UNIVERSITI TEKNOLOGI MARA

SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF ZOPFIELLAMIDE A

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of the requirements for the degree of
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AUTHOR'S DECLARATION

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

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ABSTRACT

In this study, Zopfiellamide A was chosen as a target molecule due to its unique structure and its pharmacological importance. The synthetic strategy moving towards the synthesis of Zopfiellamide A was divided accordingly based on the C-5 and C-3 substitution groups. The first approached was focused on the insertion of C-5 substituents of Zopfiellamide A which is the construction of the quaternary carbon bearing the hydroxyl, isopropyl and carboxylic acid linked *via* the methylene group at C-5 position of the pyrrolidinone ring. Therefore, the C-3 position of the pyrrolidinone ring was protected by a methyl group. Methyl acetoacetate was dialkylated, brominated and cyclised with methylamine to form the required lactam skeleton. The synthesis of C-5 substituents involved olefination, Michael addition, alkylation and mono-decarboxylation to give decarboxylated product **30,** which is closest to the target molecule **12**. There were two more steps left, which are α-hydroxylation and hydrolysis of ester. The overall yield of reaction was about 30%. Meanwhile, the *C*-acylation on C-3 was done by preparing the studied template of pyrrolidine-2,4-dione template **38**, *via* condensation, dieckmann cyclisation and decarboxylation reaction. The *C*-acylation reaction was performed using readily available acid chlorides including crotonyl, benzoyl, napthoyl, cinnamoyl, and furoyl chloride respectively. The reaction was carried out using strong and weak base, however, the product yield was very low, ranging from 1 to 14% yield to a complex mixture. Meanwhile, the chemical exploration of the pyrrolidinone intermediates produced during the reaction was also done using epoxidation, acid-catalyzed ring-opening and stereoselective reduction. The epoxidation of alkene **17** with mCPBA managed to give epoxide **31**, and treatment with diluted acid was successfully gave diols **32**. The reduction of alkene **17** with sodium borohydride in the presence of $CaCl_2$ and $MnCl_2$ was resulted in chemoselective but not stereoselective reaction. However, reduction with sodium borohydride in the presence of $MgCl_2$ and $ZnCl_2$ was found to be a chemoselective and stereoselective reaction. The reduction of Michael adduct **19** was successfully resulted in keto reduction and gave compound **35**.

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