A New Synthesis of α-Carboxy-γ-lactones and α-Methylene-γ-lactones

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α-Methylene-γ-butyrolactones have attracted attention in recent years. The tumor inhibitory activity of complex sesquiterpenes has been attributed to the α-methylenelactone group[1,2] and has led to the development of a variety of new methods for synthesizing this functionality[3,4]. The natural products containing this moiety are, however, too toxic to be considered for clinical use. Therefore, interest has shifted to the synthesis of simpler derivatives[5–8] in the hope that some of these might exhibit a more favorable therapeutic index. Activity in this field prompts us to report our investigations of a new and convenient route to simple α-methylene-γ-lactones.

α-Methylenelactones are easily prepared from the corresponding α-carboxylactones[9,10]. Previous work in our laboratory[11] suggested that such carboxylactones should be readily available from ylidenes of malonic acid derivatives. The publication of an improved procedure for the Knoevangel condensation of ketones with malonic esters[12] made it practical to investigate the lactonization of ylidenemalonates. This led to the development of a three-step process for the anellation of an α-methylene-γ-lactone to carbonyl compounds. The sequence of reactions is outlined in Scheme **A**.

In the first step of this synthesis a cycloalkanone **1** was condensed with the cyclic isopropylidene ester of malonic acid (Meldrum's acid; **2**)[13,14] using the procedure of Lehnert[12]. Our choice of the derivative **2** for these condensations was based on the expectation that the cyclic ester would hydrolyze readily and directly to the carboxylic acid in the second step of the sequence. In this second step the Knoevenagel product **3** was stirred with concentrated sulfuric acid at room temperature for 2 h. Lactonization and hydrolysis took place to give the α-carboxylactone **5**. Those carboxylactones which could not be purified as solids were converted to their methyl esters **7** for characterization. However, it was most convenient to use the crude carboxylactone for conversion to the α-methylene compound **6** by the procedure of Grieco and Hiroi[10].

We have investigated the scope of this reaction on a series of five, six, and seven-membered cycloalkanones **1** with and without α-alkyl substitution in the ring. The results of these experiments are presented in Table 1. N.M.R. data for the γ-lactones are summarized in Table 2.

The lactonization-hydrolysis of these ylidenemalonates in sulfuric acid probably proceeds via a carbenium ion interme-

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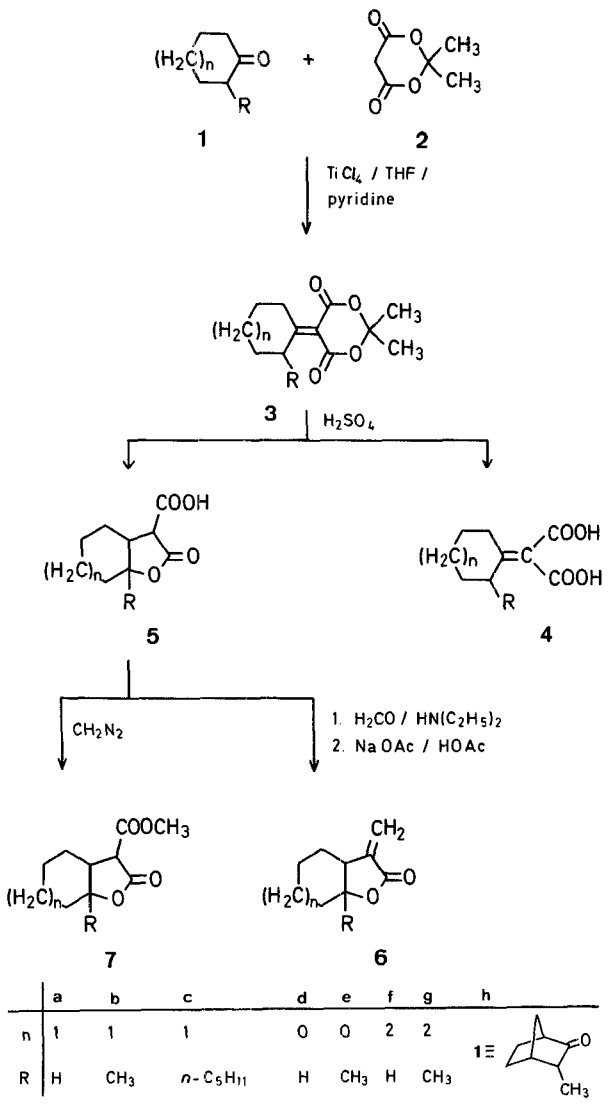

Scheme A

diate similar to the one proposed for the reaction of ylidenemalonodinitriles[11]. That the stability of this intermediate plays an important role in the lactonization step is indicated by the relatively greater yields of lactones from α-alkyl ylidenemalonates. Ring size of the carbocycle can also influence the outcome of this reaction. It is apparent from the data in Table 1 that the secondary carbenium ion intermediate from **3d** does not promote lactone ring closure to give a 5,5-ring system. Upon workup the only material isolated was the product of hydrolysis, diacid **4d**. Neither does the secondary carbenium ion intermediate from **3f** promote clean lactonization to the 7,5-ring system of **5f** but instead gives a mixture containing **5f** (51 %), **4f** (38 %), and a third unidentified component. This mixture was not separated but was subjected directly to the methylenation conditions. The acidic contaminants were washed away during workup of this reaction.

The steric constraints of a 5,5-ring system dictate that the lactone ring fusion in **5e** and **6e** be *cis*. However, both *cis*- and *trans*-fused 6,5- and 7,5-ring systems are possible. This raises the question of the nature of the ring fusion in compounds **5a–c, f–h** and **6a–c, f–h**. The most characteristic spectral feature of the lactones **6** is the N.M.R. signals for the α-methylene protons. Each proton is seen as a doublet, one at 6.25 ppm and one near 5.4–5.7 ppm (Table 2). However, in our N.M.R. spectra for compounds **6f** and **6g** each of these proton signals consisted of two doublets of unequal intensity, suggesting that we had a mixture of *cis*- and *trans*-fused isomers in our 7,5-systems. The *cis*- and *trans*-fused isomers of **6f** have been independently synthesized[15] and Table 3 compares the published N.M.R. data for these compounds with the N.M.R. data for compounds **6f** and **6g** synthesized by our method. From this information it appeared that the more upfield doublet in each pair was attributable to the *trans*-fused lactone. In that case our cyclization reaction showed a preference for formation of the *cis*-fused isomer and this preference was enhanced by alkyl substitution at the α-carbon. We have confirmed this assignment of the upfield doublets to the *trans*-isomers by the synthesis of *trans*-**6f** by the method of Marshall and Cohen[15]. When a sample of this lactone was added to our mixture of isomers, the N.M.R. spectrum showed a relative increase in the size of the upfield doublet in each pair.

Our N.M.R. spectra of compounds **6a–c, h** showed two clean doublets in the α-methylene proton region. Therefore these products must consist of a single isomer (< 95 % purity). A steric argument would suggest that in the lactonization step, ring closure to an sp^2 carbon in the intermediate ought to proceed more readily to the same side of the cyclohexane ring. This would give *cis*-fused lactone products. This argument is confirmed for **6a** by comparison of published N.M.R. data for the independently synthesized *cis*- and *trans*-fused isomers of **6a**[15] with the N.M.R. data of our product (Table 4). The appearance of the signal for the proton on C-2 as a quartet at 4.46 ppm is only consistent with the *cis*-fused structure. By analogy, the compounds **6b, c,** and **h** are also assumed to be *cis*-fused lactones.

Since the conditions of the methylenation reaction would not be expected to alter the stereochemistry of the lactone ring fusion, the compounds **5** must also be cis-fused lactones. Inspection of Table 2 shows that the crude acids **5** were usually isolated as mixtures of *cis*- and *trans*-isomers across the C-1—C-α bond. Upon recrystallization or esterification and distillation only one of these isomers was obtained.

Consideration of the results in Table 1 indicates that this synthetic route may be quite useful for the annelation of an α-methylene-γ-lactone to cyclohexanones. α-Alkylcyclopentanones are also good substrates for these reactions although unsubstituted cyclopentanones are not. The lack of stereospecific ring fusion to cycloheptanones will limit the usefulness of this synthesis to those cases in which a mixture of ring fusions can be tolerated.

Isopropylidene Ylidenemalonates (3); General Procedure:
A solution to titanium(IV) chloride (22 ml, 0.20 mol) in carbon tetrachloride (50 ml) is added dropwise under nitrogen to dry tetrahydrofuran (300 ml) with stirring and cooling in a Dry Ice/alcohol bath. This gives a bright yellow precipitate after an exothermic reaction. The dropping rate is adjusted so the internal temperature remains below 0° throughout the addition; then the Dry Ice bath is replaced by an ice/salt water bath. A solution of cycloalkanone **1** (0.10 mol) and Meldrum's acid (14.4 g, 0.10 mol) in tetrahydrofuran (50 ml) is added to the titanium(IV) chloride/tetrahydrofuran mixture. Pyridine (32 ml, 0.40 mol) in tetrahydrofuran (70 ml) is added dropwise over 1 h. The reaction mixture is stirred overnight, then quenched with water (100 ml) and ether (100 ml). The layers are separated. The aqueous layer is extracted once with ether and the combined organic fractions are washed

Table 1. α-Methylenelactones **6** via Isopropylidene Ylidenemalonates **3**

	Product **3**			Product **5**			Product **6**		
	Yield [%]	m.p. (solvent)	Molecular formula[a] or Lit. m.p.	Yield [%][b]	m.p. (solvent)	Molecular formula[a]	Yield [%]	b.p./torr or m.p. (solvent)	Molecular formula[a] or Lit. b.p.
a	38	86–88° (CH_3OH)	87–87.5°[16]	44	109° (dec.) (benzene)	$C_9H_{12}O_4$ (184.2)	39	b.p. 40°/ 0.2 torr[c]	60°/0.06 torr[15]
b	35	105–106° (CH_3OH)	$C_{13}H_{18}O_4$ (238.3)	88	101–104° (dec.) (water)	$C_{10}H_{14}O_4$ (198.2)	50	62.5–64.5° (c-C_6H_{12})	$C_{10}H_{14}O_2$ (166.2)
c	52	59–61° (CH_3OH)	$C_{17}H_{26}O_4$ (294.4)	100	—	—	66	b.p. 110–112°/ 0.3 torr	$C_{14}H_{22}O_2$ (222.3)
d	43	77–78.5° (CH_3OH)	78–79°[17]	—[d]	—		—	—	—
e	44	61–63° (C_2H_5OH)	$C_{12}H_{16}O_4$ (224.3)	80	123° (dec.) (C_2H_5OAc)	$C_9H_{12}O_4$ (184.2)	14	b.p. 32°/ 0.25 torr[c]	
f	69	56–58° (CH_3OH)	55°[18]	[e]	—	—	63	b.p. 74–76°/ 0.10 torr	b.p. 60°/ 0.06 torr[c, 15]
g	59	80–82° (CH_3OH)	$C_{14}H_{20}O_4$ (252.3)	100	—	—	84	b.p. 73°/ 0.25 torr	$C_{11}H_{16}O_2$ (180.2)
h	56	122–123° (C_2H_5OH)	$C_{14}H_{18}O_4$ (250.3)	100	137–139° (dec.) (C_2H_5OAc)	$C_{11}H_{14}O_4$ (210.2)	65	b.p. 78–81°/ 0.3 torr	$C_{11}H_{14}O_2$ (188.3)

[a] All new compounds gave satisfactory microanalyses (C ±0.3%, H ±0.3%), I.R., and ^{1}H-N.M.R. spectra.
[b] Crude products.
[c] Bath temperature.
[d] Only product is **4d**; m.p. 167° (dec.); Lit.[19] m.p. 169° (dec.).
[e] Product is a mixture of **5f** and **4f**; m.p. (**4f**): 135–138° (dec.).

Table 2. ^{1}H-N.M.R. Data for γ-Lactones **5**, **6**, and **7**

Product	Chemical shift δ [ppm], TMS as standard, $CDCl_3$ or $CDCl_3$/DMSO-d_6 solution				
	α-C—H	1-C—H	2-C—H or	2-C—CH_3	α-C=CH_2
5a	3.49 (d, J = 6 Hz, 65%); 3.85 (d, J = 6 Hz)	2.91 (broad)	4.79	—	—
7a	3.35 (d, J = 6, 5.5 Hz)	2.81 (m)	4.72 (q, J = 5.5 Hz)	—	—
6a		3.12 (m)	4.60 (q, J = 6 Hz)	—	5.59 (d), 6.24 (d, J = 3 Hz)
5b	3.62 (d, J = 14 Hz, 26%); 3.71 (d, J = 13 Hz)	2.74 (d, J = 13 Hz)		1.54	—
7b	3.68 (d, J = 13 Hz)	2.81 d of t, J = 13 Hz, J = 3 Hz)	—	1.54	—
6b		2.76 (broad)	—	1.46	5.42 (d), 6.18 (d, J = 3 Hz)
5c	3.65 (d, J = 14 Hz, 29%); 3.74 (d, J = 13 Hz)	2.82 (d, J = 13 Hz)	—	—	—
7c	3.68 (d, J = 13 Hz)	2.83 (d, J = 13 Hz)	—	—	—
6c		2.84 (broad)	—	—	5.47 (d), 6.23 (d, J = 3 Hz)
5e	3.36 (d, J = 3.5 Hz, 33%); 3.92 (d, J = 9.5 Hz)	2.80 (broad)	—	1.61 (38%); 1.53	—
7e	3.40 (d, J = 4 Hz)	2.83 (broad)	—	1.57	—
6e		3.02 (broad)	—	1.49	5.61 (d), 6.24 (d, J = 2.5 Hz)
6f		3.1 (broad)	4.73 (m)	—	see Table 3
5g	3.53 (d, J = 8 Hz, 34%); 3.58 (d, J = 8 Hz)	2.83 (broad)	—	1.53	—
7g	3.52 (d, J = 8 Hz)	2.84 (m)	—	1.51	—
6g		2.84 (broad)	—	1.43	see Table 3
5h	3.26 (d, J = 3 Hz)	2.03–2.77[a]	—	1.13–1.90[b]	—
6h		2.03–2.57[a]	—	1.44	5.68 (d), 6.26 (d, J = 2.5 Hz)

[a] This broad signal integrates for three protons—1-C and bridgehead.
[b] This broad signal integrates for nine protons—methyl and six methylene.

well with 5% sodium hydrogen carbonate and sodium chloride and dried with magnesium sulfate. Concentration gives a crude solid or an oil. In some cases crystallization of this material is effected by pouring an acetone solution into water. Recrystallization from alcohol gives **3a–h** in yields as indicated (Table 1).

2-Hydroxycycloalkylmalonic Acid Lactones (5): General Procedure:

Ylidenemalonate **3** is stirred for 2 h at room temperature with ten times its weight of concentrated sulfuric acid. The reaction mixture is poured over ice, stirred for 10 min, then saturated

Table 3. ^{1}H-N.M.R. Chemical Shifts of α-Methylene Protons of **6f** and **6g**

Compound	Solvent	δ [ppm]	Proportion of total methylene protons [%]
6f, *cis*[15]	CCl_4	6.27 (d, J = 3 Hz)	—
		5.56 (d, J = 3 Hz)	
6f, *trans*[15]	CCl_4	6.18 (d, J = 3 Hz)	—
		5.45 (d, J = 3 Hz)	
6f (this work)	$CDCl_3$	6.37 (d, J = 3 Hz)	65–69
		5.66 (d, J = 3 Hz)	
		6.27 (d, J = 3.5 Hz)	31–35
		5.57 (d, J = 3.5 Hz)	
6g (this work)	$CDCl_3$	6.30 (d, J = 2.5 Hz)	78–81
		5.55 (d, J = 2.5 Hz)	
		6.15 (d, J = 3.5 Hz)	19–22
		5.41 (d, J = 3.5 Hz)	

Table 4. Selected ^{1}H-N.M.R. Chemical Shifts for Isomers of **6a**

Compound	Solvent	δ (2-C—H) [ppm]	δ (α-methylene-H) [ppm]
6a, *cis*[15]	CCl_4	4.46 (q, J = 6 Hz)	6.05 (d, J = 2.5 Hz)
			5.44 (d, J = 2.5 Hz)
6a, *trans*[15]	CCl_4	3.9–3.4 (broad)	5.91 (d, J = 3 Hz)
			5.34 (d, J = 3 Hz)
6a (this work)	$CDCl_3$	4.60 (q, J = 6 Hz)	6.24 (d, J = 3 Hz)
			5.59 (d, J = 3 Hz)

with sodium chloride, extracted into ether, dried, and concentrated. This crude material is used directly for conversion to the α-methylene lactone. However, each of these products is purified for characterization by column chromatography (silica gel, 60–200 mesh; acetone/petroleum ether), recrystallization, or conversion to the methyl ester with diazomethane followed by distillation.

2-(2-Hydroxycycloalkyl)-propenoic Acid Lactones (6); General Procedure[10]:

Crude carboxylactone **5** (5.0 mmol) is refluxed for 30 min with diethylamine (1.82 g, 25.0 mmol) and 37% formaldehyde (5.0 ml). Then sodium acetate (500 mg) and glacial acetic acid (5.0 ml) are added and refluxing is continued for 15 min. The mixture is poured over ice, extracted into ether, washed with water, 5% sodium hydrogen carbonate and sodium chloride, dried, and concentrated. Purification by recrystallization or distillation gives α-methylene-γ-lactones **6** in the indicated yields (Table 1). A number of these liquid products become very thick and glassy upon standing for several months. This is believed to be the result of a polymerization reaction.

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