THE FIRST SYNTHESIS OF GERANYLLINALOOL ENANTIOMERS

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Dedicated to the memory of Dr Václav Černý.

(3*R*)-(–)-Geranyllinalool and its (3*S*)-(+)-isomer were synthesized in 7 steps starting from both enantiomers of citramalic acid and geranyl bromide. The synthetic sequence established the absolute configurations of naturally occurring geranyllinalools for the first time.
Keywords: Terpenoids; Diterpenes; Alcohols; Absolute configuration; Marking pheromones; Bumblebees; Cuprates; Cross-coupling reactions; Carbometallation.

Geranyllinalool (**1**) is a diterpene alcohol widely distributed in biological materials. It can be found in oleoresins[1], in plants ("Absolue de Jasmin")[2], and it is also an important insect semiochemical[3]. Chiral diterpenic alcohols such as geranylcitronellol or geranyllinalool are rather common components of marking pheromones of bumblebee and cuckoo-bumblebee males[4]. One of the important characteristics of those signals is the information about the absolute configurations of chiral pheromone components[5]. However, up-today only achiral syntheses of geranyllinalool have been developed[6] and the absolute configuration of naturally occurring geranyllinalool remains to be established. In this paper, we are reporting the first synthesis of both enantiomers of geranyllinalool (Scheme 1) establishing the absolute configurations of naturally occurring compounds.

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EXPERIMENTAL

All air-sensitive organic transformations were run in an oven-dried (120 °C) glassware. Solvents were dried and distilled prior to use: tetrahydrofuran (THF) and diethyl ether from benzophenone/Na ketyl, acetone with dry potassium carbonate in an argon atmosphere. Other reagents and solvents were purchased from commercial sources and used without further purification. NMR spectral data were recorded in $CDCl_3$ solution on a Varian UNITY-500 spectrometer at 500 MHz for ^1H and 128.2 MHz for ^{13}C, respectively. TMS was used as the internal standard and chemical shifts (in ppm) were plotted on the δ-scale. Coupling constants (*J*) are given in Hz. Infrared spectra (wavenumbers in cm^{-1}) were measured in CCl_4 solution on a Bruker IFS 88FT-IR spectrometer. Optical rotations were recorded in $CHCl_3$ or ether on a Perkin–Elmer 241 polarimeter at 20 °C; $[\alpha]_D$ values are given in 10^{-1} deg cm^2/g.

Silica gel Merck 60 (0.040–0.063 mm) or Florisil (200–300 mesh, Merck) were used for column chromatography. The purity of synthesized compounds was checked both by TLC on silica gel Merck 60 and using GC-MS with a Fisons MD 800 instrument. The capillary column used for separation was a DB-5ms (5% phenyl methyl silicone, 30 m × 0.25 mm, film thickness 0.25 μm). The temperature program started at 50 °C, while after 2 min the temperature was increased to 300 °C at a rate of 10 °C/min. Injector temperature was 220 °C, helium flow 0.94 ml/min.

(+)-(*S*)-2,2,4-Trimethyl-1,3-dioxolan-4-ethanol ((*S*)-**4**)

(+)-(*S*)-2-Hydroxy-2-methylbutanedioic acid {citramalic acid, **2**; 2.96 g, 20 mmol, $[\alpha]_D^{20}$ 23 (*c* 3, H_2O)} was dissolved in THF (20 ml). The solution was cooled to 0 °C and a borane–dimethyl sulfide complex (10 M, 5 ml) was added dropwise. Methanol was added in two portions (2 × 0.6 ml) after 20 min of stirring and subsequently after 80 min. After 30 min of further stirring the reaction mixture was heated to 60 °C for 1 h. The solvents were evaporated and the residue was chromatographed on a silica gel column (elution with 10, 30, 60% of diethyl ether in light petroleum and finally neat ether). The target product (*S*)-**3** was eluted from the column with methanol. After removal the solvent in vacuum dry acetone (142 ml), $CuSO_4$ (4.6 g) and *p*-toluenesulfonic acid (5 mg, 0.029 mmol) were added. After 3 h one major product was formed (checked by TLC, R_F 0.38, light petroleum–ethyl acetate 7 : 3). The reaction mixture was filtered and evaporated to dryness. Diethyl ether (60 ml) was added to the residue, and the solution was extracted with a saturated aqueous solution of $NaHCO_3$ (1 × 20 ml) and then with brine (1 × 20 ml). The organic phase was dried over anhydrous $MgSO_4$. After evaporation of the solvent, 1.540 g (52%) of the **4** were obtained. $[\alpha]_D^{20}$ +4.66 (*c* 1.0, diethyl ether). ^1H NMR: 1.34 (3 H, s, H-1); 1.410 and 1.414 (6 H, 2 × s, H-2, H-3); 1.77 (2 H, t, *J* = 1.8, H-5); 2.70 (1 H, t, *J* = 2.7, H-7); 3.79 (4 H, m, H-4, H-6). MS, *m/z* (%): 145 (M – 15; 31), 115 (M – 45; 24), 97 (6), 85 (32), 72 (72), 67 (13), 61 (5), 59 (12), 57 (49), 55 (32), 53 (4), 43 (100), 42 (25), 41 (22), 39 (13), 31 (14).

Similarly, (–)-(*R*)-citramalic acid {3.94 g, 32.8 mmol, $[\alpha]_D^{20}$ 23 (*c* 3, H_2O)} yielded (*R*)-**4** (1.82 g, 43%). $[\alpha]_D^{20}$ –4.33 (*c* 0.8, diethyl ether).

(+)-(*S*)-2-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)ethyl Tosylate (**5**)

The protected triol (*S*)-**4** (0.56 g, 3.5 mmol) was dissolved in THF (4 ml). *p*-Toluenesulfonyl chloride (1.58 g, 8.32 mmol) was added, and the reaction mixture was kept at –10 °C. Pow-

dered KOH (1.3 g) was added in portions to the mixture during the next 30 min. The mixture was further kept at –10 °C for 1.5 h under stirring. Brine (2 ml) was added and the temperature increased to 20 °C. Diethyl ether (20 ml) was added, and the separated organic layer was dried over anhydrous $MgSO_4$ (3 g). The filtrate was evaporated *in vacuo* and the residue was chromatographed on Florisil in light petroleum–diethyl ether mixture (5, 10, and 20%). Tosylate (*S*)-**5** (0.685 g, 62%) was obtained after evaporation of the solvents. $[\alpha]_D^{20}$ +7.06, (*c* 0.6, diethyl ether). ^{1}H NMR: 1.24 and 1.27 (6 H, 2 × s, H-2, H-3); 1.4 (1 H, s, H-1); 1.91 (2 H, t, *J* = 1.95, H-5); 2.45 (3 H, s, H-8); 3.74 (2 H, q, *J* = 3.75, H-4); 4.16 (2 H, t, *J* = 4.18, H-6); 7.5 (4 H, m, H-7). ^{13}C NMR: 21.6 (C-13), 24.8 (C-7), 26.81 (C-8), 26.84 (C-5), 38.5 (C-3), 67.0 (C-4), 74.2 (C-1), 79.2 (C-2), 109.3 (C-6), 127.9 (C-10), 129.9 (C-11), 133.0 (C-12), 144.8 (C-9). MS, *m/z* (%): 299 (M – 15; 44), 291 (9), 281 (4), 239 (7), 207 (7), 155 (48), 127 (36), 115 (26), 107 (5), 97 (8), 91 (74), 85 (100), 83 (13), 72 (65), 65 (30), 59 (14), 57 (20), 55 (12), 43 (92), 41 (16), 39 (11).

Similarly, (*R*)-**4** (0.60 g) yielded (*R*)-**5** (0.539 g, 46%). $[\alpha]_D^{20}$ –7.42 (*c* 0.4, diethyl ether).

(*E*)-6,10-Dimethylundeca-5,9-dien-1-yne[4a] (**7**)

The title compound was prepared using a slightly modified procedure[4a]. Allene (7 ml) prepared from 1,2-dichloroprop-1-ene (18 ml, 195 mmol) was treated with butyllithium (2.5 M, 20 ml, 50 mmol) to form dilithiated allene and the reaction mixture was subsequently treated at –30 °C with geranyl bromide (**6**; 3.27 ml, 16.4 mmol). After distillation, 1.629 g (46%) of pure **7** (b.p. 105 °C/15 torr) was obtained.

(1*E*,5*E*)-1-Iodo-2,6,10-trimethylundeca-1,5,9-triene[4a] (**8**)

The complex, $[ZrCl_2(\eta^5\text{-cyclopentadienyl})_2]$ (0.55 g, 1.87 mmol), was dissolved in dry dichloromethane (30 ml). The flask was cooled to –25 °C, and a solution of trimethylaluminium in toluene (1 M, 13.2 ml, 13.2 mmol) was added. After 30 min, water (240 µl) was added dropwise. Cooling to –20 °C was continued for another 30 min when acetylene **7** (1.56 g, 8.8 mmol) dissolved in dichloromethane (10 ml) was added. The reaction mixture was stirred at –20 °C for 20 min. Then, iodine (2.68 g, 10.6 mmol) dissolved in THF (10 ml) was added at –45 °C. The temperature was then increased to –5 °C and kept for 5 min. A saturated solution of Na_2CO_3 (2 ml) and $MgSO_4$ (4 g) was added at room temperature, and inorganic salts were filtered off. After evaporation of the solvents, a chromatographically pure product (R_F 0.44, light petroleum–ethyl acetate 9 : 1) was obtained. After distillation (b.p. 95–110 °C/150 Pa), 2.498 g (89.3%) of **8** were obtained. Measured spectral data on this sample were in full accord with those of the previously prepared sample[4a].

(+)-(5*E*,9*E*)-(*S*)-1,2-*O*-Isopropylidene-2,6,10,14-tetramethylpentadeca-5,9,13-triene-1,2-diol (**10**)

A solution of 2-thienyllithium in THF (1 M, 1 ml, 1 mmol) was added dropwise to a suspension of CuCN (89.6 mg, 1.4 mmol) in THF (0.5 ml) at –80 °C. The temperature was then increased to 0 °C under formation of a brown solution of dilithium cyano(2-thienyl)cuprate. Iodide **8** (398 mg, 1.25 mmol) was dissolved in THF (1 ml) in a separate flask and cooled to –90 °C in an ether/CO_2 (s) bath. A solution of *t*-BuLi (1.7 M, 1.25 ml, 2.1 mmol) in pentane was added and the reaction mixture was stirred for 20 min. This mixture was then transferred into the flask with the cuprate solution using stainless tubing and an argon over-

pressure. The solution of the formed 2-thienyl(vinyl)cuprate (**9**) was stirred at *ca* –30 °C for another 10 min. The temperature of the reaction mixture was decreased to –70 °C, and a solution of tosylate **5** (0.251 g, 0.8 mmol) in THF (1 ml) was added. The reaction was completed at 20 °C after 2 days. Ice (3 g) was added to the mixture, followed by adding a saturated solution of NH_4Cl and NH_4OH (2 : 1, 10 ml) and ether (10 ml). After 10 min stirring, the product was extracted with ether (2 × 10 ml). The combined organic phases were washed with a saturated solution of NH_4Cl and NH_4OH (2 : 1, 10 ml) and dried over anhydrous $MgSO_4$. After evaporation of the solvents the product was purified on Florisil (0, 5, 10, 20, and 50% ether in light petroleum). Compound **10**, obtained in 45% yield (0.12 g), was immediately used for the next reaction. MS, *m/z* (%): 334 (M^+; 1), 319 (M^+ – 15; 1), 291 (1), 276 (7), 265 (1), 250 (2), 189 (4), 175 (4), 161 (3), 149 (7), 136 (14), 121 (19), 115 (13), 109 (14), 107 (14), 95 (24), 93 (24), 81 (63), 69 (100), 57 (19), 41 (26).

Similarly, (*R*)-**5** (0.251 g, 0.8 mmol) yielded 0.1685 g (63%) of crude (*R*)-**10**.

(+)-(5*E*,9*E*)-(*S*)-2,6,10,14-Tetramethylpentadeca-5,9,13-triene-1,2-diol (**11**)

Pyridinium (4-toluene)sulfonate (108 mg, 0.43 mmol) and methanol (9 ml) were added to **10** (0.12g, 0.36 mmol). After 44 h of stirring at the room temperature the reaction was terminated since no additional **11** was formed (TLC, R_F 0.67, light petroleum–ethyl acetate 9 : 1). Column chromatography on Florisil (elution system 30, 50, 70, and 100% diethyl ether in light petroleum) afforded 76.2 mg (67%) of diol **11**. A substantial amount of unreacted **10** (19.2 mg) was recovered. $[\alpha]_D^{20}$ +2.52 (*c* 0.3, $CHCl_3$). ^{1}H NMR: 1.29 (3 H, s); 1.56 (3 H, s); 1.59 (3 H, s); 1.60 (3 H, s); 1.65 (3 H, s); 1.60–2.08 (6 × 2 H, m); 3.24 (2 H, s); 3.7 (2 H, bs); 5.00 (1 H, bd, *J* = 10.2); 5.10 (2 H, bt, *J* = 6.6); 5.17 (1 H, bt, *J* = 6.6). MS, *m/z* (%): 294 (M^+; 2), 276 (M^+ – 18; 1), 245 (4), 210 (5), 189 (4), 163 (6), 152 (5), 136 (22), 121 (42), 109 (26), 95 (55), 93 (61), 81 (100), 79 (25), 75 (11), 69 (91), 67 (28), 55 (32), 41 (49). HR-MS: for $C_{19}H_{34}O_2$ calculated 294.2559; found: 294.2580.

Similarly, (*R*)-**10** (0.1355 g, 0.41 mmol) yielded 0.0673 g (56%) of (*R*)-**11**. $[\alpha]_D^{20}$ –2.63 (*c* 0.4, $CHCl_3$).

(+)-(5*E*,9*E*)-(*S*)-2-Hydroxy-2,6,10,14-tetramethylpentadeca-5,9,13-trienal (**12**)

A) Oxidation with pyridinium dichromate (PDC). Dichloromethane (0.5 ml) and PDC (17.3 mg, 0.06 mmol) were added to diol **11** (10 mg, 0.034 mmol). After 10-min stirring at room temperature, the products formed were checked by TLC and GC-MS. It was found that undesired farnesyl acetone had been formed predominantly. MS, *m/z* (%): 262 (M^+; 0.5), 219 (M^+ – 43; 0.8), 193 (M^+ – 69; 1), 178 (3), 161 (3), 136 (17), 125 (9), 121 (8), 107 (24), 95 (15), 93 (17), 81 (34), 79 (10), 69 (98), 67 (23), 55 (9), 53 (49), 43 (100), 41 (62).

B) Swern oxidation. Ethyl(diisopropyl)amine (160 µl), dimethyl sulfoxide (150 µl), and dichloromethane (500 µl) were added to diol **11** (40 mg, 0.136 mmol). Under intensive stirring, sulfuryltrioxypyridinium complex (64 mg, 0.4 mmol) was then added. After 3 min, **12** was formed as the only product (checked by TLC, R_F 0.4, light petroleum–ethyl acetate 9 : 1). No traces of the starting diol **11** were detected. Ice (0.5 g) and diethyl ether (0.5 ml) were added, and the mixture was stirred for 10 min. The organic layer was extracted with ether and light petroleum (1 : 1, 2 × 1 ml). The organic phase was dried over anhydrous $MgSO_4$, filtered through a Florisil column and evaporated to dryness, yielding 24 mg (60%) of unstable hydroxyaldehyde **12**, which was immediately used for the next reaction. MS, *m/z* (%): 292 (M^+; 0.5), 249 (M^+ – 43; 1), 231 (0.8), 191 (1), 187 (1), 177 (1), 161 (3), 136

(20), 121 (12), 109 (10), 107 (11), 95 (25), 93 (20), 81 (51), 69 (100), 67 (21), 55 (12), 45 (16), 43 (29), 41 (44).

Similarly, (*R*)-**11** (24 mg, 0.0816 mmol) yielded 28.3 mg (65%) of crude (*R*)-**12**, which was submitted to Wittig reaction without purification.

(+)-(6*E*,10*E*)-(*S*)-3,7,11,15-Tetramethylhexadeca-1,6,10,14-tetraen-3-ol, [(+)-(*S*)-geranyllinalool; (*S*)-**1**]

Methyl(triphenyl)phosphonium bromide (240 mg, 0.7 mmol) was suspended in THF (1 ml). The suspension was cooled to –70 °C, and BuLi (2.5 M, 280 μl, 0.7 mmol) was added. The temperature was then increased to –10 °C (30 min), then decreased again to –55 °C. Subsequently, a solution of the hydroxyaldehyde (*S*)-**12** (24 mg) in THF (1 ml) was added. The reaction temperature was kept at 0 °C. After 1.5 h, a saturated solution of NH_4Cl (1 ml) was added. The mixture was extracted with diethyl ether and light petroleum (1 : 1, 2 × 1 ml). The organic phase was washed with a saturated solution of NaCl (1 ml) and dried over anhydrous $MgSO_4$. After evaporation of the solvents, one dominant product was found (R_F 0.72, light petroleum–ethyl acetate 9 : 1). The crude product was chromatographed on silica gel (elution with 2, 3, 5, 10, 20, 50% of diethyl ether in light petroleum) providing (*S*)-(+)-**1** in 41% yield (9.8 mg). $[\alpha]_D^{20}$ +18.2 (*c* 0.06, $CHCl_3$). ^{1}H NMR: 1.28 (3 H, s); 1.56 (3 H, s); 1.59 (3 H, s); 1.60 (3 H, s); 1.68 (3 H, s); 1.60–2.06 (12 H, 6 × m); 5.07 (1 H, bd, *J* = 10.7); 5.10 (2 H, bt, *J* = 6.6); 5.17 (1 H, bt, *J* = 6.6); 5.21 (1 H, bd, *J* = 17.3); 5.92 (1 H, dd, *J* = 10.7, 17.3). ^{13}C NMR: 15.98 (C-19), 16.01 (C-20), 17.7 (C-17), 22.7 (C-5), 25.7 (C-16), 26.6 (C-9), 26.8 (C-13), 27.9 (C-18), 39.69 (C-8), 39.71 (C-12), 42.1 (C-4), 73.5 (C-3), 111.7 (C-1), 124.2 (C-10), 124.3 (C-14), 124.4 (C-6), 131.2 (C-15), 135.6 (C-11), 135.7 (C-7), 1 145.1 (C-2). MS, *m/z* (%): 290 (M^+; 1), 272 (M^+ – 18; 2), 256 (2), 239 (1), 229 (2), 203 (4), 189 (4), 175 (3), 161 (10), 147 (8), 135 (12), 121 (15), 107 (31), 93 (52), 81 (11), 79 (17), 69 (100), 55 (22), 41 (23). HR-MS: for $C_{20}H_{34}O$ calculated 290.2610; found 290.2602. IR: 3 430 (OH); 2 962, 2 922, 2 852 (C–H); 1 645 (C=C); 1 457, 1 378 (C–H); 1 126, 1 115 (C–O); 922 (CH=CH_2).

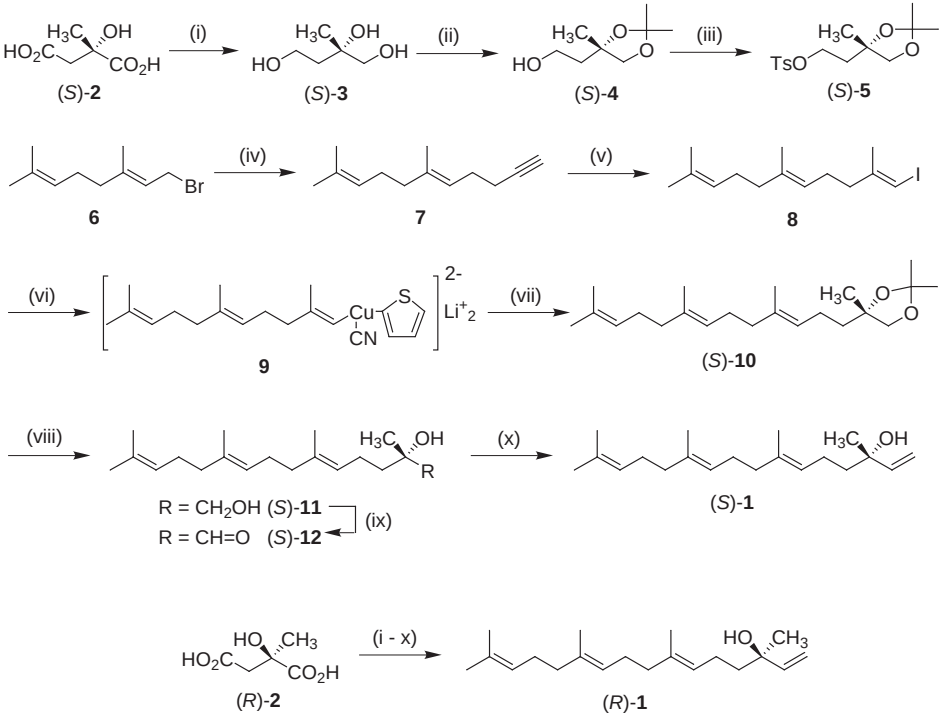
Similarly, (*R*)-**12** (28 mg, 0.053 mmol) yielded 4 mg (27%) of (*R*)-**1**. $[\alpha]_D^{20}$ –17.0 (*c* 0.1, $CHCl_3$). HR-MS: for $C_{20}H_{34}O$ calculated 290.2610; found 290.2587; other spectral data were identical to (*S*)-**1** enantiomer.

RESULTS AND DISCUSSION

For the preparation of both enantiomers of geranyllinalool (**1**) we used 2-hydroxy-2-methylbutanedioic acid (citramalic acid, **2**), commercially available in both enantiomeric forms (Aldrich, 98% e.e.).

(+)-(*S*)-2-Hydroxy-2-methylbutanedioic acid [(+)-(*S*)-citramalic acid, (*S*)-**2**] was reduced[7] using borane–dimethyl sulfide complex in THF at room temperature for 24 h affording triol[7] (*S*)-**3**. Triol (*S*)-**3** was protected with acetone[8] to afford acetonide (*S*)-**4** in 43% overall yield. Ketal **4** was converted to the tosylate (*S*)-**5** using TsCl/powdered KOH/THF/–20 °C (ref.[9]) to prevent potential deprotection of **4**. Acid (*R*)-(–)-**2** was converted to the tosylate (*R*)-**5** by using a similar reactions sequence. Iodide **8** was prepared from lithiated dianion of allene and geranyl bromide[4a,10] **6**. The initially

formed dienyne **7** was carbometallated with trimethylaluminium catalyzed by $ZrCp_2Cl_2$ complex and in the presence of 1.5 eqivalent of water[11]. The formed vinylallane was converted to vinyliodide **8** with iodine (in 89% yield based on **7**).



(i) $BH_3 \cdot Me_2S$, THF; (ii) acetone, $CuSO_4$, TsOH; (iii) TsCl, KOH powder, THF, –20 °C; (iv) $Li_2C_3H_2$, –35 °C; (v) Me_3Al, $[ZrCp_2Cl_2]$, H_2O (0.5 eq.), CH_2Cl_2, –20 °C, (vi) 1. *t*-BuLi (2 eq.), –80 °C, 2. Li(CN)Cu(2-thienyl), –70 °C to r.t.; (vii) –70 °C, **5**, –70 °C to r.t.; (viii) TsOH, MeOH, (ix) Me_2SO, $(i\text{-}Pr)_2N\text{-}Et$, pyridine$\cdot SO_3$, CH_2Cl_2, r.t.; (x) $H_2C{=}PPh_3$ (5 eq.), 0 °C

SCHEME 1

Employing higher order cuprate chemistry[12], compounds **5** and **8** were coupled to yield the protected diol **10**. Iodide **8** reacted at –90 °C with *t*-BuLi and the *in situ* formed vinyllithium compound was treated with dilithium cyano(2-thienyl)cuprate to form the cuprate **9**. The latter reacted at 0 to 20 °C with the tosylates (*S*)- and (*R*)-**5** forming (*S*)- or (*R*)-**10**. After deprotection with pyridinium (4-toluene)sulfonate in methanol, diols (*S*)- and (*R*)-**11** were obtained in 56 and 67% yields, respectively. The enantio-

meric diols **11** were oxidized using Swern oxidation[13] providing pure α-hydroxyaldehydes **12** in *ca* 5 min. When pyridinium dichromate oxidation[14] was used, farnesylacetone was the main product resulting from 1,2-diol cleavage of **11**. The aldehydes **12** were converted to **1** with an excess of CH_2=PPh_3 ylide[15]. Infrared and ^{1}H NMR data of prepared enantiomers of **1** were identical with those reported for both isolated[1a] and synthesized[6g] compounds.

Our approach using enantiopure natural compound pool and carbometallation/vinyl cuprate sequence was not previously used to construct enantiopure 4-akyl-3-methylbut-1-en-3-ols. Published routes for their preparations relayed on the enantioselective Sharpless epoxidation of 4-alkyl-3-methyl-but-2-en-1-ols and a reductive elimination of the corresponding 2,3-epoxybutan-1-iodide[16].

Knowing the optical rotation of geranyllinallool we can establish the absolute configurations of previously isolated samples from natural materials. Thus (–)-**1** previously isolated from *Picea abies*[1a] and from *Picea obovata*[1c] has the (*R*)-absolute configuration in accord with the suggested absolute configuration[1a]. Unfortunately, so far we were not able to separate the enantiomers of **1** on chiral GC columns (Lipodex E, dipentyl butyryl γ-cyclodextrin, and Cyclodex B, permethylated β-cyclodextrin) and to determine the absolute configurations of **1** found in labial glands of several bumblebees[3d]. However, further investigations in this direction are in progress.

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