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CLAISEN REARRANGEMENTS—VIII[1]

SYNTHESIS OF THE COUMARINS, AVICENNOL, DIPETALINE AND DIPETALOLACTONE

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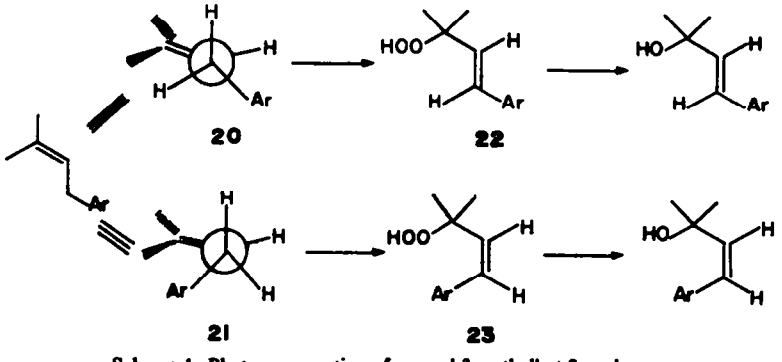
Abstract—The structures of the natural coumarins, avicennol (1) and dipetaline (2) have been confirmed by an unambiguous synthetic route from 5,7-diacetoxycoumarin. This sequence, initiated by a regiospecific O-prenylation at C-5, contains a rearrangement step which introduced the 3-methylbut-2-enyl group exclusively and in high yield at C-8. Insertion of the chromene ring gave dipetaline which on photo-oxygenation-reduction afforded avicennol as sole product. The synthesis of the dipyranocoumarin, dipetalolactone (= hortiline) (19) has also been effected.

In 1975, Gray, Waigh and Waterman reported[2] the isolation and structure of a new coumarin, avicennol (1), from the root bark of the West Indian tree *Zanthoxylum avicennae*. From spectroscopic evidence they were able to deduce that the four available positions on the benzenoid ring were substituted, with a 2,2-dimethylchromene ring, a OMe group and a *trans*-3-hydroxy-3-methylbut-1-enyl group. The latter grouping had, at this time, been encountered in only one other natural coumarin, suberenol (4), an extractive of *Z. suberosum*.[3] Despite the fact that all the functionality could be assigned, twelve possible structures remained for avicennol each varying in the position of the substituents on the fully substituted benezoid ring. The probable position of one of these substituents resulted from the addition of the lanthanide shift reagent, Eu(fod)$_3$ to avicennol trimethylsilyl ether. Although several assumptions were made in their calculations,[2] the best fit between calculated and observed chemical shift differences for the two vinyl protons in the *trans*-3-hydroxy-3-methylbutenyl group was obtained when this moiety was placed at C-8. The structure of avicennol was then uniquely determined from nuclear Overhauser experiments which required the OMe group to be adjacent to the vinyl protons of both the hydroxybutenyl substituent and the chromene ring.

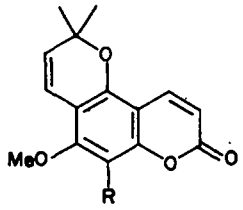
Structure 1 for avicennol has now been confirmed by a synthetic sequence in which each substituent is introduced in a regiospecific manner[4] (Scheme 2).

The synthetic plan aimed to introduce the 3-hydroxy-3-methylbutenyl group via dye-sensitised photo-oxygenation of the corresponding 8-(3-methylbut-2-enyl) coumarin (2). In the general reaction,[5] singlet oxygen abstracts an allylic H atom to form an allylic hydroperoxide in which the double bond has undergone a 1,2 shift. A *cis* cyclic ene-type mechanism has been postulated[6] in which the most favourable orientation of the C–H bond, for the allylic H atom which is transferred to oxygen, is perpendicular to the olefinic plane. An aryl 3-methylbut-2-enyl group possesses three sites at which hydrogen abstraction can occur, viz. at the benzylic position, which should be favoured mechanistatically, or at either of the terminal Me groups.

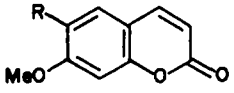
Reaction at the benzylic position could however, in principle, lead to two stereoisomeric allylic hydroperoxides (22 and 23, Scheme 1) since two conformations of the aryl 3-methylbut-2-enyl group are possible (20 and 21) which meet the mechanistic requirements of Nickon and Bagli for the reaction with singlet oxygen.[6] Conformer 20 would lead stereospecifically to the *trans* allylic hydroperoxide (22), whereas conformer (21) would afford the *cis* isomer (23). It can be seen from models that in the transition state leading from 20 to 22 there is significantly less steric congestion than that from 21 to 23 in which there is unfavourable interaction between the aryl moiety and one of the vinyl Me groups. Consequently we predicted that photo-oxygenation of 3-methylbut-2-enylaryl compounds should, when undergoing benzylic hydrogen abstraction, afford stereoselectively, if not stereospecifically, the *trans* hydroperoxide.



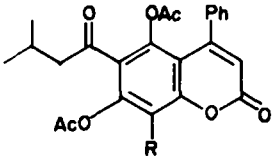
Scheme 1. Photo-oxygenation of an aryl 3-methylbut-2-enyl group.



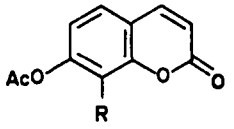
1: R = *trans* CH = CHCMe$_2$OH
2: R = CH$_2$CH = CMe$_2$
3: R = *trans* CH = CHCMe = CH$_2$



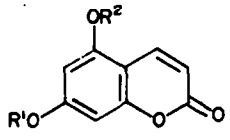
4: R = *trans* CH=CHCMe$_2$OH
5: R = CH$_2$CH=CMe$_2$
6: R = CH$_2$CHOHCMe = CH$_2$



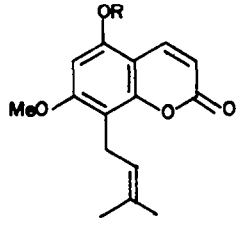
7: R = CH$_2$CH=CMe$_2$
8: R = *cis* CH=CHCMe$_2$OH



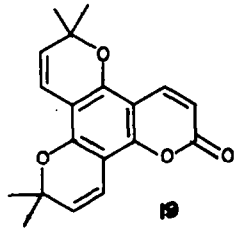
9: R = CH$_2$CH=CMe$_2$
10: R = *trans* CH=CHCMe$_2$OH



11: R' = R^2 = Ac
12: R' = Ac, R^2 = CH$_2$CH=CMe$_2$
13: R' = H, R^2 = CH$_2$CH=CMe$_2$
14: R' = Me, R^2 = CH$_2$CH=CMe$_2$
15: R' = R^2 = CMe$_2$C≡CH



16: R = CMe$_2$C≡CH
17: R = H
18: R = CO(CH$_2$)$_2$Me



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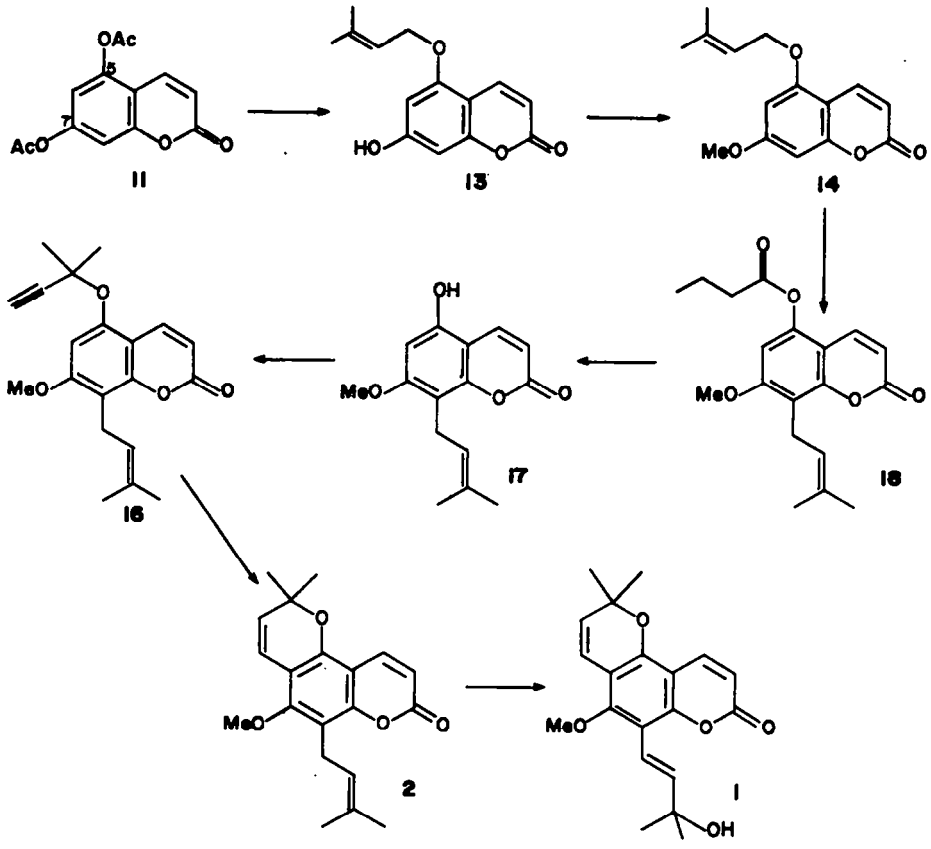
Only two examples of the photo-oxygenation of (3-methylbut-2-enyl)coumarins have been reported. Mammeisin acetate (7), after haematoporphyrin-sensitised photo-oxygenation followed by reduction, was found to give a single allylic alcohol to which the *cis* stereochemistry (8) was assigned.[7] More recently,[8] Rose Bengal-sensitised photo-oxygenation of suberosin gave a 2:1 mixture of the isomeric allylic alcohols (4 and 6) in poor yield.

Prior to embarking on a synthesis of the avicennol precursor (2), we decided to investigate the photo-oxygenation of a model compound, osthenol acetate (9). Photo-oxygenation of 9 in pyridine using haemotoporphyrin as sensitiser proceeded cleanly to give, after NaI reduction, a single product (52%) which was identified as the *trans* allylic alcohol (10) from its NMR spectrum. The possibility that an erroneous assignment of stereochemistry was made in the earlier study[7] of mammeisin acetate has recently been reached independently.[4,9] Hlubucek *et al.*[10] have shown that the 2,2-dimethylchromene ring system can be formed in high yield by pyrolysis of the appropriate 1,1-dimethylpropargyl aryl ether. This then prompted us to consider the bis ether (16) as the key intermediate for the avicennol synthesis.

A method for preparing the requisite phenolic precursor (17) of 16 from the readily available 5,7-diacetoxycoumarin (11) had been established in these laboratories.[11] The synthetic process has now been simplified and improved to provide 17 regiospecifically in good overall yield in a four step sequence. Previously we had observed that 3-methylbut-2-enylation of 11 proceeded slightly more rapidly at C-5 than at C-7 leading to a mixture of isomeric acetates from which the more abundant isomer (12) could be separated by fractional crystallization.[11] Mild base hydrolysis then gave the phenol (13). It has been found possible, by using only a slight excess of 1-bromo-3-methylbut-2-ene/K_2CO_3 in refluxing 1,2-dimethoxyethane and employing an aqueous work up, to produce 13 directly in 60% yield. After methylation, we utilised the regiospecific rearrangement of 14, first encountered during the synthesis of the coumarin toddaculin,[11] to insert the 3-methylbut-2-enyl moiety at C-8.

When 14 is heated to 180° in diethylaniline containing



Scheme 2. Synthetic route to dipetaline (2) and avicennol (1).

butyric anhydride, the *para* Claisen rearrangement product (18) is formed exclusively in 85% yield. It is indeed remarkable that no *ortho* rearrangement product can be detected even though the ether possess a vacant *ortho* position.[11] The butyrate (18) was saponified under very mild conditions to give the phenol (17) which was readily converted to the required 1,1-dimethylpropargyl ether (16). Rearrangement occurred to the remaining *ortho* position when this ether was heated at 180°, giving the pyranocoumarin (2), in an overall yield of 30% from 5,7-diacetoxycoumarin.

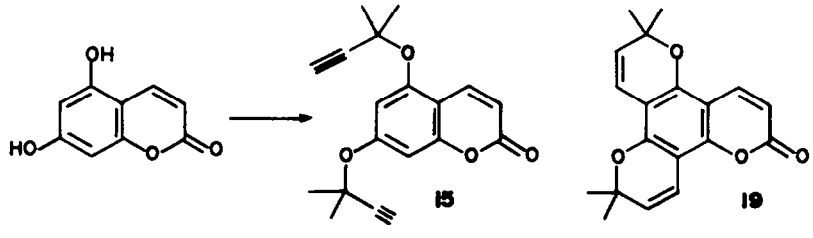
Haematoporphyrin-sensitised photo-oxygenation of 2 in pyridine produced a single hydroperoxide, which, after reduction with triphenylphosphine, afforded only the *trans* allylic alcohol (1), as had been observed with osthenol acetate (9). The synthetic avicennol and that of natural provenance were found to be completely identical. Since avicennol on controlled dehydration has been shown[2] to give avicennin (3), a coumarin from *Zanthoxylum avicennae* the structure of which[12] until recently was in doubt, our synthesis of avicennol provides a formal synthesis of avicennin, thereby confirming its structure.

Structure (2) has been tentatively assigned on spectroscopic grounds to dipetaline, a new coumarin which co-crystallised with another new coumarin, dipetalolactone, from the root bark of *Z. dipetalum* and could not be obtained in a pure state.[13] Direct comparison of synthetic and natural samples has now enabled the dipetaline assignment to be confirmed.

The unique dipyranocoumarin structure (19) has been assigned[13] to dipetalolactone and more recently to hortiline, a coumarin from the roots of *Hortia arborea*.[14] Its synthesis was readily achieved by pyrolysis at 180° of the bis(1,1-dimethylpropargyl) ether (15) obtained directly from 5,7-dihydroxycoumarin (Scheme 3).

EXPERIMENTAL

M.ps were determined with a Kofler hot stage apparatus. Microanalyses were performed by Mrs. W. Harkness and her staff. IR spectra were recorded on a Perkin Elmer 225 spec-



Scheme 3. Synthetic route to dipetalolactone (19).

trophotometer by Mrs. F. Lawrie and her staff. ^{1}H NMR spectra of solutions in $CDCl_3$ with TMS as internal standard were recorded on a Varian T-60 or by Mr. J. Gall on a Varian HA-100 spectrometer. ^{13}C NMR spectra were recorded by Dr. D. S. Rycroft on a Varian XL-100 spectrometer. Mass spectra were recorded by Mr. A. Ritchie with an AEI-GEC MS 12 Mass spectrometer. UV spectra of EtOH solutions were recorded on a Unicam SP800 spectrophotometer. Kieselgel GH_{254}(Merck) was used for preparative TLC. Light petroleum refers to the fraction of b.p. 60–80°.

Photo-oxygenation of osthenol acetate. O_2 was bubbled through a solution of osthenol acetate[15] (9; 500 mg) in pyridine (70 ml) containing haematoporphyrin (20 mg) with irradiation from a 60 watt lamp for 24 hr. The solvent was evaporated, the residue diluted with water and extracted with EtOAc. The organic layer was washed with sat. $CuSO_4$ aq, brine, dried and evaporated. The residual brown oil (520 mg) in EtOH (70 ml) was heated for 18 hr with glacial HOAc (1.8 ml) and NaI (5 g). Work up gave a brown oil (470 mg) which after purification by TLC ($CHCl_3$) furnished the *allylic alcohol* (10; 270 mg, 52%) as a colourless oil; NMR: δ 1.43(6H, s), 2.33(3H, s), 2.63(1H, bs, disappears on addition of D_2O), 6.38(1H, d, J = 9.5 Hz), 6.73(2H, s), 7.03 and 7.38(each 1H, d, J = 9 Hz), and 7.70(1H, d, J = 9.5 Hz). On addition of a small amount of Eu(fod)$_3$ the signal at 6.73 separated into two signals at 9.15 and 9.60 (each 1H, d, J = 17 Hz); $\nu_{max}^{CHCl_3}$ 3500, 1740, 1600, 1114 and 970 cm^{-1}; mass spectral peaks at *m/e* 288(4%) ($C_{16}H_{16}O_5$ requires: M$^+$ 288), 246 (12), 231(14), 228(20), 213(100) and 149(74).

Prenylation of 5,7-diacetoxycoumarin. A mixture of 11 (3.3 g), K_2CO_3 (5.9 g) and 1-bromo-3-methylbut-2-ene (6.88 ml) in 1,2-dimethoxyethane (65 ml) was refluxed for 18 hr. After filtration and evaporation, the residue was dissolved in a mixture of EtOAc and water, the organic layer washed with K_2CO_3 aq (5% w/v), brine, dried and evaporated. Purification of the yellow oil by TLC [EtOAc-light petroleum (3:7)] furnished 5,7-di((3-methylbut-2-enyloxy) coumarin (0.83 g, 21%), needles, m.p. 78–80° (lit.[11] 79–81°) and 13 (1.86 g, 60%), plates, m.p. 142–144° from ether (lit.[11] 143–145°).

Methylation of 13 *and para-Claisen rearrangement.* A mixture of 13 (1 g), K_2CO_3(1.2 g) and MeI(1.7 ml) in acetone (40 ml) was refluxed for 2 hr. Work up gave the methyl ether (14; 975 mg, 92%), m.p. 91–94° (lit.[16] 90–92°). A soln of 14 (0.7 g) in N,N-diethylaniline (5 ml) and butyric anhydride (2 ml) was refluxed for 1 hr at 175°. Work up gave the butyrate (18, 0.76 g, 85%), m.p. 98–99° (lit.[11] 98–100°) which on hydrolysis with methanolic 2% Na_2CO_3 aq gave 17 (511 mg, 86%) m.p. 195–197° (lit.[11] 195–197°).

Dipetaline. A mixture of 17 (300 mg), K_2CO_3(420 mg), KI(100 mg) and 2-chloro-2-methylbut-3-yne(500 mg) in 2% aqueous acetone (30 ml) was refluxed for 18 hr. After filtration and evaporation, the residue was dissolved in a mixture of EtOAc and water, the organic layer washed with K_2CO_3 (5% w/v), brine, dried and evaporated to give the *propargyl ether* (16; 293 mg, 78%) as a yellow oil which could not be separated from a small amount of 2; NMR signals at δ 1.63 (3H, bs), 1.72(6H, s), 1.81(3H, bs), 2.73(1H, s), 3.41(2H, bd, J = 7 Hz), 3.88(3H, s), 5.20(1H, bt, J = 7 Hz), 6.08(1H, d, J = 9.5 Hz), 7.08(1H, s) and 7.83(1H, d, J = 9.5 Hz); $\nu_{max}^{CCl_4}$ 3303, 1745 and 1605 cm^{-1}; (Found: *m/e*, 326; $C_{20}H_{22}O_4$ requires: M$^+$, 326).

A soln of 16 (300 mg) in N,N-diethylaniline (4 ml) was heated at 175° for 2 hr under N_2. The cooled soln was poured into water, extracted with EtOAc and the organic layer washed with 1 M HCl, brine dried and evaporated to give *dipetaline* (2; 264 mg, 88%), m.p. 113–114.5° (from ether–light petroleum) (Found: C, 73.3; H, 6.6. $C_{20}H_{22}O_4$ requires: C, 73.6; H, 6.8%), NMR: δ 1.46(6H, s), 1.68 and 1.84 (each 3H, bs), 3.45(2H, bd, J = 7 Hz), 3.78(3H, s), 5.22(1H, bt, J = 7 Hz). 5.63(1H, d, J = 10 Hz), 6.23(1H, d, J = 9.5 Hz), 6.57(1H, d, J = 10 Hz) and 8.00(1H, d, J = 9.5 Hz); $\nu_{max}^{CCl_4}$ 1745, 1620 and 1590 cm^{-1}; λ_{max} 229, 264, 272, 294 and 315(sh) nm (log ϵ 4.62, 4.44, 4.30, 4.52 and 4.29); mass spectral peaks at *m/e* 326(M$^+$, 30%), 311 (100), 253 (19) and 241 (13). The synthetic sample was identical with a sample of natural dipetaline[13] kindly provided by Dr. P. G. Waterman.

Avicennol. O_2 was bubbled through a soln of 2 (250 mg) in pyridine (60 ml) containing haematoporphyrin (25 mg) and the soln irradiated by a 60 watt lamp for 17 hr. Work up gave the hydroperoxide as a brown oil (302 mg) which was kept in ether (50 ml) with triphenylphosphine (270 mg) at 0° for 15 hr. Evaporation of the filtered soln gave a yellow solid (560 mg) which was purified by TLC [MeOH–$CHCl_3$ (1:99)] giving *avicennol* (1) as yellow plates (131 mg, 50%), m.p. 123.5–125° (from EtOAc–light petroleum) (lit.[2] 123–124.5°) (Found: C, 70.35; H, 6.65. Calc for $C_{20}H_{22}O_5$: C, 70.2; H, 6.45%); NMR: δ 1.59 and 1.60 (each 6H, s), 2.58 (1H, s, disappears on addition of D_2O), 3.80(3H, s), 5.69, 6.27 and 6.65 (each 1H, d, J = 10 Hz), 6.81 and 6.95 (each 1H, d, J = 16 Hz) and 8.06 (1H, d, J = 10 Hz); ν_{max}^{KBr} 3470, 1715, 1632, 1612 and 1580 cm^{-1}; λ_{max} 250, 257 and 301 nm (log ϵ 4.50, 4.63 and 4.27); mass spectral peaks at *m/e* 342 (M$^+$, 3%), 327 (78), 309 (100) and 277 (14). The synthetic sample was identical with a sample of natural avicennol[2] kindly provided by Dr. P. G. Waterman.

Dipetalolactone. A mixture of 5,7-dihydroxycoumarin (600 mg), K_2CO_3 (1.68 g), KI and 2-chloro-2methylbut-3-yne (3 g) in 2% aqueous acetone (120 ml) was refluxed for 22 hr. Work up gave the bis *ether* (15) as a yellow oil (500 mg, 43%); NMR: δ 1.73 and 1.76(each 6H, s), 2.70(2H, bs), 6.33(1H, d, J = 9.5 Hz), 7.03 and 7.45(each 1H, d, J = 2 Hz), and 7.94(1H, d, J = 9.5 Hz); $\nu_{max}^{CCl_4}$ 3300, 1745 and 1605 cm^{-1}; (Found: *m/e* 310. $C_{19}H_{18}O_4$ requires: M$^+$ 310).

A soln of 15 (500 mg) in N,N-diethylaniline (10 ml) was heated at 180° for 2 hr. The cooled soln was poured onto water and extracted with EtOAc. The EtOAc soln was washed with 1M HCl, brine, dried and evaporated to give a brown oil which after purification by TLC ($CHCl_3$) furnished *dipetalolactone* (19; 310 mg, 62%) as yellow cubes, m.p. 135–136° (ether–light petroleum) (lit.[13] 119–120°) (Found: C, 73.25: H, 5.85. $C_{19}H_{18}O_4$ requires: C, 73.55; H, 5.85%); NMR: δ 1.48(12H, s), 5.53 and 5.57 (each 1H, d, J = 10 Hz), 6.41(1H, d, J = 9.5 Hz), 6.63 and 6.80(each 1H, d, J = 10 Hz) and 7.93(1H, d, J = 9.5 Hz); $\nu_{max}^{CCl_4}$ 1744, 1645 and 1600 cm^{-1}; λ_{max} 222, 244 (sh), 250, 297, 308 and 343 nm (log ϵ 4.25, 4.47, 4.53, 4.46, 4.38 and 4.12); mass spectral peaks at *m/e* 310 (M$^+$, 30%), 295 (100) and 149 (29). The synthetic sample was identical with a sample of natural dipetalolactone kindly provided by Dr. P. G. Waterman.

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