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A Short Enantioselective Pathway for the Synthesis of the Anti-Influenza Neuramidase Inhibitor Oseltamivir from 1,3-Butadiene and Acrylic Acid

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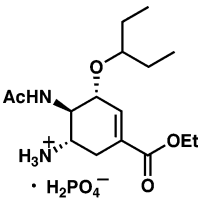
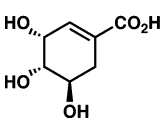
The recent emergence of the avian virus H5N1 raises the possibility of a pandemic wave of life-threatening flu that requires prompt action.[1] A four-pronged effort to avert widespread disease is now underway that consists of the following components: (1) worldwide surveillance of both wild and domesticated birds with quick culling of the latter, (2) development of recombinant vaccines against the H5N1 virus and its mutated forms whose production can be scaled up rapidly,[2] (3) procedures for quarantine, and (4) ramped up production of the orally effective, synthetic neuramidase inhibitor oseltamivir phosphate (Tamiflu) (**1**).[3] This paper describes a total synthesis of **1** that would appear to have a number of advantages over existing processes and the potential to increase the rate of production.

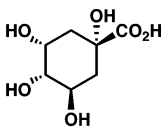
Heroic efforts by synthetic chemists at Gilead Sciences, Inc.[4] and F. Hoffman−La Roche, Ltd.[5] have resulted in the development of several synthetic pathways to **1**, culminating in the current production method.[5] That process falls short of the ideal for several reasons: (1) the starting point in the synthesis is either (−)-shikimic or (−)-quinic acid, which are complex relatively expensive and of limited availability, and (2) two steps involve potentially hazardous and explosive azide-containing intermediates. The route described herein has been used for the synthesis of oseltamivir and also its enantiomer.



1



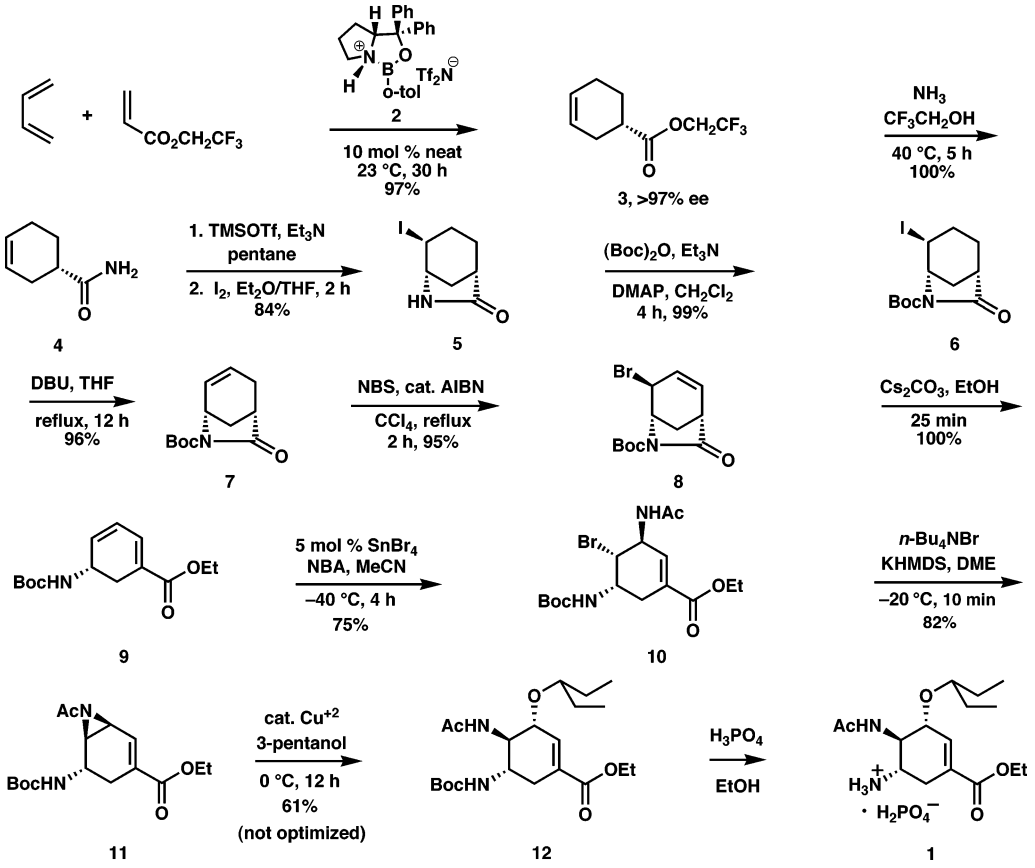
(−)-shikimic acid



(−)-quinic acid

The synthesis of **1** is summarized in Scheme 1. We have previously described the reaction of butadiene with trifluoroethyl

Scheme 1



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acrylate in the presence of the *S*-proline-derived catalyst *ent*-**2** to form the adduct *ent*-**3**.[6] Because we had a large supply of the *S*-catalyst **2**, the *R*-adduct *ent*-**3**, and racemic **3**, these were used in developing the experimental conditions for the synthetic route. These procedures were then applied to the enantioselective synthesis of **1**.[7] The initial Diels−Alder step is easily carried out at room temperature on a multigram scale in excellent yield (97%) and with >97% ee; recovery of the chiral ligand corresponding to **2** is simple and efficient. Ammonolysis of **3** produced amide **4** quantitatively. Iodolactamization of **4** using the Knapp protocol[8] generated lactam **5**, which was transformed by N-acylation with *tert*-butylpyrocarbonate into the *tert*-butoxycarbonyl (Boc) derivative **6** in very high yield. Dehydroiodination of **6** occurred cleanly with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) to give **7**, which was allylically brominated using *N*-bromosuccinimide to generate **8** very efficiently. The structure of (±)-**8** was confirmed by single-crystal X-ray diffraction analysis (see Supporting Information). Treatment of **8** with cesium carbonate in ethanol afforded the diene ethyl ester **9** quantitatively.

The next step in the synthetic sequence was a novel $SnBr_4$-catalyzed bromoacetamidation reaction which was completely regio- and stereoselective using *N*-bromoacetamide (NBA) in CH_3CN at −40 °C that converted the diene **9** to the bromodiamide **10**, the structure of which was verified by single-crystal X-ray diffraction analysis (of the racemic methyl ester). We surmise that this interesting process involves the transfer of Br^+ from an $SnBr_4$−NBA complex to the γ,δ-bond of the diene ester **9** followed by nucleophilic attack on the intermediate bromonium ion. Other applications of this useful process will be described in a separate publication. Cyclization of **10** to the *N*-acetylaziridine was rapid and efficient using in situ generated tetra-*n*-butylammonium hexamethyldisilazane and provided the bicyclic product **11**. Reaction of **11** in 3-pentanol solution containing a catalytic amount of cupric triflate at 0 °C occurred regioselectively to generate the ether **12**,[9] identical by NMR, IR, TLC, and mp with an authentic sample.[5] Finally, removal of the Boc group and salt formation with phosphoric acid in ethanol afforded **1**·H_3PO_4 (Tamiflu).

This research is continuing to increase the yields for steps **9** → **10** → **11** → **12**. It is our hope that the process described herein will be of value in improving the supply of oseltamivir and in reducing the cost. With regard to the latter, the process described herein is in the (unpatented) public domain.

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Supporting Information Available: Experimental conditions and characterization data for the transformations and compounds shown in Scheme 1. X-ray crystallographic data for (±)-**8** and the methyl ester of (±)-**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Catalyst **2**, its enantiomer, and the (*S*)- and (*R*)-amino alcohol precursors are available from Sigma Aldrich Co.

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(9) The yield for the transformation **11** → **12** has not been optimized, with regard to catalyst and temperature.

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