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A Facile Synthesis of γ-Alkylidene-α,β-unsaturated γ-Lactones

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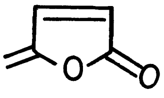
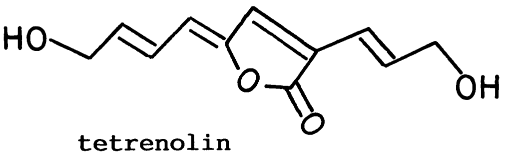
Treatment of β-allenic acid with KI_3 gave directly γ-alkylidene-α,β-unsaturated γ-lactones in moderate yields.

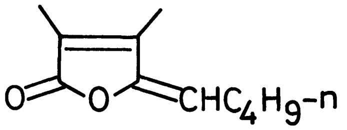
The γ-lactone ring system is a common feature in a wide variety of natural products, and a number of methods are available for its construction.[1)] It has been reported that many γ-alkylidene γ-lactones as well as α-methylene lactones exist in natural products.[2)] For example, protoanemonin,[3)] tetrenolin,[4)] and bovolide[5)] are well-known. Recently, the synthesis of these lactones has attracted the attention of organic chemists because of their biological activities and versatile use in organic synthesis.[2,6)]



protoanemonin



tetrenolin

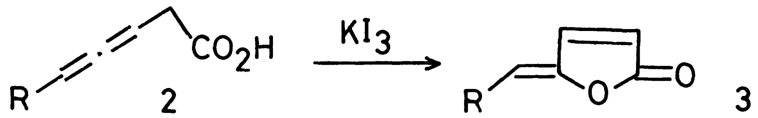


bovolide

In connection with our continuous interest in the chemistry of β-allenic esters **1**,[7)] we carried out the iodolactonization[8)] of β-allenic acid **2**. The reaction gave directly γ-alkylidene-α,β-unsaturated γ-lactones **3** in moderate yields. β-Allenic esters can be easily prepared by the reaction of sec-propargylic alcohols with orthoacetic esters.[7a)] Under mild conditions (0.2 M NaOH, r. t., 1 d), hydrolysis of **1** afforded the carboxylic acid **2** in good yield without isomerization of the allenic bond. Various γ-alkylidene-α,β-unsaturated γ-lactones **3** were prepared by the reaction of **2** with KI_3 in acetonitrile-0.5 M $NaHCO_3$ solution, and the results were summarized in Table 1. The geometry of the major product was assigned as Z-configuration by comparison of the spectral data with those of authentic samples.[9)] The synthesis of biologically active and naturally occurring protoanemonin[3)] (**3a**) was achieved by the present method in good yields.

The following synthesis of **3f** is shown as a representative example. To a mixture of 3,4-tetradecadienoic acid (**2f**) (1.15 g, 5.13 mmol), 0.5 M $NaHCO_3$, and acetonitrile (51 ml) was added a solution of KI (2.56 g, 15.4 mmol) and I_2 (3.91 g, 15.4 mmol) in water (29 ml) at 0 °C in the dark. The mixture was stirred for 1.5 day at 40 °C and then poured into water. The organic material was extracted with ethyl acetate and the combined extracts were washed with dilute $Na_2S_2O_3$ and water, and dried over $MgSO_4$. Removal of the solvent gave 1.30 g of an oil which was chromatographed on SiO_2 (hexane/ethyl acetate, 30/1) to give 826 mg (72.5%) of **3f**: TLC (SiO_2; hexane/ethyl acetate, 4/1), R_f 0.38; IR (neat) 2940, 1775, 1672, 1555,

Table 1. Synthesis of γ-Alkylidene-α,β-unsaturated γ-Lactones 3



No	R	Reaction conditions		Yield$^{a)}$/%	Z/E$^{b)}$
		Time/d	Temperature/°C		
3a$^{c)}$	H	3	25	57	
3b$^{d)}$	CH_3	2	12	42	8/1
3c$^{e)}$	C_3H_7	1.7	25	48	5/1
3d$^{e)}$	C_4H_9	4	25	51	6/1
3e	C_8H_{17}	1.7	40	59	6/1
3f	C_9H_{19}	1.5	40	73	5/1

a) Isolated yield by column chromatography. b) Determined by ^1H NMR analysis with reference to the literature (Ref. 9). c) Known compound (Ref. 3). d) Known compound; E. J. Corey and G. Schmidt, Tetrahedron Lett., 21, 731 (1980). e) Known compound (Ref. 9).

and 1465 cm^{-1}; ^1H NMR (CCl_4) δ= 0.89 (3H, t, J = 5 Hz, $(CH_2)_8C\underline{H}_3$), 1.08-1.60 (14H, m, $7CH_2$), 2.16-2.61 (2H, m, $C\underline{H}_2CH=$), 5.14 (1H, t, J = 8 Hz, $CH_2C\underline{H}=$), 6.05 (1H, J = 5 Hz, 1H, $CH=C\underline{H}CO_2$), and 7.24 (1H, d, J = 6 Hz, $C\underline{H}=CHCO_2$).

The present method provides a convenient route to γ-alkylidene-α,β-unsaturated γ-lactones because of ready availability of the starting materials and simplicity of the experimental procedure.

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