Agr. Biol. Chem., **39** (9), 1889～1890, 1975

A Synthesis of (±)-Frontalin, the Pheromone of *Dendroctonus* Bark Beetles†

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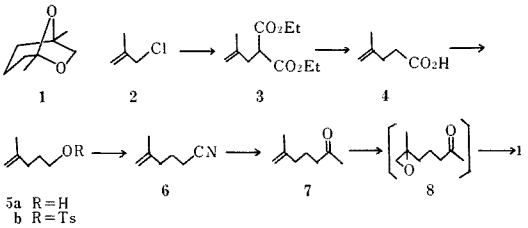
Received May 12, 1975

Frontalin is an aggregating pheromone of bark beetles with a unique bicyclic ketal strucutre, 1, 5-dimethyl-6, 8-dioxabicyclo [3. 2. 1] octane (**1**).[1] Very recently we announced the synthesis of its two enantiomers in optically pure states.[2] In connection with that work we achieved another new synthesis of (±)-frontalin by a linear and building block-type approach as shown in the scheme.[3]



Alkylation of diethyl malonate with methallyl chloride (**2**) yielded a crude diester (**3**) as described by Julia and Maumy.[4] This was saponified with potassium hydroxide and the resulting diacid was decarboxylated by heating with aqueous acetic acid to give an acid (**4**) in 52% yield. This acid readily lactonized to give γ, γ-dimethyl-γ-butyrolactone upon heating at a high temperature either in the course of the decarboxylation or during the distillation. So the mild procedure was essential for the preparation of **4**. Reduction of **4** with lithium aluminum hydride gave the known alcohol (**5a**)[4] in 60% yield. This was converted to a cyanide (**6**) *via* the corresponding tosylate in 66.5% yield from **5a**. The cyanide (**6**) was treated with methyl magnesium iodide to give a ketone (**7**) in 41% yield. An attempt was made to obtain **7** by the conjugate addition of a methallyl copper reagent to methyl vinyl ketone but in vain.

Synthesis of (±)-frontalin (**1**) from this ketone (**7**) was patterned after the work of Wasserman and Barber.[5] They prepared (±)-brevicomin (*exo*-7-ethyl-5-methyl-6, 8-dioxabicyclo [3. 2. 1] octane) by a thermal rearrangement of a δ, ε-epoxy ketone. So the ketone (**7**) was epoxidized with *m*-chloroperbenzoic acid and the resulting crude epoxide (**8**) was distilled *in vacuo* to give (±)-frontalin (**1**) as the rearranged product. In this case the rearrangement was accelerated by the presence of a small amount of *m*-chlorobenzoic acid in the crude epoxide. The yield of (±)-frontalin (**1**) from the ketone (**7**) was 59%. All the spectral data (IR, NMR, MS) of the synthetic material (**1**) was identical with those of an authentic sample.[2] The identity was further proved by GLC co-injection experiment. Although the present synthesis is somewhat lengthy, it is straightforward and can be achieved without involving any complicated purification step.

EXPERIMENTAL

All bps were uncorrected. IR spectra refer to films. NMR spectra were recorded at 60 MHz in CCl_4 with TMS as an internal standard.

4-Methyl-4-pentenoic acid (*4*)

A solution of **3** (64 g) in 95% EtOH (110 ml) was mixed with KOH aq solution (64 g in 140 ml). The mixture was heated under reflux for 2 hr with stirring and concentrated *in vacuo* to remove EtOH. After acidification with acetic acid (150 ml) the mixture was heated under reflux for 10 hr, cooled, diluted with water and extracted with ether. The ethereal solution was washed with saturated NaCl aq solution, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled to give 17.2 g (52%) of **4**, bp 59～61°C (0.85 mmHg); n_D^{21} 1.4367; IR ν_{max} cm^{-1}: 3080, 2970, 2920 (broad), 1715 (s), 1650 (m), 1450 (m), 1420 (m), 1380 (w), 1300 (m), 1250 (m), 1220 (m), 1170 (m), 890 (m), NMR δ 1.75 (3H, s), 2.40 (4H, broad), 4.73 (2H, s), 12.19 (1H,s); *Anal.* Found: C, 62.75; H, 8.63. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83%.

4-Methyl-4-penten-1-ol (*5a*)

A solution of **4** (20 g) in dry ether (100 ml) was added dropwise during 100 min to an ice-cooled and stirred suspension of $LiAlH_4$ (6.0 g) in dry ether (200 ml) at 4～8°C. After the addition, the mixture was stirred for 1 hr at 3°C and left to stand overnight at room temperature. Then the excess hydride was decomposed by the addition of water (6 ml) with stirring at 5°C. The mixture was poured into ice-water containing 40 ml of concd. HCl and extracted with ether. The ethereal solution was dried ($MgSO_4$) and concentrated. The residue was distilled to give 10.45 g (59.5%) of **5a**,

† Pheromone Synthesis, Part VII. Part VI, K. Mori, M. Tominaga and M. Matsui, *Tetrahedron*, **31**, 1846 (1975).

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bp 58~72°C (15 mmHg); n_D^{22} 1.4375 (lit.[4] $n_D^{22.5}$ 1.4378); IR ν_{max} cm^{-1}; 3360 (s), 3070 (w), 2930 (s), 2860 (m), 1650 (m), 1450 (m), 1380 (m), 1170 (w), 1060 (s), 1020 (m), 995 (w), 885 (m), NMR δ 1.71, 1.3~2.3 (7H, broad), 3.55 (2H, t, J=7Hz), 4.00 (1H, s), 4.70 (2H, s); MS; m/e 100 (M^+).

4-Methyl-4-pentenyl p-toluenesulfonate (5b)

Powdered *p*-toluenesulfonyl chloride (25 g) was added in one portion to a stirred and ice-cooled solution of **5a** (10.4 g) in dry pyridine (65 ml). The mixture was stired at 0~5°C for 1 hr and left to stand overnight in a refrigerator. Then it was poured into ice-water containing 100 ml of concd HCl and extracted with ether. The ethreal solution was washed with dil HCl, $NaHCO_3$ aq. solution and saturated NaCl aq. solution, dried ($MgSO_4$) and concentrated *in vacuo* to give 22.8 g (90%) of **5b**, IR ν_{max} cm^{-1}: 1650 (w), 1600 (m). This was employed for the next step without further purification.

5-Methyl-5-hexenenitrile (6)

Powdered NaCN (3.5 g) was added to a stirred solution of **5b** (10 g) in dimethyl sulfoxide (60 ml). The mixture was stirred at 60°C for 30 min and left to stand overnight at room temperature. Then it was diluted with water and extracted with methylene chloride. The extract was dried ($MgSO_4$) and concentrated. The residue was distilled to give 2.86 g (66.5%) of **6**, bp 74~78°C (21 mmHg), n_D^{22} 1.4340; IR ν_{max} cm^{-1}: 3080 (w), 2960 (m), 2240 (m), 1650 (m), 1450 (m), 1380 (m), 1280 (w), 1220 (w), 890 (m), 760 (m); NMR δ 1.70 (3H, s), 1.55~2.50 (6H, broad), 4.68 (2H, s); MS: m/e 109 (M^+).

6-Methyl-6-hepten-2-one (7)

A solution of **6** (2.9 g) in dry benzene (20 ml) was added dropwise to a stirred and ice-cooled solution of a Grignard reagent prepared from methyl iodide (8 g) and Mg (1.3 g) in dry ether (50 ml). After the addition, the mixture was left to stand two days at room temperature. Then it was poured into ice-water containing 20 ml of concd HCl and extracted with ether. The ethereal solution was washed with $NaHCO_3$ aq. solution containing a small amount of sodium thiosulfate and saturated NaCl aq. solution, dried ($MgSO_4$) and concentrated. The residue was distilled to give 1.38 g (41%) of **7**, bp 60~66°C (20 mmHg), n_D^{22} 1.4366; IR ν_{max} cm^{-1}: 3080 (w), 2940 (m), 1710 (s), 1650 (w), 1450 (m), 1370 (m), 1220 (w), 1160 (m), 890 (m), NMR δ 1.67 (3H, s), 2.02 (3H, s), 4.60 (2H, s). *Semicarbazone.* Prisms from EtOH, mp 124~126°C; IR ν_{max}^{nujol} cm^{-1}: 3470 (m), 3200 (w), 1690 (m), 1650 (m), 1580 (m), 1280 (w), 1210 (w), 1110 (w), 1060 (w), 970 (w), 880 (m), 760 (w), 720 (w); *Anal.* Found: C, 58.85; H, 9.17; N, 23.21. Calcd. for $C_9H_{17}ON_3$: C, 58.99; H, 9.35; N, 22.93%.

1, 5-Dimethyl-6, 8-dioxabicyclo [3. 2. 1] octane (1)

A solution of *m*-chloroperbenzoic acid (2.3 g, 85% purity) in $CHCl_3$ (30 ml) was added to an ice-cooled solution of **7** (1.26 g) in $CHCl_3$ (20 ml). The mixture was left to stand overnight in a refrigerator. Then it was poured into $NaHCO_3$ aq. solution and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated to give crude epoxy ketone (**8**) contaminated with a small amount of *m*-chlorobenzoic acid. This was distilled *in vacuo* to give 0.83 g (58.5% from **7**) of (±)-frontalin (**1**), bp 44~49°C (20 mmHg); IR ν_{max} cm^{-1}: 2980 (s), 2940 (s), 2880 (s), 2840 (m), 1490 (w), 1450 (m), 1395 (s), 1385 (s), 1350 (m), 1330 (w), 1295 (m), 1275 (s), 1245 (s), 1210 (s), 1180 (s), 1125 (s), 1065 (m), 1030 (s), 980 (w), 950 (w), 930 (m), 915 (w), 895 (m), 865 (m), 850 (s), 820 (m), 755 (m), NMR δ 1.30 (3H, s) 1.40 (3H, s) 3.42, 3.88 (2H, AB_q, J_{AB}=7Hz); MS: m/e 142 (M^+), 43 (base peak); GLC (Column SE-30 5% on Celite 545, 1.5 m×3 mm *i. d.* at 80°C, Carrier gas: N_2, 1.0 kg/cm^2): Rt 8 min 50 sec. These physical data were entirely identical with those previously reported.[2] The identity was also proved by co-injection experiment on the SE-30 column.

Acknowledgement. Thanks are due to Dr. K. Aizawa and his associates, this Department, for analytical works.

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