Synthetic Photochemistry. LXI.[1] A Total Synthesis of (±)-Valeranone, a *cis*-Decalone Sesquiterpenoid from *Valeriana officinalis*, via an Intramolecular Photocycloaddition

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Starting from the intramolecular [2+2] cycloaddition of 2,6-dimethyl-2-(3,4-dimethyl-3-cyclohexenyl)-4*H*-1,3-dioxin-4-one, (±)-valeranone, a *cis*-decalone sesquiterpenoid from *Valeriana officinalis*, was totally synthesized in stereoselective fashion.

The stereochemistry of valeranone (**1**), an interesting rearranged sesquiterpenoid with a *cis*-decalone framework isolated from several plant sources, including *Valeriana officinalis*,[2] was once a focus of dispute. The correct structure of **1** was established by Hikino et al. in the early 1960's,[3] which was soon confirmed by total syntheses of Marshall et al.[4a] and Wenkert et al.,[4b] starting from (−)-carvomenthone and (+)-carvomenthone, respectively. Since then, there have been several other synthetic achievements of **1** motivated by interests concerning the stereochemistry.[4]

We previously investigated an acetone-sensitized intramolecular photoreaction of 2-alkenyl- and 2-(cycloalkenyl)-6-methyl-4*H*-1,3-dioxin-4-ones to give cage-type [2+2] cycloadducts.[5] Herein, we describe a facile synthesis of (±)-valeranone (**1**)[6] based on this photoreaction.

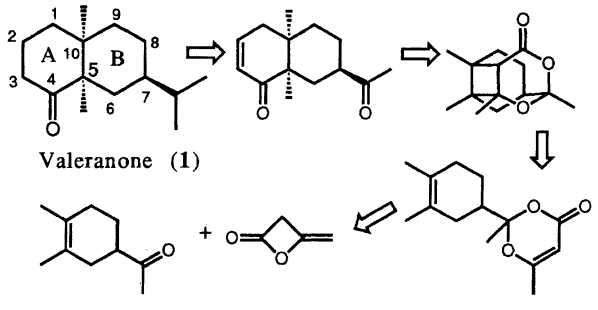
Results and Discussion

The retrosynthetic analysis shown in Scheme 1 demonstrates an attractive feature: i.e., the cage photoproduct possesses the desired *trans*-relationship between the *cis*-dimethyl group and a masked acetyl group, which can be converted into the isopropyl group of **1**.

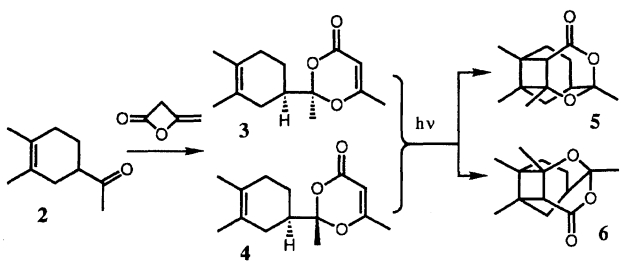
Thus, the starting material, 4-acetyl-1,2-dimethyl-1-cyclohexene (**2**), was prepared by a Diels–Alder reaction of 2,3-dimethyl-1,3-butadiene with 3-buten-2-one.[7] A subsequent treatment of **2** with diketene in the presence of *p*-tolylsulfonic acid (TsOH)[8] afforded 2,6-dimethyl-2-(3,4-dimethyl-3-cyclohexenyl)-4*H*-1,3-dioxin-4-ones (**3** and **4**) as inseparable diastereomers. The irradiation of the mixture (**3**:**4**=1:1, from ^{1}H NMR spectrometry) by means of a 400-W high-pressure mercury lamp in a mixed solution of acetone and acetonitrile (1:9) for 10 h gave isomeric [2+2] cycloadducts, **5** (98% from **3**) and **6** (32% from **4**). The different rates of conversion suggested not only the stereochemistries of **3** and **4**, but also the structures of the cage products, **5** and **6**; **5** formed in high yield must be a less-strained compound, and has a suitable structure for performing additional transformations to **1** (Scheme 2).

Subsequently, the major product, **5**, was treated with diisobutylaluminum hydride (DIBAH) and TsOH to form, via a reductive *retro*-aldol fragmentation, followed by Claisen condensation, a pair of *cis*-9-acetyl-1,6-dimethylbicyclo[4.4.0]dec-3-en-2-ones (**7a** and **7b**, 3:2), both as colorless oils. These **7a** and **7b** were not mutually interconvertible, even under acidic conditions, such as with TsOH in benzene at 80 °C, employed for the derivation, or potassium fluoride on Florisil in ethanol at 25 °C for 24 h.[9] This was rather fortunate, since their dihydro derivatives (**8a** and **8b**) obtained by a catalytic reduction were easily interconvertible on a silica-gel column.

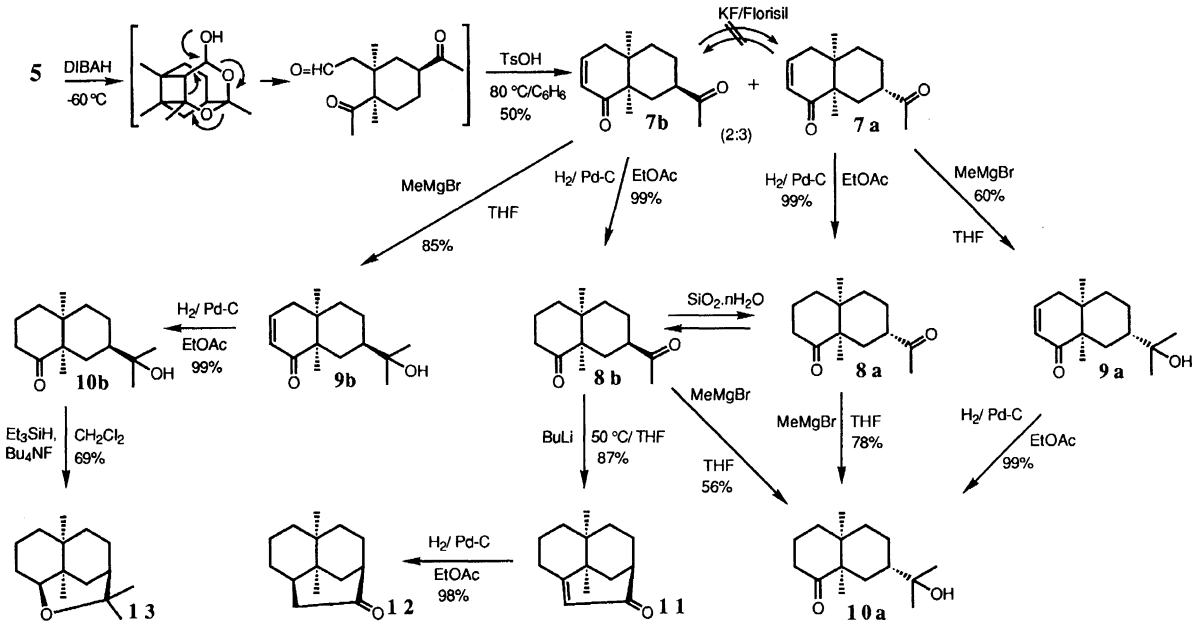
The stereostructures of **7b** and **7a** were differentiated from the nuclear Overhauser effect (NOE); irradiation of the signal at δ=1.16, ascribable to one of the angular methyl groups of **7b**, caused a signal enhancement (9.5%) of the proton located at the 1,3-diaxial relationship at δ=2.61 (tt, J=11.5, 4.0 Hz), the chemical shift of which is ascribable to the methine proton on the carbon bearing the acetyl group. However, **7a** showed no such enhancement for the corresponding proton at



Scheme 1.



Scheme 2.



Scheme 3.

δ=2.43 (tt, J=12.6, 4.0 Hz). The same was true in the cases of **8b** and **8a**; there is a clear NOE, i.e., an 8.0%-enhancement of the signal for the corresponding proton of **8b**, but none for that of **8a**. Figure 1 shows the key features of NOE.

Grignard reactions of **7a** or **7b** with methylmagnesium bromide[10] afforded a single colorless-oily tertiary alcohol (**9a** or **9b**), which was then quantitatively reduced to a dihydro derivative (**10a** or **10b**).[11] On the other hand, Grignard reactions of **8a** and **8b** resulted in the formation of the same compound, **10a**, of an unnatural series. Thus, epimerization of **8b** to **8a** under the reaction conditions took place prior to the reaction. Although an attempted methylenation of **8b** under the Wittig reaction conditions gave complicated results, a treatment of **8b** with butyl lithium resulted in the formation of a tricyclic α,β-unsaturated ketone (**11**). In its IR spectrum, a carbonyl stretching absorption appeared at 1668 cm^{-1}, thus suggesting a typical cyclohexenone moiety. Catalytic hydrogenation of **11** afforded a dihydro derivative (**12**), whose carbonyl stretching band appeared at 1701 cm^{-1}. This should provide additional evidence for the structures of **5** and its transformation products. A treatment of **10b** with triethylsilane yielded a saturated ether (**13**) in good yield. The structure of **13**, deduced from an ^1H NMR analysis, confirmed the stereochemistry of **10b** and the compounds in the same line (Scheme 3).

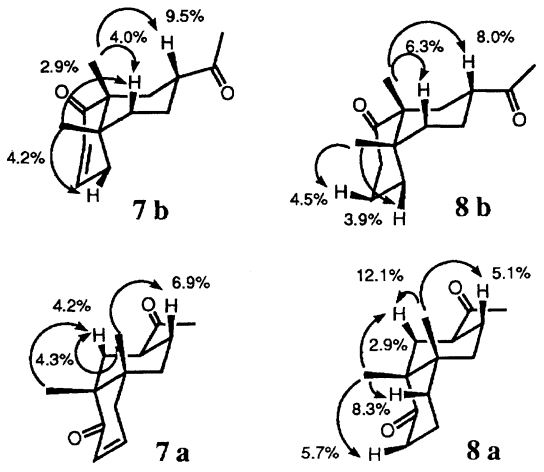
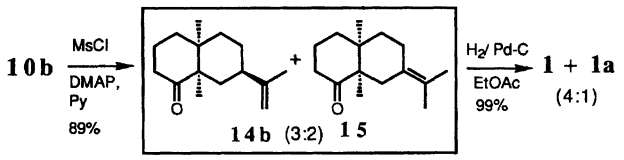


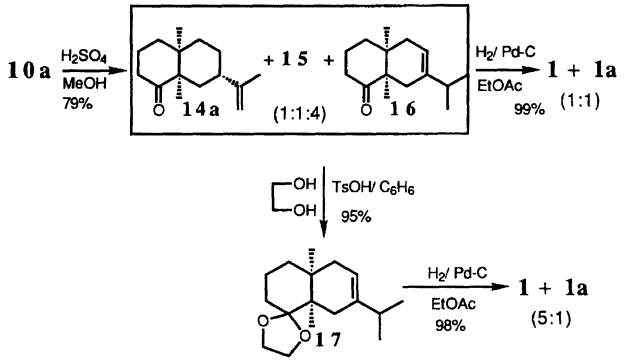
Fig. 1. NOE of **7a**, **7b**, **8a**, and **8b**.

Selective dehydration of **10b** to the desired isopropenyl compound **14b** was difficult due to its contamination by the more stable isopropylidene derivative **15**. The best result was realized by a mild treatment of **10b** with methylsulfonyl chloride in the presence of 4-dimethylaminopyridine (DMAP) in dichloromethane at 40 °C, to afford **14b** and **15** (3:2) in 89% yield (Scheme 4). A catalytic hydrogenation of the thus-obtained mixture afforded **1** and 7-*epi*-valeranone **1a** in a ratio of 4:1. The ^1H and ^{13}C NMR spectra of **1** and **1a** were identical with that of authentic samples.[4d]

Due to encountered experimental difficulty concerning the dehydration of **10b**, we turned our attention to utilize compounds belonging to the unnatural series. A treatment of **10a** with 30%-sulfuric acid by heating at 65 °C in methanol for 4 h afforded several products; the major product was a trisubstituted isomer (**16**), which was accompanied by two isomers (**14a** and **15**) (**14a**:**15**:**16**=1:1:4). After all, catalytic hydrogenation of these conformationally mobile keto olefins with various catalysts, e.g., palladium-on-carbon, iridium-black, rhodium-on-alumina, or plat-



Scheme 4.



Scheme 5.

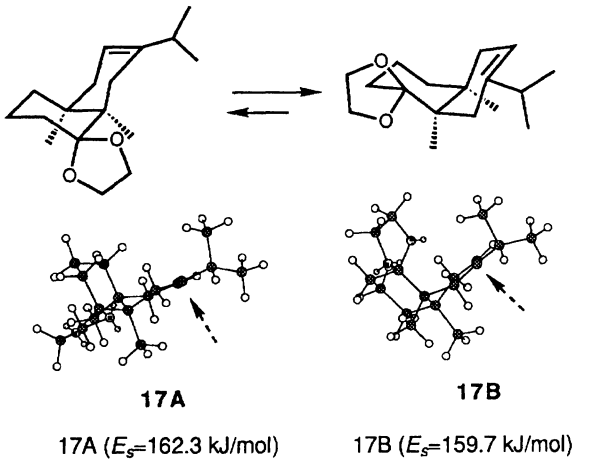


Fig. 2. Strain energies and stereoviews of **17A** and **17B**.

inum oxide, showed no stereoselectivity; a 1 : 1-mixture of **1** and **1a** was always formed.

In the hope of obtaining the desired dihydro derivative stereoselectively by changing the favored conformation of this *cis*-octalone system, the carbonyl group was converted to a bulky dioxolane group; thus, the mixture (**14a**, **15**, and **16**) was treated with 1,2-ethanediol and boron trifluoride–diethyl ether (1/1) in dichloromethane to form an acetal (**17**).[12] Subsequent hydrogenation of the acetal on platinum oxide in ethanol, followed by deacetalization with dil hydrochloric acid, furnished **1** and **1a** in a ratio of 5 : 1. The ^{1}H NMR and ^{13}C NMR spectra of the synthesized samples were again identical with those recorded in the literature[4d] (Scheme 5).

An improved formation of **1** by acetalization of the keto group in **17** is of interest. It is well known that the angularly methylated *cis*-decalines have a conformational mobility. This was frequently differentiated in terms of the steroidal and non-steroidal forms.[13] As depicted in Fig. 2, **17** may also exist in two conformers, **17A** (whose dioxolane ring is nearly coplanar with the B-ring) and **17B** (whose dioxolane ring is parallel but not coplanar with the B-ring). A direct calculation of the steric energies (E_s) for **17A** and **17B** with the Chem3D Plus program[14] gave the convergent value of 159.7 kJ mol^{-1} with the conformation of **17B**. However, the local minimum energy for **17A** was obtained with the substitution method to be 162.3 kJ mol^{-1}, indicating that **17b** is more stable than **17A**. Nevertheless, both conformers indicate that the β-side of the molecules is deeply blocked by a cyclohexane ring towards an approach of the catalyst to the double bond to be reduced. As the result, hydrogenation should preferably occur from the α-side of the molecules. This is consistent to the predominant formation of **1** from **17**. Perspective stereoviews of the minimized structures are also illustrated in Fig. 2.

In conclusion, **1** has been synthesized from the cage photocyclisate, **5**, with improved stereoselectivity, and the intramolecular photocyclization of 2-alkenyl-6-methyl-4*H*-1,3-dioxin-4-ones has opened a new entry to polysubstituted alicyclic compounds.

Experimental

The elemental analyses were carried out by Mrs. M. Miyazawa of the Institute of Advanced Material Study, Kyushu University. The mps were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The NMR spectra were measured by means of the JEOL FX 100 Model and GSX 270H Model spectrometers in $CDCl_3$ (otherwise specified); the chemical shifts were expressed in the unit of δ. The mass spectra were measured with a JEOL 01SG-2 spectrometer. The IR spectra were taken as KBr disks for crystalline compounds, or as liquid films inserted between NaCl plates for oily compounds, using a JASCO IR-A102 spectrometer. The stationary phase for column chromatography was Wakogel C-300, and the eluent was a mixture of ethyl acetate and hexane.

Preparation of 3 and 4. A mixture of diketene (1.5 cm^3) and **2**[7] (3.0 g) was heated in the presence of TsOH (10.0 mg) at 90 °C for 10 h. The reaction mixture was diluted with CH_2Cl_2, washed with dil $NaHCO_3$ and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a silica-gel column to give a colorless-oily mixture of **3** and **4** [2.8 g, 61%. ^{1}H NMR δ=1.38 (1H, m), 1.60 (3H, s), 1.61 (3H, s), 1.62 (3H, s), 1.85—2.02 (5H, m), 1.98 (3H, d, J=0.7 Hz), 2.14 (1H, m), and 5.19 (1H, d, J=0.7 Hz). ^{13}C NMR δ=18.8, 19.1, 19.5, 20.0, 23.4, 31.7, 31.8, 42.7, 93.8, 109.7, 124.0, 125.6, 161.2, and 168.6 for one isomer, ^{1}H NMR δ=1.37 (1H, s), 1.60 (3H, s), 1.61 (3H, s), 1.63 (3H, s), 1.85—2.02 (5H, m), 1.98 (3H, d, J=0.7 Hz), 2.15 (1H, m), and 5.20 (1H, d, J=0.7 Hz). ^{13}C NMR δ=18.8, 19.1, 19.5, 20.0, 23.2, 31.8, 32.0, 42.6, 93.7, 109.7, 124.1, 125.7, 161.3, and 168.6 for another isomer[15]].

Irradiation of 3 and 4. Formation of 5 and 6. A mixed solution of MeCN and acetone (9 : 1, 200 cm^3) of **3** and **4** (490.0 mg) was irradiated with a 400-W high-pressure

Hg lamp through a Pyrex-glass filter under an N_2 stream for 10 h at 0—15 °C. After evaporation of the solvents in vacuo, the residue was chromatographed on a silica-gel column to give **5** [colorless crystals, mp 118—120 °C, 237.6 mg, 98%. Found: C, 71.13; H, 8.54%. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%. ^{1}H NMR δ=1.01 (3H, s), 1.15 (3H, s), 1.29 (3H, s), 1.39 (1H, dd, J=13.0, 2.2 Hz), 1.51 (1H, dt, J=11.4, 3.7 Hz), 1.57 (3H, s), 1.62—1.72 (3H, m), 1.99 (1H, m), 2.46 (1H, m), and 2.67 (1H, s). ^{13}C NMR δ=17.4, 21.5, 22.2, 27.5, 29.6, 30.4, 38.1, 39.4, 39.8, 52.8, 60.4, 73.6, 105.5, and 170.8. MS m/z (%) 236 (M^+, 15), 152 (76), 109 (100), and 43 (26). IR ν 2920, 1733, 1471, 1386, 1295, 1130, 962, 857, and 802 cm^{-1}] and **6** [colorless needles, mp 78—80 °C, 79.2 mg, 32%. Found: C, 71.34; H, 8.55%. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%. ^{1}H NMR δ=0.98 (3H, s), 1.09 (3H, s), 1.23 (3H, s), 1.34—1.46 (2H, m), 1.58 (3H, s), 1.62—1.74 (3H, m), 1.83 (1H, m), 2.31 (1H, m), and 2.88 (1H, d, J=1.1 Hz). ^{13}C NMR δ=21.1 (2C), 22.0, 22.7, 26.5, 27.0, 33.6, 38.6, 39.7, 44.8, 51.4, 80.4, 108.3, and 169.1. MS m/z (%) 236 (M^+, 16), 152 (80), 109 (100), 85 (27), and 43 (25). IR ν 2930, 1736, 1387, 1295, 1213, 1142, and 963 cm^{-1}].

DIBAH-Reduction Followed by TsOH-Treatment of 5. Formation of 7b and 7a. To **5** (90 mg) dispersed in anhydrous ether (2 cm^3), DIBAH (1.6 cm^3, 0.93 mol dm^{-3} in hexane) was added drop-by-drop under an N_2 atmosphere, and was stirred at −60 °C for 1 h. The mixture was then treated with EtOAc, diluted with water and filtered through Celite. The filtrate was extracted with ether, washed with brine and dried over Na_2SO_4. After evaporation of the solvents, the thus-obtained residue was dissolved in benzene (20 cm^3) containing TsOH (5 mg), and refluxed with an equipped Dean–Stark apparatus for 6 h. The mixture was washed with an aqueous $NaHCO_3$ solution and brine, and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica-gel column to give **7b** [a colorless oil, 18.5 mg, 22%. Found: m/z 220.1464 (M^+). Calcd for $C_{14}H_{20}O_2$: M, 220.1464. ^{1}H NMR δ=0.94 (3H, s), 1.16 (3H, s), 1.45 (1H, tdd, J=13.5, 4.0, 1.8 Hz), 1.46 (1H, m), 1.57 (1H, dd, J=11.5, 5.5 Hz), 1.64 (1H, t, J=11.5 Hz), 1.70—1.80 (2H, m), 1.88 (1H, dd, J=19.8, 5.5 Hz), 2.16 (3H, s), 2.61 (1H, tt, J=11.5, 4.0 Hz), 2.81 (1H, dm, J=19.8 Hz), 5.98 (1H, ddd, J=9.9, 2.9, 1.1 Hz), and 6.82 (1H, ddd, J=9.9, 5.5, 2.5 Hz). ^{13}C NMR δ=16.1, 23.2, 24.4, 28.4, 33.6, 34.4, 34.9, 37.4, 44.6, 48.8, 127.5, 146.6, 203.8, and 211.1. MS m/z (%) 220 (M^+, 45), 152 (38), 123 (22), 109 (100), and 43 (21). IR ν 2936, 1709, 1668, 1461, 1387, 1248, 1184, 939, and 812 cm^{-1}] and **7a** [a colorless oil, 25.5 mg, 30%. Found: m/z 220.1465 (M^+). Calcd for $C_{14}H_{20}O_2$: M, 220.1464. ^{1}H NMR δ=1.03 (3H, s), 1.07 (3H, s), 1.25 (1H, dt, J=13.3, 3.4 Hz), 1.32 (1H, dd, J=13.3, 12.6 Hz), 1.56 (1H, tdd, J=13.3, 12.6, 3.4 Hz), 1.65 (1H, m), 1.78 (1H, td, J=13.3, 4.2 Hz), 2.02 (1H, dd, J=19.9, 5.8 Hz), 2.16 (3H, s), 2.28 (1H, ddd, J=13.3, 4.0, 2.2 Hz), 2.43 (1H, tt, J=12.6, 4.0 Hz), 2.53 (1H, dt, J=19.9, 2.8 Hz), 5.96 (1H, dd, J=10.1, 2.8 Hz), and 6.75 (1H, ddd, J=10.1, 5.8, 2.8 Hz). ^{13}C NMR δ=21.6, 21.8, 23.4, 28.4, 30.6, 34.4, 37.4, 38.6, 47.6, 49.5, 127.6, 146.2, 204.0, and 211.6. MS m/z (%) 220 (M^+, 36), 123 (100), 109 (92), and 43 (47). IR ν 2934, 1712, 1669, 1463, 1387, 1271, 1185, 1122, 984, and 840 cm^{-1}].

Hydrogenation of 7b. Formation of 8b. An EtOAc solution (2 cm^3) of **7b** (100 mg) was hydrogenated with Pd–C at room temperature. After removing the catalyst by filtration, the filtrate was evaporated and chromatographed on a silica-gel column to give **8b** [a colorless oil, 100 mg, 99%. Found: m/z 222.1619 (M^+). Calcd for $C_{14}H_{22}O_2$: M, 222.1619. ^{1}H NMR δ=0.84 (3H, s), 1.09 (3H, s), 1.34 (1H, dd, J=13.2, 3.3 Hz), 1.45 (1H, dt, J=13.7, 4.0 Hz), 1.53—1.67 (1H, m), 1.71—1.80 (4H, m), 1.88 (1H, tt, J=12.8, 4.0 Hz), 1.91 (1H, m), 2.17 (3H, s), 2.24 (1H, dm, J=14.7 Hz), 2.37 (1H, td, J=13.2, 5.1 Hz), 2.60 (1H, tt, J=13.2, 4.0 Hz), and 2.66 (1H, ddd, J=14.7, 12.8, 7.7 Hz). ^{13}C NMR δ=16.7, 21.6, 23.4, 24.5, 28.4, 31.9, 34.6, 35.1, 36.9, 38.5, 46.0, 52.2, 211.3, and 216.0. MS m/z (%) 222 (M^+, 66), 125 (100), 98 (72), 95 (20), 81 (22), and 43 (53). IR ν 2942, 1703, 1460, 1374, 1351, 1244, 1152, 1049, 933, and 828 cm^{-1}].

Hydrogenation of 7a. Formation of 8a. Similarly, **7a** (111.8 g) was reduced to **8a** [a colorless oil, 111.7 mg, 99%. Found: m/z 222.1623 (M^+). Calcd for $C_{14}H_{22}O_2$: M, 222.1619. ^{1}H NMR δ=1.01 (3H, s), 1.11 (3H, s), 1.24 (1H, t, J=12.8 Hz), 1.19—1.34 (2H, m), 1.47—1.58 (2H, m), 1.73 (1H, m), 1.80—2.06 (3H, m), 2.12 (1H, ddd, J=14.0, 3.7, 1.8 Hz), 2.17 (3H, s), 2.23 (1H, dm, J=15.0 Hz), 2.56 (1H, ddd, J=15.0, 12.8, 8.1 Hz), and 2.68 (1H, tt, J=12.8, 4.0 Hz). ^{13}C NMR δ=20.8, 22.4, 23.2, 23.5, 28.4, 31.4, 34.4, 34.8, 37.6, 38.9, 47.2, 51.8, 212.0, and 215.8. MS m/z (%) 222 (M^+, 92), 207 (29), 204 (26), 125 (100), and 43 (36). IR ν 2942, 1705, 1467, 1387, 1372, 1349, 1266, 1179, 1151, 1054, and 953 cm^{-1}].

Treatment of 8b with BuLi. Formation of 11. To an anhydrous THF solution (0.5 cm^3) of **8b** (60 mg), BuLi (0.2 cm^3, 1.68 mol dm^{-3} in hexane) was added drop-by-drop, and was stirred at 50 °C for 10 h. The reaction was quenched by water, and the solvents were evaporated in vacuo. The residue was diluted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The solution was heated in vacuo in order to remove the solvent; the thus-obtained residue was chromatographed on a silica-gel column to give **11** [colorless crystals, mp 120—121 °C, 48 mg, 87%. Found: C, 82.22; H, 9.91%. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87%. ^{1}H NMR δ=1.04 (3H, s), 1.14 (1H, m), 1.12 (3H, s), 1.61 (1H, m), 1.70—1.78 (5H, m), 1.84 (2H, m), 1.85 (1H, td, J=13.9, 2.6 Hz), 2.18 (1H, dm, J=11.7 Hz), 2.43 (1H, m), 2.54 (1H, td, J=11.7, 5.5 Hz), and 6.02 (1H, s). ^{13}C NMR δ=20.9, 21.7, 23.4, 26.3, 29.3, 32.6, 34.5, 35.3, 37.8, 40.3, 42.8, 125.8, 172.6, and 202.1. MS m/z (%) 204 (M^+, 100), 149 (51), 147 (39), 134 (41), and 121 (25). IR ν 2924, 2860, 1668, 1544, 1450, 1382, 1276, 1225, 1181, 891, and 870 cm^{-1}].

Catalytic Hydrogenation of 11. An EtOAc solution (0.5 cm^3) of **11** (20 mg) was hydrogenated with Pd–C. After removing the catalyst by filtration, the filtrate was evaporated and the residue was chromatographed on a silica-gel column to give **12** [colorless crystals, mp 140—143 °C (decomp), 19.8 mg, 98%. Found: m/z 206.1667 (M^+). Calcd for $C_{14}H_{22}O$: M, 206.1670. ^{1}H NMR δ=0.97 (3H, d, J=0.7 Hz), 0.98 (3H, s), 1.11 (2H, m), 1.26 (1H, dm, J=13.9 Hz), 1.44 (2H, m), 1.61—1.71 (3H, m), 1.75—1.96 (4H, m), 1.98 (1H, td, J=14.3, 5.1 Hz), 2.41 (2H, d, J=9.9 Hz), and 2.48 (1H, m). ^{13}C NMR δ=16.5, 24.8, 25.2, 25.3, 26.6, 32.1, 34.0, 35.1, 35.7, 38.4, 42.4, 44.8, 46.5, and 216.7. MS m/z (%) 206 (M^+, 100), 191 (30), 109 (29), 96 (20), 81 (29), and 41 (23). IR ν 2924, 1701, 1469, 1385, 1279, 1084, and 980 cm^{-1}].

Grignard Reaction of 7b. Formation of 9b. To

an anhydrous THF solution (5 cm^3) of **7b** (156 mg) was added drop-by-drop, under an N_2 atmosphere, MeMgBr (1.2 cm^3, 0.94 mol dm^{-3} in THF) at 0 °C. The mixture was further stirred at <10°C for 1 h, and quenched with dil NH_4Cl. After evaporation of THF, the mixture was extracted with CH_2Cl_2, washed with $NaHCO_3$ and brine, and dried (Na_2SO_4). The volatile materials were evaporated, and the residue was chromatographed on a silica-gel column to yield **9b** [a colorless oil, 142.3 mg, 85%. Found: *m/z* (FAB) 237.1853 $(M+1)^+$. Calcd for $C_{15}H_{25}O_2$: (M+1), 237.1854. ^{1}H NMR δ=0.91 (3H, s), 1.14 (3H, s), 1.16 (3H, s), 1.18 (3H, s), 1.10—1.26 (2H, m), 1.30—1.42 (2H, m), 1.46—1.61 (3H, m), 1.72 (1H, m), 1.82 (1H, dd, *J*=19.4, 5.9 Hz), 2.87 (1H, dt, *J*=19.4, 2.2 Hz), 5.98 (1H, dd, *J*=10.3, 2.2 Hz), and 6.83 (1H, ddd, *J*=10.3, 5.9, 2.2 Hz). ^{13}C NMR δ=16.0, 22.2, 24.7, 27.1, 27.6, 34.1, 34.5, 34.7, 37.5, 41.5, 49.3, 72.5, 127.6, 146.7, and 204.9. MS *m/z* (%) 236 (M^+, 7), 218 (48), 175 (33), 150 (58), 135 (43), 123 (100), 122 (34), 107 (93), 85 (31), 71 (48), and 57 (76). IR ν 3464, 2938, 1664, 1464, 1387, 1255, 1144, 941, and 812 cm^{-1}].

Grignard Reaction of 7a. Formation of 9a. Similarly, **7a** (158.2 mg) was converted to **9a** [a colorless oil, 102.0 mg, 60%. Found: *m/z* (FAB) 237.1854 $(M+1)^+$. Calcd for $C_{15}H_{25}O_2$: (M+1), 237.1854. ^{1}H NMR δ=1.00 (3H, s), 1.06 (3H, s), 1.14 (1H, m), 1.19 (6H, s), 1.24—1.36 (3H, m), 1.48—1.61 (2H, m), 1.76 (1H, m), 2.01 (1H, dd, *J*=19.5, 5.9 Hz), 2.22 (1H, dm, *J*=13.2 Hz), 2.51 (1H, dt, *J*=19.5, 2.6 Hz), 5.93 (1H, dd, *J*=10.3, 2.6 Hz), and 6.72 (1H, ddd, *J*=10.3, 5.9, 2.6 Hz). ^{13}C NMR δ=22.0 (2C), 22.3, 26.9, 27.1, 30.1, 35.3, 37.3, 38.5, 44.9, 49.9, 72.5, 127.8, 146.0, and 204.6. MS *m/z* (%) 218 (34), 175 (30), 150 (20), 135 (21), 123 (100), and 122 (21). IR ν 3444, 2966, 2910, 1666, 1465, 1387, 1297, 1152, 1120, 1051, 984, 917, and 831 cm^{-1}].

Hydrogenation of 9b to 10b. An EtOAc solution (2 cm^3) of **9b** (78.8 mg) was hydrogenated with Pd–C (5 mg). After the catalyst was filtered off, the filtrate was evaporated and chromatographed on a silica-gel column to afford **10b** [a colorless oil, 78.0 mg, 99%. Found: *m/z* (FAB) 239.2001 $(M+1)^+$. Calcd for $C_{15}H_{27}O_2$: (M+1), 239.2011. ^{1}H NMR δ=0.82 (3H, s), 1.07 (3H, s), 1.03—1.14 (2H, m), 1.19 (6H, s), 1.22—1.30 (2H, m), 1.41 (1H, m), 1.46—1.70 (3H, m), 1.81—1.93 (3H, m), 2.22 (1H, dm, *J*=15.0 Hz), 2.41 (1H, td, *J*=13.2, 5.9 Hz), and 2.67 (1H, ddd, *J*=15.0, 13.2, 7.7 Hz). ^{13}C NMR δ=16.7, 21.7, 21.9, 24.7, 27.2, 27.3, 32.0, 34.4, 36.0, 36.9, 38.4, 43.1, 52.9, 72.4, and 217.1. MS *m/z* (%) 238 (M^+, 1), 220 (91), 205 (56), 177 (51), 149 (58), 135 (46), 125 (100), 107 (79), and 43 (21). IR ν 3452, 2950, 2874, 1696, 1461, 1383, 1251, 1155, 1047, 934, and 732 cm^{-1}].

Hydrogenation of 9a to 10a. Similarly, **9a** (78.8 mg) was hydrogenated to **10a** [a colorless oil, 78.5 mg, 99%. Found: *m/z* (FAB) 237.1853 $(M-1)^+$. Calcd for $C_{15}H_{25}O_2$: (M−1), 237.1854. ^{1}H NMR δ=0.99 (3H, s), 1.08 (3H, s), 1.19 (3H, s), 1.20 (3H, s), 1.15—1.37 (3H, m), 1.48—1.65 (4H, m), 1.78—2.01 (3H, m), 2.08 (1H, dm, *J*=13.2 Hz), 2.21 (1H, dm, *J*=14.7 Hz), and 2.53 (1H, ddd, *J*=14.7, 13.2, 7.7 Hz). ^{13}C NMR δ=20.7, 22.4, 22.7, 23.7, 26.8, 27.2, 30.8, 34.8, 35.4, 37.7, 38.7, 44.4, 52.3, 72.6, and 216.1. MS *m/z* (%) 238 (M^+, 1), 220 (100), and 125 (50). IR ν 3460, 2936, 1698, 1470, 1373, 1313, 1149, 1102, 1052, 1013, 954, and 918 cm^{-1}].

Chemical Reduction of 10b. Formation of 13. To a stirred solution of **10b** (15 mg), Bu_4NF (43 mg), and Et_3SiH (0.026 cm^3) in CH_2Cl_2 (0.5 cm^3), was added drop-by-drop CF_3COOH (0.049 cm^3) at −20 °C. The mixture was stirred for another 1 h at −20 °C and at room temperature overnight, and then quenched with ice water. The mixture was extracted with CH_2Cl_2, washed with dil $NaHCO_3$ and brine, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on a silica-gel column to afford **13** [a colorless oil, 9.6 mg, 69%. Found: *m/z* 222.2006 (M^+). Calcd for $C_{15}H_{26}O$: M, 222.1984. ^{1}H NMR δ=0.76 (3H, s), 0.87 (3H, d, *J*=0.7 Hz), 0.78—0.92 (2H, m), 1.02 (1H, dm, *J*=13.2 Hz), 1.24 (3H, s), 1.26 (3H, s), 1.27—1.37 (2H, m), 1.44—1.75 (5H, m), 1.80—1.98 (2H, m), 2.59 (1H, td, *J*=13.6, 5.5 Hz), and 3.44 (1H, t, *J*=2.9 Hz). ^{13}C NMR δ=16.9, 22.3, 24.5, 24.7, 25.4, 27.6, 27.9, 31.4, 33.9, 34.5, 34.8, 35.4, 37.0, 74.3, and 75.8. MS *m/z* (%) 222 (M^+, 5), 85 (39), 83 (26), 71 (57), 57 (100), and 43 (20). IR ν 3432, 2926, 1647, 1385, 1261, 1032, and 806 cm^{-1}].

Dehydration of 10b Followed by Catalytic Hydrogenation to 1 and 1a. a) An HMPA (0.1 cm^3) solution of **10b** (25.0 mg) was heated at 220 °C for 1 h under an N_2 atmosphere. The mixture was diluted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on an alumina column to give a mixture of olefins (**14b**:**15**=3:2, 9.9 mg, 45%). The above-mentioned olefin mixture (9.9 mg) was dissolved in EtOAc and hydrogenated with PtO_2 under atmospheric pressure at room temperature to give **1** [a colorless oil. ^{1}H NMR δ=0.81 (3H, s), 0.86 (3H, d, *J*=6.6 Hz), 0.87 (3H, d, *J*=6.6 Hz), 1.06 (3H, s), 1.15—2.45 (13H, m), and 2.66 (1H, ddd, *J*=14.7, 13.2, 8.1 Hz). ^{13}C NMR δ=16.7, 19.7, 19.9, 21.7, 24.6, 24.8, 32.0, 32.9, 36.2, 37.0, 37.4, 38.4, 38.6, 53.1, and 217.4. (lit,[4d] ^{1}H NMR δ=0.81 (3H, s), 0.86 (6H, d), 1.06 (3H, s), and 1.15—2.45 (14H, m). ^{13}C NMR δ=16.8, 19.8, 20.0, 21.8, 24.7, 24.9, 32.1, 32.9, 36.2, 37.0, 37.5, 38.5, 38.6, 53.1, and 217.2)] and **1a** [a colorless oil. ^{1}H NMR δ=0.85 (3H, d, *J*=6.6 Hz), 0.90 (3H, d, *J*=6.6 Hz), 0.98 (3H, s), 1.05 (3H, s), and 1.00—2.60 (14H, m). ^{13}C NMR δ=19.4, 20.0, 20.6, 22.7, 23.8, 24.5, 32.9, 33.9, 35.0, 35.5, 37.7, 38.8, 39.5, 52.3, and 216.2. (lit,[4d] ^{1}H NMR δ=0.85 (3H, d, *J*=6.6 Hz), 0.89 (3H, d, *J*=6.6 Hz), 0.97 (3H, s), 1.05 (3H, s), and 1.00—2.60 (14H, m). ^{13}C NMR δ=19.4, 20.1, 20.7, 22.8, 23.8, 24.6, 32.9, 33.9, 35.0, 35.5, 37.8, 38.8, 39.5, 52.4, and 216.0)] (9.9 mg, 99%) in a ratio of 4:1.

b) To a CH_2Cl_2 (5 cm^3) solution of **10b** (17.0 mg) and DMAP (90.0 mg), $MeSO_2Cl$ (0.01 cm^3) was added drop-by-drop at 0 °C, and refluxed for 30 min. After being diluted with H_2O, the mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. After removing the volatile material, the residue was chromatographed on an alumina column to give a mixture of olefins (**14b**:**15**=3:2, 14.0 mg, 89%), which was hydrogenated in the presence of PtO_2 to afford **1** and **1a** (4:1, 14.0 mg, 99%).

Grignard Reaction of 8a. To an anhydrous THF solution (1 cm^3) of **8a** (50.0 mg), MeMgBr (0.3 cm^3, 0.94 mol dm^{-3} in THF) was added drop-by-drop at 0 °C under an N_2 atmosphere, and was further stirred at <10°C for 1 h. The mixture was then quenched with dil NH_4Cl and the solvent was evaporated. The thus-obtained residue was extracted with CH_2Cl_2, washed with $NaHCO_3$ and brine successively, and dried (Na_2SO_4). After the solvent was

evaporated, the residue was chromatographed on a silica-gel column to give **10a** (40.9 mg, 78%).

Grignard Reaction of 8b to form 10a. Similarly, **8b** (13.4 mg) was also treated with MeMgBr to form **10a** (7.1 mg, 56%).

Dehydration of 10a. To a stirred solution of **10a** (26 mg) in MeOH (1 cm^3) was added 30%-H_2SO_4 (0.5 cm^3), which was refluxed for 4 h. The mixture was diluted with water, extracted with CH_2Cl_2, washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a mixture of olefins (**14a**:**15**:**16**=1:1:4, 18.9 mg, 79%) and **10a** (4.9 mg, 19%) recovered.

Acetal Formation from the Mixture of 14a, 15, and 16. To a stirred benzene solution of a mixture of the above olefins (**14a**:**15**:**16**=1:1:4, 15 mg) and ethylene glycol (0.15 cm^3) in CH_2Cl_2 (0.5 cm^3) was added drop-by-drop BF_3–etherate at 0 °C, which was refluxed for 4 h. The reaction mixture was diluted with CH_2Cl_2, washed with dil $NaHCO_3$ and brine, and then dried over Na_2SO_4. Evaporation of the solvent and purification by chromatography on an alumina column, gave an acetal **17** [a colorless oil, 17.1 mg, 95%. ^1H NMR (C_6D_6) δ=1.04 (3H, d, J=7.0 Hz), 1.05 (3H, d, J=6.6 Hz), 1.06 (3H, s), 1.25 (3H, s), 1.02—2.25 (11H, m), 3.50 (4H, m), and 5.37 (1H, m)].

Hydrogenation of 17. Selective Formation of 1. The above **17** (15.0 mg) was hydrogenated with PtO_2 (< 1 mg) under hydrogen atmosphere for 5 d. The mixture was dissolved in a 1:1-mixture of MeOH (0.5 cm^3) and a 3 mol dm^{-3} HCl solution (0.5 cm^3), and then stirred at room temperature for 30 min. After removing MeOH, the mixture was extracted with CH_2Cl_2, washed with dil $NaHCO_3$ and brine, and dried over Na_2SO_4. Evaporation of the solvent afforded **1** and **1a** (5:1, 12.4 mg, 98%).

References

1) Part LX: H. Takeshita, Y. -S. Cui, N. Kato, A. Mori, and Y. Nagano, *Bull. Chem. Soc. Jpn.*, **65**, 2940 (1992).
2) A. Stoll, E. Seebeck, and D. Stauffacher, *Helv. Chim. Acta*, **40**, 1205 (1957).
3) H. Hikino, Y. Hikino, and T. Takemoto, *Chem. Pharm. Bull.*, **13**, 1404 (1965).
4) For former syntheses of **1**, see: a) J. A. Marchall, W. I. Fanta, and G. L. Bundy, *J. Org. Chem.*, **33**, 3913 (1968); b) E. Wenkert, D. A. Berges, and N. F. Golob, *J. Am. Chem. Soc.*, **100**, 1263 (1978); c) D. K. Banerjee and V. B. Anjadi, *Indian J. Chem.*, **11**, 511 (1973); d) G. D. Vite and T. A. Spencer, *J. Org. Chem.*, **53**, 2560 (1988); e) P. G. Sammes, L. J. Street, and R. J. Whitby, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 281.
5) H. Takeshita, Y. -S. Cui, N. Kato, A. Mori, and Y. Nagano, *Chem. Express*, **7**, 397 (1992).
6) A part of the results was preliminarily reported: H. Takeshita, Y. -S. Cui, N. Kato, and A. Mori, *Chem. Express*, **8**, 169 (1993).
7) A. A. Petrov, *J. Gen. Chem. USSR*, (*Engl. Transl.*), **11**, 309 (1941).
8) S. W. Baldwin and J. M. Wilkinson, *J. Am. Chem. Soc.*, **102**, 3634 (1980).
9) N. Kato, S. Tanaka, and H. Takeshita, *Bull. Chem. Soc. Jpn.*, **61**, 3231 (1988).
10) Purchased from Aldrich Chemical Co., Inc., Japan.
11) Ref. 4c has described a conversion of **10a** into **1** and 7-*epi*-valeranone (**1a**) (**1**:**1a**=1:4). Therefore, the present acquisition of **10a** constitutes a formal total synthesis of **1**.
12) During the acetal formation, isomerization of olefins occurred to accumulate **16**, and as the result, only **17** was identified among the products.
13) T. Nozoe, Y. S. Chen, and T. Toda, *Tetrahedron Lett.*, **1966**, 3663; C. Beeson and T. A. Dix, *J. Org. Chem.*, **57**, 4386 (1992).
14) Lisenced from Cambridge Science Computing, Inc.
15) The assignments are merely tentative.