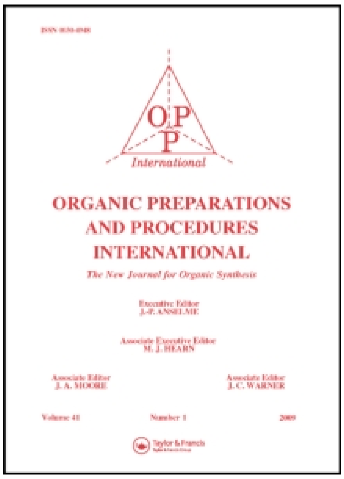

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SYNTHESIS OF SOME SPIRO α-METHYLENE-γ-LACTONES

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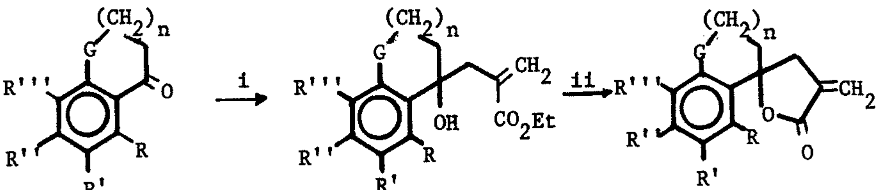
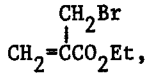
A number of natural terpenoid lactones having the α-methylene-γ-butyrolactone moiety have important biological properties including antitumor activity.[1] In connection with a search for antitumor agents, we had occasion to prepare several spiro α-methylene-γ-butyrolactones. Lactonization of the hydroxy esters resulting from the Reformatsky reaction of ethyl α-(bromomethyl) acrylate with carbonyl compounds[2] had previously been carried out by boiling in hydrochloric acid for 4 hrs., often in quite modest yields. We now report that the lactonization may





i= $CH_2{=}\overset{CH_2Br}{\overset{|}{C}}CO_2Et$, Zn, THF ii= 5% H_2SO_4, 0-5°

Cmpd	G	n	R	R'	R''	R'''
1	CH_2	0	H	H	OCH_3	H
2	CH_2	0	H	OCH_3	OCH_3	H
3	CH_2	1	H	OCH_3	OCH_3	H
4	CH_2	1	OCH_3	OCH_3	OCH_3	H
5	CH_2	1	H	OCH_3	OCH_3	OCH_3
6	CH_2	1	H	CH_3	CH_3	H
7	CH_2	2	H	H	OCH_3	H
8	O	1	H	H	H	H
9	O	1	H	Cl	H	H
10	SO_2	1	H	H	H	H

be promoted in 5-10 minutes by an ice-cold solution of 5% sulphuric acid from which the lactones crystallized in good yields (65-93%) and in 95% or greater purity. Ten new spiro lactones have been prepared from varying types of ketones by this technique (see table).

EXPERIMENTAL

Starting materials 6-methoxy-1-indanone, 5,6-dimethoxy-1-idanone, 2-methoxybenzosuberone, 4-chromanone and 6-chloro-4-chromanone were obtained commercially (Aldrich). 6,7-Dimethyl-3,4-dihydro-1-(2H)-naphthalenone was purchased from Chemical Samples Co. 3,4-Dihydro-5,6,7-trimethoxy-1(2H)-naphthalenone,[3] 3,4-dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone,[3] 6,7-dimethoxy-3,4-dihydro-1-(2H)-naphthalenone[4] and thiachroman-4-one-1,1-dioxide[5] were prepared by published procedures.

General Procedure for the Preparation of the Spiro α-Methylene-γ-lactones. Activated[6] zinc metal (20 mesh; 0.8 g, 0.012 g atom, Baker Analyzed), 3,4-dihydro-6,7,8-trimethoxy-1(2H)-naphthalenone (2.36 g, 0.01 mol) and dry (distilled from LAH) THF (15 ml) were placed in a dry three-necked, round-bottomed flask equipped with a magnetic stirrer, thermometer, nitrogen inlet and an additional funnel. A solution of ethyl α-(bromomethyl)-acrylate[7] (2.1 g, 0.011 mol) in dry THF (25 ml) was added dropwise during the course of 30 minutes, and the temperature of the reaction mixture was maintained at 40-45°. The reaction mixture turned black and a slightly exothermic reaction occurred. After being stirred at 40-45° for an additional 3 hr, the mixture was cooled and poured into ice-cold sulfuric acid, 5% (200 ml). The resulting mixture was stirred until crystallization occurred (5 to 10 min), and the product was filtered and washed several times with water, mp. 115-119°. An analytical sample was obtained upon recrystallization from methanol to yield colorless needles (2.12 g; 69%) of 4, mp. 122-123°. See table for additional data on the other compounds.

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Table I. Physical and Spectral Data of Spiro α-Methylene-γ-lactones

Cmpd	Yield (%)	MP °C	$C=CH_2$	PMR[a] Allylic CH_2	Analyses Calcd (Found) C	H	IR[b] $\nu_{C=O}$ $\nu_{C=CH_2}$
1	72	96-97[d]	5.69(t,1H) 6.29(t,1H)	3.14 (q,2H)[c]	73.02 (72.81)	6.13 (6.24)	1754 1664
2	71	115-116[d]	5.70(t,1H) 6.35(t,1H)	3.14 (q,2H)[c]	69.21 (68.97)	6.19 (6.10)	1742 1650
3	72	117-118[d]	5.68(t,1H) 6.38(t,1H)	3.04-3.12 (m,2H)	70.05 (70.07)	6.61 (6.71)	1754 1661
4	69	122-123[d]	5.56(t,1H) 6.25(t,1H)	3.08 (q,2H)[c]	67.08 (66.98)	6.62 (6.65)	1770 1667
5	67	87-88[d]	5.67(t,1H) 6.32(t,1H)	3.08 (t,2H)	67.08 (66.70)	6.62 (6.47)	1773 1639
6	76	73-74[d]	5.64(t,1H) 6.30(t,1H)	3.10 (q,2H)[c]	79.30 (79.18)	7.49 (7.41)	1770 1658
7	73	94-95[d]	5.57(t,1H) 6.29(t,1H)	3.14 (q,2H)[c]	74.39 (74.28)	7.02 (6.99)	1761 1664
8	65	82-83[e]	5.72(t,1H) 6.35(t,1H)	3.16 (q,2H)[c]	72.20 (71.96)	5.59 (5.70)	1770 1667
9	93	104-105[d]	5.77(t,1H) 6.37(t,1H)	3.15 (q,2H)[c]	62.28 (62.17)	4.42 (4.58)	1760 1658
10	62	156-157[f]	5.88(t,1H) 6.22(t,1H)	2.82 (t,2H)	59.09 (59.03)	4.57 (4.47)	1770 1653

a. PMR recorded in $CDCl_3$ on Varian XL-100(15) spectrometer, expressed in δ values relative to TMS. b. Recorded on a Beckman IR-5A Infrared spectrometer as KBr pellets and expressed in cm^{-1}. c. Complex quartet. The remaining spectral features were entirely consistent with the structures and full spectra can be obtained upon request. d. Crystallized from methanol. e. Crystallized from ethanol. f. Crystallized from 2-propanol.

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