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TETRAHEDRON: *ASYMMETRY*

Synthesis of (1*S*,2*R*,12*S*)-2-hydroxy-11-dihydroneocembrene[1]

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Abstract

Aiming at the asymmetric total synthesis of trinervitane-type diterpenes, an efficient synthetic route to the title compound was explored starting from the THP ether of pivaloyloxy geraniol **11e**. The coupling reaction with Grignard reagent **14** bearing the stereogenic carbon proceeded smoothly to give the THP ether of (11*S*)-10-dihydrogeranylgeraniol **10**. Conversion to the corresponding acid chloride through the intermediate **9**, followed by cyclization, afforded the dihydrocembrene derivative **8**, from which the title compound **7** was prepared.

1. Introduction

Two decades ago, Prestwich and his co-workers characterized[2] defense substances from termite soldiers as exemplified by compounds **1a** and **1b**, the carbon skeleton of which was named trinervitane (Fig. 1). We have been very interested in the synthesis of the trinervitane-type diterpenes and have explored a synthetic route[3] in which the formation of cembrene skeleton **3** from acyclic acid chloride **2**, followed by subsequent ring closure to the secotrinervitane skeleton **5** through the hydroxyneocembrene **4**, constitute the crucial steps to the tricyclic trinervitane skeleton **6** in racemic form, as summarized in Scheme 1.

In order to carry out the asymmetric synthesis of **1** based on our protocol as shown in Scheme 1, we chose the title compound **7** for the key intermediate corresponding to **4**. This paper deals with the preparation of the key intermediate **7** possessing the correct absolute configuration for the synthesis of trinervitanes **1** based on Scheme 1.

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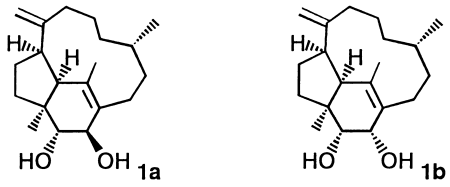
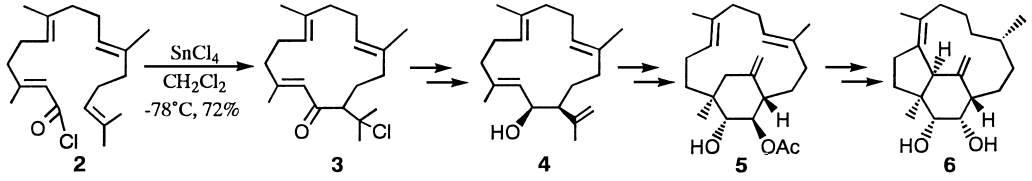


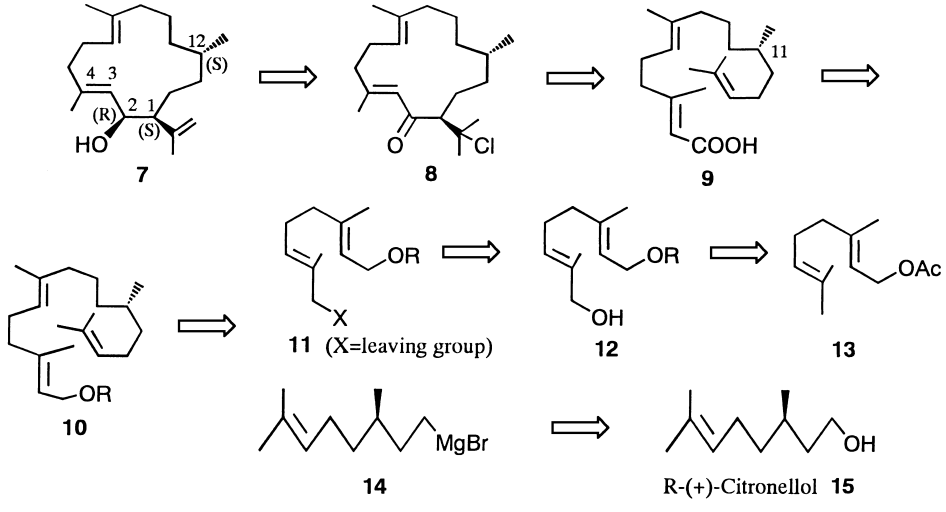
Figure 1. Typical trinervitanes from termites



Scheme 1. Synthetic route to trinervitane skeleton **6**

2. Results and discussion

Scheme 2 illustrates the retrosynthetic route to compound **7**, in which the acyclic (11*S*)-10-dihydrogeranylgeranioic acid **9** is derived from the allyl alcohol **10** (R=H). The coupling reaction of geraniol derivative **11** bearing a leaving group (X) with the Grignard reagent **14** should provide the dihydrogeranylgeraniol **10**. The leaving group (X) of **11** can be derived from the terminal hydroxyl group of **12**, which in turn was introduced by the oxidation of the terminal methyl group of geranyl acetate **13**.[4] The commercially available (*R*)-(+)-citronellol **15**[4] was selected as the chiral source of the Grignard reagent **14**.



Scheme 2. The synthetic route to the title compound **7**

The Grignard reagent was easily prepared by the sequential reactions of conversion of **15** to the tosylate, followed by replacement of the tosyl group with bromine by reaction with LiBr in acetone and finally by addition of Mg in the presence of catalytic amounts of iodine. The hydroxy geranyl acetate **12** (R=Ac) was prepared by the established method[5] of SeO_2 oxidation of geranyl acetate **13**. The terminal hydroxyl group of **12** (R=Ac) was first protected with a bulky pivaloyl group (**11**, X=OPiv, R=Ac) in order to differentiate the two allylic primary hydroxyl groups. The acetate group was selectively hydrolyzed with K_2CO_3 in MeOH to give the pivaloyloxy alcohol (**11**, X=OPiv, R=H) and then the OH

group was protected with a TBDMS group. Treatment of the pivaloyloxy TBDMS ether with KOH in MeOH provided the hydroxy TBDMS ether (**11**, X=OH, R=TBDMS), from which **11** (**a**–**d**) in Table 1 were prepared by the usual reactions as described in the Experimental. The pivaloyloxy THP ether **11e** was obtained from the pivaloyloxy alcohol (**11**, X=OPiv, R=H) by the usual procedure in high yield.

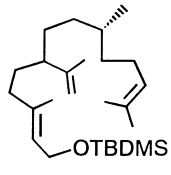
Table 1
Li_2CuCl_4-Catalyzed reaction of **11** with Grignard reagent **14**[a]

Run	Compound **11**	X	R	mol % of Li_2CuCl_4	mol % of Me_2S	Yield of **10** (%)
1	**11a**	Cl	TBDMS	——	——	65[b]
2	**11b**	OAc	TBDMS	2	5	58
3	**11b**	OAc	TBDMS	10	10	64
4	**11c**	OBz	TBDMS	10	10	60
5	**11d**	OPiv	TBDMS	10	10	65
6	**11e**	OPiv	THP	2	2	82
7	**11e**	OPiv	THP	10	10	91
8	**11e**	OPiv	THP	10	——	92

[a] The Grignard reagent **14** was added at -78 ℃ in THF and the temperature was raised to room temperature.
[b] A 1 : 1 mixture of **10** and **16**

In the C–C bond formation with the Grignard reagent, the coupling reaction of the allyl chloride **11a** gave an inseparable 1:1 mixture of the desired product **10** and its isomer **16**, the latter being formed by S_N2' displacement (run 1). The existence of **16** was shown from the observation of an isopropenyl group in the NMR spectra of the reaction products. After some trials, we found that formation of the undesired product **16** could be averted when the acetate group was selected as the leaving group. By employment of Li_2CuCl_4, as reported by Bäckvall and co-workers,[6] the α displacement predominated to give **10** in moderate yield (runs 2 and 3).[7] Changing the leaving group to benzoate and pivalate effected no improvement in the yield in the presence of Me_2S[8] (runs 4 and 5). Since the low yield of the coupling reaction might be attributed to the existence of the TBDMS as a protecting group (runs 2–5), THP was selected as the protecting group to provide **11e**, which afforded the coupling product **10** (R=THP) exclusively in 91% yield (run 7). It was also found that the addition of Me_2S is not essential for the coupling reaction (run 8).

The conversion of **10** (R=THP) to the corresponding carboxylic acid **9** was straightforward; deprotection of the THP group with *p*-TsOH in MeOH (98% yield), followed by oxidation with Dess–Martin periodinane[9] to the aldehyde (90% yield) and then $NaClO_2$ oxidation (98% yield), furnished the carboxylic acid **9**. By treatment with $SOCl_2$ and pyridine, **9** was converted to the corresponding acid chloride, which was allowed to react with $SnCl_4$ in CH_2Cl_2 at −78°C, providing the chloroketone **8** in 56% yield as a crystalline product, mp 104°C. It is evident that the 12*S* asymmetric center controlled the stereochemistry of the ring-closure reaction. The dehydrochlorination of **8** was first attempted by use of LiBr and Li_2CO_3 in DMF at 105°C, resulting in the formation of a 2:1 mixture of isopropenyl **17** (61%) and isopropylidene **18** (33%) ketones, respectively. When the LiBr–Li_2CO_3 conditions were applied to the cembrene derivative **3**, the dehydrochlorination proceeded selectively to lead to the predominant formation of the isopropenyl ketone in 77% yield.[10] After several trials, the dehydrochlorination proceeded effectively by the reaction of SiO_2 and K_2CO_3 in hexane at room temperature, providing the isopropenyl ketone **17** in 78% yield, accompanying the formation of the isomeric ketone **18** in 9% yield.



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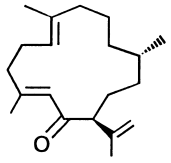

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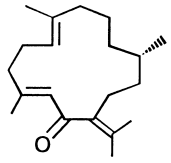

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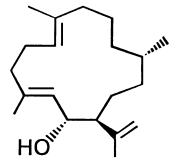

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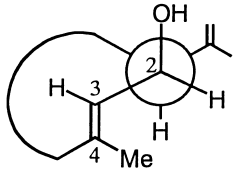
When the isopropenyl ketone **17** was submitted to reduction with DIBAH at −78°C, no stereoselectivity was observed, giving a 1:1 mixture of *cis*- and *trans*-alcohols **7** and **19**, respectively. By employment of these reduction conditions, we expected the predominant formation of the *cis*-alcohol **7**, since we had found that the reduction of the cembrene derivative **3** (isopropenyl instead of chloroisopropyl) proceeded stereoselectively under the same conditions, affording the corresponding *cis*-alcohol **4** as a major product.[11] After several attempts, we found that the reduction of **17** with DIBAH in the presence of *n*-BuLi, the conditions of which were reported by Kim and Ahn,[12] furnished a 9:1 mixture of **7** and **19** in 90% yield. The conformation of the 14-membered ring in the dihydro analog **17** seems more mobile than that of the cembrene derivative **3** due to the lack of one double bond in the 14-membered ring. The stereochemistry of the reduction products **7** and **19** was deduced from the coupling mode of the C2-protons and NOESY experiments in the NMR spectra as summarized in Table 2. The large coupling constant of 2-H with 1-H in **19** ($J_{1,2}$=9.8 Hz) indicates the *trans* relationship while the small value ($J_{1,2}$=0.9 Hz) in **7** supports the *cis* configuration, respectively. In addition to the *J* values, the existence of NOESY correlation between 2-H and 4-Me in both compounds suggests the partial conformations of **7** and **19**, as depicted in Fig. 2.[13]

Table 2
^{1}H NMR data of *cis*-**7** and *trans*-**19** alcohols (270 MHz, $CDCl_3$)

	δ (ppm)		*J* (Hz)		NOESY[a]	
	2-H	3-H	$J_{1,2}$	$J_{2,3}$	4-Me ⟷ 2-H	1-H ⟷ 2-H
7	4.44(dd)	5.35(d)	0.9	7.9	○	○
19	4.10(dd)	5.03(m)	9.8	9.2	○	×

[a] ○ and × show the presence and absence of the correlation signs between the indicated protons in the NOESY spectra.



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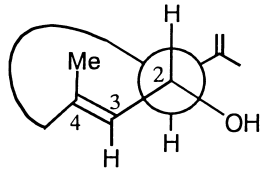

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Figure 2. Partial conformations of allyl alcohols **7** and **19**

The *cis*-alcohol **7** was converted to the benzoate, the CD spectrum of which clearly showed the positive Cotton effect with λ_{ext} ($\Delta\varepsilon$)=250.9 nm (+0.49) in MeOH, indicating (2*R*) configuration.[14] Since the *cis* relationship between the 1 and 2 positions of **7** is supported by NMR evidence, (1*S*) configuration is assignable to **7**. The title compound **7** possesses the correct configuration in relation to C-1, C-2 and C-12 stereochemistries; hence, the further cyclization to the secotrinervitane skeleton can be reasonably expected, and the result will be reported in due course.

3. Experimental

3.1. General

Unless otherwise noted, ^{1}H NMR and ^{13}C NMR spectra were recorded on solutions in $CDCl_3$ with $SiMe_4$ as an internal standard with JEOL FX-90Q (90 MHz), JNM-EX 270L (270 MHz) and GSX-500 (500 MHz) spectrometers. Chemical shifts are reported in δ_H and δ_C, and *J*-values are in Hertz. The following abbreviations were used to explain multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Infrared spectra were recorded on a Hitachi 270-30 spectrophotometer. The mass spectra were measured with a Hitachi M80B spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. CD spectra were measured with a JASCO J-725 circular dichroism polarimeter. Column chromatographic purification was carried out using Kieselgel 60, Art 7734 (70–230 mesh). Thin-layer chromatography was carried out on aluminum sheets coated with $60F_{254}$ silica. Plates were developed using a spray of 0.5% anisaldehyde in 2 M sulfuric acid. Solvents and commercially available reagents were dried and purified if necessary before use according to standard procedures. The purities of all the derivatives described in this paper were confirmed by ^{13}C NMR spectra. The usual work-up involved dilution of the reaction mixture with water, extraction with ether and evaporation after washing the organic extracts with water and brine, followed by drying over Na_2SO_4.

3.2. 8-Hydroxy-geranyl acetate **12** (R=Ac)

After a mixture of geranyl acetate **13** (115 g, 0.95 mol), 80% *tert*-butyl hydroperoxide (180 ml, 1.47 mol), SeO_2 (1.3 g, 11.7 mmol) and salicylic acid (8.92 g, 64.5 mmol) in CH_2Cl_2 (230 ml) was stirred at room temperature for 24 h, water was added and then extracted with ether. The ether solution was worked up as usual and the residue was purified by SiO_2 column chromatography eluted with hexane:AcOEt 40:1 to obtain the allyl alcohol **12** (R=Ac) (61 g, 49%) and recovered acetate **13** (38 g, 33%). **12** (R=Ac): colorless oil. EI-MS m/e (relative intensity) 212 (M^+, 1.6%), 194 (4.7), 152 (74), 134 (100) and 84 (70). IR (CCl_4) 3700–3200, 1740, 1232 and 1020 cm^{-1}. δ_H (270 MHz, $CDCl_3$) 1.49 (s, 3H), 1.67 (s, 3H), 2.06 (s, 3H), 4.00 (s, 2H), 4.59 (d, 2H, *J*=6.9 Hz), 5.33 (d, 1H, *J*=6.9 Hz) and 5.37 (t, 1H, *J*=7.1 Hz). δ_C (67.8 MHz, $CDCl_3$) 13.7 (q), 16.4 (q), 21.0 (q), 25.7 (t), 39.1 (t), 61.4 (t), 68.7 (t), 118.6 (d), 125.1 (d), 135.3 (s), 141.8 (s) and 171.3 (s).

3.3. 8-Pivaloyloxy-geranyl acetate **11** (X=OPiv, R=Ac)

After a mixture of allyl alcohol **12** (R=Ac) (18.5 g, 87.2 mmol), pivaloyl chloride (21.4 ml, 174 mmol), pyridine (212 ml, 261 mmol) and DMAP in CH_2Cl_2 (550 ml) was stirred at room temperature for 1 h, MeOH was added and the mixture was poured into water. The residue obtained by usual work-up was purified by SiO_2 column chromatography eluted with hexane:AcOEt (25:1) to give the pivaloyl ester (23.3 g, 89%). **11** (X=OPiv, R=Ac): colorless oil. EI-MS m/e (relative intensity) 296 (M^+, 4.7%), 237 (11), 194 (1.9), 134 (9) and 57 (15). IR (CCl_4) 1740, 1240 and 1162 cm^{-1}. δ_H (270 MHz, $CDCl_3$), 1.21 (s, 9H), 1.64 (s, 3H), 1.71 (s, 3H), 2.06 (s, 3H), 4.44 (s, 2H), 4.59 (d, 2H, *J*=7.3 Hz) and 5.38 (m, 2 H). δ_C (67.8 MHz $CDCl_3$) 13.8 (q), 16.4 (q), 21.0 (q), 25.8 (t), 27.2 (q, 3C), 38.8 (s), 38.9 (t), 61.3 (t), 69.7 (t), 118.7 (d), 127.8 (d), 130.8 (s), 141.6 (s), 171.0 (s) and 178.3 (s).

3.4. 8-Pivaloyloxy-geraniol **11** (X=OPiv, R=H)

After a mixture of acetoxy pivaloyl ester **11** (X=OPiv, R=Ac) (20 g, 67.6 mmol) and K_2CO_3 (11.2 g, 81.1 mmol) in MeOH (600 ml) was stirred at room temperature for 1 h, water (500 ml) was added to the mixture and extracted with ether. The residue provided by usual work-up was purified by SiO_2 column chromatography eluted with hexane:AcOEt (20:1) to afford the pivaloyloxy alcohol (15 g, 87%). **11** (X=OPiv, R=H): colorless oil. EI-MS m/e (relative intensity) 254 (M^+, 7%), 236 (3), 169 (2), 152 (35), 134 (61) and 57 (21). δ_H (270 MHz, $CDCl_3$) 1.21 (s, 9H), 1.64 (s, 3H), 1.67 (s, 3H), 4.15 (d, 2H, *J*=6.9 Hz), 4.44 (s, 2H) and 5.41 (m, 2H). δ_C (125.7 MHz, $CDCl_3$) 13.8 (q), 16.1 (q), 25.8 (t), 27.2 (q, 3C), 38.9 (s), 38.9 (t), 59.1 (t), 69.9 (t), 124.2 (d), 128.2 (d), 130.4 (s), 138.3 (s) and 178.4 (s).

3.5. 8-Pivaloyloxy-geranyl THP **11e** (X=OPiv, R=THP)

A mixture of pivaloyloxy alcohol **11** (R=H) (20.1 g, 79.3 mmol), 3,4-dihydro-2-*H*-pyrane (8.69 ml, 95.2 mmol) and *p*-TsOH (0.75 g, 4.00 mmol) in CH_2Cl_2 (600 ml) was stirred at room temperature for 1 h and then water was poured into the mixture. After usual work-up, the residue was purified by SiO_2 column chromatography eluted with hexane:AcOEt (40:1) to give the pivaloyloxy THP ether **11e** (X=OPiv, R=THP) (24.7 g, 92%): colorless oil. EI-MS m/e (relative intensity) 338 (M^+, 10%), 254 (15), 236 (11), 152 (72), 134 (100) and 57 (34). δ_H (270 MHz, $CDCl_3$) 1.21 (s, 9H), 1.64 (s, 3H), 1.68 (s, 3H), 3.51 (m, 1H), 3.97 (m, 2H), 4.24 (m, 1H), 4.44 (s, 2H), 4.63 (t, 1H, *J*=3.5 Hz) and 5.40 (m, 2H). δ_C (67.8 MHz, $CDCl_3$) 13.8 (q), 16.4 (q), 19.6 (t), 25.5 (t), 25.9 (t), 27.2 (q, 3C), 30.7 (t), 38.8 (s), 39.0 (t), 62.2 (t), 63.6 (t), 69.8 (t), 97.8 (d), 121.1 (d), 128.2 (d), 130.5 (s), 139.5 (s) and 178.2 (s).

3.6. TBDMS ethers **11 (a–d)**

A mixture of pivaloyloxy alcohol **11** (X=OPiv, R=H) (10.6 g, 41.7 mmol), *tert*-butyldimethylsilyl chloride (12.6 g, 83.4 mmol), imidazole (8.51 g, 125 mmol) and DMAP in DMF (320 ml) was stirred at room temperature for 1 h under nitrogen atmosphere. After dilution with water, the mixture was worked up as usual and the residue was purified by SiO_2 column chromatography eluted with hexane:AcOEt (15:1) to give TBDMS ether **11d** (X=OPiv, R=TBDMS) (14.1 g, 92%). After the pivaloyloxy TBDMS ether (15.3 g, 41.7 mmol) in 2N KOH–MeOH (208 ml, 0.42 mol) was stirred at room temperature for 7 h, the mixture was poured into water and treated as usual. The residue was purified by SiO_2 column chromatography eluted with hexane:AcOEt (18:1) to give TBDMS alcohol **11** (X=OH, R=TBDMS) (8.9 g, 75%). A mixture of the TBDMS alcohol (1.0 g, 3.52 mmol) and triphenylphosphine (1.66 g, 6.34 mmol) in CCl_4 (6 ml) was refluxed at 80°C for 20 h. After cooling, aq $NaHCO_3$ solution was added to the mixture and treated as usual to get the residue. The residue was purified by Florisil column chromatography eluted with hexane:AcOEt (40:1) to get allyl chloride **11a** (X=Cl, R=TBDMS) (852 mg, 80%). δ_H (90 MHz, $CDCl_3$) 0.04 (s, 6H), 0.88 (s, 9H), 1.60 (s, 3H), 1.72 (s, 3H), 2.08 (bs, 4H), 3.99 (s, 2H), 4.16 (d, *J*=7.7 Hz, 2H) and 5.38 (m, 2H). TBDMS ethers **11b** (X=OAc) were prepared from TBDMS alcohol **11** (X=OH, R=TBDMS) (1.0 g) by the action of Ac_2O (0.66 ml), pyridine (0.85 ml) and DMAP in CH_2Cl_2 (30 ml) to obtain **11b** (1.08 g, 94%) after SiO_2 column chromatography. Similarly, **11c** (X=OBz) was prepared from **11** (X=OH) (500 mg) by the action of BzCl (0.41 ml), pyridine (0.43 ml) and DMAP in CH_2Cl_2 (15 ml) in 81% yield (553 mg).

3.7. Grignard reagent **14** from (R)-citronellol **15**

After a mixture of (*R*)-(+)-citronellol (50 g, 0.32 mmol) and tosyl chloride (73 g, 0.39 mmol) in pyridine (300 ml) was stirred at 0°C for 15 h under nitrogen atmosphere, aq $NaHCO_3$ solution was added and the mixture was treated by usual work-up to obtain the tosylate (97 g, 93%) after passing through a short SiO_2 column eluted with hexane:AcOEt (80:1). Tosylate: colorless oil. EI-MS m/e (relative intensity) 310 (M^+, 7%), 173 (10), 138 (81), 123 (77), 81 (100) and 69 (60). $[\alpha]_D^{30}$=+3.0 (*c* 1.00, MeOH). δ_H (270 MHz, $CDCl_3$) 0.82 (d, 3H, *J*=6.6 Hz), 1.57 (s, 3H), 1.67 (s, 3H), 2.45 (s, 3H), 4.06 (t, 2H, *J*=6.6 Hz), 5.02 (t, 1H, *J*=7.1 Hz), 7.34 (d, 2H, *J*=8.6 Hz) and 7.79 (d, 2H, *J*=8.3 Hz). δ_C (67.8 MHz, $CDCl_3$) 17.6 (q), 19.0 (q), 21.6 (q), 25.2 (t), 25.7 (q), 28.8 (d), 35.6 (t), 36.7 (t), 69.1 (t), 124.3 (d), 127.9 (d, 2C), 129.8 (d, 2C), 131.4 (s), 133.2 (s) and 144.7 (s). A mixture of the tosylate (97 g, 0.30 mol) and LiBr (38.7 g, 0.45 mol) in anhydrous acetone (580 ml) was stirred at 56°C for 15 h, diluted with water and then extracted with hexane. The combined organic layers were successively washed with aq $Na_2S_2O_3$ solution and then brine. The organic layer was dried over Na_2SO_4 and the solvent was removed. The residue was passed through a short SiO_2 column eluted with hexane to obtain the citronellyl bromide (58 g, 89%) as a colorless oil. EI-MS m/e (relative intensity) 220 (M^++2, 9%), 218 (M^+, 9%) and 69 (100). δ_H (270 MHz, $CDCl_3$) 0.90 (d, 3H, *J*=6.3 Hz), 1.61 (s, 3H), 1.69 (s, 3H), 3.43 (m, 2H) and 5.09 (m, 1H). δ_C (67.8 MHz, $CDCl_3$) 17.7 (q), 18.9 (q), 25.3 (t), 25.7 (q), 31.4 (d), 32.0 (t), 36.6 (t), 40.0 (t), 124.4 (d) and 131.4 (s).

3.8. 10-Dihydrogeranylgeranyl THP ether **10** (R=THP)

Into the stirred anhydrous THF solution (25 ml) of pivaloyloxy THP ether **11** (X=OPiv, R=THP) (5.0 g, 14.8 mmol) and 0.1 M THF solution of Li_2CuCl_4 (7.4 ml, 0.74 mmol) was added dropwise the cooled Grignard reagent **14** in THF solution at −78°C under nitrogen atmosphere. The Grignard reagent **14** was freshly prepared from citronellyl bromide (13.0 g, 59.1 mmol) and Mg (1.7 g, 70.9 mmol) in THF (65 ml) by stirring at room temperature for 1 h under nitrogen atmosphere after addition of a catalytic amount of iodine. The reaction mixture was continuously stirred overnight after removal of the cooling bath. After careful addition of aq NH_4Cl solution, the mixture was worked up as usual. The residue was purified by SiO_2 column chromatography with hexane:AcOEt (80:1) to obtain the coupled product (5.1 g, 92%). **10** (R=THP): colorless oil. HRMS calcd for $C_{25}H_{44}O_2$: 376.3341. Found: 376.3340. $[\alpha]_D^{29}$=−2.2 (*c* 1.00, MeOH). δ_H (270 MHz, $CDCl_3$) 0.86 (d, 3H, *J*=6.3 Hz), 1.58 (s, 3H), 1.60 (s, 3H), 1.68 (s, 6H), 3.51 (m, 1H), 3.94 (m, 2H), 4.24 (m, 1H), 4.63 (t, 1H, *J*=3.5 Hz), 5.10 (m, 2H) and 5.36 (t, 1H, *J*=6.7 Hz). δ_C (125.7 MHz, $CDCl_3$) 15.9 (q), 16.4 (q), 17.6 (q), 19.6 (q), 19.7 (t), 25.4 (t), 25.6 (t, 2C), 25.7 (q), 26.3 (t), 30.8 (t), 32.3 (d), 36.6 (t), 37.1 (t), 39.7 (t), 40.0 (t), 62.2 (t), 63.6 (t), 97.7 (d), 120.7 (d), 123.7 (d), 125.1 (d), 130.9 (s), 135.6 (s) and 140.2 (s).

3.9. 10-Dihydrogeranylgeranioic acid **9**

The MeOH (670 ml) solution of the coupled product **10** (R=THP) (22.2 g, 58.9 mmol) and *p*-TsOH (1.12 g, 5.89 mmol) was kept at room temperature for 1 h and the reaction mixture was worked up as usual. The residue was purified by SiO_2 column chromatography with hexane:AcOEt (10:1) to get allyl alcohol **10** (R=H) (16.8 g, 98%): colorless oil. HRMS calcd for $C_{20}H_{36}O$: 292.2765. Found: 292.2764. $[\alpha]_D^{28}$=-3.2 (*c* 1.00, MeOH). δ_H (270 MHz, $CDCl_3$) 0.86 (d, 3H, *J*=6.6 Hz), 1.59 (s, 3H), 1.60 (s, 3H), 1.69 (s, 6H), 4.15 (d, 2H, *J*=6.9 Hz), 5.11 (m, 2H) and 5.43 (m, 1H). δ_C (67.8 MHz, $CDCl_3$) 15.9 (q), 16.3 (q), 17.6 (q), 19.6 (q), 25.4 (t), 25.6 (t), 25.7 (q), 26.3 (t), 32.3 (d), 36.6 (t), 37.1 (t), 39.6 (t), 40.0

(t), 59.3 (t), 123.4 (d), 123.6 (d), 125.1 (d), 130.9 (s), 135.7 (s) and 139.6 (s). The CH_2Cl_2 solution of Dess–Martin periodinane (28.7 g, 0.28 mol) was added to the vigorously stirred CH_2Cl_2 (500 ml) solution of the allyl alcohol (16.5 g, 56.5 mmol) and pyridine (22.9 ml, 0.28 mol) at room temperature and the stirring was continued for 30 min. After dilution with ether, aq $Na_2S_2O_3$ and then aq $NaHCO_3$ solutions were successively added and the reaction mixture was stirred for an additional 10 min. The mixture was worked up as usual and the resulting residue was purified by SiO_2 column chromatography with hexane:AcOEt (20:1) to afford the α,β-unsaturated aldehyde (14.8 g, 90%) as colorless oil. δ_H (270 MHz, $CDCl_3$) 0.86 (d, 3H, *J*=6.3 Hz), 1.60 (s, 6H), 1.68 (s, 3H), 2.17 (s, 3H), 5.11 (m, 2H), 5.88 (d, 1H, *J*=7.9 Hz) and 9.99 (d, 1H, *J*=7.9 Hz). δ_C (67.8 MHz, $CDCl_3$) 16.0 (q), 17.6 (q), 19.6 (q), 25.3 (t), 25.4 (t), 25.6 (t), 25.7 (q, 2C), 32.3 (d), 36.6 (t), 37.1 (t), 39.9 (t), 40.7 (t), 122.3 (d), 125.1 (d), 127.4 (d), 131.0 (s), 137.0 (s), 163.8 (s) and 191.2 (s). To the aldehyde (4.6 g, 15.9 mmol) in a stirred mixed solvent of CH_3CN (26 ml) and DMSO (52 ml) was dropped aqueous solution (62 ml) of NaH_2PO_4 (5.7 g, 47.7 mmol) and $NaClO_2$ (2.4 g, 27.0 mmol) at 0°C and the stirring was continued for 2 h at the same temperature. After stirring the mixture for 2 days at room temperature, the reaction mixture was acidified by adding 4N aq HCl, extracted with ether and the ether solution was worked up as usual to obtain the carboxylic acid **9** (7.0 g, 98%) as a colorless oil. HRMS calcd for $C_{20}H_{34}O_2$: 306.2559. Found: 306.2549. IR (CCl_4) 1694, 1642, 1452, 1378, 1250 and 892 cm^{-1}. δ_H (270 MHz, $CDCl_3$) 0.86 (d, 3H, *J*=6.6 Hz), 1.60 (s, 6H), 1.68 (s, 3H), 2.17 (s, 3H), 5.11 (m, 2H) and 5.69 (s, 1H). δ_C (67.8 MHz, $CDCl_3$) 15.9 (q), 17.6 (q), 19.1 (q), 19.6 (q), 25.3 (t), 25.6 (t), 25.7 (q), 25.9 (t), 32.3 (d), 36.5 (t), 37.1 (t), 39.9 (t), 41.3 (t), 115.3 (d), 122.5 (d), 125.1 (d), 130.9 (s), 136.6 (s), 162.9 (s) and 172.3 (s).

*3.10. Preparation of chloroketone **8***

Into a stirred benzene solution (60 ml) of the carboxylic acid **9** (2.0 g, 6.53 mmol) and pyridine (0.6 ml, 7.84 mmol) was added dropwise $SOCl_2$ (1.4 ml, 19.6 mmol) at 0°C and the stirring was continued for 1 h. After complete removal of the white precipitate by filtration through a glass filter, the volatile materials were removed in vacuo below 30°C to obtain crude acid chloride. The CH_2Cl_2 solution of the crude acid chloride was added dropwise to the stirred CH_2Cl_2 (212 ml) solution of $SnCl_4$ (0.23 ml, 19.6 mmol) at −78°C over 2 h and the stirring was continued for a further 20 min at the same temperature. After addition of pyridine (0.16 ml, 1.96 mmol), the CH_2Cl_2 solution was successively washed with 3N H_2SO_4 twice and then aq $NaHCO_3$ solution, and brine. The residue, obtained by evaporation of the CH_2Cl_2 solution after drying with Na_2SO_4, was purified by SiO_2 column chromatography eluted with hexane:AcOEt (50:1) to obtain chloroketone **8** (1.17 g, 56%) as white crystals. Mp 102–104°C (*n*-Hex.). HRMS calcd for $C_{20}H_{33}ClO$: 324.2220. Found: 324.2222. Anal. calcd for $C_{20}H_{33}ClO$: C, 73.93; H, 10.24. Found: C, 74.00; H, 10.40. $[\alpha]_D^{24}$=+142.1 (*c* 1.00, MeOH). IR (CCl_4) 2928, 2856, 1684, 1618, 1456, 1378 and 1116 cm^{-1}. δ_H (270 MHz, $CDCl_3$) 0.78 (d, 3H, *J*=6.4 Hz), 1.57 (s, 3H), 1.64 (s, 6H), 2.00 (s, 3H), 3.11 (dd, 1H, *J*=3.6 and 11.5 Hz), 4.96 (m, 1H) and 6.21 (s, 1H). δ_C (67.8 MHz, $CDCl_3$) 15.0 (q), 16.2 (q), 17.6 (q), 21.5 (t), 24.0 (t), 25,3 (t), 26.8 (d), 30.2 (q), 30.3 (q), 34.5 (t, 2C), 36.8 (t), 40.4 (t), 60.2 (d), 72.1 (s), 124.5 (d), 128.8 (d), 134.6 (s), 156.1 (s) and 202.7 (s).

*3.11. Dehydrochlorination of chloroketone **8***

After a mixture of the chloroketone **8** (2.54 g, 7.9 mmol), Merck silica gel (12.7 g) and K_2CO_3 (10.9 g, 79 mmol) in hexane (1270 ml) was stirred for 2 days at room temperature, the insoluble solids were removed through a SiO_2 pad and the pad was washed with benzene. The combined organic layers were removed and the residue was separated by SiO_2 column chromatography eluted with $CHCl_3$ to obtain

isopropenyl ketone (1.73 g, 78%) and isopropylidene ketone (200 mg, 9%), respectively. Isopropenyl ketone **17**: colorless oil. HRMS calcd for $C_{20}H_{32}O$: 288.2453. Found: 288.2456. $[\alpha]_D^{29}$=+86.1 (*c* 1.00, MeOH). δ_H (270 MHz, $CDCl_3$) 0.83 (d, 3H, *J*=6.6 Hz), 1.55 (s, 3H), 1.74 (s, 3H), 2.20 (s, 3H), 3.16 (dd, 1H, *J*=5.0 and 10.2 Hz), 4.89 (s, 2H), 4.95 (m, 1H) and 6.09 (s, 1H). δ_C (67.8 MHz, $CDCl_3$) 15.5 (q), 18.0 (q), 18.3 (q), 21.5 (q), 22.9 (t), 24.5 (t), 26.1 (t), 28.8 (d), 33.9 (t, 2C), 38.1 (t), 40.4 (t), 58.6 (d), 112.3 (t), 124.4 (d), 124.7 (d), 135.2 (s), 143.8 (s), 157.0 (s) and 202.2 (s). Isopropylidene ketone **18**: colorless oil. HRMS calcd for $C_{20}H_{32}O$: 288.2453. Found: 288.2448. $[\alpha]_D^{26}$=+60.6 (*c* 1.00, MeOH). δ_H (270 MHz, $CDCl_3$) 0.82 (d, 3H, *J*=6.3 Hz), 1.56 (s, 3H), 1.75 (s, 3H), 1.80 (s, 3H), 2.05 (s, 3H), 4.96 (t, 1H, *J*=6.2 Hz) and 6.08 (s, 1H). δ_C (67.8 MHz, $CDCl_3$) 15.9 (q), 18.0 (q), 19.2 (q), 20.8 (q), 22.3 (q), 23.0 (t), 24.5 (t), 27.2 (t), 30.9 (d), 34.1 (t), 36.0 (t), 38.2 (t), 40.8 (t), 124.1 (d), 126.4 (d), 134.3 (s), 135.4 (s), 139.0 (s), 155.8 (s) and 199.7 (s).

*3.12. Reduction of isopropenyl ketone **17***

The reducing reagent was prepared by addition of 1.0 M solution of *n*-BuLi in hexane (0.65 ml, 1.04 mmol) to 1.0 M solution of DIBAH in hexane (1.1 ml, 1.04 mmol) and the mixture was diluted with anhydrous toluene (15 ml). This solution of reducing reagent was added dropwise to the isopropenyl ketone **17** (100 mg, 0.35 mmol) in a stirred 1:1 mixed solvent (3 ml) of hexane and toluene at −78°C under nitrogen atmosphere. After further stirring for 1 h at the same temperature, 2N HCl was added to make the mixture acidic and then the mixture was worked up as usual. The residue was purified by SiO_2 column chromatography eluted with hexane:AcOEt (25:1) to isolate *cis*-alcohol **7** (775 mg, 78%) and *trans* isomer **19** (11.7 mg, 12%) as colorless oil. **7**: colorless oil. HRMS calcd for $C_{20}H_{34}O$: 290.2610. Found: 290.2611. $[\alpha]_D^{24}$=−54.0 (*c* 1.00, MeOH). δ_H (270 MHz,$CDCl_3$) 0.81 (d, 3H, *J*=6.6 Hz), 1.58 (s, 3H), 1.63 (s, 3H), 1.83 (s, 3H), 4.44 (dd, 1H, *J*=0.9 and 7.9 Hz), 4.82 (s, 1H), 4.95 (m, 1H), 4.99 (s, 1H) and 5.35 (d, 1H, *J*=7.9 Hz). δ_C (67.8 MHz, $CDCl_3$) 15.6 (q), 16.3 (q), 19.6 (t), 20.5 (q), 22.8 (t), 23.0 (t), 25.1 (q), 29.4 (d), 30.9 (t), 32.9 (t), 38.6 (t), 39.3 (t), 49.7 (d), 70.0 (d), 111.4 (t), 124.4 (d), 127.4 (d), 134.2 (s), 135.4 (s) and 145.9 (s). **19**: colorless oil. EIMS m/e (relative intensity) 290 (M^+, 100%), 272 (33), 239 (47), 150 (60), 97 (62), 69 (77) and 55 (58). δ_H (270 MHz, $CDCl_3$) 0.83 (d, 3H, *J*=6.9 Hz), 1.59 (s, 3H), 1.65 (s, 3H), 1.70 (s, 3H), 4.10 (dd, 1H, *J*=9.2 and 9.9 Hz), 4.89 (s, 1H), 4.90 (bs, 1H), 5.02 (s, 1H) and 5.07 (m, 1H). δ_C (67.8 MHz, $CDCl_3$) 16.5 (q), 16.9 (q), 17.5 (q), 20.5 (q), 21.1 (t), 23.0 (t), 24.7 (t), 28.8 (d), 30.5(t), 30.9 (t), 38.1 (t), 39.5 (t), 53.4 (d), 68.6 (d), 116.3 (t), 124.4 (d), 127.6 (d), 134.4 (s), 138.3 (s) and 144.7 (s).

*3.13. Benzoate of **7***

A mixture of allyl alcohol **7** (204 mg, 0.74 mmol), pyridine (0.17 ml, 1.40 mmol), benzoyl chloride (0.16 ml, 2.10 mmol) and DMAP (trace) in CH_2Cl_2 (10 ml) was stirred at room temperature for 18 h under nitrogen atmosphere. The mixture was diluted with MeOH and worked up as usual to obtain the residue. The residue was purified by SiO_2 column chromatography eluted with hexane:AcOEt (20:1) to afford the benzoate of **7** as colorless oil. HRMS calcd for $C_{27}H_{38}O_2$: 394.2872. Found: 394.2885. $[\alpha]_D^{27}$=−65.6 (*c* 1.00, MeOH). δ_H (270 MHz, $CDCl_3$) 0.84 (d, 3H, *J*=6.3 Hz), 1.59 (s, 3H), 1.76 (s, 3H), 1.79 (s, 3H), 4.78 (s, 1H), 4.84 (s, 1H), 4.97 (t, 1H, *J*=6.5 Hz), 5.37 (d, 1H, *J*=8.6 Hz), 5.81 (d, 1H, *J*=8.6 Hz), 7.49 (m, 3H) and 8.03 (m, 2H). δ_C (67.8 MHz, $CDCl_3$) 15.9 (q), 16.2 (q), 20.5 (q), 20.9 (t), 21.6 (q), 22.5 (t), 25.1 (t), 29.0 (d), 30.8 (t), 33.1 (t), 38.4 (t), 39.4 (t), 48.8 (d), 74.9 (d), 112.6 (t), 124.1 (d), 124.4 (d), 128.2 (d, 2C), 129.5 (d, 2C), 130.9 (s), 132.6 (d), 134.3 (s), 137.4 (s), 145.0 (s) and 165.8 (s).

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