# STEREOSELECTIVE TOTAL SYNTHESIS OF *γ*-BUTYROLACTONE NATURAL PRODUCTS AND (3*R*,4*S*)-ISOSTREPTENOL III

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*by*

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**Submitted**

**in fulfilment of the requirements of the degree of Doctor of Philosophy**

**to the**


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*This thesis is dedicated to my father*
*Late Mr. Surendra Kumar Sharma and*
*mother Mrs. Nirmala Sharma*
*"Dad, your guiding hand on my shoulder will*
*remain with me forever"*

# CERTIFICATE

This is to certify that thesis entitled **"Stereoselective total synthesis of *γ*-butyrolactone natural products and (3*R*,4*S*)-isostreptenol III",** being submitted by **KAPIL SHARMA** 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 him. **Mr. Kapil Sharma** 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.

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Kapil Sharma

# ABSTRACT

The thesis entitled "Stereoselective total synthesis of *γ*-butyrolactone natural products and (3*R*,4*S*)-isostreptenol III" is presenting the first stereoselective total synthesis of natural products (−)-Inohanalactone, (+)-Pseudonocardide A, (+)-Pseudonocardide C and 3-*epi*-*ent*-Pseudonocardide D from starting materials D-ribose. This thesis includes the first stereoselective total synthesis and structure revision of reported (3*R*,4*S*)-isostreptenol III.

**Chapter 1** describes the first stereoselective total synthesis of (−)-Inohanalactone. The salient features of this synthesis are highly *Z*-selective Wittig olefination and chemoselective oxidation of 1,4-diol to the *γ*-butyrolactone. The synthesis was accomplished from readily available 2,3-*O*-isopropylidene-L-erythrose derived from D-ribose in eight steps with 32% overall yield.

**Chapter 2** describes the divergent chiron approach for the first total synthesis of (+)-pseudonocardide A, (+)-pseudonocardide C and epimer of *ent*-pseudonocardide D starting from D-ribose. The significant aspects of these syntheses are highly *Z*-selective Wittig olefination, one pot formation of *γ*-butyrolactone and *γ*-butenolides [1,4] O-to-O silyl migration followed by lactonization and intramolecular oxa-Michael reaction.

**Chapter 3** describes the first total synthesis and structure revision of (3*R*,4*S*)-isostreptenol III. The structure of isolated 3*R*,4*S*-isostreptenol III was revised to 3*R*,4*R*-isostreptenol III. The salient features of this synthesis are stereoselective installation of hydroxymethyl group, highly diastereoselective Wittig olefination and regioselective epoxide opening. The synthesis was accomplished from a common intermediate readily prepared from D-ribose.

# सार

थीसिस शीर्षक "γ-**ब्यूटायरोलैक्टोन प्राकृतिक उत्पादों और (3*R*, 4*S*)-आइसोस्ट्रेप्टेनॉल III का स्टीरियोसेलेक्टिव कुल संश्लेषण**" प्राकृतिक उत्पादों (−)-इनोहेनललैक्टोन, (+)-स्यूडोनोकार्डाइड ए, (+)-स्यूडोनोकार्डाइड सी और 3-एपि-एंट-स्यूडोनोकार्डाइड डी का पहला स्टीरियोसेलेक्टिव कुल संश्लेषण प्रारंभिक सामग्री डी-राइबोज से प्रस्तुत कर रहा है। इस थीसिस में रिपोर्ट किए गए (3*R*,4*S*)-आइसोस्ट्रेप्टेनॉल III का पहला स्टीरियोसेलेक्टिव टोटल सिंथेसिस और स्ट्रक्चर रिवीजन शामिल है।

**अध्याय 1** (−)-इनोहेनललैक्टोन के पहले स्टीरियोसेलेक्टिव कुल संश्लेषण का वर्णन करता है। इस संश्लेषण की मुख्य विशेषताएं अत्यधिक *Z*-चयनात्मक विटिग ओलेफ़िनेशन और ब्यूटायरोलैक्टोन के लिए 1,4-डायोल के रसायन-चयनात्मक ऑक्सीकरण हैं। संश्लेषण आसानी से उपलब्ध 2,3-ओ-आइसोप्रोपाइलिडीन-एल-एरिथ्रोस से प्राप्त किया गया था जो डी-राइबोज से आठ चरणों में 32% समग्र उपज के साथ प्राप्त किया गया था।

**अध्याय 2** डी-राइबोस से शुरू होने वाले (+)-स्यूडोनोकार्डाइड ए, (+)-स्यूडोनोकार्डाइड सी और एंट-स्यूडोनोकार्डाइड डी के एपिमर के पहले कुल संश्लेषण के लिए अलग-अलग चिरोन दृष्टिकोण का वर्णन करता है। इन संश्लेषणों के महत्वपूर्ण पहलू अत्यधिक *Z*-चयनात्मक विटिग ओलेफ़िनेशन, ब्यूटायरोलैक्टोन और γ-ब्यूटेनॉलिड्स [१,४] का एक पॉट गठन. लैक्टोनाइज़ेशन और इंट्रामोलीक्युलर ऑक्सा-माइकल प्रतिक्रिया के बाद O-to-O silyl प्रवास है।

**अध्याय 3** (3*R*,4*S*)-आइसोस्ट्रेप्टेनॉल III के पहले कुल संश्लेषण और संरचना संशोधन का वर्णन करता है। पृथक (3*R*,4*S*)-आइसोस्ट्रेप्टेनॉल III की संरचना को 3*R*,4*R*-आइसोस्ट्रेप्टेनॉल III में संशोधित किया गया था। इस संश्लेषण की मुख्य विशेषताएं हाइड्रॉक्सीमेथाइल समूह की स्टीरियोसेक्लेक्टिव प्रतिष्ठापन, अत्यधिक डायस्टेरियोसेलेक्टिव विटिग ओलेफिनेशन और रेजियोसेलेक्टिव एपॉक्साइड ओपनिंग हैं। संश्लेषण को डी-राइबोज से आसानी से तैयार किए गए एक सामान्य मध्यवर्ती से पूरा किया गया था।

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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 Me4Si 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 $\delta$ values (parts per million, ppm) relative to the internal standard Me4Si.

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

# COMMON 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 |
| CSA | : | Camphor sulphonic acid |
| 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 |
| epi | : | epimer |
| *ent* | : | enantiomer |
| equiv. | : | 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 |
| KHMDS | : | potasium 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 |
| TsCl | : | Para-toluenesulfonyl chloride |
| Ts | : | Para-toluenesulfonyl |
| R*f* | : | Retention factor |

| | | |
|---|---|---|
| ref | : | Reference |
| 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 |
| TBSCl | : | *tertiary*-butyldimethylsilyl chloride |
| TBDPSCl | : | *tertiary*-butyldiphenyllsilyl chloride |
| TBSOTf | : | *tertiary*-butyldimethylsilyl trifluromethanesulfonate |
| TLC | : | Thin layer chromatography |
| TMS | : | Tetramethyl silane |
| tert | : | *tertiary* |
| TFA | : | trifluoroacetic acid |
| THF | : | tetrahydrofuran |
| TLC | : | thin layer chromatography |
| UV | : | ultraviolet |
| COSY | : | Correlation Spectroscopy |
| HSQC | : | Heteronuclear Single Quantum Coherence |
| NOESY | : | Nuclear Overhauser Effect Spectroscopy |
| HMBC | : | Heteronuclear Multiple Bond Correlation |