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SYNTHESIS AND STEREOCHEMISTRY OF TETRAHYDRO-3,5-DIMETHYL-6-(1-METHYLBUTYL)-2H-PYRAN-2-ONE, A COMPONENT OF THE QUEEN RECOGNITION PHEROMONE OF SOLENOPSIS INVICTA.

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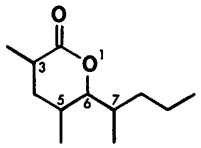
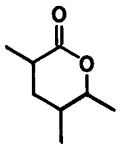
Summary. One of the diastereomers of the title compound, I, isolated from imported fire ant queens, has been prepared and named invictolide. It is responsible, in part, for "queen recognition" by workers of the species.

We have previously outlined the reasons for our interest in the queen recognition pheromone of the red imported fire ant, Solenopsis invicta (Buren), and identified one component of this pheromone as an α-pyrone (4). We have identified a second component as an aliphatic--δ-lactone, tetrahydro-3,5-dimethyl-6-(1-methylbutyl)-2H-pyran-2-one, I. A similarly substituted δ-lactone, II, has been isolated from male ants of the genus Calomyrmex, but no conclusions were drawn concerning the relative sterochemistry in the natural substance (5).



I



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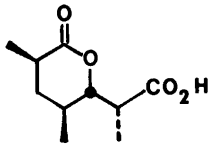
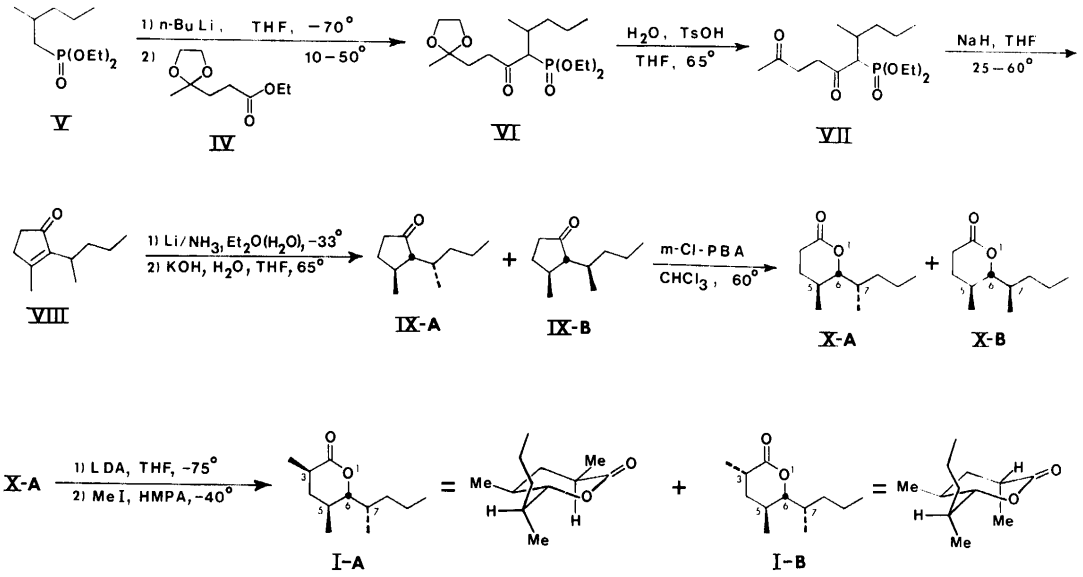


III

We could confidently assign the relative configuration at two of the chiral carbons in the natural lactone I as trans-substituted across the C-5/C-6 bond based on its ^{1}H NMR spectrum (ca. 16 μg, 300 MHz, benzene-d_6); the resonance for the proton at C-6 (3.44 ppm) is a sharp doublet with J = 10.1 Hz implying an anti-diaxial disposition of the protons at C-5 and C-6. This compares favorably with the coupling constants (9-10 Hz) for the corresponding protons on analogous trans-substituted bonds in the Prelog-Djerassi lactone, III, and related compounds (6a-e). In contrast with these compounds, however, is the absence of significant coupling between the proton at C-6 and the side-chain methine proton at C-7 in the natural lactone I; in III and related compounds coupling between the ring and side-chain methine protons is typically 2-4 Hz. This implies hindered rotation about the C-6/C-7 bond in the natural lactone I, leaving a conformation with those methine C-H bonds almost orthogonal.

We were not able to assign the relative configuration at the remaining two chiral carbons (C-3 & C-7) in the natural lactone I. For convenience in nomenclature we therefore refer to the isomer of I isolated from S. invicta queens as invictolide. Having noted the gross similarity between the proposed structure for invictolide and III, we sought a synthesis which could yield the four diastereomers of I being trans across the C-5/C-6 bond and epimeric at C-3 and C-7.

The preparation of an isomer of I with the same relative stereochemistry as invictolide, an extension of the synthesis of III by Grieco et al. (7), is shown below. The key intermediate, 3-methyl-2-(1-methylbutyl)-cyclopent-2-enone (VIII), was prepared by modifying the jasmone synthesis of Clark et al. (8).



Ethyl levulinate was protected as its ketal, IV (68% dist. yield, bp 104-5°C/7-8 Torr), with ethylene gylcol. Diethyl-2-methylpentyl phosphonate, V, was prepared by Michaelis-Arbuzov reaction (51% dist. yield, bp 94-7°/1-2 Torr) between triethyl phosphite and 1-bromo-2-methyl-pentane. Condensation of 0.5 equiv. of IV with the Li anion of V gave the protected β-keto-phosphonate, VI (59% dist. yield, bp 151-3°/0.01-.02 Torr), which was hydrolyzed to the β,ε-diketophosphonate, VII (75% dist. yield, bp 129-31°/0.01-.02 Torr). Cyclization of VII gave VIII in 61% dist. yield (bp 60-5°/0.7-.8 Torr). Spectral data for VIII are given in (12).

Reduction of VIII (9a,b) gave a mixture of four trans and cis substituted cyclopentanones in a ratio of 4:1, trans:cis (cap. GC, 30 m OV®-101). This mixture was epimerized with hydroxide giving two essentially pure trans isomers (ca. 40:1, trans:cis (10)) of 3-methyl--2-(1-methylbutyl)-cyclopentanone, (±)-IX-A&B, in a ratio of ca. 3:2, A:B. These were separated (IX-A, high R_f; IX-B, low R_f) by HPLC on silica (2% Et_2O/Hex.) and the

configurations shown tentatively assigned based on the ^{13}C NMR spectra of these epimers (12). In IX-A a methyl carbon (δ20.5), presumably on the epimeric carbon, resonates to high field of the corresponding methyl (δ21.15) in IX-B. A favorable conformation for the side-chain (models) places the methyl in IX-A below the ring plane (shielded, and perhaps anisotropically shielded by the carbonyl), but leaves the epimeric methyl in IX-B in the plane of the ring. Further evidence for the assignment of these configurations comes from the ^{1}H NMR spectra (12) of the corresponding lactones, (±)-X-A&B, obtained by Baeyer-Villiger oxidation (7) of the cyclopentanones. The resonance for the methyl at C-7 (δ0.76) in X-A is to high field of that for the methyl (δ0.96) in X-B. The same trend is seen for the analogous methyl resonances in the ^{1}H NMR spectra of III and its epimers (7a); the side-chain methyls are at higher field for the configuration which places them below the plane of the ring as in III and X-A. X-A shows a sharp doublet for the proton at C-6, whereas X-B shows a double doublet; it therefore seemed that X-A would lead to invictolide. Methylation (7,11) of X-A gave (±)-I-A&B in a ratio of 53:47, A:B. These were separated (I-A, high R_f; I-B, low R_f) by HPLC on silica (7% Et_2O/Hex.) and configurations assigned based on comparison of their spectra (12) to the IR (6b) and ^{1}H NMR (6c) spectra of III and its corresponding epimer. I-A has a lower carbonyl stretching frequency, a resonance for a less shielded ("equatorial") methyl at C-3, and a resonance for a more shielded ("axial") proton at C-3 containing an anti-diaxial coupling constant (J = ca. 13 Hz). I-A is thus more similar to III and I-B then has an "axial" methyl at C-3.

(±)-I-B is spectroscopically (IR, ^{1}H NMR, EI & CI MS) and chromatographically (GC, 30 m OV-1 and SP-2340® cap. cols.) identical with invictolide, and I-A is then (±)-3-epi-invictolide. Synthetic (±)-invictolide (99.7% by GC) is biologically active in combination with other pheromone components at ca. 5 ng/rubber "surrogate queen" (weighing ca. 20 mg). We presently do not have evidence that (±)-3-epi-invictolide is biologically active.

Notes and References

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(3) Mention of commercial products does not constitute an endorsement by the USDA.

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(10) In a separate experiment the original reduction mixture of cyclopentanones was noted to epimerize to the same ratio (ca. 40:1, trans:cis) on standing in hexane at 25° for 4 days.

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(12) The spectra for all compounds were recorded under the following conditions: FTIR--4 cm^{-1} resolution, Nicolet® 7199, ν in cm^{-1}; FT ^{1}H NMR--300 MHz, Nicolet NT-300, δ in ppm from TMS, J in Hz; FT ^{13}C NMR--75 MHz, NT-300, δ in ppm from TMS; GC EI MS - 70 eV, Finnigan® 1015/3200, reported as m/z (relative abundance).
For VIII--IR(CCl_4): 1695, 1638. ^{1}H NMR($CDCl_3$): 2.63(ddq,J = ca. 7,8,7, 1H); 2.47(2H); 2.29(2H); 2.06(s,3H); 1.69(m,1H); 1.46(m,1H); 1.19(2H); 1.14(d,J=7, 3H); 0.86(t,J=7, 3H).
^{13}C NMR($CDCl_3$): 208.9(s); 169.1(s); 143.7(s); 36.7(t); 34.6(t); 31.7(t); 30.2(d); 21.4(t); 18.6(q); 17.4(q); 14.1(q). EI MS: 166(47); 151(60); 137(50); 124(100); 109(29).
For IX-A&B--IR(CCl_4): 1739, 1459, 1381, 1152. EI MS: 168(9); 153(2); 125(9); 111(3); 109(2); 98(44); 83(100); 69(10); 55(16).
For IX-A--^{1}H NMR($CDCl_3$): 2.28(dd,J=8,17, 1H); 2.15-1.95(3H); 1.88(m,1H); 1.63(br d,J = ca. 2,10, 1H); 1.45-1.20(5H); 1.14(d,J=6, 3H); 0.92(d,J =7, 3H); 0.88(t,J=7, 3H).
^{13}C NMR($CDCl_3$): 61.2(d); 39.3(t); 36.7(t); 34.4(d); 32.0(d); 29.8(t); 20.9(t); 20.5(q); 16.9(q); 14.1(q).
For IX-B--^{1}H NMR($CDCl_3$): 2.31(dd,J=8,17, 1H); 2.20-1.95(4H); 1.70(br d, J = ca. 2,10, 1H); 1.47-1.22(5H); 1.16(d,J=6 3H); 0.89(t,J=7, 3H); 0.86(d,J=7, 3H).
^{13}C NMR($CDCl_3$): 60.9(d); 39.0(t); 37.1(t); 33.0(d); 32.3(d); 29.9(t); 21.15(q); 20.9(t); 16.8(q); 14.1(q).
For X-A&B--IR(CCl_4): 2962, 1742, 1461, 1382, 1248, 1211, 1128, 1034, 994. EI MS: 184(0.8); 142(17); 113(100); 85(35); 71(4); 69(4); 67(6); 56(26); 55(20).
For X-A--^{1}H NMR(benzene-d_6): 3.44(d,J=10, 1H); 2.18(ddd,J=4,7,17.5, 1H); 1.99(ddd,J=7,10,17.5, 1H); 1.48-1.05(7H); 0.86(t,J=7, 3H); ca. 0.8(1H); 0.76(br d,J=6, 3H); 0.42(d,J=6.5, 3H).
For X-B--^{1}H NMR(benzene-d_6): 3.31(dd,J=2,10, 1H); 2.16(ddd,J=4.5,7,17.5, 1H); 1.99(ddd,J=7,10,17.5, 1H); 1.48-1.03(7H); 0.96(d,J=7, 3H); 0.84(t,J=7, 3H); ca. 0.75(1H); 0.42(d,J=6.5, 3H).
For I-A&B--EI MS: 198(0.3); 156(18); 127(100); 99(43); 83(8); 69(24); 56(55).
For I-A--IR(CS_2): 2958, 1736, 1378, 1207, 1189, 1123, 990. ^{1}H NMR(benzene-d_6): 3.51(d,J=10, 1H/C-6); 1.94(ddq,J = ca. 7,13,7, 1H/C-3); 1.55-1.10(7H); 1.15(d,J=7, 3H, Me/C-3); 0.87(t,J=7, 3H/C-10); 0.77(br d,J=6, 3H, Me/C-7); 0.74(ddd,J = ca. 13,13,13, 1H/C-4); 0.45(d,J=6.5, 3H, Me/C-5).
For I-B--IR(CS_2): 2954, 1749, 1380, 1189, 1091, 1022, 988. ^{1}H NMR(benzene-d_6): 3.44(d,J=10, 1H/C-6); 2.03(ddq,J = ca. 7,8,7, 1H/C-3); 1.49(dddq,J = ca. 7,7,10,6.5, 1H/C-5); 1.44-1.10(6H); 1.07(d,J=7, 3H, Me/C-3); 0.97(ddd,J = ca. 7,8,13, 1H/C-4); 0.87(t,J=7, 3H/C-10); 0.81(br d,J=6, 3H, Me/C-7); 0.45(d,J=6.5, 3H, Me/C-5).

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