A New Stereocontrolled Route to (–)-Shikimic Acid

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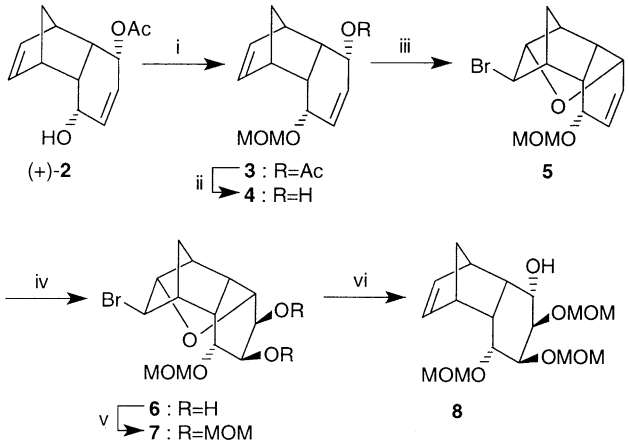
A new stereocontrolled route to (–)-shikimic acid, the component of the fruit of shikimi tree, *Illicium religiosum*, and the key biogenetic precursor of a variety of aromatic natural products, has been developed using the chiral 2,5-cyclohexadienol synthon.

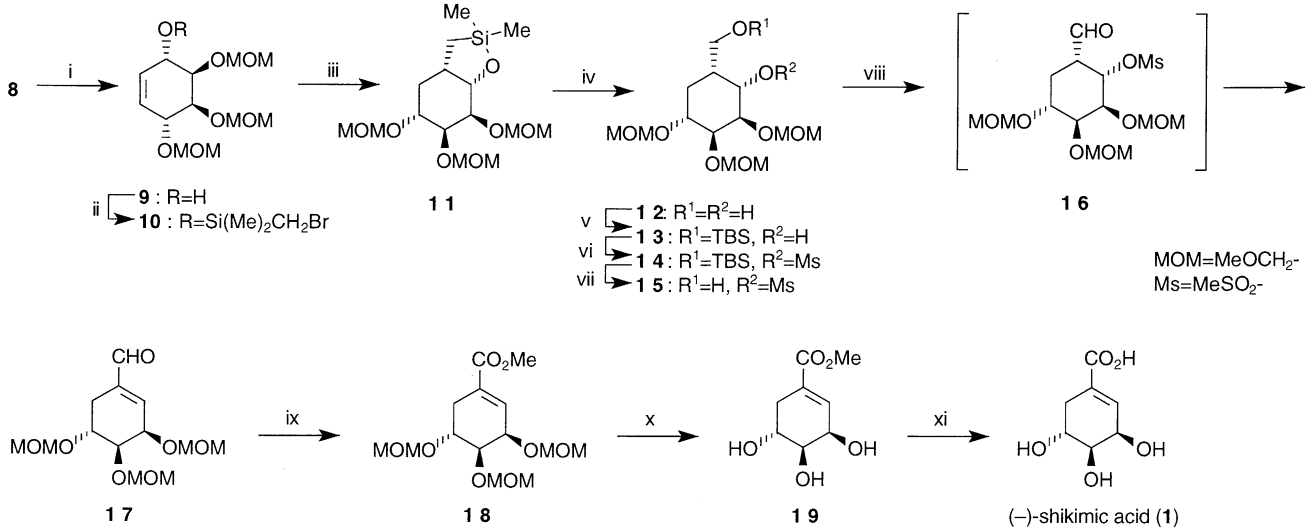
(–)-Shikimic acid (**1**), isolated from the fruit of shikimi tree, *Illicium religiosum*, in 1885[1] is known as the key biogenetic precursor of a variety of aromatic natural products though its biogenetic importance was not established until 1950s.[2,3] Since its first synthesis reported in 1960,[4] a number of approaches including chiral syntheses have been reported to date.[3,5] However, there were very limited procedures suitable for its facile stereo- and enantio-controlled construction. Because we have developed an efficient procedure for the preparation of a synthon[6] **2** serving as chiral 2,5-cyclohexadienol, either by enzymatic[7] or by catalytic[8] procedure, we were interested in using the chiral synthon **2** for the stereoselective construction of (–)-shikimic acid (**1**). We report here a new enantio- and stereo-controlled route to (–)-shikimic acid (**1**) using the synthon **2** as the starting material.

To discriminate two double bonds contained in the synthon **2**, the methoxymethyl (MOM) ether **4** generated from **2** was treated with *N*-bromosuccinimide to give the single bromo-ether[9] **5**. The remaining double bond in **5** was next dihydroxylated from the convex face to give stereoselectively the diol **6** which was transformed to the tri-MOM ether **7**. On reductive treatment, the bromo-ether **7** regenerated the olefin functionality to give **8**, $[\alpha]_D^{26}$ +22.7 (*c* 0.8, $CHCl_3$). Overall yield of **8** from (+)-**2** was 39% in six steps (Scheme 1).

Thermolysis of **8** in diphenyl ether at 260 °C smoothly caused retro-Diels-Alder reaction and gave the cyclohexenol **9**, $[\alpha]_D^{26}$ –10.1 (*c* 1.1, $CHCl_3$), in 86% yield after 30 min. Treatment of **9** with bromomethyldimethylsilyl chloride under basic conditions afforded the bromomethylsilyl ether[10,11] **10** which on treatment with tributylstannane in the presence of azobisisobutyronitrile (AIBN) furnished the single cyclic silyl



Scheme 1. *Reagents and conditions*: i) CH_3OCH_2Cl (MOM-Cl), $^iPr_2EtN$, CH_2Cl_2 (88%); ii) K_2CO_3, MeOH; iii) NBS, CH_2Cl_2 (67% from **3**); iv) OsO_4, *N*-methylmorpholine *N*-oxide (NMO), THF-H_2O (3:1 v/v) (86%); v) MOM-Cl, $^iPr_2EtN$, CH_2Cl_2 (97%); vi) Zn, EtOH-AcOH (10:1 v/v) (79%).



Scheme 2. *Reagents and conditions*: i) PhOPh, $NaHCO_3$, reflux (86%); ii) $ClSi(Me)_2CH_2Br$, Et_3N, DMAP, CH_2Cl_2, 0 °C; iii) Bu_3SnH, AIBN, benzene, 80 °C; iv) 30% H_2O_2, $KHCO_3$, MeOH-THF (1:1 v/v), reflux (89% from **9**); v) $ClSiMe_2{}^tBu$, imidazole, DMF (100%); vi) methanesulfonyl chloride, $^iPr_2EtN$, DMAP, CH_2Cl_2; vii) TBAF, THF (65% from **13**); viii) SO_3·Py, DMSO-Et_3N (3:1 v/v); ix) $NaClO_2$, NaH_2PO_4·$2H_2O$, 2-methyl-2-butene, ^tBuOH-H_2O (4:1 v/v), acid workup, then CH_2N_2, CH_2Cl_2 (77% from **15**); x) AcCl (cat.), MeOH (98%); xi) 1 M NaOH (aq.), THF-H_2O (1:1 v/v) (96%).

ether **11** by radical process.[10-12] Oxidation of **11** with hydrogen peroxide in the presence of potassium hydrogen carbonate[13] gave the diol **12**, $[\alpha]_D^{26}$ +45.8 (*c* 1.1, $CHCl_3$), in 89% overall from **9**.

Having introduced the requisite carbon framework, primary hydroxy group of **12** was selectively silylated to give the *tert*-butyldimethylsilyl (TBS) ether **13**, $[\alpha]_D^{27}$ +38.6 (*c* 1.3, $CHCl_3$), which was sequentially *O*-mesylated and de-*O*-silylated to give the primary alcohol **15**, $[\alpha]_D^{28}$ +46.1 (*c* 0.6, $CHCl_3$), *via* **14**, in 65% overall yield. The primary alcohol **15** was then oxidized with sulfur trioxide-pyridine complex[14] to afford the α,β-unsaturated aldehyde **17** *via* the formyl-mesylate **16** by concomitant elimination under the conditions. Further oxidation of the aldehyde **17** with sodium chlorite in a phosphate buffer solution[15] followed by esterification of the oxidation product with diazomethane afforded the methyl shikimate tri-MOM ether (**18**), $[\alpha]_D^{27}$ −85.5 (*c* 1.6, $CHCl_3$), in 77% overall yield from **15**. Removal of the MOM groups of **18** gave methyl shikimate[16] (**19**), mp 116.5-117.5 °C, $[\alpha]_D^{29}$ −125.5 (*c* 0.9, EtOH) {lit.: mp 113-114 °C, $[\alpha]_D^{20}$ −130 (*c* 1.88, EtOH);[16a] mp 115-116.5 °C, $[\alpha]_D^{20}$ −125 (*c* 1.8, EtOH)[16b]}, in 98% yield. Finally, alkaline hydrolysis of **18** afforded (−)-shikimic acid[16b,17] (**1**), mp 184-186 °C, $[\alpha]_D^{25}$ −163.7 (*c* 0.59, H_2O) {lit.: mp 184-186 °C, $[\alpha]_D^{20}$ −170 (*c* 0.86, H_2O);[16b] mp 183-184.5 °C, $[\alpha]_D^{21}$ −170 (*c* 1.18, H_2O)[17]}, in 96% yield after purification by ion-exchange resin. Total yield of (−)-shikimic acid (**1**) from the synthon **2** was 14% in 17 steps (Scheme 2).

In summary, the present study illustrates a new utility of the chiral synthon **2** for the construction of (−)-shikimic acid (**1**) and the procedure employed may be in particular useful for the preparation of labeled materials for biogenetic experiments.

References and Notes

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