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DIASTEREOSELECTIVE SPIROANNELATION

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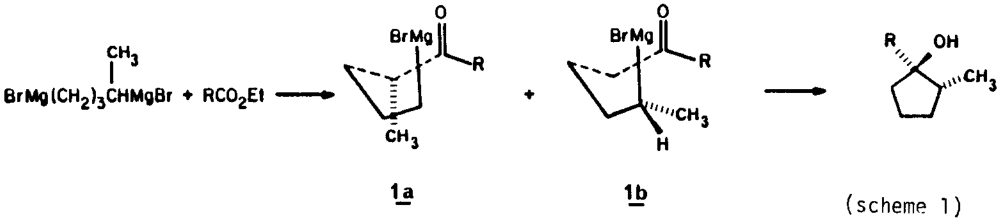
Summary. The diastereoselection in the reaction of 1,4-di-(bromomagnesio) pentane with various structures of lactones and cyclic anhydrides is described.

Recently, we have found that carboxylic acid esters are converted in good yields to the corresponding trans-2-methyl-1-substituted cyclopentanols, by reaction of 1,4-di(bromomagnesio)pentane in THF solution[1] (shceme 1).

Continuing our research in the reactions of various primary-secondary di-Grignard reagents with carboxylic acid esters, we also observe that the trans-OH diastereoisomer is preferentially formed. On the other hand, 1,4-di(bromomagnesio)pentane as well as 1,4-di(bromomagnesio)-octane leads to the formation of the same diastereoisomer[2].

In order to explain this diastereoisomer distribution, we suggest that the secondary Grignard reagent is more reactive that the primary Grignard reagent. Consequently, the intermediate 1a is more favoured than the intermediate 1b.



(scheme 1)

In the present communication, we report results concerning the influence of steric effects of the functional group (y, 2a) on the cyclization step involving an intramolecular nucleophilic addition. Thus we selected various structures of bifunctional compounds such as lactones, cyclic anhydrides and other similar compounds (1-6), in order to study the diastereoisomer distribution after hydrolysis of 3a and 3b (scheme 2).

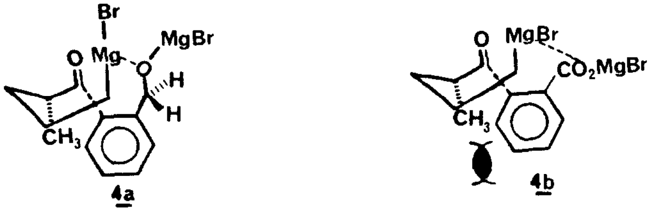


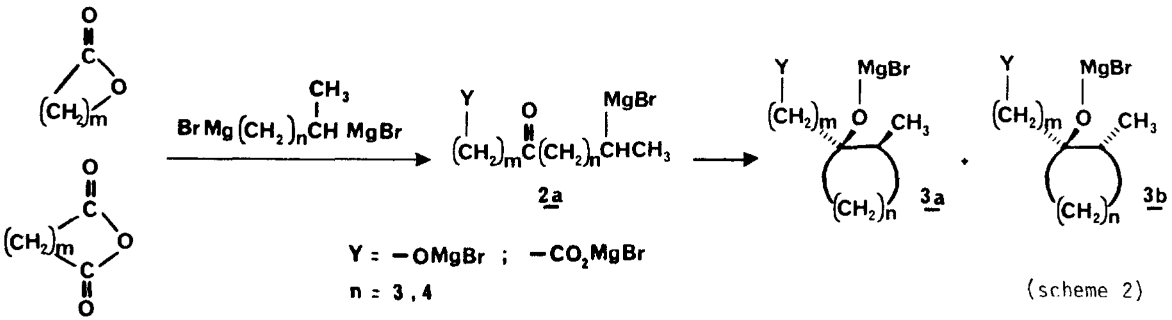
Figure 1

The choice of lactones and cyclic anhydrides allows comparison between the carboxylate and the alcoholate group. Finally, the reactions with heterocyclic compounds 2 and 6 enable a general study of this reaction[3].

The proposed methodology involves the addition of one equivalent of aromatic lactone[4] or aromatic dicarboxylic anhydride to one equivalent of 1,4-di(bromomagnesio)pentane in THF solution in order to study the influence of the existing functional group on the diastereoisomer distribution.

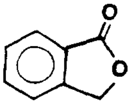
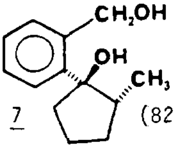
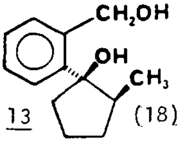
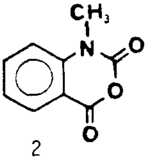
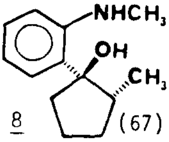
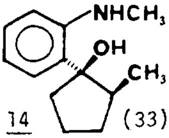
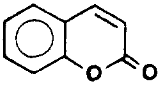
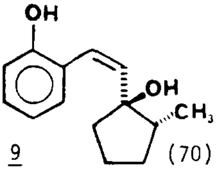
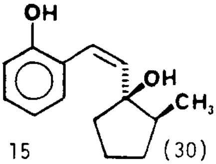
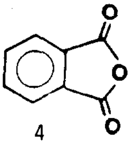
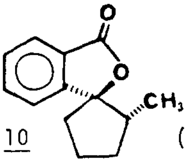
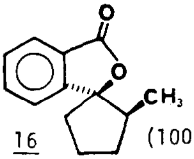
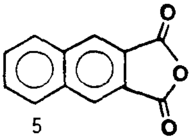
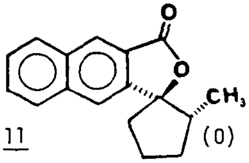
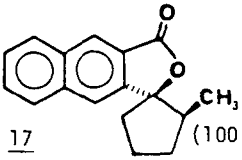
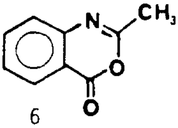
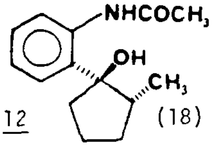
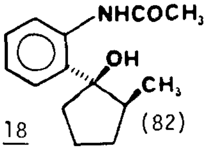
As may be gathered from table 1, this reaction showes widely different product distribution in THF. Briefly, compounds 1, 2 and 3 give mainly the trans-OH diastereoisomer whereas compounds 4, 5 and 6 give mainly the Cis-OH diastereoisomer.

These results are in contrast with those from the corresponding carboxylic acid esters. We present one possible explanation based on the structures of the intermediates formed by the reactions of phthalide and phthalic anhydride with 1,4-di(bromomagnesio)pentane.



(scheme 2)

Table 1: Reactions of 1,4-Di(bromomagnesio)pentane. Diasterioisomer Distribution[5].

Starting compound	Yield[6] (%)	*Trans*-OH Isomer (%)	δ (CH_3) ppm	*Cis*-OH Isomer (%)	δ (CH_3) ppm
 1	85	 7 (82)	0.48	 13 (18)	0.96
 2	70	 8 (67)	0.40	 14 (33)	0.97
 3	55[7]	 9 (70)	0.89	 15 (30)	0.99
 4	70	 10 (0)	-	 16 (100)	0.72
 5	65	 11 (0)	-	 17 (100)	0.73
 6	90	 12 (18)	0.41	 18 (82)	0.99

Furthermore, since there was no detectable amount of the corresponding ketoacid or hydroxyketone after hydrolysis, it follows that the cyclization step is faster than that of the first attack of the carbonyl of lactones or cyclic anhydrides. Accordingly, we suggest that the stereoselectivity of those reactions must reside in the cyclization step of the second nucleophilic attack of the 5-oxoalkyl Grignard reagent. The secondary Grignard[8] may be responsible for the first reaction with the carbonyl of each substrate (1-6). Consequently, isomer distribution is evidence of the structural geometric requirements for the annelation step (4a and 4b) where chelation of oxygen to magnesium occurs (figure 1).

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References and Notes.

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2. Results from thesis of M. Bernatchez submitted to the Université Laval (1987).
3. P. Canonne, R. Boulanger, B. Chantegrel, Tetrahedron, 43, 663 (1987).
4. P. Canonne and D. Bélanger, J. Org. Chem., 46, 3091 (1981).
5. Ratios of diastereoisomers determined by ^1H NMR.
6. Isolated product. All new compounds described here showed reasonable phenyl patterns in ^1H and ^{13}C spectroscopy and correct elemental analyses.
7. It was observed that the yield of the reaction of RMgX with coumarin 3 are generally low:
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   b) M. Abou-Assali, J. Roger, J. Dreux, Tetrahedron, 32, 1661 (1976).
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