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Highly Efficient Synthesis of (-)-Shikimic Acid from a Chiral Diels-Alder Adduct between Furan and Acrylate†

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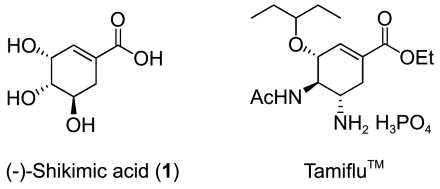
Tamiflu, a neuraminidase inhibitor, is an antiviral medication used to treat influenza virus in patients who have had symptoms for less than 2 days. The current key starting material for the production of Tamiflu is (-)-shikimic acid (**1**).[1] However, limited availability of **1** from natural Chinese star anise has led to the development of synthetic pathways to increase the supply of shikimic acid.[2] Besides its industrial uses, (-)-shikimic acid is a pivotal intermediate in the biogenetic synthesis pathway of a variety of aromatic natural products in microorganisms and plants known as the shikimate pathway.[3]

In 1983, Masamune and co-workers achieved the first enantiospecific synthesis of (-)-shikimic acid[4] based on the asymmetric Diels-Alder reaction. Since then, substantial synthetic activity has been directed toward (-)-shikimic acid.[5] In 2000, Ogasawara and co-workers reported the synthesis of (-)-shikimic acid from lipase-resolved tricyclic alcohols employing a palladium mediated elimination reaction as the key step.[6] Furthermore, an efficient synthesis of (-)-shikimic acid from D-ribose was accomplished by Vankar *et al*. in 2009.[7]

In conjunction with our interest in enantioselective Diels-Alder reactions with furans, we have found that the Diels-Alder reaction of furans with cationic chiral oxazaborolidinium catalyst **2** provides 7-oxabicyclo[2.2.1]hept-5-enes with high endo-selectivity and excellent enantioselectivity (Scheme 1).[8] In this paper, we report a method of efficient asymmetric synthesis of (-)-shikimic acid (**1**) from a chiral Diels-Alder adduct **3** between furan and acrylate.

Chiral oxazaborolidinium salts (**2**; Scheme 1) work as powerful Lewis acids and have proven to be effective catalysts for various enantioselective Diels-Alder,[9] cyanosilylation[10a,b], Michael addition[10c], 1,3-dipolar cycloaddition,[11a] three component coupling[11b] and Mukayama aldol[11c] reactions.



(-)-Shikimic acid (**1**) Tamiflu™

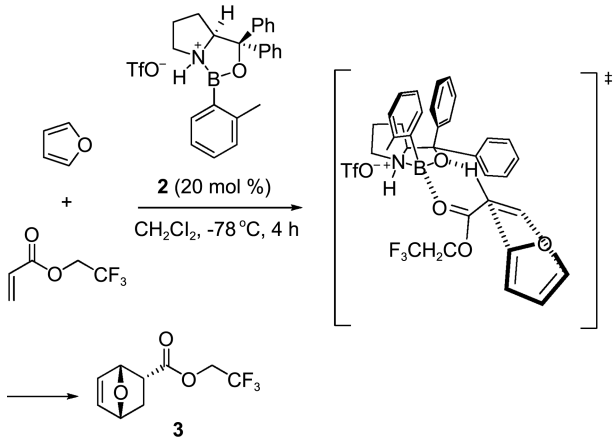
Figure 1. Structure of (-)-Shikimic acid (**1**) and Tamiflu.

With the readily available catalyst **2**, the Diels-Alder reaction of furan and 2,2,2-trifluoroethyl acrylate at −78 °C provided chiral adduct **3** in 95% yield with a high endo/exo ratio (91/9) and in more than 99% ee[12] (endo).

After chromatographic separation of the exo isomer, enantiomerically pure endo **3** was subjected to furan ring-opening with various bases. However, ring opened alcohol **5a** was obtained in very low yield (Scheme 2). Conversion of the 2,2,2-trifluoroethyl ester to an ethyl ester with weakly basic ethanolic solvent followed by ring-opening with LiHMDS gave enantiomerically enriched diene **5b** in 75% overall yield from **3**.

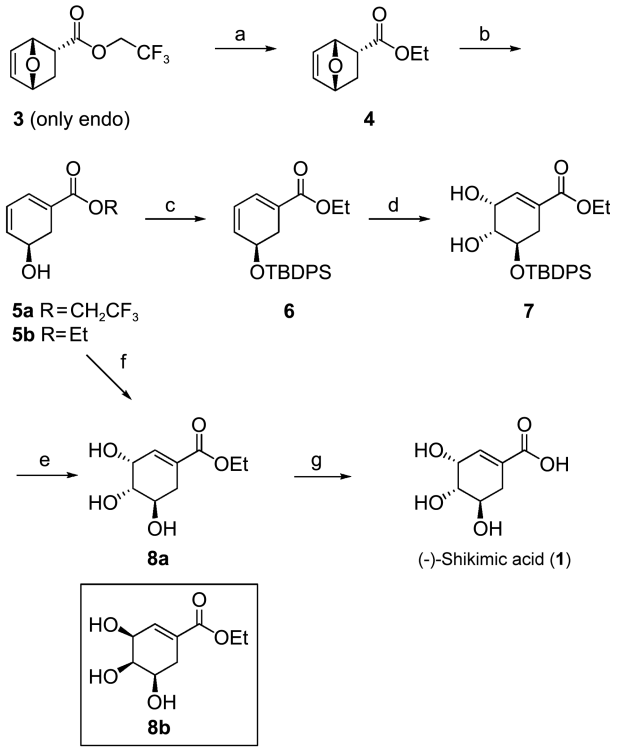
To introduce the diol with the correct stereochemistry, the free hydroxyl group in **5b** was protected with a bulky TBDPS group to afford **6** in 88% yield. Catalytic dihydroxylation of **6** provided the desired diol **7** in 80% yield with complete stereoselectivity.[13] Desilylation of **7** afforded ethyl shikimate (**8a**) in 90% yield. Additionally, treatment of allylic alcohol **5b** with osmium tetroxide afforded triol **8** in 70% yield with good stereoselectivity (**8a**/**8b**=7/1).

Finally, saponification of **8a** following a reported procedure furnished (-)-shikimic acid (**1**) in 97% yield. Identity



Scheme 1. Highly enantioselective Diels-Alder reaction catalyzed by oxazaborolidinium salt **2**.

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.



Scheme 2. Reagents and conditions (a) K_2CO_3, EtOH, 0 °C, 2 h (99%); (b) LiHMDS, THF −78 °C, 3 h (76%); (c) TBDPSCl, $^{i}Pr_2NEt$, DMAP, CH_2Cl_2, 0 °C, 18 h (88%); (d) OsO_4 (5 mol %), NMO, THF/H_2O=2/1, 0 °C, 4.5 h (80%); (e) TBAF, THF, 0 °C, 3.5 h (90%); (f) OsO_4 (5 mol %), NMO, THF/H_2O=2/1, 0 °C, 4.5 h (70%); (g) NaOH, THF/H_2O=1/1, rt, 5 h, then Amberlite IR-120 ion-exchange (plus) resin (97%).

of the synthetic material was fully established through comparisons of the ^{1}H- and ^{13}C-NMR spectra and specific rotations with literature data, $[\alpha]_D^{20} = 180.0$ (*c* 1.3, H_2O), (> 99% ee). [lit.[14] $[\alpha]_D^{20} = 179.7$ (*c* 4, H_2O)].

In summary, the total synthesis of (-)-shikimic acid was accomplished in 43.9% overall yield (*via* the TBDPS ether) or 42.5% overall yield (*via* the allylic alcohol) from commercially available furan and 2,2,2-trifluoroethyl acrylate.

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