

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

Raghao S. Mali,* Paramjeet Kaur Sandhu and Anita Manekar-Tilve

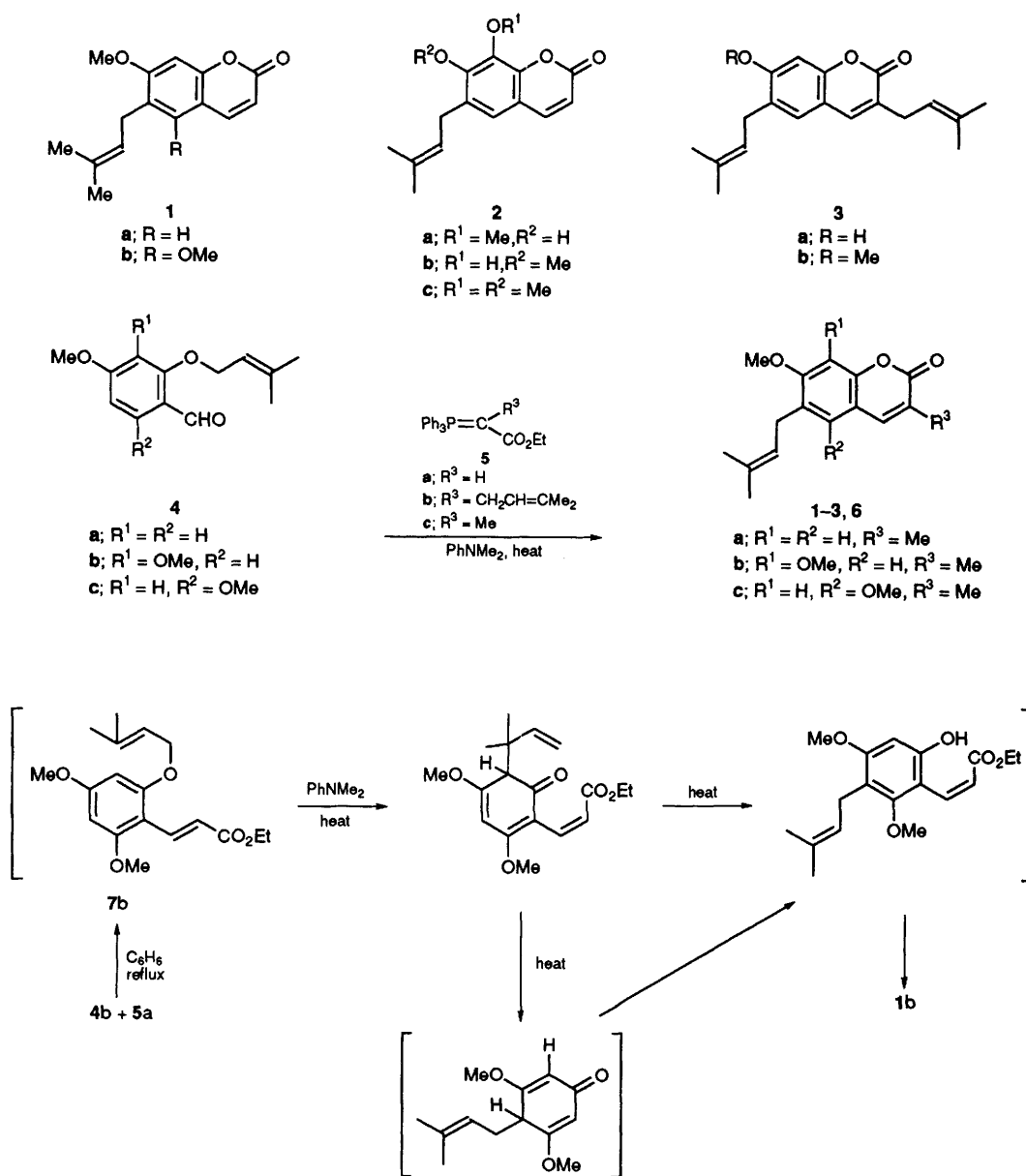
Garware Research Centre, Department of Chemistry, University of Poona, Ganeshkhind, Pune-411 007, India

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**, brosipirin **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-allyloxy-coumarins as starting materials to obtain allylcoumarins.¹

Since 7-allyloxy-coumarins 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-alkoxy-coumarins 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 propynyl 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-hydroxycoumarin¹¹ has also been reported for balsamiferone **3a**.



Scheme 1

Literature methods¹²⁻¹⁴ 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 toddaculin¹³ **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 prenylation¹³ (prenyl bromide, K₂CO₃, 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 ¹H NMR (CDCl₃) 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 ¹H 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.†

The authors thank the UGC, New Delhi for the financial support. One of them (A. M. T.) thanks the CSIR, New Delhi for the award of a Senior Research Fellowship.

Received, 9th August 1993; Com. 3/04794F

Footnote

† Selected spectral data for compound **6c**: IR (Nujol, ν_{\max} /cm⁻¹): 1720 (C=O); ¹H NMR (CDCl₃) δ : 1.8 and 1.9 (s, 3 H each, 2 \times Me), 2.2 (s, 3 H, C₃-Me), 3.4 (d, 2 H, ArCH₂), 3.8 and 3.9 (s, 3 H each, 2 \times OMe), 5.2 (t, 1 H, CH), 6.8 (s, 1 H, C₈-H), 7.8 (s, 1 H, C₄-H).

References

- 1 R. D. H. Murray, J. Mendez and S. A. Brown, *The Natural Coumarins, Occurrence, Chemistry and Biochemistry*, Wiley-Interscience New York, 1982.
- 2 R. D. H. Murray, M. M. Ballantyne and K. P. Mathai, *Tetrahedron*, 1971, **27**, 1247.
- 3 T. R. Seshadri and M. S. Sood, *Indian J. Chem.*, 1963, **1**, 291.
- 4 S. K. Koul, S. C. Taneja and K. L. Dhar, *Indian J. Chem., Sect. B.*, 1987, **26**, 574.
- 5 M. B. Raizada, S. K. Garg and S. R. Gupta, *Indian J. Chem., Sect. B*, 1981, **20**, 918.
- 6 N. H. Pardanani, Y. A. Shaikh and K. N. Trivedi, *J. Indian Chem. Soc.*, 1975, **52**, 45.
- 7 G. M. Massanet, E. Pendo, F. Rodriguez-Luis and J. Salva, *Heterocycles*, 1987, **26**, 1541.
- 8 N. Cairns, L. M. Harwood and D. P. Astles, *J. Chem. Soc. Chem. Commun.*, 1986, 1264.
- 9 N. Cairns, L. M. Harwood and D. P. Astles, *J. Chem. Soc. Chem. Commun.*, 1986, 750.
- 10 N. Cairns, L. M. Harwood and D. P. Astles, *J. Chem. Soc., Chem. Commun.*, 1987, 400.
- 11 D. Swaroop, P. B. Sharma and R. S. Kapil, *Indian J. Chem., Sect. B*, 1983, **22**, 408.
- 12 P. N. Sharma, A. Shueb, R. S. Kapil and S. P. Popli, *Indian J. Chem., Sect. B.*, 1980, **19**, 938.
- 13 R. D. H. Murray, M. M. Ballantyne, T. C. Hogg and P. H. McCabe, *Tetrahedron*, 1975, **31**, 2960.
- 14 S. Mahey, T. R. Seshadri and S. K. Mukerjee, *Indian J. Chem.*, 1974, **12**, 29.
- 15 P. W. Austin and T. R. Seshadri, *Indian J. Chem.*, 1968, **6**, 412.
- 16 S. K. Garg, S. R. Gupta and N. D. Sharma, *Phytochemistry*, 1979, **18**, 1580.