Synthetic Studies on Aphidicolane and Stemodane Diterpenes. IV.[1] A Stereoselective Formal Total Synthesis of (±)-Aphidicolin

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A formal total synthesis of (±)-aphidicolin (1) was accomplished starting from the tricyclic ketone (2) corresponding to the B/C/D ring system. The quaternary carbon center adjacent to the spirocarbon was constructed stereoselectively by conjugate addition of a methyl group to the enone (7) obtained from 2 in a four-step sequence. The tetracyclic enone (3) was obtained *via* acid-catalyzed intramolecular aldol condensation of the tricarbonyl compound (10) followed by 1,3-carbonyl transposition, in which Pd(0)-catalyzed reductive deacetoxylation of γ-acetoxy-α,β-enone (15) was a crucial step. The A-ring manipulation was performed by a similar procedure to the Ireland method to give the keto-acetonide (4), a degradation product of 1, which has already been efficiently reconverted to 1.

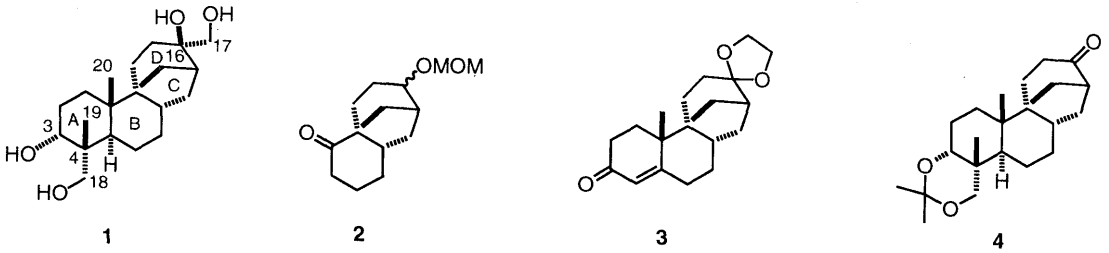
Key words aphidicolin; total synthesis; reductive deacetoxylation; γ-acetoxy-α,β-enone; stereoselective conjugate addition; 1,3-carbonyl transposition

Aphidicolin (**1**), a diterpene tetraol, was isolated as a metabolite of the fungus *Cephalosporium aphidicola* PETCH in 1972 by Hesp and coworkers. An X-ray crystallographic analysis elucidated the tetracyclic structure in which a bicyclo[3.2.1]octane moiety (C/D-ring) is fused with a *trans*-decalin (A/B-ring) in a trans manner with regard to the B/C-rings.[2] Aphidicolin (**1**) has antimitotic activity and inhibits the growth of herpes simplex virus, thereby being of interest as a candidate antiviral agent. In addition, it was found that **1** exhibited considerable antitumor activity in the C6 mouse colon and B16 mouse melanosarcoma screens and inhibited the growth of leukemic T- and B-lymphocytes.[3] The mode of action was elucidated as inhibition of DNA polymerase α.[4] These interesting biological activities and the unique tetracyclic structure have prompted various synthetic studies.[5]

In the previous paper, we reported the stereoselective synthesis of the tricyclic ketone **2** corresponding to the B/C/D ring system of **1**. In this paper, we describe a stereoselective formal total synthesis of **1**. Our final target is the keto-acetonide **4**, a degradation product of **1**, starting from **2** *via* the tetracyclic enone **3**. Compound **4** has already been converted efficiently to **1** by Rizzo and Smith.[5j]

Construction of the quaternary carbon center adjacent to the spirocarbon is one of the main problems in the stereoselective synthesis of **1**. It could be overcome by conjugate addition of a methyl group to an enone such as **7** (Chart 2), because the β-side of this enone moiety is much less congested than the α-side. So the enone **7** was synthesized as follows. The ketone **2** [*ca.* 1 : 1 diastereo mixture concerning the methoxymethoxy (MOMO) moiety] was converted to the enone **5** by α-phenylselenenylation followed by oxidative elimination. 4-Tetrahydropyranyloxybutyllithium, prepared from 4-tetrahydropyranyloxybutyl chloride and lithium,[6] was reacted with **5** to afford the 1,2-adduct **6**, which was subjected to oxidative allylic rearrangement with pyridinium chlorochromate (PCC) to give the enone **7** in good yield. 1,4-Conjugate addition to **7** with dimethylcopper lithium progressed easily to afford the ketone **8**[7] as a diastereo mixture.

Next, formation of the A-ring was achieved as follows (Chart 3). Acid treatment of **8** to remove the methoxymethyl (MOM) and tetrahydropyranyl (THP) groups gave the diol **9**, the Swern oxidation of which afforded the tricarbonyl compound **10**. Acid-catalyzed intramolecular aldol condensation of **10** provided the tetracyclic dienone **11** efficiently. After protection of the saturated ketone as an ethylene ketal (**11**→**12**), the carbonyl group of the enone moiety of **12** was reduced by lithium aluminum hydride (LAH) to afford the allylic



1 **2** **3** **4**

Chart 1

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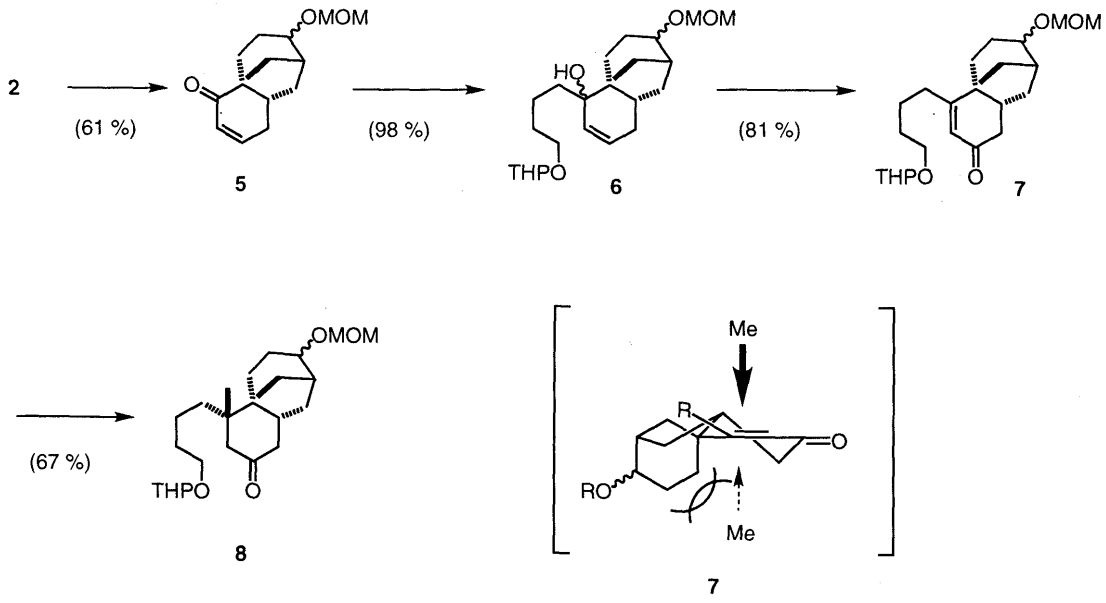

Chart 2

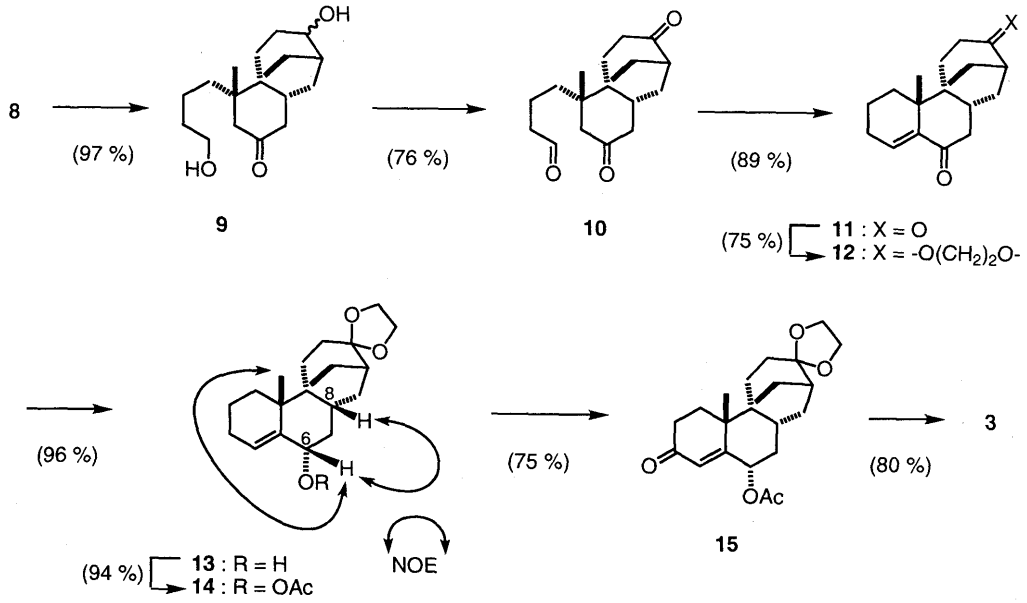

Chart 3

alcohol **13** as a single isomer. Acetylation of the hydroxyl group (**13**→**14**[7]) followed by allylic oxidation with the chromium trioxide–3,5-dimethylpyrazole system[8] afforded the enone-acetate **15**. Reductive deacetoxylation (**15**→**3**) was troublesome. Neither zinc–acetic acid nor Birch reduction afforded the desired enone **3**. Hydrogenolysis of an allylic acetate using a catalytic amount of Pd(0)[9] was fruitless. After examination of various reaction conditions, we found that the use of $Pd(PPh_3)_4$ (1.2 eq), PPh_3 (2 eq), and ammonium formate (5 eq) in refluxing dioxane afforded the desired product **3** in 64% yield. But even under these conditions, the reaction sometimes terminated prematurely. It was found later that the use of n-Bu_3P in acetonitrile[10] instead of PPh_3 in dioxane afforded a good result (80% yield). Although this hydrogenolysis reaction was originally applied to allylic acetates and was accompanied with double bond migration, to our knowledge there has been no example of applying this procedure to γ-acetoxy-α,β-enones. In this case, no β,γ-enone was obtained.

Our next task was manipulation of the A-ring. The conversion of the tetracyclic enone **3** to the keto-acetonide **4** (Chart 4) was performed according to the method developed by Ireland *et al.*[5d] The enone **3** was refluxed with paraformaldehyde, thiophenol, and triethylamine (Et_3N) in EtOH to afford the α-phenylthiomethyl derivative **16**. Birch reduction of **16** with Li in liquid NH_3 followed by trapping of the resulting lithium enolate with trimethylsilyl chloride (TMSCl) provided the enol silyl ether **17**. This (**17**) was treated with methyllithium (MeLi) to generate the lithium enolate, which was allowed to react with formalin gas to produce the α-hydroxymethyl ketone

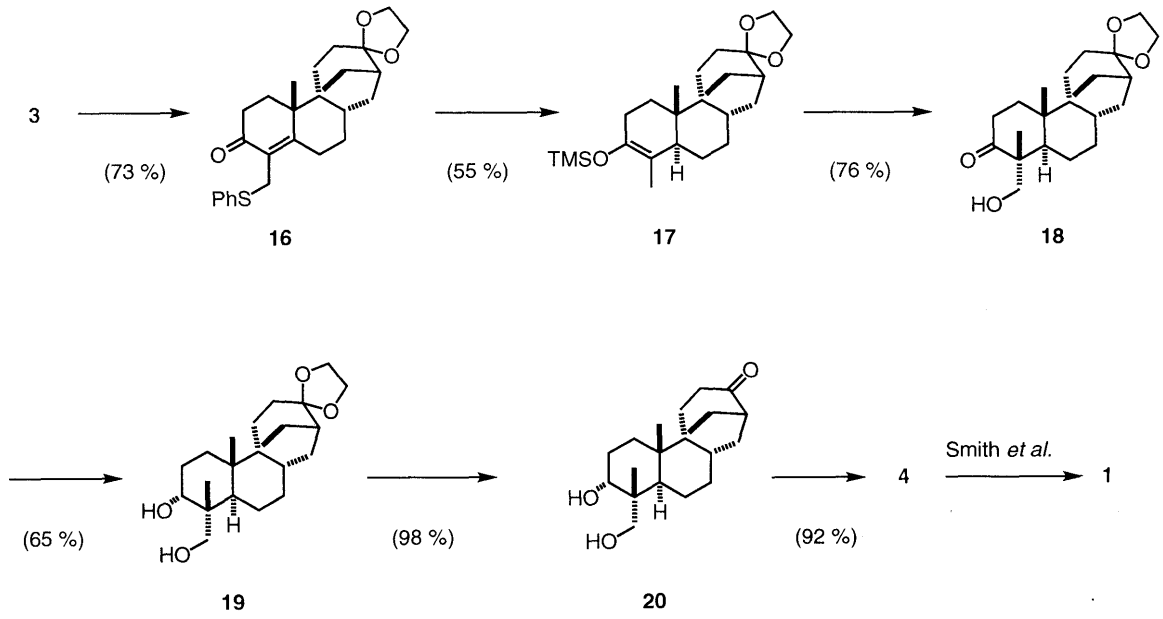

Chart 4

18. The carbonyl group of **18** was stereoselectively reduced with L-Selectride to give the diol **19**. The ketal moiety of **19** was hydrolyzed with acid to afford the keto-diol **20**, which was finally converted to the keto-acetonide **4** by reaction with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate (PPTS). Compound **4** obtained here was identical with an authentic sample of the degradation product of natural aphidicolin (**1**) on the basis of infrared (IR) and ^{1}H-NMR spectral comparison. As an efficient conversion of keto-acetonide **4** to **1** was reported by Rizzo and Smith,[5j] we have accomplished a formal total synthesis of (±)-aphidicolin (**1**).

Experimental

All melting points are uncorrected. IR spectra were recorded on a Hitachi 260-10 or a Horiba FT-210 spectrophotometer. ^{1}H-NMR spectra were obtained in $CDCl_3$ 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 GC-MS-QP1000, and high-resolution mass spectra (HR-MS) 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.

(1*RS*,6*RS*,8*RS*)-9-Methoxymethoxytricyclo[6.3.1.0^{1,6}]dodec-3-en-2-one (5) A solution of **2** (1.90 g, 7.98 mmol) in tetrahydrofuran (THF) (25 ml) was added dropwise to a lithium diisopropylamide (LDA) solution [prepared from iso-Pr_2NH (1.68 ml, 11.9 mmol) and *n*-BuLi (1.4 M in hexane, 8.57 ml, 11.9 mmol) in THF (18 ml) at −20 °C] at −78 °C, and the whole was stirred for 30 min. A solution of PhSeBr (2.83 g, 11.9 mmol) in THF (18 ml) was added all at once, and the resulting mixture was stirred for 10 min. Saturated NH_4Cl solution and water were added, then the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was dissolved in CH_2Cl_2 (30 ml), and cooled to 0 °C. Pyridine (1.9 ml, 23.9 mmol) and 15% H_2O_2 (18 ml) were added, and the whole was stirred for 15 min at room temperature. The mixture was diluted with $CHCl_3$, then the organic phase was washed with brine, dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 3 : 1) to give **5** (1.15 g, 61%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1680, 1610. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.35, 3.37 (total 3H, each s, OMe), 3.61—3.67 (1H, m, C-9H), 4.63—4.68 (2H, m, OCH_2O), 5.85—5.87 (1H, m, C-3H), 6.86—6.91 (1H, m, C-4H). UV λ nm (ε): 227 (7400). MS *m/z*: 236 (M^+). HR-MS Calcd for $C_{14}H_{20}O_3$: 236.1410. Found: 236.1409.

(1*RS*,6*RS*,8*RS*)-9-Methoxymethoxy-2-(4-tetrahydropyranyloxybutyl)-tricyclo[6.3.1.0^{1,6}]dodec-2-en-4-one (7) 1,2-Dibromoethane (0.08 ml, 0.9 mmol) was added to a suspension of lithium powder [30% lithium dispersion (1% Na) (1.0 g, 42.9 mg-atom) washed with hexane and dried] in Et_2O (8 ml) at room temperature. After 5 min, the mixture was cooled to −20 °C, and 4-tetrahydropyranyloxybutyl chloride (1.13 g, 6.2 mmol) was slowly added. The mixture was stirred for 2 h, then warmed to −5 °C, maintained at that temperature for 1 h under stirring, and then recooled to −20 °C. To the resulting mixture, a solution of **5** (293 mg, 1.24 mmol) in Et_2O (2 ml) was added dropwise, and the whole was stirred at that temperature for 2 h. Saturated NH_4Cl solution was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 3 : 2) to give (1*RS*,6*RS*,8*RS*)-9-methoxymethoxy-2-(4-tetrahydropyranyloxybutyl)-tricyclo[6.3.1.0^{1,6}]dodec-3-en-2-ol (**6**) (480 mg, 98%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3590. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.31, 3.33 (total 3H, each s, OMe), 4.50, 4.52 (total 2H, each s, OCH_2O), 5.25—5.45 (1H, m, C-4H), 5.53—5.78 (1H, m, C-3H). MS *m/z*: 310 (M^+ − DHP). HR-MS Calcd for $C_{18}H_{30}O_4$ (M^+ − DHP): 310.2142. Found: 310.2130. PCC (650 mg, 2.40 mmol) was added to a solution of **6** (480 mg, 1.22 mmol) in CH_2Cl_2 (6 ml) at 0 °C, and the mixture was stirred at room temperature for 3 h. After the addition of Et_2O (30 ml), the mixture was passed through a Florisil column, and eluted with Et_2O. The eluate was evaporated, and the residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give **7** (386 mg, 81%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1650, 1600. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.33, 3.36 (total 3H, each s, OMe), 4.62, 4.64 (total 2H, each s, OCH_2O), 5.64 (1H, br s, C-3H). UV λ nm (ε): 245 (9400). MS *m/z*: 308 (M^+ − DHP). HR-MS Calcd for $C_{18}H_{28}O_4$ (M^+ − DHP): 308.1988. Found: 308.1999.

(1*RS*,2*SR*,6*RS*,8*RS*)-9-Methoxymethoxy-2-methyl-2-(4-tetrahydropyranyloxybutyl)tricyclo[6.3.1.0^{1,6}]dodecan-4-one (8) MeLi (1.0 M in Et_2O, 5.90 ml, 5.90 mmol) was slowly added to a suspension of CuI (550 mg, 2.90 mmol) in Et_2O (4 ml) at −20 °C, and the whole was stirred for 15 min. Then a solution of **7** (379 mg, 0.97 mmol) in Et_2O (6 ml) was added at −10 °C, and the whole was stirred at 0 °C for 1 h. Saturated NH_4Cl solution was added, and the whole was extracted with AcOEt. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 4 : 1) to give **8** (diastereo mixture, 265 mg, 67%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1700. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.94 (3H, s, C-2Me), 3.35 (3H, s, OMe), 4.64 (2H, s, OCH_2O). MS *m/z*: 408 (M^+). HR-MS Calcd for $C_{24}H_{40}O_5$: 408.2841. Found: 408.2857.

(1*RS*,2*SR*,6*RS*,8*RS*)-9-Hydroxy-2-(4-hydroxybutyl)-2-methyltricyclo-[6.3.1.0^{1,6}]dodecan-4-one (9) A mixture of **8** (1.16 g, 2.84 mmol), 10% HCl (20 ml) and acetone (30 ml) was heated at 45 °C for 6 h. After

the mixture had cooled, the solvent was evaporated off, and the residue was taken up in $CHCl_3$. The organic layer was washed with brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 4) to give **9** (774 mg, 97%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3600, 1700. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.94 (3H, s, C-2Me), 3.49—3.82 (3H, m, C$\underline{H}_2$OH and C-9H). MS *m/z*: 280 (M^+). HR-MS Calcd for $C_{17}H_{28}O_3$: 280.2039. Found: 280.2050.

4-{(1*RS*,2*SR*,6*RS*,8*RS*)-4,9-Dioxo-2-methyltricyclo[6.3.1.0^{1,6}]dodecan-2-yl}butyraldehyde (10) Dimethyl sulfoxide (DMSO) (0.709 ml, 9.98 mmol) was added to a solution of oxalyl chloride (0.391 ml, 4.58 mmol) in CH_2Cl_2 (2.5 ml) at −60 °C. The mixture was stirred for 15 min, a solution of **9** (321 mg, 1.15 mmol) in CH_2Cl_2 (2 ml) was slowly added, and stirring was continued for another 15 min. Et_3N (2.90 ml, 20.8 mmol) was added slowly, and the whole was stirred for 1 h. After the addition of saturated $NaHCO_3$ solution, the mixture was extracted with Et_2O. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 2) to give **10** (240 mg, 76%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1710. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.93 (3H, s, C-2Me), 9.92 (1H, t, J = 1 Hz, CHO). MS *m/z*: 276 (M^+). HR-MS Calcd for $C_{17}H_{24}O_3$: 276.1726. Found: 276.1732.

***rac*-4,5-Didehydro-3-deoxy-17,18,19-trisnoraphidicolin-6,16-dione (11)** A mixture of **10** (740 mg, 2.68 mmol) and *p*-toluenesulfonic acid (*p*-TsOH) (5 mg) in benzene (100 ml) was refluxed under a Dean–Stark water separator for 2 h. After cooling, the mixture was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 2) to give **11** (615 mg, 89%) as colorless crystals, mp 150.0—151.0 °C (from *n*-hexane–acetone). IR ($CHCl_3$) cm^{-1}: 1710, 1680. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.16 (3H, s, C-10Me), 6.77 (1H, dd, J = 3.0, 4.9 Hz, C-4H). UV λ nm (ε): 245 (7200). MS *m/z*: 258 (M^+). *Anal.* Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.77; H, 8.80.

***rac*-4,5-Didehydro-3-deoxy-17,18,19-trisnoraphidicolin-6,16-dione 16,16-Ethylene Acetal (12)** A mixture of **11** (39.0 mg, 0.151 mmol), ethylene glycol (13.2 mg, 0.20 mmol), *p*-TsOH (2 mg), and benzene (6 ml) was refluxed under a Dean–Stark water separator for 15 min. After cooling, the mixture was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give **12** (29 mg, 64%; 75% based on the consumed starting material) as colorless crystals, mp 180.0—181.0 °C (from *n*-hexane–CH_2Cl_2). IR ($CHCl_3$) cm^{-1}: 1680, 1610. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.08 (3H, s, C-10Me), 2.59—2.68 (2H, m, C-7H$_2$), 3.83—4.02 (4H, m, OCH_2CH_2O), 6.72 (1H, dd, J = 4.3, 4.3 Hz, C-4H). UV λ nm (ε): 246 (6800). MS *m/z*: 302 (M^+). *Anal.* Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.35; H, 8.88.

***rac*-4,5-Didehydro-3-deoxy-6-hydroxy-17,18,19-trisnoraphidicolin-16-one Ethylene Acetal (13)** $LiAlH_4$ (32 mg, 0.842 mmol) was added to a solution of **12** (170 mg, 0.563 mmol) in THF (5 ml) and Et_2O (3 ml) at 0 °C, and the mixture was stirred for 1 h. After work-up with saturated Rochelle salt, the organic layer was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give **13** (165 mg, 96%) as colorless crystals, mp 144.0—145.0 °C (from *n*-hexane–CH_2Cl_2). IR ($CHCl_3$) cm^{-1}: 3600. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.09 (3H, s, C-10Me), 3.81—3.99 (4H, m, OCH_2CH_2O), 5.84 (1H, m, C-4H). MS *m/z*: 304 (M^+). HR-MS Calcd for $C_{19}H_{28}O_3$: 304.2038. Found: 304.2048.

***rac*-6-Acetoxy-4,5-didehydro-17,18,19-trisnoraphidicolin-3,16-dione 16,16-Ethylene Acetal (15)** Dimethylaminopyridine (DMAP) (150 mg, 1.23 mmol) and acetic anhydride (0.18 ml, 1.90 mmol) were added to a solution of **13** (165 mg, 0.543 mmol) in CH_2Cl_2 (10 ml) at 0 °C, and the whole was stirred at room temperature for 4 h. Water was added, and the mixture was extracted with AcOEt. The extract was washed with 1% HCl, saturated $NaHCO_3$, and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 4 : 1) to give *rac*-6-acetoxy-4,5-didehydro-17,18,19-trisnoraphidicolin-16-one ethylene acetal (**14**) (177 mg, 94%). IR ($CHCl_3$) cm^{-1}: 1750. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.13 (3H, s, C-10Me), 2.11 (3H, s, CH_3CO), 2.33 (1H, m, C-8H), 3.80—3.99 (4H, m, OCH_2CH_2O), 5.40 (1H, ddd, J = 11.1, 5.8, 2.8 Hz, C-6H), 5.58 (1H, m, C-4H). MS *m/z*: 346 (M^+). HR-MS Calcd for $C_{21}H_{30}O_4$: 346.2141. Found: 346.2131. 3,5-Dimethylpyrazole (490 mg, 5.10 mmol) was added all at once to a suspension of CrO_3 (510 mg, 5.10 mmol) in CH_2Cl_2 (2 ml) at −20 °C under vigorous stirring. After 20 min, a solution of **14** (85.0 mg, 0.246 mmol) in CH_2Cl_2 (3 ml) was added dropwise to the mixture, and the whole was stirred at −10 °C for 2 h and 0 °C for 1 h. After dilution with Et_2O, the mixture was passed through a Florisil column. The eluate was washed with 1% HCl, saturated $NaHCO_3$, and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give 15 (66.3 mg, 75%) as colorless crystals, mp 124.0—126.0 °C (from *n*-hexane–CH_2Cl_2). IR ($CHCl_3$) cm^{-1}: 1740, 1660, 1610. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.31 (3H, s, C-10Me), 2.13 (3H, s, CH_3CO), 3.74—3.98 (4H, m, OCH_2CH_2O), 5.52 (1H, m, C-6H), 5.98 (1H, d, J = 1.8 Hz, C-4H). UV λ nm (ε): 237 (10000). MS *m/z*: 360 (M^+). HR-MS Calcd for $C_{21}H_{28}O_5$: 360.1937. Found: 360.1942.

***rac*-4,5-Didehydro-17,18,19-trisnoraphidicolin-3,16-dione 16,16-Ethylene Acetal (3)** A mixture of **15** (12.8 mg, 0.036 mmol), $Pd(Ph_3P)_4$ (49.3 mg, 0.042 mmol), *n*-Bu_3P (14.4 mg, 0.071 mmol), $HCOONH_4$ (11.2 mg, 0.175 mmol), and CH_3CN (2 ml) was refluxed for 3 h under Ar. After dilution with Et_2O, the mixture was passed through a Florisil column. The eluate was washed with saturated $NaHCO_3$, and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 1) to give **3** (8.6 mg, 80%) as colorless crystals, mp 114.0—116.0 °C (from *n*-hexane–Et_2O). IR ($CHCl_3$) cm^{-1}: 1660, 1610. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.27 (3H, s), 1.31—1.44 (2H, m), 1.48—1.68 (5H, m), 1.95 (1H, m), 2.18 (1H, m), 2.28—2.53 (5H, m), 3.80—3.99 (4H, m), 5.81 (1H, d, J = 2.5 Hz). MS *m/z*: 302 (M^+). HR-MS Calcd for $C_{19}H_{26}O_3$: 302.1881. Found: 302.1901.

***rac*-4,5-Didehydro-4-phenylthiomethyl-17,18,19-trisnoraphidicolin-3,16-dione 16,16-Ethylene Acetal (16)** A mixture of **3** (68.0 mg, 0.225 mmol), paraformaldehyde (300 mg, 10 mmol), Et_3N (0.476 ml, 3.42 mmol), thiophenol (0.591 ml, 5.79 mmol), and EtOH (2.5 ml) was refluxed for 8 h under N_2. After cooling, the mixture was extracted with Et_2O. The extract was washed with cold 1 N NaOH and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give **16** (69.2 mg, 73%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1670, 1600. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.21 (3H, s, C-10Me), 3.80—3.97 (4H, m, OCH_2CH_2O), 3.88 (2H, s, C$\underline{H}_2$SPh), 7.16—7.45 (5H, m, SPh). UV λ nm (ε): 253 (15200). MS *m/z*: 424 (M^+). HR-MS Calcd for $C_{26}H_{32}O_3S$: 424.2037. Found: 424.2085.

***rac*-17-Noraphidicolin-16-one Ethylene Acetal (19)** Li (8 mg, 1.16 mg-atom) was added to liquid NH_3 (8 ml, redistilled from Na) at −78 °C, and the mixture was stirred for 10 min under N_2. A solution of **16** (67.0 mg, 0.158 mmol) in a mixture of THF (1 ml) and *tert*-BuOH (0.027 ml, 0.29 mmol) was added dropwise to the resulting solution, and the whole was stirred for 10 min. Isoprene was added to the reaction mixture until the blue color disappeared, and then the mixture was allowed to warm to room temperature while evaporating the NH_3, with protection from moisture. The residue was dried under reduced pressure, and then suspended in THF (4 ml) under N_2. Hexamethylphosphoric triamide (HMPA) (0.7 ml, 3.85 mmol) was added to the suspension at −78 °C. After 5 min, the supernatant fluid separated by centrifugation of a mixture of TMSCl (0.8 ml) and Et_3N (0.8 ml) was added dropwise, and the whole was stirred at room temperature for 1 h. After the addition of saturated $NaHCO_3$, the whole was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by a Florisil column chromatography (*n*-hexane : Et_2O = 20 : 1) to give *rac*-3,4-didehydro-3-trimethylsiloxy-17,18-dinoraphidicolin-16-one ethylene acetal (**17**) (34.0 mg, 55%). IR ($CHCl_3$) cm^{-1}: 1670. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.15 (9H, s, $SiMe_3$), 0.84 (3H, s, C-10Me), 1.49 (3H, s, C-4Me), 3.78—3.91 (4H, m, OCH_2CH_2O). MS *m/z*: 390 (M^+). HR-MS Calcd for $C_{23}H_{38}O_3Si$: 390.2588. Found: 390.2581. MeLi (1.0 M in Et_2O, 0.11 ml, 0.11 mmol) was added to a solution of **17** (34.3 mg, 0.088 mmol) in THF (1 ml) at −78 °C under N_2, and the whole was stirred at room temperature for 1 h, then recooled to −78 °C. Gaseous HCHO generated by heating paraformaldehyde at 150 °C was passed through the reaction mixture in an N_2 stream for 10 min. Then 10% AcOH in THF (0.1 ml) was added, followed by NH_3-saturated NH_4Cl (pH 7—8) in water (2 ml), and the whole was extracted with Et_2O. The extract was washed with brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 1) to give *rac*-18-hydroxy-17-noraphidicolin-3,16-dione 16,16-ethylene acetal (**18**) (23.3 mg, 76%). IR ($CHCl_3$) cm^{-1}: 3470, 1690. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.97 (3H, s, C-10Me), 1.16 (3H, s, C-4Me), 3.37, 3.67 (each 1H, d, J = 11.5 Hz, C$\underline{H}_2$OH), 3.80—3.96 (4H, m, OCH_2CH_2O). MS *m/z*: 348 (M^+). HR-MS Calcd for $C_{21}H_{32}O_4$: 348.2301. Found: 348.2323. L-Selectride (1 M in THF, 0.20 ml, 0.20 mmol) was added to a solution of **18** (16.8 mg, 0.048 mmol) at −78 °C under N_2, and the mixture was stirred for 2 h,

then warmed to room temperature. After the addition of EtOH (0.10 ml), 15% NaOH (0.15 ml) and 30% H_2O_2 (0.15 ml) were added, the whole was stirred for 3 h, then extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane: AcOEt = 1 : 1) to give **19** (11.0 mg, 65%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3470. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.70 (3H, s, C-10Me), 0.99 (3H, s, C-4Me), 3.67 (1H, dd, J = 3.5, 3.5 Hz, C-3H), 3.40 (2H, m, C$\underline{H}_2$OH), 3.80—3.96 (4H, m, OCH_2CH_2O). MS *m/z*: 350 (M^+). HR-MS Calcd for $C_{21}H_{34}O_4$: 350.2457. Found: 350.2487.

***rac*-17-Noraphidicolin-16-one (20)** A 5% HCl solution (0.5 ml) was added to a solution of **19** (10.0 mg, 0.029 mmol) in THF (1 ml), and the mixture was stirred at 40 °C for 5 h. After cooling, the mixture was extracted with AcOEt, and the extract was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 2) to give **20** (8.7 mg, 98%) as a colorless oil. IR ($CHCl_3$) cm^{-1}: 3470, 1710. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.73 (3H, s, C-10Me), 1.07 (3H, s, C-4Me), 3.44 (2H, m, C-4H), 3.74 (1H, m, C-3H). MS *m/z*: 306 (M^+). HR-MS Calcd for $C_{19}H_{30}O_3$: 306.2195. Found: 306.2202.

***rac*-3α,18-(Isopropylidenedioxy)-17-noraphidicolan-16-one (4)** A mixture of **20** (8.7 mg, 0.029 mmol), PPTS (1 mg), and 2,2-dimethoxypropane (1 ml) was stirred at room temperature for 30 min. Saturated $NaHCO_3$ was added, and the whole was extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane: AcOEt = 5 : 1) to give the expected acetonide **4** (9.2 mg, 92%) as colorless crystals, mp 143—146 °C (from *n*-hexane–Et_2O) (lit.[5j] 143—145 °C). IR ($CHCl_3$) cm^{-1}: 1720. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.73 (3H, s, C-10Me), 1.07 (3H, s, C-4Me), 1.42 (6H, s, CMe_2), 3.25, 3.61 (2H, AB, J = 11.5 Hz, C-4 CH_2–O), 3.68 (1H, dd, J = 3.5, 3.5 Hz, C-3H). MS *m/z*: 346 (M^+). HR-MS Calcd for $C_{22}H_{34}O_3$: 346.2505. Found: 346.2495.

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References and Notes

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7) Although the stereochemistry of the methyl group was speculated to be the desired one on the basis of the reaction mechanism, this could not be proved spectroscopically at the stage of compound **8**. It was confirmed by ^{1}H-NMR analysis including nuclear Overhauser effect (NOE) measurement at the stage of compound **14**, as illustrated in Chart 3. Namely, the signal of the C-6 βH appeared at δ 5.39 as ddd (J = 11.1, 5.8, 2.8 Hz), thereby showing that this proton is located at an axial position. In addition, NOE was observed between this proton and C-8H and C-10Me. These data proved not only the correct stereochemistry of compounds **13** and **14**, but also the desired introduction of the methyl group into the enone **7**.
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