

A NEW SYNTHESIS OF Δ^2 -BUTENOLIDES VIA STEREOSELECTIVE FORMATION
 OF α, β -ETHYLENIC ESTERS.

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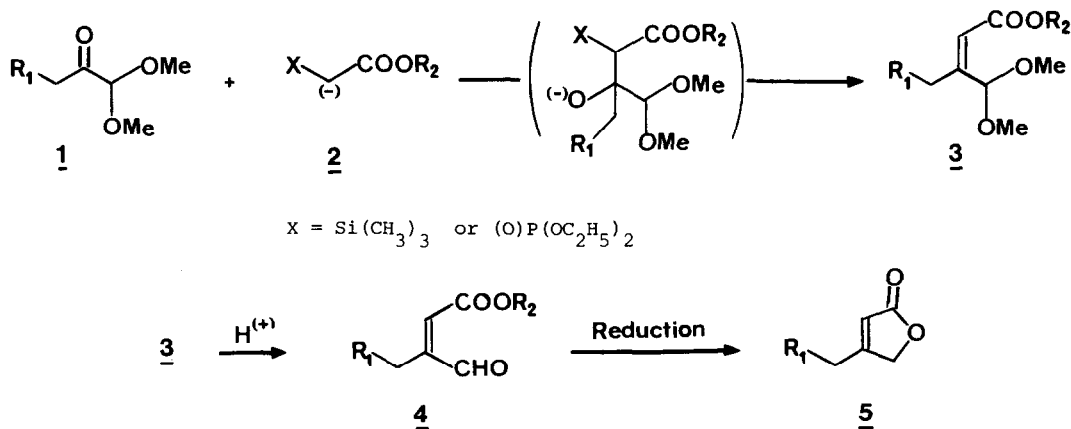
Abstract : A new synthesis of Δ^2 -butenolides is described which involves stereoselec-
 tive condensation of an α -silyl ester anion with an α -ketoacetal.

Unsaturated five membered ring lactones, butenolides, occur widely in nature and display a wide range of interesting properties (1). Despite the great variety of synthetic methods, there is not a general route to these compounds and difficulties are frequently encountered to prepare specific compounds (2).

In connection with other work, we needed an efficient route to terpenoid butenolides of structure I.



We wish to report here a new versatile preparation of these compounds based on the stereoselective formation of functional ethylenic esters according the following scheme :



Ketoacetal **1** is condensed with the lithium anion of an α -silylated or phosphorylated ester **2** to afford the ethylenic ester **3**.

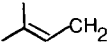
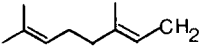
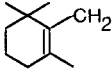
This one, after hydrolysis, gives **4** which is then reduced by sodium borohydride to butenolide **5**. The main interesting feature of this synthetic scheme lies on the introduction of R_1 as an unsaturated terpenoid C_5 or C_{10} subunit (for instance by using dimethylallyl chloride or geranyl bromide); however to be efficient, this method requires the formation of the Z ester which is the only one to lead to lactonization.

Ketoacetals **1** are readily synthesized by condensation of a halogenated compound with the anion derived from N,N-dimethyl hydrazone of pyruvaldehyde dimethylacetal followed by an acid hydrolysis (3). Initial attempts to condensate **1** with a phosphonoacetate lithium enolate **2** ($R_2 = C_2H_5$) were disappointing. Ethylenic esters were isolated in good yields, but the Z/E ratio was 45/55 only. These results are consistent with previous works which report the formation of isomeric mixtures during the condensation of phosphonate anions with ketones (4). Further modification of solvent or counter-ion have not changed this ratio significantly. Thus we have changed to α -silylated esters which are known to afford ethylenic esters by the Peterson olefination reaction (5). The condensation of methyl ester anion with **1** gives about the same ratio, but the use of hindered esters ($R_2 =$ isopropyl or tertibutyl) allows esters **3** to be obtained with good stereoselectivity and it is even possible in some cases to isolate nearly pure Z compounds.

The acetal function had to be hydrolyzed and reduced. Treatment of **3** with aqueous acid gives only complex mixtures probably due to the presence of other unsaturations in the molecule.

We succeeded in hydrolyzing by using wet silica gel (6). Thus, the aldehyde-esters **4** are isolated in nearly quantitative yields. Reduction of the aldehyde with a slight excess of sodium borohydride in methanol affords butenolide **5** directly.

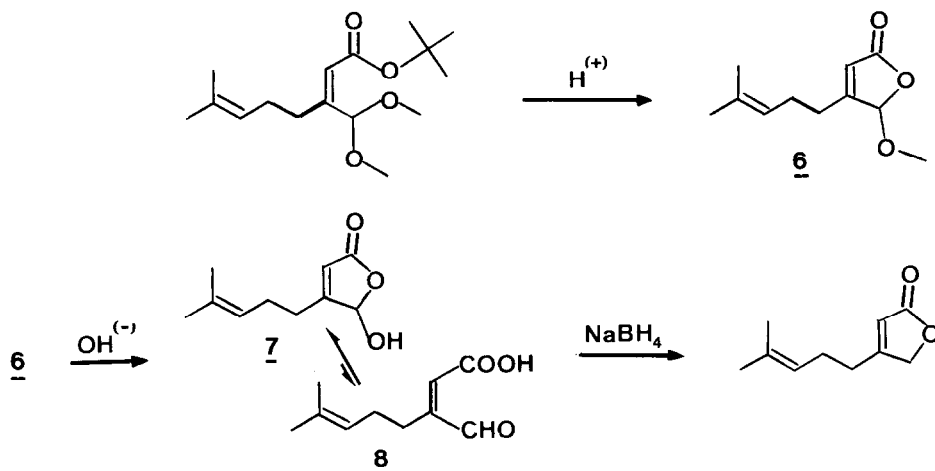
Synthesis of Δ^2 -butenolides from silylated esters.

Ketoacetal <u>1</u> (7)	Ethylene ester <u>3</u> (8)		Butenolide <u>5</u> (9)
R ₁	R ₂	Yield % Z/E ratio	Yield % ^a
H	CH ₃	55 56/44	b
H	(CH ₃) ₃ C	63 89/11	b
nC ₄ H ₉	(CH ₃) ₃ C	79 84/16	85
	CH ₃	70 43/57	83
	(CH ₃) ₂ CH	73 80/20	b
	(CH ₃) ₃ C	77 88/12	81
	(CH ₃) ₂ CH	76 70/30	b
	(CH ₃) ₃ C	81 98/2	87
	(CH ₃) ₃ C	71 90/10	80

a : yield from 3

b : lactonization was not investigated

It will be noticed that the reaction follows a slightly different path with tertio-butyl esters.



These products are much more sensitive to acidic medium and the reaction with acidic silica gel gives methoxy lactone **6** which in turn may be cleaved to hydroxy lactone **7**. Such structures are found in some natural products; they are in equilibrium with the corresponding acid-aldehydes **8** as shown by NMR spectra and may be reduced in butenolide as previously described.

Thus this method allows the preparation of difficultly accessible Δ^2 -butenolides in high yield. We are currently investigating the mechanism of α -silyl ester condensation in order to explain the stereoselectivity observed during this work.

Experimental: The anion of α -trimethylsilyl tertibutylacetate (10) (LDA-THF, 1/2 h - 78°C) is condensed with ketoacetal **1** (-78°C then 3 hours at room temp.). Hydrolysis (saturated NH_4Cl solution) gives the crude Z ethylenic ester **3** which is stirred for two hours with acidic silica gel. (for 0.01 mole; H_2SO_4 15% : 7 g, SiO_2 : 25 g) in methylene chloride. After filtration, the crude product is stirred for one hour with NaOH 1N and acidified. The reduction (1.5 equiv. of NaBH_4 in methanol) gives after chromatography (SiO_2 : CH_2Cl_2) the pure butenolide.

References and notes

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- (6) F. Huet, A. Lechevallier, M. Pellet and J.M. Conia, *Synthesis*, 63 (1978).
- (7) Yields from N,N-dimethylhydrazone of pyruvaldehyde dimethylacetal: dimethylallyl chloride: 82%; geranyl bromide: 77%; cyclogeranyl bromide: 86%.
- (8) P.M.R. in CDCl_3 (δ ppm): 1.46 ($(\text{CH}_3)_3\text{C}$, s, 9H), 1.66 and 1.74 ($(\text{CH}_3)_2\text{C}=\text{C}$, 2s, 6H) 3.36 (CH_3O , s, 6H); 4.67 (E) and 5.60 (Z) ($\text{CH}-(\text{OCH}_3)_2$, s, 1H), 5.05 ($(\text{CH}_3)_2\text{C}=\text{CH}-$, m, 1 or 2H), 5.80 (E) and 5.85 (Z) ($=\text{CH}-\text{CO}_2$, s, 1H).
- (9) PMR in CDCl_3 (δ ppm): 1.66 and 1.74 ($(\text{CH}_3)_2\text{C}=\text{C}$, 2s, 6H), 2.45 ($\text{CH}_2-\text{C}=\text{C}$, t, J=8.8 Hz, 2H), 4.80 ($\text{C}=\text{C}-\text{CH}_2\text{O}$, s, 2H), 5.15 ($\text{C}=\text{CH}-$, m, 1 or 2H), 5.92 ($=\text{CH}-\text{COOR}$, m, 1H).
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