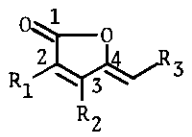
THE SYNTHESIS AND CHARACTERISATIONS OF RETINOIDAL 4-YLIDENEBUTENOLIDES

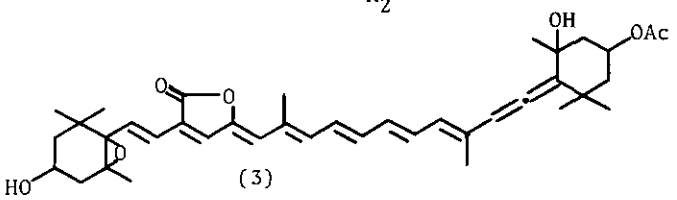
Masayoshi Ito,* Tsutomu Iwata, and Kiyoshi Tsukida
Kobe Women's College of Pharmacy, Motoyamakitamachi,
Higashinada, Kobe 658, Japan

Abstract —— *Retinoidal 4-ylidenebutenolides [(5) and (18)]* have been synthesised and their spectral characterisations have been described.

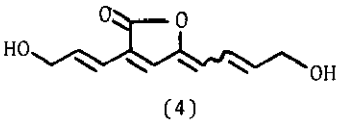
4-Ylidenebutenolides (1) occur widely in nature and many of them are known to possess a wide range of biological activities. The chemistry of natural 4-ylidenebutenolides has been well reviewed by Pattenden[1] and Yamamoto.[2] Although a number of methods for the synthesis of 4-ylidenebutenolides have been presented, there has been so far reported no synthetic pathway for natural 4-ylidenebutenolides (2) displaying extended conjugation at C-2 position such as peridinin (3)[3] and tetrenolin (4).[4] As an extension of the synthetic work[5] to develop the new antitumour retinoids, we have been interested in the preparation of the retinoidal 4-ylidenebutenolide (5).[6] In this communication, we describe the first synthesis of the retinoidal 4-ylidenebutenolides (5) and (18) and their spectral characterisations.



(1) R_1, R_2, R_3 : various kinds of substituents
(2) R_1, R_3 : conjugated polyene chains
R_2 : H



(3)



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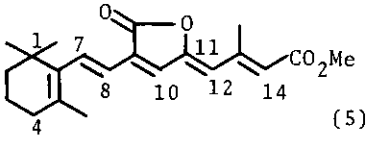
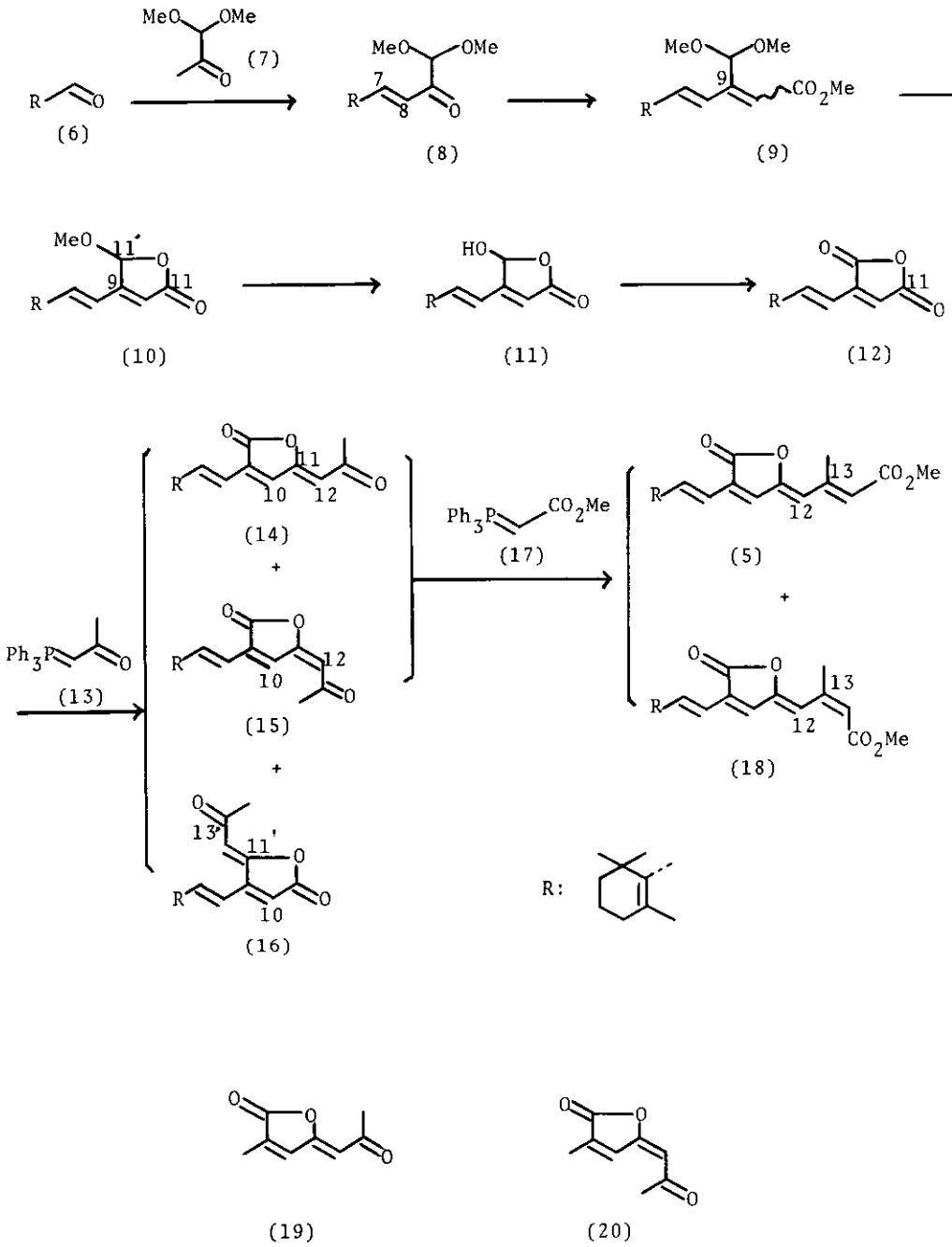


(5)

Fig. 1

The aldol condensation (piperidine/MeOH) between β-cyclocitral (6)[7] and pyruvic aldehyde dimethylacetal (7) gave the *trans* acetal-dienone (8) [δ[8] 7.59 (d,J=16,7-H), 6.46(d,J=16,8-H)] in 60% yield which was condensed with diethyl methoxycarbonylmethylphosphonate in the presence of n-butyl-lithium to afford a mixture (9) of the β-ionylidene ester derivatives [9-*cis* : 9-*trans*[9] = ca. 1 : 7 by HPLC] in 94% yield. The mixture was treated with 15% H_2SO_4 in MeOH to provide a methoxy-lactone (10) in 68% yield. The structure of this product was confirmed by its spectral data [λ 258, 319 nm; ν 1755, 1612 cm^{-1}; δ 6.90(d,J=16,7-H), 6.32 (d,J=16,8-H), 6.04(s,11'-H), 5.91(s,10-H), 3.50(s,OMe)]. Hydrolysis of the methoxy-lactone (10) with 30% H_2SO_4 in dioxan and subsequent PCC-oxidation of the resulting hydroxy-lactone (11) led to the unstable conjugated anhydride (12) [ν 1840, 1765 cm^{-1}] in ca. 60% yield which, without purification, was condensed with the phosphorane (13)[10] in dry benzene under argon to yield a mixture of the conjugated ylidenebutenolides (14)(10%), (15)(24.5%), and (16)(8.2%). The isomers (14), (15), and (16) were clearly separated by preparative TLC [SiO_2/benzene and n-hexane:ether(3:2)] and fully characterised by their spectral data (Table 1) respectively. The regioselectivity of this condensation reaction is in favour of carbanion attack at the less hindered carbonyl function (C-11) in the anhydride (10). The two isomers (14) and (15) were interconverted by heating or TLC treatment.[11] The lactonic carbonyl absorptions of the compounds (14) and (15) were shifted to the higher frequency by the effect of exocyclic double bond in the 4-ylidenebutenolide structure (2) compared with those [1740-1760 cm^{-1}] of the normal α,β-unsaturated γ-lactone ring. In the NMR data of the compounds (14) and (15), the proton signals at C-10 and C-12 were in good agreement with those at the corresponding positions in the model compounds (19) and (20).[12, 13] Therefore, extention of conjugation at the C-2 position in the 4-ylidenebutenolide ring (2) had little effect on the chemical shifts at C-10 and C-12 positions in the ylidenebutenolides (14) and (15). Stereochemistry around the newly formed Δ^{11}-double bond was determined as shown in the Fig. 2 from both the chemical shift difference of C-13-methyl signals and that of C-10-olefinic proton signals in the two isomers (14) and (15). The Wittig reaction of the keto-butenolide (14) with the phosphorane (17)[14] in a sealed bottle under argon produced a mixture of the retinoidal 4-ylidenebutenolides (5)(25.1%) and (18)(14.0%) which was separated by preparative TLC [SiO_2/benzene]. The same reaction of the isomeric keto-


MeO
OMe
(7)
R
O
(6)
7
8
(8)
9
CO2Me
(9)
11'
11
(10)
HO
(11)
(12)
10
12
(14)
+
(15)
+
13'
(16)
Ph3P
CO2Me
(17)
13
(5)
(18)
(13)
R:

(19) (20)

Fig. 2

Table 1 Spectral data of the keto-butenolides (14)-(16)

		(14)	(15)	(16)
UV	λ_{max}^{EtOH}	330 nm	335 nm	293 nm
IR	ν^{CHCl_3}	1790	1787	1785
		1665	1686	1665
		1620 cm^{-1}	1602 cm^{-1}	1643
				1610 cm^{-1}
NMR	$\delta_{ppm}^{CDCl_3}$			
	10-H	7.08 (s)	7.93 (s)	6.32 (s)
	12-H	5.51 (s)	6.14 (s)	-
	12'-H	-	-	5.72 (s)
	13-CH_3	2.56 (s)	2.33 (s)	-
	13'-CH_3	-	-	2.59 (s)

Table 2 Spectral data of the retinoidal 4-ylidenebutenolides (5) and (18)

		(5)	(18)
UV	λ_{max}^{EtOH}	356 nm	356 nm
IR	ν^{CHCl_3}	1770	1775
		1765	1760
		1712	1700
		1600 cm^{-1}	1598 cm^{-1}
NMR	$\delta_{ppm}^{CDCl_3}$		
	1-gemCH_3	1.07 (s)	1.07 (s)
	5-CH_3	1.77 (s)	1.77 (s)
	13-CH_3	2.55 (s)	2.32 (s)
	CO_2CH_3	3.73 (s)	3.72 (s)
	14-H	5.57 (s)	5.77 (s)
	12-H	6.04 (s)	7.32 (s)
	8-H	6.22 (d, J=16)	6.23 (d, J=16)
	10-H	7.00 (s)	7.09 (s)
	7-H	7.38 (d, J=16)	7.37 (d, J=16)

butenolide (15) also led to a mixture of (5)(16.8%) and (18)(9.5%). Characteristic spectral data of the retinoidal 4-ylidenebutenolides (5) and (18) are summarised in Table 2. Stereochemistry of the Δ^{13}-double bond was determined from the follow-

ing NMR data. The methyl signal at C-13 in the 13-*trans* isomer (5) is extremely deshielded by the effect of both enolic oxygen in the butenolide ring and the carbonyl group of ester. The proton signal at C-12 in the 13-*cis* isomer (18) is also deshielded by the anisotropic effect of the carbonyl group of ester. The biological activities of the retinoidal 4-ylidenebutenolides prepared here are now under investigation. The present synthetic route could be expected to extend to the studies towards the synthesis of the 4-ylidenebutenolide (2).

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