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EFFICIENT SYNTHESES OF THE COUMARINS, NORDENTATIN, DENTATIN AND CLAUSARIN

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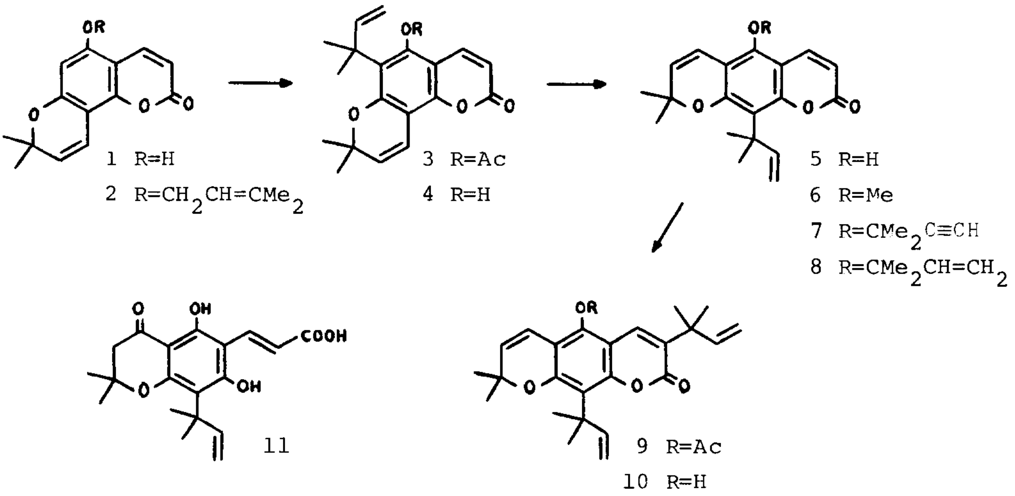
Abstract. A convenient synthetic route to the linear pyranocoumarins, nordentatin (5) and dentatin (6), has been established. A novel out-of-ring Claisen rearrangement has been employed in the synthesis of clausarin (10). The structure of clausenidinaric acid has been reassigned as 11.

In 1977 a novel coumarin, clausarin, was isolated[1] from *Clausena pentaphylla* roots where it co-occurs with dentatin,[2] the revised[3] structure (6) of which has been confirmed by synthesis.[4] Clausarin, which is assigned the linear pyranocoumarin structure (10) on spectroscopic evidence,[1] is unique is possessing two 1,1-dimethylallyl groups and is the only coumarin in which all but C-4 of the nucleus bears a substituent. Synthetic confirmation for structure (10) was thus desirable but posed considerable problems, not least the regiospecific introduction of the 1,1-dimethylallyl groups at C-3 and C-8. Clausarin has recently been found in *C. excavata*[6] where it co-occurs with nordentatin (5). It was also of interest to provide an efficient synthetic route to this phenol which possesses important antibacterial properties.



1 R=H
2 R=$CH_2CH=CMe_2$
3 R=Ac
4 R=H
5 R=H
6 R=Me
7 R=$CMe_2C\equiv CH$
8 R=$CMe_2CH=CH_2$
11
9 R=Ac
10 R=H

Our convenient three-step synthesis[7] of the angular pyranocoumarin (1) provided an intermediate suitable for transformation into nordentatin. The derived prenyl ether (2, 98%) rearranged smoothly in refluxing acetic anhydride-NaOAc[8] to 3 (97%) introducing the potential C-8 1,1-dimethylallyl group initially at C-6. Exposure of 3 to 1% NaOH (2 eq) in MeOH for 3 h afforded the corresponding phenol (4, 100%). Base-induced lactone-ring isomerisation[9] of this 5-hydroxycoumarin to nordentatin (5, 96%), m.p. 183-184° (lit.[2] 182°) was accomplished with 1% NaOH (5 eq) in MeOH for 50 h. Nordentatin was more conveniently obtained directly from 3 with 1% NaOH (10 eq) in MeOH for 20 h. Methylation (MeI, K_2CO_3, acetone) of 5 gave dentatin (6, 99%), m.p. 93-94° (lit.[2] 95°).

With an efficient synthesis of nordentatin established it was of interest to determine if a 1,1-dimethylallyl group could be introduced at C-3 to give clausarin (10). In the synthesis of rutacultin,[5] this moiety was introduced, albeit in low yields, by triple Claisen rearrangement of a 7-prenyloxycoumarin. Although such an approach is not possible with nordentatin, it was envisaged that a double Claisen rearrangement of the 1,1-dimethylallyl ether (8) might result in a similar out-of-ring migration to C-3 since rearrangement to give an *ortho* or *para*-substituted phenol is precluded. Reaction of 5 with 3-chloro-3-methylbut-1-yne, K_2CO_3, KI in dry acetone gave the ether (7, 77%) which was partially hydrogenated over 5% Pd-$BaSO_4$ to the desired 1,1-dimethylallyl ether (8, 100%). Rearrangement of 8 in acetic anhydride-NaOAc for 2 h gave clausarin acetate (9, 82%), m.p. 123-124° (lit.[1] 120°) which was deacetylated with 1% NaOH (2 eq) in MeOH for 1 min to clausarin (10), m.p. 201-204° (lit.[1] 208°).

A new compound, clausenidinaric acid, was recently obtained from *C. excavata*.[6] Its structure was secured by its formation from the coumarin clausenidin. However, the original[2] and not the revised[3] structure of clausenidin was the basis for this assignment; consequently clausenidinaric acid should be reformulated as 11.

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