Pergamon

Tetrahedron 54 (1998) 1395–1406

TETRAHEDRON

Regiospecific Bromination-Cyclization of Spirocyclic Cyclohexanones and Its Application to the Synthesis of (±)-Laurencial

Kazuyuki Miyashita, Akira Tanaka, Hiroyuki Shintaku, and Chuzo Iwata*

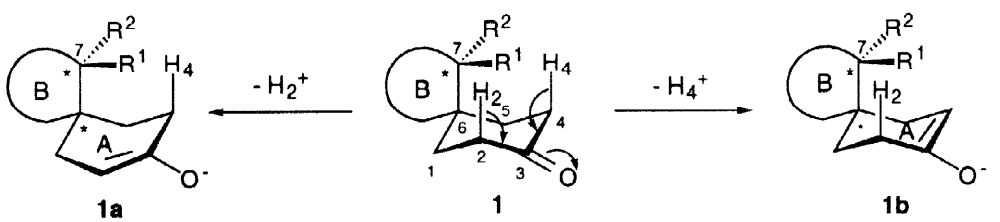
Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565, Japan

Received 29 September 1997; accepted 17 November 1997

Abstract: Stereospecific bromination-cyclization of spirocyclic cyclohexanones having an isopropylidenedioxy group was found to proceed under thermodynamically controlled conditions, which was applied to the first synthesis of (±)-laurencial and its epimer.

Introduction

The stereoselective formation of a quartenary carbon center has been an important and challenging problem in the field of synthetic organic chemistry.[1] We have been interested in the construction of an asymmetric spirocyclic carbon center, as few methodologies addressing this problem are available.[2] As a novel method for this purpose, we planned to examine the regioselective enolization of the spirocyclic cyclohexanone system: the axially oriented substituent at C-4 having an asymmetric center would participate in the regioselectivity of enolization, as shown in Scheme 1. In compounds such as **1**, the rotation of the C6-7 bond is restricted by the B-ring structure. Therefore, one of the substituents at C-7, R^1, or R^2, could be positioned in proximity of the axial hydrogen at C-2 or C-4 and, as a consequence, deprotonation of one of the axial hydrogens (H_2 vs. H_4) would be facilitated, giving rise to **1a** or **1b**, regioselectively. This means that a novel chirality is simultaneously induced at the spiro-carbon atom in a stereoselective manner.

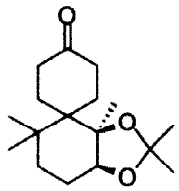


1a **1** **1b**

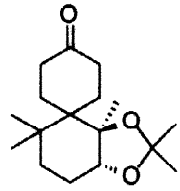
Scheme 1

As a model for this concept, we selected the spirocyclic cyclohexanones having an isopropylidenedioxy group such as **2** and **3**, and we examined the α-bromination of these compounds. In this study, an anomalous cyclization to the tetrahydrofuran derivatives was found to proceed, and we then applied this result to the first synthesis of the chlorinated sesquiterpene, (±)-laurencial (**4a**), isolated from *Laurencia nipponica* by Kurosawa and coworkers,[3] as well as its epimer **4b**.

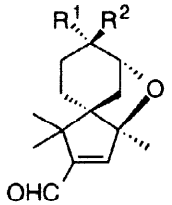
0040-4020/98/$19.00
PII: S0040-4020(97)10378-7



2



3

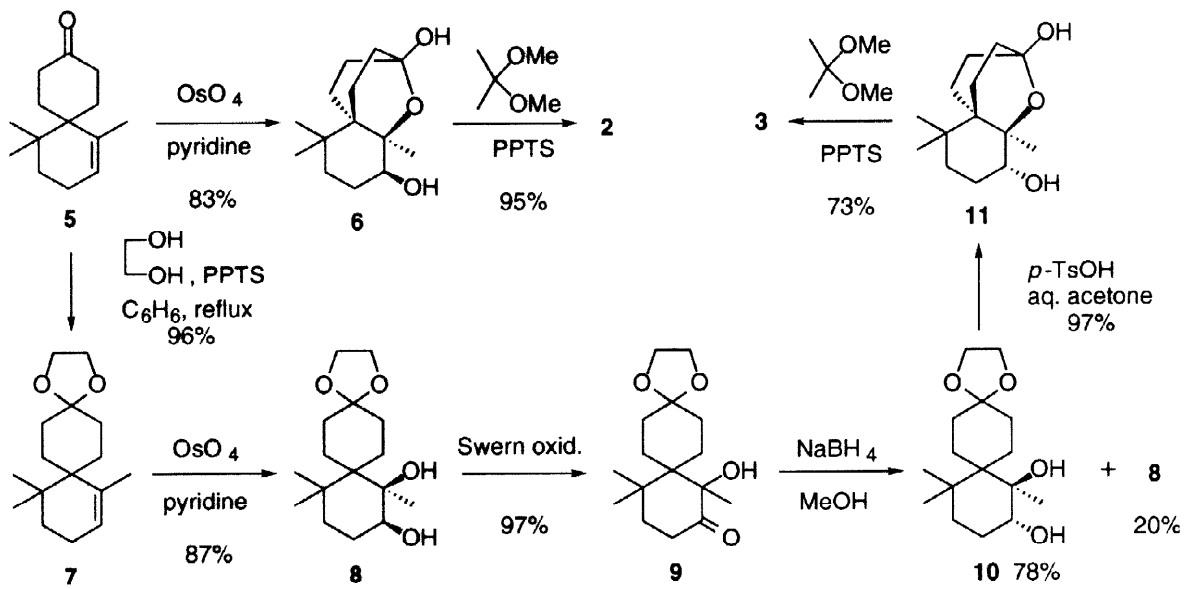


laurencial (**4a**) : R^1 = Cl, R^2 = Me
3-epilaurencial (**4b**) : R^1 = Me, R^2 = Cl

Fig. 1

Results and Discussion

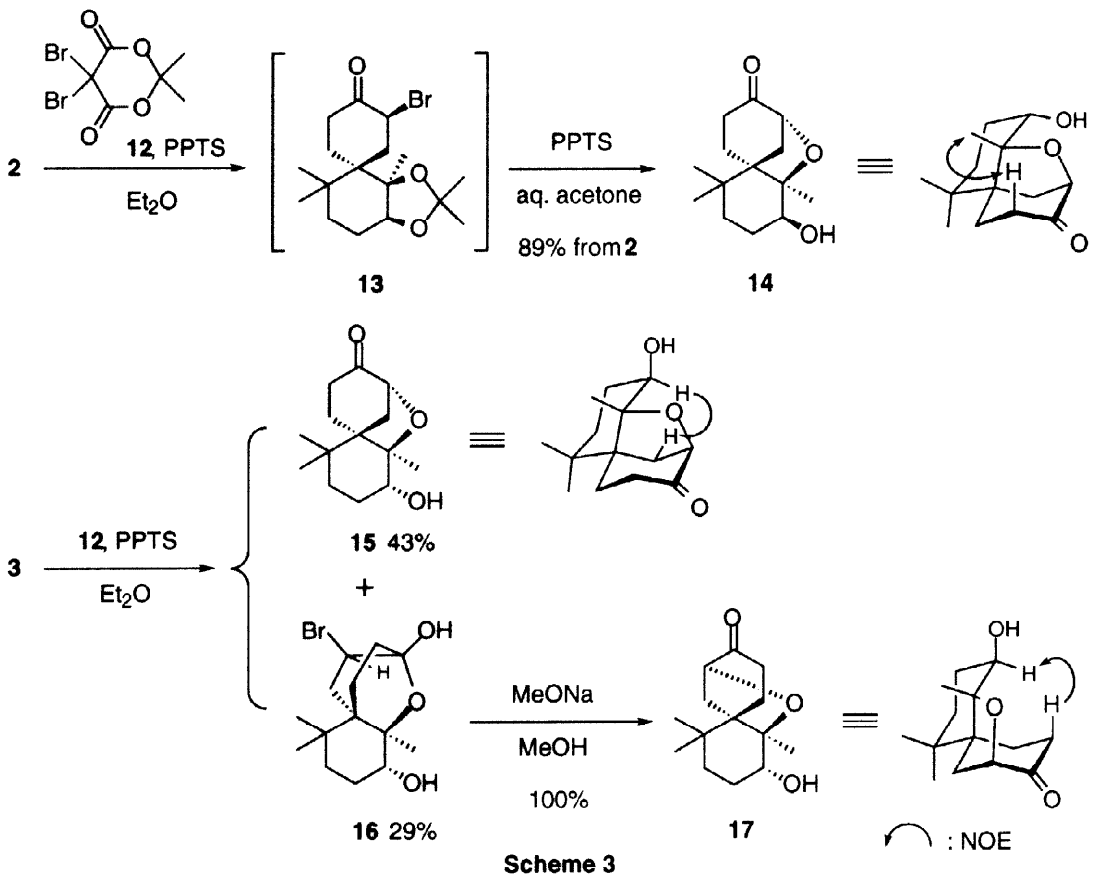
Syntheses of **2** and **3** were achieved starting from **5**[4] as shown in Scheme 2. The *cis*-isomer **2** was obtained in 79% overall yield by *cis*-dihydroxylation with osmium tetroxide, and the subsequent acetonization of **6** was achieved by treatment with 2,2-dimethoxypropane. The *trans*-isomer **3** was also prepared from **5**, which was acetalized and oxidized with osmium tetroxide to afford the *cis*-diol **8** in 84% overall yield. A Swern oxidation[5] of **8** and the subsequent reduction of **9** with $NaBH_4$ afforded the *trans*-diol **10** as a main product in 76% yield, which was deacetalized and then treated with 2,2-dimethoxypropane to give the desired *trans*-isomer **3** in 71% yield.



Scheme 2

The bromination of **2** and **3** under kinetically controlled conditions [treatment with lithium diisopropylamide (LDA) at -78 °C then with Br_2 at -78 °C] afforded a complex mixture of brominated products. However, upon bromination under thermodynamically controlled conditions [treatment with 5,5-dibromo-2,2-dimethyl-1,3-dioxan-4,6-dione (**12**)[6] and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) at room temperature], cyclized compounds were obtained from both compounds **2** and **3**. The reaction of **2** under the described conditions afforded unstable bromide **13**, and a subsequent acidic treatment of **13** without isolation afforded **14** as a single product in good yield. In contrast, the tricyclic compounds **15** and **16** were directly obtained by the reaction of **3** in the ratio of ca. 4 : 3. Although the bromide **13** was not isolated,[7] the

stereochemistries of **13** and **16** were assumed to be as shown from the reaction mechanism described later. Ring transformation of **16** occurred by treatment with a base, yielding the regioisomeric tetrahydrofuran derivative **17** in quantitative yield. The structures of these cyclized compounds **14**, **15**, and **17** were confirmed from spectral evidence. The stereochemistries were assigned based on their NOE differential spectra, and the characteristic NOE data are shown in Scheme 3.



Scheme 3

This regiospecific cyclization obviously takes place *via* an α-bromoketone.[7] Taking into account the thermodynamically controlled reaction conditions, the regiospecificity of the bromination appears to depend on the thermodynamic stability of the regioisomeric enols generated from **2** and **3**. In the compound **2**, the following four conformations appear to exist; (axial C_6-C_7, equatorial C_7-O, axial C_8-O)-, (equatorial C_6-C_7, equatorial C_7-O, axial C_8-O)-, (axial C_6-C_7, axial C_7-O, equatorial C_8-O)-, and (equatorial C_6-C_7, axial C_7-O, equatorial C_8-O)-conformers. Among them, the (axial C_6-C_7, equatorial C_7-O, axial C_8-O)-conformer was suggested to be most likely from the following ^{1}H NMR data: the hydrogen at C-8 was observed at 4.15 ppm with a t-like shape (J = 4.2 Hz); upon irradiation of the hydrogens at C-2 and C-4, the NOE relations were observed with one of the C-7 methyl groups and one of the acetonide methyl groups, respectively. Similarly, although two conformations of **3**, (axial C_6-C_7)- and (equatorial C_6-C_7)-conformers, are possible, the former one was supported from the ^{1}H NMR data. In addition, the easy cyclizations involving the oxygen at C-7 to **14**, **15** and **16** would also support the significant contribution of the conformations of **2** and **3** having an axial C_6-C_7 bond. These findings certainly do not exclude the existence of the other conformations, but apparently suggest that both compounds **2** and **3** have suitable conformations to examine our concept shown in Fig. 1.

Therefore we focused on and analyzed the conformations of **2** and **3** corresponding to that shown in Fig. 1. The (axial C_6-C_7)-conformers of **2** and **3** were minimized by PM3 calculations[8] and are shown in Fig. 2. The thermodynamic stability of the corresponding regioisomeric enols **2a, b** and **3a, b**, which were generated from the conformations of **2** and **3**, were compared by means of PM3 calculations. Although in every case two conformers having s-cis and s-trans enol bonds, respectively, were obtained, a s-cis conformer was always shown to be more stable than the s-trans one. The s-cis conformations of **2a, b** and **3a, b** and the values of the heat of formation for the s-cis and s-trans conformations are shown in Fig. 2. Concerning the regiospecificity, both the enols s-cis and s-trans **2a** generated by the deprotonation of H_2 of the ketone **2** were shown to be more stable than the corresponding regioisomeric enols **2b**. In contrast, this significant difference in the energies of the conformations was not observed between the regioisomeric enols **3a** and **b** generated from the ketone **3**. These findings appear to convincingly explain the experimental results.

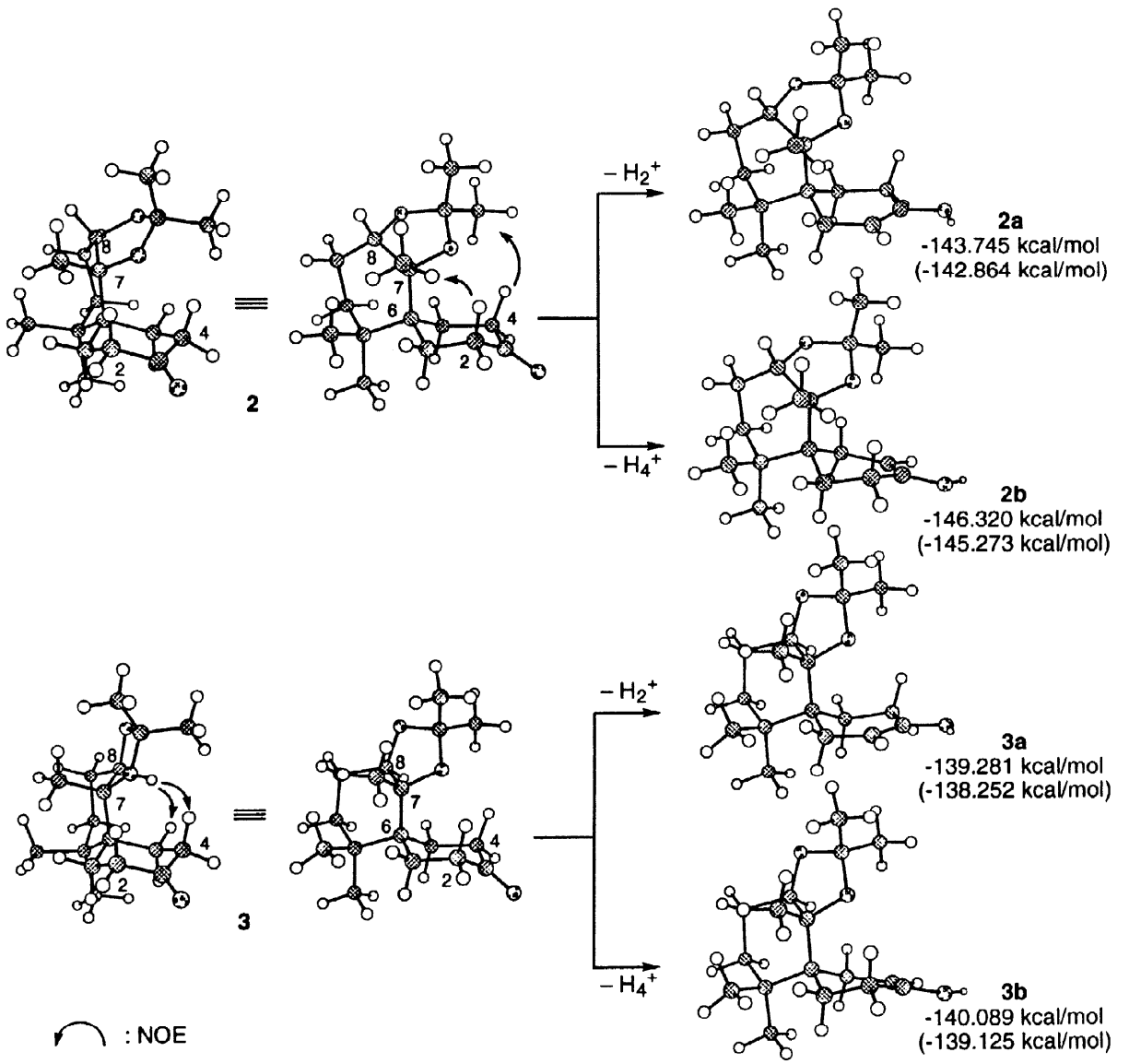


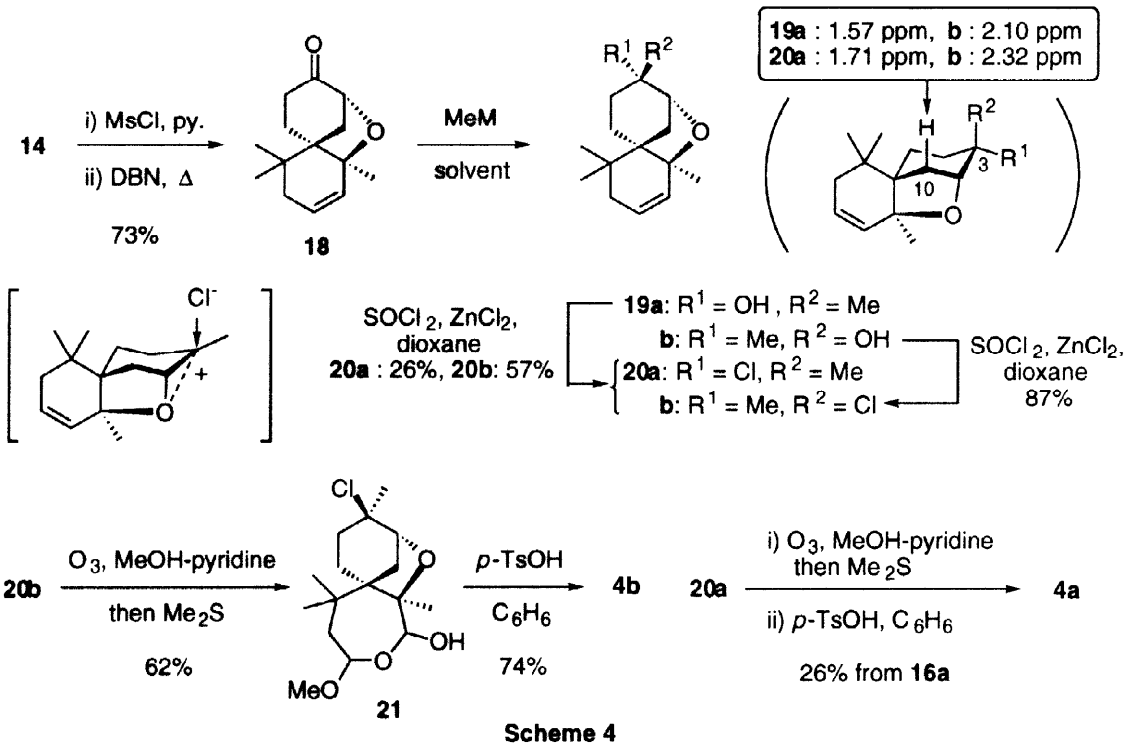
Fig. 2. Conformations of ketones, **2** and **3**, and the enols, **2a, b** and **3a, b**. Only s-cis conformations are shown. The values of heat of formations for the corresponding s-trans conformations are in the parentheses .

Although the factor which produces the differences in stability between the two regioisomeric enols **2a** and **b** is undefined, the distance between the α-hydrogen and the neighboring oxygen might be responsible. In the conformation of **2**, the distances between the oxygen at C-7 and the axial hydrogens (H_2 and H_4) at C-2 and C-4 are 2.70 and 2.31 Å, respectively, while those in the conformation of **3** are 2.55 and 2.38 Å, indicating that the hydrogen closer to the oxygen seems to be deprotonated more easily. These findings suggest that the oxygen could affect the neighboring hydrogen sterically and/or electronically, facilitating the depotonation of one of the two axial hydrogens as a consequence. Although, from the present study, it is impossible to define, the following steric and electronic effects can be proposed: i) the enol, generated by the release of the steric repulsion between the closer hydrogen and the oxygen in the parent ketone, is more stable; ii) the lone pair of the neighboring oxygen works as a base to accelerate the deprotonation of the closer hydrogen. In the former case, the neighboring methyl group as well as the oxygen function would work similarly. In the latter case, not only a distance, but also a direction, would be important. In addition, it is most likely that the attack of the bromonium ion takes place from the less hindered lower side of the respective enols shown in Fig. 2 and, when the oxygen at C-7 occupies a suitable position for the nucleophilic replacement of bromine, a subsequent cyclization would proceed preferably by the acidic treatment or in one pot to afford the corresponding tricyclic derivative **14** or **15**, rather than the α-bromoketones.

Application to the Synthesis of (±)-Laurencial

We applied this methodology to the synthesis of (±)-laurencial (**4a**) and its epimer **4b**, as shown in Scheme 4. Dehydration of **14** by mesylation and its subsequent treatment with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) afforded the olefin **18**. The stereoselectivity of the nucleophilic introduction of the methyl group at C-3 was affected by the organometallic reagent and the solvent used, and the results are outlined in the Table. To our knowledge, there are few reports concerning the stereochemistry of the nucleophilic reaction of cyclohexanones having an axially oriented oxygen function at the α-position.[9] These stereochemical outcomes appear to be clearly explained by considering the following two models shown in Fig. 3.[10] Nucleophilic attack of a bulky reagent formed from methyllithium by solvation with tetrahydrofuran (THF)[11] would proceed from the antiparallel direction of the oxygen at the α-position to afford **19a** (Run 1, non-coordination model). On the other hand, an intramolecular reaction *via* the formation of a complex from **18** and a reagent having a Lewis acidic character (methylmagnesium iodide) in a less basic solvent like ether appears to be favored over an intermolecular nucleophilic attack, giving rise to **19b** (Run 4, coordination model). The stereochemistries of **19a** and **b** were confirmed by comparing their ^1H NMR spectra, in which the axial hydrogen at C-10 of **19b** appeared at a lower field than that of **19a**, due to the deshielding effect of the axial hydroxy group at C-3 as shown. The hydroxy group of **19b** was displaced by chlorine with retention of the stereochemistry at C-3 by treatment with $SOCl_2$ and $ZnCl_2$ in dioxane as reported,[12] to give **20b** in 87% yield. In contrast, the reaction of **19a** under the same conditions unexpectedly afforded an isomeric mixture of **20a** and **b** in the ratio of ca. 1 : 2, which could be explained by taking into account the participation of the neighboring oxygen function, as shown in Fig. 4. The stereochemistries of **20a** and **b** were determined similarly to the method described for **19a** and **b**. Transformation of **20b** to (±)-3-epilaurencial (**4b**) was achieved in 46% overall yield by ozonolysis and the subsequent treatment of **21**[13] with acid. Synthesis of (±)-laurencial (**4a**) was also carried out as follows. After chromatographic separation, the

isomer **20a** was transformed in 26% overall yield according to a similar procedure to that described above to afford (±)-laurencial (**4a**), with IR and ^{1}H NMR spectra identical to those of an authentic sample.



Scheme 4

Table Reaction of **18** with MeM

Run	MeM	Solvent	Yield (**19a** : **19b**)
1	MeLi	THF	92 (12 : 1)
2	MeLi	Et_2O	78 (1 : 8)
3	MeMgI	THF	76 (1 : 3)
4	MeMgI	Et_2O	81 (1 : 19)

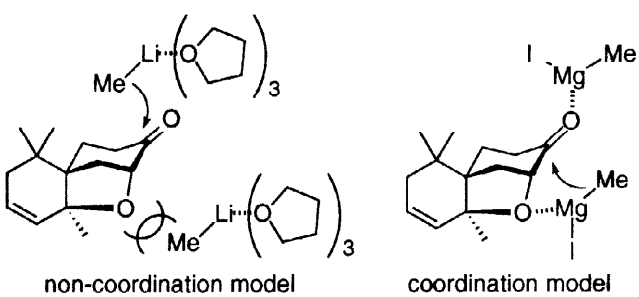


Fig.3

Experimental

Mps measured on a Yanagimoto micromelting point apparatus are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were recorded on a Hitachi R-22 (90 MHz), a JEOL JNM-FX90Q (90 MHz) or a JEOL GX-500 (500 MHz) spectrometer with tetramethylsilane (TMS) as internal standard. *J* values are given in Hz. Low-resolution mass spectra (MS) were obtained with a Shimadzu GCMS-QP1000 or a JEOL JMS-D300 instrument, and high-resolution mass spectra (High-MS) with a JEOL JMS-D300 instrument. For column chromatography, Merck Kieselgel 60 (0.063-0.200 mm) was used.

(8*SR*,8a*RS*)-2,4a-Ethano-3,4,5,6,7,8-hexahydro-2,8-dihydroxy-5,5,8a-trimethylchromene (6) Osmium tetroxide (244 mg, 0.96 mmol) was added to a stirred solution of the olefin **5** (198 mg, 0.96 mmol) in pyridine (4 ml) and the whole was stirred for 3.5 h at 60 °C. After cooling, a solution of sodium bisulfite (500 mg, 4.8 mmol) in H_2O (8 ml) and pyridine (6 ml) was added to the reaction mixture, which was kept stirring for 1 h at room temperature then extracted with AcOEt. The AcOEt layer was washed with H_2O and saturated NaCl

solution, dried over $MgSO_4$, and concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography (C_6H_6-AcOEt, 1:1) to give the diol **6** (90.8 mg, 83%) as colorless crystals, mp 125-127 °C (hexane); IR ($CHCl_3$) ν: 3570, 3400, 2950, 1710 (weak), 1150, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.86, 0.98 (each 3H, s, C_5-Me), 1.38 (3H, s, C_{8a}-Me), 3.10, 3.28 (each 1H, br, OH), 3.62 (1H, m, C_8-H); EI-MS *m/z*: 240 (M^+, 11%); *Anal.* Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 69.84; H, 10.03.

(7*RS*,8*SR*)-7,8-Dihydroxy-7,11,11-trimethylspiro[5.5]undecan-3-one acetonide (2) A catalytic quantity of PPTS was added to a stirred solution of the diol **6** (29.3 mg, 0.12 mmol) in 2,2-dimethoxypropane (3 ml) and the whole was refluxed for 2 h. The reaction mixture was diluted with AcOEt and the organic solution was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6-AcOEt, 5:1) to afford the acetonide **2** (32.6 mg, 95%) as a colorless oil; IR ($CHCl_3$) ν: 1705, 1380, 1265, 1070, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.98, 1.03 (each 3H, s, C_{11}-Me), 1.38, 1.44 (each 3H, s, acetonide Me), 1.50 (3H, s, C_7-Me), 4.15 (1H, t-like, J = 4.2, C_8-H); EI-MS *m/z*: 280 (M^+, 100%); HR-MS *m/z*: Calcd for $C_{17}H_{28}O_3$: 280.2039. Found: 280.2039.

7,11,11-Trimethylspiro[5.5]undec-7-en-3-one ethylene acetal (7) A mixture of **5** (220 mg, 1.1 mmol), ethylene glycol (1.5 ml, 27 mmol), and PPTS (26.0 mg, 0.10 mmol) in C_6H_6 (50 ml) was stirred under refluxing for 2 h with a Dean-Stark trap. After cooling, the reaction mixture was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6) to afford the acetal **7** (258 mg, 96%) as a colorless oil; IR ($CHCl_3$) ν: 2952, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.90 (6H, s, C_{11}-Me), 1.82 (3H, s, C_7-Me), 3.91 (4H, s, acetal H), 5.27 (1H, m, C_8-H); EI-MS *m/z*: 250 (M^+, 13%); HR-MS *m/z*: Calcd for $C_{16}H_{26}O_2$: 250.1933. Found: 250.1939.

(7*RS*,8*SR*)-7,8-Dihydroxy-7,11,11-trimethylspiro[5.5]undecan-3-one ethylene acetal (8) Olefin **7** (201 mg, 0.80 mmol) was treated with osmium tetroxide (204 mg, 0.80 mmol) according to the same method as described for **6**. After purification of the crude product by silica gel column chromatography (C_6H_6-AcOEt, 1:1), diol **8** (200 mg, 87%) was obtained as colorless crystals, mp 139-140 °C (hexane-AcOEt); IR ($CHCl_3$) ν: 3550, 2950, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.99, 1.16 (each 3H, s, C_{11}-Me), 1.42 (3H, s, C_7-Me), 3.55 (1H, m, C_8-H), 3.92 (4H, s, acetal H); EI-MS *m/z*: 284 (M^+, <0.1); *Anal.* Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.44; H, 10.23.

1-Hydroxy-1,5,5-trimethylspiro[5.5]undecan-2,9-dione 9-ethylene acetal (9) Under a nitrogen atmosphere, a CH_2Cl_2 solution of oxalyl chloride (0.46 M, 0.43 ml, 0.20 mmol) was added dropwise to a stirred solution of **8** (49.5 mg, 0.17 mmol) in CH_2Cl_2 at -78 °C and stirring was continued for 5 min at the same temperature. Dimethyl sulfoxide (0.56 M in CH_2Cl_2, 0.63 ml, 0.35 mmol) and, after 30 min, triethylamine (1.77 M in CH_2Cl_2, 0.53 ml, 0.94 mmol) were added dropwise to the reaction mixture at -78 °C. The whole mixture was gradually warmed to room temperature and then poured into a saturated $NaHCO_3$ solution After extraction with AcOEt, the organic layer was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt, 3:2) to give the ketone **9** (47.6 mg, 97%) as colorless crystals, mp 71-72 °C; IR ($CHCl_3$) ν: 3470, 2980, 1705, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.05, 1.91 (each 3H, s, C_5-Me), 1.46 (3H,

s, C_1-Me), 3.91 (4H, s, acetal H), 4.20 (1H, s, OH); EI-MS *m/z*: 282 (M^+, 2.5); HR-MS *m/z*: Calcd for $C_{16}H_{26}O_4$: 282.1831. Found: 282.1831.

(7*RS*,8*RS*)-7,8-Dihydroxy-7,11,11-trimethylspiro[5.5]undecan-3-one ethylene acetal (10) To a stirred solution of **9** (103 mg, 0.37 mmol) in methanol (5 ml) was added $NaBH_4$ (21.0 mg, 0.56 mmol) under ice-cooling. After stirred for 15 min at the same temperature, the reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with H_2O and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6-AcOEt, 1:1) to afford **10** (80.7 mg, 78%) as colorless crystals and **8** (21.0 mg, 20%). **10**, mp 128-130 °C; IR ($CHCl_3$) ν: 3480, 1480, 1105, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.99 (6H, s, C_{11}-Me), 1.33 (3H, s, C_7-Me), 3.75 (1H, m, C_8-H), 3.92 (4H, s, acetal H); EI-MS *m/z*: 284 (M^+, 1.1%); HR-MS *m/z*: Calcd for $C_{16}H_{28}O_4$: 284.1988. Found: 284.1991.

(8*RS*,8a*RS*)-2,4a-Ethano-3,4,5,6,7,8-hexahydro-2,8-dihydroxy-5,5,8a-trimethylchromene (11) To a stirred solution of **10** (32.0 mg, 0.11 mmol) in 70% aqueous acetone was added a catalytic amount of *p*-TsOH and the whole was stirred at 55 °C for 21 h. After evaporation of acetone under reduced pressure, the reaction mixture was extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, H_2O, and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) to afford the diol **11** (26.2 mg, 97%) as colorless crystals, mp 84-86 °C; IR ($CHCl_3$) ν: 3420, 2980, 1490, 1145, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.84, 0.99 (each 3H, s, C_5-Me), 1.40 (3H, s, C_{8a}-Me), 3.31, 3.76 (each 1H, br, OH), 4.04 (1H, m, C_8-H); EI-MS *m/z*: 240 (M^+, 4.4%); HR-MS *m/z*: Calcd for $C_{14}H_{24}O_3$: 240.1723. Found: 240.1713.

(7*RS*,8*RS*)-7,8-Dihydroxy-7,11,11-trimethylspiro[5.5]undecan-3-one acetonide (3) Diol **11** (26.2 mg, 0.11 mmol) was treated with 2,2-dimethoxypropane and PPTS according to the same method as described for **2**. The crude product was purified by silica gel column chromatography (C_6H_6-AcOEt, 7:1) to afford the acetonide **3** (22.4 mg, 73%) as colorless crystals, mp 62-63 °C; IR ($CHCl_3$) ν: 2990, 1715, 1470, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.03, 1.07 (each 3H, s, C_{11}-Me), 1.36 (3H, s, C_7-Me), 1.33, 1.46 (each 3H, s, acetonide Me), 3.70 (1H, m, C_8-H); EI-MS *m/z*: 280 (M^+, 13%); HR-MS *m/z*: Calcd for $C_{17}H_{28}O_3$: 280.2039. Found: 280.2033.

(2*RS*,5a*RS*,9*SR*,9a*RS*)-2,3,4,5,6,7,8,9-Octahydro-9-hydroxy-2,5a-methano-6,6,9a-trimethyl-1-benzoxepin-3-one (14) To a stirred solution of acetonide **2** (40.6 mg, 0.14 mmol) in ether (20 ml) were added **12** (43.7 mg, 0.14 mmol) and a catalytic amount of PPTS at room temperature. After being stirred for 16 h at the same temperature, the reaction mixture was washed with H_2O, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over $MgSO_4$ and concentrated under reduced pressure. The resultant residue was immediately dissolved in acetone-H_2O (1 : 1, 20 ml) containing a catalytic amount of PPTS and the whole was stirred for 4 h at room temperature. After evaporation of the acetone under reduced pressure, the aqueous phase was extracted with ether. The ethereal solution was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to afford a crude product, which was purified by silica gel column chromatography (C_6H_6-AcOEt, 1:1) to give **14** (30.8 mg, 89%) as colorless crystals, mp 137-140 °C (hexane); IR ($CHCl_3$) ν: 3580, 1730, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.98, 1.01 (each 3H, s, C_6-Me), 1.41 (3H, s, C_{9a}-Me), 3.63 (1H, m, C_9-H), 4.12 (1H, d, J = 7.9 Hz, C_2-H); EI-MS *m/z*: 238 (M^+, 57%); *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.26; H, 9.62.

(2*RS*,5a*RS*,9a*RS*)-2,3,4,5,6,7,8,9-Octahydro-9-hydroxy-2,5a-methano-6,6,9a-trimethyl-1-benzoxepin-3-one (15) and (2*RS*,4a*SR*,8*RS*,8a*RS*)-3-Bromo-2,4a-ethano-3,4,5,6,7,8-hexahydro-2,8-dihydroxy-5,5,8a-trimethylchromene (16) To a stirred solution of **3** (11.4 mg, 0.041 mmol) in ether were added **12** (12.3 mg, 0.041 mmol) and a catalytic amount of PPTS and the whole was stirred for 50 h at room temperature. The reaction mixture was diluted with ether, washed with H_2O, saturated $NaHCO_3$ solution, and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6-AcOEt, 1:1) to afford **15** (4.2 mg, 43%) and **16** (3.8 mg, 29%). **15**, colorless crystals, mp 117-120 °C; IR ($CHCl_3$) ν: 3580, 3450, 2960, 1730, 1470, 1090 cm^{-1}; ^1H NMR (C_6D_6) δ: 0.48, 0.58 (each 3H, s, C_6-Me), 1.22 (3H, s, C_{9a}-Me), 3.39 (1H, m, C_9-H), 4.05 (1H, d, J = 7.5, C_2-H); EI-MS *m/z*: 238 (M^+, 43%); HR-MS *m/z*: Calcd for $C_{14}H_{22}O_3$: 236.1569. Found: 238.1560. **16**, a colorless oil; IR ($CHCl_3$) ν: 3410, 2940, 1730 (weak), and 1040; ^1H NMR ($CDCl_3$) δ: 0.86, 0.98 (each 3H, s, C_5-Me), 1.37 (3H, s, C_{8a}-Me), 3.46 (1H, br, OH), 3.90-4.38 (2H, m, C_3- and C_8-H); EI-MS *m/z*: 318, 320 (M^+, 0.4%, 0.4%); HR-MS *m/z*: Calcd for $C_{14}H_{23}{}^{79}BrO_3$: 318.0829. Found: 318.0829.

(2*SR*,5a*SR*,9*RS*,9a*RS*)-2,3,4,5,6,7,8,9-Octahydro-9-hydroxy-2,5a-methano-6,6,9a-trimethyl-1-benzoxepin-3-one (17) To a stirred solution of **16** (3.8 mg, 0.012 mmol) was added a methanolic solution of sodium methoxide (0.13 M, 0.19 ml, 0.025 mmol) and the whole reaction mixture was stirred at room temperature for 30 min. After dilution with AcOEt, the organic solution was washed with H_2O and saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to afford **17** (2.9 mg, 100%) as colorless crystals, mp 140-142 °C; IR ($CHCl_3$) ν: 3440, 2950, 1730, 1055 cm^{-1}; ^1H NMR (C_6D_6) δ: 0.55, 0.66 (each 3H, s, C_6-Me), 1.20 (3H, s, C_{9a}-Me), 3.81 (1H, m, C_9-H), 4.11 (1H, d, J = 8.1, C_2-H); EI-MS *m/z*: 238 (M^+, 16%); HR-MS *m/z*: Calcd for $C_{14}H_{22}O_3$: 236.1569. Found: 238.1581.

(2*RS*,5a*RS*,9a*SR*)-2,3,4,5,6,7-Hexahydro-2,5a-methano-6,6,9a-trimethyl-1-benzoxepin-3-one (18) To a stirred solution of **14** (113 mg, 0.47 mmol) in dry pyridine (5 ml) at room temperature was added methanesulfonyl chloride (0.17 ml, 2.2 mmol) dropwise and the whole mixture was stirred for 10 h at the same temperature. The reaction mixture was poured into ice-saturated $NaHCO_3$ solution, and extracted with AcOEt. The combined organic layer was washed with saturated $NaHCO_3$ solution, 2% HCl, H_2O, and saturated NaCl solution, dried, and concentrated under reduced pressure to afford the crude mesylate. Without purification, the crude mesylate was dissolved in DBN (1.4 ml) and the solution was heated at 150 °C for 1.5 h under an argon atmosphere. After being cooled to the room temperature, the reaction mixture was directly applied on silica gel column chromatography (C_6H_6-AcOEt, 20:1) to afford **18** (76.6 mg, 73%) as colorless crystals, mp 70-71 °C (hexane); IR ($CHCl_3$) ν: 2970, 1720, 1380, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.30-5.65 (2 H, m, olefinic protons), 4.03 (1 H, d, J = 7.5, C_2-H), 1.51 (3 H, s, C_{9a}-Me), 1.01 (6 H, s, C_6-Me_2); EI-MS *m/z*: 220 (M^+, 38%); *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 75.85; H, 9.35.

(2*RS*,3*SR*,5a*RS*,9a*SR*)-2,3,4,5,6,7-Hexahydro-3-hydroxy-2,5a-methano-3,6,6,9a-tetramethyl-1-benzoxepin (19a) Methyllithium (1 M in ether, 0.21 ml, 0.21 mmol) was added dropwise to a stirred solution of **18** (45.6 mg, 0.21 mmol) in dry THF (8 ml) under a nitrogen atmosphere at -78 °C and the whole mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ether. The combined ethereal layer was washed with H_2O and saturated NaCl solution, dried, and concentrated under reduced pressure. The residue was purified by silica gel column

chromatography (C_6H_6-AcOEt, 3:1) to afford **19a** (41.6 mg, 85%) as colorless crystals and **19b** (3.5 mg, 7%). : mp 75-78 °C; IR ($CHCl_3$) ν: 3450, 2970, 1390, 1375, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.30-5.50 (2 H, m, olefinic protons), 3.72 (1 H, d, J = 7.0, C_2-H), 1.42, 1.15 (each 3 H, s, C_3- and C_{9a}-Me), 0.95 (6 H, s, C_6-Me_2); EI-MS *m/z*: 236 (M^+, 35%); HR-MS *m/z*: Calcd for $C_{15}H_{24}O_2$: 236.1776. Found: 236.1771.

(2*RS*,3*SR*,5a*RS*,9a*SR*)-2,3,4,5,6,7-Hexahydro-3-hydroxy-2,5a-methano-3,6,6,9a-tetramethyl-1-benzoxepin (19b) Methylmagnesium iodide (1 M in ether, 0.3 ml, 0.3 mmol) was added dropwise to a stirred solution of **18** (13.3 mg, 0.060 mmol) in dry ether (2 ml) under a nitrogen atmosphere at 0 °C and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was worked up according to the same procedure as described above and the resultant residue was purified by silica gel column chromatography (C_6H_6-AcOEt, 5:1) to afford **19b** (11.0 mg, 77%) as colorless crystals and **19a** (0.6 mg, 4%). : mp 76-80 °C; IR ($CHCl_3$) ν: 3450, 2970, 1375, 1045 cm^{-1};^1H NMR ($CDCl_3$) δ: 5.25-5.55 (2 H, m, olefinic protons), 3.67 (1 H, d, J = 5.3, C_2-H), 1.37, 1.25 (each 3 H, s, C_3- and C_{9a}-Me), 0.93, 0.98 (each 3 H, s, C_6-Me_2); EI-MS *m/z*: 236 (M^+, 42%); HR-MS *m/z*: Calcd for $C_{15}H_{24}O_2$: 236.1776. Found: 236.1776.

(2*RS*,3*RS*,5a*RS*,9a*SR*)-3-Chloro-2,3,4,5,6,7-hexahydro-2,5a-methano-3,6,6,9a-tetramethyl-1-benzoxepin-3-one (20b) Thionyl chloride (0.09 ml, 1.2 mmol) was added to a stirred suspension of $ZnCl_2$ (3.0 mg, 0.022 mmol) in a solution of **19b** (52.3 mg, 0.22 mmol) in dry ether (2.9 ml) and dry 1,4-dioxane (2.9 ml) under an argon atmosphere at 0 °C and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with ether, washed with saturated $NaHCO_3$ solution and saturated NaCl solution, dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6-hexane, 1:1) to afford **20b** (49.0 mg, 87%) as a colorless oil; IR ($CHCl_3$) ν: 2960, 1450, 1375, 1275, 1030, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.20-5.55 (2 H, m, olefinic protons), 3.87 (1 H, d, J = 6.2, C_2-H), 1.58, 1.38 (each 3 H, s, C_3- and C_{9a}-Me), 0.99, 0.93 (each 3 H, s, C_6-Me_2); EI-MS *m/z*: 254, 256 (M^+, 75, 26%); HR-MS *m/z*: Calcd for $C_{15}H_{23}{}^{35}ClO$: 254.1438. Found: 254.1425.

(1*RS*,3*RS*,9*RS*,12*RS*)-12-Chloro-4-hydroxy-6-methoxy-3,8,8,12-tetramethyl-2,5-dioxatricyclo-[7.3.1.0^{3,9}]tridecane (21) Dry ozone was passed through a solution of **20b** (20.2 mg, 0.080 mmol) in dry MeOH (5 ml) containing pyridine (0.07 ml, 0.87 mmol) at -78 °C for 1 h. After excess ozone was removed by passing dry nitrogen at -78 °C, dimethyl sulfide (0.2 ml, 2.7 mmol) was added to the reaction mixture at -78 °C and stirring was continued at the same temperature for 1 h, at 0 °C for 5 h, then at room temperature overnight. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ether, washed with H_2O and saturated NaCl solution, dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6-AcOEt, 30:1) to afford **21** (15.7 mg, 62%) as a colorless oil; IR ($CHCl_3$) ν: 3560, 2960, 1450, 1380, 1140, 1100, 1040, 1005, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.96 (1 H, s, C_4-H), 4.60 (1 H, dd, J = 9.2, 5.7, C_6-H), 3.94 (1 H, d, J = 5.7, C_1-H), 3.43 (3 H, s, C_6-OMe), 1.58, 1.39 (each 3 H, s, C_3- and C_{12}-Me), 1.09, 1.01 (each 3 H, s, C_8-Me_2); EI-MS *m/z*: 272, 274 [$(M-CH_3OH-CH_3)^+$, 13, 4%].

(±)-3-Epilaurencial (4b) A solution of (15.7 mg, 0.049 mmol) in dry C_6H_6 (10 ml) containing a catalytic amount of *p*-TsOH was refluxed for 15 min. After cooling, the reaction mixture was washed with saturated $NaHCO_3$ solution, H_2O, and saturated NaCl solution, dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (C_6H_6-AcOEt, 30:1) to afford (±)-3-epilaurencial (9.8 mg, 74%) as colorless crystals, mp 157-161 °C (isopropyl ether); IR ($CHCl_3$) ν: 2950, 1690, 1615, 1455,

1380, 1120, 1030, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.70 (1 H, s, C_{10}-CHO), 6.58 (1H, s, C_8-H), 3.99 (1 H, d, J = 6.2, C_2-H), 1.60, 1.40 (each 3 H, s, C_3- and C_7-Me), 1.21, 1.13 (each 3 H, s, C_{11}-Me_2); EI-MS *m/z*: 268, 270 (M^+, 65, 23%); HR-MS *m/z*: Calcd for $C_{15}H_{21}{}^{35}ClO_2$: 268.1229. Found: 268.1218. .

(2*RS*,3*SR*,5a*RS*,9a*SR*)-3-Chloro-2,3,4,5,6,7-hexahydro-2,5a-methano-3,6,6,9a-tetramethyl-1-benzoxepin (20a) Thionyl chloride (0.07 ml, 0.96 mmol) was added to a stirred suspension of $ZnCl_2$ (2.2 mg, 0.016 mmol) in a solution of **19a** (37.3 mg, 0.16 mmol) in dry 1,4-dioxane (2.5 ml) and the reaction mixture was worked up according to the same procedure as described for the preparation of. Purification by silica gel column chromatography (C_6H_6-hexane, 10:1) afforded **20a** (12.1 mg, 26%) as a colorless oil and **20b** (25.9 mg, 57%). : IR ($CHCl_3$) ν: 2970, 1475, 1385, 1270, 1095, 1075, 1040, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 5.20-5.55 (2 H, m, olefinic protons), 4.01 (1 H, d, J = 7.3, C_2-H), 1.59, 1.48 (each 3 H, s, C_3- and C_{9a}-Me), 0.95 (6 H, s, C_6-Me_2); EI-MS *m/z*: 254, 256 (M^+, 26, 9%); HR-MS *m/z*: Calcd for $C_{15}H_{23}{}^{35}ClO$: 254.1438. Found: 254.1458.

(±)-Laurencial (4a) Dry ozone was passed through a solution of **20a** (5.9 mg, 0.023 mmol) in dry MeOH (1.5 ml) containing pyridine (0.02 ml, 0.25 mmol) at -78 °C for 40 min. After excess ozone was removed by passing dry nitrogen at -78 °C, dimethyl sulfide (0.2 ml, 2.72 mmol) was added to the reaction mixture at -78 °C and stirring was continued at the same temperature for 1 h then at 0 °C for 5 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in ether, washed with H_2O and saturated NaCl solution, dried, and concentrated under reduced pressure. The residue was dissolved in dry C_6H_6 (5 ml) containing a catalytic amount of *p*-TsOH and refluxed for 15 min. The reaction mixture was washed with saturated $NaHCO_3$ solution, H_2O, and saturated NaCl solution, dried, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt, 10:1) to afford (±)-laurencial (**4a**, 1.6 mg, overall 26%) as colorless crystals, ^1H NMR and IR spectra of which were identical with those of authentic sample. : mp 120-121 °C (isopropyl ether); IR ($CHCl_3$) ν: 2930, 1675, 1600, 1240, 1220, 1120, 1080, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.70 (1 H, s, C_{10}-CHO), 6.66 (1H, s, C_8-H), 4.09 (1 H, d, J = 6.7, C_2-H), 1.61, 1.57 (each 3 H, s, C_3- and C_7-Me), 1.18, 1.13 (each 3 H, s, C_{11}-Me_2); EI-MS *m/z*: 268, 270 (M^+, 60, 21%); HR-MS *m/z*: Calcd for $C_{15}H_{21}{}^{35}ClO_2$: 268.1229. Found: 268.1229.

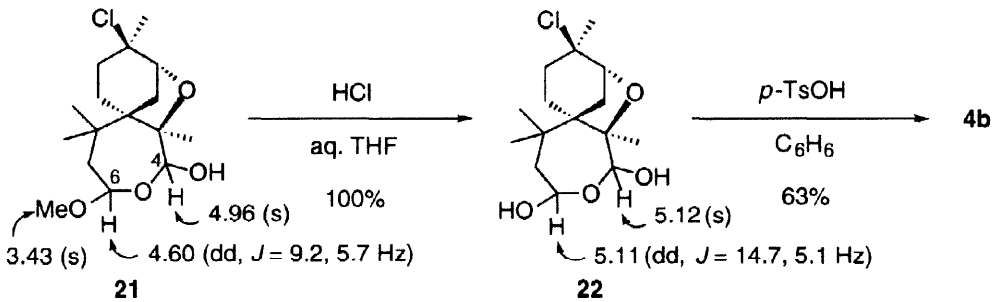
Acknowledgment

We thank Dr. M. Suzuki at Hokkaido University for kindly providing us IR and ^1H NMR spectra of natural laurencial.

References and Notes

1. For review articles, Fuji, K. *Chem. Rev.*, **1993**, *93*, 2037-2066 and references cited therein.
2. McCurry, Jr., P. M.; Singh, R. K. *J. Chem. Soc., Chem. Commun.*, **1976**, 59-60; Martin, S. F. *J. Org. Chem.*, **1976**, *41*, 3337-3338; Iwata, C.; Miyashita, K.; Ida, Y.; Yamada, M. *J. Chem. Soc., Chem. Commun.*, **1981**, 461-463; Iwata, C.; Akiyama, T.; Miyashita, K. *Chem. Pharm. Bull.*, **1988**, *36*, 2872-2877; Tanaka, T.; Okuda, O.; Murakami, K.; Yoshino, H.; Mikamiyama, H.; Kanda, A.; Kim, S.-W.; Iwata, C. *Chem. Pharm. Bull.*, **1995**, *43*, 1017-1023.
3. Kurata, K.; Suzuki, T.; Suzuki, M.; Kurosawa, E.; Furusaki, A.; Matsumoto, T. *Chem. Lett.*, **1983**, 299-300.

4. Iwata, C.; Miyashita, K.; Koga, Y.; Shinoo, Y.; Yamada, M.; Tanaka, T. *Chem. Pharm. Bull.*, **1983**, *31*, 2308-2312.
5. Omura, K.; Swern, D. *Tetrahedron*, **1978**, *34*, 1651-1660; Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.*, **1978**, *43*, 2480-2482.
6. Bloch, R. *Synthesis*, **1978**, 140-142.
7. Several attempts to isolate the bromides, **13** and the precursor of **15**, resulted in failure to afford an unidentified mixture.
8. Stewart, J. J. P. *Comput. Chem.*, **1989**, *10*, 209; Stewart, J. J. P. *Comput. Chem.*, **1989**, *10*, 221.
9. Guillerm-Dron, D.; Capmau, M.-L.; Chodkiewicz, W. *Tetrahedron Lett.*, **1972**, 37-40; Ashby, E. C.; Laemmle, J. T. *Chem. Rev.*, **1975**, *75*, 521-546.
10. Eliel, E. L. In *Asymmetric Synthesis*, Morrison, J. D. Eds.; Academic Press: New York, 1983, Vol. 2; pp 125-155.; Eliel, E. L.; Frye, S. V.; Hortelano, E. R.; Chen, X.; Bai, X. *Pure Appl. Chem.*, **1991**, 63, 1591-1598.
11. Jackman, L. M.; Lange, B. C. *J. Am. Chem. Soc.*, **1981**, *103*, 4494-4499; Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta*, **1981**, *64*, 2617-2621; Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta*, **1981**, *64*, 2622-2626.
12. Squires, T. G.; Schmidt, W. W.; McCandlish, Jr., C. S. *J. Org. Chem.*, **1975**, *40*, 134-136; Iwata, C.; Akiyama, T.; Miyashita, K. *Chem. Pharm. Bull.*, **1988**, *36*, 2878-2886.
13. Although **21** was obtained as a single isomer, and the stereochemistries at C-4 and C-6 were unknown, the methoxy group was assingn to be at C-6 and not at C-4 based on the following observation. Upon acidic treatment in aqueous THF, **21** was transformed to diol **22** in quantitative yield, as shown in Scheme 5. In their ^{1}H NMR spectra, the shift of the hydrogen at C-6 was greater than that of the hydrogen at C-4 due to this reaction, supporting the above assignment. (±)-Epilaurencial (**4b**) was obtained from **22** as well under the same conditions as described for the preparation from **21**.



21 **22**

Scheme 5