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ABSOLUTE CONFIGURATION OF (+)-IPSDIENOL, THE PHEROMONE OF *IPS PARACONFUSUS* LANIER, AS DETERMINED BY THE SYNTHESIS OF ITS (R)-(-)-ISOMER

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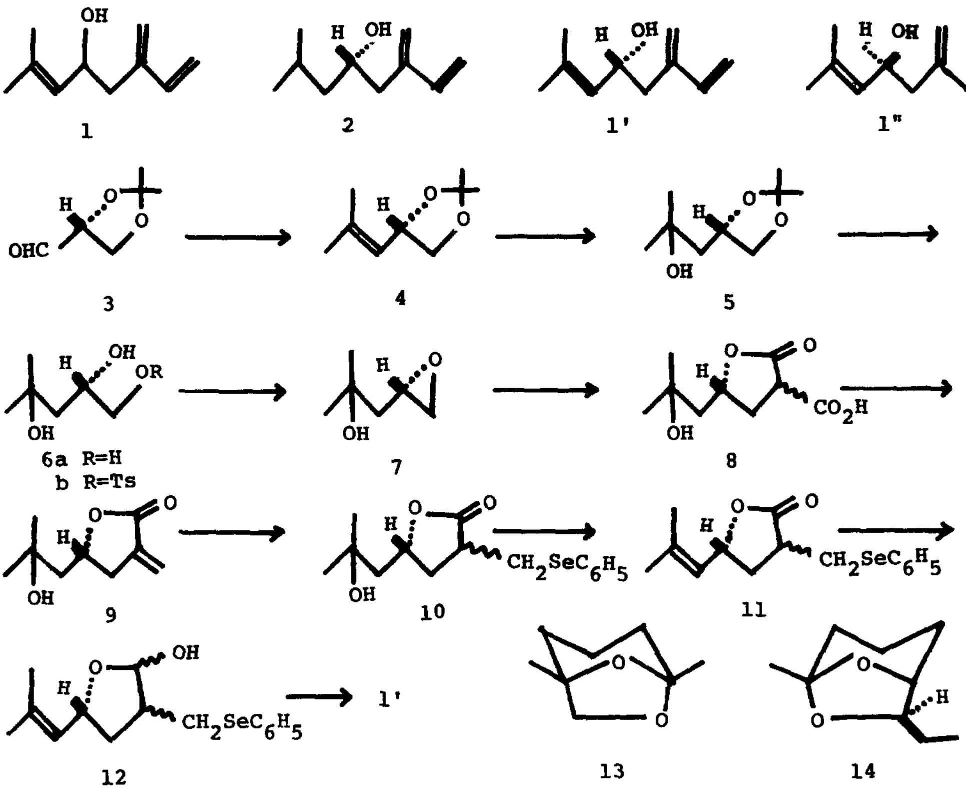
(+)-Ipsdienol (2-methyl-6-methylene-2,7-octadien-4-ol, 1) is one of the aggregation pheromones of a bark beetle, *Ips paraconfusus* Lanier.[1,2] The structure (1) proposed for it on the basis of spectral data was confirmed by syntheses of its racemate.[3-5] However, its absolute configuration remained unknown. None of the reported syntheses was applicable to the preparation of optically active ipsdienol of known absolute configuration. As a part of our project to synthesize optically active pheromones,[6] we have now synthesized (*R*)-(-)-ipsdienol(1') unambiguously establishing the absolute configuration of the pheromone (1) to be *S* (1").

In contrast with the synthesis of (*S*)-(-)-ipsenol (2) which started from an amino acid (leucine),[7] the present synthesis started from a sugar derivative, (*R*)-(+)-glyceraldehyde acetonide (3), which was readily obtainable from *D*-mannitol.[9] The Wittig reaction between 3 and a phosphorane $[(C_6H_5)_3\overset{+}{P}(CHMe_2)\overset{-}{I}/NaH/DMSO]$ yielded an olefin (4), bp 72-75°/20 mm ; n_D^{22} 1.4374 ; $[\alpha]_D^{22}$ - 16.7° (c=2.98, C_6H_6). The oxymercuration-demercuration $[Hg(OAc)_2/THF\text{-}H_2O/NaBH_4]$[10] of 4 gave an alcohol (5), bp 75-77°/7mm; n_D^{22} 1.4344 ; $[\alpha]_D^{22}$ + 10.6° (c=2.87, acetone). The protecting group was removed (*N*-HCl-95% EtOH) to give a triol (6a) as a crude oil. This was converted (1 eq TsCl/C_5H_5N) to a monotosylate (6b). Without further purification, this was reacted with KOH aq soln to give an epoxide (7), bp 78-



80°/10mm ; n_D^{23} 1.4368 ; $[\alpha]_D^{23}$ - 13.7° (c=1.91, $CHCl_3$). Hereafter we followed our route for the synthesis of (S)-(-)-ipsenol[7] with an additional step to re-introduce the trisubstituted double bond (10 →11). Condensation of 7 with diethyl malonate (NaOEt/EtOH) followed by alkaline hydrolysis (KOH aq soln) and acidification (H_2SO_4 aq soln) gave an α-carboxy-γ-lactone (8). This was treated with CH_2O aq soln and Et_2NH to give an α-methylene-γ-lactone (9), bp 130-132°/1.2 mm; n_D^{22} 1.4754; $[\alpha]_D^{22}$-32.6° (c=1.25, EtOH); ν_{max} (film) 3420, 1770, 1670 cm^{-1}. The methylene group was protected by the Michael addition of C_6H_5SeH.[11] The resulting seleno compound (10) was dehydrated ($POCl_3/C_5H_5N$) to give an olefinic lactone (11) after chromatographic purification (SiO_2-$AgNO_3$), δ (60MHz, CCl_4) 1.66 (3H, d, J=2Hz), 1.70 (3H, d, J=2Hz), 1.9-3.6 (5H), 4.80 (1H), 5.10 (1H), 7.2 -7.7 (5H, m). Reduction of 11 with i-Bu_2AlH/THF (-60°, 1hr) gave a lactol (12), ν_{max} (film) 3380 cm^{-1}. This was converted by the Wittig reaction $[(C_6H_5)_3\overset{+}{P}(CH_3)$-$Br^-$/NaH/DMSO$]$ to (R)-ipsdienol (1') with concomitant removal of the protecting group by a retro-Michael reaction. The product, after chromatographic purification (Al_2O_3) and distillation, exhibited the following properties : bp (bath temp) 80-90°/7mm ; n_D^{20} 1.4893 ; $[\alpha]_D^{20}$ -5.0 (c=0.558, MeOH); ν_{max} (film) 3320 (s) 3080 (m), 1670 (w), 1630 (w), 1595 (vs), 1020 (s), 990 (vs), 895 (vs) cm^{-1}; δ (100 MHz, $CDCl_3$) 1.66 (3H, s), 1.71 (3H, s), 2.37 (2H, d, J=7Hz), ~3.5 (1H, -OH), 4.45 (1H, dt J_1=7, J_2=6 Hz), 4.90-5.40 (5H, m), 6.34 (1H, dd, J_1=16, J_2= 10Hz); MS : m/e 134.1118 ($C_{10}H_{14}=M^+-H_2O$). The spectral data were identical with those of the natural and racemic pheromones.[2,5] The optical rotation of the natural ipsdienol was reported to be : $[\alpha]_D^{20}$ + 10° ± 0.9° (c=1, MeOH).[1,2] Our synthetic (*R*)-(-)-ipsdienol (**1'**) was therefore of 50% optical purity. Milder reaction conditions should be sought to improve this value.[12,13]

In conclusion the natural pheromone possesses *S*-configuration as represented by **1"**. This absolute stereochemistry is the opposite of that of the natural and biologically active ipsenol (**2**). A similar stereochemistry-biological activity relationship was encountered recently : the biologically active enantiomer of *exo*-brevicomin possesses I*R* : 7*R* - configuration (**14**), while that of frontalin possesses the opposite *S*-configuration (**13**).[6a,b,14]

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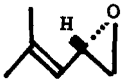

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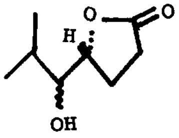

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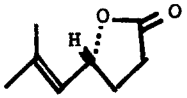

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