Tetrahedron. Vol. 31, pp. 1381 to 1384 Pergamon Press 1975. Printed in Great Britain

SYNTHESIS OF OPTICALLY ACTIVE FORMS OF FRONTALIN

THE PHEROMONE OF *DENDROCTONUS* BARK BEETLES[a]

K. MORI*
Department of Agricultural Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113, Japan

(*Received in Japan 2 November 1974; Received in the UK for publication 28 January 1975*)

Abstract—(*R*)-(+)-Frontalin (**1**) and its antipode (**1'**) were synthesized from (*R*)-(+)-2-hydroxy-2-methylpentane-1,5-dioic acid 5→2 lactone (**2**) and its antipode (**2'**), respectively. This established the absolute configurations of both enantiomers of frontalin and afforded key materials to study the relationship between pheromone activity and chirality.

Our recent synthesis of the both optical isomers of *exo*-brevicomin (**A**) opened the way to clarify the chiral nature of the pheromone receptor of the western pine beetle, *Dendroctonus brevicomis* Le Conte.[1] Indeed only the (*R*)-(+)-isomer of *exo*-brevicomin (**A**) was shown to be biologically active.[2] This very interesting observation prompted us to synthesize optically active forms (**1** and **1'**) of frontalin, an aggregating pheromone of bark beetles.

Frontalin was first detected in the hindgut of females of the southern pine beetle, *Dendroctonus frontalis* Zimmerman, and later isolated from hindgut extracts of male western pine beetles.[3] Its structure was revealed to be 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (**1** or **1'**) by spectroscopic data and confirmed by the synthesis of its racemate.[3] Due to the scarcity of the pure natural pheromone (~0·3 mg), it was impossible to measure its optical rotation. Therefore its absolute stereochemistry remained unknown. Although two other syntheses of (±)-frontalin are recorded, none of them can be modified to give optically active products.[4,5] This paper describes the successful synthesis of both enantiomers of frontalin together with assignment of absolute stereochemistry to them.

As the resolution of (±)-frontalin itself is beyond the scope of the conventional resolution methods, our synthesis must follow either of the following two ways. One was to employ an optically active natural product of known absolute stereochemistry as the starting material just like what we did in the synthesis of brevicomin (**A**).[1] For this purpose optically active linalool seemed to be the best starting point as illustrated by the Cornforth synthesis of optically active mevalonolactone.[6] A drawback to this approach was the very limited availability of the optically pure linalool. After several attempts we had to abandon this route from linalool. The second and successful approach involves the resolution of a simple intermediate, (±)-2-hydroxy-2-methylpentane-1,5-dioic acid 5→2 lactone (**2**+**2'**), and will be detailed below.

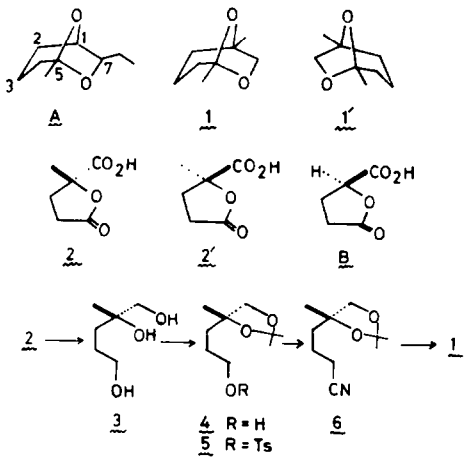
A quantity of the racemic lactonic acid (**2**+**2'**) could readily be prepared from levulinic acid by cyanohydrin formation and acid hydrolysis.[7] Its optical resolution with quinine was reported to give (+)-lactonic acid.[8] In our hands two diastereomeric quinine salts of the lactonic acid were successfully separated by careful fractional crystallization from EtOH. The less soluble salt afforded (+)-lactonic acid after acidification. So this was the salt recorded by Adams.[8] The other salt was more soluble in EtOH and exhibited distinctly different IR spectrum with that of the salt of the (+)-acid. This gave the (−)-acid after acidification. The (−)-acid was more easily obtainable by resolution with cinchonine. The cinchonine salt of (−)-acid was highly crystalline, while the antipodal (+)-acid gave non-crystalline salt. Recrystallization of the resolved acids gave pure enantiomers (**2** and **2'**), $[\alpha]_D^{23} \pm 16{\cdot}2°$ (H_2O).

In order to assign the absolute configurations to the resolved acids, their CD spectra were compared with that of (*S*)-(−)-2-hydroxypentane-1,5-dioic acid 5→2 lactone (**B**).† Although it might not be appropriate to apply the lactone sector rule[9] in the presence of an adjacent CO_2H, the rule predicted a positive Cotton effect for the (*S*)-lactonic acid (**B**). This was shown to be the case. The (*S*)-lactone (**B**) exhibited a positive CD extremum at 213 nm ($\Delta\epsilon = +1{\cdot}72$). Since CO_2H is far more bulky than Me, the (*S*)-lactonic acid (**2'**) was expected to exhibit a positive Cotton effect curve similar to that of the (*S*)-lactone (**B**). The (−)-lactonic acid obtained by resolution was found to possess a positive CD extremum at 215 nm ($\Delta\epsilon = +1{\cdot}80$), while the (+)-lactonic acid showed a negative one at 215 nm ($\Delta\epsilon = -1{\cdot}75$). Thus it is concluded that the (−)-acid possesses the (*S*)-configuration (**2'**), while the (+)-one belongs to the *R*-series (**2**).

The conversion of the lactonic acid to frontalin was first tried with the racemate to optimize the reaction conditions. (±)-Lactonic acid (1/2 **2**+1/2 **2'**) was reduced with LAH to give a triol [(±)-**3**]. This was dissolved in acetone and treated with *p*-TsOH yielding an acetonide [(±)-**4**]. The corresponding tosylate [(±)-**5**] was treated with NaCN in DMSO to give a nitrile [(±)-**6**]. Addition of MeMgI and subsequent acidification converted the nitrile into (±)-frontalin (1/2 **1**+1/2 **1'**). After chromatographic purification and distillation, the product showed the IR, NMR and mass (M^+ 142. 1015) spectra entirely identical with those reported for the natural and synthetic frontalins.[3-5]

[a]Pheromone Synthesis—V. Part IV: k. Mori, *Tetrahedron* **30**, 4223 (1974).

†This was a gift of Mr. Y. Ozawa of Ajinomoto Co., Inc., Kawasaki, who prepared it in a conventional manner from L-(+)-glutamic acid.



The same sequence of transformations afforded (*R*)-(+)-frontalin (**1**), $[\alpha]_D^{23}$ + 53·4° (ether), and its antipode (*S*)-(−)-**1'**, $[\alpha]_D^{23}$ − 52·0° (ether), starting from (*R*)-(+)-lactone (**2**) and (*S*)-(−)-**2'**, respectively. For the confirmation of the absolute stereochemistry of our products, the ORD curve of (1*R*:7*R*)-(+)-*exo*-brevicomin (**A**) was compared with those of the optical isomers of frontalin. Positive plain curves were observed for (+)-*exo*-brevicomin (**A**) and (+)-frontalin (**1**). This supports the *R*-configuration at C-1 of the latter. (−)-Frontalin (**1'**) exhibited a negative plain curve. This established the correlation between the optical rotation and absolute stereochemistry of two enantiomers of frontalin. The absolute configuration of the natural frontalin, however, remains unknown until enough material for rotation measurement is re-isolated in future.

Finally the optical purity of our products was checked with the NMR optishift reagent, Eu(facam)$_3$.[10,11]† In the case of (±)-frontalin, the addition of the shift reagent induced a remarkable downfield shift of every signal. Moreover, the Me singlets were separated into two sets of enantiotopic signals, a signal due to $-(CH_2)_3-$ was broadened and the AB quartet due to $-OCH_2O-$ was broadened to a pair of multiplets. On the other hand, the NMR spectrum of (*R*)-(+)-frontalin (**1**) suffered little change in pattern after the addition of the shift reagent. Of course a large downfield shift of each signal was induced, but the set of Me singlets and the $-OCH_2O-$ AB quartet were both remained unresolved. This clearly indicates the satisfactory optical purity of the (+)-pheromone (**1**). In the case of (*S*)-(−)-frontalin, however, the two Me signals and the lower field doublet of the $-OCH_2O-$ AB quartet showed a small splitting (2 ~ 3 Hz). This splitting may be due to the presence of two ether oxygen atoms in the frontalin molecule as the possible sites of coordination with Eu. As our frontalin optical isomers show $[\alpha]_D$ values of the same magnitude of opposite sign, we can regard our (*S*)-(−)-frontalin (**1'**) to be optically pure, although the optishift study gave somewhat anomalous result.

In conclusion the optically active forms of frontalin were synthesized in enough quantities (1·5 g of **1** and 1·2 g of **1'**) to study the relationship between absolute stereochemistry and phenomone activity. The biological result will be published elsewhere by our co-workers in entomological laboratories.

†Tris[3 - (trifluoromethylhydroxymethylene) - *d* - camphorato]europium (III).

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra refer to films unless otherwise specified and were determined on a Jasco IRA-1 spectrometer. NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer. Optical rotations were measured on a Jasco DIP-4 polarimeter. ORD and CD spectra were recorded on a Jasco J-20 spectropolarimeter. GLC analyses were performed on a Yanaco G 80 gas chromatograph.

Optical resolution of (±)-2-*hydroxy*-2-*methylpentane*-1,5-*dioic acid* 5→2 *lactone* (2 + 2')

(a) *With quinine.* The (±)-acid (117 g) and quinine (267 g) were dissolved in hot 95% EtOH (2000 ml). The soln was left to stand overnight in a refrigerator to give less soluble crystals A-1 (249 g). This was recrystallized from 95% EtOH to give crystals A-2(135 g). The mother liquor after removal of A-2 was concentrated *in vacuo* and the residue was recrystallized from 95% EtOH to give A-3 (60 g). Recrystallization of A-3 from 95% EtOH gave A-4 (17 g). Since the crystals A-2 and A-4 exhibited the same IR and $[\alpha]_D$ values, they were combined to give pure salt A (152 g, 38%). *The salt A* was less soluble in EtOH than the salt B described below and had the following properties: needles from EtOH, m.p. 222 ~ 224° (dec); $[\alpha]_D^{23}$ − 138° (c = 0·74%, EtOH) [lit.[8] m.p. 199·5 ~ 201·3°; $[\alpha]_D^{28}$ − 134·41° (c = 0·5%, EtOH)]; ν_{max} (nujol) ~ 3100 (m), 1765 (s), 1615 (m), 1590 (m), 1510 (m), 1405 (m), 1375 (m), 1305 (w), 1280 (m), 1260 (s), 1220 (m), 1195 (w), 1170 (m), 1150 (w), 1095 (s), 1080 (m), 1040 (w), 1000 (w), 980 (w), 940 (m), 925 (w), 915 (m), 900 (w), 885 (w), 870 (w), 850 (w), 805 (m), 785 (w), 760 (w), 715 (m) cm^{-1}. (Found: C, 66·78; H, 6·77; N, 5·82. $C_{26}H_{32}O_6N_2$ requires: C, 66·65; H, 6·88; N, 5·98%). The mother liquors obtained after removals of A-1, A-3 and A-4 were combined and concentrated *in vacuo*. The residue was recrystallized from 95% EtOH to give crystals B-1 (87 g). The mother liquor gave further crystals (B-2, 33·5 g) after concentration *in vacuo*. Since B-1 and B-2 showed the same IR and $[\alpha]_D$ values, they were combined (salt B, 120·5 g, 30%). An analytical sample was obtained by further recrystallization from EtOH. *The salt B* crystallized from EtOH as prisms, m.p. 224 ~ 225° (dec); $[\alpha]_D^{23}$ − 133·6° (c = 0·68%, EtOH); ν_{max} (nujol) ~ 3200 − ~ 3000 (m), 1775 (s), 1615 (m), 1590 (s), 1510 (m), 1400 (m), 1380 (m), 1305 (w), 1280 (w), 1240 (s), 1220 (m), 1145 (m), 1095 (s), 1060 (w), 1030 (m), 1000 (w), 980 (w), 945 (m), 915 (m), 855 (m), 830 (m), 800 (w), 720 (m) cm^{-1}. (Found: C, 66·83; H, 6·83; N, 5·95. $C_{26}H_{32}O_6N_2$ requires: C, 66·65; H, 6·88; N, 5·98%).

(b) *With cinchonine.* The (±)-acid (50 g) and cinchonine (95 g) were dissolved in hot 95% EtOH (600 ml). The soln was left to stand overnight in a refrigerator to give crystalline salt (74 g). This was recrystallized from 95% EtOH to give 50 g (41%) of the salt. This crystallized from EtOH as prisms, m.p. 228 ~ 230° (dec); $[\alpha]_D^{23}$ + 147° (c = 0·81%, EtOH); ν_{max} (nujol) ~ 3160 (m), 1785 (s), ~ 1570 (m), 1400 (s), 1305 (m), 1250 (m), 1215 (s), 1140 (m), 1120 (m), 1110 (m), 1040 (w), 1010 (w), 995 (w), 950 (m), 930 (m), 920 (m), 880 (w), 860 (w), 840 (w), 800 (m), 790 (m), 780 (m), 750 (m), 720 (w) cm^{-1}. (Found: C, 68·54; H, 6·83; N, 6·22. $C_{25}H_{30}O_5N_2$ requires: C, 68·47; H, 6·90; N, 6·39%).

(R)-(+)-2-*Hydroxy*-2-*methylpentane*-1,5-*dioic acid* 5→2 *lactone* (2)

A soln of the quinine salt A (151 g) in 10% HCl (2500 ml) was extracted continuously with ether for 3 days. The ether soln was concentrated *in vacuo*, The residue was mixed with C_6H_6 and concentrated *in vacuo* to remove trace of H_2O. The residue was recrystallized from C_6H_6-CCl_4 (1 : 1) to give crude acid (39 g, 83%). This was recrystallized from C_6H_6-CCl_4 (1 : 1). Further recrystallization from EtOAc-C_6H_6 gave pure **2** (27·2 g, 58%). The acid **2** crystallized from EtOAc-light petroleum as elongated prisms, m.p. 87·5 ~ 88·5° (lit.[8] 87·8 ~ 89·8°); $[\alpha]_D^{24}$ + 16·2° (*c* = 3·15%, H_2O) [lit.[8] $[\alpha]_D^{28}$ + 15·39° (*c* = 2·5%, H_2O)]; ν_{max} (nujol) ~ 3200 (m), ~ 2600 (m), 1760 (s), 1710 (s), 1290 (m), 1280 (s), 1250 (s), 1220 (m), 1180 (s), 1160 (m), 1110 (s), 1080 (m), 1000 (w), 980 (w), 950 (w), 850 (w), 800 (w), 760 (w), 715 (w) cm^{-1}; CD (*c* = 0·302%, EtOH): $[\theta]_{255}$, 0; $[\theta]_{215}$ − 5770 (min); $[\theta]_{200}$ − 3100. (Found: C, 49·96; H, 5·45. $C_6H_8O_4$ requires: C, 50·00; H, 5·60%).

(S)-(−)-2-*Hydroxy*-2-*methylpentane*-1,5-*dioic acid* 5→2 *lactone* (2')

(a) *From quinine salt B.* A soln of the salt B (120 g) in 10% HCl (saturated with NaCl, 3000 ml) was extracted continuously with ether for 3 days. The ether soln was concentrated *in vacuo*. The residue was mixed with C_6H_6 and concentrated *in vacuo*. The residual crystalline product was recrystallized from EtOAc-C_6H_6 to give 21·0 g (57%) of 2'.

(b) *From cinchonine salt.* A soln of the cinchonine salt (50 g) in 10% HCl (500 ml) was continuously extracted with ether for 2 days. The ether soln was diluted with C_6H_6 and concentrated *in vacuo*. The residue was recrystallized from EtOAc-C_6H_6 to give 10·5 g (64%) of 2'. The above two crops were combined (31·5 g) and further recrystallized from EtOAc-C_6H_6 to give pure 2' (25·9 g). An analytical sample crystallized as elongated prisms from EtOAc-light petroleum, m.p. 88·0 ~ 89·0°; $[\alpha]_D^{23}$ − 16·2° (*c* = 1·86%, H_2O); δ ($CDCl_3$) 1·68 (3 H, s), ~ 2·10 − ~ 2·90 (4 H, m), 9·99 (1 H, br. s); CD (*c* = 0·329%, EtOH): $[\theta]_{255}$ 0; $[\theta]_{215}$ + 5950; $[\theta]_{200}$ + 3090. (Found: C, 49·91; H, 5·45. $C_6H_8O_4$ requires: C, 50·00; H, 5·60%).

(S)-(−)-2-*Hydroxypentane*-1,5-*dioic acid* 5→2 *lactone* (B)

This is a gift from Mr. Y. Ozawa, m.p. 72°; $[\alpha]_D^{22}$ − 4·1° (*c* = 3·97%, H_2O); CD (*c* = 0·306%, EtOH): $[\theta]_{252}$ 0; $[\theta]_{213}$ + 5700 (max); $[\theta]_{200}$ + 3400.

2-*Methylpentane*-1,2,5-*triol*

(a) *Racemate* (1/2 3 + 1/2 3'). A soln of (±)-lactonic acid (1/2 2 + 1/2 2', 43·2 g) in dry ether (200 ml) was added to a stirred and ice-cooled suspension of LAH (17·1 g) in dry ether (1000 ml) at 0 ~ 5° during 1·5 hr. The stirring was continued for 2 hr at 0 ~ 25°. The mixture was left to stand overnight at room temp. Then the stirred mixture was ice-cooled and decomposed by successive addition of H_2O (17 ml), 15% NaOH soln (17 ml) and H_2O (50 ml). The mixture was diluted with THF (500 ml) and acetone (500 ml), stirred for 4 hr at room temp and filtered. The filter cake was washed several times with acetone and the combined filtrates were evaporated to dryness. The residual oil was distilled to give 15 g (37·5%) of the triol, b.p. 133 ~ 135°/0·2 mm, n_D^{32} 1·4721; ν_{max} ~ 3300 (s), 1140 (m), 1050 (s), 940 (m), 900 (w) cm^{-1}; δ (C_5D_5N) 1·41 (3 H, s), ~ 2·00 (4 H, m), 3·78 (2H, s), 3·85 (2 H, m), 5·64 (3 H, br. s, −OH). (Found: C, 53·59; H, 10·49. $C_6H_{14}O_3$ requires: C, 53·71; 10·52%).

(b) (R)-(−)-*Isomer* (3). This was obtained from (*R*)-(+)-lactone (2, 26·0 g) in 39·6% (9·5 g) yield, b.p. 136 ~ 137°/0·5 mm, n_D^{23} 1·4732; $[\alpha]_D^{23}$ − 1·2° (*c* = 1·7%, EtOH).

(c) (S)-(+)-*Isomer* (3'). This was obtained from (*S*)-(−)-lactone (2', 25·0 g) in 32% (7·4 g) yield, b.p. 137°/0·5 mm, n_D^{23} 1·4740; $[\alpha]_D^{23}$ + 1·7° (*c* = 1·85%, EtOH). The optically active products showed the same IR and NMR spectra as those of the racemate in every case hereafter described.

1,2-0-*Isopropylidene*-2-*methylpentane*-1,2,5-*triol*

(a) *Racemate* (1/2 4 + 1/2 4'). *p*-TsOH (0·5 g) was added to a soln of (±)-triol (1/2 3 + 1/2 3', 10 g) in acetone (500 ml) and the mixture was left to stand overnight at room temp. Powdered K_2CO_3 was added to the mixture and it was stirred for 10 min at room temp. Acetone was removed *in vacuo* and the residue was dissolved in EtOAc-H_2O. The EtOAc soln was washed with K_2CO_3 soln, dried (K_2CO_3) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 11·4 g (88%) of (±)-acetonide, b.p. 80 ~ 85°/0·4 mm, n_D^{28} 1·4370; ν_{max} 3350 (s), 2980 (s), 2930 (s), 2870 (s), 1450 (m), 1380 (s), 1250 (s), 1215 (s), 1160 (m), 1120 (m), 1060 (s), 980 (w), 940 (w), 900 (w), 850 (w), 805 (w) cm^{-1}; δ ($CDCl_3$) 1·28 (3 H, s), 1·48 (6 H, s), 1·63 (4H, s), 2·75 (2 H, s), 3·62 (1 H, br. s), 3·72 (2 H, s). (Found: C, 61·67; H, 10·26. $C_9H_{18}O_3$ requires: C, 62·04; H, 10·41%).

(b) (R)-(+)-*Isomer* (4). This was obtained from (*R*)-(−)-triol (3, 8·5 g) in 63·6% yield (7·0 g), b.p. 83°/0·4 mm, n_D^{22} 1·4388; $[\alpha]_D^{23}$ + 0·8° (*c* = 1·6%, acetone).

(c) (S)-(−)-*Isomer* (4'). This was prepared from (*S*)-(+)-triol (3', 6·4 g) in 83% yield (6·9 g), b.p. 83°/0·4 mm, n_D^{23} 1·4405; $[\alpha]_D^{23}$ − 0·5° (*c* = 2·25%, acetone).

1,2 - 0 - *Isopropylidene* - 2 - *methylpentane* - 1,2,5 - *triol* - 5 - p - *toluenesulfonate*

(a) *Racemate* (1/2 5 + 1/2 5'). *p*-TsCl (16·0 g) was added to a soln of (±)-acetonide (1/2 4 + 1/2 4', 11·2 g) in dry C_5H_5N (60 ml) with stirring at 0 ~ 5°. The mixture was stirred for 1 hr at 0 ~ 5° and then for another hr at room temp. It was poured into ice-water and extracted with ether. The ether soln was washed with $CuSO_4$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated *in vacuo* to give 23 g of an oily tosylate, ν_{max} 3040 (w) 2980 (s), 2930 (m), 2860 (m), 1600 (m), 1360 (s), 1250 (m), 1215 (a), 1190 (s), 1175 (s), 1110 (m), 1060 (m), 960 (m), 920 (m), 815 (m), 740 (m), 680 (m), 665 (m) cm^{-1}. This was employed for the next step without further purification.

(b) (R)-*Isomer* (5). (*R*)-(+)-Acetonide (4, 6·6 g) was converted into 11·1 g of crude 5.

(c) (S)-*Isomer* (5'). (*S*)-(−)-Acetonide (4', 5·9 g) was converted into 10·0 g of crude 5'.

1,2 - 0 - *Isopropylidene* - 2 - *methyl* - 5 - *cyanopentane* - 1,2 - *diol*

(a) *Racemate* (1/2 6 + 1/2 6'). Powdered NaCN (6·0 g) was added to a soln of (±)-tosylate (1/2 5 + 1/2 5', 23 g) in DMSO (100 ml) with stirring (exothermic). The mixture was stirred for 10 min at 50°, then left to stand overnight at room temp, poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was distilled *in vacuo* to give 9·0 g (77% from 4) of the cyanide, b.p. 83°/0·3 mm, n_D^{26} 1·4347; ν_{max} 2970 (s), 2920 (s), 2850 (m), 2240 (w), 1450 (m), 1420 (w), 1380 (s), 1245 (s), 1210 (s), 1110 (s), 1050 (s), 1010 (w), 975 (w), 915 (w), 860 (w), 800 (w) cm^{-1}; δ ($CDCl_3$) 1·29 (3 H, s), 1·38 (6 H, s), 1·75 (4 H, br. s), 2·42 (2 H, m), 3·76 (2 H, s). (Found: C, 65·60; H, 9·24; N, 7·44. $C_{10}H_{17}O_2N$ requires: C, 65·54; H, 9·35; N, 7·64%).

(b) (R)-(−)-*Isomer* (6). This was obtained from (*R*)-tosylate (5, 11·1 g) in 65% yield (4·5 g), b.p. 83°/0·3 mm, n_D^{23} 1·4375; $[\alpha]_D^{23}$ − 2·6° (*c* = 2·9%, acetone).

(c) (S)-(+)-*Isomer* (6'). This was obtained from (*S*)-tosylate (5', 10·0 g) in 66% yield (4·1 g) from 4', b.p. 84 ~ 86°/0·4 mm, n_D^{23} 1·4378; $[\alpha]_D^{23}$ + 2·3° (*c* = 2·0%, acetone).

Frontalin (1,5-*dimethyl*-6,8-*dioxabicyclo*[3.2.1] *octane*)

(a) *Racemate* (1/2 1 + 1/2 1'). A Grignard reagent was prepared from MeI (18·4 g) and Mg (2·8 g) in dry ether (60 ml). The cyanide (1/2 6 + 1/2 6', 8·5 g) in dry ether (20 ml) was added dropwise to the stirred MeMgI at room temp. The mixture was left to stand overnight at room temp and then cautiously poured into ice and dil HCl (25 ml of concd HCl + 100 ml of ice-water) in a round bottomed flask. The mixture was heated at 50 ~ 60° for 20 min. During that period, ether was almost distilled off. After cooling, the aqueous layer was saturated with NaCl and extracted with ether. The ether soln was washed with $NaHCO_3$-$Na_2S_2O_4$ soln and sat NaCl soln, dried ($MgSO_4$) and concentrated. As the product is highly volatile, care should be taken not to evaporate frontalin. The residue was chromatographed over alumina (Woelm, neutral, grade II, 60 g, 10 × 3 cm in light petroleum). Elution with light petroleum (500 ml) gave pure frontalin. This was distilled to give 3·2 g (49%) of (±)-frontalin, b.p. 92 ~ 93°/100 mm (lit.[5] b.p. 91°/100 mm), n_D^{27} 1·4345 (lit.[5] n_D^{20} 1·4386); ν_{max} 2960 (m, sh), 2920 (s), 2860 (m), 2810 (w), 1445 (w), 1390 (m), 1380 (m), 1340 (w), 1325 (w), 1285 (w), 1270 (m), 1240 (m), 1200 (m), 1170 (m), 1120 (s), 1060 (m), 1020 (s), 970 (w), 925 (m), 910 (w) 890 (m), 860 (m), 840 (s), 815 (m), 750 (w) cm^{-1}; δ ($CDCl_3$) 1·49 (3 H, s), 1·59 (3 H, s), ~ 1·80 (6 H, br. s), 3·58, 4·04 (2 H, ABq, J_{AB} = 7 Hz); NMR with Eu (facam)$_3$ [30 mg of (±)-frontalin and 100 mg of Eu (facam)$_3$ in 0·3 ml of CCl_4] δ (CCl_4) 1·64 (1·5 H, s), 1·74 (1·5 H, s), 2·20 (1·5 H, s), 2·29 (1·5 H, s), 3·72 (6 H, br. s, shoulder at 3·68), 4·64 (1 H, br. m), 5·12 (1 H, br. m); MS: *m/e* 27·0203 (6%, C_2H_3), 39·0269 (16%, C_3H_3), 41·0428 (19%, C_3H_5), 43·0214 (100%, C_2H_3O), 54·0473 (11%, C_4H_6), 67·0551 (13%, C_5H_7), 71·0494 (21%, C_4H_7O), 72·0580 (78%, C_4H_8O), 100·0867 (35%, $C_6H_{12}O$), 112·0860 (12%, $C_7H_{12}O$), 142·1015 (13%, M^+, $C_8H_{14}O_2$ requires: 142·0994); GLC (5% SE-30 on Celite 545, 1·5 m × 3 mm i.d. at 80°; Carrier gas N_2, 1·0 kg/cm^2): R, 8·8 min (94%), 11·6 min (2%), 13·8 min (3%), 14·6 min (1%).

(b) (R)-(+)-*Frontalin* (1). This was obtained from (*R*)-(−)-nitrile (6, 4·1 g) in 47% yield (1·5 g), b.p. 100–103°/121 mm, n_D^{23}

1·4356; $[\alpha]_D^{23}$ + 53·4° (*c* = 2·757%, ether); ORD (*c* = 0·629%, ether): $[\phi]_{450}$ + 134°; $[\phi]_{350}$ + 253°; $[\phi]_{240}$ + 536°; NMR with Eu (facam)$_3$ [30 mg of I and 100 mg of Eu (facam)$_3$ in 0·3 ml of CCl_4] δ (CCl_4) 1·66 (3 H, s), 2·24 (3 H, s), 3·57 (6H, br. s), 4·67, 5·26 (2 H, ABq, J_{AB} = 7 Hz); GLC (5% SE-30 on Celite 545, 1·5 m × 3 mm i.d. at 80°; Carrier gas, N_2, 1·0 kg/cm^2): Rt 8·8 min (96%), 13·8 min (3%). 14·6 min (1%).

(c) (S)-(−)-*Frontalin* (**1**). This was obtained from (*S*)-(+)-nitrile (6′, 3·8 g) in 41% yield (1·2 g), b.p. 99 ~ 100°/120 mm, n_D^{24} 1·4354; $[\alpha]_D^{23}$ − 52·0° (*c* = 1·63%, ether); ORD (*c* = 0·621%, ether): $[\phi]_{450}$ − 141°; $[\phi]_{350}$ − 256°; $[\phi]_{240}$ − 560°; NMR with Eu (facam)$_3$ [30 mg of 1′ and 100 mg of Eu (facam)$_3$ in 0·3 ml of CCl_4, measured after 2 h] δ (CCl_4) 1·63 (3 H, d, J = 3 Hz), 2·18 (3 H, d, J = 2·5 Hz), 3·70 (6 H, br. s), 4·50 (1 H, d, J = 7 Hz), 5·00 (1 H, dd, J_1 = 7 Hz, J_2 = 2·5 Hz); GLC (5% SE-30 on Celite 545, 1·5 m × 3 mmi.d. at 80°; Carrier gas N_2, 1·0 kg/cm^2): R, 8·8 min (96%), 13·8 min (3%), 14·6 min (1%).

(1 R:7 R)-(+)-exo-*Brevicomin* (*A*). Due to the scarcity of the material, a sample recovered after $[\alpha]_D$ measurement was used for this ORD study. So it was highly probable that the sample contained a small amount of ether which was the solvent for $[\alpha]_D$ measurement. This means that pure A possesses somewhat greater $[\phi]$ values than those reported here. ORD (*c* = 0·621%, ether): $[\phi]_{450}$ + 115°; $[\phi]_{350}$ + 160°; $[\phi]_{240}$ + 275°.

Acknowledgements—I thank Prof. M. Matsui, the Dean, Faculty of Agriculture of this University, for encouragements. My thanks are due to Mr. L. E. Browne, University of California, for stimulating me to carry out this work by showing me his olfactometer and western pine beetles attracted by a mixture of brevicomin, frontalin and myrcene. Messers K. Kurihara and S. Muraki of Takasago Perfume Industry, Tokyo, kindly gave me (−)-linalool used in the early phase of this work. I also thank Dr. K. Aizawa and his associates, this Department, for MS and elemental analyses. Help of Mr. T. Takigawa in GLC and ORD-CD analyses is acknowledged with thanks.

REFERENCES

[1]K. Mori, *Tetrahedron* **30**, 4223 (1974)
[2]Unpublished observation of Prof. D. L. Wood, Mr. L. E. Browne and their associates at University of California, Berkeley. This result was presented by K. M. at the IX*th International Symposium on the Chemistry of Natural Products*, Ottawa, June 27 (1974)
[3]G. W. Kinzer, A. F. Fentiman, Jr., T. F. Page, Jr., R. L. Foltz, J. P. Vite and G. B. Pitman, *Nature* **221**, 447 (1969)
[4]B. P. Mundy, R. D. Otzenberger and A. R. De Bernardis, *J. Org. Chem.* **36**, 2390 (1971)
[5]T. D. J. D'Silva and D. W. Peck, *Ibid.* **37**, 1828 (1972)
[6]R. H. Cornforth, J. W. Cornforth and G. Popják, *Tetrahedron* **18**, 1351 (1962)
[7]Y. Iwanami and Y. Kawai, *Kogyokagaku Zasshi* (*J. Ind. Chem. Soc. Japan*) **65**, 1492 (1962)
[8]R. Adams and F. B. Hauserman, *J. Am. Chem. Soc.* **74**, 694 (1952)
[9]P. Crabbé, *ORD and CD in Chemistry and Biochemistry, an Introduction* pp. 50 ~ 54; and refs therein. Academic Press, New York and London (1972)
[10]H. L. Goering, J. N. Eikenberry and G. S. Koermer, *J. Am. Chem. Soc.* **93**, 5913 (1971)
[11]H. L. Goering, J. N. Eikenberry, G. S. Koermer and C. J. Lattimer, *Ibid.* **96**, 1493 (1974)