Synthesis of Linear Coumarins *via para*-Claisen Rearrangement of Coumarate Ester Derivatives: Total Syntheses of Suberosin, Demethylsuberosin, and Ostruthin

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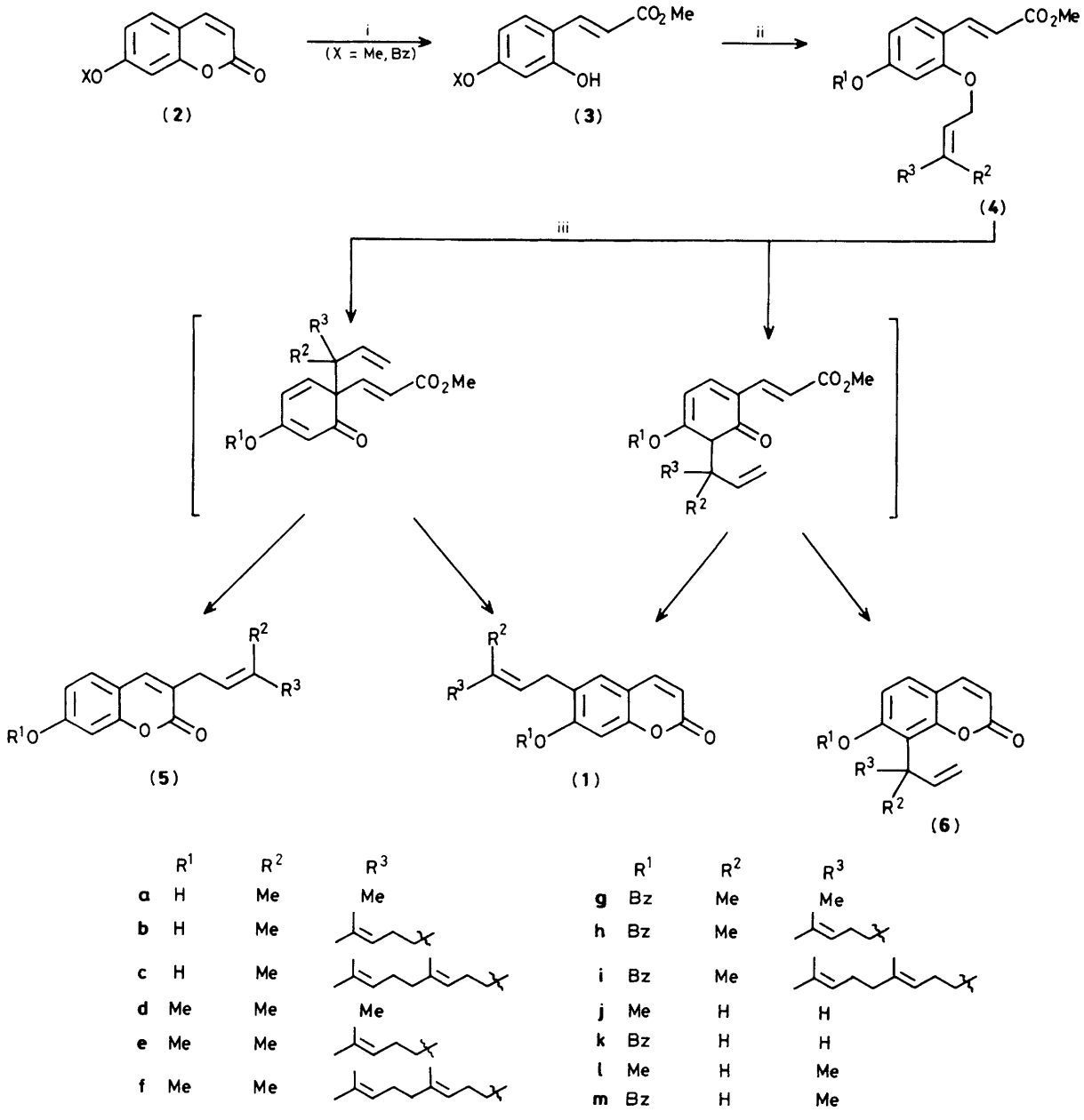
Heating 2′-*O*-prenylated derivatives of 4′-*O*-methyl and 4′-*O*-benzyl methyl coumarates (**3**) furnishes the corresponding linear prenylated umbelliferones (**1**) directly *via* sequential *para*-Claisen rearrangement and relactonisation.

We have recently reported the regioselective Lewis acid catalysed *ortho*-Claisen rearrangement of 4′-allyloxycoumarate esters[1] and have successfully applied this approach to the synthesis of the naturally occurring linear coumarin demethylsuberosin (**1a**),[2] isolated from *Ruta graveolens*.[3] This procedure utilises 7-(1,1-dimethyl)allyloxycoumarin, derived initially from the readily available 3-chloro-3-methylbut-1-yne.[4] However, extension of this approach to the synthesis of geranyl and farnesyl prenylogues of (**1**) would necessitate the use of the less readily obtained dehydrolinaloyl or dehydronerolidyl halides. Since the double inversion of a *para*-Claisen rearrangement would permit the use of ethers derived from more readily available prenyl, geranyl, and farnesyl halides, we have investigated the application of such an approach to the synthesis of structures (**1**).[5]

The 2′-*O*-allyl ethers (**4d**—**f**) were readily prepared from 7-methoxycoumarin (**2**, X = Me) *via* cleavage to the coumarate ester (**3**, X = Me) (NaOMe, MeOH, reflux, 92%)



Scheme 1. *Reagents:* i, NaOMe, MeOH, reflux; ii, K_2CO_3, $R^2R^3C{=}CHCH_2Br$, acetone, reflux; iii, $PhNEt_2$, reflux.

followed by allylation with the requisite bromides [(**4d**), 96%; (**4e**), 91%; (**4f**), 89%].† (Scheme 1.)

Heating these substrates in refluxing diethylaniline for 2 hours gave the desired 6-allylated umbelliferone methyl ethers in good yield [(**1d**), 80%; (**1e**), 80%; (**1f**), 78%], with reclosure to the coumarin following the *para*-Claisen rearrangement. This procedure constitutes a direct, efficient synthesis of suberosin, (**1d**), a coumarin constituent of *Pastinaca* species (Umbelliferae).[6] Accompanying the desired materials were lesser amounts of 3-allylated by-products [(**5d**), 12%; (**5e**), 14%; (**5f**), 14%], the formation of which can be rationalised by initial rearrangement to the 1′-position followed by 3,3-sigmatropic rearrangement to the side chain and relactonisation.[7]

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

Since attempted cleavage of the methyl ethers would probably result in concomitant cyclisation of the *ortho* side chains[2] the corresponding benzyl derivatives (**4g—i**) were prepared by the same procedure in high overall yield from 7-benzyloxycoumarin (**2**, X = Bz): [(**4g**), 86%; (**4h**), 82%; (**4i**) 82%]. Rearrangement as before furnished the desired 6-allylated coumarins [(**1g**), 78%; (**1h**), 72%; (**1i**), 72%], again accompanied by lesser amounts of the 3-allylated coumarins [(**5g**), 10%; (**5h**), 13%; (**5i**), 15%]. The 6-allyl-7-benzyloxycoumarins were smoothly debenzylated [(**1g**) BCl_3, CH_2Cl_2 saturated with ethylene, −50 °C;‡ (**1h,i**) Raney Ni, H_2, EtOH] to furnish demethylsuberosin (**1a**),[2] ostruthin (**1b**) (isolated

‡ Attempts at similar debenzylations in the coumarate ester series were unsuccessful. This may be connected with the relative electron withdrawing capacities of the coumarin lactone and coumarate ester moieties for the benzyl ether oxygen.

Table 1.

Substrate	Product, % isolated yield		
(**4**)	(**1**)	(**5**)	(**6**)
d	80	12	0
g	78	10	0
j	4	7	84
k	6	8	76
l	28	9	53
m	27	8	50

from *Pastinaca ostruthium*[8]), and the farnesyl derivative (**1c**) in 84, 82, and 77% purified yields respectively.

Examination of the ^{1}H 300 MHz n.m.r. spectra of the geranyl and farnesyl *para* rearrangement products (**1**) and (**5**) indicated that the double inversion had regenerated the initial 2′-(*E*)-double bond geometry of the side chain, as evidenced by the absence of duplication of absorptions, particularly the doublet corresponding to the side chain benzylic CH_2 group.

The allyl ethers (**4j**), (**4k**) and crotyl ethers (**4l**), (**4m**) were also prepared in order to assess the effect of γ-substitution of the allyl ether upon the *para*-rearrangement process. The allyl ethers furnished largely the 8-substituted products (**6j**) and (**6k**) (Table 1), identified by a mutual *ortho* coupling (10 Hz) of the aromatic protons, whereas the crotyl ethers furnished a mixture of 8-(1′-methyl)allyl [(**6l**), (**6m**)] and 6-crotyl umbelliferones [(**1l**), (**1m**)], [(**6**) : (**1**) *ca.* 2 : 1]. These results appear to reflect the degree of steric crowding at the benzylic position of the 8-substituted products. Interestingly, the yield of 3-substituted umbelliferones (**5**) produced appeared insensitive to the nature of the migrating group in all instances.

The *para*-Claisen rearrangement approach described above permits the ready and efficient preparation of 6-prenylated derivatives of umbelliferone, particularly the higher prenylogues, and is complemented by our *ortho*-Claisen rearrangement approach to 6-allylumbelliferone.[1]

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