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Enantiospecific total synthesis of (+)-laevigatin

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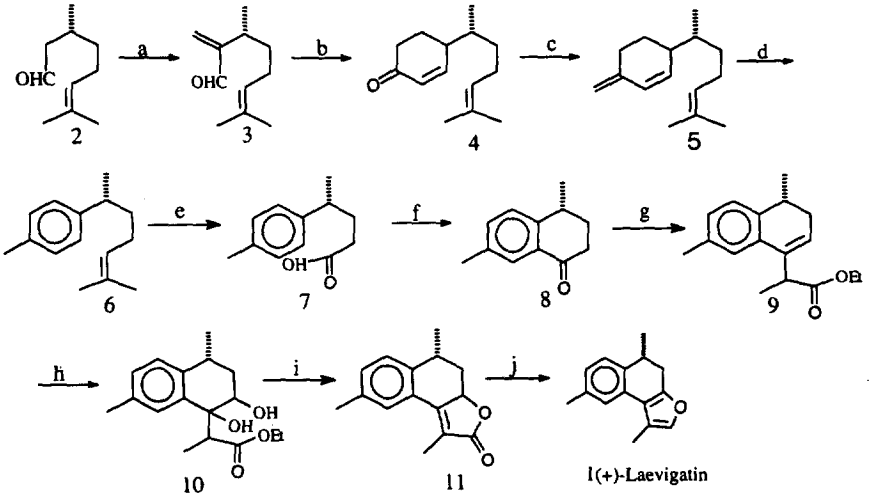
Abstract: The first enantiospecific, total synthesis of (+)-laevigatin from (+)-citronellal is described. © 1997 Published by Elsevier Science Ltd

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 of β,γ-unsaturated esters[3] 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, Piperdine acetate reflux b: Methylacetoacetate, MeOH, MeONa, reflux c: $(Ph)_3PCH_3I$, BuLi, THF 0°C

d: Sulfur, DMF reflux e: OsO_4 (cat), Jones reagent, R.T. f: TFA, TFAA, 0°C g: ethylbromopropionate, Zn, H^+

h: OsO_4, NMO, CH_3CN i: TsOH, C_6H_6, 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 methylenation[6] of **4** gave triene **5** in good yield (80%). The aromatization[7] 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 bond[8] *via* the corresponding diol to acid **7** was achieved in 84% yield. Cyclisation of acid **7** by trifluoroacetic anhydride[9] 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 reaction[3] 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-H[10] 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, lit[1] 65–66°C, specific rotation $[\alpha]_D$=+89 (c=2.3, $CHCl_3$). Lit.[1] $[\alpha]_D$=+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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