Notes

A Total Synthesis of Grifolin

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An antibiotic, grifolin, was synthesized in seven steps starting from orcinol by utilizing a biogenetic-type olefination.

In a preceding paper, we reported a mild biogenetic-type olefination coordinated with dehydrative decarboxylation (Chart 1).[1] This paper deals with an application of the olefination to a total synthesis of a terpenoid antibiotic, grifolin (4).[2]
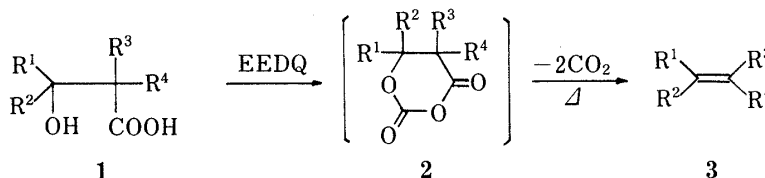

Chart 1

Grifolin (4) is an antibiotic isolated from *Grifola confluens* by Goto and coworkers in 1968[2] and several total syntheses have been reported.[3] We planned to synthesize 4 by an application of the olefination reaction starting from orcinol (5). The two phenolic hydroxyl groups of orcinol (5) were protected with methoxymethyl groups by treatment with chlorodimethyl ether in the presence of sodium hydride in dimethylformamide (DMF). Formylation of the ether (6) thus obtained was carried out by treatment with n-butyllithium (n-BuLi) at $-78\,^\circ$C followed by addition of DMF to give 2,6-bismethoxymethyloxy-4-methylbenzaldehyde (7) in 68.9% yield. The structure of the product (7) was confirmed by its proton nuclear magnetic resonance (^{1}H-NMR) spectrum, all signals of which are symmetric; therefore, the product is not 7' but is 7. The aldehyde (7) was converted to the corresponding cinnamic acid (8) by a modified Perkin reaction[4] in 84.3% yield. The acid (8) was hydrogenated in the presence of 5% Pd-charcoal in a usual manner to give a 3-phenylpropionic acid (9) in quantitative yield. The corresponding methyl ester was prepared as an analytical sample by treatment with an ethereal solution of diazomethane.

On the other hand, sterically pure geranyl chloride (10) was prepared starting from myrcene according to Takabe *et al.*[5] Then, ethyl acetoacetate was alkylated with 10 in the usual manner followed by decarboxylation of the intermediate (11) to give pure (E)-geranylacetone (12). The overall yield of 12 from myrcene was 53.7%. The purity of the (E)-geranylacetone (12) was checked by 300 MHz ^{1}H-NMR spectroscopy.[6]
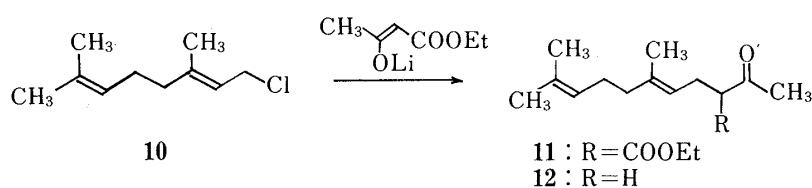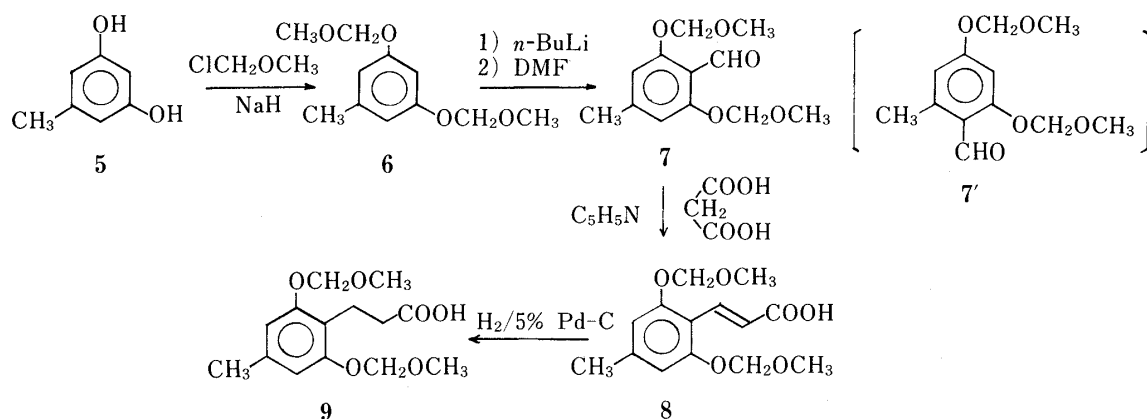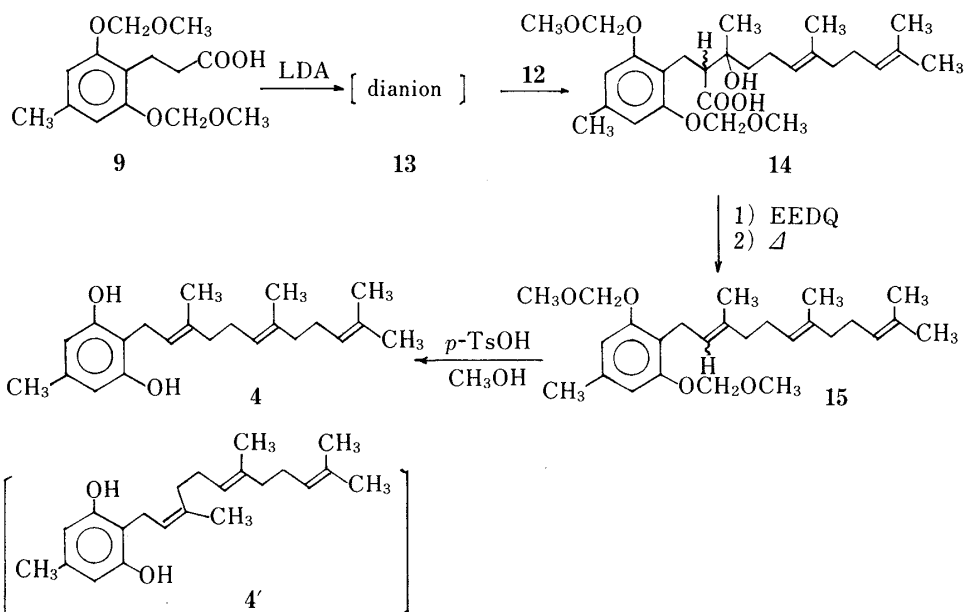
Chart 2

Chart 3

Aldol reaction of the lithium enolate (13) of 9 with (E)-geranylacetone (12) was carried out according to the reported method[7] to give a viscous 3-tert-hydroxypropionic acid (14) in 83.9% yield. The crude product (14) was subjected to olefination[1] with N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) to give a crude product, which was purified by chromatography on silica gel to isolate an oily material (15) in 52.7% yied. The infrared (IR) spectrum of the product (15) showed no carbonyl group absorption near 1700 cm^{-1} but exhibited olefinic absorptions at 1610 and 1580 cm^{-1}. Removal of the two methoxymethyl groups was somewhat difficult because grifolin is known to be unstable in an acidic medium.[2] For example, the olefinic ether (15) afforded a complex mixture upon refluxing in methanol containing a small amount of concentrated hydrochloric acid. All attempts to cleave the ether linkages with trimethylsilyl iodide[8] resulted in complex mixtures, which contained only a

trace amount of the desired product, grifolin (4). Surprisingly, the best result was obtained by treating **15** with a small amount of *p*-toluenesulfonic acid in methanol at room temperature, and grifolin (**4**; mp 35—37 °C) was obtained in 43.9% yield. The spectral characteristics of the synthetic grifolin were identical with those of natural grifolin.

Experimental

All melting points are uncorrected. IR spectra were taken with a Shimadzu IR-410 spectrometer. ^{1}H-NMR spectra were obtained at 80 MHz on a Varian CFT-20 spectrometer and at 300 MHz on a Varian XL-300 spectrometer, and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^{1}H-NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). The ultraviolet (UV) spectrum was taken with a Shimadzu UV-200S spectrometer. Mass spectra (MS) were obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure by using a rotary evaporator in the usual work-up procedure. Unless otherwise stated, anhydrous sodium sulfate was used as a drying agent. A Kugel-Rohr apparatus was used for vacuum distillation of crude oils. Silica gel (Merck Art. 7734) was used in column chromatography.

Bismethoxymethyl Ether (6) of Orcinol (5)——A solution of orcinol (11.78 g, 95 mmol) in dry DMF (42 ml) was added at below 75 °C under a nitrogen atmosphere to a stirred suspension of NaH (5.13 g, 214 mmol) in dry DMF (55 ml). The mixture was stirred at room temperature for 2 h, and then chlorodimethyl ether (16.0 ml, 211 mmol) was added at below 60 °C, followed by stirring at room temperature overnight. Ice water (310 ml) was added to the reaction mixture and insoluble materials were filtered off. The filtrate was extracted with benzene (125 ml × 4) and the organic layer was evaporated after drying with solid K_2CO_3 to give a red-brown oil. The oil was purified by column chromatography on silica gel (eluent: Et_2O) followed by vacuum distillation. bp_5 155 °C. Yield, 16.71 g (83.0%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600 (benzene), 1140, 1035 (C–O). ^{1}H-NMR (80 MHz in CDCl$_3$) δ: 2.29 (s, 3H, Ar–C$\underline{H}_3$), 3.47 (s, 6H, OC$\underline{H}_3$ × 2), 5.13 (s, 4H, OC$\underline{H}_2$O), 6.53 (s, 3H, Ar-H).

2,6-Bis(methoxymethyloxy)-4-methylbenzaldehyde (7)——An ethereal solution (140 ml) of the protected orcinol (**6**; 16.71 g, 78.8 mmol) was added over 15 min to a stirred ethereal solution of 1.6 M *n*-BuLi in hexane (55.4 ml, 90 mmol) at −78 °C under a nitrogen atmosphere. The mixture was refluxed for 1 h at 40 °C. Dry DMF (8.1 ml, 105 mmol) was added at room temperature and the reaction mixture was stirred overnight. Water and ether were added, and the aqueous layer was extracted thoroughly with ether. The combined ethereal layer was washed with saturated NH$_4$Cl (120 ml × 3), 5% NaOH (120 ml × 2) and saturated NaCl, and dried with solid K_2CO_3. The solvent was evaporated off to give a yellow crystalline residue, recrystallization of which from Et_2O–*n*-hexane afforded colorless prisms, mp 40— 42 °C. Yield, 13.00 g (68.9%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (ArCHO). ^{1}H-NMR (80 MHz in CDCl$_3$) δ: 2.35 (s, 3H, Ar–C$\underline{H}_3$), 3.50 (s, 6H, OC$\underline{H}_3$ × 2), 5.24 (s, 4H, OC$\underline{H}_2$O × 2), 6.65 (s, 2H, Ar-H), 10.48 (s, 1H, C$\underline{H}$O). MS *m/z*: 240 (M$^+$, 6%). High-resolution MS *m/z*: Calcd for $C_{12}H_{16}O_5 = 240.0998$. Found $= 240.0996$. *Anal.* Calcd: C, 59.99; H, 6.71. Found: C, 59.75; H, 6.62.

(*E*)-3-[2,6-Bis(methoxymethyloxy)-4-methylphenyl]acrylic Acid (8)——A mixture consisting of the aldehyde (**7**; 13.03 g, 54.3 mmol), malonic acid (6.86 g, 65.5 mmol), piperidine (0.5 ml) and pyridine (25 ml) was heated at 90 °C for 2.5 h. Water and ethyl acetate were added, and the organic layer was dried and evaporated. Xylene was added to the oily residue, and the mixture was evaporated. This operation was repeated three times to give finally pale yellow crystals, which were corrected by filtration and washed with a small amount of ethyl acetate. The crude product was recrystallized from ethyl acetate–*n*-hexane to give colorless prisms, mp 167.5—170.5 °C. Yield, 12.90 g (84.3%). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O), 2700, 2600 (OH). ^{1}H-NMR (80 MHz in CDCl$_3$) δ: 2.33 (s, 3H, Ar–C$\underline{H}_3$), 3.50 (s, 6H, OC$\underline{H}_3$ × 2), 5.25 (s, 4H, OC$\underline{H}_2$O), 6.66 (s, 2H, Ar-H), 6.85 (d, 1H, Ar-CH=C$\underline{H}$, *J* = 16 Hz), 8.40—8.80 (br s, 1H, COO$\underline{H}$). MS *m/z*: 282 (M$^+$, 12%). *Anal.* Calcd for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.44; H, 6.44.

[2,6-Bis(methoxymethyloxy)-4-methylphenyl]propionic Acid (9)——A solution of the acrylic acid (**8**; 700 mg, 2.48 mmol) in ethyl acetate (35 ml) was hydrogenated at atmospheric pressure in the presence of 5% Pd–C (700 mg). Hydrogen uptake (1 mol) was complete within about 2 h. The solvent was evaporated off after removal of the catalyst by filtration to give a white solid (710 mg, quantitative). The product was recrystallized from ethyl acetate–*n*-hexane to give colorless needles, mp 66—70 °C. Yield, 613 mg (87.0%). A sample for MS was obtained by esterification with ethereal diazomethane. IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O), 2700, 2600 (OH). ^{1}H-NMR (80 MHz in CDCl$_3$): 2.29 (s, 3H, Ar–C$\underline{H}_3$), 2.54 (t, 2H, C$\underline{H}_2$CO-, *J* = 2.6 Hz), 2.64 (t, 2H, Ar–C$\underline{H}_2$CH$_2$–), 3.48 (s, 6H, OC$\underline{H}_3$ × 2), 5.17 (s, 4H, OC$\underline{H}_2$O × 2), 6.60 (s, 2H, Ar-H), 8.75—7.50 (br, 1H, COO$\underline{H}$). MS *m/z*: 298 (M$^+$ of the methyl ester, 25%). *Anal.* Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.08; H, 7.26.

(*E*)-Geranylacetone (12)——A mixture of ethyl acetoacetate (286 mg, 2.2 mmol), LiH (19 mg, 2.4 mmol) and dry DMF (5 ml) was stirred under a nitrogen atmosphere at room temperature for 30 min. Then, geranyl chloride (**10**; 500 mg, 2.4 mmol)[5] was added to the mixture, and the whole was stirred at 40—50 °C. Pentane and water were added to the mixture, and the organic layer was dried with anhydrous MgSO$_4$. Removal of the solvent gave [11] as a colorless oil [520 mg, 88.9%; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1720 (C=O); MS *m/z*: 266 (M$^+$, 4%)], 340 mg (1.28 mmol) of which was

stirred in 10% NaOH (1 ml) at room temperature for 2 h then at 60 °C overnight. The mixture was acidified with 10% HCl and extracted with ethyl acetate. The organic layer was evaporated to give an oily residue, which was dissolved in benzene (3 ml) and refluxed for 1 h. The oil obtained by evaporation of the benzene was purified by column chromatography on silica gel (eluent: $CHCl_3$) followed by vacuum distillation to give a colorless oil. bp_5 105 °C. Yield, 190 mg (76.6%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (C=O). ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 1.59 and 1.61 (s each, 3H, each, =CC$\underline{H}_3 \times 2$), 1.68 (s, 3H, =CC$\underline{H}_3$), 1.93—2.07 (m, 4H, =CHC$\underline{H}_2$C$\underline{H}_2$CH=), 2.14 (s, 3H, COC$\underline{H}_3$), 2.28 (q, 2H, C$\underline{H}_2$CH$_2$CO, J=7.5 Hz), 2.46 (t, 2H, C$\underline{H}_2$CO, J=7.5 Hz), 5.07 (t-like, 2H, =C$\underline{H}$-$\times 2$, J=7.7 Hz). MS m/z: 194 (M$^+$, 24%).

Aldol Reaction of 9 with 12——A lithium diisopropylamide (LDA; 20 mmol) solution in tetrahydrofuran (THF) (40 ml) was prepared at -78 °C in the usual manner. The carboxylic acid (**9**; 2.84 g, 10 mmol) was added in the presence of a small amount of 2,2′-bipyridyl to the LDA solution, and then the mixture was stirred at 40—45 °C for 2.5 h to form a dark-red pasty solution. Geranylacetone (**12**; 2.20 ml, 10 mmol) was added to the solution at -78 °C followed by stirring for 10 min after removal of the cooling bath. Ether and water were added to the reaction mixture, and the aqueous layer was acidified with 10% HCl. The separated material was extracted with ethyl acetate. The dried extract was evaporated to give a pale yellow viscous material, purification of which by column chromatography on silica gel (eluent: Et_2O : n-hexane = 5 : 1) gave a pale yellow viscous material. Yield, 4.01 g (83.9%). The methyl ester as a sample for MS was prepared by treatment with ethereal diazomethane in the usual manner. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500—2500 (OH, COOH), 1710 (C=O). ^{1}H-NMR (80 MHz in $CDCl_3$) δ: 1.30, 1.68 (s each, 6H each, C$\underline{H}_3 \times 4$), 2.00—2.09 (m, 8H, =CHC$\underline{H}_2$-$\times 3$ and CH$_2$C-OH), 2.28 (s, 3H, Ar-C$\underline{H}_3$), 2.85 (m, 2H, Ar-C$\underline{H}_2$-), 3.00—3.07 (m, 1H, C$\underline{H}$COOH), 3.45 (s, 6H, OC$\underline{H}_3 \times 2$), 5.07—5.16 (m, 2H, =C$\underline{H}$-$\times 2$), 5.11 (s, 4H, OC$\underline{H}_2$O$\times 2$), 5.50—6.00 (br, 2H, O$\underline{H}$ and COO$\underline{H}$), 6.58 (s, 2H, Ar-H). MS m/z: 492 (M$^+$ of the methyl ester, 0.2%). High-resolution MS m/z Calcd for $C_{28}H_{44}O_7$ = 492.3087. Found = 492.3073. The ^{1}H-NMR indicated that the product was a diastereomeric mixture.

Treatment of 14 with EEDQ——A mixture consisting of **14** (4.01 g, 8.39 mmol), EEDQ (2.90 g, 11.74 mmol) and dry benzene (30 ml) was stirred under a nitrogen atmosphere at room temperature overnight. Evaporation of the solvent afforded an oily material, which was purified by column chromatography on silica gel to give a pale yellow oil [4.40 g; presumed to be the corresponding anhydride (**2**)]. A solution of the intermediate in dry toluene (15 ml) was refluxed for 5 h and evaporated to give an oily product (3.98 g). Purification of the product by column chromatography on silica gel (Et_2O : n-hexane = 1 : 1) gave a colorless oil (**15**). Yield, 1.84 g (52.7%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1610, 1580 (C=C). ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 1.56—1.69 (complex, 9H, =C-C$\underline{H}_3 \times 3$), 1.78 (s, 3H, ArCH$_2$CH=C-C$\underline{H}_3$), 1.94—2.06 (m, 8H, =C-C$\underline{H}_2$-$\times 4$), 2.29 (s, 3H, Ar-C$\underline{H}_3$), 3.35—3.37 (d-like, 2H, Ar-C$\underline{H}_2$-), 3.47 (s$\times 2$, 6H, OC$\underline{H}_3 \times 2$), 5.08 (m, 2H, -C$\underline{H}$ = $\times 2$), 5.17 (s, 4H, OC$\underline{H}_2$O$\times 2$), 5.20 (m, 1H, Ar-CH$_2$C$\underline{H}$=), 6.59 (s, 2H, Ar-H). MS m/z: 416 (M$^+$, 14%). High-resolution MS m/z Calcd for $C_{26}H_{40}O_4$ = 416.2927. Found = 416.2935. The ^{1}H-NMR spectrum indicated that the product was a diastereomeric mixture.

Grifolin (4)——A mixture consisting of **15** (260 mg, 0.625 mmol), p-toluenesulfonic acid mono-hydrate (10 mg) and methanol (15 ml) was stirred under a nitrogen atmosphere at 40 °C for 24 h. The mixture was evaporated after addition of triethylamine (few drops) to leave a yellow oil, purification of which by a preparative thin-layer chromatography on silica gel (Merck Art. 7747) (eluent: Et_2O : n-hexane = 1 : 1) afforded a crystalline residue (142 mg, 69.2%). The ^{1}H-NMR spectrum (300 MHz in $CDCl_3$) indicated that the crude product was a diastereomeric mixture.[9] Recrystallization of the crude product from petroleum ether gave colorless needles of grifolin (**4**), mp 35—37 °C (lit. mp 40—42 °C).[3a] Spectral data of the product were consistent with the reported values[2,3e] as shown below. Yield, 90 mg (43.9%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 2920 (CH), 1635, 1585 (C=C). ^{1}H-NMR (300 MHz in $CDCl_3$) δ: 1.58, 1.60, 1.68 (s each, 3H each, =C-C$\underline{H}_3 \times 3$), 1.82 (s, 3H, ArCH$_2$CH=C-C$\underline{H}_3$), 1.96—2.27 (m, 8H, =C-C$\underline{H}_2$-$\times 4$), 2.21 (s, 3H, Ar-C$\underline{H}_3$), 3.38 (d, 2H, Ar-C$\underline{H}_2$-, J=7.0 Hz), 5.02 (s, 2H, Ar-O$\underline{H} \times 2$), 5.05—5.08 (m, 2H, =C$\underline{H}$-$\times 2$), 5.26 (t, 1H, ArCH$_2$C$\underline{H}$=, J=7.0 Hz), 6.23 (s, 2H, Ar-H). UV (in EtOH) λ_{max} (ε): 272 (1107), 281 nm (1025). MS m/z: 328 (M$^+$, 8%). High-resolution MS m/z Calcd for $C_{22}H_{32}O_2$ = 328.2402. Found = 328.2396.

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9) The ^{1}H-NMR spectrum indicates that the crude product before recrystallization probably includes about 25% of the (Z)-isomer (**4'**).