Synthetic Studies on Aphidicolane and Stemodane Diterpenes. V.[1] A Facile Formal Total Synthesis of (±)-Aphidicolin *via* a Lewis Acid-Mediated Stereoselective Spiroannelation

Tetsuaki TANAKA,[a] Osamu OKUDA,[a] Kazuo MURAKAMI,[a] Hitoshi YOSHINO,[a] Hidenori MIKAMIYAMA,[a] Atsushi KANDA,[a] Sang-Wong KIM,[b] and Chuzo IWATA*,[a]

Faculty of Pharmaceutical Sciences, Osaka University,[a] 1–6 Yamadaoka, Suita, Osaka 565, Japan and Faculty of Pharmaceutical Sciences, Josai University,[b] 1–1 Keyakidai, Sakado, Saitama 350–02, Japan.
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Formal total synthesis of (±)-aphidicolin (1) was achieved *via* a Lewis acid-mediated stereoselective spiroannelation reaction as a key step. The bisbenzyl acetal (2) was synthesized from the readily available dimethyl acetal (4). Treatment of 2 with trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded a 69:31 mixture of the spirocyclic enones (9 and 10) in excellent yield. The tricyclic ketal-ketone (3) corresponding to the B/C/D rings of 1 was easily generated from the enone (9) by intramolecular alkylation and catalytic hydrogenation as principal steps. The A-ring construction was performed by a procedure similar to one used previously. Barbier reaction of 14, followed by oxidative rearrangement, stereoselective 1, 4-addition of a methyl group, and subsequent intramolecular aldol-condensation afforded the tetracyclic enone (18), which has already been transformed into (±)-aphidicolin (1).

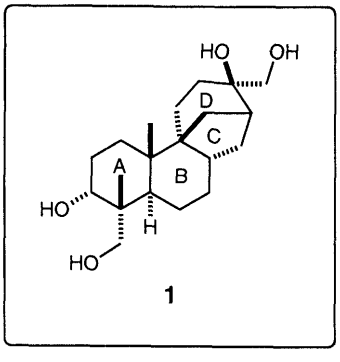
Key words aphidicolin; formal total synthesis; stereoselective spiroannelation; trimethylsilyl trifluoromethanesulfonate; benzyl acetal

Aphidicolin (**1**) is a tetracyclic diterpenoid produced by the fungus *Cephalosporium aphidicola* PETCH[2a] and other fungi[2b] (Chart 1). In 1972, the absolute structure of **1** was determined by Hesp and co-workers by means of X-ray crystallographic analysis.[2a] The diterpenoid (**1**) has eight stereogenic centers and comprises a bicyclo-[3.2.1]octane moiety (C/D-rings) fused with a *trans*-decalin moiety (A/B-ring). In spite of its simple functionality, **1** displays remarkable anti-viral[3a] and anti-tumor activities.[3b] These biological activities are due to its specific inhibitory effects on DNA polymerase-α, so that it does not interfere with mitochondrial DNA synthesis, or with RNA , protein, and nucleic acid precursors synthesis.[3c] Hence, **1** is expected to be an anti-cancer or anti-psoriasis agent for clinical use.[3c] Because of its unique structural features together with its exciting biological properties, **1** has been an attractive synthetic target to many organic chemists.[1,4]

Our synthetic studies on aphidicolin (**1**) have been based on the strategy of constructing the B/C/D-ring, followed by A-ring cyclization.[5] In connection with our strategy for the ring construction sequence,[5] we hoped to establish an alternative and facile synthetic route to aphidicolin (**1**) by utilizing the recently developed stereoselective spiroannelation reaction.[6] The substrate for the spiroannelation reaction was selected to be the bisbenzyl acetal (**2**) in view of the facile subsequent transformations into the tricyclic intermediate (**3**) (Chart 1).[7] In this paper, we present a facile formal total synthesis of (±)-aphidicolin (**1**) *via* a stereoselective spiroannelation.

The bisbenzyl acetal (**2**), the substrate for the spiroannelation reaction, was synthesized as follows (Chart 2): The easily obtainable dimethyl acetal (**4**)[6] was converted to the benzyl acetal (**5**) by treatment with benzyl alcohol in *n*-hexane in the presence of *p*-toluenesulfonic acid (*p*-TsOH) and molecular sieves 3A (MS 3A). Deconjugative alkylation of the α,β-unsaturated ester (**5**) with 4-bromobutanal dibenzyl acetal (**6**)[8] afforded **7** by treatment with sodium hydride (NaH) and 1,3-dimethyl-2-imidazolidinone (DMI) in tetrahydrofuran (THF) at room temperature. After reduction of **7** with lithium aluminum hydride (LAH), the resulting alcohol (**8**) was mesylated to give **2**.

The important tricyclic intermediate (**3**) for **1** was synthesized by utilizing the TMSOTf-mediated stereoselective spiroannelation[6] as follows (Chart 3): Treatment of



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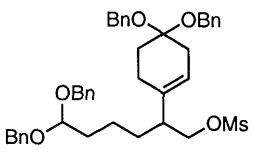

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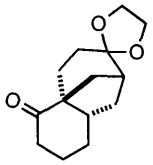

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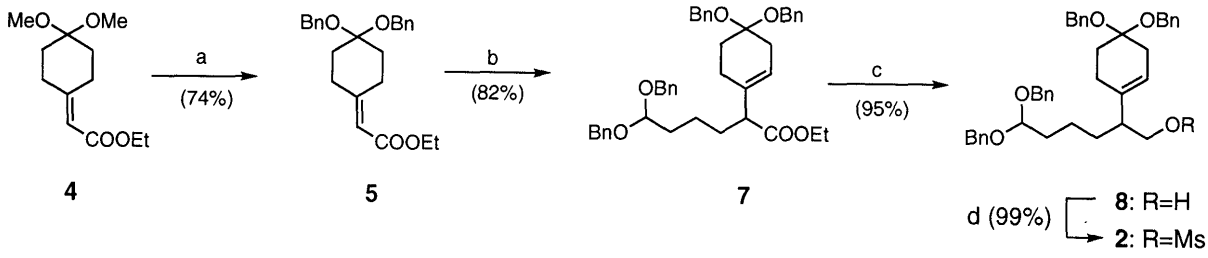
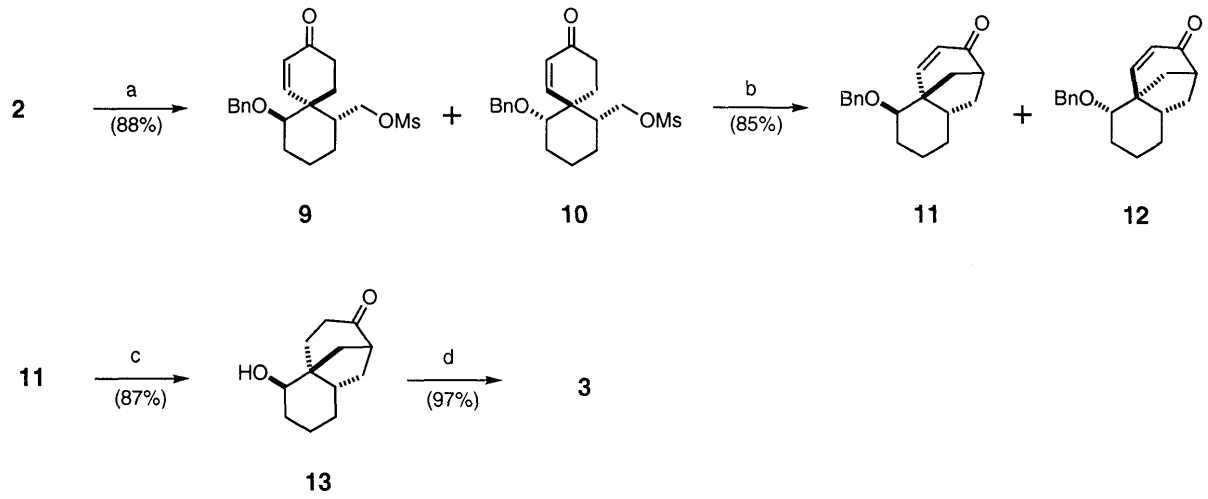
Chart 1

* To whom correspondence should be addressed.



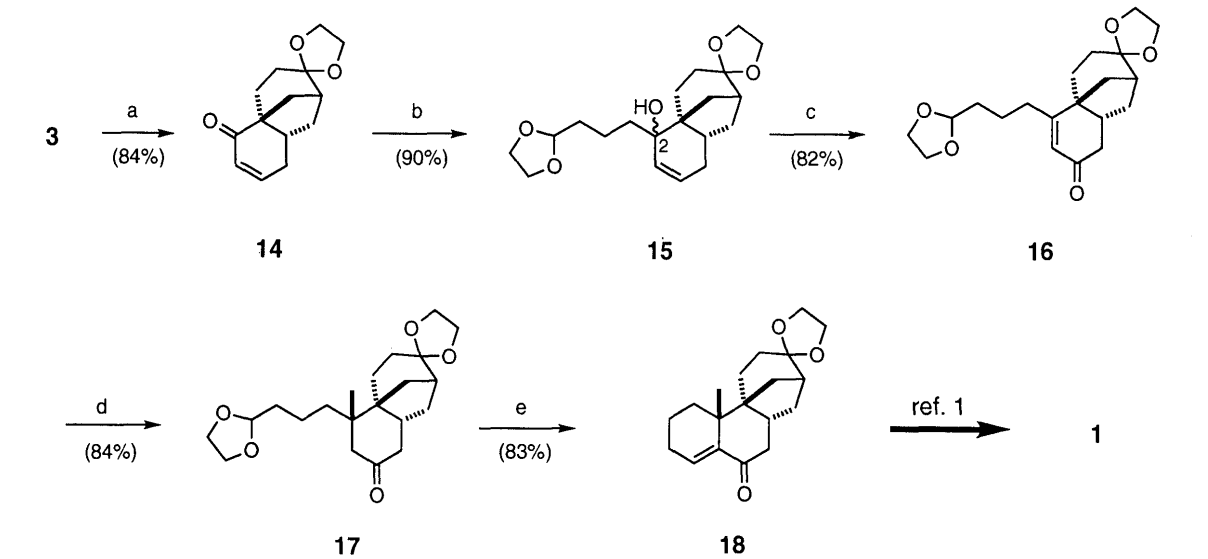
a) *p*-TsOH, BnOH, *n*-hexane, b) NaH, DMI, $(BnO)_2CH(CH_2)_3Br$ (**6**), THF c) LAH, Et_2O d) MsCl, Et_3N, DMAP, CH_2Cl_2

Chart 2



a) TMSOTf, CH_3CN/CH_2Cl_2, -78 °C, b) *t*-BuOK, Et_2O, c) H_2(5 atm), Pd-C, AcOEt, 40-50 °C, d) ethylene glycol, PPTS, benzene; PCC, CH_2Cl_2

Chart 3



a) LDA, PhSeBr, THF; H_2O_2, pyridine, CH_2Cl_2, b) Li, 4-bromobutanal ethylene acetal, Et_2O, ultrasonic irradiation, c) PCC, CH_2Cl_2, d) Me_2CuLi, Et_2O, e) *p*-TsOH, benzene

Chart 4

the bisbenzyl acetal (**2**) with TMSOTf in a 1:1 mixture of CH_2Cl_2 and CH_3CN at −78 °C readily furnished a 69:31 mixture of the spirocyclic compounds (**9** and **10**) in excellent yield. Since the diastereomeric mixture did not tolerate column chromatographic separation due to its lability on silica gel, the next transformation was performed on the mixture. The mixture of **9** and **10** was treated with potassium *tert*-butoxide (*t*-BuOK) to afford the tricyclic enones (**11** and **12**). At this stage, **11** was purified by ordinary chromatography. Medium-pressure

catalytic hydrogenation of the benzyl ether (**11**) in the range of 40 to 50 °C gave cleanly the keto-alcohol (**13**) in excellent yield (87%). Because compound **13** was identical with the compound previously synthesized,[6] the correct stereochemistry was verified. Compound **13** was ketalized followed by oxidation with pyridinium chlorochromate (PCC) to afford the ketal-ketone (**3**).

Next, the stereoselective construction of the A-ring of **1** was accomplished by employing our synthetic sequence reported recently, with a slight modification (Chart 4).[1] The ketal-ketone (**3**) was converted into the enone (**14**) by the usual α-selenenylation-oxidation sequence. The Barbier reaction[9] under ultrasonic irradiation was applied to **14** with 4-bromobutanal ethylene acetal[10] to afford the 1,2-adduct (**15**). Oxidative allylic rearrangement of **15** with PCC gave the enone (**16**). Compound **16** was treated with dimethyl copper lithium to give the 1,4-adduct (**17**) as a single diastereomer. Although we speculated that the methyl group would have been introduced from the less hindered β-face, the stereochemistry of the methyl group could not be determined at this stage. Therefore, the stereochemistry was established by the transformation of **17** into the known enone (**18**).[1] Without deprotection of the acetal moiety, an acid treatment of **17** in benzene afforded the desired enone-acetal (**18**) directly. Compound **18** was identical with the compound previously reported.[1] Since the enone (**18**) has been transformed into **1**,[1] we have accomplished the formal total synthesis of (±)-aphidicolin (**1**).

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 or a Horiba FT-210 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in $CDCl_3$ solution on a Varian VXR 200 (200 MHz), a Hitachi R-250HT (250 MHz), a JEOL EX270 (270 MHz), or a JEOL JNM-GX500 (500 MHz) spectrometer. Mass spectra (MS) were obtained with a Shimadzu GCMS-QP-1000, and high-resolution mass spectra (HRMS) were measured with a JEOL JMS-D300 mass spectrometer. Column chromatography was performed on Merck Kieselgel 60 unless otherwise noted. All extracts were dried over anhydrous Na_2SO_4 before evaporation.

Ethyl 4,4-Dibenzyloxycyclohexylideneacetate (5) A solution of ethyl 4,4-dimethoxycyclohexylideneacetate (**4**)[6] (100 mg, 0.44 mmol) in *n*-hexane (1 ml) was added to a suspension of benzyl alcohol (BnOH) (0.1 ml, 1.03 mmol), *p*-TsOH·H_2O (17 mg, 0.09 mmol), and MS 3A (500 mg) in *n*-hexane (2 ml) and the mixture was stirred for 22 h at room temperature. MS 3A was filtered off and saturated $NaHCO_3$ aqueous solution was added. The whole was extracted with ether. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 10 : 1) to afford **5** (123 mg, 74%) as a colorless oil. IR (KBr) cm^{-1}: 1713, 1651. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.27 (3H, t, J = 7.2 Hz, $CH_2C\underline{H}_3$), 1.94—2.06 (4H, m, $(C\underline{H}_2)_2(OBn)_2$), 2.28—2.41 (2H, m, $CH_2C{=}C_{trans}$), 2.93—3.05 (2H, m, $CH_2C{=}C_{cis}$), 4.14 (2H, q, J = 7.2 Hz, $C\underline{H}_2CH_3$), 4.59 (4H, s, $2(C\underline{H}_2Ar)$), 5.67 (1H, s, CH = C), 7.20—7.41 (10H, s, 2Ar). MS *m/z* (%): 289 (M^+ − Bn, 2.0). *Anal.* Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.41. Found: C, 75.96; H, 7.40.

4-Bromobutanal Dibenzyl Acetal (6) A mixture of 4-bromobutanal[8] (1.51 g, 10.0 mmol), BnOH (2.14 ml, 22.0 mmol), *p*-TsOH·H_2O (0.19 g, 1.0 mmol), and benzene (50 ml) was refluxed under a Dean-Stark water separator for 3 h, then allowed to cool. Saturated $NaHCO_3$ aqueous solution was added and the mixture 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 : Et_3N = 15 : 1 : 0.01) to give **6** (2.58 g, 74%), as a colorless oil. IR (KBr) cm^{-1}: 1603. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.84—2.06 (4H, m, $C\underline{H}_2C\underline{H}_2CH$), 3.41 (2H, t, J = 6.2 Hz, $C\underline{H}_2Br$), 4.56, 4.67 (4H, each d, J = 11.6 Hz, $2(C\underline{H}_2Ar)$), 4.76 (1H, t, J = 5.2 Hz, CH), 7.34 (10H, s, 2Ar). MS *m/z* (%): 240 (M^+ − 1 − BnOH, 4.7). HRMS Calcd for $C_{11}H_{13}BrO$ (M^+ − 1 − BnOH): 240.0147. Found: 240.0146.

Ethyl 6,6-Dibenzyloxy-2-(4,4-dibenzyloxy-1-cyclohexenyl)hexanoate (7) A solution of **6** (1.19 g, 3.41 mmol) in THF (0.2 ml) was added to a suspension of **5** (1.00 g, 2.63 mmol), NaH (60% in oil, 188 mg, 4.7 mmol), and DMI (0.17 ml, 1.58 mmol) in THF (1.0 ml). The whole was stirred for 12 h at room temperature. Saturated NH_4Cl aqueous solution and water were added and the whole was extracted with EtOAc. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 6 : 1) to afford **7** (1.39 g, 82%) as a colorless oil. IR (KBr) cm^{-1}: 1728, 1606. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.20 (3H, t, J = 7.1 Hz, $CH_2C\underline{H}_3$), 1.25—2.21 (11H, m), 2.38—2.55 (2H, m, $C\underline{H}_2CH{=}C$), 2.86—3.02 (1H, m, CHC = C), 4.10 (2H, q, J = 7.1 Hz, $C\underline{H}_2CH_3$), 4.47—4.75 (total 9H, m, $4(C\underline{H}_2Ar)$ and $C\underline{H}(OBn)_2$), 5.46 (1H, br s, CH = C), 7.18—7.41 (20H, m, 4Ar). MS *m/z* (%): 648 (M^+, 0.06), 540 (M^+ − BnOH, 0.17), 434 (M^+ − 2BnOH, 6.0). HRMS Calcd for $C_{35}H_{40}O_5$ (M^+ − BnOH): 540.2873. Found: 540.2873.

6,6-Dibenzyloxy-2-(4,4-dibenzyloxy-1-cyclohexenyl)hexan-1-ol (8) A solution of **7** (350 mg, 0.54 mmol) in diethyl ether (Et_2O) (1 ml) was added dropwise to a stirred suspension of LAH (41 mg, 1.08 mmol) in Et_2O (1.3 ml) at 0 °C and the stirring was continued for 15 min at room temperature. Water (0.04 ml), 10% NaOH aqueous solution (0.04 ml) and water (0.12 ml) were successively added at 0 °C and the mixture was stirred for 30 min at room temperature, then filtered, and the filtrate was evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 2 : 1) to afford **8** (312 mg, 95%) as a colorless oil. IR (KBr) cm^{-1}: 3469, 1605, 1585. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.20—2.54 (13H, m), 3.34—3.50 (2H, m, $C\underline{H}_2OH$), 4.46—4.73 (total 9H, m, $4(C\underline{H}_2Ar)$ and $C\underline{H}(OBn)_2$), 5.35—5.48 (1H, m, CH = C), 7.18—7.41 (20H, m, 4Ar). MS *m/z* (%): 606 (M^+, 0.08), 390 (M^+ − 2BnOH, 0.6). HRMS Calcd for $C_{26}H_{30}O_3$ (M^+ − 2BnOH): 390.2195. Found: 390.2196.

6,6-Dibenzyloxy-2-(4,4-dibenzyloxy-1-cyclohexenyl)hexyl Methanesulfonate (2) Methanesulfonyl chloride (0.12 ml, 1.58 mmol) was added dropwise to a solution of **8** (800 mg, 1.32 mmol) and Et_3N (0.37 ml, 2.64 mmol) in CH_2Cl_2 at 0 °C. The solution was stirred for 3 h at room temperature, then water was added at 0 °C, and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 3 : 1) to afford **2** (898 mg, 99%) as a colorless oil. IR (KBr) cm^{-1}: 1606, 1585. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.28—2.54 (11H, m), 2.82 (3H, s, CH_3), 4.00—4.18 (2H, m, CH_2OMs), 4.46—4.73 (total 9H, m, $4(C\underline{H}_2Ar)$ and $C\underline{H}(OBn)_2$), 5.34—5.45 (1H, m, CH = C), 7.18—7.41 (20H, m, 4Ar). MS *m/z* (%): 282 (M^+ − 2BnOH − Bn − OMs, 2.4), 266 (M^+ − 3BnOH − OMs, 0.7). HRMS Calcd for $C_{19}H_{22}O_2$ (M^+ − 2BnOH − Bn − OMs): 282.1617. Found: 282.1605.

(6*RS*,7*RS*,11*SR*)- and (6*RS*,7*SR*,11*SR*)-7-Benzyloxy-11-mesyloxymethylspiro[5.5]undec-1-en-3-one (9 and 10) Under an argon atmosphere, TMSOTf (20 μl, 0.10 mmol) was added to a solution of **2** (23.4 mg, 0.034 mmol) in CH_2Cl_2 (3.4 ml) and CH_3CN (3.4 ml) at −78 °C and the mixture was stirred for 30 min. Saturated $NaHCO_3$ aqueous solution was added, and the whole was washed with water and brine, then dried, and evaporated. The residue was purified by chromatography (*n*-hexane : AcOEt = 1 : 1) to give a 69 : 31 mixture of **9** and **10** (11.4 mg, 88%), as a colorless oil. IR (KBr) cm^{-1}: 1705, 1678, 1608. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.18—2.93 (11H, m), 2.97 (3H, s, CH_3), 3.27 (1 × 31/100H, dd, J = 3.9, 10.3 Hz, $C\underline{H}OBn$), 3.75—3.78 (1 × 69/100H, m, $C\underline{H}OBn$), 3.93—4.85 (total 4H, m, $C\underline{H}_2OMs$ and $C\underline{H}_2Bn$), 6.03 (1 × 69/100H, d, J = 10.4 Hz, CH = C$\underline{H}$C = O), 6.14 (1 × 31/100H, d, J = 10.2 Hz, CH = C$\underline{H}$C = O), 6.53 (1 × 31/100H, d, J = 10.2 Hz, C$\underline{H}$ = CHC = O), 7.06 (1 × 69/100H, dd, J = 1.5, 10.4 Hz, C$\underline{H}$ = CHC = O), 7.13—7.43 (5H, m, Ar-H). MS *m/z* (%): 378 (M^+, 5.9). HRMS Calcd for $C_{20}H_{26}O_5S$: 378.1501. Found: 378.1513.

(1*RS*,2*RS*,6*SR*,8*RS*)- and (1*RS*,2*RS*,6*RS*,8*SR*)-2-Benzyloxytricyclo[6.3.1.0^{1,6}]dodec-10-en-9-one (11 and 12) A solution of **9** and **10** (1.23 g, 3.25 mmol) in Et_2O (5 ml) was added to a suspension of *tert*-BuOK (730 mg, 6.5 mmol) in Et_2O (60 ml) at 0 °C. The whole was stirred for 30 min at room temperature. Water was added and the mixture was extracted with EtOAc. The extract was washed with water and brine, then dried, and evaporated. The residue was purified by flash column chromatography (*n*-hexane : AcOEt = 4 : 1) to give **11** (542 mg, 59%) and **12** (241 mg, 26%), each as a colorless oil. For **11**, IR (KBr) cm^{-1}: 1682,

1605. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.04—2.19 (11H, m), 2.79—2.91 (1H, m, CHC(=O)), 3.61—3.66 (1H, m, CHOBn), 4.42, 4.70 (2H, each d, J=11.4, 11.4 Hz, CH_2Bn), 5.81 (1H, dd, J=1.7, 9.8 Hz, C-10H), 7.25—7.42 (5H, m, Ar), 7.60 (1H, dd, J=2.0, 9.8 Hz, C-9H). MS m/z (%): 282 (M^+, 3.9). HRMS Calcd for $C_{19}H_{22}O_2$: 282.1620. Found: 282.1622. For **12**, IR (KBr) cm^{-1}: 1686, 1603. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.02—2.20 (11H, m), 2.82—2.98 (1H, m, CHC(=O)), 3.62 (1H, dd, J=4.7, 10.7 Hz, CHOBn), 4.60 (2H, each d, J=12.0, 12.2 Hz, CH_2Bn), 5.82 (1H, dd, J=1.8, 9.8 Hz, C-10H), 6.86 (1H, d, J=9.8 Hz, C-9H), 7.25—7.46 (5H, m, Ar). MS m/z (%): 282 (M^+, 2.0). HRMS Calcd for $C_{19}H_{22}O_2$: 282.1619. Found: 282.1624.

(1*RS*,2*SR*,6*RS*,8*SR*)-2-Hydroxytricyclo[6.3.1.0^{1,6}]dodecan-9-one (13) Pd–C (10%, 56 mg) was added to a solution of **11** (565 mg, 2.00 mmol) in AcOEt (40 ml), and the mixture was stirred for 12 h under 5 atm of H_2 at 40—50°C. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 1) to give **13** (337 mg, 87%) as a colorless oil, which was identical with the compound synthesized previously.[6]

(1*RS*,6*RS*,8*SR*)-Tricyclo[6.3.1.0^{1,6}]dodecane-2,9-dione 9,9-Ethylene Acetal (3) Compound **3** was prepared from **13** by use of the reported procedures.[6b]

(1*RS*,6*RS*,8*SR*)-Tricyclo[6.3.1.0^{1,6}]dodec-3-ene-2,9-dione 9,9-Ethylene Acetal (14) A solution of **3** (228 mg, 0.97 mmol) in THF (3 ml) was added dropwise to a lithium diisopropylamide (LDA) solution [prepared from iso-Pr_2NH (0.23 ml, 1.53 mmol) and *n*-BuLi (1.64 M in *n*-hexane, 0.88 ml, 1.46 mmol) in THF (3 ml) at 0 °C] at −78 °C, and the whole was stirred for 30 min. A solution of PhSeBr (343 mg, 0.97 mmol) in THF (3 ml) was added all at once, and the resulting mixture was stirred for 10 min. Saturated NH_4Cl aqueous solution and water were added, then the whole was extracted with AcOEt. The extract was washed with brine, then dried, and evaporated. The residue was dissolved in CH_2Cl_2 (4 ml), and the solution was cooled to 0 °C. Then pyridine (0.16 ml, 1.94 mmol) and 15% H_2O_2 (2.4 ml) were added, and the whole was stirred for 15 min at room temperature. The mixture was diluted with $CHCl_3$, and the organic phase was washed with brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 3 : 1) to give **14** (191 mg, 84%) as colorless crystals, mp 79.0—80.0 °C (from *n*-hexane). IR (KBr) cm^{-1}: 1678, 1603. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.52—2.58 (12H, m), 3.81—4.03 (4H, m, OCH_2CH_2O), 5.85—5.90 (1H, m, CH=CH–CO), 6.89 (1H, ddd, J=1.7, 5.6, 9.8 Hz, CH=CH–CO). MS m/z (%): 236 (M^+, 100). *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.55; H, 7.70.

(1*RS*,6*SR*,8*SR*)-2-(4,4-Ethylenedioxybutyl)tricyclo[6.3.1.0^{1,6}]dodec-2-ene-4,9-dione 9,9-Ethylene Acetal (16) A solution of **14** (20.0 mg, 0.085 mmol) and 4-bromobutanal ethylene acetal[9] (82.9 mg, 0.43 mmol) in Et_2O (0.8 ml) was added to a suspension of lithium powder [30% lithium dispersion (1% Na) (30 mg, 1.28 mg-atom) washed with hexane and dried] in Et_2O (0.8 ml) at room temperature. The mixture was ultrasonicated for 1 h at room temperature. MeOH and saturated NH_4Cl aqueous solution were added successively, 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 = 1 : 1) to give (1*RS*,6*RS*,8*SR*)-2-(4,4-ethylenedioxybutyl)-2-hydroxytricyclo[6.3.1.0^{1,6}]dodec-3-ene-4,9-dione 9,9-ethylene acetal (**15**) (27.1 mg, 90%) as a colorless oil. A solution of **15** (152 mg, 0.43 mmol) in CH_2Cl_2 (3 ml) was added to a suspension of PCC (370 mg, 1.72 mmol), AcONa (71 mg, 0.86 mmol), and alumina (2.0 g) in CH_2Cl_2 (5.6 ml) at 0 °C, and the mixture was stirred at room temperature for 8 h. After the addition of Et_2O (8.6 ml), the suspension was applied to a Florisil column, and eluted with Et_2O. The eluate was evaporated, and the residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 1) to give **16** (124 mg, 82%) as a colorless oil. IR (KBr) cm^{-1}: 1664, 1603. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.57—2.83 (19H, m), 3.90—4.22 (8H, m, 2(OCH_2CH_2O)), 4.87 (1H, t, J=4.3, CH(OCH_2-CH_2O)), 5.70 (1H, s, C=CH). MS m/z (%): 348 (M^+, 0.7). HRMS Calcd for $C_{20}H_{28}O_5$: 348.1936 Found: 348.1943.

(1*RS*,2*RS*,6*SR*,8*SR*)-2-(4,4-Ethylenedioxybutyl)-2-methyltricyclo-[6.3.1.0^{1,6}]dodecane-4,9-dione 9,9-Ethylene Acetal (17) MeLi (1.09 M in Et_2O, 0.95 ml, 1.03 mmol) was slowly added to a suspension of CuI (98.5 mg, 0.52 mmol) in Et_2O (1.0 ml) at −20 °C, and the whole was stirred for 15 min. A solution of **16** (90.0 mg, 0.258 mmol) in Et_2O (1.6 ml) was further added at 0 °C, and the whole was stirred at room temperature for 3 h. Saturated NH_4Cl aqueous 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 = 1 : 1) to give **17** (78.7 mg, 84%) as a colorless oil. IR (KBr) cm^{-1}: 1707. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.96 (3H, s, C-2 Me), 1.18—2.52 (20H, m), 3.80—4.06 (8H, m, 2(OCH_2-CH_2O)), 4.85 (1H, t, J=4.4 Hz, CH(OCH_2)$_2$. MS m/z (%): 364 (M^+, 0.08). HRMS Calcd for $C_{21}H_{32}O_5$: 364.2247. Found: 364.2237.

***rac*-17,18,19-Trisnoraphidicol-4-ene-6,16-dione 16,16-Ethylene Acetal (18)** A mixture of **17** (9.2 mg, 0.025 mmol) and *p*-TsOH (0.5 mg, 0.0026 mmol) in benzene (5 ml) was stirred for 24 h at 75 °C (bath temperature). Saturated $NaHCO_3$ aqueous solution was added and the resulting mixture was extracted with AcOEt. The organic layer was washed with water and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give **18** (6.3 mg, 83%) as colorless crystals, mp 180.0—181.0 °C (from *n*-hexane–CH_2Cl_2). The compound obtained here was identical with the compound synthesized previously.[1]

References and Notes

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7) Originally, the dimethyl acetal instead of the dibenzyl acetal was used for the development of the spiroannelation reaction. However, in the synthetic sequence, the methyl ether cleavage suffered from unsatisfactory yield. In order to establish an efficient and facile synthetic route to aphidicolin (**1**), the benzyl analogue was considered appropriate. For details, see reference 6*b*.

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