

UNIVERSITI TEKNOLOGI MARA

**AN APPROACH TOWARDS THE
SYNTHESIS OF DYSIDAMIDE C
AND ITS DERIVATIVES**

SHARIFAH EDAYU SYED MONUDEEN KHAN

Thesis submitted in fulfillment
of the requirements for the degree of
Master of Science

Faculty of Applied Sciences

May 2013

AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any other degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of mu study and research.


Name of Student : Sharifah Edayu binti Syed Monudeen Khan

Student's ID No. : 2008263028

Programme : AS780

Faculty : Faculty of Applied Sciences

Thesis Title : An Approach towards the Synthesis of Dysidamide C and Its Derivatives

Signature of Student : 

Date : May 2013

ABSTRACT

Dysidamide C was chosen in this study as the synthetic target due to its unique skeletal structure and its interesting pharmacological activities. This thesis has been divided into five main sections. Chapter one is a review on our target compounds-Dysidamide C. Chapter two focus on the synthetic strategies of compound which have similar skeleton to Dysidamide C by different research groups, whilst chapter three consists of our synthetic works. Experimental details including the spectroscopic data are provided in chapter four and finally, future works are recommended in chapter five. Our synthetic approach towards the synthesis of Dysidamide C was divided into two different routes. The first route began by couple up readily available starting material known as glycine methyl ester and methyl malonate potassium through condensation reaction followed by Dieckmann cyclisation to give pyrrolidine ring known as the β,β -diketoester. Letting β,β -diketoester undergo a series of successive chemical reactions, which include demethoxycarbonylation, dialkylation at C-3 position, olefin formation at C-5, successfully gave our desire template known as methylene ketone type of compounds, **125** (with an overall yield of 21%). For the second route, methylene ketone type of compounds, **125**, was obtained in four steps using methyl acetoacetate as the starting material. The first step was known as dimethylation, followed by brominations, intercyclization reaction and finally olefin formations at C-5 (with an overall yield of 26%). This entire attempt was successfully furnished us with over 35 pyrrolidine type of compounds. Apart from that, we manage to manipulate the important intermediates **125**, to produce Dysidamide C-derivative known as diesterified compound and *isoxazoline* in 4 steps. In brief, we have developed a mild and operationally simple procedure towards the synthesis of Dysidamide C. The result extracted from this study thus far may be used to develop new scientific knowledge and remarkable findings.

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation and sincere gratitude to my supervisor Professor Dr. Ahmad Sazali Hamzah, for his valuable advice and assistance through useful comments, suggestions, and guidance. I am very grateful to him for putting at my disposal every facility that he had which I need during the course of my work.

I would like to register my heartfelt thanks to my co-supervisor Dr Yaser Bathich for his criticisms, suggestions and generous help especially during my research in laboratories. May I register my gratitude to Professor Madya Dr. Zurina Shaameri for her guidance and a very helpful critical reading of the manuscript, without which it would not have been possible for me to shape the thesis in the present form.

My profound thanks and appreciations to all staffs in the Organic Synthesis and Natural Product laboratory, Puan Irmazatul, Puan Zaleha and Encik Shahrizan for their invaluable assistance and unfailing support. I would also like to thank all my friends and colleagues, especially Dr. Fazli, Norsaliyana, Sharifah Hidayah, Shulehaf, Asmah, Che puteh, Jihah, Fatimah and Najah for their assistance whenever it was needed. I would express my special thanks to my mother Puan Jamiaah, for her prayer, patience and untiring support in every way during my study, and not forgetting my sibling Rahim, Adi and Adzham for their motivation and confident in me. Most of all, I am very grateful to Allah for blessing me with good health and a lot of patience, without which this work will not be complete.

Finally, I would like to acknowledge gratitude to Ministry of Higher Education (MOSTI) and Universiti Teknologi MARA for financial support and for giving me the opportunities to pursue my study.

TABLE OF CONTENTS

	Page
AUTHOR'S DECLARATION	ii
ABSTRACT	iii
ACKNOWLEDGEMENTS	iv
TABLE OF CONTENTS	v
LIST OF TABLES	xii
LIST OF FIGURES	xiii
LIST OF ABBREVIATIONS	xiv
CHAPTER ONE: INTRODUCTION	
1.1 Marine Natural Product as a Potential Source for Drug Discover.	1
1.2 Pharmacy of Deep Marine-Sponges	2
1.3 Dysidamide C	4
1.4 Objectives of Research	6
CHAPTER TWO: LITERATURE REVIEW	
2.1 Synthesis of (+)-Lactacystin by Omura	7
2.2 Synthesis of (+)-Lactacystin by Wenxin	11
2.3 Synthesis of (+)-Lactacystin by Hayes	15
2.4 Synthesis of (+)-Lactacystin by Shibasaki	20
2.5 Synthesis of (-)-Salinosporamide A by Corey	23
2.6 Synthesis of (-)-Salinosporamide A by Romo	26
2.7 Synthesis of (-)-Salinosporamide A by Danishefsky	27
2.8 Synthesis of Janolusimide A by Sodano	30