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CLAISEN REARRANGEMENTS–XIV[1,2]

SYNTHESIS OF THE COUMARIN, BENAHORIN AND REVISION OF THE STRUCTURE OF MARMELIDE

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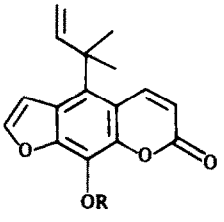
Abstract—The natural coumarin, benahorin **1** has been synthesised in five steps from xanthotoxol **4**. Marmelide has been shown to be the 3,3-dimethylallyl ether of xanthotoxol (imperatorin **9**) and not as believed the 1,1-dimethylallyl ether **7**.

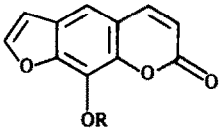
Benahorin **1**[3,4] is a unique natural coumarin in possessing a 1,1-dimethylallyl substituent at C-5.[5] This 5-carbon variant of the more commonly encountered 3,3-dimethylallyl (prenyl) moiety is normally found at either C-3 or C-8[5] of the coumarin nucleus with only clausarin[6] having both positions thus substituted. When the 1,1-dimethylallyl group is at C-8, it is always *ortho* to two oxygen functions, at C-7 and the pyran ring, and both have been used to introduce the C-8 alkenyl group by *ortho*-Claisen prenyl ether rearrangement. Initially, 7-prenyloxycoumarins were employed[7] but recently O-prenylation of a lactone-ring opened coumarin followed by Claisen rearrangement provided[8] an alternative synthetic route to furopinnarin,[9] the isomer of benahorin in which the substituents at C-5 and C-8 are interchanged. Since there is no oxygen function *ortho* to the 1,1-dimethylallyl group in benahorin, neither of these approaches is possible. Consequently we envisaged that the 1,1-dimethylallyl group could be introduced by the *para*-Claisen rearrangement of xanthotoxol 1,1-dimethylallyl ether **7**, a procedure we introduced for the first synthesis of furopinnarin.[10]

Xanthotoxol **4** has been obtained synthetically from pyrogallol[11] but is more conveniently prepared by hydriodic acid demethylation of xanthotoxin **5**,[12] which has been synthesised from 7,8-dihydroxycoumarin[13] and is available commercially.

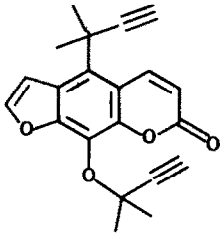
The established method for preparing a 1,1-dimethylallyl ether is by semi-hydrogenation of the corresponding 1,1-dimethylpropargyl ether,[10,14] the latter normally being obtained by etherification of



1 R = Me
2 R = Ac
3 R = H



4 R = H
5 R = Me
6 R = $CMe_2C{\equiv}CH$
7 R = $CMe_2CH{=}CH_2$
8 R = CMe_2CH_2Me
9 R = $CH_2CH{=}CMe_2$



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a phenol with 3-chloro-3-methylbut-1-yne in the presence of potassium carbonate and potassium iodide in acetone.[10,14,15] Xanthotoxol however was recovered intact after prolonged exposure to these reagents as it was with the propargyl halide in the presence of sodium carbonate in acetone, with and without 18-crown-6, and sodium hydride in either benzene or 1,3-dimethyl-2-imidazolidinone.[16] TLC monitoring of the first reaction indicated extremely slow etherification of the hindered phenol so the reaction was repeated for 60 hr in a closed system to prevent evaporation of the volatile halide. This gave the desired ether **6** in 50% yield and 9% of a crystalline $C_{21}H_{18}O_4$ by-product.

The ^{1}H NMR spectrum of **6** is in accord with the proposed structure with the doublets for H-4 and H-3′ centred at δ7.75 and 6.82, respectively, the normal positions for linear furanocoumarins unsubstituted at C-5.[17] Partial hydrogenation of **6** over 5% Pd–$BaSO_4$ gave the requisite 1,1-dimethylallyl ether **7** (85%) accompanied by the tetrahydro product **8** (8%). **7** underwent rapid and quantitative *para*-Claisen rearrangement[10] to the acetate **2** in acetic anhydride containing sodium acetate.[18] The ^{1}H NMR spectrum of **2** differs substantially from that of its precursor. A 1,1-dimethylallyl unit is still present, but not the aromatic proton, while the H-4 and H-3′ doublets have both shifted downfield to δ8.44 and 7.22, respectively, consistent with C-5 substitution. Hydrolysis of **2** with 1% methanolic NaOH for 5 min gave the corresponding phenol **3**, methylation of which gave benahorin **1** having an identical m.p. and spectroscopic properties with those published.[3,4] Direct comparison confirmed the identity.

The molecular formula and ^{1}H NMR spectrum of the by-product indicated that it was the *C,O*-bis-(1,1-dimethylpropargyl)[10,19] derivative **10**, signals being present for two 1,1-dimethylpropargyl residues with no benzenoid resonance. Whereas the H-3 doublet is centred at the normal position of δ6.33 (xanthotoxin **5**, δ6.32[17]), the doublet for the neighbouring C-4 proton has experienced spectacular deshielding to δ9.08, by far the lowest value encountered for H-4 of any coumarin[5] and downfield by 1.36 ppm from that of xanthotoxin.[17] Prior to this example, benahorin possessed the lowest known H-4 resonance (δ8.45), the bulky 1,1-dimethylallyl group at C-5 having strong *peri* interactions[20] with H-4 and H-3′ resulting in the shifts to lower fields of these resonances. For benahorin, the H-3′ doublet is centred at δ7.26 compared with δ6.78 for xanthotoxin. Similarly the H-3′ doublet of **10** is centred at δ7.19. Thus compared with 1,1-dimethylallyl, the 1,1-dimethylpropargyl group at C-5 is seen to have an additional deshielding effect on H-4, but not on H-3′. Consequently it appears that the 1,1-dimethylpropargyl substituent at C-5 in **10** adopts a conformation in solution in which the triple bond is in close proximity to the proton at C-4.[21]

In 1978, Chakraborty *et al.*[22] reported the isolation of a new $C_{16}H_{14}O_4$ ether, marmelide, from *Aegle marmelos* fruits and showed that acid treatment gave xanthotoxol **4**. Marmelide was thus an ether of xanthotoxol carrying a C_5H_9 residue which was deduced to be 1,1-dimethylallyl from the 60 MHz ^{1}H NMR spectrum—two terminal methylene protons at δ 4.8 and 5.05, one vinylic proton at δ5.6 and a 6-proton singlet at δ1.8 for the *gem*-dimethyl group. The structure of the synthetic 1,1-dimethylallyl ether of xanthotoxol **7** has been secured from its conversion into benahorin. In contrast with that of marmelide, its ^{1}H NMR spectrum exhibits the characteristic splitting pattern for the AXY system of a vinyl group with the geminal methyls resonating as a sharp 6-proton singlet at δ1.56.[5] Thus marmelide cannot be the 1,1-dimethylallyl ether of xanthotoxol. Prof. Chakraborty has kindly sent us copies of the ^{1}H NMR and IR spectra of marmelide from which it is clear that the natural product should be reformulated as the corresponding 3,3-dimethylallyl ether, imperatorin **9**. The signals at δ4.8 and 5.05 are reassigned to the two branches of the methylene doublet (*J* 7 Hz) while the methine signal at δ5.6 appears in the original spectrum as a broadened triplet (*J* 7 Hz) centred at this position. Typical of a 8-prenyloxy linear furanocoumarin the methyl signals appear as a 6-proton broadened singlet instead of the more usual two 3-proton broadened singlets.[5,23] Imperatorin is a well-known constituent of *A. marmelos* fruits having first been isolated from this source in 1930 when it was named marmelosin.[24] The revision of the structure of marmelide leaves only two natural coumarin 1,1-dimethylallyl ethers[25,26] both of which are also linear furanocoumarins.

EXPERIMENTAL

M.ps. were determined with a Kofler hot stage apparatus. Microanalyses were performed by Mrs. W. Harkness and her staff. IR spectra of solns in $CHCl_3$ were recorded by Mrs. F. Lawrie and her staff. ^{1}H NMR spectra of solns in $CDCl_3$ with TMS as internal standard were recorded on a Perkin–Elmer R32 90 MHz spectrometer. Mass spectra were recorded by Mr. A. Ritchie and his staff on an AEI–GEC MS 12 mass spectrometer. Light petroleum refers to the fraction of b.p. 40–60°.

Dimethylpropargylation of xanthotoxol **4**

A mixture of **4** (280 mg), K_2CO_3 (600 mg), KI (100 mg), 3-chloro-3-methylbut-1-yne (1.5 ml) and 2% aqueous acetone (30 ml) was refluxed with stirring in a closed system. After 12 hr, more K_2CO_3 (200 mg), KI (50 mg) and 3-chloro-3-methylbut-1-yne (1.5 ml) were added and refluxing continued for another 12 hr. Two more additions of 3-chloro-3-methylbut-1-yne (1.5 ml each) were made after 36 and 48 hr. After 60 hr, the cooled mixture was filtered through celite, the solids washed with acetone and the filtrate evaporated. The residue was partitioned between EtOAc and water, the organic layer washed with 5% Na_2CO_3 soln, brine, dried and evaporated. The residual yellow oil was chromatographed on silica gel (Merck 60), gradient elution with EtOAc–light petroleum (1:9 to 2:3) affording

(i) 5-(1,1-*Dimethylpropargyl*) - 8 - (1,1-*dimethylpropargyloxy*)*psoralen* **10** (43 mg, 9%) tan-yellow plates, m.p. 125–126° (from EtOAc–light petroleum). (Found: C, 75.25; H, 5.4. $C_{21}H_{18}O_4$ requires: C, 75.45; H, 5.45%); ν_{max} 3300, 1725 and 1575 cm^{-1}; NMR signals at δ1.83 (6H, s), 1.94 (6H, s), 2.28 (1H, s), 2.46 (1H, s), 6.33 (1H, d, *J* 9.5 Hz), 7.19 (1H, d, *J* 2.5 Hz), 7.62 (1H, d, *J* 2.5 Hz) and 9.08 (1H, d, *J* 9.5 Hz).

(ii) 8-(1,1-*Dimethylpropargyloxy*)*psoralen*, **6** (185 mg, 50%) colourless needles, m.p. 136–137° (from EtOAc–light petroleum). (Found: C, 71.4; H, 4.35. $C_{16}H_{12}O_4$ requires: C, 71.65; H, 4.45%); ν_{max} 3310, 1725, 1630 and 1585 cm^{-1}; NMR signals at δ1.86 (6H, s), 2.30 (1H, s), 6.35 (1H, d, *J* 9.5 Hz), 6.82 (1H, d, *J* 2.5 Hz), 7.44 (1H, s), 7.67 (1H, d, *J* 2.5 Hz), and 7.75 (1H, d, *J* 9.5 Hz).

Partial hydrogenation of **6**

A soln of **6** (32 mg) in EtOAc (10 ml) was hydrogenated over 5% Pd–$BaSO_4$ (11 mg) for 2 hr. After freeing from catalyst and solvent, residual solid was flash chromatographed[27] on silica gel (Fluka GF 254). Elution with EtOAc–light petroleum (1:4) gave (i) **8** (2.5 mg, 8%) colourless needles, m.p. 81–83° (from EtOAc–light petroleum); NMR signals at δ1.12 (3H, t, J 7.5 Hz), 1.38 (6H, s), 1.93 (2H, q, J 7.5 Hz), 6.25 (1H, d, J 9.5 Hz), 6.80 (1H, d, J 2.5 Hz), 7.40 (1H, s), 7.66 (1H, d, J 2.5 Hz) and 7.75 (1H, d, J 9.5 Hz) and (ii) 8-(1,1-*dimethylallyloxy*)*psoralen* **7** (27 mg, 85%) colourless needles, m.p. 114–116° (from EtOAc–light petroleum). (Found: C, 71.25; H, 5.1. $C_{16}H_{14}O_4$ requires: C, 71.1; H, 5.2%); ν_{max} 1725, 1625 and 1585 cm^{-1}; NMR signals at δ1.56 (6H, s), 5.02 (1H, dd, J 10 and 2 Hz), 5.13 (1H, dd, J 17.5 and 2 Hz), 6.34 (1H, d, J 9.5 Hz), 6.34 (1H, dd, J 17.5 and 10 Hz), 6.80 (1H, d, J 2.5 Hz), 7.40, (1H, s), 7.65 (1H, d, J 2.5 Hz) and 7.74 (1H, d, J 9.5 Hz).

Para-Claisen rearrangement

A mixture of **7** (30 mg), NaOAc (50 mg) and Ac_2O (1.5 ml) was refluxed with stirring for 30 min. The cooled mixture was filtered and evaporated and the residue partitioned between EtOAc and brine. The organic layer was washed with brine, dried and evaporated to give 8-*acetoxy*-5-(1,1-*dimethylallyl*)*psoralen* **2** (33 mg, 95%) colourless needles, m.p. 144–145° (from EtOAc–light petroleum). (Found: C, 69.4; H, 5.15. $C_{18}H_{16}O_5$ requires: C, 69.2; H, 5.15%); ν_{max} 1780, 1732, 1635 and 1590 cm^{-1}; NMR signals at δ1.70 (6H, s), 2.47 (3H, s), 5.00 (1H, dd, J 17.5 and 2 Hz), 5.12 (1H, dd, J 10 and 2 Hz), 6.23 (1H, d, J 9.5 Hz), 6.31 (1H, dd, J 17.5 and 10 Hz), 7.22 (1H, d, J 2.5 Hz), 7.60 (1H, d, J 2.5 Hz) and 8.44 (1H, d, J 9.5 Hz).

Benahorin **1**

A soln of **2** (23 mg, 0.085 mmole) in MeOH (5 ml) and 1% NaOH/MeOH (1 ml, 0.25 mmole) was stirred at room temp for 5 min. After careful neutralisation the solvent was evaporated and the residue partitioned between EtOAc and brine. Work up as above gave 8-*hydroxy*-5-(1,1-*dimethylallyl*)*psoralen* **3** (20 mg, 100%) tan-yellow plates, m.p. 168–170° (from EtOAc–light petroleum). (Found: C, 70.9; H, 5.1. $C_{16}H_{14}O_4$ requires: C, 71.1; H, 5.2%); ν_{max} 3550, 1730, 1640 and 1595 cm^{-1}; NMR signals at δ1.70 (6H, s), 4.98 (1H, dd, J 17.5 and 2 Hz), 5.12 (1H, dd, J 10 and 2 Hz), 6.26 (1H, d, J 9.5 Hz), 6.30 (1H, dd, J 17.5 and 10 Hz), 7.21 (1H, d, J 2.5 Hz), 7.65 (1H, d, J 2.5 Hz) and 8.47 (1H, d, J 9.5 Hz).

A mixture of **3** (15.5 mg), K_2CO_3 (100 mg), MeI (0.5 ml) and acetone (10 ml) was refluxed with stirring for 30 min. Work up gave benahorin **1** (16 mg, 98%) colourless plates, m.p. 89–90° (lit. 88–90°) (from light petroleum). (Found: C, 71.7; H, 5.6. Calc for $C_{17}H_{16}O_4$: C, 71.8; H, 5.65%); mass spectral peaks at m/z 284 (M^+, 100%), 269 (62), 241 (63), 238 (45), 213 (40), 210 (70), 197 (30), 141 (42) and 115 (71); ν_{max} 1730, 1620 and 1580 cm^{-1}; NMR signals at δ1.72 (6H, s), 4.25 (3H, s), 4.99 (1H, dd, J 17.5 and 2 Hz), 5.15 (1H, dd, J 10 and 2 Hz), 6.27 (1H, d, J 9.5 Hz), 6.32 (1H, dd, J 17.5 and 10 Hz), 7.26 (1H, d, J 2.5 Hz), 7.65 (1H, d, J 2.5 Hz) and 8.45 (1H, d, J 9.5 Hz) identical (mmp, UV and TLC) with an authentic sample.

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