# Synthesis of (+)- and (−)-Methyl Shikimate from Benzene

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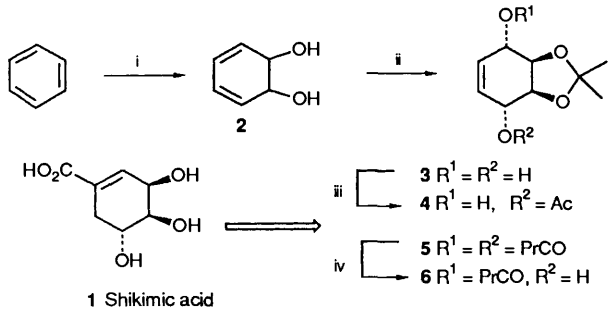
*cis*-Cyclohexa-3,5-diene-1,2-diol **2**, the product of oxidation of benzene by mutants of *Pseudomonas putida*, was transformed into optically pure **4** in a sequence involving asymmetrization of *meso*-diol **3** in organic media with *Pseudomonas cepacia* lipase. Alcohol **4** was converted into the title compounds by processes utilizing α-iodination of the derived enones **8** and **9** followed by $Pd^0$-catalysed coupling of the α-iodoenones with 2-tributylstannylfuran and $RuO_4$-catalysed oxidation of the 2-furyl groups to carboxylic acids.

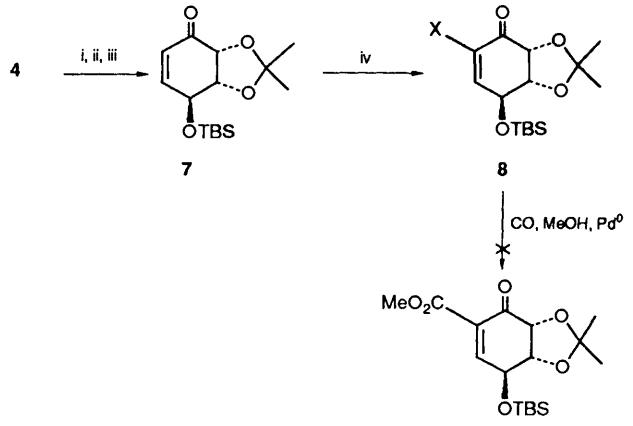
(−)-Shikimic acid **1** is a biosynthetic precursor responsible for the 'benzene' moiety of aromatic amino acids.[1] In this paper we describe the synthesis of (+)- and (−)-shikimic acid by a pathway that, amusingly, could be viewed as 'contra-biosynthetic' in that the starting point is benzene. Benzene is oxidized by mutants of the microorganism *Pseudomonas putita* to the diol **2**;[2] this diol was converted into *meso*-diol **3** which has been asymmetrized to mono-acetate **4** utilizing *Pseudomonas cepacia* lipase in isopropenyl acetate[3] (Scheme 1). During the course of our investigation a synthesis of unnatural (+)-shikimic acid from **6**, obtained by lipase-catalysed hydrolysis of **5** was reported by the Vandewalle group.[4,5] Their route involved reduction of the double bond of **6**, dehydration, epoxidation and nucleophilic opening of the epoxide with dithiane.[4b]




**Scheme 1** *Reagents and conditions:* i, *Pseudomonas putida*[2]; ii, see refs. 3 and 4; iii, *Pseudomonas cepacia* lipase, isopropenyl acetate[3]; iv, recombinant cutinase from *Fusarium solani pisi*[4a]

Our initial plan for the synthesis involved the chemistry illustrated in Scheme 2. In our hands the key carbonylation[6] of α-bromoenone **8** (X = Br) failed. We reasoned that a more reactive α-iodoenone might serve our needs and this was the impetus for our recent development of a general procedure for the production of this little studied class of enones.[7] Much to our disappointment, with the iodo compound **8** (X = I), in the presence of CO, MeOH and $Pd^0$ only phenolic products were obtained. As an alternative we choose to explore the use of the 2-furyl group as a carboxylate surrogate.[8] The syntheses of both enantiomers of methyl shikimate based on this strategy are detailed below.

The enone **9** was prepared by the PCC oxidation[9] of the allylic alcohol **4** (Scheme 3). Treatment of the enone **9** with iodine in carbon tetrachloride–pyridine furnished the α-iodoenone **10** in 80% yield. Furan **11** was isolated in quantitative yield when the α-iodoenone **10** and 2-tributylstannylfuran were coupled under Stille conditions;[10] the reaction was complete within 1 min of the reagents being mixed at room temperature. Attempts to conjugatively reduce the enone **11** under a variety of literature procedures failed; starting material was isolated or extensive decomposition was observed. The enone **11**, when subjected to the Luche reduction conditions,[11] furnished a mixture of the readily separable

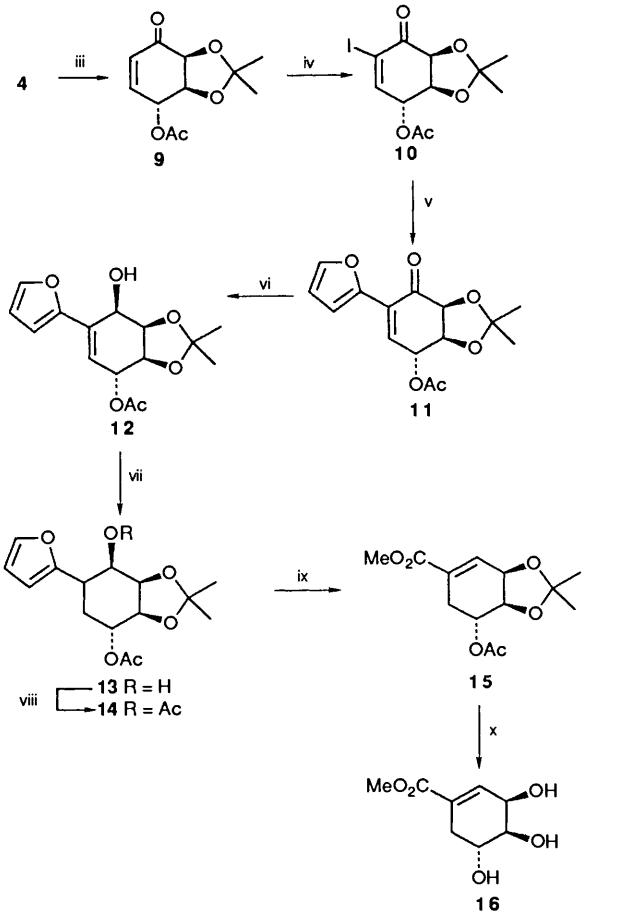



**Scheme 2** *Reagents and conditions:* i, *tert*-butyldimethylsilyl chloride (TBSCl), imidazole, DMF; ii, $K_2CO_3$–MeOH; iii, pyridinium chlorochromate (PCC)–$CH_2Cl_2$–molecular sieves[9]; iv, X = I, $I_2$–pyridine–$CCl_4$[7]

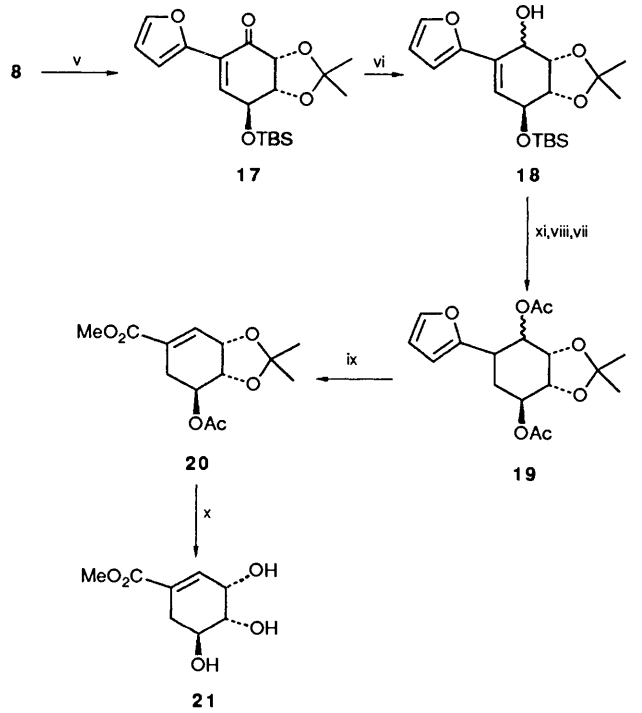
epimeric allylic alcohols (6:1 ratio, 88%). The major isomer **12** was determined by NMR experiments to be that which possessed the β-hydroxy configuration ($J_{3a\alpha\text{-H},4\alpha\text{-H}}$ 3.6 Hz). The tri-substituted olefinic bond of **12** was hydrogenated in 83% yield to produce the alcohol **13** as a single diastereoisomer. The relative stereochemistry of **13**, although predicted to be that from hydrogenation from the lesser hindered α-face of the molecule, was not determined. Acylation of the alcohol **13** was accomplished under standard conditions to produce the diacetate **14** in 88% yield. Oxidation of the furan group of **14** with ruthenium tetroxide,[12] followed by esterification of the crude acid with diazomethane and elimination of the acetate furnished the α,β-unsaturated ester **15** {$[\alpha]_D^{25}$ −54.0 (*c* 0.26, $CHCl_3$)} in 69% yield. Concomitant deprotection of the three hydroxy groups was accomplished by treatment of **15** with toluene-*p*-sulfonic acid in boiling methanol to deliver (−)-methyl shikimate **16** (89% yield), {$[\alpha]_D^{25}$ −126.4 (*c* 0.25, EtOH); lit.,[5b] $[\alpha]_D^{25}$ −128 (*c* 1.79, EtOH)}.

The unnatural (+)-methyl shikimate was prepared by the route outlined in Scheme 4. Furan **17** was prepared from iodoenone **8** in 93% yield. Luche reduction of this compound afforded a 1:1 mixture of the epimeric alcohols (87% yield). Exposure of the alcohols **18** to palladium on carbon under a hydrogen atmosphere over 24 h led to quantitative recovery of the starting material. The sterically demanding *tert*-butyldimethylsilyl group was removed and the crude diol mixture was diacetylated in 85% overall yield. Hydrogenation of the diacetate mixture was complete in 15 min to deliver the diastereoisomeric mixture **19** which was purified by filtration through silica (97% yield). Oxidation, esterification, and elimination in the manner previously described for the enantiomer furnished the α,β-unsaturated ester **20** (88% yield), {$[\alpha]_D^{25}$ −59.8 (*c* 1.4, $CHCl_3$)}. The acetate and acetonide

protecting groups were removed in acidic methanol to provide (+)-methyl shikimate **21** {$[\alpha]_D^{25}$ +131.0 (*c* 0.21, EtOH); lit.,[4b] $[\alpha]_D^{25}$ +131.2 (*c* 0.8, EtOH)}.




**Scheme 3** *Reagents and conditions:* see Scheme 2; v, 2-tributylstannylfuran–Pd(PhCN)$_2$Cl$_2$–CuI, $Ph_3As$–*N*-methylpyrrolidone[10]; vi, $CeCl_3$–$NaBH_4$–MeOH, −78 °C[11]; vii, $H_2$ (1 atm)–Pd on C–EtOH; viii, $Ac_2O$–4-dimethylaminopyridine–$Et_3N$/$CH_2Cl_2$; ix, (*a*) $RuO_2$·$H_2O$–$NaIO_4$–$CCl_4$–$H_2O$–$CH_3CN$[12]; (*b*) $CH_2N_2$–$Et_2O$; (*c*) DBU–$CH_2Cl_2$, 20 °C, 12 h; x, TsOH–MeOH, reflux




**Scheme 4** *Reagents and conditions:* see Scheme 3; xi, tetrabutylammonium fluoride–THF, 25 °C, 24 h

## Experimental

(−)-7-*Acetoxy*-5-(2-*furyl*)-3a$\alpha$,4,7$\alpha$,7a$\alpha$-*tetrahydro*-2,2-*dimethyl*-1,3-*benzodioxol*-4-*one* **11**.—The iodoenone **10** (0.547 g, 1.63 mmol) was dissolved in *N*-methylpyrrolidone (5 cm$^3$) and the flask was charged with bis(benzonitrile)palladium(II) chloride (5 mol%, 36 mg), copper(I) iodide (36 mg, 0.16 mmol) and triphenylarsine (50 mg, 0.16 mmol). To the stirred solution was added 2-tributylstannylfuran (0.641 g, 1.79 mmol) *via* dropwise addition. When the addition was complete the suspension was diluted with ethyl acetate (20 cm$^3$). The organic layer was washed sequentially with 20% aqueous potassium fluoride (10 cm$^3$) and 20% aqueous ammonium hydroxide (3 × 10 cm$^3$). The combined aqueous layers were extracted with ethyl acetate (3 × 10 cm$^3$) and then the combined organic layers were washed with brine (50 cm$^3$) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica (5–10% ethyl acetate–light petroleum) to give ketone **11** (499 mg, 100%) as a viscous yellow oil; $[\alpha]_D^{25}$ −99.7 (*c* 0.18, $CHCl_3$); $\delta_C$($CDCl_3$) 190.6, 169.3, 146.4, 142.6, 133.2, 129.2, 112.1, 111.5, 110.3, 75.6, 74.7, 67.0, 26.7, 25.23 and 20.3 (Calc. for $C_{15}H_{16}O_6$ *M*, 292.0948. Found $M^+$, 292.0948).

(−)-*Methyl* 7-*Acetoxy*-3a$\alpha$,6,7$\alpha$,7a$\alpha$-*tetrahydro*-2,2-*dimethyl*-1,3-*benzodioxole*-5-*carboxylate* **15**.—Oxidation of diacetate **14** {m.p. 106 °C, $[\alpha]_D^{25}$ +10.0 (*c* 0.56, $CHCl_3$)} under Sharpless conditions,[12] esterification with diazomethane and elimination of acetic acid by exposure to diazobicycloundecene (DBU) in dichloromethane at 20 °C provided the protected shikimic acid derivative **15**; $[\alpha]_D^{25}$ −54.0 (*c* 0.26, $CHCl_3$); $\delta_C$($CDCl_3$) 170.1, 166.3, 134.1, 129.4, 109.9, 73.8, 71.8, 69.8, 52.0, 27.7, 26.3, 25.9 and 21.0.

## Acknowledgements

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