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### HIGHLY STEREOSELECTIVE SYNTHESIS OF NERYLGERANIOL-18-OIC ACID

Zuosheng Liu<sup>a</sup>, Lizeng Peng<sup>a</sup>, Tao Zhang<sup>a</sup> & Yulin Li<sup>b</sup>

<sup>a</sup> National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou, 730000, People's Republic of China

<sup>b</sup> National Laboratory of Applied Organic Chemistry and Institute of Organic Chemistry, Lanzhou University, Lanzhou, 730000, People's Republic of China

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## HIGHLY STEREOSELECTIVE SYNTHESIS OF NERYLGERANIOL-18-OIC ACID

Zuosheng Liu, Lizeng Peng, Tao Zhang, and Yulin Li\*

National Laboratory of Applied Organic Chemistry and  
Institute of Organic Chemistry, Lanzhou University,  
Lanzhou, 730000, People's Republic of China

### ABSTRACT

A stereoselectively total synthesis of nerylgeraniol-18-oic acid from geraniol was described. The key steps were the iodization-rearrangement of 2, 3-epoxy alcohol **4**, stereoselective Claisen rearrangement and *Horner-Emmons* olefination reaction.

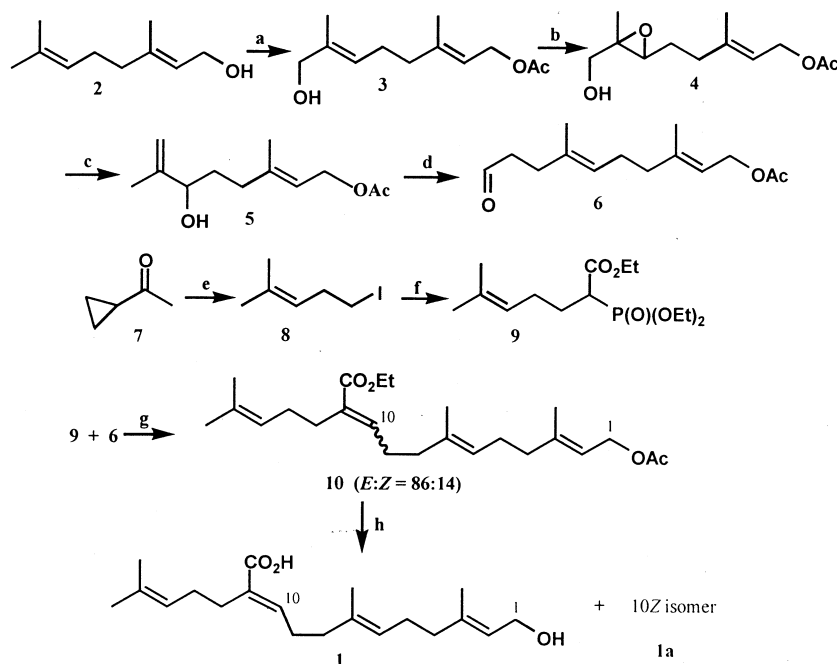
Nerylgeraniol-18-oic acid (**1**), a novel nerylgeraniol derivative, was isolated by Zdero and co-workers from the aerial part of *Heteropappus altaicus*<sup>1</sup> and *cutierrezia espinosae*.<sup>2</sup> The structure was elucidated by spectroscopic methods. Herein, we report the first total synthesis of **1** from geraniol (**2**).

The total synthesis of nerylgeraniol-18-oic (**1**) is detailed in scheme 1. Allylic alcohol **3**, readily available from geraniol (**2**) in two steps,<sup>3</sup> was treated by VO(acac)<sub>2</sub> and *t*-BuOOH to give the 2,3-epoxy alcohol **4** in 90% yield.<sup>4</sup> By our method,<sup>5</sup> allylic alcohol **5** was obtained in 94% yield with Ph<sub>3</sub>P, pyridine, I<sub>2</sub> and H<sub>2</sub>O. On treatment with a large excess of ethyl vinyl ether containing

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\*Corresponding author. E-mail: liyl@lzu.edu.cn

freshly recrystallized mercuric acetate,<sup>6</sup> the allylic alcohol **5** was converted into the corresponding allyl vinyl ether. The allyl vinyl ether was pyrolysed in a sealed tube at 110°C under Ar for 1 h to obtain the aldehyde **6** in 90% yield.<sup>7</sup> The *trans*:*cis* isomer ratio, which was determined by GC, was 93:7.



Scheme 1.

Reagents and conditions: a) ref. 3, two steps, 72%; b) VO(acac)<sub>2</sub>, *t*-BuOOH, C<sub>6</sub>H<sub>6</sub>, reflux, 2h, 90%; c) Ph<sub>3</sub>P, I<sub>2</sub>, pyridine, Et<sub>2</sub>O/CH<sub>3</sub>CN (5/3), 0°C, 1h, then added 1 *eq* H<sub>2</sub>O, 38°C, 6h, 93%; d) 1) Hg(OAc)<sub>2</sub>, ethyl vinyl ether, reflux, 24h, 83%; 2) sealed tube, 110°C, 1h, 90%; e) MeMgI, Et<sub>2</sub>O, reflux, 2h then 30% H<sub>2</sub>SO<sub>4</sub>, 0°C, 1h, 77%; f) NaH, (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, DMF, 60°C, 6h, 88%; g) LiHMDS, -50°C, 30 min., then aldehyde **6**, -50°C, 16h, 64%; h) KOH, EtOH-H<sub>2</sub>O, reflux, 2h, 100%.

By Biernacki's method, treatment methyl cyclopropane ketone **7** with methylmagnesium iodide, then acidification of the cyclopropylcabinol derivative gave homoprenyl iodide **8** in 77% yield.<sup>8</sup> Alkylation of triethyl



## NERYLGERANIOL-18-OIC ACID

2551

phosphonate with homoprenyl iodide **8** gave phosphono ester **9** in 88% yield. The *Horner-Emmons* reaction of phosphono ester **9** with aldehyde **6** in the presence of LiHMDS<sup>9</sup> gave a mixture of ethyl esters **10** in 64% yield (*E:Z* = 86:14, by <sup>1</sup>H NMR). Hydrolysis of the esters **10** with KOH in EtOH-H<sub>2</sub>O gave the nerylgeraniol-18-oic acid (**1**) in 86% yield and geranylgeraniol-18-oic acid (**1a**) in 14% yield after column chromatography on silica gel.

## EXPERIMENTAL

<sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker AC-80 or Bruker AM-400 spectrometer in CDCl<sub>3</sub> solution using TMS as internal reference. IR spectra were obtained using a FT-170SX spectrophotometer. Mass spectra were measured on a HP 5988 spectrometer by direct inlet at 70 eV, and signals were given in *m/z* with relative intensity (%) in brackets. GC was measured on a HP 5890 spectrometer. Elemental analyses were determined on a Vario El instrument. All solvents were freshly purified and dried by standard techniques prior to use. Purification of products was conducted by flash column chromatography (FCG) on silica gel (200~300 mesh) purchased from Qing Dao Marine Chemical Co.

### (*E,E*)-3, 7-Dimethyl-6, 7-epoxy-8-hydroxy-2, 6-decadien-1-ol acetate (4)

To a well-stirred suspension of VO(acac)<sub>2</sub> (50 mg) and alcohol **3** (7.2 g, 33.96 mmol) in dry benzene (30 mL) was added *t*-BuOOH (10.98 mL, 3.4 M in toluene, 37.36 mmol) in dry benzene (30 mL) under Ar atmosphere at 80°C. After reflux for 2 h, the mixture was extracted with Et<sub>2</sub>O (3 × 50 mL). The organic phases were washed with 10% aq. KOH solution, saturated NaHCO<sub>3</sub> solution, H<sub>2</sub>O, brine and dried. Evaporation of the solvent was followed by flash column chromatography (pet. ether: ethyl acetate 3:1, v/v) to afford the epoxy alcohol **4** (6.95 g, 90%) as a colorless oil. IR (film):  $\nu_{\max}$  = 3400, 2980, 1732, 1670, 1237, 1028, 967 cm<sup>-1</sup>; <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>):  $\delta$  5.38 (t, 1H, *J* = 6.7 Hz, CH=), 4.62 (d, 2H, *J* = 6.7 Hz, CH<sub>2</sub>OAc), 3.66 (d, 1H, *J* = 12.1 Hz, CHO), 3.56 (d, 1H, *J* = 12.1 Hz, CHO), 3.02 (t, 1H, *J* = 6.2 Hz, epoxy H), 2.12–2.25 (m, 2H, CH<sub>2</sub>), 2.05 (s, 3H, CH<sub>3</sub>CO), 1.66–1.77 (m, 2H, CH<sub>2</sub>), 1.72 (s, 3H, CH<sub>3</sub>), 1.28 (s, 3H, CH<sub>3</sub>); Anal. calcd for C<sub>12</sub>H<sub>20</sub>O<sub>4</sub>: C, 63, 15; H, 8.82; found: C, 63.02; H, 8.79.



**(*E*)-3, 7-Dimethyl-6-hydroxy-2, 7-decadien-1-ol acetate (5)**

To a stirred solution of epoxy alcohol **4** (6.95 g, 30.48 mmol) in dry Et<sub>2</sub>O-CH<sub>3</sub>CN (5:3, 56 mL) was added sequentially of Ph<sub>3</sub>P (24 g, 91.4 mmol), pyridine (9.85 mL, 121.9 mmol) and I<sub>2</sub> (11.61 g, 45.7 mmol) at 0°C. After being stirred for 2 h at 0°C, H<sub>2</sub>O (0.55 mL, 30.48 mmol) was added into the system. The reaction mixture was refluxed for 6 h at 38°C, then 20% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (aq) (5 mL) and saturated NaHCO<sub>3</sub> solution (5 mL) were added to quench the reaction and organic layers were extracted with ether (3 × 50 mL). The combined ether extracts were washed with 5% HCl (4 × 10 mL), saturated NaHCO<sub>3</sub> (10 mL), H<sub>2</sub>O, brine and dried. Evaporation of the solvent was followed by flash column chromatography (pet. ether: ethyl acetate 6:1, v/v) to afford allylic alcohol **5** (6.0 g, 93%) as a colorless oil. IR (film):  $\nu_{\max}$  = 3472, 3074, 2942, 2861, 1727, 1671, 1650, 1296, 1024, 953, 900 cm<sup>-1</sup>; EIMS (*m/z*): 213 (0.1%, M+1), 185 (0.1), 152 (1.4), 134 (5), 119 (8), 84 (38), 67 (38), 43 (100), 41 (38); <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>):  $\delta$  5.36 (1H, t, *J* = 7.0 Hz, CH=), 4.93, 4.84 (2H, s, CH<sub>2</sub>=), 4.57 (2H, d, *J* = 7.0 Hz, CH<sub>2</sub>OAc), 4.04 (1H, t, *J* = 5.6 Hz, CHO), 2.12–2.02 (2H, m, CH<sub>2</sub>), 2.04 (3H, s, CH<sub>3</sub>CO), 1.68–1.62 (2H, m, CH<sub>2</sub>), 1.72 (3H, s, CH<sub>3</sub>), 1.75 (3H, s, CH<sub>3</sub>); Anal. calcd for C<sub>14</sub>H<sub>20</sub>O<sub>3</sub>: C, 67.89; H, 9.54; found: C, 67.76; H, 9.47.

**(*E,E*)-4, 8-Dimethyl-10-acetoxyl-4, 8-octadienal (6)**

To a solution of alcohol **5** (4.93 g, 23.25 mmol) in ethyl vinyl ether (27 mL) was added Hg(OAc)<sub>2</sub> (3 g, freshly recrystallized from anhydrous EtOH). The mixture was refluxed for 24 h. The reaction mixture was extracted with Et<sub>2</sub>O (3 × 50 mL). The organic phases were washed by H<sub>2</sub>O, brine and dried. Evaporation of the solvent was followed by flash column chromatography (pet. ether: ethyl acetate 15:1, v/v) to afford the vinyl ether (4.6 g, 83%) as a colorless oil. The vinyl ether (3.28 g, 13.78 mmol) was heated in sealed tube under Ar atmosphere at 110°C for 1 h. The crude product was purified by flash column chromatography (pet. ether: ethyl acetate 8:1, v/v) to afford the aldehyde **6** (2.95 g, 90%) as a colorless oil. IR: (film):  $\nu_{\max}$  = 2928, 2858, 2721, 1736, 1445, 1377, 1234, 1023, 954 cm<sup>-1</sup>. EIMS (*m/z*): 196 (0.2%, M-43), 178 (1), 163 (1.2), 134 (4), 119 (5), 93 (21), 67 (19), 55 (26), 43 (100). <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>):  $\delta$  9.77 (t, 1H, *J* = 1.6 Hz, CHO), 5.35 (t, 1H, *J* = 6.8 Hz, CH=), 5.14 (t, 1H, *J* = 6.4 Hz, CH=), 4.60 (d, 2H, *J* = 6.8 Hz, CH<sub>2</sub>OAc), 2.25–2.54 (m, 4H, 2CH<sub>2</sub>), 2.07 (s, 3H, CH<sub>3</sub>CO), 1.95–2.14 (m, 2H, CH<sub>2</sub>), 1.71 (s, 3H, CH<sub>3</sub>), 1.63 (s, 3H, CH<sub>3</sub>); Anal. calcd for C<sub>14</sub>H<sub>22</sub>O<sub>3</sub>: C, 70.56; H, 9.30; found: C, 70.35; H, 9.26.



**Ethyl 2-(Diethylphosphono)-6-methyl-5-heptaenoate (9)**

To a stirred suspension of NaH (80%, 920 mg, 30 mmol) in anhydrous DMF (20 mL) was added dropwise a solution of ethyl (diethylphosphono)-acetate (4.45 mL, 22 mmol) in DMF (10 mL). The mixture was stirred at room temperature for 2 h and a solution of iodide **8** (4.2 g, 20 mmol) was added. The resulting solution was stirred at 60°C for 6 h and partitioned between Et<sub>2</sub>O (20 mL) and H<sub>2</sub>O (10 mL). The reaction mixture was extracted with Et<sub>2</sub>O (3 × 50 mL). The organic phases were washed with H<sub>2</sub>O, brine and dried. Evaporation of the solvent was followed by flash column chromatography (pet. ether: ethyl acetate 3:1, v/v) to afford the phosphono ester **9** (5.44 g, 88%) as a colorless oil. IR (film):  $\nu_{\max}$  = 2983, 2935, 1734, 1445, 1258, 1031, 969 cm<sup>-1</sup>; EIMS  $m/z$ : 306 (10%, M), 261 (12), 224 (100), 197 (82), 169 (31), 152 (84), 123 (44), 109 (32), 81 (51), 67 (29), 55 (52), 41 (91); <sup>1</sup>H NMR (80 MHz, CDCl<sub>3</sub>):  $\delta$  5.01 (1H, t,  $J$  = 7.2 Hz, CH=), 3.93–4.30 (6H, m, 3CH<sub>2</sub>), 2.70–3.10 (1H, m, CH), 1.90–2.16 (4H, m, 2CH<sub>2</sub>), 1.64 (3H, s, CH<sub>3</sub>), 1.54 (3H, s, CH<sub>3</sub>), 1.16–1.38 (9H, m, 3CH<sub>3</sub>); Anal. calcd for C<sub>14</sub>H<sub>27</sub>O<sub>5</sub>P: C, 54.89; H, 8.88; found: C, 54.79; H, 8.85.

**(*E,E,E*)-1-Acetoxy-11-carboethoxy-3,7,15-trimethyl-hexa-deca-2,6,10-tetraene (10)**

To a stirred solution of hexamethyldisilazane (0.912 mL, 1.44 mmol) in anhydrous DME(25 mL) was added dropwise *n*-BuLi (2.34 mL, 1.55 M, 3.63 mmol) at –50°C over 5 min. After being stirred for an additional 30 min at that temperature, a solution of phosphonate **9** (1.016 g, 3.32 mmol) in DME(15 mL) was added dropwise *via* syringer. After 45 min at –50°C, a solution of aldehyde **6** (720 mg, 3.025 mmol) in DME(10 mL) was added. The resulting mixture was stirred at –50°C for 16 h, the saturated NH<sub>4</sub>Cl(10 mL) was added to quench the reaction. The mixture was extracted with Et<sub>2</sub>O(3 × 50 mL), the organic phases were washed with H<sub>2</sub>O, brine and dried. Evaporation of the solvent was followed by flash column chromatography (pet. ether: ethyl acetate 8:1, v/v) to give the mixture of *E* and *Z* isomers of ester **10** (760 mg, 64%) as a colorless oil. IR(film):  $\nu_{\max}$  = 2971, 2928, 2859, 1740, 1712, 1651, 1446, 1374, 1233, 1025, 955 cm<sup>-1</sup>; EIMS  $m/z$ : 290 (0.1%, M), 330 (0.1, M-AcOH), 300 (0.9), 272 (1), 232 (3), 212 (5), 189 (2), 161 (4), 138 (5), 107 (10), 93 (20), 67 (19), 43 (100); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  6.72(1H, t,  $J$  = 7.4 Hz, trans CH=), 5.90 (1H, t,  $J$  = 7.3 Hz, cis CH=), 5.33 (1H, t,  $J$  = 7.0 Hz, CH=), 5.13 (1H, t,  $J$  = 7.0 Hz, CH=), 4.58 (2H, d,  $J$  = 7.0 Hz, CH<sub>2</sub>OAc), 4.18 (2H, q,  $J$  = 7.2 Hz, CH<sub>2</sub>O), 2.23–2.32 (4H, m, 2CH<sub>2</sub>), 2.03–2.13 (8H, m, 4CH<sub>2</sub>), 2.04 (3H, s, CH<sub>3</sub>CO), 1.70 (3H, s, CH<sub>3</sub>),



1.67 (3H, s, CH<sub>3</sub>), 1.61 (3H, s, CH<sub>3</sub>), 1.59 (3H, s, CH<sub>3</sub>), 1.28 (3H, t, *J* = 7.2 Hz, CH<sub>3</sub>); Anal. calcd for C<sub>24</sub>H<sub>38</sub>O<sub>4</sub>: C, 73.81; H, 9.81; found: C, 73.62; H, 9.85.

### Nerylgeraniol-18-oic acid (**1**)

A mixture of ester **10** (36 mg, 0.092 mmol) and KOH (20 mg, 0.36 mmol) in 3 mL of EtOH-H<sub>2</sub>O (1:1) was refluxed for 2 h. The solution was cooled to room temperature, diluted with Et<sub>2</sub>O (5 mL), acidified with 5% aq. HCl solution and stirred for 10 min at room temperature. The mixture was extracted with Et<sub>2</sub>O (50 mL). The organic layers were washed with H<sub>2</sub>O, brine and dried. Evaporation of the solvent was followed by flash column chromatography (pet. ether: ethyl acetate 3:1, *v/v*) to give nerylgeraniol-18-oic acid (**1**) (25 mg, 86%) and geranylgeraniol-18-oic acid (**1a**) (4 mg, 14%). nerylgeraniol-18-oic acid (**1**): IR (film):  $\nu_{\max}$  = 3347, 2965, 2925, 1686, 1638, 1445, 1276, 991 cm<sup>-1</sup>; EIMS *m/z*: 302 (0.2%, M), 287 (0.1), 259 (0.4), 234 (0.3), 219 (1.1), 201 (1.1), 189 (2.2), 151 (6), 135 (10), 121 (14), 107 (15), 93 (26), 81 (20), 69 (100), 41 (71); <sup>1</sup>H NMR (400 MHz) (CDCl<sub>3</sub>):  $\delta$  6.86 (1H, t, *J* = 7.0 Hz, CH=), 5.41 (1H, t, *J* = 7.0 Hz, CH=), 5.14 (2H, t, *J* = 7.2 Hz, CH=), 4.16 (2H, d, *J* = 7.0 Hz, CH<sub>2</sub>O), 2.27–2.33 (4H, m, 2CH<sub>2</sub>), 2.05–2.12 (8H, m, 4CH<sub>2</sub>), 1.68 (3H, s, CH<sub>3</sub>), 1.67 (3H, s, CH<sub>3</sub>), 1.62 (3H, s, CH<sub>3</sub>), 1.60 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (100 MHz) (CDCl<sub>3</sub>):  $\delta$  172.57, 145.08, 139.32, 133.98, 132.30, 131.29, 124.94, 123.64, 123.55, 59.39, 39.33, 38.36, 27.62, 27.20, 26.80, 26.10, 25.68, 17.62, 16.19, 15.92; Anal. Calcd for C<sub>20</sub>H<sub>32</sub>O<sub>3</sub>: C, 74.96; H, 10.06; found: C, 74.90; H, 10.02; geranylgeraniol-18-oic acid (**1a**): <sup>1</sup>H NMR (400 MHz) (CDCl<sub>3</sub>):  $\delta$  5.94 (1H, t, *J* = 6.8 Hz, CH=), 5.41 (1H, t, *J* = 7.0 Hz, CH=), 5.12 (2H, t, *J* = 7.2 Hz, CH=), 4.18 (2H, d, *J* = 7.0 Hz, CH<sub>2</sub>O), 2.27–2.33 (4H, m, 2CH<sub>2</sub>), 2.05–2.12 (8H, m, 4CH<sub>2</sub>), 1.69 (3H, s, CH<sub>3</sub>), 1.68 (3H, s, CH<sub>3</sub>), 1.62 (3H, s, CH<sub>3</sub>), 1.60 (3H, s, CH<sub>3</sub>); Anal. Calcd for C<sub>20</sub>H<sub>32</sub>O<sub>3</sub>: C, 74.96; H, 10.06; found: C, 74.88; H, 10.11.

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**NERYLGERANIOL-18-OIC ACID**

**2555**

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