Stereo selective total synthesis of macrolides 11-β-Methoxy curvularin, (3S), (7R)-de-O-methyl botryosphaereodiplodin and development of novel methodologies using glucal as precursor

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To
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By
CHITTETI. DIVYA VANI
Reg. No: 09CHPH19

Supervisor
Dr. J.S. Yadav FNA, FNASc, FTWAS

Director's Research Group

Division of Natural Products

Indian Institute of Chemical Technology

(An Associate Institution of UNIVERSITY OF HYDERABAD)

HYDERABAD-500 007

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DECLARATION

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

Place: Hyderabad **CHITTETI. DIVYA VANI**
Date: **(Candidate)**

CERTIFICATE

I hereby certify that the research work embodied in this thesis entitled **“Stereo selective total synthesis of macrolides 11-β-Methoxy curvularin, (3S), (7R)-de-O-methyl botryosphaereodiplodin and development of novel methodologies using glucal as precursor”** has been carried out by **Miss. CHITTETI. DIVYAVANI** under my supervision at Indian Institute of Chemical Technology, Hyderabad. I state that no part or full has been submitted elsewhere for any degree or diploma.

Place: Hyderabad

Date:

Dr. J. S. YADAV

(Supervisor)

DEDICATED

TO MY

BELOVED

PARENTS

AND MY GUIDE

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DIVYAVANI.CHITTETI

GENERAL REMARKS

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

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

ABBREVIATIONS

Ac	:	Acetyl
AcOH	:	Acetic acid
Ag_2O	:	Silver-II-Oxide
AlI_3	:	Aluminum iodide
Aq	:	Aqueous
Ar	:	Aryl
(S,S)-BINOL	:	Binaphthol
(S,S)-BINOL	:	Binaphthol
^{n}Bu	:	*normal*-Butyl
Bn	:	Benzyl
BnOH	:	Benzyl alcohol
Cacld	:	Calculated
CCl_4	:	Carbon tetrachloride
$CeCl_3$	:	Cerium Chloride
m-CPBA	:	*meta*-Chloroperbenzoic acid
CrO3	:	Chromium trioxide
CuCN	:	Copper cyanide
DCC	:	N,N’-Dicyclohexyl-Carbodiimide
DCM	:	Dichloromethane
DCE	:	Dichloroethane
L(+)-DIPT	:	L(+)- Diisopropyl tartarate
DMAP	:	4-Dimethyl aminopyridine
DMF	:	N,N-Dimethylformamide
DMSO	:	Dimethyl sulfoxide
EI-MS	:	Electron impact mass spectrometry
ESI-MS	:	Electrospray ionization mass spectrometry
Et	:	Ethyl
EtMgBr	:	Ethyl magnesium bromide
EtOAc	:	Ethyl acetate

Et_2O : Diethyl ether

$Fe(NO_2)_3$: Ferric nitrate

H : Hour

HMPA : Hexamethyl phosphoramide

$(HCHO)_n$: Paraformaldehyde

HCl : Hydrochloric acid

HRMS : High Resolution Mass Spectrometry

H_2O_2 : Hydrogen peroxide

H_2SO_4 : Sulphuric acid

Hz : Hertz

I_2 : Iodine

IBX : Iodoxy benzoic acid

$InCl_3$: Indium trichloride

IR : Infrared

LAH : Lithium aluminium hydride

LC-MS : Liquid chromatography mass spectrometry

LiCl : Lithium chloride

$LiNH_2$: Lithium amide

Me : Methyl

Min : Minute(s)

MeOH : Methyl alcohol

MOM : Methoxy methyl

4 A^o MS : 4 A^o Molecular sieves

MHz : Megahertz

MeI : Methyl iodide

NaH : Sodium hydride

NaOH : Sodium hydroxide

NMR : Nuclear magnetic resonance

Pd/C : Palladium Carbon

$Pd(PPh_3)_4$: Tetrakis Palladium

Ph : Phenyl

^{i}Pr : *iso*-propyl
Quant : Quantitative
Rt : room temperature
R_f : Retardation factor
$SOCl_2$: Thionyl Chloride
TBAF : Tetra-*n*-butyl ammonium iodide
TBHP : *tertiary*-butylhydroperoxide
TBSCl : *tertiary*-butyl dimethyl silyl chloride
TFA : Trifluoro acetic acid
TFAA : Trifluoro acetic anhydride
$TiCl_4$: Titanium tetrachloride
$Ti(O_iPr)_4$: Titanium isopropoxide
TLC : Thin layer chromatography
TPP : Triphenyl phosphine

CONTENTS

Section C: InCl3-catalysed novel and efficient Synthesis of sugar annulated N-aryl tetrahydro Pyridine

INTRODUCTION

Organic synthesis is a versatile branch of chemical synthesis and is concerned with the construction of organic molecules through organic reactions hence the molecules can often contain a higher level of complexity when compared to purely other inorganic compounds, so the synthesis of natural products has developed into one of the most important branches of organic chemistry. 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. Ever since synthetic organic chemists realized their ability to assemble molecules from the elements and other simple starting materials, natural products served to fascinate and challenge them. The chemical syntheses of natural molecules without the aid of enzymes often present formidable challenges to human ingenuity and skill. The structure of natural products in an almost infinite range of complexity and stability therefore often present distinct synthetic problems, which require strategies and tactics for their solutions. It is the almost unlimited variation in structure and the constant discovery of new molecular constructs that keep the field of natural products synthesis so attractive and vibrant. The dazzling biological properties exhibited by many natural products and the attendant opportunities these molecules offer for probing biological questions also serve as major attractions in this field of investigation.

Robert Burns Woodward, won the Nobel Prize for chemistry in 1965 for several total synthesis (e.g. his 1954 synthesis of strychnine), is regarded as the father of modern organic synthesis. Other notable example is Wender's, Holton’s, Nicolaou’s, and Danishefsky’s synhthesis of Taxol. The term *macrocycle* refers to medium and large ring compounds, with respectively, 8–11 and 12 or more atoms in the ring. Macrolides belong to the polyketide class of natural products. Macrocyclic structures that have one or more ester linkages are generally referred to as macrolides or macrocyclic ring lactones[1] in some cases, macrocyclic lactams have also been described as macrolides. Originally macrolides denoted a class of antibiotics derived from species of *Streptomyces* and containing a highly substituted macrocyclic lactone ring aglycone with few double bonds and one or more sugars, which may be aminosugars, non-nitrogen sugars or both[2] a large macrocyclic lactone ring to which one or more deoxy sugars, usually cladinose and desosamine, may be attached. To our knowledge the largest naturally occurring macrolides are the 60-membered quinolidomicins and the largest constructed macrolide is the 44-membered swinholide.[3] Trivial names are widely used, especially for naturally occurring macrocyclic lactones. According to IUPAC rules, macrolides as well as other lactones formed from aliphatic acids should be named by adding “olide” as a suffix to the name of the hydrocarbon with the same number of carbon atoms. The numbering starts from the ester carbonyl carbon. The IUPAC rules also give an alternative way of naming lactones based on the rules for naming heterocycles. According to this rule the lactones are named as oxacyclo ketones and the numbering starts from the ring oxygen. AutoNom naming program uses this latter rule although the “olide” naming is generally used in the literature. By way of example, Figure 1 shows the alternative names of two macrolides **1** and **2**.

The tremendous interest in macrolide chemistry can be understood if one takes a look at the diversity of the structures and physiological effects of macrolides. Natural products containing a macrolactone framework are found in plants, insects, and bacteria and they may be of terrestrial or marine origin. The useful properties of macrolides range from perfumery to biological and medicinal activity. The new findings in the field of antitumour active and other antibiotic macrolides, together with pheromones and plant growth regulators with macrolactone framework, are an inspiration to chemists to study macrolides. The isolation and structural elucidation of almost all of the known ten-membered-ring lactones were reported in the last 30 years. Before 1975, the only described decalactone was the jasmine ketolactone, identified in Italian jasmine oil in 1942. From the monocyclic lactones diplodialides (isolated in 1975) to the bicyclic lactone 642305 (isolated in 2003) and very recently isolated Botryolides (isolated in

2008), more than ten structural groups, several of which possess three or even more lactones with different structures, were isolated.

Kerschbaum and co workers[4] in 1927 was isolated the first macrocyclic lactones, Exaltolide **3** and ambrettolide **4**, from angelica root and ambrette seed oil, respectively. The discovery of these vegetable musk oils aroused interest in finding synthesis routes to these and related macrolides owing to their commercial importance in the fragrance industry. Even today Exaltolide **3** is one of the most widely produced macrocyclic musk lactones. The great breakthrough in macrolide chemistry came in 1950 when Brockmann and Henkel[5] isolated the first macrolide antibiotic picromycin **5** from an *Actinomyces* culture.

Macrolide antibiotics play a therapeutically important role. They are regarded as among the safest of antibiotics and they have successfully been used to treat infections caused by gram-positive organisms, certain gram-negative and anaerobic bacteria. Natural macrolide antibiotics can be classified according to the size of the aglycone ring. The most commonly used macrolide antibiotics, erythromycin and josamycin, belong to the groups of 14-membered and 16- membered ring derivatives, respectively.[6] A variety of macrolides can be looking at figure **3** some examples are Chainin **6**, Maytansin **7**, Cytochalasan B **8**, and Carpaine **9**.

The synthesis and antimicrobial activity of a new class of macrolide antibiotics which consist of a macrolide scaffold and a quinolone unit covalently connected by an appropriate linker are described. Optimization of several synthetic steps and structural properties of lead compounds are discussed. The structure-activity relationships of these compounds were studied and the screening results showed that compounds exhibited moderate antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis* and *Escherichia coli*, where as some compounds showed potent antifungal activity against all the fungal species tested, showing a promising broad-spectrum antifungal activity. All the compounds have been studied *in vitro* for the hemolytic activity as a measure of their cytotoxicity, showing that these compounds have low lytic properties.

New macrolides, such as clarithromycin and azithromycin, are active agents to Mycobacterium avium complex (MAC). Both clarithromycin and azithromycin are well-known for the ability to improve the prognosis of AIDS patients with disseminated MAC infection. Which is a macrolide antibiotics used to treat pharyngitis, tonsillitis, acute maxillary sinusitis, acute bacterial chronic bronchitis, pneumonia (especially a typical pneumonias associated with Chlamydia pneumoniae or TWAR), skin infections.

In addition, it is sometimes used to treat Legionellosis, Helicobacter pyloro, and Lyme disease.

Some of the macrolides such as methymycin **10** have proved to be antibiotic activity. A novel antitumourally active macrolide group is represented by epothilone B **11**.[7] Epothilones are considered as the most promising new candidates for cancer chemotherapy. Epothilones are also the first naturally occurring compounds whose biological profile has been shown to bear a similarity to the clinically important anticancer agent Taxol.[8]

Curvularin is a 12-membered macrocyclic lactone incorporating a resorcinyl moiety produced by a number of fungal species across several genera including Curvularia, Penicillium and Alternaria. Curvularins has been shown cytotoxicity towards sea urchin embryogenesis, inhibit cell division[9] by disrupting mitotic spindle formation and is known to be phytotoxic. More recent investigations have been shown that curvularin is a highly selective transcription-based inhibitor of the iNOS-dependent NO production, [10a] acting on the Janus tyrosine kinase-STAT pathway. This action offers an approach to the development of drugs inhibiting iNOS associated with NO pathophysiology. Curvularins also reported to cause hepatic necrosis.[10b] Because of an interesting macro cyclic skelton, adopting some flexible conformations and novel biological properties Curvularin and related macrolides have been receiving much attention of synthetic chemists.

11, 12-Dehydrocurvularin (**13**) co-occurs with curvularin in *Drechslera australiensis*.[11]

In 1988 kobyashi and coworkers isolated Curvularin, 8-dehydrocurvularin, and 8-hydroxycurvularin as well as a minor new metabolite, 8-methoxycurvularin, as fungal metabolites having cytotoxic activity towards sea urchin embryogenesis. Curvularin induced barrel-shaped mitotic spindles and 8-dehydrocurvularin caused miniature spindles. They were shown to act on components of mitotic apparatus and effectively inhibit cell division.

In recent years, Yamamura and co workers[12] reported the isolation of several curvullarin type metabolites from the mycelium of the hybrid strain ME 0005 derived from *Pencillium citrociride B* although curvularin was first isolated in 1956 from the curvularia species. Some other related curvullarins which are also isolated from the hybrid strain ME 0005 derived from *Pencillium citrociride* species, having cytotoxic, antimicrobial, anticancer drug discovery.[13] 12-Oxo curvularin and cireofuran have shown attractive physiological properties. They also possess an unusual oxygen function at C-12 position in their structures.

Shosuke Yamamura and co workers in 1991 isolated four new curvularin-type metabolites 11-α-methoxycurvularin, 11-β-methoxycurvularin, 11,12-dihydroxy-curvularin, and 12-hydroxy-10, 11-trans-dehydrocurvularin from the mycelium of the hybrid strain ME 0005 derived from *penicillium citreocitreociride* B.

11-β-Methoxycurvularin, a 12-membered macrolide, was recently isolated from hybrid strain ME 0005 derived from *Pencillium citrociride* 4692 and 6200, and showed cytotoxicity towards panel of human cancer cell lines (NCI-H460,MCF-7 and SF-268)[11]. The structure was elucidated by revision of spectroscopic data analysis of the originally proposed structures[14] methoxy curvularin. Curvularin exhibits a distinctly different biological profile to the structurally similar resorcylic acid lactones such as the zearalananones, radicilol and antibiotic LL Z1640-2.

Chemical investigations of the cytotoxic extract of the marine fungus *Curvularia* sp. (strain no. 768), isolated from the red alga *Acanthophora spicifera*, yielded the novel macrolide apralactone A, as well as the antipodes of curvularin macrolides **22–24**. Compound **25**, a dimeric curvularin was recognized as an artefact. In the current study, we were able to isolate and identify the novel fungal macrolide **21**, which on the one hand is characterised by a 14-membered macrolide like in RALs (e.g., zearalenone and radicicol), but resembles the phenylacetic acid lactone moiety of the curvularins on the other hand. Such nonaketide-based carbon skeletons as for curvularins found in **21** have so far exclusively appeared in a Japanese patent as lead structure concerning the inhibition of neuropeptide Y receptor for anti-obesity programs. The structural type of **21** is unprecedented, due to the incorporation of a 4-chromanone moiety within a macrolactone. Moreover, here we describe the new stereochemical series of curvularin macrolides **22–24**. The majorities of the isolated macrolactones 21-25 were evaluated for their cytotoxic activity towards a panel of up to 36 human tumor cell lines and were found to be considerably cytotoxic in some cases. The novel macrolide **21** showed concentration-dependent cytotoxicity with a mean IC50 value of 9.87 µM. The most active metabolite, compound **22**, displayed concentration-dependent cytotoxicity with a mean IC50 value of 1.25 µM, combined with significant *in vitro* tumor cell selectivity towards nine of the 36 tested tumor cell lines, which indicates 25% of selectivity.

Peter Proksch and co-workers[15] isolated fungal isolates of *Penicillium cf. montanense* were obtained from the marine sponge *Xestospongia exigua* collected from the Bali Sea, Indonesia. Culture filtrates of the fungi yielded three novel decalactone metabolites sporostatin **28**.

Xestodecalactones A, B, and C (**26** & **27**) (Figure **9**), consisting of 10-membered macrolides with a fused 1, 3-dihydroxybenzene ring. These compounds, of which **26a** and **26b**, due to the additional stereocenter at C-9, are diastereomeric compounds, are structurally related to a number of biologically active metabolites found in terrestrial fungal strains. Compound **27a** was found to be active against the yeast *Candida albicans.*

Other 12-membered macrolides:

Cladosporolide A, B, C, D is also 12-memnered lactones, produced by Cladosporium. Cladosporolides FI-113 is a root growth inhibitor of lettuce seedlings. Its structure and stereochemistry, [(2E, 4R, 5S, 11R)-4,5-dihydroxy-2-dodecen-11-olide] were illucidated by Hirota from spectroscopic studies and X-ray analysis.

Relatively simple macrolides such as macrolide A26771B **33**[16] and patulolides A **34**,[17] B **35**, and C **36**[18] are antimicrobial compounds. Interestingly, even very simple macrolides possess properties that make them worth studying.

The pheromones of the saw-toothed grain beetle, *Oryzaephilus surinamensis,* and related cucujid species *O.mercator, Cryptolestes ferrugineus, C.turcicus,* and *C.pusillus,* have rather simple macrolactone. These grain beetles are major pests of cereal and grain on a world wide scale and some of these pheromones have been patented as attractants for insect traps.[19]

14-Membered macrolides:

Fungal macrolides, such as zearalenone, radicicol, and the curvularin macrolides have recently attracted attention due to their interesting biological activities. Zearalenone was shown to have estrogen agonistic properties,[20] whereas radicicol and the curvularin macrolides were found to be inhibitors of HSP90, a promising target for anticancer drug discovery. From the chemical point of view, the macrolides zearalenone and radicicol belong to the family of resorcylic acid lactones (RALs) possessing a C-18 backbone with a 14-membered macrolide.[21] In contrast, the curvularins are octaketides composed of a 12-membered macrolide skeleton attached to a 3,5-dihydroxy-phenylacetic acid.

Hair loss or hair thinning is a common complaint of people living in today's stressful world. Some drugs to counteract such hair loss, such as minoxidil and finasteride have been developed, but their therapeutic effects have been limited. Consequently, there is a need for a new drug that induces hair-growth through a new mechanism. Human hair follicles are made up of epithelial and mesenchymal dermal cells such as keratinocytes, dermal papilla cells, fibroblasts, and sebaceous cells, and the hair-growth cycle (hair cycle) is controlled *via* interactions among these cells. The hair shaft is formed by the proliferation and differentiation (keratinization) of follicular keratinocytes. Dermal papillae regulate the proliferation, differentiation and apoptosis of these follicular keratinocytes, which play a key role in the control of the hair cycle. WNT-5A (wingless-type mouse mammary tumor virus integration site family, member 5A) is a secretory glycoprotein that belongs to the WNT family. WNTs are important intercellular signaling molecules that regulate axis formation and organ formation during the fetal stage. 6, 7 to develop a hair-growth stimulant, we have been studying molecules that regulate the proliferation of dermal papilla cells. We recently found that WNT-5A was highly expressed in the dermal papillae of depilated skin, by using inhibitory activity against WNT-5A expression as a guide for bioassay.

In 2009, Shinonaga and co-workers[22] disclosed four unique pochonin family structures (pochonins G-J) from the culture broth of *Pochonia chlamydosporia var. chlamydosporia.* These compounds were isolated via bioassay-guided fractionation against WNT-5A expression in search of novel hair-growth stimulants. The structures of pochonins G-J were elucidated by means of a combination of 1D and 2D spectroscopic techniques. The entire family of pochonin natural products (A-P) has been shown to share a common structural motif of a 14-membered macrocyclic resorcylic acid lactone core (RAL). In addition, all pochonins except F and J are chlorinated at C13 of the aromatic ring analogous to radicicol and monorden. Similarly, pochonins J and F demonstrate more semblances to the aigialomycin family of natural products and hypothemycin, due in part to the lack of C13 chlorination. Because of their diverse biological functions and curious skeletal connectivities, members of these families of natural products have been met with interest giving rise to innovative synthetic approaches towards their assembly. Here we have shown some group of Pochonin macrolides in figure **13**.

Aigialomycin D 1, which possesses potent antitumour (IC50: 3.0 mg/ml against KB cells) and anti-malarial activity (IC50: 6.6 mg/ml against Plasmodium falciparum), is a member of a group of 14-membered resorcinylic macrolides isolated from the marine mangroove fungus Aigialus parvus BCC 5311. Some kinases, in particular cyclin-dependant kinase (CDK) and glycogen synthase kinase (GSK-3), have recently been identified as its antitumor targets of action.[23]

CONTEMPORARY WORKS:

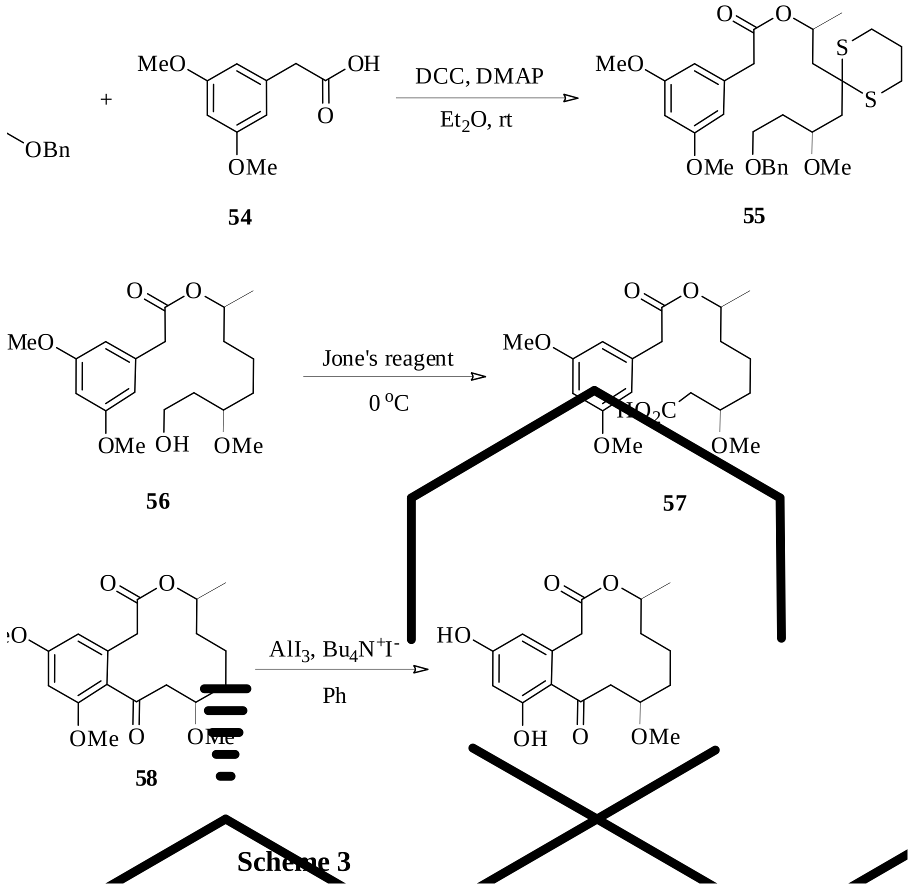
This thesis focuses on the synthesis and reactions of simple 12-membered macrolide 11-β-methoxycurvularin. Despite its simplicity significance and its low natural abundance, have made them as an attractive synthetic target. Consequently, there have been some reports on the total synthesis of 11-β-methoxycurvularin following multi step synthetic sequences.

Xinfu Pan et al synthesis[24]:

The first total synthesis of 11-β-methoxycurvularin was reported by Xinfu Pan et al in 2007. The design of this synthesis started with a three-component, one-flask Linchpin coupling employing 2-*tert*-(butyldimethylsilyl)-1,3-dithiane **47** with two different epoxide electrophiles **48** to construct unsymmetrical adducts **49** exploited a solvent-controlled Brook rearrangement[25](Scheme 1). This route leads to the rapid, efficient, and stereocontrolled assembly of highly functionalized intermediates for complex molecule synthesis[26] in this note, they reported the application of this tactic for the efficient construction of the target molecule.

The synthesis is commenced from (S)- 1,2-epoxy-4-butanol **50**, which was prepared from (S)-(-)-malic acid according to the route made by Kenji Mori and its NMR data and optical rotation were identical with those reported in the literature. As shown in Scheme **2**, the multicomponent linchpin coupling was employed with commercially available (*S*)-(-)-methyloxirane and epoxide **51**, and the latter is readily prepared from (*R*)-4 with BnBr and NaH. Pleasingly, with lithiation of dithiane in THF *n*-BuLi (-78 ^{o}C to -10 °C) was used, followed by the addition of epoxide (*S*) (-78 °C), warming to -40 °C, and stirring for an additional 1 h at -40 °C, and then adding HMPA (3 equiv) and epoxide **5** in THF, letting it warm to 0 °C for 1 h. Last MeI (3 equiv) was added and the mixture was stirred for 0.5 h at 0 °C, furnishing **52** in 74% isolated yield. This on TBS deprotection gave 98% of the desired compound **53**.

Esterification of **53** with 3,5- dimethoxyphenylacetic acid **54**[27] using DCC and DMAP gave the ester **55** in 98% yield. The dithiane and benzyl groups of **55** were removed with Raney Ni under reflux for 6 h, affording **56** in 75.4% yield. Oxidation of the hydroxy group of **56** with Jones reagent (5 equiv) in acetone at 0 °C for 15 min gave the acid **57** in 86% yield in 7 h. The macrolide **58** was obtained by intramolecular Friedel-Crafts reaction of the carboxylic acid **57** in a mixture of TFA and TFAA.[28] Deprotection of the methoxy groups at C5 and C7 of macrolide **58** with freshly prepared AlI_3 completed the synthesis 11-β-methoxycurvularin. Like wise the 11-α-methoxy curvullarin has also been synthesized from (*R*)-1, 2-epoxy-4-butanol.



Scheme 3

J.Madhusudhan Rao's[29] synthesis:

J.M.Rao et al has reported a new route for the stereoselective synthesis of 11- α methoxycurvularin and 11-β-methoxycurvularin featuring a Maruoka allylation to install stereocentre at C-11 and Grubbs cross metathesis reaction for the construction of the key fragment. The most distinguished feature of this synthesis is the efficient and reagent controlled asymmetric construction of key fragment in six steps from inexpensive 1,3-propanediol in 55% overall yield.

The total synthesis was initiated with the known 1,3-propanediol **59**, which was selectively protected as benzyl ether **60** using BnBr, NaH and a catalytic amount of TBAI (Scheme 4). IBX oxidation of **60** gave aldehyde **61**, which was subjected to an enantioselective Maruoka allylation[30] using titanium complex (*S, S*)-I and allyltri-n-butyl tin to furnish the homoallylic alcohol **62** in 86% yield with excellent enantioselectivity of 97% ee (determined by chiral HPLC). Homoallylic alcohol **62** was then converted to its corresponding methyl ether **63** using MeI and NaH in THF in 96% yield (Scheme 4). The merging of two alkenes **63** and methyl vinyl ketone was then investigated *via* olefin cross-metathesis reaction with second generation Grubbs catalyst (5 mol % Grubbs II) in dichloromethane under reflux conditions provided the cross-metathesis product **64** in 86% yield.[31] The α, β-unsaturated ketone **64** was treated with (*R*)-(+)-2-methyl-CBS-oxazaborolidine[32] and BH_3DMS at -40 ^{o}C to furnish allyl alcohol **65** with an (*S*)-configuration in 90% yield with 97% de.

Esterification of **65** with 3, 5- dimethoxyphenylacetic acid **66** using DCC and DMAP gave the ester **67** in 98% yield. Oxidation of the hydroxy group of compound with Jones reagent (5 equiv) in acetone at 0 °C for 15 min gave the acid in 86% yield.

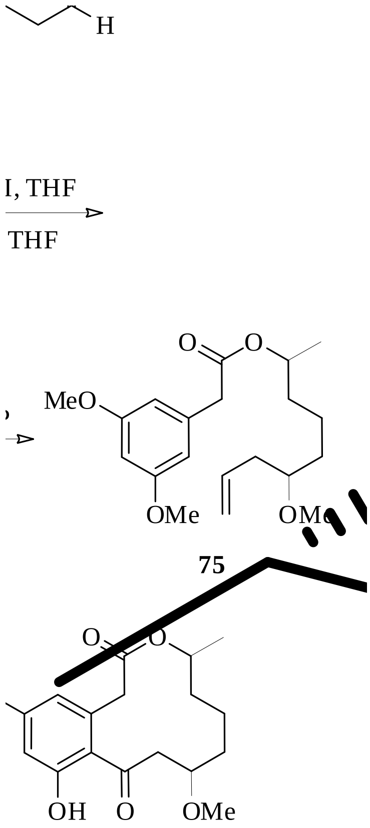
The macrolide was obtained by intramolecular Friedel-Crafts reaction of a mixture of TFA and TFAA. Deprotection of the methoxy groups at C5 and C7 of macrolide with freshly prepared AlI_3 completed the synthesis of 11-β-methoxycurvularin. 11-α-methoxy curvullarin has also been synthesized by using (*S*, *S*) **-** catalyst in Mourako allylation.

11- β-Methoxycurvularin

heme 5

J.S.Yadav's[33] Synthesis:

Previously our group has reported the stereoselective total synthesis of 11-α and 11-β-methoxycurvularins using Jacobsen hydrolytic kinetic resolution (KHR) and Maruoka allylation reactions to create the two stereogenic centers. With Jacobsen hydrolytic kinetic resolution (KHR) of propylene oxide afford (*S*) propylene oxide **68**.[34] The resulting propylene oxide **68** was regioselectively opened with 1-[(2-propynyloxy) methyl] benzene to provide the secondary alcohol **69**. Compound **69** was subjected to tert butyl dimethyl silyl (TBS) protection to give **70** which was hydrogenated with Pd/C to provide the primary alcohol **71** which was oxidized to aldehyde **72**. This was subjected to Marouka asymmetric allylation reaction to establish the C-11 stereocenter of both natural products by using different 1, 1-binaphthol ligands. The secondary alcohol **73** was protected as its methyl ether **74**.



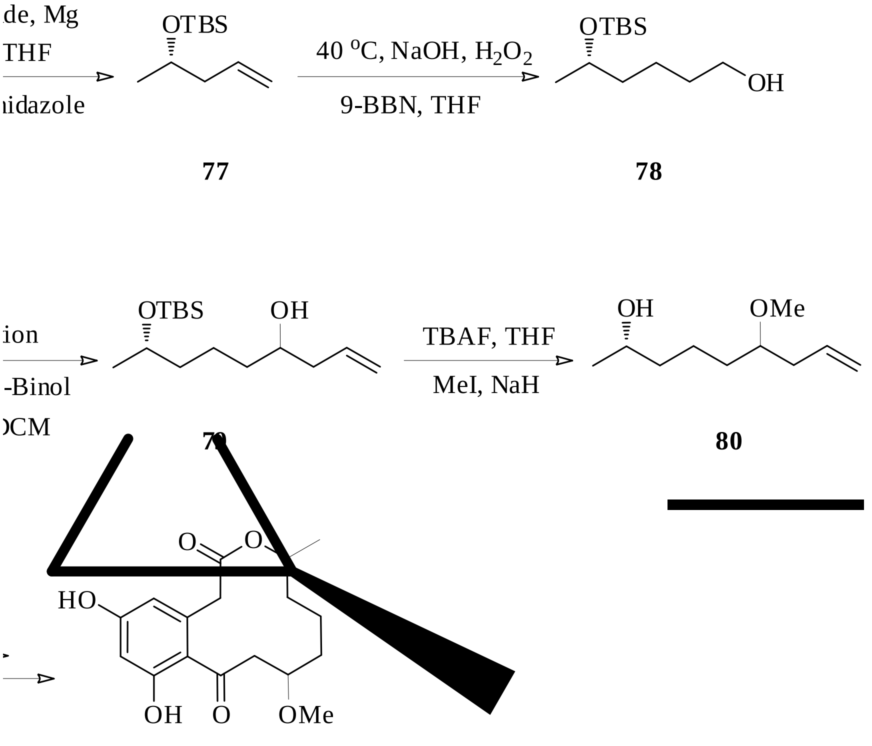
75

Scheme 6

Which undergo esterification with 3, 5-dimethoxy phenyl acetic acid to give an ester compound **75** which on further subjection of jones oxidation to give an acid, which was transformed to 11-β-methoxycurvularin using the same procedure described in Scheme 3.

Y.Venkateswarlu[35] synthesis:

Another total synthesis of 11-β-methoxycurvularin was reported by Venkateswarlu et al. The synthesis of 11-β-methoxycurvularin initiated from commercially available oxirane **76**, was subjected to a CuCN mediated regioselective nucleophilic opening with allylmagnesium chloride to provide an alcohol. Alcohol was protected as its *t*-BuMe$_2$Si ether by reaction with *t*-BuMe$_2$SiCl (tert-butyldimethylsilyl chloride) to obtain 77. Protected **77**, on selective hydroboration with 9-BBN-H (9-borabicyclo [3.3.1] nonane) in THF, followed by treatment with NaOH and H$_2$O$_2$, gave alcohol **78** in 90% yield.[36] The primary-alcohol function in **78** was oxidized with IBX (2-iodoxybenzoic acid) in DMSO to afford the corresponding aldehyde which was subjected to catalytic asymmetric allylation with allyltributylstannane, a procedure developed by Keck and co-workers, to furnish the homoallylic alcohol **79** in 80% yield with an excellent diastereoselectivity of 95% de. The homoallylic alcohol **79** on treatment with MeI/NaH, afforded methyl ether. The *t*-BuMe$_2$Si group in **79** was removed with 1M Bu$_4$NF in THF at room temperature to give **80** in 97% yield, which was esterified with 3,5-dimethoxybenzeneacetic acid in the presence of dicyclohexylcarbodiimide (DCC) and N,N-(4)-dimethylaminopyridin (DMAP). Further synthesis is reported using the same procedure.



Scheme 7

PRESENT WORK

Synthesis of 11-β-methoxycurvularin:

Synthetic organic chemistry is perhaps the most expressive branch 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 a quest to construct the most complex and challenging of nature's products, this endeavor-perhaps more that 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. 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. The choice of the strategy for any synthesis lies on the availability of the starting materials, selectivity of the reactions and the yield of the reactions.

As an ongoing project on the synthesis of biologically active natural products, we have initiated a programme on the stereoselective total synthesis of 11-β-Methoxy-curvularin, a 12-membered macrolide first isolated from the mycelium of hybrid strain ME-0005 which is a polyketide metabolite of various *curvularia, pencillium, and alternaria* and *cochiobolous* species. It was found to be cytotoxic[37] and antimicrobial activities[38] particularly four human cancer cell lines such as [NCI-H460, MCF-7, SF-268, 41A Pa Ca-2].[39] Moreover it has been indicated that, they have effects on the spindle formation of embryos of sea urchin cells to give barrel like spindles and terminate the first step of cell division.

This is a promising tool for anticancer drug discovery further it has also been demonstrated that stereo chemical features important for tubulin binding of these agents. Structurally 11-β-methoxycurvularin shows different stereochemistry at C-11 in the 12-membered lactone ring. The first total synthesis of these natural products has been reported by Liang et al which also presented in this thesis, which led to the revision of the spectral data of originally proposed structures.

Retrosynthetic analysis:

The target molecule 11-β-methoxycurvularin, 12-membered macrolide lactone comprises a fused 1,3-dihydroxy benzene ring with two stereogenic centers at C-11, C-15. Other researchers, as discussed in earlier started with a three-component, one-flask linchpin coupling employing 2-*tert*-(butyldimethylsilyl)-1,3-dithiane with two different epoxide electrophiles to construct unsymmetrical adducts exploited a solvent-controlled Brook rearrangement, propane diol, epoxides to prepare the key fragment. We used a simple and commercially available homopropargyl alcohol as a starting material to originate our synthetic scheme. The retrosynthesis of 11-β-methoxycurvularin is outlined in the following scheme 7.Our synthetic design of 11-β-methoxycurvularin makes use of the well known Sharpless asymmetric epoxidation to introduce absolute stereo centre at C-11 and Jacobson’s kinetic hydrolytic resolution at C-15 methyl centre for the construction of the key fragment **82**, which has been synthesized from commercially inexpensive starting material homopropargyl alcohol **88**. We wish to report a concise route for stereoselective total synthesis of 11-β-methoxycurvularin. This strategy was schematically illustrated in scheme **7** as below.

The later process is also expected to facilitate the incorporation of esterification of readily available 1,3-dimethoxyphenylaceticacid[47] **83**. Compound **83** on disconnection of the unique 12-membered lactone ring leads to **78** with the key fragment **81,** which in turn could be prepared from **82** and **83**.

Synthesis of Fragment 82:

Our synthesis commenced with easily available and commercially inexpensive homopropargyl alcohol **88** which was protected as benzyl ether **87** by using BnBr, NaH[48] in dry THF at 0 °C-rt for 4 h in 93% yield (Scheme 9). In the PMR spectrum of the obtained product **87** apppearence of signals at δ 7.21-7.31 as multiplet, 4.52 as singlet confirmed the structure of benzyl ether **87**. The ether was treated with the

Grignard reagent prepared from ethyl bromide and magnesium metal followed by quenching with para formaldehyde in dry THF to afford compound **89** in 72% yield (Scheme 9). The PMR spectrum of compound **89** clearly showed a broad singlet at δ 4.16 for hydroxymethylene protons. In IR spectrum an absorbance at 3373 cm^{-1} for the hydroxy functional group and in the EI-mass spectrum appearance of a molecular ion peak at m/z 189 [M-H] further confirmed the product. In order to get the *trans*-allyl alcohol, compound **89** was treated with lithium alumunium hydride[40] in dry THF refluxed for 2 h, which reduced the alkyne to the desired *trans* olefin **90** in 90% yield. The PMR spectrum showed a multiplet at δ 5.68-5.72 for the olefinic protons. In the IR spectrum a characteristic C=C stretch at 1686 cm^{-1}, a C-H deformation stretch at 971 cm^{-1} for the *trans* C-H protons and hydroxyl absorption at 3379 cm^{-1} has observed. The structure of the olefin **90** was further confirmed by the EI-mass spectrum, which showed a molecular ion peak at *m/z* 191 [M-H]. (Scheme 8)

In the next step, olefin **90** was subjected to Sharpless asymmetric epoxidation[41] using L(+)-DIPT, Ti(O$_i$Pr)$_4$ and 4.5M *tertiary* butyl hydroperoxide to furnish the desired epoxide **86** in 70% yield (scheme 10). The two-epoxy protons in the PMR spectrum of **86** resonated as multiplets at δ 2.87-2.91 and δ 3.00-3.10, while the IR spectrum showed absorptions at 3403 cm^{-1} for the hydroxyl function and 1277 cm^{-1} for the epoxy linkage. The structure of the epoxy alcohol **86** was further confirmed by the molecular ion peak at *m/z* 231 [M+Na]$^{+}$ in its ESI-mass spectrum.

The epoxy alcohol **86** was converted into the corresponding chloride **91** with CCl_4, Ph_3P, and $NaHCO_3$ and it is refluxed for overnight in 80% yield. The PMR spectrum of **91** showed multiplet at δ 2.99-3.12 for three protons corresponding to the two oxirane ring protons and one of the methylene proton adajacent to the chloro group. All other protons resonated at their respective chemical shift values. A molecular ion peak at *m/z* 249 $[M+Na]^+$ further confirmed the structure of product **91**. Compound **91** which on reductive elimination with Li in liquid ammonia and ferric nitrate[42] at -33 ^oC for 2 h afforded chiral propargyl alcohol **92** in 70% yeild. The formation of compound **92** was well characterized by PMR, mass spectral studies. The PMR spectrum of compound **92** showed alkynyl protons resonating at δ 2.37 as singlet. Mass spectrum showed a molecular ion peak at *m/z* value 189 $[M-H]^+$ further confirmed the structure of product **92** (Scheme 11). The secondary hydroxyl of **92** was protected as the methyl ether with MeI and NaH in dry THF at 0 ^oC to room temperature to afford the compound **84** in 85% yield. The PMR spectrum of **84** showed singlet at δ 3.38 for methyl protons. Mass spectrum showed a molecular ion peak at *m/z* value 227 $[M+Na]^+$ further confirmed the structure of product **84** (Scheme 11).

Regioselective ring opening of (*S*) - methyl oxirane by methyl protected propargyl alcohol **84**, with the help of n-BuLi, BF_3OEt_2 in dry THF at -78 ^oC gave **82** in

65% overall yield. The obtained desired product was characterized by PMR, IR, mass spectral studies. The PMR spectrum of compound **82** showed methyl protons resonating at δ 1.23 as doublet, hydroxy attached protons at 3.85-3.91 as multiplet. While the IR spectrum showed absorption at 3422 cm^{-1} for the hydroxyl function. Mass spectrum showed a molecular ion peak at *m/z* value 263 $[M+H]^{+}$ further confirmed the structure of product **82** (Scheme 12).

Thus with the assistance of later process, as shown in the scheme 13, esterification[43] of **82** with 3,5-dimethoxy phenyl acetic acid **83** using DCC and DMAP at rt afforded compound **93** in 80% yield. The obtained product was characterized by PMR, IR, mass spectral studies. The PMR spectrum of compound **93** showed protons resonating at δ 4.90-5.04 as multiplet. While the IR spectrum showed absorption at 1702 cm^{-1} for the ester function. Mass spectrum showed a molecular ion peak at *m/z* value 458 $[M+NH_4]$ further confirmed the structure of product **93** (Scheme 13).

Subsequently deprotection of benzyl group and reduction of triple bond were carried out by hydrogenation using 10% Pd/C[44] in ethyl acetate for 12 h to furnish alcohol **94** in 70% yield. The obtained product was characterized by PMR, IR, mass spectral studies. The PMR spectrum of compound **94** showed hyrroxy attached methylene protons resonating at δ 3.65–3.74 as multiplet. While the IR spectrum showed absorption at 3327 cm^{-1} for the hydoxy function. Mass spectrum showed a molecular ion peak at *m/z* value 458 [M+NH$_4$] further confirmed the structure of product **94**. (Scheme 14) After oxidation of **94** by using Jones reagent (CrO$_3$, H$_2$O, H$_2$SO$_4$ and acetone 0 ^{o}C-rt) the desired carboxylic acid **81** was obtained in 80% yield.

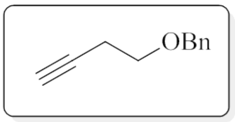
The intramolecular friedel crafts acylation was occurred smoothly by a mixture of trifloro acetic acid and trifloro acetic anhydride to give 50% yield of macrolide,[45] obtained product was characterized by PMR, IR, mass spectral studies. The PMR spectrum of compound **95** showed methylene protons resonating at δ 2.16 as triplet, while the IR spectrum showed absorption at 1659 cm^{-1} for the keto function. Mass spectrum showed a molecular ion peak at *m/z* value 373 [M+Na]$^{+}$ further confirmed the structure of product **95** (Scheme 15).

Finally treatment of **95** with freshly prepared AlI_3, TFA and TFAA in benzene by catalytic usage of TBAI completed the synthesis of 11-β-Methoxycurvularin[46] in 65% yield as colourless oil. The obtained desired target was characterized by PMR, IR, mass spectral studies. The PMR spectrum of target molecule showed methylene protons resonating at δ 3.25 as singlet. While the IR spectrum showed absorption at 3390 cm^{-1} for the hydroxy function. The product **5** was also confirmed by mass spectrum showed a molecular ion peak at *m/z* value 345 $[M+Na]^+$ further confirmed the structure of 11-β-methoxycurvularin (Scheme 15).

In conclusion, the stereoselective total synthesis of 11-β-Methoxycurvularin has been accomplished through Sharpless asymmetric epoxidation, and intramolecular Friedel crafts acylation establish the 12-membered macro cyclic lactone 11-β-methoxycurvularin by using commercially inexpensive homopropargyl alcohol as starting material.

EXPERIMENTAL SECTION

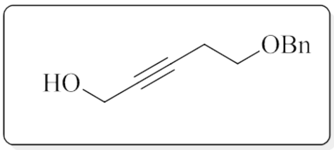
((but-3-ynyloxy) methyl) benzene (87):



To a suspension of NaH (1.13 g, 27.85 mmol) in THF (50 mL), was added alcohol **88** (1.50 g, 21.42 mmol) at 0 °C. After stirring for 20 min, BnBr (3.66 g, 21.42 mmol) was added slowly and the resulting mixture was stirred for another 4 h. After completion, the reaction was quenched with ice-cold H_2O (20 mL) and extracted with EtOAc (2×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane 1:9) to afford compound **87** (3.1 g, 90%) as yellow oily liquid.

IR (neat) υ_{max}	:	3031, 2916, 2865, 2120, 1454, 1363, 1204, 1028, 820, 739, 698 cm^{-1}.
^{1}H NMR:($CDCl_3$, 500 MHz)	:	δ 7.21-7.31 (m, 5H), 4.52 (s, 2H), 3.56 (t, 2H, J = 6.83 Hz), 2.46 (td, 2H, J = 2.92, 6.83 Hz), 1.88 (t, 1H, J = 2.92 Hz).
EI-MS	:	m/z [M-H] 159

5-(Benzyloxy) pent-2-yn-1-ol (89):



To a suspension of Mg metal (2.5 g, 15.62 mmol) in dry THF (50 mL) was added ethyl bromide (1.7 mL, 23.43 mmol) solely at 0 ^oC. The mixture was stirred for 30 min at room temperature, and then compound **87** in dry THF was added at 0 ^oC. After stirring for 2 h at room temperature, paraformaldehyde was added slowly at 0 ^oC. The resulting mixture was stirred for another 5-6 h. After completion, the reaction was quenched with saturated NH_4Cl (20 mL) and extracted with EtOAc (2×50 mL) and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane 2:8) as the eluent to afford **89** (1.65 g, 93%) as a colorless oil.

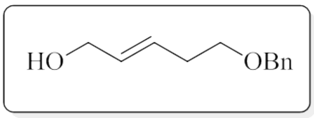
IR (neat) υ_{max} : 3373, 3064, 3031, 2289, 2237, 1958, 1718, 1417, 1363, 1273, 1137, 1014, 744, 699 cm^{-1}

^{1}H NMR:(CDCl$_3$, 300 MHz) : *δ* 7.20 -7.35 (m, 5H), 4.52 (s, 2H), 4.16 (s, 2H), 3.54 (t, 2H, *J* = 6.83 Hz), 2.49 (t, 2H, *J* = 6.83 Hz), 1.89-195 (bs, 1H)

^{13}C NMR: (CDCl$_3$, 75 MHz) : *δ* 137.3, 127.8, 127.1, 127.1, 81.0, 79.4, 76.1, 72.2, 67.7, 50.0, 19.5

EI – MS : m/z [$M^{-}H$] 189

(*E*)-5-(Benzyloxy) pent-2-en-1-ol (90):



To a suspension of LiAlH$_4$ (540 mg, 14.21 mmol) in THF (30 mL) was added a solution of **89** (1.8 g, 9.47 mmol) in THF (10 mL) dropwise. After stirring the mixture for 2 h at reflux, water was added. The resulting mixture was filtered through a short pad of celite and washed with EtOAc (3×50 mL). The filtrate was dried over Na$_2$SO$_4$. The solvent was removed and the residue purified on a silica gel column using (EtOAc /hexane 2:8) as the eluent to afford **90** (1.65 g, 90%) as a colourless oil.

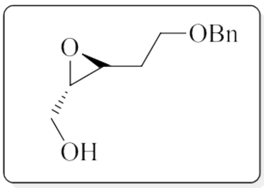
IR (neat) υ_{max} : 2862, 2359, 1686, 1453, 1363, 1309, 1205, 1098, 971, 910, 739, 698 cm^{-1}

^{1}H NMR:(CDCl$_3$, 300 MHz) : *δ* 7.21 -7.33 (m, 5H), 5.68 (td, 2H, *J* = 4.53, 18.8 Hz,), 4.48 (s, 2H), 4.04 (d, 2H, *J* = 2.83 Hz,), 3.52(t, 2H, *J* = 2.83 Hz), 2.34 (td, 1H, *J* = 2.83, 4.53 Hz)

^{13}C NMR: (CDCl$_3$, 75 MHz) : *δ* 137.8, 130.9, 128.0, 127.3, 127.2, 72.4, 69.2, 62.6, 32.2

EI-MS : m/z [M-1] 191

((2*S*, 3*S*) -3-(2-(Benzyloxy) ethyl) oxiran – 2- yl) methanol (86):

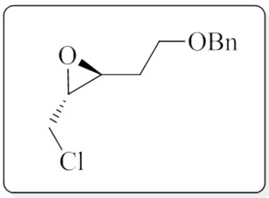


To a suspension of 4 Å molecul ar sieves (1.5 g) in 30 mL CH_2Cl_2 were added L(+)-diisopropyltartarate (0.18 mL, 0.782 mmol), $Ti(O_iPr)_4$ (0.22 mL, 0.782 mmol), and TBHP(4.5 M in toulene (2.6 ml, 11.71 mmol) sequentially at -27 ^oC. The reaction mixture was stirred for 30 min before compound **90** (2.06 g, 10 mmol) was added. The reaction mixture was then stored overnight (12h) in the freezer at -25 ^oC without stirring. The reaction was then warmed to -25 ^oC and quenched by the addition of 10% NaOH/saturated aqueous NaCl (4.0 mL). Upon further warming to -10 ^oC the mixture was diluted with Et_2O (100 mL), and then treated with $MgSO_4$ (4.0 g) and Celite (1.0 g), and stirred for an additional 15 min. The resulting mixture was then allowed to settle for 1 h before filtration through celite using Et_2O and then concentrated under reduced pressure. The residue was purified on silica gel column chromatography using (EtOAc /hexane 3:7) as the eluent to afford compound **86** (1.0 g, 70%) as colourless oil.

$[\alpha]_D^{27}$ + 2.8 (0.5c, $CHCl_3$).

IR (neat) υ_{max}	:	2927,2872, 1719, 1453, 1277, 1098, 1074, 1027, 750, 716, 699 cm^{-1}
^{1}H NMR:($CDCl_3$, 300 MHz)	:	δ 7.21 -7.32 (m, 5H), 4.49 (s, 2H), 3.20 (dd, 1H, *J* = 2.26, 10.57 Hz), 3.50 – 3.59 (m, 3H), 3.04 (td, 1H, *J* = 2.26, 6.79 Hz), 2.87 – 2.91 (m, 1H), 2.34 – 2.41 (bs, 1H), 1.71 – 1.95 (m, 2H)
^{13}C NMR: ($CDCl_3$, 75 MHz)	:	δ 137.6, 127.8, 127.5, 127.3, 123.9, 125.9, 72.4, 66.3, 61.3, 58.2, 53.2, 31.5, 31.0
ESI – MS	:	m/z (%) 231 (100) $[M+Na]^+$
HRMS (ESI)	:	$[M+Na]^+$ 231.0997; found 231.0996

(2*S*,3*R*)-2-(2-(Benzyloxy)ethyl)-3-(chloromethyl)oxirane (91) :



To a stirred solution of **86** (800 mg, 3.84 mmol) in anhydrous CCl_4 (15 ml) was added triphenylphosphine (102 g, 4.61 mmol) under nitrogen atmosphere and then sodium bicarbonate (969 mg, 11.5 mmol) was added. The mixture was heated under reflux until triphenyl phosphine oxide separated from the reaction mixture. After 6 h, the mixture was filtered and the solvent was removed from the filtrate under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc /hexane 1:9) to afford compound **91 (**691 mg, 80%) as a colourless liquid.

$[\alpha]_D^{27}$ +7.7 (0.5c, $CHCl_3$).

IR (neat) υ_{max} : 3031, 2921, 2852, 2359, 1454, 1360, 1264, 1028, 878, 736, 698 cm^{-1}

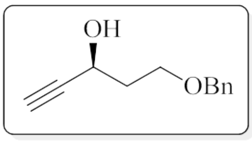
^{1}H NMR:($CDCl_3$, 300 MHz) : δ 7.22-7.34 (m, 5H), 4.50 (*s*, 2H), 3.56 (tdd, 3H, *J* = 5.2, 6.04, 11.3 Hz), 3.44 (dd, 1H, *J* = 5.2, 11.3 Hz), 2.99 (td, 2H, *J* = 2.26, 5.2, 6.04, Hz), 1.73-1.96 (m, 2H)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 137.8, 128.0, 127.2, 127.7, 72.6, 67.5, 66.2, 66.2, 56.7, 56.2, 44.4, 31.6

ESI – MS : m/z (%) 251 (100) $[M+Na]^+$

HRMS (ESI) : Cacld for $C_{12}H_{15}O_2Na$ $[M+Na]^+$ 249.0658; found 249.0660

(*S*) -5-(Benzyloxy) pent -1 –yn-3-ol (92):



To a freshly distilled ammonia (25 mL) in a 100 mL two neck round bottom flask fitted with a cold finger condenser, was added catalytic amount of ferric nitrate, followed by the piecewise addition of lithium metal (166 mg, 18.5 mmol) at -33 °C. The resulting grey colour suspension was stirred for 30 min. To this was added the chloride **91** (600 mg, 2.64 mmol) in dry THF (3 mL) over a period of 5 min. After stirring the reaction mixture for 30 min, solid NH_4Cl (2 g) was added and ammonia was allowed to evaporate. The residue was partitioned between water and ether and the aqueous layer was extracted with (2×50 mL) ether. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane 2.5:7.5) to afford compound **92** (346 mg, 70%) as a colourless liquid.

$[\alpha]_D^{27}$ + 4.5 (0.5c, $CHCl_3$).

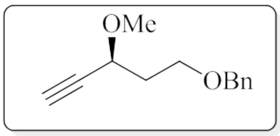
IR (neat) υ_{max} : 3410, 3292, 2926, 2866, 1724, 1601, 1450, 1364, 1206, 1084, 01023, 740, 696 cm^{-1}

^{1}H NMR:($CDCl_3$, 300 MHz) : δ 7.21 - 7.35 (m, 5H), 4.46 – 4.66 (m, 3H), 3.83 (td, 1H, J = 4.52, 9.82 Hz), 3.65 (td, 1H, J = 4.52, 9.82 Hz), 2.89 – 2.94 (bs, 1H), 2.37 (d, 1H, J = 2.26 Hz), 2.02 –2.15 (m, 1H), 1.86-1.97 (m, 1H)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 137.6, 128.3, 127.6, 127.5, 126.8, 84.2, 73.1, 72.8, 67.2, 64.9, 60.7, 36.5, 29.5

EI-MS : m/z [M-1] 189

(*S*)- ((3-Methoxypent-4-ynyloxy) methyl) benzene (84):



To a suspension of NaH (1.26 mg, 3.15 mmol) in THF (10 mL), was added alcohol **92** (300 mg, 1.57 mmol) at 0 °C. After stirring for 20 min, MeI (448 mg, 3.15 mmol) was added slowly and the resulting mixture was stirred for a further 2 h. After completion, the reaction was quenched with ice-cold H_2O (10 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc /hexane1:9) to afford compound **84**. (275 mg, 75%) as yellow oily liquid.

$[\alpha]_D^{27}$ + 4.2 (c, 0.5, $CHCl_3$).

IR (neat) υ_{max} : 3292, 3030, 2931, 2863, 1728, 1454, 1362, 1108, 1028, 739, 696 cm^{-1}

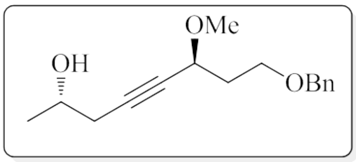
^1H NMR:($CDCl_3$, 300 MHz) : *δ* 7.20 -7.33 (m, 5H), 4.48 (s, 2H), 4.12 (td, 1H, *J* = 2.26, 6.04 Hz), 3.58 (td, 2H, *J* = 2.26, 6.04 Hz), 3.38 (s, 3H), 2.35 (d, 1H, *J* = 2.26 Hz), 1.88 – 2.08 (m, 2H)

^{13}C NMR: ($CDCl_3$, 75 MHz) : *δ* 138.2, 128.1, 127.7, 127.4, 82.2, 73.8, 72.8, 67.9, 65.9, 56.3, 35.7

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

HRMS (ESI) : Cacld for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1047; found 227.1048

(2*S*,6*S*)-8-(Benzyloxy)-6-methoxyoct-4-yn-2-ol (82):



n-BuLi (1.6 M in hexane, 1.22 mL, 1.83 mmol) was added dropwise to a solution of **84** (250 mg, 1.22 mmol) in anhydrous THF (20 mL) at –78 °C under N_2 atmosphere. The mixture was allowed to stir for 30 min, and then treated with $BF_3{\cdot}OEt_2$ (270 mg, 1.83 mmol). After 10 min, a solution of (*S*)-propyleneoxide (142 mg, 2.45 mmol) in anhydrous THF (5 mL) was added and the mixture was allowed to stir for 3 h at -78 °C. The resulting mixture was quenched with saturated $NaHCO_3$ (10 mL) and NH_4Cl (10 mL) solution at –78 °C. The mixture was then allowed to warm to room temperature and extracted with EtOAc (3×20 mL), washed with H_2O (10 mL) and dried over Na_2SO_4 removal of the solvent followed by purification on silica gel column chromatography (AcOEt/hexane 3:7) to afford compound **82**. (220 mg, 65%) as colourless oil.

$[\alpha]_D^{27}$ + 21.3 (c, 0.5, $CHCl_3$).

IR (neat) υ_{max} : 3422,3030, 2967, 2930, 2867, 1726, 1453, 1367, 1206, 1107, 940, 742, 699 cm^{-1}

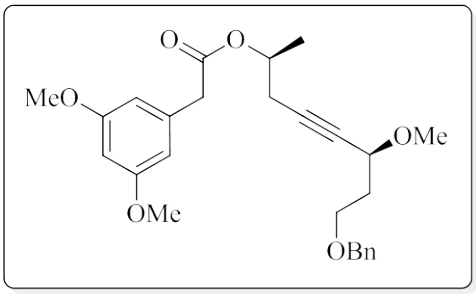
^{1}H NMR:(CDCl$_3$, 500 MHz) : δ 7.21 -7.33 (m, 5H), 4.47 (s, 2H), 4.10 (t, 1H, *J* = 6.76 Hz), 3.85 – 3.91 (m, 1H), 3.57 (t, 2H, *J* = 5.79 Hz), 3.35 (s, 3H), 2.28-2.41 (m, 2H), 1.86–2.03 (m, 2H), 1.23 (d, 3H, *J* = 6.76 Hz)

^{13}C NMR: (CDCl$_3$, 75 MHz) : *δ* 138.2, 128.2, 127.5, 127.5, 82.7, 81.0, 74.4, 74.0, 72.9, 68.5, 66.2, 66.2, 56.3, 36.0, 29.1, 22.2

ESI-MS : m/z: (%) 263 (100) 280 (30) [M+Na]$^+$

HRMS (ESI) : Cacld for $C_{16}H_{23}O_3$ [M+H]$^+$ 263.1647; found 263.1657

(2*S*,6*S*)-8-(Benzyloxy)-6-methoxyoct-4-yn-2-yl2-(3,5dimethoxyphenyl) acetate (93):



To a stirred solution of **82** (150 mg, 0.56 mmol) in CH_2Cl_2 (10 ml) at 0 °C was added DCC (232 mg, 1.12 mmol), followed by a catalytic amount of DMAP after 5 min. Later 3,5-dimethoxybenzeneacetic acid (121 mg, 0.62 mmol) was added, and the resulting mixture was stirred for 1 h at room temperature.Upon completion the mixture was quenched with water (10 ml) and then extracted with CH_2Cl_2 (20 ml). The organic layer was washed successively with 10% aq. HCl solution, followed by saturated $NaHCO_3$ solution and brinesolution. The oraganic layer was dried over Na_2SO_4, and concentrated in *vacuo* and the residue was purified by column chromatography (EtOAc /hexane 2:8) to afford compound **93** (200 mg, 80%).

$[\alpha]_D^{27}$ -16.6 (0.5 c, $CHCl_3$).

IR (neat) υ$_{max}$: 3448, 2936, 1722, 1600, 1462, 1290, 1203, 1154, 1107, 1065, 960, 837, 744, 695 cm^{-1}

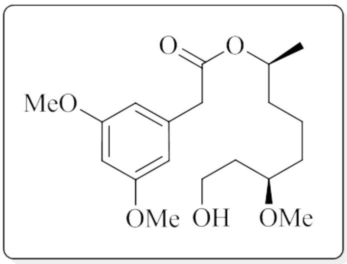
^{1}H NMR:(CDCl$_3$, 500 MHz) : *δ* 7.17 -7.30 (m, 5H), 6.37 (d, 2H, *J* = 6.76 Hz), 6.29 (s, 1H), 4.90–5.04 (m, 1H), 4.42 (s, 2H) 3.94–4.08 (m, 2H), 3.71 (s, 9H), 3.43–3.56 (m, 5H), 2.35-2.47 (m, 2H), 1.27 (d, 3H, *J* = 5.79 Hz), 1.15 (d, 2H, *J* = 6.76 Hz)

^{13}C NMR: (CDCl$_3$, 75 MHz) : *δ* 170.5, 160.6, 138.3, 135.9, 128.2, 127.5, 107.1, 99.0, 81.5, 80.7, 72.8, 70.3, 69.7, 68.3, 66.2, 56.2, 25.6, 19.0

ESI-MS : m/z (%) 441 (30) [M+H]$^+$, 458 (100) [M+NH$_4^+$]

HRMS (ESI) : Cacld for $C_{26}H_{36}O_6$ [M+NH$_4^+$] 458.2542; found 458.2558

(2*S*,6*R*)-8-Hydroxy-6-methoxyoctan-2-yl 2-(3,5-dimethoxyphenyl)acetate (94) :



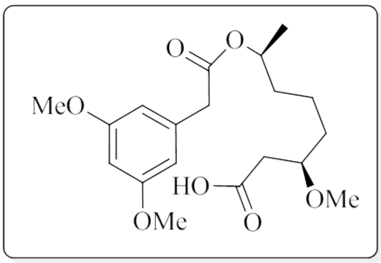
To stirred solution of **93** (200 mg, 0.45 mmol) in EtOAc (10 mL), 10% Pd/C (25 mg) was added and the mixture was stirred under H_2 atmosphere at room temperature for 12 h. After complete conversion the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure and then purified by silica gel column chromatography (EtOAc /hexane 6:4) as eluent to afford compound **94** (152 mg, 80%). **[α]$_D^{27}$** -0.9 (0.5 c, CHCl$_3$).

IR (neat) υ$_{max}$: 3327, 2923, 2849, 1702, 1612, 1463,1417, 1334, 1294, 1238, 1205, 1152, 1062, 915, 818, 735, 654 cm^{-1}

^{1}H NMR:(CDCl$_3$, 300 MHz) : *δ* 6.38 (d, 2H, *J* = 6.75 Hz), 6.28 (m, 1H), 4.83-4.94 (m, 1H), 3.76 (s, 9H), 3.65-3.74 (m, 2H), 3.52 (s, 1H), 3.47 (s, 1H), 3.30 (s, 2H), 1.24-1.64 (m, 8H), 1.21 (d, 3H, *J* = 6.23 Hz)

ESI-MS : m/z (%) 458 (100) [M+NH_4^+]

(3*R*,7*S*)-7-(2-(3,5-Dimethoxyphenyl) acetoxy)-3-methoxyoctanoicacid (81):



Compound **94** (15mg, 0.38 mmol) was taken in 5 mL of distilled acetone at 0 °C. Then freshly prepared Jones reagent was added dropwise at the same temperature until the orange brown colour persists. The mixture was allowed to attain room temperature and stirring was continued for further 30 min. The mixture was then quenched with water and extracted with EtOAc purification by silica gel column chromatography gave the compound **81** as a viscous liquid (100 mg) in 70% yield.

$[\alpha]_D^{27}$ +9.1 (0.8 c, $CHCl_3$).

IR (neat) υ_{max} : 3447, 2928, 1721, 1596, 1458, 1301, 1267, 1198, 1165, 1035, 765, 637 cm^{-1}

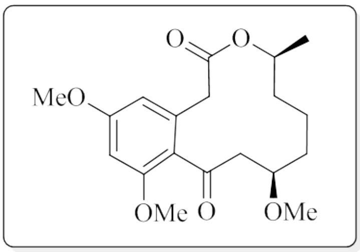
^{1}H NMR:($CDCl_3$, 300 MHz) : δ 6.75 (s, 2H), 6.30 (s, 1H), 4.81 – 4.94 (m, 1H), 3.78 (s, 6H), 3.49 (m,1H), 3.45 (s, 2H), 3.30 (s, 3H), 2.47 (dd, 1H, *J* = 15.7, 6.3 Hz), 2.35 (dd, 1H, *J* = 15.7, 5.3 Hz), 1.21 – 1.61 (m 6H), 1.98 (d, 3H, *J* = 6.2)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 175.4, 171.2, 170.2, 159.9, 137.2, 107.2, 99.7, 78.3, 70.2, 55.9, 55.1, 41.7, 38.7, 35.3, 32.2

ESI-MS : m/z (%) 385 (100) [M+NH_4^+]

HRMS (ESI) : Cacld for $C_{19}H_{27}O_7Na$ $[M+Na]^+$ 391.1732; found 391.1714

(*4S,8R*)-8,11,13-Trimethoxy-4-methyl-4,5,6,7,8,9-hexahydro-1H-benzo[d][1]oxacyclododecine-2,10-dione(95) :

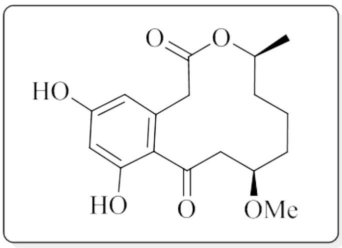


The compound **81** (100 mg, 0.27 mmol) was taken in a round bottom flask under N_2 atmosphere was dissolved in CF_3COOH (7.5 mL) and $(CF_3CO)_2O$ (1.2 mL). The solution was stirred for 12 h at room temperature and poured into an excess of $NaHCO_3$ solution. The mixture was extracted with Et_2O (3.5 mL), and the extract was dried over Na_2SO_4 and concentrated, in *vacuo* and the residue was purified by silica gel column chromatography (EtOAc / hexanes 1: 5) to afford compound **95** (52 mg, 50%) as Colourless oil.

$[\alpha]_D^{27}$ -16 (0.8 c, $CHCl_3$).

IR (neat) υ_{max}	:	3387, 2936, 1728, 1659, 1601, 1457, 1310, 1271, 1157, 1084, 973, 681 cm^{-1}
^{1}H NMR:($CDCl_3$, 300 MHz)	:	δ 6.51 (s, 1H), 6.42 (s, 1H), 6.21 (d, 1H, *J* =15.4 Hz), 4.85 (t, 1H, *J* = 6.3, Hz), 3.81 (s, 2H), 3.80 (s, 6H), 3.31 (d, 3H, *J* = 18.6 Hz), 2.31 (t, 1H, *J* = 6.7 Hz), 2.16 (t, 1H, *J* = 6.7 Hz), 1.90 -1.73 (m, 2H), 1.51-1.36 (m, 4H), 1.13 (d, 3H, *J* = 6.3 Hz)
^{13}C NMR: ($CDCl_3$, 75 MHz)	:	δ 198.3, 170.2, 160.7, 157.3, 156.2, 133.0, 122.3, 106.3, 97.5, 72.7, 55.3, 55.1, 55.0, 39.3, 34.0, 39.9, 24.1, 20.1
ESI-MS	:	m/z (%) 373 (100) $[M+Na]^+$
HRMS (ESI)	:	Cacld for $C_{19}H_{26}O_6Na$ $[M+Na]^+$ 373.1629; found 373.1627

(*4S,8R*)-11,13-Dihydroxy-8-methoxy-4-methyl-4,5,6,7,8,9-hexahydro-1H benzo[d][1]oxacyclododecine2,10dione:



To a stirred solution of Iodine (1.1 g, 4.33 mmol) in dry benzene (10 mL) was added Al powder (167 mg, 4.70 mmol). The mixture was refluxed for 30 min and cooled to 10 ^{o}C. To this mixture $Bu_4N^+I^-$ (253 mg) and compound **95** (50 mg, 0.14 mmol) in dry benzene (4 mL) were added. The mixture was stirred for 15 min at 10 ^{o}C and quenched with 2M HCl at 0 ^{o}C. The mixture was then extracted with ethylacetate (3×20 mL), the organic phase was washed with $NaHCO_3$ solution and followed by brine solution, dried over Na_2SO_4, and concentrated in *vacuo*, and the residue was purified by silica gel column chromatography (EtOAc /hexane 2 : 1) to afford 11-β-methoxycurvularin (30 mg, 65%) as colourless oil.

$[\alpha]_D^{27}$ -9.0 (0.4 c, EtOH).

IR (neat) υ_{max} : 3390, 2921, 2850, 1709, 1618, 1532, 1319, 1258, 1157, 1028, 976, 841, 750, 643 cm^{-1}

^{1}H NMR:(CDCl$_3$, 300 MHz) : δ 6.50 (s, 1H), 6.19 (s, 1H), 4.90 (t, 1H, *J* = 6.2 Hz), 3.87 (d, 1H, *J* =15.7 Hz), 3.71 (d, 1H, *J* = 14.09 Hz), 3.57 (d, 1H, *J* = 16.3 Hz), 3.30 (d, 1H, *J* = 5.1 Hz), 3.25 (s, 3H), 3.12 (dd, 1H, *J* = 14.1, 8.1 Hz), 1.51 – 1.83 (m, 6H), 1.21(d, 3H, *J* = 5.1 Hz)

^{13}C NMR: (CDCl$_3$, 75 MHz) : δ 170.7, 160.2, 157.3, 133.0, 117.2, 112.4, 101.7, 73.9, 72.1, 54.1, 49.2, 41.0, 31.2, 30.4, 19.2, 17.2

ESI-MS : m/z (%) 345 (100) $[M+Na]^+$

HRMS (ESI) Cacld for $C_{17}H_{22}O_6Na$ $[M+Na]^+$ 345.1307; found 345.1311

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INTRODUCTION

The benzannulated 12-membered macro lactones are an ever-growing class of natural products with potential therapeutic and agrochemical applications[1] various types of compounds were isolated from the genus *Botryosphaeria*. Some of them showed interesting biological activities such as antibacterial primin, antiseptic mellein, phytotoxic 4-hydroxymellein, and antimicrobial lasiodiplodin.[2] Lasiodiplodin, isolated from the fungus *Botrysdiplodia theobromae* and the wood of *Euphorbia splendens* and *E. fidjiana*, together with its de-O-methyl congener, a secondary metabolite found in Chinese traditional medicine, has shown an efficient prostaglandin biosynthesis inhibition and significant anti leukemic activity.[3] The remarkable range of potent biological properties displayed by such compounds has attracted a great deal of attention. Indeed, a number of representative examples of these types of natural products include radicicol (a HSP-90 inhibitor), zearalenone (an estrogen agonist), hypothemycin (a MAP kinase inhibitor) and L-783, 277 (a MEK inhibitor) resembled structures with orsellinic acid precursors. The bioactive metabolites from endophytic fungi, the broth extracts of two endophytic fungi, B. rhodina PSU-M35 and PSU-M114, displayed antibacterial activity against Staphylococcus aureus, both standard ATCC 25922 (SA) and methicillin-resistant (MRSA) strains.[4] Along with Botryosphaereodiplodin few other macrolides were isolated. Such as (*3S*)-lasiodiplodin (1), (*5R*)-hydroxylasiodiplodin (**1a**), (*5S*)-hydroxylasiodiplodin (**1b**), (*R*)-(-)-mellein (**4**), cis-(*3R*,*4R*)-(-)-4-hydroxymellein (**4a**), (*R*)-(-)-2 octeno d hydroxyl lactone (**5**) and tetrahydro-4-hydroxy-6-propylpyran-2-one (**5a**) in figure 1.

The proposed structure **3** was different from natural Botryosphaeriodiplodin **2** by comparing the ^{1}H NMR and MS of the natural product and this leads them to de-O-methyl botryosphaeriodiplodin. Botryosphaeriodiplodin was obtained as colorless gum with $[\alpha]_D$ -9.8 (c 0.7, $CHCl_3$). IR and ^{1}H spectral data were similar to that of lasiodiplodin molecule, here I was synthesized (*3S*), (*7R*) de-O-methyl botryosphaerio-diplodin which was derived from the Botryosphaeriodiplodin **2** natural product, the NMR, IR data was matched with the natural product except with O - methyl signals, and hence the proposed structure de-O-methyl botryosphaeriodiplodin has been synthesized enclosed in this thesis.

Lasiodiplodia species are common, especially in tropical and subtropical regions where they cause a variety of diseases (Punithalingam 1980). According to Sutton (1980) the genus is based on *Lasiodiplodia theobromae*. The main features that distinguish this genus from other closely related genera are the presence of pycnidial paraphyses and longitudinal striations on mature conidia. Thus far 20 species have been described and they are differentiated on the basis of conidial and paraphyses morphology. The more recently described species (described since 2004) have been separated not only on morphology, but also on the basis of ITS and EF-1α sequence data. Punithalingam (1976) included several of the species known at that time as synonyms of *L. theobromae* since he could not separate them on morphological characters. However, on account of its morphological variability and wide host range it seems likely that *L. theobromae* is a species complex. Recent studies based on sequence data have confirmed this and eight new species have been described since 2004 (Pavlic et al. 2004, 2008, Burgess et al. 2006, Damm et al. 2007, Alves et al. 2008). There have been no studies on the *Lasiodiplodia* species in Iran apart from a few reports of L. theobromae. In a survey of Botryosphaeriaceae in Iran some Lasiodiplodia isolates that differed from *L. theobromae* in terms of morphology and ISSR fingerprinting profile were found. The aim of this study was to characterize these isolates in terms of anamorphous morphology and phylogenetic analysis.[5] (figure 2)

Figure 2: Lasodiploidia citricola holophyte a) Conidiomata on pine needles in culture.; b) Conidia developing on conidiogenous cells between paraphyses.; c) annelations., d,e)

Paraphyses., f) hyaline, immature conidia.; g,h) mature conidia in two different focal planes to show the longitudinal striations.

Factors effecting on the construction of medium ring compounds:

Medium ring compounds (those are having a ring size in the range 7 to 11) are becoming increasingly important in organic chemistry, as they are contained in an ever-growing number of natural products. Hydrocarbons, as well as heterocyclic compounds (ethers, lactones, amines, amides) have been isolated and these compounds have specific characteristics which had been recognized by, at the beginning of this century, and it was soon observed that they were much more difficult to synthesize by cyclisation methods than other cyclic compounds including macrocyclic compounds (ring sizes $\geq$ 12). These difficulties are caused by the fact that the formation of these cyclic compounds are disfavored by entropy as well as enthalpy (*vide infra*). Increase in carbon chain length disfavor the entropic factor, and thus the probability of a reaction taking place between the two chain termini decreases. The enthalpic factor is mainly created by steric interactions. There are three different interactions:

1. Torsional effects in single bonds (Pitzer strain)
2. Deformation of bond angles from their optimal values (Bayer’s strain)
3. Transannular strain, particularly important in medium size ring compounds.

A stereo electronic factor can also pertain in the case of heterocyclic compounds. Strong repulsions between non-bonded atoms have been reported in compounds like cyclodecanes. In this compound, Dunitz has calculated that the *trans* annular H…H distances are on average 1.85 Å (instead of 1.95–2.00 Å to avoid interactions), while the distance between carbons 1 and 5 is 3.29 Å. The strain of medium ring hydrocarbons is also evidenced by their heat of formation and their relative (to cyclohexane) strain energy (**Table 1**).

Table1: Heats of formation and relative strain energies in cycloalkanes

Ring size	d, H_0 Kcal/mole	strain energy Kcal/mole
6	-29.5	0
7	-28.2	6.2
8	-29.7	9.6
9	-31.7	12.5
10	-36.3	12.9
11	-42.9	11.2
12	-55.0	4.0

The negative entropy is necessary for cyclisations. In medium size ring lactones the entropic factor is outweighed by the enthalpic factor from strain energy in the ring being formed, but for the intramolecular reaction in the large ring lactones the entropic factor is increased while the enthalpic factor has decreased since the rings formed is almost strain free. That is the reason why medium ring lactones disfavor the cyclisation, and in fact favors the intermolecular reaction. This phenomenon can be counteracted by utilizing high dilution conditions, as was first suggested by Ruggli.[6] Two different techniques can be used.

1) The compound to be cyclised is introduced in one portion, at the beginning of the reaction, in to a large volume of solvent.
2) The compound is introduced slowly in a small volume of solvent to maintain its concentration at a very low level (influxion procedure). This second technique, first introduced by Ziegler,[7] is generally more convenient. A kinetic treatment of these intra and intermolecular reactions has been reported which showed that if k_r (rate constant for the formation of the cyclic monomer) and k_p (rate constant for the formation of the dimer) are known optimal concentration conditions can be determined.[8]

$$1.\ \text{Linear monomer} \xrightarrow{k_r} \text{Cyclic monomer}$$

$$2.\ \text{Linear monomers} \xrightarrow{k_p} \text{Dimer}$$

Methods have been even under these conditions, medium ring formation remains difficult, and numerous developed to improve or avoid the cyclisation step.

Macrolides by ring closure:

Ring closure by lactonisation

The direct esterification of long chain hydroxy acids is usually an inefficient way to prepare macrolides. Very dilute solutions of starting materials are needed and even then polymers are formed. However, if the linear precursor is rigid and the conformation of the acyclic skeleton allows the two interacting sites to reach each other easily, this method can be used successfully.

Activation of one or both interacting sites of a hydroxy acid precursor greatly improves the lactonization,[9] many methods have been developed for the activation. The Corey double activation method (also called the Corey-Nicolaou method) involves the idea of activating the carboxyl and hydroxyl groups simultaneously.[10] the double activation is achieved by preparing 2-pyridinmethiol ester **8** form the hydroxy acid **6**. Usually 2,2^1-dipyridyl disulfide **7** is the activating reagent, but also other nitrogen-containing disulfides have been used. The basic nitrogen of the pyridine nucleus facilitates proton transfer from the hydroxy group to the carboxylic oxygen and a dipolar intermediate **9** is formed. This intermediate undergoes a facile, electrostatically driven cyclization without the need for basic or acidic catalysis (Scheme 1). This is known as Corey double activation method for macrolactonization.

In the Mukaiyama[11a] method the hydroxy acid is activated with 1-methyl-2-chloropyridinium iodide. The mechanism of this reaction is fairly similar to that of the Corey double activation method. Also other 2-chloro pyridinium salts have been used for the activation.[11b]

The activating effect of the thiol ester is also utilized in the Masamune[12] macrolactonization reaction. A rapid lactonisation occurs when *S-tert* butyl thiolester of hydroxy acid reacts with an electrophilic Hg (Π)-compound such as mercuric trifluoroacetate. The mechanism of the Masamune method has not been fully clarified and two intermediates **13** and **14**, have been suggested (Figure 3).

A very common way to activate the carboxyl group of a long chain hydroxy acid is to convert it to a mixed anhydride. The anhydride reacts with the hydroxyl group under base-catalyzed reaction conditions, leading to a lactonized product. It has been utilized with success, for example, in most of the total syntheses of patulolides. The Yamaguchi reaction consists of two steps the formation of the mixed anhydride **17** and the alcoholysis of this anhydride (Scheme 2).[13]

2,4,6-Trichlorobenzoyl chloride **16** is used to prepare the mixed anhydride **17**, for two reasons, it forms a good leaving group and it is sterically hindered towards nucleophilic attack. The alcoholysis reaction is catalysed by DMAP, which is highly active in acyl transfer reactions. In a modification of the Yamaguchi lactonisation reaction, 2,4-dichlorobenzoyl chloride has been used instead of 2,4,6-trichlorobenzoyl chloride to prepare the mixed anhydride.[14] The concentration of DMAP in the alcoholysis step has also been modified in order to increase its activation effect.[15] Besides chlorobenzoyl chlorides several other reagents, such as pivoloyl chloride, trifluoroacetic acid, *p*-toluenesulfonyl chloride and di-*tert*-butyl dicarbonate have been used to prepare mixed anhydrides.

In the Mitsunobu lactonisation procedure[16] the hydroxy group is activated by the formation of a dipolar alkoxyphosphonium salt **21** from the hydroxy acid, PPh_3 and diethyl azodicarboxylate (DEAD). This activated intermediate reacts by an SN^2 displacement giving the lactone product **22** with inversion of the configuration of the alcohol (Scheme 3). High dilution conditions are used in the preparation of large-ring lactones. The Mitsunobu reaction conditions are mild and neutral.

Lipase enzymes have been used to promote the macrolactonization of long chain ω-and (ω-1)-hydroxy acids and esters. In addition to the lactonisation methods discussed above, several other methods have been used for the preparation of macrolides. These include carbodiimide or organotin reagent mediated reactions, intramolecular ketene trapping and activated ester methods.[17]

Ring closure by C–C and C=C bond formation:

Metal-catalyzed coupling reactions, such as oxidative coupling of ω,ω'-diacetylenic esters with $Cu(OAc)_2$, coupling of allylic dibromides with nickel carbonyl, intramolecular palladium catalyzed coupling of stabilized anions with allylic acetates and intramolecular palladium catalyzed coupling of acid chlorides and *β*-stannylalkenoates in the presence of Co, have been utilized to prepare macrolides of different size. Also other intramolecular C–C bond formation reactions such as Dieckmann condensation and Diels–Alder reaction have been applied in the preparation of macrolides. Ring closure by Diels–Alder reaction is particularly useful in the construction of cytochalasans and their skeleton structures.[18]

For macrolide ring closure by C=C bond formation, intramolecular Wittig-like reactions are useful and generally give good yields. A relatively new but very efficient route to macrolides through C=C bond formation is the ruthenium carbene catalyzed reaction of 1,ω-dienes by ring-closing metathesis (RCM) (Scheme 4).[19a] The RCM method for macrolide ring closure has been utilized, for example, in the Nicolaou synthesis of epothilones.[19b]

PRESENT WORK

The total synthesis of usually very heavily substituted macrolide antibiotics represents an enormous challenge to chemists, both in the construction of the macrocycle and in the control of the stereochemistry of the macrolide aglycone and the attached sugars. Since the synthesis of these structurally very complicated macrolide antibiotics was not a part of this work, the literature review of the synthesis of macrolides that follows is mainly concerned with simple macrolide structures. The compounds discussed in this chapter are limited to benzannulated 12-membered macrolide de-O-methyl botryosphaeriodiplodin, the prosperity of its biological significance and chemical structure prompted us to initiate a program aimed at the total synthesis of de-O-methyl botryosphaeriodiplodin.

Retro synthetic strategy for the (*3S*), (*7R*)-de-O-methyl botryosphaeriodiplodin was summarized in Scheme 5. We have envisaged that total synthesis of (*3S*), (*7R*)-de-O-methyl botryosphaeriodiplodin **3** can be achieved by macrocyclization based on ring closing metathesis (RCM) of diene **26**. Initially aromatic substituted styrene **27** has to be synthesized by Stille coupling. Which upon undergoes esterification by initially synthesized 1,5–diol **28** system utilizing Jacobson’s kinetic hydrolytic resolution and Marouka asymmetric chiral allylation.

The key fragment **26** with 1,5-diol system could be achieved from hex-5-en-1-ol **30** by Jacobson's kinetic hydrolytic resolution, Maoraka asymmetric allylation, involving esterification with aromatic substituted styrene **27** which in turn could be synthesized from 2,4,6-trihydroxy benzoicacid **29** by Stille conditions.

Synthesis of fragment 28:

Our synthesis commenced from hex-5-en-1-ol **30**, the alcohol was protected as benzyl ether **31** by using benzyl bromide and NaH in dry THF at 0 ^{o}C-rt 2 h in 90% yield. Which was subjected to epoxidation by utilizing m-CPBA[20] in dry DCM at 0 ^{o}C -rt for 5 h gave an epoxide **32** in 90% yield. Jacobsen's kinetic hydrolytic resolution[21] of epoxide **32** using (*R*,*R*)−(salen)Co(II) precatalyst, AcOH and H_2O (0.55 equiv) for 12 h resulted in (*R*)-2-(4-(benzyloxy)butyl)oxirane **33** in 49% yield. This was ascertained by epoxide proton signals in ^{1}H NMR at δ 3.44 as triplet, 2.83-2.88 as multiplet and 2.68 as triplet. Compound **33** was also characterized by its IR spectrum, which showed an absorption band at 3037 cm^{-1} for –OH stretching. The enantiomeric purity of the chiral epoxide **33** was calculated as 95% employing chiral HPLC technique.

The reduction of **33** with Lithium Aluminium Hydride[22] in THF at 0 ^{o}C for 4 h afforded secondary alcohol **34** in 82% yield. The formation of the compound **34** was confirmed by ^{1}H NMR, ^{13}C NMR, mass and IR spectral data. In the ^{1}H NMR spectrum of compound **34** methyl groups resonated as doublets at δ 1.16 (*J* = 6.04 Hz). IR spectrum shows absorption at 3404 cm^{-1} clearly indicated the presence of hydroxyl functional group and ESI mass spectrum showed a molecular ion peak at *m/z* 209 [M+H]. The secondary alcohol **34** was protected as methyl ether **35** with methyl iodide and NaH in THF in 80% yield. In the ^{1}H NMR spectrum of **35** appearances of methyl signals in the region at δ 3.33 as singlet confirmed the structure of methyl protected alcohol **35**. Appearance of molecular ion peak at *m/z* value 270 [M+NH$_4^+$] in its mass spectrum further confirmed its structure. The deprotection of benzyl group in compound **35** with LiNH$_2$ in THF afforded compound **36** in 75% yield. The ^{1}H NMR spectrum of compound **36** showed the absence of peaks in aromatic region confirmed the removal of benzyl group. The mass spectrum showed molecular ion peak at *m/z* 163 [M+H]

The primary hydroxyl group of compound **36** was oxidized to aldehyde by using IBX, DMSO in DCM 0 ºC-rt. Thus aldehyde was subjected under Marouaka[23] asymmetric chiral allylation to yield 1,5-diol **37** by using (*R*,*R*)-Binol complex, allyltributyltin in 75% yield with 95% ee can be determined by ^{1}H NMR studies. The product was ascertained by ^{1}H NMR, ^{13}C NMR, mass and IR spectral data. In the ^{1}H NMR spectrum of compound **37** allyl group resonated as multiplet at δ 5.71-5.87, doublet of doublet at 4.59 (*J* = 6.79, 16.43 Hz), ^{13}C NMR spectrum of compound **37** resonates at δ 134.7, 117.4. ESI mass spectrum showed a molecular ion peak at *m/z* 220 [M+NH$_4^+$].

Further the secondary hydroxyl group of compound **37** was protected as its benzyl ether **38** by using NaH, BnBr in dry THF at 0 °C-rt for 2 h in 75% yield. This was confirmed by ^1H NMR spectral data. In ^1H NMR spectrum aromatic protons resonates at δ 7.16-7.29 as multiplet. The IR absorption at 3447 cm^{-1} clearly indicated the presence of hydroxyl functional group and ESI mass spectrum showed a molecular ion peak at *m/z* 310 $[M+NH_4]$. The afforded compound **38** was subjected to MOM deprotection with $CeCl_3$ in $CH_3CN/MeOH$ to yield 70% desired 1,5-diol fragment **28**. The disappearance of the signal corresponding to methoxy methyl protons at δ 4.95-5.05 doublet, 3.28 as singlet, in ^1H NMR spectrum which was confirmed the deprotection of methoxy methyl group in compound **28**. IR spectrum showed the characteristic absorption at 3461 cm^{-1} due to secondary free hydroxyl function. It was further confirmed by its ESI mass spectrum, which showed a $[M+H]^+$ peak at *m/z* 249. (Scheme 9)

Synthesis of aromatic substituted styrene 27:

Our research was also focused on the aromatic substituted styrene fragment **28**, which was initiated by 2,4,6-trihydroxy benzoic acid **39** this on acetonide protection with acetone and thionyl chloride to afford acetonide protected orsellinic acid **29** in 85% yield. A subsequent chemo selective protection of the more reactive phenol moiety as benzyl ether with benzyl alcohol, TPP in THF to afford compound **40** in 92% yield. The additional five aromatic protons at δ 7.40-7.26, singlet at 5.05 and also acetonide protons at δ 1.50 as singlet for 3H and δ 1.44 as singlet for 3H as characterized the compound **40**. It was further characterized by its IR and mass spectrum, which showed a strong absorption at 1638 cm^{-1} due to conjugated ester group, whereas HRMS(ESI) showed [M+Na]$^+$ peak at *m/z* 323. Aryl triflate **41** was obtained by using triflic anhydride in 90% yield. The disappearance of phenolic OH at δ 10.4 as singlet, and also acetonide protons at δ 1.50 as singlet for 3H and δ 1.44 as singlet for 3H as characterized the compound **41**. It was further characterized by its IR and mass spectrum, which showed a strong absorption at 1734 cm^{-1} due to conjugated ester group, whereas HRMS(ESI) showed [M+Na]$^+$ peak at *m/z* 455. (Scheme 10)

Thus aryl triflate was further subjection to Stille coupling[24] to gave required substituted aromatic styrene fragment **28**, by using LiCl, vinyl stanane and Pd(PPh$_3$)$_4$ catalyst to gave **28** in 90%. (Scheme 7) The substituted styrene was identified by the additional olefin peaks resonated at δ 7.70 as doublet of doublet for 1H coupling constant *J* = 10.95,17.37 Hz, 5.62 as doublet of doublet, coupling constant *J* = 1.32, 17.37 Hz, and 5.38 as doublet of doublet, 1H, coupling constant *J* = 1.32, 10.95 Hz, as characterized the styrene compound **28**. It was further characterized by its IR and mass spectrum, which showed a strong absorption at 2992 cm^{-1} due to C=C stretching, whereas HRMS (ESI) showed [M+Na]$^+$ peak at *m/z* 333.1.

Our synthesis was turned towards the target molecule **3** by readily synthesized aromatic substituted styrene compound **28**, aliphatic fragment **29**, those two were undergoing esterification under Mukiyama condition insitu deprotection of acetonide by using NaH in DMF/THF (1:1 ratio) to afford an excellent yield of diene **26** in 77% yeild[25] the additional olefin peaks resonated in ^{1}H NMR at δ 5.74-5.90 as multiplet for 1H, δ 5.38 as multiplet, δ 4.96 as doublet of doublet for 1H with coupling constant J =17.1, 3.9 Hz, five aromatic protons resonates at δ 7.40−7.26 and also disappearance of acetonide protons at δ 1.50 as singlet for 3H and δ 1.44 as singlet for 3H as characterized the diene compound **26**. It was further confirmed by HRMS (ESI) mass spectrum showed $[M+Na]^+$ peak at *m/z* 523.1.

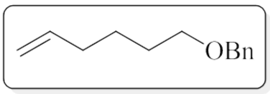
This diene compound **26** was subjected to 10 mol% Grubb’s second generation catalyst[26] in refluxing dichloromethane in 2 h the RCM product **42** in 70% yield (Scheme 13). The disappearance of the signal corresponding to terminal vinylic protons along with other required signals indicated the formation of compound **42**. In the HRMS (ESI) mass spectra, peak at *m/z* 495.2 $[M+Na]^+$ also supported the formation of the RCM product.

The cyclized product **42** was subjected to reduction with 10 mol% Pd/C in MeOH in 12 h afforded the desired compound **3** in 62% yield. The disappearance of the signal corresponding to benzyl, olefin protons along with other required signals indicated the formation of compound **3**. ^{13}C NMR spectrum and HRMS ESI mass peak at *m/z* 317.1 $[M+Na]^+$ analysis ensured the formation of desired compound.

In conclusion, we have finished the first stereo selective total synthesis of (3S), (7R)- de-O-methyl botryosphaereodiplodin **3**, unique applications such as Jacobson's kinetic resolution, Marouka asymmetric allylation, Stille coupling, esterification and ring closing metathesis were employed to complete the target molecule **3** by using commercially in expensive starting materials hex5-en-1-ol and 2,4,6-trihydroxy benzoic acid.

EXPERIMENTAL SECTION

((Hex-5-enyloxy) methyl) benzene (31):



To a stirred suspension of NaH (0.15 g, 6.26 mmol) in THF (10 mL) under N_2, was added alcohol **30** (2.5 g, 25 mmol) in THF (25 mL) at 0 ^oC in a drop wise manner. The mixture was stirred at 0 ^oC for 45 min, then benzyl bromide (4.2 g, 24.5 mmol) was added drop wise over 10 min. The mixture was stirred for 2 h at room temperature, then cold H_2O (10 mL) was added to the reaction mixture slowly. The layers were separated and aq. layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with H_2O (2 x 10 mL), brine (2 x10 mL) and dried over Na_2SO_4. The solvent was removed in *vacuo* and the crude product was purified by silica gel column chromatography to afford benzyl ether **31 (**5 g, 90%).

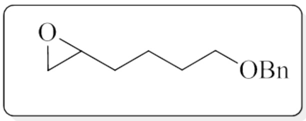
IR (neat) υ_{max} : 3420, 2933, 2857, 1721, 1639, 1453, 1362, 1104, 994, 910, 736, 697 cm^{-1}

^{1}H NMR:(CDCl$_3$, 300 MHz) : *δ* 7.19-7.32 (m, 5H), 5.68-5.83 (m, 1H), 4.93 (dt, 2H, *J* = 1.70, 10.3, 17.3 Hz), 4.46 (s, 2H), 3.43 (t, 2H, *J* = 6.23 Hz), 2.05 (q, 2H, *J* = 7.17 Hz), 1.61 (q, 2H, *J* = 6.2, 8.1 Hz), 1.48 (q, 2H, *J* = 6.71, 7.17 Hz)

^{13}C NMR: (CDCl$_3$, 75 MHz) : δ 138.7, 128.3, 127.5, 127.4, 114.4, 72.8, 70.2, 33.5, 29.1, 28.4

EI-MS : *m/z* (%) 191 (100) $[M+H]^+$

2-(4-(Benzyloxy)butyl)oxirane (32):



To a stirred solution of compound **31** (4 g, 21.05 mmol) in CH_2Cl_2 (50 mL) at 0 ^oC, *m*-CPBA (4.7 g, 27.3 mmol) dissolved in CH_2Cl_2 (50 mL), was added to the reaction mixture and stirred for 5 h. The reaction mixture was filtered, the filtrate washed with saturated $NaHCO_3$ (3 x 20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography to obtain (4 g, 90 %) compound **32** as a colourless liquid.

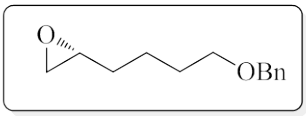
IR (neat) υ_{max} : 3422, 2935, 2860, 1719, 1602, 1453, 1362, 1274, 1105, 1027, 840, 742, 610 cm^{-1}

^{1}H NMR:($CDCl_3$, 300 MHz) : δ 7.19-7.33 (m, 5H), 4.47 (s, 2H), 3.44 (t, 2H, *J* = 6.04, 6.71 Hz), 2.80-2.86 (m, 1H), 2.67 (td, 1H, *J* = 1.5, 3.7 Hz), 2.39 (dd, 1H, *J* = 2.26, 3.02 5.28 Hz), 1.48-1.70 (m, 6H)

^{13}C NMR: ($CDCl_3$, 50 MHz) : δ 138.0, 129.6, 128.7, 127.6, 72.1, 62.9, 64.0, 51.3, 46.1, 31.6, 31.3, 28.8, 22.6

ESI-MS : *m/z* (%) 224 (100) [$M+NH_4^+$]

(*R*)-2-(4-(Benzyloxy)butyl)oxirane (33):



A mixture of (*R,R*)-bis(3,5-di-*tert*-butylsalicylide)-1,2-cyclohexanediamino-Co(II) complex (0.58 g, 0.96 mmol), toluene (0.5 mL) and acetic acid (0.2 g, 3.8 mmol) was stirred in open air for 1 h at rt. The solvent was removed in a rotary evaporator under reduced pressure and the brown residue [(*R,R*)-bis (3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino-Co(III)-acetate, (salen) Co(III)(OAc) complex] was dried under vacuum. To the brown residue racemic epoxide **32** (4 g, 19.41 mmol) was added and the stirring mixture was then cooled in an ice-water bath. Water (0.19 mL, 10.67 mol) was slowly added keeping the bath temperature 15 ^{o}C, after 20 min addition was completed, the ice-water bath was removed and the reaction mixture was stirred at room temperature for 12 h. The crude reaction mixture was purified by silica gel column chromatography to afford the chiral epoxide **33** (2 g, 49%).

$[\alpha]_D^{27}$: -0.26 (*c* = 2, $CHCl_3$).

IR (neat) υ_{max} : 3447, 2925, 2856, 1716, 1634, 1454, 1275, 1106, 709 cm^{-1}

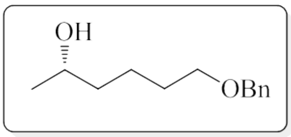
^{1}H NMR:(CDCl$_3$, 300 MHz) : *δ* 7.21-7.32 (m, 5H), 4.47 (s, 2H), 3.44 (t, 2H, *J* = 5.85, 6.23 Hz), 2.83-2.88 (m, 1H), 2.68 (t, 1H, *J* = 4.91 Hz), 2.40 (dd, 1H, *J* = 2.6, 5.09 Hz), 1.45-1.70 (m, 6H)

^{13}C NMR: (CDCl$_3$, 75 MHz) : *δ* 138.3, 128.0, 127.3, 127.2, 72.6, 69.7, 51.8, 46.7, 31.9, 29.3, 32.5

ESI – MS : *m/z* (%) 224 (100) [M+NH$_4^+$]

HRMS (ESI) Calcd for $C_{13}H_{18}O_2Na$ [M+Na]$^+$ 229.1204; found 229.0995

(*S*)-6-(Benzyloxy) hexan-2-ol (34):



To a stirred suspension of LiAlH$_4$ (0.5 g, 14.56 mmol) in dry THF (10 mL) at 0 ^{o}C was added drop wise, a solution of compound **33** (2.0 g, 9.70 mmol) in dry THF (20 mL). The reaction mixture was allowed to warm to room temperature, and was stirred for 4 h. It was then cooled to 0 ^{o}C, diluted with ether, and quenched with drop wise addition of saturated aq. Na$_2$SO$_4$ (5 mL). The solid material was filtered and washed thoroughly with hot ethyl acetate for several times. The combined organic layers were dried over anhydrous Na$_2$SO$_4$. The solvent was removed under vacuum and the residue was purified by silica gel column chromatography to afford the compound **34** (1.65 g, 82%) as a viscous liquid.

$[\alpha]_D^{27}$: +7.84 (*c* = 1, CHCl$_3$).

IR (neat) υ_{max} : 3404, 2934, 2860, 1716, 1638, 1454, 1307, 1204, 1101, 939, 737, 697 cm^{-1}

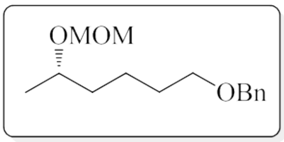
^{1}H NMR:(CDCl$_3$, 300 MHz) : *δ* 7.23-7.32 (m, 5H), 4.46 (s, 2H), 3.71-3.78 (m, 1H), 3.44 (t, 2H, *J* = 6.04 Hz), 1.38-1.66 (m, 6H), 1.16 (d, 3H, 6.04 Hz)

^{13}C NMR: (CDCl$_3$, 75 MHz) : *δ* 138.1, 128.5, 127, 127.1, 72.5, 69.9, 67.1, 38.6, 29.3, 22.9, 22.0

EI – MS : *m/z* (%) 209 (100) $[M+H]^+$

HRMS (ESI) : Calcd for $C_{13}H_{20}O_2Na$ $[M+Na]^+$ 231.1360; found, 231.1355

(*S*)-((5-(Methoxymethoxy)hexyloxy)methyl)benzene (35):



To alcohol **34** (1.65 g, 7.93 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C were added diisopropylethylamine (3.09 g, 23.7 mmol), catalytic DMAP (7 mg) and MOMCl (1.19 g, 15.86 mmol) successively and the mixture was stirred for 4 h at room temperature and then quenched by adding water (5 mL) and extracted with CH_2Cl_2. The organic extracts were washed with brine (5 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 (1.6 g, 80%) **35** as a colourless oil.

$[\alpha]_D^{27}$: +4.05 (*c* = 1, $CHCl_3$).

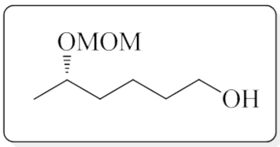
IR (neat) υ_{max} : 3322, 2934, 1719, 1453, 1373, 1275, 1100, 1039, 917, 743 cm^{-1}

^{1}H NMR:($CDCl_3$, 300 MHz) : *δ* 7.21-7.32 (m, 5H), 4.58 (dd, 2H, *J* = 6.79, 6.98 Hz), 4.46 (s, 2H), 3.59-3.67 (m, 1H), 3.43 (t, 2H, *J* = 6.42 Hz), 3.33 (s, 3H), 1.34-1.65 (m, 6H), 1.14 (d, 3H, 6.23 Hz)

^{13}C NMR: ($CDCl_3$, 75 MHz) : *δ* 134.4, 129.4, 128.9, 128.2, 127.5, 94.7, 73.0, 70.1, 55.1, 36.7, 36.6, 32.6, 29.7, 22.1, 20.2

ESI – MS : *m/z* (%) 270 (100) $[M+NH_4^+]$

(*S*)-5-(Methoxymethoxy)hexan-1-ol (36):



To a solution of lithium (0.44 g, 63.49 mmol) in liquid NH_3 (75 ml) was added compound **35** (1.6 g, 6.34 mmol) in dry THF (20 ml). The mixture was stirred for 5 min and quenched with solid NH_4Cl (350 mg). Ammonia was allowed to evaporate and the residual mixture was taken in ether (20 ml) and washed with water (50 ml), brine (10 ml) and dried (Na_2SO_4). Removal of the solvent and purification by column chromatography of the crude product afforded alcohol **36** (0.6 g, 75%) as a colorless liquid.

$[\alpha]_D^{27}$: +19.18 (*c* = 1, $CHCl_3$).

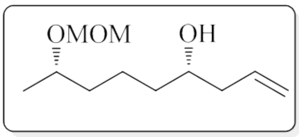
IR (neat) υ_{max} : 3419, 2932, 1732, 1455, 1375, 1244, 1104, 1038, 916, 754 cm^{-1}

^{1}H NMR:($CDCl_3$, 300 MHz) : δ 4.60 (dd, 2H, *J* = 6.79, 15.86 Hz), 3.65-3.74 (m, 1H), 3.61(t, 2H, *J* = 4.53 Hz), 3.33 (s, 3H), 1.82-1.87 (m, 1H), 1.34-1.59 (m, 6H), 1.15 (d, 3H, 6.04 Hz)

^{13}C NMR: ($CDCl_3$, 50 MHz) : δ 171.1, 94.6, 93.1, 72.5, 70.5, 67.4, 64.2, 62.8, 54.9, 38.4, 36.8, 28.3, 23.0, 19.9

EI – MS : *m/z* (%) 163 (100) $[M+H]^+$

(*4S, 8S*)-8-(Methoxymethoxy) non-1-en-4-ol (37):



To a stirred solution of $TiCl_4$ (0.26 g 1.4 mmol, 0.5 equiv) in anhydrous CH_2Cl_2 (10 mL) was added dried $Ti(O_iPr)_4$ (0.12 mL, 0.42 mmol, 0.15 equiv) at 0 ^oC under Ar. The solution was allowed to warm to room temperature. After 1 h Silver oxide (0.2 eq) was added at room temperature and the whole reaction mixture was stirred for 5 h under the exclusion of direct light. The mixture was diluted with CH_2Cl_2 (15 mL) and treated with (*S*)-binaphthol (0.3 eq) at room temp for 2 h to furnish chiral bis IV oxide (*S,S*)-I. The insitu generated (*S, S*)-I (0.2 eq) in anhydrous CH_2Cl_2 (15 mL) was cooled to -15 ^oC

and treated sequentially with aldehyde and allyl tributyl tin (2 eq, 1.8 mL) at -15 °C. The whole mixture was allowed to warm to 0 °C and stirred there for 4 h. The reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$ (20 mL) and then extracted with ether, and the organic extracts were dried over anhydrous $NaSO_4$, filtered, and concentrated in vacuum. Purification of the residue by column chromatography (silica, 15% ethyl acetate in hexanes) afforded **37** as a pale yellow oil. The absolute configuration and purity of the product was determined to be 99% ee. (0.4 g, 75% yield).
$[\alpha]_D^{27}$: +9.6 (c = 1.5, $CHCl_3$).

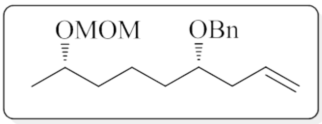
IR (neat) υ_{max} : 3424, 2926, 2856, 1727, 1626, 1459, 1377, 1213, 1143, 1037, 915, 749 cm^{-1}

^{1}H NMR:($CDCl_3$, 300 MHz) : δ 5.71-5.87 (m, 1H), 5.12 (d, 2H, J = 1.70, 12.65 Hz), 4.59 (dd, 2H, J = 6.79, 16.43 Hz), 3.56-3.69 (m, 2H), 3.34 (s, 3H), 2.20-2.31 (m, 2H), 1.23-1.68 (m, 6H), 1.15 (d, 3H, J = 6.23 Hz)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 134.7, 117.8, 94.7, 73.0, 70.4, 55.1, 41.8, 36.8, 36.6, 21.5, 20.2

ESI – MS : m/z (%) 220 (100) $[M+NH_4^+]$

(((*4S,8S*)-8-(Methoxymethoxy)non-1-en-4-yloxy)methyl)benzene (38):



To a stirred suspension of NaH (0.1 g, 2.57 mmol) in THF (10 mL) under N_2, was added compound **37** (0.4 g, 1.98 mmol) in THF (5 mL) at 0 °C in a drop wise manner. The mixture was stirred at 0 °C for 45 min, then benzyl bromide (0.33 g, 1.98 mmol) was added drop wise over 10 min. The mixture was stirred for 2 h at rt, then cold H_2O (10 mL) was added to the reaction mixture slowly. The layers were separated and aq. layer was extracted with EtOAC (3 x 15 mL). The combined organic layers were washed with H_2O (2 x 10 mL), brine (2 x10 mL) and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by silica gel column chromatography to afford benzyl ether **38** (0.3 g, 75%).

$[\alpha]_D^{27}$: +6.32 (*c* = 0.5, $CHCl_3$).

IR (neat) υ_{max} : 3447, 2925, 2856, 1716, 1634, 1454, 1275, 1106, 709 cm^{-1}

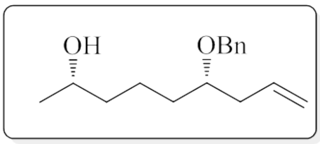
^{1}H NMR:($CDCl_3$, 300 MHz) : *δ* 7.16-7.29 (m, 5H), 5.70-5.85(m, 1H), 4.95-5.05 (m, 2H), 4.37-4.62 (m, 4H), 3.52-3.63 (m, 1H), 3.31-3.40 (m, 1H), 3.28 (s, 3H), 2.30-2.31 (m, 2H), 1.16-1.54 (m, 6H), 1.07 (d, 3H, *J* = 6.04 Hz)

^{13}C NMR: ($CDCl_3$, 75 MHz) : *δ* 138.8, 134.9, 128.2, 127.4, 116.8, 84.8, 78.3, 73.02, 70.8, 55.2, 38.0, 37.0, 33.8, 21.4

ESI – MS : *m/z* (%) 310 $[M+NH_4^+]$

HRMS (ESI) : Calcd for $C_{18}H_{28}O_3Na$ $[M+Na]^+$ 315.1936; found 315.1943

(*2S*,*6S*)-6-(Benzyloxy)non-8-en-2-ol (28):



To a stirred solution of compound **38** (0.3 g, 1.027 mmol) in CH_3CN/MeOH (1:1) (30 mL) at reflux condition was added $CeCl_3.7H_2O$ (0.009 g, 0.02 mmol) and stirred at reflux for 48 h. The reaction mixture was evaporated and the residue was purified by column chromatography to afford **28** (0.1 g, 70% yield) as a colorless liquid.

$[\alpha]_D^{25}$: 4.96 (*c* = 1, $CHCl_3$).

IR (neat) υ_{max} : 3414, 3071, 2923, 2856, 1712, 1639, 1453, 1348, 1070, 912, 737 cm^{-1}

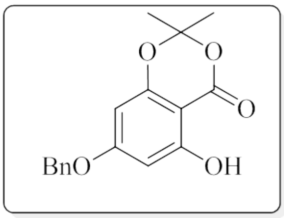
^{1}H NMR:($CDCl_3$, 300 MHz) : *δ* 7.25-7.37 (m, 5H), 5.86 (ddt,1H, *J* =6.79,10.57,17.3 Hz), 5.08 (dd, 2H, *J* =10.57, 17.3 Hz), 4.95-5.05 (m, 2H), 4.54 (q, 2H, *J* =6.79 Hz), 3.74-3.84 (m, 1H), 3.42-3.51 (m, 1H), 2.27-2.42 (m, 2H), 1.34-1.69 (m, 6H), 1.18 (d, 3H, 6.04 Hz)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 138.6, 134.7, 128.2, 127.8, 116.8, 78.2, 70.9, 67.8, 39.1, 38.1, 33.6, 22.3, 21.6

ESI-MS : *m/z* (%) 249 (100) $[M+H]^+$

HRMS (ESI) : Calcd for $C_{16}H_{24}O_2Na$ $[M+Na]^+$ 271.1673; found 271.1686

7-(Benzyloxy)-5-hydroxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (40):



To a stirred solution of **29** (0.13 g, 0.61 mmol, 1.00 equiv) in dry THF (5.0 mL) was added Benzyl alcohol (0.1 mL, 0.915 mmol, 1.50 equiv) and TPP at 0 °C under Ar. The reaction mixture was warmed to room temp for 2 h at rt, The solution was then diluted with EtOAc washed thrice with H_2O (15 mL) and with brine solution. Dried over $NaSO_4$, filtered, and concentrated in *vacuo* and the residue was purified by chromatography to afforded compound **40** as a white crystalline solid (0.175 g, 92% yield).

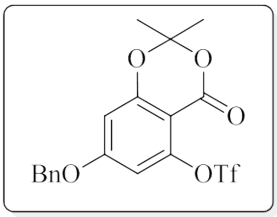
IR (neat) υ_{max} : 3420, 2928, 1682, 1638, 1583, 1466, 1387, 1315, 1159, 1091, 964, 904, 820, 731, 693, 629 cm^{-1}

^{1}H NMR:($CDCl_3$, 300 MHz) : δ 10.41 (s, 1H), 7.28-7.45 (m, 5H), 6.17 (d, 1H, J = 2.26 Hz), 6.00 (d, 1H, J = 2.26 Hz), 5.05 (s, 2H), 1.73 (s, 6H)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 138.6, 134.7, 128.2, 127.8, 116.8, 78.2, 70.9, 67.8, 39.1, 38.1, 33.6, 22.3, 21.6

ESI – MS : *m/z* (%) 301 (30) $[M+H]^+$, 323(70) $[M+Na]^+$

7-(Benzyloxy)-2,2-dimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (41):



To a stirred solution of **40** (0.175 g, 0.583 mmol, 1.00 equiv) in anhydrous pyridine (5.0 mL) was added Tf$_2$O (0.15 mL, 0.875 mmol, 1.50 equiv) at 0 ^{o}C under Ar. The reaction mixture was stirred for 18 h at rt, at which time the reaction temperature was lowered to 0 ^{o}C and quenched with a saturated aqueous solution of NaHCO$_3$ (5 mL) and deionized water (5 mL) and then allowed to reach rt. The aqueous layer was extracted with EtOAc (3 ^{o}C, 10 mL), and the combined organic extracts were washed with a saturated aqueous solution of CuSO$_4$ (20 mL) to remove excess pyridine, dried over MgSO$_4$, filtered, and concentrated in *vacuum* and the residue was purified by coloumn chromatography to afforded compound **41** as a white crystalline solid (90% yield).

IR (neat) υ_{max} : 3446, 3041, 1734, 1631, 1573, 1499, 1428, 1390, 1330, 1293, 1160, 1036, 976, 910, 841, 817, 738, 627 cm^{-1}

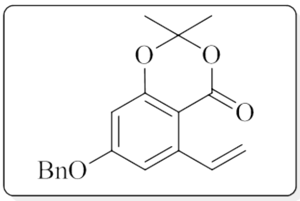
^{1}H NMR:(CDCl$_3$, 300 MHz) : δ 7.33-7.42 (m, 5H), 6.58 (d, 1H, J = 2.26 Hz), 6.50 (d, 1H, J = 2.26 Hz), 5.09 (s, 2H), 1.74 (s, 6H)

^{13}C NMR: (CDCl$_3$, 75 MHz) : δ 164.6, 158.8, 149.7, 128.7, 134.8, 128.7, 127.6, 116.6, 105.7, 102.0, 71.19, 25.5

ESI – MS : m/z (%) 433 (70) [M+H]$^{+}$, 450 (100) [M+ NH$_4^{+}$]$^{+}$

HRMS (ESI) : Calcd for C$_{18}$H$_{15}$O$_7$Na [M+Na]$^{+}$ 455.0428; found 455.0417

7-(Benzyloxy)-2,2-dimethyl-5-vinyl-4H-benzo[d][1,3]dioxin-4-one (27):



To a stirred solution of **41** (0.23 g, 0.523 mmol, 1.00 equiv) in THF (20 mL) were added LiCl (0.069 g, 1.62 mmol, 3.00 equiv), $Pd(PPh_3)_4$ (0.06 g, 0.047 mmol, 0.10 equiv), and stirred for 30 min at room temperature under N_2. Vinyl stanane (0.21 mL, 1.28 mmol, 2.00 equiv) was then added and the reaction mixture was stirred for 18 h at reflux (40 ^{o}C) and allowed to reach rt, at which time the reaction was quenched with deionized water (5 mL). The aqueous layer was extracted with EtOAc (3x10 mL), and the organic extracts were dried over NaSO4, filtered, and concentrated in *vacuum* and the residue was purified by coloumn chromatography to afforded compound **27** as white solid (0.15 g, 90% yield).

IR (neat) υ_{max} : 3422, 2992, 2924, 1721, 1602, 1571, 1423, 1383, 1319, 1272, 1212, 1160, 1036, 981, 847, 757, 634 cm^{-1}

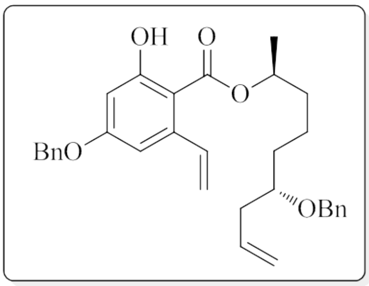
^{1}H NMR:($CDCl_3$, 300 MHz) : *δ* 7.70 (dd, 1H, *J* = 10.95,17.37 Hz), 7.31-7.40 (m, 5H), 6.82 (d, 1H, *J* = 2.45 Hz), 6.39 (d, 1H, *J* = 2.46 Hz), 5.62 (dd, 1H, *J* = 1.32, 17.37 Hz), 5.38 (dd, 1H, *J* = 1.32, 10.95 Hz), 5.09 (s, 2H), 1.70 (s, 6H)

^{13}C NMR: ($CDCl_3$, 75 MHz) : *δ* 135.4, 128.4, 127.6, 117.6, 109.1, 101.5, 70.3, 27.7, 26.8, 25.5

ESI – MS : m/z: (%) 311 (100) $[M+H]^+$

HRMS (ESI) : Calcd for $C_{19}H_{18}O_4Na$ $[M+Na]^+$ 333.1102; found 333.1108

(*2S,6S*)-6-(Benzyloxy) non-8-en-2-yl 2,4-dihydroxy-6-vinyl benzoate (26):



To a stirred solution of compound **28** (100 mg, 0.403 mmol, 1.00 equiv) in a 1:1 mixture of DMF/THF (10 mL) was added NaH (60% dispersion in mineral oil, 62 mg, 1.48 mmol, 3.5 equiv) at 0 °C under Ar. To this mixture compound **27** was added (145 mg, 0.483 mmol, 1.25 equiv), and the resulting mixture was allowed to stir at room temperature. After 12 h, the resulting suspension was cooled to 0 °C and quenched with deionized water (10 mL). The mixture was allowed to stir at room temperature for 30 min, at which time the aqueous layer was extracted with EtOAc (3 x10 mL), and the organic extracts were dried over $NaSO_4$, filtered, and concentrated in *vacuo* and the residue was purified by coloumn chromatography to afforded compound **26** as a yellow viscous oil (150 mg, 77% yield).

$[\alpha]_D^{25}$: + 16 (c = 0.5, $CHCl_3$).

IR (neat) υ_{max} : 3387, 2918, 2868, 1712, 1488, 1451, 1364, 1272, 1212, 1100, 1016, 819, 743 cm^{-1}

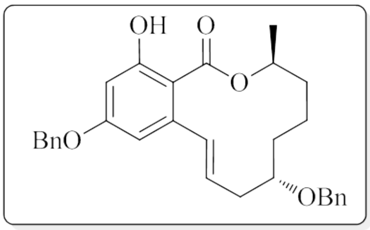
^{1}H NMR:($CDCl_3$, 300 MHz) : δ 11.79 (s, 1H), 7.19-7.45 (m, 11H), 6.55 (d, 1H, J = 2.07 Hz), 6.48 (d, 1H, J = 2.67 Hz), 5.74-5.90 (m, 1H), 5.38 (d, 1H, J = 17.18 Hz), 5.15 (d, 2H, J = 11.31 Hz), 5.02-5.11 (m, 4H), 4.56 (d, 1H, J = 11.50 Hz), 4.45 (dd, 1H, J = 3.9, 11.5 Hz), 3.37-3.49 (m, 1H), 2.42-2.40 (m, 2H), 1.48-1.63 (m, 6H), 1.34 (dd, 3H, J = 2.07, 6.23 Hz)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 170.7, 165.0, 163.0, 138.5, 134.7, 128.6, 128.2, 128.1, 127.7, 127.5, 117.0, 115.3, 108.2, 101.1, 96.1, 78.1, 72.7, 70.9, 70.0, 38.2, 35.9, 33.5, 21.4, 20.2

ESI – MS : m/z (%) 501 (100) $[M+H]^+$, 523 (90) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{32}H_{36}O_5Na$ $[M+Na]^+$ 523.1065; found 523.1072

(*3S,7S*,E)-7,12-bis(Benzyloxy)-14-hydroxy-3-methyl-3,4,5,6,7,8-hexahydro-1H-benzo[c][1]oxacyclododecin-1-one (42):



Grubbs's catalyst II (25 mg, 0.03 mmol, 10 mol %) was dissolved in CH_2Cl_2 (5 mL) and was added drop wise to a refluxing solution of the compound **26** (150 mg, 0.326 mmol) in CH_2Cl_2 (20 mL) refluxing was continued for 3 h by which time all the starting material was consumed (TLC). The solvent was removed in *vacuo*, and the crude residue was purified by column chromatography to afford **42** (100 mg, 70% yield).

$[\alpha]_D^{25}$: - 45 (c = 0.5, $CHCl_3$).

IR (neat) υ_{max} : 3448, 2922, 2853, 1646, 1611, 1573, 1456, 1353, 1315, 1255, 1210, 1163, 1089, 757, 696 cm^{-1}

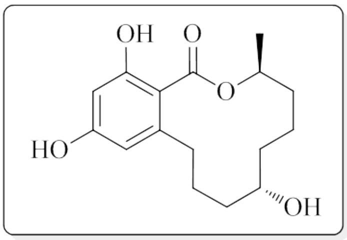
^{1}H NMR:($CDCl_3$, 300 MHz) : δ 11.52 (s, 1H), 7.14-7.34 (m, 12H), 6.75 (d, 1H, J = 15.92 Hz), 6.36 (d, 1H, J = 7.39 Hz), 5.48-5.73 (m, 1H), 5.15-5.28 (m, 1H), 4.99 (s, 2H), 4.44-4.53 (m, 2H), 3.51-3.67 (m, 1H), 2.23-2.41 (m, 1H), 1.47-1.67 (m, 4H), 1.28 (d, 3H, J = 5.62 Hz)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 170.7, 164.6, 143.5, 138.7, 135.3, 134.5, 128.6, 127.5, 127.3, 126.6, 108.4, 100.5, 77.7, 72.1, 70.3, 69.8, 35.5, 33.8, 32.7, 32.2, 31.8, 29.7, 19.7, 18.7, 17.4

ESI – MS : m/z (%) 473 (50) $[M+H]^+$, 495 (50) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{30}H_{32}O_5Na$ $[M+Na]^+$ 495.2147; found 495.2141

(*3S*,*7R*)-7,12,14-Trihydroxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclododecin-1-one (3):



To stirred solution of **42** (100 mg, 0.211 mmol) in MeOH (10 mL), 10% Pd/C (20 mg) was added and the mixture was stirred under H_2 atmosphere at room temperature for 12 h. When the reaction was complete the mixture was filtered through celite and the filtrate was concentrated under reduced pressure purification on silica gel column chromatography (EtOAc/hexane 6:4) to afford desired compound **3** (100 mg, 62%). **$[\alpha]_D^{27}$**: - 14.3 (c = 0.35, $CHCl_3$).

IR (neat) υ_{max} : 3464, 3292, 2925, 2854, 1647, 1613, 1458, 1309, 1255, 1206, 1161, 1100, 1065, 993, 840, 717, 662, 616 cm^{-1}

^{1}H NMR:($CDCl_3$, 300 MHz) : δ 11.38 (s, 1H), 9.73 (s, 1H), 6.12 (d, 2H, J = 7.39 Hz), 5.0 -5.19 (m, 2H), 4.18-4.19 (m, 1H), 3.58-3.93 (m, 1H), 2.40- 2.54 (m, 2H), 2.11-2.36 (m, 2H), 1.88-2.05 (m, 2H), 1.53-.173 (m, 6H), 1.30 (d, 3H, J = 6.03 Hz)

^{13}C NMR: ($CDCl_3$, 75 MHz) : δ 168.5, 160.8, 159.6, 157.4, 144.4, 141.6, 108.2, 98.3, 93.5, 72.5, 69.7, 36.5, 33.8, 32.6, 29.9, 20.2, 19.5

ESI-MS : m/z (%) 295 (100) $[M+H]^+$, 317 (30) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{16}H_{12}O_5Na$ $[M+Na]^+$ 317.1364; found 317.1358

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INTRODUCTION

Naturally occurring carbohydrates and their derivatives have been useful during the last few decades as “chiral pool” constituents in the enantioselective synthesis of biologically active natural and non natural products. Synthetic organic chemistry is not only a tool for obtaining compounds that can be utilized for understanding biological functions and the behavior of materials, but it also leads to the creation of a novel drug or drug like candidates and for novel materials with interesting properties. The ever-increasing importance of the role of carbohydrates in biological processes relating to immunology, virology, cancer, antibiotic action, and a host of life-threatening diseases has heightened the interest in the accessibility of specific sugar-based molecules. The ready availability of a wide range of carbohydrates in nature and their multichiral architecture, coupled with their well defined stereochemistry, make them attractive starting materials in organic synthesis. The first glycal was synthesized by Hermann Emil Fisher and Karl Zach in 1913. They synthesized this 1,2-unsaturated sugar from D-glucose and named their product D-glucal. Various elimination procedures conducted on appropriate pyranoid and furanoid carbohydrate derivatives, especially on O-protected glycosyl halides afford cyclic vinyl ethers which Fischer (inappropriately) named glycals. These are used extensively in general organic synthesis and for the preparation of non-carbohydrate natural products as well as biologically important complex carbohydrates and glycoconjugates. The best known member, tri-O-acetyl-D-glucal, is normally made from tetra-O-acetyl-α-D-glucopyranosyl bromide, is commercially available, and is used very frequently in this chapter to represent the family in examples of the reactions under discussion. By the time he discovered his mistake, the name “glycal” was adopted as a general name for all sugars with a double bond between carbon atoms 1 and 2.

Synthesis of D-Glucal: The original Fischer glycal synthesis was shown in scheme 1 was started from D-glucose **2** with acetic anhydride and molten anhydrous sodium acetate at 120 ºC gives exclusively the D-glucose penta-acetate **3**, which on treatment with hydrogen bromide/acetic acid leads to the glucosyl bromide **4**. This on Reductive elimination with zink-copper affords tri-*O*-acetyl glucal **1**, a monosaccharide starting material synthetic route is as follows.

Applications of glucal: Because of the pronounced region and stereoselectivities with which their addition reactions can be conducted, glycal derivatives are of major importance in synthesis. They also, however, take part in rearrangement processes that, likewise, have proved useful for synthesis. The principal one involves nucleophilic substitution of the allylic group with allylic rearrangement and results in products having double bonds in the 2, 3 positions and new substituents at the anomeric centers. By far the simplest and most commonly used way to this conversion involves the removal of the allylic substituent of the glycal and the generation of highly resonance-stabilized oxocarbenium ion intermediate. This may then react with nucleophiles at the anomeric center to give products as mixture of diastereomers. Many examples and variations of this theme are described and form the major part of this chapter, but other ways are also considered. Important building blocks for both solution- and solid-phase synthesis of oligosaccharides. Almost no formal mechanistic studies have been carried out on the reactions in this chapter. Categorization of mechanism required for the treatment of this topic has been done on the basis of conditions used, product identification and largely, chemical intuition.

Importance of Catalyst: Developing the catalytic organic reactions using air-stable and water-tolerant inorganic salts such as Lewis acid catalysts is one of the promising and challenging subjects in modern synthetic chemistry. Recently, InX_3 (X=Cl, Br, I, OTf) have been attracting considerable attention because of its broad applications as catalysts in organic synthesis.[1] In particular, InX_3 have been the efficient catalysts for the carbon–carbon bond formation.[2] For a few decades, more attention has been paid to the development of new synthetic methods using indium chloride, which is non toxic, readily available catalyst for various transformations under mild and convenient conditions, affording the corresponding products in excellent yields with high selectivity which is also compatible with water and air[3] tolarent reactions. Which imparting high region, chemo and stereoselectivity in various organic transformations compared to conventional lewis acids, indium trichloride has advantages of low catalyst loading, moisture stability and catalyst recycling.

The synthetic advantaged of using indium-mediated, reactions in aqueous has been developed. However, the full synthetic potential of such raections is still waiting to be explored.It can be expected that the use of indium-mediated and catalyzed reactions for synthetic purposes will gain further attention. Recently, in our research we have been reported some $InCl_3$-mediated reactions[5] which are enclosed in this chapter as section A and section C.

INTRODUCTION

The ready availability of a wide range of carbohydrates in nature and their multi-chiral architecture, coupled with their well-defined stereochemistry, make them attractive starting materials in organic synthesis.[4,5] In particular, glycals (1,5-anhydro-hex-1-enitols), i.e. 1,2-unsaturated derivatives of pentoses and hexoses, are among the most versatile chiral building blocks.[6] They are ambident electrophiles capable of reacting with various nucleophiles under the influence of acid catalysts or oxidants to produce 2,3-unsaturated glycosides.[7] They are very useful precursors in oligosaccharide synthesis.[8] Recently, the multistage reaction has always been a part of organic synthesis, which is known as “one-pot reaction”, which means, “chemical conversions consisting of a number of sequential transformations are brought about in one reaction step”. This approach is not only selective but also highly efficient, saving time, energy and raw materials and adds chemists aim to use the mildest possible conditions, ideally temperature of 25 ^{o}C, atmosphere pressure, an environmentally safe solvent and finding suitable nontoxic catalyst, and one of the major concerns of the pharmaceutical industry getting shape right. Multicomponent one-pot synthesis has received great attention because of its wide range of applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for drug discovery.[9]

PRESENT WORK

We report a versatile approach via a three component coupling (3CC) involving the condensation of glycals, 1, 3-dicarbonyl compounds and arylamines. The 3CC reaction was carried out in the presence of an acid catalyst, usually 10 mol% of indium (III) chloride. This robust approach allows for the preparation of a diverse range of products and suited our requirements in the continuation of a synthetic program aimed at the generation of combinatorial libraries for drug discovery. Initially, we first studied a three-component coupling of D-glucal, acetylacetone and aniline using 10 mol% indium (III) chloride as a novel glycosyl activator. The unusual bicyclic adduct **4a** was isolated in 93% yield with high stereo selectivity (Scheme 1). The other isomer is also formed in trace amounts it cannot be isolated by coloumn chromatography.

The product **4a** was characterized thoroughly with the help of various NMR experiments including extensive ^{1}H decoupling, 2-D Nuclear Overhauser enhancement spectroscopy (NOESY), heteronuclear single-quantum correlation spectroscopy (HSQC) and heteronuclear multiple bond correlation spectroscopy (HMBC). The NMR data suggest that the molecular structure of **4a** consists of a [2.3.3] bicyclononene like structure. The location of the methylene group in the bridge of a bicyclononene like structure was confirmed by small couplings with the bridgehead protons H1 and H3 ($J_{\mathrm{H1\text{-}H2}\ (pro\text{-}S)}$ = 3.0 Hz, $J_{\mathrm{H1\text{-}H2}\ (pro\text{-}R)}$ = 2.2 Hz, $J_{\mathrm{H2}\ (pro\text{-}S)\mathrm{\text{-}H3}}$ = 3.0 Hz, and $J_{\mathrm{H2}\ (pro\text{-}S)\mathrm{\text{-}H3}}$ = 4.3 Hz; Figure 1). The two six-membered rings of the bicyclononene moiety differ in their conformations. For the pyranose ring, $J_{\mathrm{H4\text{-}H5}}$ = 10.3 Hz and the NOESY cross peak H2$_{(pro\text{-}S)}$/H4 support the $^4C_1$ chair form. nOe correlations, H5/H$_{\mathrm{ortho}}$ and H1/ H$_{\mathrm{ortho}}$ further confirm that the *N*-Ph group is on same side as the ring oxygen, while the location of methyl group adjacent to ring nitrogen was amply supported by nOe, C11/ H_{ortho}. Additionally, HMBC correlations, H4/C13, H3/C12 and H1/C12 are in complete agreement with the proposed structure. Interestingly, the structure differs from that expected from our earlier studies on glycals.[10] Further, the energy-minimized structure of **4a** was obtained from molecular mechanics calculations is shown in Figure 1.[11]

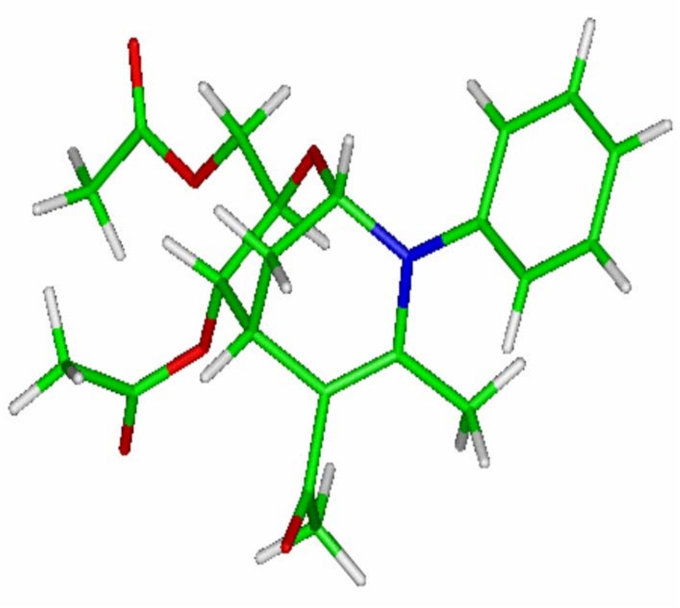
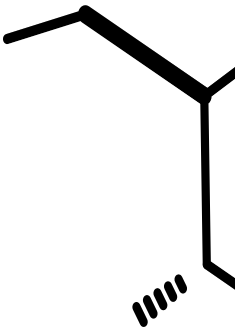


Figure 1: Characteristic nOe interactions and the energy-minimized structure of **4a**



Catalytic studies of various Lewis salts:

The efficacy of various Lewis acids such as $InCl_3$, $BiCl_3$, $CeCl_3{\cdot}7H_2O$, YCl_3 and $YbCl_3$ was tested. Indium trichloride was found to be the most effective catalyst in terms of conversion and selectivity. For instance, treatment of D-glucal with acetyl acetone and aniline in the presence of 10 mol% $InCl_3$, 10 mol% $BiCl_3$ and 10 mol% $CeCl_3{\cdot}7H_2O$ for 5 h afforded the **4a** yields of 93%, 78%, and 65% respectively. Alternatively, 10 mol% $InBr_3$ was found to be equally effective for this conversion.

However, in the absence of either $InCl_3$ or $InBr_3$, the reaction did not proceed even after an extended time. Various triflates were screened $In(OTf)_3$, $Sc(OTf)_3$, $Bi(OTf)_3$, $Yb(OTf)_3$, $Dy(OTf)_3$, and $Sm(OTf)_3$ but none of them gave satisfactory yields.

The scope of this method was investigated with respect to various glucal derivatives, 1,3-dicarbonyl compounds and a range of anilines and the results are presented in the Table 2. Simple cyclic enol ethers such as 3,4-dihydro-2H-pyran and 2,3-dihydrofuran afforded the corresponding tetrahydroquinoline derivatives under similar reaction conditions.[12] Furthermore, the reaction also proceeded with protic acids, specifically montmorillonite KSF or PMA/SiO_2, at 80 °C in 1,2-dichloroethane to yield the same products.

This unexpected result prompted us to apply this process to various glycals, 1, 3-dicarbonyl compounds and arylamines. Substituted arylamines such as *p*-toludine, *p*-anisidine, *p*-chloroaniline, *p*-fluoroaniline, 3, 4-methylenedioxyaniline, *o*-toludine, and 1-naphthylamine participated in this reaction to produce the corresponding heterobicycles in good yields (Table 1). Other glucal derivatives including 3,4,6-tri-*O*-methyl- and 3,4,6-tri-*O*-allyl-D-glucal reacted efficiently with enamines generated *in situ* from 1,3-diones and arylamines to produce cyclic adducts (Table 1). Besides acetyl acetone, methyl acetoacetate also participated. A plausible mechanism for the formation of products **4** is depicted in Scheme 2.

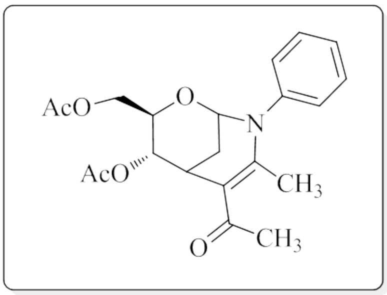
This method is a highly stereo selective, one-pot synthesis of unusual bicyclic heterocycles under mild conditions.

In conclusion, we present in this section a three-component one-pot synthesis of novel carbohydrate derivatives, oxa-aza-heterobicycles, from glycals, 1,3-dicarbonyls and aryl amines using a catalytic amount of indium trichloride under mild conditions. This is an entirely new approach to functionalize glycals with 1,3-dicarbonyl compounds and arylamines, leading to oxa-aza bicyclononene scaffolds.

EXPERIMENTAL

General Procedure: A mixture of glucal triacetate (272 mg, 1 mmol), aniline (103 mg, 1.1 mmol), pentane-2,4-dione (110 mg, 1.1 mmol) and $InCl_3$ (0.1 mmol) in dichloroethane (10 mL) was heated at 80 ºC for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with water followed by brine and dried over anhydrous Na_2SO_4. Removal of solvent followed by purification on silica gel column using a mixture of ethyl acetate: *n*-hexane (3:7) afforded pure product.

((*3R,4S*)-4-Acetoxy-6-acetyl-7-methyl-8-phenyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4a):

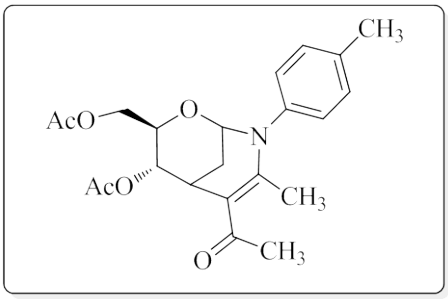


Colorless solid, mp 123^0 C.

IR (KBr) υ_{max}	:	2924, 2832, 1731, 1705, 1643, 1530, 1490, 1414, 1385, 1291, 1215, 1120, 1093, 1066, 1018, 981, 831, 721, 599, 553, 507 cm^{-1}
^{1}H NMR:($CDCl_3$, 500 MHz)	:	δ 7.40 (t, 2H, *J* = 7.7 Hz), 7.32 (t, 1H, *J* = 7.1 Hz), 7.19 (d, 2H, *J* = 7.9 Hz), 5.01 (m, 1H), 4.92 (dd, 1H, *J* = 4.3, 10.3 Hz), 4.17 (dd, 1H, *J* = 5.6, 11.9 Hz), 4.07 (dd, 1H, *J* = 2.5, 11.9 Hz), 3.83 (ddd, 1H, *J* = 2.5, 5.6, 10.4 Hz), 3.59 (m, 1H), 2.27 (dt, 1H, *J* = 3.0, 12.8 Hz), 2.22 (s, 3H), 2.15 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.92 (ddd, 1H, *J* = 2.2, 4.3, 12.8 Hz)
LC – MS	:	*m/z* (%) 388 (70) $[M+H]^+$, 410 (100)$[M+Na]^+$

HRMS (ESI) : Calcd for $C_{21}H_{26}NO_6$ $[M+H]^+$ 388.1760; found 388.1756

((*3R,4S*)-4-Acetoxy-6-acetyl-7-methyl-8-p-tolyl-2-oxa-8-azabicyclo[3.3.1]non-6- en-3-yl)methyl acetate (4b):



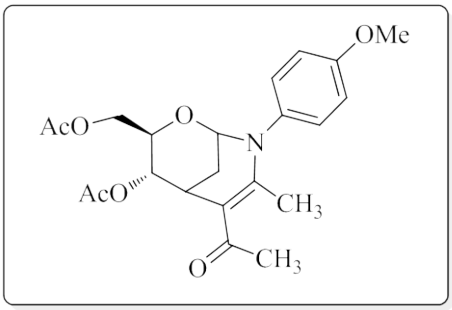
Pale yellow liquid.

^{1}H NMR:($CDCl_3$, 300 MHz) : δ 6.94 (d, 2H , *J* = 9.0 Hz), 6.77 (d, 2H , *J* = 9.0 Hz), 5.87–5.72 (m, 2H), 5.16 (d, 2H , *J* = 16.6 Hz), 5.07 (d, 2H , *J* = 11.3 Hz), 5.02 (t, 1H, *J* = 6.0 Hz), 4.82 (m, 1H), 4.06 (dd, 1H, *J* = 6.0, 12.8 Hz), 3.95 (dd, 1H, *J* = 3.0, 12.8 Hz), 3.92–3.85 (m, 2H), 3.72 (s, 3H), 3.50-3.49 (m, 4H), 2.19 (s, 3H), 2.10 (dt, 1H, *J* = 3.0, 12.8 Hz), 2.01 (s, 3H), 1.80 (ddd, 1H, *J* = 2.2, 4.3, 12.8 Hz)

ESI – MS : *m/z* (%) 424 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{22}H_{27}NO_6Na$ $[M+H]^+$ 424.1736; found 424.1716

((*3R,4S*)-4-Acetoxy-6-acetyl-8-(4-methoxyphenyl)-7-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4c):



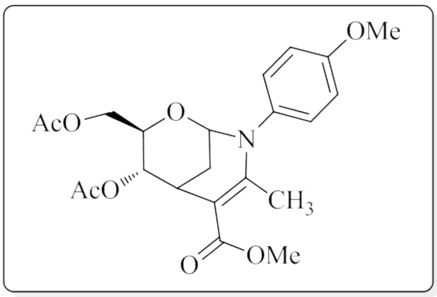
Pale yellow liquid

IR (KBr) υ_{max} : 2925, 2854, 1735, 1641, 1508, 1460, 1378, 1292, 1212, 1124, 1032, 993, 925, 831, 757, 545 cm^{-1}.

^{1}H NMR:(CDCl$_3$, 500 MHz) : δ 7.02 (d, 2H, J = 8.3 Hz), 6.87 (d, 2H, J = 8.3 Hz), 4.88-4.96 (m, 2H), 4.15-4.23 (m, 1H), 3.82 (s, 3H), 3.54-3.60 (m, 1H), 2.22-2.20 (m, 2H), 2.16 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.87-1.95 (m, 1H)

ESI – MS : *m/z* (%) 418 (100) [M+H]$^+$, 440 (70) [M+Na]$^+$

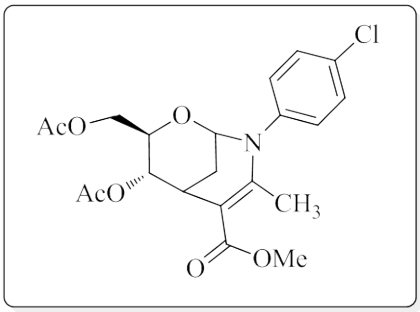
(*3R,4S*)-Methyl 4-acetoxy-3-(acetoxymethyl)-8-(4-methoxyphenyl)-7-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-ene-6-carboxylate (4d):



Pale yellow liquid

IR (Neat) υ_{max}	:	2927, 2854, 1742, 1638, 1609, 1508, 1459, 1375, 1243, 1176, 1125, 1038, 992, 901, 833, 759, 588 cm^{-1}

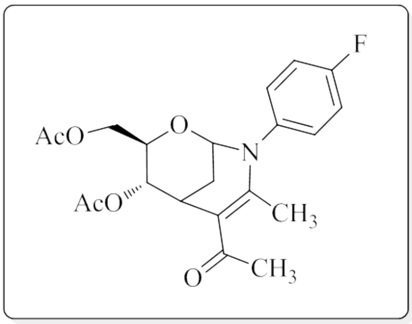
(*3R,4S*)-Methyl 4-Acetoxy-3-(acetoxymethyl)-8-(4-chlorophenyl)-7-methyl-2-oxa-8-azabicyclo [3.3.1] non-6-ene-6-carboxylate (4e):



Pale yellow liquid.

IR (Neat) υmax	:	2926, 1701, 1638, 1527, 1492, 1383, 1294, 1119, 1125, 1063, 988, 832, 765, 594 cm^{-1}
1H NMR:(CDCl3, 200 MHz)	:	*δ* 7.15 (d, 2H, *J*= 6.9 Hz), 6.83 (d, 2H, 6.9 Hz) 4.91-4.98 (m, 1H), 4.71-4.86 (m, 1H), 4.12-4.25 (m, 3H), 3.72-3.91 (m, 1H), 3.65 (s, 3 H), 3.49-3.51 (m,1H), 2.10-2.23 (m, 1H), 2.05 (s, 3H), 1.98 (s, 3H), 1.91 (s, 3H), 1.71-1.81 (m, 1H)
ESI – MS	:	m/z: (%) 460 (100) [M+Na]$^{+}$

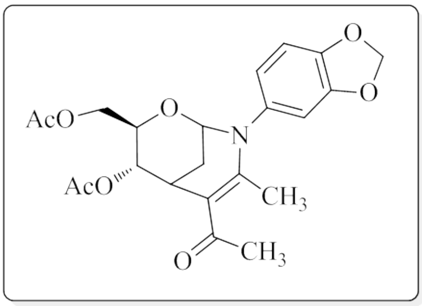
(3R,4S)-4-acetoxy-6-acetyl-8-(4-fluorophenyl)-7-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4f):



Pale yellow liquid

IR (Neat) ט$_{max}$	:	2928, 2827, 1701, 1639, 1531, 1507, 1423, 1323, 1290, 1120, 1064, 989, 836, 759, 584 cm^{-1}
^{1}H NMR:(CDCl$_3$, 200 MHz)	:	δ 6.99 (d, 4H, J= 6.6 Hz), 4.92-5.05 (m, 1H), 4.76-4.87 (m, 1H), 3.90-4.14 (m, 3H), 3.64-3.75 (m, 1H), 3.43-3.52 (m,1H), 2.11-2.24 (m, 1H), 2.07 (s, 3H), 1.94 (s, 3H), 1.93 (s, 3H), 1.75-1.83 (m, 1H)
ESI – MS	:	*m/z* (%) 428 (100) [M+Na]$^+$

((*3R*,*4S*)-4-Acetoxy-6-acetyl-8-(benzo[d][1,3]dioxol-5-yl)-7-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4g):



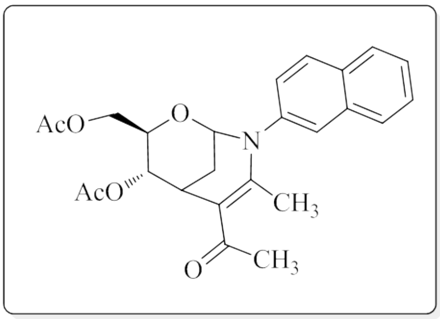
Pale yellow liquid.

IR (Neat) ט$_{max}$	:	2926, 1741, 1637, 1484, 1374, 1297, 1231, 1123, 1039, 991, 860, 756, 632 cm^{-1}
^{1}H NMR:(CDCl$_3$, 300 MHz)	:	*δ* 6.77 (d, 1H, *J*= 8.12 Hz), 6.60 (s, 2H), 6.02 (s, 2H), 4.86-4.95 (m, 1H), 4.04-4.01 (m, 2H),

3.82-3.74 (m, 1H), 3.58-3.53 (m, 1H), 2.22-2.29 (m,1H), 2.16 (s, 3H), 2.14 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H),1.94-1.92 (m, 1H)

ESI – MS : *m/z* (%) 432 (100) $[M+H]^+$, 454 (30)$[M+Na]^+$

((*3R,4S*)-4-Acetoxy-6-acetyl-7-methyl-8-(naphthalen-2-yl)-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4h):



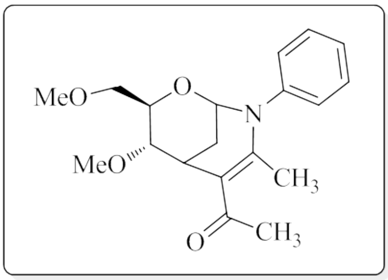
Pale yellow liquid.

IR (Neat) υ_{max} : 2926, 1742, 1640, 1532, 1432, 1375, 1297, 1226, 1119, 1043, 804, 777, 673 cm^{-1}

^{1}H NMR:($CDCl_3$, 300 MHz) : *δ* 7.83-7.93 (m, 1H), 7.44-.7.64 (m, 4H), 7.25-7.33 (m, 2H), 4.95-5.01 (m, 1H), 4.81-4.84 (m, 1H), 3.98-4.28 (m, 3H), 3.66-3.71 (m, 1H), 2.33-2.40 (m, 1H), 2.21 (s, 3H), 2.08 (s, 3H), 2.06 (s, 6H), 1.21-1.27 (m, 1H)

ESI – MS : *m/z* (%) 438 (100) $[M+H]^+$

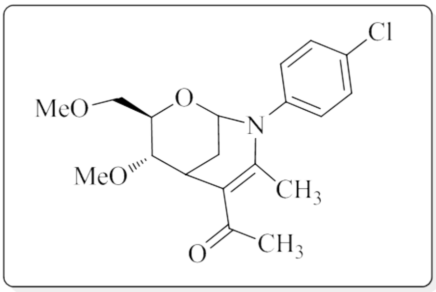
1-((*3R,4S*)-4-methoxy-3-(methoxymethyl)-7-methyl-8-phenyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-6-yl)ethanone (4i):



Pale yellow liquid.

IR (Neat) υ$_{max}$	:	2924, 2853, 1741, 1510, 1459, 1374, 1242, 1038, 833, 759 cm^{-1}
^{1}H NMR:(CDCl$_3$, 200 MHz)	:	*δ* 7.23-7.42 (m, 3H), 7.10 (d, 2H, *J*= 6.64 Hz), 4.94-5.0 (m, 1H), 3.43-3.63 (m, 5H), 3.41 (s, 3H), 3.35 (s, 3H), 2.28 (s, 3H), 2.12-2.21 (m, 1H), 2.09 (s, 3H), 1.82-1.94 (m, 1H)

1-((*3R,4S*)-8-(4-Chlorophenyl)-4-methoxy-3-(methoxymethyl)-7-methyl-2-oxa-8-azabicyclo [3.3.1]non-6-en-6-yl)ethanone(4j):

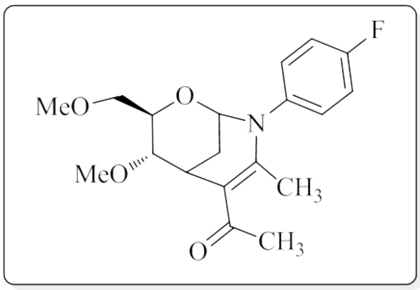


Pale yellow liquid

IR (Neat) υ$_{max}$	:	2929, 2827, 1701, 1640, 1530, 1490, 1383, 1293, 1213, 1120, 1093, 1065, 1013, 989, 831, 722, 599, 570 cm^{-1}
^{1}H NMR (CDCl$_3$, 500 MHz)	:	*δ* 7.38 (d, 2H, *J* = 8.6 Hz), 7.05 (d, 2H, *J* = 8.6 Hz), 4.95 (m, 1H), 3.52 (dd, 1H, *J* = 4.3, 10.3 Hz), 3.49 (dd, 1H, *J* = 5.6, 11.9 Hz), 3.45 (dd, 1H, *J* = 2.5, 11.9 Hz), 3.40 (ddd, 1H, *J* = 2.5, 5.6, 10.4 Hz), 3.38 (m, 1H), 3.41 (s, 3H), 3.35 (s, 3H), 2.21 (s, 3H), 2.09 (dt, 1H, *J* = 3.0, 12.8 Hz,), 2.01 (s, 3H), 1.80 (ddd, 1H, *J* = 2.2, 4.3, 12.8 Hz)
^{13}C NMR (CDCl$_3$, 75 MHz)	:	*δ* 198.2, 152.5, 142.2, 133.0, 129.6, 129.5, 109.7, 82.5, 78.5, 71.5, 59.2, 58.3, 31.8, 30.3, 29.6, 22.6, 20.2
ESI-MS	:	*m/z* (%) 366 (100) [M+H]$^+$

HRMS (ESI)	:	Calcd for $C_{19}H_{25}NO_4Cl$ $[M+H]^+$ 366.1472; found 366.1476

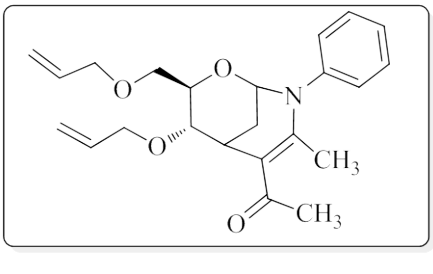
1-((*3R,4S*)-8-(4-Fluorophenyl)-4-methoxy-3-(methoxymethyl)-7-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-6-yl)ethanone (4k):



Pale yellow liquid.

IR (Neat) υ_{max}	:	2926, 1742, 1640, 1532, 1432, 1375, 1297, 1226, 1119, 1043, 804, 777, 673 cm^{-1}
^{1}H NMR ($CDCl_3$, 200 MHz)	:	δ 7.08 (m, 4H), 4.83-4.93 (m, 1H), 3.43-3.63 (m, 4H), 3.40 (s, 3H), 3.36 (s, 3H), 2.31-2.37 (m, 1H), 2.28 (s, 3H), 2.11-2.21 (m, 1H), 2.07 (m, 3H), 1.82-1.93 (m, 1H)
ESI-MS	:	*m/z* (%) 350 (100) $[M+H]^+$

1-((*3R,4S*)-4-(Allyloxy)-3-(allyloxymethyl)-7-methyl-8-phenyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-6-yl)ethanone (4l):



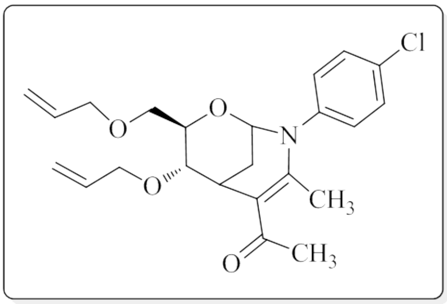
Pale yellow liquid.

^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 7.23-7.39 (m, 3H), 7.07-.7.14 (m, 2H), 5.74-5.94 (m, 2H), 4.94-5.29 (m, 4H), 3.91-4.18 (m, 5H), 3.50-3.62 (m, 5H), 2.88 (s, 3H),

2.13-2.22 (m, 1H), 2.09 (s, 3H), 1.80-1.93 (m, 1H)

ESI-MS : *m/z* (%) 384 (100) $[M+H]^+$

1-((*3R,4S*)-4-(Allyloxy)-3-(allyloxymethyl)-8-(4-chlorophenyl)-7-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-6-yl)ethanone (4m):



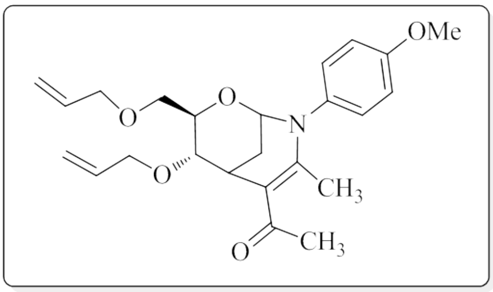
Pale yellow liquid.

IR (Neat) ν_{max} 2924, 2856, 1641, 1596, 1530, 1423, 1295, 1213, 1123, 1089, 933, 829, 765, 663 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.35 (d, 2H, J = 6.9 Hz), 7.03 (d, 2H, J = 6.9 Hz), 6.53 (d, 2H), 5.75-5.91 (m, 2H), 5.12-5.29 (m, 2H) 4.97 (s, 1H), 3.97-4.10 (m, 5H), 2.29 (s, 3H), 2.09 (s, 3H), 1.85-1.92 (m, 1H)

ESI-MS : *m/z* (%) 440 (100) $[M+Na]^+$

1-((*3R,4S*)-4-(Allyloxy)-3-(allyloxymethyl)-8-(4-methoxyphenyl)-7-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-6-yl) ethanone (4n):



Pale yellow liquid.

IR (Neat) ν_{max} : 2925, 2854, 1735, 1641, 1508, 1460, 1378, 1292, 1212, 1124, 1032, 933, 925, 831, 757, 545 cm^{-1}

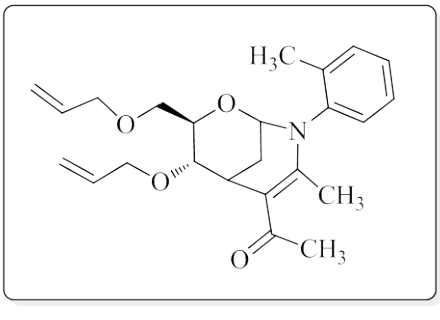
^{1}H NMR (CDCl$_3$, 500 MHz) : δ 7.03 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.8 Hz), 5.95-5.85 (m, 2H), 5.26 (dd, 4H , J = 1.6, 2.7 Hz), 5.16 (dd, 1H, J = 1.6, 3.3 Hz), 4.95 (m, 1H), 4.16 (dt, 1H, J = 1.6 Hz), 4.05-3.95 (m, 3H), 3.81 (s, 3H), 3.65-3.56 (m, 3H), 2.30 (s, 3H), 2.14 (dt, 1H, J = 2.7, 3.3 Hz) 2.30 (s, 3H), 2.14 (s, 3H)

^{13}C NMR (CDCl$_3$, 75 MHz) : δ 198.0, 158.5, 153.7, 136.5, 134.7, 134.4, 129.4, 117.3, 116.9, 114.5, 108.8, 82.7, 78.1, 72.4, 71.3, 71.2, 69.0, 55.4, 30.4, 29.6, 29.3, 28.6, 20.0

ESI-MS : m/z (%) 414 (100) [M+H]$^+$

HRMS (ESI) : Calcd for $C_{24}H_{32}NO_5$ [M+H]$^+$ 414.2280; found 414.2277

1-((*3R,4S*)-4-(Allyloxy)-3-(allyloxymethyl)-7-methyl-8-o-tolyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-6-yl)ethanone (4o):

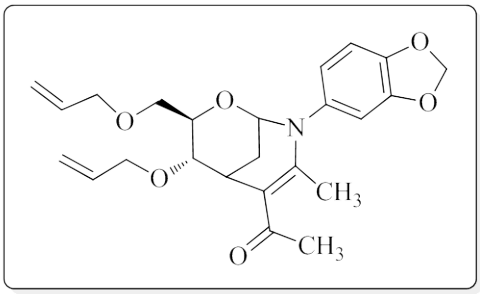


Pale yellow liquid.

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 7.16-7.14 (m, 3H), 7.07 (d, 1H, J = 3.02 Hz), 5.79-5.93 (m, 2H), 5.10-5.29 (m, 4H), 4.63-4.66 (m, 1H), 4.07-4.12 (m, 1H), 3.93-4.03 (m, 3H), 3.51-3.70 (m, 5H), 2.85-2.37

		(m, 1H), 2.26 (s, 3H), 2.14 (s, 3H), 1.99 (s, 3H), 1.85-1.93 (m, 1H)
ESI-MS	:	*m/z* (%) 398 (100) $[M+H]^+$

4p) 1-((*3R,4S*)-4-(Allyloxy)-3-(allyloxymethyl)-8-(benzo[d][1,3]dioxol-5-yl)-7-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-6-yl)ethanone:



Pale yellow liquid.

IR (Neat) ν_{max}		2924, 2855, 1734, 1637, 1527, 1503, 1424, 1998, 1242, 1124, 1058, 1037, 993, 930, 812, 728, 669 cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 6.75 (d, 1H, *J* = 8.1 Hz), 6.61(s, 2H), 6.06 (s, 2H) 5.79-5.90 (m, 2H), 5.12-5.32 (m, 4H), 4.90 (s, 1H), 3.92-4.10 (m, 5H), 3.49-3.60 (m, 4H), 2.23 (s, 3H), 2.12 (s, 3H), 1.82-1.89 (m, 1H)
ESI-MS	:	*m/z* (%) 428 (100) $[M+H]^+$

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INTRODUCTION

Among the various protocols and manipulations of carbohydrates in the course of synthetic strategy, glycosydations are prominent because of their centrality within carbohydrate chemistry. Glycosidation of glycols has been widely used for the synthesis of biologically interesting oligosaccharides and glycoconjugates and for the preparation of 2-deoxy glycosides, which are common structural units in many biologically active natural products such as antibiotics or cardiac glycosides as well as versatile synthetic intermediates. Thioglycosides are important chiral building blocks for the synthesis of various biologically active natural products.[1] Thioglycosides are used as glycosyl donors as they are stable under mild acidic or basic conditions and can be selectively activated by thiophilic reagents.[2] they are usually prepared by reaction of glycals with thiols in the presence of acid catalysts. The acid catalyzed allylic rearrangement of glycals in presence of alcohols or thiols is known as Ferrier rearrangement, which is widely used to prepare 2,3-unsaturated glycosides.[3]

The reaction, as originally reported by Ferrier, involves intermediacy of a cyclic allylic oxocarbenium ion to which the nucleophile adds preferentially in quasi-axial orientation. Consequently, there have been some reports on the preparation of thioglycosides using Lewis acids such as $SnCl_4$,[4] $BF_3.OEt_2$[5] $LiBF_4$[6] and $Sc(OTf)_3$.[7] However, many of these reagents are corrosive, moisture sensitive and are required in stoichiometric amounts and also involve poor regioselectivity[4,5] and low yields due to the formation of mixture of products containing 3-thioglycals[4] and 1,3-dithioadducts.[5] Recently, molecular iodine has gained importance as low cost, non-toxic and readily available catalyst for various organic transformations affording the corresponding products with high selectivity in excellent yields.[8] The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts. Owing to advantages associated with this eco-friendly catalyst, molecular iodine has been explored as a powerful reagent in organic synthesis.[9]

PRESENT WORK

In continuation of our interest on the use of molecular iodine for various organic transformations, [10] we herein report an efficient and practical method for the thia-glycosidation of glycals with thiols in dichloromethane using a catalytic amount of molecular iodine under mild conditions. Accordingly, treatment of tri-O-acetyl-D-glucal (**1**) with thiophenol (**2**) in the presence of 5 mol% of molecular iodine gave the 1-phenylthio-2,3-unsaturated glycoside **3a** in 85% yield (Scheme 1).

Similarly, various aryl and alkyl thiols reacted well with tri-O-acetyl-D-glucal to furnish the aryl and alkyl 2,3-unsaturated thioglycosides in high yields. It is of interest to note that α-anomer was exclusively obtained in this reaction (entries b-g, Table 1). In case of propane-1,3-dithiol, mono-thioglycoside was obtained instead of dithioglycoside (entry g, Table 1). The reaction is a highly stereoselective affording α-anomer exclusively with tri-O-acetyl D-glucal (entries a-g, Table 1). However, thioglycosidation of 3,4,6-tri-O-methyl-, 3,4,6-tri-O-benzyl-, and 3,4,6-tri-O-allyl-D-glucal with thiols gave the products in good yields but with low selectivity when compared to acylated analogues. The predominant formation of α-anomer in the thiaglycosidation must arise from the thermodynamic anomeric effect.[11] the ratio of the α-anomer was increased by long reaction time because the configuration at the anomeric position isomerizes by the exposure of the product to the acidic conditions. The ratio of α and β-anomers was determined on the basis of integrated ratios of anomeric hydrogens in the ^{1}H NMR spectrum of the product and also by isolation of pure isomers on column chromatography. The configuration of the products was assigned by comparison of their spectral data with authentic compounds[4] the spectroscopic data of the products was identical with the data reported in the literature. The results are summarized in Table 1.

The mild lewis acid element Iodine has been used for the thioglycosidation of glycals with various aromatic thiols to generate thioglycals. Here we used 5 mol% of molecular Iodine to give the desired product and got predominantly the α-anomer.

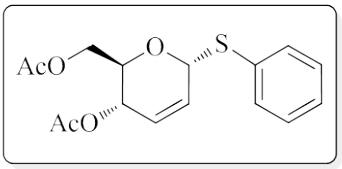
The scope and generality of the reaction is illustrated with respect to various thiols and glycals. This method offers significant advantages such as high yields, short reaction times, high α-selectivity and mild conditions over classical thia-Ferrier conditions. No 3-thioglycals and 1,3-dithioadducts were formed under these reaction conditions, which are normally observed either by stoichiometric amount of $BF_3.OEt_2$ or by $SnCl_4$.

In conclusion, iodine has proved to be an effective catalyst for the synthesis of thioglycosides from glycals and thiols by means of thia-Ferrier rearrangement. The method has advantages of mild reaction conditions, high conversions, short reaction times, remarkable selectivity and simple experimental/work-up procedures, which makes it useful and alternative process for the synthesis of thioglycosides.

EXPERIMENTAL

General procedure: A mixture of 3,4,6-tri-O-acetyl-D-glucal (1 mmol) thiophenol (1 mmol) and molecular iodine (5 mol%) in dichloromethane (15 mL) was stirred at room temperature for 3 h. After complete conversion, as indicated by TLC, the mixture was diluted with saturated sodium thiosulfate (10 mL) and extracted twice with dichloromethane (2 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* and purified by column chromatography on silica gel (Merck, 100-200 mesh, ethyl acetate-hexane, 2:8) to afford pure thioglycoside in 85% yield.

((*2R,3S,6R*)-3-Acetoxy-6-(phenylthio)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3a):



Solid, m.p. 58-60 °C.

IR (Neat) υ_{max} : 3458, 3059, 2926, 1742, 1581, 1475, 1440, 1372, 1232, 1124, 1046, 975, 899, 784, 745 cm^{-1}

^{1}H NMR ($CDCl_3$, 500 MHz) : δ 7.52-7.47 (m, 2H), 7.31-7.24 (m, 3H), 6.05 (dt, 1H, J = 2.4, 10.3 Hz), 5.85 (dt, 1H, J = 1.5, 10.3 Hz), 5.74-5.70 (m, 1H), 5.37-5.32 (m, 1H), 4.43 (td, 1H, J = 2.4, 6.3 Hz), 4.27 (dd, 2H, J = 6.3, 11.8), 2.11 (s, 3H), 2.05 (s, 3H)

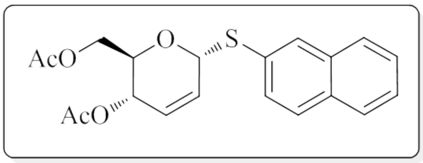
^{13}C NMR ($CDCl_3$, 50 MHz) : δ 170.6, 170.2, 134.8, 132.6, 129.8, 128.9, 128.7, 128.5, 127.6, 127.1, 83.6, 67.3, 65.4, 63.2, 63.0, 20.9

ESI-MS : *m/z* (%) 345 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{16}H_{18}O_5NaS$ 345.0772; found

345.0762

((*2R,3S,6R*)-3-Acetoxy-6-(naphthalen-2-ylthio)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3b):

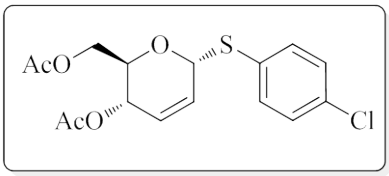


IR (Neat) υ_{max} : 2926, 1744, 1644, 1587, 1500, 1369, 1056, 947, 854, 784, 635 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : δ 7.60 -7.70 (m, 4H), 7.30-7.40 (m, 3H), 6.40 (d, 1H, *J* = 6.0 Hz), 5.10 (dd, 1H, *J* = 4.5 Hz), 4.90 (t, 1H, *J* = 5.2 Hz), 4.30-4.40 (m, 3H), 4.25 (dt, 1H, *J* = 4.5, 2.2 Hz), 2.04 (s, 3H), 2.02 (s, 3H)

ESI-MS : *m/z* (%) 395 (100) [M+Na]$^+$

((*2R,3S,6R*)-3-Acetoxy-6-(4-chlorophenylthio)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3c):



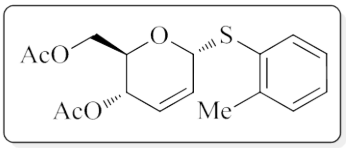
IR (Neat) υ_{max} : 2925, 1743, 1477, 1437, 1231, 1086, 1055, 976, 905, 785, 649, cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) : δ 7.42-7.49 (d, 2H, *J* = 8.7 Hz), 7.20 (d, 2H, *J* = 8.7 Hz), 5.91-6.01 (m, 1H), 5.83-5.89 (m, 1H), 5.29-5.37 (m, 1H), 5.65-5.68 (m, 1H) 4.39 (q, 1H, *J* = 4.3 Hz), 4.22 (d, *J* = 4.3 Hz, 2H), 2.11 (s, 3H), 2.07 (s, 3H)

^{13}C NMR (CDCl$_3$, 50 MHz) : δ 170.1, 169.7, 133.9, 133.4, 132.9, 129.1, 128.1, 128.0, 83.6, 67.4, 65.0, 62.9, 20.9, 20.7

ESI-MS : *m/z* 356 (100) [M+Na]$^+$

((*2R,3S,6R*)-3-Acetoxy-6-(o-tolylthio)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3d):

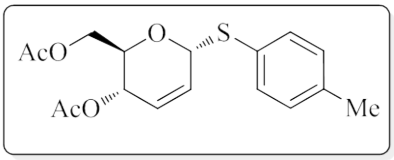


IR (Neat) υ_{max} : 2928, 2190, 1749, 1646, 1565, 1499, 1451, 1370, 1239, 1052, 809, 780, 656 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.59 (m, 1H), 7.14 (m, 3H), 6.09-6.06 (m, 1H), 5.88-5.82 (m, 1H), 5.72-5.69 (m, 1H), 4.42-4.35 (m, 1H), 4.32-4.23 (m, 1H), 4.16 (d, 1H, *J* = 2.0 Hz), 2.42 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H)

LC-MS : *m/z* (%) 359 (100) $[M+Na]^+$

((*2R,3S,6R*)-3-Acetoxy-6-(p-tolylthio)-3,6-dihydro-2H-pyran-2-yl)methyl acetate (3e):

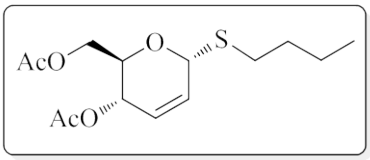


IR (Neat) υ_{max} : 2925, 2090, 1741, 1641, 1492, 1451, 1370, 1231, 1052, 809, 780 cm^{-1}

^{1}H NMR ($CDCl_3$ + DMSO, 200 MHz) : δ 7.35 (d, 2H, *J* = 7.5 Hz), 7.08 (d, 2H, *J* = 7.5 Hz), 6.01-6.06 (m, 1H), 5.80-5.84 (m, 1H), 5.61-5.64 (m, 1H), 5.30-5.35 (m, 1H), 4.38- 4.44 (m, 1H), 4.16-4.27 (m 2H), 2.34 (s, 3H), 2.11 (s, 3H), 2.07 (s, 3H)

ESI-MS : *m/z* (%) 359 (100) $[M+Na]^+$

((*2R,3S,6R*)-3-Acetoxy-6-(butylthio)-3,6-dihydro-2H-pyran-2-yl) methyl acetate (3f):



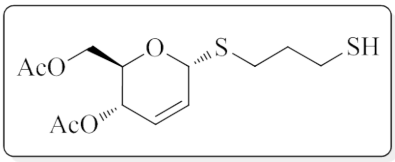
IR (Neat) υ_{max} : 2958, 2928, 2869, 1744, 1645, 1455, 1370, 1233, 1050, 975, 905, 792 cm^{-1}

^{1}H NMR (CDCl$_3$, 300 MHz) : *δ* 5.96-5.87 (m, 1H), 5.77-6.72 (m, 1H), 5.48 (brs, 1H), 5.33-5.28 (m, 1H), 4.27-4.11 (m, 3H), 2.76-2.56 (m, 2H), 2.08 (s, 6H), 1.68-1.58 (m, 2H), 1.49-1.37 (m, 2H), 0.94 (t, 3H, *J* = 7.6 Hz)

ESI-MS : *m/z* (%) 325 (100) [M+Na]$^+$

HRMS (ESI) : Calcd for $C_{14}H_{22}O_5NaS$ 325.1085; found 325.1088

((*2R,3S,6R*)-3-Acetoxy-6-(3-mercaptopropylthio)-3,6-dihydro-2H-pyran-2-yl) methylacetate (3g):



IR (Neat) υ_{max} : 2926, 1743, 1649, 1372, 1222, 1103, 1042 cm^{-1}

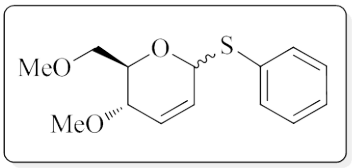
^{1}H NMR (CDCl$_3$, 200 MHz) : *δ* 5.90 (dt, 1H, *J* = 1.5, 10.1 Hz), 5.76 (dt, 1H, *J* = 1.5, 10.1 Hz), 5.51- 5.47 (m, 1H), 5.35-5.25 (m, 1H), 4.25 (t, 1H, *J* = 4.6 Hz), 4.19 (dd, 2H, *J* = 3.1, 9.3 Hz), 1.95-1.97 (m, 2H) 2.88-2.58 (m, 4H), 2.09 (s, 6H), 1.27 (t, 1H, *J* = 7.8 Hz)

^{13}C NMR (CDCl$_3$, 75 MHz) : *δ* 190.0, 189.7, 148.3, 146.4, 118.1, 100.0, 96.9, 93.5, 84.4, 82.4, 53.0, 49.1, 40.4, 40.3, 20.5

ESI-MS : *m/z* (%) 343 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{13}H_{20}O_5NaS_2$ 343.0649; found 343.0648

(*2R,3S,6R*)-3-Methoxy-2-(methoxymethyl)-6-(phenylthio)-3,6-dihydro-2H-pyran (3h):



IR (Neat) υ_{max} : 3054, 2962, 2822, 1581, 1472, 1384, 1313, 1193, 1106, 974, 848, 782 cm^{-1}

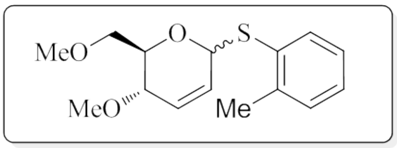
^{1}H NMR ($CDCl_3$, 200 MHz) : δ 7.51-7.45 (m, 2H), 7.27-7.16 (m, 3H), 6.02-5.89 (m, 2H), 5.69-5-65 (m, 1H), 4.11 (dd, 1H, *J* = 2.2, 4.4 Hz), 4.15-4.07 (m, 1H), 3.90-3.86 (m, 1H), 3.64-3.58 (m, 2H), 3.38 (s, 6H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 135.7, 131.2, 128.7, 128.5, 128.2, 127.0, 96.1, 84.0, 81.7, 72.2, 71.5, 69.2, 56.2, 29.7

ESI-MS : *m/z* (%) 289 (100) $[M+Na]^+$

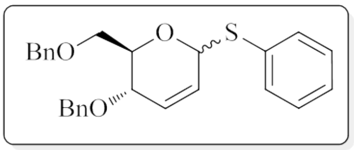
HRMS (ESI) : Calcd for $C_{14}H_{18}O_3NaS$ 289.0874; found 289.0871

(*2R,3S,6R*)-3-Methoxy-2-(methoxymethyl)-6-(p-tolylthio)-3,6-dihydro-2H-pyran (3i):



IR (Neat) υ$_{max}$	:	2926, 2822, 1730, 1588, 1463, 1382, 1314, 1193, 1110, 1051, 975, 949, 849, 782, 749, 711, 527 cm^{-1}
^{1}H NMR (CDCl$_3$+DMSO, 200 MHz)	:	δ 7.51-7.60 (m, 1H), 7.08-7.13 (m, 3H), 5.94-6.05 (m, 2H), 4.07-4.13 (q, 1H, *J* = 2.6 Hz), 3.93-3.97 (t, 1H, *J* = 1.5 Hz), 3.54-3.6 (d, 2H, *J* = 3.7 Hz), 3.42 (s, 2H), 3.30 (s, 3H), 2.30 (s, 3H)
ESI-MS	:	*m/z* (%) 303 (100) [M+Na]$^+$

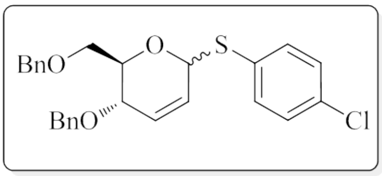
(*2R,3S,6R*)-3-(Benzyloxy)-2-(benzyloxymethyl)-6-(p-tolylthio)-3,6-dihydro-2H-pyran (3j):



Liquid

IR (Neat) υ$_{max}$	:	3030, 2919, 2862, 1725, 1645, 1493, 1452, 1371, 1306, 1206, 1179, 1080, 1023, 949, 849, 809, 780, 738, 698, cm^{-1}
^{1}H NMR (CDCl$_3$, 200 MHz)	:	δ 7.39 (d, 2H, *J* = 8.3 Hz), 6.99-7.10 (d, 2H, *J* = 8.3 Hz), 7.23-7.30 (m, 10H), 5.95-5.97 (m, 1H), 5.62-5.63 (m, 1H), 4.5-4.58 (m, 2H), 3.75-3.72 (m, 2H), 2.31 (s, 3H)
ESI-MS	:	*m/z* (%) 455 (100) [M+Na]$^+$

(*2R,3S,6R*)-3-(Benzyloxy)-2-(benzyloxymethyl)-6-(4-chlorophenylthio)-3,6-dihydro-2H-pyran (3k):

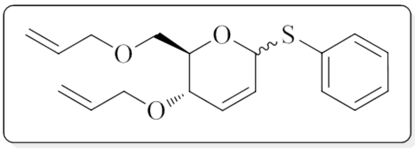


IR (Neat) υ$_{max}$: 2924, 2855, 1743, 1646, 1544, 1549, 1458, 1089, 922, 741, 693, 585 cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) : *δ* 7.53-7.30 (m, 2H), 7.27-7.20 (m, 2H), 5.92-5.70 (m, 3H), 5.60 (d, 1H, *J* = 5.1 Hz), 5.3-5.10 (m, 6H), 4.0-3.90 (m, 6H), 3.7-3.20 (m, 2H)

LC-MS : *m/z* (%) 341 (100) [M+Na]$^+$

(*2R,3S,6R*)-3-(Allyloxy)-2-(allyloxymethyl)-6-(phenylthio)-3,6-dihydro-2H-pyran (3l):

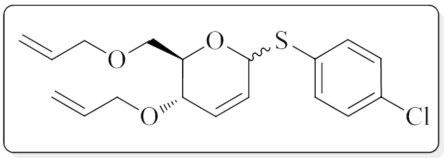


IR (Neat) υ$_{max}$: 2920, 2865, 1763, 1678, 1532, 1521, 1470, 1078, 932, 742, 698, 535 cm^{-1}

^{1}H NMR (CDCl$_3$, 200 MHz) : *δ* 7.48-7.45 (m, 1H), 7.41 (d, 2H, *J* = 7.9 Hz), 7.32-7.20 (m, 10H), 7.13 (d, 2H, *J* = 7.9 Hz), 5.96 (dt, 2H, *J* = 10.1, 1.4 Hz), 5.67-5.60 (m, 1H), 4.61-4.40 (m, 5H), 3.71 (d, 2H, *J* = 3.6 Hz)

LC-MS : *m/z* (%) 475.5 (100) [M+Na]$^+$

(*2R,3S,6R*)-3-(Allyloxy)-2-(allyloxymethyl)-6-(4-chlorophenylthio)-3,6-dihydro-2H-pyran (3m):



Liquid

IR (Neat) υ_{max}	:	2958, 2924, 2854, 2362, 1736, 1646, 1459, 1375, 1270, 1081, 996, 922, 770 cm^{-1}
^{1}H NMR ($CDCl_3$, 300 MHz)	:	δ 7.48 (d, 2H, *J* = 6.7 Hz), 7.23 (d, 2H, *J* = 6.7 Hz), 5.76-6.02 (m, 4H), 5.63-5.65 (m, 1H), 5.16-5.30 (m, 4H), 3.96-4.22 (m, 6H), 3.60 (d, 2H, *J* = 3.0 Hz)
ESI-MS	:	*m/z* (%) 375 (100) [M+Na]$^+$

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INTRODUCTION

The dihydropyridines are biologically, medicinally and synthetically important class of compounds in the field of drugs and pharmaceuticals.[1] They act as potent vasodilators, antihypertensives, branchodilators, antiatherosclerotics, hepatoprotective, antitumor, antimutagenic, geroprotective and antidiabetic agents.[2] DHPs are commercially used as calcium channel blockers such as Nifedipine, Nitrendipine Nimodipine and Lacidipine for the treatment of cardiovascular diseases.[3] A number of DHP calcium antagonists have been introduced as potential drugs for the treatment of congestive heart failure.[4] They are also useful as cognition enhancers, neuroprotectants and platelet antiaggregatory agents.[5] Nifidipine, Nitridipine, Nimodipine and Lasodipine (**Figure 1**) belongs to the same group such as dihyropyridine units which are calcium channel blockers, used in the treatment of hypertension originally developed for the treatment of high blood pressure. Which were available as tablets containing 2 or 4 mg.

Some of these 1,4-dihydropyridines acts as NADH mimics for the reduction of carbonyl compounds and their derivatives.[6] Generally 1,4-dihydropyridines are synthesized by Hantzsh method,[7] which involves cyclocondensation of aldehyde, β-ketoester and ammonia either in acetic acid or in refluxing ethanol.[8] Subsequently, 1,4-dihydropyridines have also been synthesized from α,β-unsaturated aldehydes using organocatalysis.[9] However, the development of novel approaches for the synthesis of sugar fused *N*-aryl tetrahydropyridine scaffolds would be useful for drug discovery program.

PRESENT WORK

In continuation of our interest, this result provided incentive for further study of reactions with other arylamines such as *p*-fluoroaniline, *p*-chloroaniline, *p*-methylaniline, *p*-methoxylaniline and 3,4-methylenedioxyaniline to produce the respective *N*-aryl tetrahydropyridine derivatives in good yields (entries c-f and h-i, Table 1). The structure of the sugar fused *N*-aryl tetrahydropyridine **4h** was established with the help of NMR experiments including ^{1}H decoupling, 1D, nOe, ^{13}C, DEPT and 2D-double quantum filtered correlation spectroscopy (DQFCOSY), 2D-nuclear over Hauser effect spectroscopy (NOESY) and hetero nuclear correlation spectroscopy (HSQC and HMBC). The NMR data suggest that the molecular structure of **4h** consists of an aryl substitution at nitrogen and a sugar fusion at 4,6-positions of the pyridine ring with an unsaturation at 9,10-positions (J_{H9-H10} = 7.7 Hz, *cis* orientation) of the pyridine ring. The H-2 (δ 4.01), H-3 (δ 4.88) and H-5 (δ 2.82) are occupied at axial and H-4 (δ 3.13-3.20), H-7 (δ 1.30) and acetate groups are in equatorial orientation. The ring fusion appears to be a chair form which is confirmed by the NOESY cross peaks between H-4 (δ 3.13-3.20) H-10 (δ 4.93) and H-7 (δ 1.30), H-16 (δ 6.71). Other important nOe correlations are depicted in Figure 2. Additionally, heteronuclear correlations were in agreement with the proposed structure.

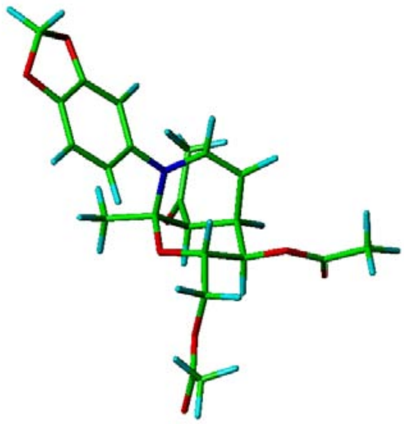


Figure 2: Characteristic nOe cross peaks and energy-minimized structure of **4h**

NOESY Expansion of 4h

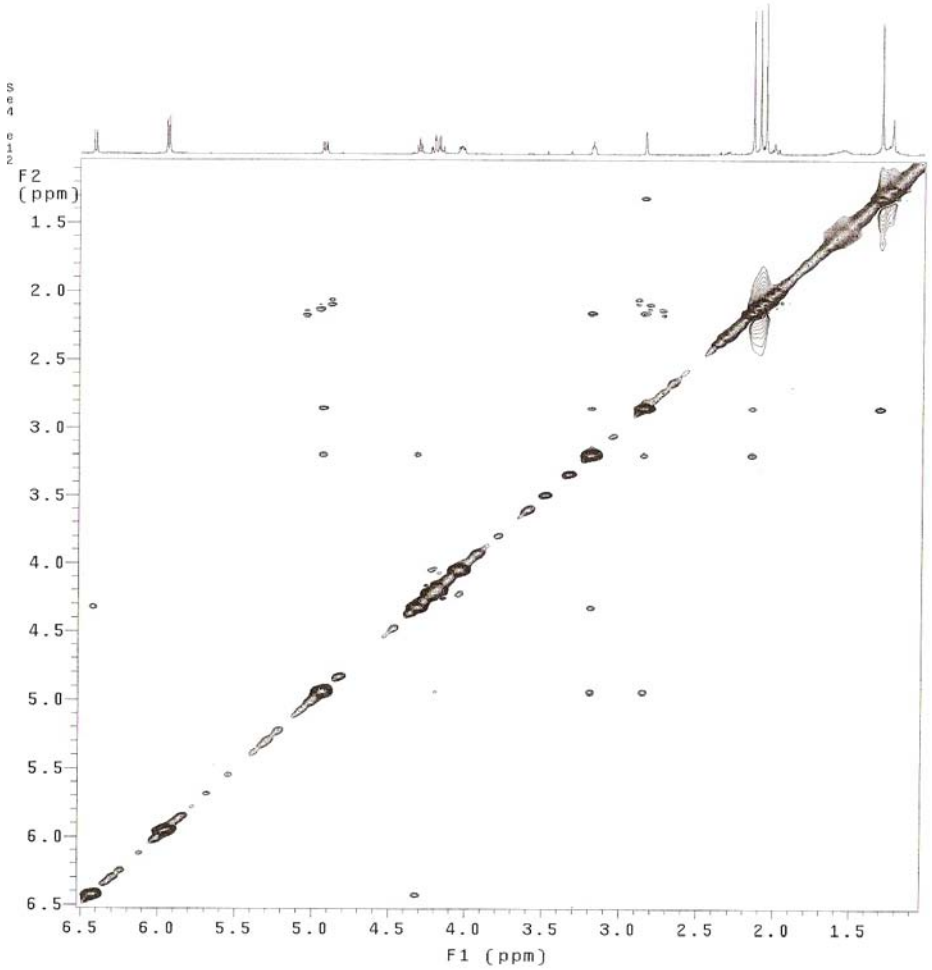


Figure 3

COSY Expansion of 4h

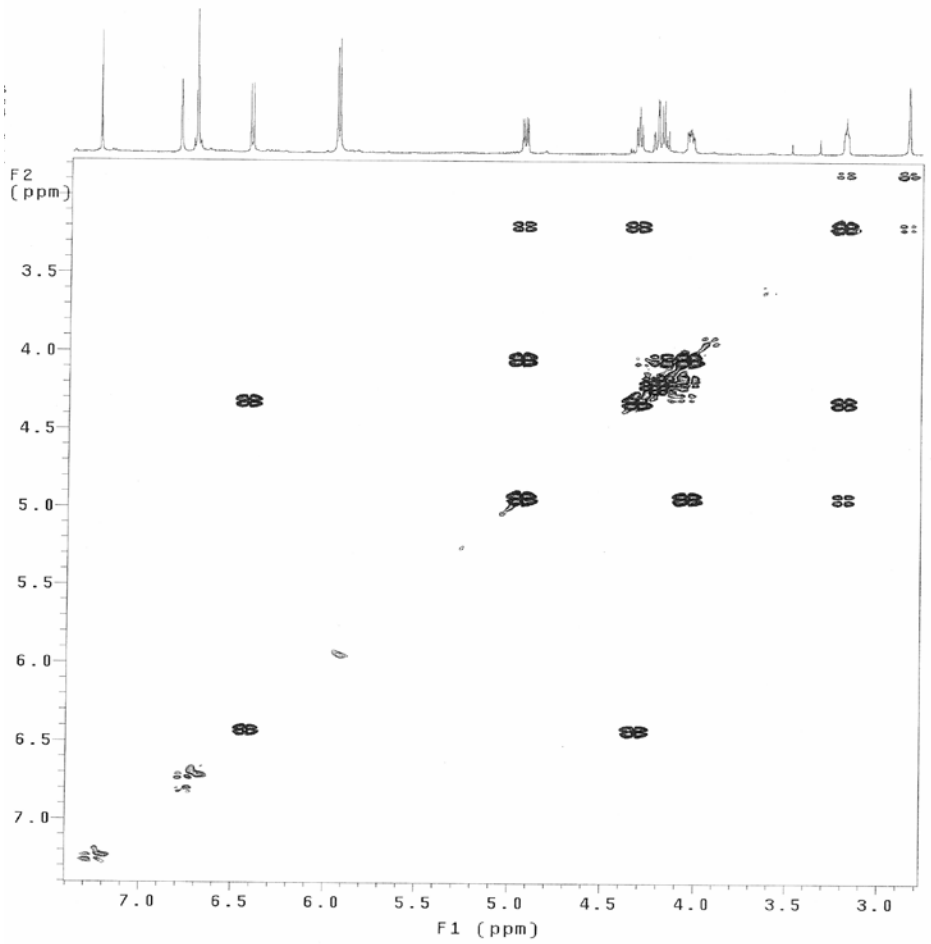
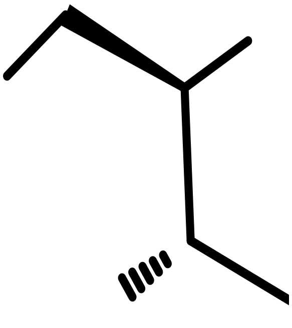


Figure 4

The NMR data suggest that the molecular structure of **4h** consists of an aryl substitution at nitrogen and a sugar fusion at 4,6-positions of the pyridine ring with an unsaturation at 9,10-positions ($J_{H9\text{-}H10}$ = 7.7 Hz, *cis* orientation) of the pyridine ring. The ring fusion appears to be a chair form which is confirmed by the NOESY cross peaks in figure 3.

Various 1,3-diones such as acetyl acetone, methyl acetoacetate and ethyl acetoacetate underwent smooth coupling with aryl amines and δ-hydroxy-α,β-unsaturated aldehyde to furnish the corresponding *N*-aryl tetrahydropyridines (Table 1). The structures of the products were established by ^{1}H NMR, IR and mass spectroscopy. In all cases, the reactions proceeded readily at -10 °C under mild conditions to give the respective products in good yields and with high selectivity.



Catalytic studies of various Lewis acids:

The effect of various Lewis acids such as $BiCl_3$, $CeCl_3.7H_2O$, YCl_3 and $YbCl_3$ was studied in the preparation of **4a**. The reactions were performed using 10 mol% of the catalyst. Of these, $InCl_3$ was found to be the most effective catalyst in terms of conversion. The reactions were sluggish in tetrahydrofuran, dimethoxyethane and acetonitrile. As solvent, CH_2Cl_2 appeared to give the best results.

However, aliphatic amines and cyclic ketones failed to give the desired products. Notably, no cyclization was observed in the absence of $InCl_3$ even after a long reaction time (12 h). The scope and generality of this process is illustrated with respect to various aryl amines and 1,3-diones and the results are presented in Table 2

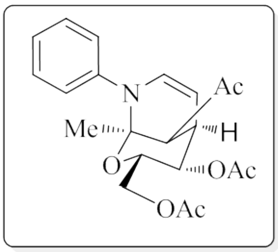
Mechanistically, the reaction proceeds *via* an enamine formation and a subsequent Hantzch cyclization. The resulting dihydropyridne may possibly undergo an intramolecular oxy-Michael reaction to afford the desired tetrahydropyridine (Scheme 2).

In conclusion, we have developed a new strategy that provides a novel class of *N*-aryl tetrahydropyridines in high yields from perlin aldehyde, 1,3-diketones and aryl amines using a catalytic amount of $InCl_{3.}$ This method is mild and convenient for the preparation of highly substituted *N*-aryl tetrahydropyridines in a single-step operation.

EXPERIMENTAL

General procedure: To a mixture of 1,3-diketone, aryl amine (1 mmol) and $InCl_3$ (10 mol%) in dichloromethane (5 mL) was added δ-hydroxy-α,β-unsaturated aldehyde (1 mmol) at -10 °C. The resulting mixture was allowed to stir at the same temperature for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the mixture was quenched with water and extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100-200 mesh, ethyl acetate-hexane, 2:8) gave the pure *N*-phenyltetrahydropyridine. The products thus obtained were characterized by IR, NMR and mass spectroscopy.

(4-Acetoxy-9-acetyl-1-methyl-8-phenyl-2-oxa-8-azabicyclo [3.3.1] non-6-en-3-yl) methyl acetate (4a):



Liquid: $[\alpha]_D^{27}$ +15.9 (c 0.025, $CHCl_3$).

IR (Neat) υ_{max} : 2925, 2853, 2360, 2088, 1740, 1601, 1496, 1438, 1370, 1237, 1144, 1043, 972, 753, 699, 667 cm^{-1}

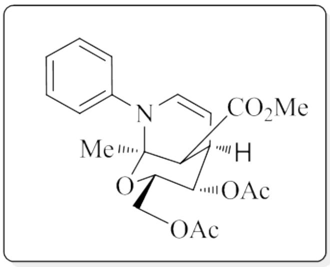
^{1}H NMR ($CDCl_3$, 400 MHz) : *δ* 7.33 (t, 2H, *J*= 7.63 Hz), 7.27 (d, 2H, *J* = 7.63 Hz), 7.21 (t, 1H, *J* = 7.63 Hz), 6.55 (d, 1H, *J* = 7.63 Hz), 4.99 (dd, 1H, *J* = 4.24, 9.33 Hz), 4.39 (td, 1H, *J* = 1.69, 7.63 Hz), 4.19 - 4.29 (m, 2H), 4.08 (ddd, 1H, *J* = 2.54, 5.08, 7.63 Hz), 3.21-3.26 (m, 1H), 2.89-2.92 (m, 1H), 2.19 (s, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.58 (s, 3H)

^{13}C NMR ($CDCl_3$, 150 MHz) : *δ* 197.4, 170.9, 170.3, 144.0, 135.3, 129.4, 127.8, 119.9, 118.6, 108.2, 97.7, 82.5, 71.1, 68.5, 63.3, 30.6, 29.2, 23.4, 21.3

ESI-MS : *m/z* (%) 410 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{21}H_{25}NO_6Na$ 410.1579; Found 410.1575

Methyl-4-acetoxy-3-(acetoxymethyl)-1-methyl-1-methyl-8-phenyl-2-oxa-8azabicyclo[3.3.1]non-6-ene-9-carboxylate (4b):



Pale yellow liquid: $[\alpha]_D^{27}$ +0.036 (c 0.5, $CHCl_3$).

IR (Neat) υ_{max} : 2948, 1741, 1690, 1568, 1493, 1433, 1370, 1236, 1123, 1097, 1083, 1044, 976, 897, 864, 759, 666 cm^{-1}

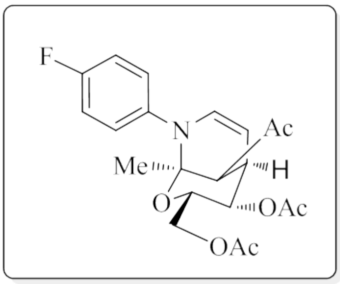
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.31 (t, 2H, *J* = 7.32 Hz), 7.25 (d, 2H, *J* = 7.32 Hz), 7.17 (t, 1H, *J* = 7.32 Hz), 6.53 (d, 1H, *J* = 8.05 Hz), 4.91 (dd, 1H, *J* = 4.39, 10.2 Hz), 4.39 (td, 1H, *J* = 1.46, 6.59 Hz), 4.12-4.2 (m, 2H), 4.04 (ddd, 1H, *J* = 2.9, 8.05, 10.2 Hz), 3.68 (s, 3H), 3.19-3.23 (m, 1H), 2.87-2.89 (m, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 1.40 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.8, 170.2, 168.0, 153.6, 143.9, 130.9, 129.2, 129.1, 96.7, 82.5, 82.0, 65.2, 64.2, 64.1, 60.3, 28.9, 23.0, 21.4, 21.0

ESI-MS : *m/z* (%) 426 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{21}H_{25}NO_7Na$ 426.1528; Found 426.1518

(4-Acetoxy-8-(4-fluorophenyl)-1,9-dimethyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4c):



Brown liquid**:** $[\alpha]_D^{27}$ +4.8 (c 0.03, $CHCl_3$).

IR (Neat) υ_{max} : 3416, 3019, 2930, 2857, 1725, 1465, 1375, 1216, 1045, 756, 668 cm^{-1}

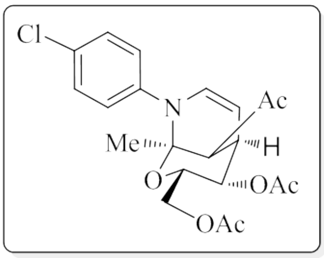
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.16 (d, 2H, J = 8.52 Hz), 6.94 (d, 2H, J = 8.52 Hz), 6.38 (d, 1H, J = 7.55 Hz), 4.91 (dd, 1H, J = 4.65, 10.07 Hz), 4.31 (t, 1H, J = 6.97), 4.13- 4.19 (m, 2H), 3.96 - 4.02 (ddd, 1H, J = 2.9, 4.65, 10.07 Hz), 3.14 – 3.18 (m, 1H), 2.82 (s, 1H), 2.11 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.23 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 204.0, 170.8, 170.1, 161.9, 159.4, 140.1, 138.7, 128.8, 115.6, 89.3, 84.1, 71.8, 68.4, 63.4, 54.8, 32.8, 29.6, 27.9, 23.1, 20.9

ESI-MS : *m/z* (%) 428 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{21}H_{24}NO_6FNa$ 428.1485; Found 428.1474

(4-acetoxy-8-(4-chlorophenyl)-1,9-dimethyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4d):



Brown liquid: $[\alpha]_D^{27}$ +2.2 (c 0.07, $CHCl_3$).

IR (Neat) υ_{max} : 3459, 2924, 2853, 1741, 1639, 1595, 1490, 1454, 1367, 1237, 1127, 1085, 1043, 978, 834 cm^{-1}

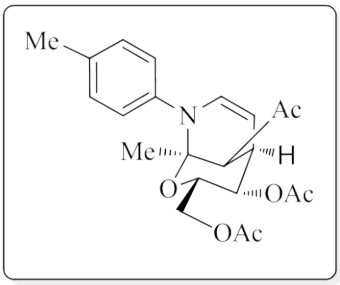
^{1}H NMR ($CDCl_3$, 400 MHz) : δ 7.20 (d, 2H, *J* = 8.52 Hz), 7.10 (d, 2H, *J* = 8.52 Hz), 6.38 (d, 1H, *J* = 7.75 Hz), 4.89 (dd, 1H, *J* = 4.65, 10.07 Hz), 4.33 (t, 1H, *J* = 6.97 Hz), 3.91-4.19 (m, 3H), 3.13–3.17 (m, 1H), 2.81 (s, 1H), 2.08 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 1.25 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 203.9, 170.8, 170.1, 142.6, 138.4, 131.2, 129.6, 128.9, 128.1, 90.0, 84.1, 71.7, 68.5, 63.4, 55.0, 32.8, 29.6, 27.9, 23.1

ESI-MS : *m/z* (%) 422 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{21}H_{24}NO_6NaCl$ 444.1189; Found 444.1179

(4-Acetoxy-1,9-dimethyl-8-p-tolyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4e):



Liquid: **[α]** +16.16 (c 0.025, $CHCl_3$).

IR (Neat) υ_{max} : 3458, 2946, 1741, 1637, 1512, 1366, 1236, 1042, 972, 825, 754, 692, 633, 557 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.05 - 7.14 (m, 5H), 6.45 (d, 1H, *J* = 6.04 Hz), 4.91 (dd, 1H, *J* = 3.02, 6.04 Hz), 3.99 - 4.33 (m, 3H), 3.15 - 3.21 (m, 1H), 2.83 (s, 1H), 2.35 (s, 3H), 2.16 (s, 3H), 2.11 (s, 3H), 2.07

(s, 3H), 1.30 (s, 3H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 196.3, 170.0, 161.0, 155.7, 153.9, 141.2, 130.1, 127.4, 106.7, 89.2, 82.2, 72.1, 70.3, 65.0, 60.3, 29.9, 29.6, 23.2, 22.6, 21.0

ESI-MS : *m/z*: (%) 424 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{22}H_{27}NO_6Na$ 424.1736; Found 424.1730

(4-acetoxy-8-(4-methoxyphenyl)-1,9-dimethyl-2-oxa-8-azabicyclo[3.3.1]non-6-en-3-yl)methyl acetate (4f):

Brown liquid, $[\alpha]_D^{27}$ +5.7 (c 0.7, $CHCl_3$).

IR (Neat) υ_{max} : 3452, 2928, 1740, 1636, 1510, 1443, 1368, 1238, 1178, 1039, 834, 562 cm^{-1}

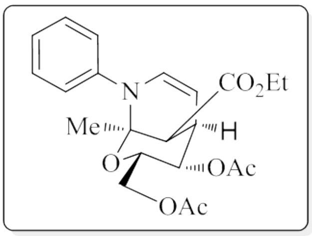
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 7.15 (d, 2H, *J* = 8.87 Hz), 6.80 (d, 2H, *J* = 8.87 Hz), 6.40 (d, 1H, *J* = 7.55 Hz), 4.99 (dd, 1H, *J* = 4.34, 10.09 Hz), 4.11-4.33 (m, 3H), 3.99 - 4.07 (m, 3H), 3.80 (s, 3H), 3.68 - 3.73 (m, 1H), 3.15 - 3.21 (m, 1H), 2.17 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.26 (s, 3H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 199.0, 156.5, 146.3, 138.0, 137.6, 133.3, 128.3, 127.6, 118.1, 116.3, 117.9, 92.9, 83.1, 73.3, 72.6, 72.0, 70.6, 55.5, 29.6, 20.3

ESI-MS : *m/z* (%) 440 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{22}H_{27}NO_7Na$ 440.1685; Found 440.1671

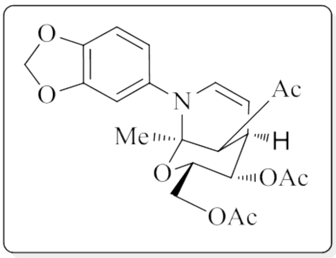
Ethyl4-acetoxy-3-(acetoxymethyl)-8-(4-methoxyphenyl)-1-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-ene-9-carboxylate (4g):



Pale yellow liquid: $[\alpha]_D^{27}$ +0.57 (c 0.5, $CHCl_3$).

IR (Neat) υ_{max}	:	2976, 1742, 1688, 1571, 1493, 1443, 1368, 1341, 1236, 1205, 1170, 1143, 1096, 1040, 968, 913, 861, 769, 702, 646 cm^{-1}
^{1}H NMR ($CDCl_3$, 400 MHz)	:	δ 7.30 (t, 2H, *J* = 7.31 Hz), 7.23 (d, 2H, *J* = 7.31 Hz), 7.15 (t, 2H, *J* = 7.31 Hz), 6.51 (d, 1H, *J* = 8.03 Hz), 4.90 (dd, 1H, *J* = 4.35, 10.02 Hz), 4.40 (q, 2H, *J* = 7.17 Hz), 4.37 (td, 1H, *J* = 1.44, 6.57 Hz), 4.10 - 4.08 (m, 2H), 4.02 (ddd, 1H, *J* = 2.9, 8.03, 10.02 Hz), 3.66 (s, 3H), 3.17 - 3.21 (m, 1H), 2.85 - 2.87 (m, 3H), 2.10 (s, 3H), 2.04 (s, 3H), 1.71 (t, 3H, *J* = 7.17 Hz,), 1.20 (s, 3H)
^{13}C NMR ($CDCl_3$, 50 MHz)	:	δ 201.1, 170.5, 169.7, 167.4, 152.9, 144.0, 129.2, 127.6, 127.2, 97.2, 82.2, 71.8, 70.5, 65.1, 59.4, 31.8, 29.0, 21.1, 20.7, 19.1
ESI-MS	:	*m/z* (%) 440 (100) $[M+Na]^+$
HRMS (ESI)	:	Calcd for $C_{22}H_{27}NO_7Na$ 440.1581; Found 440.1576

(4-acetoxy-9-acetyl-8-(benzo[d][1,3]dioxol-5-yl)-1-methyl-2-oxa-8-azabicyclo[3.3.1] non-6-en-3-yl)methyl acetate (4h):



Reddish brown liquid: $[\alpha]_D^{27}$ +0.24 (c 0.04, $CHCl_3$).

IR (Neat) υ_{max} : 2925, 1739, 1637, 1485, 1442, 1370, 1233, 1133, 1037, 971, 932, 813, 755, 634 cm^{-1}

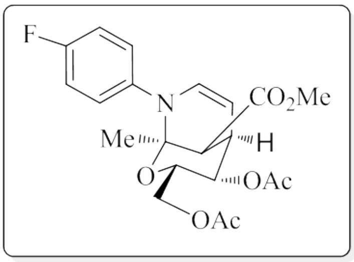
^{1}H NMR ($CDCl_3$, 300 MHz) : δ 6.78 (s, 1H), 6.71 (s, 2H), 6.40 (d, 2H, *J* = 7.74 Hz), 5.90 (d, 2H, *J* = 3.20 Hz), 4.88 (dd, 1H, *J* = 4.34, 10.01 Hz), 4.27 (td, 1H, *J* = 1.32, 6.98 Hz), 4.18 (d, 2H, *J* = 3.2 Hz), 4.01 (ddd, 1H, *J* = 3.3, 6.9, 10.0 Hz), 3.13 - 3.20 (m, 1H), 2.82 (s, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 1.30 (s, 3H)

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 170.8, 170.1, 147.5, 139.1, 138.1, 120.5, 108.9, 107.7, 101.2, 88.7, 84.2, 71.9, 68.3, 63.5, 54.8, 32.9, 31.8, 29.5, 27.8

ESI-MS : *m/z*: (%) 454 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{22}H_{25}NO_8Na$: 454.1493; Found 454.1477

Methyl4-acetoxy-3-(acetoxymethyl)-8-(4-fluorophenyl)-1-methyl-2-oxa-8-azabicyclo[3.3.1]non-6-ene-9-carboxylate (4i):



Reddish brown liquid: $[\alpha]_D^{27}$ +2.13 (c 0.15, $CHCl_3$).

IR (Neat) υ_{max} : 2925, 1739, 1637, 1485, 1442, 1370, 1233, 1133, 1037, 971, 932, 813, 755, 634 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz) : δ 7.01 - 7.06 (m, 4H), 6.98 (d, 1H, *J* = 7.75 Hz), 4.77 (dd, 1H, *J* = 4.65, 10.85 Hz), 4.12 (t, 1H, *J* = 2.32 Hz), 3.97 - 4.10 (m, 2H), 3.80 - 3.85 (m, 1H), 3.68 - 3.71 (m, 1H), 3.58 (s, 3H), 3.15-3.19 (m,1H), 2.82 (s, 1H), 2.14 (s, 3H), 2.05 (s,3H), 2.03 (s, 3H), 1.18 (s, 3H)

^{13}C NMR ($CDCl_3$, 50 MHz) : δ 209.6, 170.7, 169.8, 168.4, 160.3, 155.3, 139.4, 129.9, 116.4, 97.1, 82.6, 70.8, 68.2, 65.1, 63.4, 50.8, 31.8, 29.6, 28.6, 20.8

ESI-MS : *m/z* (%) 454 (100) $[M+Na]^+$

HRMS (ESI) : Calcd for $C_{21}H_{24}NO_7FNa$ 444.1434; Found 444.1423

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The thesis is based on the following original research publications, refered in the text by their numerals:

1. The stereoselective total synthesis of (3S), (7R)-de-O-methyl botryospheareodiplodin. J. S. Yadav,* **Ch.Divyavani**,K.Ananthalakshmi, N.Thrimurtulu and B. V. Subba Reddy.
   (*Manuscript under preparation*).

2. Efficient stereoselective total synthesis of 11-β-methoxycurvularin.
   J. S. Yadav,* **Ch.Divyavani**, B. V. Subba Reddy.
   (*Manuscript under preparation*).

3. The first examples of cyclisation of a glycal with enamines leading to oxa-azabicyclononenes scaffolds. J.S. Yadav,* B.V. Subba Reddy, M.Srinivas, **Ch.Divyavani**, A.C.Kunwar and Ch.Madavi
   Tetrahedron Letters, **2007**,*48,* 8301−8305.

4. Highly Stereoselective synthesis of 2,3-Unsaturated Thioglycopyranosides Employing molecular Iodine. B. V. Subba Reddy*,**Ch.Divyavani**, Jhillu S. Yadav
   Synthesis, **2010**, *10*, 1617-1621−8305.

5. Indium (III) chloride catalyzed novel and efficient synthesis of sugar annulated N-aryl tetrahydropyridines
   B. V. Subba Reddy*,**Ch.Divyavani**, zubeda begum,Jhillu S. Yadav, T.Prabhakarrao
   Synthesis, **2011**,168-172.

6. Three component reaction of Aldose Sugars, Aryl amines, and 1,3-Diones: A novel synthesis of annulated pyrroles.
   Jhillu.S. Yadav, *[+]Basi.V. Subba Reddy, [+]Mende.Srinivas, [+]Chitteti.Divyavani, [+]Shaik Jeelani Basha,[++] and Akella V.S. Sarma.[++]

*J.Org. Chem.***2008**,*73*, 3252−3254.

7. Three component reaction of a δ- hydroxyl-α, β- unsaturated aldehydes with aryl amines and 1,3-diketones; A novel synthesis of oxa-aza bicycles.
   B. V. Subba Reddy*,**Ch.Divyavani**, zubeda begum,Jhillu S. Yadav.
   Synthesis, **2010**, *10*, 1719-1723

SYNOPSIS

Title of the thesis : Stereoselectivetotal synthesis of macrolides 11-β-Methoxy curvullarin, (3S), (7R)-de-O-methyl botryosphaereodiplodin and developement of novel methodologies using glucal as precursor.

Name of the student: DIVYAVANI.CHITTETI (09CHPH19)

Research supervisor: Dr. J. S. YADAV, FNA, FTWAS, Director IICT

The thesis entitled **"Stereoselective total synthesis of macrolides 11-β-Methoxy curvularin, (3S), (7R)-de-O-methyl botryosphaereodiplodin and Development of novel Methodologies using glucal as precursor"** consists of three chapters.

Chapter–I: This chapter describes introduction to macrolides, previous synthetic reports, and stereoselective total synthesis of 11-β-methoxycurvullarin.

Chapter–II: Stereoselective total synthesis of (3S), (7R)-de-O methyl botryosphaereodiplodin.

Chapter–III: Devolepment of novel methodologies using glucal as precursor. This chapter is then sub divided into Section A, Section B and Section C.

Section A: Cyclizations of a glycal with enamines leading to oxa-aza bicyclononene.

Section B: Conversion of glucals into thioglycals by using iodine as catalyst.

Section C: $InCl_3$-catalyzed novel and efficient synthesis of sugar annulated *N*-aryl tetrahydropyridine.

CHAPTER–I

Stereoselective total synthesis of 11-β-methoxy curvularin:

The choice of the strategy for any synthesis lies on the availability of the starting materials, selectivity of the reactions and the yield of the reactions. As an ongoing project on the synthesis of biologically active natural products, we have initiated a programme on the stereoselective total synthesis of 11-β-methoxycurvularin, which is a 12 membered macrolide isolated from hybrid strain ME-0005 derived from *Penicillium citreoviride* have been found to exhibit cytotoxicity towards panel of human cancer cell lines (NCI-H460, MCF-7, and SF-268), cytotoxic against sea urchin embryogenesis. It was shown to act on components of the mitotic apparatus and to effectively inhibit cell division. Macrolides, particularly lactones with medium-sized rings (10–12 membered) attracted considerable attention from medicinal chemists as well as chemical biologists because of their fascinating structural diversity and important biological activities. Structurally, 11-β-methoxycurvularin 12-membered macrolide lactone contain a fused 1,3-dihydroxybenzene ring. The potential biological importance as well as unique structural feature of these molecules made an attention to synthesize by Xuegong She et al. and determined the absolute configuration of 11-α-methoxycurvularin and 11-β,-methoxycurvularin, by their stereoselective synthesis. The absolute configurations of 11-β-methoxycurvularin was assigned as (11*R*, 15*S*) by comparing the ^{1}H NMR data with 11-α-methoxycurvularin respectively. The favorable bioactivities as well as interesting structures inspired our synthesis of 11-β-methoxycurvularin. Herein, a concise stereoselective total synthesis of the natural product 11-β-methoxycurvularin **1** (Figure 1) has been presented.

The first total synthesis of these natural products has been reported by Liang et al, and some of the synthetic approaches were disclosed in the literature. As part of our program towards the synthesis of 11-β-methoxycurvularin, herein we devised a concise route for stereoselective total synthesis of 11-β-methoxycurvularin. The retrosynthetic strategy is schematically illustrated in scheme 1.

The total synthesis of 11-β-methoxycurvularin was achieved by the coupling of the 1, 3-dimethoxyphenyl aceticacid **4** and the fragment **3** by esterification. The required compound was isolated by using column chromatography and the structure was confirmed from spectral studies. Which was synthesized unique 12 membered lactone ring leads to **1** with the key fragment **3** this inturn could be synthesized from **5** & **6**, the key fragment was synthesized from homo propargyl alcohol **9**. Which was protected as benzyl ether **8** by using BnBr, NaH (scheme 2) followed by formylation of paraformaldehyde magnesium turnings and ethylbromide gave 93% yield of **10**, which was on reduction with LAH furnished allyl alcohol **11**. Allyl alcohol **11** was subjected to Sharpless asymmetric epoxidation by using titanium isopropoxide, L (+) DIPT, 4.5 M TBHP gave an epoxide **7** in 70% yield with 95% ee.

This chiral epoxy alcohol **7** was then converted to chloro compound **12** with CCl_4 in reflux conditions. It was further converted to propargyl alcohol **13**. This was converted to its corresponding methyl ether **5** by using NaH and MeI with 85% yield. Regio selective ring opening of (S)-methyl oxirane **6** with **5**, using n-butyl litium and opening of (S) -methyl oxirane **6** with methyl protected propargyl alcohol **5**, with the help of n-BuLi, BF_3OEt_2 gave **3** in 65% overall yield. (Scheme 3)

Thus with the assistance of later process, as shown in the scheme 3, esterification of 3 with 3,5-dimethoxy phenyl acetic acid **4** using DCC and DMAP at rt afforded **14** in

80%yield. Subsequently deprotection of benzyl group and reduction of triple bond were carried out by hydrogenation using 10% Pd/C in ethyl acetate to furnish alcohol **15** in 70% yield. After oxidation of **15** by using Jones reagent (CrO_3, H_2O, H_2SO_4, Acetone, 0 ^oC - rt) the desired carboxylic acid **2** was obtained in 80% yield. (Scheme 4)

Intramolecular Friedel Craft's acylation of compound **2** using a mixture of TFA and tri fluoro acetic anhydride to gave macrolide **16** in 50% yield. The deprotection of methyl groups in **16** with freshly prepared AlI_3 in benzene gave the target molecule, 11-β-methoxycurvularin **1** in 65% yield as colourless oil. (Scheme 5)

CHAPTER-II

Stereo selective total synthesis of (3R), (7R)-de-O-methyl lasodiplodin:

Benzannulated macrolactones are an ever-growing class of natural products with potential therapeutic and agrochemical applications. Lasodiplodins considered as an important leads in the biological ativities such as antibacterial primin, antiseptic mellien, phytotoxic 4-hydroxymellien and antimicrobial. These were also identified to be very efficient inhibitors of prostaglandin biosynthesis, antileukemic and potato micro tuber induced activities. Botryosphaeriodiplodin belongs to lasodiploidins, naturally occurring bioactive metabolites, isolated from mycelial extracts of endophytic fungi Botryosphaeria rhodina PSU-M35 and PSU – M114, which shows antibacterial activity against *Staphylococcus aureas*, both standard ATCC 25922 (SA) and methicillin resistant (MRSA) strains. The structures were resembled with orsellinic acid type macrolides such as zearalenone, curvularin, resorcylide and hydroxy-de-O-methyllasiodiplodin. Several natural products with oresellinic acid type structural units are found to exhibit a wide range of biological activities. As a part of our interest on the synthesis of biologically active molecules, here in we enclose the synthesis of (3S), (7R) -de-O-methyl botryosphaereodiplodin **17**. This is a derivative of botryospheareodiplodin (Figure 2).

Herein we demonstrate the first stereoselective total synthesis of de-O-methyl (3S), (7R)-botryosphealriodiplodin. Our synthesis is a modular one that corresponds two fragments that includes aromatic core and aliphatic 1, 5 – diol of target molecule **17**. The key steps are shown in the retrosynthetic analysis and involve, in order of execution, Jacobson's kinetic resolution, Maruoka asymmetric allylation, Stille cross coupling, Esterification and ring Closing Meta thesis processes displayed in the following. (Scheme 6)

Thus subjection of commercially inexpensive starting material from hex-5-en-1-ol **23** to benzylation using NaH and BnBr to produce benzylether **24** in 90% yield, which was subjected to m-CPBA epoxidation to produce epoxide **25** in 90% of yield, now this epoxide was undergone Jacobson's kinetic resolution to afford resoluted epoxide **22** in 49% of yield. (Scheme 7)

This was readily converted into secondary alcohol **26** by using LAH in THF to afford **26** in 82% yield. Which on protection with MOMCl to produce MOM protected alcohol **27** in 80% yield. Which on debenzylation with $LiNH_2$ gave primary alcohol **28** in 75% yield, this on PCC oxidation to gave an aldehyde. This readily convertible aldehyde was further subjected to Marouka Assymmetric allylation to afford an allyacohol **21** in 75% yields with 99% ee. (Scheme 8)

This allyl alcohol was subjected to benzylation with NaH and BnBr to yield secondary benzyl ether **29** in 75% yield. This was itself converted under cerium chloride to afford a key fragment 20 in 70% yield (Scheme 9).

Our focus was on the construction of aromatic core **19**, which commenced with acetonide formation of commercially available 2,4,6-trihydroxybenzoic acid **30** in the presence of $SOCl_2$, DMAP and acetone to gave aryl acetonide **23** in 85% yield as shown in scheme 10. A subsequent chemoselective protection of the more reactive phenol hydroxy as benzyl ether with benzyl alcohol, TPP to afford **31** in 92% yield. Aryl triflate **32** was obtained by using triflic anhydride in 90% yield. Thus aromatic triflate was subjected to Stille cross coupling to gave desired aromatic core **19**, by using LiCl, vinyl stannane and Pd catalyst to gave **19** in 90%. (Scheme 10)

Our synthesis was turned towards the target molecule **17** by readily synthesized aromatic core **19**, alkyl 1,5 - diol fragment **20**, those two were undergoing esterification insitu deprotection of acetonide by using NaH, DMF/THF (1:1 ratio) to afford diene **18** in 77% yield. This diene was subjected to ring closing metathesis by using Grubbs II generation catalyst in DCM to provide a macrolide **33** in 70% yield. Ultimately, the synthesis was accomplished by hydrogenation of macrolide **17** by 10 mol% Pd/C in MeOH to afford a target molecule **1** in 62% as viscous compound.

In conclusion, we have demonstrated the first stereoselective total synthesis of (*3S*), (*7R*)- de-O-methyl botryosphaereodiplodin **1**7, unique applications such as Jacbson's kinetic resolution, Marouka asymmetric allylation, Stille coupling, esterification and ring Closing metathesis was employed to complete the target molecule **17** by using commercially in expensive starting materials hex-5-en-1-ol and 2,4,6- trihydroxy benzoic acid.

CHAPTER–III

This chapter describes the novel methodologies developed by using glucal as precursor. The ready availability of a wide range of carbohydrates in nature and their multichiral architecture, coupled with their well defined stereochemistry, make them attractive starting materials in organic synthesis. The first glycal was synthesized by Hermann Emil Fisher and Karl Zach in 1913. They synthesized this 1, 2-unsaturated sugar from D-glucose and named their product D-glucal. These are used extensively in general organic synthesis and for the preparation of non-carbohydrate natural products as well as biologically important complex carbohydrates and glycoconjugates. The best known member, tri-O-acetyl-D-glucal, is commercially available, and is used very frequently in this chapter to represent the family in examples of the reactions under discussion. This chapter can be further subdivided into three sections.

Section A: Cyclizations of a glycal with enamines leading to oxa-aza bicyclononene.

In this section, we report smooth coupling of glycols **34** with β-enaminoketones and β-enaminoesters generated *in situ* from 1,3-dicarbonyl compounds **35** and arylamines **36** using 10 mol% of $InCl_3$ as catalyst under reflux with dichloroethane to produce oxa-aza-bicyclononene scaffolds **37** in excellent yields with high selectivity (Scheme 11). Treatment of D-glucal derivatives (3,4,6-tri-O-benzoyl, 3,4,6-tri-O-allyl and 3,4,6-tri-O-methyl -D-glucal) gives the corresponding oxa-aza-bicyclononene scaffolds in very excellent yield. The use of $InCl_3$ makes this protocol quite simple, convenient and easy to scale-up.

Mechanistically, the reaction is initiated by $InCl_3$ catalysed coupling of glycols with β-enaminoketones and β-enaminoesters resulting the formation of the corresponding bicyclonones. (Scheme 12)

Among various triflates were screened $In(OTf)_3$, $Sc(OTf)_3$, $Bi(OTf)_3$, $Yb(OTf)_3$, $Dy(OTf)_3$, and $Sm(OTf)_3$ but none of them gave satisfactory yields employed for this transformation, indium trichloride was found to be the most effective catalyst in terms of conversion selectivity and reaction rates.

Section B: This section deals with the conversion of glucals into thioglycals by using iodine as catalyst.

The principal one involves nucleophilic substitution of the thio group with allylic rearrangement and results in products having double bonds in the 2, 3 positions and new thio substituents at the anomeric centers by using molecular iodine. Molecular iodine has been utilized for the first time for the thioglycosidation of D-glycals with various thiols to afford the corresponding 2, 3-unsaturated thioglycosides in high yields (Scheme 13), in case of tri-O-acetyl-D-glucal, α-anomer was obtained exclusively. But in the case of derivatives of (3,4,6-tri-O-benzyl, 3,4,6-tri-O-allyl and 3,4,6-tri-O- methyl -D-glucal) gave both isomers with less selectivity.

The use of inexpensive readily available iodine makes this method quite simple, more convenient and practical.

Scetion C: This section describes the $InCl_3$-catalyzed novel and efficient synthesis of sugar annulated *N*-aryl tetrahydropyridines.

The dihydropyridines are biologically, medicinally and synthetically important class of compounds in the field of drugs and pharmaceuticals. DHPs are commercially used as calcium channel blockers such as Nifedipine, Nitrendipine and Nimodipine for the treatment of cardiovascular diseases. δ-hydroxy-α, β-unsaturated aldehydes undergo smooth coupling with enamine derived from aryl amine and 1, 3-diketone in the presence of 10 mol% $InCl_3$ in dichloromethane under mild reaction conditions to afford sugar fused *N*-aryltetrahydropyridine derivatives in good yields with high selectivity. (Scheme 14)

Mechanistically, the reaction proceeds *via* an enamine formation and a subsequent Hantzch cyclization. The resulting dihydropyridne may possibly undergo an intramolecular oxy-Michael reaction to afford the desired tetrahydropyridine. (Scheme 15)

Use of catalytic amount of $InCl_3$ in makes this reaction simple. The salient features of this method are high conversions, mild reaction conditions, short reaction times, high selectivity and operational simplicity.

The thesis is based on the following original research publications, refered in the text by their numerals:

1. The stereoselective total synthesis of (3S), (7R)-de-O-methyl botryosphaereodiplodin.
   J. S. Yadav,* **Ch.Divyavani**, K.Anantha lakshmi, N.Thrimurtulu and B. V. Subba Reddy.
   (*Manuscript under preparation*).

2. Efficient stereoselective total synthesis of 11-β-methoxycurvularin.
   J. S. Yadav,* **Ch.Divyavani**, B. V. Subba Reddy.
   (*Manuscript under preparation*).

3. The first examples of cyclisation of a glycal with enamines leading to oxa-aza bicyclononenes scaffolds.
   J. S. Yadav,* B. V. Subba Reddy, M.Srinivas, **Ch.Divyavani**, A.C.Kunwar and Ch.Madavi
   Tetrahedron Letters, **2007**, *48*, 8301−8305.

4. Highly Stereoselective synthesis of 2,3-Unsaturated Thioglycopyranosides Employing molecular Iodine
   B. V. Subba Reddy*, **Ch.Divyavani**, Jhillu S. Yadav
   Synthesis, **2010**, *10*, 1617-1621−8305.

5. Indium (III) chloride catalyzed novel and efficient synthesis of sugar annulated N-aryl tetrahydropyridines
   B. V. Subba Reddy*, **Ch.Divyavani**, zubeda begum, Jhillu S. Yadav, T.Prabhakar rao
   Synthesis, **2011**, 168-172.

6. Three component reaction of Aldose Sugars, Aryl amines, and 1,3-Diones: A novel synthesis of annulated pyrroles.

Jhillu. S. Yadav,*[+] Basi. V. Subba Reddy, [+] Mende.Srinivas, [+] Chitteti.Divyavani, [+] Shaik Jeelani Basha, [++] and Akella V.S.Sarma. [++]
J.Org. Chem. **2008**, *73*, 3252−3254.

7. Three component reaction of a δ- hydroxyl-α, β- unsaturated aldehydes with aryl amines and 1,3-diketones; A novel synthesis of oxa-aza bicycles.
   B. V. Subba Reddy*, **Ch.Divyavani**, zubeda begum, Jhillu S. Yadav.
   Synthesis, **2010**, *10*, 1719-1723.