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SYNTHESIS OF (±)-LINEATIN, THE UNIQUE TRICYCLIC PHEROMONE OF TRYPODENDRON LINEATUM (OLIVIER)

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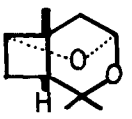
Summary : (±)-3,3,7-Trimethyl-2,9-dioxatricyclo[4.2.1.$0^{4,7}$]nonane 1 and (±)-3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$]nonane 2 were synthesized. The latter was shown to be (±)-lineatin, an ambrosia beetle pheromone.

Lineatin is an attractant compound isolated from frass produced by female beetles of Trypodendron lineatum (Olivier) boring in Douglas fir.[2] Its structure has been proposed to be one of the two isomeric tricyclic acetals (1 or 2 without assignment of the absolute configuration).[2] It therefore seems to be biogenetically related to grandisol 3, one of the components of the boll-weevil pheromone.[3] In continuation of our work on the synthesis of 3,[4] we have now accomplished the synthesis of the racemates of 1 and 2 and established that the structure of lineatin is 2.



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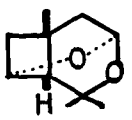

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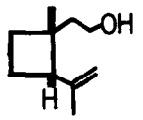

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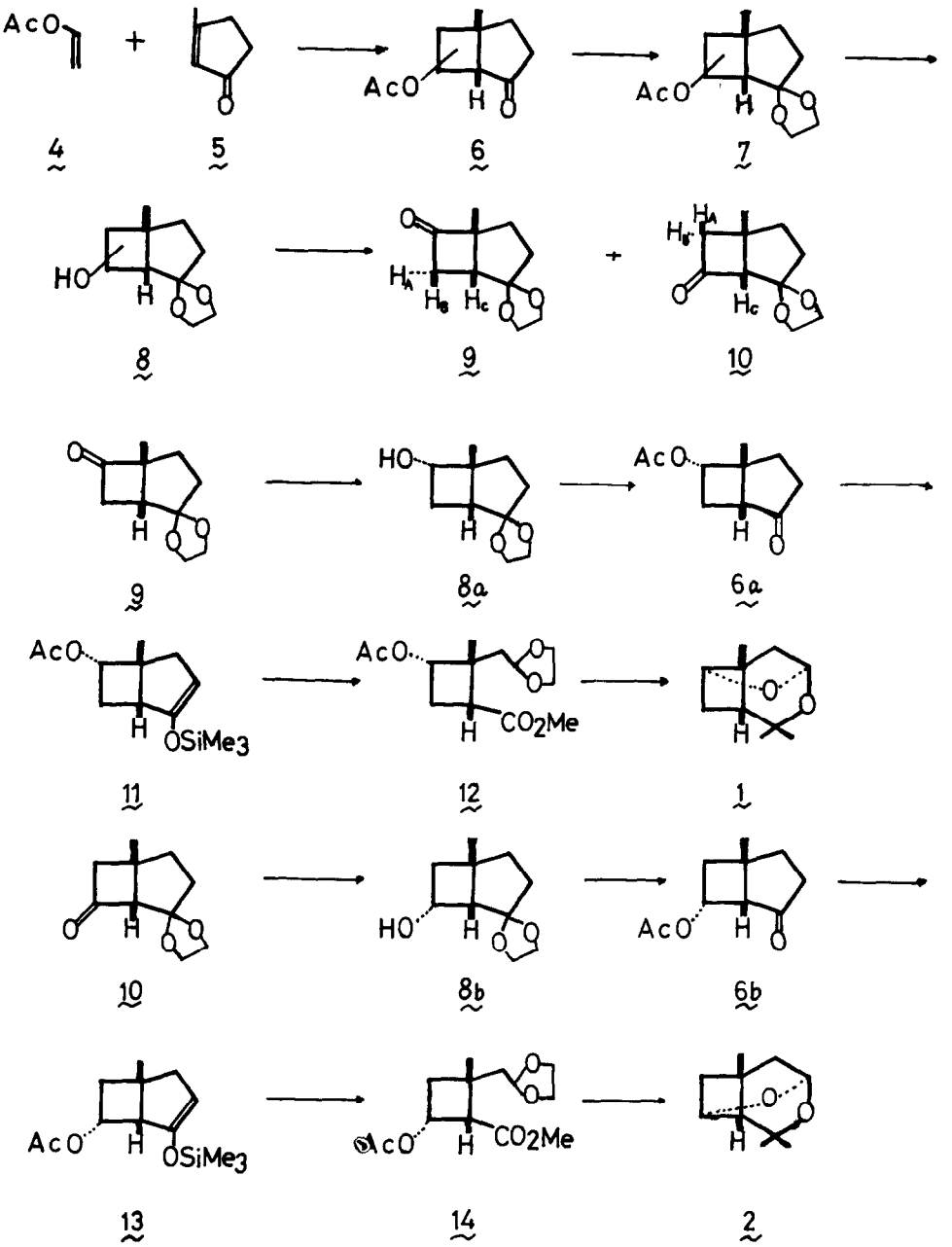
The construction of the cyclobutane ring was carried out by the photocycloaddition (4 + 5 → 6). Irradiation (450W Ushio UM-452 UV lamp) of vinyl acetate 4 and an enone 5[5] in benzene for 60 hrs at 4~6° gave the adduct 6, bp 73-75°/0.3mm, n_D^{22} 1.4650, in 60% yield as a mixture of four possible stereo-

isomers.[6] Since it was impossible to separate the four isomers completely, the mixture 6 was employed directly for the next step. Treatment of 6 with butanone ethyleneacetal in the presence of p-TsOH gave a mixture 7 of acetoxy acetals, bp 93~97°/0.5 mm, n_D^{20} 1.4620, in 91.5% yield. This was converted to



a mixture 8 of hydroxy acetals, bp 93~103°/0.4mm, in 93% yield by treatment with KCN in 95% EtOH.[7] Oxidation of 8 with CrO_3-C_5H_5N-HCl in CH_2Cl_2[8] gave in 75% yield a mixture of two isomeric ketones 9 and 10. These were separable by chromatography over silicic acid (Mallinckrodt CC-7). The major product 9, bp 86~89°/1.0mm, n_D^{22} 1.4735, was eluted in earlier fractions, amounting to 78% of the total. The minor product 10 (22% of the total), bp 92~100°/1.0mm n_D^{20} 1.4810, was eluted later. Both were gas chromatoraphically pure and their structures were supported by the following NMR data : δ (100 MHz, CCl_4) 2.24 (1H, dd J_{AC}=6, J_{BC}=10Hz, Hc), 2.80 (1H, dd, J_{AC}=6, J_{AB}=20Hz, H_A), 3.16 (1H, dd, J_{BC}=10, J_{AB}=20Hz, H_B) for 9 and 2.52-3.00 (3H, m, H_A, H_B, H_C) for 10.

The major ketone 9 was converted to (±)-1 in the following manner. Reduction of 9 with L-selectride ($Li(sec\text{-}Bu)_3BH$)[9] in THF gave a mixture of an endo-alcohol 8a (89% pure) contaminated with a small amount (11%) of its exo-isomer, bp 102~110°/0.6 mm, n_D^{22} 1.4830. The endo stereochemistry 8a of the major alcohol was assigned on the basis of the NMR evidence that the 3H-singlet due to the angular Me group shifted less significantly upon addition of Eu-$(fod)_3$ in the case of the major isomer than in the case of the minor one. Since the separation of these two isomers was difficult, the synthesis was carried through to the completion employing impure 8a.[10] Acetylation (Ac_2O/C_5H_5N) of 8a gave the corresponding acetate which was heated in 50% AcOH to give 6a, bp 85~89°/0.5mm, n_D^{20} 1.4670, in 71% yield from 8a. The acetoxy ketone 6a was treated with $LiN(i\text{-}Pr)_2$ and Me_3SiCl in THF to give 11. This was dissolved in CH_2Cl_2 and reacted with O_3. Reductive work-up (Ph_3P) of the ozonide followed by mild acid treatment (AcOH), esterification (CH_2N_2) and acetalization with methyl ethylene orthoformate and p-TsOH in CH_2Cl_2 (2 days at room temp.) yielded 12 in 11% yield from 11. This was treated with MeMgI in ether and the reaction was acidified with dil HCl (30 min at room temp.) to give (±)-3,3,7-trimethyl-2,9-dioxatricyclo[$4.2.1.0^{4,7}$]nonane 1 in 28% yield from 12. Its spectral data[11] were quite different from those of lineatin.[2] The proposed structure 1 was therefore excluded.

The synthesis of a racemate with the alternative structure 2 was carried out in the same manner starting from the isomeric ketone 10. In this case,

however, 8b and the corresponding hydroxy ketone were unstable and apt to suffer cyclobutane ring cleavage. The hydroxy ketal 8b was therefore immediately acetylated to give the corresponding acetate, which afforded 6b after hydrolysis with 50% AcOH. The rest of the synthetic sequence went smoothly to give the desired product 2. Its spectral data[12] were in very good accord with the published charts.[2] The complicated finger-print region of the IR spectrum of our (±)-2 coincided with that of lineatin.[2]

The structure of lineatin was thus established as 3,3,7-trimethyl-2,9-dioxatricyclo[3.3.1.$0^{4,7}$]nonane 2. The biological activity of synthetic 1 and 2 on Trypodendron lineatum and T. domesticum will be reported in due course by Prof. J.P. Vité, University of Freiburg. Synthesis of optically pure lineatin is now in progress to determine the absolute stereochemistry of the natural pheromone.[13,14]

REFERENCES AND FOOTNOTES

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6 Satisfactory spectral (IR and NMR) and analytical (combustion and/or MS) data were obtained for all the compounds described in this paper.

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10 It should be mentioned that the exo-isomer could not yield any intramolecular tricyclic acetal because of the unfavorable orientation of the OH group and hence caused no trouble in securing the final product 1.

11 ν_{max} (CCl_4) 2960 (s), 2920 (s), 2850 (m), 1455 (m), 1385 (m), 1370 (m), 1360 (w), 1350 (w), 1330 (m), 1305 (w), 1260 (w), 1240 (w), 1215 (m), 1200 (m), 1180 (w), 1160 (w), 1150 (s), 1120 (s), 1100 (m), 1050 (s), 1040 (w), 1020 (m), 1000 (m), 990 (w), 980 (w), 950 (w), 940 (s), 920 (w), 910 (s), 895 (s), 850 (w) cm^{-1} ; δ (100MHz, CCl_4) 1.06 (3H, s), 1.20 (3H, s), 1.37 (3H, s), 1.50-2.60 (5H, m), 3.88 (1H, -CHOR), 5.24 (1H, -CH(OR)OR'), MS : m/e 168 (M^+), 124, 109, 83, 81, 71, 69, 55, 43 (base peak), 41, 39.

12 ν_{max} (CCl_4) 2960 (s), 2920 (s), 2850 (m), 1465 (m), 1450 (m), 1380 (m), 1365 (m), 1340 (w), 1315 (m), 1240 (w), 1225 (m), 1205 (m), 1185 (m), 1170 (s), 1125 (s), 1100 (m), 1075 (m), 1015 (w), 995 (m), 960 (s), 920 (w), 900 (s), 830 (w) cm^{-1}; δ (100 MHz, CCl_4) 1.09 (3H, s), 1.14 (6H, s), 1.50-2.40 (5H, m, ~1.60, ~1.76, ~1.94), 4.34 (1H, -CHOR), 4.86 (1H, -CH(OR)OR'); MS:m/e 168 (M^+), 153, 140, 125, 111, 109, 107, 96, 85 (base peak), 83, 69, 56, 55, 43, 41.

13 We thank Prof. J.P. Vité for discussions. Our thanks are due to Sumitomo Chemical Co. for financial support.

14 A synthesis of a mixture of (±)-1 and (±)-2 is briefly stated in ref.2 without experimental details.

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