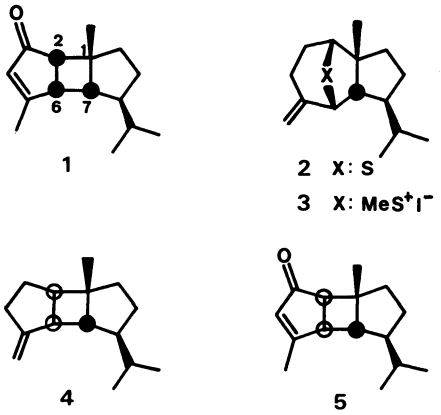
Stereospecific Synthesis of 3-Oxo-α-bourbonene and the Cisoid Isomer for Structural Determination of the Toxic Component of *Lansium domesticum*

Tadao UYEHARA,* Ichiro SUZUKI, and Yoshinori YAMAMOTO
Department of Chemistry, Faculty of Science, Tohoku University, Aramaki-Aoba, Sendai 980
(Received December 2, 1987)

Synopsis. The cis-cisoid-cis isomer of 3-oxo-α-bourbonene, (**1**), the original structure proposed for the toxic principle of *Lansium domesticum*, has been prepared from (−)-mintsulfide. Neither spectral data of **1** nor of 3-oxo-α-bourbonene itself, derived from β-bourbonene, are not identical with those of the toxic componet.

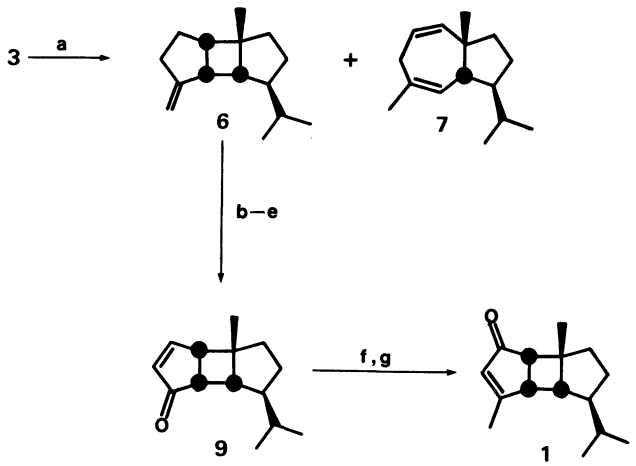
Recently, it has been reported that one of the toxic principles (fish poisons) of *Lansium domesticum* Jack v.duku, a Meliaceous plant, is the cis-cisoid-cis isomer of 3-oxo-α-bourbonene, (**1**).[1] Because of this unique cisoid-[5–4–5] fused-ring skeleton, we have designed a stereospecific synthesis of **1** starting from the sulfur-bridged sesquiterpene, (−)-mintsulfide (**2**) whose absolute stereostructure had been established.[2] We report herein the synthesis of **1** from **2**, a similar transformation of β-bourbonene (**4**) into 3-oxo-α-bourbonene (**5**), and the findings that the toxic component has not any [5–4–5] fused ring skeleton.



Results and Discussion

The methylsulfonium iodide of (−)-mintsulfide, (**3**),[3] is the actual starting material of the synthesis of **1**. By treating with alkyllithium, **3** reacts in competitively. One is the [2,3]sigmatropic rearrangement of the resulting sulfonium methylide to give the homologous sulfur-bridged compound. The other is the sulfide extrusion to yield the cis-cisoid-cis isomer of β-bourbonene, **6**, and the [5–7] fused-ring diene **7** via the hypothetical diradical intermediate.[3,4] The ratio of these products was reported to depend upon the reaction conditions, while **6** was the minor product.[3] After several attempts, the yield of **6** was increased up to 41% by treating with methyllithium at 0 °C.

Ozonization of **6** in ethanol followed by treatment with zinc dust gave the cyclopentanone (**8**) in 85% yield. In order to transform **8** into the α,β-unsaturated ketone **9** by palladium-catalyzed oxidation,[5] the allyl enol carbonate was derived from **8** using potassium *t*-butoxide and allyl chloroformate. Treatment of the carbonate with palladium acetate (10%) in boiling acetonitrile gave **9** in 84% overall yield from **8**. Conversion of **9** into **1** was achieved by consecutive treatment with methyllithium and pyridinium chlorochromate (PCC)[6] in 85% yield.



Scheme 1. Preparation of *cis-cisoid-cis*-3-oxo-α-bourbonene (**1**).
(a): MeLi, THF, (b): O_3, EtOH, (c): Zn, AcOH, EtOH–H_2O, (d) *t*-BuOK, THF, $ClCOOCH_2CH=CH_2$, (e): $Pd(OAc)_2$, CH_3CN, (f): MeLi, ether, (g): PCC, CH_2Cl_2.

Compound **1** shows reasonable spectral characteristics. The cis-cisoid-cis arrangement of **1** is clearly supported by the ^1H NMR spectrum ($J_{2,6}$=5.8 Hz and $J_{6,7}$=9.6 Hz) and the NOEDIF spectra which show certain interactions between the C-1 methyl protons (δ=1.33) and the C-2 proton (δ=2.60), the C-2 proton and the C-6 proton (δ=3.24), and the C-6 proton and the C-7 proton (δ=2.33). Upon irradiation of the C-1 methyl protons, NOE enhancement was also observed at C-7 proton. However, the spectral data of **1** are completely different from those of the toxic principle of *Lansium domesticum*.

Cis-transoid-cis isomer of **1**, namely **5**,[7] has been prepared in a similar manner as above starting from β-bourbonene (**4**) which was derived photochemically from (−)-germacrene-D.[8] The spectral characteristics of **5**, including ^{13}C NMR spectrum, are also different from those of that fish poison. Now it is clear that the

toxic principle has no [5–4–5] fused ring skeletons. Remaining candidates for the toxic principle seem to be ylangene or copaene type compounds containing an *r*-1, *t*-2, *c*-3, *t*-4-tetrasubstituted cyclobutane ring.

Experimental

General. Melting points were determined with a Yamato MP-21 capillary melting point apparatus and are uncorrected. UV and IR spectra were recorded on Hitachi Model 323 and 215 spectrometers, respectively. NMR spectra were obtained on JEOL JNM-PMX60, Varian EM-390, Varian XL-200, and JEOL GX-400 NMR spectrometers, using tetramethylsilane as an internal standard. The mass spectral studies were conducted using a Hitachi M-52 spectrometer and a JEOL DX-303 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter. Elemental analyses were performed by the Microanalytical Laboratory of Tohoku University. All reactions were monitored by analytical TLC using E. Merck precoated silica gel $60F_{254}$ plates. Column chromatography was carried out with E. Merck silica gel 60 (70—230 mesh ASTM). Ozone was generated using a Nippon Ozone type O-1-2 laborastory ozonator.

(1*S*)-*cis*-1-*cisoid*-1,2-*cis*-2-Bourbonene ((1*S*)-*cis*-8-Isopropyl-1-methyl-5-methylenetricyclo[5.3.0.$0^{2,6}$]decane 6). The procedure used for preparation of **6** was essentially that of Ohnuma[9] with following modification. To a mixture of methylsulfonium iodide of mintsulfide (**3**, 4.42 g, 11.7 mmol) and THF (40 ml) was added 1 M methyllithium solution (1 M=1 mol dm^{-3}) in ether (14 ml, 1.2 equiv) at 0 °C under argon and stirred for 30 min. To the reaction mixture was added saturated aqueous ammonium chloride solution and extracted with three portions of ether. The combined extracts were washed with water and saturated brine, and dried over $MgSO_4$. After removal of the solvent, the remaining oil (2.61 g) was chromatographed on silica gel (50 g; hexane) to yield a mixture of hydrocarbons (1.85 g). Silver nitrate impregnated silica-gel chromatography (50 g; hexane) of the mixture gave **6** (0.946 g, 4.74 mmol, 41% yield) **7** (0.579 g, 2.83 mmol, 24% yield), and a mixture of them (0.109 g). **6**: Colorless oil; $[\alpha]_D^{25}$+188.41° (*c* 0.0820, $CHCl_3$); IR (CCl_4) 3070 (w), 1640 (w), and 890 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.83 (3H, d, *J*=6.8 Hz), 0.86 (3H, d, *J*=6.8 Hz), 1.12 (3H, s), 1.1—1.8 (9H, m), 1.86 (1H, m), 2.3—2.5 (2H, m), 3.12 (1H, dd, *J*=9.5 and 8.1 Hz), 4.68 (1H, broad s, $W_{1/2}$=4.0 Hz), and 5.00 (1H, $W_{1/2}$=4.0 Hz); ^{13}C NMR ($CDCl_3$) δ=21.86 (q), 21.98 (q), 27.73 (t), 30.23 (q), 31.79 (t), 33.02 (t), 34.48 (d), 36.32 (t), 41.49 (d), 44.72 (s), 46.20 (d), 49.50 (d), 52.10 (d), 107.73 (t), and 155.15 (s). Found: C, 88.42; H, 11.73%. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84%.

(1*R*)-*cis*-8-Isopropyl-1,5-dimethyl-*cis*-bicyclo[5.3.0]deca-2.5-diene 7: Colorless oil; $[\alpha]_D^{25}$ −97.80° (*c* 1.452, $CHCl_3$); IR (CCl_4) 1460 (w), 820 (w), 730 (w), 705 (m), and 680 (w) cm^{-1}; ^1H NMR (CCl_4) δ=0.85 (3H, d, *J*=6.8 Hz), 0.88 (3H, d, *J*=6.8 Hz), 1.09 (3H, s), 1.72 (3H, broad s), 1.1—2.2 (7H, m), 2.63 (1H, dd, *J*=21.3 and 3.3 Hz), 2.83 (1H, broad d. *J*=21.3 Hz. $W_{1/2}$=7.8Hz), 5.25 (1H, d, *J*=12.0 Hz), and 5.00 (1H, $W_{1/2}$=4.0 Hz). Found: C, 88.15: H, 11.90%. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84%.

(1*R*)-*cis*-10-Isopropyl-7-methyl-*cis*-1-*cisoid*-1,2-*cis*-2-tricyclo[5.3.0.$0^{2,6}$]decan-3-one (8). To a solution of **6** (844.1 mg, 4.13 mmol) in ethanol (20 ml) at −78 °C was treated with ozone until it was faintly blue. The reaction mixture was diluted with water (30 ml) and then treated with zinc (1.37 g) and acetic acid (2.4 ml). The resulting suspension was stirred at room temperature for 2 h and then filtered. The filtrate was diluted with saturated aqueous ammonium chloride solution and extracted with three portions of ether. The combined extracts were washed with saturated sodium hydrogencarbonate solution and saturated brine, and dried over $MgSO_4$. Removal of the solvent followed by chromatography of the remaining oil (847.3 ml) on silica gel (25 g; 10:1 hexane–ethyl acetate) gave **8** (720.3 mg, 3.49 mmol, 85% yield); colorless oil; $[\alpha]_D^{20}$ +251.2° (*c* 0.400, $CHCl_3$) 1720cm^{-1}; ^1H NMR (CCl_4) δ=0.87 (6H, d, *J*=6.0 Hz), 1.18 (3H, s), and 1.2—2.8 (13H, m). Found *m/z* 206.1668. Calcd for $C_{14}H_{22}O$: M, 206.1670.

(1*R*)-*cis*-10-Isopropyl-7-methyl-*cis*-1-*cisoid*-1,2-*cis*-2-tricyclo[5.3.0.$0^{2,6}$]dec-4-en-3-one (9). To a solution of potassium *t*-butoxide (580 mg, 6.10 mmol) in THF (20 ml) was added a solution of **8** (614.4 mg, 3.0 mmol) in THF (20 ml) at −70°C under argon and the resulting mixture was stirred for 1 h. Allyl chloroformate (0.80 ml, 909 mg, 8.0 mmol) was added to the deep yellow solution and the mixture was stirred for 1 h at −78°C and then allowed to warm to room temperature. After stirring overnight, the mixture was treated with saturated aqueous NH_4Cl solution (40 ml) and then extracted with three portions of ether. The combined extracts were washed with saturated brine, dried over $MgSO_4$, and concentrated. Chromatography of the remaining oil (1.105 g) on silica gel (30 g; 20:1 hexane–ethyl acetate) gave the allyl enol carbonate (743.4 mg, 3.00 mmol) as a colorless oil.

Palladium acetate (67 mg, 0.30 mmol) was added to a solution of the carbonate in acetonitrile (10 ml) and the mixture was heated at 80 °C for 1 h under nitrogen. After filtration through a Celite layer, the solvent was romoved in vacuo. Chromatography of the residue on silica gel (50 g; 20:1 hexane–ethyl acetate) gave **9** (510.3 mg, 2.50 mmol, 84%); colorless oil; $[\alpha]_D^{20}$ +487.8° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 1685 (s) cm^{-1}; ^1H NMR δ=0.85 (3H, d, *J*=6 Hz), 0.92 (3H, d, *J*=6 Hz), 1.33 (3H, s), 2.13 (1H, broad dd, *J*=11.7 and 3.8 Hz), 2.77 (1H, dd, *J*=11.7 and 5.9 Hz), 2.77 (1H, dddd, *J*=5.9, 3.3, 1.2, and 0.9 Hz), 6.25 (1H, dd, *J*=5.6 and 1.8 Hz), and 7.48 (1H, ddd, *J*=5.6, 3.3, and 0.7 Hz); MS *m/z* (rel intensity) 204 (M^+, 12.5), 189 (8.1), 161 (48.8), 123 (100), and 81 (95). Found *m/z* 204.1514. Calcd for $C_{14}H_{20}O$: M, 204.1513.

(1*S*)-*cis*-8-Isopropyl-1,5-dimethyl-*cis*-1-*cisoid*-1,2-*cis*-2-tricyclo[5.3.0.$0^{2,6}$]dec-4-en-3-one (1). To a solution of **9** (314.6 mg, 1.54 mmol) in THF (10 ml) was added 1 M methyllithium solution in ether (3 ml) at −78 °C under argon and stirred for 30 min. To the reaction mixture was added saturated aqueous ammonium chloride solution and extracted with three portions of ether. The combined extracts were washed with saturated brine, and dried over $MgSO_4$. Removal of the solvent gave a colorless oil (351 mg). To a solution of PCC (665 mg, 3.08 mmol) in dichloromethane (16 ml) was added a solution of the product in dichloromethane (12 ml) and the mixture was stirred for 3.2 h. The resulting mixture was diluted with ether (40 ml) and the supernatant was decanted from the black solid. The residue was washed with several portions of ether. The combined ethereal solutions were washed successively with 5% NaOH solution, 5% HCl, saturated $NaHCO_3$ solution, and saturated brine, dried over $MgSO_4$, and concentrated. Chromatography of the residue (389 mg) on silica gel (23 g; 10:1 hexane–ethyl acetate)gave **1** (289.5 mg, 1.31 mmol, 85% yield); colorless prisms; mp 50.5—51.5 °C (ether); $[\alpha]_D^{20}$ −331.5° (*c* 0.97); UV (EtOH) λ_{max} 238 (ε 9370) and 318 nm (94); IR ($CHCl_3$) 1680 (broad s) and 1610 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.86 (3H, d, *J*=6.2 Hz), 0.90 (3H, d, *J*=6.4 Hz), 1.25—1.52 (4H, m), 1.33 (3H, s), 1.54—1.68 (2H, m), 2.11 (3H, broad s, $W_{1/2}$=2.5 Hz), 2.23 (1H, dd, *J*=9.6 and 3.8 Hz), 2.60 (broad, d, *J*=5.8 Hz, $W_{1/2}$=2 Hz), 3.24 (1H, dddd, *J*=9.6, 5.8, 0.8, and 0.8 Hz), and

6.11 (1H, brosd s, $W_{1/2}$=3.5 Hz); ^{13}C NMR ($CDCl_3$) δ=19.29 (5-Me), 20.85 (-CHMe-Me), 21.94 (-CHMe-Me), 28.70 (1-Me), 32.12 (9 or 10), 33.33 (-CHMe$_2$), 35.58 (9 or 10), 41.96 (6), 46.65 (1), 50.03 (8), 50.90 (7), 52.90 (2), 135.68 (4), 179.35 (5), and 211.08 (3). MS *m/z* (rel intensity) 218 (M^+, 12.3), 203 (6.5), 189 (4.0), 175 (20.5), 149 (18.0), 123 (100), and 81 (69.5). Found *m/z* 218.1671. Calcd for $C_{15}H_{22}O$: M, 218.1670.

Transformation of β-Bourbonene (4) into 3-Oxobourbonene ((1*S*)-*cis*-8-Isopropyl-1,5-dimethyl-*cis*-1-*transoid*-1,2-*cis*-2-tricyclo[5.3.0.0^{2,6}]dec-4-en-3-one (5)). β-Bourbonene was derived photochemically by using the literature procedure[7] from (−)-germacrene-D which was isolated from peppermint oil (*Mentha peperita*). In a procedure similar to that employed for the synthesis of **9**, **4** was transformed into (1*R*)-*cis*-10-isopropyl-7-methyl-*cis*-1-*transoid*-1,2-*cis*-tricyclo-[5.3.0.0^{2,6}]dec-4-en-3-one (^{1}H NMR ($CDCl_3$) δ=0.88 (3H, d, *J*=6.5 Hz), 0.90 (3H, d, *J*=6.5 Hz), 1.03 (3H, s), 1.30 (1H, d-sept, *J*=9.5 and 6.5 Hz), 1.58 (1H, ddd, *J*=13.0, 10.5, and 6.8 Hz), 1.65 (1H, m, 10-H), 1.72 (1H, ddd, *J*=13.0, 6.8, and 3.5 Hz), 1.80 (1H, dddd, *J*=16.5, 7.0, 3.5, and 1.0 Hz), 1.93 (1-H, broad s), 1.96 (1H, ddd, *J*=13.4, 10.8, and 6.5), 2.33 (2-H, ddd, *J*=4.9, 3.8, and 0.2 Hz), 2,97 (6-H, ddd, *J*=4.9, 3.2, and 1.2 Hz), 6.40 (4-H, ddd, *J*=5.6, 1.2, and 0.2 Hz), and 7.73 (5-H, ddd, *J*=5.6, 3.2, and 0.3 Hz); Found *m/z* 204.1519). This α,β-unsaturated ketone was converted into **5** in a manner similar to that adopted to prepare **1** from **9**. **5**: Colorless oil; $[\alpha]_D^{20}$ +336.3° (*c* 0.30, $CHCl_3$); UV (EtOH)λ_{max} 234 (ε 11700) and 315 nm (95); IR ($CHCl_3$) 1675 (s) and 1615 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.90 (3H, d, *J*=6.3 Hz), 0.91 (3H, d, *J*=6.3 Hz), 1.07 (3H, s), 1.34 (1H, d-sept, *J*=9.2 and 6.3 Hz), 1.50 (ddd, *J*=13.0, 11.0 and 6.5 Hz), 1.52—1.62 (1H, m), 1.78 (1H, dddd, *J*=13.0, 6.8, 3.0, and 0.8 Hz), 1.82 (1H, $W_{1/2}$=5 Hz), 1.93 (1H, dddd, *J*=13.0, 11.0, 6.5, and 6.5 Hz), 2.12 (3H, d, *J*=1.2 Hz), 2.57 (2,6-H, broad s, $W_{1/2}$=1.5 Hz), and 5.98 (4-H, q, *J*=1.2 Hz); ^{13}C NMR ($CDCl_3$) δ=17.08 (5-Me), 21.26 (-CHMe-Me), 21.65 (-CHMe-Me), 24.12 (1-Me), 29.35 (9 or 10), 30.54 (-CHMe$_2$), 40.72 (9 or 10), 45.79 (1), 47.06 (2 or 6), 50.82 (8), 53.32 (2 or 6), 54.60 (7), 132.10 (4), 180.87 (5), and 211.20 (3); MS (25 eV) *m/z* (rel intensity) 218 (M^+, 0.8), 175 (15.9), 124 (5.1), 123 (100), 122 (25.0), and 81 (47.3). Found *m/z* 218.1663. Calcd for $C_{12}H_{22}O$: M, 218.1670.

We wish to thank Professor Yuji Hayashi of Osaka City University for fruitful discussion and Takasago Perfumery Co., Ltd., for generous gift of peppermint oil (*Mentha piperita*). We also thank Professor Kuninobu Kabuto of Tohoku University for measurement of optical rotations.

References

1) H. Ikeda, M. Nishizawa, T. Tokuyama, and Y. Hayashi, 31 st Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Kyoto, September 1987, Symposium paper, pp. 209—211.

2) Y. Yoshida, S. Muraki, K. Takahashi, T. Kato, C. Kabuto, T. Suzuki, T. Uyehara, and T. Ohnuma, *J. Chem. Soc., Chem. Commun.*, **1979**, 512.

3) T. Uyehara, T. Ohnuma, T. Saito, T. Kato, T. Yoshida, and K. Takahashi, *J. Chem. Soc., Chem. Commun.*, **1981**, 127.

4) T. Uyehara, M. Takahashi, and T. Kato, *Tetrahedron Lett.*, **25**, 3003 (1984); **26**, 1241 (1985).

5) J. Tsuji, I. Minami, I. Shimizu, and H. Kataoka, *Chem. Lett.*, **1984**, 1133.

6) W. G. Dauben and D. M. Michno, *J. Org. Chem.*, **42**, 682 (1977).

7) M. Brown, *J. Org. Chem.*, **33**, 162 (1968).

8) K. Yoshihara, Y. Ohta, T. Sakai, and Y. Hirose, *Tetrahedron Lett.*, **1969**, 2263.

9) T. Ohnuma, Master Thesis, Tohoku University, 1980; Ref. 3.