

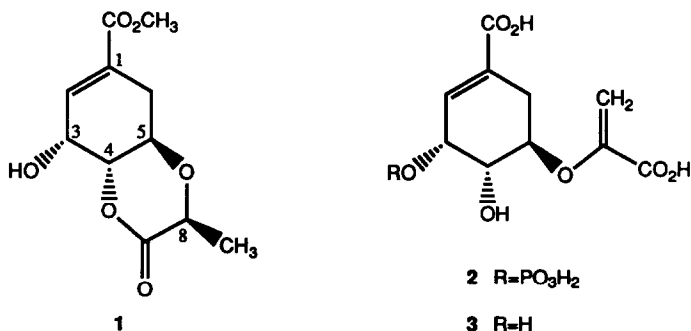
ENANTIOSELECTIVE SYNTHESIS OF (-)-METHYL 5-LACTYLSHIKIMATE LACTONE

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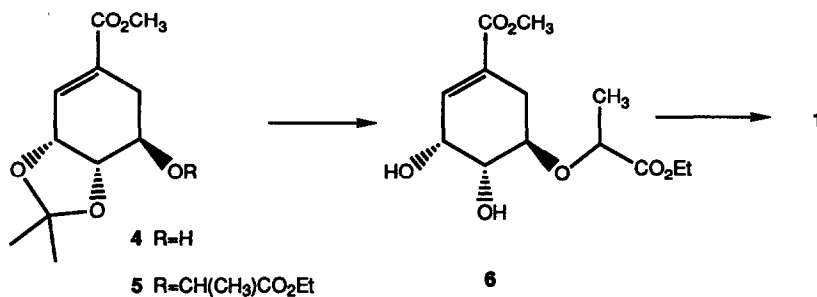
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Abstract -- A short synthesis of enantiomerically pure (-)-methyl 5-lactylshikimate lactone **1** from (-)-shikimic acid is described, which, along with NOE measurements, establishes its absolute stereostructure.

In the course of identifying and screening new fungal metabolites for biological activity, Isogai *et al.* recently reported a new shikimate-derived metabolite **1** isolated from *Penicillium* sp. K-114.¹ The structure of lactone **1** is noteworthy for several reasons. It represents the first lactone (and first O-lactyl derivative) isolated in the shikimate/chorismate pathway.^{2,3} Its biosynthesis is also intriguing, since **1** might originate along the main stem of the pathway from 5-enolpyruvylshikimate-3-phosphate **2** or from the dead-end metabolite 5-enolpyruvylshikimic acid **3** (Compound Z-1).⁴ In either case, reduction of the enolpyruvyl double bond is required as in the formation of UDP-N-acetylmuramic acid, an intermediate in bacterial cell wall peptidoglycan synthesis.⁵ Here we disclose a short, enantioselective synthesis of **1** confirming its absolute stereostructure as shown. The lactyl ether appendage is attached by a diazo coupling reaction whose mild conditions are compatible with both acid-sensitive and electrophilic groups.



Treating the known acetonide **4** of methyl shikimate⁶ with ethyl diazopropionate (5 equiv, catalytic HBF₄, CH₂Cl₂, 0°C) gave diester **5** in 25% yield as a mixture of C-8 diastereomers.⁷ Since the direct conversion of **5** to **1** failed using various solvent/acid combinations, the acetonide protecting group in **5** was first hydrolyzed (4:1 HOAc:H₂O, 75°C, 6 h) to afford **6** (83%). When both diastereomers of **6** were suspended in dry benzene and boiled for 10 h with a catalytic amount of pyridinium *p*-toluenesulfonate,⁸ lactonization and C-8 equilibration led to methyl 5-lactylshikimate lactone **1** which was obtained as a single isomer after flash chromatography: (68%, mp 128-129°C, lit¹ mp 133-135°C). Spectral, analytical and chiroptical data for synthetic **1** matched values reported for the natural product. Moreover a nuclear Overhauser effect (5%) between H5 and H8 confirmed the equatorial C8-methyl in **1** and established the overall 3R,4R,5R,8S-configuration.⁹



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