Synthetic Studies on Aphidicolane and Stemodane Diterpenes. II.[1] Neighboring Hydroxyl Group Participation in Stereoselective Syntheses of Tricyclo[6.3.1.0^{1,6}]dodecanes Corresponding to the B/C/D-Ring Systems[2]

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Tricyclo[6.3.1.0^{1,6}]dodecane derivatives (5 and 6) corresponding to the B/C/D-ring systems of aphidicolane and stemodane diterpenes were synthesized stereoselectively *via* a spirodienone-alcohol (4) as a common intermediate. Participation of the neighboring hydroxyl group in 4 is crucial for controlling the stereochemistry of the spirocenters.

Keywords tricyclo[6.3.1.0^{1,6}]dodecane; aphidicolane; stemodane; hydroxyl group participation; spirodienone; regioselective reduction

The aphidicolane (**2**) and stemodane (**3**) families are tetracyclic diterpenes that have the same carbon framework, a tetracyclo[10.3.1.0^{1,10}.0^{2,7}]hexadecane (**1**).[3] Although the A/B-ring is a *trans*-fused decaline system in both families, aphidicolanes have a *trans*-B/C ring junction and stemodanes have a *cis*-junction. Aphidicolane-type compounds are mainly found as metabolites of microorganisms, whereas stemodane-type compounds are plant products. Aphidicolin (**2a**) exhibits potent antiviral and antitumor activities, in spite of its simple functionalities. It is also a specific inhibitor of DNA polymerase α.[4] Because of the diverse substitution patterns on the skeleton (**1**), the structure–activity relationship among these diterpenes is of interest.

Although several total syntheses and synthetic approaches to **2a** and **3** have been reported so far,[5] most of the studies have involved the construction of the C- and D-ring on the pre-formed A/B-ring systems. Most of the structural differences in these families are centered on the A-ring. Therefore, it would be more effective for the synthesis of compounds belonging to these families if the B/C/D-ring were constructed first, followed by cyclization to form the A-ring. It would also be useful if both of the B/C/D-ring systems (**5** and **6**) could be obtained selectively from a common intermediate. In this paper, we describe a stereoselective synthesis of two types of tricyclo[6.3.1.0^{1,6}]-dodecane derivatives (**5** and **6**) corresponding to the B/C/D-ring systems of aphidicolane and stemodane diterpenes, respectively, *via* a spirodienone alcohol (**4**), in which neighboring hydroxyl group participation is crucial.

The following two points are pivotal in the strategy of this synthetic study.

1. Synthesis of **4** as a common intermediate for the tricyclic compounds (**5** and **6**) by the catalytic decomposition of a phenolic α-diazoketone (**13**), followed by stereo- and chemoselective reduction of the saturated ketone.

2. Differentiation of the two double bonds in **4** through the participation of the neighboring hydroxyl group to introduce an asymmetry to the spirocenter; this makes possible a regioselective reduction of the double bond near the hydroxyl group, and a selective intramolecular protection of the same double bond by the formation of a

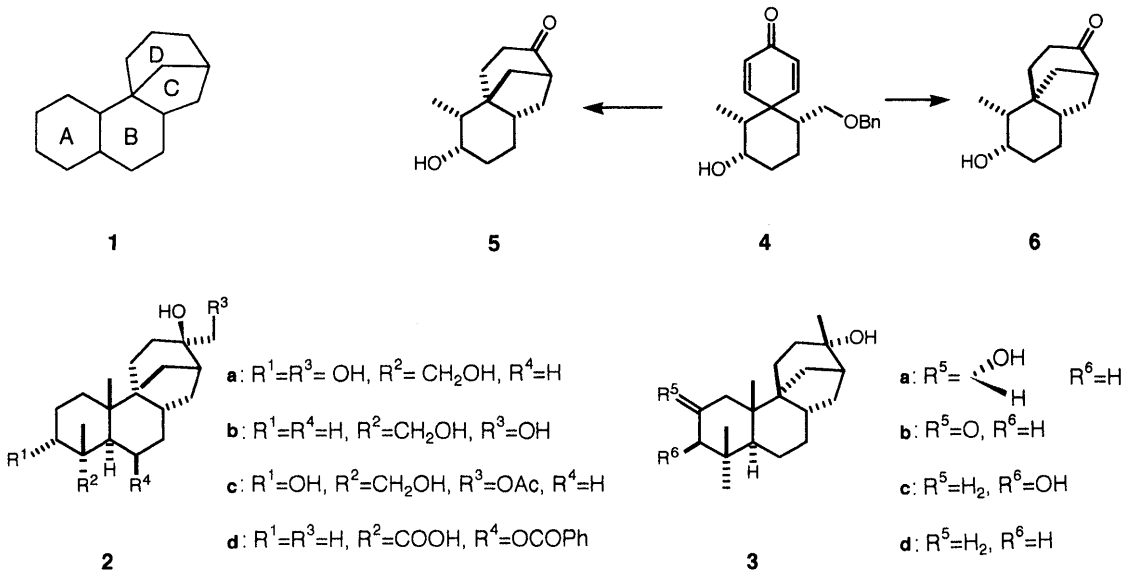

Chart 1

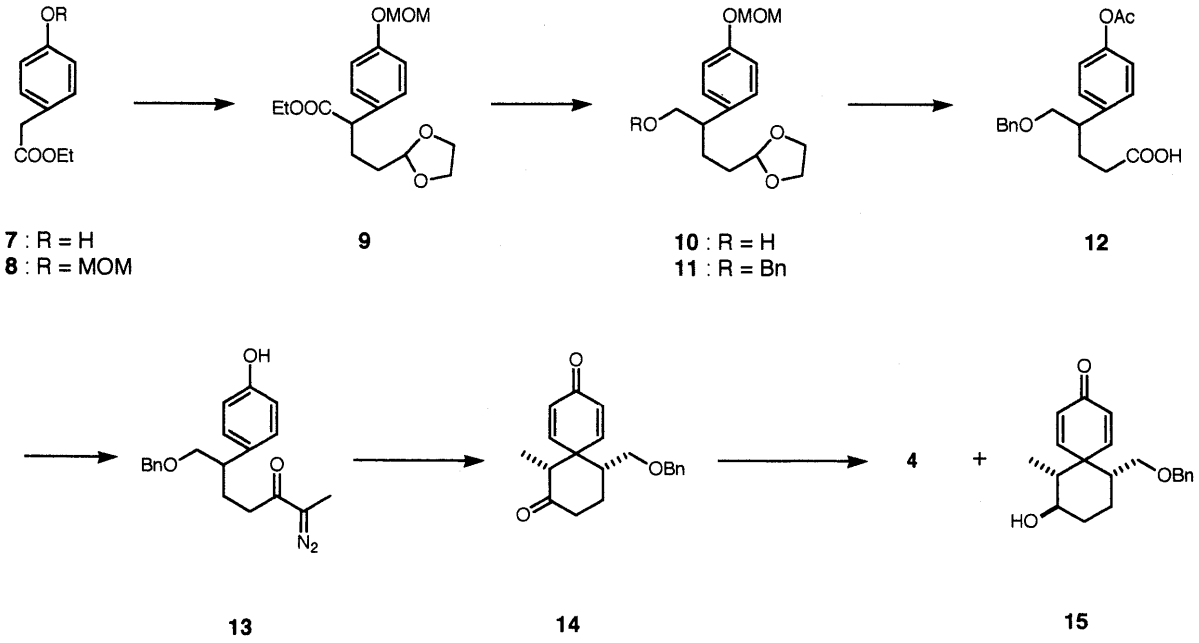

Chart 2

cyclic ether.

First, we synthesized the spirodienone-alcohol (**4**) as shown in Chart 2. The methoxymethyl (MOM) ether (**8**) of ethyl 4-hydroxyphenylacetate (**7**) was alkylated with 2-(2-bromoethyl)-1,3-dioxolane using sodium amide in the presence of hexamethylphosphoric triamide (HMPA) to afford **9** (73% yield from **7**), which was reduced with lithium aluminum hydride (LAH) to give an alcohol (**10**). The hydroxyl group of **10** was protected as a benzyl (Bn) ether (**11**). Deprotection of MOM and the acetal of **10** with 10% hydrochloric acid, and acetylation of the phenolic hydroxyl group followed by Jones oxidation gave a carboxylic acid (**12**) in 70% yield from **9**. The acid (**12**) was treated with oxalyl chloride in benzene to afford an acid chloride, which was converted to a diazoketone by reaction with diazoethane in ether. A phenolic α-diazoketone (**13**) was obtained by hydrolysis of the acetate with sodium carbonate in the presence of sodium bicarbonate. Copper(II) chloride-catalyzed decomposition[6] of **13** in boiling chloroform produced a spirodienone (**14**). Selective reduction[7] of the saturated ketone of **14** with sodium borohydride at −30 °C in methanol gave the desired spirodienone-alcohol (**4**) in 42% yield from **12**, along with a small amount of the diastereomer (**15**).

The *cis*-stereochemistry for the C(7)- and C(11)-substituents of **14** was determined by comparison of the proton nuclear magnetic resonance (^{1}H-NMR) spectrum with that of the saturated ketone (**16**) obtained from **14** by hydrogenation (Chart 3). In compound **14**, the C(7)-methyl and C(11)-methylene proton signals appeared at about 0.4 ppm higher fields than those of **16**. This means that both substituents are shielded, being located above the dienone ring, and the C(11)-proton is deshielded due to its location near the plane of the dienone ring.[8] Namely, both substituents apparently adopt equatorial positions, with a *cis*-relationship.

The axial orientation of the hydroxyl group of **4** was determined as follows. The C(8)-proton of **4** appeared at

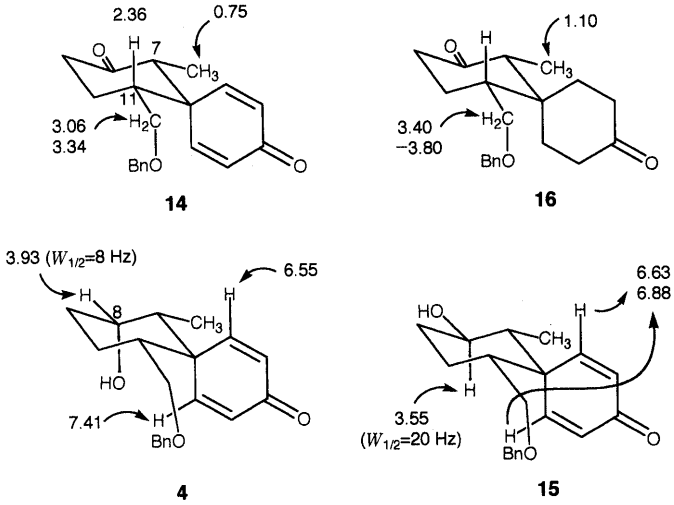

Chart 3

3.93 ppm with a half width, $W_{1/2} = 8$ Hz, and that of the isomer **15** was seen with $W_{1/2} = 20$ Hz. These values indicate that the former hydroxyl group is axial and the latter is equatorial. Furthermore, one of the olefinic protons of **4** was seen at 7.41 ppm with a significant downfield shift. This shows that this olefinic proton is located near the C(8)-hydroxyl group.

The proximity of the hydroxyl group and one of the β-positions of the dienone moiety is a key point in control of the stereochemistry of the spirocenter. Namely, the chemical environment of the two double bonds would be greatly affected by the axial hydroxyl group. We set about the stereoselective construction of the C-ring utilizing the axially oriented hydroxyl group (Chart 4). We have already developed a regioselective reduction method for one double bond adjacent to the hydroxyl group in the dienone moiety.[9] So, the hydroxy-enone (**4**) was subjected to the Birch reduction to reduce selectively the double bond

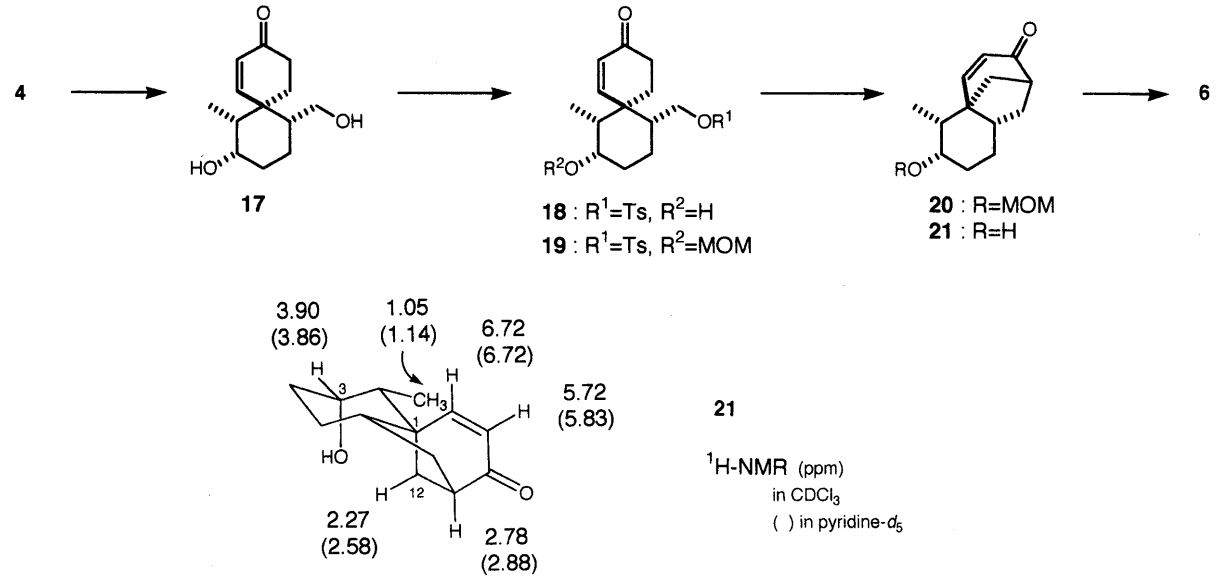

Chart 4

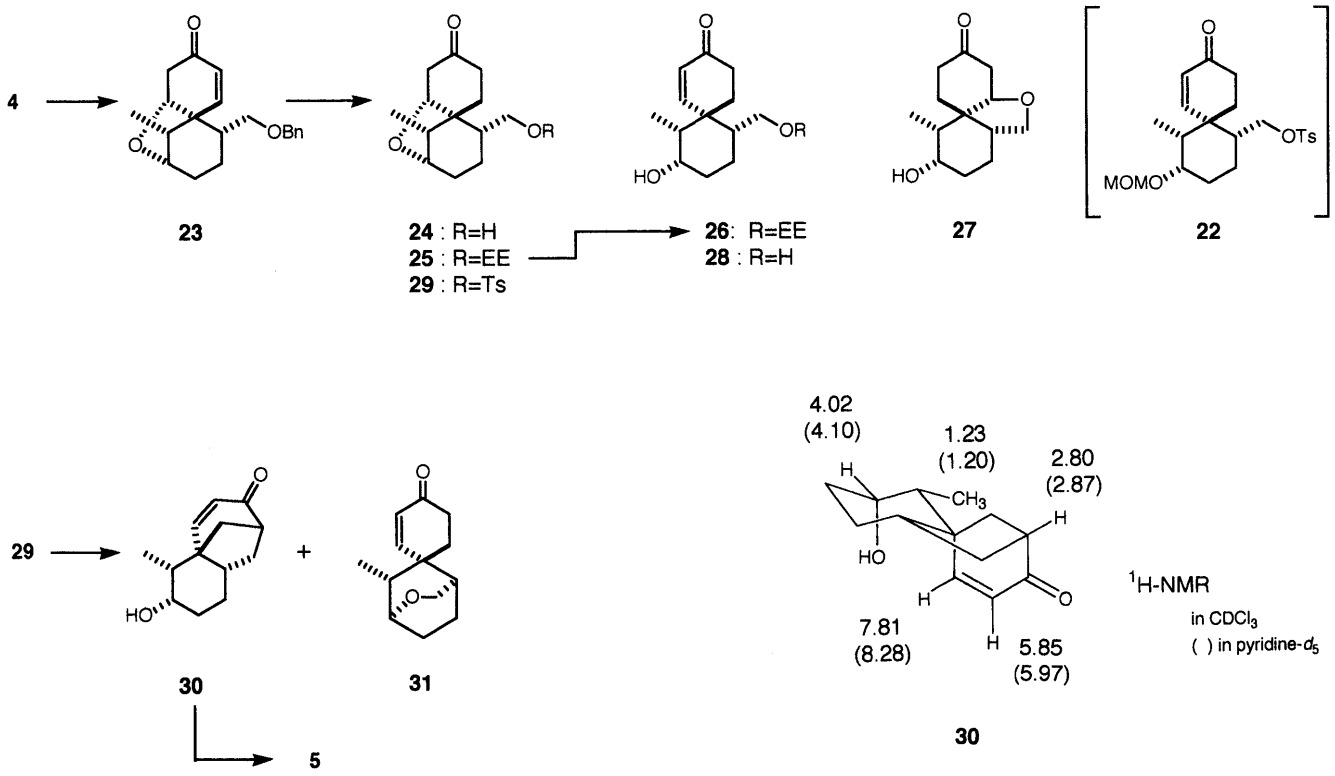

Chart 5

neighboring the hydroxyl group concurrently with a reductive debenzylation. Compound **4** was treated with 5 eq of lithium in liquid ammonia at −78 °C for 5 min to produce an enone-diol (**17**) selectively in 70% yield. Next, the primary hydroxyl group was tosylated (**17**→**18**), and then the secondary alcohol was protected as the MOM ether (**18**→**19**). The keto-tosylate (**19**) was treated with potassium *tert*-butoxide in tetrahydrofuran (THF) at 0 °C to afford a tricyclic enone (**20**) in 97% yield. Hydrolysis of the MOM group with 10% hydrochloric acid afforded an enone-alcohol (**21**) in 91% yield. The stereochemistry of the product (**21**) was confirmed by comparison of its ^{1}H-NMR spectra in chloroform-d_1 ($CDCl_3$) and in pyridine-d_5.[10] One of the C(12)-protons appeared at 2.27 ppm in $CDCl_3$, while the same proton was seen at 2.58 ppm in pyridine-d_5. This notable downfield shift indicates that the proton is located near the C(3)-hydroxyl group as shown in Chart 4. Compound **21** was hydrogenated to give the stemodane-type tricyclic compound (**6**) in 92% yield.

On the other hand, similarly to the case of the enone-tosylate (**19**), the synthesis of another enone-tosylate (**22**), an epimer of **19** at the spirocenter, would lead to the aphidicolane-type tricyclic compound (**5**). To this end, compound **4** was treated with sodium amide in liquid

ammonia to produce a tricyclic ether (**23**, 84% yield based on the consumed starting material), which was converted to a keto-alcohol (**24**) by hydrogenation and hydrogenolysis with 10% palladium–charcoal (Pd–C) in ethanol–ethyl acetate (1 : 1). After protection of the hydroxyl group as the ethoxyethyl (EE) ether (**25**), an enone-alcohol (**26**) was obtained by the treatment of **25** with tetra-*n*-butylammonium fluoride in THF. In compound **25**, deprotection of the EE afforded a tricyclic ether (**27**) preferentially instead of the desired diol (**28**). Because of the failure to obtain **28**, we turned back to the hydroxy-ketone (**24**), which was converted to a tosylate (**29**). Treatment of **29** with potassium *tert*-butoxide in THF at −10 °C afforded a tricyclic enone-alcohol (**30**) directly in 59% yield with a cyclic ether (**31**, 9% yield) as a by-product. Similarly to the determination of the stereochemistry of **20**, the structure of **30** was confirmed by the ^{1}H-NMR spectral comparison in $CDCl_3$ and in pyridine-d_5. The C(11)-olefinic proton appeared at 7.81 ppm in $CDCl_3$, while it appeared at 8.28 in pyridine-d_5, with a significant downfield shift (Chart 5). Finally, hydrogenation of **30** gave the aphidicolane-type tricyclic compound (**5**).

As described above, a stereoselective synthesis of tricyclo-[6.3.1.0^{1,6}]dodecane derivatives (**5** and **6**) corresponding to the B/C/D-ring systems of aphidicolane and stemodane diterpenes *via* a spirodienone-alcohol (**4**) as a common intermediate has been accomplished.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in $CDCl_3$ solution on a Hitachi R-22 (90 MHz) or a Varian VXR-200 (200 MHz). Mass spectra (MS) were obtained with a Shimadzu GCMS-QP1000, and high-resolution mass spectra (HRMS) were measured with a JEOL JMS-D300 mass spectrometer. Column chromatography was performed on Merck Kieselgel 60, and Merck Kieselgel 60 PF_{254} was used for preparative thin layer chromatography (PTLC). All extracts were dried over anhydrous Na_2SO_4 before evaporation.

Ethyl 4-(1,3-Dioxolan-2-yl)-2-(4-methoxymethoxyphenyl)butyrate (9) Diisopropylethylamine (157 ml, 0.90 mol) and chloromethyl methyl ether (MOMCl) (60 ml, 0.78 mol) were added to a stirred solution of **7** (63.6 g, 0.35 mol) in methylene chloride (400 ml) at 0 °C, and the mixture was stirred overnight at room temperature. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with methylene chloride. The extract was washed with water and brine, then evaporated. The residue was purified by column chromatography (hexane : AcOEt = 5 : 1) to afford a MOM ether (**8**, 72 g, 91%) as a pale yellow oil. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR δ: 1.21 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.43 (3H, s, $OCH_2OC\underline{H_3}$), 4.18 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 5.10 (2H, s, $O\underline{CH_2}OCH_3$), 6.89—7.21 (4H, AA′BB′-type aromatic protons). MS m/z: 224 (M^+). HRMS Calcd for $C_{12}H_{16}O_4$: 224.1049. Found: 224.1065. The ester (**8**, 33.0 g, 0.15 mol) and HMPA (60 ml) were added to a suspension of $NaNH_2$ (11.7 g, 0.39 mol) in ether (600 ml) at 0 °C, and the mixture was refluxed for 1 h. To the resulting mixture, 2-(2-bromoethyl)-1,3-dioxolane (40 g, 0.22 mol) was added dropwise during 30 min, and the whole was refluxed for 3 h, then allowed to cool. Saturated NH_4Cl solution was added, and the mixture was extracted with ether. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (hexane : AcOEt = 5 : 1) to give **9** (38 g, 80%) as a pale yellow oil. IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR δ: 1.24 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 3.51 (3H, s, $OCH_2OC\underline{H_3}$), 3.8—4.1 (4H, m, OCH_2CH_2O), 4.14 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 4.86 (1H, t, J=4 Hz, O–CH–O), 5.15 (2H, s, $O\underline{CH_2}OCH_3$), 6.90—7.33 (4H, AA′BB′-type aromatic protons). *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.99; H, 7.43.

1-Benzyloxy-4-(1,3-dioxolan-2-yl)-2-(4-methoxymethoxyphenyl)butane (11) A solution of the ester (**9**, 10 g, 31 mmol) in ether (20 ml) was added to a suspension of lithium aluminum hydride (3.6 g, 95 mmol) in ether (300 ml) at 0 °C, and the mixture was stirred at room temperature for 1 h, and then cooled to 0 °C. Water (3.6 ml), 10% NaOH solution (3.6 ml) and water (10.8 ml) were slowly added in that order, and stirring was continued until the grayish precipitates turned white. The precipitates were filtered off, the filtrate was concentrated, and the residue was purified by column chromatography (hexane : AcOEt = 2 : 1) to give the alcohol (**10**, 8.3 g, 95%) as a colorless oil. IR ($CHCl_3$): 3580, 3490 cm^{-1}. ^{1}H-NMR δ: 2.75 (Ar-CH), 3.49 (3H, s, $OCH_2OC\underline{H_3}$), 3.58—4.10 (6H, $HOC\underline{H_2}$ and OCH_2CH_2O), 4.79 (1H, t, J=4 Hz, O–CH–O), 5.13 (2H, s, $O\underline{CH_2}OCH_3$), 6.90—7.16 (4H, AA′BB′-type aromatic protons). *Anal.* Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.60; H, 7.72. A solution of **10** (8.3 g, 29 mmol) in THF (50 ml) was added to a stirred suspension of sodium hydride (2.3 g, 57 mmol) in THF (300 ml) and HMPA (5 ml). After 1 h, benzyl bromide (5.7 ml, 44 mmol) and Bu_4NI (1.7 g, 4.6 mmol) were added dropwise, and the mixture was stirred overnight at room temperature. After the addition of NH_4Cl solution, the mixture was extracted with benzene, and the extract was washed with brine, dried, and then evaporated. The residue was purified by column chromatography (hexane : AcOEt = 5 : 1) to give **11** (11 g, 98%) as a colorless oil. IR ($CHCl_3$): 2960, 2896, 1510, 1220 cm^{-1}. ^{1}H-NMR δ: 2.88 (1H, m, Ar-CH), 3.45 (3H, s, $OCH_2OC\underline{H_3}$), 3.52 (2H, d, J=6 Hz, $BnOC\underline{H_2}$), 4.76 (1H, t, J=4 Hz, O–CH–O), 5.10 (2H, s, $O\underline{CH_2}OCH_3$), 6.86—7.12 (4H, AA′BB′-type aromatic protons), 7.23 (5H, s-like, $OCH_2\underline{Ph}$). *Anal.* Calcd for $C_{22}H_{28}O_5$: C, 70.95; H, 7.58. Found: C, 70.99; H, 7.62.

4-(4-Acetoxyphenyl)-5-benzyloxypentanoic Acid (12) A mixture of **11** (10.8 g, 29 mmol), 10% HCl (30 ml) and THF (150 ml) was refluxed for 6 h. After cooling, the mixture was extracted with $CHCl_3$, and the extract was washed with water and brine, dried, and then evaporated. The residue was purified by column chromatography (hexane : AcOEt = 2 : 1) to give a hydroxy-aldehyde (7.2 g, 87%). IR ($CHCl_3$): 3580, 3350, 1725 cm^{-1}. ^{1}H-NMR δ: 3.54 (2H, d, J=6 Hz, $BnOC\underline{H_2}$), 4.45 (2H, s, $PhC\underline{H_2}O$), 6.65—7.01 (4H, AA′BB′-type aromatic protons), 7.25 (5H, s-like, $\underline{Ph}C\underline{H_2}$), 9.86 (1H, t, J=3 Hz, CHO). The hydroxy-aldehyde (7.2 g, 25 mmol) was dissolved in pyridine (6.0 ml), and acetic anhydride (4.4 ml, 47 mmol) was added at 0 °C. After 15 min, the mixture was acidified with 10% HCl, and extracted with ether. The extract was washed with brine, dried, and then evaporated. The residue was dissolved in acetone (15 ml), and Jones reagent was added at 0 °C until the starting material was no longer detectable on TLC. Excess reagents were decomposed with isopropanol, and the mixture was evaporated. AcOEt and water were added to the residue, and the mixture was extracted with AcOEt. The extract was washed with brine, dried, and then evaporated. The residue was passed through a short silica gel column (hexane : AcOEt = 1 : 1) to afford **12** (7.5 g, 87%) as a colorless oil. IR ($CHCl_3$): 3600—2300, 1748, 1208 cm^{-1}. ^{1}H-NMR δ: 2.24 (3H, s, OAc), 2.80 (1H, m, $BnOCH_2C\underline{H}$), 3.56 (2H, d, J=6 Hz, $BnOC\underline{H_2}$), 4.47 (2H, s, $PhC\underline{H_2}O$), 6.97—7.15 (4H, AA′BB′-type aromatic protons), 7.21 (5H, s-like, $\underline{Ph}CH_2$). *Anal.* Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.90; H, 6.60.

(7*RS*,11*RS*)-11-Benzyloxymethyl-7-methylspiro[5.5]undeca-1,4-diene-3,8-dione (14) Oxalyl chloride (6.3 ml, 72 mmol) was added to a stirred solution of **12** (5.3 g, 15 mmol) in benzene (6 ml) at 0 °C, and the mixture was stirred at room temperature for 40 min. After the solvent and excess reagent were evaporated off, the residue was dissolved in methylene chloride (6 ml). The resulting solution was added to an ethereal solution of excess diazoethane at 0 °C. After 30 min, the mixture was concentrated, and MeOH (100 ml), water (90 ml), Na_2CO_3 (9 g), and $NaHCO_3$ (8 g) were added. The mixture was stirred for 2 h, and the MeOH was evaporated off. After the addition of water, the mixture was extracted with AcOEt, and the extract was washed with water and brine, dried, and then evaporated to give a phenolic diazoketone (**13**). IR ($CHCl_3$): 3580, 3350, 2080, 1620 cm^{-1}. A solution of **13** in $CHCl_3$ (20 ml) was added to boiling $CHCl_3$ (800 ml) containing $CuCl_2$ (2.1 g, 16 mmol). After cooling, the mixture was passed through a Florisil column and the eluate was concentrated. Purification of the residue by column chromatography (hexane : AcOEt = 2 : 1) gave **14** (2.4 g, 54%) as a colorless oil. IR ($CHCl_3$): 1710, 1660, 1620 cm^{-1}. ^{1}H-NMR δ: 0.75 (3H, d, J=8 Hz, C(7)-CH_3), 3.06 (1H, dd, J=10, 8 Hz), 3.34 (1H, dd, J=10, 4 Hz), 4.32 (2H, s, $PhC\underline{H_2}$), 6.30—6.57 (4H, AA′BB′-type olefinic protons), 7.20 (5H, s-like, Ph). *Anal.* Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.13; H, 7.27.

(7*RS*,8*SR*,11*RS*)-11-Benzyloxymethyl-8-hydroxy-7-methylspiro[5.5]-undeca-1,4-dien-3-one (4) Sodium borohydride (43 mg, 1.13 mmol) was added to a solution of **14** (1.4 g, 4.5 mmol) in MeOH (14 ml) at −30 °C, and the mixture was stirred for 10 min. Saturated $NaHCO_3$ solution was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, dried, and then evaporated. The residue was purified by column chromatography (hexane : AcOEt = 1 : 1) to give **4** (1.1 g, 78%)

and **15** (0.1 g, 7%). **4**: IR ($CHCl_3$): 3600, 3430, 1660, 1618 cm^{-1}. ^{1}H-NMR δ: 0.74 (3H, d, J=7 Hz, C(7)-CH_3), 2.90—3.30 (2H, m, C(11)-CH_2), 3.93 (1H, m, $W_{1/2}$=8 Hz, C(8)-H), 4.27 (2H, s, PhCH_2), 6.28 (2H, br d, J=11 Hz, C(2)-H and C(4)-H), 6.55 and 7.41 (each 1H, dd, J=11, 3 Hz, C(1)-H and C(5)-H), 7.25 (5H, s, Ph). *Anal.* Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.76; H, 7.67. **15**: IR ($CHCl_3$): 3600, 3425, 1665, 1625 cm^{-1}. ^{1}H-NMR δ: 0.84 (3H, d, J=7 Hz, C(7)-CH_3), 3.02 and 3.28 (each 1H, dd, J=10, 7 Hz, C(11)-CH_2), 3.55 (1H, m, $W_{1/2}$=20 Hz, C(8)-H), 4.36 (2H, s, PhCH_2), 6.35 and 6.40 (each 1H, dd, J=10, 2 Hz, C(2)-H and C(4)-H), 6.63 and 6.88 (each 1H, dd, J=10, 4 Hz, C(1)-H and C(5)-H). HRMS Calcd for $C_{20}H_{24}O_3$: 312.172. Found: 312.175.

(7*RS*,11*RS*)-11-Benzyloxymethyl-7-methylspiro[5.5]undecane-3,8-dione (16) A mixture of **14** (300 mg, 0.96 mmol), 10% Pd–C (300 mg), and AcOEt (15 ml) was stirred under 1 atm of H_2 for 20 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by PTLC (hexane : AcOEt = 2 : 1) to give **16** (286 mg, 94%) as a colorless oil. IR ($CHCl_3$): 1705 cm^{-1}. ^{1}H-NMR δ: 1.11 (3H, d, J=7 Hz, C(2)-CH_3), 3.40—3.80 (2H, m, CH_2OBn), 4.55 (2H, s, CH_2Ph), 7.32 (5H, s, aromatic protons). HRMS Calcd for $C_{20}H_{26}O_3$: 314.188. Found: 314.191.

(6*RS*,7*SR*,8*RS*,11*SR*)-8-Hydroxy-11-hydroxymethyl-7-methylspiro-[5.5]undec-1-en-3-one (17) The dienone **4** (80 mg, 0.26 mmol) dissolved in dry THF (0.5 ml) was added to a solution of lithium metal (11 mg, 1.6 mg-atom) in liquid NH_3 (12 ml) at −78 °C. After 5 min, solid NH_4Cl was added to the reaction mixture until the blue color of the solution had disappeared, and ammonia was evaporated off at room temperature. After the addition of water, the mixture was extacted with AcOEt, and the extract was washed with brine, dried, and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to afford **17** (40 mg, 70%) as a colorless oil. IR ($CHCl_3$): 3600, 3430, 1670 cm^{-1}. ^{1}H-NMR δ: 1.01 (3H, d, J=7 Hz, C(7)-CH_3), 3.38—3.82 (2H, m, C(11)-CH_2), 3.92 (1H, m, $W_{1/2}$=8 Hz, C(8)-H), 6.00 and 6.30 (each 1H, d, J=11 Hz, C(2)-H and C(1)-H). HRMS Calcd for $C_{13}H_{20}O_3$: 224.141. Found: 224.141.

(6*RS*,7*SR*,8*RS*,11*SR*)-8-Hydroxy-7-methyl-11-tosyloxymethylspiro-[5.5]undec-1-en-3-one (18) Triethylamine (0.06 ml, 0.43 mmol), *p*-TsCl (55 mg, 0.29 mmol), and 4-dimethylaminopyridine (DMAP) (27 mg, 0.22 mmol) were added to a solution of **17** (50 mg, 0.22 mmol) in $CHCl_3$ (1 ml) at 0 °C, and the mixture was stirred at room temperature for 2 h. After the addition of $NaHCO_3$ solution, the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **18** (61 mg, 73%) as a colorless oil. IR ($CHCl_3$): 3600, 3450, 1675, 1365, 1180 cm^{-1}. ^{1}H-NMR δ: 1.01 (3H, d, J=7 Hz, C(7)-CH_3), 2.42 (3H, s, Ar-CH_3), 3.65—4.15 (2H, m, C(11)-CH_2), 3.96 (1H, m, C(8)-H), 5.95 (1H, d, J=11 Hz, C(2)-H), 6.29 (1H, d, J=11 Hz, C(1)-H), 7.25—7.67 (4H, AA′BB′-type aromatic protons). HRMS Calcd for $C_{20}H_{26}O_5S$: 378.149. Found: 378.149.

(6*RS*,7*SR*,8*RS*,11*SR*)-8-Methoxymethoxy-7-methyl-11-tosyloxymethyl-spiro[5.5]undec-1-en-3-one (19) Diisopropylethylamine (0.04 ml, 0.23 mmol) and MOMCl (0.018 ml, 0.22 mmol) were added to a solution of **18** (60 mg, 0.16 mmol) in CH_2Cl_2 (1 ml) at 0 °C, and the mixture was stirred at room temperature for 7 h. After the addition of saturated $NaHCO_3$ solution, the resulting mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **19** (55 mg, 81%) as a colorless oil. IR (CCl_4): 1690, 1380, 1185 cm^{-1}. ^{1}H-NMR δ: 0.99 (3H, d, J=7 Hz, C(7)-CH_3), 2.43 (3H, s, Ar-CH_3), 3.25 (OCH_2OCH_3), 3.65 (1H, m, $W_{1/2}$=8 Hz, C(8)-H), 4.45—4.55 (2H, AB-q, J=6 Hz, OCH_2OCH_3), 5.85 (1H, d, J=10 Hz, C(2)-H), 6.10 (1H, d, J=10 Hz, C(1)-H), 7.26—7.67 (4H, AA′BB′-type aromatic protons). HRMS Calcd for $C_{22}H_{30}O_6S$: 422.176. Found: 422.176.

(1*RS*,2*RS*,3*SR*,6*SR*,8*SR*)-3-Methoxymethoxy-2-methyltricyclo-[6.3.1.0^{1,6}]dodec-10-en-9-one (20) Potassium *tert*-butoxide (11 mg, 0.098 mmol) was added to a solution of **19** (33 mg, 0.078 mmol) in dry THF (0.3 ml) at 0 °C. After 30 min, water was added, and the resulting mixture was extracted with AcOEt. The extract was washed with brine, dried, and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 2 : 1) to give **20** (19 mg, 97%) as a colorlss oil. IR (CCl_4): 1680 cm^{-1}. ^{1}H-NMR δ: 1.05 (3H, d, J=8 Hz, C(2)-CH_3), 2.70 (1H, m, C(8)-H), 3.30 (3H, s, OCH_2OCH_3), 3.67 (1H, m, $W_{1/2}$=7 Hz, C(3)-H), 4.44—4.58 (2H, AB-q, J=6 Hz, OCH_2OCH_3), 5.63 (1H, dd, J=10, 2 Hz, C(10)-H), 6.58 (1H, dd, J=10, 2 Hz, C(11)-H). HRMS Calcd for $C_{15}H_{22}O_3$: 250.157. Found: 250.156.

(1*RS*,2*RS*,3*SR*,6*SR*,8*SR*)-3-Hydroxy-2-methyltricyclo[6.3.1.0^{1,6}]dodec-10-en-9-one (21) A mixture of **20** (15 mg, 0.06 mmol), 10% HCl (0.1 ml), and acetone (0.2 ml) was stirred at room temperature for 34 h. The mixture was extracted with $CHCl_3$, and the extract was washed with water and brine, dried, and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **21** (11 mg, 91%) as a colorless solid, mp 102.5—103.5 °C. IR ($CHCl_3$): 3610, 3440, 1670 cm^{-1}. ^{1}H-NMR δ: 1.05 (3H, d, J=7 Hz, C(2)-CH_3), 2.27 (1H, ddd, J=12, 5, 2 Hz, C(12)-H), 2.78 (1H, m, C(8)-H), 3.90 (1H, m, $W_{1/2}$=6 Hz, C(3)-H), 5.72 (1H, dd, J=9, 2 Hz, C(10)-H), 6.72 (1H, dd, J=9, 2 Hz, C(11)-H). In pyridine-d_5 δ: 1.14 (3H, d, J=8 Hz, C(2)-CH_3), 2.58 (1H, ddd, J=12, 5, 2 Hz, C(12)-H), 2.88 (1H, m, C(8)-H), 3.86 (1H, m, $W_{1/2}$=6 Hz, C(3)-H), 5.72 (1H, dd, J=9, 2 Hz, C(10)-H), 6.72 (1H, dd, J=9.2 Hz, C(11)-H). HRMS Calcd for $C_{13}H_{18}O_2$: 206.130. Found: 206.130.

(1*RS*,2*RS*,3*SR*,6*SR*,8*SR*)-3-Hydroxy-2-methyltricyclo[6.3.1.0^{1,6}]-dodecan-9-one (6) A mixture of 10% Pd–C (50 mg) in AcOEt (6 ml) was stirred under an H_2 atmosphere for 10 min, then a solution of **21** (104 mg, 0.5 mmol) was added and the resulting mixture was stirred for 2 h under the same atmosphere as above. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **6** (96 mg, 92%) as a colorless solid, mp 114—116 °C (hexane : benzene = 2 : 1). IR ($CHCl_3$): 3160, 3425, 1710 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.10 (3H, d, J=7.3 Hz, C(2)-CH_3), 2.59 (1H, m, C(8)-H), 3.87 (1H, m, C(3)-H). *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.81; H, 9.94.

(1*RS*,6*RS*,8*SR*,11*RS*,12*RS*)-11-Benzyloxymethyl-12-methyl-7-oxatricyclo[6.3.1.0^{1,6}]dodec-2-en-4-one (23) Sodium metal (501 mg, 22 mg-atom) and a catalytic amount of $FeCl_3$ were added to liquid NH_3 (85 ml), and the mixture was refluxed until the blue color of the solution had just disappeared. To the resulting solution was added **4** (850 mg, 2.7 mmol) in THF (2 ml) at −78 °C, and stirring was continued for 2 h. After the addition of solid NH_4Cl, the NH_3 was evaporated at room temperature, and water was added. The mixture was extracted with AcOEt, and the extract was washed with brine, dried, and then evaporated. The residue was purified by column chromatography (hexane : AcOEt = 2 : 1) to give **23** (145 mg, 17%) as a colorless oil, with recovery of the starting material (677 mg, 80%). **23**: IR (CCl_4): 1690 cm^{-1}. ^{1}H-NMR δ: 1.04 (3H, d, J=7 Hz, C(12)-CH_3), 2.35 (1H, dd, J=16, 10 Hz, one of C(5)-H), 2.76 (1H, dd, J=16, 8 Hz, one of C(5)-H), 3.16 (2H, d-like, CH_2OBn), 4.02 (1H, d, J=4 Hz, C(8)-H), 4.25 (2H, s, CH_2Ph), 4.38 (1H, dd, J=10, 8 Hz, C(6)-H), 5.87 (1H, d, J=10 Hz, C(3)-H), 6.51 (1H, d, J=10 Hz, C(2)-H), 7.12 (5H, s, Ph). HRMS Calcd for $C_{20}H_{24}O_3$: 312.173. Found: 312.175.

(1*RS*,6*RS*,8*SR*,11*RS*,12*RS*)-11-Hydroxymethyl-12-methyl-7-oxatricyclo-[6.3.1.0^{1,6}]dodecan-4-one (24) A mixture of **23** (145 mg, 0.46 mmol), 10% Pd–C (140 mg), AcOEt (2.5 ml), and EtOH (2.5 ml) was stirred under 1 atm of H_2 at 40 °C for 36 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by PTLC (hexane : AcOEt = 2 : 1) to give **24** (96 mg, 92%) as a colorless solid, mp 93.0—95.0 °C. IR ($CHCl_3$): 3600, 3425, 1710 cm^{-1}. ^{1}H-NMR δ: 1.15 (3H, d, J=7 Hz, C(12)-CH_3), 2.53 (1H, dd, J=16, 10 Hz, C(5)-H), 2.78 (1H, dd, J=16, 7 Hz, C(5)-H), 4.08 (1H, m, $W_{1/2}$=8 Hz, C(8)-H), 4.35 (1H, dd, J=10, 7 Hz, C(6)-H). *Anal.* Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.33; H, 9.30.

(1*RS*,6*RS*,8*SR*,11*RS*,12*RS*)-11-(1-Ethoxyethoxymethyl)-12-methyl-7-oxatricyclo[6.3.1.0^{1,6}]dodecan-4-one (25) Ethyl vinyl ether (0.1 ml, 1.2 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (2 mg) were added at 0 °C to a solution of **24** (26 mg, 0.12 mmol) in $CHCl_3$ (0.5 ml), and the mixture was stirred at room temperature for 6 h. After the addition of saturated $NaHCO_3$, the mixture was extracted with AcOEt, and the extract was washed with water and brine, dried, and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **25** (32 mg, 90%) as a colorless oil. IR ($CHCl_3$): 1715 cm^{-1}. ^{1}H-NMR δ: 2.51 (1H, dd, J=16, 12 Hz, C(5)-H), 2.74 (1H, dd, J=16, 6 Hz, C(5)-H), 4.06 (1H, m, $W_{1/2}$=6 Hz, C(8)-H), 4.43 (1H, dd, J=12, 6 Hz, C(6)-H), 4.55 (1H, q, J=5 Hz, O–CH–O). HRMS Calcd for $C_{17}H_{28}O_4$: 296.202. Found: 296.201.

(6*RS*,7*RS*,8*SR*,11*RS*)-11-(1-Ethoxyethoxymethyl)-8-hydroxy-7-methyl-spiro[5.5]undec-1-en-3-one (26) A solution of *n*-Bu_4NF in THF (1 M, 0.48 ml, 4.9 mmol) was added to a solution of **25** (96 mg, 3.2 mmol) in THF (5 ml), and the mixture was stirred for 2 h. Water was added and THF was evaporated off. The residue was extracted with AcOEt, and the extract was washed with saturared $NaHCO_3$, water, and brine, dried, and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **26** (43 mg, 40%) with recovery of the starting material (45 mg). **26**: colorless oil. IR ($CHCl_3$): 3600, 3450, 1670 cm^{-1}. ^{1}H-NMR δ: 3.85 (1H, m, $W_{1/2}$=7 Hz, C(8)-H), 4.58 (1H, m, O–CH–O), 6.00 (1H, d, J=11 Hz, C(2)-H), 7.17 (1H, d, J=11 Hz, C(1)-H). HRMS Calcd for $C_{17}H_{28}O_4$:

296.198. Found: 296.201.

Attempted Deprotection of **26**: PPTS (2 mg) was added to a solution of **26** (13 mg, 0.044 mmol) in MeOH (1 ml), and the mixture was stirred for 4 h. After the addition of water, the mixture was extracted with AcOEt. The extract was washed with water and brine, dried, and then evaporated. The residue afforded a tricyclic ether (**27**, 9 mg, 91%). **27**: IR ($CHCl_3$): 1710 cm^{-1}. ^{1}H-NMR δ: 1.17 (3H, d, J=7 Hz), 3.56 (1H, dd, J=8, 4 Hz), 3.8—4.1 (2H, m), 4.70 (1H, t, J=3 Hz).

(1*RS*,6*RS*,8*SR*,11*RS*,12*RS*)-12-Methyl-7-oxa-11-tosyloxymethyltricyclo-[6.3.1.0^{1,6}]dodecan-4-one (29) *p*-TsCl (44 mg, 0.23 mmol) and DMAP (28 mg, 0.23 mmol) were added to a solution of **24** (39 mg, 0.17 mmol) in $CHCl_3$ (1 ml) at 0 °C, and the mixture was stirred at room temperature for 4 h. After the addition of water, the mixture was extracted with AcOEt, and the extract was washed with water and brine, dried and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **29** (55 mg, 85%) as a colorless oil. IR ($CHCl_3$): 1730, 1380, 1180 cm^{-1}. ^{1}H-NMR δ: 1.12 (3H, d, J=7 Hz, C(12)-CH_3), 2.45 (3H, s, Ar-CH_3), 3.74—4.15 (4H, m),7.28—7.68 (4H, AA'BB'-type aromatic protons). HRMS Calcd for $C_{20}H_{26}O_5S$: 378.144. Found: 378.147.

(1*RS*,2*SR*,3*RS*,6*RS*,8*RS*)-3-Hydroxy-2-methyltricyclo[6.3.1.0^{1,6}]dodec-10-en-9-one (30) *tert*-BuOK (34 mg, 0.3 mmol) was added to a stirred solution of **29** (57 mg, 0.15 mmol) in THF (0.6 ml) at −10 °C, and the stirring was continued for 30 min at the same temperature. After the addition of water, the mixture was extracted with AcOEt, and the extract was washed with brine, dried, and then evaporated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **30** (18 mg, 59%) as a colorless solid (mp 99.5—101.0 °C) together with **31** (3 mg, 9%). **30**: IR ($CHCl_3$): 3610, 3450, 1675 cm^{-1}. ^{1}H-NMR δ: 1.13 (3H, d, J=7 Hz, C(2)-CH_3), 2.80 (1H, m, C(8)-H), 4.02 (1H, m, $W_{1/2}$=6 Hz, C(3)-H), 5.85 (1H, dd, J=10, 2 Hz, C(10)-H), 7.81 (1H, dd, J=10, 2 Hz, C(11)-H). In pyridine-d_5 δ: 1.20 (3H, d, J=7 Hz, C(2)-CH_3), 2.87 (1H, m, C(8)-H), 4.10 (1H, m, $W_{1/2}$=6 Hz, C(3)-H), 5.97 (1H, dd, J=10, 2 Hz, C(10)-H), 8.28 (1H, dd, J=10, 2 Hz, C(11)-H). HRMS Calcd for $C_{13}H_{18}O_2$: 206.130. Found: 206.130. **31**: mp 73.0—75.0 °C. IR ($CHCl_3$): 1670, 1610 cm^{-1}. ^{1}H-NMR δ: 1.80 (3H, d, J=7 Hz), 3.52 (1H, br t), 3.80 (1H, d, J=9 Hz), 4.05 (1H, dt, J=9, 2 Hz), 6.00 (1H, d, J=10 Hz), 7.24 (1H, d, J=10 Hz). MS *m/z*: 206 (M^+).

(1*RS*,2*SR*,3*RS*,6*RS*,8*RS*)-3-Hydroxy-2-methyltricyclo[6.3.1.0^{1,6}]-dodecan-9-one (5) A mixture of **30** (7 mg, 0.034 mmol), 10% Pd–C (10 mg), and AcOEt (1 ml) was hydrogenated under 1 atm of H_2 for 23 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was purified by PTLC (hexane : AcOEt = 1 : 1) to give **5** (7 mg, 99%) as a colorless solid, mp 99.0—100.0 °C (from hexane : AcOEt = 5 : 1). IR ($CHCl_3$): 3610, 3425, 1710 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.06 (3H, d, J=7.3 Hz, C(2)-CH_3), 2.67 (1H, m, C(8)-H), 3.88 (1H, m, C(3)-H). *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.80; H, 9.51.

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