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Retinoids and Related Compounds. VII.[1] Synthesis of Retinoidal 4-Ylidenebutenolides and Their Homologues

MASAYOSHI ITO,* TSUTOMU IWATA, and KIYOSHI TSUKIDA

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

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Retinoidal ylidenebutenolides (XVIa, b and XVIIa, b) and their homologues have been synthesized in several steps starting from β-cyclocitral (IIIa) or 3-methoxy-β-cyclocitral (IIIb). The spectral characteristics of the 4-ylidenebutenolides (II) are described in comparison with those of methyl all-(*E*)-retinoate (XX).

Keywords——retinoidal ylidenebutenolide; antitumor retinoid; spectral characterization; aldol condensation; Emmons–Horner reaction; Wittig reaction

A number of products possessing an α,β-unsaturated γ-lactone ring ($\Delta^{\alpha,\beta}$-butenolide) have been discovered in nature and many of them have attracted interest because of their wide range of biological activities. Among them, most of the 4-ylidene derivatives (4-ylidenebutenolides) (I and II) have been found as natural products in the past two decades, and excellent reviews have been given by Pattenden[2] and Yamamoto.[3] Although a number of approaches to the synthesis of I have been made, there has been no report on synthetic studies for II (*e.g.* peridinin[4] and tetrenolin[5]), displaying extended conjugation at the C-2 position. In a previous communication,[6] we described the first synthesis and characterizations of retinoidal 4-ylidenebutenolides as an extension of synthetic work[7,8] to develop a new antitumor retinoidal compound.[9] We now give a full account of the results.

β-Cyclocitral (IIIa)[10] was condensed with pyruvic aldehyde dimethylacetal (IV) in the presence of piperidine in methanol to give the (*E*)-acetal-dienone (Va) in 60% yield. This aldol condensation was investigated under various conditions (base, solvent, molar ratio of reactants, reaction temperature, and reaction time) and a reasonable yield was obtained when the molar ratio of IIIa, IV, and piperidine was 1 : 5 : 2 and methanol was used as a solvent. The ultraviolet (UV) (λ_{max} 307 and 236 nm) and infrared (IR) absorptions (ν 1693 cm^{-1}) of Va were almost identical with those of β-ionone. The newly formed double bond was determined to be (*E*) on the basis of the coupling constant ($J = 16$ Hz) between 7-H[11] (δ 7.59) and 8-H (δ 6.46) in the ^{1}H-nuclear magnetic resonance (NMR) spectrum. An Emmons–Horner reaction of the acetal-dienone (Va) with diethyl methoxycarbonylmethylphosphonate (VI) in the presence of *n*-butyl lithium gave a mixture of the (9*E*)- and (9*Z*)-acetal-ester (VIIa) in 94% yield, and this was immediately refluxed in methanol in the presence of sulfuric acid for 1 h to afford the methoxy-lactone (VIIIa) in 68% yield after silica gel column chromatographic purification. The structure of VIIIa was confirmed by the following spectral data compared with the spectral data of the model compound (IXc) derived from the acetoxy-ester (VIIc)[12]: IR absorption due to the α,β-unsaturated γ-lactone at 1790 and 1755 cm^{-1}; singlet signals in the NMR spectrum at δ 6.04 (10′-H), δ 5.91 (10-H), and δ 3.50 (OCH_3); UV absorption maxima at 319 and 258 nm. Attempts to extend the conjugation by appropriate reactions (*e.g.* Horner,[13] Wittig, and Grignard reactions) at the lactone carbonyl group were unsuccessful. The methoxy-lactone (VIIIa) was hydrolyzed in dioxane containing dil. sulfuric acid at the

refluxing temperature in a stream of argon for 3.5 h to give the hydroxy-lactone (IXa) in 91% yield; IXa was also obtained directly in 74% yield by treatment of the isomeric mixture (VIIa) under the same conditions. PCC-oxidation of IXa in dry CH_2Cl_2 led to the unstable conjugated anhydride (Xa) in 69% yield. Without purification, Xa was condensed with the

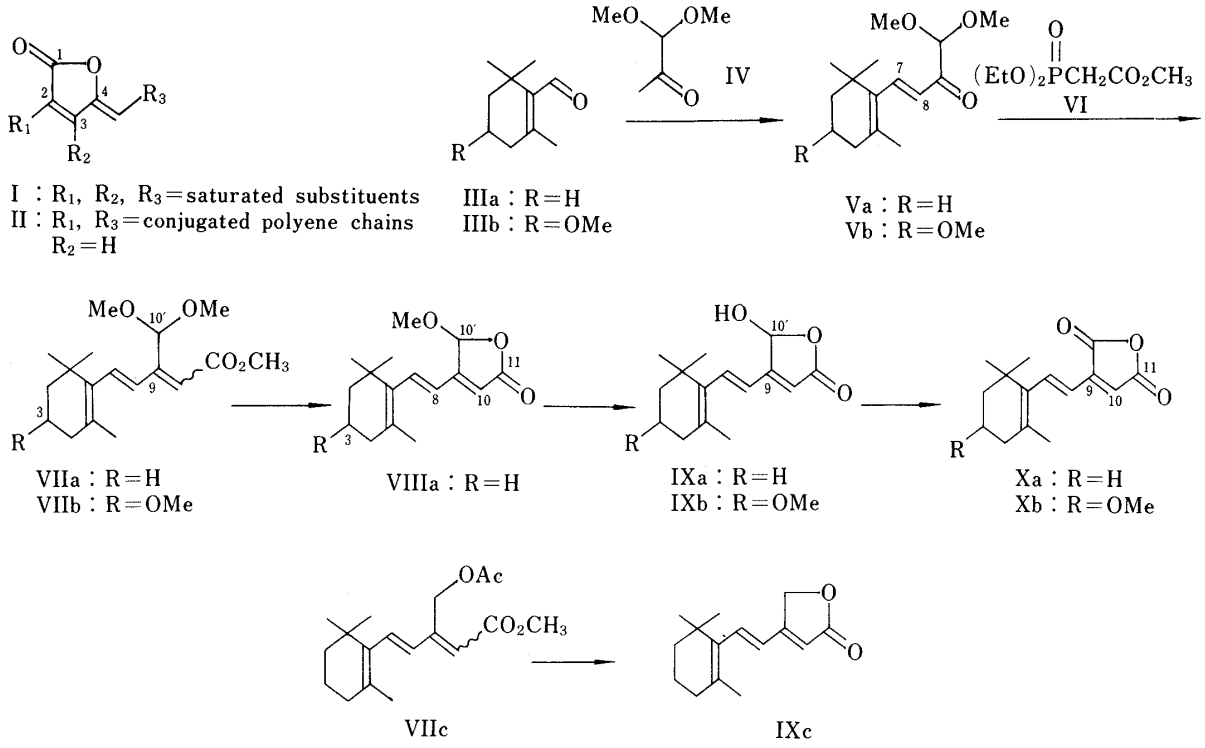

Chart 1

acetyl phosphorane (XI)[14] in dry benzene under reflux for 2 h in a stream of argon to afford a mixture of three keto-lactones (XIIa, 10%), (XIIIa, 24.5%), and (XIVa, 8.2%) which were clearly separated by preparative thin layer chromatography (TLC). The two isomers (XIIa) and (XIIIa) with UV absorption maxima at longer wavelengths (λ 330 and 335 nm, respectively, Table I) were considered to be the products arising from attack of the phosphorane at the less hindered carbonyl group (C-11). The lactone carbonyl absorptions (Table I) of XIIa and XIIIa were in good agreement with those of the model compounds (XVIII) and (XIX).[15] The stereochemistry of the Δ^{11} double bond in XIIa and XIIIa was definitely determined from the NMR spectra (Table I). It has been noted in the literature[15-17] that in XVIII and XIX, the chemical shift of the vinyl proton on the exocyclic double bond is at lower field in the (*E*)-isomer (XIX) than in the (*Z*)-isomer (XVIII), probably due to the deshielding effect of the lactone oxygen. Thus, the isomer (XIIIa) with 12-H at δ 6.14 was assigned the (11*E*)-configuration and the isomer (XIIa) with δ 5.51 (12-H) was assigned the (11*Z*)-configuration. These assignments were further supported by the chemical shift difference of the 10-H signals and that of the methyl signals (C-13) of XIIa and XIIIa. From a comparison of the IR and NMR data for XIIa and XIIIa with those[15,18] of XVIII and XIX, it appears that the extending of conjugation at the C-2 position in II has no effect on the lactone carbonyl absorption or on the chemical shifts of 10-H and 12-H in the conjugated ylidenebutenolide. Heating or TLC of XIIa and XIIIa provided an equilibrium mixture (*ca.* 1 : 1) of them. Spectral data (Table I) of the third isomer (XIVa), which showed a UV absorption maximum at a shorter wavelength (λ 293 nm), were also in accord with the proposed structure. The (11*Z*)-isomer (XIIa) was treated with the phosphorane (XV)[19] in dry

TABLE I. Spectral Data for the Keto-butenolides [(XII), (XIII), and (XIV)]

	XII		XIII		XIV	
	a	b	a	b	a	b
UV λ_{max}^{EtOH}, nm	330	363 307	335	366 320	293	294
IR $\nu_{max}^{CHCl_3}$, cm^{-1}	1790 1665 1620	1790 1668 1607	1787 1686 1602	1791 1694 1600	1785 1665 1643 1610	1781 1660 1644 1608
NMR $\delta_{ppm}^{CDCl_3}$						
10-H	7.08 (s)	7.08 (s)	7.93 (s)	7.95 (s)	6.32 (s)	6.33 (s)
12-H	5.51 (s)	5.51 (s)	6.14 (s)	6.16 (s)		
11′-H					5.72 (s)	5.70 (s)
13-CH_3	2.56 (s)	2.56 (s)	2.33 (s)	2.33 (s)		
12′-CH_3					2.59 (s)	2.59 (s)

toluene at 140 °C for 3 h in a sealed bottle containing argon to furnish the mixture of butenolide-esters (XVIa, 25.1%) and (XVIIa, 14.0%), which were separated by preparative TLC. Characteristic spectral data are summarized in Table II. Unexpectedly, UV maxima of both products were observed at 356 nm, close to that (354 nm)[20] of methyl retinoate (XX), and the lactone carbonyl absorptions of XVIa and XVIIa showed standard values for general $\Delta^{\alpha,\beta}$-butenolides. The configuration of the methylated trisubstituted double bond (Δ^{13}) was decided from the NMR data. The C-13 methyl signal in the (13*E*)-isomer (XVIa) appeared at extremely low field (δ 2.55) compared with that[21] (δ 2.36) of the all-(*E*)-retinoate. This is due to the deshielding effect of both the enolic oxygen in the butenolide ring and the carbonyl group of the ester. The C-12 proton signal of the (13*Z*)-isomer (XVIIa) is also deshielded by the anisotropic effect of the carbonyl group of the ester. The Wittig reaction of XIIIa with XV as in the case of XIIa also produced a mixture of XVIa (16.8%) and XVIIa (9.5%). The intensity of ketonic carbonyl absorption of XIIIa in the IR spectrum was very weak in comparison with that of the isomer (XIIa), suggesting low reactivity of the ketone group of XIIIa. On the basis of the facts that XIIa and XIIIa are equilibrated by heating and TLC, and produce a mixture of XVIa and XVIIa in a similar ratio, it is suggested that Wittig reaction of XIIIa with XV proceeded after predominant conversion to XIIa.

By using the same pathway as described above, the 3-methoxy-derivatives (XVIb) and (XVIIb) of retinoidal ylidenebutenolides (XVIa) and (XVIIa) were synthesized starting from 3-methoxy-β-cyclocitral (IIIb), which was itself prepared by ozonolysis of 3-methoxy-β-ionone[22] at low temperature. Spectral characterizations of XVIb, XVIIb, and intermediates in the synthesis of the 3-methoxy analogue are summarized in Tables I and II, together with those for the 3-desmethoxy compounds. All the spectral data for XVIb and XVIIb were consistent with the proposed structures. The 7-H signal in the NMR spectra of XVI and XVII is observed at very low field (δ 7.3—7.4) as compared with that (δ 6.3) of methyl all-(*E*)-retinoate, suggesting an anisotropic effect of the lactone carbonyl group. The chemical shift values (*ca.* δ 7.0—7.1) of 10-H in XIIa, XIIb, XVIa, XVIb, XVIIa, XVIIb, and XVIII could

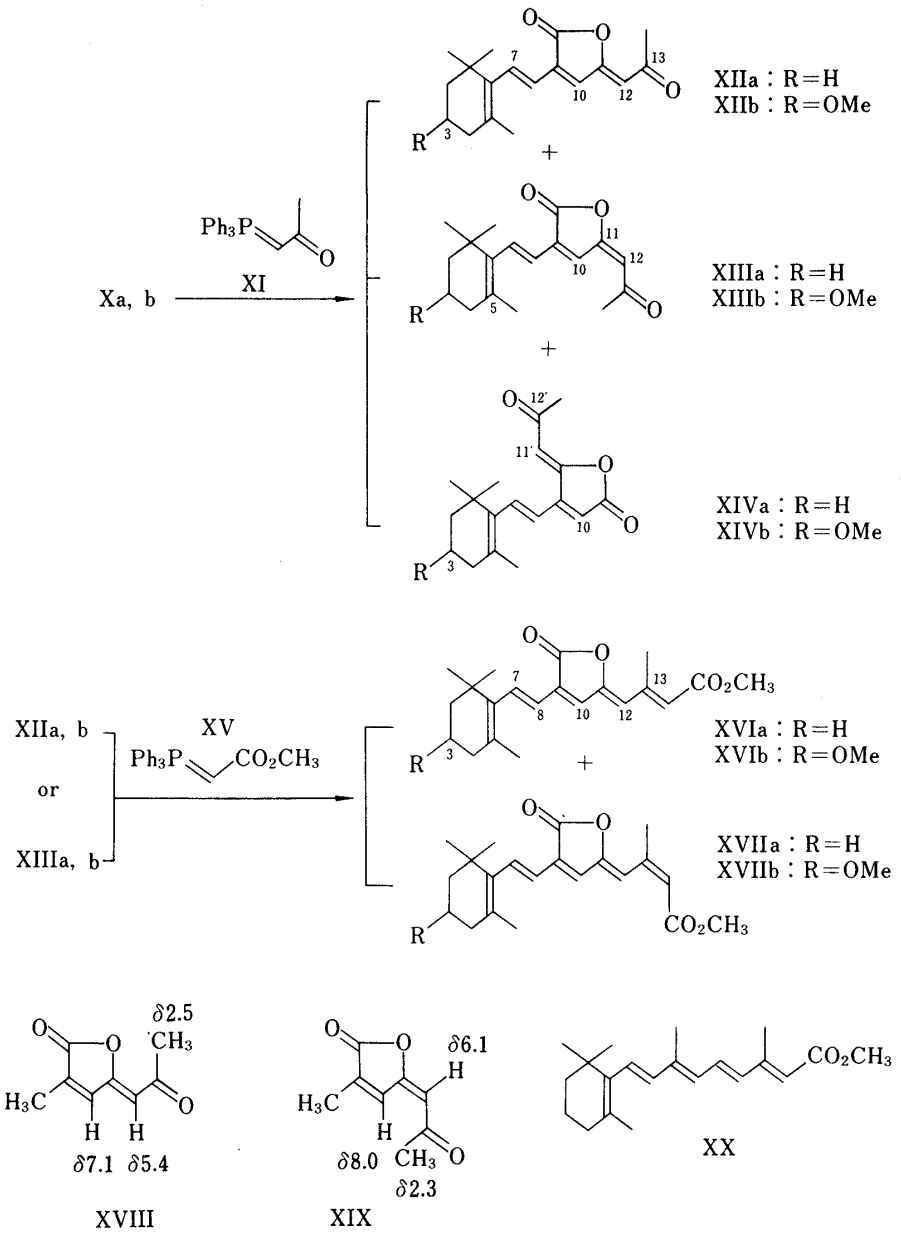

Chart 2

be regarded as a diagnostic value of 3-H in the II system. This might also apply to the chemical shifts (*ca.* δ 7.9—8.0) of 10-H in XIIIa, XIIIb, and XIX.

The present synthetic route may also be applicable to the synthesis of the 4-ylidenebutenolide (II). Cytotoxic activity of the retinoidal butenolides obtained here on mouse neuroblastoma and rat glioma cells is now under investigation. The results will be reported elsewhere.

Experimental

UV spectra were recorded on a Shimadzu UV 200S instrument and IR spectra on a Shimadzu IR-27G spectrometer. NMR spectra at 60 or 200 MHz were determined on a JEOL JNM-PMX 60 or a Varian XL-200 superconducting FT-NMR spectrometer in $CDCl_3$. Mass spectra (MS) were determined on a JEOL JMS-01SG or a Hitachi M-80 double-focusing GC mass spectrometer; high resolution measurements were made relative to perfluorokerosene as a reference. Preparative 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

TABLE II. Spectral Data for the Retinoidal Ylidene-butenolides (XVI) and (XVII)

	XVI		XVII	
	a	b	a	b
UV λ_{max}^{EtOH}, nm	356 (ε 35400)	368 (ε 30000)	356 (ε 35300)	364 (ε 30100)
IR $\nu_{max}^{CHCl_3}$, cm^{-1}	1770 (sh)	1775 (sh)	1775 } (split)	1775 } (split)
	1765	1765	1760 }	1760 }
	1712	1710	1700	1703
	1600	1600	1598	1600
NMR $\delta_{ppm}^{CDCl_3}$				
13-CH_3	2.55 (s)	2.55 (s)	2.32 (s)	2.33 (s)
14-H	5.57 (s)	5.59 (s)	5.77 (s)	5.78 (s)
12-H	6.04 (s)	6.05 (s)	7.32 (s)	7.34 (s)
10-H	7.00 (s)	7.03 (s)	7.09 (s)	7.11 (s)
8-H	6.22 (d)	6.22 (d)	6.23 (d)	6.23 (d)
	(J=16 Hz)	(J=16 Hz)	(J=16 Hz)	(J=16 Hz)
7-H	7.38 (d)	7.33 (d)	7.37 (d)	7.33 (d)
	(J=16 Hz)	(J=16 Hz)	(J=16 Hz)	(J=16 Hz)

0.063—0.200 mm, 70—230 mesh ASTM). Unless otherwise noted, solvent extracts were dried on anhydrous Na_2SO_4.

10,10-Dimethoxy-β-ionone (Va)——β-Cyclocitral (IIIa,[10] 1.5 g), pyruvic aldehyde dimethylacetal (IV, 5.9 g), and piperidine (2.0 g) were dissolved in methanol (20 ml). The solution was refluxed for 27 h, then concentrated under a vacuum, and the residue was purified by alumina column chromatography (eluent: 10% ether in hexane) to give the acetal-dienone (Va, 1.5 g (60%)) as a light yellow oil. UV λ_{max}^{EtOH} nm (ε): 236 (6700), 307 (8200); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1693 (conj. C=O); NMR δ (200 MHz): 1.09 (6H, s, *gem*CH_3), 1.81 (3H, s, 5-CH_3), 3.42 (6H, s, 2×OCH_3), 4.72 (1H, s, 10-H), 6.46 (1H, d, J=16 Hz, 8-H), 7.59 (1H, d, J=16 Hz, 7-H); MS m/z 252.171 (M^+, $C_{15}H_{24}O_3$ requires 252.172).

3-Methoxy-β-cyclocitral (IIIb)——Ozone gas was introduced into a rapidly stirred solution of 3-methoxy-β-ionone[22] (15.0 g) in methanol (127 ml) at −20 °C for 3 h. Nitrogen gas was introduced into the reaction solution for 5 min, and zinc dust (7.0 g) and 50% acetic acid (53 ml) were added at *ca.* −5 °C. The mixture was stirred for 1 h at room temperature, then poured into ice-water, and the whole was extracted with CH_2Cl_2. The organic layer was neutralized with satd. $NaHCO_3$ solution and washed with brine. Removal of the dried solvent under reduced pressure left an oil which was distilled at 60—70 °C (0.15—0.20 mmHg) to give IIIb (11.4 g (93%)) as a light yellow oil. UV λ_{max}^{EtOH} nm: 245; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665 (CO); NMR δ (60 MHz): 1.22, 1.23 (each 3H, s, *gem*CH_3), 2.11 (3H, s, 5-CH_3), 3.35 (3H, s, 3-OCH_3), 10.08 (1H, s, 7-H).

3,10,10-Trimethoxy-β-ionone (Vb)——The methoxy-aldehyde (IIIb, 11.4 g) was treated in the same manner as described for Va to give Vb (10.5 g (59%)) as a light yellow oil. UV λ_{max}^{EtOH} nm (ε): 232 (7200), 304 (10800); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1692 (conj. C=O), 1584 (C=C); NMR δ (200 MHz): 1.12, 1.14 (each 3H, s, *gem*CH_3), 1.82 (3H, s, 5-CH_3), 3.37 (3H, s, 3-OCH_3), 3.42 (6H, s, 2×OCH_3), 4.70 (1H, s, 10-H), 6.46 (1H, d, J=16 Hz, 8-H), 7.53 (1H, d, J=16 Hz, 7-H); MS m/z 282.185 (M^+, $C_{16}H_{22}O_4$ requires 282.183).

Methyl 10′,10′-Dimethoxy-β-ionylideneacetate (VIIa)——A solution (38 ml) of *n*-butyl lithium (15% (w/v) in hexane solution) was added to a stirred solution of diethyl methoxycarbonylmethylphosphonate (VI, 18.2 g) in dry tetrahydrofuran (THF) (20 ml) with ice-cooling under a stream of argon. The mixture was stirred at room temperature for 0.5 h and the acetal-dienone (Va, 9.9 g) in dry THF (20 ml) was then added dropwise. The reaction mixture was refluxed for 1 h and allowed to cool to room temperature. Satd. NH_4Cl solution was added and the mixture was extracted with ether. The ethereal solution was washed with brine and dried. Removal of the solvent *in vacuo* gave an oil, which was purified by alumina column chromatography (eluent: 10% ether in hexane) to afford a mixture of the isomers of the β-ionylidene ester (VIIa, 11.4 g (94%)) as a light yellow oil from which the (*Z*)-isomer was isolated in pure form by additional alumina column chromatography (eluent: hexane). The (9*Z*)-isomer of VIIa; UV λ_{max}^{EtOH} nm: 275, 310 (sh); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1709 (CO_2CH_3), 1604 (C=C); NMR δ (200 MHz): 1.03 (6H, s, *gem*CH_3), 1.72 (3H, s, 5-CH_3), 3.43 (6H, s, 2×OCH_3), 3.73 (3H, s, CO_2CH_3), 6.02 (1H, s, 10- or 10′-H), 6.07 (1H, d, J=16 Hz, 8-H), 6.10 (1H, s, 10′- or 10-H), 6.90 (1H, d, J=16 Hz, 7-H); MS m/z 308.200 (M^+, $C_{18}H_{28}O_4$ requires 308.199). A small amount of the (9*E*)-isomer of VIIa was isolated in a pure form by repeated alumina column chromatography (eluent: hexane) and preparative TLC (developing solvent: 10% ether in hexane). The (9*E*)-isomer

of VIIa; UV λ_{max}^{EtOH} nm: 265, 316; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1709 (CO_2CH_3), 1603 (C=C); NMR δ (200 MHz): 1.06 (6H, s, *gem*CH_3), 1.78 (3H, s, 5-CH_3), 3.31 (6H, s, 2×OCH_3), 3.72 (3H, s, CO_2CH_3), 5.19 (1H, s, 10′-H), 6.07 (1H, s, 10-H), 6.83 (1H, d, J=16.5 Hz, 7-H), 7.38 (1H, d, J=16.5 Hz, 8-H); MS *m/z* 308.198 (M^+, $C_{18}H_{28}O_4$ requires 308.199).

Methyl 3,10′,10′-Trimethoxy-β-ionylideneacetate (VIIb)——A solution (13 ml) of 15% *n*-butyl lithium in hexane was added to a stirred solution of diethyl methoxycarbonylmethylphosphonate (VI, 6.0 g) in dry dimethoxyethane (6 ml) with ice-cooling under a stream of argon. The mixture was stirred at room temperature for 0.5 h and the acetal-dienone (Vb, 3.0 g) in dry dimethoxyethane (6 ml) was then added dropwise. The reaction mixture was refluxed for 3 h, then cooled to room temperature. Satd. NH_4Cl solution was added and the mixture was extracted with ether. The organic layer was washed with brine and dried. Removal of the solvent by evaporation *in vacuo* gave an oil which was purified by alumina column chromatography (eluent: 10% ether in hexane) to afford a mixture of the ester isomers (VIIb, 2.5 g (69%)) from which only the (*Z*)-isomer was isolated in pure form by additional alumina column chromatography (eluent: hexane). The (9*Z*)-isomer of VIIb; UV λ_{max}^{EtOH} nm (ε): 252 (9100), 294 (10500); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO_2CH_3), 1605 (C=C); NMR δ (200 MHz): 1.07 (6H, s, *gem*CH_3), 1.74 (3H, s, 5-CH_3), 3.37 (3H, s, 3-OCH_3), 3.43 (6H, s, 2×OCH_3), 3.73 (3H, s, CO_2CH_3), 6.02 (1H, s, 10- or 10′-H), 6.06 (1H, d, J=16 Hz, 8-H), 6.10 (1H, s, 10′- or 10-H), 6.84 (1H, d, J=16 Hz, 7-H); MS *m/z* 338.208 (M^+, $C_{19}H_{30}O_5$ requires 338.209).

10′-Hydroxy-10′-methoxy-β-ionylideneacetic Acid Lactone (VIIIa)——A mixture of the ester isomer (VIIa, 6.6 g) and 15% aq. H_2SO_4 (15 ml) in methanol (60 ml) was refluxed for 1 h, cooled to room temperature, poured into ice-water, and extracted with ether. The organic layer was neutralized with satd. $NaHCO_3$ solution and washed with brine. Removal of the dried solvent under reduced pressure left an oil which was purified by silica gel column chromatography (eluent: 10% ether in hexane) to give the methoxy-lactone (VIIIa, 3.8 g (68%)) as a colorless oil. UV λ_{max}^{EtOH} nm (ε): 258 (12500), 319 (12600); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1790 (sh) and 1755 (α,β-unsaturated γ-lactone), 1612 (C=C); NMR δ (200 MHz): 1.06, 1.08 (each 3H, s, *gem*CH_3), 1.78 (3H, s, 5-CH_3), 3.50 (3H, s, OCH_3), 5.91 (1H, s, 10-H), 6.04 (1H, s, 10′-H), 6.32 (1H, d, J=16 Hz, 8-H), 6.90 (1H, d, J=16 Hz, 7-H); MS *m/z* 262.156 (M^+, $C_{16}H_{22}O_3$ requires 262.157).

10′,10′-Dihydroxy-β-ionylideneacetic Acid Lactone (IXa)——Method A: Aq. H_2SO_4 (30%, 70 ml) was added to a solution of VIIIa (5.0 g) in dioxane (100 ml). The mixture was refluxed under argon for 3.5 h, cooled to room temperature, poured into ice-water, extracted with ether, and dried. Removal of the solvent by evaporation *in vacuo* gave an oil, which was purified by silica gel column chromatography (eluent: benzene) to afford the hydroxy-lactone (IXa, 4.3 g (91%)) as a colorless oil.

Method B: Aq. H_2SO_4 (30%, 60 ml) was added to a solution of VIIa (a mixture of (*E*)- and (*Z*)-isomers, 4.2 g) in dioxane (80 ml). The mixture was refluxed under argon for 3.5 h, cooled to room temperature, poured into ice-water, and extracted with ether. The organic layer was washed with brine and dried. Removal of the solvent by evaporation under reduced pressure gave an oil, which was purified by silica gel column chromatography (eluent: benzene) to afford the hydroxy-lactone (IXa, 2.5 g (74%)) as a colorless oil. UV λ_{max}^{EtOH} nm: 260, 315; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3325 (OH), 1750 and 1735 (α,β-unsaturated γ-lactone), 1635 and 1614 (C=C); NMR δ (200 MHz): 1.07 (6H, s, *gem*CH_3), 1.78 (3H, s, 5-CH_3), 4.94 (1H, s, OH), 5.86 (1H, s, 10-H), 6.30 (1H, s, 10′-H), 6.32 (1H, d, J=17 Hz, 8-H), 7.00 (1H, d, J=17 Hz, 7-H); MS *m/z* 248.140 (M^+, $C_{15}H_{20}O_3$ requires 248.140).

10′,10′-Dihydroxy-3-methoxy-β-ionylideneacetic Acid Lactone (IXb)——The trimethoxy-ester (VIIb, 2.5 g) was treated according to method B described for IXa to give the hydroxy-lactone (IXb, 1.2 g (57%)) as crystals, mp 84—86 °C. UV λ_{max}^{EtOH} nm (ε): 253 (8600), 315 (12600); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3295 (OH), 1755 (lactonic C=O), 1614 (C=C); NMR δ (200 MHz): 1.10, 1.11 (each 3H, s, *gem*CH_3), 1.79 (3H, s, 5-CH_3), 3.37 (3H, s, 3-OCH_3), 5.39 (1H, d, J=8 Hz, OH), 5.88 (1H, s, 10-H), 6.29 (1H, d, J=8 Hz, 10′-H), 6.32 (1H, d, J=17 Hz, 8-H), 6.94 (1H, d, J=17 Hz, 7-H); MS *m/z* 278.151 (M^+, $C_{16}H_{22}O_4$ requires 278.152).

9-Carboxy-β-ionylideneacetic Acid Anhydride (Xa)——A solution of the hydroxy-lactone (IXa, 0.3 g) in dry CH_2Cl_2 (freshly distilled over P_2O_5, 1.5 ml) was added to a stirred suspension of pyridinium chlorochromate (PCC, 0.9 g) in dry CH_2Cl_2 (7 ml) under argon. The mixture was refluxed for 3.5 h, cooled to room temperature, and filtered. The filtrate was concentrated *in vacuo* to give an unstable yellow oil (Xa, 0.207 g (69%)), which was used in the following step without purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1840 and 1765 (CO–O–CO); NMR δ (60 MHz): 1.08 (6H, s, *gem*CH_3), 1.82 (3H, s, 5-CH_3), 6.42 (1H, s, 10-H), 6.92 (1H, d, J=16 Hz, 8-H), 7.63 (1H, d, J=16 Hz, 7-H); MS *m/z* 246.128 (M^+, $C_{15}H_{18}O_3$ requires 246.126).

9-Carboxy-3-methoxy-β-ionylideneacetic Acid Anhydride (Xb)——The hydroxy-lactone (IXb, 0.2 g) was treated in the same manner as described for Xa to give an unstable yellow oil (Xb), which was used in the following step without purification. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1838 and 1765 (CO–O–CO).

Reaction of Xa with XI——A solution of the crude anhydride (Xa, 0.2 g) in dry benzene (2 ml) was added to a suspension of the acetyl phosphorane (XI,[14] 0.5 g) in dry benzene (8 ml). The mixture was refluxed for 2 h under argon and concentrated *in vacuo*. The residue was subjected to preparative TLC (developing solvent: benzene) to give XIIIa as a yellow oil (57 mg (24.5%)) and a mixture of XIIa and XIVa, from which pure XIIa (23 mg (10.0%)) and XIVa (19 mg (8.2%)) were obtained, each as a yellow oil, by additional preparative TLC (developing solvent: 40% ether in hexane).

(7*E*),(11*Z*)-XIIa: NMR δ (200 MHz): 1.09 (6H, s, *gem*CH_3), 1.79 (3H, s, 5-CH_3), 2.56 (3H, s, 13-CH_3), 5.51 (1H,

s, 12-H), 6.28 (1H, d, J=16 Hz, 8-H), 7.08 (1H, s, 10-H), 7.52 (1H, d, J=16 Hz, 7-H); MS m/z 286.157 (M^+, $C_{18}H_{22}O_3$ requires 286.157).

(7*E*),(11*E*)-XIIIa: NMR δ (200 MHz): 1.08 (6H, s, *gem*CH_3), 1.79 (3H, s, 5-CH_3), 2.33 (3H, s, 13-CH_3), 6.14 (1H, s, 12-H), 6.29 (1H, d, J=16 Hz, 8-H), 7.50 (1H, d, J=16 Hz, 7-H), 7.93 (1H, s, 10-H); MS m/z 286.159 (M^+, $C_{18}H_{22}O_3$ requires 286.157).

(7*E*),(10′*Z*)-XIVa: NMR δ (200 MHz): 1.08 (6H, s, *gem*CH_3), 1.79 (3H, s, 5-CH_3), 2.59 (3H, s, 12′-CH_3), 5.72 (1H, s, 11′-H), 6.15 (1H, d, J=16 Hz, 8-H), 6.32 (1H, s, 10-H), 7.07 (1H, d, J=16 Hz, 7-H); MS m/z 286.154 (M^+, $C_{18}H_{22}O_3$ requires 286.157).

Reaction of Xb with XI——The crude anhydride (Xb) was condensed with XI[14] (0.5 g) according to the procedure described for the preparation of XIIa, XIIIa, and XIVa to yield XIIb (28 mg (12.3%)), XIIIb (68 mg (30.0%)), and XIVb (25 mg (11.0%)), each as a yellow oil.

(7*E*),(11*Z*)-XIIb: NMR δ (200 MHz): 1.13 (6H, s, *gem*CH_3), 1.80 (3H, s, 5-CH_3), 2.56 (3H, s, 13-CH_3), 3.38 (3H, s, 3-OCH_3), 5.51 (1H, s, 12-H), 6.28 (1H, d, J=16 Hz, 8-H), 7.08 (1H, s, 10-H), 7.47 (1H, d, J=16 Hz, 7-H); MS m/z 316.168 (M^+, $C_{19}H_{24}O_4$ requires 316.168).

(7*E*),(11*E*)-XIIIb: NMR δ (200 MHz): 1.12 (6H, s, *gem*CH_3), 1.80 (3H, s, 5-CH_3), 2.33 (3H, s, 13-CH_3), 3.38 (3H, s, 3-OCH_3), 6.16 (1H, s, 12-H), 6.29 (1H, d, J=16 Hz, 8-H), 7.45 (1H, d, J=16 Hz, 7-H), 7.95 (1H, s, 10-H); MS m/z 316.168 (M^+, $C_{19}H_{24}O_4$ requires 316.168).

(7*E*),(10′*Z*)-XIVb: NMR δ (200 MHz): 1.12 (6H, s, *gem*CH_3), 1.81 (3H, s, 5-CH_3), 2.59 (3H, s, 12′-CH_3), 3.38 (3H, s, 3-OCH_3), 5.70 (1H, s, 11′-H), 6.16 (1H, d, J=16 Hz, 8-H), 6.33 (1H, s, 10-H), 7.01 (1H, d, J=16 Hz, 7-H); MS m/z 316.168 (M^+, $C_{19}H_{24}O_4$ requires 316.168).

Retinoidal Ylidenebutenolides [(XVIa) and (XVIIa)]——The phosphorane (XV,[19] 1.0 g) and the butenolide (XIIa, 0.15 g) in dry toluene (4 ml) were heated together at *ca.* 140 °C for 3 h in a sealed glass bottle under argon. The mixture was concentrated under reduced pressure and separated by preparative TLC (developing solvent: benzene) to give the retinoidal ylidenebutenolide as a yellow oil (XVIa, 45 mg (25.1%)) and XVIIa as yellow crystals (25 mg (14.0%)), mp 77—79 °C. By the same procedure, XVIa (30 mg (16.8%)) and XVIIa (17 mg (9.5%)) were obtained from the butenolide (XIIIa, 0.15 g).

(7*E*),(11*Z*),(13*E*)-Retinoidal Ylidenebutenolide (XVIa): NMR δ (200 MHz): 1.07 (6H, s, *gem*CH_3), 1.77 (3H, s, 5-CH_3), 2.55 (3H, s, 13-CH_3), 3.73 (3H, s, CO_2CH_3), 5.57 (1H, s, 14-H), 6.04 (1H, s, 12-H), 6.22 (1H, d, J=16 Hz, 8-H), 7.00 (1H, s, 10-H), 7.38 (1H, d, J=16 Hz, 7-H); MS m/z 342.184 (M^+, $C_{21}H_{26}O_4$ requires 342.183).

(7*E*),(11*Z*),(13*Z*)-Retinoidal Ylidenebutenolide (XVIIa): NMR δ (200 MHz): 1.07 (6H, s, *gem*CH_3), 1.77 (3H, s, 5-CH_3), 2.32 (3H, s, 13-CH_3), 3.72 (3H, s, CO_2CH_3), 5.77 (1H, s, 14-H), 6.23 (1H, d, J=16 Hz, 8-H), 7.09 (1H, s, 10-H), 7.32 (1H, s, 12-H), 7.37 (1H, d, J=16 Hz, 7-H); MS m/z 342.183 (M^+, $C_{21}H_{26}O_4$ requires 342.183).

3-Methoxy-retinoidal Ylidenebutenolides [(XVIb) and (XVIIb)]——The butenolide (XIIb, 0.15 g) was condensed with XV[19] (1.0 g) by the same method as described for the preparation of XVIa and XVIIa to yield XVIb (26 mg (14.7%)) and XVIIb (22 mg (12.4%)), each as a yellow oil. By the same procedure, XVIb (25 mg (14.2%)) and XVIIb (21 mg (11.9%)) were obtained from the butenolide (XIIIb, 0.15 g).

(7*E*),(11*Z*),(13*E*)-3-Methoxy-retinoidal Ylidenebutenolide (XVIb): NMR δ (200 MHz): 1.11 (6H, s, *gem*CH_3), 1.78 (3H, s, 5-CH_3), 2.55 (3H, s, 13-CH_3), 3.38 (3H, s, 3-OCH_3), 3.73 (3H, s, CO_2CH_3), 5.59 (1H, s, 14-H), 6.05 (1H, s, 12-H), 6.22 (1H, d, J=16 Hz, 8-H), 7.03 (1H, s, 10-H), 7.33 (1H, d, J=16 Hz, 7-H); MS m/z 372.192 (M^+, $C_{22}H_{28}O_5$ requires 372.194).

(7*E*),(11*Z*),(13*Z*)-3-Methoxy-retinoidal Ylidenebutenolide (XVIIb): NMR δ (200 MHz): 1.11 (6H, s, *gem*CH_3), 1.79 (3H, s, 5-CH_3), 2.33 (3H, s, 13-CH_3), 3.38 (3H, s, 3-OCH_3), 3.72 (3H, s, CO_2CH_3), 5.78 (1H, s, 14-H), 6.23 (1H, d, J=16 Hz, 8-H), 7.11 (1H, s, 10-H), 7.33 (1H, d, J=16 Hz, 7-H), 7.34 (1H, s, 12-H); MS m/z 372.193 (M^+, $C_{22}H_{28}O_5$ requires 372.194).

10′-Hydroxy-β-ionylideneacetic Acid Lactone (IXc)——A mixture of the acetoxy-ester (VIIc,[12] 2.0 g) and 15% aq. H_2SO_4 (3 ml) in methanol (20 ml) was refluxed for 1 h, cooled to room temperature, poured into ice-water, and extracted with ether. The organic layer was washed with 5% aq. $NaHCO_3$ and brine. Removal of the dried solvent under reduced pressure left an oil, which was purified by silica gel column chromatography (eluent: 15% ether in hexane) to give the lactone (IXc, 1.0 g (67%)) as a colorless oil. UV λ_{max}^{EtOH} nm: 250, 312; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775, 1735 (α,β-unsaturated γ-lactone); NMR δ (200 MHz): 1.06 (6H, s, *gem*CH_3), 1.72 (3H, s, 5-CH_3), 5.02 (2H, s, 10′-H), 5.87 (1H, s, 10-H), 6.38 (1H, d, J=17 Hz, 8-H), 6.57 (1H, d, J=17 Hz, 7-H); MS m/z 232.147 (M^+, $C_{15}H_{20}O_2$ requires 232.146).

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