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An Enantioconvergent Route to (−)-Shikimic Acid via a Palladium-Mediated Elimination Reaction

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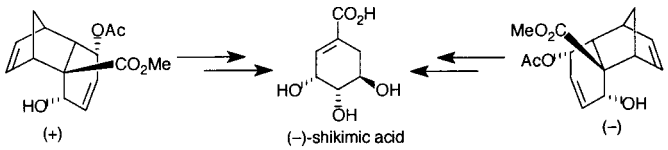
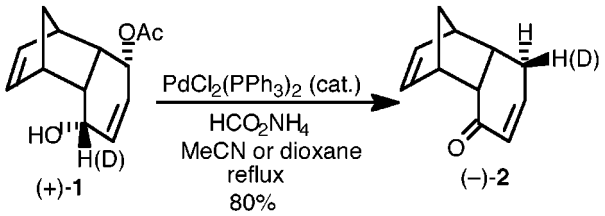
ABSTRACT



(−)-Shikimic acid, the key intermediate in the shikimate pathway in plants and microorganisms, has been synthesized in an enantioconvergent manner from both enantiomeric starting materials by employing a palladium-mediated elimination reaction as the key step.

We found[1] a novel palladium-mediated reaction to convert the *cis*-1,4-enediol monoacetate (+)-**1** into the α,β-unsaturated ketone (−)-**2** by elimination of acetic acid involving a suprafacial 1,4-hydrogen shift, without losing its original chiral integrity (Scheme 1).

Scheme 1



Quite recently, we also found[2] that the tricyclic diol (±)-**3**, readily prepared[3] from methyl 2,5-dihydroxybenzoate, is resolved under lipase-mediated transesterification conditions to give the acetate (+)-**4** and the alcohol (+)-**3** in high enantiomeric purity (Scheme 2). In this paper we report a diastereoselective synthesis[4] of (−)-shikimic acid **5**, starting from either of the resolved products, (+)-**3** and (+)-**4** and by employing the palladium-mediated reaction above as the key step. (−)-Shikimic acid is the pivotal biogenetic precursor in the biosynthesis of a variety of aromatic natural products in the biogenetic pathway in plants and microorganisms known as the shikimate pathway.[5]

To acetylate the more hindered hydroxy functionality, the diol (+)-**3** (>97% ee) was first silylated at the less hindered site and then acetylated to give (+)-**6**, $[\alpha]_D^{29}$ +35.5 (*c* 0.97, $CHCl_3$), which was further desilylated to give the desired

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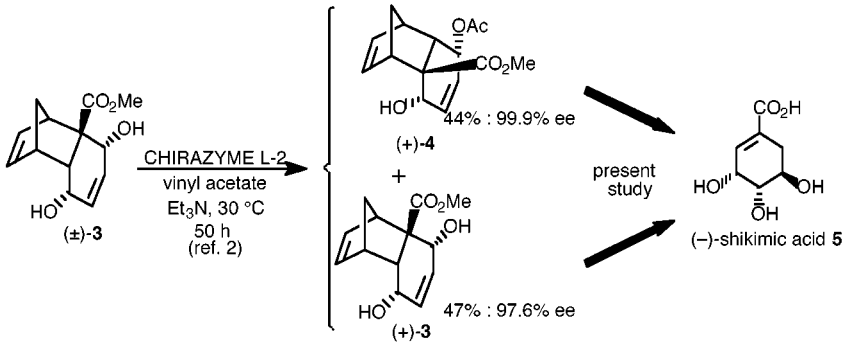
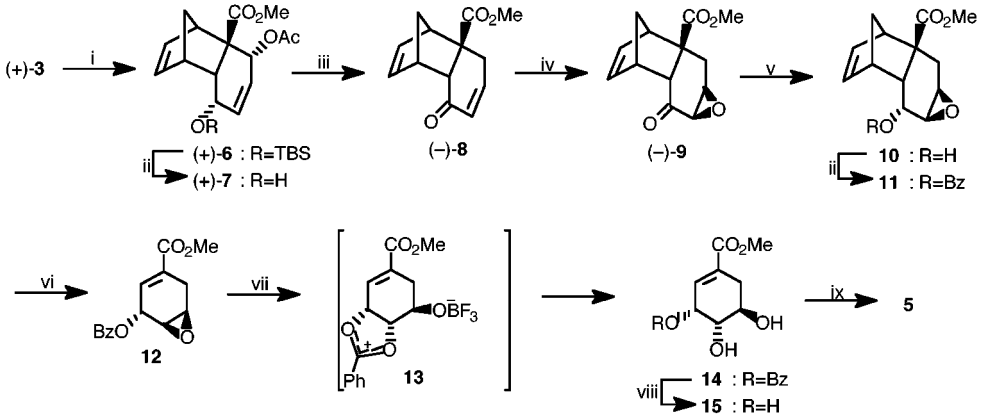
Scheme 2



Scheme 3[a]



[a] Reagents and conditions: i, (a) TBS−Cl, imidazole, DMF, 0 °C to room temperature; (b) AcCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C to room temperature. (81%). ii, TBAF, THF, room temperature (80%). iii, $PdCl_2(PPh_3)_2$ (cat.), HCO_2NH_4, MeCN, reflux, 30 min (79%). iv, 30% H_2O_2, Triton B, THF, 0 °C, 1 h, (75%). v, (a) $NaBH_4$, 0.5 N NaOH−MeOH (1:20 v/v), 0 °C; (b) BzCl, 40% NaOH, BuNCl, toluene, 5 °C, 50 min (59%). vi, diphenyl ether, 300 °C, 1 h (52%). vii, BF_3·OEt_2, toluene, room temperature (94%). viii, K_2CO_3, MeOH (72%). ix, KOH, THF (ref 4).

monoacetate (+)-**7**, $[\alpha]_D^{29}$ +58.3 (*c* 0.58, $CHCl_3$), in 65% overall yield. When (+)-**7** was refluxed with ammonium formate in acetonitrile in the presence of a catalytic amount of palladium(II) chloride bistriphenylphosphine (2 mol %)[1b,6] for 20 min, the single enone (−)-**8**, $[\alpha]_D^{29}$ −48.7 (*c* 2.6, $CHCl_3$), was obtained in 79% yield. Owing to the biased structure,[7] (−)-**8** afforded the *exo*-epoxide (−)-**9**, $[\alpha]_D^{29}$ −26.9 (*c* 2.0, $CHCl_3$), diastereoselectively, which allowed convex face-selective reduction of the ketone functionality to give the *endo*-alcohol **10**. Benzoylation of **10** followed by thermolysis of the resulting benzoate **11**, $[\alpha]_D^{29}$ −29.2 (*c* 1.4, $CHCl_3$), in diphenyl ether at 280 °C induced a retro-Diels−Alder reaction[7] to give the cyclohexenecarboxylate **12**, $[\alpha]_D^{30}$ −37.1 (*c* 4.7, $CHCl_3$). The overall yield of **12** from **8** was 23% in four steps.

On exposure to boron trifluoride etherate,[8,9] the epoxybenzoate **12** afforded, diastereoselectively, the monobenzoate **14**, $[\alpha]_D^{29}$ −159.1 (*c* 2.0, $CHCl_3$), which was treated with potassium carbonate in methanol to give methyl shikimate **15**, mp 115−116 °C, $[\alpha]_D^{30}$ −128.0 (*c* 0.1, EtOH) [lit.[4g,h] mp 116.5−117.5 °C, $[\alpha]_D^{29}$ −125.5 (*c* 0.9, EtOH)]. The overall yield of **15** from **12** was 67%. Diastereoselective generation of the monobenzoate **14** was presumed to be due to the neighboring effect of the benzoate functionality to form a transient oxonium intermediate **13**. Transformation of **15** into (−)-shikimic acid **5** has been done[4g,h] (Scheme 3).

In the other route, the acetate (+)-**4** (>99% ee) was first deacetylated to give the diol (−)-**3**, $[\alpha]_D^{29}$ −12.5 (*c* 0.2, $CHCl_3$), which was converted into (−)-**7**, $[\alpha]_D^{29}$ −58.2 (*c* 0.6, $CHCl_3$), via the TBS ether (+)-**6**, $[\alpha]_D^{29}$ −35.3 (*c* 1.0, $CHCl_3$), by employing the same procedure for the enantiomer (+)-**7**. Upon treatment with ammonium formate in acetonitrile in the presence of a catalytic amount of the palladium catalyst above (2 mol %), (−)-**7** afforded the enantiomeric enone (+)-**8**, $[\alpha]_D^{30}$ +49.1 (*c* 1.1, $CHCl_3$). This was then

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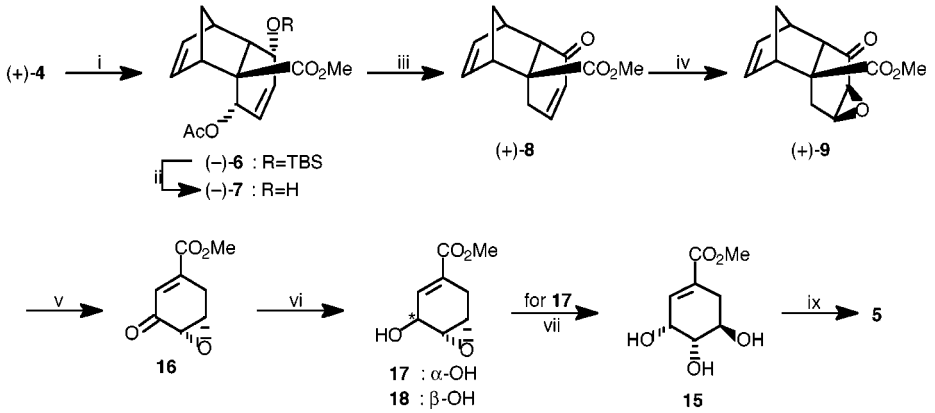
Scheme 4[a]



[a] Reagents and conditions: i, (a) MeOH, K_2CO_3, room temperature; (b) TBS−Cl, imidazole, DMF, 0 °C to room temperature; (c) AcCl, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C to room temperature (55%). ii, TBAF, THF, room temperature (89%). iii, $PdCl_2(PPh_3)_2$ (cat.), HCO_2NH_4, MeCN, reflux, 30 min (81%). iv, 30% H_2O_2, Triton B, THF, 0 °C, 1 h, (79%). v, diphenyl ether, 300 °C, 10 min (47%). vi, $NaBH_4$−$CeCl_3 \cdot 7H_2O$, MeOH, −78 °C (40% of **17** and 13% of **18**). vii, (a) 80% AcOH, reflux, 1 h; (b) NaOMe, MeOH (55%). viii, TPAP (cat.), NMO, 4A sieves, CH_2Cl_2 (82%). ix, KOH-THF (ref 4).

transformed diastereoselectively into the enantiomeric *exo*-epoxide (+)-**9**, $[\alpha]_D^{30}$ +26.8 (*c* 0.6, $CHCl_3$), on reaction with alkaline hydrogen peroxide. The overall yield of the epoxide (+)-**9** from the acetate (+)-**4** was 31% in six steps.

Retro-Diels−Alder reaction was carried out at this stage by heating (+)-**9** in diphenyl ether to give the cyclohexenone **16**, $[\alpha]_D^{30}$ +58.3 (*c* 0.1, $CHCl_3$), in 47% yield. Although diastereoselectivity was less than satisfactory, treatment of the enone with sodium borohydride and cerium(III) chloride[10] allowed chemoselective 1,2-reduction to afford a mixture of two isomeric products from which the desired α-alcohol **17**, mp 80−82 °C, $[\alpha]_D^{30}$ −54.8 (*c* 1.1, $CHCl_3$), having *all-cis* stereochemistry was obtained in 40% yield after separation of the undesired epimeric *β*-alcohol **18**, $[\alpha]_D^{30}$ +51.9 (*c* 0.1, $CHCl_3$), in 13% yield by silica gel column chromatography. The latter compound was reverted to the enone **16** by oxidation using tetrapropylammonium perruthenate[11] (TPAP) in the presence of *N*-methylmorphorine *N*-oxide (NMO) and recycled. An attempt to obtain the α-alcohol **17** from the *β*-alcohol **18** by Mitsunobu inversion as well as from (+)-**9** via a sequence involving the generation of *ent*-**10** followed by Mitsunobu inversion and retro-Diels−Alder reaction resulted in a formation of a complex mixture. The (−)-alcohol **17** has been obtained by Pawlak and Berchtold[12] by employing a different procedure and has been transformed into (−)-shikimic acid **5**. By following the reported procedure,[12] **17** was transformed diastereoselectively into methyl shikimate **15**, mp 116−117 °C, $[\alpha]_D^{30}$ −129.0 (*c* 0.1, EtOH), in 55% yield by refluxing with acetic acid, followed by alkaline methanolysis (Scheme 4).

Thus, an enantioconvergent synthesis of (−)-shikimic acid **5** has been established by employing the palladium-mediated elimination reaction we found as the key step. The enantioconvergency and stereoselectivity demonstrated are all due to the biased framework and the thermal instability of the tricyclic substrate that we used in the present study.

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