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SYNTHESIS AND BIOLOGICAL ACTIVITY OF BOTH (*E*)- AND (*Z*)-ISOMERS OF OPTICALLY PURE (*S*)-14-METHYL-8-HEXADECENAL (TROGODERMAL), THE ANTIPODES OF THE PHEROMONE OF THE KHAPRA BEETLE†

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Abstract—Both (*E*)- and (*Z*)-isomers of (*S*)-14-methyl-8-hexadecenal (trogodermal) were synthesized from 100% optically pure (*R*)-(+)-citronellic acid. These antipodes of the khapra beetle pheromone were 1/500 to 1/1000 times as active as the natural (*R*)-pheromone. Determination of the optical purities of citronellic acid and related compounds was achieved by hplc method. Warning was made not to forget the measurement of density in expressing the optical rotation of a neat liquid as $[\alpha]_D$ (neat).

In 1969 Rodin *et al.* isolated (*Z*)-(−)-14-methyl-8-hexadecen-1-ol 21 and methyl (*Z*)-(−)-14-methyl-8-hexadecenoate as the sex pheromone of the female dermestid beetle (*Trogoderma inclusum*) by extracting whole insects.[1] The absolute configuration of these compounds was shown by us to be *R* by synthesizing their antipodes from (*S*)-(−)-2-methyl-1-butanol.[2] Indeed this was the first example of the determination of the absolute stereochemistry of a pheromone by synthesis.[3] In 1976 Cross *et al.*[4] isolated the genuine sex pheromone of *T. inclusum*, *T. variabile*, *T. glabrum* and *T. granarium*. They identified (*Z*)-14-methyl-8-hexadecenal in *T. inclusum* and *T. variabile* and the corresponding (*E*)-isomer in *T. glabrum*. Both isomers were found in *T. granarium* in a *Z* : *E* ratio of 92 : 8. The above aldehydes were named (*Z*)- and (*E*)-trogodermal (Fig. 1).[2a] In 1978 we synthesized both enantiomers of (*Z*)-trogodermal 1 and its (*E*)-isomer 2.[5,6] Bioassay of our materials revealed only the (*R*)-enantiomers, (*R*)-1 *and* (*R*)-2, to be bioactive on male dermestid beetles, *T. glabrum*, *T. inclusum*, *T. variabile* and *T. granarium* (German strain).[7,8]

However, in 1978, Rossi and Niccoli[9] reported that the (*S*)-enantiomers of (*E*)- and (*Z*)-trogodermals were extremely active on *T. granarium* (Italian strain) employing the samples prepared by Rossi *et al.*[10] Later they published a synthesis of (*R*, *E*)-trogodermal and its (*Z*)-isomer.[11] They claimed that the biological response of the male khapra beetle (*T. granarium*, Italian strain) to both enantiomers of 1 and 2 indicated the (*S*)-enantiomers to be the pheromone, while the antipodal (*R*)-1 and (*R*)-2 were far less active.[12] This was contrary to our observation.

Here we report that the high optical purities of our previous samples of trogodermal enantiomers were confirmed by repeating our synthetic procedure starting from 100% optically pure (*R*)-(+)-citronellic acid.

Determination of the optical purities of citronellic acid and related compounds. Since the chiral center in trogodermal molecule is far separated from the functional groups, it is rather difficult to determine its optical purity directly by physical methods such as NMR measurement in the presence of optishift reagents. What we can do is to determine the optical purity of the starting material precisely, to execute the synthesis carefully avoiding racemization during the process, and to assume that the final product retains the optical purity of the starting material. As to the determination of the optical purity of citronellic acid, our starting material, the most reliable way is the hplc analysis of its amide derivatives prepared from chiral amines, because the $[\alpha]_D$ value of citronellic acid is not so large and fluctuates owing to contamination

†Pheromone Synthesis. Part 52. Part 51, K. Mori and H. Ueda, *Tetrahedron* 38, 1227 (1982).

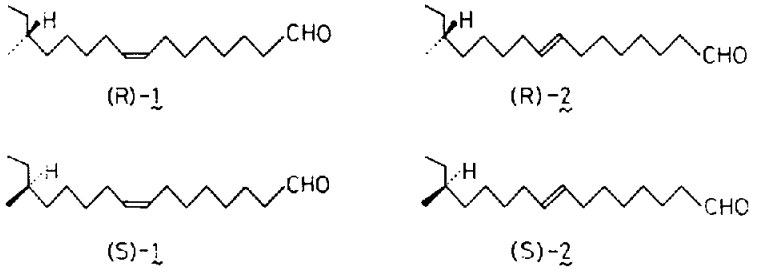

Fig. 1. Structure of stereoisomers of trogodermal.

of even a trace amount of impurities.[13,14] To ascertain the capability of the hplc method we analyzed optically impure citronellic acid **4a** and its derivatives, **5a**, **8a** and **10a**, which were prepared from optically impure (−)-isopulegol **3** in the conventional manner as shown in Fig. 2 (Experimental). These acids were converted to the corresponding (*R*)-(+)-α-(1-naphthyl)ethylamides, **4b**, **5b**, **8b** and **10b**. Except **8b**, the separation of the diastereomeric amides by hplc was complete using a Zorbax SIL column with *n*-hexane–THF (10:1) as the solvent. The degree of separation of the diastereomeric amides decreased in the order **10b** > **4b** ~ **5b** ≫ **8b**. It is to be noted that the order of elution of two diastereomeric amides is rather confusing. In the cases of **4b** and **5b**, the amides derived from (*R*)-acids and (*R*)-amine were eluted earlier. On the other hand, in the cases of **8b** and **10b**, which are higher and lower homologs of **5b**, the order of elution was reversed and the amides derived from (*S*)-acids and (*R*)-amine were eluted earlier (Experimental). We then analyzed (*R*)-(+)-citronellic acid **4a** derived from purified (−)-isopulegol **3** and found it to be 92% optically pure.[15] This was the common starting material for our syntheses of optically active pheromones such as (3*R*,4*R*)-4-methyl-3-heptanol,[16] (*Z*)-trogodermal **1**,[5] (*E*)-trogodermal **2**,[6] 10-methyldodecyl acetate,[17] the pine sawfly pheromone[18] and the German cockroach pheromone.[15] These synthetic pheromones including trogodermal were therefore of 92% optical purities, since we carefully planned the syntheses to avoid racemization.

Synthesis and biological activity of optically pure (S,Z)- *and* (S,E)-*trogodermals, the antipodes of the natural pheromone components.* After Rossi's claim that the (*S*)-enantiomers of (*E*)- and (*Z*)-trogodermals were far more active than the (*R*)-enantiomers, we decided to study the pheromone activity of our 92% optically pure samples of trogodermal enantiomers[5,6] on the Italian strain of *T. granarium* which was used by Rossi *et al.*[9–12] Through the courtesy of Dr. A. Niccoli, Firenze, we obtained it and found that even on the Italian strain the (*R*)-enantiomers of **1** and **2** were far more active than the (*S*)-enantiomers.[19] This was in complete agreement with our previous results,[7,8] but in contradiction to Rossi's claims.[9–12] Then we felt it desirable to repeat our synthesis starting from 100% optically pure (*R*)-(+)-citronellic acid **4a** so as to compare the specific rotations of pure intermediates with those reported by us[5,6] and by Rossi *et al.*[10,11] Another reason for the repetition was to know whether highly optically pure (*S*)-enantiomers of (*Z*)- and (*E*)-trogodermals are completely devoid of biological activity or not. These antipodes of the natural pheromone components with 92% optical purities failed to induce copulation in unmated males but produced receptor potentials in antennae, although they were very low.[7,8] Since the (*S*)-enantiomers employed for the bioassay were not 100% optically pure, it was possible that the apparent activity of the (*S*)-enantiomers might be largely due to contamination by the bioactive (*R*)-enantiomers.[7,8] Highly optically pure (*S*)-**1** and (*S*)-**2** were necessary to clarify this.

(*R*)-(+)-Pulegone **11** was selected as our starting material because it was available in 100% optically pure state and convertible into (*R*)-(+)-citronellic acid **4a**.[20] The optical purity of this **4a** was estimated to be 100% by the hplc analysis of the corresponding amide **4b**. The synthetic route[5,6] is shown in Fig. 3. The intermediates and the final products, (*S*)-**1** and (*S*)-**2**, were highly purified (96 ~ 99.7% as checked by GLC) whenever possible, while in the previous synthesis,[5] rigorous purification of the intermediate such as (*R*)-**17**, (*R*)-**18** and (*R*)-**19** had been omitted because of the ease of purification at later stages (**20b**, **21**, **22**).

As we had still in our hands the samples of intermediates used in the previous synthesis,[5,6] we measured the specific rotations of both the previous and the present samples of some intermediates. The measurements were carried out as $CHCl_3$ solns. A few results are shown in Table 1. This clearly indicates that our previous samples are also more than 90% optically pure, if we believe the high chemical and optical purities of our new

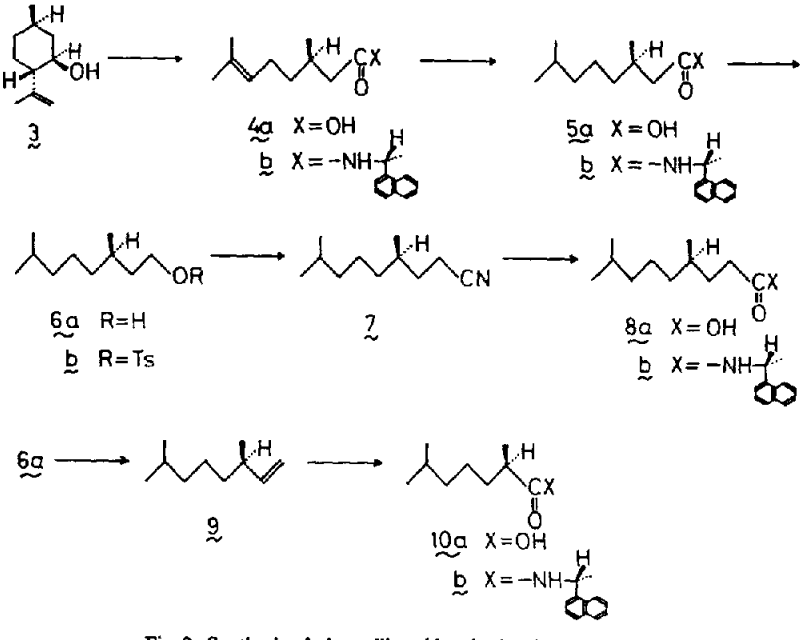

Fig. 2. Synthesis of citronellic acid and related compounds.

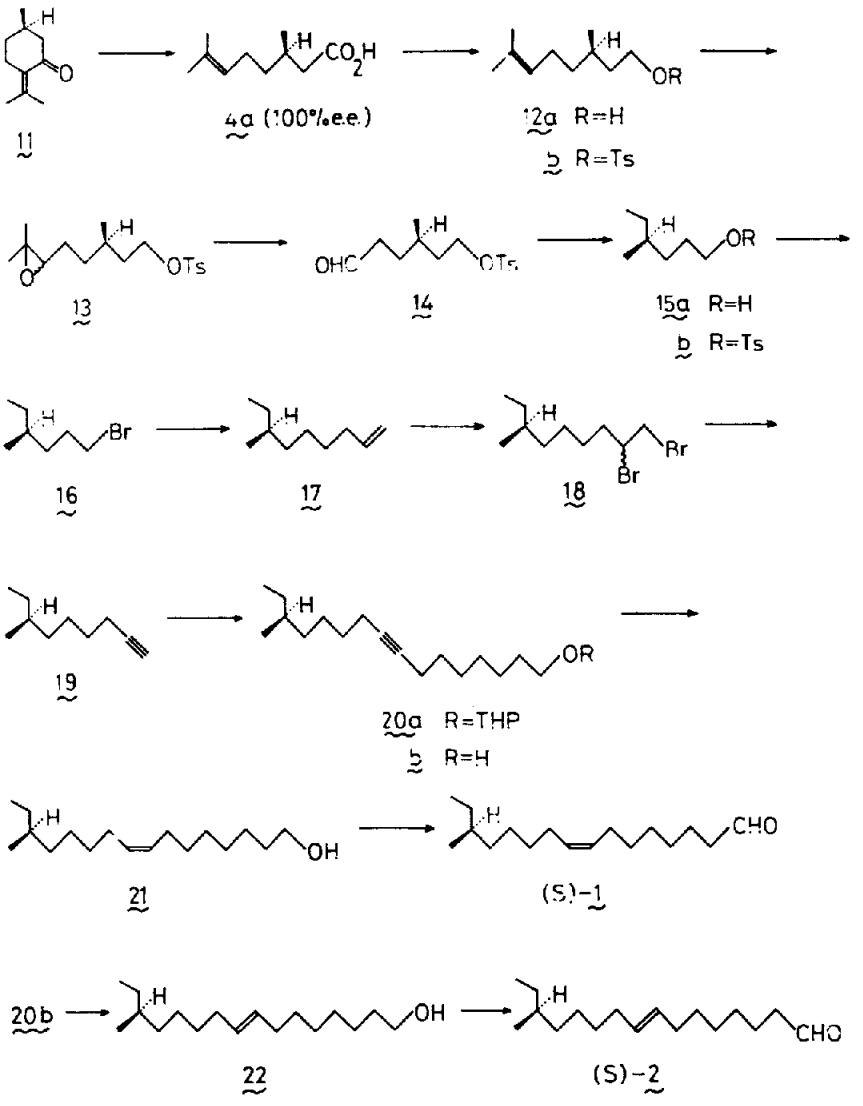

Fig. 3. Synthesis of (*S*, *Z*)- and (*S*, *E*)-trogodermals.

Table 1. Specific rotations of some synthetic intermediates

Compound	$[\alpha]_D^{23}$ (measured as $CHCl_3$ soln) of the previous samples prepared by Suguro[5]	the present samples prepared by Kuwahara
(S)-15a	8.33° (c=2.83)	8.62° (c=3.65)
(S)-16	10.19° (c=3.85)	10.33° (c=3.84)
(S)-17	9.06° (c=1.74)	9.94° (c=2.96)

samples. Table 2 summarizes the specific rotations of (*Z*)- and (*E*)-trogodermals **1**, **2** and related compounds **20b**, **21** and **22** as reported in the past.[2,5,6,10,11,21] Our data on newly synthesized samples of (*S*)-series are also included. Examination of the data in Table 2 also supports the high purities of our samples. Rossi's following statement is therefore untrue: "it is possible to infer that any conclusion of Mori *et al.* on the evaluation of the optical purity of the compounds from them synthesized, is very probably erroneous."[11]

We then tested the newly synthesized optically pure samples of (*S*)-**1** and (*S*)-**2** for male khapra beetles (*T. granarium*) of the Italian and the German strain and compared their activities with those of (*R*)-**1** and (*R*)-**2**. (*R*,*Z*)-Trogodermal synthesized in 1978[5] was about 10^3 times more active than the pure (*S*, *Z*)-trogodermal and

Table 2. Specific rotations of both enantiomers of (*E*)- and (*Z*)-trogodermals and related compounds

Compound	$[\alpha]_D^{21\sim27.5}$ as reported by			
	Mori[2,5,6]	Rossi[10,11]	Schäfer[21]	this paper
20	+5.23°[a] -5.11°[a] +5.97°[a]	-4.93°[b] +5.34°[b]	-5.13°[a]	+6.23°[a]
21	+5.31°[b] -5.43°[b] +5.57°[b]	-5.27°[b] +5.33°[b]	-5.20°[b]	+6.06°[b]
22	-5.48°[b] +5.52°[b]	-5.45°[b] +5.11°[b]	-5.12°[b]	+5.86°[b]
1	-5.94° +6.02°[b]	-5.90°[c] +6.05°[c]	-	+6.15°[b]
2	-5.99° +6.18°[c]	-5.04°[c] +5.62°[c]	-	+6.92°[c]

[a] Measured as MeOH soln. [b] Measured as $CHCl_3$ soln.

[c] Measured as Et_2O soln. (R)-Enantiomers are levorotatory while (S)-isomers are dextrorotatory.

(*R*)-**2** prepared in 1978[6] was likewise about 0.5×10^3 times more active than (*S*)-**2** in evoking receptor potentials in the antennae of male *T. granarium* of both German and Italian strains. Some of the receptor potentials obtained are given in Table 3. These findings indicate that the high chemical and optical purities of the (*S*)-enantiomers did not significantly increase the gap between the activities of the (*R*)- and (*S*)-enantiomers of **1** and **2**. It became obvious that (*S*)-**1** or (*S*)-**2** alone induces relatively low receptor potentials. This is not so surprising, as 8-hexadecenal also induces low receptor potentials probably due to the presence of the CHO group.[7]

A comment on expressing the optical rotation of a neat liquid. Optical purity is classically measured by comparing the rotation of a sample to the rotation of "optically pure" reference material. Although the accuracy of this method is questionable in view of the recent advent of NMR or chromatographic techniques, specific rotation or $[\alpha]_D$ value is still important like m.p. or b.p.

Specific rotation is defined as $[\alpha]_D^T = \alpha_D^T/(1 \times c)$. So as to calculate the specific rotation we must know α_D^T as expressed by degree, 1 as expressed by dm and c as expressed by g/ml. Carelessly in some cases we did not measure the densities of our samples whose optical rotations were observed as neat liquids, partly because of the paucity of the materials. Therefore our data in refs. 2, 5, 16–18 and 22–24 expressed as specific rotations $[\alpha]_D^T$ X° (neat) should read observed rotations α_D^T (neat, $1 = 1$ dm).† These mistakes, however, have nothing to do with the high optical purities of the pheromone enantiomers reported in our papers.[2,5,16–18,22–24] These are mistakes not in the facts but in their expressions. Needless to say these do not hurt the validity of all biological works resulting from our syntheses.[25]‡

This same mistake as ours is now prevailing among recent literatures. There are many cases where specific rotations of neat liquids are reported without specifying their densities. This is accelerated by recent trend to execute micro-scale experiments. Through the availability of a sensitive automatic polarimeter, it has become possible to measure the optical rotation of a small amount of a neat liquid. The measurement of density, on the other hand, requires a substantial amount of the material.

In conclusion, hplc analysis of diastereomeric derivatives is the method of choice in determining optical purities, and the (*S*)-enantiomers of (*E*)- and (*Z*)-trogodermals induce low but definite receptor potentials in the antennae of male khapra beetles.

EXPERIMENTAL

All b.ps were uncorrected. IR spectra were determined as film for oils on a Jasco A-102 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated. Optical rotations were measured on a Jasco DIP-140 polarimeter. Hplc analyses were performed on a Shimadzu LC-2 chromatograph. Glc analyses were performed on a JEOL JGC-20K or Yanaco GCG-550F gas chromatographs.

(R)-(+)-*Dihydrocitronellic acid* **5a**. (*R*)-(+)-**4a** was prepared from crude (−)-**3** as reported.[15] 10% Pd-C (3 g) was added to a soln of this **4a** (14 g) in 95% EtOH and the mixture was shaken under H_2 for 3.5 hr. Subsequent work-up gave 13.4 g (94.6%) of **5a** after distillation, b.p. 79–87°/0.42 mm, n_D^{22} 1.4316; $[\alpha]_D^{21.5}$ +7.42° ($c = 5.10$, $CHCl_3$); ν_{max} ~3000 (br), 2950 (s), 2920 (s), 2860 (s), 1710 (vs), 1470 (m), 1415 (m), 1385 (m), 1370 (w), 1300 (m), 1220

†In K. M.'s recent review on pheromone synthesis,[3] these mistakes have been corrected, except one which escaped his checking: ref. 3, p. 112, $[\alpha]_D^{23}$ −4.54° (neat) should read α_D^{23} −4.54° (neat, $1 = 1$ dm).

‡We measured densities of several compounds reported in our previous syntheses of dermestid beetle pheromones.[2,5] For example, the density of (*S*)-(+)-4-methyl-1-hexanol **15a**[5] was d_4^{22} 0.8182 (lit.[26] d_4^{25} 0.8236). Therefore its $[\alpha]_D^{20} = (+6.63°/0.8182) = +8.10°$ (neat) instead of +6.63° as reported.[5] This value is almost as high as that (+8.16°) reported for "optically pure" (*S*)-**15a** in 1961.[26] Due to the non-availability at that time of modern NMR or chromatographic techniques, the exact optical purity of the "optically pure" (*S*)-**15a** remains unknown. Its reported $[\alpha]_D$ value, however, supports the high optical purity of our (*S*)-**15a**. Reestimated $[\alpha]_D$ values of **16**, **17**, **18** and **19** are described in the Experimental Section. In our first synthesis of (*S*)-**21** from (*S*)-(−)-2-methyl-1-butanol, the specific rotation of the latter was erroneously reported as $[\alpha]_D^{23}$ −4.54°(neat).[2] With its density as d_4^{22} 0.8213, it should be corrected as $[\alpha]_D^{23} = (-4.54/0.8213) = -5.53°$ (neat). Since the highest observed $[\alpha]_D$ value of this compound is −5.90°,[27] the optical purity of our (*S*)-(−)-2-methyl-1-butanol was not 77% as reported previously[2] but 93%. Our dermestid beetle pheromone reported in ref. 2 was therefore of 93% optical purity. It should be added that Rossi himself reported specific rotations of neat liquids without specifying their densities.[10,11]

Table 3. Receptor potentials recorded from the antennae of male khapra beetles, *Trogoderma granarium* pertaining an Italian and a German strain

Dose (μg)	Compound	Receptor potential[a,b] (average m V)	Compound	Receptor potential[a,b] (average m V)
0.01	(R)-1	1.7	(R)-2	1.2
	(S)-1	0.4	(S)-2	0.2
0.1	(R)-1	3.2	(R)-2	1.8
	(S)-1	0.6	(S)-2	0.5
1	(R)-1	4.3	(R)-2	2.1
	(S)-1	1.2	(S)-2	0.7

[a] Extracellular DC potentials were obtained from the terminal antennal segment by glass microelectrodes containing Beadle-Ephrussi's Ringer solution.

[b] No significant difference between the olfactory responses recorded from both strains.

(m), 935 (m) cm^{-1}; δ 0.87 (6H, d, J = 5 Hz), 0.96 (3H, d, J = 6 Hz), 1.1–2.0 (8H, br), 2.0–2.5 (2H, m), 11.85 (1H, s). After glc purification this showed $[\alpha]_D^{21.5} + 7.26°$ (c = 3.89, $CHCl_3$). (Found: C, 69.31; H, 11.71. Calc. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70%).

(R)-(+)-*Dihydrocitronellol* **6a**. A soln of **5a** (11.0 g) in dry ether (20 ml) was added to a stirred and ice-cooled suspension of LAH (4.86 g) in dry ether (200 ml). The mixture was stirred for 1.5 hr at room temp. After usual work-up 8.67 g (85.8%) of **6a** was obtained, b.p. 58–62°/0.55 mm, $n_D^{22.5}$ 1.4315; $[\alpha]_D^{22.5} + 3.54°$ (c = 4.79, $CHCl_3$); ν_{max} 3300 (m), 2945 (s), 2915 (s), 2860 (s), 1470 (m), 1385 (m), 1370 (m), 1050 (m), 1010 (m) cm^{-1}; δ 0.87 (9H, d, J = 5 Hz), 1.0–1.9 (10H, br), 2.97 (1H, s), 3.56 (2H, t, J = 6 Hz); glc (Column, 3% SE-30, 1.5 m × 2 mm at 100° + 8°/min; Carrier gas, N_2, 0.7 kg/cm^2): Rt 4.4 min (100%). (Found: C, 75.36; H, 14.18. Calc. for $C_{10}H_{22}O$: C, 75.88; H, 14.01%).

(R)-*Dihydrocitronellyl cyanide* **7**. *p*-TsCl (24.17 g) was added to a stirred and ice-cooled soln of **6a** (10 g) in dry C_5H_5N (100 ml). The mixture was stirred for 3 hr at 0–5°. Subsequent work-up yielded 21.2 g of crude **6b**. This was dissolved in DMSO (175 ml) and NaCN (4.83 g) was added to the soln. The mixture was stirred overnight at 60–65°. Subsequent work-up yielded 9.0 g (84.8%) of **7**, b.p. 102–112.5°/11.5 mm, ν_{max} 2950 (s), 2920 (s), 2860 (s), 2245 (m), 1470 (m), 1430 (m), 1390 (m), 1370 (m) cm^{-1}. This was employed for the next step without further purification.

(R)-(−)-*4,8-Dimethylnonanoic acid* **8a**. NaOH (42.8 g) in H_2O (60 ml) was added to a soln of **7** (8.95 g) in 95% EtOH (80 ml). The mixture was heated under reflux for 2 days. Subsequent work-up yielded 8.54 g (73.2% from **6a**) of **8a**, b.p. 115–117°/0.62 mm, $n_D^{22.5}$ 1.4341; $\alpha_D^{22.5} - 0.54°$ (neat, l = 1 dm); ν_{max} ~ 3000 (br), 2930 (s), 2900 (s), 2840 (s), 1700 (s), 1460 (m), 1405 (m), 1380 (m), 1360 (m), 1280 (m), 925 (m) cm^{-1}; δ 0.86 (9H, d, J = 5 Hz), 1.0–2.0 (10H, br), 2.29 (2H, t, J = 7 Hz), 11.93 (1H, s); glc (Column, 5% SE-30, 0.75 m × 2 mm at 134°; Carrier gas, N_2, 0.88 kg/cm^2): Rt 4.05 min (100%). (Found: C, 70.78; H, 11.88. Calc. for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90%).

(R)-3,7-*Dimethyl*-1-*octene* **9**. A soln of **6a** (12.6 g) in CS_2 (6.3 ml) was added dropwise to a suspension of 50% NaH (4.19 g) in THF (37 ml) under water-cooling. After the addition, the mixture was heated under reflux for 30 min and then cooled to room temp. MeI (14.15 g) was added to the mixture. Then it was heated under reflux for 30 min and poured into ice-water. The mixture was extracted with ether. The ether soln was washed with sat NH_4Cl and brine, dried ($MgSO_4$) and concentrated. The residual crude xanthate was heated at 220–250° (bath temp) to effect pyrolysis. The distillate (b.p. 100–115°) was collected and redistilled to give 6.36 g (54%) of an oil, b.p. 97.5–99°/147 mm, ν_{max} 3070 (w), 2950 (s), 2900 (s), 2860 (s), 1825 (w), 1640 (m), 1470 (m), 1420 (w), 1390 (m), 1370 (m), 995 (m), 910 (s) cm^{-1}; δ 0.87 (6H, d, J = 5 Hz), 0.97 (3H, d, J = 7 Hz), 1.1–1.8 (7H, br), ~2.1 (1H, m, br), 4.7–5.1 (2H, m), 5.35–6.0 (1H, m). This was employed for the next step without further purification.

(R)-2,6-*Dimethylheptanoic acid* **10a**. O_3 was bubbled into a soln of **9** (3.0 g) in AcOH (35 ml) for 1 hr under ice-cooling. 35% H_2O_2 (20 ml) was added to the stirred and ice-cooled AcOH soln. The mixture was stirred for 23 hr at room temp and then for another 23 hr at 50°. The excess H_2O_2 was destroyed by the addition of a small amount of Adams' Pt. The mixture was concentrated *in vacuo*, diluted with water and extracted with ether. The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 1.45 g (42.8%) of crude **10a**, b.p. 82–91°/0.77 mm. This was further purified by removing neutral impurities. The ether soln of crude **10a** was shaken with $NaHCO_3$ soln. The aq soln was acidified with HCl and extracted with ether. Subsequent work-up yielded 0.92 g of pure **10a**, b.p. 106–108°/1.75 mm, n_D^{22} 1.4250; $\alpha_D^{22} - 13.20°$ (neat, l = 1 dm); ν_{max} ~ 3000 (br), 2940 (s), 2860 (s), 1710 (s), 1470 (m), 1420 (m), 1390 (m), 1375 (m), 1300 (m), 1255 (m), 1240 (m), 1205 (m), 940 (m) cm^{-1}; δ 0.87 (6H, d, J = 5 Hz), 1.16 (3H, d, J = 7 Hz), 1.1–2.1 (7H, br), ~2.35 (1H, m), 11.88 (1H, s). glc (Column, 5% SE-30, 0.75 m × 2 mm at 107°; Carrier gas, N_2, 0.88 kg/cm^2): Rt 4.0 min (100%).

Hplc analyses of amides **4b**, **5b**, **8b** and **10b**. These amides were prepared from the acids **4a**, **5a**, **8a** and **10a** and (*R*)-(+)-α-(1-naphthyl)ethylamine.[15] The analytical conditions are: Column, Zorbax SIL 25 cm × 6.2 mm; Eluent, n-hexane-THF (10 : 1); Flow rate, 0.8 ml/min; Pressure, 6–7 kg/cm^2; Detector, 254 nm. *Analysis of* **4b** *from crude* **3**: R_t 76.1 min [81.6%, (*R*)-acid + (*R*)-amine], 87.4 min [18.4%, (*S*)-acid + (*R*)-amine]; ΔR_t 11.3 min; optical

purity of **4a** = 63.1%. *Analysis of* **5b**: R_t 66.0 min [78.4%, (*R*)-acid + (*R*)-amine], 80.0 min [21.6%, (*S*)-acid + (*R*)-amine]; ΔR_t 14.0 min; optical purity of **5a** = 56.8%. *Analysis of* **8b**: R_t 77.4 min [(*S*)-acid + (*R*)-amine], 80.3 min [(*R*)-acid + (*R*)-amine]; ΔR_t 2.9 min = incomplete separation. *Analysis of* **10b**: R_t 33.4 min [22%, (*S*)-acid + (*R*)-amine], 55.5 min [78%, (*R*)-acid + (*R*)-amine]; ΔR_t 22.1 min; optical purity of **10a** = 56.0%. Under exactly the same condition **4b** prepared from pure (*R*)-(+)-pulegone **11** showed a single peak indicating 100% optical purity of (*R*)-(+)-citronellic acid obtained from **11**.

(R)-*Citronellyl tosylate* **12b**. Pure (*R*)-**4a** was reduced with LAH to give **12a** $[\alpha]_D^{22} + 5.26°$ ($c = 4.77$, $CHCl_3$); glc (Column, 5% FFAP, 1.5 m × 2 mm at 130°; Carrier gas, N_2, 1.4 kg/cm²): R_t 5.8 min (single peak). Thus obtained **12a** (16.2 g) yielded 38.9 g of **12b** as described in Ref. 5.

(3R)-*Epoxycitronellyl tosylate* **13**. Crude **12b** (38.9 g) and MCPBA (30.6 g) yielded 46.3 g of crude **13** as described in Ref. 5.

(R)-6-*Tosyloxy-4-methylhexanal* **14**. Crude **13** (46.3 g) and $HIO_4 \cdot 2H_2O$ (35 g) yielded 34.8 g of crude **14** as described in Ref. 5.

(S)-(+)-4-*Methyl-1-hexanol* **15a**. Crude **14** (34.8 g) was reduced with LAH (14 g) as described in Ref. 5 to give 7.07 g (58.7% from **12a**) of **15a**, b.p. 94–99°/38 mm, whose IR and NMR coincided with those reported in Ref. 5. This was further purified by prep glc to give a pure sample of **15a**, n_D^{23} 1.4205; $[\alpha]_D^{23} + 8.62°$ ($c = 3.65$, $CHCl_3$); glc (Column, 5% PEG 20M, 2 m × 4 mm at 90°; Carrier gas, N_2, 1.0 kg/cm²): R_t 6.3 min (99.3%). (Found: C, 72.10; H, 14.01. Calc. for $C_7H_{16}O$: C, 72.35; H, 13.88%).

(S)-(+)-1-*Bromo-4-methylhexane* **16**. TsCl (26.8 g) and **15a** (8.16 g) yielded 21.1 g of crude **15b**, which yielded 7.76 g (61.6% from **15a**) of **16** by treatment with LiBr (17 g). The IR and NMR spectra of **16** were identical with those reported in Ref. 5. The physical properties of **16** were: b.p. 60–68°/22 mm, $n_D^{24.5}$ 1.4466, $[\alpha]_D^{24.5} + 10.33°$ ($c = 3.84$, $CHCl_3$); $\alpha_D^{22} + 11.04°$ (neat, $l = 1$ dm), $d_4^{20.8}$ 1.0960 ∴ $[\alpha]_D^{22} + 10.07°$ (neat); glc (Column, 5% PEG 20M, 2 m × 4 mm at 67°; Carrier gas, N_2, 0.75 kg/cm²): R_t 5.9 min (97.3%). (Found: C, 47.20; H, 8.44. Calc. for $C_7H_{15}Br$: C, 46.94; H, 8.44%).

(S)-(+)-7-*Methyl-1-nonene* **17**. A Grignard reagent was prepared from **16** (10.21 g) and Mg (1.52 g) in dry ether (55 ml). This was added to a stirred and cooled soln of allyl bromide (8.28 g) in dry ether (15 ml) below −5°. The mixture was stirred for 7 hr at room temp. Subsequent work-up yielded 4.78 g (59.9%) of **17**, b.p. 92.5–95°/97 mm, $n_D^{25.5}$ 1.4175; $[\alpha]_D^{25.5} + 9.94°$ ($c = 2.96$, $CHCl_3$, with the present material); $\alpha_D^{23} + 7.14°$ (neat, $l = 1$ dm, with previously reported material[5] of 80% glc purity), d_4^{23} 0.7359 ∴ $[\alpha]_D^{23} + 9.70°$ (neat, with 80% pure material); glc (Column, 5% OV-17, 2 m × 4 mm at 64°; Carrier gas, N_2, 1.2 kg/cm²): R_t 2.4 min (97.1%); MS: *m/z* 141 ($M^+ + 1$), 140 (M^+). The IR and NMR spectra were identical with those reported in Ref. 5.

(S)-(+)-1,2-*Dibromo-7-methylnonane* **18**. A soln of **17** (4.42 g) in CCl_4 (45 ml) was treated with Br_2 (5.4 g) as described in Ref. 5 to give 8.10 g (85.5%) of **18**, b.p. 100–105°/1.05 mm, n_D^{24} 1.4890; $[\alpha]_D^{24} + 5.71°$ ($c = 3.12$, $CHCl_3$); $\alpha_D^{23} + 7.20°$ (neat, $l = 1$ dm),[5] $d_4^{22.8}$ 1.3449 ∴ $[\alpha]_D^{23} + 5.35°$ (neat); glc (Column, 5% OV-17, 2 m × 4 mm at 130°; Carrier gas, N_2, 1.55 kg/cm²): kt: R_t 8.9 min (98.2%). (Found: C, 39.98; H, 6.78. Calc. for $C_{10}H_{20}Br_2$: C, 40.03; H, 6.72%). The IR and NMR spectra of **18** were identical with those reported in Ref. 5.

(S)-(+)-*Methyl-1-nonyne* **19**. A soln of **18** (8.0 g) in dry ether (10 ml) was added to a stirred and cooled suspension of $NaNH_2$ (from 2.6 g of Na) in liq NH_3 (80 ml) below −50°. The mixture was stirred at −40° for 2 hr. Subsequent work-up as described in Ref. 5 yielded 3.04 g (82.6%) of **19**, b.p. 92–93°/73 mm, n_D^{25} 1.4222; $[\alpha]_D^{25} + 10.3°$ ($c = 2.57$, $CHCl_3$, with the present material); $\alpha_D^{19} + 8.84°$ (neat, $l = 1$ dm, with previously reported material of 95% glc purity),[5] $d_4^{22.7}$ 0.7628 ∴ $[\alpha]_D^{19} + 11.6°$ (neat, with 95% pure material) (lit.[10] $[\alpha]_D^{20} + 9.55°$ (neat) with no *d*]; glc (Column, 5% OV-17, 2 m × 4 mm at 62°; Carrier gas, N_2, 1.1 kg/cm²): R_t 4.8 min (97.7%). (Found: C, 86.36; H, 13.10. Calc. for $C_{10}H_{18}$: C, 86.88; H, 13.12%). The IR and NMR spectra of **19** were identical with those reported in Ref. 5.

(S)-(+)-14-*Methyl-8-hexadecyn-1-ol* **20b**. A soln of *n*-BuLi in *n*-hexane (1.5N, 15.7 ml) was added to a soln of **19** (2.85 g) in dry THF (20 ml) with stirring and cooling (ice-NaCl) below 0°. The mixture was stirred for 20 min at 0°. Then a soln of 1-tetrahydropyranyloxy-7-bromoheptane (7.1 g) in dry HMPA (35 ml) was added to it with stirring and ice-cooling. The stirring was continued for 2.5 hr at room temp. The mixture was poured into ice-water and extracted with *n*-hexane. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 9.49 g of crude **20a**. This was dissolved in MeOH (70 ml) containing TsOH (0.45 g). The soln was stirred at 60–65° for 8 hr. Subsequent work-up gave 7.07 g of crude **20b**. This was chromatographed over SiO_2 (70 g). Elution with *n*-hexane-ether yielded 4.07 g (78.2% from **19**) of **20b**, b.p. 152–153°/0.7 mm; $n_D^{27.5}$ 1.4582; $[\alpha]_D^{27.5} + 6.23°$ ($c = 3.43$, MeOH); glc (Column, 5% OV-17, 2 m × 4 mm at 198°; Carrier gas, N_2, 1.5 kg/cm²): R_t 7.1 min (99.1%). (Found: C, 80.75; H, 12.84. Calc. for $C_{17}H_{32}O$: C, 80.88; H, 12.78%). The IR and NMR spectra of **20b** were identical with those reported in Ref. 5.

(S, Z)-(+)-14-*Methyl-8-hexadecen-1-ol* **21**. This was prepared from **20b** (2.5 g) in exactly the same manner (semi-hydrogenation) as described in Ref. 5 to give 2.05 g (81.4%) of pure **21**, b.p. 149.5–150°/0.58 mm, $n_D^{25.5}$ 1.4549; $[\alpha]_D^{25.5} + 6.06°$ ($c = 2.97$, $CHCl_3$); glc (Column, 5% OV-17, 2 m × 4 mm at 184°; Carrier gas, N_2, 1.3 kg/cm²): R_t 10.3 min (97.5%). (Found: C, 80.26; H, 13.41. Calc. for $C_{17}H_{34}O$: C, 80.24; H, 13.47%). The IR and NMR spectra of **21** were identical with those reported in Ref. 5.

(S, Z)-(+)-14-*Methyl-8-hexadecenal* (*trogodermal*) (*S*)-**1**. The crude (*S*)-**1** (2.05 g) obtained from **21** (2.00 g) in the same manner (PCC oxidation) as described in Ref. 5 was chromatographed over Mallinckrodt SiO_2 CC-7 (30 g). Elution with *n*-hexane-ether gave 1.34 g (67.5%) of (*S*)-**1**, b.p. 129–134°/0.8 mm, n_D^{25} 1.4500; $[\alpha]_D^{24} + 6.15°$ ($c = 2.89$, $CHCl_3$); glc (Column, 5% OV-17, 2 m × 4 mm at 178°; Carrier gas, N_2, 1.45 kg/cm²): R_t 8.1 min (97.3%). (Found: C, 80.83; H, 12.89. Calc. for $C_{17}H_{32}O$: C, 80.88; H, 12.78%). The spectral data coincided with those reported in Ref. 5. For the purpose of bioassay this was further purified by preparative glc (5% PEG 20M) to give glc purity of 99% on a 5% OV-17 column.

(S, E)-(+)-14-*Methyl-8-hexadecen-1-ol* **22**. The crude **22** (1.6 g) obtained from **20b** (1.396 g) in the same manner (LAH reduction) as described in Ref. 6 was chromatographed over SiO_2–$AgNO_3$ prepared from Mallinckrodt SiO_2 AR-100 mesh (30 g), $AgNO_3$ (2.5 g) and H_2O (7 ml). Elution with *n*-hexane-ether gave 0.991 g (70.4%) of **22**, b.p. 117–118°/0.06 mm, n_D^{24} 1.4545; $[\alpha]_D^{24} + 5.86°$ ($c = 3.14$, $CHCl_3$); glc (Column, 5% OV-17, 2 m × 4 mm at 184°; Carrier gas, N_2, 1.55 kg/cm²): R_t 8.2 min (99.7%). (Found: C, 80.23; H, 13.51. Calc. for $C_{17}H_{34}O$: C, 80.24; H, 13.47%). The IR and NMR spectra of **22** was identical with those reported in Ref. 6.

(S, E)-(+)-14-*Methyl-8-hexadecenal* (*trogodermal*) (*S*)-**2**. The crude (*S*)-**2** obtained from **22** (0.95 g) in the same manner (PCC oxidation) as described in Ref. 6 was chromatographed over Mallinckrodt SiO_2 CC-7 (29 g). Elution with *n*-hexane-ether yielded 0.65 g (69.0%) of (*S*)-**2**, b.p. 113–114°/0.11 mm. This was further purified by preparative glc (5% PEG 20M). The purified sample showed the following properties: n_D^{23} 1.4490; $[\alpha]_D^{23} + 6.92°$ ($c = 3.66$, ether); glc (Column, 5% OV-17, 2 m × 4 mm at 177°; Carrier gas, N_2, 1.4 kg/cm²): R_t 7.7 min (96.0%). (Found: C, 80.61; H, 12.85. Calc. for $C_{17}H_{32}O$: C, 80.88; H, 12.78%). The spectral data of (*S*)-**2** were identical with those reported in Ref. 6.

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