ABSOLUTE CONFIGURATION OF (-)-4-METHYLHEPTAN-3-OL, A PHEROMONE OF THE SMALLER EUROPEAN ELM BARK BEETLE, AS DETERMINED BY THE SYNTHESIS OF ITS (3R,4R)-(+)- AND (3S,4R)-(+)-ISOMERS

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Abstract—Nerol and geraniol were stereoselectively converted to (+)-threo- and (+)-erythro-4-methylheptan-3-ol respectively. (R)(+)-Citronellic acid was converted to a mixture of (3R.4R)(+)-threo- and (3S.4R)(+)-erythro-isomers which was separable by GLC. These syntheses established the absolute configuration of the naturally occurring (-)-4-methylheptan-3-ol to be 3S.4S.

(-)-4-Methylheptan-3-ol 1 and α -multistriatin (2,4 dimethyl - 5 - ethyl - 6,8 - dioxabicyclo [3.2.1] octane) are beetle-produced pheromones responsible for the aggregation of the smaller European elm bark beetle, *Scolytus multistriatus* Marsham.¹ Our recent synthesis of (-)- α multistriatin established its absolute stereochemistry as 1*S*, 2*R*, 4*S*, 5*R*.² The absolute configuration of (-) - 4 methylheptan - 3 - ol 1, however, remained unknown. The present paper describes the solution of this problem by synthetic means.



In the course of their structure elucidation of 1, Silverstein et al reduced (\pm) -4-methylheptan-3-one to a diastereomeric mixture of (\pm) -1'. They observed that the synthetic diastereomers were separable by GLC. The natural pheromone corresponded to the diastereomer of shorter retention time on a Carbowax 20M column. However, they were unable to decide whether the natural alcohol was *threo* (1a or 1a') or *erythro* (1b or its antipode). The first phase of our work was therefore to devise stereoselective synthetic routes to racemic *threo* -((\pm)-1a) and *erythro* -((\pm)-1b) isomers of the alcohol. This was achieved by employing the hydroboration of stereochemically pure olefins as the key step. Nerol 2a and geraniol 11 were particularly useful as the sources of (Z) and (E)-olefins.¹ The former was converted to (\pm) -threoisomer 1a, while the latter to (\pm) -erythro-isomer 1b as described below.

Nervl acetate 2b was treated with N-bromosuccinimide to give bromohydrin 3. This was converted to an epoxy acetate 4 by treatment with KOH soln followed by Ac₂O. Oxidation with HIO, cleaved the epoxide 4 to an aldehyde 5. Wolff-Kishner reduction of 5 afforded (Z)-3methylhex-2-en-1-ol 6a whose homogeneity was proved by GLC and NMR (C = CMe at δ = 1.70). The hydroboration-oxidation of the corresponding THP ether 6b gave an alcohol 7a which was hydrolyzed to give a diol 7b. This was the 2,3-threo-isomer, since the hydroboration was known to proceed via anti-Markownikoff cis-addition.4 This was converted to an epoxide 10 according to the general method of Golding et al.' to obtain chiral epoxides. Thus treatment of the diol 7b with HBr-AcOH gave a mixture of 8 and 9, which was treated with base to yield 10. Reaction of the epoxide 10 with Me₂CuLi⁶ gave (±)-threo-4-methylheptan-3-ol Ia with retention of configuration at C-3.⁺ The product was stereochemically homogeneous as revealed by GLC (94.5-98% purity) and NMR (CHOH at $\delta = 3.30$ (dt, $J_1 = 5$, $J_2 = 2Hz$)). In the same manner, geraniol 11 was converted to (±)-erythro-4-methylheptan-3-ol 1b. Upon Wolff-Kishner reduction, the known aldehyde 12° gave the (E)-alcohol 13a, which was homogeneous on the basis of GLC and NMR (C = CMe at δ = 1.62). The corresponding THP ether 13b gave the 2,3-erythro-diol 14b by hydroboration-oxidation followed by hydrolysis. This was converted to epoxide 17 via 15 and 16. Cleavage of epoxide 17 with Me₂CuLi gave the desired alcohol 1b in stereochemically homogeneous state as judged by GLC (95.3-97% purity) and NMR (CHOH at $\delta = 3.20$ (dt, $J_1 = 4$, $J_2 = 2Hz$)). GLC comparison of the diastercomers on a Carbowax 20M column showed the racemic three-isomer (1a, $R_c = 11.7$ min) to be of shorter retention time than the racemic erythro-isomer (1b, $R_i = 12.1$ min). The natural pheromone was therefore the threo-isomer. The IR and NMR spectra of the natural pheromone kindly provided by Prof. R. M. Silverstein were identical with those of our threo-isomer.

Pheromone Synthesis-XIII. Part XII, K. Mori, N. Mizumachi and M. Matsui, Agric. Biol. Chem., 40, 1611 (1976).

⁺3-Methylhexan-2-one (i) seemed to be a by-product (2% by GLC). A small signal was observable at $\delta = 2.05$ (MrCC) of i) in the NMR spectrum of the distilled alcohol (1a).



The next phase was the synthesis of optically active 4methylheptan-3-ol 1 of known absolute configuration. (R)-(+)-Citronellic acid 18a was chosen as the starting material, since it was known to be readily obtainable from pulegone in almost optically pure state.⁸⁹ The chirality at C-3 of 18a was retained throughout the synthesis to give a mixture of (3R, 4R)- and (3S, 4R)-4-methylheptan-3-ol, 1a and 1b, which could be separated by GLC.

Methyl (R)-(+)-citronellate (18b), prepared by esterification of acid 18a with CH₂N₂, was oxidized with m-chloroperbenzoic acid to give (+)-epoxide 19. This was cleaved by treatment with HIO, to give an aldehyde 20. The Wolff-Kishner reduction of 20 gave (R)-(+)-3methylhexanoic acid 21a. This was converted to (R)-(-)-N.N-dimethylamide 21c via acyl chloride 21b. Reduction of the amide 21c with LiAlH₄ gave (R)-(-)-amine 22. Pyrolysis of the corresponding N-oxide 23 according to Cope^{10,11} yielded an olefin 24. This was oxidized with m-chloroperbenzoic acid to give (R)-(-)-epoxide 25 as a diastereomeric mixture. The epoxide opening with Me₂-CuLi gave a mixture, $[\alpha]_D^{21}$ +10.28° (neat), of (3R,4R)threo-alcohol 1a and its (3S,4R)-erythro-isomer 1b. In order to correlate these alcohols to a known compound, a small portion of the diastereomeric mixture was oxidized with Jones' reagent to give (R)-(-)-4-methylheptanone (26), $[\alpha]_D^{23}$ -22.1° (*n*-hexane). This was the antipode of the alarm pheromone of the leaf-cutting ant, Atta texana, whose reported $[\alpha]_D$ value was -21.5° (*n*-hexane).¹² The comparison of these two rotation values proved the high optical purity of our ketone 26 and confirmed the retention of configuration at C-3 of 18a throughout the synthesis.

The GLC separation of the threo-isomer la from the erythro-alcohol 1b was carried out on a PEG 20M column. Although the complete separation could not be achieved, both isomers of 80-90% purities were secured. The rotation value of the (3R,4R)-threo-isomer la contaminated with 21% of the erythro-isomer was $[\alpha]_{D}^{23} + 21^{\circ}$ (n-hexane), while that of the (3S,4R)-erythro-isomer 1b contaminated with 8% of threo-isomer was $[\alpha]_{D}^{23} + 13^{\circ}$ (*n*-hexane). The calculated $[\alpha]_D$ value of the pure (3R,4R)-threo-isomer 1a was therefore +23° (n-hexane). Since the natural pheromone was levorotatory $([\alpha]_p)^2$ -15°),¹ its absolute configuration was concluded to be 3S,4S as represented by 1a'. It is interesting to note that both this pheromone la' and the Atta texana pheromone (antipode of 26) share 4S-stereochemistry. This suggests the existence of a similar stereochemical control in the course of the pheromone biosynthesis in these two quite different insects.

In conclusion the absolute configuration of the pheromone was established to be 1a' starting with only



two items of evidence (GLC retention order and $[\alpha]_D$ value) at the outset.[†]

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded as CCL solns at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. Optical rotations were measured on a Jasco DIP-4 polarimeter. GLC analyses were performed on a Yanaco G80 gas chromatograph.

6.7-Epoxyneryl acetate 4

To a soln of 2b (43 g) in dimethoxyethane (150 ml) and water (100 ml), N-bromosuccinimide (44 g) in dimethoxyethane (240 ml) and H₂O (160 ml) was added with stirring and cooling (5 \sim 12°). The mixture was stirred for 2 h at room temp., then poured into water and extracted with ether. The ether soln was washed with water and NaCl soln, dried (MgSO₄) and concentrated in vacuo to give 84 g of crude 3. This was dissolved in MeOH (250 ml) and mixed with aq KOH (100 g in 250 ml) under ice-cooling. The mixture was left to stand overnight at room temp, concentrated in vacuo, diluted with water and extracted with ether. The ether soln was washed with water and NaCl soln, dried (K2CO3) and concentrated in racuo to give 35 g of crude 6,7-epoxynerol. This was dissolved in C₄H₅N (75 ml) and mixed with Ac₂O (125 ml). The mixture was left to stand overnight at room temp, poured into water and extracted with ether. The ether extract was washed with water, NaHCO, soln and NaCl soln, dried (MgSO₄) and concentrated in vacuo. The residue was distilled to give 36 g (78%

⁺Attempts to convert ii, obtainable from (R)-(+)-citronellol, into 24 failed. Another synthesis of the optically active pheromone (vi) was attempted starting from D-glyceraldehyde acetonide (iii) via iv and v. However, racemization in the course of the synthesis was so extensive that the final diastereometric mixture (vi) was only slightly optically active ($[\alpha]_{D}^{21} \cdot 0.99^{\circ}$ (ether)).



from **2b**) of 4. b.p. 108–110⁶/2 mm, n_D^{21} 1.4544; ν_{max} 2940 (m), 1750 (vs), 1660 (w), 1440 (m), 1390 (s), 1250 (vs), 1120 (m), 1030 (m), 945 (m), 890 (w), 850 (w) cm⁻¹; δ 1.24 (6H, s), 1.78 (3H, s), 1.98 (3H, s), 4.53 (2H, d, J = 7 Hz), 5.38 (1H, t, J = 7 Hz). (Found: C, 67.40; H, 9.16. C₁₂H₂₀O₃ requires: C, 67.89; H, 9.50%).

(Z)-4-Methyl-6-acetoxyhex-4-enal 5

A soln of 4 (36 g) in ether (500 ml) was added dropwise during 30 min to a stirred and ice-cooled soln of HIO₄·2H₂O (45 g) in THF (200 ml). The mixture was stirred for 30 min at room temp, and then diluted with water. The ether layer was separated and the aq layer was extracted with ether. The combined ether soln was washed with water, NaHCO₃ soln and NaCl soln, dried (MgSO₄) and concentrated *in vacuo*. The residue was distilled to give 23.5 g (82%) of 5, b.p. 102-105⁹/2 mm, n_p²³ 1.4581; ν_{max} 2920 (m), 2720 (w), 1740 (vs), 1660 (w), 1445 (m), 1380 (s), 1370 (s), 1240 (vs), 1020 (s), 950 (m) cm⁻¹; δ 1.75 (3H, s), 1.96 (3H, s), 2.45 (4H, br.s), 4.48 (2H, d, J = 7 Hz), 5.33 (1H, t, J = 7 Hz). (Found: C, 62.80; H, 8.31. C₉H₁Q₀ requires C, 63.51; H, 8.29%).

(Z)-3-Methylhex-2-en-1-ol 6a

Hydrazine hydrate (85%; 24 ml) was added to a soln of 5 (23.5 g) in diethylene glycol (140 ml) and the mixture was heated under reflux for 30 min. Then KOH (19 g) in water (20 ml) was added and the mixture was heated under reflux for another 30 min. Then the bath temp. was gradually raised to 210°. Water (100 ml) was added portionwise to the mixture during 2h. This effected the steam-distillation of the reduction product. Organic layer in the distillate was separated and the aq layer was extracted with ether. The combined organic soln was washed with dil. HCl, NaHCO, soln and NaCl soln, dried (K₂CO₃) and concentrated by fractional distillation with a Vigreux column. The residue was distilled to give 10.5 g (67%) of 6a, b.p. 108-112^e/68 mm, n_D^{21} 1.4495; ν_{max} 3300 (s), 2970 (s), 2940 (s), 2880 (s), 1665 (w), 1470 (m), 1450 (m), 1385 (m), 1310 (w), 1260 (w), 1235 (w), 1180 (w), 1120 (w), 1065 (m), 1040 (m), 1000 (s), 900 (w), 870 (w), 740 (w) cm⁻¹; δ 0.88 (3H, deformed t, J = 7 Hz), 1.70 (3H, s), 3.25 (1H, -OH), 4.05 (2H, d, J - 7 Hz), 5.41 (1H, t, J = 7 Hz); GLC (Column, 5% Carbowax 20M, 0.75 m × 3 mm i.d. at 100°; carrier gas, N2, 0.6 kg/cm2): Rt 7.0 min. (Found: C, 73.65; H, 12.21. C,H, O requires: C, 73.63; H, 12.36%).

(Z)-3-Methylhex-2-en-1-ol THP ether 6b

Dihydropyran (10.5 g) and p-TsOH (0.1 g) were added to a soln of **6a** (10.5 g) in dry ether (50 ml) and the mixture was left to stand for 2 h at room temp. Then the mixture was washed with K₃CO₃, soln, dried (K₃CO₃) and concentrated *in vacuo*. The residue was distilled to give 17.2 g (99%) of **6b**, b.p. 85-90⁶/4 mm, n_p^{23} 1.4579; ν_{max} 1670 (w), 1210 (m), 1140 (m), 1120 (s), 1080 (s), 1060 (m), 1025 (s) cm⁻¹; δ 0.90 (3H, deformed t, J = 7 Hz), 1.60 (~10H, br.), 1.72

(3H, s), 3.20–4.20 (4H, m), 4.58 (1H, br.s), 5.36 (1H, t, J = 7 Hz). (Found: C, 72.38; H, 11.02. $C_{12}H_{22}O_2$ requires: C, 72.68; H, 11.18%).

2.3-threo-3-Methylhexane-1,2-diol 7b

0.8M-B₂H₄ in THF (55 ml) was added dropwise during 1 h to a stirred and ice-cooled soln of 6b (17 g) in dry THF (60 ml) at 0-10° under N₂. The mixture was left to stand overnight at room temp. Then water (2 ml) was added to destroy the excess B₂H₄. NaOH soln (2 g in 16 ml) and 30% H₂O₂ (16 ml) were added dropwise and the mixture was stirred for 1 hr at 30-50°. After cooling, solid NaCl was added to the mixture. The THF layer was separated and the aq layer was extracted with ether. The combined organic soln was washed with NaCl soln, dried (K2CO3) and concentrated in vacuo to give 20 g of 7a. This was mixed with water (60 ml) and conc. HCl (10 ml) and the mixture was stirred and heated at 80-90° for 30 min. The dark soln was concentrated in vacuo. The residue was distilled to give 7.7 g (68%) of 7b, b.p. 105-110°/3 mm, np²³ 1.4490; ν_{mex} 3300 (s), 1060 (s), 1030 (s) cm ⁻¹; δ (CDCl₃) 0.90 (3H, t), 0.89 (3H, d, J = 7 Hz), 1.1-1.8 (5H, m), 3.20 (2H, s), 3.40-3.80 (3H, m). (Found: C, 62.99; H, 11.66. C₃H₁₆O₂ requires: C, 63.59; H, 12.20%).

2,3-threo-1,2-Epoxy-3-methylhexane 10

A sat soln of HBr in AcOH (50 g) was added to stirred and ice-cooled 7b (7.7g). After 5 min, the ice-bath was removed and the mixture was stirred at room temp. for 30 min. Then it was diluted with ice-water, neutralized with Na₂CO₃ and extracted with ether. The ether soln was dried (MgSO₄) and concentrated in vacuo to give 14 g of a mixture of 8 and 9, ν_{max} 1740 (s), 1370 (m), 1245 (s), 1030 (m) cm⁻¹. This was dissolved in ethylene glycol (50 ml) and mixed with KOH soln (25 g in 30 ml water). The mixture was stirred for 1 h at room temp., diluted with water and extracted with a small amount of ether. The ether soln was washed with water and NaCl soln, dried (K2CO3) and fractionated through a Vigreux column. The residue was distilled to give 1.9 g (29%) of 10, b.p. 68–72°/72 mm, n_D^{24} 1.4112; ν_{max} 3050 (w), 2970 (s), 2930 (s), 2880 (s), 1490 (w), 1465 (m), 1420 (w), 1385 (w), 1320 (w), 1270 (w), 1240 (w), 1130 (w), 1070 (w), 1040 (w), 965 (w), 920 (w), 900 (m), 870 (w), 850 (w), 825 (m), 780 (w), 740 (w) cm⁻¹; δ ~ 0.94 (6H, m), ~1.30 (5H, m), 2.30-2.70 (3H, m); MS: m/e 114 (M*).

3,4-threo-4-Methylheptan-3-ol (racemic 1a)

MeLi soln was prepared from Li (2.5 g), MeBr (43 g) and dry ether (130 ml). This was added to a stirred and cooled suspension of Cu₂I₂ (11.4 g) in dry ether (30 ml) at $-30^{\circ} \sim -40^{\circ}$ under N₂ and the mixture was stirred for 1 h at this temp. A soln of 10 (1.9 g) in dry ether (20 ml) was added to the soln of Me₂CuLi with stirring and cooling at $25 \sim -30^\circ$. The mixture was stirred for 1 h at -30 ~ -40° and left to stand overnight. Then it was poured into sat NH₄Cl soln and ice. The ether layer was separated and the aq layer was extracted with ether. The combined ether soln was washed with NaCl soln, dried (K2CO3) and concentrated at atmospheric pressure by fractional distillation with a Vigreux column. The residue was distilled to give 1.9 g (90%) of (+)-1a, b.p. $110^{\circ}/123 \text{ mm}, n_{D}^{23} 1.4264; \nu_{max} 3360 (s), 2970 (s), 2940 (s), 2880 (s),$ 1710 (w, due to i), 1470 (s), 1385 (m), 1340 (w), 1310 (w), 1250 (w), 1150 (w), 1110 (m), 1075 (m), 1040 (w), 1020 (w), 970 (s), 950 (sh), 910 (w), 880 (w), 860 (w), 820 (w), 780 (w), 750 (w) cm $^{-1}$; δ (100 MHz) 0.8-1.0 (9H, m, 0.80, 0.85, 0.92, 0.99), 1.0-1.6 (7H, m), 2.38 (1H, s, -OH), 3.30 (1H, dt, $J_1 = 5$, $J_2 = 2 Hz$); GLC (Column, 5% Carbowax 20M, 0.75 m × 3 mm i.d. at 70°; Carrier gas, N₂, 0.6 kg/cm²): 2.4 min (2%, due to i), 11.7 min (98%). (Found: C, 73.60; H. 13.61. C₈H₁₈O requires: C, 73.78; H, 13.92%).

(E)-3-Methylhex-2-en-1-ol 13a

This was prepared, in the same manner as described for the preparation of 6a, from 12 (14 g) to give 7.0 g (74%) of 13a, b.p. $112-120^{\circ}/78 \text{ mm}, n_D^{-24} 1.4485; \nu_{max} 3300 (s), 2970 (s), 2930 (s), 2880 (s), 1670 (w), 1460(m), 1385(m), 1310(w), 1245(w), 1185(w), 1120 (w), 1070 (m), 1000 (s), 890 (w), 830 (w), 780 (w), 750 (w) cm <math>^{+}; \delta$ 0.88 (3H, deformed t, J ~ 6 Hz), 1.62 (3H, s), 3.15 (1H, s, -OH), 4.04

(2H, d, J = 6 Hz), 5.37 (1H, t, J = 6 Hz); GLC (5% Carbowax 20M, 0.75 m × 3 mm i.d. at 100°; Carrier gas, N₂, 0.6 kg/cm²): Rt 8.0 min. (Found: C, 73.81; H, 12.27, C-H₁₄O requires; C, 73.63; H, 12.36%).

(E)-3-Methylhex-2-en-1-ol THP ether 13b

This was prepared in the manner described for the preparation of **6b**, from **13a** (7.0 g) to give 11.1 g (96%) of **13b**, b.p. 92-96³/5 mm, n_{12}^{24} 1.4563; ν_{max} 1670 (w), 1210 (s), 1140 (s), 1120 (s), 1085 (s), 1025 (s) cm⁻¹; δ 0.88 (3H, deformed t, J = 6 Hz), 1.62 (s), 5.34 (1H, t, J = 6 Hz). (Found: C, 72.63; H, 11.20. C₁₂H₂₂O₂ requires: C, 72.68; H, 11.18%).

2,3-erythro-3-Methylhexane-1,2-diol 14b

This was prepared, in the manner described for the preparation of 7b, from 13b (11.1g) to give 4.0g (55%) of 14b, b.p. 105-110°/3 mm, n_{10}^{21} 1.4472; ν_{max} 3300 (s), 1060 (s) cm ⁻¹; δ (CDC1,) 0.86 (3H, d, J = 6 Hz), 0.90 (3H, deformed t, J = 6 Hz), 3.50 (2H, s, -OH), 3.4-3.8 (3H, m). (Found: C, 62.97; H, 11.74. C₃H₁₄O₂ requires: C, 63.59; H, 12.20%).

2,3-erythro-1,2-Epoxy-3-methylhexane 17

This was prepared, in the same manner as described for the preparation of 10, from 14b (4.0 g) to give 0.9 g (26%) of 17, b.p. 65°/66 mm, n_0^{-21} 1.4099; ν_{max} 3050 (w), 2970 (s), 2940 (s), 2880 (s), 1490 (w), 1460 (m), 1420 (w), 1380 (m), 1260 (w), 1130 (w), 1075 (w), 1040 (w), 960 (w), 935 (m), 900 (m), 860 (w), 855 (w), 820 (m), 780 (w), 740 (w) cm⁻¹; $\delta \sim 0.92$ (6H, m), ~ 1.35 (5H, m), 2.20–2.65 (3H, m); M); M/S: m/e 114 (M⁺).

3.4-crythro-4-Methylheptan-3-ol (racemic 1b)

This was prepared, in the manner described for the preparation of racemic 1a, from 852 mg of 17 to give 667 mg (69%) of (\pm)-1b, b.p. 110-112°/125-130 mm, n_D²³ 1.4268: ν_{max} 3360 (s), 2970 (s), 2940 (s), 2880 (s), 1720 (w, C+O due to i), 1475 (s), 1390 (m), 1340 (w), 1320 (w), 1260 (w), 1160 (w), 1120 (m), 1085 (w), 1050 (w), 1030 (w), 980 (s), 960 (sh), 910 (w), 880 (w), 860 (w), 820 (w), 780 (w), 750 (w) cm⁻¹; δ (100 MHz) 0.8-1.0 (9H, m, 0.80, 0.88, 0.92, 0.98), 1.0-1.6 (7H, m), 2.04 (1H, s), 3.20 (1H, dt, J₁ = 4, J₂ = 2 Hz); GI,C (5% Carbowax 20M, 0.75 × 3 mm i.d. at 70°; Carrier gas, N₂, 0.6 kg/cm⁻²): Rt 2.4 min (3%, due to i), 12.1 min (97%). (Found: C, 73.38; H, 13.62; C_aH₁₀O requires: C, 73.78; H, 13.92%).

Methyl (R)-(+)-citronellate 18b

(*R*)-(+)-Citronellic acid (18a, 52.5 g, b.p. 130-135°/4 mm, n_D^{23} 1.4533; $[\alpha]_D^{23} + 11.0^\circ$ (c = 2.8, CHCl₃)) was treated with ethereal CH₂N₂ to give 53 g (93%) of 18b, b.p. 82-84°/1.7 mm, n_D^{24} , 1.4426; $[\alpha]_D^{24} + 7.40$ (neat); ν_{max} 1740 (s), 1440 (m), 1380 (m), 1240 (m), 1200 (m), 1160 (m), 1110 (w), 1085 (w), 1010 (w), 830 (w) cm ⁻¹; δ 0.94 (3H, d, J = 6 Hz), 1.60 (3H, s), 1.68 (3H, s), 3.62 (3H, s), 5.12 (1H, t, J = 7 Hz). (Found: C, 71.39; H, 10.58. C₁₁H₂₆O₂ requires: C, 71.69; H, 10.94%).

Methyl (R)-(+)-6,7-epoxycitronellate 19

m-Chloroperbenzoic acid (85% purity, 60 g) was added portionwise to a soln of **18b** (53 g) in CHCl, (500 ml) with stirring and ice-cooling below 25°. The mixture was stirred for 1 h at room temp, and filtered. The filtrate was washed with dil Na₃CO, soln and dried (MgSO₄). The solid on the filter was washed with light petroleum. The light petroleum soln was washed with dil Na₃CO, soln and dried (MgSO₄). The combined organic soln was concentrated *in vacwo*. The residue was distilled to give 52.5 g (92%) of 19, b.p. 95-105°/1.7 mm, n_D²⁴ 1.4375; [α]_D²⁴ +5.30 (neat); ν_{mx} , 1740 (s), 1460 (m), 1440 (m), 1385 (m), 1300 (m), 1240 (m), 1210 (m), 1170 (m), 1120 (m), 1010 (w), 900 (w), 870 (w), 800 (w) cm '; δ 0.95 (3H, d, J = 6 Hz), 1.20 (3H, s), 1.24 (3H, s), 2.52 (1H, m), 3.62 (1H, s). (Found: C, 66.03; H, 9.75. C₁₁H₂₀₀, requires: C, 65.97; H, 10.07%).

Methyl (R)-(+)-6-oxo-3-methylhexanoate 20

This was prepared in the manner described for the preparation of 5, from 52.5 g of 19 to give 36.5 g (88%) of 20, b.p. 70–80°/1 mm, n_D^{24} 1.4386; [α] $_D^{24}$ +7.36° (neat); ν_{max} 2950 (m), 2720 (w), 1730 (s), 1440 (m), 1370 (m), 1300 (m), 1270 (m), 1210 (m), 1170 (s), 1100 (m), 1010 (m) cm⁻¹; δ 0.95 (3H, d, J = 6 Hz), 3.62 (3H, s), 9.75 (1H, t, J = 1 HZ). (Found: C, 60.35; H. 8.75. C₈H₁₄O₁ requires: C, 60.74; H, 8.92%).

(R)-(+)-3-Methylhexanoic acid 21a

Hydrazine hydrate (85%; 30 ml) was added to a soln of 20 (36 g) in diethylene glycol (200 ml) and the mixture was heated under reflux for 30 min. Then aq KOH (30 g in 30 ml) was added and the mixture was heated under reflux for another 30 min. The bath temp, was gradually raised to 160° and kept there for 3 h. A higher bath temp, could not be attained because of the foaming of the soln. After cooling, the soln was diluted with ice-water, acidified with conc HCl and extracted with ether. The ether soln was washed with NaCl soln, dried (MgSO2) and concentrated in vacuo. The residue was distilled to give 10.0 g (34%) of 21a, b.p. 118-125'/20 mm, n_0^{24} 1.4229; $[\alpha]_0^{24}$ +3.20' (neat); $\nu_{max} \sim 3200$, ~2600, 1710 (s), 1460 (m), 1410 (m), 1380 (w), 1300 (m), 1240 (w), 1195 (w), 1155 (w), 1130 (w), 1100 (w), ~920 (w) cm⁻¹; δ 0.90 (3H, deformed t, J = 6 Hz, 0.95 (3H, d, J = 6 Hz), 1.2-1.5 (5H, m), ~2.15 (2H, m), 11.46 (1H, s). (Found: C, 64.59; H, 10.56. C:H14O2 requires: C, 64.58; H, 10.84%).

(R)-(-)-3-Methylhexanoic acid N,N-dimethylamide 21c

SOCI₂ (15 ml) was added to a soln of 21a (10 g) in dry C.H. (20 ml) and the mixture was stirred and heated under reflux for 1 h. Then C.H. was distilled off under atmospheric pressure. The residue was dissolved in dry C.H. (50 ml) and concentrated again (to remove SOCI₂) to give crude 21b, ν_{max} 1810 cm⁻¹. This was dissolved in dry C.H. (20 ml) and added dropwise to a stirred and ice-cooled soln of 30% Me2NH (60 ml) and water (20 ml). The mixture was stirred for 1 h. Then organic layer was separated and aq layer was extracted with ether. The combined organic soln was washed with water, dried (MgSO₄) and concentrated in vacuo. The residue was distilled to give 8.5 g (71%) of 21c, b.p. 78-80°/3 mm, n_D^{24} 1.4449; $[\alpha]_D^{24}$ 6.95° (neat); ν_{max} 1660 (s, sh), 1640 (s), 1495 (m), 1460 (m), 1400 (m), 1350 (w), 1270 (w), 1160 (m), 1120 (m), 1060 (w), 970 (w), 740 (w) cm 1 ; δ 0.88 (3H, d, J - 6 Hz), 0.90 (3H, t, J = 6 Hz), 2.86 (3H, s), 2.97 (3H, s). (Found: C, 68.92; H, 11.84; N, 8.51. C.H., ON requires: C, 68.74; H, 12.18; N, 8.91%).

(R)-()-N.N-Dimethyl-3-methylhexylamine 22

A soln of 21c (8.5 g) in dry ether (50 ml) was added to a stirred and ice-cooled suspension of LiAlH₄ (2.2 g) in dry ether (50 ml) and the mixture was stirred overnight at room temp. Water (2.5 ml), 10% NaOH soln (2.5 ml) and water (7.5 ml) were added successively to the stirred and ice-cooled mixture. After stirring for 1 h, the mixture was dried (K₅CO₅) and filtered. The solvent was removed at atmospheric pressure through a Vigreux column. The residue was distilled to give 6.3 g (82%) of 22, b.p. 60-62°/25 mm, n_D²⁴ 1.4167, $[\alpha]_{12}^{24}$ = 5.72° (neat); ν_{max} 2920 (s), 2860 (s), 2800 (s), 2760 (s), 1460 (m), 1380 (m), 1310 (w), 1270 (w), 1190 (w), 1160 (w), 1115 (w), 1100 (w) to60 (w, sh), 1040 (w), 1010 (w), 850 (w), 830 (w), 75.19; H, 14.57; N, 9.65. C₃H₂₁N requires: C, 75.44; H, 14.77; N, 9.78%).

(R)-3-Methylhex-1-ene 24

35% H₂O₂ (5 ml) was added to a soln of 22 (6.2 g) in MeOH (6 ml) under ice-cooling. After 2 h, and again after an additional 2 h, 35% H₂O₂ (5 ml portions each time) was added with swirling and the soln was left to stand overnight at room temp. The soln was negative to phenolphthalein test after this period. The excess H₂O₂ was destroyed by the cautious addition of Pt catalyst. After 1 h the mixture was filtered. The filtrate was concentrated *in vacwo* below 60° to give 23 as white foamy solid. Then 23 was heated at 160–180°/20–30 mm to effect pyrolysis. The vigorous reaction continued for about 30 min. The product was collected in a trap well-cooled by a Dry ice-acetone bath. The upper hydrocarbon layer in the trap was washed with water, cold dil HCl, NaHCO, soln and NaCl soln. The yield of 24 was 2.5 g (69% from 22). δ (CDCl₃) 0.92 (3H, deformed t, J = 6 Hz), 0.98 (3H, d, J = 7 Hz).

1.2-1.6 (4H, m), 2.12 (1H, m), 4.8-6.1 (3H, m, 4.85, 5.05, 5.12, 5.52, 5.65, 5.68, 5.81, 5.94, 5.99, 6.10). Owing to its high volatility, 24 was employed for the next step without further purification.

(3R)-(-)-1,2-Epoxy-3-methylhexane 25

m-Chloroperbenzoic acid (6.0 g) was added to a stirred and ice-cooled soln of 24 (2.5 g) in CH₂Cl₂ (40 ml). The mixture was left to stand overnight in a refrigerator. Then it was washed with cold NaOH soln, dried (K₂CO₃) and fractionated through a Vigreux column to remove CH₂Cl₂. The residue was distilled to give 2.5 g (86%) of 25, b.p. 70-71°/85 mm, n_D²³ 1.4092; [α]_D²³ - 1.60 (neat); ν_{mx} 3050 (w), 2970 (s), 2940 (s), 2880 (s), 1490 (w), 1460 (m), 1420 (w), 1380 (m), 1265 (w), 1130 (w), 960 (w), 935 (w), 900 (m), w70 (w), 850 (w), 820 (m), 780 (w), 740 (w) cm⁻¹; δ ~0.90 (6H, m), --1.30 (5H, 2.2-2.7 (3H, m)); MS: *m/e* 114 (M⁻).

(3R)-(+)-4-Methylheptan-3-ol 1a + 1b

This was prepared in the manner described for the preparation of (+)-1a, from 2.3 g of 25 to give 1.5 g (60%) of 1a + 1b, b.p. 105-115'/118 mm, n_D^{23} 1.4231; $[\alpha]_D^{23}$ +10.28° (neat); GLC (5% Carbowax 20M, 0.75 m × 3 mm i.d. at 70°; Carrier gas, N., 0.6 kg/cm²); Rt 11.7 min (1a, ~55%), 12.1 min (1b, ~45%). (Found: C, 73.41; H, 13.46. C_aH₁₀O requires: C, 73.78; H, 13.92%). The IR and NMR spectra corresponded to those of the mixture of (+)-1a and (+)-1b.

(3R)-()-4-Methylheptan-3-one 26

Jones' reagent (1 ml) was added to a soln of 1a + 1b (300 mg) in acetone (3 ml) under ice-cooling and swirling. The mixture was left to stand for 10 min at room temp. poured into water and extracted with ether. The ether soln was washed with water, NaHCO₃ soln and NaCl soln, dried (MgSO₄) and fractionated under atmospheric pressure with a Vigreux column to remove ether. The residue was distilled to give 127 mg (43%) of 26, b.p. 88–90°/118 mm. nc³¹ 1.4110; $[\alpha]_D^{21} \cdot 22.1^{\circ}$ (c = 0.78, *n*-hexane); ν_{max} 2960 (s), 2940 (s), 2880 (s), 1715 (s), 1460 (m), 1420 (w), 1380 (m), 1240 (w), 1180 (w), 1110 (m), 1020 (w), 975 (w) cm⁻¹; δ 0.90–1.20 (9H, m, 0.94, 0.99, 1.01, 1.12, 1.15), 1.20–1.70 (4H, m), 2.20–2.70 (3H, m, 2.26, 2.38, 2.49, 2.61); GLC (5% Carbowax 20M, 0.75 m × 3 mm i.d. at 50°; Carrier gas, N₂, 0.4 kg/cm⁻²): Rt 1.7 min (6%), 2.0 min (4%), 3.0 min (90%, 26). This was so volatile that correct elemental analytical data could not be obtained.

Separation of (3R, 4R)-threo- and (3S, 4R)-erythro-isomers 1a and 1b

The separation was carried out on a Hitachi K-53 gas chromatograph using a PEG 20 M Column (2 m \times 3 cm i.d.) at 80° with N₂ as the carrier gas (1.2 kg/cm²).

(3R, 4R)-threo-(+)-4-Methylheptan-3-ol 1a. About 40 mg of this isomer was obtained from 1.2 g of the mixture. Its purity was checked by GLC on a Shimazu 6 AM gas chromatograph: PEG 20M, 30 m × 0.28 mm i.d. at 80°; Carrier gas, N₂: Rt 9.5 (1a, 79%), 9.85 (1b, 21%) min. This sample was therefore of 79% purity. Its IR spectrum as film was identical with that of (\pm)-1a. The rotation of this sample was: $[\alpha]_D^{23} + 21^{\circ} \pm 1^{\circ} (c \sim 0.373, n-hexane).$

(3S, 4R)-erythro-(+)-4-Methylheptan-3-ol 1b. About 50 mg of this isomer was obtained. Its purity was checked by GLC as described for 1a; Rt 9.61 (1a, 8%), 10.02 (1b, 91%) min. This sample was therefore of 91% purity. Its IR spectrum as film was completely identical with that of (=)-1b. The rotation of this sample was: $[\alpha]_D^{3^*} + 13^* \pm 1^* (c = 0.456, n-hexane)$. From these $[\alpha]_D$ values, the optical rotations of pure 1a and 1b were calculated to be: $[\alpha]_D^{3^*} + 23^* (n-hexane)$ for 1a and $+9^* (n-hexane)$ for 1b. GLC analyses of (*)-1b and the mixture of 1a and 1b were also carried out by the PEG 20M capillary column, 30 m × 0.28 mm i.d. at 80^*: Rt 9.70 ((±)-1a, 94.5% purity), 10.11 min ((±)-1b, 95.3% purity). The mixture was composed of 52% 1a and 48% 1b.

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REFERENCES

- ¹G. T. Pearce, W. E. Gore, R. M. Silverstein, J. W. Peacock, R. A. Cuthbert, G. N. Lanier and J. B. Simeone, J. Chem. Ecol. 1, 115 (1975).
- ²K. Mori, Tetrahedron 32, 1979 (1976).
- ³G. Stork, M. Gregson and P. A. Grieco, *Tetrahedron Letters* 1391 (1969).
- ⁴H. C. Brown, Organic Syntheses via Boranes, pp. 6–8. Wiley, New York (1975).

- ⁵B. T. Golding, D. R. Hall and S. Sakrikar, J. Chem. Soc. Perkin I 1214 (1973).
- *R. W. Herr, D. M. Wieland and C. R. Johnson, J. Am. Chem. Soc. 92, 3813 (1970).
- ^{*}M. Ohki, K. Mori and M. Matsui, Agr. Biol. Chem. 38, 175 (1974). ^{*}C. G. Overberger and H. Kaye, J. Am. Chem. Soc. 89, 5640 (1967).
- D. Valentine, Jr., K. K. Chan, C. G. Scott, K. K. Johnson, K. Toth and G. Saucy, J. Org. Chem. 41, 62 (1976).
- ¹⁰A. C. Cope and E. R. Trumbull, Organic Reactions 11, 317 (1960).
- "A. C. Cope and E. Ciganek, Org. Synth. Col. Vol. 4, 612 (1963).
- ¹²R. G. Riley, R. M. Silverstein and J. C. Moser, *Science* 183, 760 (1974).