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ONE-STEP SYNTHESIS OF (±)-FRONTALIN

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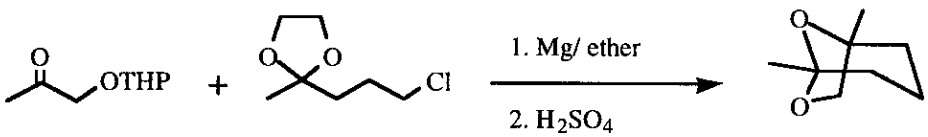
ABSTRACT

(±)-Frotalin was synthesized in one step by Grignard reaction procedure.

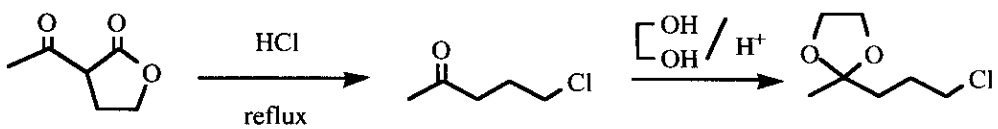
Frontalin **(1)** is the aggregation pheromone of southern pine beetle *Dendroctonus frontalis*[1]. Several groups have synthesized this compound in both racemic[2] as well as enantiomeric[3] forms.

We have developed a novel method for the synthesis of frontalin by using palladium (II) catalysed cyclisation as a key step[4,5]. Now we wish to report a simple, one step synthesis of frontalin. Our synthesis is based upon a Grignard reaction of a protected chloro ketone **(3)** and hydroxy protected ketone **(2)** as shown by the following equation.



(2) **(3)** **(1)**

The protected α-hydroxy ketone **(2)** was easily prepared according to the procedure reported previously[6]. The protected 5-chloro-2-pentanone **(3)** could be obtained from the corresponding ketone, 5-chloro- 2-pentanone which was easily prepared from 2-acetyl butyrolactone[7].



(3)

The Grignard reaction between the ketone **(2)** and **(3)** was carried out in the presence of a catalyst 1,2-dibromoethane. Acid hydrolysis yielded frontalin **(1)** in 61%.

IR spectra were recorded on Jusco A-302 spectrometer. ^1H spectra were recorded on Varian T-60A or Bruker WH 400 spectrometer. Chemical shifts are given in ppm relative to internal TMS(δ scale). MS data were obtained at 70ev AET.MS 902 instrument.

5-CHLOROPENTAN-2-ONE

2-Acetyl butyrolactone (20g, 0.16 mmol) was added dropwise to a refluxing mixture of 48% hydrochloric acid (25 ml) and water (27 ml). When addition was completed, it was continued refluxing for 4h. The product was collected by azeotropic distillation with a Dean-Stark separator. The oily layer of the distillate was separated and dissolved in chloroform(100 ml) then washed with water and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the residue was distilled to give a colorless liquid (13.12g, 70%), b.p. 57-59°C/10 Tor, lit.[7] b.p.70-72°C/20 Tor. ^1H NMR ($CDCl_3$) δ : 1.80-2.15 (m, 2H, CH_2), 2.17 (s, 3H, $CO-CH_3$), 2.63 (t, J = 7Hz, 2H, $CO-CH_2$), 3.57 (t, J = 6Hz, CH_2-Cl).

2-ETHYLENEKETAL-5-CHLOROPENTAN-2-ONE[3]

A mixture of 5-chloropentan-2-one (13.12 g, 10.9 mmol), ethylene glycol (19.57 g, 31.6 mmol) and p-toluene sulphonic acid (25 mg, 0.02 mmol) in dry benzene (50 ml) was refluxed for 20 h. The water formed was removed by azeotropic distillation with Dean-Stark separator. The reaction mixture was cooled to room temperature and washed with 5% aqueous sodium hydrogen carbonate, water, brine and dried over anhydrous sodium sulphate. Solvent was removed then the residue was distilled to give a colorless liquid (11.62 g, 65%); b.p. 73-75°C/7 Torr. ^1H NMR ($CDCl_3$) δ : 1.31 (s, 3H, CH_3),1.76-1.94 (m, 4H, CH_2-CH_2), 3.57 (t, J = 6Hz, 2H, CH_2Cl), 3.93 (s, 4H, $O-CH_2.CH_2-O$).

FRONTALIN [1]

A suspension of magnesium turning (1.37 g, 5.71 mmol) in dry ether (11 ml) was stirred at room temperature under nitrogen atmosphere. A solution of 2-ethyleneketal-5-chloropentan-2-one (4.64g, 2.83 mmol) and dibromoethane (4.99 g, 2.68 mmol) in dry ether (31 ml) was added dropwide into the stirred mixture at such a rate as to allow the solvent to reflux gently. To the resulting Grignard reagent was added dropwise a solution of acetonyl tetrahydropyranyl ether (4.05 g, 2.56 mmol) in dry ether (120 ml) and refluxed for 1.5h. After cooling the reaction mixture to room temperature some crushed ice was added and then acidified with 30% aqueous sulphuric acid (14 ml), stirred at room temperature for 1.5h. The mixture was extracted with ether and the combined ether was washed with water,dried over anhydrous sodium sulphate. The solvent was removed under vacuum to give a yellowish liquid (3.02 g). Glc analysis (SE 30, 90°C) of the crude product showed three components which are frontalin **(1)**, 5-chloropentan-2-one and unidentified compound in the ratio of 20:3:2. The separation of each components was accomplished by HPLC. Yield of frontalin based on protected α-hydroxy acetone was 61.2%. IR (neat) 2900, 1120 and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ :1.26(s, 3H, CH_3), 1.30(s, 3H, CH_3), 1.5-1.8(m, 6H, 3xCH_2), 3.48 and 3.78(dd, J = 7Hz, 1H each). MS(m/e): 142(M^+, 13), 112(12), 100(35), 72(78),54(11), 43(100)

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บทคัดย่อ

ได้บรรยายถึงวิธีการสังเคราะห์สารประกอบ frontalin เพียงขั้นตอนเดียวจากปฏิกิริยา Grignard