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A Short and Efficient Synthesis of (±) Laevigatin

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Abstract : A short and efficient total synthesis of (±) Laevigatin starting from 4,7 dimethyl tetralone *via* butenolide is described. © 1997 Published by Elsevier Science Ltd.

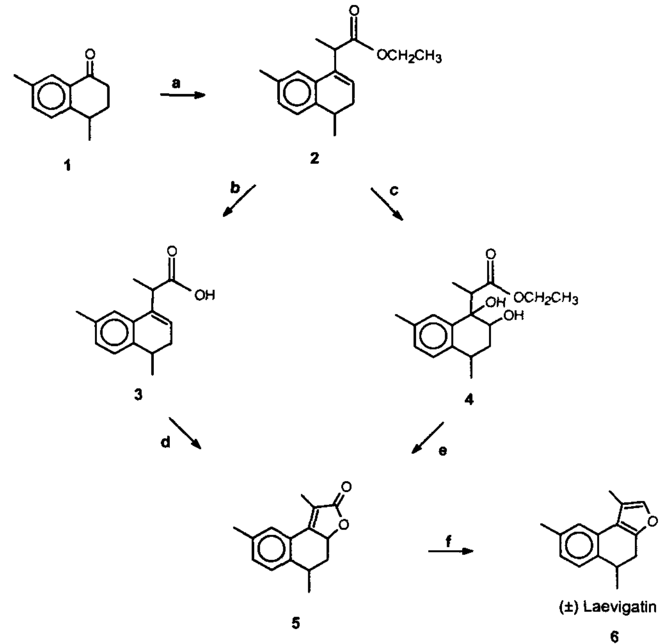
Laevigatin, a sesquiterpene furan was first isolated from *Eupatorium laevigatum* by de Oliveira, *et.al*[1]. Only two racemic synthesis of this compound have been reported so far[2]. We have recently achieved the first chiral synthesis of (+) laevigatin[3]. Because of its unusual skeleton and as a continuation of our interest in the synthesis of compounds like Heritol, Heritonin and other related compounds which have the same skeletal framework, we undertook the synthesis of (±) laevigatin.

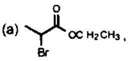
We have earlier developed two efficient methodologies to generate butenolides *via* osmylation of β,γ-unsaturated esters[4] and direct oxidative conversion of β,γ-unsaturated acids to butenolides by ceric ammonium nitrate at room temperature[5].

In this communication, we wish to describe the application of the above protocols for the synthesis of the butenolide and its further conversion to (±) laevigatin.

Reformatsky reaction of ethyl bromopropionate on 4,7 dimethyl tetralone (**1**)[6] furnished the corresponding β, γ-unsaturated ester **2**. The ester was then hydrolyzed to the acid **3** and was further converted to the butenolide using CAN, as a mixture of diastereomers. The butenolide **5** was also made by subjecting the β, γ-unsaturated ester **2** to an osmylation reaction to yield the diol **4** which on further heating with PTSA yielded the butenolide **5**. Since the chiral center at the butenolide was of no consequence as far as the synthesis of laevigatin is concerned (as it would be destroyed later), no attempt was made to separate the diastereomers. The butenolide **5** was then treated with DIBAL at -78°C to give (±) laevigatin in 70% yield. The spectral data of (±) laevigatin were in agreement to those reported for naturally occurring (+) laevigatin. [H^1NMR ($CDCl_3$) : δ 1.3 (d, 3H, J=7.5Hz), 2.3 (s, 3H), 2.33 (s, 3H), 2.7 (dd, 1H), 3.1 (m, 2H), 7.0 - 7.5 (m, 3H)]

The whole sequence of reactions for the synthesis of (±) laevigatin are simple, mild, efficient and are easy to perform.



(a)  , Zn/I_2, dry ether (80%) (b) KOH/MeOH , △ , (83%) (c) OsO_4, NMO, $Na_2S_2O_5$, CH_3CN/H_2O (78%)

(d) CAN, $NaHCO_3/CH_3CN$, R.T (74%) (e) PTSA/Benzene, △ , (78%) (f) DIBAL-H, dry toluene, -78 °C, (70%)

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