Pawinee Wichienukul 2011: Total Synthesis of an Anti-avian Influenza Drug Oseltamivir Phosphate (Tamiflu) and Advance Intermediate to Tamiphosphor from D-Ribose. Master of Science (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Boonsong Kongkathip, Ph.D. 115 pages.

Oseltamivir phosphate (Tamiflu) is used as an orally active drug for treatment and prevention of influenza viruses infections. It is hydrolyzed by an esterase enzyme to the corresponding carboxylic acid, which is a potent inhibitor of neuraminidases A and B. Recently Tamiphosphor, a phosphonate congener of Tamiflu, has been synthesized and showed more potent activity against the wild-type neuraminidase of H5N1 and H1N1 viruses. The current manufacturing process of Tamiflu uses (-)-shikimic acid as the starting compound which is not always readily available in consistently pure form. Thus, alternative approaches starting from other substrates were explored. Herein, we report a synthesis of Tamiflu and advance intermediate to Tamiphosphor from an alternative starting material D-ribose which is cheap and commercially available.

The main features of this approach comprise a metal (Zn, In)-mediated domino reaction of 5-iodo derivative of D-ribofuranose and ring-closing olefin metathesis (RCM) of the resultant functionalized dienes to produce the Tamiflu skeleton. The synthesis represents a new and efficient transformation of a 5-epi-hydroxy shikimate derivative into a 1,2-diamino compound which involved oxidation of an alcohol followed by reductive amination, regioselective reductive ring opening of 3-pentylidene ketal and stereospecific nucleophilic replacement of a triflate with an azide.

In summary, we have accomplished an efficient synthesis of Tamiflu in 14 steps and advance intermediate to Tamiphosphor in 9 steps with 5% and 2% overall yield respectively, using cheap and abundant D-ribose as the starting material. The key features of the synthesis include a metal-mediated domino reaction, ring-closing olefin metathesis (RCM), reductive amination and regioselective reductive ring opening of 3-pentylidene ketal.

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