A Synthesis of Frontalin and Brevicomin

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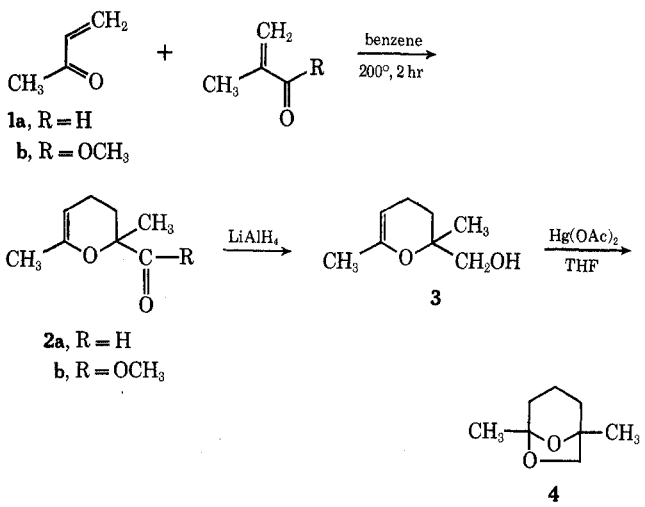
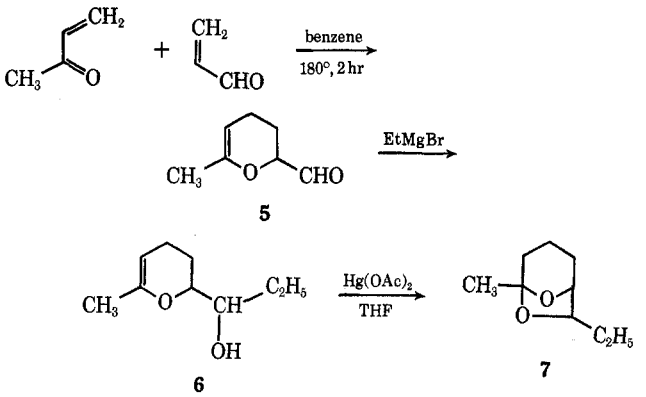
Frontalin, 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane is an aggregating pheromone of the southern pine beetle, *Dendroctonus frontalis*.[2] A Diels–Alder reaction of methyl vinyl ketone and methacrolein (**1a**) does not afford the correct adduct (**2a**) for further elaboration to frontalin (**4**). However, use of methyl methacrylate (**1b**) affords a mixture containing only the dimer of methyl vinyl ketone and **2b**. Lithium aluminum hydride reduction of **2b** gives **3** which is immediately cyclized to **4**. The yield of **4** from **2b** is 40%, and it seems reasonable that the overall conversion could be improved.[3]



Similarly, we have obtained brevicomin (**7**), a pheromone of *Dendroctonus brevicomis*, the western pine beetle. Treatment of the Diels–Alder adduct **5** with the ethyl Grignard reagent affords **6**.[4] This is converted, without purification, to a mixture containing 9% brevicomin. Although this process does not afford a high yield of the pheromone, the simplicity makes it considerably more attractive than the previously reported syntheses.[5]



Experimental Section[6]

Methyl 2,3,4-Trihydro-2,6-dimethylpyran-2-carboxylate (2b).—A mixture of 14.0 g of methyl vinyl ketone, 20.0 g of methyl methacrylate, and 25 ml of benzene was heated for 2 hr at 200° in an autoclave. Distillation gave 13.0 g of a mixture composed of 67% **2b** and 33% methyl vinyl ketone dimer. Separation of the dimer from **2b** was achieved by way of a bisulfite addition complex. The ir spectrum of **2b** had major absorptions at 3020, 2910, 2830, 1750, 1730, 1680, 1455, 1435, 1380, 1315, 1295, 1220, 1190, 1168, 1113, 1105, 1070, 985, and 760 cm^{-1}. The nmr spectrum of **2b** exhibited a singlet at δ 1.49 (3 H), a singlet at 1.8 (3 H), a methylene envelope from 1.85 to 2.4 (4 H), a singlet at 3.72 (3 H), and a triplet at 4.50 (1 H).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.49; H, 8.31. Found: C, 63.70; H, 8.61.

Preparation of Frontalin (4).—The 3.5 g of **2b** was reduced by 0.4 g of lithium aluminum hydride in anhydrous THF under dry nitrogen to give 2.4 g of a colorless liquid (**3**). This was treated with 6.0 g of mercuric acetate in 20 ml of dry THF. After it stirred at room temperature for 20 hr, 20 ml each of solutions containing 3 *M* potassium hydroxide, 0.5 *M* sodium borohydride in 3 *M* potassium hydroxide, saturated sodium chloride, and water were added in turn. Extraction with methylene chloride gave 1.8 g of colorless liquid which was 65% frontalin (**4**) by glc (20 ft × 3/8 in. column packed with 30% SE-30 on Chromosorb W at 150° with a 150–200-ml/min flow rate). Ir and nmr[2a] spectra of a sample collected from preparative glc were identical with those of an authentic sample of frontalin obtained from the U. S. Forest Service.

Synthesis of Brevicomin (7).—In a process similar to that for frontalin, 15 g of methyl vinyl ketone, 30 g of acrolein, and 80 ml of benzene were heated in an autoclave at 180° for 2 hr. The crude product was partially purified by short-path distillation, yielding 18 g of a product mixture, bp 35–40° (2 mm). This product (4 g) was added to a Grignard solution prepared from 1.2 g of magnesium and 5.4 g of ethyl bromide in 80 ml of anhydrous ether. After work-up, the mixture containing **1b** (4.0 g) was stirred with 9.6 g of mercuric acetate in 75 ml of dry THF. The product mixture, isolated as previously discussed, was subjected to glc analysis and was shown to contain 9% brevicomin. The ir and nmr spectra were identical with those of an authentic sample. The nmr and mass spectra were identical with those reported by Silverstein.[7]

Registry No.—**2b**, 29765-30-8; **4**, 22625-04-3; **7**, 20290-99-7.

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(1) NDEA Predoctoral Fellow, 1968–1971.

(2) (a) G. W. Kinzer, A. F. Fentman, T. F. Page, R. L. Foltz, J. P. Vite, and G. B. Pitman [*Nature*, **221**, 477 (1969)] reported the isolation, identification, and synthesis of this pheromone; (b) W. D. Bedard, R. M. Silverstein, and D. L. Wood (*Science*, **167**, 1638 (1970)] discussed nomenclature problems associated with frontalin and questioned the importance of this compound as an active pheromone.

(3) The previously reported synthesis of frontalin[2a] gave no Experimental Section and was based on a Diels–Alder reaction of methallyl alcohol and acrolein which resulted in a direct 21% yield of 1-methyl-6,8-dioxabicyclo-[3.2.1]octane [C. W. Smith, D. G. Morton, and S. A. Ballard, *J. Amer. Chem. Soc.*, **73**, 5270 (1951)]. We repeated the work of Kinzer, *et al.*,[2a] and have obtained a 6.7% yield of frontalin. Our reported synthesis with no attempt to maximize yields gave an equivalent overall yield and has the potential to be improved. For example, the separation of the methyl vinyl ketone dimer and **2b** *via* the bisulfite addition product was only attempted once giving a 37% recovery of **2b**.

(4) The synthesis of brevicomin was carried out without isolation of intermediate products.

(5) (a) T. E. Bellas, R. G. Brownlee, and R. M. Silverstein, *Tetrahedron*, **25**, 5149 (1969); (b) H. H. Wasserman and E. H. Barker, *J. Amer. Chem. Soc.*, **91**, 3674 (1969).

(6) Melting points and boiling points are uncorrected. Nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Infrared spectra were recorded on a Beckman IR-5 instrument. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

(7) R. M. Silverstein, *J. Chem. Educ.*, **45**, 794 (1968). We also obtained some of the endo isomer, but in lesser amount than brevicomin. The simple mass spectral fragmentation patterns are different for the exo and endo isomers, and the occurrence of several metastables in the exo product is the most powerful proof of the authenticity of our synthetic material.