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Efficient Short Step Synthesis of Corey's Tamiflu Intermediate

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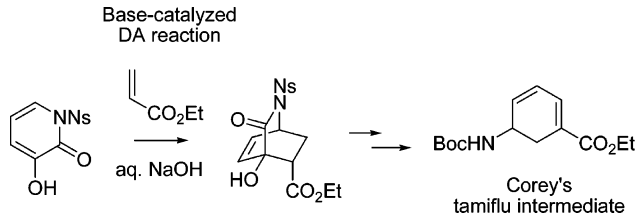
ABSTRACT



Corey's tamiflu intermediate was synthesized from a bicyclolactam adduct obtained by base-catalyzed Diels–Alder reaction of *N*-nosyl-3-hydroxy-2-pyridone with ethyl acrylate. A compound that has the same array of functional groups with the Corey's intermediate was obtained in four steps from the DA adduct in 47% overall yield. The intermediate itself was also prepared efficiently by simply changing the protective group.

Tamiflu (oseltamivir phosphate) **1** is a potent neuraminidase inhibitor and the most widely used anti-influenza drug. Since its development in 1996 by Gilead Science, Inc. and launching by F. Hoffman-La Roche, Ltd., 42 million people have been treated with Tamiflu until November 2006.[1] Roche's group has already developed its practical synthetic route for commercial supply.[2] However, more a efficient process using easily available starting material and safer reactions is still required for stockpiling the drug in preparation for a possible flu pandemic, and thus active researches have been carried out.[3,4] In addition, since the emergence of influenza viruses with reduced sensitivity to neuraminidase inhibitors have been reported recently,[5] syntheses of modified Tamiflu are also of high interest.

Our research group found a unique base-catalyzed Diels−Alder (DA) reaction of 3-hydroxy-2-pyridones that gave sterically controlled and highly functionalized bicyclolactams **4** as products.[6] These compounds seemed to be good building blocks for aminocyclitols having C7N structures,[7] and indeed, (±)-validamine and its epimers were synthesized from the DA adduct in short steps.[8]

Since Tamiflu is also structurally related to aminocyclitols, we planed its short and efficient synthesis. Considering the known synthetic pathway, Corey's synthesis seemed to be superior because no expensive starting material and no hard-to-deal-with azide reagent were needed,[3] and if the steps could be reduced, the process would be much more attractive as a practical production method. In the Corey's synthesis, the intermediate **2a** has a simple C7N structure (see Figure 1), and thus we chose it as a primary target of our synthesis

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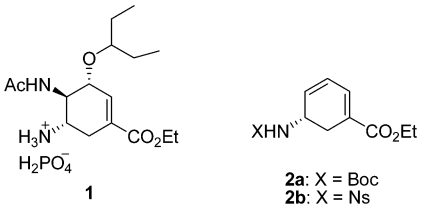


Figure 1. Tamiflu **1** and Corey's intermediate **2a**.

using the DA adduct **4b** as the starting material. Here, we report a short and efficient synthesis of (±)-**2a** and its equivalent (±)-**2b**.

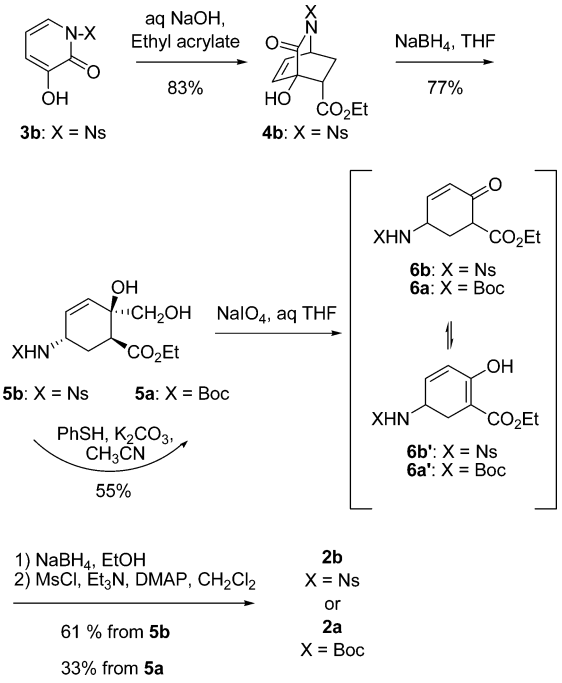
The starting material **4b** was prepared by the base-catalyzed DA reaction of **3b** and ethyl acrylate in good yield.[9] Chemoselective reduction of the lactam carbonyl group was achieved by $NaBH_4$ in THF to give diol **5b**. After oxidative cleavage of the 1,2-diol moiety, the corresponding ketone was obtained as a relatively unstable mixture of two diastereomers and one enol tautomer (**6b** and **6b′**). Reduction of the mixture using $NaBH_4$ followed by elimination of the resulting alcohol by mesylation gave **2b** that has the same array of functional groups as does Corey's intermediate (**2a**).[3]

Changing the protective group from Ns (2-nitrobenzenesulfonyl) to Boc was nicely accomplished by mild deprotection using thioglycolic acid and K_2CO_3[10] followed by a Boc protection in aqueous solution,[11] and the formation of **2a** was established by ^{1}H NMR. Unfortunately, purification of **2a** was difficult due to a contamination of side products of the deprotection.

An alternative synthetic pathway for **2a** in pure form was next examined. The conversions of functional groups were essentially the same as those of the above-mentioned synthetic route, and the only change was deprotection of the Ns group and introduction of Boc protective group at the earlier stage of the synthesis (**4b** → **5b** → **5a**). After obtaining the Boc-protected compound **5a**, oxidative cleavage and subsequent reduction−elimination were again successfully accomplished to give pure **2a**.

As shown in Scheme 1, the DA adduct **4b** was easily obtained from an aqueous "green" DA reaction that was possible to scale-up until multigram quantity without significant loss of the yield. All the subsequent processes for **2b** were only four steps that required regular reactions using inexpensive reagents and easy operations. Availability of the appropriate starting material and ease of the synthetic steps

Scheme 1. Synthesis of Tamiflu Intermediates



are important factors for industrial preparations, and thus the synthesis described here could be considered as a practical method.

Although the resulting products in this synthesis were all racemate, asymmetric synthesis of **4b** has been currently investigated in our group. Until now, we have already reported the asymmetric DA reaction of 3-hydroxy-2-pyrone and acrylates having chiral auxiliaries[12] in the presence of cinchona alkaloids as chiral catalysts. Considering the structural similarity of the substrates and products, this approach would be promising to give an optically active compound related to **4b**[13] that will provide efficient asymmetric synthesis Tamiflu **1** and its related compounds.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds shown in Scheme 1. This material is available via the Internet at http://pubs.acs.org.

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(9) The details of the base-catalyzed DA reaction of **3b** are mentioned in the Supporting Information.

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(13) As a preliminary examination, we found that the asymmetric DA reaction of **3a** and chiral acrylate derivative gave optically active product up to 91% de. Further optimization of the reaction conditions is currently being investigated.