STEREOSELECTIVE TOTAL SYNTHESES OF CYCLOALKENONE NATURAL PRODUCTS AND CALLYSPONGIDIC ACIDS.

SAYANI DAS

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY DELHI

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by

SAYANI DAS
DEPARTMENT OF CHEMISTRY

Submitted

In fulfillment of the requirements of the degree of DOCTOR OF PHILOSOPHY

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Dedicated to

My Beloved Family

CERTIFICATE

This is to certify that thesis entitled **"Stereoselective total syntheses of cycloalkenone natural products and callyspongidic acids.",** being submitted by **SAYANI DAS** to the Indian Institute of Technology Delhi, for the award of the degree of **Doctor of Philosophy**, is a record of bonafide research work carried out by her. **Ms Sayani Das** has worked under my supervision and guidance and has fulfilled all the requirements for the submission of a Ph.D. thesis, which to my knowledge, has reached the requisite standard and is worthy of consideration for the award of PhD degree.

The work embodied in this thesis has not been submitted, in part or full, to another University or Institute for the award of any degree or diploma.

Prof. Shivajirao L. Gholap
Thesis Supervisor
Assistant Professor,
Department of Chemistry
Indian Institute of Technology Delhi
Hauz Khas, New Delhi-110016, INDIA

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ABSTRACT

The thesis titled "**Stereoselective total syntheses of cycloalkenone natural products and callyspongidic acids.**" presents the work carried out on the total synthesis of a chiral cyclohexenone, cyclopentenone bioactive natural products and a family of amphiphilic lipidic tyrosine derivatives named callyspongidic acids.

Chapter 1 describes the stereoselective total syntheses of anti-fungal cyclohexenones bioactive natural products (−)-Pseudohygrophorone A^{12} and (−)-Pseudohygrophorone B^{12} starting from commercially available inexpensive chiral starting material (−)-quinic acid. The salient features of these syntheses are the diastereoselective addition of dodecyl magnesium bromide to highly oxygenated ketone derived from (−)-quinic acid and α-oxidation of the enone.

Chapter 2 describes the stereoselective total syntheses of anti-fungal cyclopentenones natural products (−)-Hygrophorone A^{12}, (−)-4-*O*-Acetyl-hygrophorone A^{12} and (+)-Hygrophorone B^{12} in high overall yield from D-(−)-tartaric acid. The key step of this syntheses is an aqueous KOH mediated diastereoselective intramolecular aldol reaction to form *β*-hydroxy ketone with three contiguous chiral centres, which was further elaborated to (−)-hygrophorone A^{12} and (+)-hygrophorone B^{12}.

Chapter 3 describes the first short and expeditious total syntheses of (±)-Callyspongidic acids and 2-*epi*-(±)-Callyspongidic acids from epoxy ester derived from L-tartaric acid. The notable features of these syntheses are the stereoselective opening of epoxide with organocuprates and chemoselective addition of Grignard reagent to ketone in the presence of ester.

सार

थीसिस शीर्षक "**साइक्लोएलकेनोन प्राकृतिक उत्पादों और कैलीस्पोंगिडिक एसिड के स्टीरियोसेलेक्टिव कुल संश्लेषण।**" एक चिरल साइक्लोहेक्सेनोन, साइक्लोपेंटेनोन बायोएक्टिव प्राकृतिक उत्पादों और एम्फीफिलिक लिपिडिक टाइरोसिन डेरिवेटिव्स परिवार के कैलीस्पोंजिडिक एसिड के कुल संश्लेषण पर किए गए कार्य को प्रस्तुत करता है।

अध्याय 1 व्यावसायिक रूप से उपलब्ध सस्ती चिरल प्रारंभिक सामग्री (−)-क्विनिक एसिड से शुरू होने वाले स्टीरियोसेक्लेक्टिव कुल संश्लेषण से एंटी-फंगल साइक्लोहेक्सेनोन बायोएक्टिव प्राकृतिक उत्पादों (−)-स्यूडोहाइग्रोफोरोन ए[12] और (−)-स्यूडोहाइग्रोफोरोन बी[12] का वर्णन करता है। इन संश्लेषणों की मुख्य विशेषताएं डोडेसिल मैग्नीशियम ब्रोमाइड का डायस्टेरियोसेलेक्टिव जोड़ हैं जो अत्यधिक ऑक्सीजन युक्त कीटोन से (−)-क्विनिक एसिड और एनोन के α-ऑक्सीकरण से प्राप्त होता है।

अध्याय 2 में एंटी-फंगल साइक्लोपेंटेनोन प्राकृतिक उत्पादों (−)-हाइग्रोफोरोन ए[12], (−)-4-ओ-एसिटिल-हाइग्रोफोरोन ए[12] और (+)-हाइग्रोफोरोन बी[12] के डी-(−)-टारटरिक एसिड से उच्च समग्र उपज के स्टीरियोसेलेक्टिव कुल संश्लेषण का वर्णन किया गया है। इस संश्लेषण का मुख्य चरण एक जलीय KOH मध्यस्थता डायस्टेरियोसेलेक्टिव इंट्रामोल्युलर एल्डोल प्रतिक्रिया है जो तीन सन्निहित चिरल केंद्रों के साथ β-हाइड्रॉक्सी कीटोन बनाता है, जिसे आगे (−)-हाइग्रोफोरोन ए[12] और (+)-हाइग्रोफोरोन बी[12] के लिए विस्तृत किया गया था।

अध्याय 3 एल-टार्टरिक एसिड से प्राप्त एपॉक्सी एस्टर से (±)-कैलीस्पॉन्गिडिक एसिड और 2-एपी-(±)-कैलीस्पॉन्गिडिक एसिड के पहले लघु और त्वरित कुल संश्लेषण का वर्णन करता है। इन संश्लेषणों की उल्लेखनीय विशेषताएं एपॉक्साइड के स्टिरियोसेलेक्टिव ओपनिंग के साथ ऑर्गनोक्यूप्रेट्स और एस्टर की उपस्थिति में कीटोन के लिए ग्रिग्नार्ड अभिकर्मक के कीमोसेलेक्टिव जोड़ हैं।

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GENERAL EXPERIMENTAL CONSIDERATIONS

All solvents employed were purified by standard procedures. Anhydrous solvents were dried over sodium wire (THF, diethyl ether, benzene) or molecular sieves (CH_2Cl_2, $CHCl_3$, DMF). Nitrogen or Argon gas used for creating an inert atmosphere was freed from oxygen prior to entry into the reaction vessel.

Commercially sourced TLC plates were used, and the spots were visualized by exposure to iodine or by dipping in $KMnO_4$. Column chromatography was carried out on silica gel (230–400 mesh) using hexane and ethyl acetate mixtures as eluent unless otherwise mentioned.

Optical rotations were recorded on an Autopol V (Rudolph Research Flanders, NJ) instrument. All the rotations were measured at 589 nm (sodium D-line).

All melting points reported in this thesis are uncorrected and were taken on an electric melting point apparatus (Ambassador, India).

IR spectra were taken within the range 4000–600 cm^{-1} either as KBr pellets or neat on a Nicolet (Madison, USA) FT-IR spectrophotometer (Model Protégé 460).

^{1}H-NMR spectra were recorded on 300 MHz or 400 MHz, or 500 MHz Bruker Spectrospin DPX FT-NMR instruments. The solvents employed were $CDCl_3$ or CD_3OD with Me_4Si as the internal standard. The multiplicities are denoted as s-singlet, brs-broad singlet, d-doublet, brm-broad multiplet, t-triplet, q-quartet, dt-doublet triplet and m-multiplet. ^{13}C-NMR spectra were recorded at 75 MHz or 100 MHz, or 125 MHz instruments. The chemical shifts are reported in δ values (parts per million, ppm) relative to the internal standard Me_4Si.

High-resolution mass spectra were recorded with a Q-TOF Bruker instrument, using electrospray ionization (ESI) as the ionization method.

X-ray crystallography

Suitable crystal of compounds was obtained by slow evaporation of their saturated solutions in chloroform-methanol solvent mixture or water. BRUKER AXS SMART-APEX diffractometer equipped with CCD area detector (Kα=0.71073Å, monochromator: graphite). Frames were collected at T=298K by ω, φ and 2θ-rotation with full quadrant data collection strategy (four domains each with 600 frames) at 10s per frame with SMART. The measured intensities were reduced to F^2 and corrected for absorption with SAINT. Structure solution and refinement were carried out with the SHELXTL package by direct methods. Non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in idealized positions, and a riding model was used for the refinement. Images were created with the program Diamond.

LIST OF ABBREVIATIONS

Ac	:	acetyl
Ac_2O	:	acetic anhydride
Anhyd.	:	anhydrous
Ar	:	aryl
aq	:	aqueous
Bn	:	benzyl
brs	:	broad singlet
C	:	concentration
calcd	:	calculated
cat.	:	catalytic
cm	:	centimeter
DCM	:	dichloromethane
dd	:	doublet of a doublet
ddd	:	doublet of a doublet of a doublet
ddt	:	doublet of a doublet of a triplet
dt	:	doublet of a triplet
DIPA	:	*N*, *N*-diisopropylamine
DIPEA	:	*N*, *N*-diisopropylethylamine
DMF	:	*N*, *N*-dimethylformamide
DMAP	:	4-(*N*,*N*-dimethylamino)pyridine
2,2-DMP	:	2,2-dimethoxy propane
DMP	:	Dess-Martin periodinane
DMSO	:	dimethylsulfoxide
dr	:	diastereomeric ratio
dt	:	doublet of a triplet
ent	:	enantiomer
eq.	:	equivalents
Et	:	ethyl
Fig.	:	figure
g	:	gram(s)
h	:	hour(s)

HRMS	:	high resolution mass spectrum
Hz	:	hertz
IC_{50}	:	half maximal inhibitory concentration
^{i}Pr	:	isopropyl
IR	:	infrared
liq	:	liquid
Lit.	:	literature
LiHMDS	:	lithium hexamethyldisilazide
m	:	multiplet
m-CPBA	:	*meta*-chloroperbenzoic acid
Me	:	methyl
mg	:	milligram(s)
MHz	:	megahertz
min	:	minute(s)
mL	:	milliliter(s)
mmol	:	millimole
MOM	:	methoxymethyl
M.p.	:	melting point
MS	:	Molecular sieves
NMR	:	Nuclear Magnetic Resonance
p	:	para
Ph	:	phenyl
ppm	:	parts per million
PPTS	:	pyridinium para-toluenesulphonate
p-TSA	:	*para*-toluenesulfonic acid
py	:	pyridine
pent.	:	pentet
q	:	quartet
rt	:	room temperature
s	:	singlet
sat.	:	saturated
^{t}Bu	:	*tertiary*-Butyl
t	:	triplet

td	:	triplet of a doublet
TBAF	:	tetra-*n*-butylammonium fluoride
TBS	:	*tertiary*-butyldimethylsilyl
TBDMSCl	:	*tertiary*-butyldimethylsilyl chloride
TBDMSOTf	:	*tertiary*-butyldimethylsilyl trifluromethanesulfonate
tert	:	*tertiary*
TFA	:	trifluoroacetic acid
THF	:	tetrahydrofuran
TLC	:	thin layer chromatography
UV	:	ultraviolet