165. Synthesis of (*R*)- and (*S*)-4-Methyl-6-2′-methylprop-1′-enyl-5,6-dihydro-2*H*-pyran (Nerol oxide) and Natural Occurrence of its Racemate

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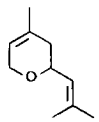
Summary

Following a known procedure, a mixture of (−)-(2*S*,3*R*)- and (+)-(2*R*,3*R*)-2,3-epoxy-citronellols (**5**) was prepared from (−)-(*R*)-linalool (**3**) *via* epoxy alcohol **4** and then reduced to (−)-(*R*)-3-hydroxy-citronellol (**6**). Sensitized photooxygenation of (−)-(*R*)-diol **6** led in part to (−)-(*R*)-triol **8** which was cyclodehydrated by dilute acid to a mixture of diastereoisomeric tetrahydropyran-4-ols **9** and **10**. Dehydration of hydroxy ethers **9** and **10** afforded (−)-(*S*)-nerol oxide (**11**) and (+)-(*R*)-nerol oxide (**12**), respectively, with an optical purity of 91%. Nerol oxide isolated from Bulgarian rose oil (0.038%) proved to be racemic. These results shed some light on the formation of nerol oxide in plants.

Nerol oxide (**1**) is a valuable base material in perfumery [1] [2] and occurs naturally as an ingredient of Bulgarian rose oil [3] and grape juice [4]. Nerol (**2**) was the starting material for the industrial manufacture of the racemic dihydropyran derivative **1** [5]. However, the formation of nerol oxide (**1**), which has a



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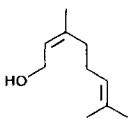

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chiral centre, in plants has remained a mystery. A knowledge of the absolute configuration and optical purity of **1** would allow conclusions to be drawn about its biochemical formation, but so far the optical rotation of the natural ether **1** is unknown. We have now tackled the solution of this problem on two experimental planes. First, we have isolated ether **1** from natural sources, and we have also unambiguously synthesized the enantiomeric nerol oxides **11** and **12**.

The optically active ethers **11** and **12** were prepared from (−)-(*R*)-linalool (**3**) by conversion to its monoepoxide **4** according to *Sharpless & Michaelson* [6] [7]

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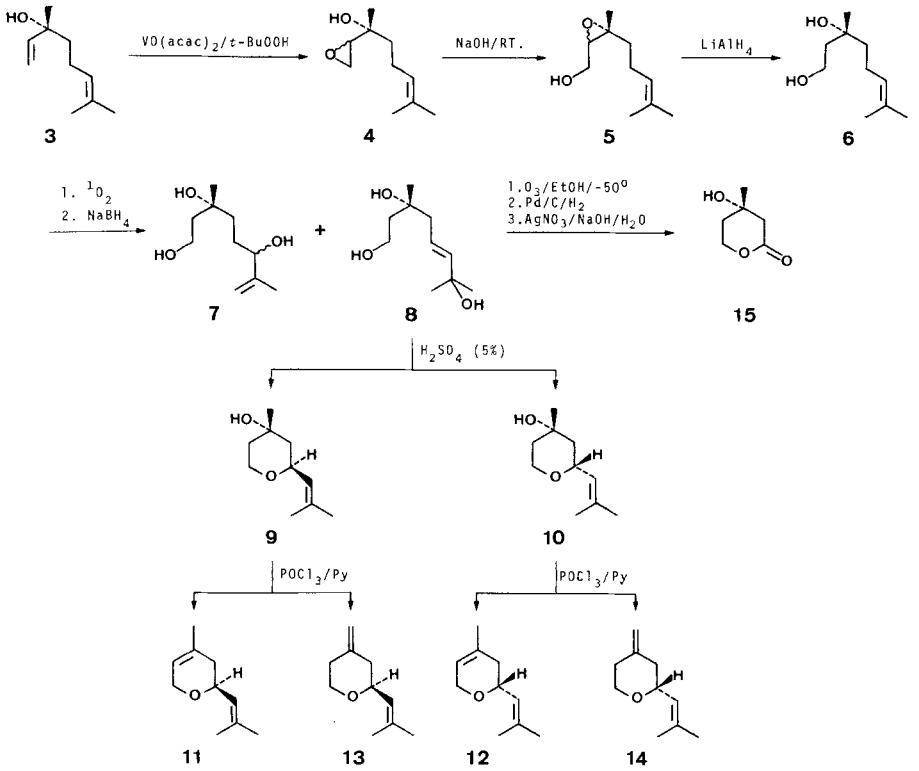
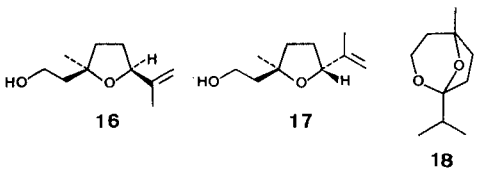


and base-catalyzed isomerization [8] of the epoxide. An equilibrium mixture of the epoxy alcohols **4** and **5** in a ratio of 5:95 was thus obtained. The erythro and threo isomers (2:1) of **5** were separated by means of preparative gas chromatography. Reduction of the epoxide mixture **5** with $LiAlH_4$ gave diol **6**[2]). Photooxygenation of **6** and reduction of the resulting allyl hydroperoxides with $NaBH_4$ afforded a 55:45 mixture of triols **7** and **8** which were easily separated by gas chromatography. This result is all the more surprising as the treatment of the comparable β-citronellol with $^1O_2$ results in a reversed ratio of 45:55 of secondary and tertiary allyl hydroperoxides [9]. When 5% sulfuric acid is added to the mixture of triols **7** and **8** at room temperature, in analogy to the rose oxide synthesis [9], only triol **8** was attacked and converted into a mixture of the diastereoisomeric hydroxy ethers **9** and **10**, separable by chromatography on SiO_2. On stron-



[2]) Diol **6** was isolated from Bulgarian rose oil (0.92‰) by one of the authors (*E. D.*, 1970). No data relating to its optical rotation are available.

ger acid treatment, triol **7** was converted into the cyclic ethers **16** to **18**. Whereas the diastereoisomeric hydroxy tetrahydrofuran derivatives **16** and **17** were formed with retention of optical activity, the cyclic acetal **18** was formed as racemate. Treatment of the individual diastereoisomeric hydroxy ethers **9** and **10** with $POCl_3$ in pyridine afforded the enantiomers of nerol oxide **11** and **12**, respectively, in addition to the double bond isomeric ethers **13** and **14**, the ratio of endocyclic to exocyclic compounds being 9:1. Oxide **13** was exclusively formed when the acetate of **9** was pyrolyzed at 440°.

The critical steps in the preparation of (−)-(*S*)-nerol oxide (**11**) and of (+)-(*R*)-nerol oxide (**12**) from (−)-(*R*)-linalool (**3**) begin with the conversion of epoxy alcohol **4** into diol **6** *via* **5**. In order to determine the optical yield of this reaction sequence (−)-(*R*)-triol **8** was exhaustively ozonized, the ozonization product reduced with H_2 on Pd/C and the reduction product oxidized in a basic medium. Thus, there was obtained 35% of (+)-(*S*)-mevalo lactone (**15**), $[\alpha]_D^{20} = +21°$, corresponding to an optical purity of 91%, based on the highest value observed so far in an enantiomeric mevalo lactone ($[\alpha]_D^{20} = -23°$) [10]. From this result an absolute rotation of $[\alpha]_D^{20} = -22.5°$[3]) can be calculated for linalool ($[\alpha]_D^{20} = -20.5°$), showing that the formation of diol **6** from (−)-(*R*)-linalool (**3**) occurs with complete retention of configuration. The dehydration of the pure diastereoisomers **9** and **10** to the enantiomeric nerol oxides **11** and **12** appears to take place regioselectively, independently of their configuration and without racemization. (−)-(2*S*,4*S*)-4-Methyl-2-2′-methylprop-1′-enyl-tetrahydropyran-4-ol (**9**) yielded (−)-(*S*)-nerol oxide (**11**) with $[\alpha]_D^{20} = -105.1°$, whereas the diastereoisomeric (+)-(2*R*,4*S*)-compound **10** was converted into (+)-(*R*)-nerol oxide (**12**) with $[\alpha]_D^{20} = +106°$.

In order to check the optical activity of natural nerol oxide [3] 1019 g of commercial Bulgarian rose oil were subjected to four fractional distillations combined with four chromatographic separations on silica gel, affording 2.42 g of an enriched mixture containing about 10% of nerol oxide (including other, less interesting fractions, this corresponded to a total content of nearly 0.038% of nerol oxide in the rose oil). Four further separations by GC. and liquid chromatography on silica gel/$AgNO_3$ 9:1 finally afforded 15 mg of nerol oxide (**1**) (99% pure by GC.). This compound, identified by its ^{1}H-NMR. and mass spectra, was racemic.

The results of these investigations lead to the assumption that nerol oxide is not formed directly in the plant but from a precursor which is pre-formed to a large extent. Nerol (**2**) is a potential precursor, and $^1O_2$ might act as an active agent for the introduction of a second allylic hydroxyl group; its reaction with nerol (**2**) has been investigated [1a]. Assuming that the diastereoisomers of (−)-rose oxide are formed from (−)-citronellol by photooxygenation [9] [12], it is conceivable that (±)-nerol oxide (**1**) is formed in a similar manner from nerol (**2**) in Bulgarian rose oil[4]).

[3]) The highest values measured for optically active linalool were $[\alpha]_D^{20} = -21.53°$; lit. [11] = +21.62°.

[4]) A racemization during the formation of the natural product is improbable. The optical rotation of a 10% solution of (−)-(*S*)-nerol oxide (**11**) in ethanol or chloroform remained unchanged after 24 h at room temperature, even in the presence of catalytic amounts of BF_3 [13].

Sensory evaluation. – The olfactory properties of the enantiomeric nerol oxides **11** and **12** are comparable to those of the diastereoisomeric rose oxides as regards tonality and strength [14]. (*S*)-Oxide **11** is dominated by a powerful greenish-spicy note of the geranium-type corresponding to the odour of (–)-*cis*-rose oxide [15]. The odour profile of (*R*)-oxide **12** with its striking greenish-floral note is less complex than that of (*S*)-oxide **11** and is rather similar to the diastereoisomeric (+)-rose oxides [15] in tonality and strength. Racemic nerol oxide **11/12** is dominated by the odour profile of (*S*)-enantiomer **11** which is more interesting from the perfumer's point of view.

Although a rose oxide-like odorous character is recognizable to a certain extent in the enantiomeric exo-cyclic double bond isomers **13** and **14**, this odour is less differentiated than in the enantiomeric nerol oxides **11** and **12**. (*S*)-Oxide **13**, which has a floral note of greenish vegetable-like tonality, differs only slightly from (*R*)-oxide **14**. Racemate **9/10** has a fragrance similar to that of the rose oxides. Whereas the (2*S*)-compound **9** has a powerful spicy note, diastereoisomer **10** presents a striking green note with a floral nuance. As in the case of the enantiomeric rose oxides, the nerol oxides **11** and **12** and their double bond isomers **13** and **14**, it was observed that among the alcohols the (2*S*)-derivative **9** has a more powerful odour than the (2*R*)-compound **10**.

Experimental Part

General. – Specific rotations $[\alpha]_D^{20}$ (for solutions) and rotations α_D^{20} (for neat liquids) were measured in a 1 dm tube on the models Polatronic 1 *(Schmidt & Haensch)* and *Perkin-Elmer* 141 polarimeter. The infrared (IR). spectra were taken on a *Perkin-Elmer* 125 instrument; characteristic maxima in cm^{-1}. ^1H-NMR. spectra were recorded on a *Varian* A-60 and/or on a *Bruker* HFX-90/15″ instrument, using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are expressed in ppm (δ scale) downfield from TMS as internal standard; abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, br. = broad, *J* = spin-spin coupling constant (Hz). Mass spectra (MS.) were measured on an *Atlas* CH_4 spectrometer, inlet temperature *ca.* 150°, electron energy *ca.* 70 eV; the molecular ions (M^+) and fragment ions are given as *m/z* with relative peak intensities in % of the most abundant peak. Gas chromatography (GC.) was performed on *Varian* Aerograph instruments (models 1700 and 2700), carrier gas: He (~40 ml/min); using Carbowax 20 M or SE-30, 10% on Chromosorb W 95, 60–80 mesh (4 mm × 3 m). RT. = room temperature.

1. *(–)-(2S,3R)- and (–)-(2R,3R)-1,2-Epoxy-3,7-dimethyloct-6-en-3-ol* (**4**) [6] [7]. A stirred mixture of 5 g of vanadium acetylacetonate *(Fluka)* and 100 g of (*R*)-linalool (**3**) ($[\alpha]_D^{20} = -20.5°$; $c = 10$, $CHCl_3$) in 700 ml of toluene was heated to 80°, 120 g of *t*-butylhydroperoxide (79% peroxide content) were added dropwise over 2 h, and stirring was continued for 5 h. After cooling, the mixture was washed with hydrogensulfite-solution, hydrogencarbonate-solution and water, then concentrated and the residue distilled. Yield: 74 g (67% of **4**), b.p. 70–80°/0.01 Torr. GC. showed the (2*S*,3*R*)- and the (2*R*,3*R*)-isomers of **4** in a ratio of 3:1. The pure diastereoisomers were obtained by preparative GC.

(2*S*,3*R*)-**4**: $[\alpha]_D^{20} = -4.5°$ ($c = 9$, $CHCl_3$). – IR. ($CDCl_3$): 3550, 1215. – ^1H-NMR.: 1.18 (*s*, $H_3C-C(3)$); 1.65 (*s*, $H_3C-C(7)$); 1.7 (*s*, $H_3C-C(7)$); 2.7 (*m*, $H_2C(1)$); 2.79 (*t*, $J = 3.5$, $H-C(2)$); 5.12 (*m*, $H-C(6)$). – MS.: 170 (0, M^+), 168 (6), 152 (7), 137 (9), 125 (12), 109 (32), 97 (18), 82 (54), 69 (56), 55 (93), 43 (100), 27 (26).

(2*R*,3*R*)-**4**: $[\alpha]_D^{20} = -24.8°$ ($c = 2.5$, $CHCl_3$). – IR. ($CDCl_3$): 3550. – ^1H-NMR.: 1.3 (*s*, $H_3C-C(3)$); 1.63 (*s*, $H_3C-C(7)$); 1.7 (*s*, $H_3C-C(7)$); 2.8 (*m*, $H_2C(1)$ and $H-C(2)$); 5.12 (*m*, $H-C(6)$). – MS.: 170 (5, M^+), 168 (3), 152 (4), 137 (5), 123 (10), 109 (26), 97 (19), 82 (50), 67 (38), 55 (100), 43 (93), 27 (19).

2. *(–)-(2S,3R)- and (+)-(2R,3R)-2,3-Epoxy-3,7-dimethyl-oct-6-en-1-ol* (= 2,3-epoxycitronellol, **5**) [8]. A mixture of 242 g of epoxide **4** and 1.5 l of 0.5N NaOH were vigorously stirred at RT. Equilibrium was reached after 6 h (5% of **4** and 95% of **5**). After extraction with ether, the extract was washed until neutral, concentrated, and the residue distilled. Yield: 225 g (93% of **5**), b.p. 80–90°/0.1 Torr. GC. showed the (2*S*,3*R*)- and (2*R*,3*R*)-isomers of **5** in a ratio of 2:1. The pure diastereoisomers were obtained by preparative GC.

(2S,3R)-**5**: $[\alpha]_D^{20} = -21°$ ($c = 6$, $CHCl_3$). – IR. ($CDCl_3$): 3500. – ^{1}H-NMR.: 1.32 (*s*, $H_3C-C(3)$); 1.62 and 1.68 (*s*, $2\,H_3C-C(7)$); 2.95 (*t*, $J = 5.5$, H–C(2)); 3.75 (*m*, $H_2C(1)$); 5.1 (*m*, H–C(6)). – MS.: 170 (1, M^+), 152 (4), 109 (21), 82 (100), 69 (73), 41 (86), 29 (26).

(2R,3R)-**5**: $[\alpha]_D^{20} = +4°$ ($c = 4.9$, $CHCl_3$). – IR. ($CDCl_3$): 3480. – ^{1}H-NMR.: 1.27 (*s*, $H_3C-C(3)$); 1.6 and 1.68 (*s*, $2\,H_3C-C(7)$); 2.97 (*t*, $J = 5.5$, H–C(2)); 3.73 (*m*, $H_2C(1)$); 5.1 (*m*, H–C(6)). – MS.: 170 (0.5, M^+), 152 (1), 109 (30), 82 (100), 67 (85), 55 (41), 41 (99), 29 (30).

3. (–)-*(R)-3,7-Dimethyloct-6-en-1,3-diol* (= 3-hydroxycitronellol, **6**). A solution of 223 g of epoxide **5** in 1 l of ether was added dropwise to a stirred solution of 30 g of $LiAlH_4$ in 500 ml of abs. ether. After completion of the addition the reaction mixture was refluxed for 1 h. After cooling, water (30 ml), 15% sodium hydroxide solution (30 ml) and water (150 ml) were added dropwise. The precipitate was filtered off, washed 3 times with ether, and the combined solvent phases were concentrated. The residue was distilled on a 20 cm *Vigreux* column. A fraction (171 g, 76%) with b.p. 100–107°/0.1 Torr consisted of diol **6**. $\alpha_D^{20} = -4°$. – IR. ($CDCl_3$): 3410. – ^{1}H-NMR.: 1.23 (*s*, $H_3C-C(3)$); 1.63 and 1.7 (*s*, $2\,H_3C-C(7)$); 3.9 (*t*, $J = 5.5$, $H_2C(1)$); 5.15 (*m*, H–C(6)). – MS.: 172 (0, M^+), 154 (30), 121 (43), 109 (69), 69 (70), 43 (100).

4. (–)-*(3R,6R)- and (3R,6S)-3,7-Dimethyloct-7-ene-1,3,6-triol* (**7**) *and* (–)-*(R,E)-3,7-dimethyloct-5-ene-1,3,7-triol* (**8**). A solution of 165 g of diol **6** in 3.5 l of ethanol was photooxidized in the presence of 2 g of Bengal rose and 1 g of sodium acetate [9]. After absorption of 22 l of O_2 (92%) 35 g of $NaBH_4$ were added to the mixture. After the usual treatments there were obtained 161 g (89.5%) of a mixture of triols **7** and **8**. For analytical purpose **7** and **8** were purified by preparative GC.

Triol **7**: $[\alpha]_D^{20} = -0.7°$ ($c = 15$, $CHCl_3$). – ^{1}H-NMR.: 1.2 (*s*, $H_3C-C(3)$); 1.7 (br. *s*, $H_3C-C(7)$); 3.9 (*m*, $H_2C(1)$ and H–C(6)); 4.8 and 4.9 (2*s*, $H_2C(8)$). – MS.: 188 (0, M^+), 85 (70), 83 (100), 47 (25).

Triol **8**: $[\alpha]_D^{20} = -2.4°$ ($c = 4.2$, $CHCl_3$). – ^{1}H-NMR.: 1.21 (*s*, $H_3C-C(3)$); 1.28 (*s*, $2\,H_3C-C(7)$); 3.83 (*m*, $H_2C(1)$); 5.67 (*m*, H–C(5) and H–C(6)). – MS.: 188 (0, M^+), 172 (27), 144 (32), 129 (36), 91 (15), 67 (15), 55 (19), 43 (100).

5. (–)-*(2S,4S)- and* (+)-*(2R,4S)-4-Methyl-2-2'-methylprop-1'-enyl-tetrahydropyran-4-ol* (**9** and **10**). A solution of 60 g of triol mixture **7**/**8** in 1 l of 5% aq. sulfuric acid was stirred for 2 h at RT., then extracted 3 times with ether. The combined ether phases were washed with aq. $NaHCO_3$-solution and brine until neutral, concentrated and distilled. Yield: 17 g of **9** and **10**, b.p. 82–100°/0.1 Torr. The aqueous acid phase containing triol **7** was used for the preparation of **16**, **17** and **18**. Pure hydroxy ethers **9** and **10** were obtained by chromatography on silica gel with ether.

Hydroxyether **9**: $[\alpha]_D^{20} = -54°$ ($c = 11.3$, $CHCl_3$). – IR. (film): 3450. – ^{1}H-NMR.: 1.23 (*s*, $H_3C-C(4)$); 1.89 (br. *s*, $2\,H_3C-C(2')$); 3.84 (*m*, $H_2C(6)$); 4.37 (*d*, *t*, $J_1 = 5$, $J_2 = 8$, H–C(2)); 5.14 (*d*, $J = 8$, H–C(1')). – MS.: 170 (41, M^+), 155 (100), 137 (35), 85 (75), 71 (99), 43 (90).

Hydroxyether **10**: $[\alpha]_D^{20} = +54.3°$ ($c = 11$, $CHCl_3$). – IR. (film): 3450. – ^{1}H-NMR.: 1.33 (*s*, $H_3C-C(4)$); 1.7 (br. *s*, $2\,H_3C-C(2')$); 3.5 (*m*, H–C(2)); 3.95 (*m*, $H_2C(6)$); 5.15 (*d*, $J = 8$, H–C(2')). – MS.: 170 (30, M^+), 155 (100), 137 (30), 85 (78), 71 (93), 58 (25), 43 (98), 29 (21).

6. (–)-*(S)-Nerol oxide* (**11**). To an ice-cold solution of 2.6 g of hydroxy ether **9** in pyridine (15 ml) were added dropwise 2.5 ml of $POCl_3$. After 3 h at RT. the solution was diluted with ether and water and washed until neutral with dil. sulfuric acid, $NaHCO_3$-solution and brine. Concentration yielded 1.8 g of a mixture of 75% of nerol oxide (**11**) and 25% of (*S*)-4-methylidene-2-2'-methylprop-1'-enyl-tetrahydropyran (dehydro-rose oxide, **13**). Pure oxide **11** was obtained by prep. GC. $[\alpha]_D^{20} = -105.1°$ ($c = 10.3$, $CHCl_3$). – ^{1}H-NMR.: 1.7 (br. *s*, $H_3C-C(4)$ and $2\,H_3C-C(2')$); 4.15 (*m*, $H_2C(2)$ and H–C(6)); 5.21 (*m*, H–C(1')); 5.4 (br. *s*, H–C(3)). – MS.: 152 (11, M^+), 137 (1), 109 (8), 96 (11), 83 (75), 68 (100), 53 (23), 41 (36), 27 (17).

7. (–)-*(S)-4-Methylidene-2-2'-methylprop-1'-enyl-tetrahydropyran* (**13**). To 2.7 g of hydroxy derivative **9** in dimethylaniline (7 ml) 1.2 ml of acetic anhydride and 2 ml of acetyl chloride were added dropwise with ice-cooling and stirring. The solution was then heated to 50° for 5 h. After cooling, it was taken up in ether, washed (dil. H_2SO_4-solution, $NaHCO_3$, brine) and concentrated to yield 3.7 g of (2*S*,4*S*)-4-methyl-2,2'-methylprop-1'-enyl-tetrahydropyran-4-yl acetate. For analysis a small amount was distilled (bulb to bulb). $[\alpha]_D^{20} = -10°$. – IR. (film): 1730. – ^{1}H-NMR.: 1.46 (*s*, $H_3C-C(4)$); 1.68 (*t*, $J = 1$, $2\,H_3C-C(2')$); 2.01 (*s*, $H_3COOC-C(4)$); 3.75 (*m*, $H_2C(6)$);

4.2 (*m*, H–C(2)); 5.12 (*m*, H–C(1')). – MS.: 212 (0, M^+), 152 (55), 137 (100), 109 (6), 85 (46), 69 (35), 43 (68).

The ester was pyrolyzed in a 3 m column in a N_2 stream at 440°. The pyrolysate was taken up in ether, washed (dil. NaOH-solution, brine), concentrated and distilled (bulb to bulb, b.p. 100° (bath temp.)/8 Torr), to yield 1.1 g of pure **13**. $[\alpha]_D^{20} = -22.2°$ ($c = 9$, $CHCl_3$). – IR. ($CDCl_3$): 910. – ^{1}H-NMR.: 1.7 (neat *m*, $2\,H_3C{-}C(2')$); 3.2–4.2 (*m*, $H_2C(6)$ and H–C(2)); 4.72 (*s*, $H_2C{=}C(4)$); 5.2 (*m*, H–C(1')). – MS.: 152 (67, M^+), 137 (100), 107 (20), 85 (86), 67 (75), 53 (28), 41 (44).

8. (+)-(R)-*Nerol oxide* (**12**) *and* (+)-(R)-*4-methylidene-2-2'-methylprop-1'-enyl-tetrahydropyran* (**14**). $POCl_3$/pyridine was added to 3.3 g of hydroxy derivative **10** as described in experiment 6. After the usual treatments 1.2 g of a mixture (9:1) of compounds **12** and **14** were obtained. Both isomers were obtained in a pure state by prep. GC. *Oxide* **12**: $[\alpha]_D^{20} = +106°$ ($c = 9.7$, $CHCl_3$). *Oxide* **14**: $[\alpha]_D^{20} = +28.5°$ ($c = 10$, $CHCl_3$). The spectra were identical with those of compounds **11** and **13**, respectively.

9. (+)-(S)-*Mevalolactone* (**15**). A solution of 10 g of triol **8** in ethanol (200 ml) was ozonized at −50° (2.6 g of O_3). The crude ozonization mixture was hydrogenated in the presence of Pd/C (5%). The calculated amount of H_2 was absorbed in 30 min. After concentration 8.5 g of a crude product were obtained which were directly added to a solution of 33 g of $AgNO_3$ in water (100 ml) and ethanol (30 ml). To this mixture, 10 g of NaOH in water (150 ml) were added dropwise with stirring. After standing overnight, the precipitate was removed by filtration and washed 5 times with ether and the aq. phase was acidified (hydrochloric acid). Continuous extraction with CH_2Cl_2 gave 5.5 g of an extract which, after chromatography on 100 g of silica gel in CH_2Cl_2/acetone 9:1 yielded 2.2 g of pure mevalolactone **16** (32%); b.p. 150° (bath temp.)/0.1 Torr. $[\alpha]_D^{20} = +21°$ ($c = 11.7$, ethanol); [10]: $[\alpha]_D^{20} = +22.8°$ ($c = 10$, ethanol); [16]: $[\alpha]_D^{20} = +21.8°$/ethanol. – IR. ($CDCl_3$): 3400, 1725. – ^{1}H-NMR.: identical pattern to [17]. – MS.: 130 (0, M^+), 112 (2), 82 (4), 71 (19), 59 (54), 43 (100), 31 (42), 28 (60).

10. (+)-(2R,5S)- *and* (−)-(2R,5R)-*2-2'-Hydroxyethyl-5-isopropenyl-2-methyl-tetrahydrofuran* (**16** and **17**). One half of the aq. acidic phase obtained in the preparation of **9** and **10** (experiment 5) was continuously extracted with CH_2Cl_2, then concentrated. The residual triol **7** (5 g) was heated in a mixture of petroleum ether and toluene in a water separator with addition of 0.5 g of *p*-toluenesulfonic acid. After 10 h **7** had completely disappeared. Washing to neutrality and concentration gave two products which were separated by preparative GC.

Hydroxyether **16**: $[\alpha]_D^{20} = +11.7°$ ($c = 10.7$, $CHCl_3$). – IR. ($CDCl_3$): 3500. – ^{1}H-NMR.: 1.27 (*s*, $H_3C{-}C(2)$); 1.7 (*d*, $J = 1$, $H_3C{-}C(1')$); 3.8 (*m*, CH_2OH); 4.4 (*m*, H–C(5)); 4.78 and 5.0 (2 br. *s*, $H_2C(2')$). – MS.: 170 (8, M^+), 155 (6), 137 (5), 125 (49), 107 (13), 84 (22), 67 (47), 55 (21), 43 (100).

Hydroxyether **17**: $[\alpha]_D^{20} = -32°$ ($c = 11.3$, $CHCl_3$). – IR. ($CDCl_3$): 3500. – ^{1}H-NMR.: 1.27 (*s*, $H_3C{-}C(2)$); 1.7 (br. *s*, $H_3C{-}C(1')$); 3.8 (*m*, CH_2OH); 4.4 (*m*, H–C(5)); 4.8 and 4.96 (2 br. *s*, $H_2C(2')$). – MS.: 170 (0, M^+), 86 (73), 84 (100), 49 (19), 47 (26).

11. (+)-*1-Isopropyl-5-methyl-2,8-dioxabicyclo[3.2.1]octane* (**18**). The other half of the acidic phase obtained from experiment 5 was refluxed for 1 h, then extracted with ether and washed to neutrality. After concentration, the residue was distilled. Yield: 11 g of **18**, b.p. 85°/8 Torr. $\alpha_D^{20} = \pm 0°$. – IR.: does not show any functional groups. – ^{1}H-NMR.: 0.935 (*d*, $J = 7$, $H_3C{-}C(1')$); 0.985 (*d*, $J = 7$, $H_3C{-}C(1')$); 1.32 (*s*, $H_3C{-}C(5)$); 3.9 (*m*, $H_2C(3)$). – MS.: 170 (13, M^+), 155 (1), 142 (5), 127 (8), 109 (4), 99 (69), 82 (51), 71 (80), 67 (73), 55 (21), 43 (100).

12. *Isolation of nerol oxide* (**1**) *from Bulgarian rose oil.* Bulgarian rose oil (1019 g) was distilled at 75°/0.001 Torr (max. bath temp. 130°) through a 20 cm *Vigreux* column. The fractions with b.p. 30°/50 Torr to 85°/0.001 Torr were combined and carefully refractionated three times at 130–10 Torr (max. bath temp. 123°), using a refluxing head. The subfraction b.p. 45–105°/10 Torr (92.8 g) was collected and subjected to four successive chromatographic separations on 10 to 30 parts of silica gel[5]) in the presence of hexane/ether 19:1 to 2:1. Most constituents whose polarity differed markedly from that of nerol oxide were thus removed from the mix-

[5]) Silica gel for column chromatography, 70–230 mesh (*Merck AG*).

ture. The progress of this enrichment was followed by capillary GC. (OV-1, 100°, 50 m × 0.3 mm column), by observing the increasing intensity of the nerol oxide peak. 2.42 g of an enriched mixture containing about 10% of nerol oxide were obtained. Further separation of this fraction by semi-preparative GC. (5% Carbowax, 120°, 3.5 m column) yielded 140 mg of crude nerol oxide (purity ~80%), which was chromatographed twice on silica gel/$AgNO_3$ 9:1 (using 7 g, then 10 g of adsorbent) in the presence of hexane/ether 99:1 to 97:3. This in turn afforded 50 mg of 95% nerol oxide, the final purification of which was achieved by GC. (10% TCEP[6]), 110°, 5 m column). The resulting nerol oxide (**1**) (15 mg, 99% pure) was optically inactive. – ^{1}H-NMR.: 1.70–1.74 (2 *s*, H_3C–C(4) and 2 H_3C–C(2′)); 1.82 (*d*, *J* = 17, H–C(5)); 2.03 (*m*, H–C(5)); 4.17 (*m*, H_2C(2) and H–C(6)); 5.22 (*d*, *J* = 8, H–C(1′)); 5.42 (br. *s*, H–C(3)). – MS.: 152 (9, M^+), 85 (25), 83 (67), 69 (17), 68 (100), 67 (60), 53 (20), 41 (29).

REFERENCES

[1] a) *G. Ohloff, K.H. Schulte-Elte & B. Willhalm,* Helv. *47,* 602 (1964); b) *G. Ohloff & B. Lienhard,* Helv. *48,* 182 (1965).

[2] *G. Ohloff,* in 'Progress in the Chemistry of Organic Natural Products' *35,* 470 (founded by L. Zechmeister, ed. by W. Herz, H. Grisebach, G.W. Kirby), Springer Verlag, Wien – New York 1978.

[3] *E. sz. Kováts,* private communication (1965); *Ch. Ehret & P. Teisseire,* Recherches *1974,* 287.

[4] *P. Schreier & F. Drawert,* Z. Lebensm.-Unters. Forsch. *154,* 273 (1974).

[5] *Studiengesellschaft Kohle mbH,* Mülheim (Erfinder: G. Ohloff, E. Klein & G. Schade), Deutsches Pat. 1443338 (28.2.1974; Anmeldg. 18.5.1961, St 17836 IVb/12qu) = Fr. P. 1322612 (18.2. 1962); Chem. Abstr. *59,* 11439a (1963); see also [1a].

[6] *K.B. Sharpless & R.C. Michaelson,* J. Am. Chem. Soc. *95,* 6136 (1973).

[7] *E.D. Mihelich,* Tetrahedron Lett. *1979,* 4729; *B.E. Rossiter, T.R. Verhoeven & K.B. Sharpless,* Tetrahedron Lett. *1979,* 4733.

[8] *G.B. Payne,* J. Org. Chem. *27,* 3819 (1962); *J.-L. Pierre, P. Chautemps & P. Arnaud,* Bull. Soc. Chim. Fr. *1969,* 1317.

[9] *G. Ohloff, E. Klein & G.O. Schenck,* Angew. Chem. *73,* 578 (1961).

[10] *R.H. Cornforth, J.W. Cornforth & G. Popják,* Tetrahedron *18,* 1351 (1962).

[11] *G. Ohloff & E. Klein,* Tetrahedron *18,* 37 (1962).

[12] *G. Ohloff,* Pure Appl. Chem. *43,* 481 (1975).

[13] *K.H. Schulte-Elte,* Int. Pat. Appl. WO 79/00509 (Aug. 9, 1979).

[14] *G. Ohloff,* in «Kosmetika, Riechstoffe und Lebensmittelzusatzstoffe», p.35 (editors: H. Aebi, E. Baumgartner, H.P. Fiedler und G. Ohloff), Georg Thieme Verlag, Stuttgart 1979.

[15] *G. Ohloff,* in 'Olfaction and Taste', IV, 156. Proc. of the 4th Internat. Symp. Starnberg, Germany, August 2–4, 1971 (D. Schneider, ed.), Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1972.

[16] *F.C. Huang, L.F. Hsu Lee, R.S.D. Mittal, P.R. Ravikumar, J.A. Chan & C.J. Sih,* J. Am. Chem. Soc. *97,* 4144 (1975).

[17] VARIAN-catalog, spectrum No. 466.

[6] 1,2,3-Tris-(2-cyano-ethoxy)-propane or 'Fractonitril III' *(Merck AG).*