UNIVERSITI TEKNOLOGI MARA

CHEMICAL STUDIES TOWARDS THE SYNTHESIS OF JANOLUSIMIDE, A MARINE NEUROTOXIN FROM *Janolus cristatus*

NURULHUDA BINTI KAMARUDDIN

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ABSTRACT

Janolusimide **19** was chosen to be the synthetic target molecule due to having a unique tripeptide structure besides showing a neurotoxin activity. Our synthetic approach towards the synthesis of janolusimide involved the construction of a core lactam system derived from L-valine using EDC.HCl followed by dimethylation using four different conditions. Dimethylation at C-3 position of **133** affords (5*S*)-3,3-dimethyl-5-*iso*propylpyrrolidine-2,4-dione **26** in 72% yield using TBAF as a phase transfer catalyst. In this dimethylation step, a characteristic of ambident anion also can be observed. Multiple positions of alkylation had occurred due to enolate's ambident character of which *C*,*O*-alkylated and *O*-alkylated side products were observed. While the effort to synthesize the dipeptide chain was carried out using aldol reaction, *N*-alkylation of **26** and *N*-acylation of a template, 2-pyrrolidinone **139** and lactam **26** with several electrophiles. Four general protocols (Method A-D) to *N*-acylate 2-pyrrolidinone and lactam **26** were examined. These methods can be used as an alternative method to perform *N*-acylation of other lactam analogues. From these steps, two main precursors **144** and **147** towards the synthesis of janolusimide were afforded. In order to carry out mono-alkylation of β-keto amide **143**, monomethylation to our template **140** was performed to optimize the reaction conditions. Mono-alkylation of β-keto amide **143** was carried out using several electrophiles such as methyl iodide, benzyl bromide, *iso*propyl iodide and allyl bromide afforded compounds **147**, **148**, **149** and **150** in 85, 64, 50 and 76% yields respectively. Chemical exploration of the lactam **133** through electrophilic substitution at C-3 afforded unique compounds **151** and **152** derived from unusual bond migration. In addition, the study of ester hydrolysis of compound **143** had proven the sensitivity of amide bond towards acid and base. Meanwhile, reduction of *N*-acylated lactams **144** and **147** *via* $NaBH_4$ affording reduced lactam adduct **155** due to the amide hydrolysis. Besides, reduction of keto compound **147** mediated by sodium triacetoxyborohydride produced the diastereomeric mixture of reduced products **156** in 14% yield.

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CHAPTER ONE
INTRODUCTION

1.1 MARINE NATURAL PRODUCTS

Natural products are frequently called secondary metabolites because they are not biosynthesized by general metabolic pathways and have no primary function directly involved in the normal growth such as development or reproduction of an organism. These metabolites are usually used by organism to control ecological relationship that comprises competition for food and space, interspecies communication for the purposes of mating and defense against predation (Martins, Vieira, Gaspar and Santos, 2014). Natural products have long been used as medicines, foods, pigments, fragrances and insecticides. Terrestrial plants have been the major sources of medicinally useful products especially in traditional medicines due to their easy access (Jha and Rong, 2004). Nowadays, modern technologies have uncovered vast areas of research for the isolation of natural compounds originated from oceans and sea organisms.

Marine life is an enormous resource for providing food, medicine and raw materials. The ocean which covers 70% of the Earth's surface is also the source of the structurally unique natural products. Research into the use of marine natural products in the pharmaceutical field is still in early stages even the vast biodiversity in marine environment far exceeds that of the terrestrial environment (Jha and Rong, 2004). The ocean is an extremely promising source of new drug candidates, however it still remains largely unexplored (Skropeta, Pastro and Zivanovic, 2011). Remarkably, overexploiting of many marine resources, predominantly the fisheries, the planktonic compartment consists of zooplankton, phytoplankton, bacteria and viruses which represents 95% of marine biomass; thus far its diversity remains largely unknown and underexploited (Abida *et al.*, 2013). Many compounds originated from living organisms in the ocean, show pharmacological activities and are significantly important for the invention and discovery of metabolites especially for deadly diseases such as cancer, arthritis and AIDS (Jha and Rong, 2004). In association with the pharmaceutical industry, the cosmeceutical industry is gradually turning to the sea