ASYMMETRIC SYNTHESIS OF SOME BIOLOGICALLY RELEVANT OXYGENATED HETEROCYCLIC COMPOUNDS

By

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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.

Papiya Ghosh

List of Publications arising from the thesis

Journals

1. Ghosh, P.; Chattopadhyay, A. A practical procedure of propargylation of aldehydes. *Tetrahedron Lett*. **2012**, *53*, 5202–5205. (published)
2. Ghosh, P.; Gamre, S. S.; Chatterjee, S.; Chattopadhyay, S.; Sharma, A. An Enantioselective Synthesis of Clonostachydiol. *Asian J. Org. Chem*. (under revision)

Conferences

1. P. Dey, S. Gamre, A. Sharma, S. Chattopadhyay. Asymmetric synthesis of Clonostachydiol –a DOS mediated approach, National Conference on Chirality-2015
2. P. Dey, B. B. Dhotare, K. S. Ajish Kumar, A. Sharma. A Practical Asymmetric Synthesis of the Tumor –imaging Agent, 18F-FLT, 6th International Symposium on Current Trends in Drug Discovery and Research (CTDDR)-2016

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Dedicated to……

My Parents……

And to some wonderful persons whose love and support made this journey successful

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BOD, BARC

CONTENTS

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SYNOPSIS OF Ph. D. THESIS

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Preamble

Nature abounds in chiral organic molecules, and the stereochemistry of many of them governs their biological activities. This has provided significant impetus to organic chemists to develop efficient and scalable routes to asymmetric synthesis that produces chiral compounds with predictable stereochemistry. Thus, design and development of efficient asymmetric syntheses continue to challenge synthetic chemists with the growing demand of enantiomerically pure compounds.[1] In view of these, the present work was focused on the development of some chemical and biocatalytic enantioselective routes, and their applications for the syntheses of a few bioactive naturally occurring oxygenated heterocyclic compounds. These are presented in four chapters of the thesis as detailed below. The bibliography of all the chapters is presented collectively in Chapter IV.

CHAPTER I: INTRODUCTION TO ASYMMETRIC TRANSFORMATIONS

This chapter deals with a broad review on asymmetric synthesis and covers aspects such as (i) genesis and importance of chirality; (ii) different methods of enantiomeric syntheses; (iii) thermodynamics and kinetics of preparing stereomers; and (iv) methods of determining enantiomeric purities. In addition a brief summary of the natural oxygen-heterocyclic compounds with special emphasis on the chosen targets is presented. One of the major foci of the investigations was the design of chemoenzymatic syntheses of some complex natural products. Hence, a brief account on biocatalytic reactions has also been provided.[2] Finally a brief outline of the work carried out during the investigation is provided and rationalized.

Chapter II: DEVELOPMENT OF ASYMMETRIC BARBIER TYPE ALLYLATION/PROPARGYLATION REACTIONS

This chapter deals with formulation of asymmetric allylation/propargylation protocols and use of some of the derived products for the syntheses of two target molecules. These are sequentially presented after a brief preamble as follows.

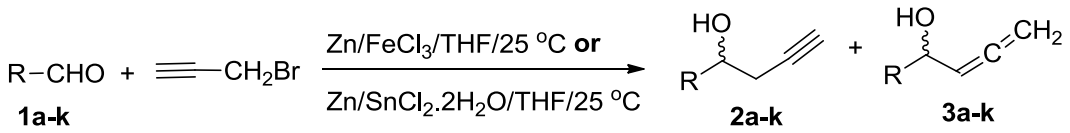
II.1: Preamble

Chiral carbinols are one of the most versatile synthons for synthesis of various target molecules with structural diversities.[3] The Barbier-type allylation/propargylation of aldehydes/ketones offers easy access to the carbinols and is extensively pursued, since the terminal alkene/alkyne functions of the resultant products are amenable to further functionalization for synthesizing various target molecules.[4] To this end, substrate-controlled approaches using (*R*)-cyclohexylideneglyceraldehyde[5] as the chiral template were explored for asymmetric version of these reactions. The resultant alcohol stereomers with two adjacent secondary carbinol stereogenic centres are proven intermediates in asymmetric syntheses of various target natural products. Since the diastereoselectivity of the asymmetric Barbier-type reaction is governed by the nature of the metal and reaction medium,[6] this aspect was investigated by carrying out the reaction of the above aldehyde with allyl and propargyl bromides using different combinations of metals and solvents. Finally, applications of the resultant homoallylic alcohol stereomers in the synthesis of two bioactive compounds were demonstrated. These are sequentially described in this chapter.

II.2: A Bimetallic Redox Strategy for Propargylation

The bimetallic redox strategy involves spontaneous reduction of a metal salt ($\mathbf{M_1X}$) in aqueous environment with another metal ($\mathbf{M_2}$) that have higher oxidation

potential, to produce the activated metal ($\mathbf{M_1}$). This, in turn, would react with propargyl bromide to give the active propargyl-metal species for its subsequent reaction with the glyceraldehyde derivative **4a**. Based on its higher oxidation potential compared to Fe, Co, Cu and Sn, Zn-metal was chosen as the reducing metal in separate combinations with the commercially available salts *viz*. $Zn/CuCl_2.2H_2O$, $Zn/CoCl_2.6H_2O$, $Zn/FeCl_3$ and $Zn/SnCl_2.2H_2O$. One of the major challenges of propargylation is to control the formation of the desired homopropargylic alcohols over the corresponding allenic alcohols. Hence, the reaction was initially standardized using benzaldehyde (**1a**) as the model substrate. Amongst the Zn-metal salts combinations, $Zn/FeCl_3$ (*reagent 1*) and $Zn/SnCl_2.2H_2O$ (*reagent 2*) were effective to furnis the desired alcohol **2a** in good yield and insignificant formation of the allenic alcohol **3a**. These reagents were subsequently used for the propargylation of several other aromatic **1b-f** and aliphatic **1g-k** aldehydes to obtain the corresponding homopropargylic alcohols **2b-f** and **2g-k** respectively, with varying amounts of the allenic alcohols **3b-k** (**Scheme II.2.1.**). The summarized results (**Table II.2.1.**) clearly established the efficacy of the protocol. Both the reagents showed similar results, although in certain cases the reactions with *reagent 2* were marginally slow. Amongst the substrates, **1b**, **1c**, and **1k** furnished 11-17% of the corresponding allenic alcohols with *reagent 2*. On the other hand, the aldehydes **1d** and **1g** furnished appreciable amounts of the undersired alcohols **3d** and **3g**, irrespective of the reagent used. Overall, an operationally simple and potentially scalable propargylation protocol with high chemo-selectivity was developed using inexpensive materials.[7]



1a-k **2a-k** **3a-k**

R = **a:** Ph; **b:** 3-Br-Ph; **c:** 3-MeO-Ph; **d:** 4-Br-Ph; **e:** 4-Et-Ph; **f:** 4-EtO-Ph; **g:** *n*-C_4H_9; **h:** *n*-C_6H_{13}; **i:** *n*-C_8H_{17}; **j:** *n*-C_9H_{19}; **k:** *n*-$C_{11}H_{23}$.

Scheme II.2.1.

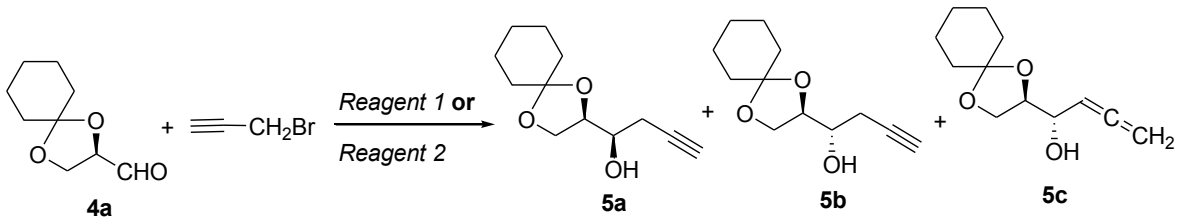
Table II.2.1. Reaction course of propargylation[a]

Entry	R (substrate)	Reagent	Time (h)	Yield (%)	**2:3**[b]
1	Ph (**1a**)	1	3	75	95:5
2	Ph (**1a**)	2	5	81	100:0
3	3-Br-Ph (**1b**)	1	14	84	100:0
4	3-Br-Ph (**1b**)	2	14	81	88:12
5	3-MeO-Ph (**1c**)	1	14	81	100:0
6	3-MeO-Ph (**1c**)	2	14	87	89:11
7	4-Br-Ph (**1d**)	1	3	81	85:15
8	4-Br-Ph (**1d**)	2	5	85	54:46
9	4-Et-Ph (**1e**)	1	15	89	94:6
10	4-Et-Ph (**1e**)	2	16	86	100:0
11	4-EtO-Ph (**1f**)	1	16	80	93:7
12	4-EtO-Ph (**1f**)	2	14	81	100:0
13	*n*-C_4H_9 (**1g**)	1	1	79	86:14
14	*n*-C_4H_9 (**1g**)	2	3	73	88:12
15	*n*-C_6H_{13} (**1h**)	1	4	77	94:6
16	*n*-C_6H_{13} (**1h**)	2	7	81	68:32
17	*n*-C_8H_{17} (**1i**)	1	4	95	94:6
18	*n*-C_8H_{17} (**1i**)	2	8	83	93:7
19	*n*-C_9H_{19} (**1j**)	1	16	98	95:5

20	*n*-C_9H_{19} (**1j**)	2	17	97	91:9
21	*n*-$C_{11}H_{23}$ (**1k**)	1	18	93	97:3
22	*n*-$C_{11}H_{23}$ (**1k**)	2	18	92	83:17

[a]All reactions were carried out in moist THF on a 2 mmol scale at 25 [o]C. [b]Based on the ^{1}H NMR spectra of the products. *Reagent 1*: Zn/$FeCl_3$; *Reagent 2*: Zn/$SnCl_2.2H_2O$.

Next, the suitability of the protocol in asymmetric transformation was explored using the chiral aldehyde **4a** (**Scheme II.2.2.**), and the results are shown in **Table II.2.2**. For this, besides Zn-metal, Al foils were also used to reduce $SnCl_2.2H_2O$ (entry 2). The reaction was much faster with this combination. All the reactions produced the homopropargylic alcohol as a mixture of the *syn* and *anti*-epimers, **5a** and **5b** in appreciable yields (75-80%) and moderate diastereoselectivities without producing the allenic alcohol **5c**.



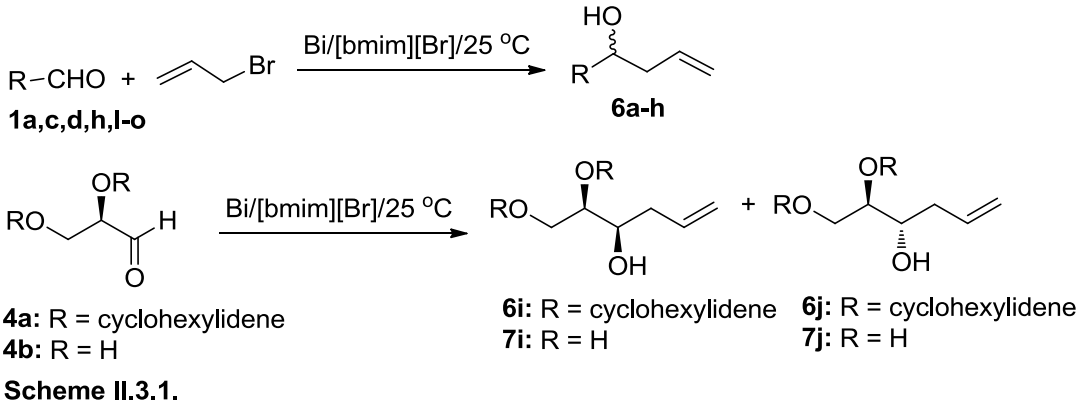
Scheme II.2.2.

Table II.2.2. Reaction course of propargylation of **4a**[a]

Entry	M_1X/M_2	Time (h)	Yield (%)	**5a:5b**[b]
1	$SnCl_2.2H_2O$/Zn	3	78	25:75
2	$SnCl_2.2H_2O$/Al	0.5	80	24:76
3	$FeCl_3$/Zn	2	75	12:88

II.3: Bismuth-mediated allylation protocol

Earliler, our group has shown that due to its stronger oxidizing power and moderate acidity, the hydrophilic RTIL, [bmim][Br] acts both as a solvent and a metal activator in the Ga-mediated allylation/crotylation of various aldehydes including **4a** even at room temperature.[8] The crotylation of **4a** also proceeded with an excellent diastereoselectivity.[8a] Hence, the primary motivation of the present work was to explore if the inexpensive, safe and environmentally benign Bi-metal can carry out allylation of aldehydes, and if this combination can offer any diastereoselectivity with **4a**.



Scheme II.3.1.

Table II.3.1. Reaction course of Bi-mediated allylation in [bmim][Br][a]

Entry	Substrate	R	Allyl bromide (eq.)	Bi (eq.)	Time (h)	Product	Yield (%)
1	**1a**	Ph	1.5	1.0	3	**6a**	75
2	**1c**	3-MeO-Ph	1.7	1.3	6	**6b**	74
3	**1d**	4-Br-Ph	1.7	1.3	6	**6c**	78
4	**1l**	4-NO_2-Ph	1.7	1.3	3	**6d**	74
5	**1m**	4-MeO-Ph	1.7	1.3	3	**6e**	74

6	**1n**	PhCH=CH	1.5	1.0	3	**6f**	71
7	**1h**	n-C_5H_{11}	1.5	1.4	3	**6g**	71
8	**1o**	n-C_6H_{13}	1.5	1.4	6	**6h**	66

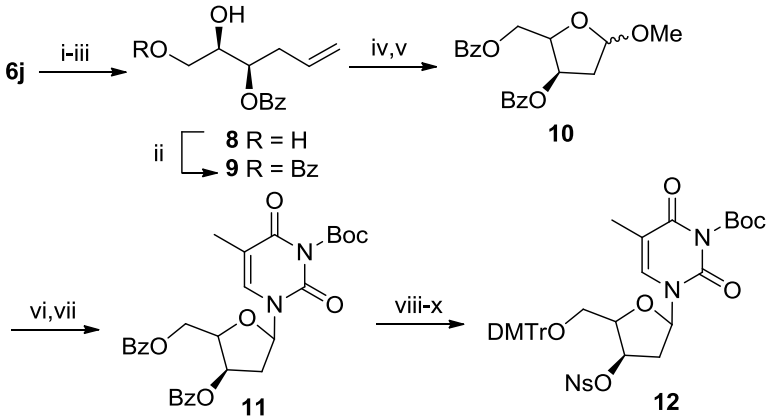
[a]All reactions were carried out on a 2 mmol scale at 25 ^oC in [bmim][Br] (3 mL/mmol).

To probe the feasibility of the first objective, the Bi-mediated allylation of various aromatic and aliphatic aldehydes **1a,c,d,h,l-o** was carried out in [bmim][Br] (**Scheme II.3.1.**), and the results are summarized in **Table II.3.1**. The protocol was equally effective for both aromatic and aliphatic aldehydes. With the aromatic aldehydes, the products **6a-f** were obtained in good (71−78%, entries 1-6) yields, irrespective of the presence of any electron-withdrawing or -donating group in the aromatic ring. Likewise, the aliphatic aldehydes also furnished the corresponding allylated products **6g,h** in good yields (entries 7,8). The reaction also proceeded with complete chemoselectivity with the conjugated aldehyde **1n**, furnishing the 1,2-addition product **6f** exclusively. Regarding the asymmetric allylation, the reaction with **4a** proceeded to furnish the alcohol epimers **6i/6j** in 32:68 ratio in 75% yield. However, allylation with the unprotected aldehyde **4b** proceeded with better diasteroselectivity to furnish **7i/7j** in 2:8 ratio, albeit in 45% yield due to high polarity of the product. With both **4a** and **4b**, the reaction was accomplished using allyl bromide (1.5 eq.) and Bi (1.0 eq.) with respect to the substrates.

II.4: Asymmetric synthesis of a ^{18}FLT precursor

Cellular proliferation and DNA synthesis are related to thymidine kinase I (TK1) activity.[9a] As fluorothymidine, the nucleoside thymidine analog is a substrate for TK1, 3′-deoxy-3′-([^{18}F]Fluoro)-fluorothymidine, (^{18}F-FLT, **12**) has been proposed as an imaging biomarker for tumor detection.[9b] In the present work, compound **12**, an

excellent precursor of ^{18}F-FLT was synthesized (**Scheme II.4.1.**) starting from **6j**, the allylation product of **4a**. The alcohol on Mitsunobu inversion,[10] benzoylation and deacetalization with aqueous trifluoroacetic acid (TFA) furnished the diol **8**. After benzoylating its primary hydroxyl group, the product **9** was subjected to reductive ozonolysis followed by glycosidation to obtain **10**. Introduction of the thymine group at the anomeric site and subsequent Boc-protection gave **11**. Its debenzoylation and column chromatography gave the diol with the required β-thymine moiety. Sequential DMTr and Ns protection of its primary and secondary hydroxyl groups respectively afforded the target compound **12**.



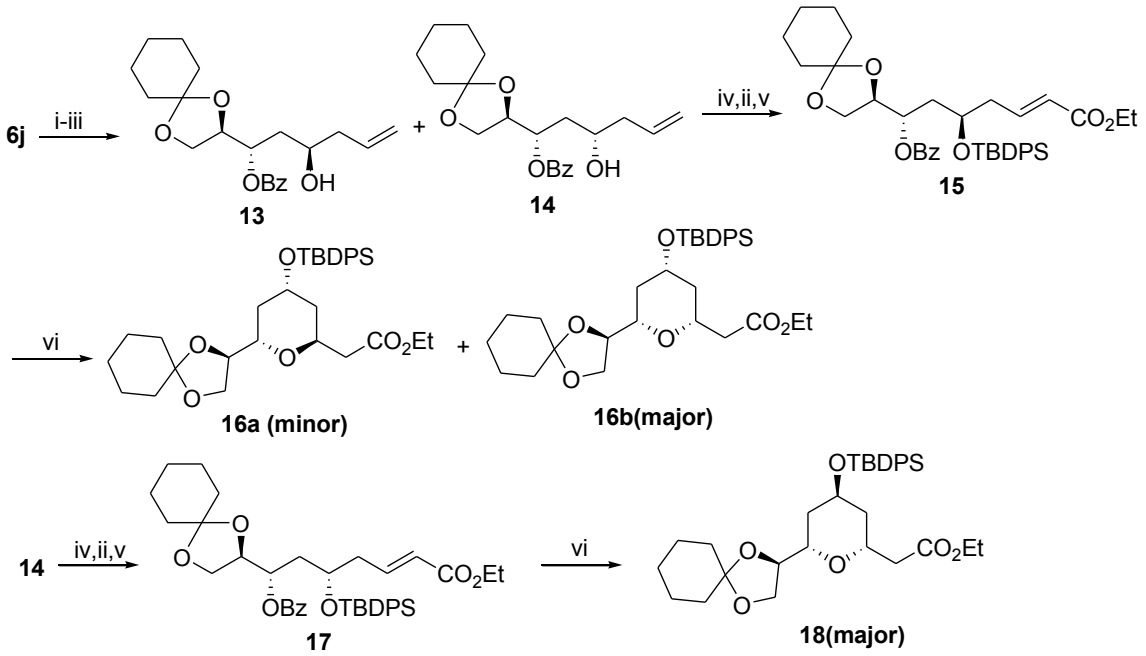
i) *p*-Nitrobenzoic acid/Ph_3P/DEAD/THF/25 ^oC/20 h (91%); KOH/MeOH/25 ^oC/ 6 h (88%), ii) BzCN/Et_3N/ CH_2Cl_2/3 h (95% for **8**, 77% for **9**), iii) Aqueous TFA/CH_2Cl_2/25 ^oC/3 h (86%), iv) O_3/Ph_3P/CH_2Cl_2/-78-25 ^oC/18 h (82%), v) MeOH/*p*-TsOH/25 ^oC/5 h (85%), vi) Thymine/BSA/TMS-triflate/MeCN/25 ^oC/7 d (67%), vii) Boc_2O/DMAP/25 ^oC/2 h (72%), viii) K_2CO_3/MeOH/25 ^oC/5 h (81%), ix) DMTrCl/pyridine/25 ^oC/12 h (81%), x) NsCl/pyridine/25 ^oC/22 h (72%).

Scheme II.4.1.

II.5: Asymmetric synthesis of tetrahydropyrans

Oxygen-containing heterocycles are widely sought for their significant biological properties.[11] Pyran and benzopyran motifs, are ubiquitous structural elements in biologically relevant small molecules. In this investigation, asymmetric synthesis of some tetrahydropyrans via 1,4-addition of alkoxide to the conjugated esters, derived from **6j** was explored. Thus, compound **6j** was converted to the tetrol derivative epimers **13** and **14** via benzoylation, reductive ozonolysis, Barbier-type

allylaltion and column chromatographic separation. Compounds **13** and **14** were individually silylated with *tert*-butyldiphenylsilyl chloride (TBDPSCl)/imidazole, their olefinic function cleaved by ozonolysis and the resultant aldehyde subjected to a Wittig-Horner reaction with triethyl phosphonoacetate to obtain the conjugated esters **15** and **17** respectively. Treatment of **15** with K_2CO_3 in MeOH afforded the tetrahydropyrans **16a** and **16b** in 1:4 ratio. Likewise, the ester **17** gave the tetrahydropyran **18** as the major product along with its C-3 epimer (not shown in the Scheme) in 1:2 ratio. The diastereomers of **16** and **18** were separated by column chromatography (**Scheme II.5.1.**) and their relative stereochemistry confirmed by 2D NMR experiments.



i) $BzCN/Et_3N/CH_2Cl_2/25\ ^oC$ (96%), ii) $O_3/CH_2Cl_2/Ph_3P/-78\ ^oC$ (78% for **13**, 80% for **15**, 81% for **17**), iii) Allyl bromide/Zn/NH_4Cl/THF/25 ^oC/4 h (80%), iv) TBDPSCl/imidazole/CH_2Cl_2/25 ^oC (89% for **15**, 90% for **17**), v) NaH/$(EtO)_2P(0)CH_2HCO_2Et$/THF/0-25 ^oC/4 h (87% for **15**, 91% for **17**), vi) K_2CO_3/MeOH/25 ^oC (40% for **16**, 38% for **18**).

Scheme II.5.1.

CHAPTER III: CHEMOENZYMATIC SYNTHESES OF TWO MACROLIDES

III.1: Preamble

Designing a common strategy, referred to as diversity-oriented organic synthesis (DOS) of various bioactive molecules has vital significance in organic synthesis. This can provide economic access to an array of discrete compounds from a single starting molecule.[12] The 14-membered unsymmetrical bismacrolides, clonostachydiol (**III**) and acremodiol (**IV**) contain two common structural motifs *viz.* hept-6-ene-2,5-diol derivatives (unit **A** or **A'**) shown in bold lines (**Fig. III.1.1.**) and the C6-dihydroxy acids (unit **B** or **B'**). It was envisaged that both the compounds can be synthesized by the DOS approach by esterification of the unit **B** with the unit **A** (for compound **III**) or of the unit **B'** with **A'** (for compound **IV**) under Mitsunobu conditions,[10] followed by removal of the protecting group, acroylation of the resultant carbinol and subsequent ring closing metathesis (RCM) reaction.[13]

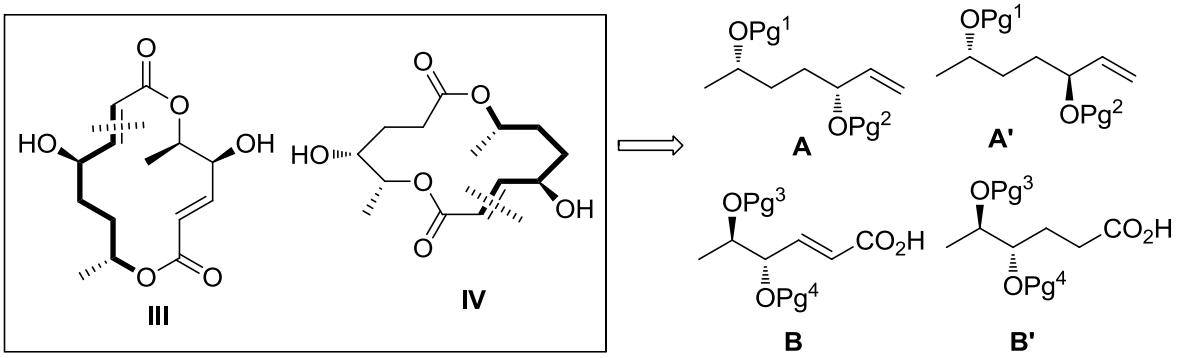


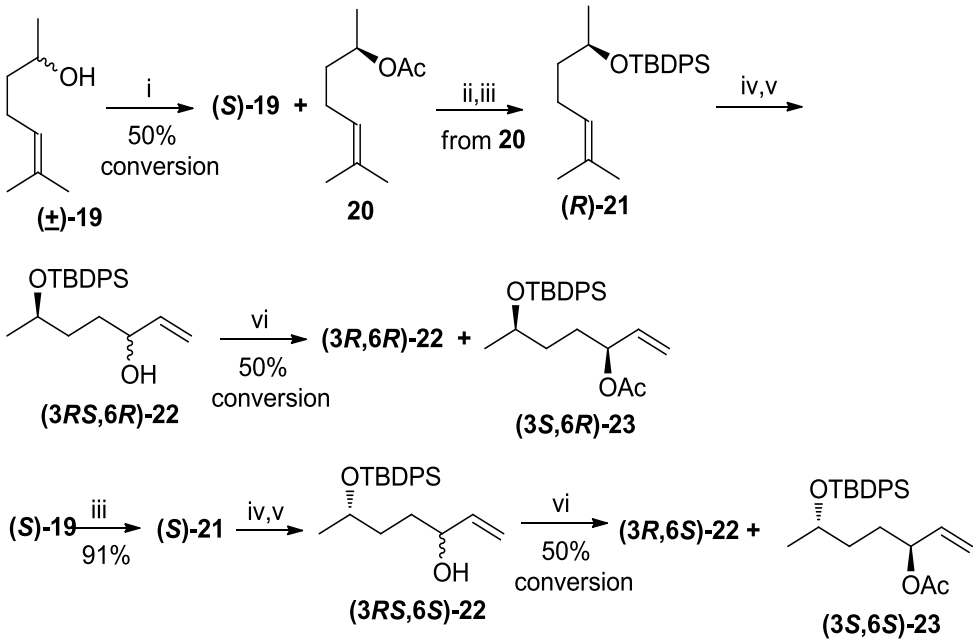
Fig. III.1.1. Chemical structures and partial retrosynthesis of clonostachydiol and acremodiol.

We planned to synthesize the **A** or **A'** units by a biocatalytic route, a viable and sustainable option in the syntheses of natural products and their congeners.[14] On the other hand, the aldehyde **4a**[5] appeared to provide the **B** or **B'** units easily. The target macrolide **III** was isolated from the marine algae-derived fungus *Gliocladium* sp. and

Clonostachys cy lindrospora (strain FH-A 6607),[15a] while **IV** was isolated from a soil sample of the Bermuda Islands, Acremonium-like anamorphic fungus.[15b] The syntheses of **III** and **IV** are sequentially presented in this chapter.

III.2: Chemoenzymatic synthesis of the A-unit stereomers

Kinetic resolution of (±)-sulcatol (**19**) via a Novozym 435®-catalyzed acetylation with vinyl acetate gave (*S*)-**19** and the (*R*)-acetate **20** (both >98% ees) at 50% conversion. The acetate **20** on $LiAlH_4$ reduction and silylation with TBDPSCl/imidazole/4-dimethylaminopyridine (DMAP) gave **21**. Its reductive ozonolysis followed by reaction with vinylmagnesium bromide furnished (3*RS*,6*R*)-**22**, which on another Novozym 435®-catalyzed-acetylation afforded (3*R*,6*R*)-**22** and (3*S*,6*R*)-**23** both with >98% ees. To utilize (*S*)-**19**, it was converted to (3*R*,6*S*)-**22** and (3*S*,6*S*)-**23** following the same sequence of reactions as above (**Scheme III.2.1.**).

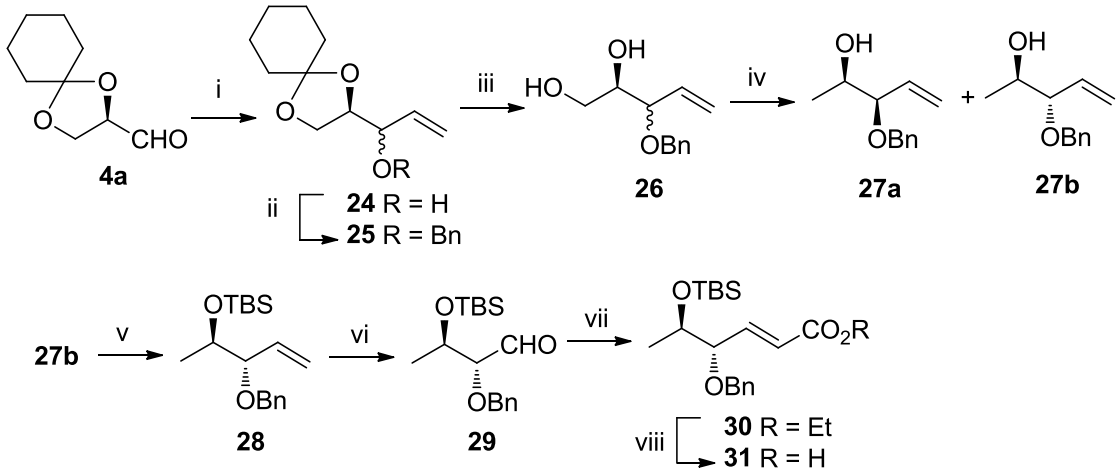


i) Novozyme 435/vinyl acetate/hexane/50 min, ii) $LiAlH_4/Et_2O$/0 °C/2 h (92%), iii) TBDPSCl/ imidazole/DMAP/CH_2Cl_2/25 °C/7 h (88% and 91% for (*R*)-**21** and (*S*)-**21** respectively), iv) O_3/CH_2Cl_2/-78 °C /1.5 h; Ph_3P/-78-25 °C/18 h (81% and 82% for (3*RS*,6*R*)-**22** and (3*RS*,6*S*)-**22** respectively), v) CH_2=CHMgBr/THF/-78 °C/3 h (84% for both (3*RS*,6*R*)-**22** and (3*RS*,6*S*)-**22**), vi) Novozyme 435/vinyl acetate/25 °C/6 h.

Scheme III.2.1

III.3: Chemoenzymatic synthesis of the B and B'-units

For the synthesis of the **B** unit, the aldehyde **4a** was reacted with vinylmagnesium bromide to obtain the allylic alcohol **24** as an inseparable mixture of the C-3 epimers. After its benzylation, the product **8** was subjected to deacetalization with aqueous TFA to get the diol **26**. Its tosylation using Martinelli's procedure (Bu_2SnO/*p*-TsCl/Et_3N)[16] furnished the corresponding primary monotosylate. This on $LiAlH_4$ reduction gave the epimeric mixture of the secondary alcohol **27a** and **27b** in 28:72 ratio (based on isolated yields), which were separable by column chromatography. The major carbinol epimer **27b** was silylated with *tert*-butyldimethylsilyl chloride (TBSCl)/imidazole/DMAP to obtain **28**. This, on reductive ozonolysis, afforded the aldehyde **29**, which on a Wittig-Horner reaction with triethyl phosphonoacetate furnished the *E*-ester **30**. Its alkaline hydrolysis with LiOH/THF-H_2O furnished the acid **31** (**B** unit) (**Scheme III.3.1.**).

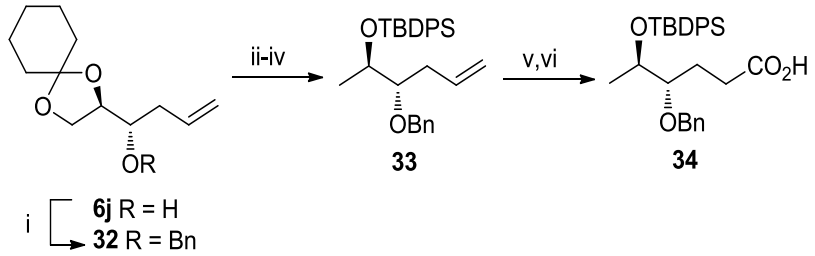


i) CH_2=CHMgBr/THF/-78 ^oC/12 h (80%),ii) NaH/BnBr/Bu_4NI/THF/reflux/4 h (98%), iii) Aqueous TFA/CH_2Cl_2/25 ^oC/24 h (92%), iv) *p*-TsCl/Bu_2SnO/Et_3N/CH_2Cl_2/25 ^oC/6 h (92%); $LiAlH_4$/THF/reflux/8 h (89%), v) TBSCl/ imidazole/DMAP/CH_2Cl_2/25 ^oC/3 h (84%), vi) O_3/Ph_3P/CH_2Cl_2/-78 ^oC/6 h (88%), vii) NaH/THF/$(EtO)_2P(O)CH_2CO_2Et$/0 ^oC/6 h (89%), viii) LiOH.H_2O/H_2O:THF:MeOH/25 ^oC/8 h (84%)

Scheme III.3.1.

The synthesis (**Scheme III.3.2.**) of the **B'** unit started from the alcohol **6j**, which on benzylation gave **32**. Its acid-catalyzed deacetalization, regioselective

tosylation,[16] $LiAlH_4$ reduction and silylation with TBDPSCl/imidazole/DMAP afforded **33**. A hydroboration-oxidation of its alkene function followed by Pinnick oxidation furnished **34** (**B'** unit).

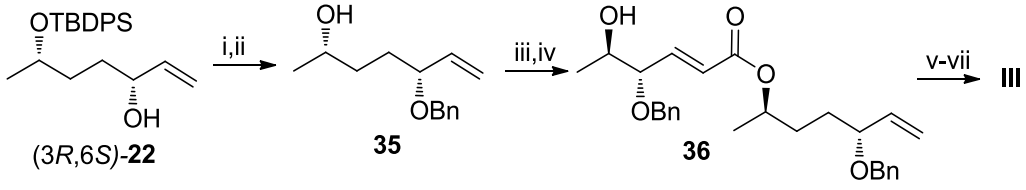


i) NaH/BnBr/Bu_4NI/THF/reflux/6 h (98%), ii) MeOH/HCl/H_2O/25 ^oC/4 h (89%), iii) *p*-TsCl/Bu_2SnO/Et_3N/ CH_2Cl_2/25 ^oC/6 h (90%); $LiAlH_4$/THF/reflux/8 h (90%), iv) TBDPSCl/ imidazole/DMAP/CH_2Cl_2/25 ^oC/3 h (81%), v) $BH_3.Me_2S$/THF/0 ^oC/3 h; aqueous NaOH/H_2O_2 (88%), vi) NaH_2PO_4/$NaClO_2$/30% H_2O_2/MeCN/0-25 ^oC/6 h (84%).

Scheme III.3.2.

III.4: Synthesis of clonostachydiol (III).

For the synthesis, (3*R*,6*S*)-**22** was converted to the benzyl ether **35** by reaction with BnBr/NaH in THF, and used for esterification with the acid **31** under Mitsunobu conditions (Ph_3P/DIAD). The product was desilylated with trimethylchlorosilane (TMSCl) in aqueous acetonitrile[17] to obtain the ester **36**. Its reaction with acryloyl chloride/Hunig's base, followed by an RCM reaction,[18] and debenzylation with DDQ[19] yielded **III** (**Scheme III.4.1.**).

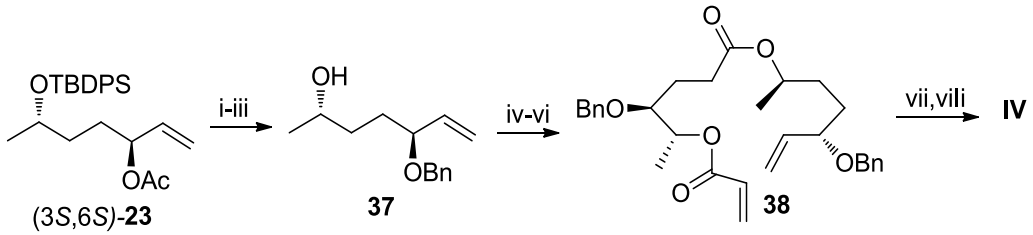


i) NaH/BnBr/Bu_4NI/THF/reflux/7 h (95%), ii) Bu_4NF/THF/0 ^oC/7 h (88%), iii) **31**/Ph_3P/DIAD/THF/0-25 ^oC/18 h (78%), iv) TMSCl/aqueous CH_3CN/0 ^oC/1 h (89%), v) Acryloyl chloride/ DIPEA/ CH_2Cl_2/ 0-25 ^oC/3 h (87%), vi) Hoveyda-Grubbs II/toluene/80 ^oC/22 h (65%), vii) DDQ/CH_2Cl_2/H_2O/25 ^oC/5 h (71%).

Scheme III.4.1.

III.5: Synthesis of acremodiol (IV). For the synthesis (**Scheme III.4.2.**), the acetate (3*R*,6*S*)-**23** was subjected to alkaline hydrolysis, the resultant alcohol benzylated and

the silyl protection removed with Bu_4NF to obtain the alcohol **37**. Its esterification with the acid **34** under Mitsunobu conditions, desilylation with HF-pyridine and acryloylation of the resultant alcohol furnished **38.** This on an RCM reaction followed by $TiCl_4$-calatalyzed debenzylation afforded the target macrolide **IV**.



i) K_2CO_3/MeOH/25 ^oC/18 h (91%), ii) NaH/BnBr/Bu_4NI/THF/reflux/7 h (93%), iii) Bu_4NF/THF/0 ^oC/7 h (88%), iv) **34**/Ph_3P/DIAD/THF/0-25 ^oC/18 h (75%), v) HF-pyridine/THF/pyridine//25 ^oC/16 h (90%), vi) Acryloyl chloride/DIPEA/CH_2Cl_2/ 0-25 ^oC/3 h (84%), vii) Grubbs I/CH_2Cl_2/40 ^oC/48 h (69%), viii) $TiCl_4$/CH_2Cl_2/0 ^oC/0.5 h (91%).

Scheme III.4.2.

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

3 (a) Miller, S.J.; Blackwell, H.E.; Grubbs, R.H. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614; (b) Loh. T.P.; Hu. Q.Y.; Ma. L.T. *J. Am. Chem. Soc.* **2001**, *123*, 2450–2451; (c) Adam. W.; Saha-Moller, C.R.; Schmidt, K.S. *J. Org. Chem*. **2001**, *66*, 7365–7371.

4 (a) Pu, L.; Yu, H.-B. *Chem. Rev*. **2001**, *101*, 757–824.

5 Sugiyama, T.; Sugawara, H.; Watanabe, M.; Yamashita, K. *Agric. Biol. Chem*. **1984**, *48*, 1841–1844.

6 Denmark, S. E.; Fu, J. *Chem. Rev.* **2003,** *103,* 2763–2793.

7 Ghosh, P.; Chattopadhyay, A. *Tetrahedron Lett*. **2012**, *53*, 5202–5205.

8 (a) Goswami, D.; Chattopadhyay, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1957–1961; (b) Goswami, D.; Chattopadhyay, A.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem*. **2012**, *77*, 11064–11070.

9 Sherley, J. L.; Kelly, T. J. *J. Biol. Chem*. **1988**, *263*, 8350–8358; (b) Bertagna, F.; Biasiotto, G.; Giubbini, R.; *Clin .Transl. Imaging* **2013**, *1*, 77-97.

10 (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) R. Dembinski, *Eur. J. Org. Chem*. **2004**, 2763–2772.

11 (a) Ellis, G. P.; Lockhart, I. M. The Chemistry of Heterocyclic Compounds, Chromenes, Chromanones, and Chromones; Wiley: New York, 2007; (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc*. **2000**, *122*, 9968–9976.

12 (a) Spring, D. R. *Org. Biomol. Chem*. **2003**, *1*, 3867–3870; (b) Tan, D. S. *Nature Chem. Biol*. **2005**, *1*, 74–84.

13 (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18–29; (b) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471(7339)*, 461–466.

14 (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.

15 (a) Grabley, S.; Hammann, P.; Thiericke, R.; Wink, J.; Philipps, S.; Zeeck, A. *J. Antibiot.* **1993**, *46*, 343–345; (b) Berg, A.; Notni, J.; Dorfelt, H.; Grafe, U. *J. Antibiot*. **2002**, *55*, 660–662.

16 Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett*. **1999**, *1*, 447–450.

17 Grieco, P. A.; Markworth, C. J. *Tetrahedron Lett*. **1999**, *40*, 665–666.

18 Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

19 Zhu, B.; Panek, J. S. *Org. Lett*. **2000**, *2*, 2575–2578.

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CHAPTER I

INTRODUCTION TO ASYMMETRIC TRANSFORMATIONS

I.1: Preamble

Organic chemistry had its genesis in the study of naturally occurring substances, and this remains a constant source of information and intellectual challenge.[1] Natural products have traditionally played an important role in drug development with a considerable number of marketed drugs being derived from naturally occurring compounds.[2a] They also can be excellent leads for drug development despite often having complex structures and limited oral bioavailability.[2b,c] Thus, organic synthesis is expected to play a pivotal role in developing functional molecules, as it can provide the target compounds in sufficient amounts and also assist in tailoring the molecular properties of the functional entities. A large majority of the naturally occurring secondary metabolites, derived from terrestrial and marine kingdom are chiral, and their stereochemistry crucially governs the biological activity. This emphasizes the importance of developing efficient routes for enantiomeric synthesis in synthetic organic chemistry.[3] The ideal and challenging version of this task is to formulate catalytic asymmetric organic transformations, which is usually achieved using metal complexes and/ or biocatalysts so that higher degree of selectivity is achieved with minimum waste generation.

Hence, the major focus of the present investigation was asymmetric synthesis. 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 also discussed, since this methodology has been extensively used in the present investigation.

I.2: Important Aspects of Asymmetric Synthesis

Lack of certain symmetry elements in a molecule endows it with chirality

(handedness) that is manifested in the form of its ability to rotate the plane of a polarized light to the left or right from its original direction. In most of the cases, presence of an asymmetric centre in the organic molecules contributes to their chirality. Chirality may also arise due to the presence of an axis of chirality (an axis about the substituents are held in a spatial arrangement that is not superimposable on its mirror image) or restricted rotation (atropisomerism), but is rare.[4]

The importance of enantiomerically pure compounds comes from the fact that physiological properties of chiral molecules are different for the stereomers, and the differences are often wide. There exists several examples of drugs,[5a] agrochemicals[5b] and other chemical compounds where the desired biological property is related to their absolute configurations. A brief account of the importance of chirality on biological activities is provided below.

I.2.1. **Importance of chirality on bioactivity:** 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. In most cases, the action of drugs involves molecular recognition of a biologically active molecule by chiral non-racemic receptors/enzymes. Since two enantiomers of a molecule can't bind equally to the receptors/enzymes, different biological responses are observed. Thus, often only one enantiomer of the drugs show the desired biological activity, while the other enantiomer is inactive or possesses a different activity, and may even cause toxic effects. Even when the other enantiomer of a drug is non-toxic, it is desirable to use only the active enantiomer. Use of a racemic mixture of the drug would otherwise require double the quantity. Moreover, long-term biological effect (if any) of the inactive drug enantiomer also needs proper

consideration. This is the case with ibuprofen as its *S*-enantiomer is a pain reliever, whereas the *R*-form is inactive. However, the problems that arise with optically impure pharmaceuticals even when employed at high enantiomeric excess (ee), are no less significant and can even be ominous. Enantiomers may be competitive antagonists, as reported with (+)- and (-)-isoproterenol enantiomers, which act differently on the α_1-adrenergic receptors in rats.[5c] Different enantiomers can also show different pharmacological profiles, all of which may be beneficial. For example, *S*-propanolol is a β-blocker, but the *R*-isomer is a contraceptive.

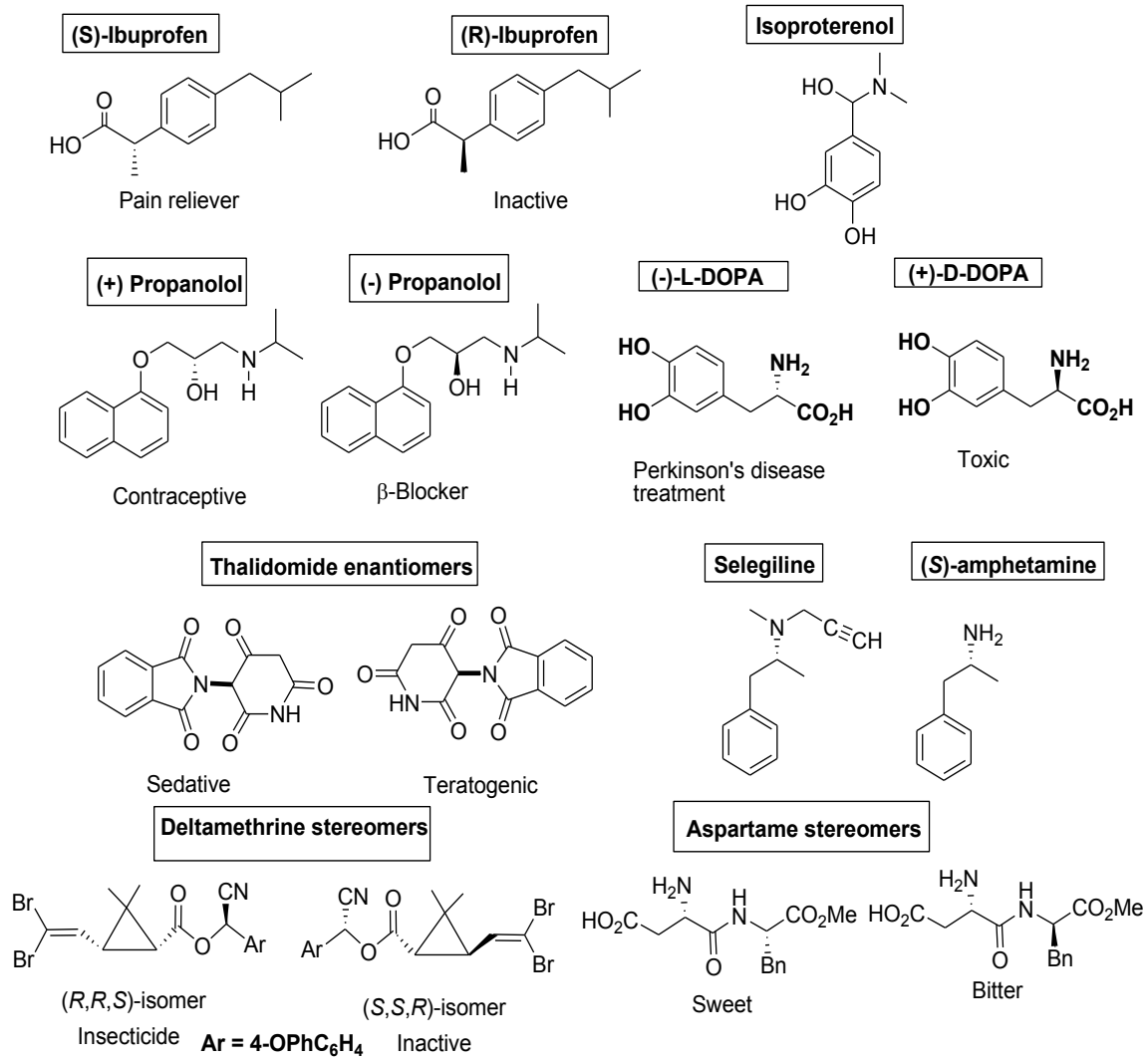


Figure I.2.1. Examples of chirality-governed biological activities.

However, the most damaging possibility is encountered when the non-beneficial enantiomer contributes to toxicity and/ or severe side effects. For e.g. (-)-L-DOPA is used for the treatment of Perkinson's disease whereas its enantiomer (+)-D-DOPA is toxic. The thalidomide tragedy is perhaps the most well-known example of this category. While, its (*R*)-enantiomer was earlier used for morning sickness of pregnant women, the (*S*)-enantiomer was found to be teratogenic causing wide spread birth defects. Another similar example was reported with selegiline, an antidepressant and a drug for Parkinson's disease. It was found that its less active (*S*)-isomer is converted into (*S*)-(+)-amphetamine in vivo, which causes undesired CNS stimulation.[5d] Amongst the eight isomers of deltamethrin, the (*R*,*R*,*S*)-isomer is the most powerful insecticide, but the (*R*,*S*,*S*)-stereoisomer is inactive.[5e] (*S*,*S*)-Aspartame is used as an artificial sweetener, while its (*S*,*R*)-isomer is bitter and must be avoided in the manufacturing process. Some selective examples highlighting this aspect is shown in **Figure I.2.1.**

From the foregoing, the importance of chirality especially on drugs, agrochemicals, perfumeries and food-additives are obvious. The enantiomers of chiral drugs are considered as two separate compounds and use of them as racemates require firm establishment of the physiological actions of each stereomers. Hence, the pharmaceutical industries are adopting different strategies for enantiomeric synthesis of target compounds, as explained below.

***I.2.2. Strategies of enantiomeric synthesis*:** Several methods are available to obtain enantiomerically pure compounds, which include classical optical resolution by fractional crystallization of diastereomers or chromatographic separation using chiral columns, chiral pool synthesis, enzymatic/microbial routes, and asymmetric synthesis.

***Resolution of racemates*:** This is the oldest, but one of the most important industrial methods[6] in obtaining enantiomerically pure compounds, and generally involve preferential crystallization of diastereomeric derivatives or covalently bonded diastereomers. In the crystallization method, a racemic mixture is reacted with an optically pure resolving agent to obtain a separable mixture of diastereomers, ensuring its resolution. Hence, it is restricted only to compounds having functional groups such as amines, alcohols, carboxylic acids etc. Some of the commonly used resolving agents are: (i) tartaric acid, for resolution of secondary alcohols and secondary amines, (ii) alkaloids such as brucine salts or amines such as α-phenylethyl amine, for resolution of chiral acids. Ideally the resolving agent should be available in its enantiomeric forms with high optical purity and furnish crystalline diastereomeric derivatives. Also, 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*:** The vast repertoire of chiral pool materials, obtained from various natural sources are often synthetically transformed into the target molecules. In this type of synthesis, the stereogenic centres of the target molecules are inherited from that present in the starting chiral materials, without generating any new stereogenic centre(s). This necessitates design of suitable reaction conditions to avoid any alteration of the existing stereogenic centres of the starting materials or racemization during the reaction sequence. Alternatively, the synthesis should ensure change in the stereogenicity in a predictable manner. Amongst the natural chiral pool materials, the α-amino acids, steroids, carbohydrates, alkaloids and terpenes are important starting materials in enantiomeric syntheses.[7] Some easily available and widely-used 'chiral pool' materials are shown in **Figure I.2.2**.

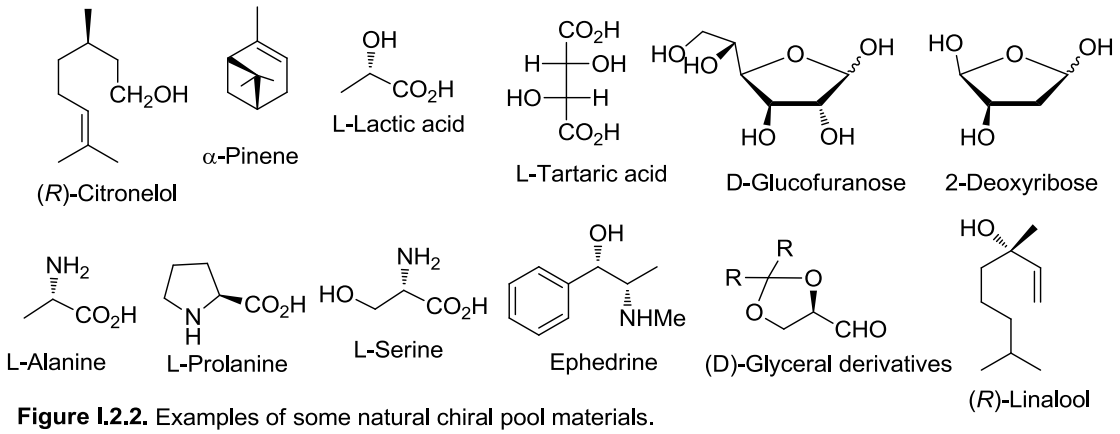


Figure I.2.2. Examples of some natural chiral pool materials.

Despite its proven success for the synthesis a large number of enantiomerically pure compounds, this approach is limited by the availability of inexpensive starting materials with the right sense of chirality. Some of the natural chiral pool materials are available only as a single enantiomer, or the other stereomers are expensive. For example, only the D- or L-sugars and amino acids exist in natural sources. Thus, when the synthesis of a target compound requires the other enantiomer of these starting materials, the synthesis becomes lengthy and inefficient. In these cases, other methods may be more efficient and economic.

The carbohydrates contain several stereogenic centres, and may provide suitable steric bias for the subsequent transformations. Hence, these are the most preferred 'chiral pool' materials for enantiomeric syntheses of various target molecules. However, due to the presence of several similar functionalities in the carbohydrates, several protection and deprotection steps are required using these materials. Moreover, their use in the syntheses of simple compounds with one or two stereogenic centrs, is undesirable. Many of the alkaloids, steroids and triterpenes are also not useful for the enantiomeric syntheses of structurally unrelated targets.

***Asymmetric reactions*:** By definition, an asymmetric reaction is a reaction that converts an achiral unit in an ensemble of substrate molecules to stereoisomeric

products in unequal amounts.[8] Thus, it is a protocol for controlled and preferential creation of new stereogenic centres. The transition states $R^{\#}$ and $S^{\#}$ of such reactions are enantiomeric and therefore, isoenergic. Hence, the energetic consideration favours formation of racemates. As a consequence, development of an asymmetric synthesis warrants formation of diastereomeric transition states so that their potential energies are different, ensuring their formation at different rates. Hence, these would be produced in unequal amounts, making the processes enantio- or diastereoselective (or both). In turn, this may give rise to enantiomerically pure products. This can happen only if the newly generated stereogenic centre is not the first one in the ensemble. Such a scenario can be achieved only by using a chiral reagent, substrate, solvent, catalyst or physical forces such as circularly polarized light to control the reaction. Under these conditions, the reactions can be stereo-differentiating to "induce" chirality at the newly formed stereogenic centers. An asymmetric synthesis may involve 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.**).[9]

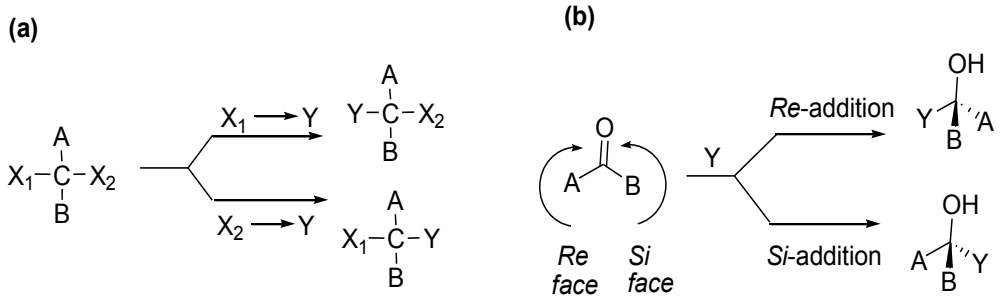


Figure I.2.3. Modalities of asymmetric reactions (**a**) enantiotopic substitution, (**b**) face-selective addition.

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 the diastereomers. In the first category, the most widely encountered situation is the regent-controlled "asymmetric induction" and some important achievements in this area include, but not limited are the asymmetric catalytic hydrogenation of dehydroamino acids, as described by Knowles *et al.*[10a] Sharpless epoxidation[10b,c] and dihydroxylation of alkenes,[10d] and catalytic hydrogenation of tri-substituted olefins, developed by Noyori *et al.*[10e]

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 many chiral molecules can be produced by one catalyst molecule. Chirality multiplication is a known characteristic of both biocatalysts and chemical catalysts. Some industrially useful chemical asymmetric reactions are the production of *L*-menthol by asymmetric isomerization,[10f,g] asymmetric cyclopropanation[10h] and synthesis of *L*-dopa by asymmetric hydrogenation.[10i]

Although metal/metal salt-catalyzed reactions remain the mainstay in asymmetric synthesis, greater emphasis is currently being given on developing methods using metal-free small organic molecules (organocatalysis).[11a,b] Spectacular successes have also been achieved in terms of extremely high enantioselectivity in some cases. Besides, they also offer notable preparative advantages because (i) the catalysts are inexpensive and stable; (ii) the reactions can usually be performed even in wet solvents without any inert atmosphere; (iii) the catalysts can be anchored on to

a solid support and reused. Overall, these methods are 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 also known as artificial enzymes or enzyme mimetics.[11c]

Addition of nucleophiles to ketones and aldehydes is perhaps the most popular protocol for creating chiral molecules, since the resultant alcohols are of wide occurrence in nature, and are precursors to varied types of other molecules such as macrolides, spiroketals, amines 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[12]: 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 (R^1M, R^1 = alkyl or H), 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 model. In the open chain model, the C=O group of the ketone is placed such that it is flanked by the two smaller groups (R_S and R_M), while the large group (R_L) is 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 R^1 group or H atom to the triagonal 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.

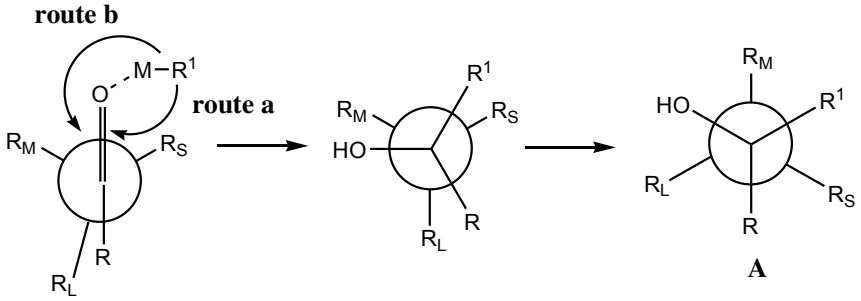


Figure I.2.4a. Cram's open chain model.

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.

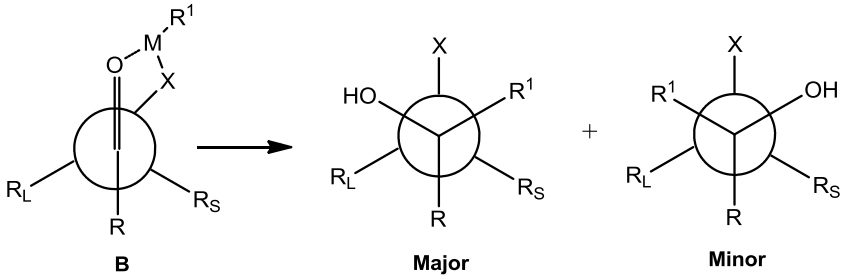


Figure I.2.4b. Cram's cyclic chelate model

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**.

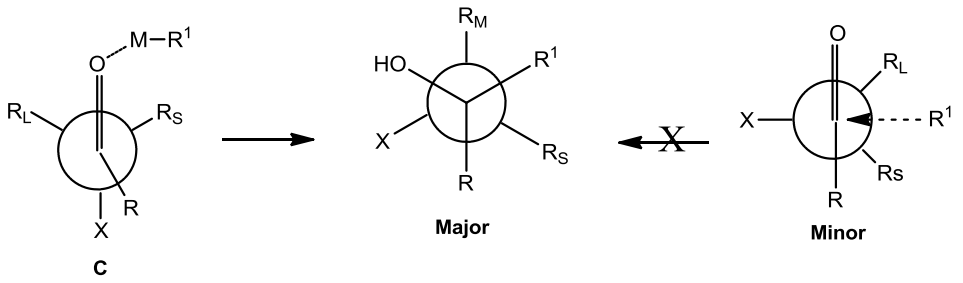


Figure I.2.4c. Cram's dipolar model.

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. Amongst the few alternative models, the Felkin-Anh model predicts the stereochemical outcome of the designated reactions in more quantitative terms, and is discussed below.

Felkin-Anh model[13]**:** 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 due to unfavorable steric interactions.

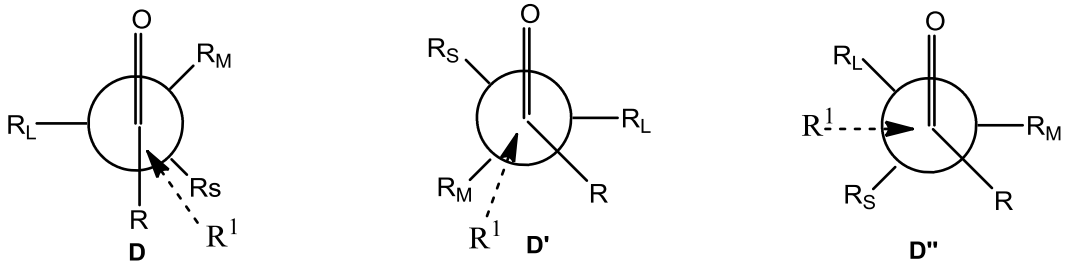


Fig. I.2.5. Felkin-Anh model.

I.2.3. Energy considerations in asymmetric synthesis: The reactions with competing pathways such as in asymmetric transformations lead to different products. The outcome of such a reaction is decided by the relative stability of the products (*thermodynamic factors*) or the rate of product formation (*kinetic factors*). For an irreversible enantioselective reaction, the stereomeric composition of the products is governed by the difference of the energies of activation ($\Delta\Delta G^*$) of their formation, and the faster reaction pathways prevail to give the kinetically controlled enantiomers. This implies that the most abundant product is that originating *via* the lowest activation energy.

When the products in the asymmetric synthesis are diastereomeric, the selectivity can also be dictated by the difference in kinetic energies (kinetic control), but when the reaction is reversible, the selectivity at equilibrium depends on the difference between the free energies of the diastereomeric products ($\Delta G°$). Thus, under thermodynamic control, the most stable diastereomeric product is obtained. 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 $\Delta\Delta G^{\#} \geq 1.0$ kcal/mol for achieving a diastereo-/enantio-selectivity 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. Despite

good understanding of a large numbers 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 steric interactions, hydrogen bonds, selective solvation *etc*. Moreover, as 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.

I.2.4. Protocols for determination of enantiomeric purities: Accurate and reliable methods of measuring the enantiomeric composition of an asymmetric reaction have become prerequisites in enantioselective syntheses. Enantiomeric excess (ee), defined as the difference between the mole fractions of the enantiomers, is a measure of the enantiomeric purity of a chiral molecule. The methods of determining % ees are based on (i) formation of suitable diastereoisomers of a chiral analyte, either transiently via a reversible diastereotopic non-covalent interaction with a chiral reagent, or by a covalent attachment using one of its functional groups, followed by (ii) separation/analysis of the diastereoisomers using various instrumental techniques such as HPLC, GC and NMR spectroscopy. The non-covalent HPLC or GC techniques using appropriate chiral columns are widely used for analyzing % ees of all types of analytes. The % ees can also be determined using chiral paramagnetic lanthanide complexes that can reversibly bind to certain chiral molecules *via* the metal centre to form two diastereomeric complexes. 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 an alternative approach, the analyte is converted to a pair of diastereoisomers by covalent attachment with another enantiomerically pure molecule. The diastereoisomers can then be separated by normal chromatography using an achiral column, or analyzed by 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 (≥ 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 spectra can be used to determine the % ees. The Mosher's derivatives can also be used to determine the absolute configuration of a stereocentre using the δ differences (Δδ).[14c] Various other derivatizing agents, notably some chiral mandelic acid derivatives are also used for this purpose.[14d]

I.3: Biocatalytic Organic Reactions

Enzymes or the biocatalysts are used by all living systems *viz*. microbes, plants and animals to carry out essential cellular reactions in an energy-efficient manner under moderate conditions of temperature, pH in both aqueous and hydrophobic environments.

Learning from nature, humans have perfected the art of producing cheese, wine, beer etc. using whole cell microorganisms as the enzymes' source, since time immemorial. During the past few decades, there has been a steady growth in the application of biocatalysis to produce several pharmaceuticals and intermediates.[15]

Nevertheless, several factors such as (i) non-availability of many enzymes in large enough quantities and at affordable cost; (ii) narrow substrate specificity and moderate stereo- and/or regioselectivity; and (iii) insufficient stability under the operating conditions impeded the applications of biocatalysts in synthetic organic chemistry. However, many of these problems are adequately addressed through recombinant DNA technology. Currently, biocatalysis has become a part of the toolkit of synthetic organic chemists, as they can furnish various desired compounds with minimum wastes generation via atom-economic and green protocols.[16]

Like their chemical counterparts,[17a] biocatalysts accelerate the rate of a reaction by stabilizing its transition states, without affecting the equilibrium. However, they offer some unique advantages such as higher rate enhancement and catalytic turnover number, and most importantly excellent selectivity over the 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. Similarly, only 0.005-0.05 mol% of biocatalysts is required to achieve a chemical conversion *vis-à-vis* that (5-50 mol%) required by chemical catalysts. Moreover, the stereo-, regio-, and chemo-selectivities, offered by the biocatalysts may minimize the number of protection/deprotection steps as well as side reactions in a chemical synthesis, and assist easier isolation of the desired products with less environmental problems.

Many of the unique characteristics of these sophisticated enzymes systems can be explained in terms of their built-in feedback mechanisms and subtle intra- and intermolecular cooperation.[17b] Enzymes are proteins with three-dimensional architectures containing primarily hydrophobic and a few polar sites, allowing them to effectively 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. Best ES complex formation occurs when the substrate size and the disposition of their groups match well with the enzyme conformation. This "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, on binding with substrates, the entrapped water molecules in the enzymes get released to increase the entropy and decrease the dielectric constant, thus intensifying the electrostatic effects. 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.

The secondary and tertiary structures of enzymes are stabilized by various weak non-covalent forces *viz*. hydrogen bonding, hydrophobic interaction and dipolar/ionic interactions. Hence, it is possible to modulate the enzyme conformation marginally by 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, if carried out in water. Although the enzymatic reactions are reversible, the thermodynamic equilibria of the reverse processes are unfavorable in water. For example, the lipases and proteases catalyzes hydrolysis of lipids and

proteins in water. But they also 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 is also easier. Moreover, although the bound water molecules are essential to maintain the activity of the enzymes, their denaturation is also induced in aqueous environment. Hence replacement of the free water by organic solvents prevents their denaturation, 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. Based on their functions, 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] Use of the isolated enzymes offer several benefits, including simpler reaction apparatus, higher productivity owing to higher catalyst concentration, and simpler product purification. However, a whole-cell system is more useful for the cofactor-requiring enzymes such as oxidoreductases, lyases etc., since they have built-in cofactors

recycling systems. It can also carry out selective synthesis using cheap and abundant raw materials. However, the whole-cell systems require expensive equipments and tedious work-up, have low productivity and may result in undesirable side reactions. Another drawback in whole-cell systems is that the cell membrane may prevent easy mass transport between the substrates and the enzymes. The whole-cell approach is typically used when a specific biotransformation requires multiple enzymes or when it is difficult to isolate the enzyme.

Enzymes such as oxidoreductases, proteases (α-chymotrypsin, papain, and subtilisin), esterases and lipases are widely used in various industrial processes, developed with the whole cell systems as well as isolated enzymes. The oligosaccharides and polysaccharides that are vital for cellular functions are industrially synthesized using transferases. Amongst the isomerases, glucose isomerase is used 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 over its counterpart for a specific reaction. The maximum yield in KR can be only 50%. The oxidoreductases, present in many microorganisms including common baker's yeast are often used for the asymmetric reduction of ketones. The same enzyme can also 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, some lipases were found to carry out reactions akin to those expected. Some examples in this category include: (i) use of *Candida antarctica* lipase for Michael

addition reactions,[20a] (ii) use of another *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]

Many of the perceived drawbacks of enzymes, such as limited operating regions, substrate or product inhibition, and operation only in aqueous solutions have now been proven to be wrong. Many commercially used enzymes show excellent stability with half-lives of months or even years under process conditions. Many enzymes accept non-natural substrates and convert them into desired products, both in aqueous and non-aqueous media.

I.4: Objectives of the Present Work

Impressive progress notwithstanding, development of simple, efficient and scalable strategies remains a challenging and important goal in asymmetric organic syntheses.[21] 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,[22] and the concept of multiple-targets- rather than target-specific syntheses have become the buzzword of modern organic synthesis. The present work was primarily targeted in consideration of the above challenges. Thus, the primary motivation of the present investigations was focused to develop operationally simple and practically viable asymmetric transformations and establishing their utility in the syntheses of some chiral biologically active compounds. The choice of the target molecules was decided in consideration of our own interest in immunomodulatory, anti-inflammatory, and anti-neoplastic agents as well as their structural complexity.[23]

Chirality in a majority of the organic molecules originates due to the presence of asymmetric carbon atoms, possessing methyl branched alkane segment [-CH(Me)-] or a secondary/tertiary carbinol moiety or both. Besides being present in various natural products, chiral carbinols are also precursors for a large variety of molecules such as lactones, macrolides, spiroketals, amines and heterocycles. From this perspective, enantio- and diastereoselective construction of carbinols assumes great importance in synthetic chemistry. To this end, initially the Barbier-type of protocols for propargylation and allylation of aldehydes were developed using a wide range of aliphatic and aromatic substrates. The optimized method was subsequently used in formulating the substrate-controlled asymmetric strategies. The mannitol-derived compound, (*R*)-2,3-cyclohexylideneglyceraldehyde appeared to be an ideal chiral template for this purpose, because it is amenable to various diastereoselective transformations using commonly available, inexpensive reagents.[24] Presently, we decided to use the aldehyde as the required chiral substrate to carry out both the designated transformations. In the pursuit of green chemistry, the room temperature ionic liquids (RTILs) have emerged as good, eco-friendly alternative reusable solvents for a wide range of organic transformations. Likewise, Bi-metal is one of the non-toxic metals that are used in organic syntheses. Hence, the allylation reaction was developed using a combination of Bi-metal and an RTIL. However, for the propargylation reaction, an innovative bi-metallic strategy was designed by generating active Fe or Sn by reducing their salts with Zn-metal. The substrate-controlled approaches provided economic options to carry out both the reactions.

Besides the chemical routes, enzymatic transformations can also give access to the carbinol enantiomers. In particular, the lipase-catalyzed *trans*-esterification of secondary alcohols or hydrolysis of esters under kinetic control often proceeds with

good to excellent enantioselectivity. Moreover, these protocols provide both the enantiomers of secondary alcohols. Hence, with the objective of developing some operationally simple asymmetric syntheses of the target compounds, the metal-mediated allylation and biocatalytic routes were judiciously used to obtain several target compounds. Amongst the *O*-heterocyles, a nucleoside analog, some 2,6-disubstituted tetrahydropyrans and two macrolides were synthesized.

CHAPTER II

DEVELOPMENT OF ASYMMETRIC BARBIER TYPE ALLYLATION/PROPARGYLATION REACTIONS

II.1: Preamble

Asymmetric allylation of aldehydes is one of the most extensively used carbon–carbon bond forming reactions, driven in part by versatility of the homoallylic alcohols as synthetic intermediates.[25] A useful extension of allylation chemistry is the asymmetric carbonyl propargylation reaction that has attracted recent attention. The synthetic utility of these methods has been demonstrated in the context of several polyketide natural product syntheses.[26,27] The Barbier-type protocols are more convenient for these transformations, since the reactive metal-allyl/propargyl-metal complexes are produced *in situ*. Amongst the various metals used for the Barbier-type allylation, the group 13 metals, In[28a,b] and Ga[28c-g] are being extensively used of late. On the other hand, for Barbier-type propargylation, Zn is used extensively,[29a] along with In,[29b] Sn,[29c] or Ti-metals[29d] to promote the reaction. The asymmetric version of these reactions can be accomplished by incorporating a chiral auxiliary in the substrate and/ or the reagent. While the design and synthesis of the required chiral reagent provide adequate challenge, the efforts are often taxing, and at times frustrating. Further, syntheses of the sterically robust chiral auxiliaries may require several steps, and involve expensive reagents. Instead, a substrate-controlled method using natural chiral pool-derived templates might provide suitable alternatives for the designated transformations. Hence, one of the major objectives of the present investigations was formulation of asymmetric allylation/propargylation strategies that are sequentially presented bellow.

II.2: Carbonyl Propargylation: Importance and Synthetic Strategies

II.2.1. Importance: The alkyne functional group is found in many bioactive natural products and is the key to many important chemical transformations developed over

recent years.[30] The terminal alkyne functionality is amenable for cross-coupling, metathesis, and heterocycle synthesis.[31] Many chiral homopropargylic alcohols were used as building blocks for the synthesis of complex molecules of pharmaceutical interest.[32]

II.2.2. Synthetic Strategies: In view of the importance of the homopropargylic alcohols, numerous protocols for carbonyl propargylation using allenylmetal reagents have been developed.[33] These include reaction of the carbonyl with allenic Grignard reagents, allenic stannanes, allenylchromium, allenylsilicon and allenylboron reagents. The allenylmetal reagents can also be prepared *in situ* from propargylic iodides and metals salts. Most importantly, these can be chirally modified at the metal/metalloid center to carry out propargylation of aldehydes enantioselectively. For example, chiral allenylboron reagents have been used in asymmetric propargylation.[34a,b] Likewise, allenylstannanes, chirally modified at the Sn center also induce asymmetric carbonyl propargylation, as was first reported by Minowa and Mukaiyama.[34c] Significant advances in the area of asymmetric carbonyl propargylation have been made by the groups of Marshall,[34d,e] and Hayashi.[34f] Since their introduction by Keck *et al*.,[35a] and Denmark and Wynn,[35b] chiral Lewis acids or bases are also increasingly being used for the same purpose. More recently, reaction of allenylboronates in the presence of chiral phosphoric acids,[35c,d] and a bromo-BINOL derivative[35e] allowed conversion of a broad range of aryl, polyaryl, heteroaryl, α,β-unsaturated, and aliphatic aldehydes to the corresponding chiral homopropargylic alcohols in good enantioselectivity.

Despite several advantages, the allenylation strategy warrants use of anhydrous organic solvents. Hence, the more environmentally benign Barbier type protocols aided by different metals have been developed for propargylation. Thus,

reports on non-asymmetric propargylation of carbonyls promoted by In,[36a-e] Zn,[36f,g] and low valent Ba[36h] are available in literature. Also, homopropargyl alcohols have been synthesized by (i) Zn-catalyzed addition of propargyl boronates to aldehydes;[37a] (ii) Mn-mediated asymmetric propargylation of aldehydes in the presence of Cr(salen) complex,[37b] or titanocene (III) complex;[37c] (iii) addition of 1-substituted propargyl mesylate to carbonyls in the presence of $SnI_2/Bu_4NI/NaI$;[37d] and (iv) electrochemical reaction using Pt cathode and Zn or Al anode.[37e]

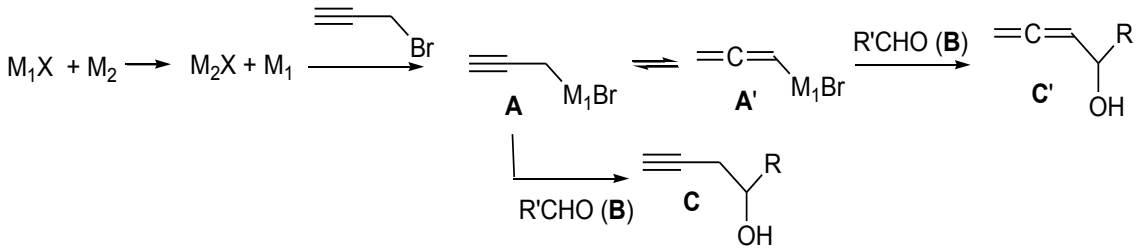
II.3: Present work: A Bimetallic Redox Strategy for Carbonyl Propargylation

Despite impressive progress, synthesis of homopropargylic alcohols remains arduous. Two main complications are i) the lower reactivity of the allenylic and propargylic substrates in comparison to allylic substrates; and ii) the difficulties associated in controlling the reaction regioselectivity.[30a] Many of the metal-catalyzed propargylations of aldehydes furnishes the desired homopropargylic alcohol **C** together with varying amount of the allenic alcohols **C'** (**Scheme II.3.1.**). This has been attributed to the metallotropic rearrangements between the intermediate propargyl metals **A** and the corresponding allenyl metals **A'** during the reaction. This is classically suppressed by the addition of poisonous $HgCl_2$ catalyst, or carrying out the reaction in the presence of $ZnBr_2$, as reported more recently.[38] Alternatively, homopropargylic alcohols could be prepared with high regio-selectivity by reacting carbonyls with allenylmetals.[25d,33c-e,39]

On the other hand, most of the current enantioselective methods of propargylation rely on the use of chiral reagents.[34a,40] However, several of these methods suffer from i) the use of reagents that are relatively difficult to prepare or are unstable to air and/or moisture; ii) the use of undesirable metal reagents or catalysts; and iii) regioselectivity concerns. Alternative catalytic methods have been developed, but are limited to the use of allenylic or propargylic metal-based reagents or intermediates.[25d] The limitations of the available protocols of propargylation of aldehydes presented an opportunity to formulate an alternate synthetic strategy. In particular, the primary aim was to develop a conceptually simple, but unexplored method that is practically viable using inexpensive and commercially available materials. It was also of interest to avoid using any anhydrous organic solvent, and

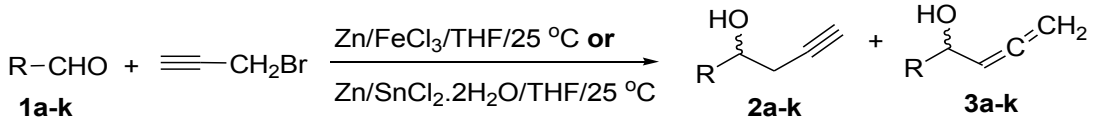
achieve high regioselectivity to maximize the yields of the homopropargylic alcohols. To this end, a plan of using bi-metallic systems as the promoter was conceived.

In this mission, a low valent metal mediator (M_1) was freshly prepared *in situ* in highly active form following a spontaneous redox reaction between its commercially available hydrated salt (M_1X) with a reducing metal (M_2). In consideration of the redox potentials of the following couples: $E^0_{Zn} = Zn^{2+} + 2e$ (+0.761 V), $E^0_{Cu} = Cu^{2+} + 2e$ (-0.337 V), $E^0_{Fe} = Fe^{2+} + 2e$ (+ 0.441 V), $E^0_{Fe^{2+}} = Fe^{3+} + e$ (- 0.771 V) and $E^0_{Sn} = Sn^{2+} + 2e$ (+0.140 V), Zn dust was chosen as the reducing metal. However, even Mg was also used in some of the earlier studied reactions by our group.[41a,b] For the present studies, three different combinations of M_1X/M_2, *viz.* (a) $FeCl_3$/Zn, (b) $SnCl_2.2H_2O$/Zn, and (c) $CuCl_2.2H_2O$/Zn were used to carry out the reaction between propargyl bromide and a host of aldehydes in THF. It was envisaged that the higher surface area of Zn dust would be advantageous for the reduction of the metal salts to produce the active Cu, Fe and Sn respectively. The freshly prepared M_1 would react with the propargyl halide immediately to produce the corresponding organometallics **A** or its tautomer **A**'. These can subsequently participate in nucleophilic addition to the substrate aldehydes **B** to yield the corresponding addition products (**Scheme II.3.1.**). Thus, the reaction can be carried out without any additional metal activator. Similar strategies has been employed by our group in formulating allylation,[41c,d] crotylation,[41e-g] Reformatsky reaction,[41e] and benzylation[41b] of aldehydes, but not for propargylation.



Scheme II.3.1. Schemetic representation of carbonyl propargylation using bi-metallic strategy.

Initially, the efficacy of $Zn/FeCl_3$ (*reagent 1*) and $Zn/SnCl_2.2H_2O$ (*reagent 2*) combinations was tested using PhCHO (**1a**) as the model compound. This furnished the desired alcohol **2a** in 75% yield and insignificant formation of the allenic alcohol **3a**. The reactions were carried out with **1a** (1.0 equiv) using excess (3.0 equiv.) of Zn-dust, metal salts, and propargyl bromide. Next, the generality of the protocol was established by performing the reaction with several aromatic **1b-f** and aliphatic aldehydes **1g-k** under the above conditions. The aromatic substrates differed in terms of presence of either electron-withdrawing or donating substituents at different positions of the phenyl moiety, while the aliphatic substrates were of varied alkyl chain lengths. The synthetic scheme (**Scheme II.3.2.**) and combined results (**Table II.3.1.**) of the investigations are shown below.



Scheme II.3.2. Carbonyl propargylation using the bi-metallic strategy.

Table II.3.1. Reaction course of propargylation[a]

Entry	Aldehyde	Reagent	Time (h)	Yield (%)	**2:3**[b]
1	PhCHO (**1a**)	1	3	75	95:5
2	PhCHO (**1a**)	2	5	81	100:0
3	3-Br-PhCHO (**1b**)	1	14	84	100:0
4	3-Br-PhCHO (**1b**)	2	14	81	88:12

5	3-MeO-PhCHO (**1c**)	1	14	81	100:0
6	3-MeO-PhCHO (**1c**)	2	14	87	89:11
7	4-Br-PhCHO (**1d**)	1	3	81	85:15
8	4-Br-PhCHO (**1d**)	2	5	85	54:46
9	4-Et-PhCHO (**1e**)	1	15	89	94:6
10	4-Et-PhCHO (**1e**)	2	16	86	100:0
7	4-EtO-PhCHO (**1f**)	1	16	80	93:7
8	4-EtO-PhCHO (**1f**)	2	14	81	100:0
9	*n*-C_4H_9CHO (**1g**)	1	1	79	86:14
10	*n*-C_4H_9CHO (**1g**)	2	3	73	88:12
11	*n*-C_6H_{13}CHO (**1h**)	1	4	77	94:6
12	*n*-C_6H_{13}CHO (**1h**)	2	7	81	68:32
13	*n*-C_8H_{17}CHO (**1i**)	1	4	95	94:6
14	*n*-C_8H_{17}CHO (**1i**)	2	8	83	93:7
15	*n*-C_9H_{19}CHO (**1j**)	1	16	98	95:5
16	*n*-C_9H_{19}CHO (**1j**)	2	17	97	91:9
17	*n*-$C_{11}H_{23}$CHO (**1k**)	1	18	93	97:3
18	*n*-$C_{11}H_{23}$CHO (**1k**)	2	18	92	83:17

[a]All reactions were carried out in moist THF on a 2 mmol scale at 25 ^oC. [b]Based on the ^1H NMR spectra of the products. *Reagent 1*: Zn/$FeCl_3$; *Reagent 2*: Zn/$SnCl_2.2H_2O$.

All the reactions proceeded uneventfully, albeit at different rates using both reagents giving good yields of the desired products **2a-k**. Both the reagents showed similar results, although in certain cases the reactions with *reagent 2* were marginally

slow. Amongst the substrates, **1b**, **1c**, and **1k** furnished 11-17% of the corresponding allenic alcohols with *reagent 2* (entries 4, 6 and 18). On the other hand, the aldehydes **1d** and **1h** furnished appreciable amounts of the undersired alcohols **3d** and **3h** with *reagent 2* (entries 8 and 12). The regio-selectivity of the propargylation with **1g** was moderate, irrespective of the reagent used (entries 9 and 10). Among the chosen substrates, two aromatic (**1a** and **1d**) and three aliphatic (**1g-i**) aldehydes reacted faster, while the others reacted somewhat sluggishly in the presence of both the reagents. Unfortunately, no reaction took place with any of the aldehydes **1a–k** with $CuCl_2.2H_2O$/Zn combination. This is in marked contrasts to other reactions done earlier under similar reactions condition.[41b–d]

The ratios of the homopropargyl alcohols (**2a-k**) and the allenic alcohols (**3a-k**) were determined from the ^{1}H NMR integrations of the carbinol protons of homopropargyl and allenic alcohols of the respective mixtures. The carbinol proton resonances appeared at different δ values for the homopropargylic and allenic alcohols, and that also differed for the aromatic and aliphatic products. For the aromatic homopropargylic and allenic alcohols, the resonances were at δ 4.86 and δ 5.44 respectively. For the aliphatic alcohols the corresponding resonances were at δ 3.76 and δ 4.17 respectively. Formation of the homopropargyl alcohols **2a–k** was confirmed from the alkyne IR bands at ~3300 cm^{-1} (C-H stretching) and at ~2100-2260 cm^{-1} (C≡C stretching) and appearance of ^{1}H NMR triplets at ~δ 2.07 (C≡C-**H**) and multiplets at ~δ 2.36-2.40 (-C**H**$_2$-C≡C-) and the ^{13}C resonances at δ ~65 and ~80 (C≡C). The ^{1}H NMR resonances of the allenic moiety in **3a–k** alcohols appeared at ~δ 4.95 (m, -C=C=C**H**$_2$) and ~δ 5.24 (m, C**H**=C=C-), while the ^{13}C resonances appeared at δ ~94 and ~207. The representative ^{1}H and ^{13}C NMR for the reaction of **1d** and **1h** are shown in **Figures. II.3.1.-II.3.4**. Overall, an operationally simple and potentially

scalable propargylation protocol with high chemo-selectivity was developed using inexpensive materials.[42]

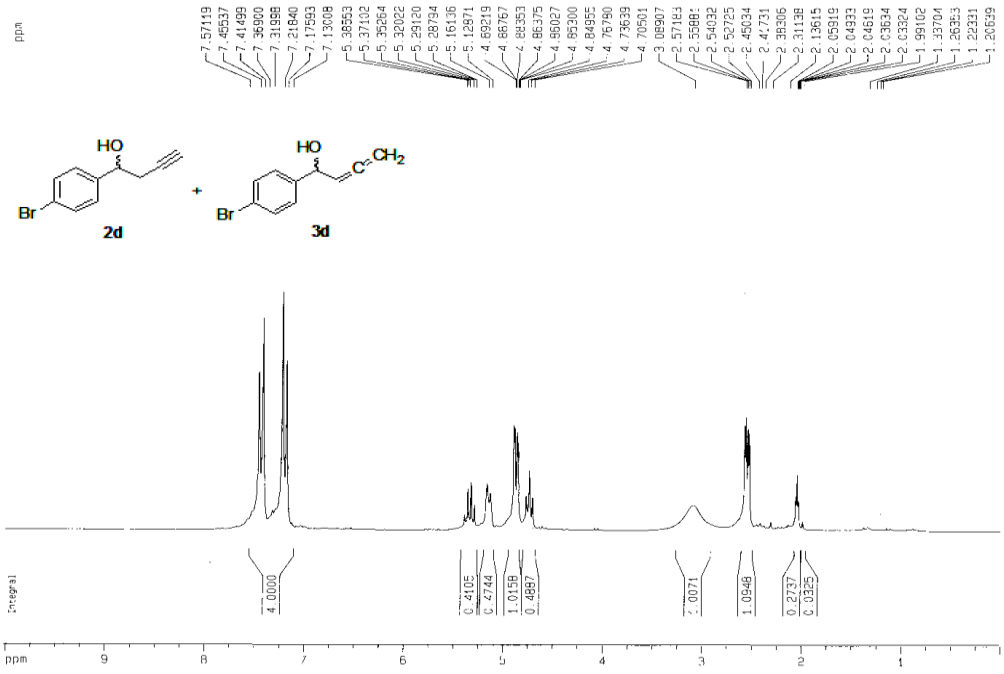


Figure II.3.1. ^{1}H NMR spectrum for reaction of **1d** with *reagent 2*

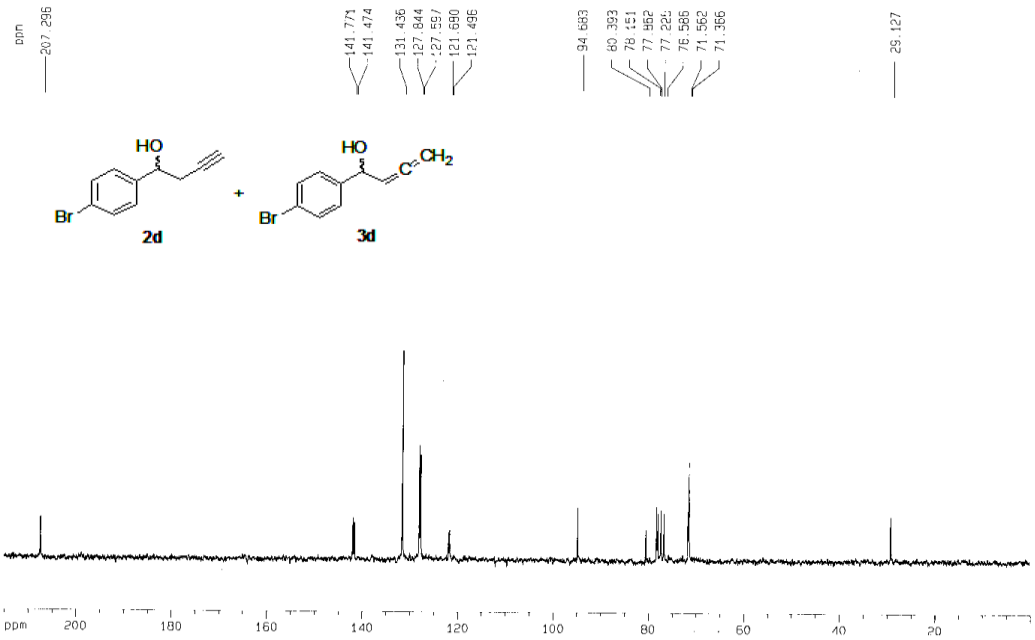


Figure II.3.2. ^{13}C NMR spectrum for reaction of **1d** with *reagent 2*

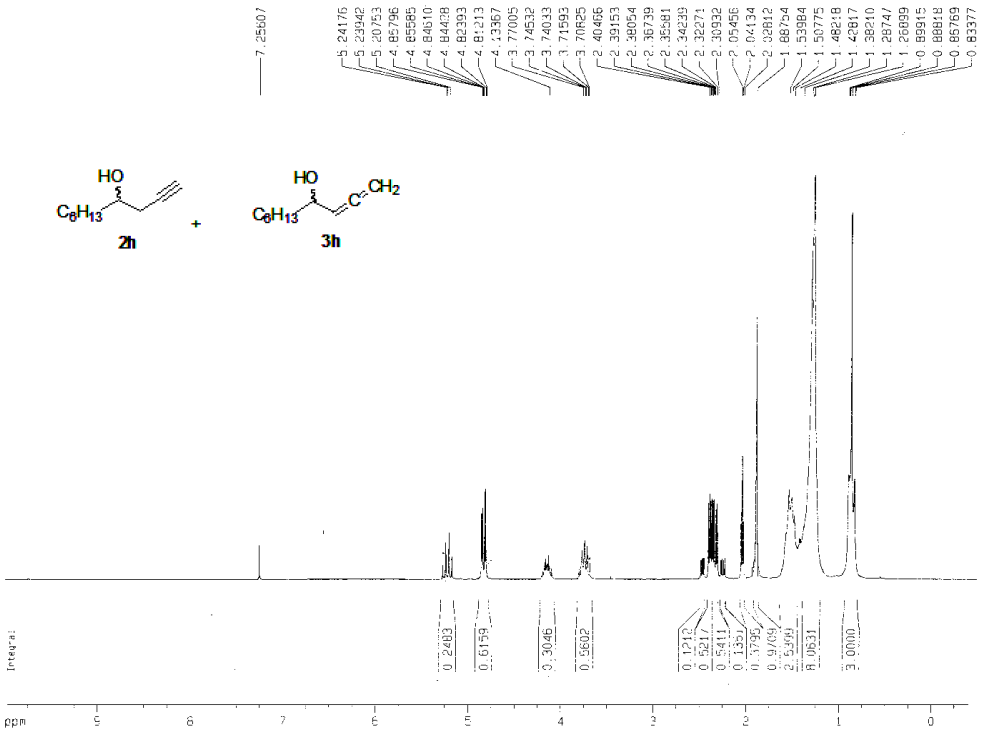


Figure II.3.3. ^{1}H NMR spectrum for reaction of **1h** with *reagent 2*

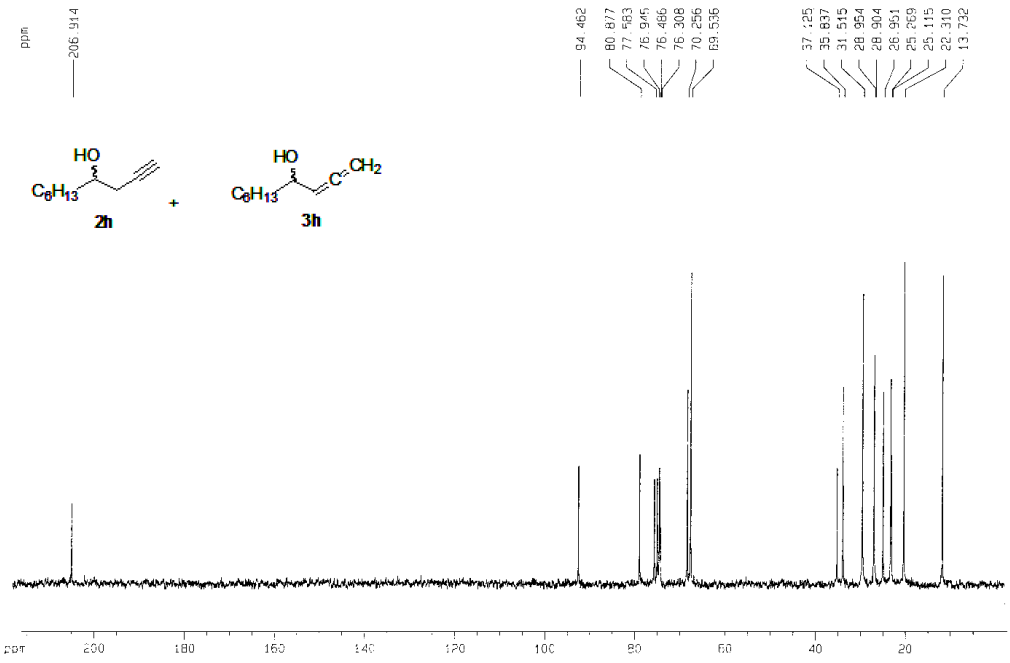
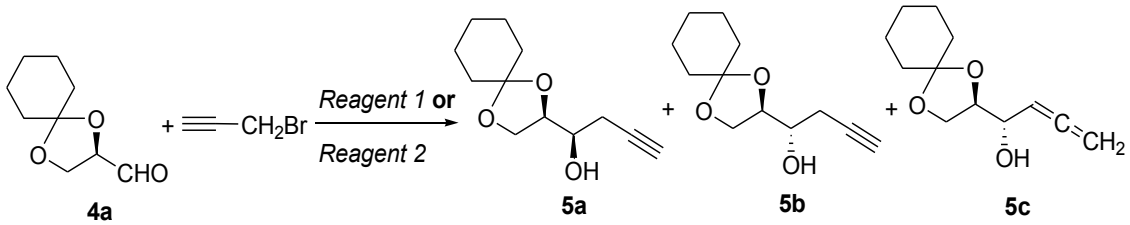


Figure II.3.4. ^{13}C NMR spectrum for reaction of **1h** with *reagent 2*

***Diastereoselective propargylation*:** The diastereoselectivity of aldehyde propargylation reactions, in many occasions, are only moderate, in particular in reactions with aldehydes lacking α-branches or advanced aldehyde intermediates.[43] Furthermore, the requirement of strong Lewis acids to attain *syn*-selectivity is often incompatible with ornately functionalized aldehyde substrates. Moreover, highly diastereoselective syntheses of the *anti*-homopropargyl alcohol stereoisomers via these procedures are generally lacking. Therefore, the development of a mild, highly diastereo- and enantioselective carbonyl propargylation reaction remains an important objective.

Hence, a substrate-controlled method using a natural chiral pool-derived template with the above bimetallic strategy was attempted. The aldehyde **4a** appeared to be a good template for this, as it is enriched with diverse functionalities, and both (*R*)- and (*S*)-**4a** are amenable from the inexpensive D-mannitol and L-ascorbic acid respectively.[44] Further, its cyclohexylidene moiety provides considerable steric bias in the addition of organometallics to its aldehyde function, and ensures easy separation of the resultant epimeric carbinols by column chromatography. To probe this, compound **4a** was subjected to propargylation as above (**Scheme II.3.2.**), and the results are shown in **Table II.3.2**. For this, besides Zn-metal, Al foils were also used to reduce $SnCl_2.2H_2O$ (entry 2). The reaction was much faster with this combination. All the reactions produced the homopropargylic alcohol in appreciable yield (75-80%) without formation of the allenic alcohol **5c**, but with a moderate diastereoselectivity. Fortunately, the resultant *syn* and *anti*-epimers, **5a** and **5b** were easily separated by column chromatography.



4a 5a 5b 5c

Scheme II.3.2. Diastereoselectivity of propargylation of **4a** by the bi-metallic strategy.

Table II.3.2. Reaction course of propargylation of **4a**[a]

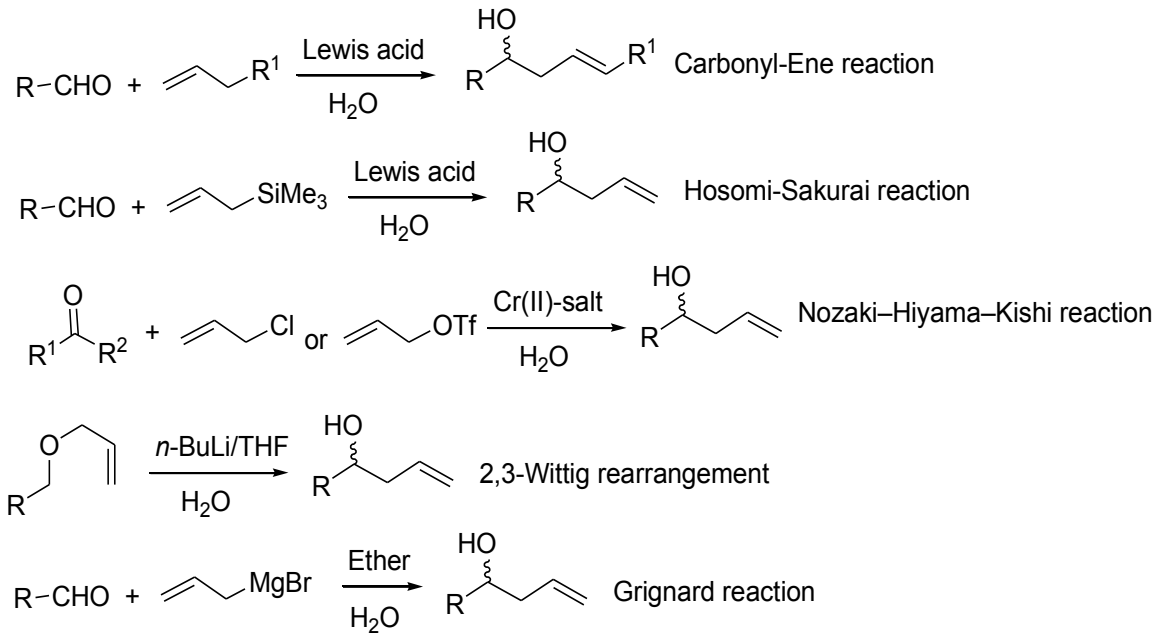
Entry	M_1X/M_2	Time (h)	Yield (%)	**5a:5b**[b]
1	$SnCl_2.2H_2O/Zn$	3	78	25:75
2	$SnCl_2.2H_2O/Al$	0.5	80	24:76
3	$FeCl_3/Zn$	2	75	12:88

Mechanistic considerations. The amount of moisture content in distilled THF ensured partial (Cu) and good (Fe and Sn) solubility of the metal salts in the reaction medium. This, in turn, facilitated bimetal redox reactions and subsequent C–C bond formition. This was ascertained from the fact that no reaction was observed earlier, when attempted in anhydrous THF employing this strategy.[41b–h] The predominant formation of the homopropargyl alcohols may be due to higher reactivity of both propargyl-Fe and propargyl-Sn reagents with the aldehyde substrates *vis-à-vis* that of their conversion into the corresponding allenyl metal reagents.

II.4: Allylation of Carbonyl Compounds: Importance and synthetic strategies

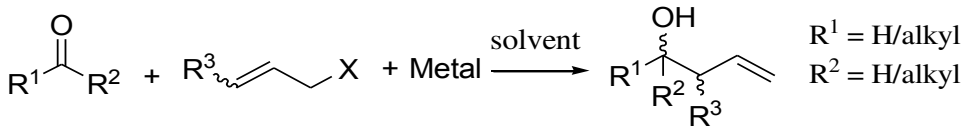
II.4.1. Importance: Allylation of carbonyl compounds is mechanistically similar to the analogous propargylation reaction, but more widely pursued. This is because the terminal alkene moiety of the resultant carbinols is amenable to a wider variety of chemical transformations such as ozonolysis, hydroboration, cycloaddition, hydroformylation and olefin metathesis. In addition, Sharpless' asymmetric dihydroxylation and epoxidation of the alkene function are extensively used to generate multiple stereogenic centres. Furthermore, alkenes are widely distributed in many biological active molecules like macrolides, polyhydroxylated natural products, polyether antibiotics and alkaloids.[45]

II.4.2. Synthetic strategies: Various methods such as carbonyl-ene reaction,[46a] Hosomi-Sakurai reaction,[46b] Nozaki-Hiyama coupling reaction,[46c] 2,3-Wittig rearrangement, Grignard addition etc. have been developed for the synthesis of homoallylic alcohols (**Scheme II.4.1.**). Several of these are useful in diastereoselective syntheses. However, these reactions are invariably carried out in anhydrous organic solvents and require chiral catalysts.



Scheme II.4.1. Some non-Barbier type carbonyl allylation protocols.

Instead, the Barbier type metal-mediated strategy is most popular for allylation of aldehydes due to better efficiency and ease of operation. While the reaction allyl halides generates a stereogenic carbinol centre, the γ-substituted allyl halides (R-CH=CHCH$_2$X, R = Aryl, alkyl; X = Cl, Br) produce two stereogenic centres due to the allylic rearrangement in the allylic-metal reagents (**Scheme II.4.2.**). More importantly, use of a chiral auxiliary and/ or presence of a chiral moiety in R^1/R^2 can proceed with diastereoselectively to furnish the homoallylic alcohols with good to excellent enantiselectively.



Scheme II.4.2. Reaction course in Barbier-type carbonyl allylation.

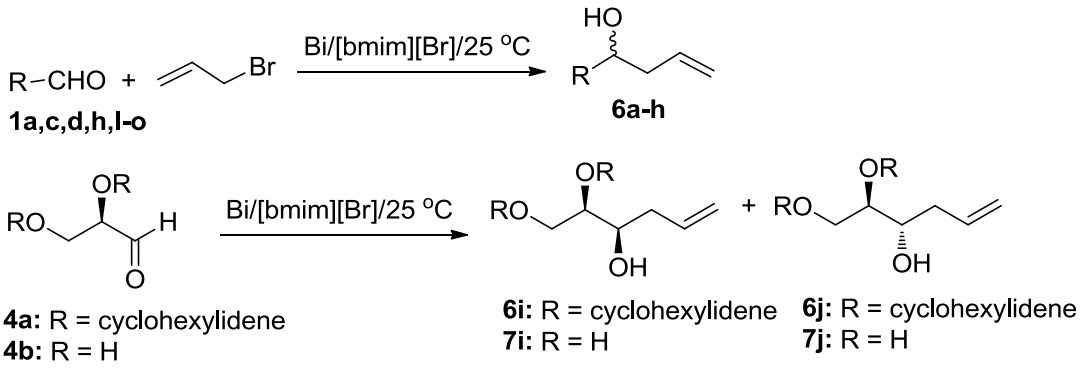
II.5: Present Work: A Bismuth-mediated Carbonyl Allylation Protocol

Despite impressive progress, the need for an environmentally benign diastereoselective allylation was felt. This prompted us to explore the possibility of using Bi-mediated allytaion in a room temperature ionic liquid (RTIL). Towards controlling the disateroeslectivity, allylation of **4a** and its congener **4b** was planned, while the combination of Bi-RTIL appeared well-suited for a green synthetic route. Green chemistry plays an important role in reducing and eventually eliminating the impact of chemical industries on the environment. Bismuth (Bi) metal is one of the best options to develop to develop green chemical synthetic routes. Bi is an inexpensive, safe and environmentally benign metal. It is also used in cosmetics and anti-viral creams, and as a component of an oral gastrointestinal formulation.[47] The readily available Bi powder has been used for allylation of aldehydes in organic solvents (DMF, THF and acetonitrile),[48a-c] water,[48d] and under solvent-free conditions.[48e] New protocols for metal activation such as use of bimetallic systems (Al–$BiCl_3$ and Zn–Bi-trihalides),[48b,49a-d] nanometer-sized Bi,[49e] as well as ball milling[49f] have been used to carry out the Bi-mediated carbonyl allylation.

Currently, the room temperature ionic liquids (RTILs) have emerged as good, eco-friendly, alternative reusable solvents for a wide range of organic transformations.[50] These have excellent stability to air, moisture and heat, possess very low vapor pressure, and can dissolve various organic and inorganic materials.[51] The RTILs are easy to prepare, and their properties can be tailored by changing the ionic components. The hydrophobic RTILs are preferred for carrying out various organic reactions including the Barbier-type protocols. However, we have shown that due to its stronger oxidizing power and moderate acidity, the hydrophilic RTIL, [bmim][Br] can act both as a solvent and a metal activator in the Ga-mediated

allylation/crotylation of various aldehydes including **4a** even at room temperature.[52] The key issue for this type of transformations is metal activation that is usually accomplished by Rieke's activation method,[53a] the metal−graphite method,[53b] and addition of a catalytic amount of a second metal to the target metal.[53c−h] Indeed, different strategies have also been adopted to activate Bi metal.[51,52] It was envisaged that because of its strong oxidizing power (E^o = 0.641 V, measured by cyclic voltammetry using a standard calomel electrode as reference), [bmim][Br] may activate Bi-metal without any additional chemical additive.

To probe this, the Bi-mediated allylation of benzaldeyde (**1a**) was carried out in different media *viz*. THF, H_2O, aqueous THF, DMF and [bmim][Br] at room temperature (RT, 25 ^oC) or with with additional metal activation (**Scheme II.5.1.**). As shown in the summarized results (**Table II.5.1.**), the reaction in DMF at RT was complete in 3 h to furnish **6a** in good yield (65%) (entry 1). However, the reactions in MeCN/THF/aqueous THF/H_2O were incomplete even after stirring overnight (ON, 18-22 h) at RT and gave lower yields of **6a** (42-68%) (entries 2-5). The reactions in these solvents remained incomplete even after sonication for 4 h (entries 6-9). The reactions carried out overnight in MeCN and THF at RT with aqueous 10% KF as the additive,[54] did not improve the results (entries 10,11). However, in water, marginal metal activation by KF was observed (entry 12). However, the reaction was complete in 3 h in [bmim][Br] furnishing **6a** in 72% yield, as obtaind in 10% aqueous KF (entry 13).



Scheme II.5.1.

Table II.5.1. Reaction course of Bi-mediated allylation of **1a** under different conditions[a]

Entry	Solvent	Time (h)	Conditions	Yield (%)	Completion (%)[b]
1	DMF	3	RT	65	100
2	MeCN	ON	RT	52	70
3	THF	ON	RT	56	60
4	THF:H_2O	ON	RT	60	75
5	H_2O	ON	RT	45	75
6	MeCN	4	Sonication	42	75
7	THF	4	Sonication	48	70
8	THF:H_2O	4	Sonication	65	90
9	H_2O	4	Sonication	48	85
10	MeCN[c]	ON	RT	65	90
11	THF[c]	ON	RT	40	70
12	H_2O[c]	3	RT	72	100
13	[bmim][Br]	3	RT	72	100

[a]All reactions were carried out on a 2 mmol scale using allyl bromide (1.5 equiv.) and Bi metal (1.0 equiv.) with respect to the substrate. [b]Based on disappearance of **1a** as

revealed by thin layer chromatography. [c]The reactions were carried out in the presence of aqueous 10% KF as the additive.

Next its scope was established using various aromatic and aliphatic aldehydes **1c,d,h,l-o**, and the results are summarized in **Table II.5.2**. The reactions were complete with slight excesses of the reagents, allyl bromide (1.5-1.7 equiv.) and Bi-metal (1.3-1.4 equiv.) (entries 2-5,7 and 8) with respect to the substrates. The notable exceptions were for **1a** and **1n** that required only stoichiometric (1.0 equiv.) amount of Bi-metal (entries 1 and 6 respectively). The results are significantly better than those reported so far in most of the Barbier-type allylation protocol. The protocol was equally effective for both aromatic and aliphatic aldehydes. With the aromatic aldehydes, the products **6a-f** were obtained in good (71−78%, entries 1-6) yields. No effect of the presence of any electron-withdrawing or -donating group in the aromatic ring in the reaction outcome was observed. Likewise, the aliphatic aldehydes also furnished the corresponding allylated products **6g,h** in good yields (entries 7,8). The reaction also proceeded with complete chemoselectivity with the conjugated aldehyde **1n**, furnishing the 1,2-addition product **6f** exclusively.

Regarding the asymmetric allylation, the reaction with **4a** proceeded to furnish the alcohol epimers **6i/6j** in 32:68 ratio in 75% yield. However, allylation with the unprotected aldehyde **4b** proceeded with better diasteroselectivity to furnish **7i/7j** in 2:8 ratio, albeit in 45% yield. The distereomeric ratio was confirmed by converting them to the corresponding cyclohexylidene derivatives **6i/6j** and isolating the individual products. The modest yields of **7i/7j** were due to their high polarity that posed problem in isolation from the viscous reaction medium. However, with both **4a** and **4b**, the reaction was accomplished using allyl bromide (1.5 eq.) and Bi (1.0 eq.)

with respect to the substrates. The stereochemistry of **6i** and **6j** was confirmed from their ^{1}H NMR spectra (**Figures II.5.1.-II.5.4.**) as described previously.[24a,e]

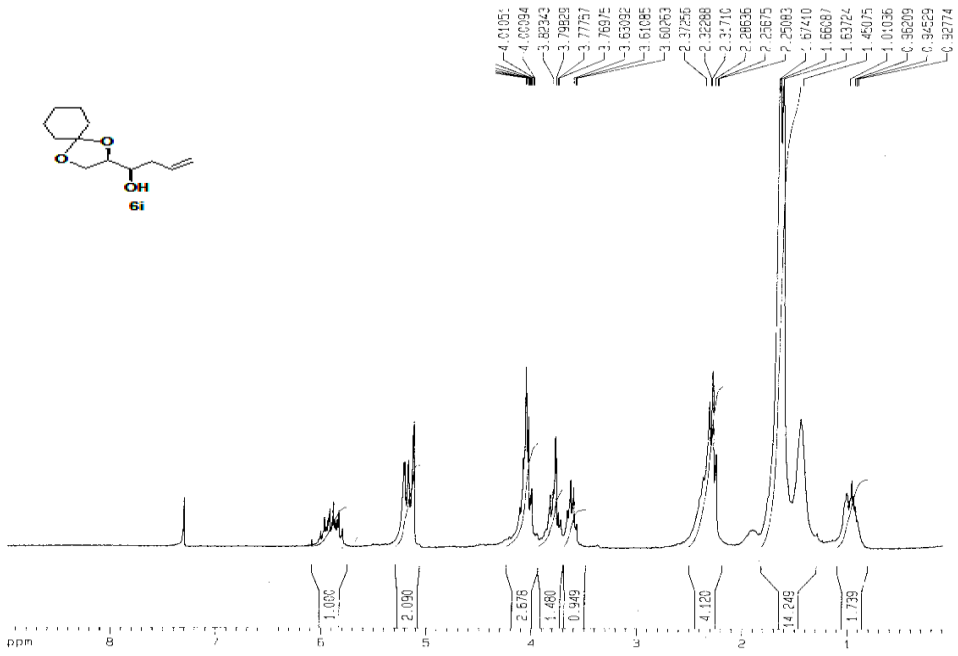


Figure II.5.1. ^{1}H NMR spectrum of **6i**

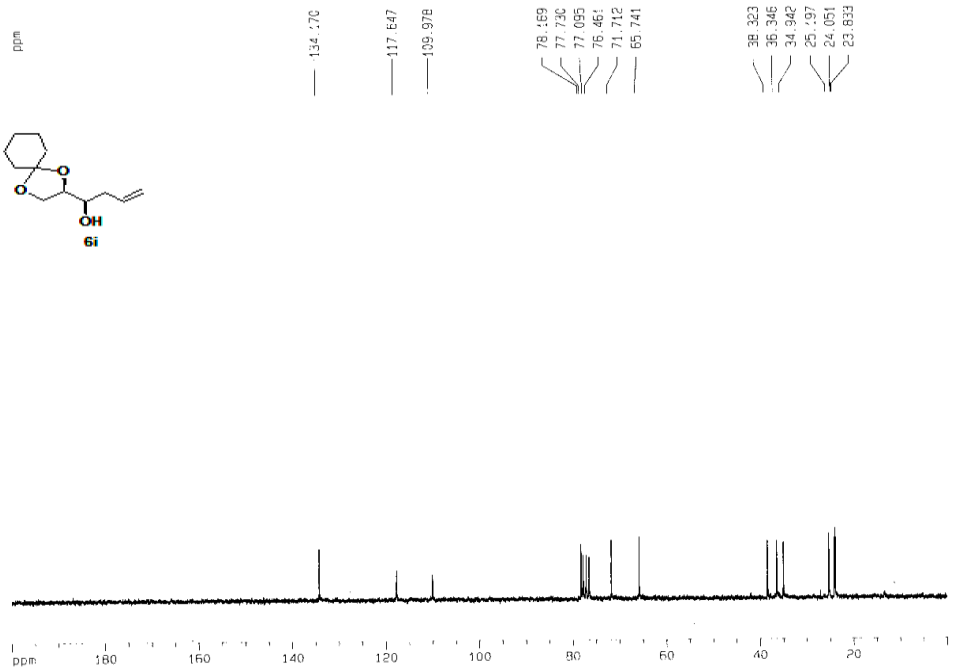


Figure II.5.2. ^{13}C NMR spectrum of **6i**

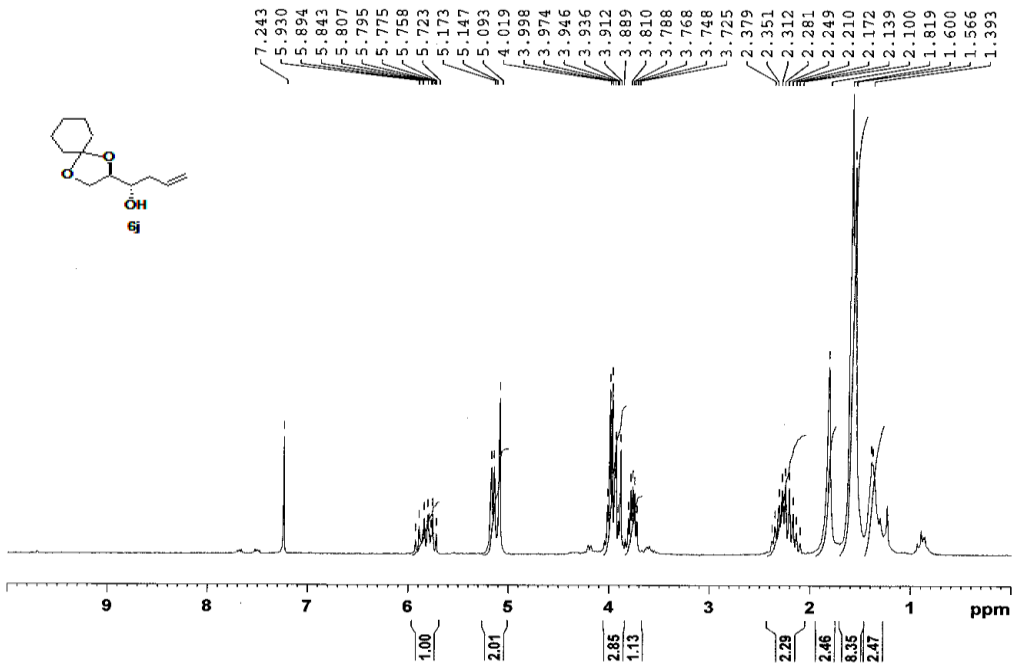


Figure II.5.3. ^{1}H NMR spectrum of **6j**

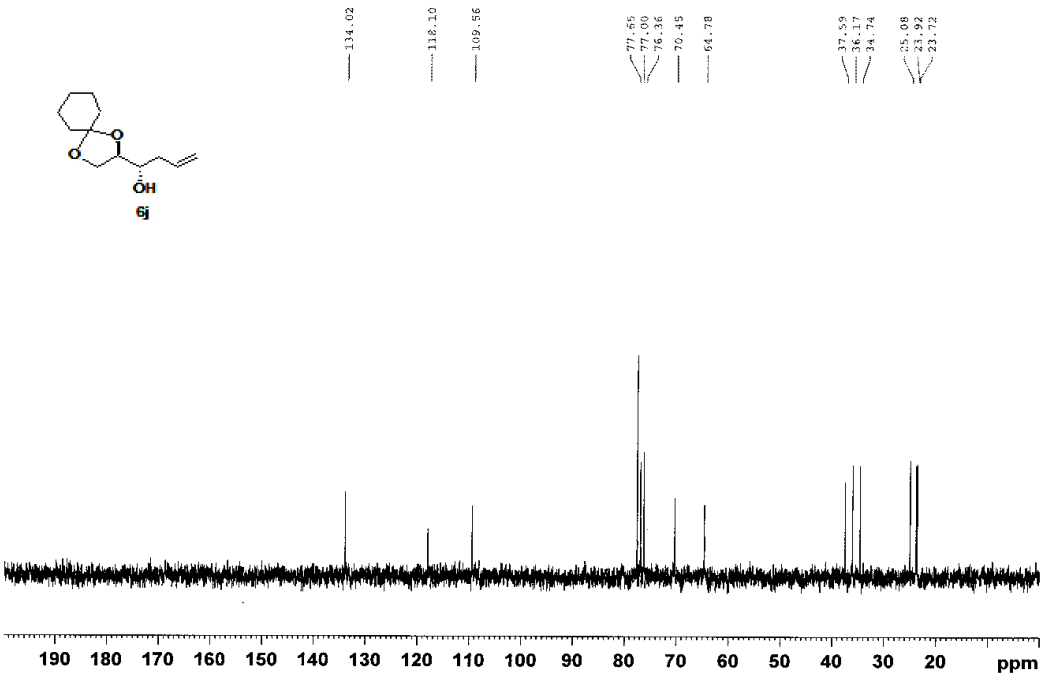


Figure II.5.4. ^{13}C NMR spectrum of **6j**

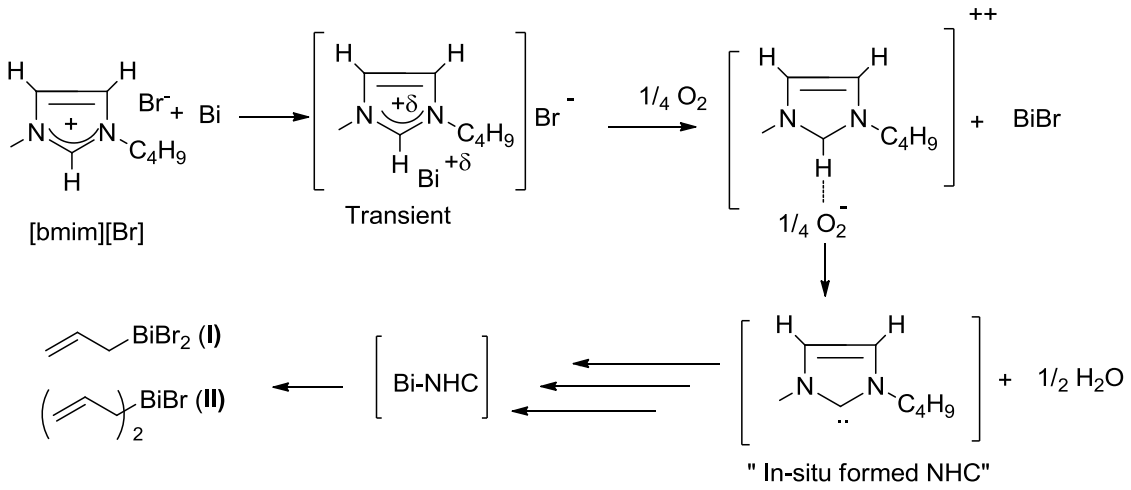
Table II.5.2. Reaction course of Bi-mediated allylation in [bmim][Br][a]

Entry	Substrate	R	Allyl bromide (eq.)	Bi (eq.)	Time (h)	Product	Yield (%)
1	**1a**	Ph	1.5	1.0	3	**6a**	75
2	**1c**	3-MeO-Ph	1.7	1.3	6	**6b**	74
3	**1d**	4-Br-Ph	1.7	1.3	6	**6c**	78
4	**1l**	4-NO_2-Ph	1.7	1.3	3	**6d**	74
5	**1m**	4-MeO-Ph	1.7	1.3	3	**6e**	74
6	**1n**	PhCH=CH	1.5	1.0	3	**6f**	71
7	**1h**	n-C_5H_{11}	1.5	1.4	3	**6g**	71
8	**1o**	n-C_6H_{13}	1.5	1.4	6	**6h**	66

[a]All reactions were carried out on a 2 mmol scale at RT [bmim][Br] (3 mL/mmol).

***Mechanistic aspects*:** With regard to the activation of Bi metal, we envisaged a dipole induced dipole interaction with [bmim][Br]. After incubating Bi (1.0 mmol) in [bmim][Br] for 30 min, the ^{1}H NMR spectrum of the reaction mixture showed upfield shifts of the [bmim][Br] protons, with maximum shifts for H-2 (20 Hz), and H-3 and H-4 (each 18 Hz). As expected, considering the maximum positive charge density at C-2 of the imidazole ring, the shifts gradually decreased with increasing distance of the protons from the imidazolium core. Likewise, the terminal –CH_3 protons of the butyl chain showed minimum shift. Since such magnitudes of ^{1}H NMR shifts are generally attributed to charge transfer phenomenon,[55a-c] it is proposed that the combination of Bi and [bmim][Br] initially forms ion pairs with an activated Bi. This is consistent with the remarkable ability of the imidazolium-based ILs to promote

electron transfer reactions.[55d-f] Earlier, the dipole induced dipolar interaction between Ga and [bmim][Br] helped in the transfer of one electron to the oxygen dissolved in the RTIL.[52b,56] The resultant superoxide radical anion is stabilized by the acidic C-2 hydrogen of [bmim][Br], facilitating the process.[57] The hypothesis was substantiated from the fact that the reaction is possible only in [bmim][Br], but not in [bmim][BF_4] and requires the presence of O_2 (data not shown). Possibly, the non-acidic nature of C-2 hydrogen of [bmim][BF_4] prevented electron transfer from Bi to O_2, precluding the reaction. As observed with Ga, this may lead to an *N*-heterocyclic carbene (NHC), which would form a NHC-Bi complex. Due to poor stability of the sterically less hindered cyclic NHCs, the complex would eventually furnish the active crotyl-Bi species (**Scheme II.5.2.**). Although we could not isolate any NHC-Bi complex, the proposed type of reaction is well established in M-NHC chemistry, but the mechanism remains unclear.[58] Our hypothesis of direct adduct formation of an NHC with Bi metal-is based on fast chemical conversion of imidazolium ion to the NHC on the surface of a nanoparticle.[59] Moreover, a similar oxidative addition of the imidazolium salts to Pt(0) was shown to be exothermic by DFT calculations.[60] However, without clear evidence, any further mechanistic rationalization of the of Bi-metal activation by [bmim][Br] would only be hypothetical.



Scheme II.5.2. Probable mechanism of Bi activation by [bmim][Br].

Next we probed the nature of the organometallic species responsible for the reaction. To this end, we attempted to identify the allyl-Bi reagent by *in situ* ^{1}H NMR spectroscopy of the reaction mixture, comprising of allyl bromide and Bi in [bmim][Br]. For this, the mixture was stirred for 1 h at 25 ^{o}C, and the ^{1}H NMR spectra of the aliquots in CD_2Cl_2 were recorded as such or after cooling the sample to -70 °C. The ^{1}H NMR spectrum, recorded at room temperature did not show any additional peak corresponding to the allyl-Bi species. However, the spectrum recorded after cooling the sample to -70 ºC showed two doublets sat δ 2.45 and δ 2.61, in 1:2 ratio, along with new olefinic multiplets at δ 5.19, 6.35 and 6.70, indicating formation of a η^1-Bi-allyl coordination complex. This is consistent with the fluxional behaviour, reported earlier for the crotylbismuth species.[61] We assigned formation of a η^1-complex, since the ^{1}H NMR spectrum of the alternative η^3-complex would be broad without well-defined peaks, unlike that observed in this study.

We excluded the possibility of formation of tris(allyl)-bismuth as the reported[61] doublet at δ 2.33 due to its allylic protons was absent in the ^{1}H NMR spectrum of the reaction mixture before addition of the aldehydes. Instead, formation of allylbismuth dibromide (**I**) and diallylbismuth bromide (**II**) (in 2:0.5 ratio) was

inferred. The structures of the allyl-Bi specie are shown in **Scheme II.5.2**. Earlier, we could carry out the Ga-mediated allylation of aldehydes/ketones using 0.5 eq. of Ga-metal, due to formation of diallyl-GaBr as the active allylating species.[52a] Given that one mole of **II** is expected to react with two moles of the aldehydes, the possibility of substoichiometric amount of Bi-metal was explored using **4a** as the substrate. However the reaction was incomplete, indicating the lower reactivity of **II** compared to **I** in the reaction mixture. Consistent with this, presently 1.0-1.7 equiv. of Bi-metal was required for the completion of the reaction with all the substrates. A recent report described **I** as the most active allylating species in water medium.[49d] In analogy, we presume that **I** is also the active species for the present protocol.

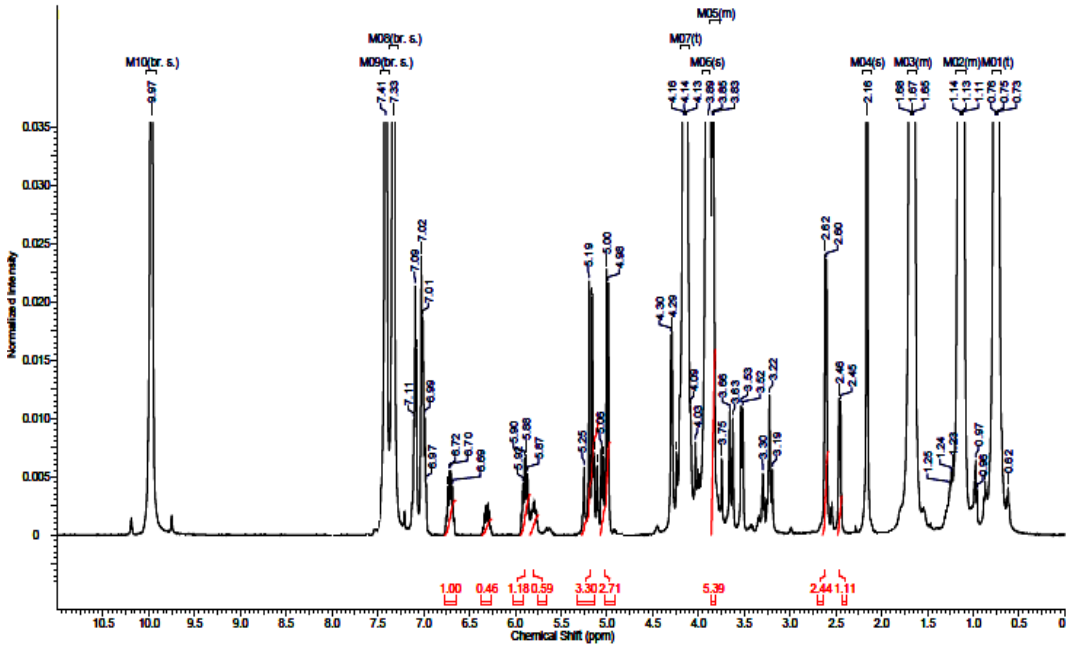


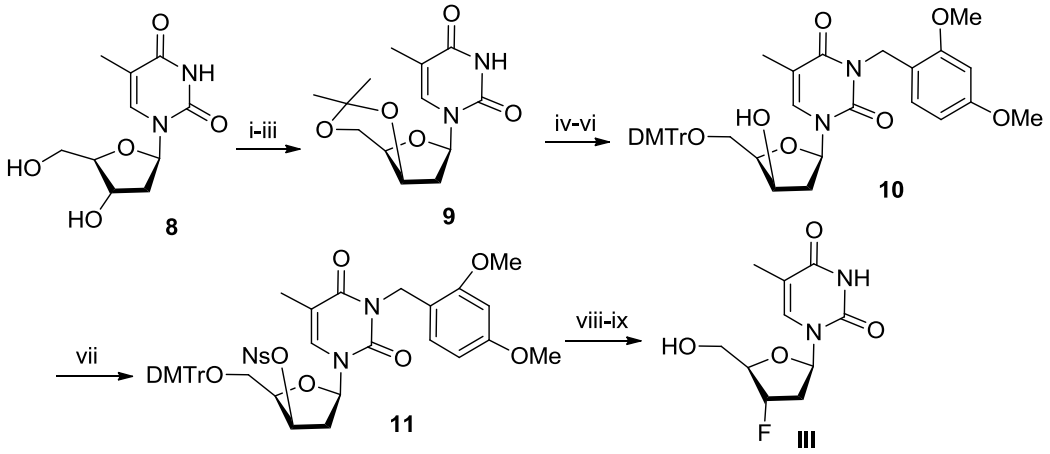
Figure II.5.5. ^{1}H NMR spectrum of allyl-Bi species, generated in [bmim]Br

II.6: 3´-Deoxy-3´-^{18}F-fluorothymidine (^{18}F-FLT): Importance and Synthetic Strategies

***II.6.1. Importance*:** Molecular imaging tools have gained importance for tumor detection and assessment of its prognosis as well as development of therapeutic strategies. To this end, positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is being extensively used in clinical practice for diagnosis, staging and restaging of a wide variety of tumor types, and in the evaluation of the treatment regime. However, ^{18}F-FDG may not be tumor-specific, since glucose is metabolized in all types of cells. Instead, a ^{18}F-radio-labeled thymidine analog is hypothesized to be an alternative to ^{18}F-FDG for in vivo imaging of proliferating tissues and malignant tumors. The hypothesis is based on that fact that the measurement of tumor growth and DNA synthesis are attractive targets for imaging in clinical oncology. Fluorothymidine (FLT), a nucleoside thymidine analog is a substrate for thymidine kinase 1 (TK1) and TK1 activity is thought to be proportional to cellular proliferation and DNA synthesis.[62] Hence the thymidine analog, 3'-deoxy-3'-^{18}F-fluorothymidine (^{18}F-FLT, **III**) has been proposed as an alternative to ^{18}F-FDG for in vivo imaging of proliferating tissues and malignant tumors.[63] The hypothesis is based on the premises that the cellular concentration of FLT is proportional to TK1 activity, and therefore, to cellular proliferation. Being a substrate for only TK1, but not for mitochondrial TK2, it is a more specific tracer for assessing cellular proliferation. FLT permeates the cell membrane by a carrier-mediated mechanism, as well as by facilitated diffusion.[64] Because the fluorine is placed at the 3'-position in the sugar, **III** may function as a terminator of the growing DNA chain, ensuring its insignificant accumulation in DNA. But it will be retained in the cells due to the TK-1 (an S-phase specific enzyme)-catalyzed phosphorylation to

3-fluorothymidine MP (FLT-MP).[65] The phosphorylation results in intracellular trapping of FLT-MP that is not significantly degraded in vivo as it is not a substrate for thymidine phosphorylase. As a result, it is retained in the cells without being incorporated into the DNA due to the substitution of OH with ^{18}F in the 5-prime position.

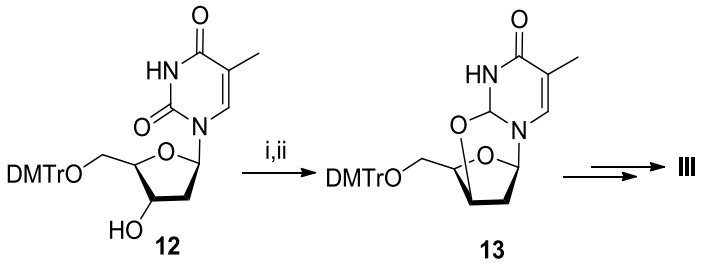
II.6.2. Synthetic Strategies: Considerable interest in FLT as an imaging agent has been developed over the past decade. Synthesis of **III** can be achieved by nucleophilic substitution at C-3 of a suitable thymidine precursor with F^- followed by deprotection and HPLC purification. However, the seemingly simple synthesis is fraught with several key issues such as good radiochemical yield and ease of automation in the process. The low radiochemical yields of many of the existing methods have been a major obstacle in its routine use as a PET imaging agent. Therefore a convenient synthetic scheme with short reaction steps from a suitable precursor is desirable. The first practical synthesis of ^{18}F-FLT was short, but the radiochemical yield was low.[66a] Subsequently another synthesis used a precursor having a nosyl (Ns) group at 3′O position, O-4,4′-dimethoxytrityl (DMTr) group at 5′O position and a 2,4-dimethoxybenzyl protection at 3-N (**Scheme II.6.1.**). However, this involved seven long chemical reaction steps for precursor synthesis followed by three more steps for ^{18}F-labeling. Moreover, the final deprotection step involved use of ceric ammonium nitrate (CAN) resulting in precipitation of ceric salt and causing problems in the automated synthesis.[66b]



i) DIAD/Ph_3P/MeCN/-15 ^oC/H_2O; (ii) LiOH/H_2O/acidic resin; iii) Acetone/PPTS/reflux, iv) 2,4-Dimethoxybenzyl chloride/ K_2CO_3/methyl ethyl ketone/reflux/phase transfer catalyst, v) EtOH/H_2O/PPTS/reflux; vi) DMTrCl/ pyridine, vii) 4-NBSCl/ AgOTf/pyridine/0 ^oC, viii) K_2CO_3/KR/^{18}F-fluoride (n.c.a.)/MeCN/100 ^oC, (ix) CAN/ MeOH/EtOH/H_2O/100 ^oC; HPLC.

Scheme II.6.1.

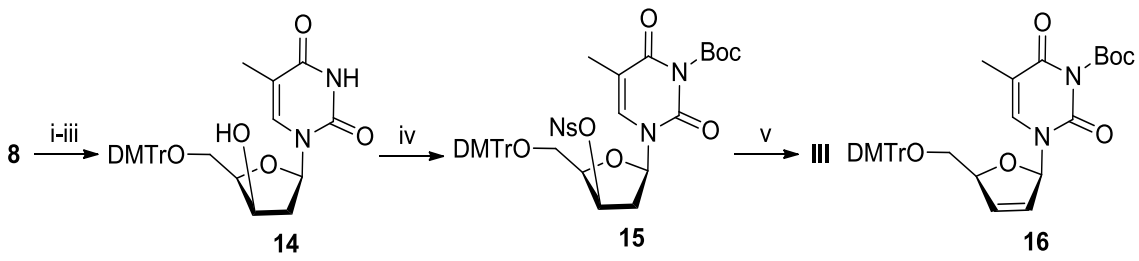
A few syntheses of **III** reported thereafter with minor alterations did not offer any significant advantage and are not discussed.[66c,d] In a conceptually different synthesis, 2,3′-anhydro-5′-O-DMTr thymidine was used as the precursor (**Scheme II.6.2.**).[66e] As an activated electrophilic group, the anhydro group facilitated nucleophilic substitution with ^{18}F, while protecting the 3-N group also. However its reduced nucleophilic character required high temperature for the removal, and the use of high boiling solvents like DMF and DMSO posed difficulty in final HPLC purification. A Ns precursor with an *N*-Boc-protecting group on the pyrimidine ring gave the best results and also provided the advantage of one step hydrolysis for the Boc group in a homogeneous solution.



(i) MsCl/ Et_3N; (ii) DBU

Scheme II.6.2.

In their effort, Martin *et al*.[66f] screened different protecting groups like mesyl, tosyl and nosyl group at the 3′O position and DMTr and trityl groups at the 5′O position for the synthesis of **III**. In the latest synthesis of **III**, the 5′-hydroxy group of thymidine (**8**) was protected with DMTrCl followed C-3 epimerization to obtain **14**. This was nosylated and its pyrimidine NH group protected with *t*-BOC anhydride to afford compound **15**. This on ^{18}F-fluorination and acidic hydrolysis furnished **III**. Attempted direct fluorination of the nosylated product of **14** (without Boc protection) with BuN_4F led to substantial elimination to furnish 3′-deoxy-5′-*O*-DMTr-thymidinene (**16**) as the major product with very little amount of **III** (**Scheme II.6.3.**).[66g]



i) DMTrCl/pyridine/0 ^{o}C, (ii) MsCl, iii) 10N NaOH/EtOH; iii) 4-NBSCl/AgOTf/pyridine/0 ^{o}C, v) (*t*-Boc)$_2$O/ THF, vi) ^{18}F-fluoride/K_{222}/MeCN; 1N HCl.

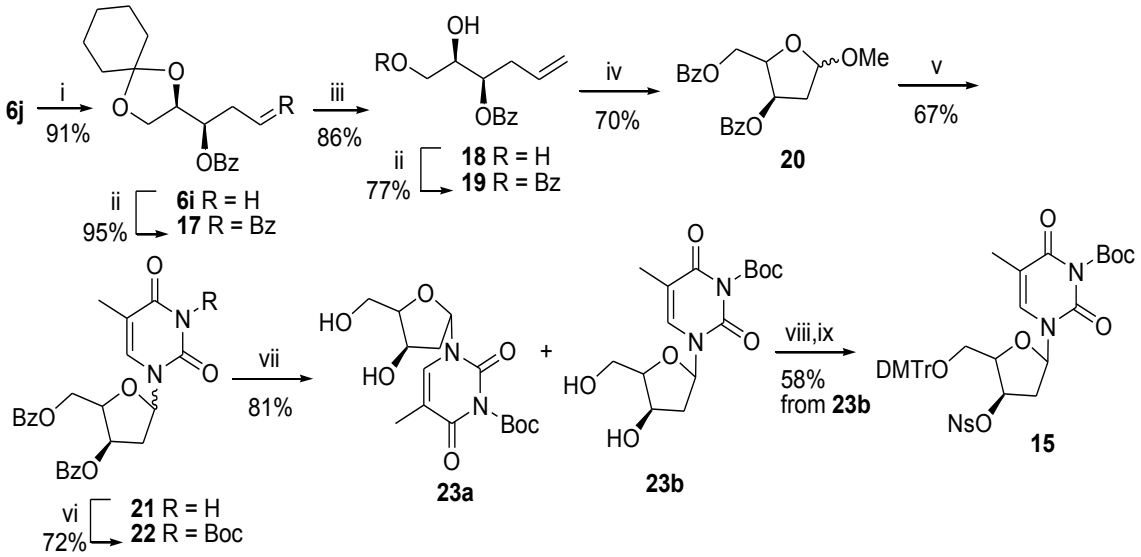
Scheme II.6.3.

II.7: Present Work: Chiral Template-driven Synthesis of a ^{18}FLT Precursor

Because of the low half-life (110 min) of ^{18}F, compound **III** needs to be synthesized just prior to use from its precursor. In the light of previous reports, compound **15** is considered as an advanced precursor of **III**. From the foregoing it is evident that the earlier syntheses of **III** were accomplished starting from the commercially available, but expensive thymidine (**8**). Hence, in the present effort, it was planned to construct the precursor **15** from the homoallylic alcohol **6j**. The alcohol is easily available by the Ga-mediated allylation of the aldehyde **4a** with allyl bromide.[52a]

For the synthesis, compound **6j** was converted to **6i** by a Mitsunobu inversion.[19c-e] Its benzoylation with BzCN gave the ester **17**. Formation of the benzoate was confirmed from the appearance of the ester IR band (1735 cm^{-1}) in place of the hydroxyl bands, the ^{1}H NMR aromatic resonances and the ^{13}C NMR carbonyl peak at δ 168. This on treatment with aqueous trifluoroacetic acid (TFA) furnished the diol **18**. A strong IR band at 3405 cm^{-1} and a broad ^{1}H NMR signal at δ 2.47 for the OH group in place of the ^{1}H NMR resonances for the cyclohexyl protons confirmed its identity. Benzoylation of **18** as above proceeded chemo-selectively at the primary carbinol site to furnish the mono-benzoylate **19**. This was characterized from the IR hydroxyl stretching band (3455 cm^{-1}) and the NMR resonances for the Bz groups at δ 7.35-7.57 (m), and δ 7.96-8.09 (m) that accounted for 10 aromatic protons and two ester carbonyl groups resonances at δ 166.0 and 166.6 in ^{13}C NMR. Reductive ozonolysis (O_3/Ph_3P) of **19** followed by treatment with MeOH/*para*-toluene sulphonic acid (*p*-TsOH) directly afforded the furanose **20** as a mixture of anomers, which could not be separated by column chromatography. Its formation was revealed from the disappearance of olefinic protons in the ^{1}H NMR spectra and appearance of multiplets

at δ 5.45-5.50 for the anomeric protons. Also, presence of a peak at 3405 cm^{-1} in its IR spectrum confirmed the formation of furanose ring structure. The required introduction of the thymine moiety at the anomeric centre of **20** was achieved in presence of bis-(trimethylsilyl)trifluoroacetamide (BSA) and trimethylsilyl trifluoromethanesulphonate (TMSOTf) to obtain **21**.[67] Next the NH group of the pyrimidine was protected with di-*tert*-butyldicarbonate (Boc_2O) and 4-dimethylaminopyridine (DMAP) to obtain compound **22**. Unlike a previous report,[66g] the Boc protection was achieved smoothly in only 2 h. Debenzoylation of **22** with K_2CO_3/MeOH furnished the corresponding diol anomers. Gratifyingly the α- and β-anomers, **23a** and **23b** respectively were separated at this stage by column chromatography and were obtained in 3:7 ratio (based on isolated yield of the individual isomers).



i) *p*-Nitrobenzoic acid/Ph_3P/DEAD/THF/25 ^oC/20 h; KOH/MeOH/25 ^oC/6 h, ii) BzCN/Et_3N/ CH_2Cl_2/3 h, iii) Aqueous TFA/CH_2Cl_2/25 ^oC/3 h, iv) O_3/Ph_3P/CH_2Cl_2/-78-25 ^oC/18 h; MeOH/*p*-TsOH/25 ^oC/5 h, v) Thymine/ BSA/TMS-triflate/MeCN/25 ^oC/7 d, vi) Boc_2O/DMAP/25 ^oC/2 h, vii) K_2CO_3/MeOH/25 ^oC/5 h, viii) DMTrCl/ pyridine/25 ^oC/12 h, ix) NsCl/pyridine/25 ^oC/22 h.

Scheme II.7.1.

Compound **23b** was used for the synthesis of **III**. Thus, its primary and secondary hydroxyl groups were sequentially protected with DMTrCl and 4-nitrobenzenesulphonylchloride (NsCl) respectively to obtain the desired precursor **15** (**Scheme II.7.1.**). The reaction with DMTrCl proceeded chemoselectively without furnishing any sencondary carbinol protected or diprotected products. Compound **15** was characterized from its NMR spectra (**Figure II.7.1-II.7.2**) that matched very well with the reported values.[66g]

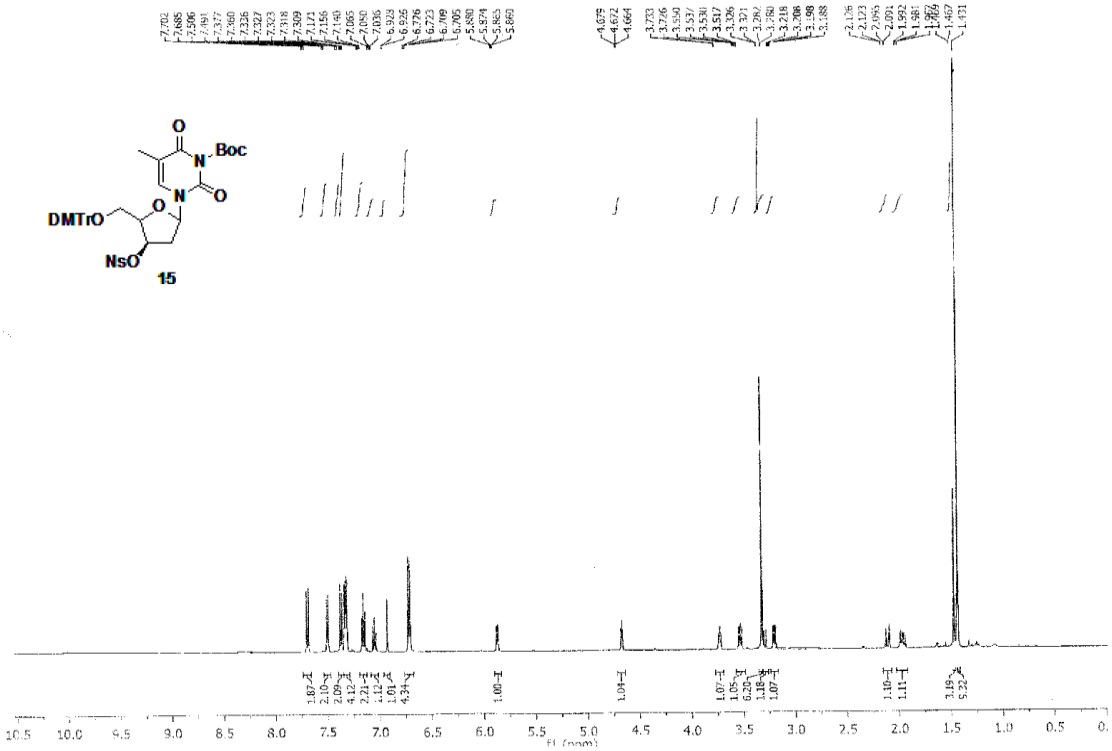


Figure II.7.1. ^{1}H NMR spectrum of **15**

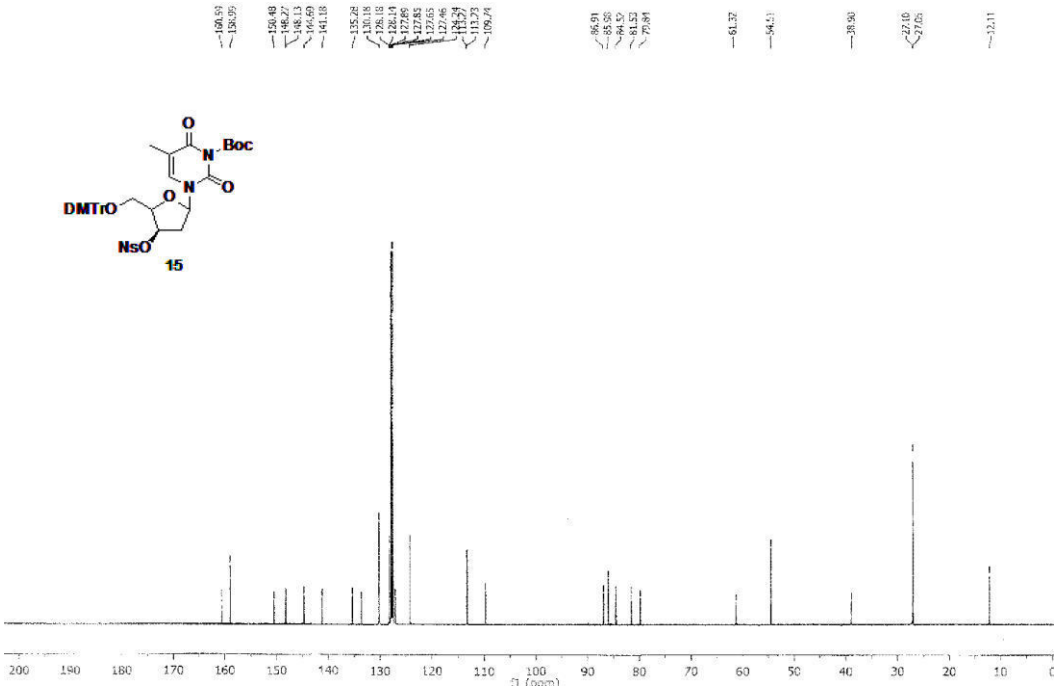


Figure II.7.2. ^{13}C NMR spectrum of **15**

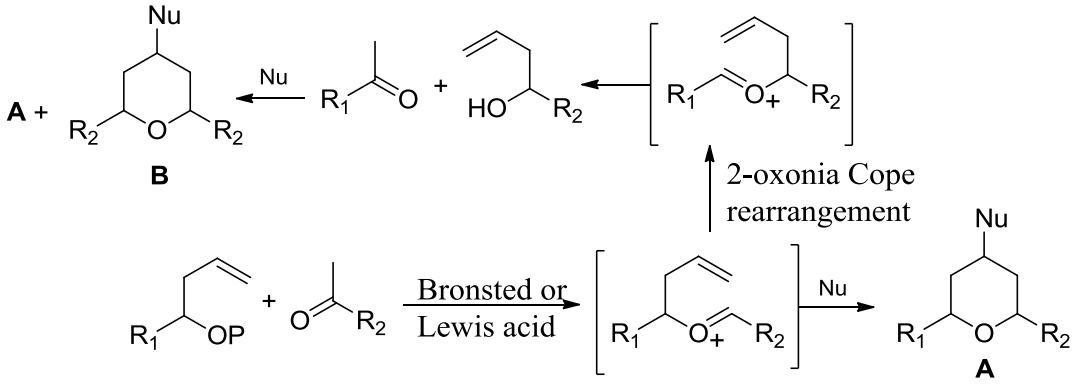
II.8: Tetrahydropyrans (THPs): Importance and Synthetic Strategies

II.8.1. Importance: An ever increasing number of biologically significant natural products, especially those of marine origin, possess functionalized tetrahydropyran rings as critical substructural motifs. Prominent examples include phorboxazoles A and B,[68a] brayostatins,[68b] (-)-centrolobine,[68c] and some pheromones[68d]. Tetrahydropyran derivatives are also used as materials in photographic films[69] and host–guest chemistry.[70] In particular, 2,4,6-trisubstituted tetrahydropyrans such as the 4-oxygenated, 4-halogenated, 4-sulfonyl- and 4-azido/amido tetrahydropyrans are widely present as biologically active core structures.[71]

II.8.2. Synthetic Strategies: Amongst the methods adopted for the construction of THP rings, Prins cyclisation has become most commonplace, undoubtedly because of its convergent and efficient nature for the formation of THP ring. This involves an acid-catalyzed condensation of a homoallylic alcohol with an aldehyde. For this, several Brønsted acids *viz*. TFA,[72a] AcOH, $MeSO_3H$,[72b] $Sc(OTf)_3$,[72c] $O_3ReOSiPh_3$,[72d] TMSBr,[72e] or Lewis acids *viz*. $TiCl_4$,[72f] $AlCl_3$,[72g] $InCl_3$,[72h] $HBF_4{\cdot}OEt_2$,[72i] $InBr_3$,[72j] $TiBr_4$,[72k] Fe(III) compounds,[72l] and $BF_3{\cdot}OEt_2$[72m] have been used. In addition, polymer supported reagents,[73a] $BiCl_3$/microwave[73b] and Pd(0)/Sn(II)-mediated three component cascade coupling[73c] were also employed to effect Prins cyclisation. While different solvents have been screened for the reaction, use of the ionic liquid, 1-n-Butyl-3-methylimidazolium chloroaluminate accelerated the reaction dramatically even at room temperature.[73d]

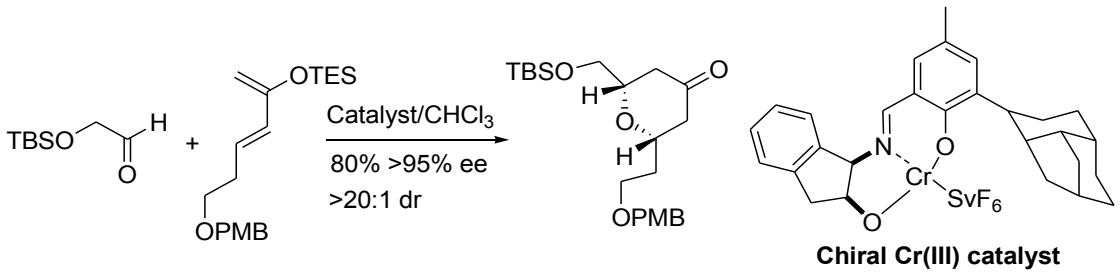
However, the reaction often proceeds with moderate yields and low enantiomeric excesses of the desired unsymmetrical product **A** because of the competing 2-oxonia Cope rearrangement that can furnish a mixture of products **A** and **B** (**Scheme II.8.1.**). Extended reaction times and/or strong acidic conditions can

account for this. Use of $SnBr_4$ as the acid catalyst promotes the cyclisation faster than the conventionally used acids such as $BF_3 \cdot OEt_2$/AcOH, thereby suppressing the competing 2-oxonia Cope process.[73e] Crosby *et al*. suggested that presence of an electron-rich aromatic ring in the homoallylic alcohol favors an oxonia-Cope rearrangement to yield the symmetrical tetrahydropyrans as the major product via a side-chain exchange process. The type **A** tetrahydropyrans are obtained with electron-deficient aromatic rings.[73f] Recently, a combination of *p*-TsOH and 4Å molecular sieves was found to furnish the 2,4,6-trisubstituted tetrahydropyrans in excellent yields and shorter reaction times.[73g]



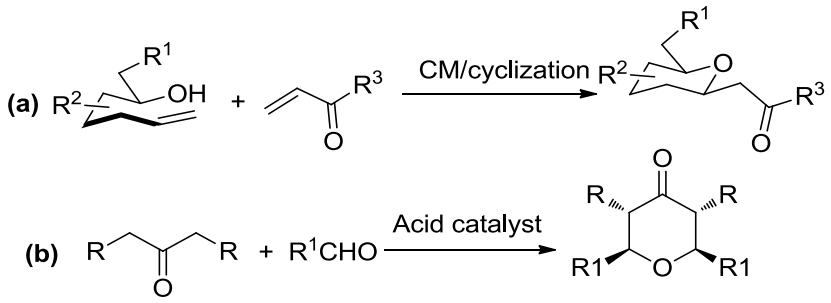
Scheme II.8.1. Reaction course of Prins cyclization.

Hetero-Diels–Alder cyclisation (HDA) has also been used by several groups for the synthesis of functionalised THP units. This involves cycloaddition of an aldehyde to a diene in an unsymmetrical fashion.[74a,b] A more significant growth on enantioselective HDA reaction has been pioneered by Jacobsen's group,[74c-e] employing a chiral tridentate Schiff base chromium (III) complex as the catalyst. This furnished the 2,6-*cis*-THPs with high stereoselectivity (**Scheme II.8.2.**).



Scheme II.8.2. HDA approach for enantioselective synthesis of THPs.

Some other reactions for the construction of THP ring are: (i) Pd(0) and Pd(II)-catalyzed cyclization[75a-c] of alcohols; (ii) radical cyclization of β- or α,β-alkoxyacrylates;[75d,e] as well as (iii) more venerable methods such as cyclisation onto epoxides.[75f,g] Carbohydrate precursors have also been extensively used for accessing both 2,6-*cis* and 2,6-*trans* isomers of THPs.[76] However, for that both the stereoisomers of the starting materials should be available, which often lead to lengthy processes. Cross metathesis (CM) followed by tandem S_N2' oxa-conjugate cyclization have been used develop protecting-group-free synthesis of THPs from base-sensitive substrates (**Scheme II.8.3a.**).[77] In addition, the multi-component Maitland-Japp reaction can give rapid access to THPs present in natural products (**Scheme II.8.3b.**).[78]



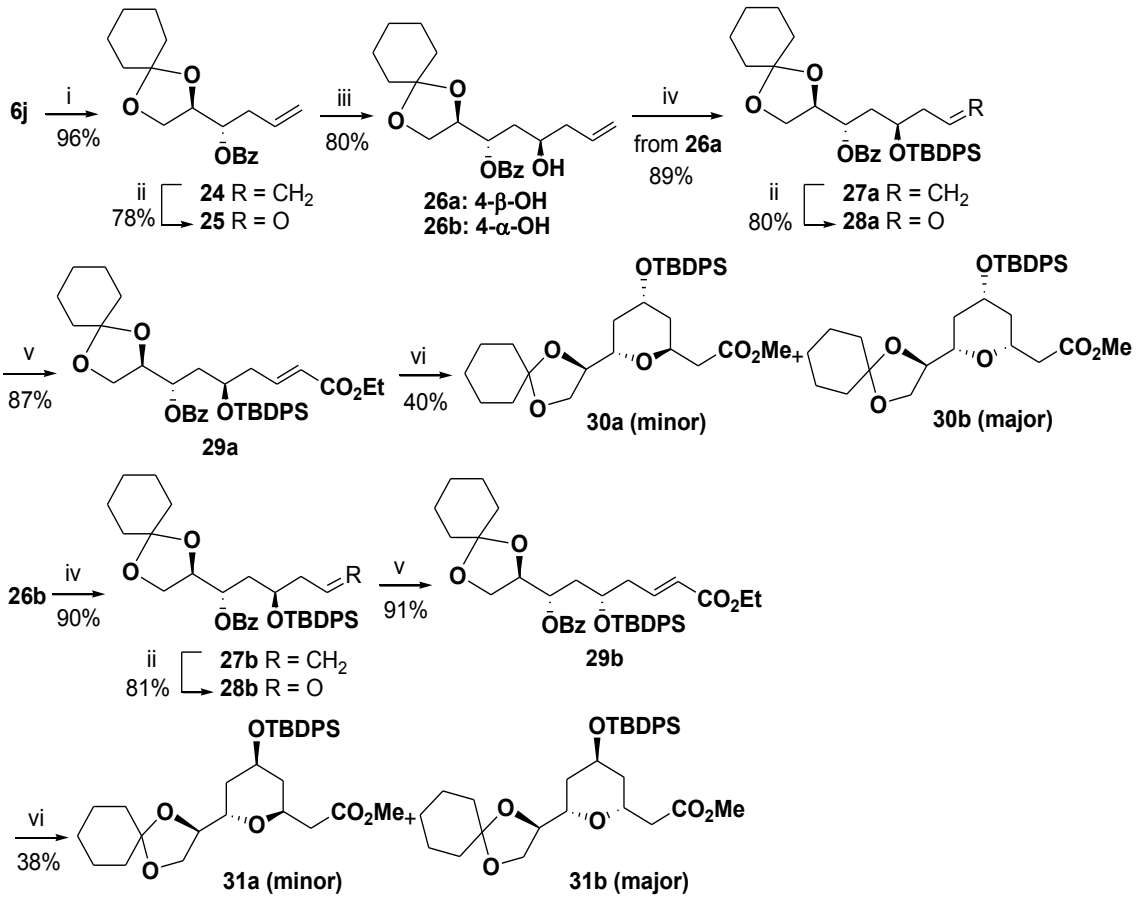
Scheme II.8.3. THP synthesis via (a) CM reaction; (b) multi-component Maitland-Japp reaction .

II.9: Present Work: Asymmetric Synthesis of THPs

Despite distinct advantages, all of the above reactions have their own limitations such as regio- and stereochemical outcome issues, highly sensitive reaction conditions and incompatibility of the labile functional groups under the reaction conditions. Moreover, most of these methods gave thermodyanamically more stable 2,6-*cis* isomer. Designing a flexible and efficient strategy to get both 2,6-*cis* and 2,6-*trans* THP isomers starting from a common substrate is still a challenge. Given that the pyran motif is an ubiquitous structural element in various biologically relevant small molecules,[79] we have developed a new method to access both 2,6-*cis* and 2,6-*trans* isomers of substituted THPs. The synthetic strategy was designed based on easy availability of the enantiomerically pure carbinols **6i** and **6j**. It was hypothesized that oxidative olefinic cleavage of either **6i**, **6j** or their hydroxy protected derivatives and subsequent allylation by any of the protocols developed during this investigation (*vide supra*) would furnish 2-4 stereomers of the resultant 1,3-diol. These compounds could then be derivatized to the required THPs, exploiting the rich olefin chemistry. Moreover, employing stereoisomers of the crotylated product of **4a**, different isomers of 4-hydroxy-2,3,6-tetrahydropyran derivatives can be obtained.

To probe the hypothesis, we attempted synthesis of some stereomers of both 2,6-*cis* and 2,6-*trans* substituted THPs from the alcohol **6j** (**Scheme II.9.1.**). For this, **6j** was benzoylated to obtain **24**. Its IR spectrum showed carbonyl band at 1740 cm^{-1} in place of the hydroxyl peak, while the ^{1}H NMR spectrum showed resonances at the aromatic region and the ^{13}C NMR signal at δ 168.6. Its reductive ozonolysis furnished the aldehyde **25** (IR band at 2711 and 1710 cm^{-1} and NMR resonances *viz*. δ_H 9.68 (t, J = 2.0 Hz, 1H) and δ_C 201.7, characteristics of a CHO group). Its allylation by

Luche's method[80] gave a mixture of two diastereomeric alcohols **26a** and **26b** which were conveniently separated by column chromatography. Appearance of the IR band at 3405 cm^{-1}, ^{1}H NMR olefinic resonances (δ 4.8-6.2) in place of the corresponding aldehyde signals as well as absence of the ^{13}C NMR carbonyl peak confirmed its formation. Although the diastereoselectivity of the allylation was modest, availability of both **26a** and **25b** was well-suited for the synthesis of different stereomers of the THPs. The compounds **26a** and **26b** were individually silylated with *tert*-butyldiphenylsilyl chloride (TBDPSCl)/ imidazole/DMAP to obtain **287** and **27b** respectively. Their ^{1}H NMR singlets at δ 1.04 and δ 1.01 respectively as well as the ^{13}C NMR peaks in the aromatic region were as per expectation.



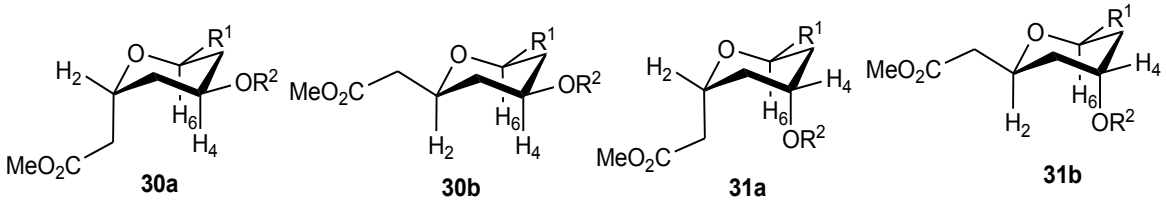
i) BzCN/Et_3N/CH_2Cl_2/0 ^oC/5 h, ii) O_3 /CH_2Cl_2/PPh_3/-78-25 ^oC/18 h, iii) Allyl bromide/Zn/NH_4Cl/THF/25 ^oC/3.5 h, iv) TBDPSCl/ imidazole/CH_2Cl_2/25 ^oC/6 h, v) NaH/$(EtO)_2P(O)CH_2CO_2Et$/THF/0-25 ^oC/18 h, vi) K_2CO_3/MeOH/0-25 ^oC/5 h.

Scheme II.9.1.

Michael addition reaction has gained immense importance in synthetic community due to its ability to form new C-C bonds via addition of nucleophiles to various Michael acceptors. We planned to construct the THP ring via the Michael oxa-conjugate addition reaction using the alkoxide that can be generated by alkaline hydrolysis of the OBz group. For the synthesis of the suitable Michael acceptors, compounds **27a** and **27b** were converted to the corresponding aldehydes **28a** and **28b** by reductive ozonolysis as above (IR band at 2711 and 1710 cm^{-1} and NMR resonances *viz*. δ_H 9.65 (t, J = 1.6 Hz) and δ_C 201.5). The aldehydes were individually subjected to the Wittig-Horner reaction with triethylphosphonoacetate to obtain the

α,β-unsaturated esters **29a** and **29b** respectively. The ^{1}H the NMR doublets at δ 5.67 (J = 16.2 Hz, 1H) for **29a** and δ 5.85 (d, J = 15.2 Hz, 1H) for **29b** confirmed the presence of *E*-conjugated olefinic moiety. Treatment of **29a** with K_2CO_3 in MeOH afforded the tetrahydropyrans **30a** and **30b** in 1:4 ratio (**Scheme II.9.1.**). Likewise, the ester **30b** gave the tetrahydropyran **31b** as the major product along with its C-3 epimer **31a** in 2:1 ratio with poor overall yield due to hydrolysis of the ester group as well as formation trans-esterified products.

From the point of view of stability, the THP isomers (**30a/b** and **31a/b**) can be represented by their respective chair conformations (**Figure II.9.1.**). All the bulky groups of the 2,4,6-all *syn*-isomer **30b**, are equatorially disposed in this conformation. Hence it will be thermodynamically more stable than **30a** that has its CH_2CO_2Me disposed axially. This explains preferential formation of **30b** over **30a**. With **31a/b** however, the bulky OTBDPS groups will always be axially placed, resulting in significant loss of diastereoselectivity in cyclization. Nevertheless, between **31a/b**, the latter (**31b**), containing the equatorial CH_2CO_2Me will be more stable, explaining a slight preponderance of its formation over **31a**.

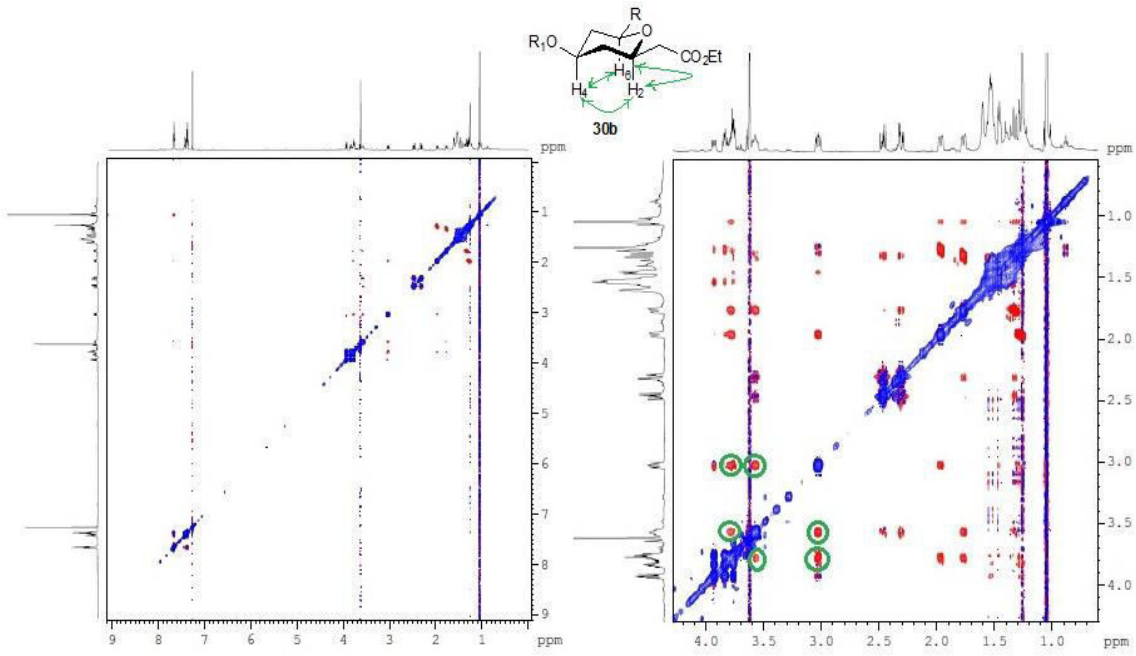


R^1 = Cyclohexylidenedioxy, R^1 = TBDPS

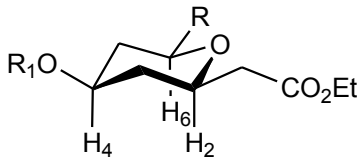
Figure II.9.1. Preferred confomations of **30** and **31**.

The diastereomers of **30** and **31** were separated by column chromatography and their relative stereochemistry confirmed by 2D NMR experiments. The ROESY spectra of **30b** (**Figure II.9.2.**) showed three strong cross peaks (shown by green circles): (i) between the peaks at δ 3.02-3.05 and δ 3.75-3.81 due to H_2-H_4 interaction;

(ii) between the peaks at δ 3.02-3.05 and δ 3.55-3.60 due to H_4-H_6 interaction; and (iii) between the peaks at δ 3.55-3.60 and δ 3.75-3.81 due to H_2-H_6 interaction. This established the proposed all *syn* geometry of **30b**. Given that the stereochemistry of **30a** varied onlt the the C2-centre, it would possess the 2,6-*anti* stereochemistry.



Key ROESY data of compound **30b**



30b

Signal	Cross peaks observed
H_2	H_4, H_6
H_4	H_2, H_6
H_6	H_2, H_4

Figure II.9.2. ROESY spectra of 30b

The ROESY data of compound **31b** (**Figure II.9.3.**) showed only one very weak cross peak (shown by green circles) between δ 3.37-3.40 and δ 3.72-3.77 due to H_2-H_6 interaction. No interaction was found for H_2 and H_4 interaction. This confirms the 2,6-anti conformation of the **31b** isomer.Therfore the other isomer **31a** should possess 2,6-anti-stereochemistry.

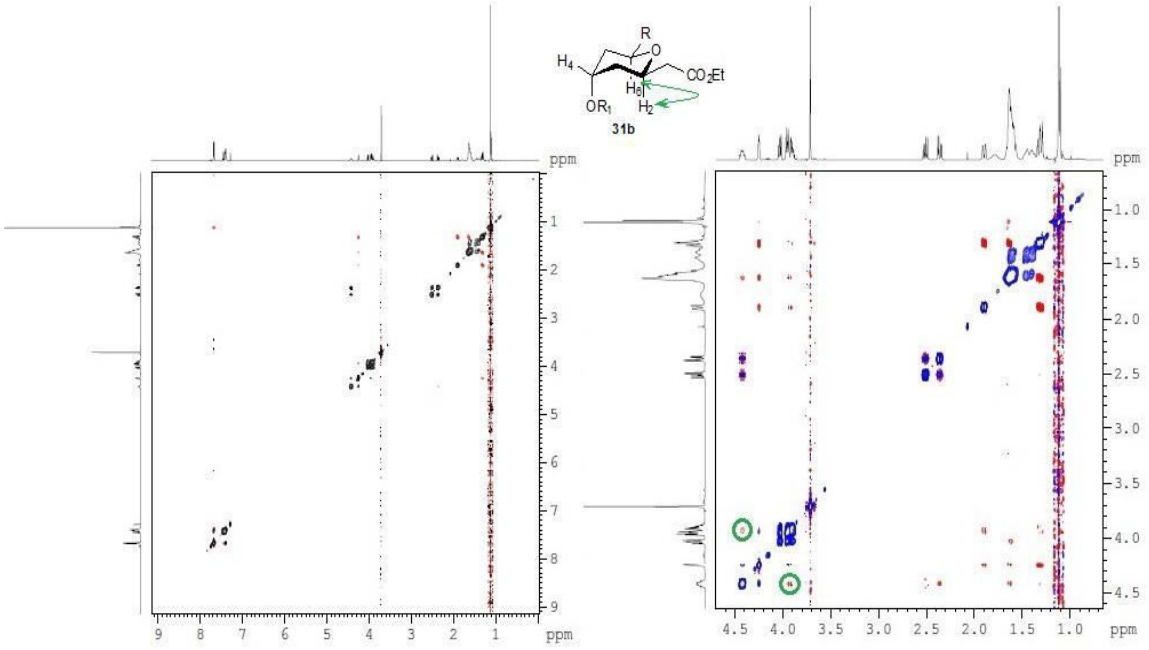


Figure II.9.3. ROESY spectra of 31b

II.10: 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 ^1H 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). ROSEY spectra were taken with 300 ms mixing time.

***General procedure of Bi-metalic propargylation*:** A mixture of the aldehyde **1a-k** (0.01 mol), propargyl bromide (3.57 g, 0.03 mol), and $FeCl_3$ or $SnCl_2.2H_2O$ or $CuCl_2.2H_2O$ (0.03 mol) in THF (100 mL) was stirred at 10–15 ^oC for 10 min. To the reaction mixture was added Zn-dust (Aldrich make, 1.95 g, 0.03 mol) in portions in 15 min and stirring continued at 25 ^oC for the period shown in Table **II.3.1**. The mixture was treated successively with Et_2O (100 mL) and H_2O (50 mL), stirred for 10 min, filtered, the filtrate treated with aqueous 2% HCl to dissolve any suspended particles. The organic layer was separated, the aqueous layer extracted with EtOAc (2 × 20 mL), the combined organic layers washed with H_2O (2 × 20 mL) and brine (1 × 10 mL), and dried. Solvent removal in vacuo afforded the crude residue, which was passed through a short silica gel pad eluting with 20% EtOAc/hexane and the eluent concentrated in vacuo to get a residue that was analyzed by NMR spectroscopy to determine the ratio of the respective homopropargyl (**2a-k**) and allenyl (**3a-k**)

alcohols. Column chromatography of the residues (silica gel, 0-10% EtOAc/hexane) gave the individual alcohols.

2a/3a (by reagent I): ^{1}H NMR: δ 2.07 (t, J = 2.6 Hz, 1H), 2.40 (broad s, 1H), 2.62-2.68 (m, 2H), 4.87 (t, *J* = 6.3 Hz, 1H), 4.93-4.95 (m, 0.1H), 5.29-5.30 (m, 0.05H), 5.45-5.46 (m, 0.05H), 7.30-7.41 (m, 5H); ^{13}C NMR: δ 29.0, 70.9, 72.2, 80.8, 94.9, 125.8, 127.8, 128.9, 133.3, 142.5, 207.2. (by reagent II): ^{1}H NMR: δ 2.07 (t, *J* = 2.6 Hz, 1H), 2.40 (broad s, 1H), 2.63-2.64 (m, 2H), 4.87 (t, *J* = 6.3 Hz, 1H), 7.30-7.41(m, 5H). ^{13}C NMR: δ 29.4, 71.0, 72.4, 80.7, 125.8, 128.0, 128.5, 130.1, 142.5.

2b/3b (by reagent I): ^{1}H NMR: δ 2.09 (t, *J* = 2.6 Hz, 1H), 2.60-2.64 (m, 2H), 4.20 (broad s, 1H), 4.85 (t, *J* = 6.3 Hz, 1H), 7.25-7.58 (m, 4H); ^{13}C NMR: δ 14.2, 29.5, 71.5, 71.7, 80.1, 124.5, 129.0, 130.1, 131.1, 144.7; (by reagent II): ^{1}H NMR: δ 2.09 (t, *J* = 2.6 Hz, 1H), 2.60-2.63 (m overlapped with broad s, 4H), 4.83 (t, *J* = 6.2 Hz, 1H), 4.93-4.96 (m, 0.32 H), 5.21-5.28 (m, 0.16 H), 5.36-5.42 (m, 0.16H), 7.29-7.55 (m, 4H). ^{13}C NMR: δ 14.0, 29.7, 71.7, 72.5, 80.1, 94.2, 122.6, 128.8, 130.2, 133.2, 144.8, 206.5.

2c/3c (by reagent I): ^{1}H NMR: δ 2.08 (t, *J* = 2.7 Hz, 1H), 2.62-2.65 (m, 2H), 3.81 (s overlapped with a broad s, 4H), 4.85 (t, *J* = 6.2 Hz, 1H), 6.83-7.30 (m, 4H); ^{13}C NMR: δ 29.4, 55.2, 65.8, 70.9, 72.2, 78.1, 80.7, 113.5, 118.4, 129.5, 144.2, 160.1.

(by reagent II): ^{1}H NMR: δ 2.08 (t, *J* = 2.6 Hz, 1H), 2.38 (broad s, 1H), 2.61-2.67 (m, 2H), 3.80 (s, 3H), 4.86 (t, *J* = 6.3 Hz, 1H), 4.93-4.95 (m, 0.24H), 5.25-5.26 (m, 0.12H), 5.43-5.44 (m, 0.12H), 6.84-7.29. (m, 4H). ^{13}C NMR: δ 29.4, 55.2, 65.8, 70.9, 71.9, 78.3, 94.1, 111.4, 113.5, 118.4, 129.5, 144.2, 159.7.

2d/3d (by reagent I): ^{1}H NMR: δ 2.07 (t, *J* = 2.6 Hz, 1H), 2.40 (broad s, 2H), 2.57-2.63 (m, 2H), 4.81 (t, *J* = 6.3 Hz, 1H), 4.89-4.93 (m, 0.34H), 5.13-5.25 (m, 0.17H), 5.36-5.39 (m, 0.17H), 7.23-7.50 (m, 4H); ^{13}C NMR: δ 29.3, 72.0, 77.9, 80.4, 94.5,

112.2, 121.7, 127.5, 128.1, 131.1, 131.5, 141.4, 207.1; (by reagent II): ^{1}H NMR: δ 2.05 (t, *J* = 2.6 Hz, 1H), 2.52-2.57 (m, 2H), 3.0 (broad s, 2H), 4.84 (t, *J* = 6.3 Hz, 1H), 4.85-4.89 (m, 1.68H), 5.12-5.26 (m, 0.84H), 5.32-5.38 (m, 0.84H), 7.13-7.57 (m, 4H). ^{13}C NMR: δ 28.9, 71.1, 77.9, 80.1, 94.4, 121.2, 121.4, 127.6, 127.8, 131.4, 141.8, 207.3.

2e/3e (by reagent I): ^{1}H NMR: δ 1.25 (t, *J* = 4.0 Hz, 3H), 2.08 (t, *J* = 2.6 Hz, 1H), 2.48 (broad s, 1H), 2.51-2.55 (m, 4H), 4.86 (t, *J* = 6.3 Hz, 1H), 4.92-4.94 (m, 0.12 H), 5.25-5.26 (m, 0.06H), 5.44-5.45 (m, 0.06 H), 7.20-7.33 (m, 4H); ^{13}C NMR: δ 15.5, 28.5, 29.2, 70.8, 72.2, 80.9, 94.6, 125.8, 126.1, 127.9, 139.8, 144.0, 206.5. (by reagent II): ^{1}H NMR: δ 1.25 (t, *J* = 4.0 Hz, 3H) 2.05 (t, *J* = 2.6 Hz, 1 H), 2.50-2.72 (m overlapped with a broad s, 5H), 4.83 (t, *J* = 6.3 Hz, 1H), 7.12-7.33 (m, 4H). ^{13}C NMR: δ 15.4, 28.4, 29.1, 70.7, 72.1, 80.8, 119.0, 125.7, 127.8, 139.7, 143.9.

2f/3f (by reagent I): ^{1}H NMR: δ 1.34 (t, *J* = 4.0 Hz, 3H), 2.08 (t, *J* = 2.6 Hz, 1 H), 2.53-2.60 (m, 2H), 3.96 (q, *J* = 6.8 Hz, 2H), 4.32 (broad s, 1H), 4.73 (t, *J* = 6.3 Hz, 1H), 4.93 (m, 0.16H), 5.25-5.29 (m, 0.08 H), 5.42-5.44 (m, 0.08H), 6.81-6.87 (m, 2H), 7.18-7.28 (m, 2H); ^{13}C NMR: δ 14.2, 28.7, 63.5, 70.6, 71.9, 80.6, 94.5, 114.1, 126.7, 134.5, 159.1.

(by reagent II): ^{1}H NMR: δ 1.34 (t, *J* = 4.0 Hz, 3H), 2.02 (t, *J* = 2.6 Hz, 1H), 2.54-2.59 (m, 2H), 3.05 (broad s, 1H), 3.96 (q, *J* = 6.8 Hz, 2H), 4.74 (t, *J* = 6.3 Hz, 1H), 6.81-6.87 (m, 2H), 7.18-7.28 (m, 2H). ^{13}C NMR: δ 14.5, 28.9, 63.1, 70.5, 71.6, 80.8, 114.0, 126.8, 134.4, 158.2.

2g/3g (by reagent I): ^{1}H NMR: δ 0.91 (t, *J* = 3.5 Hz, 3H), 1.32-1.37 (m, 4H), 1.50-1.63 (m, 2H), 2.05 (t, *J* = 2.7 Hz, 1H), 2.33-2.45 (m overlapped with a broad s, 3H), 3.72-3.80 (m, 1H), 4.12-4.33 (m, 0.16 H), 4.85-4.90 (m, 0.32H), 5.24–5.43 (m, 0.16H); ^{13}C NMR: δ 13.8, 22.2, 25.0, 34.0, 37.3, 69.9, 70.7, 80.8, 94.6, 206.2; (by

reagent II): ^{1}H NMR: δ 0.90 (t, *J* = 3.5 Hz, 3H), 1.32 (m, 4H), 1.51-1.58 (m, 2H), 2.05 (t, *J* = 2.7 Hz, 1H), 2.30-2.42 (m overlapped with a broad s, 3H), 3.76-3.80 (m, 1H), 4.17-4.20 (m, 0.14 H), 4.85-4.92 (m, 0.28 H), 5.21-5.42 (m, 0.14 H); ^{13}C NMR: δ 14.1, 22.6, 29.5, 33.8, 36.0, 69.8, 70.6, 80.9, 94.8, 206.5.

2h/3h (by reagent I): ^{1}H NMR: δ 0.88 (t, *J* = 2.2 Hz, 3H), 1.26-1.28 (m, 8H), 1.38-1.53 (m, 2H), 1.88 (broad s, 1H), 2.04 (t, *J* = 2.6 Hz, 1H), 2.26-2.46 (m, 2H), 3.74-3.77 (m, 1H), 4.14-4.17 (m, 0.06H), 4.83-4.85 (m, 0.12H), 5.22-5.44 (m, 0.06H); ^{13}C NMR: δ 13.9, 22.4, 25.4, 27.1, 29.0, 31.6, 36.0, 37.3, 69.7, 70.4, 77.6, 81.0, 94.6, 207.0. (by reagent II): ^{1}H NMR: δ 0.87 (t, *J* = 3.0 Hz, 3H), 1.27-1.54 (m, 10H), 1.89 (s, 4H), 2.05 (t, J = 2.7 Hz, 1H), 2.31-2.41 (m, 2H), 3.75-3.76 (m, 1H), 4.19-4.25 (m, 0.24H), 4.85 (m, 0.48H), 5.24 (m, 0.24H). ^{13}C NMR: δ 13.8, 22.4, 25.2, 27.0, 28.9, 29.0, 31.5, 35.8, 37.1, 69.6, 70.3, 77.6, 80.9, 94.5, 207.0.

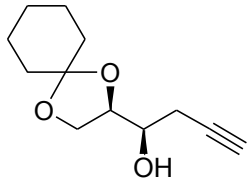
2i/3i (by reagent I): ^{1}H NMR: δ 0.88 (t, *J* = 3.0 Hz, 3H), 1.33 (m, 12H), 1.51-1.68 (m, 2H), 1.7 (broad s, 1H), 2.05 (t, *J* = 2.7 Hz, 1H), 2.33-2.45 (m, 2H), 3.74-3.77 (m, 1H), 4.11-4.20 (m, 0.06H), 4.81-4.89 (m, 0.12H), 5.24-5.32 (m, 0.06H); ^{13}C NMR: δ 14.0, 22.4, 25.7, 27.1, 29.1, 29.4, 29.5, 31.9, 36.2, 37.6, 69.9, 70.7, 80.9, 94.7, 206.9; (by reagent II): ^{1}H NMR: δ 0.87 (t, *J* = 3.0 Hz, 3H), 1.32 (m, 12H), 1.50-1.67 (m overlapped with a broad s, 3H), 2.05 (t, *J* = 2.7 Hz, 1H), 2.30-2.41 (m, 2H), 3.74-3.77 (m, 1H), 4.11-4.20 (m, 0.07H), 4.81-4.89 (m, 0.14H), 5.23-5.32 (m, 0.07H). ^{13}C NMR: δ 14.2, 22.6, 25.5, 27.2, 29.2, 29.4, 29.7, 31.8, 36.2, 37.4, 69.8, 70.6, 81.0, 94.8, 207.1.

2j/3j (by reagent I): ^{1}H NMR: δ 0.88 (t, *J* = 3.0 Hz, 3H), 1.2-1.3 (m, 14H), 1.52-1.55 (m overlapped with a broad s, 3H), 2.05 (t, *J* = 2.7 Hz, 1H), 2.33-2.45 (m, 2H), 3.73-3.77 (m, 1H), 4.15-4.17 (m, 0.05H), 4.83-4.86 (m, 0.1H), 5.20-5.26 (m, 0.05H); ^{13}C NMR: δ 14.2, 22.0, 25.4, 27.2, 29.1, 29.4, 29.5, 29.6, 29.7, 29.8, 30.3, 69.7, 70.5,

80.9, 94.7, 207.1; (by reagent II): ^{1}H NMR: δ 0.87 (t, *J* = 3.0 Hz, 3H), 1.2-1.3 (m, 14H), 1.52-1.54 (m, 2H), 2.06 (t, *J* = 2.7 Hz, overlapped with a broad s, 2H), 2.33-2.47 (m, 2H), 3.73-3.77 (m, 1H), 4.15-4.17 (m, 0.1H), 4.83-4.86 (m, 0.2H), 5.20-5.26 (m, 0.1H). ^{13}C NMR: δ 14.1, 22.6, 25.6, 27.3, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 31.8, 69.9, 70.6, 81.0, 94.8, 207.0.

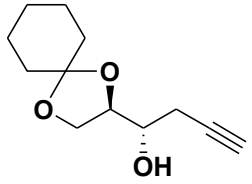
2k/3k (by reagent I): ^{1}H NMR: δ 0.88 (t, *J* = 3.0 Hz, 3H), 1.22-1.28 (m, 18H), 1.52-1.64 (m, 2H), 1.90 (broad s, 1H), 2.05 (t, *J* = 2.7 Hz, 1H), 2.30-2.44 (m, 2H), 3.74-3.77 (m, 1H), 4.17-4.20 (m, 0.03H), 4.84-4.85 (m, 0.06H), 5.24 (m, 0.03H); ^{13}C NMR: δ 14.1, 22.7, 25.6, 27.3, 29.3, 29.6, 31.9, 36.3, 69.9, 70.7, 90.9, 94.5, 207.1; (by reagent II): ^{1}H NMR: δ 0.88 (t, *J* = 3.0 Hz, 3H), 1.23-1.30 (m, 18H), 1.5-1.6 (m overlapped with a broad s, 3H), 2.05 (t, *J* = 2.6 Hz, 1H), 2.25-2.39 (m, 2H), 3.70-3.79 (m, 1H), 4.17-4.21 (m, 0.21H), 4.80-4.84 (m, 0.42H), 5.23-5.24 (m, 0.21H); ^{13}C NMR: δ 14.0, 22.6, 25.3, 25.5, 27.2, 29.3, 31.8, 36.1, 69.8, 70.5, 78.0, 80.9, 94.7, 207.0.

(2*R*,3*R*)-1,2-Cyclohexylidenedioxy-5-hexyne-3-ol (5a):



colorless oil; ^{1}H NMR: δ 1.29-1.45 (m, 2H), 1.57-1.60 (m, 8H), 2.01-2.04 (m, 1H), 2.40-2.44 (m, 2H), 2.57 (broad s, 1H), 3.66-4.19 (m, 4H). ^{13}C NMR: δ 23.6, 23.9, 25.0, 34.5, 36.0, 36.2, 65.5, 70.2, 76.9, 80.0, 110.0.

(2*R*,3*S*)-1,2-Cyclohexylidenedioxy-5-hexyne-3-ol (5b):



colorless oil; ^{1}H NMR: δ 1.25-1.50 (m, 2H), 1.54-1.75 (m, 8H), 2.03-2.07 (m, 1H), 2.46-2.52 (m, 2H), 2.86 (broad s, 1H), 3.75-3.78 (m, 1H), 3.94-4.16 (m, 3H). ^{13}C NMR: δ 23.5, 23.6, 23.9, 25.0, 34.5, 36.3, 65.4, 70.1, 71.1, 76.8, 79.9, 109.9.

General procedure for Barbier-type allylation in aqueous or organic media. Finely divided Bi powder (2.0 mmol) was added to a mixture of **1a** (2.0 mmol) and allyl bromide (1.5 equiv.) in different solvents (20 mL) and the mixture was magnetically stirred. The reactions in THF, aqueous THF, MeCN and H_2O were also were also carried out using an aqueous solution of KF (10 mol%) or ultrasonication as the activator. The solvent compostions, reaction conditions and periods are specified in **Table II.5.1**. The mixture was filtered and extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with aqueous saturated NH_4Cl, dried, concentrated in vacuo, and the residue subjected to column chromatography (silica gel, 0-10% Et_2O/hexane) to obtain pure **6a**.

General procedure for Bi-mediated allylation of aldehydes in [bmim][Br]. To a magnetically stirred mixture of the aldehyde (2.0 mmol) and allyl bromide (1.5-1.7 equiv.) in [bmim][Br] (6 mL) was added Bi powder (1.0-1.5 equiv.) in portions. After stirring the mixture for different periods, it was extracted with Et_2O (3 × 10 mL), concentrated in vacuo, and the residue subjected to column chromatography (silica gel, 0-15% EtOAc/hexane) to obtain the pure homoallylic alcohols. The chosen aldehydes, reaction conditions and periods are specified in **Table II.5.2**. A similar procedure was followed under Ar using N_2 (g)-purged [bmim][Br], when the mixture was stirred for 24 h. The allylation reaction with **1a** was also carried out [bmim][BF_4] under otherwise similar conditions.

1-Phenyl-but-3-en-1-ol (6a). colorless oil; IR: 3468, 922 cm^{-1}; ^1H NMR: δ 1.94 (broad s, 1H), 2.45-2.56 (m, 2H), 4.74 (t, *J* = 6.8 Hz, 1H), 5.10-5.25 (m, 2H), 5.65-5.93 (m, 1H), 7.26-7.40 (m, 5H); ^{13}C NMR: δ 43.8, 73.2, 118.4, 125.8, 127.5, 128.4, 134.4, 143.8. Anal. Calcd. for $C_{10}H_{12}O$: C, 81.06; H, 8.16%. Found: C, 81.26; H, 7.89%.

1-(3-Methoxyphenyl)-but-3-en-1-ol (6b). colorless oil; IR: 3418, 916 cm^{-1}; ^1H NMR: δ 2.18 (broad s, 1H), 2.49-2.53 (m, 2H), 3.80 (s, 3H), 4.69 (t, *J* = 6.2 Hz, 1H), 5.10-5.19 (m, 2H), 5.70-5.91 (m, 1H), 6.79-6.91 (m, 3H), 7.21-7.29 (m, 1H); ^{13}C NMR: δ 43.7, 55.2, 73.2, 111.3, 112.9, 118.1, 118.3, 129.4, 134.4, 145.6, 159.7. Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%. Found: C, 73.86; H, 7.68%.

1-(4-Bromophenyl)-but-3-en-1-ol (6c). colorless oil; IR: 3389, 910 cm^{-1}; ^1H NMR: δ 2.14 (broad s, 1H), 2.34-2.53 (m, 2H), 4.67 (t, *J* = 6.6 Hz, 1H), 5.10-5.17 (m, 2H), 5.65-5.86 (m, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR: δ 43.8, 72.5, 118.8, 121.2, 127.5, 131.4, 133.9, 142.8. Anal. Calcd. for $C_{10}H_{11}BrO$: C, 52.89; H, 4.88%. Found: C, 52.66; H, 4.72%.

1-(4-Nitrophenyl)but-3-en-1-ol (6d).[81a] colorless liquid; ^1H NMR: δ 2.41-2.47 (m, 2H), 2.51-2.55 (m, 1H), 4.84 (dd, *J* = 8.0 and 5.0 Hz, 1H), 5.13−5.17 (m, 2H), 5.74−5.81 (m, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 8.16 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR: δ 43.7, 72.1, 119.4, 123.5, 126.5, 133.2, 147.1, 151.2.

1-(4-Methoxyphenyl)but-3-en-1-ol (6e).[81b] colorless liquid; ^1H NMR: δ 2.37 (broad s, 1H), 2.48 (t, *J* = 6.5 Hz, 2H), 3.79 (s, 3H), 4.65 (t, *J* = 6.5 Hz, 1H), 5.10−5.15 (m, 2H), 5.76−5.81 (m, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.26 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR: δ 43.5, 55.1, 72.9, 113.6, 117.9, 127.0, 134.6, 136.0, 158.8.

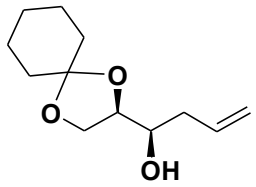
(*E*)-1-Phenylhexa-1,5-dien-3-ol (6f). colorless oil; IR: 3425, 916 cm^{-1}; ^1H NMR: δ 1.84 (broad s, 1H), 2.33-2.42 (m, 2H), 4.31-4.41 (m, 1H), 5.13-5.22 (m, 2 H), 5.75-

5.93 (m, 1H), 6.18-6.29 (dd, *J* = 6.2 Hz and 16.0 Hz, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 7.23-7.40 (m, 5H); ^{13}C NMR: δ 41.8, 71.6, 118.3, 126.3, 127.5, 128.4, 130.2, 131.4, 133.9, 136.5. Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10%. Found: C 82.56; H 7.94%.

Non-1-en-4-ol (6g).[81c] colorless liquid; ^{1}H NMR: δ 0.91 (t, *J* = 7.0 Hz, 3H), 1.24-1.38 (m, 6H), 1.44-1.47 (m, 2H), 1.68 (broad s, 1H), 2.12-2.18 (m, 1H), 2.28-2.33 (m, 1H), 3.63-3.68 (m, 1H), 5.12−5.16 (m, 2H), 5.79−5.86 (m, 1H); ^{13}C NMR: δ 14.0, 22.6, 25.3, 31.8, 36.8, 41.9, 70.7, 118.0, 134.9.

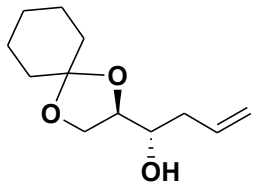
1-Decen-4-ol (6h). colorless oil; IR: 3408, 912 cm^{-1}; ^{1}H NMR: δ 0.85 (t, *J* = 6.4 Hz, 3H), 1.22-1.60 (m, 10H), 1.92 (broad s, 1H), 2.02-2.29 (m, 2H), 3.52-3.65 (m, 1H), 4.98-5.17 (m, 2H), 5.65-5.93 (m, 1H); ^{13}C NMR: δ 14.0, 22.6, 25.6, 29.3, 31.8, 36.8, 41.9, 70.6, 117.8, 134.9. Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90%. Found: C 76.61; H 13.05%.

(2*R*,3*R*)-1,2-Cyclohexylidenedioxy-5-hexene-3-ol (6i).



colorless oil; $[\alpha]_D^{24}$ +5.5 (*c* 1.12, $CHCl_3$) (lit.[24e] $[\alpha]_D^{23}$ +5.3 (*c* 1.34, $CHCl_3$)); IR: 3451, 1640, 1098, 1042 cm^{-1}; ^{1}H NMR: δ 1.25-1.37 (m, 2H), 1.56-1.61 (m, 8H), 2.22 (t, *J* = 6.5 Hz, 2H), 2.31(d, *J* = 4.8 Hz, D_2O exchangeable, 1H), 3.52-3.58 (m, 1H), 3.68-3.76 (m, 1H), 3.93-4.02 (m, 2H), 5.06-5.16 (m, 2H), 5.77-5.91 (m, 1H); ^{13}C NMR: δ 23.5, 23.7, 24.8, 34.5, 35.9, 37.9, 65.4, 71.3, 77.8, 109.6, 117.4, 133.8.

(2*R*,3S)-1,2-Cyclohexylidenedioxy-5-hexene-3-ol (6j).



colorless oil; $[\alpha]_D^{24}$ +10.6 (*c* 1.38, $CHCl_3$) (lit.[24e] $[\alpha]_D^{25}$ +10.2 (*c* 1.41, $CHCl_3$)); IR: 3453, 1642, 1101, 1044 cm^{-1}; ^1H 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. Anal.Calcd.for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%. Found: C, 67.79; H,9.42%.

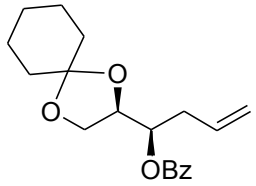
NMR experiments. A mixture of the Bi (1.0 mmol) and [bmim][Br] (3 mL) as such or along with allyl bromide (1.0-2.0 mmol) was magnetically stirred at room temperature. Aliquots (35 μL) of reaction mixture were taken at different time intervals, and the ^1H NMR spectra were recorded in CD_2Cl_2.

Inversion of the carbinol stereochemistry of 6j. To a mixture of **6j** (3.0 g, 14.15 mmol), PPh_3 (5.56 g, 21.23mmol), *p*-nitrobenzoic acid (2.84 g, 16.98 mmol) and DIAD (4.3 mL, 21.23mmol) in THF (50 mL) was stirred at RT for 20 h. The mixture was concentrated in vaccuo, taken in EtOAc (50 mL), the organic extract washed with H_2O (2 × 20 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0-5% EtOAc/hexane) to afford pure ester (4.65 g, 91%). Colorless oil; $[\alpha]_D^{24}$ +13.1 (*c* 1.02, $CHCl_3$); IR: 1529, 1347 cm^{-1}; ^1H NMR: δ 1.17-1.46 (m, 2H), 1.48-1.72 (m, 8H), 2.46-2.54 (m, 2H), 3.77 (q, *J* = 6.2 Hz, 1H), 4.06 (q, *J* = 6.6 Hz, 1H), 4.30 (q, *J* = 6.2 Hz , 1H), 5.04-5.28 (m, 3H),

5.72-5.86 (m,1H), 8.17-8.30 (m, 4H); ^{13}C NMR: δ 23.8, 23.9, 25.1, 34.8, 35.5, 36.0, 65.3, 74.6, 75.6, 110.3,118.7, 123.5, 130.8, 132.6, 135.6, 150.6, 164.3.

A mixture of the above ester (4.60 g, 12.74 mmol) and K_2CO_3 (5.28 g, 38.23mmol) in MeOH (25 mL) was stirred at RT for 6 h. The mixture was concentrated in vaccuo, the residue diluted with H_2O (10 mL), and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with H_2O (2 × 15 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. The residue was purified by colum chromatography (silica gel, 0-15% EtOAc/hexane) to obtain **6i** (2.37 g, 88%). colorless oil; IR: 3434, 2985 cm^{-1}; $[\alpha]_D^{25}$ +6.3 (*c* 0.92, $CHCl_3$); ^{1}H NMR: δ 1.20-1.23 (m, 2H), 1.61- 1.62 (m, 8H), 2.20-2.27 (m, 2H), 3.52-3.61 (m 1H), 3.67-3.77 (m,1H), 3.95-4.03 (m, 2H), 5.07-5.16 (m, 2H), 5.75- 5.95(m, 1H); ^{13}C NMR: δ 23.7, 23.9,25.0, 34.7, 36.1, 38.1, 65.6, 71.5, 76.4, 109.8, 117.6, 134.0. Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50%. Found: C, 68.18; H, 9.42%.

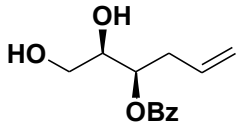
(4*R*,5*R*)-4-Benzoyloxy-5,6-cyclohexylidenedioxy-1-hexene (17).



To a cooled (0 °C) and stirred solution of **6i** (2.32 g, 10.94 mmol) and Et_3N (1.8 mL, 13.13 mmol) in CH_2Cl_2 (30 mL) was added BzCN (1.72 g, 13.13 mmol). After consumption of the starting material (*cf.* TLC, ~3 h) the reaction mixture was treated with ice-cold H_2O (30 mL). The organic layer was separated, the aqueous portion extracted with $CHCl_3$ (2 × 25 mL), the combined organic extracts 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 **17** (3.29 g, 95%). colorless oil; $[\alpha]_D^{26}$ +15.2 (*c* 1.06, $CHCl_3$); IR: 1641, 1463 cm^{-1}; ^{1}H NMR: δ

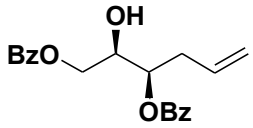
1.38-1.41 (m, 2H), 1.56-1.64 (m, 8H), 2.46-2.55 (m, 2H), 3.74-3.82 (m, 1H), 3.99-4.07 (m, 1H), 4.26-4.32 (m, 1H), 5.02-5.08 (m, 1H), 5.16-5.24 (m, 2H), 5.74-5.83 (m, 1H), 7.38-7.55 (m, 3H), 8.02-8.06 (m, 2H); ^{13}C NMR: δ 23.8, 23.9, 25.1, 34.8, 35.4, 35.8, 65.1, 73.0, 75.6, 110.0, 118.2, 128.3, 129.6, 130.1, 132.9, 133.0, 166.0. Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65%. Found: C, 72.40; H, 7.44%.

(2*R*,3*R*)-3-Benzoyloxyhex-5-ene-1,2-diol (18).



A mixture of **17** (3.25 g, 10.28 mmol) and aqueous 80% TFA (5 mL) in CH_2Cl_2 (15 mL) was stirred at 0 ^{o}C till completion of the reaction (*cf.* TLC, ~3 h). The reaction mixture was neutralized with aqueous saturated $NaHCO_3$, extracted with $CHCl_3$ (3 × 20 mL), the organic extract washed with H_2O (3 × 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 **18** (2.09 g, 86%). colorless oil; $[\alpha]_D^{24}$ + 8.0 (*c* 1.04, $CHCl_3$); IR: 3405 cm^{-1}; ^{1}H NMR: δ 2.47 (broad s, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 3.63 (d, *J* = 5.6 Hz, 2H), 3.87-3.98 (m, 1H), 5.05-5.14 (m, 2H), 5.19-5.30 (m, 1H), 5.71-5.88 (m, 1H), 7.39-7.46 (m, 2H), 7.53-7.60 (m, 1H), 8.00-8.09 (m, 2H); ^{13}C NMR: δ 34.9, 63.2, 72.5, 73.8, 118.1, 128.2, 129.5, 129.6, 133.0, 166.5. Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%. Found: C, 65.78; H, 6.71%.

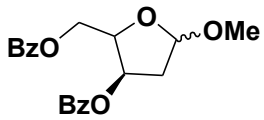
(2*R*,3*R*)-1,3-Dibenzoyloxyhex-5-ene-2-ol (19).



As described earlier, benzoylation of **18** (2.05 g, 8.69 mmol) with BzCN (1.25 g, 9.55 mmol) and Et_3N (1.33 mL, 9.55 mmol) in CH_2Cl_2 (30 mL) followed by usual isolation and column chromatography (silica gel, 0-15% EtOAc/hexane) furnished **19**

(2.18 g, 77%). Colorless oil; IR: 3455, 1642, 1463 cm^{-1}; ^1H NMR: δ 2.03 (s, 1H), 2.59-2.68 (m, 2H), 4.09-4.23 (m, 1H), 4.44-4.47 (m, 2H), 5.08-5.23 (m, 2H), 5.31-5.39 (m, 1H), 5.78-5.86 (m, 1H), 7.35-7.57 (m, 6H), 7.96-8.09 (m, 4H); ^{13}C NMR: δ 34.8, 65.9, 70.0, 73.7, 118.5, 128.2, 129.4, 129.5, 129.6, 129.7, 132.9, 133.0, 166.0, 166.6. Anal. Calcd. for $C_{20}H_{22}O_4$: C, 70.57; H, 5.92%. Found: C, 70.69; H, 5.80%.

Methyl 3,5-O-dibenzoyl-2-deoxy-α,β-D-lyxofuranoside (20).



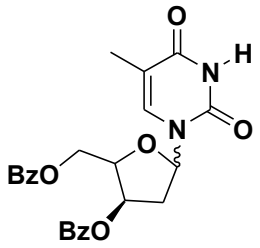
O_3 was bubbled through a cooled (-78 ^oC) and stirred solution of **19** (2.1 g, 6.44 mmol) in CH_2Cl_2 (100 mL) until a blue color persisted. After 15 min, excess O_3 was removed by flushing with N_2, PPh_3 (2.03 g, 7.73 mmol) was added into the mixture and stirring continued for 18 h at 25 ^oC. The mixture was concentrated in vacuo, the residue taken in hexane (30 mL) and concentrated to obtain a residue that was column chromatographed (silica gel, 0-5% MeOH/$CHCl_3$) to obtain the intermediate furanose (1.81 g, 82%). Colorless oil; IR: 3406 cm^{-1}; ^1H NMR: δ 1.89-2.18 (m, 2H), 4.18-4.26 (m, 1H), 4.42-4.78 (m, 3H), 5.45-5.52 (m, 1H), 7.35-7.57 (m, 6H), 7.95-8.09 (m, 4H); ^{13}C NMR: δ 39.0, 39.7, 61.9, 62.7, 72.6, 73.9, 80.3, 80.6, 84.4, 110.9, 111.4, 128.4, 128.6, 128.8, 129.0, 129.3, 129.7, 133.3, 133.4, 133.7, 133.9, 135.2, 135.7, 150.2, 150.3, 165.2, 165.5.

A solution of the above furanose (1.76 g, 5.15 mmol) and *p*-TsOH (89 mg, 0.515 mmol) in MeOH (50 mL) was stirred at 25 ^oC for 5 h. The mixture was neutralized with aqueous 10% $NaHCO_3$, concentrated in vacuo, and the residue column chromatographed (silica gel, 0-25% EtOAc/hexane) to afford **20** (1.56 g, 85%). colorless oil; IR: 1150 cm^{-1}. A small sample of the compound was subjected to preparative TLC (silica gel, 0-25% EtOAc/hexane) to obtain two anomers.

Top-isomer: $[\alpha]_D^{24}$+ 11.7 (*c* 1.03, $CHCl_3$); ^1H NMR: δ 2.29-2.54 (m, 2H), 3.41 (sharp s, 3H), 4.54-4.64 (m, 3H), 5.24-5.28 (m, 1H), 5.72-5.79 (m, 1H), 7.37-7.44 (m, 4H), 7.51-7.58 (m, 2H), 7.98-8.02 (m, 4H); ^{13}C NMR: δ 40.3, 55.1, 62.5, 73.9, 76.4, 103.9, 128.1, 128.2, 129.4, 129.5, 132.8, 133.1, 165.4, 165.9. Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66%. Found: C, 67.71; H, 5.43%.

Bottom-isomer: $[\alpha]_D^{24}$ -68.3 (*c* 0.93, $CHCl_3$); ^1H NMR: δ 2.22-2.30 (m, 1H), 2.45-2.55 (m, 1H), 3.43 (s, 3H), 4.59-4.66 (m, 3H), 5.13-5.16 (m, 1H), 5.73-5.78 (m, 1H), 7.35-7.43 (m, 4H), 7.49-7.57 (m, 2H), 7.96-8.07 (m, 4H); ^{13}C NMR: δ 39.5, 55.1, 64.1, 72.6, 74.8, 78.6, 104.6, 128.2, 128.3, 129.6, 129.7, 132.9, 133.1, 165.8, 166.2. Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66%. Found: C, 67.30; H, 5.54%.

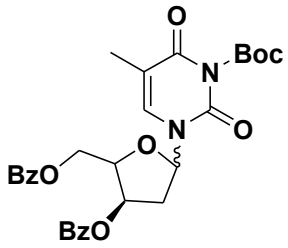
1-[3,5-*O*-Dibenzoyl-2-Deoxy-α,β-D-lyxofuranosyl]-thymine (21).



To a stirred suspension of **20** (1.51 g, 4.24 mmol) and thymine (1.60 g, 12.72 mmol) in anhydrous CH_3CN (30 mL) under Ar was dropwise added BSA (5.2 mL, 21.21 mmol) at 25 °C. The mixture was stirred for 3 h, cooled to -30°C and treated with TMSOTf (3.1 mL, 16.97 mmol). After stirring for 7 d at 25 °C, the mixture was diluted with CH_2Cl_2 (30 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ (1 × 10 mL), H_2O (2 × 20 mL), brine (1 × 5 mL), and dried. After removal of solvent in vacuo, the residue was purified by column chromatography (silica gel, 0-5% MeOH/$CHCl_3$) to obtain **21** (1.28 g, 67%) as an inseparable mixture of α and β anomers. colorless oil; $[\alpha]_D^{22}$ +34.9 (*c* 0.66, $CHCl_3$); IR: 3455 cm^{-1}; ^1H NMR: δ 1.25 (s, 3H), 2.30-2.44 (m, 2H), 4.54-4.83 (m, 3H), 5.65-5.68 (m, 2H), 7.38-7.67 (m, 6H),

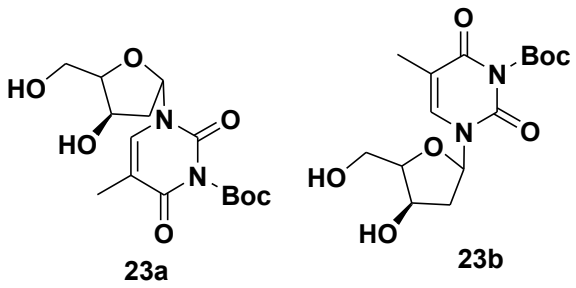
8.05-8.07 (m, 4H), 10.3 (broad s, 1H); ^{13}C NMR: δ 12.4, 12.5, 29.6, 38.9, 39.6, 61.9, 62.7, 72.6, 73.9, 77.6, 80.3, 80.5, 84.4, 87.3, 110.6, 127.9, 128.0, 128.3, 128.6, 128.7, 129.0, 133.0, 133.7, 150.0, 163.4, 165.2. Anal. Calcd. for $C_{24}H_{22}N_2O_7$: C, 63.99; H, 4.92; N, 6.22%. Found: C, 63.88; H, 4.73; N, 6.41%.

3-*N*-Boc-1-[3,5-O-dibenzoyl-2-deoxy-α,β-D-lyxofuranosyl]thymine (22).



To a solution of **21** (1.23 g, 2.73 mmol) in THF (50 mL) was added DMAP (0.67 g, 5.46 mmol) followed by a Boc_2O (1.19 g, 5.46 mmol). The mixture was stirred for 2 h at RT, diluted with EtOAc (20 mL), the organic extract washed with H_2O (2 × 20 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-35% EtOAc/hexane) of the residue gave pure **22** (1.08 g, 72%). colorless oil; $[\alpha]_D^{22}$ +26.6 (*c* 0.83, $CHCl_3$); IR: 1782, 1720 cm^{-1}; ^{1}H NMR: δ 1.53 (s, 9H), 1.64 (s, 3H), 2.52-3.04 (m, 2H), 4.04-4.15 (q, *J* = 7.2 Hz, 1H), 4.58-4.91 (m, 3H), 5.72-5.91 (m, 1H), 6.24-6.35 (m, 1H),7.37-7.60 (m, 6H),7.92-8.00 (m, 4H); ^{13}C NMR: δ 12.2, 12.3, 13.9, 20.7, 27.1, 29.4, 38.6, 39.3, 60.1, 61.7, 62.5, 72.4, 73.7, 80.1, 80.4, 84.5, 86.5, 87.4, 110.2, 110.6, 128.2, 128.4, 128.5, 128.7, 128.8, 129.1, 129.3, 129.4, 133.0, 133.1, 133.4, 133.7, 134.4, 135.2, 147.6, 148.2, 160.9, 161.0, 164.9, 165.2, 165.8, 170.8. Anal. Calcd. for $C_{29}H_{30}N_2O_9$: C, 63.27; H, 5.49; N, 5.09%. Found: C, 63.55; H, 5.66; N, 4.86%.

3-*N*-Boc-1-[2-deoxy-β-D-lyxofuranosyl]-thymine (23a and **23b)**.

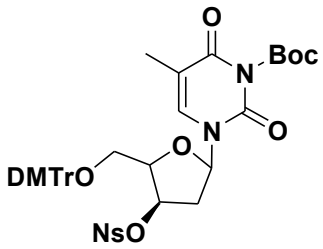


A mixture of **22** (1.02 g, 1.85 mmol) and K_2CO_3 (639 mg, 4.63 mmol) in MeOH (25 mL) was stirred for 5 h. It was concentrated in vacuo, the residue diluted with H_2O (10 mL), and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried and concentrated in vacuo to obtain the crude product, which was purified by column chromatography (silica gel, 0-5% MeOH/$CHCl_3$) to obtain **23a** and **23b** (510 mg, 81%, 30:70).

23a: colorless oil; $[\alpha]_D^{24}$ -11.0 (*c* 0.49, MeOH); IR: 3456 cm^{-1}; ^1H NMR (CD_3OD): δ 1.28 (s, 3H), 1.57 (s, 6H), 1.90 (d, *J* = 6.2 Hz, 3H), 2.20-2.50 (m, 2H), 3.79 (d, *J* = 5.4Hz, 2H), 4.31-4.35 (m, 1H), 4.47-4.49 (m, 1H), 4.86 (s, 2H), 6.18-6.28 (m, 1H), 7.49-7.55 (m, 1H); ^{13}C NMR (CD_3OD): δ 12.4, 27.7, 30.7, 42.4, 61.9, 72.6, 86.1, 86.4, 87.7, 87.9, 88.6, 111.2, 111.6, 137.9, 149.3, 149.9, 163.3. Anal. Calcd. for $C_{15}H_{22}N_2O_7$: C, 52.63; H, 6.48; N, 8.18%. Found: C, 52.41; H, 6.67; N, 8.30%.

23b: colorless oil; $[\alpha]_D^{23}$ +2.9 (*c* 0.49, MeOH); IR: 3455 cm^{-1}; ^1H NMR (CD_3OD): δ 1.28 (s, 3H), 1.57 (s, 6H), 1.90 (s, 3H), 1.98-2.15 (m, 1H), 2.57-2.71 (m, 1H), 3.89-3.96 (m, 3H), 4.36-4.40 (m, 1H), 4.86 (s, 2H), 6.10-6.15 (m, 1H), 7.89-7.98 (m, 1H); ^{13}C NMR (CD_3OD): δ 12.6, 23.7, 27.7, 30.4, 30.7, 42.4, 61.5, 70.8, 70.9, 86.1, 86.5, 86.8, 87.8, 110.3, 110.8, 139.0, 139.3, 149.4, 150.1, 163.3. Anal. Calcd. for $C_{15}H_{22}N_2O_7$: C, 52.63; H, 6.48; N, 8.18%. Found: C, 52.42; H, 6.36; N 8.36%

3-*N*-Boc-1-[3-O-Nosyl-5-O-(4,4´-dimethoxytrityl)-2-deoxy-β-D-lyxofuranosyl]thymine (15).

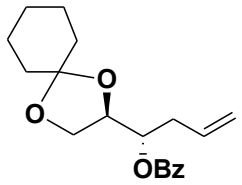


To a stirred solution of **23b** (460 mg, 1.34 mmol) in dry pyridine (7 mL) under Ar was added DMTrCl (546 mg, 1.61 mmol). After stirring for 12 h at 25 ^{o}C, the reaction mixture was poured into ice-cold water (100 mL), stirred for 0.5 h, and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried and concentrated in vacuo to obtain the crude product, which was purified by column chromatography (silica gel, 0-35% EtOAc/hexane) to obtain the corresponding 5-O-DMTr product (700 mg, 81%). colorless syrup; IR: 1175 cm^{-1}; ^{1}H NMR: δ 1.78 (d, *J* = 0.8 Hz, 3H), 2.14 (dd, *J* = 15.1, 2.0 Hz, 1H), 2.57 (ddd, *J* = 15.0, 8.2, 5.4 Hz, 1H), 3.51 (dd, *J* = 10.2, 5.7 Hz, 1H), 3.62 (dd, 10.2, 5.3 Hz, 1H), 3.79 (s, 6H), 4.01 (ddd, *J* = 5.2, 5.2, 3.0 Hz, 1H), 4.43-4.49 (m, 1H), 6.19 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.80-6.88 (m, 4H), 7.19-7.47 (m, 9H), 7.66 (q, *J* = 1.2 Hz, 1H), 8.92 (broad s, 1H); ^{13}C NMR: δ 15.5, 28.5, 40.4, 55.9, 63.6, 70.8, 78.8, 85.0, 86.9, 88.3, 110.9, 114.8, 126.3, 128.3, 129.3, 136.2, 137.5, 143.9, 149.7, 154.3, 158.2, 162.3.

To a cooled (0 ^{o}C) and stirred solution of the above compound (410 mg, mmol) in pyridine (7 mL) under Ar was added NsCl (280 mg, 1.27 mmol). After stirring for 1 h, the reaction mixture was brought to room temperature and stirred further for 21 h. It was diluted with EtOAc (20 mL), filtered, the filtrate washed with ice-cold H_2O (2 × 20 mL) and brine (1 × 5 mL), dried, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0-25% EtOAc/hexane) to

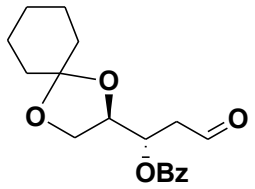
obtain pure **15** (385 mg, 72%). yellow solid; m.p.: 108 °C; (lit.[66g] mp: 106 °C); ^{1}H NMR: δ 1.43 (s, 9H), 1.47 (s, 3H), 1.97-1.99 (m, 1H), 2.11 (dd, *J* = 15.5, 2.0 Hz, 1H), 3.20 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.32 (s, 6H), 3.53 (dd, *J* = 16.5, 6.5 Hz, 1H), 3.72-3.73 (m, 1H), 4.67 (t, *J* = 3.5 Hz, 1H), 5.87 (dd, *J* = 7.5, 3.0 Hz, 1H), 6.71-6.73 (m, 4H), 6.93 (d, *J* = 1.0 Hz, 1H), 7.04-7.07(m, 1H), 7.14-7.17 (m, 2H), 7.31-7.34 (m, 4H), 7.36-7.38 (m, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR : δ 12.1, 27.1, 38.9, 54.5, 61.3, 79.8, 81.5, 84.5, 86.0, 86.9, 109.7, 113.2, 113.3, 124.2, 127.5, 127.7, 127.9, 128.1, 128.2, 130.2, 135.3, 141.2, 144.7, 148.1, 148.3, 150.5, 159.0, 160.6. Anal. Calcd. for $C_{43}H_{45}N_3O_{13}S$: C, 61.20; H, 5.37; N, 4.98; S, 3.80 %. Found: C, 61.44; H, 5.54; N, 5.36; S, 3.71%.

(2*R*,3*S*)-1,2-*O*-Cyclohexylidene-3-benzoyloxy-5-hexene (24).



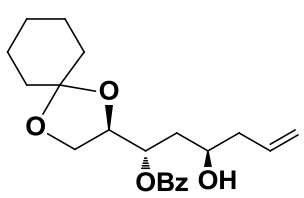
Benzoylation of **6j** (3.0 g, 14.15 mmol) with BzCN (2.22 g, 16.98 mmol) and Et_3N (2.36 mL, 16.98 mmol) in CH_2Cl_2 (70 mL) at 0 °C (5 h) followed by usual isolation and column chromatography (silica gel, 0-15% EtOAc/hexane) furnished **24** (4.3 g, 96%). colorless oil; IR: 1721, 1642 cm^{-1}; ^{1}H NMR: δ 1.2-1.60 (m, 10H), 2.38-2.52 (m, 2H), 3.85-3.93 (m, 1H), 4.00-4.07 (m, 1H), 4.19-4.28 (m, 1H), 5.00-5.13 (m, 2H), 5.21-5.30 (m, 1H), 5.71-5.91 (m, 1H), 7.35-7.51 (m, 3H), 8.01 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR: 23.7, 23.8, 25.0, 34.7, 35.5, 36.0, 65.7, 73.3, 75.8, 110.0, 118.1, 128.2, 129.5, 130.0, 132.9, 165.6. Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.12; H, 7.64%. Found: C, 71.88; H, 7.84%.

(3*S*,4*R*)-4,5-Cyclohexylidenedioxy-3-benzoyloxypentanal (25).

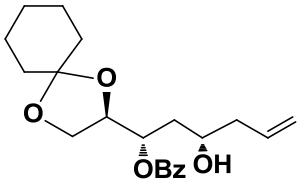


Reductive ozonolysis of **26** (4.20 g, 13.20 mmol) in CH_2Cl_2 (100 mL) followed by reaction with PPh_3 (4.15 g, 15.85 mmol) followed by usual isolation and column chromatography (silica gel, 0-15% EtOAc/hexane) furnished **26** (3.30 g, 78%). colorless oil; IR: 2857, 2711 cm^{-1}.

(4*R*,6*S*,7*R*)- and **(4*R*,6*S*,7*R*)-7,8-Cyclohexylidenedioxy-6-benzoyloxyoct-1-en-4-ols (26a** and **26b).**



26a



26b

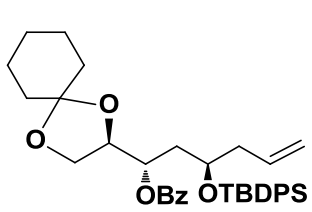
To a well-stirred mixture of **25** (2.80 g**,** 8.81 mmol), allyl bromide (1.97 mL, 17.61 mmol), and Zn dust (1.14 g, 17.61 mmol) in THF (100 mL) was added aqueous saturated NH_4Cl (7 mL) in portions in 20 min. After stirring for another 3.5 h till complete disappearance of the starting material (TLC), the mixture was filtered and washed thoroughly with EtOAc (3 × 15 mL). The combined organic extracts were washed with aqueous 5% HCl (10 mL), H_2O (2 × 10 mL) and brine, and dried. Solvent removal in vacuo and column chromatography (silica gel, 0-20% EtOAc/ hexane) of the residue afforded pure **26a** and **26b** in 55:45 ratio (total yield 2.53 g, 80%).

26a: colorless oil; $[\alpha]_D^{23}$ +12.8 (*c* 1.03, $CHCl_3$); IR: 3455, 1642 cm^{-1}**;** ^{1}H NMR: δ 1.28-1.40 (m, 2H), 1.57 (broad s, 8H), 1.87-2.03 (m overlapped with broad s, 3H),

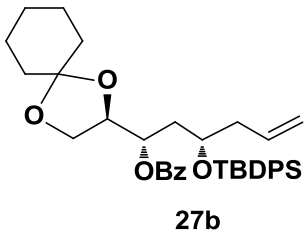
2.17-2.35 (m, 2H), 3.85-3.92 (m, 2H), 4.05-4.13 (m, 1H), 4.26-4.36 (m, 1H), 5.08-5.15 (m, 2H), 5.26-5.35 (m, 1H), 5.74-5.82 (m, 1H), 7.39-7.47 (m, 2H), 7.53-7.99 (m, 1H), 8.00 (d, *J* = 7.0 Hz, 2H); ^{13}C NMR: δ 23.5, 23.6, 24.8, 29.4, 34.5, 35.8, 37.8, 41.5, 65.5, 67.7, 72.1, 110.1, 117.9, 128.1, 129.4, 129.7, 132.9, 134.1, 165.8. Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83%. Found: C, 70.16; H, 7.62%.

26b: colorless oil; $[\alpha]_D^{23}$ +10.9 (*c* 1.09, $CHCl_3$); IR: 3456, 1640 cm^{-1}**;** ^{1}H NMR: δ 1.25 (t, *J* = 2.4 Hz, 2H), 1.35-1.38 (m, 2H), 1.53-1.61 (m, 8H), 1.75-1.86 (m, 2H), 2.04 (sharp s, 1H), 2.24-2.29 (m, 2H), 3.65-3.68 (m, 1H), 3.90-3.92 (m, 1H), 4.09-4.13 (m, 2H), 4.26-4.29 (m, 1H), 5.06-5.10 (m, 2H), 5.34-5.37 (m, 1H), 5.78-5.85 (m, 1H), 7.45 (t, *J* = 2.6 Hz, 2H), 7.58 (t, *J* = 2.4 Hz, 1H), 8.05 (d, *J* = 2.4 Hz, 2H); ^{13}C NMR: δ 15.9, 22.7, 25.5, 25.6, 26.8, 36.4, 37.7, 40.7, 43.4, 62.3, 67.6, 68.3, 74.1, 112.2, 119.3, 130.2, 131.2, 131.6, 135.1, 136.4, 168.6. Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83%. Found: C, 69.65; H, 7.71%.

(2*R*,3*S*,5*R*)- and **(2*R*,3*S*,5*S*)-1,2-Cyclohexylidenedioxy-3-benzoyloxy-5-*tert*-butyldiphenylsilyloxy-oct-7-ene (27a/b).**



27a



27b

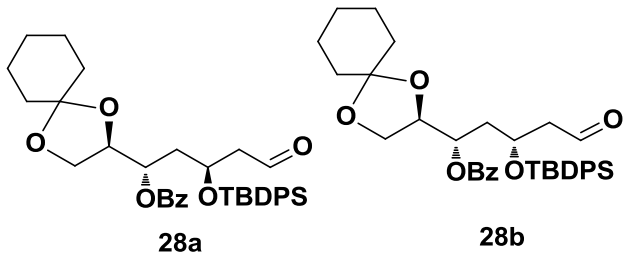
To a stirred solution of **26a/b** (950 mg, 2.64 mmol), imidazole (0.22 g, 3.17 mmol) and DMAP (10 mol%) in CH_2Cl_2 (50 mL) was added TBDPSCl (0.87 g, 3.17 mmol) and the reaction mixture was stirred for 6 h. It was poured in H_2O (30 mL), the organic layer separated and the aqueous layer extracted with $CHCl_3$ (2 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL),

and dried. Solvent removal and column chromatography of the residue (silica gel, 0-5% EtOAc/hexane) afforded **27a** (1.40 g, 89%) and **27b** (1.44 g, 90%) respectively.

27a: colorless oil; $[\alpha]_D^{23}$ +3.62 (*c* 0.94, $CHCl_3$);); IR: 1641 cm^{-1}; ^1H NMR: δ 1.02 (s, 9H), 1.50-1.55 (m, 10H), 1.78-1.82 (m, 1H), 1.95-1.99 (m, 1H), 2.19-2.25 (m, 2H), 3.78-3.81 (m, 1H), 3.94-3.97 (m, 1H), 4.10-4.14 (m, 1H), 4.16-4.19 (m, 1H), 4.86-4.89 (m, 1H), 4.95-4.96 (m, 1H), 5.31-5.34 (m, 1H), 5.60-5.67 (m, 1H), 7.19-7.21 (t, *J* = 2.4 Hz, 2H), 7.26-7.29 (m, 1H), 7.32-7.34 (m, 2H), 7.37-7.42 (m, 4H), 7.61-7.66 (m, 4H), 7.94-7.96 (m, 2H); ^{13}C NMR: δ 12.7, 15.9, 19.6, 20.9, 25.5, 25.6, 26.8, 28.2, 28.7, 36.5, 37.5, 38.8, 43.4, 62.1, 67.3, 71.8, 73.5, 111.9, 119.3, 129.1, 129.2, 129.4, 129.9, 131.2, 131.3, 131.4, 132.0, 134.6, 135.1, 135.8, 136.1, 136.5, 137.6, 137.6, 167.5. Anal. Calcd. for $C_{37}H_{46}O_5Si$: C, 74.21; H, 7.74%. Found: C, 74.09; H, 7.42%.

27b: colorless oil; $[\alpha]_D^{24}$ -1.89 (*c* 1.06, $CHCl_3$); IR: 1641 cm^{-1}; ^1H NMR: δ 1.04 (s, 9H), 1.21-1.45 (m, 2H), 1.46-1.70 (m, 8H), 1.79-1.92 (m, 2H), 2.22-2.35 (m, 2H), 3.68-3.75 (m, 1H), 3.86-3.94 (m, 2H), 4.06-4.13 (m, 1H), 4.96-5.05 (m, 2H), 5.23-5.31 (m, 1H), 5.75-5.96 (m, 1H), 7.21-7.38 (m, 8H), 7.51-7.64 (m, 5H), 7.80-7.84 (m, 2H); ^{13}C NMR: δ 19.2, 23.7, 23.8, 25.0, 26.9, 34.6, 35.7, 36.5, 39.7, 65.0, 69.3, 70.8, 76.4, 110.1, 117.7, 127.4, 128.2, 129.5, 129.6, 129.9, 132.9, 133.7, 133.9, 134.1, 135.7, 165.7. Anal. Calcd. for $C_{37}H_{46}O_5Si$: C, 74.21; H, 7.74%. Found: C, 74.06; H, 7.55%.

(3*R*,5*S*,6*R*)- and **(3*S*,5*S*,6*R*)-1,2-Cyclohexylidenedioxy-3-benzoyloxy-5-(tert)-butyldiphenylsilyloxyheptanal (28a/b).**



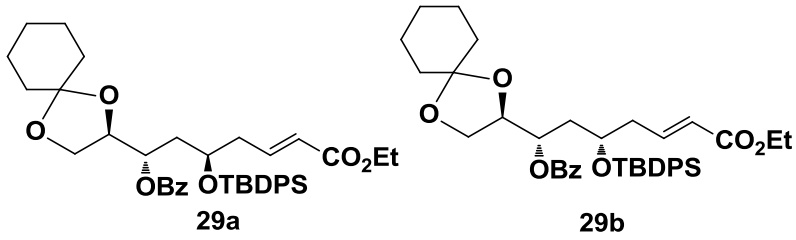
28a **28b**

Reductive ozonolysis of **27a** (1.35 g, 2.26 mmol) and **27b** (1.40 g, 2.34 mmol) in CH_2Cl_2 (100 mL) followed by reaction with PPh_3 (0.71 g, 2.71 mmol for **27a**, 0.74 g, 2.81 mmol for **27b**) followed by usual isolation and column chromatography (silica gel, 0-15% EtOAc/hexane) furnished **28a** (1.08 g, 80%) and **28b** (1.14 g, 81%) respectively.

28a: colorless oil; $[\alpha]_D^{21}$ +20.0 (*c* 0.94, $CHCl_3$); IR: 2857, 2711 cm^{-1}; ^1H NMR: δ 1.01 (s, 9H), 1.46-1.56 (m, 10H), 1.97-2.04 (m, 2H), 2.54-2.59 (m, 2H), 3.71-3.73 (m, 1H), 3.92-3.94 (m, 1H), 4.08-4.10 (m, 1H), 4.33-4.39 (m, 1H), 7.31-7.49 (m, 9H), 7.54-7.57 (m, 1H), 7.62-7.64 (m, 4H), 7.70-7.72 (m, 1H), 7.95-7.97 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR : δ 19.2, 23.7, 23.8, 23.9, 25.0, 26.5, 26.8**,** 34.6, 35.8, 38.5, 50.7, 65.6, 66.4, 71.7, 76.6, 110.3, 127.7, 128.3, 128.4, 128.5, 128.6, 129.7, 129.8, 129.9, 130.1, 132.9, 133.1, 133,5, 134.7, 135.7, 135.8, 165.7, 200.8. Anal. Calcd. for $C_{36}H_{44}O_6Si$: C, 71.97; H, 7.38%. Found: C, 71.64; H, 7.58%.

28b: colorless oil; $[\alpha]_D^{24}$ -8.03 (c 0.77, $CHCl_3$); IR: 2856, 2712 cm^{-1}; ^1H NMR: δ 1.02 (s, 9H), 1.25-1.62 (m, 10H), 1.92-2.04 (m, 2H), 2.55-2.68 (m, 2H), 3.65-3.72 (m, 1H), 3.87-3.95 (m, 1H), 4.03-4.09 (m, 1H), 4.26-4.33 (m, 1H), 5.15-5.23 (m, 1H), 7.27-7.44 (m, 8H), 7.53-7.64 (m, 5H), 7.79-7.83 (m, 2H), 9.65 (d, *J* = 1.6 Hz, 1H); ^{13}C NMR: δ 19.1, 23.6, 23.7, 24.8, 26.8, 34.5, 35.8, 37.9, 49.2, 65.2, 66.3, 70.7, 110.3, 127.5, 127.6, 128.2, 129.4, 129.6, 129.8, 132.8, 133.1, 133.4, 135.7, 165.7, 201.5. Anal. Calcd. for $C_{36}H_{44}O_6Si$: C, 71.97; H, 7.38%. Found: C, 72.16; H, 7.48.

(2*E*,5*R*,7*S*,8*R*)- and **(5*S*,7*S*,8*R*)-8,9-Cyclohexylidenedioxy-7-benzoyloxy-5-*tert*-butyldiphenylsilyloxy-ethyl-2-nonenoate (29a/b).**



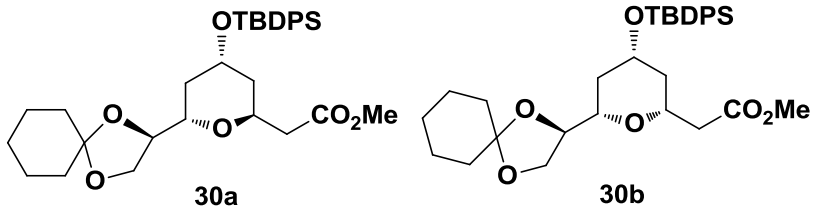
29a **29b**

To a cooled (0 ^{o}C) and stirred suspension of hexane-washed NaH (98 mg, 2.04 mmol for **28a**, 105 mg, 2.20 mmol for **28b**, 50% suspension in oil) in THF (10 mL) was injected triethyl phosphonoacetate (0.4 mL, 2.04 mmol) in THF (10 mL), followed by **28a** (1.02 g, 1.70 mmol) or **28b** (1.10 g, 1.83 mmol) in THF (20 mL) after 15 min. After stirring for 18 h at 25 ^{o}C, the mixture was poured into ice-cold H_2O (30 mL) and extracted with Et_2O (3 × 10 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 **29a** (990 mg, 87%) and **29b** (1.12 g, 91%).

29a: colorless oil; $[\alpha]_D^{21}$ +8.72 (*c* 1.03, $CHCl_3$); IR: 1715, 1685, 928 cm^{-1}. ^{1}H NMR: δ 1.02 (s, 9H), 1.33-1.39 (m, 2H), 1.49-1.57 (m, 8H), 1.85-1.95 (m, 2H), 2.30-2.38 (m, 2H), 3.75-3.77 (m, 1H), 3.94-3.97 (m, 2H), 4.10-4.17 (m, 3H), 5.25-5.27 (m, 1H), 5.67 (d, *J* = 16.2 Hz, 1H), 6.78-6.83 (m, 1H), 7.22-7.24 (m, 2H), 7.29-7.34 (m, 3H), 7.37-7.43 (m, 3H), 7.54-7.57 (m, 1H), 7.61-7.65 (m, 4H), 7.95 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR: δ 14.2, 19.2, 23.7, 23.8, 25.0, 26.9, 34.7, 35.8, 37.7, 39.9, 60.1, 65.6, 69.5, 71.7, 76.7, 110.3, 123.8, 127.5, 127.6, 128.2, 129.6, 129.9, 132.9, 133.1, 133.9, 135.7, 135.8, 144.4, 165.7, 166.1. Anal. Calcd. for $C_{40}H_{50}O_7Si$: C, 71.61; H, 7.51%. Found: C, 71.38; H, 7.41%.

29b: colorless oil; $[\alpha]_D^{22}$ -0.97 (c 1.44, $CHCl_3$). IR; 1720, 1689, 927 cm^{-1}; ^1H NMR: δ 1.08 (s, 9H), 1.29-1.36 (m, 2H), 1.48-1.56 (m, 8H), 1.85-1.97 (m, 2H), 2.47-2.49 (m, 2H), 3.70-3.77 (m, 1H), 3.91-4.10 (m, 2H), 4.13-4.27 (m, 4H), 5.18-5.35 (m, 1H), 5.85 (d, *J* = 15.2 Hz, 1H), 6.90-7.15 (m, 1H), 7.25-7.49 (m, 8H), 7.58-7.68 (m, 5H), 7.84 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR: δ 14.0, 18.9, 23.4, 23.6, 24.8, 34.4, 35.7, 37.2, 37.9, 59.8, 65.0, 68.7, 70.5, 76.4, 109.9, 123.9, 127.3, 128.0, 129.4, 129.5, 132.8, 133.1, 133.5, 135.5, 144.5, 165.4, 168.8. Anal. Calcd. for $C_{40}H_{50}O_7Si$: C, 71.61; H, 7.51%. Found: C, 71.74; H, 7.65%.

2β- and **2*α*-(acetic acid ethyl ester)-4β-*tert*-butyldiphenylsilyloxy-6β-(1″,2″-cyclohexylidenedioxy)tetrahydropyran 30a/b.**



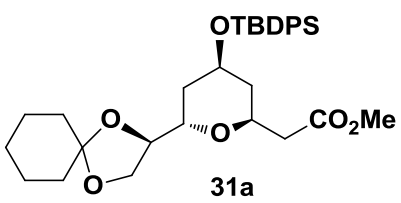
To a cooled (0 ^oC) and well-stirred solution of **29a** (300 mg, 0.447 mmol) in MeOH (15 mL) was added powdered K_2CO_3 (154 mg, 1.12 mmol). After stirring for 5 h, till completion of the reaction (*cf*. TLC), the mixture was concentrated in vacuo to afford a residue. It was dissolved in $CHCl_3$ (15 mL), washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal in vacuo afforded a residue, which on column chromatography (silica gel, 0-10% EtOAc/ hexane) gave **30a** and **30b** in 1:4 ratio with a total yield of 101 mg (40%).

30a: colorless oil; $[\alpha]_D^{24}$ +46.9 (c 0.49, $CHCl_3$); ^1H NMR: δ 1.05 (s, 9H), 1.26 (t, J = 2.0 Hz, 2H), 1.39-1.40 (m, 2H), 1.44-1.47 (m, 2H), 1.53-1.58 (m, 8H), 1.90-1.93 (m, 1H), 2.12 (dd, *J* = 15.0, 5.4 Hz, 1H), 2.44 (dd, *J* = 15.0, 9.0 Hz, 1H), 3.37-3.40 (m, 1H), 3.64 (s, 3H), 3.72-3.74 (m, 1H), 3.95-3.99 (m, 1H), 4.02-4.05 (m, 1H), 4.26-4.29 (m, 1H), 4.39-4.43 (m, 1H), 7.35-7.44 (m, 6H), 7.65-7.70 (m, 4H); ^{13}C NMR: δ 19.0,

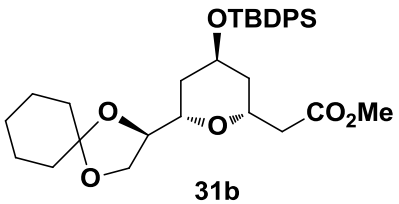
23.7, 24.0, 25.1, 26.8, 29.6, 34.8, 35.6, 36.5, 37.9, 38.4, 51.6, 65.4, 67.2, 67.8, 72.2, 76.3, 109.7, 127.5, 127.6, 129.6, 133.8, 134.0, 135.7, 135.8, 171.3. Anal. Calcd. for $C_{32}H_{44}O_6Si$: C, 69.53; H, 8.02%; Found: C, 69.50; H, 8.03%.

30b: colorless oil; $[\alpha]_D^{21}$ +9.23 (*c* 0.65, $CHCl_3$); ^1H NMR: δ 1.04 (s, 9H), 1.29-1.36 (m, 2H), 1.44-1.46 (m, 2H), 1.49-1.57 (m, 8H), 1.75-1.78 (m, 1H), 1.91-2.00 (m, 1H), 2.31 (dd, *J* = 15.0, 4.8 Hz, 1H), 2.47 (dd, *J* = 15.0, 8.4 Hz, 1H), 3.00-3.03 (m, 1H), 3.55-3.59 (m, 1H), 3.62 (s, 3H), 3.74-3.85 (m, 3H), 3.91-3.94 (m, 1H), 7.35-7.74 (m, 6H); 7.65-7.70 (m, 4H); ^{13}C NMR: δ 19.1, 23.8, 24.0, 25.1, 26.9, 27.0, 29.7, 34.9, 36.4, 37.7, 40.6, 40.9, 41.9, 51.6, 66.6, 69.1, 72.3, 77.2, 109.8, 127.6, 129.7, 134.1, 134.2, 135.7, 171.3. Anal. Calcd. for $C_{32}H_{44}O_6Si$: C, 69.53; H, 8.02%; Found: C, 69.52, 8.00%.

2β- and **2α-(acetic acid ethyl ester)-4β-*tert*-butyldiphenylsilyloxy-6β-(1″,2″-cyclohexylidenedioxy)tetrahydropyran 31a/b.**



31a



31b

As above, debenzoylation of **29b** (400 mg, 0.596 mmol) with K_2CO_3 (206 mg, 1.49 mmol) in MeOH (15 mL), followed by isolation and purification by column chromatography (silica gel, 0-10% EtOAc/hexane) gave **31a** and **31b** in 1:2 ratio with a total yield of 128 mg (38%).

31a: colorless oil; $[\alpha]_D^{22}$ +6.1 (*c* 1.80, $CHCl_3$); IR: 1742 cm^{-1}. ^1H NMR: δ 1.07 (s, 9H), 1.28-1.29 (m, 2H), 1.37-1.41 (m, 2H), 1.49-1.57 (m, 8H), 1.68-1.80 (m, 2H), 2.54 (dd, *J* = 15.4, 4.9 Hz, 1H), 2.92 (dd, *J* = 15.4, 9.1 Hz, 1H), 3.67 (s, 3H), 3.72-3.74 (m, 1H), 3.83-3.85 (m, 1H), 3.91-3.95 (m, 1H), 3.98-4.00 (m, 1H), 4.10-4.14 (m, 1H), 4.16-4.19 (m, 1H), 7.32-7.42 (m, 6H), 7.62-7.65 (m, 4H); ^{13}C NMR: δ 15.8,

20.8, 25.5, 25.7, 26.9, 28.7, 31.4, 36.4, 36.6, 38.1, 39.1, 41.6, 53.3, 67.3, 68.7, 70.2, 72.2, 77.5, 111.6. Anal. Calcd. for $C_{32}H_{44}O_6Si$: C, 69.53; H, 8.02%. Found: C, 69.35; H, 8.18%.

31b: colorless oil; $[\alpha]_D^{22}$ -3.48 (*c* 1.61, $CHCl_3$); IR: 1743 cm^{-1}; ^1H NMR: δ 1.09 (s, 9H), 1.25-1.30 (m, 2H), 1.34-1.43 (m, 2H), 1.54-1.63 (m, 9H), 1.86-1.88 (m, 1H) , 2.33 (dd, *J* = 15.4, 4.9 Hz, 1H), 2.48 (dd, *J* = 15.4, 7.0 Hz, 1H), 3.68 (s, 3H), 3.85-3.93 (m, 3H), 4.00-4.01 (m, 1H), 4.20-4.24 (m, 1H), 4.38-4.41 (m, 1H), 7.36-7.44 (m, 6H), 7.61-7.73 (m, 4H); ^{13}C NMR: δ 19.2, 23.7, 24.0, 25.1, 26.5, 26.9, 34.9, 35.1, 36.4, 38.4, 41.1, 51.5, 65.4, 66.5, 68.9, 73.3, 77.6, 109.8, 127.6, 129.6, 133.7, 133.9, 134.7, 135.6, 171.4. Anal. Calcd. for $C_{32}H_{44}O_6Si$: C, 69.53; H, 8.02%. Found: C, 69.38; H, 7.80%.

CHAPTER III

CHEMOENZYMATIC SYNTHESES OF TWO MACROLIDES

III.1: Preamble to Diversity-Oriented Synthesis

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. To this end, building small-molecule libraries via diversity-oriented syntheses (DOS) *vis-à-vis* the conventional target-oriented syntheses is appealing. Generation of high levels of stereochemical and skeletal diversity is especially challenging, and the DOS approach helps to incorporate a high degree of structural diversity efficiently.[82] Generation of structurally diverse compounds is 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.[83] Increasing the size and number of rigidifying elements (macrocycles, polycycles, olefins, etc.) in small molecules is equally essential for these compounds to bind to sites of protein-protein interactions. 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 approach is crucial to achieve stereochemical diversity, since each substrate might react with a different diastereoselectivity to the 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 target compounds of interest. More recently, our group has been interested in developing divergent synthetic strategies, as these are particularly best suited for our long-standing interest in anti-inflammatory, anti-neoplastic and immunomodulatory activities of natural compounds.[23,84] Amongst the various targets, macrolides are of wide occurrence in various natural sources, and often show impressive medicinal and other biological activities.[85] 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.[86] Moreover, several of these provide synthetic challenges.

During literature search for the macrolides of our interests, several compounds **IV-VIII** (**Figure III.1.1.**) were identified to contain the hept-6-ene-2,5-diol derivatives **A** (different stereomers and Pgs) as the common structural motif (shown in bold bonds in **Figure III.1.1.**). 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 different stereomers of **A** as the ideal small-molecule chiral DOS-intermediates. Very recently, we have synthesized the unit **A** through a chemoenzymatic approach and used some of its stereomers and/ or derivatives for the synthesis of stagonolide E and pyrenophorol.[84a] In the present work, we synthesized all the stereomers of **A** in considerably higher amounts and used two of its diastereomers to synthesize two 14-membered bis-macrolides clonostachydiol (**IV**) and acremodiol (**V**).

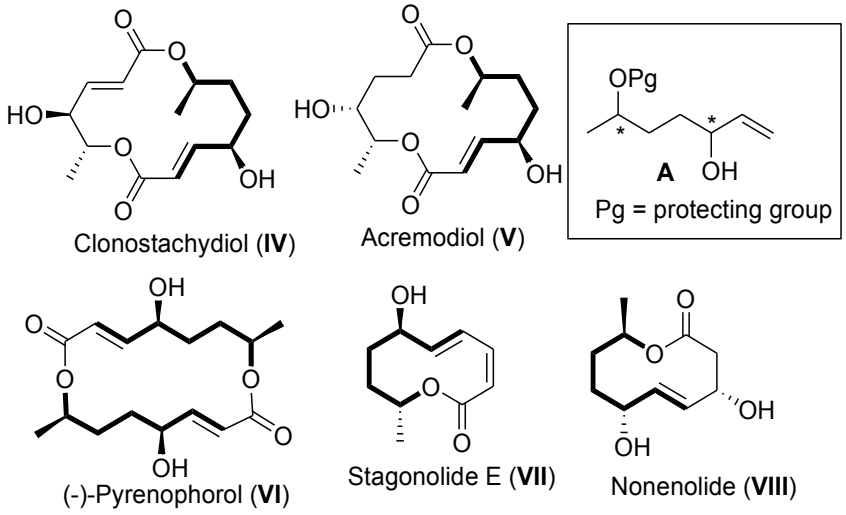


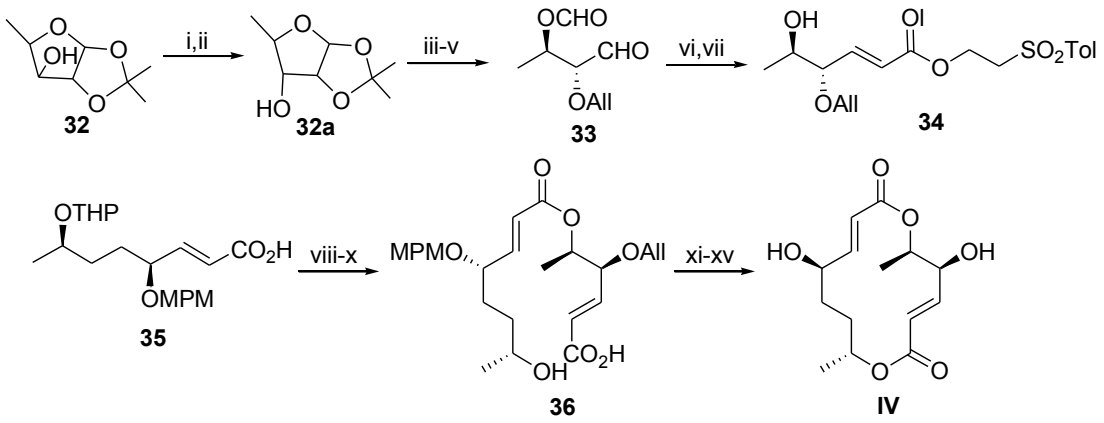
Figure III.1.1. Some representative natural products bearing the hept-6-ene-2,5-diol structural motif.

Compound **IV** was isolated from the marine algae-derived fungus *Gliocladium* sp. and *Clonostachys cylindrospora* (strain FH-A 6607).[87a] In the MTT reduction assay, it showed significant anti-proliferative property against human leukemia (L1210), colon carcinoma (HT29), and non-small-cell lung carcinoma (A549) cell lines, with IC_{50} values of 4.5, 4.2 and 5.7 μg/mL respectively. Subcutaneous administration of **IV** (2.5 mg/kg) also reduced *Haemunchus cortortus*, one of the most pathogenic nematodes of ruminants by 80-90%.[87a] Despite being only moderately cytotoxic (IC_{50} 25 μM) against murine leukemic P388 cell line, it is a precursor for 4-ketoclonostachydiol, which is highly cytotoxic (IC_{50} 0.55 μM) against the same cell line and also shows significant growth inhibition against *Bacillus subtilis* and the fungi, *Trichophyton mentagrophytes and Cladosporium resinae*.[87b] Its other oxidation products *viz.* 10-ketoclonostachydiol and the corresponding diketone are also significantly cytotoxic and exhibit antimicrobial property.[87b] On the other hand, the macrolide **V** was isolated from a soil sample of the Bermuda islands, Acremonium-like anamorphic fungus. Its structure was assigned based on the NMR, ESI-MS, and FABMS spectroscopy.[87c] It showed inhibitory property against a series of Gram positive bacteria and fungi, unlike another bis-macrolide, colletodiol.[87d] It

was also active in cellular phagocytosis assay using dog PMNL cells and reduced the oxidative burst at concentrations ≥ 4 μg/mL. Compound **IV** has four stereogenic centres with (2*R*,3*S*,8*R*,11*R*)-configuration that was established by the first asymmetric synthesis.[88] However, the absolute configuration of **V** remains unresolved. The proposed absolute configuration as 5*R*,6*R*,11*R*,14*R* of natural **V** has been refuted by Sharma *et al.* based on their synthesis of the same isomer of **V**.[89]

III.2: Previous Syntheses of Clonostachydiol

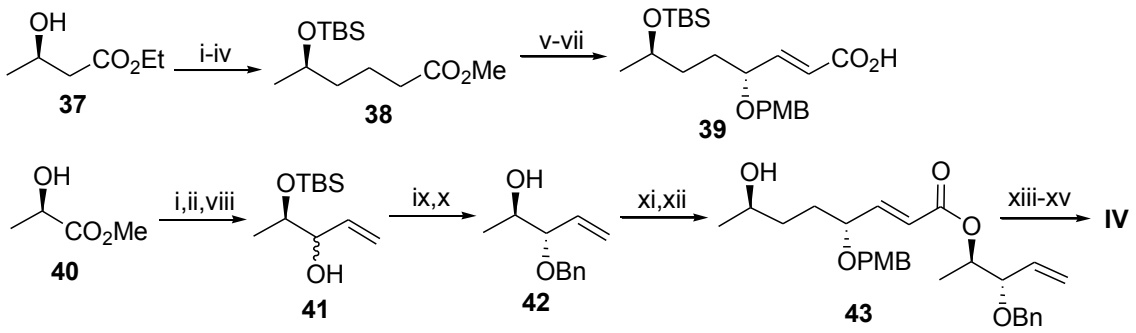
Despite these biological attributes, only three syntheses of **IV** have been reported so far. Rama Rao *et al*. carried out the first total synthesis (**Scheme III.2.1.**) of clonostachydiol.[88] This involved conversion of the xylose derived compound **32** to its C-4 epimer **32a** by PDC oxidation followed by $NaBH_4$ reduction. Its *O*-allylation followed by acidic deacetalization gave an intermediate lactol, which on reaction with $NaIO_4$ furnished the aldehyde **33**. Its Wittig reaction with a suitable phosphorane and acid catalyzed de-O-formylation afforded **34**. The other acid component **35** was synthesized in 14 steps starting from 1,2-O-isopropylidene D-glyceraldehyde. Esterification of **35** with **34** by the Yamaguchi protocol, depyranylation and selective saponification gave the seco-acid **36**. Another Yamaguchi reaction and selective removal of the MPM group, Mitsunobu inversion of the resultant alcohol, deacetylation with thiourea and deallylation gave **IV**.



i) PDC/Ac_2O/CH_2Cl_2/40 ^oC, ii) $NaBH_4$/EtOH, iii) NaH/allyl bromide/THF, iv) Conc. H_2SO_4/ 60% aqueous AcOH/60 ^oC, v) $NaIO_4$/MeOH, vi) $Ph_3P{=}CHCO_2(CH_2)_2SO_2Tol$/$C_6H_6$/80 ^oC, vii) 2% HCl/1:1 dioxane-water, viii) 2,6-Trichlorobenzoyl chloride/Et_3N/THF; DMAP/toluene/room temp., ix) Cat. conc. HCl/1:1 MeOH-EtOAc, x) DBN/C_6H_6/room temp., xi) 2,6-Trichlorobenzoyl chloride/Et_3N/THF; DMAP/toluene/95 ^oC, xii) DDQ/CH_2Cl_2-H_2O, xiii) $ClCH_2CO_2H$/DEAD/Ph_3P/THF, xiv) Thiourea/MeOH-$CHCl_3$/room temp., xv) 10% Pd-C/PTSA/MeOH/60 ^oC.

Scheme III.2.1.

Yadav *et al.*[90a] employed racemic epichlorohydrin as a precursor and used Jacobsen's hydrolytic kinetic resolution and asymmetric reactions like Sharpless asymmetric dihydroxylation and Sharpless epoxidation for making the desired fragments towards the synthesis of clonostachydiol. In the latest synthesis,[90b] the hydroxy ester **37** was two-carbon homologated to compound **38** via silylation, DIBAL-H reduction, followed by Wittig reaction of the resultant aldehyde with a C2-ylide and a chemoselective olefin reduction. Its DIBAL-H reduction, followed by a one-pot asymmetric MacMillan α-hydroxylation,[91] Horner–Emmons olefination and $CuSO_4$-mediated O–N bond cleavage, and alkaline hydrolysis furnished the key conjugated acid **39**. For the synthesis of the other fragment, the hydroxy ester **40** was silylated, its ester function reduced with DIBAL-H and the product aldehyde reacted with CH_2=CHMgBr to obtain **41** as a mixture of C-3 epimers. This on benzylation and desilylation gave **42** as a pure enantiomer, which on a DCC-mediated reaction with **39** and subsequent desilylation afforded **43**. Its acrolylation, debenzylation and ring-closing metathesis (RCM) provided **IV** (**Scheme III.2.2.**).

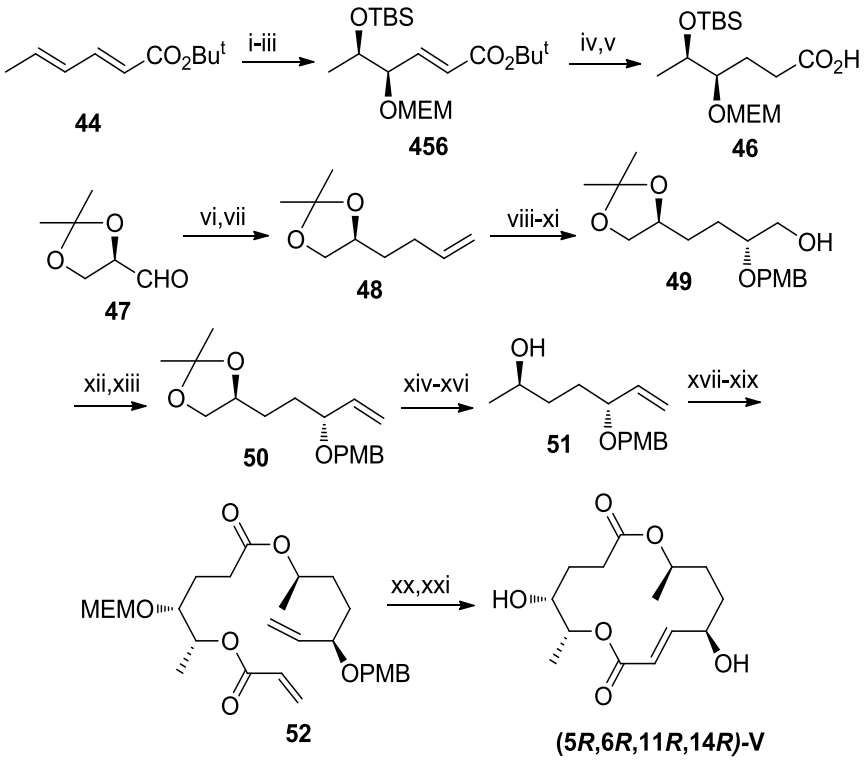


i) TBSCl/imidazole/CH_2Cl_2/room temp./6 h, ii) DIBAL-H/CH_2Cl_2/-78 ^oC/0.5 h, iii) Ph_3PCHCO_2Me/ CH_2Cl_2/room temp./6 h, iv) $NiCl_2.6H_2O/NaBH_4$/MeOH/room temp./1 h, v) Nitrosobenzene/L-proline/DMSO/ 20 ^oC/25 min; triethyl phosphonoacetate/DBU/LiCl/0 ^oC/1 h; MeOH/$CuSO_4.5H_2O$/room temp./overnight, vi) PMB imidate/PTSA/CH_2Cl_2/room temp./8 h, vii) $LiOH.H_2O$/aqueous THF/8 h, viii) vinylmagnesium bromide/Et_2O/-78 ^oC/ 2 h, ix) NaH/BnBr/Bu_4NI/THF/room temp./8 h, x) Bu_4NF/THF/room temp./8 h, xi) **39/**DCC/DMAP/CH_2Cl_2/0 ^oC/12 h, xii) PTSA/MeOH/^oC/0.5 h, xiii) Et_3N/acryloyl chloride/CH_2Cl_2/0 ^oC/0.5 h, xiv) $TiCl_4/CH_2Cl_2$/0 ^oC/1 h, xv) Hoveyda–Grubbs-II/toluene/80 ^oC/0.5 h.

Scheme III.2.2.

III.3: Previous Synthesis of Acremodiol

In the only synthesis of **V** (**Scheme III.3.1.**) reported so far,[89] the ester **44** was subjected to Sharpless' asymmetric dihydroxylation with AD-mix-β and the resultant diol was converted to compound **45** by silylation of one of the carbinols followed by MEM protection of the other. Its catalytic hydrogenation and alkaline hydrolysis gave **46**. In a parallel sequence of reactions, the aldehyde **47** was converted to the alkene **48** by allylation followed by tosylation and $LiAlH_4$ reduction. Epoxidation of **48**, hydrolytic kinetic resolution of the product with (*S*,*S*)-Jacobsen's catalyst, reaction of the resultant diol with anisaldehyde dimethyl acetal and DIBAL-H reduction gave **49**. This on Swern oxidation and Wittig olefination with methylphosphorane afforded **50**. Its deacetalization, tosylation and $LiAlH_4$ reduction furnished **51**. Esterification of **51** with the acid **46** under Yamaguchi conditions, desilylation and acrylation gave **52**. This on an RCM reaction followed by removal of the PMB and MEM groups afforded the target compound.



(i) AD-mix-β/methane sulfonamide/tert-BuOH-H_2O, (ii) TBSCl/Et_3N/DMAP/CH_2Cl_2, (iii) MEMCl/DIPEA/CH_2Cl_2, (iv) H_2/PtO_2/EtOAc/40 psi, (v) Aqueous NaOH/MeOH, (vi) Allylation; *p*-TsCl/Et_3N/DMAP/CH_2Cl_2, (vii) $LiAlH_4$/THF/reflux, (viii) *m*-CPBA/$CHCl_3$, (ix) (*S*,*S*)-Jacobsen catalyst/AcOH/toluene; H_2O, (x) PPTS/Anisaldehyde dimethylacetal/CH_2Cl_2, (xi) DIBAL-H/CH_2Cl_2, (xii) $(COCl)_2$/DMSO/Et_3N/CH_2Cl_2/-78 ^oC, (xiii) Ph_3PCH_3I/*n*-BuLi/THF, (xiv) Aqueous 60% AcOH, (xv) *p*-TsCl/Et_3N/DMAP/CH_2Cl_2, (xvi) $LiAlH_4$/THF/0 - r. t., (xvii) 2,4,6-Trichlorobenzoyl chloride/Et_3N/THF/**46**/DMAP/toluene, (xviii) $ZrCl_4$/CH_3CN/0 ^oC, (xix) Acryloyl chloride/DIPEA/CH_2Cl_2, (xx) Grubbs' I/CH_2Cl_2/reflux, (xxi) $TiCl_4$/CH_2Cl_2.

Scheme III.3.1.

III.4: Present Work

From the foregoing it is evident that the previous syntheses of **IV** were all target-specific, while the only synthesis of **V** did not provide its naturally occurring enantiomer. Moreover, most of these were unsuitable to provide the stereomers of **IV**. The diverse biological activities of the steromers of clonostachydiol diastereomers and/ or derivatives,[87a,b] coupled with limited syntheses of **IV** and **V** warrant formulation of a flexible synthetic strategy for both the target compounds.

Based on our identification of **A** as a key DOS-unit for both **IV** and **V**, the initial task was the preparation of different stereomers of **A** or its equivalent as these. We paid particular attention to using commercially available and inexpensive materials to obtain the products in high yields under operationally simple reaction conditions. Because the chirality in the **A**-unit was derived from two stereogenic carbinol centres, a lipase acylation strategy seemed ideal to obtain its stereomers. For this, we relied on the Novozym 435®-catalyzed acylation strategy using vinyl acetate as the acyl donor and synthesized all the four stereomers of **A** (Pg = TBDPS).

The retrosyntheses of **IV** and **V**, syntheses of the stereomers/derivatives of the DOS intermediate and their conversions to the target molecules are sequentially presented in the following.

III.5: Retrosyntheses of Compounds IV and V

Based on retrosynthesis, we envisioned that the synthesis of **IV** (**Figure III.5.1.**) could be achieved by a RCM of the unit **B** which, in turn, could be obtained by esterification between the hept-6-ene-2,5-diol derivative $\mathbf{A^1}$ and the 4,5-dihydroxyhex-2-enoic acid derivative **C** under Mitsunobu conditions. We planned to use (*R*)-2,3-cyclohexylidene glyceraldehydes (**4a**) as the chiral template to synthesize unit $\mathbf{C^1}$, the precursor of **C**. Due to its diverse functionalities, our group has

extensively used **4a** for the syntheses of a wide range of biologically active natural compounds.[24]

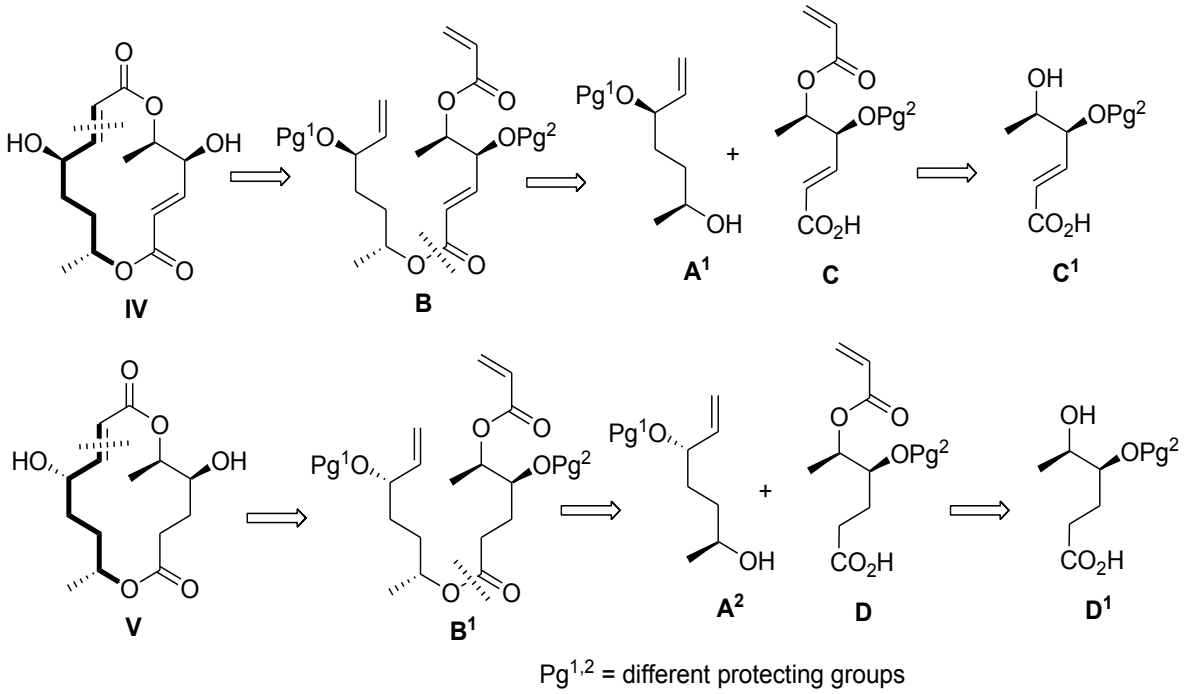


Figure III.5.1. Retrosynthesis of clonostachydiol (**IV**) and (5*S*,11*S*)-acremodiol (**V**).

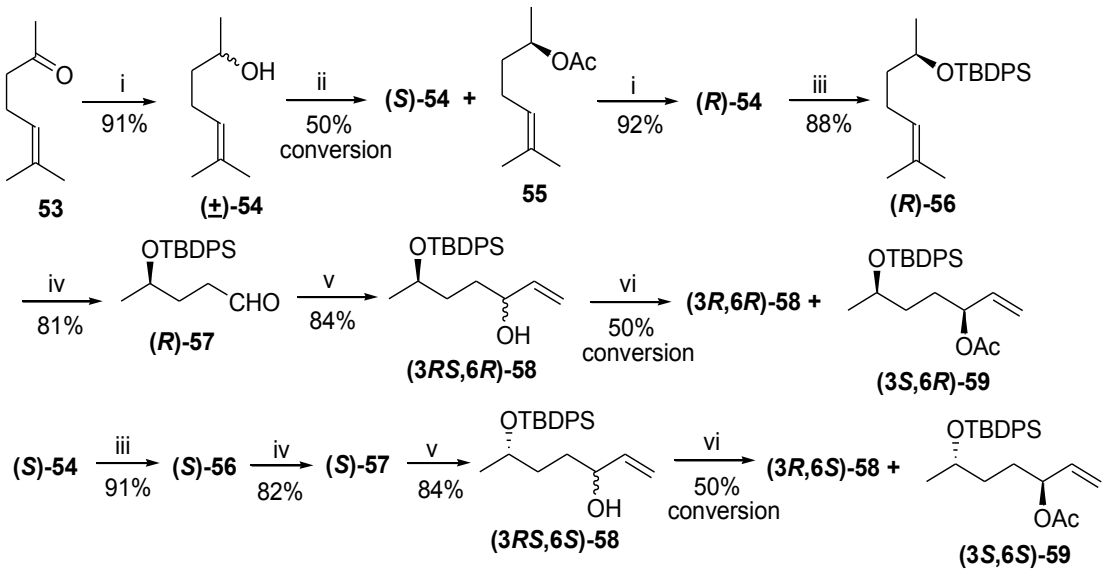
Compound **V** could also be accessed following a similar synthetic strategy as above. However, instead of **C**[1]**/C** units the hydrogenated derivatives of their C-4 epimer **D**[1]**/D** were required for the synthesis. We planned to synthesis the (5*S*,6*R*,11*S*,14*R*)-isomer of **V**, because the originally proposed structure of **V** was proved wrong.[89] In view of this, the (3*S*,6*S*)-stereomer of the DOS intermediate **A**[2] was used as the **A** unit.

III.6: Preparation of the DOS Intermediates

For the synthesis (**Scheme III.6.1.**), the commercially available ketone **53** was reduced with $LiAlH_4$ to furnish the alcohol (±)-**54**. Its IR hydroxyl band at 3370 cm^{-1} in place of the carbonyl band, and the NMR resonances *viz.* δ_H 1.16 (d, 3H, CH_3-CH(OH)), 3.76-3.92 (m, 1H, -CH(OH)) and δ_C 67.8 (carbinol) confirmed its structure. The enantiomers of **54** have been earlier prepared using chiral starting materials,[92a] by its lipase-catalyzed kinetic resolution,[92b-e] or microbial oxidation,[92f] by asymmetric reduction of **53** with baker's yeast or alcohol dehydrogenases,[92g-i] as well as by chemical kinetic resolution.[92j] The alcohol (±)-**54** was subjected to a Novozym 435®-catalyzed acetylation with vinyl acetate in hexane at room temperature to obtain the (*R*)-acetate **55** and (*S*)-**54**, both in >98% ees (E≥195) at 50% conversion (*cf.* GC, 50 min). A similar previously reported protocol using a *C. antarctica B* lipase preparation required 30 h for the conversion.[92d] Compared to that, the present protocol is better. The IR band at 1735 cm^{-1} and NMR resonances at δ_H 2.03 (s) and δ_C 170.3 of (*R*)-**55** accounted for the OAc functionality, confirming its structure. Its reduction with $LiAlH_4$ furnished the alcohol (*R*)-**54**. The % ees of (*R*)- and (*S*)-**54** were determined from the relative intensities of the methoxyl resonances of the corresponding MTPA esters,[14b] while their configurations were assigned based on the reported optical rotations of the individual enantiomers.[93a] In a recent paper, same sign of the specific rotations of (*S*)-**54** and (*R*)-**55** have been reported.[93b] However, our results are consistent with those reported by another group,[93c] and have been derived by carrying out the reaction 10-15 times at different scales. Earlier, two groups have reported different reaction rates for the CAL-B lipase-catalyzed acylation of (±)-**54** under similar reaction conditions.[92d,93b] Steinreiber et al.,[92e] reported higher yield and % ee of (*R*)-**55** by combining the lipase-catalyzed acylation with *in situ* inversion or,

alternatively, dynamic kinetic resolution (DKR) using a Ru-catalyst. Because we wanted to prepare all the stereomers of the DOS intermediate, both (*R*)- and (*S*)-**54** were required. Hence, the DKR protocol was unsuitable for the present work.

Silylation of the individual enantiomers of **54**, as previously described gave (*R*)- and (*S*)-**56**. Their ^{1}H NMR spectra were similar, and showed peaks at δ ~1.05 (s, *t*-Bu) and multiplets for the aryl protons at δ 7.34-7.44 (6H) and δ 7.68-7.72 (4H), confirming their structures. Reductive ozonolysis (O_3/Ph_3P) of (*R*)- and (*S*)-**56** in CH_2Cl_2 furnished the aldehydes (*R*)- and (*S*)-**57** [IR: 2713, 1720 cm^{-1}; NMR: δ_H 9.69 (s, 1H) and δ_C 202.1] respectively. Reaction of (*R*)-**57** with commercially available vinylmagnesium bromide furnished the allylic alcohol (3*RS*,6*R*)-**58** as a 1:1 mixture of C-3 epimers. Its ^{1}H NMR spectrum showed CH(OH) multiplets at δ 3.96-4.02 (1H), olefinic multiplets at δ 5.04-5.25 (2H) and δ 5.65-5.82 (1H), while the ^{13}C NMR spectrum showed peaks at δ ~ 73.1 (carbinol) and δ 114.5 (terminal alkene). This on a Novozym 435®-catalyzed acetylation furnished (3*R*,6*R*)-**58** and (3*S*,6*R*)-**59** in >98% ees at 50% conversion (~ 6 h). A similar sequence of reaction with (3*RS*,6*S*)-**58** also proceeded uneventfully and provided the target intermediate diastereomers (3*R*,6*S*)-**58** and (3*S*,6*S*)-**59** in enantiomerically pure forms (**Scheme III.6.1.**). The second lipase-catalyzed acylation reactions for the syntheses of the diastereomers of the **A**-unit were highly stereoselective, and did not proceed further even under extended shaking.



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.

Scheme III.6.1.

The NMR spectra of the diastereomeric acetates (3*S*,6*R*)- and (3*S*,6*S*)-**59** showed characteristic -$OCOCH_3$ resonances such as δ_H ~2.01 (s, 3H) and δ_C ~170.3. The Novozym 435®-catalyzed acetylation of allylic alcohols is reported to furnish the (*S*)-acetate.[94] In analogy, the absolute configurations of the alcohol and acetate were empirically assigned. This is also consistent with Kazlauskas' empirical rule.[95] Taken together the above results suggested that chirality at the distant C-6 centre did not have any effect on the diastereoselectivity of the lipase-catalyzed resolution of **58**. Different immobilized CAL-B lipase preparations was earlier reported to show different enantioselectivities in the hydrolysis of certain racemic esters.[96] Hence, we also attempted acetylation of (3*RS*,6*R*)- and (3*RS*,6*S*)-**58** 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 and hence, abandoned.

Previously, Enders and Nguyen described the synthesis of the analogs of (3*R*,6*S*)-**58** and (3*S*,6*S*)-**59** containing the *tert*-butyldimethylsilyl protection at C-6.[97] For this, the C-3 stereogenic centre was instilled by carrying out a lipase PS "Amano"-catalyzed acetylation with vinyl acetate in diisopropyl ether at 40 ^{o}C for 72 h. 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*R*,6*S*)-**58**, and (3*S*,6*R*)-**59** are shown in **Figures III.6.1.**-**III.6.6**.

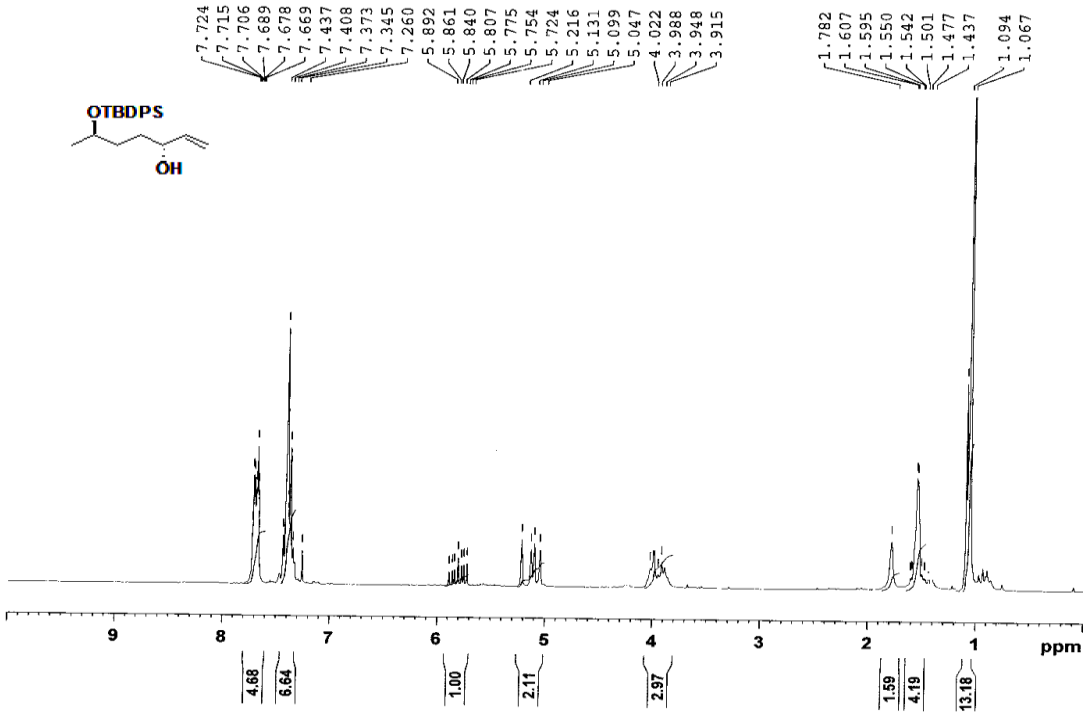


Figure III.6.1. ^{1}H NMR spectrum of (3*R*,6*R*)-**58**

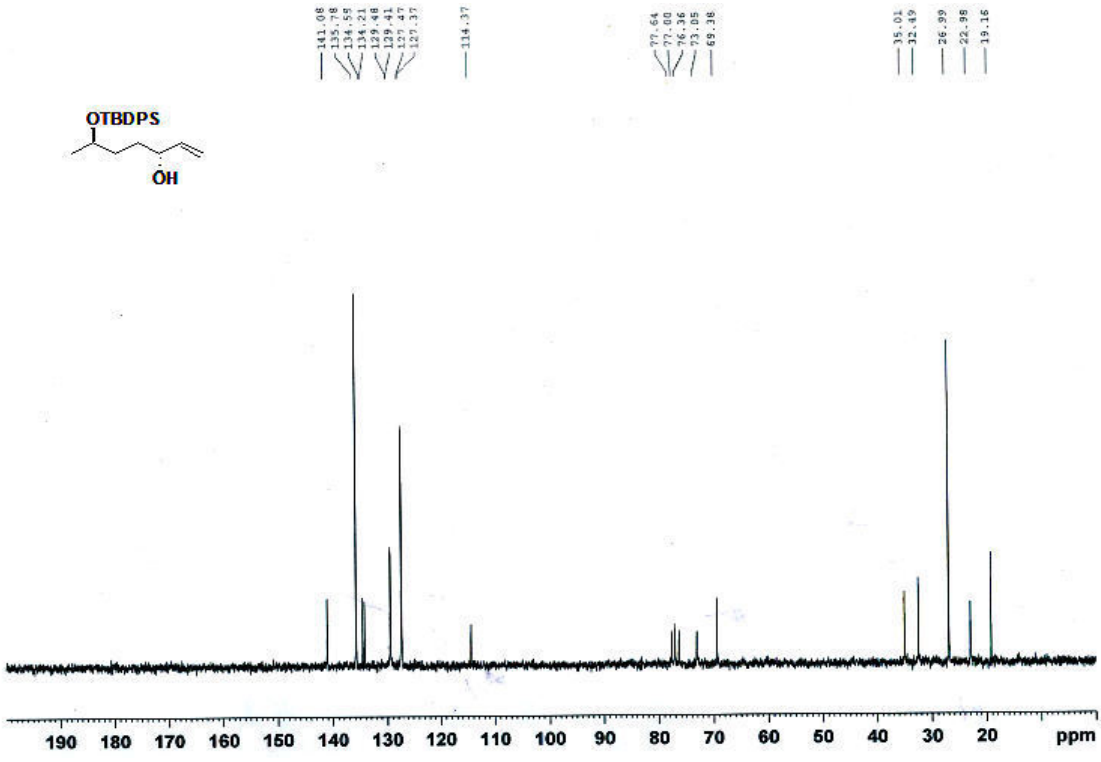


Figure III.6.2. ^{13}C NMR spectrum of (3*R*,6*R*)-**58**

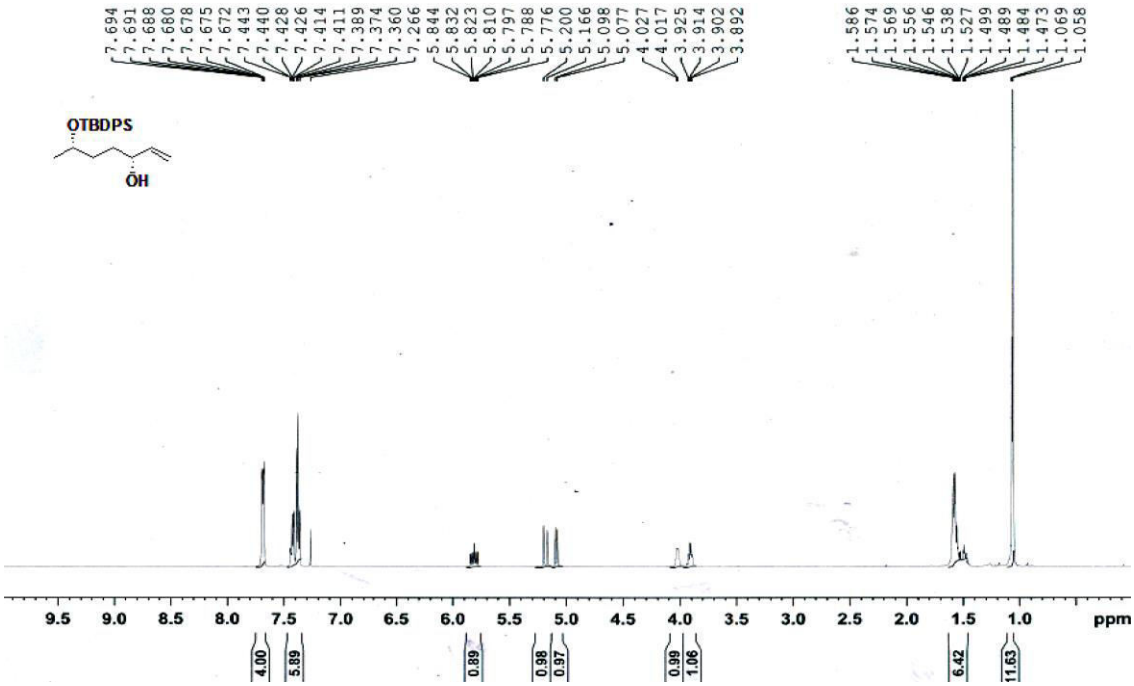


Figure III.6.3. ^{1}H NMR spectrum of (3*R*,6*S*)-**58**

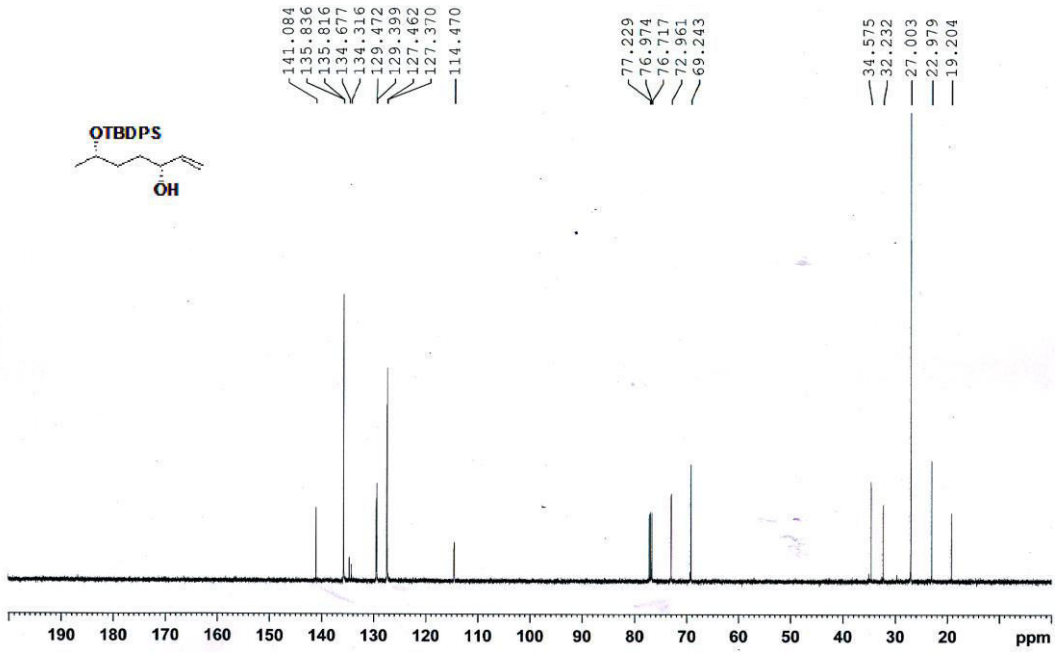


Figure III.6.4. ^{13}C NMR spectrum of (3*R*,6*S*)-**58**

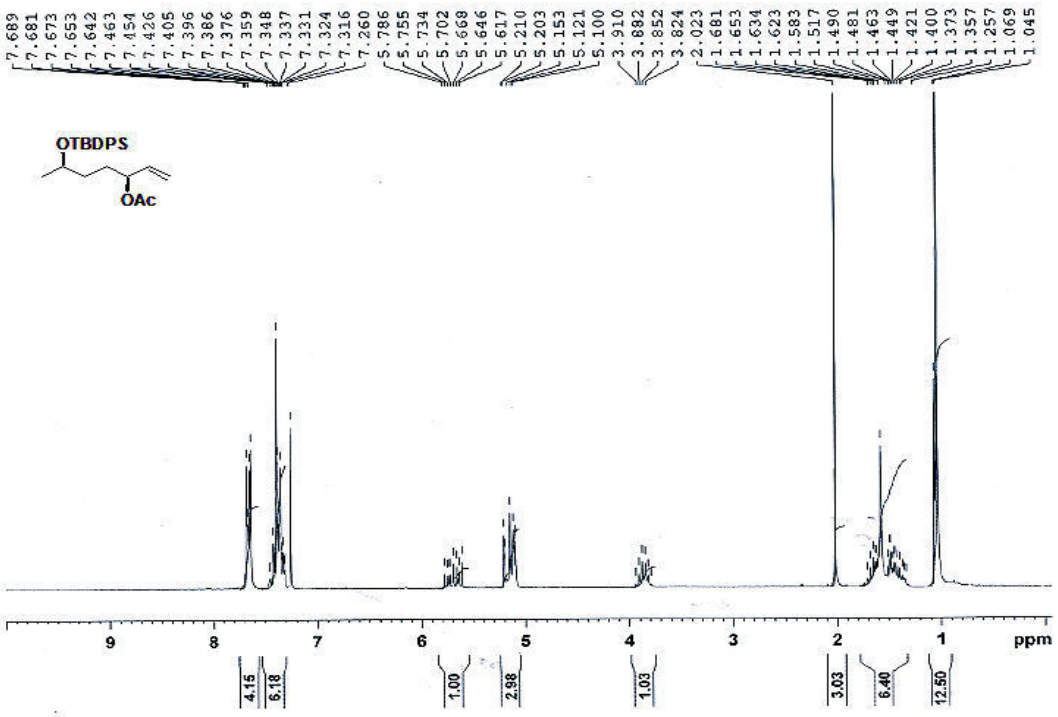


Figure III.6.5. ^{1}H NMR spectrum of (3*S*,6*R*)-**59**

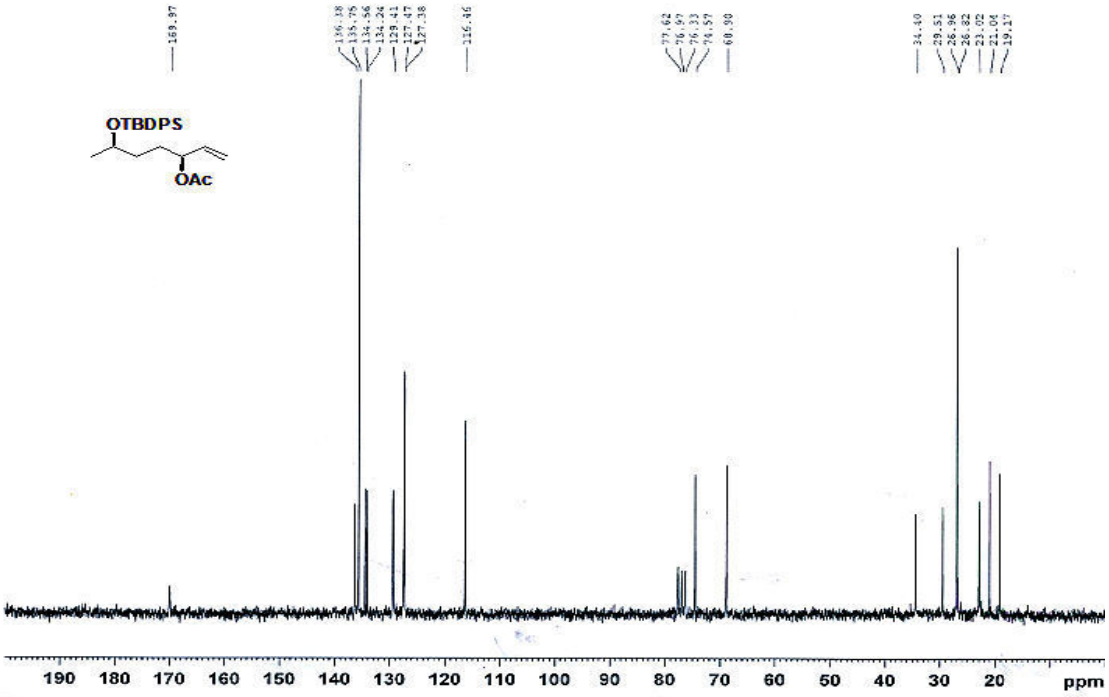


Figure III.6.6. ^{13}C NMR spectrum of (3*S*,6*R*)-**59**

III.7: Synthesis of Clonostachydiol (IV)

The synthesis (**Scheme III.7.1.**) commenced with the alcohol (3*R*,6*S*)-**58** was converted to the benzyl ether **60** by reaction with BnBr/NaH in THF. Its ^{1}H NMR doublets at δ 4.30 and 4.56 (each 1H, J = 12.0 Hz, $PhCH_2$-) and the multiplets at δ 7.25-7.29 (5H) were indicative of the Bn group. This on desilylation with Bu_4NF furnished the alcohol **61** (**A**^{1}-unit equivalent, IR band at 3456 cm^{-1} and absence of NMR resonances for the TBDPS moiety) for its subsequent use in esterification with fragment **C**. For the synthesis of the **C1** fragment, the aldehyde **4a** was reacted with vinylmagnesium bromide to obtain the allylic alcohol **62** as an inseparable mixture of the C-3 epimers. The compound was characterized from the ^{1}H NMR resonances at δ 4.07-4.38 (two m, 1H, allylic CH(OH)), olefinic multiplets at δ 5.18-5.42 (2H) and 5.70-5.89 (1H), and ^{13}C NMR peaks at δ 77.5 and δ 77.9, 73.2 (carbinol), and 116.0 (terminal alkene).

Earlier, we have observed appreciable *anti*-selectivity in the addition of long chain alkyl Grignard reagent to **4a**, and the resultant diastereomeric products can be conveniently separated by column chromatography.[24] Clearly that was not the case in the addition of short chain alkenyl (vinyl) group to **4a**. Nevertheless, we proceeded with the synthesis. Thus, the alcohol **62** was benzylated as done for **60**. Presence of two one-proton multiplets at δ 4.38-4.52 and 4.62-4.73 ($PhCH_2$-) at δ 7.26-7.35 (5H, Ph) confirmed the presence of a -Bn group. However, we could not separate the diastereomers of **63** by column chromatography. Its deacetalization with aqueous TFA furnished the diol **64** (IR band at 3405 cm^{-1}, ^{1}H NMR resonance at δ 2.48 (broad s, 2H)). Its tosylation using Martinelli's procedure (Bu_2SnO/*p*-TsCl/Et_3N)[98] furnished the corresponding primary monotosylate (IR band at 1642 cm^{-1} and ^{1}H NMR singlet at δ 2.46 (3H, CH_3Ph)) without the formation of any secondary tosylate or ditosylate.

This on $LiAlH_4$ reduction gave the epimeric mixtures of the secondary alcohol **65a** and **65b**. Gratifyingly, the stereomers were separable by column chromatography and were obtained in 28:72 ratio (based on isolated yields). The ^1H and ^{13}C NMR spectra of **65a** and **65b** are shown in **Figures III.7.1-III.7.4**. Presence of the MeCH(OH) doublets at δ 1.14/1.15 (J = 6.4 Hz, 3H) along with other expected resonances confirmed their structures. The major carbinol epimer **65b** was silylated with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole and DMAP to obtain **66**. Absence of IR hydroxyl peak and ^1H NMR singlets at δ 0.03 (3H), 0.04 (3H) and 0.87 (9H) confirmed the TBS moiety. This on reductive ozonolysis afforded the aldehyde **67**. Its IR spectrum showed bands at 2711 and 1736 cm^{-1}, while the ^1H NMR contained a one-proton doublet at δ 9.67 (J = 2.4 Hz), typical of the aldehyde group. This on a Wittig-Horner reaction with triethyl phosphonoacetate furnished the ester **68**. The *E*-stereochemistry of its olefinic function was confirmed from the ^1H NMR resonances *viz*. at δ 6.03 (d, J = 15.8 Hz, 1H) and δ 6.92 (dd, J = 15.8, 6.0 Hz, 1H). Its alkaline hydrolysis with LiOH/THF-H_2O furnished the acid **69** (**C1** unit) as was evident from the IR peaks-broad peak at 3300-2500 cm^{-1} and 1714 cm^{-1} and NMR resonance at δ_C 171.5.

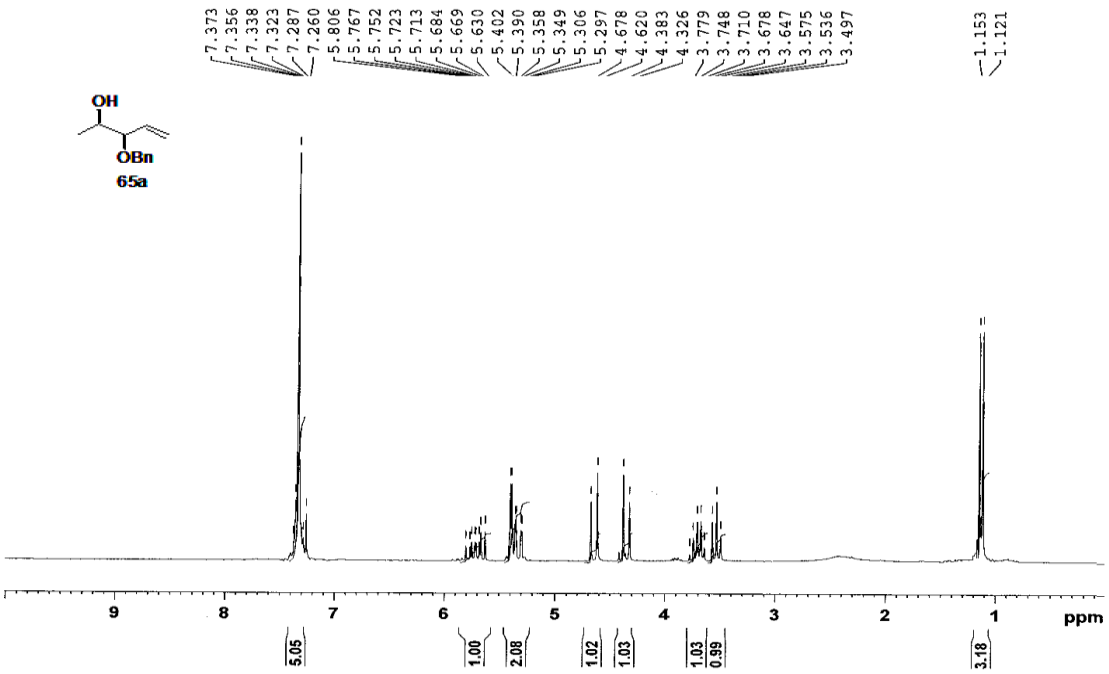


Figure III.7.1. ^{1}H NMR spectrum of **65a**

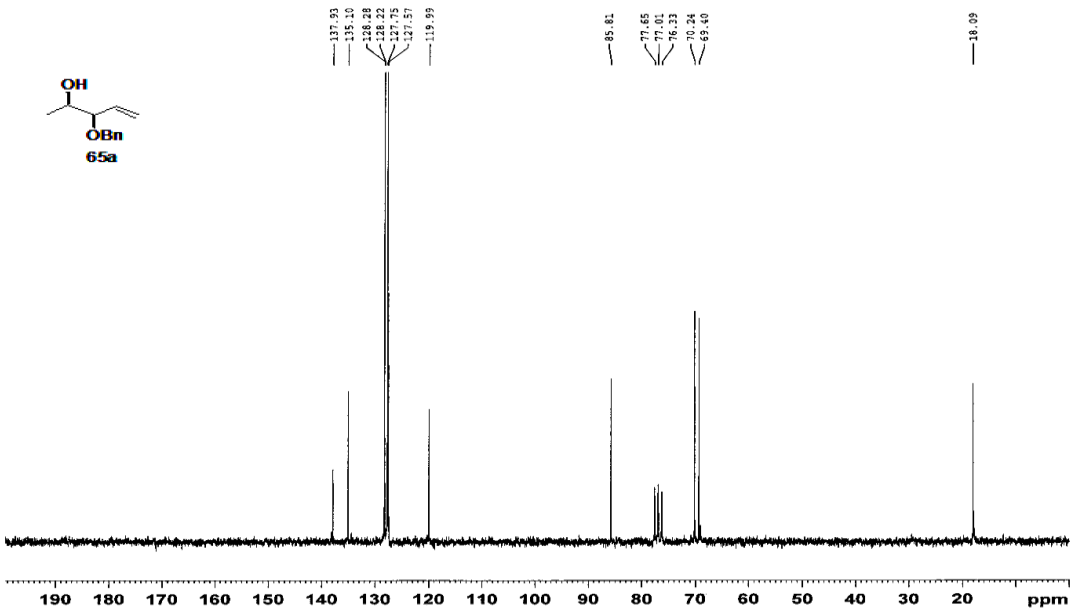


Figure III.7.2. ^{13}C NMR spectrum of **65a**

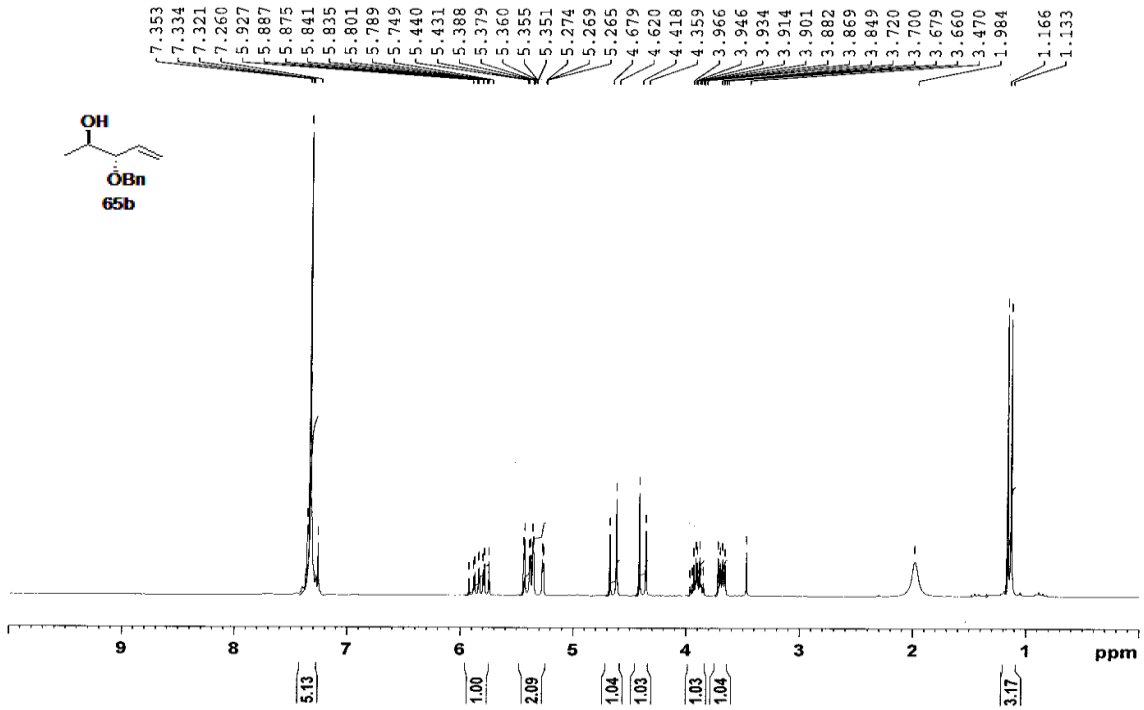


Figure III.7.3. ^{1}H NMR spectrum of **65b**

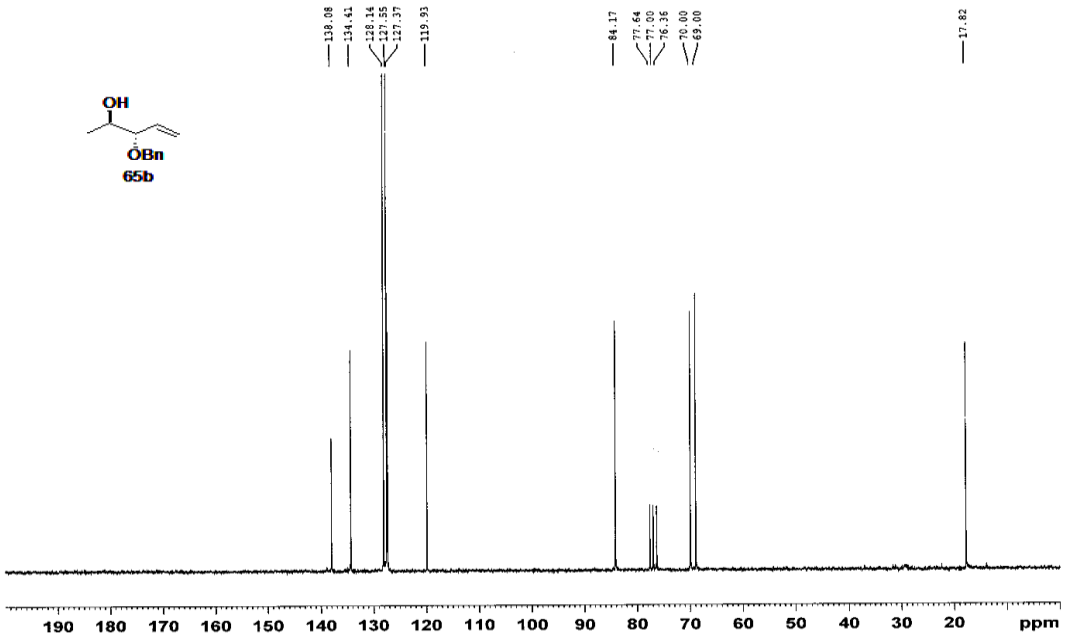
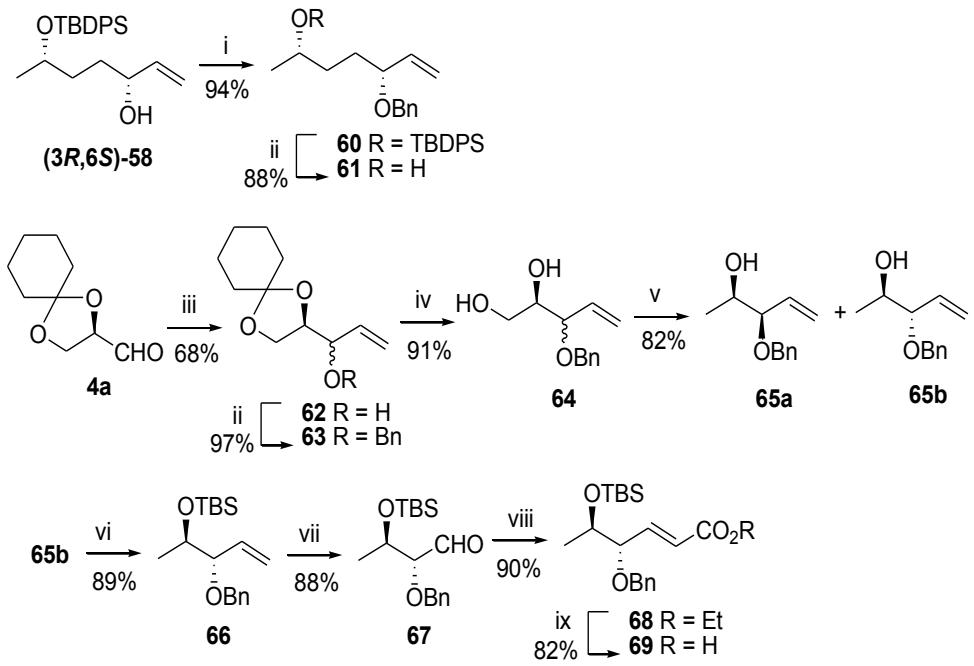


Figure III.7.4. ^{13}C NMR spectrum of **65b**

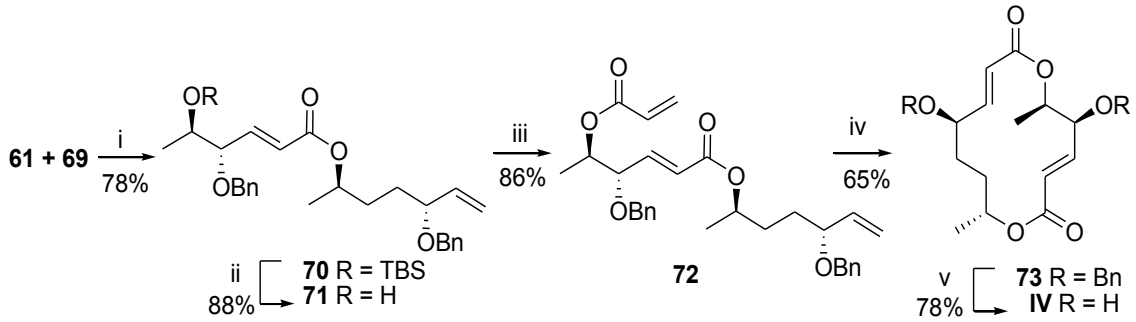


i) NaH/BnBr/Bu_4NI/THF/reflux/4 h, ii) Bu_4NF/THF/0 ^oC/7 h, iii) CH_2=CHMgBr/THF/-78 ^oC/12 h, iv) Aqueous TFA/CH_2Cl_2/0 ^oC/ 3 h, v) *p*-TsCl/Bu_2SnO/Et_3N/CH_2Cl_2/25 ^oC/6 h; $LiAlH_4$/THF/reflux/8 h, vi) TBSCl/ imidazole/DMAP/CH_2Cl_2/25 ^oC/3 h, vii) O_3/Ph_3P/CH_2Cl_2/-78 ^oC/6 h, viii) NaH/THF/ $(EtO)_2P(O)CH_2CO_2Et$/0 ^oC/6 h, ix) $LiOH.H_2O$/H2O:THF:MeOH(1:5:5)

Scheme III.7.1.

With compounds **61** and **69** in hand, the stage was set for their esterification under Mitsunobu conditions (Ph_3P/DIAD) to obtain the ester **70**. Attempted desilylation of **70** with Bu_4NF/THF proved disastrous, because even at -78 ^oC, it resulted into hydrolysis of the ester moiety and also produced additional unidentified degradation products. So it was treated with catalytic trimethylchlorosilane (TMSCl) in aqueous acetonitrile to obtain **71** in 89% yield.[99] There was no ester hydrolysis under this condition. Compound **71** was characterized from IR peak at 3456 cm^{-1} (OH) and absence NMR resonances for the TBS group. Its conversion to the corresponding acrylate **72** with acryloyl chloride/Hunig's base in CH_2Cl_2 proceeded uneventfully. The terminal olefins in **72** were now predisposed for the RCM reaction. This was realized with Hoveyda-Grubbs II catalyst in toluene at 80 ^oC under high dilution conditions to obtain the macrodiolide **73**. The *E*-geometry of the incipient

olefin is consistent with the proposed reaction mechanism for RCM.[100] Debenzylation of **73** with $TiCl_4/CH_2Cl_2$[101] led to a disappointingly poor yield of the target product **IV**. Instead, the mild oxidative protocol using $DDQ/CH_2Cl_2/H_2O$ (4:1)[102] furnished **IV** in 71% yield (**Scheme III.7.2.**). It is worth mentioning that the water concentration in the reaction medium was found to be crucial. Lowering its concentration slowed down the reaction considerably, while at the higher H_2O concentration decomposition of DDQ furnished an acidic product that decomposed the substrate. The spectral (^1H and ^{13}C NMR spectra of **IV** shown in **Figures III.7.5** and **III.7.6.**) and optical data of synthetic **IV** were commensurate with its structure and in agreement with the reported values.[87a]



i) Ph_3P/DIAD/THF/0-25 ^oC/18 h, ii) TMSCl/aqueous CH_3CN/0 ^oC/1 h, iii) Acryloyl chloride/ DIPEA/CH_2Cl_2/ 0-25 ^oC/3 h, iv) Hoveyda-Grubbs II/toluene/80 ^oC/22 h, v) DDQ/CH_2Cl_2-H_2O (18: 1)/25 ^oC/5 h.

Scheme III.7.2.

In summary, we have developed a highly enantioselective convergent synthesis of natural clonostachydiol (**IV**) wherein its macrodiolide skeleton was assembled via Mitsunobu esterification between the hept-6-ene-2,5-diol derivative (**A**^{1}-unit) and the pent-4-ene-2,3-diol acid derivative (**C** unit), followed by an RCM reaction as the key steps. However, due to the availability of all the stereomers of the **A** unit, the other C-10/C-13 stereomers of **IV** can be synthesized easily. Moreover, the enantiomers of **65a** and **65b** can also be accessed starting from (*S*)-**4a**. This would ensure availability of the other stereomers of the **C** unit. Taken together, the present

strategy offers sufficient flexibility for synthesizing different stereomers of **IV**. One apparent limitation of the present synthesis is non-utilization of **65a**. However, this can be converted to the C4-epimer of the **C** unit that is a proven intermediate for the synthesis of acremodol.[89] Compared to the previous relatively lengthy and low yielding syntheses of **IV**, our scheme is simple and concise.

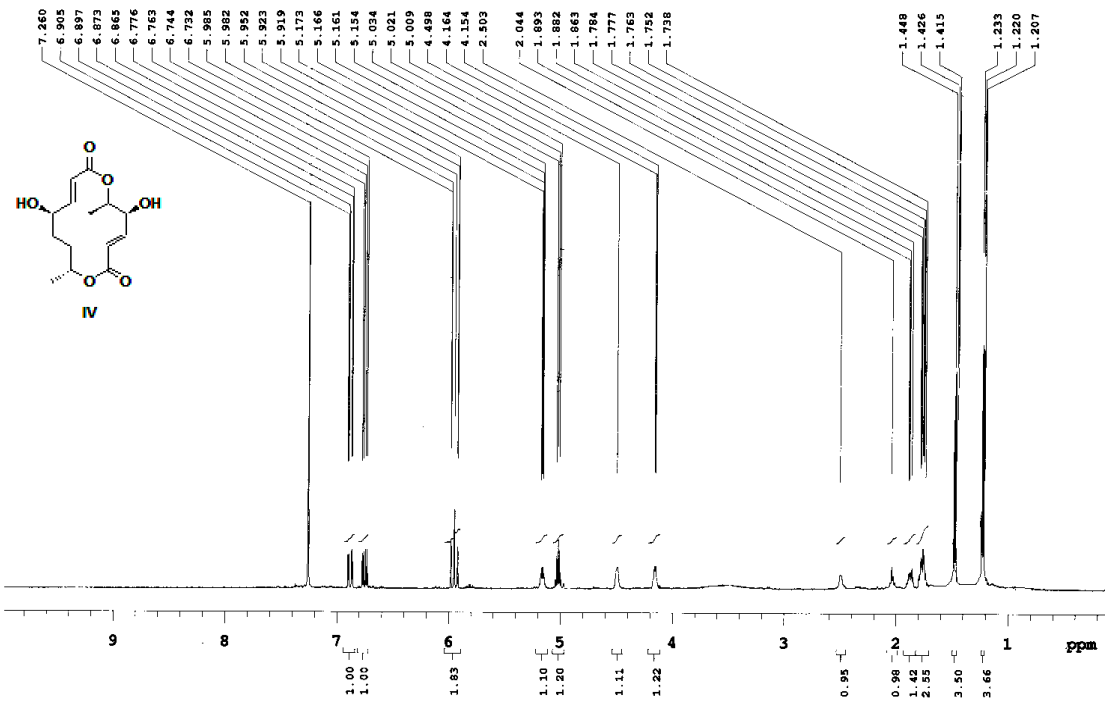


Figure III.7.5. ^{1}H NMR spectrum of **IV**

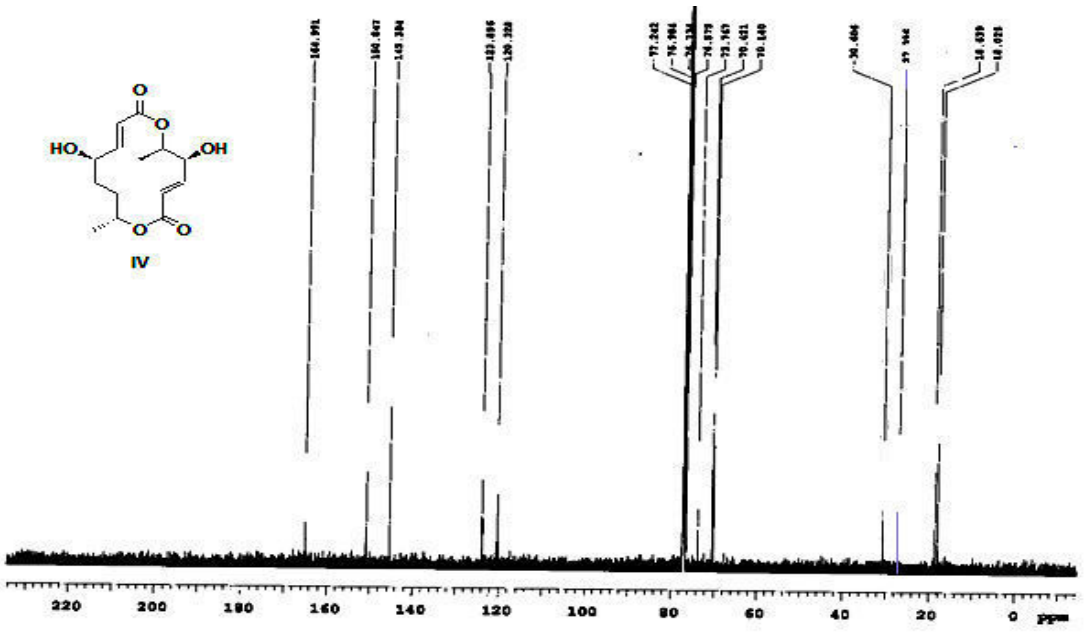


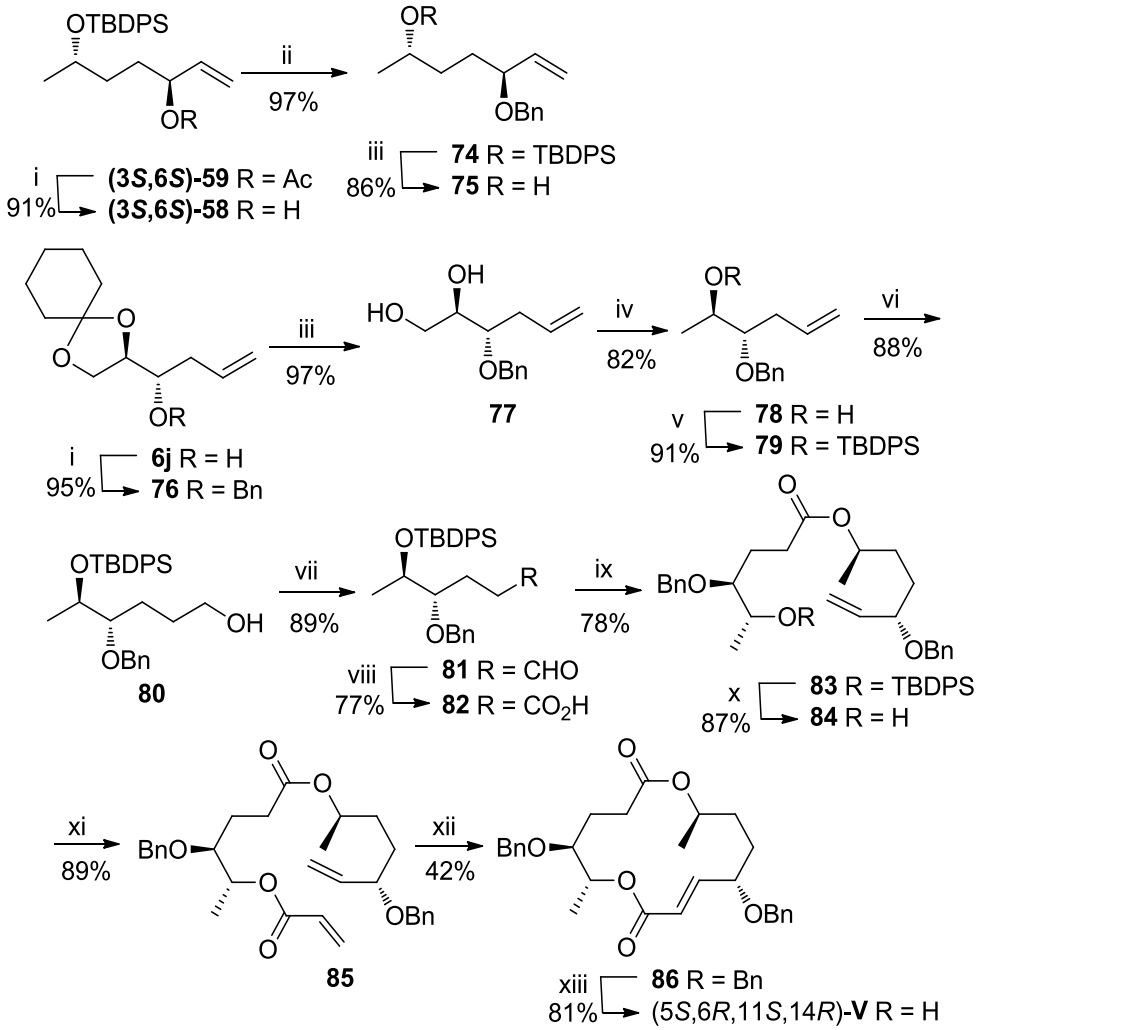
Figure III.7.6. ^{13}C NMR spectrum of **IV**

III.8: Synthesis of (5*S*,6*R*,11*S*,14*R*)-Acremodiol (V)

For the synthesis (**Scheme III.8.1.**), the acetate (3*S*,6*S*)-**59** was converted to the corresponding alcohol by alkaline hydrolysis. Appearance of the IR hydroxyl band at 3420 cm^{-1} in place of IR and NMR peaks for the acetate group confirmed its formation. This was converted to the benzyl ether **74** by reaction with BnBr/NaH in THF. Its desilylation with Bu_4NF furnished the alcohol **75** (**A**[1]-unit equivalent, IR: 3456 cm^{-1}). The synthesis of the required **D1** fragment commenced by a recently reported Ga-mediated allylation of the aldehyde **4a** in the room temperature ionic liquid, [bmim][Br], developed in our laboratory.[52a] The reaction proceeded with excellent diastereoselectivity to furnish **6j** as the major product in good yield and 95:5 diastereomeric ratio. The pure *anti*-isomer **6j** was easily isolated by column chromatography and the relative stereochemistry of its stereogenic centres were confirmed from the ^1H NMR multiplets at δ 3.71-3.79 (m, 1H) and δ 3.88-4.01 (m, 3H) for the carbinol (-CHO and $–CH_2O$) protons. This was benzylated with NaH/BnBr/Bu_4NI to obtain compound **76**. In ^1H NMR AB quartets (J = 11.4 Hz, 2H) at δ 4.61, multiplets at δ 7.29-7.33 (5H) and the ^{13}C NMR peak at δ 79.0 confirmed its Bn group. This on treatment with aqueous TFA furnished the diol **77**. A strong IR band at 3398 cm^{-1} and a broad ^1H NMR signal at δ 1.75 for the OH group in place of the ^1H NMR resonances for the cyclohexyl protons confirmed its identity. Reaction of **77** with *p*-TsCl in the presence of Bu_2SnO and Et_3N proceeded regioselectively at the primary carbinol function to furnish the corresponding monotosylate (IR bands at 1362 and 1177 cm^{-1} and a ^1H NMR singlet at δ 2.41 (Me-Ph)). Its reduction with $LiAlH_4$ furnished the alcohol **78**, which showed the expected ^1H NMR 3-proton doublets at δ 1.18 (J = 6.4 Hz) for the C**H**$_3$CH(OH) moiety. This on silylation (TBDPSCl/imidazole/ DMAP) furnished **79** (absence of IR hydroxyl band and

appearance of NMR resonances for the TBDPS group). It was regioselectively hydroborated with BH_3-Me_2S (BMS) and the intermediate tri-alkyl borane oxidized with H_2O_2/NaOH to afford the alcohol **80**. Appearance of the hydroxyl IR band (3433 cm^{-1}) and the five-proton ^1H NMR multiplets (δ 3.34-3.93) for the CH_2OH and CHOH groups in place of the olefinic resonances confirmed its formation. This on oxidation with PCC afforded the aldehyde **81** (IR bands at 2714 and 1729 cm^{-1}; NMR resonances: δ_H 9.64 (t, *J* = 1.4 Hz, 1H) and δ_C 202.5). Its oxidation gave the acid **82** (IR bands at 3500-2500 and 1712 cm^{-1}, and δ_C 179.8).

As done for the synthesis of **IV**, esterification of the acid **82** with the alcohol **75** under Mitsunobu conditions (Ph_3P/DIAD) gave compound **83**. The ^1H and ^{13}C NMR spectra of **83** are shown in **Figures III.8.1** and **III.8.2**. It desilylation with HF-pyridine furnished the desired alcohol **84** without any ester hydrolysis. The peak at 3427 cm^{-1} in its IR spectrum and disappearance of the TBDPS resonances in the NMR spectrum confirmed its formation. Its conversion to the corresponding acrylate **85** with acryloyl chloride/Hunig's base in CH_2Cl_2 proceeded uneventfully. Appearance of two ester IR peaks at 1718 and 1714 cm^{-1} and the down-field ^1H NMR resonances at δ 5.83 (d, *J* = 10.5 Hz, 1H), 6.13 (dd, *J* = 17.5, 10.5 Hz, 1H) and 6.41 (d, *J* = 17.5 Hz, 1H) were the indicators of its assigned structure. The required RCM reaction between the terminal olefin moieties in **85** with Grubbs I catalyst in CH_2Cl_2 at 40 ^oC gave the macrodiolide **86**. The *E*-geometry of the incipient olefin was confirmed from the ^1H NMR olefinic resonances *viz*. at δ 5.86 (d, *J* = 16.0 Hz, 1H) and δ 6.64 (dd, *J* = 16.0, 9.5 Hz, 1H). Finally, debenzylation of **86** with $TiCl_4/CH_2Cl_2$[105] afforded the target compound **V** in 88% yield. The spectral (^1H and ^{13}C NMR spectra of **V** shown in **Figures III.8.3** and **III.8.4.**) and optical data of synthetic **V** were commensurate with its structure and in agreement with the reported values.[87c]



i) K_2CO_3/MeOH//25 ^oC/4 h, ii) NaH/BnBr/Bu_4NI/THF/reflux/4 h, iii) Bu_4NF/THF/0 - 25 ^oC/7 h, iv) HCl/ Aqueous MeOH/25 ^oC/4 h, v) *p*-TsCl/Bu_2SnO/Et_3N/ CH_2Cl_2/0-25 ^oC/6 h, $LiAlH_4$/Er_2O/25 ^oC/8 h, vi) TBDPSCl/imidazole/DMAP/ CH_2Cl_2 /25 ^oC/4 h, vii) $BH_3.Me_2S$/ THF/0 ^oC/3 h; aqueous NaOH/H_2O_2/0 ^oC/3 h; 25 ^oC/12 h, viii) PCC/NaOAc/CH_2Cl_2/0 ^oC/3 h, ix) $NaClO_2$/$NaHPO_4.2H_2O$/H_2O_2/aqueous MeCN/0 -15 ^oC/6 h, x) **75**/Ph_3P/DIAD/THF/0 to 25 ^oC/18 h, xi) HF-Pyr/THF/pyridine/25 ^oC/6 h, xii) Acryloyl chloride/DIPEA/CH_2Cl_2/25 ^oC/3 h, xiii) Grubbs' I catalyst/CH_2Cl_2/40 ^oC/48 h, xiv) $TiCl_4$/CH_2Cl_2/0 to 25 ^oC/0.5 h.

Scheme IV.8.1.

In summary, we have developed an efficient synthesis of (5*S*,6*R*,11*S*,14*R*)-**V** using a DOS-based strategy. The versatility of the chosen DOS intermediate **59/60** has been ably demonstrated given that two of its different stereomers were used for the synthesis of both **IV** and **V**. Surprisingly, the optical rotation data of the synthetic compound was similar to the reported[89] value of its 5*R*,11*R*-stereomer. This suggested that (5*S*,6*R*,11*S*,14*R*)-**V** may not be the natural **V**. As before, due to availability of the

key DOS intermediates **A** and **D** in their diastereomeric forms, the present method is flexible enough to furnish the other stereomers of **V**.

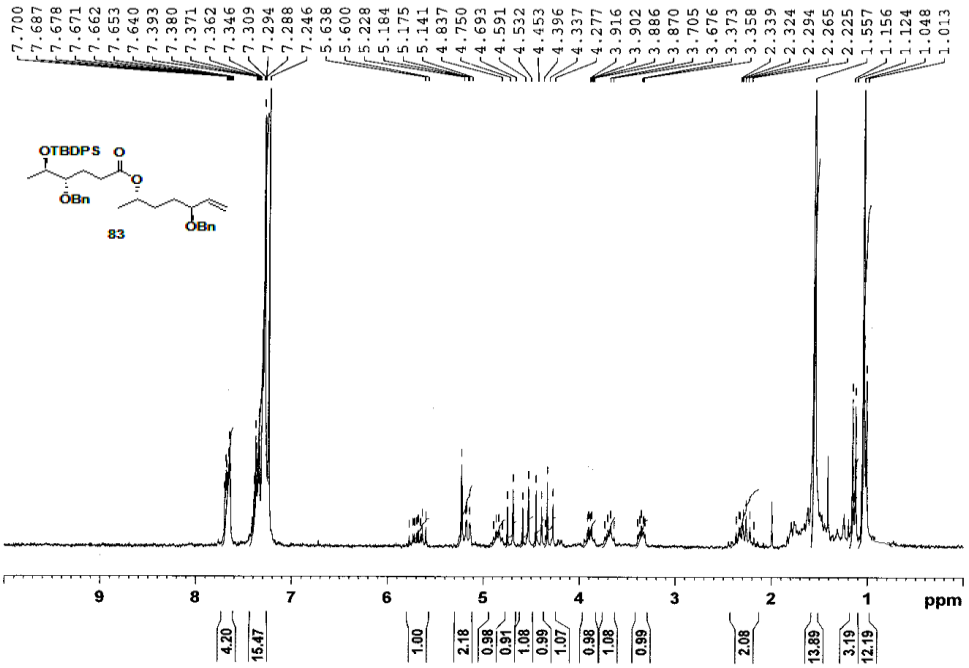


Figure III.8.1. ^{1}H NMR spectrum of **83**

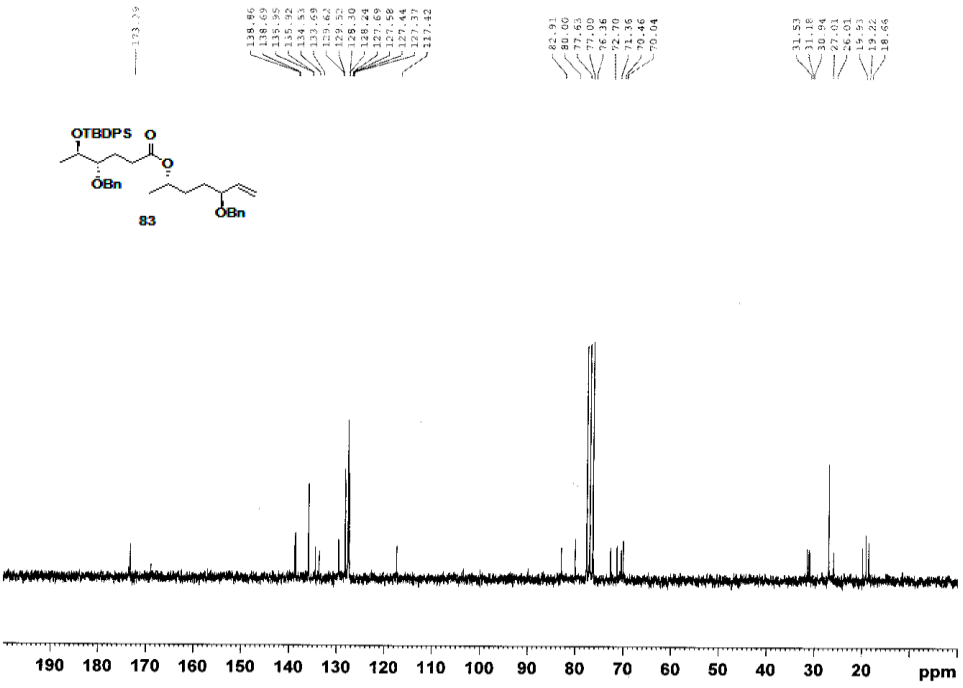


Figure III.8.2. ^{13}C NMR spectrum of **83**

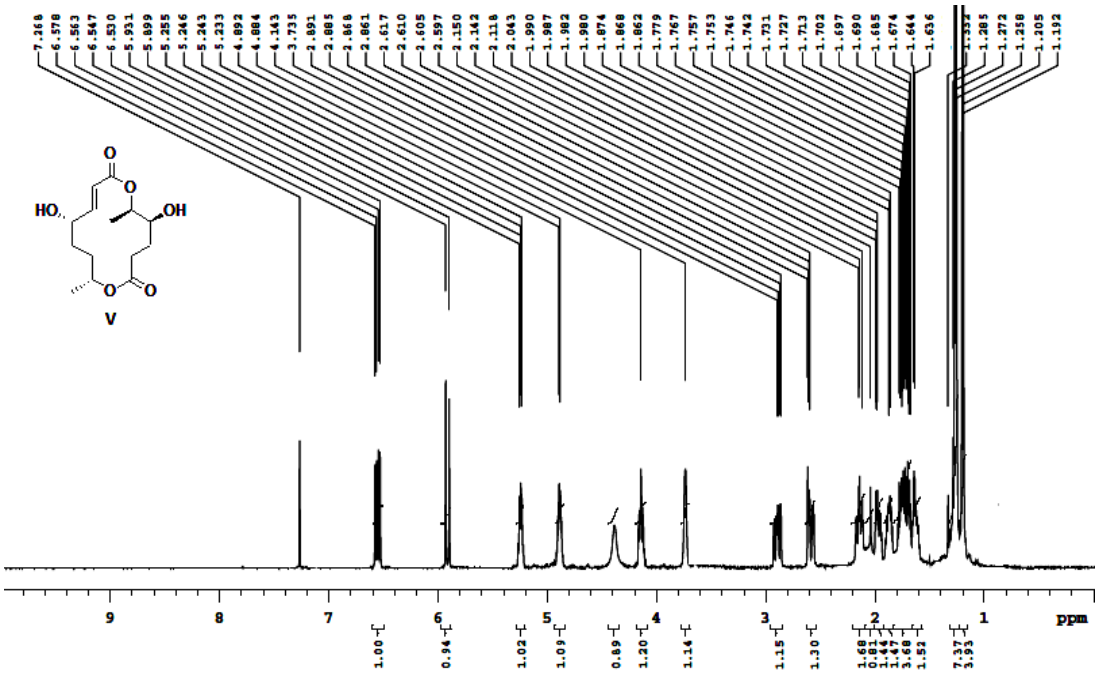


Figure III.8.3. ^{1}H NMR spectrum of **V**

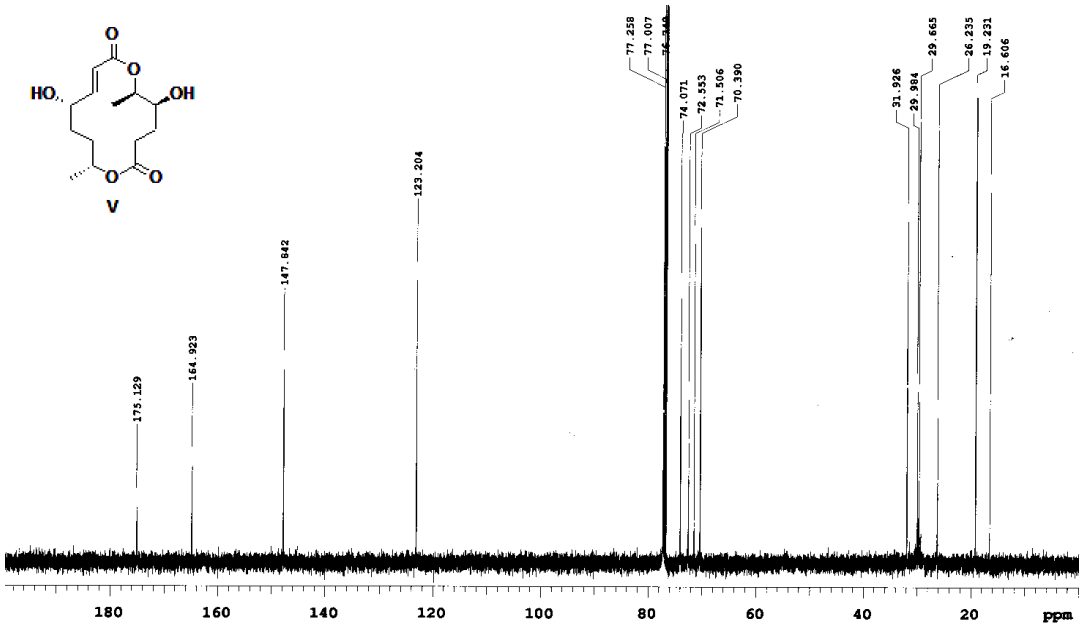
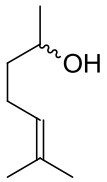


Figure III.8.4. ^{13}C NMR spectrum of V

III.9: Experimental Section

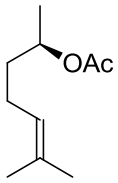
***General details*.** The general experimental details were same as those mentioned in Chapter II.

(±)-6-Methyl-5-hepten-2-ol (54).



To a cooled (0 ^{o}C) and stirred suspension of $LiAlH_4$ (6.33 g, 166.68 mmol) in Et_2O (100 mL) was dropwise added **53** (30.00 g, 238.11 mmol) in Et_2O (200 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 **54** (27.6 g, 91%). colorless oil; bp: 92 ^{o}C/20 mm; IR: 3370, 1641 cm^{-1}; ^{1}H NMR: δ 1.16 (d, *J* = 6.0 Hz, 3H), 1.46-1.58 (m, 2H), 1.67 (s, 3H), 1.72 (s, 3H), 2.02-2.16 (m, 3H), 3.76-3.92 (m, 1H), 5.12-5.20 (m, 1H); ^{13}C NMR: δ 17.6, 23.2, 24.5, 25.6, 39.2, 67.8, 124.2, 131.9.

(*R*)-6-Acetoxy-2-methyl-2-heptene (55).

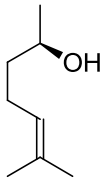


A mixture of (±)-**54** (15.0 g, 117.18 mmol), vinyl acetate (16.2 mL, 175.78 mmol) and Novozym 435® (1.5 g, ~12 mg/mmol) in hexane (60.0 mL) was agitated on an orbital shaker at 110 rpm for 50 min. The reaction mixture was filtered, and the solution concentrated in vacuo to get a residue which on column chromatography (silica gel, 0-10% EtOAc/hexane) gave pure (*S*)-**54** (6.2 g, 41%) and (*R*)-**55** (8.8 g, 44%).

(*S*)-**54:** colorless oil; $[\alpha]_D^{24}$ +10.2 (*c* 1.26, $CHCl_3$) (lit.[92b] $[\alpha]_D^{25}$ +10.5 (*c* 0.4, $CHCl_3$)); IR: 3437 cm^{-1}; ^1H NMR: δ 1.16 (d, *J* = 6.0 Hz, 3H), 1.42-1.58 (m, 2H), 1.63 (s, 3H), 1.70 (s, 3H), 1.95 (broad s, 1H), 2.02-2.16 (m, 2H), 3.82 (sextet, *J* = 6.2 Hz, 1H), 5.14-5.24 (m, 1H); ^{13}C NMR: δ 17.8, 23.2, 24.6, 25.8, 39.4, 67.8, 124.2, 131.8. Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58%; Found: C, 74.87; H, 12.78%.

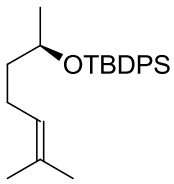
(*R*)-**55:** colorless oil; $[\alpha]_D^{24}$ -7.0 (*c* 1.21, $CHCl_3$), (lit.[92c] $[\alpha]_D^{23}$ +7.7 (*c* 0.03, EtOH)); IR: 1735, 1244 cm^{-1}; ^1H NMR: δ 1.23 (d, *J* = 6.5 Hz, 3H), 1.42-1.58 (m, 2H), 1.60 (s, 3H), 1.69 (s, 3H), 1.96-2.04 (merged m and s at δ 2.03, 5H), 4.85-4.92 (m, 1H), 5.03-5.12 (m, 1H); ^{13}C NMR: δ 17.4, 21.5, 24.2, 25.8, 29.6, 36.0, 70.8, 123.6, 132.3, 170.3. Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%; Found: C, 70.68; H, 10.46%.

(*R*)-6-Methyl-5-hepten-2-ol (*R*)-(54).



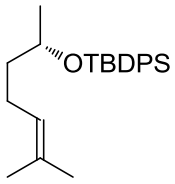
Reduction of (*R*)-**55** (8.1 g, 47.64 mmol) with $LiAlH_4$ (1.44 g, 38.10 mmol) in Et_2O (200 mL) followed by work up as above furnished pure (*R*)-**54** (5.7 g, 92%). colorless oil; $[\alpha]_D^{22}$ -11.2 (*c* 1.26, $CHCl_3$); IR: 3060, 1641 cm^{-1}; ^1H NMR: δ 1.14 (d, *J* = 6.2 Hz, 3H), 1.38-1.56 (m, 2H), 1.58 (s, 3H), 1.69 (s, 3H), 1.82 (broad s, 1H), 2.04-2.10 (m, 2H), 3.74-3.82 (m, 1H), 5.04-5.20 (m, 1H); ^{13}C NMR : δ 17.4, 23.6, 24.7, 25.9, 39.0, 67.8, 124.2, 132.0. Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58%; Found: C, 74.67; H, 12.62%.

(*R*)-6-*tert*-Butyldiphenylsilyloxy-2-methyl-2-heptene (*R*)-(56).



To a stirred solution of (*R*)-**54** (5.2 g, 40.62 mmol), imidazole (3.60 g, 52.81 mmol) and DMAP (catalytic) in CH_2Cl_2 (50 mL) was dropwise added TBDPSCl (14.52 g, 52.81 mmol) in CH_2Cl_2 (20 mL). After stirring the mixture for 7 h at room temperature, it was poured into ice-cold H_2O (40 mL), the organic layer was separated and the aqueous portion extracted with $CHCl_3$ (2 × 30 mL). The combined organic extracts were washed with H_2O (2 × 20 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 (*R*)-**56** (13.10 g, 88%). colorless oil; $[\alpha]_D^{24}$ +11.5 (*c* 1.14, $CHCl_3$); IR: 3060, 3010 cm^{-1}; ^1H NMR: δ 1.06 (merged s and d, *J* = 5.8 Hz, 12H), 1.16-1.25 (m, 2H), 1.54 (s, 3H), 1.68 (s, 3H), 1.88-2.03 (m, 2H), 3.80-3.85 (m, 1H), 4.96-5.02 (m, 1H), 7.34-7.44 (m, 6H), 7.68-7.72 (m, 4H); ^{13}C NMR: δ 17.5, 18.2, 19.5, 23.0, 24.2, 25.8, 26.4, 26.8, 39.5, 69.2, 124.4, 127.4, 127.6, 127.8, 129.4, 129.5, 131.1, 134.3, 134.8, 135.0, 135.6, 136.0. Anal. Calcd. for $C_{24}H_{34}OSi$: C, 78.63; H, 9.35%. Found: C, 78.58; H, 9.48%.

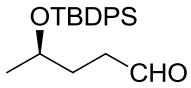
(*S*)-6-*tert*-Butyldiphenylsilyloxy-2-methyl-2-heptene (*S*)-(56).



As above, silylation of (*S*)-**54** (5.94 g, 46.41 mmol) using TBDPSCl (16.52 g, 60.32 mmol), imidazole (4.10 g, 60.32 mmol) and DMAP (catalytic) in CH_2Cl_2 (60 mL) furnished (*S*)-**56** (15.4 g, 91%). colorless oil; $[\alpha]_D^{25}$ -11.5 (*c* 1.12, $CHCl_3$); IR: 3070, 3050, 997 cm^{-1}; ^1H NMR: δ 1.04 (merged s and d, *J* = 6.0 Hz, 12H), 1.42-1.45 (m, 1H), 1.51-1.56 (m containing a s at δ 1.54, 4H), 1.64 (s, 3H), 1.89-2.03 (m, 2H), 3.84-3.87 (m, 1H), 4.95-4.98 (m, 1H), 7.36-7.45 (m, 6H), 7.64-7.69 (m, 4H); ^{13}C NMR: δ

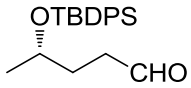
17.8, 18.3, 19.2, 23.4, 24.2, 25.6, 26.9, 27.0, 39.8, 69.2, 124.8, 127.6, 127.7, 129.4, 129.6, 131.4, 134.6, 135.2, 135.6, 136.1. Anal. Calcd. for $C_{24}H_{34}OSi$: C, 78.63; H, 9.35%. Found: C, 78.39; H, 9.43%.

(*R*)-4-*tert*-Butyldiphenylsilyloxypentanal (*R*)-(57).



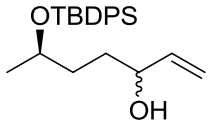
Reductive ozonolysis of (*R*)-**56** (8.23 g, 22.47 mmol) using O_3 and Ph_3P (8.84 g, 33.73 mmol) in CH_2Cl_2 (200 mL) followed by work-up and column chromatography (silica gel, 0-10% Et_2O/hexane) gave pure (*R*)-**57** (6.12 g, 81%). colorless oil; $[\alpha]_D^{22}$ +2.8 (*c* 1.06, $CHCl_3$); IR: 3072, 2713, 1720 cm^{-1}; ^1H NMR: δ 1.05 (merged s and d, *J* = 6.2 Hz, 12H), 1.71-1.84 (m, 2H), 2.45-2.52 (m, 2H), 3.90-3.94 (m, 1H), 7.38-7.44 (m, 6H), 7.65-7.69 (m, 4H), 9.69 (s, 1H); ^{13}C NMR: δ 19.2, 23.1, 27.0, 27.3, 31.5, 39.8, 68.2, 127.6, 127.7, 129.5, 129.6, 134.3, 134.5, 135.7, 135.9, 202.1. Anal. Calcd. for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29%. Found: C, 74.20; H, 8.42%.

(*S*)-4-*tert*-Butyldiphenylsilyloxypentanal (*S*)-(57).



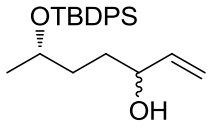
Reductive ozonolysis of (*S*)-**56** (9.01 g, 24.64 mmol) with O_3 and Ph_3P (9.68 g, 36.95 mmol) in CH_2Cl_2 (210 mL) followed by isolation as above furnished pure (*S*)-**57** (6.84 g, 82%). colorless oil; $[\alpha]_D^{22}$ -2.1 (*c* 1.09, $CHCl_3$); IR: 1725, 2717, 3050 cm^{-1}; ^1H NMR: δ 1.05 (merged s and d, *J* = 5.8 Hz, 12H), 1.72-1.85 (m, 2H), 2.46-2.49 (m, 2H), 3.91-3.97 (m, 1H), 7.38-7.43 (m, 6H), 7.65-7.68 (m, 4H), 9.72 (s, 1H); ^{13}C NMR: δ 19.2, 23.0, 27.0, 27.3, 31.2, 39.8, 68.2, 127.3, 127.4, 127.6, 127.8, 129.5, 129.8, 134.2, 134.6, 135.6, 135.8, 136.2, 202.5. Anal. Calcd. for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29%. Found: C, 74.26; H, 8.45%. \

(3*RS*,6*R*)-6-*tert*-Butyldiphenylsilyloxyhept-1-en-3-ol (3*RS*,6*R*)-(58).



To a cooled (-78 ^{o}C) and stirred solution of (*R*)-**57** (6.0 g, 17.65 mmol) in THF (150 mL) was added vinylmagnesium bromide (35.3 mL, 35.3 mmol, 1 M in THF). After stirring for 3 h, the mixture was treated with aqueous saturated NH_4Cl (20 mL) and poured in H_2O (80 mL). The organic layer was separated, the aqueous portion extracted with EtOAc (3 ×50 mL), the combined organic extracts 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, 0-10% Et_2O/hexane) to obtain (3*RS*,6*R*)-**58** (5.35 g, 84%). colorless liquid; $[\alpha]_D^{24}$ +35.9 (*c* 1.26, $CHCl_3$); IR: 3350, 3070, 3040, 1640 cm^{-1}; ^{1}H NMR: δ 1.05 (merged s and d, *J* = 6.2 Hz, 12H), 1.43-1.67 (m, 5H), 3.86-3.89 (m, 1H), 3.96-4.02 (m, 1H), 5.04-5.25 (m, 2H), 5.65-5.82 (m, 1H), 7.32-7.46 (m, 6H), 7.62-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 23.0, 27.2, 29.9, 32.5, 32.6, 34.8, 35.2, 69.4, 69.6, 73.1, 73.2, 114.5, 127.4, 127.6, 129.4, 129.6, 134.6, 134.8, 135.0, 136.6, 141.3. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C, 74.88; H, 8.62%.

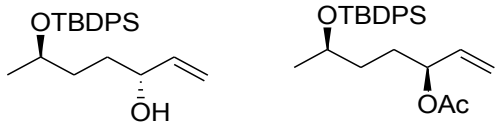
(3*RS*,6*S*)-6-*tert*-Butyldiphenylsilyloxyhept-1-en-3-ol (3*RS*,6*S*)-(58).



As above, reaction of (*S*)-**57** (6.44 g, 18.92 mmol) with vinylmagnesium bromide (38.1 mL, 38.1 mmol, 1 M in THF) in THF (80 mL) and usual purification afforded pure (3*RS*,6*S*)-**58** (5.88 g, 84%). colorless liquid; $[\alpha]_D^{24}$ -12.5 (*c* 1.20, $CHCl_3$); IR: 3365, 3076, 997 cm^{-1}; ^{1}H NMR: δ 1.06 (merged s and d, *J* = 6.2 Hz, 12H), 1.47-1.65 (m containing a s at 1.58, 5H), 3.82-3.89 (m, 1H), 3.93-4.05 (m, 1H), 5.04-5.26 (m,

2H), 5.69-5.84 (m, 1H), 7.36-7.42(m, 6H), 7.62-7.69 (m, 4H); ^{13}C NMR: δ 19.0, 23.1, 27.2, 32.3, 32.5, 34.8, 35.1, 69.2, 69.5, 73.0, 73.3, 114.6, 127.3, 127.5, 129.3, 129.5, 136.0, 141.1. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C, 75.08; H, 8.81%.

Resolution of (3*RS*,6*R*)-(58).



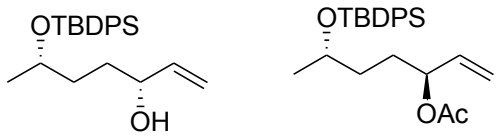
(3*R*,6*R*)-**58** (3*S*,6*R*)-**59**

Acetylation of (3*RS*,6*R*)-**58** (5.0 g, 13.56 mmol) with vinyl acetate (6 mL) and Novozym435® (0.60 g, ~50 mg/mmol) was carried out as described above to obtain pure (3*R*,6*R*)**-58** (2.4 g, 48%) and (3*S*,6*R*)-**59** (2.5 g, 46%).

(3*R*,6*R*)-**58:** colorless oil; $[\alpha]_D^{26}$ +10.2 (*c* 1.02, $CHCl_3$); ^{1}H NMR: δ 1.07 (merged s and d, *J* = 5.6 Hz, 12H), 1.53-1.63 (m, 5H), 3.85-4.01 (m, 2H), 5.04-5.22 (m, 2H), 5.72-5.88 (m, 1H), 7.34-7.43 (m, 6H), 7.65-7.71 (m, 4H); ^{13}C NMR: δ 19.2, 23.0, 27.0, 32.5, 35.0, 69.4, 73.1, 114.4, 127.4, 127.5, 129.4, 129.5, 134.2, 134.6, 135.8, 141.1. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C,74.85; H, 8.82%.

(3*S*,6*R*)-**59:** colorless oil; $[\alpha]_D^{25}$ +12.6 (*c* 1.03, $CHCl_3$); IR: 3070, 1742, 1645 cm^{-1}; ^{1}H NMR: δ 1.05 (merged s and d, *J* = 7.2 Hz, 12H), 1.26-1.68 (m, 4H), 2.02 (s, 3H), 3.82-3.91 (m, 1H), 5.10-5.21 (m, 3H), 5.62-5.79 (m, 1H), 7.32-7.43 (m, 6H), 7.64-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 21.0, 23.0, 26.8, 27.0, 29.5, 34.4, 68.9, 74.6, 116.5, 127.4, 127.5, 129.4, 134.2, 134.6, 135.8, 136.4, 170.0. Anal. Calcd. for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35%. Found: C,73.45; H, 8.42%.

Resolution of (3*RS*,6*S*)-(58).



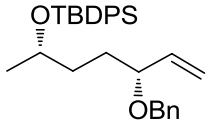
(3*R*,6*S*)-**58** (3*S*,6*S*)-**59**

Following the same procedure as above, (3*RS*,6*S*)-**58** (5.8 g, 15.73 mmol) was acetylated in vinyl acetate (15.3 mL) using Novozym 435® (0.76 g, ~50 mg/mmol) to obtain pure (3*R*,6*S*)-**58** (2.62 g, 45%) and (3*S*,6*S*)-**59** (3.1 g, 47%).

(3*R*,6*S*)-**58:** colorless oil; $[\alpha]_D^{25}$ -17.2 (*c* 1.04 , $CHCl_3$); IR: 3365, 3070, 997 cm^{-1}; ^1H NMR: δ 1.07 (merged s and d, *J* = 5.5 Hz, 12H), 1.47-1.59 (m, 4H), 3.89-3.92 (m, 1H), 4.02-4.03 (m, 1H), 5.09 (d, *J* = 10.5 Hz, 1H), 5.18 (d, *J* = 17.0 Hz, 1H), 5.78-5.84 (m, 1H), 7.36-7.44 (m, 6H), 7.67-7.69 (m, 4H); ^{13}C NMR: δ 19.2, 23.0, 27.0, 32.2, 34.6, 69.2, 73.0, 114.5, 127.4, 127.5, 129.4, 129.5, 134.3, 134.7, 135.8, 141.1. Anal. Calcd. for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75%. Found: C, 75.08; H, 8.62%.

(3*S*,6*S*)-**59:** colorless oil; $[\alpha]_D^{24}$ -12.9 (*c* 1.23, $CHCl_3$); IR: 1739, 1225 cm^{-1}; ^1H NMR: δ 1.06 (merged s and d, *J* = 6.2 Hz, 12H), 1.37-1.54 (m, 2H), 1.55-1.63 (m, 2H), 2.02 (s, 3H), 3.77-3.89 (m, 1H), 5.07-5.22 (m, 3H), 5.65-5.72 (m, 1H), 7.34-7.43 (m, 6H), 7.65-7.71 (m, 4H); ^{13}C NMR: δ 19.2, 21.7, 23.5, 27.0, 29.7, 34.8, 69.3, 74.6, 116.8, 127.3, 127.5, 129.3, 129.4, 134.6, 134.7, 135.8, 136.7, 170.5. Anal. Calcd. for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35%. Found: C, 73.42; H, 8.15%.

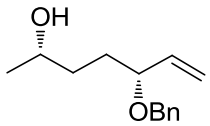
(3*R*,6*S*)-3-Benzyloxy-6-*tert*-butyldiphenylsilyloxyhept-1-ene (60).



To a stirred hexane-washed suspension of NaH (586mg, 50% suspension in oil, 12.21 mmol) in THF (15 mL) was added a solution of (3*R*,6*S*)-**58** (3.00 g, 8.14 mmol) in THF (15 mL) under Ar. After the evolution of H_2 subsided, the mixture was refluxed for 1 h, brought to room temperature, Bu_4NI (10 mol%) and a solution of BnBr (1.2 mL, 9.77 mmol) in THF (10 mL) was dropwise added. The mixture was refluxed till consumption of the starting material (*cf*. TLC, ~4 h), brought to room temperature, and treated with ice-cold H_2O (30 mL). The organic layer was separated and the

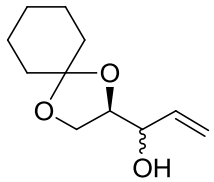
aqueous portion extracted with Et_2O (2 × 25 mL). The combined organic extracts were washed with H_2O (2 ×10 mL) and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-5% EtOAc/hexane) of the residue furnished pure **60** (3.5 g, 94%). colorless oil; $[\alpha]_D^{27}$ -2.2 (*c* 1.04, $CHCl_3$); IR: 1641, 1420 cm^{-1}; ^1H NMR: δ 1.06 (merged s and d, *J* = 6.0 Hz, 12H), 1.40-1.70 (m, 4H), 3.58-3.68 (m, 1H), 3.83-3.91 (m, 1H), 4.30 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 5.11-5.23 (m, 2H), 5.61-5.79 (m, 1H), 7.31-7.43 (m, 11H), 7.66-7.71 (m, 4H); ^{13}C NMR: 19.1, 23.1, 26.8, 27.0, 30.7, 34.7, 69.1, 69.8, 80.2, 116.7, 127.1, 127.3, 127.4, 127.5, 128.1, 128.2, 128.3, 129.3, 134.3, 134.6, 135.7, 138.7, 138.9. Anal.Calcd. for $C_{30}H_{38}O_2Si$: C, 78.55; H, 8.35%. Found: C, 78.16; H, 8.32%.

(2*S*,5*R*)-5-Benzyloxyhept-6-en-2-ol (61).



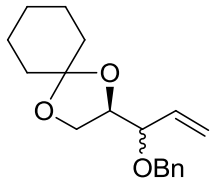
To a cooled (0 °C) and stirred solution of **60** (3.00 g, 6.54 mmol) in THF (15 mL) was added Bu_4NF (7.9 mL, 7.85 mmol, 1M in THF). After stirring for 7 h, the reaction mixture was poured into ice-cold H_2O (15 mL) and extracted with EtOAc (2 × 10 mL). The organic extract was washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent followed by column chromatography of the residue (silica gel, 0-10% EtOAc/hexane) furnished **61** (1.3 g, 88%). colorless oil; $[\alpha]_D^{27}$ +21.2 (*c* 0.76, $CHCl_3$); IR: 3456, 1641 cm^{-1}; ^1H NMR: δ 1.17 (d, *J* = 6.2 Hz, 3H), 1.47-1.80 (m, 4H), 1.91 (broad s, 1H), 3.72-3.81 (m, 2H), 4.35 (d, *J* = 11.8 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 5.18-5.27 (m, 2H), 5.67-5.84 (m, 1H), 7.29-7.35 (m, 5H); ^{13}C NMR : 23.2, 31.6, 34.8, 67.4, 69.9, 80.3, 117.2, 127.3, 127.5, 127.7, 128.1, 138.2, 138.5. Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%. Found: C, 76.00; H, 8.98%.

(2*R*,3*RS*)-1,2-Cyclohexylidenedioxy-pent-4-en-3-ol (62).



Reaction of **4a** (12.00 g, 70.50 mmol) with vinylmagnesium bromide (84.6 mL, 84.60 mmol, 1 M in THF) in THF (80 mL) at -78 ^{o}C for 4 h, followed by work-up and column chromatography (silica gel, 0-15% EtOAc/hexane) gave **62** (9.5 g, 68%). colorless oil; $[\alpha]_D^{25}$ +2.5 (*c* 1.07, $CHCl_3$); IR: 3456, 1641, 1100, 1042 cm^{-1}; ^{1}H NMR: δ 1.33-1.47 (m, 2H), 1.51-1.63 (m, 8H), 2.11 (broad s, 1H), 3.68-4.05 (two m, 2H), 4.01-4.05 (m, 1H), 4.07-4.38 (two m, 1H), 5.18-5.42 (m, 2H), 5.70-5.89 (m, 1H); ^{13}C NMR: δ 23.4, 23.6, 24.8, 34.3, 34.4, 35.8, 35.9, 64.5, 65.0, 71.8, 73.8, 77.5, 77.9, 109.6, 109.9, 116.0, 117.2, 135.9, 136.2. Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15%. Found: C, 66.67, H, 8.84%.

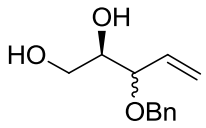
(3*RS*,4*R*)-3-Benzyloxy-4,5-cyclohexylidenedioxy-1-pentene (63).



Benzylation of **62** (6.00 g, 30.26 mmol) using hexane-washed NaH (1.74 g, 50% suspension in oil, 45.39 mmol), BnBr (4.3 mL, 36.32 mmol) and Bu_4NI (10 mol%) in THF (50 mL) followed by work-up and column chromatography (silica gel, 0-10% EtOAc/ hexane) afforded **63** (8.5 g, 97%). colorless oil; $[\alpha]_D^{27}$ +15.8 (*c* 0.65, $CHCl_3$); IR: 1641, 1463, 1216 cm^{-1}; ^{1}H NMR: δ 1.40-1.43 (m, 2H), 1.60 (m, 8H), 3.70-3.81 (m, 1H), 3.84-4.22 (m, 3H), 4.38-4.52 (m, 1H), 4.62-4.73 (m, 1H), 5.29-5.40 (m, 2H), 5.65-5.92 (m, 1H), 7.26-7.35 (m, 5H); ^{13}C NMR: δ 23.7, 23.9, 25.1, 34.8, 36.0, 36.1, 65.2, 66.3, 70.2, 70.5, 77.2, 81.0, 109.9, 110.1, 119.2, 119.7, 127.3, 127.5, 127.6,

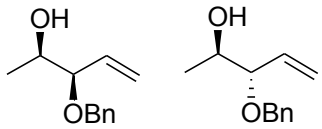
127.7, 128.1, 128.2, 134.2, 135.3, 138.1, 138.2. Anal.Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39%. Found: C, 75.08; H, 8.09%.

(2*R*,3*RS*)-3-Benzyloxypent-4-ene-1,2-diol (64).



Deacetalization of **63** (8.20 g, 28.43 mmol) with aqueous 80% TFA (10 mL) in CH_2Cl_2 (50 mL) for 3 h at 0 °C, followed by work-up and column chromatography (silica gel, 0-5% MeOH/$CHCl_3$) furnished pure **64** (5.4 g, 91%). colorless oil; $[\alpha]_D^{27}$ + 9.0 (*c* 0.66, $CHCl_3$); IR: 3405, 1642 cm^{-1}; ^1H NMR: δ 2.48 (broad s, 2H), 3.55-3.71 (m, 3H), 3.74-3.94 (m, 1H), 4.35 and 4.36 (two d, *J* = 11.6 Hz each, 1H), 4.64 and 4.65 (two d, *J* = 11.6 Hz each, 1H), 5.32-5.43 (m, 2H), 5.70-5.87 (m, 1H), 7.29-7.35 (m, 5H); ^{13}C NMR: δ 62.9, 63.1, 70.4, 70.5, 73.2, 73.8, 81.3, 81.8, 120.0, 120.4, 127.7, 127.8, 127.9, 128.3, 128.4, 134.6, 134.9, 137.7, 137.8. Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%. Found: C, 69.14; H, 7.91%.

(2*R*,3*R*)-and **(2*R*,3*S*)-3-Benzyloxypent-4-en-2-ol (65a** and **65b).**



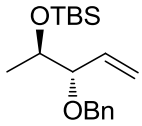
65a **65b**

To a cooled (0 ^oC) and stirred solution of **64** (5.40 g, 25.93 mmol) and Et_3N (4.3 mL, 32.15 mmol) in CH_2Cl_2 (50 mL) was added *p*-TsCl (5.44 g, 28.52 mmol) followed by Bu_2SnO (194 mg, 0.78 mmol). After stirring for 6 h at room temperature, H_2O (15 mL) was added to the mixture, the organic layer separated and the aqueous layer extracted with $CHCl_3$ (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 the

corresponding primary monotosylate (8.6 g, 92%). colorless oil; $[\alpha]_D^{27}$ +8.9 (*c* 1.4, $CHCl_3$); IR: 3405, 1642 cm^{-1}; ^1H NMR: δ 1.62 (broad s, 1H), 2.46 (s, 3H), 3.78-4.01 (m, 2H), 4.08-4.18 (m, 2H), 4.33 (d, *J* = 11.6 Hz, 1H), 4.61 (dd, *J* = 11.6, 4.8 Hz, 1H),5.31-5.46 (m, 2H), 5.70-5.88 (m, 1H), 7.28-7.36 (m, 7H), 7.79-7.83 (m, 2H); ^{13}C NMR: δ 21.5, 69.9, 70.4, 70.5, 71.0, 71.3, 79.7, 80.2, 120.6, 120.8, 127.6, 127.7, 127.8, 128.2, 128.3, 129.7, 132.5, 133.8, 134.1, 137.4, 137.6, 144.8. Anal. Calcd. for $C_{19}H_{22}O_5S$: C, 62.96; H, 6.12; S, 8.85%. Found: C, 62.75; H, 6.27; S, 8.45%.

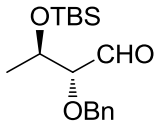
To a suspension of $LiAlH_4$ (776 mg, 20.42 mmol) in THF (30 mL) was dropwise added the above tosylate (7.40 g, 20.42 mmol) in THF (20 mL). The mixture was refluxed for 8 h, brought to room temperature, and the excess hydride decomposed with aqueous saturated Na_2SO_4. The mixture was filtered, the filtrate concentrated in vacuo and the residue purified by column chromatography (silica gel, 0-15% EtOAc/hexane) to obtain **65a** and **65b** (3.5 g, 89%, 28:72). **65a:** colorless oil; $[\alpha]_D^{27}$ -40.3 (*c* 1.00, $CHCl_3$); IR: 3446, 3073, 1643, 994, 927 cm^{-1}; ^1H NMR: δ 1.14 (d, *J* = 6.4 Hz, 3H), 2.42 (broad s, 1H), 3.50-3.58 (m, 1H), 3.65-3.78 (m, 1H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 5.30-5.40 (m, 2H), 5.63-5.81 (m, 1H), 7.29-7.37 (m, 5H); ^{13}C NMR: δ 18.1, 69.4, 70.2, 85.8, 120.0, 127.6, 127.8, 128.2, 128.3, 135.1, 137.9. Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%. Found: C, 74.66; H, 8.33%. **65b:** colorless oil; $[\alpha]_D^{27}$ +42.3 (*c* 1.00, $CHCl_3$); IR: 3400, 3029, 1637 cm^{-1}; ^1H NMR: δ 1.15 (d, *J* = 6.6 Hz, 3H), 1.98 (broad s, 1H), 3.66-3.72 (m, 1H), 3.85-3.97 (m, 1H), 4.39 (d, *J* = 11.8 Hz,1H), 4.65 (d, *J* = 11.8 Hz, 1H), 5.26-5.44 (m, 2H), 5.75-5.93 (m, 1H), 7.32-7.35 (m, 5H); ^{13}C NMR: δ 17.8, 69.0, 70.0, 84.2, 119.9, 127.4, 127.6, 128.1, 134.4, 138.1. Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%. Found: C, 74.69; H, 8.36%.

(2*R*,3*S*)-3-Benzyloxy-5-*tert*-butyldimethylsilyloxypentene (66).



To a stirred solution of **65b** (2.50 g, 13.00 mmol), imidazole (1.06 g, 15.60 mmol) and DMAP (catalytic) in CH_2Cl_2 (20 mL) was dropwise added TBSCl (2.35 g, 15.60 mmol). After stirring the mixture for 7 h at room temperature, it was poured into ice-cold H_2O (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 × 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 **66** (3.5 g, 89%). colorless oil; $[\alpha]_D^{27}$ +15.7 (*c* 0.72, $CHCl_3$); IR: 1658, 1462, 1252, 1112 cm^{-1}; ^1H NMR: δ 0.03 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.17 (d, *J* = 6.0 Hz, 3H), 3.56 (dd, *J* = 7.6, 5.2 Hz, 1H), 3.83 (quintet, *J* = 5.8 Hz, 1H), 4.40 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 5.20-5.33 (m, 2H), 5.71-5.88 (m, 1H), 7.28-7.34 (m, 5H); ^{13}C NMR: δ -4.6, -4.5, 18.1, 20.2, 25.9, 70.5, 70.9, 85.2, 118.6, 127.3, 127.7, 128.2, 136.4, 138.8. Anal. Calcd. for $C_{18}H_{30}O_2Si$: C, 70.53; H, 9.87%. Found: C, 70.86, H, 9.67%.

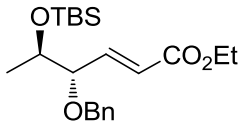
(2*R*,3*R*)-2-Benzyloxy-3-*tert*-butyldimethylsilyloxybutanal (67).



Reductive ozonolysis of **66** (3.16 g, 10.31 mmol) in CH_2Cl_2 (40 mL) -78 ^oC, followed by reaction with (3.24 g, 12.37 mmol) for 18 h at 25 ^oC, usual isolation and column chromatography (silica gel, 0-10% Et_2O/hexane) furnished **67** (2.8 g, 88%). colorless oil; $[\alpha]_D^{25}$ -16.5 (*c* 1.07, $CHCl_3$); IR: 2931, 2857, 2711, 1736 cm^{-1}; ^1H NMR: δ 0.03 (s, 6H), 0.87 (s, 9H), 1.31 (d, *J* = 6.6 Hz, 3H), 3.59-3.62 (m, 1H), 4.09-4.24 (m, 1H),

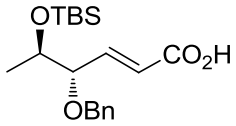
4.57-4.71 (m, 2H), 7.34 (s, 5H), 9.67 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR: δ -4.9, -4.5, 14.2, 17.9, 20.2, 25.7, 29.7, 60.4, 69.5, 72.9, 87.3, 127.9, 128.0, 128.5, 137.4, 203.0. Anal. Calcd. for $C_{17}H_{28}O_3Si$: C, 66.19; H, 9.15%. Found: C, 65.84, H, 9.09%.

Ethyl (4*S*,5*R*,2*E*)-4-Benzyloxy-5-*tert*-butyldimethylsilyloxyhex-2-enoate (68).



Wittig-Horner reaction between **67** (2.00 g, 6.48 mmol) and triethylphosphonoacetate (1.5 mL, 7.78 mmol) in THF (20 mL) at 25 ^{o}C for 18 h, usual isolation and column chromatography (silica gel, 0-10% Et_2O/hexane) afforded pure **68** (2.2 g, 90%). colorless oil; $[\alpha]_D^{27}$ +9.4 (*c* 1.36, $CHCl_3$); IR: 1722, 1656, 983, 916 cm^{-1}; ^{1}H NMR: δ 0.03 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 1.20 (d, *J* = 5.8 Hz, 3H),1.30(t, *J* = 7.2 Hz, 3H), 3.73-3.89 (m, 2H), 4.22 (q, *J* = 7.2 Hz, 2H),4.43 (d, *J* = 11.8 Hz, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 6.03 (d, *J* = 15.8 Hz, 1H), 6.92 (dd, *J*= 15.8, 6.0 Hz, 1H), 7.30-7.35 (m, 5H); ^{13}C NMR: δ -4.9, -4.6, 14.2, 18.0, 20.4, 25.7, 29.7, 60.3, 70.9, 71.6, 83.0, 123.3, 127.6, 127.7, 128.3, 138.0, 146.5, 166.1. Anal. Calcd. for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05%. Found: C, 66.69; H, 9.04%.

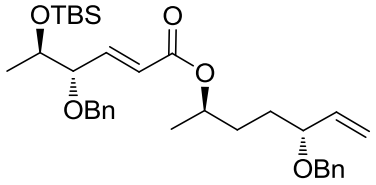
(4*S*,5*R*,2*E*)-4-Benzyloxy-5-*tert*-butyldimethylsilyloxyhex-2-enoic acid (69).



A mixture of **68** (1.60 g, 4.23 mmol) and $LiOH.H_2O$ (887 mg, 21.13 mmol) in THF-H_2O (1:1, 10 mL) was stirred for 8 h at room temperature. The mixture was concentrated in vacuo, the residue diluted with H_2O (10 mL), acidified with $KHSO_4$ and the aqueous layer extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried and concentrated in vacuo to obtain the crude product, which was purified by colum chromatography (silica gel, 0-30%

EtOAc/hexane) to obtain **69** (1.2 g, 82%). colorless oil; $[\alpha]_D^{27}$ +17.4 (*c* 1.03, $CHCl_3$); IR: 3300-2500, 1714, 1656, 988 cm^{-1}; ^1H NMR: δ 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.20 (d, *J* = 5.8 Hz, 3H), 3.80-3.88 (m, 2H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.62 (d, *J* = 11.8 Hz, 1H), 6.06 (d, *J* = 15.8 Hz, 1H), 7.06 (dd, *J* = 15.8, 5.8 Hz, 1H), 7.33-7.42 (m, 5H); ^{13}C NMR: δ -4.9, -4.6, 17.9, 20.4, 25.7, 70.8, 71.7, 82.8, 122.5, 127.7, 127.8, 128.4, 137.8, 149.4, 171.5. Anal. Calcd. for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63%. Found: C, 65.00; H, 8.55%.

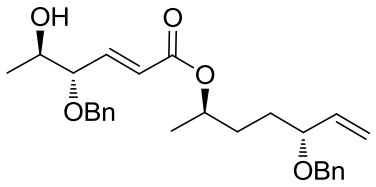
(4*S*,5*R*,2*E*)-[(2*R*,5*R*)-5-Benzyloxy]hept-6-en-2-yl 4-benzyloxy-5-*tert*-butyldimethyl silyloxyhex-2-enoate (70).



To a cooled (0 ^oC) and stirred solution of **61** (566 mg, 2.57 mmol), **69** (900 mg, 2.57 mmol) and PPh_3 (1.01 g, 3.85 mmol) in THF (30 mL) was added DIAD (0.8 mL, 3.85 mmol). After stirring for 18 h at room temperature, the mixture was extracted with EtOAc (2 × 15 mL), the combined organic extracts 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 **70** (1.11 g, 78%). colorless oil; $[\alpha]_D^{27}$ +22.2 (*c* 1.28, $CHCl_3$); IR: 1776, 1717, 1658, 988, 927 cm^{-1}; ^1H NMR: δ 0.01 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.56-1.65 (m, 4H), 3.71-3.85 (m, 3H), 4.39 (dd, *J* = 17.4, 11.8 Hz, 2H), 4.60 (d, *J* = 11.8, 5.4 Hz, 2H), 4.94-5.03 (m, 1H), 5.18-5.26 (m, 2H), 5.64-5.82 (m, 1H), 6.00 (d, *J* = 15.8 Hz, 1H), 6.88 (dd, *J* = 15.8, 6.2 Hz, 1H), 7.30-7.34 (m, 10H); ^{13}C NMR: δ -4.8, -4.6, 17.9, 20.0, 20.4, 25.7, 29.6, 31.4, 31.8, 70.1, 70.8, 71.0, 71.6, 80.4, 83.1, 117.4, 123.8, 127.4, 127.6, 127.7, 128.3, 128.6, 132.1, 132.3, 138.0,

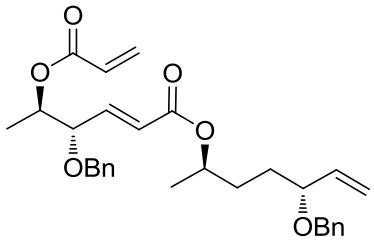
138.6, 138.7, 146.2, 165.6. Anal. Calcd. for $C_{33}H_{48}O_5Si$: C, 71.70; H, 8.75%. Found: C, 71.74; H, 8.21%.

(4*S*,5*R*,2*E*)-[(2*R*,5*R*)-5-Benzyloxy]hept-6-en-2-yl 4-benzyloxy-5-hydroxyhex-2-enoate (71).



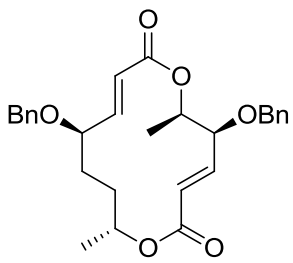
To a cooled (0 ^oC) and stirred solution of **70** (800 mg, 1.45 mmol) in CH_3CN (6 mL) was added TMSCl (37 µL, 0.29 mmol) in CH_3CN (2 mL) followed by H_2O (26 µL, 1.45 mmol). After stirring at 25 ^oC for 1 h, the reaction mixture treated with aqueous 10% $NaHCO_3$, diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried, concentrated in vacuo and the residue purified by column chromatography (silica gel, 0-25% EtOAc/hexane) to furnish **71** (560 mg, 88%). colorless oil; $[\alpha]_D^{26}$ +41.8 (*c* 1.27, $CHCl_3$); IR: 3456, 1714, 988 cm^{-1}; ^1H NMR: δ 1.16 (d, *J* = 6.6 Hz, 3H), 1.25 (d, *J* = 5.4 Hz, 3H), 1.59-1.71 (m, 4H), 3.72-3.75 (m, 1H), 3.90-3.96 (m, 2H), 4.35 (d, *J* = 12 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.65 (d, *J* = 12 Hz, 1H), 4.96-4.99 (m, 1H), 5.21-5.26 (m, 2H), 5.70-5.76 (m, 1H), 6.04 (d, *J* = 15.6 Hz, 1H), 6.88 (dd, *J* = 15.6, 7.2 Hz, 1H), 7.27-7.37 (m, 10H); ^{13}C NMR: δ 17.9, 19.9, 31.3, 31.7, 69.2, 70.1, 71.3, 80.3, 81.9, 117.5, 125.1, 127.4, 127.7, 127.9, 128.3, 128.5,137.6, 138.6, 143.7, 165.3. Anal. Calcd. for $C_{27}H_{34}O_5$: C, 73.94; H, 7.81%. Found: C, 73.78; H, 7.63%.

(4*S*,5*R*,2*E)*-[(2*R*,5*R*)-5-Benzyloxy]hept-6-en-2-yl-4-benzyloxy-5-acryloyloxyhex-2-enoate (72).



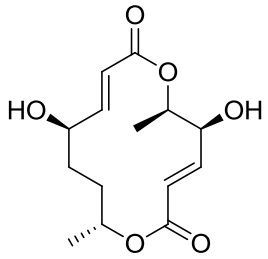
To a solution of **71** (300 mg, 0.68 mmol) in CH_2Cl_2 (10 mL) at 0 ^oC were added DIPEA (0.2 mL, 1.36 mmol) and acryloyl chloride (0.1 mL, 1.37 mmol) and the mixture stirred at 25 ^oC for 3 h. The mixture was extracted with $CHCl_3$ (3 × 20 mL). The organic layer was washed with H_2O (2 × 20 mL) and brine (1 × 10 mL), concentrated in vacuo and the residue purified by column chromatography (silica gel, 0-20 % EtOAC/ hexane) to obtain **72** (290 mg, 86%). colorless oil; $[\alpha]_D^{27}$ +73.3 (*c* 1.17, $CHCl_3$); IR: 1716, 1658, 985, 928 cm^{-1}; ^1H NMR: δ 1.28 (d, *J* = 6.5 Hz, 3H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.61-1.72 (m, 4H), 3.74-3.76 (m, 1H), 4.11-4.13 (m, 2H), 4.36 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.99-5.01 (m, 1H), 5.12-5.13 (m, 1H), 5.21-5.27 (m, 1H), 5.71-5.82 (m, 2H), 6.08-6.13 (m, 2H), 6.39 (d,*J* = 17.0 Hz,1H), 6.87 (dd, *J* = 16.0, 6.5Hz, 1H), 7.26-7.34 (m, 10H); ^{13}C NMR: δ 15.0, 20.0, 29.7, 31.4, 31.8, 70.1, 71.4, 71.7, 79.5, 80.4, 117.7, 124.7, 127.5, 127.7, 127.8, 128.4, 131.1, 137.7, 138.7, 143.6, 165.5. Anal. Calcd. for $C_{30}H_{36}O_6$: C, 73.15; H, 7.37%. Found: C, 73.09; H, 7.23%.

Clonostachydiol benzyl ether (73).



A mixture of **72** (200 mg, 0.43 mmol) and Hoveyda-Grubbs II catalyst (27 mg, 0.043 mmol, 10 mol%) in toluene (730 mL) was heated at 80 ^{o}C for 22 h. After concentrating the mixture in vacuo, the residue was subjected to column chromatography (silica gel, 0-25% EtOAc/hexane) to give pure **73** (123 mg, 65%); colorless oil; $[\alpha]_D^{27}$ +65.5 (*c* 1.27, $CHCl_3$); IR: 1722, 983 cm^{-1}; ^{1}H NMR: δ 1.20 (d, *J* = 6.5Hz, 3H), 1.41 (d, *J* = 6.5Hz, 3H), 1.53-1.65 (m, 2H), 1.79-1.83 (m, 1H), 2.07-2.12 (m, 1H), 3.76 (t, *J* = 9.0 Hz, 1H), 4.22-4.26 (m, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 4.66 (d, *J* = 12.5 Hz, 1H), 5.07-5.13 (m, 1H), 5.18-5.21 (m, 1H), 5.92 (dd, *J* = 15.5, 9.0 Hz, 2H), 6.71 (dd, *J* = 16.0, 9.0 Hz, 1H), 6.81 (dd, *J* = 16.0, 5.5 Hz, 1H), 7.28-7.38 (m, 10H); ^{13}C NMR: δ 17.6, 17.9, 27.3, 29.7, 69.6, 70.2, 70.6, 71.7, 76.5, 83.0, 122.5, 126.8, 127.4, 127.6, 127.9, 128.4, 137.4, 138.0, 145.6, 150.0, 164.7, 165.2. Anal. Calcd. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94%. Found: C, 72.42; H, 7.08%.

Clonostachydiol (IV).

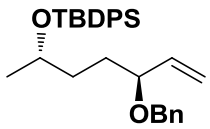


To a solution of **73** (80 mg, 0.17 mmol) in CH_2Cl_2-H_2O (4:1) was added DDQ (117 mg, 0.52 mmol). After completion of reaction (*cf*. TLC) the mixture was filtered, the filtrate concentrated in vacuo, and the residue purified by preparative TLC (5% MeOH/$CHCl_3$) to obtain pure **IV** (37 mg, 78%). white solid; mp: 165 ^{o}C (lit.[90b] mp 164 ^{o}C); $[\alpha]_D^{27}$ +112.5 (*c* 1.06, MeOH) (lit.[90b] $[\alpha]_D^{25}$ +101.6 (*c* 0.5, MeOH)) IR: 3417, 1729, 968, 910 cm^{-1}; ^{1}H NMR: δ 1.23 (d, *J* = 6.5 Hz, 3H), 1.48 (d, *J* = 6.5 Hz, 3H), 1.73-1.80 (m, 2H), 1.85-1.89 (m, 1H), 2.00-2.06 (m, 1H), 2.49 (broad s, 1H), 4.15-

4.16 (m, 1H), 4.49 (broad s, 1H), 4.99-5.05 (m, 2H), 5.12-5.19 (m, 1H), 5.91-5.98 (m, 2H), 6.75 (dd, *J* = 16.0, 6.0 Hz, 1H), 6.89 (dd, *J* = 16.0, 4.0 Hz, 1H); ^{13}C NMR: δ 18.0, 18.6, 27.4, 30.6, 70.1, 70.4, 73.8, 76.6, 120.3, 123.8, 145.4, 150.8, 165.0. Anal. Calcd. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09%. Found: C, 59.47; H, 7.30%.

(3*S*,6*S*)-6-*tert*-Butyldiphenylsilyloxyhept-1-en-3-ol (3*S*,6*S*)-58. Alkaline hydrolysis of (3*S*,6*S*)-**59** (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*)-**58** (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%.

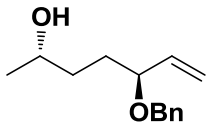
(3*S*,6*S*)-3-Benzyloxy-6-*tert*-butyldiphenylsilyloxyhept-1-ene (74).



As described earlier, benzylation of (3*S*,6*S*)-**58** (5.23 g, 14.19 mmol) with BnBr (2.19 mL, 18.45 mmol) and Bu_4NI (10 mol%) in the presence of hexane-washed NaH (1.36 g, 28.38 mmol, 50% suspension in oil) in THF (40 mL), followed by work-up and column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **74** (6.3 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

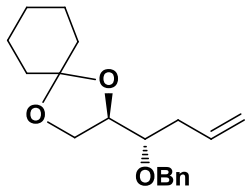
NMR: δ 19.2, 23.2, 27.0, 31.0, 35.0, 69.5, 69.9, 80.7, 117.1, 127.4, 127.6, 127.7, 128.3, 129.4, 134.4, 134.8, 135.9, 138.8, 138.9. Anal. Calcd. for $C_{30}H_{38}O_2Si$: C, 78.55; H, 8.35%. Found: C, 78.37; H, 8.28%.

(2*S*,5*S*)-5-Benzyloxyhept-6-en-2-ol (75).



Desilylation of **74** (6.32 g, 13.78 mmol) with Bu_4NF (20.67 mL, 20.67 mmol, 1M in THF) in THF (40 mL) at 0 ^oC, followed by usual isolation and purification by column chromatography (silica gel, 0-30% EtOAc/hexane) afforded pure **75** (2.6 g, 86%). colorless oil; $[\alpha]_D^{25}$ -20.6 (*c* 1.06, $CHCl_3$); IR: 3400, 3065, 3030, 1643 cm^{-1}; ^1H 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%.

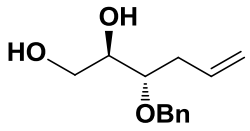
(4*S*,5*R*)-4-Benzyloxy-5,6-cyclohexylidenedioxy-1-hexene (76).



Benzylation of **6j** (4.00 g, 18.84 mmol) with BnBr (2.69 mL, 22.61 mmol) and Bu_4NI (10 mol%) in the presence of hexane-washed NaH (1.81 g, 50% suspension in oil, 37.68 mmol) in THF (65 mL), followed by work-up and column chromatography (silica gel, 0-10% EtOAc/hexane) afforded pure **76** (5.4 g, 95%). colorless oil; $[\alpha]_D^{25}$ +27.5 (*c* 1.47, $CHCl_3$); IR: 3060, 1644 cm^{-1}; ^1H NMR: δ 1.26-1.44 (m, 2H), 1.55-1.62 (m, 8H), 2.34-2.44 (m, 2H), 3.52-3.60 (m, 1H), 3.83-3.92 (m, 1H), 3.98-4.12 (m, 2H), 4.61 (AB quartet, *J* = 11.4 Hz, 2H), 5.05-5.18 (m, 2H), 5.78-5.99 (m, 1H), 7.29-7.33

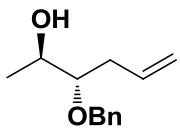
(m, 5H); ^{13}C NMR: δ 23.8, 24.0, 25.2, 34.9, 35.7, 36.3, 66.1, 72.5, 76.8, 79.0, 109.5, 117.4, 127.6, 127.7, 128.3, 134.3, 138.4. Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H 8.67%; Found: C, 75.29; H, 8.99%.

(2*R*,3*S*)-3-Benzyloxyhex-5-ene-l,2-diol (77).



A mixture of **76** (5.35 g, 17.69 mmol) and aqueous methanolic HCl (5 mL, 2N) was stirred at 25 ^{o}C till completion of the reaction (*cf*. TLC, 4 h). It was diluted with methanol (10 mL), concentrated 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 × 20 mL), aqueous 10% $NaHCO_3$ (2 × 10 mL), H_2O (2 × 20 mL) and brine (1 × 10 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-5% MeOH/$CHCl_3$) of the residue gave pure **77** (3.8 g, 97%) colorless oil; $[\alpha]_D^{26}$ +35.2 (*c* 1.05, $CHCl_3$); IR: 3398, 1063 cm^{-1}; ^{1}H NMR: δ 1.75 (broad s, 2H), 2.41-2.44 (m, 2H), 3.63-3.73 (m, 4H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.66 (d, *J* = 11.4 Hz, 1H), 5.12-5.19 (m, 2H), 5.78-5.92 (m, 1H), 7.25-7.33 (m, 5H); ^{13}C NMR: δ 34.9, 63.3, 72.4, 80.2, 117.6, 127.8, 128.4, 134.2, 137.9. Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%; Found: C, 70.39; H, 8.21%.

(2*R*,3*S*)-3-Benzyloxyhex-5-en-2-ol (78)

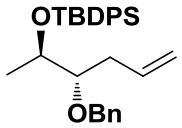


Tosylation of **77** (3.83 g, 17.23 mmol) with *p*-TsCl (3.61 g, 18.95 mmol), Bu_2SnO (129 mg, 0.52 mmol) and Et_3N (2.88 mL, 20.68 mmol) in CH_2Cl_2 (50 mL) for 6 h, followed by work-up and column chromatography (silica gel, 0-15% EtOAc/hexane) afforded the parimary monotosylate of **78** (5.5 g, 85%). colorless oil; $[\alpha]_D^{25}$ +33.9 (*c*

1.06, $CHCl_3$); IR: 3528, 1362 cm^{-1}; ^1H NMR: δ 1.85 (broad s, 1H), 2.33-2.48 (m containing a s at δ 2.41, 5H), 3.47-3.56 (m, 1H), 3.80-3.88 (m, 1H), 4.05-4.24 (m, 2H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 5.06-5.16 (m, 2H), 5.71-5.92 (m, 1H), 7.24-7.33 (m, 7H), 7.75-7.79 (m, 2H); ^{13}C NMR: δ 21.4, 34.2, 70.3, 71.3, 71.9, 78.1, 117.8, 127.6, 127.8, 128.2, 129.7, 132.3, 133.6, 137.7, 144.8. Anal. Calcd. for $C_{20}H_{24}O_5S$: C, 63.81; H, 6.43%. Found: C, 64.03; H, 6.82%.

Reduction of the monotosylate (4.20 g, 11.16 mmol) with $LiAlH_4$ (424 mg, 11.16 mmol) in Et_2O (50 mL) followed by work-up as described earlier furnished **78** (2.2 g, 96%). colorless oil; $[\alpha]_D^{26}$ +5.8 (*c* 1.01, $CHCl_3$); IR: 3434, 1640 cm^{-1}; ^1H NMR: δ 1.18 (d, *J* = 6.4 Hz, 3H), 2.00 (broad s, 1H), 2.23-2.46 (m, 2H), 3.38-3.46 (m, 1H), 3.87-3.97 (m, 1H), 4.60 (q, *J* = 11.4 Hz, 2H), 5.04-5.17 (m, 2H), 5.77-5.95 (m, 1H), 7.31-7.35 (m, 5H); ^{13}C NMR: δ 17.7, 34.0, 68.1, 71.9, 82.3, 116.8, 127.5, 127.6, 128.2, 135.0, 138.3. Anal Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80%. Found: C, 75.98; H, 9.07%.

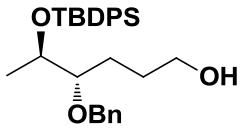
(4*S*,5*R*)-4 -Benzyloxy-5-*tert*-butyldiphenylsilyloxy-1-pentene (79).



Silylation of **78** (2.20 g, 10.67 mmol) with TBDPSCl (3.32 mL, 12.80 mmol), imidazole (1.09 g, 16.00 mmol) and DMAP (catalytic) in CH_2Cl_2 (35 mL), followed by work-up and column chromatography (silica gel, 0-5% EtOAc/hexane) afforded pure **79** (4.3 g, 91%). colorless oil; $[\alpha]_D^{26}$ -6.0 (*c* 1.24, $CHCl_3$); IR: 3070, 1639 cm^{-1}; ^1H NMR: δ 1.07 (merged s and d, *J* = 6.2 Hz, 12H), 2.18-2.33 (m, 2H), 3.39-3.43 (m, 1H), 3.89-3.94 (m, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 11.6 Hz, 1H), 4.95-5.04 (m, 2H), 5.61-5.79 (m, 1H), 7.31-7.39 (m, 11H), 7.65-7.71 (m, 4H); ^{13}C NMR: δ 18.3, 19.2, 27.0, 35.8, 71.4, 72.7, 83.5, 116.5, 127.3, 127.4, 127.5, 127.6, 128.2,

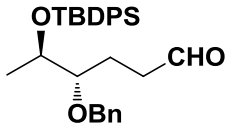
129.5, 129.6, 133.9, 134.5, 135.5, 136.0, 139.1. Anal. Calcd. for $C_{29}H_{36}O_2Si$: C,78.33; H, 8.16%. Found: C, 78.62; H, 7.93%.

(4*S*,5*R*)-4-Benzyloxy-5-*tert*-butyldiphenylsilyloxyhexan-1-ol (80).



To a stirred and cooled (0 °C) solution of **79** (4.30 g, 9.67 mmol) in THF (20 mL) was added $BH_3.Me_2S$ (644 μL, 95% purity, 6.45 mmol), and the mixture stirred for 3 h. Aqueous NaOH (3.87 mL, 3N) was added into it, followed by aqueous 30% H_2O_2 (3.87 mL). After stirring for 3 h at 0 ^oC 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 pure **80** (3.9 g, 88%). colorless oil; $[\alpha]_D^{25}$ -4.0 (*c* 1.01, $CHCl_3$); IR: 3433 cm^{-1}; ^1H NMR: δ 1.06 (merged s and d, *J* = 6.2 Hz, 12H), 1.48-1.55 (m, 5H), 3.34-3.38 (m, 1H), 3.48-3.54 (m, 2H), 3.88-3.93 (m, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.81 (d, *J* = 11.6 Hz, 1H), 7.29-7.38 (m, 11H), 7.64-7.71 (m, 4H); ^{13}C NMR: δ 18.4, 19.2, 27.0, 27.4, 29.2, 62.8, 71.9, 72.8, 83.7, 127.5, 127.6, 127.8, 128.3, 129.6, 133.9, 134.5, 136.0, 138.8. Anal. Calcd. for $C_{29}H_{38}O_3Si$: C, 75.28; H, 8.28%. Found: C, 75.57; H, 8.11%.

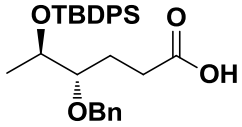
(4*S*,5*R*)-4-Benzyloxy-5-*tert*-butyldiphenylsilyloxyhexanal (81).



Oxidation of **80** (3.63 g, 7.85 mmol) with PCC (2.54 g, 11.77 mmol) and NaOAc (10 mol%) in CH_2Cl_2 (30 mL) for 3 h, followed by work-up and column chromatography

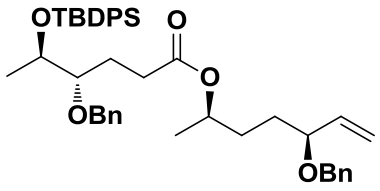
(silica gel, 0-5% EtOAc/hexane) furnished **81** (3.2 g, 89%). colorless oil; $[\alpha]_D^{26}$ -8.4 (*c* 1.30, $CHCl_3$); IR: 2714, 1729 cm^{-1}; ^1H NMR: δ 1.06 (merged s and d, *J* = 6.2 Hz, 12H), 1.76-1.84 (m, 2H), 2.38 (dt, *J* = 7.2, 1.4 Hz, 2H), 3.28-3.37 (m, 1H), 3.89-3.94 (m, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 7.28-7.41 (m, 11H), 7.64-7.70 (m, 4H), 9.64 (t, *J* = 1.4 Hz, 1H); ^{13}C NMR: δ 18.7, 19.2, 23.1, 27.0, 40.3, 71.1, 72.4, 82.6, 127.5, 127.6, 127.7, 127.8, 128.2, 129.6, 129.7, 133.6, 134.3, 135.9, 138.5, 202.5. Anal. Calcd. for $C_{29}H_{36}O_3Si$: C, 75.61; H, 7.88%. Found: C, 75.97; H, 7.48%.

(4*S*,5*R*)-4-Benzyloxy-5-*tert*-butyldiphenylsilyloxyhexanoic acid (82).



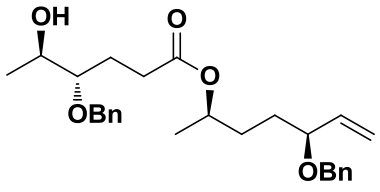
Oxidation of **81** (3.00 g, 6.51 mmol) using $NaH_2PO_4.2H_2O$ (203 mg, 1.30 mmol), $NaClO_2$ (1.18 g, 13.02 mmol) and aqueous 30% H_2O_2 (810 μL, 7.16 mmol) in CH_3CN (10 mL), followed by work-up and column chromatography (silica gel, 10% EtOAc/hexane) furnished **82** (2.4 g, 77%). colorless thick oil; $[\alpha]_D^{26}$ -8.3 (*c* 1.1 0, $CHCl_3$); IR: 3500-2500, 1712 cm^{-1}; ^1H NMR: δ 1.06 (merged s and d, *J* = 6.0 Hz, 12H), 1.69-1.91 (m, 2H), 2.35-2.42 (m, 2H), 3.35-3.43 (m, 1H), 3.87-3.98 (m, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 11.6 Hz, 1H), 7.29-7.41 (m, 11H), 7.65-7.72 (m, 5H); ^{13}C NMR: δ 14.2, 18.6, 19.2, 25.5, 27.0, 30.4, 71.2, 72.6, 82.6, 127.5, 127.6, 127.7, 128.3, 129.6, 129.7, 133.7, 134.4, 135.9, 138.7, 179.8. Anal. Calcd. for $C_{29}H_{36}O_4Si$: C,73.07; H, 7.61%. Found: C, 72.93; H, 7.26%.

(4*S*,5*R*)-[(2*R*,5*S*)-5-Benzyloxyhept-6-en-2-yl]-4-benzyloxy-5-tert-butyldiphenylsilyloxy hexanoate (83).



Esterification of **82** (2.22 g, 4.66 mmol) with **75** (1.03 g, 4.66 mmol) using PPh_3 (1.83 g, 6.99 mmol) and DIAD (1.38 mL, 6.99 mmol) in THF (20 mL) for 18 h, followed by work up, usual isolation and column chromatography (silica gel, 0-20% EtOAc/hexane) gave pure **83** (2.5 g, 78%). colorless oil; $[\alpha]_D^{26}$ -17.1 (*c* 1.01, $CHCl_3$); IR: 1715, 1657, 995 cm^{-1}; ^1H NMR: δ 1.03 (merged s and d, *J* = 7 Hz, 12H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.52-1.62 (m, 6H), 2.18-2.37 (m, 2H), 3.32-3.40 (m, 1H), 3.64-3.74 (m, 1H), 3.87-3.92 (m, 1H), 4.31 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.72 (d, *J* = 11.4 Hz, 1H), 4.80-4.89 (m, 1H), 5.14-5.23 (m, 2H), 5.60-5.77 (m, 1H), 7.28-7.39 (m, 16H), 7.64-7.70 (m, 4H); ^{13}C NMR: δ 18.7, 19.2, 19.9, 26.0, 27.0, 30.9, 31.2, 31.5, 70.0, 70.5, 71.4, 72.7, 80.0, 82.9, 117.4, 127.4, 127.6, 127.7, 128.2, 128.3, 129.5, 129.6, 133.7, 134.5, 135.9, 136.0, 138.7, 138.9, 173.3. Anal. Calcd. for $C_{43}H_{54}O_5Si$: C, 76.07; H, 8.02%. Found: C, 76.21; H, 8.10%.

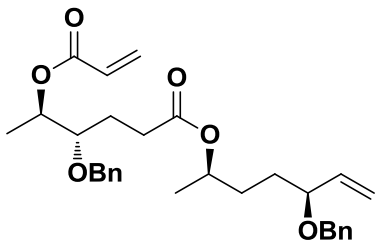
(4*S*,5*R*)-[(2*R*,5*S*)-5-Benzyloxyhept-6-en-2-yl]-4-benzyloxy-5-hydroxyhexanoate (84).



To a mixture of **83** (1.40 g, 2.06 mmol) and pyridine (20 mL) in THF (20 mL) in a teflon vessel was added HF-Pyr (70:30, 2 mL). After stirring at room temperature for 6 h, the mixture was extracted with EtOAc (3 × 20 mL). The organic extract was

washed with H_2O (2 × 10 mL) and brine (1 × 10 mL), dried, concentrated in vacuo, and the residue column chromatographed (silica gel, 0-25% EtOAc/hexane) to afford pure **84** (790 mg, 87%). colorless oil; $[\alpha]_D^{27}$ -11.3 (*c* 1.03, $CHCl_3$); IR: 3427, 3030, 1714, 990 cm^{-1}; ^1H NMR: δ 1.19 (d, *J* = 7.0 Hz, 6H), 1.48-1.53 (m, 2H), 1.64-1.73 (m, 2H), 1.81-1.95 (m, 3H), 2.32-2.39 (m, 1H), 2.44-2.51 (m, 1H), 3.34-3.37 (m, 1H), 3.70-3.74 (m, 1H), 3.93-3.98 (m, 1H), 4.33 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 12.5 Hz, 1H), 4.59 (d, *J* = 12.5 Hz, 1H), 4.87-4.91 (m, 1H), 5.20-5.25 (m, 2H), 5.67-5.75 (m, 1H), 7.27-7.36 (m, 10H); ^{13}C NMR: δ 18.0, 20.0, 23.6, 30.3, 31.3, 31.6, 67.4, 70.1, 70.8, 72.1, 80.0, 81.9, 117.5, 127.5, 127.7, 127.8, 127.9, 128.3, 128.5, 138.2, 138.6, 138.7, 173.5. Anal. Calcd. for $C_{27}H_{36}O_5$: C, 73.61; H, 8.24%. Found: C, 73.95; H, 8.62%.

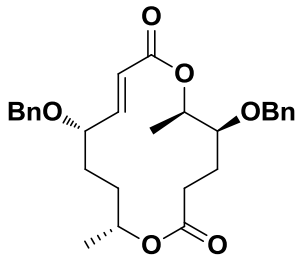
(4*S*,5*R*)-[(2*R*,5*S*)-5-Benzyloxyhept-6-en-2-yl]-5-acryloyloxy-4-benzyloxyhexanoate (85).



Reaction of **84** (790 mg, 1.79 mmol) with acryloyl chloride (0.29 mL, 3.59 mmol) and DIPEA (0.60 mL, 3.59 mmol) in CH_2Cl_2 (15 mL) at room temperature for 3 h, followed by isolation and purification by column chromatography (silica gel, 0-20 % EtOAC/hexane) yielded **85** (790 mg, 89%). colorless oil; $[\alpha]_D^{26}$ -26.1 (*c* 1.22, $CHCl_3$); IR: 1718, 1714, 985 cm^{-1}; ^1H NMR: δ 1.18 (d, *J* = 6.5 Hz, 3H), 1.31 (d, *J* = 6.0 Hz, 3H), 1.49-1.55 (m, 2H), 1.64-1.71 (m, 2H), 1.82-1.89 (m, 2H), 2.33-2.39 (m, 1H), 2.43-2.48 (m, 1H), 3.51-3.55 (m, 1H), 3.70-3.75 (m, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.87-

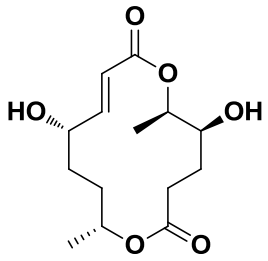
4.91 (m, 1H), 5.16-5.25 (m, 3H), 5.68-5.76 (m, 1H), 5.83 (d, *J* = 10.5 Hz, 1H), 6.13 (dd, *J* = 17.5, 10.5 Hz, 1H), 6.41 (d, *J* = 17.5 Hz, 1H), 7.26-7.34 (m, 10H); ^{13}C NMR: δ 15.0, 19.9, 25.8, 29.7, 30.7, 31.2, 31.6, 70.1, 70.7, 71.7, 72.6, 79.8, 80.0, 117.4, 127.4, 127.7, 127.9, 128.3, 128.4, 128.8, 130.7, 138.2, 138.7, 165.5, 173.0. Anal. Calcd. for $C_{30}H_{38}O_6$: C,72.85; H, 7.74%. Found: C, 72.46; H, 7.62%.

Acremodiol benzyl ether (86).



RCM reaction of **85** (300 mg, 0.61 mmol) in the presence of Grubbs' I catalyst (150 mg, 0.18 mmol) in degassed CH_2Cl_2 (300 mL) at 40 ºC for 48 h, followed by isolation and purification by thin layer chromatography (TLC, silica gel, 10% EtOAC/hexane) gave pure **86** (100 mg, 42% based on conversion) and recovered **85** (50 mg). white solid; mp: 91-93°C; $[\alpha]_D^{28}$ -45.3 (*c* 1.11, $CHCl_3$); IR: 1713 cm^{-1}; ^{1}H NMR: δ 1.13 (d, *J* = 6.5 Hz, 3H), 1.34 (d, *J* = 6.0 Hz, 3H), 1.51-1.58 (m, 1H), 1.66-1.70 (m, 1H), 1.82-1.89 (m, 2H), 1.99-2.10 (m, 2H), 2.32-2.41 (m, 2H), 3.30-3.34 (m, 1H), 3.73-3.78 (m, 1H), 4.37 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 4.53 (d, *J* = 10.5 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.73-4.76 (m, 1H), 5.15-5.21 (m, 1H), 5.86 (d, *J* = 16.0 Hz, 1H), 6.64 (dd, *J* = 16.0, 9.5 Hz, 1H), 7.27-7.37 (m, 10H); ^{13}C NMR: δ 17.6, 18.8, 24.4, 28.1, 28.6, 31.7, 69.1, 70.5, 71.3, 72.0, 78.4, 81.7, 125.0, 127.7, 128.2, 128.5, 137.8, 138.0, 147.9, 164.8, 172.3. Anal. Calcd. for $C_{28}H_{34}O_6$: C,72.08; H, 7.35%. Found: C, 72.38; H, 7.25%.

Acremodiol (V).



To a cooled (0 ^{o}C) and stirred solution of **86** (25 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) was added $TiCl_4$ (11.8 µL, 0.11 mmol) and the mixture stirred at room temperature for 0.5 h. After concentration in vacuo, the residue was purified by preparative TLC (silica gel, 15% EtOAC/hexane) to get pure **V** (12 mg, 81%). white solid; mp: 133-135 ºC (lit.[89] mp: 118-120 ºC); $[\alpha]_D^{25}$ -52.0 (*c* 1.20, $CHCl_3$), (lit.[87c] $[\alpha]_D^{25}$ +98 (c 0.33, MeOH) for natural **V**); IR: 3420, 1724, 982 cm^{-1}; ^{1}H NMR: δ 1.20 (d, *J* = 6.5 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.60-1.69 (m, 1H), 1.70-1.79 (m, 2H), 1.84-1.89 (m, 1H), 1.94-2.00 (m, 1H), 2.11-2.17 (m, 1H), 2.56-2.61 (m, 1H), 2.86-2.92 (m, 1H), 3.74 (broad s, 1H), 4.11-4.17 (m, 2H), 4.39 (broad s, 1H), 4.87-4.90 (m, 1H), 5.22-5.27 (m, 1H), 5.92 (d, *J* = 16.5 Hz, 1H), 6.56 (dd, *J* = 16.5, 8.5 Hz, 1H); ^{13}C NMR: δ 16.6, 19.2, 26.2, 29.7, 30.0, 31.9, 70.4, 71.5, 72.6, 74.1, 123.2, 147.8, 164.9, 175.1. Anal. Calcd. for $C_{14}H_{22}O_6$: C,58.73; H, 7.74%. Found: C, 59.07; H, 7.68%.

CHAPTER IV

BIBLIOGRAPHY

References

1. Clardy, J.; Walsh, C. *Nature* **2004,** *432,* 829–837.
2. (a) Butler, M. S.; Robertson, A. A. B.; Cooper, M. A. *Nat. Prod. Rep*. **2014**, *31*, 1612–1661; (b) Zhang, M. -Q.; Wilkinson, B. *Curr. Opin. Biotechnol*. **2007**, *18*, 478–488; (c) Ganesan, A. *Curr. Opin. Chem. Biol*. **2008**, *12*, 306–317.
3. (a) Ward, R. S. In: *Selectivity in Organic Synthesis*. Wiley, 1999; (b) Hoz A. D. L.; Diaz-Ortiz, A.; Moreno, A. *Curr. Org. Chem*. **2004**, *8*, 903–918.
4. (a) Eliel, E. L. In: Stereochemistry of Carbon Compounds; McGraw-Hill, 1962; (b) Stephenson, G. R. In: Advanced Asymmetric Synthesis; Chapman and Hall, 1996.
5. (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.
6. (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, J. Wiley & Sons, Inc., New York, 1981, 447 S.
7. (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.
8. (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.); John Wiley & Sons, 2013.
9. (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.
10. (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.

11. (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.
12. (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.
13. (a) Cherest, M.; Felkin, H. *Tetrahedron Lett*. **1968**, *9*, 2205–2208; (b) Anh, N. T. *Top. Curr. Chem*. **1980**, *88*, 145–170.
14. (a) 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. (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.
16. Liese, Andreas; Seelbach, Karsten; Wandrey, Christian, ed. (2006). *Industrial Biotransformations* (2nd ed.). John Wiley & Sons. p. 556.
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. Klibanov, A. M. *Nature* **2001**, *409*, 241–246.
19. (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.

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. (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*; Wiley: New York, 1994.
22. (a) Wardencki, W.; Curylo, J.; Namieśnik, J. *Pol. J. Env. Stud*. **2005**, *14*, 389–395; (b) Sheldon, R. A. *Chem. Soc. Rev.* **2012**, *41*, 1437–1451.
23. (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) Patro, B. S.; Maity, B.; Chattopadhyay, S. *Antioxidant Redox. Signal*. **2010**, *12*, 945–960; (d) Yadav, S. K.; Adhikary, B.; Chand, S.; Maity, B.; Bandyopadhyay, S. K.; Chattopadhyay S. *Free Radic. Biol. Med*. **2012**, *52*, 1175–1187; (e) Maity, B.; Yadav, S. K.; Patro, B. S.; Bandyopadhyay, S. K.; Chattopadhyay S. *Free Radic. Biol. Med*. **2012**, *52*, 1680–1691.
24. (a) Salaskar, A.; Sharma, A.; Chattopadhyay, S. *Tetrahedron Asymm*. **2005**, *17*, 325–329. (b) Sharma, A.; Gamre, S.; Roy, S.; Goswami, D.; Chattopadhyay, A.; Chattopadhyay, S. *Tetrahedron Lett*. **2008**, *49*, 3902–3905; (c) Sharma, A.; Das, P.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2008**, *19*, 2167–2170; (d) Roy, S.; Sharma, A.; Mula, S.; Chattopadhyay, S. *Chem. A Eur. J*. **2009**, *15*, 1713–1722; (e) Chattopadhyay, A; Mamdapur, V. R. *J. Org. Chem*. **1995**, *60*, 585–587.
25. (a) Roush, W. R. Comprehensive Organic Synthesis. Trost, BM., editor. Vol. 2. Pergamon Press; Oxford: 1991. p. 1; (b) Yamamoto, Y.; Asao, N. *Chem Rev*. **1993**, *93*, 2207–2293; (c) Denmark, S. E. Almstead, N. G. Modern Carbonyl Chemistry. Otera, J., editor. Wiley-VCH; Weinheim: 2000. p. 299; (d) Denmark, S. E.; Fu, J. *Chem Rev*. **2003**, *103*, 2763–2793; (e) Lachance, H.; Hall, D. G. *Org React*. **2008**, *73*, 1; (f) Yus, M.; Gonzalez-Gomez, J. C.; Foubelo, F. *Chem Rev*. **2011**, *111*, 7774–7854.
26. (a) Marshall, J.; Johns, B. *J. Org. Chem*. **1998**, *63*, 7885–7892; (b) Marshall, J. A.; Adams, N. D. *J. Org. Chem*. **2002**, *67*, 733–740; (c) Marshall, J. A.;

Bourbeau, M. P. *J. Org. Chem*. **2002**, *67*, 2751–2754; (d) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem*. **2003**, *68*, 7428–7432; (e) Brodmann, T.; Janssen, D.; Kalesse, M. *J. Am. Chem. Soc*. **2010**, *132*, 13610–13611.

27. (a) Marshall, J. A.; Schaaf, G. *J. Org. Chem*. **2001**, *66*, 7825–7831; (b) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem*. **2004**, *69*, 4626–4647; (c) Lepage, O.; Kattnig, E.; Furstner, A. *J. Am. Chem. Soc*. **2004**, *126*, 15970–15971; (d) Furstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc*. **2006**, *128*, 9194–9204; (e) Belardi, J. K.; Micalizio, G. C. *Org. Lett*. **2006**, *8*, 2409–2412; (f) Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc*. **2007**, *129*, 3826–3827; (g) Chatterjee, A.; Richer, J.; Hulett, T.; Iska, V. B. R.; Wiest, O.; Helquist, P. *Org. Lett*. **2010**, *12*, 832–834; (h) Chen, Q.; Schweitzer, D.; Kane, J.; Davisson, V. J.; Helquist, P. *J. Org. Chem*. **2011**, *76*, 5157–5169; (i) Carter, C. F.; Lange, H.; Sakai, D.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J*. **2011**, *17*, 3398– 3405.
28. (a) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959–1982; (b) Augé, J.; Lubin-Germain, N. Uziel, J. *Synthesis* **2007**, 1739–1764; (c) Araki, S.; Ito, H.; Butsugan, Y. *Appl. Organomet. Chem*. **1988**, *2*, 475–478; (d) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Tetrahedron Lett*. **2004**, *45*, 243–248; (e) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc*. **2001**, *123*, 9168–9169; (f) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett*. **2005**, *7*, 3577–3579; (g) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Organometallic Chem*. **2007**, *692*, 505–513.
29. (a) Wang, J .-X.; Jia, X.; Meng, T.; Xin, L. *Synthesis*, **2005**, 2669–2672; (b) Haddad, T. D.; Hirayama, L. C.; Buckley, J. J.; Singaram, B. *J. Org. Chem.*, **2012**, *77*, 889–898; (c) Yan, Z.; Hua, Z.; Ling-Yan, L.; Xin, W.; Wei-Xing, C.; Jing, L. *Chem. J. Chin. Univ. – Chin. Ed*. **2012**, *33*, 2447–2451. DOI: 10.7503/cjcu20120380; (d) Muñoz-Bascón, J.; Sancho-Sanz, I., Alvarez-Manzaneda, E., Rosales, E., Oltra, J. E. *Chem. Eur. J*. **2012**, *18*, 14479–14486.
30. (a) Yamamoto, H. In: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 81–85; (b) Epsztein, R. In: *Comprehensive Carbanio Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1984; p 107. Chapter 3; (c) Kleinman, E. F.; Volkmann, R. A. In: *Comprehensive Organic Synthesis*; Trost, B. M.,

Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 975; (d) Stang, P. J.; Diederich, F. In: *Modern Acetylene Chemistry*; VCH: New York, 1995.

31. For selected examples, see: (a) Trost, B. M.; Dumas, J.; Villa, M. *J. Am. Chem. Soc*. **1992**; *114*, 9836–9845; (b) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc*. **1996**; *118*, 6648–6659; (c) Schmidt, D. R.; O'Malley, S. J.; Leighton, J. L. *J. Am. Chem. Soc*. **2003**, *125*, 1190–1191; (d) O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. A.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Holmes, A. B. *J. Am. Chem. Soc*. **2004**, *126*, 2194–2207; (e) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485–488; (f) Francais, A.; Leyva, A.; Etxebarria-Jardi, G.; Ley, S. V. *Org Lett*. **2010**, *12*, 340–343.
32. (a) Dolhem, F.; Al Tahali, F.; Lievre, C.; Demailly, G. *Eur. J. Org. Chem*. **2005**, *23*, 5019–5023; (b) Bahadoor, A. B.; Micalizio, G. C. *Org. Lett*. **2006**, *8*, 1189–1191; (c) Saito, N.; Masuda, M.; Saito, H.; Takenouchi, K.; Ishizuka, S.; Namekawa, J.-i.; T. –K., M.; Kittaka, A. *Synthesis* **2005**, 2533–2543; (d) Kobayishi, Y.; Fukuda, A.; Kimachi, T.; Ju-Ichi, M.; Takemoto, Y. *Tetrahedron* **2005**, *61*, 2607–2622; (e) Broadrup, R. L.; Sunder, H. M.; Swindell, C. S. *Bioorg. Chem*. **2005**, *33*, 116–133; (f) Chavan, S. P.; Praveen, C. *Tetrahedron Lett*. **2005**, *46*, 1939–1941; (g) Schwartz, B. D.; Hayes, P. Y.; Kitching, W.; De Voss, J. *J. Org. Chem*. **2005**, *70*, 3054–3065; (h) Cases, M.; Gonzalez lopez de Turiso, F.; Hadjisoterio, M. S.; Pattenden, G. *Org. Biomol. Chem*. **2005**, *3*, 2786–2804; (i) Hansen, E. C.; Lee, D. *Tetrahedron Lett*. **2004**, *45*, 7151–7155; (j) Marshall, J. A.; Adams, N. D. *Org. Lett*. **2000**, *2*, 2897–2900; (k) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Org. Chem*. **1989**, *54*, 5198–5200; (l) Carter, R. G.; Weldon, D. J. *Org. Lett*. **2000**, *2*, 3913–3916; (m) O'Sullivan, P. T.; Buhr, W.; Fuhry, M. A. M.; Harrison, J. R.; Davies, J. E.; Feeder, N.; Marshall, D. R.; Burton, J. W.; Homes, A. B. *J. Am. Chem. Soc*. **2004**, *126*, 2194–2207; (n) Trost, B. M.; Dong, G. B. *Nature* **2008**, *456*, 485–488; (o) Liu, S. B.; Kim, J. T.; Dong, G. C.; Kishi, Y. *Org. Lett*. **2009**, *11*, 4520–4523; (p) Francais, A.; Leyva, A.; Etxebarria-Jardi, G.; Ley, S. V. *Org. Lett*. **2010**, *12*, 340–343.
33. For reviews on carbonyl propargylation employing allenylmetal reagents, see: (a) Moreau, J. -L. In: *The Chemistry of Ketenes, Allenes and Related*

Compounds; Patai, S., Ed.; Wiley; New York: 1980. p. 363–413; (b) Marshall, J. A. *Chem. Rev*. **1996**, *96*, 31–48; (c) Gung, B. W. *Org. React*. **2004**, *64*, 1–113; (d) Marshall, J. A.; Gung, B. W.; Grachan, M. L. In: *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K., Eds;. Wiley-VCH; Weinheim: 2004. p. 493–592; (e) Marshall, J. A. *J. Org. Chem*. **2007**, *72*, 8153–8166.

34. (a) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc*. **1982**, *104*, 7667–7669; (b) Corey, E. J.; Yu, C. M.; Lee, D. H. *J. Am. Chem. Soc*. **1990**, *112*, 878–879; (c) Minowa, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 3697–3704; (d) Marshall, J. A.; Wang, X. J. *J. Org. Chem*. **1991**, *56*, 3211–3213; (e) Marshall, J. A.; Maxson, K. *J. Org. Chem*. **2000**, *65*, 630–633; (f) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *J. Chem. Soc. Chem. Commun*. **1993**, 1468–1469.
35. (a) Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett*. **1994**, *35*, 8323–8324; (b) Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc*. **2001**, *123*, 6199–6200; (c) Jain, P.; Wang, H.; Houk, K. N.; Antilla, J. C. *Angew. Chem., Int. Ed*. **2012**, *51*, 1391–1394; (d) Reddy, L. R. *Org. Lett*. **2012**, *14*, 1142–1145; (e) Barnett, D. S.; Schaus, S. E. *Org. Lett.*, **2011**, *13*, 4020–4023.
36. (a) Loh, T.-P.; Lin, M.-J.; Tan, K.-L. *Tetrahedron Lett*. **2003**, *44*, 507–509; (b) Haddad, T. D.; Hirayama, L. C.; Buckley, J. J.; Singaram, B. *J. Org. Chem*. **2012**, *77*, 889–898. and references cited therein; (c) Miao, W.; Chan, T. S. *Synthesis* **2003**, 785–789; (d) Lin, M.-J.; Loh, T. P. *J. Am. Chem. Soc*. **2003**, *125*, 13042–13043; (e) Miao, W.; Lu, W.; Chan, T. H. *J. Am. Chem. Soc*. **2003**, *125*, 2412–2413; (f) Bieber, L. W.; da Silva, M. F.; da Costa, R. C.; Silva, L. O. S. *Tetrahedron Lett*. **1998**, *39*, 3655–3658; (g) Jögi, A.; Mäeorg, U. *Molecules* **2001**, *6*, 964–968; (h) Yanagisawa, A.; Suzuki, T.; Koide, T.; Okitsu, S.; Arai, T. *Chem. Asian. J*. **2008**, *3*, 1793–1800.
37. (a) Fandrick, D. R.; Fandrick, K. R.; Reeves, J. T.; Tan, Z.; Johnson, C. S.; Lee, H.; Song, J. J.; Yee, N. K.; Sananayake, C. H. *Org. Lett*. **2010**, *12*, 88–91; (b) Bandini, M.; Gozzi, P. G.; Melchiorre, P.; Tino, R.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1063–1069; (c) Justicia, J.; Sancho-Sanz, I.; Alvarez-Manzaneda, E.; Oltra, J. E.; Cuerva, J. M. *Adv. Synth. Catal*. **2009**, *351*, 2295–2300; (d) Masuyama, Y.; Watabe, A.; Ito, A.; Kurusu, Y. *Chem. Commun*. **2000**, 2009–2010; (e) Kurono, N.; Sugita, K.; Tokuda, M. *Tetrahedron* **2000**, *56*, 847–854.

38. Achartya, H. P.; Miyoshi, K.; Kobayashi, Y. *Org. Lett*. **2007**, *9*, 3535–3538.
39. Patman, R. L.; Williums, V. M.; Bower, J. F.; Kische, M. J. *Angew. Chem. Int. Ed*. **2008**, *47*, 5220–5223, and references cited therein.
40. (a) Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc*. **1986**, *108*, 483–486; (b) Corey, E. J.; Yu, C. M.; Lee, D. H. *J. Am. Chem. Soc*. **1990**, *112*, 878–879; (c) Lee, K. C.; Lin, M. J.; Loh, T. P. *Chem. Commun*. **2004**, 2456–2457; (d) Lai, C.; Soderquist, J. A. *Org. Lett*. **2005**, *7*, 799–802.
41. (a) Chattopadhyay, A.; Dubey, A. *J. Org. Chem*. **2007**, *72*, 9357–9359; (b) Dubey, A. K.; Goswami, D.; Chattopadhyay, A. *ARKIVOC* **2010**, 137–145; (c) Dhotare, B.; Chattopadhyay, A. *Tetrahedron: Asymmetry* **2009**, *20*, 2007–2013; (d) Vichare, P.; Chattopadhyay, A. *Tetrahedron: Asymmetry* **2008**, *19*, 598–602; (e) Chattopadhyay, A.; Goswami, D.; Dhotare, B. *Tetrahedron Lett*. **2006**, *47*, 4701–4705; (f) Chattopadhyay, A.; Goswami, D.; Dhotare, B. *Tetrahedron Lett*. **2010**, *51*, 3893–3896; (g) Gowami, D.; Chattopadhyay, A. *Lett. Org. Chem*. **2006**, *3*, 922–925.
42. Ghosh, P.; Chattopadhyay, A. *Tetrahedron Lett*. **2012**, *53*, 5202–5205.
43. (a) Marshall, J. A.; Schaaf, G. *J. Org. Chem*. **2001**, *66*, 7825–7831; (b) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem*. **2004**, *69*, 4626–4647; (c) Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc*. **2004**, *126*, 15970–15971; (d) Fürstner, A.; Kattnig, E.; Lepage, O. *J. Am. Chem. Soc*. **2006**, *128*, 9194–9204; (e) Belardi, J. K.; Micalizio, G. C. *Org. Lett*. **2006**, *8*, 2409–2412; (f) Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc*. **2007**, *129*, 3826–3827; (g) Chatterjee, A.; Richer, J.; Hulett, T.; Iska, V. B. R.; Wiest, O.; Helquist, P. *Org. Lett*. **2010**, *12*, 832–834; (h) Chen, Q.; Schweitzer, D.; Kane, J.; Davisson, V. J.; Helquist, P. *J. Org. Chem*. **2011**, *76*, 5157–5169; (i) Carter, C. F.; Lange, H.; Sakai, D.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J*. **2011**, *17*, 3398–3405.
44. (a) Yamashita, K. *Agric. Biol. Chem*. **1984**, *48*, 1841–1844; (b) Benaglia, M.; Caporale, M.; Puglisi, A. *Enantiomer* **2002**, *7*, 383–385.
45. (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem. Int. Ed. Engl*. **2002**, *41*, 3701–3704; (b) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc*. **1997**, *119*, 7974–7991; (c) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2–72; (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624; (e) Germay, O.; Kumar,

N.; Thomas, E. J. *Tetrahedron Lett*. **2001**, *42*, 4969–4974; (f) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc*. **1993**, *115*, 7906–7907; (g) Kobayashi, J.; Ishibashi, M. *Chem. Rev*. **1993**, *93*, 1753–1769; (h) Doi, Y.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 4573–4580, and references cited therein.

46. (a) Okachi, T.; Onaka, M. *J. Am. Chem. Soc*. **2004**, *126*, 2306–2307; (b) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc*. **2005**, *127*, 14556–14557; (c) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc*. **2003**, *125*, 1140–1141.
47. (a) Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis*, **1997**, 249–267; (b) Sadler, P. J.; Li, H.; Sun, H. *Coord. Chem. Rev.* **1999**, *185-186*, 689–709.
48. (a) Wada, M.; Akiba, K-y. *Tetrahedron Lett*. **1985**, *26*, 4211–4212; (b) Wada, M.; Ohki, H.; Akiba, K-y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1738–1747; (c) Miyoshi, N.; Nishio, M.; Murakami, S.; Fukuma, T.; Wada, M. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 689–692; (d) Miyamoto, H.; Daikawa, N.; Tanaka, K. *Tetrahedron Lett*. **2003**, *44*, 6963–6964; (e) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Green Chem.* **2001**, *3*, 313–315.
49. (a) Wada, M.; Fukuma, T.; Morioka, M.; Takahashi, T.; Miyoshi, N. *Tetrahedron Lett*. **1997**, *38*, 8045–8048; (b) Wada, M.; Ohki, H.; Akiba, K.-y. *J. Chem. Soc. Chem. Commun*. **1987**, 708–709; (c) Donnelly, S.; Thomas, E. J.; Fielding, M. *Tetrahedron Lett*. **2004**, *45*, 6779–6782; (d) Jadhav, B. D.; Pardeshi, S. K. *Tetrahedron Lett*. **2014**, *55*, 4948–4952; (e) Xu, X.; Zha, Z.; Miao, Q.; Wang, Z. *Synlett* **2004**, 1171–1174; (f) Wada, S.; Hayashi, N.; Suzuki, H. *Org. Biomol. Chem*. **2003**, *1*, 2160–2163.
50. For reviews: (a) Wasserscheid, P.; Keim, W. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3772–3789; (b) Wasserscheid, P.; Welton, T. Ionic Liquids in Synthesis. Wiley-VCH, 2002. (c) Adams, D. J.; Dyson, P. J.; Taverner, S. J. Chemistry in Alternative Reaction Media. Wiley, 2003. For some recent papers: (d) Alizadeh, A.; Khodaei, M. M.; Eshgi, A. *J. Org. Chem.* **2010**, *75*, 8295–8298; (e) Aridoss, G.; Laali, K. K. *J. Org. Chem.* **2011**, *76*, 8088–8094; (f) Kumar, A.; Rao, V. K. *Synlett* **2011**, 2157–2162; (g) Sarkar, D.; Bhattarai, R.; Headley, A. D.; Ni, B. *Synthesis* **2011**, 1993–1997; (h) Sobhani, S.; Honarmand, M. *Synlett*, **2013**, *24*, 236–240; (i) Sarkar, A.; Roy, S. R.; Parikh, N.; Chakraborti, A. K. *J. Org. Chem.* **2011**, *76*, 7132–7140.

51. (a) Nelson, W. M. In *Green Chemistry*; Anastas, P. T., Williamson, T. C., Eds.; Oxford Univ. Press: Oxford, **1998**; p 200; (b) Welton, T. *Chem. Rev*. **1999**, *99*, 2071–2084; (c) Law, M. C.; Wong, K. Y.; Chan, T. H. *Green Chem*. **2002**, *4*, 161–164.
52. (a) Goswami, D.; Chattopadhyay, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2009**, *20*, 1957–1961; (b) Goswami, D.; Chattopadhyay, A.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem*. **2012**, *77*, 11064–11070.
53. (a) Rieke, R. D. *Aldrichimica Acta* **2000**, *33*, 52–60; (b) Fürstner, A. *Active Metals: Preparation, Characterization, Application*; VCH: Weinheim, 1996; (c) Li−Na: Kamienski, C. W.; Esmay, D. L. *J. Org. Chem*. **1960**, *25*, 1807–1808; (d) Smith, W. N., Jr. *J. Organomet. Chem*. **1974**, *82*, 1–5; (e) Shank, R. S.; Shechter, H. *J. Org. Chem*. **1959**, *24*, 1825–1826; (f) LeGoff, E. *J. Org. Chem*. **1964**, *29*, 2048–2050; (g) Takai, K.; Ueda, T.; Hayashi, T.; Moriwake, T. *Tetrahedron Lett*. **1996**, *37*, 7049–7052; (h) Takai, K.; Ikawa, Y. *Org. Lett*. **2002**, *4*, 1727–1729.
54. Smith, K.; Lock, S.; El-Hiti, G. A.; Wada, M.; Miyoshi, N. *Org. Biomol. Chem.* **2004**, *2*, 935–938.
55. (a) Hanna, M. W.; Ashbaugh, A. L. *J. Phys. Chem*. **1964**, *68*, 811−816; (b) Bhattacharya, S.; Nayak, S. K.; Chattopadhyay, S.; Banerjee, M.; Mukherjee, A. K. *J. Phys. Chem. A* **2001**, *105*, 9865−9868; (c) Bhattacharya, S.; Ghosh, K.; Bauri, A. K.; Chattopadhyay, S.; Banerjee, M. *J. Mol. Struct*. **2006**, *784*, 124−137; (d) *Ionic Liquids in Synthesis*, Chap 6, (Eds.: Endres, F.; Welton, T. in Wasserscheid, P.; Welton, T.), Wiley-VCH Verlag GmbH & Co. KGaA, **2002**, 289–318; (e) Dai, J. C.; Wu, X. T.; Hu, S. M.; Fu, Z. Y.; Zhang, J. J.; Du, W. X.; Zhang, H. H.; Sun, R. Q. *Eur. J. Inorg. Chem.* **2004**, 2096–2106; (f) Choi, D. S.; Kim, D. H.; Shin, U. S.; Deshmukh, R. R.; Lee, S.-g.; Song, C. E. *Chem.. Commun*. **2007**, 3467–3469.
56. The imidazolium ionic liquids are known to dissolve substantial amount of O_2. Husson-Borg, P.; Majer, V.; Gomes, M. F. C. *J. Chem. Engg. Data*. **2003**, *48*, 480–485.
57. (a) Fukuzumi, S.; Mori, H.; Imahori, H.; Suenobu, T.; Araki, Y.; Ito, O.; Kadish, K. M. *J. Am. Chem. Soc*. **2001**, *123*, 12458–12465; (b) Kim, Y- J.; Steritwieser, A. *J. Am. Chem. Soc*. **2002**, *124*, 5757–5761; (c) Fukuzumi, S.;

Yuasa, J.; Miyagawa, T.; Suenobu, T. *J. Phys. Chem. A* **2005**, *109*, 3174–3181.

58. Chianese, A. R.; Crabtree, R. H. Activation and functionalization of C-H bonds. Goldberg, K. I.; Goldman, A. S. eds., *Am. Chem. Soc*. **2004**, 169–183.
59. Ott, L. S.; Cline, M. L.; Deetlefs, M.; Seddon, K. R.; Finke, R. G. *J. Am. Chem. Soc*. **2005**, *127*, 5758–5759.
60. McGuinness, D. S.; Cavell, K. J.; Yates, B. F. *Chem. Commun*. **2001**, 355–356.
61. Lichtenberg, C.; Pan, F.; Spaniol, T. P.; Englert, U.; Okuda, J. *Angew. Chem. Int. Ed*. **2012**, *51*, 13011–13015, and references cited therein.
62. Sherley, J. L.; Kelly, T. J. *J. Biol. Chem*. **1988**, *263*, 8350–8358.
63. Shields, A. F.; Grierson, J. R.; Dohmen, B. M.; Machulla, H. J.; Stayanoff, J. C.; Lawhorn-Crews, J. M.; Obradovich, J. E.; Muzik, O.; Mangner, T. J. *Nat Med*. **1998**, *4*, 1334–1336.
64. (a) Belt, J. A.; Marina, N. M.; Phelps, D. A.; Crawford, C. R. *Adv. Enzyme Regul*. **1993**, *33*, 235–252; (b) Mackey, J. R.; Mani, R. S.; Selner, M.; Mowles, D.; Young, J. D.; Belt, J. A.; Crawford, C. R.; Cass, C. E. *Cancer Res*. **1998**, *58*, 4349–4357.
65. (a) Mier, W.; Haberkorn, U.; Eisenhut, M. *Eur. J. Nucl. Med. Mol. Imaging* **2002**, *29*, 165–169; (b) Rasey, J. S.; Grierson, J. R,.; Wiens, L. W.; Kolb, P. D.; Schwartz, J. L. *J. Nucl. Med.* **2002**, *43*, 1210–1217.
66. (a) Grierson, J. R.; Shields, A. F. *J. Labelled Compd. Radiopharm*. **1999**, *42*, S525–S526; (b) Grierson, J. R.; Shields, A. F. *Nucl. Med. Biol*. **2000**, *27*, 143–156; (c) Machulla, H. J.; Blocher, A.; Kuntzsch, M.; Piert, M.; Wei, R.; Grierson, J. R. *J. Radioanal. Nucl. Chem.* **2000**, *243*, 843–846; (d) Wodarski, C.; Eisenbarth, J.; Weber, K.; Henze, M.; Haberkorn, U.; Eisenhut, M. *J. Labelled Cpd. Radiopharm*. **2000**, *43*, 1211–1218; (e) Matsuda, A. *Nucleoside Nucleotide* **1990**, *9*, 587–597; (f) Martin, S. J.; Eisenbarth, J. A.; Wagner, U.; Mier, W.; Henze, M.; Pritzkow, H.; Haberkorn, U.; Eisenhut, M. *Nucl. Med. Biol*. **2002**, *29*, 263–273; (g) Yun, M.; Oh, S. J.; Ha, H.-J.; Ryu, J. S.; Moon, D. H. *Nucl. Med. Biol*. **2003**, *30*, 151–157.
67. Blain, J. C.; Ricardo, A.; Szostak, J. W. *J. Am. Chem. Soc*. **2014**, *136*, 2033–2039.

68. (a) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 9422–9423; (b) Prasad, K. R.; Anbarasan, P. *Tetrahedron* **2007**, *63*, 1089–1092; (c) Szallasi, Z.; Du, L.; Levine, R.; Lewin, N. E.; Nguyen, P. N.; Williams, M. D.; Pettit, G. R.; Blumberg, P. M. *Cancer Res*. **1996**, *56*, 2105–2111; (d) Schwarz, M.; Graminski, G. F.; Waters, R. M. *J. Org. Chem*. **1986**, *51*, 260–263.

69. Sakata, H.; Yasukawa, H. Jpn. Kokai Tokkyo Koho JP 2003121964 A, **2003**; pp 42 ff.

70. McGarvey, G. J.; Stepanian, M. W.; Bressette, A. R.; Sabat, M. *Org. Lett*. **2000**, *2*, 3453–3456.

71. (a) Zhang, W. -C.; Li, C. -J. *Tetrahedron* **2000**, *56*, 2403–2411; (b) Hu, Y.; Skalitzky, D. J.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 8679–8682; (c) Kataoka, K.; Ode, Y.; Matsumoto, M.; Nokami, J. *Tetrahedron* **2006**, *62*, 2471–2483; (d) Sabitha, G.; Bhikshapathi, M.; Nayak, S.; Yadav, J. S. *Synth. Commun*. **2010**, *41*, 8–15.

72. (a) Hart, D. J.; Bennett, C. E. *Org. Lett*. **2003**, *5*, 1499–1502; (b) Jervis, P. J.; Kariuki, B. M.; Cox, L. R. *Org. Lett*. **2006**, *8*, 4649–4652; (c) Zhang, W.-C.; Viswanathan, G. S.; Li, C.-J. *Chem. Commun.* **1999**, 291–292; (d) Tadpetch, K.; Rychnovsky, S. D. *Org. Lett*. **2008**, *10*, 4839–4842; (e) Liu, F.; Loh, T.-P. *Org. Lett*. **2007**, *9*, 2063–2066; (f) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem*. **1988**, *53*, 911–913; (g) Dobbs, A. P.; Guesne, S. J. J.; Martinovic, S.; Coles, S. J.; Hursthouse, M. B. *ChemInform*. **2004**, 35; (h) Viswanathan, G. S.; Yang, J.; Li, C. -J. *Org. Lett*. **1999**, *1*, 993–995; (i) Yadav, J. S.; Reddy, B. V. S.; Anusha, B.; Reddy, U. V. S.; Reddy, V. V. B. *Tetrahedron Lett*. **2010**, *51*, 2872–2874; (j) Yang, J.; Viswanathan, G. S.; Li, C.-J. *Tetrahedron Lett*. **1999**, *40*, 1627–1630; (k) Patterson, B.; Marumoto, S.; Rychnovsky, S. D. *Org. Lett*. **2003**, *5*, 3163–3166; (l) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martín, V. S. *Org. Lett*. **2003**, *5*, 1979–1982; (m) Launay, G. G.; Slawin, A. M. Z.; O'Hagan, D. *Beilstein J. Org. Chem.* **2010**, *6*, No. 41, http://dx.doi.org/10.3762/bjoc.6.41.

73. (a) Kumar, H. M. S.; Qazi, N. A.; Shafi, S.; Kumar, V. N.; Krishna, A. D.; Yadav, J. S. *Tetrahedron Lett*. **2005**, *46*, 7205–7207; (b) Yadav, J. S.; Reddy, B. V. S.; Venugopal, C.; Srinivas, R.; Ramalingam, T. *Synth. Commun*. **2002**, *32*, 1803–1808; (c) Roy, U. K.; Jana, P. K.; Roy, S. *Tetrahedron Lett*. **2007**,

48, 1183–1186; (d) Yadav, J. S.; Reddy, B.V.S.; Reddy, M. S.; Niranjan, N.A.; Prasad, R.; *Eur. J. Org. Chem*. **2003**, 1779–1783; (e) Marumoto, S.; Jaber, J.J.; Vitale, J.P.; Ryknovsky, SD.; *Org. Lett*. **2002**, *4*, 3919–3922; (f) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett*. **2002**, *4*, 577–580; (g) Ahmed, N.; Konduru, N. K.; *Beilstein J. Org. Chem*. **2012**, *8*, 177–185. doi:10.3762/bjoc.8.19.

74. (a) Jorgensen, K.A; Eur. *J. Org. Chem.* **2004**, 2093–2102; (b) Larson, E.R.; Danishefsky, S.; *J. Am. Chem. Soc.* **1983**, *104*, 6715–6716; (c) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773; (d) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403–405; (e) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **1999**, *38*, 2398–2400.
75. (a) Qian, H.; Han, X.; Widenhoefer, R.A.; *J Am chem Soc*. **2004**, *126*, 9536–9537; (b) Coulembel, L.; Favier, I.; Dunach, E.; *Chem Comm*. **2005**, 2286–2288; (c) Yang, C.G.; Reich, NW.; Shi, Z.; He, C.; *Org. Lett*. **2005**, *7*, 4553–4556; (d) Lee, E.; Choi, S. J.; Kim, H.; Han, H. O.; Kim, Y. K.; Min, S. J.; Son, S. H.; Lim, S. M.; Jang, W. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 176–178; (e) Song, H. Y.; Joo, J. M.; Kang, J. W.; Kim, D. -S.; Jung, C. -K.; Kwak, H. S.; Park, J. H.; Lee, E.; Hong, C. H.; Jeong, S. W.; Jeon, K.; Park, J. H. *J. Org. Chem*. **2003**, *68*, 8080–8087; (f) McDonald, F. E.; Wei, X. *Org. Lett*. **2002**, *4*, 593–595; (g) Smith III, A. B.; Fox, R. J. *Org. Lett*. **2004**, *6*, 1477–1480.
76. (a) Hanessian, S. Total Synthesis of Natural products: The "Chiron Approach" (Ed.: J. E. Baldwin), Pergamon, Oxford, 1983; (b) Esteveza, J. C.; Fairbanks, A. J.; Fleet, G. W. J. *Tetrahedron*. **1998**, *54*, 13591–13620.
77. (a) Cortez, G. A.; Baxter, C. A.;. Schrock, R. R.; Hoveyda, A. H. *Org. Lett*. **2007**, *9*, 2871–2874; (b) Lee, K.; Kim, H.; Hong, J. *Org. Lett*. **2009**, *11*, 5202–5205; (c) Fuwa, H.; Noguchi, T.; Noto, K.; Sasaki, M. *Org. Biomol. Chem.* **2012**, *10*, 8108–8112.
78. Clarke, P. A.; Santos, S.; Mistry, N.; Burroughs, L.; Humphries, A. C. *Org. Lett.*, **2011**, *13*, 624–627.
79. Ellis, G. P.; Lockhart, I. M. The Chemistry of Heterocyclic Compounds, Chromenes, Chromanones, and Chromones; Wiley: New York, 2007.
80. Luche, J. L.; Damiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 7926–7927.

81. (a) Freitas, J. J. R.; Couto, T. R.; Cavalcanti, I. H.; Freitas, J. C. R.; Oliveira, R. A.; Menezes, P. H. *Ultrason. Sonochem.* **2014**, *21,* 1609–1614; (b) Li, N.; Qiu, R.; Zhang, X.; Chen, Y.; Yin, S-F.; Xu, X. *Tetrahedron* **2015**, *71,* 4275–4281; (c) Freitas, J. J. R.; Couto, T. R.; Cavalcanti, I. H.; Freitas, J. C. R.; Oliveira, R. A.; Menezes, P. H. *Ultrason. Sonochem.* **2014**, *21,* 1609–1614.
82. (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
83. (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.
84. (a) Chatterjee, S.; Ghadigaonkar, S.; Sur, P.; Sharma, A.; Chattopadhyay, S. *J. Org. Chem*. **2014**, *79*, 8067−8076; (b) Ajish Kumar, K. S.; Rathee, J. S.; Subramanian, M.; Chattopadhyay, S. *J. Org. Chem*. **2012**, *78*, 7406−7413; (c) Chatterjee, S.; Sharma, A.; Chattopadhyay, S. *RSC Adv*. **2014**, *4*, 42697-42705.
85. (a) Õmura, S. In: *Macrolide Antibiotics. Chemistry, Biology and Practice*, Õmura, S. Ed.; Academic Press, Orlando 1984, pp. 509–552; (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624; (c) Tadashi, N. In *Macrolide Antibiotics: Chemistry, Biology and Practice*, 2nd ed.; S. Omura, Ed.; Academic Press: San Diego, 2002; pp. 181–284.
86. 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.
87. (a) Grabley, S.; Hammann, P.; Thiericke, R.; Wink, J.; Philipps, S.; Zeeck, A. *J. Antibiot.* **1993**, *46*, 343–345; (b) Lang, G.; Mitova, M. I.; Ellis, G.; Sar, S.; Phipps, R. K.; Blunt, J. W.; Cummings, N. J.; Cole, A. L. J.; Munro, M. H. *J. Nat. Prod.* **2006**, *69*, 621–624; (c) Berg, A.; Notni, J.; Dorfelt, H.; Grafe, U. *J. Antibiot*. **2002**, *55*, 660–662; (d) Grove, J. F.; Speake, R. N.; Ward, G. *J. Chem. Soc.* **1966**, 230–234.
88. Rama Rao, A. V.; Murthy, V. S.; Sharma, G. V. M. *Tetrahedron Lett*. **1995**, *36,* 143–146.
89. Sharma, G. V. M.; Mallesham, S.; Chandra Mouli, C. *Tetrahedron: Asymmetry* **2009**, *20*, 2513–2529.

90. (a) Yadav, J. S.; Swamy, T.; Subba Reddy, B. V. *Synlett* **2008**, 2773–2776; (b) Ramulu, U.; Ramesh, D.; Rajaram, S.; Reddy, S. P.; Venkatesham, K.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2012**, *23*, 117–123.

91. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2003**, *125*, 10808–10809.

92. (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.

93. (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.

94. (a) Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; Van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc.* **2004**, *126*, 187–193; (b) Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622–2628.

95. Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991,** *56,* 2656–2665.

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

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

98. Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett*. **1999**, *1*, 447–450.

99. Grieco, P. A.; Markworth, C. J. *Tetrahedron Lett*. **1999**, *40*, 665–666.

100. (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res*. **2001**, *34*, 18–29; (b) 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; (c) Chatterjee, A. K.; Choi, T.-L.;Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.*, **2003**, *125*, 11360–11370.

101. Sharma, G. V. M.; Reddy, C. G.; Krishna, P. R. *J. Org. Chem*. **2003**, *68*, 4574–4575.
102. Zhu, B.; Panek, J. S. *Org. Lett*. **2000**, *2*, 2575–2578.