

The Synthesis of Phycopsisenone, a New Phenolic Secondary Metabolite from the Sponge *Phycopsis* sp.

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A short first total synthesis of phycopsisenone (**1**) utilizing microwave irradiation-induced aldol condensation and TiCl_4 -catalyzed reaction of silyl enol ether (**3**) with acetone as key steps has been achieved in 29.4% overall yield.

Several prenylated aromatic compounds have been isolated from marine flora and fauna¹ and are known to be biologically active. Venkateswarlu et al.² investigated the sponge *Phycopsis* sp. collected from the Tuticorin coast, Tamilnadu, India. A CH_2Cl_2 –MeOH (1:1) extract of this organism exhibited antibacterial activity against *E. coli* and *B. subtilis*. One of the components of this extract was phycopsisenone (**1**), the structure of which was assigned on the basis of its spectroscopic studies.² We wish to report a simple synthesis of compound **1** (Scheme 1).

Microwave irradiation-induced aldol condensation of 4-hydroxybenzaldehyde and acetone in aqueous NaOH solution afforded the α,β -unsaturated ketone in 65% yield. Compound **2** on treatment with trimethylchlorosilane and DBU as a base at 40 °C for 30 min gave the enol ether **3**.³ Further condensation of **3** with acetone using TiCl_4 ⁴ as the Lewis acid at –78 °C furnished the title compound **1** after column chromatography using petroleum ether–EtOAc (9:1) in 60% yield (29.4% overall yield). The spectral data of the synthetic sample agree well with those reported in the literature.²

Experimental Section

General Experimental Procedures. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a 300 MHz Bruker spectrometer using TMS as internal standard. IR spectra were recorded on a Perkin-Elmer 337 spectrophotometer. Mass spectra were determined on VG 70S with an 11-250 J+ data system. A BPL domestic microwave oven with a power output of 700 W was used. Unless otherwise stated, all organic extracts were dried over anhydrous sodium sulfate. Silica gel (ASC, Bombay) impregnated with calcium sulfate was used for TLC.

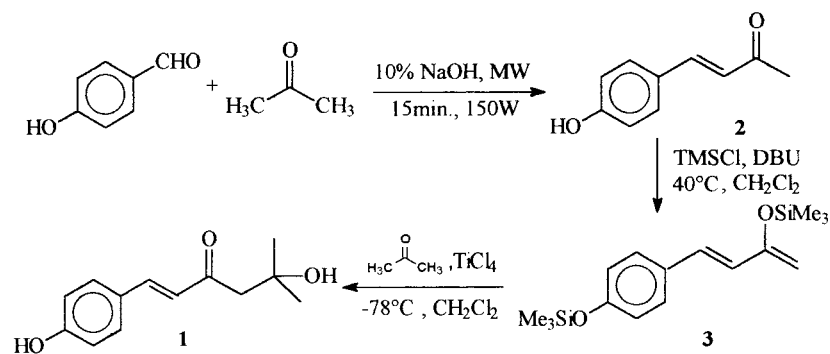
4-(4'-Hydroxyphenyl)but-3-en-2-one (2). To a clear solution of 4-hydroxybenzaldehyde (2.5 g, 20.4 mmol) in 10% NaOH (7 mL) was added acetone (7.0 g, 120.6 mmol) at 25 °C followed by remaining 10% NaOH

solution (10 mL) in open beaker covered by a watch glass and subjected to microwave irradiation for 15 min at a power level of 150 W. The deep red solution was acidified with 10% HCl solution and extracted with ether (4 × 25 mL). The combined organic extracts were dried and evaporated to obtain crude product **2**, which was recrystallized from benzene to afford **2** as yellow solid: mp 102–103 °C (2.15 g, 65%); IR (KBr) ν_{max} 3450 (OH), 1680 (C=O), 1640, 1540 cm^{-1} ; ^1H NMR δ 2.6 (3H, s, H-1), 6.2–6.3 (1H, d, H-3, J = 13.5 Hz), 6.5–6.7 (2H, d, H-3' and H-5', J = 7 Hz), 7.0–7.4 (3H, m, H-4, H-2' and H-6').

1-[4'-(Trimethylsiloxy)phenyl]-3-(trimethylsiloxy)buta-1,3-diene (3). A dry solution of **2** (0.5 g, 3.08 mmol) in CH_2Cl_2 (10 mL), trimethylchlorosilane (0.86 mL, 6.7 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.12 g, 7.3 mmol) under N_2 was stirred at 40 °C for 2 h. The mixture was diluted with hexane (10 mL), washed successively with 1% HCl (2 × 10 mL) and 5% NaHCO_3 (2 × 10 mL), dried, evaporated, and distilled to give **3** (0.37 g; 39%): IR (neat) ν_{max} 1660, 1635, 1640, 1560 cm^{-1} ; ^1H NMR δ 0.17 (18H, s, $\text{Si}(\text{CH}_3)_3 \times 2$), 4.2 (2H, d, H-4, J = 1.7 Hz), 6.2–6.3 (1H, d, H-2, J = 13.5 Hz), 6.5–6.7 (2H, d, H-3' and H-5', J = 7 Hz), 7.0–7.4 (3H, m, H-1, H-2' and H-6').

5-Hydroxy-1-(4'-hydroxyphenyl)-5-methyl-1-hex-ene-3-one (1). Acetone (0.1 mL, 5 mmol) and anhydrous CH_2Cl_2 solution (10 mL) were cooled to –78 °C under N_2 , and TiCl_4 (0.17 mL, 5 mmol) was added. Silyl enol ether **3** (0.355 mg, 5 mmol) was added dropwise to this solution and stirred for 3 h at –78 °C followed by stirring at room temperature for 16 h. The dark red solution was quenched with aqueous NaHCO_3 , stirred for 5 h, and then extracted with ether (5 × 10 mL). The ether extract was dried and evaporated to give a crude product that was purified by column chromatography using petroleum ether–EtOAc (9:1) as an eluent to give a pure colorless solid **1** (0.153 mg, 60%): mp 135 °C; IR (KBr) ν_{max} 3450 (OH), 1680 (C=O), 1640, 1560 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.3 (6H, s), 2.8 (2H, s, H-4), 6.5 (1H, d, H-2, J = 13.5 Hz), 6.8 (2H, d, H-3' and H-5', J = 7 Hz), 7.45 (2H, d, H-2' and H-6', J = 7 Hz), 7.5 (1H, d, H-1, J = 13.5 Hz); ^{13}C NMR (CDCl_3) δ 201.7, 158.4,

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Scheme 1. Synthesis of Phycopsisenone

143.7, 130.5, 126.7, 124.5, 116.1, 70.6, 50.5, 29.4, 29.2;
 EIMS (70 ev) m/z [M⁺] 220, 202, 162, 147 (100), 107;
anal. C 70.70%, H 7.21%, calcd for C₁₃H₁₆O₃, C 70.88%,
 H 7.32%.

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References and Notes

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