

Studies on Natural Odoriferous Compounds

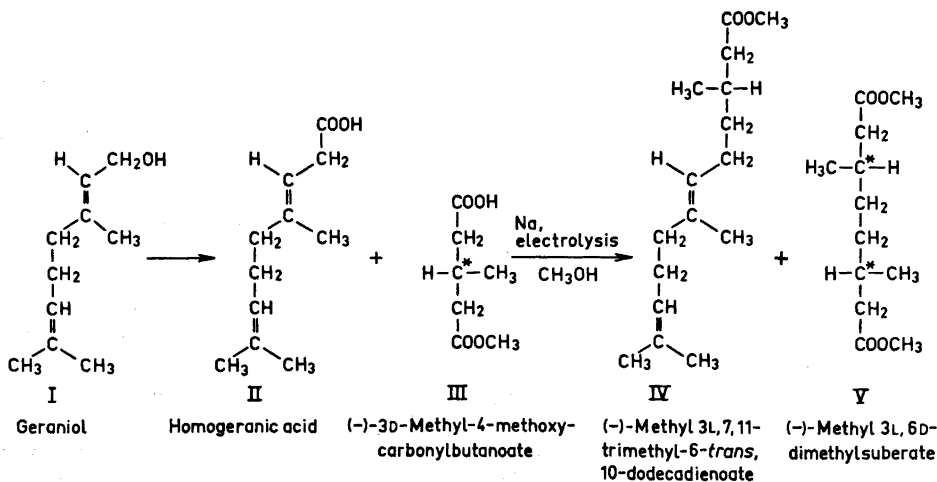
III. Synthesis of (+)- and (-)-3,7,11-Trimethyl-6-trans, 10-dodecadien-1-ol

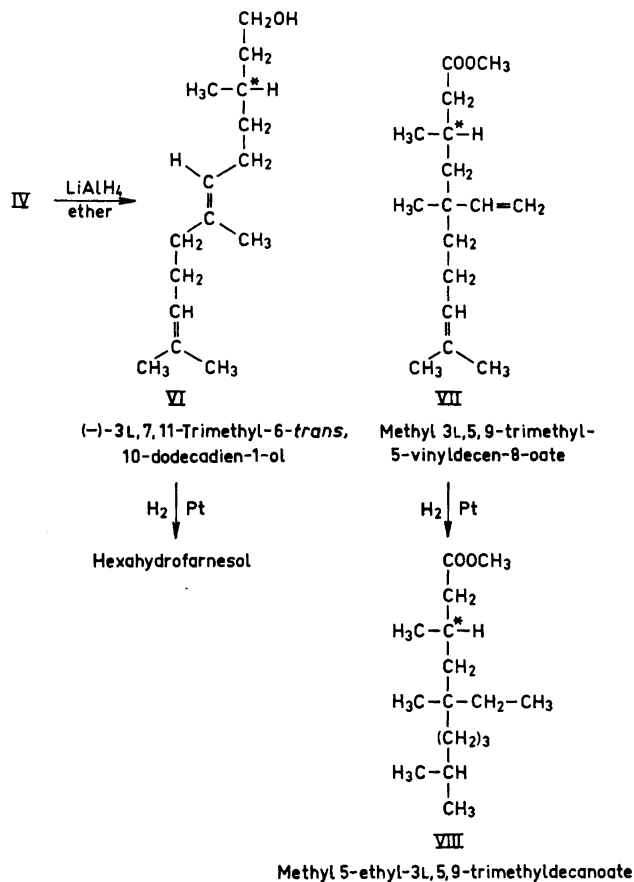
LARS AHLQUIST and STINA STÄLLBERG-STENHAGEN

Institute of Medical Biochemistry, University of Göteborg, S-400 33 Göteborg, Sweden

Terrestrol and its enantiomer have been synthesized by stereospecific routes from geraniol *via* homogeric acid. The chain of the latter acid is lengthened through mixed electrolysis with the enantiomeric methyl hydrogen 3-methylglutarates, whose absolute configurations are known. The enantiomeric methyl (-)-3L- and (+)-3D,7,11-trimethyldodeca-6-*trans*,10-dienoates thus prepared on reduction with lithium aluminium hydride give, respectively, terrestrol and its enantiomer.

It has been shown^{1,2} that the marking perfume of male bumble bees of the species *Bombus terrestris* L. contains, as the main component, (-)-2,3-dihydro-6-*trans*-farnesol ((-)-3L,7,11-trimethyl-6-*trans*,10-dodecadien-1-ol).





The present paper deals with the stereospecific synthesis of the enantiomers. Both enantiomers were needed for biological work.

It appeared that the simplest synthetic route would be that outlined in Chart 1. Geraniol (3,7-dimethylocta-2-*trans*,6-dien-1-ol) (I) is converted into homogeric acid (4,8-dimethylnona-3-*trans*,7-dienoic acid) (II) by the method of Barnard and Bateman.³ Mixed electrolysis of (II) with optically active methyl hydrogen 3-methylglutarate (III) of known absolute configuration⁴ would be expected to give the corresponding enantiomers of the methyl ester (IV) of 3,7,11-trimethyl-6-*trans*,10-dodecadienic acid, which on reduction with lithium aluminium hydride should give the desired enantiomeric 3,7,11-trimethyldodeca-6-*trans*,10-dien-1-ols (VI).

In practice, the purification needed at each step was difficult and time-consuming. Homogeric acid (I), prepared and purified by distillation only as described by Barnard and Bateman,³ was found to contain isomers and minor amounts of other compounds, and had to be extensively purified by

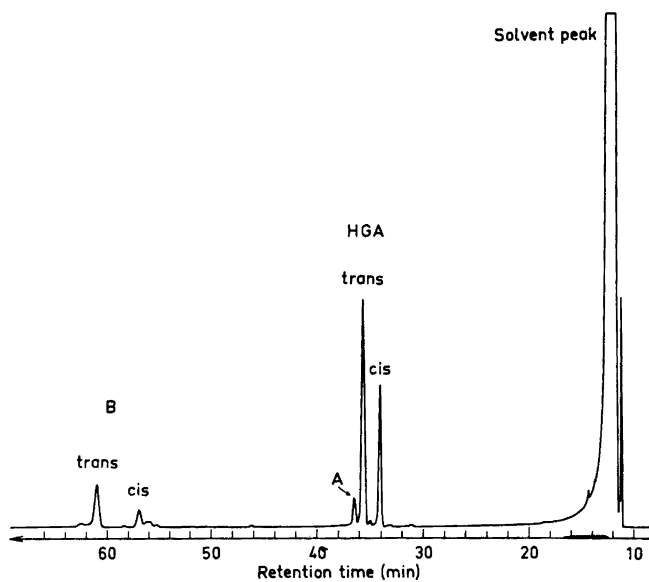


Fig. 1. Gas chromatograms of crude methyl ester of homogeric acid. Glass capillary column. Cf. Ref. 2.

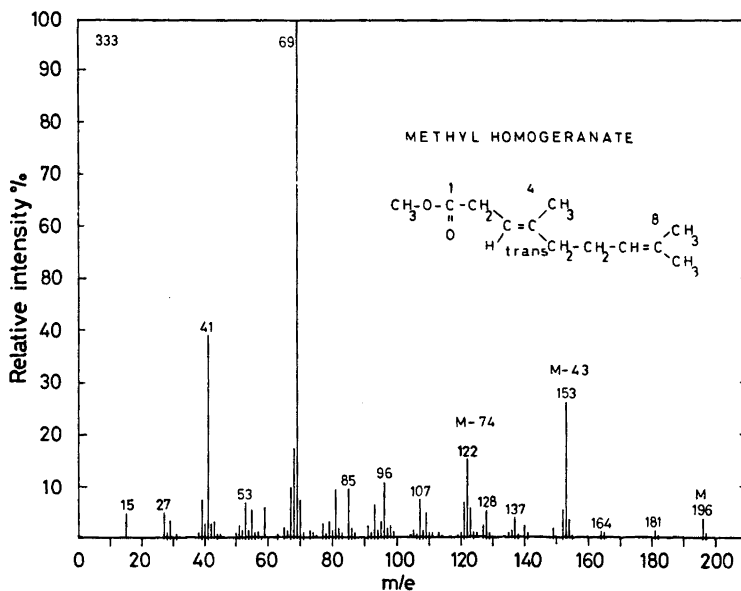


Fig. 2. Mass spectrum of methyl homogerate.

chromatography of the methyl ester on silicic acid and on silver nitrate impregnated silicic acid, respectively.

The gas chromatogram of the methyl ester of the crude acid (Fig. 1) indicated the presence of about 50 % of the desired *trans*-isomer, 25 % of the *cis*-isomer, and about 25 % of other compounds. The last mentioned group contains 3 major and several minor components.

The mass spectra of the methyl ester of *trans*-homogeranic acid (Fig. 2) and the *cis*-isomer (methyl 4,8-dimethylnona-3-*cis*,7-dienoate) are very much alike. Characteristic peaks occur at m/e 196 (molecule ion), m/e 122 ($=M-74$) and m/e 153 ($=M-43$). The base peak is due to an alkenyl ion of m/e 69, which is found in the mass spectra of acyclic sesquiterpenes.¹ After catalytic hydrogenation, the same mass spectrum was given by both esters.

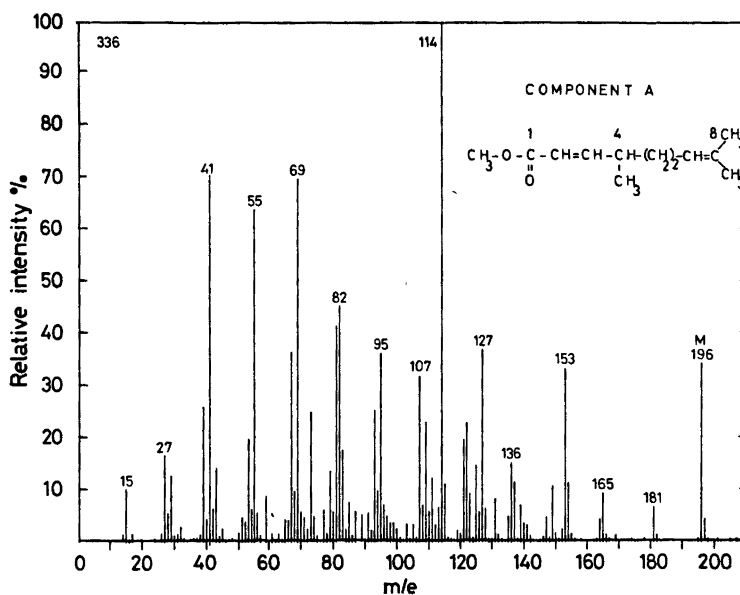
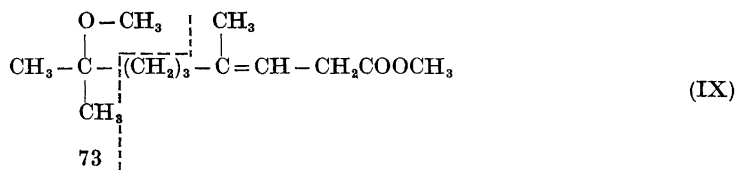


Fig. 3. Mass spectrum of component A.

The mass spectrum of component A (Fig. 3) is very different from that shown in Fig. 2. After catalytic hydrogenation, the saturated ester gave a mass spectrum identical with that of the hydrogenated methyl homogeranate, which shows that component A has the same carbon skeleton. The infrared spectrum of component A showed strong -C=C- stretching absorption at 1660 cm^{-1} , which points to the presence of double bond conjugation.^{5,6,7} A strong absorption band at 983 cm^{-1} and the absence of strong absorption at 910 cm^{-1} and 890 cm^{-1} seems to exclude the presence of a methylene end group. The mass spectra of the components *cis*-B and *trans*-B of Fig. 1 are very much alike, but they are quite different from those of component A and the methyl *cis*- and *trans*-homogeranates. The infrared spectrum of *trans*-B suggested that

the B-compounds possess a terminal isopropyl group (doublet of 1360, 1375 cm^{-1}).⁵ Although the molecular weight appeared to be 196, the mass spectrum of the hydrogenated ester showed a peak at m/e 215. This, together with the strong infrared band at 1085 cm^{-1} , suggested the presence of a methoxyl group which leads to a molecular weight of 230 for the hydrogenated ester, the peak at m/e 215 being an ion formed through loss of a methyl group. This would correspond to a molecular weight of 228 for the initial ester. The peak at m/e 196 is due to the ion formed through loss of methanol from the molecule ion, a process characteristic of monounsaturated methyl esters.⁸ On hydrogenation of a mixture of *cis*-B and *trans*-B, a single peak appeared in the gas chromatogram.

The available evidence suggests that the B-compounds are the geometrical isomers of methyl 8-methoxy-4,8-dimethylnona-3-enoate (IX), formed through addition of methanol to the 7,8 double bond of homogeric acid and its



cis-isomer during esterification. The formation of (IX) can be suppressed by using a low concentration of sulphuric acid and a short reaction time (< 10 min).

Homogeric acid is a β,γ -unsaturated acid and might thus be expected to give low yields in mixed Kolbe synthesis.⁹ The chromatographic analyses

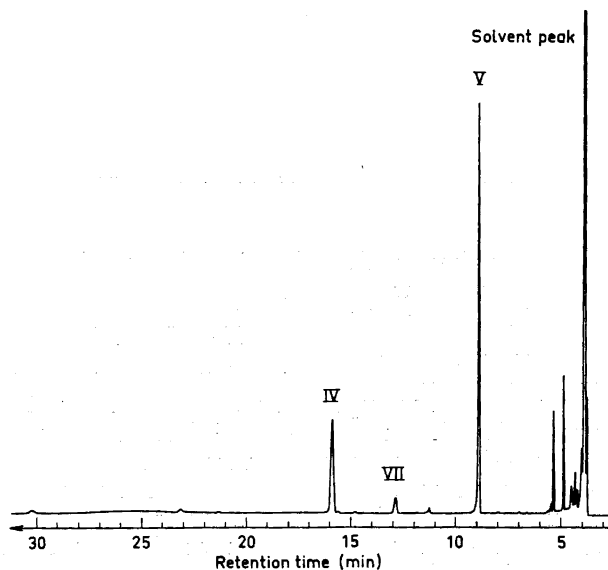


Fig. 4. Gas chromatogram of crude products from Kolbe electrosynthesis.

indicate that the yields of (IV) in the electrolysis were about 20 % of the theoretical, calculated on the homogeranic acid (II) used. A capillary gas chromatogram of a crude reaction product is shown in Fig. 4. The optical rotations of the 3,6-dimethylsuberates (V), obtained as by-products in the reaction, afford a convenient control of the optical purity of the material used.¹⁰

The component from the electrolysis mixture that was most difficult to remove from the desired product (IV) was component (VII) in the gas chromatogram shown in Fig. 4. The final purification had to be performed by preparative gas chromatography. The mass spectrum of (VII) (Fig. 5)

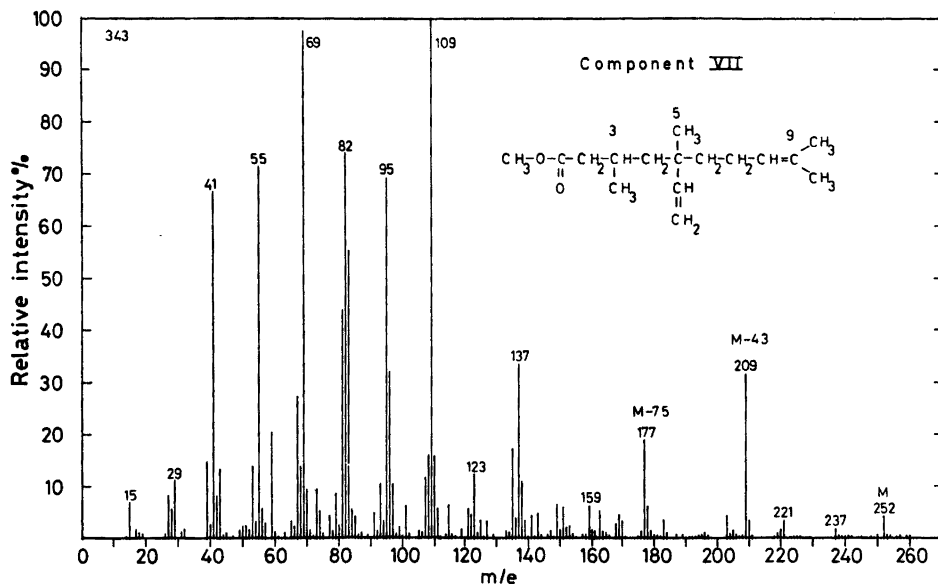


Fig. 5. Mass spectrum of component (VII).

differs significantly from that of (IV) (Fig. 6). After catalytic hydrogenation, the mass spectrum of Fig. 7 was obtained. The extremely small M^+ peak and the very strong peaks at m/e 227 ($=M-29$) and m/e 195 ($=M-29-32$) suggest the presence of an ethyl group attached to a quaternary carbon atom. The presence of a significant methoxycarbonyl type peak at $m/e=171$ ($=M-85$) and two hydrocarbon type peaks about m/e 140 to 141 is consistent with the structure (VIII) shown in Chart 1.¹¹ This indicates that the ester (VII) has the structure shown in Chart 1, and is the result of allylic rearrangement during the electro-synthesis. The appearance of the peak due to fraction (VII) in the gas chromatogram does not indicate that (VII) is a mixture of diastereoisomers, but the gas chromatogram of the hydrogenated product showed the presence of two diastereoisomers.

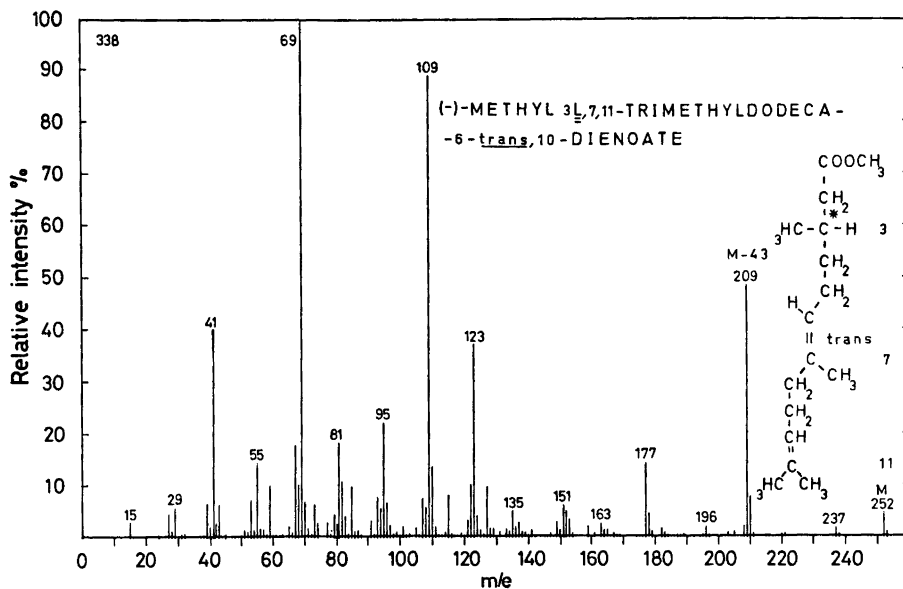


Fig. 6. Mass spectrum of component (IV).

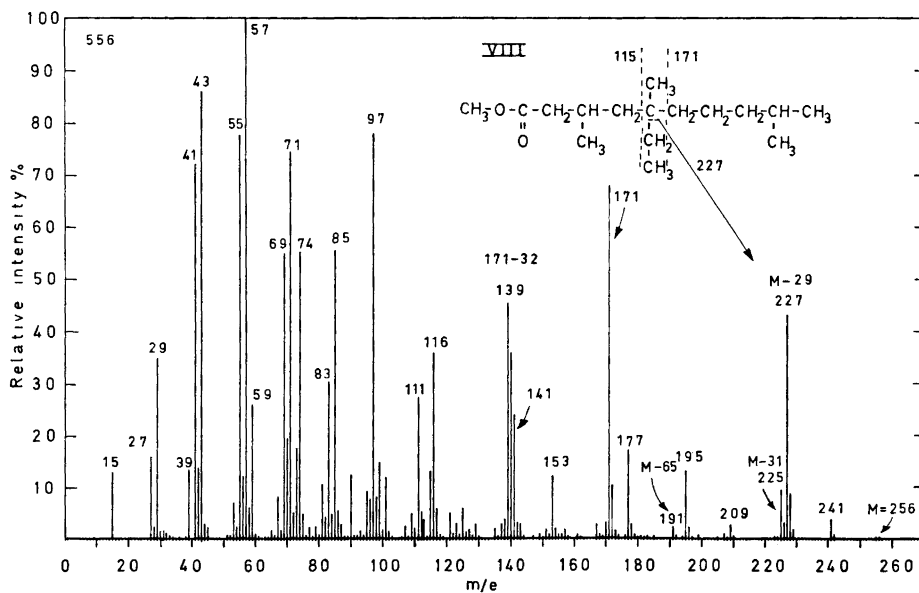


Fig. 7. Mass spectrum of compound (VIII), obtained by catalytic hydrogenation of (VII).

No difficulty was encountered in the reduction step. The enantiomeric 3,7,11-trimethyl-6-*trans*,10-dodecadien-1-ols had $[\alpha]_{5461}^{23} + 4.7 \pm 0.2^\circ$ and $-4.4 \pm 0.5^\circ$, respectively.

For comparison with the synthetic enantiomers, terrestrol was isolated from *B. terrestris* on a scale to give an amount of material sufficient for measuring the optical rotation.⁸ The rotation was $\alpha_{5461}^{23} - 0.018^\circ$ (chloroform: *c*, 3.5; *l*, 0.12; $[\alpha]_{5461}^{23} - 4.4^\circ$, which tallies with the rotation found for the synthetic *levo*-alcohol. The mass spectra and the infrared spectra of the synthetic enantiomers were identical with those of the racemic compound (see Ref. 1).

EXPERIMENTAL

Gas chromatographic analyses were performed with glass capillary columns constructed in the laboratory (*cf.* Ref. 2). Combined GC-MS analyses were carried out, using an instrument constructed in our laboratory. The electron energy was 70 eV. Infrared spectra were run on a Perkin Elmer model 157 instrument. Optical rotations were measured with a Bendix-Ericsson photoelectric polarimeter.

Homogeranic acid (II). Geraniol (I) (Fluka) (200 g) was converted into geranyl chloride as described by Barnard and Bateman.³ (The geraniol used contained about 25 % of citronellol, but no component with one double bond was present in the homogeranic acid obtained.) Sodium (26.7 g) was dissolved in dry ethanol (500 ml). A mixture of diethyl malonate (198 g) and dimethyl carbonate (250 ml) was added, and the resulting mixture was evaporated to dryness. Dimethyl carbonate (800 ml) was added. A solution of geranyl chloride (177 g of n_D^{20} 1.4710) was then added, with stirring and cautious heating, over a period of 1.5 h. After refluxing for 4 h, most of the solvent was evaporated. After acidification by means of dilute hydrochloric acid, the organic material was taken up in ether. Distillation gave 172 g of diethyl geranylmalonate, b.p. 118–124°, 0.2 torr. n_D^{20} 1.4615.

In the preparation of the α -oximinogeranylacetic acid, the original procedure of Barnard and Bateman was modified as follows:

Sodium (7.3 g) was dissolved in dry ethanol (180 ml). Diethyl geranylmalonate (90 g) was added at 0°C, followed by amyl nitrite (39 g) under further cooling with ice. After standing at room temperature for 45 min, the solvent was evaporated, the temperature not being allowed to exceed 30°C. To the residue was added crushed ice (120 g) and 25 % sulphuric acid (90 ml). After extraction with ether in the normal manner and evaporation of the solvent, the residue was hydrolyzed by adding a solution of potassium hydroxide (34 g) in water (70 ml) and ethanol (270 ml). These operations were performed at room temperature. After standing overnight, water was added, and the neutral product removed by extraction with ether. The water solution was acidified and extracted with ether in the normal manner. The residue was mixed with light petroleum (180 ml of b.p. 60–70°) and acetic anhydride (90 ml), and the mixture kept at 50°C for 1.5 h. The top layer was taken up in ether. Distillation gave 28.4 g of material, b.p. 80–87°, 0.7 torr. n_D^{25} 1.4667. The mass spectrum indicated a molecular weight of 163. The base peak was at *m/e* 69, and other significant peaks occurred at *m/e* 41, *m/e* = *M* – 15, and *m/e* = *M* – 40 (loss of $-\text{CH}_2-\text{C}\equiv\text{N}$). The data tally with those expected for geranyl cyanide. The cyanide (28.4 g) was hydrolyzed by refluxing with potassium hydroxide (28.4 g) and 450 ml of 80 % ethanol for 24 h. After extraction of neutral products with ether, the solution was acidified and extracted in the standard manner. The crude homogeranic acid (I) was distilled, giving 27.5 g of b.p. 102–103°C, 0.3 torr. n_D^{25} 1.4728 (Barnard and Bateman³ give n_D^{30} 1.4743). The acid was converted to methyl ester by means of methanol and sulphuric acid in the standard manner.

Methyl *trans*-homogeranate was isolated in pure form by repeated chromatography on silver nitrate impregnated silicic acid (Silicar CC-4, 100–200 mesh, Mallinckrodt) (*cf.* Ref. 1). The results are given in Table 1. Corresponding fractions from different runs were combined and rechromatographed on silicic acid. From 97 g of crude product was finally obtained 18.4 g of methyl *trans*-homogeranate in a purity of >99 %, as indicated

Table 1.

| Fraction number | Eluent: light petr.(40–60°): ethylether | Weight mg | Composition % | Mol. weight | Strongest peaks |
|-----------------|---|-------------|---|-------------|---|
| 8–11 | 20 : 1 | 325 | 80 component A (Fig. 1) 20 other components | 196 | 114, 41, 69, 55, 82 |
| 12–15 | 4 : 1 | 679 | mixture of several components | | |
| 16–20 | 4 : 1 | 1420 | 90 methyl <i>cis</i> -homogeranate 10 other components | 196 | 69, 41, 153, 122, 68 |
| 21–23 | 4 : 1 | 1825 | 20 methyl <i>cis</i> -homogeranate 78 <i>trans</i> -homogeranate 2 component B (Fig. 1) | 196 228 | 69, 41, 153, 68, 122 73, 140, 81, 98, 85 |
| 24–27 | 4 : 1 | 2186 | 5 methyl <i>cis</i> -homogeranate 91 <i>trans</i> homogeranate 4 component B | | |
| 28–32 | 4 : 1 | 1392 | 1 methyl <i>cis</i> -homogeranate 59 <i>trans</i> -homogeranate 40 component B | | |
| 33–42 | 4 : 1 | 876 8703 | 20 methyl <i>trans</i> -homogeranate 80 component B | | |

by gas chromatography, using a SE-30 capillary column. *trans*-Homogeranic acid was prepared by hydrolysis of the methyl ester (5 g) with potassium hydroxide (5 g) in water (5 ml) and 96 % ethanol (20 ml). After refluxing for 1 h, the free acid was isolated in the standard manner.

(–)-Methyl 3*L*,7,11-trimethyl-6-*trans*,10-dodecadienoate (IV). *trans*-Homogeranic acid (II) (3.5 g) and D(–)-methyl hydrogen 3-methylglutarate (III) (14 g)⁴ were mixed. To a solution of sodium (0.21 g) in dry methanol (100 ml) was added one third of the mixture just described, and electrolysis was carried out between platinum electrodes (cf. Ref. 6). When the pH had risen to 7, new additions of the mixture were made, finally followed by 2 g of (III). The electrolysis mixture was worked up as described in Ref. 6. The neutral products were subjected to gas chromatography on a capillary column (Fig. 4). The separation of components (IV) and (VII) on silicic acid was difficult, and preparative gas chromatography had to be resorted to. The stationary phase was 15 % OV-1 on Chromosorb WAW DMCS, 60–80 mesh, with nitrogen as carrier gas. The overall yield of pure (IV), calculated on (II), was about 8 % of the theoretical. *levo*-(IV) was a colourless oil of $\alpha_{5461} -0.061^\circ$ (chloroform: *c*, 7.9; *l*, 0.1); $[\alpha]_{5461}^{23} -4.7^\circ$. The optical rotation of the (+)-methyl 3,6-dimethylsuberate (fraction V, Fig. 4) was $\alpha_D^{23} +10.36^\circ$ (in substance).

(–)-3*L*,7,11-Trimethyl-6-*trans*,10-dodecadien-1-ol (VI). Lithium aluminium hydride (0.1 g) was dissolved in dry ether, and 0.199 g of a solution of *levo*-(IV) in 2 ml dry, ether was added dropwise. When all had been added, the mixture was left at room temperature for 20 min. The mixture was cooled with ice, and water and dilute sulphuric acid added. The alcohol was taken up in ether, and the ether solution was washed with water and dried. Evaporation of the solvent gave 0.173 g of *levo*-(VI), $\alpha_{5461}^{23} 0.092^\circ$ (chloroform; *c*, 20; *l*, 0.1); $[\alpha]_{5461}^{23} -4.4^\circ$.

(+)-3D,7,11-Trimethyl-6-trans,10-dodecadien-1-ol (dextro-(VI)) was prepared on a completely analogous manner, starting with L(+)-methyl hydrogen 3-methylglutarate. (-)-Methyl 3,6-dimethylsuberate from the electrolysis had $\alpha_D^{25} - 10.32^\circ$. (+)-Methyl 3D,7,11-trimethyl-6-trans,10-dodecadienoate was reduced to dextrorotatory alcohol of $\alpha_{5461}^{25} + 0.097^\circ$ (chloroform; c, 10.3: l, 0.2); $[\alpha]_{5461}^{25} + 4.7^\circ$.

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