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Microwave-assisted Efficient Synthesis of Alliodorin and (±)-Curcuhydroquinone†

Goverdhan L. Kad,* Anupam Khurana, Vasundhara Singh and Jasvinder Singh

Department of Chemistry, Panjab University, Chandigarh-160014, India

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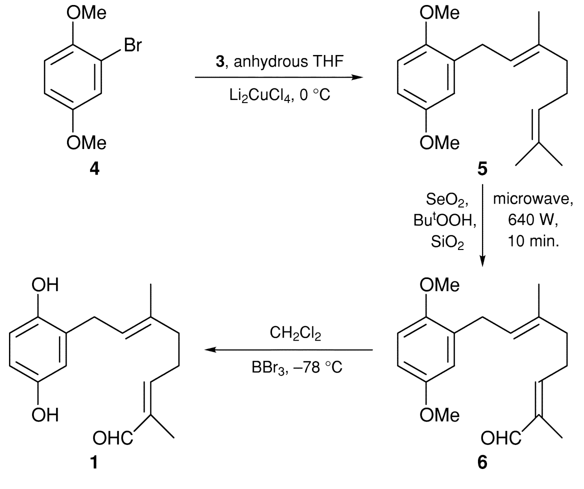
Terpenoids **1** and **2** have been synthesized from readily available starting materials using Li_2CuCl_4-catalysed coupling of Grignard reagents with alkyl/aryl bromides and microwave-assisted oxidation of allylic methyl groups, using SeO_2/Bu^tOOH adsorbed over SiO_2 as key steps.

Alliodorin (**1**) a terpenoid and immediate precursor of the cardiochromes was isolated[1] from the heartwood of *Cordia alliodora*, a Panamanian tree belonging to the family Boraginaceae. (±)-Curcuhydroquinone (**2**), a bisabolane was isolated[2] from the gorgonian sea plume *Pseudopterogorgia rigida* collected off the coasts of Belize and Tobago, West Indies. It shows modest antibacterial activity against *Staphylococcus aureus* and the marine pathogen *Vibrio anguillarum*. There are literature[3–5] reports of the synthesis of **1** and **2**.

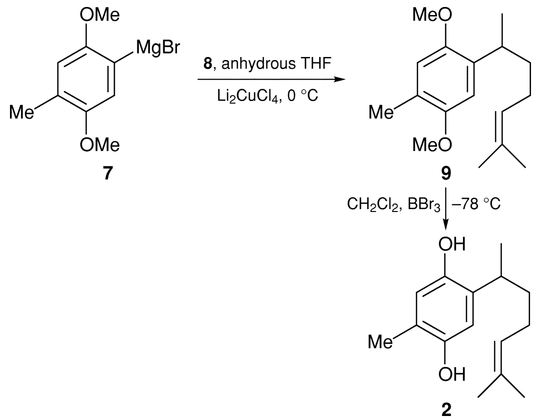
The applications of domestic microwave ovens in organic synthesis are well documented in the literature.[6] Microwave and ultrasound aid in giving a shorter, simpler, time-saving and higher yielding route to the synthesis of organic compounds. As part of our continuing efforts towards the use both of microwaves under solventless conditions[7] and of ultrasonic waves,[8,9] the syntheses of compounds **1** and **2** have been achieved and are outlined in Schemes 1 and 2.

Li_2CuCl_4-catalysed coupling[10] of geranyl magnesium bromide (**3**) with 2-bromo-1,4-dimethoxybenzene (**4**) in anhydrous THF at 0 °C gave **5** in 74% yield. The microwave-assisted allylic oxidation[7] of **5** using SeO_2/Bu^tOOH on SiO_2 as solid support gave **6** in 25% yield which upon demethylation[11] using BBr_3 in anhydrous CH_2Cl_2 at –78 °C furnished pure **1** in 17.6% overall yield.



Scheme 1

Ultrasonic irradiation of a mixture of 1-bromo-2,5-dimethoxy-4-methylbenzene and Mg in anhydrous THF afforded 2,5-dimethoxy-4-methylphenylmagnesium bromide (**7**) which upon subsequent coupling with 6-bromo-2-methylhept-2-ene (**8**) using Li_2CuCl_4 as catalyst in anhydrous THF at 0 °C afforded **9** in 74% yield. Demethylation of **9** using BBr_3 in anhydrous CH_2Cl_2 at –78 °C furnished **2** in 70.9% overall yield.



Scheme 2

Experimental

IR (ν_{max}/cm^{-1}) spectra were recorded on a Perkin Elmer model 1430 spectrophotometer and the ^1H NMR spectra with a Varian EM-360 (90 MHz) NMR spectrometer. Chemical shifts (δ) are reported in ppm with Me_4Si as internal standard. Elemental analyses were carried out using a Perkin Elmer 2400 elemental analyser. A Branson B-2200 EI (60 W, 47 kHz) ultrasonic cleaner was used for sonication. Microwave-induced reactions were carried out in a BPL BMO 700 T (640 W) microwave oven. Unless otherwise stated, all organic extracts were dried over anhydrous Na_2SO_4.

2,6-*Dimethyl*-8-(2,5-*dimethoxyphenyl*)*octa*-2,6-*diene* (**5**).—To the ice-cooled solution of the Grignard reagent, prepared from Mg turnings (0.48 g, 20 mmol) and geranyl bromide (4.34 g, 20 mmol) in anhydrous THF (40 ml) under a nitrogen atmosphere, was added dropwise a solution of 2-bromo-1,4-dimethoxybenzene (4.12 g, 19 mmol) in anhydrous THF (50 ml). After stirring for 45 min, Li_2CuCl_4 (0.1 M) in THF (2 ml) was added as a catalyst. The resultant mixture was then cooled to –10 °C, stirred for 3 h and the contents were left overnight at room temperature. The reaction mixture was then quenched with a saturated solution of NH_4Cl and extracted with diethyl ether (2 × 50 ml). The ethereal layer was washed successively with water and brine and then dried. Solvent evaporation followed by purification by column chromatography over silica gel using light petroleum (bp 60–80 °C)–diethyl ether (9:1) as eluent afforded **5** in 74% yield (4.05 g). δ_H 1.5 (s, 3 H), 1.7 (s, 6 H, vinyl methyls), 2.2, 2.5 (2 m, 4 H), 3.3 (d, 2 H, $J = 7$ Hz), 3.7, 3.8 (2 s, 6 H, 2 × OMe), 5.1, 5.3 (2 brt, 2 H, $J = 7$ Hz), 6.6–6.8 (3 H, Ar). ν_{max}/cm^{-1} 3030, 1610, 1520, 1470. (Found: C, 78.7; H, 9.3. $C_{18}H_{26}O_2$ requires C, 78.8; H, 9.5%.)

2,6-*Dimethyl*-8-(2,5-*dimethoxyphenyl*)*octa*-2,6-*dienal* (**6**).—A mixture of **5** (0.876 g, 3.2 mmol), SeO_2 (0.176 g, 1.6 mmol) and Bu^tOOH (70%, 0.576 g, 4.48 mmol) was dissolved in a small amount of CH_2Cl_2. Silica (1 g) was added to form a slurry and excess solvent was evaporated off to obtain free flowing silica which was then exposed to microwave irradiation at power level 9 (640 W) for 10 min. Diethyl ether (2 × 50 ml) was added and the mixture was filtered. The filtrate was washed (10% KOH, brine) and dried. Solvent removal and purification over silica gel gave **6** in 25% yield. δ_H 1.5 (s, 3 H), 1.7 (s, 6 H, vinyl methyls) 2.1, 2.6 (2 m, 4 H), 3.3

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*To receive any correspondence.

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(d, 2 H, $J = 7$ Hz), 3.7, 3.8 (2 s, 6 H, 2 × OMe), 5.3 (t, 1 H, $J = 7$ Hz), 6.4 (t, 1 H, $J = 7$ Hz), 6.6–6.8 (3 H, Ar), 9.3 (s, 1 H, CHO). ν_{max}/cm^{-1} 2720, 1675. (Found: C, 79.6; H, 6.3. $C_{18}H_{24}O_3$ requires C, 75.0; H, 8.4%.)

Alliodorin (**1**).—To a well stirred solution of **6** (0.72 g, 2.5 mmol) in anhydrous CH_2Cl_2 (15 ml) at −78 °C was added BBr_3 (0.65 g, 2.6 mmol). The solution was allowed to reach room temperature and then decomposed with water (2 ml), extracted with diethyl ether and dried. Evaporation of the solvent furnished pure compound **1** (0.626 g, 96%): δ_H 1.5 (s, 3 H), 1.7 (s, 6 H), 2.2, 2.4 (2 m, 4 H), 3.3 (d, 2 H, $J = 7$ Hz), 5.2 and 5.5 (2 s, 2 H, D_2O exchangeable), 5.3 (t, 1 H, $J = 7$ Hz), 6.5 (t, 1 H, $J = 7$ Hz), 6.6–6.8 (3 H, Ar), 9.3 (s, 1 H, CHO). ν_{max}/cm^{-1} 3350, 2720, 1675, 1698, 1602. (Found: C, 73.4; H, 7.5. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%.)

2,6-*Dimethyl*-6-(4-*methyl*-2,5-*dimethoxyphenyl*)*hex*-2-*ene* (**9**).—To an ice-cooled solution of the Grignard reagent prepared from 1-bromo-2,5-dimethoxy-4-methylbenzene (4.16 g, 20 mmol) and Mg (0.48 g, 20 mmol) in anhydrous THF (40 ml) *via* ultrasonic irradiations in an inert atmosphere was added dropwise a solution of 6-bromo-2-methylhept-2-ene (3.62 g, 19 mmol) in THF (50 ml). After stirring for 45 min, Li_2CuCl_4 (0.1 M) in THF (2 ml) was added to it; the resultant mixture cooled to −10 °C and stirred for 3 h and left overnight at room temperature. The reaction mixture was worked-up as described earlier to afford **9** in 74% yield. δ_H 1.2 (d, 3 H, $J = 7$ Hz), 1.5 (s, 3 H), 1.6–1.7 (m, 2 H), 1.8 (s, 3 H), 1.9 (m, 2 H), 2.1 (s, 3 H), 2.9 (m, 1 H, $J = 7$ Hz), 3.7–3.8 (2 s, 6 H, 2 × OMe), 5.1 (brt, 1 H, $J = 7$ Hz), 6.5, 6.7 (2 s, 2 H, Ar). ν_{max}/cm^{-1} 3030, 2920, 1590, 1480, 1245. (Found: C, 77.3; H, 9.6. $C_{17}H_{26}O_2$ requires C, 77.7; H, 9.9%.)

(±)-*Curcuhydroquinone* (**2**).—Demethylation of **9** (0.655 g, 2.5 mmol) in anhydrous CH_2Cl_2 (15 ml) at −78 °C using BBr_3 (0.65 g, 2.6 mmol) as described above gave **2** (0.56 g, 96% yield). δ_H 1.2 (d, 3 H, $J = 7$ Hz), 1.5 (s, 3 H), 1.6–1.7 (m, 2 H), 1.8 (s, 3 H), 1.9 (m, 2 H), 2.2 (3 H, s), 3.1 (m, 1 H, $J = 7$ Hz), 4.5 (2 H, brs, OH), 5.1 (brt, 1 H, $J = 7$ Hz), 6.5, 6.7 (s, 2 H, Ar.). ν_{max}/cm^{-1} 3400, 1590, 1480, 1245. (Found: C, 76.6; H, 9.1. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.4%.)

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