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SYNTHESIS OF COMPLEX CHALCONES OF *FLEMINGIA* SPP.

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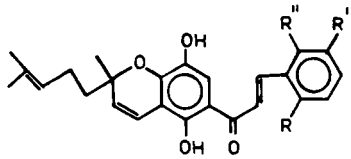
ABSTRACT.—The synthesis of naturally occurring 2′,5′-dihydroxy-2″,2″-dimethyl-2*H*-pyrano(3′,4′:5″,6″) chalcone and bioactive 2′,5′-dihydroxy-2-methoxy-2″-methyl-2″-(4-methyl-3-pentenyl)-2*H*-pyrano-(3′,4′:5″,6″) chalcone is described. An intramolecular oxypalladation reaction has been utilized for the synthesis of the intermediate chromene components.

The 2,2-dimethyl-2*H*-chromenes are an important class of naturally occurring heterocyclic compounds possessing a wide range of physiological activities (1,2). Also, they are useful intermediates in the synthesis of complex natural products.

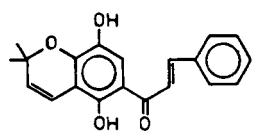
"Wars" is a drug obtained from the seed pods of *Flemingia rhodocarpa* Baker (Leguminosae). It is used as a medication in East Africa, and it also finds application as a cosmetic, dye, and adulterant. Cardillo *et al.* (3) isolated the three orange red chalcones, flemingins A [**1**], B [**3**], and C [**4**], from the extract of the seed pods of the plant. These compounds have a 2′,4′,5′,2-tetrahydroxylation pattern which is not commonly encountered.

An important feature of the flemingins is that they possess a C_{10}-alkylated unit that is cyclized to a six-membered ring. One other natural product, chromenochalcone [**5**], has also been isolated by Cardillo *et al.* (4) from *F. rhodocarpa*. Compound **5** is similar to the flemingins except for the fact that it is 2,2-dimethyl substituted and there is no oxygenation in ring A. It has been suggested that *Flemingia* spp. have the peculiar ability to introduce hydroxy groups para to those coming from the acetate pathway. Flemingin A trimethyl ether [**6**], flemingin B tetramethyl ether [**7**], and flemingin C tetramethyl ether [**8**] have been synthesized by Crombie *et al.* (5).

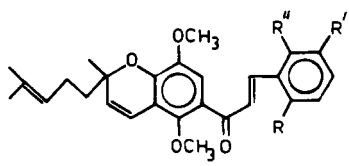
Chromenochalcone and the flemingins are interesting synthetic targets in view of their unusual oxygenation pattern. In continuation of our studies on the synthesis of 2,2-dimethyl-2*H*-chromenes (6), we report here the syntheses of chromenochalcone [**5**] and the monomethyl ether **2** of flemingin A. The synthetic methodology adopted is shown in Scheme 1. Our initial targets were the acetylchromenes **12** and **16**. Resacetophenone [**9**] was condensed with 2-methyl-3-buten-2-ol in BF_3-etherate to yield the isopentenyl derivatives **10** (33%) and **11**. The required substrate **10** was intramolecularly cyclized



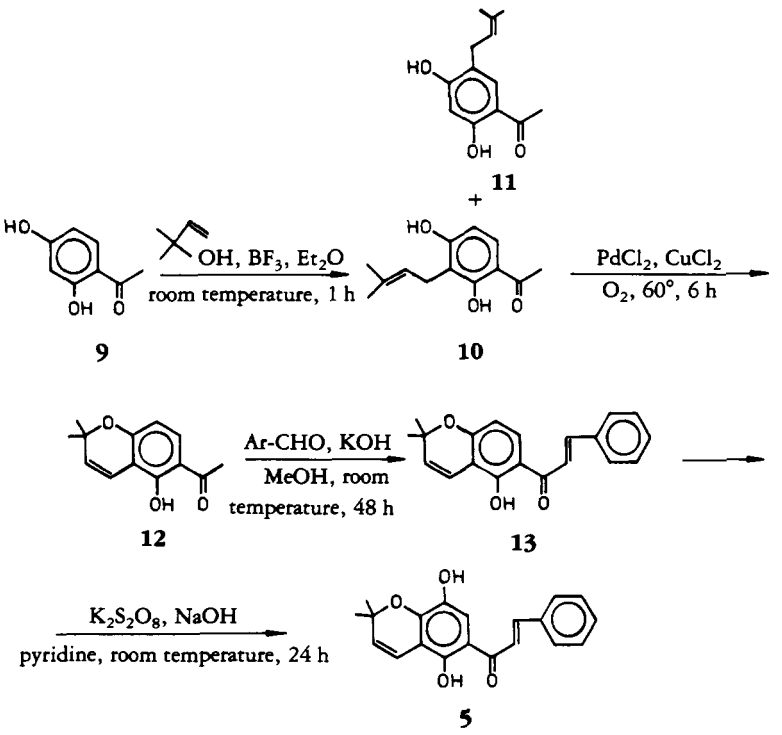
1 R=OH, R′=R″=H
2 R=OMe, R′=R″=H
3 R=OH, R′=H, R″=OH
4 R=OH, R′=OH, R″=H



5



6 R=OMe, R′,R″=H
7 R,R″=OMe, R′=H
8 R,R′=OMe, R″=H



SCHEME 1

using $PdCl_2$ and $CuCl_2$. Intramolecular oxypalladation has been used by other authors for chromene synthesis (7–9). 6-Acetyl-5-hydroxy-2,2-dimethyl-2*H*-chromene [**12**] was obtained exclusively in 50% yield. Base-catalyzed condensation of the acetylchromene **12** with benzaldehyde yielded the naturally occurring chalcone lonchocarpin [**13**]. Finally, the hydroxy chalcone **13** was reacted under Elbs oxidation conditions (10) to afford chromenochalcone [**5**] in 15% yield.

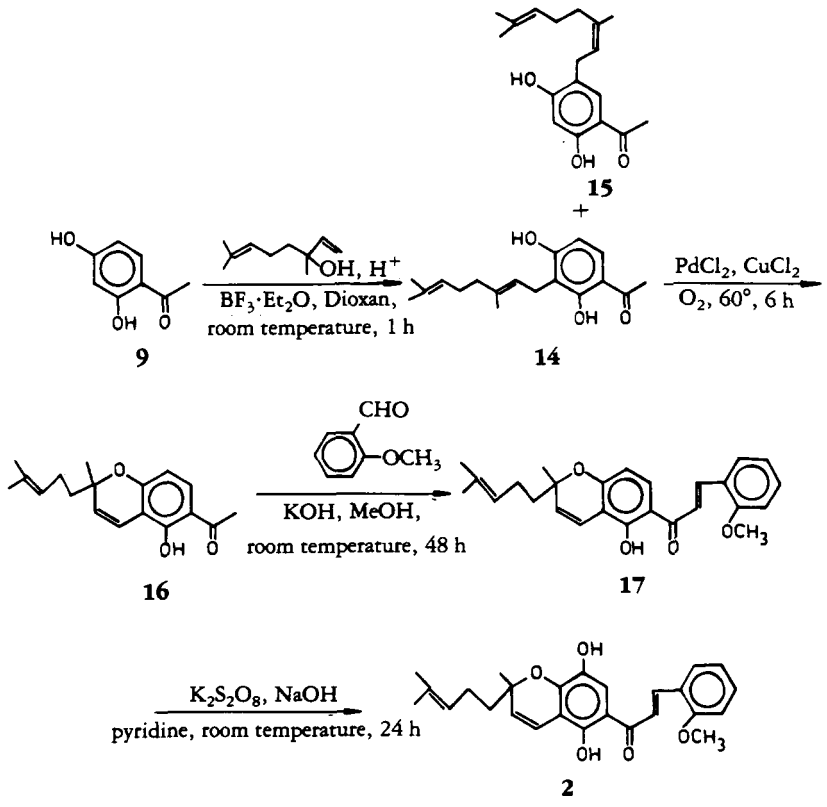
Similarly, reaction of resacetophenone [**9**] with 3,7-dimethyl-3-hydroxy-1,6-octadiene in the presence of BF_3-etherate gave the products **14** and **15**. The 3-alkenylated compound **14** was oxidatively cyclized to the chromene **16** by the oxypalladation reaction. The acetylchromene **16** was condensed with salicylaldehyde methyl ether to give the chalcone **17** after careful chromatographic separation. Elbs oxidation of the chalcone **17** using $K_2S_2O_8$ in pyridine afforded the monomethyl ether **2** of flemingin A in 15% yield.

Thus, the syntheses of the complex, naturally occurring chalcones has been achieved through a five-step reaction sequence. The chromene intermediates for the synthesis have been synthesized through an intramolecular Wacker oxidation (12–14).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—All melting points are uncorrected. The ir spectra in Nujol were recorded on a Perkin-Elmer model 681 spectrometer. The ^1H nmr spectra in $CDCl_3$ were recorded on a Varian VXR-300 spectrometer (300 MHz) with TMS as internal standard. Mass spectra were run on a Shimadzu QP-1000 spectrometer. $PdCl_2$ was purchased from Johnson Matthey. $CuCl_2$ was purchased from S.D. Fine Chemicals.

2,4-DIHYDROXY-3(3-METHYL-2-BUTENYL) ACETOPHENONE [**10**].—The phenol **9** (2.2 g, 14.2 mmol) was dissolved in dry dioxan (8 ml), and the solution was stirred at room temperature. BF_3-etherate (0.6 ml) and 2-methylbut-3-en-2-ol (1.2 g) were added and the reaction was allowed



SCHEME 2

to proceed for 1 h. The mixture was diluted with Et_2O (10 ml). The ethereal solution was washed with H_2O (15 ml) and dried over Na_2SO_4. Chromatography of the residue over Si gel using 50% C_6H_6/petroleum ether as eluent gave the product **10** (0.72 g, 33%): mp 148° [lit. (11) mp 148°], ir ν 3200, 1620, 1380, 1060 cm^{-1}; ^1H nmr δ 1.81 (6H, s, 2 × Me), 2.55 (3H, s, Ac), 3.43 (2H, d, $ArOCH_2$), 5.24 (1H, t, olefinic), 6.05 (1H, s, OH), 6.36 (1H, d, J = 9 Hz, aromatic), 7.55 (1H, d, J = 9 Hz, aromatic), 13.09 (1H, s, chelated OH). Likewise by condensation of resacetophenone [**9**] with 3,7-dimethyl-3-hydroxy-1,6-octadiene, 2,4-dihydroxy-3-(3,7-dimethyl-2,6-octadienyl) acetophenone **14** was obtained: ir ν 3200, 1630, 1380, 1050 cm^{-1}; ^1H nmr δ 1.40 (s, 2 × Me), 1.52 (C=C-Me), 2.20 (m, 2 × CH_2), 2.40 (s, Ac), 3.30 (d, Ar-CH_2) 4.40 (bs, OH), 5.10 (m, olefinic), 6.50–6.80 (m, aromatic), 1250 (s, chelated OH).

6-ACETYL-5-HYDROXY-2,2-DIMETHYL-2*H*-CHROMENE [**12**].—A solution of the phenol **10** (0.200 g, 0.9 mmol) in EtOH (5 ml) was stirred at 60°. To the stirred solution were added $PdCl_2$ (0.006 g, 0.036 mmol), $CuCl_2$ (0.012 g, 0.09 mmol), and H_2O (0.5 ml). A slow stream of O_2 was passed through the solution. After 6 h, the mixture was diluted with H_2O (10 ml) and extracted with Et_2O (3 × 5 ml). The organic layer was washed with H_2O (10 ml) and dried over Na_2SO_4. The chromene **12** was obtained after Si gel cc (25% petroleum ether/C_6H_6). Compound **12** (0.09 g, 45%): mp 103° [lit. (11) mp 102–103°]; ir ν 3480, 1630, 1380, 1030 cm^{-1}; ^1H nmr δ 1.45 (6H, s, 2 × Me), 2.48 (3H, s, Ac), 5.60 (1H, d, J = 10 Hz, H-3), 6.32 (1H, d, J = 9 Hz, aromatic), 6.65 (1H, d, J = 10 Hz, H-4), 7.45 (1H, s, J = 9 Hz, aromatic), 13.00 (1H, s, chelated OH). Similar oxidative cyclization of the phenol **14** gave 6-acetyl-5-hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-2*H*-chromene [**16**] as an oil: ir ν 3460, 1630, 1480, 1380, 1040 cm^{-1}; ^1H nm,r δ 1.40 (3H, s, Me), 1.62 (6H, d, 2 × Me), 2.02 (4H, m, 2 × CH_2), 5.08 (1H, t, olefinic), 5.56 (1H, d, J = 10 Hz, H-3), 6.30 (1H, d, J = 9 Hz, aromatic), 6.68 (1H, d, J = 10 Hz, H-4), 7.40 (1H, d, J = 9 Hz, aromatic), 13.00 (1H, s, chelated OH).

LONCHOCARPIN [**13**].—The chromene **12** (2.6 g, 11.8 mmol) was dissolved in MeOH (25 ml). A solution of aqueous KOH (40%) was added followed by dropwise addition of benzal-

dehyde (1.0 ml). The reaction was stirred at 70° for 1 h and at room temperature for 48 h. The resultant solution was acidified with dilute HCl and extracted with Et_2O (20 ml). The ethereal solution was washed with saturated NaCl solution (10 ml) and H_2O (10 ml) and dried over Na_2SO_4. Evaporation of the solvent left a residue (2 g) which was crystallized from MeOH to afford yellow crystals of **13** (1.5 g, 75%): mp 109° [lit. (5) mp 109°]; ir ν 3460, 1660, 1380, 1050 cm^{-1}; ^1H nmr 1.45 (6H, s, Me), 5.60 (1H, d, $J = 10$ Hz, H-3), 6.40 (1H, d, $J = 9$ Hz, H-5′), 6.80 (1H, d, $J = 10$ Hz, H-4), 7.20–7.60 (7H, aromatic, C_α-H), 7.82 (1H, d, $J = 15$ Hz, C_β-H), 13.60 (1H, s, chelated OH).

CHROMENOCHALCONE [**5**].—The chalcone **13** (1.6 g, 5.2 mmol) was dissolved in pyridine (30 ml) to which an aqueous solution of NaOH (8%) was added. A solution of $K_2S_2O_8$ (2.8 g, 10.4 mmol) in H_2O (30 ml) was added over a period of 2 h. After 24 h, the mixture was acidified with dilute HCl, and $CHCl_3$ (2 × 25 ml) was added. The solution was refluxed for 1 h. The mixture was extracted with $CHCl_3$ (25 ml), washed with saturated NaCl solution (15 ml), and dried over Na_2SO_4. The residue obtained after the removal of the solvent was chromatographed on Si gel (15% $CHCl_3/C_6H_6$) to yield chromenochalcone [**5**] (0.24 g, 15%): mp 191–192° [lit. (4) mp 190–191°]; ir ν 3480, 1660, 1380, 1050 cm^{-1}; ^1H nmr 1.47 (6H, s, 2 × Me) 5.10 (1H, s, OH), 5.56 (1H, d, $J = 10$ Hz, H-3″), 6.79 (1H, d, $J = 10$ Hz, H-4″), 7.30–7.65 (7H, aromatic, C_α-H), 8.00 (1H, d, $J = 15$ Hz, C_β-H), 13.61 (1H, s, chelated OH); eims *m/z* (rel. int.) 322 (100), 307 (90).

FORMATION OF CHALCONE **17**.—A solution of the acetyl chromene **16** (2 g, 6.9 mmol) in MeOH (20 ml) was stirred at 70°. To the stirred solution, aqueous KOH (40%) was added followed by the dropwise addition of salicylaldehyde methyl ether (0.9 g). After 48 h, the mixture was acidified with dilute HCl and extracted with Et_2O (15 ml). The solution was washed with saturated NaCl solution (10 ml) and H_2O (10 ml) and dried over Na_2SO_4. Si gel chromatography of the residue using C_6H_6 gave the chalcone **17** (1.1 g, 55%): ir ν 3450, 1650, 1610, 1380, 1050 cm^{-1}; ^1H nmr δ 1.46 (3H, s, Me), 1.63 (6H, d, 2 × Me), 2.10–2.12 (4H, m, 2 × CH_2), 3.93 (3H, s, OMe), 5.08 (2H, m, olefinic), 5.56 (1H, d, $J = 10$ Hz, H-3″), 6.40 (1H, d, $J = 10$ Hz, H-5′), 6.78 (1H, d, $J = 10$ Hz, H-4″), 7.38–7.68 (6H, m, aromatic, C_α-H), 7.78 (1H, d, $J = 15$ Hz, C_β-H), 13.28 (1H, s, chelated OH).

FLEMINGIN A MONOMETHYL ETHER [**2**].—A solution of chalcone **17** (3.75 g, 9.28 mmol) in pyridine (30 ml) and NaOH solution (8%) was stirred at room temperature. $K_2S_2O_8$ (5.01 g, 18.57 mmol) dissolved in H_2O (20 ml) was added during 2 h. After 24 h, the reaction mixture was acidified with dilute HCl and refluxed for 1 h after addition of $CHCl_3$ (25 ml). The solution was then extracted with $CHCl_3$ (20 ml), washed with saturated NaCl solution (15 ml) and H_2O (10 ml), and dried over Na_2SO_4. Evaporation of the solvent followed by Si gel chromatography (5% $CHCl_3/C_6H_6$) afforded flemingin A monomethyl ether [**2**] (0.56 g, 15%); ir ν 3480, 1660, 1610, 1580, 1380, 1050 cm^{-1}; ^1H nmr δ 1.47 (3H, s, Me), 1.63 (6H, d, 2 × Me), 2.10–2.12 (4H, m, 2 × CH_2), 3.93 (3H, s, OMe) 5.08 (2H, m, olefinic), 5.16 (1H, s, OH), 5.56 (1H, d, $J = 10$ Hz, H-3″), 6.79 (1H, d, $J = 10$ Hz, H-4″), 7.38–7.70 (6H, m, aromatic, C_α-H), 7.79 (1H, d, $J = 16$ Hz, C_β-H), 13.10 (1H, s, chelated OH); eims *m/z* (rel. int.) $[M]^{+1}$ 420 (100).

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