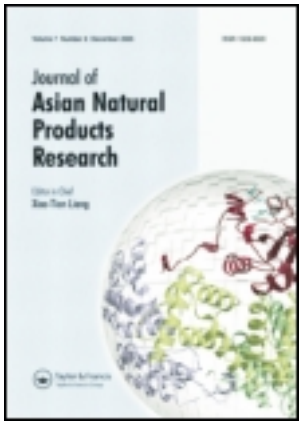

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Total synthesis of 3,7-dimethyl-7-hydroxy-2-octen-1,6-olide and 3,7-dimethyl-2,6-octadien-1,6-olide

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Total synthesis of 3,7-dimethyl-7-hydroxy-2-octen-1,6-olide and 3,7-dimethyl-2,6-octadien-1,6-olide

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3,7-Dimethyl-7-hydroxy-2-octen-1,6-olide (**1**) and 3,7-dimethyl-2,6-octadien-1,6-olide (**2**), the natural bioactive compounds isolated from the fruit of *Litsea cubeba* and the liverwort *Plagiochila rutilans*, were totally synthesized using easily available *cis*-geraniol as raw material in short, convenient, and low-cost, five-step reactions including three steps of oxidation, cyclization, and dehydration, with an overall yield of 47.5% and 37.3%.

Keywords: total synthesis; 3,7-dimethyl-7-hydroxy-2-octen-1,6-olide; 6-olide; 3,7-dimethyl-2,6-octadien-1,6-olide

1. Introduction

As all we know, a large number of natural products have the structures of five- or six-membered lactone ring as well as medium-ring lactone including 8-, 9-, 10-, and 11-membered ring [1–4]. For example, clausamines A–C and clausevatines D–G (Figure 1) were first isolated from dried branches of *Clausena anisata* in Thailand [5]. Some of them may display interesting biological activities including antimalaria, anti-TB, cytotoxicity, and stimulating glucose uptake in L6 myotubes [6–8]. However, there are a few natural products having the structure of seven-membered lactone rings [9]. (6R)-3,7-Dimethyl-7-hydroxy-2-octen-6-olide (**1**) was first isolated from the honey bee fungal entomopathogen *Ascosphaera apis* [10], as well as the fruit of plant *Litsea cubeba* in Tibet [11], and exhibited good antifungal and antioxidant activities. 3,7-Dimethyl-2,6-octadien-1,6-olide (**2**) is a natural product, which was first isolated from the Costa Rican liverwort *Plagiochila rutilans*. They have a very unique structure of a seven-membered lactone ring with an olefin or isopropanol side chain [12]. Sesquiterpene lactone (**4**) was also isolated from *Drypetes molunduana* (Figure 2) and showed anti-inflammatory and analgesic activities [13,14]. Because they all have novel strain seven-membered lactone ring structure, there are very practical difficult to synthesis them. So far, only a few synthetic methods of natural and nonnatural seven-membered lactones were reported by oxidative lactonization, the palladium-catalyzed carbonylative annulation of internal alkynes, the ring-closing metathesis synthesis of unsaturated lactones and enzymatic synthesis [15–18]. The only crystal structure of seven-membered lactone (*S*)-6-methyl-ε-caprolactone was also reported [19]. Therefore, there has been great demand for highly efficient synthetic methods for natural and nonnatural seven-membered lactones.

Lactonization of epoxy carboxylic acid was a new synthetic strategy, and we will report the total synthesis of natural products 3,7-dimethyl-7-hydroxy-2-octen-1,6-olide (**1**) and 3,7-dimethyl-2,6-octadien-1,6-olide (**2**) using this protocol as the key step in this paper. Based on the

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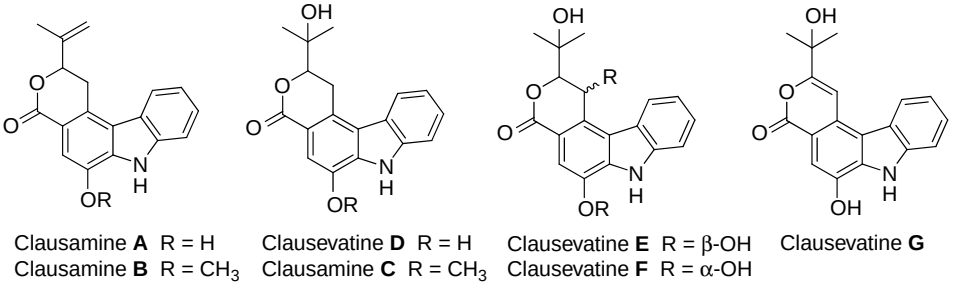


Figure 1. Structures of clausamines A–C and clausevatines D–G.

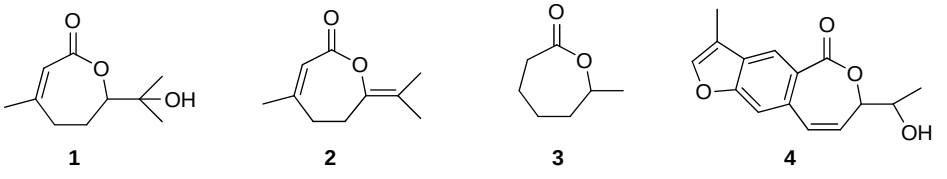
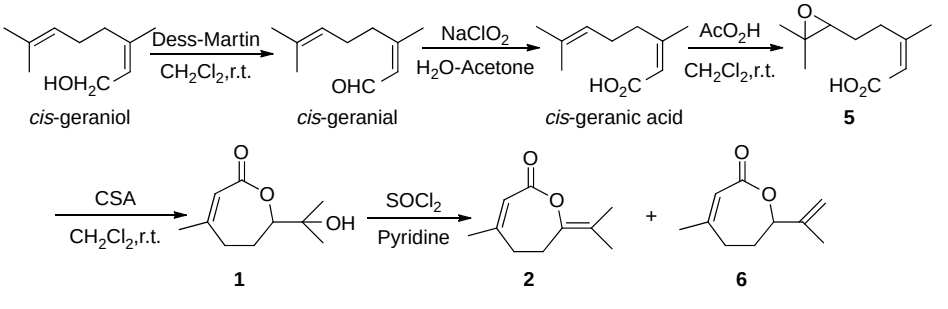


Figure 2. Structures of some typical natural products with seven-membered lactone ring.

above methodology, a short, convenient, and low-cost synthesis routes of natural products 3,7-dimethyl-7-hydroxy-2-octen-1,6-olide (**1**) and 3,7-dimethyl-2,6-octadien-1,6-olide (**2**) including four- or five-step reactions were established with an overall yields of 47.5% and 37.3%, respectively (Scheme 1), and it was suitable for synthesis of the other seven-membered lactones. This work was in progress in our laboratory.

2. Results and discussion

We investigated the synthesis of *cis*-geranial using *cis*-geraniol as the key starting material. First, pyridinium dichromate or pyridinium chlorochromate was used to oxidize hydroxyl into aldehyde group, and all attempts under various conditions showed that only a mixture of *cis*- and *trans*-geranial was obtained in the ratio of about 1:3 (from ^{1}H NMR spectrum). But the *cis*-isomer was our desired product. Then, the Dess-Martin



Scheme 1. Synthetic route of compounds **1** and **2**.

oxidant reagent was luckily found to afford *cis*-isomer with no *cis–trans* isomerization by repeated experiments using various oxidant reagents [20]. *cis*-Geranial was oxidized to *cis*-geranic acid with $NaClO_2$ without *cis–trans* isomerization [21]. The selective epoxidation of *cis*-geranic acid was achieved successfully in CH_2Cl_2–water solvent system with peracetic acid. After the key intermediate **5** in hand, we found that it could automatically cyclize to afford 3,7-dimethyl-7-hydroxy-2-octen-1,6-olide **1** in the presence of catalytic quantity of camphorsulfonic acid [22]. This new synthetic strategy by lactonization of epoxy carboxylic acid to prepare lactones including the seven-membered as well as the other-membered ring was seldomly referred in literatures. Finally, dehydration of compound **1** with $SOCl_2$ in pyridine gave the final products **2** and the byproduct **6** in 15 min [23]. As given in Table 1, compound **2** became the major product along with the isomer **6** as the minor product when the temperature dropped. The overall yield of 47.5% for **1** was much better than 3% yield in the chemical transformation of citral as the byproduct [24], and compound **6** was also prepared as fragrance [25].

In conclusion, 3,7-dimethyl-7-hydroxy-2-octen-1,6-olide (**1**) and 3,7-dimethyl-2,6-octadien-1,6-olide (**2**) were synthesized through four- or five-step reactions with overall yields of 47.5% and 37.3%, respectively.

Table 1. The temperature effect on the product of compounds **2** and **6**.

Reaction temperature (°C)	Ratio[a] of **2**:**6**	Yields[b] of **2** and **6** (%)
15	2:3	38.9 and 58.3
0	3:2	55.6 and 36.1
−20	7:1	78.4 and 11.6

[a] Ratio values were from ^{1}H NMR.
[b] Isolated yields.

3. Experimental

3.1 General experimental procedures

Melting points were measured on a Yanagimoto apparatus (Yanagimoto MFG Co., Kyoto, Japan) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Brüker DPX 300 NMR Spectrometer (Brüker Biospin Co., Stuttgart, Germany) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. HR–MS were obtained on Brüker Apex II mass spectrometer (Brüker Co., Bremen, Germany) using nitrobenzoyl alcohol and sodium chloride as matrix. The solvents were analytical grade and newly distilled before usage.

3.2 General procedures for the synthetic compounds

3.2.1 Synthesis of cis-geranial

To a solution of *cis*-geraniol (10.8 g, 70.0 mmol) in CH_2Cl_2 (60 ml) was added the Dess-Martin oxidant reagent (33.9 g, 80.0 mmol). The reaction mixture was stirred for 1.5 h at room temperature. After the reaction was finished as detected by thin-layer chromatography (TLC), the mixture was diluted with saturated $Na_2S_2O_3$ (50 ml) and extracted with CH_2Cl_2 (3×100 ml). The combined organic phases were washed with brine (3×30 ml), dried with sodium sulphate anhydrous, and concentrated *in vacuo*. Flash chromatography on silica gel (10:1, v/v; petroleum ether:EtOAc) afforded a yellow oil *cis*-geranial 10.3 g, yield 96.3%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.89 (d, $J = 8.2$ Hz, 1H, CHO), 5.87 (d, $J = 8.2$ Hz, 1H, CH═), 5.13–5.07 (m, 1H, CH═), 2.56 (t, $J = 7.4$ Hz, 2H, CH_2), 2.28–2.17 (m, 2H, CH_2), 1.99 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), and 1.59 (s, 3H, CH_3).

3.2.2 Synthesis of cis-geranic acid

A solution of 27.8 g (0.246 mol) of 80% sodium chlorite and 44.7 g (0.286 mol) of NaH_2PO_4 in 250 ml of distilled water was added dropwise to a stirred mixture of 5.13 g (33.8 mmol) of *cis*-geranial and

55 ml 2-methylbut-2-ene in 210 ml of acetone over 5 h at ambient temperature. The mixture was stirred for anther 2 h at ambient temperature. After the reaction was finished as detected by TLC, the acidic products were extracted with 300 ml of EtOAc three times. The organic phase was combined and dried over magnesium sulphate. Evaporation of solvent under reduced pressure, and then flash chromatography on silica gel (10:1, v/v; petroleum ether:EtOAc) produced a yellow oil *cis*-geranic acid 4.84 g, yield 85.1%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.93 (br, 1H, OH), 5.68 (s, 1H, CH═), 5.17–5.12 (m, 1H, CH═), 2.64 (t, $J = 7.5$ Hz, 2H, CH_2), 2.20–2.12 (m, 2H, CH_2), 1.93 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), and 1.62 (s, 3H, CH_3).

3.2.3 *Synthesis of* cis*-6,7-epoxygeranic acid (**5**)*

To a solution of *cis*-geranic acid (10.7 g, 63.9 mmol) in CH_2Cl_2 (300 ml) was added the peracetic acid solution (123 ml = 10 × 12.3 ml) and anhydrous sodium carbonate (42.1 g = 10 × 4.21 g). The reaction mixture was stirred for 1.5 h at room temperature. After the reaction was finished as detected by TLC, the mixture was diluted with saturated $Na_2S_2O_3$ (50 ml) and extracted with CH_2Cl_2 (3 × 100 ml). The combined organic phases were washed with brine (3 × 100 ml), dried with sodium sulphate anhydrous, and concentrated *in vacuo* to give a white solid **5** 10.5 g, yield 89.2%. mp 46–48°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.75 (br, 1H, OH), 5.74 (s, 1H, CH═), 2.89–2.66 (m, 3H, CHO + CH_2), 1.95 (s, 3H, CH_3), 1.81–1.66 (m, 2H, CH_2), 1.31 (s, 3H, CH_3), 1.28 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.4, 162.3, 116.3, 63.8, 58.6, 30.2, 27.6, 25.5, 24.8, 18.6.

3.2.4 *Synthesis of 3,7-dimethyl-7-hydroxy-2-octen-1,6-olide (**1**)*

To a 1000 ml three-necked flask were added 12.0 g (65.1 mmol) compound **5**, 560 ml CH_2Cl_2 and 0.33 g camphorsulfonic acid. The mixture was stirred for 4 h at room temperature. After the reaction was finished, the organic phase was washed with 5% Na_2CO_3 solution and brine, dried with sodium sulphate anhydrous, and concentrated *in vacuo*. Flash chromatography on silica gel (3:1, v/v; petroleum ether:EtOAc) afforded a light yellow oil (**1** 7.8 g, yield 65.0%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.86 (brq, $J = 1.2$ Hz, 1H, CH═), 4.04 (dd, $J = 9.0$, 2.2 Hz, 1H, CHO), 2.89 (br, 1H, OH), 2.53 (dt, $J = 17.8$, 6.0 Hz, 1H, CH_2), 2.38–2.33 (m, 1H, CH_2), 2.19–2.09 (m, 1H, CH_2), 1.97 (s, 3H, CH_3), 1.96–1.87 (m, 1H, CH_2), 1.28 (s, 3H, CH_3), 1.26 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.1, 154.9, 118.1, 84.3, 71.4, 33.5, 27.1, 26.1, 26.0, 24.8. HR-ESI-MS *m/z*: 185.11705 $[M + H]^+$ (cacld for $C_{10}H_{17}O_3$,185.11722).

3.2.5 *Synthesis of 3,7-dimethyl-2,6-octadien-1,6-olide (**2**) and its isomer (**6**)*

$SOCl_2$ (1.60 ml, 22.0 mmol) was added to solutions of compound **1** (0.405 g, 2.20 mmol) in dry pyridine (20 ml) at −20°C. The reaction mixture was stirred for 15 min, then poured into ice-water (100 ml), and extracted with EtOAc (2 × 50 ml). The combined organic layer was sequentially washed with 10% HCl, 5% $NaHCO_3$ solution, and brine, dried with Na_2SO_4, and evaporated to produce the residues, which were purified by column chromatography on silica gel (10:1, v/v; petroleum ether:EtOAc) and produced a colorless solid **2** (0.286 g, yield 78.4%) and a colorless oily liquid **6** (0.0402 g, yield 11.0%). Compound **2**, mp 67–69°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.83 (s, 1H, CH═), 2.61 (t, $J = 6.3$ Hz, 2H, CH_2), 2.39 (t, $J = 6.3$ Hz, 2H, CH_2), 1.92 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.66 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.1, 155.5, 141.5, 118.0, 117.0, 34.6, 27.4, 26.1, 18.0, 17.1. HR-ESI-MS *m/z*: 167.10654 $[M + H]^+$ (cacld for $C_{10}H_{15}O_2$, 167.10665). Compound **6**, ^{1}H

NMR (300 MHz, $CDCl_3$) δ: 5.88 (s, 1H, CH═), 5.04 (d, $J = 2.0$ Hz, 1H, ═CH_2), 4.90 (d, $J = 2.0$ Hz, 1H, ═CH_2), 4.69 (dd, $J = 8.4$ and 2.4 Hz, 1H, CHO), 2.55–2.30 (m, 2H, CH_2), 2.21–2.00 (m, 2H, CH_2), 1.97 (s, 3H, CH_3), 1.82 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.9, 153.6, 142.8, 118.6, 112.7, 81.1, 33.2, 31.2, 26.0, 17.8. HR-ESI-MS *m/z*: 167.10655 $[M + H]^+$ (cacld for $C_{10}H_{15}O_2$, 167.10666).

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