

A new approach to the C₅-homologation of linear monoterpenols

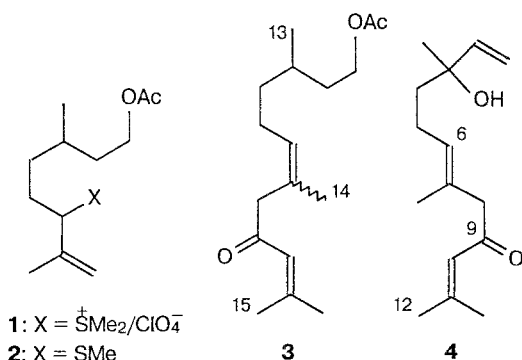
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Both possible geometric isomers of 9-oxo-2,3-dihydrofarnesyl acetate, which are structurally related to the natural linear sesquiterpenes bearing the keto-function at position 9, have been prepared by a six-stage procedure starting from citronellyl acetate.

Key words: C₅-homologation, oxo- and hydroxydihydrofarnesols, allylsulfonium salts, [2,3]-sigmatropic rearrangement.

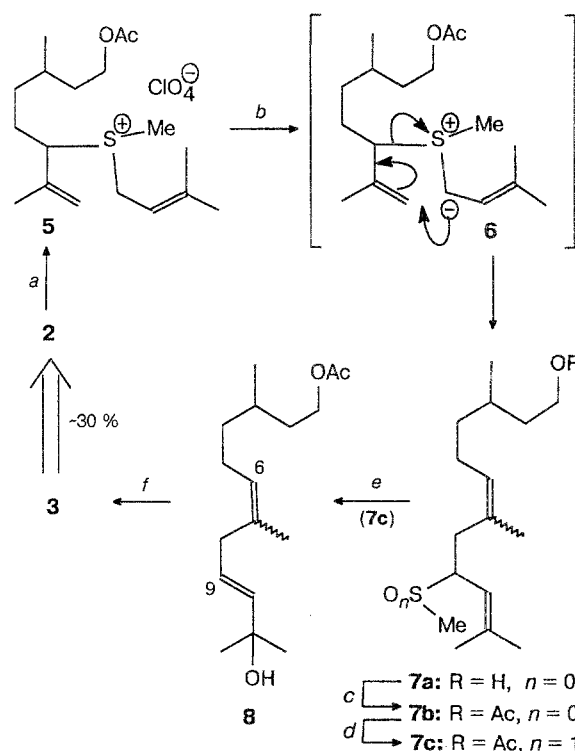
The elaboration of methods for obtaining functionalized isoprenologs of simple linear terpenols is primarily aimed at the further expansion of their synthetic potential. Bearing this in mind and continuing our previous investigations,¹ we now report the transformation of dimethylsulfonium salt **1**, which is readily available from citronellyl acetate,² to 9-oxofarnesols (**3**) structurally related to phytoalexine 9-oxonerolidol (**4**) and similar sesquiterpenoids.^{3,4}



According to the plan accepted by us, perchlorate **1** was smoothly converted to sulfide **2**, which we previously described as a side product formed in the transformations of this sulfonium salt by the action of a series of nucleophiles.² It turned out that this demethylation reaction (**1**→**2**) becomes predominant when compound **1** is treated with ~5 equivalents of pyridine in MeCN. Subsequent S-prenylation of compound **2** by the action of a twofold amount of prenyl chloride (PreCl) and silver mesylate (MsOAg) in the presence of LiClO₄ gave high yields of diastereomeric sulfonium salts (**5**), which were isolated by double precipitation with pentane from chloroform (Scheme 1).

In the scheme suggested for the synthesis of sesquiterpenes **3**, we employed at the key stage the well known ability of type **6** allylsulfonium ylides to undergo [2,3]-sigmatropic rearrangement.⁵ For example, the treatment of salts **5** with ~2 equivalents of MeONa in MeOH

Scheme 1



Reagents and conditions (yield): a, AgOMs/PreCl, LiClO₄, CH₂Cl₂, 10→25 °C, 1 h (90 %); b, MeONa/MeOH, 25 °C, 30 min (82 %); c, Ac₂O/Py; d, H₂O₂/AcOH, MeOH, SeO₂ (cat.), 25 °C, 10 min (90 %); e, P(OMe)₃, MeOH, 65 °C, 2 h (94 %); f, PCC, CH₂Cl₂, 25 °C, 2.5 h (50 %).

† Deceased.

at 25 °C smoothly gives hydroxysulfides **7a** in high yields, while the amount of the products of competing processes, including the 1,2-shift according to Stevens,⁵ does not exceed 15 % (¹H NMR data). The structure of the hitherto unknown alcohol **7a** was confirmed by spectral data and by obtaining the respective acetate **7b** which was then characterized by elemental analysis and spectral data.

Transformation of compound **7** to the target compound **3** at the next stage presumes the replacement of the sulfide group by the keto moiety. Of the possible variants, we chose the approach based on sequential sulfoxide-sulfenate rearrangement^{6,7} and allylic oxidation of the resulting alcohol.⁸ For example, standard SeO₂-catalyzed treatment of sulfides **7b** with peracetic acid in MeOH gives moderately stable diastereomeric sulfoxides **7c** in ~90 % yield (Scheme 1). The latter are stereospecifically transformed under the conditions of the Mislow–Evans reaction by the action of P(OMe)₃ in boiling MeOH to give alcohols **8** with a 9*E*-configuration in the ratio 6*Z*-**8**/6*E*-**8** ≈ 1 : 1 (¹H NMR data). The former product was quantitatively isolated in the individual form by HPLC. Its subsequent oxidation with pyridinium chlorochromate (PCC) in CH₂Cl₂ was accompanied by complete allylic isomerization and resulted in ketone 6*Z*-**8** (50 %). Under the same conditions, the above mixture of alcohols **8** was transformed to ketones 6*Z*-**3** and 6*E*-**3** isolated in equal amounts by HPLC, overall yield ~40 %. It should be noted that since the sequence of transformations **7a**→**3** was performed without the involvement of the C=C(6) double bond, the observed ratio of target ketones **3** corresponds to that for the products of the [2,3]-sigmatropic rearrangement at the key stage, **7a**.

The structures of the hitherto unknown alcohols **8** and ketones **3** was confirmed on the basis of spectral analysis data, including high-resolution mass spectrometry. The configuration of the C=C(6) double bond in compounds **3** was unambiguously determined by observation of the nuclear Overhauser effect (NOE) between the protons at the C(8) atom and the vinyl proton at the C(6) atom in ketone *Z*-**3** and the absence of this effect in compound *E*-**3**, and confirmed by comparing the ¹³C NMR spectra of these compounds with those for related compounds reported in the literature.^{3,9} Moreover, the observation of the NOE between the protons in H₂C(8) and H₃C(14) made it possible to assign with certainty the signals of the methyl group in the ¹H NMR spectra of both isomers **3**.

Thus, using the example of citronellyl acetate, we demonstrated the possibility of regular C₅-homologation of linear isoprenoids with the formation of a keto moiety at the position where the isoprene unit is attached.

Experimental

IR spectra (ν/cm⁻¹) for CCl₄ solutions were recorded on a UR-20 spectrophotometer. ¹H and ¹³C NMR spectra (δ) for CDCl₃ solutions were obtained on Bruker WM-250 and Bruker

AX-200 spectrometers, respectively. Mass spectra (EI, 70 eV) were recorded on Varian MAT CH-6 and Varian MAT 311A instruments. The values of *R_f* are given for a fixed SiO₂ layer (Silufol, ethyl acetate — heptane, 1 : 4).^{*} Semipreparative HPLC was performed on a column with Silasorb 600 silica gel (10 mm, 250 × 24 mm).

6-Methylthio-3,7-dimethyl-7-octen-1-ol acetate (2). A solution of sulfonium salt **1**² (2.02 g, 5.63 mmol) and piperidine (2.58 g, 30.3 mmol) in MeCN (12 mL) was stirred for 3 h at 25 °C and then concentrated. The residue (1.15 g) was distilled to give 1.06 g (77 %) of acetoxy sulfide **2** as a colorless liquid, b.p. 73–74 °C (0.06 Torr), *n*_D²⁰ 1.4845. The product was practically identical (¹H NMR data) to the previously described sample of this compound.²

(8-Acetoxy-2,6-dimethyl-1-octen-3-yl)methyl(phenyl)sulfonium perchlorate (5). A vigorously stirred (Ar, at 10 °C) suspension of compound **2** (0.56 g, 2.29 mmol) and LiClO₄ (0.25 g, 2.35 mmol) in CH₂Cl₂ (6 mL) was successively treated three times with portions of MsOAg (0.31 g, 1.5 mmol) and prenyl chloride (0.16 g, 1.53 mmol). Each time, the reaction mixture was heated to 25 °C and kept for 20 min at this temperature. The resulting mixture was diluted with CHCl₃ (50 mL), washed with saturated NaHCO₃ and water, dried with MgSO₄, and concentrated at a reduced pressure. The residue (1.4 g) was purified three times by precipitation with pentane from CH₂Cl₂ and dried *in vacuo* to give product **5** (0.85 g, 90 %) as a light yellow oil. ¹H NMR: 0.90 and 0.91 (d, *J* = 5.8 Hz, 3 H, CH₃C-6); 1.1–2.0 (m, 7 H, CH, CH₂); 1.78, 1.81, 1.83, and 1.85 (br.s, 9 H, CH₃); 2.02 (s, 3 H, CH₃CO); 2.70 and 2.89 (br.s, 3 H, CH₃S); 3.83, 4.04, 4.17, and 4.37 (m, 5 H, CHS, CH₂S, CH₂O); 5.1–5.4, 5.35, and 5.45 (m, 3 H, HC=C, H₂C=C).

9-Methylthio-3,7,11-trimethyl-6*E*/*Z*,10-dodecadien-1-ol (7a) and its acetate (7b). A 2*M* solution of MeONa in MeOH (5.4 mL) was added in one portion at 25 °C (Ar) to a stirred solution of compound **5** (0.76 g, 1.84 mmol) in MeOH (5 mL). The reaction mixture was stirred for 30 min at 25 °C, diluted with ether (50 mL), and treated with saturated NH₄Cl. The aqueous layer was extracted with ether. The combined organic layer was dried with MgSO₄ and concentrated *in vacuo*. The residue (0.47 g) was chromatographed on 30 g of SiO₂. Gradient elution from hexane to ether (up to 30 % of the latter) gave 0.41 g (82 %) of alcohol **7a** as a colorless oil with *R_f* 0.23. ¹H NMR: 0.90 (d, *J* = 5.3 Hz, 3 H, CH₃C-3); 1.0–2.3 (m, 9 H, CH, CH₂); 1.59, 1.62, 1.69, and 1.74 (br.s, 12 H, CH₃); 1.97 and 1.99 (s, 3 H, CH₃S); 3.59 and 3.65 (m, 3 H, CHS, CH₂O); 4.94 and 5.15 (m, 2 H, HC=C).

Acetate **7b** was obtained by ordinary acylation of alcohol **7a** with Ac₂O (3.25 g) and Py (1.47 g) as a colorless oil, *R_f* 0.57. IR: 1055, 1240, 1365, 1375, 1440, 1742, 2920, 2950, 2970. ¹H NMR: 0.90 (d, *J* = 5.4 Hz, 3 H, CH₃C-3); 1.0–2.2 (m, 7 H, CH, CH₂); 1.59, 1.62, 1.69, and 1.74 (br.s, 9 H, CH₃); 1.97 and 1.99 (s, 3 H, CH₃S); 2.03 (s, 3 H, CH₃CO); 2.25 (m, 2 H, HC-8); 3.60 (m, 1 H, CHS); 4.08 (m, 2 H, CH₂O); 4.93 and 5.13 (m, 2 H, HC=C). MS, *m/z*: 312 [M]⁺. Found (%): C, 68.81; H, 10.60; S, 10.23. C₁₈H₃₂O₂S. Calculated (%): C, 69.18; H, 10.32; S, 10.26. Mol. weight 312.5.

9-Methylsulfinyl-3,7,11-trimethyl-6*E*/*Z*,10-dodecadien-1-ol acetate (7c). AcOH (0.33 g, 5.5 mmol), 30 % H₂O₂ (0.57 mL), and SeO₂ (~5 mg) were successively added at 25 °C to a stirred solution of compound **7b** (0.28 g, 0.9 mmol) in a MeOH/Et₂O (1 : 1) mixture. The reaction mixture was kept for 10 min at 25 °C, diluted with ether (10 mL), and

* Unless stated otherwise.

treated with saturated NaHCO₃. The aqueous layer was extracted with ether. The combined organic layer was dried with MgSO₄ and concentrated *in vacuo*. The residue (0.29 g) was chromatographed on 10 g of SiO₂. Gradient elution from hexane to ether and further to an ether-methanol mixture (up to 5 % of the latter) gave 0.26 g (88 %) of sulfoxide **7c** as a colorless oil, *R_f* 0.46 (ethyl acetate). ¹H NMR: 0.90 and 0.92 (d, *J* = 6.2 Hz, 3 H, CH₃C-3); 1.1–2.8 (m, 9 H, CH, CH₂); 1.61, 1.68, 1.71, 1.78, and 1.83 (br.s, 9 H, CH₃); 2.04 (s, 3 H, CH₃CO); 2.36, 2.39, 2.49, and 2.52 (s, 3 H, CH₃S); 3.3–3.7 (m, 1 H, CHS); 4.08 (m, 2 H, CH₂O); 4.8–5.3 (m, 2 H, HC=C).

3,7,11-Trimethyl-6Z,9E-dodecadien-1,11-diol 1-acetate (6Z-8) and 3,7,11-trimethyl-6E,9E-dodecadien-1,11-diol 1-acetate (6E-8). A solution of compound **7c** (0.26 g, 0.79 mmol) and P(OMe)₃ (0.2 g, 1.61 mmol) in MeOH (3 mL) was refluxed for 2 h (Ar) and concentrated *in vacuo*. The residue (0.24 g) was chromatographed on SiO₂ (10 g). Gradient elution from hexane to ether (up to 50 % of the latter) gave 0.21 g (94 %) of a mixture of alcohols **8** and an unidentified compound **9** in the ratio 6Z-8 : 6E-8 : **9** ≈ 2 : 2 : 1 (calculated on the basis of ¹H NMR data and by quantitative isolation of compound 6Z-8, see below) as a colorless oil, *R_f* 0.21. HPLC of 160 mg of the mixture obtained (ethyl acetate – heptane, 13 : 87 as the eluent) gave 64 mg of 6Z-8 as an individual compound).

IR spectrum of compound 6Z-8: 910, 970, 1055, 1152, 1240, 1365, 1460, 1740, 2930, 2950, 3585, 3590, 3610. ¹H NMR spectrum of compound 6Z-8: 0.91 (d, *J* = 6 Hz, 3 H, CH₃); 1.1–1.8 (m, 5 H, CH, CH₂); 1.32 (s, 6 H, CH₃C-11); 2.00 (m, 2 H, HC-5); 2.06 (s, 3 H, CH₃CO); 2.73 (br.d, *J* = 5.3 Hz, 2 H, HC-8); 4.11 (m, 2 H, CH₂O); 5.17 (t, *J* = 7 Hz, 1 H, HC-6); 5.4–5.7 (m, 2 H, HC-9,10).

¹H NMR spectrum of compound 6E-8: 0.90 (d, *J* = 6 Hz, 3 H, H₃C-3); 1.1–1.8 (m, 5 H, CH, CH₂); 1.32 (s, 6 H, CH₃C-11); 2.00 (m, 2 H, HC-5); 2.06 (s, 3 H, CH₃CO); 2.67 (br.d, *J* = 5.3 Hz, 2 H, H₂C-8); 4.09 (m, 2 H, CH₂O); 5.12 (t, *J* = 7 Hz, 1 H, HC-6); 5.4–5.7 (m, 2 H, HC-9,10).

3,7,11-Trimethyl-9-oxo-6Z,10-dodecadien-1-ol acetate (Z-3). Compound 6Z-8 (54 mg, 0.19 mmol) in CH₂Cl₂ (1 mL) was added in one portion at 25 °C to a vigorously stirred (Ar) suspension of PCC (165 mg, 0.77 mmol) in CH₂Cl₂ (2.5 mL). The reaction mixture was kept for 2.5 h at 25 °C, diluted with hexane (10 mL), and treated with saturated NaHCO₃. The aqueous layer was extracted with hexane. The combined organic layer was dried with MgSO₄/celite (1 : 1) and concentrated *in vacuo*. The residue (0.7 g) was chromatographed on SiO₂ (10 g). Gradient elution from hexane to ether (up to 30 % of the latter) gave successively 26 mg (49 %) of compound Z-3 and 9 mg (17 %) of compound 6Z-8.

Ketone Z-3 is a colorless oil, *R_f* 0.40. IR: 1055, 1105, 1240, 1365, 1380, 1445, 1620, 1740, 2930, 2950, 2960. ¹H NMR: 0.92 (d, *J* = 6.0 Hz, 3 H, CH₃); 1.1–1.8 (m, 5 H, CH, CH₂); 1.70 (br.s, 3 H, H₃C-14); 1.88 (d, *J* = 1.0 Hz, 3 H, H₃C-12); 2.01 (m, 2 H, HC-5); 2.04 (s, 3 H, CH₃CO); 2.14 (br.s, *J* = 1.2 Hz, 3 H, H₃C-15); 3.11 (br.s, 2 H, HC-8); 4.09 (m, 2 H, CH₂O); 5.33 (t, *J* = 7 Hz, 1 H, HC-6); 6.07 (br.s, 1 H, HC-10). ¹³C NMR: 19.26 (C-13); 20.65 (C-15); 20.94 (CH₃CO); 24.12 (C-14); 25.61 (C-5); 27.65 (C-12); 29.40 (C-3); 35.29 (C-2); 36.74 (C-4); 47.72 (C-8); 62.85 (C-1); 122.81 (C-10); 128.50 (C-6); 129.05 (C-7); 155.83 (C-11); 171.13 (CH₃CO); 198.49 (C-9).

3,7,11-Trimethyl-9-oxo-6E,10-dodecadien-1-ol acetate (E-3) and ketone Z-3. Similarly to the procedure for com-

pound Z-3, a mixture of compounds **3** (85 mg, 42 %) was obtained in 1.5 h from the mixture of alcohols **8** (0.2 g, 0.71 mmol) and PCC (0.77 g, 3.57 mmol) in CH₂Cl₂ (12 mL). Separation of the mixture by HPLC (ethyl acetate – heptane, 1 : 9) gave successively 40 mg (20 %) of ketone Z-3 and 40 mg (20 %) of ketone E-3.

The IR spectral data and *R_f* values for ketone E-3 are virtually identical to those given above for ketone Z-3. ¹H NMR: 0.92 (d, *J* = 6.2 Hz, 3 H, CH₃); 1.1–1.8 (m, 5 H, CH, CH₂); 1.62 (br.s, 3 H, H₃C-14); 1.88 (d, *J* = 1.1 Hz, 3 H, H₃C-12); 2.04 (s, 3 H, CH₃CO); 2.05 (m, 2 H, HC-5); 2.14 (br.s, *J* = 1.1 Hz, 3 H, H₃C-15); 3.03 (br.s, 2 H, HC-8); 4.09 (m, 2 H, CH₂O); 5.23 (t, *J* = 7 Hz, 1 H, HC-6); 6.12 (br.s, 1 H, HC-10). ¹³C NMR: 16.31 (C-14); 19.31 (C-13); 20.61 (C-15); 20.96 (CH₃CO); 25.46 (C-5); 27.64 (C-12); 29.47 (C-3); 35.34 (C-2); 36.59 (C-4); 55.33 (C-8); 62.91 (C-1); 122.81 (C-10)**; 129.33 (C-6)**; 129.59 (C-7); 155.56 (C-11); 171.15 (CH₃CO); 199.33 (C-9).

Mass spectrum for ketones **3**, *m/z*: 280[M]⁺. High resolution mass spectrum: 280.20516; calculated for C₁₇H₂₈O₃: 264.20891.

* The chemical shifts for the atoms were assigned using ¹³C–¹H correlation spectroscopy. When the chemical shifts are compared to the data reported in Ref. 3 for similar data for the same atoms in a related ketone **4** (122.8 for C-6 and 129.2 for C-10), the validity of the assignments for the above centers made in that work seems doubtful.

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