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Protective Group-Free Syntheses of (±)-Frontalin, (±)-*endo*-Brevicomin, (±)-*exo*-Brevicomin, and (±)-3,4-Dehydro-*exo*-brevicomin: Racemic Pheromones with a 6,8-Dioxabicyclo[3.2.1]octane Ring*

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Protective group-free syntheses of four racemic pheromones with a 6,8-dioxabicyclo[3.2.1]octane ring were achieved in five or six steps from commercially available (±)-3-butyn-2-ol (6) and 2-alkenyl halides or 2-alken-1-ol by employing Lewis acid-catalyzed acetalization of δ, ε-epoxy ketones as the key reaction. (±)-Frontalin (1) was prepared in a 25% overall yield in five steps from methallyl chloride (5a), (±)-*endo*-brevicomin (2) was prepared in a 23% overall yield in five steps from (*E*)-2-pentenyl bromide (5b), and (±)-*exo*-brevicomin (3) and (±)-3,4-dehydro-*exo*-brevicomin (4) were both prepared in a 4% overall yield in six steps based on (*Z*)-2-penten-1-ol (12).

Key words: *endo*-brevicomin; *exo*-brevicomin; 3,4-dehydro-*exo*-brevicomin; frontalin; pheromone

The 6,8-dioxabicyclo[3.2.1]octane ring system is one of the prevailing structural motifs among pheromones.[2] Frontalin (**1**, Fig. 1),[3] *endo*-brevicomin (**2**),[4] and *exo*-brevicomin (**3**)[4] have been discovered as the aggregation pheromones of bark beetles, while 3,4-dehydro-*exo*-brevicomin (**4**) has been identified as the sex pheromone produced by the male house mouse.[5] Frontalin (**1**) has recently been shown to be the sex pheromone of male Asian elephants.[6] The absolute configurations of their pheromonally active enantiomers have been determined as shown in Fig. 1 by enantioselective syntheses and subsequent bioassays.[7] Their opposite enantiomers are not inhibitory against the pheromone activities of the natural enantiomers,[7] making their racemates half as active as the pheromones. Accordingly, their racemates are practically useful as attractants.

Over a hundred reports have been presented to date on the synthesis of these pheromones with the 6,8-dioxabicyclo[3.2.1]octane ring system,[8,9] including my first synthesis of the enantiomers of **1**[10] and that of **3**.[11] Almost all of the published syntheses have utilized the intramolecular acetalization of keto diol **A** (Fig. 2) to give acetal **B** as the final step. Keto diol **A** is usually prepared by acid-catalyzed deprotection of intermediate **C**, **D** or **E**, and spontaneous cyclization of **A** under acidic conditions gives **B**. Using the protective groups present in **C**, **D** and **E**, however, is against the recent trend to carry out syntheses under protective group-free conditions. Protective group-free synthesis is considered to be better on the basis of atom economy and is regarded as a so-called green process.

I therefore planned to employ a rearrangement reaction of epoxy ketone **F** to give acetal **B** as the final acetalization step. The reactions of epoxides with ketones are known to give acetals,[12] and Wasserman and Barber were the first to employ this rearrangement for the synthesis of (±)-*exo*-brevicomin (**3**).[13] We have used this reaction in our synthesis of (±)-frontalin (**1**).[14] Wasserman *et al.* later synthesized 3,4-dehydro-*exo*-brevicomin (**4**) by this rearrangement (**G** → **4**).[15,16] The purpose of the present study is to prepare (±)-**1**, (±)-**2**, (±)-**3** and (±)-**4** by epoxy ketone rearrangement (**F** → **B**) and to evaluate its effect on the efficiency of synthesizing these pheromones. It is of particular interest to learn whether or not the synthesis of (±)-**4** by such rearrangement of **G** → **4** would be better than our previous method with pure (1*R*,5*S*,7*R*)-**4** employing protective groups.[17,18]

Results and Discussion

*Syntheses of (±)-frontalin (1) and (±)-*endo*-brevicomin (2)*

Scheme 1 summarizes the syntheses of (±)-frontalin (**1**) and (±)-*endo*-brevicomin (**2**). The carbon framework of (±)-**1** was constructed from methallyl chloride (**5a**) and (±)-3-butyn-2-ol (**6**) by alkylating the dianion of (±)-**6** with **5a** to give (±)-**7a**.[19] Oxidation of (±)-**7a** with pyridinium chlorochromate (PCC) afforded acetylenic ketone **8a**. *m*-Chloroperbenzoic acid (MCPBA) selectively epoxidized the double bond of **8a** to give epoxy ketone **9a**. This in ethyl acetate was hydrogenated over palladium-charcoal in the presence of a small amount of triethylamine to give epoxy ketone **10a**. Treating **10a** with zinc chloride in diethyl ether finally yielded (±)-frontalin (**1**) after distillation. Its IR, ^{1}H- and ^{13}C-NMR, and mass spectral data were identical to those of an authentic sample. The overall yield of (±)-**1** was 25% in five steps based on **5a**. This protective group-free synthesis was far more efficient than our previous synthesis of (±)-**1** in 1975 [a 4.4% overall yield in eight steps based on **5a**], and proved to be convenient for preparing gram quantities of (±)-**1** in a short time.

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* Pheromone Synthesis, Part 246. See ref. 1 for Part 245.

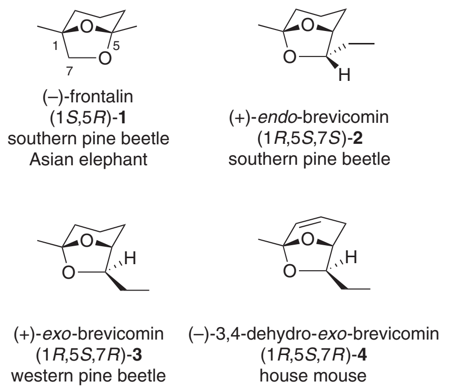


Fig. 1. Structures of the Pheromones with a 6,8-Dioxabicyclo-[3.2.1]octane Ring System.

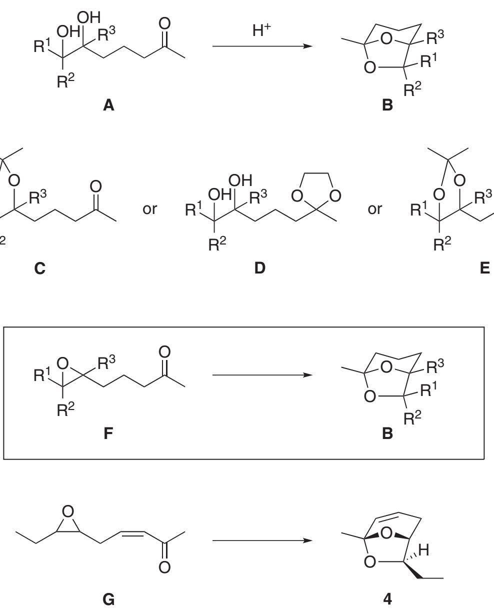
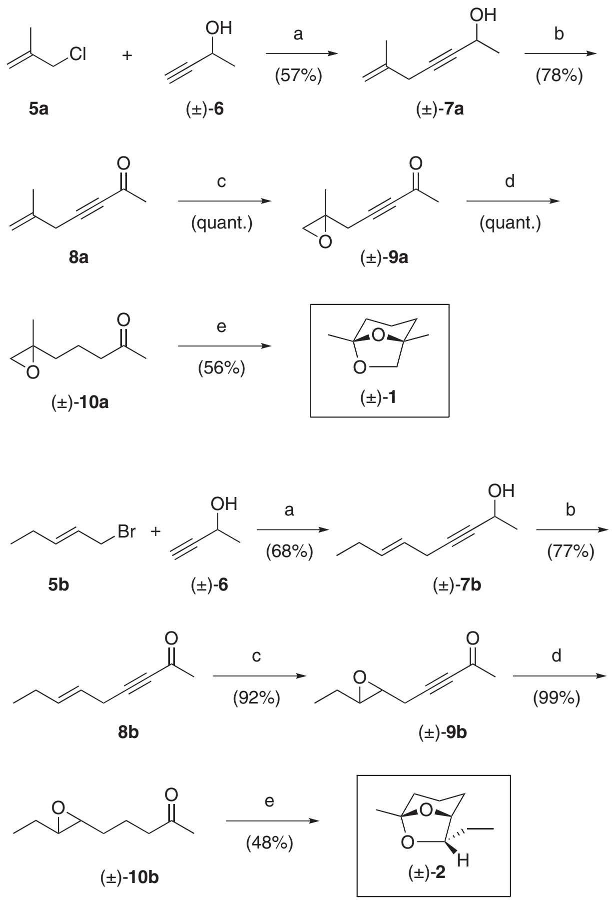


Fig. 2. Synthetic Plan.

The synthesis of ($\pm$)-*endo*-brevicomin (**2**) started with slightly lachrymatory bromide **5b**, which had been prepared in a 62% yield from commercially available (*E*)-2-penten-1-ol, being treated with phosphorus tribromide in diethyl ether.[15] The subsequent steps to ($\pm$)-**9b** were carried out in the same manner as that reported by Wasserman *et al.*[15] Accordingly, the dianion of ($\pm$)-**6** was alkylated with **5b** to give ($\pm$)-**7b**. PCC oxidation of ($\pm$)-**7b** afforded **8b** which was epoxidized with MCPBA to give ($\pm$)-**9b**. Hydrogenation of ($\pm$)-**9b** with palladium-charcoal in ethyl acetate in the presence of triethylamine furnished epoxy ketone ($\pm$)-**10b**. This was treated with zinc chloride in diethyl ether to yield ($\pm$)-*endo*-brevicomin (**2**). Its spectral data were identical to those of an authentic specimen. The overall yield of ($\pm$)-**2** was 23% based on **5b** in five steps. ($\pm$)-*endo*-Brevicomin (**2**) could thus be efficiently synthesized in a straightforward manner.

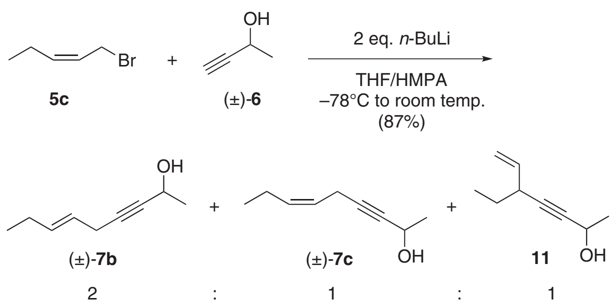
*Syntheses of (±)-*exo*-brevicomin (3) and (±)-3,4-dehydro-*exo*-brevicomin (4)*

($\pm$)-*exo*-Brevicomin (**3**) was initially thought to be obtainable through a route similar to that used for the synthesis of ($\pm$)-*endo*-brevicomin (**2**). Accordingly, as



Scheme 1. Syntheses of ($\pm$)-Frontalin (**1**) and ($\pm$)-*endo*-Brevicomin (**2**).

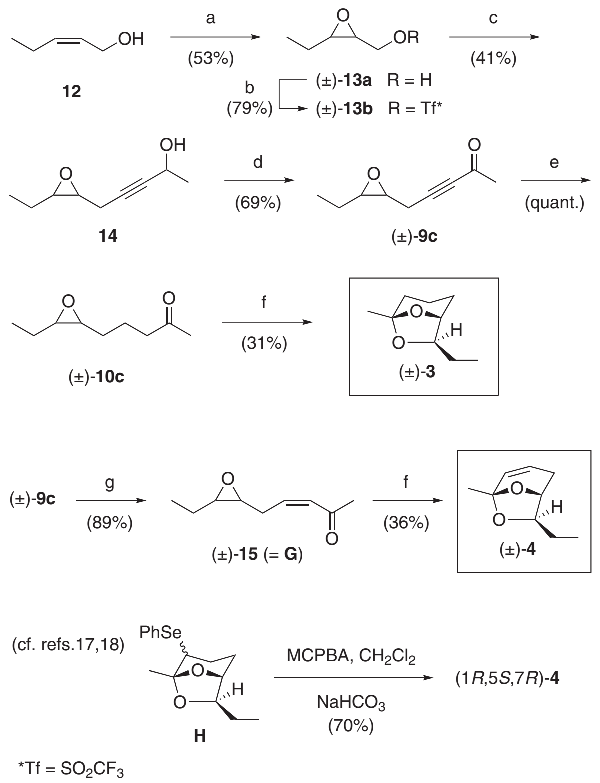
Reagents and conditions: (a) *n*-BuLi (2 eq.), THF, HMPA; $-40\,^{\circ}C$ to room temperature, overnight; (b) PCC, NaOAc, SiO_2, CH_2Cl_2; 0–5 °C, 1 h; room temperature, 2 h; (c) MCPBA, CH_2Cl_2; 0–5 °C, 1.5–2 h; (d) H_2, Pd–C, Et_3N, EtOAc; room temperature, 1–1.5 h; (e) $ZnCl_2$, Et_2O; 0–5 °C, 45 min–1 h.



Scheme 2. Attempted Preparation of **7c**.

shown in Scheme 2, extremely lachrymatory bromide **5c**, which had been prepared from commercially available (*Z*)-2-penten-1-ol by a treatment with phosphorus tribromide, was subjected to attack by the dianion derived from ($\pm$)-**6** in THF/HMPA (10:1). This alkylation, however, took place with allylic rearrangement and *E*/*Z*-isomerization to give a mixture of three enyne alcohols, ($\pm$)-**7b**, ($\pm$)-**7c** and **11** (2:1:1). Desired ($\pm$)-**7c** was not, however, the major product. The synthetic route leading to ($\pm$)-**3** was therefore modified to that shown in Scheme 3.

Epoxidation of (*Z*)-2-penten-1-ol (**12**) with MCPBA furnished epoxy alcohol ($\pm$)-**13a**. As with the



Scheme 3. Syntheses of (±)-*exo*-Brevicomin (**3**) and (±)-3,4-Dehydro-*exo*-brevicomin (**4**).

Reagents and conditions: (a) MCPBA, CH_2Cl_2; 0–5 °C, 2 h; (b) Tf_2O, Et_3N, CH_2Cl_2; −70 °C, 20 min; (c) (±)-**6**, *n*-BuLi (2 eq.), THF; −30 to −20 °C; then room temperature, 1 h; (d) PCC, NaOAc, SiO_2, CH_2Cl_2; 0–5 °C, 2 h; (e) H_2, Pd–C, Et_3N, EtOAc; room temperature, 1 h; (f) $ZnCl_2$, Et_2O; 0–5 °C, 20–30 min; (g) H_2, Lindlar's Pd (Aldrich), quinoline, cyclohexane; 0–5 °C, 1 h.

Wasserman synthesis of (±)-3,4-dehydro-*exo*-brevicomin (**4**), (±)-**13a** was converted to corresponding triflate (±)-**13b**, this being employed for alkylation of the dianion derived from (±)-**6**. It must be added that triflate (±)-**13b** was unstable and readily polymerized when dissolved in THF containing peroxides. Dianion alkylation of (±)-**6** with (±)-**13b** yielded **14**, whose PCC oxidation gave (±)-**9c**. Hydrogenation of (±)-**9c** over palladium-charcoal furnished (±)-**10c** which was treated with zinc chloride in diethyl ether to give (±)-*exo*-brevicomin (**3**). Its IR, ^{1}H- and ^{13}C-NMR, and mass spectral data were identical to those of an authentic specimen. The overall yield of (±)-**3** was 4% in six steps based on **12**.

Wasserman's route[16] was employed for converting (±)-**9c** to (±)-3,4-dehydro-*exo*-brevicomin (**4**). Accordingly, (±)-**9c** was hydrogenated over Lindlar's palladium catalyst in the presence of quinoline in cyclohexane to give (*Z*)-enone (±)-**15** which was treated with zinc chloride in diethyl ether to afford (±)-**4**. GC-MS analysis showed a significant content (24%) of (±)-**3** resulting from over-reduction in the course of the Lindlar hydrogenation of (±)-**9c**. With the exception of signals due to contaminating (±)-**3**, synthetic (±)-**4** showed IR, ^{1}H- and ^{13}C-NMR, and mass spectral data identical to those of the authentic specimen. The overall yield of (±)-**4** in six steps was 4% based on **12**. The respective cyclization reactions of epoxy ketones (±)-**10c** and (±)-**15** to pheromones (±)-**3** and (±)-**4** unfortuanately proceeded in rather low yields (31% and 36%), leaving a non-volatile and oily residue after distillation.

Although the present method was convenient for preparing (±)-**4** as reported by Wasserman,[15,16] contamination with (±)-**3** was almost inevitable due to our reliance on Lindlar hydrogenation for converting (±)-**9c** to (±)-**15**. Our previous synthesis of **4** with introduction of the 3,4-double bond at the final stage (**H** → **4**) seems to have been a better method for yielding pure **4** without contamination by **3**.[17,18]

Conclusion

Protective group-free syntheses of (±)-frontalin (**1**), (±)-*endo*-brevicomin (**2**), (±)-*exo*-brevicomin (**3**), and (±)-3,4-dehydro-*exo*-brevicomin (**4**) were accomplished. The four synthetic routes were all shorter (five or six steps) than the conventional ones, and guaranteed good overall yields in the cases of (±)-**1** and (±)-**2**. Although short, the synthesis of (±)-**3** as well as that of (±)-**4** proceeded in rather poor overall yields (4%) mainly due to the instability of epoxy triflate (±)-**13b**.

Experimental

General. Refractive index data (n_D) were measured with an Atago DMT-1 refractometer, and IR spectra were measured with a Jasco FT/IR-410 spectrometer. ^{1}H-NMR spectra (400 MHz, TMS at $\delta = 0.00$ as an internal standard) and ^{13}C-NMR spectra (100 MHz, $CDCl_3$ at $\delta = 77.0$ as an internal standard) were recorded by a Jeol JMN-AL 400 spectrometer. GC-MS data were recorded by an Agilent Technologies 5975 inert XL instrument, and HRMS data were measured with a Jeol JMS-SX 102A spectrometer. Column chromatography was carried out on Merck Kieselgel 60 Art 1-07734.

(±)-6-Methyl-6-hepten-3-yn-2-ol (7a). A solution of *n*-BuLi in hexane (1.6 M, 100 mL, 160 mmol) was added dropwise to a stirred and cooled solution of (±)-3-butyn-2-ol (**6**, 5.50 g, 80 mmol) in dry THF (100 mL) and dry HMPA (10 mL) at −20 °C under Ar. The paste-like mixture was stirred for 30 min at −20 to 0 °C. It was then further cooled to −40 °C, and a solution of methallyl chloride (**5a**, 6.30 g, 10 mmol) in dry THF (15 mL) was added dropwise to the stirred mixture. Stirring was continued overnight, after which the reaction mixture had reached room temperature. The mixture was quenched with an NH_4Cl solution and then extracted with hexane. The resulting extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was distilled to give 5.03 g (57%) of (±)-**7a** as a colorless oil, bp 70–73 °C at 5 Torr, $n_D^{25} = 1.4648$. IRν_{max} (film) cm^{-1}: 3317 (m), 3080 (w), 2979 (s), 2931 (m), 2883 (m), 2251 (w), 1657 (m), 1153 (s), 1078 (vs), 1003 (s), 891 (vs). ^{1}H-NMR δ_H ($CDCl_3$): 1.45 (3H, d, $J = 6.4$ Hz), 1.79 (3H, s), 2.01 (1H, br. s), 2.92 (2H, s), 4.56 (1H, br. s), 4.83 (1H, s), 4.99 (1H, s). GC-MS [HP-5MS column, 5% phenylmethylsiloxane, 30 m × 0.25 mm i.d.; He carrier gas at 60.7 kPa pressure and 70–230 °C (+10 °C/min) temperature] t_R: 5.42 min [92%, (±)-**7a**], 6.53 min (3.0%), 9.22 min (1.8%). MS of (±)-**7a** (70 eV, EI) *m/z*: 124 (4) (M^+), 123 (11), 109 (100), 91 (16), 81 (21), 79 (38), 77 (13), 65 (13), 53 (13), 45 (7), 43 (21), 41 (11), 39 (17). HRMS: calcd. for $C_8H_{12}O$ (M^+), 124.0888; found, 124.0884.

6-Methyl-6-hepten-3-yn-2-one (8a). A solution of **7a** (4.40 g, 35.5 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise over 10 min to a stirred and ice-cooled mixture of PCC (15.5 g, 72 mmol), NaOAc (0.9 g, 11 mmol) and SiO_2 (15.5 g) in dry CH_2Cl_2 (180 mL) at 5–10 °C. Stirring was continued for 1 h at 0–5 °C and then for 2 h at room temperature. The mixture was diluted with Et_2O and filtered. The SiO_2 layer was washed with Et_2O. The combined filtrate and washings were concentrated *in vacuo* to give a dark oil which was chromatographed over SiO_2 (60 g). Elution with hexane/EtOAc (50:1–20:1) gave 3.39 g (78%) of **8a** as a yellowish oil, $n_D^{25} = 1.4668$. IRν_{max} (film) cm^{-1}: 3087 (w), 2978 (m), 2939 (m), 2268 (w), 2212 (s), 1678 (vs), 1300 (s), 1230 (vs), 899 (s). ^{1}H-NMR δ_H ($CDCl_3$): 1.81 (3H, s), 2.35 (3H, s), 3.08 (2H, s), 4.90 (1H, s), 5.50 (1H, s). GC-MS (same conditions as those for **7a**) t_R: 5.38 min (88.1%, **8a**), 5.50 min (5.1%), 6.30 min (3.3%), 9.36 min (2.6%). MS of **8a** (70 eV, EI) *m/z*: 122 (42) (M^+), 107 (85), 77 (100), 43 (31), 39 (19). HRMS: calcd. for $C_8H_{10}O$ (M^+), 122.0732; found, 122.0733.

*(±)-6,7-Epoxy-6-methyl-3-heptyn-2-one (**9a**).* MCPBA (65% purity, 6.40 g, 24 mmol) was added portionwise to a stirred and ice-cooled solution of **8a** (2.80 g, 22.6 mmol) in dry CH_2Cl_2 (70 mL) at 5–10 °C. The mixture was stirred for 1.5 h at 0–5 °C and then left to stand for 40 h in a refrigerator at 5 °C. The mixture was filtered to remove solid *m*-chlorobenzoic acid, before the filter cake was washed with hexane. The combined filtrate and washings were washed with an aqueous solution of Na_2CO_3 containing a small amount of $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated *in vacuo* to give 2.96 g (quant.) of (±)-**9a**, $n_D^{25} = 1.4658$. IRν_{max} (film) cm^{-1}: 3055 (w), 2989 (m), 2970 (m), 2925 (m), 2268 (m), 2214 (s), 1678 (vs), 1360 (s), 1230 (s). ^{1}H-NMR δ_H ($CDCl_3$): 1.45 (3H, s), 2.34 (3H, s), 2.60–2.81 (4H, m). GC-MS (same conditions as those for **7a**) t_R: 5.35 min (2.9%), 7.43 min [86.1%, (±)-**9a**], 7.51 min (2.0%), 12.11 min (3.5%). MS of (±)-**9a** (70 eV, EI) *m/z*: 138 (10) (M^+), 123 (16), 109 (30), 95 (58), 67 (46), 65 (26), 55 (22), 43 (100), 39 (24). HRMS: calcd. for $C_8H_{10}O_2$ (M^+), 138.0681; found, 138.0685.

*(±)-6,7-Epoxy-6-methyl-2-heptanone (**10a**).* 10% Pd–C (0.4 g) was added to a solution of (±)-**9a** (2.70 g, 20 mmol) and Et_3N (0.5 mL) in EtOAc (35 mL). The suspension was vigorously stirred under H_2 (balloon) for 1 h at room temperature, when the H_2 absorption ceased. The mixture was filtered through Celite, and the Celite layer was washed with Et_2O. The filtrate and washings were concentrated *in vacuo* to give 2.78 g (quant.) of (±)-**10a**, $n_D^{25} = 1.4350$. IRν_{max} (film) cm^{-1}: 2956 (m), 1712 (s), 1363 (m), 1163 (m), 899 (m). ^{1}H-NMR δ_H ($CDCl_3$): 1.32 (3H, s), 1.50–1.58 (2H, m), 1.64–1.74 (2H, m), 2.14 (3H, s), 2.47 (2H, t-like $J = 7.2$ Hz), 2.58 (1H, d, $J = 4.6$ Hz), 2.60 (1H, d, $J = 4.6$ Hz). This compound [(±)-**10a**] decomposed under MS conditions to give (±)-**1**.

*(±)-Frontalin (1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane, **1**).* A solution of (±)-**10a** (2.70 g, 19 mmol) in dry Et_2O (20 mL) was added dropwise to a stirred and ice-cooled suspension of $ZnCl_2$ (700 mg, 5.1 mmol) in dry Et_2O (10 mL) at 0–5 °C. The mixture was stirred for 45 min at 0–5 °C, diluted in an ice-water mixture, and the organic layer was separated. The aqueous layer was extracted with a small amount of Et_2O. The combined Et_2O solution was washed with brine, dried ($MgSO_4$), and concentrated under atmospheric pressure by fractional distillation through a Vigreux column. The resulting residue was distilled to give 1.51 g (56%) of (±)-**1** as a colorless oil with a camphor-like odour, bp 74–77 °C at 52 Torr, $n_D^{25} = 1.4358$. IRν_{max} (film) cm^{-1}: 2976 (m), 2937 (s), 2877 (m), 1454 (m), 1387 (m), 1379 (m), 1263 (m), 1240 (m), 1201 (m), 1173 (m), 1120 (s), 1065 (m), 1030 (s), 931 (m), 895 (m), 868 (m), 849 (s), 820 (m). ^{1}H-NMR δ_H ($CDCl_3$): 1.32 (3H, s), 1.43 (3H, s), 1.50–1.70 (5H, m), 1.70–1.95 (1H, m), 3.45 (1H, d-like $J = 5.6$ Hz), 3.91 (1H, d, $J = 6.8$ Hz). ^{13}C-NMR δ_C ($CDCl_3$): 18.1, 23.1, 24.7, 34.0, 34.6, 74.2, 80.0, 108.0. GC-MS (same conditions as those for **7a**) t_R: 3.10 min (2.7%), 4.36 min [90.7%, (±)-**1**], 4.41 min (1.2%), 4.49 min (4.9%). MS of (±)-**1** (70 eV, EI) *m/z*: 142 (25) (M^+), 112 (27), 100 (81), 72 (100), 71 (38), 43 (98). HRMS: calcd. for $C_8H_{14}O_2$ (M^+), 142.0994; found, 142.0991.

*(±)-(*E*)-6-Nonen-3-yn-2-ol (**7b**).* A solution of *n*-BuLi (1.6 M, 82 mL, 131 mmol) was added dropwise to a stirred and cooled solution of (±)-**6** (4.40 g, 65 mmol) in dry THF (80 mL) and dry HMPA (10 mL) at −78 °C under Ar. Stirring was continued for 1 h at −78 °C to 0 °C. After further stirring for 10 min at 0–5 °C, the mixture was cooled again to −40 °C. A solution of **5b** (6.75 g, 45 mmol) in dry THF (10 mL) was added dropwise to the stirred mixture, and it was left to stand overnight at room temperature. The mixture was then diluted with an ice and NH_4Cl solution, and extracted with hexane. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was distilled to give 4.27 g (68%) of (±)-**7b** as a colorless oil, bp 76–78 °C at 3 Torr, $n_D^{22} = 1.4708$. IRν_{max} (film) cm^{-1}: 3357 (s), 2964 (s), 2247 (w), 1641 (w), 1155 (m), 1080 (s), 968 (s). ^{1}H-NMR δ_H ($CDCl_3$): 0.99 (3H, t, $J = 7.6$ Hz), 1.45 (3H, d, $J = 6.4$ Hz), 1.98 (1H, br.), 2.04 (2H, m), 2.92 (2H, m), 4.50 (1H, q, $J = 6.4$ Hz), 5.35–5.42 (1H, m), 5.67–5.75 (1H, m). GC-MS (same conditions as those for **7a**) t_R: 7.22 min [1.2%, (*Z*)-isomer], 7.35 min [82.9%, (±)-**7b**], 7.61 min (3.5%, $M^+ = 138$, unidentified), 7.65 min (12.4%, $M^+ = 170$, unidentified). MS of (±)-**7b** (70 eV, EI) *m/z*: 138 (2) (M^+), 137 (3), 123 (35), 109 (37), 105 (77), 95 (100), 93 (20), 91 (37), 81 (58), 79 (57), 77 (57), 67 (52), 55 (45), 43 (69), 39 (33). HRMS: calcd. for $C_9H_{14}O$ (M^+), 138.1045; found, 138.1037.

*(*E*)-6-Nonen-3-yn-2-one (**8b**).* A solution of (±)-**7b** (5.07 g, 37 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to a stirred and ice-cooled mixture of PCC (17.2 g, 80 mmol), NaOAc (0.6 g, 7 mmol) and SiO_2 (20 g) in dry CH_2Cl_2 (200 mL) at 5–10 °C. Stirring was continued for 1 h at 0–5 °C and then for 2 h at room temperature. The mixture was diluted with Et_2O and filtered, the resulting filter cake being washed with Et_2O. The combined filtrate and washings were concentrated *in vacuo* to give a dark oil which was chromatographed over SiO_2 (50 g). Elution with hexane/EtOAc (10:1) gave 3.87 g (77%) of **8b** as a yellowish oil, $n_D^{21} = 1.4710$. IRν_{max} (film) cm^{-1}: 2966 (s), 2933 (m), 2210 (s), 1678 (s), 1360 (s), 1228 (s), 970 (s). ^{1}H-NMR δ_H ($CDCl_3$): 1.00 (3H, t, $J = 7.2$ Hz), 2.02–2.09 (2H, m), 2.34 (3H, s), 3.07–3.09 (2H, m), 5.33–5.41 (1H, m), 5.70–5.77 (1H, m). GC-MS (same conditions as those for **7a**) t_R: 5.89 min (6.7%, $M^+ = 136$, unidentified), 7.30 min [2.6%, (*Z*)-isomer], 7.42 min (88.1%, **8b**), 7.74 min (1.7%, $M^+ = 136$, unidentified). MS of **8b** (70 eV, EI) *m/z*: 136 (11) (M^+), 135 (5), 121 (100), 95 (18), 93 (42), 91 (63), 82 (21), 79 (79), 77 (93), 65 (27), 55 (25), 53 (17), 51 (20), 43 (88), 39 (26). HRMS: calcd. for $C_9H_{11}O$ ($M^+ - H$), 135.0810; found, 135.0810. HRMS: calcd. for C_8H_9O ($M^+ - CH_3$), 121.0653; found, 121.0652.

*(±)-*trans*-6,7-Epoxy-3-nonyn-2-one (**9b**).* MCPBA (65% purity, 8.10 g, 30 mmol) was added portionwise to a stirred and ice-cooled solution of **8b** (3.80 g, 28 mmol) in CH_2Cl_2 (100 mL) at 5–10 °C. The mixture was stirred for 1 h at 0–5 °C, and then left to stand for 65 h in a refrigerator at 5 °C. The mixture was filtered, and the resulting filter cake was washed with hexane. The filtrate and washings were washed with an aqueous solution of Na_2CO_3 containing a small amount of $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated *in vacuo* to give 3.90 g (92%) of (±)-**9b** as a yellowish oil, $n_D^{21} = 1.4658$. IRν_{max} (film) cm^{-1}: 2972 (s), 2937 (m), 2877 (m), 2214 (s), 1678 (vs), 1360 (s), 1228 (vs). ^{1}H-NMR δ_H ($CDCl_3$): 1.01 (3H, t, $J = 7.6$ Hz), 1.57–1.65 (2H, m), 2.34 (3H, s), 2.69 (2H, dq, $J = 5.2$, 17.6 Hz), 2.85 (1H, dt, $J = 2$, 5.6 Hz), 2.93 (1H, dt, $J = 2$, 6 Hz). GC-MS (same conditions as those for **7a**) t_R: 5.89 min [5.8%, $M^+ = 136$, unidentified], 8.49 min (1.7%, $M^+ = 152$, unidentified), 9.06 min [89.0%, (±)-**9b**], 9.15 min [0.6%, (±)-**9c**], 9.21 min (2.9%, unidentified). MS of (±)-**9b** (70 eV, EI) *m/z*: 152 (9) (M^+), 137 (14), 123 (9), 109 (48), 95 (55), 81 (38), 79 (52), 67 (13), 53 (18), 43 (100). HRMS: calcd. for $C_9H_{11}O_2$ ($M^+ - H$), 151.0759; found, 151.0764. HRMS: calcd. for $C_8H_9O_2$ ($M^+ - CH_3$), 137.0603; found, 137.0594.

*(±)-*trans*-6,7-Epoxy-2-nonanone (**10b**).* 10% Pd–C (0.5 g) was added to a solution of (±)-**9b** (3.86 g, 26 mmol) and Et_3N (0.7 mL) in EtOAc (50 mL). The suspension was vigorously stirred under H_2 (balloon) for 1.5 h at room temperature, after which the H_2 absorption ceased. The mixture was filtered through Celite, and the Celite layer was washed with Et_2O. The filtrate and washings were concentrated *in vacuo* to give 3.90 g (99%) of (±)-**10b** as an oil, $n_D^{21} = 1.4402$. IRν_{max} (film) cm^{-1}: 2968 (s), 2937 (s), 1712 (vs), 1462 (m), 1367 (m), 1167 (m), 887 (m). ^{1}H-NMR δ_H ($CDCl_3$): 0.99 (3H, t, $J = 7.6$ Hz), 1.35–1.65 (5H, m), 1.70–1.77 (2H, m), 2.15 (3H, s), 2.37–2.53 (2H, m), 2.62–2.70 (1H, m). Compound (±)-**10b** decomposed under MS conditions to give (±)-**2**.

*(±)-*endo*-Brevicomin (*endo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]-octane, **2**).* A solution of (±)-**10b** (3.80 g, 24 mmol) in dry Et_2O (20 mL) was added dropwise to a stirred and ice-cooled suspension of

$ZnCl_2$ (1.10 g, 8 mmol) in dry Et_2O (20 mL) at 0–5 °C. The mixture was stirred for 1 h at 0–5 °C, poured into an ice-water solution, and left until the organic layer had separated. The aqueous layer was extracted with a small amount of Et_2O. The combined Et_2O solution was washed with brine, dried ($MgSO_4$), and concentrated by fractional distillation through a Vigreux column under atmospheric pressure. The residue was distilled to give 1.84 g (48%) of (±)-**2** as a colorless oil with a camphor-like odour, bp 92–96 °C at 45 Torr, $n_D^{21} = 1.4462$. IRν_{max} (film) cm^{-1}: 2960 (s), 2877 (m), 1463 (m), 1379 (s), 1348 (w), 1307 (w), 1257 (m), 1238 (s), 1198 (m), 1173 (s), 1108 (s), 1032 (s), 1001 (s), 968 (m), 903 (m), 870 (w), 852 (s). ^{1}H-NMR δ_H ($CDCl_3$): 0.99 (3H, dt, $J = 2$, 7.6 Hz), 1.43 (3H, d, $J = 2$ Hz), 1.53–1.70 (6H, m), 1.75–1.90 (2H, m), 3.95–4.03 (1H, m), 4.19–4.25 (1H, m). ^{13}C-NMR δ_C ($CDCl_3$): 11.0, 17.6, 21.9, 23.6, 25.0, 34.4, 76.5, 81.6, 106.9. GC-MS (same conditions as those for **7a**) t_R: 11.9 min [3.1%, (±)-**3**], 12.6 min (8.1%, $M^+ = 142$, unidentified), 12.8 min [88.8%, (±)-**2**]. MS of (±)-**2** (70 eV, EI) *m/z*: 156 (4) (M^+), 114 (63), 98 (59), 86 (32), 81 (23), 71 (29), 68 (29), 67 (17), 57 (15), 55 (15), 43 (100), 41 (15), 39 (10). HMRS: calcd. for $C_9H_{16}O_2$ (M^+), 156.1150; found, 156.1148.

*(±)-*cis*-2,3-Epoxy-1-pentanol (**13a**).* MCPBA (65% purity, 41.3 g, 156 mmol) was added portionwise over 30 min to a stirred and ice-cooled solution of **12** (13.4 g, 156 mmol) in CH_2Cl_2 (250 mL) at 5–10 °C. Stirring was continued for 2 h at 0–5 °C, and the mixture was then filtered and the filter cake washed with hexane. The filtrate and washings were washed with a solution of Na_2CO_3 containing a small amount of $Na_2S_2O_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue was distilled to give 8.36 g (53%) of (±)-**13a** as a colorless oil, bp 77–78 °C at 8 Torr or 68–69 °C at 5 Torr, $n_D^{20} = 1.4359$. IRν_{max} (film) cm^{-1}: 3419 (s), 2972 (s), 2937 (m), 2879 (m), 1460 (m), 1043 (s), 895 (m), 818 (m), 800 (m). ^{1}H-NMR δ_H ($CDCl_3$): 1.05 (3H, dt, $J = 2$, 7.6 Hz), 1.49–1.68 (2H, m), 2.52–2.85 (1H, br.), 2.99–3.05 (1H, m), 3.14–3.22 (1H, m). 3.62–3.70 (1H, m), 3.81–3.90 (1H, m). GC-MS (same conditions as those for **7a**) t_R: 6.85 min [0.98%, *trans*-isomer], 8.07 min [99.02%, (±)-**13a**]. MS of (±)-**13a** (70 eV, EI) *m/z*: 102 (<1) (M^+), 59 (100), 57 (20), 55 (11), 44 (29), 43 (39), 41 (46), 39 (18), 31 (38). HRMS: calcd. for C_5H_8O ($M^+ - H_2O$), 84.0575; found, 84.0576.

*(±)-*cis*-2,3-Epoxypentyl triflate (**13b**).* A solution of Tf_2O (7.6 mL, 12.7 g, 45 mmol) in dry CH_2Cl_2 (45 mL) was added dropwise over 20 min to a stirred and cooled solution of (±)-**13a** (3.06 g, 30 mmol) and Et_3N (13.6 mL, 100 mmol) in dry CH_2Cl_2 (70 mL) at −70 °C under Ar. The mixture was stirred for 20 min at −70 °C, before being transferred to a separatory funnel, successively washed with water and an aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and filtered through a short column of SiO_2 (30 g) in CH_2Cl_2. The column was washed with a small amount of CH_2Cl_2, and the combined filtrate and washings were concentrated *in vacuo* to give crude (±)-**13b** as an oil (5.52 g, 79%). IRν_{max} (film) cm^{-1}: 2979 (m), 2945 (w), 2885 (w), 1415 (s), 1248 (s), 1209 (s), 1144 (s), 941 (s), 615 (m). ^{1}H-NMR δ_H ($CDCl_3$): 1.09 (3H, t, $J = 7.6$ Hz), 1.50–1.67 (2H, m), 3.00–3.10 (1H, m), 3.30–3.34 (1H, m), 4.47–4.56 (1H, m), 4.64–4.71 (1H, m). Triflate (±)-**13b** was extremely unstable and spontaneously polymerized by an exothermic reaction in the presence of air to give a dark-colored and viscous oil. Crude (±)-**13b** was immediately employed in the next step.

*(±)-*cis*-6,7-Epoxy-3-nonyn-2-ol (**14**).* A solution of *n*-BuLi in hexane (1.6 M, 50 mL, 80 mmol) was added dropwise to a stirred and cooled solution of (±)-**6** (2.80 g, 40 mmol) in dry THF (200 mL) at −70 °C to −50 °C under Ar. The resulting sticky suspension was stirred without cooling to warm the mixture to −10 °C. It was then cooled again to −30 °C to −20 °C, and a solution of (±)-**13b** (5.52 g, 23.6 mmol) in dry C_6H_6 (40 mL) was added dropwise over 10 min to the vigorously stirred mixture to make it homogeneous. Stirring was continued for 1 h without cooling, before the mixture was poured into a solution of ice and NH_4Cl, and extracted with Et_2O. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue (3.69 g) was chromatographed over SiO_2 (80 g), elution with hexane/EtOAc (8:1 to 5:1) giving 1.71 g (41%) of (±)-**14** as a colorless oil, $n_D^{20} = 1.4694$. IRν_{max} (film) cm^{-1}: 3417 (vs), 2976 (s), 2937 (m), 2879 (m), 2249 (w), 1454 (m), 1371 (m), 1290 (m), 1153 (s), 1078 (vs), 1003 (s), 935 (m), 893 (m), 820 (m), 793 (m). ^{1}H-NMR δ_H ($CDCl_3$): 1.08 (3H, t, $J = 7.6$ Hz), 1.44 (3H, d, $J = 6.4$ Hz), 1.49–1.66 (2H, m), 2.02 (1H, d, $J = 4.8$ Hz), 2.28–2.37 (1H, m), 2.56–2.64 (1H, m), 2.92–2.98 (1H, m), 3.12–3.18 (1H, m), 4.53 (1H, m). GC-MS (same conditions as those for **7a**) t_R: 9.38 min [99.2%, (±)-**14**]. MS of (±)-**14** (70 eV, EI) *m/z*: 153 (4) (<1) ($M^+ - 1$), 136 (3), 125 (4), 121 (10), 109 (37), 95 (54), 91 (21), 81 (87), 79 (37), 77 (33), 67 (49), 55 (29), 53 (34), 45 (29), 43 (100), 41 (57), 39 (40). HRMS: calcd. for $C_9H_{13}O_2$ ($M^+ - H$), 153.0921; found, 153.0915.

*(±)-*cis*-6,7-Epoxy-3-nonyn-2-one (**9c**).* A solution of (±)-**14** (1.65 g, 10.7 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to a vigorously stirred and ice-cooled suspension of PCC (6.45 g, 40 mmol), NaOAc (1.90 g, 23 mmol) and SiO_2 (6.0 g) in dry CH_2Cl_2 (80 mL). The mixture was stirred at 0–5 °C for 2 h, diluted with Et_2O, and filtered. The filtrate was concentrated *in vacuo*, and the residue (*ca.* 1.6 g) was chromatographed over SiO_2 (20 g). Elution with hexane/EtOAc (20:1) gave 1.12 g (69%) of (±)-**9c** as a yellowish oil, $n_D^{20} = 1.4702$. IRν_{max} (film) cm^{-1}: 2972 (s), 2937 (m), 2879 (m), 2214 (s), 1678 (vs), 1360 (m), 1230 (s). ^{1}H-NMR δ_H ($CDCl_3$): 1.09 (3H, t, $J = 7.6$ Hz), 1.49–1.67 (2H, m), 2.34 (3H, s), 2.49 (1H, dd, $J = 6.8$, 17.6 Hz), 2.75 (1H, dd, $J = 5.6$, 17.6 Hz), 2.94–2.98 (1H, m), 3.12–3.22 (1H, m). GC-MS (same conditions as those for **7a**) t_R: 9.25 min [90.0%, (±)-**9c**], 9.32 min (3.8%, *trans*-isomer), 11.41 min (6.2%, unidentified). MS of (±)-**9c** (70 eV, EI) *m/z*: 152 (4) (M^+), 137 (13), 123 (8), 109 (29), 95 (54), 81 (38), 79 (56), 67 (13), 53 (18), 43 (100), 41 (21), 39 (23). HRMS: calcd. for $C_9H_{11}O_2$ ($M^+ - H$), 151.0765; found, 151.0760.

*(±)-*cis*-6,7-Epoxy-2-nonanone (**10c**).* 10% Pd–C (0.25 g) and Et_3N (0.3 mL) were added to a solution of (±)-**9c** (1.02 g, 6.7 mmol) in EtOAc (20 mL). The suspension was stirred under an H_2 atmosphere (balloon) for 1 h at room temperature and then filtered through Celite. The Celite layer was washed with Et_2O, and the filtrate and washings were combined and concentrated *in vacuo* to give 1.10 g (quant.) of (±)-**10c** as a colorless oil, $n_D^{21} = 1.4442$. IRν_{max} (film) cm^{-1}: 2970 (s), 2937 (s), 2877 (m), 1714 (vs), 1367 (m), 1242 (m), 906 (m). ^{1}H-NMR δ_H ($CDCl_3$): 1.04 (3H, t, $J = 7.6$ Hz), 1.40–1.65 (4H, m), 1.77 (2H, m), 2.15 (3H, s), 2.50–2.61 (1H, m), 2.84–2.94 (1H, m). Oily (±)-**10c** was immediately employed in the next step.

*(±)-*exo*-Brevicomin (*exo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]-octane, **3**).* A solution of (±)-**10c** (1.00 g, 6.4 mmol) in dry Et_2O (10 mL) was added dropwise to a stirred and ice-cooled suspension of $ZnCl_2$ (1.00 g, 3.7 mmol) in dry Et_2O (30 mL) at 0–5 °C. After stirring for 30 min at 0–5 °C, the mixture was quenched with an NH_4Cl solution and extracted with Et_2O. The extract was washed with brine, dried ($MgSO_4$), and concentrated under atmospheric pressure by fractional distillation through a Vigreux column. The residue was distilled to give 310 mg (31%) of (±)-**3** as a colorless oil with a camphor-like odour, bp 81–82 °C at 29 Torr, $n_D^{21} = 1.4408$. IRν_{max} (film) cm^{-1}: 2939 (s), 2877 (m), 2848 (m), 1462 (m), 1381 (s), 1346 (w), 1333 (w), 1238 (s), 1174 (s), 1107 (m), 1032 (m), 1007 (m), 970 (m), 926 (m), 879 (m), 847 (s), 615 (w). ^{1}H-NMR δ_H ($CDCl_3$): 0.92 (3H, t, $J = 7.6$ Hz), 1.42 (3H, s), 1.45–1.61 (1H, m), 1.61–1.65 (2H, m), 1.75–1.85 (2H, m), 1.85–1.95 (1H, m), 3.94 (1H, t, $J = 7.6$ Hz), 4.14 (1H, br. s). ^{13}C-NMR δ_C ($CDCl_3$): 9.8, 17.2, 25.1, 28.0, 28.6, 34.9, 78.3, 81.2, 107.7. GC-MS (same conditions as those for **7a**) t_R: 11.96 min [97.2%, (±)-**3**], 12.83 min [1.4%, (±)-**2**]. MS of (±)-**3** (70 eV, EI) *m/z*: 156 (12) (M^+), 127 (11), 114 (100), 99 (15), 98 (36), 86 (31), 85 (81), 81 (17), 68 (27), 43 (100). HRMS: calcd. for $C_9H_{16}O_2$ (M^+), 156.1150; found, 156.1142.

*(±)-(Z)-*cis*-6,7-Epoxy-3-nonen-2-one (**15**).* Lindlar's Pd catalyst on $CaCO_3$ with Pb^{2+} (Aldrich, 100 mg) and quinoline (1 drop) were added to a solution of (±)-**9c** (381 mg, 2.5 mmol) in cyclohexane (15 mL). The mixture was stirred under an H_2 atmosphere (balloon) at 0–5 °C for 1 h and was then filtered through SiO_2 (3.0 g). The SiO_2 column was washed with hexane/EtOAc (20:1), and the combined filtrate and washings were concentrated *in vacuo* to give 344 mg (89%) of crude (±)-**15**, $n_D^{21} = 1.4662$. IRν_{max} (film) cm^{-1}: 2972 (s), 1693 (s), 1616 (m), 1415 (m), 1358 (m), 1180 (s), 968 (m), 928 (m), 808 (m). ^{1}H-NMR δ_H ($CDCl_3$): 1.02 (3H, t, $J = 7.6$ Hz), 1.42–1.65 (2H, m), 2.23 (3H, s), 2.69–2.73 (1H, m), 2.85–2.94 (1H, m), 3.01–3.10 (2H, m),

6.15–6.22 (1H, m), 6.29 (1H, d-like, $J = 12$ Hz). (±)-**15** was immediately employed in the next step.

(±)-3,4-Dehydro-exo-*brevicomin (*exo-*7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]oct-3-ene,* ***4****).* $ZnCl_2$ (0.5 g, 3.7 mmol) was added to a stirred and ice-cooled solution of (±)-**15** (340 mg, 2.2 mmol) in dry Et_2O (5 mL). The mixture was stirred at 0–5 °C for 20 min, and then quenched by adding an NH_4Cl solution, before the mixture was extracted with Et_2O. The Et_2O solution was washed with brine, dried ($MgSO_4$), and concentrated under atmospheric pressure by fractional distillation through a Vigreux column. The residue was distilled to give 121 mg (36%) of (±)-**4** contaminated with (±)-**3** as a colorless and camphor-smelling oil, bp 88–89 °C at 38 Torr, $n_D^{20} = 1.4542$. IRν_{max} (film) cm^{-1}: 3039 (w), 2962 (s), 1641 (w), 1462 (w), 1394 (m), 1381 (s), 1317 (w), 1254 (s), 1198 (s), 1041 (m), 1016 (s), 966 (s), 922 (m), 903 (m), 858 (s), 710 (m), 526 (w), 505 (m). ^{1}H-NMR δ_H ($CDCl_3$): 0.94 (3H, t, $J = 7.6$ Hz), 1.53 (3H, s), 1.55–1.65 (2H, m), 1.82–1.90 (1H, m), 2.60–2.68 (1H, m), 3.76–3.80 (1H, m), 4.72–4.76 (1H, m), 5.66–5.73 (1H, m), 5.80–5.84 (1H, m). ^{13}C-NMR δ_C ($CDCl_3$): 9.8, 22.1, 27.5, 32.1, 77.1, 82.0, 102.5, 124.3, 132.0. GC-MS (same conditions as those for **7a**) t_R: 11.93 min [24.0%, (±)-**3**], 12.25 min [73.1%, (±)-**4**]. MS of (±)-**4** (70 eV, EI) m/z: 154 (8) (M^+), 136 (5), 125 (49), 112 (21), 111 (100), 97 (29), 96 (43), 95 (79), 83 (46), 81 (43), 79 (13), 69 (20), 57 (35), 53 (17), 43 (100), 41 (24), 39 (19). HRMS: calcd. for $C_9H_{14}O_2$ (M^+), 154.0994; found, 154.0999.

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