

Springer Theses

Recognizing Outstanding Ph.D. Research

For further volumes:
<http://www.springer.com/series/8790>

Aims and Scope

The series “Springer Theses” brings together a selection of the very best Ph.D. theses from around the world and across the physical sciences. Nominated and endorsed by two recognized specialists, each published volume has been selected for its scientific excellence and the high impact of its contents for the pertinent field of research. For greater accessibility to non-specialists, the published versions include an extended introduction, as well as a foreword by the student’s supervisor explaining the special relevance of the work for the field. As a whole, the series will provide a valuable resource both for newcomers to the research fields described, and for other scientists seeking detailed background information on special questions. Finally, it provides an accredited documentation of the valuable contributions made by today’s younger generation of scientists.

Theses are accepted into the series by invited nomination only and must fulfill all of the following criteria

- They must be written in good English.
- The topic should fall within the confines of Chemistry, Physics, Earth Sciences, Engineering and related interdisciplinary fields such as Materials, Nanoscience, Chemical Engineering, Complex Systems and Biophysics.
- The work reported in the thesis must represent a significant scientific advance.
- If the thesis includes previously published material, permission to reproduce this must be gained from the respective copyright holder.
- They must have been examined and passed during the 12 months prior to nomination.
- Each thesis should include a foreword by the supervisor outlining the significance of its content.
- The theses should have a clearly defined structure including an introduction accessible to scientists not expert in that particular field.

Jianxian Gong

Total Synthesis of (±)-Maoecrystal V

Doctoral Thesis accepted by
Peking University, Beijing, China

 Springer

Author

Dr. Jianxian Gong
School of Chemical Biology and
Biotechnology
Peking University Shenzhen Graduate
School
Shenzhen, Guangdong
People's Republic of China

Supervisor

Prof. Zhen Yang
College of Chemistry and Molecular
Engineering
Peking University
Beijing
People's Republic of China

ISSN 2190-5053

ISSN 2190-5061 (electronic)

ISBN 978-3-642-54303-6

ISBN 978-3-642-54304-3 (eBook)

DOI 10.1007/978-3-642-54304-3

Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2014931688

© Springer-Verlag Berlin Heidelberg 2014

This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed. Exempted from this legal reservation are brief excerpts in connection with reviews or scholarly analysis or material supplied specifically for the purpose of being entered and executed on a computer system, for exclusive use by the purchaser of the work. Duplication of this publication or parts thereof is permitted only under the provisions of the Copyright Law of the Publisher's location, in its current version, and permission for use must always be obtained from Springer. Permissions for use may be obtained through RightsLink at the Copyright Clearance Center. Violations are liable to prosecution under the respective Copyright Law. The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

While the advice and information in this book are believed to be true and accurate at the date of publication, neither the authors nor the editors nor the publisher can accept any legal responsibility for any errors or omissions that may be made. The publisher makes no warranty, express or implied, with respect to the material contained herein.

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

Parts of this thesis have been published in the following journal articles:

Gong J, Lin G, Li C-C et al. (2009) Synthetic study toward the total synthesis of maoecrystal V. *Org Lett* 11:4770–4773 (Reprinted with permission. Copyright (2010) American Chemical Society.)

Gong J, Lin G, Sun W-B et al. (2010) Total Synthesis of (\pm) Maoecrystal V. *J. Am. Chem. Soc.* 132:16745–16746 (Reprinted with permission. Copyright (2009) American Chemical Society.)

Supervisor's Foreword

The field of total synthesis of natural products is practiced in a scientific and artistic way. The strategy should be balanced based on the dimensions, geometries, and symmetries of the molecules. During the pursuit of total synthesis, the artistic taste was exercised in the way combining chemical reactions to arrive at a strategy that will lead to the target molecule. The powerful methodology and sophisticated instrumentation available today have profoundly affected the way in which organic molecules are synthesized and characterized. In spite of the great advances that have enormously facilitated our operations, the synthesis of organic molecules even of medium levels of complexity still faces practical, theoretical, and logical challenges.

This thesis focuses on the total synthesis of Maoecrystal V. Maoecrystal V, a natural product with potent biological activity, is a novel diterpenoid which was isolated from the leaves of Chinese medicinal herb, *Isodon eriocalyx*, by Prof. Handong Sun and co-workers. The synthesis challenge exists in the novel pentacyclic ring system and six chiral centers, including four continuous chiral centers, three all quaternary carbon centers.

Many distinguished synthetic groups have carried out the total synthesis toward Maoecrystal V due to the complexity of the structure and the importance of its bioactivity. The thesis mainly focuses on two aspects: the first part is the stereo-selective construction of the tetracyclic model system and the second part is the first total synthesis of natural product Maoecrystal V. Based on the model study, the total synthesis of Maoecrystal V is accomplished in 17 steps, 1.2 % yield.

In such an exciting field, only a tip of the iceberg in terms of molecular diversity from nature has been just touched by the synthesis. With the development of organic synthesis, I strongly believe that we are going to see a lot of creative and efficient strategies for the synthesis of complex molecules. As Prof. K. C. Nicolaou said "It's rather complicated to even define art, science, and technology. There is a triangle of art, which is the pursuit of something new, usually associated with esthetics; science, the pursuit of something new, perhaps the understanding of nature; and technology, the application of science." Keeping ourselves busy inventing and discovering new generations of medicine used in the pharmaceutical and biotechnology industries will always be our unremitting pursuit.

Beijing, March 2013

Zhen Yang

Contents

1	Research Background of Total Synthesis of Natural Product Maoecrystal V and Its Family	1
1.1	Introduction to the Research Background of Total Synthesis of Natural Products	1
1.2	Terpenoids	4
1.3	Ent-Kaurane Diterpene	5
1.4	Isolation and Structure Identification of Diterpenoid Natural Product Maoecrystal V	7
1.5	Biosynthetic Hypothesis for Maoecrystal V	8
1.6	Bioactivity of Maoecrystal V	8
1.7	A Brief Review on Synthesis Works of Maoecrystal V	9
1.7.1	The Synthetic Strategy of Our Group	9
1.7.2	The Synthesis Research of Baran's Group	17
1.7.3	The Synthesis Research of Danishefsky's Group	18
1.7.4	The Synthesis Research of Nicolaou's Group	21
1.7.5	The Synthesis Research of Singh's Group	22
1.7.6	The Synthesis Research of Thomson's Group	23
1.7.7	The Synthesis Research of Trauner's Group	25
1.7.8	The Synthesis Research of Zakarian's Group	25
1.8	Brief Summary	26
	References	27
2	Model Study of Maoecrystal V	29
2.1	Model Study of Maoecrystal V: Synthesis Strategy	29
2.2	The Model Synthesis of Maoecrystal V	29
2.2.1	Pinhey Arylation	31
2.2.2	The Development and Synthetic Application of Diels–Alder Reaction	31
2.2.3	Construction of [2.2.2] System via Sequential Oxidative Dearomatization/IMDA Reaction	35
2.2.4	The Model Study of Maoecrystal V	38

2.3	Experimental Section	48
2.3.1	Experimental Materials and Equipment	48
2.3.2	Experimental Process and NMR Data of Model Study. . .	49
2.4	Summary	69
	References	70
3	Total Synthesis of Maoecrystal V	73
3.1	Retro-synthetic Analysis of Maoecrystal V	73
3.2	Strategy 1 of Total Synthesis: DA/Oxa-bridge Formation	73
3.2.1	Retro-synthetic Analysis	73
3.2.2	The Preparation of 1,3-Keto Ester	74
3.2.3	Diastereoselective Reduction of Ketone Carbonyl Group of 1,3-Keto Ester	76
3.2.4	Intramolecular Diels–Alder/Oxa-bridge Strategy	79
3.3	Oxa-bridge/IMDA: Intramolecular S _N 2 to Form Oxa-bridge	84
3.4	Oxa-bridge/IMDA Strategy: Intramolecular Oxa-Michael Reaction	86
3.5	Oxa-bridge/IMDA Strategy: Rh(II)-catalyzed Intramolecular O–H Insertion	89
3.6	The Experimental Process and NMR Data of Total Synthesis . . .	96
3.7	Summary	134
	References	135
4	Summary	137

Abbreviations

Ac	Acetyl
AVMA	Asymmetric vinylogous Mukaiyama aldol
Bn	Benzyl
Boc	<i>t</i> -butoxycarbonyl
BOM	Benzyloxymethyl
<i>i</i> -Bu	<i>i</i> -butyl
<i>n</i> -Bu	<i>n</i> -butyl
<i>t</i> -Bu	<i>t</i> -butyl
Bu	Butyl
CAN	Cerium(IV) ammonium nitrate
Cp	Cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	<i>N,N</i> -4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess–Martin Periodinane
DMSO	Dimethylsulfoxide
<i>dr</i>	Diastereoselective ratio
EA	Ethyl Acetate
EE	2-ethoxyethyl
Et	Ethyl
eq.	Equivalent
HMPA	Hexamethylphosphoramide
<i>i</i> -Pr	<i>i</i> -propyl
LDA	Lithium Diisopropylamide
LiHMDS	Lithium Hexamethyldisilazide
NaHMDS	Sodium Hexamethyldisilazide
Me	Methyl
MEM	(2-methoxyethoxy) Methyl
MES	Mesityl
MOM	Methoxymethyl

MS	Molecular Sieves
OTf	Triflate
PE	Petroleum Ether
PG	Protective Group
Ph	Phenyl
Piv	Pivaloyl
PPTS	Pyridinium <i>p</i> -toluenesulfonate
Py	Pyridine
RCM	Ring Closing Metathesis
RT	Room Temperature
SM	Starting Material
TBAF	Tetrabutylammonium fluoride
TBS	<i>t</i> -butyldimethylsilyl
TBDPS	<i>t</i> -butyldiphenylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TIPS	Triisopropylsilyl
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride
Ts	<i>p</i> -toluenesulfonyl