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δ-LACTONES FROM GRIGNARD REACTIONS

THEIR ISOLATION AND STRUCTURE CHARACTERIZATION

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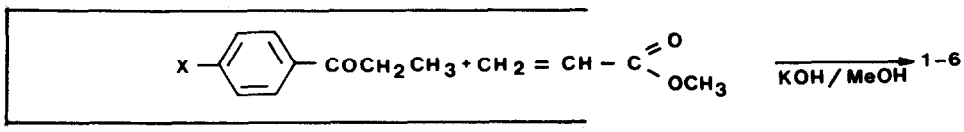
Abstract—Grignard reactions on methyl 4-methyl, 5-oxo, 5-phenyl (pX substituted) pentanoates **1–6** (X = H, Me, F, Cl, Br, OMe) produced mixtures of *cis*-(**7–11**) and *trans*-(**12–16**) tetrahydro 5,6 dimethyl-6-phenyl-2H-pyran-2-ones. They were isolated by HPLC and characterized by ^1H and ^{13}C techniques. The stereochemistry of Grignard reactions in THF with CH_3MgCl was determined at 0° and 60°.

Many examples are reported about the behaviour of alkylation reactions on bifunctional conformationally mobile compounds. Recently a comprehensive review has been published[1] summarizing different methods in stereocontrolling reactions in acyclic systems. Moreover at present no extensive studies have been carried out about the characterization of δ-lactones by ^{13}C NMR spectroscopy. As a matter of fact interesting results have been obtained only on rigid polycyclic systems,[2] or on 3,5 disubstituted compounds[3] and monosubstituted compounds.[4a,b]

On this ground we were induced to synthesize a series of δ-ketoesters **1–6** and we tested the reactivity of these compounds in Grignard reactions:



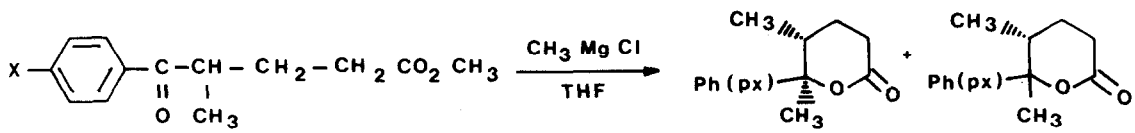
The object of the present work is to obtain: (1) the isolation of lactones **7–16**; (2) the characterization of their structure; (3) the stereochemical outcome of Grignard reactions on compounds **1–6** in THF with MeMgCl.

RESULTS AND DISCUSSION

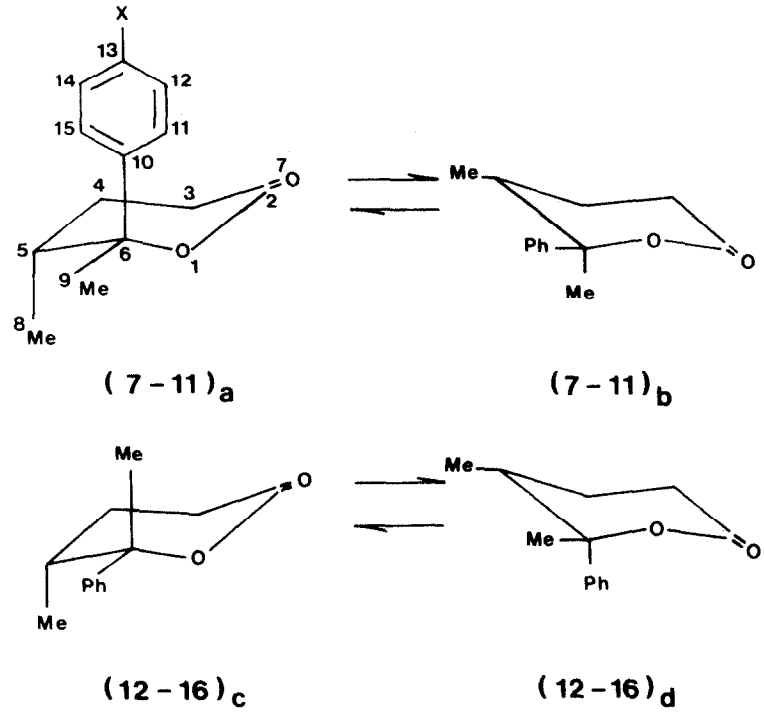
The 4-methyl 5-oxo 5-phenyl pentanoates **1–6** were synthesized by a Michael reaction with methyl acrylate on the suitable propiophenones. Grignard reactions on compounds **1–5** in THF with MeMgCl produced lactones **7–16**. Compound **6** resisted till now all of our attempts of alkylation in the above mentioned conditions even at 60°.

Lactones **7–16** can exist in a conformational equilibrium of $(7–11)_a$, $(7–11)_b$ and $(12–16)_c$, $(12–16)_d$ respectively (Scheme 1).

In a previous work[5] in which we reported Grignard reactions on different conformationally mobile δ-ketoesters among which was also compound **1** we could not



X =		7	12
H	1	7	12
CH_3	2	8	13
F	3	9	14
Cl	4	10	15
Br	5	11	16
OCH_3	6	–	–



Scheme 1.

isolate lactones **7** and **12** from each other and their structural characterization was attained on the basis of ^{1}H NMR studies and potential energy calculations.

It was clear from our results that conformers $\mathbf{7}_a$ and $\mathbf{12}_c$ are energetically favoured with respect to $\mathbf{7}_b$ and $\mathbf{12}_d$. At present we succeeded in isolating the lactones arising from reactions on **1–5** only by HPLC (lactones **7–11** have retention times always higher than lactones **12–16**, see Experimental), being GLC techniques inadequate to resolve them. Each of compounds **7–16** was submitted to usual spectroscopic analyses (^{1}H and ^{13}C NMR, IR) MS analyses and C, H analyses (Experimental).

Structure characterization of δ-lactones. The ^{1}H NMR spectra exhibit singlets at δ1.73–1.55 attributed to C9 Me group. The chemical shift differences between **7–11** and **12–16** series compounds are attributable respectively to an equatorial and an axial Me position (Table 1). The C8 Me group shows a doublet at δ0.81–1.04. Compounds **7–11** show signals at higher field with respect to the same signals of lactones **12–16**. This is attributable to a deshielding effect of the phenyl group, whose distance from the C8 Me group is different in the two lactonic series.[5]

This further evidences that the conformational equilibrium of the two isomers is highly shifted towards conformers having the greatest number of axial substituents $(\mathbf{7–11})_a$ and $(\mathbf{12–16})_c$.

Proton noise decoupled ^{13}C NMR spectra of samples **8**

Table 1. ^{1}H NMR chemical shifts of compounds **7–16** in CCl_4 at 25° (data in ppm from TMS)

Compounds	C9: δCH_3 (s, 3H)	C8: δCH_3 (d, 3H) J=6.7 Hz	δ Ph	δ_X
7	1.73	0.85	7.27 (5H)	
8	1.70	0.82	7.07 (4H)	2.32(s, 3H)
9	1.71	0.81	6.8-7.4 (4H)	
10	1.69	0.81	7.16 (4H)	
11	1.69	0.81	6.9-7.5 (4H)	
12	1.58	1.01	7.24 (5H)	
13	1.54	1.04	7.10 (4H)	2.30(s, 3H)
14	1.55	0.99	6.8-7.4 (4H)	
15	1.55	1.03	7.20 (4H)	
16	1.55	1.04	7.0-7.5 (4H)	

and **13** are shown in Figs. 1(a) and 1(b). Carbon atoms chemical shifts of the samples **7–16** and their corresponding assignments are reported in Table 2. The assignments have been performed on the basis of off resonance experiments, selective decoupling experiments, empirical rules,[6a] comparison with model compounds,[4a,b] variable temperature experiments.

The low field region includes the sp^2 carbons of the molecule, i.e. the aromatic (114–140 ppm) C atoms of the *para* substituted benzene ring and the CO group ($\approx$ 170 ppm) on the lactonic group. The high field region (from 0 to 90 ppm) is due to the sp^3 aliphatic carbons of the δ lactonic ring and to their Me substituents.

Aromatic resonances can be assigned by empirical rules for substituted benzenes. By considering **7** and **12** samples as models for the corresponding series, C-11–C-15, C-14–C-12 and C-13 experimental and calculated ^{13}C chemical shifts are completely in agreement in both series and show to be affected only by substituent effect in 13 position.

In each series also C-10 C atom shows a chemical shift closely depending on the substituent in 13 position which exhibits a relevant shift (2.7–3.5 ppm) downfield in going from **12** to **16** series compounds to the corresponding **7–11** series. Such an effect can be attributed to the equatorial position of the phenyl group in the **12–16** series.

δ-Lactonic ring quaternary (C-6), methynic (C-5), methylenic (C-3 and C-4), methylic (C-8 and C-9) C atoms have been identified by off resonance experiments; unequivocal assignments between C-3 and C-4 and between C-8 and C-9 has been performed by ^1H selective decoupling experiments and comparison with model compounds.[4a,b] An interesting difference between **7–11** and **12–16** series compounds is shown by downfield shift (4.6–5 ppm) of C-9 Me group in the **7–11** series compounds with respect to the **12–16** series. In similar systems[3] a Me group in equatorial position shows downfield shift with respect to a Me group in axial position (about 4 ppm).

No further information can be derived from other C atoms, due to little variations of their chemical shift.

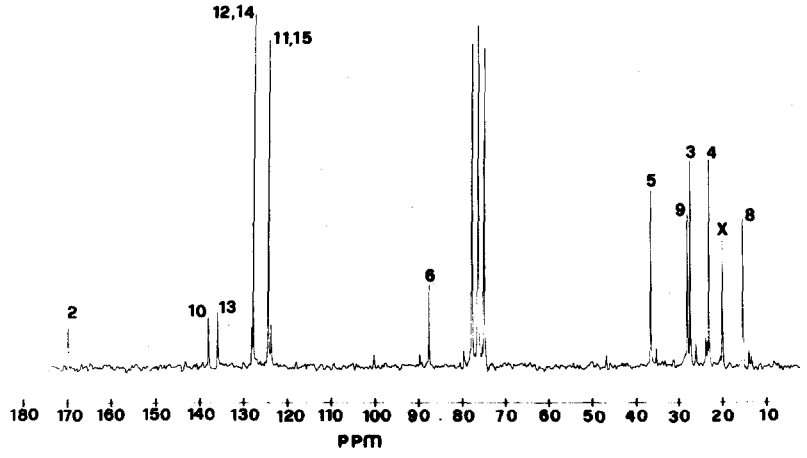


Fig. 1(a).

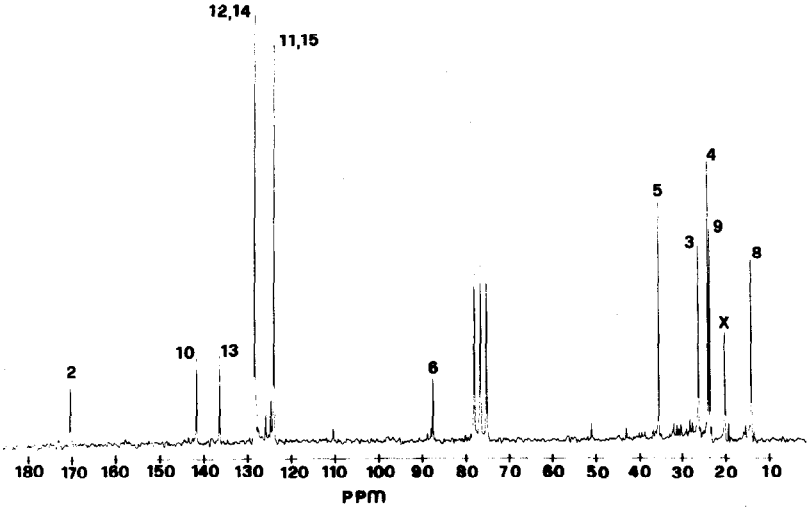


Fig. 1(b).

Fig. 1. Proton decoupled ^{13}C NMR spectrum at 22.63 MHz of samples (a) 8 and (b) 13. X symbol indicates methyl group on C-13 carbon atom.

Table 2. ^{13}C NMR chemical shifts of compounds 7–16 in $CDCl_3$ at 25° (data in ppm from TMS)

Compound		C2	C3	C4	C5	C6	C8	C9	C10	C11-15	C12-14	C13	X
7	-H	170.96	28.07	23.88	36.89	88.27	15.94	28.95	141.85	125.31	128.05	127.30	
8	p-CH_3	171.46	28.28	23.94	37.21	88.28	15.98	28.86	138.97	125.37	128.80	136.90	20.83
9	p-F	171.01	27.76	23.75	36.82	87.77	15.79	29.05	138.06	126.99	114.95	161.95	
10	p-Cl	170.88	27.63	23.75	36.69	87.64	15.72	28.93	140.91	126.73	128.35	133.27	
11	p-Br	170.81	27.63	23.75	36.63	87.57	15.72	28.93	141.49	127.06	131.33	121.36	
12	-H	170.96	26.74	24.41	36.00	88.05	14.53	24.23	145.29	124.65	128.40	127.30	
13	p-CH_3	171.60	26.92	24.65	35.92	87.89	14.62	24.26	142.40	124.60	129.06	137.02	20.83
14	p-F	171.20	27.18	24.26	36.37	87.57	14.75	24.07	140.98	126.61	115.21	161.95	
15	p-Cl	170.90	27.11	24.39	36.24	87.44	14.68	24.26	143.95	126.34	128.67	133.53	
16	p-Br	170.96	26.74	24.10	36.00	87.60	14.40	24.01	144.28	126.85	131.26	121.21	

On regard to conformational isomerism, by low temperature ^{13}C NMR spectra only one conformational form has been evidenced for each configurational isomer at least at the examined temperatures. In fact additional splittings have not been found for Me resonances highly sensitive to conformational changes.[6b]

All ^{1}H and ^{13}C data are in agreement with the potential energy calculations pointed out above, and confirm that the conformational equilibrium for the *cis*-(**7–11**) and *trans*-(**12–16**) series compounds is almost completely shifted toward (**7–11**)$_a$ and (**12–16**)$_e$ conformations.

Stereochemistry of Grignard reactions. Grignard reactions on compounds **1–6** were performed in THF with MeMgCl 0.1 N at 0° and 60°. The stereochemical ratios of lactones *cis*-(**7–11**) and *trans*-(**12–16**) are collected in Table 3. The results are derived from at least six reactions for each substrate in each temperature condition adopted.

It is evident that, for reactions carried out at 60°, the ratios *cis*/*trans* are almost the same for all the examined ketoesters.

These results may exclude, for all the substrates in the examined condition, the existence of interactions between the keto and the ester group due to a different influence of the *para* phenyl substituted group on the rotational states of molecules in the reaction transition states.

Moreover the stereochemical behaviour doesn't agree with Cram's rule.[7a,b,c]. This suggests that one of the most energetically favoured rotamers in the reaction transition state is that showed in Scheme 2.

The reactions carried out at 0° show a decrease in the stereochemical ratio *cis*/*trans* for at least three substrates, and a loss of reactivity of compounds **1** and **2**. This temperature variation causes an increase in the difference of rotamers activation energy in the reaction transition state, favouring in this way the (1) attack.

EXPERIMENTAL

IR spectra were recorded using a Perkin–Elmer 457 spectrophotometer. ^{1}H NMR spectra were recorded on a Jeol-C-60 HL and on a Bruker WH 90 spectrometer.

^{13}C NMR spectra were obtained at room temp. (28°) in a 10 mm sample tube on a Bruker WH 90 instrument operating at 22.63 MHz in the Fourier Transform mode. The sample concentration was 50 mg × ml^{-1} in $CDCl_3$ used as ^{2}D internal lock. The same samples were used for both ^{1}H and ^{13}C NMR experiments. Measurements conditions were as follows: pulse width 4.5 sec (30° pulse), acquisition time 0.682 sec, spectral width 6000 Hz, number of data points 8 K, number of scans 3000.

^{13}C chemical shifts were measured taking the chemical shift of $CDCl_3$ as 77.02 ppm relative to TMS and are considered to be accurate to 0.05 ppm.

The low temp. ^{13}C NMR spectra were obtained at 10°–40° and −80° on Bruker variable temp. accessory in CD_2Cl_2 solns.

The CD_2Cl_2 chemical shifts were determined at −80° in respect to CS_2.

The single resonance spectra were obtained at decoupler off. The number of scans was 15,000.

Specific ^{1}H decouplings were performed at a power 0.5 W. MS were recorded on a AE1 MS 12 spectrometer: the relative intensities of the peaks (in parenthesis) are referred to the most intense one taken as 100%. The spectra were recorded at 70 eV. GLC analyses were carried out on a Carlo Erba Fractovap G1 using a 2 m, 2 mm i.d. column packed with SP 2250 on Supelcoport 100/120 mesh. The GLC analysis conditions were $T_{det} = T_{inj} = 260°$, N_2 flow = 30 ml/min, $T_{oven} = 248°$, theoretical plates = 3000.

HPLC analyses and separations were carried out on a Waters apparatus equipped with a detector UV Perkin–Elmer LC 55 at $\lambda = 265$ nm, using respectively a 30 cm × 3.9 mm i.d. μ Porasil Waters and a 30 cm × 7.9 mm i.d. μ Porasil Waters columns.

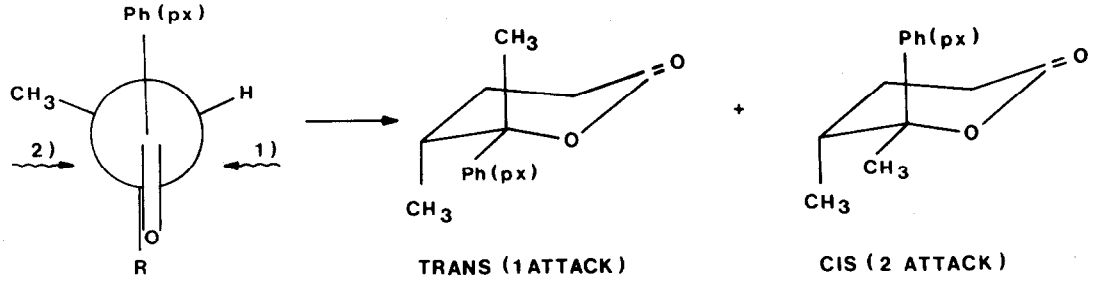
Starting materials. Compounds **1–6** were synthesized using the method of Bertocchio and Dreux.[8] We used propiophenone (Merck), 4-Me propiophenone (K & K), 4-F propiophenone and 4-Br propiophenone (EGA CHEMIE), 4-Cl propiophenone (Shilling), 4-Me propiophenone (Fluka) and methyl acrylate (Fluka).

MeOH was purified and dried as described.[9] In a 500-ml two-necked dry flask, equipped with refrigerator, $CaCl_2$ tube and

Table 3. Stereochemical product ratios for Grignard reactions in THF with Me_3MgCl at 0° and 60° on compounds **1–6**

Starting compound	0°C cis/trans [a]	Yields %	60°C cis/trans [a]	Yields %
1	—	—	0.70	75
2	—	—	0.69	65
3	0.45	48	0.64	81
4	0.51	40	0.68	73
5	0.49	38	0.66	65
6	—	—	—	—

a) Mean deviation error: ± 0.05



Scheme 2.

dropping funnel were placed 1 mole of the selected propiophenone with 21 ml (0.25 mole) of methyl acrylate. 2N KOH methanolic soln (5 ml) was dropped into the flask in about 3 min. The reaction was refluxed for 2 hr, cooled and then hydrolysed with 200 ml water, and neutralized with conc HCl. The mixture was extracted 3 times with diethyl ether and the ethereal layers were collected, dried over Na_2SO_4 and distilled. The crude product was purified as further described for each pentanoate **1–6**.

Methyl,4 - methyl - 5 - oxo - 5 - phenyl pentanoate **1**. The crude product was distilled in order to remove the excess propiophenone (b.p. 65°/2 mm Hg). The residual was distilled (133°/2 mm Hg) (146°/2.5 mm Hg[8]) to give 25.3 g of **1** as colourless oil (yield 48%). Compound **1** was analyzed by GLC in the above mentioned conditions (ret. time: 1 min, 39 sec).

NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ: 1.15 (0.95) d, $J = 6.7$ Hz, 3H; 3.52 (3.28) s, 3H; 7.1–7.9 multiplet, 5H. MS spectra *m/e*: 39(20), 59(20), 77(64), 105(100), 133(20), 220(1), 221(0.1).

IR spectra showed ν_{max}^{film} cm^{-1}: 3060w, 3040w, 2980m, 2960m, 2940sh, 2880w, 1740s, 1685s, 1600m, 1585m, 1460sh, 1450s, 1440m, 1425sh, 1380m, 1365sh, 1320w, 1290sh, 1265m, 1225m; 1205sh, 1175m, 1080w, 1005m, 980s, 800m, 710s. (Found C, 70.7; H, 7.23. $C_{13}H_{16}O_3$ requires C, 70.91; H, 7.27%.)

Methyl 4-methyl-5-oxo-5(4' methyl)phenyl pentanoate **2**. The crude product was distilled in order to remove the excess 4-methyl propiophenone (b.p. 137–139°/0.7 mm Hg). The residual was chromatographed on silica gel (Merck) (R = 1:60) using benzene/EtOAc, 9/1 as eluant. The fractions containing **2** were collected as a colourless oil and distilled (b.p. 160–162°/0.2 mm Hg) to give 27.5 g of **2** (yield 47%). **2** was analyzed by GLC in the specified conditions (ret. time: 2 min, 16 sec).

NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ: 1.14 (1.03) d, $J = 6.7$, 3H; 2.40 (2.03) s, 3H; 3.55 (3.32) s, 3H; 7–7.8 multiplet, 4H. MS *m/e*: 91(22), 119(100), 120(9), 148(3), 161(2); 175(3), 203(5), 234(9), 235(1).

IR spectra showed ν_{max}^{film} cm^{-1}: 3060w, 3040w, 2985sh, 2975m, 2940w, 1740s, 1680s, 1610s, 1570w, 1560w, 1460sh, 1450sh, 1435m, 1410m, 1375m, 1315w, 1290w, 1260m, 1230m, 1205m, 1185sh, 1170m, 1120w, 1065w, 1040w, 1020w, 990sh, 975m, 850sh, 830m, 790w, 750m. (Found C, 71.72; H, 7.65, $C_{14}H_{18}O_3$ requires C, 71.79; H, 7.69%.)

Methyl 4-methyl-5-oxo-5(4' fluoro)-phenyl pentanoate **3**. The crude product was distilled in order to remove the excess 4-fluoro propiophenone (b.p. 88–90°/0.2 mm Hg). The residual was chromatographed on silica gel (Merck) (R = 1:70) using CCl_4/EtOAc, 9/1 as eluant. The fractions containing **3** were collected as a colourless oil and distilled (b.p. 108/110°/0.1 mm Hg) to give 20.8 g of **3** (yield 35%). **3** was analyzed by GLC in the above specified conditions (ret. time: 1 min, 50 sec).

NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ: 1.18 (0.96) d; $J = 6.7$ Hz 3H; 3.60 (3.31) s 3H; 6.9–8.1 m, 4H. MS *m/e*: 75(9), 95(34), 123(100), 124(9), 152(7), 238(5), 239(0.6).

IR spectra showed ν_{max}^{film} cm^{-1}: 3040w, 3020w, 2990m, 2980m, 2975sh, 2940w, 1745s, 1690s, 1605s, 1515sh, 1510m, 1465m, 1455sh, 1445m, 1415m, 1380m, 1370sh, 1325sh, 1305w, 1265w, 1235s, 1205sh, 1180sh, 1165s, 1135w, 1125w, 1105w, 1075w, 1030sh, 1020w, 985m, 855m, 825w, 770m. (Found C, 65.41 H, 6.27; $C_{13}H_{15}FO_3$ requires C, 65.55; H, 6.30%.)

Methyl 4-methyl-5-oxo-5(4' chloro)-phenyl pentanoate **4**. The crude product was distilled in order to remove the excess 4-chloro propiophenone (b.p. 123–125°/10 mm Hg). The residual was chromatographed on silica gel (Merck) (R = 1:70) using CCl_4/EtOAc, 9/1 as eluant. The fractions containing **4** were collected as a pale yellow viscous oil and distilled (b.p. 160–162°/5 mm Hg) to give 27.3 g of **4** (yield 43%). **4** was analyzed by GLC in the above specified conditions (ret. time: 2 min, 23 sec).

NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ: 1.15 (0.93) d $J = 6.7$ Hz 3H; 3.52 (3.28) s 3H; 7.2–7.8 m 4H. MS *m/e*: 75(5), 111(14), 139(100), 140(7), 141(27), 195(4), 222(5), 223(7), 254(12), 255(2), 256(4).

IR spectra showed ν_{max}^{film} cm^{-1}: 3040w, 3020w, 2985m, 2975m, 2970m, 2940w, 1740s, 1685s, 1590m, 1570sh, 1485w, 1460w, 1440m, 1420w, 1400m, 1380m, 1210s, 1175s, 1095s, 1015m, 975s, 840s, 765sh, 745m. Found C, 61.60, H, 5.86; $C_{13}ClO_3$ requires C, 61.42 H, 5.91.%)

Methyl 4-methyl-5-oxo-5(4' bromo)-phenyl pentanoate **5**. The crude product was distilled in order to remove the excess 4-bromo propiophenone (114–117°/0.3 mm Hg). The residual was chromatographed on silica gel (Merck) (R = 1:70) using CCl_4/EtOAc, 9/1 as eluant. The fractions containing **5** were collected as a pale yellow viscous oil and distilled (b.p. 158–160°/0.3 mm Hg) to give 26.2 g of **5** (yield 35%). **5** was analyzed in the above specified conditions (ret. time: 3 min, 27 sec).

NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ: 1.18 (0.90) d $J = 6.7$ Hz 3H; 3.60 (3.30) s 3H; 7.25–8.00 m 4H. MS *m/e*: 75(28), 76(31), 155(30), 157(30), 184(100), 186(94), 212(11), 214(11), 299(2), 300(1), 301(1).

IR spectra showed ν_{max}^{film} cm^{-1}: 3040w, 3020w, 2985sh, 2950m, 2940sh, 1735s, 1680s, 1585s, 1485w, 1460sh, 1450sh, 1435m, 1420w, 1395m, 1370m, 1365sh, 1305w, 1275sh, 1260m, 1215s, 1170s, 1125w, 1110w, 1070s, 1010m, 975s, 900w, 840m, 765sh, 750m. (Found C, 52.12; H, 5.07. $C_{13}H_{15}BrO_3$ requires: C, 52.17; H, 5.02%.)

Methyl 4-methyl-5-oxo-5(4' methoxy)phenyl pentanoate **6**. The crude product was distilled in order to remove the excess 4-methoxy propiophenone (b.p. 142–143°/10 mm Hg). The residual was chromatographed on silica gel (Merck) (R = 1:70) using benzene/EtOAc, 9/1 as eluant. The fractions containing **6** were collected as a colourless viscous oil and distilled (b.p. 168–170°/5 mm Hg) to give 25 g of **6** (yield 40%). **6** was analyzed by GLC in the above specified conditions (ret. time: 2 min, 40 sec).

NMR spectra in CCl_4 (and in benzene d_6) showed the following peaks δ: 1.12 (1.03) d $J = 6.7$ Hz 3H; 3.52 (3.25) s 3H; 3.78 (3.15) s 3H; 6.6–7.8 m 4H. MS *m/e*: 77(78), 78(11), 92(42), 107(71), 135(71), 164(44), 176(10), 191(22), 219(60), 250(100), 251(15).

IR spectra showed ν_{max}^{film} cm^{-1}: 3040w, 3020w, 3000w, 2980m, 2970m, 2960sh, 2940w, 2920w, 1740s, 1675s, 1600s, 1580sh, 1575m, 1510m, 1460m, 1440m, 1420m, 1375m, 1365sh, 1310m, 1260s, 1240sh, 1170s, 1130w, 1115w, 1065w, 1025m, 1010sh, 975m, 840m, 800w, 760m. (Found C, 67.15; H, 7.18. $C_{14}H_{18}O_4$ requires C, 67.20; H, 7.20%.)

Purification of THF. This was done as described.[5]

Preparation of MeMgCl *in THF.* This was done as described;[5] the reagent was subsequently titrated.[10]

Grignard reactions on **1–6**. A soln 0.1 N MeMgCl in THF was added dropwise to a rapidly stirred soln of 2.5 mmol of **1–6** dissolved in 25 ml anhydrous THF. The reaction was carried out in a temp. controlled apparatus. Reactions were interrupted after 40 min by adding a sat NH_4Claq. and a weighed amount of GLC standard. Reaction mixtures were extracted with diethyl ether; the ethereal solns washed with water were combined, dried over Na_2SO_4, filtered and evaporated. The residue was analyzed by GLC on SP 2250 to measure the total material balance which was always in the range of 90–98%. Lactones **7–12**, **8–13**, **9–14**, **10–15** and **11–16** are the only products of the Grignard reactions on **1**, **2**, **3**, **4** and **5** respectively in the employed conditions. Ketoester **6** was recovered from reaction in 95% yield. We were not able to separate into two peaks the lactonic fractions in all the GLC conditions on packed or capillary columns employed.

Isolation of lactones **7–12**. The crude Grignard product on **1** was chromatographed by HPLC on the described apparatus, using hexane/EtOAc, 80/20 as eluant, $\varphi = 7.0$ ml/min. We obtained as pure fractions, in order of elution the residual portion of **1**, 260 mg of *trans*-**12** and 110 mg of *cis*-**7**.

The purity of **7** and **12** was tested by HPLC on analytical column Ret. times at $\varphi = 3.0$ ml/min (hexane/EtOAc, 80/20): 3 min 39 sec for **12** and 4 min 12 sec for **7**.

For compound **7**: b.p. 140°/3 mm Hg.

MS *m/e*: 44(31), 56(93), 77(22), 84(35), 105(100), 121(52), 161(15), 189(21), 204(32), 205(4).

IR spectra showed ν_{max}^{film} cm^{-1}: 3080w, 3050w, 3020w, 2970s, 2925m, 2870m, 1725s, 1600w, 1490m, 1455sh, 1445m, 1415w, 1380m, 1345sh, 1325m, 1290sh, 1250s, 1225sh, 1210sh, 1190w, 1160s, 1125m, 1105m, 1085m, 1070sh, 1060m, 1035m, 1010w, 1000sh, 975s, 920w, 895w, 875w, 825w, 790m, 765s, 705s. (Found C, 76.30, H, 7.80; $C_{13}H_{16}O_2$ requires: C, 76.44; H, 7.90%.)

For compound **12**: b.p. 140°/3 mm Hg.

MS *m/e*: 44(31), 56(93), 77(35), 84(44), 105(100), 121(52), 161(15), 189(21), 204(32), 205(4).

IR spectra showed ν_{max}^{film} cm^{-1}: 3080w, 3050w, 3020w, 2970s, 2925m, 2870m, 1725s, 1600w, 1490m, 1460sh, 1450m, 1390m, 1330m, 1270sh, 1260m, 1235m, 1210sh, 1170m, 1115sh, 1105w, 1090w, 1065m, 1040sh, 1030w, 1010m, 1000sh, 975m, 965sh, 760s, 700s. (Found C, 76.40, H, 7.85. $C_{13}H_{16}O_2$ requires C, 76.44, H, 7.90%.)

Isolation of lactones **8–13**. The crude product on **2** was chromatographed by HPLC on the described apparatus using hexane/EtOAc, 80/20 as eluant, $\varphi = 7.0$ ml/min.

We obtained as pure fractions, in order of elution the residual portion of **2**, 170 mg of *trans*-**13** and 170 mg of *cis*-**8**.

The purity of **8** and **13** was tested by HPLC on analytical column: ret. times at $\varphi = 3.0$ ml/min (hexane/EtOAc, 80/20): 3 min 18 sec for **13** and 3 min 48 sec for **8**.

For compound **8**, b.p. 140°/3 mm Hg; MS *m/e*: 56(31), 65(9), 84(9), 91(23), 99(5), 105(7), 115(7), 119(100), 120(9), 131(12), 135(54), 136(6), 143(8), 146(6), 158(6), 159(8), 175(9), 203(14), 218(25), 219(4).

IR spectra showed ν_{max}^{film} cm^{-1}: 3080w, 3050w, 3020w, 2970m, 2940m, 2880m, 1740sh, 1730s, 1515m, 1460m, 1450m, 1380m, 1345m, 1330m, 1285sh, 1255s, 1230sh, 1215sh, 1195w, 1160m, 1120w, 1105m, 1080m, 1060m, 1035m, 1020w, 1010w, 975m, 950sh, 820m, 805sh. (Found C, 77.00, H, 8.05. $C_{14}H_{18}O_2$ requires C, 77.06, H, 8.26%.)

For compound **13**; b.p. 140°/3 mm Hg; MS *m/e*: 56(31), 65(9), 84(9), 91(33), 99(5), 105(7), 115(7), 119(100), 120(9), 131(12), 135(62), 136(6), 143(8), 146(6), 158(6), 159(8), 175(9), 203(14), 218(25), 219(4).

IR spectra showed ν_{max}^{film} cm^{-1}: 3080w, 3050w, 3020w, 2970m, 2950m, 2880w, 1740sh, 1730s, 1515m, 1510sh, 1460sh, 1450m, 1415w, 1385m, 1375sh, 1360w, 1350w, 1330m, 1300sh, 1290sh, 1260s, 1240sh, 1215w, 1190w, 1170m, 1115sh, 1105m, 1075s, 1065sh, 1040m, 1020m, 1010m, 975m, 970sh, 955sh, 910m, 840sh, 825m, 810sh, 725m. (Found C, 77.02, H, 8.10; $C_{14}H_{18}O_2$ requires: C, 77.06, H, 8.26%.)

Isolation of lactones **9–14**. The crude Grignard product on **3** was chromatographed by HPLC on the described apparatus using hexane/EtOAc, 80/20 as eluant, $\varphi = 7.0$ ml/min. We obtained as pure fractions, in order of elution, the residual portion of **3**, 180 mg of *trans*-**9**, 200 mg of *cis*-**14**. The purity of **9** and **14** was tested by HPLC on analytical column. Ret. times at $\varphi = 3.0$ ml/min (hexane/EtOAc, 80/20) 5 min, 18 sec for **14** and 6 min, 6 sec for **9**.

For compound **9**, b.p. 165°/3 mm Hg; MS *m/e*: (55(14), 56(95), 75(9), 84(50), 95(18), 109(14), 123(100), 133(9), 135(18), 136(9), 138(13), 139(31), 150(9), 179(17), 194(9), 207(23), 222(30), 223(5).

IR spectra showed ν_{max}^{film} cm^{-1}: 3080w, 2970m, 2940m, 2920sh, 2880w, 1740sh, 1730s, 1605m, 1510s, 1480w, 1465m, 1450sh, 1410w, 1385m, 1350m, 1330m, 1305w, 1295w, 1250sh, 1240s, 1225sh, 1170sh, 1160s, 1120w, 1100m, 1080m, 1060m, 1035m, 1015m, 980m, 920w, 845s, 820m, 790w, 780w, 765w. (Found C, 70.08, H, 6.05. $C_{13}H_{15}FO_2$ requires: C, 70.27, H, 6.16%.)

For compound **14**; b.p. 160°/3 mm Hg; MS *m/e*: 55(14), 56(95), 75(9), 84(50), 95(27), 109(14), 123(100), 133(9), 135(28), 136(11), 138(13), 139(31), 150(9), 179(17), 194(9), 207(23), 222(30), 223(5).

IR spectra showed ν_{max}^{film} cm^{-1}: 3070w, 3050w, 2970m, 2940m, 2880m, 1740sh, 1730s, 1600m, 1510s, 1470m, 1460m, 1450m, 1410m, 1385m, 1375w, 1305w, 1265m, 1255sh, 1230s, 1175sh, 1165s, 1120sh, 1110m, 1075m, 1060m, 1040w, 1015m, 1005m, 995sh, 980m, 965m, 905w, 845s, 820w, 790m, 775w, 765w, 730w. (Found C, 70.10, H, 6.08. $C_{13}H_{15}FO_2$ requires: C, 70.27, H, 6.16%.)

Isolation of lactones **10–15**. The crude Grignard product on **4** was chromatographed by HPLC on the described apparatus using hexane/EtOAc, 85/15 as eluant, $\varphi = 9.0$ ml/min. We obtained, in order of elution, as pure fractions, the residual portion of **4**, 180 mg of *trans*-**15** and 160 mg of *cis*-**10**. The purity of **10** and **15** was tested by HPLC on analytical column. Ret. times at $\varphi = 3.0$ ml/min (hexane/EtOAc, 85/15) 7 min, 36 sec for **15** and 9 min, 18 sec for **10**.

For compound **10**; b.p. 170°/3 mm Hg; MS *m/e*: 55(37), 56(100), 71(61), 75(34), 77(49), 78(35), 84(63), 99(40), 100(40), 103(42), 135(20), 139(60), 141(37), 238(30), 239(5), 240(10).

IR spectra showed ν_{max}^{film} cm^{-1}: 3070w, 2970m, 2940m, 2880w, 1735s, 1600w, 1495s, 1465w, 1455w, 1420w, 1405w, 1380w, 1350w, 1330w, 1305w, 1285m, 1270sh, 1250s, 1230sh, 1210sh, 1190w, 1160m, 1125w, 1105m, 1080m, 1060m, 1040m, 1015s, 980s, 960sh, 920w, 890w, 835m, 790w, 760w, 725w, 715w, 700w. (Found C, 65.47, H, 6.18. $C_{13}H_{15}ClO_2$ requires: C, 65.55, H, 6.30%.)

For compound **15**; b.p. 165°/3 mm Hg; MS *m/e*: 55(37), 56(100), 71(61), 75(34), 77(49), 78(35), 84(63), 99(40), 100(48), 103(55), 135(30), 139(60), 141(37), 238(30), 239(5), 240(10).

IR spectra showed ν_{max}^{film} cm^{-1}: 3070w, 2980sh, 2970m, 2950m, 2880w, 1735s, 1600w, 1495s, 1465w, 1455w, 1420w, 1405m, 1390w, 1380w, 1360w, 1350w, 1330m, 1305w, 1280sh, 1265sh, 1255s, 1240s, 1210sh, 1170m, 1120m, 1105sh, 1100s, 1075s, 1065m, 1040m, 1015s, 980sh, 965m, 950sh, 910w, 845s, 820w, 795s, 765w, 725w, 710w. (Found C, 65.48, H, 6.20. $C_{13}H_{15}ClO_2$ requires: C, 65.55, H, 6.30%.)

Isolation of lactones **11–16**. The crude Grignard product on **5** was chromatographed by HPLC on the described apparatus using hexane/EtOAc, 86/14 as eluant, $\varphi = 9.9$ ml/min. We obtained, in order of elution, as pure fractions, the residual portion of **5**, 90 mg of *trans*-**16** and 100 mg of *cis*-**11**.

The purity of **11** and **16** was tested by HPLC on analytical column. Ret. times at $\varphi = 4.5$ ml/min (hexane/EtOAc, 88/12): 6 min, 45 sec for **16** and 8 min, 30 sec for **11**.

For compound **11**; b.p. 170°/3 mm Hg; MS *m/e*: 55(17), 56(100), 75(11), 76(12), 77(11), 84(89), 115(10), 116(10), 128(9), 129(9), 131(11), 155(8), 157(8), 183(40), 185(42), 198(11), 199(12), 200(9), 201(12), 239(9), 241(9), 267(11), 269(11), 283(17), 284(3), 285(17), 286(3).

IR spectra showed ν_{max}^{film} cm^{-1}: 3070w, 3010w, 2980m, 2940m, 2880w, 1735s, 1720sh, 1595w, 1490m, 1460m, 1455sh, 1420w, 1400m, 1380sh, 1350m, 1330m, 1305w, 1280m, 1250s, 1225sh, 1210sh, 1190w, 1160s, 1125m, 1100m, 1080s, 1060m, 1040m, 1010s, 980s, 920w, 890w, 880sh, 840sh, 825m, 790s, 765m, 720w, 695w. (Found C, 55.03, H, 5.27. $C_{13}H_{15}BrO_2$ requires: C, 55.12, H, 5.30%.)

For compound **16**; b.p. 165°/3 mm Hg; MS *m/e*: 55(17), 56(100), 75(11), 76(12), 77(11), 84(89), 115(14), 116(14), 128(9), 129(9), 131(11), 155(13), 157(13), 183(48), 185(47), 198(11), 199(12), 200(9), 201(12), 239(9), 241(9), 267(11), 269(11), 283(17), 284(3), 285(17), 286(3).

IR spectra showed ν_{max}^{film} cm^{-1}: 3070w, 2980m, 2940m, 2880w, 1735sh, 1730s, 1590w, 1485m, 1475m, 1455m, 1415w, 1395m, 1385sh, 1375sh, 1325m, 1280sh, 1255s, 1235sh, 1205w, 1170m, 1115m, 1105sh, 1080sh, 1070s, 1060sh, 1035w, 1010s, 975sh, 965m, 905w, 840m, 835sh, 815w, 790m, 720w, 700w, 690w. (Found C, 55.07, H, 5.28. $C_{13}H_{15}BrO_2$ requires: C, 55.12, H, 5.30%.)

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