Convenient Synthetic Route to 6,8-Dioxabicyclo[3.2.1]octanes, the Aggregation Pheromone Components of Bark Beetles [1]

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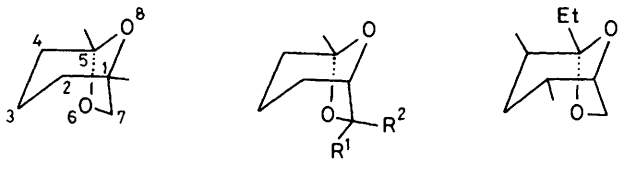
Convenient syntheses of (±)-frontalin (I) and (±)-brevicomins (IIa) and (IIb) were achieved from pent-4-en-1-ol (2) and pent-4-yn-1-ol (3). In a few simple and unambiguous steps, the alkenol (2) and the alkynol (3) were transformed into the acetal bromide (7) and the alkenyl bromides (14) and (17), respectively. Acylation of the Grignard reagents of these bromides provided the corresponding methyl ketones (8), (15), and (18), the key intermediates for the synthesis of the title bicyclic acetals. The ketone (8) was converted into the olefin (9) which, on epoxidation followed by acid hydrolysis, yielded (±)-frontalin, whereas epoxidation of the alkenones (15) and (18) and subsequent cyclisation afforded *exo*- and *endo*-brevicomin, stereoselectively.

Bark beetles are insect pests inhabiting the subcortical tissues of trees, and account for much of the loss of timber in coniferous forests throughout the northern hemisphere. Interestingly, all the aggregation pheromones (identified so far) of these beetles contain dioxabicyclo[3.2.1]octanes, *e.g.* frontalin (I),[2] brevicomins (IIa) and (IIb),[3] and multistriatin (III).[4] Amongst these, frontalin (I) was identified as the principal component of the aggregation pheromone of the southern pine beetle, *Dendroctonus frontalis*.[2] In the case of the western pine beetle, *D. brevicomis*, the pheromone was found to consist of two isomeric compounds, *viz.* *exo*-brevicomin (IIa), the active principle, and the *endo*-isomer (IIb), an inactive component.[3] However, later studies [5] revealed that (IIb) inhibits the response of *D. frontalis* towards (I). Further investigations [6] on these compounds showed that only (−)-(I) and (+)-(IIa) are the active enantiomers, the corresponding antipodes being inactive. Nevertheless, the racemic mixtures are sufficiently potent for their practical application. On account of their structural novelty and economic value, these compounds have been studied extensively.[7] By now, several syntheses (racemic as well as asymmetric) have been reported for frontalin [8] and the brevicomins.[9]

We have devised convenient synthetic routes to the above bicyclic acetals, starting from tetrahydrofurfuryl alcohol (1), an easily accessible raw material. The alcohol (1) can be converted into two important C_5-units, *viz.* the alkenol (2) [10] and the alkynol (3).[11] These bifunctional intermediates were earlier exploited by us [12] for the synthesis of jasmonoids. As depicted in the Scheme, the alcohol (1) proved to be an ideal starting material for the synthesis of the three pheromone components (I), (IIa), and (IIb).

For the synthesis of (I), the acetate of the alkenol (2) was treated with Jones reagent in the presence of mercury(II) acetate,[13] to obtain the keto acetate (4). Acetalisation of the ketone (4) followed by reduction with lithium aluminium hydride provided the acetal alcohol (6). Alternatively, the alcohol (6) was also derived in 78% overall yield from ethyl levulinate (5).† Mesylation (methanesulphonation) [14] of the alcohol (6), and subsequent treatment with lithium bromide, afforded the corresponding bromide (7). Recently, Sato *et al.*[15] have reported an excellent preparative method for ketones which involves acylation of Grignard reagents in tetrahydrofuran (THF) at low temperature. Following this procedure, the bromide (7) was transformed into the corresponding methyl ketone (8). A Wittig reaction between the ketone (8) and methyltriphenylphosphonium iodide led to the regioselective introduction of an *exo*-methylene group. The resulting olefin (9), on epoxidation to (10) followed by acid hydrolysis, directly afforded (±)-frontalin (I) whose analytical data (b.p., n_D, and spectra) were in good agreement with those reported in the literature.[16]



(I) (II) (III)

a; R^1 = H, R^2 = Et
b; R^1 = Et, R^2 = H

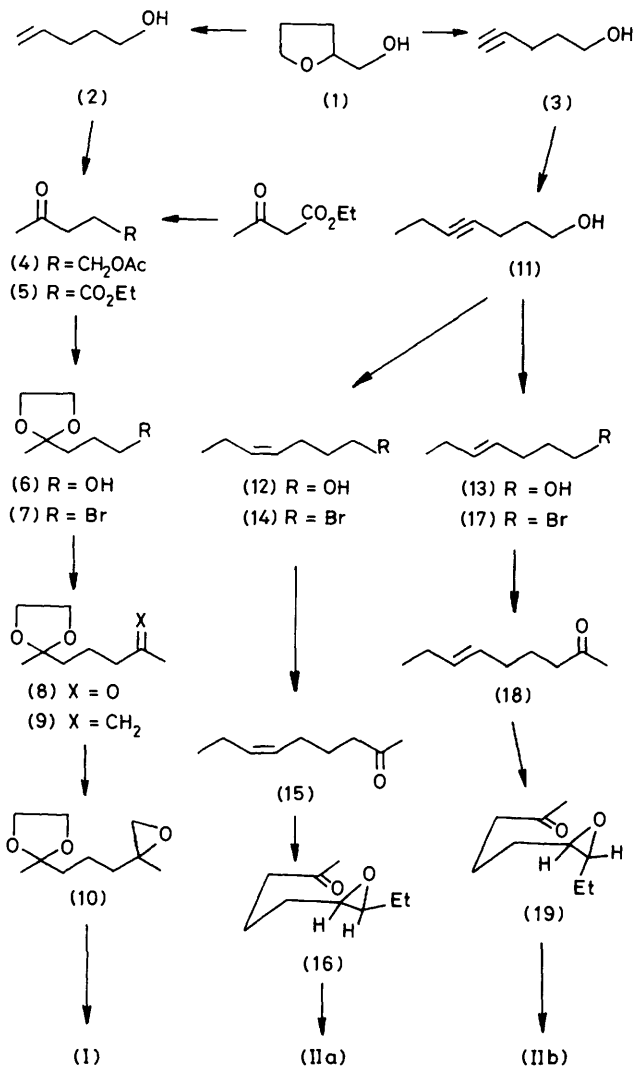
The synthesis of (±)-brevicomins (IIa) and (IIb) was so devised as to use a common intermediate for both the isomers. The alkynol (11), an appropriate intermediate for this purpose, was easily obtained by the alkylation of the alkynol (3) with bromoethane. Partial reduction of the acetylene (11) with hydrogen in the presence of a poisoned palladium catalyst,[17] and with sodium–ammonia,[18] gave the (*Z*)-alkenol (12) and the (*E*)-alkenol (13), respectively. Bromination of the alkenol (12) with triphenylphosphonium dibromide (PPh_3:Br_2 complex) [19] provided the corresponding bromide (14) which, *via* its Grignard reagent, was converted into the (*Z*)-alkenone (15) in high overall yield. Epoxidation of the olefin (15) gave the epoxy ketone (16) which, on treatment with toluene-*p*-sulphonic acid in diethyl ether, yielded the expected compound, *viz.* (±)-*exo*-brevicomin (IIa).

A similar sequence of reactions on the (*E*)-alkenol (13) resulted in the synthesis of the *endo*-isomer (IIb). G.l.c. analysis showed that the products were contaminated (3—4%) with their corresponding isomers which obviously arose in the final (cyclisation) step. The spectral data of both the compounds were identical with those reported for authentic brevicomins.[20]

Experimental

All the b.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer Infracord 137-B spectrophotometer. ^{1}H N.m.r. spectra were determined on a Varian A-60A spectrometer, using $SiMe_4$ as internal reference. Unless otherwise indicated, the spectra were taken using thin films (i.r.) and solutions in

† An ingenious preparation of this well known intermediate (5) involved alkylation of ethyl acetoacetate with ethyl bromoacetate, and subsequent de-ethoxycarbonylation with boric acid.



Scheme.

CCl_4 (^1H n.m.r.). Mass spectra were recorded on a VG Micromass 7070F instrument. The purity of all the products was checked by g.l.c. which was carried out on a 5% OV-17 column (6 ft × ¼ in), and using nitrogen (15 lb in^{-2}) as the carrier gas. All the reactions involving organometallic reagents were conducted under argon, and the solvents and reagents were transferred with the help of syringes.

4-Oxopentyl Acetate (4).—Acetylation of compound (2) with acetic anhydride–pyridine provided the corresponding acetate which was functionalised *via* an oxidation, described by Rogers *et al.*[13] This involved treatment of a solution of the alk-1-enyl acetate (12.8 g, 0.1 mol) in acetone (200 ml) with mercury(II) acetate (6.36 g, 0.02 mol) followed by 2M Jones reagent (70 ml). The reaction product was purified by fractional distillation to obtain the keto acetate (4) (8.0 g, 65%), b.p. 136—140 °C/100 mmHg (lit.,[21] 100—105 °C/13 mmHg); $\nu_{max.}$ 2 960, 1 745, 1 460, 1 245, and 1 030 cm^{-1}; δ 1.6—2.0 (4 H, m, $[CH_2]_2$), 2.04 (3 H, s, $COCH_3$), 2.13 (3 H, s, CH_2COCH_3), and 3.98 (2 H, t, CH_2OCOCH_3).

4,4-Ethylenedioxypentan-1-ol (6).—Following the standard procedures, the keto acetate (4) and ethyl levulinate (5) were separately acetalised, and the resulting acetals were reduced with lithium aluminium hydride to obtain the ketal alcohol (6) [75—80% from (4) or (5)], b.p. 112—114 °C/10 mmHg (lit.,[22] 62—64 °C/0.4 mmHg). The spectral properties of the product were identical with those reported [22] for (6).

1-Bromo-4,4-ethylenedioxypentane (7).—To a stirred and cooled (−10 °C) solution of the alcohol (6) (7.3 g, 50 mmol) and triethylamine (7.6 g, 75 mmol) in anhydrous dichloromethane (100 ml), was added a solution of methanesulphonyl chloride (6.3 g, 55 mmol) in dichloromethane (10 ml) during 0.5 h. After being stirred at 0—5 °C for a further 2 h, the reaction mixture was washed in turn with ice-cold water and saturated aqueous ammonium chloride. The organic phase was dried over anhydrous sodium sulphate and concentrated under reduced pressure to provide the corresponding mesylate as a pale yellow viscous liquid (11.2 g, *ca.* 100%), $\nu_{max.}$ 2 985, 2 940, 1 360, 1 180, 1 060, 980, 955, 930, and 820 cm^{-1}.

The above mesylate (crude) was immediately dissolved in acetone (100 ml) and anhydrous lithium bromide (7 g, *ca.* 80 mmol) was added. The solution was stirred overnight at the ambient temperature, and then under reflux for 4 h. Thereafter, it was concentrated under reduced pressure, and the residue was dissolved in cold water and extracted with light petroleum (b.p. 40—60 °C). Usual work-up then afforded the acetal bromide (7) (8.3 g, 79%), b.p. 94—97 °C/10 mmHg (lit.,[23] 103—105 °C/20 mmHg); $\nu_{max.}$ 2 985, 1 445, 1 380, 1 255, 1 120, 1 050, 950, and 865 cm^{-1}; δ 1.25 (3 H, s, CH_3), 1.5—2.2 (4 H, m, $[CH_2]_2$), 3.42 (2 H, t, CH_2Br), and 3.83 (4 H, s, OCH_2CH_2O).

6,6-Ethylenedioxyheptan-2-one (8).—Following the conventional procedure, a Grignard reagent was prepared from magnesium (960 mg, 40 mg-atom) and the bromide (7) (6.27 g, 30 mmol) in THF (30 ml). The solution was cooled to −70 °C and treated with a solution of freshly distilled acetic anhydride (3.06 g, 30 mmol) in THF (5 ml). After the addition, the mixture was slowly (during 2 h) warmed to room temperature. Thereafter, it was poured into ice-cold water (150 ml) and extracted with diethyl ether. The extract was washed in turn with 1M sodium hydroxide and brine, and was then worked up as usual to afford the *ketone* (8) (3.7, 71%), b.p. 114—116 °C/10 mmHg; $\nu_{max.}$ 2 995, 1 725, 1 380, 1 250, 1 070, 950, and 870 cm^{-1}; δ 1.22 (3 H, s, CH_3), 1.4—1.9 (4 H, m, $[CH_2]_2$), 2.05 (3 H, s, $COCH_3$), 2.35 (2 H, distorted t, CH_2CO), and 3.87 (4 H, s, OCH_2CH_2O) (Found: C, 62.7; H, 9.45. $C_9H_{16}O_3$ requires C, 62.77; H, 9.36%).

6,6-Ethylenedioxy-2-methylhept-1-ene (9).—To a stirred and cooled (0—5 °C) suspension of methyltriphenylphosphonium iodide (9.7 g, 24 mmol) in anhydrous THF (30 ml) was added n-butyl-lithium (12 ml of a 2M solution in hexane; 24 mmol) during 15—20 min. The cooling bath was then removed, the reaction mixture was stirred at ambient temperature for 1 h, and the resulting orange solution was treated with the ketone (8) (3.44 g, 20 mmol). After being stirred overnight at ambient temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride (2 ml), the solvent was removed under reduced pressure, and the residue was thoroughly extracted with diethyl ether. The product obtained after removal of solvent was purified by column chromatography [neutral alumina; 0—20% (gradient) diethyl ether in hexane as eluant] followed by a ' short path ' distillation to provide the *olefin* (9) [2.5 g, 74% from (7)]; b.p. 82—84 °C/10 mmHg; $\nu_{max.}$ 3 145, 2 780, 1 660, 1 450, 1 380, 1 070, 945, 885, and 865 cm^{-1}; δ 1.23 (3 H, s, CH_3), 1.3—2.2 (6 H, m, $[CH_2]_3$), 1.72 (3 H, s, $CH_2=CCH_3$), 3.85 (4 H, s, OCH_2CH_2O), and 4.68 (2 H, s, $CH_2=C$) (Found: C, 70.65; H, 10.65. $C_{10}H_{18}O_2$ requires C, 70.72; H, 10.80%).

(±)-*Frontalin* (I).—Treatment of the acetal olefin (9) (1.7 g. 10 mmol) with perbenzoic acid (30 ml of a 0.5M solution in dichloromethane; 15 mmol) for 24 h at 0—5 °C gave the corresponding epoxide (10) in quantitative yield. This was dissolved in THF (10 ml), 2M sulphuric acid (2.5 ml) was added, and the mixture was stirred for 4 h, diluted with diethyl ether (30 ml), washed thoroughly with brine, dried over anhydrous sodium sulphate, and carefully concentrated. The residue was distilled under reduced pressure to obtain (±)-frontalin (I) (1.09 g, 77%), b.p. 76—78 °C/50 mmHg; n_D^{21} 1.4365 (lit.,[16] b.p. 91 °C/100 mmHg; n_D^{20} 1.4386); g.l.c. (100 °C) R_t 3.8 min (>98%); $\nu_{max.}$ 2 960, 1 455, 1 380, 1 265, 1 245, 1 205, 1 175, 1 125, 1 070, 1 030, 935, 900, 870, 850, and 820 cm^{-1}; δ 1.25 (3 H, s, 1-CH_3), 1.32 (3 H, s, 5-CH_3), 1.5—1.8 (6 H, m, $[CH_2]_3$), and 3.55 and 3.78 (together 2 H, ABq, J_{AB} 7 Hz, 7-H_2).

Hept-4-yn-1-ol (11).—Following the procedure described earlier from this laboratory,[24] the alkynol (11) was obtained by the alkylation of pent-4-yn-1-ol (3) with bromoethane.

(Z)-*Hept-4-en-1-ol* (12).—To a solution of the alkynol (11) (11.2 g, 0.1 mol) and triethylamine (0.70 ml) in freshly distilled THF (100 ml) was added 5% palladium–calcium carbonate (1.0 g) and the mixture was stirred vigorously under hydrogen. After the uptake of the required volume of hydrogen, the reaction mixture was diluted with hexane (100 ml) and filtered through a short pad of silica gel. Removal of solvent, followed by distillation of the residue, provided the alkenol (12) (5.1 g, 89%), b.p. 84—86 °C/20 mmHg (lit.,[25] 74—76 °C/11 mmHg); $\nu_{max.}$ 3 380, 2 940, 1 460, 1 065, 1 040, and 725 cm^{-1}; δ 0.93 (3 H, t, CH_3), 1.3—1.8 (2 H, m, CH_2), 1.8—2.3 (4 H, m, $CH_2CH{=}CHCH_2$), 3.55 (2 H, t, CH_2CH), 3.98 (1 H, s, D_2O-exchangeable, OH), and 5.37 (2 H, m, CH=CH).

(E)-*Hept-4-en-1-ol* (13).—To a vigorously stirred solution of the alkynol (11) (11.2 g, 0.1 mol) in anhydrous ammonia (500 ml) was added sodium (9.2 g, 0.4 g-atom) (in small pieces) during 1 h. The resulting dark blue solution was stirred under reflux for 6 h, quenched cautiously with ammonium chloride (24 g), and kept overnight. The residue was dissolved in ice-cold water and extracted with diethyl ether, and the extract was worked up as usual to furnish the alkenol (13) (9.6 g, 84%), b.p. 83—85 °C/20 mmHg (lit.,[26] 74—76 °C/11 mmHg); $\nu_{max.}$ 3 405, 2 960, 1 455, 1 065, and 965 cm^{-1}.

7-*Bromohept-3-enes* (14) *and* (17).—To a stirred and cooled solution of triphenylphosphine (14.4 g, 55 mmol) in anhydrous dichloromethane (50 ml) was added bromine (10 ml of a 5.5M solution in CCl_4; 55 mmol) during *ca.* 10 min. The resulting thick white suspension was treated with a solution of the alkenol (12) (5.7 g, 50 mmol) in pyridine (4.5 ml). A mildly exothermic reaction ensued, which was completed by stirring the mixture for 1 h at ambient temperature. The contents of the flask were carefully distilled under reduced pressure, and the distillate was fractionated to obtain (*Z*)-7-bromohept-3-ene (14) (7.2 g, 81%), b.p. 73—75 °C/20 mmHg; $\nu_{max.}$ 2 975, 1 455, 1 440, 1 250, and 730 cm^{-1}.

Likewise, the corresponding (*E*)-alkenol (13) was converted into the corresponding bromide (17) (7.1 g, 81%), b.p. 74—76 °C/20 mmHg (lit.,[27] 35—40 °C/0.5 mmHg).

Non-6-en-2-ones (15) *and* (18).—As described for the preparation of the methyl ketone (8), the (*Z*)-alkenyl bromide (14) (3.54 g, 20 mmol) was transformed into the ketone (15) (2.21 g, 79%), b.p. 94—96 °C/20 mmHg (lit.,[28] 56 °C/6 mmHg); $\nu_{max.}$ 2 975, 1 720, 1 465, 1 365, and 1 160 cm^{-1}; δ 0.97 (3 H, t, CH_3), 1.3—2.4 (8 H, m, 4 × CH_2), 2.05 (3 H, s, $COCH_3$), and 5.32 (2 H, m, CH=CH).

Similarly, the (*E*)-alkenyl bromide (17) was converted into the corresponding ketone (18) (2.16 g, 77%), b.p. 93—95 °C/20 mmHg; $\nu_{max.}$ 2 960, 1 720, 1 370, 1 165, and 965 cm^{-1}; the ^1H n.m.r. spectrum was almost identical with that of the alkenone (15) (Found: C, 77.0; H, 11.6. $C_9H_{16}O$ requires C, 76.91; H, 11.65%).

(±)-*Brevicomins* (IIa) *and* (IIb).—Epoxidation of compound (15) (1.40 g, 10 mmol) with perbenzoic acid (24 ml of a 0.5M solution in CH_2Cl_2; 12 mmol) afforded the corresponding epoxy ketone (16) in *ca.* 100% yield. The crude product was dissolved in diethyl ether (20 ml) containing a catalytic amount (*ca.* 10 mg) of toluene-*p*-sulphonic acid, and the solution was stirred at ambient temperature for 3 h. Thereafter, the solvent was removed, and the residue was distilled under reduced pressure to provide (±)-*exo*-brevicomin (Ia) (1.36 g, 87%), b.p. 86—88 °C/50 mmHg (lit.,[29] 70 °C/20 mmHg); g.l.c. (100 °C) R_t 4.4 min (96—97%); $\nu_{max.}$ 2 990, 1 570, 1 470, 1 390, 1 245, 1 150, 1 115, 1 095, 980, 935, 885, and 855 cm^{-1}; δ 0.90 (3 H, t, CH_2CH_3), 1.32 (3 H, s, 5-CH_3), 1.45—1.78 (8 H, m, 4 × CH_2), 3.85 (1 H, t, 7-H), and 4.05 (1 H, br s, 1-H); *m/z* 156 (M^+), 114, 85, 68, 43 (100%), and 29.

Following the above procedure, the (*E*)-alkenone (18) (10 mmol) was transformed *via* the epoxide (19) into (±)-*endo*-brevicomin (IIb) (1.31 g, 84%), b.p. 82—84 °C/50 mmHg (lit.,[29] 60 °C/20 mmHg); g.l.c. (100 °C) R_t 5.2 min (96—97%); $\nu_{max.}$ 2 950, 1 560, 1 460, 1 380, 1 240, 1 175, 1 110, 1 035, 1 005, 980, 905, and 855 cm^{-1}; δ 0.91 (3 H, t, CH_2CH_3), 1.30 (3 H, s, 5-CH_3), 1.47—1.82 (8 H, m, 4 × CH_2), 3.82 (1 H, m, 7-H), and 4.06 (1 H, br s, 1-H); *m/z* 156, 140, 85, 68, 43, and 29.

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