

ALKYLATION OF  $\delta$ -KETOESTERS : A MECHANISM CHANGE DEPENDING ON CONFORMATIONAL MOBILITY AND SUBSTITUENT EFFECTS ON STEREOSELECTION.

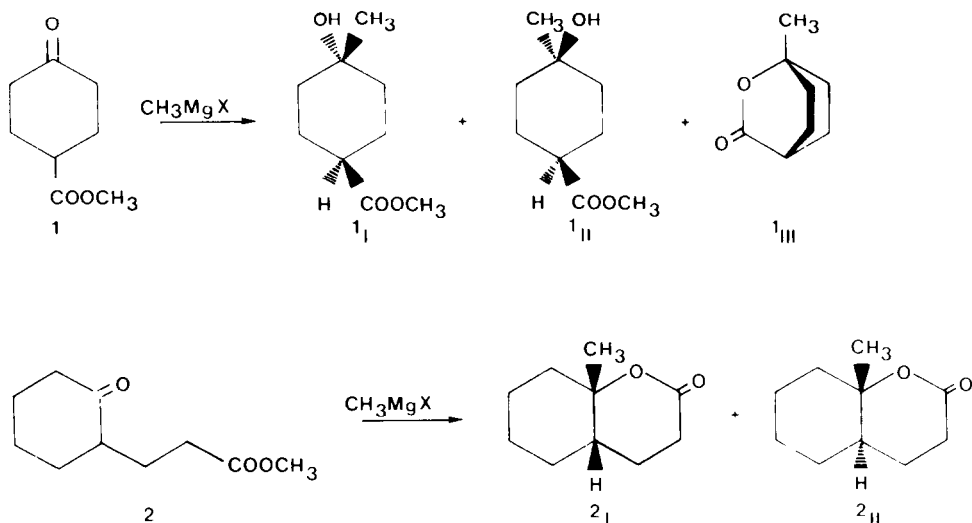
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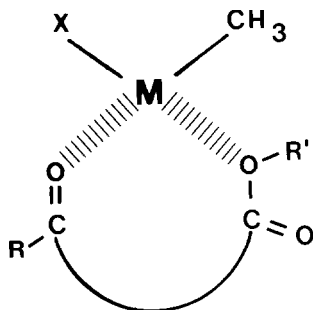
SUMMARY: Kinetic evidence shows that the two groups of a  $\delta$ -ketoester can interact in the transition state of a Grignard reaction. This promotes high stereoselectivity by chiral center far from the ketonic group and produces good correlations between stereoselection and electronic effects of substituents.

Considerable attention has been focused in recent years on the study of the control of stereochemistry during carbon-carbon bond formation. We are currently searching for reaction conditions which could promote interactions between the two functional groups of conformationally mobile  $\delta$ -ketoesters as a basic synthetic strategy to stereoselection in alkylation reactions at the carbonyl group <sup>1,3</sup>. In fact such interactions may either modify the stereoselectivity usually produced by a preexisting chiral center at the reaction site, or promote stereoselection when the chiral center is far from it and close to the ester group. Reactivity measurements, carried out on  $\delta$ -ketoesters of different conformational mobility, suggest interactions occurring through complexation of a molecule of the alkylating agent by the two functional groups. The present communication gives an example of this kind, indicating that  $\delta$ -ketoesters 1 and 2, differing from one another in conformational mobility, do not have the same reaction order in Grignard reactant when reactions are carried out in  $C_6H_6$  with  $CH_3MgI$ , and that the reaction order is the same for reactions in THF with  $CH_3MgCl$ . The relative reactivities of compounds 1 and 2 have been measured at 25°C in competitive reactions on equimolecular mixtures of them (total ketonic conc. .05 M) using three different concentrations of the added Gri-

gnard reagent (0.5 , 0.1 , 0.01 M). The results have been obtained by GLC determination of the reaction yield.<sup>4</sup> The relative reaction rates  $k_1/k_2$  , computed hypothesizing that reactions are first order in ketone both for 1 and 2 , were 11.7 , 11.2 , 11.8 in THF and 1.7 , 1.4 , 0.8 in  $C_6H_6$ .



The systematic decrease of the relative rate of compound 1 with respect to 2 as the concentration of the added reactant is lowered (reactions in  $C_6H_6$ ), indicates an higher reaction order for 1. We recently showed<sup>3</sup> that the ester group of compound 1 complexes a molecule of Grignard reactant when reactions are performed in  $C_6H_6$ . Since the ester group of compound 2 should have the same ability in complexing a molecule of Grignard reactant, our explanation for the difference in the reaction order is that in an early step of the alkylation sequence a molecule of the Grignard reactant complexes together the ester and the keto group in a cyclic intermediate (representable as in Fig.) which then evolves to the end products. Such a complex is forbidden for compound 1 owing to its higher conformational restrictions.



Stereochemistry of Grignard reactions on 2-methyl, 5-oxo 5-phenyl methyl pentanoate  $\underline{3}$ <sup>5</sup> both confirms the above kinetic results and indicates useful applications. Lactones  $\underline{3}_I$  and  $\underline{3}_{II}$  are the only reaction products, and their ratio  $\underline{3}_I/\underline{3}_{II}$  is equal to 1 in THF with  $\text{CH}_3\text{MgCl}$ . This ratio raises to 2.3 in  $\text{C}_6\text{H}_6$  with  $\text{CH}_3\text{MgI}$ . As far as we know this figure represents the higher stereoselection produced by a chiral center three  $\sigma$  bonds away from the reacting site.



Results in THF point to a complete absence of interactions, whereas those in  $\text{C}_6\text{H}_6$  indicate that the chiral center has been carried close to the keto group by the complexation phenomenon depicted in Figure.

Interestingly, when the alkylation was carried out with  $\text{CH}_3\text{Li}$  in  $\text{Et}_2\text{O}$ , the ratio  $\underline{3}_I/\underline{3}_{II}$  was reversed (0.67), suggesting that the geometry of the complexation phenomenon depends on the nature of the alkylating agent.

Moreover in the last reaction condition, the extent of the complexation phenomenon depends on the electronegativity of the Z ring substituent in compounds  $\underline{4}$ <sub>(a-h)</sub>. These, in fact, give lactones  $\underline{4}_I$ <sub>(a-h)</sub> and  $\underline{4}_{II}$ <sub>(a-h)</sub> in the ratios reported in Table I. For  $\underline{4}$ ,  $\underline{4}_I$ ,  $\underline{4}_{II}$ : Z = p- $\text{CH}_3$  (a); H (b); m- $\text{OCH}_3$  (c); p-F (d); p-Cl (e); p-Br (f); m-Br (g); m-CN (h)<sup>6</sup>.

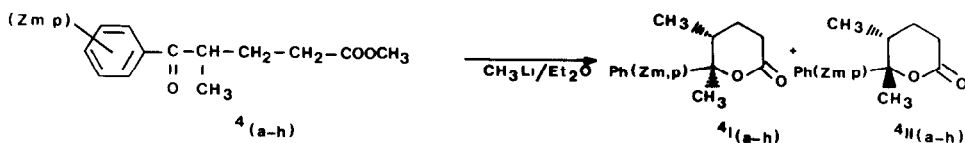


Table I : Stereochemical ratios  $\underline{4}_I$ <sub>(a-h)</sub>/ $\underline{4}_{II}$ <sub>(a-h)</sub> obtained in alkylation reactions on  $\underline{4}$ <sub>(a-h)</sub> with  $\text{CH}_3\text{Li}$  in  $\text{Et}_2\text{O}$ .

Substituent Z	p- $\text{CH}_3$	H	m- $\text{OCH}_3$	p-F	p-Cl	p-Br	m-Br	m-CN
$\underline{4}_I$ <sub>(a-h)</sub> / $\underline{4}_{II}$ <sub>(a-h)</sub>	1.60	1.67	1.70	1.80	2.02	1.97	2.14	2.38

A plot of  $\log \underline{4}_I$ <sub>(a-h)</sub>/ $\underline{4}_{II}$ <sub>(a-h)</sub> vs Hammett  $\sigma$ 's has  $\rho = 0.25$  (correlation coefficient = 0.97) : to the best of our knowledge this is the first example in which a change in acyclic stereoselection correlates with the electronegativity of the substituent which, owing to the folding up phenomena, is able

to modify the rotamer population in the transition state.

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References:

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- (4) For the isolation and identification of compounds  $1_I$ ,  $1_{II}$  and  $1_{III}$  see ref. (3);  $2_I$  and  $2_{II}$ : Di Maio, G.; Pellegrini, M.T.; Tardella, P.A.; Ric. Sci. 1968 38 229-234.
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- (6) The characterization of lactones  $3_I$  and  $3_{II}$  and the synthesis and characterization of compounds ( $4_I$ ,  $4_{II}$ )<sub>c,g,h</sub> to be described in a full paper. For the synthesis and characterization of compounds ( $4_I, 4_{II}$ )<sub>a,b,d,e,f</sub> see: Delfino, M.; Lociuoro, S.; Vecchi, E.; Zeuli, E.; Tetrahedron 1982 (to be published).

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