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## Note

# A facile three-step synthesis of (*dl*)-6,8 dedihydroxyagrimonolide

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3-[2-(4′-methoxyphenyl)ethyl]isocoumarin **2** has been prepared by the condensation of 4-methoxyphenyl-propanoyl chloride with homophthalic acid. Alkaline hydrolysis of **2** yields the keto-acid 3 which is reconverted back to **2** either by treatment with acetic anhydride or with slightly acidified methanol. The keto-acid **3** on reaction with methyl iodide or dry methanol in the presence of a catalytic amount of sulfuric acid affords the methyl keto-Ester-4. (*dl*)-6,8-Dedihydroxyagrimonolide **6** is obtained by reduction of **3** to the racemic hydroxyacid **5** followed by cyclodehydration using acetic anhydride.

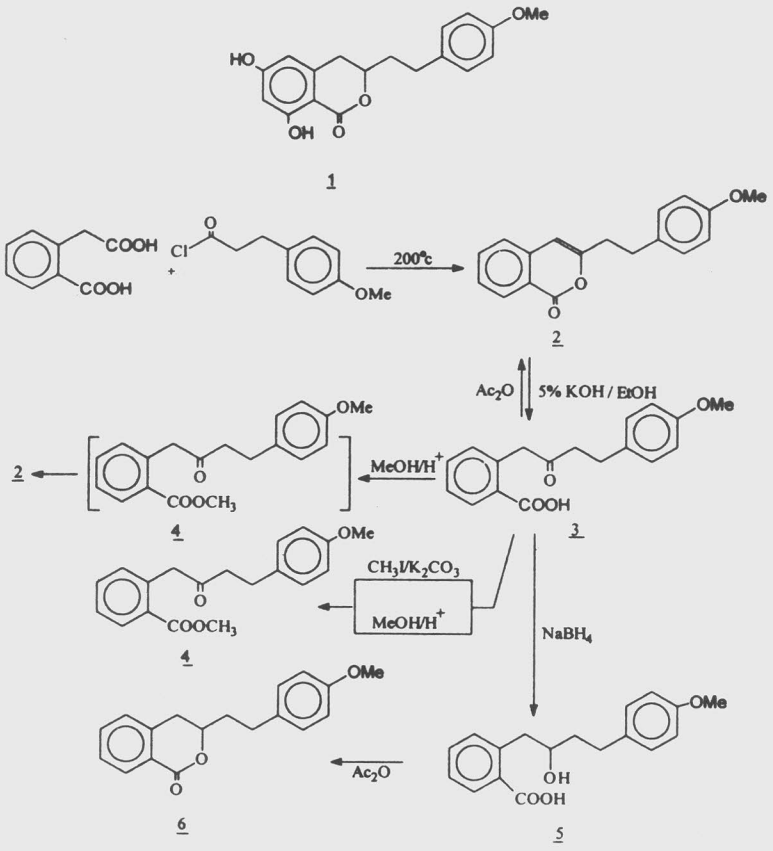
Agrimonolide is a phenolic constituent of the Rhizome of *Agrimonia pilosa* Ledeb, isolated[1] in 1958. The determination of its structure was extensively studied by Yamato *et al.*[2] who finally confirmed its structure by synthesis as 6,8-di-hydroxy-3-[2-ethyl-(4′-methoxyphenyl)-3, 4-dihy-droxyisocoumarin **1**. In 1969, Arakawa[3] determined its absolute configuration as *R*. Liu[4] reported its strong anthelmintic activity against tape worms. Scanning electron microscopic (SEM) obser-vations have shown that its anthelmintic effects are due to its destructive effect on the body walls of the tape worms.

In this article we describe a facile three-step synthesis of 6,8-dedihydroxyagrimonolide **6** (Scheme I) as model for the synthesis of agri-monolide **1** and to study its possible anthelmintic effects. Thus, direct condensation[5] of 4-methoxy-phenylpropanoyl chloride with homophthalic acid at elevated temperature afforded the 3-[2-(4′-methoxyphenyl)ethyl]isocoumarin **2** which showed a characteristic 1H singlet at δ 6.20 for $C_4$-H and the lactonic carbonyl absorption at 1720 $cm^{-1}$. Alkaline hydrolysis of **2** afforded the keto-acid **3** which showed a 2H singlet at δ 3.99 for $C_1$-$CH_2$. The absorption for ketonic and carbony groups were observed at 1683 and 1716 $cm^{-1}$ respectively. Isocoumarin **2** was obtained by refluxing of **3** with acetic anhydride. Following an already reported[6] procedure, the keto-acid **3** when refluxed with dry acidic methanol for 8 hr furnished the keto-ester **4** as indicated by TLC. It may be pointed out that the work-up of this reaction mixture involved the use of sodium bicarbonate which might have hydrolyzed the keto-ester **4** to the corresponding keto-acid **3** which under the work-up conditions was converted back to the lactone **2**, identical in all respect with that prepared earlier. Methylation of **3** with excess of methyl iodide or with dry acidic methanol under reflux for 8 hr without using sodium bcarbonate in the work-up also yielded the methyl keto-ester **4**. The appearance of carbonyl absorptions at 1720 and 1684 $cm^{-1}$ for ester and keto groups respectively in the IR spectrum and a 3H singlet at δ 3.81 in the $^1$H NMR spectrum of **4** confirmed the esterifi-cation. It is presumed that sodium borohydride reduction of **3** afforded the corresponding racemic hydroxyacid **5** (not isolated) which under the direct influence of acetic anhydride produced the (*dl*)-6,8-dedihydroxy-agrimonolide **6**. The dihydroiso-coumarin **6** exhibited the carbonyl absorption at 1715 $cm^{-1}$ in the IR spectrum and the typical *ABX* pattern of $C_3$-H and the typical *AB* pattern of $C_4$-H proton in the $^1$H NMR spectrum. Thus, each proton of $C_4$-$H_2$ showed a doublet of a doublet (δ 2.87-2.90 and 2.96-3.03 respectively). The multiplet for $C_3$-H was observed at δ 4.45-4.52.

## Experimental Section

Melting points were taken in a melting point apparatus (Toshniwal, India) and are uncorrected. IR spectra were recorded on a Hitachi 270-50 infrared spectrophotometer as KBr discs or as neat liquids. $^1$H NMR (500 MHz) spectra were recorded in $CDCl_3$ on a Bruker AM-500 instrument using TMS as internal standard and EIMS on a MAT-112-S machine.

**3-[2-(4′-Methoxyphenyl)ethyl]isocoumarin 2.** A mixture of homophthalic acid (1.1 g, 0.006 mole) and 4-methoxyphenylpropanoyl chloride (4.4 g, 0.022 mole) was heated on an oil-bath at




**Scheme I**

200°C for 3 hr. The residue after concentration was chromatographed over silica gel column using pet. ether (60-80°) as eluant to give 3-[2-(4′-methoxyphenyl)ethyl]isocoumarin **2** (0.8 g, 0.0029 mole, 46.6%) which was recrystallized from methanol, m.p. 84-86°; IR (KBr): 1720, 1665, 1615 $cm^{-1}$; $^1H$ NMR: δ 2.76-2.80 (2H, t, *J*=7.23 Hz, H-1′), 2.95-2.99 (2H, t, *J*=7.18 Hz, H-2′), 3.76 (3H, s, OMe), 6.10 (1H, s, H-4), 6.79-6.84 (2H, dt, *J*=3.03, 5.13, Hz, H-3″, H-5″), 7.09-7.13 (2H, dt, *J*=2.98, 5.06 Hz, H-2″, H-6″), 7.25-7.31 (1H, d, *J*=7.76 Hz, H-5), 7.41-7.45 (1H, ddd, *J*=1.12, 7.08, 8.19 Hz, H-7), 7.62-7.66 (1H, ddd, *J*=1.35, 7.6, 8.89 Hz, H-6), 8.23-8.25 (1H, dd, *J*=0.65, 7.97, Hz, H-8); MS (70 eV): m/z 280 (7.4%) [$M^+$], 252 (23.7) [$M^+$–CO], 118 (100) [$C_{18}H_{16}O_3$: Calcd 280.1099; Found 280.1092 (MS)].

**2-[2-Oxobutyl-(4′-methoxyphenyl)]benzoic acid 3.** A suspension of **2** (350 mg, 1.25 mmoles) in ethanol (15 mL) and potassium hydroxide (5%, 30 mL) was refluxed for 5 hr. After cooling, ethanol was removed by evaporation under reduced pressure. Cold water (20 mL) was then added and the mixture acidified with dil. hydrochloric acid, extracted with dichloromethane (2×15 mL), dried ($Na_2SO_4$), and solvent removed on a rotary evaporator to yield a solid residue which was recrystallized from ethyl acetate and pet. ether (60-80°) affording **3** (0.3 g, 0.001 mole, 93.7%), m.p. 128-29°; IR (KBr): 1715, 1683 $cm^{-1}$; $^1H$ NMR: δ 2.78 (2H, t, *J*=6.93 Hz, H-3′), 2.87 (2H, t, *J*=7.1 Hz, H-4′), 3.76 (3H, s, OMe), 3.99 (2H, s, H-1′), 6.79-6.83 (2H, d, *J*=8.62 Hz, H-3″, H-5″), 7.09-7.10 (2H, d, *J*=8.50 Hz, H-2″, H-6″), 7.16-7.18 (1H, d, *J*=7.41 Hz, H-3), 7.36-7.40 (1H, ddd, *J*=1.13, 7.61, 8.21 Hz, H-5), 7.50-7.54 (1H, ddd, *J*=1.16, 7.51, 8.64 Hz, H-4), 8.12-8.14 (1H, dd, *J*=1.14, 7.75 Hz, H-6), 10.2 (1H, s, $D_2O$ exchangeable, COOH); MS (70 eV): m/z 298 (3.1%) [$M^+$], 280 (8.6) [$M^+$–$H_2O$], 118 (100) [$C_{18}H_{18}O_4$]: Calcd 298.1205; Found 298.1210 (MS).

**3-[2-(4′-Methoxyphenyl)ethyl]isocoumarin 2. Method A.** Compound **3** (50 mg, 0.17 mmole) was refluxed with acetic anhydride (0.5 mL) for 12 hr. After cooling, the reaction mixture was poured into

ice water (5 mL), extracted with ethyl acetate (2×10 mL). The extract was washed with sodium bicarbonate (2×10 mL, 5%), dried ($Na_2SO_4$) and concentrated to give an oily product which solidified on standing. It was recrystallized from methanol to afford **2** (40 mg, 0.14 mmole, 85%), m.p. 84-86°, m.m.p. 85-86°. $R_f$ value, mass, high resolution mass, IR and $^1H$ NMR spectral data were in good agreement with those of the already synthesized **2**.

**Method B.** A solution of compound **3** (150 mg, 0.5 mmole) in dry methanol (30 mL) and conc. sulfuric acid (as a catalyst) was refluxed for 8 hr. The reaction mixture was neutralized with solid sodium bicarbonate, filtered and methanol rotary evaporated to afford an oil which solidified on cooling and recrystallized from diethyl ether to furnish **2** (0.11 g, 3.9m mole, 78%), m.p. 84-86°, m.m.p. 84-86°.

**Methyl 2-[2-oxobutyl-(4′-methoxyphenyl)]benzoate 4. Method A.** Compound **3** (100 mg, 0.33 mmole), methyl iodide in excess and anhydrous potassium carbonate (1.0 g) in dry acetone (10 mL) were heated under reflux for 2 hr. The reaction mixture was filtered when hot. The cake was washed with warm dry acetone (10 mL) and the solvent evaporated *in vacuo* leaving an oil which solidified on standing and recrystallized from ether to afford **4** (90 mg, 0.29 mmole, 86%), m.p. 53-54°. IR (KBr): 1720, 1684 $cm^{-1}$; $^1H$ NMR: δ 2.82-2.85 (2H, t, *J*=7.16 Hz, H-3′), 2.86-2.89 (2H, t, *J*=7.07 Hz, H-4′), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 4.05 (2H, s, H-1′), 6.79-6.83 (2H, dd, *J*=3.12, 5.28 Hz, H-3″, H-5″), 7.09-7.12 (2H, dd, *J*=3.15, 11.60 Hz, H-2″, H-6″), 7.14-7.18 (1H, d, *J*=0.91 Hz, H-3), 7.31-7.35 (1H, ddd, *J*=0.97, 3.62, 7.61 Hz, H-5), 7.42-7.46 (1H, ddd, *J*=0.92, 3.68, 7.62 Hz, H-4), 7.99-8.02 (1H, dd, *J*=1.16, 7.78 Hz, H-6); MS (70 eV): m/z 312 (1.2%) [$M^+$], 281 (28.3) [$M^+$–OMe], 280 (100) [$M^+$–MeOH], 118 (50.3) [$C_{19}H_{20}O_4$: Calcd 312.1361; Found 312.1361 (MS)].

**Method B.** A solution of compound **3** (150 mg, 0.5 mmole) in dry methanol (100 mL) and conc. sulfuric acid (two drops) was refluxed for 8 hr. water (50 mL) was then added and methanol removed under reduced pressure. The reaction mixture was extracted with ether (2×20 mL). The combined extract was dried ($Na_2SO_4$) and the solvent removed under reduced pressure leaving an oil which solidified on standing. The crude solid was recrystallized from diethyl ether. The isolated compound was further purified by preparative chromatography to furnish **4** (0.1 g, 3.2m mole, 63.6%), m.p. 53-54°, m.m.p. 53°; IR (KBr): 1720, 1680 $cm^{-1}$; $^1H$ NMR: δ 2.82-2.85 (2H, t, *J*=7.14 Hz, H-3′), 2.86-2.89 (2H, t, *J*=7.1 Hz, H-4′), 3.78 (3H, s, OMe), 3.81 (3H, s, OMe), 4.05 (2H, s, H-1′), 6.79-6.83 (2H, dd, *J*=3.12, 5.28 Hz, H-3″, H-5″), 7.09-7.12 (2H, dd, *J*=3.15, 11.60 Hz, H-2″, H-6″), 7.14-7.18 (1H, d, *J*=0.91 Hz, H-3), 7.29-7.35 (1H, ddd, *J*=0.97, 3.62, 7.61 Hz, H-5), 7.43-7.47 (1H, ddd, *J*=0.92, 3.68, 7.62 Hz, H-4), 7.99-8.02 (1H, dd, *J*=1.16, 7.78 Hz, H-6); MS (70 eV): m/z 312 (1.6%) [$M^+$], 281 (25.3) [$M^+$–OMe], 280 (100) [$M^+$–MeOH], 118 (54.3) [$C_{19}H_{20}O_4$: Calcd 312.1361; Found 312.1361 (MS)].

**(*dl*)-6,8-Dedihydroxyagrimonolide 6.** Compound **3** (150 mg, 0.5 mmole) was heated under reflux with sodium borohydride (0.15 g) in absolute ethanol (20 mL) for 4 hr. Ethanol was then rotatory evaporated and the residue diluted with cold water and acidified with dil. sulfuric acid to give a precipitate which was extracted with ethyl acetate (2×15 mL). The solvent was evaporated to leave a solid residue **m** (0.12 g). This crude compound was dissolved in acetic anhydride (1.5 mL) and heated under reflux for 2 hr. The reaction mixture was then cooled, water (15 mL) added and the solid that separated out on stirring was extracted with dichloromethane (2×10 mL). The extracts were combined, treated with sodium bicarbonate (2×10 mL, 5%), washed with water, dried ($Na_2SO_4$) and filtered. Solvent was removed from the filtrate to give a solid which was recrystallized from methanol to furnish **6** (110 mg, 0.39 mmole, 78%), m.p. 105-6°; IR (KBr): 1715, 1610 $cm^{-1}$; $^1H$ NMR: δ 1.92-2.01 (1H, m, H-1′), 2.13-2.22 (1H, m, H-1′),2.74-2.79 (1H, m, H-2′), 2.81-.2.85 (1H, m, H-2′), 2.87-2.90 (*AB* pattern, 1H, dd, $J_{vic}$=5.91, $J_{gem}$=9.23 Hz, H-4), 2.96-3.03 (*AB* pattern, 1H, dd, $J_{vic}$=11.34, $J_{gem}$=16.22 Hz, H-4), 3.76 (3H, s, OMe), 4.45-4.52 (1H, m, H-3), 6.80-6.84 (2H, dt, *J*=2.97, 5.12 Hz, H-3″, H-5″), 7.11-7.14 (1H, dt, *J*=2.97, 5.09 Hz, H-2″, H-6″), 7.19-7.23 (1H, d, *J*=7.56 Hz, H-5), 7.34-7.37 (1H, ddd, *J*=1.4, 7.51, 8.91 Hz, H-7), 7.48-7.52 (1H, ddd, *J*=1.4, 7.50, 8.90 Hz, H-6), 8.07-8.09 (1H, dd, *J*=1.26, 7.78 Hz, H-8); MS (70 eV): m/z 282

(43.2%) [$M^+$], 254 (10.6), 118 (100) [$C_{18}H_{18}O_3$: Calcd 282.1256; Found 282.1249 (MS)].

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