Chem. Pharm. Bull.
34(10)4346—4351(1986)

Synthesis and Spectral Characterization of γ-Hydroxy-$\Delta^{\alpha,\beta}$-butenolides Possessing a Conjugated Substituent at the β-Position

MASAYOSHI ITO,* TSUTOMU IWATA, and KIYOSHI TSUKIDA

Kobe Women's College of Pharmacy, 4–19–1 Motoyamakita-machi, Higashinada-ku, Kobe 658, Japan

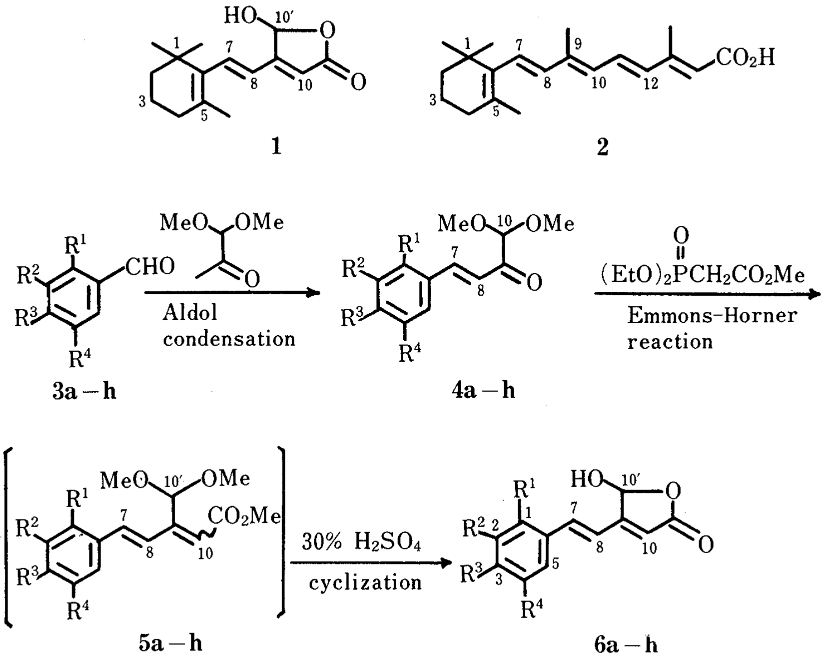
(Received March 28, 1986)

Conjugated γ-hydroxybutenolides (**6a**—**h**, **10**, and **11**) were synthesized in three steps starting from various aldehydes (**3a**—**h** and **7**), and their spectral characteristics were compared with those of unconjugated butenolides (**12** and **13**).

Keywords——conjugated γ-hydroxybutenolide; antitumor agent; aldol condensation; Emmons–Horner reaction; deshielding effect

In the previous papers,[1] we reported the first synthesis and characterization of retinoidal 4-ylidenebutenolides as an extension of synthetic work aimed at developing new antitumor retinoidal compounds. Cytotoxic activity of the retinoidal butenolides on mouse neuroblastoma and rat glioma cells has been examined,[2] and **1** was found to be the most potent. The ED_{50} of **1** for both types of cells was about 5×10^{-7} M; thus, **1** is about 90 times more potent than retinoic acid (**2**), which is well known to have anti-tumor activity on skin papilloma and carcinoma.[3] Since extensive chemical modification[4] of **2** led to the discovery of more active aromatic retinoids, aromatic analogues and higher homologues of the new type of antitumor agent (**1**) have been synthesized with the aim of developing more active compounds. Inhibitory effects of some of these compounds (**6a**—**h** and **10**) on deoxyribonucleic acid synthesis in neuro *in vitro* system have been observed.[2] In this paper, we wish to describe the synthesis and spectral characterization of both aromatic analogues (**6a**—**h**) and higher homologues (**10** and **11**) of **1**.

Synthesis of the conjugated γ-hydroxybutenolides was carried out by the same pathway (Chart 1) as that[1] used for the preparation of **1**. Aldol condensation of commercially available benzaldehydes (**3a**—**h**) with pyruvic aldehyde dimethylacetal using piperidine as a base proceeded smoothly to give acetal-enone compounds (**4a**—**h**), which were easily purified by distillation or column chromatography and characterized by spectral means. The configuration of the newly formed double bond was determined to be (*E*) on the basis of the coupling constant ($J = 16$ Hz) between 7-H and 8-H[5] in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum. An Emmons–Horner reaction of the acetal-enones with diethyl methoxycarbonylmethylphosphonate in the presence of *n*-butyl lithium, and cyclization of the resulting acetal-esters using an acid catalyst afforded the corresponding hydroxylactones (**6a**—**h**) in moderate yields. Characteristic spectral data are compiled in Table I. Higher homologues (**10** and **11**) of **1** were also synthesized in an analogous fashion (Chart 2) starting from the dienal (**7**)[6] by way of **8** and **9**. The structures of the hydroxybutenolide isomers (**10** and **11**) were determined from the spectral data (summarized in Table II), together with those of **1**. The configurations of the two disubstituted double bonds in **10** were confirmed to be (*E*) on the basis of the coupling constants ($J_{7,8} = J_{9,10} = 16$ Hz) and the results



a: $R^1=R^2=R^3=R^4=H$
b: $R^1=OMe$, $R^2=R^3=R^4=H$
c: $R^1=R^2=R^4=H$, $R^3=OMe$
d: $R^1=Me$, $R^2=R^3=R^4=H$
e: $R^1=R^2=R^4=H$, $R^3=Me$
f: $R^1=R^2=OMe$, $R^3=R^4=H$
g: $R^1=R^4=H$, $R^2=R^3=OMe$
h: $R^2=R^3=H$, $R^1=R^4=OMe$

Chart 1

TABLE I. Characteristic Spectral Data for the γ-Hydroxybutenolides (**6a**—**h**)

	UV (EtOH) nm	IR (Nujol) cm^{-1}	^{1}H-NMR (d_6-acetone) δ 7-H[5]	8-H	10-H	10′-H
6a	313 (ε 34200)	3210, 1729, 1704, 1628, 1591	7.40 (d, $J=16$)	7.20 (d, $J=16$)	6.12 (s)	6.46 (s)
6b	342 (ε 19900) 302 (ε 17900)	3309,[a] 1742,[a] 1623,[a] 1593[a]	7.59[b] (d, $J=16$)	7.00[b] (d, $J=16$)	5.97[b] (s)	6.37[b] (s)
6c	341 (ε 33900)	3330, 1709, 1601, 1582	7.34 (d, $J=16$)	7.04 (d, $J=16$)	6.03 (s)	6.39 (s)
6d	316 (ε 28500)	3200, 1711, 1619, 1594	7.66 (d, $J=16$)	7.09 (d, $J=16$)	6.13 (s)	6.50 (d, $J=8$)
6e	322 (ε 35500)	3250, 1714, 1625, 1595	7.36 (d, $J=16$)	7.13 (d, $J=16$)	6.07 (s)	6.43 (d, $J=8$)
6f	317 (ε 32600)	3300, 1742, 1711, 1629, 1570	7.67 (d, $J=17$)	7.19 (d, $J=17$)	6.11 (s)	6.47 (br s)
6g	352 (ε 27300)	3340, 1707, 1622, 1593	7.33 (d, $J=16$)	7.07 (d, $J=16$)	6.01 (s)	6.41 (d, $J=7$)
6h	370 (ε 16300) 306 (ε 27000)	3340, 1701, 1609, 1572	7.65 (d, $J=17$)	7.23 (d, $J=17$)	6.06 (s)	6.43 (d, $J=8$)

a) In $CHCl_3$, *b*) in $CDCl_3$, *J* in Hz (200 MHz).

Table II. Characteristic Spectral Data for the γ-Hydroxybutenolides (**10**, **11**, and **1**)

		10	**11**	**1**
UV (EtOH) nm		318 (ε 23400)	318	315, 260
IR ($CHCl_3$) cm^{-1}		3280, 1752, 1729, 1618, 1600	3280, 1751, 1619	3325, 1750, 1735, 1635, 1614
^{1}H-NMR ($CDCl_3$) δ_{ppm}	7-H	6.57 (d, $J=16$)	6.41 (d, $J=16$)	7.00 (d, $J=17$)
	8-H	6.23 (dd, $J=11$, 16)	6.89 (dd, $J=10$, 16)	6.32 (d, $J=17$)
	9-H	6.99 (dd, $J=11$, 16)	6.26 (t-like, $J=10$)	
	10-H	6.36 (d, $J=16$)	6.35 (d, $J=10$)	
	12-H (10-H)	5.88 (s)	5.89 (s)	5.86 (s)
	12′-H (10′-H)	6.27 (d, $J=8$)	6.18 (br s)	6.30 (s)

J in Hz (200 MHz).

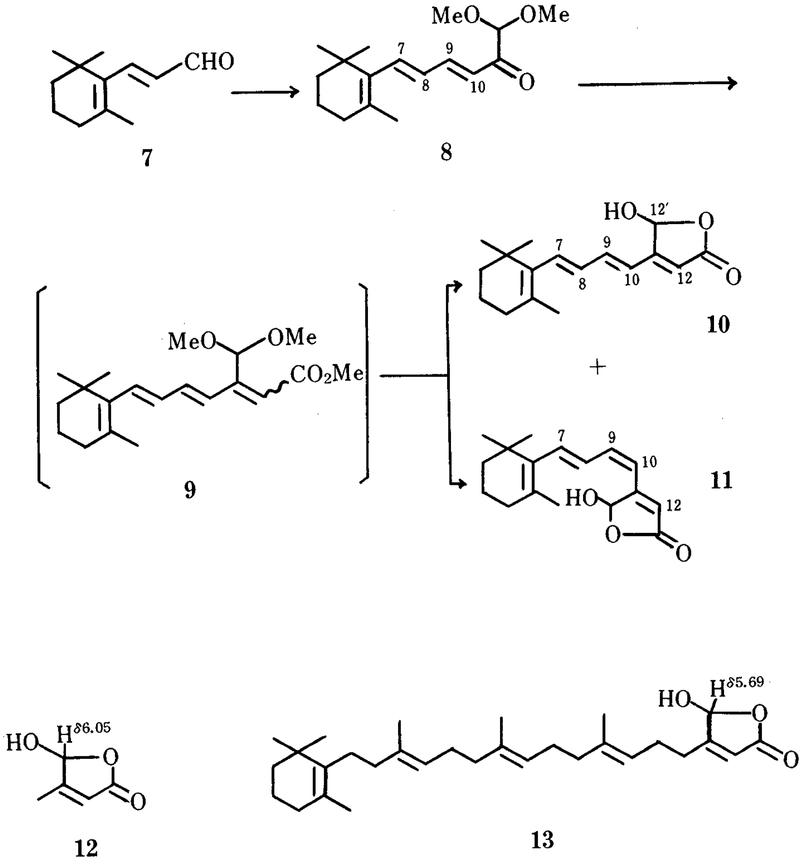


Chart 2

of ^{1}H-NMR decoupling experiments. The low-field shift of the C-9 proton is due to the deshielding effect of the hydroxyl group. The stereochemistry of double bonds in **11** was assigned as (7*E*, 9*Z*) from the ^{1}H-NMR coupling constants ($J_{7,8}=16$ Hz, $J_{9,10}=10$ Hz) compared with those of **10**. The chemical shift of the C-8 proton is at lower field in **11** than in **10**, probably due to the deshielding effect of both the 11, 12-double bond and the hydroxyl group at the C-12′ position. As can be seen from Tables I and II, the chemical shift of the proton at the γ-position in the γ-hydroxybutenolides possessing a conjugated chain at the β-position was observed at relatively lower field (δ *ca.* 6.3) than in the unconjugated γ-hydroxybutenolides (**12**[7]) and **13**[8])). This suggests a deshielding effect of a conjugated double bond at the β-position. These values should be diagnostic in the structural elucidation of unknown conjugated γ-hydroxybutenolide compounds.

Experimental

Ultraviolet (UV) spectra were recorded on a Shimadzu UV 200S instrument and infrared (IR) spectra on a Shimadzu IR-27G spectrometer. ^{1}H-NMR spectra at 60 or 200 MHz were determined on a JEOL JNM-PMX 60 or a Varian XL-200 superconducting FT-NMR spectrometer. Mass spectra (MS) were determined on a Hitachi M-80 double-focusing GC mass spectrometer; high-resolution measurements were made relative to perfluorokerosene as a reference. Preparative thin layer chromatography (TLC) was carried out on silica gel plates (Merck Silica gel 60F$_{254}$ precoated plates, 0.25 or 0.5 mm thickness). Alumina used for column chromatography was Merck aluminium oxide 90 standardized (activity II-III). Silica gel used for column chromatography was Merck Kieselgel 60 (particle size 0.063—0.200 mm, 70—230 mesh ASTM). Unless otherwise stated, solvent extracts were dried on anhydrous Na_2SO_4.

General Procedure for the Aldol Condensation——An aldehyde (*ca.* 5 g), pyruvic aldehyde dimethylacetal, and piperidine (the molar ratio of aldehyde : acetal : piperidine = 1 : *ca.* 4 : *ca.* 3) were dissolved in methanol (*ca.* 90 ml). The solution was refluxed under argon for 3—6.5 h (the progress of the reaction was followed by TLC), then concentrated *in vacuo*, and the residue was purified by distillation or alumina column chromatography.

(*E*)-1,1-Dimethoxy-4-phenyl-3-buten-2-one (4a)——A light yellow oil. bp 177 °C/0.2 mmHg. Yield 73%. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 298. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1690 (conj. C=O), 1607 (C=C). ^{1}H-NMR (200 MHz, $CDCl_3$)δ: 3.45 (6H, s, 2 × OMe), 4.74 (1H, s, 10-H),[5]) 7.07 (1H, d, J=16 Hz, 8-H), 7.35—7.46 (3H, m, 2-, 3-, and 4-H), 7.55—7.67 (2H, m, 1-, 5-H), 7.80 (1H, d, J=16 Hz, 7-H). MS (CI, isobutane) m/z: 207.101 ($(M+H)^+$, $C_{12}H_{15}O_3$ requires 207.102).

(*E*)-1,1-Dimethoxy-4-(2-methoxyphenyl)-3-buten-2-one (4b)——A light yellow oil. Yield 86%. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 340, 292. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1690 (conj. C=O), 1599 (C=C), ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.42 (6H, s, 2 × OMe), 3.83 (3H, s, 1-OMe), 4.70 (1H, s, 10-H), 7.02 (1H, d, J=16 Hz, 8-H), 6.70—7.03 (2H, m, 3-, 4-H), 7.17—7.33 (1H, m, 2-H), 7.40—7.63 (1H, m, 5-H), 8.07 (1H, d, J=16 Hz, 7-H). MS m/z: 236.105 (M^+, $C_{13}H_{16}O_4$ requires 236.105).

(*E*)-1,1-Dimethoxy-4-(4-methoxyphenyl)-3-buten-2-one (4c)——A light yellow oil. Yield 98%.UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 330. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1684 (conj. C=O), 1595 (C=C). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.45 (6H, s, 2 × OMe), 3.84 (3H, s, 3-OMe), 4.73 (1H, s, 10-H), 6.90 (2H, d, J=9 Hz, 2-, 4-H), 6.95 (1H, d, J=16 Hz, 8-H), 7.55 (2H, d, J=9 Hz, 1-, 5-H), 7.77 (1H, d, J=16 Hz, 7-H), MS m/z: 236.104 (M^+, $C_{13}H_{16}O_4$ requires 236.105).

(*E*)-1,1-Dimethoxy-4-(2-methylphenyl)-3-buten-2-one (4d)——A light yellow oil. Yield 44%. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 302. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1690 (conj. C=O), 1606, 1592 (C=C). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.43 (3H, s, 1-Me), 3.42 (6H, s, 2 × OMe), 4.68 (1H, s, 10-H), 6.99 (1H, d, J=16 Hz, 8-H), 7.12—7.70 (4H, m, ArH), 8.03 (1H, d, J=16 Hz, 7-H), MS (CI, isobutane) m/z: 221.116 ($(M+H)^+$· $C_{13}H_{17}O_3$ requires 221.118).

(*E*)-1,1-Dimethoxy-4-(4-methylphenyl)-3-buten-2-one (4e)——A light yellow oil. Yield 61%. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 310. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1690 (conj. C=O), 1600 (C=C), ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 2.37 (3H, s, 3-Me), 3.42 (6H, s, 2 × OMe), 4.68 (1H, s, 10-H), 6.93 (1H, d, J=16 Hz, 8-H), 7.13, 7.43 (2 × 2H, 2 × d, each J=8 Hz, ArH), 7.73 (1H, d, J=16 Hz, 7-H). MS (CI, isobutane) m/z: 221.120 ($(M+H)^+$, $C_{13}H_{17}O_3$ requires 221.118).

(*E*)-1,1-Dimethoxy-4-(2,3-dimethoxyphenyl)-3-buten-2-one (4f)——A light yellow oil. Yield 59%. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 303. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1691 (conj. C=O), 1602, 1578 (C=C). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.42 (6H, s, 2 × 10-OMe), 3.83 (6H, s, 2 × Ar-OMe), 4.70 (1H, s, 10-H), 6.75—7.04 (2H, m, ArH), 7.00 (1H, d, J=16 Hz, 8-H), 7.10—7.30 (1H, m, ArH), 8.05 (1H, d, J=16 Hz, 7-H). MS m/z: 266.115 (M^+, $C_{14}H_{18}O_5$ requires 266.115).

(*E*)-1,1-Dimethoxy-4-(3,4-dimethoxyphenyl)-3-buten-2-one (4g)——A light yellow oil. Yield 73%. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 345. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1689 (conj. C=O), 1591, 1578 (C=C), ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.43 (6H, s, 2 × 10-OMe), 3.88 (6H, s, 2 × Ar-OMe), 4.68 (1H, s, 10-H), 6.80—7.37 (3H, m, Ar-H), 6.85 (1H, d, J=16 Hz, 8-H), 7.70 (1H, d, J=16 Hz, 7-H). MS m/z: 266.117 (M^+, $C_{14}H_{18}O_5$ requires 266.115).

(*E*)-1,1-Dimethoxy-4-(2,5-dimethoxyphenyl)-3-buten-2-one (4h)——A light yellow oil. Yield 48%. UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 372, 295. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1688 (conj. C=O), 1599 (C=C). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 3.45 (6H, s, 2 × 10-OMe), 3.79, 3.84 (each 3H, each s, Ar-OMe), 4.77 (1H, s, 10-H), 6.84 (1H, d, J=9 Hz, 2-H), 6.94 (1H, dd, J=3,9 Hz, 3-H), 7.08 (1H, d, J=16 Hz, 8-H), 7.12 (1H, d, J=3 Hz, 5-H), 8.12 (1H, d, J=16 Hz, 7-H). MS m/z: 266.116 (M^+, $C_{14}H_{18}O_5$ requires 266.115).

5-Hydroxy-4-[2-phenyl-(*E*)-ethenyl]-2(5*H*)-furanone (6a)——This procedure is representative of the preparation of γ-hydroxy-butenolides from the acetal-enones. A solution (14.1 ml) of *n*-butyl lithium (15% (w/v) in *n*-hexane solution) was added to a stirred solution of diethyl methoxycarbonylmethylphosphonate (6.7 g) in dry tetrahydrofuran (THF) (7.4 ml) with ice-cooling under a stream of argon. The mixture was stirred at room temperature for 0.5 h and the acetal-dienone (**4a**, 3.0 g) in dry THF (7.4 ml) was added dropwise. The reaction mixture was refluxed for 40 min and allowed to cool to room temperature. The reaction was quenched by the addition of cold satd. aq. NH_4Cl solution. The mixture was extracted with ether, and the extract was washed with brine, then dried. Removal of the solvent *in vacuo* gave an oil, which was purified by alumina chromatography (eluent: *n*-hexane) to afford a mixture (9*E*:9*Z*=*ca.* 1:2 from ^{1}H-NMR) of isomers of the ester (**5a**, 3.8 g (99%)) as a light yellow oil. Small amounts of the (*E*)- and (*Z*)-isomers of **5a** were isolated in pure form by preparative TLC (developing solvent: 10% ether in *n*-hexane) (9*E*)-isomer[1,9]: UV λ_{max}^{EtOH} nm: 315. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1707 (conj. CO_2Me), 1624 (C=C). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.37 (6H, s, 2×OMe), 3.77 (3H, s, CO_2Me), 5.20 (1H, s, 10′-H), 6.13 (1H, s, 10-H), 7.13 (1H, d, J=16 Hz, 7-H), 7.16—7.63 (5H, m, ArH), 8.13 (1H, d, J=16 Hz, 8-H). (9*Z*)-Isomer: UV λ_{max}^{EtOH} nm: 314. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1709 (conj. CO_2Me), 1608 (C=C). ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 3.45 (6H, s, 2×OMe), 3.73 (3H, s, CO_2Me), 6.12 (1H, s, 10′-H), 6.15 (1H, s, 10-H), 6.72 (1H, d, J=16 Hz, 8-H), 7.15—7.58 (5H, m, ArH), 7.28 (1H, d, J=16 Hz, 7-H).

Aqueous H_2SO_4 (30%, 40 ml) was added to a solution of **5a** (a mixture of (9*E*)- and (9*Z*)-isomers, 3.8 g) in dioxane (60 ml). The mixture was refluxed under argon for 1.5 h, cooled to room temperature, poured into ice-water, and extracted with ether. The organic layer was washed with brine and dried. Evaporation of the solvent under reduced pressure gave an oil, which was purified by silica gel column chromatography (eluent: 10% acetone in benzene) to afford the hydroxybutenolide (**6a**, 1.3 g (45%)) as light yellow needles, mp 163—164 °C (benzene–acetone). UV and IR: see Table I. ^{1}H-NMR (200 MHz, d_6-acetone) δ: see Table I, 6.89 (1H, s, OH), 7.37—7.50 (3H, m, ArH), 7.58—7.70 (2H, m, ArH). MS *m*/*z*: 202.061 (M^+, $C_{12}H_{10}O_3$ requires 202.063).

5-Hydroxy-4-[2-(2-methoxyphenyl)-(*E*)-ethenyl]-2(5*H*)-furanone (6b)——A light yellow oil. Yield 27%. UV and IR: see Table I. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: see Table I. 3.88 (3H, s, OMe), 4.97 (1H, s, OH), 6.92 (1H, t, J=8 Hz, 3-H), 7.06 (1H, d, J=8 Hz, 2-H), 7.32 (1H, dt, J=2, 8 Hz, 4-H), 7.51 (1H, dd, J=2, 8 Hz, 5-H). MS *m*/*z*: 232.072 (M^+, $C_{13}H_{12}O_4$ requires 232.073).

5-Hydroxy-4-[2-(4-methoxyphenyl)-(*E*)-ethenyl]-2(5*H*)-furanone (6c)——Light yellow needles, mp 164—167 °C (benzene–acetone). Yield 21%. UV and IR: see Table I. ^{1}H-NMR (200 MHz, d_6-acetone) δ: see Table I, 3.84 (3H, s, OMe), 6.81 (1H, br s, OH), 6.98, 7.59 (2×2H, 2×d, each J=9 Hz, ArH). MS *m*/*z*: 232.076 (M^+, $C_{13}H_{12}O_4$ requires 232.073).

5-Hydroxy-4-[2-(2-methylphenyl)-(*E*)-ethenyl]-2(5*H*)-furanone (6d)——Light yellow needles, mp 129—131 °C (*n*-hexane–acetone). Yield 43%. UV and IR: see Table I. ^{1}H-NMR (200 MHz, d_6-acetone) δ: see Table I, 2.41 (3H, s, 1-Me), 6.92 (1H, d, J=8 Hz, OH), 7.18—7.32 (3H, m, 2-, 3-, and 4-H), 7.65—7.74 (1H, m, 5-H). MS *m*/*z*: 216.079 (M^+, $C_{13}H_{12}O_3$ requires 216.079).

5-Hydroxy-4-[2-(4-methylphenyl)-(*E*)-ethenyl]-2(5*H*)-furanone (6e)——Light yellow plates, mp 154—155 °C (*n*-hexane–acetone). Yield 33%. UV and IR: see Table I. ^{1}H-NMR (200 MHz, d_6-acetone) δ: see Table I, 2.35 (3H, s, 3-Me), 6.84 (1H, d, J=8 Hz, OH), 7.24, 7.52 (2×2H, 2×d, each J=8 Hz, ArH). MS *m*/*z*: 216.079 (M^+, $C_{13}H_{12}O_3$ requires 216.079).

5-Hydroxy-4-[2-(2,3-dimethoxyphenyl)-(*E*)-ethenyl]-2(5*H*)-furanone (6f)——Light yellow needles, mp 148—150 °C (*n*-hexane–acetone). Yield 28%. UV and IR: see Table I. ^{1}H-NMR (200 MHz, d_6-acetone) δ: see Table I, 3.81, 3.87 (each 3H, each s, 2×OMe), 6.92 (1H, br s, OH), 7.04—7.14 (2H, m, ArH), 7.30 (1H, dd, J=2, 7 Hz, ArH). MS *m*/*z*: 262.085 (M^+, $C_{14}H_{14}O_5$ requires 262.084).

5-Hydroxy-4-[2-(3,4-dimethoxyphenyl)-(*E*)-ethenyl]-2-(5*H*)-furanone (6g)——Light yellow needles, mp 138—141 °C (benzene–acetone). Yield 32%. UV and IR: see Table I. ^{1}H-NMR (200 MHz, d_6-acetone) δ: see Table I, 3.85, 3.87 (each 3H, each s, 2×OMe), 6.78 (1H, d, J=7 Hz, OH), 6.98 (1H, d, J=8 Hz, 4-H), 7.16 (1H, dd, J=2, 8 Hz, 5-H), 7.28 (1H, s-like, 1-H). MS *m*/*z*: 262.086 (M^+, $C_{14}H_{14}O_5$ requires 262.084).

5-Hydroxy-4-[2-(2,5-dimethoxyphenyl)-(*E*)-ethenyl]-2(5*H*)-furanone (6h)——Light yellow needles, mp 148—150 °C (benzene–acetone). Yield 20%. UV and IR: see Table I. ^{1}H-NMR (200 MHz, d_6-acetone) δ: see Table I, 3.79, 3.85 (each 3H, each s, 2×OMe), 6.84 (1H, d, J=8 Hz, OH), 6.94 (1H, dd, J=3, 9 Hz, 3-H), 7.01 (1H, d, J=9 Hz, 2-H), 7.23 (1H, d, J=3 Hz, 5-H). MS *m*/*z*: 262.085 (M^+, $C_{14}H_{14}O_5$ requires 262.084).

(3*E*, 5*E*)-1,1-Dimethoxy-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3,5-hexadien-2-one (8)——The dienal (7,[6]) 1.0 g) was treated in the same manner as described for **4** to give **8** (0.9 g (56%)) as a yellow oil. UV λ_{max}^{EtOH} nm: 333, 275 (sh). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1687 (conj. C=O), 1583 (C=C). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.05 (6H, s, *gem*-Me), 1.75 (3H, s, 5-Me), 3.42 (6H, s, 2×OMe), 4.69 (1H, s, 12-H), 6.28 (1H, dd, J=11, 15 Hz, 8-H), 6.45 (1H, d, J=15 Hz, 10-H), 6.72 (1H, d, J=15 Hz, 7-H), 7.48 (1H, dd, J=11, 15 Hz, 9-H). MS *m*/*z*: 278.186 (M^+, $C_{17}H_{26}O_3$ requires 278.188).

5-Hydroxy-4-[4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-(1*E*/*Z*, 3*E*)-butadienyl]-2(5*H*)-furanone (10) and (11)——The acetal (**8**, 0.8 g) was treated in the same manner as described for **6a** to give **10** (53 mg (13%)) and **11** (16 mg (4%)), each as a yellow oil. **10**: UV and IR: see Table II. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: see Table II, 1.06 (6H, s, *gem*-Me), 1.76 (3H, s, 5-Me), 3.98 (1H, d, J=8 Hz, OH). MS *m*/*z*: 274.159 (M^+, $C_{17}H_{22}O_3$ requires 274.157). **11**: UV and IR: see Table II. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: see Table II, 0.98 (6H, s, *gem*-Me), 1.62 (3H, s, 5-Me), 3.72 (1H, br s, OH), MS *m*/*z*: 274.158 (M^+, $C_{17}H_{22}O_3$ requires 274.157).

Acknowledgement We thank Misses S. Ikezoe and A. Imai for technical assistance.

References and Notes

1) M. Ito, T. Iwata, and K. Tsukida, *Heterocycles*, **19**, 1385 (1982); *idem, Chem. Pharm. Bull.*, **32**, 1709 (1984).
2) H. Higashida, N. Miki, M. Ito, T. Iwata, and K. Tsukida, *Int. J. Cancer*, **33**, 677 (1984).
3) W. Bollag, *Experientia*, **27**, 90 (1971).
4) H. Mayer, W. Bollag, R. Hänni, and R. Rüegg, *Experientia*, **34**, 1105 (1978); P. Loeliger, W. Bollag, and H. Mayer, *Eur. J. Med. Chem.*, **15**, 9 (1980).
5) Retinoid numbering (*J. Biol. Chem.*, **258**, 5329 (1983)) is employed in the formulae.
6) P. J. van den Tempel and H. O. Huisman, *Tetrahedron*, **22**, 293 (1966).
7) G. Pattenden and B. C. L. Weedon, *J. Chem. Soc. (C)*, **1968**, 1984.
8) M. B. Yunker and P. J. Scheuer, *J. Am. Chem. Soc.*, **100**, 307 (1978).
9) M. Ito, K. Hirata, A. Kodama, K. Tsukida, H. Matsumoto, K. Horiuchi, and T. Yoshizawa, *Chem. Pharm. Bull.*, **26**, 925 (1978); M. Ito, T. Iwata, K. Tsukida, Y. Shichida, and T. Yoshizawa, *J. Nutr. Sci. Vitaminol.*, **30**, 577 (1984).