

Note

Synthesis of (\pm)-(*E*)-2,6-dimethyl-6-hydroxy-2,7-octadienoic acid, its methyl ester and (\pm)-(*E*)-2,6-dimethyl-octa-2,7-diene-1,6-diol over solid support using microwave

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A simple, exceedingly mild, ecofriendly and efficient methodology for the synthesis of (\pm)-(*E*)-2,6-dimethyl-6-hydroxy-2,7-octadienoic acid, its methyl ester and (\pm)-(*E*)-2,6-dimethyl-octa-2,7-diene-1,6-diol by utilization of microwave energy has been achieved.

Keywords: Microwave, natural products, monoterpenoid, solid support.

The monoterpenoid (\pm)-(*E*)-2,6-dimethyl-6-hydroxy-2,7-dienoic acid (linalool-1-oic acid) isolated as a free natural product for the first time from *Kickxia spuria*¹ and from fruits of *Gymnocladus chinesis*². This linalool-1-oic acid and its methyl ester have been isolated from *Artemisia siberi* and *Piper aduncum*³, respectively and (\pm)-(*E*)-2,6-dimethyl-octa-2,7-diene-1,6-diol has been isolated from aerial parts of *Artemisia Xerophytica*⁴. The structural assignments of these compounds were done on the basis of spectral data. Optical rotation of these compounds has not been reported, indicating thereby that the isolated natural products are racemic in nature. Literature⁵⁻⁷ reports the synthesis of these compounds using conventional techniques which are found to be time consuming.

The exploitation of microwaves for assisting different organic reactions⁸ has blossomed into an important tool in synthetic organic chemistry. Due to the timeless, ease of workability and eco-friendliness, microwaves provide an alternative to environmentally unacceptable procedures which may be time consuming or use toxic and expensive reagents. The microwave enhanced chemical reactions on solid support⁹ have clear advantage over the usual homogeneous and heterogeneous reactions as they

can be conducted rapidly and provide pure products in quantitative yields without use of solvents.

Herein we report a simple, exceedingly mild, eco-friendly synthesis of these compounds by utilizing microwave energy in excellent yield.

The linalool **1** was converted into (\pm)-(*E*)-2,6-dimethyl-3-hydroxy-2,7-octadienal **2** on oxidation with SeO₂, Bu^tOOH over SiO₂ in microwave at 640 W for 10 min with 85% yield^{8b}. α,β -Unsaturated dienal **2** was converted into (\pm)-(*E*)-2,6-dimethyl-2,7-octadienoic acid **3** using silica supported chromium trioxide under microwave irradiation. The reduction of dienal **2** with sodium borohydride supported on neutral alumina in microwave furnished pure (\pm)-(*E*)-2,6-dimethyl-octa-2,7-diene-1,6-diol **4** in 87% yield (**Scheme I**). Esterification of **3** was done with methanol in the presence of silica supported sodium hydrogen sulphate¹⁰. The heterogeneous catalyst, NaHSO₄.SiO₂ has been found to be highly efficient in carrying out the conversion of acid into corresponding ester in very high yield. The yield of reaction was observed to be low when the same reaction was carried out with NaHSO₄ alone without using silica support. In recent years such heterogeneous catalysts has been preferred for carrying out various chemical transformation due to enviro-economic factors.

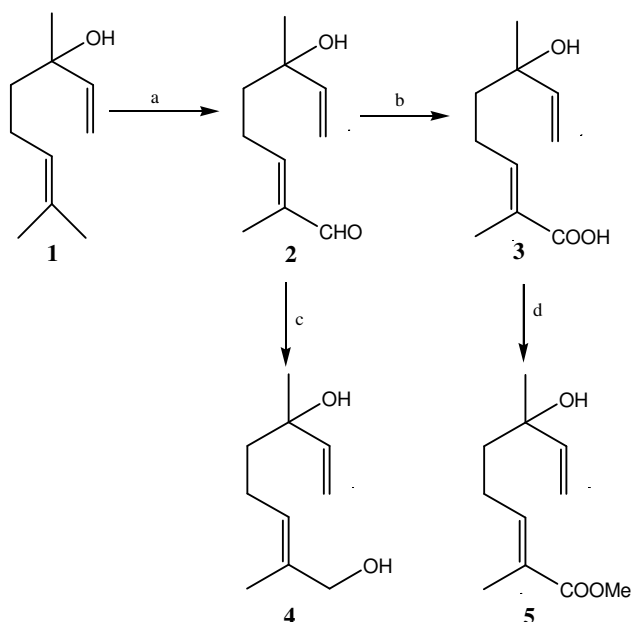
In conclusion, we have developed a simple, inexpensive and efficient synthesis of these natural products. The mild reaction conditions, experimental simplicity, short reaction time and excellent yields are main advantages of this procedure.

Experimental Section

The IR spectra were recorded on a Perkin-Elmer R X 1 FT-IR spectrophotometer, and ¹H NMR spectra were recorded on a FT JEOL, 300MHz spectrometer with CDCl₃ or CCl₄ as solvent. Chemical shifts are reported as ppm downfield from Me₄Si. Mass spectra (MS) were recorded at 70 eV using a VG-Analytical 11-250-J70-S spectrometer.

Procedure

(\pm)-(*E*)-2,6-Dimethyl-3-hydroxy-2,7-octadienal 2. Linalool **1** (2 g, 12.98 mmoles), SeO₂ (0.70 g,



a) SeO_2 , Bu^tOOH , SiO_2 , MWI 640 W, 10 min. b) CrO_3 , SiO_2 , MWI, 480 W, 4 min. c) $\text{NaBH}_4/\text{Al}_2\text{O}_3$, MWI, 640 W, 1 min. d) CH_3OH , NaHSO_4 , SiO_2 , MWI, 320 W, 4 min.

Scheme I

6.4 mmol) and Bu^tOOH (70%, 1.75 g, 19.47 mmol) were dissolved in 2 mL of dichloromethane in a 50 mL conical flask. Silica (1 g) was added to form a slurry and excess solvent was evaporated to obtain free flowing solid, which was exposed to microwave irradiation at power level 640 W for 10 min. The product was extracted with diethyl ether and filtered. The filtrate was washed (10% KOH, brine) and then dried. Removal of solvent followed by column chromatographic purification over silica gel afforded pure product **2** in 85% yield.

IR (neat): 3410, 2916, 1685, 1635, 1411, 1070, 910 cm^{-1} ; ^1H NMR: δ 9.3 (s, 1H, $-\text{CHO}$), 5.7 (m, 1H, $-\text{CH}=\text{CH}_2$), 5.2 (t, 2H, $J=12$ Hz, $-\text{CH}=\text{CH}_2$), 4.96 (t, 1H, $J=9$ Hz, $-\text{CH}=\text{C}<$), 3.8 (bs, 1H, OH, D_2O exchangeable), 2.2 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}=\text{C}<$), 1.7 (s, 3H, $>\text{C}(\text{CHO})\text{CH}_3$), 1.5 (m, 2H, $-\text{CH}_2-\text{CH}=\text{C}<$) and 1.2 (s, 3H, $>\text{C}(\text{OH})\text{CH}_3$); MS: 168 $[\text{M}]^+$, 151, 150, 135, 123, 111, 93, 81, 71, 85, 59.

(\pm)-(E)-2,6-Dimethyl-6-hydroxy-2,7-octadienioc acid 3. The dienal **2** (0.4 g, 2 mmol) and silica supported chromium trioxide (0.2 g, 2 mmol) (prepared by mixing equal molar amounts of silica and chromium trioxide in pestle mortar) were subjected to microwave irradiation at 480 W for 4 min. The product was extracted with diethyl ether and filtered. The filtrate was washed with brine, dried and evaporated to give pure acid **3** in 90% yield.

IR (neat): 3430-3260 (br), 2940, 1709, 1635, 1410, 1190, 1060, 905 cm^{-1} ; ^1H NMR: δ 6.93 (bs, 1H, COOH, D_2O exchangeable), 5.73 (m, 1H, $-\text{CH}=\text{CH}_2$), 5.3 (t, 2H, $J=11$ Hz, $-\text{CH}=\text{CH}_2$), 5.06 (bt, 1H, $-\text{CH}=\text{C}<$), 2.3 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}=\text{C}<$), 3.8 (bs, 1H, OH, D_2O exchangeable), 1.6 (s, 3H, $>\text{C}(\text{OH})\text{CH}_3$), 1.43 (m, 2H, $-\text{CH}_2-\text{CH}=\text{C}<$) and 1.26 (s, 3H, $>\text{C}(\text{COOH})\text{CH}_3$); MS: 183 $[\text{M}]^+$, 166, 143, 110, 99, 85, 81, 71, 59.

(\pm)-(E)-2,6-Dimethyl-octa-2,7-diene-1,6-diol 4.

To the dienal (0.4 g, 2 mmol) was added freshly prepared $\text{NaBH}_4/\text{Al}_2\text{O}_3$ (0.11 g, 3 mmol) in conical flask and the conical flask was put in neutral alumina-bath. The reaction-mixture was irradiated at 640 W for 1 min, cooled the product and extracted with diethyl ether. The product was washed with brine and dried over sodium sulphate. Removal of solvent followed by column chromatographic purification over silica gel using hexane-ethylacetate (9:1) as eluent afforded pure product **4** in 89% yield.

IR (neat): 3460, 2970, 1550, 1460, 1380, 1260, 1015 cm^{-1} ; ^1H NMR: δ 5.77 (m, 1H, $-\text{CH}=\text{CH}_2$), 5.22 (t, 2H, $J=11$ Hz, $-\text{CH}=\text{CH}_2$), 5.07 (t, 1H, $J=9$ Hz, $-\text{CH}=\text{C}<$), 3.99 (bs, 3H, $-\text{CH}_2\text{OH}$), 2.96 (bs, 1H, OH, D_2O exchangeable), 2.08 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}=\text{C}<$), 1.66 (bs, 3H, $>\text{C}(\text{OH})\text{CH}_3$), 1.30 (s, 3H, $>\text{C}(\text{CH}_2\text{OH})\text{CH}_3$); MS: 170 $[\text{M}]^+$, 85, 71.

(\pm)-(E)-2,6-Dimethyl-6-hydroxy-2,7-octadienioc acid methyl ester 5. The acid **4** (0.2 g, 1.08 mmol), methanol (0.1 g, 3 mmol), and silica supported sodium hydrogen sulphate (0.1 g, 0.7 mmol) were taken in conical flask and exposed to microwave irradiation at 320 W for 4 min. The product was extracted with diethylether washed with sodium bicarbonate, water, brine and dried. Evaporation of solvent under reduced pressure yielded crude product which was purified by silica gel column chromatography using 5% ethyl acetate in *n*-hexane as elutant to give ester **5** in 90% yield.

IR (CCl_4): 1710, 1645, 999, 921 cm^{-1} ; ^1H NMR: δ 5.88 (m, 1H, $-\text{CH}=\text{CH}_2$), 5.20 (t, 2H, $J=11$ Hz, $-\text{CH}=\text{CH}_2$), 5.07 (t, $J=9$ Hz 1H, $-\text{CH}=\text{C}<$), 3.70 (s, 3H, $>\text{C}(\text{COOCH}_3)\text{CH}_3$), 3.1 (bs, 1H, OH, D_2O exchangeable), 2.1 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}=\text{C}<$), 1.50 (m, 2H, $-\text{CH}_2-\text{CH}=\text{C}<$), 1.80 (s, 3H, $>\text{C}(\text{COOCH}_3)\text{CH}_3$), 1.30 (s, 3H, $>\text{C}(\text{OH})\text{CH}_3$); MS: 198 $[\text{M}]^+$, 180, 165.

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References

- 1 Nicoletti M, Tomassini L & Seraffini M, *Fitoterapia*, 60, **1989**, 252.
- 2 Konoshima T & Sawada T, *Chem Pharm Bull*, 32, **1984**, 2617.
- 3 Macro J A, Sanz-Cervera J F, Sancenon F, Jakupovic J, Rustaiyan A & Mohamadi F, *Phytochemistry*, 34, **1993**, 1061.
- 4 Bohlmann F, Jakupovic J, Tan R X, Zia Z J & Huneck S, *Phytochemistry*, 30, **1991**, 583.
- 5 Liu H X, Chen X H & Huang C S, *Chem Res in Chinese Universities*, 19, **2003**, 425.
- 6 Sharma M L & Chand T, *Proc Indian Acad Sci Chem Sci*, 108, **1996**, 21.
- 7 Carda M, Murga J & Macro J A, *Tetrahedron Lett*, 51, **1995**, 2755.
- 8 (a) Kad G L, Kaur J, Nayyar S, Kaur I & Singh J, *Indian J Chem*, 40B, **2001**, 715; (b) Singh J, Sharma M, Kad G L & Chhabra B R, *J Chem Res (S)*, **1997**, 264; (c) Kad G L, Bhandari M, Kaur J & Singh J, *Green Chem*, 3, **2001**, 275; (d) Kad G L, Kaur K P, Singh V & Singh J, *Tetrahedron Lett*, 38, **1997**, 1079; (e) Singh J, Bhandari M, Kaur J & Kad G L, *Indian J Chem*, 42B, **2003**, 405.
- 9 (a) Singh V, Khurana A, Kaur I, Sapeliyia V, Kad G L & Singh J, *J Chem Soc Perkin trans 1*, **2002**, 1766; (b) Singh J, Kaur J, Nayyar S & Kad G L, *J Chem Res (S)*, **1998**, 280; (c) Singh J, Sharma M, Chibber M, Kaur J & Kad G L, *Synth Commun*, 30, **2000**, 3941. .
- 10 Nath N R, Ramu R, Reddy M R & Das B, *Synth Commun*, 34, **2004**, 3135.