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

Sung Ho Shin, Jae Hyun Han, Sung Il Lee, Young Baeck Ha,‡ and Do Hyun Ryu*†

Department of Chemistry, Sungkyunkwan University, Suwon 440-746, Korea. *E-mail: dhryu@skku.edu
‡Department of Graphic Arts Media, Shingu College, Seongnam 462-743, Korea

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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 acid4 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 cyanosilylation10b, Michael addition10c, 1,3-dipolar cycloaddition,11a three component coupling11b and Mukayama aldol11c reactions.

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 (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

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

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

Scheme 1. Highly enantioselective Diels-Alder reaction catalyzed by oxazaborolidinium salt 2.
Scheme 2. Reagents and conditions (a) K$_2$CO$_3$, EtOH, 0 °C, 2 h (99%); (b) LiHMDS, THF –78 °C, 3 h (76%); (c) TBDPSCl, Pr$_2$NEt, DMAP, CH$_2$Cl$_2$, 0 °C, 18 h (88%); (d) OsO$_4$ (5 mol %), NMO, THF/H$_2$O=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$_2$O=2/1, 0 °C, 4.5 h (70%); (g) NaOH, THF/H$_2$O=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, [α]$_D^{20}$ = 180.0 (c 1.3, H$_2$O), (–99% ee). [lit.14 [α]$_D^{20}$ = 179.7 (c 4, H$_2$O)].

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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References
12. The enantioselectivity was determined after hydrogenation with H$_2$ in the presence of 10% Pd/C and GC analysis.
13. Other protecting groups such as TBS or Bz groups provided lower regioselectivities compared to TBDPS group.