STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF DOLABELIDES A-C (C1-C14), SIPHONARIENAL, SIPHONARIENONE, PECTINATONE AND APPLICATIONS OF FERRIER REARRANGEMENT

A THESIS

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BY

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Dedicated
To
My Beloved Parents

DECLARATION

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

(D. NARASIMHA ACHARY)

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GENERAL REMARKS

- Boiling points and melting points are uncorrected. Melting points were recorded on Buchi R-535 apparatus.
- Infrared spectra were recorded on Perkin-Elmer infrared-683 spectrophotometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1601 cm^{-1}.
- Mass measurements were carried out on CEC-21-110B double focusing mass spectrometer operating at 70 eV using direct inlet systems and are given in mass units (*m*/*z*).
- Proton magnetic resonance spectra were recorded on Varian Gemini-200, Avance 300, Varian Unity-400, Inova-500 and Bruker 600MHz. Most of the samples were made in CCl_4/chloroform-d (1:1) using tetramethylsilane (Me_4Si) as the internal standard and are given in the δ scale. The standard abbreviations s, d, t, q, m, dd, dt, br s, refer to singlet, doublet, triplet, quartet, multiplet, double doublet, doublet triplet, broad singlet respectively.
- The optical rotations were measure on JASCO DIP-360 Digital polarimeter.
- All reactions involving air-sensitive compounds were conducted in oven-dried glassware at 90-110 ^{0}C for 6-12 h. Solutions were transferred with syringes or cannulas (double-ended needles) *via* nitrogen pressure.
- Analytical thin-layer chromatography (TLC) was performed on precoated silica gel-60 F_{254} (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapour or UV light or by spraying sulphuric-β-naphthol or phosphomolybdic acid-sulphuric acid or sulphuric acid-anisaldehyde and heating the plates at 120 ^{0}C.
- All the reactions were monitored by employing TLC techniques using appropriate solvent systems for development. Anhydrous DMF, THF, diethyl ether, hexane and toluene were obtained from an Innovative Technologies solvent purification system. *n*-Pentane, petroleum-ether (boiling range 35 ^{0}C to 60 ^{0}C) were distilled over P_2O_5 and stored over pressed sodium wire; dry ether, dry benzene and dry THF were made by distilling them from sodium-benzophenone ketyl. All chlorinated solvents, pyridine, DMF and TEA were distilled over

CaH_2 and stored over 4 A^o molecular sieves. Acetone was distilled over potassium permanganate and potassium carbonate.

- All solvent extracts were concentrated at reduced pressure on Buchi-RE-121 rotary evaporator below 50 ^{0}C. Yields reported are isolated yields of material judged homogenous by TLC and PMR spectroscopy.
- All solvents used for silica gel column chromatography were distilled prior to use. Silica gel used was either 60-120 or 100-200 mesh.

ABBREVIATIONS

Ac	:	acetyl
Ac_2O	:	acetic anhydride
Ar	:	aryl
BOC	:	*tert*- butyloxy carbonyl
Bn	:	benzyl
Bz	:	benzoyl
$BF_3.Et_2O$	:	boron trifluoride diethyl ether
n-BuLi	:	*n*-Butyllithium
t-BuOH	:	*tert*- butanol
t-BuOK	:	potassium *tert*-butoxide
CSA	:	camphor sulphonic acid
CAN	:	ceric ammonium nitrate
DCC	:	dicyclohexylcarbodimide
DCM	:	dichloromethane
DDQ	:	2,3 dichloro-5,6-dicyano-1,4- benzoquinone
DEAD	:	diethyl azodicarboxylate
DET	:	diethyl tartrate
DHP	:	dihydropyran
DIBAL	:	Diisobutylaluminium hydride
DIPEA	:	*N*,*N*-Diisopropylethylamine
DMAP	:	4-dimethylaminopyridine
DME	:	dimethoxy ethane
DMS	:	dimethyl sulphide
DMSO	:	dimethylsulfoxide
DMF	:	*N*,*N*-dimethylformamide
ESI	:	Electro Spray Ionization
Et	:	ethyl
EtOH	:	ethanol
FAB	:	Fast Atom Bombardment
Hz	:	Hertz
$InBr_3$	:	indium tribromide
$InCl_3$	:	indium trichloride

IR	:	infra red
KSF	:	montmorillonite clay
LAH	:	lithium aluminium hydride
Me	:	methyl
MeOH	:	methanol
MOM	:	methoxy methyl
MW	:	microwave
NMR	:	nuclear magnetic resonance
NaH	:	sodium hydride
NaHMDS	:	*N*-sodiumhexamethyldisilazane
NaH_2PO_4	:	sodium hydrogen phosphate
$NaCNBH_3$	:	sodiumcyanoborohydride
NBS	:	*N*-bromosuccinimide
*p*TSA	:	*p*-toluenesulphonic acid
PCC	:	pyridinium chlorochromate
Ph	:	phenyl
PMB-Br	:	*para*-methoxy benzyl bromide
^{1}H NMR	:	proton magnetic resonance
PPTS	:	pyridinium *para*-toluene sulphonate
PTSA	:	*para*-toluenesulfonic acid
Py	:	pyridine
r.t.	:	room temperature
Red-Al	:	sodium *bis*(methoxyethoxy)aluminiumhydride
$Sc(OTf)_3$	:	scandium trifluoromethanesulfonate
TBAF	:	tetra-*n*-butylammonium fluoride
TEA	:	triethyl amine
TFA	:	trifluoroacetic acid
THF	:	tetrahydrofuran
THP	:	tetrahydropyran
Ts	:	*p*-toluene sulphonyl
TPP	:	triphenyl phosphine
TBDMS or TBS	:	*tert*-butyl dimethylsilyl
TBDPS	:	*tert*-butyl diphenylsilyl

CONTENTS

CHAPTER I: SECTION A

Introduction and previous approaches to Dolabelides.

Introduction to Prins cyclization

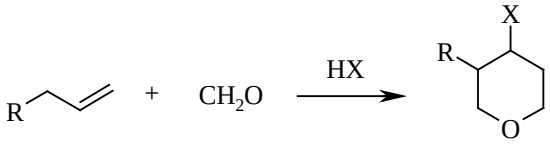
The acid catalyzed condensation of olefins with aldehydes is known as the Prins reaction.[1] This reaction affords a mixture of compounds; the major products of classical Prins reaction are normally 1,3-glycols, unsaturated alcohols and the products obtained from acid-catalyzed polymerization of the olefins (Scheme 1).

Scheme 1

The analogous reaction, the so-called carbonyl-ene reaction,[2] exclusively affords homoallyl alcohols from carbonyl compounds and either mono- or di-substituted olefins in the presence of Lewis acids (Scheme 2).

Scheme 2

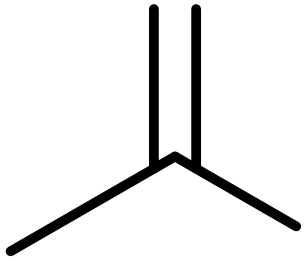
In the late 1960s, Stapp[3] briefly examined the direct synthesis of tetrahydropyran derivatives *via* the Prins cyclization (Scheme 3).



Scheme 3

The Prins cyclization reaction has been very useful for the construction of oxygen-containing heterocyclic units that appear in many natural products.[4] This reaction typically involves the reaction between an aldehyde (**1**) and a homoallylic alcohol (**2**) promoted by an acid as shown in Scheme 4. This reaction is believed to proceed *via* an oxocarbenium ion intermediate (**4a**) that largely adopts *E*-geometry as the most stable geometrical isomer.[5] Mechanistically, it can be affected by the competing cationic oxa-Cope rearrangement. This 3,3-sigmatropic rearrangement has been shown to be of great relevance in the distribution of products. The equilibrium is affected by substituents on

the double bonds and at the allylic position. The stability of the two isomers **4a** and **4b** relate to product ratios. The Prins cyclization reaction itself proceeds largely through a chair-like transition state that allows for control of stereoisomers in the course of the reaction. This organization of the reaction, in principle, should allow one to set four relative stereogenic centers in one step. In addition, capture of the positive cationic intermediate **5** can introduce a fifth stereogenic center. It is notable that this reaction can also provide tetrahydrofurans. The product ring size usually depends on olefin substituents in intermediates **4a** and **4b**, that is, which carbon can best stabilize the resulting positive charge. [5-6]



Scheme 4

The relevance of this reaction as a carbon-carbon bond forming reaction has led to the study and application of many variations. Some of these variations are:

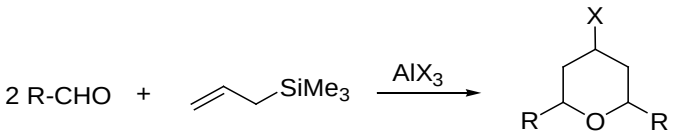
a) the use of Lewis acids to promote the reaction (such as $BF_3 \cdot Et_2O$, $SnCl_4$, $TiCl_4$, $TiBr_4$, $FeCl_3$, $InCl_3$).[6-7]

b) the use of acetals, mixed acetals and α-acetoxy ethers to generate the oxonium ion.[6-8]

c) the use of alkynes, allylsilanes, alkenes, and enolsilanes as the π-component.[6-8]

d) termination of the cyclization with a variety of nucleophiles (Cl, Br, F, allylsilanes)[6-8]

The utility of this method lies in its ability to simultaneously form carbon-carbon bonds and introduce heterofunctionality in a predictable and stereocontrolled manner. A variety of heteroatom-stablized carbocations have been cyclized including oxenium, thienium, dithienium, and iminium carbocations. The cyclization proceeds through the addition of dioxenium cations onto unactivated olefins resulting in the formation of 4-hetero-substituted pyranosides. Recently, the potential of Prins-cyclization in the formation of tetrahydropyran derivatives has been recognized. In the literature,[9] Chan as well as Coppi reported that the coupling between allylsilanes and aldehydes could be used to prepare 2,6-disubstituted-4-halotetrahydropyrans (Scheme 5).



Scheme 5

Coppi and co-workers[10] found that an analogous condensation could be achieved by directly mixing aldehydes and unsaturated alcohols at 0 °C in the presence of Lewis acid (Scheme 6).

Scheme 6

A variety of Lewis acids have been used to mediate such a cyclization. In most cases, the cyclization products are 2,6-disubstituted dihydropyran or 2,4,6-trisubstituted tetrahydropyran derivatives.

The Prins-cyclization of homoallyl mercaptans with aldehydes in the presence of indium trichloride afforded 2,4,6–trisubstituted thiacyclohexanes[11] as an 8:1 mixture of diastereomers (Scheme 7).

Scheme 7

Interestingly, the reactions of both *cis*- and *trans*-mercaptans with aldehydes generated the cyclized product with the major *cis*-*trans*-*cis*-configuaration but different selectivity.[11]

Scheme 8

The reaction of *cis*-mercaptan gave a mixture of *cis*-*cis*-*cis* and *cis*-*trans*-*cis*-thiacyclohexane derivatives with the latter as the predominant product whereas *trans*-mercaptan generated exclusively a *cis*-*trans*-*cis* thiacyclohexane derivative (Scheme 8).

Furthermore, the aldol-Prins reactions of enol allylsilanes in the presence of camphorsulphonic acid afforded the tetrahydropyran derivative with *cis*-diastereo-selectivity.[12] The aldol-Prins reactions of enol allylsilanes with aldehydes led to the formation of *cis*-2,6-disubstituted tetrahydropyran derivatives (Scheme 9).

Scheme 9

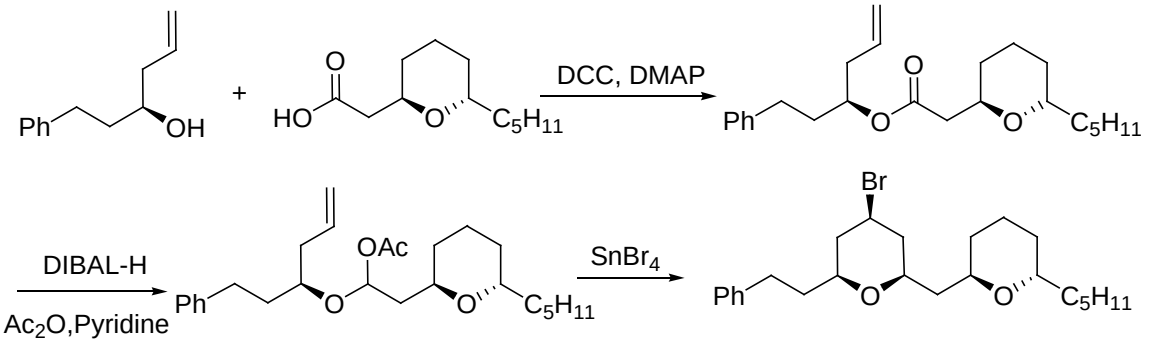
Leucascandrolide A was isolated from the sponge *Leucascandra cavealata* in 1996 and shows potent cytotoxicity against P388 cancer cells.[12] This aldol-Prins cyclization method has been adopted for the synthesis of Leucascandrolide A as described in Scheme 9.

Scheme 10

Recently, the segment-coupling Prins-cyclization has been reported[13] involving esterification, reductive acetylation and Lewis acid promoted cyclization (Scheme 11).

Scheme 11

Phorboxazoles A and B are potent anticancer agents isolated from the marine sponge *Phorbas sp*. Both compounds inhibit the growth of tumor cells *in vitro* and show selectivity against solid tumor cells.[14] The segment-coupling Prins-cyclization reaction has been applied to a short synthesis of the C22-C26 tetrahydropyran segment of the natural product, Phorboxazole as described in Scheme 12.

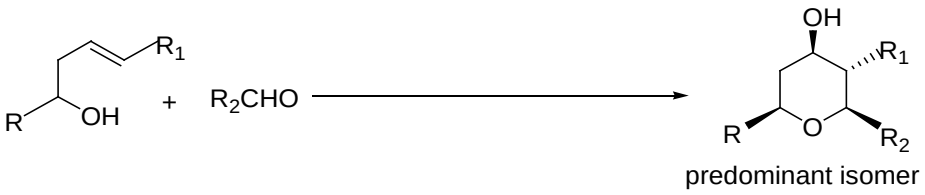


Scheme 12

Similarly the Prins cyclization was used successfully in the synthesis of Okadaic acid, a complex natural product first isolated by Tachibana *et al*., from the marine sponges *Halichondria okadai* and *Halichondria melanodocia*,[15] and Roflamycin, an antifungal agent, isolated from *Streptomyces roseoflavus*.[16]

On the other hand, the formation of oxygenated, instead of halogenated, tetrahydropyran derivatives would often be more desirable synthetically. Furthermore,

pyranosides hydroxylated at the 4-position are key sub structures in a number of naturally occurring substances such as the avermectins, aplysiatoxin-oscillatoxins, latrunculins, talaromycins and acutiphycin, among others.[17] Hence there have been few catalytic systems developed for the construction of pyrans with hydroxyl group at the 4th position (Scheme 13).[18]



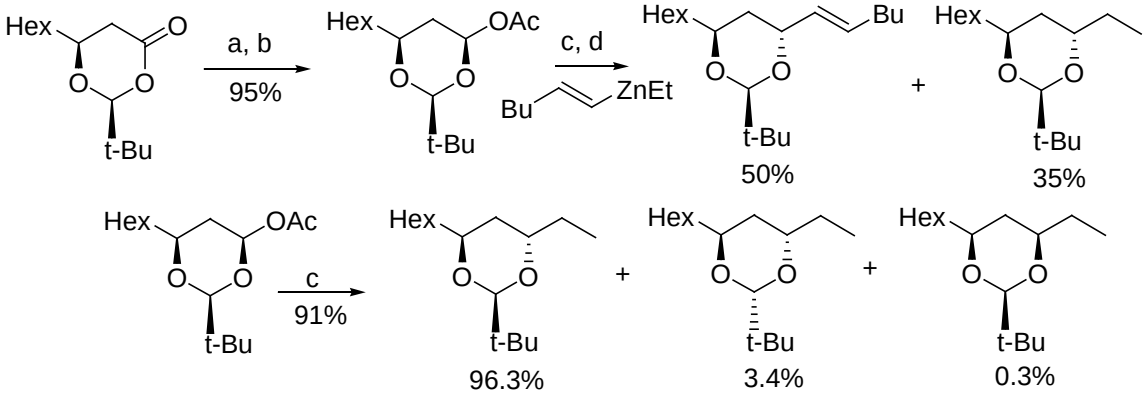
Scheme 13

Reagents and conditions: TFA, CH_2Cl_2 then K_2CO_3, MeOH (OR) $BF_3.OEt_2$, AcOH, CH_2Cl_2 then K_2CO_3, MeOH (OR) $Sc(OTf)_3$, $CHCl_3$ or (OR) H-ZSM-5/ion exchange resin ionic liquid or (OR) Amberlist, CH_2Cl_2.

Despite the potential of the reaction to build up structural complexity rapidly, the Prins cyclization remains underutilized as a synthetic tool. Thus the potentiality of the Prins cyclization in the construction of various carbocycles and heterocycles prompted us to study extensively for the synthesis of various acyclic and cyclic polyketide intermediates.

<u>Contemporary approaches to the synthesis of 1,3-diol units.</u>

Rychnovsky's approach:



Scheme 14

Reagents and conditions: (a) DIBAL-H, CH_2Cl_2; (b) Ac_2O, DMAP, Py; (c) $BF_3.OEt_2$, CH_2Cl_2; (d) Et_2Zn TMSOTf.

Rychnovsky *et al.*[19] described an *anti*-selective coupling reaction between 4-acetoxy-1,3-dioxanes and dialkylzinc reagents (Scheme 14) in presence of TMSOTf.

Colobert's approach[20]

Scheme 15

Reagents and conditions: (a) LDA, THF; (b) SmI_2 (2 equiv); (c) DIBAL-H (2 eqiv.), THF; (d) DIBAL-H (4 equiv.), $Yb(OTf)_3$ (2.4 equiv), THF.

Chiral nonracemic α-bromo-α′-sulfinyl ketones (**10**) were shown to react with aldehydes in the presence of SmI_2 in a Reformatsky-type reaction to give the corresponding adduct **11** with high *syn* diastereoselectivity. Reduction of the Reformatsky adducts furnished *anti*- and *syn*-2-methyl-1,3-diol moieties **12** and **13** in good yields and diastereoselectivities (Scheme 15).

Cossy's approach:

Cossy *et al.*[21] achieved the preparation of unprotected *syn*- and *anti*-1,3-diols through enantioselective allyltitanation. Chiral allylation of aldehydes of type 31 using either (*R*,*R*)-I 14 or (*S*,*S*)-I 15 yielded homoallyl alcohols 17 or 21 which, without protection, on periodate mediated cleavage resulted in required starting materials, β-hydroxy aldehydes 18 or 22. The sensitive β-hydroxy aldehydes were subjected again to chiral allyltitanation using either (*R*,*R*)-I 14 or (*S*,*S*)-I 15 to furnish *syn*- or *anti*-1,3-diols (Scheme 16).

Scheme 16

Reagents and conditions: (a) Ether, -78 ^{o}C; (b) OsO_4, $NaIO_4$, ether, H_2O.

Chakraborty's approach:

Scheme 17

Reagents and conditions: **(**a) cp_2TiCl_2, Zn, $ZnCl_2$, THF; (b) *m*-CPBA, CH_2Cl_2.

Chakraborty *et al*.[22] described a radical-mediated opening of chiral 2,3-epoxy alcohols regioselectively at the 2-position, using cp_2TiCl_2 (Scheme 17). The reaction precursors **26**, obtained from Sharpless asymmetric resolution, were used for the

construction of *anti*-1,3-diols **28**, whereas precursors **29** obtained from *m*CPBA mediated epoxidation of allylic alcohols **27** were used for the construction of *syn*-1,3-diols **31**

Kiyooka's approach:

Kiyooka *et al*.[23] described a chiral oxazaborolidinone (**33** or **34**) catalyzed aldol reaction of a silyl ketene (**35**) acetal involving a dithiolane moiety with aldehydes to yield β-hydroxy esters **36** or **37** which on protection, controlled reduction and again chiral oxazaborolidinone-catalysed aldol reaction produced *syn*- and *anti*-1,3-diols (**39** or **40**) with complete stereoselectivity by the choice of the stereochemistry of the catalyst (Scheme 18).

Scheme 18

Introduction to Dolabelides:

A new 22-membered macrolide, Dolabelide A (**41**)[24] and its deacetyl derivative Dolabelide B (**42**) have been isolated as cytotoxins from the Japanese specimens sea hare *Dolabella auricularia* (Figure 4). The gross structure of **41** and **42** was determined by spectroscopic analysis, and their absolute stereochemistry was elucidated by a combination of chemical means and the NMR spectroscopic methods. Two years later,

two new members of this class of natural products, Dolabelides C (**43**) and D (**44**) were reported.[25]

Extraction:

The sea hare *Dolabella auriculuria (40 kg.* wet wt) collected in Mie Prefecture, Japan, was subjected to the operations for extraction and partition. The material obtained from 90% aqueous MeOH portion (40 g) was subjected to chromatography by four times using silica gel and ODS silica gel to afford crude samples of Dolabelide A (**41**) and Dolabelide B (**42**). Final purification by reversed-phase HPLC (Develosil ODS 10.75% aqueous MeCN for **41** and 70% aqueous MeCN for **42**) yielded **41** (35.2 mg) and **42** (9.6 mg) as colorless oils. Dolabelides A and B showed cytotoxicities against HeLa-S_3 cells with IC_{50} of 6.3 and 1.3 μg/mL respectively.

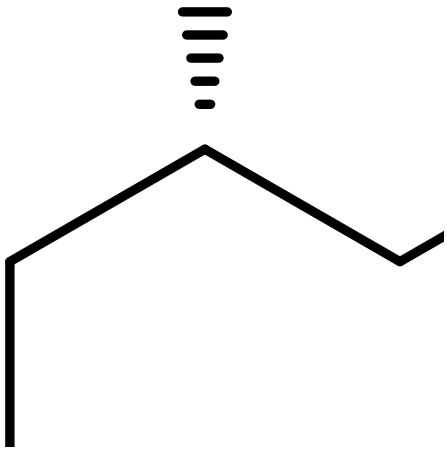


Table 1. NMR Data for Dolabelide A (41) in C_5D_5N

Position	^1H	^{13}C	HMBC	Position	^1H	^{13}C	HMBC
1.	-	174.5 s	H-2, 21, 2-Me	20	2.16 m	36.4 t	H-21
2.	2.94 dq (9.2, 7.0)	46.9 d	2-Me	21	6.31 dt (4.8, 7.0)	72.7 d	H-20, 22, 22-Me
2-Me	1.25 d (7.0)	14.1 q	H-2	22	2.70 ddq (9.2, 4.8, 7.0)	42.6 d	H-21, 22-Me
3.	4.09 m	75.3 d	H-2, 2-Me, 4-Me	22-Me	1.10 d (7.0)	10.5 q	H-21
4.	1.82 m	34.2 d	4-Me	23	4.53 dd (9.2, 8.4)	69.5 d	H-22, 22-Me
4-Me	0.95 d (5.1)	13.2 q		24.	5.57 d (8.4)	132.3 d	H-26, 25-Me
5.	1.56, 1.82 m	29.8 t	4-Me	25	-	133.3 s	H-23, 26, 27, 25-Me
6.	1.81, 1.90 m	32.7 t		25-Me	1.80 s	17.1 q	H-24, 26
7.	5.42 m	69.9 d		26	2.25 dd (13.4, 5.7)	45.2 t	
8.	1.92, 2.16 m	38.4 t			2.34 dd (13.4, 7.5)		
9.	5.21 m	68.2 d		27	5.26 m	72.0 d	H-26, 28
10.	1.92, 2.02 m	39.2 t		28	1.53 m	36.3 t	H-26, 27, 30
11.	1.61, 1.86 m	31.6 t		29	1.29, 1.35 m	18.9 t	H-27, 28, 30
12.	2.07 m	35.4 t		30	0.84 t (7.7)	14.0 q	H-28
13.	2.07 m	35.1 t	H-15, 14-Me	OAc	1.98 s	20.9 q, 170.7 s	Ac (δ 1.98)
14.	-	132.9 s	14-Me	OAc	2.04 s	21.0 q, 170.5 s	Ac (δ 2.04)
14-Me	1.61 s	15.3 q		OAc	2.05 s	21.1 q, 170.6 s	Ac (δ 2.05), H-27
15	5.33 t (7.0)	127.1 d	14-Me	OAc	2.12 s	21.2 q, 170.2 s	Ac (δ 2.12)
16	2.04 m	29.0 t	H-15	3-OH	6.06 br d (6.6)		
17	1.54, 1.82 m	27.5 t		19-OH	5.87 br s		
18	1.67 m	39.7 t		23-OH	6.30 br s		
19	4.17 m	68.1 d	H-18				

Figure 4

Dolabelide A (**41**): $[\alpha]_D$ -13.5 (*c* 1.45, $CHCl_3$), has a molecular formula of $C_{43}H_{72}O_{13,}$ which was determined by HRFABMS [*m/z* 819.4878 $(M + Na)^+$] and NMR spectroscopy.

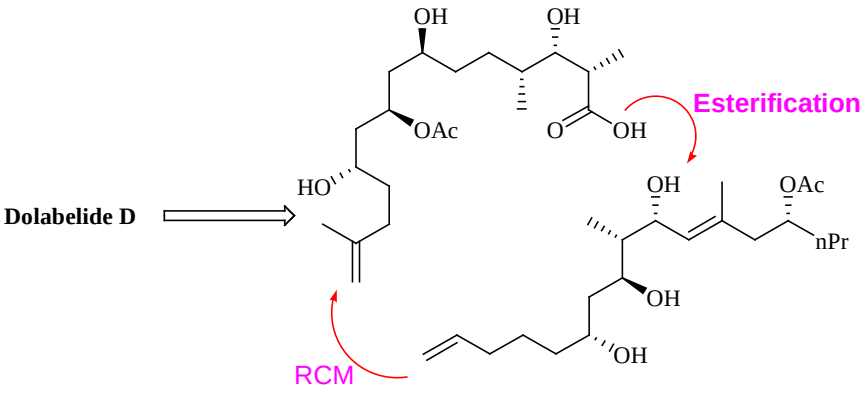
The presence of hydroxyl and ester groups in **41** was shown by IR bands at 3600-3150 (br), 1730 and 1260 cm^{-1}. The ^{13}C NMR spectrum includes five carbonyl signals (δ 174.5, 170.7, 170.6, 170.5 and 170.2). Four of which are assigned to acetate groups considering the ^1H NMR signals at δ 1.98, 2.04, 2.05 and 2.12 (3H s each). The presence of three hydroxyl groups was shown by observation of the signals due to D_2O exchangeable protons at δ 6.29, 6.06 and 5.87 and confirmed by acetylation of **41** to give triacetyl Dolabelide A. Detailed analyses of phase-sensitive DQF-COSY and ^{13}C - ^1H COSY spectra of **41** allowed constructing three partial structures.

Dolabelide B (**42**): $[\alpha]_D$ +4.0 (*c* 0.43, $CHCl_3$) was considered to be a monodeacetyl derivative of Dolabelide A (**41**) from the molecular formula of $C_{41}H_{70}D_{12}$ which was determined by HRFABMS: *m/z* 777.4756 $[M+Na]^+$ and comparison of NMR spectra between **41** and **42**. The high-field chemical shift at H 11 (δ 4.04) of **42** revealed that **42** was the 11-Odeacetyl derivative of **41**. Since acetylation of **42** gave the acetate that was identical with triacetyl Dolabelide A (**41**) in all respects, the absolute stereochemistry of **42** was found to be identical with that of **41**.

Previous approaches:

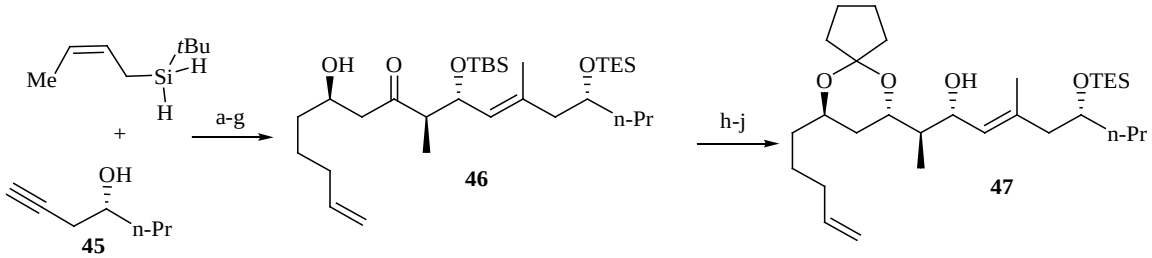
Leighton approach for the Total Synthesis of Dolabelide D:

Leighton *et al.*[26] reported the first total synthesis with an application of recently developed catalytic asymmetric silane alcoholysis and tandem silylformylation-crotylsilylation methods.



Scheme 19

Key steps of this synthesis include the catalytic asymmetric silane alcoholysis with alcohol **45** and *tert.* butyl-*cis*-crotylsilane, Rhodium-catalyzed tandem silylformylation-crotylsilylation and ring closing metathesis (RCM).



Scheme 20

(a) 4 mol % CuCl, 4 mol % *t*-BuONa, 4 mol % (*R*,*R*)-BDPP, PhH; (b) i. 2 mol % $[Rh(acetone)_2$- $(P(OPh)_3)_2]BF_4$, CO, PhH, 60 °C; ii. MeLi, Et_2O, -78 to 23 °C; (c) TESCl, Et_3N, CH_2Cl_2, -20 °C; (d) *n*-BuLi, THF, -78 °C; CuBr.Me_2S, DMPU, 23 °C; MeI, -78-23 °C; (e) 25 mol % $PdCl_2$, CuCl, DMF, THF, H_2O, O_2; (f) Ac_2O, pyridine, DMAP, CH_2Cl_2; (g) $(+)$-$(ipc)_2BCl$, Et_3N, 5-hexenal, Et_2O, -78-23 °C; (h) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, THF, -40 to -20 °C; (i) 1,1-Dimethoxycyclopentane, PPTS, CH_2Cl_2; (j) *n*-Bu_4NF, THF.

Scheme 21

Reagents and conditions: (a) **52**, CH_2Cl_2, -20 °C; (b) NaH, PMBBr, THF, reflux; (c) 25 mol % $PdCl_2$, CuCl, DMF, H_2O, O_2; (d) 9-BBN, THF, -78 to 23 °C; H_2O_2, NaOH; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, t-BuOH, H_2O; (g) K_2CO_3, CH_2=$CHCH_2Br$, acetone, reflux; (h) PPTS, acetone, H_2O, reflux; (i) *n*-Bu_2BOTf, i-Pr_2NEt, Et_2O, -110 °C; (j) TESCl, imidazole, CH_2Cl_2; (k) *L*-

Selectride, CH_2Cl_2, -78 °C; (l) Ac_2O, pyridine, DMAP, CH_2Cl_2; (m) 10 mol % $Pd(PPh_3)_4$, morpholine, THF.

Scheme 22

(a) Et_3N, DMAP, toluene, -78 ^oC-rt; (b) PPTS, MeOH; (c) DDQ, CH_2Cl_2, pH 7 Buffer; (d) 25 mol% Gr-II, CH_2Cl_2, reflux.

Paul R. Hanson's Phosphate-Mediated Approach for the Total synthesis of Dolabelide C:

Hanson and his co-workers have reported[50] the first total synthesis by utilizing a phosphate tether-mediated approach.

Scheme 23

Dolabelide C can be disconnected into C1-C14 and C15-C30 subunits, **55** and **56**, respectively (Scheme). The final coupling for this approach is similar to Leighton's strategy toward Dolabelide D, employing a macrocyclization sequence to install the C14/C15 trisubstituted olefin through a late-stage ring-closing metathesis (RCM) reaction. Macrocyclization, *via* RCM, is preceded by Yamaguchi coupling between the C1 carboxylic acid of the northern subunit **55** and the C23 carbinol center in the southern

subunit **56**. Central to this approach are the 1,3 anti-diol motifs at C7/C9 and C19/C21, which can be assembled and elaborated from bicyclic phosphates **58** and **60**, respectively, utilizing a phosphate tether mediated approach.

Synthesis of C1-C14 Carbon Framework:

Scheme 24

Reagents and conditions: (a) Hoveyda Grubbs catalyst (6 mol %), DCE, 90 ^{o}C, 72%; (b) o-$NO_2C_6H_5SO_2NHNH_2$, Et_3N, CH_2Cl_2, 72%; (c) $Pd(OAc)_2$ (5 mol %), HCO_2H, Et_3N, DCE, 40 ^{o}C, then MeOH, $TMSCHN_2$, 87%. (d) $LiAlH_4$, Et_2O, 75%; (e) PPTS, 2,2-DMP, CH_2Cl_2, 96%; (f) O_3, pyridine, 1:1 MeOH/CH_2Cl_2, -78 ^{o}C, then Me_2S, 72%; (g) 1-iodo-3-methylbutene, Mg, Et_2O, -78 ^{o}C, 95%; (h) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 90%; (i) $CeCl_3.7H_2O$, H_2O/MeCN (1:7), 87%; (j) Et_2BOMe, $NaBH_4$, THF/MeOH 4:1,-78 ^{o}C , ds $\geq$ 20:1, 60% (95% brsm).(k) Ac_2O, DMAP, pyridine, 95%; (l) TBAF, THF, 93%; (m) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (n) $NaClO_2$, 2-methyl- 2-butene, H_3PO_4, 81% over two steps.

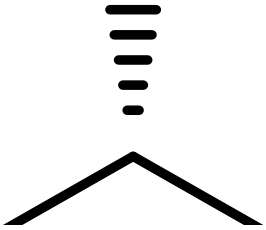
Second-Generation Synthesis of C15-C30 Subunit:

Scheme 25

Reagents and conditions: (a) Hoveyda Grubbs catalyst (6 mol %), **63**, DCE, 90 ^{o}C, 82%; (b) o-$NO_2C_6H_5SO_2NHNH_2$, Et_3N, CH_2Cl_2, 75%; (c) (1) CuCN . 2 LiCl, Me_2Zn, THF, -30 ^{o}C to rt; (2) $TMSCHN_2$, MeOH, 91%; (d) $LiAlH_4$, Et_2O, 0 ^{o}C, 92%; (e) 2,2-DMP,

PPTS, CH_2Cl_2, 96%; (f) OsO_4, NMO, t-BuOH/THF/H_2O, then $NaIO_4$, phosphate buffer pH 7, then $NaBH_4$, EtOH, 0 ^oC, 81%; (g) TBSCl, pyridine, 95%; (h) H_2, Pd/C, EtOAc, $NaHCO_3$, 90%; (i) Ph_3P, I_2, imidazole, then t-BuOK, THF, 94%; (j) TBAF, THF, 98%; (k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to rt; (l) *t*-BuLi, Et_2O, 39, -78 to 0 ^oC, 30 min, 28, -78 ^oC,~1:1 syn:anti, 79% over two steps; (m) Dess-Martin Periodinane, CH_2Cl_2, 85%; (n) $NaBH_4$, MeOH, 0 ^oC, 89%, ~2.7:1 syn:anti.

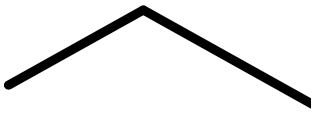
Coupling of both the fragments:



Scheme 26

Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, toluene, 77%; (b) TBAF, 94%; (c) Ac_2O, pyridine, DMAP, 98%; (d) PPTS, 83%; (e) DDQ, phosphate buffer pH =7, CH_2Cl_2, 95%; (f) Grubbs 2nd generation (20 mol %), CH_2Cl_2 (0.5 mM), 57%, E:Z = ~1:1.

Genet *at el.*[28] reported the synthesis of C1-C13 fragment of Dolabelides using ruthenium SYNPHOS catalyzed asymmetric hydrogenation (Scheme 27). The C3, C7, C9 and C11 hydroxyl-bearing stereo centers were installed using ruthenium mediated asymmetric hydrogenation reaction of the adequate β-keto ester and β-hydroxy ketone.



Scheme 27

Reagents and conditions: (a). $PMBOC(NH)CCl_3$, CSA,CH_2Cl_2 (b). LDA, *t*-BuOAc, THF, -40 ^oC (c). [Ru(*S*)-SYNPHOS]Br_2, H_2 (d). LDA, THF, -40 ^oC (e). HMPA, MeI, THF, -40 ^oC (f). TIPSOTf, 2,6-lutidine, CH_2Cl_2 (g). DMP,CH_2Cl_2, 0 ^oC (h). [Ru(*S*)-SYNPHOS]Br_2, H_2 (i). $(CH_3O)_2$, CH_2, P_2O_5, $CHCl_3$ (j). LDA, t-BuOAc, THF, -40 ^oC (k). [Ru(*S*)-SYNPHOS]Br_2, H_2 (l). TBSOTf, 2,6-lutidine, CH_2Cl_2 (m). DIBAl-H, toleune, -78 ^oC (n). *n*-BuLi, $MeP(O)(OEt)_2$, THF, -78 ^oC (o). DMP, CH_2Cl_2, 0 ^oC.

Scheme 28

Reagents and conditions: (a). LiCl, DIPEA, MeCN, rt (b). 1%HCl, EtOH, rt (c). [Ru(*S*)-SYNPHOS]Br_2, H_2 (d). 2,2-DMP, PPTS, acetone, rt.

Keck *et al.*[29] reported C1-C13 segment of Dolabelide β (Scheme 29). A key element of the synthesis entails BITIP catalysed asymmetric methallylation to establish the C7 and C11 centers through Evans reduction and 1,5-anti aldol condensation.

Scheme 29

Reagents and conditions: (a). (*Z*)-crotyltributyltin, $TiCl_4$ (b). TBSOTf, Et_3N, CH_2Cl_2 (c). O_3, CH_2Cl_2, PPh_3 (d). $(C_6H_5)_3P{=}CHCO_2C_2H_5$ (e). SmI_2, MeOH, DMA (f).DIBAL-H, THF, -78 ^oC (g). $(COCl)_2$, DMSO, Et_3N, -78 ^oC.

Scheme 30

Reagents and conditions: (a). **78**, (*R*)-BINOL, $Ti(^iOPr)_4$, 4 A^o-MS, CH_2Cl_2, -20 ^oC (b). PMBBr, NaH, THF (c). OsO_4, NMO, *t*-BuOH/THF/H_2O (d). $NaIO_4$, CH_2Cl_2 (e). acrolein, $(C_6H_{11})_2BCl$, Et_3N (f). TBSOTf, 2,6-lutidine, THF (g). DDQ, 10:1 CH_2Cl_2/p^H 7 buffer (h). $Me_4NBH(OAc)_3$, 1:1 actonitrile/AcOH (i). Ac_2O, DMAP, pyridine, r.t.

Prunet *et al* [30] reported Enantioselective Synthesis of the C1–C15 Fragment of Dolabelide C; the key step is a diastereoselective Mukaiyama aldol reaction to form the C6–C7 bond, followed by reduction and deoxygenation of the carbonyl group at C5. The trisubstituted vinyl iodide is introduced *via* the corresponding vinyl boronate by cross metathesis.

Scheme 31

Reagents and conditions: (a). VinylMg Br, CuI, 96% (b). Grubbs 2nd generation, Methyl acrylate, 94% (c). PhCHO, t-BuOK, 74% (d) DIBAL-H, –95 °C, CH_2Cl_2, 94 %.(e) TMS Cl, Et_3N, LiHMDS, quant.

The Mukaiyama aldol reaction between silyl enol ether **90** and aldehyde **88** is controlled by the aldehyde, furnishing the 1,3-*anti* product **91** as the major diastereomer (82:18 ratio) in 93% yield

Scheme 32

Reagents and conditions: (a). $BF_3{\cdot}OEt_2$, 93% (b). TBSOTf, Et_3N, 98% (c) $NaBH_4$, MeOH, 99%, (d). NaH, CS_2, MeI, 91% (e) AIBN, Bu_3SnH,92% (f) H_2, Raney Ni, EtOH, 86% (g) IBX, 93% (h) MeMgBr,THF (i) IBX (j) $CH_3Ph_3P^+Br^-$, BuLi, 52% in 3 steps (k) Grubbs 2nd generation, I_2, NaOH, 55%.

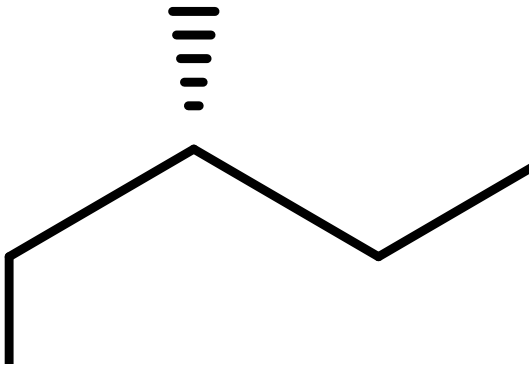
CHAPTER I: SECTION B

Towards the total synthesis (C1-C14 Subunit) of Dolabelides A-C via Prins cyclization and cross metathesis strategy.

PRESENT WORK

We predicted that the total synthesis of this molecule would not only provide an access to larger quantities for further biological studies, but also help to design and build more potent synthetic analogs. The wealth of biological functions and chemical structure prompted us to initiate a program aimed at the total synthesis of Dolabelide A. The Dolabelide A is a 22-membered macrolide consisting of 11 stereogenic centers, eight of which bear oxygen, and two *E*-configured trisubstituted olefins. Other structural features possessed by this family of macrolactones include 1,3-anti-diol fragments found at C7/C9 and C19/C21, along with an accompanying 1,3-syn-diol at C9/C11 and polypropionate fragments at C1/C4 and C21/ C23. The stereochemical complexity and biological profile of this class of compounds as well as their limited availability from natural sources make them attractive targets for synthetic challenge of the dolabelides.

In our retrosynthetic analysis (Scheme 33), we envisioned that Dolabelide A could be divided into two fragments, arising from bond disconnection at the macrolactone and about the C14–C15 olefin. We have planned the coupling of fragments **95** and **96** by esterification and ring-closing metathesis.



Scheme 33

Retro synthetic analysis of C1-C14 segment of Dolabelides A-C:

The synthesis of target fragment **97** is planned by regioselective cross metathesis (CM) between fragments **98** and **99** (scheme 34).

Scheme 34

RESULTS AND DISCUSSION

The synthesis commenced from *S*-(-)-benzyl glycidyl ether **101** (Scheme 6). Jacobson resolution[31] of (-/+)-benzyl glycidyl using (*R*,*R*)-(salen)Co(II) precatalyst, AcOH and H_2O (0.51 equiv) for 22 hours resulted in (*S*)-benzyl glysidyl ether. Regioselective opening of epoxide **101** with vinylmagnesium bromide (generated by addition of vinyl bromide to Mg in THF) in the presence of CuCN gave homoallylic alcohol **103**. ^{1}H NMR spectrum of the compound **103** exhibited two multiplets due to olefinic protons at δ 5.91-5.61 and δ 5.20-4.93 ppm integrating for one and two protons respectively. Oxygen attached C-H signals integrated for five protons confirming that the regioselectivity was in anticipated line. In addition, IR spectrum showed hydroxyl absorption at 3360 cm^{-1} and ESI-MS showed $[M+H]^+$ signal at *m/z* 193, further confirming the structure. Substrate **103** on treatment with lithium in liquid NH_3 underwent (Birch Reduction)[32] debenzylation to produce diol **104**. (Scheme 35)

Scheme 35

In ^{1}H NMR spectrum of **104**, disappearance of peaks due to benzyl group and appearance of broad singlet due to hydroxyl protons at δ 3.16 integrating two protons confirmed the conversion.

Aldehyde required for the Prins cyclization was prepared from 1,3-propanediol as shown in Scheme 36. Monoprotection of commercially available 1,3-propanediol with benzyl bromide and sodium hydride gave 3-benzyloxy propanol **105a** in 70% yield. Appearance of signals at δ 7.29 as multiplet integrating for 5 protons corresponding to Ph*H* and a singlet integrating for 2 protons at δ 4.5 corresponding to OCH_2Ph group in the ^{1}H NMR spectrum of compound **105a** confirmed the monoprotection. In addition to this, a signal at *m/z* 167 in the ESI–MS spectrum of compound **105a** that corresponds to the $[M+H]^+$ was additional support for the formation of the product. The alcohol **105a** was oxidized with PCC in 4 h to furnish 3-benzyloxy propanal **105** in quantitative yield which was taken forward to next reaction, after a flash column chromatography, without any further characterization.

Scheme 36

Then the stage was set for crucial Prins cyclisation (Scheme 37). Subjection of homo allyl alcohol (**104)** and three equivalents of aldehyde (**105**) to Prins cyclisation in the presence of TFA in CH_2Cl_2 resulted in trifluoroacetate **106**. Constant persuasion of thin layer chromatography showed the complete consumption of homoallylic alcohol **104** after 3 hours. After work up, the crude trifluoroacetate **106** on hydrolysis with K_2CO_3 in

MeOH yielded desired trisubstituted pyran **104**. Stereochemistry was assumed to be in anticipated line as it was well examined and established previously.[33]

Scheme 37

The structure assigned to **100** was supported by its ^{1}H NMR spectrum, which revealed disappearance of olefinic protons at δ 5.91-5.63 and δ 5.13-5.04, and appearance of five aromatic protons resonating at δ 7.33-7.20, along with other required signals. IR spectrum showed a strong absorption at 3415 cm^{-1} further confirming the construction in Prins cyclisation.

Proposed mechanism for Prins cyclisation:

Figure 5: Formation of the *syn*−THP ring

A plausible mechanism for the *syn*−selectivity is showed in Figure 5. Competition exists between the sterically stable and favored transition state T.S−1 and unstable T.S−2, which has 1,3-diaxial interactions. [34] The favored T.S1 leads to the conventional *syn*−isomer A whereas T.S−2 leads to *anti*−isomer B. In both cases, axial nucleophilic

attack by the external nucleophile at the 4−position is prevented. Obviously, *syn*−isomer is the major product, which comes from favored transition state.

Chemo selective tosylation[35a] of **100** with 1.1 equivalents of tosyl chloride in the presence of TEA in CH_2Cl_2 produced primary tosylate **107** (Scheme 38). ^{1}H NMR spectrum of tosylate **107** exhibited a doublet at δ 7.74 integrating for two protons, a multiplet at δ 7.32-7.20 integrating for seven protons and a singlet at δ 2.42 integrating for three protons confirmed the mono tosylation. IR spectrum showed absorption at 3452 cm^{-1} due to secondary hydroxyl group. Compound **107** on exposure to NaI in refluxing acetone[33f] gave the corresponding iodide **108** in 12 hours.

Scheme 38

Disappearance of tosyl group signals and presence of other required signals in ^{1}H NMR spectrum characterized the compound **108**. It was further supported by ESI-MS, which showed (M+H) peak at *m/z* 399. Iodo compound **108** on exposure to activated Zn in refluxing EtOH furnished key open chain intermediate **109** with the required *anti*-1,3-diol system,[35b] which was confirmed by the appearance of quaternary carbon in the ^{13}C NMR of its acetonide protected compound **109a** at 100.2 ppm. Appearance of characteristic terminal olefinic proton signals at δ 5.87-5.72 and δ 5.13-5.03 integrating for one and two protons respectively along with other required signals in ^{1}H NMR spectrum and a strong absorption at 3422 cm^{-1} in IR spectrum confirmed the structure of **109**.

Having succeeded in achieving the key intermediate with required stereochemistry, attention was turned on to chain elongation (Scheme 39). Thus, the newly created anti 1,3 diol of **109** was protected as its MOM ether[36] **110** in presence of MOM chloride, DIPEA and DMAP in CH_2Cl_2 to give **110** in 90% yield. Appearance of

characteristic $-OCH_2$ protons at δ 4.67-4.58 integrating for four protons and two singlet peaks at δ 3.34, 3.33 indicates the presence of two $-OCH_3$ in the corresponding molecule.

Scheme 39

Ozonolytic cleavage[37] of the olefinic bond of **110** resulted in aldehyde **111** after quenching the corresponding ozonide. Aldehyde **111**, after work up, on subjection to Wittig olefination with stable ylide $Ph_3P{=}CHCO_2Et$, in benzene gave *α*,β-unsaturated ester **112**.

In ^1H NMR spectrum, appearance of two olefinic peaks, each integrated for one-proton, at δ 5.84 as doublet with coupling constant J =15.8 Hz and at δ 6.99-6.85 as multiplet characterized the compound **112**. It was further characterized by its IR spectrum, which showed a strong absorption at 1718 cm^{-1} due to conjugated ester group. (Scheme 39)

Scheme 40

Substrate **112** on exposure to DIBAL-H at 0 ^oC in CH_2Cl_2 underwent reduction of ester to produce *E*-allylic alcohol compound **113** in 85% yield. Disappearance of the carbonyl carbon signal in the ^{13}C NMR spectrum of compound **113** proved the transformation. In addition to this, presence of a broad signal at 3448 cm^{-1} in the IR spectrum of the compound **113** also suggested the presence of –OH functionality. In the high resolution ESI mass spectrum of compound **113**, a signal at *m/z* 391.2091 corresponding to $[M+Na]^+$ (calcd 391.2096) lent support for the reduction.

Allylic alcohol **113** on Sharpless asymmetric epoxidation[38] with (-)-DIPT, Ti ($^iOPr)_4$ and *tert*-butyl hydroperoxide for 10 h at -20 ^oC yielded epoxide **114** in 75% yield.

In the ^{1}H NMR of **114** epoxide protons resonated at δ 2.87-2.822 as multiplet and at δ 3.03-2.96 as multiplet while remaining protons resonated at expected chemical shifts. In the high resolution ESI mass spectrum of compound **114** peaks at *m/z* 407.2038 corresponding to $[M+Na]^+$ (calcd 407.2045) lent support for the presence of epoxide. (Scheme 40)

Scheme 41

Regioselective opening of the epoxide using Red-Al[39] yielded 1,3-diol **115** in 84% yield. The contamination of the 1,2 -diol was eliminated by exposing the crude reaction mixture to $NaIO_4$ followed by silica gel column chromatography (2:3, EtOAc/hexane) to give pure 1,3 diol. Disappearance of the epoxide protons in ^{1}H NMR spectrum and ESI mass spectrum of compound **115** showing peaks at *m/z* 409.2073 corresponding to $[M+Na]^+$ (calcd 409.2080) confirmed the presence of 1,3 diol.

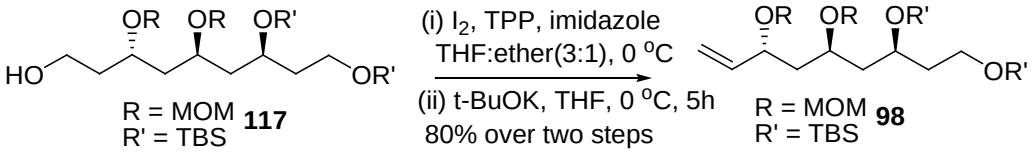
Protection of alcohols (1^o and 2^o) as TBS ethers was achieved by using *tert*-butyl dimethylsilyl [trifluoromethanesulfonate] and 2,6-lutidine in CH_2Cl_2 resulting in the di-TBS ether **116** in high yield. Resonance at δ 0.88 as a singlet, integrating for eighteen protons determines the presence of two *tert*.butyl moities and two singlet peaks at δ 0.05, 0.03 indicates the presence of six silyl attached methylenic protons of both the alcohols (1^o and 2^o). The compound **116** was also confirmed by mass spectrometry, which in its ESI-MS displayed $(M+Na)^+$ peak at *m/z* 637. (Scheme 41)

Scheme 42

Hydrogenolysis of **116** over 10% Pd-C in MeOH resulted debenzylated primary alcohol **117** in 92% yield at room temperature. The product was characterized by ^{1}H NMR study, which showed the disappearance of resonance for aromatic protons and there is no chemical shift at 7.32-7.16 ppm. The presence of primary free alcohol was confirmed by its IR spectroscopy that showed the absorption band at 3450 cm^{-1}. The

compound **117** was also confirmed by mass spectrometry, which in its ESI-MS displayed (M^++H) peak at *m*/*z* 547.

The primary alcohol **117 (**Scheme 42) was transformed to its iodo derivative by standard protocol[40] using I_2, TPP and imidazole which on immediate treatment with *t*-BuOK in Dry THF at 0 ^oC gave a (1,2 eliminated) terminal olefin[41] **98** in 80% yield.



Scheme 43

^{1}H NMR spectrum of the compound **98** exhibited two multiplets due to olefinic protons at δ 5.72-5.60 and δ 5.26-5.13 integrating for one and two protons respectively. The compound **98** was also confirmed by ESI-MS which displayed (M^++H) peak at *m*/*z* 477. **(**Scheme 43)

Synthesis of fragment 99:

Commercially-available enantiomerically-pure (*R*)-Roche ester was protected with TBDPSCl and imidazole with catalytic amount of DMAP in dry DCM at room temperature to afford **102** in 97% ylide. Resonance at 7.67-7.60, 7.42-7.31 ppm in ^{1}H NMR spectrum indicated the presence of ten diphenylic protons along with the characteristic –C(C**H**$_3$)$_3$ protons of TBDPS.

Scheme 44

Compound **102** was partially reduced using DIBAL-H at -78 ^oC over a time period of 30 min to give an aldehyde[42] which was used for the next reaction immediately. The aldehyde was subjected to Wittig olefination using stabilized ylide (Ph_3P=$CHCO_2Et$) in benzene to furnish α,β-unsaturated ester **118** in 85% overall yield (Scheme 44). The newly introduced protons corresponding to α,β-unsaturated ester group in ^{1}H NMR of **118** resonated at δ 5.89 (dd, *J* = 7.5, 15.8 Hz, 1H), 5.79 (dd, *J* = 1.5, 15.8

Hz, 1H), and ethyl ester –OCH_2– corresponds to δ 4.16(q, J = 7.5, 14.3 Hz, 2H) and -CH_3 corresponds to appear as a triplet at δ 1.29 (t, J = 6.7 Hz, 3H) confirming the product as an α,β-unsaturated ester. The coupling constant at 15.8 Hz indicate the formation of α,β-unsaturated ester group as *E*-geometry. In the IR spectrum a characteristic strong absorption at 1720 cm^{-1} for α,β-unsaturated ester functional group has observed. The structure of **118** was further confirmed by mass spectrum, which showed a molecular ion peak at *m/z* 419 $[M+H]^+$.

Substrate **118** on exposure to DIBAL-H at 0 ^oC in CH_2Cl_2 underwent reduction of ester to produce *E* - allylic alcohol compound **119** in 90% yield. Disappearance of the carbonyl carbon signal in the ^{13}C NMR spectrum of compound **119** proved the transformation. In addition to this, presence of a broad signal at 3383 cm^{-1} in the IR spectrum of the compound **119** also suggested the presence of –OH functionality. In the high resolution ESI mass spectrum of compound **119**, a signal at *m/z* 391.2091 corresponding to $[M+Na]^+$ (calcd 391.2096) lent support for the reduction.

Scheme 45

Allylic alcohol **119** on Sharpless asymmetric epoxidation[38] with (-)-DIPT, Ti ($^iOPr)_4$ and *tert*-butyl hydroperoxide for 6 h at -30 ^oC yielded epoxide **120** in 82% yield. Disappearance of olefinic protons and presence of epoxide protons resonated at δ 3.01-2.97 as multiplet and at δ 2.86 (dd, J = 2.2 Hz, 1H) in the ^1H NMR of **120**, while remaining of the protons resonated at expected chemical shifts. In the high resolution ESI mass spectrum of compound **120** peaks at *m/z* 393.1874 corresponding to $[M+Na]^+$ (calcd 393.1861) lent support for the presence of epoxide. (Scheme 45)

The chiral epoxy alcohol **120** was subjected to Gilman's[43] opening, using Me_2CuLi in dry ether at – 30 ^oC to afford the inseparable mixture of regioisomers 1,3-diol **121** and 1,2-diol**.** The crude mixture was subjected to $NaIO_4$ chopping in THF/H_2O (4:1) to give the pure compound **121** (Scheme 46).

Scheme 46

Disappearance of epoxide protons and appearance of two methyl doublets at δ 0.98(d, *J* = 6.7 Hz, 3H) and 0.74(d, *J* = 7.5 Hz, 3H) indicates the presence of compound **121**. In addition to this, presence of a broad signal at 3420 cm^{-1} in the IR spectrum of the compound **121** also suggested the presence of –OH functionality. In the high resolution ESI mass spectrum of compound **121**, a signal at *m/z* 409.2179 corresponding to $[M+Na]^+$ (calcd 409.2179) lent support for Gillman's product **121**.

The diol compound **121** was protected as its *para*-methoxybenzyledene acetal **122** with PMB acetal in DCM using catalytic amount of *p*-toluenesulfonic acid (PTSA) at 0 ^oC. The ^1H NMR spectrum of compound **122** revealed the presence of PMB group, which was resonated at 5.35 ppm as singlet for –OC**H**O- and three –OC$\mathbf{H}_3$ protons at 3.80 ppm as a singlet. Disappearance of hydroxyl absorption bands at 3420 cm^{-1} and 3413 cm^{-1} in IR spectrum confirmed the formation of PMB compound.

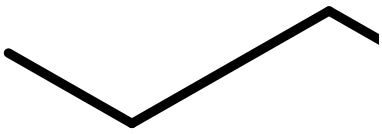
Scheme 47

Deprotection of silyl ether derivative in **122** with tetrabutylammonium fluoride (TBAF) in THF at room temperature furnished the primary alcohol **123**. The product was characterized by ^1H NMR study which showed the disappearance of resonance for aromatic protons and there is no chemical shift at 1.05 ppm as singlet for *tert*-butyl protons from TBDPS moiety. The presence of primary free alcohol was confirmed by its IR spectroscopy that showed the absorption band at 3420 cm^{-1}. The compound **123** was also confirmed by mass spectrometry, which in its ESI-MS displayed $(M^+ + Na)^+$ peak at *m*/*z* 289 (Scheme 47).

Oxidation of the primary alcohol **123** using Dess-martin periodinane[44] in CH_2Cl_2 in catalytic amt. of $NaHCO_3$ gives an aldehyde, which was subjected to Wittig olefination[45] by using $Ph_3P=CH_2$ and *n*-BuLi in dry THF at -20 ^oC to give the required fragment **99** in 80% yield.

Scheme 48

^1H NMR spectrum of the compound **99** exhibited two multiplets due to olefinic protons at δ 6.03-5.96 and δ 5.08-4.97 integrating one and two protons respectively. The compound **99** was also confirmed by mass spectrometry, In the high resolution ESI mass spectrum of compound **99**, a signal at *m/z* 285.1465 corresponding to $[M+Na]^+$ (calcd 285.1466) (Scheme 48).



Scheme 49

Now, the stage was set to prepare the compound **124** by olefin cross-metathesis reaction. However, cross-metathesis reaction[46] between fragment **98** and another

fragment **99** in the presence of Grubbs' 2nd generation catalyst (**A**) in Toluene was found to be an effective solvent for coupling of both the fragments. (In case of CH_2Cl_2 as solvent takes longer reaction time and low yields) Reaction was carried under refluxing temperature for 24 h, yields the product in 65%.

The product was characterized by ^{1}H NMR, appearance of almost all the peaks in the resulted spectra which shows two methyl doublets and TBS functionality and methoxy protons of the mom ether, and also the internal olefin resonated at δ 5.8 (dd, *J* = 7.5 Hz, 15.8 Hz, 1H), 5.34-5.26 (m, 1H). In the high resolution ESI mass spectrum of compound **124** peaks at *m/z* 763.4625corresponding to $[M+Na]^+$ (calcd 763.4612) lent support for the coupled product **124** (Scheme 49).

Saturation of the double bond of compound **124** was carried by treating with Raney Ni [47] in ethanol under hydrogen atmosphere, yielded the product **125** in 90% . The product was confirmed by the disappearance of olefinic protons at δ 5.8 (dd, *J* = 7.5 Hz, 15.8 Hz, 1H), 5.34-5.26 (m, 1H) in the ^{1}H NMR spectrum. Which was also confirmed by the ESI mass spectrum of compound **125**, a signal at *m/z* 765.4754 corresponding to $[M+Na]^+$ (calcd : 765.4763).

The primary TBS group of **125** was deprotected by HF/pyridine [48] in pyridine to give **126** in 85% yield. The product was confirmed by ^{1}H NMR spectrum, which shows integral value 6 protons at δ 0.10 ppm and 9 protons at δ 0.90 ppm, and also a strong absorption band at 3477 cm^{-1} in IR spectrum shows the presence of primary hydroxyl functionality. The high resolution ESI mass spectrum of compound **126** peaks at *m/z* 651.3888 corresponding to $[M+Na]^+$ (calcd : 651.3898) leads for the support for the mono silyl deprotection (Scheme 49).

Scheme 50

Oxidation of the primary alcohol **126** using Dess-martin periodinane[44] in CH_2Cl_2 in catalytic amt. of $NaHCO_3$ gives an aldehyde, which was subjected to Grignard reaction and the crude allyl alcohol was protected as acetyl ester *in situ* conditions. The product **127** was confirmed by the presence of olefinic protons at δ 4.90 - 4.78 ppm and methyl protons of acetyl group appears as a singlet at δ 2.18 ppm, which is also confirmed by mass spectrometry, which displayed $(M+Na)^+$ peak at *m*/*z* 734. The IR spectrum shows carbonyl functionality at 1709 cm^{-1}

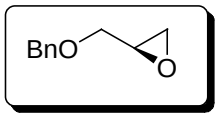
Palladium-catalyzed hydrogenolysis with ammonium formate and tributylphosphine according to a modification of the Tsuji protocol [49] provided terminal olefin **97** in an 88% yield with no detectable internal olefin regioisomer. The product was confirmed by ^1H NMR which shows the presence of olefinic protons and disappearance of acetyl group at 2.18 ppm, also confirmed by the ESI mass spectrum of compound **97**, a signal at *m/z* 675.4271 corresponding to $[M+Na]^+$ (calcd : 675.4262) (Scheme 50).

Experimental Section:

(2*R*)-2-[(benzyloxy)methyl]oxirane: 101

To the (*S*,*S*)-(salen)Co(II) precatalyst (151 mg, 0.250 mmol, 0.5 mol%) in a flask was charged sequentially with (±)-benzyl glycidyl ether (8.20 g, 50.0 mmol) and AcOH (57 μL, 1.0 mmol, 0.02 equiv). After the reaction mixture turned from a red suspension to a dark brown solution, the flask was cooled to 0 ^oC and THF (0.5 mL) followed by H_2O (495 μL, 27.5 mmol, 0.55 equiv) were added. The reaction mixture was allowed to warm

to room temperature over 2 h and stir for an additional 20 h. Distillation of the reaction mixture under *vacuum* (75 ^{o}C, 11 mmHg) gave unreacted (*R*)-benzyl glycidyl ether **101** (3.77 g, 46% yield) as a colorless oil. R_f = 0.6 (SiO_2, 20% EtOAc in hexane).



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

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

MASS (ESI-MS) : *m/z* 165 $(M+H)^+$

$[\alpha]_D^{25}$: -5.2 (*c* 2.0, $CHCl_3$).

(2*R*)-1-benzyloxy)pent-4-en-2-ol: 103

To the magnesium (1.18 g, 48.78 mmol) in dry THF (35 mL) at room temperature was sequentially added 1,2-dibromoethane (3 drops) and freshly prepared vinyl bromide (3.45 mL, 48.78 mmol) in a drop wise manner. CuCN (10.9 mg, 5 mol%) was added after allowing the reaction mixture to stir for 0.5 h. Then the mixture was cooled to –78 ^{o}C and added epoxide **101** (4.0 g, 24.39 mmol) in THF (6 mL) and warmed the mixture to –40 ^{o}C and stirred for 4 h. Quenched with saturated NH_4Cl solution (30 mL) and extracted with EtOAc (2x30 mL). Combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography afforded **103** (4.30 g, 92%) as a colorless liquid. R_f = 0.45 (SiO_2, 20% EtOAc in hexane).

^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.31 (m, 5H), 5.91-5.69 (m, 1H), 5.20-4.93 (m, 2H), 4.52 (s, 2H), 4.00-3.63 (m, 1H), 3.49 (dd, *J* =

9.5, 3.7 Hz, 1H), 3.32 (dd, *J* = 9.5, 6.5 Hz, 1H), 2.48 (brs, 1H), 2.23 (t, *J* = 6.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 138.3, 134.2, 128.5, 127.9, 127.7, 117.7, 73.8, 73.4, 69.7, 37.9.

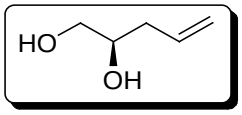
MASS (ESI-MS) : *m/z* 193 $(M+H)^+$.

IR (Neat) : 3360, 3021, 1637, 1494, 1450 cm^{-1}.

$[\alpha]_D^{25}$: -2.32 (*c* 1.2, $CHCl_3$).

(*R*)-pent-4-ene-1,2-diol: 104

To a solution of lithium (0.72 g, 104.1 mmol) in liquid NH_3 (25 ml) was added compound **103** (4.0 g, 20.8 mmol) in dry THF (8 ml). The mixture was stirred for 20 min and quenched with solid NH_4Cl (5.5 g) was added. Ammonia was allowed to evaporate and to the residual mixture was added ether and filtered through Celite. The filtrate was dried over Na_2SO_4. Removal of the solvent and purification by column chromatography of the crude product afforded alcohol **104** (1.59 g, 75% yield) as a colorless oil. R_f = 0.25 (SiO_2, 80% EtOAc in hexane).



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 5.91-5.63 (m, 1H), 5.13-5.04 (m, 2H), 3.90 (brs, 2H), 3.75-3.55 (m, 2H), 3.38 (dd, *J* = 11.0, 7.6 Hz, 1H), 2.18 (t, *J* = 6.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 135.1, 117.2, 71.3, 66.0, 37.5.

IR (Neat) : 3388, 2927, 1645, 1440, 1075 cm^{-1}.

$[\alpha]_D^{25}$: +3.6 (*c* 2.8, $CHCl_3$).

3−(Benzyloxy)propan−1−ol (105 a):

To the suspension of NaH (2.6 g, 65.78 mmol) in dry THF (35 mL) cooled to 0° C was added 1,3-propanediol (5.0 g, 65.78 mmol) in THF (130 mL) in a drop wise manner. The reaction mixture was stirred at room temperature for 30 min. and cooled to 0° C. After addition of BnBr (7.77 mL, 65.78 mmol), reaction was left to room temperature and stirred for 6 h, cooled to 0° C and quenched with saturated NH_4Cl solution (60 mL)

carefully. Then added EtOAc (150 mL), organic layer was separated, washed with H_2O (3×30 mL) and brine solution (30 mL) and dried *in vacuo*. Column chromatography of crude product afforded **105a** as colorless oil (6.65 g, 70%) along with 18% recovered starting material.

***R*f :** 0.4 (SiO_2, 30% EtOAc in hexane).

^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.32−7.28 (m, 5H), 4.50 (s, 2H), 3.75 (t, 2H, J = 5.7 Hz), 3.63 (t, 2H, J = 5.7 Hz), 2.17 (brs, 1H, O*H*), 1.86−1.84 (m, 2H).

3−(Benzyloxy)propanal (105):

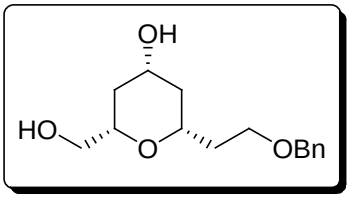
Freshly prepared pyridinium chlorochromate (7.7 g, 36.0mmol) was added portion wise to a solution of alcohol **105a** (4 g, 24.0 mmol), activated molecular sieves(4 g) and silica gel (4 g) in dry CH_2Cl_2 (50 mL) at 0° C under nitrogen atmosphere. The turbid solution was allowed to warm to room temperature and stirred for 4 h. When TLC analysis shows that most of the starting material is consumed, the solids suspended in the reaction and the chromium species are removed by filtration through a pad of silica gel and the pad is washed with ether. The organic phases were concentrated, followed by purification by column chromatography afforded the pure aldehyde **105** (3.55 g, quant.) as colorless oil. This aldehyde was taken forward to next step with any further characterization.

***R*f :** 0.4 (SiO_2, 10% EtOAc in hexane).

(2*S*,4*R*,6*S*)-2-(2-(benzyloxy)ethyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-4-ol: 100

Trifluoroacetic acid (15.6.0 ml) was added slowly to a solution of the homoallylic alcohol **104** (1.0 g, 9.61 mmol) and 3-(benzyloxy)propanal **105** (4.73 g, 28.8 mmol) in CH_2Cl_2 (30 mL) at 0 ^oC under nitrogen atmosphere. The reaction mixture was stirred for 3.0 h and then saturated sodium hydrogen carbonate solution (30 mL) was added and p^H was adjusted to >7 by addition of triethylamine. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4x20 ml) and the organic layers were combined and the solvent was removed under reduced pressure. The trifluoroacetate **106** obtained in this reaction was directly used in the next reaction without purification.

The residue was dissolved in methanol (25 ml), added potassium carbonate (5.0 g) and the mixture was stirred for 0.5 h. The methanol was then removed under reduced pressure and water (15 mL) was added. The mixture was extracted with dichloromethane (3 × 20 ml) and the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the crude by column chromatography on silica yielded **100** (1.4 g, 55%) as a colorless liquid. R_f = 0.2 (SiO_2, 40% EtOAc in hexane).

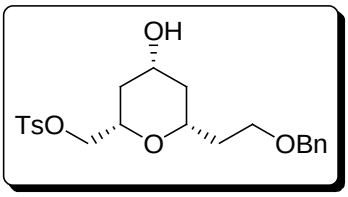


^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 7.33-7.20 (m, 5H), 4.44 (q, *J* = 12.0, 15.8 Hz, 2H), 3.76-3.64 (m, 1H), 3.60-3.41 (m, 5H), 3.39-3.29 (m, 1H), 3.17-3.08 (brs, 2H),1.93-1.66 (m, 3H), 1.26-1.04 (m, 2H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: 138.2, 128.3, 127.6, 75.8, 72.9, 72.6, 67.6, 66.4, 65.4, 40.9, 36.5, 35.9.
MASS (ESI-MS)	: *m/z* 267 $(M+Na)^+$.
HRMS (ESI)	: calcd. for $C_{15}H_{22}O_4Na$: 289.1415; found: 289.1427.
IR (Neat)	:3415, 2921, 2856, 1092, 1026, 741 cm^{-1}.
$[\alpha]_D^{25}$	: +16.7 (*c* 2.0, MeOH);

[(2*S*,4*R*,6*S*)-6-(2-(benzyloxy)ethyl)-4-hydroxy-tetrahydro-2H-pyran-2-yl]methyl 4-ethylbenzenesulfonate: 107

To solution of diol **100** (2.0 g, 7.5 mmol) in dry CH_2Cl_2 (20.0 mL), was added triethylamine (2.10 mL, 15 mmol) at 0 ^oC, and tosyl chloride (1.71 g, 9.0 mmol) over 2 h. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was treated with aqueous 1N HCl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with saturated $NaHCO_3$ (15 mL) and water (15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced

pressure. Flash chromatography of the crude afforded tosylate **107** (2.58 g, 82%) as a gummy liquid. R_f = 0.5 (SiO_2, 40% EtOAc in hexane).

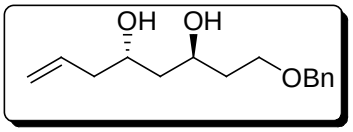


^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.32-7.20 (m, 7H), 4.43 (q, *J* = 12.4 Hz, 2H), 3.96 (dd, *J* = 6.2, 10.0 Hz, 1H), 3.90 (dd, *J* = 4.2, 10.0 Hz, 1H), 3.75-3.67 (m,1H), 3.52-3.40 (m, 4H), 2.42 (s, 3H), 1.90-1.65 (m, 5H), 1.14-1.04 (m, 2H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 144.7, 138.3, 132.8, 129.7, 128.3, 127.8, 127.5, 127.5, 72.9. 72.6, 71.8, 67.4, 66.2, 40.7, 36.7, 35.8, 29.6, 21.5.
MASS (ESI-MS)	: *m/z* 443 $(M+Na)^+$
HRMS (ESI)	: calcd. for $C_{22}H_{28}O_6SNa$: 443.1504; found: 443.1500.
IR (Neat)	: 3452, 2921, 1630, 1357, 989, 661 cm^{-1}.
$[\alpha]_D^{25}$	: -23.3 (*c* 3.0, $CHCl_3$);

(3*S*,5*S*)-1-(benzyloxy)oct-7-ene-3,5-diol: 109

NaI (4.45 g, 29.7 mmol) was added to a solution of **107** (2.5 g, 5.9 mmol) in 30 mL of acetone and heated to reflux for 24 h. Acetone was removed under reduced pressure. To the residue was added water and EtOAc and the organic layer was separated, dried over Na_2SO_4, concentrated and chromatographed to afford **108** (2.01 g, 90%) as a colourless liquid. R_f = 0.7 (SiO_2, 10% EtOAc in hexane).

To the iodide **108** (2.01 g, 5.35 mmol) in ethanol (50 mL), commercial zinc dust (5.2 g, 80.25 mmol) was added. The mixture was refluxed for 1 h and then cooled to 25 ^oC. Addition of solid ammonium chloride (8.17 g) and ether (120 mL) followed by stirring for 5 min gave a gray suspension. The suspension was filtered through Celite and filtrate was concentrated in *vacuo*. Purification by flash chromatography gave **109** (1.17 g, 88%) as a colourless liquid. R_f = 0.2 (SiO_2, 50% EtOAc in hexane).



^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.36-7.23 (m, 5H), 5.87-5.72 (m, 1H), 5.13-5.03 (m, 2H), 4.50 (s, 2H), 4.18-3.83 (m, 2H), 3.74-3.58 (m, 2H), 2.27-2.13 (m, 2H), 1.92-1.47 (m, 3H), 1.27-1.21 (m, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 137.6, 134.8, 128.3, 127.7, 127.6, 117.5, 73.2, 69.0, 68.8, 67.9, 42.1, 41.9, 36.2.

MASS (ESI-MS) : *m/z* 273 $(M+Na)^+$.

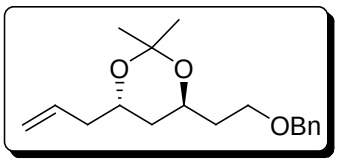
HRMS (ESI) : calcd. for $C_{15}H_{22}O_3Na$: 273.1466; found: 273.1469.

IR (Neat) : 3422, 2923, 1639, 1093, 744 cm^{-1}.

$[\alpha]_D^{25}$: + 5.1 (*c* 2.2, $CHCl_3$).

(4S,6S)-4-allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane: 109a

To an ice-bath cooled solution of diol **109** (388 mg, 1.52 mmol), catalytic amount of CSA in anhydrous CH_2Cl_2 (7 mL) was added 2,2-dimethoxypropane (0.28 mL, 2.28 mmol) at 0 ^{o}C. The reaction mixture was stirred for 1h at rt. After complete consumption of the starting material, solid $NaHCO_3$ (300 mg) was added and stirred for 30 min. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a crude mixture that was purified by silica gel column chromatography by using ethyl acetate and hexane (1:20) afford compound **109 a** (423 mg, 96%) as colourless liquid;



^{1}H NMR ($CDCl_3$ 300 MHz) : 7.36-7.31 (m, 5H), 5.79 (ddt, *J* = 7.0, 10.0, 17.0 Hz, 1H), 5.12-5.02 (m, 2H), 4.49 (dd, *J* = 11.9, 13.9 Hz, 2H), 4.03-3.95 (m, 1H), 3.90-3.82 (m,

1H), 3.60-3.50 (m, 2H), 2.34-2.26 (m, 1H), 2.23-2.14 (m, 1H), 1.81-1.73 (m, 2H), 1.65-1.57 (m, 2H), 1.33 (s, 3H), 1.32 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 138.5, 134.4, 128.3, 127.6, 127.5, 116.7, 100.2, 73.1, 66.6, 66.2, 63.7, 40.1, 38.0, 36.0, 24.8 ppm.

MASS (ESI-MS) : *m/z* 313 $(M+Na)^+$

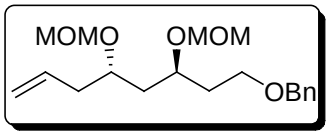
HRMS (ESI) : calcd. for $C_{18}H_{26}O_3Na$: 313.1779; found: 313.1790.

IR (Neat) : 2990, 2940, 1442, 1379, 1223, 1171, 1118, 1028, 998, 925, 758, 698 cm^{-1}

$[\alpha]_D^{25}$: + 14.7 (*c* 0.65, $CHCl_3$).

1-[((3*S*,5*S*)-3,5-bis(methoxymethoxy)oct-7-enyloxy)methyl]benzene: 110

To alcohol **109** (1.5 g, 6.0 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 ^oC were added diisopropylethylamine (8.3mL, 48 mmol) and MOMCl (1.3mL, 1.9 g, 24mmol) successively and the mixture was stirred for 3 h at room temperature and then quenched by adding water (10 mL) and extracted with CH_2Cl_2 (3 × 12 mL). The organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to remove the solvent and the crude was purified by column chromatography to afford the pure product **110** (1.82 g, 90%). R_f = 0.1 (SiO_2, 10% EtOAc in hexane).



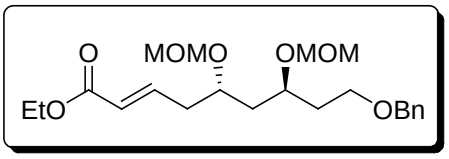
^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.35-7.18 (m, 5H), 5.86-5.70 (m, 1H), 5.09-5.01 (m, 2H), 4.67-4.58 (m, 4H), 4.46 (s, 2H), 3.87-3.70 (m, 2H), 3.88-3.69 (m, 2H), 3.51 (t, *J* = 6.0 Hz, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 2.33-2.27 (m, 2H), 1.64-1.57 (m, 2H).

^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 138.3, 134.2, 128.2, 127.5, 127.4, 117.3, 96.2, 95.9, 74.4, 73.0, 73.0, 72.8, 66.6, 55.5, 40.5, 39.7, 35.5.
MASS (ESI-MS)	: *m/z* 361 $(M+Na)^+$
HRMS (ESI)	: calcd. for $C_{19}H_{30}O_5Na$: 361.2032; found: 361.2041.
IR (Neat)	: 2927, 1640, 1448, 1150, 1040, 916, 739 cm^{-1}.
$[\alpha]_D^{25}$	: + 4.9 (*c* 2.5, $CHCl_3$).

5*S*,7*S*,*E*)-ethyl 9-(benzyloxy)-5,7-bis(methoxymethoxy)non-2-enoate: 112

Ozone was bubbled through a solution of **110** (2.0 g, 5.9 mmol) in CH_2Cl_2 (15 mL) at –78 ^oC until no unreacted starting material was observerd on TLC. The reaction mixture was purged with N_2 to remove the excess ozone and cooled to 0 ^oC, Ph_3P (3.1 g, 11.8 mmol) was added, and the mixture was stirred for 2 h. The mixture was concentrated in *vacuo*. After adding hexane, the mixture was filtered through celite pad. Washed the residue with hexane, filtrate was dried over Na_2SO_4, concentrated under reduced pressure and the crude aldehyde **111** was subjected to the next reaction without further purification.

To the solution of aldehyde **111** in benzene (20 mL) was added carbethoxy methylenetriphenylphosphorane (4.1 g, 11.8 mmol) in one portion at refluxing temperature. Stirred for 2 h at the same temperature, removed the benzene under reduced pressure, added EtOAc (15 mL), washed with brine (5 mL), dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography afforded **112** (2.1 g, 90%, 2 steps) as a colorless oil. R_f = 0.4 (SiO_2, 10% EtOAc in hexane).



^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 7.32-7.20 (m, 5H), 6.99-6.85 (m, 1H), 5.84 (d, *J* = 15.8 Hz, 1H), 4.67-4.58 (m, 4H), 4.46 (s, 2H), 4.17 (q, *J* = 14.3 Hz, 2H), 3.88-3.78 (m, 2H), 3.50 (t, *J* =

6.0 Hz, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 2.50-2.41 (m, 2H), 1.85-1.75 (m, 2H), 1.65-1.56 (m, 2H), 1.29 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.1, 144.6, 128.2, 127.5, 127.4, 123.7, 96.2, 96.2, 74.0, 73.0, 72.9, 66.5, 60.1, 55.7, 55.6, 40.8, 38.2, 35.4, 14.2.

MASS (EIMS) : *m/z* 433 $(M+Na)^+$.

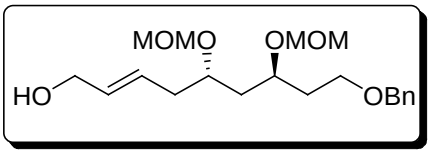
HRMS (ESI) : calcd. for $C_{22}H_{34}O_7Na$: 433.2202; found: 433.2223.

IR (Neat) : 2933, 1718, 1654, 1037 cm^{-1}

$[\alpha]_D^{25}$: + 0.7 (*c* 1.4, $CHCl_3$).

(5*S*,7*S*,*E*)-9-(benzyloxy)-5,7-bis(methoxymethoxy)non-2-en-1-ol: 113

To a solution of **112** (2.0 g, 4.8 mmol) in CH_2Cl_2 (15 mL) at 0 ºC, a solution of DIBAL-H in toluene (1.5 M, 6.9 mL, 12.2 mmol) was added drop wise and stirred for 1 h at this temperature. The reaction was quenched by the addition of few drops of MeOH followed by saturated aqueous sodium potassium tartrate solution. It was warmed to 0 ^oC and stirred for 2 h. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude by column chromatography afforded **113** (1.52 g, 85%) as an oil. R_f = 0.2 (SiO_2, 50% EtOAc in hexane).

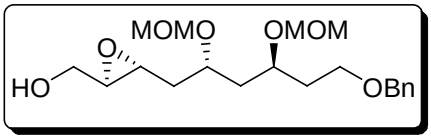


^{1}HNMR ($CDCl_3$ 300 MHz) : δ 7.33-7.21 (m, 5H), 5.70-5.63 (m, 2H), 4.65-4.56 (m, 4H), 4.47 (s, 2H), 4.05-4.00 (m, 2H), 3.85-3.67 (m, 2H), 3.51 (t, *J* = 6.2 Hz, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 2.29 (t, *J* = 4.9 Hz, 2H), 1.79 (q, *J* = 12.0 Hz, 2H), 1.72-1.54 (m, 2H).

^{13}CNMR ($CDCl_3$, 75 MHz)	: δ 138.4, 132.3, 128.3, 128.0, 127.6, 127.5, 96.2, 95.8, 74.3, 73.0, 72.8, 66.5, 63.5, 55.5, 40.3, 37.9, 35.5.
MASS (EIMS)	: *m/z* 391 $(M+Na)^+$.
HRMS (ESI)	: calcd. for $C_{20}H_{32}O_6Na$: 391.2096; found: 391.2091.
IR (Neat)	: 3448, 2926, 1635, 1449, 1097, 1036, 915 cm^{-1}.

(2*R*,3*R*)-3-((2*R*,4*S*)-6-(benzyloxy)-2,4-bis(methoxymethoxy)hexyl)oxiran-2-yl)methanol: 114

In a two neck round-bottomed flask was weighed, 1 g of 4 A^o molecular sieves (dry powder) under nitrogen atmosphere and was added dry CH_2Cl_2 (5 mL) and the solution was cooled to –20 ^{o}C. To this cold suspension was added $Ti(O^iPr)_4$ (0.33 mL, 1.08 mmol) followed by D-(+)-diethyl tartrate (0.23 mL, 1.08 mmol) and the mixture was stirred vigorously at -20 ^{o}C for 45 min. The allyl alcohol **113** (2.0 g, 5.4 mmol) in CH_2Cl_2 (10 mL) and *tert*-butyl hydrogen peroxide(3.3 mL, 13.5 mmol) were added to the reaction mixture subsequently at the same temperature and stirred for 8 h. After completion of the reaction (by TLC), the reaction mixture was filtered. The filtrate was quenched by addition of water (8 mL) and 3 mL of 20% NaOH solution, stir for 1 h at 0 ^{o}C. The filtrate was dried over anhydrous Na_2SO_4 and concentrated to afford the crude epoxy alcohol, which was purified by silica gel column chromatography using Hexane/EtOAc (7:3) to afford **114** (1.5 g, 75% yield).



^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 7.34-7.20 (m, 5H), 4.68-4.59 (m, 4H), 4.47 (s, 2H), 3.89-3.57 (m, 4H), 3.52 (t, *J* = 6.0 Hz, 2H), 3.35 (s, 3H), 3.34 (s, 3H), 3.03-2.96 (m, 1H), 2.87-2.82 (m, 1H), 1.86-1.64 (m, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 138.2, 128.2, 127.5, 127.4, 96.1, 96.1, 73.0, 72.8, 66.4, 61.5, 58.5, 52.9, 41.2, 41.0, 37.3, 35.4.

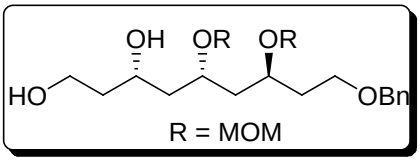
MASS (EIMS) : *m/z* 407 $(M+Na)^+$.

HRMS (ESI) : calcd. for $C_{20}H_{32}O_7Na$: 407.2045; found: 407.2038.

$[\alpha]_D^{25}$: +1.6 (*c* 1.35, $CHCl_3$)

(3*S*,5*S*,7*S*)-9-(benzyloxy)-5,7-bis(methoxymethoxy)nonane-1,3-diol: 115

To a cold (0 ^oC) solution of epoxide **114** (2.0 g, 5.20 mmol) in THF (20 mL) was added Red-Al (1.5 mL, 70 wt % in toluene, 10.4 mmol) drop wise. After 2 h at 0 ^oC, the reaction mixture was quenched carefully by drop wise addition of saturated aqueous sodium potassium tartrate. EtOAc (30 mL) was added and mixture was allowed to warm to room temperature. The organic layer was washed with brine and the combined aqueous layers were extracted with EtOAc (3 × 20 mL). The combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on Silica gel to provide **115** (1.6 g, 84%) as a colorless oil. R_f = 0.3 (60% EtOAc in hexane)



^1H NMR ($CDCl_3$ 300 MHz) : δ 7.34-7.20 (m, 5H), 4.73-4.56 (m, 4H), 4.46 (s, 2H), 4.11-3.69 (m, 4H), 3.51 (t, *J* = 6.0 Hz, 2H), 3.36 (s, 3H), 3.34 (s, 3H), 1.85-1.13 (m, 9H).

MASS (EIMS) : *m/z* 407 $(M+Na)^+$.

HRMS (ESI) : calcd. for $C_{20}H_{32}O_7Na$: 407.2065; found 384.2073.

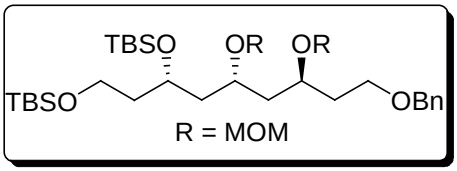
IR (Neat) : 3285, 292, 2850, 1460, 1080 cm^{-1}.

$[\alpha]_D^{25}$: +2.0 (*c* 1.25, $CHCl_3$).

1-[((3*S*,5*R*,7*S*)-7,9-bis(tert-butyldimethylsilyloxy)-3,5-is(methoxymethoxy)nonyloxy) methyl] benzene: 116

To a solution of **115** (2.0 g, 5.20 mmol) in dry CH_2Cl_2 (20 ml) was added 2,6-lutidine (3.0mL, 26.0 mmol) in one portion followed by *tert*-butyl dimethylsilyl [trifluoromethanesulfonate] (2.8 mL, 13 mmol) in two portions. The reaction mixture was

stirred for 6 h with the temperature slowly reaching room temperature. It was quenched with the saturated NH_4Cl solution (30 ml), diluted with EtOAc (30 ml), washed with brine (25 ml), dried (Na_2SO_4) and concentrated in *vacuo*. Purification of the crude product by column chromatography afforded **116** (2.8 g, 90%) as a colorless liquid. R_f = 0.2 (SiO_2, 10% EtOAc in hexane).



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.32-7.16 (m, 5H), 4.66-4.53 (m, 4H), 4.47 (s, 2H), 3.93-3.61 (m, 4H), 3.56-3.44 (m, 2H), 3.33 (s, 3H), 3.32 (s, 3H), 1.90-1.48 (m, 6H), 1.35-1.19 (m, 2H), 0.88 (s, 18H), 0.05 (s, 6H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 138.4, 128.2, 127.5, 127.4, 96.3, 95.9, 73.0, 72.9, 66.7, 66.5, 59.7, 55.5, 43.6, 41.6, 40.2, 35.6, 25.9, 25.8, 18.2, 17.9, -4.5, -5.3.

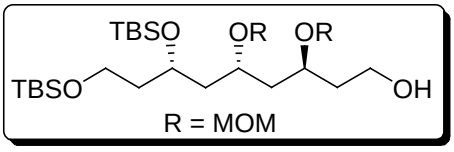
MASS (ESI-MS) : *m/z* 637 $(M+Na)^+$.

IR (Neat) : 2952, 2855, 1466, 1098, 1039, 836 cm^{-1}.

$[\alpha]_D^{25}$: -12.6 (*c* 1.0, $CHCl_3$).

(3S,5R,7S)-7,9-bis(tert-butyldimethylsilyloxy)-3,5-bis(methoxymethoxy)nonan-1-ol: 117

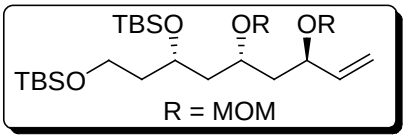
To a stirred solution of compound **116** (2.5 g, 4 mmol) in EtOAc (10 mL) was added 10 % Pd/C (0.2 g) at room temperature The flask was evacuated and pressurized with H_2 (balloon) and the mixture was then stirred for 10 h. The mixture was then filtered through a pad of Celite. After washing thoroughly with EtOAc, the filtrate was concentrated to get a debenzylated product **117**. Purification of the crude product by column chromatography afforded **117** (1.9 g, 92%) as a colorless liquid. R_f = 0.2 (SiO_2, 30% EtOAc in hexane).



^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 4.66-4.55 (m, 4H), 3.96-3.86 (m, 2H), 3.82-3.61 (m, 4H), 3.40 (s, 3H), 3.36 (s, 3H), 1.93-1.47 (m, 7H), 1.37-1.20 (m, 2H), 0.88 (s, 18H), 0.33 (s,12H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 96.7, 95.6, 73.9, 72.7, 66.4, 59.4, 55.7, 43.3, 41.4, 40.2, 37.8, 25.8, 25.7, 18.1, 17.9, -4.5, -5.4.
MASS (ESI-MS)	: *m/z* 547 $(M+H)^+$.
HRMS (ESI)	: calcd. for $C_{25}H_{56}O_7Si_2Na$: 547.3462; found 547.3456.
IR (Neat)	: 3450, 2929, 2857, 1253, 1096, 1037, 836 cm^{-1}.
$[\alpha]_D^{25}$	: -22.4 (*c* 2.5, $CHCl_3$).

(3*R*,5*R*,7*S*)-7,9-bis(tert-butyldimethylsilyloxy)-3,5-bis(methoxymethoxy)non-1-ene: 98

To a solution of **117** (1.5 g, 2.8 mmol) in CH_3CN:Et_2O (1:3) (12 mL), imidazole (584 mg, 8.5 mmol) was added with stirring. After imidazole was dissolved the reaction mixture was cooled to 0 ^oC and TPP (1.10 g, 4.2 mmol) was added followed by the addition of I_2 (850 mg, 3.3 mmol). The temperature was maintained at 0 ^oC and the mixture ws stirred vigorously for 30 minutes. The reaction mixture was filtered and residue was washed with ether several times. The filtrate was concentrated on rota vaccum and crude residue was purified by flash chromatography to afford the iodo compound, a pale yellow liquid by column chromatography on silica gel (60-120 mesh) using EtOAc/hexane (2%) as an eluent. To a solution of iodo compound (1.74g, 2.7 mmol) in THF (9 ml) at rt was added *t*-BuOK (760 mg, 6.85 mmol) and stirred it for 4 h. After the completion of the reaction as checked by TLC it was quenched by water and diluted with EtOAc. The layers were separated and aqueous layer was extracted with EtOAc (2 times). The combined organic layers were washed (water and brine solution), dried, concentrated under reduced pressure and purified by flash chromatography to afford the olefin compound **98** (1.1 gm, 80%) as a yellow liquid by column chromatography on silica gel (60-120 mesh) using EtOAc/hexane as an eluent. R_f = 0.4 (10% EtOAc/hexane).



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 5.72-5.60 (m, 1H), 5.26-5.13 (m, 2H), 4.69-4.57 (m, 4H), 4.17-4.07 (m, 1H), 3.97-3.74 (m, 2H), 3.65 (t, *J* = 6.0 Hz, 2H), 3.37 (s, 3H), 3.35 (s, 3H), 1.85-1.50 (m, 6H), 0.88 (s, 18H), 0.03 (s, 12H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 138.7, 116.8, 96.0, 94.1,76.9, 74.6, 72.5, 66.5, 59.7, 55.7, 43.5, 41.9, 40.2, 25.9, 18.0, 18.2, -4.4, -5.3.

MASS (ESI-MS) : *m/z* 529 $(M+Na)^+$.

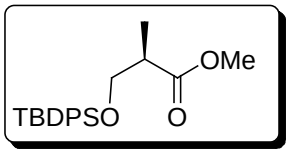
HRMS (ESI) : calcd. for C_{25} H_{54} O_6Si_2Na: 529.3351; found: 529.3344.

IR (Neat) : 2953, 2931, 2889, 2857, 1468, 1096, 1036, 836 cm^{-1}.

$[\alpha]_D^{25}$: -22.4 (*c* 2.5, $CHCl_3$).

(*R*)-methyl 3-(tert-butyldiphenylsilyloxy)-2-methylpropanoate: 102

To an ice cooled solution of Roche ester (2.0 g, 16.9 mmol) and imidazole (2.3 g, 33.8 mmol) in dry dichloromethane (40 mL) was added TBDPS-Cl (4.8 g, 18.6 mmol) in dichloromethane. After stirring for 15 min. at 0 °C then reaction mixture was brought to room temperature and the stirring was continued for another 5 h, completion of the reaction was monitored by TLC. Reaction mixture was quenched using saturated NH_4Cl solution and extracted with dichloromethane (2 × 30 mL). The combined extracts was washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness. The residue was purified on column chromatography using silica gel to afford the pure mono protected silyl ether **102** (5.7 g, 95% yield) as a viscous liquid.



^{1}H NMR ($CDCl_3$ 300 MHz) : ^{1}H NMR ($CDCl_3$ 300 MHz): δ 7.68-7.63 (m, 4H), 7.45-7.35 (m, 6H), 3.86-3.71 (m, 2H), 3.68 (s, 3H),

2.78-2.65 (m, 1H), 1.15 (d, *J* = 7.5 Hz, 3H), 1.03 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 175.3, 135.5, 133.4, 129.6, 127.6, 65.8, 51.5, 42.3, 26.6, 19.2, 13.4 ppm.

MASS (ESI-MS) : *m/z* 379 $(M+Na)^{+\cdot}$

HRMS (ESI) : calcd. for $C_{21}H_{28}O_3Si$ Na: 379.1699; found: 379.1698.

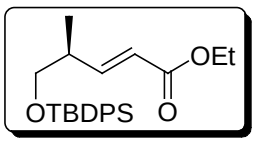
IR (Neat) : 3453, 2935, 2858, 1740, 1429, 1109, 703 cm^{-1}.

$[\alpha]_D^{25}$: -15.4 (*c* 1.4, $CHCl_3$).

(*S,E*)-ethyl 5-(tert-butyldiphenylsilyloxy)-4-methylpent-2-enoate: 118

To a solution of **102** (2.0 g, 5.6 mmol) in CH_2Cl_2 (20 mL) at –78 ^oC, a solution of DIBAL-H in toluene (3.5 mL, 6.1 mmol) was added drop wise and stirred for 30min at the same temperature. The reaction was quenched by the addition of few drops of MeOH followed by saturated aqueous sodium potassium tartrate solution. It was warmed to 0 ^oC and stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 (2x10 mL) and washed with brine (10 mL), dried over Na_2SO_4 concentrated under reduced pressure and the crude aldehyde was subjected to the next reaction without further purification.

To a solution of the aldehyde in dry benzene (15 mL) was added (carbethoxymethylene)triphenylphosphorane (3.8 g, 11.2 mmol) in one portion at refluxing temperature, continued for 2 h at the same temperature. Removal of benzene under reduced pressure, added EtOAc (15 mL), washed with brine (5 mL), dried over Na_2SO_4 and concentrated in *vacuo*. Purification by column chromatography afforded **118** (1.8, 85%, 2 steps) as a colorless oil. R_f = 0.5 (SiO_2, 10% EtOAc in hexane).



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.64-7.58 (m, 4H), 7.40-7.31 (m, 6H), 5.89(dd, *J* = 7.5, 15.8 Hz, 1H), 5.79 (dd, *J* = 1.5, 15.8 Hz, 1H), 4.16 (q, *J* = 14.3 Hz, 2H), 3.60-3.52 (m, 2H), 2.59-2.48 (m, 1H), 1.29 (t *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.04 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.6, 151.2, 135.5, 133.5, 129.6, 127.6, 121.0, 67.5, 60.1, 39.0, 26.7, 19.0, 15.5, 14.2.

MASS (ESI-MS) : *m/z* 419 $(M+Na)^+$.

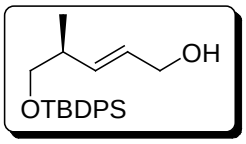
HRMS (ESI) : calcd. for $C_{24}H_{32}O_3SiNa$: 419.2012; found: 419.2004.

IR (Neat) : 2959, 2858, 1720, 1110, 703 cm^{-1}.

$[\alpha]_D^{25}$: 13.8 (*c* 0.9, $CHCl_3$).

(*S*,*E*)-5-(tert-butyldiphenylsilyloxy)-4-methylpent-2-en-1-ol: 119

To a cooled (0 ^oC) solution of **118** (1.8 g, 4.54 mmol) in dry CH_2Cl_2 (20 mL), DIBAL-H (6.4 mL, 11.36 mmol) was added slowly for 15 min, stirred for 2 h at 0 ^oC, before being quenched with methanol (3 mL) and sodium potassium tartarate solution (10 mL). The reaction mixture was passed through a short pad of celite. The filtrate was concentrated and purified the residue by column chromatography (1:4, EtOAc/hexane) to furnish allyl alcohol **119** (1.44 g, 90%) as a colorless liquid.



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.74 (d, 2H, *J* = 8.3 Hz), 7.30-7.18 (m, 7H), 4.24 (dd, 1H, *J* = 11.3, 1.5 Hz), 4.10-3.99 (m, 2H), 3.98-3.81 (m, 1H), 3.77-3.67 (m, 1H), 2.42 (s, 3H), 2.01-1.95 (m, 1H), 1.88-1.82 (m, 1H), 1.52-1.24 (m, 2H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 141.5, 129.7, 128.2, 128.0, 127.5, 125.9, 77.7, 73.3, 72.1, 68.3, 43.3, 37.2, 25.7, 21.31, 13.8, -4.5.

MASS (ESI-MS) : *m/z* 377 $(M+Na)^+$.

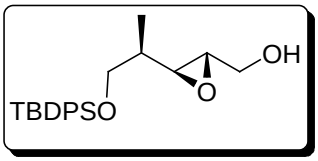
HRMS (ESI) : calcd. for C_{22} H_{30} O_2 Si Na: 377.1907; found: 377.1907.

IR (Neat) : 3383, 2931, 2858, 1427, 1109, 703 cm^{-1}.

$[\alpha]_D^{25}$: 5.5 (*c* 1.3, $CHCl_3$).

((2*S*,3*S*)-3-((*R*)-1-(tert-butyldiphenylsilyloxy)propan-2-yl)oxiran-2-yl)methanol: 120

To a stirred solution of (+) DIPT (0.4 mL, 1.4 mmol) in dry CH_2Cl_2 (10 mL) at -30 ^oC containing MS 4 Å (3.5 g), sequentially Ti $(O^iPr)_4$ (0.3mL, 1.4 mmol) and TBHP (3.8mL, 15.5 mmol) were added and stirred for 30 min. A solution of allyl alcohol **119** (2.5 g, 7.0 mmol) in CH_2Cl_2 (20 mL) was added and stirred for 10 h at -30 ^oC. It was then quenched with 15 mL of water and 20% aqueous NaOH and saturated with NaCl (5 mL). The resulting mixture stirred vigorously for another 30 min at room temperature. The resulting mixture was vacuum filtered through celite and the filter cake was washed well with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). Combined organic phases were washed with brine and dried over Na_2SO_4. Removal of solvent under reduced pressure and purification by column chromatography (2:8, EtOAc/hexane) afforded **120** (2.14 g, 82%) as a viscous liquid.

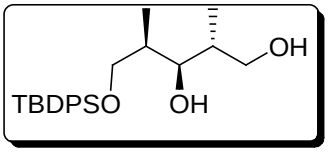


^1H NMR ($CDCl_3$ 300 MHz)	: δ 7.66-7.59 (m, 4H), 7.43-7.32 (m, 6H), 3.90-3.84 (m, 1H), 3.64-3.53 (m, 2H), 3.01-2.97 (m, 1H), 2.86 (dd, *J* = 2.2 Hz, 1H), 1.69-1.41 (m, 3H), 1.04 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 135.4, 133.3, 129.6, 127.6, 66.2, 61.6, 58.7, 58.4, 38.3, 26.7, 19.1, 13.3 ppm
MASS (ESI-MS)	: *m/z* 393 $(M+Na)^+$.
HRMS (ESI)	: calcd. for $C_{22}H_{30}O_3$ Si Na: 393.1861; found: 393.1874.
IR (Neat)	: 3442, 2958, 1427, 1108, 702 cm^{-1}.
$[\alpha]_D^{25}$	: -15.4 (*c* 3.4, $CHCl_3$).

(2*R*,3*R*,4*R*)-5-(tert-butyldiphenylsilyloxy)-2,4-dimethylpentane-1,3-diol: 121

To a cold (0 ^oC) suspension of copper (I) cyanide (1.93 g, 21.6 mmol) in dry ether (10 mL), MeLi (21.6 mL, 43.2 mmol, 2.0M) in dry ether (10 mL) was added drop wise until it become a clear solution. After 30 minutes at this temperature the solution was cooled to -30 ^oC and the epoxy alcohol **120** (2 g, 5.4 mmol) in ether 10 mL was added

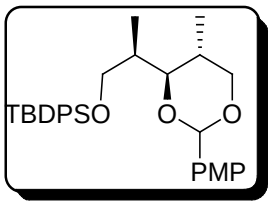
drop wise. After being stirred for 2 h at -30 ^{o}C, and then 1hour at -20 ^{o}C, the mixture was poured in to satutated aqueous NH_4Cl and the blue aqueous layer was thoroughly extracted with ether (3x10 mL). The combined organic layer were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The contamination of the 1,2 -diol was eliminated by exposing the crude reaction mixture to $NaIO_4$ followed by silica gel column chromatography (2:8, EtOAc/hexane) gave pure 1,3 diol **121** (1.81 g, 87%).



^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 7.66-7.61 (m, 4H),7.44-7.36 (m, 6H), 3.85-3.77 (m, 2H), 3.70-3.59 (m, 2H), 1.88-1.69 (m, 2H), 1.44-1.39 (m, 1H), 1.06 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.74(d, *J* = 7.5 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 135.6, 132.8, 129.8, 127.7, 80.4, 69.5, 68.8, 37.3, 36.2, 26.8, 19.1, 13.4, 9.1 ppm.
MASS (ESI-MS)	: *m/z* 409 $(M+Na)^{+}$.
HRMS (ESI)	: calcd. for $C_{23}H_{34}O_3SiNa$: 409.2174; found: 409.2179.
IR (Neat)	: 3420, 2960, 2930, 1427, 1109, 703 cm^{-1}.
$[\alpha]_D^{25}$	: -7.8 (*c* 2.5, $CHCl_3$).

tert-butyl((2R)-2-((4*R*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propoxy)diphenylsilane: 122

To a stirred solution of **121** (1.5 g, 3.88 mmol) and PTSA (65 mg, 0.38 mmol) in dry CH_2Cl_2 (50 mL), anisaldehyde dimethylacetal (0.9 mL, 7.76 mmol) was added at 0 °C and stirred at room temperature for 2 h. The reaction mixture was neutralized with Et_3N, solvent evaporated and the residue purified by column chromatography (60-120 Silica gel, 1:9 EtOAc:Hexane) to give **122** (1.5 g, 80%) as yellowish red syrup.



^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 7.66-7.55 (m, 4H), 7.38-7.15 (m, 8H), 6.84-6.79 (m, 2H), 5.35 (s, 1H), 4.11-4.05 (m, 1H), 3.80 (s, 3H), 3.77-3.70 (m, 1H), 3.53-3.43 (m, 3H), 2.08-1.98 (m, 2H), 1.05 (s, 9H), 0.86 (d, *J* = 6.9 Hz, 3H), 0.76(d, *J* = 6.7 Hz, 3H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 159.6, 135.5, 133.8, 131.5, 129.5, 127.5, 127.3, 111.3, 100.7, 81.1, 73.2, 65.2, 55.2, 36.4, 30.1, 26.8, 19.2, 12.0, 9.6ppm.
MASS (ESI-MS)	: *m/z* 527 $(M+Na)^+$.
IR (Neat)	: 3447, 2958, 2929,2855, 1247, 1107, 703 cm^{-1}.
$[\alpha]_D^{25}$	: -24.1 (*c* 2.0, $CHCl_3$).

(2*R*)-2-((4*S*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)propan-1-ol: 123

To a solution of **122** (1.5 g, 2.97 mmol) in dry THF (6 ml), TBAF (3.5 mL, 1 M in THF, 3.5 mmol) was added at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 4 h. It was quenched with saturated aqueous NH_4Cl solution, extracted with EtOAC, washed with brine, dried (Na_2SO_4) and concentrated *in vacuum*. The residue was purified by silica gel column chromatography (by eluting with hexanes-ethyl acetate, 9:1) to obtained the product **123** (0.71 g, 90%) as a colorless liquid.

^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 7.31 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.42 (s, 3H), 4.12-4.05 (m, 1H), 3.79 (s, 3H),

3.70-3.65 (m, 3H), 3.51-3.44 (m, 1H), 2.12-1.91 (m, 1H), 1.02 (m, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 159.8, 131.0,127.2, 113.5, 100.9, 84.5, 73.0, 66.5, 55.2, 35.5, 30.3, 11.8, 9.6 ppm.

MASS (ESI-MS) : *m/z* 266 $(M+Na)^+$.

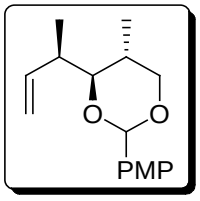
IR (Neat) : 3420, 2963, 2846, 1248, 1031, 828 cm^{-1}.

$[\alpha]_D^{25}$: -22.5 (*c* 1.5, $CHCl_3$).

(4*S*,5*R*)-4-((*R*)-but-3-en-2-yl)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxane: 99

To a stirred solution of alcohol **123** (1.0 g, 3.7 mmol) in CH_2Cl_2 (15 mL) was added Dess-Martin periodinane (2.37 g, 5.6 mmol), $NaHCO_3$ (62 mg, 0.74 mmol) at 0 ^oC and the reaction mixture was left to stir at room temperature. After 30 min, the reaction was diluted with hexanes (10 mL) and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography using hexane/EtOAc (90:10) to afford aldehyde as colorless liquid.

Methyltriphenylphosphonium iodide (6.1 g, 14.8 mmol) in THF (20 ml) at 0 °C was treated with *n*-BuLi (9.2 ml, 1 M in THF, 9.25 mmol), and the resulting solution was stirred at 0 °C for 30 min. The aldehyde in THF (10.0 ml) was added, at -20 °C and the mixture was allowed to stir at the same temperature for a period of 4h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined Et_2O fractions were washed with brine and dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluting with hexanes-ethyl acetate, 95:5) to afford compound **99** (780 mg, 80%) as a colorless liquid.



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.35 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.03-5.96 (m, 1H), 5.38 (s, 1H), 5.08-4.97 (m,

2H), 2.52-2.41 (m, 2H), 2.06-1.97 (m, 1H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 159.7, 142.3, 131.4, 127.2, 113.5, 113.4, 100.8, 85.9, 73.0, 55.2, 38.9, 30.9, 13.2, 12.2 ppm.

MASS (ESI-MS) : *m/z* 285 $(M+Na)^+$.

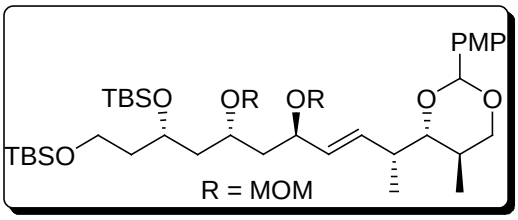
HRMS (ESI) : calcd. for $C_{16}H_{22}O_3Na$: 285.1466; found 285.1465.

IR (Neat) : 2962, 2928, 1516, 1248, 1034, 827 cm^{-1}.

$[\alpha]_D^{25}$: -33.2 (*c* 0.5, $CHCl_3$).

(5*R*,7*R*,9*S*)-9-((tert-butyldimethylsilyl)oxy)-7-(methoxymethoxy)-5-((3*R*,*E*)-3-((4*S*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)but-1-en-1-yl)-13,13,14,14-tetramethyl-2,4,12-trioxa-13-silapentadecane: 124

To a solution of **98** (100 mg, 0.197 mmol) in anhydrous Toluene (3 mL) under N_2, was added **99** (103 mg, 0.395 mmol, 2 equiv.). Catalyst **A** (16 mg, 0.0197 mmol, 0.1 equiv.) was added and the mixture was heating at 110 °C. After 20h, the solvent was evaporated under reduced pressure. Purification of the residual product by silica gel chromatography (AcOEt/Haxene2:8) afforded **124** (95 mg, 65%) as a colorless oil.



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.31 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 5.8 (dd, *J* = 7.5 Hz, 15.8 Hz, 1H), 5.35 (s, 1H), 5.34-5.26 (m, 1H), 4.68-4.41 (m, 4H), 4.44 (d, *J* = 6.7 Hz, 1H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.48-3.35 (m, 2H), 3.34 (s, 3H), 3.31 (s, 3H), 2.58-2.49 (m, 1H), 2.06-1.94 (m, 1H), 1.81-1.51 (m, 6H), 1.07 (d, *J* = 7.50 Hz, 3H), 0.88(s, 18H), 0.78 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 12H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 159.7, 137.5, 131.3, 129.5, 127.2, 113.4, 100.8, 96.0, 93.6, 85.9, 73.8, 72.9, 72.5, 66.4, 59.7, 55.6, 55.2, 43.5, 42.1, 40.1, 37.5, 30.8, 29.6, 25.9, 25.8, 18.5, 13.5, 12.2, -4.5, -5.3 ppm.

MASS (ESI-MS) : *m/z* 763 $(M+Na)^+$.

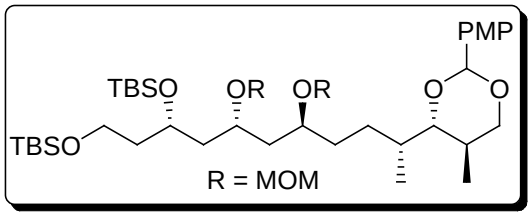
HRMS (ESI) : calcd. for $C_{39}H_{72}O_9Na\ Si_2$: 763.4612; found: 763.4625.

IR (Neat) : 2924, 2853, 1734, 1462, 1383, 1251, 1082, 1036, 832, 773 cm^{-1}.

$[\alpha]_D^{25}$: -23.8 (*c* 2.0, $CHCl_3$).

(5*S*,7*R*,9*S*)-9-((tert-butyldimethylsilyl)oxy)-7-(methoxymethoxy)-5-((3*R*)-3-((4*S*,5*R*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)butyl)-13,13,14,14-tetramethyl-2,4,12-trioxa-13-silapentadecane: 125

A suspension of olefin derivative **124** (100 mg, 0.134 mmol) and Raney-Ni (200 mg) in ethanol (4 mL) was flushed with hydrogen gas and stirred under hydrogen (20 psi) atmosphere at room temparature for 6 h. The reaction mixture was filtered through a plug of filter aid, washed with ethyl acetate thoroughly (3 × 10 mL), and concentrated. Purification of crude product by column chromatography (10% ethyl acetate in petroleum ether) yielded hydrogenated product **125** (90 mg, 90%) as a colorless oil. *Rf* = 0.3 (hexane/EtOAc 9:1).



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.33 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.36 (s, 1H), 4.63-4.55 (m, 4H), 4.06 (dd, *J* = 4.3 Hz, 15.8 Hz, 1H), 3.93-3.85 (m, 1H), 3.78 (s, 3H), 3.68-3.61 (m, 2H), 3.43 (t, *J* = 11.4 Hz, 1H), 3.36-3.31 (m, 8H), 2.09-1.94 (m, 1H), 1.81-1.45 (m, 8H), 1.31-1.24 (m, 4H), 0.96 (d, *J* = 6.1 Hz,

3H), 0.87 (s, 18H), 0.74 (d, *J* = 6.1 Hz, 3H), 0.06-0.02 (m, 12H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 159.7, 131.6, 127.3, 113.3, 100.0, 96.2, 95.9, 85.3, 75.4, 73.1, 72.9, 66.7, 66.5, 59.6, 55.6, 55.5, 43.6, 41.2, 40.3, 34.0, 33.3, 30.6, 29.7, 29.0, 26.0, 18.0, 13.2, 12.2, -4.3, -5.2 ppm.

MASS (ESI-MS) : *m/z* 765 $(M+Na)^+$.

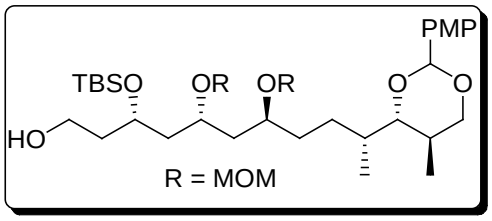
HRMS (ESI) : calcd. for $C_{39}H_{74}O_9Si_2Na$: 765.4763; found: 765.4754.

IR (Neat) : 3448, 2922, 2852, 1638, 1461, 1216, 1108, 760 cm^{-1}.

$[\alpha]_D^{25}$: -15.5 (*c* 2.0, $CHCl_3$).

(3*S*,5*R*,7*S*,10*R*)-3-((tert-butyldimethylsilyl)oxy)-5,7-bis(methoxymethoxy)-10-((4*S*,5*R*)-2-(4- methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)undecan-1-ol: 126

HF/pyridine in pyridine (4.0 mL, prepared by slow addition of 1.2 mL pyridine to 0.3 mL HF/pyridine complex, followed by dilution with 2.5 mL THF), from the liquor solution 0.5mL was added to a solution of TBS ether **125** (100 mg, 0.134 mmol) in THF (4 mL). The mixture was stirred overnight at room temperature and quenched with saturated $NaHCO_3$ (100 mL). The aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were washed with saturated $CuSO_4$ (3 × 10 mL), dried over Na_2SO_4, and concentrated. Flash column chromatography (EtOAc/hexane 1:9) afforded (72 mg, 85%) of alcohol **126** as colorless oil:



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.34 (d, *J* = 8.3 Hz, 2H), 6.83(d, *J* = 9.3 Hz, 2H), 5.37 (s, 1H), 4.69 - 4.54 (m, 4H), 4.07 (dd, *J* = 4.6 Hz, 2H), 3.80 (s, 3H), 3.77-3.61 (m, 2H), 3.44 (t, *J* = 11.1 Hz, 3H), 3.35 (s, 3H), 3.34 (s, 3H), 2.11-1.98

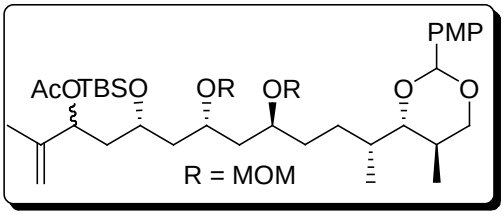
	(m, 2H), 1.92-1.48 (m, 6H), 1.47-1.23 (m, 6H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.90 (s, 9H), 0.75 (d, *J* = 6.5 Hz, 3H), 0.10 (s, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 159.7, 131.5, 127.2, 113.4, 100.9, 96.1, 95.9, 85.3, 75.4, 73.1, 68.7, 60.0, 55.6, 55.6, 55.2, 43.1, 41.2, 37.8, 33.9, 33.0, 30.6, 28.9, 29.6, 25.8, 13.1, 12.0, -4.4, -4.6 ppm.
MASS (ESI-MS)	: *m/z* 651 $(M+Na)^+$.
HRMS (ESI)	: calcd. for $C_{33}H_{60}O_9SiNa$: 651.3898; found: 651.3888.
IR (Neat)	: 3477, 2931, 2855, 1615, 1463, 1250, 1150, 1036, 833, 744 cm^{-1}.
$[\alpha]_D^{25}$	: -23.8 (*c* 1.0, $CHCl_3$).

(5R,7R,9S,12R)-5-((tert-butyldimethylsilyl)oxy)-7,9-bis(methoxymethoxy)-12-((4S,5R)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-2-methyltridec-1-en-3-yl acetate: 127

To a stirred solution of alcohol **126** (80.0 mg, 0.127 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin periodinane (80 mg, 0.190 mmol), $NaHCO_3$ (2 mg, 0.02 mmol) at 0 ^oC and the reaction mixture was left to stir at room temperature. After 30 min, the reaction was diluted with hexanes (5 mL) and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel chromatography using hexane/EtOAc (95:5) to afford aldehyde as colorless liquid, the aldehyde was used for the next reaction without any characterization.

To a stirred solution of aldehyde in THF was added Isopropenyl MgBr (0.25 mL, 0.5M, 0.25mmol) at -20 °C, the solution was stirred for 1 h at the same temperature and bring up to room temperature over 2 h. The reaction mixture was then quenched with sat. NH_4Cl (3 mL), and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with sat. $NaHCO_3$ (3 mL), water (5 mL), and brine (5 mL), dried over Na_2SO_4 and concentrated *via* rotary evaporation. The resulting oil was dissolved in pyridine (5

mL) and acetic anhydride (0.3 mL) was added. After stirring for 1 h, the flask was placed on the rotary evaporator at low pressure and the volume was reduced to about 1 mL. The crude oil was diluted with 1:1 hexanes-EtOAc (100 mL) and washed with Cu_2SO_4 (5 mL), H_2O (5 mL), $NaHCO_3$ (5 mL), H_2O (5 mL), and brine (5 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by flash plug chromatography (95:5 hexanes/AcOEt) to yield a diastereomeric mixture of allyl acetates **127** as colorless oil.



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.40 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 5.41 (s, 1H), 4.97 - 4.82 (m, 2H), 4.68-4.60 (m, 4H), 4.16-4.02 (m, 2H), 3.79 (s, 3H), 3.48 (t, *J* = 11.0 Hz, 2H), 3.36 (s, 6H), 2.40-2.29 (m, 4H), 2.18 (s, 3H), 2.12-1.99 (m, 6H), 1.88-1.55 (m, 8H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 9H), 0.75 (d, *J* = 6.7 Hz, 3H), 0.07 (s, 6H).

MASS (ESI-MS) : *m/z* 734 $(M+Na)^+$.

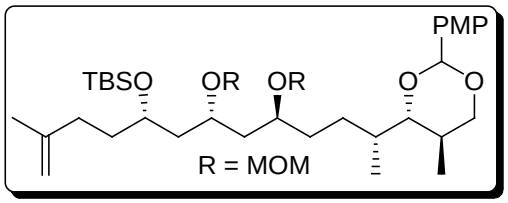
IR (Neat) : 2956, 2921, 2846, 1709, 1613, 1253, 1151, 1037, 833, 773 cm^{-1}.

$[\alpha]_D^{25}$: -18.6 (*c* 0.8, $CHCl_3$).

(5S,7R,9S)-7-(methoxymethoxy)-5-((3R)-3-((4S,5R)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)butyl)-11,11,12,12-tetramethyl-9-(3-methylbut-3-en-1-yl)-2,4,10-trioxa-11-silatridecane 97

Dioxane (2.0mL) was added to a mixture of ammonium formate (10 mg, 0.168) and $Pd(PPh_3)_4$ (5 mg, 0.0042 mmol) in a dry flask under argon atmosphere. PBu_3 (5 μL, 0.0212 mmol) was added and the mixture heated at reflux. The evolution of gas was observed prior to reaching reflux temperature. A solution of allyl acetates **127** (30 mg, 0.0422 mmol) in dioxane (2 mL) was added *via* cannula to the heated reaction mixture. The reaction was stirred at reflux for 3 hours, cooled to r.t, diluted with hexanes (10mL),

washed with H_2O, sat. $NaHCO_3$, brine, and dried over Na_2SO_4. Purification by flash chromatography (95:5 hexanes/AcOEt) yielded terminal olefin **97** (24 mg, 88%) as a colorless oil. No internal olefin could be detected by NMR spectroscopy



^{1}H NMR ($CDCl_3$ 300 MHz)	: δ 7.40 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.41 (s, 1H), 4.70 - 4.59 (m, 6H), 4.09 (dd, *J* = 4.6 Hz, 1H), 3.79 (s, 3H), 3.78-3.75 (m, 1H), 3.47 (t, *J* = 11.0 Hz, 2H), 3.36 (s, 6H), 2.37-2.29 (m, 4H), 2.08-1.95 (m, 6H), 1.87-1.78 (m, 2H), 1.71 (s, 3H), 1.68-1.41 (m, 4H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.74 (d, *J* = 6.6 Hz, 3H), 0.06 (s, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 159.7, 145.2, 131.6, 127.2, 113.4, 109.6, 100.9, 96.1, 95.8, 85.4, 75.4, 73.1, 72.9, 69.0, 55.6, 55.6, 55.2, 43.0, 41.1, 33.9, 33.2, 30.6, 29.0, 27.8, 25.9, 22.6, 18.0, 13.8, 12.0 -4.4 ppm.
MASS (ESI-MS)	: *m/z* 675 $(M+Na)^+$.
HRMS (ESI)	: calcd. for $C_{36}H_{64}O_8SiNa$: 675.4262; found: 675.4271.
IR (Neat)	: 2952, 2919, 2851, 1705, 1613, 1463, 1251, 1151, 1037, 833, 773 cm^{-1}.
$[\alpha]_D^{25}$	: -5.2 (*c* 0.8, $CHCl_3$).

REFERENCES

1. a) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. b) Chandrasekhar, S.; Reddy, B. V. S. *Synlett* **1998**, 851. c) Tateiwa, J.; Hashimoto, K.; Yamauchi, T.; Uemura, S. *Bull. Chem. Soc. Jpn*. **1996**, *69*, 2361.
2. a) Snider, B. B. Prins and Carbonyl-Ene Reactions: In Comprehensive Organic Synthesis; Trost, B. M. Ed.; Pergamon: Oxford, **1991**, *Vol, 2*, pp 527-561. b) Aggarwal, V. K.; Vennall, G. P.; Davey, P. N.; Newman, C. *Tetrahedron Lett.* **1998**, *39*, 1997. c) Tateiwa, J.; Kimura, A.; Takasuka, M. ; Uemura, S. *J. Chem. Soc. Perkin Trans*. *1*, **1997**, 2169.
3. Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479.
4. a) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc*. **2001**,*123*, 9033-9044. b) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. . *J. Am. Chem. Soc*. **2003**, *125*, 6650-6652.
5. Lolkema, L. D. M.; Hiemstra, H.; Mooiweer, H. H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 6365-6368
6. a) Roush, W. R.; Dilley, G. J. *Synlett* **2001**, 955-959. b) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426-3427. c) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115-7128. d) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129-7140.
7. a) Miranda, P. O.; Díaz, D. D.; Padron, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979-1982. b) Dobbs, A. P.; Guesné, S. J. J.; Martinovič, S.; Coles, S. J.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880-7883. c) Dobbs, A. P.; Martinovič, S. *Tetrahedron Lett.* **2002**, *43*, 7055-7057. d) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679-4686
8. a) Blumenkopf, T. A.; Bratz, M.; Castañeda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386-4399. b) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 277-279.
9. Wei, Z. Y.; Li, J. S.; Wang, D.; Chan, T. H. *Tetrahedron Lett.* **1987**, *28*, 3441.
10. Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 913.

11. Yang, X. F.; Li, C. J. *Tetrahedron Lett.* **2000**, *41*, 1321.
12. Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2001**, *123*, 8420.
13. Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271.
14. a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. b) Molinski, T. b) *Tetrahedron Lett*. **1996**, *37*, 7879. c) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271.
15. Marko, I. E.; Chelle, F. *Tetrahedron Lett.* **1997**, *38*, 2895.
16. a) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3023. b) Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc.* **1997**, *119*, 2058.
17. Perron, F.; Albizati, *J. Org. Chem.* **1987**, *52*, 4130.
18. (a) Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett*. **2003**, *5*, 2429-2432; (b) Yang, X. -F.; Mague, J. T.; Li, C. -J. *J. Org. Chem.* **2001**, *66*, 739-747; c) Zhang, W. C.; Li, C, J. *Tetrahedron* **2000**, *56*, 2403. (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N. *J. Mol. Catal. A: Chem.* **2004**, *210*, 99-103; e) Yadav, J. S.; Reddy, B. V. S.; Sekhar, K. C.; Gunasekar, D. *Synthesis* **2001**, *6*, 885-888;
19. Rychnovsky, S. D.; Powell, N. A. *J. Org. Chem*. **1997**, *62*, 6460-6461.
20. Obringer, M.; Colobert, F.; Neugnot, B.; Solladie, G. *Org. Lett*. **2003**, *5*, 629-632.
21. BouzBouz, S.; Cossy, J. *Org. Lett*. **2000**, *2*, 501-504.
22. (a) Chakraborty, T. K.; Dutta, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1257-1259. (b) Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2002**, *43*, 2313-2315.
23. Kiyooka, S.; Yamaguchi, T.; Maeda, H.; Kira, H.; Hena, M. A.; Horiike, M. *Tetrahedron Lett.* **1997**, *38*, 3553-3556.
24. Ojika, Ms; Nagoya, T; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491.
25. Suenaga, K.; Nagoya, T.; Shibata, T; Kigoshi, H; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155.
26. Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796.
27. Hanson, P.R.; Rambabu, C.; Nguyen, J.; Thomas, C. D.; Waetzig, J. D.; Whitehead, A.; *J. Org. Chem*. 2011, *76*, 4358.
28. Roux, R. L.; Desroy, N.; Phansavath, P.; Genet, J. P. *Synlett*, **2005**, 429.

29. Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911.

30. Vincent, A.; Prunet, J.; *Synlett*, **2006**, 2269.

31. Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *68*, 6776-6777.

32. Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133−2136.

33. (a) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397−4401. (b) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4937−4941. (c) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4995−4998. (d) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Synlett* **2007**, 2049−2052. (e)) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133-2136. (f) Yadav, J. S.; Rao, P. P.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2008**, *49*, 5427-5430, and the references cited therein.

34. Chan, K. P.; Seow, A. H.; Loh, T. P. *Tetrahedron Lett.* **2007**, *48*, 37–41.

35. (a) Gerspacher, M.; Rapoport, H.; *J. Org. Chem.* **1991**, *56*, 3700. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.

36. a) Stork, G.; Takahashi, T.; *J. Am. Chem. Soc.* **1977**, *99*, 1275. b) Askin, D.; Volante, R. P.; Reamer, R. A.; Ryan, K. M.; Shinkai, I.; *Tetrahedron Lett.* **1988**, *29*, 277.

37. (a) Criegee, R. *Angew. Chem., Int. Ed. Engl*. **1975**, *14*, 745-752. (b) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1; 1982; Vol. 2. (c) Kuczkowski, R. *Chem. Soc. Rev*. **1992**, 79-83.

38. (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J.Am. Chem. Soc.* **1987**, *109*, 5765-5780 (b) Johnson, R. A.; Sharpless, K. B. In *CatalyticAsymmetric Synthesis*, Ojima, I., Ed.; VCH: New York, **1993**; 103-158.

39. (a) Ma, P.; Martin, V, S.; Masamune, S.; Sharpless, K. B.; Viti, S, M. *J. Org. Chem.* **1982**, *47*, 1378-1380. (b) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719-2722. (c) Viti, S. M. *Tetrahedron Lett.* **1982**, *23*, 4541-4544.

40. Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladourus, E. A.; Abe, Y.; Carroll, O. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040-3054.

41. Chandrasekhar, S.; Mahipal, B.; Kavitha, M. *J. Org. Chem*. **2009**, *74*, 9531.

42. Zakharkin, L. L.; Khorlina, I. M.; *Tetrahedron Lett.* **1962**, *3*, 619.

43. Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem*. **2004**, *116*, 4441.

44. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.

45. Wittig, G.; Geissler, G.; *Liebigs Ann*. **1953**, 44–57.

46. For a recent review on cross-metathesis, (a) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H.; *J. Am. Chem. Soc*. **2003**, *125*, 11360 (b)BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465; (c) Comin, M. J.; Parrish, D. A.; Deschamps, J. R.; Marquez, V. E. *Org. Lett.* **2006**, *8*, 705; (d) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900; (e) Hoveyda, A. H.; Gillingham, D. G.; Van Veldhuizen, J. J.; Kataoka, O.; Garber, S. B.; Kingsbury, J. S.; Harrity, J. P. A. *Org. Biomol. Chem.* **2004**, *2*, 8;

47. Vincent, A.; Prunet, J.; *Tetrahedron Lett.* **2006**, *47*, 4075.

48. (a) Shin, Y.; Fournier, J. H.; Bruckner, A.; Madiraju, C.; Balachandran, R.; Raccor, B. S.; Edler, M. C.; Ernest Hamel, E.; Sikorski, R. P.; Vogt, A.; Daya, B. W.; Curran, D. P.; *Tetrahedron* **2007**, *63*, 8537. (b) Joo, J. M.; Kwak, H. S.; Park, J. H.; Song, H. Y.; Eun Lee; *Bioorganic & Medicinal Chemistry Letters*, **2004**, *14*, 1905.

49. Tsuji, J.; Yamakawa, T.; *Tetrahedron Lett.*, **1979**, 20, 613.(b) Alexander, M. D.; Fontaine, S. D.; La Clair,J. J; DiPasquale, A. G.; Rheingold, A. L.; Michael D. Burkart, M. D.; *Chem. Commun.*, **2006**, 4602–4604.(c) Das, P. P.; Lysenko, I. L.; Cha, J. K.; *Angew. Chem. Int. Ed.*, **2011**, *50*, 9459.

CHAPTER II: SECTION A

Introduction and previous approaches to Siphonarienal, Siphonarienone and Pectinatone.

INTRODUCTION

The greatest biodiversity on Earth is found in the world's oceans, which cover greater than 70% of earth's surface.[1] They contain more than 300 000 described plants and animals[2] which represents approximately 75% of all living organisms, with 34 of the 36 phyla of life present. Many marine organisms are soft bodied and have a sedentary life style necessitating chemical means of defense. To resist the ecological pressures, they have evolved the ability to synthesize toxic compounds or to obtain them from marine microorganisms. These compounds help them deter predators, competition for space, fouling of the surface; predation and successfully reproducing have required these species to develop chemical defense systems in addition to various physical defense systems they possess. Several of these compounds show pharmacological activities and are helpful for the invention and discovery of bioactive compounds, primarily for deadly diseases like Cancer, Acquired Immuno-Deficiency Syndrome (AIDS), Arthritis etc., while other compounds have been developed as analgesics or to treat inflammation etc., The live saving drugs are mainly found abundantly in micro-organisms, algae and invertebrates, while they are scarce in vertebrates. Modern technologies have opened vast areas of research for the extraction of biomedical compounds from Oceans and Seas.[1]

"Poison kills the poison", the famous proverb is the basis for researchers in finding the biomedical metabolites from living organisms. Natural products released into the water are rapidly diluted, highly potent, immense biological diversity in the sea as a whole, it is increasingly recognized that a huge number of natural products and novel chemical entities exist in the oceans, with diverse biological activities that may be useful in finding drugs with greater efficacy and specificity for the treatment of many human diseases.

Marine organisms have provided a array of novel structures since the launch of marine natural product chemistry in the late 1960s-1970s. The catalyst for the search for pharmaceutical products from the ocean came in 1969 when Weinheimer and Spraggins[3] discovered large quantities of the prostaglandins, in the gorgonian coral *Plexaura homomalla*. Interest in the search for drugs from the sea was stimulated because the prostaglandins had previously been identified as important mediators involved in

managing inflammatory diseases, pain and fever. Following this discovery three dominant areas of research quickly emerged in marine natural products chemistry; marine toxins, marine biomedicines and marine chemical ecology, which will each be discussed.

Marine toxins

Majority of marine toxins have large polyether structures, which have been described as "ladder-like", for example brevetoxin B (Figure 1). Some of these toxins pose a significant risk to human health. Paralytic and diarrhetic toxins accumulate in the flesh of filter feeders and in some tropical fish when they feed on dinoflaggelates which produce the toxins. Amnesic shellfish[4] poisoning is a serious condition arising when shellfish contaminated with diatoms are ingested.[5] An example of such poison is domoic acid, produced by the diatom *Psedonitzschina pungens* forma *multiseries*, which causes gastrointestinal symptoms and in more severe cases of poisoning, neurological disorders, coma or even death.

Figure 1

MARINE ORGANISMS AS POTENTIAL SOURCE OF DRUGS:

The isolation and characterization of marine natural products has been focused over the past 30 years in search for bioactive active compounds. A large number of marine-derived natural products have progressed to preclinical and clinical trials for assessment in treating a range of conditions such as cancer, pain, neuropathic pain, epilepsy, inflammation and asthma. However, many do not progress to development as commercial drugs due to formulation problems, undesirable side effects or inactivity. The journey of a potential drug target from identification and structural elucidation through to

clinical trials can be extremely long so there are a significant number of compounds currently under investigation as potential pharmaceutical drugs.

In this review, the examples given of pharmacologically active compounds which are under clinical and preclinical trials, range of structures reported and also the variety of marine animals, plants and microorganisms from which they have been isolated.

ANTI-MICROBIAL COMPOUNDS:

The cephalosporins are good examples of drugs which owe their origin to a marine source. From the marine fungus, *Cephalosporium acremonium*, Cephalosporin C (Figure 2) was isolated. A semi-synthetic derivative of this, cephalothin sodium, has been widely used as an antibiotic drug. Istamycins are reported to have invitro activity against both gram-negative and gram-positive bacteria, including those with known resistance to the amino-glycoside antibiotics.[6]

Figure 2

ANTIVIRAL COMPOUNDS:

Many marine organisms have been screened for antiviral activity and a wide range of active compounds has been isolated and characterized. However, the only compound reported to have significant therapeutic activity is ara-A,[7](Figure 3) which is a semi-synthetic substance based on the arabinosyl nucleosides isolated from the sponge *Tethya Crypta*. Other antiviral compounds include Avarol and Avarone (Figure 3) inhibit the immunodeficiency virus, have high therapeutic indices and the ability to cross the blood-brain barrier.

Figure 3

CYTOTOXIC COMPOUNDS:

Many of the compounds isolated from marine organisms have been tested for cytotoxicity in the search for drugs active against cancer. Several established cancer drugs are DNA interactive agents. These compounds, including the platinum drugs cisplatin and carboplatin, are characterized by strong cytotoxic activity, but they also show a total lack of specificity for cancer verses normal cells. ET743[8] (Yondelis [TM]) is a marine natural product, which is under clinical trials, distinguish the both normal and cancer cells. ET743 is one of a family of tunicate derived anti-tumor compounds originally isolated from ecteinascidins, named after *Ecteinascidia turbinata,* a colonial ascidian. Other cytotoxic compounds, source of origin and status of the compounds are listed below.

Figure 4

ANTI-INFLAMMATORY COMPOUNDS:

A variety of inflammatory diseases are due to the production of arachidonic acid, the precursor of prostaglandins and leukotrienes. The quintessential marine-sourced compound that exhibited anti-inflammatory agent was the sponge metabolite manolide.[10] (Figure 5) this compound was originally isolated from the marine sponge *Luffariella variabilis*, a potent inhibitor of the enzyme phospholipase $A_{2,}$ which is intimately involved in the initial step of the inflammatory response. The other compound, which shows anti-inflammatory activity, is IPL576092, [11](Figure 5) a synthetic analogue of the steroid contignasteron isolated from the sponge *Petrosia contignata* is in phase II clinical trials as a leukocyte-suppressing anti-inflammatory drug.

Figure 5

ANTI-PARASITIC COMPOUNDS:

Digenia simplex, a red alga, has been used as a vermifuge for very many years. Its active component, α-Kainic acid,[12] is marketed for the treatment of parasitic round worm, whip worm and tape worm. Marine animals have been tested as source of anti-parasitic compounds for example, Bengamide F[13] which has anthelmintic properties. (Figure 6)

Figure 6

Chemical Ecology:

Studies on marine chemical ecology comprise the remaining area of research in marine natural products chemistry. A large proportion of bioactive products are isolated from soft-bodied, sessile or slow moving marine invertebrates which lack physical defence system such as shells or spines. For this reason biosynthesis or bioaccumulation of bioactive compounds can enhance the survival of the producing organism. Some algal metabolites use chemical defence to combat predation. Shellless molluscs were able to evolve from their shelled counterparts due to their ability to store defensive chemicals biosynthesized by the organisms ingested. In sessile organisms metabolites are also thought to act as anti-fouling agents. The chemical defensive agents employed by marine organisms are highly potent perhaps accounting for the significant number of these compounds entering clinical trials. Upon excretion by the organism these agents are heavily diluted by sea water, thus their elevated potency overcomes this problem.[14] The generally accepted reason for the presence of such a variety of bioactive compounds within marine organisms is chemical defence. However, relatively little is known about the exact mode of action of these compounds or their biosynthesis/bioaccumulation within the organism. Numerous reviews of research in each of these areas, in particular marine biomedicinals, have been, and continue to be, published each year.

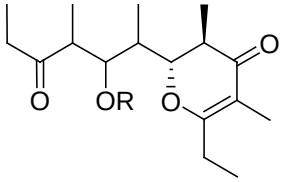
MARINE POLYPROPIONATE NATURAL PRODUCTS:

Marine natural products derived from polyketides and polypropionates have attracted a lot of attention during the past 50 years and a great deal of research has concerned itself with their isolation, biological activity, biogenesis and total synthesis. These polypropionates represent a diverse array of structurally complex compounds, having a wide range of biological activity (typically antibiotic, antimicrobial, antifungal,

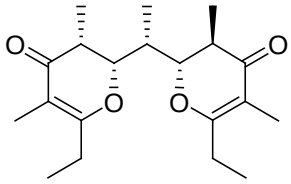
antitumour, antiparasitic or immuno modulatory action). Polypropionate subunits are aliphatic chains bearing alternating hydroxyl and methyl groups with distinct stereochemistry.

The original role of these bioactive substances has been considered to be a defensive function from predators, prevention of fouling, inhibition of over growth, and protection from ultraviolet radiation.

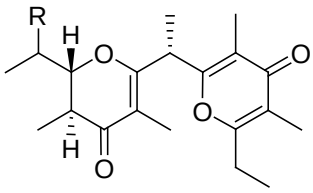
Polypropionates are typified by the macrolide antibiotics and many such compounds are important medicines. This class includes a number of compounds isolated from molluscs of the genus Siphonaria, including baconipyrone, siphonarin, denticulatin and muamvatin. The biological activity (typified by the macrolide antibiotics) often exhibited by this class of compounds makes these compounds important targets for stereo selective synthesis. These natural products (Membrenones,[15] Vallartanones,[16] Denticulatins,[17] Auripyrones[18] and Siphonarines[19])are characterized by possessing highly oxygenated linear carbon chains with methylation at alternate carbons.



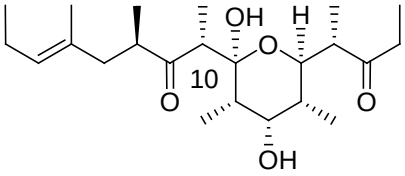
Membrenone A (R = (R)-2-methylbutyryl)
Membrenone B (R = propionyl)



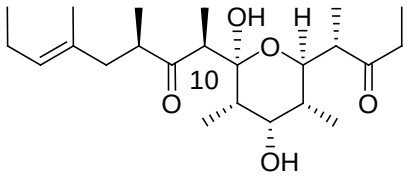
(+)-Membrenone C



Vallartanone A : R = CH_3
Vallartanone B : R = H



Denticulatin A



Denticulatin B

Figure 7

There are many naturally occurring deoxypolypropionates have been isolated and a broad range of biological activities are associated with these deoxypropionates. Different structural deoxypropionates have been reported so far e.g.; cytostatics: Borrelidin[20] and Doliculide,[21] pheromones: Lardolure,[22] waxes: 4,6,10,16,18-hexamethyldocosane,[23] and virulent markers: PDIM A,[24] calcium ionophores: Ionomycin,[25] Siphonarienolone[26] and TMC-151A[27]. A wide variety of synthetic methods for the construction of polypropionates has been described over last decades, especially the aldol condensation based on chiral auxiliary, developed by Evans and others. This strategy contributed to a large extent to the synthesis of polypropionates.[28,29] Many synthetic strategies have also been developed for deoxypropionate units because of its abundant presence in natural products. These strategies are often based on the selective introduction of methyl subunits in a consecutive (iterative) fashion, either *syn* or *anti*, and can be divided into two catagories: non-catalytic and catalytic pathways.

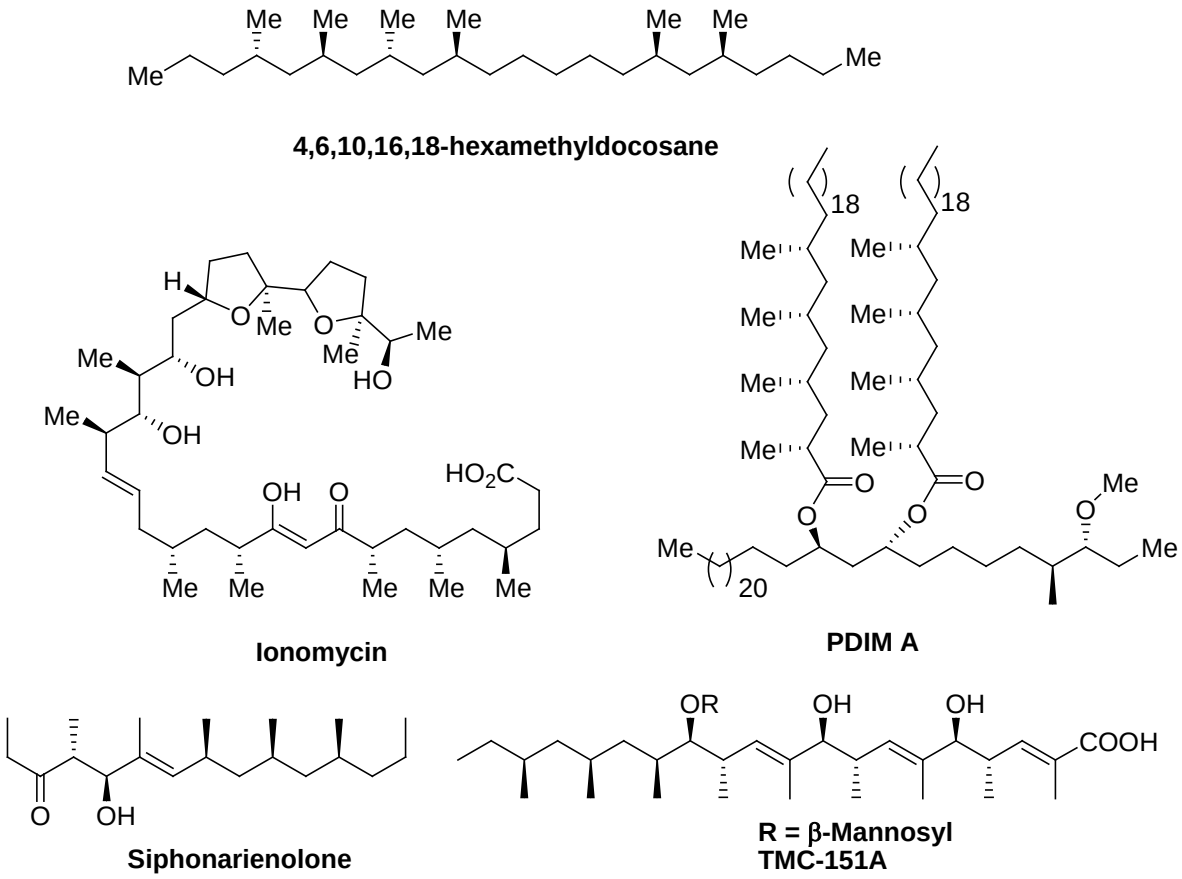


Figure 8

Siphonarienes and Pectinatone:

Figure 9

Marine molluscs of the genus *Siphonaria* is the rich source of polypropionates,[30] polyether antibiotics[31] and macrolides.[32] Natural products derived from marine mollusks

gained interest for their bio-active secondary metabolites[33] and unusual structures. Siphanarienes **1**,2 and Pectinatone **3** are marine polypropionate natural products produced from the genus *Siphonaria* such as *Siphonariea grisea*[34] and *Siphonaria pectinata*[35] respectively collected from intertidal region of the Mediterranean sea and Atlantic ocean.

They are active against Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), yeast (*Candida albicans* and *Saccharomyces cervisiae*) and several human cancer cell lines.[34b,37] The structures of **1**, **2** and **3** were established on the basis of their spectroscopic data and X-ray diffraction analysis.[34a,38] The members of this class all contain an alternating 1,3-*syn* arrangement of methyl substituents with an *S* configuration in their respective aliphatic chains connected through an olefinic linker to a more polar oxygen containing group.[36] This structural motif offers a significant challenge for asymmetric synthesis.

Previous synthetic approaches of polypropionates 1, 2 and 3:

Teck-Peng Loh's Catalytic Asymmetric Conjugate Addition approach for the synthesis of Siphonarienal and Siphonarienone:

Teck-Peng Loh *et al*.[39] reported from commercially available methyl *trans*-2-hexenoate (**4**), the first methyl stereogenic center was installed using (*S*)-Tol-BINAP to give methyl ester (**5**) in 68% yield (Scheme 1).

Scheme 1

Reagents and conditions: (a) MeMgBr, CuI, *S*-Tol-BINAP, *t*-BuOMe, -20 °C, 68%;(b) DIBAL-H, hexane, -78 °C, 1.5 h; (c) $MeO_2CCH=PPh_3$, THF, reflux, 7 h, 64%; (d) MeMgBr, CuI, *S*-Tol-BINAP, *t*-BuOMe, -20 °C, 66%; (e) DIBAL-H, hexane, -78 °C, 1.5 h; (f) $MeO_2CCH=PPh_3$, THF, reflux, 7 h, 58%; (g) MeMgBr, CuI, *S*-Tol-BINAP, *t*-BuOMe, -20 °C, 68%; (h) Br_2; (i) DIBAL-H, hexane, -40 °C, 2 h; (j) Zn, AcOH, THF, reflux, 16 h, 44%; (k) O_3, CH_2Cl_2, -78 °C, 30 min, then Me_2S; (l) $PPh_3P(Me)CCO_2Me$, DCE, reflux, 14 h, 42%; (m) DIBAL-H, hexane, 0 °C, 1.5 h; (n) IBX, DMSO, rt, 4 h, 63% (o) MeNHOMe.HCl, ^{i}PrMgBr, THF, -20 °C 1.5 h; (p) EtMgBr, THF, rt, 16 h, 67%.

After the one-pot DIBAL-*H* reduction, Wittig olefination protocol to (*E*)-enoate (**6**) (64% yield), the second stage methyl addition was performed under the same catalytic conditions to afford the *syn*- deoxypropionate unit (**7**). The similar elongation protocol furnished the second (*E*)- enoate (**8**).

The third and final stage methyl addition using (*S*)-Tol-BINAP was modified by using neat bromine as an enolate trapping reagent to effect the following one- carbon dehomologation. Without further purification, the α-bromomethyl ester (**9**) obtained was reduced to the alcohol using DIBAL-H, and this reduced alcohol was used without further isolation for the next step. Treating this alcohol in THF with zinc dust and glacial acetic acid gave the terminal olefin (**10**). A one-pot ozonolysis and Wittig olefination protocol gave the α,β-unsaturated ester (**11**). No epimerization of the third methyl

stereogenic center was observed by comparing the ^{13}C NMR to a diastereomeric mixture of the same α,β-unsaturated ester. From the α,β-unsaturated ester (**11**), a two-step DIBAL-H reduction and IBX oxidation furnished Siphonarienal (**1**). Likewise, from α,β-unsaturated ester (**11**), the application of Weinreb's ketone synthesis using MeNHOMe.HCl with ^{i}PrMgCl followed by treatment of the Weinreb amide with EtMgBr in THF gave Sipharienone (**2**)

Ei-ichi Negishi's Zr-Catalyzed Asymmetric Carboalumination approach for the synthesis of Siphonarienal and Siphonarienone:

Ei-ichi Negishi *et al.*[40] developed an efficient and general method for the synthesis of reduced polypropionates *via Zr*-catalyzed asymmetric carboalumination application to the synthesis of a couple of structurally related siphonarienes, i.e., Siphonarienal (**1**) and Siphonarienone (**2**).

All previous syntheses of **1**-**3** and other related siphonarienes have employed (2*S*,4*S*,6*S*)-2,4,6-trimethyl-1-nonanol (**16**) and/or the corresponding aldehyde (**17**) as key intermediates. The *Zr*-catalyzed asymmetric carboalumination method recently developed has provided (2*S*,4*S*,6*S*)-2,4,6-trimethyl-1-nonanol (**16**) in 23% overall yield over seven (or six isolation) steps from 3-buten-1-ol (**12**), as shown in Scheme 2.

Scheme 2

Reagents and conditions: (a) $^{n}Pr_3Al$ (2.5 eq), IBAO, 5% (+)-$(NMI)_2ZrCl_2$, (b) H_3O^+, 88%; (c) Swern oxid.; (d) $Ph_3P{=}CH_2$, 84%; (e) Me_3Al (1.5 eq), MAO (0.3 eq), % (+)-$(NMI)_2ZrCl_2$, then O_2, 79%; (f) Iodination; (g) Pd-cat. Vinylation; (h) Swern oxid.; (i) *s*-

BuLi, THF, -78 °C to -20 °C, 1 h, and then CF_3CO_2H, 0 °C, 85%; (j) EtMgBr, THF; (k) Dess-Martin periodinane.

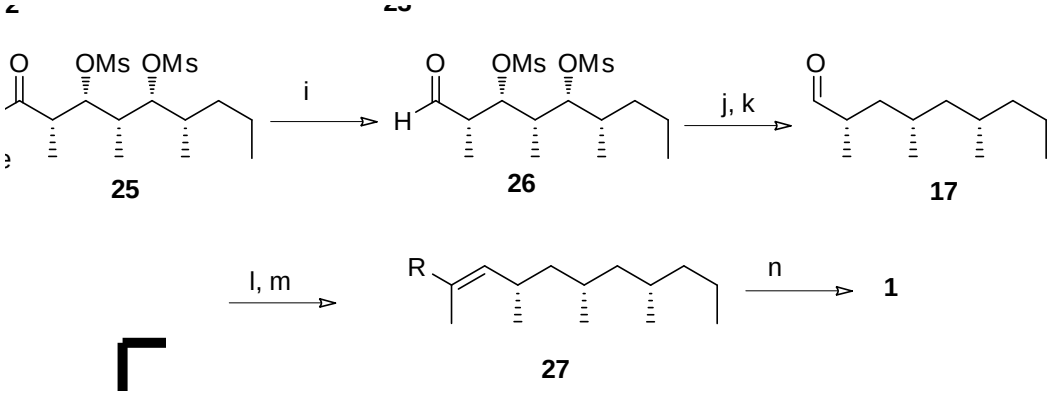
(3*S*)- 3-Methyl-1-hexanol (**13**) was prepared from 3-buten-1-ol in one step. The alcohol thus obtained was used without enantiomeric separation to prepare (2*S*,4*S*)-2,4-dimethyl-1- heptanol (**15**). A three-step protocol consisting of iodination, Pd-catalyzed vinylation, and *Zr*-catalyzed asymmetric carboalumination-oxidation furnished (**16**) in 46% combined yield over three steps.

Oxidation of **16** with $(COCl)_2$, DMSO and Et_3N produced the corresponding aldehyde (**17**). Without isolation-purification, it was treated with 1.3 equiv of $Et_3SiCH(Me)CHNCy$ and BuLi (1.2 equiv) in THF at -78 to 20 °C for 1 h. The reaction mixture was quenched with CF_3COOH at 0 °C in THF to give Siphonarienal (**1**) in 85% yield over two steps (Scheme 3). Conversion of Siphonarienal (**1**) into Siphonarienone (**2**) was achieved by the reaction of **1** with EtMgBr in 88% yield, followed by oxidation with Dess-Martin periodinane in 90%.

Michael A. Calter's Catalytic, Asymmetric approach for the synthesis of Siphonarienal

Michael A. Calter *et al*[41] describes the synthesis of the marine natural product, Siphonarienal. The key step of this synthesis is an aldol reaction that constructs most of the skeleton and sets all three stereocenters of the target in one step from commercially available starting materials.

Deoxygenation and chain homologation steps complete the synthesis of **1**, however, starts with a catalytic, asymmetric reaction. They preveously reported a convenient procedure for the conversion of propionic anhydride to polypropionates by a ketene formation/dimerization/opening/aldol reaction sequence, and that a similar sequence of deoxygenation and homologation afforded Siphonarienal (**1**).



Scheme 3

Reagents and conditions: (a) HN(OMe)Me, 5 mol% Py, THF, 0 °C; (b) $Zn(OTf)_2$, $NaBH_4$, THF, -78 °C; (c) CS_2, MeI, NaH, THF, 0 °C, 86%; (d) Bu_3SnH, AIBN, Toluene, 110 °C, 96%; (e) DIBAL-H, Et_2O, -78 °C, 75%; (f) LiN(OMe)Me, **18**, THF, -78 °C, 55%; (g) $Zn(BH_4)_2$, Et_2O, -78 °C, 71%; (h) MsCl, Py, DMAP, CH_2Cl_2, 89%; (i) $LiAlH_4$, THF, -78 °C; (j) $LiAlH_4$, Et_2O, -78 °C - 0 °C; (k) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 92%; (l) $Ph_3P=C(CH_3)CO_2Et$, Toluene/CH_2Cl_2, reflux, 81%; (m) DIBAL-H, CH_2Cl_2, -78 °C, 90%; (n) MnO_2, Hexane, 95%.

Dieter Enders Iterative Alkylation Approach for the total synthesis of Pectinatone by SAMP-Hydrazone Method:

Dieter Enders *et al.*[42] in 1998 reported first total synthesis of Pectinatone *via* iterative alkylation of propanal SAMP-hydrazone with β-branched iodides.

Scheme 4

Reagents and conditions: (a) LiTMP, THF, 0.5M, 0 °C, 45 min; (b) *n*-propyl iodide, -78 °C; (c) Mel, reflux, 90 min then 4N HCl,pentane, 90 min.; (d) $BH_3.Me_2S$, 0 °C, then MeOH and HCl; (e) 4-nitrophanyl sulfonyl chloride, pyridine, DMAP, CH_2Cl_2, rt; (f) LiI, THF, 1 M, rt, 3 h, then pentane and -78 °C; (g) hydrazone **28**, (a) and inverse addition -78 °C; (h) $Ph_3PC(CH_3)CO_2Et$, toluene, reflux, 5 h; (i) *N*-methoxy, *N*-methyl amine.HCl, ^{i}PrMgCl, THF, -20 °C - 0 °C, 64%; (j) LDA, THF, 0 °C, $CH_3CH_2COCH(CH_3)CO_2Et$, inverse addition, then DBU, toluene, reflux, 3 h, 29% overall (35% recovered starting material) and 20% amide.

The highly reactive aza-enolates derived from SAMP hydrazones react readily with secondary iodides and β-branched iodides and bromides at low temperatures. The hydrazone **28**, derived from propanal was utilised as the source of the methyl stereogenic center. Generation of the aza-enolate, alkylation, hydrazone cleavage, reduction to the alcohol and finally conversion into the iodide **32** gives the first methyl stereocenter. Further iteration generates the 'skip' 1,3-motif **34** (Scheme 1). Treatment of the hydrazone **28** with lithium tetramethylpiperidide (LiTMP) gave complete deprotonation. Alkylation of the aza-enolate with *n*-propyl iodide at - 78 °C gave the hydrazone **29**. Reduction of the aldehyde was conveniently carried out using borane dimethyl sulfide complex. The alcohol **30** was directly derivatised as the nosylate **31**.

The *insitu* conversion of the sulfonate **31** to the iodide **32** and subsequent alkylation would prove useful in the manipulation of volatile alkyl iodides as compared

with the usual PPh_3, I_2, imidazol protocol. Employing, the crystalline nosylate **31**, iodide displacement occurred rapidly at ambient temperature in THF. Inverse addition of the aza-enolate of **28** to a solution of the *in situ* iodide **32** gave the desired hydrazone **33**. Quaternization, acidic hydrolysis and subsequent reduction gave the alcohol which was converted into the nosylate **34** in 32% overall yield from **31**. *Insitu* conversion into the iodide as before, alkylation with the aza-enolate derived from **28**, quaternization, acidic hydrolysis and then reaction with phosphorane gave the α,β-unsaturated ester **27**. Conversion of **27** into the Weinreb amide as an intermediate Weinreb amide was used in generation of the β-ketoester dianion of dialkylated acetoacetate ester using LDA and addition to the amide at 0 °C occurred smoothly to give the tricarbonyl intermediate. Treatment of the crude reaction mixture with DBU in boiling toluene to affect cyclization to the α-pyrone gave Pectinatone (**3**) (Scheme 4).

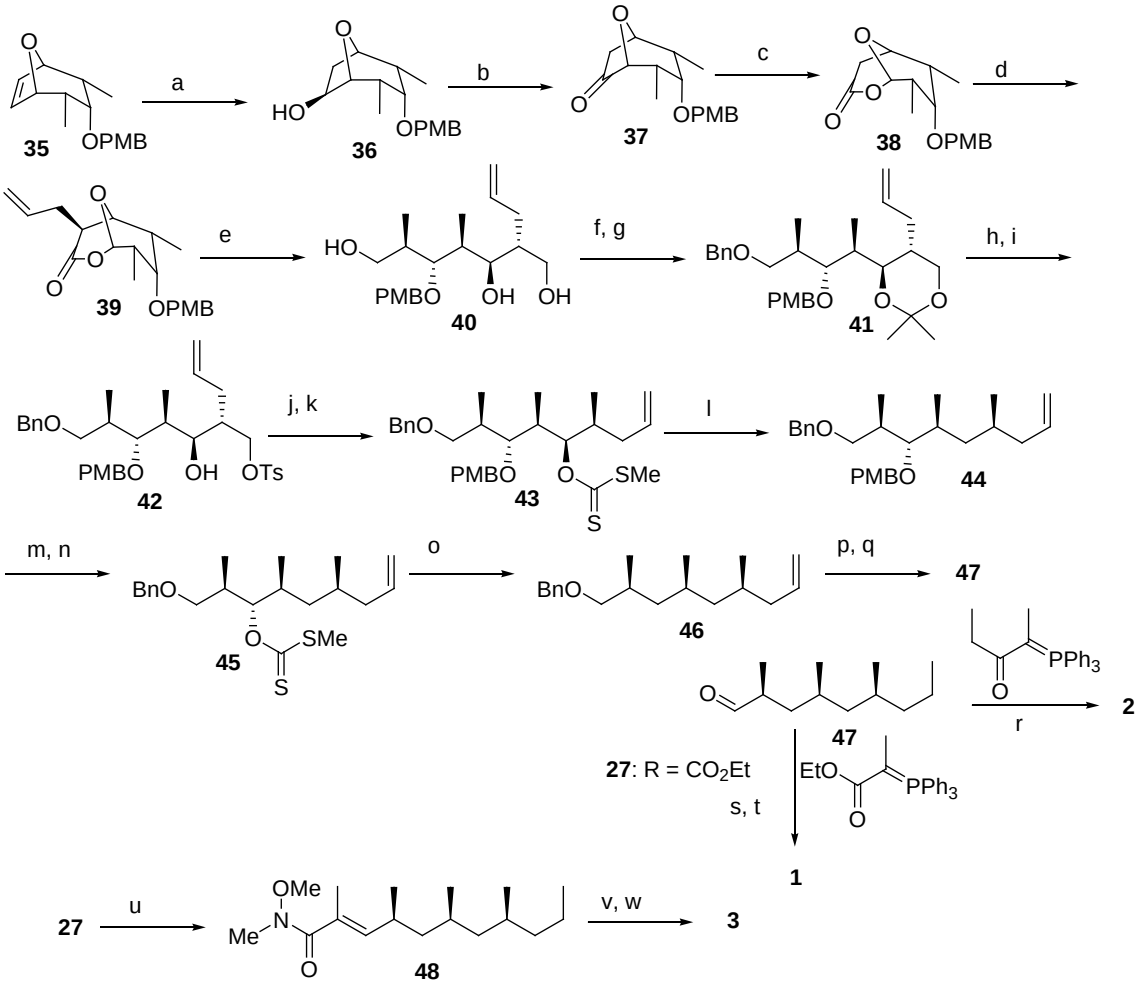
Gowravaram Sabitha's Desymmetrization approach for the synthesis of Siphonarienal, Siphonarienone and Pectinatone

G. Sabitha *et al*.[43] reported the total synthesis of all the three natural products by using desymmetrization method.

Accordingly, allylation of **38** with allyl bromide in the presence of LHMDS in anhydrous THF at -78 °C gave compound **39**. Reductive ring opening of **39** with LAH in THF gave triol **40**. The 1,3-diol of **40** were protected as acetonide using 2,2-dimethoxypropane and a catalytic amount of CSA, in CH_2Cl_2/Et_2O followed by protection of the primary hydroxyl group as its benzyl ether **41**. Then, the acetonide group was hydrolyzed to diol and the primary hydroxyl group was selectively tosylated with TsCl, Et_3N, and DMAP in CH_2Cl_2, followed by reductive cleavage ($LiAlH_4$, THF, 80%) of the sulfonate, and the secondary hydroxyl group was converted into the xanthate ester and reduced to compound **44**. The PMB group has deprotected oxidatively using DDQ, which was converted to the xanthate and reduced to compound **46**. Debenzylation and reduction of the terminal olefin were successfully achieved in one-pot using Pd/C and H_2, in EtOAc to produce alcohol, which on oxidation using IBX provided the corresponding aldehyde **47.**

The aldehyde **47** was subjected to a Wittig reaction to give siphonarienone **2**. To prepare target compounds **1** and **3,** aldehyde **47** was subjected to a Wittig reaction to give

ester **27**. The ester was reduced to allylic alcohol, and further oxidized to afford siphonarienal **1**. Whereas treatment of ester **27** with N-methoxy, N-methyl ammonium chloride, and ^{i}PrMgCl, in THF, at -20 °C to 0 °C afforded Weinreb amide **48**, which on treatment with ethyl 2-methyl-3-oxopentanoate followed by cyclization of the resulting β, δ -diketo ester with 1,8- diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene gave the target molecule, pectinatone **3**



Scheme 5

Reagents and conditions: (a) (-) -Ipc_2BH, (+)-α-pinene, 95% (b) PCC, CH_2Cl_2, r.t., 90% (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 25 0 °C (d) LHMDS, Allyl bromide, THF, -78 °C, 94% (e) $LiAlH_4$, THF, 0 °C - 25°C (f) 2, 2 DMP, CSA, CH_2Cl_2, Et_2O, 93% (g) NaH, BnBr, THF, Reflux, 92% (h) 2M HCl, THF/H_2O, 25 °C, 90% (i) TsCl, Et_3N, DMAP, CH_2Cl_2, 92% (j) $LiAlH_4$, THF, 0 °C - 25°C, 80% (k) CS_2, MeI, NaH, 0 °C - 25 °C, 89% (l) *n*-Bu_3SnH, AIBN, Toluene, reflux, 91% (m) DDQ, CH_2Cl_2, p^H 7 buffer (9:1) 0 °C -25

°C, 89% (n) CS_2, MeI, NaH, 0 °C - 25 °C, 91% anhydrous THF, (o) *n*-Bu_3SnH, AIBN, Toluene, reflux (p) Pd/C, H_2,88%, (q) IBX/DMSO 81% (r) dry benzene, reflux, 56% (s) dry benzene, reflux, 81% (t) DIBAL-H, -78 °C - r.t, 72%, CH_2Cl_2; IBX/DMSO, 72%. (u) HN(MeO)Me·HCl, 2eq ^{i}PrMgCl, THF, -20 °C - 0 °C, 71% (v) LDA, THF, 0 °C, $CH_3CH_2COCH(CH_3)CO_2Et$ (w) DBU, Toluene, reflux, 30%.

CHAPTER II: SECTION B

Enantioselective total synthesis of Siphonarienal, Siphonarienone and Pectinatone.

Present work:

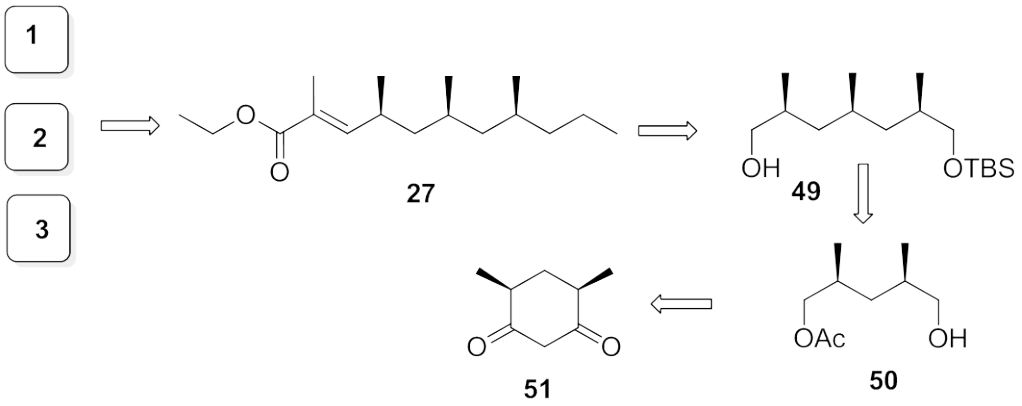
Synthetic organic chemistry is perhaps the most expressive branch of the science of chemistry in view of its creative power and unlimited scope. To appreciate its impact on modern humanity one only has to look around and recognize that this science is a pillar behind pharmaceuticals, high-tech materials, polymers, fertilizers, pesticides, cosmetics and clothing. The engine that drives forward and sharpens our ability to create such molecules through chemical synthesis is total synthesis. It is quest to construct the most complex and challenging of nature's products, this endeavor-perhaps more than any other–becomes the prime driving force for the advancement of the art and science of organic synthesis.

Although the theme of natural product synthesis is attracting a lively interest in research laboratories around the world today, the reasons for practicing it vary. Advances in the elucidation of biological processes have generated a demand for the efficacious synthesis of biologically active compounds in enantiomerically pure form. Isolation from natural sources usually does not provide sufficient amount of material to complete biological studies. In addition, structural modification of a natural substrate often provides valuable information about a system not afforded by the parent molecule. In order to fulfill these needs, a major focus of synthetic organic chemistry has been the enantiomeric synthesis of molecules and their analogues for the study of the expanding number of biological pathways that continue to be investigated.

As an ongoing project on the synthesis of biologically active natural products, we have initiated a programme on the total synthesis of Siphonarienal, Siphonarienone and Pectinatone.

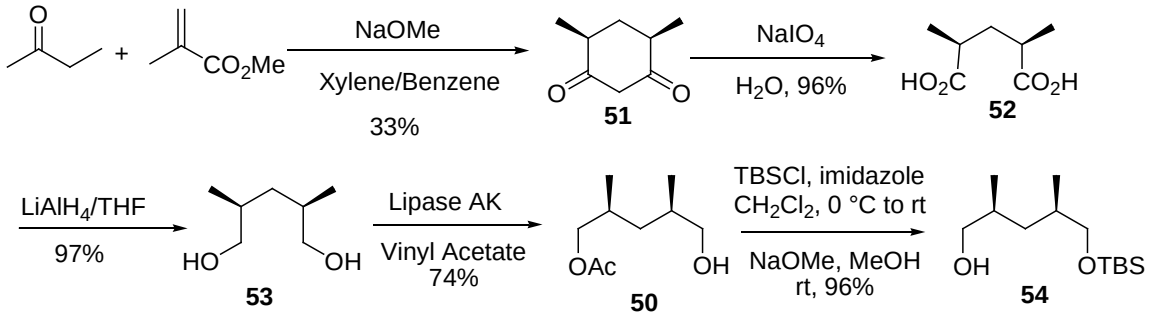
Retro synthetic analysis:

Retro synthetically, we envisaged that the target molecules siphonarienal, siphonarienone and pectinatone could be synthesized from a common precursor **27.** The chiral precursor **27** was then proposed to be synthesized from **49** in two steps involving oxidation and C3-homologation reactions. The intermediate **49** was assumed to be synthesized in a stereoselective manner involving enzymatic desymmetrization approach, Wittig reaction, and Evan's asymmetric alkylation (Scheme 6).



Scheme 6

Our synthesis began with the preparation of meso-4,6-dimethylcyclohexane-1,3-dione **51**. To a stirred solution of NaOMe in benzene at 0 °C was added methylmethacrylate followed by the addition of butanone to prepare diketone **51** as a white precipitate with 33% yield.[44] The ^{1}H NMR of compound **51** showed a signal at δ 3.45 (d, *J* = 16.1 Hz, 1H) and 3.35 (d, *J* = 16.1 Hz, 1H) ppm corresponding to the two –CH_2 protons attached to the keto group and δ 2.76-2.54 (m, 2H) ppm corresponding to two –CH protons attached to the keto group and 2.27-2.01 (m, 2H) ppm corresponding to other two –CH_2 protons. Further confirmation was obtained from EI-MS data which showed [M^+] peak at *m/z* 140. Diketone **51** was converted into the diacid **52** by periodate oxidation.[45] The ^{1}H NMR spectrum showed a strong evidence for oxidation in which proton signals at the region of δ 3.45 (d, *J* = 16.1 Hz, 1H) and 3.35 (d, *J* = 16.1 Hz, 1H) ppm corresponding to the two –CH_2 protons attached to the keto group disappeared and shifting of δ values of the two –CH protons attached to the keto group was observed at δ 2.47-2.61(m, 2H) ppm. Further confirmation was obtained from the EI-MS data which showed [M+] peak at *m/z* 140.



Scheme 7

$LiAlH_4$ reduction of the diacid **52** in THF at room temperature gave the *meso*-diol **53** in 97% yield. The formation of *meso*-diol **53** was confirmed by the appearance of the peak at δ 3.56-3.29 (m, 4H) ppm corresponding to the four $–CH_2OH$ protons in ^1H NMR spectrum and from the ^{13}C NMR which showed no characteristic signal for carbonyl group. Desymmetrization of meso-diol using Lipase-AK and vinyl acetate (as acylating agent) in THF at ambient conditions furnished the mono acetate **50** in 74% yield and at least 95% *ee* along with the *meso*diacetate.[46] It is noteworthy to mention that the *meso*-diacetate obtained was again converted back to the *meso*-diol by treatment with CH_3ONa in methanol in quantitative yield for further utilizations. Compound **50** was characterized by the appearance of the proton signal at the region of δ 3.97 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.85 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.49 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.42 (dd, *J* = 10.5, 6.0 Hz, 1H) ppm corresponding to the four $–CH_2OH$ protons and proton signal at δ 2.05 (s, 3H) ppm corresponding to the acetyl group confirmed the formation. Further confirmation was obtained from ^{13}C NMR spectrum which showed the carbonyl peak at δ 171.3 ppm for the acetyl group. Compound **50** showed Specific rotation $[\alpha]^D$ 25 of + 9.8 (*c* 0.6 in $CHCl_3$) which was almost identical with the reported one.[46a, 46f]

The mono acetate **50** was protected as its silyl ether using TBSCl and imidazole in dichloromethane and then treated with CH_3ONa in methanol to furnish the desired terminalalcohol **54** in 96% yield over two steps. Alcohol **54** was characterized by the disappearance of the proton signal at the region of δ 2.05 (s, 3H) ppm in ^1H NMR spectrum corresponding to acetyl group and appearances of the peak at δ 0.89 (s, 9H) and 0.03 (s, 6H) ppm in ^1H NMR spectrum clearly indicates the presence of TBS group. Further confirmation was obtained from the ^{13}C NMR spectroscopy which showed characteristic peaks at δ 25.8, 18.2, −5.4 ppm referred to TBS group (Scheme 7).

Scheme 9

Oxidation of alcohol **54** was done by Swern oxidation[47] conditions followed by two carbons extension by means of Wittig reaction gave us the *α,β*-unsaturated ester **55** in 86% yield in overall two steps. The formation of the product was confirmed by appearance of signals of the two olefinic protons at δ 6.76 (dd, *J* = 15.8, 8.3 Hz, 1H) and 5.75 (d, *J* = 15.8 Hz, 1H) ppm in ^{1}H NMR spectrum confirmed product as *trans*-olefin, also showed characteristic resonances as a quartet at δ 4.17 (q, *J* = 14.3, 6.7 Hz, 2H) and triplet at δ 1.29 (t, *J* = 6.7 Hz, 3H) ppm in ^{1}H NMR spectrum which corresponds to the presence of *α,β*-unsaturated ethyl ester. Compound **55** was also characterized by HRMS [ESI] data which showed the $[M+Na]^+$ peak at *m/z* 337.2174.

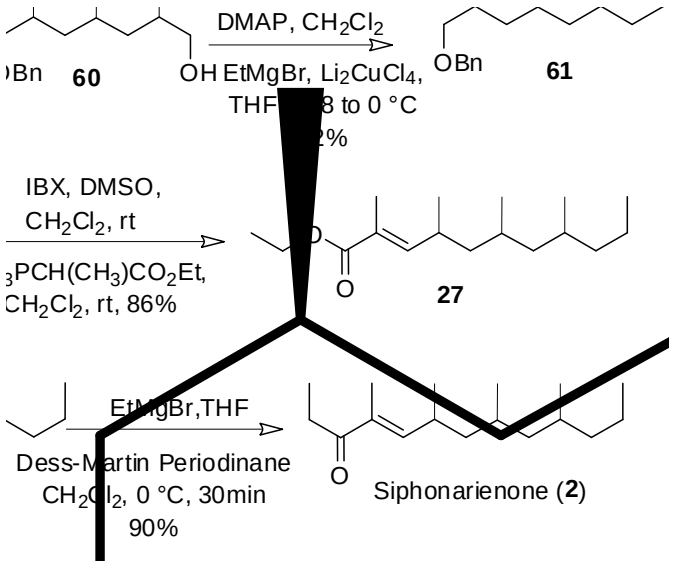
Reduction of double bond of **55** was achieved with Pd/C in ethyl acetate to afford the saturated ester **56** with 96% yield. This transformation was confirmed from ^{1}H NMR spectroscopy which showed no characteristic resonance at the region of δ 6.76 (dd, *J* = 15.8, 8.3 Hz, 1H) and 5.75 (d, *J* = 15.8 Hz, 1H) ppm correspond to olefinic protons. Further confirmation was obtained from HRMS [ESI] data which showed the $[M+Na]^+$ peak at *m/z* 339.2321. Saturated ester **56** was then hydrolyzed under basic conditions to furnish the corresponding carboxylic acid **57** in 93% yields. This hydrolysis was confirmed by ^{1}H NMR spectroscopy which showed disappearances of the proton signals at the region of δ 4.17 (q, *J* = 14.3, 6.7 Hz, 2H) and 1.29 (t, *J* = 6.7 Hz, 3H) ppm

corresponding to the ethyl ester group. Further confirmation was obtained from the HRMS[ESI] data which showed $[M+Na]^+$ peak at *m/z* 311.2028 and from IR spectrum which showed an absorption band at 1711 cm-1 due to C=O stretching frequency of acid group.

Coupling of carboxylic acid **57** with the Evan's chiral oxazolidinone using pivaloyl chloride in presence of triethylamine and LiCl furnished the required compound **58** in 93% yield.[48] Compound **58** was characterized by the resonance of five aromatic protons as multiplet between δ 7.15 to 7.38 ppm and appearance of peak at the region of δ 2.78-3.03 (m, 2H) ppm corresponding to benzyl group. Further confirmation was obtained from IR spectrum which showed disappearances of absorption band at 1711 cm^{-1} due to C=O stretching frequency of acid group and appearances of absorption band at 1784 cm^{-1} due to C=O stretching frequency of keto group and from HRMS[ESI] data which showed the $[M+Na]^+$ peak at *m/z* 470.2714.

Diastereoselective methylation of Na-enolate of compound **58** with MeI in THF furnished the desired compound **59** in 91% yield and in >97:3[49] diastereoselectivity (confirmed by ^1H NMR). Compound **59** was characterized by 1H NMR spectroscopy which showed peak at δ 1.20 (d, J = 6.7 Hz, 3H) ppm for the newly formed methyl center and from HRMS [ESI] data which showed the $[M+Na]^+$ peak at *m/z* 484.2875. Compound **59** was then reduced under $NaBH_4$ in MeOH to obtain the desired primary alcohol **49** having 3 chiral centres in place with 92% yield (Scheme 9). The formation of product was confirmed by ^1H NMR spectroscopy which showed no characteristic proton signals at the aromatic region and from the IR spectroscopy which showed absorption band at 3351 cm^{-1} due to OH stretching frequency. Further evidence was obtained by the appearance of peak at *m/z* 311.2398 for $[M+Na]^+$ in HRMS[ESI] data.

Primary hydroxyl group present in **49** was protected as its benzyl ether (**60a**) by using benzyl bromide and NaH in catalytic amount of TBAI, afforded benzyl ether was treated with TBAF in THF yielded desilylated primary alcohol (**60**) in 91% (over two steps). Compound **60** was confirmed by the disappearance proton signals at δ 0.89 (s, 9H) and δ 0.03 (s, 6H) ppm corresponding to TBS ether group and from the IR spectroscopy which showed strong absorption band at the region of 3418 cm^{-1} confirmed the presence of hydroxyl group.



Scheme 10

Primary hydroxyl group present in **60** was protected as its tosyl derivative by TsCl and Et_3N in presence of catalytic amount of DMAP and then subjected to Grignard reaction[50] with EtMgBr in Et_2O in presence of 5 mol% Li_2CuCl_4 to afford **61** in 90% yield for two steps. Grignard compound **61** was characterized by the disappearance of two proton signals as a multiplet at the region of δ 3.36-3.27 ppm corresponding to the $–CH_2OH$ protons in ^1H NMR spectroscopy and disappearance of OH stretching absorption at 3418 cm^{-1} in IR spectroscopy.

Hydrogenolysis of **61** over 10% Pd-*C* in ethyl acetate at room temperature, resulted debenzylated primary alcohol **16** in 95 % yield. The product was characterized by ^1H NMR study, which showed the disappearance of resonance for aromatic protons and there is no chemical shift at 7.35-7.21 ppm. The presence of primary free alcohol was confirmed by its IR spectroscopy that showed the absorption band at 3450 cm^{-1}. The 1^0 alcohol group in **16** was oxidized with IBX to the corresponding aldehyde, followed by three-carbon homologation using $Ph_3PCH(CH_3)CO_2Et$ in benzene to furnish the (*E*)-*α,β*-unsaturated ester **27** in 86% overall yield. The ^1H NMR spectrum of **27** showed resonances at δ 6.44 for one olefin proton and quartet at δ 4.20 (J = 7.1 Hz) shows $–CH_2$ protons of the ester ($-CH_2-CH_3$), and the presence of carbonyl functionality was also

confirmed by IR spectroscopy, it shows a stong absorption band at 1648 cm^{-1}. Further evidence was obtained by the appearance of peak at *m/z* 291.2322 for $[M+Na]^+$ in HRMS [ESI] data.

The target molecule, Siphonarienal **1** was readily achieved in 88% yield by reduction of **27** with DIBAL-*H* at -78 $^{\circ}C$.

Final product **1** was confirmed by ^1H NMR spectroscopy which showed a peak as singlet at the region of δ 9.39 (1 H) ppm, corresponding to aldehyde proton and from ^{13}C NMR spectroscopy which showed characteristic peak at δ 195.4 ppm corresponding to carbon resonance of aldehyde group. Further evidence was obtained from IR spectrum which showed absorption band of C=O stretching frequency of aldehyde at 1690 cm^{-1}.

Siphonarienal to Siphonarienone was simply achieved by treating with Grignard reaction on Siphonarienal (**1**) with EtMgBr followed by oxidation with Dess-Martin periodinane gave the Siphonarienone (**2**) in 85% over two steps. The compound **2** was well characterized by its ^1H NMR, ^{13}C NMR, IR and mass spectral properties. In the ^1H NMR spectrum the vinylic proton resonated at δ 6.34 as a doublet, methyl attached to sp^2 carbon resonated as singlet at δ 1.80, and from ^{13}C NMR spectroscopy which showed characteristic peak at δ 202.8 ppm corresponding to carbon resonance of conjugated keto group The mass spectrum ESI (MS) showed $[M+H]^+$ peak at *m/z* 253 and an absorption band at 1672 cm^{-1} in the IR spectrum further confirmed the Siphonarienone **2** (Scheme 10).

Scheme 11

Weinreb amide **48** was prepared from ester **27** using 2 eq of ^{i}PrMgCl, N(MeO)Me.HCl in THF in 71% yield. Formation of the product was confirmed by ^1H NMR spectrum, which

showed two new singlets at δ 3.38 and 1.88 corresponding to methoxy and methyl groups of amide respectively. IR absorption showed at 1624 cm-1 corresponding to C=O stretching of amide. MS(ESI) mass showed a molecular ion peak at *m/z* 284 $[M+H]^+$ further confirming the amide **48** (Scheme 11).

The amide **48** was converted into diketoester **63** using the enolate of ethyl 2-methyl-3-oxopentanoate (**62**). Without further purification, DBU was added to the diketoester **63** in refluxing anhydrous toluene to give (+)-pectinatone in 51% over two steps (Scheme 11). The spectral and analytical data for compound **3** were in good agreement with those reported earlier[35,42] (Scheme 11).

The ^1H and ^{13}C NMR spectral data of our synthetic compounds (**1**, **2** & **3**) were in good agreement with the data previously reported in the literature.[35,42,51]

EXPERIMENTAL SECTION

meso-4,6-Dimethylcyclohexane-1,3-dione (51):

To a stirred solution of NaOMe (43.2 g, 0.8 mol) in benzene (450 mL) at 0 °C was added methylmethacrylate (105 mL, 0.94 mol) followed by the addition of butanone (32.7 mL, 0.36 mol). The reaction mixture was stirred for 0.5 h at same temperature, and then 8 h at room temperature. Water (200 mL) was added to the reaction mixture, stirred for another hour, the aqueous and benzene layers were separated and the aqueous layer was acidified with glacial acetic acid at 0 °C. A white precipitate was formed which on filtration gave pure diketone **51** (16.7 g, 33%). *Rf* = 0.4 (20% EtOAc/hexane).

M.P. : 111-113 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 3.45 (d, *J* = 16.1 Hz, 1H), 3.35 (d, *J* = 16.1 Hz, 1H), 2.76-2.54 (m, 2H), 2.27-2.01 (m, 2H), 1.18 (d, *J* = 6.6 Hz, 6H).

Mass (EI-MS) *m/z* : 140 $[M]^+$.

meso- 2,4-Dimethylpentanedioic acid (52):

To a stirred suspension of diketone **51** (8.0 g, 57 mmol) in water (400 mL) at 0 °C was added sodium periodate (120 g, 0.56 mol) dissolved in 1.6 L water dropwise at 0 °C. After complete addition, reaction mixture was warmed to room temperature and stirred for 24 h. The aqueous reaction mixture was extracted with EtOAc (5 × 800 mL) and organic layer were dried over Na_2SO_4, concentrated under reduced pressure to afford crude *meso*-2,4- dimethylglutaric acid **52** as a white solid (8.77 g, 96%). *Rf* = 0.4 (50% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 2.61-2.47 (m, 2H), 2.19-2.06 (m, 1H), 1.49 (dt, *J* = 6.7, 14.3 Hz, 1H), 1.21 (d, *J* = 6.7 Hz, 6H).

MASS (ESI-MS) *m/z* : 160 $(M+Na)^+$

***meso*-2,4-dimethylpentane-1,5-diol (53):**

To a stirred suspension of $LiAlH_4$ (12.2 g, 0.32 mol) in anhydrous THF (200 mL) at 0 ºC was added the dimethyl glutaric acid **52** (16.0 g, 0.1 mol) dissolved in THF (100 mL) dropwise. The reaction mixture was allowed to stir for 12 hours at room temperature and then quenched by the slow addition of moistened Na_2SO_4 at 0 °C and mixture was stirred overnight. The solid was filtered through pad of celite and washed with EtOAc (5 × 100 mL). The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (EtOAc/hexane, 50%) to afford diol **53** as a viscous liquid (12.8 g, 97%). *Rf* = 0.4 (30% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 3.56-3.29 (m, 4H), 1.78-1.57 (m, 3H), 1.29-1.16 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 17.6, 32.9, 36.8, 67.3.

(2*S*,4*R*)-5-Hydroxy-2,4-dimethylpentyl acetate (50):

To a stirred solution of meso-diol **53** (4.0 gm, 30.30 mmol, 1.0 equiv.) in THF (40 mL) was cooled to 0 ºC. At this temperature, Amano Lipase AK (220 mg) and vinyl acetate (4.20 mL, 3.90 g, 45.4 mmol, 1.50 equiv) were added. The reaction mixture was stirred for 30 min at 0^{o}C and 7h at 5 ^{o}C. The enzyme was removed by suction filtration through Celite. The residue was further washed with diethyl ether (2 × 30mL) and dried over Na_2SO_4. The homogeneous filtrate was concentrated *in vacuo* and purified by chromatography on silica gel (1:5, EtOAc/hexane) to afford the monoacetate **50** (3.902 g, 74%).)

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 3.97 (dd, *J* = 10.5, 5.2 Hz, 1H), 3.85 (dd, *J* = 10.5, 6.7 Hz, 1H), 3.49 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.42 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.05 (s, 3H), 1.96-1.82 (m, 1H), 1.78-1.64 (m, 1H), 1.43 (br, s, 1H), 1.49-1.39 (m, 1H), 1.30-1.15 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 171.3, 69.1, 67.9, 37.2, 32.9, 29.9, 20.9, 17.8, 17.2.

$[\alpha]_D^{25}$: + 9.8 (*c* 0.6, $CHCl_3$).

(2*S*,4*R*)-5-(*tert*-butyldimethylsilyloxy)-2,4-dimethylpentan-1-ol (54):

To a cold (0 °C) solution of alcohol **50** (5.0 g, 28.7 mmol) in anhydrous CH_2Cl_2 (80 mL) was added imidazole (3.9 g, 57.4 mmol) and *tert*-butyldimethylsilylchloride (5.16 g, 34.4 mmol). The resulting mixture was stirred at room temperature for 3 h. After completion of the reaction as indicated by TLC, the mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to furnish crude acetate. To the above mixture in MeOH (80 ml) was added sodium methoxide (2.3 g, 43.05 mmol) at room temperature. Then the mixture was stirred for 1 h at room temperature and concentrated under reduced pressure. The residue was then quenched by the addition of saturated NH_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated in vacuum. The resulting crude product was purified by silica gel column chromatography (1:9 EtOAc/hexane) to give the product as a colorless oil **54** in (6.77 g, 96%) yield. *Rf* = 0.4 (10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 3.50-3.32 (m, 4H), 1.77-1.60 (m, 2H), 1.50-1.36 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz) : 68.2, 67.9, 37.2, 33.1, 25.8, 18.2, 17.7, 17.6, −5.4.

IR (Neat) : 3348, 2954, 2928, 2857, 1466, 1252, 1097, 837, 775 cm^{-1}.

$[\alpha]_D^{25}$: + 0.9 (*c* 1.2, $CHCl_3$).

(*4S,6R,E*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-4,6-dimethylhept-2-enoate(55):

To a stirred solution of IBX (11.4 g, 40.8 mmol) in DMSO (30 mL) at 25 °C, was added slowly dropwise a solution of alcohol **54** (6.70 g, 27.2 mmol) in CH_2Cl_2 (80 mL). The resulting mixture was stirred at 25 °C for 3 h. The solid was filtered and washed with ether. The filtrate was washed with saturated aqueous $NaHCO_3$ solution, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to furnish crude aldehyde. To the above crude mixture (4.94 g, 20.1 mmol) in CH_2Cl_2 (150 ml) was added (ethoxycarbonylmethylene) triphenyl phosphorane (17.0 g, 48.9 mmol) and resulting mixture was stirred for 12 hours at room temperature. The reaction mixture was concentrated under reduced pressure and purified on silica gel chromatography (5% EtOAc/hexane) to afford the unsaturated ester **55** (7.3 g, 86% over two steps) as a colourless liquid. *Rf* = 0.5 (10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 6.76 (dd, *J* = 15.8, 8.3 Hz, 1H), 5.75 (d, *J* = 15.8 Hz, 1H), 4.17 (q, *J* = 14.3, 6.7 Hz, 2H), 3.37 (dd, *J* = 5.2, 1.5 Hz, 2H), 2.51-2.32 (m, 1H), 1.67-1.44 (m, 2H), 1.29 (t, *J* = 6.7 Hz, 3H), 1.15-1.06 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 166.7, 154.3, 119.7, 68.3, 60.0, 39.8, 34.1, 33.3, 25.8, 20.4, 18.2, 16.5, 14.2, −5.4.

MASS (ESI-MS) : *m/z* 337 $(M+ Na)^+$.

HRMS (ESI) : calcd. for $C_{17}H_{34}O_3NaSi$: 337.2174; found 337.2174.

IR (Neat) : 2957, 2859, 1722, 1652, 1465, 1367, 1259, 1180, 1094, 1042, 840, 775 cm^{-1}

$[\alpha]_D^{25}$: +17.9 (*c* = 1.0 in $CHCl_3$).

(4*R*,6*R*)-ethyl 7-(*tert*-butyldimethylsilyloxy)-4,6-dimethylheptanoate (56):

To a cooled (0 °C) solution of **55** (7.2 g, 22.9 mmol) and $NiCl_2.6H_2O$ (1.08 g, 4.58 mmol) in MeOH (100 mL), was added $NaBH_4$ (2.0 g, 54.9 mmol) in small portions to the solution. During addition of $NaBH_4$, the reaction temperature was maintained at 0 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred for 1 h at room temperature and the resulting black precipitate was filtered and then washed with MeOH. The solvent was removed under reduced pressure and then diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. Removal of solvent under reduced pressure followed by purification on silica gel column chromatography using ethyl acetate/hexane (5% EtOAc/hexane) gave the product **96** (6.9 g, 96% yield) as a colorless oil. *Rf* = 0.5 (10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 4.10 (q, *J* = 14.3, 6.7 Hz, 2H), 3.41 (dd, *J* = 9.8, 6.0 Hz, 1H), 3.33 (dd, *J* = 9.8, 6.0 Hz, 1H), 2.34-2.18 (m, 2H), 1.75-1.28 (m, 6H), 1.26 (t, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 6.0 Hz, 3H)), 0.02 (s, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 174.0, 68.2, 60.1, 40.7, 33.0, 31.8, 31.5, 29.6, 25.9, 20.0, 18.2, 17.3, 14.2, −5.4.
MASS (ESI-MS)	: *m/z* 339 $(M+Na)^+$.
HRMS (ESI)	: calcd. for $C_{17}H_{36}O_3NaSi$: 339.2331; found 339.2321.
IR (Neat)	: 2956, 1738, 1636, 1253, 1094, 772, 570 cm^{-1}.
$[\alpha]_D^{25}$	: +3.8 (*c* = 1.2 in $CHCl_3$).

(4*R*,6*R*)-7-(*tert*-butyldimethylsilyloxy)-4,6-dimethylheptanoic acid (57):

$LiOH.H_2O$ (2.7 g, 64.5 mmol) was added portion wise to a cooled solution (0 °C) of ester **56** (6.8 g, 21.5 mmol) in 80 mL of CH_3OH:H_2O (4:1) and the stirring was continued for

2 h at room temperature. The reaction mixture was then concentrated in vacuum and the residue was diluted with EtOAc (80 mL) and washed with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Removal of solvent followed by column chromatography using 20% EtOAc/hexane afforded the acid **57** (5.7 g, 93% yield) as a colorless liquid. *Rf* = 0.3 (10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 3.45-3.30 (m, 2H), 2.42-2.24 (m, 2H), 1.78-1.06 (m, 6H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 3H)), 0.03 (s, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 180.2, 68.1, 40.6, 33.0, 31.5, 31.2, 29.6, 25.9, 19.9, 18.3, 17.4, −5.3.
MASS (ESI-MS)	: *m/z* 311 $(M+Na)^+$.
HRMS (ESI)	: calcd. for $C_{15}H_{32}O_3NaSi$: 311.2018; found 311.2028
IR (Neat)	: 2956, 2930, 2858, 1711, 1464, 1414, 1253, 1094, 938, 839, 775, 667 cm^{-1}.
$[\alpha]_D^{25}$	: +5.0 (*c* = 0.7 in $CHCl_3$).

(4*R*)-4-benzyl-3-((4*R*,6*R*)-7-(*tert*-butyldimethylsilyloxy)-4,6-dimethylheptanoyl) dihydrofuran-2(3H)-one (58):

To a stirred solution of acid **57** (5.6 g, 19.4 mmol) in THF (100 mL) at −20 °C was added Et_3N (6.74 mL, 48.5 mmol) followed by PivCl (2.4 mL, 19.4 mmol). After stirring for 1 h at –20 °C, LiCl (1.23 g, 29.1 mmol) followed by (*S*)-oxazolidinone (3.77 g, 21.3 mmol) were added to it at the same temperature. The stirring was continued for 1 h at −20 °C and then 2 h at 0 °C. It was then quenched with saturated NH_4Cl solution (50 mL) and extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate

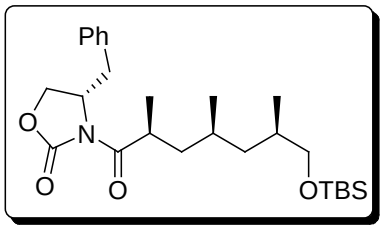
and hexane (1:16) to gave **58** (8.0 g, 93 %) as a viscous liquid. *Rf* = 0.5 (10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 7.38-7.15 (m, 5H), 4.67-4.54 (m, 1H), 4.23-4.09 (m, 2H), 3.43 (dd, *J* = 9.8, 5.2 Hz, 1H), 3.40-3.25 (m, 2H), 3.03-2.78 (m, 2H), 2.69 (dd, *J* = 13.5, 9.8 Hz, 1H), 1.80-1.08 (m, 6H), 0.95 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 173.6, 153.3, 135.3, 129.3, 128.8, 127.2, 68.2, 66.0, 55.1, 40.8, 37.8, 33.1, 33.0, 30.8, 29.7, 25.9, 20.0, 18.3, 17.4, −5.3.
MASS (ESI-MS)	: *m/z* 470 $(M+Na)^+$.
HRMS (ESI)	: calcd. for $C_{25}H_{41}NO_4Si$ Na: 470.2702; found 470.2714.
IR (Neat)	: 2954, 2928, 2857, 1784, 1700, 1461, 1386, 1353, 1251, 1208, 1093, 839, 772, 701, 591cm^{-1}.
$[\alpha]_D^{25}$	: +38.8 (*c* = 1.0 in $CHCl_3$).

(4*R*)-4-benzyl-3-((2*S*,4*S*,6*R*)-7-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptanoyl) dihydrofuran-2(3H)-one (59):

To a stirred solution of **58** (4.0 g, 8.9 mmol) in anhydrous THF (80 mL) at −78 °C, NaHMDS (1M solution in THF, 13.35 mL, 13.35 mmol) was added slowly dropwise with stirring under nitrogen atmosphere. After stirring at −78 °C for 30 min, MeI (1.56 mL, 26.7 mmol) was added dropwise to the reaction mixture and then stirring was continued for another 2 h at −78 °C. Then the mixture was quenched with saturated NH_4Cl (50 mL) and warmed to room temperature and then extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried over

anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:19) to afford the product **59** as a colorless liquid (3.73 g, 91 %). *Rf* = 0.6 (10% EtOAc/hexane).



^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.37-7.17 (m, 5H), 4.68-4.55 (m, 1H), 4.22-4.08 (m, H), 3.93-3.77 (m, 1H), 3.47-3.22 (m, 3H), 2.70 (dd, *J* = 12.8, 9.8 Hz, 1H), 1.98-1.25 (m, 5H), 1.20 (d, *J* = 6.7 Hz, 3H), 1.12-0.96 (m, 1H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 6H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 177.2, 152.9, 135.2, 129.4, 128.8, 127.2, 68.3, 65.9, 55.2, 41.2, 40.4, 37.8, 35.2, 33.0, 28.1, 25.9, 20.7, 18.5, 18.3, 17.4, −5.3.

MASS (ESI-MS) : *m/z* 484 $(M+Na)^+$.

HRMS (ESI) : calcd. for $C_{26}H_{43}O_4$ Si Na: 484.2859; found 484.2875.

IR (Neat) : 2954, 2928, 2857, 1784, 1700, 1461, 1386, 1353, 1251, 1208, 1093, 839, 772, 701, 591cm^{-1}.

$[\alpha]_D^{25}$: +41.6 (*c* = 1.3 in $CHCl_3$).

(2*S*,4*R*, 6*R*)-7-(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptan-1-ol (49):

To a stirred solution of **59** (5.0 g, 10.8 mmol) in MeOH (40 mL) at 0 ºC was added $NaBH_4$ portion wise (1.23 g, 32.4 mmol). The reaction mixture was allowed to stir for 1 hour at same temperature and then quenched with saturated NH_4Cl solution. The solvent was removed under reduced pressure and the resulting residue was diluted with water and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (10%, EtOAc/hexane) to afford the pure product **49** (2.86 g, 92%) as a viscous liquid. R_f = 0.5 (10% EtOAc/hexane).

^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 3.55-3.29 (m, 4H), 2.60 (s, 1H), 1.88-0.96 (m, 7H), 0.93 (d, *J* = 7.5 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 68.1, 67.9, 41.2, 41.0, 33.0, 27.6, 25.9, 21.0, 18.3, 17.9, 17.5, −5.3.
MASS (ESI-MS)	: *m/z* 289 $(M+H)^+$.
HRMS (ESI)	: calcd. for $C_{16}H_{36}O_2$ Si Na: 311.2382; found 311.2398.
IR (Neat)	: 3351, 2956, 2928, 2858, 1465, 1383, 1253, 1098, 1040, 838, 775, 667 cm^{-1}.
$[\alpha]_D^{25}$	: –5.8 (*c* = 1.0 in $CHCl_3$).

((2R,4R,6S)-7-(benzyloxy)-2,4,6-trimethylheptyl)oxy)(tert-butyl)dimethylsilane:(60a)

To a stirred solution of sodium hydride (0.55g [50% with mineral oil], 11.46 mmol) in dry THF (10 mL) was added alcohol **49** (3.0 g, 10.42 mmol) in dry THF (20 mL) at 0 °C. The mixture was allowed to stir for 20 min and then a solution of benzyl bromide (1.3 mL, 10.42 mmol) in excess anhydrous THF was added slowly drop wise. The resulting mixture was allowed to stir at ambient temperature for 2h. Up on completion, the reaction was quenched with water and extracted with ethyl acetate (3 × 20 mL). The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation of the solvent followed by purification of the crude product on flash chromatography (4% EtOAc/ hexane) afforded the benzyl ether (3.62 g, 92%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.33-7.18 (m, 5H), 4.45 (s, 2H), 3.45-3.37 (m, 1H), 3.33-3.25 (m, 2H), 3.15 (dd, *J* = 6.9 Hz, 1H), 1.88-1.77 (m, 1H), 1.70-1.50 (m, 2H), 1.37-1.23 (m, 4H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.88-0.82 (m, 15H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 128.2, 127.4, 127.3, 75.9, 72.9, 68.0, 41.7, 41.1, 33.0, 30.8, 26.6, 25.9, 21.0, 18.2, 17.9, -5.3

MASS (ESI-MS) : *m/z* 401 $(M+Na)^+$.

IR (Neat) : 3452, 2955, 2928, 2856, 1462, 1252, 1097, 838, 774cm^{-1}.

$[\alpha]_D^{25}$: +1.8 (*c* = 2.1 in $CHCl_3$).

(2*R*,4*S*,6*S*)-7-(Benzyloxy)-2,4,6-trimethylheptan-1-ol (60):

The crude product (**60a**) was dissolved in dry THF (20 mL) at 0 ºC, and then 9.6 mL of TBAF (1M in THF) was added. The resulting mixture was allowed to stir at room temperature for 6h. After completion, it was quenched with saturated NH_4Cl solution (10 mL) and then extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane mixture (1:9) to give the product **60** (2.3g, 90 %) as a viscous liquid.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.34-7.19 (m, 5H), 4.50-4.42 (m, 2H), 3.46 (dd, J = 4.9, 9.8 Hz, 1H), 3.36-3.27 (m, 2H), 3.23-3.18 (m, 2H), 1.87- 1.80 (m, 1H), 1.61-1.55 (m, 1H), 1.40-1.26 (m, 2H), 0.97- 0.84 (m, 12H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 138.6, 128.2, 127.4, 127.3, 75.7, 72.93, 68.0, 41.5, 41.0, 32.9, 30.8, 27.6, 20.9, 18.2, 17.5;

MASS (ESI-MS) : *m/z* 282 $(M+ NH_4)^+$.

IR (Neat) : 3418, 2956, 2919, 2869, 1457, 1370, 1101, 1034, 740 cm^{-1};

$[\alpha]_D^{25}$: +7.5 (c = 2.5, $CHCl_3$);

(2*S*,4*S*,6*S*)-2,4,6-Trimethylnoyloxy)benzene (61):

To a stirred solution of alcohol (**60**) (2.0 g, 7.6 mmol) in dry CH_2Cl_2(20 mL) were added triethylamine (1.3 mL, 9.1 mmol), *p*-toluenesulfonyl chloride (1.50g, 7.6 mmol), and a catalytic amount of DMAP (46 mg, 0.37 mmol). The resulting mixture was stirred for 3h. After complete conversion as confirmed by TLC, the mixture was quenched with NH_4Cl solution and then extracted with EtOAc (3 × 20 mL). Removal of the solvent followed by purification on silica gel column chromatography (5% ethyl acetate/hexane) gave the pure tosyl derivative. To a round-bottom flask equipped with an activated Mg-turnings (0.59 g, 24.0 mmol, 3.4 eq) was added slowly ethyl bromide (1.86 mL, 25.2 mmol, 3.5 eq) in diethyl ether (20 mL). After complete addition, the mixture was heated to reflux(~30 min) until initiation of the reaction. The reaction mixture was cooled to -20 ^oC and then tosylate (3.0g, 7.18 mmol) was added slowly. To this mixture, a solution of Li_2CuCl_4 (0.1M in tetrahydrofuran, 7 mL, 0.718 mmol, 0.1eq) was slowly added at -20 ^oC. The resulting mixture was stirred vigorously overnight at room temperature and then quenched with saturated aqueous NH_4Cl (20 mL) at 0 ^oC and then extracted with diethyl ether (3 × 20 mL). Removal of the solvent followed by column chromatography gave the product **61** as a colorless liquid with 82% yield.

^1H NMR ($CDCl_3$, 300 MHz) : δ 7.35-7.21 (m, 5H), 4.51-4.42 (m, 2H), 3.30(dd, J = 5.2 Hz, 1H), 3.18 (dd, J = 6.7 Hz, 1H), 1.90-1.78 (m,1H), 1.65-1.44 (m, 2H), 1.44-1.15 (m, 6H), 1.03-0.79 (m, 14H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 138.8, 128.2, 127.4, 127.3, 75.9, 73.0, 45.2, 41.8, 38.9, 30.9, 29.7, 27.6, 20.9, 20.4, 20.0, 18.4, 14.5.

MASS (ESI-MS) : *m/z* 294 $(M+ NH_4)^+$.

IR (Neat) : 3449, 2955, 2919, 2857, 1637, 1457, 1371, 1101, 760 cm^{-1}.

$[\alpha]_D^{25}$: +2.0 (c = 1.0, $CHCl_3$);

(2*S*,4*S*,6*S*)-2,4,6-Trimethylnonan-1-ol (16):

To a stirred solution of benzyl ether (1.6 g, 5.8 mmol) in ethyl acetate (10 mL), under N_2 atmosphere was added palladium on activated carbon (10%, 35 mg). The solution was flushed with nitrogen and then stirred under H_2 atmosphere for about 2h until complete consumption of the starting material. The resulting mixture was diluted with ether (60 mL) and then filtered through a pad of celite and concentrated in *vacuo*. The crude product was purified by silica gel column chromatography using ethyl acetate/hexane mixture (1:9) to yield the compound **16** (1.1g, 95% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 3.54-3.32 (m, 2H), 2.06-1.96 (m, 1H), 1.77-1.42 (m, 3H), 1.37-1.11 (m, 6H), 0.95-0.79 (m, 14H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 68.2, 45.1, 41.2, 38.7, 33.0, 29.7, 27.4, 20.8, 20.4, 19.9, 17.5, 14.4.

IR (Neat) : 3449, 2955, 2919, 2857, 1637, 1457, 1371, 1101, 760 cm^{-1}.

$[\alpha]_D^{25}$: -7.7 (*c* = 2.1, $CHCl_3$)

(4*S*,6*S*,8*S*,*E*)-Ethyl 2,4,6,8-trtramethylundec-2-enoate (27):

To a stirred solution of IBX (2.48 g, 8.85 mmol) in DMSO (6 mL) at 25 ^oC, was added slowly drop wise a solution of alcohol (**16**) (1.1 g, 5.9 mmol) in CH_2Cl_2 (15 mL). The resulting mixture was stirred at 25 ^oC for 3h. The solid was filtered and washed with ether. The filtrate was washed with saturated aqueous $NaHCO_3$ solution, water, and brine then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to furnish the crude aldehyde. To the above aldehyde in CH_2Cl_2 (20 mL) was added ylide, ethyl 2-(triphenylphosphoranylidene)propanoate (3.30 g, 9.46 mmol) and the resulting mixture was stirred for 12 h at room temperature. The solvent was concentrated under

reduced pressure and purified on silica gel chromatography (3% EtOAc/hexane) to afford the unsaturated ester (**27**) (1.3 g, 86%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 6.44 (d, J = 10.1 Hz, 1H) 4.20 (q, J = 7.1 Hz, 2H), 2.66-2.53 (m, 1H), 1.84 (s, 3H), 1.46-1.14 (m, 10H), 1.12-0.77 (m, 15H);
^{13}C NMR ($CDCl_3$, 75 MHz)	: δ 168.3, 148.0, 126.1, 60.2, 45.5, 44.3, 39.2, 30.8, 29.6, 28.1, 20.5, 20.4, 19.9, 14.3, 14.2, 12.3.
MASS (ESI-MS)	: *m/z* 291 $(M+ Na)^+$.
HRMS (ESI)	: calcd. for $C_{17}H_{32}O_2Na$ 291.2342; found 291.2322.
IR (Neat)	: 3449, 2958, 2924, 2871, 1713, 1648, 1457, 1268, 1101, 1035, 751 cm^{-1}
$[\alpha]_D^{25}$	: +17.9 (c = 1.0, $CHCl_3$)

(4*S*,6*S*,8*S*,*E*)-2,4,6,8-Tetramethyl-2-undecenal (1): Siphonarienal

To a cooled (-78 ^oC) solution of **27** (250 mg, 0.93 mmol) in dry CH_2Cl_2 (3 mL), DIBAL-H (1.0 mL, 1.0 mmol, 20% solution in toluene) was added slowly over 5 min. The resulting mixture was allowed to stir for 30 min at -78 ^oC, before being quenched with sodium potassium tartarate solution (5 mL). The mixture was then stirred at room temperature until it becomes clear solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were concentrated in *vacuo*. Purification of the residue by flash column chromatography (2:98, EtOAc/hexane) gave the target Siphonarienal (**1**) as a colorless liquid in 80% yield.

^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 9.39 (s, 1H), 6.22 (d, J = 9.8 Hz, 1H), 2.91-2.76 (m, 1H), 1.77 (s, 3H), 1.53-1.25 (m, 4H), 1.24-1.10

(m, 3H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.95-0.78 (m, 12H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ δ 195.4, 160.6, 137.93, 45.5, 44.2, 39.2, 31.2, 29.6, 28.2, 20.4, 20.3, 20.0, 19.9, 14.3, 9.3.

IR (Neat) : 3447, 2959, 2924, 2871, 2706, 1690, 1644, 1459, 1378, 1014, 809 cm^{-1};

$[\alpha]_D^{25}$: +15.8 (*c* = 1.0, $CHCl_3$).

Lit. $[\alpha]_D^{30}$: +16.5 (*c* = 1.0, $CHCl_3$).

[(6*S*,8*S*,10*S*,*E*)-4,6,8,10-tetramethyltridec-4-3-one] (2): Siphonarienone

To a stirred solution of **1** (150 mg, 0.66 mmol) in dry THF was added EtMgBr (0.4 mL of 2M solution), at -78 ^oC and stirred for 2h. The reaction mixture was then quenched with saturated NH_4Cl and extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed sequentially with water and brine, dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure afforded the diastereomeric mixture of allylic alcohol (1:1), which was then dissolved in dry DCM (6 mL) and treated with Dess-Martin periodinane (450 mg) at 0 ^oC for 30 min. The reaction mixture was filtered through a pad of celite, washed with DCM and quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was then extracted with DCM (3 × 5mL) and washed with water and then brine. The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to furnish the crude product which was then purified by silica gel column chromatography using ethyl acetate/hexane mixture (2:98) to yield the compound **2** in 90% yield.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 6.34 (d, *J* = 9.2 Hz, 1H), 2.75-2.64 (m, 3H), 1.80 (s, 3H), 1.54-1.15 (m, 10H), 1.10 (t, *J* = 7.3 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 202.8, 148.2, 135.3, 45.5, 44.4, 39.2, 31.2, 30.3, 29.6, 28.2, 20.6, 20.4, 19.9, 19.9, 14.3, 11.5, 8.9.

IR (Neat) : 3451, 2958, 2925, 2871, 1672, 1639, 1458, 1376, 1256, 1047, 799 cm^{-1}

$[\alpha]_D^{25}$: 25.2 (*c* = 1.5, $CHCl_3$);

Lit. $[\alpha]_D^{30}$: 26.4 (*c* = 1.4, $CHCl_3$)

_N_-1-Methoxy-_N_-1,2,4,6,8-pentamethyl-(_E_,4_S_,6_S_,8_S_)-2-undecenamide (48):

To a stirred solution of ester (**27**) (300 mg, 1.34 mmol) and hydroxylamine hydrochloride (4.0 g, 4.0 mmol) in anhydrous THF (10 mL) was added ^{i}PrMgCl (2.68 mL, 5.36 mmol, 2M solution in THF) at -20 ^{o}C and allowed it to stir for 1h. Upon completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and washed with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc/hexanes, 5:95) to give the compound **48** (280 mg, 75%) as a liquid.

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 5.44 (d, *J* = 10.3 Hz, 1H), 3.38 (s, 3H), 2.69-2.54 (m, 1H), 1.88 (s, 3H), 1.55–0.93 (m, 14H), 0.99 (d, *J* = 6.7Hz, 3H), 0.88 (t, *J* = 6.7 Hz, 2H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz);

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 168.7, 141.7, 126.5, 45.6, 44.4, 39.1, 37.8, 30.2, 29.6, 29.5, 28.2, 28.8, 20.2, 20.1, 19.9, 14.3, 13.9.

MASS (ESI-MS) : *m/z* 284 $(M+ H)^+$.

IR (Neat) : 3448, 2923, 2855, 1624, 1456, 1219, 769, 668 cm^{-1}

$[\alpha]_D^{25}$: +11.1 (*c* = 1.0, $CHCl_3$)

(4-Hydroxy-3, 5-dimethyl-6-[(_E_, 3_S_, 5_S_, 7_S_)-1, 3, 5, 7-tetramethyl-1-decenyl]-2_H_-2-pyranone) (3): Pectinatone

To a freshly prepared 1.0 M solution of LDA (1.20 mL) in anhydrous THF at -20 ^{o}C was added a solution of **48** (150 mg, 0.53 mmol) in anhydrous THF (5 mL) dropwise and

allowed to stir for 30 min at 0 ^{o}C. To this mixture, a solution of **62** (252 mg, 1.59 mmol) in anhydrous THF (5 mL) was added dropwise at 0 ^{o}C and allowed it to stir for another 30 min at the same temperature. After completion, the reaction mixture was quenched with saturated aqueous NH_4Cl (6 mL) at 0 ^{o}C and allowed to warm to room temperature. The aqueous layer was separated and washed with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo to afford the crude compound **63** (415 mg) as a liquid. Without further purification, the compound **63** was treated with DBU (1.0 mL, 6.811 mmol) in anhydrous toluene under reflux for 4h. The solvent was removed under reduced pressure and then the residue was diluted with CH_2Cl_2 (10 mL) and washed with water (3 mL). The aqueous layer was again washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4 , concentrated in *vacuo*, and purified by silica gel column chromatography using ethyl acetate/hexane mixture (1:4)to give the compound **3** as a solid. m.p. = 126–128 ^{o}C;

^{1}H NMR ($CDCl_3$, 300 MHz)	: δ 5.37-5.32 (m, 1H), 2.68-2.58 (m, 1H), 2.03 (s, 3H), 1.97 (s, 3H), 1.86 (s, 3H), 1.52-1.42 (m, 2H), 1.40-1.01 (m, 8H), 0.91 (t, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 6.0 Hz, 3H), 0.85 (d, *J* = 6.0 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H);
^{13}C NMR ($CDCl_3$, 75 MHz)	: 165.2, 164.5, 159.6, 146.9, 126.2, 105.4, 98.7, 45.9, 44.8, 39.4, 30.6, 29.5, 28.3, 21.4, 20.2, 20.1, 20.0, 14.8, 14.4, 11.5, 8.5.
MASS (ESI-MS)	: *m/z* 352 $(M+ NH_4)^{+}$.
IR (Neat)	: 3201, 2923, 2858, 1655, 1455, 1375, 1226, 755 cm^{-1};
$[\alpha]_D^{25}$	: +58 (*c* = 0.2, $CHCl_3$);
Lit. $[\alpha]_D^{30}$	: +62 (*c* = 0.11, $CHCl_3$);

References:

1. a) Harvey, A.; *Drug. Discov. Today*. **2000**, *5*, 294; b) Mc Carthy, P. J.; Pomponi, S. A.; *Marine Biomed. Res.* **2004**, 1; c) Donia, M.; Hamann, M. T.; *The Lancet*. **2003**, *3*, 338; d) Haefner, B.; *Drug. Discov. Today*. **2003**, *8*, 536; e) Faulkner, D. *J. Oceanus*. **1992**, *35*, 29.
2. Pomponi, S. A. *J. Biotechnol.* **1999**, *70*, 5.
3. Weinheimer, A. J.; Spraggins, R. L. *Tetrahedron Lett*. **1969**, *15*, 5185.
4. a) Lundholm, N.; Skov, J., Pocklington, R.; Moestrup, O.; *Phycologia*. **1994**, *33*, 475; b) Dechraoui, M. Y.; Naar, J.; Pauillac, S.; Legrand, A. M.; *Toxin*. **1999**, *37*, 125; c) Kodama, M.; Ogata, T.; Sato, S. *Agric. Biol. Chem.* **1988**, *52*, 1075; d) Yasumoto, T.; Murata, M.; Oshima, T.; Sano, M.; Matsumoto, G. K.; Clardy, J.; *Tetrahedron*. **1985**, *41*, 1019.
5. Blunden, G. *Phytother. Res.* **2001**, *15*, 89.
6. a) Okami, Y.; Hotta, K.; Yoshida, M.; Ikeda, D.; Kondo, S.; Umezawa, H.; *J. Antibiot*. **1979**, *32*, 964; b) Jang, W. S.; Kim, K. N.; Lee, Y. S.; Nam, M. H.; Lee, I. H.; *FEBS Lett.* **2002**, *81*, 521.
7. a) Marcelletti, J. F. *Antiviral Research.* **2002**, *56*, 153; b) Ballatore, C.; Mc Guigan, C.; Clercq, E. D.; Balzarini, J. *Antiviral Research.* **2000**, *46*, A63; c) Dusheiko, G. M. *Pharmacology & Therapeutics*, **1995,** *65*, 47.
8. a) Haefner, B. *Drug. Discov. Today* **2003**, *8*, 536; b) Blay, J.-Y.; Cesne, A. L.; Verweij, J.; Scurr, M.; Seynaeve, C.; Bonvalot, S.; Hogendoom, P.; Jimeno, J.; Evrard, V.; Glabbeke, M.V.; Judson, I. *Eur. J. Cancer* **2004**, *40*, 1327.
9. a) Mutter, R.; Wills, M. *Bioorg. Med. Chem.* **2000**, *8*, 1841; b) Hale, K. J.; Hummersone, M. C.; Manaviazar, S.; Frigerio, M. *Nat. Prod. Rep.* **2002**, *19*, 413; c) Pettit, G. R.; Herald, C. L.; Hogan, F. In *Anticancer Drug Developement*, Baguley, B. C.; Kerr, D. J.; Eds. Academic Press: San Diego, CA, **2002**: pp. 203
10. a) de Silva, E. D.; Scheuer, P. *Tetrahedron Lett*. **1980**, *21*, 1611; b) Kernan, M. R.; Faulkner, D. J.; Jacobs, R. S. *J. Org. Chem*. **1987**, *52*, 3081; c) De Rosa, M.; Soriente, A.; Sodano, G.; Scettri, A. *Tetrahedron* **2000**, *56*, 2095.

11. a) Yang, L.; Andersen, R. J. *J. Nat. Prod.* **2002**, *65*, 1924; b) Coulson, F. R.; O' Donnell, S. R. *Inflamm. Res.* **2000**, *49*, 123; c) Shen, Y.; Burgoyne, D. L. *J. Org. Chem.* **2002**, *67*, 3908.
12. a) Murukami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn*. **1953**, *73*, 1026; b) Nilta, I.; Watase, H.; Tomic, Y. *Nature* **1958**, *181*, 761.
13. Miyamoto, T.; Togawa, K.; Higuchi, R.; Komori, T.; Sasaki, T. *Liebigs. Ann. Chem*, **1990**, 453.
14. Newmann, D. J.; Cragg, G. M. *J. Nat. Prod*. **2004**, *67*, 1216.
15. Ciavatta, M. C.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett*. **1993**, *34*, 6791.
16. Manker, D. C.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 5374.
17. Hochlowski, J. E.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc*. **1983**, *105*, 7413.
18. Suenaga, K.; Kigoshi, H.; Yamada, K. *Tetrahedron Lett*. **1996**, *37*, 5151.
19. Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. M.; Qi-tai, Z.; Cun-heng, H.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748.
20. Lumb, M.; Macey, P. E.; Spyvee, J.;Whitmarsh, J. M.; Wright, R. D. *Nature* **1965**, *206*, 263-268.
21. Ishiwata, H.; Nemoto, M.; Ojika, M.; Yamada, K. *J. Org. Chem*. **1994**, *59*, 4710-4711.
22. a) Mazery, R.; Pullez, M.; López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa. B. L. *J. Am. Chem. Soc.* **2005**, *127*, 9966-9967; b) Mori, K.; Kuwahara, S. *Tetrahedron* **1986**, *42*, 5539-5544; c) Hanaki, N.; Ishihara, K.; Kaino, M.; Naruse, Y.; Yamamoto, H. *Tetrahedron* **1996**, *52*, 7297-7320; d) For the stereochemistry of lardolure, see: Mori, K.; Kuwahara S. *Tetrahedron* **1986**, *42*, 5545-5550.
23. a) Chow, S.; Fletcher, M. T.; Lambert, L. K.; Gallagher, O. P.; Moore, C. J.; Cribb, B. W.; Allsopp, P. G.; Kitching, W. *J. Org. Chem.* **2005**, *70*, 1808-1827; (b) Fletcher, M. T.; Chow, S.; Lambert, L. K.; Gallagher, O. P.; Cribb, B. W.; Allsopp, P. G.; Moore, C. J.; Kitching, W. *Org. Lett*. **2003**, *5*, 5083-5086.

24. a) Casas-Arce, E.; ter Horst, B.; Feringa, B. L. Minnaard, A. J. *Chem. Eur. J.* **2008**, *14*, 4157-4159. For a review on deoxypropionates in mycobacteria see: Minnikin, D. E.; Kremer, L.; Dover, L. G.; Besra, G. S. *Chem. Biol.* **2002**, *9*, 545-553.
25. a) Liu, C.-M.; Hermann, T. E. *J. Biol. Chem.* **1978**, *253*, 5892-5894.
26. Norte, M.; Cataldo, F.; Gonza´lez, A. G.; *Tetrahedron Lett*. **1988**, *29*, 2879.
27. Kohno, J.; Nishio, M.; Sakurai, M.; Kawano, K.; Hajime, H.; Kameda, N.; Kishi, N.; Yamashita, T.; Okuda, T.; Komatsubara, S. *Tetrahedron* **1999**, *55*, 7771.
28. For a review see: Schetter, B.; and Mahrwald, R. *Angew. Chem., Int. Ed*., **2006**, *45*, 7506.
29. a) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, *21*, 4675; (b) Evans, D.; Bartroli, A. J.; Shih, T. L. *J. Am. Chem. Soc*. **1981**, *103*, 2127.
30. Davies-Coleman, M. T.; Garson, M. *J. Nat. Prod. Rep.* **1998**, *15*, 477-493.
31. (a) Garson, M. J. *Chem. Rev*. **1993**, *93*, 1699; (b) Garson, M. J.; Jones, D. D.; Small, C. J.; Liang, J.; Clardy, J. *Tetrahedron Lett*. **1994**, *35*, 6921; (c) Garson, M. J.; Goodman, J. M.; Paterson, I. *Tetrahedron Lett*. **1994**, *35*, 6929.
32. Norcross, R. D.; Paterson, I. *Chem. Rev*. (Washington, D.C.) **1995**, *95*, 2041.
33. a) Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem*. **1989**, *54*, 5371. b) Roll, D. M.; Bisakupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc*. **1986**, *108*, 6680.
34. a) Norte, M.; Ferna´ndez, J. J.; Padilla, A. *Tetrahedron Lett.* **1994**, *35*, 3413-3416. b) Norte, M.; Cataldo, F.; Gonza´ lez, A. G.; Rodrı´guez M. L.; Ruiz-Perez, C. *Tetrahedron* **1990**, *46*, 1669-1678.
35. Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett.* **1983**, *24*, 3055-3058.
36. Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054-2070.
37. Paul, M. C.; Zubia, E.; Ortega, M. J.; Salva, J. *Tetrahedron* **1997**, *53*, 2303-2308.
38. Garson, M. J.; Small, C.; Skelton, B. W.; Thinapong, P and White, A. H. *J.Chem. Soc. Perkin Trans I* **1990**, 805-807.
39. Lum, T-K.; Wang, S-Y.; Loh, T.P. *Org. Lett.* **2008**, *10*, 761-764
40. Magnin-Lachaux, M.; Tan, Z.; Liang, B. and Negishi, E.-I. *Org. Lett.* **2004**, *6*,1425-1427

41. Calter, M. A.; Liao, W.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500-7504
42. Birkbeck, A. A.; Enders, D. *Tetrahedron Lett.* **1998**, *39*, 7823-7826
43. Sabitha, G.; Gopal, P.; Yadav, J. S.; *Tetrahedron Asymmetry* **2009**, *20*, 2205-2210.
44. a) Miller, J. J. ; Benneville, P. L.; De *J. Org. Chem.* **1957**, *22*, 1268; b) Stork, G.; Nair, V. *J. Am. Chem. Soc.* **1979**, *101*, 1315.
45. Wolfrom, M. L.; Bobbitt, J. M. *J. Am. Chem. Soc.* **1956**, *78*, 2489.
46. a) Fujita, K.; Mori, K.; *Eur. J. Org. Chem.* **2001**, 493-502.b) Schmidt, Y.; Lehr, K.; Breuninger, U.; Brand, G.; Reiss, T.; Breit, B.; *J. Org. Chem.* **2010**, *75*, 4424-4433.c) Tsuji, K.; Terao, Y.; Achiwa, K.; *Tetrahedron Lett.* **1989**, *30*, 6189-6192. d) Lin, G.; Xu, W.; *Tetrahedron* **1996**, *52*, 5907-5912; e) Anderson, J. C.; Ley, S. V.; Marsden, S. P.; *Tetrahedron Lett.* **1994**, *35*, 2087-2087. f) McAllister, G. D.; Taylor, R. J. K.; *Tetrahedron Lett.* **2004**, *45*, 2551-2554.
47. a) Omura, K.; Swern, D.; *Tetrahedron* **1978**, *34*, 1651–1660.b) Mancuso, A. J.; Brownfain, D. J.; Swern, D.; *J. Org. Chem.* **1979**, *44*, 4148-4150.
48. a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737; b) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775.
49. Weise, C. F.; Pischl, M.; Pfaltz, A.; Schneider, C. *Chem Commun.* **2011**, *47*, 3248.
50. Breit, B.; Schmidt, Y. *Org. Lett.* **2009,** *11***,** 4767-4769.
51. a) M.Norte, J. J. Fernández, A. Padilla, *Tetrahedron Lett.* **1994**, *35*, 3413-3416; b) Y. Galeyeva, M. Morr, A. Baro, M. Nimtz, F. Sasse, S. Laschat, *Synthesis* **2005**, 2875-2880.c) T.-K. Lum, S.-Y. Wang, T.-P. Loh, *Org. Lett.* **2008**, *10*, 761-764.

CHAPTER III: SECTION A

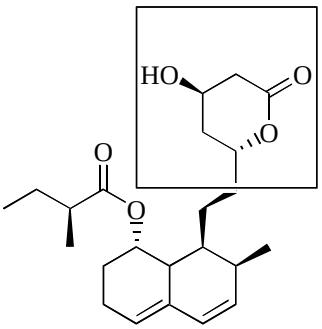
Introduction to Ferrier rearrangement.

Introduction

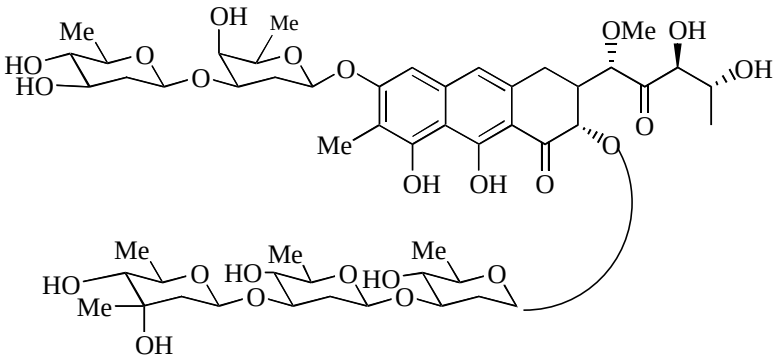
The field of carbohydrate chemistry has been occupied the minds and hearts of many scientists for over a hundred years and it continues to be both vigorous and challenging. Among the most exciting aspects of organic chemistry in the last few decades has been the interplay between the specialized sub disciplines of carbohydrate chemistry and total synthesis. The abundance of carbohydrates in nature and their diverse roles in biological systems make them attractive as subjects for chemical and biological research and they found as monomers, oligomers, or polymers, or as components of biopolymers and other naturally occurring substances. As domains of natural products, they play important roles in conferring certain physical, chemical, and biological properties to their carrier molecules. Due to their importance as building blocks, synthetic targets, and biological tools, and their potential as drug candidates, investigations into these compounds have been on the rise for some time. They have been implicated in many cellular processes, including cell -cell recognition, cellular transport, and adhesion; they appear in all cells in some form or another, for example, as peptido- and proteoglycans, glycoproteins, nucleic acids, lipopolysaccharides, or glycolipids.[1]

Glycals are versatile building blocks in synthetic chemistry via 2-deoxyglycosides and 2,3-unsaturated glycosides and have been extensively investigated for the synthesis of various important molecules.[2] 2-Deoxyglycosides are common structural elements of natural products, especially antibiotics with antitumor activity, such as the anthracycline antibiotic daunorubicin, β-rhodomycinone A, aureolic acid, compactin, thromboxane B 2, avermectin B1a and the erythromycin A (Figure 1). The anthracycline quinone antibiotics daunorubicin (DNR) and doxorubicin are potent antitumor agents against a variety of solid tumors. Both, α- or β -glycosidic linkages to the aglycon are found in these bioactive natural products.. While the specific therapeutic effect is thought to be caused by the aglycon, the carbohydrate residue is assumed to be responsible mainly for regulating the pharmacokinetics. The glycosydation of glycols was achieved in a number of manners.

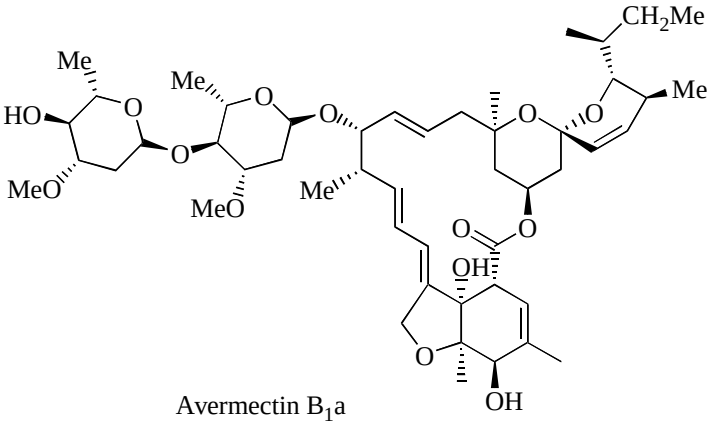
The chemistry of glycosyl transfer represents an enormous research endeavor. The most frequently used methodologies for forging the glycosidic linkage involve generation of a leaving group at the anomeric carbon of the glycosyl donor which is then displaced by a nucleophilic group from the glycosyl acceptor.



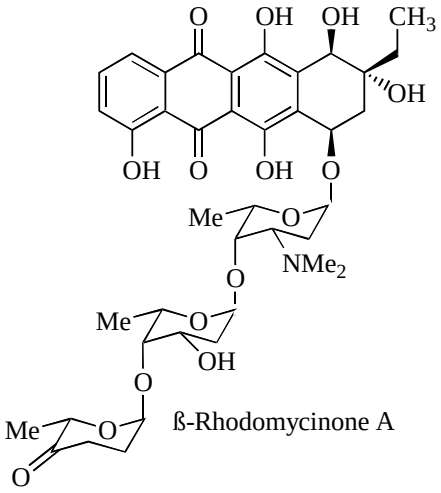
(+) - Compactin



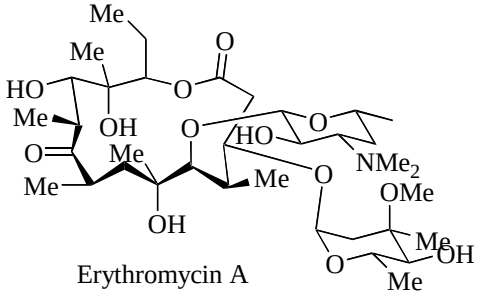
Aureolic acid



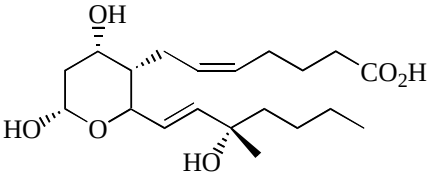
Avermectin B_1a



ß-Rhodomycinone A



Erythromycin A

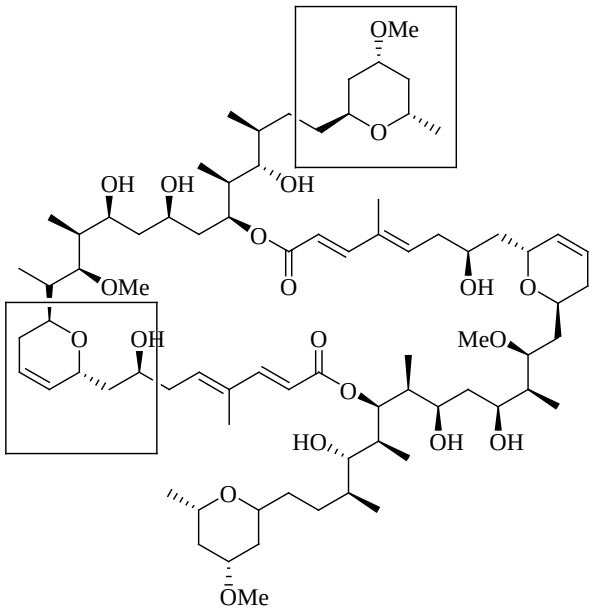


(+) - Thromboxane

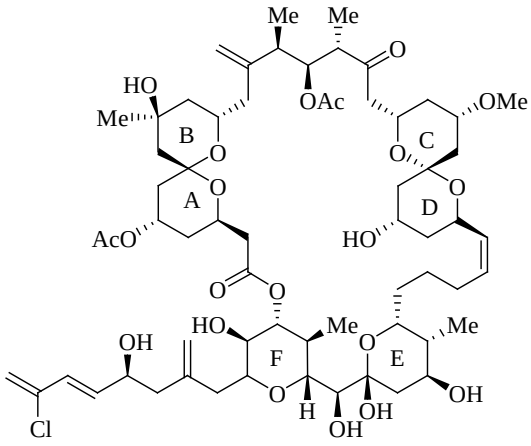
Figure 1

The art and subtlety of this step are found in a complicated algorithm which includes solvent, leaving group, Lewis acid catalyst, and the influence of the neighboring group at C-2 that can be reductively removed after its control features are no longer needed.[3]

Carbohydrate analogs in which a carbon atom substitutes for the glycosidic oxygen are called *C*-glycosides. During the last two decades, the synthesis of *C*-glycosides has become an area of intense study among carbohydrate chemists and biochemists because: 1) The discovery of naturally occurring *C*-nucleosides with important pharmacological properties gave impetus to synthetic efforts for preparing active carbohydrate analogs; 2) The requirement of *C*-glycoside chiral building blocks in the synthesis of biologically important macromolecules, such as palytoxin,[4] spongistatin [5] and swinholides[6] (Fig. 2); 3) *C*-glycosides are potential inhibitors of carbohydrate processing enzymes and are stable analogs of glycans involved in important intra- and inter-cellular processes.[7]



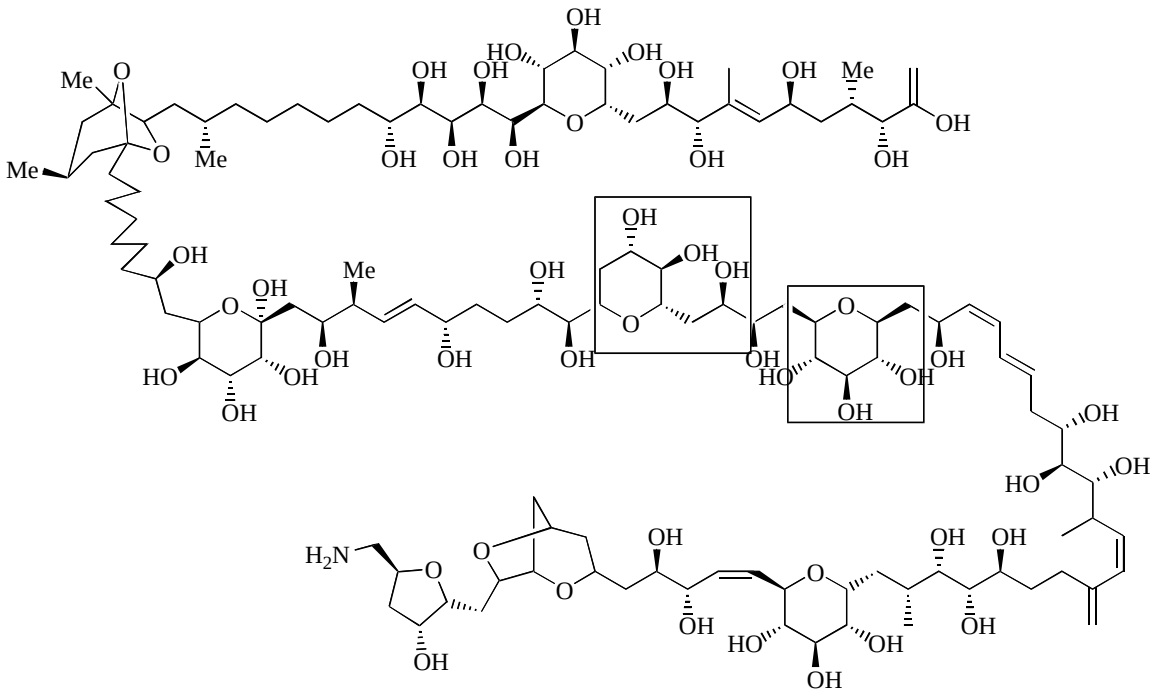
Swinholide A



Spongistatin 1

Figure 2: The swinholides are a series of complex macrodiolides, isolated from the marine sponge *Theonella swinhoei,* which displayed potent cytotoxicity.

The spongistatins (altohyrtins) were recently isolated from *Sopongia sp.* and have been found to be extraordinarily effective against a variety of chemo resistant tumor types, which comprise the NCI- panel of 60 human cancer cell lines.

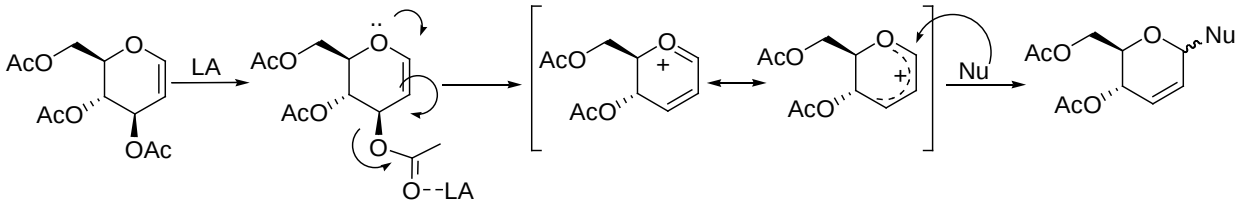


Palytoxin

Figure 2c: Palytoxin is a marine alkaloid isolated from *palythoa nelliae*. It is a potent non-12-O-tetradecanoylphorbol-13-acetate (TPA)-type skin tumor inhibitor.

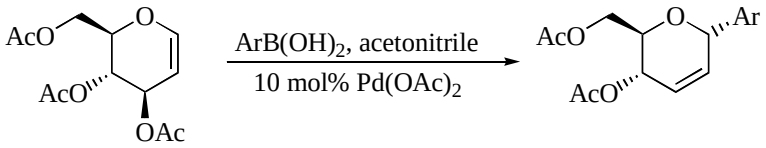
Ferrier rearrangement:

The acid-catalyzed allylic rearrangement of glycols in the presence of nucleophiles such as alcohols, thiols, azides etc., known as Ferrier rearrangement[8] and widely employed to obtain 2,3-unsaturated glycosides.



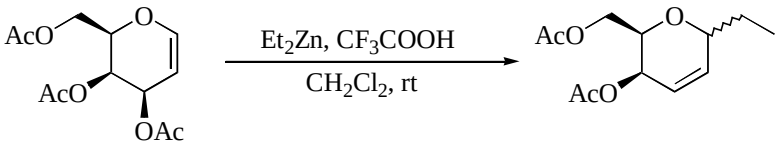
Previous Approaches

Maddaford *et al*[9] reported the *C*-glycosidation of the glycals with aryl boronic acids in presence of catalytic amount of palladium acetate in acetonitrile at ambient temparature (Scheme 1).



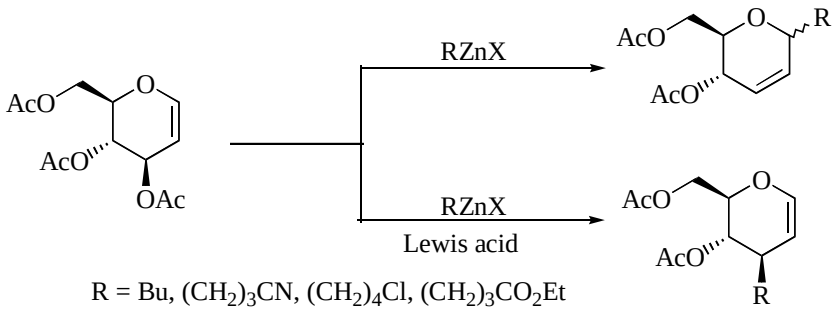
Scheme 1

Song Xue *et al*[10] reported the glycosidation of glycal with diethyl zinc in the presence of CF_3COOH to furnish the corresponding glycosides with α:β ratio 2.5:1 in 97% yield (Scheme 2).



Scheme 2

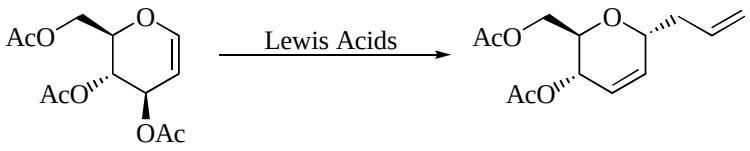
Gallagher *et al*[11] reported the reaction of glycals with simple and functionalized alkyl Zn/Cu reagents in the presence of $BF_3.Et_2O$ afforded C(3)-branched carbohydrates with retention of configuration at C(3) whereas in absence of Lewis acid, C(1)-adduct was obtained predominantly with high β-selectivity (Scheme 3).



R = Bu, $(CH_2)_3CN$, $(CH_2)_4Cl$, $(CH_2)_3CO_2Et$

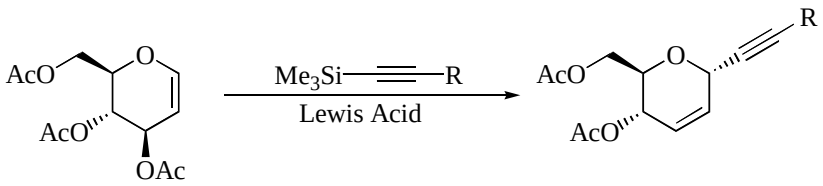
Scheme 3

Glycals underwent Ferrier reaction with allyltrimethyl silane in the presence of different Lewis acids such as BF_3Et_2O or $TiCl_4$, DDQ etc., to give allyl C-glycosides in high yields (Scheme 4).[12]



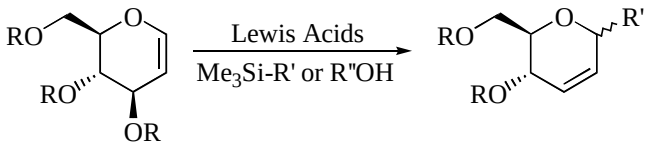
Scheme 4

Nishikawa *et al*[13] reported *C*-Glycosidation of glycals with silyl acetylenes in the presence of Lewis acids such as $SnCl_4$, $BF_3.Et_2O$, $TiCl_4$, TMSOTf and iodine gave sugar acetylenes with high α-selectivity (Scheme 5).



Scheme 5

Yadav *et al*[14,15,16] disclosed the synthesis of *C*-glycosides and *O*-glycosides using allyltrimethylsilane, trimethylsilylcyanide, bistrimethylsiylacetylenes and alcohols as nucleophiles in the presence of Lewis acids scandium triflate, indium chloride, indium bromide, lithium tetrafluoroborate ($LiBF_4$) and $CeCl_3.7H_2O$ (Scheme 6).



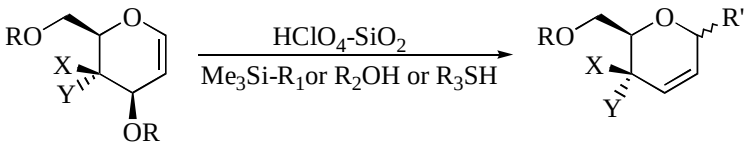
R' = allyl, TMSacetylenyl, cyanide, azide, R"O

R = Ac, Bz, Piv

Scheme 6

Mishra *et al*[17] reported the $HClO_4$-SiO_2 catalyzed synthesis of *C*-glycosides, *O*-glycosidess and *S*-glycosides from preacetylated glycals using allyltrimethylsilane and

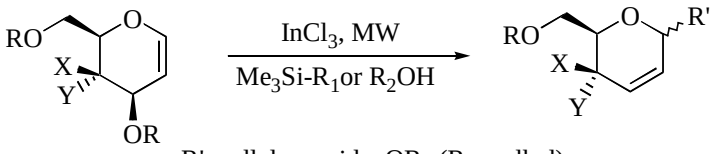
active methylene compounds, alcohols and thiols as nucleophiles in acetonitrile at ambient temparature (Scheme 7).



R' =R_1= allyl, -$CH(COOEt)_2$, -$CH(COMe)_2$, cyanide,
R' = OR_2, SR_3 (R_2 = R_3 = alkyl or aryl)
Glucal: R = Ac, X = H; Y = Ac; Galactal:R = Ac, X = Ac; Y = H

Scheme 7

Kumar Das *et al*[18] reported the microwave assisted synthesis of C-glycosides and O-glycosides from per-*O*-acetyl glycals using silanes and alcohols as nucleophiles in the presence of $InCl_3$ to obtain α-glycosides exclusively (Scheme 8).



R' = allyl, cyanide, OR_2 (R_2 = alkyl)
Glucal: R = Ac, X = H; Y = Ac;
Galactal:R = Ac, X = Ac; Y = H

Scheme 8

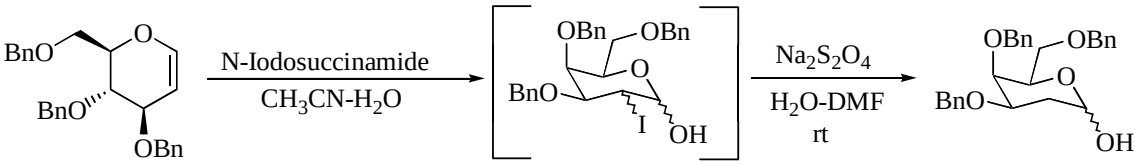
Schmidt *et al*[19] reported the glycals reacted with silyl enol ethers and alcohols in the presence of ytterbium triflate to furnish C(1)-adducts with a high α-selectivity in organic solvents as well as in ionic liquids (Scheme 9).

Scheme 9

Balasubramanian *et al*[20] reported, treatment of tri-O acetyl-D-glucal with diverse thiols in the presence of $LiBF_4$ in CH_3CN, furnished aryl/alkyl 2,3-unsaturated thioglycopyranosides 56-72% with low anomeric selectivity (Scheme 10).

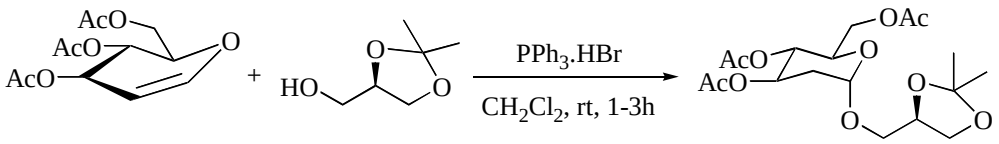
Scheme 10

Costantino *et al*[21] reported synthesis of the 2-deoxyglycosides from glycals by treatment with *N*-iodosuccinimide in CH_3CN-H_2O (95:5) and removal of the iodide group using $Na_2S_2O_4$ in DMF/H_2O at room temparature. 2-Deoxyglycosides obtained as a mixtrure of α-anomers (Scheme 11).



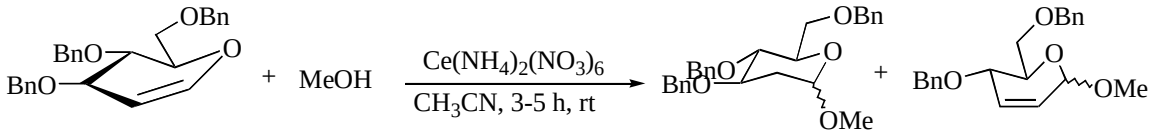
Scheme 11

Falk *et al*[22] syntheisized 2-deoxyglycosides by treatment of glycals with hydroxylic nucleophiles in the presence of the catalytic amount of triphenyl phosphine hydrogen bromide (TPHB) (5 mol %) in anhydrous CH_2Cl_2 at ambient temperature for 3 hours (Scheme 12).



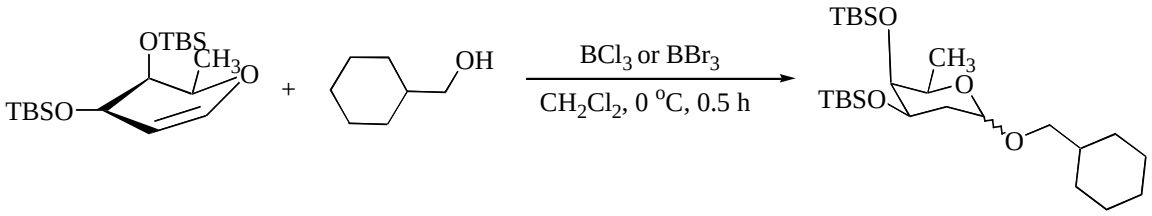
Scheme 12

According to Kandasamy *et al*[23] glycals under went addition of alcohols in presence of 2 mol % CAN to form the corresponding 2-deoxy-O-glycosides[7]with varying α/β ratio of the *O*-glycosides along with the formation of the Ferrier products, albeit, in only trace amounts (Scheme 13).



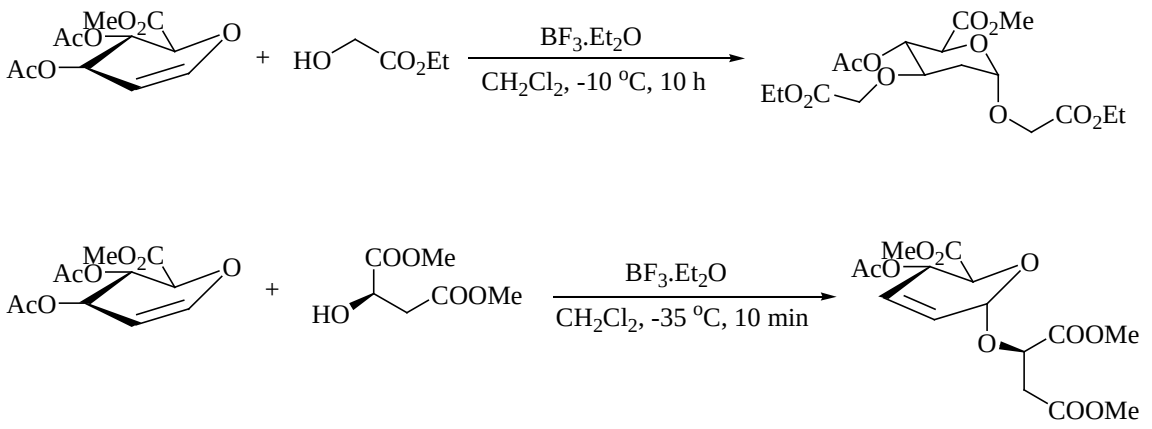
Scheme 13

Toshima *et al*[24] achieved the glycosidations of silylated glycals with alcohols using 10 mol % of BCl_3 or BBr_3 at 0 °C for 0.5 h to afford the corresponding anomeric mixture of 2-deoxyglycosides (Scheme 14).



Scheme 14

Thiem *et al*[25] reported the reaction of methyl 3,4-di-O-acetyl-1,2-dideoxy-D-*arabino*-hex-1-enopyranuronate with ethyl hydroxy acetate catalyzed by $BF_3.Et_2O$ gave saturated 2-deoxyglycosides, having the nucleophiles attached both at C-1 and C-3 (Scheme 15).


MeO2C
AcO
AcO
O
+
HO
CO2Et
BF3.Et2O
CH2Cl2, -10 °C, 10 h
CO2Me
O
AcO
O
EtO2C
O
CO2Et
MeO2C
AcO
AcO
O
+
COOMe
HO
COOMe
BF3.Et2O
CH2Cl2, -35 °C, 10 min
MeO2C
AcO
O
O
COOMe
COOMe

Scheme 15

References:

1. M. Sznaidman in Bioorganic Chemistry: Carbohydrates (Ed. S. M. Hecht), Oxford University Press, New York, **1999**, pp. 1 - 56;
2. Williams, L. J.; Garbaccio, R. M.; Danishefsky, S. J. In Carbohydrates in Chemistry and Biology; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, **2000**; Vol. *1*, pp 61–92.
3. a) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734; b) Barresi, F.; Hindsgaul, O. *J. Carbohydr. Chem.* **1995**, *14*, 1043.
4. Lewis, M. D.; Cha, J. K.; Kishi, Y. J. *Am. Chem. Soc.* **1982**, *104*, 4976.
5. a).Paterson, L.; Keown, L.E. *Tetrahedron Lett.* **1997**, *38*, 5727; b) Smith, III., A.B.; Zhuang, L.; Brook, C.S.; Boldi, A.M.; McBriar, M.D. et. al. *Tetrahedron Lett.* **1997**, *38*, 8667.
6. Kashman, Y.; Carmely, S. *Tetrahedron Lett.* **1985**, *26*, 511.
7. Nicotra, F. *Topics Curr. Chem.* **1997**, *187*, 55; b) Weatherman, R. V.; Mortell, K. H.; Chervenak, M.; Kiessling, L. L.; Toone, E. J. *Biochemistry* **1996**, *35*, 3619; c) Weatherman, R.; Kiessling, L. L. J. *Org. Chem.* **1996**, *61*, 534; d) Sutherlin, D. P.; Stark, T. M.; Hughes, R.; Armstrong, R. W. J. *Org. Chem.* **1996**, *61*, 8350.
8. (a) Ferrier, R. J. *J. Chem. Soc. (C*) **1964**, 5443; b) Ferrier, R. J.; Ciment, D. M. *J. Chem. Soc. (C)* **1966**,441; c) Ferrier, R. J.; Prasad, N. *J. Chem. Soc.(C)* **1969**,570; d) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. (C)* **1969**,581; e) Danishefsky, S.; Keerwin, J. F. *J. Org. Chem*. **1982**, *47*, 3803. f) Ferrier; R. J. *J. Chem. Soc., Perkin Trans.* **1979**, *1*: 1455–1458.
9. Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013.
10. Xue, S.; Lin He, Han, K.-Z.; Zheng, X.-Q.; Guo, Q-X. *Carbohy. Res.* **2005**, *340*, 303.
11. Thorn, S. N.; Gallagher, T. *Synlett*, **1996**, 856.

12. a) Ichikawa, Y.; Isobe, M.; Konobe, M.; Goto, T. *Carbohydr. Res.* **1987**, *171*, 193; b) Danishefsky, S. J.; Keerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803; c)Toshimam K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Chem. Lett*. **1993**, 2013.
13. Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *J. Chem. Soc*. *Chem. Commun.* **1998**, 2665.
14. a) Yadav, J. S.; Subba Reddy, B. V.; Chand, P. *Tetrahedron Lett*. **2001**, *42*, 4045; b) Yadav, J. S.; Subba Reddy, B. V.; Murthy, C. V. S. R.; Kumar, G. M. *Synlett*, **2000**, 1450.
15. a) Yadav, J. S.; Reddy, B. V. S.; Raman, J. V.; Niranjan, N.; Kumar, S. K.; Kunwar, A. C. *Tetrahderon Lett*. **2002**, *43*, 2095; b) Yadav, J. S.; Reddy, B. V. S. *Synthesis* **2002**, 511; c) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K.; Rao, C. V. *Tetrahderon Lett*. **2002**, *43*, 5437.
16. a) Yadav, J. S.; Reddy, B. V. S.; Chandraiah, L.; Reddy, K. S. *Carbohydr. Res*. **2001**, *332*, 221.b) Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Satyanarayana, M. *Tetrahderon Lett*. **2002**, *43*, 7009.
17. a) Tiwari, P.; Agnihotri, G.; Misra, A. K. *Carbohydr. Res*. **2005**, *340*, 749; b) Misra, A. K.; Tiwari, P.; Agnihotri, G. *Synthesis*, **2005**, *2*, 260.
18. a) Das, S. K.; Reddy, K. A.; Roy, J. *Synlett*, **2003**, *11*, 1607; b) Das, S. K.; Reddy, K. A.; Abbineni, C.; Roy, J.; Rao, K. V. L. N.; Sachwani, R. H.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 4507.
19. a) Takhi, M.; Abdel-Rahman, A. A.-H.; Schmidt, R. R. *Tetrahderon Lett*. **2001**, *42*, 4053; b) Takhi, M.; Abdel-Rahman, A. A-H.; Schmidt, R. R. *Synlett*, **2001**, 427.
20. Babu, B. S.; Balasubramanian, K. K. *Tetrahderon Lett*. **1999**, *40*, 5777.
21. Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *Tetrahedron Lett*. **2002**, *43*, 9047.
22. Bolitt, V.; Mioskowski, C.; Lee, S-G.; Falck, J. R. *J. Org. Chem*. **1990**, *55*, 5812.
23. Pachamuthu, K.; Vankar, Y. D. *J. Org. Chem.* **2001**, *66*, 7511.
24. Toshima, K.; Nagai, H.; Ushiki, Y.; Matsumara, S. *Synlett* **1998**, 1007.
25. Wieczorek, E.; Thiem, J. *Synlett* **1998**, 467.

CHAPTER III: SECTION B

A tandem Ferrier and Click reaction: a facile synthesis of, triazolyl-2,3-dideoxypyranosides.

Introduction

Organic molecules generally have frameworks of carbon atoms; one of the biggest challenges in chemical synthesis is finding ways to link two carbon atoms together to make C–C bonds. In natural this often happens *via* generic reactions. Sharpless feels that organic chemists have long made the error of thinking that they should mimic nature in finding ways of creating new C–C bonds. But most synthetic reactions that exist to do this have only a very modest thermodynamic driving force – which means that they happen inefficiently, giving low yields. That is a huge burden for pharmaceutical chemists, because every low-yield step in a multi-step synthesis of some biologically active molecule slashes the final yield of product and makes the synthesis wasteful and costly. It also makes the process of drug discovery slow, because it is expensive in labor, time and materials to make new candidate drugs.

So Sharpless argues that, rather than slogging away at what we do badly, we should focus on what we can do well. Nature's chemistry isn't just about making C–C bonds, he says; in fact, the small-molecule building blocks of nature's key compounds – proteins, nucleic acids and polysaccharides – generally have no more than six consecutive C–C bonds. They are full of heteroatom bonds, in which carbon is linked to atoms of a different element, mostly oxygen or nitrogen. The heteroatom X often bridges two carbons, creating C–X–C units.

Linkages of this sort, he says, are much easier to make efficiently. So why not focus on them? In other words, we can start with molecules that have all the C–C bonds we need, and think about how to link up these reagents in the right way via heteroatom bonds made using efficient reactions. This, he says, turns the philosophy of drug development on its head. Rather than choosing some daunting molecular target and then slaving at the bench for years to try to make it, we should pay greater attention to molecules that we know how to make, using reliable and effective heteroatom chemistry.

Click Chemistry:

Nobel laureate Barry Sharpless, Scripps Institute, US, coined the term click chemistry. Sharpless and other converts to the 'click' concept have concentrated on finding reactions with a large thermodynamic driving force, which give virtually complete conversion of reagents to a single product. Such reactions are 'spring-loaded' – they start with 'high-energy' compounds

that will 'click' together in a predictable way with very little prompting. Ideally, such reactions should proceed under relatively mild reaction conditions – no intensive cooking, which run the risk of breaking down some reagents or products into unwanted byproducts. And they should work in solvents that are benign, especially water. All of this potentially makes click chemistry both clean (it doesn't produce anything you don't want) and green. 'The lack of byproducts and quantitative yields are the big advantages of click chemistry for materials chemistry,' says polymer chemist Craig Hawker of the University of California in Santa Barbara, US.

In 2009, 94% of the top grossing pharmaceuticals were nitrogen-containing molecules. As pharmaceutical agents containing nitrogen atoms in their structure become increasingly common, growing interest has been generated in the synthesis of molecules that incorporate nitrogen. Therefore, synthetic chemists aim to incorporate nitrogen-containing heterocyclic in their target compounds in the most efficient way. In the last decade, 1,2,3-triazoles (Figure 1.1) have received much attention, as their intriguing physical and biological properties, as well as their excellent stability, render them promising drug core structures.

Compounds containing 1,2,3-triazoles have been shown to exhibit a wide range of biological activity, including anticancer[1], antiparasitic[2] and antiviral[3] behavior.

In addition to substituted 1,2,3-triazoles, fused 1,2,3-triazoles have also demonstrated relevance in the pharmaceutical industry. As compounds containing fused 1,2,3-triazoles become increasingly common in pharmaceutical targets and biologically active substances, such as

chemotherapeutic[4] and cardiovascular[5] agents (Figure 1.3), new strategies to synthesize this class of molecules are highly desirable.[6]

The copper-catalyzed azide-alkyne cycloaddition (CuAAC)

Since 1,2,3-triazoles are extremely important in the chemical and biological community, immense effort has been put into the design of efficient and high-yielding methods for their preparation. The most prominent way to access 1,4-disubstituted 1,2,3-triazoles is the copper-catalyzed azide-alkyne cycloaddition (CuAAC),[7]as pioneered by Meldal[8] and Sharpless.[9] In this process, an azide is reacted with an alkyne in a [3+2] cycloaddition, in the presence of a Cu(I) catalyst. Due to its reliability and specificity, the CuAAC has become the gold standard of "click chemistry".[10] A "click" reaction generates substances quickly and reliably by joining small units together. The term describes reactions that are modular, widely applicable, high-yielding, environmentally friendly, and stereo specific. The process should also employ simple reaction conditions, readily available starting materials and reagents, a lack of solvent or a solvent that is not harmful and easily removed, and straightforward isolation of the product, which should remain stable under air and room temperature. The abovementioned criteria are achieved by the CuAAC and other click reactions, owing to their high thermodynamic driving force (>20 kcal/mol), which allows the reactions to go to completion and to be highly selective for a single product.

The original reaction, the azide–alkyne (Huisgen) cycloaddition,[11] was performed using a heat source, producing a mixture of 1,4-disubstituted 1,2,3-triazoles and 1,5-disubstituted 1,2,3-triazoles. This result contradicted several of the requirements for a click reaction. In 2002, Sharpless[9] and Meldal[8] independently observed the exclusive formation of the 1,4-regioisomer when using a Cu(I) catalyst in the cycloaddition of the azide with the alkyne. Not only did the

Cu(I) catalytic system produce a single regioisomer, but it also accelerated the reaction and allowed for it to proceed at room temperature. The Cu(I) catalyst can either be generated *in situ* from copper(II) sulfate, used together with sodium ascorbate as a reducing agent, or it can consist of a copper(I) halide, along with a stabilizing ligand. Jia reported the use of a Ru(II) catalyst in the cycloaddition, which generated only the 1,5-disubstituted 1,2,3-triazole (Scheme 1).[12]

Scheme 1

Proposed catalytic cycle for Cu (I)-catalyzed ligation:

The mechanistic proposal for the catalytic cycle is shown in Scheme 1. It begins unexceptionally with the formation of the copper (I) acetylide **I** (i.e. no reaction is observed with internal alkynes). Then proceeds *via* stepwise annealing sequence **B-1** to **B-2** to **B-3** not in B-directly (this is strongly disfavored by extensive density functional theory calculations-according to this 12-15 kcal-energy is required for concerted [2+3] cycloaddition). This **B-2** proceeds *via* the intriguing six-membered copper-containing intermediate **III**, hence the term "ligation" came for this mechanism (Figure 1).[9] finally, and cleavage of metal complex leads to the formation of triazoles.

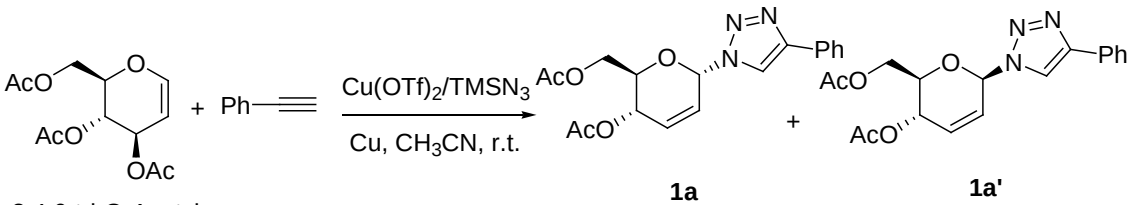
Figure 1

Present work

Since triazole linked glycoconjugates have become increasingly useful and important in glycobiology, the development of a simple and efficient method for their synthesis in a single step operation is desirable.

In this section, we have described a direct one-pot method for the synthesis of triazole-linked glycoconjugates from readily available D-glucal, TMS azide and alkyne involving a tandem Ferrier and Click reaction.[13]

In a preliminary study, 3,4,6-tri-O-acetyl-D-glucal (**1**) was treated with trimethylsilyl azide and phenylacetylene (**2**) in the presence of 10 mol% of $Cu(OTf)_2$ and 1 eq. of metallic copper in acetonitrile. The reaction proceeded smoothly at room temperature and the product, 1,2,3-triazole-linked glycoside was obtained in 85% yield as a mixture of α-**1a**, and β-isomers **1a'** in 3:2 ratio favoring α-isomer **1a** (Scheme 2).



3,4,6-tri-O-Acetyl D-glucal

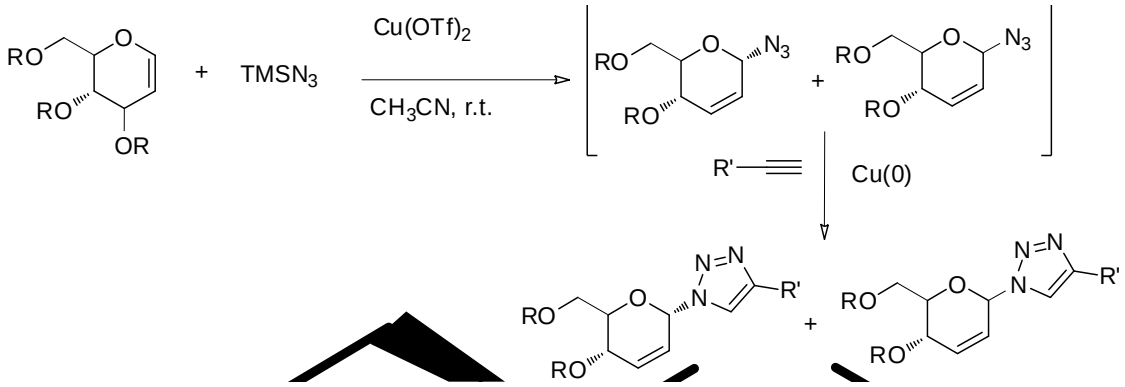
1a **1a'**

Scheme 2

The stereoisomers **1a** and **1a'** could be easily separated by column chromatography. This result provided the incentive for further study of reactions with various other alkynes such as 1-octyne, 1-hexyne, 4-phenyl-1-butyne and propargyl ether. These alkynes reacted readily with glycosyl azides under identical conditions to produce triazole-linked glycosides in high yields (entries b-m, Table 1). Other glucal derivatives such as 3,4,6-tri-*O*-methyl, 3,4,6-tri-*O*-benzyl, 3,4,6-tri-*O*-TBDMS and 3,4,6-tri-*O*-allyl-D-glucal also underwent smooth coupling with trimethylsilyl azide and alkynes to produce 1,2,3-triazole- linked 2,3-dideoxypyranosides in good yields.

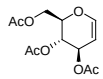
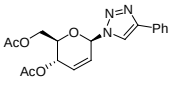
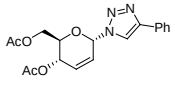
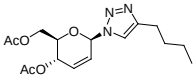
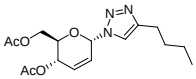
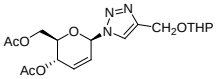
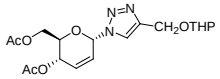
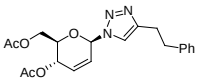
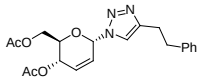
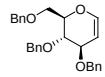
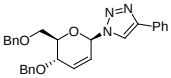
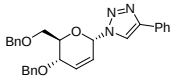
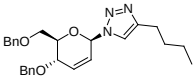
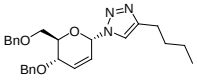
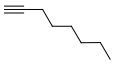
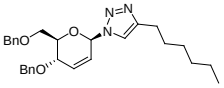
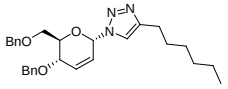
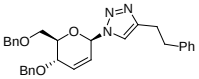
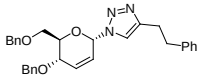
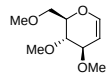
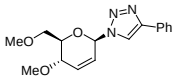
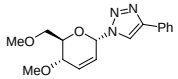
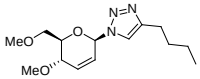
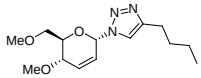
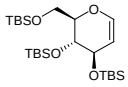
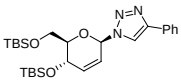
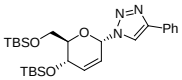
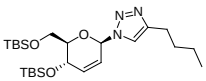
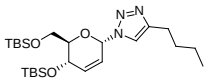
This method tolerates highly acid labile protecting groups such as THP and TBDMS ethers. However, in the absence of either copper triflate or copper (0), the reaction did not give the expected triazole even after long reaction times (8-12 h).

Both copper triflate and copper metal are essential for the success of the reaction. As solvent, acetonitrile appears to give the best results. The scope and generality of this process is illustrated in Table 1. The reaction may proceed via the Ferrier rearrangement followed by [3+2] cycloaddition as depicted in (Scheme 3).



Scheme 3

Table 1: Synthesis of triazole linked glycosides via the Ferrier and Click reactions

Entry	Glucal	Alkyne	Products	Time (h)	Yield (%)b	a:a'
a			 	4.5	85	6:4
b	"		 	5.0	80	8:2
c	"		 	5.0	70	7:3
d	"		 	4.5	75	7:3
e			 	4.5	85	6:4
f	"		 	5.5	80	9:1
g	"		 	6.0	80	8:2
h	"		 	5.5	70	6:4
i			 	4.5	80	6:4
j	"		 	5.0	75	8:2
k			 	6.0	70	7:3
l	"		 	6.5	65	8:2
m				6.5	65	7:3

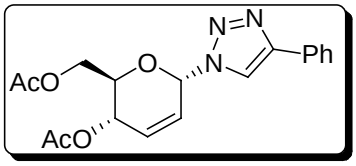
a) All products were characterized by NMR, IR and mass spectrometry.
b) Yield refers to pure products after chromatography.

In conclusion, we have developed a direct one-pot glycosylation method for the synthesis of 1,2,3-triazole bridged glycoconjugates. By executing several reaction steps in a single step and purifying only at the final stage, this procedure excludes the isolation of azide intermediate, which significantly reduces the reaction time and improves the overall yield. This method provides an easy access to build a metabolically stable triazole linkage between carbohydrates and other functional groups, which can be used as a new strategy for the bioconjugation of carbohydrates.

Experimental procedure:

A mixture of glucal triacetate (0.5 mmol), $TMSN_3$ (0.6 mmol) and $Cu(OTf)_2$ (5 mol %) in acetonitrile (2 mL) was stirred at room temperature for 2 h. Then phenyl acetylene (0.55 mmol) and Cu-powder (10 mol %) were added and the resulting mixture was stirred at room temperature for another 2.5 h. After completion of the reaction, as monitored by TLC, the product was extracted with ethyl acetate (3x10 mL) and dried over anhydrous Na_2SO_4. Removal of solvent *in vacuo*, followed by purification on silica gel using hexane–ethyl acetate (8:2) afforded pure 1,2,3-triazole. Spectral data for selected products:

(2*R*,3*S*,6*S*)-2-[(acetyloxy)methyl]-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3,6-dihydro-2*H*-3-pyranyl acetate: (**1a**)



Solid; m.p. : 104-106 ^oC

^1H NMR ($CDCl_3$ 300 MHz) : δ 7.90-7.76 (m, 3H) , 7.51-7.19 (m, 3H) , 6.80 (d, J = 6.0 Hz, 1H), 5.60 (t, J = 5.2 Hz, 1H) , 5.23 (dd, J = 5.2, 6.5 Hz, 1H) , 5.09 (t, J = 5.2 Hz, 1H), 4.35-4.09 (m, 3H), 2.05 (s, 3H), 2.04 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.3, 169.6, 148.2, 128.8, 128.2, 125.6, 119.5, 95.2, 70.2, 66.5, 61.7, 52.1, 29.6, 20.5.

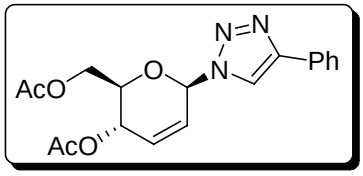
MASS (ESIMS) : *m/z* 380 (M+Na)

HRMS : calcd for $C_{18}H_{19}N_3O_5Na$ $[M+Na]^+$: 380.1222; Found: 380.1215.

IR (KBr) υ_{max} : 3452, 3136, 2925, 2854, 1745, 1652, 1458, 1370, 1227, 1076, 1048, 892, 768 cm^{-1}.

$[\alpha]_D^{25}$: 210 (*c* = 0.7, chloroform);

(2*R*,3*S*,6*R*)-2-[(acetyloxy)methyl]-6-(4-phenyl-1*H*-1,2,3-triazol-1-yl)-3,6-dihydro-2*H*-3-pyranyl acetate: (**1a'**)



Solid; m.p. : 112-114 °C

^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.93 (s, 1H), 7.87-7.78 (m, 2H), 7.47-7.22 (m, 3H), 6.38-6.20 (m, 3H), 5.46-5.38 (m, 1H), 4.28-3.89 (m, 3H), 2.12 (s, 3H), 2.06 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.3, 169.6, 148.2, 128.8, 128.2, 125.6, 119.5, 95.2, 70.2, 66.5, 61.7, 52.1, 29.6, 20.5.

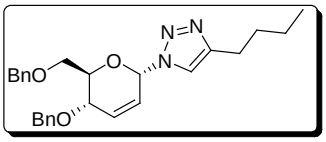
MASS (ESIMS) : *m/z* 380 (M+Na)

HRMS : calcd for $C_{18}H_{19}N_3O_5Na$ $[M+Na]^+$: 380.1222; Found: 380.1215.

IR (KBr) υ_{max} : 3465, 3136, 2927, 2855, 1743, 1655, 1455, 1371, 1234, 1097, 1037, 975, 764 cm^{-1}.

$[\alpha]_D^{25}$: -29.6 (*c* = 0.8, chloroform).

1-(2*R*,5*S*,6*R*)-5-(benzyloxy)-6-[(benzyloxy)methyl]-5,6-dihydro-2*H*-2-pyranyl-4-butyl-1*H*-1,2,3-triazole: (1f)



Liquid;

^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.39-6.96 (m, 10H), 6.67 (d, *J* = 6.0 Hz, 1H), 5.47 (t, *J* = 5.2 Hz, 1H), 4.82-4.94 (m, 1H), 4.67-4.44 (m, 3H), 4.14-3.97 (m, 2H), 3.70 (d, *J* = 3.0 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.73-1.60 (m, 2H), 1.47-1.26 (m, 2H), 1.02-0.88 (m, 5H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 147.6, 146.4, 132.9, 128.4, 128.4, 127.9, 127.8, 127.7, 120.5, 119.9, 95.48, 73.6, 73.2, 72.1, 71.8, 68.4, 52.2, 31.4, 25.3, 22.3, 13.7.

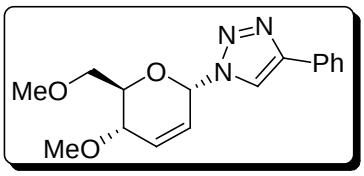
MASS (ESIMS) : *m/z* 456 (M+Na).

HRMS : calcd for $C_{26}H_{31}N_3O_3Na$ $[M+Na]^+$: 456.2263; Found: 456.2265.

IR (KBr) υ_{max} : 3064, 3031, 2924, 2856, 1725, 1652, 1454, 1364, 1256, 1114, 1046, 744, 699 cm^{-1}.

$[\alpha]_D^{25}$: 169 (*c* = 0 .75, chloroform);

1-[(2*S*,5*S*,6*R*)-5-methoxy-6-(methoxymethyl)-5,6-dihydro-2*H*-2-pyranyl]-4-phenyl-1*H*-1,2,3-triazole: (1i)



Solid; m.p. : 102-104 °C

^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.86-7.79 (m, 3H), 7.43-7.24 (m, 3H), 6.59-6.55 (m, 1H), 5.32-5.27 (m, 2H), 4.84-4.80 (m, 1H), 3.99-3.63 (m, 3H), 3.42 (s, 3H), 3.15 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 148.0, 128.7, 127.9, 128.2, 125.8, 125.5, 119.4, 95.2, 74.1, 72.9, 70.6, 59.4, 57.9.

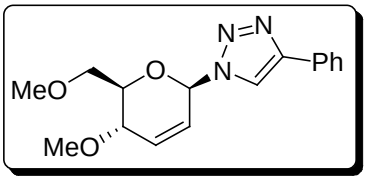
MASS (ESIMS) : *m/z* 324 (M+Na)

HRMS : calcd for $C_{16}H_{19}N_3O_3Na$ $[M+Na]^+$: 324.1324; Found: 324.1327.

IR (KBr) υ_{max} : 3421, 2923, 2853, 1726, 1652, 1460, 1215, 1091, 1043, 761 cm^{-1}.

$[\alpha]_D^{25}$: 198 (*c* = 0.5, chloroform);

1-[(2*R*,5*S*,6*R*)-5-methoxy-6-(methoxymethyl)-5,6-dihydro-2*H*-2-pyranyl]-4-phenyl-1*H*-1,2,3-triazole: (1i')



Solid; m.p. : 108-110 °C

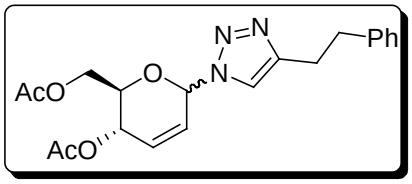
^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.93 (s, 1H), 7.86-7.75 (m, 2H), 7.45-7.19 (m, 3H), 6.70 (dd, *J* = 1.5 Hz, 1H), 5.57-5.51 (m, 2H), 4.98-4.93 (m, 1H), 4.05-3.81 (m, 3H), 3.52 (s, 3H), 3.41 (s, 3H).

MASS (ESIMS) : *m/z* 324 $(M+Na)^+$.

IR (Neat) : 3447, 2923, 2852, 1650, 1460, 1243, 1046, 765 cm^{-1}.

$[\alpha]_D^{25}$: -13.4 (*c* = 0.5, chloroform);

((2R,3S,6S)-3-acetoxy-6-(4-phenethyl-1H-1,2,3-triazol-1-yl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate: (1d)



Solid; m.p. : 98-100 ^oC

^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.31-7.08 (m, 6H) , 6.25-6.08 (m, 2H), 5.36 (d, *J* = 9.5 Hz, 1H), 4.26-3.99 (m, 3H), 3.82-3.72 (m, 1H), 3.07-2.95 (m, 2H), 2.12 (s, 3H), 2.04 (s, 3H).

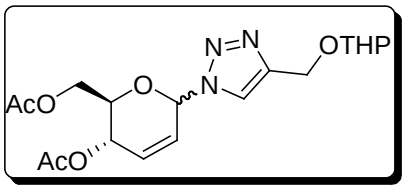
^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.6, 170.2, 148.0, 142.3, 130.1, 129.8, 126.0, 124.9, 120.3, 95.4, 71.2, 68.3, 63.5, 53.6, 34.6, 31.1, 26.4, 20.5.

MASS (ESIMS) : *m/z* 408 $(M+Na)^+$.

IR (KBr) υ_{max} : 3442, 3125, 2970, 2845, 1720, 1632, 1470, 1320, 1230, 1076, 864, 758 cm^{-1}.

$[\alpha]_D^{25}$: 132 (*c* = 0.5, chloroform);

((2R,3S)-3-acetoxy-6-(4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate: (1c)



Solid;

m.p. : 118-120 ^oC

^1H NMR ($CDCl_3$ 300 MHz) : δ 7.73 (s, 1H), 6.30-6.12 (m, 2H), 5.46-5.38 (m, 1H), 6.30-6.12 (m, 2H), 4.31-4.05 (m, 3H), 4.91-4.57 (m, 3H), 4.31-4.05 (m, 3H), 3.94-3.82 (m, 2H), 3.60-3.49 (m, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 1.72-1.50 (m, 4H), 1.30-1.23 (m, 2H).

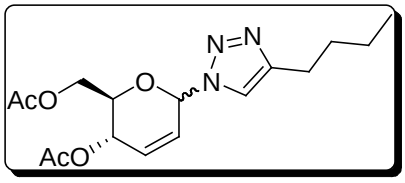
MASS (ESIMS) : *m/z* 324 (M+Na)

HRMS : calcd for $C_{16}H_{19}N_3O_3Na$ $[M+Na]^+$: 324.1324; Found: 324.1327.

IR (KBr) υ_{max} : 3052, 3020, 2924, 2846, 1740, 1635, 1426, 1352, 1264, 1134, 1056, 754, 699 cm^{-1}.

$[\alpha]_D^{25}$: -92 (*c* = 0.8, chloroform);

((2R,3S)-3-acetoxy-6-(4-butyl-1H-1,2,3-triazol-1-yl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate: (1b)



Solid; m.p. : 102-104 ^oC

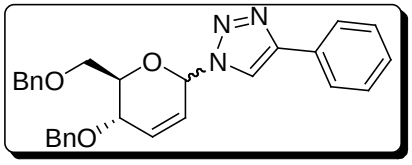
^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.70 (s, 1H), 6.60 (d, *J* = 6.0 Hz, 1H), 5.62 (t, *J* = 5.1 Hz, 1H), 5.24 (m, 1H), 4.41-4.05 (m, 4H), 2.60 (t, *J* = 5.1 Hz, 2H), 2.08 (s, 3H), 2.04 (s, 3H), 1.72-1.50 (m, 2H), 1.42-1.32 (m, 2H), 0.92 (t, *J* = 5.1 Hz, 3H).

MASS (ESIMS) : *m/z* 360 (M+Na)

IR (KBr) υ_{max} : 3442, 3136, 2925, 2834, 1735, 1642, 1428, 1358, 1232, 1104, 1038, 734, 702 cm^{-1}.

$[\alpha]_D^{25}$: 120 (*c* = 0.6, chloroform);

1-((5S,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-5,6-dihydro-2H-pyran-2-yl)-4-phenyl-1H-1,2,3-triazole: (**1e**)



Liquid;

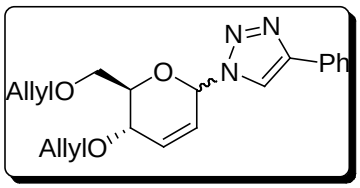
^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.67-7.55 (m, 2H), 7.40-6.98 (m, 14H), 6.67-6.52 (m, 1H), 5.48-5.38 (m, 1H), 4.92-4.72 (m, 2H), 4.63-4.39 (m, 4H), 4.12-3.94 (m, 3H).

MASS (ESIMS) : *m/z* 476 (M+Na).

IR (KBr) υ_{max} : 3072, 3018, 2930, 2840, 1730, 1648, 1496,1454, 1352, 1234, 1146, 1097, 1037, 752, 696 cm^{-1}.

$[\alpha]_D^{25}$: 118 (*c* = 0 .6, chloroform);

1-((5S,6R)-5-(allyloxy)-6-((allyloxy)methyl)-5,6-dihydro-2H-pyran-2-yl)-4-phenyl-1H-1,2,3-triazole: (1m)



Liquid;

^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.89-7.79 (m, 3H), 7.47-7.27 (m, 3H), 6.64-6.53 (m, 1H), 6.01-5.82 (m, 1H), 5.61-5.44 (m, 1H)M 5.38-5.16 (m,

	4H), 5.08-4.81 (m, 2H), 4.25-3.94 (m, 4H), 3.88-3.62 (m, 4H)
MASS (ESIMS)	: *m/z* 376 (M+Na).
IR (KBr) υ_{max}	: 3412, 3125, 2972, 2835, 1612, 1470, 1322, 1236, 1056, 868, 758 cm^{-1}.
$[\alpha]_D^{25}$	: -68 (*c* = 0.5, chloroform);

REFRENCES:

1. Jagerovic, N.; Gomez-de La, O. C.; Goya-laza, M. P.; Dordal Zueras, A.; Cuberes-altisrnt, M. R. European Patent 1,921,072, May 14, 2008.
2. Maurya, S. K.; Gollapalli, D. R.; Kirubakaran, S.; Zhang, M.; Johnson, C. R.; Benjamin, N. N.; Hedstrom, L.; Cuny, G. D. *J. Med. Chem*. **2009**, *52*, 4623
3. Puig-Basagoiti, F.; Qing, M.; Dong, H.; Zhang, B.; Zou, G.; Yuan, Z.; Shi, P.-Y. *Antiviral Res.* **2009**, *83*, 71.
4. Kallander, L. S.; Lu, Q.; Chen, W.; Tomaszek, T.; Yang, G.; Tew, D.; Meek, T. D.; Hofmann, G. A.; Schulz-Pritchard, C. K.; Smith, W. W.; Janson, C. A.; Ryan, M. D.; Zhang, G.-F.; Johanson, K. O.; Kirkpatrick, R. B.; Ho, T. F.; Fisher, P. W.; Mattern, M. R.; Johnson, R.K.; Hansbury, M. J.; Winkler, J. D.; Ward, K. W.; Veber, D. F.; Thompson, S. K. *J. Med. Chem*. **2005**, *48*, 5644.
5. Chackalamannil, S.; Chelliah, M. V.; Wang, Y.; Xia, Y. WO 2,008,042,422, April 10, 2008.
6. Basolo, L.; Beccalli, E. M.; Borsini, E.; Broggini, G.; Pellegrino, S. *Tetrahedron Lett.* **2008**, *64*, 8182
7. Reviews on the CuAAC and its applications: (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (b) Bock, V. D.; Hiemstra, H.; Van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, 51. (c) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun*. **2007**,*28*, 15. (d) Lutz, J. F. *Angew. Chem., Int. Ed*. **2007**, *46*, 1018. (e) Tornøe, C. W.; M. Meldal. *Chem. Rev*. **2008**, *108*, 2952. (f) Gramlich, P. M. E.; Wirges, C. T.; Manetto, A.; Carell, T. *Angew. Chem. Int. Ed*. **2008**, *47*, 8350. (g) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev*. **2010**, *39*, 1302.
8. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.
9. Rostovtsev, V. V.; Green, L. G., Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2002**, *41*, 2596.
10. Reviews on click chemistry: (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004. (b) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev*. **2007**, *36*, 1674. (c) Nandivada, H.; Jiang, X.; Lahann, *J. Adv. Mater*. **2007**, *19*, 2197. (d) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev*. **2007**, *36*, 1249. (e) Fournier, D.; Hoogenboom, R.; Schubert, U. S. *Chem. Soc. Rev*. **2007**, *36*, 1369.

11. Huisgen, R. *Angew. Chem*. **1963**, *75*, 604.
12. Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B. Fokin, V. V. Jia, G. *J. Am. Chem. Soc*. **2005**, *127*, 15998
13. (a) Ferrier, R. J.; Prasad, N. J. *J. Chem. Soc. C* **1969**, 570-572; (b) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem*. **1969**, *24*, 199-266; c) Fraser-Reid, B. *Acc. Chem. Res*. 1985, *18*, 347-354; d) Yadav, J. S.; Reddy, B. V. S.; Chand, P. K. *Tetrahedron Lett.* **2001**, *42*, 4057–4059.

CHAPTER III: SECTION C

First example of the Carbon-Ferrier rearrangement of glycals with Isocyanides: a novel synthesis of C- glycosyl amides.

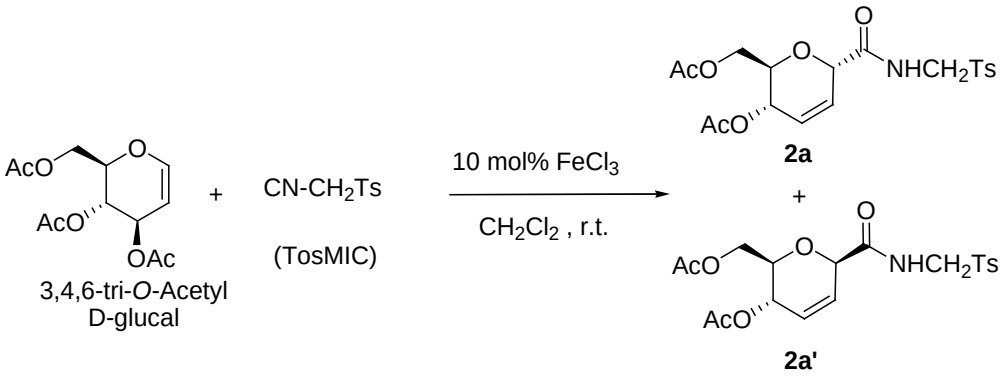
Introduction

C-Glycosidation is an important tool for the synthesis of optically active compounds, since it allows the introduction of carbon chains to sugar chirons and the use of sugar nuclei as chiral pool reagents as well as a carbon sources.[1] *C*-Glycosides are versatile chiral building blocks for the synthesis of many biologically interesting natural products such as palytoxin, spongistatin, halichondrin and many others.[2]

The discovery of naturally occurring *C*-nucleosides with important pharmacological properties gave impetus to synthetic efforts for preparing active carbohydrate analogs.[3] In addition, *C*-glycosides are potential inhibitors of carbohydrate processing enzymes and they are stable analogs of glycans involved in important intra- and inter-cellular processes.[4] Of these *C*-glycosides, 2,3-unsaturated glycosides (pseudoglycals) are versatile synthetic intermediates and also constitute the structural units of several antibiotics.[5]

Pseudoglycals are traditionally obtained by an acid catalyzed allylic rearrangement of glycals in the presence of nucleophiles, a reaction known as the Ferrier rearrangement.[6] Lewis acids are known to promote *C*-glycosidation with various nucleophiles such as allyltrimethylsilane, trimethylsilylcyanide and alkynylsilanes.[7-9] However, there have been no reports on the allylic nucleophilic substitution of glycals (S_N2') with isocyanides to produce *C*-glycosyl amides.[10]

In continuation of our interest on glycosidation, we disclose a versatile approach for the preparation of *C*-glycosyl amides from glucal and isonitriles by means of a carbon-Ferrier rearrangement. Initially, we attempted the Passerini type coupling of an isonitrile, a carboxylic acid and a glycal instead of a carbonyl compound to produce ω-hydroxy carboxamides. Surprisingly, we observed the formation of glycosyl amides instead of open chain hydroxyl amides.



Scheme 1

This provided incentive for an extensive study. Initially, we examined the reaction of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with tosylmethylisocyanide (**2**, Tosmic) in the presence of 10 mol% of $FeCl_3$. The reaction was complete within 30 min and the desired product was obtained in 92% yield as a mixture of α-**2a** and β-**2a'** anomers in a 9:1 ratio favoring α-anomer **2a** (Scheme 1).

Similarly, various other D-glucal derivatives such as 3,4,6-tri-*O*-benzoyl-, 3,4,6-tri-*O*-benzyl-, 3,4,6-tri-*O*-methyl-, and 3,4,6-tri-*O*-allyl-D-glucal reacted effectively with isonitriles to produce the corresponding *C*-glycosides in good yields (entries **b**-**k**, Table 1). The reaction was also effective with the TBS derivative of D-glucal without affecting the TBS functionality (entries **l** and **m**, Table 1). This method is applicable for both ester and ether derivatives of D-glucal. In each case, the α-anomer was obtained predominantly.

The ratio of anomers was determined by ^{1}H NMR spectroscopy of the crude products obtained in the *C*-glycosidation. The predominant formation of the α-anomer may be explained by electronic effects on the oxocarbenium intermediate involved in this transformation. Kinetically preferred axial addition of the carbon nucleophile was observed in most cases.[11]

The structures of **2a** and **2a'** were thoroughly studied by various NMR techniques including 1D ^{1}H NMR, homo-nuclear decoupling, double quantum filtered correlation spectroscopy (DQFCOSY) and nuclear Overhauser effect spectroscopy (NOESY). The

spectral assignments were obtained from DQFCOSY experiments. Since the configurations at C2 and C3 are fixed, for the major isomer **2a**, the coupling constant between protons H2 and H3 ($^3J_{H2\text{-}H3}$= 5.9 Hz) support the equatorial disposition of H2 and H3, thereby implying axial orientation of the substituents at C2 and C3. The presence of nOe correlations between H1-H3 and H1-H6 suggest that all these three protons lie on the same side of the C3-C4-C5-C6 plane. These observations in turn indicate that the substituent at C6 is on the other side of this plane, which is additionally supported by the nOe correlation between NH and H2. The characteristic nOe's and energy minimized structure of **2a** are shown in Figure 1.

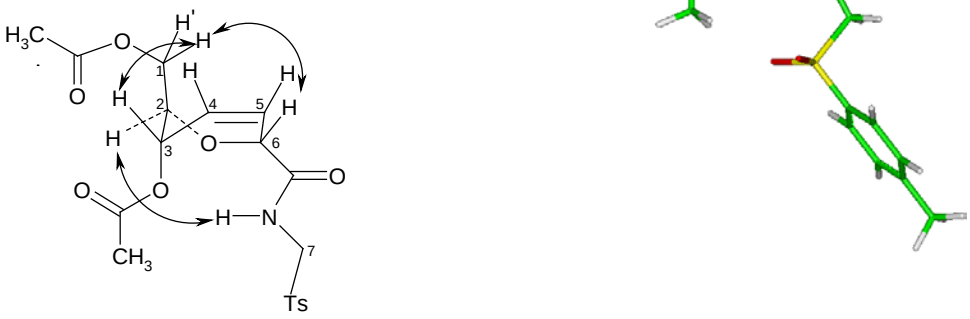


Figure 1. Characteristic nOe's and energy minimized structure of **2a**

For the minor isomer, a large coupling constant ($^3J_{H2\text{-}H3}$= 9.2 Hz) between protons H2 and H3 indicates that they occupy axial positions in the six-membered ring. Further, the presence of a strong nOe correlation between H2 and H6 indicates that these protons occupy 1,3-diaxial positions, which in turn provides support for the equatorial orientation of all the three substituents on the ring. The characteristic nOe's and energy minimized structure of **2a'** are shown in Figure 2.

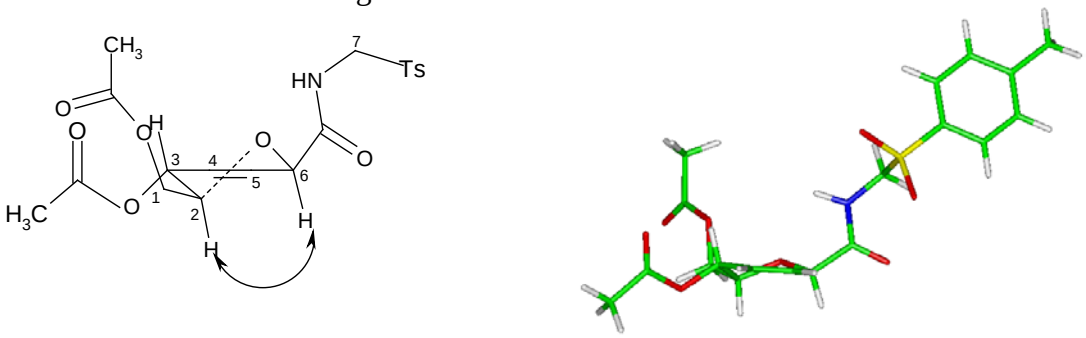
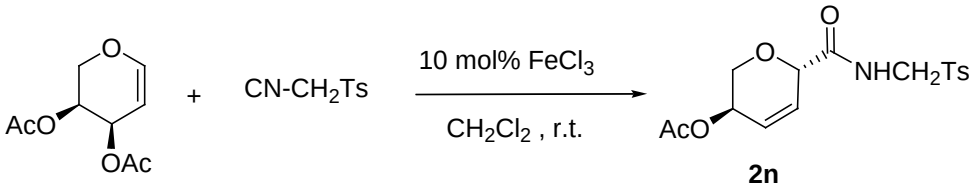


Figure 2. Characteristic nOe's and energy-minimized structure of **2a'**

Similarly, di-*O*-acetyl-L-arabinal also underwent the Ferrier type rearrangement to produce C-glycosyl amide 5n with α-selectivity. The presence of strong correlations between H1′ /H5 and H1 / H2 and medium correlations between H1′/ H2 protons and the coupling constant 3JH1-H2 = 5.2 and 3JH1'-H2 = 7.4 Hz, provide ample support for the structure shown in Figure 3, with substituents at C4 trans to the O-acetyl group at C1. The characteristic nOe's and energy minimized structure of 2n are shown in Figure 3.



Scheme 4

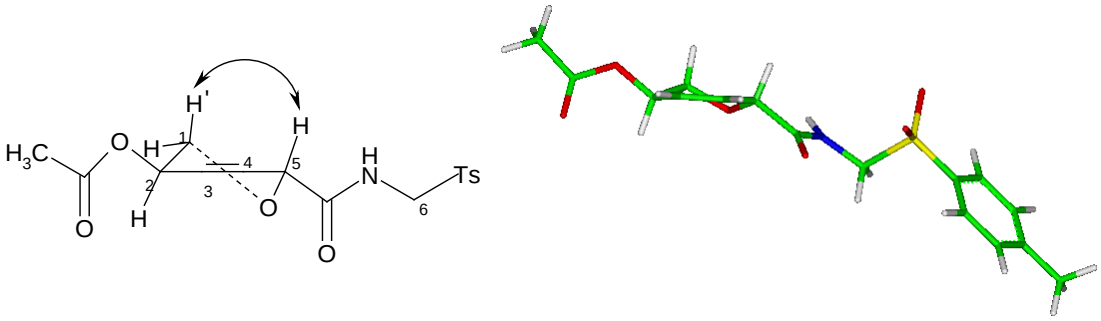
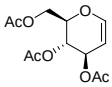
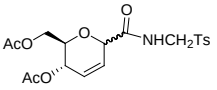
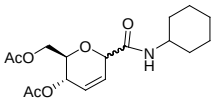
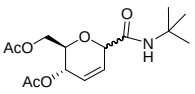
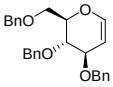
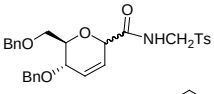
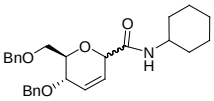
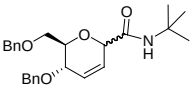
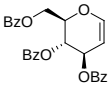
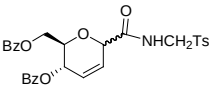
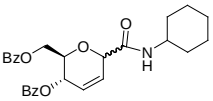
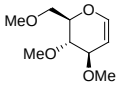
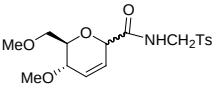
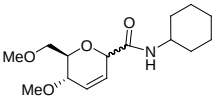
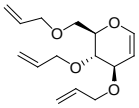
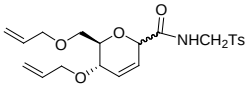
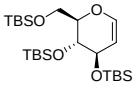
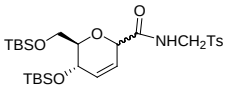
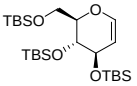
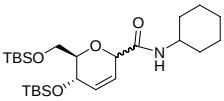
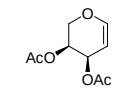
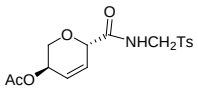


Figure 3.Charecteristic nOe's and energy minimized structure of 2n

Table 2: $FeCl_3$-catalyzed Ferrier rearrangement of glycals with isocyanides

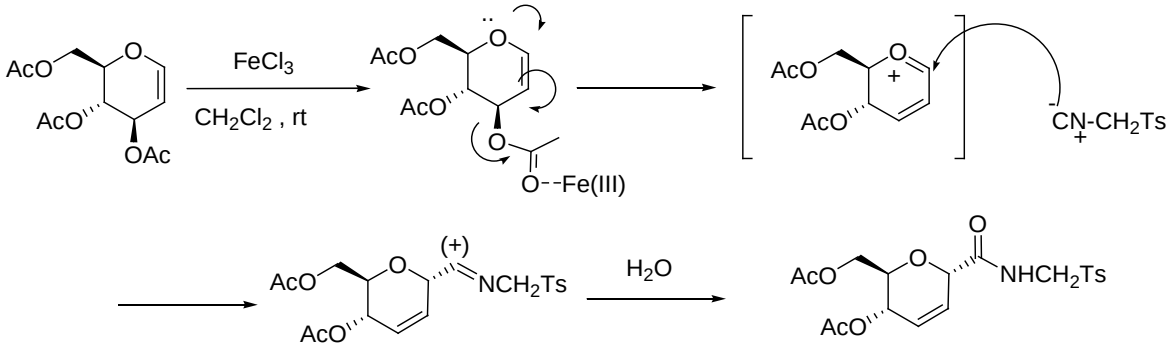
Entry	Glucal	Isonitrile	Products[a]	Time (min)	Yield (%)[b]	Ratio (a:a')[c]
a		Tosmic		30	92	9:1
b	"			30	85	9:1
c	"			50	75	9:1
d		Tosmic		35	90	9:1
e	"			45	85	6:1
f	"			55	70	9:1
g		Tosmic		30	85	9:1
h	"			45	80	9:1
i		Tosmic		25	90	9:1
j	"			30	85	6:1
k		Tosmic		45	75	9:1
l		Tosmic		50	70	9:1
m				40	65	
n		Tosmic		30	89	-

a. All products were characterized by NMR, IR and mass spectrometry.
b. Yield refers to pure products after chromatography.
c. Ratio was determined by ^1H NMR spectrum of crude product.

The products were characterized by ^{1}H, ^{13}C NMR and IR spectra and by mass spectrometry. In the absence of catalyst, no reaction was observed even after an extended reaction time (12 h). As solvent, CH_2Cl_2 gave the best results. In all the cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and no side products were detected under these conditions as determined from the NMR spectra of the crude products. There are several advantages in the use of $FeCl_3$ as catalyst for this transformation, which include high conversions, short reaction times and high α-selectivity. In addition, this method avoids the use of expensive reagents and does not require any additives or stringent reaction conditions. This method is quite simple and convenient affording the desired products in good yields.

The efficacy of various metal halides such as $FeCl_3$, $InBr_3$, $InCl_3$, $GaCl_3$, YCl_3 and $YbCl_3$ was studied for this transformation. Of these catalysts, $FeCl_3$ was found to be more effective in terms of conversion. For example, treatment of 3,4,6-tri-*O*-acetyl-D-glucal with TosMIC in the presence of 10 mol% $FeCl_3$ and 10 mol% $InCl_3$ over 30 min afforded 92% and 75% yields, respectively.

The scope and generality of this process is illustrated with respect to various glucal derivatives and isonitriles and the results are presented in Table 2. Mechanistically, the reaction proceeds via an oxocarbenium ion intermediate by a Ferrier rearrangement. Subsequent axial attack of the isonitrile on the oxocarbenium ion would give a carbimminium intermediate which is probably hydrolyzed to the product amide (Scheme 5).



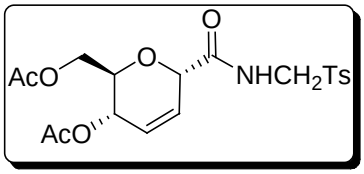
Scheme 5. A plausible reaction mechanism

In summary, we have described a novel method for the synthesis of *C*-pseudoglycals from glycals and isonitriles using a catalytic amount of $FeCl_3$ under mild reaction conditions. This method provides high yields of *C*-glycosyl amides in short reaction times with high anomeric selectivity, which makes it a useful and attractive process for carbon-carbon bond formation at the anomeric position of sugars.

Experimental procedure

To a stirred solution of glucal triacetate (0.5 mmol) in CH_2Cl_2 (2 mL) were added TosMIC (0.6 mmol) and $FeCl_3$ (10 mol%). The resulting mixture was stirred at room temperature for 30 min. After complete conversion as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 10 mL) and the combined organics dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo*, followed by purification on silica gel using hexane–ethyl acetate (3:1) afforded the pure *C*-glycosyl amide. Spectral data for selected products:

((2R,3S,6S)-3-acetoxy-6-((tosylmethyl)carbamoyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate: (2a)



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.72 (m, 2H, Ar), 7.27 (t, *J* = 6.9 Hz, 1H, NH), 7.31 (m, 2H, Ar), 5.98 (ddd, *J* = 10.5, 3.0, 1.7 Hz, 1H, H4), 5.86 (dt, *J* = 10.4, ~2.9 Hz, 1H, H5), 5.06 (ddt, *J* = 5.9, 1.7, ~3.0 Hz, 1H, H3), 4.70 (dd, *J* = 13.9, 7.4 Hz, 1H, H7), 4.54 (q, *J* = ~2.8 Hz, 1H, H6), 4.51 (dd, *J* =13.9, 6.4 Hz, 1H, H7′), 4.21 (dd, *J* = 11.9, 3.7 Hz, 1H, H1), 4.17 (dd, *J* = 11.9, 7.5 Hz, 1H, H1′), 3.90 (ddd, *J* = 7.5, 5.9, 3.7 Hz, 1H, H2), 2.46 (s, 3H, Me), 2.19 (s, 3H, OAc), 2.14 (s, 3H, OAc).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.8, 170.1, 168.2, 145.5, 133.5, 129.9, 128.8, 127.6, 124.8, 72.8, 71.9, 64.0, 62.6, 59.6, 21.6, 20.8, 20.6.

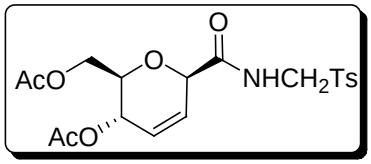
MASS (ESIMS) : *m/z* 448.0 (M+Na)

HRMS : calcd for $C_{19}H_{23}NO_8NaS$ $[M+Na]^+$: 448.1015; Found: 448.1012.

IR (KBr) υ_{max} : 3393, 2924, 2853, 1740, 1694, 1597, 1513, 1453, 1372, 1322, 1232, 1143, 1084, 1045, 758 $cm^{-1.}$

$[\alpha]_D^{25}$: 11.6 (*c* = 2.5, chloroform);

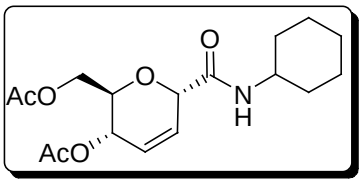
((2R,3S,6R)-3-acetoxy-6-((tosylmethyl)carbamoyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate: (2a')



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.72(m, 2H, Ar), 7.31 (m, 2H, Ar), 7.23 (t, *J* = 6.6 Hz, 1H, NH), 5.80 (dt, *J* = 10.5, ~1.6 Hz, 1H, H4), 5.76 (dt, *J* = 10.5, ~1.6 Hz, 1H, H5), 5.28 (ddd, *J* = 9.2, 3.3, 1.6 Hz, 1H, H3), 4.73 (dd, *J* = 13.9, 7.4 Hz, 1H, H7), 4.56 (dt, *J* = 3.3, ~1.6 Hz, 1H, H6), 4.44 (dd, *J* = 13.9, 5.7 Hz, 1H, H7′), 4.31 (dd, *J* = 12.4, 2.6 Hz, 1H, H1), 4.25 (dd, *J* = 12.4, 5.2 Hz, 1H, H1′), 3.76 (ddd, *J* = 9.2, 5.2, 2.5 Hz, 1H, H2), 2.46 (s, 3H, Me), 2.17 (s, 3H, OAc), 2.10 (s, 3H, OAc).

$[\alpha]_D^{25}$: 5.3 (*c* = 0.5, chloroform);

((2R,3S,6S)-3-acetoxy-6-(cyclohexylcarbamoyl)-3,6-dihydro-2H-pyran-2-yl)methyl acetate: (2b)



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 6.55 (d, *J* = 8.2 Hz, 1H), 5.92-5.81 (m, 2H), 5.12-5.05 (m, 1H), 4.63-4.59 (m, 1H), 4.22-4.10 (m, 2H), 3.95-3.85 (m, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 1.98-1.10 (m, 11H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.8, 170.2, 169.9, 145.0, 133.1, 73.0, 71.6, 64.3, 62.2, 47.0, 32.9, 25.3, 24.6, 20.8, 20.6.

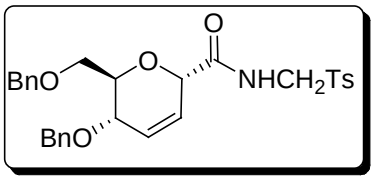
MASS (ESIMS) : *m/z* 362 (M+Na)

HRMS : calcd for $C_{17}H_{25}NO_6$ Na $[M+Na]^+$: 362.1579; Found: 362.1591.

IR (KBr) υ_{max} : 3408, 2929, 1715, 1656, 1515, 1455, 1374, 1346, 1177, 1068, 986, 759 cm^{-1}

$[\alpha]_D^{25}$: 49.8 (*c* = 1.0, chloroform);

(2S,5S,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-N-(tosylmethyl)-5,6-dihydro-2H-pyran-2-carboxamide: (2d)



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.79-7.67 (m, 3H), 7.38-7.18 (m, 12H), 5.98-5.84 (m, 2H), 4.62-4.39 (m, 7H), 3.80-3.63 (m, 3H), 3.49 (dd, *J* = 9.8, 7.5 Hz, 1H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 169.2, 144.9, 137.5, 133.6, 129.6, 128.6, 128.3, 128.2, 127.6, 127.5, 127.3, 125.9, 125.3, 74.5, 73.3, 72.7, 70.6, 69.2, 68.7, 59.6, 21.4.

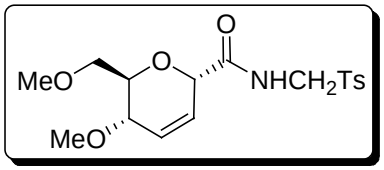
MASS (ESIMS) : *m/z* 544 (M+Na)

HRMS : calcd for $C_{29}H_{31}NO_6NaS$ $[M+Na]^+$: 544.1769; Found: 544.1761.

IR (KBr) υ_{max} : 3132, 2929, 2856, 2657, 1630, 1510, 1384, 1255, 1086, 835, 773, 699, 624 cm^{-1}.

$[\alpha]_D^{25}$: -7.7 (*c* = 1.13, chloroform);

(2S,5S,6R)-5-methoxy-6-(methoxymethyl)-N-(tosylmethyl)-5,6-dihydro-2H-pyran-2-carboxamide: (2i)



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.75-7.70 (m, 3H) , 7.30 (d, *J* = 8.3 Hz, 2H) , 5.87-6.60 (m, 2H), 4.54-4.67 (m, 2H), 4.40-4.44 (m, 1H), 3.52-3.71 (m, 2H), 3.46 (s, 3H), 3.38 (s, 3H), 2.44 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 169.4, 145.5, 133.4, 129.7, 128.7, 126.9, 125.4, 74.2, 72.6, 71.4, 71.2, 59.8, 59.2, 56.1, 21.5.

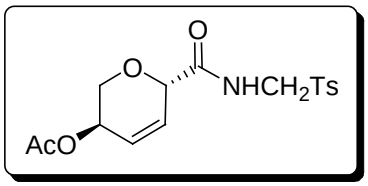
MASS (ESIMS) : *m/z* 392 (M+Na)

HRMS : calcd for $C_{17}H_{23}NO_6NaS$ $[M+Na]^+$: 392.1143; Found: 392.1154.

IR (KBr) υ_{max} : 3350, 2989, 2930, 2826, 1693, 1596, 1514, 1456, 1396, 1322, 1144, 1087, 753 cm^{-1}.

$[\alpha]_D^{25}$: -28.4 (*c* = 1.15, chloroform)

(3R,6S)-6-((tosylmethyl)carbamoyl)-3,6-dihydro-2H-pyran-3-yl acetate: (2n)



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.75 (m, 2H, Ar), 7.33 (m, 2H, Ar), 7.31 (t, *J* = 7.0 Hz, 1H, NH), 5.93 (dt, *J* = 10.5, ~1.7 Hz, 1H, H3), 5.76 (dt, *J* = 10.5, ~2.3 Hz, 1H, H4), 5.27(m, 1H, H2), 4.71 (dd, *J* = 14.2, 7.3 Hz, 1H, H6), 4.60 (dd, *J* = 14.2, 6.8 Hz, 1H, H7′), 4.50 (q, *J* ~ *2.3* Hz, 1H, H6), 4.17 (dd, *J* = 11.2, 5.2 Hz, 1H, H1), 3.60 (dd, *J* = 11.2, 7.4 Hz, 1H, H1̀), 2.44 (s, 3H, Me), 2.09 (s, 3H, OAc).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.3, 168.6, 145.4, 133.4, 129.9, 128.8, 128.1, 125.8, 73.7, 65.3, 63.6, 59.4, 21.6, 20.8.

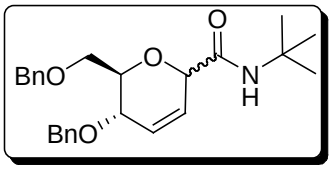
MASS (ESIMS) : *m/z* 376 (M+Na)

HRMS : calcd for $C_{16}H_{19}NO_6NaS$ $[M+Na]^+$: 376.0830; found, 376.0828.

IR (KBr) υ_{max} : 3344, 2927, 2857, 1734, 1693, 1596, 1515, 1372, 1322, 1238, 1144, 1086, 954, 815, 752 cm^{-1}.

$[\alpha]_D^{25}$: -136.7 (*c* = 0.6, chloroform);

(5S,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-N-(tert-butyl)-5,6-dihydro-2H-pyran-2-carboxamide: (2f)



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.40-7.22 (m, 10H), 6.27-5.91 (m, 2H), 4.73-4.42 (m, 5H), 3.86-3.41 (m, 4H), 1.26 (s, 9H).

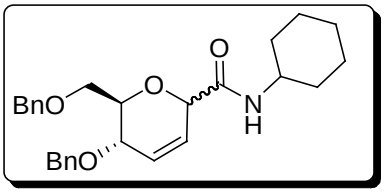
MASS (ESIMS) : *m/z* 432 (M+Na)

HRMS : calcd for $C_{25}H_{31}NO_4Na$ $[M+Na]^+$: 432.2150; found, 432.2131.

IR (KBr) υ_{max} : 3374, 2924, 2868, 1734, 1671, 1527, 1454, 1366, 1091, 1024, 740, 698 cm^{-1}

$[\alpha]_D^{25}$: 34 (*c* = 0.8 chloroform);

(5S,6R)-5-(benzyloxy)-6-((benzyloxy)methyl)-N-cyclohexyl-5,6-dihydro-2H-pyran-2-carboxamide: (2e)



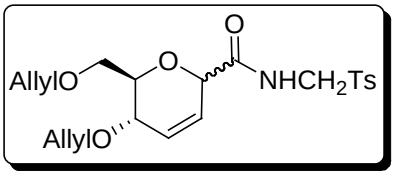
^1H NMR ($CDCl_3$ 300 MHz) : δ 7.36-7.17 (m, 10H), 6.06-5.94 (m, 1H), 5.83-5.73 (m, 1H), 5.36-5.29 (m, 1H), 4.64-4.42 (m, 4H), 4.11-3.94 (m, 3H), 3.70-3.49 (m, 2H), 1.93-0.77 (m, 10H).

MASS (ESIMS) : *m/z* 458 (M+Na).

IR (KBr) υ_{max} : 3352, 3132, 2968, 2856, 1724, 1641, 1517, 1404, 1386, 1084, 1024, 753, 672 cm^{-1}.

$[\alpha]_D^{25}$: -12 (*c* = 0.6 chloroform);

(5S,6R)-5-(allyloxy)-6-((allyloxy)methyl)-N-(tosylmethyl)-5,6-dihydro-2H-pyran-2-carboxamide: (2k)



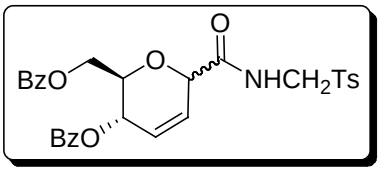
^{1}H NMR ($CDCl_3$ 300 MHz) : δ 7.76 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.3 Hz, 2H), 5.99-5.73 (m, 2H), 5.32-5.02 (m, 8H), 4.22-3.51 (m, 9H), 2.5(s, 3H).

MASS (ESIMS) : *m/z* 444 (M+Na).

IR (KBr) υ_{max} : 3312, 2958, 2926, 2856, 1692, 1582, 1526, 1438, 1322, 1334, 1120, 1052, 753 cm^{-1}.

$[\alpha]_D^{25}$: -28.4 (*c* = 1.15, chloroform)

((2R,3S)-3-(benzoyloxy)-6-((tosylmethyl)carbamoyl)-3,6-dihydro-2H-pyran-2-yl)methyl benzoate: (2g)



^{1}H NMR ($CDCl_3$ 300 MHz) : δ 8.12-8.02 (m, 4H), 7.73 (d, J = 8.1Hz, 2H), 7.66-7.39 (m, 6H), 7.35-7.23 (m, 2H), 6.01-5.77 (m, 2H), 4.75-4.30 (m, 5H), 4.17-3.96 (m, 1H), 3.81-3.67 (m, 1H), 2.43(s, 3H).

MASS (ESIMS) : *m/z* 572 (M + Na).

IR (KBr) υ_{max} : 3372, 2912, 2822, 1736, 1684, 1582, 1523, 1416, 1342, 1364, 1224, 1185, 1024, 954, 752 $cm^{-1.}$

$[\alpha]_D^{25}$: 20.6 (*c* = 0.8, chloroform);

REFERENCES:

1. a) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545. b) Hanessian, S. C. Total Synthesis of Natural Products: The Chiron Approach: Pergamon Press: Oxford, **1984**.

2. a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc*. **1982**, *104*, 4976. b) Paterson, L.; Keown, L. E. *Tetrahedron Lett*. **1997**, *38*, 5727. c) Horita, K.; Sakurai, Y.; Nagasawa, M.; Hachiya, S.; Yonemistu, O. *Synlett* **1994**, 43.

3. Suhadolnik, R. J. Nucleoside Antibiotics; Wiley-Interscience: New York, **1970**.

4. Weatherman, R. V.; Mortell, K. H.; Chervenak, M.; Kiessling, L. L.; Toone, E. J. *Biochemistry* **1996**, *35*, 3619.

5. Williams, N. R.; Wander, J. D. *The Carbohydrates*. *Chemistry and Biochemistry*; Academic Press: New York, **1980**; pp. 761–798.

6. a) Ferrier, R. J. *J. Chem. Soc*. (*C*) **1964**, 5443. b) Ferrier, R. J.; Ciment, D. M. *J. Chem. Soc*. (*C*) **1966**, 441. c) Ferrier, R. J.; Prasad, N. *J. Chem. Soc*. (*C*) **1969**, 570. d) For a recent review on the Ferrier rearrangement, see: Ferrier, R. J. *Topics Curr. Chem*. **2001**, *15*, 153.

7. a) Danishefsky, S. J.; Denin, S.; Lartey, P. *J. Am. Chem. Soc*. **1987**, *109*, 2082. b) De Raadt, A.; Griegl, H.; Klempic, N.; Stutz, A. E. *J. Org. Chem*. **1993**, *58*, 3179. c) De-Las Heras, F. G.; Felix, A. S.; Ferdanzandez-Risa, P. *Tetrahedron* **1983**, *39*, 1617. d) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Chem. Lett*. **1993**, 2013. e) Toshima, K.; Miyamito, N.; Matsuo, G.; Nakata, M.; Matsumura, S. *J. Chem. Soc., Chem. Commun.* **1996**, 1379.

8. a) Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun*. **1981**, 1180. b) Hayashi, M.; Kawabata, H.; Inoue, K. *Carbohydr. Res*. **2000**, *325*, 68. c) Takhi, M.; Adel, A. -H. A. R; Schimdt, R. R. *Tetrahedron Lett*. **2001**, *42*, 4053. d) Yadav, J. S.; Reddy, B. V. S.; Chand, P. K. *Tetrahedron Lett*. **2001**, *42*, 4057. e) Danishefsky, S. J.; Keerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803.

9. a) Tsukiyama, T.; Isobe, M. *Tetrahedron Lett*. **1992**, *33*, 7911. b) Huang, G.; Isobe, M. *Tetrahedron* **2001**, *57*, 10241. c) Tsukiyama, T.; Peters, S. C.; Isobe, M. *Synlett* **1993**, 413. d) Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett*. **1998**, *39*, 1917.

10. Nicotra, F. *Topics Curr. Chem*. **1997**, *187*, 55.

11. a) McMillan, K. G.; Tackett, M. N.; Dawson, A.; Fordyce, E.; Paton, R. M. *Carbohydr. Res*. **2006**, *341*, 41. b) Smith, M. D.; Long, D. D.; Marquess, D. G.; Claridge, T. D. W.; Fleet, G. W. J. *Chem. Commun*. **1998**, 2039.

LIST OF PUBLICATIONS

1. Towards the Total Synthesis of Dolabelides A-C: C1-C14 segment" Yadav, J. S.; **D.Narasimha Chary** ; **(Manuscript Ready for *Eur. J. Org. Chem*).**
2. "Towards the Total Synthesis of Oasomycin A: C1-C16 segment" Yadav, J. S.; **D.Narasimha Chary**; Sandip Sengupta **(Manuscript Under preparation)**
3. "Enantioselective Total synthesis of Siphonarienal, Siphonarienone and Formal synthesis of Pectinatone " Yadav, J. S.; **D.Narasimha Chary**, Nagendranath Yadav, Sandip Sengupta, Subba Reddy, B.V.; **communicated to *Helv.Chim. Acta.***
4. "Stereoselective synthesis of methyl branched chiral deoxypropionate units: a new route for synthesis of insect pheromone (-lardolure and (2*R*,4*R*,6*R*,8*R*) 2,4,6,8-tetramethylundecanoic acid'' Yadav, J. S.; Sandip Sengupta, Nagendranath Yadav, **D.Narasimha Chary** ; Ahmad Alkhazim Al Ghamd; ***Tetrahedron Letters*, 2012, *53*, 5952-5954.**
5. "First example of the carbon-Ferrier rearrangement of glycals with isocyanides: a novel synthesis of *C*-glycosyl amides" J. S. Yadav, B. V. S. Reddy, **D. Narasimha Chary**, C. Madavi, A. C. Kunwar; ***Tetrahedron Letters*, 2009, *50*, 81-84.**
6. "A tandem Ferrier and Click reaction: a facile synthesis of triazolyl-2,3-dideoxypyranosides" J. S. Yadav, B. V. Subba reddy, **D. Narasimha Chary**, Ch. Suresh Reddy; ***Tetrahedron Letters*, 2008, *49*, 2649-2652.**
7. "Three component, regioselective, one-pot synthesis of β-hydroxytriazoles from epoxides *via* 'click reactions" J. S. Yadav, B. V. Subba reddy, G. Madhusudhan Reddy, **D. Narasimha Chary** ; ***Tetrahedron Letters*, 2007, *48*, 8773-8776.**
8. "InX_3-catalyzed haloamidation of vinyl arenes: a facile synthesis of α-bromo- and α-fluoroamides." J. S. Yadav, B. V. Subba Reddy, **D. Narasimha Chary**, D. Chandrakanth; ***Tetrahedron Letters*, 2009, *50*, 1136-1138**.
9. "Iron(III) Chloride as Mild and Efficient Reagent for the a-Thiocyanation of Ketones: An Expedient Synthesis of a-Oxo Thiocyanates" J.S. Yadav, B.V. Subba Reddy, U. V. Subba Reddy, **D. Narasimha Chary**; ***Synthesis* 2008, *8*, 1283-1287.**

SPECTRA

SYNOPSIS

Title of the thesis:	"Studies directed towards the total synthesis of Dolabelides A-C (C1-C14), Siphonarienal, Siphonarienone, Pectinatone and applications of Ferrier Rearrangement"
Name of the student:	D. Narasimha Achary (09CHPH23)
Research supervisor:	Dr. J. S. Yadav

The thesis entitled **"Studies directed towards the total synthesis of Dolabelides A-C (C1-C14), Siphonarienal, Siphonarienone, Pectinatone and applications of Ferrier Rearrangement"** consists of three chapters.

Chapter–I:

Section A: Introduction and previous approaches to Dolabelides.

Section B: Towards the total synthesis (C1-C14 Subunit) of Dolabelides A-C *via* Prins cyclization and cross metathesis strategy.

Chapter–II:

Section A: Introduction and previous approaches to Siphonarienal, Siphonarienone and Pectinatone.

Section B: Enantioselective total synthesis of Siphonarienal, Siphonarienone and Pectinatone.

Chapter–III:

Section A: Introduction to Ferrier rearrangement.

Section B: A tandem Ferrier and Click reaction: a facile synthesis of, triazolyl-2,3-dideoxypyranosides.

Section C: First example of the Carbon-Ferrier rearrangement of glycals with Isocyanides: a novel synthesis of *C*- glycosyl amides.

CHAPTER–I

Section A: Introduction and previous approaches to Dolabelides.

Section B: Stereo selective synthesis of C1-C14 Subunit of Dolabelides A-C *via* Prins cyclization and cross metathesis strategy.

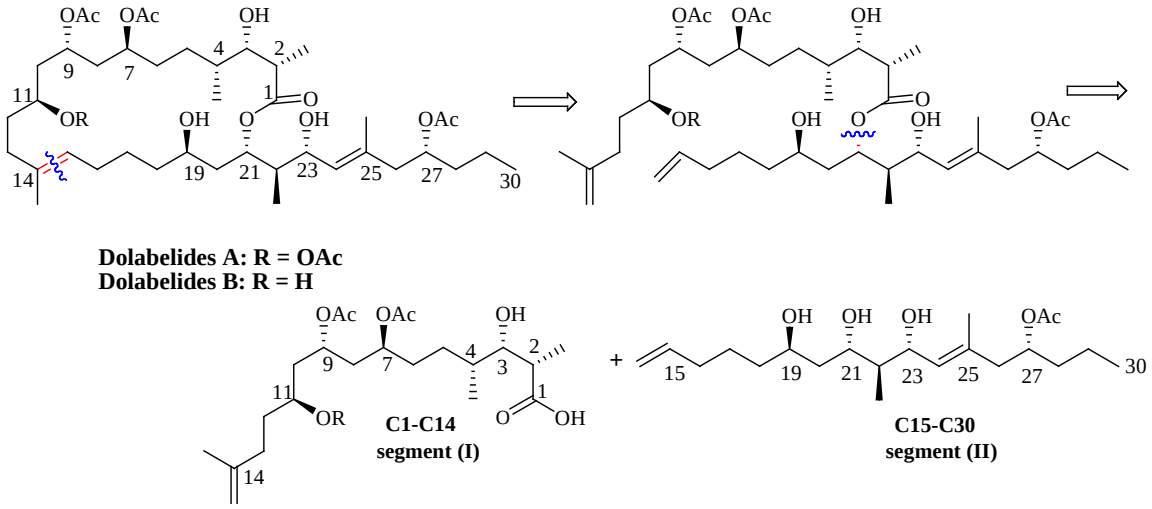
In 1995, the 22 membered macrolides Dolabelides A and B were isolated and charecterised by Yamada and coworkers from *Dolabella auricularia* ((family Aplysiidae). The Dolabelides C and D were also a similar 24 membered macrolactones exctracted from the same marine natural product (From sea hare, *Dolabella auricularia*) in 1997. The macrolactones were found to possess cytotoxicity against HeLa-S3 cells with IC_{50} values of 6.3, 1.3, 1.9, and 1.5 μg/mL, respectively (Figure 1).

Figure 1

Common features among the Dolabelide family are 11 stereogenic centers, eight of which bear oxygen, and two *E*-configured trisubstituted olefins. Other structural features possessed by this family of macrolactones include 1,3-anti-diol fragments found at C7/C9 and C19/C21, along with an accompanying 1,3-syn-diol at C9/C11 and polypropionate fragments at C1/C4 and C21/ C23. The stereochemical complexity and biological profile of this class of compounds as well as their limited availability from natural sources made them attractive targets for synthetic challenge of the Dolabelides. Consequently, there have been some reports on the total synthesis of Dolabelides following multi-step synthetic sequences. We were interested in the synthesis of Dolabelides using Prins cyclization and cross metathesis as key steps for the C1-C14 segment.

In recent days, Prins cyclization has become a powerful synthetic tool for the construction of tetrahydropyran systems and has been utilized in the synthesis of several natural products. Our group has made a significant effort to explore the utility of Prins cyclization in the synthesis of various polyketide intermediates and applied it to the total synthesis of some natural products. As a part of our ongoing program on the total synthesis of biologically active natural products, we herein report the total synthesis of Dolabelides.

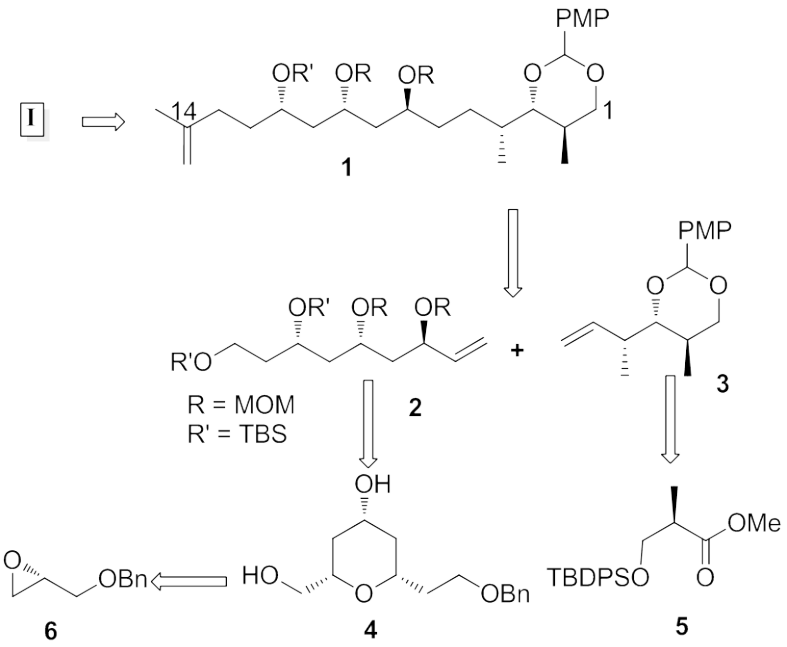
In our retrosynthetic analysis (Scheme 1), we envisioned that Dolabelide A could be divided into two fragments, arising from bond disconnection at the macrolactone and about the C14–C15 olefin. We have planned the coupling of fragments **I** and **II** by esterification and ring-closing metathesis.



Scheme 1: Retrosynthetic plan for Dolabelide A

Retro synthetic analysis of C1-C14 segment of Dolabelides A-C:

The synthesis of target fragment **1** was planned by regioselective cross metathesis (CM) between fragments **2** and **3** (scheme 2) while the sub segment **2** could be synthesized from known (*S*)-benzyl glycidyl ether (**6)**, and another fragment **3** could be synthesized by using commercially available (*R*) Roche ester.



Scheme 2: Retrosynthetic analysis for C1-C14 segment

Synthesis of the Olefin fragment 2:

The synthesis of fragment **2** began with a homoallylic alcohol (**7**) which was prepared from (*S*)-benzyl glycidyl ether (**6**). The Prins cyclization of compound **7** with aldehyde (**8**) (an aldehyde of mono benzylated propane diol) in presence of TFA in CH_2Cl_2 followed by hydrolysis of the resulting trifluoroacetate with K_2CO_3 in methanol gave the 4-hydroxytetrahydropyran (**4)** in 65% yield (Scheme 3).

Chemoselective tosylation of primary alcohol (**4**) with 1.1 equiv. of tosyl chloride in the presence of TEA in CH_2Cl_2 gave the corresponding tosylate (**9**) in 82% yield. Treatment of tosylate (**9**) with NaI in refluxing acetone gave the respective iodide, which when treated with Zn in refluxing EtOH furnished the key intermediate **10** with the

required *anti*-1,3- diol system in 88% yield over two steps. MOM protection of the secondary *anti*-1,3- diol (**10**) with methoxymethyl chloride in DIPEA provided the corresponding MOM ether (**11**) in 90% yield (Scheme 3).

Scheme 3: Synthetic plan for compound **11**

Ozonolytic cleavage of the olefinic bond of **11** followed by Wittig olefination of resulting aldehyde with $Ph_3P{=}CHCO_2Et$ afforded the α,β-unsaturated ester (**12**). The α,β-unsaturated ester (**12**) upon reduction with DIBAL-H afforded the an *E*-allylic alcohol compound (**13**) in 85% yield. This allyl alcohol (**13**) on treatment with (–)-DET, Titanium(IV)isopropoxide and *tert*-butyl hydroperoxide in CH_2Cl_2 under anhydrous conditions at –20 $^{\circ}$C yielded epoxy alcohol (**14**) in 75%. Regioselective reduction of the epoxide using Red-Al yielded 1,3-diol (**15**) in 84% yield.

Scheme 4: Synthetic plan for compound **15**

Protection of alcohols (1^{o} and 2^{o})**,** as TBS ethers was performed in the presence of *tert*-butyl dimethylsilyl [trifluoromethanesulfonate] and 2,6-lutidine in CH_2Cl_2 to produce **16** in 90% yield. Hydrogenolysis of the compound **16** using Pd/C in MeOH at

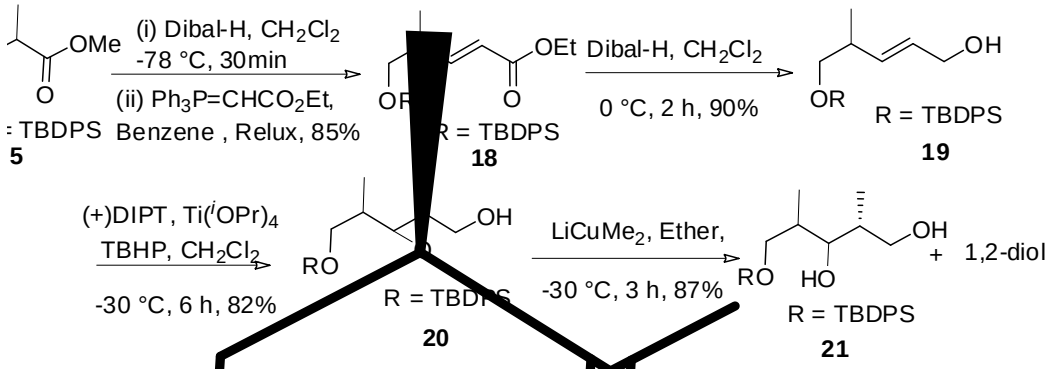
room temperature resulted in primary alcohol (**17**) in 92% yield. The primary alcohol (**17**) was transformed to its iodo derivative by standard I_2, TPP, imidazole protocol which on immediate treatment with ^{t}BuOK in Dry THF at 0 $^{\circ}$C gave a terminal olefin (**2**) in 80% yield (Scheme 5).

Scheme 5: Synthesis of fragment **2**

Synthesis of the Olefin fragment 3:

Commercially available (*R*)-Roche ester was protected with TBDPSCl in the presence of imidazole and catalytic amount of DMAP gave compound **5** in quantitative yield. Partial reduction of compound **5** using DIBAL-H at –78 $^{\circ}$C over a time period of 30 min gave the corresponding aldehyde which upon treatement with $Ph_3P{=}CHCO_2Et$, produced an α,β-unsaturated ester (**18**) in 85% yield over two steps.

The chemoselective reduction of α,β-unsaturated ester (**18**) using DIBAL-H as reducing agent afforded an *E*-allylic alcohol (**19**) in 90% yield. Sharpless asymmetric epoxidation of allyl alcohol (**19**) with (+)-DIPT, $Ti(O^{i}Pr)_4$ and TBHP in dry CH_2Cl_2 gave chiral epoxy alcohol (**20**) in 82%. The chiral epoxy alcohol (**20**) was subjected to Gilmans opening, using Me_2CuLi in dry ether at –30 $^{\circ}$C, to afford the unseparable mixture of regioisomers 1,3-diol (**21**) and 1,2-diol**.** The crude mixture was subjected to $NaIO_4$ chopping in THF/H_2O (4:1) to provide the pure compound **21** (Scheme 6).



Scheme 6: Synthetic plan for compound **21**

The 1,3-diol (**21**), on reaction with anisaldehyde dimethylacetal in dry CH_2Cl_2 gave **22** as PMP-acetal. Desilylation of compound **22** was carried out by using TBAF in THF to provide primary alcohol (**23**) in 90% yield. Oxidation of the primary alcohol (**23**) by using Dess-Martin periodinane in CH_2Cl_2 in catalytic ammount of $NaHCO_3$, gives an aldehyde, which when subjected to Wittig olefination with $Ph_3P=CH_2$ and *n*-BuLi in dry THF at -20 $^{\circ}$C, gave the required fragment **3** in 80% yield (Scheme 7).

Scheme 7: Synthetic analysis of fragment **3**

Coupling of both the fragments 2 & 3 by Cross-Metathesis approach:

The two fragments **2** and **3** (Scheme 8) were subjected to cross-metathesis reaction by using Grubbs' 2nd generation catalyst in refluxing toluene to give the

expected product **24** along with the formation of alkene dimer of **3**. Reduction of the compound **24** by using Raney-Ni in ethanol under hydrogen atmosphere, resulted in saturation of the olefinic bond to get **25** in 90% yield. Selective deprotection of primary silyl group of **25** was simply achieved, by treating with HF-Pyridine in THF to give the compound **26** in 85% yield.

Scheme 8: Synthetic plan for compound **26**

The primary alcohol (**26**) was oxidized by using Dess-Martin periodinane in CH_2Cl_2 using catalytic amount of $NaHCO_3$ to give the aldehyde, which was immediately treated with 2-propenylmagnesium bromide and the resulting magnesium alkoxide product was trapped *in situ* with acetic anhydride and pyridine to deliver a diastereomeric mixture of allylic acetates (**27**) in 89% yield. Palladium-catalyzed hydrogenolysis with ammonium formate and tributylphosphine according to a modification of the Tsuji protocol provided terminal olefin (**1**) in an 88% yield with no detectable internal olefin regioisomer, which is our required segment for construction of Dolabelide A.

Scheme 9: Synthesis of targeted C1-C14 fragment

In summary, our investigations into the Prins-cyclization, Gilmans' opening of epoxide, cross metathesis and Palladium-catalyzed hydrogenolysis has led to a concise synthesis of C1-C14 fragment of Dolabelides A-C, which proceeded only in a 14-step longest linear sequence with 6.7% overall yield starting from a known homo allyl alcohol (**7**).

CHAPTER–II

Section A: Introduction and previous approaches to Siphonarienal, Siphonarienone and Pectinatone.

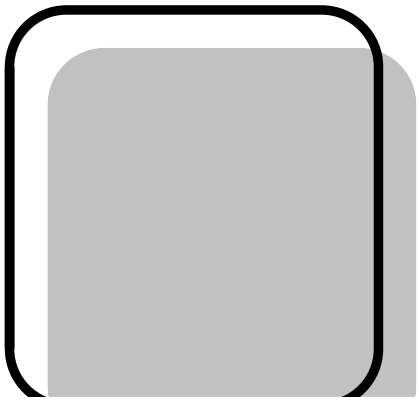
Section B: Enantioselective total synthesis of Siphonarienal, Siphonarienone and Pectinatone.

The siphonarienes belongs to a class of polypropionates, polyether antibiotics and macrolides. Deoxypropionate is a common recurring motif in many deoxypolyketide natural products which are known to exhibit various biological activities. In particular, *syn*/*syn*-deoxypropionate unit was found in many natural products such as TMC-151A, pectinatone, and siphonarienes (and its congeners). Of these, siphonarienes (1 & 2) and pectinatone (3) are the marine polypropionate natural products and were isolated from the genus *Siphonaria* such as *Siphonariea grisea* and *Siphonaria pectinata*, respectively. The members of this class consist of (2*S*),(4*S*),(6*S*)-trimethylnonane segment which is connected to a more polar oxygen-containing group through the olefinic linker (Figure 1).

Figure 1. Representative structures of Siphonarienal (**1**), Siphonarienone (**2**) and Pectinatone (**3**)

They are active against gram positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), Yeast (*Candida albicans* and *Saccharomyces cervisiae*), and several human cancer cell lines. The structures of **1**, **2** and **3** were established on the basis of their spectral data. Furthermore, the structure of **3** was confirmed by X-ray diffraction analysis.

Retrosynthetically, we envisaged that the target molecules Siphonarienal, Siphonarienone and Pectinatone could be synthesized from a common precursor **4.** The chiral precursor **4** was then proposed to be synthesized from **5** in two steps involving oxidation and C3-homologation reactions. The intermediate **5** was assumed to be synthesized in a stereoselective manner involving enzymatic desymmetrization approach, Wittig reaction, and Evans' asymmetric alkylation (Scheme1).



Scheme 1. Retrosynthetic analysis of Siphonarienal (**1**), Siphonarienone (**2**) and Pectinatone (**3**).

Accordingly, we began our synthesis from *cis*-4,6-dimethyl-cyclohexan-1,3-

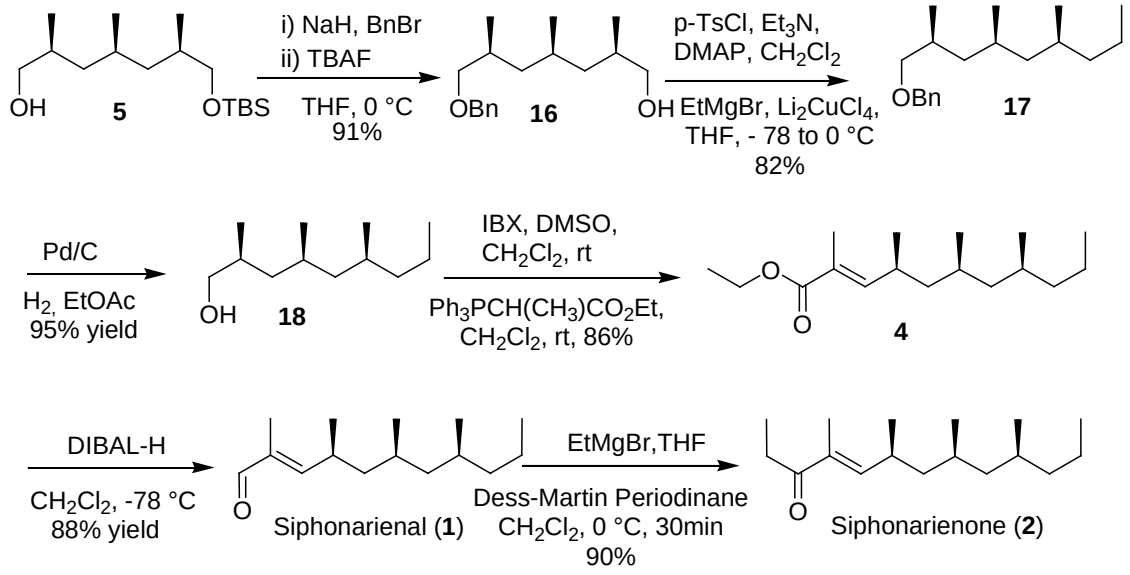
dione, which was synthesized by the condensation of methyl methacrylate with 2-butanone in the presence of NaOMe. Thus obtained 1,3-dione (**7**) was then converted into the corresponding diacid (**8**) by means of periodate oxidation. Reduction of diacid with $LiAlH_4$ in THF at 0 $^{\circ}$C gave the meso-diol (**9**) in 98% yield. Desymmetrization of me so-diol using Lipase-AK and vinyl acetate (as acylating agent) in THF at ambient conditions gave the mono acetate (**6**) in 74% yield with >95% ee along with the meso-diacetate. Thus obtained meso-diacetate was again converted into meso-diol using K_2CO_3 in methanol. The mono acetate (**6**) was protected as its silyl ether using TBSCl and imidazole in CH_2Cl_2 and then treated with K_2CO_3 in methanol to furnish the desired terminal alcohol (**10**) in 96% yield.

Scheme 2. Synthetic route for compound **10**

Subsequent oxidation of alcohol (**10**) followed by elongation of two carbons by means of Wittig reaction gave the *α,β*-unsaturated ester (**11**) in 86% yield over two steps. Chemoselective reduction of the double bond with Pd/C in EtOAc afforded the saturated ester (**12**) in 96% yield which was then subjected to hydrolysis under basic conditions to furnish the corresponding carboxylic acid (**13**) in 93% yield. The coupling of acid (**13**) with Evan's chiral oxazolidinone using pivaloyl chloride in presence of triethylamine and LiCl gave the compound **14** in 93% yield. Diastereoselective methylation of Li-enolate of compound **14** was achieved with MeI using a freshly prepared LDA (1.0 M) to furnish the desired compound **15** with >97:3 diastereoselectivity. Reduction of **15** with $LiBH_4$ in THF gave the primary alcohol (**5**) in 92% yield with all three chiral centers

Scheme 3. Synthetic route for compound **5**

The alcohol **5** was then protected as its benzyl derivative using NaH and benzyl bromide in presence of catalytic amount of TBAI, followed by removal of silyl group using HF-Pyridine in THF gave the alcohol (**16**) in 91% over two steps.Tosylation of primary alcohol (**16**) with TsCl in the presence of Et_3N in dry CH_2Cl_2, at 0 $^{\circ}$C followed by Grignard reaction with EtMgBr in dry diethyl ether at -20^{o}C in the presence of a catalytic amount of Li_2CuCl_4 gave the product (**17**) in 82% yield. Deprotection of benzyl group of (**17**) with Pd/C in EtOAc under H_2 atmosphere gave the primary alcohol (**18**) in 95% yield. Swern oxidation of primary alcohol (**18**) gave the required aldehyde, which was then subjected to C-3 Wittig reaction to afford the *α,β*-unsaturated ester **4** (*E*-isomer) as a major product in 86% yield over two steps, which is a common precursor for the synthesis of all the three natural products (1,2 &3).



Scheme 4. Synthesis of Siphonarienal (**1)**, Siphonarienone (**2**).

The target molecule, Siphonarienal **1** was readily achieved in 88% yield by reduction of **4** with DIBAL-H at -78 °C. Grignard reaction of Siphonarienal (**1**) with EtMgBr followed by oxidation with Dess-Martin periodinane gave the Siphonarienone (**2**) in 85% yield over two steps. The spectral data of **1** and **2** were in good agreement with the data reported in literature.

Scheme 5. Synthesis of Pectinatone (**3**).

In order to achieve the next target compound **3**, the ester **4** was treated with *N*-methoxy-*N*-methylammonium chloride and ^{i}PrMgCl in anhydrous THF, at -20 to 0 °C to afford the Weinreb amide **(19**) in 71% yield. Upon treatment of **19** with ethyl 2-methyl-3-

oxopentanoate (**20**) followed by cyclization of the resulting β, δ-diketoester (**21**) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene gave the target molecule, pectinatone (**3**).

In summary, we have demonstrated the total synthesis of Siphonarienal (**1**), Siphonarinone (**2**) and Pectinatone (**3**) in a highly enantioselective and divergent manner. The synthetic route involves very simple and straight forward reactions such as enzymatic desymmetrization of meso-diol, Wittig olefination and Evan's asymmetric alkylation as key steps.

CHAPTER–III

Section A: Introduction to Ferrier rearrangement.

Section B: A tandem Ferrier and Click reaction: a facile synthesis of triazolyl-2,3-dideoxypyranosides.

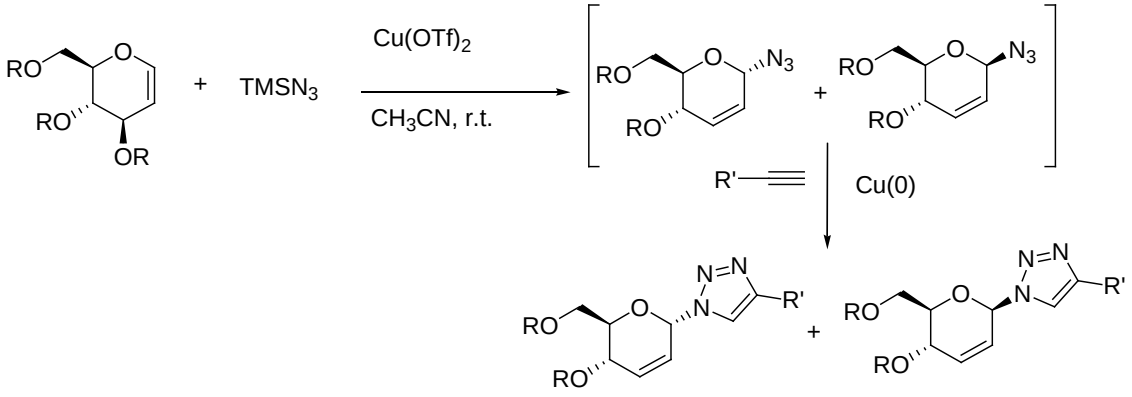
1,2,3-Triazoles are potential targets for drug discovery as they exhibit a broad spectrum of biological properties such as antiviral, antibacterial, antiepileptic and antiallergic behavior. They have also found applications as optical brighteners, light stabilizers, fluorescent whiteners and corrosion retarding agents. The classical method for the preparation of 1,2,3-triazoles is the Huisgen reaction. However, this uncatalyzed cycloaddition results in products with poor regioselectivity and low yields. The Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC), one of the most reliable click reactions, has enabled practical and efficient preparation of 1,4-disubstituted-1,2,3-triazoles, from wide range of substrates with excellent selectivity, which cannot be attained with the traditional Huisgen uncatalyzed thermal approaches. This powerful and reliable Cu-catalyzed 1,3-dipolar cycloaddition has found widespread applications in combinatorial chemistry for drug discovery, material science, and bioconjugation. Since triazole linked glycoconjugates have become increasingly useful and important in glycobiology, the development of a simple and efficient method for their synthesis in a single step operation is desirable.

We report a direct one-pot method for the synthesis of triazole-linked glycoconjugates from readily available D-glucal, TMS azide and alkyne involving a

tandem Ferrier and Click reaction. In a preliminary study, 2,4,6-tri-O-acetyl-D-glucal (**1**) was treated with trimethylsilyl azide and phenylacetylene (**2**) in the presence of 10 mol% of $Cu(OTf)_2$ and 1 eq. of metallic copper in acetonitrile. The reaction proceeded smoothly at room temperature and the product, 1,2,3-triazole-linked glycoside was obtained in 85% yield as a mixture of α-**3a**, and β-isomers **3b** in 3:2 ratio favoring α-isomer **3a** (Scheme 1).

Scheme1

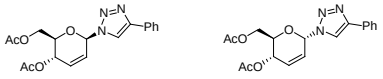
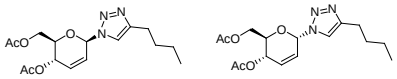
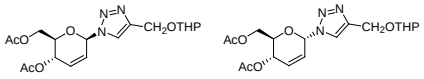
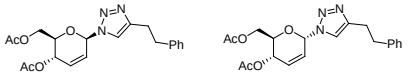
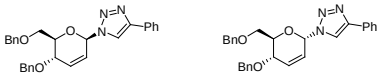
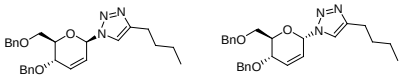
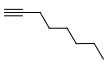
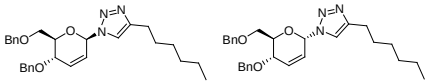
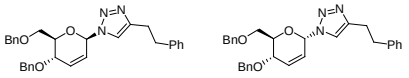
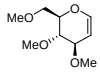
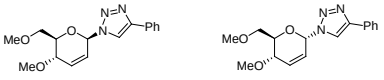
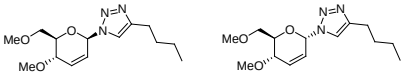
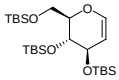
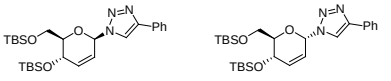
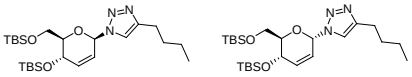
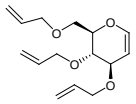
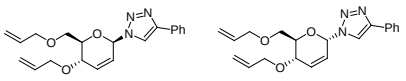
The stereoisomers **3a** and **3b** could be easily separated by column chromatography. This result provided the incentive for further study of reactions with various other alkynes such as 1-octyne, 1-hexyne, 4-phenyl-1-butyne and propargyl ether. These alkynes reacted readily with glycosyl azides under identical conditions to produce triazole-linked glycosides in high yields (entries b-m, Table 1). Other glucal derivatives such as 2,4,6-tri-*O*-methyl, 2,4,6-tri-*O*-benzyl, 2,4,6-tri-*O*-TBDMS and 2,4,6-tri-*O*-allyl-D-glucal also underwent smooth coupling with trimethylsilyl azide and alkynes to produce 1,2,3-triazole- linked 2,3-dideoxypyranosides in good yields. This method tolerates highly acid labile protecting groups such as THP and TBDMS ethers. However, in the absence of either copper triflate or copper (0), the reaction did not give the expected triazole even after long reaction times (8-12 h). Both copper triflate and copper metal are essential for the success of the reaction. As solvent, acetonitrile appears to give the best results. The scope and generality of this process is illustrated in Table 1. The reaction may proceed via the Ferrier rearrangement followed by [3+2] cycloaddition as depicted in (Scheme 2).



Scheme2

A mixture of glucal triacetate (0.5 mmol), $TMSN_3$ (0.6 mmol) and $Cu(OTf)_2$ (5 mol %) in acetonitrile (2 mL) was stirred at room temperature for 2 h. Then phenyl acetylene (0.55 mmol) and Cu-powder (10 mol %) were added and the resulting mixture was stirred at room temperature for another 2.5 h. After completion of the reaction, as monitored by TLC, the product was extracted with ethyl acetate (3x10 mL) and dried over anhydrous Na_2SO_4. Removal of solvent *in vacuo*, followed by purification on silica gel using hexane–ethyl acetate (8:2) afforded pure 1,2,3-triazole.

Table 1: Synthesis of triazole linked glycosides via the Ferrier and Click reactions

Entry	Glucal	Alkyne	Products	Time (h)	Yield (%)b	a:b
a				4.5	85	6:4
b	"			5.0	80	8:2
c	"			5.0	70	7:3
d	"			4.5	75	7:3
e				4.5	85	6:4
f	"			5.5	80	9:1
g	"			6.0	80	8:2
h	"			5.5	70	6:4
i				4.5	80	6:4
j	"			5.0	75	8:2
k				6.0	70	7:3
l	"			6.5	65	8:2
m				6.5	65	7:3

a) All products were characterized by NMR, IR and mass spectrometry.
b) Yield refers to pure products after chromatography.

In conclusion, we have developed a direct one-pot glycosylation method for the synthesis of 1,2,3-triazole bridged glycoconjugates. By executing several reaction steps in a single step and purifying only at the final stage, this procedure excludes the isolation of azide intermediate, which significantly reduces the reaction time and improves the

overall yield. This method provides an easy access to build a metabolically stable triazole linkage between carbohydrates and other functional groups, which can be used as a new strategy for the bioconjugation of carbohydrates.

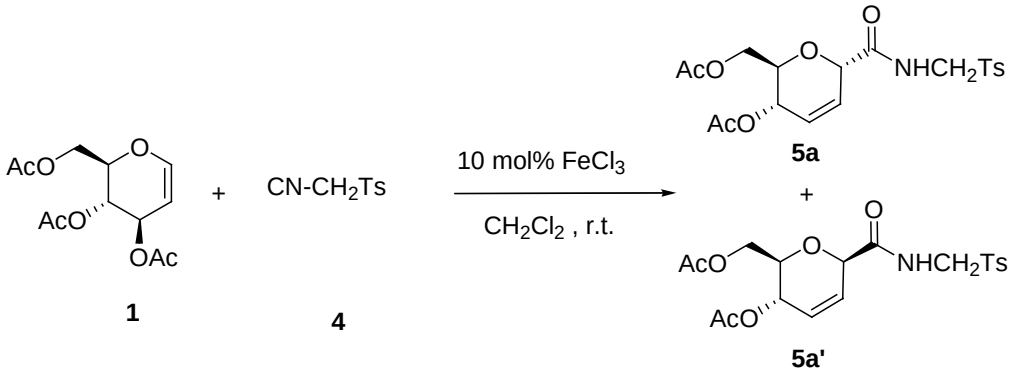
Section C:

First example of the carbon-Ferrier rearrangement of glycals with isocyanides: a novel synthesis of *C*-glycosyl amides.

C-Glycosidation is an important tool for the synthesis of optically active compounds, since it allows the introduction of carbon chains to sugar chirons and the use of sugar nuclei as chiral pool reagents as well as a carbon sources. *C*-Glycosides are versatile chiral building blocks for the synthesis of many biologically interesting natural products such as palytoxin, spongistatin, halichondrin and many others. The discovery of naturally occurring *C*-nucleosides with important pharmacological properties gave impetus to synthetic efforts for preparing active carbohydrate analogs. In addition, *C*-glycosides are potential inhibitors of carbohydrate processing enzymes and they are stable analogs of glycans involved in important intra- and inter-cellular processes. Of these *C*-glycosides, 2,3-unsaturated glycosides (pseudoglycals) are versatile synthetic intermediates and also constitute the structural units of several antibiotics. Pseudoglycals are traditionally obtained by an acid catalyzed allylic rearrangement of glycals in the presence of nucleophiles, a reaction known as the Ferrier rearrangement. Lewis acids are known to promote *C*-glycosidation with various nucleophiles such as allyltrimethylsilane, trimethylsilylcyanide and alkynylsilanes. However, there have been no reports on the allylic nucleophilic substitution of glycals (S_N2') with isocyanides to produce *C*-glycosyl amides.

Continuation of our interest on glycosidation, we disclose a versatile approach for the preparation of *C*-glycosyl amides from glucal and isonitriles by means of a carbon-Ferrier rearrangement. Initially, we attempted the Passerini type coupling of an isonitrile, a carboxylic acid and a glycal instead of a carbonyl compound to produce ω-hydroxy carboxamides. Surprisingly, we observed the formation of glycosyl amides instead of open chain hydroxyl amides. This provided incentive for an extensive study. Initially, we

examined the reaction of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with tosylmethylisocyanide (**4**, Tosmic) in the presence of 10 mol% of $FeCl_3$. The reaction was complete within 30 min and the desired product was obtained in 92% yield as a mixture of α-**5a** and β-**5 a'** anomers in a 9:1 ratio favoring α-anomer **5a** (Scheme 3).



Scheme 3

To a stirred solution of glucal triacetate (0.5 mmol) in acetonitrile (2 mL) were added Tosmic (0.6 mmol) and $FeCl_3$ (10 mol %). The resulting mixture was stirred at room temperature for 30 min. After complete conversion as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (3x10 mL) and the combined organics dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo*, followed by purification on silica gel using hexane–ethyl acetate (3:1) afforded the pure *C*-glycosyl amide.

Similarly, various other D-glucal derivatives such as 3,4,6-tri-*O*-benzoyl-, 3,4,6-tri-*O*-benzyl-, 3,4,6-tri-*O*-methyl-, and 3,4,6-tri-*O*-allyl-D-glucal reacted effectively with isonitriles to produce the corresponding *C*-glycosides in good yields (entries **b**-**k**, Table 2). The reaction was also effective with the TBS derivative of D-glucal without affecting the TBS functionality (entries **l** and **m**, Table 2). This method is applicable for both ester and ether derivatives of D-glucal. In each case, the α-anomer was obtained predominantly. The ratio of anomers was determined by ^{1}H NMR spectroscopy of the crude products obtained in the *C*-glycosidation. The predominant formation of the α-anomer may be explained by electronic effects on the oxocarbenium intermediate involved in this transformation. Kinetically preferred axial addition of the carbon

nucleophile was observed in most cases.The structures of **5a** and **5a'** were thoroughly studied by various NMR techniques including 1D ^{1}H NMR, homo-nuclear decoupling, double quantum filtered correlation spectroscopy (DQFCOSY) and nuclear Overhauser effect spectroscopy (NOESY). The spectral assignments were obtained from DQFCOSY experiments. Since the configurations at C2 and C3 are fixed, for the major isomer **5a**, the coupling constant between protons H2 and H3 ($^{3}J_{H2\text{-}H3}$= 5.9 Hz) support the equatorial disposition of H2 and H3, thereby implying axial orientation of the substituents at C2 and C3. The presence of nOe correlations between H1-H3 and H1-H6 suggest that all these three protons lie on the same side of the C3-C4-C5-C6 plane. These observations in turn indicate that the substituent at C6 is on the other side of this plane, which is additionally supported by the nOe correlation between NH and H2. The characteristic nOe's and energy minimized structure of 5**a** are shown in Figure 1.

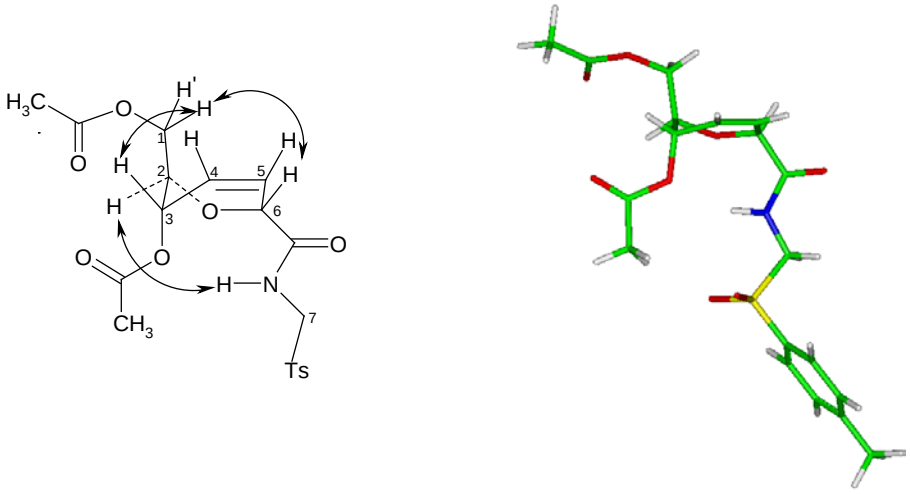


Figure 1. Characteristic nOe's and energy minimized structure of **5a**

For the minor isomer, a large coupling constant ($^{3}J_{H2\text{-}H3}$= 9.2 Hz) between protons H2 and H3 indicates that they occupy axial positions in the six-membered ring. Further, the presence of a strong nOe correlation between H2 and H6 indicates that these protons occupy 1,3-diaxial positions, which in turn provides support for the equatorial orientation of all the three substituents on the ring. The characteristic nOe's and energy minimized structure of **5 a'** are shown in Figure 2.

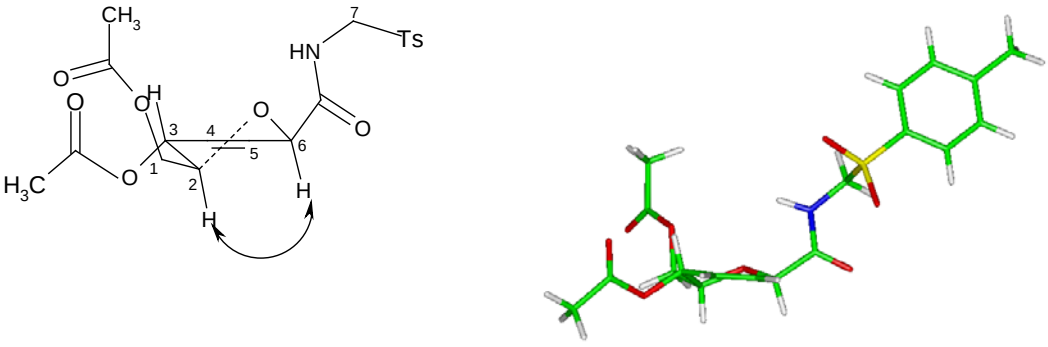
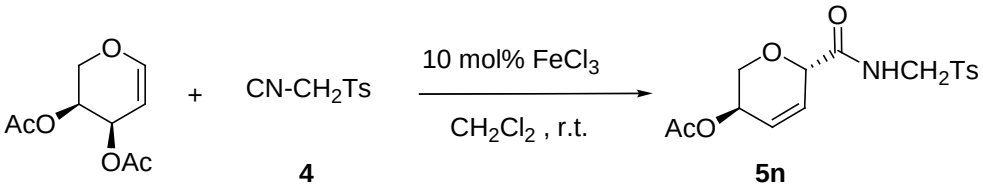


Figure 2. Characteristic nOe's and energy-minimized structure of **5a'**

Similarly, di-O-acetyl-L-arabinal also underwent the Ferrier type rearrangement to produce C-glycosyl amide 5n with α-selectivity. The presence of strong correlations between H1′ /H5 and H1 / H2 and medium correlations between H1′/ H2 protons and the coupling constant 3JH1-H2 = 5.2 and 3JH1'-H2 = 7.4 Hz, provide ample support for the structure shown in Figure 3, with substituents at C4 trans to the O-acetyl group at C1. The characteristic nOe's and energy minimized structure of **5n** are shown in Figure 3.



Scheme 4

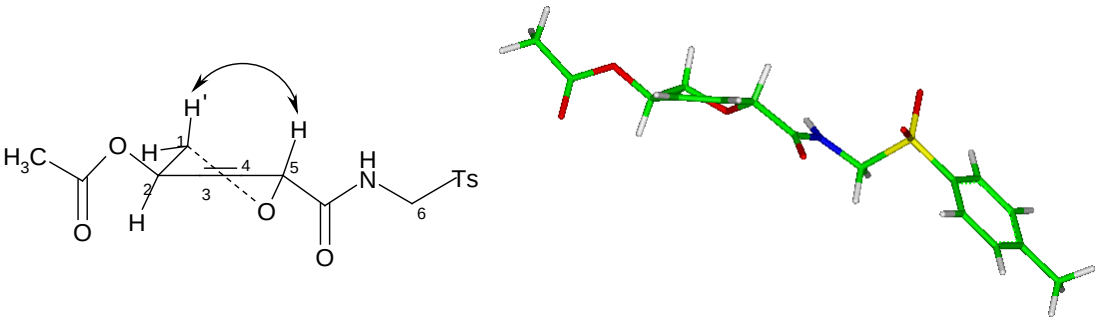


Figure 3.Characteristic nOe's and energy minimized structure of **5n**

The products were characterized by ^{1}H, ^{13}C NMR and IR spectra and by mass spectrometry. In the absence of catalyst, no reaction was observed even after an extended reaction time (12 h). As solvent, acetonitrile gave the best results. In all the cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and no side products were detected under these conditions as determined from the NMR spectra of the crude products. There are several advantages in the use of $FeCl_3$ as catalyst for this transformation, which include high conversions, short reaction times and high α-selectivity. In addition, this method avoids the use of expensive reagents and does not require any additives or stringent reaction conditions. This method is quite simple and convenient affording the desired products in good yields.

The efficacy of various metal halides such as $FeCl_3$, $InBr_3$, $InCl_3$, $GaCl_3$, YCl_3 and $YbCl_3$ was studied for this transformation. Of these catalysts, $FeCl_3$ was found to be more effective in terms of conversion. For example, treatment of 3,4,6-tri-*O*-acetyl-D-glucal with Tosmic in the presence of 10 mol% $FeCl_3$ and 10 mol% $InCl_3$ over 30 min afforded 92% and 75% yields, respectively.

The scope and generality of this process is illustrated with respect to various glucal derivatives and isonitriles and the results are presented in Table 1. Mechanistically, the reaction proceeds via an oxocarbenium ion intermediate by a Ferrier rearrangement. Subsequent axial attack of the isonitrile on the oxocarbenium ion would give a carbimminium intermediate which is probably hydrolyzed to the product amide (Scheme5).

Scheme 5. A plausible reaction mechanism

In summary, we have described a novel method for the synthesis of *C*-pseudoglycals from glycals and isonitriles using a catalytic amount of $FeCl_3$ under mild reaction conditions. This method provides high yields of *C*-glycosyl amides in short reaction times with high anomeric selectivity, which makes it a useful and attractive process for carbon-carbon bond formation at the anomeric position of sugars.