SYNTHESIS OF 6,8-DIOXABICYCLO [3.2.1] OCTANES. TOTAL SYNTHESES OF (±)-FRONTALIN AND (±)-BREVICOMIN.

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The syntheses of two pheromones: (±)-frontalin (1) and (±)-brevicomin (2) are described starting from 2-methylcyclohexanone (3) and 3,4-dihydro-2H-pyran (13), respectively.

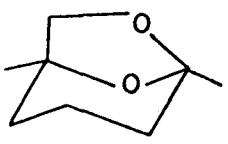
Keywords: Pheromones; (±)-frontalin; (±)-brevicomin.

INTRODUCTION

Frontalin (1) and *exo*-brevicomin (2) were identified as the principal components of the aggregation pheromone of the southern pine beetle *Dendroctonus frontalis*[1] and *Dendroctonus brevicomis*,[2] respectively. These pheromones have a 6,8-dioxabicyclo [3.2.1] octane system, which is often found as an integral part of sugars[3], alkaloids[4] and terpenoids[5].

Although in 1974 Mori and collaborators[6] had demonstrated, through the synthesis and study of the biological activity of both enantiomers, that the natural frontalin (1) has a 1S,5R configuration, in 1976 Wood and collaborators[7] showed that the racemic mixture also had a good aggregating activity. Similar results were also observed with the racemic *exo*-brevicomin (2).

We now report the synthesis of (±)-frontalin (1)[8], starting from 2-methylcyclohexanone (3a) in nine steps and the synthesis of (±)-brevicomin (2)[9] in seven steps from 3,4-dihydro-2H-pyran (13), using simple and classic reactions.



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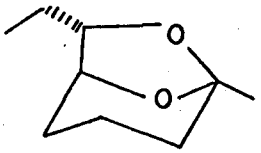

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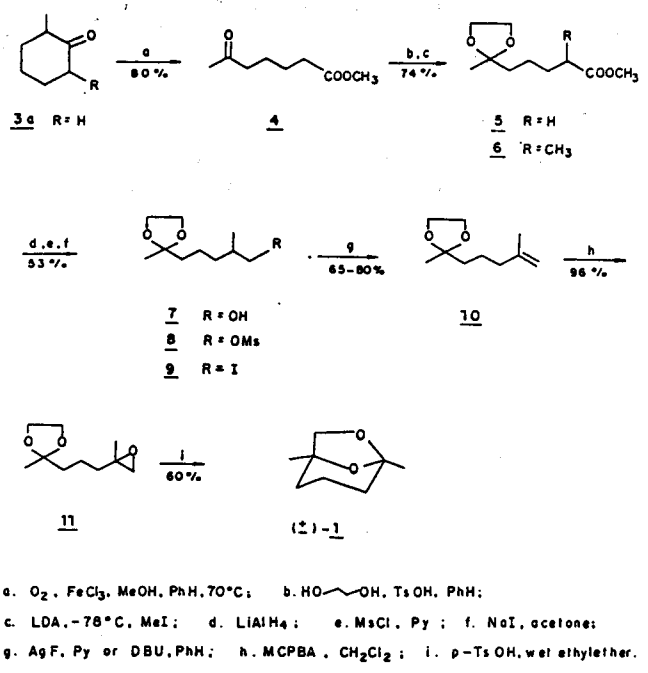
(±)-Frontalin (1).

As can be seen in Scheme I, the ester methyl-6-oxo-heptanoate (4) was prepared from 3a according to Matsumoto's procedure[10] in 80% yield. This keto-ester was protected as its 1,3-dioxolane with 1,2-ethyleneglycol by the normal procedure (82% yield for 5) and then alkylated with methyl iodide (LDA at -78°C) to provide 6 in 90% yield. The spectroscopic evidence for the formation of the monoalkylated product was a doublet at 1.00 ppm (J= 6.0 Hz) for the methyl group at C-2 and was consistent with the ^{13}C NMR spectra in which the C-2 carbon appears at 38.6 ppm as a doublet.

Compound 6 was also obtained from 2,6-dimethylcyclohexanone (3b) using the same oxidation and protection conditions (Scheme II). Using this sequence, 6 was produced in 24% yield and we therefore prefer the first sequence (Scheme I, 59%), even though LDA has to be used as a base.

Resuming our synthesis following Scheme I, ester 6 was reduced with $LiAlH_4$ to the corresponding alcohol 7 in 96% yield and then converted to the methanesulfonyl ester 8

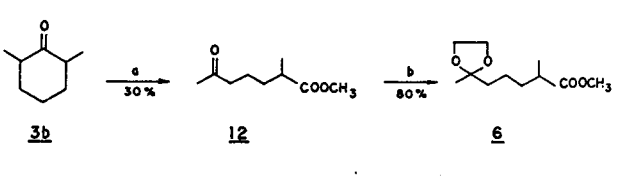
Scheme I



a. O_2, $FeCl_3$, MeOH, PhH, 70°C; b. HO~OH, TsOH, PhH; c. LDA, -78°C, MeI; d. $LiAlH_4$; e. MsCl, Py; f. NaI, acetone; g. AgF, Py or DBU, PhH; h. MCPBA, CH_2Cl_2; i. p-TsOH, wet ethylether.

(MsCl, Py, 72% yield). Treatment of 8 with NaI in acetone gave 9 (76% yield) and elimination of iodide with AgF in pyridine or DBU in benzene gave 10[11] in 80% and 65% respectively. Finally the epoxidation of olefin 10 with MCPBA in CH_2Cl_2 gave the epoxide 11[11] in 96% yield, which was treated with p-TsOH in wet ethyl ether to furnish (±)-frontalin (1) in 60% yield. The structure of 1 was confirmed by the ^1H NMR, IR and MS data, which were in good agreement with those reported in the literature[1,6-8] for the natural product.

Scheme II



a. O_2, $FeCl_3$, MeOH, PhH, 70°C; b. HO~OH, p-TsOH, PhH

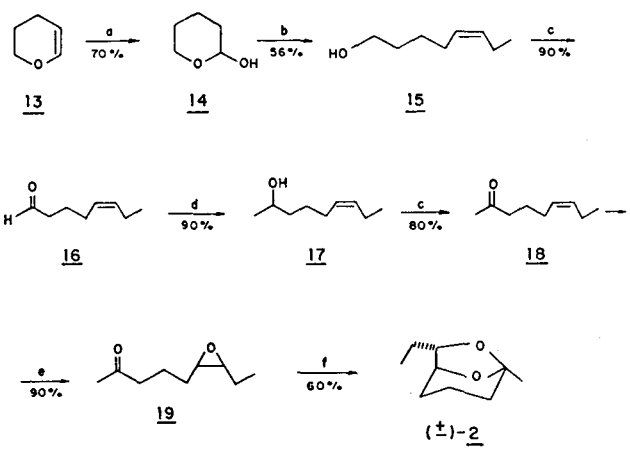
(±)-Brevicomin (2).

As shown in Scheme III, the hydroxy-olefin 15 was prepared in two steps from 3,4-dihydro-2H-pyran (13) following Wood's procedure[12] (13 → 14, 70% yield) and Ohloff's procedure[13] (14 → 15 , 56% yield). The presence of Z isomer was confirmed by the $W_{1/2}$ = 6.4 Hz of the olefinic proton at 5.28 ppm measured on the spectrum acquired irradiating the allylic methylenic protons.

Oxidation of alcohol 15 with PCC[14] furnished the corresponding aldehyde 16 in 90% yield. Treatment of this aldehyde with 1.2 equivalent of MeMgI gave alcohol 17 in 90% yield, which was oxidized again with PCC to furnish the key intermediate ketone 18[11] in 80% yield.

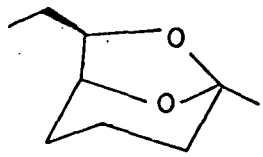
The epoxidation of the keto-olefin 18 with MCPBA in CH_2Cl_2 gave epoxide 19[11] in 90% yield. Treatment of this epoxide for 4h with p-TsOH in wet ethyl ether furnished directly (±)-brevicomin (2) in 60% yield as a mixture of 4:1 *exo/endo*-brevicomin (2/20) revealed by GC/MS analysis. This shows that in our case the Wittig reaction was not as selective as reported in the literature (97:3; Z/E)[13], even though it was carried out under identical conditions. We should also like to point out that the separation of these isomers by GC on the capillary column was only possible in the final product, the intermediates showing only one peak on HP 05 capillary column.

SCHEME III



a. H^+, H_2O ; b. $Ph_3\overset{\oplus}{P}CH_2CH_2CH_3\overset{\ominus}{Br}$, DMSO , NaH ; c. PCC , CH_2Cl_2 ;

d. CH_3MgI, Et_2O ; e. MCPBA , CH_2Cl_2 ; f. p-TsOH, wet ethylether.



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CONCLUSION

In 1983, at the begining of this work, few total syntheses of frontalin (1) and brevicomin (2) had been reported[15], but since then the number has increased to over 35 for 1 and over 100 for 2, showing that these molecules are still viewed as a challenge by chemists searching for good targets to test new methodologies or to devise more economic routes for these important compounds.

The synthesis of (±)-frontalin (1) was achieved in nine steps from 2-methylcyclohexanone (3) with 15% overall yield and the synthesis of (±)-brevicomin (2), in seven steps from 3,4-dihydro-2H-pyran (13) with 14% overall yield, as a mixture of *exo:endo* isomers (4:1).

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian T-60 (60 MHz) or on a Bruker WP-80 (80 MHz) instrument and ^{13}C NMR spectra were recorded on a Varian XL-100 (25.2 MHz) instrument with tetramethylsilane (TMS) as internal standard. IR spectra were obtained on a Perkin-Elmer 399B instrument and mass spectra (MS) were obtained on a Varian MAT-311 instrument. Column chromatographies were performed with silica gel 60 (0.06-0.2 mm) purchased from Merck. GC/MS spectra was obtained on a Hewlett-Packard VDC 5890-A instrument (HP 05 Capillary column).

Table I - ^{13}C NMR Data for the Compounds 4-7.[a]

	4	5	6	7
C-1	172.9 (s)[b]	172.4 (s)	175.4 (s)	67.0 (t)
C-2	33.8 (t)	33.5 (t)	38.6 (d)	35.4 (d)
C-3	24.6 (t)	24.8 (t)	33.7 (t)	33.4 (t)
C-4	23.4 (t)	23.8 (t)	21.4 (t)	21.3 (t)
C-5	43.1 (t)	38.5 (t)	38.6 (t)	39.3 (t)
C-6	205.9 (s)	109.4 (s)	108.4 (s)	109.4 (s)
C-7	29.7 (q)	23.6 (q)	23.6 (q)	23.6 (q)
Me-(C-2)	-	-	16.8 (q)	16.7 (q)
OMe	51.2 (q)	50.6 (q)	50.6 (q)	-
$-OCH_2CH_2O-$	-	2x64.2 (t)	2x64.2 (t)	2x64.2 (t)

a. The solvent used was CCl_4 and the chemical shifts were measured in ppm using TMS as an internal standard.
b. The multiplicity was obtained using the SFORD mode spectra

Methyl-6,6-ethylenedioxyheptanoate (5).

A mixture of 4[10] (6.20g, 39.0 mmol), ethylene glycol (6.20g, 103.0 mmol) and 15 mg of p-TsOH in benzene (190 ml) was refluxed for 20h using a Dean-Stark apparatus to collect the water. The reaction mixture was cooled and washed with 10% aqueous solution of $NaHCO_3$ followed by brine. The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to leave an oil, which was distilled to give 5 (6.50g, 82%, b.p. 76-81°/1 mm); ^1H NMR (60 MHz, CCl_4) δ 1.23 (s, 3H), 1.38-1.60 (m, 6H), 2.08-2.30 (m, 2H), 3.61 (s,3H), 3.85 (s, 4H); ^{13}C NMR see Table I; IR (neat) 1735 cm^{-1}; MS, m/z (relative intensity) 187 ($M^{+\cdot}$ -15, 14), 97 (100).

Methyl-6,6-ethylenedioxy-2-methylheptanoate (6).

A solution of 5 (2.54g, 12.5 mmol) in anhydrous THF (20 ml), was added dropwise to a cold (-78°C) magnetically stirred solution of LDA (15ml) in same solvent (20 ml). After lh, methyl iodide (2.30g, 15. mmol) was introduced and stirred for 2h. After removing the cooling bath, the temperature was allowed to rise to room temperature and reaction mixture was quenched with NH_4Cl solution (30 ml). The product was extracted with ethyl ether (5 x 20 ml), washed with brine (3 x 20 ml), dried over Na_2SO_4 filtered and concentrated. The residue was chomatographed on silica gel with hexane:ethyl ether (19:1) as eluent yielding 6 as oil (2.4g, 90%); ^1H NMR (60 MHz, CCl_4) δ 1.00 (d, J= 6.0 Hz, 3H), 1.10 (s, 3H),

1.22-1.75 (m, 6H), 2.05-2.37 (m,1H), 3.48 (s, 3H), 3.70 (s, 4H); ^{13}C NMR see Table I, IR (neat) 1735 cm^{-1}; MS, m/z (relative intensity) 201 ($M^{+\cdot}$ -15, 11), 87 (100).

6,6-Ethylenedioxy-2-methylheptan-1-ol (7).

To a stirred suspension of $LiAlH_4$ (1.00g, 26.3 mmol) in dry ethyl ether (80 ml) at 0°C and under N_2 was added dropwise a solution of ester 6 (2.80g, 12.9 mmol) in the same solvent (10 ml). After 2h at 0°C, the reaction mixture was slowly quenched with 5% aqueous NaOH solution to destroy the excess hydride, the mixture filtered through a Celite pad, washed with ether, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane:ethyl ether 9:1) to give 7 as an oil (2.34g, 96%); ^1H NMR (60 MHz, CCl_4) δ 0.90 (d, J= 6.0 Hz, 3H), 1.23 (s,3H), 1.33-1.55 (m,7H), 1.80 (bs, 1H), 3.36 (d, J= 6.0 Hz, 2H), 3.85 (s, 4H); ^{13}C NMR see Table I; IR (neat) 3500 cm^{-1}; MS, m/z (relative intensity) 173 ($M^{+\cdot}$ -15, 9), 87 (100).

6,6-Ethylenedioxy-2-methylheptan-1-methanesulfonate (8).

To a solution of 7 (1.30g, 6.9 mmol) in dry pyridine (4ml) at 0°C was added methanesulfonyl chloride (1.90g, 16.8 mmol). After stirring for 5h at room temperature, the reaction mixture was quenched with cold water (20 ml) and extracted with CH_2Cl_2 (3 x 20 ml). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product (1.30g, 72%) was used in next step without further purification. ^1H NMR (60 MHz, CCl4) δ 1.00 (d, J= 6.0 Hz, 3H), 1.21 (s, 3H), 1.33-1.56 (m, 7H), 2.91 (s, 3H), 3.83 (s, 4H), 4.00 (d, J= 6.0 Hz, 2H); IR (neat) 1460, 1380 and 1060 cm^{-1}.

1-Iodo-2-methyl-6,6-ethylenedioxyheptane (9).

The above mesylate (1,30g, 4.9 mmol) was dissolved in acetone (100 ml) and NaI (1.50g, 10.0 mmol) was added. The solution was refluxed for 12h and then concentrated under reduced pressure. The residue was dissolved in water (20 ml), and extracted with CH_2Cl_2 (5 x 20 ml), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane: ethyl ether 19:1) to give 9 as an oil (1.1g, 76%); ^1H NMR (60 MHz, CCl4) δ 1.00 (d, J= 6.0 Hz, 3H), 1.23 (s, 3H), 1.31-1.53 (m, 7H), 3.16 (d, J= 4.8 Hz, 2H), 3.86 (s, 4H); MS, m/z (relative intensity) 283 ($M^{+\cdot}$ -15, 12), 87 (100).

2-Methyl-6,6-ethylenedioxyhept-1-ene (10).

Method A - To a solution of 9 (0.50g, 1.6 mmol) in dry pyridine (5 ml) was added AgF (1.30g, 10.0 mmol). After stirring for 5h at room temperature, the reaction mixture was diluted with ethyl ether and filtered on a small pad of silica. The solvent was concentrated to give 10 as an oil (0.23g, 80%).

Method B - To a solution of 9 (1.30g, 4.36 mmol) in benzene (15 ml) was added DBU (1.32g, 8.72 mmol) and the mixture was refluxed for 20h. After cooling to room temperature, the reaction mixture was diluted with ethyl ether and filtered through silica pad. The solvent was concentrated to give 10 as an oil (0.48g, 65%); ^1H NMR (60 MHz, CCl_4) δ 1.25 (s, 3H), 1.40-1.60 (m, 4H), 1.70 (bs, 3H), 1.90-2.08 (m, 2H), 3.85 (s, 4H), 4.66 (bs, 2H); IR (neat) 1650 cm^{-1}.

2-Methyl-6,6-ethylenedioxy-1,2-epoxy-heptane (11).

To a stirred and cooled (0°C) solution of 10 (0.19g, 1.1 mmol) in CH_2Cl_2 (3 ml) was added MCPBA (0.25g, 1.45 mmol). After 2h the solvent was evaporated and the residue was filtered on a small alumina column (hexane:ethyl ether 9:1) to give 11 as an oil (0.19g, 96%); ^1H NMR (60 MHz, CCl_4) δ 1.20 (s, 3H), 1.22 (s, 3H), 1.42-1.52 (m,6H), 2.42 (bs, 2H), 3.82 (s, 4H); IR (neat) 3000, 1460, 1370 cm^{-1}; MS, m/z (relative intensity) 171 ($M^{+\cdot}$ -15, 2), 43 (100).

(±)-Frontalin (1)[1]

To a solution of epoxide 11 (0.12g, 0.6 mmol) in wet ethyl ether (30 ml) was added a catalytic amount of p-toluenesulfonic acid (3 mg) and the resulting mixture was stirred at room temperature for 12h. The solvent was evaporated and the residue was filtered on a small alumina column (hexane) to give (±)-frontalin (1) as an oil (49 mg, 60%); ^1H NMR (60 MHz, CCl_4) d 1.20 (s, 3H), 1.27 (s,3H), 1.45-1.65 (m, 6H), 3.27, and 3.75 (2d, AB, J_{AB}= 7.0 Hz, 2H); IR (neat) 2920, 1460, 1370, 1270, 1080 cm^{-1}; MS, m/z (relative intensity) 142 ($M^{+\cdot}$, 2), 62 (100).

5-Octen-1-al (16).

To a solution of 15 [12,13] (500mg, 3.9 mmol) in anhydrous CH_2Cl_2 (50 ml) at room temperature was added PCC[14] (1.7g, 7.9 mmol), Celite (800 mg) and $MgSO_4$ (800 mg). After stirring 1h, the reaction mixture was passed through a silica gel pad and the solvent removed to give 16 as a colourless oil (442 mg, 90%). ^1H NMR (80 MHz, CCl_4) δ 0.95 (t, J= 8.0 Hz, 3H), 1.60 (q, J=8.0 Hz, 2H), 2.00 (m, 4H), 2.35 (t, J= 8.0 Hz, 2H), 5.30 (m, 2H) and 9.70 (s, 1H); IR (neat) 1730 cm^{-1}.

6-Nonen-2-ol (17).

To a solution of MeMgI, prepared from MeI (674 mg, 4.4 mmol) and Mg (78 mg. 3.3 mmol), in anhydrous ethyl ether (20 ml), was added dropwise a solution of 16 (400 mg, 3.2 mmol) in anhydrous ethyl ether. After 1h of stirring, the reaction was quenched carefully by adding H_2O (20 ml) and acidified with 0.1N HCl until disappearance of the emulsion. The mixture was extracted with ethyl ether (5 x 30 ml), the organic layer washed with 0.1 N $NaHCO_3$ (30 ml), dried over Na_2SO_4 and concentrated in vacuo. The crude oil was purified by silica gel flash chromatography (hexane:AcOEt, 9:1) to give 17 (405 mg, 90%). ^1H NMR (80 MHz, CCl_4) δ 0.93 (t, J= 8.0 Hz, 3H), 1.12 (d, J= 6.4 Hz, 3H), 1.25-1.32 (m, 6H), 1.90-2.05 (m, 3H), 3.68 (m, 1H) and 5.28 (m, 2H); IR (neat) 2960, 1720 and 1460 cm^{-1}.

6-Nonen-2-one (18).

To a solution of 17 (300 mg, 2.1 mmol) in anhydrous CH_2C1_2 at room temperature, was added PCC[14] (500 mg, 2.3 mmol), Celite (500 mg) and $MgSO_4$ (500 mg). After 1h of stirring, the reaction mixture was filtered through a silica gel pad and solvent removed to give 18 as an oil (240 mg, 80%). ^1H NMR (80 MHz, CCl_4) δ 0.94 (t, J= 8.0 Hz, 3H), 1.40-1.76 (m, 6H), 2.04 (s, 3H), 2.32 (t, J= 8.0 Hz, 2H) and 5.28 (m, 2H); IR (neat) 2960, 1720 and 1460 cm^{-1}.

6,7-Epoxy-nonan-2-one (19).

To a stirred solution of 18 (160 mg, 1.3 mmol) in anhydrous CH_2Cl_2 (10 ml) was added MCPBA (344 mg, 2.0 mmol). After 1h, the solution was washed with 0.1 N $NaHCO_3$ (20 ml), dried over Na_2SO_4 and concentrated in vacuo. The crude oil was chromatographed on a small alumina column (CH_2Cl_2) to give 19 (160 mg, 90%). ^1H NMR (80 MHz, CCl_4) δ 1.00 (t, J= 8.0 Hz, 3H), 1.00-1.90 (m, 6H), 2.05 (s, 3H), 2.20-2.40 (m, 3H) and 2.70 (m, 1H); IR (neat) 2980 and 1720 cm^{-1}.

(±)-Brevicomin (2).[2]

To a solution of 19 (110 mg, 0.71 mmol) in wet ethyl ether (10 ml) at room temperature, was added a catalytic amount of p-toluenesulfonic acid (3 mg). After stirring for 4h, the mixture was washed with 0.1 N $NaHCO_3$ (2 x 5 ml), dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel column (ethyl ether) gave (±)-brevicomin (2/20) (ratio 4:1) (73 mg, 60%). ^1H NMR (80 MHz, CCl_4) δ 0.86 (t, J= 7.0 Hz, 3H), 1.32 (s, 3H), 1.40-1.78 (m, 8H), 3.80 (t, J= 6.4 Hz, 1H) and 4.00 (bs, 1H); IR (neat) 2940, 1460, 1380, 1240, 1175, 1010, 970 and 850 cm^{-1}; MS, m/z (relative intensity) 156 ($M^{+}\cdot$, 12), 114 (66), 98 (82), 85 (97), 71 (73), and 67 (100).

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