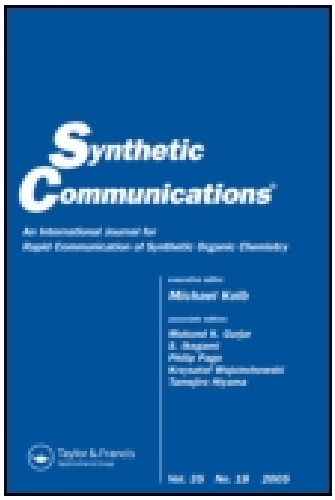

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# HIGHLY STEREOSELECTIVE SYNTHESIS OF NERYLGERANIOL-18-OIC ACID

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# HIGHLY STEREOSELECTIVE SYNTHESIS OF NERYLGERANIOL-18-OIC ACID

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## 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*[1] and *cutierrezia espinosae*.[2] 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,[3] was treated by $VO(acac)_2$ and *t*-BuOOH to give the 2,3-epoxy alcohol **4** in 90% yield.[4] By our method,[5] allylic alcohol **5** was obtained in 94% yield with $Ph_3P$, pyridine, $I_2$ and $H_2O$. On treatment with a large excess of ethyl vinyl ether containing

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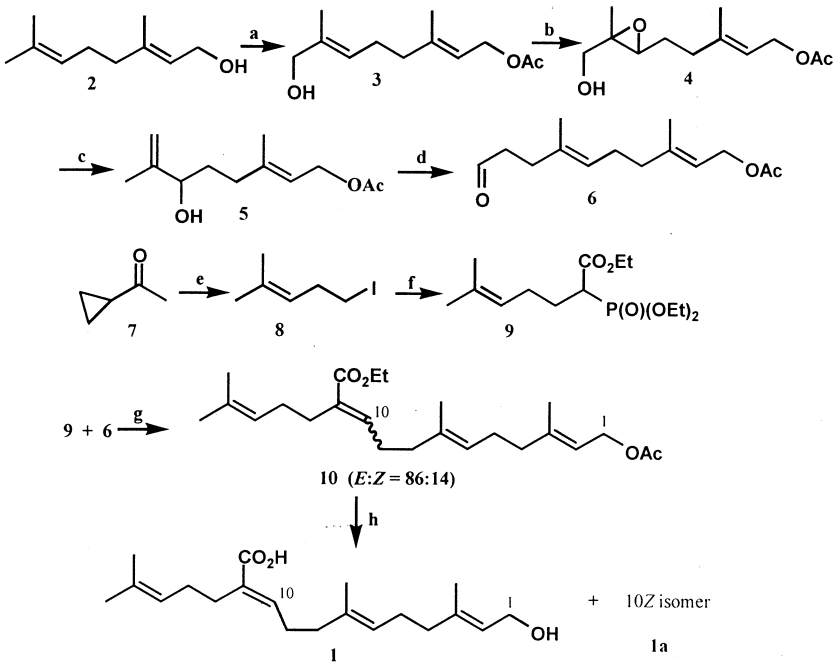
freshly recrystallized mercuric acetate,[6] the allylic alcohol **5** was converted into the corresponding allyl vinyl ether. The allyl vinyl ether was pyrolysed in a sealed tube at 110°C under Ar for 1 h to obtain the aldehyde **6** in 90% yield.[7] The *trans* : *cis* isomer ratio, which was determined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




*Scheme 1.*

Reagents and conditions: a) ref. 3, two steps, 72%; b) $VO(acac)_2$, *t*-BuOOH, $C_6H_6$, reflux, 2h, 90%; c) $Ph_3P$, $I_2$, pyridine, $Et_2O/CH_3CN$ (5/3), 0°C, 1h, then added 1 *eq* $H_2O$, 38°C, 6h, 93%; d) 1) $Hg(OAc)_2$, ethyl vinyl ether, reflux, 24h, 83%; 2) sealed tube, 110°C, 1h, 90%; e) MeMgI, $Et_2O$, reflux, 2h then 30% $H_2SO_4$, 0°C, 1h, 77%; f) NaH, $(EtO)_2P(O)CH_2CO_2Et$, DMF, 60°C, 6h, 88%; g) LiHMDS, −50°C, 30 min., then aldehyde **6**, −50°C, 16h, 64%; h) KOH, EtOH-$H_2O$, reflux, 2h, 100%.

By Biernacki's method, treatment methyl cylcopropane ketone **7** with methylmagnesium iodide, then acidification of the cyclopropylcabinol derivative gave homoprenyl iodide **8** in 77% yield.[8] Alkylation of triethyl





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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[9] gave a mixture of ethyl esters **10** in 64% yield ($E:Z = 86:14$, by $^1$H NMR). Hydrolysis of the esters **10** with KOH in EtOH-$H_2O$ 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

$^1$H NMR and $^{13}$C NMR spectra were recorded on a *Bruker* AC-80 or *Bruker* AM-400 spectrometer in $CDCl_3$ 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 $VO(acac)_2$ (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 $Et_2O$ ($3 \times 50$ mL). The organic phases were washed with 10% aq. KOH solution, saturated $NaHCO_3$ solution, $H_2O$, 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): $\nu_{max} = 3400, 2980, 1732, 1670, 1237, 1028, 967\ cm^{-1}$; $^1$H NMR (80 MHz, $CDCl_3$): δ 5.38 (t, 1H, $J = 6.7$ Hz, CH=), 4.62 (d, 2H, $J = 6.7$ Hz, $CH_2OAc$), 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, $CH_2$), 2.05 (s, 3H, $CH_3CO$), 1.66–1.77 (m, 2H, $CH_2$), 1.72 (s, 3H, $CH_3$), 1.28 (s, 3H, $CH_3$); Anal. calcd for $C_{12}H_{20}O_4$: C, 63, 15; H, 8.82; found: C, 63.02; H, 8.79.





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### *(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 $Et_2O$-$CH_3CN$ (5:3, 56 mL) was added sequentially of $Ph_3P$ (24 g, 91.4 mmol), pyridine (9.85 mL, 121.9 mmol) and $I_2$ (11.61 g, 45.7 mmol) at 0°C. After being stirred for 2 h at 0°C, $H_2O$ (0.55 mL, 30.48 mmol) was added into the system. The reaction mixture was refluxed for 6 h at 38°C, then 20% $Na_2S_2O_3$ (aq) (5 mL) and saturated $NaHCO_3$ solu tion (5 mL) were added to quench the reaction and organic layers were extracted with ether ($3 \times 50$ mL). The combined ether extracts were washed with 5% HCl ($4 \times 10$ mL), saturated $NaHCO_3$ (10 mL), $H_2O$, 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 $cm^{-1}$; 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); $^1$H NMR (80 MHz, $CDCl_3$): δ 5.36 (1H, t, $J = 7.0$ Hz, CH=), 4.93, 4.84 (2H, s, $CH_2$=), 4.57 (2H, d, $J = 7.0$ Hz, $CH_2OAc$), 4.04 (1H, t, $J = 5.6$ Hz, CHO), 2.12–2.02 (2H, m, $CH_2$), 2.04 (3H, s, $CH_3CO$), 1.68–1.62 (2H, m, $CH_2$), 1.72 (3H, s, $CH_3$), 1.75 (3H, s, $CH_3$); Anal. calcd for $C_{14}H_{20}O_3$: 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 $Hg(OAc)_2$ (3 g, freshly recrystallized from anhydrous EtOH). The mixture was refluxed for 24 h. The reaction mixture was extracted with $Et_2O$ ($3 \times 50$ mL). The organic phases were washed by $H_2O$, 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 $cm^{-1}$. 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). $^1$H NMR (80 MHz, $CDCl_3$): δ 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, $CH_2OAc$), 2.25–2.54 (m, 4H, $2CH_2$), 2.07 (s, 3H, $CH_3CO$), 1.95–2.14 (m, 2H, $CH_2$), 1.71 (s, 3H, $CH_3$), 1.63 (s, 3H, $CH_3$); Anal. calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30; found: C, 70.35; H, 9.26.





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### 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 $Et_2O$ (20 mL) and $H_2O$ (10 mL). The reaction mixture was extracted with $Et_2O$ ($3 \times 50$ mL). The organic phases were washed with $H_2O$, 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 $cm^{-1}$; 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); $^1H$ NMR (80 MHz, $CDCl_3$): δ 5.01 (1H, t, $J = 7.2$ Hz, CH=), 3.93–4.30 (6H, m, $3CH_2$), 2.70–3.10 (1H, m, CH), 1.90–2.16 (4H, m, $2CH_2$), 1.64 (3H, s, $CH_3$), 1.54 (3H, s, $CH_3$), 1.16–1.38 (9H, m, $3CH_3$); Anal. calcd for $C_{14}H_{27}O_5P$: 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 $NH_4Cl$(10 mL) was added to quench the reaction. The mixture was extracted with $Et_2O$($3 \times 50$ mL), the organic phases were washed with $H_2O$, 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 $cm^{-1}$; 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); $^1H$ NMR (400 MHz, $CDCl_3$): δ 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, $CH_2OAc$), 4.18 (2H, q, $J = 7.2$ Hz, $CH_2O$), 2.23–2.32 (4H, m, $2CH_2$), 2.03–2.13 (8H, m, $4CH_2$), 2.04 (3H, s, $CH_3CO$), 1.70 (3H, s, $CH_3$),





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1.67 (3H, s, $CH_3$), 1.61 (3H, s, $CH_3$), 1.59 (3H, s, $CH_3$), 1.28 (3H, t, $J = 7.2$ Hz, $CH_3$); Anal. calcd for $C_{24}H_{38}O_4$: 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-$H_2O$ (1:1) was refluxed for 2 h. The solution was cooled to room temperature, diluted with $Et_2O$ (5 mL), acidified with 5% aq. HCl solution and stirred for 10 min at room temperature. The mixture was extracted with $Et_2O$ (50 mL). The organic layers were washed with $H_2O$, 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 $cm^{-1}$; 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); $^1$H NMR (400 MHz) ($CDCl_3$): δ 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, $CH_2O$), 2.27–2.33(4H, m, $2CH_2$), 2.05–2.12(8H, m, $4CH_2$), 1.68(3H, s, $CH_3$), 1.67(3H, s, $CH_3$), 1.62(3H, s, $CH_3$); 1.60 (3H, s, $CH_3$); $^{13}$C NMR(100 MHz) ($CDCl_3$): δ 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 $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; found: C, 74.90; H, 10.02; geranylgeraniol-18-oic acid (**1a**): $^1$H NMR(400 MHz) ($CDCl_3$): δ 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, $CH_2O$), 2.27–2.33(4H, m, $2CH_2$), 2.05–2.12(8H, m, $4CH_2$), 1.69(3H, s, $CH_3$), 1.68 (3H, s, $CH_3$), 1.62(3H, s, $CH_3$), 1.60(3H, s, $CH_3$); Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; found: C, 74.88; H, 10.11.

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