Synthesis of Clavulone Derivatives. Selective Cleavage of Ester Bonds and Elongation of α-Side Chain in Clavulone

Kazuo IGUCHI, Soichiro KANETA, Hiroto NAGAOKA and Yasuji YAMADA*

Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan. *Received June 15, 1989*

Several clavulone derivatives were synthesized from clavulone I (1) and clavulone II (2). The carboxylic acid 3 and 4-*O*-deacetyl derivative 4 were synthesized by selective enzymatic hydrolysis of 2 using porcine liver esterase and orange peel acetylesterase, respectively. From the carboxylic acid 3, the benzyl ester 5, *tert*-butyl ester 6 and amide 7 were prepared. The 12-*O*-deacetyl derivative 9 was synthesized by organocuprate reduction of the epoxide 8 which was prepared from 2. The derivatives 13—15, which possess an elongated α-side chain, were synthesized from 1 *via* the hemiacetal 12.

Keywords marine prostanoid; clavulone I; clavulone II; clavulone derivative; enzymatic hydrolysis; porcine liver esterase; orange peel acetylesterase; lithium dimethylcuprate

Much attention has been paid to the coral-derived marine prostanoids, clavulones[1] and their congeners,[2] owing to their unique structural features and strong antileukemic activities.[3] In order to elucidate the structure–activity relationship, we have been synthesizing various derivatives of clavulones[4,5] and examining the biological activity of the derivatives.[6] In our previous paper,[7] the synthesis of clavulone derivatives modified on the cyclopentenone ring was reported. The present paper deals with the synthesis of clavulone derivatives modified mainly on the α-side chain by selective cleavage of the ester bonds and elongation of the α-side chain.[8]

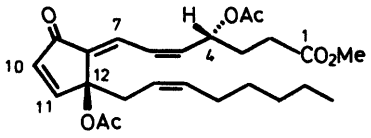
Selective Cleavage of Ester Bonds in Clavulone The selective cleavage of the ester bonds at C-1, -4 and -12 in clavulones became an important problem for the present study for the following reasons: 1) the biological activity of the alcohol or carboxylic acid, obtained by the selective cleavage of the ester bonds, was of interest, and 2) a variety of derivatives could be supplied by further modification of the alcohol or carboxylic acid obtained by the selective ester cleavage.

Usual acid-catalyzed hydrolysis (*e.g.* with hydrochloric acid) and base-catalyzed reactions (*e.g.* with sodium hydroxide, potassium carbonate, and sodium methoxide) of clavulone II (**2**) were initially attempted under various conditions, but these reactions yielded mixtures of many products and selective cleavage of the ester bond was not observed.

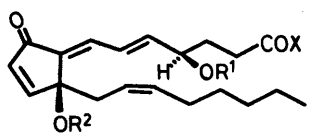
The methyl ester at C-1 and acetic acid ester of the secondary alcohol at C-4 in **2** were selectively hydrolyzed by means of enzymatic reactions using porcine liver esterase (PLE)[9] and orange peel acetylesterase, respectively. Treatment of **2** in acetone and phosphate buffer solution (pH = 8.0) with PLE in aqueous ammonium sulfate solution at 40 °C gave exclusively the carboxylic acid **3** in 96% yield. On the other hand, treatment of **2** in acetone and phosphate buffer solution (pH = 6.5) with orange peel acetylesterase at 40 °C gave exclusively the alcohol **4** in 91% yield. The use of baker's yeast or porcine pancreatic lipase (PPL), both of which were employed for the hydrolysis of the methyl ester in prostaglandin syntheses,[10] did not give good results. In the former case a mixture of many products including reduced products was formed, while in the latter case the reaction did not proceed.

From the carboxylic acid **3** thus obtained, the esters, **5** and **6**, and the amide **7** were synthesized. Treatment of **3** with benzyl alcohol in the presence of dicyclohexylcarbodiimide (DCC) and *N*,*N*-dimethylaminopyridine (DMAP) gave the benzyl ester **5** in 85% yield. Similar reaction of **3** with *tert*-butyl alcohol gave the *tert*-butyl ester **6** in 47% yield. The amide **7** was also obtained by the reaction of **3** with *tert*-butylamine in the presence of DCC and DMAP in 20% yield.

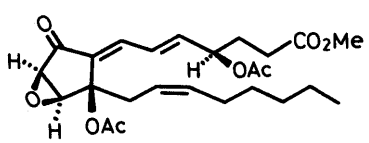
The selective cleavage of the acetic acid ester of the tertiary alcohol at C-12 was chemically done *via* the epoxide **8**, which was prepared by epoxidation of **2** with *tert*-butyl hydroperoxide.[7] The acetic acid ester at C-12 in the epoxide **8** was cleaved by the organocuprate-induced reaction which involved neighboring participation of the acetoxyl group at C-12. Reaction of **8** with lithium dimethylcuprate in ether at −78 °C gave the alcohol **9** in 52% yield. Compound **9** is presumably formed by the reaction pathway shown in Chart 1. Reduction of the carbonyl group at C-9 with lithium dimethylcuprate gives the intermediate (a), and then cleavage of the epoxide followed by further electron transfer to the oxygen at C-11 takes



1 clavulone I



2 : X=OMe, $R^1=R^2=Ac$ clavulone II
3 : X=OH, $R^1=R^2=Ac$
4 : X=OMe, $R^1=H$, $R^2=Ac$
5 : X=OCH_2Ph, $R^1=R^2=Ac$
6 : X=O-*tert*-Bu, $R^1=R^2=Ac$
7 : X=NH-*tert*-Bu, $R^1=R^2=Ac$
9 : X=OMe, $R^1=Ac$, $R^2=H$



8

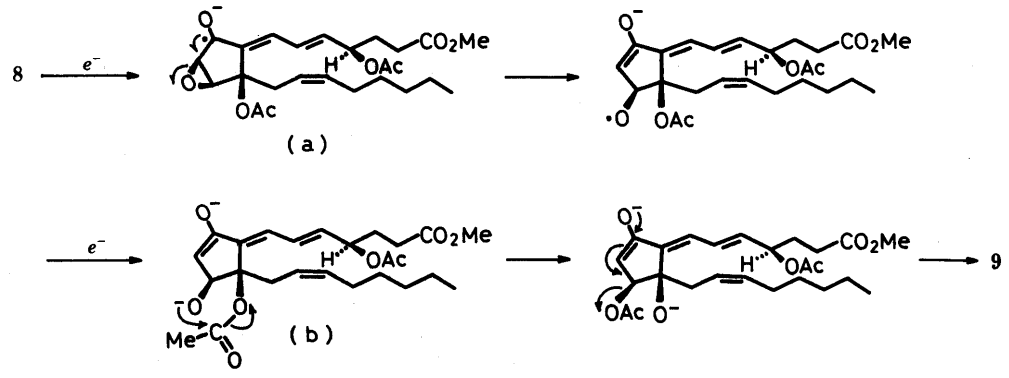


Chart 1

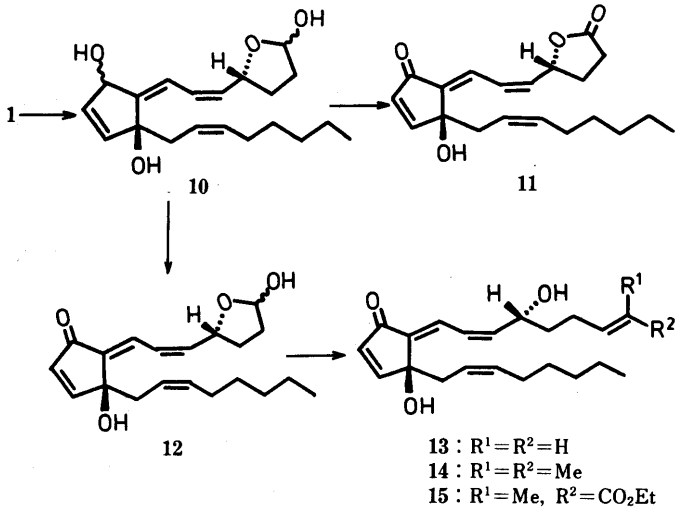


Chart 2

place to give (b). Acetyl migration from the 12-oxygen to the 11-oxygen in (b) followed by elimination of the acetoxyl group and protonation at the 12-oxygen during the work-up procedure gave rise to **9**. This reaction, which resulted in both reduction of the epoxide and cleavage of the acetic acid ester, is of interest in view of the organocuprate-induced reaction of α,β-epoxy ketones.[11]

Elongation of α-Side Chain It is of interest to clarify how the length of the side chains of clavulones affects the antileukemic activity. From this viewpoint we have investigated the elongation of the α-side chain of clavulones. The derivatives **13**—**15** having the elongated α-side chain were synthesized from clavulone I (**1**) *via* the hemiacetal **12**. Reaction of **1** with diisobutylalminium hydride (DIBAH) at −78 °C gave the triol **10** as an unstable diastereomeric mixture. Jones oxidation of **10** gave the lactone **11** in 62% yield from **1**, while oxidation of **10** with active manganese (IV) oxide gave the hemiacetal **12** as a diastereomeric mixture in 32% yield from **1**. Wittig reaction of **12** with methylenetriphenylphosphorane in tetrahydrofuran (THF) gave **13** in 24% yield. Similar reaction of **12** with isopropylidenetriphenylphosphorane gave **14** in 29% yield. In the case of the reaction using a stable ylid, the yield of the product increased: reaction of **12** with ethyl 2-triphenylphosphoranylidenepropionate at 70 °C gave the α,β-unsaturated ester **15** in 79% yield. The *E* geometry of the newly formed carbon–carbon double bond was indicated by the chemical shift of the olefinic proton [δ 6.70 (1H, br dt, J=1.4, 7.4 Hz) ppm], and the formation of the geometrical isomer was not observed.

The antileukemic activities of **3**, **4**, **9**, **11**, **12**, **13**, **14** and **15** against HL-60 cells were measured, and remarkable enhancement of the activity was observed for **9**, **11**, **12**, **13** and **14**. The details have been described in a separate paper.[12]

Experimental

Optical rotations were measured with a JASCO DIP-360 automatic polarimeter. Infrared (IR) spectra were recorded with a Perkin-Elmer FT-IR 1710 spectrophotometer and ultraviolet (UV) spectra with Hitachi 124 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Bruker AM-400 (400 MHz) spectrometer. Chemical shifts are given on a δ (ppm) scale with tetramethylsilane (TMS) as an internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Mass spectra (MS) were taken with a Hitachi M-80 spectrometer. Column chromatography was carried out on Merck Silica gel 60 (70—230 mesh), and preparative thin layer chromatography (PTLC) was carried out on Silica gel F_{254} TLC plates. The enzyme solutions were available from Sigma Chemical Company.

Hydrolysis of 2 with PLE Phosphate buffer solution (pH=8.0, 20 ml) and PLE in 3.2 M $(NH_4)_2SO_4$ solution (0.21 ml) were successively added to a solution of clavulone II (**2**) (215 mg) in acetone (2 ml). The mixture was vigorously stirred at 40 °C for 14 h, then acidified to pH=3 by addition of 0.5 M HCl, and extracted with a mixture of ether and methylene chloride (2:1). The organic layer was successively washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane:ethyl acetate=1:2 as an eluent) to give **3** (200 mg).

1-*O*-Demethylclavulone II (**3**): Colorless oil. $[\alpha]_D$ +12.2° (c=2.0, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3400—2800, 1742, 1708, 1644. UV λ_{max}^{EtOH} nm (ε): 232 (13400), 294 (15100). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.8 Hz), 1.94 (1H, br q, J=7.0 Hz), 2.04 (1H, br q, J=3.6 Hz), 2.07 (3H, s), 2.43 (1H, t, J=7.3 Hz), 2.68 (1H, dd, J=7.1, 14.3 Hz), 2.88 (1H, dd, J=7.1, 14.3 Hz), 5.19 (1H, m), 5.43 (1H, br q, J=6.3 Hz), 5.52 (1H, m), 6.03 (1H, dd, J=7.1, 14.9 Hz), 6.41 (1H, d, J=6.1 Hz), 6.76 (1H, ddd, J=0.9, 12.0, 14.9 Hz), 6.87 (1H, d, J=12.0 Hz), 7.47 (1H, dd, J=0.7, 6.1 Hz). EIMS m/z: 432 (M^+). High-resolution MS Calcd for $C_{24}H_{32}O_7$ (M^+): 432.2145. Found: 432.2132.

Hydrolysis of 2 with Orange Peel Acetylesterase Phosphate buffer solution (pH=6.5, 2 ml) and orange peel acetylesterase in 2.5 M $(NH_4)_2SO_4$ solution (0.2 ml) were successively added to a solution of **2** (30 mg) in acetone (0.2 ml). The mixture was vigorously stirred at 40 °C for 24 h. The reaction mixture was diluted with ether, and washed successively with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC to give **4** (24.6 mg).

4-*O*-Deacetylclavulone II (**4**): Colorless oil. IR ν_{max}^{film} cm^{-1}: 3470, 1739, 1700, 1641. UV λ_{max}^{EtOH} nm (ε): 234 (12200), 295 (14100). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.8 Hz), 2.04 (3H, s), 2.48 (2H, dt, J=3.3, 7.1 Hz), 2.70 (1H, dd, J=8.2, 13.9 Hz), 2.96 (1H, dd, J=7.4, 13.9 Hz), 3.69 (3H, s), 4.42 (1H, m), 5.18 (1H, m), 5.51 (1H, m), 6.20 (1H, dd, J=5.2, 14.9 Hz), 6.41 (1H, dd, J=6.1 Hz), 6.80 (1H, ddd, J=1.5, 12.5, 14.9 Hz), 6.94 (1H, d, J=12.0 Hz), 7.48 (1H, dd, J=0.7, 6.1 Hz). CIMS m/z: 387 (M^++1−H_2O), 345 (M^++1−AcOH). High-resolution MS Calcd for $C_{21}H_{28}O_4$ (M^+

−AcOH): 344.1988. Found: 344.1973.

Esterification of 3 with Benzyl Alcohol Powdered molecular sieves (5A, 10 mg), DCC (5.4 mg) and DMAP (0.3 mg) were successively added to a solution of **3** (10 mg) in dry methylene chloride (0.4 ml) under an argon atmosphere, and the mixture was stirred at room temperature for 5 min. After addition of benzyl alcohol (5.2 μl), the mixture was stirred at room temperature for 20 min. The reaction mixture was diluted with ether, washed successively with 5% acetic acid solution, water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC to give **5** (9.8 mg).

(4*S*)-4-Acetoxy-5*E*-[(4*R*)-4-acetoxy-6-benzyloxycarbonyl-2*E*-hexenylidene]-4-(2*Z*-octenyl)-2-cyclopenten-1-one (**5**): Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.1 Hz), 1.93 (2H, br q, J=7.2 Hz), 2.03 (3H, s), 2.05 (3H, s), 2.42 (2H, t, J=7.3 Hz), 2.66 (1H, dd, J=8.2, 13.8 Hz), 2.87 (1H, dd, J=6.5, 13.8 Hz), 5.12 (2H, s), 5.19 (1H, m), 5.41 (1H, br q, J=6.9 Hz), 5.51 (1H, m), 6.01 (1H, dd, J=7.2, 14.9 Hz), 6.41 (1H, d, J=6.1 Hz), 6.74 (1H, ddd, J=0.9, 12.0, 14.9 Hz), 6.86 (1H, d, J=12.0 Hz), 7.34 (5H, m), 7.47 (1H, dd, J=0.8, 6.1 Hz). EIMS m/z: 522 (M^+).

Esterification of 3 with *tert*-Butyl Alcohol The carboxylic acid **3** (10 mg) was reacted with *tert*-butyl alcohol (5 μl) under conditions similar to those used for the esterification of **3** with benzyl alcohol, to give **6** (4 mg).

(4*S*)-4-Acetoxy-5*E*-[(4*R*)-4-acetoxy-6-*tert*-butyloxycarbonyl-2*E*-hexenylidene]-4-(2*Z*-octenyl)-2-cyclopenten-1-one (**6**): Colorless oil. $[\alpha]_D$ +16.0° (c=0.1, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1739, 1707, 1646. UV λ_{max}^{EtOH} nm (ε): 230 (17300), 295 (21500). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.8 Hz), 1.45 (9H, s), 1.96 (2H, m), 2,07 (6H, s), 2.28 (2H, t, J=8.0 Hz), 2.68 (1H, dd, J=6.4, 13.5 Hz), 2.88 (1H, dd, J=6.4, 13.5 Hz), 5.19 (1H, m), 5.41 (1H, br q, J=6.8 Hz), 5.52 (1H, m), 6.03 (1H, dd, J=7.4, 15.0 Hz), 6.41 (1H, d, J=6.1 Hz), 6.74 (1H, ddd, J=0.9, 12.0, 15.0 Hz), 6.87 (1H, d, J=12.0 Hz), 7.47 (1H, dd, J=0.8, 6.1 Hz). EIMS m/z: 432 ($M^+-(CH_3)_2C=CH_2$), 428 (M^+−AcOH). High-resolution MS Calcd for $C_{24}H_{32}O_7$ ($M^+-(CH_3)_2C=CH_2$): 432.2186. Found: 432.2129.

Reaction of 3 with *tert*-Butylamine The carboxylic acid **3** (10 mg) was reacted with *tert*-butylamine (5.3 μl) under conditions similar to those used for the esterification of **3** with benzyl alcohol, giving **7** (2.3 mg).

(4*S*)-4-Acetoxy-5*E*-[(4*R*)-4-acetoxy-6-*tert*-butylcarbamoyl-2*E*-hexenylidene]-4-(2*Z*-octenyl)-2-cyclopenten-1-one (**7**): Colorless oil. IR ν_{max}^{film} cm^{-1}: 3350, 1741, 1648. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.0 Hz), 1.12 (9H, s), 1.96 (2H, m), 2.09 (3H, s), 2.11 (3H, s), 2.27 (2H, t, J=8.0 Hz), 2.66 (1H, dd, J=7.1, 13.9 Hz), 2.86 (1H, dd, J=6.7, 13.9 Hz), 5.19 (1H, m), 5.41 (1H, br q, J=6.8 Hz), 5.53 (1H, m), 6.03 (1H, dd, J=7.4, 14.9 Hz), 6.40 (1H, d, J=6.0 Hz), 6.74 (1H, ddd, J=0.9, 11.9, 14.9 Hz), 6.87 (1H, d, J=11.9 Hz), 7.46 (1H, dd, J=0.9, 6.0 Hz).

Reaction of 8 with Lithium Dimethylcuprate A solution (82 μl) of methyllithium in ether (1.0 M) was added dropwise to a suspension of copper(I) iodide (7.8 mg) in dry ether (0.8 ml) at −10 °C under an argon atmosphere. The mixture was stirred at −10 °C for 20 min and then cooled to −78 °C. To this mixture, a solution of **8** (16 mg) in dry ether (0.5 ml) was added dropwise, and the whole was stirred for 20 min. The reaction mixture was poured into NH_4Cl–NH_4OH solution, and extracted with ether. The ether layer was successively washed with water and saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC to give **9** (7.1 mg).

12-*O*-Deacetylclavulone II (**9**): Pale yellow oil. $[\alpha]_D$ −51.9° (c=0.31, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3456, 1739, 1642. UV λ_{max}^{EtOH} nm (ε): 230 (11600), 295 (12100). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.8 Hz), 1.95 (1H, br q, J=6.6 Hz), 2.08 (3H, s), 2.38 (2H, t, J=7.4 Hz), 2.64 (1H, br dd, J=7.9, 14.3 Hz), 2.74 (1H, br dd, J=7.5, 14.3 Hz), 3.67 (3H, s), 5.21 (1H, m), 5.43 (1H, br q, J=6.4 Hz), 5.51 (1H, m), 6.07 (1H, dd, J=6.4, 14.8 Hz), 6.33 (1H, d, J=6.1 Hz), 6.87 (1H, d, J=11.9 Hz), 6.96 (1H, ddd, J=1.1, 11.8, 14.8 Hz), 7.32 (1H, dd, J=0.5, 6.1 Hz). EIMS m/z: 404 (M^+), 344 (M^+−AcOH). High-resolution MS Calcd for $C_{21}H_{28}O_4$ (M^+−AcOH): 344.1986. Found: 344.1996.

Reduction of 1 with DIBAH and Successive Oxidation with Jones Reagent A solution (1.9 ml) of DIBAH in hexane (1.0 M) was added to a solution of **1** (200 mg) in dry ether (20 ml) at −78 °C under an argon atmosphere, and the mixture was stirred at −78 °C for 15 min. Methanol (0.1 ml) was added and the reaction mixture was stirred for 5 min, then diluted with ether. Saturated NaCl solution (2 ml) was added. The mixture was stirred for 6 h, and the organic solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue containing **10** was dissolved in acetone (10 ml) and Jones reagent was added to the solution at 0 °C until the color of the solution became dark brown. After reaction for 5 min, 2-propanol was added and the reaction mixture was diluted with water and then saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane: AcOEt = 1 : 1 as an eluent), to give **11** (89 mg).

(4*S*)-4-Hydroxy-4-(2*Z*-octenyl)-5*E*-[3-((5*R*)-2-oxo-5-tetrahydrofuranyl)-2*Z*-propenylidene]-2-cyclopenten-1-one (**11**): Pale yellow oil. $[\alpha]_D$ −90° (c=1.1, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350, 1770, 1690, 1640. UV λ_{max}^{EtOH} nm (ε): 227 (10700), 287 (13100). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.8 Hz), 2.61 (1H, d, J=9.6 Hz), 2.62 (1H, dd, J=1.5, 9.6 Hz), 2.67 (1H, dd, J=7.7, 14.3 Hz), 2.81 (1H, dd, J=7.7, 14.3 Hz), 5.24 (1H, ttd, J=1.6, 7.7, 10.9 Hz), 5.57 (1H, m), 6.03 (1H, dd, J=8.6, 10.9 Hz), 6.39 (1H, d, J=6.0 Hz), 6.94 (1H, ddd, J=1.2, 10.9, 12.7 Hz), 7.13 (1H, br d, J=12.7 Hz), 7.36 (1H, dd, J=0.7, 6.0 Hz). EIMS m/z: 330 (M^+), 312 (M^+-H_2O). High-resolution MS Calcd for $C_{20}H_{26}O_4$ (M^+): 330.1830. Found: 330.1842.

Oxidation of 10 with Activated Manganese(IV) Oxide Activated manganese(IV) oxide (700 mg) was added to a solution of the hemiacetal **10**, which was prepared from **1** (400 mg) by the above-mentioned reduction, in methylene chloride (20 ml) and the mixture was stirred at 20 °C for 15 min. The reaction mixture was diluted with methylene chloride, filtered through a Celite column, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column (hexane: AcOEt = 1 : 1 as an eluent) to give **12** (96 mg) as a mixture of diastereomeric isomers.

(4*S*)-4-Hydroxy-5*E*-[3-((2ξ,5*R*)-2-hydroxy-5-tetrahydrofuranyl)-2*Z*-propylidene]-4-(2*Z*-octenyl)-2-cyclopenten-1-one (**12**): Pale yellow oil. IR ν_{max}^{film} cm^{-1}: 3404, 1694, 1633.

Reaction of 12 with $(C_6H_5)_3P=CH_2$ A solution of butyllithium in hexane (1.53 M) was added to a mixture of methyltriphenylphosphoranyl iodide (450 mg) in dry THF (3.5 ml) at 0 °C under an argon atmosphere. The mixture was stirred for 10 min, then cooled to −78 °C and a solution of **12** (46 mg) in dry THF (2 ml) was added. The reaction mixture was stirred at 0 °C for 45 min, and poured into a mixture of ether and saturated NH_4Cl solution. The organic layer was washed with water and then saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC (hexane: AcOEt = 1 : 1 as a development solvent) to give **13** (11 mg).

(4*S*)-4-Hydroxy-5*E*-[(4*R*)-2*Z*,7-octadienylidene]-4-(2*Z*-octenyl)-2-cyclopenten-1-one (**13**): Pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1695, 1630, UV λ_{max}^{EtOH} nm (ε): 232 (11000), 295 (13200). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=6.8 Hz), 2.66 (1H, dd, J=7.9, 14.6 Hz), 2.83 (1H, dd, J=7.9, 14.6 Hz), 4.84 (1H, br q, J=6.7 Hz), 5.01 (1H, tdd, J=1.3, 1.8, 10.2 Hz), 5.06 (1H, tdd, J=1.3, 1.8, 17.1 Hz), 5.24 (1H, td, J=7.6, 10.9 Hz), 5.55 (1H, td, J=7.4, 11.0 Hz), 5.84 (1H, tdd, J=6.7, 10.2, 17.1 Hz), 5.99 (1H, ddd, J=1.2, 8.9, 10.9 Hz), 6.37 (1H, d, J=6.0 Hz). 6.81 (1H, ddd, J=1.1, 11.0, 12.2 Hz), 7.24 (1H, d, J=12.2 Hz), 7.34 (1H, dd, J=0.8, 6.0 Hz).

Reaction of 12 with $(C_6H_5)_3P=C(CH_3)_2$ A solution (0.104 ml) of butyllithium in hexane (1.53 M) was added to a mixture of isopropyltriphenylphosphoranyl bromide (123 mg) in dry THF (2 ml) at 0 °C under an argon atmosphere. The mixture was stirred for 10 min, then cooled to −78 °C and a solution of **12** (18 mg) in dry THF (1.5 ml) was added. The reaction mixture was stirred at 0 °C for 30 min, and poured into a mixture of ether and saturated NH_4Cl solution. The organic layer was washed with water and then saturated NaCl solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by PTLC (hexane: AcOEt = 1 : 1 as a development solvent) to give **14** (5.5 mg).

(4*S*)-4-Hydroxy-5*E*-[(4*R*)-4-hydroxy-8-methyl-2*Z*,7-nonadienylidene]-4-(2*Z*-octenyl)-2-cyclopenten-1-one (**14**): Pale yellow oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300, 1700. UV λ_{max}^{EtOH} nm (ε): 234 (10500), 294 (12200). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=6.8 Hz), 1.60 (3H, s), 1.70 (3H, d, J=1.0 Hz), 2.66 (1H, br dd, J=7.6, 14.3 Hz), 2.83 (1H, br dd, J=7.6, 14.3 Hz), 4.82 (1H, br q, J=7.9 Hz), 5.13 (1H, m), 5.24 (1H, ttd, J=1.6, 7.7, 10.9 Hz), 5.55 (1H, ttd, J=1.3, 7.4, 10.9 Hz), 5.98 (1H, ddd, J=1.1, 8.9, 11.0 Hz), 6.36 (1H, d, J=6.0 Hz), 6.79 (1H, ddd, J=1.0, 11.0, 12.7 Hz), 7.25 (1H, d, J=12.7 Hz), 7.33 (1H, dd, J=0.7, 6.0 Hz). EIMS m/z: 358 (M^+), 340 (M^+-H_2O).

Reaction of 12 with $(C_6H_5)_3P=C(CH_3)CO_2C_2H_5$ Ethyl 2-triphenylphosphoranylidenepropionate (20 mg) was added to a solution of **12** (5.2 mg) in 1,2-dichloroethane (0.8 ml), and the mixture was stirred at 70 °C for 20 min. The reaction mixture was passed through a silica gel short column, and the eluate was concentrated under reduced pressure. The residue was purified by PTLC (hexane: AcOEt = 1 : 2 as a development solvent) to give **15** (4.9 mg).

(4*S*)-5*E*-[(4*R*)-8-Ethoxycarbonyl-4-hydroxy-2*Z*,7*E*-nonadienylidene]-4-hydroxy-4-(2*Z*-octenyl)-2-cyclopenten-1-one (**15**): Pale yellow oil. $[\alpha]_D$ +0.7° (c=0.28, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3426, 1738, 1694, 1634. UV λ_{max}^{EtOH}

nm (ε): 220 (22100), 300 (15700). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J= 6.8 Hz), 1.28 (3H, t, J=7.1 Hz), 1.81 (3H, s), 1.98 (2H, q, J=6.9 Hz), 2.66 (1H, dd, J=7.6, 14.4 Hz), 2.81 (1H, dd, J=7.6, 14.4 Hz), 4.16 (2H, q, J= 7.1 Hz), 4.82 (1H, br q, J=6.6 Hz), 5.22 (1H, br td, J=7.6, 11.0 Hz), 5.53 (1H, br td, J=7.4, 11.0 Hz), 5.96 (1H, dd, J=9.8, 10.2 Hz), 6.35 (1H, d, J=6.0 Hz), 6.70 (1H, br dt, J=1.4, 7.4 Hz), 6.81 (1H, br t, J=11.6 Hz), 7.20 (1H, d, J=12.7 Hz), 7.33 (1H, d, J=5.8 Hz). EIMS m/z: 416 (M^+), 398 ($M^+ - H_2O$). High-resolution MS Calcd for $C_{25}H_{36}O_5$ (M^+): 416.2564. Found: 416.2560.

Acknowledgement We are grateful to Prof. Y. Mori and Dr. A. Honda, Laboratory of Biochemistry, Tokyo College of Pharmacy, for measurement of the antileukemic activity and helpful discussions. This work was supported by a grant from the Science Research Fund of the Japan Private School Promotion Foundation.

References and Notes

1) H. Kikuchi, Y. Tsukitani, K. Iguchi and Y. Yamada, *Tetrahedron Lett.*, **23**, 5171 (1982); *idem, ibid.*, **24**, 1549 (1983). See also the reports on claviridenones: M. Kobayashi, T. Yasuzawa, M. Yoshihara, H. Akutsu, Y. Kyogoku and I. Kitagawa, *ibid.*, **23**, 5331 (1982); I. Kitagawa, M. Kobayashi, T. Yasuzawa, B. W. Son, M. Yoshihara and Y. Kyogoku, *Tetrahedron*, **41**, 995 (1985).
2) K. Iguchi, S. Kaneta, K. Mori, Y. Yamada, A. Honda and Y. Mori, *Tetrahedron Lett.*, **26**, 5787 (1985); K. Iguchi, S. Kaneta, K. Mori and Y. Yamada, *Chem. Pharm. Bull.*, **35**, 4375 (1987) and other references cited therein.
3) M. Fukushima and S. Narumiya, *Ensho*, **4**, 152 (1984); M. Fukushima, T. Kato, Y. Yamada, I. Kitagawa, S. Kurozumi and P. J. Scheuer, *Proc. Am. Assoc. Cancer Res.*, **26**, 249 (1985); A. Honda, Y. Yamamoto, Y. Mori, Y. Yamada and H. Kikuchi, *Biochem. Biophys. Res. Commun.*, **130**, 515 (1985).
4) We used clavulones as a starting material for the synthesis of clavulone derivatives, because clavulones are abundant in the soft coral *Clavularia viridis* (about 0.4% yield based on the freeze-dried organisms) and total syntheses of clavulones have already been accomplished.[5)]
5) For example: E. J. Corey and M. M. Mehrotra, *J. Am. Chem. Soc.*, **106**, 3384 (1984); H. Nagaoka, T. Miyakoshi and Y. Yamada, *Tetrahedron Lett.*, **25**, 3621 (1984); M. Shibasaki and Y. Ogawa, *ibid.*, **26**, 3841 (1985).
6) A. Honda, Y. Mori, K. Iguchi and Y. Yamada, *Mol. Pharmacol.*, **32**, 530 (1987).
7) K. Iguchi, S. Kaneta, C. Tsune and Y, Yamada, *Chem. Pharm. Bull.*, **37**, 1173 (1989).
8) A part of this work has been published in a preliminary form; K. Iguchi, S. Kaneta, H. Nagaoka and Y. Yamada, *Chem. Lett.*, **1989**, 157.
9) A. Hazato, T. Tanaka, K. Toru, N. Okamura, K. Bannai, S. Sugiura, K. Manabe and S. Kurozumi, *Nippon Kagaku Kaishi*, **9**, 1390 (1983).
10) A. F. Kluge, K. G. Untch and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972); C. J. Sih, R. G. Salomon, P. Price, S. Sood and G. Peruzzotti, *ibid.*, **97**, 857 (1975).
11) J. R. Bull and H. H. Lachmann, *Tetrahedron Lett.*, **1973**, 3055.
12) A. Honda, Y. Mori, K. Iguchi and Y. Yamada, *Prostaglandins*, **36**, 621 (1988).