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SYNTHESIS OF OPTICALLY ACTIVE FORMS OF IPSENOL, THE PHEROMONE OF *IPS* BARK BEETLES†

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Abstract—(*S*)-(−)-Ipsenol 1′ and its antipode 1″ were synthesized from (*S*)-(+)-leucine **10** and its antipode **10′**, respectively. This established the *S*-configuration of the naturally occurring (−)-ipsenol. Only the natural (*S*)-(−)-enantiomer was biologically active on *Ips grandicollis*.

(−)-Ipsenol was first isolated from a bark beetle, *Ips paraconfusus* Lanier, as one of its aggregation pheromones.[1,2] The structure **1** proposed for it on the basis of spectral data was confirmed by syntheses of its racemate.[3-6] However, its absolute configuration has remained unknown. None of the reported synthesis is applicable to the preparation of optically active ipsenol of known absolute configuration. As a part of our project to synthesize optically active pheromones,[7-10] we have completed the synthesis of both enantiomers of ipsenol (**1′** and **1″**) starting from the readily available amino acid, leucine. This unambiguously established the *S*-configuration of the natural (−)-ipsenol.[11] Our synthesis is based on the idea that an optically active α-methylene-γ-lactone **2′** may be converted into ipsenol 1′ via a lactol intermediate **A** or its equivalent.

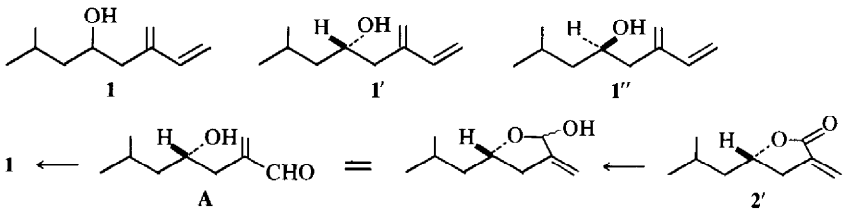
The first phase of this work was a model study with racemates to find a successful route from the (±)-lactone **2** to (±)-ipsenol **1**. For this purpose the lactone **2** was prepared in a conventional manner from methyl isobutyl ketone. The starting ketone was converted to the known β-keto ester **3**[12] with $CO(OEt)_2$ in the presence of NaH. Alkylation of **3** with methyl bromoacetate gave a diester **4**. This was heated with conc. HCl to give a crystalline keto acid **5**. Reduction of **5** with $NaBH_4$ followed by acidification yielded a γ-lactone **6**. This was carboxylated with magnesium methyl carbonate ($MeOMgOCO_2Me$)[13] to give an α-carboxy lactone **7** which was smoothly converted to the key intermediate **2** when treated with CH_2O and Et_2NH.[14] Direct reduction of the methylene lactone **2** with *i*-Bu_2AlH in THF gave an intractable mixture of products. The protection of the methylene group therefore seemed necessary. This was readily carried out by the Michael addition of C_6H_5SeH as described by Grieco.[15] The resulting seleno compound **8** was reduced with *i*-Bu_2AlH in THF to give a lactol **9**. When this was treated with an excess of methylene triphenyl phosphorane in DMSO, (±)-ipsenol **1** was the only isolable product. Obviously during the Wittig reaction a retro-Michael process took place resulting in the removal of the selenophenyl protecting group. The racemic ipsenol **1** exhibited IR and NMR spectra identical to those of the natural pheromone recorded in the literature.[1]

†Pheromone Synthesis—IX. Part VIII, K. Mori, *Tetrahedron*, **31**, 3011 (1975).

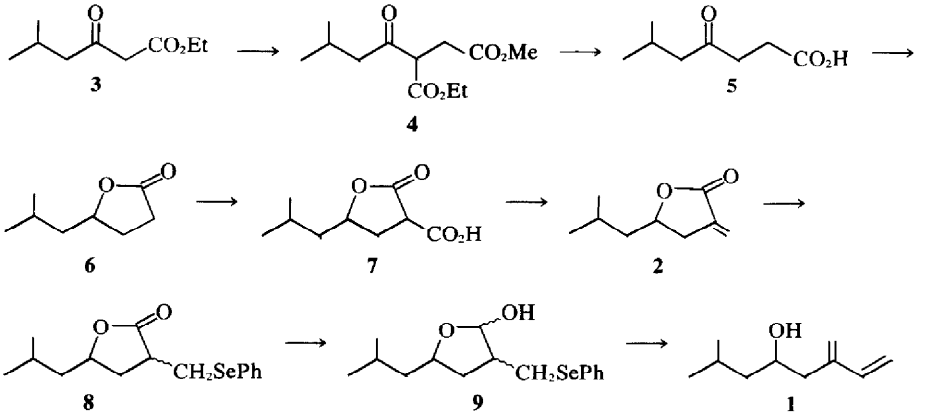
The next stage was to develop a synthetic route to the optically active α-methylene-γ-lactone **2′**. Subsequent to several unsuccessful attempts to prepare **2′** from (*S*)-(+)-glutamic acid, we noticed that leucine **10** was a very promising starting material, since its deamination with HNO_2 was known to proceed with full retention of configuration.[16] It seemed feasible to convert it to an optically active epoxide **14** and hence to the lactone **2′**. Both enantiomers of **2′** were synthesized this way.

(*S*)-(+)-Leucine **10** was treated with HNO_2 to give (*S*)-(−)-leucic acid **11a**.[17] This was recrystallised three times to ensure high optical purity. In our hands the highest rotation value of **11a** after purification was $[\alpha]_D^{20} - 26.9°$ (c 1.55%, N–NaOH) (cf. lit.[17a] $[\alpha]_D^{20} - 27.7°$ (c 1.0%, N–NaOH)). This was esterified to give the ethyl ester **11b**. After protection of the OH group as THP (tetrahydropyranyl) ether, the ester **11c** was reduced with $LiAlH_4$ to give an alcohol **12a**. This was treated with tosyl chloride in pyridine to give a tosylate **12b**. The THP-protecting group was removed by treatment with AcOH–THF–H_2O (2:1:1) to give a hydroxy tosylate **13b**. This gave the optically active epoxide **14**, $[\alpha]_D^{23} - 17.9°$ (c 1.42%, EtOH), upon treatment with KOH. This (*S*)-epoxide **14** could be obtained by a shorter route. (*S*)-(−)-Leucic acid **11a** was reduced with $LiAlH_4$ to give a glycol **13a**. This was treated with 1 eq of tosyl chloride to give crude mono-tosylate **13b**, which gave the epoxide **14** by treatment with KOH. However, the epoxide **14** prepared by this route was of lower optical purity, $[\alpha]_D^{22} - 16.1°$ (c 1.83%, EtOH). Formation of a small amount of the undesired monotosylate at the secondary OH group of **13a** in the course of the tosylation would generate (*R*)-epoxide and hence lower the optical purity of the epoxide **14**.

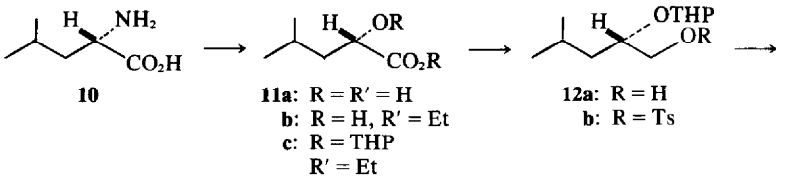
Condensation of the epoxide **14** with diethyl malonate (NaOEt/EtOH) followed by alkaline hydrolysis (KOH aq) and acidification (dil. H_2SO_4) gave an α-carboxy-γ-lactone **7′**.[cf 18] This was treated with CH_2O aq soln and Et_2NH[19,20] to give the optically active α-methylene-γ-lactone **2′**, $[\alpha]_D^{25} - 66·6°$ (c 1.83%, EtOH). This was the (*S*)-lactone **2′**, since Levene had demonstrated as early as 1931 the retention of configuration at the secondary carbon of an epoxide similar to **14** in the course of reaction with carbanions.[21] The IR and NMR spectra of this key intermediate were identical to those of the racemic lactone **2**. Hereafter we followed the route successfully employed in the synthesis of the racemic ipsenol. Thus the lactone **2′** was reacted with C_6H_5SeH to



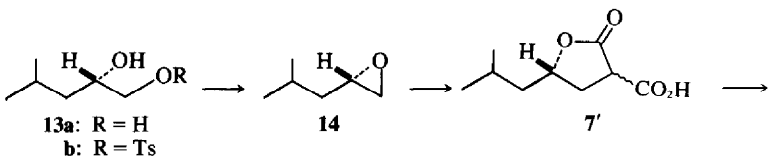
Scheme 1.



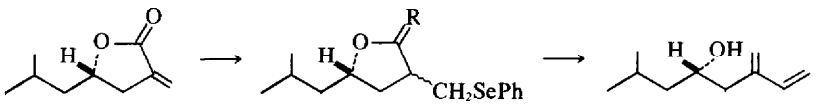
Scheme 2.



11a: R = R′ = H
b: R = H, R′ = Et
c: R = THP
R′ = Et

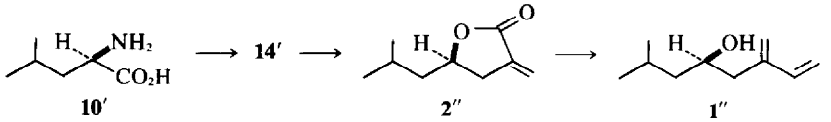


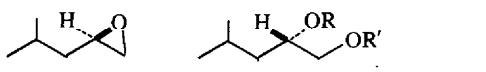
13a: R = H
b: R = Ts



8′: R = O
9′: R = H, OH

Scheme 3.





15a: R = THP R′ = CH_2Ph
b: R = H R′ = CH_2Ph
c: R = Ts R′ = CH_2Ph
d: R = Ts R′ = H
e: R = Ac R′ = CH_2Ph
f: R = Ac R′ = H
g: R = Ac R′ = THP
h: R = H R′ = THP
i: R = Ts R′ = THP

Scheme 4.

give **8'**, which was reduced with *i*-Bu_2AlH yielding α lactol **9'**. Methylene triphenyl phosphorane reacted with **9'** to give (*S*)-ipsenol **1'**. It exhibited a negative optical rotation, $[\alpha]_D^{24} - 16.5°$ (c 1.47%, EtOH). The rotation value of the natural ipsenol was reported to be: $[\alpha]_D^{25} - 17.5° \pm 0.7°$ (c 1%, EtOH).[1] It is therefore evident that the natural ipsenol possesses *S*-configuration as represented by **1'**. It should be emphasized that this assignment was made possible only through the present synthetic approach, since the available amount of the natural pheromone was too small for its degradation to a known compound.

For the purpose of studying the relationship between chirality and pheromone activity, it was absolutely necessary to synthesize the unnatural (*R*)-(+)-ipsenol **1''** of high optical purity. The obvious way to achieve this was to employ unnatural (*R*)-(−)-leucine **10'** as the starting material.† This synthesis in the *R*-series proceeded smoothly as in the case of *S*-series to give (*R*)-(+)-epoxide **14'**, $[\alpha]_D^{24} + 17.5°$ (c 2.44%, EtOH). This afforded (*R*)-(+)-lactone **2''**, $[\alpha]_D^{24} + 67.0°$ (c 1.44%, EtOH). The NMR spectra of the (*R*)- and (*S*)-lactones (**2''** and **2'**) were examined in the presence of the chiral shift reagent $Eu(facam)_3$,[22] but no large difference was observable. (*R*)-(+)-Ipsenol **1''**, $[\alpha]_D^{25} + 17.3°$ (c 1.58%, EtOH) was prepared from **2''** in the same manner as in the cases of (±)-and (*S*)-(−)-ipsenols. The enantiomeric ipsenols showed quite different NMR spectra when measured in the presence of $Eu(facam)_3$ (see Experimental) and no sign of cross contamination was detectable. This fact, combined with the rotation value, supports the high enantiomeric purities of our products.

In conclusion both the natural (*S*)-(−)- and unnatural (*R*)(+)-forms of ipsenol were synthesized in large enough quantities (1.0 g of **1'** and 0.9 g of **1''**) to study the relationship between absolute stereochemistry and pheromone activity. Professor J. P. Vité, University of Freiburg, kindly carried out the bioassay and showed that only the natural (*S*)-(−)-enantiomer was biologically active on *Ips grandicollis*.[23] This result strongly suggests the chiral nature of the pheromone receptor of the insect. The biological study by Vité *et al.* will be published elsewhere.

†Prior to this approach we attempted to convert (*S*)-(+)-leucine **10** to (*R*)-(+)-epoxide **14'**, for the amino acid of the natural *S*-series was far cheaper than its antipode. Attempts were made to obtain a tosylate **15d** which is a position isomer of **13b** and hence should afford (*R*)-epoxide **14'** after treatment with a base. The first attempt was quite disappointing. The alcohol **12a** was treated with benzyl bromide and NaH to give a benzyl ether **15a**. The THP protecting group was removed with AcOH–THF–H_2O (2:1:1) to give an alcohol **15b**. This was tosylated to afford **15c**. Hydrogenolysis of **15c** over Pd–C was unsuccessful in our hands when tried on the scale of 66-123 g of **15c** and resulted in the recovery of most of **15c** affording no pure **15d** after chromatographic separation. The second attempt was more successful but still unsatisfactory. The alcohol **15b** was acetylated ($AcCl/C_5H_5N$) to give an acetate **15e**. This was smoothly hydrogenolyzed over Pd–C to give an alcohol **15f**. The free OH group was protected as THP ether and the resulting **15g** was treated with NaOH to give an alcohol **15h**. This was tosylated to yield **15i**. The removal of the THP group gave the desired monotosylate **15d**. However, these numerous operations resulted in the partial racemization at the asymmetric carbon atom. This was evident from the rotation values of the (*R*)-epoxide **14'**, $[\alpha]_D^{24} + 10.6°$ (c 2.0%, EtOH), and the (*R*)-lactone **2''**, $[\alpha]_D^{25} + 43.6°$ (c 1.83%, EtOH), derived from this monotosylate **15d**. The optical purities were 59–65%. At this point we abandoned this approach and started from the expensive (*R*)-(−)-leucine **10'**.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films unless otherwise specified and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded 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 G 80 gas chromatograph.

Ethyl 3-oxo-5-methylhexanoate **3**

The original procedure[12] was modified to use NaH instead of $NaNH_2$. A 10 ml-portion of a soln of 4-methylpentan-2-one (67 g) in $CO(OEt)_2$ (50 ml) was added to a stirred suspension of 50% NaH (64 g) in dry C_6H_6 (300 ml) and $CO(OEt)_2$ (200 ml). The mixture was stirred and heated under reflux until a vigorous exothermic reaction set in, then heating was discontinued and the remainder of the ketone was added dropwise to maintain reflux. After the addition, the mixture was stirred and heated under reflux for 1 h. After cooling it was poured into ice water containing AcOH (100 ml). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic soln was washed with $NaHCO_3$ soln and NaCl soln, dried ($MgSO_4$) and concentrated. The residue was distilled to give 97.5 g (80.5%) of **3**, b.p. 94–96°/12 mm, n_D^{21} 1.4296; ν_{max} 2960 (s), 2860 (m), 1750 (s), 1720 (s), 1640 (m), 1320 (m), 1245 (s), 1160 (m), 1030 (m) cm^{-1}, δ (CCl_4) 0.88 (6H, d, J = 7 Hz), 1.23 (3H, t, J = 7 Hz), 1.98 (1H, m), 2.28 (2H, br, s), 3.22 (2H, s), 4.10 (2H, q, J = 7 Hz). (Found: C, 62.80; H, 9.17. $C_9H_{16}O_3$ requires: C, 62.76; H, 9.36%).

4-Oxo-6-methylheptanoic acid **5**

The β-keto ester (**3**, 190 g) was added to a soln of NaOEt (prepared from 26 g of Na) in EtOH (450 ml) and C_6H_6 (900 ml). Then methyl bromoacetate (180 g) was added to the mixture with stirring. The mixture was stirred and heated under reflux for 1 h. After cooling, it was washed with water and concentrated *in vacuo* to give 301 g of crude **4**. This was mixed with conc. HCl (1.2 l) and heated under reflux for 15 h. After cooling, the mixture was extracted with ether. The ether soln was washed with water and NaCl soln, dried ($MgSO_4$), decolorized with charcoal and concentrated. The residue was distilled to give 113 g (62%) of **5**, b.p. 130–131°/5 mm; needles from ether-pet. ether, m.p. 46.5–47.5°; ν_{max} (nujol) ~ 3200 (m), ~2650 (m), 1720 (s), 1700 (s), 1270 (s), 1240 (s), 1180 (m), 1150 (w), 1070 (m), 1030 (w), 940 (s), 860 (w), 820 (w), 770 (w) cm^{-1}; δ (CCl_4) 0.95 (6H, d, J = 6 Hz), ~2.1 (1H, m), 2.32 (2H, br. s), 2.68 (4H, br. s), 11.05 (1H, br. s). (Found: C, 60.44; H. 8.68. $C_8H_{14}O_3$ requires: C, 60.74; H, 8.92%).

4-Hydroxy-6-methylheptanoic acid **1→4** *lactone* **6**

A soln of $NaBH_4$ (15 g) in water (100 ml) was added during a 15 min period to an ice-cooled and stirred soln of **5** (110 g) in NaOH (30 g)-water (350 ml). The mixture was left to stand at 0–5° for 1.5 h and extracted with ether to remove neutral impurities. The aq layer was acidified with dil. HCl and extracted with ether. The ether soln was washed with NaCl soln, dried ($MgSO_4$) and concentrated. (This lactone **6** was hydrolyzed by washing with $NaHCO_3$ soln.) The residue was distilled to give 96.5 g (97%) of **6**, b.p. 88–89°/5 mm, n_D^{22} 1.4422; ν_{max} 2960 (s), 2860 (m), 1775 (vs), 1470 (m), 1230 (m), 1190 (s), 1170 (s), 1140 (m), 1015 (m), 980 (m), 915 (m), 800 (w) cm^{-1}; δ (CCl_4) 0.96 (6H, d, J = 6 Hz), 1.3 ~ 2.1 (5H, m), 2.1 ~ 2.6 (2H, m), 4.46 (1H, m). (Found: C, 67.08; H, 9.65. $C_8H_{14}O_2$ requires: C, 67.57; H, 9.93%).

2-Carboxy-4-hydroxy-6-methylheptanoic acid **1→4** *lactone* **7**

Magnesium methyl carbonate in DMF was prepared as reported.[13] The lactone **6** (7 g) and magnesium methyl carbonate (50 ml) were heated at 140° for 6 h under CO_2 atm. After cooling, the mixture was slowly added to an ice-cooled 6N–HCl (200 ml) and ether (200 ml). The ether layer was separated and the aqueous layer was extracted with ether. The ether soln was washed with water, and NaCl soln, dried ($MgSO_4$) and concentrated below 40°. The residue (**7**, 10.0 g) was employed in the next step without further purification. ν_{max} ~ 3400 (m), ~3200 (m), ~2600 (m), ~1780-~1700 (vs, br), 1470 (m), 1370 (m), 1180 (s), 1120 (m), 1000 (m), 950 (w) cm^{-1}.

Leucic acid

(a) *(S)-(−)-Isomer* **11a**. This was prepared by the method of Scheibler and Wheeler[17a] with slight modification in isolation procedure. A soln of $NaNO_2$ (63 g) in water (200 ml) was added dropwise during 3 h to an ice-cooled and stirred soln of *(S)*-(+)-leucine (**10**, 75 g) in N H_2SO_4. The mixture was stirred for an additional 2 h after the addition at 0–5° and left to stand overnight at room temp. The resulting clear soln was concentrated *in vacuo*. The residual semi-solid was extracted with ether and the ether soln concentrated *in vacuo*. The residue was mixed with C_6H_6 and concentrated to remove a trace of water. The above operations were repeated to give 108 g of crude leucic acid from 150 g of leucine. The crude acid crystallised when cooled. This was recrystallised three times from ether-pet. ether to give 85.5 g (57%) of pure **11a**, m.p. 80–81° (lit.[17a] m.p. 81–82°), as rods, $[\alpha]_D^{23} - 26.9°$ (c 1.55%, N NaOH) (lit.[17a] $[\alpha]_D^{20} - 27.7°$ (c 10%, N NaOH)); ν_{max} (Nujol) 3410 (s), ~2600, 1720 (s), 1280 (s), 1215 (m), 1140 (m), 1080 (s), 900 (m) cm^{-1}; δ ($CDCl_3$) 0.95 (6H, d, J = 6 Hz), 1.66 (2H, q, J = 6 Hz), ~1.90 (1H, m), 4.31 (1H, t, J = 6 Hz), 7.16 (2H, br. s).

(b) *(R)-(+)-Isomer* **11a'**. This was obtained from *(R)*-(−)-leucine (75 g) in 50.7% yield (38 g). Rods from ether pet. ether, m.p. 79–80° (lit.[17a] m.p. 80°); $[\alpha]_D^{24} + 26.5°$ (c 1.52%, N NaOH) (lit.[17a] $[\alpha]_D^{20} + 26.3°$ (c 9.1, N NaOH)).

Ethyl leucate

(a) *(S)-(−)-Isomer* **11b**. A soln of **11a** (70 g) in 99% EtOH (400 ml) was mixed with toluene (200 ml) and conc. HCl (2.5 ml). The mixture was heated on a boiling water bath for 1.5 h with slow removal of the solvent. The concentrated residue was diluted with 99% EtOH (200 ml) and toluene (120 ml). The soln was again heated on a boiling water bath for 1 h with removal of the solvent. The residue was fractionally distilled to give 74 g (87%) of **11b**, b.p. 85–87°/16 mm, n_D^{23} 1.4222; $[\alpha]_D^{23} - 10.8°$ (neat) (lit.[17a] $[\alpha]_D^{20} - 11.07°$ (neat)); ν_{max} 3480 (m), 2970 (s), 2880 (m), 1740 (vs), 1480 (m), 1400 (m), 1380 (m), 1280 (m), 1220 (s), 1150 (s), 1095 (m), 1030 (m), 935 (w), 860 (w), 750 (w) cm^{-1}; δ (CCl_4) 0.95 (6H, d, J = 6 Hz), 1.29 (3H, t, J = 7 Hz), 1.50 (2H, t), 1.95 (1H, m), 2.85 (1H, s), 4.10 (1H, t, J = 6 Hz), 4.20 (2H, q, J = 7 Hz). (Found: C, 59.61; H, 9.97. $C_8H_{16}O_3$ requires: C, 59.98; H, 10.07%).

(b) *(R)-(+)-Isomer* **11b'**. This was prepared from **11a'** (38 g) in 89% yield (41 g), b.p. 84–86°/15 mm; n_D^{25} 1.4214: $[\alpha]_D^{25} + 10.86°$ (neat).

THP ether of ethyl leucate

(c) *(S)-(−)-Isomer* **11c**. Dihydropyran (50 g) and *p*-TsOH (0.1 g) was added to a soln of **11b** (83 g) in dry ether (200 ml). The mixture was left to stand overnight at room temp. Then the soln was washed with K_2CO_3 aq, dried (K_2CO_3) and concentrated. The residue was distilled to give 123 g (97%) of **11c**, b.p. 99–100°/1.3 mm, n_D^{23} 1.4403; $[\alpha]_D^{23} - 52.8°$ (c 1.24%, acetone); ν_{max} 2960 (s), 2880 (m), 1755 (vs) 1480 (m), 1395 (m), 1370 (m), 1280 (m), 1210 (s), 1190 (s), 1155 (s), 1130 (s), 1080 (m), 1035 (s), 980 (s), 915 (m), 870 (m), 810 (m), 760 (m) cm^{-1}; δ (CCl_4) 0.95 (6H, d, J = 6 Hz), 1.20 (3H, t, J = 7 Hz), 1.60 (~7H, br.), ~3.0–4.4 (7H, m), 4.56 (1H). (Found: C, 63.87; H, 9.74. $C_{13}H_{24}O_4$ requires: C, 63.90; H, 9.90%).

(b) *(R)-(+)-Isomer* **11c'**. This was prepared from **11b'** (41 g) in 97% yield (61 g), b.p. 104–108°/1.4 mm; n_D^{24} 1.4404; $[\alpha]_D^{24} + 56.7°$ (c 1.56%, acetone).

4-Methylpentane-1,2-diol-2-THP ether

(a) *(S)-(−)-Isomer* **12a**. A soln of **11c** (122 g) in dry ether (200 ml) was added during 30 min to an ice-cooled and stirred suspension of $LiAlH_4$ (15 g) in dry ether (800 ml). The mixture was stirred for 2 h at 0–5° and left to stand overnight at room temp. Then the stirred mixture was ice-cooled and decomposed by successive addition of water (15 ml), 20% NaOH soln (15 ml) and water (45 ml). The mixture was stirred for 1.5 h and filtered. The filter cake was washed thoroughly with ether. The combined ether soln was dried (K_2CO_3) and concentrated. The residue was distilled to give 99 g (99%) of **12a**, b.p. 97–98°/1.2 mm, n_D^{23} 1.4521; $[\alpha]_D^{23} - 35.4°$ (c 2.8%, acetone); ν_{max} 3400 (m), 2950 (s), 2850 (s), 1460 (m), 1360 (m) 1260 (w), 1200 (m), 1160 (m), 1125 (s), 1105 (m), 1065 (s), 1015 (s), 970 (m), 895 (w), 860 (m), 800 (m) cm^{-1}; δ (CCl_4) 0.95 (6H, d, J = 6 Hz), ~1.60 (9H), ~3.50-~3.95 (~7H), 4.60, 4.86. (Found: C, 65.03; H, 10.87. $C_{11}H_{22}O_3$ requires: C, 65.31; H, 10.96%).

(b) *(R)-(+)-Isomer* **12a'**. This was prepared from **11c'** (61 g) in 89% yield (45 g), b.p. 100–105°/1.5 mm; $[\alpha]_D^{24} + 36.1°$ (c 2.13%, acetone).

4-Methylpentane-1,2-diol-1-tosylate-2-THP ether

(a) *(S)-Isomer* **12b**. Powdered *p*-TsCl (46 g) was added to an ice-cooled and stirred soln of **12a** (40 g) in dry C_5H_5N (200 ml). The mixture was stirred for 1 h at 0–5°, then poured into ice-water and extracted with ether. The ether extract was washed with water, $CuSO_4$ soln, water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 80 g of crude **12b**, ν_{max} 2950 (s), 2860 (m), 1600 (m), 1500 (w), 1465 (m), 1450 (m), 1365 (s), 1190 (s), 1180 (s), 1120 (m), 1095 (m), 1080 (m), 1030 (s), 980 (s), 920 (m), 860 (w), 810 (m) cm^{-1}. This was employed in the next step without further purification.

(b) *(R)-Isomer* **12b'**. This was prepared from **12a'** (45 g) to give 80 g of crude **12b'**.

(S)-(−)-4-Methylpentane-1,2-diol **13a**

A soln of *(S)*-(−)-leucic acid (**11a**, 44.5 g) in dry THF (200 ml) was added dropwise to an ice-cooled and stirred suspension of $LiAlH_4$ (16.0 g) in dry ether (800 ml) during 1.5 h. After stirring for 1 h at 0–5°, the mixture was left to stand overnight at room temp. Then the stirred mixture was ice-cooled and decomposed by successive addition of water (16 ml), 15% NaOH soln (16 ml) and water (48 ml). The mixture was diluted with acetone (600 ml), stirred for 1 hr and filtered. The filter cake was washed several times with acetone and the combined filtrates were concentrated. The residue was distilled to give 20.0 g (50%) of **13a**, b.p. 89–95°/5 mm (main b.p. 91°/5 mm), n_D^{23} 1.4405; $[\alpha]_D^{23} - 24.4°$ (c 1.84%, EtOH); ν_{max} 3300 (s), 2950 (s), 1480 (s), 1070 (s), 1030 (s) cm^{-1}; δ ($CDCl_3$) 0.91 (6H, d, J = 6 Hz), ~1.3 (2H), ~1.7 (1H), 3.56 (5H, br). (Found: C, 60.70; H, 11.42. $C_6H_{14}O_2$ requires: C, 60.98; H, 11.94%).

4-Methylpentane-1,2-diol-1-tosylate

(a) *(S)-Isomer* **13b**. The crude **12b** (80 g) was dissolved in a mixture of AcOH (200 ml), THF (100 ml) and water (100 ml). The soln was left to stand overnight at room temp, warmed at 50–60° for 2 h, poured into water and extracted with ether. The ether soln was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated. The residual **13b** (70 g) was used for the next step without further purification, ν_{max} ~ 3480 (m), 2960 (s), 1600 (m), 1500 (w), 1470 (m), 1360 (s), 1320 (w), 1300 (w), 1220 (w), 1195 (s), 1185 (s), 1100 (m), 1020 (w), 980 (m), 950 (m), 900 (w), 850 (m), 840 (m), 820 (m), 790 (w) cm^{-1}.

(b) *(R)-Isomer* **13b'**. This was prepared from **12b'** (80 g) to give 65 g of crude **13b'**.

1,2-Oxido-4-methylpentane

(a) *(S)-(−)-Isomer* **14**. A soln of KOH (100 g) in water (100 ml) was added to a stirred and ice-cooled soln of **13b** (70 g) in ethylene glycol (100 ml). The mixture soon solidified. It was diluted with water and shaken vigorously to dissolve the solid. The mixture was extracted with a small amount of ether. The ether soln was washed with water and NaCl soln, dried (K_2CO_3) and filtered. The ether soln was fractionated through a Vigreux column. Careful fractional distillation was essential. The epoxide **14** was obtained in 53% yield from **12a** (10.7 g), b.p. 64–66°/150 mm, n_D^{23} 1.4006; $[\alpha]_D^{23} - 17.9°$ (c 1.42%, EtOH); ν_{max} 3040 (m), 2960 (s), 2920 (s), 2870 (s), 1470 (s), 1430 (w), 1420 (m), 1395 (m), 1380 (m), 1350 (w), 1290 (w), 1270 (m), 1240 (w), 1180 (w), 1150 (w), 1130 (w), 1070 (w), 1020 (w), 960 (w), 950 (w), 920 (m), 880 (w), 850 (m), 840 (s), 810 (m), 785 (w), 760 (m) cm^{-1}; δ (CCl_4) 0.95 (6H, d, J = 6 Hz), 1.22 (2H, t, J = 6 Hz), ~1.70 (1H, m), ~2.20 (1H, q), ~2.4–~2.8 (2H, m). MS: *m/e* 100 (M^+).

(b) *(R)-(+)-Isomer* **14'**. This was prepared from **13b'** (65 g) in 36% yield from **12a'** (8.1 g), b.p. 54–56°/135 mm, n_D^{24} 1.3995; $[\alpha]_D^{24} + 17.5°$ (c 2.44%, EtOH).

2-Methylene-4-hydroxy-6-methylheptanoic acid **1→4** *lactone*

(a) *Racemate* **2**. 37% CH_2O aq soln (30 ml) and Et_2NH (5 ml) were added to crude **7** (10.0 g) and the mixture was heated at 70–80° for 30 min. Then AcONa (3 g) and AcOH (30 ml) were added to the mixture and it was heated at 70–80° for 15 min. The mixture was poured into ice-water and extracted with ether. The ether soln was washed with N HCl and NaCl soln, dried ($MgSO_4$) and concentrated. The residue was distilled to give 4.9 g (65%) of **2**, b.p. 93°/2 mm, n_D^{21} 1.4806; ν_{max} 2960 (s), 2860 (m), 1770 (vs), 1665 (m), 1470 (m), 1440 (w), 1400 (m), 1375 (w), 1360 (m), 1340 (w), 1285 (s), 1260 (m), 1220 (w), 1195 (m), 1160 (m), 1125 (s), 1070 (w), 1025 (m), 1005 (m), 985 (m), 950 (m), 880 (w), 865 (w), 810 (m) cm^{-1}; δ (CCl_4) 0.96 (6H, d, J = 6 Hz), 1.24–1.68 (2H, m), 1.68–2.08 (1H, m), 2.20–3.33 (2H, m), 4.48 (1H, quint), 5.50 (1H, t, J = 2 Hz), 6.00 (1H, t, J = 2 Hz). (Found: C, 69.62; H, 9.05. $C_9H_{14}O_2$ requires: C, 70.10; H, 9.15%).

(b) *(S)-(−)-Isomer* **2'**. Diethyl malonate (22 g) was added to a soln of NaOEt (prepared from 2.7 g of Na) in EtOH (100 ml). *(S)*-(−)-Epoxide (**14**, 11.0 g) in EtOH (20 ml) was added dropwise to a stirred soln of NaCH $(CO_2Et)_2$ and the mixture was stirred and heated under reflux for 5 h. Then a soln of KOH (12 g) in water (80 ml) was added and the mixture was stirred and heated under reflux for 1 h to effect hydrolysis. The mixture was concentrated *in vacuo* to remove EtOH, acidified with conc H_2SO_4 (30 ml) and ice-water, and thoroughly extracted with ether. The ether soln was washed with NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give crude **7'**, ν_{max} ~3400, ~1780–~1700, 1200 cm^{-1}. This was mixed with 37% CH_2O aq soln (45 ml) and Et_2NH (7.5 ml), and heated at 80–90° for 30 min. The mixture was diluted with water and extracted with ether. The ether extract was washed with water, dil HCl and NaCl soln, dried ($MgSO_4$) and concentrated. The residue was distilled to give 5.8 g (34% from **14**) of *(S)*-lactone **2'**, b.p. 86°/0.14 mm, n_D^{25} 1.4576; $[\alpha]_D^{25}$ − 66.6° (c 1.83%, EtOH); δ (CCl_4, 100 MHz) 0.98 (6H, d, J = 6 Hz), 1.24–1.68 (2H, m), 1.68–2.04 (1H, m), 2.36–3.28 (2H, m), 4.55 (1H, q, J = 6 Hz), 5.58 (1H, t, J = 2 Hz), 6.12 (1H, t, J = 2 Hz); δ (CCl_4, 60 MHz, **2'** (30 mg) + Eu(facam)$_3$ (100 mg)) 1.15 (3H, d, J = 6 Hz), 1.20 (3H, d, J = 6 Hz), ~2.10, ~3.55, 5.55 (1H, m), 6.54 (1H), 8.53 (1H).

(c) *(R)-(+)-Isomer* **2''**. This was prepared from 8.1 g of **14'** in the same manner as described for **2'** in 18% yield (2.3 g), b.p. 102–106°/6 mm, n_D^{24} 1.4579; $[\alpha]_D^{24}$ + 67.0° (c 1.44%, EtOH); δ (CCl_4, 60 MHz, **2''** (30 mg) + Eu(facam)$_3$ (100 mg)) 1.16 (6H, d, J = 6 Hz), ~2.10, ~3.60, 5.45 (1H, m), 6.42 (1H), 8.32 (1H).

2-Phenylselenomethyl-4-hydroxy-6-methylheptanoic acid **1→4** *lactone*

(a) *Racemate* **8**. $NaBH_4$ (1.2 g) was added portionwise to an ice-cooled and stirred suspension of $C_6H_5SeSeC_6H_5$ (5.1 g) in abs. EtOH (70 ml) under N_2 atm. The yellow colour of the diselenide disappeared rapidly. A soln of **2** (4.5 g) in abs. EtOH (30 ml) was added to the above soln of C_6H_5SeNa and the mixture was stirred for 2 h at room temp. Then it was poured into 0.1N HCl (500 ml) and extracted with ether. The ether soln was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated. The residue was chromatographed over Mallinckrodt AR 100 mesh silicic acid (200 g, 37 × 4 cm) in *n*-hexane. Elution with 1.6 l of *n*-hexane yielded a small amount of $C_6H_5SeSeC_6H_5$. Subsequent elution with 1.2 l of *n*-hexane-ether (9:1) gave 9.1 g (quantitative) of pale yellow oily **8**. Analytical sample distilled at 160–170°/0.15 mm, n_D^{22} 1.5524; ν_{max} 3060 (w), 2960 (s), 2860 (m), 1770 (vs), 1580 (m), 1480 (m), 1440 (m), 1385 (w), 1360 (m), 1340 (w), 1285 (m), 1200 (s), 1175 (s), 1135 (m), 1065 (w), 1020 (m), 1000 (m), 980 (m), 940 (w), 900 (w), 740 (s), 690 (m) cm^{-1}; δ (CCl_4) 0.92 (6H, d, J = 6 Hz), ~1.1–~2.0 (3H, m), ~2.2–3.0 (2H, m), 3.30 (1H, m), 4.30 (1H, br, m), ~7.2–~7.6 (5H, m); MS: *m/e* 312 (M^+, 100%), 310 (41%), 228 (54%), 226 (29%), 157 (39%), 134 (29%), 109 (37%), 78 (29%), 77 (32%), 69 (88%), 55 (73%), 41 (95%). (Found: C, 58.19; H, 6.56. $C_{15}H_{20}O_2Se$ requires: C, 58.00; H, 6.48%).

(b) *(S)-Isomer* **8'**. This was prepared from **2'** (4 g) in a quantitative yield (8.5 g).

(c) *(R)-Isomer* **8''**. This was prepared from **2''** (2.3 g) in a quantitative yield (5.0 g).

2-Phenylselenomethyl-4-hydroxy-6-methylheptanal **1→4** *lactol*

(a) *Racemate* **9**. *i*-Bu_2AlH (25% in *n*-hexane, 10 ml) was added dropwise to a stirred and cooled soln of **8** (3.2 g) in dry THF (30 ml) during 6 min at −60–−55° under N_2. The soln was stirred for 1 h at −60°. The reaction was quenched by the addition of sat NH_4Cl aq soln (10 ml) at −60°. Then the mixture was poured into ice-dil. HCl and extracted with ether. The ether extract was washed with water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 3.1 g (97%) of **9**, ν_{max} 3400 (m), 3260 (w), 2970 (s), 2940 (s), 2880 (m), 1580 (m), 1480 (m), 1445 (m), 1390 (w), 1380 (w), 1340 (w), 1280 (w), 1030 (s), 880 (w), 820 (w), 750 (s), 700 (m) cm^{-1}; δ (CCl_4) 0.88 (6H, d, J = 6 Hz), 1.1 ~ 2.0 (3H, m), 2.0 ~ 2.4 (2H, m), 2.80 (2H, m), 4.15 (1H, m), 4.40 (1H, br. s), 5.20 (1H), 7,10 ~ 7.70 (5H, m). This was employed in the next step without further purification.

(b) *(S)-Isomer* **9'**. This was prepared from **8'** (8.0 g) in a quantitative yield (8.0 g).

(c) *(R)-Isomer* **9''**. This was prepared from **8''** (5.0 g) in a quantitative yield (5.0 g).

Ipsenol (*2-methyl-6-methyleneoct-7-en-4-ol*)

(a) *Racemate* **1**. Triphenylmethylphosphonium bromide (10.7 g) was added to a soln of $NaCH_2SOMe$ (from 1.3 g of 50% NaH) in dry DMSO (50 ml) under N_2 with stirring at room temp. The mixture was stirred for 10 min to yield an orange soln of the Wittig reagent. A soln of **9** (3.1 g) in dry THF (10 ml) was added dropwise to the stirred soln. The mixture turned red and deep red solid separated. This was stirred for 3 h at room temp., poured into ice-water and extracted with *n*-hexane. The extract was washed with 80% MeOH aq soln (5 ml × 2), water and NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over Woelm neutral alumina (activity grade II, 20 g, 10 × 1.8 cm) in pet. ether. Elution with pet. ether gave some hydrocarbon impurities. Subsequent elution with pet. ether–ether (9:1–4:1, 350 ml) gave 0.7 g (44%) of (±)-ipsenol, b.p. 66–67°/5 mm, n_D^{22} 1.4664; ν_{max} ~3360 (s), 3080 (m), 2960 (vs), 2920 (s), 2860 (s), 1800 (w), 1630 (w), 1590 (s), 1465 (s), 1385 (m), 1370 (m), 1340 (w), 1320 (w), 1280 (w), 1230 (w), 1170 (w), 1140 (m), 1070 (m), 1020 (m), 985 (s), 890 (vs), 840 (w), 820 (w), 760 (w) cm^{-1}; δ (CCl_4, 100 MHz) 0.88 (3H, d, J = 6 Hz), 0.92 (3H, d, J = 6 Hz) ~1.20 (2H, q), 1.76 (1H, s), ~1.80 (1H, m), 2.28 (2H, m), 3.72 (1H, sept), ~5.00–~5.30 (3H, m), 6.19–6.48 (1H, q); MS (70 eV): *m/e* 39.0245 (C_3H_3, 13%), 41.0401 (C_3H_5, 43%), 43.0562 (C_3H_7, 47%), 45.0353 (C_2H_5, 26%), 53.0394 (C_4H_5, 10%), 57.0711 (C_4H_9, 14%), 67.0549 (C_5H_7, 28%), 68.0625 (C_5H_8, 100%, base peak), 69,0699 (C_5H_9, 65%), 85.0645 (C_5H_9O, 15%), 136.1244 ($C_{10}H_{16} = M^+ - H_2O$, 1%). GLC (Column 5% LAC-2R-446, 1.5 m × 3 mmi.d. at 100°, Carrier gas, N_2, 1.0 kg/cm^2): Rt 6.4 min (99.5% purity). (Found: C, 77.64; H, 11.46. $C_{10}H_{18}O$ requires: C, 77.86; H, 11.76%).

(b) *(S)-(−)-Isomer* **1'**. In the same manner as described above *(S)*-**9'** (8.0 g) gave **1'** (1.0 g, 25% from **2'**), b.p. 63–64°/5 mm, n_D^{24} 1.4633; $[\alpha]_D^{24}$ − 16.5° (c 1.47%, EtOH) (lit.[1] $[\alpha]_D^{25}$ − 17.5 ± 0.7° (c 1%, EtOH)). These figures indicate that the optical purity of **1'** is at least 94%.; δ (CCl_4, 60 MHz), 0.86 (3H, d, J = 6 Hz), 0.90 (3H, d, J = 6 Hz), 1.28 (2H, q), 1.45 ~ 2.00 (1H, m), 1.70 (1H, s), ~2.30 (2H, m), 3.74 (1H, sept), ~4.90–~5.40 (5.10, 5.37; 3H, m), 6.10–6.70 (6.18, 6.34, 6.47, 6.64; 1H, dd, J = 17 Hz, J' = 10 Hz); δ (60 MHz, **1'** (51 mg) + Eu (facam)$_3$ (125 mg) in 0.4 ml CCl_4) 1.98 (3H, d, J = 6 Hz), 2.06 (3H, d, J = 6 Hz), ~4.2 (1H, m), ~5.1 (1H, m), 5.64, 5.80, 6.10, 6.42, 6.54, 6.82, 6.98, 7.24, 7.42, 7.54, 7.72, 10.22 (1H, m).

(c) *(R)-(+)-Isomer* **1''**. In the same manner as described above *(R)*-**9''** (5.0 g) gave **1''** (0.9 g, 39% from **2'**), b.p. 62–64°/5 mm, n_D^{25} 1.4626; $[\alpha]_D^{25}$ + 17.3° (c 1.58%, EtOH). This figure indicates that **1''** is at least 99% optically pure; δ (60 MHz, **1''** (40 mg) + Eu (facam)$_3$ (102 mg) in 0.4 ml CCl_4) 1.99 (6H, dd, J = 6 Hz, J' = 1.5 Hz), ~4.2 (1H, m), ~5.0 (1H, m), 5.62, 5.80, 6.08, 6.52, 6.82, 7.20, 7.38, 7.50, 7.68, 10.22 (1H, m). The IR and NMR spectra of **1**, **1'** and **1''** were completely identical with those of the natural pheromone recorded in the literature.[1]

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