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SYNTHESIS AND STRUCTURE REVISION OF THE COUMARIN, CELERIN

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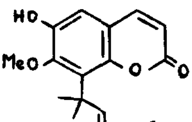
Abstract. The four possible structures (2, 4, 6 and 8) for celerin have been synthesised and the structure of the natural product revised to 8-hydroxy-7-methoxy-5-(1,1-dimethylallyl)coumarin (8).

Recently, a new coumarin, celerin, m.p. 154-156° was isolated from *Apium graveolens* seeds.[1] Synthetic studies revealed however that the proposed structure (1) was untenable.[2] On biogenetic grounds, either the OMe or OH must be at C-7 but the absence of a UV bathochromic shift with base precludes the latter possibility.[1] Since the H-4 doublet centred at δ 8.28 necessitates C-5 substitution,[2,3] we decided to resolve the problem by synthesising all four possible structures (2, 4, 6 and 8) for celerin.

The two isomers (2 and 4) having the OH at C-5 and the 1,1-dimethylallyl unit at C-6 and C-8 were obtained as follows. Previously we observed that 5-prenyloxy-7-acetoxycoumarin underwent exclusive *para*-Claisen rearrangement in Ac_2O giving 5,7-diacetoxy-8-prenylcoumarin.[4] 5-Prenyloxy-7-methoxycoumarin behaves similarly but when heated in Ac_2O containing NaOAc,[2] a mixture of the *ortho*- (3, 86%) and *para*- (11%) rearrangement products was obtained. Hydrolysis



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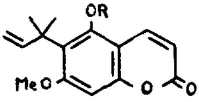
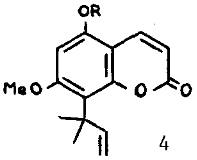
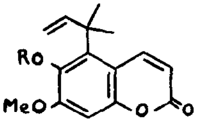


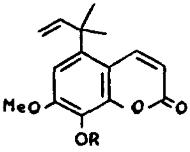
2 R = H
3 R = Ac



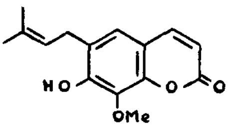
4 R = H
5 R = Me



6 R = H
7 R = Ac



8 R = H
9 R = Ac



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of 3 with 1 eq 0.5% NaOH/MeOH for 4 h gave the corresponding phenol (2, 75%), m.p. 105-107° and the lactone-ring isomerisation[4] product (4, 6%), m.p. 175-177°. An equilibrium mixture of 4 (91%) and 2 (9%) was obtained by exposure of 3 to 10 eq 3% NaOH/MeOH for 12 h. Methylation of 4 completed an alternative synthetic route to pinnarin (5).[5] The singlet benzenoid protons of 2 and 4 resonate at 6.47 and 6.52, compared with 7.03 for celerin,[1] with H-4 centred at 7.98 and 8.05, respectively. Consequently the 1,1-dimethylallyl group and not the OH must be the C-5 substituent.

The third possibility (6) for celerin was obtained by ortho-Claisen rearrangement of 6-prenyloxy-7-methoxycoumarin in Ac_2O/NaOAc which gave the acetate (7, 80%) and 6-acetoxy-7-methoxycoumarin (14%). Hydrolysis of 7 with 8 eq 2% NaOH/MeOH for 8 h gave a mixture of the phenol (6, 65%), m.p. 92-94° and the corresponding 2,3,3-trimethyldihydrofuranocoumarin (31%). Treatment of 7 with 150 eq 10% NaOH/MeOH for 10 min however gave 6 (97%) uncontaminated with the cyclised isomer. Although the ^{1}H NMR signals of 6 are close to those reported for celerin with H-4 centred at 8.30 and the aromatic proton at 6.73, the large m.p. difference (62°) rules out this structure.

For the final possibility (8), 8-hydroxy-7-methoxycoumarin was condensed with 3-chloro-3-methylbut-1-yne, Cs_2CO_3 in acetone in a closed system for 36 h to give the 1,1-dimethylpropargyl ether (46%), no reaction occurring using the normal etherification conditions.[6] Semi-hydrogenation gave the corresponding 1,1-dimethylallyl ether (71%) which quantitatively underwent the desired para-Claisen rearrangement[6] in Ac_2O/NaOAc giving 9. Hydrolysis of 9 with 1% NaOH/MeOH gave 8, m.p. 158-159.5°, the ^{1}H NMR (H-4, 8.22; H-6, 6.93), UV and mass spectra of which are, like the m.p., similar to those recorded for celerin.[1]

Apart from 5-methylcoumarins, only eight C-5 alkylated coumarins are known[3] all of which possess a 7,8-dioxygenated coumarin nucleus as significantly does apigravin (10)[7] and three more of the twelve *A. graveolens* coumarins.[3] Celerin is therefore reformulated as 8-hydroxy-7-methoxy-5-(1,1-dimethylallyl)coumarin (8) and is the second example of a coumarin with a 1,1-dimethylallyl group at C-5.[3]

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