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SYNTHESIS OF THE NATURAL COUMARINS, MURRAOL (CM-c_2), *TRANS*-DEHYDROOSTHOL AND SWIETENOCOUMARIN G

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Key Word Index—*Cnidium monnieri*; Umbelliferae; fruit; coumarin syntheses; CM-c_2; murraol; *trans*-dehydroosthol; swietenocoumarin G.

Abstract—The coumarin CM-c_2 from *Cnidium monnieri*, 7-methoxy-8-(3-hydroxy-3-methylbut-1-enyl) coumarin, has been synthesized by palladium acetate-catalysed condensation of 7-methoxy-8-iodocoumarin with 2-methylbut-3-en-2-ol. Its stereochemistry follows from its conversion to *trans*-dehydroosthol. The identity of CM-c_2 and murraol has been established. Swietenocoumarin G has been prepared similarly from bergaptol.

INTRODUCTION

The fruit of *Cnidium monnieri* (L.) Cuss. is used in Japan as a topical agent for skin conditions such as eczema and pruritis. During a recent investigation of possible anti-allergic principles from the fruit, a number of coumarins were isolated [1] including a new $C_{15}H_{16}O_4$ coumarin mp 138–141° designated CM-c_2 for which structure **1** was proposed from its ^{1}H and ^{13}C NMR spectra. However, structure **1** can represent two coumarins since stereoisomers are possible differing in the orientation of the groups about the double bond. Although it is normally possible to assign the stereochemistry of a disubstituted alkene from the coupling constants of the signals for the two vinyl protons, such a method is not suitable in this case for the two olefinic protons gave rise to a singlet at δ6.88.

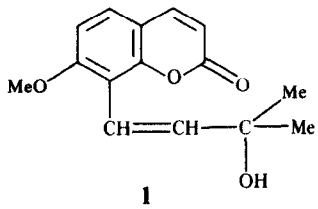
The 3-hydroxy-3-methylbut-1-enyl moiety, albeit a relatively rare biogenetic modification of the prenyl unit, has been encountered in the *E* form in a number of naturally occurring oxygen heterocycles [2–7]. In the spectra of suberenol [2] and avicennol [3] the first natural coumarins found with this grouping, the two olefinic protons appeared as an AB quartet with the characteristic coupling constant of about 16 Hz. More recently however the same protons in swietenocoumarin G (**2**) and swietenocoumarin H (**3**) were found to have identical chemical shifts appearing therefore as two-proton singlets at δ7.10 and 7.18, respectively [4]. Since similar accidental equivalence of such vinyl protons was observed in the spectra of the synthetic coumarin (**6**) [8] and of two natural flavanones [5, 6] it seemed likely that CM-c_2 was the *E* isomer (**7**).

RESULTS AND DISCUSSION

We envisaged that the stereoisomer (**7**) could be prepared by dye-sensitized photo-oxygenation of osthol (**10**) followed by reduction of the intermediate allylic hydroperoxide. This singlet-oxygen process had worked well in our synthesis of avicennol [8]. Moreover we had employed osthenol acetate (**9**) as a model compound and found that it could be converted into the allylic alcohol (**6**) in moderate yield. When the corresponding methyl ether (**10**) was subjected to photooxygenation in pyridine with haematoporphyrin as sensitizer, the mp 122–123° of the product was significantly lower than that reported for CM-c_2. However, it was almost identical with that reported [1] for the isomer CM-c_1, another *C. monnieri* constituent, commonly known as auraptenol (**11**) [9]. Confirmation of this came from the ^{1}H NMR spectrum which revealed a 2-hydroxy-3-methylbut-3-enyl side chain. Thus in the photo-oxygenation of osthol the allylic hydrogen atom preferentially abstracted by singlet oxygen came from a terminal methyl group rather than as anticipated from the benzylic position.

An alternative synthetic route to CM-c_2 was thus required. We found that Heck condensation of 7-methoxy-8-iodocoumarin with 2-methylbut-3-en-2-ol could be effected in good yield at 90° in the presence of palladium acetate, sodium hydrogencarbonate and tetrabutylammonium bromide [10, 11]. The ^{1}H NMR spectrum and mp 138–142° of the product (**7**) were in complete agreement with those reported for CM-c_2. In a recent ergot alkaloid synthesis, Somei and Yamada [12] have shown that condensation of 3-formyl-4-iodoindole with 2-methylbut-3-en-2-ol in the presence of palladium acetate and triethylamine resulted in the introduction of an (*E*)-3-hydroxy-3-methylbut-1-enyl moiety. We considered that dehydration to dehydroosthol, both stereoisomers of which are now known to occur naturally [13, 14], could be used to determine the stereochemistry of CM-c_2. The tertiary allylic alcohol (**7**) was resistant to attempted dehydration with molecular sieves [15] while a complex mixture was produced using phosgene in toluene [3]. However, refluxing a pyridine solution of the alcohol with toluene-*p*-sulphonyl chloride afforded only *trans*-dehydroosthol [13] thereby confirming the *E* configuration of CM-c_2.

In their very recent paper on the isolation of *cis*-dehydroosthol from *Murraya exotica*, Ito and Furukawa also reported [14] another new coumarin mp 105–107° which they named murraol. The latter was deduced to have the structure (**7**) which we had assigned by synthesis



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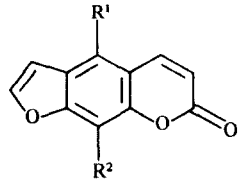
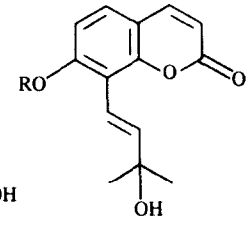
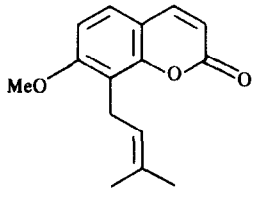


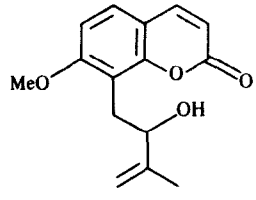
2 R^1 = OMe, R^2 = (*E*)CH=CHCMe$_2$OH
3 R^1 = H, R^2 = (*E*)CH=CHCMe$_2$OH
4 R^1 = OH, R^2 = H
5 R^1 = OMe, R^2 = I



6 R = Ac
7 R = Me
8 R = H



9 R = Ac
10 R = Me



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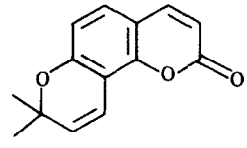

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to CM-c_2 which also has a significantly higher melting point. The fragment ions in the mass spectrum were identical to those we have observed and the ^{1}H NMR signals of murraol were almost identical to ours except that the two olefinic protons gave rise to a pair of doublets, $J = 16.4$ Hz at δ7.02 and 6.93. Although Professor Furukawa was unable to provide us with a sample of murraol due to the paucity of natural product, he was able to show that our synthetic sample gave identical IR, UV, ^{1}H and ^{13}C NMR and mass spectra. The anomalous behaviour of the olefinic signals in the ^{1}H NMR spectra was shown to be a consequence of the spectrum of murraol having been recorded at 270 MHz while that of the synthetic sample, and presumably CM-c_2 also, had been obtained at lower field.

The problem of differing melting points remained until Professor H. Furukawa [personal communication] isolated murraol from a second source, *Murraya paniculata* leaves. Now the murraol was found to have the same melting point as our synthetic sample. Confirmation of bimorphism came from recrystallizing the lower melting form of murraol from acetone and seeding with a crystal of our synthetic sample. The higher melting form was now obtained [H. Furukawa, personal communication] confirming the identity of murraol, CM-c_2 and our synthetic coumarin.

The phenol (**8**), of which murraol is the methyl ether, has not yet been recognized as a natural product. We wished however to effect its synthesis since potentially it is a precursor of structurally more complex natural coumarins [16]. As it was unlikely that sufficiently mild conditions could be found to selectively demethylate murraol, we chose to prepare it from 7-acetoxy-8-iodocoumarin. When the Heck condensation with 2-methylbut-3-en-2-ol was carried out at 105°, the sole product was not **6** as had been anticipated. Although a five-carbon moiety had indeed been introduced, the condensation had proceeded with concomitant elimination of acetic acid. Six pairs of doublets in the ^{1}H NMR spectrum and the electron-impact MS base peak characteristically [17] at [M − 15] showed conclusively that the pyranocoumarin seselin (**12**) had been produced [16, 18]. When the Heck reaction was repeated at 65° the required acetoxycoumarin (**6**) was now the only product. Mild alkaline hydrolysis rapidly afforded the desired crystalline phenol (**8**).

A similar synthetic route was envisaged for swietenocoumarin G (**2**). Only one synthesis of bergaptol (**4**) has been recorded [19] but its geranyl ether bergamottin is a major constituent of bergamot oil and bergaptol is obtained readily on acid hydrolysis [20]. Iodination of bergaptol was effected with iodine and yellow mercury(II)

oxide in acetone–chloroform [21]. The derived methyl ether (**5**) underwent the Heck reaction with 2-methylbut-3-en-2-ol to give swietenocoumarin G the melting point and spectroscopic properties of which were identical with those reported for the natural coumarin [4].

EXPERIMENTAL

For general experimental see ref. [22].

Photo-oxygenation of osthol. Oxygen was bubbled through a soln of **10** (108 mg) in pyridine (30 ml) containing haematoporphyrin (7 mg) with irradiation from a 60 W lamp for 24 hr [8]. The solvent was evapd, the residue diluted with water and extracted with EtOAc. The organic layer was washed with satd $CuSO_4$ aq., brine, dried and evapd. The residual brown oil (128 mg) in EtOH (17 ml) was heated for 24 hr with HOAc (0.4 ml) and NaI (1.3 g). Work-up and purification by TLC [EtOAc–petrol (2:3)] gave (±)-auraptenol (**11**) as needles (34 mg), mp 122–123° (EtOAc–petrol) (lit [1] 119–122°); ^{1}H NMR δ: 1.88 (3H, *s*), 2.20 (1H, *br s*), 3.15 (2H, *m*), 3.92 (3H, *s*), 4.38 (1H, *br t*), 4.80 and 4.90 (each 1H, *br s*), 6.22 (1H, *d*, J = 9.5 Hz), 6.82 and 7.32 (each 1H, *d*, J = 9 Hz) and 7.62 (1H, *d*, J = 9.5 Hz).

(E)-7-*Methoxy*-8-(3-*hydroxy*-3-*methylbut*-1-*enyl*)*coumarin* (*CM-c*$_2$). A mixture of 7-methoxy-8-iodocoumarin (530 mg), 2-methylbut-3-en-2-ol (1.16 g), tetrabutylammonium bromide (1.93 g), $NaHCO_3$ (500 mg) and $Pd(OAc)_2$ (40 mg) in DMF (10 ml) under Ar was heated in an oil bath at 90° for 24 hr. The cooled mixture was filtered through Celite and the filtrate diluted with EtOAc, washed with brine, dried and evapd. Purification by chromatography on silica gel (Merck 60) and elution with $CHCl_3$–petrol (1:4 to 4:1) gave (*E*)-7-Methoxy-8-(3-hydroxy-3-methylbut-1-enyl)coumarin (**7**) as needles (400 mg), mp 138–142° (EtOAc–petrol) (lit. [1] 138–141°) (Found: C, 68.95; H, 6.19. $C_{15}H_{16}O_4$ requires: C, 69.21; H, 6.19%); ^{1}H NMR δ: 1.48 (6H, *s*), 3.88 (3H, *s*), 6.25 (1H, *d*, J = 9.5 Hz), 6.84 (1H, *d*, J = 9 Hz), 6.88 (2H, *s*), 7.30 (1H, *d*, J = 9 Hz) and 7.60 (1H, *d*, J = 9.5 Hz); IR ν_{max}^{KBr} 3420, 1720, 1600, 1250, 1050 and 837 cm^{-1}; EIMS *m/z* 260.1047 (M^+, 15%) ($C_{15}H_{16}O_4$ requires M^+ 260.1029), 242 (90), 227 (27), 217 (100), 183 (52), 155 (36), 128 (32) and 115 (30).

trans-*Dehydroosthol.* A soln of the allylic alcohol (**7**; 65 mg) and toluene-*p*-sulphonyl chloride (54 mg) in pyridine (2 ml) was refluxed under Ar for 2 hr. Work-up and purification by TLC [EtOAc–petrol (1:4) then (2:3)] gave *trans*-dehydroosthol as needles (20 mg), mp 81–82° (Et_2O–petrol) (lit [13] 84°); ^{1}H NMR δ: 2.00 (3H, *br s*), 3.82 (3H, *s*), 4.90 (2H, *m*), 6.15 (1H, *d*, J = 9.5 Hz), 6.77 (1H, *d*, J = 8.5 Hz), 6.80 (1H, *d*, J = 15 Hz), 7.18 (1H, *d*, J = 8.5 Hz), 7.42 (1H, *d*, J = 15 Hz) and 7.50 (1H, *d*, J = 9.5 Hz); IR $\nu_{max}^{CHCl_3}$ 1735, 1605, 1500 and 835 cm^{-1}; EIMS *m/z* 242.0899 (M^+, 14%) ($C_{15}H_{14}O_3$ requires M^+ 242.0897), 228 (24), 212 (52), 187 (15), 183 (16), 155 (24), 131 (34), 115 (47) and 91 (100).

Condensation of 7-*acetoxy*-8-*iodocoumarin with* 2-*methylbut*-3-*en*-2-*ol.* (i) At 65°. A mixture of 7-acetoxy-8-iodocoumarin (530 mg), 2-methylbut-3-en-2-ol (1.16 g), tetrabutylammonium bromide (1.93 g), $NaHCO_3$ (530 mg) and $Pd(OAc)_2$ (80 mg) in DMF (10 ml) under Ar was heated at 65° for 24 hr. Work-up and chromatography on silica gel and elution with EtOAc–petrol (1:1) gave (*E*)-7-acetoxy-8-(3-hydroxy-3-methylbut-1-enyl) coumarin (**6**) as an oil (368 mg); ^{1}H NMR δ: 1.43 (6H, *s*), 2.33 (3H, *s*), 2.63 (1H, *br s*), 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); EIMS *m/z* 288 (M^+, 4%), 246 (15), 231 (14), 228 (20), 213 (100) and 149 (74). A soln of **6** (220 mg) in MeOH (8 ml) was stirred with Na_2CO_3 aq (2% w/v, 2 ml) for 15 min. After neutralization with 0.1 M HCl, work-up using EtOAc gave (*E*)-7-hydroxy-8-(3-hydroxy-3-methylbut-1-enyl) coumarin (**8**) as needles (170 mg), mp 159–160° (EtOAc–petrol) (Found: C, 68.29; H, 5.69. $C_{14}H_{14}O_4$ requires: C, 67.99; H, 5.81%); ^{1}H NMR δ: (DMSO-d_6) 1.32 (6H, *s*), 4.64 (1H, *br s*), 6.18 (1H, *d*, J = 9.5 Hz), 6.78 (1H, *d*, J = 16 Hz), 6.94 (1H, *d*, J = 8.5 Hz), 6.96 (1H, *d*, J = 16 Hz), 7.35 (1H, *d*, J = 8.5 Hz), 7.90 (1H, *d*, J = 9.5 Hz) and 10.91 (1H, *s*); IR $\nu_{max}^{CHCl_3}$ 3600, 3500, 2980, 1735, 1620 and 1610 cm^{-1}; UV λ_{max}^{EtOH} 226 (log ε 4.43), 286 (4.17) and 328 (4.24) nm; EIMS *m/z* 246 (M^+, 0.1%), 228 (24), 213 (100) and 185 (22). (ii) At 105°. A mixture of 7-acetoxy-8-iodocoumarin (120 mg), 2-methylbut-3-en-2-ol (200 mg), tetrabutylammonium bromide (420 mg), $NaHCO_3$ (100 mg) and $Pd(OAc)_2$ (7 mg) in DMF (5 ml) under Ar was heated at 105° for 24 hr. Work-up and chromatography on silica gel and elution with $CHCl_3$–petrol (1:4) gave seselin (**12**) as needles (48 mg), mp 120–121° (MeOH) (lit [16] 119–120°); ^{1}H NMR δ: 1.50 (6H, *s*), 5.85 (1H, *d*, J = 10 Hz), 6.26 (1H, *d*, J = 9.5 Hz), 6.75 (1H, *d*, J = 9 Hz), 6.93 (1H, *d*, J = 10 Hz), 7.25 (1H, *d*, J = 9 Hz) and 7.63 (1H, *d*, J = 9.5 Hz); EIMS *m/z* 228 (M^+, 13%), 213 (100), 185 (25) and 128 (16).

Swietenocoumarin G. HgO (1.16 g) and I_2 (1.36 g) were added alternately portionwise to a stirred solution of bergaptol (**4**; 1.32 g) in Me_2CO (80 ml) and $CHCl_3$ (20 ml) and the mixture refluxed for 24 hr. The cooled mixture was filtered through Celite and the filtrate evapd. The residue was extracted with EtOAc, washed with $Na_2S_2O_3$ aq., brine, dried and evapd. A soln of the residual solid (1.80 g) in Me_2CO was refluxed with K_2CO_3 (1.7 g) and MeI (4.4 ml) for 6 hr. Work-up and purification by chromatography on silica gel and elution with EtOAc–petrol (1:4 to 4:1) gave 8-iodobergapten (**5**) as yellow needles (0.53 g), mp 197–199° (EtOAc–petrol); IR ν_{max}^{KBr} 1732, 1610 and 1350 cm^{-1}; ^{1}H NMR δ: 4.30 (3H, *s*), 6.25 (1H, *d*, J = 9.5 Hz), 7.06 and 7.50 (each 1H, *d*, J = 2 Hz) and 8.20 (1H, *d*, J = 9.5 Hz); EIMS *m/z* 342 (M^+, 39%), 216 (100), 201 (35), 173 (75) and 145 (39).

A mixture of 8-iodobergapten (50 mg), 2-methylbut-3-en-2-ol (103 mg), tetrabutylammonium bromide (172 mg), $NaHCO_3$ (50 mg) and $Pd(OAc)_2$ (9 mg) in DMF (4 ml) under Ar was heated at 95° for 24 hr. Work-up gave swietenocoumarin G (**2**) as yellow needles (37 mg), mp 187–188° (EtOAc–petrol) (lit [4] 190°); UV λ_{max}^{EtOH} 224 (log ε 4.35), 238 (4.35), 245 (4.30), 277 (4.38), 287 (4.45) and 312 (4.10) nm; ^{1}H NMR δ: 1.50 (6H, *s*), 4.20 (3H, *s*), 6.30 (1H, *d*, J = 9.5 Hz), 7.05 (1H, *d*, J = 2 Hz), 7.10 (2H, *s*), 7.65 (1H, *d*, J = 2 Hz) and 8.10 (1H, *d*, J = 9.5 Hz); EIMS *m/z* 300 (M^+, 26%), 285 (67), 282 (53), 257 (41), 243 (29) and 229 (100).

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