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Total Synthesis of Optically Active Cotylenol, a Fungal Metabolite Having a Leaf Growth Activity. Intramolecular Ene Reaction for an Eight-Membered Ring Formation[1]

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Abstract: Starting from condensation of two iridoid synthons, (3*S*,8*R*)-benzyloxy-1-iriden-7-al and (3*R*)-7-chloro-1-iridene, cotylenol, one of the representative fusicoccane diterpenoids having 5-8-5-membered tricyclic carbon framework, is now synthesized for the first time *via* an eight-membered ring formation by an intramolecular ene reaction and subsequent introduction of an α-hydroxyl group.

Introduction

There have been many 5-8-5-membered tricyclic diterpenoids[2,3] and sesterterpenoids[4] isolated from various organisms. These natural products vary stereochemistries of the ring junctures depending on the sources of these compounds. Due to the unique structural elements, total synthesis of these tricyclic higher terpenoids are continuously attracted attentions from synthetic organic chemists. Other than the further bio-transformed metabolites, dictymal,[5] sordaricin,[6] plagiospirolides A and B,[7] and crinipellin B,[8] several natural products of this family have been synthesized up to date; those indeed included were all least substituted derivatives, *i.e.*, cycloaraneosene,[9] hydroxycycloaraneosene,[10] ceroplastols I[11] and II,[12] albolic acid,[12] and ophiobolin C.[13] Since the most of the bio-active metabolites are in the highly oxidized state, synthesizing those oxygenated derivatives are currently a focus of interests. With this regard, the fusicoccins and cotylenins, whose common feature is an 8β,9α-glycol function on the eight-membered ring, are worth to synthesize.

As an extension of our synthetic studies of these tricyclic higher terpenoids, we have now succeeded in stereoselective introduction of the *trans*-glycol function on the tricyclic carbon skeleton to solve the most crucial step in the synthesis.

The direct construction of the tricyclic *trans*-glycol system from various dialdehydic precursors *via* titanium (II) chloride-mediated cyclization[14] has been explored to obtain the requisite 8β,9α-diol system, but it has been hitherto unsuccessful to get the desired cyclization product.

Cotylenins, diterpenoid glycosides isolated from the culture filtrate of an unidentified species of *Cladosporium*, stimulate the growth of cotyledons in Chinese cabbage seedlings,[15] and are structurally related closely to fusicoccins which were isolated as phytotoxic substances responsible to a wilting disease of peach and almond trees.[3,16]

The cotylenins and fusicoccins commonly possess the *trans*-8β,9α-glycol system on their central eight-membered ring and the stereochemistry of this glycol is reported to be important for their unique biological activities.[17] However, since the derivations of this glycol system from natural sources are limited to give only 7-*epi-cis*-8β,9β-isomer,[18] the biological activities of other stereoisomers are not yet clear. Among them, cotylenol (1)[19,20] is the only characterized sugar-free natural product of these classes of compounds; therefore, synthesizing not only 1 but also its stereoisomers of the glycol system are desirable to clarify the structure-activity relationships and the mechanisms of the biological action.

Cotylenol (1)

As has been already reported,[21] the carbon framework of 1 can be constructed *via* an eight-membered ring formation by an ene reaction on an appropriately functionalized *B-seco*-fusicoccane derivative. Herein reported is the first total synthesis[22] of 1 utilizing this methodology, which is potentially applicable for all stereoisomeric glycol functions.
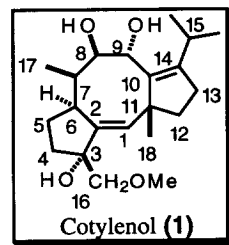
Results and Discussion

Synthesis of (3S)-1,2-Epoxy-6-methoxyirid-8-en-7-al.   At the beginning, the C_{10}-synthon for the A-ring of **1** was derived from (3S)-irida-1,8-dien-7-ol (**2**)[14] as follows. An epoxy alcohol, (3S)-1,2-epoxyirid-8-en-6-ol (**3**),[23] obtained by Sharpless epoxidation[24] of **2**, was consecutively treated with aluminum isopropoxide and *tert*-butyldimethylsilyl (TBS) chloride to form an allylic alcohol (**4a**) and its TBS ether (**4b**). Allyl alcohol **4b** was oxidized by pyridinium chlorochromate (PCC) and was reduced with sodium borohydride to obtain an allylic alcohol (**5a**) and an epoxy alcohol (**6a**). The major product **5a** was then methylated (to **5b**), deprotected (to **5c**), and epoxidized again under the Katsuki-Sharpless conditions[25] to afford an epoxy alcohol (**6c**). The minor product **6a** was also employed to form **6c** by a methylation (to **6b**) and a deprotection procedure. Subsequently, **6c** was oxidized to (3S)-1,2-epoxy-6-methoxyirid-8-en-7-al (**7**) by treating with pyridinium dichromate (PDC).
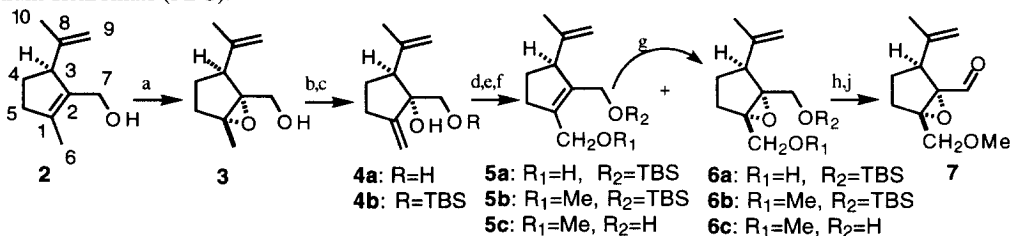
Scheme 1. a) ref. 22; b) Al(i-PrO)₃/toluene; c) TBSCl, imidazole/DMF; d) PCC/CH₂Cl₂; e) NaBH₄/MeOH; f) MeI, NaH/THF; g) Ti(i-PrO)₄, Et₂ tartrate, t-BuO₂H/CH₂Cl₂; h) Bu₄NF/THF; j) PDC/CH₂Cl₂

Low-Valent Chromium Coupling Reaction.   The aldehyde **7** was then condensed with another C_{10}-synthon of the C-ring, (3R)-7-chloroirid-1-ene (**8**)[14] by use of low-valent chromium species[26] in *N,N*-dimethylformamide (DMF) to give a desired condensate, 2α,3α-epoxy-16-methoxy-8,9-secofusicocca-7,9-dien-1α-ol (**9a**), together with 16-methooxy-8,9-secofusicocca-2,7,9-trien-1α-ol (**10a**). The minor product **10a** must be arisen from a deoxygenated Δ²-aldehyde, formed prior to the condensation, since α,β-epoxyaldehydes are very reactive towards reducing agents. The observed stereoselection of α-hydroxy function in **9a** and **10a** is consistent to the previous findings; usually high α-selection was achieved in DMF, *e.g.*, the coupling of **8** and (3S)-8-benzyloxyirid-1-en-7-al (**A**) afforded a 1α-condensate, 8-benzyloxy-8,9-secofusicocca-2,9-dien-1α-ol (**Ba**) in 85% yield over its 1β-epimer (**Bb**, 10% yield). In the present case, the combined yield of **9a** and **10a**, 65%, was not so satisfactory, and failure to characterize 1β-epimers should not necessarily mean their absence. After protecting the secondary hydroxyl of **9a** as a trimethylsilyl (TMS) ether, the site and stereoselective hydroboration[14] on C-8 was performed by 9-borabicyclo[3.3.1]nonane (9-BBN) to afford **11a**. A methanesulfonate **11d**, derived from **11a** in three steps, was reductively converted into **12a** in a moderate yield. In this Birch type reduction step, the addition of iron(III) salt[27] was indispensable to minimize an over-reduction product.
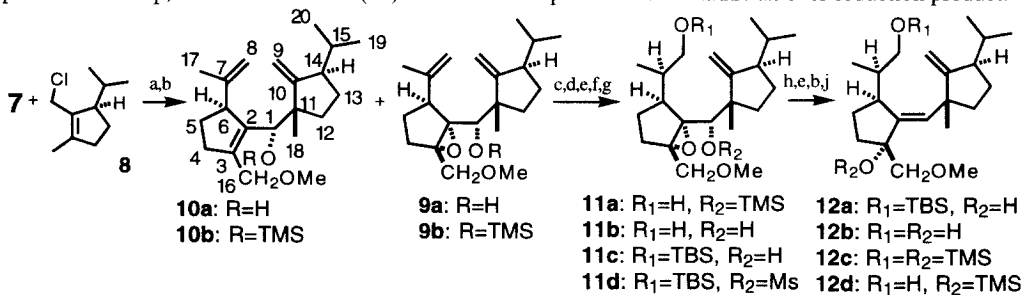

Scheme 2. a) CrCl₃-LAH/THF-DMF; b) TMSCl/pyridine; c) 9-BBN/THF; d) H₂O₂, NaOH; e) Bu₄NF/THF; f) TBSCl, imidazole/DMF; g) MsCl/pyridine; h) Na, FeCl₃/ liq. NH₃; j) PPTS/aq. THF.

Ene Cyclization to Construct the Tricyclic System and Conversion into Cotylenol.   After
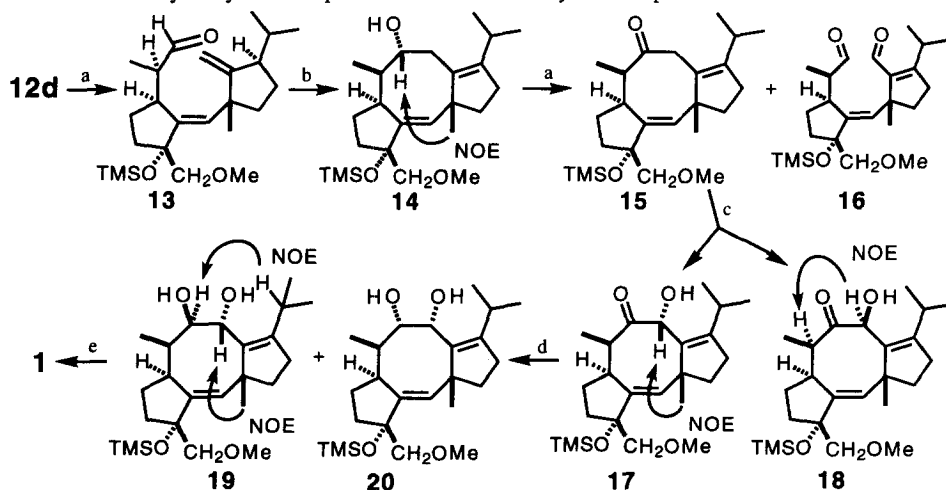
protection of C-3 hydroxyl and deprotection of C-8 hydroxyl of **12a** to **12d**, the aldehyde **13**, the precursor for the ene reaction, was obtained by PDC-oxidation. The thermally-induced ene reaction of **13** occurred in xylene to give a cyclisate, 16-methoxy-3α-(trimethylsilyloxy)fusicocca-1,10(14)-dien-8α-ol (**14**) in a good yield. The α-orientation of C-8 hydroxyl was clarified by the NOE experiment; an enhancement of 8β-H was observed by irradiation of C-11-Me signal. For the observed stereospecific formation of **14**, two points should be taking into account; one is smooth occurrence of the reaction, and this is attributable to the abstraction of 14α-hydrogen from the α-face of the ring C, which is predictable from the stereochemistry of the methyl group on C-11. The other is stereogenesis of 8α-hydroxyl group, and this could be explained in terms of a cyclic mechanism involved; due to the presence of C-1 double bond, the freedom for conformations of the secofusicoccane **13** is quite limited, and only two conformations, **13a** and **13b** (Chart 1) should be taken into account; obviously, **13a** is favorable for the ene reaction, while **13b** is disfavorable in a large steric strain to form the six-membered cyclic transition state of the reaction.

The stereo-chemical outcome of the ene reaction is easily explainable from the molecular orbital calculations (MNDO/PM3[28]) of the transition states with the model compound, which lacks two oxygenous substituents on the C-3 and C-16 in **13**. Thus, there is a large energy difference in two transition states **TSA** and **TSB** of model compound for **13**, a 3-dehydroxy-16-demethoxy-**13** (Figure 1). In **TSA**, which gives a cyclizate with an α-oriented hydroxyl corresponding to **14**, an ideal chair-like six-membered transition structure is realized.

Chart 1. Plausible conformers of **13**.
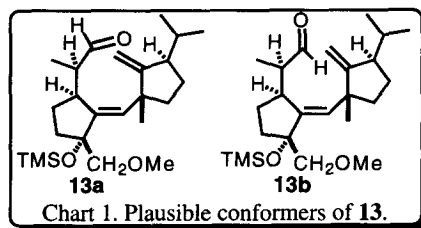
Whereas an alternate transition state **TSB** is clearly more energetic due to having an *anti*-Bredt's-like strain at C-8, a bridge-head carbon of a transient bicyclic system. **13A** forms less energetic transition state, and the transition state from **13B** is more energetic. This should explain the exclusive formation of the product **14**.

For the introduction of C-9 hydroxyl, **14** was oxidized to a ketone **15**. Then the enolate, generated with lithium hexamethyldisilazide (LiHMDS), was oxidized by oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH)[29] to give an isomeric mixture of α- and β-hydroxy ketones (**17** and **18**). The configuration of the C-9 hydroxyl of each product was confirmed by NOE experiments shown in Scheme 3.

Scheme 3. a)PDC/CH₂Cl₂; b) Δ /xylene; c) BuLi, (TMS)₂NH/ THF, MoOPH/THF; d) NaB(OAc)₃H/THF; e) Bu₄NF/THF.

As similar to the model studies,[21] reduction of **17** with sodium triacetoxyborohydride mainly gave a desired *trans*-8β,9α-isomer (**19**) together with a *cis*-8α,9α-isomer (**20**), a minor product. The stereochemistry of **19** was confirmed again by NOE experiments as shown in scheme 3. The conversion of **19** to the target, cotyl-
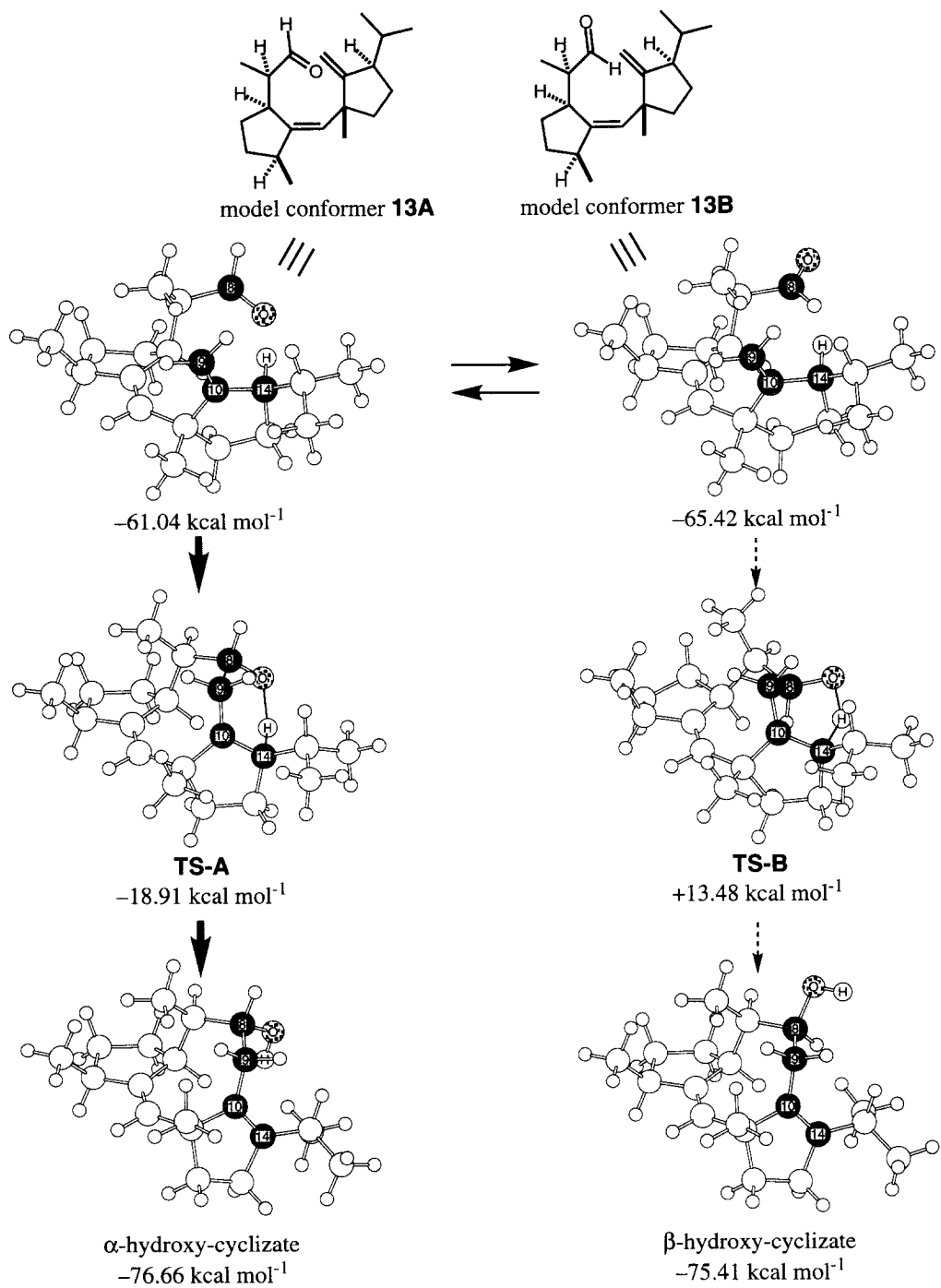
Figure 1. Transition states and heats of formations of ene reaction process of a model for **13** to **14** (MNDO/PM3).

enol (1), simply required a deprotection of TMS ether of C-3 hydroxyl; it was accomplished by an ammonium fluoride treatment. Synthetic 1 [colorless prisms, m.p. 160 °C[19], $[\alpha]_D^{30}$ -30° (lit.[19] -26°)] was identical with natural 1 in respects of direct comparisons of physicochemical properties.

Thus, the first total synthesis of 1 has been completed. Although this synthetic pathway involves several non-stereospecific steps, the by-products obtained are considered to be useful for the synthesis of isomers of 1; e.g., 9β-hydroxy ketone 18 is a promising precursor for the 8β,9β- and 8α,9β-isomers. Since, as mentioned above, those isomeric glycols are of interest in regards of the structure-activity relationships, results on the syntheses and biological activities will be reported in elsewhere.

Experimental

The elemental analyses were carried out by Miss S. Maehata of the Institute of Advanced Material Study, Kyushu University. The melting points were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. The NMR spectra were measured by means of JEOL FX 100 Model and GSX 270H Model spectrometers in CDCl$_3$; the chemical shifts are expressed in δ units. The mass spectra were measured with a JEOL 01SG-2 spectrometer; among the data, only the molecular ion peak, or the nearest peak as the alternative, and the base peak were recorded for each sample. The IR spectra were taken as KBr disks for crystalline compounds or as liquid films inserted between NaCl plates for oily compounds, using a JASCO IR-A102 spectrometer. The stationary phase for column chromatography was Wakogel C-300 and the eluent was a mixture of hexane and EtOAc.

Synthesis of (3S)-7-(tert-Butyldimethylsilyloxy)irida-1(6),8-dien-2-ol (4b). A toluene solution of 3 (6.1 g, 36.4 mmol) was refluxed under an N$_2$ atmosphere in the presence of Al(OCHMe$_2$)$_3$ (18.6 g, 91.0 mmol) for 2 h. The mixture was then fractionated with aq. Na$_2$SO$_4$ and EtOAc. The organic layer was washed with aq. NaHCO$_3$ and aq. NaCl, dried over MgSO$_4$, and evaporated in vacuo. The residue thus obtained was chromatographed on a silica gel column to give a colorless oily allyl alcohol (4a) [5.7 g, 93%; ^{1}H NMR: δ 1.70–1.82 (2H, m), 1.91 (3H, br s), 2.25 (1H, ddm, J=7, 6.5 Hz), 2.45–2.52 (2H, m), 2.58 (1H, dd, J=12, 7.5 Hz), 2.96 (1H, s), 3.30 (1H, dd, J=12, 6.5 Hz), 3.59 (1H, dd, J=12, 6 Hz), 4.83 (1H, br s), 4.92 (1H, br s), 5.06 (1H, tm, J=2 Hz), and 5.14 (1H, tm, J=2.5 Hz); ^{13}C NMR: δ 23.9, 24.8, 28.2, 54.2, 64.5, 82.0, 108.7, 111.4, 144.9, and 154.5; IR: ν 3430, 3100, 2980, 1645, 1440, 1385, 1290, 1160, 1090, 1050, 920, and 880 cm^{-1}], an anhydrous DMF solution (300 cm^3) of which (9.7 g, 57.4 mmol) was then treated with TBSCl (10.4 g, 69 mmol) and imidazole (11.7 g, 172 mmol) at room temperature and stirred for 4 h under an N$_2$ atmosphere. The mixture was then diluted with aq. NaHCO$_3$ and extracted with ether. The organic extract was dried over MgSO$_4$ and evaporated in vacuo. The residue thus obtained was chromatographed on a silica gel column to give 4b [a colorless oil, 15.9 g, 98%; $[\alpha]_D^{30}$ -15.2° (c 1.15, CHCl$_3$); MS m/z(%), 282 (M$^+$, 4.6) and 75 (100); ^{1}H NMR: δ 0.03 (6H, s), 0.89 (9H, s), 1.63-1.79 (2H, m), 1.86 (3H, s), 2.30–2.62 (3H, m), 3.10 (1H, s), 3.33 (1H, d, J=10 Hz), 3.53 (1H, d, J=10 Hz), 4.75 (1H, br s), 4.84 (1H, br s), 5.01 (1H, tm, J=2 Hz), and 5.11 (1H, tm, J=2.5 Hz); ^{13}C NMR: δ -5.7, -5.6, 18.3, 23.5, 25.0, 25.8 (3C), 28.5, 54.6, 65.8, 80.7, 108.3, 111.2, 144.5, and 154.7; IR: ν 3450, 2950, 2850, 1640, 1460, 1250, 1090, 880, and 820 cm^{-1}. Anal. Calcd. for C$_{16}$H$_{30}$O$_2$Si: C, 68.03; H, 10.70%. Found: C, 68.00; H, 10.74%].

Conversion of 4b to (3S)-7-(tert-Butyldimethylsilyloxy)irida-1,8-dien-6-ol (5a), an Allyl Alcohol, and (3S)-7-(tert-Butyldimethylsilyloxy)-1,2-epoxyirid-8-en-6-ol (6a), an Epoxy Alcohol. To a CH$_2$Cl$_2$ solution (500 cm^3) of 4b (15.9 g, 56.1 mmol) was added Celite (37 g) and PCC (36.3 g, 168.3 mmol) and stirred at room temperature for 12 h. The mixture was then diluted with ether and passed through a short Florisil column. The filtrate was evaporated in vacuo and the residue was chromatographed on a silica gel column to give a mixture of aldehydes (12.1 g), which was directly dissolved in MeOH (300 cm^3) and treated with NaBH$_4$ (2.1 g, 50 mmol) in portionwise. After being stirred for 1 h, the mixture was diluted with aq. NaHCO$_3$ and extracted with ether. The extract was dried over MgSO$_4$ and chromatographed on a silica gel column to give 5a [a colorless oil, 6.4 g, 40%; $[\alpha]_D^{29}$ +92.8° (c 3.62, CHCl$_3$); MS m/z (%), 225 ([M–57]$^+$, 35.1) and 133 (100); ^{1}H NMR: δ 0.07 (3H, s), 0.08 (3H, s), 0.90 (9H, s), 1.63 (3H, br s), 1.68 (1H, m), 2.05 (1H, m), 2.31–2.56 (2H, m), 3.27 (1H, br s), 3.36 (1H, m), 4.08 (1H, dm, J=13.5 Hz), 4.21 (dm, J=13.5 Hz), 4.23 (2H, br s), and 4.71 (2H, br s); ^{13}C NMR: δ -5.6, -5.5, 18.2, 19.0, 25.8 (3C), 27.9, 34.6, 56.1, 59.4, 60.0, 110.9, 137.4, 140.7, and 147.3; IR: ν 3450, 2950, 2850, 1650, 1460,

1380, 1260, 1080, 1010, 890, and 820 cm^{-1}] and **6a** [a colorless oil, 140 mg, 8%; $[\alpha]_D^{29}$ +23.3° (c 1.46, CHCl$_3$); MS *m/z*(%), 298 (M$^+$, 0.9), and 241 (100); ^{1}H NMR: δ 0.07 (6H, s), 0.90 (9H, s), 1.43 (1H, m), 1.70 (1H, m), 1.72 (3H, br s), 1.93–2.13 (2H, m), 2.70 (1H, br), 2.91 (1H, d, *J*=8.5 Hz), 3.82 (1H, dd, *J*=12, 5.5 Hz), 3.93 (2H, s), 3.94 (1H, dd, *J*=12, 7.5 Hz), 4.75 (1H, m), and 4.78 (1H, m); ^{13}C NMR: δ −5.8, −5.6, 18.2, 20.6, 25.5, 25.8 (3C), 28.8, 49.4, 61.9, 62.3, 72.1, 72.3, 112.5, and 145.7; IR: ν 3450, 2900, 2850, 1640, 1450, 1250, 1090, 880, and 830 cm^{-1}. Anal. Calcd. for C$_{16}$H$_{30}$O$_3$Si: C, 64.38; H, 10.13%. Found: C, 64.54; H, 10.20%].

Methylation of 5a. Formation of (3S)-7-(*tert*-Butyldimethylsilyloxy)-6-methoxyirida-1,8-diene (5b).   To an anhydrous THF solution (50 cm^3) of **5a** (1.27 g, 4.5 mmol) was added NaH (220 mg, 5.4 mmol) under an N$_2$ atmosphere and stirred for 30 min. Then the mixture was treated with MeI (0.56 cm^3, 9.0 mmol). After being stirred for 12 h, the mixture was diluted with ether, washed with aq. NaCl, dried over MgSO$_4$, and evaporated *in vacuo* to remove the solvent. Silica gel column chromatography of the residue afforded **5b** [a colorless oil, 1.33 g, 100%; ^{1}H NMR: δ 0.03 (3H, s), 0.04 (3H, s), 0.89 (9H, s), 1.64 (3H, br s), 1.67 (1H, m), 2.05 (1H, m), 2.32–2.54 (2H, m), 3.29 (3H, s), 3.49 (1H, dm, *J*=10.5 Hz), 3.99 (1H, dm, *J*=11.5 Hz), 4.09 (2H, br s), 4.24 (1H, dm, *J*=11.5 Hz), and 4.70 (2H, m); ^{13}C NMR: δ −5.4 (2C), 18.4, 19.4, 25.9 (3C), 28.0, 34.0, 54.7, 57.8, 58.1, 68.6, 110.8, 137.1, 140.5, and 147.4. Anal. Calcd. for C$_{17}$H$_{32}$O$_2$Si: C, 68.86; H, 10.88%. Found: C, 68.63; H, 10.81%].

Deprotection of 5b to (3S)-6-Methoxyirida-1,8-dien-7-ol (5c).   An anhydrous THF solution (50 cm^3) of **5b** (1.33 g, 4.5 mmol) was treated with Bu$_4$NF (1 M solution in THF; 5.3 cm^3) for 4 h. The mixture was then diluted with aq. NaHCO$_3$ and extracted with ether. The organic extract was washed with aq. NaCl, dried over MgSO$_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column to give **5c** [a colorless oil, 698 mg, 85%; $[\alpha]_D^{30}$ +155.1° (c 2.14, CHCl$_3$); MS *m/z*(%), 182 (M$^+$, 8.2) and 164 (100); ^{1}H NMR: δ 1.65 (3H, br s), 1.72 (1H, tdd, *J*=13.5, 9, 5 Hz), 2.07 (1H, dtd, *J*=13.5, 9, 7 Hz), 2.33–2.60 (3H, m), 3.35 (3H, s), 3.49 (1H, br m), 4.01 (1H, d, *J*=13 Hz), 4.05 (1H, d, *J*=13.5 Hz), 4.09 (1H, d, *J*=13.5 Hz), 4.19 (1H, d, *J*=13 Hz), and 4.73–4.78 (2H, m); ^{13}C NMR: δ 19.0, 27.8, 34.6, 55.9, 58.2, 58.3, 69.4, 111.3, 137.5, 140.5, and 147.8; IR: ν 3450, 2950, 1640, 1460, 1380, 1100, 1010, and 900 cm^{-1}. Anal. Calcd. for C$_{11}$H$_{18}$O$_2$: C, 72.49; H, 9.95%. Found: C, 72.70; H, 10.04%].

Oxidation of 5c to (3S)-1,2-Epoxy-6-methoxyirid-8-en-7-ol, an Epoxy Alcohol (6c).

To an anhydrous CH$_2$Cl$_2$ suspension (150 cm^3) of Molecular Sieves (4A, 2.1 g) was added diethyl tartrate (0.47 cm^3, 2.76 mmol), Ti(OCHMe$_2$)$_4$ (0.68 cm^3, 2.3 mmol), and anhydrous Me$_3$COOH (7.0 cm^3, 23 mmol) and stirred for 30 min. To the mixture, anhydrous CH$_2$Cl$_2$ solution (10 cm^3) of **5c** (2.1 g, 11.5 mmol) was introduced in dropwise at −20 °C and stirred for 12 h. The mixture was then diluted with 30% NaOH and aq. NaCl, and gradually wormed to room temperature. The organic layer was collected by decantation, dried over MgSO$_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column to give **6c** [a colorless oil, 2.1 g, 100%; $[\alpha]_D^{30}$ +60.0° (c 1.75, CHCl$_3$); MS *m/z*(%), 181 ([M−17]$^+$, 0.9) and 107 (100); ^{1}H NMR: δ 1.44 (1H, ddt, *J*=13, 8, 1.5 Hz), 1.72 (3H, br s), 1.73 (1H, m), 1.91–2.11 (3H, m), 2.97 (1H, br d, *J*=8 Hz), 3.41 (3H, s), 3.72 (2H, s), 3.73 (1H, dd, *J*=12.5, 6.5 Hz), 3.97 (1H, dd, *J*=12.5, 6.5 Hz), and 4.79 (2H, br s); ^{13}C NMR: δ 20.6, 25.4, 28.9, 48.4, 59.3, 59.9, 71.2, 71.6, 72.1, 112.5, and 145.5. Anal. Calcd. for C$_{11}$H$_{18}$O$_3$: C, 66.64; H, 9.15%. Found: C, 66.79; H, 9.18%], which was used directly for the next transformation.

Methylation and Deprotection of 6a. Formation of 6c.   To an anhydrous THF solution (150 cm^3) of **6a** (2.34 g, 7.8 mmol) was added NaH (400 mg, 9.4 mmol) under an N$_2$ atmosphere and stirred for 30 min. Then the mixture was treated with MeI (1.0 cm^3, 16.1 mmol). After being stirred for 12 h, the mixture was diluted with ether, washed with aq. NaCl, dried over MgSO$_4$, and evaporated *in vacuo* to remove the solvent. After silica gel column chromatography of the resultant methyl ether (**6b**) [a colorless oil, 2.37 g, 97%; $[\alpha]_D^{25}$ +39.0° (c 1.42, CHCl$_3$); MS *m/z*(%), 255 ([M−57]$^+$, 52.6) and 223 (100); ^{1}H NMR: δ 0.04 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 1.38 (1H, m), 1.70 (1H, m), 1.72 (3H, br s), 1.86–2.10 (2H, m), 2.95 (1H, d, *J*= 8 Hz), 3.39 (3H, s), 3.61 (1H, d, *J*=11 Hz), 3.64 (1H, d, *J*=11.5 Hz), 3.71 (1H, d, *J*=11 Hz), 4.03 (1H, d, *J*=11.5 Hz), and 4.74 (2H, m); ^{13}C NMR: δ −5.6, −5.4, 18.3, 21.2, 25.6, 25.8 (3C), 28.8, 48.1, 59.2, 61.5, 70.3, 71.9, 72.2, 111.9, and 145.9] was dissolved in an anhydrous THF solution (100 cm^3) and treated with Bu$_4$NF (1 M solution in THF; 9.1 cm^3) while being stirred for 4 h under an N$_2$ atmosphere. The mixture was then diluted with aq. NaHCO$_3$, washed with aq. NaCl, and dried over MgSO$_4$. The organic solu-

tion was evaporated *in vacuo* to remove the solvent, and the residue was chromatographed on a silica gel column to give **6c** (1.34 g, 89%), which was identical with the sample prepared from **5a**.

Preparation of (1S,2R,3S)-2,3-Epoxy-2-formyl-1-methoxyirid-8-ene (7). An anhydrous CH_2Cl_2 solution (150 cm^3) of **6c** (2.0 g, 10.0 mmol) with added Molecular Sieves (4A, 6.5 g) and PDC (5.9 g, 15.8 mmol) was stirred for 12 h under an N_2 atmosphere. The mixture was then diluted with ether and passed through a short Florisil column. After evaporation of the solvent, the residue was chromatographed on a silica gel column to give **7** [a colorless oil, 1.65 g, 84%; $[\alpha]_D^{22}$ -60.0° (c 0.5, $CHCl_3$); ^1H NMR: δ 1.49 (1H, dddd, J=12.5, 5.5, 2.5, 0.5 Hz), 1.77 (1H, m), 1.82 (3H, br s), 2.00–2.15 (2H, m), 3.01 (1H, d, J=8 Hz), 3.38 (3H, s), 3.73 (1H, d, J=11 Hz), 3.77 (1H, d, J=11 Hz), 4.75 (1H, br s), 4.86 (1H, m), and 9.61 (1H, s); ^{13}C NMR: δ 21.9, 26.5, 28.1, 46.2, 59.5, 70.3, 72.0, 75.0, 112.2, 144.7, and 196.2; IR: ν 2850, 1740, 1460, 1100, and 900 cm^{-1}].

Condensation of 7 and (3R)-7-Chloroiri-1-dene (8) to 2α,3α-Epoxy-16-methoxy-8,9-secofusicocca-7,9-dien-1-ol (9a), and 16-Methoxy-8,9-secofusicocca-2,7,9-trien-1-ol (10a). To an anhydrous THF suspension (20 cm^3) of $CrCl_3$ (1.7 g, 11 mmol) was added LAH (210 mg, 5.5 mmol) at 0–5 °C and stirred for 30 min. From the mixture THF was removed by evaporation, and the residue was dissolved in an anhydrous DMF (20 cm^3), to which **8** (940 mg, 5.5 mmol) dissolved in anhydrous DMF (5 cm^3) was introduced and stirred for 2 h. After raising the temperature to 15–20 °C, **7** (360 mg, 1.85 mmol) was added in dropwise and stirred for further 12 h. The mixture was then diluted with water and extracted with ether. The organic extract was washed with aq. NaCl, dried over $MgSO_4$, and chromatographed on a silica gel column to partly give **9a** [colorless needles, m.p. 82 °C; $[\alpha]_D^{25}$ +97° (c 0.35, $CHCl_3$); MS *m/z*(%), 335 ([M+1]$^+$, 38.3), 334 (M$^+$, 38.4), and 317 (100); ^1H NMR: δ 0.77 (3H, d, J=6.5 Hz), 0.99 (3H, d, J=7 Hz), 1.15 (3H, s), 1.25–1.49 (3H, m), 1.58–1.72 (2H, m), 1.72 (3H, br s), 1.85–2.11 (4H, m), 2.53 (1H, m), 2.68 (1H, d, J=5 Hz, OH), 2.77 (1H, br d, J=8 Hz), 3.42 (3H, s), 3.88 (1H, d, J=11 Hz), 3.92 (1H, d, J=11 Hz), 4.07 (1H, d, J=5 Hz), 4.73 (1H, br s), 4.79 (1H, m), 4.86 (1H, d, J=2.5 Hz), and 4.98 (1H, d, J=3 Hz); ^{13}C NMR: δ 16.3, 21.6, 22.1, 22.9, 24.1, 25.6, 28.3, 28.6, 33.7, 50.4, 51.6, 52.3, 59.2, 71.1, 72.1, 72.4, 74.3, 105.7, 112.0, 146.7, and 161.3; IR: ν 3460, 2950, 1640, 1450, 1380, 1100, and 900 cm^{-1}. Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25%. Found: C, 75.50; H, 10.19%] and a mixture of **9a** and **10a** (a colorless oil).

Isolation of 9a and 10a as 2α,3α-Epoxy-16-methoxy-1-trimethylsilyloxy-8,9-secofusicocca-7,9-diene (9b) and 16-Methoxy-1-trimethylsilyloxy-8,9-secofusicocca-2,7,9-diene (10b). The mixture of **9a** and **10a** (464 mg) in an anhydrous pyridine solution (5 cm^3) was treated with TMSCl (1.1 cm^3) and stirred for 12 h. The mixture was then diluted with aq. $NaHCO_3$ and extracted with ether. The organic extract was washed with aq. $KHSO_4$, aq. $NaHCO_3$, and aq. NaCl, dried over $MgSO_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column to give **9b** [a colorless oil, 307 mg, 54%; ^1H NMR: δ 0.11 (9H, s), 0.76 (3H, d, J=7 Hz), 0.99 (3H, d, J=7 Hz), 1.07 (3H, s), 1.16-1.40 (3H, m), 1.55–1.85 (3H, m), 1.73 (3H, br s), 1.92–2.14 (2H, m), 2.29 (1H, m), 2.71 (1H, m), 2.83 (1H, d, J=8 Hz), 3.43 (3H, s), 3.88 (1H, d, J=12 Hz), 3.89 (1H, d, J=12 Hz), 4.25 (1H, s), 4.76 (1H, br s), and 4.83 (3H, m); ^{13}C NMR: δ 1.1 (3C), 15.9, 21.6, 22.1, 22.4, 26.0, 27.2, 27.8, 28.2, 33.0, 50.5, 52.0, 53.5, 58.9, 72.7, 73.1, 75.4, 75.7, 105.3, 112.7, 146.8, and 160.2. Anal. Calcd. for $C_{24}H_{42}O_3Si$: C, 70.88; H, 10.41%. Found: C, 70.74; H, 10.35%] and **10b** [a colorless oil, 180 mg, 33%; $[\alpha]_D^{25}$ +163° (c 1.36, $CHCl_3$); MS *m/z*(%), 256 ([M–134]$^+$, 4.2) and 254 (100); ^1H NMR: δ 0.09 (9H, s), 0.79 (3H, d, J=7 Hz), 0.99 (3H, d, J=6.5 Hz), 1.05 (3H, s), 1.25–1.38 (2H, m), 1.67 (3H, br s), 1.55-2.01 (5H, m), 2.23 (1H, m), 2.38-2.50 (2H, m), 3.34 (1H, m), 3.36 (3H, s), 4.15 (1H, br s), 4.34 (2H, br s), 4.69 (1H, m), 4.73 (1H, m), 4.84 (1H, d, J=2.5 Hz), and 4.93 (1H, d, J=3 Hz); ^{13}C NMR: δ 0.5 (3C), 16.7, 19.5, 22.2, 23.6, 26.2, 28.3, 28.5, 33.2, 33.9, 51.6, 52.0, 57.6, 58.6, 70.7, 77.6, 105.9, 111.2, 139.5, 140.2, 148.3, and 160.1; IR: ν 2900, 2850, 1680, 1490, 1400, 1280, 1130, 1100, 910, and 860 cm^{-1}. Anal. Calcd. for $C_{24}H_{42}O_2Si$: C, 73.78; H, 10.84%. Found: C, 73.67; H, 10.88%].

Hydroboration of the TMS Ether (9b) of 9a. Formation of 2α,3α-Epoxy-16-methoxy-1-trimethylsilyloxy-8,9-secofusicocca-9-en-8-ol (11a). To an anhydrous THF solution (70 cm^3) of **9b** (1.2 g, 3.0 mmol) was added 9-BBN (2.4 g, 10.5 mmol) under an N_2 atmosphere, and stirred for 3 h. The mixture was then treated with 3 M NaOH (52 cm^3) and 35% H_2O_2 (38 cm^3) at 40 °C for 40 min. The mixture was extracted with ether, which was washed with aq. NaCl and dried over $MgSO_4$, and evaporated *in vacuo*. The residue thus obtained was chromatographed on a silica gel column to give **11a** [a colorless oil, 1.1 g, 83%;

$[\alpha]_D^{25}$ +43.5° (c 0.85, CHCl$_3$); MS *m/z*(%), 361 ([M−63]$^+$, 1.1) and 197 (100); ^{1}H NMR: δ 0.07 (9H, s), 0.67 (3H, d, *J*=6.5 Hz), 0.89 (3H, d, *J*=7 Hz), 0.90 (3H, d, *J*=6.5 Hz), 1.03 (3H, s), 1.05–1.43 (5H, m), 1.52 (1H, m), 1.63 (1H, br s, OH), 1.85–1.97 (2H, m), 2.00–2.11 (2H, m), 2.24 (1H, m), 2.62 (1H, m), 3.19 (1H, br t, *J*=9.5 Hz), 3.31 (3H, s), 3.48 (1H, br d, *J*=9.5 Hz), 3.75 (1H, d, *J*=11.5 Hz), 3.77 (1H, d, *J*=11.5 Hz), 4.31 (1H, s), and 4.71 (2H, m); ^{13}C NMR: δ 1.0 (3C), 15.9, 17.0, 20.2, 22.0, 22.4, 27.2, 27.9, 28.7, 33.0, 36.1 49.4, 50.4, 52.1, 58.8, 63.9, 72.9, 73.0, 73.9, 75.3, 105.0, and 160.4; IR: ν 3500, 2950, 1640, 1460, 1260, 1080, 880, and 840 cm^{-1}. Anal. Calcd. for C$_{24}$H$_{44}$O$_4$Si: C, 67.88; H, 10.44%. Found: C, 67.57; H, 10.51%].

Conversion of 11a to 8-(*tert*-Butyldimethylsilyloxy)-16-methoxy-8,9-secofusicocca-1,9-dien-3α-ol (12a) *via* 2α,3α-Epoxy-16-methoxy-8,9-secofusicocc-9-en-1,8-diol (11b), 2α,3α-Epoxy-16-methoxy-8-(*tert*-butyldimethylsilyloxy)-8,9-secofusicocc-9-en-1-ol (11c), and 2α,3α-Epoxy-1-mesyloxy-16-methoxy-8-(*tert*-butyldimethylsilyloxy)-8,9-secofusicocc-9-ene (11d). To an anhydrous THF solution (50 cm^3) of **11a** (1.1 g, 2.5 mmol) was added Bu$_4$NF (1 M solution in THF; 3.8 cm^3) and stirred for 4 h. The mixture was then treated with aq. NaHCO$_3$ and extracted with ether, which was washed with aq. NaCl, dried over MgSO$_4$, and evaporated *in vacuo*. The residue thus obtained was chromatographed on a silica gel column to give a diol **11b** [a colorless oil, 850 mg, 88%; ^{1}H NMR: δ 0.79 (3H, d, *J*=7 Hz), 0.85 (3H, d, *J*=7 Hz), 1.00 (3H, d, *J*=7 Hz), 1.16 (3H, s), 1.30–1.83 (6H, m), 1.87–2.06 (3H, m), 2.12 (1H, dm, *J*=9.5 Hz), 2.37 (1H, m), 2.57 (1H, m), 3.13 (1H, m), 3.40 (3H, s), 3.46 (2H, m), 3.63 (1H, m), 3.83 (1H, d, *J*=10.5 Hz), 3.94 (1H, d, *J*=10.5 Hz), 4.31 (1H,br s), 4.82 (1H, d, *J*=2.5 Hz), and 5.03 (1H, d, *J*=3 Hz); ^{13}C NMR: δ 16.2, 17.1, 19.5, 22.0, 22.9, 24.7, 28.2, 29.6, 33.7, 35.4, 49.2, 50.5, 50.8, 59.0, 64.8, 71.4, 71.8, 72.7, 75.7, 104.9, and 161.9].

To an anhydrous DMF solution (30 cm^3) of **11b** (670 mg, 1.7 mmol) was added imidazole (350 mg, 5.1 mmol) and TBSCl (390 mg, 2.6 mmol) and stirred for 4 h. Then the mixture was diluted with aq. NaHCO$_3$ and extracted with ether, which was washed with aq. NaCl, dried over MgSO$_4$, and evaporated *in vacuo*. The residue thus obtained was chromatographed on a silica gel column to give a mono-TBS ether **11c** [a colorless oil, 790 mg, 100%; $[\alpha]_D^{30}$ +33.0° (c 1.15, CHCl$_3$); MS *m/z*(%), 450 ([M−16]$^+$, 58.0) and 404 (100); ^{1}H NMR: δ 0.06 (3H, s), 0.07 (3H, s), 0.78 (3H, d, *J*=6.5 Hz), 0.91 (9H, s), 0.93 (3H, d, *J*=6.5 Hz), 0.99 (3H, d, *J*=6.5 Hz), 1.17 (3H, s), 1.30–1.55 (4H, m), 1.55–1.72 (2H, m), 1.87–2.07 (3H, m), 2.10–2.20 (2H, m), 2.54 (1H, m), 2.87 (1H, d, *J*=4 Hz), 3.31 (1H, dd, *J*=10.5, 7.5 Hz), 3.40 (3H, s), 3.63 (1H, dd, *J*=10.5, 5.5 Hz), 3.87 (2H, s), 4.20 (1H, d, *J*=4 Hz), 4.83 (1H, d, *J*=2.5 Hz), and 5.03 (1H, d, *J*=3 Hz); ^{13}C NMR: δ −5.4, −5.3, 16.4, 17.1, 18.6, 20.1, 22.1, 23.0, 24.5, 26.1 (3C), 28.4, 29.6, 33.7, 36.4, 48.5, 50.7, 51.2, 59.0, 64.7, 71.7, 71.8, 72.5, 74.7, 105.2, and 161.8; IR: ν 3450, 2950, 1640, 1460, 1360, 1240, 1080, and 820 cm^{-1}. Anal. Calcd. for C$_{27}$H$_{50}$O$_4$Si: C, 69.48; H, 10.80%. Found: C, 69.52; H, 10.76%], an anhydrous pyridine solution (10 cm^3) of which (198 mg, 0.42 mmol) was treated with MsCl (0.13 cm^3) and stirred for 12 h. The mixture was then treated with aq. NaHCO$_3$ and extracted with ether. The organic extract was washed with aq. NaCl, dried over MgSO$_4$, and evaporated *in vacuo*. The residue thus obtained was chromatographed on a silica gel column to give **11d** [a colorless oil; ^{1}H NMR: δ 0.035 (3H, s), 0.041 (3H, s), 0.76 (3H, d, *J*=7 Hz), 0.89 (9H, s), 0.99 (6H, d, *J*=6.5 Hz), 1.22 (3H, s), 1.22–1.48 (3H, m), 1.52–1.74 (3H, m), 1.94–2.08 (2H, m), 2.33–2.46 (2H, m), 2.39 (1H, m), 2.74 (1H, m), 3.04 (3H, s), 3.34 (1H, dd, *J*=10.0, 7.0 Hz), 3.43 (3H, s), 3.68 (1H, dd, *J*=10, 3.5 Hz), 3.70 (1H, d, *J*=11.5 Hz), 4.05 (1H, d, *J*=11.5 Hz), 4.93 (2H, m), and 5.37 (1H, s)].

Finally, to liquid NH$_3$ (30 cm^3) was added Na (11 mg, 0.42 mmol) and FeCl$_3$ (cat. amount) at −78 °C. After the resultant blue coloration was fade away, the solution was treated with Ca (30 mg, 0.70 mmol) while stirring. The solution was diluted with THF (10 cm^3) and was treated with an anhydrous THF solution (4 cm^3) of **11d** (78 mg, 0.14 mmol) for 2 h. The mixture was then treated with PhCOONa and stirred further 8 h. From the mixture, the most of NH$_3$ was removed by vaporization and the residue was diluted with aq. NaHCO$_3$ and extracted ether. The organic extract was dried over MgSO$_4$ and evaporated *in vacuo*. The residue was chromatographed on a silica gel column to give **12a** [a colorless oil, 46 mg, 72%; $[\alpha]_D^{24}$ +40° (c 0.25, CHCl$_3$); MS *m/z*(%), 450 (M$^+$, 100); ^{1}H NMR: δ 0.03 (6H, s), 0.78 (3H, d, *J*=7 Hz), 0.89 (9H, s), 0.92 (3H, d, *J*=7 Hz), 0.98 (3H, d, *J*=6.5 Hz), 1.19 (3H, s), 1.36–2.05 (10H, m), 2.26 (1H, br s, OH), 2.47 (1H, m), 3.04 (1H, br m), 3.30 (2H, s), 3.36 (1H, dd, *J*=9.5, 7 Hz), 3.40 (3H, s), 3.54 (1H, dd, *J*=9.5, 3.5 Hz), 4.80 (1H, d, *J*=2 Hz), 4.90 (1H, d, *J*=3 Hz), and 5.64 (1H, d, *J*=2 Hz); ^{13}C NMR: δ −5.42, −5.37, 16.3, 16.4, 18.4, 22.0, 23.2, 25.96 (4C), 26.02, 28.8, 35.5, 38.2, 39.2, 42.5, 48.7, 49.7, 59.4, 65.8, 79.7, 81.5, 105.2, 135.5,

145.6, and 162.9; IR: ν 3450, 2950, 2850, 1460, 1250, 1100, and 820 cm^{-1}. Anal. Calcd. for $C_{27}H_{50}O_3Si$: C, 71.94; H, 11.18%. Found: C, 71.76; H, 11.06%], together with **12i** [a colorless oil, 5 mg, 10%; ^1H NMR: δ 0.04 (6H, s), 0.78 (3H, d, J=7 Hz), 0.90 (9H, s), 0.96 (3H, d, J=6.5 Hz), 0.98 (3H, d, J=6.5 Hz), 1.23 (3H, s), 1.25–1.85 (8H, m), 1.95–2.08 (2H, m), 2.13–2.25 (1H, m), 2.55–2.70 (2H, m), 3.29 (1H, d, J=9.5 Hz), 3.36 (1H, m), 3.38 (3H, s), 3.53 (1H, d, J=9.5 Hz), 3.59 (1H, dd, J=10, 4 Hz), 4.80 (1H, d, J=2.5 Hz), 4.97 (1H, d, J=3 Hz), and 5.61 (1H, d, J=2 Hz)], a geometrical (Z-) isomer at the C_1=C_2.

Conversion of 12a into 16-Methoxy-3α-(trimethylsilyloxy)-8,9-secofusicocca-1,9-dien-8-ol (12d), *via* 16-Methoxy-8,9-secofusicocca-1,9-dien-3α,8-diol (12b) and 16-Methoxy-3α,8-di(trimethylsilyloxy)-8,9-secofusicocca-1,9-diene (12c). An anhydrous THF solution (7 cm^3) of **12a** (80 mg, 0.19 mmol) was treated with Bu$_4$NF (1 M solution in THF; 0.3 cm^3) at room temperature for 4 h. The mixture was then extracted with ether and subsequently chromatographed on a silica gel column to give **12b** [a colorless oil, 55 mg, 84%; $[α]_D^{30}$ +86.9° (c 1.75, CHCl$_3$); ^1H NMR: δ 0.78 (3H, d, J=7 Hz), 0.92 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.22 (3H, s), 1.35–2.10 (12H, m), 2.49 (1H, m), 3.04 (1H, m), 3.32 (1H, d, J= 9.5 Hz), 3.35 (1H, dd, J=11, 6.5 Hz), 3.39 (1H, d, J=9.5 Hz), 3.39 (3H, s), 3.57 (1H, dd, J=11, 6 Hz), 4.82 (1H, d, J=2.5 Hz), 4.91 (1H, d, J=3 Hz), and 5.65 (1H, d, J=2 Hz); ^{13}C NMR (C$_6$D$_6$): δ 16.6, 16.7, 22.1, 23.4, 24.9, 26.0, 29.1, 36.2, 39.3, 39.8, 43.2, 48.9, 49.9, 59.0, 65.4, 78.8, 81.8, 105.4, 135.4, 146.6, and 163.3].

Then, an anhydrous pyridine solution (7 cm^3) of **12b** (55 mg, 0.16 mmol) and TMSCl (0.1 cm^3, 0.8 mmol) was stirred at room temperature for 12 h, and the mixture was extracted with ether and chromatogrpahed on a silica gel column to give **12c** [a colorless oil, 71 mg, 92%; $[α]_D^{30}$ +15.4° (c 0.65, CHCl$_3$); ^1H NMR: δ 0.08 (9H, s), 0.09 (9H, s), 0.78 (3H, d, J=7 Hz), 0.92 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.18 (3H, s), 1.37–2.05 (10H, m), 2.47 (1H, m), 2.93 (1H, m), 3.12 (1H, d, J=10 Hz), 3.21 (1H, d, J=10 Hz), 3.26 (1H, dd, J=9.5, 8 Hz), 3.35 (3H, s), 3.52 (1H, dd, J=9.5, 3.5 Hz), 4.77 (1H, d, J=2.5 Hz), 4.90 (1H, d, J=3 Hz), and 5.61 (1H, d, J=2 Hz); ^{13}C NMR: δ –0.5 (3C), 2.2 (3C), 16.3, 16.5, 22.0, 23.2, 25.3, 25.5, 28.9, 34.4, 38.0, 38.9, 42.0, 48.3, 49.6, 59.2, 65.0, 79.1, 84.9, 104.8, 135.0, 145.3, and 163.6].

Finally, a moistened THF solution (8 cm^3) of **12c** (71 mg, 0.14 mmol) and PPTS (a catalytic amount) was stirred at room temperature for 4 h. Chromatographic purification of the mixture through a silica gel column afforded **12d** [a colorless oil, 50 mg, 86%; $[α]_D^{30}$ +35.0° (c 1.20, CHCl$_3$); ^1H NMR: δ 0.09 (9H, s), 0.79 (3H, d, J=7.0 Hz), 0.90 (3H, d, J=7.0 Hz), 0.99 (3H, d, J=7.0 Hz), 1.22 (3H, s), 1.40–2.05 (10H, m), 2.19 (1H, m), 2.51 (1H, m), 2.94 (1H, m), 3.22 (1H, d, J=9.5 Hz), 3.29 (1H, dd, J=11, 6 Hz), 3.33 (1H, d, J=9.5 Hz), 3.35 (3H, s), 3.56 (1H, dd, J=11, 6.5 Hz), 4.80 (1H, d, J=2.5 Hz), 4.91 (1H, d, J=3 Hz), and 5.63 (1H, d, J=2.5 Hz); ^{13}C NMR: δ 2.3 (3C), 16.4, 16.8, 22.0, 23.2, 23.3, 26.1, 28.9, 35.5, 38.4, 38.8, 42.8, 48.2, 49.7, 59.1, 65.3, 77.6, 85.0, 104.7, 135.3, 145.2, and 164.3].

Conversion of 12d into 16-Methoxy-3α-trimethylsilyloxy-8,9-secofusicocca-1,9-dien-8-al (13). To an anhydrous CH$_2$Cl$_2$ solution (10 cm^3) of **12d** (50 mg, 0.12 mmol) was added Molecular Sieves (4A, 100 mg) and PDC (70 mg, 0.18 mmol) under an N$_2$ atmosphere and stirred for 12 h. The mixture was then diluted with ether and passed a short Florisil column, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on a silica gel column to give **13** [a colorless oil, 35 mg, 70%; ^1H NMR: δ 0.09 (9H, s), 0.80 (3H, d, J=6.5 Hz), 0.98 (3H, d, J=7 Hz), 0.99 (3H, d, J=7 Hz), 1.23 (3H, s), 1.20-1.35 (2H, m), 1.40–1.75 (3H, m), 1.75–2.05 (4H, m), 2.47 (1H, m), 2.94 (1H, qd, J=7, 6.5 Hz), 3.14 (1H, m), 3.15 (1H, d, J=9.5 Hz), 3.19 (1H, d, J=9.5 Hz), 3.32 (3H, s), 4.80 (1H, d, J=2.5 Hz), 4.91 (1H, d, J=3 Hz), 5.75 (1H, d, J=2.5 Hz), and 9.61 (1H, d, J=1 Hz); ^{13}C NMR: δ 2.3 (3C), 12.2, 16.4, 21.9, 23.1, 24.9, 27.3, 28.9, 34.8, 38.0, 41.7, 48.1, 49.1, 49.7, 59.1, 78.4, 84.6, 105.3, 135.9, 144.2, 162.9, and 206.5].

Intramolecular Ene Reaction of 13 to 16-Methoxy-3α-(trimethylsilyloxy)fusicocca-1,10(14)-dien-8α-ol (14). A xylene solution (8 cm^3) of **13** (32 mg, 0.078 mmol) was degassed and sealed in a pressure bottle containing Na$_2$CO$_3$ (30 mg) and heated in an autoclave at 160 °C for 24 h. The mixture was then chromatographed on a silica gel column to give **14** [a colorless oil, 29 mg, 90 %; ^1H NMR: δ 0.07 (9H, s), 0.86 (3H, d, J=7 Hz), 0.96 (3H, d, J=7 Hz), 0.98 (3H, d, J=7 Hz), 1.18 (3H, s), 1.40 (1H, m), 1.60–2.22 (9H, m), 2.31 (1H, dq, J=14.5, 3 Hz), 2.61 (1H, dd, J=14.5, 9.5 Hz), 2.85 (1H, sept, J=7 Hz), 3.21 (1H, d, J=10.5 Hz), 3.31 (1H, d, J=10.5 Hz), 3.35 (1H, m), 3.37 (3H, s), 3.64 (1H, br m), and 5.48 (1H, d, J=2 Hz); ^{13}C NMR: δ 2.3 (3C), 13.7, 20.4, 21.2, 27.27, 27.30, 27.5, 29.0, 32.5, 35.7, 36.5, 40.8, 45.7, 53.3, 59.3, 73.2, 78.8, 85.3, 133.6, 135.0, 141.5, and 143.8].

**Oxidation of 14 to 16-Methoxy-3α-(trimethylsilyloxy)fusicocca-1,10(14)-dien-8-one
(15).** A CH_2Cl_2 solution (7 cm^3) of **14** (47 mg, 0.11 mmol) with Molecular Sieves (4A, 70 mg) was treated with PDC (65 mg, 0.17 mmol) and stirred for 12 h. The mixture was then diluted with ether and passed a short Florisil column. The filtrate was evaporated *in vacuo*, and the residue was chromatographed on a silica gel column to give **15** [a colorless oil, 27.0 mg, 70%. ^{1}H NMR: δ 0.08 (9H, s), 0.97 (3H, d, *J*=7 Hz), 0.98 (3H, d, *J*=7 Hz), 0.99 (3H, d, *J*=7 Hz), 1.11 (3H, s), 1.25–1.54 (3H, m), 1.72–1.89 (3H, m), 2.09 (1H, m), 2.26 (2H, tm, *J*=6.5 Hz), 2.72 (1H, sept, *J*=7 Hz), 2.81 (1H, dt, *J*=15.5, 2 Hz), 3.00 (1H, dd, *J*=10.5, 1 Hz), 3.11 (1H, d, *J*=10.5 Hz), 3.21 (1H, d, *J*=15.5 Hz), 3.25 (1H, m), 3.35 (3H, s), and 5.51 (1H, d, *J*=2 Hz); ^{13}C NMR: δ 2.3 (3C), 12.5, 20.2, 21.0, 26.6, 27.26, 27.31, 27.7, 34.2, 39.8, 40.5, 40.8, 45.4, 52.2, 59.3, 78.2, 85.1, 133.8, 134.0, 143.5, 144.9, and 213.4] and a *seco*-dialdehyde **16** [a colorless oil, 6 mg, 15%; ^{1}H NMR: δ 0.10 (9H, s), 0.99 (3H, d, *J*=7 Hz), 1.08 (3H, d, *J*=7 Hz), 1.10 (3H, d, *J*=7 Hz), 1.38 (3H, s) 1.55–1.95 (4H, m), 2.02 (1H, m), 2.22–2.38 (2H, m), 2.55–2.63 (2H, m), 2.90 (1H, qd, *J*=7, 6.5 Hz), 3.13 (1H, d, *J*=10 Hz), 3.18 (1H, d, *J*=10 Hz), 3.31 (3H, s), 3.43 (1H, sept, *J*=7 Hz), 5.91 (1H, d, *J*=3 Hz), 9.49 (1H, d, *J*=1 Hz), and 9.91 (1H, s)].

**Oxidation of 15 to 9α-Hydroxy-16-methoxy-3α-(trimethylsilyloxy)fusicocca-1,10(14)-
dien-8-one and 9β-Hydroxy-16-methoxy-3α-(trimethylsilyloxy)fusicocca-1,10(14)-dien-8-
one (17 and 18).** To an anhydrous THF solution (10 cm^3) of LiBu (3.4 cm^3, 5.4 mmol in hexane) was introduced (TMS)$_2$NH (1.3 cm^3) at -78 °C. To the mixture, **15** (25 mg) was added in drop by drop at −78 °C and stirred for another 1 h. The mixture was then treated with MoOPH (304 mg, 0.7 mmol) at −40 °C and continued stirring for further 1 h. The mixture was then treated with NaHSO$_3$ and extracted with ether. The organic extract was washed with aq. NaHCO$_3$, water, and aq. NaCl, dried over MgSO$_4$, and evaporated *in vacuo*. The residue was chromatographed on a silica gel column to give **17** [colorless needles, m.p. 87–88 °C, 10.0 mg, 44%; ^{1}H NMR: δ 0.10 (9H, s), 0.81 (3H, d, *J*=6.5 Hz), 1.00 (3H, d, *J*=6.5 Hz), 1.08 (3H, d, *J*=7.5 Hz), 1.32 (3H, s), 1.49 (1H, m), 1.76–2.24 (7H, m), 2.67 (1H, qd, *J*=7.5, 1.5 Hz), 2.75 (1H, sept, *J*=6.5 Hz), 3.07 (1H, dd, *J*=10, 1 Hz), 3.23 (1H, tm, *J*=9 Hz), 3.31 (1H, d, *J*=10 Hz), 3.36 (3H, s), 3.80 (1H, br d, *J*=4.5 Hz, OH), 4.82 (1H, d, *J*=4.5 Hz), and 5.63 (1H, d, *J*=2.5 Hz); ^{13}C NMR: δ 2.3 (3C), 13.5, 19.6, 21.1, 26.3, 27.1, 27.6, 30.3, 34.2, 39.1, 40.9, 50.1, 52.5, 59.2, 69.4, 77.5, 85.1, 133.3, 135.5, 139.8, 150.8, and 212.0] and **18** [a colorless oil, 6.5 mg, 28%; ^{1}H NMR: δ 0.06 (9H, s), 1.05 (3H, d, *J*=7 Hz), 1.06 (3H, d, *J*=7 Hz), 1.11 (3H, s), 1.12 (3H, d, *J*=6.5 Hz), 1.51–2.05 (6H, m), 2.20–2.26 (2H, m), 2.85 (1H, qd, *J*=6.5, 6 Hz), 3.00 (1H, sept, *J*=7 Hz), 3.15 (1H, d, *J*=10.5 Hz), 3.25 (1H, d, *J*=10.5 Hz), 3.36 (3H, s), 3.76 (1H, m), 3.90 (1H, br d, *J*=3.5 Hz, OH), 5.10 (1H, d, *J*=3.5 Hz), and 5.43 (1H, d, *J*=2.5 Hz); ^{13}C NMR: δ 2.3 (3C), 10.8, 20.5, 21.6, 27.0, 27.4, 27.5, 28.0, 35.7, 38.3, 41.8, 47.4, 52.6, 59.2, 72.8, 78.2, 84.8, 134.6, 135.3, 143.7, 151.0, and 213.3].

**Reduction of 17 with Sodium Triacetoxyborohydride to 16-Methoxy-3α-(trimethylsilyl-
oxy)fusicocca-1,10(14)-dien-8β,9α-diol (19) and 16-Methoxy-3α-(trimethylsilyloxy)fusicoc-
ca-1,10(14)-dien-8α,9α-diol (20).** To an anhydrous THF solution (4 cm^3) of **17** (10.0 mg) was added NaBH(OAc)$_3$ (10. 5 mg) gradually at room temperature and stirred for 12 h under an N$_2$ atmosphere. The mixture was then diluted with aq. NaHCO$_3$ and extracted with ether. The organic extract was evaporated *in vacuo*, and the silica gel column chromatography of the residue afforded **19** [a colorless oil, 4.5 mg, 70%; ^{1}H NMR: δ 0.09 (9H, s), 0.82 (3H, d, *J*=7.5 Hz), 0.95 (3H, d, *J*=6.5 Hz), 1.04 (3H, d, *J*=6.5 Hz), 1.21 (3H, s), 1.40 (1H, m), 1.67 (1H, m), 1.77 (1H, br s), 1.79–1.98 (4H, m), 2.05–2.15 (3H, m), 2.82 (1H, td, *J*=7, 2 Hz), 2.91 (1H, dd, *J*=10.5, 1.5 Hz), 2.95 (1H, br s), 3.28 (1H, sept, *J*=7 Hz), 3.29 (1H, d, *J*=10.5 Hz), 3.36 (3H, s), 3.92 (1H, dd, *J*= 10, 4 Hz), 4.09 (1H, d, *J*=10 Hz), and 5.40 (1H, d, *J*=2.5 Hz); ^{13}C NMR: δ 2.2 (3C), 8.0, 20.4, 21.4, 26.5, 27.0, 28.0, 31.2, 33.7, 39.8, 41.2, 42.7, 51.6, 59.3, 68.0, 77.2, 77.8, 85.3, 133.8, 136.8, 140.0, and 150.1] and **20** [a colorless oil, 1.5 mg, 24%; ^{1}H NMR: δ 0.08 (9H, s), 0.83 (3H, d, *J*=7.5 Hz), 1.00 (3H, d, *J*=7 Hz), 1.03 (3H, d, *J*=7 Hz), 1.19 (3H, s), 1.43–2.25 (10H, m), 2.27 (1H, br d, *J*=5.5 Hz), 3.00 (1H, dd, *J*=10.5, 1.5 Hz), 3.19 (1H, tm, *J*=6 Hz), 3.29 (1H, d, *J*=10.5 Hz), 3.36 (3H, s), 3.44 (1H, sept, *J*=7 Hz), 3.82 (1H, br m), 4.36 (1H, br s), and 5.46 (1H, d, *J*=2.5 Hz); ^{13}C NMR: δ 2.3 (3C), 13.1, 20.8, 22.6, 27.20, 27.24, 28.6, 31.0, 34.5, 34.6, 42.0, 42.2, 52.3, 59.3, 69.8, 77.7, 78.1, 85.3, 134.1, 135.3, 140.7, and 150.4].

Conversion of 19 to Cotylenol (1). An anhydrous THF solution (3 cm^3) of **17** (6.0 mg) was treated with Bu$_4$NF (1 M solution in THF; 0.07 cm^3) at room temperature for 4 h under an N$_2$ atmosphere. The mixture was then diluted with aq. NaHCO$_3$ and extracted with ether. The organic extract was washed with aq. NaCl, dried over MgSO$_4$, and evaporated *in vacuo*. Silica gel column chromatography of the residue afforded

1 [colorless prisms, 5 mg, 100%, m.p. 160 °C (lit.[19] 157–158 °C); [α]$_D^{30}$ –30° (lit.[19] –26°); ^{1}H NMR: δ 0.81 (3H, d, J=7.5 Hz), 0.96 (3H, d, J=7 Hz), 1.04 (3H, d, J=7 Hz), 1.22 (3H, s), 1.25–1.46 (2H, m), 1.69 (1H, ddd, J=12.0, 10.0, 8.5 Hz), 1.78 (1H, br s, OH), 1.85 (1H, ddd, J=12, 6, 3 Hz), 1.90–2.22 (5H, m), 2.53 (1H, br s, OH), 2.94 (1H, td, J=8.5, 2.5 Hz), 2.96 (1H, br s, OH), 3.09 (1H, dd, J=9.5, 1 Hz), 3.27 (1H, sept, J=7 Hz), 3.36 (1H, d, J=9.5 Hz), 3.41 (3H, s), 3.94 (1H, dd, J=10, 4.5 Hz), 4.07 (1H, d, J=10 Hz), and 5.52 (1H, d, J=2.5 Hz); ^{13}C NMR: δ 8.4, 20.3, 21.5, 26.5, 27.1, 28.1, 31.6, 35.3, 40.2, 41.7, 42.5, 51.8, 59.3, 67.9, 77.4, 77.5, 82.0, 134.3, 136.9, 139.7, and 150.4].

Computational Analysis of the Ene Reaction of 13 to 14. The semi-empirical molecular orbital calculations were performed with MNDO/PM3[28] implemented in the MOPAC ver.6.10 program included in the CAChe system[30] (SONY-Tektronix). The structures of the transition states for the model of **13** were optimized by 'TS' with 'PRECISE' option, and it was confirmed that both **TSA** and **TSB** have only one imaginary frequency by vibrational-frequency-calculation analyses (1289.4 i cm^{-1} for **TSA** and 1760.9 i cm^{-1} for **TSB**).

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