Efficient Synthesis of 6-Prenylcoumarins; Total Syntheses of Suberosin, Toddaculin, *O*-Methylapigravin (*O*-Methylbrosiperin) and *O*-Methylbalsamiferone

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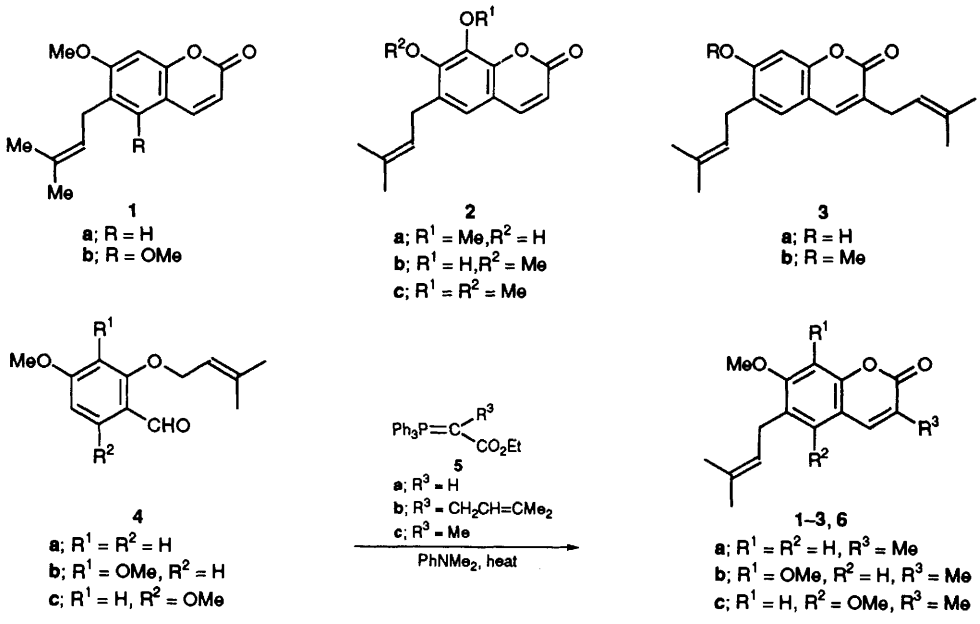
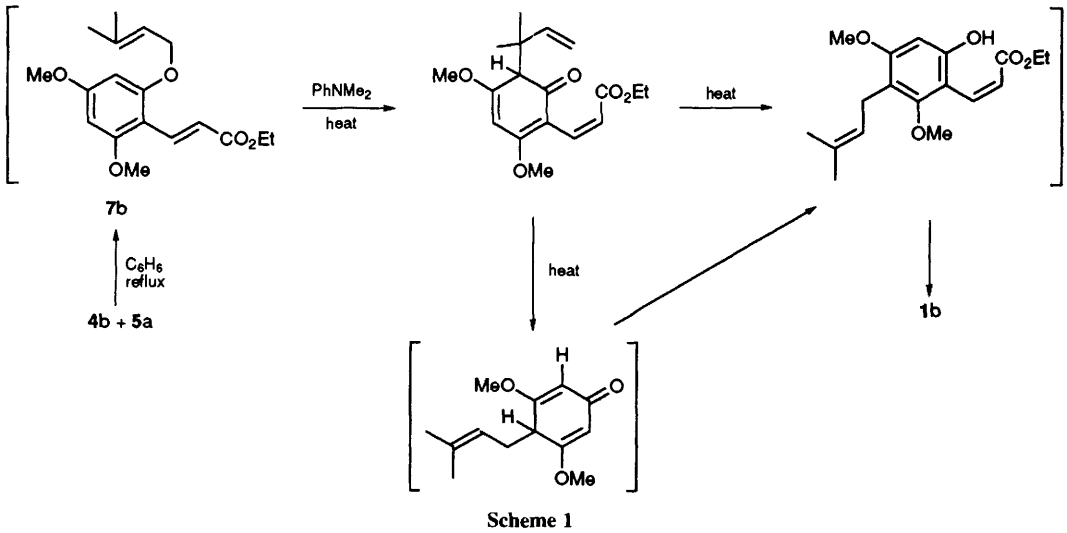
Synthesis of naturally occurring 6-prenylcoumarins **1a**, **b**, **2c**, and **3b** and their derivatives **6a–c** is described, starting from 2-prenyloxybenzaldehydes **4a–c**, using a tandem Claisen rearrangement and Wittig reaction.

Several 6-prenylcoumarins such as suberosin **1a**, toddaculin **1b**, apigravin **2a**, brosiperin **2b** and balsamiferone **3a** have been isolated from natural sources.[1] A large number of 6-allyl- and 6-prenyl-coumarins have been used as intermediates for the synthesis of biologically active compounds,[1] naturally occurring 6-substituted coumarins and linear furocoumarins.[1–3] In view of this, various approaches have been developed[1,4,5] for 6-allyl- and 6-prenyl-coumarins.

Claisen rearrangement of allyloxy benzene provides *ortho*-allylphenol; most of the reported methods utilize 7-allyloxycoumarins as starting materials to obtain allylcoumarins.[1] Since 7-allyloxycoumarins on Claisen rearrangement provide exclusively 8-allylcoumarins,[1] the C-8 position is blocked to obtain 6-allylcoumarins.[6,7] In a recent approach 7-alkoxycoumarins have been initially converted to methyl 2-allyloxy-4-alkoxycinnamates and then to 6-allylcoumarins such as suberosin **1a** and related compounds.[8] In an alternative approach the propynylic ether of umbeliferone has been used for the synthesis of demethylsuberosin,[9] which was subsequently converted to 3,6-diprenyl-7-hydroxycoumarin (balsamiferone **3a**).[10] A route utilizing 3-prenyl-7-hydroxycoumarin[11] has also been reported for balsamiferone **3a**.





Scheme 1

Literature methods[12–14] for toddaculin **1b** either involve multistep sequences and/or provide **1b** in very low yields. Most of these approaches[13,14] utilize 5,7-dihydroxycoumarin as the starting material. As 7-(1,1-dimethylallyloxy)coumarins provide 8-allylcoumarins on Claisen rearrangement, it was necessary to synthesize 5-(1,1-dimethylallyloxy)-7-methoxycoumarin to obtain toddaculin[13] **1b**. The major obstacle in this case was the selective allylation of C-5-hydroxyl group of 5,7-dihydroxycoumarin.

All the known methods, for the synthesis of 6-allyl and 3,6-diallylcoumarins make use of preformed coumarins.[8–10] We report herein a novel and general route for naturally occurring 6-prenylcoumarins **1a**, **b**, **2c** and **3b** and their derivatives **6a–c** from 2-prenyloxybenzaldehydes **4a–c**. The aldehydes **4a–c** were prepared by prenylation[13] (prenyl bromide, K_2CO_3, tetrabutylammonium iodide, acetone, reflux) of the corresponding 2-hydroxybenzaldehydes. Thus, the reaction of **4a** with phosphorane **5a** in *N*,*N*-dimethylaniline at 200 °C for 6 h under nitrogen atmosphere, directly gave suberosin **1a**, mp 87 °C (lit.[15] 87–88 °C) in 47% yield. A similar reaction of **4c** and **4b** with phosphorane **5a** for 8 and 12 h provided toddaculin **1b**, mp 93 °C (lit.[13] 93–94 °C) and *O*-methylapigravin (*O*-methylbrosiperin, **2c**), mp 93 °C (lit.[16] 93–95 °C) in 50 and 55% yields, respectively. It was anticipated that the reaction of **4a–c** with **5a** would initially give (*E*)-esters **7a–c**, which would isomerise thermally to the (*Z*)-isomer and then cyclize after Claisen rearrangement to give **1a**, **b** and **2c** (Scheme 1). Thus, when **4b** was reacted with **5a** in refluxing benzene for 6 h the (*E*)-ester **7b**, mp 92 °C, was obtained, which on heating in refluxing *N*,*N*-dimethylaniline at 200 °C for 6 h provided toddaculin **1b**. The α and β olefinic protons in **7b** appeared in ^{1}H NMR ($CDCl_3$) as doublets (*J* 16 Hz) at δ 7.00 and 8.42, respectively, which confirmed its geometry. *O*-Methylbalsamiferone **3b** was obtained in 49% yield, by a similar reaction of **4a** with phosphorane **5b**.

To demonstrate the generality of this approach the aldehydes **4a–c** were reacted with phosphorane **5c** to obtain coumarins **6a–c** in 48, 58 and 45% yields, respectively. The present approach, which does not require preformed coumarin, demonstrates the synthetic utility of this tandem Claisen rearrangement and Wittig reaction for the synthesis of 6-prenyl- and 3,6-diprenyl-coumarins. IR and ^{1}H NMR spectral data of coumarins **1a**, **b** and **2c** are identical with literature data.[5,13,15] The new coumarins **3b** and **6a–c** also exhibited satisfactory analytical and spectral data.†

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† *Selected spectral data* for compound **6c**: IR (Nujol, ν_{max}/cm^{-1}): 1720 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.8 and 1.9 (s, 3 H each, 2 × Me), 2.2 (s, 3 H, C_3–Me), 3.4 (d, 2 H, $ArCH_2$), 3.8 and 3.9 (s, 3 H each, 2 × OMe), 5.2 (t, 1 H, CH), 6.8 (s, 1 H, C_8–H), 7.8 (s, 1 H, C_4–H).

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