GLYCAL BASED APPROACH TO THE SYNTHESIS OF (+)-KIRKAMIDE, AMINO-POLYHYDROXY CARBOCYCLES AND SUGAR-IMINOSUGAR HYBRID MOLECULES

ABHISHEK KULSHRESTHA

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY DELHI
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by

ABHISHEK KULSHRESTHA
DEPARTMENT OF CHEMISTRY

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This thesis is dedicated to my beloved parents

Mr. Ashok Kulshrestha and **Mrs. Praveena Kulshrestha**

For their love, endless support, and encouragement

CERTIFICATE

This is to certify that the thesis entitled **"GLYCAL BASED APPROACH TO THE SYNTHESIS OF (+)-KIRKAMIDE, AMINO-POLYHYDROXY CARBOCYCLES AND SUGAR-IMINOSUGAR HYBRID MOLECULES"**, being submitted by **Mr. ABHISHEK KULSHRESTHA** 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. ABHISHEK KULSHRESTHA** 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 Ph.D. degree.

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

Prof. N. G. Ramesh
Supervisor
Department of Chemistry
Indian Institute of Technology
Delhi
Hauz Khas, New Delhi – 110016
India.

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(ABHISHEK KULSHRESTHA)

ABSTRACT

The thesis titled **"GLYCAL BASED APPROACH TO THE SYNTHESIS OF (+)-KIRKAMIDE, AMINO-POLYHYDROXY CARBOCYCLES AND SUGAR-IMINOSUGAR HYBRID MOLECULES"** presents the research work carried out on the synthesis of (+)-kirkamide, amino-polyhydroxy carbocycles and sugar-iminosugar hybrid molecules utilizing precursors derived from tri-*O*-benzyl-D-glucal.

The research work embodied in the thesis has been divided into three chapters.

Chapter I describes the synthesis of the C7N aminocyclitol natural product (+)-kirkamide. Two distinct synthetic strategies were explored: (a) ring-closing metathesis (RCM) and (b) the Baylis–Hillman reaction. Both strategies commenced from tri-*O*-benzyl-D-glucal. The RCM approach facilitates the formation of a C7N aminocyclitol, while the Baylis–Hillman strategy used to synthesize (+)-kirkamide through an alternative route provided an unexpected product.

Chapter II describes the use of the ring-closing metathesis approach to the synthesis of the core analogue of C6N aminocyclitol (–)-neplanocin A. This approach highlights the utility of metathesis in C6N aminocyclitol synthesis and offers a versatile platform for the development of (–)-neplanocin A analogues with potential biological applications.

Chapter III A few sugar-iminosugar hybrid molecules comprising oxa-aza fused skeletons were designed and synthesized using the diversity-oriented synthetic (DOS) approach from tri-*O*-benzyl-D-glucal derived common intermediate involving ring-closing metathesis as a key step along with the Wittig reaction, Grignard reaction, Barbier reaction and dihydroxylation reaction. These sugar-iminosugar oxa-aza hybrid molecules are pyrrolidino-pyran, pyrrolidino-oxepane and pyrrolidino-oxocane. The interesting thing in all these hybrid molecules is that one of the

common moiety in all these molecules is a five-membered pyrrolidino ring while other moieties are different, such as -pyran, a six-membered ring, -oxepane, a seven-membered ring and -oxocane, an eight-membered ring.

सारांश

थीसिस शीर्षक **"ग्लाइकल आधारित (+)-किर्कामाइड, एमिनो-पॉलीहाइड्रॉक्सी कार्बोसाइक्ल्स और शुगर-इमिनोशुगर हाइब्रिड अणुओं का संश्लेषण"** उस अनुसंधान कार्य को प्रस्तुत करता है जो (+)-किर्कामाइड, एमिनो-पॉलीहाइड्रॉक्सी कार्बोसाइक्ल्स तथा शुगर-इमिनोशुगर हाइब्रिड अणुओं के संश्लेषण पर आधारित है। इस कार्य में संश्लेषण के लिए ट्राई-ओ-बेंज़िल-डी-ग्लूकाल से प्राप्त अग्रद्रव्यों का उपयोग किया गया है।

इस शोध कार्य को तीन अध्यायों में विभाजित किया गया है।

अध्याय I में C7N एमिनोसाइक्लिटोल प्राकृतिक उत्पाद (+)-किर्कामाइड के संश्लेषण का वर्णन किया गया है। इसमें दो भिन्न संश्लेषणीय रणनीतियों का अन्वेषण किया गया: (क) रिंग-क्लोज़िंग मेटाथेसिस (RCM) (ख) बेइलिस-हिलमैन प्रतिक्रिया। दोनों ही रणनीतियाँ ट्राई-ओ-बेंज़िल-डी-ग्लूकाल से प्रारंभ होती हैं। RCM पद्धति C7N एमिनोसाइक्लिटोल के निर्माण को सुगम बनाती है, जबकि बेइलिस-हिलमैन रणनीति का उपयोग वैकल्पिक मार्ग से (+)-किर्कामाइड के संश्लेषण हेतु किया गया, लेकिन इस प्रक्रिया में एक अप्रत्याशित उत्पाद प्राप्त हुआ।

अध्याय II में रिंग-क्लोज़िंग मेटाथेसिस (RCM) पद्धति का उपयोग करके C6N एमिनोसाइटोल (-)-नेप्लैनोसिन A के कोर एनालॉग का संश्लेषण प्रस्तुत किया गया है। यह पद्धति C6N एमिनोसाइटोल के संश्लेषण में मेटाथेसिस की उपयोगिता को दर्शाती है तथा संभावित जैविक गतिविधियों वाले (-)-नेप्लैनोसिन A के विभिन्न एनालॉग्स को विकसित करने का एक बहुआयामी मंच प्रदान करती है।

अध्याय III में कुछ शुगर-इमिनोशुगर हाइब्रिड अणुओं का डिज़ाइन और संश्लेषण किया गया है, जिनमें ऑक्सा-एज़ा संयुक्त कंकाल हैं। ये अणु डाइवर्सिटी-ओरिएंटेड सिंथेटिक (DOS) दृष्टिकोण द्वारा ट्राई-ओ-बेंज़िल-डी-ग्लूकाल से प्राप्त एक सामान्य मध्यवर्ती से बनाए गए हैं। इसमें रिंग-

क्लोज़िंग मेटाथेसिस को एक मुख्य चरण के रूप में अपनाया गया, और इसके साथ-साथ विटिग प्रतिक्रिया, ग्रिगनार्ड प्रतिक्रिया, बार्बियर प्रतिक्रिया तथा डायहाइड्रोक्सीलेशन प्रतिक्रिया का भी प्रयोग किया गया। इन शुगर-इमिनोशुगर ऑक्सा-एज़ा हाइब्रिड अणुओं में पाइरोलिडिनो-पाइरान, पायरोलीडिनो-ऑक्सेपेन और पायरोलीडिनो-ऑक्सोकैन शामिल हैं। सभी हाइब्रिड अणुओं में एक रोचक तथ्य यह है कि इनमें एक सामान्य अणु पाँच-सदस्यीय पाइरोलिडिनो रिंग पाया गया, जबकि अन्य रिंग संरचनाएँ भिन्न थीं, जैसे की: पाइरान (छह-सदस्यीय रिंग), ऑक्सेपेन (सात-सदस्यीय रिंग), तथा ऑक्सोकैन (आठ-सदस्यीय रिंग)।

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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, toluene) or molecular sieves (CH_2Cl_2, $CHCl_3$, DMF, CH_3CN).

Nitrogen or Argon gas used for creating inert atmosphere was freed from oxygen prior to entry into the reaction vessel.

Thin-layer chromatography (TLC) was performed on Merck silica gel pre-coated on aluminium plates and the spots were visualized by exposure to UV light, iodine, or by dipping in KMnO4 solution. Column chromatography was carried out on silica gel (230–400 mesh) using mixtures of hexane and ethyl acetate 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).

Freeze-drying of samples was done on a Freezone 2.5 (Labconco, USA) lyophilizer.

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

^{1}H-NMR spectra were recorded on 300 MHz, 400 MHz, 500 MHz Bruker Spectrospin DPX FT-NMR instruments or 400 MHz Jeol instrument. The solvents employed were $CDCl_3$, D_2O or DMSO-d_6 with Me_4Si as the internal standard. The multiplicities are denoted as s-singlet, br s-broad singlet, d-doublet, t-triplet, q-quartet, dt-doublet triplet, dd-doublet of doublet. ^{13}C-NMR spectra were recorded at 75 MHz, 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 and on Xevo G2-XS QTof.

COMMON ABBREVIATIONS

Ac	:	Acetyl
Ac_2O	:	acetic anhydride
AcOH	:	acetic acid
ADMP	:	aminodeoxy-DMDP
AIBN	:	Azobisisobutyronitrile
Atm	:	atmospheric pressure
Aq	:	Aqueous
Bn	:	Benzyl
Boc	:	tertiary-butoxycarbonyl
^{t}Bu	:	tertiary butyl
C	:	Concentration
Cat	:	Catalyst
Cbz	:	Carbobenzyloxy
COSY	:	correlation spectroscopy
CSA	:	camphor-10-sulfonic acid
DCC	:	*N*, *N*'-dicyclohexylcarbodiimide
DCM	:	Dichloromethane
DEAD	:	diethyl azodicarboxylate
DMAP	:	4-dimethylaminopyridine

DMF	:	*N*, *N*'-dimethylformamide
DMSO	:	Dimethylsulfoxide
Dr	:	diastereomeric ratio
Equiv	:	Equivalent
ESI	:	electrospray ionization
Et	:	Ethyl
EtOAc	:	ethyl acetate
G	:	Gram
GalNAcase	:	*N*-acetyl-α-D-galactosaminidase
Hr	:	Hour
HRMS	:	high resolution mass spectrometry
HSQC	:	heteronuclear single quantum coherence
Hz	:	Hertz
IC_{50}	:	half maximal inhibitory concentration
Imi	:	Imidazole
^{i}Pr	:	Isopropyl
IR	:	Infrared
LAH	:	lithium aluminum hydride
LDA	:	lithium diisopropylamide
LiHMDS	:	lithium hexamethyldisilamide

m-CPBA	:	meta-chloro perbenzoic acid
Me	:	Methyl
Mg	:	Milligrams
Min	:	Minute
mL	:	Milliliters
mM	:	Millimolar
Mmol	:	Millimoles
M.P	:	melting point
Ms	:	Mesyl
MS	:	molecular sieves
MHz	:	Megahertz
m/z	:	mass-to-charge ratio
NAc	:	*N*-acetyl
NCS	:	*N*-chlorosuccinimide
NIS	:	*N*-iodosuccinimide
NMO	:	*N*-methylmorpholine *N*-oxide
NMR	:	nuclear magnetic resonance
NOESY	:	nuclear overhauser effect spectroscopy
Nu	:	Nucleophile
Pd/C	:	palladium on activated carbon

PPh_3	:	triphenyl phosphine
Ph	:	Phenyl
Py	:	Pyridine
p-TSA	:	para-toluenesulfonic acid
RCM	:	ring closing metathesis
R_f	:	retention factor
Ref	:	Reference
Rt	:	room temperature
TBAF	:	tetra-*N*-butyl ammonium fluoride
TBS	:	tertiary-butyldimethyl silyl
TCDI	:	1,1′-thiocarbonyldiimidazole
TFA	:	trifluoroacetic acid
THF	:	Tetrahydrofuran
TLC	:	thin layer chromatography
TMS	:	trimethyl silyl
Tr	:	trityl (triphenyl methyl)
Ts	:	tosyl (*p*-toluenesulfonyl)