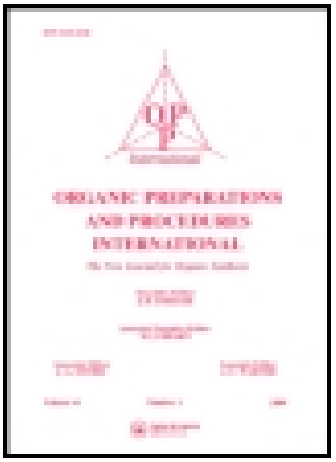

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SYNTHESIS OF OCTANDRENOLONE, FLEMICULOSIN, (±)-3-DEOXY-MS-II AND LAXICHALCONE

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SYNTHESIS OF OCTANDRENOLONE, FLEMICULOSIN, (±)-3-DEOXY-MS-II AND LAXICHALCONE

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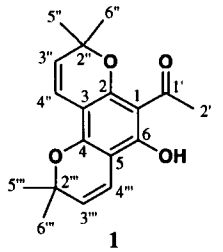
Flavonoids are widely distributed in the plant kingdom and play a vital role in the ecology of plants. Many flavonoids have been shown to possess a wide range of biological activities including antioxidant,[1] anticancer,[2] anti-inflammatory[3] and antiviral.[4]



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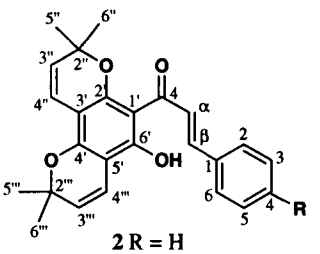

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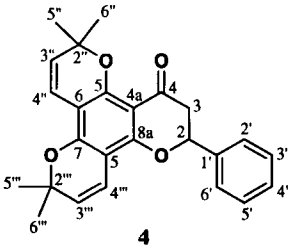
3 R = OH



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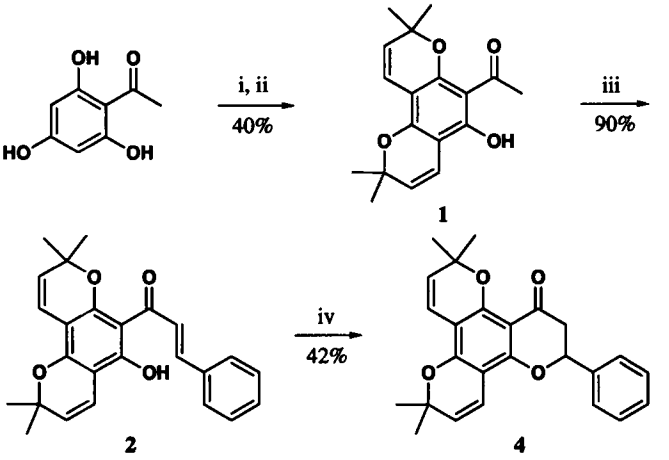
Octandrenolone (**1**) was first isolated from the leaves of *Melicome octandra*[5] and later from *Melicope erromangensis*.[6] The related chalcone structure flemiculosin (**2**), was isolated from leaves of *Flemengia fruticulosa*[7] and its structure was confirmed by X-ray crystallography.[8] A closely related analogue laxichalcone (**3**), was isolated from the roots of *Derris laxiflora* and

its structure was established on the basis of spectroscopic data.[9,10] Kingston *et al.*[11] isolated (-)-3-deoxy-MS-II (**4**) from the bark and leaf extracts of *Mundulea chapelieri* and reported its potent cytotoxicity against human ovarian cancer cell line. Prior to its isolation as a natural product, octandrenolone had been synthesized by reaction of phloroacetophenone with 3-hydroxy-3-methylbutanal dimethyl acetal in 4% yield.[12] Although the synthesis of octandrenolone **1** is known, syntheses of **2-4** have not been described previously.

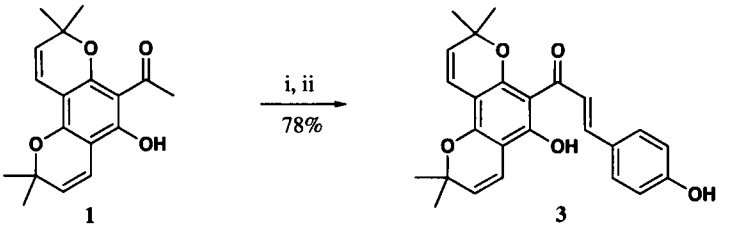
A copper(I) iodide-catalyzed reaction of phloroacetophenone with 3-chloro-3-methylbut-1-yne has been reported to give **1** in 78% yield.[13] However, in our hands, attempted synthesis of **1** by this procedure led to a mixture of compounds from which only a very small amount of the desired product could be isolated. Assuming that uncyclized intermediates were present in the reaction mixture,[13] we decided to heat the crude product with *N,N*-dimethylaniline and *N,N*-dimethylformamide (1:12) at 140°C for 2 hr.[14] TLC analysis of the reaction mixture showed formation of **1** as the major product along with two other impurities. Octandrenolone could be isolated quite easily in 40% yield from this mixture by column chromatography (*Scheme 1*).



i) 3-Chloro-3-methylbut-1-yne, K_2CO_3, KI, CuI, acetone, reflux 3 h; ii) *N,N*-Dimethylaniline, *N,N*-dimethylformamide, 140°C, 2 h; iii) Benzaldehyde, KOH, ethanol, rt, 6 h; iv) Sodium acetate, ethanol, reflux 48 h

Scheme 1

Condensation of octandrenolone with benzaldehyde in the presence of excess potassium hydroxide in ethanol afforded flemiculosin in 90% yield. Cyclization of **2** was achieved by refluxing with sodium acetate in ethanol for 48 hr to give (±) 3-deoxy-MS-II (**4**) in 42% yield after aqueous work-up (*Scheme 1*). Attempts to condense octandrenolone with 4-hydroxybenzaldehyde using KOH in ethanol were unsuccessful. However, treatment of **1** with 4-methoxymethoxybenzaldehyde[15] in *N,N*-dimethylformamide using sodium hydride as the base, followed by work-up with conc. hydrochloric acid in ethanol, led to the formation of laxichalcone in high yield as a consequence of the concomitant removal of the methoxymethyl protecting group (*Scheme 2*).



1 3

i) 4-Methoxymethoxybenzaldehyde, NaH, DMF; ii) Conc. HCl, aqueous ethanol

Scheme 2

The melting points and UV, IR, ^{1}H NMR and ^{13}C NMR spectra of the synthesized compounds were identical to the reported values.[5,7,9,11] Moreover the structure of (±) 3-deoxy-MS-II (**4**) was confirmed by two dimensional NMR experiments such as COSY and HMBC.

EXPERIMENTAL SECTION

Melting points are uncorrected and were determined on a Kofler hot stage micromelting point apparatus. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker DPX 300F spectrometer. Infrared spectra were recorded with a Mattson Genesis FTIR spectrometer. The electrospray mass spectra were acquired using a Bruker BioApex-2 7T FTICR mass spectrometer. UV spectra were determined on a Varian Cary 100 spectro-photometer. Column chromatography was carried out using Merck silica gel 60H (Art 7736).

Octandrenolone (**1**).- To a suspension of phloroacetophenone (1 g, 5.9 mmol), potassium iodide (1.78 g, 10.7 mmol) and potassium carbonate (1.6 g, 11.5 mmol) in dry acetone (10 mL) was added copper (I) iodide (10 mg, 0.05 mmol). The reaction mixture was stirred at reflux for 15 min followed by the dropwise addition of 3-chloro-3-methylbut-1-yne (5.5 g, 53.6 mmol) over a period of 1.5 hr. The refluxing was continued for further 3 hr. TLC analysis showed absence of starting material and formation of five products. The reaction mixture was cooled and water (25 mL) was added. The product was extracted with ethyl acetate (3 x 25 mL) and the combined organic extracts were dried over anhydrous sodium sulfate. The crude product obtained from evaporation of ethyl acetate was dissolved in a mixture of *N,N*-dimethylaniline (1 mL) and *N,N*-dimethylformamide (12 mL), and heated for 2 hr at 140°C under an argon atmosphere. TLC analysis showed the presence of one major spot and disappearance of two other spots from the crude starting material. The reaction mixture was cooled to room temperature and diluted with 1M hydrochloric acid (50 mL). The mixture was then extracted with light petroleum (3 x 30 mL), dried over anhydrous sodium sulfate and evaporated to yield a pale yellow oil which was chromatographed using 0.5% ethyl acetate in light petroleum as the eluent to yield octandrenolone (0.71 g, 40%) as yellow prisms. An analytical sample was obtained by recrystallization from pentane, mp. 88-90°C, *lit.*[5] mp. 90°C. IR (KBr): 3444, 2972, 1646, 1596, 1468, 1361, 1281, 1138, 1115, 872, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 6H, H2''), 1.49 (s, 6H, H2'''), 2.65

(s, 3H, $C\underline{H}_3CO$-), 5.43 (2 x d, 2H, J 10.2 Hz, H3", H3'''), 6.58 (d, 1H, J 10.2 Hz, H4'''), 6.64 (d, 1H, J 10.2 Hz, H4"), 13.99 (s, 1H, -OH). ^{13}C NMR ($CDCl_3$): δ 27.9, 28.3, 33.1, 78.1, 78.2, 102.1, 102.2, 105.4, 116.1, 116.3, 124.6, 125.3, 154.9, 156.6, 160.5, and 203.2. UV-Vis λ_{max} (EtOH): 240 (sh), 268 (ε = 24911), 280 (sh), 294 (sh) nm. HR-MS: Found: 323.126321. Calcd. for $C_{18}H_{20}O_4Na$ 323.125384.

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.07; H, 6.98

Flemiculosin (2).- To a solution of **1** (300 mg, 1 mmol) and benzaldehyde (260 mg, 2.5 mmol) in absolute ethanol (10 mL) was added a solution of potassium hydroxide (2.5 g) in water (2.5 mL). The dark brown mixture was stirred at ambient temperature under an argon atmosphere for 6 hr. The reaction mixture was poured into water (50 mL) and acidified to pH 5 using 3N hydrochloric acid. The product was extracted with ethyl acetate (3 x 25 mL), dried over anhydrous sodium sulfate and the combined extracts were evaporated under vacuum to yield brown oil which was chromatographed using light petroleum/acetone (99:1) as the eluent to yield pure flemiculosin (350 mg, 90%) as red needles. An analytical sample was prepared by re-crystallization from pentane, mp. 98-99°C, *lit.*[7] mp. 99°C. IR (KBr): 3444, 2970, 1633, 1601, 1588, 1546, 1341, 1184, 1141, 703 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (s, 6H, H5", H6"), 1.54 (s, 6H, H5''', H6'''), 5.47 (d, 2H, J 10.2 Hz, H3", H3'''), 6.61 (d, 1H, J 10.2 Hz, H4'''), 6.69 (d, 1H, J 10.2 Hz, H4"), 7.4 (m, 3H, H2, H4, H6), 7.61 (m, 2H, H3, H5), 7.76 (d, 1H, J 15.5 Hz, Hα), 8.09 (d, 1H, J 15.5 Hz, Hβ). ^{13}C NMR ($CDCl_3$): δ 28.0, 28.3, 77.1, 78.2, 102.4, 102.5, 105.9, 116.2, 116.6, 124.7, 125.3, 127.6, 128.1, 128.5, 128.8, 129.9, 135.6, 142.0, 155.2, 156.1, 161.4 and 192.8. UV-Vis λ_{max} (MeOH): 202 (ε = 14900), 277 (ε = 16750), 306 (ε = 17050), 359 (ε = 14150) nm. HR-MS: Found 411.156889. Calcd. for $C_{25}H_{24}O_4Na$: 411.156699.

Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.29; H, 6.22. Found: C, 77.03; H, 6.43

Laxichalcone (3).- A solution of **1** (200 mg, 0.66 mmol) and 4-methoxymethoxybenzaldehyde (165 mg, 0.99 mmol) in dry dimethylformamide (2 mL) was cooled to 0°C under an argon atmosphere. Sodium hydride (80 mg, 2 mmol) was added in three lots. The mixture was stirred for 1 hr at 0°C. Ethanol (15 mL) was slowly added followed by addition of water (2 mL) and conc. hydrochloric acid (2 mL). The mixture was heated at 60°C for 3 hr. Ethanol was distilled off under reduced pressure and the residue was diluted with water (25 mL). The product was extracted in dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate and solvent removed under vacuum. The crude product was purified by chromatography using 20% ethyl acetate in light petroleum as the eluent to yield pure laxichalcone as red needles (210 mg, 78%). mp. 174-176°C (EtOH), *lit.*[11] 174-176°C. IR (KBr): 3382, 3235, 1648, 1628, 1603, 1584, 1442, 1345, 1185, 1153, 971cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.39 (s, 6H, H5", H6"), 1.48 (s, 6H, H5''', H6'''), 5.60 (d, 2H, J 10.2 Hz, H3'''), 5.61 (d, 2H, J 10.2 Hz, H3"), 6.49 (d, 1H, J 10.2 Hz, H4'''), 6.52 (d, 1H, J 10.2 Hz, H4"), 6.84 (d, 2H, J 8.7 Hz, H3, H5), 7.52 (d, 2H, J 8.7 Hz, H2, H6), 7.68 (d, 1H, J 15.5 Hz, Hα), 7.84 (d, 1H, J 15.5 Hz, Hβ), 10.16 (bs, 1H, 4-OH), 14.42 (s, 1H, 2'-OH). ^{13}C NMR (DMSO-d_6): δ 28.0, 28.3, 78.6, 78.7, 102.3, 102.5, 105.7, 115.7, 116.0, 116.5, 123.6,

126.1, 126.3, 126.6, 130.8, 143.8, 154.6, 155.8, 160.6, 160.6 and 192.6. UV-Vis λ_{max} (MeOH): 203 (ε = 18876), 252 (ε = 22179), 266 (ε = 21685), 276 (ε = 22764), 376 (ε =31797) nm.

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.24; H, 5.98. Found: C, 74.35; H, 6.21

(±) 3-Deoxy-MS-II (4).- To a solution of anhydrous sodium acetate (1.2 g, 14.6 mmol) in ethanol (40 mL) was added **2** (400 mg, 1 mmol). The reaction mixture was refluxed in an oil bath for 48 hr. Ethanol was distilled off under vacuum and residue was dissolved in water (20 mL). The product was extracted with dichloromethane (3 x 20 mL), dried over anhydrous sodium sulfate and the extracts were evaporated under vacuum to yield a yellow oil. The crude product was purified by chromatography using 5% ethyl acetate in light petroleum as eluent to yield unreacted starting material (140 mg). Further elution with 10% ethyl acetate in light petroleum yielded 3-deoxy-MS-II (**4**, 170 mg, 42%) as yellow crystals, mp. 145-147°C (light petroleum). IR (KBr): 2976, 1640, 1591, 1573, 1434, 1140, 1014, 728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (s, 3H, H5'''), 1.45 (s, 3H, H6'''), 1.48 (s, 3H, H5''), 1.52 (s, 3H, H6''), 2.77 (dd, 1H, J 3.1, 16.6 Hz, H3), 2.96 (dd, 1H, J 12.8, 16.6 Hz, H3), 5.39 (dd, 1H, J 3.0, 12.8 Hz, H2), 5.46 (d, 1H, J 10.1 Hz, H3'''), 5.50 (d, 1H, J 10.1 Hz, H3''), 6.57 (d, 1H, J 10.1 Hz, H4'''), 6.60 (d, 1H, J 10.1 Hz, H4''), 7.35-7.46 (m, 5H, H2' H3', H4', H5', H6'). ^{13}C NMR ($CDCl_3$): δ 27.8, 28.0, 28.1, 28.4, 45.8, 77.7, 77.8, 78.9, 102.3, 104.5, 105.5, 115.7, 116.2, 126.1, 126.3, 126.5, 128.6, 128.7, 139.0, 154.2, 155.9, 157.4 and 188.6. UV-Vis λ_{max} (MeOH): 267 (ε = 31818), 315 (sh), 368 (ε = 3181) nm. HR-MS: Found 411.156116. Calcd. for $C_{25}H_{24}O_4Na$: 411.156699.

Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.29; H, 6.22. Found: C, 77.38; H, 6.40

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