

SYNTHESIS AND ABSOLUTE CONFIGURATION OF
(-)-IPSENOL (2-METHYL-6-METHYLENE-7-OCTEN-4-OL),
THE PHEROMONE OF IPS PARACONFUSUS LANIER

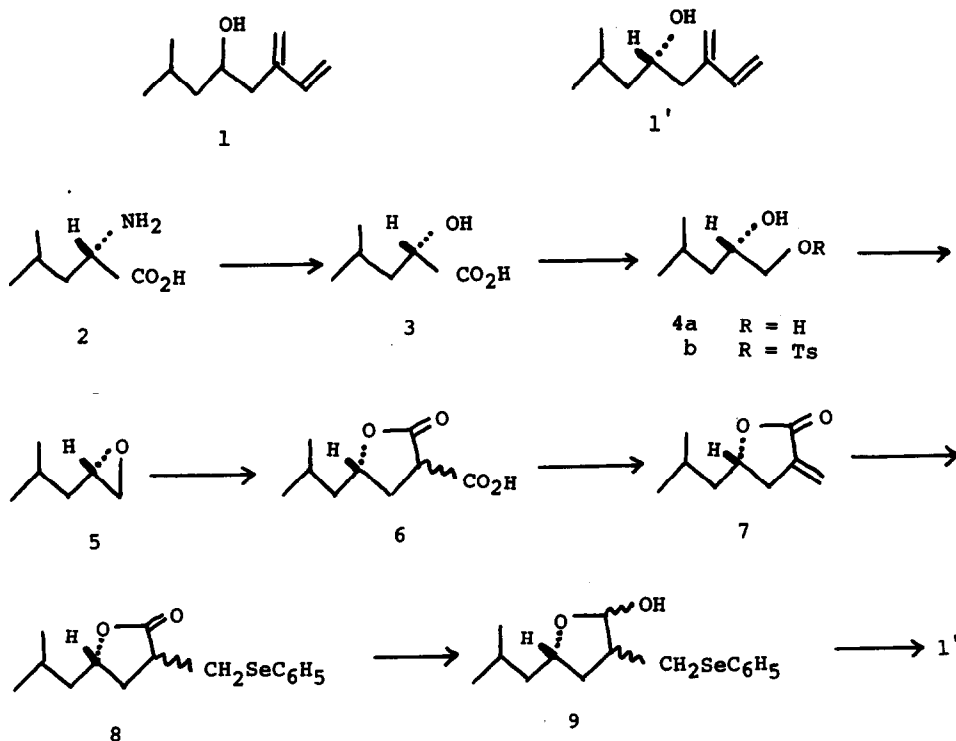
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(-)-Ipsenol is one of the aggregation pheromones of a bark beetle, Ips paraconfusus Lanier.^{1,2} The structure (1) proposed for it on the basis of spectral data has been confirmed by syntheses of its racemate.³⁻⁵ However, its absolute configuration has remained unknown. None of the reported syntheses is applicable to the preparation of optically active ipsenol of known absolute configuration. As a part of our project to synthesize optically active pheromones,⁶ we have converted L-(+)-leucine (2, S-configuration) into (S)-(-)-ipsenol (1'), thus establishing the absolute configuration of the pheromone. The key intermediate in the present synthesis is an optically active α -methylene- γ -lactone (7).

L-(+)-Leucine (2) was treated with HNO_2 to give (S)-(-)-leucic acid (3), mp 78-80°; $[\alpha]_D^{22} -24.8^\circ$ (c=1.47, N-NaOH), [lit.⁷ $[\alpha]_D^{20} -27.7^\circ$ (c=1.0, N-NaOH)]. This reaction is known to proceed with full retention of configuration.⁸ The rotation value indicated that our leucic acid was of 90% optical purity. This was reduced with LiAlH_4 to give a glycol (4a), bp 89-91°/5mm; n_D^{23} 1.4405; $[\alpha]_D^{23} -24.7^\circ$ (c=1.84, EtOH). Tosylation (1 eq of P-TsCl/ $\text{C}_5\text{H}_5\text{N}$) gave crude monotosylate (4b). This was treated with KOH aq soln to give an epoxide (5), bp 62-65°/150 mm; n_D^{22} 1.4050; $[\alpha]_D^{22} -16.1^\circ$ (c=1.83, EtOH).^{cf.9}



Condensation of 5 with diethyl malonate (NaOEt/EtOH) followed by alkaline hydrolysis (KOH aq) and acidification (H₂SO₄ aq soln) gave an α -carboxy- γ -lactone (6).^{10,cf.11} This was treated with CH₂O aq soln and Et₂NH¹² to give an α -methylene- γ -lactone (7), bp 95° / 3mm; n_D^{23} 1.4600; $[\alpha]_D^{23}$ -54.4° (c=1.11, EtOH); ν_{\max} (film) 1770, 1665 cm⁻¹. The IR and NMR spectra of this key intermediate (7) was identical with those of its racemate prepared from (i)-4-hydroxy-6-methylheptanoic acid lactone, bp 88-89° / 5 mm, n_D^{22} 1.4422, by the standard carboxylation-methylenation method.¹³ The methylene group of 7 was protected by the Michael addition of C₆H₅SeH.¹⁴ The resulting seleno compound (8), ν_{\max} (film) 1770, 1580 cm⁻¹, was treated with *i*-Bu₂AlH/THF (-60°, 1 hr) to give a hemiacetal (9), ν_{\max} (film) 3400 cm⁻¹. This was converted by the Wittig reaction [(C₆H₅)₃P(CH₃)Br/NaH/DMSO, room temp, 2 hr] to (S)-(-)-ipse-nol (1') with concomitant removal of the selenophenyl protecting group due to a retro-Michael process. The product, after chromatographic purification

(Al₂O₃) and distillation, exhibited the following properties : bp 65-66° / 5 mm; n_D^{23} 1.4656; $[\alpha]_D^{23}$ -13.9° (c=1.41, EtOH) ; ν_{\max} (film) 3360 (s), 3080 (m), 1590 (s), 1465 (s), 1370 (m), 1070 (m), 1020 (m), 985 (s), 890 (s) cm⁻¹ ; δ (100 MHz, CCl₄) 0.88 (3H, d, J=6Hz), 0.92 (3H, d, J=6Hz), ~1.20 (2H, q), 1.76 (1H, s, -OH), ~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 136. 1244 (C₁₀H₁₆ =M⁺ -H₂O). The spectral data of our product was identical with those of the natural pheromone recorded in the literature.¹ The rotation value of the natural ipsenol was reported to be : $[\alpha]_D^{25}$ -17.5° ± 0.7° (c=1, EtOH).¹ Our product is therefore of 80% optical purity.^{15,16}

In conclusion the natural ipsenol possesses (S)-configuration as represented by 1'. Our work is continuing to obtain optically pure enantiomers of ipsenol in order to test their biological activities.

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 15. Formation of a small amount of the undesired monotosylate at the secondary hydroxyl group of 4a in the course of the tosylation would cause the genesis of (R)-epoxide and hence lower the optical purity of the epoxide (5).
 16. All the compounds described in this paper gave reasonable spectral (IR and NMR) and analytical (combustion or MS) data.