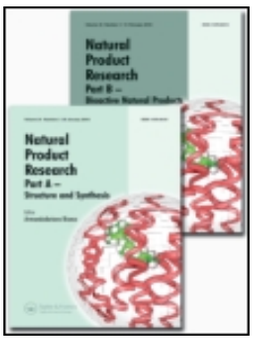

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A short and facile synthesis of 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol and 1-(3'-methoxypropanoyl)-2,4,5-trimethoxybenzene isolated from Cordia alliodora

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A short and facile synthesis of 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol and 1-(3′-methoxypropanoyl)-2,4,5-trimethoxybenzene isolated from *Cordia alliodora*

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A novel synthesis of 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol and 1-(3′-methoxypropanoyl)-2,4,5-trimethoxybenzene has been carried out by making use of an easily available starting material, acceleration by MW irradiation and the use of water as a green solvent in the key steps.

Keywords: microwave irradiation; aqueous media; aldol reaction; Heck reaction; prenylated hydroquinone

1. Introduction

A variety of biologically active prenylated hydroquinones have been extracted from plant extracts (Danelutte, Lago, Young, & Kato, 2003; Yamaguchi, Lago, Tanizaki, Mascio, & Kato, 2006). A prenylated hydroquinone, 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol (**4**), and 1-(3′-methoxypropanoyl)-2,4,5-trimethoxybenzene (**7**) have been isolated from the root bark of *Cordia alliodora*, (Aknin, Dayan, Rudi, Kashman, & Gaydon, 1999; Ioset, Marston, Gupta, & Hostettmann, 2000), also known as *Cerdana alliodora* Ruiz and Pavon. It is a tall tree frequently encountered in Central America, South America and the Caribbean. In Panama, *C. alliodora* is the most widespread species. A decoction of the leaves is used as a tonic for pulmonary diseases in traditional Mexican medicine, and is applied on bruises and swelling in Salvador. An ointment made of the plant seeds is employed to treat skin diseases. Compound **4** also showed antifungal properties against the pythogenic mould *Cladosporium cucumerinum*. The title compound **7** is reported to have antifungal and larvicidal activities against the phytopathogenic mould *C. cucumerinum* and the larvae of yellow fever transmitting mosquito, *Aedes aegypti*, respectively.

One of the main goals of organic synthesis has been the search for new compounds that exhibit novel physical, chemical and biological properties as well as

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synthesis of molecules of nature. The use of clean technology tools is adding a new dimension towards greening the synthesis of natural products. Water is a very attractive solvent as a reaction medium (Matsushita, Kamata, Yamaguchi, & Mizuno, 2005). It is safe, harmless, non-flammable, non-toxic and extremely eco-friendly. Ionic liquids may be viewed as an alternative to volatile organic solvents, representing a new class of non-molecular ionic solvents (Holbrey & Seddon, 1999; Wasserchied & Keim, 2000; Welton, 1999). Ionic liquids have been extensively studied in the past few years as media for organic synthesis and catalysis in particular (Dupont, de Souza, & Suarez, 2002; Song, 2004).

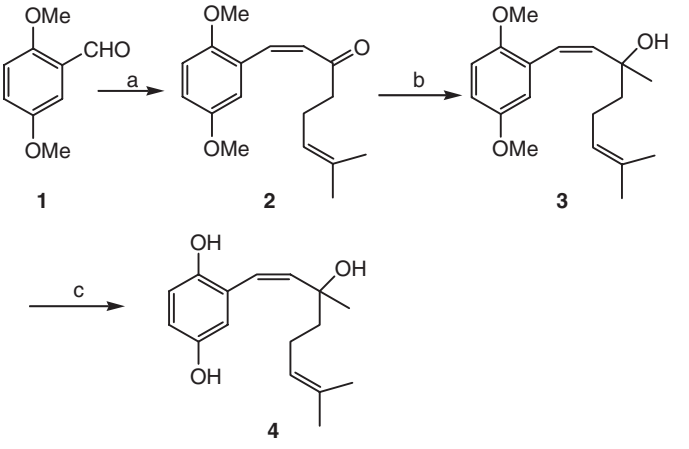
Microwave heating has been used to accelerate organic chemical transformations. The many advantages of this enabling technology, such as reduced reaction times, increased product yields and enhanced product purities (De La Hoz, Diaz-Ortiz, & Moreno, 2005; Hayes, 2002, 2004; Kappe, 2004; Kappe & Sandler, 2005; Kingston & Haswell, 1997; Loupy, 2002; Perreux & Loupy, 2001; Strauss, 2002) have not only been exploited for organic synthesis in the context of medicinal chemistry/drug discovery (Kappe & Dallinger, 2006; Larhed & Hallberg, 2001; Shipe, Wolkenberg, & Lindsley, 2005; Wathey, Tierney, Lidstrom, & Westman, 2002), but have also penetrated fields such as polymer synthesis (Bogdal, Penczek, Pielichowski, & Prociak, 2003; Wiesbrock, Hoogenboom, & Schubert, 2004), material sciences (Barlow & Marder, 2003; Zhu, Wang, Qi, & Hu, 2004), nanotechnology (Tsuji, Hashimoto, Nishizawa, Kubokawa, & Tsuji, 2005) and biochemical processes (Orrling, Nilsson, Gullberg, & Larhed, 2004). We report the synthesis of two bioactive natural products, 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol (**4**) and 1-(3′-methoxypropanoyl)-2,4,5-trimethoxybenzene (**7**), by making use of clean technologies, such as microwave irradiation, aqueous media and ionic liquids.

2. Discussion

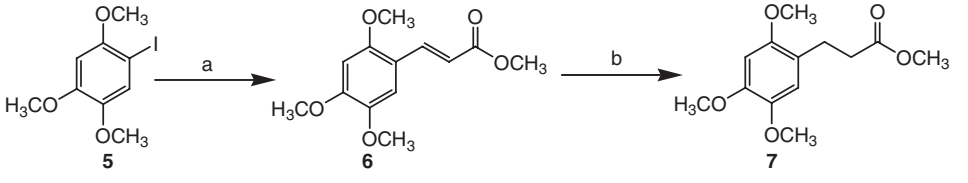
The literature does not record any synthesis of 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol (**4**). Keeping in mind the medicinal value of the compound, its synthesis has been undertaken. Aldol condensation in aqueous media and a Grignard reaction in the presence of $CeCl_3$ have been employed as key steps in the novel synthesis of the title compound **4**. A diagrammatic representation of the different steps used in this multi-step synthesis is shown in Scheme 1.

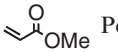
Aldol condensation (Kad, Singh, & Kaur, 1999) of 2,5-dimethoxybenzaldehyde with 6-methylhept-5-en-2-one using aq. NaOH under MW was carried out to yield a transparent liquid (**2**) in 84% yield. MeMgI in THF, upon Grignard reaction (Imamoto, Takiyama, Wakamura, Hatajima, & Kamiya, 1989) in the presence of $CeCl_3$ with 2-(1Z)-(7-methyl-3-oxoocta-1,6-dienyl)-1,4-dimethoxybenzene gave a 1,2-addition product (**3**) in 87% yield. $CeCl_3$ was used to get exclusively the 1,2 addition product instead of the 1,4 addition in the Grignard reaction.

Deprotection (Demuynck, Clercq, & Vandewalle, 1979) of (**3**) using BBr_3 in DCM at $-78^{\circ}C$ furnished the title compound **4** as a yellow viscous liquid in 85% yield. The spectral data of this title compound matched well with that reported in the literature (Aknin et al., 1999; Ioset et al., 2000). The title compound **4** has been obtained in 62.1% overall yield.



Scheme 1. Reagents and conditions: (a) aq. NaOH, MW, 7-methyl-5-hepten-2-one, (b) MeMgI, $CeCl_3$, THF, (c) BBr_3, DCM, 78°C.



Scheme 2. Reagents and conditions: (a)  $Pd(OAc)_2$ (1 mol%), NaOAc, (bmim)Br, (b) $ZnCl_2$, Mg, H_2O.

Several synthesis methods of the title compound **7** have been reported in the literature (Aguilar, Benavides, & Tamariz, 2004; Sinha, Joshi, Sharma, Kumar, & Kaul, 2003; Sinha, Sharma, & Kumar, 2006; Vanisree, Kavitha, & Subbaraja, 2002).

We herein report a simple, inexpensive and short synthesis of 1-(3′-methoxypropanoyl)-2,4,5-trimethoxybenzene from readily available starting materials using the Heck reaction of the unactivated ring and an appropriate alkene as the key steps. The reaction sequence employed is as shown in Scheme 2.

The Heck reaction (Bianco, Claudia, & Marcella, 2004; Xu, Chen, & Xiao, 2000) of 1-iodo-2,4,5-trimethoxybenzene (**5**) using $Pd(OAc)_2$ as catalyst and (bmim)Br as solvent, with methyl acrylate, led to the formation of methyl 2,4,5-trimethoxy cinnamate (**6**). The $Mg/ZnCl_2$-mediated selective reduction (Anil, Gopal, & Chandra, 2005) of C=C in aqueous media led to the formation of the final compound **7** in 55.4% overall yield. Its ^1H NMR, ^{13}C NMR and IR spectra were found to be in agreement to that reported for the original compound (Aknin et al., 1999; Ioset et al., 2000).

To conclude, a short synthesis of two biologically active products, 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol (**4**) and 1-(3′-methoxypropanoyl)-2,4,5-trimethoxybenzene (**7**), isolated from the root bark of *C. alliodora*, have been carried out using easily available starting materials, and in good overall yields.

The synthesis has been carried out using green methodologies, such as aqueous media, ionic liquids and microwave irradiations.

3. Experimental

Melting points were determined with a Sunbim melting point apparatus. IR spectra were recorded on a Perkin-Elmer model 1430 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Joel 300 MHz spectrometer. Chemical shifts are reported in parts per million with tetramethylsilane as the internal standard. Microwave-induced reactions were carried out in a domestic microwave (MG-396W A, 2450 MHz, 800 W).

3.1. *2-(1Z)-(7-methyl-3-oxoocta-1,6-dienyl)-1,4-dimethoxybenzene (2)*

A mixture of 2,5-dimethoxybenzaldehyde (1.9 mmol), 6-methylhept-5-en-2-one (11.7 mmol) and 10% aq. NaOH (3.25 mL) was taken in a 50 mL conical flask and was irradiated in a microwave oven at 150 W for 10 min. Then the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined extract was washed with water and dried to get a colourless liquid (**2**) in 84% yield, after purification on silica gel column chromatography using 3% ethyl acetate in *n*-hexane as eluant.

IR ($CDCl_3$)/ν_{max} cm^{-1}: 3032, 1680, 1660, 1240. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (d, 1H, $J = 7.2$ Hz, Ar–C**H**=CH–), 6.69–6.96 (m, 3H, Ar–**H**), 6.50 (d, 1H, $J = 7.2$ Hz, Ar–CH=C**H**–), 5.08 (m, 1H, $(CH_3)_2$C=C**H**–), 3.87 (s, 3H, –OC**H**$_3$), 3.72 (s, 3H, –OC**H**$_3$), 2.62 (t, 2H, $J = 7.2$, –CO–C**H**$_2$), 2.28 (m, 2H, –C**H**$_2$CH=C$(CH_3)_2$), 1.64 (s, 6H, –CH=C(C**H**$_3)_2$). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 198.2, 153.7, 152.7, 136.9, 132.0, 129.0, 125.4, 123.6, 55.9, 55.4, 40.3, 25.9, 23.0, 21.6.

3.2. *2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-dimethoxybenzene (3)*

$CeCl_3 \cdot 7H_2O$ (2.0 mmol) was quickly and finely ground to powder in a mortar and placed in a 30 mL two necked flask. The flask was immersed in an oil bath and heated gradually to 135–140°C with evacuation. After maintaining the $CeCl_3$ at a constant temperature for 1 h, a magnetic bead was placed in the flask and $CeCl_3$ was completely dried in vacuum with stirring at the same temperature for an additional 1 h. While the flask was still hot, nitrogen gas was introduced, the flask was then cooled in an ice bath and THF (6 mL) was added at once with vigorous stirring. The ice bath was removed and the suspension was stirred overnight at room temperature under nitrogen. The flask was then immersed in an ice bath and MeMgI (2.0 mmol) was added. After stirring for 1.5 h at 0°C, the compound 2-(1Z)-(7-methyl-3-oxoocta-1,6-dienyl)-1,4-dimethoxybenzene (1.3 mmol) was added, and stirring was continued for an additional 2 h. Then the reaction mixture was treated with 10% aqueous CH_3COOH (12 mL). The product was extracted with diethyl ether (3 × 10 mL) and the combined extract was washed with water (1 × 5 mL), aq. $NaHCO_3$ solution, brine, and then dried with Na_2SO_4. The solvent was evaporated to furnish product (**3**) in 87% yield after purification on silica gel column chromatography using 10% ethyl acetate in *n*-hexane as eluant.

IR ($CDCl_3$)/ν_{max} cm^{-1}: 3450, 3032, 1660, 1240. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.69–6.53 (m, 3H, Ar–**H**), 6.25 (d, 1H, $J = 7.2$ Hz, Ar–C**H**=CH–), 5.21 (d, 1H, $J = 7.2$ Hz, Ar–CH=C**H**–), 5.08 (m, 1H, $(CH_3)_2C$=C**H**–), 3.72 (s, 3H, –OC**H**$_3$), 3.87 (s, 3H, –OC**H**$_3$), 2.18 (m, 2H, –C**H**$_2$CH=C$(CH_3)_2$), 1.81 (t, 2H, $J = 7.4$ Hz, –C**H**$_2$–C(OH)), 1.36 (s, 3H, (OH)C–C**H**$_3$), 1.61 (d, 6H, $J = 11.4$ Hz, –CH_2=C(C**H**$_3)_2$). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 153.2, 149.7, 134.6, 132.3, 126.9, 124.4, 116.2, 115.6, 114.2, 111.0, 72.3, 55.3, 55.1, 29.1, 25.5. Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; O, 18.29. Found: C, 73.65; H, 8.39; O, 17.96.

3.3. *2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-benzenediol (4)*

To a stirred solution of 2-(1Z)-(3-hydroxy-3,7-dimethylocta-1,6-dienyl)-1,4-dimethoxybenzene (0.08 mmol) in dried DCM (4 mL) was added a solution of BBr_3 (0.05 mL, 0.05 mmol) in 1.0 mL DCM at −78°C. After 1 h the reaction mixture was quenched with $NaHCO_3$ and extracted with DCM (2 × 10 mL). The combined extract was washed with water (5 mL) and dried over $CaCl_2$. The crude product, on column chromatography using 20% ethyl acetate in *n*-hexane as eluant, yielded the title compound **4** in 85% yield.

IR ($CDCl_3$, cm^{-1}): 3450, 3032, 2880, 1628, 1660. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.64–6.48 (m, 3H, Ar–**H**), 6.25 (d, 1H, $J = 7.2$ Hz, Ar–C**H**=CH–), 5.41(d, 1H, $J = 7.2$ Hz, Ar–CH=C**H**–), 5.19 (br s, 1H, –O**H**), 5.08 (m, 1H, $(CH_3)_2C$=C**H**), 4.12 (br s, 1H, –O**H**), 2.09 (m, 2H, –C**H**$_2$CH=C$(CH_3)_2$), 1.81 (t, 2H, –C**H**$_2$–C(OH)), 1.36 (s, 3H, (OH)C–C**H**$_3$), 1.61 (s, 6H, $J = 11.4$ Hz, –CH_2=C(C**H**$_3)_2$). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 156.3, 146.6, 130.2, 129.6, 123.9, 123.0, 122.4, 115.3, 114.8, 113.7, 80.1, 41.3, 27.2, 25.3, 22.5, 16.7.

3.4. *Methyl 2,4,5-trimethoxycinnamate (6)*

In a 50 mL flame dried, two necked round bottom flask fitted with a septum and reflux condenser were placed (bmim)Br (3 mL), 1-iodo-2,4,5-trimethoxybenzene (3 mmol), anhydrous sodium acetate (3.3 mmol) and palladium acetate (0.03 mmol). To that was added methyl acrylate (4 mmol) through the septum, and the reaction mixture was heated and maintained at 100°C in an oil bath for 24 h. The reaction mixture was then cooled and extracted with ethyl acetate (3 × 5 mL). The combined organic extract was washed with water (2 × 2 mL), brine and dried over anhydrous magnesium sulphate. The solvent was evaporated on vacuum and the product was separated by column chromatography using hexane : ethyl acetate (8.5 : 1.5) as eluant to obtain the pure product **6** in 84% yield.

IR (nujol)/ν_{max} cm^{-1}: 3030, 2880, 1717, 1624, 1610. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.51 (d, 1H, $J = 9.6$, Ar–C**H**=CH–), 7.12 (s, 1H, Ar–**H**), 6.67 (s, 1H, Ar–**H**), 6.20 (d, 1H, $J = 9.6$, Ar–CH=C**H**–), 3.87 (s, 3H, –OC**H**$_3$), 3.80 (s, 3H, –OC**H**$_3$), 3.74 (s, 3H, –OC**H**$_3$), 3.71 (s, 3H, –OC**H**$_3$). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 170.2, 153.3, 145.1, 139.1, 122.6, 120.4, 115.3, 111.0, 99.6, 58.5, 58.0, 57.7, 52.5.

3.5. *1-(3′-Methoxypropanoyl)-2,4,5-trimethoxybenzene (7)*

To the suspension of methyl 2,4,5-trimethoxycinnamate (1.8 mmol) in distilled water (10 mL) taken in a 50 mL round bottom flask was added magnesium metal (2.7 mmol) and zinc chloride (2.7 mmol). The reaction mixture was stirred at room temperature for 30 min and extracted with dichloromethane (3 × 5 mL). The organic extracts were dried over calcium chloride. Evaporation of the solvent followed by purification through column chromatography on silica gel, with hexane : ethyl acetate (9 : 1) gave the pure compound (**7**) in 66% yield.

IR (nujol)/ν_{max} cm^{-1}: 3024, 2990, 1743, 1649, 1518, 1162. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.77 (s, 1H, Ar–**H**), 6.54 (s, 1H, Ar–**H**), 3.88 (s, 3H, –OC**H**$_3$), 3.83 (s, 3H, –OC**H**$_3$), 3.79 (s, 3H, –OC**H**$_3$), 3.67 (s, 3H, –OC**H**$_3$), 2.89 (t, 2H, $J = 7.6$, Ar–C**H**$_2$–), 2.59 (t, 2H, $J = 7.6$, –C**H**$_2$–COOCH$_3$). ^{13}C NMR ($CDCl_3$, 300 MHz) δ: 174.8, 150.5, 148.3, 144.4, 122.6, 114.3, 99.6, 57.6, 56.9, 51.7, 34.5, 27.3. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13; O, 31.44. Found: C, 61.54; H, 7.06; O, 31.39.

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