Synthetic Studies on Aphidicolane and Stemodane Diterpenes. III.[1] An Alternative Stereoselective Access to Aphidicolane-Type B/C/D-Ring System

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Compound 2, corresponding to the B/C/D-ring for aphidicolane-type diterpenes, was synthesized stereoselectively from a perhydroindane derivative (3) which was obtained by rhodium–alumina catalyzed hydrogenation of an indane ester (4) as a key step.

Keywords aphidicolane; stemodane; tricyclo[6.3.1.0^{1,6}]dodecane; catalytic hydrogenation; *cis*-perhydroindane

In the previous report,[1] we described the stereoselective syntheses of the B/C/D-ring systems of aphidicolane and stemodane diterpenes in the sequence D→B/D→B/C/D. In connection with our strategy for the ring construction sequence,[1] we planned another approach, B/C→B/C/D, for a synthesis of aphidicolin (**1**).[2] From a consideration of the angular protons H_a and H_b in the tricyclic compound (**2**), a *cis*-perhydroindane derivative (**3**) was selected as a precursor of **2**, because intramolecular alkylation of **3** would easily afford **2** stereoselectively. Namely, the C-2 proton (H_c) and C-7a proton (H_d) must be *cis* in compound **3**. Catalytic hydrogenation of the 2-substituted indane derivative (**4**) should afford the required stereochemistry. Namely, the C-7a hydrogen atom (H_d) is expected to be introduced from the opposite side to the C-2 ester group. Furthermore, as the substituent at C-2 becomes bulkier, better stereoselectivity should be obtained. In this paper, we describe a synthesis of the tricyclic compound **2** *via* the stereoselective reduction of the indane derivative (**4**) as a crucial step.

First, a *cis*-perhydroindane derivative (**10**) was synthesized starting from commercially available indanone (**5**). Compound **5** was converted to the methyl ether (**6**), and then transformed into the β-keto ester (**7**) by reaction with dimethyl carbonate and sodium hydride in the presence of a catalytic amount of potassium hydride.[3] Hydrogenolysis of the C-1 ketone (**7**→**8**) followed by hydrolysis with hydrogen bromide afforded the phenolic carboxylic acid (**9**). At this point, in order to make the C-2 substituent bulkier, the carboxylic acid of **9** was converted to a *sec*-butyl ester using *sec*-butyl bromide and diazabicyclo-[5.4.0]undecene (DBU). As expected, rhodium–alumina-catalyzed hydrogenation[4] of **4** at 120 atm/40 °C afforded stereoselectively the desired *cis*-perhydro compound **10** in excellent yield. No diastereomer was detected. The stereochemistry of **10** was confirmed by the formation of the lactone (**11**) *via* hydrolysis of the ester followed by treatment with acetic anhydride and sodium acetate in refluxing benzene.[5] Compound **10** is the only lactonizable compound among the diastereomers.

With the perhydroindane derivative (**10**) having the required stereochemistry in hand, we addressed the task of manipulating the C-2 substituent for the D-ring formation. The hydoxyl group of **10** was protected as the *tert*-butyldimethylsilyl (TBS) ether (**12**), the ester group of which was reduced with lithium aluminum hydride (LAH) to afford the alcohol (**13**). Pyridinium chlorochromate (PCC) oxidation of **13** gave the aldehyde (**14**), which was treated with vinylmagnesium bromide to afford the allylic alcohol (**15**). After the protection of the hydroxyl group as a methoxymethyl (MOM) ether (**15**→**16**), it was found that compound **15** was an inseparable *ca.* 1:1 diastereomeric mixture regarding the newly formed hydroxyl group (corresponding to the C-9 position of **2**). As the separation of the diastereomers was not necessary at this stage, because of the disappearance of the asymmetry in a subsequent step, compound **16** was used for the next step as it was. Hydroboration–oxidation of the olefin of **16** produced the primary alcohol (**17**). The TBS group of **17** was removed with tetrabutylammonium fluoride (TBAF) to give the dihydroxy compound (**18**). Selective oxidation of the secondary alcohol with bromine in the presence of hexamethylphosphoric triamide (HMPA) and sodium bicarbonate[6] afforded a keto-alcohol (**19**). The primary alcohol of **19** was converted to a tosylate (**20**), and it was converted to the bromide by treatment with lithium bromide in acetone to afford the desired keto-bromide (**3**). Finally, **3** was treated with potassium *tert*-butoxide in refluxing benzene to afford the

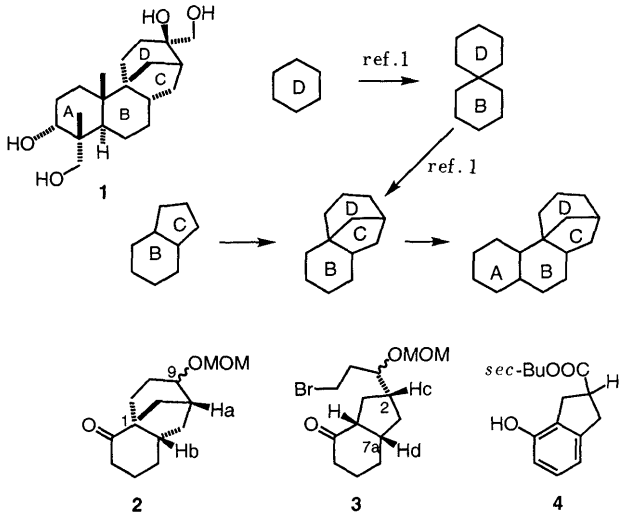

Chart 1

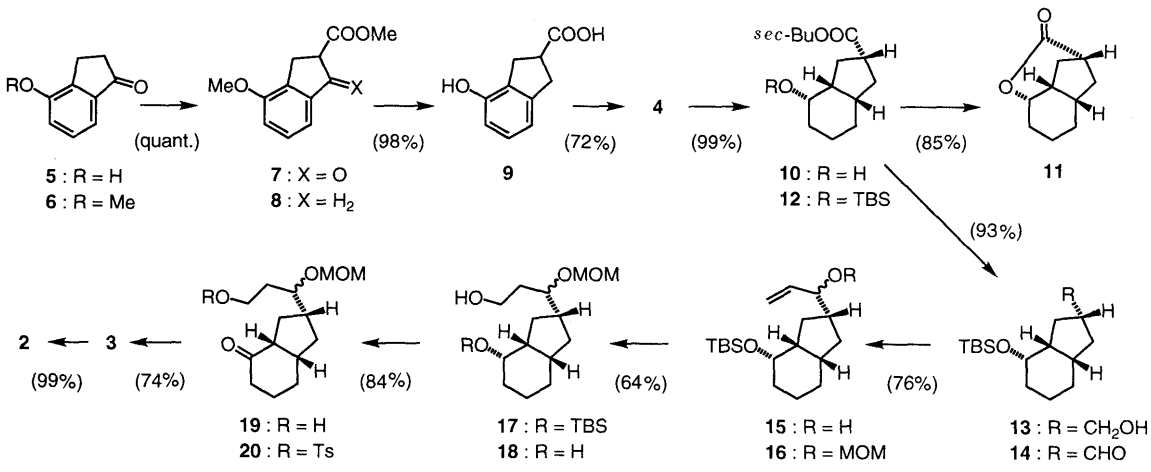

Chart 2

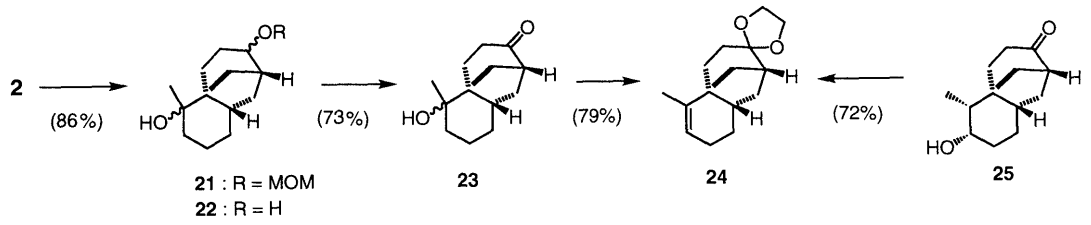

Chart 3

tricyclic compound (**2**)[7] corresponding to the B/C/D-ring system of aphidicolin (**1**).

The structure of **2** was confirmed as follows. Compound **2** was treated with methyllithium to give a diastereomeric mixture of alcohols (**21**). The MOM group of **21** was removed by treatment with aqueous acid to afford the dihydroxy compound (**22**). Compound **22** was oxidized to the keto-alcohol (**23**), which was treated with ethylene glycol in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in refluxing benzene to give a ketal-olefin (**24**) *via* simultaneous ketalization and dehydration. Compound **24** was identical to the compound obtained independently from the known keto-alcohol (**25**)[1] *via* ketalization, mesylation of the alcohol followed by elimination of methanesulfonic acid.

As described above, a new route to the B/C/D-ring system of aphidicolane diterpenes was developed through the stereoselective catalytic hydrogenation of the indane ester derivative (**4**) as a key step.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 or a Horiba FT-210 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in a $CDCl_3$ solution on a Hitachi R-22 (90 MHz), a JEOL JNM-FX90Q (90 MHz), a Varian VXR 200 (200 MHz), or a JEOL JNM-GX500 (500 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. All extracts were dried over anhydrous Na_2SO_4 before evaporation.

Methyl 4-Methoxyindan-2-carboxylate (8) MeI (24.0 ml, 386 mmol) was added dropwise to a mixture of **5** (10.0 g, 67.5 mmol), K_2CO_3 (23 g, 166 mmol), and acetone (600 ml), and the whole was refluxed for 8 h. After the acetone was evaporated off, the residue was extracted with benzene. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane: AcOEt = 5 : 1) to give **6** (10.9 g, 100%) as pale yellow crystals. A small part of a solution of **6** (10.9 g, 67.3 mmol) in tetrahydrofuran (THF) (100 ml) was added to a mixture of NaH (60% in oil, 9.8 g, 245 mmol, pre-washed with hexane and dried), dimethyl carbonate (20.0 ml, 237 mmol), and THF (300 ml), and the whole was refluxed for 15 min, then a small amount of KH was added to initiate the reaction, and the remaining solution of **6** was added dropwise under refluxing. The whole was refluxed for 6 h, and cooled to 0 °C. Ice-water was added slowly until gas evolution ceased, and the whole was acidified with 10% HCl, then extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane: AcOEt = 5 : 1) to give **7** (14.8 g, 100%) as a pale yellow oil. Concentrated HCl (3 ml) and 10% Pd–C (460 mg) were added to a solution of **7** (5.40 g, 24.5 mmol) in MeOH (200 ml), and the whole was stirred under 4 atm of H_2 for 12 h. The catalyst was filtered off, then the filtrate was concentrated. The residue was dissolved in AcOEt, and washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane: AcOEt = 8 : 1) to give **8** (4.97 g, 98%) as colorless crystals, mp 62.5—63.5 °C (from EtOH). IR ($CHCl_3$): 1740, 1600 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 3.1—3.4 (5H, m, $(C\underline{H}_2)_2C\underline{H}COO$), 3.72 (3H, s, OMe), 3.82 (3H, s, COOMe), 6.68 (1H, d, J = 8 Hz, C-7H), 6.83 (1H, d, J = 7.6 Hz, C-5H), 7.15 (1H, dd, J = 7.6, 7.8 Hz, C-6H). MS *m/z*: 206 (M^+, 63), 136 (100). *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.93; H, 6.78.

4-Hydoxyindan-2-carboxylic Acid (9) A mixture of **8** (20.8 g, 101 mmol), 48% HBr (200 ml), and AcOH (200 ml) was refluxed for 4 h. After cooling, the solvent was evaporated off, then water was added and the mixture was extracted with AcOEt. The AcOEt solution was extracted with aqueous $NaHCO_3$ solution, then the extract was acidified with concentrated HCl, and extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by chromatography (AcOEt) to give **9** (18.0 g, 100%) as colorless crystals, mp 154.5–155.5 °C (from iso-PrOH). IR (KBr): 3650—2200, 1705, 1600 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 3.23 (2H, d, J = 8.5 Hz, C-1H), 3.28 (2H, d, J = 6.3 Hz, C-3H), 3.40 (1H, m, C-2H), 6.61 (1H, d, J = 8.5 Hz, C-7H), 6.81 (1H, d, J = 8.5 Hz, C-5H), 7.06 (1H, dd, J = 8.5, 8.5 Hz, C-6H). MS *m/z*: 178 (M^+, 76), 132 (100). *Anal.* Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.13; H, 5.58.

***sec*-Butyl 4-Hydoxyindan-2-carboxylate (4)** *sec*-BuBr (15 ml) was added dropwise to a stirred mixture of **9** (11.0 g, 61.7 mmol), DBU (14 ml, 93.8 mmol) and benzene (250 ml), and the whole was refluxed for 12 h. After cooling, the mixture was washed with water and brine, then

dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 2 : 1) to give **4** (10.4 g, 72%) as a colorless oil. IR ($CHCl_3$): 3575, 1725, 1600 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.90 (3H, t, J = 8 Hz, $CH_2C\underline{H}_3$), 1.22 (3H, d, J = 7 Hz, $CHC\underline{H}_3$), 1.45—1.84 (2H, m, $C\underline{H}_2CH_3$), 4.95 (1H, m, $COOC\underline{H}$–), 6.70 (1H, d, J = 7 Hz, C-5H), 6.86 (1H, d, J = 7 Hz, C-7H), 7.13 (1H, dd, J = 7, 7 Hz, C-6H). MS m/z: 234 (M^+, 34), 132 (100). HRMS Calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1259.

(2*RS*,3a*RS*,4*SR*,7a*SR*)-*sec*-Butyl 4-Hydroxyperhydroindan-2-carboxylate (10) The catalyst, 5% Rh–Al_2O_3 (2.5 g), was added to a solution of **4** (18.0 g, 76.9 mmol) in EtOH (100 ml) and the whole was hydrogenated at 120 atm/40 °C in an autoclave for 8 h. The mixture was filtered, and the filtrate was evaporated to give the residue, which was purified by chromatography (*n*-hexane : AcOEt = 4 : 1) to give **10** (18.0 g, 99%) as a colorless oil. IR ($CHCl_3$): 3600, 1715 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.91 (3H, t, J = 8 Hz, $CH_2C\underline{H}_3$), 1.22 (3H, d, J = 7 Hz, $CHC\underline{H}_3$), 2.88 (1H, m, C-2H), 3.97 (1H, m, C-4H), 4.95 (1H, m, $COOC\underline{H}$–). MS m/z: 240 (M^+, 12), 121 (100). *Anal.* Calcd for $C_{14}H_{24}O_3$: C, 69.93; H, 10.07. Found: C, 69.88; H, 9.98.

(2*RS*,3a*RS*,4*SR*,7a*SR*)-Perhydroindan-2,4-carbolactone (11) NaOH (177 mg) was added to a solution of **10** (265 mg, 1.10 mmol) in EtOH (5 ml), and the whole was stirred for 1 h at room temperature. Water (5 ml) was added, and the mixture was acidified with 10% HCl, and then extracted with AcOEt. The extract was washed with brine, then dried, and evaporated. The residue was dissolved in benzene (10 ml), and then Ac_2O (0.216 ml, 2.2 mmol) and AcONa (45 mg, 0.55 mmol) were added. The whole was refluxed for 3 h. After cooling, the mixture was extracted with AcOEt. The extract was washed with saturated $NaHCO_3$, water and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 2 : 1) to give **11** (156 mg, 85%) as colorless crystals, mp < 30 °C. IR ($CHCl_3$): 1735 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 2.94 (1H, m, C-2H), 4.62 (1H, m, C-4H). MS m/z: 166 (M^+, 4), 81 (100). HRMS Calcd for $C_{10}H_{14}O_2$: 166.0991. Found: 166.0985.

(2*RS*,3a*RS*,4*SR*,7a*SR*)-*sec*-Butyl 4-*tert*-Butyldimethylsilyloxyperhydroindan-2-carboxylate (12) **10** (7.00 g, 29.1 mmol) was dissolved in *N*,*N*-dimethylformamide (DMF) (14 ml), and then imidazole (5.17 g, 75.9 mmol) and TBSCl (5.72 g, 37.9 mmol) were added, and the whole was stirred at room temperature for 3 h. After the addition of water, the whole was extracted with Et_2O. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 20 : 1) to give **12** (9.80 g, 95%) as a colorless oil. IR ($CHCl_3$): 1715 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.02 (6H, s, $SiMe_2$), 0.88 (9H, s, *tert*-Bu), 0.91 (3H, t, J = 8 Hz, $CH_2C\underline{H}_3$), 1.22 (3H, d, J = 7 Hz, $CHC\underline{H}_3$), 2.85 (1H, m, C-2H), 3.95 (1H, m, C-4H), 4.93 (1H, m, $COOC\underline{H}$–). MS m/z: 297 ($M^+ - tert$-Bu). HRMS Calcd for $C_{16}H_{29}O_3Si$ ($M^+ - tert$-Bu): 297.1886. Found: 297.1888.

(2*RS*,3a*RS*,4*SR*,7a*SR*)-4-*tert*-Butyldimethylsilyloxy-2-hydroxymethylperhydroindan (13) LAH (2.5 g, 65.8 mmol) was added portionwise to a solution of **12** (27.8 g, 78.4 mmol) in Et_2O (300 ml), and the mixture was stirred at room temperature for 2 h. Saturated Rochelle salt solution was slowly added to the reaction mixture and the whole was stirred for 1 h, then extracted with AcOEt. The extract was washed with brine, then dried, and evaporated to give **13** (21.9 g, 98%) as a colorless oil. The residue was used for the next reaction without purification. IR ($CHCl_3$): 3600 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.02 (6H, s, $SiMe_2$), 0.88 (9H, s, *tert*-Bu), 3.52—4.21 (3H, m, $C\underline{H}_2OH$ and SiOCH). MS m/z: 227 ($M^+ - tert$-Bu). HRMS Calcd for $C_{12}H_{23}O_2Si$ ($M^+ - tert$-Bu): 227.1467. Found: 227.1478.

(2*RS*,3a*RS*,4*SR*,7a*SR*)-4-*tert*-Butyldimethylsilyloxyperhydroindan-2-carboxaldehyde (14) The crude alcohol (**13**: 5.00 g, 17.6 mmol) was dissolved in CH_2Cl_2 (80 ml), AcONa (1.5 g, 18.3 mmol) was added, and the whole was cooled to 0 °C. To this solution, PCC (7.59 g, 35.2 mmol) was added portionwise, then the whole was stirred for 2 h at room temperature. After dilution with Et_2O, the whole was filtered through a Florisil column and the eluate was concentrated. The residue was passed through a short silica gel column to give crude **14** (4.50 g, 91%) as a colorless oil. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.02 (6H, s, $SiMe_2$), 0.88 (9H, s, *tert*-Bu), 9.43 (1H, d, J = 2 Hz, CHO). MS m/z: 225 ($M^+ - tert$-Bu). HRMS Calcd for $C_{12}H_{21}O_2Si$ ($M^+ - tert$-Bu): 225.1308. Found: 225.1282.

(2*RS*,3a*RS*,4*SR*,7a*SR*)-4-*tert*-Butyldimethylsilyloxy-2-(1-hydroxy-2-propenyl)perhydroindan (15) A solution of the crude aldehyde **14** (4.50 g, 16.0 mmol) in THF (20 ml) was added to vinylmagnesium bromide solution [prepared from vinyl bromide (6.5 g, 60.7 mmol) and Mg (1.5 g, 61.7 mg-atom) in THF (10 ml)] at 0 °C. After 30 min, saturated NH_4Cl 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 chromatography (*n*-hexane : AcOEt = 8 : 1) to give **15** (4.10 g, 83%) as a colorless oil. IR ($CHCl_3$): 3580 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.02 (6H, s, $SiMe_2$), 0.88 (9H, s, *tert*-Bu), 5.41—5.48 (2H, m, $=CH_2$), 6.00 (1H, m, –CH=). MS m/z: 253 ($M^+ - tert$-Bu).

(2*RS*,3a*RS*,4*SR*,7a*SR*)-4-*tert*-Butyldimethylsilyloxy-2-(1-methoxymethoxy-2-propenyl)perhydroindan (16) iso-Pr_2NEt (11.0 ml, 64.7 mmol) was added to a solution of **15** (4.10 g, 13.2 mmol) in CH_2Cl_2 (150 ml), and then MOMCl (4.5 ml, 60.9 mmol) was added, and the whole was stirred overnight at room temperature. Saturated $NaHCO_3$ was added, and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 20 : 1) to give **16** (3.60 g, 77%) as a colorless oil. IR ($CHCl_3$): 1640 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.02 (6H, s, $SiMe_2$), 0.89 (9H, s, *tert*-Bu), 3.44 (3H, s, OMe), 4.52—4.86 (2H, m, OCH_2O), 5.13—5.38 (2H, m, $=CH_2$), 5.73 (1H, m, –CH=). MS m/z: 297 (M^+-*tert*-Bu). HRMS Calcd for $C_{16}H_{29}O_3Si$ ($M^+ - tert$-Bu): 297.1886. Found: 297.1907.

(2*RS*,3a*RS*,7a*SR*)-4-*tert*-Butyldimethylsilyloxy-2-(3-Hydroxy-1-methoxymethoxypropyl)perhydroindan (17) Borane–THF complex (1 M in THF, 39 ml) was added dropwise to a solution of **16** (9.10 g, 25.7 mmol) in THF (50 ml) at 0 °C, and the whole was stirred for 2 h. Ice-water was added slowly until the gas evolution ceased, and then 3 N NaOH (25 ml) and 30% H_2O_2 (25 ml) were added, and the resulting mixture was stirred for 2 h. After salting out with NaCl, the whole was extracted with AcOEt. The extract was washed with saturated $Na_2S_2O_3$ and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 5 : 1) to give **17** (7.90 g, 83%) as a colorless oil. IR ($CHCl_3$): 3475 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 0.04 (6H, s, $SiMe_2$), 0.89 (9H, s, *tert*-Bu), 3.44 (3H, s, OMe), 3.52—3.99 (2H, m, $C\underline{H}_2OH$), 4.73 (2H, s, OCH_2O). MS m/z: 327 ($M^+ - CH_2OCH_3$). HRMS Calcd for $C_{20}H_{40}O_4Si$ (M^+): 372.2693. Found: 372.2688.

(2*RS*,3a*RS*,7a*SR*)-2-(3-Hydroxy-1-methoxymethoxypropyl)perhydroindan-4-ol (18) *n*-Bu_4NF (1 M in THF, 18 ml, 18 mmol) was added to a solution of **17** (2.64 g, 7.10 mmol) in THF (18 ml), and the whole was stirred at 50 °C for 48 h, then cooled with ice-water. Water was added, and the mixture was extracted with AcOEt. The extract was washed with brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 1 : 5) to give **18** (1.81 g, 99%) as a colorless oil. IR ($CHCl_3$): 3450 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 3.38 (3H, s, OMe), 3.50—3.97 (4H, m, $C\underline{H}_2OH$, C-4H, $C\underline{H}$OMOM), 4.67 (2H, s, OCH_2O). MS m/z: 197 ($M^+ - OMOM$). HRMS Calcd for $C_{12}H_{21}O_2$ ($M^+ - OMOM$): 197.1542. Found: 197.1567.

(2*RS*,3a*RS*,7a*SR*)-2-(3-Hydroxy-1-methoxymethoxypropyl)perhydroindan-4-one (19) HMPA (0.74 ml, 4.3 mmol) and 8% $NaHCO_3$ (50 ml) were added to a solution of **18** (3.69 g, 14.3 mmol) in CH_2Cl_2 (70 ml) at 0 °C, and the whole was stirred for 5 min, then Br_2 (3.43 g, 21.5 mmol) in CH_2Cl_2 (10 ml) was added. The resulting mixture was stirred for 15 min, and saturated $Na_2S_2O_3$ was added. The whole was extracted with $CHCl_3$, and the extract was washed with brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 1 : 5) to give **19** (3.11 g, 85%) as a colorless oil. IR ($CHCl_3$): 3480, 1700 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 3.46, 3.48 (total 3H, each s, OMe), 3.62—3.95 (3H, m, $C\underline{H}_2OH$, $C\underline{H}$OMOM), 4.77, 4.80 (total 2H, each s, OCH_2O). MS m/z: 256 (M^+, 0.1), 87 (100). HRMS Calcd for $C_{14}H_{24}O_4$: 256.1675. Found: 256.1688.

(2*RS*,3a*RS*,7a*SR*)-2-(1-Methoxymethoxy-3-tosyloxypropyl)perhydroindan-4-one (20) TsCl (2.30 g, 12.0 mmol) was added to a solution of **19** (1.53 g, 6.00 mmol) in pyridine (10 ml) at 0 °C, and the whole was stirred for 3 h. After the addition of water, the whole was extracted with AcOEt. The extract was washed with saturated $CuSO_4$, water, and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 1:1) to give **20** (1.83 g, 75%) as a colorless oil. IR ($CHCl_3$): 1700, 1600 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 2.42 (3H, s, Ar-$C\underline{H}_3$), 3.29 (3H, s, OMe), 4.14 (2H, t, J = 7 Hz, $C\underline{H}_2OTs$), 4.55, 4.58 (total 2H, each s, OCH_2O), 7.22—7.83 (4H, AA′BB′ type aromatic H). MS m/z: 378 ($M^+ - MeOH$). HRMS Calcd for $C_{20}H_{26}O_5S$ ($M^+ - MeOH$): 378.1498. Found: 378.1488.

(2*RS*,3a*RS*,7a*SR*)-2-(3-Bromo-1-methoxymethoxypropyl)perhydroindan-4-one (3) LiBr (5.10 g, 58.7 mmol) was added to a solution of **20** (4.80 g, 11.7 mmol) in acetone (80 ml) at 0 °C, and the whole was stirred at room temperature for 24 h. After the addition of water, the acetone

was evaporated off, and the residue was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 5 : 2) to give **3** (3.50 g, 98%) as a colorless oil. IR ($CHCl_3$): 3480, 1700 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 3.37 (3H, s, OMe), 3.48 (2H, t, J = 7 Hz, CH_2Br), 4.66, 4.68 (total 2H, each s, OCH_2O). MS *m/z*: 273 ($M^+ - 1$-MeOH), 275 ($M^+ + 1$-MeOH). HRMS Calcd for $C_{12}H_{18}BrO_2$ ($M^+ - 1$-MeOH): 273.0491. Found: 273.0491.

(1*RS*,6*RS*,8*SR*,9*SR*)- and (1*RS*,6*RS*,8*SR*,9*RS*)-9-Methoxymethoxytricyclo[6.3.1.0^{1,6}]dodecan-2-one (2a and 2b) **3** (1.84 g, 6.01 mmol) was added to a mixture of *tert*-BuOK (0.78 g, 6.91 mmol) and benzene (25 ml), and the whole was refluxed for 30 min, then allowed to cool. Water was added, and the resulting mixture was extracted with benzene. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 2 : 1) to give a diastereomeric mixture of **2** (1.42 g, 99%) as a colorless oil. IR ($CHCl_3$): 1700 cm^{-1}. Separation by HPLC (*n*-hexane : AcOEt = 7 : 1) afforded **2a** (α-OMOM). ^{1}H-NMR (500 MHz) δ: 3.35 (3H, s, OMe), 3.62 (1H, ddd, J = 13.4, 3.1, 3.1 Hz, C-9H), 4.62, 4.66 (2H, AB q, J = 6.6, 20 Hz, OCH_2O). MS *m/z*: 238 (M^+, 16), 182 (100). *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.65; H, 9.30. **2b** (β-OMOM): ^{1}H-NMR (500 MHz) δ: 3.32 (3H, s, OMe), 3.55 (1H, m, $W_{1/2}$ = 8 Hz, C-9H), 4.59, 4.62 (2H, AB q, J = 6.7, 15 Hz, OCH_2O). MS *m/z*: 238 (M^+, 16), 182 (100). HRMS Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1568.

Compound **2a** (27 mg, 0.113 mmol) was dissolved in THF (1 ml), then 10% HCl (0.5 ml) was added to the solution, and the whole was heated at 40 °C for 2 h. After evaporation of the THF, the residue was extracted with AcOEt. The extract was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was dissolved in CH_2Cl_2 (1 ml), then PCC (35 mg, 0.162 mmol) was added, and the whole was stirred for 2 h. After the addition of Et_2O (1 ml), the resulting mixture was passed through a Florisil column, and the eluate was evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 1 : 1) to give (1*RS*,6*RS*,8*SR*)-tricyclo[6.3.1.0^{1,6}]dodecane-2,9-dione (19 mg, 88%) as colorless crystals, mp 48.0—49.0 °C (from hexane). IR ($CHCl_3$): 1710 cm^{-1}. ^{1}H-NMR (200 MHz) δ: 1.45 (1H, m), 1.62—2.68 (14H, m), 2.72 (1H, m). MS *m/z*: 192 (M^+, 80), 151 (100). HRMS Calcd for $C_{12}H_{16}O_2$: 192.1151. Found 192.1151. Compound **2b** was converted to the same diketone by a similar procedure.

(1*RS*,6*RS*,8*SR*)-2-Methyltricyclo[6.3.1.0^{1,6}]dodec-2-en-9-one Ethylene Acetal (24) from 2 Excess MeLi was added to a solution of **2** (200 mg, 0.84 mmol) in Et_2O (5 ml) at 0 °C, and the whole was stirred for 1 h. After the addition of saturated NH_4Cl, the resulting mixture was extracted with Et_2O. The extract was washed with brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 2 : 1) to give **21** (182 mg, 86%). Compound **21** (95 mg) was dissolved in acetone, and 10% HCl was added, then the whole was stirred at 40 °C for 2 h. After neutralization with saturated $NaHCO_3$, the acetone was evaporated off, then the residue was extracted with AcOEt. The extract was washed with brine, then dried, and evaporated to give a crude diol **22**, which was dissolved in CH_2Cl_2 (3 ml). PCC (160 mg, 0.74 mmol) was added, and the whole was stirred for 1 h. The reaction mixture was diluted with Et_2O, and the whole was filtered through a Florisil column. The filtrate was evaporated to leave a residue, which was purified by chromatography (*n*-hexane : AcOEt = 3 : 1) to give **23** (57 mg, 73%) as a colorless oil. IR ($CHCl_3$): 3600, 1710 cm^{-1}. ^{1}H-NMR (90 MHz) δ: 1.21 (3H, s, C-2 Me). MS *m/z*: 208 (M^+, 26), 95 (100). HRMS Calcd for $C_{13}H_{20}O_2$: 208.1461. Found: 208.1443. A mixture of **23** (105 mg), ethylene glycol (0.4 ml, 7.2 mmol), and *p*-TsOH (small amount) in benzene (30 ml) was refluxed under a Dean–Stark water separator for 5 h. After cooling, the mixture was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 5 : 1) to give **24** (93 mg, 79%) as a colorless oil. IR ($CHCl_3$): 1645 cm^1. ^{1}H-NMR (90 MHz) δ: 3.73—4.04 (4H, m, OCH_2CH_2O), 5.40 (1H, br s, $W_{1/2}$ = 8 Hz, C-3H). MS *m/z*: 234 (M^+, 2), 99 (100). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.02; H, 9.34.

From 25 A mixture of **25** (140 mg, 0.67 mmol), ethylene glycol (0.4 ml, 7.2 mmol), pyridinium *p*-toluenesulfonate (catalytic amount), and benzene (10 ml) was refluxed for 6 h under a Dean–Stark water separator. After cooling, the mixture was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was dissolved in CH_2Cl_2 (7 ml), and MsCl (0.13 ml, 1.7 mmol) and Et_3N (0.28 ml, 2.0 mmol) were added at 0 °C, then the whole was stirred for 1 h. Saturated $NaHCO_3$ was added, and the whole was extracted with CH_2Cl_2. The extract was washed with brine, then dried, and evaporated. The residue was dissolved in benzene (10 ml), then DBU (0.5 ml, 3.3 mmol) was added, and the whole was refluxed for 4 h. After cooling, the mixture was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 5 : 1) to give **24** (114 mg, 72%), which was identical with the compound obtained from **2**.

References and Notes

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7) The fact that **2** was a diastereomeric mixture (**2a** and **2b**) at the C-9 MOMO group was proven by the fact that each isomer afforded the same tricyclododecane-2,9-dione derivative by the hydrolysis of MOM group followed by PCC oxidation (see Experimental).