Synthetic Studies on Aromadendrane-Type Compounds. I. Stereoselective Construction of Aromadendrane- and Alloaromadendrane-Type Skeletons

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As a preliminary study for the synthesis of aromadendrane- and alloaromadendrane-type compounds, *trans* and *cis* B/C-ring compounds (18 and 22) were synthesized from (+)-(1*S*,2*R*,4*R*,7*R*)-3,3,7-trimethyltricyclo[6.3.0.0^{2,4}]undec-8-en-10-one (3) as a common intermediate, which was obtained from (+)-3-carene *via* an intramolecular aldol condensation as a crucial step.

Keywords aromadendrane; alloaromadendrane; stereoselective reduction; aldol condensation; tricyclo[6.3.0.0^{2,4}]-undecane; (+)-3-carene

The 3,3,7,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane skeleton (I) is found in a number of natural products, which can be divided into two groups according to the stereochemistry of C-8. In the aromadendrane group Ia, the relationship between the C-8 proton and the cyclopropane ring (A) is *trans*. On the other hand, it is *cis* in the alloaromadendrane group Ib. In other words, the B/C-ring junction is *trans* in the former group (a) and *cis* in the latter (b). It is of interest that there are compounds having the same planar structure, for instance (+)-aromadendrene **1**[1] in group a and (−)-alloaromadendrene **2**[2] in group b, and bearing an isonitrile group[3] or a sugar moiety,[4] and furthermore, the enantiomer of **1** has been found in nature.[5] Various biological activities, *e.g.*, olfactory,[6] antifungal,[1,7] allelopathic[7] and cytotoxic activities,[3] have been reported. Recently, some compounds coupled with other organic moieties were found.[8] Some of them exhibit HIV-RTase inhibitory activities. Compounds bearing the skeletons Ia and Ib are quite widely distributed; they have been obtained from various land and marine animals and plants. Thus, new compounds exhibiting interesting biological activities are likely to be found. Although several synthetic studies on individual natural product have been reported so far,[5,9] no systematic study has been done with regard to the B/C-ring junction.[10] Efficient general synthetic routes to these compounds are required. Here we report a stereoselective construction of *trans*- and *cis*-B/C-ring systems from a common intermediate.

We selected (+)-(1*S*,2*R*,4*R*,7*R*)-3,3,7-trimethyltricyclo-[6.3.0.0^{2,4}]undec-8-en-10-one (**3**) as a common intermediate for a model study to construct the *trans*- and *cis*-B/C-ring systems. Stereoselective reduction of the C-8–C-9 double bond of **3** would lead to selective formation of both B/C-ring systems.

First, we synthesized a bicyclic ketone **11** starting from optically active and inexpensive (+)-3-carene (**4**) as follows. Ozonolysis[11] of **4** followed by selective acetalization of the aldehyde (**5**) with ethylene glycol catalyzed by pyridinium *p*-toluenesulfonate (PPTS) afforded a keto-acetal **6**, which was converted to a β-keto ester **7** by treating **6** with sodium hydride and dimethyl carbonate in tetrahydrofuran (THF) in the presence of a catalytic amount of potassium hydride.[12] Compound **7** was treated with 15% sulfuric acid in acetone to afford a 7-membered cyclic enone **8**,[13] which was hydrogenated on palladium–carbon (Pd–C) to give a cyclic β-keto ester **9** as an inseparable mixture regarding the configuration of the ester group. Treatment of the sodium salt of the β-keto ester **9** with methyl iodide in *N*,*N*-dimethylformamide (DMF) afforded only one methylated product **10**. Although very little work has been done on the stereochemistry of bicyclo[5.1.0]octane derivatives,[11b,c] it was found from the investigation of the 500 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectra that the 7-membered ring takes a chair conformation, as shown in Chart 2. The methyl group would have been introduced from the less hindered side of the enolate anion **9′**. The stereochemistry was further confirmed by the observation of nuclear Overhauser effect (NOE) between the newly introduced methyl group and the C-2 and C-6 axial protons. Ketonic cleavage of the β-keto ester **10** with aqueous potassium hydroxide afforded equatorial- and axial-methyl compounds **11** and **12** in a ratio of 8:1. Compound **12** afforded a mixture of **11** and **12** in a ratio

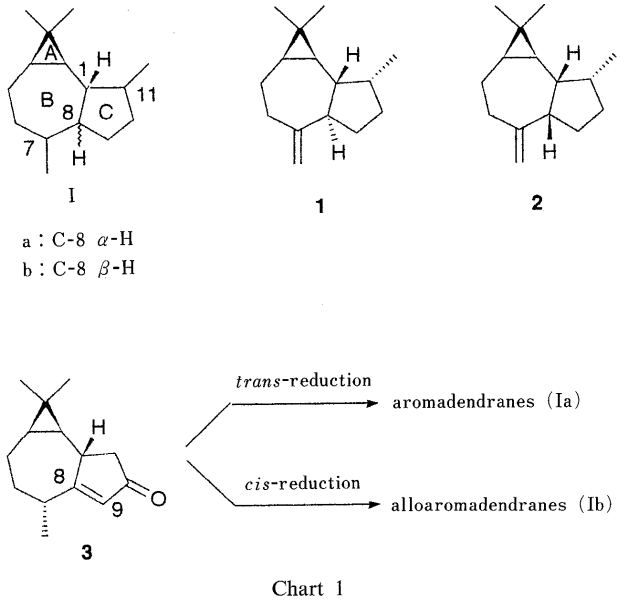

Chart 1

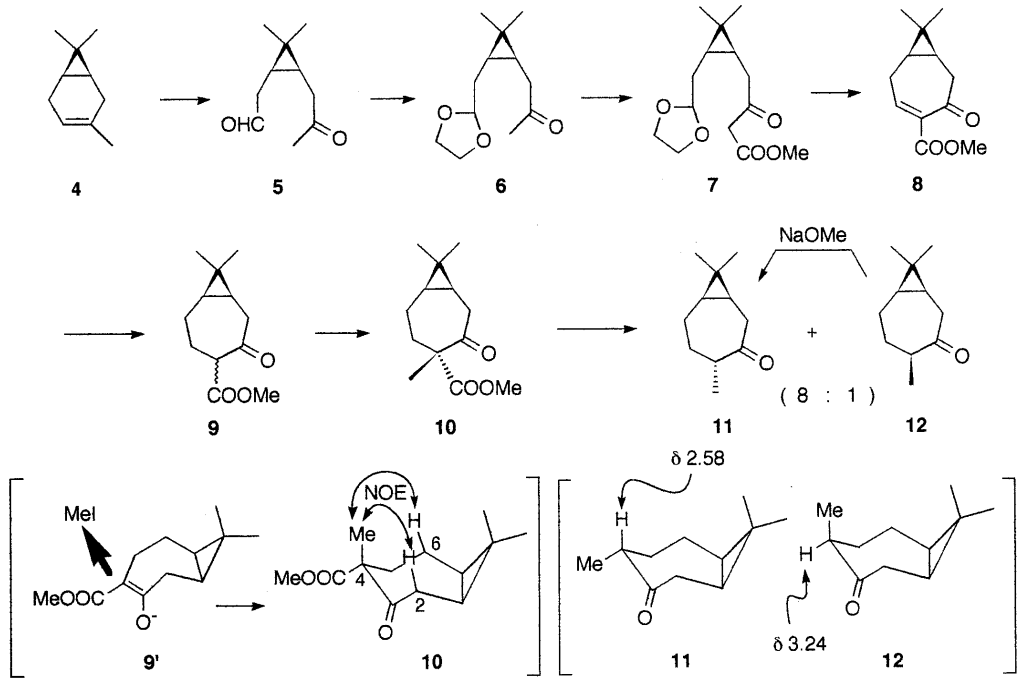

Chart 2

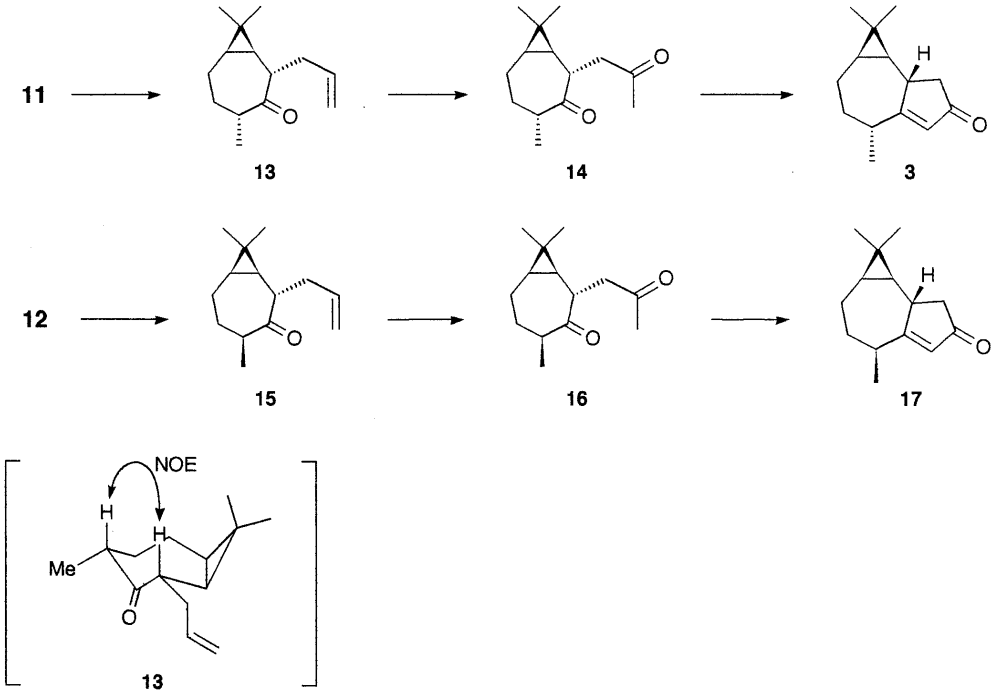

Chart 3

of 8 : 1 upon treatment with sodium methoxide. ^{1}H-NMR spectral analysis revealed that both compounds had the same chair conformation of the 7-membered ring, and the C-4 proton signal of **11** appeared at δ 2.58 and that of **12** at δ 3.24. These data show that the methyl group of **11** is equatorial and that of **12** is axial, as shown in Chart 2.

Next, we set about the construction of the C-ring. Allylation at C-2 from the less hindered α-side was accomplished by the treatment of **11** with lithium dissopropylamide (LDA) followed by alkylation with allyl bromide to give **13**. The stereochemistry was confirmed by the observation of NOE between the C-2 and C-4 protons, both of which were located in axial positions. The allyl group of **13** was converted to a methyl ketone by Wacker oxidation[14] to afford a diketone **14**. The intramolecular aldol condensation of **14** to the enone **3** was more difficult than expected. No method has been reported for the construction of a 5-membered enone on a 7-membered ring by the aldol reaction. Furthermore, a severe $A^{1,3}$-strain between the C-7 methyl group and C-9

proton is expected in the resulting enone **3**. This might cause isomerization at C-7. After various examinations (Table I), we found conditions which did not cause isomerization at C-7. Namely, the diketone **14** was treated with sodium hydride in refluxing benzene in the presence of a catalytic amount of *tert*-amyl alcohol[15] for 10 min to afford the desired enone **3** in over 90% yield. These reaction conditions were also applicable to the C-7 methyl

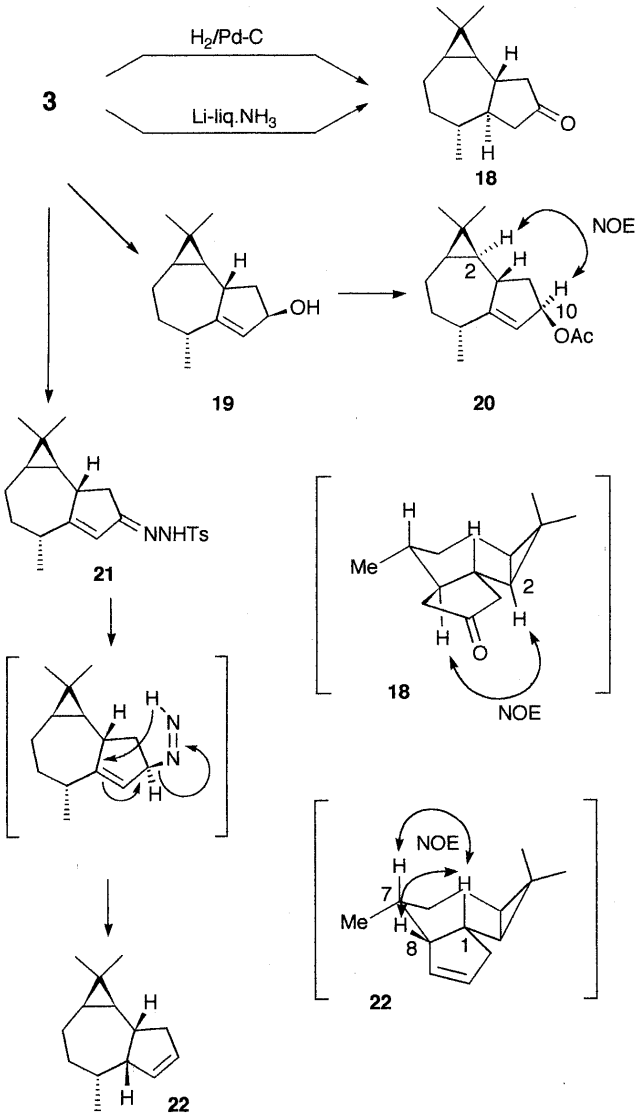

Chart 4

isomeric series (**12**→**15**→**16**→**17**) without any isomerization.

This left the final step in the preliminary study: stereoselective construction of the B/C-ring systems for Ia and Ib. Catalytic hydrogenation of **3** over Pd–C afforded a *trans* B/C-ring compound **18** exclusively. The Birch reduction of **3** also produced only **18**. Although the *trans* compound was easily obtained, some modifications were necessary to obtain the *cis* compound. The reduction of **3** with the sodium borohydride–cerium trichloride system[16] afforded exclusively an allylic alcohol **19**, which was converted to an acetate **20**. The stereochemistry of **20** was confirmed by the observation of NOE between the C-2 cyclopropyl proton and the C-10 proton. These results show that the attack of a hydride at C-10 carbonyl carbon occurred from the α-side stereospecifically. On the basis of these facts, we planned an intramolecular-type reduction. Namely, the enone **3** was converted to a tosylhydrazone **21**, which was treated with catechol borane.[17] At this point, the attack of a hydride at C-10 occurred from the α-side, as in the case where **3** produced **19**, and subsequent intramolecular hydride migration from the β-side to C-8 took place accompanied by elimination of nitrogen gas to afford a B/C-*cis* compound **22** in 77% yield as illustrated in Chart 4. The stereochemistry of **22** was confirmed by the observation of NOE between the C-1 and C-8 protons.

As described above, stereoselective methods for the construction of aromadendrane- and alloaromadendrane-type skeletons (Ia, b) were developed by controlling the stereochemistry of the reduction of the tricyclic enone **3** as a common intermediate.

Experimental

All melting and boiling points were measured without correction. Infrared (IR) spectra were recorded with a Hitachi 260-10 spectrometer. ^{1}H-NMR spectra were measured with a Hitachi R-22 (90 MHz), a JEOL JNM FX-90Q (90 MHz), or a JEOL JNM-GX-500 (500 MHz) instrument. The chemical shifts are given as δ (ppm) values with tetramethylsilane (TMS) as an internal standard. Optical rotations were recorded with a JASCO DIP-360 polarimeter. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a Shimadzu QP-1000 or a JEOL JMS D-300 mass spectrometer. For column chromatography, Kieselgel 60 (E. Merck) was used. All organic extracts were dried over anhydrous $MgSO_4$ before evaporation.

(−)-(1*S*,3*R*)-2,2-Dimethyl-3-(1,3-dioxolan-2-yl)-1-(2′-oxopropyl)cyclopropane (6) (+)-3-Carene (**4**) (60.0 g, 44.1 mmol) was dissolved in a mixture of MeOH (400 ml) and CH_2Cl_2 (50 ml), and O_3 (generated by passing O_2 through an ozonizer) was bubbled through the solution at

Table I. Intramolecular Aldol Cyclization of **14** and **16**

Substrate	Reagent	Solvent	Time	Temp. (°C)	Products **3**:**17**	Yield (%)
14	NaH	C_6H_6 + *tert*-AmOH	10 min	Reflux	100:0	92
16	NaH	C_6H_6 + *tert*-AmOH	10 min	Reflux	0:100	94
14	KO*tert*-Bu	*tert*-BuOH	12 h	40	45:55	60
16	KO*tert*-Bu	*tert*-BuOH	6 h	40	41:59	63
14	K_2CO_3	MeOH	24 h	Reflux		0[a]
14	KOH	MeOH	24 h	Reflux		0[a]
14	*p*-TsOH	C_6H_6	3 h	Reflux	[b]	0
14	PPTS	C_6H_6	24 h	Reflux		0[a]

a) Starting material was recovered. *b*) A complex mixture was obtained.

−78 °C for 10 h. After flushing the solution with N_2 to remove excess O_3, Me_2S (60 ml) was added, and the mixture was stirred overnight at room temperature. The mixture was concentrated, and the residue was dissolved in AcOEt. This solution was washed with water and brine, then dried, and evaporated. The residue was distilled under reduced pressure to give (+)-(1*R*,2*S*)-(2-acetonyl-3,3-dimethylcyclopropyl)acetaldehyde (**5**, 64.9 g, 88%) as a pale yellow oil, bp 115—120 °C/9 mmHg, $[\alpha]_D^{21}$ +49.2° (*c*=4.58, $CHCl_3$). IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.82—1.22 (2H, m, C-1 H, C-2 H), 0.90 and 1.15 (each 3H, s, C-3 Me × 2), 2.10 (3H, s, COMe), 9.79 (1H, m, CHO). MS *m/z*: 168 (M^+). A mixture of **5** (55.1 g, 32.8 mmol), ethylene glycol (16.5 ml, 29.5 mmol), PPTS (catalytic amount) and benzene (400 ml) was refluxed under a Dean–Stark water separator for 2 h. After cooling, the mixture was washed with water and brine, then dried, and evaporated. The residue was distilled under reduced pressure to give **6** (57.0 g, 91%) as a pale yellow oil, bp 120—125 °C/8 mmHg, $[\alpha]_D^{27}$ −17.3° (*c*=1.00, $CHCl_3$). IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.91 and 1.12 (each 3H, s, C-2 Me × 2), 2.10 (3H, s, COMe), 3.61—4.00 (4H, m, OCH_2CH_2O), 4.74 (1H, t, *J*=10 Hz, OCHO). MS *m/z*: 212 (M^+). HRMS Calcd for $C_{12}H_{20}O_3$: 212.1410. Found: 212.1409.

Methyl (−)-(1*S*,3*R*)-4-[2-(1,3-Dioxolan-2-yl)methyl-3,3-dimethylcyclopropyl]-3-oxobutanoate (7) A mixture of NaH (60% in oil, 5.15 g, 129 mmol), dimethyl carbonate (19.3 g, 429 mmol), a small part of the solution of **6** (9.10 g, 42.9 mmol) in THF (40 ml) and THF (80 ml) was refluxed for 15 min. After the addition of a catalytic amount of KH, the remaining solution of **6** was added dropwise under reflux for 1 h, and the stirring was continued for another 1 h. After cooling, the excess base was decomposed by the slow addition of ice-water, then the mixture was acidified with 10% HCl, and extracted with Et_2O. The extract was washed with water and brine, then dried, and evaporated. The residue was distilled under reduced pressure to give **7** (9.15 g, 79%) as a pale yellow oil, bp 135—140 °C/1 mmHg, $[\alpha]_D^{25}$ −16.6° (*c*=1.04, $CHCl_3$). IR ($CHCl_3$): 1745, 1720 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.91 and 1.12 (each 3H, s, C-2 Me × 2), 3.35 (2H, s, CH_2COO), 3.70 (3H, s, COOMe), 4.76 (1H, t, *J*=9.0 Hz, OCHO). MS *m/z*: 270 (M^+). HRMS Calcd for $C_{14}H_{22}O_5$: 270.1468. Found: 270.1459.

Methyl (+)-(1*S*,7*R*)-8,8-Dimethyl-3-oxobicyclo[5.1.0]oct-4-ene-4-carboxylate (8) A 15% H_2SO_4 solution was added to a solution of **7** (1.25 g, 4.63 mmol) in acetone (25 ml), and the mixture was stirred at room temperature for 24 h. Saturated $NaHCO_3$ was added, the mixture was concentrated, and the residue was dissolved in AcOEt. This solution was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give **8** (0.79 g, 82%) as a pale yellow oil, $[\alpha]_D^{24}$ +161.4° (*c*=0.485, $CHCl_3$). IR ($CHCl_3$): 1720, 1695 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.10 and 1.18 (each 3H, s, C-8 Me × 2), 3.70 (3H, s, COOMe), 7.17 (1H, m, C-5 H). MS *m/z*: 208 (M^+). HRMS Calcd for $C_{12}H_{16}O_3$: 208.1100. Found: 208.1100.

Methyl (+)-(1*S*,7*R*)-8,8-Dimethyl-3-oxobicyclo[5.1.0]octane-4-carboxylate (9) A suspension of 5% Pd–C (20 mg) in MeOH (5 ml) was stirred for 1 h under an H_2 atmosphere, and a solution of **8** (100 mg, 0.48 mmol) in MeOH (1 ml) was added. The resulting mixture was stirred for 24 h under the same atmosphere. The catalyst was removed by filtration, the filtrate was concentrated, and the residue was purified by column chromatography (*n*-hexane : AcOEt = 6 : 1) to give **9** (83 mg, 82%, colorless solid), mp below 30 °C, as a diastereomeric mixture (*ca.* 1 : 1) at C-4. IR ($CHCl_3$): 1740, 1705 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.60 (ddd, *J*=6.7, 9.2, 11.0 Hz, C-1 H), 0.70—0.83 (m, C-1 H, C-7 H), 1.01, 1.05, 1.06 and 1.08 (s, C-8 Me), 1.02—1.27 (m, C-6 H), 1.83—2.29 (m, C-2 H, C-5 H, C-6 H), 2.68 (dd, *J*=6.7, 12.8 Hz, C-2 H), 3.34 (t, *J*=7.3 Hz, C-4 H), 3.72 (s, COOMe), 3.74 (s, COOMe), 3.95 (t, *J*=6.7 Hz, C-4 H). MS *m/z*: 210 (M^+). HRMS Calcd for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1245.

Methyl (+)-(1*S*,4*R*,7*R*)-3-Oxo-4,8,8-trimethylbicyclo[5.1.0]octane-4-carboxylate (10) A solution of **9** (2.76 g, 13.1 mmol) in DMF (5 ml) was added at 0 °C to a stirred suspension of NaH (60% in oil, 631 mg, 15.8 mmol) in DMF (15 ml). After 10 min, MeI (0.98 ml, 15.8 mmol) was added, and the resulting mixture was stirred at room temperature for 30 min. Cold water and 10% HCl were added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to give **10** (2.67 g, 91%) as a colorless oil, $[\alpha]_D^{26}$ +79.8° (*c*=0.63, $CHCl_3$). IR ($CHCl_3$): 1745, 1705 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.49 (1H, ddd, *J*=7.9, 8.5, 8.8 Hz, C-1 H), 0.82 (1H, ddd, *J*=4.8, 8.8, 11.6 Hz, C-7 H), 0.88—1.00 (1H, m, C-6 βH), 0.97 and 1.05 (each 3H, s, C-8 Me × 2), 1.31 (3H, s, C-4 Me), 1.48 (1H, ddd, *J*=2.3, 5.0, 14.5 Hz, C-5 βH), 1.89 (1H, dddd, *J*=2.3, 4.8, 5.0, 14.0 Hz, C-6 αH), 2.18 (1H, dd, *J*=8.5, 18.3 Hz, C-2 βH), 2.62 (1H, ddd, *J*=5.0, 14.0, 14.5 Hz, C-5 αH), 2.86 (1H, dd, *J*=7.9, 18.3 Hz, C-2 αH), 3.76 (3H, s, COOMe). MS *m/z*: 224 (M^+). HRMS Calcd for $C_{13}H_{20}O_3$: 224.1413. Found: 224.1440.

(+)-(1*S*,4*R*,7*R*)- and (+)-(1*S*,4*S*,7*R*)-4,8,8-Trimethylbicyclo[5.1.0]-octan-3-one (11 and 12) A mixture of **10** (2.28 g, 10.2 mmol), KOH (1.40 g, 25 mmol), MeOH (10 ml), and water (15 ml) was refluxed for 14 h. After cooling, the mixture was extracted with AcOEt, and the extract was washed with water and brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give a mixture of **11** and **12** (1.34 g, 79%). The mixture was dissolved in MeOH (10 ml) and $NaBH_4$ (305 mg, 8.07 mmol) was added at 0 °C, then the resulting mixture was stirred for 30 min. Saturated $NaHCO_3$ was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to give the (4*R*)-3-ol and (4*S*)-3-ol derivatives in a ratio of 8 : 1. Each alcohol was dissolved in acetone and Jones' reagent was added until the red color persisted for more than 5 min. Excess reagent was decomposed by the addition of isopropanol, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 3 : 1) to give **11** (1.12 g, 84% from **10**) as a colorless oil, and **12** (142 mg, 11% from **10**) as a colorless oil. **11**: $[\alpha]_D^{26}$ +97.2° (*c*=0.98, $CHCl_3$). IR ($CHCl_3$): 1705 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.58 (1H, ddd, *J*=6.1, 6.7, 11.3 Hz, C-1 H), 0.70 (1H, ddd, *J*=6.3, 6.7, 11.0 Hz, C-7 H), 1.04 (3H, d, *J*=6.1 Hz, C-4 Me), 1.06 and 1.08 (each 3H, s, C-8 Me × 2), 1.18—1.36 (2H, m, C-5 αH, C-6 βH), 1.90 (1H, dd, *J*=5.5, 12.2 Hz, C-5 βH), 2.08 (1H, ddd, *J*=5.5, 6.3, 13.8 Hz, C-6 αH), 2.13 (1H, t, *J*=11.3 Hz, C-2 βH), 2.38 (1H, m, C-4 H), 2.51 (1H, dd, *J*=6.1, 11.6 Hz, C-2αH). MS *m/z*: 166 (M^+). HRMS Calcd for $C_{11}H_{18}O$: 166.1358. Found: 166.1359. **12**: $[\alpha]_D^{26}$ +248.4° (*c*=0.56, $CHCl_3$). IR ($CHCl_3$): 1705 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.75—0.86 (2H, m, C-1 H, C-7 H), 0.96—1.11 (1H, m, C-6 βH), 1.00 and 1.09 (each 3H, s, C-8 Me × 2), 1.03 (3H, d, *J*=6.7 Hz, C-4 Me), 1.41 (1H, m, C-5 βH), 1.85 (1H, m, C-6 αH), 1.93 (1H, m, C-5 αH), 2.14 (1H, dd, *J*=8.3, 17.7 Hz, C-2 βH), 2.60 (1H, dd, *J*=7.9, 17.7 Hz, C-2 αH), 3.26 (1H, m, C-4 H). MS *m/z*: 166 (M^+). HRMS Calcd for $C_{11}H_{18}O$: 166.1358. Found: 166.1358.

(+)-(1*R*,2*S*,4*R*,7*R*)-2-(2-Propenyl)-4,8,8-trimethylbicyclo[5.1.0]octan-3-one (13) *n*-BuLi (1.6 M in hexane, 2.10 ml, 3.37 mmol) was added to a solution of diisopropylamine (0.47 ml, 3.37 mmol) in THF (10 ml) at −20 °C and the mixture was stirred for 20 min. To the resulting LDA solution, a solution of **11** (430 mg, 2.59 mmol) in THF (2 ml) was added at −78 °C, and the whole was stirred for 30 min at this temperature. HMPA (1 ml) and allyl bromide (0.29 ml, 3.37 mmol) were added, and the resulting mixture was gradually warmed to room temperature under stirring. After 12 h, saturated NH_4Cl solution and water were added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **13** (473 mg, 89%) as a colorless oil, $[\alpha]_D^{22}$ +186.7° (*c*=0.475, $CHCl_3$). IR ($CHCl_3$): 1690, 1630 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.20 (1H, dd, *J*=9.2, 10.4 Hz, C-1 H), 0.69 (1H, m, C-7 H), 1.04 and 1.05 (each 3H, s, C-8 Me × 2), 1.08 (3H, d, *J*=7.9 Hz, C-4 Me), 1.90 (1H, m, C-6 αH), 2.05 (1H, m, C-5 βH), 2.25 (1H, m, C-2 H), 2.45 (1H, m, C-4 H), 4.97—5.08 (2H, m, $=CH_2$), 5.72 (1H, m, $-CH=$). MS *m/z*: 206 (M^+). HRMS Calcd for $C_{14}H_{22}O$: 206.1672. Found: 206.1677.

(+)-(1*R*,2*S*,4*R*,7*R*)-2-(2-Oxopropyl)-4,8,8-trimethylbicyclo[5.1.0]-octan-3-one (14) A mixture of **13** (142 mg, 0.68 mmol), $PdCl_2$ (60 mg, 0.34 mmol), CuCl (134 mg, 1.36 mmol), water (1 ml) and DMF (5 ml) was stirred at room temperature for 12 h under an O_2 atmosphere. Water was added, and the whole was extracted with Et_2O. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 7 : 1) to give **14** (158 mg, 100%) as a colorless oil, $[\alpha]_D^{27}$ +129.0° (*c*=0.885, $CHCl_3$). IR ($CHCl_3$): 1715, 1705 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.18 (1H, dd, *J*=9.2, 11.0 Hz, C-1 H), 0.70 (1H, ddd, *J*=6.4, 9.2, 11.0 Hz, C-7 H), 1.04 and 1.06 (each 3H, s, C-8 Me × 2), 1.05 (3H, d, *J*=7.3 Hz, C-4 Me), 1.25—1.34 (2H, m, C-5 αH, C-6 βH), 1.93 (1H, m, C-6 αH), 2.06 (1H, m, C-5 βH), 2.13 (3H, s, MeCO), 2.45 (1H, dd, *J*=3.7, 18.0 Hz,

one of C-2 CH_2–CO), 2.58 (1H, m, C-4 H), 2.61 (1H, ddd, J=3.7, 11.0, 11.0 Hz, C-2 H), 3.22 (1H, dd, J=11.0, 18.0 Hz, one of C-2 CH_2–CO). MS m/z: 222 (M^+). HRMS Calcd for $C_{14}H_{22}O$: 222.1621. Found: 222.1624.

(+)-(1*S*,2*R*,4*R*,7*R*)-3,3,7-Trimethyltricyclo[6.3.0.0^{2,4}]undec-9-en-10-one (3) A solution of **14** (35.0 mg, 0.158 mmol) in benzene (0.3 ml) was added to a suspension of NaH (60% in oil, 4.5 mg, 0.110 mmol) in a mixture of benzene and *tert*-AmOH (1 ml, benzene : *tert*-AmOH = 300 : 1), and the mixture was refluxed for 10 min. Ice-water was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to give **3** (29.7 mg, 92%) as a colorless oil, $[\alpha]_D^{26}$ +94.2° (c=1.32, $CHCl_3$). IR ($CHCl_3$): 1695, 1600 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.24 (1H, dd, J=9.1, 9.1 Hz, C-2 H), 0.68 (1H, ddd, J=6.1, 9.1, 11.6 Hz, C-4 H), 1.00—1.27 (1H, m, C-5 βH), 1.04 and 1.11 (each 3H, s, C-3 Me × 2), 1.23 (3H, d, J=6.1 Hz, C-7 Me), 1.37 (1H, m, C-6 αH), 1.94 (1H, m, C-6 βH), 2.04 (1H, m, C-5 αH), 2.22 (1H, d, J=17.1 Hz, C-11 αH), 2.29 (1H, m, C-7 H), 2.58 (1H, dd, J=6.7, 9.1 Hz, C-1 H), 2.64 (1H, dd, J=6.7, 17.1 Hz, C-11 βH), 5.85 (1H, d, J=1.3 Hz, C-9 H). MS m/z: 204 (M^+). HRMS Calcd for $C_{14}H_{20}O$: 204.1515. Found: 204.1492.

(+)-(1*R*,2*S*,4*S*,7*R*)-2-(2-Propenyl)-4,8,8-trimethylbicyclo[5.1.0]octan-3-one (15) Compound **15** was prepared from **12** (153 mg, 0.922 mmol) in a manner similar to that described for **13** in 85% yield (161 mg, a colorless oil), $[\alpha]_D^{26}$ +204.0° (c=1.44, $CHCl_3$). IR ($CHCl_3$): 1690, 1635 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.34 (1H, dd, J=9.1, 9.9 Hz, C-1 H), 0.58—0.92 (1H, m, C-7 H), 1.01 and 1.06 (each 3H, s, C-8 Me × 2), 1.04 (3H, d, J=6.0 Hz, C-4 Me), 2.75—3.20 (1H, m, C-4 H), 4.88—5.20 (2H, m, =CH_2), 5.40—5.98 (1H, m, –CH=). MS m/z: 206 (M^+). HRMS Calcd for $C_{14}H_{22}O$: 206.1672. Found: 206.1654.

(+)-(1*R*,2*S*,4*R*,7*R*)-2-(2-Oxopropyl)-4,8,8-trimethylbicyclo[5.1.0]-octan-3-one (16) Compound **16** was prepared from **15** (145 mg, 0.70 mmol) in a manner similar to that described for **14** in 91% yield (135 mg, a colorless oil), $[\alpha]_D^{22}$ +234.2° (c=1.69, $CHCl_3$). IR ($CHCl_3$): 1715, 1700 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.26 (1H, dd, J=9.0, 10.1 Hz, C-1 H), 0.58—0.92 (1H, m, C-7 H), 1.05 (6H, s, C-8 Me × 2), 1.19 (3H, d, J=7.0 Hz, C-4 Me), 2.14 (3H, s, MeCO). MS m/z: 222 (M^+). HRMS Calcd for $C_{14}H_{22}O$: 222.1621. Found: 222.1616.

(+)-(1*S*,2*R*,4*R*,7*S*)-3,3,7-Trimethyltricyclo[6.3.0.0^{2,4}]undec-9-en-10-one (17) Compound **17** was prepared from **16** (131 mg, 0.618 mmol) in a manner similar to that described for **3** in 94% yield (119 mg, a colorless oil), $[\alpha]_D^{26}$ +135.8° (c=0.655, $CHCl_3$). IR ($CHCl_3$): 1685, 1605 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.29 (1H, dd, J=9.2, 9.2 Hz, C-2 H), 0.70 (1H, ddd, J=7.0, 9.2, 9.7 Hz, C-4 H), 1.05 and 1.11 (each 3H, s, C-3 Me × 2), 1.14 (3H, d, J=7.3 Hz, C-7 Me), 2.20 (1H, d, J=17.7 Hz, C-11 αH), 2.62 (1H, dd, J=6.7, 17.7 Hz, C-11 βH), 2.72 (1H, dd, J=6.7, 9.1 Hz, C-1 H), 3.19 (1H, m, C-7 H), 5.79 (1H, s, C-9 H). MS m/z: 204 (M^+). HRMS Calcd for $C_{14}H_{20}O$: 204.1515. Found: 204.1529.

(−)-(1*R*,2*R*,4*R*,7*R*,8*S*)-3,3,7-Trimethyltricyclo[6.3.0.0^{2,4}]undecan-10-one (18) i) Catalytic Hydrogenation: A suspension of 5% Pd–C (2 mg) in MeOH (1 ml) was stirred for 1 h under an H_2 atmosphere, then a solution of **3** (18.3 mg, 0.090 mmol) was added, and the whole was stirred for 2 h under the same atmosphere. After removal of the catalyst by filtration, the filtrate was evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **18** (16.8 mg, 91%) as a colorless oil.

ii) Birch Reduction: A solution of **3** (21.6 mg, 0.106 mmol) in THF (0.5 ml) was added at −78 °C to a solution of Li (2.0 mg, 0.288 mg-atom) in liquid NH_3 (10 ml), and the resulting mixture was refluxed for 1 h. The NH_3 was evaporated off at room temperature, then water was added, and the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The purified product (18.3 mg, 84%) was shown to be identical with that obtained by catalytic hydrogenation. **18**: $[\alpha]_D^{23}$ −136.0° (c=2.98, $CHCl_3$). IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.40 (1H, dd, J=9.2, 9.8 Hz, C-2 H), 0.70 (1H, ddd, J=6.3, 9.2, 11.3 Hz, C-4 H), 0.92 (3H, d, J=6.1 Hz, C-7 Me), 1.03 and 1.04 (each 3H, s, C-3 Me × 2), 1.20—1.32 (1H, m, C-7 H), 1.64—1.76 (3H, m, C-1 H, C-5 αH, C-8 H), 1.83 (1H, dd, J=11.6, 19.5 Hz), 2.46 (1H, dd, J=7.3, 18.0 Hz, C-9 βH), 2.54 (1H, dd, J=3.9, 19.5 Hz, C-11 βH). MS m/z: 206 (M^+). HRMS Calcd for $C_{14}H_{22}O$: 206.1668. Found: 206.1667.

(+)-(1*R*,2*R*,4*R*,7*R*,10*R*)-3,3,7-Trimethyltricyclo[6.3.0.0^{2,4}]undec-8-en-10-ol (19) $CeCl_3 \cdot 6H_2O$ (57.7 mg, 0.139 mmol) was dissolved in a solution of **3** (28.3 mg, 0.139 mmol), and $NaBH_4$ (5.1 mg, 0.139 mmol) was added at −60 °C. The mixture was stirred for 15 min, and then saturated $NaHCO_3$ solution was added. The whole was extracted with AcOEt, and the extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give **19** (26.9 mg, 94%) as a colorless oil, $[\alpha]_D^{23}$ +88.2° (c=1.08, $CHCl_3$). IR ($CHCl_3$): 3570, 3425, 1635 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.27 (1H, dd, J=9.2, 9.2 Hz, C-2 H), 0.28—0.64 (1H, m, C-4 H), 1.01 and 1.06 (each 3H, s, C-3 Me × 2), 1.14 (3H, d, J=6.4 Hz, C-7 Me), 5.04 (1H, m, C-10 H), 5.34 (1H, s, C=CH–). MS m/z: 206 (M^+). HRMS Calcd for $C_{14}H_{22}O$: 206.1672. Found: 206.1690.

(+)-(1*R*,2*R*,4*R*,7*R*,10*R*)-10-Acetoxy-3,3,7-trimethyltricyclo[6.3.0.0^{2,4}]-undec-8-ene (20) Acetic anhydride (0.012 ml, 0.131 mmol) was added at 0 °C to a stirred mixture of **19** (26.9 mg, 0.131 mmol), dimethylaminopyridine (40.0 mg, 0.262 mmol) and CH_2Cl_2 (0.5 ml), and the resulting mixture was stirred for 2 h. Water was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to give **20** (29.8 mg, 92%) as a colorless oil, $[\alpha]_D^{23}$ +88.2° (c=1.85, $CHCl_3$). IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.23 (1H, dd, J=9.2, 9.2 Hz, C-2 H), 0.46 (1H, ddd, J=6.0, 9.2, 11.3 Hz, C-4 H), 0.94 and 0.99 (each 3H, s, C-3 Me × 2), 1.08 (3H, d, J=6.7 Hz, C-7 Me), 1.98 (3H, s, COMe), 2.23 (1H, dd, J=7.3, 13.5 Hz, C-11 αH), 2.32 (1H, dd, J=8.0, 9.2 Hz, C-1 H), 5.26 (1H, s, C-9 H), 5.81 (1H, m, C-10 H). MS m/z: 248 (M^+). HRMS Calcd for $C_{16}H_{24}O_2$: 248.1777. Found: 248.1749.

(+)-(1*R*,2*R*,4*R*,7*R*,8*S*)-3,3,7-Trimethyltricyclo[6.3.0.0^{2,4}]undec-9-ene (22) A mixture of **3** (113.5 mg, 0.556 mmol), tosylhydrazine (134 mg, 0.723 mmol) and EtOH (3 ml) was refluxed for 6 h under an Ar atmosphere. The solvent was evaporated off, and water was added, then the whole was extracted with $CHCl_3$. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give (−)-(1*S*,2*R*,-4*R*,7*R*)-3,3,7-trimethyltricyclo[6.3.0.0^{2,4}]undec-8-en-10-one tosylhydrazone (**21**) (153 mg, 74%) as a yellow oil, $[\alpha]_D^{23}$ −6.53° (c=1.03, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.02—0.82 (2H, m, C-3 H, C-4 H), 1.01 and 1.07 (each 3H, s, C-3 Me × 2), 1.15 (3H, d, J=6.6 Hz, C-7 Me), 2.42 (3H, s, aromatic Me), 5.88 (1H, s, C-9 H), 7.86 (4H, AA'BB' type aromatic H). MS m/z: 372 (M^+). Catecholborane (0.08 ml, 0.663 mmol) was added to a solution of **21** (192 mg, 0.51 mmol) in $CHCl_3$ (3 ml) at 0 °C, and the mixture was stirred for 1 h. Stirring was continued at room temperature for another 1 h, then $AcONa \cdot 3H_2O$ (90.2 mg, 0.663 mmol) was added, and the resulting mixture was refluxed for 1 h. After the mixture had cooled, water (3 ml) was added, and the whole was extracted with hexane. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane) to give **22** (74.6 mg, 77%) as a colorless oil, $[\alpha]_D^{23}$ +51.6° (c=1.02, $CHCl_3$). IR ($CHCl_3$): 1620 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.44 (1H, dd, J=6.7, 8.5 Hz, C-2 H), 0.55 (1H, m, C-4 H), 1.00 and 1.05 (each 3H, s, C-3 Me × 2), 1.07 (3H, d, J=7.3 Hz, C-7 Me), 1.96 (1H, m, C-7 H), 2.14 (1H, ddd, J=2.4, 7.3, 15.9 Hz, C-11 αH), 2.34 (1H, m, C-1 H), 2.70 (1H, dd, J=9.2, 15.9 Hz, C-11 βH), 2.80 (1H, d, J=9.2 Hz, C-8 H), 5.50 (1H, m, C-10 H), 5.70 (1H, m, C-9 H). MS m/z: 190 (M^+). HRMS Calcd for $C_{14}H_{20}$: 190.1719. Found: 190.1713.

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