Pergamon

Tetrahedron Letters 43 (2002) 2641–2643

TETRAHEDRON
LETTERS

(*S*)-3,7-Dimethyl-2-oxo-6-octene-1,3-diol: an aggregation pheromone of the Colorado potato beetle, *Leptinotarsa decemlineata* (Say)

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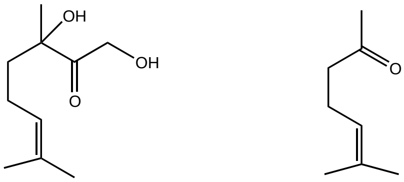
Received 23 January 2002; accepted 6 February 2002

Abstract—(*S*)-3,7-Dimethyl-2-oxo-6-octene-1,3-diol has been identified as a male-produced pheromone from the Colorado potato beetle. Its gross structure was deduced from its mass and NMR spectra plus synthesis from geraniol. The absolute configuration was determined to be (*S*) by syntheses of both enantiomers from (*R*)- and (*S*)-linalool, respectively. Published by Elsevier Science Ltd.

The use of pheromone(s) by the Colorado potato beetle (CPB, *Leptinotarsa decemlineata* (Say)) has been the subject of controversy for many years, as has been discussed by Dickens, et al.[1] In that paper we reported the discovery, by gas chromatography with electroantennogram detection, of a volatile pheromone produced by male CPB but recognized by both sexes, and also described behavioral responses of both sexes to synthetic pheromone. We here describe in detail the identification and synthesis of the novel pheromone as the terpenoid ketodiol **1**.

Compound **1** was initially encountered as a minor peak in a complex gas chromatogram produced from volatiles collected above adult male CPB feeding on potato leaves. A majority of the components were sesquiterpenes produced by the potato plants, but **1** could occasionally be observed as a barely detectable peak in gas chromatograms of samples derived from males, but never in female-derived samples. The discovery[1] that production of **1** could be enhanced by both topical application of juvenile hormone III and by antennectomy facilitated its study by gas chromatography–mass spectrometry (GC–MS), and eventually permitted isolation of enough material by preparative gas chromatography to acquire NMR spectra.[2]

A pivotal observation was that gas chromatograms (obtained from any of several columns) containing a peak for **1** seemed to invariably contain a peak representing 6-methyl-5-heptene-2-one (**2**), but that the ratios of the two weren't necessarily constant. A possible explanation was that **2** was being formed thermally from **1**, and some similar features in the electron ionization (EI) mass spectra of **1** and **2** seemed to support a possible relationship between the two compounds. The EI spectrum of **1**[2] did not contain a molecular ion, but its chemical ionization (CI) spectrum (ammonia as reagent gas) displayed an adduct ion at *m*/*z* 204, indicating a probable molecular weight of 186. Significantly, the CI spectrum also contained strong ions at *m*/*z* 144 and 127 just as did the CI spectrum of **2** ($M+NH_4^+$ and $M+H^+$, respectively). The CI spectrum of **1** with deuteroammonia as reagent gas displayed an ammonium adduct with *m*/*z* 210, consistent with a compound with mw 186 containing two exchangeable



1a racemic
1b 3-(*S*)
1c 3-(*R*)

2

Figure 1.

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0040-4039/02/$ - see front matter. Published by Elsevier Science Ltd.
PII: S0040-4039(02)00349-0

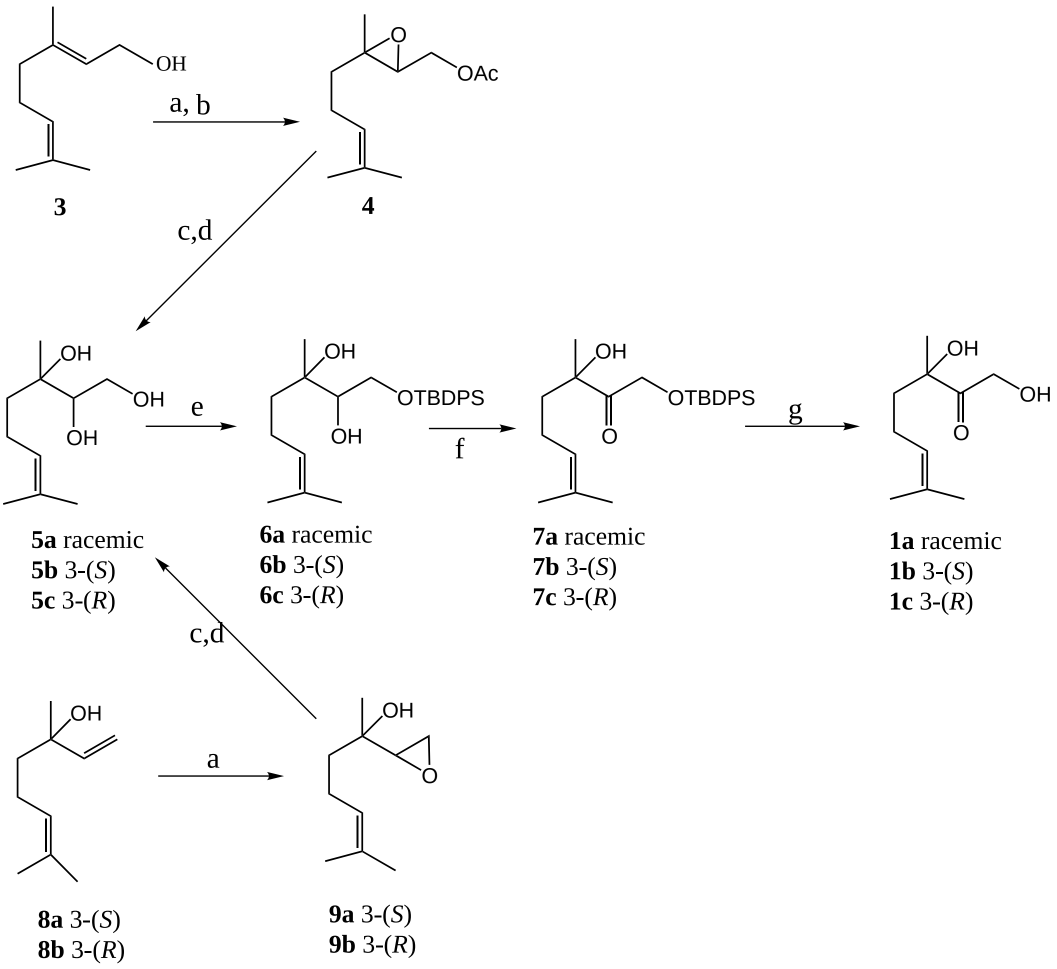
hydrogens. The deuteroammonia spectrum also contained fragment ions indicative of **2**. These observations collectively suggested an empirical formula of $C_{10}H_{18}O_3$ with two of the oxygens being OH's and eight of the carbons configured such as to allow facile fragmentation to **2**. Of the few possible structures meeting these requirements, the most probable appeared to the rather highly oxygenated terpene **1** (Fig. 1).

3,7-Dimethyl-2-oxo-oct-6-ene-1,3-diol **1** appears in the literature once, having been proposed as a geraniol metabolite produced by the soil pseudomonad, *Pseudomonas incognita*.[3] No attempts to synthesize the compound or establish its absolute configuration were reported. To confirm the gross structure, we first synthesized racemic **1** from geraniol (**3**) (Scheme 1).

Regioselective epoxidation of **3** was achieved as described by Mori, et al.[4] After acetylation (Ac_2O, Py), epoxyacetate **4** was hydrolyzed ($HClO_4$/DMF followed by K_2CO_3/MeOH saponification)[5] to triol **5a**.[6] Reaction of **5a** with one equivalent of *t*-butylchlorodiphenylsilane provided the mono silyl ether **6a**.[6] Oxidation of **6a** with pyridinium chlorochromate afforded primarily *t*-butyldiphenylsilanol and ketone **2**, but Swern[7] oxidation proceeded smoothly to give **7a**.[6] Desilylation with TBAF provided the desired **1a** whose gas chromatographic and mass spectral properties[2] matched those of the natural product.

Racemic **1a** was readily resolved on a chiral GC column;[8] comparison with the natural product established that the latter was a single enantiomer (the later-eluting of the two). Linalool (**8**, absolute configuration not described) has been converted to monoepoxide **9** with *t*-BuOOH/VO(acac)$_2$,[9] similar to the conversion of **3** to **4** (Scheme 1). We repeated the epoxidation with commercially available (Fluka) (*R*)-linalool **8b**, and hydrolyzed the product **9b** as described above to give **5c**.[6] Repeating the remainder of the sequence just described gave **1b**, which, on chiral GC, proved to be the earlier-eluting enantiomer (about 96:4, reflecting the composition of the starting linalool), indicating that the absolute configuration of the natural product must be (*S*).

In contrast to the (*R*)-enantiomer, (*S*)-linalool **8a** is not readily available. We developed a procedure for isolation and purification of (*S*)-linalool from oil of coriander,[10] and repeated the above sequence. The product,



Scheme 1. (a) *t*-BuOOH, VO(acac)$_2$; (b) Ac_2O, Py; (c) $HClO_4$, DMF; (d) K_2CO_3, MeOH; (e) TBDPS-Cl, imidazole; (f) Swern oxidation; (g) TBAF

1b, of essentially 100% chiral purity, was identical to the natural product in all respects, including ^{1}H and ^{13}C NMR spectra.[2] Synthetic **1b** stimulates a response when applied to antennae[1] of beetles of either sex, and attracts walking beetles of both sexes in a Y-tube olfactometer.[1] The (*R*)-enantiomer **1c** was inactive (indistinguishable from controls) in both tests.

Acknowledgements

Dr. J. A. Klun performed preparative gas chromatography, Mr. E. David DeVilbiss conducted mass spectrometric experiments, and Drs. John Davis and Ben Hollister collected insect volatiles and performed insect behavioral experiments. We thank Dr. Ashot Khrimian for assistance with chiral gas chromatography. Mention of a proprietary product or company does not imply endorsement.

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2. The initial NMR spectra were recorded in deuterobenzene because of concern about possible instability of the natural product to chloroform. Spectra of the synthetic material have been recorded in both benzene and chloroform: Compound **1b**: ^{1}H NMR (d_6-benzene, 500 MHz): δ 4.95 (1H, tm, J=7.2, 1.4 Hz, H-6); 4.24 (1H, dd, J=19.7, 4.5, H-1a); 4.14 (1H, dd, J=19.7, 4.5, H-1b); 2.93 (1H, t, J=4.5 Hz, OH); 2.27 (1H, s, OH); 1.96 (1H, m, H-5a); 1.81 (1H, m H-5b); 1.59 (3H, m, H-8); 1.44 (3H, broad s, H-9); 1.46 (1H, ddd, J=14.0, 10.4, 5.4 Hz, H-4a); 1.33 (1H, ddd, J=14.0, 10.4, 5.4 Hz, H-4b); 0.88 (3H, s, H-10). ^{13}C NMR δ 214.44 (C-2); 132.50 (C-7); 123.83 (C-6); 78.13 (C-3); 64.79 (C-1); 40.12 (C-4); 25.82 (C-10); 25.66 (C-8); 22.42 (C-5); 17.52 (C-9). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.04 (1H, tm, J=7.2, 1.4 Hz, H-6); 4.51 (1H, d, J=19.7 Hz, H-1a); 4.47 (1H, d, J=19.7 Hz, H-1b); 2.94 (2H, broad s, OH); 2.08 (1H, m, H-5a); 1.89 (1H, m, H-5b); 1.79 (1H, ddd, J=14.1, 9.7, 6.0 Hz, H-4a); 1.71 (1H, ddd, J=14.1, 9.7, 6.0 Hz, H-4b); 1.66 (3H, m, H-8); 1.58 (3H, broad s, H-9); 1.37 (3H, s, H-10). ^{13}C NMR δ 214.15 (C-2); 133.32 (C-7); 122.95 (C-6); 78.47 (C-3); 64.65 (C-1); 39.92 (C-4); 26.13 (C-10); 25.63 (C-9); 22.16 (C-5); 17.66 (C-8). Mass spectrum (m/z, %) 127 (6), 109 (37), 104 (10), 86 (7), 83 (7), 71 (11), 70 (5), 69 (88), 67 (9), 58 (5), 55 (10), 53 (6), 43 (100), 41 (72). $[\alpha]^{D}_{25}$ 0.73 ($CHCl_3$).
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6. Triols **5a**–**5c** occur as mixtures of diastereomers and have been characterized as such;[9] we made no effort to separate the isomers or to characterize them beyond their mass spectra (essentially identical to each other): m/z (%) 170 (2), 152 (4), 110 (14), 109 (46), 71 (14), 69 (74), 67 (20), 55 (20), 44 (11), 43 (100), 41 (67). The DPTB ethers **6a**–**6c** and **7a**–**7c** were purified by flash chromatography on silica gel; **6a**–**6c** (mixture of diastereomers) eluted with 20% ethyl acetate in hexanes, mass spectrum (probe introduction) m/z (%) 351 (18), 200 (17), 199 (70), 197 (11), 183 (12), 181 (12), 162 (16), 139 (28), 136 (14), 135 (100), 127 (11), 109 (40), 107 (28), 93 (35), 91 (11), 78 (10), 77 (16), 71 (10), 69 (72), 67 (10), 57 (14), 55 (27), 43 (28), 41 (58). Ketones **7a**–**7c** eluted from silica gel with 10% ethyl acetate in hexanes, mass spectrum (probe introduction) m/z (%) 349 (8), 310 (10), 309 (39), 289 (12), 231 (12), 200 (10), 199 (54), 197 (14), 181 (17), 163 (15), 143 (13), 139 (25), 135 (39), 133 (15), 123 (10), 109 (39), 107 (12), 105 (18), 93 (11), 91 (13), 77 (16), 71 (14), 69 (100), 59 (10), 57 (12), 55 (21), 43 (77), 41 (64).
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