An Iterative Procedure for the Synthesis of the Diprenylated Coumarins Balsamiferone and Gravelliferone from Umbelliferone *via* Multiple [3.3] Sigmatropic Rearrangements

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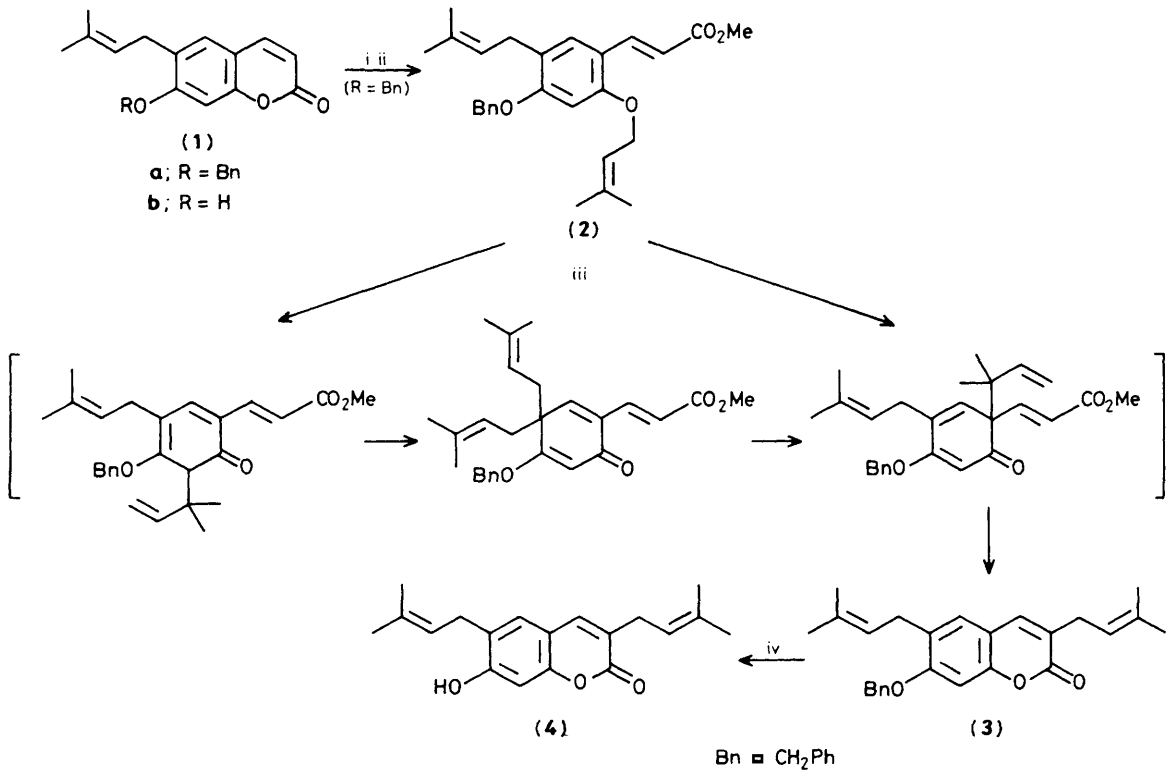
Repeated sequences of [3.3] sigmatropic rearrangements initiated by a Claisen rearrangement permit the synthesis of the 3,6-disubstituted umbelliferone derivatives balsamiferone (**4**) and gravelliferone (**6**) from umbelliferone.

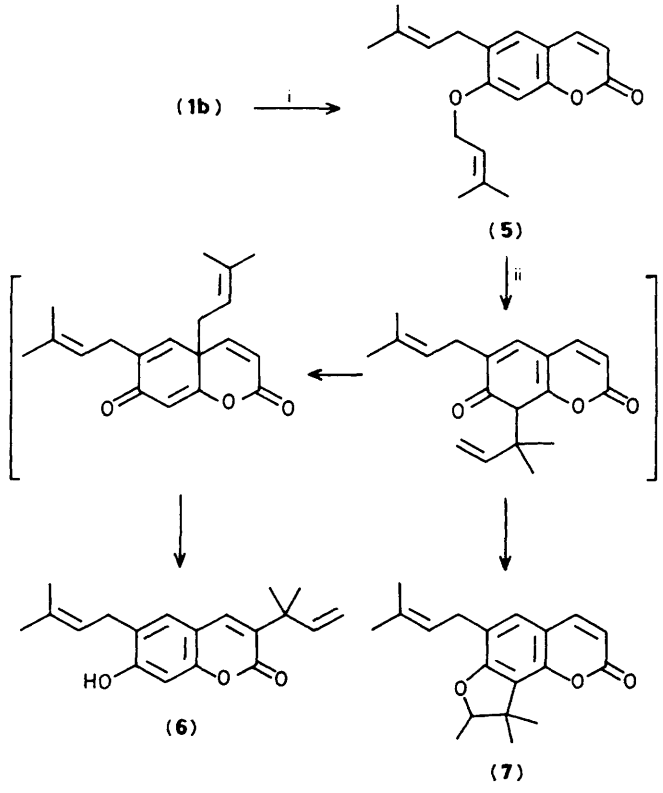
We have recently reported an efficient synthesis of the linear coumarin demethylsuberosin together with its geranyl and farnesyl analogues from 2′-*O*-prenylated derivatives of 4′-*O*-benzyl methyl coumarate by a procedure involving sequential *para*-Claisen rearrangement and relactonisation.[1] As a consequence of the double inversion this sequence permits utilisation of the readily available prenyl bromide or its prenyl homologues as alkylating agents to prepare the rearrangement precursors. Along with the desired 6-prenylated products were isolated smaller quantities (*ca.* 10%) of the 3-prenylated derivatives arising from an alternative rearrangement pathway. We now report that, having blocked the 6-position, this alternative pathway operates to furnish 3,6-diprenylated products, permitting synthetic access to balsamiferone (**4**) (isolated from *Amyris balsamifera*)[2] and gravelliferone (**6**) (isolated from *Ruta graveolens*).[3]

The lactone ring of 7-benzyloxy-6-prenylcoumarin (**1a**) (obtained in 65% overall yield in four steps from umbelliferone[1]) was cleaved to give the methyl coumarate ester (NaOMe, MeOH, reflux) and the free phenolic group prenylated (K_2CO_3, prenyl bromide, acetone, reflux) to furnish (**2**) in 85% overall yield (Scheme 1).† On heating in refluxing diethylaniline, (**2**) smoothly rearranged, resulting in prenyl substitution at the free C-3 position with concomitant relactonisation to produce 7-*O*-benzyl balsamiferone (**3**) in 95% yield [n.m.r., 300 MHz, $CDCl_3$: δ 6.85 (1H, s, H-8), 7.17 (1H, s, H-5), and 7.32—7.47 (6H, m with superimposed s at δ

† All novel compounds isolated gave spectroscopic and analytical data in keeping with their assigned structures.



Scheme 1. *Reagents and conditions:* i, NaOMe, MeOH, reflux, 3 h, 92%; ii, prenyl bromide, K_2CO_3, acetone, reflux, 5 h, 95%; iii, $PhNEt_2$, reflux, 3 h, 95%; iv, BCl_3, CH_2Cl_2, −50 °C, 1 h, 90%.



Scheme 2. *Reagents and conditions:* i, Prenyl bromide, K_2CO_3, acetone, reflux, 5 h, 95%; ii, $PhNEt_2$, reflux, 3 h, (**6**) 20%, (**7**) 8%, (**1b**) 56%.

7.37, benzyl H, H-4)]. Deprotection (BCl_3, CH_2Cl_2, −50 °C, 90% yield) furnished the target product (**4**) [m.p. 134.5—136.0 °C, lit.[2] 135—137 °C; n.m.r., 300 MHz, $CDCl_3$: δ 6.95 (1H, s, H-8) (typical value, H-8 chemical shift concentration dependent[4]) and 7.14 (1H, s, H-5)]. This compound has been prepared previously in 13 steps from umbelliferone 3-carboxylic acid in <1% overall yield.[5]

The conversion of (**2**) into (**3**) is remarkably efficient in view of the requirement for at least two and possibly four rearrangements.

Gravelliferone (**6**), which possesses a 1,1-dimethylallyl substituent at C-3, was prepared by an analogous procedure from demethylsuberosin (**1b**), itself prepared from (**1a**) in 87% yield[1] (Scheme 2). Prenylation of (**1b**) occurred in 95% yield to give the ether (**5**) which on heating in refluxing diethylaniline underwent a triple rearrangement to furnish gravelliferone (**6**) (m.p. 165—166 °C, lit.[3] 166—168 °C) in 20% purified yield, accompanied by 56% of the starting demethylsuberosin (**1b**). In addition, *ca.* 8% of the *ortho*-rearrangement derived product (**7**) could be detected in the crude reaction mixture [n.m.r., 300 MHz, $CDCl_3$: δ 1.36 (3H, d, *J* 6 Hz,O–C–Me), 1.45 (6H, s, $-CMe_2$), 3.30 (1H, q, *J* 6 Hz, O–CH), and 7.03 (1H, s, H-5)].

Such a triple rearrangement has been proposed as the biogenetic sequence for the formation of 3-(1,1-dimethylallyl) umbelliferones[6] and has experimental precedent.[7] Although less efficient than the rearrangement in the balsamiferone series, this migration is still remarkable in view of the sterically unfavourable processes involved. Despite the low yield in the final step, this approach permits the synthesis of gravelliferone in 10% overall yield from umbelliferone which compares favourably with the previous synthesis of this molecule.[8]

Thus balsamiferone (**4**) and gravelliferone (**6**) have been

prepared in 48%‡ and 10% overall yields respectively from umbelliferone, demonstrating further the synthetic utility of multiple [3.3] sigmatropic rearrangements for constructing prenyl substituted coumarins.

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‡ The procedure may also be carried out without separation of the 3- and 6-prenylated coumarins resulting from the first rearrangement.[1] Methoxide induced cleavage and prenylation led to a mixture of (**2**) and its 3-prenyl isomer, both of which yielded the desired product (**3**) on thermal rearrangement. The overall yield of balsamiferone from umbelliferone is 55% using this procedure.

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