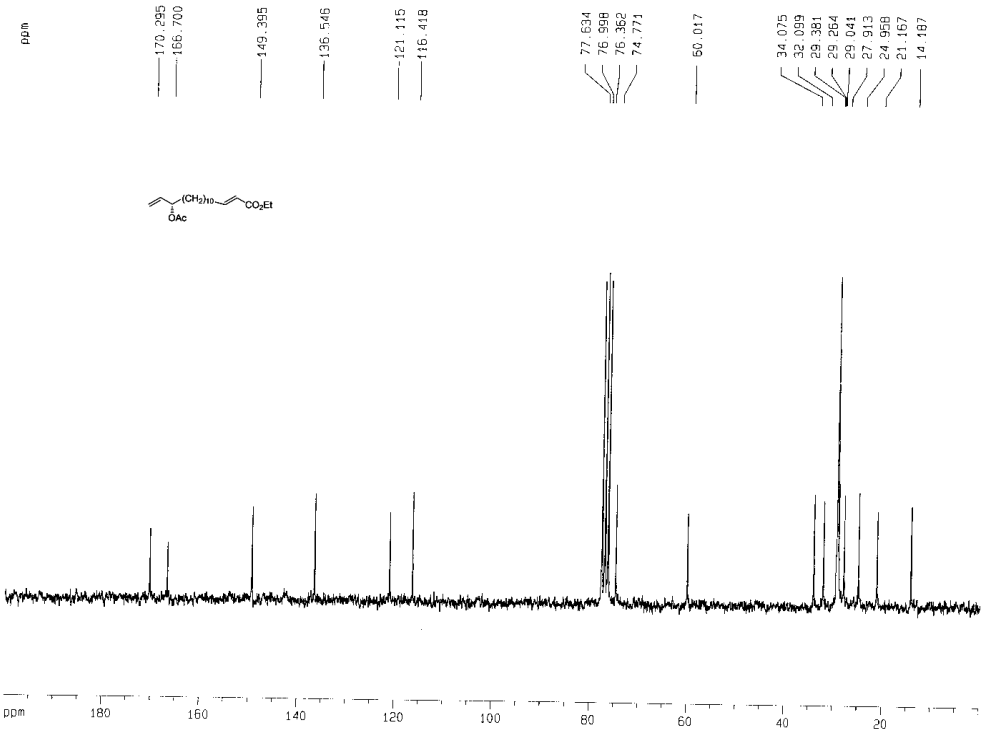


Figure II.2.4. ^{13}C NMR spectrum of **45.**

presence of NaH produced compound **47**. The ^{1}H NMR signals at δ 4.51-4.73 (m, 2H) and at δ 7.29-7.34 (m, 5H) accounted for its Bn group. This on an acid (aqueous HCl)-catalyzed deacetalization furnished the diol **48** that showed absence of NMR resonances for the cyclohexylidene moiety and presence of an IR band at 3398 cm^{-1}. Its reaction with trimethylsilyl chloride (TMSCl) in the presence of Et_3N in EtOAc followed by mesylation of the resultant product with mesyl chloride (MsCl), and subsequent desilylation with aqueous HCl furnished the intermediate C-2 mesylate. After isolation, this was treated with K_2CO_3 in MeOH to furnish the epoxide **49** with inversion of configuration at C-2. The characteristic features of its epoxy group were the ^{1}H NMR resonances at δ 2.48-2.52 (dd, 1H), δ 2.79 (t, 1H) and δ 2.99-3.06 (m, 2H), along with the ^{13}C NMR peaks at δ 43.1 and δ 55.1. The epoxide **49** was subsequently one-carbon homologated with Me_3SI/*n*-BuLi, as before to obtain the allylic alcohol **50**. Appearance of the ^{1}H NMR 2:1 multiplets at δ 5.21-5.41 and δ 5.84-5.95 and the ^{13}C NMR peaks at δ 116.8 and δ 127.8 were indicative of its terminal alkene group.

In the final sequence of reactions, the alcohol **50** was subjected to a cross-metathesis reaction with the allylic acetate **45** in the presence of Grubbs' II catalyst to furnish the desired alcohol **51** (61%, based on conversion of **50**) along with the unreacted alcohols **45** and **50**. The homo-dimerized products of **45** and **50** were obtained in trace amounts. We used the alcohol **50** in excess in view of its easy availability. Further, its dimerizaton (if any) would produce a highly polar product, which can be easily separated from the alcohol **51**. As before, the unprotected alcohol **50** was used directly for the metathesis reaction to ensure good reactivity. The ^{1}H NMR resonances of the newly generated olefinic protons and that at C-2 position appeared together as complex multiplets, precluding the assignment of the geometry of the newly generated olefin function. However, this was not important for the present synthesis. Catalytic hydrogenation of **51** gave the acetoxy ester **52** (absence of olefin NMR

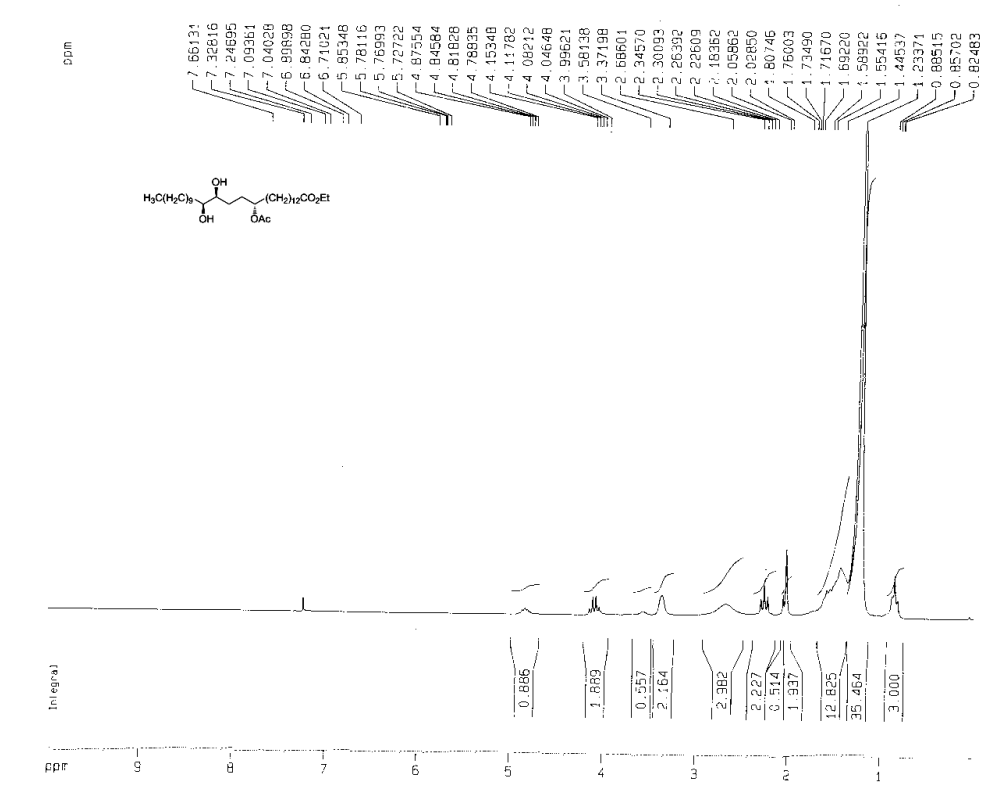


Figure II.2.5. ^{1}H NMR spectrum of **52.**

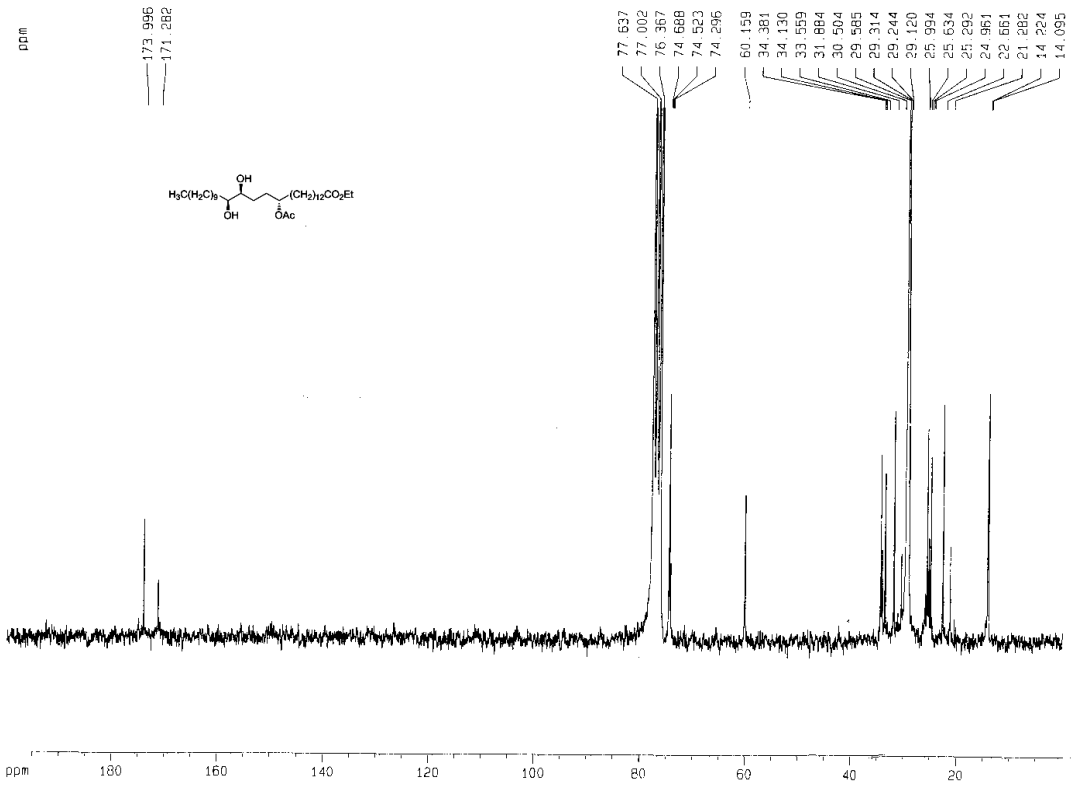


Figure II.2.6. ^{13}C NMR spectrum of **52.**

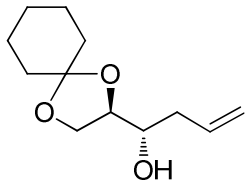
resonances, shown in **Figures II.2.5.** and **II.2.6.**), which was converted to the target hydroxy ester **53** by an acid (Amberlyst 15®)-catalyzed *trans*-esterification with ethanol. Its ^{1}H and ^{13}C NMR resonances were commensurate with its structure.

II.3. EXPERIMENTAL SECTION

General experimental details

The chemicals (Fluka and Lancaster) were used as received. Other reagents were of AR grade. All anhydrous reactions were carried out under an Ar atmosphere, using freshly dried solvents. The organic extracts were dried over anhydrous Na_2SO_4. The IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker (200/300/400/500/700 MHz) spectrometers. The optical rotations were recorded with a Jasco DIP 360 digital polarimeter. The chemical purities of the compounds were determined by CHN analyses with an elemental analyzer (vario Micro cube, Elementar, Germany).

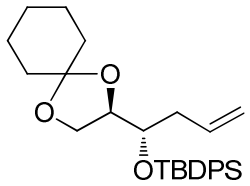
(2*R*,3S)-1,2-Cyclohexylidenedioxy-5-hexene-3-ol 11.



A mixture of Ga metal (0.690 g, 10 mmol) and allyl bromide (1.45 g, 12.0 mmol) in [bmim][Br] (30 mL) was stirred at room temperature for 0.5 h, followed by addition of **10** (1.7 g, 10 mmol). After stirring at room temperature for 4 h, the mixture was extracted with Et_2O (2 × 20 mL), the ether extract evaporated in vacuo and the residue purified by column chromatography (silica gel, 0-15% EtOAc/hexane) to obtain **11** (1.7 g, 81%). colourless oil; $[\alpha]_D^{24}$ +10.2 (*c* 1.38, $CHCl_3$); IR: 3453, 1642, 1101, 1044 cm^{-1}; ^{1}H NMR: δ 1.36-1.38 (m, 2H), 1.55-1.59 (m, 8H), 2.13-2.33 (m overlapped with broad s, 3H), 3.71-3.79 (m, 1H), 3.88-

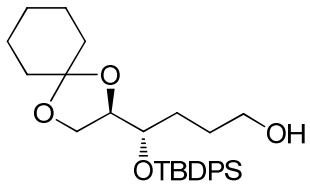
4.01 (m, 3H), 5.13-5.16 (m, 2H), 5.75-5.88 (m,1H); ^{13}C NMR: δ 24.1, 24.3, 25.5, 35.2, 36.6, 38.0, 65.2, 71.0, 78.0, 110.0, 118.6, 134.4.

(4*S*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxyhex-1-ene 12.



To a stirred and cooled (-30 °C) solution of the mixture of **11** (1.48 g, 6.95 mmol), imidazole (0.80 g, 11.80 mmol) and DMAP (catlytic) in CH_2Cl_2 (25 mL) was dropwise added TBDPSCl (2.86 g, 10.4 mmol) in CH_2Cl_2 (10 mL). After stirring the mixture for 10 h at room temperature, it was poured into ice cold H_2O (25 mL), the organic layer was separated and the aqueous portion extracted with $CHCl_3$ (2 × 15 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by purification of the residue by column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **12** (2.8 g, 88%). colorless oil; $[\alpha]_D^{24}$ +16.8 (*c* 1.13, $CHCl_3$); IR: 3070, 1639 cm^{-1}; ^{1}H NMR: δ 1.07 (s, 9H), 1.38-1.44 (m, 2H), 1.50-1.64 (m, 8H), 2.12-2.21 (m, 2H), 3.68-3.79 (m, 1H), 3.89-3.96 (m, 2H), 4.04-4.09 (m, 1H), 4.87-4.99 (m, 2H), 5.74-5.78 (m, 1H), 7.36-7.44 (m, 6H), 7.67-7.76 (m, 4H); ^{13}C NMR: δ 19.3, 23.8, 23.9, 25.2, 26.9, 34.8, 36.1, 38.7, 65.8, 73.1, 77.3, 109.2, 117.4, 127.4, 127.5, 129.6, 129.7, 133.5, 133.8, 133.9, 135.9. Anal. Calcd. for $C_{28}H_{38}O_3Si$: C, 74.62; H, 8.50%. Found: C, 74.48; H, 8.36%.

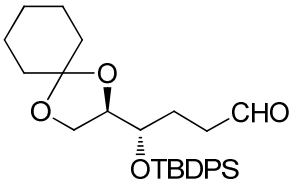
(4*S*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxyhexan-1-ol 13.



To a stirred and cooled (0 °C) solution of **12** (3.52 g, 7.82 mmol) in THF (20 mL) was added BMS (0.52 mL, 5.2 mmol), and the mixture stirred for 3 h at the same temperature. Aqueous

3N NaOH (3.13 mL) was added into it at 0 ^{o}C, followed by H_2O_2 (30%, 3.13 mL). After stirring for 3 h at 0 ^{o}C and 12 h at room temperature, the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 10 mL), aqueous 10% HCl (1 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-15% EtOAc/hexane) of the residue furnished **13** (3.4 g, 93%). colorless oil; $[\alpha]_D^{25}$ +3.4 (*c* 1.13, $CHCl_3$); IR: 3433 cm^{-1}; ^{1}H NMR: δ 1.04 (s, 9H), 1.32-1.39 (m, 2H), 1.41-1.52 (m, 13H), 3.39 (t, *J* = 6.2 Hz, 2H), 3.64-3.72 (m, 1H), 3.78-3.83 (m, 1H), 3.92-4.13 (m, 2H) 7.32-7.47 (m, 6H), 7.64-7.77 (m, 4H); ^{13}C NMR: δ 19.4, 23.8, 23.9, 25.1, 26.9, 27.2, 30.2, 34.8, 36.1, 60.4, 62.7, 66.8, 73.6, 109.5, 127.5, 129.7, 133.5, 133.9, 135.8, 135.9. Anal. Calcd. for $C_{28}H_{40}O_4Si$: C, 71.75; H, 8.60%. Found: C, 71.64; H, 8.78%.

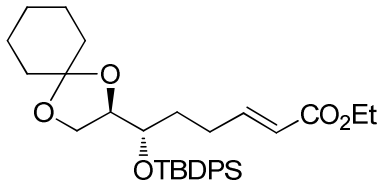
(4*S*,5*R*)-4-*tert*-Butyldiphenylsilyloxy-5,6-cyclohexylidenedioxyhexanal 14.



To a cooled (0 °C) and stirred suspension of PCC (1.90 g, 8.82 mmol) and NaOAc (10 mol%) in CH_2Cl_2 (20 mL) was added the alcohol **13** (2.70 g, 5.77 mmol) in one lot. After stirring for 3 h, the reaction mixture was diluted with Et_2O (30 mL) and the supernatant passed through a pad of silica gel (2" x 1"). Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-10% EtOAc/hexane) furnished pure **14** (2.2 g, 81%). colorless oil; $[\alpha]_D^{24}$ +7.7 (*c* 1.24, $CHCl_3$); IR: 2714, 1729 cm^{-1}; ^{1}H NMR: δ 1.04 (s, 9H), 1.32-1.36 (m, 2H), 1.45-1.52 (m, 8H), 1.81-1.88 (m, 2H), 2.25-2.54 (m, 2H), 3.48-3.62 (m, 1H), 3.67-3.77 (m, 1H), 3.88-4.00 (m, 2H), 7.34-7.43 (m, 6H), 7.62-7.68 (m, 4H), 9.14 (t, *J* = 1.2 Hz, 1H); ^{13}C NMR: δ 19.4, 23.8, 25.1, 26.3, 26.9, 34.7, 36.1, 38.8, 67.2, 73.3, 77.6,

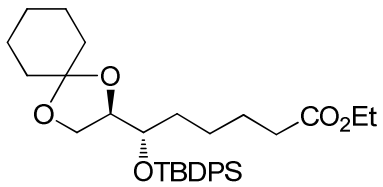
109.7, 127.7, 129.8, 133.3, 133.5, 135.9, 202.2. Anal. Calcd. for $C_{28}H_{38}O_4Si$: C, 72.06; H, 8.21%. Found: C, 72.21; H, 8.18%.

Ethyl (6*S*,7*R*)-6-*tert*-Butyldiphenylsilyloxy-7,8-cyclohexylidenedioxyoct-2*E*-enoate 15.



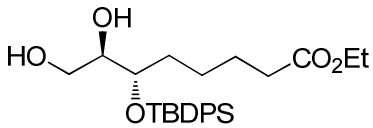
To a stirred suspension of pentane-washed NaH (0.444 g, 9.24 mmol, 50% suspension in oil) in THF (20 mL) was added triethyl phosphonoacetate (1.85 mL, 9.24 mmol) in THF (5 mL). After 15 min, when the solution became clear, the mixture was cooled to 0 ^oC, and the aldehyde **14** (2.15 g, 4.61 mmol) in THF (5 mL) was dropwise added into it. After stirring at room temperature for 18 h, the mixture was poured into ice-water and extracted with Et_2O (3 × 20 mL). The ether layer was washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), dried, and concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0-10% Et_2O/hexane) furnished pure **15**. Yield: 2.3 g (91%); colorless oil; $[\alpha]_D^{24}$ +12.7 (*c* 1.07, $CHCl_3$); IR: 1716, 997 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.33-1.37 (m, 2H), 1.45-1.59 (m, 8H), 1.65-1.76 (m, 2H), 2.12-2.21 (m, 2H), 3.58-3.66 (m, 1H), 3.70-3.76 (m, 1H), 3.90-4.05 (m, 2H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.66 (d, *J* = 16.0 Hz, 1H), 6.71-6.79 (m, 1H), 7.32-7.43 (m, 6H), 7.62-7.68 (m, 4H); ^{13}C NMR: δ 14.2, 19.3, 23.7, 23.8, 25.0, 26.9, 32.1, 34.7, 36.0, 59.9, 67.0, 73.5, 77.4, 109.5, 121.1, 127.5, 129.7, 133.3, 133.6, 135.7, 135.8, 148.7, 166.5. Anal. Calcd. for $C_{32}H_{44}O_5Si$: C, 71.60; H, 8.26%. Found: C, 71.44; H, 8.48%.

Ethyl (6*S*,7*R*)-6-*tert*-Butyldiphenylsilyloxy-7,8-cyclohexylidenedioxyoctanoate 16.



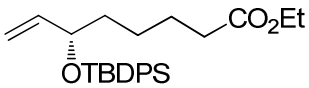
A mixture of **15** (1.3 g, 2.42 mmol) and 10% Pd-C (0.05 g) in EtOH (10 mL) was magnetically stirred at 25 ^{o}C for 22 h under a positive pressure of H_2. The mixture was diluted with Et_2O (30 mL) and passed through a small pad of silica gel. Removal of solvent in vacuo furnished pure **16** (1.2 g, ~quant.). colorless oil; $[\alpha]_D^{24}$ +7.7 (*c* 1.06, $CHCl_3$); IR: 1735 cm^{-1}; ^{1}H NMR: δ 1.04 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.20-1.48 (m, 8H), 1.50-1.60 (m, 8H), 2.07-2.15 (m, 2H), 3.63-3.78 (m, 2H), 3.89-3.97 (m, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 7.32-7.42 (m, 6H), 7.63-7.70 (m, 4H); ^{13}C NMR: δ 14.1, 19.3, 23.6, 23.7, 23.8, 24.8, 25.1, 26.9, 33.6, 34.1, 34.7, 36.0, 60.0, 66.5, 73.5, 77.5, 109.3, 127.5, 129.6, 133.5, 134.0, 135.8, 173.5. Anal. Calcd. for $C_{32}H_{46}O_5Si$: C, 71.33; H, 8.61%. Found: C, 71.34; H, 8.47%.

Ethyl (6*S*,7*R*)-6-*tert*-Butyldiphenylsilyloxy-7,8-dihydroxyoctanoate 17.



A mixture of **16** (1.20 g, 2.23 mmol) in CH_2Cl_2 (15 mL) and aqueous 80% TFA (8 mL) was stirred at 0 ^{o}C for 3 h and at 25 ^{o}C till completion of the reaction (*cf*. TLC, 24 h). Most of the solvent was removed in vacuo, the residue diluted with H_2O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed successively with H_2O (3 × 10 mL), aqueous 10% $NaHCO_3$ (2 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-5% MeOH/$CHCl_3$) of the residue gave pure **17** (0.830 g, 81%). colorless oil; $[\alpha]_D^{25}$ +26.5 (*c* 1.08, $CHCl_3$); IR: 3455, 1731 cm^{-1}; ^{1}H NMR: δ 1.06 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.32-1.43 (m, 6H), 2.04-2.12 (m, 2H), 2.43 (broad s, 2H), 3.63-3.72 (m, 3H), 3.80-3.84 (m, 1H), 4.07 (q, *J* = 7.2 Hz, 2H), 7.36-7.47 (m, 6H), 7.64-7.70 (m, 4H); ^{13}C NMR: δ 14.2, 19.4, 24.7, 27.0, 29.7, 32.5, 33.9, 60.2, 63.1, 73.4, 75.1, 127.6, 127.8, 129.9, 133.0, 133.5, 135.8, 173.6. Anal. Calcd. for $C_{26}H_{38}O_5Si$: C, 68.08; H, 8.35%. Found: C, 67.86; H, 8.53%.

Ethyl (6*S*)-6-*tert*-Butyldiphenylsilyloxyoct-7-enoate 18.

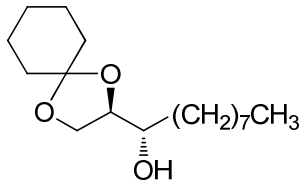


To a cooled (0 ^{o}C) and stirred solution of **17** (0.820 g, 1.79 mmol) in pyridine (8 mL) was added *p*-TsCl (0.750 g, 3.94 mmol). The reaction mixture was brought to room temperature and stirred for 24 h. It was poured in ice-cold water (30 mL) and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed successively with H_2O (2 × 10 mL), aqueous 2N HCl (2 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-10% EtOAc/hexane) of the residue gave the pure ditosylate as a mixture of rotamers (1.22 g, 89%). colorless oil; $[\alpha]_D^{24}$ +20.9 (*c* 1.03, $CHCl_3$); IR: 1370, 1177 cm^{-1}; ^{1}H NMR: δ 1.00 (m, 9H), 1.23-1.51 (m, 7H), 1.60-1.80 and 1.90-2.10 (m, 2H), 2.45 (s, 6H), 3.80-3.88 (m, 1H), 4.03-4.28 (m, 3H), 4.34-4.43 (m, 1H), 4.56-4.70 (m, 1H), 7.30-7.48 (m, 8H), 7.50-7.69 (m, 10H); ^{13}C NMR: δ 14.2, 19.3, 21.7, 24.3, 26.8, 33.5, 33.8, 60.2, 67.0, 73.7, 80.8, 127.5, 127.7, 127.9, 128.1, 129.9, 130.0, 135.7, 136.1, 144.9, 145.1, 172.7.

A mixture of the above compound (1.22 g, 1.59 mmol), NaI (1.43 g, 9.53 mmol) and Zn-dust (0.650 g, 10.0 mmol) in DMF (10 mL) was heated at 90 ^{o}C for 8 h (*cf*. TLC). The mixture was brought to room temperature, poured in H_2O (30 mL) and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed successively with 10% aqueous $Na_2S_2O_3$ (1 × 10 mL), H_2O (3 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-10% Et_2O/hexane) of the residue gave pure **18** (0.565 g, 84%). colorless oil; $[\alpha]_D^{24}$ +21.3 (*c* 1.01, $CHCl_3$); IR: 1735, 997 cm^{-1}; ^{1}H NMR: δ 1.05 (s, 9H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.39-1.58 (m, 6H), 2.16 (t, *J* = 7.0 Hz, 2H), 4.08 (q, *J* = 7.2 Hz, 2H), 4.92-5.01 (m, 3H), 5.70-5.80 (m, 1H), 7.33-7.38 (m, 6H), 7.61-7.68 (m, 4H); ^{13}C NMR: δ 14.2, 19.3, 23.9, 24.8, 26.9, 34.2, 37.0, 60.1, 74.3, 114.3, 127.3, 127.4,

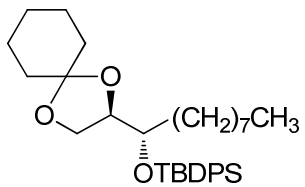
129.4, 129.5, 134.1, 134.3, 135.8, 135.9, 140.6, 173.6. Anal. Calcd. for $C_{26}H_{36}O_3Si$: C, 73.54; H, 8.54%. Found: C, 73.78; H, 8.71%.

(2*R*,3*S*)-1,2-Cyclohexylidenedioxyundecan-3-ol 19.



To a cooled (-78 ^oC) and stirred solution of $C_8H_{17}Li$ [prepared from 1-bromooctane (11.60 g, 60.0 mmol) and Li (0.890 g, 127.1 mmol)] in THF (80 mL) was added **10** (5.10 g, 30.0 mmol) in THF (20 mL). After stirring the mixture for 3 h at -78 ^oC, it was gradually brought to room temperature and treated with aqueous saturated NH_4Cl, the supernatant was decanted and the residue washed with Et_2O (2 × 20 mL). The combined organic extracts were washed with aqueous saturated NH_4Cl (1 × 10 mL), dried and concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0-15% EtOAc/hexane) furnished **19** (7.32 g, 86%). colorless oil; $[\alpha]_D^{24}$ +12.6 (*c* 1.02, $CHCl_3$), (lit.[36] $[\alpha]_D^{24}$ +6.2 (*c* 1.15, $CHC1_3$)); IR: 3457 cm^{-1}; ^1H NMR: δ 0.86 (t, *J* = 6.4 Hz, 3H), 1.17-1.43 (m containing a s at δ 1.21, 16H), 1.56-1.79 (m, 8H), 1.94 (broad s, 1H), 3.70-3.78 (m, 1H), 3.86-3.97 (m, 3H); ^{13}C NMR: δ 13.9, 22.5, 23.7, 23.9, 25.0, 25.7, 29.1, 29.4, 29.5, 31.7, 32.5, 34.8, 36.0, 63.9, 70.5, 78.2, 109.3. Anal. Calcd. for $C_{17}H_{32}O_3$: C, 71.79; H, 11.34%. Found: C, 71.94; H, 11.50%.

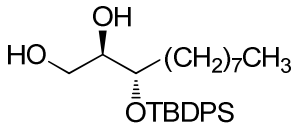
(2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxy-1,2-cyclohexylidenedioxyundecane 20.



As described earlier, silylation of **19** (2.87 g, 10.10 mmol) with TBDPSCl (3.53 g, 12.85 mmol), imidazole (0.87 g, 12.85 mmol) and DMAP (catalytic) in CH_2Cl_2 (40 mL), followed by work up and column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **20**

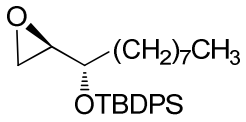
(4.54 g, 86%). colorless oil; $[\alpha]_D^{24}$ +15.5 (*c* 1.06, $CHCl_3$); IR: 3072, 3050 cm^{-1}; ^1H NMR: δ 0.89 (t, *J* = 6.4 Hz, 3H), 1.14-1.38 (m containing a s at δ 1.06, 25H), 1.48-1.72 (m, 8H), 3.66-3.75 (m, 2H), 3.80-3.87 (m, 1H), 3.93-4.10 (m, 1H), 7.34-7.47 (m, 6H), 7.67-7.75 (m, 4H); ^{13}C NMR: δ 14.1, 19.4, 22.6, 23.8, 23.9, 24.2, 25.2, 26.9, 29.1, 29.3, 29.6, 31.8, 34.1, 34.8, 36.1, 66.4, 73.7, 77.7, 109.3, 127.4, 129.5, 133.8, 134.3, 135.8, 135.9. Anal. Calcd. for $C_{33}H_{50}O_3Si$: C, 75.81; H, 9.64%. Found: C, 75.74; H, 9.48%.

(2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxyundecane-1,2-diol 21.



As described earlier, compound **20** (2.87 g, 5.50 mmol) was deacetalized in CH_2Cl_2 (20 mL) with aqueous 80% TFA (8.0 mL). Usual work up and column chromatography (silica gel, 0-5% MeOH/$CHCl_3$) afforded pure **21** (2.0 g, 84%). colorless oil; $[\alpha]_D^{24}$ +21.0 (*c* 1.04, $CHCl_3$); IR: 3398 cm^{-1}; ^1H NMR: δ 0.89 (t, *J* = 6.8 Hz, 3H), 1.09-1.35 (m containing a s at δ 1.10, 21H), 1.45-1.55 (broad m, 4H), 3.65-3.72 (m, 3H), 3.78-3.89 (m, 1H), 7.35-7.49 (m, 6H), 7.68-7.75 (m, 4H); ^{13}C NMR: δ 14.1, 19.4, 22.6, 24.8, 27.0, 29.1, 29.2, 29.4, 31.7, 32.9, 63.1, 73.6, 75.5, 127.5, 127.7, 129.7, 129.8, 133.1, 133.7, 135.9. Anal. Calcd. for $C_{27}H_{42}O_3Si$: C, 73.25; H, 9.56%. Found: C, 73.14; H, 9.72%.

(2*R*,3*S*)-3-*tert*-Butyldiphenylsilyloxy-1,2-epoxyundecane 22.

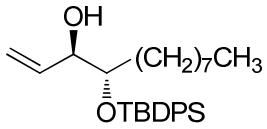


Tosylation **21** (1.10 g, 2.49 mmol) with *p*-TsCl (0.475 g, 2.49 mmol) and pyridine (8 mL), followed by work-up and column chromatography (silica gel, 0-10% EtOAc/hexane) furnished the monotosylate (1.30 g, 84%). colorless oil; $[\alpha]_D^{24}$ +19.5 (*c* 1.16, $CHCl_3$); IR: 3528, 1362, 1177 cm^{-1}; ^1H NMR: δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.02 (s, 9H), 1.25-1.42 (m, 14H), 2.18 (broad s, 1H), 2.45 (s, 3H), 3.75-3.87 (m, 2H), 3.98-4.04 (m, 1H), 4.21-4.27 (m, 1H),

7.31-7.45 (m, 8H), 7.61-7.66 (m, 4H), 7.78 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR: δ 14.0, 19.3, 21.5, 22.5, 24.5, 26.9, 28.9, 29.2, 29.3, 31.7, 32.7, 71.3, 71.5, 74.2, 127.4, 127.6, 127.9, 129.8, 132.5, 132.9, 133.5, 135.7, 144.8.

A mixture of the above compound (1.20 g, 2.01 mmol) and anhydrous K_2CO_3 (0.63 g, 4.58 mmol) in MeOH (10 mL) was stirred for 3 h at room temperature. The supernatant was decanted, the solid residue washed with EtOAc (20 mL) and the combined organic extracts concentrated in vacuo. The residue was taken in EtOAc (30 mL) washed with H_2O (3 × 15 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. Column chromatography (silica gel, 0-5% EtOAc/hexane) of the residue gave pure **22** (0.770 g, 90%). colorless oil; $[\alpha]_D^{24}$ +20.2 (*c* 1.14, $CHCl_3$); IR: 1110 cm^{-1}; ^{1}H NMR: δ 0.89 (t, *J* = 6.4 Hz, 3H), 1.08 (s, 9H), 1.22-1.40 (m, 12H), 1.53-1.59 (m, 2H), 2.11-2.16 (m, 1H), 2.43-2.48 (m, 1H), 2.86-2.91 (m, 1H), 3.37-3.43 (m, 1H), 7.32-7.48 (m, 6H), 7.64-7.72 (m, 4H); ^{13}C NMR: δ 13.9, 19.2, 22.5, 24.1, 26.7, 29.0, 29.2, 29.5, 31.7, 35.2, 45.9, 54.1, 73.1, 127.3, 127.4, 129.4, 129.5, 133.6, 133.7, 135.7. Anal. Calcd. for $C_{27}H_{40}O_2Si$: C, 76.36; H, 9.49%. Found: C, 76.42; H, 9.27%.

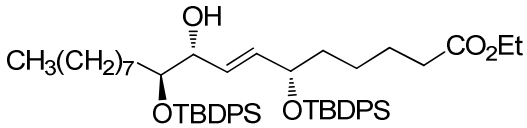
(3*R*,4*S*)-4-*tert*-Butyldiphenylsilyloxydodec-1-en-3-ol 23.



To a cooled (-40 ^{o}C) and stirred suspension of Me_3SI (1.25 g, 6.13 mmol) in THF (20 mL) was added *n*-BuLi (3.0 mL, 1.5 M in hexane, 4.91 mmol). After stirring for 1 h, compound **22** (0.522 g, 1.23 mmol) in THF (5.0 mL) was injected into the mixture, stirring continued at -40 ^{o}C for 3 h and at room temperature for 12 h. H_2O (15 mL) was added to the mixture, the organic layer separated, and the aqueous layer extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H_2O (1 × 10 mL), and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-15% EtOAc/hexane) of the residue gave pure **23** (0.436 g, 81%). colorless oil; $[\alpha]_D^{24}$ +16.5 (*c*

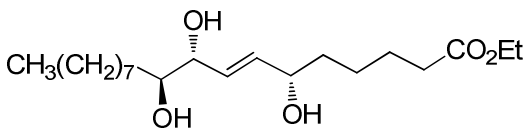
1.08, $CHCl_3$); IR: 3475, 997, 925 cm^{-1}; ^1H NMR: δ 0.86 (t, *J* = 6.4 Hz, 3H), 1.08 (s, 9H), 1.14-1.39 (m, 14H), 1.96 (broad s, 1H), 3.48-3.52 (m, 1H), 4.01-4.07 (m, 1H), 4.93-5.23 (m, 2H), 5.74-5.95 (m, 1H), 7.34-7.43 (m, 6H), 7.61-7.65 (m, 4H); ^{13}C NMR: δ 14.1, 19.3, 22.6, 25.4, 26.9, 29.1, 29.2, 29.4, 31.8, 31.9, 74.3, 77.9, 117.6, 127.4, 127.5, 127.6, 129.7, 129.8, 133.4, 133.6, 135.5, 135.7, 135.9, 136.4. Anal. Calcd. for $C_{28}H_{42}O_2Si$: C, 76.66; H, 9.65%. Found: C, 76.84; H, 9.48%.

Ethyl (6*S*,9*R*,10*S*)-6,10-Di-*tert*-butyldiphenylsilyloxy-9-hydroxyoctadeca-7*E*-enoate 24.



A mixture of **18** (0.97 g, 0.23 mmol), **23** (0.153 g, 0.35 mmol) and Grubbs' II catalyst (5 mol%) in CH_2Cl_2 (5 mL) was stirred for 22 h under Ar. After concentrating the mixture in vacuo, the residue was subjected to column chromatography (silica gel, 0-15% EtOAc/hexane) to give pure **24** (0.120 g, 63% based on **18**). colorless oil; $[\alpha]_D^{25}$ +16.3 (*c* 1.02, $CHCl_3$); IR: 3583, 1736 cm^{-1}; ^1H NMR: δ 0.86 (t, *J* = 6.8 Hz, 3H), 1.19-1.44 (m containing a s at δ 1.12, 36H), 1.48-1.74 (m, 6H), 2.16 (t, *J* = 7.2 Hz, 2H), 3.41-3.48 (m, 1H), 4.01-4.14 (m containing a q at δ 4.07, *J* = 7.2 Hz, 4H), 5.68-5.72 (m, 2H), 7.35-7.41 (m, 12H), 7.61-7.68 (m, 8H); ^{13}C NMR: δ 14.1, 14.2, 19.3, 22.6, 23.9, 24.8, 25.5, 26.9, 29.2, 29.4, 31.8, 31.9, 34.2, 37.0, 60.1, 74.2, 74.4, 78.0, 114.3, 127.3, 127.4, 127.6, 129.4, 129.5, 129.7, 129.8, 133.4, 133.7, 134.1, 134.4, 135.5, 135.8, 135.9, 140.6, 173.6. Anal. Calcd. for $C_{52}H_{74}O_5Si_2$: C, 74.77; H, 8.93%. Found: C, 74.98; H, 9.09%.

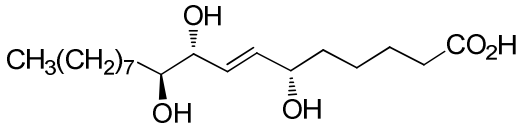
Ethyl (6*S*,9*R*,10*S*)-6,9,10-Trihydroxyoctadeca-7*E*-enoate 25.



To a cooled (0 °C) and stirred solution of **24** (0.300 g, 0.36 mmol) in THF (5 mL) was added Bu_4NF (0.57 mL, 1 M in THF, 0.57 mmol). The reaction mixture was brought to room

temperature and stirred until the reaction was complete (*cf.* TLC, 3 h). The mixture was poured into ice-cold water (15 mL) and extracted with EtOAc (2 × 10 mL). The organic extract was washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent followed by column chromatography of the residue (silica gel, 0-15% EtOAc/hexane) furnished **25** (0.112 g, 87%). colorless oil; $[\alpha]_D^{24}$ +3.3 (*c* 1.22, $CHCl_3$); IR: 3435, 1729 cm^{-1}; ^1H NMR: δ 0.88 (t, *J* = 6.4 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 1.26-1.39 (m, 14H), 1.42-1.54 (m, 6H), 2.25 (t, *J* = 7.0 Hz, 2H), 2.50 (broad s, 1H), 2.71 (broad s, 2H), 3.51-3.56 (m, 1H), 4.01-4.17 (m, 4H), 5.56-5.68 (m, 2H); ^{13}C NMR: δ 14.2, 18.9, 24.8, 26.2, 26.6, 31.2, 31.5, 34.2, 36.5, 37.2, 73.0, 74.2, 75.0, 78.3, 131.2, 137.1, 173.7. Anal. Calcd. for $C_{20}H_{38}O_5$: C, 67.00; H, 10.68%. Found: C, 67.26; H, 10.88%.

(6*S*,9*R*,10*S*)-6,9,10-Trihydroxyoctadeca-7*E*-enoic acid Id.



A solution of **25** (0.1 g, 0.28 mmol) in aqueous-ethanolic KOH (2M, 5 mL) was stirred at room temperature for 4 h. Most of the solvent was removed in vacuo, the residue taken in $CHCl_3$ (10 mL) and the extract washed with water (2 × 5 mL) and brine (1 × 5 mL), and dried. Removal of solvent followed by preparative thin layer chromatography of the residue (silica gel, 5% MeOH/$CHCl_3$) furnished pure **Id** (0.087 g, 95%). semi-solid; $[\alpha]_D^{24}$ +5.7 (*c*, 0.831, $CHCl_3$) (lit.[31] $[\alpha]_D^{25}$ -10.5 (*c* 0.15, MeOH) for natural **Id**); IR: 3630-3550, 3488, 1729 cm^{-1}; ^1H NMR: δ 0.86 (t, *J* = 6.2 Hz, 3H), 1.22-1.39 (m, 14H), 1.40-1.61 (m, 6H), 2.25 (t, *J* = 6.8 Hz, 2H), 1.83 (broad s, 1H), 2.41 (broad s, 2H), 3.52-3.55 (m, 1H), 4.04-4.10 (m, 2H), 5.56 (dd, *J* = 15.4, 5.4 Hz, 1H), 5.67 (dd, *J* = 15.4, 5.4 Hz, 1H); ^{13}C NMR: δ 14.2, 23.8, 26.4, 26.9, 30.7, 30.8, 31.2, 33.9, 34.2, 37.7, 73.2, 75.0, 76.8, 130.8, 137.0, 177.2.

12-*tert*-Butyldiphenylsilyloxydodecan-1-ol 39.

$TBDPSO(CH_2)_{12}OH$

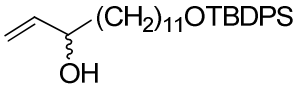
As described above, **38** (7.0 g, 34.65 mmol) was silylated with TBDPSCl (10.0 g, 36.42 mmol), imidazole (2.82 g, 41.48 mmol), and DMAP (cat.) in CH_2Cl_2 (50 mL), followed by work-up and column chromatography (silica gel, 0-15% EtOAc/hexane) to obtain **39** (10.4 g, 68%). colourless oil; IR: 3348, 3071, 3049 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.17-1.40 (m, 16H), 1.44 (broad s, 1H), 1.53-1.65 (m, 4H), 3.58-3.67 (m, 4H), 7.25-7.41 (m, 6H), 7.64-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 25.7, 26.8, 29.4, 29.6, 32.6, 32.7, 63.1, 63.9, 127.5, 129.4, 134.1, 135.5. Anal. Calcd. for $C_{28}H_{44}O_2Si$: C, 76.30; H, 10.06%. Found: C, 76.14; H, 9.88%.

12-*tert*-Butyldiphenylsilyloxydodecanal 40.

$TBDPSO(CH_2)_{11}CHO$

Oxidation of **39** (6.4 g, 14.55 mmol) with PCC (4.71 g, 21.83 mmol) and NaOAc (10 mol%) in CH_2Cl_2 (30 mL), followed by usual work-up and column chromatography (silica gel, 0-10% EtOAc/hexane) furnished pure **40** (5.9 g, 92%). colorless oil; IR: 2712, 1726 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.25-1.42 (m, 14H), 1.44-1.62 (m, 4H), 2.37-2.45 (m, 2H), 3.64 (t, J = 6.4 Hz, 2H), 7.34-7.42 (m, 6H), 7.64-7.69 (m, 4H), 9.75 (t, J = 1.2 Hz, 1H); ^{13}C NMR: δ 19.2, 22.1, 25.7, 26.9, 29.1, 29.4, 29.5, 32.6, 43.9, 64.0, 127.5, 129.5, 134.1, 135.6, 203.0. Anal. Calcd. for $C_{28}H_{42}O_2Si$: C, 76.66; H, 9.65%. Found: C, 76.48; H, 9.81%.

(±)-14-*tert*-Butyldiphenylsilyloxytetradec-1-en-3-ol 41.

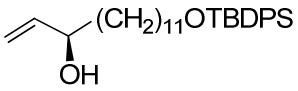


To a stirred solution of **40** (5.60 g, 12.78 mmol) in THF (25 mL) was slowly added CH_2=CHMgBr (36.5 mL, 25.57 mmol, 0.7 M in THF), and the mixture stirred for 6 h. The reaction was quenched with aqueous saturated NH_4Cl, the mixture filtered and concentrated in vacuo. The residue was dissolved in Et_2O (30 mL), the organic layer washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal in vacuo and column chromatography (silica gel, 0-10% Et_2O/hexane) of the residue afforded (±)-**41** (4.6 g, 77%).

colorless oil; IR: 3357, 997 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.26-1.42 (m, 16H), 1.45-1.60 (m, 5H), 3.64 (t, *J* = 6.4 Hz, 2H), 4.07-4.17 (m, 1H), 5.06-5.26 (m, 2H), 5.78-5.98 (m, 1H), 7.31-7.44 (m, 6H), 7.64-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 25.3, 25.7, 26.8, 29.4, 29.6, 32.6, 37.0, 64.0, 73.3, 114.5, 127.5, 129.4, 134.1, 135.5, 141.3. Anal. Calcd. for $C_{30}H_{46}O_2Si$: C, 77.19; H, 9.93%. Found: C, 77.34; H, 9.78%.

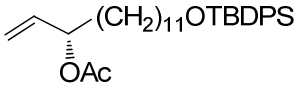
(*S*)-3-Acetoxy-14-*tert*-butyldiphenylsilyloxytetradec-1-ene 42. A mixture of (±)-**41** (2.0 g, 4.29 mmol), vinyl acetate (5 mL) and Novozym 435® (0.250 g) was agitated on an orbital shaker at 110 rpm for 5.5 h. The reaction mixture was filtered, and the solution was concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0-10% EtOAc/hexane) gave pure (*R*)-**41** and (*S*)-**42**.

(*R*)-**41:**



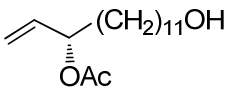
Yield: 0.780 g (39%); colorless oil; $[\alpha]_D^{22}$ -3.0 (c 1.07, $CHCl_3$);

(*S*)-**42:**



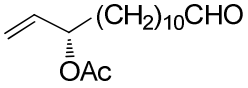
Yield: 0.960 g (44%); colorless oil; $[\alpha]_D^{22}$ -4.4 (*c* 1.11, $CHCl_3$); IR: 1740, 1033, 930 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.15-1.42 (m, 16H), 1.43-1.65 (m, 4H), 2.04 (s, 3H), 3.65 (t, *J* = 6.4 Hz, 2H), 5.12-5.26 (m, 3H), 5.69-5.80 (m, 1H), 7.31-7.46 (m, 6H), 7.64-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 21.2, 25.1, 25.8, 26.9, 29.4, 29.6, 32.6, 34.2, 64.0, 74.8, 116.5, 127.6, 129.5, 134.1, 135.6, 136.7, 170.2. Anal. Calcd. for $C_{32}H_{48}O_3Si$: C, 75.54; H, 9.51%. Found: C, 75.39; H, 9.37%.

(*S*)-12-Acetoxytetradec-13-en-1-ol 43.



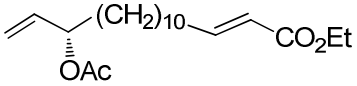
Desilylation of **42** (0.950 g, 1.87 mmol) with Bu_4NF (1.87 mL, 1 M in THF, 1.87 mmol) in THF (5 mL), subsequent work-up and column chromatography (silica gel, 0-15% EtOAc/hexane) furnished **43** (0.470 g, 93%). colorless oil; $[\alpha]_D^{22}$ -6.1 (*c* 1.08, $CHCl_3$); IR: 3421, 1738 cm^{-1}; ^1H NMR: δ 1.22-1.39 (m, 16H), 1.52-1.61 (m, 4H), 2.05 (s, 3H), 3.62 (t, *J* = 6.6 Hz, 2H), 5.16-5.25 (m, 3H), 5.68-5.84 (m, 1H); ^{13}C NMR**:** δ 21.2, 25.0, 25.7, 29.3, 29.4, 32.6, 34.1, 62.9, 74.8, 116.4, 136.5, 170.4. Anal. Calcd. for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18%. Found: C, 70.88; H, 11.07%.

(*S*)-12-Acetoxytetradecan-13-enal 44.



As described for **14**, oxidation of the alcohol **43** (0.800 g, 2.96 mmol) with PCC (0.958 g, 4.44 mmol) and NaOAc (10 mol%) in CH_2Cl_2 (25 mL), followed by work up gave **44** (0.700 g, 88%). colorless oil; $[\alpha]_D^{22}$ -4.6 (*c* 1.04, $CHCl_3$); IR: 2716, 1737 cm^{-1}; ^1H NMR: δ 1.19-1.32 (m, 14H), 1.56-1.65 (m, 4H), 2.02 (s, 3H), 2.36-2.41 (m, 2H), 5.09-5.21 (m, 3H), 5.67-5.78 (m, 1H), 9.72 (t, *J* = 1.5 Hz, 1H); ^{13}C NMR**:** δ 21.1, 21.9, 24.9, 29.0, 29.2, 29.3, 34.0, 43.8, 74.7, 116.4, 136.5, 170.3, 202.1. Anal. Calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52%. Found: C, 71.68; H, 10.67%.

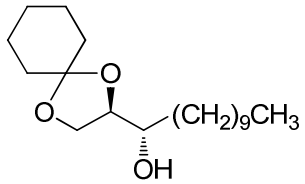
Ethyl (*S*)-14-Acetoxyhexadeca-2*E*,15-dienoate 45.



Wittig-Horner reaction of **44** (0.650 g, 2.42 mmol) with triethyl phosphonoacetate (0.652 g, 2.91 mmol) in THF (15 mL), using NaH (0.140 g, 2.91 mmol, 50% suspension in oil) as the base, usual work up and column chromatography (silica gel, 0-10% Et_2O/hexane) furnished pure **45** (0.630 g, 77%). colorless oil; $[\alpha]_D^{22}$ -5.4 (*c* 1.03, $CHCl_3$); IR: 1739, 1722, 982 cm^{-1}; ^1H NMR: δ 1.05-1.31 (m, 17H), 1.42-1.61 (m, 4H), 2.05 (s, 3H), 2.12-2.22 (m, 2H), 4.17 (q, *J* = 7.2 Hz, 2H), 5.11-5.25 (m, 3H), 5.63-5.84 (m containing a d at δ 5.79, *J* = 15.8 Hz, 2H),

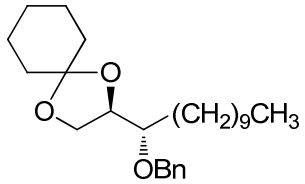
6.88-7.02 (m, 1H); ^{13}C NMR: δ 14.2, 21.2, 24.9, 27.9, 29.0, 29.3, 29.4, 32.0, 34.1, 60.0, 74.8, 116.4, 121.1, 136.5, 149.4, 166.7, 170.3. Anal. Calcd. for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12%. Found: C, 71.16; H, 10.16%.

(2*R*,3*S*)-l,2-Cyclohexylidenedioxytridecan-3-ol 46.



Reaction of **10** (6.0 g, 35.29 mmol) with 1-decyl-Li [prepared from 1-bromodecane (15.60 g, 70.59 mmol) and Li (1.1 g, 155.29 mmol)] in THF (100 mL) at -78 ^{o}C, usual isolation and column chromatography (silica gel, 0-15% EtOAc/hexane) furnished **46** (8.90 g, 81%). colorless oil; $[\alpha]_D^{22}$ +5.1 (*c* 1.14, $CHCl_3$), (lit.[48] $[\alpha]_D^{22}$ +4.21 (*c* 0.83, $CHCl_3$)); IR: 3418 cm^{-1}; ^{1}H NMR: δ 0.86 (dist. t, *J* = 6.8 Hz, 3H), 1.20-1.40 (m, 20H), 1.56-1.62 (m, 8H), 1.94 (broad s, 1H), 3.63 (t, *J* = 6.4 Hz, 1H), 3.87-3.97 (m, 3H); ^{13}C NMR: δ 13.9, 22.4, 23.5, 23.7, 24.9, 25.5, 29.1, 29.4, 31.7, 32.4, 34.6, 35.9, 63.9, 70.4, 78.1, 109.2. Anal. Calcd. for $C_{19}H_{36}O_3$: C 73.03, H 11.61; Found: C 73.17, H 11.47.

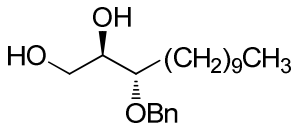
(2*R*,3*S*)-3-Benzyloxy-l,2-cyclohexylidenedioxytridecane 47.



To a stirred suspension of NaH (1.44 g, 50% suspension in oil, 29.97 mmol) in THF (30 mL) was added **46** (8.5 g, 27.24 mmol) in THF (30 mL) under Ar. After the evolution of H_2 subsided, the mixture was refluxed for 1 h, brought to room temperature, and Bu_4NI (10 mol%) and BnBr (5.59 g, 32.69 mmol) in THF (30 mL) added into it. The mixture was refluxed till consumption of **46** (*cf*. TLC, ~4 h), brought to room temperature, and treated with ice-cold H_2O (30 mL). The organic layer was separated, the aqueous portion extracted

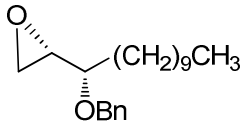
with Et_2O (2 × 25 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-10% EtOAc/hexane) of the residue furnished **47** (10.19 g, 93%). colorless oil; $[\alpha]_D^{22}$ +5.0 (*c* 1.16, $CHCl_3$); IR: 3060, 1644 cm^{-1}; ^1H NMR: δ 0.87 (dist. t, *J* = 6.4 Hz, 3H), 1.15-1.39 (m, 20H), 1.51-1.61 (m, 8H), 3.48-3.56 (m, 1H), 3.86-3.90 (m, 1H), 3.95-4.04 (m, 2H), 4.51-4.73 (m, 2H), 7.29-7.34 (m, 5H); ^{13}C NMR: δ 14.1, 22.7, 23.8, 24.0, 25.0, 25.2, 29.3, 29.6, 29.7, 31.4, 31.9, 34.9, 36.2, 65.8, 72.9, 77.6, 79.0, 109.4, 127.5, 127.8, 128.3, 138.7. Anal. Calcd. for $C_{26}H_{42}O_3$: C 77.56, H 10.51; Found: C 77.71, H 10.47.

(2*R*,3*S*)-3-Benzyloxytridecane-l,2-diol 48.



A mixture of **47** (5.0 g, 12.44 mmol) and aqueous HCl (6 mL, 2N) was stirred at 25 °C till completion of the reaction (*cf.* TLC, 6 h). Most of the solvent was removed in vacuo, the residue diluted with H_2O (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed successively with H_2O (3 × 10 mL), 10% aqueous $NaHCO_3$ (2 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-5% MeOH/$CHCl_3$) of the residue gave pure **48** (3.0 g, 75%). colorless oil; $[\alpha]_D^{22}$ +7.3 (*c* 1.12, $CHCl_3$), (lit.[49] $[\alpha]_D$ +6.4 (*c* 1.07, CH_2Cl_2)); IR: 3398, 1620, 1063 cm^{-1}; ^1H NMR δ 0.87 (dist. t, *J* = 6.8 Hz, 3H), 1.21-1.59 (m, 18H), 2.72 (broad s, 2H), 3.56-3.69 (m, 1H), 3.72-3.78 (m, 3H), 4.51-4.65 (m, 2H), 7.27-7.36 (m, 5H); ^{13}C NMR: δ 14.0, 22.6, 25.2, 29.5, 29.7, 30.3, 31.8, 63.3, 72.5, 72.7, 80.8, 127.7, 127.8, 128.3, 138.1. Anal. Calcd. for $C_{20}H_{34}O_3$: C 74.49, H 10.63; Found: C 74.35, H 10.80.

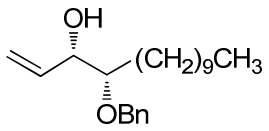
(2*S*,3*S*)-3-Benzyloxy-l,2-epoxytridecane 49.



To a cooled (-20 ^{o}C) and stirred solution of **48** (1.16 g, 3.60 mmol) and Et_3N (1.76 mL, 12.6 mmol) in EtOAc (12 mL) was added TMSCl (0.46 mL, 3.6 mmol). After stirring for 20 min, Et_3N (0.8 mL, 5.76 mmol) and MsCl (0.334 mL, 4.32 mmol) were successively added into the mixture. After stirring for another 30 min, the mixture was brought to 25 ^{o}C, aqueous 2N aqueous HCl (7.0 mL) was added and stirring continued for 1 h. The organic layer was separated, the aqueous portion extracted with EtOAc (2 × 15 mL) and the combined organic extracts were washed successively with H_2O (3 × 10 mL), aqueous 2N HCl (2 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal afforded the corresponding 1-hydroxy-2-mesylate. IR: 1456, 1350 cm^{-1}.

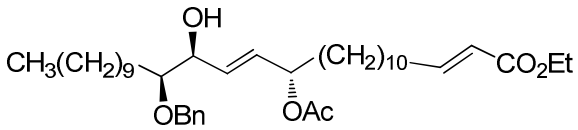
A mixture of the above compound (1.14 g, 2.83 mmol) and anhydrous K_2CO_3 (1.17 g, 8.48 mmol) in MeOH (20 mL) was stirred for 3 h at room temperature. The supernatant was decanted, the solid residue washed with EtOAc (20 mL) and the combined organic extracts concentrated in vacuo. The residue was taken in EtOAc (30 mL) washed with H_2O (3 × 15 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. Column chromatography (silica gel, 0-5% EtOAc/hexane) of the residue gave pure **49** (0.722 g, 84%). colorless oil; $[\alpha]_D^{22}$ -22.5 (*c* 1.28, $CHCl_3$), (lit.[49] $[\alpha]_D$ -17 (*c* 1.16, CH_2Cl_2) for (2*R*,3*S*)**-49**); IR: 1254, 850 cm^{-1}; ^{1}H NMR: δ 0.87 (dist. t, *J* = 6.8 Hz, 3H), 1.26 (broad s, 18H), 2.48-2.52 (dd, t, *J* = 1.8 Hz, 3.0 Hz, 1H), 2.79 (t, *J* = 3.0 Hz, 1H), 2.99-3.06 (m, 2H), 4.58 (d, *J* = 11.7 Hz, 1H), 4.84 (d, *J* = 11.7 Hz, 1H), 7.26-7.40 (m, 5H); ^{13} C NMR: δ 14.1**,** 22.7, 25.5, 29.3, 29.5, 29.6, 31.9, 32.3, 43.1, 55.1, 71.6, 80.5, 127.4, 127.8, 128.3, 138.7. Anal. Calcd. for $C_{20}H_{32}O_2$: C 78.90, H 10.59; Found: C 78.75, H 10.43.

(3*S*,4*S*)-4-Benzyloxytetradec-1-en-3-ol 50.



As described earlier, compound **49** (0.470 g, 1.55 mmol) was reacted with the sulphorane [prepared from Me_3SI (1.57 g, 7.73 mmol) and *n*-BuLi (4.31 mL, 1.5 M in hexane, 6.46 mmol) at -40 ^oC in THF (25 mL), and the product **50** (0.393 g, 80%) was isolated by work-up and column chromatography (silica gel, 0-15% EtOAc/hexane). colorless oil; $[\alpha]_D^{22}$ +3.1 (*c* 0.980, $CHCl_3$); IR: 3444, 992, 922 cm^{-1}; ^1H NMR: δ 0.89 (dist. t, *J* = 6.4 Hz, 3H), 1.27 (broad, s, 16H), 1.57-1.63 (m, 2H), 2.55 (broad s, 1H), 3.32-3.39 (m, 1H), 4.08-4.17 (m, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 5.21-5.41 (m, 2H), 5.84-5.95 (m, 1H), 7.34-7.38 (m, 5H); ^{13} C NMR: δ 14.1, 22.7, 25.1, 29.4, 29.6, 29.7, 29.9, 30.4, 31.9, 72.6, 74.4, 82.3, 116.8, 127.8, 127.9, 128.5, 137.7. Anal. Calcd. for $C_{21}H_{34}O_2$: C 79.19, H 10.76; Found: C 79.05, H 10.59.

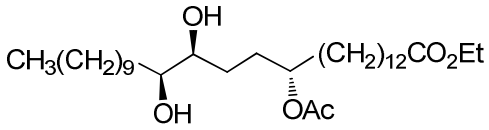
Ethyl (14*S*,17*S*,18*S*)-14-Acetoxy-17-hydroxy-18-benzyloxyoctacosa-2*E*,15*E/Z*-dienoate 51.



A mixture of **45** (0.130 g, 0.38 mmol), **50** (0.180 g, 0.56 mmol) and Grubbs' II catalyst (4 mol%) in CH_2Cl_2 (15 mL) was stirred for 22 h. After concentrating the mixture in vacuo, the residue was subjected to column chromatography (silica gel, 0-15% EtOAc/hexane) to give pure **51** (0.146 g, 61% based on conversion of **50**). colorless oil; $[\alpha]_D^{22}$ -9.3 (*c* 1.03, $CHCl_3$); IR: 3461, 1735, 1722, 972 cm^{-1}; ^1H NMR: δ 0.85 (dist. t, *J* = 6.2 Hz, 3H), 1.24-1.58 (m containing a s at δ 1.30, 39H), 2.03 (s, 3H), 2.15-2.24 (m, 3H), 3.27-3.35 (m, 1H), 4.07-4.28 (m, 4H), 4.47-4.65 (m, 2H), 5.22-5.25 (m, 1H), 5.70-5.83 (m, 2H), 6.98 (d, *J* = 16.2 Hz, 1H), 7.35-7.39 (m, 5H); ^{13}C NMR: δ 14.0, 21.2, 22.6, 24.9, 25.0, 27.9, 29.0, 29.3, 29.4, 29.5, 29.8,

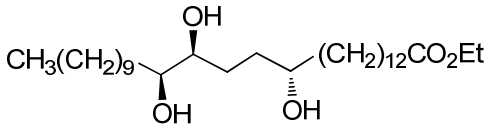
30.3, 31.8, 32.1, 34.3, 60.0, 72.4, 73.2, 74.1, 82.3, 121.1, 127.7, 128.3, 130.5, 132.3, 138.1, 149.4, 166.7, 170.2. Anal. Calcd. for $C_{39}H_{64}O_6$: C 74.48, H 10.26; Found: C 74.72, H 10.45.

Ethyl (14*S*,17*S*,18*S*)-14-Acetoxy-17,18-dihydroxyoctacosanoate 52.



Catalytic hydrogenation of **51** (0.125 g, 0.20 mmol) over 10% Pd-C (0.05 g) in EtOH (10 mL), work-up and column chromatography (silica gel, 0-15% EtOAc/hexane) furnished pure **52** (0.095 g, 88%). colourless oil; $[\alpha]_D^{22}$ +13.2 (*c* 1.14, $CHCl_3$); IR: 3457, 1740, 1730 cm^{-1}; ^1H NMR: δ 0.86 (dist. t, *J* = 6.4 Hz, 3H), 1.23-1.60 (containing a s at δ 1.32, 47H), 2.03 (s, 3H), 2.26 (t, *J* = 7.2 Hz, 2H), 2.69 (broad s, 2H), 3.47-3.58 (m, 2H), 4.08 (q, *J* = 7.0 Hz, 2H), 4.28-4.36 (m, 1H); ^{13}C NMR: δ 14.1, 14.2, 21.3, 22.7, 25.0, 25.6, 26.0, 29.1, 29.2, 29.3, 29.6, 30.5, 31.9, 33.6, 34.1, 60.2, 74.3, 74.5, 74.7, 171.3, 174.0. Anal. Calcd. for $C_{32}H_{62}O_6$: C 70.80, H 11.51; Found: C 70.54, H 11.72.

Ethyl (14*S*,17*S*,18*S*)-14,17,18-Trihydroxyoctacosanoate 53.



A mixture of **52** (0.09 g, 0.17 mmol) and Amberlyst 15® (0.05 g) in EtOH (5 mL) was magnetically stirred at 25 ^oC for 18 h. After filtering the mixture, it was concentrated in vacuo, and the residue subjected to preparative chromatography (silica gel, 15% EtOAc/hexane) to obtain pure **53** (0.077 g, 91%). colourless oil; $[\alpha]_D^{22}$ -11.7 (*c* 0.912, $CHCl_3$); IR: 3446, 1742 cm^{-1}; ^1H NMR: δ 0.87 (dist. t, *J* = 6.4 Hz, 3H), 1.27-1.56 (containing a s at δ 1.30, 47H), 2.32 (t, *J* = 6.8 Hz, 2H), 2.44 (broad s, 2H), 2.82 (broad s, 1H), 3.44-3.65 (m, 3H), 4.10 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR: δ 14.2, 21.2, 22.5, 25.0, 25.3, 25.5, 27.3, 27.7, 29.2, 29.3, 29.8, 30.2, 31.2, 31.9, 32.1, 34.4, 60.7, 72.4, 74.4, 74.7, 169.2. Anal. Calcd. for $C_{30}H_{60}O_5$: C 71.95, H 12.08; Found: C 70.54, H 11.72.

CHAPTER III

"Chemoenzymatic Syntheses of Two Macrolides"

III.1 ENANTIOMERIC SYNTHESES OF THE MACROLIDE ANTIBIOTIC (-)-A26771B

III.1.1 Introduction

The macrolides are of wide occurrence in various natural sources and several of these show impressive medicinal and other biological activities.[24] The antimicrobial spectrum of macrolides is wider than that of penicillin, making them attractive substitutes for patients with a penicillin allergy. Several highly oxygenated, conformationally restricted marine macrolides possess outstanding cell growth antiproliferative properties, and some of these are under preclinical and/or clinical trials.[51] The 16-membered macrolide, (-)-A26771B (**V**), isolated from the fungus *Penicillium turbatum* showed moderate activity against the gram-positive bacteria, mycoplasma, and fungi.[52] Its macrolide skeleton also contains an additional keto moiety that may broaden the antimicrobial spectrum. All these have generated tremendous interest among organic chemists leading to several racemic[53] and enantioselective syntheses of **V**.[54]

III.1.2: Previous Syntheses

The first enantiomeric synthesis of **V** employed D-glucose and a chromatographic separation to instill the 5*S*- and 15*R*-stereochemistry respectively.[54a] The required 15*R* stereocentre of **V** has been generated using (*R*)-(+)-methyloxirane in several other syntheses.[54b-e] In an innovative approach, both the stereogenic centres of **V** were introduced in a single Sharpless asymmetric dihydroxylation (ADH) step,[54f] while the ADH reaction in combination with a lipase-catalyzed *trans*-acylation were the key steps in its another synthesis.[54g] Sharpless' kinetic resolution[54c,d] or ADH reaction[54e] of 2-furylcarbinols were used to obtain the required 5*S*-carbinol as well as the γ-keto-*E*-α,β-unsaturated carboxylic acid moieties of **V**. However, many of the reported syntheses of **V** were targeted to the lactone **Va**, or followed the known

procedure[54a] of converting **Va** to **V** (**Figure III.1.1.**). Some of the previous syntheses are briefly described below.

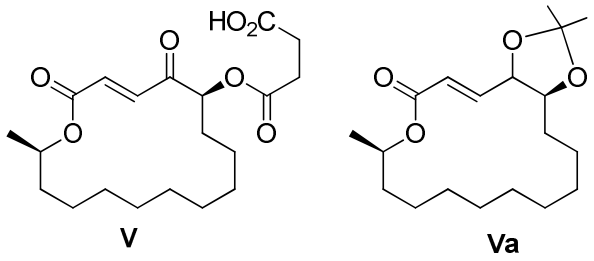
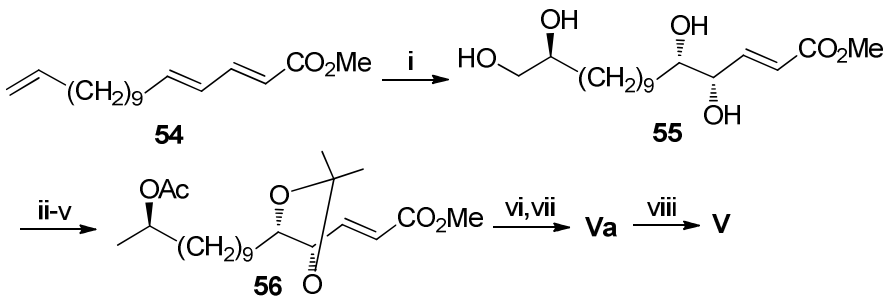


Figure III.1.1. The chemical structures of the macrolide and its precursor.

In one of these (**Scheme III.1.1.**),[54f] the conjugated ester **54** was subjected to Sharpless ADH reaction with AD-mix-α reagent to obtain the tetrol **55**. This was converted to **56** by acetonide protection of the two α-glycol moieties, selective removal of the terminal acetonide function, bromination of the primary hydroxyl function with acetyl bromide and reductive debromination. Alkaline hydrolysis of its ester functions and Yamaguchi lactonization ($C_6H_2Cl_3COCl/Et_3N/DMAP$) gave **Va**, which was deacetalized and the released carbinol succinoylated to obtain **V**.

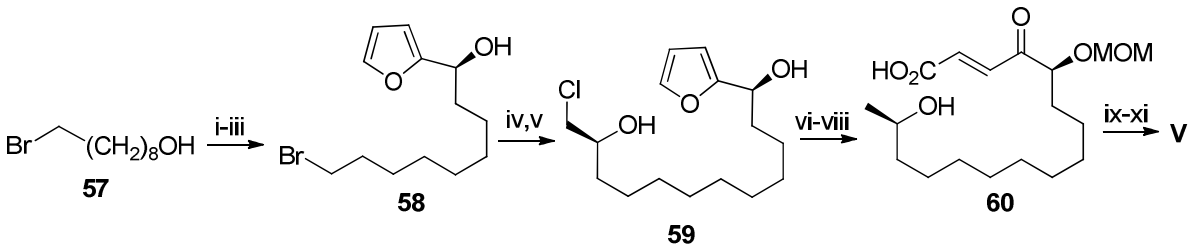


i) AD-mix-α, ii) 2,2-Dimethoxypropane/PTS/acetone, iii) $MeCO_2H/H_2O$, iv) $(EtO)_3CCH_3$/PPTS/ CH_3COBr, v) Bu_3SnH/benzene, vi) LiOH/THF-H_2O, vii) Yamaguchi lactonization, viii) CHF_2CO_2H/ MeOH; succinic anhydride/i-Pr_2EtN; Ac_2O/DMSO.

Scheme III.1.1.

In another synthesis (**Scheme III.1.2.**),[54c] the bromo alcohol **57** was oxidized to the corresponding aldehyde by Swern oxidation, reacted with 2-furyl lithium and subsequently

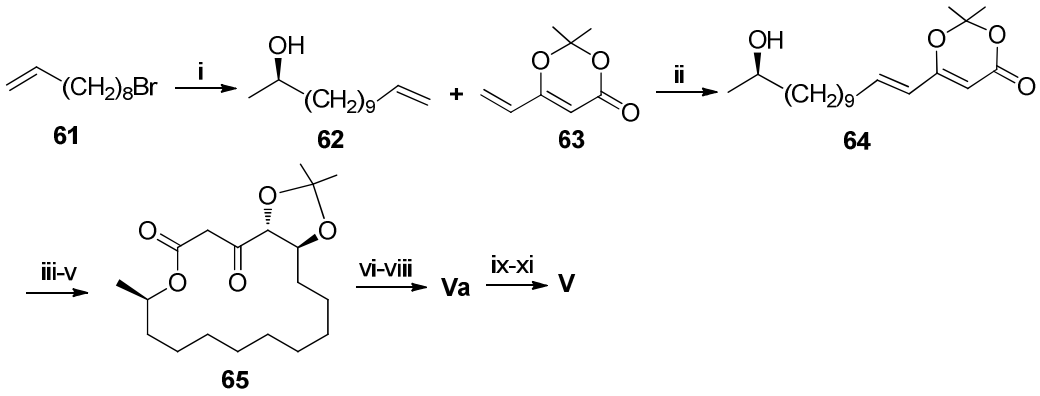
subjected to a kinetic resolution using Sharpless epoxidation to obtain **58**. After protecting its alcohol function, its Grignard reagent was reacted with (*R*)-epichlorohydrin to get the chorohydrin **59**. Reductive removal of its chlorine atom and oxidative cleavage of the furan ring gave the acid **60**. This was converted to **V** by Yamaguchi lactonization followed by some routine sequence of reactions, used in **Scheme III.1.1**.



i) $(COCl)_2$/DMSO/Et_3N, ii) 2-Furyl lithium/THF, iii) *tert*-BuOOH/$Ti(OPr)_4$/(D)-DIPT/-15 ^oC, iv) MOMCl/i-Pr_2EtN /CH_2Cl_2, v) Mg/$Br(CH_2)_2Br$/THF/heat; (*R*)-epichlorohydrin/CuCN/-50 to -30 ^oC, vi) $LiAlH_4$/THF, vii) NBS/ $NaHCO_3$/acetone-H_2O/-15 ^oC; furan/-15 ^oC; pyridine/room temperature, viii) $NaClO_2$/2-methyl-2-butene/pH 3.6 phosphate buffer, ix) Yamaguchi lactonization, x) TFA/CH_2Cl_2, xi) Succinic anhydride/DMAP.

Scheme III.1.2.

In a more recent synthesis (**Scheme III.1.3.**),[54e] the alcohol **62** was obtained by reacting (*R*)-epichlorohydrin with the Grignard reagent, prepared from **61**. Its cross-metathesis with **63** gave compound **64**, which on a Sharpless ADH reaction with AD-mix-α reagent, acetonide protection and heating furnished the keto macrolide **65**. This was transformed to **Va** by reduction of the ketone function, mesylation of the resultant alcohol and a base-catalyzed elimination. Conversion of **Va** to **V** was achieved, as described previously.



i) Mg/THF/(*R*)-methyloxirane/CuCN/-78 °C, ii) Hoveyda Grubbs' II catalyst/CH_2Cl_2/40 °C, iii) AD-mix-α/*tert*-BuOH-H_2O, iv) Acetone/PTS, v) Heptane/reflux, vi) $NaBH_4$/MeOH, vii) MsCl/pyridine, viii) DBU/CH_2Cl_2, ix) TFA/MeCN-H_2O, x) TEMPO/PTS/CH_2Cl_2, xi) Succinic anhydride/DMAP/CH_2Cl_2.

Scheme III.1.3.

III.1.3. PRESENT WORK

Compound **V** contains a methylcarbinol moiety, $CH_3CH(OH)$ that often contributes to the chirality of many biochemicals and pharmaceuticals.[55] Usually this moiety is obtained using the "chiral pool" compounds such as lactic acid or alanine. However, this approach provides only the (*S*)-methylcarbinols, while its antipode is accessible only via circuitous routes. The biocatalytic reactions are now a viable option to develop low-waste asymmetric syntheses of pharmaceuticals, chiral intermediates, and complex target molecules.[56] The whole cell microorganisms such as bakers' yeast,[19a,b] *Rhizopus arrhizus*,[57a-c] *Geotrichum candidum*[57d,e] etc. have been effectively used for the asymmetric reduction of methyl ketones to the corresponding chiral methylcarbinols. Nevertheless, microbial reduction often proceeds with low enantioselectivity, and usually follows Prelog's rule to furnish only the (*S*)-methylcarbinols. Use of commercially available alcohol dehydrogenases[32f] for asymmetric reduction of ketones is restricted due to the prohibitive cost of the enzymes and the cofactors. From this perspective, the lipase-catalyzed kinetic resolution of alcohols is more promising, as it provides the carbinol enantiomers, and if required, the efficiency of the resolution-based protocol can be improved by invoking dynamic kinetic resolution[58a,b] or stereo-inversion under the Mitsunobu conditions.[58c-e] Lipases are commercially available, affordable, display good stereoselectivity, work in organic or aqueous media, and are easily handled by organic chemists.[59] The chemoenzymatic approaches involving lipase-catalyzed asymmetric reactions have been extensively used by our group to synthesize a diverse array of target compounds including the macrolides.[29d,e] Presently, a new enantioselective synthesis of the macrolide core **Va** of the antibiotic was developed using two lipase-catalyzed acylation reactions as the key steps for incorporating the stereogenic centres. This protocol was further extended to develop an operationally simple synthesis of (-)-**V**.

The synthetic plan of **V** was conceived in consideration of the efficacy of the inexpensive and robust lipase preparation, Novozym 435® in resolving methylcarbinols,[29i] and allylic alcohols.[49] While the importance of the resolution of methylcarbinols is obvious, the chiral allylic alcohol moiety with a terminal alkene function was useful in constructing the macrolide structure via an RCM reaction.[37] The synthesis (**Scheme III.1.4.**) commenced from 11-bromo-1-undecene (**66**), which was converted to the corresponding Grignard reagent and subsequently reacted with acetaldehyde to furnish the alcohol (±)-**67**. The ^{1}H NMR 3H-doublets at δ 1.17, and 1H-mutiplets at δ 3.73-3.82, and the ^{13}C NMR peak at δ 67.7 confirmed its $CH_3CH(OH)$- moiety. This was subjected to a *trans*-acetylation with vinyl acetate in hexane or diisopropyl ether in the presence of different commercial lipase preparations (porcine pancreatic lipase (PPL), *Candida rugosa* lipase (CRL), an immobilized-CRL (Sigma-Aldrich, 80841), and Novozym 435®). The results are shown in **Table III.1.1**. PPL and the immobilized-CRL were ineffective in both the solvents, while the CRL-catalyzed acetylation proceeded in diisopropyl ether, but without any enantioselectivity. The Novozym 435®-catalyzed acetylation of (±)-**67** in diisopropyl ether furnished the acetate (*R*)-**68** (97% ee, E = 126) (IR band at 1738 cm^{-1} and ^{1}H and ^{13}C NMR resonances at δ 2.01 and at δ 169.9 respectively) and (*S*)-**67** (84% ee) after 40% conversion (*cf.* GC, 75 min). When the reaction was allowed to proceed up to 51% conversion (*cf.* GC, 2 h), (*S*)-**67** was obtained in 96% ee. Alternatively, the resolved alcohol (*S*)-**67** (obtained at 40% conversion) was enantiomerically enriched to 98% ee by a second Novozym 435®-catalyzed acetylation (15% conversion) as above. The reaction was repeated several times at various scales with reproducible results.

Table III.1.1. Resolution of (±)-**67** with different lipases[a]

Entry	Lipase	Solvent	Time	% Conversion	% ee of **67**	% ee of **68**
1	PPL	hexane	48 h	<10	--	--
2	PPL	diisopropyl ether	48 h	<10	--	--
3	immobilized-CRL	hexane	48 h	Nil	--	--
4	immobilized-CRL	diisopropyl ether	48 h	Nil	--	--
5	CRL	diisopropyl ether	48 h	25[b]	--	--
6	Novozym 435®	diisopropyl ether	75 min	40	84	97
7	Novozym 435®	diisopropyl ether	2 h	51	96	92
8	Novozym 435®	diisopropyl ether	8-10 h	15	98[b]	--

[a]The experiments were carried out using (±)-**67** (2 mmol) and vinyl acetate (3 mmol) at 25 ^{o}C.
[b]In this case, (*R*)-**67**, obtained from entry 6 was used.

Alkaline hydrolysis of the acetate (*R*)-**68** with K_2CO_3/aqueous MeOH furnished the alcohol (*R*)-**67** (IR band at 3349 cm^{-1}; absence of the NMR resonances for the acetate group). The % ees of the enantiomeric alcohols (*R*)- and (*S*)-**67** were determined from the relative intensities of the methoxyl resonances of the corresponding (*R*)-MTPA esters.[14b] The configurations of the alcohols were assigned by converting a small aliquot of the respective alkenol enantiomers into tridecan-2-ol enantiomers and comparing their optical rotations with the reported values.[60] As per the requirement of the synthesis and to make the synthesis enantioconvergent, (*S*)-**67** was converted to its enantiomer (*R*)-**67** under the Mitsunobu

conditions (Ph_3P/DIAD/*p*-nitrobenzoic acid/THF/8 h; K_2CO_3/MeOH/25 ^oC/3 h, 91-95%).[57c] The alcohol (*R*)-**67** was silylated with TBDPSCl/imidazole/DMAP to furnish (*R*)-**69**. Its ^1H NMR signals at δ 1.07, δ 7.38-7.48 and δ 7.66-7.74 as well as the ^{13}C NMR peaks in the aromatic region were as per expectation. Dihydroxylation of the alkene function in compound **69** with OsO_4/*N*-methylmorpholine *N*-oxide (NMO) gave the diol **70**. Its ^1H NMR resonances at δ 3.65-3.88 (m, 3H) and ^{13}C peaks at δ 66.8, δ 69.6 and δ 72.3 in place of the alkene NMR resonances confirmed its formation. Cleavage of its α-glycol function with $NaIO_4$ gave the aldehyde (*R*)-**71** (IR: 2712 and 1727 cm^{-1}; NMR: δ_H 9.80 (t, 1H) and δ_C 179.6). This on reaction with vinylmagnesium bromide gave the alcohol **72** as a mixture of C-3 epimers. Expectedly, its ^1H NMR showed terminal olefinic mutiplets at δ 5.07-5.25 (2H) and 5.76-5.96 (1H).

Next, the alcohol **72** was subjected to another Novozym 435®-catalyzed acetylation with vinyl acetate in diisopropyl ether to produce the acetate **73** (95% ee, E = 145) and (3*R*,13*R*)-**72** (98% ee) after 50% conversion (*cf.* GC, 6 h). The stereochemical outcome of the transesterification was consistent with our previous results,[29h,i,49] and followed Kazlauskas' empirical rule.[61] For determination of the % ees of the products, the acetate **73** was subjected to alkaline hydrolysis to obtain (3*S*)-**72**. Subsequently, both (3*S*)- and (3*R*)-**72** were converted to their respective (*R*)-MTPA esters and analyzed by ^1H NMR spectra as above. Next, in order to increase the yield of the synthesis, the alcohol (3*R*,13*R*)-**72** was converted to the required alcohol (3*S*,13*R*)-**72** by a Mitsunobu inversion. Its ^1H and ^{13}C NMR spectra are shown in **Figures III.1.2.** and **III.1.3**.

The carbinol function in (3*S*,13*R*)-**72** was protected with 3,4-dihydropyran (DHP) in the presence of pyridinium *p*-toluenesulphonate (PPTS) in CH_2Cl_2 to furnish **74**. Its one proton ^1H NMR multiplets at δ 4.63-4.68 and ^{13}C peaks at δ 95.0 and 97.7 (epimeric acetal carbon)

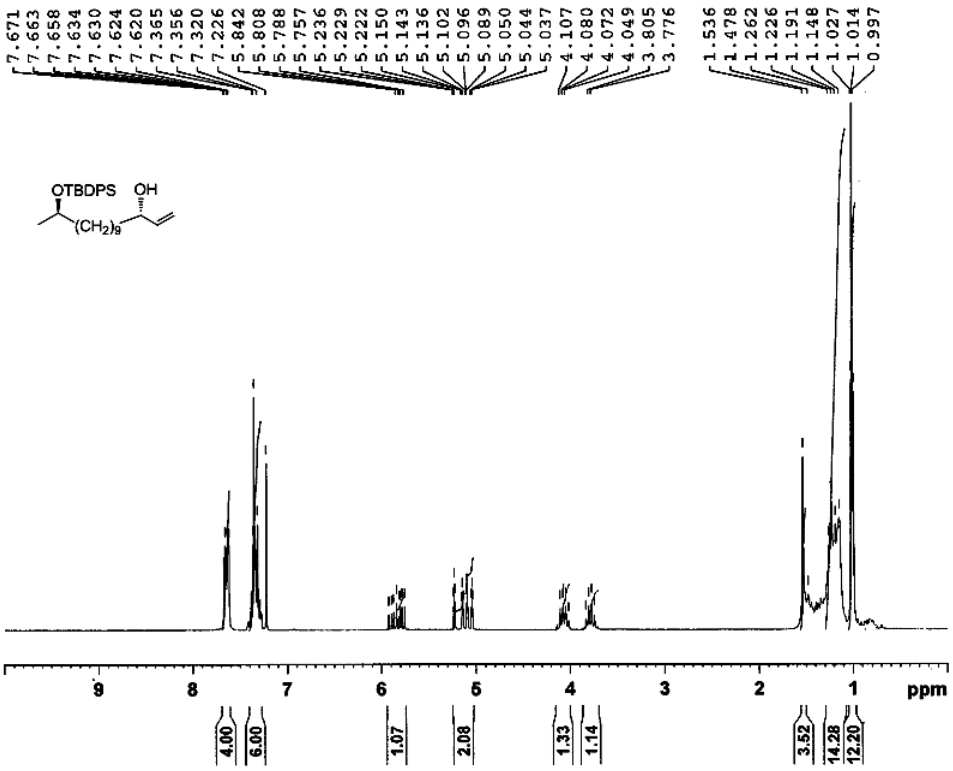


Figure III.1.2. ^{1}H NMR spectrum of (3*S*,13*R*)-**72.**

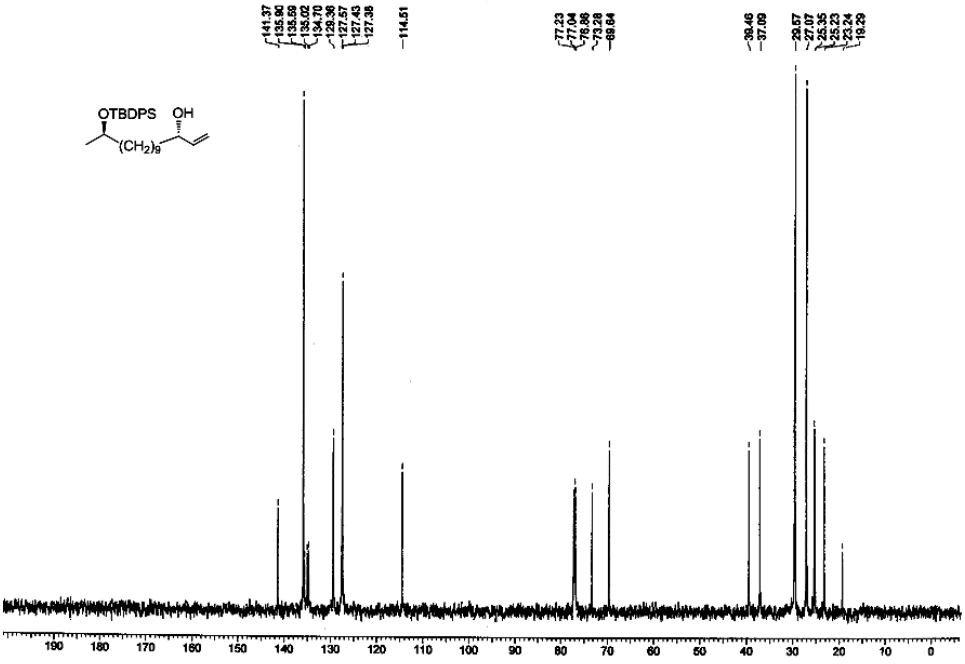


Figure III.1.3. ^{13}C NMR spectrum of (3*S*,13*R*)-**72.**

revealed the –OTHP function. As above, dihydroxylation of the alkene **74** gave **75**, which on reaction with $NaIO_4$ furnished the aldehyde **76**. This was converted to the allylic alcohol **77** by reaction of with vinylmagnesium bromide. The compounds **75**-**77** were characterized by their NMR spectra that showed expected changes, discussed earlier. However, due to the presence of additional stereogenic centres (carbinol and/ or OTHP) in them, the NMR spectra of **75**-**77** showed more peaks. Since the C-3 carbinol function of **77** would be eventually converted to the keto group in the target compound, the synthesis was continued using the C-3 epimeric mixtures of **77**. Thus, it was depyranylated with MeOH/PPTS and the resultant diol reacted with 2,2-dimethoxypropane (2,2-DMP) in the presence of PPTS to furnish the acetonide **78**. The acetonide Me protons appeared at δ 1.37 and δ 1.42 in the ^{1}H NMR spectrum, while the quaternary carbon was seen at δ 108.0 and 108.5 in the ^{13}C NMR spectrum, consistent with its epimeric nature. This was desilylated with Bu_4NF in THF to furnish the alcohol **79** (absence of TBDPS NMR signals). This on reaction with ethyl acrylate in the presence of Novozym 435® as the catalyst afforded the acrylate ester **80**. Besides the IR ester band at 1723 cm^{-1}, its ^{1}H NMR resonances at δ > 5.1 and ^{13}C NMR peak at δ 165.9 confirmed its structure. Finally, an RCM reaction of **80** in the presence of Grubbs' II catalyst in refluxing CH_2Cl_2 furnished the desired macrolide **Va** in good (81%) yield. The spectral data (^{1}H and ^{13}C NMR spectra shown in **Figures III.1.4.** and **III.1.5**.) of the synthesized **Va** were in conformity with its structure and corresponded well with the reported values.[52] In particular, the ^{1}H the NMR resonances at δ 6.00 (d) and δ 6.83 (dd) with J = 15.6 Hz also confirmed the *E* geometry of the olefin.

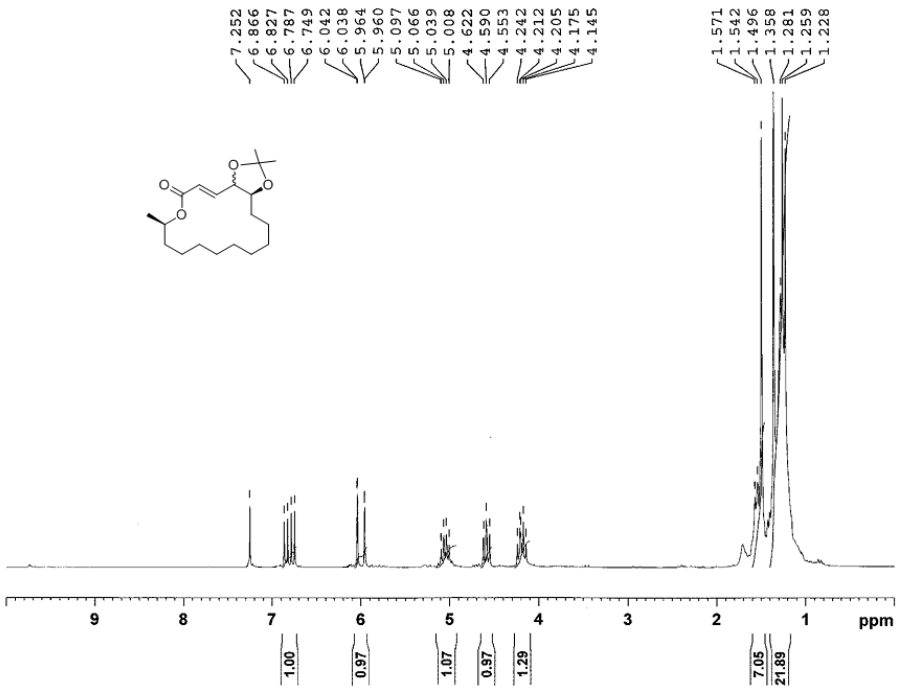


Figure III.1.4. ^{1}H NMR spectrum of **Va.**

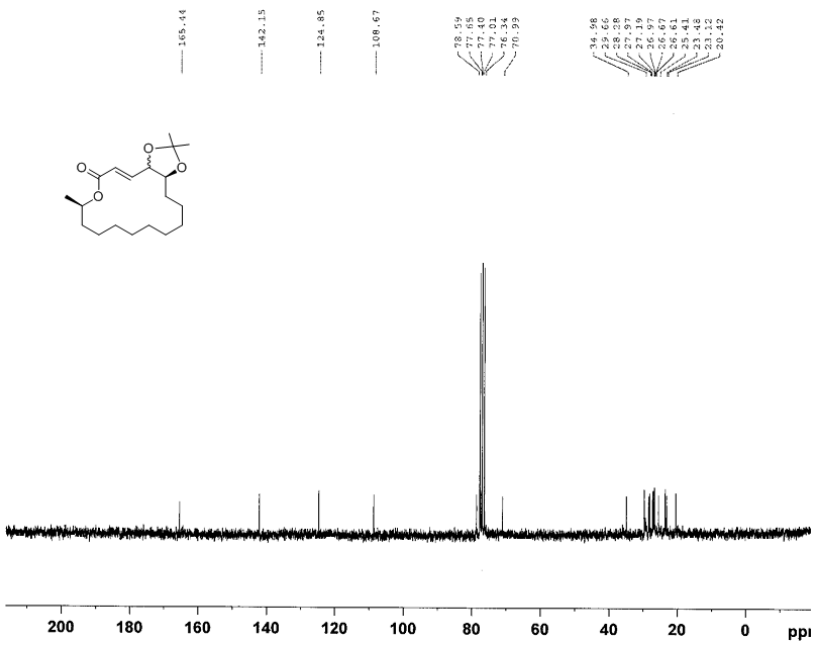
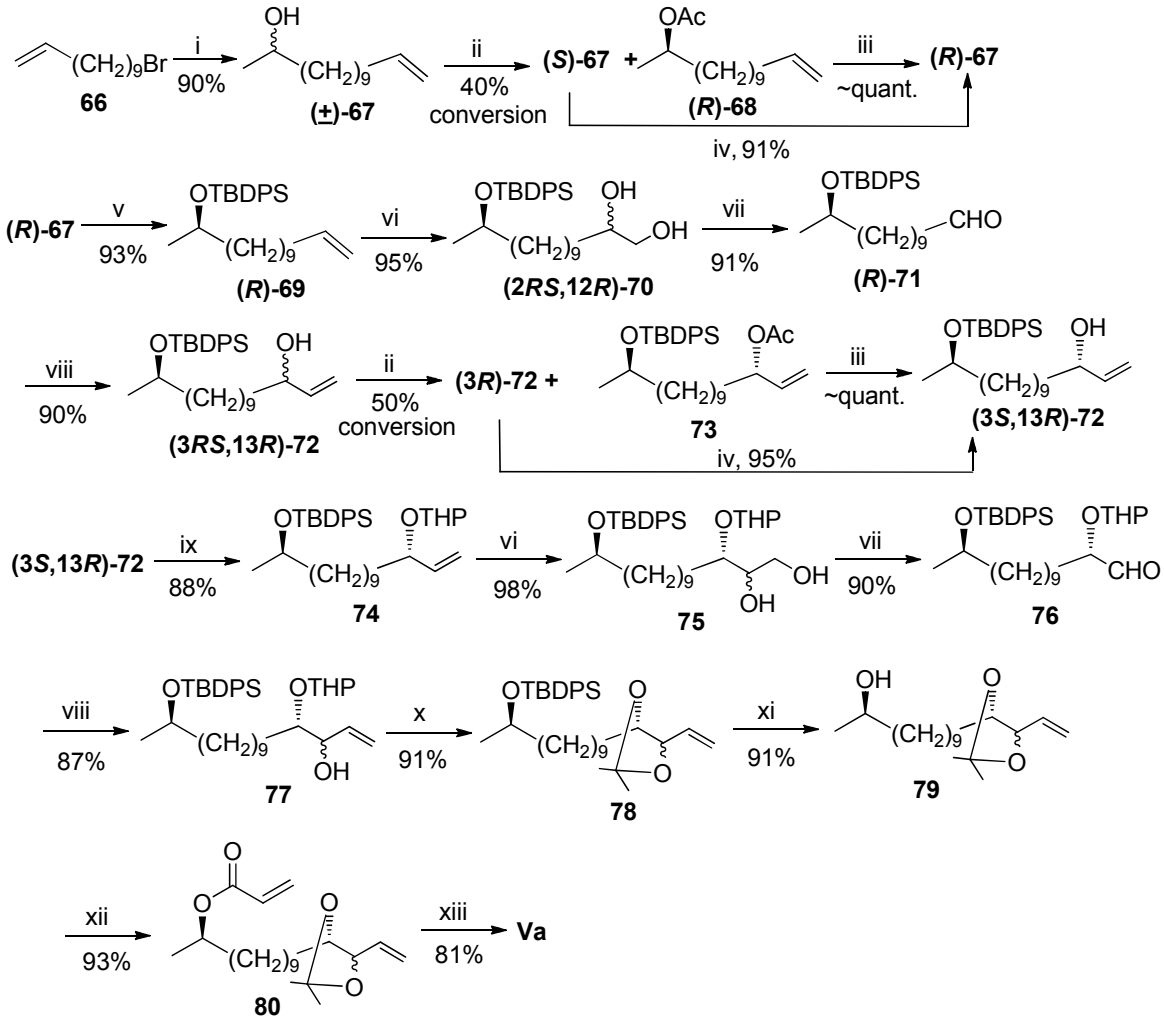


Figure III.1.5. ^{13}C NMR spectrum **Va.**

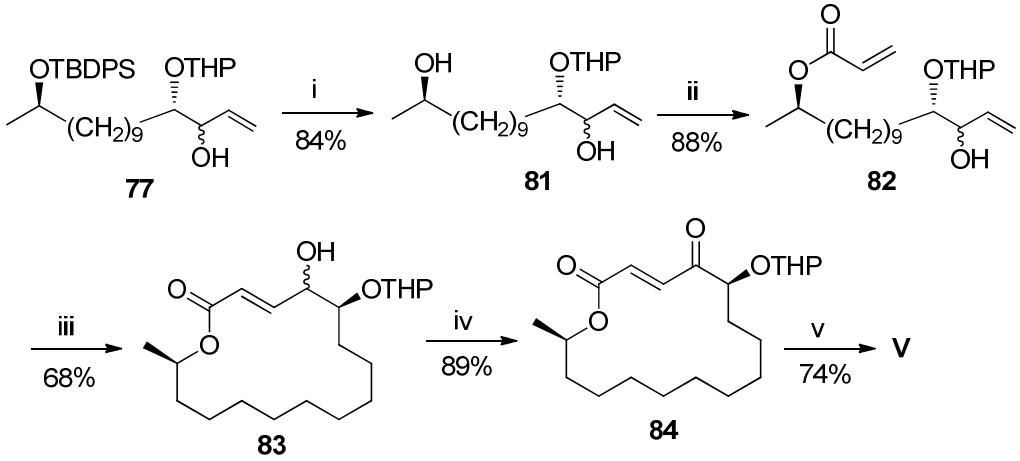


i) Mg/THF/25 ^{o}C/CH_3CHO/3 h, ii) Vinyl acetate/ diisopropyl ether/Novozym 435®/25 ^{o}C/75 min (for **(±)-67**); 6 h (for (3*RS*,13*R*)-**72**), iii) K_2CO_3/aqueous MeOH/25 ^{o}C/6 h, iv) DIAD/Ph_3P/*p*-$NO_2C_6H_4CO_2H$/THF/8 h; K_2CO_3/aqueous MeOH, v) TBDPSCl/imidazole/4-DMAP/CH_2Cl_2/0 to 25 ^{o}C/7 h, vi) OsO_4/NMO/acetone-H_2O (8:1)/*t*-BuOH/25 ^{o}C/10 h, vii) $NaIO_4$/MeCN-H_2O/0 ^{o}C/2 h, viii) CH_2=CHMgBr/THF/-78 ^{o}C/1 h, ix) DHP/PPTS /CH_2Cl_2/25 ^{o}C/4 h, x) PPTS/MeOH/25 ^{o}C/6 h; 2,2-DMP/PPTS/25 ^{o}C/12 h, xi) Bu_4NF/THF/0 ^{o}C/4 h, xii) CH_2=$CHCO_2Et$/ Novozym 435®/25 ^{o}C/24 h, xiii) Grubbs' II catalyst/CH_2Cl_2/Δ/8 h.

Scheme III.1.4.

Synthesis of the macrolide **V** from **Va** requires hydrolysis of the acetonide function, followed by the regioselective installation of a succinic acid moiety onto the C-5 carbinol function and oxidation of the C-4 carbinol moiety. Previous attempts for selective oxidation of the unnecessary C-4-hydroxyl group in the presence of those at the C-5 and C-15 positions were

unsuccessful. The earlier syntheses of macrolide **V** from **Va** was achieved using multiple steps.[54a-c] In view of these, presently, the **Scheme III.1.4** was slightly modified to formulate an improved total synthesis of **V**. For this (**Scheme III.1.5**), the alcohol **77** was desilylated with Bu_4NF in THF to obtain the diol **81**. Its Novozym 435-catalyzed reaction with ethyl acrylate proceeded regioselectively at the methylcarbinol centre, without affecting the allylic carbinol function to furnish **82**. The IR and NMR spectra of **82** were similar to that of **80** and showed features, typical of its constituent acrylate functionality.



i) Bu_4NF/THF/0 °C/4 h, ii) CH_2=$CHCO_2Et$/Novozym 435/25 °C/72 h, iii) Grubbs' II catalyst/CH_2Cl_2/ 50 °C/4 h, iv) PCC/NaOAc/CH_2Cl_2/2 h, v) TFA/moist THF/0 °C/3 h; succinic anhydride/DMAP (cat.)/ CH_2Cl_2/2 h.

Scheme III.1.5.

The lipase-catalyzed acrylation has been extensively studied, owing to its potential application in chemical industries.[62] Till date there is only one report of using it for the kinetic resolution of alcohols.[63] However, this was achieved with the activated ester, vinyl acrylate that needed to be synthesized separately. Instead, we achieved the acrylation using commercially available ethyl acrylate. Despite being a slow reaction, we found several advantages in the enzymatic acrylation, compared to the conventional base-catalyzed reaction with acryloyl chloride. The enzymatic reaction could be carried out with **79** (*vide supra*) and **81** avoiding the

hygroscopic, hazardous and toxic acryloyl chloride. With both the compounds, the reaction proceeded without any side reaction or formation of any colored products, and the acrylate esters **80** and **82** were conveniently isolated by filtering the reaction mixture, solvent removal and column chromatography. In particular, the result of the Novozym 435®-catalyzed acrylation of **81** is noteworthy. Given that Novozym 435® is known to acylate both 2-alkanols and 3-alkenols,[29h,i] the exclusive formation of **82** suggested that the chosen lipase discriminated between the designated carbinol functionalities. Further, the 14*R*-stereochemistry of the alcohols **79** and **81** also matched with the inherent enantioselectivity of the chosen lipase. Hence this strategy may be useful in asymmetric syntheses of compounds, possessing a chiral methylcarbinol moiety. At present we don't have any explanation for the observed chemo-selectivity of the reaction. Nevertheless, the results are valuable in organic synthesis, and unprecedented to the best of our knowledge. Finally, an RCM reaction of **82** in the presence of Grubbs' II catalyst furnished the macrolide **83** in good (68%) yield. Appearance of two olefinic multiplets at δ 6.04-6.18 and δ 6.82-6.95 (each, 1H) in its ^{1}H NMR spectrum confirmed the RCM reaction. This on oxidation with buffered PCC gave the ketone **84** (IR band at 1725 cm^{-1} in place of the OH band) uneventfully. The notable changes in its NMR spectra *viz*. the downfield shifts of the olefinic resonances to δ_H 6.78 (d, J = 15.8 Hz, 1H) and δ_H 7.28 (d, J = 15.8 Hz, 1H), and δ_C 199.7 were consistent with the introduction of the keto group, α-to the alkene functionality. Depyranylation of **84** with aqueous TFA, followed by a base-catalyzed succinoylation produced the target compound **V**. The spectral data (^{1}H and ^{13}C NMR spectra shown in **Figures III.1.6.** and **III.1.7.**.) of the synthesized **V** were in conformity with its structure and corresponded well with the reported values.[64]

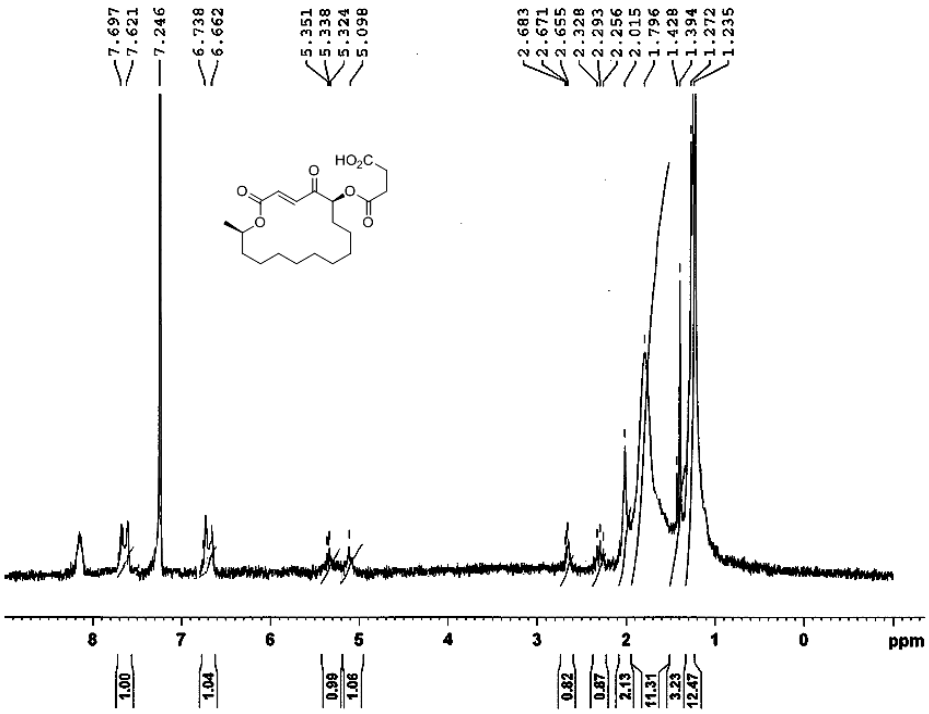


Figure III.1.6. ^{1}H NMR spectrum of **V.**

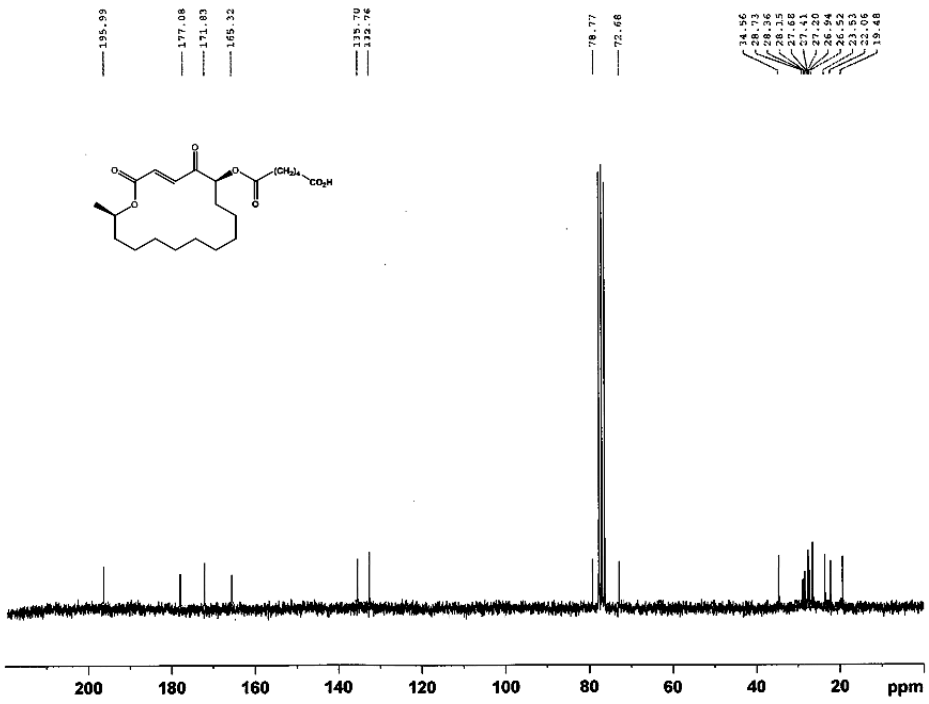


Figure III.1.7. ^{13}C NMR spectrum **V.**

Overall, a formal and a total synthesis of the macrolide antibiotic (-)-A26771B have been developed using a chemoenzymatic approach. The required stereogenic centres of the target molecules were instilled using the green biocatalytic reactions as the key steps. We also used Mitsunobu inversion after the lipase-catalyzed acylation steps to offset the limitation of a resolution-based synthesis by making it enantio-convergent. This improved the yield of the synthesis. Since our methodology gives access to all possible stereoisomers of the key intermediate **72**, it would be possible to access all the stereomers of the macrolide based on the described methodology. This strategy also provided easy access to the enantiomers of chiral methylcarbinol $CH_3CH(OH)$ and secondary allylic alcohol moieties that are very useful for the syntheses of many bioactive compounds. Further, the unprecedented Novozym 435®-catalyzed protocol for the chemo-selective acrylation using a non-traditional acyl donor (ethyl acrylate) is particularly noteworthy and elevates the significance of the work. This strategy may be useful in kinetic resolution of chiral $CH_3CH(OH)$ moiety to furnish the corresponding acrylates for their subsequent conversion to a diverse array of natural products. Use of inexpensive reagents/materials, and application of operationally simple reactions were the other attractive features of the flexible, efficient and scalable syntheses.

Alternate Synthesis of V. Most of the previous syntheses of **V** including the present one, discussed above involve introduction of the unnecessary C(4)-hydroxyl group followed by its conversion to the keto group. This is achieved by differentiation of the C(4)-carbinol centre from the other hydroxyl groups, necessitating the use of different orthogonal carbinol protecting/deprotecting strategies. Hence an alternative, short synthesis of **V** (**Scheme III.1.6**) was also developed.

In this case, we used the alcohol (*S*)-**67**, which on silylation with TBDPSCl/imidazole/DMAP furnished (*S*)-**69**. Its NMR spectral features were similar to that of its enantiomer and consistent with its chemical structure. Cleavage of its alkene function by ozonolysis (O_3/Ph_3P) gave the aldehyde (*S*)-**71** [IR: 2710 and 1717 cm^{-1}; NMR: δ_H 9.76 (t, *J* = 1.8 Hz, 1H) and δ_C 202.5]. Next, the aldehyde (*S*)-**71** was reacted with allyl$(Bu)_3Sn$ in the presence of $InCl_3$ and activated 4Å molecular sieves using (*R*)-BINOL[65] as the chiral auxiliary in CH_2Cl_2 to obtain the alcohol **85** as a single diastereomer. The ^1H NMR resonances (^1H and ^{13}C NMR spectra shown in **Figures III.1.8.** and **III.1.9**.) at δ 2.16-2.27 (m, 2H), and at δ 5.09-5.16 (m, 2H) and δ 5.76-5.96 (m, 1H) accounted for the allyl group in **85**. Its carbinol function was protected as the tetrahydropyranyl ether **86** with DHP/PPTS in CH_2Cl_2 (NMR: δ_H 4.64-4.70 (m, 1H), δ_C 96.7 and 97.9). This was desilylated with Bu_4NF in THF to furnish the alcohol **87**, which was subsequently esterified with acrylic acid under the Mitsunobu conditions to obtain the acrylate **88** (NMR: δ_H 6.37 (dd, *J* = 1.7, 17.2 Hz, 1H, one of the terminal conjugated olefinic protons), δ_C 166.1). An RCM reaction[37] of **88** in the presence of Grubbs' II catalyst in refluxing CH_2Cl_2 furnished the desired macrolide **89** in good (75%) yield. One of the olefinic resonances of **89** appeared at δ 5.84 (broad d, *J* = 15.6 Hz, 1H), accounting for the *E*-geometry of the olefin function installed by the RCM reaction. Following a reported method,[66] compound **89** was subjected to a SeO_2-catalyzed allylic oxidation to obtain the intermediate γ-oxo compound **84**, which on aqueous TFA-mediated depyranylation, followed by a base-catalyzed succinoylation produced the target compound **V**.

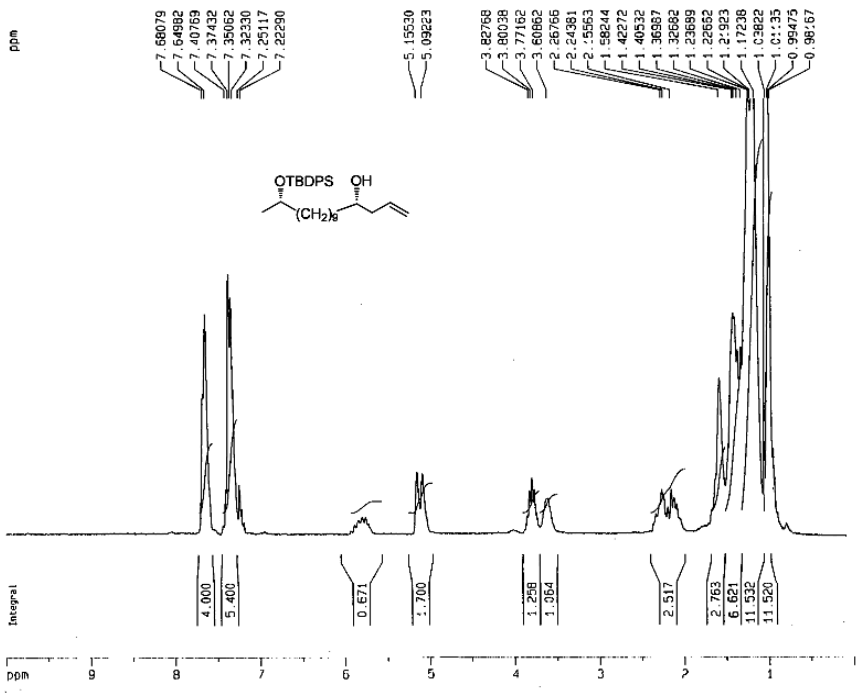


Figure III.1.8. ^{1}H spectrum of **85**

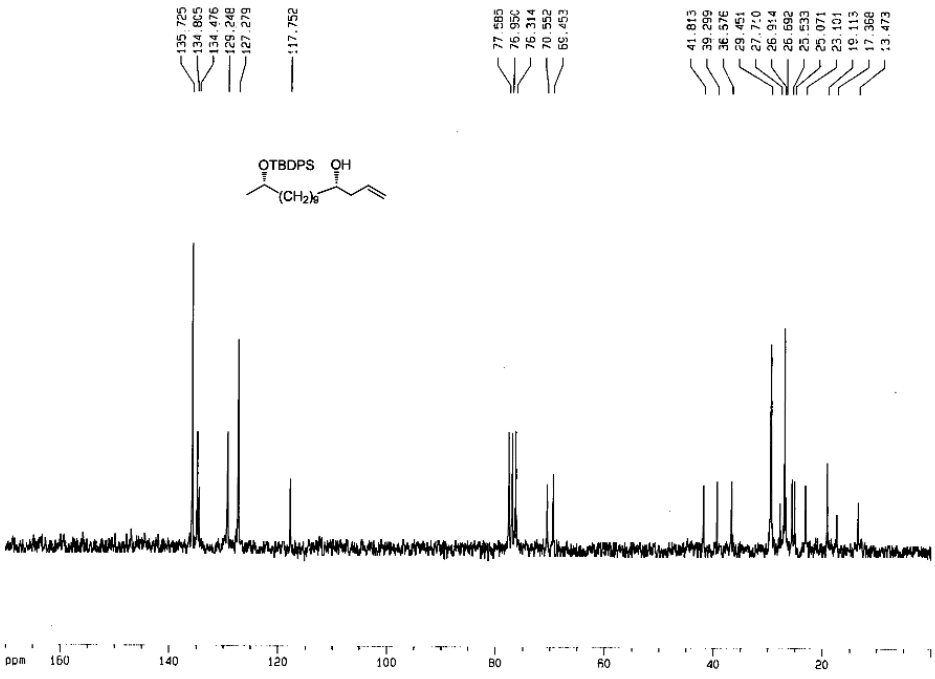
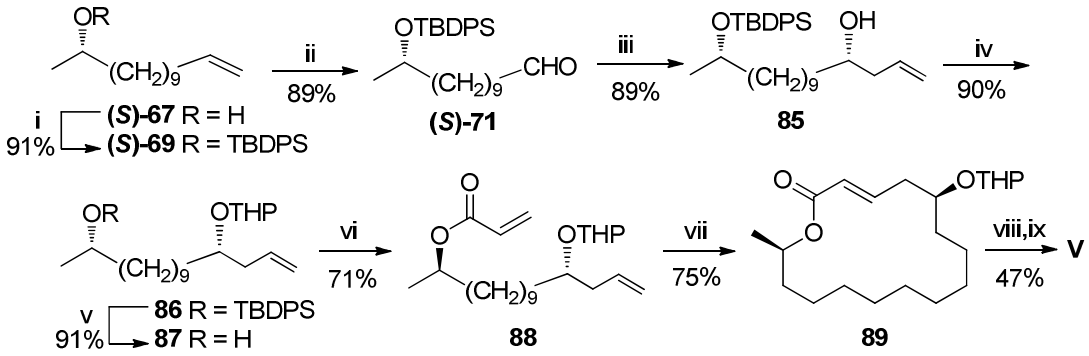


Figure III.1.9. ^{13}C NMR spectrum of **85.**



i) TBDPSCl/imidazole/DMAP/CH_2Cl_2/25 ^oC/7 h, ii) O_3/MeOH/-78 ^oC/1 h; Ph_3P/-40 ^oC/3 h/25 ^oC/12 h, iii) $AllylSnBu_3$/$InCl_3$/molecular sieve 4Å/(*R*)-BINOL/THF/-78 ^oC/4 h; 25 ^oC/8 h, iv) DHP/PPTS/CH_2Cl_2/25 ^oC/4 h, v) Bu_4NF/THF/0 ^oC/4 h, vi) Ph_3P/DIAD/CH_2=$CHCO_2H$/THF/12 h, vii) Grubbs' II catalyst/CH_2Cl_2/ reflux/8 h, viiii) SeO_2/1,4-dioxane/reflux/24 h, ix) TFA/ moist THF/0 ^oC/3 h; succinic anhydride/DMAP (catalytic)/CH_2Cl_2/2 h.

Scheme III.1.6.

III.2. DIVERSITY-ORIENTED SYNTHESIS OF PYRENOPHOROL ENANTIOMERS

III.2.1. Introduction

With the rapid advancements in biological and material sciences, the organic chemists are facing the challenge of synthesizing collections of molecules, instead of a single molecule. This is because the structural/stereochemical complexity and diversity of the molecules govern their function. This has led to a paradigm shift in organic chemistry research from the target-oriented syntheses to diversity-oriented syntheses (DOS), which represents an approach towards small-molecule library synthesis that seeks to incorporate a high degree of structural diversity efficiently.[67] Generation of high levels of stereochemical and skeletal diversity is especially challenging. Increasing the size and number of rigidifying elements (macrocycles, polycycles, olefins, etc.) in small molecules is essential for these compounds to bind to sites of protein-protein interactions. The generation of structurally diverse compounds is equally important, as the eventual target of a compound in phenotypic screens can be any one of the cell's or organism's entire collection of proteins. Indeed, numerous modulators of challenging biological targets have been identified from DOS-derived compound collections.[68] For achieving skeletal diversity, Schreiber proposed the *branching reaction pathways*, in which a single molecular skeleton is exposed to different reaction conditions to effect unique rearrangements into alternative skeletons. However, a reagent-based stereocontrol is crucial in order to achieve stereochemical diversity, since each substrate might react with a different diastereoselectivity to an achiral reagent leading to variable stereochemical outcomes.

Designing flexible and stereo-divergent protocols, leading to several targets from a single starting molecule has vital significance in organic synthesis. Small chiral intermediates with high functional density and multiple stereogenic centres are especially attractive to synthesize targets

of structural and stereochemical diversities. This warrants identification of such a core intermediate that can be efficiently derivatized into various complex target compounds of interest. Based on a literature search on the macrolides, we identified several bioactive compounds **VI-XI** (**Figure III.2.1.**) that contain the hept-6-ene-2,5-diol derivatives **C** (different stereomers and Pgs) as the common structural motif. This structural feature offered a remarkable opportunity to formulate a divergent strategy for the synthesis of a wide array of complex target molecules starting from the diol derivatives **C** as the ideal small-molecule chiral DOS-intermediates. As explained before, use of biocatalysts, in particular, the lipases have enriched organic synthesis immensely. Hence, in the present work, we have formulated a highly efficient biocatalytic route to all the four stereomers of **C** (Pg = TBDPS) as well as two stereomers of another derivative (Pg = PMB), and used some of these DOS-intermediates to devise asymmetric syntheses of the natural macrodiolide (-)-pyrenophorol (**VI**) as well as its enantiomer. Compound **VI** was isolated from *Byssochlamys nivea*,[69a] *Pyrenophora avenae,*[69b] and *Stemphylium radicinum*[69c] cultures as well as from the imperfect fungus *Alternaria alternate*.[69d] It is specifically phytotoxic to the host *Avena sterilis* (wild oat), but not to other related plant species,[70a] and also inhibited the growth of *Microbotryum violaceum*, *Chlorella fusca*, *Escherichia coli* and *Bacillus megaterium.*[70b,c] In addition, it is a promising nootropic and antidepressant agent.[70d,e] The compound possesses interesting structural features like stereochemically pure carbinol appendages and/ or properly placed olefinic moieties of well-defined geometries. These, coupled with its biological activity make it an attractive and challenging synthetic target.

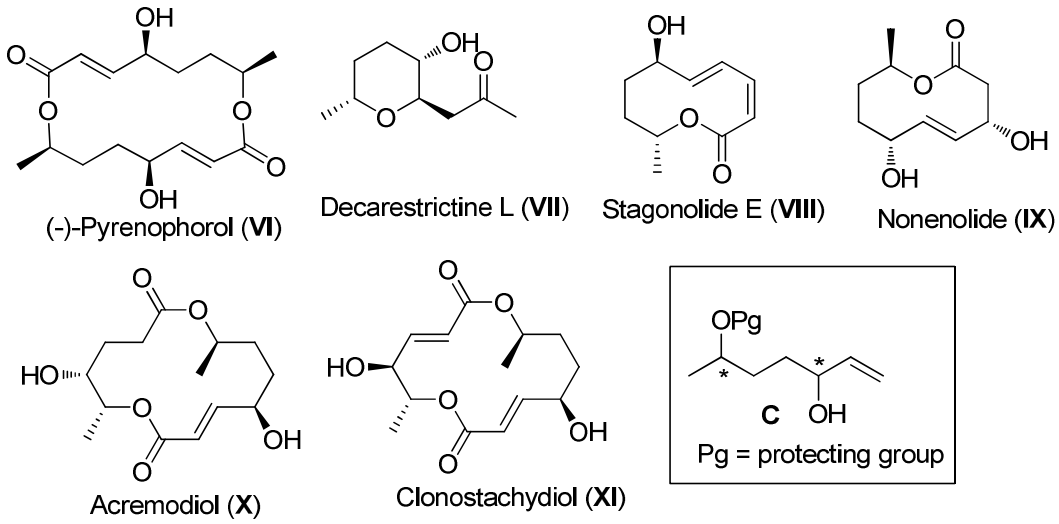
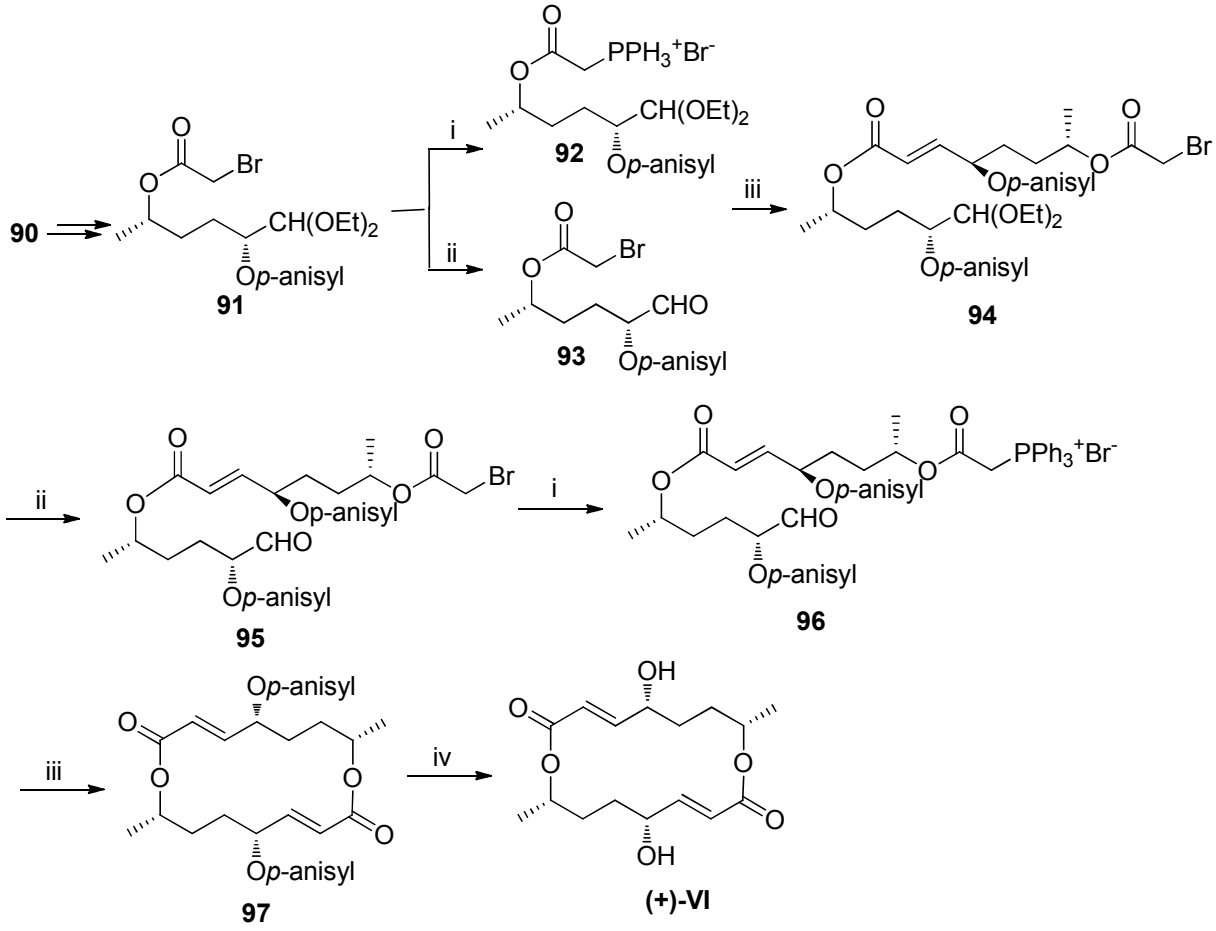


Fig. III.2.1. Some representative natural products bearing the hept-6-ene-2,5-diol structural motif.

III.2.2. Previous Syntheses

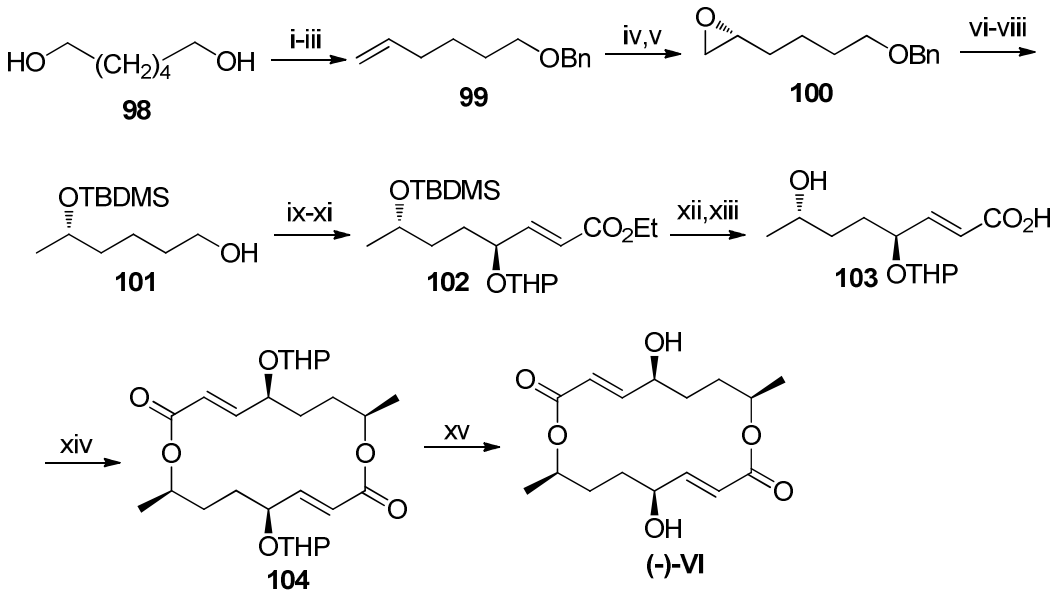
Several enantiomeric syntheses of **VI** have been reported,[71] which are briefly discussed in this section. Using a novel asymmetric catalytic alkynylation of acetaldehyde as the key step, a concise synthesis of the tetrahydro analogue of **VI** has been recently developed.[72] A few of these syntheses are described in the following. In one of the earlier synthesis of (+)-**VI** (**Scheme III.2.1.**),[71c] the bromoacetal **91** (derived from (*S*)-ethyl lactate **90**) was converted to the phosphonium salt **92** and the aldehyde **93** respectively, via two parallel sequences of conventional reactions. A Wittig reaction between these compounds gave the bromo acetal **94**, which on acidic hydrolysis furnished the aldehyde **95**. Its transformation to the corresponding Wittig salt **96** followed by an intramolecular Wittig reaction furnished the macrolide **97**. This was converted to (+)-**VI** by an acid-catalyzed deprotection.



i) PPh_3/CH_3CN, ii) HCO_2H, iii) TEA/CH_3CN/heat, iv) CAN/CH_3CN-H_2O/-10°C.

Scheme III.2.1.

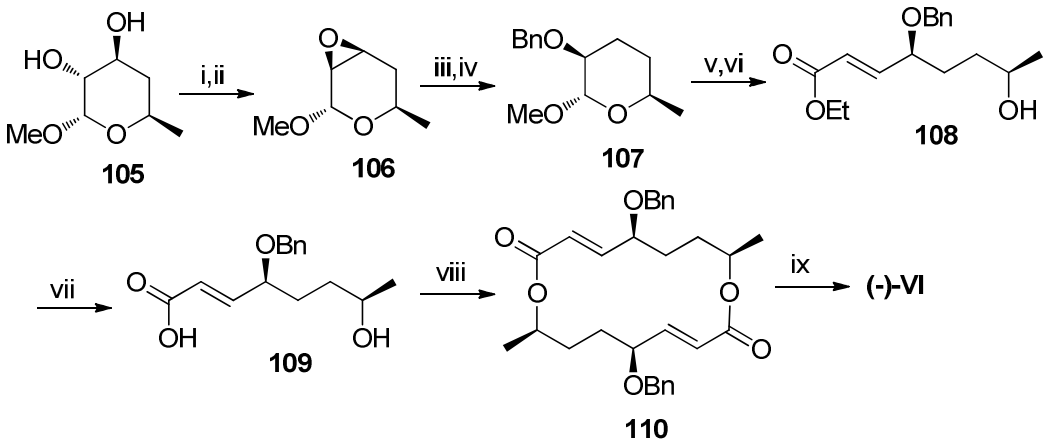
In an asymmetric synthesis of (-)-**VI** (**Scheme III.2.2.**),[71d] the diol **98** was monobenzylated and converted to the alkenol derivative **99** by iodination of the hydroxyl function and a base-catalyzed elimination. Its epoxidation followed by a hydrolytic kinetic resolution furnished the chiral epoxide **100**, which on $LiAlH_4$ reduction, silylation and catalytic hydrogenation gave **101**. This on Swern oxidation, MacMillan α-hydroxylation, Horner–Wadsworth–Emmons reaction and tetrahydropyranylation gave the ester **102**. This was converted to the acid **103** by conventional alkaline hydrolysis and desilylation. Its Mitsunobu cyclization and depyranylation furnished (-)-**VI**.



i) NaH/Bu_4NI/BnBr/DMF, ii) I_2/imidazole/Ph_3P/THF, iii) *tert*-BuOK/THF, iv) MCPBA/CH_2Cl_2, v) (*R*,*R*)-Salen-Co-(OAc)/ H_2O, vi) $LiAlH_4$/THF, vii) TBDMSCl/imidazole/CH_2Cl_2, viii) H_2/10% Pd-C/EtOAc, ix) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2/-78 ^oC, x) Nitrosobenzene/D-proline/DMSO; $(EtO)_2P(O)CH_2CO_2Et$/ DBU/LiCl/0 ^oC; MeOH/NH_4Cl/$Cu(OAc)_2$, xi) 3,4-Dihydropyran/ CSA/CH_2Cl_2, xii) Aqueous 20% NaOH/MeOH, xiii) Bu_4NF/THF/80 ^oC, xiv) Ph_3P/DEAD/toluene-THF-25 ^oC, xv) *p*-TsOH/MeOH.

Scheme III.2.2.

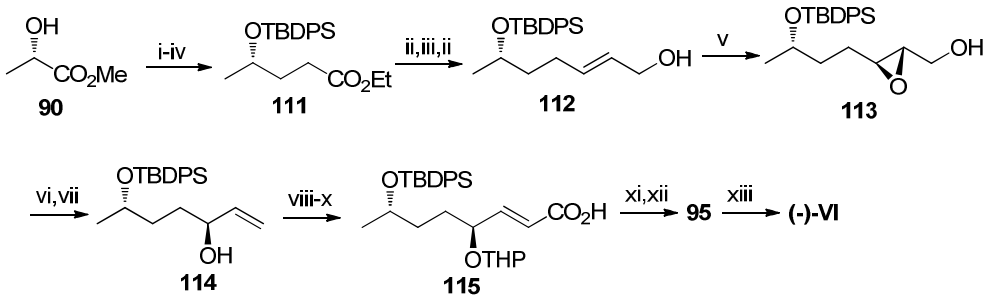
In another synthesis of (-)-**VI** (**Scheme III.2.3.**),[71e] the chiral pool-derived material, methyl α-D-glucopyranoside (**105**) was transformed to the epoxide **106** by mono-tosylation and base treatment. Regioselective reduction of its oxirane group and benzylation gave **107**. This on acid-catalyzed deacetalization followed by a two-carbon homologation via the Wittig route afforded the conjugated ester **108**, which after alkaline hydrolysis to **109** and Yamaguchi lactonization gave **110**. This was converted to the target compound by debenzylation.



i) *p*-TsCl/pyridine, ii) *tert*-BuOK/benzene, iii) $LiAlH_4/Et_2O$, iv) NaH/BnBr/Bu_4NI/THF, v) H_2SO_4/AcOH,vi) $Ph_3P{=}CHCO_2Et$/benzene, vii) LiOH/THF/MeOH-H_2O, viii) Yamaguchi lactonization, ix) $TiCl_4/CH_2Cl_2$.

Scheme III.2.3.

More recently, (*S*)-ethyl lactate (**90**) was used for the synthesis of (-)-**VI** (**Scheme III.2.4.**).[71f] Thus, compound **90** was silylated, reduced with DIBAL-H, two-carbon homologated by a Wittig reaction and hydrogenated to obtain **111**.



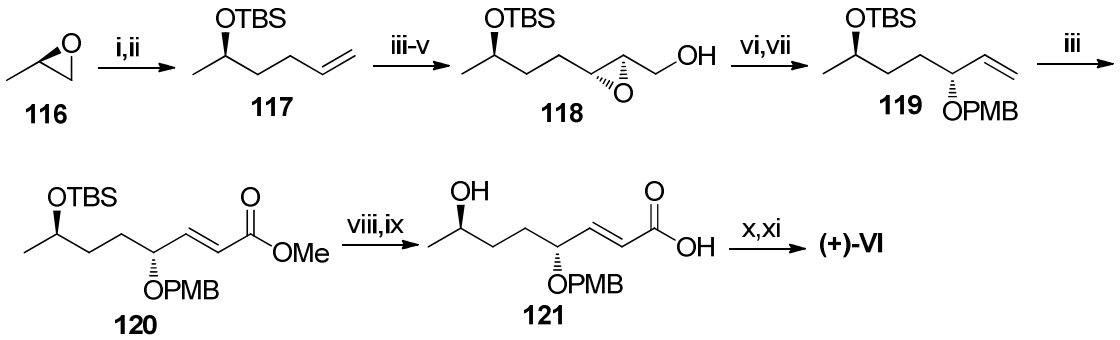
i) TBDPSCl/imidazole/CH_2Cl_2, ii) DIBAL-H/CH_2Cl_2/-78°C, iii) $Ph_3P{=}CHCO_2Et$/benzene/reflux, iv) $NiCl_2.6H_2O/NaBH_4$/MeOH/0 °C, v) (L)-DIPT/Ti(O^iPr)$_4$/TBHP/CH_2Cl_2/-20 °C, vi) I_2/imidazole/PPh_3/THF-MeCN, vii) Zn/MeOH/reflux, viii) $CH_2{=}CHCO_2Et$/Grubbs catalyst, ix) 3,4-Dihydropyran/CSA/CH_2Cl_2, x) Aqueous 20% NaOH/MeOH, xi) Bu_4NF/THF/60 °C, xii) Ph_3P/DEAD/toluene-THF, xiii) *p*-TsOH/MeOH.

Scheme III.2.4.

This was converted to the allylic alcohol **112** using a similar sequence of reactions involving DIBAL-H reduction and Wittig olefination. Its Sharpless epoxidation to **113** followed by iodination of the alcohol group and reductive elimination afforded the secondary allylic alcohol **114**. This on a cross-metathesis with ethyl acrylate, tetrahydropyranylation and alkaline

hydrolysis gave the acid **115**. The rest of the synthesis followed a similar route as described earlier.

In the latest synthesis (**Scheme III.2.5.**),[71g] the (*R*)-oxirane **116** was reacted with the allyl Grignard reagent and the resultant alcohol silylated to obtain **117**. Its ozonolysis, Wittig reaction, DIBAL-H reduction and Sharpless epoxidation with (-)-DIPT/cumene hydroperoxide/Ti(OPr^i)$_4$ gave the alcohol **118**. This on reduction with Na and PMB protection afforded **119**. Its cross-metathesis with ethyl acrylate to **120** followed by alkaline hydrolysis and desilylation gave the acid **121**, which on Mitsunobu cyclization and deprotection furnished (+)-**VI**.



i) Allymagnesium chloride/Et_2O/-78 ° C, ii) TBSCl/imidazole/CH_2Cl_2, iii) O_3/CH_2Cl_2/-78 ° C; Ph_3P=$CHCO_2Et$/ CH_2Cl_2, iv) DIBAL-H/CH_2Cl_2/-78 ° C, v) Sharpless epoxidation, vi) Na/Et_2O, vii) PMBBr/NaH/THF, viii) LiOH/ THF-MeOH-H_2O, ix) Bu_4NF/THF, x) Ph_3P/DEAD/toluene-THF, xi) DDQ/CH_2Cl_2:H_2O.

Scheme III.2.5.

III.2.3. Present Work

From the foregoing it is evident that the previous syntheses of **VI** were all target-specific, and most of these were unsuitable to access the stereomers of **VI**. Moreover, the previous syntheses of the natural and other stereomers of **VI** were relatively lengthy (14 to 21 steps), and often suffered from low yields. However, the focus of the present investigation was to develop a DOS route to various target molecules including **VI**. To realize this objective, the initial task was the preparation of different stereomers of **C** or its equivalent. We paid particular attention to using commercially available and inexpensive materials to obtain the products in high yields under operationally simple reaction conditions. For this, we relied on the Novozym 435®-catalyzed acylation strategy using vinyl acetate as the acyl donor. The syntheses of the stereomers/derivatives of the DOS intermediate and their conversions to the target molecules are sequentially presented in the following.

Preparation of the DOS intermediates. The synthesis (**Scheme III.2.6.**) commenced from the commercially available, 6-methyl-5-hepten-2-one (**122**) that on reduction with $LiAlH_4$ furnished the alcohol (±)-**123**. This was characterized from the IR hydroxyl band at 3373 cm^{-1} in place of the carbonyl band, and the NMR resonances *viz*. δ_H 1.14 (d, 3H, CH_3-CH(OH)), 3.74-3.90 (m, 1H, -CH(OH)) and δ_C 67.7 (carbinol). Several protocols for the preparation of (*R*)- or (*S*)-**123** have been reported earlier. These include use of chiral starting materials,[73a] kinetic resolution of (±)-**123** by lipase-catalyzed acylation[73b-e] or microbial oxidation,[73f] asymmetric reduction of **122** with baker's yeast or alcohol dehydrogenases,[73g-i] as well as chemical kinetic resolution.[73j] In the present studies, the alcohol (±)-**123** was efficiently resolved by carrying out its acetylation with vinyl acetate in hexane at room temperature to obtain the (*R*)-acetate **124** and (*S*)-**123** in >98% enantiomeric excesses (E≥195) after 50% conversion (*cf*. GC, 50 min). This protocol is better

than a similar protocol reported earlier using a *C. antarctica B* lipase preparation that required 30 h.[73d] Compound (*R*)-**124** showed typical spectral peaks due to the OAc functionality. *viz*. IR band at 1736 cm^{-1} and NMR resonances at δ_H 2.03 (s) and δ_C 170.8. Reduction of the acetate (*R*)-**124** with $LiAlH_4$ furnished the alcohol (*R*)-**123**. The % ees of (*R*)- and (*S*)-**123** were determined from the relative intensities of the methoxyl resonances of the corresponding MTPA esters.[14b] The configurations of (*S*)- and (*R*)-**123** were assigned based on their reported optical rotations.[74a] This also ascertained the configuration of (*R*)-**124**. In a recent paper, same sign of the specific rotations of (*S*)-**123** and (*R*)-**124** have been reported.[51b] Hence we carried out the reaction at least 10-12 times to report the $[\alpha]_D$ values. Moreover, our results are consistent with those reported by another group.[51c] It is worth mentioning that despite using CAL-B lipase and similar reaction conditions, the reaction kinetics were found to be significantly different by two groups.[73d,74b] Earlier, Faber and his group have obtained (*R*)-**124** in high yield and % ee by combining the lipase-catalyzed acylation with *in situ* inversion or, alternatively, dynamic kinetic resolution using a Ru-catalyst.[73e] However, this protocol is unsuitable for the present work, because we wanted to synthesize all the stereomers of the DOS intermediate that warranted the availability of both (*R*)- and (*S*)-**123**.

The enantiomers of the alcohol **123** were individually silylated, as previously described to obtain (*R*)- and (*S*)-**125**. The ^1H NMR spectra of both these compounds were similar, and showed peaks at δ ~1.05 (s, *t*-Bu) and multiplets for the aryl protons at δ 7.32-7.44 (6H) and δ 7.65-7.70 (4H), confirming their structures. Next, the olefin functions in (*R*)- and (*S*)-**125** were individually subjected to reductive ozonolysis (O_3/Ph_3P) in CH_2Cl_2 to get the aldehydes (*R*)- and (*S*)-**126** [IR: 2717, 1726 cm^{-1}; NMR: δ_H 9.68 (s, 1H) and δ_C 202.4] respectively. Reaction of (*R*)-**126** with commercially available vinylmagnesium bromide furnished the allylic alcohol

(3*RS*,6*R*)-**127** as a 1:1 mixture of C-3 epimers. The compound was characterized from the ^{1}H NMR CH(OH) multiplets at δ 3.98-4.00 (1H), olefinic multiplets at δ 5.01-5.20 (2H) and δ 5.69-5.86 (1H), and ^{13}C NMR peaks at δ ~ 73.2 (carbinol) and 114.5 (terminal alkene). Its Novozym 435®-catalyzed acetylation furnished (3*R*,6*R*)-**127** and (3*S*,6*R*)-**128** in >98% ees at 50% conversion (~ 6 h). The reaction was highly stereoselective, and did not proceed further even under extended shaking (**Scheme III.2.6.**). A similar sequence of reaction with (*S*)-**127** also proceeded uneventfully and provided the target intermediate diastereomers (3*R*,6*S*)-**127** and (3*S*,6*S*)-**128** in enantiomerically pure forms. The NMR spectra of the diastereomeric acetates **128** showed characteristic -$OCOCH_3$ resonances *viz.* δ_H ~2.01 (s, 3H) and δ_c ~170.3. The absolute configurations of the alcohol and acetate were empirically assigned based on the fact that the Novozym 435®-catalyzed acetylation of allylic alcohols has been found to furnish the (*S*)-acetate.[29h,i,,75] This is also consistent with Kazlauskas' empirical rule.[61] These results suggested that chirality at the distant C-6 centre did not have any bearing on the diastereoselectivity of the chosen lipase-catalyzed resolution of **127**. Earlier, depending on the choice of hydrophobic supports, different immobilized CAL-B lipase preparations showed different enantioselectivities in the hydrolysis of certain racemic esters.[76] Hence, the acetylation of (3*RS*,6*R*)- and (3*RS*,6*S*)-**127** was also attempted using another recombinant CAL-B lipase preparation (Sigma, L4777), expressed in *Aspergillus niger* and adsorbed on a macroporous acrylic resin. However, the reaction was too slow to be of any use in preparative chemistry. Previously, the synthesis of the analogs of (3*R*,6*S*)-**127** and (3*S*,6*S*)-**128** containing the *tert*-butyldimethylsilyl protection at C-6 has been described by Enders and Nguyen.[77] In this protocol, the C-3 stereogenic centre was installed using a lipase PS "Amano"-catalyzed acetylation with vinyl acetate in diisopropyl ether. However, the reaction required higher temperature (40 ^{o}C) and extended stirring (72 h).

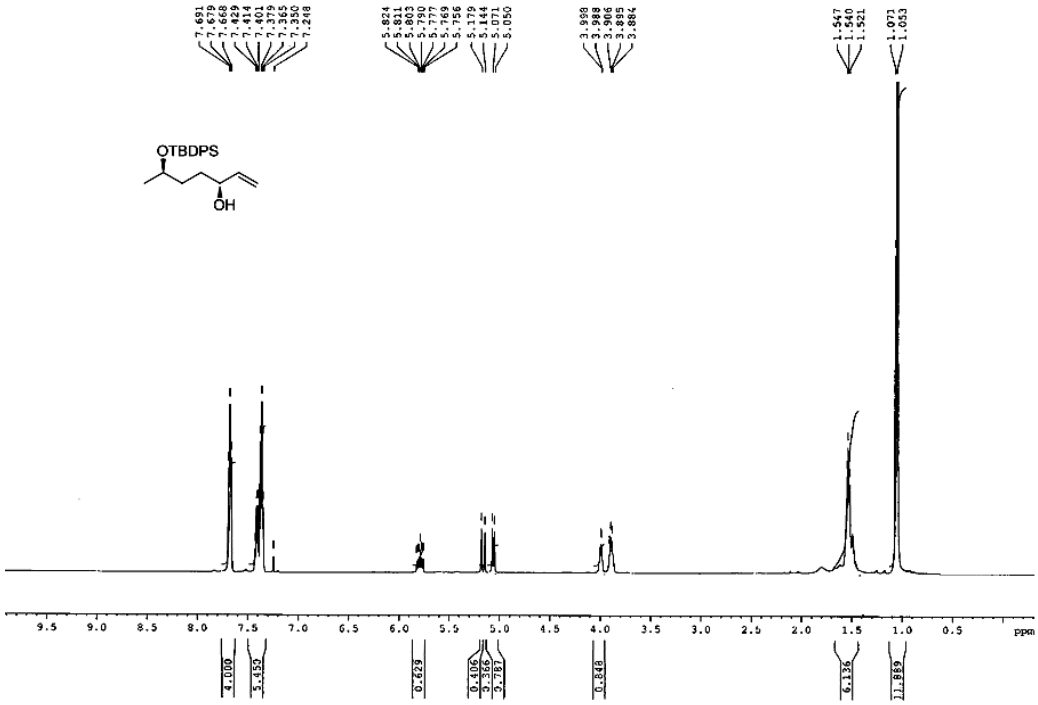


Figure III.2.2. ^{1}H NMR spectrum of (3*R*,6*R*)-**127**

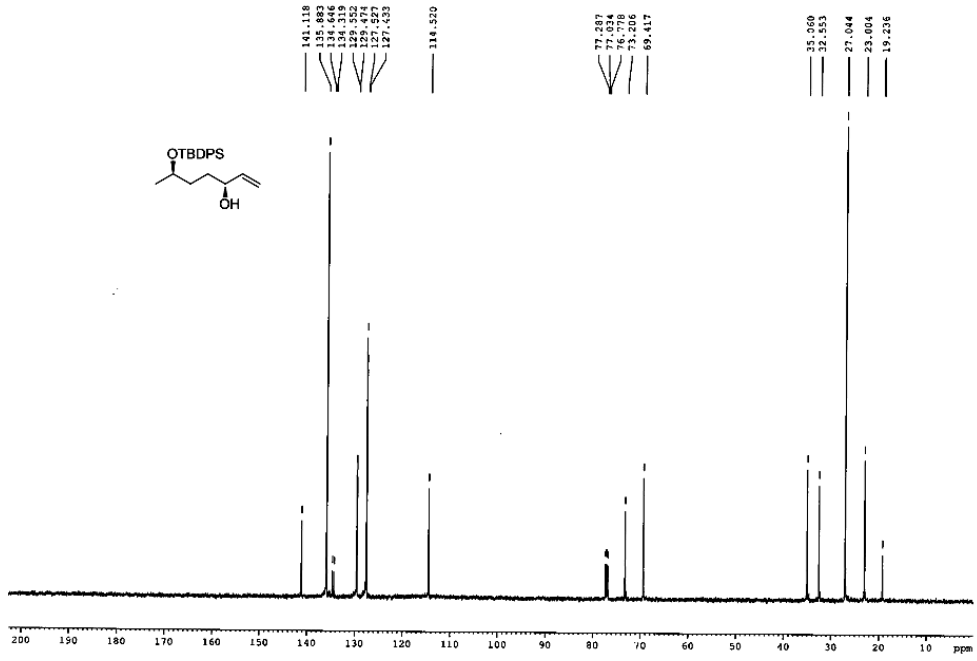


Figure III.2.3. ^{13}C NMR spectrum of (3*R*,6*R*)-**127**

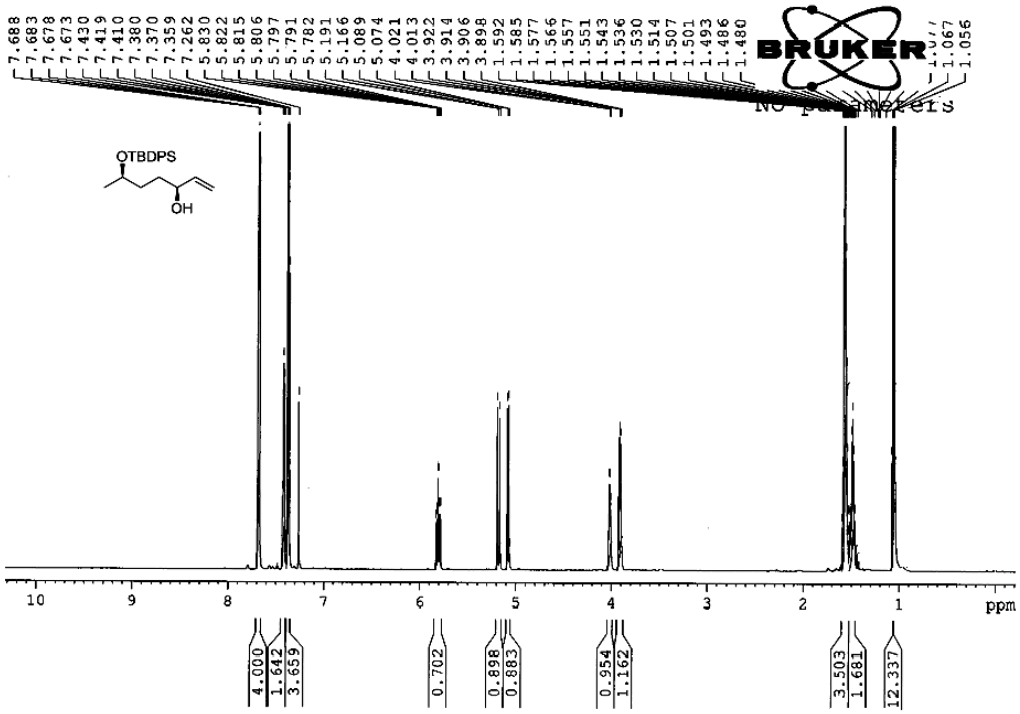


Figure III.2.4. ^{1}H NMR spectrum of (3*S*,6*R*)-**127**

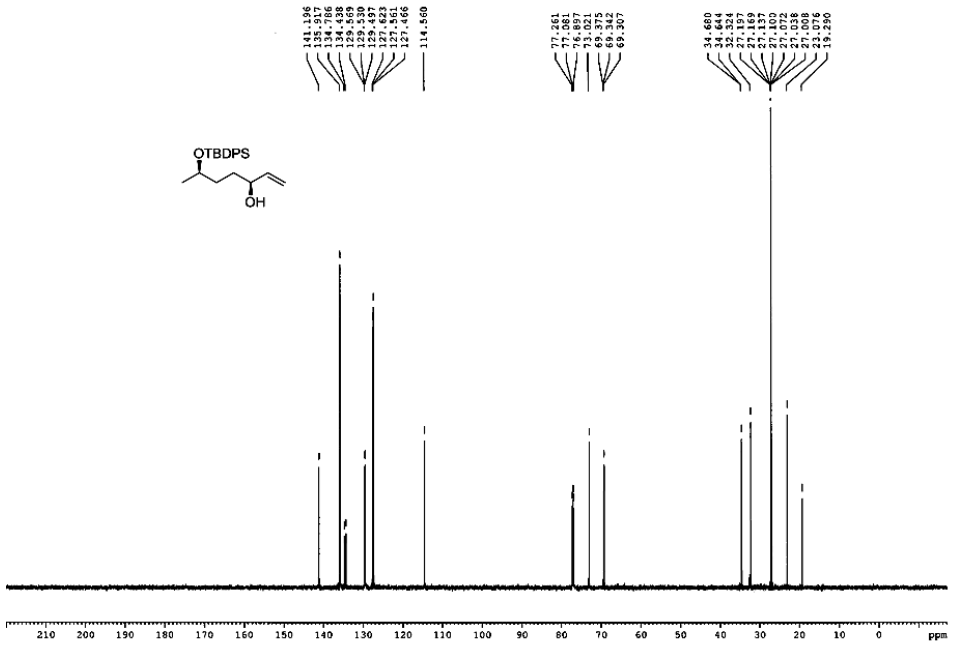


Figure III.2.5. ^{13}C NMR spectrum of (3*S*,6*R*)-**127**

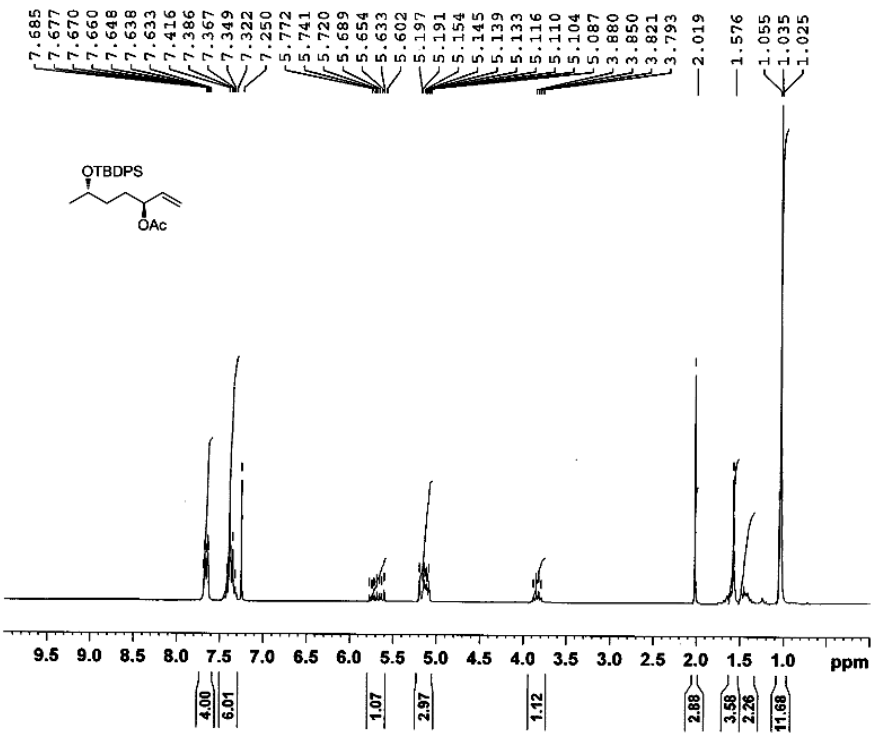


Figure III.2.6. ^{1}H NMR spectrum of (3*S*,6*S*)-**128**

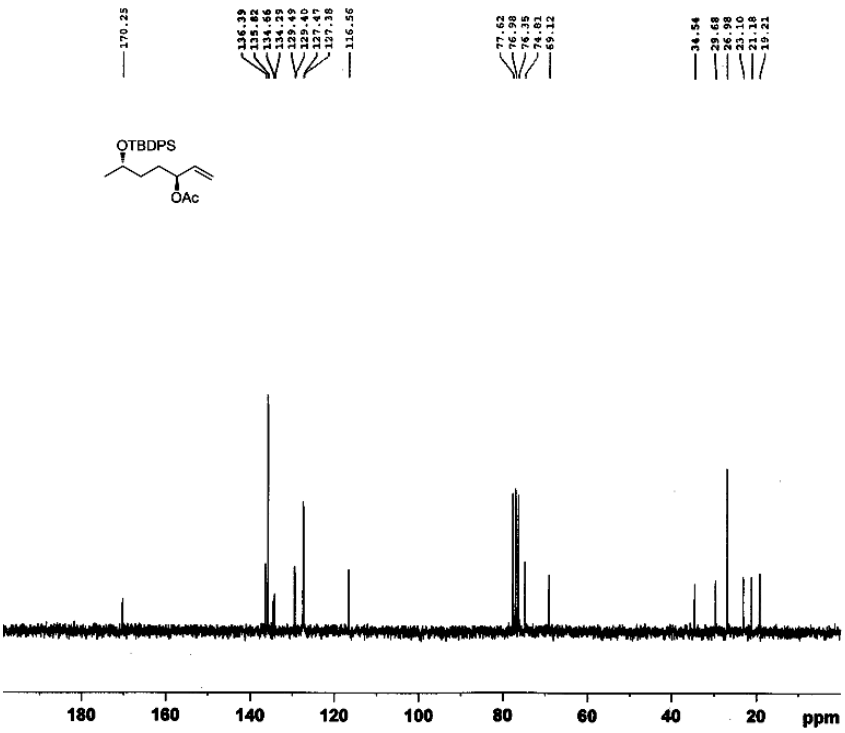
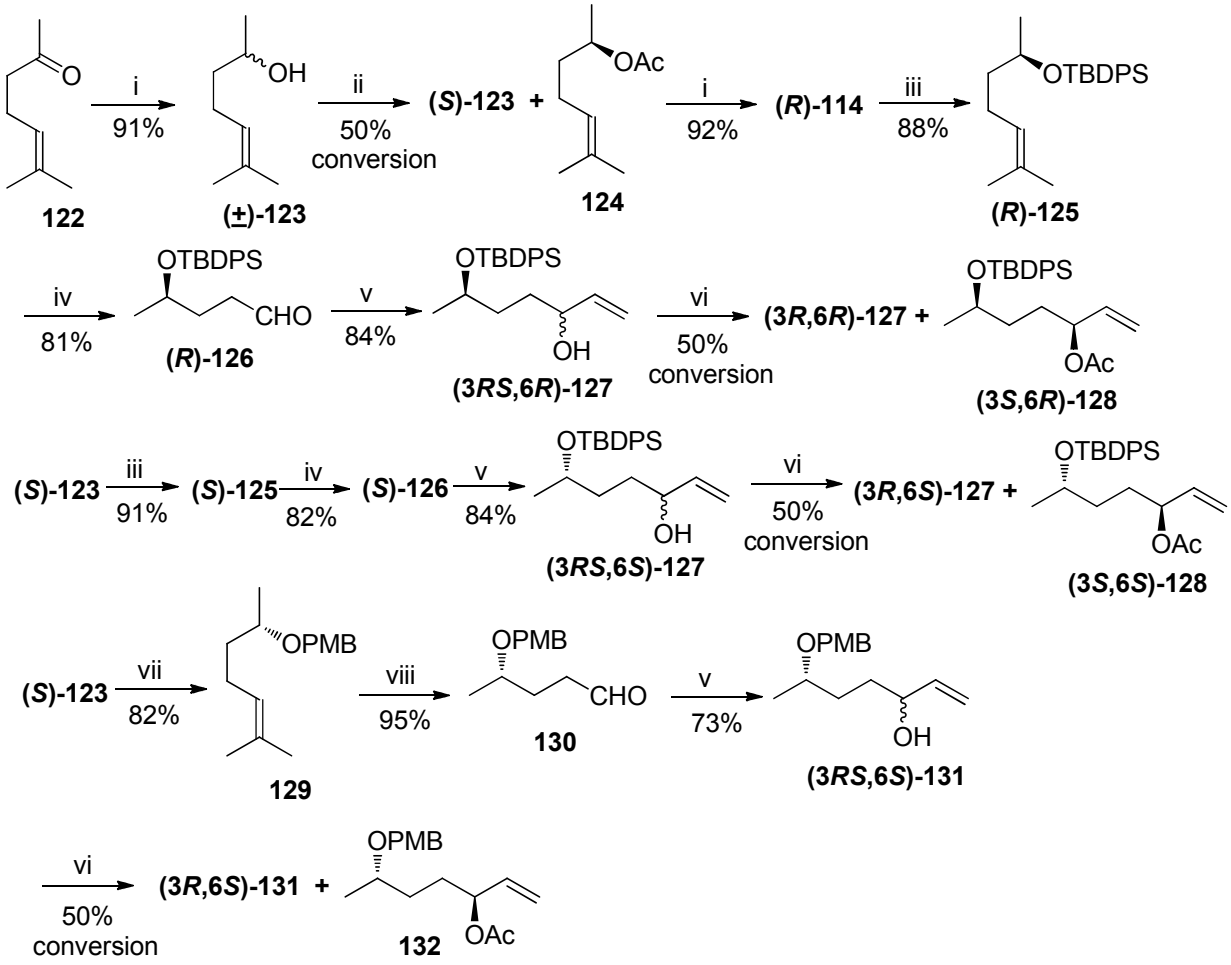


Figure III.2.7. ^{13}C NMR spectrum of (3*S*,6*S*)-**128**

Moreover, this protocol is not amenable to the corresponding 6*R*-stereomers as it was derived from (*S*)-ethyl lactate. The representative ^{1}H and ^{13}C NMR spectra of (3*R*,6*R*)- and (3*S*,6*R*)-**127**, and (3*S*,6*S*)-**128** are shown in **Figures III.2.2. - III.2.7**.

To exclude any possible involvement of the protecting group at C-6 in the reaction, the alcohol (*S*)-**123** was converted to the *para*-methoxybenzyl (PMB) derivative (*S*)-**129** with *para*-methoxybenzyl chloride (PMBCl) in the presence of NaH. The three-proton ^{1}H NMR singlet at δ 3.79 (OMe), two aromatic doublets at δ 6.86 and δ 7.26 (each 2H, J = 7.0 Hz) along with the ^{13}C NMR peaks at δ 55.2 (OMe) and at the aromatic region confirmed its PMB function. Oxidative cleavage (OsO_4/NMO; $NaIO_4$) of its olefin function, followed by addition of vinylmagnesium bromide to the resultant aldehyde **130** gave (3*RS*,6*S*)-**131**, another derivative of the DOS intermediate. Its IR and NMR spectra showed expected peaks due to the allylic carbinol moiety. As expected, the Novozym 435®-catalyzed acetylation of (3*RS*,6*S*)-**131** also furnished (3*R*,6*S*)-**131** and (3*S*,6*S*)-**132** in excellent ees at ~50% conversion (~ 6 h). The E-values of all the lipase-catalyzed acetylation reactions were >195. Overall, the above simple synthetic strategy provided the target DOS intermediate in its diastereomeric forms, and as differently protected derivatives. With all the stereomers of the intermediate in hand, we proceeded for the synthesis of the target compounds, (-)- and (+)-**VI**. This also confirmed the assigned configurations of the silylated DOS intermediates ('**C**' unit equivalents).

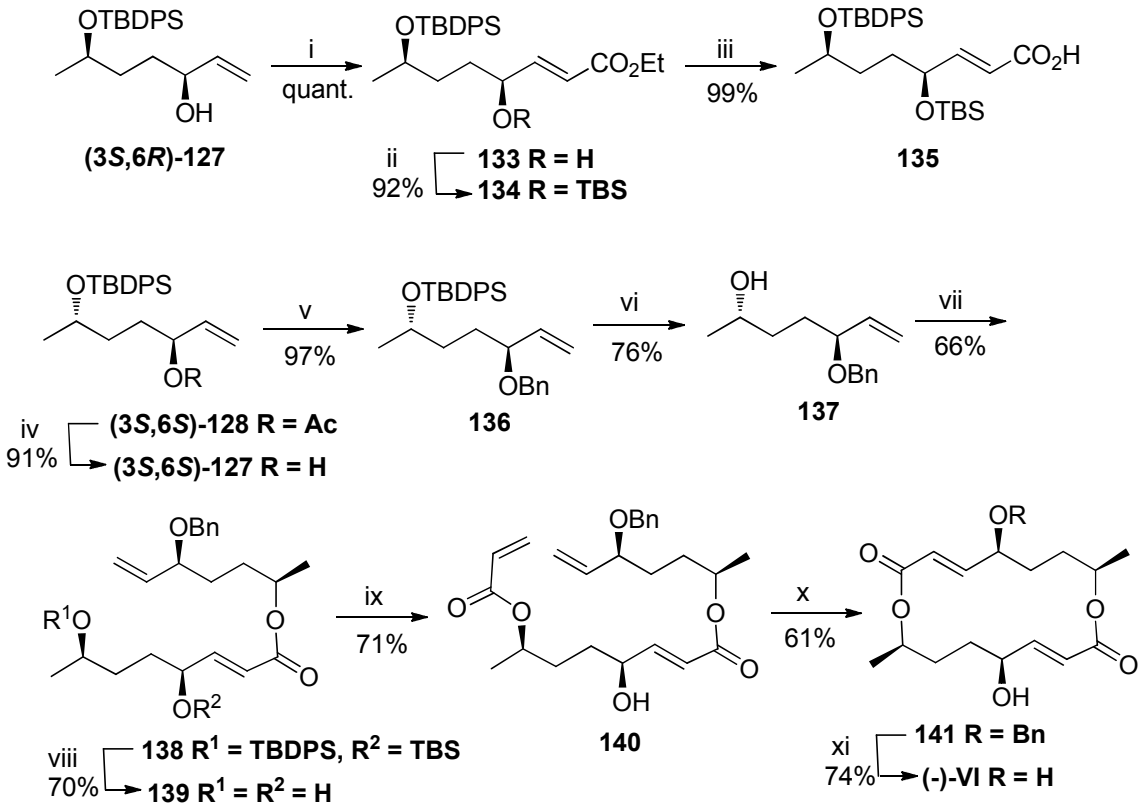


i) $LiAlH_4/Et_2O$/0 ^oC/2 h, ii) Novozym 435®/vinyl acetate/hexane/50 min, iii) TBDPSCl/ imidazole/DMAP/CH_2Cl_2/25 ^oC/7 h, iv) O_3/CH_2Cl_2/-78 ^oC /1.5 h; Ph_3P/-78 ^oC to 25 ^oC/18 h,v) CH_2=CHMgBr/THF/-78 ^oC/3 h, vi) Novozym 435®/vinyl acetate/25 ^oC/6 h, vii) NaH/PMBCl/DMF/-5 ^oC/4 h. viii) OsO_4/NMO/*t*-BuOH-acetone-H_2O/25 ^oC/24 h; $NaIO_4/CH_3CN$-H_2O/10 ^oC/2 h.

Scheme III.2.6.

Synthesis of the natural pyrenophorol enantiomer (-)-VI. For the synthesis, the alcohol (3*S*,6*R*)-**127** was subjected to a cross-metathesis reaction with ethyl acrylate in the presence of Hoveyda Grubbs' II catalyst to furnish the ester **133**. Its ^{1}H NMR spectrum showed a quartet at δ 4.20 (-CO_2CH_2) and resonances at δ 5.99 and δ 6.88 for the conjugated olefinic moiety. The *E*-olefinic geometry was affirmed from the *J*–value (15.6 Hz) of olefinic resonances. Its carbinol function was silylated with *tert*-butyldimethylsilyl chloride (TBSCl)/imidazole/DMAP to obtain

134. Its ^{1}H NMR singlets at δ -0.04 (6H) and 0.85 (9H) confirmed the TBS moiety. This on alkaline hydrolysis furnished the acid **135** (IR bands at 3500-2500 and 1698 cm^{-1}). In a parallel sequence, the acetate (3*S*,6*S*)-**128** was converted to the alcohol (3*S*,6*S*)-**127** by treatment with K_2CO_3 in MeOH. The spectral data of (3*S*,6*S*)-**127** were similar to that of its other stereomers. Its carbinol function was benzylated with BnBr in the presence of NaH as the base to furnish **136**. Its ^{1}H and ^{13}C NMR spectra were complex, suggesting it to be a mixture of rotamers. Nevertheless, the ^{1}H NMR doublets at δ 4.30 and 4.54 (each 1H, *J* = 11.8 Hz, $PhCH_2$-) and the multiplets at δ 7.25-7.29 (5H) were indicative of the Bn group. Its desilylation with Bu_4NF furnished the alcohol **137** (IR band at 3400 cm^{-1} and absence of NMR resonances for the TBDPS moiety). Esterification of the acid **135** with **137** under the Mitsunobu conditions afforded the ester **138** (IR 1715 cm^{-1}, δc 166.1) as a mixture of rotamers. This was desilylated with aqueous HF in CH_3CN to obtain the diol **139** (broad IR band at 3417 cm^{-1} and absence of NMR resonances due to the TBDPS and TBS groups). The Novozym 435®-catalyzed acrylation of **139** with ethyl acrylate furnished the desired acrylate **140** exclusively. The spectral features of **140** *viz*. IR peak 1728 cm^{-1} and the NMR resonances such as δ_H 5.66-5.83 (m, 2H), δ_H 6.38 (dd, *J* = 1.6, 17.2 Hz, 1H) and δc 165.9 were commensurate with its structure. As observed in the synthesis of **V**, in this case also, Novozym 435® was found to preferentially acylate the $CH_3CH(OH)$- moiety without affecting the free allylic alcohol functionality.



i) CH_2=$CHCO_2Et$/Hoveyda Grubbs' II catalyst/CH_2Cl_2/25 ^oC/3 h, ii) TBSCl/imidazole/DMAP/CH_2Cl_2/25 ^oC/7 h, iii) Aqueous 20% NaOH/MeOH/25 ^oC/2 h, iv) K_2CO_3/MeOH/25 ^oC/6 h, v) NaH/BnBr/Bu_4NI/THF/reflux/4 h, vi) Bu_4NF/THF/0 to 25 ^oC/8 h, vii) **135**//Ph_3P/DIAD/THF/0 to 25 ^oC/18 h, viii) Aqueous HF/MeCN/25 ^oC/16 h, ix) CH_2=$CHCO_2Et$/Novozyme 435/diisopropyl ether/25 ^oC/30 h, x) Grubbs' II catalyst/CH_2Cl_2/reflux/72 h, xi) $TiCl_4$/CH_2Cl_2/0 to 25 ^oC/0.5 h.

Scheme III.2.7.

The stage was now set for the RCM reaction of **140** for constructing the required macrocyclic structure of (-)-**VI**. This was achieved with Grubbs' II catalyst in CH_2Cl_2 to obtain **141** in modest yield after refluxing for 72 h. Control of the olefin geometry in the RCM-mediated macrocyclization is difficult, as the Ru-catalysts often induce the undesirable olefin isomerization as a secondary step. This leads to E/Z olefin mixtures with preponderance of the *E*-olefin. The composition of the geometrical isomers of products is governed by factors such as solvent, catalyst, temperature, substrate structure, and product ring size. Nevertheless, we did not

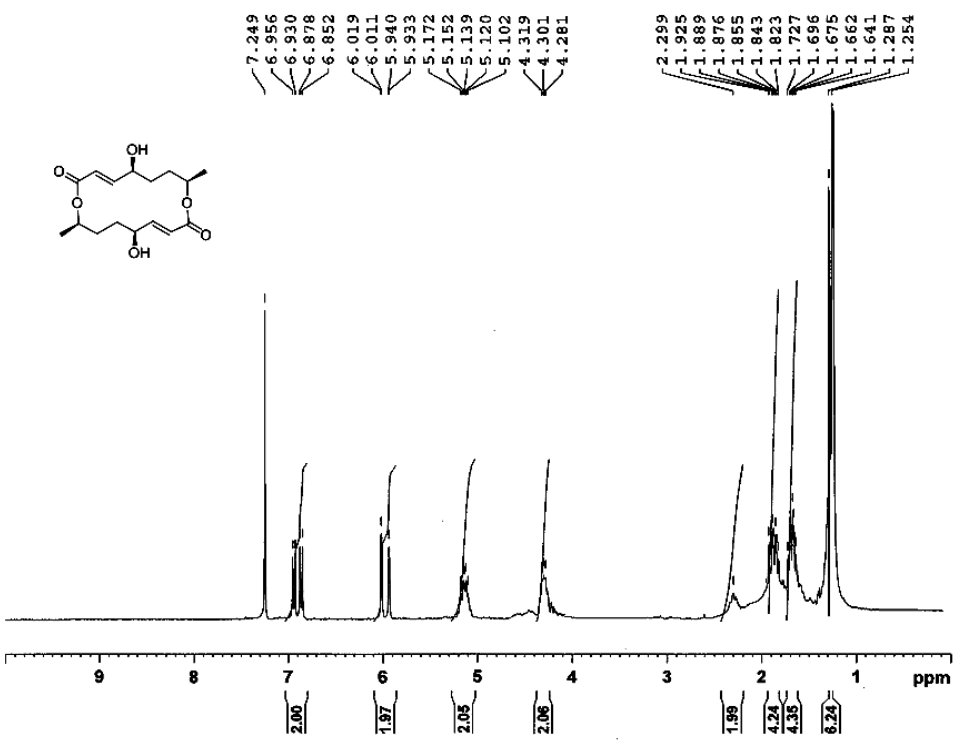


Figure III.2.8. ^{1}H NMR spectrum of (-)-**VI**

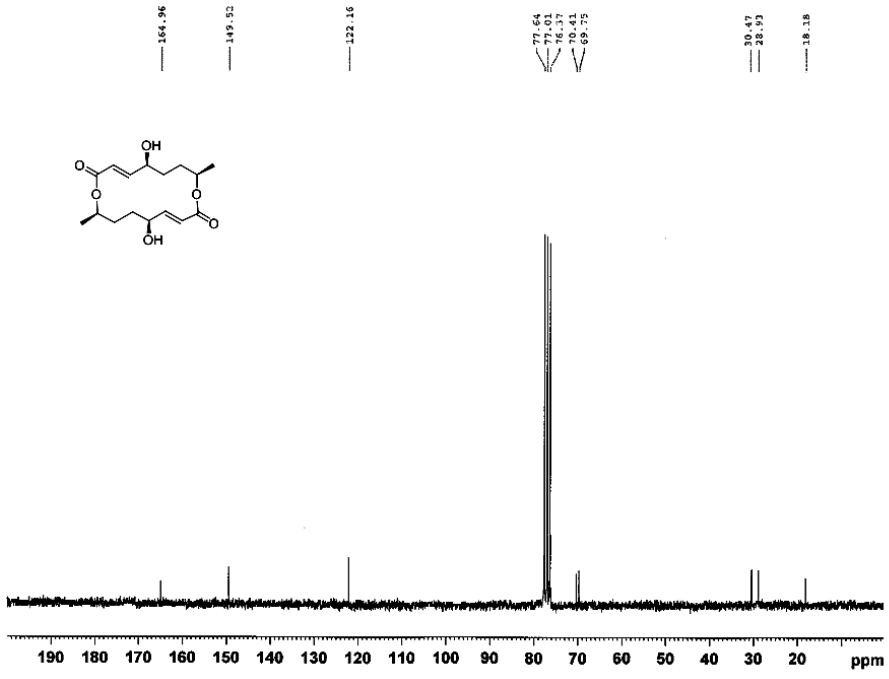


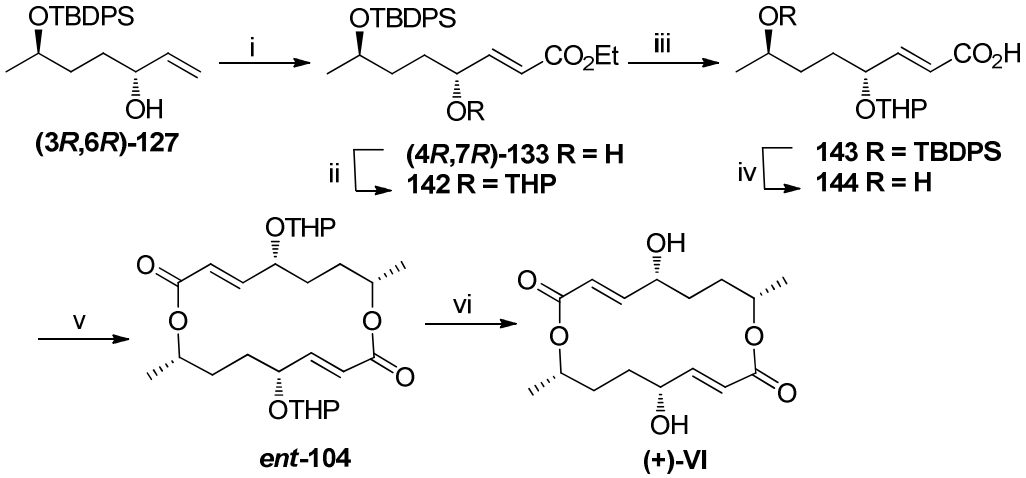
Figure III.2.9. ^{13}C NMR spectrum of (-)-**VI**

isolate any *Z*-isomer in the conversion of **140** to **141** as revealed from the ^{1}H NMR spectrum [δ_H 5.91 (d, *J* = 16.0 Hz, 2H), 6.74 (dd, *J* = 7.8, 16.0 Hz, 1H), 6.82 (dd, *J* = 6.8, 15.6 Hz, 1H)]. A $TiCl_4$-catalyzed debenzylation[78] of **141** completed the synthesis of (-)-**VI** (**Scheme III.2.7.**). The spectral (^{1}H and ^{13}C NMR spectra shown in **Figures III.2.8.** and **III.2.9**.) and optical data of (-)-**VI** matched very well with the reported values.[70f]

Synthesis of the pyrenophorol enantiomer (+)-VI. The versatility of the DOS synthons was established by converting them to different other complex natural products, and part of this is also published.[39] In the preceeding section, the alcohol stereomers *viz*. (3*S*,6*R*)- and (3*S*,6*S*)-**127** were used for the synthesis of (-)-**VI**. It was hypothesized that since pyrenophorol is a C_2-symmetric molecule with four stereogenic carbinol centres, its non-natural stereomers can also be synthesized using different stereomers of **127**. To explore the possibility, (3*R*,6*R*)-**127** was converted to the ester (4*R*,7*R*)-**133** by a cross-metathesis reaction with ethyl acrylate in the presence of Grubbs' II catalyst. The IR peaks at 1716 and 981 cm^{-1}, and the NMR resonances *viz*. δ_H 5.99 (d, *J* = 15.5 Hz, 1H) and 6.87 (dd, *J* = 5.0, 15.5 Hz, 1H) as well as δ_C 166.6 confirmed the presence of the *E*-olefinic ester moiety in **133**. The ^{1}H and ^{13}C NMR spectra of (4*R*,7*R*)-**133** are shown in **Figures III.2.10.** and **III.2.11**.

Protection of its carbinol function as the OTHP derivative **142** (δ_H: 4.51-4.62 (m, 1H) and δ_C: 94.6, 95.9, 97.0) followed by alkaline hydrolysis of the ester function furnished the acid **143** (IR: 3500-2500, 1697 cm^{-1}). Its desilylation with Bu_4NF furnished the alcohol **144**, as confirmed from the absence of the TBDPS moiety in its NMR spectra. This on cyclo-dimerization under the Mitsunobu conditions afforded the pyrenophorol derivative *ent*-**104**, which was characterized by comparing the reported data of its enantiomer.[71d] This was converted to (+)-**VI** by an acid-

catalyzed depyranylation (**Scheme III.2.8.**). The compound was characterized from its reported chiro-optical and spectral data.[71c]



i) CH_2=$CHCO_2Et$/Grubbs II catalyst/CH_2Cl_2/25 °C/3 h, ii) 3,4-DHP/PPTS/CH_2Cl_2/25 °C/7 h, iii) NaOH/MeOH/25 °C/0.5 h, iv) Bu_4NF/THF/80 °C/2 h, v) TBDPSCl/imidazole/DMAP/CH_2Cl_2, vi) Ph_3P/THF/toluene/DEAD/-25 to 25°C /10 h, vi) PTS/MeOH/25°C /0.5 h.

Scheme III.2.8.

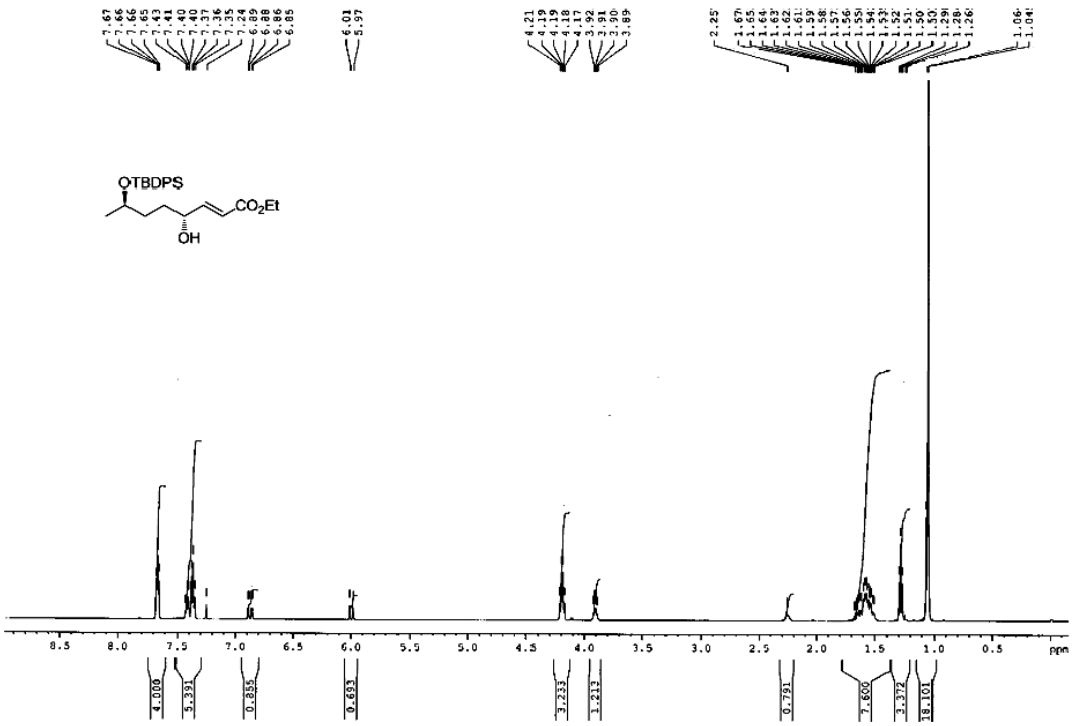


Figure III.2.10. ^{1}H NMR spectrum of (4*R*,7*R*)-**133.**

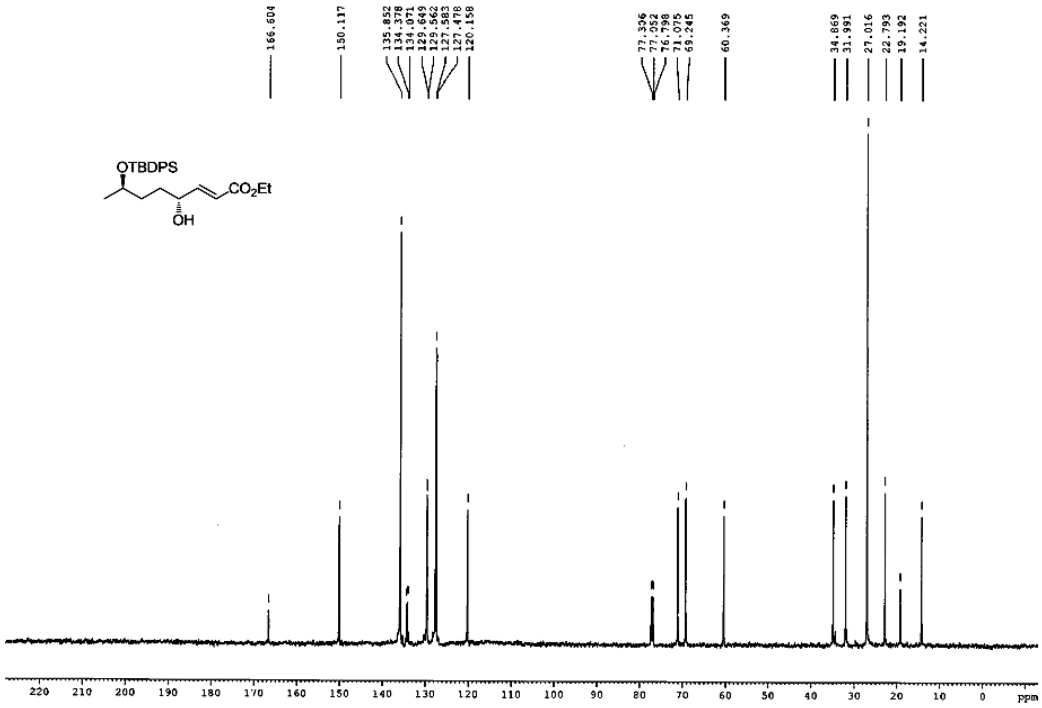
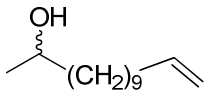


Figure III.2.11. ^{13}C NMR spectrum of (4*R*,7*R*)-**133.**

III.3 EXPERIMENTAL SECTION

General methods. The general experimental details were same as those mentioned in Chapter II.

(±)-Tridec-12-en-2-ol (67).

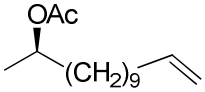


To a stirred solution of the Grignard reagent prepared from **66** (10.0 g, 43.1 mmol) and Mg (1.25 g, 51.8 mmol) in THF (170 mL) was added acetaldehyde (3.61 mL, 64.7 mmol) in THF (20 mL). After stirring for 3 h, the mixture was treated with aqueous saturated NH_4Cl, the organic layer separated, and the aqueous portion extracted with Et_2O (3 × 80 mL). The combined organic extracts were washed with H_2O (3 × 15 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0-10% Et_2O/hexane) to afford pure (±)-**67** (7.7 g, 90%). colorless oil; IR: 3374, 1640 cm^{-1}; ^1H NMR: δ 1.17 (d, *J* = 6.2 Hz, 3H), 1.28-1.52 (m containing a s at δ 1.29, 17H), 1.97-2.04 (m, 2H), 3.73-3.82 (m, 1H), 4.89-5.01 (m, 2H), 5.73-5.87 (m, 1H); ^{13}C NMR: δ 23.2, 25.7, 28.8, 29.0, 29.3, 29.4, 29.5, 33.7, 39.2, 67.7, 113.9, 138.9. Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21%. Found: C, 78.58; H, 12.93%.

Optimization of the lipase-catalyzed acetylation of (±)-67. A mixture (±)-**67** (2 mmol), vinyl acetate (3 mmol) and different lipases in hexane or diisopropyl ether (3 mL) was agitated on an orbital shaker at 110 rpm at 25 ^oC for different periods (**Table III.1.1.**). The extent of conversion was determined by analyzing an aliquot of the reaction mixture by GC. The GC analyses were carried out with a Shimadzu GC–2010 Plus instrument (Shimadzu Corporation, Kyoto, Japan) equipped with a split/splitless injector, FID detector using a DB-5 (5%-phenyl)-methylpolysiloxane, J&W Scientific, Folsom, CA, USA) capillary column (length, 30 m; i.d., 0.25 mm and film thickness, 0.25 μm). The operating conditions were: column temperature

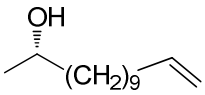
programmed from 80 to 200 ºC at the rate of 4 ºC/min, held at initial temperature for 5 min and at 200 ºC for 2 min and further to 280 ºC at the rate of 10 ºC/min, held at final temperature for 10 min; injection port temperature: 210 ºC; carrier gas He (flow rate, 1.0 mL/min). Samples (0.1 μL) were injected in the splitless mode.

(*R*)-12-Acetoxytridec-1-ene 68.



A mixture of (±)-**67** (3.5 g, 17.7 mmol), vinyl acetate (2.4 mL, 26.4 mmol) and Novozyme 435® (0.175 g) in diisopropyl ether (25 mL) was agitated on an orbital shaker at 110 rpm for (75 min). The reaction mixture was filtered, and the solution concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0-10% EtOAc/hexane) gave pure (*S*)-**67** (1.9 g, 54%) and (*R*)-**68** (1.5 g, 35%). (*S*)-**67**: colorless oil; $[\alpha]_D^{24}$ +5.7 (*c* 1.15, $CHCl_3$). (*R*)-**68**: colorless oil; $[\alpha]_D^{24}$ -1.7 (*c* 1.06, $CHCl_3$); IR: 1738, 1243 cm^{-1}; ^1H NMR: δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.22-1.63 (m containing a s at δ 1.25, 16H), 1.98-2.10 (m containing a s at δ 2.01, 5H), 4.82-5.01 (m, 3H), 5.77-5.81 (m, 1H); ^{13}C NMR: δ 19.5, 20.8, 25.1, 28.6, 28.8, 29.1, 29.2, 33.5, 35.6, 70.4, 113.8, 138.5, 169.9. Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74%. Found: C, 74.71; H, 12.03%.

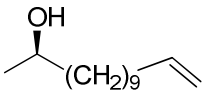
(*S*)-Tridec-12-en-2-ol (*S*)-67.



Following the same procedure, (*S*)-**67** (1.9 g, 9.60 mmol) (obtained from the above experiment) was acetylated with vinyl acetate till 15% conversion, and the product purified by column chromatography to obtain enantiomerically pure (*S*)-**67** (1.5 g, 80%). colorless oil; $[\alpha]_D^{26}$ +6.7 (*c* 1.50, $CHCl_3$); IR: 3348, 1641, 992 cm^{-1}; ^1H NMR *δ* 1.17 (d, *J* = 6.2 Hz, 3H), 1.26-1.53 (m containing a s at δ 1.53, 17H), 1.97-2.08 (m, 2H), 3.71-3.83 (m, 1H), 4.89-5.03 (m, 2H), 5.70-

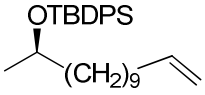
5.90 (m, 1H); ^{13}C NMR: δ 23.3, 25.7, 28.8, 29.0, 29.4, 29.5, 29.6, 33.7, 39.2, 67.9, 114.0, 139.0. Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21%. Found: C, 78.60; H, 13.44%.

(*R*)-Tridec-12-en-2-ol (*R*)-67.



A mixture of (*R*)-**68** (2.18 g, 9.10 mmol) and 2M K_2CO_3 in 10% aqueous MeOH (20 mL) was stirred at room temperature for 6 h. The mixture was filtered, concentrated in vacuo, H_2O (30 mL) added into it, and extracted with EtOAc (2 × 20 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-10% EtOAc/hexane) afforded pure (*R*)-**67** (1.7 g, ~quant.). colorless oil; $[\alpha]_D^{25}$ -6.3 (*c* 1.15, $CHCl_3$); IR: 3371, 1640, 991 cm^{-1}; ^{1}H NMR: δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.23-1.54 (m containing a s at δ 1.28, 17H), 1.99-2.06 (m, 2H), 3.75-3.81 (m, 1H), 4.90-5.04 (m, 2H), 5.75-5.88 (m, 1H); ^{13}C NMR: δ 23.4, 25.7, 28.9, 29.1, 29.4, 29.5, 29.6, 33.8, 39.3, 68.1, 114.0, 139.2. Anal. Calcd. for $C_{13}H_{26}O$: C, 78.72; H, 13.21%. Found: C, 78.35; H, 13.56%.

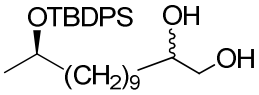
(*R*)-12-*tert*-Butyldiphenylsilyloxytridec-1-ene 69.



Silylation of (*R*)-**67** (1.6 g, 8.08 mmol) with TBDPSCl (2.67 g, 9.70 mmol), imidazole (0.82 g, 12.12 mmol) and DMAP (catalytic) in CH_2Cl_2 (20 mL) followed by work-up and column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **69** (3.3 g, 93%). colorless oil; $[\alpha]_D^{26}$ +16.3 (*c* 1.16, $CHCl_3$); IR: 997, 910 cm^{-1}; ^{1}H NMR: δ 1.07 (merged s and d, *J* = 6.0 Hz, 12H), 1.22-1.65 (m, 16H), 2.01-2.09 (m, 2H), 3.78-3.90 (m, 1H), 4.90-5.10 (m, 2H), 5.74-5.94 (m, 1H), 7.38-7.48 (m, 6H), 7.66-7.74 (m, 4H); ^{13}C NMR: δ 19.3, 23.2, 25.2, 27.0, 28.9, 29.1,

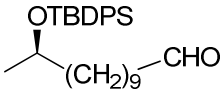
29.5, 29.6, 33.8, 39.5, 69.6, 114.1, 127.3, 127.4, 129.4, 134.7, 135.0, 135.9, 139.2. Anal. Calcd. for $C_{29}H_{44}OSi$: C, 79.75; H, 10.15%. Found: C, 79.56; H, 10.47%.

(2*RS*,12*R*)-12-*tert*-Butyldiphenylsilyloxytridecane-1,2-diol 70.



To a stirred solution of **69** (3.54 g, 8.12 mmol) and NMO (2.19 g, 16.24 mmol) in acetone-H_2O (8:1, 20 mL) was added OsO_4 (0.103 g, 0.41 mmol) in *tert*-BuOH (4 mL). After consumption of **69** (*cf*. TLC, 10 h), the reaction mixture was treated with aqueous saturated Na_2SO_3 and stirred for 1 h. The organic layer was separated and the aqueous portion extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with H_2O (2 × 30 mL) and brine (1 × 10 mL), dried and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0-40% EtOAc/hexane) to afford pure **70** (3.6 g, 95%). colorless oil; $[\alpha]_D^{27}$ +12.0 (*c* 1.05, $CHCl_3$); IR: 3375 cm^{-1}; ^1H NMR: δ 1.08 (merged s and d, *J* = 6.0 Hz, 12H), 1.15-1.47 (m, 18H), 1.69 (broad s, 2H), 3.43-3.52 (m, 1H), 3.65-3.88 (m, 3H), 7.35-7.48 (m, 6H), 7.67-7.78 (m, 4H); ^{13}C NMR: δ 19.2, 23.2, 25.2, 25.5, 27.0, 29.5, 29.6, 33.2, 39.4, 66.8, 69.6, 72.3, 127.3, 127.4, 129.3, 134.7, 135.0, 135.8. Anal. Calcd. for $C_{29}H_{46}O_3Si$: C, 73.99; H, 9.85%. Found: C, 73.78; H, 9.75%.

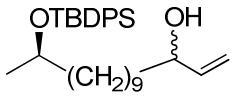
(*R*)-11-*tert*-Butyldiphenylsilyloxydodecanal 71.



To a cooled (0 °C) and stirred solution of **70** (3.86 g, 8.21 mmol) in MeCN-H_2O (3:2, 15 mL) was added $NaIO_4$ (3.52 g, 16.43 mmol). After stirring for 2 h, the mixture was concentrated in vacuo, the residue taken in EtOAc (30 mL) and washed successively with H_2O (1 × 10 mL), aqueous 10% $NaHSO_3$ (1 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent

removal furnished the pure aldehyde **71** (3.2 g, 91%). colorless oil; $[\alpha]_D^{27}$ +14.9 (*c* 1.03, $CHCl_3$); IR: 2712, 1727 cm^{-1}; ^1H NMR: δ 1.09 (merged s and d, *J* = 6.2 Hz, 12H), 1.18-1.40 (m, 12H), 1.60-1.80 (m, 4H), 2.46 (dt, *J* = 1.8, 7.2 Hz, 2H), 3.79-3.95 (m, 1H), 7.35-7.48 (m, 6H), 7.72-7.83 (m, 4H), 9.80 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR: δ 19.0, 21.9, 23.0, 24.5, 25.0, 26.8, 28.8, 29.0, 29.1, 29.2, 29.3, 33.8, 39.2, 43.7, 69.4, 127.1, 127.2, 129.2, 134.5, 134.8, 135.7, 179.6. Anal. Calcd. for $C_{28}H_{42}O_2Si$: C, 76.66; H, 9.65%. Found: C, 76.33; H, 9.84%.

(3*RS*,13*R*)-13-*tert*-Butyldiphenylsilyloxytetradec-1-en-3-ol (3*RS*,13*R*)-72.

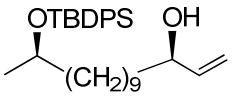


To a cooled (-40 °C) and stirred solution of **71** (3.0 g, 6.84 mmol) in THF (20 mL) was added CH_2=CHMgBr (13.7 mL, 1M in THF, 13.7 mmol). After stirring for 1 h, H_2O (15 mL) was added to the mixture, the organic layer separated, and the aqueous layer extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H_2O (1 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-15% EtOAc-hexane) of the residue gave pure (3*RS*,13*R*)-**72** (2.9 g, 90%). colorless oil; $[\alpha]_D^{27}$ +14.2 (*c* 1.08, $CHCl_3$); IR: 3359, 996, 920 cm^{-1}; ^1H NMR: δ 1.03 (merged s and d, *J* = 6.0 Hz, 12H), 1.15-1.35 (m, 12H), 1.45-1.68 (m containing a s at 1.56, 7H), 3.73-3.85 (m, 1H), 4.03-4.13 (m, 1H), 5.07-5.25 (m, 2H), 5.76-5.96 (m, 1H), 7.29-7.41 (m, 6H), 7.63-7.78 (m, 4H); ^{13}C NMR: δ 19.2, 23.2, 25.2, 25.3, 27.0, 29.5, 37.0, 39.4, 69.6, 73.2, 114.5, 127.3, 127.4, 129.3, 129.4, 134.6, 134.9, 135.8, 141.3. Anal. Calcd. for $C_{30}H_{46}O_2Si$: C, 77.19; H, 9.93%. Found: C, 77.44; H, 10.21%.

(3*S*,13*R*)-3-Acetoxy-13-*tert*-butyldiphenylsilyloxytetradec-1-ene 73. Acetylation of (3*RS*,13*R*)-**72** (2.1 g, 4.51 mmol) with vinyl acetate (0.58 g, 6.76 mmol) in diisopropyl ether (25 mL) and Novozym 435® (0.035 g) for 6 h, followed by usual work up, isolation and purification

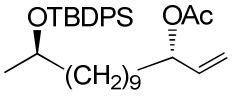
by column chromatography (silica gel, 0-10% EtOAc/hexane) gave pure (*3R,13R*)-**72** (0.860 g, 41%) and **73** (0.860 g, 45%).

(*3R,13R*)-**72:**



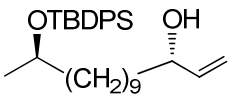
colorless oil; $[\alpha]_D^{22}$ +11.9 (*c* 1.05, $CHCl_3$); IR: 3367, 991, 927 cm^{-1}; ^1H NMR: δ 1.01 (merged s and d, *J* = 5.8 Hz, 12H), 1.15-1.26 (m, 14H), 1.44-1.55 (m, 4H), 2.01 (s, 1H), 3.78-3.81 (m, 1H), 4.05-4.11 (m, 1H), 5.04-5.24 (m, 2H), 5.76-5.84 (m, 1H), 7.32-7.37 (m, 6H), 7.62-7.67 (m, 4H); ^{13}C NMR: δ 19.2, 23.2, 25.2, 26.9, 29.6, 37.1, 39.3, 69.5, 73.3, 114.8, 127.6, 129.4, 134.9, 135.8, 141.3. Anal. Calcd. for $C_{30}H_{46}O_2Si$: C, 77.19; H, 9.93%. Found: C, 77.29; H, 9.71%.

73:



colorless oil; $[\alpha]_D^{22}$ +9.1 (*c* 1.02, $CHCl_3$); IR: 1732, 1246, 997 cm^{-1}; ^1H NMR: δ 1.05 (s, 9H), 1.20-1.28 (m, 17H), 1.42-1.66 (m, 4H), 2.07 (s, 3H), 3.81-3.84 (m, 1H), 5.15-5.17 (m, 1H), 5.22-5.26 (m, 2H), 5.75-5.80 (m, 1H), 7.35-7.46 (m, 6H), 7.70-7.78 (m, 4H); ^{13}C NMR: δ 19.3, 21.3, 23.3, 25.1, 25.2, 27.1, 29.4, 29.5, 29.6, 29.7, 32.6, 34.2, 39.5, 69.6, 74.9, 116.5, 127.4, 127.5, 127.6, 129.4, 134.7, 135.0, 135.6, 135.9, 136.7, 170.4. Anal. Calcd. for $C_{32}H_{48}O_3Si$: C, 75.74; H, 9.51%. Found: C, 75.82; H, 9.86%.

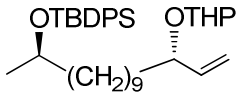
(3*S*,13*R*)-13-*tert*-Butyldiphenylsilyloxytetradec-1-en-3-ol (3*S*,13*R*)-72.



Hydrolysis of **73** (0.80 g, 1.57 mmol) with 2M K_2CO_3 in aqueous MeOH (25 mL) followed by work-up and column chromatography (silica gel, 0-10% EtOAc/hexane) afforded pure (3*S*,13*R*)-

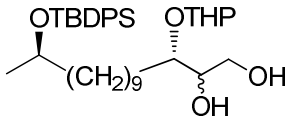
72 (0.725 g, ~quant.). colorless oil; $[\alpha]_D^{23}$ +14.7 (*c* 1.01, $CHCl_3$); IR: 3367, 1006, 927 cm^{-1}; ^1H NMR: δ 1.03 (merged s and d, *J* = 6.0 Hz, 12H), 1.15-1.26 (m, 14H), 1.47-1.56 (m, 4H), 3.75-3.82 (m, 1H), 4.05-4.11 (m, 1H), 5.04-5.24 (m, 2H), 5.76-5.88 (m, 1H), 7.36-7.39 (m, 6H), 7.62-7.67 (m, 4H); ^{13}C NMR: δ 19.3, 23.2, 25.2, 25.4, 27.1, 29.6, 37.1, 39.5, 69.6, 73.3, 114.5, 127.4, 127.6, 129.4, 134.7, 135.0, 135.6, 135.9, 141.4. Anal. Calcd. for $C_{30}H_{46}O_2Si$: C, 77.19; H, 9.93%. Found: C, 77.37; H, 10.28%.

(3*S*,13*R*)-13-*tert*-Butyldiphenylsilyloxy-3-tetrahydropyranyloxytetradec-1-ene 74.



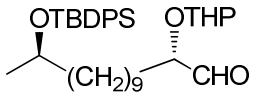
A mixture of (3*S*,13*R*)-**72** (0.7 g, 1.5 mmol), DHP (0.2 mL, 2.25 mmol) and PPTS (catalytic) in CH_2Cl_2 (10 mL) was stirred for 4 h at room temperature. The mixture was poured into ice-cold aqueous 10% $NaHCO_3$ (20 mL), the organic layer separated and the aqueous portion extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 10 mL), and dried. Removal of solvent in vacuo followed by purification of the residue by column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **74** (0.73 g, 88%). colorless oil; $[\alpha]_D^{29}$ +8.9 (*c* 1.07, $CHCl_3$); IR: 1320, 1259, 1077 cm^{-1}; ^1H NMR: δ 1.04 (merged s and d, *J* = 6.0 Hz, 12H), 1.16-1.25 (m, 14H), 1.49-1.65 (m, 10H), 3.42-3.52 (m, 1H), 3.76-3.89 (m, 2H), 4.03-4.07 (m, 1H), 4.63-4.68 (m, 1H), 5.11-5.24 (m, 2H), 5.56-5.86 (m, 1H), 7.34-7.38 (m, 6H), 7.64-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 19.6, 23.2, 25.0, 25.2, 25.5, 27.0, 29.5, 29.6, 30.8, 35.6, 39.4, 62.3, 69.6, 95.0, 97.7, 114.7, 117.2, 127.3, 127.4, 129.3, 129.4, 134.6, 135.0, 135.9, 138.7, 139.8. Anal. Calcd. for $C_{35}H_{54}O_3Si$: C, 76.31; H, 9.88%. Found: C, 76.71; H, 10.28%.

(2*RS*,3*S*,13*R*)-13-*tert*-Butyldiphenylsilyloxy-3-tetrahydropyranyloxytetradecane-1,2-diol 75.



Dihydroxylation of **74** (0.7 g, 1.27 mmol) with NMO (0.171 g, 2.54 mmol) and OsO_4 (0.016 g, 0.06 mmol) in acetone-H_2O (8:1, 10 mL) followed by usual isolation and column chromatography (silica gel, 0-40% EtOAc/hexane) afforded pure **75** (0.730 g, 98%). colorless oil; $[\alpha]_D^{26}$ +4.5 (*c* 1.03, $CHCl_3$); IR: 3410, 1389, 1183 cm^{-1}; ^1H NMR: δ 1.03 (merged s and d, *J* = 6.0 Hz, 12H), 1.17-1.24 (m, 14H), 1.44-1.86 (m, 10H), 1.89-2.19 (m, 2H), 3.47-3.57 (m, 2H), 3.63-3.76 (m, 4H), 3.79-3.88 (m, 1H), 4.06-4.10, 4.29-4.39 and 4.72-4.75 (three m, 1H), 7.34-7.41 (m, 6H), 7.64-7.68 (m, 4H); ^{13}C NMR: δ 19.1, 19.9, 21.6, 23.1, 24.8, 25.1, 25.2, 25.4, 25.9, 26.9, 29.4, 29.7, 30.8, 31.2, 31.3, 32.2, 39.3, 63.0, 63.2, 65.8, 69.5, 72.7, 73.2, 79.2, 83.1, 99.1, 102.4, 127.2, 127.3, 129.2, 129.3, 134.5, 134.8, 135.8. Anal. Calcd. for $C_{35}H_{56}O_5Si$: C, 71.87; H, 9.65%. Found: C, 71.48; H, 9.77%.

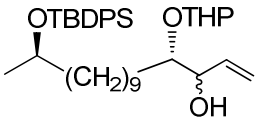
(2*S*,12*R*)-12-*tert*-Butyldiphenylsilyloxy-2-tetrahydropyranyloxytridecanal 76.



Reaction of **75** (0.73 g, 1.25 mmol) with $NaIO_4$ (0.535 g, 2.50 mmol) in MeCN-H_2O (3:2, 15 mL) at 0 ^oC, followed by usual work-up furnished the pure aldehyde **76** (0.620 g, 90%). colorless oil; $[\alpha]_D^{25}$ -16.7 (*c* 1.01, $CHCl_3$); IR: 2707, 1734 cm^{-1}; ^1H NMR: δ 1.04 (merged s and d, *J* = 6.2 Hz, 12H), 1.17-1.25 (m, 12H), 1.31-1.88 (m, 12H), 3.46-3.56 (m, 1H), 3.74-3.92 (m, 2H), 4.17 (dt, *J* = 1.4, 7.2 Hz, 1H), 4.53-4.56 and 4.67-4.70 (two m, 1H), 7.35-7.41 (m, 6H), 7.62-7.70 (m, 4H), 9.63 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR: δ 19.2, 19.3, 23.2, 25.1, 25.2, 25.3, 27.0, 29.3, 29.4, 29.5, 30.0, 30.5, 39.4, 62.6, 69.5, 79.8, 83.6, 97.6, 100.9, 127.3, 127.4, 129.3, 129.4, 134.6,

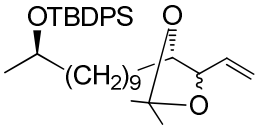
134.9, 135.8, 203.4, 203.9. Anal. Calcd. for $C_{34}H_{52}O_4Si$: C, 73.86; H, 9.48%. Found: C, 73.75; H, 9.88%.

(3*RS*,4*S*,14*R*)-14-*tert*-Butyldiphenylsilyloxy-4-tetrahydropyranyloxypentadec-1-en-3-ol 77.



As described above, reaction of **76** (0.600 g, 1.09 mmol) with CH_2=CHMgBr (2.2 mL, 1M in THF, 2.20 mmol) in THF (10 mL) at -78 ^oC, followed by usual work up, and column chromatographic purification (silica gel, 0-20% EtOAc/hexane) afforded pure **77** (0.547 g, 87%). colorless oil; $[\alpha]_D^{27}$ -6.4 (*c* 1.09, $CHCl_3$); IR: 3433, 996, 921 cm^{-1}; ^1H NMR: δ 1.02 (merged s and d, *J* = 6.2 Hz, 12H), 1.06-1.29 (m, 15H), 1.31-1.66 (m, 8H), 1.77-1.82 (m, 2H), 3.44-3.66 (m, 2H), 3.71-4.04 (m, 3H), 4.18-4.45 and 4.62-4.78 (two m, 1H), 5.10-5.33 (m, 2H), 5.76-5.93 (m, 1H), 7.21-7.41 (m, 6H), 7.60-7.68 (m, 4H); ^{13}C NMR: δ 13.9, 19.0, 19.7, 21.0, 23.1, 24.8, 25.0, 25.2, 25.7, 25.8, 26.9, 29.3, 29.5, 30.7, 31.1, 31.8, 36.9, 39.2, 62.7, 63.0, 64.9, 69.4, 72.8, 73.5, 74.7, 79.1, 85.2, 97.3, 99.1, 102.1, 114.0, 116.0, 116.3, 127.2, 127.3, 129.1, 129.2, 134.4, 134.7, 135.6, 136.6, 136.8, 138.0, 141.4. Anal. Calcd. for $C_{36}H_{56}O_4Si$: C, 74.43; H, 9.72%. Found: C, 74.19; H, 9.97%.

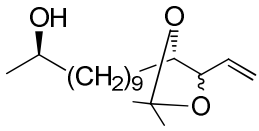
(3*RS*,4*S*,14*R*)-14-*tert*-Butyldiphenylsilyloxy-3,4-isopropylidenedioxypentadec-1-ene 78.



A solution of **77** (0.23 g, 0.40 mmol) and PPTS (20 mol%) in MeOH (5 mL) was stirred for 6 h at room temperature. Concentration of the mixture in vacuo gave the crude product, which was diluted with 2,2-DMP (1 mL) and stirred for 12 h at room temperature. The mixture was concentrated in vacuo, H_2O (15 mL) added into it, and extracted with EtOAc (2 × 15 mL). The

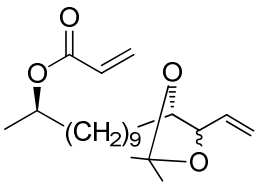
organic layer was washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-10% EtOAc/hexane) afforded pure **78** (0.190 g, 91%). colorless oil; $[\alpha]_D^{21}$ +28.8 (*c* 1.04, $CHCl_3$); IR: 3399, 992, 926 cm^{-1}; ^1H NMR: δ 1.04 (merged s and d, 12H), 1.21-1.29 (m, 10H), 1.37-1.66 (m containing two s at δ 1.37 and 1.42, 14H), 3.62-3.70, 3.81-3.84, 3.95-3.98, 4.13-4.14, and 4.46-4.48 (five m, 3H), 5.22-5.37 (m, 2H), 5.79-5.84 (m, 1H), 7.35-7.45 (m, 6H), 7.65-7.75 (m, 4H); ^{13}C NMR: δ 19.3, 23.2, 25.2, 25.7, 26.2, 27.1, 28.3, 29.5, 29.6, 29.7, 30.4, 39.5, 69.6, 78.3, 79.9, 80.7, 82.8, 108.0, 108.5, 118.1, 118.7, 127.4, 127.6, 129.3, 129.4, 134.7, 135.0, 135.6, 135.9. Anal. Calcd. for $C_{34}H_{52}O_3Si$: C, 76.07; H, 9.76%. Found: C, 75.91; H, 9.79%.

(2*R*,12*S*,13*RS*)-12,13-Isopropylidenedioxypentadec-14-en-2-ol 79.



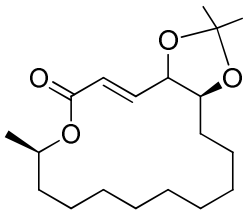
To a cooled (0 °C) and stirred solution of **78** (0.26 g, 0.49 mmol) in THF (5 mL) was added Bu_4NF (0.97 mL, 0.97 mmol, 1 M in THF). After stirring for 4 h, the mixture was concentrated in vacuo, the residue taken in EtOAc (10 mL) and the combined organic extracts washed with H_2O (1 × 5 mL) and brine (1 × 5 mL), and dried. The residue was purified by column chromatography (silica gel, 0-30% EtOAc/hexane) to afford pure **79** (0.131 g, 91%). colorless oil; $[\alpha]_D^{24}$ -3.3 (*c* 1.10, $CHCl_3$); IR: 3399, 992, 926 cm^{-1}; ^1H NMR: δ 1.15-1.55 (m containing a d at δ 1.17, *J* = 6.2 Hz, and two s at δ 1.39 and δ 1.47, 27H), 3.59-3.83, 3.93-4.17 and 4.42-4.49 (three m, 3H), 5.19-5.39 (m, 2H), 5.71-5.90 (m, 1H); ^{13}C NMR: δ 23.2, 25.5, 25.6, 25.9, 26.0, 26.8, 27.2, 28.1, 29.3, 29.4, 29.5, 30.2, 31.7, 39.1, 68.0, 78.2, 79.7, 80.5, 82.6, 107.9, 108.3, 118.0, 118.6, 134.4, 135.4. Anal. Calcd. for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48%. Found: C, 72.46; H, 11.61%.

(3*RS*,4*S*,14*R*)-14-Acryloxy-3,4-isopropylidenedioxypentadec-1-ene 80.



A mixture of **79** (0.12 g, 0.40 mmol), ethyl acrylate (0.33 mL, 3.20 mmol) and Novozym 435® (0.10 g) was agitated on an orbital shaker at 110 rpm for 24 h. The reaction mixture was filtered, and concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0-30% EtOAc/hexane) gave pure **80** (0.100 g, 93% based on conversion) along with unreacted **79** (16%). colorless oil; $[\alpha]_D^{23}$ -4.9 (*c* 1.03, $CHCl_3$); IR: 1723, 986 cm^{-1}; ^1H NMR: δ 1.20-1.67 (m containing a d at δ 1.22, *J* = 6.2 Hz, and two s at δ 1.35 and 1.47, 27H), 3.65-3.82, 3.93-4.00, 4.07-4.16, and 4.42-4.49 (four m, 2H), 4.91-5.00 (m, 1H), 5.18-5.38 (m, 2H), 5.71-5.89 (m, 2H), 6.01-6.15 (m, 1H), 6.35 (dd, *J* = 1.8, 17.2 Hz, 1H); ^{13}C NMR: δ 19.9, 25.3, 25.7, 26.0, 26.8, 27.3, 28.2, 29.3, 29.5, 30.2, 31.8, 35.9, 71.2, 78.2, 79.9, 80.7, 82.7, 107.9, 108.4, 118.0, 118.7, 129.0, 130.1, 134.6, 135.5, 165.9. Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29%. Found: C, 71.46; H, 10.61%.

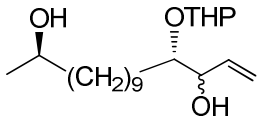
(4*RS*,5*S*,15*R*)-4,5-Dihydroxyhexadec-2-en-15-olide 4,5-acetonide (Va).



A mixture of **80** (0.05 g, 0.14 mmol) and Grubbs' II catalyst (5 mol%) in CH_2Cl_2 (10 mL) was refluxed for 8 h. The reaction mixture was concentrated in vacuo and the residue subjected to column chromatography (silica gel, 0-40% EtOAc/hexane) to afford pure **Va** (0.037 g, 81%). viscous gum; $[\alpha]_D^{24}$ -20.9 (*c* 1.10, $CHCl_3$); IR: 1713, 982 cm^{-1}; ^1H NMR: δ 1.12-1.42 (m

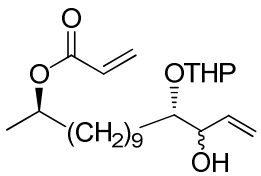
containing a d at δ 1.27, *J* = 6.4 Hz and two s at δ 1.36 and δ 1.50, 20H), 1.50-1.60 (m, 7H), 4.15-4.24 (m, 1H), 4.55-4.62 (m, 1H), 4.98-5.10 (m, 1H), 6.00 (d, *J* = 15.6 Hz, 1H), 6.83 (dd, *J* = 7.8, 15.6 Hz, 1H); ^{13}C NMR: δ 20.4, 23.1, 23.5, 25.4, 26.6, 26.7, 27.0, 27.2, 28.0, 28.3, 29.7, 35.0, 71.0, 76.3, 78.6, 108.7, 124.9, 142.2, 165.4. Anal. Calcd. for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94%. Found: C, 70.57; H, 9.83%.

(3*RS*,4*S*,14*R*)-4-Tetrahydropyranyloxypentadec-1-ene-3,14-diol 81.



Desilylation of (3*RS*,4*S*,14*R*)-**77** (0.73 g, 1.26 mmol) with Bu_4NF (2.5 mL, 1 M in THF, 2.5 mmol) in THF (10 mL) at 0 °C, followed by usual isolation and purification by column chromatography (silica gel, 0-30% EtOAc/hexane) afforded pure **81** (0.360 g, 84%). colorless oil; $[\alpha]_D^{25}$ -17.8 (*c* 1.08, $CHCl_3$); IR: 3399, 992, 925 cm^{-1}; ^{1}H NMR: δ 1.18 (d, *J* = 6.2 Hz, 3H), 1.21-1.87 (m, 26H), 3.45-3.56 (m, 1H), 3.59-3.84 (m, 2H), 3.85-4.03 (m, 2H), 4.20-4.54 and 4.65-4.88 (two m, 1H), 5.16-5.46 (m, 2H), 5.82-5.99 (m, 1H); ^{13}C NMR: δ 19.5, 19.7, 20.9, 23.1, 24.7, 25.1, 25.5, 25.6, 29.2, 29.3, 29.4, 29.6, 30.5, 31.0, 31.6, 36.8, 39.0, 62.5, 64.8, 67.4, 72.6, 73.4, 74.5, 79.1, 84.9, 97.3, 101.9, 113.8, 115.8, 116.2, 136.5, 136.8, 137.8, 141.3. Anal. Calcd. for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18%. Found: C, 69.74; H, 11.55%.

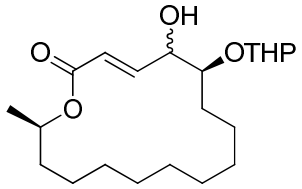
(3*RS*,4*S*,14*R*)-14-Acryloxy-4-tetrahydropyranyloxypentadec-1-en-3-ol 82.



A mixture of **81** (0.30 g, 0.88 mmol) and Novozym 435® (0.20 g) in ethyl acrylate (0.80 mL, 7.04 mmol) was agitated on an orbital shaker at 110 rpm for 72 h. The reaction mixture was

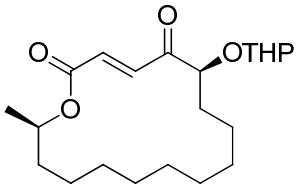
concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0-30% EtOAc/hexane) gave pure **82** (0.236 g, 88% based on conversion) and unreacted **81** (23%). colorless oil; $[\alpha]_D^{25}$ -5.1 (*c* 1.18, $CHCl_3$); IR: 3429, 1723, 1638, 1618, 986, 921 cm^{-1}; ^1H NMR: δ 1.19-1.69 (m, 27H), 1.76-1.88 (m, 1H), 3.35-3.70 (m, 2H), 3.82-4.12 (m, 2H), 4.37-4.46 (m, 1H), 4.90-5.12 (m, 1H), 5.15-5.45 (m, 2H), 5.75-5.94 (m, 2H), 6.01-6.14 (m, 1H), 6.32-6.50 (m, 1H); ^{13}C NMR: δ 14.0, 19.8, 21.2, 22.6, 24.8, 25.2, 25.9, 29.3, 29.6, 31.2, 32.0, 35.8, 36.9, 65.2, 71.1, 73.0, 74.8, 85.4, 102.0, 102.3, 114.2, 116.5, 117.2, 129.0, 130.0, 136.7, 137.0, 141.3, 165.8. Anal. Calcd. for $C_{23}H_{40}O_5$: C, 69.66; H, 10.17%. Found: C, 69.35; H, 10.53%.

(5*RS*,6*S*,16*R*,3*E*)-5-Hydroxy-16-methyl-6-(tetrahydropyranyloxy)oxacyclohexadec-3-en-2-one 83.



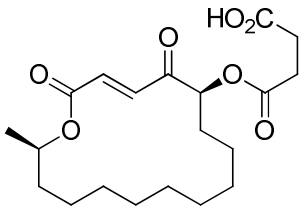
A mixture of **82** (0.10 g , 0.25 mmol) and Grubbs' II catalyst (20 mol%) in CH_2Cl_2 (10 mL) was refluxed for 4 h. Usual work-up, and purification by column chromatography (silica gel, 0-40% EtOAc/hexane) afforded pure **83** (0.063 g, 68%). colorless oil; $[\alpha]_D^{27}$ -17.0 (*c* 1.00, $CHCl_3$); IR: 3404, 1711, 985 cm^{-1}; ^1H NMR: δ 1.18-1.46 (m, 28H), 3.49-3.54, 3.70-3.76, 3.91-3.94 and 4.18-4.22 (four m, 3H), 4.59-4.62 (m, 1H), 4.72-4.81 (m, 1H), 4.88-5.10 (m, 1H), 6.04-6.18 (m, 1H), 6.82-6.95 (m, 1H); ^{13}C NMR: δ 20.3, 20.6, 22.3, 22.7, 23.4, 23.8, 25.2, 26.1, 27.0, 27.4, 27.7, 27.8, 28.9, 29.3, 29.5, 29.7, 30.3, 31.0, 31.1, 31.9, 35.1, 35.6, 63.0, 70.9, 71.3, 78.3, 82.5, 96.1, 100.4, 122.1, 123.0, 145.1, 145.8, 165.6, 166.1. Anal. Calcd. for $C_{21}H_{36}O_5$: C, 68.44; H, 9.85%. Found: C, 68.62; H, 9.52%.

(6*S*,16*R*,3*E*)-16-Methyl-6-(tetrahydropyranyloxy)oxacyclohexadec-3-ene-2,5-dione 84.



As described in the previous chapter, oxidation of **83** (0.03 g, 0.08 mmol) with PCC (0.027 g, 0.12 mmol) and NaOAc (10 mol%) in CH_2Cl_2 (5 mL) followed by work-up and column chromatography (silica gel, 0-15% EtOAc/hexane) furnished pure **84** (0.027 g, 89%). colorless oil; $[\alpha]_D^{25}$ -53.0 (*c* 1.00, $CHCl_3$); IR: 1725, 980 cm^{-1}; ^1H NMR: δ 1.14-1.88 (m, 27H), 3.46-3.54 (m, 1H), 3.80-3.88 (m, 1H), 4.40-4.58 (m, 1H), 4.86-5.12 (m, 1H), 6.78 (d, *J* = 15.8 Hz, 1H), 7.28 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR: δ 19.4, 20.1, 22.0, 22.7, 23.6, 25.3, 26.6, 27.5, 27.6, 28.9, 29.1, 29.3, 29.7, 30.5, 30.6, 31.9, 33.8, 34.7, 62.9, 72.6, 80.0, 97.7, 132.1, 134.9, 165.0, 199.7. Anal. Calcd. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35%. Found: C, 68.40; H, 9.49%.

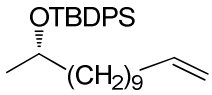
Antibiotic (-)-A26771B (V).



To a cooled (0 ^oC) and stirred solution of **84** (0.025 g, 0.07 mmol) in moist THF (5 mL) was added TFA (0.27 mL). After stirring for 3 h, the mixture was concentrated in vacuo to afford the corresponding depyranylated product (0.02 g). To a solution of the above crude product in CH_2Cl_2 (5 mL) was added DMAP (catalytic), followed by succinic anhydride (0.011 g, 0.11 mmol). After stirring for 2 h, the reaction mixture was concentrated and the residue subjected to preparative TLC (8% MeOH/$CHCl_3$) to afford pure **V** (0.019 g, 74%). white powder; mp: 122 ^oC (lit.[63] mp: 121-123 ^oC); $[\alpha]_D^{25}$ -12.2 (*c* 0.5, MeOH), (lit.[63] $[\alpha]_D^{12}$ -13 (*c* 0.2, MeOH)); IR: 3420,

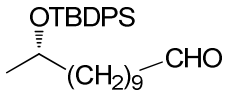
1748, 1713, 1701 cm^{-1}; ^1H NMR: δ 1.24-1.43 (m containing a d at δ 1.28, *J* = 6.5 Hz, 15H), 1.56-2.01 (m, 6H), 2.29 (t, *J* = 7.0 Hz, 2H), 2.65-2.69 (m, 2H), 5.10-5.15 (m, 1H), 5.34 (t, *J* = 5.4 Hz, 1H), 6.67 (d, *J* = 15.2 Hz, 1H), 7.63 (d, *J* = 15.2 Hz, 1H), 8.16 (broad s, 1H); ^{13}C NMR: δ 19.5, 22.1, 23.5, 26.5, 26.9, 27.2, 27.4, 27.7, 28.2, 28.4, 28.7, 34.6, 72.7, 78.8, 122.8, 135.7, 165.3, 171.8, 177.1, 196.0. Anal. Calcd. for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91%. Found: C, 63.18; H, 8.03%.

(*S*)-12-*tert*-Butyldiphenylsilyloxytridec-1-ene (*S*)-69.



Silylation (*S*)-**67** (4.24 g, 21.41 mmol) with TBDPSCl (7.06 g, 25.70 mmol), imidazole (2.18 g, 32.12 mmol) and DMAP (catalytic) in CH_2Cl_2 (40 mL) followed by usual work-up and purification by column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure (*S*)-**69** (8.54 g, 91%). colorless oil; $[\alpha]_D^{23}$ -16.1 (*c* 1.02, $CHCl_3$); IR: 997, 909 cm^{-1}; ^1H NMR: δ 1.07 (merged s and d, *J* = 6.0 Hz, 12H), 1.22-1.65 (m, 16H), 2.01-2.09 (m, 2H), 3.78-3.90 (m, 1H), 4.90-5.10 (m, 2H), 5.74-5.94 (m, 1H), 7.38-7.48 (m, 6H), 7.66-7.74 (m, 4H); ^{13}C NMR: δ 19.3, 23.2, 25.2, 27.0, 28.9, 29.0, 29.5, 29.6, 33.8, 39.4, 69.6, 114.1, 127.4, 129.3, 134.6, 135.0, 135.9, 139.2. Anal. Calcd. for $C_{29}H_{44}OSi$: C, 79.75; H, 10.15%. Found: C, 79.36; H, 10.18%.

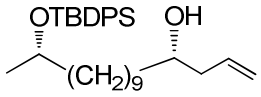
(*S*)-11-*tert*-Butyldiphenylsilyloxydodecanal (*S*)-71.



Ozone was bubbled through a cooled (-78 ^oC) solution of (*S*)-**69** (2.23 g, 5.11 mmol) in MeOH (20 mL) for 1 h. After 0.5 h, the excess O_3 was removed by purging with N_2, Ph_3P (2.01 g, 7.67 mmol) added, the mixture stirred for 12 h at room temperature and concentrated in vacuo. The residue was taken in hexane (10 mL), filtered, the filtrate concentrated in vacuo, and the product

purified by column chromatography (silica gel, 0-15% EtOAc/hexane) to obtain pure (*S*)-**71** (1.99 g, 89%). colorless oil; $[\alpha]_D^{24}$ -14.7 (*c* 1.02, $CHCl_3$); IR: 2710, 1717 cm^{-1}; ^1H NMR: δ 1.04 (merged s and d, *J* = 5.2 Hz, 12H), 1.17-1.25 (m, 12H), 1.59-1.64 (m, 4H), 2.39 (dt, *J* = 1.7, 7.3 Hz, 2H), 3.79-3.83 (m, 1H), 7.30-7.41 (m, 6H), 7.64-7.69 (m, 4H), 9.76 (t, *J* = 1.8 Hz, 1H); ^{13}C NMR: δ 19.1, 21.9, 23.1, 25.1, 26.9, 29.0, 29.1, 29.2, 29.3, 29.4, 39.3, 43.7, 69.4, 127.3, 129.3, 134.5, 134.8, 135.7, 202.5. Anal. Calcd. for $C_{28}H_{42}O_2Si$: C, 76.66; H, 9.65%. Found: C, 76.78; H, 9.69%.

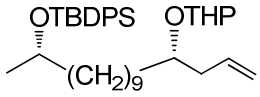
(4*S*,14*S*)-14-(*tert*)-Butyldiphenylsilyloxypentadec-1-en-4-ol 85.



To a stirred solution of $InCl_3$ (0.197 g, 0.89 mmol) [azeotropically dried with dry THF] in CH_2Cl_2 (10 mL) was added (*R*)-BINOL (0.282 g, 0.98 mmol) followed by molecular sieves 4Å (0.012 g). After 2 h, allylBu_3Sn (2.8 mL, 8.94 mmol) was added to this mixture, stirred for 10 min, cooled to -78 °C and (*S*)-**71** (1.96 g, 4.47 mmol) in CH_2Cl_2 (10 mL) was added. After stirring for 4 h at -78 °C and for 8 h at room temperature the mixture was treated with aqueous saturated $NaHCO_3$ and extracted with $CHCl_3$ (3 × 10 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0-10% EtOAc/hexane) furnished pure **85** (1.9 g, 89%). colourless oil; $[\alpha]_D^{27}$ -15.7 (*c* 1.12, $CHCl_3$); IR: 3389, 997, 913 cm^{-1}; ^1H NMR: δ 1.02 (merged s and d, *J* = 5.4 Hz, 12H), 1.17-1.58 (m, 19H), 2.16-2.27 (m, 2H), 3.55-3.62 (m, 1H), 3.77-3.83 (m, 1H), 5.09-5.16 (m, 2H), 5.76-5.96 (m, 1H), 7.32-7.41 (m, 6H), 7.63-7.69 (m, 4H); ^{13}C NMR: δ 13.5, 17.4, 19.1, 23.1, 25.1, 25.5, 26.7, 26.9, 27.7, 29.5, 36.7, 39.3, 41.8, 69.5, 70.6, 117.8, 127.3, 129.2, 134.5, 134.8, 135.7. Anal. Calcd. for $C_{31}H_{48}O_2Si$: C, 77.44;

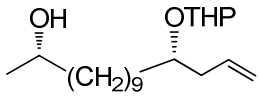
H, 10.06%. Found: C, 77.51; H, 10.21%.

(4*S*,14*S*)-14-(*tert*)-Butyldiphenylsilyloxy-4-tetrahydropyranyloxypentadec-1-ene 86.



Pyranylation of **85** (1.43 g, 2.98 mmol) with DHP (0.540 mL, 5.96 mmol) and PPTS (catalytic) in CH_2Cl_2 (20 mL) followed by work-up and column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **86** (1.5 g, 90%). colorless oil; $[\alpha]_D^{25}$ -15.2 (*c* 1.05, $CHCl_3$); IR: 997, 911, 869 cm^{-1}; ^{1}H NMR: δ 1.04 (merged s and d, *J* = 5.4 Hz, 12H), 1.17-1.47 (m, 14H), 1.50-1.74 (m, 10H), 2.25-2.33 (m, 2H), 3.44-3.52 (m, 1H), 3.61-3.65 (m, 1H), 3.80-3.93 (m, 2H), 4.64-4.70 (m, 1H), 5.00-5.10 (m, 2H), 5.72-5.93 (m, 1H), 7.33-7.40 (m, 6H), 7.64-7.68 (m, 4H); ^{13}C NMR: δ 19.2, 19.7, 23.2, 25.0, 25.1, 25.5, 27.0, 29.5, 29.7, 30.9, 31.1, 33.3, 34.7, 37.9, 39.4, 39.7, 62.3, 69.5, 75.2, 76.6, 96.7, 97.9, 116.4, 116.8, 127.3, 129.3, 134.5, 134.7, 134.8, 135.4, 135.8. Anal. Calcd. for $C_{36}H_{56}O_3Si$: C, 76.54; H, 9.99%. Found: C, 77.29; H, 9.71%.

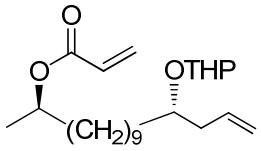
(2*S*,12*S*)-12-Tetrahydropyranyloxypentadec-1-en-2-ol 87.



Desilylation of **86** (1.52 g, 2.66 mmol) with Bu_4NF (5.3 mL, 5.31 mmol, 1 M in THF) in THF (10 mL) followed by work-up and column chromatography (silica gel, 0-30% EtOAc/hexane) gave **87** (0.810 g, 92%). colorless oil; $[\alpha]_D^{24}$ -2.8 (*c* 1.09, $CHCl_3$); IR: 3367, 1006, 927 cm^{-1}; ^{1}H NMR: δ 1.15 (d, *J* = 6.2 Hz, 3H), 1.18-1.32 (m, 12H), 1.38-1.88 (m, 13H), 2.19-2.34 (m, 2H), 3.42-3.48 (m, 1H), 3.62-3.93 (m, 3H), 4.63-4.67 (m, 1H), 5.03-5.08 (m, 2H), 5.66-5.92 (m, 1H); ^{13}C NMR: δ 19.7, 23.3, 25.0, 25.5, 25.7, 29.5, 29.6, 29.7, 30.9, 31.1,

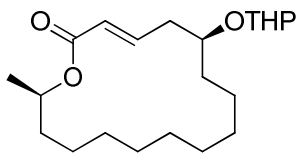
33.3, 34.7, 38.0, 39.3, 39.7, 62.4, 67.9, 75.5, 76.7, 96.8, 97.9, 116.3, 116.7, 134.8, 135.5. Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73%. Found: C, 73.22; H, 11.70%.

(2*R*,12*S*)-2-Acryloxy-12-tetrahydropyranyloxypentadec-1-ene 88.



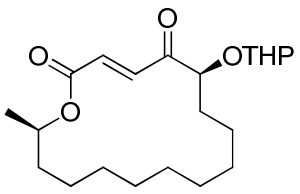
To a cooled (0 °C) and stirred solution of **87** (0.610 g, 1.87 mmol), PPh_3 (0.735 g, 2.81 mmol) and acrylic acid (0.270 g, 3.74 mmol) in THF (15 mL) was dropwise added DIAD (0.55 mL, 2.81 mmol). After stirring the mixture for 12 h at room temperature, it was poured into ice-cold water (20 mL), the organic layer separated and the aqueous portion extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal in vacuo followed by column chromatography (silica gel, 0-30% EtOAc/hexane) of the residue gave pure **88** (0.500 g, 71%). colorless oil; $[\alpha]_D^{25}$ -10.2 (*c* 1.08, $CHCl_3$); IR: 1722, 987 cm^{-1}; ^1H NMR: δ 1.22-1.40 (m containing a d at δ 1.23, *J* = 6.5 Hz, 15H), 1.43-1.76 (m, 12H), 2.24-2.36 (m, 2H), 3.46-3.50 (m, 1H), 3.57-3.68 (m, 1H), 3.87-3.94 (m, 1H), 4.65-4.69 (m, 1H), 4.94-5.10 (m, 3H), 5.75-5.85 (m, 2H), 5.97-6.03 (m, 1H), 6.37 (dd, *J* = 1.7, 17.2 Hz, 1H); ^{13}C NMR: δ 20.0, 20.1, 25.2, 25.5, 25.7, 25.8, 29.6, 29.7, 29.9, 31.1, 31.2, 33.5, 34.9, 36.1, 38.1, 39.9, 62.7, 71.4, 75.5, 76.8, 97.0, 98.2, 116.7, 117.1, 129.3, 130.3, 135.0, 135.7, 166.1. Anal. Calcd. for $C_{23}H_{40}O_4$: C, 72.59; H, 10.59%. Found: C, 72.71; H, 10.72%.

(6*S*,16*R*,3*E*)-16-Methyl-6-(tetrahydropyranyloxy)-1-oxacyclohexadec-3-ene-2-one 89.



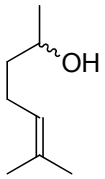
A mixture of **88** (0.210 g, 0.55 mmol) and Grubbs' II catalyst (10 mol%) in CH_2Cl_2 (50 mL) was refluxed for 8 h. The reaction mixture was concentrated in vacuo and the residue subjected to column chromatography (silica gel, 0-25% EtOAc/hexane) to afford pure **89** (0.147 g, 75%). colorless oil; $[\alpha]_D^{26}$ -23.0 (*c* 1.14, $CHCl_3$); IR: 1712, 887 cm^{-1}; ^1H NMR: δ 1.22-1.50 (m, 19H), 1.56-1.86 (m, 8H), 2.30-2.39, 2.42-2.53 and 2.63-2.69 (three m, 2H), 3.45-3.51 (m, 1H), 3.68-3.90 (m, 2H), 4.61-4.70 (m, 1H), 4.95-5.21 (m, 1H), 5.84 (broad d, *J* = 15.6 Hz, 1H), 6.80-6.96 (m, 1H); ^{13}C NMR: δ 19.4, 19.7, 20.0, 20.3, 22.6, 22.8, 23.3, 23.6, 25.4, 26.3, 26.8, 27.2, 27.4, 27.5, 27.8, 29.6, 30.9, 31.0, 31.3, 32.0, 34.6, 34.8, 37.9, 62.2, 62.6, 70.6, 72.9, 75.7, 95.5, 98.8, 124.4, 144.3, 144.8, 165.6, 165.8. Anal. Calcd. for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29%. Found: C, 71.47; H, 10.12%.

(6*S*,16*R*,3*E*)-16-Methyl-6-(tetrahydropyranyloxy)-1-oxacyclohexadec-3-ene-2,5-dione 84.



A mixture of **89** (0.100 g, 0.28 mmol) and SeO_2 (0.048 g, 0.43 mmol) in 1,4-dioxane (10 mL) was refluxed for 24 h. After bringing to room temperature, the mixture was filtered, the filtrate concentrated in vacuo, and the residue subjected to column chromatography (silica gel, 0-25% EtOAc/hexane) to obtain pure **84** (0.065 g, 63%). Its optical and spectral (^1H and ^{13}C NMR) data were identical with that of the sample, prepared earlier. Anal. Calcd. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35%. Found: C, 68.64; H, 9.49%.

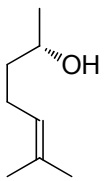
(±)-6-Methyl-5-hepten-2-ol 123.



To a cooled (0 ^{o}C) and stirred suspension of $LiAlH_4$ (2.11 g, 55.56 mmol) in Et_2O (30 mL) was dropwise added **122** (10.00 g, 79.37 mmol) in Et_2O (70 mL). After stirring for 2 h, the mixture was treated with aqueous saturated Na_2SO_4, diluted with Et_2O, and the supernatant filtered. The filtrate was carefully concentrated, and the residue distilled to obtain pure **123** (9.2 g, 91%). colorless oil; bp: 90 ^{o}C/20 mm; IR: 3373, 1642 cm^{-1}; ^{1}H NMR: δ 1.14 (d, *J* = 6.2 Hz, 3H), 1.48-1.59 (m, 2H), 1.65 (s, 3H), 1.71 (s, 3H), 2.00-2.15 (m, 3H), 3.74-3.90 (m, 1H), 5.11-5.19 (m, 1H); ^{13}C NMR: δ 17.5, 23.3, 24.4, 25.6, 39.1, 67.7, 124.0, 131.8.

(*R*)-6-Acetoxy-2-methyl-2-heptene 124. A mixture of (±)-**123** (7.50 g, 58.59 mmol), vinyl acetate (8.1 mL, 87.89 mmol) and Novozym 435® (0.75 g, ~12 mg/mmol) in hexane (30.0 mL) was agitated on an orbital shaker at 110 rpm for 50 min. The reaction mixture was filtered, and the solution concentrated in vacuo to get a residue which on column chromatography (silica gel, 0-10% EtOAc/hexane) gave pure (*S*)-**123** (3.1 g, 41%) and (*R*)-**124** (4.4 g, 44%).

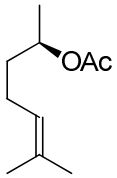
(*S*)-**123:**



colorless oil; $[\alpha]_D^{24}$ +10.9 (*c* 1.30, $CHCl_3$) (lit.[73b] $[\alpha]_D^{25}$ +10.5 (*c* 0.4, $CHCl_3$)); IR: 3437 cm^{-1}; ^{1}H NMR: δ 1.19 (d, *J* = 6.0 Hz, 3H), 1.41-1.57 (m, 2H), 1.62 (s, 3H), 1.69 (s, 3H), 1.93 (broad s, 1H), 2.00-2.14 (m, 2H), 3.80 (sextet, *J* = 6.0 Hz, 1H), 5.12-5.22 (m, 1H); ^{13}C NMR: δ 17.7, 23.4,

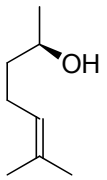
24.5, 25.7, 39.2, 67.9, 124.1, 132.0. Anal Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58%; Found: C, 74.77; H, 12.68%.

(*R*)-**124:**



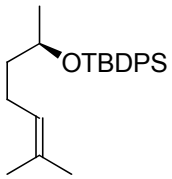
colorless oil; $[\alpha]_D^{24}$ -6.5 (*c* 1.01, $CHCl_3$), $[\alpha]_D^{25}$ -6.8 (*c* 1.23, EtOH) (lit.[73c] $[\alpha]_D^{23}$ +7.7 (*c* 0.03, EtOH)); IR: 1736, 1243 cm^{-1}; ^1H NMR: δ 1.21 (d, *J* = 6.6 Hz, 3H), 1.43-1.57 (m, 2H), 1.59 (s, 3H), 1.68 (s, 3H), 1.97-2.04 (merged m and s at δ 2.03, 5H), 4.83-4.91 (m, 1H), 5.05-5.11 (m, 1H); ^{13}C NMR: δ 17.6, 21.4, 24.0, 25.7, 29.7, 36.0, 70.7, 123.5, 132.1, 170.8. Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%; Found: C, 70.38; H, 10.36%.

(*R*)-6-Methyl-5-hepten-2-ol (*R*)-123.



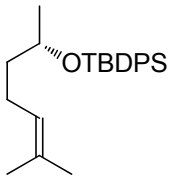
Reduction of (*R*)-**124** (2.70 g, 15.88 mmol) with $LiAlH_4$ (0.480 g, 12.70 mmol) in Et_2O (60 mL) followed by work up as above furnished pure (*R*)-**123** (1.9 g, 92%). colorless oil; $[\alpha]_D^{22}$ -11.7 (*c* 1.06, $CHCl_3$); IR: 3050, 1642 cm^{-1}; ^1H NMR: δ 1.16 (d, *J* = 6.0 Hz, 3H), 1.39-1.55 (m, 2H), 1.59 (s, 3H), 1.68 (s, 3H), 1.83 (broad s, 1H), 2.00-2.09 (m, 2H), 3.72-3.83 (m, 1H), 5.03-5.18 (m, 1H); ^{13}C NMR : δ 17.7, 23.5, 24.5, 25.8, 39.2, 67.9, 124.1, 132.0. Anal Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58%; Found: C, 74.77; H, 12.68%.

(*R*)-6-*tert*-Butyldiphenylsilyloxy-2-methyl-2-heptene (*R*)-125.



Silylation of (*R*)-**123** (2.50 g, 19.53 mmol) with TBDPSCl (6.98 g, 25.39 mmol), imidazole (1.73 g, 25.39 mmol) and DMAP (catalytic) in CH_2Cl_2 (20 mL) followed by work-up and column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure (*R*)-**125** (6.3 g, 88%). colorless oil; $[\alpha]_D^{24}$ +11.7 (*c* 1.04, $CHCl_3$); IR: 3050, 3013 cm^{-1}; ^1H NMR: δ 1.05 (merged s and d, *J* = 6.0 Hz, 12H), 1.18-1.26 (m, 2H), 1.53 (s, 3H), 1.63 (s, 3H), 1.88-2.01 (m, 2H), 3.79-3.87 (m, 1H), 4.95-5.00 (m, 1H), 7.32-7.44 (m, 6H), 7.65-7.70 (m, 4H); ^{13}C NMR: δ 17.6, 18.4, 19.3, 23.2, 24.0, 25.7, 26.8, 26.9, 39.6, 69.4, 124.5, 127.4, 127.5, 127.6, 129.4, 129.5, 131.2, 134.3, 134.6, 135.0, 135.6, 135.9. Anal. Calcd. for $C_{24}H_{34}OSi$: C, 78.63; H, 9.35%. Found: C, 78.68; H, 9.51%.

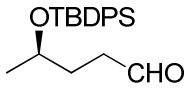
(*S*)-6-*tert*-Butyldiphenylsilyloxy-2-methyl-2-heptene (*S*)-125.



As above, silylation of (*S*)-**123** (2.20 g, 17.19 mmol) using TBDPSCl (6.12 g, 22.34 mmol), imidazole (1.52 g, 22.34 mmol) and DMAP (catalytic) in CH_2Cl_2 (20 mL) furnished (*S*)-**125** (5.7 g, 91%). colorless oil; $[\alpha]_D^{25}$ -11.8 (*c* 1.03 , $CHCl_3$); IR: 3071, 3049, 998 cm^{-1}; ^1H NMR: δ 1.03 (merged s and d, *J* = 6.2 Hz, 12H), 1.40-1.45 (m, 1H), 1.50-1.55 (m containing a s at δ 1.54, 4H), 1.63 (s, 3H), 1.89-2.01 (m, 2H), 3.84-3.86 (m, 1H), 4.96-4.99 (m, 1H), 7.35-7.42 (m, 6H), 7.67-7.69 (m, 4H); ^{13}C NMR: δ 17.7, 18.5, 19.4, 23.2, 24.1, 25.8, 26.9, 27.1, 39.7, 69.4, 124.5, 127.5,

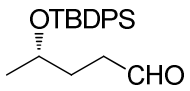
127.7, 129.5, 129.6, 131.3, 134.7, 135.0, 135.6, 136.0. Anal. Calcd. for $C_{24}H_{34}OSi$: C, 78.63; H, 9.35%. Found: C, 78.31; H, 9.23%.

(*R*)-4-*tert*-Butyldiphenylsilyloxypentanal (*R*)-126.



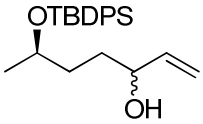
Reductive ozonolysis of (*R*)-**125** (4.84 g, 13.22 mmol) using O_3 and Ph_3P (5.20 g, 19.84 mmol) in CH_2Cl_2 (20 mL) followed by work-up and column chromatography (silica gel, 0-10% Et_2O/hexane) gave pure (*R*)-**126** (3.6 g, 81%). colorless oil; $[\alpha]_D^{22}$ +2.2 (*c* 1.01, $CHCl_3$); IR: 3070, 2717, 1726 cm^{-1}; ^1H NMR: δ 1.06 (merged s and d, *J* = 6.3 Hz, 12H), 1.70-1.83 (m, 2H), 2.44-2.51 (m, 2H), 3.91-3.95 (m, 1H), 7.37-7.43 (m, 6H), 7.66-7.68 (m, 4H), 9.68 (s, 1H); ^{13}C NMR: δ 19.3, 23.0, 27.0, 27.1, 31.3, 39.6, 68.5, 127.5, 127.7, 129.6, 129.7, 134.1, 134.5, 135.8, 135.9, 202.4. Anal. Calcd. for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29%. Found: C, 74.18; H, 8.51%.

(*S*)-4-*tert*-Butyldiphenylsilyloxypentanal (*S*)-126.



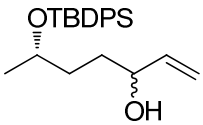
Reductive ozonolysis of (*S*)-**125** (5.01 g, 13.69 mmol) with O_3 and Ph_3P (5.38 g, 20.53 mmol) in CH_2Cl_2 (20 mL) followed by isolation as above furnished pure (*S*)-**126** (3.8 g, 82%). colorless oil; $[\alpha]_D^{22}$ -1.9 (*c* 1.19, $CHCl_3$); IR: 1727, 2717, 3050 cm^{-1}; ^1H NMR: δ 1.07 (merged s and d, *J* = 6.1 Hz, 12H), 1.71-1.83 (m, 2H), 2.47-2.49 (m, 2H), 3.92-3.96 (m, 1H), 7.37-7.43 (m, 6H), 7.66-7.68 (m, 4H), 9.68 (s, 1H); ^{13}C NMR: δ 19.3, 23.0, 27.0, 27.1, 31.3, 39.6, 68.5, 127.4, 127.5, 127.6, 127.7, 129.6, 129.7, 134.1, 134.5, 135.8, 135.9, 136.0, 202.4. Anal. Calcd. for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29%. Found: C, 74.18; H, 8.51%.

(3*RS*,6*R*)-6-*tert*-Butyldiphenylsilyloxyhept-1-en-3-ol (3*RS*,6*R*)-127.



Reaction of (*R*)-**126** (3.14 g, 9.24 mmol) with vinylmagnesium bromide (18.5 mL, 18.5 mmol, 1 M in THF) in THF (30 mL) at -78 ^{o}C followed by work-up and column chromatography (silica gel, 0-10% Et_2O/hexane) gave (3*RS*,6*R*)-**127** (2.8 g, 84%). colorless liquid; $[\alpha]_D^{23}$ +36.1 (*c* 1.22, $CHCl_3$); IR: 3365, 3070, 3050, 1644 cm^{-1}; ^{1}H NMR: δ 1.04 (merged s and d, *J* = 6.2 Hz, 12H), 1.45-1.69 (m, 5H), 3.85-3.87 (m, 1H), 3.98-4.00 (m, 1H), 5.01-5.20 (m, 2H), 5.69-5.86 (m, 1H), 7.30-7.40 (m, 6H), 7.63-7.68 (m, 4H); ^{13}C NMR: δ 19.3, 23.1, 27.1, 29.7, 32.3, 32.6, 34.7, 35.1, 69.3, 69.5, 73.0, 73.2, 114.5, 127.5, 127.6, 129.5, 129.6, 134.4, 134.7, 135.0, 136.4, 141.2. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C, 74.78; H, 8.84%.

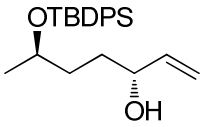
(3*RS*,6*S*)-6-*tert*-Butyldiphenylsilyloxyhept-1-en-3-ol (3*RS*,6*S*)-127.



As above, reaction of (*S*)-**126** (2.30 g, 6.76 mmol) with vinylmagnesium bromide (13.6 mL, 13.6 mmol, 1 M in THF) in THF (20 mL) and usual purification afforded pure (3*RS*,6*S*)-**127** (2.1 g, 84%). colorless liquid; $[\alpha]_D^{24}$ -12.1 (*c* 1.16, $CHCl_3$); IR: 3364, 3071, 997 cm^{-1}; ^{1}H NMR: δ 1.04 (merged s and d, *J* = 6.2 Hz, 12H), 1.45-1.62 (m containing a s at 1.58, 5H), 3.85-3.87 (m, 1H), 3.96-4.02 (m, 1H), 5.01-5.20 (m, 2H), 5.69-5.86 (m, 1H), 7.33-7.40 (m, 6H), 7.63-7.67 (m, 4H); ^{13}C NMR: δ 19.2, 23.0, 27.0, 32.2, 32.5, 34.6, 35.0, 69.3, 69.4, 73.0, 73.2, 114.5, 127.4, 127.5, 129.4, 129.5, 135.9, 141.1. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C, 75.18; H, 8.51%.

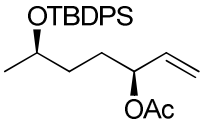
(3*S*,6*R*)-3-Acetoxy-6-*tert*-butyldiphenylsilyloxyhept-1-ene (3*S*,6*R*)-128. Acetylation of (3*RS*,6*R*)-**127** (4.16 g, 11.30 mmol) with vinyl acetate (5.0 mL) and Novozym 435® (0.50 g, ~50 mg/mmol) was carried out as described above to obtain pure (3*R*,6*R*)-**127** (2.0 g, 48%) and (3*S*,6*R*)-**128** (2.1 g, 46%).

(3*R*,6*R*)-**127:**



colorless oil; $[\alpha]_D^{26}$ +10.4 (*c* 1.14, $CHCl_3$); ^{1}H NMR: δ 1.06 (merged s and d, *J* = 6.0 Hz, 12H), 1.47-1.55 (m, 5H), 3.88-3.91 (m, 1H), 3.98-4.00 (m, 1H), 5.01-5.18 (m, 2H), 5.76-5.82 (m, 1H), 7.35-7.43 (m, 6H), 7.67-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 23.0, 27.0, 32.6, 35.1, 69.4, 73.2, 114.5, 127.4, 127.5, 129.5, 129.6, 134.3, 134.6, 135.9, 141.1. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C,75.15; H, 8.92%.

(3*S*,6*R*)-**128:**

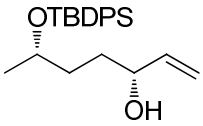


colorless oil; $[\alpha]_D^{26}$ +13.1 (*c* 1.03, $CHCl_3$); IR: 3070, 1739, 1647 cm^{-1}; ^{1}H NMR: δ 1.04 (merged s and d, *J* = 7.2 Hz, 12H), 1.35-1.52 (m, 2H), 1.54-1.70 (m, 2H), 2.01 (s, 3H), 3.81-3.90 (m, 1H), 5.09-5.20 (m, 3H), 5.61-5.78 (m, 1H), 7.31-7.42 (m, 6H), 7.63-7.68 (m, 4H); ^{13}C NMR: δ 19.3, 21.2, 23.1, 27.0, 27.1, 29.6, 34.5, 69.0, 74.7, 116.6, 127.5, 129.5, 129.6, 134.4, 134.7, 135.8, 135.9, 136.0, 136.5, 170.3. Anal. Calcd. for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35%. Found: C,73.15; H, 8.32%.

(3*S*,6*S*)-3-Acetoxy-6-*tert*-butyldiphenylsilyloxyhept-1-ene (3*S*,6*S*)-128. Following the same procedure as above, (3*RS*,6*S*)-**127** (1.90 g, 5.16 mmol) was acetylated in vinyl acetate (5.0 mL)

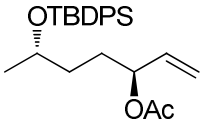
using Novozym 435® (0.25 g, ~50 mg/mmol) to obtain pure (3*R*,6*S*)-**127** (0.860 g, 45%) and (3*S*,6*S*)-**128** (1.0 g, 47%).

(3*R*,6*S*)-**127:**



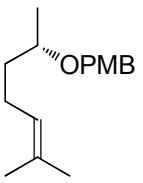
colorless oil; $[\alpha]_D^{25}$ -17.7 (*c* 1.24 , $CHCl_3$); IR: 3360, 3065, 998 cm^{-1}; ^1H NMR: δ 1.02 (merged s and d, *J* = 6.0 Hz, 12 H), 1.45-1.59 (m, 5H), 3.84-3.93 (m, 1H), 3.96-4.02 (m, 1H), 5.04-5.21 (m, 2H), 5.71-5.87 (m, 1H), 7.30-7.41 (m, 6H), 7.64-7.68 (m, 4H); ^{13}C NMR: δ 19.2, 23.0, 27.0, 32.3, 34.6, 69.3, 73.0, 114.6, 127.4, 127.5, 129.5, 134.4, 134.7, 135.9, 141.1. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C, 75.18; H, 8.51%.

(3*S*,6*S*)**-128:**



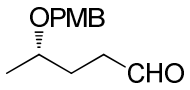
colorless oil; $[\alpha]_D^{24}$ -13.5 (*c* 1.05, $CHCl_3$); IR: 1736, 1231 cm^{-1}; ^1H NMR: δ 1.04 (merged s and d, *J* = 6.0 Hz, 12H), 1.35-1.50 (m, 2H), 1.52-1.68 (m, 2H), 2.02 (s, 3H), 3.79-3.88 (m, 1H), 5.10-5.20 (m, 3H), 5.60-5.77 (m, 1H), 7.32-7.42 (m, 6H), 7.63-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 21.2, 23.1, 27.0, 29.7, 34.5, 69.1, 74.8, 116.6, 127.4, 127.5, 129.4, 129.5, 134.3, 134.7, 135.8, 136.4, 170.3. Anal. Calcd. for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35%. Found: C, 73.32; H, 8.04%.

(2*S*)-6-*para*-Methoxybenzyloxy-2-methylhept-2-ene 129.



To a cooled (-5 ^{o}C) and stirred suspension of hexane-washed NaH (4.52 g, 94.14 mmol, 50% suspension in oil) in DMF (10 mL) was added (*S*)-**123** (4.82 g, 37.66 mmol) in DMF (10 mL). After 1 h, PMBCl (6.13 mL, 45.19 mmol) was dropwise added into the mixture and stirring continued till completion of the reaction (*cf*. TLC). After addition of H_2O (20 mL), the mixture was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), dried and concentrated in vacuo to get a residue which on column chromatography (silica gel, 0-5% Et_2O/hexane) afforded pure (*S*)-**129** (7.6 g, 82%). colorless liquid; $[\alpha]_D^{23}$ +29.9 (*c* 1.08, $CHCl_3$); IR: 3090, 1613 cm^{-1}; ^{1}H NMR: δ 1.18 (d, *J* = 7.0 Hz, 3H), 1.43-1.44 (m, 2H), 1.60 (s, 3H), 1.68 (s, 3H), 2.04-2.06 (m, 2H), 3.47-3.50 (m, 1H), 3.79 (s, 3H), 4.38 (d, *J* = 14.0 Hz, 1H), 4.49 (d, *J* = 14.0 Hz, 1H), 5.09 (t, *J* = 2.4 Hz, 1H), 6.86 (d, *J* = 7.0 Hz, 2H), 7.26 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR: δ 17.6, 19.6, 24.1, 25.7, 36.7, 55.2, 69.9, 74.1, 113.7, 124.3, 129.1, 131.2, 131.5, 159.0. Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74%. Found: C, 77.33; H, 9.61%.

(4*S*)-4-*para*-Methoxybenzyloxypentanal 130.

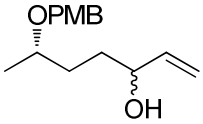


Dihydroxylation of (*S*)-**129** (4.46 g, 17.98 mmol) in acetone : water (8:1, 30 mL) with NMO (4.20 g, 35.96 mmol) and OsO_4 (0.230 g, 0.89 mmol) in *t*-BuOH (2 mL), followed by work-up and column chromatography (0-30% EtOAc/hexane) furnished the corresponding 1,2-diol (4.8 g, 95%). colorless oil. $[\alpha]_D^{24}$ +29.2 (*c* 1.03, $CHCl_3$); IR: 3418, 1341, 1138 cm^{-1}; ^{1}H NMR: δ 1.12-1.26 (merged s and d, *J* = 6.4 Hz, 9H), 1.56-1.81 (m, 4H), 2.56 (broad s, 2H), 3.34 (t, *J* = 7.4 Hz, 1H), 3.45-3.61 (m, 1H), 3.78 (s, 3H), 4.37 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR: 19.4, 19.5, 23.3, 23.4, 26.4, 26.5, 27.5,

27.6, 33.7, 33.8, 55.3, 70.1, 72.9, 73.0, 74.5, 74.7, 78.4, 113.8, 129.4, 129.5, 130.5, 130.7, 159.2. Anal. Calcd. for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28%. Found: C, 67.88; H, 9.61%.

The above diol (4.08 g, 14.47 mmol) was cleaved with $NaIO_4$ (6.19 g, 28.92 mmol) in in aqueous 60% CH_3CN (20 mL). Usual work-up and column chromatography (silica gel, 0-10% EtOAc/hexane) furnished pure (*S*)-**130** (3.2 g, quant.). colorless liquid; $[\alpha]_D^{24}$ +45.5 (*c* 1.03, $CHCl_3$); IR: 2724, 1723 cm^{-1}; ^1H NMR: δ 1.20 (d, *J* = 6.0 Hz, 3H), 1.79-1.86 (m, 2H), 2.46-2.54 (m, 2H), 3.50-3.56 (m, 1H), 3.80 (s, 3H), 4.36 (d, *J* = 11.4 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 9.74 (t, *J* = 1.5 Hz, 1H); ^{13}C NMR: δ 19.6, 29.3, 40.3, 55.4, 70.2, 73.5, 113.9, 129.4, 130.7, 159.2, 202.7. Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%. Found: C, 70.05; H, 8.08%.

(3*RS*,6*S*)-6-*para*-Methoxybenzyloxyhept-1-en-3-ol 131.

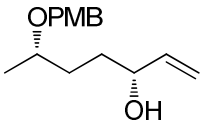


As described earlier, reaction of (*S*)-**130** (2.28 g, 10.27 mmol) with vinylmagnesium bromide (15.40 mL, 15.40 mmol, 1M in THF) (30 mL) followed by usual isolation and purification furnished (3*RS*,6*S*)-**131** (1.9 g, 73%). colorless liquid; $[\alpha]_D^{24}$ +16.3 (*c* 1.02, $CHCl_3$); IR: 3410 cm^{-1}; ^1H NMR: δ 1.15 (d, *J* = 6.3 Hz, 3H), 1.47-1.66 (m, 4H), 2.50 (broad s, 1H), 3.44-3.52 (m, 1H), 3.74 (s, 3H), 3.98-4.05 (m, 1H), 4.33 (d, *J* = 11.4 Hz, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 5.01-5.18 (m, 2H), 5.74-5.86 (m, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ 19.5, 32.4, 33.0, 55.3, 70.0, 72.9, 74.3, 74.5, 113.8, 114.4, 129.4, 130.8, 141.3, 159.1. Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%. Found: C, 72.21; H, 8.88%.

(3*S*,6*S*)-3-Acetoxy-6-*para*-methoxybenzyloxyhept-1-ene 132. As described earlier, acetylation of (3*RS*,6*S*)-**131** (1.80 g, 7.20 mmol) with vinyl acetate (1.0 mL, 10.8 mmol) in the presence of

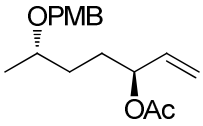
Novozym 435® (0.540 mg, ~75 mg/mmol) in diisopropyl ether (25 mL) followed by isolation furnished (3*R*,6*S*)-**131** (0.756 g, 42%) and **132** (0.946 g, 45%).

(3*R*,6*S*)-**131:**



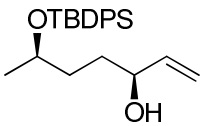
colorless liquid; $[\alpha]_D^{23}$ +20.7 (*c* 1.00, $CHCl_3$); IR: 3410 cm^{-1}; ^1H NMR: δ 1.19 (d, *J* = 6.3 Hz, 3H), 1.54-1.72 (m, 4H), 2.43 (broad s, 1H), 3.49-3.59 (m, 1H), 3.79 (s, 3H), 4.03-4.11 (m, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 5.07-5.26 (m, 2H), 5.80-5.91 (m, 1H), 6.87 (d, *J* = 8.7 Hz, 2H), 7.26 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR: δ 19.5, 32.4, 33.0, 55.3, 70.1, 72.9, 74.5, 113.8, 114.5, 129.4, 130.8, 141.2, 159.1. Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%. Found: C, 72.15; H, 8.75%.

132:



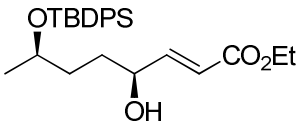
colorless liquid; $[\alpha]_D^{24}$ +12.4 (*c* 1.01, $CHCl_3$); IR : 1736, 1646, 990 cm^{-1}; ^1H NMR: δ 1.18 (d, *J* = 6.3 Hz, 3H), 1.39-1.80 (m, 4H), 2.03 (s, 3H), 3.46-3.56 (m, 1H), 3.80 (s, 3H), 4.36 (d, *J* = 11.4 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, 1H), 5.13-5.25 (m, 3H), 5.70-5.81 (m, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR: δ 19.6, 21.3, 30.1, 32.0, 55.3, 70.0, 73.9, 74.7, 113.8, 116.7, 129.2, 131.0, 136.5, 159.1, 170.4. Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%. Found: C, 69.88; H, 8.33%.

(3*S*,6*R*)-6-*tert*-Butyldiphenylsilyloxyhept-1-en-3-ol (3*S*,6*R*)-127.



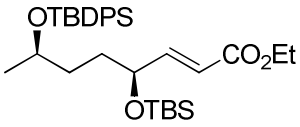
A mixture of (3*S*,6*R*)-**128** (3.20 g, 7.80 mmol) and K_2CO_3 (1.30 g, 9.36 mmol) in MeOH (20 mL) was magnetically stirred till completion of the reaction (*cf*. TLC, ~6 h). After solvent removal in vacuo, H_2O (25 mL) was added to the residue followed by extraction with EtOAc (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), dried and concentrated in vacuo to get a residue which on column chromatography (silica gel, 0-15% EtOAc/hexane) furnished pure (3*S*,6*R*)-**127** (2.7 g, 92%). colorless liquid; $[\alpha]_D^{24}$ +15.0 (*c* 1.12, $CHCl_3$); IR: 3420, 3050, 997 cm^{-1}; ^1H NMR: δ 1.07 (merged s and d, *J* = 6.3 Hz, 12H), 1.42-1.60 (m, 5H), 3.85-3.92 (m, 1H), 3.96-4.02 (m, 1H), 5.07-5.19 (m, 2H), 5.78-5.83 (m, 1H), 7.35-7.43 (m, 6H), 7.67-7.69 (m, 4H); ^{13}C NMR: δ 19.3, 23.1, 27.0, 27.2, 32.3, 34.6, 69.3, 73.0, 114.6, 127.5, 127.6, 129.5, 129.6, 134.4, 134.8, 135.9, 141.2. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C, 74.77; H, 8.43%.

Ethyl (*2E*,4*S*,7*R*)-4-Hydroxy-7-*tert*-butyldiphenylsilyloxyoct-2-enoate 133.



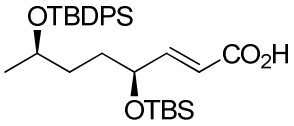
Cross-metathesis between (3*S*,6*R*)-**127** (0.730 g, 1.98 mmol) and ethyl acrylate (1.99 g, 19.8 mmol) in the presence of Hoveyda Grubbs' II catalyst (5 mol) in CH_2Cl_2 (15 mL), followed by isolation furnished **133** (0.870 g, quant.). colorless oil; $[\alpha]_D^{28}$ +28.9 (*c* 1.02, $CHCl_3$); IR: 3453, 1720, 1656, 984 cm^{-1}; ^1H NMR: δ 1.04 (merged s and d, *J* = 6.0 Hz, 12H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.59-1.67 (m, 5H), 3.85-3.94 (m, 1H), 4.14-4.25 (merged m and q at δ 4.20, *J* = 7.2 Hz, 3H), 5.99 (dd, *J* = 1.6, 15.6 Hz, 1H), 6.88 (dd, *J* = 4.6, 15.6 Hz, 1H), 7.35-7.42 (m, 6H), 7.63-7.68 (m, 4H); ^{13}C NMR: δ 14.2, 19.2, 22.9, 27.0, 31.6, 34.2, 60.4, 69.1, 70.8, 120.2, 127.4, 127.6, 129.5, 129.6, 134.0, 134.4, 135.8, 135.9, 150.1, 166.5. Anal. Calcd. for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.23%. Found: C, 70.65; H, 8.36%.

Ethyl (*2E*,4*S*,7*R*)-4-*tert*-Butyldimethylsilyloxy-7-*tert*-butyldiphenylsilyloxyoct-2-enoate 134.



As described earlier, silylation of **133** (0.870 g, 1.98 mmol) with TBSCl (0.445 g, 2.97 mmol), imidazole (0.202 g, 2.97 mmol) and DMAP (catalytic) in CH_2Cl_2 (15 mL) furnished **134** (1.0 g, 92%) after isolation and purification. colorless oil; $[\alpha]_D^{22}$ +25.8 (*c* 1.04, $CHCl_3$); IR: 3071, 3048, 1720, 1656, 997 cm^{-1}; ^1H NMR: δ -0.04 (s, 6H), 0.85 (s, 9H), 1.01 (merged s and d, *J* = 6.0 Hz, 12H), 1.23-1.31 (m containg a t at δ 1.28, *J* = 7.0 Hz, 4H), 1.44-1.50 (m, 3H), 3.77-3.83 (m, 1H), 4.08-4.22 (merged m and q at δ 4.17, *J* = 7.0 Hz, 3H), 5.88 (dd, *J* = 1.8, 15.6 Hz, 1H), 6.82 (dd, *J* = 4.6, 15.6 Hz, 1H), 7.28-7.40 (m, 6H), 7.61-7.65 (m, 4H); ^{13}C NMR: δ 14.3, 18.1, 19.2, 23.2, 25.8, 27.0, 32.8, 34.4, 60.3, 69.2, 71.4, 119.8, 127.4, 127.5, 129.4, 129.5, 134.4, 134.8, 135.8, 135.9, 150.9, 166.7. Anal. Calcd. for $C_{32}H_{50}O_4Si_2$: C, 69.26; H, 9.08%. Found: C, 69.47; H, 9.23%.

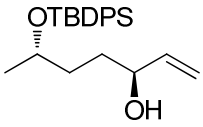
(*2E*,4*S*,7*R*)-4-*tert*-Butyldimethylsilyloxy-7-*tert*-butyldiphenylsilyloxyoct-2-enoic acid 135.



To a stirred solution of **134** (1.01 g, 1.82 mmol) in MeOH (20 mL) was added aqueous 20% NaOH (8 mL). After stirring for 2 h at room temperature, the mixture was concentrated in vacuo. The residue was acidified with aqueous 2N HCl and extracted with Et_2O (3 × 30 mL). The organic layer was washed with H_2O (2 × 20 mL) and brine (1 × 10 mL). Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-30% EtOAc/hexane) afforded pure **135** (0.948 g, 99%). colorless oil; $[\alpha]_D^{24}$ +27.1 (*c* 1.17, $CHCl_3$); IR: 3500-2500, 1698 cm^{-1}; ^1H NMR: δ 0.01 (s, 6H), 0.90 (s, 9H), 1.06 (merged s and d, *J* = 6.2 Hz, 12H), 1.27-

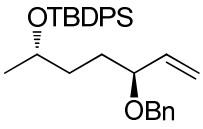
1.30 (m, 2H), 1.51-1.63 (m, 3H), 3.82-3.88 (m, 1H), 4.11-4.19 (m, 1H), 5.96 (dd, *J* = 1.2, 15.6 Hz, 1H), 6.98 (dd, *J* = 4.4, 15.6 Hz, 1H), 7.34-7.42 (m, 6H), 7.66-7.70 (m, 4H); ^{13}C NMR: δ 18.1, 19.2, 23.2, 25.8, 27.0, 29.7, 32.7, 34.3, 69.1, 71.2, 119.1, 127.4, 127.5, 129.4, 129.6, 134.3, 134.7, 135.8, 135.9, 153.7, 172.2. Anal. Calcd. for $C_{30}H_{46}O_4Si_2$: C, 68.39; H, 8.80%. Found: C, 68.04; H, 9.19%.

(3*S*,6*S*)-6-*tert*-Butyldiphenylsilyloxyhept-1-en-3-ol (3*S*,6*S*)-127.



Alkaline hydrolysis of (3*S*,6*S*)-**128** (1.20 g, 2.93 mmol) with K_2CO_3 (0.490 g, 3.55 mmol) in MeOH (15 mL) followed by usual isolation as above furnished pure (3*S*,6*S*)-**127** (0.981 g, 91%). colorless liquid; $[\alpha]_D^{24}$ -10.1 (*c* 1.06, $CHCl_3$); IR: 3420, 3050, 997 cm^{-1}; ^{1}H NMR: δ 1.04 (merged s and d, *J* = 5.6 Hz, 12H), 1.50-1.61 (m, 5H), 3.84-3.98 (m, 2H), 5.00-5.19 (m, 2H), 5.69-5.85 (m, 1H), 7.31-7.40 (m, 6H), 7.62-7.68 (m, 4H); ^{13}C NMR: δ 19.0, 22.7, 26.8, 32.3, 34.8, 69.1, 73.0, 114.3, 127.2, 127.3, 129.2, 129.3, 134.4, 135.6, 140.9. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C, 74.71; H, 8.83%.

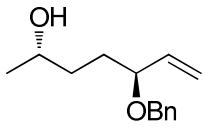
(3*S*,6*S*)-3-Benzyloxy-6-*tert*-butyldiphenylsilyloxyhept-1-ene 136.



Benzylation of (3*S*,6*S*)-**127** (0.690 g, 1.88 mmol) using hexane-washed NaH (0.14 g, 5.64 mmol, 50% suspension in oil), BnBr (0.48 g, 2.82 mmol) and Bu_4NI (10 mol%) in THF (15 mL) followed by work-up and column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **136** (0.835 g, 97%). colorless oil; $[\alpha]_D^{23}$ -25.0 (*c* 1.20, $CHCl_3$); IR: 3069, 1643 cm^{-1}; ^{1}H NMR: δ 1.03 (merged s and d, *J* = 6.0 Hz, 12H), 1.49-1.57 (m, 4H), 3.56-3.66 (m, 1H), 3.78-

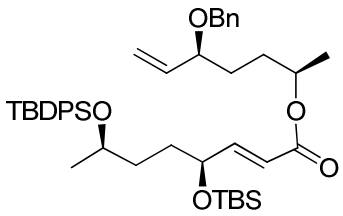
3.89 (m, 1H), 4.30 (d, *J* = 11.8 Hz, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 5.06-5.19 (m, 2H), 5.55-5.73 (m, 1H), 7.25-7.29 (m, 5H), 7.32-7.43 (m, 6H), 7.63-7.68 (m, 4H); ^{13}C NMR: δ 19.2, 23.2, 27.0, 31.0, 35.0, 69.5, 69.9, 80.7, 117.1, 127.4, 127.6, 127.7, 128.3, 129.4, 134.4, 134.8, 135.9, 138.8, 138.9. Anal. Calcd. for $C_{30}H_{38}O_2Si$: C, 78.55; H, 8.35%. Found: C, 78.37; H, 8.28%.

(2*S*,5*S*)-5-Benzyloxyhept-6-en-2-ol 137.



Desilylation of **136** (0.742 g, 1.62 mmol) with Bu_4NF (3.23 mL, 3.23 mmol, 1 M in THF) in THF (10 mL) at 0 °C, followed by isolation, as described earlier furnished **137** (0.271 g, 76%); colorless oil; $[\alpha]_D^{25}$ -20.6 (*c* 1.06, $CHCl_3$); IR: 3400, 3065, 3030, 1643 cm^{-1}; ^{1}H NMR: δ 1.17 (d, *J* = 6.0 Hz, 3H), 1.64-1.66 (m, 5H), 3.72-3.83 (m, 2H), 4.34 (d, *J* = 11.8 Hz, 1H), 4.59 (d, *J* = 11.8 Hz, 1H), 5.17-5.26 (m, 2H), 5.67-5.84 (m, 1H), 7.25-7.32 (m, 5H); ^{13}C NMR: δ 23.3, 31.6, 34.9, 67.6, 70.1, 80.5, 117.3, 127.4, 127.7, 128.3, 138.3, 138.6. Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%. Found: C, 76.37; H, 9.51%.

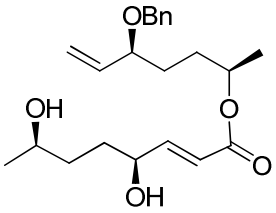
(*9E*,3*S*,6*R*,11*S*,14*R*)-3-Benzyloxy-11-*tert*-butyldimethylsilyloxy-14-*tert*-butyldiphenylsilyloxy-6-methyl-7-oxa-8-oxopenta-1,9-diene 138.



To a stirred solution of **137** (0.270 g, 1.23 mmol) in THF (10 mL) were added PPh_3 (0.48 g, 1.85 mmol) and **135** (0.775 g, 1.47 mmol). The reaction mixture was cooled to 0 °C, DIAD (0.36 g, 1.85 mmol) added, and the mixture stirred for 18 h. The mixture was extracted with EtOAc (2 × 15 mL), the organic extract washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. After

concentrating in vacuo, the residue was subjected to column chromatography (silica gel, 0-20% EtOAc/hexane) to give pure **138** (0.592 g, 66%). colorless oil; $[\alpha]_D^{23}$ +7.7 (*c* 1.06, $CHCl_3$); IR: 1715, 1657, 995 cm^{-1}; ^1H NMR: δ -0.03 (s, 6H), 0.86 (s, 9H), 1.03 (merged s and d, *J* = 6.0 Hz, 12H), 1.22 (d, *J* = 6.2 Hz, 3H), 1.46-1.57 (m, 8H), 3.72-3.85 (m, 2H), 4.12-4.14 (m, 1H), 4.33 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.93-4.97 (m, 1H), 5.16-5.25 (m, 2H), 5.63-5.77 (m, 1H), 5.86 (dd, *J* = 1.6, 15.6 Hz, 1H), 6.80 (dd, *J* = 4.6, 15.6 Hz, 1H), 7.31-7.37 (m, 11H), 7.63-7.67 (m, 4H); ^{13}C NMR: δ 18.0, 19.1, 19.9, 23.2, 25.8, 27.0, 31.1, 31.5, 32.8, 34.4, 69.1, 70.0, 70.4, 71.3, 79.9, 117.3, 120.1, 127.3, 127.4, 127.6, 128.2, 129.3, 129.4, 134.2, 134.6, 135.7, 138.5, 138.7, 150.5, 166.1. Anal. Calcd. for $C_{44}H_{64}O_5Si_2$: C, 72.48; H, 8.85%. Found: C, 72.52; H, 8.70%.

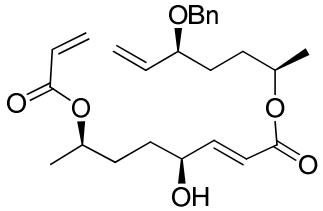
(*6E,2R,5S,10R,13S*)-13-Benzyloxy-10-methyl-9-oxa-8-oxopenta-6,14-diene-2,5-diol 139.



A mixture of **138** (0.583 g, 0.80 mmol) in CH_3CN (10 mL) and aqueous HF (0.4 ml) in a teflon vessel was stirred at room temperature for 16 h. The mixture was concentrated in vacuo, and the residue extracted with EtOAc (3 × 20 mL). The organic layer was washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), concentrated in vacuo, and the residue column chromatographed (silica gel, 0-40% EtOAc/hexane) to afford pure **139** (0.210 g, 70%). colorless oil; $[\alpha]_D^{23}$ -24.0 (*c* 1.05, $CHCl_3$); IR: 3417, 3087, 3030, 1714, 990 cm^{-1}; ^1H NMR: δ 1.17 (d, *J* = 6.0 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.49-1.75 (m, 8H), 3.14 (broad s, 2H), 3.70-3.82 (m, 2H), 4.29-4.35 (merged m and d, *J* = 11.8 Hz, 2H), 4.57 (d, *J* = 11.8 Hz, 1H), 4.92-4.96 (m, 1H), 5.16-5.25 (m, 2H), 5.62-5.79 (m, 1H), 5.99 (dd, *J* = 1.4, 15.6 Hz, 1H), 6.89 (dd, *J* = 4.8, 15.6 Hz, 1H), 7.26-7.33 (m, 5H); ^{13}C

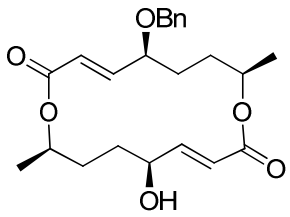
NMR: δ 19.9, 23.6, 31.1, 31.6, 33.2, 35.1, 68.1, 70.0, 70.8, 71.0, 80.0, 117.5, 120.4, 127.4, 127.7, 128.3, 138.5, 138.6, 150.0, 166.3. Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57%. Found: C, 69.84; H, 8.53%.

(*6E,2R,5S,10R,13S*)-2-Acryloxy-13-benzyloxy-10-methyl-9-oxa-8-oxopenta-6,14-dien-5-ol 140.



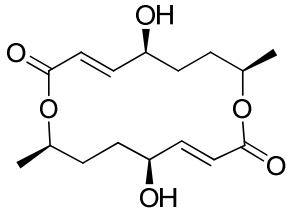
A solution of **139** (0.210 g, 0.56 mmol), ethyl acrylate (0.450 g, 4.48 mmol) and Novozym 435® (0.50 g, ~890 mg/mmol) in diisopropyl ether (5 mL) was agitated on an orbital shaker at 120 rpm for 30 h. The reaction mixture was filtered, the filtrate concentrated in vacuo, and the residue column chromatographed (silica gel, 0-25% EtOAc/hexane) to furnish pure **140** (0.171 g, 71%). colorless oil; $[\alpha]_D^{23}$ -7.1 (*c* 1.13, $CHCl_3$); IR: 3479, 3065, 1728, 1714, 1657, 985 cm^{-1}; ^1H NMR: δ 1.22 (d, *J* = 6.2 Hz, 3H), 1.25 (d, *J* = 6.4 Hz, 3H), 1.54-1.80 (m, 8H), 3.51 (broad s, 1H), 3.68-3.79 (m, 1H), 4.29-4.35 (merged m and d, *J* = 11.8 Hz, 2H), 4.58 (d, *J* = 11.8 Hz, 1H), 4.88-5.06 (m, 2H), 5.16-5.25 (m, 2H), 5.66-5.83 (m, 2H), 5.95-6.15 (m, 2H), 6.38 (dd, *J* = 1.6, 17.2 Hz, 1H), 6.88 (dd, *J* = 5.0, 15.8 Hz, 1H), 7.29-7.33 (m, 5H); ^{13}C NMR: δ 20.0, 31.1, 31.4, 31.6, 32.0, 70.0, 70.5, 70.7, 70.9, 80.0, 117.5, 120.8, 127.4, 127.7, 128.3, 128.7, 130.6, 138.5, 138.6, 149.5, 165.9, 166.0. Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96%. Found: C, 69.44; H, 7.94%.

(*5S,8R,13S,16R*)-Pyrenophorol monobenzyl ether 141.



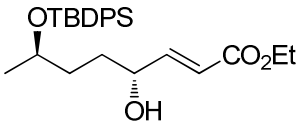
A stirred solution of **140** (0.142 g, 0.33 mmol) and Grubbs' II catalyst (20 mol%) in degassed CH_2Cl_2 (10 mL) was refluxed for 72 h. The reaction mixture was concentrated in vacuo, and the residue subjected to preparative thin layer chromatography (TLC) to obtain pure **141** (57 mg, 61% based on conversion) and recovered **140** (40 mg). colorless oil; $[\alpha]_D^{25}$ -39.0 (*c* 1.07, $CHCl_3$); IR: 3470, 1713, 1643 cm^{-1}; ^1H NMR: δ 1.24 (t, *J* = 6.2 Hz, 6H), 1.60-1.86 (m, 9H), 3.78-3.88 (m, 1H), 4.13-4.22 (m, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 5.03-5.17 (m, 2H), 5.91 (d, *J* = 16.0 Hz, 2H), 6.74 (dd, *J* = 7.8, 16.0 Hz, 1H), 6.82 (dd, *J* = 6.8, 15.6 Hz, 1H), 7.32 (s, 5H); ^{13}C NMR: δ 13.9, 18.4, 29.7, 30.9, 33.4, 43.7, 69.8, 70.7, 77.2, 79.2, 83.4, 124.5, 127.7, 128.6, 146.9, 178.1. Anal. Calcd. for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51%. Found: C, 68.56; H, 7.78%.

(*5S,8R,13S,16R*)-Pyrenophorol (-)-VI.



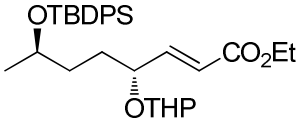
A mixture of **141** (40 mg, 0.1 mmol) and $TiCl_4$ (11.0 µL, 0.1 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature till the completion of the reaction (*cf.* TLC, 30 min). After concentration in vacuo, the residue was purified by preparative TLC to get pure (*5S,8R,13S,16R*)-**VI** (23 mg, 74%). sticky solid; $[\alpha]_D^{25}$ -2.9 (*c* 1.00, acetone), (lit.[70f] $[\alpha]_D^{25}$ -3.2 (*c* 0.25, acetone); IR: 3440, 1714, 1651, 985 cm^{-1}; ^1H NMR: δ 1.26 (d, *J* = 6.6 Hz, 6H), 1.64-1.93 (m, 8H), 2.30 (broad s, 2H), 4.26-4.32 (m, 2H), 5.10-5.17 (m, 2H), 5.98 (dd, *J* = 1.6, 15.6 Hz, 2H), 6.90 (dd, *J* = 5.2, 15.6 Hz, 2H); ^{13}C NMR: δ 18.2, 28.9, 30.5, 69.8, 70.4, 122.2, 149.5, 165.0. Anal. Calcd. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74%. Found: C, 61.45; H, 7.92%.

Ethyl (4*R*,7*R*)-4-Hydroxy-7-*tert*-butyldiphenylsilyloxyoct-2-enoate (4*R*,7*R*)-133.



The cross-metathesis between (3*R*,6*R*)-**118** (1.5 g, 4.08 mmol) and ethyl acrylate (2.28 g, 22.85 mmol, 2.5 mL) in the presence of Grubbs II catalyst (5 mol%, 170 mg) in CH_2Cl_2 (15 mL) at 25 ^oC for 3 h, followed by work-up and column chromatography (silica gel, 0-15% EtOAc/hexane) gave pure (4*R*,7*R*)-**133** (1.4 g, 78%). colourless oil; $[\alpha]_D^{23}$ +6.6 (*c* 1.04, $CHCl_3$); IR: 3502, 1716, 981 cm^{-1}; ^1H NMR: δ 1.05 (merged s and d, *J* = 6.2 Hz, 12H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.51-1.73 (m, 4H), 2.26 (broad s, 1H), 3.89-3.92 (m, 1H), 4.19 (merged m and q, *J* = 7.0 Hz, 3H), 5.99 (d, *J* = 15.5 Hz, 1H), 6.87 (dd, *J* = 5.0, 15.5 Hz, 1H), 7.32-7.45 (m, 6H), 7.63-7.69 (m, 4H); ^{13}C NMR: δ 14.2, 19.2, 22.8, 27.0, 32.0, 34.9, 60.4, 69.2, 71.1, 120.2, 127.5, 127.6, 129.5, 129.6, 134.1, 134.4, 135.9, 150.1, 166.6; Anal. Calcd. for $C_{26}H_{36}O_4Si$: C, 70.87, H, 8.23%. Found: C, 70.65, H, 8.36%.

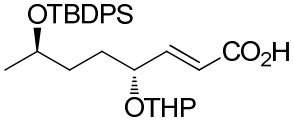
Ethyl (4*R*,7*R*)-4-Tetrahydropyranyloxy-7-*tert*-butyldiphenylsilyloxyoct-2-enoate 142.



As described earlier, tetrahydropyranylation of (4*R*,7*R*)-**133** (1.2 g, 2.73 mmol) with DHP (0.50 mL, 5.46 mmol) and PPTS (10 mol%) in CH_2Cl_2 (15 mL), usual work-up and column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **142** (1.38 g, 96%). colourless oil; $[\alpha]_D^{23}$ +22.9 (*c* 1.01, $CHCl_3$); IR: 1716, 821, 756, 742 cm^{-1}; ^1H NMR: δ 1.04 (merged s and d, *J* = 6.2 Hz, 12H), 1.30 (t, *J* = 3.5 Hz, 3H), 1.36-1.66 (m, 6H), 1.67-1.87 (m, 4H), 3.35-3.52 (m, 1H), 3.76-3.91 (m, 2H), 4.15-4.25 (m, 2H), 4.51-4.62 (m, 1H), 4.92-4.96 (m, 1H), 5.87 and 5.99 (two d, *J* = 15.5 Hz, 1H), 6.71 and 6.87 (two dd, *J* = 6.4, 15.5 Hz, 1H), 7.33-7.41 (m, 6H),

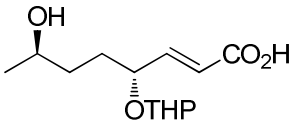
7.65-7.67 (m, 4H); ^{13}C NMR: δ 14.2, 19.2, 19.3, 19.7, 22.2, 23.1, 23.2, 23.8, 25.3, 25.4, 26.0, 27.0, 29.0, 30.6, 34.0, 34.8, 60.2, 60.4, 62.1, 62.3, 62.7, 65.7, 68.6, 69.3, 69.4, 74.4, 74.7, 79.3, 94.6, 95.9, 97.0, 120.5, 122.1, 127.4, 129.4, 129.5, 134.4, 134.6, 134.7, 135.8, 138.0, 148.8, 166.2, 166.5. Anal. Calcd. for $C_{31}H_{44}O_5Si$: C, 70.95, H, 8.45%. Found: C, 70.82, H, 8.55%.

(4*R*,7*R*)-4-Tetrahydropyranyloxy-7-*tert*-butyldiphenylsilyloxyoct-2-enoic acid 143.



Alkaline hydrolysis of **142** (1.1 g, 2.10 mmol) with aqueous 20% NaOH (10 mL) in MeOH (10 mL), work-up and purification by column chromatography (silica gel, 0-30% EtOAc/hexane) afforded pure **143** (0.90 g, 87%). colourless oil; $[\alpha]_D^{24}$ +20.9 (*c* 1.01, $CHCl_3$); IR: 3500-2500, 1697 cm^{-1}; ^{1}H NMR: δ 1.06 (merged s and d, *J* = 6.0 Hz, 12H), 1.44-1.75 (m, 10H), 3.42-3.52 (m, 1H), 3.67-3.90 (m, 2H), 4.20-4.32 (m, 1H), 4.51-4.68 (m, 1H), 5.89 and 6.02 (two d, *J* = 15.5 Hz, 1H), 6.83 and 6.98 (two dd, *J* = 6.0, 15.5 Hz, 1H), 7.33-7.50 (m, 6H), 7.65-7.79 (m, 4H); ^{13}C NMR: *δ* 14.2, 19.2, 19.3, , 23.1, 23.2, 25.3, 27.0, 29.0, 30.6, 34.0, 34.8, 62.1, 62.2, 62.3, 69.3, 69.4, 119.7, 121.12, 127.4, 127.5, 129.4, 129.5, 129.6, 134.4, 134.7, 135.8, 135.9, 150.9, 151.7, 171.2, 171.5. Anal. Calcd. for $C_{29}H_{40}O_5Si$: C, 70.12, H, 8.12%. Found: C, 70.36, H, 8.50%.

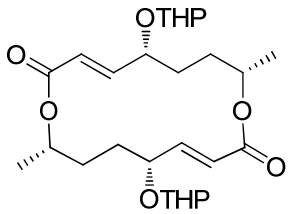
(4*R*,7*R*)-4-Tetrahydropyranyloxy-7-hydroxyoct-2-enoic acid 144.



Desilylation of **143** (0.70 g, 1.41 mmol) with Bu_4NF (2.82 mL, 1 M in THF, 2.82 mmol) in THF (15 mL) under refluxing conditions, work-up and purification by column chromatography (silica gel, 0-40% EtOAc/hexane) furnished **144** (0.25 g, 69%); colourless oil; $[\alpha]_D^{23}$ +22.4 (*c* 1.16, $CHCl_3$); IR: 3500-2500, 1698 cm^{-1}; ^{1}H NMR: δ 1.16-1.27 (m, 5H), 1.45-1.83 (m, 8H), 3.07

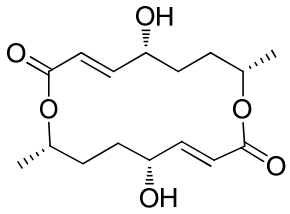
(broad s, 1H), 3.43-3.57 (m, 1H), 3.73-3.94 (m, 2H), 4.29-4.50, 4.52-4.60 and 4.69-4.80 (three m, 2H), 5.94 and 6.07 (two d, *J* = 15.8 Hz, 1H), 6.88 and 7.03 (two dd, *J* = 6.2, 15.8 Hz, 1H); ^{13}C NMR: δ 18.8, 19.1, 23.5, 25.8, 29.8, 30.5, 32.0, 34.0, 35.0, 63.1, 63.5, 68.0, 74.0, 75.0, 77.0, 78.0, 96.8, 97.3, 121.0, 122.0, 127.7, 130.0, 135.0, 149.0, 151.0, 169.0, 170. Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.45, H, 8.58%. Found: C, 60.35, H, 8.77%.

(5*R*,8S,11*R*,16*S*)-5,11-Ditetrahydropyranyloxy pyrenophorol *ent*-104.



To a cooled (-25 °C) and stirred solution of **135** (0.15 g, 0.58 mmol) in THF (16 mL) was added PPh_3 (0.80 g, 2.91 mmol) in toluene (160 mL) followed by DIAD (0.59 g, 2.91 mmol, 0.60 mL). After stirring for 10 h, the mixture was extracted with EtOAc (2 × 15 mL), the organic extract washed with H_2O (2 × 5 mL) and brine (1 × 5 mL), and dried. After concentrating in vacuo, the residue was subjected to column chromatography (silica gel, 0-30% EtOAc/hexane) to give pure *ent*-**104** (0.07 g, 50%). colourless oil; $[\alpha]_D^{22}$ +22.3 (*c* 1.12, $CHCl_3$); IR: 1722 cm^{-1}; ^{1}H NMR: δ 1.22-1.31 (m, 6H), 1.45-1.88 (m, 20H), 3.41-3.50 (m, 2H), 3.77-3.86 (m, 2H), 4.11-4.18 (m, 2H), 4.50-4.54 (m, 1H), 4.70-4.74 (m, 1H), 4.93-5.04 (m, 2H), 5.83-5.96 (m, 2H), 6.66-6.83 (m, 2H); ^{13}C NMR: δ 18.1, 18.4, 18.5, 18.8, 19.3, 19.7, 21.7, 21.9, 25.3, 25.4, 27.2, 27.3, 28.7, 28.8, 28.9, 29.1, 29.3, 29.5, 29.7, 30.7, 62.3, 62.9, 69.4, 69.6, 69.8, 70.3, 72.3, 74.0, 74.1, 74.4, 76.6, 96.4, 96.6, 122.8, 122.9, 124.4, 124.7, 146.4, 146.9, 165.0, 165.6. Anal. Calcd. for $C_{26}H_{40}O_8$: C, 64.98; H, 8.39%. Found: C, 64.79; H, 8.12%.

(5*R*,8S,11*R*,16*S*)-Pyrenophorol (+)-VI.



A mixture of *ent*-**104** (0.07 g, 0.22 mmol) and PTS (10 mol%) in MeOH (5 mL) was stirred at room temperature for 30 min. After concentration in vacuo, the residue was extracted with EtOAc (2 × 5 mL), the organic extract washed with H_2O (2 × 4 mL) and brine (1 × 2 mL) and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-40% EtOAc/hexane) of the residue afforded pure (+)-**VI** (0.02 g, 44%). colourless oil; $[\alpha]_D^{25}$ +2.7 (*c* 1.00, $CHCl_3$); IR: 3448, 1719 cm^{-1}; ^1H NMR: δ 1.22 (d, *J* = 6.6 Hz, 6H), 1.62-1.95 (m, 8H), 2.24 (broad s, 2H), 4.22-4.28 (m, 2H), 5.08-5.19 (m, 2H), 5.95 (dd, *J* = 1.6, 15.6 Hz, 2H), 6.93 (dd, *J* = 5.2, 15.6 Hz, 2H); ^{13}C NMR: δ 18.3, 29.1, 30.5, 69.3, 70.8, 121.9, 148.8, 166.2. Anal. Calcd. for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74%. Found: C, 61.56; H, 7.66%.

CHAPTER IV

"Bibliography"

References

1. (a) Ward, R. S. In: *Selectivity in Organic Synthesis*; 1999, Wiley; (b) Hoz A. D. L.; Diaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem*. **2004**, *8*, 903–918.
2. Clardy, J.; Walsh, C. *Nature* **2004,** *432,* 829–837.
3. (a) Eliel, E. L. In: *Stereochemistry of Carbon Compounds*; 1962, McGraw-Hill; (b) Stephenson, G. R. In: *Advanced Asymmetric Synthesis*; 1996, Chapman and Hall.
4. (a) Chen, A. S. M. *Chem. Tech.* **1993**, 46; (b) Tombo, R. G. M.; Bellus, D., *Angew. Chem. Intl. Ed. Engl*. **1991**, *30*, 1193–1215; (c) Ariens, E. J. *Proc. 1st Int. Pharmacol. Meet*. Vol 7, Pergamon Press, Oxford, 1963, 247; (d) Renynolds, G. P.; Elsworth, J. D.; Blau, K.; Sandler, M.; Lees, A. J.; Stern, G. M. *Br. J. Clin. Pharmacol*. **1978**, *6*, 542–544; (e) Tessier, J.; Herve, J. J. *Deltamethrine*, Uclaf, R. (Ed.); 1982, 25.
5. (a) Blaschke, G. *Angew. Chem. Intl. Ed. Engl*. **1980**, *19*, 13–24; (b) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904–3906; (c) Dobashi, A.; Oka, K.; Hara, S. *J. Am. Chem. Soc.* **1980**, *102*, 7122–7123; (d) Jaques, J.; Collet, A.; Wilen, S. H. In: *Enantiomers, Racemates, and Resolutions*; 1981, 447 S, J. Wiley & Sons, Inc., New York.
6. (a) Hanessian, S. In: *Total Synthesis of Natural Products, the "Chiron" Approach*; Pergamon Press, Elmsford. NY, 1983; (b) Crosby, J. *Tetrahedron* **1991**, *47*, 4789–4846; (c) Blaser, H.-U. *Chem. Rev*. **1992**, *92*, 935–952.
7. (a) In: *Asymmetric Synthesis* (Morrison, J. D., Ed.); Academic Press: NY, 1983, Vol. 2, Chapter 2; (b) Gawley, R. E.; Aube, J. Principles of Asymmetric Synthesis, In: *Catalytic Asymmetric Synthesis*, (Ojima, I., Ed.); 2013, John Wiley & Sons.
8. (a) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem. Intl. Ed. Engl*. **1966**, *5*, 385–415; (b) Eliel, E. L. *Tetrahedron* **1974**, *30*, 1503–1513.

9. (a) Knowles, W. S. Sabacky, M. J. *J. Chem. Soc. Chem. Comm.* **1968**, 1445–1446; (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976; (c) Hanson, R. M.; Sharpless, K. B. *J. Org, Chem.*, **1986**, *51*, 1922–1925; (d) Kolb, H. C.; van Nieuwenhuize, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (e) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345–1376; (f) Noyori, R. *Science* **1990**, *248*, 1194–1199; (g) Otsuka, S.; Tani, K. *Synthesis* **1991**, 665–680; (h) Aratani, T. *Pure and Appl. Chem.* **1985**, *57*, 1839–1844, and the references cited therein; (i) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauf, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567–2568.

10. (a) Stinson, S. C. *Chem. Eng. News* **2000**, *78*, 55–79; (b) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed*. **2001**, *40*, 3726–3748; (c) Breslow, R. *Science* **1982**, *218*, 532–537.

11. (a) Cram, D. J.; Elhafez, A. *J. Am. Chem. Soc*. **1952**, *74*, 5828–5835; (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc*. **1959**, *81*, 2748–2755.

12. (a) Cherest, M.; Felkin, H. *Tetrahedron Lett*. **1968**, *9*, 2205–2208; b) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145–170.

13. (a) Okamoto, Y.; Ikai, T. *Chem. Soc. Rev.* **2008**, *37*, 2593–2608; (b) Stalcup, A. M. *Annu. Rev. Anal. Chem. (Palo Alto Calif.)* **2010**, *3*, 341–363. doi: 10.1146/annurev.anchem.111808.073635; (c) Maftouh, M.; Granier-Loyaux, C.; Chavana, E.; Marini, J.; Pradines, A.; Heyden, Y. V.; Picard, C. *J. Chromatogr. A*. **2005**, *1088(1-2)*, 67–81.

14. Wenzel, T. J. In: *Discrimination of Chiral Compounds Using NMR Spectroscopy*; 2007, Wiley-Interscience; (b) Dale, J. A.; Mosher, S. H. *J. Am. Chem. Soc*. **1973**, *95*, 512–519; (c) Okatani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc*.

1991, *113*, 4092–4096; (d) Moon, L. S.; Jolly, R. S.; Kasetti, Y.; Bharatam, P. V. *Chem. Commun.* **2009**, 1067–1069.

15. Liese, Andreas; Seelbach, Karsten; Wandrey, Christian, (Eds.). In: *Industrial Biotransformations*; 2006, p. 556, 2nd ed., John Wiley & Sons.
16. (a) Wong, C. H.; Whitesides, G. M. In: *Enzymes in Synthetic Organic Chemistry*; 1994, Elsevier Science; (b) Santiniello, E.; Ferraboschi, P.; Grisenti, P.; Manzocchi, A. *Chem. Rev*. **1992**, *92*, 1071–1140.
17. Rothenberg, G. In: Catalysis: Concepts and Green Applications; 2008, Wiley-VCH Verlag; (b) Kirby, A. J. *Angew. Chem. Int. Ed.* **1996**, *35*, 707–725.
18. (a) Gupta, M. N. (Ed.); *Methods in Non-Aqueous Enzymology*, 2000, Birkhäuser Basel; (b) Klibanov, A. M. *Nature* **2001**, *409*, 241–246.
19. (a) Jones, J. B.; Beck, J. F. In: *Application of Biochemical Systems in Organic Chemistry. Part 1*; (Jones, J. B.; Sih, C. J.; Perlman, D. Eds.); 1976; Vol. X, pp 236–401, Wiley: New York; (b) Roberts, S. M.; Turner, A. J.; Willetts, A. J.; Turner, M. K. In: *Introduction to Biocatalysis Using Enzymes and Microorganisms*; 1995, Cambridge University Press: New York.
20. (a) Svedendahl, M.; Hult, K.; Berglund, P. *J. Am. Chem. Soc*. **2005**, *127*, 17988–17989; (b) Arora, B.; Pandey, P. S.; Gupta, M. N. *Tetrahedron Lett*. **2014**, *55*, 3920–3922; (c) Le, Z. -G.; Guo, L. -T.; Jiang, G. -F.; Yang, X. -B.; Liu, H. -Q. *Green Chem. Lett. Rev*. **2013**, *6*, 277–281.
21. Chow, C. K. Ed. *Fatty Acids in Foods and their Health Implications*; 2008, Third Edition, CRC Press, Taylor & Francis, USA.
22. Downing D. T. *Rev. Pure Appl. Chem*. **1961**, *11*, 196–211.

23. (a) Patel, D. K.; Archana, G.; Kumar, G. N. *Curr. Microbiol*. **2008**, *56*, 168–174; (b) Schulz, H.; Vetterlein, D. *J. Plant Nutr. Soil Sci*. **2007**, *170*, 640–644; (c) Polgar, N. *Top Lipid Chem*. **1971**, *2*, 207–246.

24. (a) Turner, W. B.; Aldridge, D. C. in *Fungal Metabolites* II; 1983, Academic Press, London,. (b) Gardner, H. W. *J. Lipid Res*. **1970**, *11*, 311–321. (c) Kawagishi, H.; Ando, M.; Micno, T.; Yokota, H.; Konishi, S. *Agric. Biol. Chem*. **1990**, *54*, 1329–1331. (d) Kuga, H.; Ejima, A.; Mitui, I.; Sato, K.; Ishihara, N. Fukunda, K.; Saito, F.; Uenaki, K. *Biosci. Biotech. Biochem*. **1993**, *57*, 1020–1021. (e) Simon, B.; Anke, T.; Sterner, O. *Phytochem*. **1994**, *36*, 815–816.

25. (a) Kawagishi, H.; Ando, M.; Micno, T.; Yokota, H.; Konishi, S. *Agric. Biol. Chem*. **1990**, *54*, 1329–1331. (b) Kuga, H.; Ejima, A.; Mitui, I.; Sato, K.; Ishihara, N. Fukunda, K.; Saito, F.; Uenaki, K. *Biosci. Biotech. Biochem*. **1993**, *57*, 1020-1021. (c) Gardner, H. W. *J. Lipid Res*. **1970**, *11*, 311–321.

26. Arnone, A.; Nasini, G.; De Pava, O. V. *Phytochem*. **1998**, *48*, 507–510; (b) Simon, B.; Anke, T.; Sterner, O. *Phytochem*. **1994**, *36*, 815–816; (c) Nagai, T.; Kiyohara, H.; Munakata, K.; Shirahata, T.; Sunazuka, T.; Harigaya, Y.; Yamada, H. *Int. Immunopharm.* **2002**, *2*, 1183–1193.

27. (a) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed*. **2000**, *39*, 44–122; (b) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed*. **1998**, *37*, 388–401; (c) Noyori, R. In: *Asymmetric Catalysis in Organic Synthesis*; 1994, Wiley: New York.

28. (a) Maity, B.; Chattopadhyay, S. *Curr. Bioact. Comp*. **2008**, *4*, 225-244; (b) Guha, P.; Dey, A.; Sarkar, B.; Dhyani, M.V.; Chattopadhyay, S.; Bandyopadhyay, S. K. *J. Exp. Pharmacol. Ther*. **2009**, *328*, 1–10; (c) Guha, P.; Dey, A.; Chatterjee, A.; Chattopadhyay, S.; Bandyopadhyay, S. K. *Brit. J. Pharmacol*. **2010**, *159*, 726–734;

(d) Patro, B. S.; Maity, B.; Chattopadhyay, S. *Antioxidant Redox. Signal*. **2010**, *12*, 945-960; (e) Yadav, S. K.; Adhikary, B.; Chand, S.; Maity, B.; Bandyopadhyay, S. K.; Chattopadhyay S. *Free Radic. Biol. Med*. **2012**, *52*, 1175–1187; (f) Maity, B.; Yadav, S. K.; Patro, B. S.; Bandyopadhyay, S. K.; Chattopadhyay S. *Free Radic. Biol. Med*. **2012**, *52*, 1680–1691.

29. (a) Sharma, A.; Gamre, S.; Roy, S.; Goswami, D.; Chattopadhyay, A.; Chattopadhyay, S. *Tetrahedron Lett*. **2008**, *49*, 3902–3905; (b) Sharma, A.; Das, P.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2008**, *19*, 2167–2170; (c) Roy, S.; Sharma, A.; Mula, S.; Chattopadhyay, S. *Chem. A Eur. J*. **2009**, *15*, 1713–1722; (d) Sankaranarayanan, S.; Sharma, A.; Kulkarni, B. A.; Chattopadhyay, S. *J. Org. Chem.* **1995**, *60*, 4251–4254; (e) Sharma, A.; Sankaranarayanan, S.; Chattopadhyay, S. *J. Org. Chem.* **1996**, *61*, 1814–1816; (f) Sharma, A.; Chattopadhyay, S. *J. Org. Chem*. **1999**, *64*, 8059–8062; (g) Sharma, A.; Chattopadhyay, S. *J. Mol. Cat. B. Enzymatic* **2000**, *10*, 531–534; (h) Sharma, A.; Mahato, S.; Chattopadhyay, S. *Tetrahedron Lett*. **2009**, *50*, 4986–4988; (i) Sharma, A.; Gamre, S.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1164–1167; (j) Ghadigaonkar, S.; Koli, M. R.; Gamre, S. S.; Choudhary, M. K.; Chattopadhyay, S.; Sharma, A. *Tetrahedron: Asymmetry* **2012**, *23*, 1093–1099.

30. (a) Brack Egg, A. In: *Diccionario Enciclopedico de Plantas utiles del Peru´*; 1999; p 187, Centro de Estudios Regionales Andinos Bartolome de las Casas: Cuzco, Peru. (b) Miyake, M.; Sasaki, K.; Ide, K.; Matsukura, Y.; Shijima, K.; Fujiwara, D. *J. Immunol.* **2006**, *176*, 5797–5804. (c) Lovera, A.; Bonilla, C.; Hidalgo, J. *Rev. Peru´ Med. Exp. Salud Publica* **2006**, *23*, 177–181.

31. Benavides, A.; Napolitano, A.; Bassarello, C.; Carbone, V.; Gazzerro, P.; Malfitano, AM.; Saggese, P.; Bifulco, M.; Piacente, S.; Pizza, C. *J. Nat. Prod.* **2009**, *72*, 813–817.

32. Vyavahare, V. P.; Chakraborty, C.; Maity, B.; Chattopadhyay, S.; Puranik, V. G.; Dhavale, D. D. *J. Med. Chem*. **2007**, *50*, 5519-5523.

33. (a) Chatterjee, S.; Kanojia, S. V.; Chattopadhyay, S.; Sharma, A. *Tetrahedron: Asymmetry* **2011**, *21*, 367–372; (b) Saikia, B.; Joymati Devi, T.; Barua, N. C. *Tetrahedron* **2013**, *69*, 2157–2166; (c) Wadavrao, S. B.; Ghogare, R. S.; Venkat Narsaiah, A. *Tetrahedron Lett*. **2012**, *53*, 3955–3958.

34. (a) Chattopadhyay, A. *J. Org. Chem*. **1996**, *61*, 6104–6107; (b) Goswami, D.; Chattopadhyay, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1957–1961.

35. Sharma, A.; Gamre, S.; Chattopadhyay, S. *Tetrahedron Lett*. **2007**, *48*, 633–634.

36. Chattopadhyay, A.; Mamdapur, V. R. *J. Org. Chem*. **1995**, *60*, 585–587.

37. For reviews on olefin metathesis, see: (a) Armstrong, S. K. *J. Chem. Soc. Perkin Trans. 1*, **1998**, 371–388; (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141–8153; (c) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58–71; (d) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18–29; For some leading references, see: (f) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.*, **2003**, *125*, 11360–11370; (g) Galan, B. R.; Kalbarczyk, K. P.; Szczepankiewicz, S.; Keister, J. B.; Diver, S. T. *Org. Lett.* **2007**, *9*, 1203–1206; (h) Lipshutz, B. H.; Aquinaldo, G. T.; Ghorai, S.; Voigtritter, K. *Org. Lett.* **2008**, *10*, 1325–1328; (i) Ferrié, L.; Bouzbouz, S.; Cossy, J. *Org. Lett.* **2009**, *11*, 5446–5448; (j) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org.*

Chem., **2011**, *76*, 4697–4702; (k) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471(7339)*, 461–466.

38. "The Nobel Prize in Chemistry 2005" (Press release). Nobelprize.org. 5 October 2005.
39. (a) Chatterjee, S.; Ghadigaonkar, S.; Sur, P.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem*. **2014**, *79*, 8067–8076; (b) Chatterjee, S.; Sharma, A.; Chattopadhyay, S. *RSC Adv*. **2014**, *4*, 42697–42705.
40. Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; Van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc.* **2004**, *126*, 187–193.
41. (a) Burgoyne, D. L.; Miao, S.; Pathirana, C.; Andersen, R. J.; Ayer, W. A.; Singer, P. P.; Kokke, W. C. M. C.; Ross, D. M. *Can. J. Chem.* **1991**, *69*, 20–27. (b) Ohba, M.; Nishimura, Y.; Kato, M.; Fujii, T. *Tetrahedron* **1999**, *55*, 4999–5016. (c) Nakao, Y.; Maki, T.; Matsunaga, S.; Van, Soest, R. W. M.; Fusetani, N. *Tetrahedron* **2000**, *56*, 8977–8987.
42. Bowen, E. G.; Wardrop, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 6062–6063.
43. (a) Nakao, Y.; Maki, T.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Nat. Prod.* **2004**, *67*, 1346–1350. (b) Nakao, Y.; Maki, T.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *Tetrahedron* **2000**, *56*, 8977–8987.
44. (a) Braun, C.; Brayer, G. D.; Withers, S. G. *J. Biol. Chem.* **1995**, *270*, 26778–26781. (b) Mehta, A.; Zitzmann, N.; Rudd, P. M.; Block, T. M.; Dwek, R. A. *FEBS Lett.* **1998**, *430*, 17–22. (c) Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N. *Nat. Rev. Drug Discovery* **2002**, *1*, 65–75.
45. For a review of glycosidase inhibitors, see: Jung, M.; Park, M.; Lee, H. C.; Kang, Y.-H.; Kang, E. S.; Kim, S. K. *Curr. Med. Chem.* **2006**, *13*, 1203–1218.

46. (a) Kuntiyong, P.; Akkarasamiyo, S.; Eksinitkun, G. *Chem. Lett.* **2006**, *35*, 1008–1009; (b) Gurjar, M. K.; Pramanik, C.; Bhattasali, D.; Ramana, C. V.; Mohapatra, D. K. *J. Org. Chem.* **2007**, 72, 6591–6594; (c) Liu, G.; Romo, D. *Org. Lett*. **2009**, *11*, 1143–1146.

47. Che, C.; Zhang, Z.-N.; Huang, G.-L.; Wang, X.-X. *Chin. J. Org. Chem*. **2004**, *24*, 1281–1283.

48. Dhotare, B.; Salaskar, A.; Chattopadhyay, A. *Synthesis* **2003**, 2571–2575.

49. Biswas, S.; Chattopadhyay, S.; Sharma, A. *Tetrahedron: Asymmetry* **2010**, *21*, 27–32.

50. Gravier-Pelletier, C.; Le Merrer, Y. ; Depezay, J. –C. *Tetrahedron* **1995**, *51*, 1663–1674.

51. For reviews on biology and synthesis: (a) Napolitano, J. G.; Daranas, A. H.; Norte, M.; Fernandez, J. J. *Anticancer Agents Med. Chem*. **2009**, *9*, 122–137; (b) Hale, K. J.; Manaviazar, S. *Chem. Asian J*. **2010**, *5*, 704–754.

52. Michel, K. H.; Demarco, P. V.; Nagarajan, R. *J. Antibiot*. **1977**, *30*, 571–575.

53. (a) Hase, T. A.; Nylund, E. -L. *Tetrahedron Lett.* **1979**, *20*, 2633–2636; (b) Asaoka, M.; Yanagida, N.; Takai, H. *Tetrahedron Lett*. **1980**, *21*, 4611–4614; (c) Asaoka, M.; Mukuta, T.; Takai, H. *Chem. Lett.* **1982**, 215–218; (d) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568–575; (e) Fujisawa, T.; Okada, N.; Takeuchi, M.; Sato, T. *Chem. Lett*. **1983**, 1271–1272; (f) Bestmann, H. J.; Schobert, R. *Angew. Chem. Int. Ed. Engl.* **1986**, *24*, 791–792; (g) Bienz, S.; Hew, M. *Helv. Chim. Acta* **1987**, *70*, 1333–1340; (h) Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *J. Chem. Soc. Chem. Commun.* **1991**, 940–942.

54. (a) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3248–3253; (b) Quinkert, G.; Kueber, F.; Knauf, W.; Wacker, M.; Koch, U.; Becker, H.; Nestler, H. P.; Dürner, G.; Zimmermann, G.; Bats, J. W.; Egert, E.

Helv. Chim. Acta **1991**, *74*, 1853–1923; (c) Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, *65*, 612–615; (d) Lee, W.; Shin, H. J.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 29–31; (e) Gebauer, J.; Blechert, S. *J. Org. Chem.* **2006**, *71*, 2021–2025; (f) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 7789–7796; (g) Nagarajan, M. *Tetrahedron Lett.* **1999**, *40*, 1207–1210.

55. (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem. Int. Ed. Engl*. **1977**, *16*, 585–607; (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683–710; (c) Back, T. G. *Tetrahedron* **1977**, *33*, 3041–3059; (d) Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298; (e) Simpson, T. J. *Nat. Prod. Rep*. **1987**, *4*, 339–376.
56. For some reviews: (a) Michels, P. C.; Khmelnitsky, Y. L. J. S. Dordick and D. S. Clark, *Trends Biotechnol*., 1998, **16**, 210–215; (b) Garcia-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev*. **2005**, *105*, 313–354; (c) van Rantwijk, F.; Sheldon, R. *Chem. Rev*. **2007**, *107*, 2757–2785; (d) Hudlicky, T.; Reed, J. W. *Chem. Soc. Rev*. **2009**, *38*, 3117–3132; (e) Clouthierzab, C. M.; Pelletier, J. N. *Chem. Soc. Rev*. **2012**, *41*, 1585–1605.
57. (a) Salvi, N. A.; Chattopadhyay, S. *Tetrahedron* **2001**, *57*, 2833–2839; (b) Salvi, N. A.; Chattopadhyay, S. *Bioorg. Med. Chem*. **2006**, *14*, 4918–4922; (c) Salvi, N. A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2008**, *19*, 1992–1997; (d) Zhou, B. N.; Gopalan, A. S.; Van Middlesworth, F.; Shieh, W. Ru; Sih, C. J. *J. Am. Chem. Soc*. **1983**, *105*, 5925-5926; (e) Manzocchi, A.; Fiecchi, A.; Santaniello, E. *J. Org. Chem*. **1988**, *53*, 4405–4407 and references cited therein; (f) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A. *J. Org. Chem*. **1992**, *57*, 3631–3637.
58. (a) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal*. **2001**, *343*, 5–26; (b) Lee, J. H.; Han, K.; Kim, M. -J.; Park, J. *Eur. J. Org. Chem*. **2010**, 999–1015; (c) Mitsunobu, O. *Synthesis*, **1981**, 1–28; (d) Dembinski, R. *Eur. J. Org. Chem*. **2004**,

2763–2772; (e) Swamy, K. C.; Kumar, N. N.; Balaraman, E.; Kumar, K. V. *Chem. Rev*. **2009**, *109*, 2551–2651.

59. (a) Reetz, M. T. *Curr. Opin. Chem. Biol*. **2002**, *6*, 145–150; (b) Faber, K.; *Biotransformations in Organic Chemistry*; Springer: Heidelberg, Germany, 5th Ed. 2004; (c) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic Synthesis*; Wiley-VCH: Weinheim. Germany, 2nd Ed. 2005; (d) Gotor-Fernández, V.; Busto, E.; Gotor, V. *Adv. Synth. Catal*. **2006**, 797–812.
60. Sharma, A.; Pawar, A. S.; Chattopadhyay, S. *Synth. Commun*. **1996**, *26*, 19–25.
61. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991,** *56,* 2656–2665.
62. (a) Martin, B. D.; Ampofo, S. A.; Linhardt, R. J.; Dordick, J. S. *Macromol*. **1992**, *25*, 7081–7085; (b) Haughton, L.; Williams, J. M. J.; Zimmermann, J. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1697–1701; (c) Athawale, V.; Manjrekar, N. *J. Mol. Catal. B: Enz*. **2000**, *10*, 551–554; (d) Petersson, A. E. V.; Adlercreutz, P.; Mattiasson, B. *Biotechnol. Bioeng*. **2007**, *97*, 235–241; (e) Nordblad, M.; Adlercreutz, P. *Biotechnol. Bioeng*. **2008**, *99*, 1518–1524.
63. Sundby, E.; Perk, L.; Anthonsen, T.; Aasen, A. J.; Hansen, T. V. *Tetrahedron* **2004**, *60*, 521–524.
64. Arai, K.; Rawlings, B. J.; Yoshizawa, Y.; Vederas, J. C. *J. Am. Chem. Soc.* **1989**, *111,* 3391–3399.
65. (a) Teo, Y. -C.; Tan, K. -T.; Loh, T. -P. *Chem. Commun*. **2005**, 1318–1320; (b) Goswami, D.; Sur, P.; Chattopadhyay, A.; Sharma, A.; Chattopadhyay, S. *Synthesis* **2011**, 1626–1632.
66. Bestmann, H. J.; Schobert, R. *Angew Chem. Int. Ed. Engl*. **1985**, *24*, 791–792.

67. (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58; (b) Galloway, W. R. J. D.; Isidro-Llobet, A.; Spring, D. R. *Nature Commun.* **2010**, *1*, 80. doi:10.1038/ncomms1081.

68. (a) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613–618; (b) Wetzel, S.; Bon, R. S.; Kumar, K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 10800–10826.

69. (a) Kis, Z.; Furger, P.; Sigg, H. P. *Experientia* **1969**, *25*, 123–124; (b) Nozoe, S.; Hirai, K.; Tsuda, K.; Ishibashi, K.; Shirasak, M. *Tetrahedron Lett.* **1965**, 4675–4677; (c) Grove, J. F. *J. Chem. Soc*. **1971**, *12*, 2261–2263; (d) Kind, R.; Zeeck, A.; Grabley, S.; Thiericke, R.; Zerlin, M. *J. Nat. Prod*. **1996**, *59*, 539–540.

70. (a) Kastanias, M. A.; Chrysayi-Tokousbalides, M. *Pest Manag. Sci*. **2000**, *56*, 227–232; (b) Karsten, K.; Umar, F.; Ulrich, F.; Barbara, S.; Siegfried, D.; Gennaro, P.; Piero, S.; Sándor, A.; Tibor, K. *Eur. J. Org. Chem*. **2007**, 3206–3211; (c) Zhang, W.; Krohn, K.; Egold, H.; Draeger, S.; Schulz, B. *Eur. J. Org. Chem*. **2008**, 4320–4328; (d) Kind, R.; Zeeck, A.; Grabley, S.; Thiericke, R.; Zerlin, M. *J. Nat. Prod*. **1996**, *59*, 539–540. (e) C. Christner, G. Kullertz, G. Fischer, M. Zerlin, S. Grabley, R. Thiericke, A. Taddei, A. Zeeck, *J. Antibiot*. **1998**, *51*, 368–371.

71. (a) Dommerholdt, E. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1499–1502; (b) Machinaga, N.; Kibayashi, C. *Tetrahedron Lett.* **1993**, *34*, 841–844; (c) Amigoni, S.; Le Floc'h, Y. *Tetrahedron:Asymmetry* **1997**, *8*, 2827–2831; (d) Yadav, J. S.; Reddy, U. V. S.; Reddy, B. V. S. *Tetrahedron Lett.* **2009**, *50*, 5984–5986; (e) Oh, H.-S.; Kang, H.-Y. *Bull. Korean Chem. Soc*. **2011**, *32*, 2869–2870; (f) Yadav, J. S.; Reddy, G.; Rao, T. S.; Reddy, B. V. S.; Ghamdi, A. A. K. A. *Synthesis* **2012**, 783–787; (g) Nuguri, S; Vuppula, N. K.; Eppakayala, L.; Prasad K. R. *J. Pharm. Res*. **2013**, *6/7*, 559–564.

72. Trost, B. M.; Quintard, A. *Angew. Chem. Int. Ed*. **2012**, *51*, 6704 –6708.

73. (a) Mori, K. *Tetrahedron* **1981**, *37*, 1341–1342; (b) Nakamura, K.; Kinoshita, M.; Ohno, A. *Tetrahedron* **1995**, *51*, 8799–8808; (c) Kinoshita, M.; Ohno, A. *Tetrahedron* **1996**, *52*, 5397–5406; (d) Steinreiber, A.; Stadler, A.; Mayer, S. F.; Faber, K.; Kappe, C. O. *Tetrahedron Lett*. **2001**, *42*, 6283–6286; (e) Steinreiber, A.; Edegger, K.; Mayer, S. F.; Faber, K. *Tetrahedron: Asymmetry* **2001**, *12*, 2067–2071; (f) Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Fontana, S. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2367–2373; (g) Belan, A.; Bolte, J.; Fauve, A.; Gourcy, J. G.; Veschambre, H. *J. Org*. *Chem*. **1987**, *52*, 256–260; (h) Fantin, G.; Fogagnolo, M.; Giovannini, P. P.; Medici, A.; Pedrini, P. *Tetrahedron*: *Asymmetry* **1995**, *6*, 3047–3053; (i) Clair, N. S.; Wang, Y.-F.; Margolin, A. L. *Angew*. *Chem*. **2000**, *112*, 388–391; (j) Chen, S. L.; Hu, Q. Y.; Loh, T. P. *Org. Lett*. **2004**, *6*, 3365–3367.

74. (a) Patil, P. N.; Chattopadhyay, A.; Udupa, S. R.; Banerji, A. *Biotech Lett*. **1993**, *15*, 367–372; (b) Ferreira, H. V.; Rocha, L. C.; Severino, R. P.; Viana, R. B.; da Silva, A. B. F.; Porto, A. L. M. *J. Iran. Chem. Soc.* **2010**, *7*, 883–889; (c) Burgess, K.; Henderson, I. *Tetrahedron: Asymmetry* **1990**, *1*, 57–60.

75. Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622–2628.

76. Cabrera, Z.; Fernandez-Lorente, G.; Fernandez-Lafuente, R.; Palomo, J. M.; Guisan, J. M. *J. Mol. Cat. B: Enz.* **2009**, *57*, 171–176.

77. Enders, D.; Nguyen, D. *Synthesis* **2000**, 2092–2098.

78. Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2003**, *44*, 2873–2875.