Tetrahedron. Vol. 34, pp. 357 to 362. Pergamon Press 1978. Printed in Great Britain

STEREOCHEMISTRY OF GRIGNARD REACTIONS ON SOME CONFORMATIONALLY MOBILE δ-KETO ESTERS

THE EFFECTS OF CHANGING SOLVENT AND REACTANT†

A. COLANTONI, G. DI MAIO*, E. VECCHI and E. ZEULI
Istituto di Chimica Organica dell'Università, Rome, Italy

and

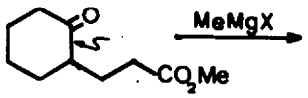
C. QUAGLIATA
Istituto di Chimica Fisica dell'Università, Rome, Italy

(*Received in UK 24 June 1977; Accepted for publication 1 August 1977*)

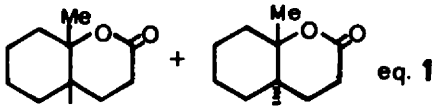
Abstract—Methyl 4-methyl-5-oxo-hexanoate (4) and methyl 4-methyl-5-oxo-5-phenyl-pentanoate (5) yield mixtures of *cis* and *trans* tetrahydro-5, 6-dimethyl-6-phenyl-2H-pyran-2-one (6 + 7) on reacting with PhMgX and MeMgX, respectively. Ratios 6/7 were measured for reactions performed in benzene, diethyl ether (with X = I) and tetrahydrofuran (with X = Cl). A comparison is made of the results obtained with those of methyl (2-oxo-cyclohexyl)-propionate (1). It is suggested that the ester group and the keto group can interact in the transition states of the reaction performed in the less polar solvent and that in polar solvents they are remote from one another during the reaction. These conformational changes are believed to be responsible for the observed stereochemical differences in the reactions.

It is well known that changes of solvent, reactant and temperature may produce changes in stereospecificity and steric direction in Grignard reactions.[1-5]

One of us[4] found that Grignard reactions on methyl (2-oxo-cyclohexyl)-propionate (1) proceed with unusual changes in stereospecificity with varying reactant and solvent. Thus lactones 2 and 3 were produced in the ratio 2/3 = 1.3 when benzene was the solvent and X = I, whereas 2/3 = 14.4 when Grignard reactions were carried out in THF with X = Cl. Identical changes in solvent and reactant caused variations in the same direction, but smaller, with all the other α-substituted cyclohexanones we examined[5] and this is in agreement with other authors.[6]



1



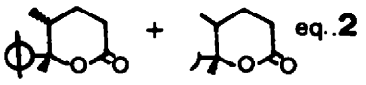
eq. 1

2 3

This suggests that, with bifunctional, conformationally mobile systems, changes in reaction conditions could modify the interactions between functional groups in the transition state with consequent changes in stereochemistry.

δ-Keto esters 4 and 5 differ from 1 and from each other in their rotational freedom around bonds CO-C_α (see arrows) and the transition states of their reactions can attain different conformations: the stereochemistry of their reactions with Grignard reagents are studied in the hope of gaining a better understanding of the factors involved.

4 R_1 = Me R_2 = Ph when R_1 = Me
5 R_1 = Ph R_2 = Me when R_1 = Ph



eq. 2

6

RESULTS

Grignard reactions on γ or δ-keto esters generally yield γ- or δ-lactones.[4,7] This was also the case for compounds 4 and 5 when reacting with phenyl and methyl Grignard reagents, respectively: the lactonic fractions invariably showed P peak at 204 *m/e* (Experimental for the complete fragmentation pattern). IR spectra show normal lactonic bands at 1740 cm^{-1}.‡ These lactonic fractions resisted till now all our attempts to separate 6 from 7 but NMR spectra (Figs. 1 and 2) clearly show that they are present in variable amounts depending on both the starting material (4 and 5) and the reaction conditions. Also NMR spectra allow quantitative determination of 6 and 7.

†We thank the Consiglio Nazionale delle Ricerche for financial support.

‡No bands at frequencies higher than 1750 cm^{-1}, characteristic of the boat conformation of the δ-lactonic ring,[8] appear in the IR spectra.

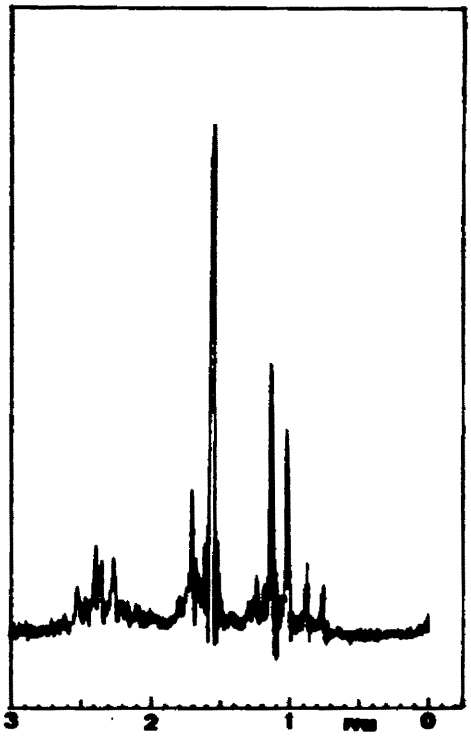


Fig. 1. NMR spectrum of a lactonic fraction deriving from reaction of 4 with PhMgI in Et_2O. (solvent CCl_4)

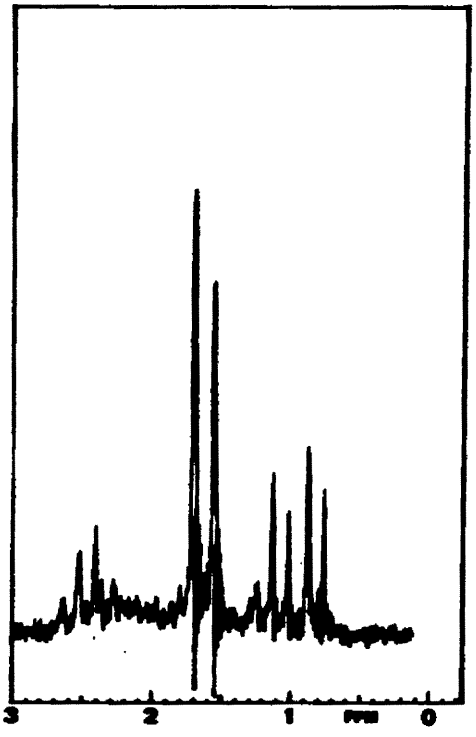
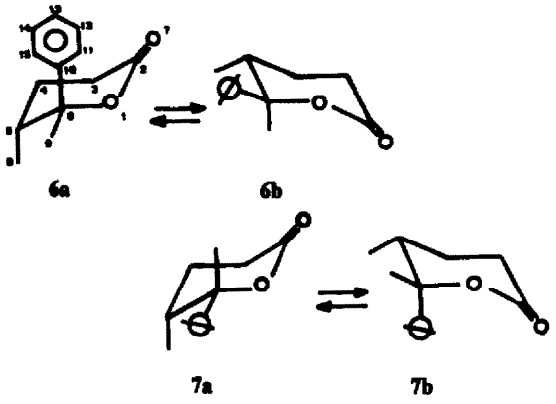


Fig. 2. NMR spectrum of a lactonic fraction deriving from reaction of 5 with MeMgI in C_6H_6. (solvent CCl_4)

Structures of lactones **6** *and* **7**. Figures 1 and 2 represent the NMR spectra of the lactonic fraction deriving from the reaction of 4 with PhMgI in Et_2O at 25° and from 5 with MeMgI in benzene (same reaction temp.), respectively.

From the spectra it is evident that the lactone showing the singlet Me signal at 1.73δ shows the Me doublet at 0.85δ and that the Me singlet at 1.58δ and the doublet at 1.10δ belong to the same lactone. Since both **6** and **7** might be equilibrium mixtures of **6a**, **6b** and **7a**, **7b** respectively, we calculated the potential energies of the above four structures and the pertinent interatomic distances at the minima in order to facilitate the interpretation of NMR spectra.



Potential energy calculations. The numbers in Fig. 6a were assigned to the atoms (C, O) of all four structures **6a**, **6b** **7a** and **7b** in calculations of this section. Intramolecular potential energy E was computed as a function of the angle φ around the C6–C10 bond.

In Table 1 are reported the coefficients of the semiempirical potential functions employed in the generalized form: $a.\exp(-br)/r^d - cr^{-6}$, where r is the atom-atom distance. In many cases these functions, suitable to describe van der Waals interactions, have been successfully used in predicting the most stable conformations of molecules, macromolecules, as well as in solving the phase problem in crystals.[9] It should be noted that the employement of a potential function for the Me group, treated as an atom, reduces the degree of freedom from three to one in the present case.

The choice of a starting model for calculations was not straightforward, since the crystal structures of closely similar compounds are lacking in the literature. The geometry of the lactone ring, as far as the atoms O1, C2, C3, C4, C5, C6, O7 are concerned, was assumed as it results at the end of refinement of *cis*-oxa-1 trimethyl-7, 7, 10-decalinedione-2, 5[10] (**8**), the lactone ring being a fragment of this last compound. Torsion angles are

Table 1. Coefficients of potential functions†

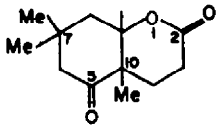
Interaction	a 10^{-3}	b	c	d
H–H	6.6	4.080	49.2	0
H–C	44.8	2.040	125.0	6
H–O	42.0	2.040	132.7	6
H–CH_3	49.1	3.705	380.5	0
C–C	301.2	0.000	327.2	12
C–O	278.7	0.000	342.3	12
C–CH_3	291.1	1.655	981.1	6
O–O	259.0	0.000	358.0	12
O–CH_3	272.7	1.665	1026.3	6
CH_3–CH_3	273.9	3.329	2942.0	0

†The energy is in Kcal per atom pair if the interatomic distance is in Å.

Table 2. Torsional angles (°) in 6 and 7 corresponding to the lactone ring geometry assumed in calculations

O1–C2–C3–C4	14.6
C6–O1–C2–C3	−15.3
C5–C6–O1–C2	37.1
C2–C3–C4–C5	−36.0
C3–C4–C5–C6	55.9
C4–C5–C6–O1	−56.2

defined according to the IUPAC rules.[11] Computed values are shown in Table 2. Bond distances and bond angles are in good agreement with standard values.



8

The coordinates of all other atoms were generated by means of a program, Calcor,[12] by assuming: C–H = 1.08 Å, C–C = 1.54 Å, HCC and CCC = 109.5° in the lactone ring and C–H = 1.08 Å, C–C = 1.40 Å, HCC and CCC = 120.0° in the phenyl ring. The starting position was defined by dihedral angle φ C11–C10–C6–C5 equal to 0°. E values were computed by taking into account all the interactions between atoms whose distance depends on φ, which was varied from 0° to 180°, taking account of the phenyl ring symmetry, with increments of 5°. The behaviour of E as a function of φ is shown in Fig. 3 for **6a** and **6b** and in Fig. 4 for **7a** and **7b**. On inspecting the corresponding curves, it is clear that conformers **6a** and **7a** are energetically favoured with respect to **6b** and **7b** in the solid state. Table 3 summarizes the results of calculations.

The distances from C9 to the plane and to the axis of the benzene ring are practically the same in both **6a** and **7a**. Then, the difference in chemical shift between the two methyl singlets arises from their being axial and equatorial, respectively, to the lactonic ring. We then assigned *trans* structure **7** to the lactone with signals at 1.58δ (s) and 1.10δ (d) and *cis* structure **6** to the lactone with signals at 1.73δ (s) and 0.85δ (d).

Stereochemistry of Grignard reactions. Grignard reactions were carried out (a) in THF with RMgCl at 60°, (b) in benzene with RMgI at 25°, and (c) in Et_2O with RMgI at 25°. R = Ph in reactions with **4** and R = Me in reactions with **5**. Conditions (a) and (b) are those for which the extreme differences were reached in the stereospecificity for keto ester 1.[4]† Reaction yields were determined using a GLC standard (Exp. part) whereas ratios **6**/**7** were determined by NMR. We found very reproducible **6**/**7** ratios, although reactions yields varied from run to run. The sum **6** + **7** + starting product was always in the range 89–97%. Table 4 collects our results together with those

†Grignard reactions in benzene at 60° and 25° show very small differences in the ratios **6**/**7** but those at 60° produce a more complex reaction mixture containing variable amounts of unsaturated acids. This behaviour parallels the results for keto ester 1.[4]

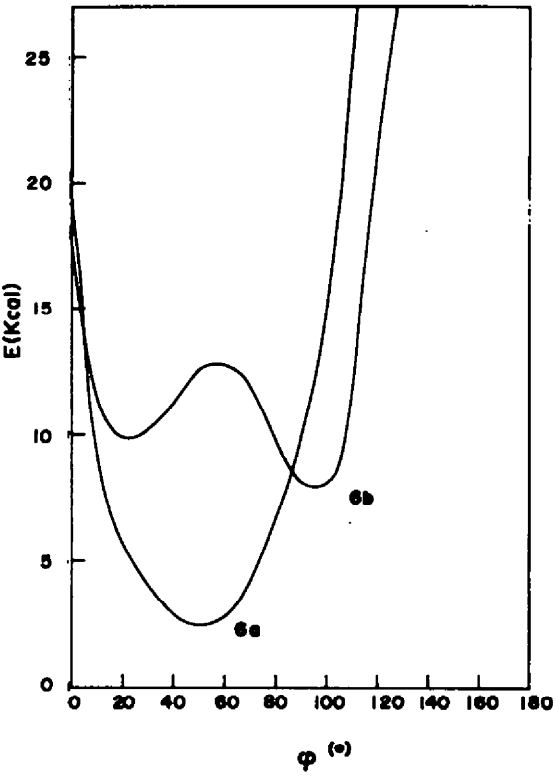


Fig. 3. Intramolecular potential energy E vs dihedral angle φ for **6a** and **6b**.

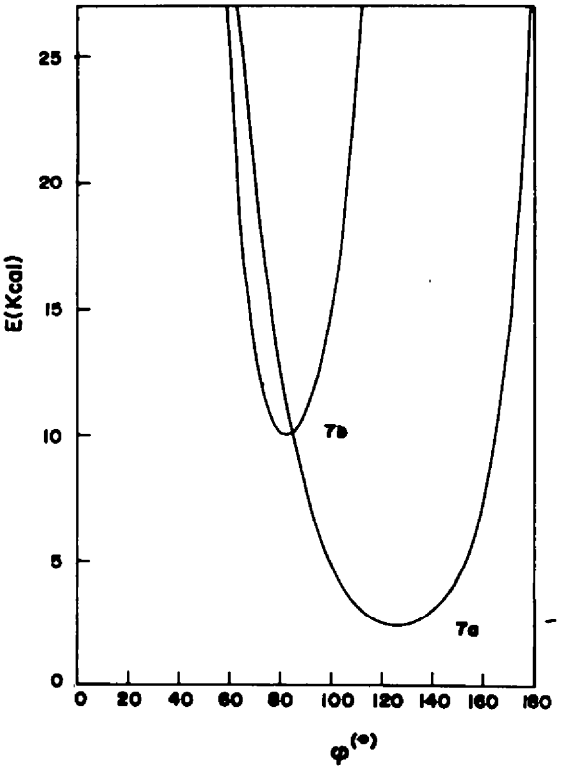


Fig. 4. Intramolecular potential energy E vs dihedral angle φ for **7a** and **7b**.

Table 3. Distances of C8 and C9 to the plane and to the axis of the benzene ring for **6a**, **6b**, **7a**, **7b** in conformations corresponding to potential energy minima designated by φ_m

formula	φ_m(°)	E (Kcal)	Distances (A°)† to the Ph plane C8	Ph plane C9	Ph axis C8	Ph axis C9
6a	50	2.4	1.04	1.68	5.44	3.56
6b	95	7.8	2.16	1.01	3.41	3.81
7a	130	2.4	2.79	1.69	2.80	3.55
7b	85	10.1	2.15	1.10	3.21	3.78

†Computed from the centre of hydrogen atoms on C8 and C9.

Table 4. Stereochemical product ratios for Grignard reactions of keto ester 4 with PhMgX and of keto esters 5 and 1 with MeMgX

Solvent	X	Ratios 6/7 R_1 = Me† R_2 = Ph†	Ratios 6/7 R_1 = Ph† R_2 = Me†	Ratios 2/3‡
C_6H_6	I	0.30	1.23	1.3
Et_2O	I	0.35	0.83	2.5
THF	Cl	0.48	0.70	14.4

†Eqn (2).
‡Ref. 4.

relative to keto ester 1.[4] Each result is the mean value of several runs.

†In these conditions Grignard reactions on α-methyl and α-n-propyl cyclohexanones are more stereospecific giving ratios axial/equatorial = 4.6 and 3.4 respectively for the two isomeric alcohols.[5]

‡An analogous change in steric direction has been described by Collins *et al.*[1] They attributed this change to different rotamers of the rigid cyclic intermediate.

§If it is supposed, that in the hydrocarbon solvent the ester group preferentially interacts with the keto group from the equatorial side it can also be explained why ketoester 1 gives less stereospecific Grignard reactions than α-methyl-and α-n-propyl cyclo-hexanones do in the same conditions.[5]

DISCUSSION

Compound 7, which is the main product in the reactions with 4 has the two Me groups (i.e. the substituents preexisting to the Grignard reaction) *trans* to each other. The corresponding atoms in lactone 2, that is the two methylene groups joining the lactone ring to the rest of the molecule, are instead *cis* to each other. This comparison leads to the conclusion that 1 and 4 react with largely opposite stereochemistry, which means that the geometry of the transition state of Grignard reactions from 4 is inacessible to keto ester 1 at least for reactions in THF. Nevertheless, this comparison also reveals a kind of continuity in the variations: stereospecificity is low (2/3 = 1.3) for reactions of 1 in benzene with MeMgI†, it increases when reactions are made in Et_2O with MeMgI (2/3 = 2.5) and again increases for reactions in THF with MeMgCl (2/3 = 14.4). In the last solvent for reactions with PhMgCl stereochemistry is reversed (6/7 = 0.48) for keto ester 4‡, which reaches the maximum stereospecificity when reactions are performed in benzene with PhMgI. Reactions in diethyl ether with PhMgI lie in between. The results in general suggest a high sensitivity to reaction conditions which excludes cyclic transition states having both functional groups coordinated by the metal atom; rather, this sensitivity indicates less energetic intramolecular interactions varying with reaction conditions.

Inspection of models shows that owing to the distance existing between the two functional groups of a δ-keto ester it is possible that they interact. When, as in our case, with compounds 4 and 5 the molecules are not symmetric this interaction can favour one of the two diastereoisomeric transition states. We believe that this applies to reactions in less polar solvents. In a polar solvent the equilibrium might shift towards transition states in which the two functional groups with their solvent cage are remote from each other. For keto ester 1.§ Fig. 5 tentatively represents a way for this phenomenon to occur in terms of equatorial (a)⇌skew boat (b)⇌axial (c) equilibrium.

This conformational change is accompanied by an enhancement of steric crowding on one side of the molecule with respect to the other and, since the direction of preferential attack remains unchanged (see arrows), this turns out in a higher stereospecificity.

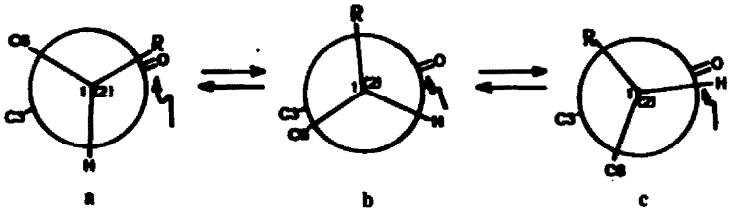


Fig. 5. Newman projections along bond C1, C2 of keto ester 1 (R = $(CH_2)_2CO_2Me$).

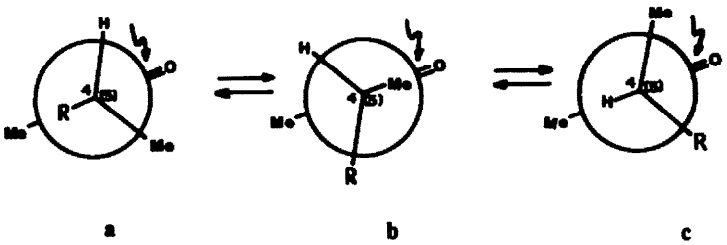


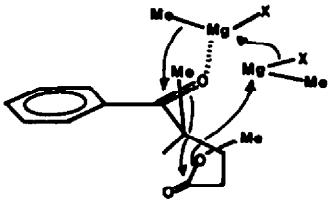
Fig. 6. Newman projections along bond C4, C5 of keto ester 4 (R = $(CH_2)_2CO_2Me$).

On the other hand, ketoester 4 (Fig. 6) has no restriction to rotation about CO–C_α bond imposed by the existence of a ring so that in the polar solvent the lower transition state might correspond to conformation a with a consequent change in steric direction of attack (see arrows). In the hydrocarbon solvent again the two polar groups tend to approach each other. Owing to Me/Me skew interactions, conformations b and c in Fig. 6 are likely to be less energetic than those attainable from conformation a by a clockwise rotation of the atom C4. Thus no changes in steric direction are expected and the stereospecificity can be higher, as observed, since one side of the keto group is protected by the ester group.

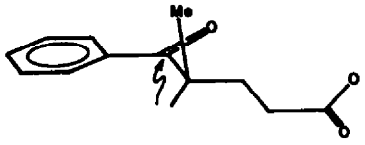
If the above is a correct interpretation of the experimental data, it is reasonable to think that lactone 2, at least for reactions in THF with MeMgCl is mainly formed by axial attack to the axial conformer of 1.

Data pertaining to ketoester 5 (Table 4 R_1 = Ph, R_2 = Me) show a change in steric direction with changing reaction conditions. They can be interpreted much in the same way as before: in this case rotation about the CO–C_α bond is very restricted by the interaction between the aromatic ring protons and the C_α alkyl substituents and this might be one reason for the change in steric direction.

We believe that structures **5a**† and **5b** can represent the preferred conformations for transition states of 5 in benzene and in THF respectively. Clearly, they predict a change in steric direction of attack (see arrows).



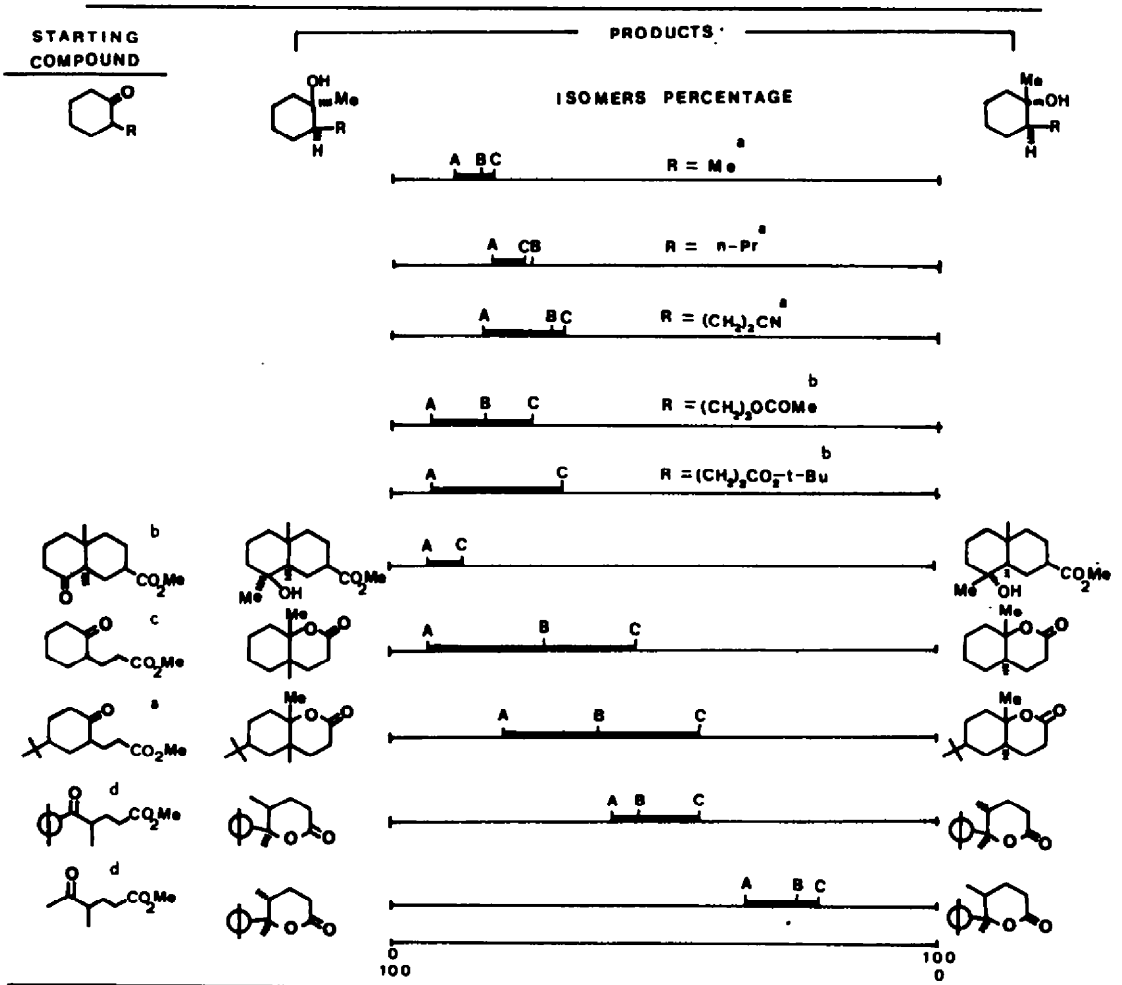
5a



5b

†We are suggesting structure **5a** for transition state of reactions in benzene since in these conditions, conformationally mobile δ-ketoesters react faster, in Grignard reactions, than their rigid analogues.[13]

Table 5. Percentages of diastereoisomers obtained from Grignard reactions conducted in THF with RMgCl (A), in Et_2O (B) and in benzene (C) with RMgI



[a]Ref. 5; [b]Ref. 13; [c]Ref. 4; [d]This paper.

The present data, those of our previous studies[4,5] and some yet unpublished results are summarised in Table 5; here the left hand end of each thick line (A) represents the percentage of the two diastereoisomers resulting from reactions in THF with RMgCl whereas the right hand end limits (C) represents the percentages of the same diastereoisomers from reactions in benzene with RMgI. The intermediate mark (B) refers to reactions conducted in Et_2O with RMgI. It appears that changes in reaction conditions have parallel effects on all the substrates examined so far with the exception of point *B* for α-n-propyl cyclohexanone. On the ground of Table 5 it is possible to deduce the following generalization: the percentage of the diastereoisomer in which the newly introduced group and the hydrogen on the asymmetric C_α are *trans* increases in going from reactions performed in THF with RMgCl to reactions in benzene with RMgI. (It is likely that this generalization is not valid for reactions with cyclic or dipolar models.)

This generalization could be useful when the structures of products from Grignard reactions are not easily deduced from their spectral properties: lactones **6** and **7** represent a typical example of this kind.

EXPERIMENTAL

IR spectra were recorded using a Perkin Elmer Infracord 257 spectrophotometer.

NMR spectra were recorded on a Jeol JNM-C-60 HL.

MS were recorded on AEI MS 12: the relative intensities of the peaks (in parenthesis) are referred to the most intense one taken as 100%.

GLC–MS were recorded on the same instrument (AEI MS 12) coupled to a Varian 1400 gaschromatograph.

GLC analyses were carried out on a Carlo Erba Fractovap G1 apparatus using a 2 m, 2 mm i.d. column packed with 2% OV 17 on silanized Chromosorb W 80–100 mesh.

The GLC analysis conditions were $T_{det} = T_{inj} = 230°$; N_2 flow = 26 ml/min; oven temperatures: initial linear program from 130° to 200° in 10 min in analysis of mixtures from **4**; $T_{oven} = 200°$ in analysis of mixtures from **5**.

Starting materials. Compound **4** was syntesised using the method of Baumgarte and Eifert.[14] Compound **5** was synthesised by the method described.[15] Mg turnings (Grignard grade) from Carlo Erba were used.

Purification of solvents. Ether, THF and benzene were distilled from Na wire and then from LAH directly into the flask in which they were to be used.

Preparation of Grignard reagents. Grignard reagents in Et_2O and THF were prepared directly in these solvents in the usual way from Mg turnings and the proper methyl or phenyl halide.

In the preparation of MeMgCl in THF the flask was equipped with a dry-ice acetone condenser during the Mg dissolution and MeCl was dried by passing it through a $CaCl_2$ column.

Grignard reagents in benzene were prepared by the solvent-substitution method, i.e. the ether solns were evaporated to dryness and then an equal volume of dry benzene was added, evaporated and added again.

Ppts were allowed to settle and the supernatant clear liquid was titrated by the Zerewitinoff method[16] for methyl Grignard reagents and by the acid titration method[17] for phenyl Grignard reagents.

Aliquots of these stock solns were withdrawn and diluted (in the dropping funnel) with the same solvent to 0.05 + 0.1 M concentrations just before Grignard reactions.

Grignard reactions. All reactions were carried out under pure N_2; those in Et_2O and benzene at 25°, those in THF at 60°. Typically: a soln of the Grignard reagent of the above mentioned concentration (4.0 mmol) in the chosen solvent was added dropwise to a rapidly stirred soln of 3.0 mmol of **4** or **5** dissolved in 30 ml of the same solvent.

Reactions in benzene and Et_2O were interrupted after 10 min and those in THF after 60 min, both by adding a sat. soln of NH_4Cl.

A weighed amount of n-heptadecane was added at this point as GLC standard to the mixtures of **4**. n-Hexadecane was used for the same purpose in the reactions of **5**. Reaction mixtures were then extracted with diethyl ether; solns washed with water were combined, dried over Na_2SO_4, filtered and evaporated. The residue was analysed by GLC to measure the total material balance **6** + **7** + starting material and by NMR to determine the **6**/**7** ratios: for this purpose we measured the height of singlets at 1.73δ and 1.58δ which have the same half band width as measured at 108 cycles sweep width on a pure lactonic fraction.

Lactonic fraction isolation. 1 g of a mixture from **4** was chromatographed on silica gel (R = 100) using hexane/diethyl ether, 2:1 as eluant. 25 ml fractions were collected. Fractions 40–50 contained lactones **6** + **7** as a colourless viscous oil which distilled at 95° (external temp.) at 0.1 mm Hg.

NMR spectra in CCl_4 (and in benzene-d_6) showed the following peaks δ: 7.31(7.14) sharp; 7.28(7.14) sharp: 2.65–1.90(2.5–1.9) multiplet; 1.73(1.40) s; 1.58(1.27) s; 1.10(0.60) d, J = 6.9 cps; 0.85(0.46) d, J = 6.9 cps.

MS spectra: *m/e* 44(31%); 56(93); 77(27); 84(41); 105(100); 121(52); 161(15); 189(21); 204(32); 205(4).

IR spectra showed ν_{max}^{film} cm^{-1}: 3080 w, 3050 w, 3020 w, 2960 m, 2925 m, 2870 m, 1725 s (at 1740 cm^{-1} in CCl_4†), 1600 w, 1490 m, 1455 sh, 1445 m, 1415 w, 1380 m, 1370 sh, 1345 sh, 1325 m, 1290 sh, 1250 s, 1210 sh, 1190 w, 1170 sh, 1155 m, 1115 sh, 1105 m, 1085 m, 1060 m, 1030 m, 1005 m, 1000 m, 975 m, 915 w, 905 w, 890 w, 875 w, 825 w, 790 w, 765 s, 705 s.

Found: C, 76.2; H, 7.8. $C_{13}H_{16}O_2$ requires: C, 76.44; H, 7.90%.

Similarly reaction mixtures from **5** (1 g.) were purified by chromatography on silica gel (R = 100) using benzene as eluant. 50 ml Fractions were collected. Fractions 28–43 contained **6** and **7** as shown by GLC, IR, NMR and MS comparison.

Acknowledgements—We wish to thank Professors E. Giglio and A. L. Segre for helpful discussions and Messrs L. Palombini, A. C. Russo and L. Turrio Baldassarri for technical assistance.

REFERENCES

[1]J. H. Stocker, P. Sidisunthorn, B. M. Benjamin and C. J. Collins, *J. Am. Chem. Soc.* **82**, 3913 (1960).
[2]D. J. Cram and D. R. Wilson, *Ibid.* **85**, 1245 (1963).
[3]T. J. Leitereg and D. J. Cram, *Ibid.* **90**, 4019 (1968).
[4]G. Di Maio, M. T. Pellegrini and P. A. Tardella, *Ric. Sci.* **38**, 234 (1968).
[5]G. Di Maio, M. T. Pellegrini and P. A. Tardella, *Ibid*, **38**, 240 (1968).
[6]E. C. Ashby and J. T. Laemmle, *Chem. Rev.* **75**, 521–46 (1975); and refs cited.
[7]S. M. McElvain and R. B. Clampitt, *J. Am. Chem. Soc.* **81**, 5590 (1959).
[8]K. K. Cheung, K. H. Overton and G. A. Sim, *Chem. Com.* 634 (1965).
[9]N. V. Pavel, C. Quagliata and N. Scarcelli, *Z. Kristallogr.* **144**, 64 (1976).
[10]R. Roques, N. Chezan and J. Lapasset, *Acta Cryst.* B **32**, 1885 (1976).
[11]*IUPAC, Nomenclature of Org. Chem.*, Section E, Stereochemistry, rule E-5.4.
[12]E. Gavuzzo, S. Pagliuca, V. Pavel and C. Quagliata, *Acta Cryst.* B **28**, 1968 (1972).
[13]Unpublished results.
[14]H.E. Baumgarten, R. L. Eifert, *J. Org. Chem.* **18** 1177–82 (1953).
[15]R. Bertocchio, J. Dreux, *Bull. Soc. Chim.* Fr. 823–7 (1) (1962).
[16]Zerewitinoff, *Ber. Dtsch. Chem. Ges.* **40**, 2023–31 (1907).
[17]Kharasch and Reinmuth, *Grignard Reactions of Non-metallic Substances*, p. 94. Prentice Hall, New York (1954).
[18]R. N. Johnson and N. V. Riggs, *Aust. J. Chem.* **24**, 1643 (1971).

†Johnson and Riggs[18] already described this shift of δ-lactonic band in going from CCl_4 solution to solid phase (Nujol).