

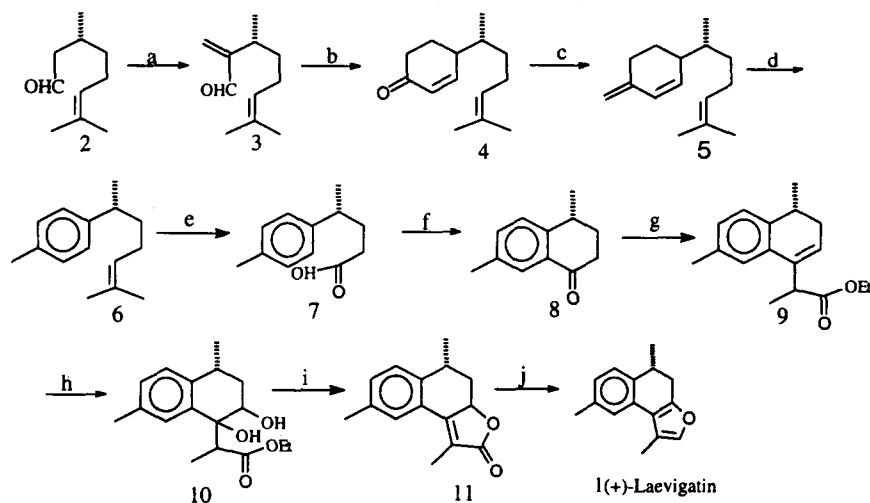
Enantiospecific total synthesis of (+)-laevigatin

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Abstract: The first enantiospecific, total synthesis of (+)-laevigatin from (+)-citronellal is described. © 1997 Published by Elsevier Science Ltd

Laevigatin **1**, a naturally occurring terpene having an unusual skeleton, was isolated in optically active form from *Eupatorium laevigatum*¹ So far there have been only two syntheses of (±)-**1** published,² but there has been no report of a synthesis of enantiomerically pure laevigatin. As a part of our interest in synthesis of Heritol, Heritonin and related compounds, two convenient and efficient methodologies to generate butenolides have been developed: (1) *via* osmylation of β,γ -unsaturated esters³ and (2) direct oxidative conversion of β,γ -unsaturated acids to butenolides mediated by CAN at room temperature.⁴ Earlier^{2c} based on this strategy we have synthesized (±)-**1**.



a: HCHO, Piperidine acetate, reflux; b: Methylacetoacetate, MeOH, MeONa, reflux; c: (Ph)₃PCH₂I, BuLi, THF, 0°C
 d: Sulfur, DMF, reflux; e: OsO₄ (cat), Jones reagent, R.T.; f: TFA, TFAA, 0°C; g: ethylbromopropionate, Zn, H⁺
 h: OsO₄, NMO, CH₃CN; i: TsOH, C₆H₆, reflux; j: DIBAL-H, THF, -40°C

We now wish to report the first enantiospecific synthesis of (+)-**1**, using the above protocol for the synthesis of the butenolide and its conversion into naturally occurring laevigatin. The key intermediate, optically active tetralone **8** was obtained from commercially readily available citronellal **2**. (+)-Citronellal **2** was converted to enone **4** following a reported procedure.⁵ Wittig methylenation⁶ of **4** gave triene **5** in good yield (80%). The aromatization⁷ of **5** was achieved by refluxing it in DMF in the presence of sulfur to furnish the aromatic compound **6** in 70% yield. One pot oxidative cleavage of the double bond⁸ *via* the corresponding diol to acid **7** was achieved in 84% yield. Cyclisation of acid **7** by trifluoroacetic anhydride⁹ furnished enantiomerically pure tetralone **8** (80%).

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Having achieved the synthesis of chiral tetralone, the next task was the straightforward transformation of **8** to butenolide **11** by the protocol developed in this laboratory and its further conversion to (+)-laevigatin **1**. Accordingly, the Reformatsky reaction³ on tetralone **8** afforded the β,γ -unsaturated ester **9** in 78% yield. Dihydroxylation of **9** furnished the corresponding diol **10** as a mixture of diastereoisomers in 80% yield. Since the stereochemistry at the newly created centres was of no consequence as far the synthesis of (+)-laevigatin is concerned as they would be destroyed in the subsequent steps, no attempt was made to separate the isomers. The acid catalyzed cyclization of the diol **10** with a catalytic amount of p-TsOH in refluxing benzene furnished the corresponding butenolide **11** in 73% yield. Reduction of butenolide **11** with DIBAL-H¹⁰ in THF at -40°C provided (+)-laevigatin **1** in 77% yield. The spectroscopic and physical properties of (+)-laevigatin thus obtained were found to be identical in all respects with the reported values for (+)-**1** obtained from natural sources. m.p. 66°C , lit¹ $65\text{--}66^{\circ}\text{C}$, specific rotation $[\alpha]_{\text{D}}^{25} = +89$ ($c = 2.3$, CHCl_3). Lit.¹ $[\alpha]_{\text{D}}^{25} = +88$.

Thus, the first enantiospecific synthesis of (+)-laevigatin has been achieved from readily available (+)-citronellal. All reaction steps are very simple, mild and proceed with excellent yields and are easy to perform.

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