UNIVERSITI TEKNOLOGI MARA

THE SYNTHESIS OF OSELTAMIVIR PHOSPHATE KEY INTERMEDIATE, *tert*-BUTYL (5-(PENTAN-3-YLOXY)-6-((TRIMETHYLSILYL)OXY)CYCLOHEX-3-EN-1-YL)CARBAMATE AND SYNTHESIS OF (1*S*,2*S*)-HYDROXYCYCLOHEXENE-1,2,3-TRIAZOLE DERIVATIVES

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ABSTRACT

Oseltamivir phosphate also known as Tamiflu is an active neuraminidase inhibitor for the treatment of influenza A and B. In this study, a new method on synthesizing a key intermediate of oseltamivir phosphate was established by using commercially available 1,4-cyclohexadiene as the starting materials. In the first part, *tert*-butyl (5-(pentan-3-yloxy)-6-((trimethylsilyl)oxy)cyclohex-3-en-1-yl)carbamate **14** (Tamiflu intermediate) was synthesized from 1,4-cyclohexadiene via epoxidation using *m*-CPBA to give cyclohexene epoxide **8**, followed by epoxide ring opening with trimethyl silane azide using Salen catalyst complex to afford azide **9** and **10**. Then the azide **9** was reduced by using $Pd(OH)_2/C$ and the resulted amine was protected with di*tert*-butyldicarbonate to give **11** and **12**, followed by allylic oxidation of **11** with SeO_2 and TBHP to afford **13**. The compound **14**, was synthesized via etherification reaction of dialcohol **11** with 3-pentanol catalyzed by $BF_3.OEt_2$ with the overall yield of 13%. The second part focused on the synthesis triazole derivatives **15a-15d** using azide **10** as the starting material via click reaction employing iodocopper $CuI[P(OEt)_3]$ complex in toluene to afford triazole derivatives **15a-15d** with the yield of 17- 29%. Both oseltamivir phosphate key intermediate and triazole derivatives explore new synthetic approaches towards the development of new chemicals for bioactivity purposes.

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CHAPTER ONE
INTRODUCTION

1.1 Background of study

1.1.1 Drug discovery

World Health Organization (WHO) had recommended Tamiflu, the commercial medicine name of oseltamivir phosphate **1** (OP) as a prophylactic and therapeutic treatment drug for avian influenza outbreaks (Wang et al., 2015). Oseltamivir phosphate **1** has been designed as the neuraminidase inhibitors. Mostly, the studies aimed at the advancement of new synthetic routes for this neuraminidase inhibitor (Magano, 2009). For example, the worldwide outbreak of swine flu (H1N1 human flu) and potential threat of avian flu have attracted serious concern to secure anti-influenza drugs in order to safeguard public health (Oh & Kang, 2012).

Over the years, the creation of a new drug emerged when scientists learn about a biological target that included in a biological function which can be impaired in patients with a disease. The advantages over existing drugs in terms of drug synthesis, efficiency, safety, tolerability and mechanism of drug use are considered for the success of a new drug (Mohs & Greig, 2017). The process of drugs development took over years to be tested and synthesized until it get to be consumed by patients. There are also some challenges in developing drugs such as a huge cost or high degree of uncertainty of drug development. These elements should be considered in developing new drugs other than knowing the significance of the drugs (Rotella, 2016).

There are many successful studies on drugs that include natural product for medical purposes. Biologically active molecules will continue to provide a strong incentive for discovery of new chemical reaction (Esposito & Principi, 2016). With the information of the behavior of active molecules, many researchs had conducted to develop chemical and medical research. Different types of disease and infection had been discovered and known for their causes of illness, prevention and cure. For example in year 1918, Spanish flu pandemic got the attention of the world that deaths was estimated to be at least 50 million worldwide. The virus has been discovered and evaluated which lead to discovery of vaccination (Chuanopparat et.al, 2012).