One-Step Synthesis of Drimenin and Cinnamolide

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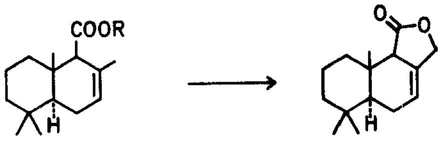
In a previous paper[1], we have reported the synthesis of *drimenin*[2] (**2**) by photo-oxidation of methyl bicyclofarnesate (**1 b**) and subsequent lactonization with concomitant hydrolysis of the oxidized product (**3**). *Cinnamolide*[3] (**5**) was also prepared from drimenin by a multistage synthesis[4].

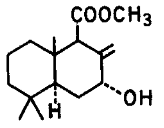
From a biogenetical point of view, the direct oxidation of a methyl group attached to an olefinic carbon atom is of particular interest since the γ-lactone group of drimenin (**2**) and cinnamolid (**5**) might be derived *in vivo* from the oxidation of the methyl group of bicyclofarnesic acid (**1a**) or bicyclofarnesol (**4**), respectively.

In vivo, oxidation of the methyl group in the 2-position of **1a** and **4** is presumed to proceed enzymatically through a π-complex (**6**, M = enzyme). We tried the analogous *in vitro* oxidation of **1a** and **4** using palladium(II)-chloride which is reported to form π-complexes with olefinic double bonds[5] (**6**, M = $PdCl_2$). Direct oxidation of the methyl group in **1a** and **4** to give drimenin (**2**) and cinnamolide (**5**), respectively, was achieved by refluxing the precursors **1a** and **4** with palladium(II)-chloride in an aqueous organic solvent.



1a R=H
1b R=CH_3

2



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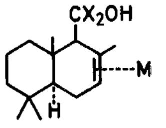
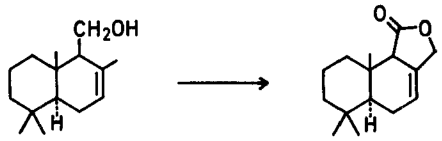


6 $X_2 = H_2$ or O



4

5

Drimenin (2): A mixture of bicyclofarnesic acid (**1a**; 200 mg), palladium chloride (100 mg), copper(II)-chloride (300 mg), dimethylformamide (10 ml), and water (5 ml) was refluxed for 4 days with stirring. Aqueous hydrochloric acid was then added and the reaction mixture extracted with ether. From the ethereal extract there was obtained 190 mg of a crude oil. This was dissolved in hexane and the solution kept in an refrigerator to afford a colorless crystalline product; yield: 18 mg (10%); m.p. 97–98°. The product was identical with authentic drimenin.

Cinnamolide (5): A mixture of bicyclofarnesol (**4**; 200 mg), palladium chloride (100 mg), diisopropyl ether (1 ml), and water (5 ml) was refluxed with stirring for 48 hr and then extracted with ether. The extract was washed with aqueous sodium hydroxide solution and then water and the ether was evaporated. The crude oil (190 mg) thus obtained was chromatographed on a 5% silver nitrate/silica gel column. Elution with benzene afforded 20 mg of crystalline **5** which was identical with an authentic specimen; m.p. 88°.

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