Biomimetic Synthesis of Marine Sponge Derived Natural Products

Kevin Kuan Kar Weng

B. Sc. (Hons.) Chem

A thesis submitted in total fulfilment of the requirements for the degree of Doctor of Philosophy

THE UNIVERSITY of ADELAIDE

2015

Department of Chemistry

University of Adelaide

In memory of my grandmother, Gan Lian See

24.09.1925 – 06.01.2013

Table of Contents

Chapter Four: Progress Towards the Biomimetic Synthesis of (–)-Frondosin A

Abstract

There is a longstanding interest in the total synthesis of meroterpenoid natural products. These secondary metabolites of marine sponge origin not only display interesting biological activity, but also possess an intriguing molecular architecture, and thus have emerged as appealing targets for total synthesis. Herein this thesis, we report the synthesis of several marine natural products starting from (+)-sclareolide, a cheap and commercially available chiral pool starting material. A brief account on the recent applications of (+)-sclareolide in the field of total synthesis is first described in chapter one.

An improved total synthesis of (+)-liphagal is reported in chapter two. The key intermediate can be obtained from (+)-sclareolide in just 10 steps. The construction of the 6,7,5,6-tetracyclic framework was achieved via a pinacol ring expansion methodology, followed by formation of the hemiacetal, and subsequent dehydration to form the benzofuran moiety. Alternatively, this ring expansion can also proceed from the *ortho*-quinone methide generated *in-situ* under acidic conditions. Furthermore, the feasibility of a biomimetic conversion of (+)-siphonodictyal B, a co-isolated natural product, to (+)-liphagal was also investigated using a simplified model system. While the results from the model study proved to be encouraging, the formation of a stable *ortho*-quinone methide was observed while attempting this one-pot epoxidation-ring expansion approach.

The preparation of (+)-aureol from (+)-sclareolide is described in chapter three. Key transformations include a series of bioinspired stereospecific [1,2]-hydride and methyl shifts to form the aureane skeleton, and a late stage biomimetic cycloetherification reaction under acidic conditions to afford the desired natural product. In addition, simple modification of the cycloetherification reaction produced a novel tetracyclic molecule with an unprecedented seven-membered cycloether ring.

Finally, recent progress towards frondosin A is described in chapter four. While a convergent strategy approach utilising the key intermediate in chapter three failed to deliver the target molecule, a structural isomer of the natural product could be obtained from a novel ring expansion cascade. This sequence involved a dehydration, ring expansion, di-TBS deprotection, and cycloether formation in a one-pot operation. Preliminary attempts to convert this structural isomer to frondosin A or its quinone derivative are reported.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library catalogue and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

……..

Kevin Kuan

……..

Date

Acknowledgements

First and foremost, I'd like to thank my supervisor, Dr. Jonathan George, for his support and guidance over the past few years. Being able to work with Jonathan has been a very rewarding experience; Jonathan is very passionate about organic chemistry, and I am often amazed by his creative ideas and his insightful approach towards contemporary synthetic chemistry challenges. This positive attribute of his has served as an inspiration not only to myself, but to other members of the George group as well.

I'd like to thank the members of the George group over the course of my candidature. Special mention goes out to Justin Spence and Hilton Lam, both of which I consider to be very diligent and talented individuals. It has been a great pleasure to share a fume cupboard with Justin, and I am grateful to Hilton for running computational simulations on my molecules. Both Justin and Hilton have been of tremendous help whenever I hit a roadblock with my research; I was able to bounce ideas and ask for feedback from the two of them, and they are always passionate about chemistry, sometimes leading to endless discussions about mechanisms and NMR spectra late into the night. I'd also like to extend my thanks to Michelle Cruickshank, for proof reading the final draft of my thesis and baking delicious cakes for our group meetings and birthday celebrations. It has been a real pleasure and privilege to be working with you all.

Next, I'd like to acknowledge my peers, Dr. Alex Gentleman, Dr. Bradley Visser, and Dr. William Tieu for always lending an ear when in need. Alex and Brad have kept me motivated about life and science, and the lively discussions we had whilst walking back to our cars late at night will always be the most memorable part of my PhD years. My thanks also goes out to Will, for general discussions and help with HPLC purifications.

Special thanks goes out to the technical staff in the Chemistry department, in particular Mr. Phil Clements for running NMR experiments on the 600 MHz spectrometer, Mr. Gino Farese, for memorable times in the undergraduate teaching labs, Mr. Peter Apoefis, for the general maintenance and servicing of the lab equipment, and Mr. John Cameron, for keeping the chemistry store adequately stocked.

To my friends outside of the chemistry department, I'd like to acknowledge Dr. Tiong Jingwen, Dr. Anja Winterstein, Denise Cheah, and Yen Kinsern for their moral support and encouragement through some of the tougher moments of my candidature. In particular, it was great that Jingwen and Anja were able to relate to similar issues that every PhD student encounters. Their thoughts and advices were invaluable, if not refreshing, and often manages to revitalise my enthusiasm towards scientific research.

This journey would have not been possible without the blessing and approval from my family. I'd like to take this opportunity to thank my parents, Kuan Khai Chuan and Tham Yin Foong, for allowing me to pursue this lifelong ambition of mine. Thank you for being patient, for lending moral and financial support, and for being the greatest parents a child can ever ask for.

Finally, I'd like to thank Marie-Ann Chin, my partner, for being by my side and cheering me up when I'm frustrated. This journey would have not been possible without you.

List of Abbreviations

$[\alpha]_D$	specific rotation at wavelength of sodium D line
Å	angstrom(s)
aq.	aqueous
Asp	aspartic acid
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-butyl
c	concentration for specific rotation measurements
CAN	ceric ammonium nitrate
^{13}C	carbon-13 isotope
cat.	catalytic
°C	degrees Celsius
cm^{-1}	wavenumber(s)
conc.	concentrated
CSA	camphorsulfonic acid
1,2-DCE	1,2-dichloroethane
1,2-DCB	1,2-dichlorobenzene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

(–)-DET	**D**-(–)-diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N*,*N*-dimethylformamide
EI	electron impact
epi	epimer
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
g	gram(s)
gCOSY	gradient-selected Correlation Spectroscopy
h	hour(s)
^{1}H	proton
HFIP	hexafluoroisopropanol
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
hv	light
Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximum inhibitory concentration
IR	infrared (spectroscopy)

J	coupling constant
KHMDS	potassium hexamethyldisilazide
MeOH	methanol
λ	wavelength
L	litre
Lys	lysine
m	multiplet or milli
m-CPBA	*meta*-chloroperoxybenzoic acid
m/z	mass to charge ratio
μ	micro
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMO	*N*-methylmorpholine N-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
PDC	pyridinium dichromate

PhH	benzene
PhMe	toluene
PPTS	pyridinium *para*-toluenesulfonate
p-TsOH	*para*-toluenesulfonic acid
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
pyr	pyridine
q	quartet
RCM	Ring closing metathesis
R_f	retention factor
ROESY	Rotating Frame Overhauser Enhancement Spectroscopy
rt	room temperature
s	singlet or seconds
t	triplet
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMEDA	*N, N, N', N'*-tetramethylethylenediamine
TMS	trimethylsilyl
Tr	triphenylmethyl (trityl)
Ts	*p*-toluenesulfonyl (tosyl)
Tyr	tyrosine
UV	ultraviolet
W	watt