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Reactions of β-Lactones with Lewis Acids: Ring Enlargement Versus β-Elimination

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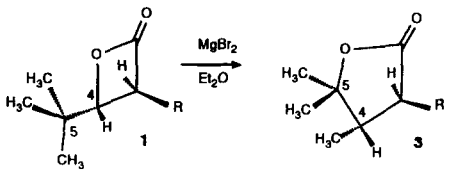
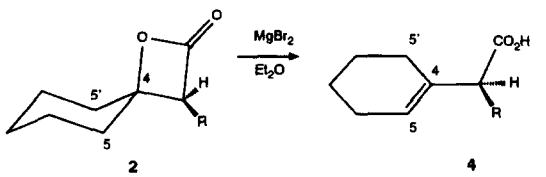
Abstract: *On treatment with $MgBr_2$ the β-spirolactones **7** and **10** undergo ring enlargement to the γ-lactones **8** and **11**, whereas the β-spirolactones **13** show diastereoselective β-elimination to form the β,γ-unsaturated acids **14**. The Lewis acid influence on the migratory aptitude of Me versus H is studied for β-lactone **18**.*

As we found more than ten years ago, β-lactones undergo two types of reaction on treatment with anhydrous $MgBr_2$ (*Scheme 1*): ring enlargement (type A)[1] and β-elimination (type B)[2,3]. Later it was claimed by Black[4,5] that the substitution at C-4 determines the reaction type: β-lactones with secondary C-4 (such as **1**) follow type A and those with a tertiary C-4 (typically spirofused lactones such as **3**) follow type B. We now report that Black's assertion is not correct; additionally some other interesting mechanistic details of A and B type reactions are communicated.

Type A Ring Enlargement

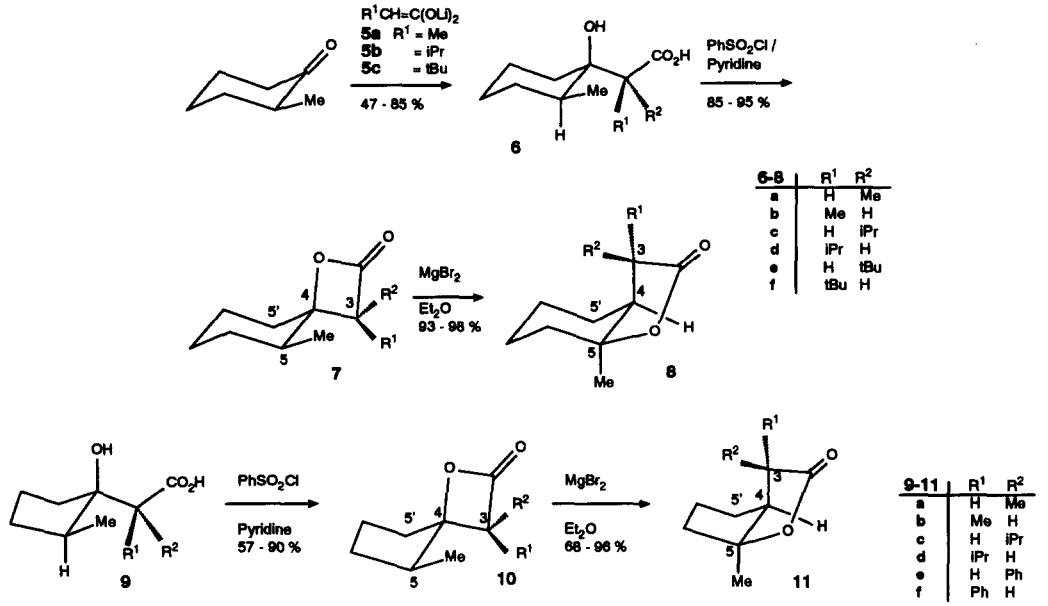


Type B β-Elimination



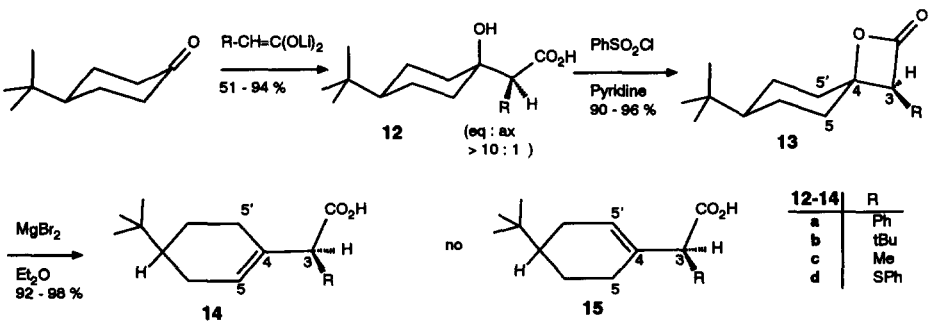
Scheme 1: Reactions of β-Lactones with $MgBr_2$

As a test case for Black's hypothesis spirolactones **7**, **10** and **13** were prepared (*Schemes 2 and 3*). The addition of the dilithiated carboxylic acids **5a-c** to 2-methylcyclohexanone proceeded with high (> 95 %) equatorial selectivity. With respect to the relative position of R^1/R^2 a significant stereoselection was observed (**6a** : **b** = 2 : 1, **6c** : **d** = 5 : 1 and **6e** : **f** = 4 : 1). The epimeric mixtures were cyclized to β-lactones **7**, which were separated by chromatography. If Black's hypothesis were correct, **7a** - **f** should undergo β-elimination under treatment with $MgBr_2$. Instead, clean ring enlargement to **8** was observed. The structure of **8** followed from the IR and ^1H NMR spectra (*Table 1*). Most remarkable is the downfield shift of the ring-methyl (ca. 0.4 ppm) of **8** compared to **7**. The configuration at C-3 can be deduced from the $J_{3,4}$ - values (11 - 12 Hz for the diaxial H in **8b, d, f**) and the downfield position of the endo-3-H in **8b, d, f** compared to **8a, c, e**). The ring enlargements **7** -> **8** proceeded in > 90 % yield. Similar results were obtained in the cyclopentanone series **9** - **11**. Again only the "equatorial" β-hydroxy acids were formed as epimeric mixtures of **9ab**, **9cd** and **9ef** with low selectivities (e.g. **9a** : **b** = 2 : 1).

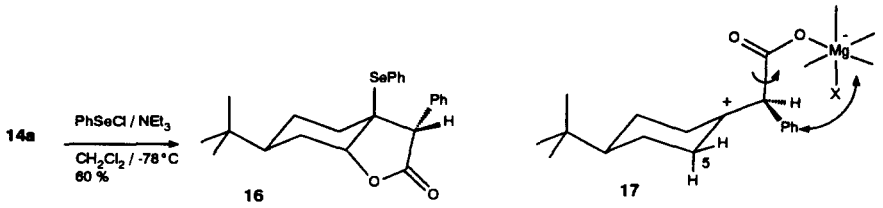


Scheme 2: Synthesis and Ring Enlargement of Spirofused β-Lactones 7 and 10 with $MgBr_2$ in Diethyl Ether

This means that Black's hypothesis has to be corrected to the effect that it is both the 4- and the 5-position of the β-lactone that determine the reaction type. *Only if C-4 is tertiary and both C-5 positions are secondary, β-elimination occurs.* As an additional testcase spirolactones **13** were prepared as shown in Scheme 3. The hydroxy acids **12** were formed with > 10 : 1 -equatorial selectivity. In **13** the 5- and 5'-positions are diastereotopic. Quite remarkably, the β-elimination proceeded with high (> 95 %) selectivity in favor of 5-H to generate **14** as the sole product. Although **14a** - **c** were crystalline no suitable crystals for X-ray crystal structure determination were obtained. Therefore, **14a** was converted into **16** (via a diaxial anti-Markownikoff selenolactonisation[6] - *Scheme 4*) and this lactone was submitted to an X-ray analysis (*Fig. 1*)[7]. The diastereoselectivity of the β-elimination may be rationalized via transition state **17**; after ring opening the O-$MgBr_2$ moiety is rotated away from the phenyl substituent to release the steric strain. In this way the syn-5-H is removed by the basic oxygen to form **14** selectively.



Scheme 3: Diastereotopos-Selective β-Elimination of Spirofused β-Lactones (13 -> 14)



*Scheme 4: Selenolactonisation of **14a***

Compound	mp [°C]	^{1}H-NMR ($CDCl_3$, TMS)	$J_{3/4}$ [Hz]	IR [1/λ, cm^{-1}]
7a	liquid	1.03 (5-Me); 3.51 (H-3)	-	1820
7b	liquid	1.05 (5-Me); 3.26 (H-3)	-	-
8a	-	1.37 (5-Me); 3.09 (H-3)	7	1760
8b	liquid	1.46 (5-Me); 2.62 (H-3)	11.5	-
10a	liquid	1.04 (5-Me); 3.44 (H-3)	-	1825
10b	liquid	1.07 (5-Me); 3.55 (H-3)	-	-
11a	liquid	1.47 (5-Me); 2.93 (H-3)	9	1760
11b	liquid	1.51(5-Me); 2.93 (H-3)	-	-
13a	125	4.46 (H-3)	-	1805
14a	140	4.22 (H-5); 5.63 (olefinic-H)	-	1792
15a	157	3.98 (H-3); 4.37 (H-5)	-	1765
18	liquid	4.24 (H-4); 4.44 (H-3)	4.5	1825
19	61	2.26, 2.60 (H-4); 4.05 (H-3)	8.5, 11.5	1774
20	62	2.72 (H-4); 3.42 (H-3); 4.42 (H-5)	11	1753
21	liquid	2.19 (H-4); 3.38 (H-3); 4.21 (H-5)	12	1775

*Table 1: Selected Analytical Data of Compounds **7, 8, 10, 11, 13, 14, 16, 18, 19, 20 and 21.***

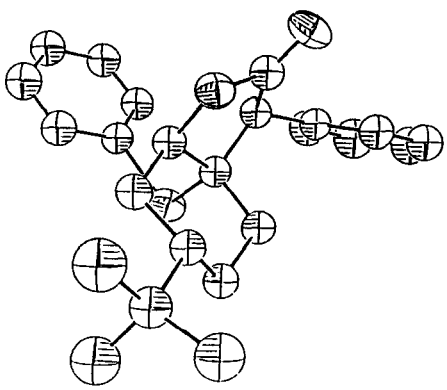
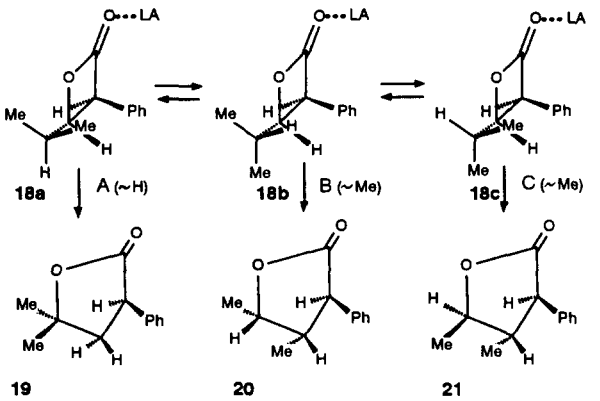


Figure** 1: X-Ray Crystal Structure of **16

An important aspect of the ring enlargement is the relative migratory aptitude of the C-5-substituents, if these are different. It was described earlier[1], that β-lactone **18** undergoes ring enlargement via the reactive conformations **18a - c**; in each conformer the migrating substituent adopts an antiperiplanar arrangement with respect to the C-4-O-1 bond (*Scheme 5*). The influence of the solvent and the Lewis acid (LA) on the relative participation of the pathways A - C was now investigated (*Table 2*). As it turns out the solvent is of minor importance. There is, however, a considerable effect with regard to the Lewis acid. With weak Lewis acids (such as $MgBr_2$) pathway A predominates, whereas for strong Lewis acids (e.g. $AlBr_3$) methyl migration (pathways B and C) significantly gains in importance. This may be interpreted in terms of an interplay of electonic and steric factors. Electronically, the complexation with the Lewis acid lowers the energy of the σ* (C-4-O-1) orbital. This means that for weak Lewis acids the substituent with the highest donating effect, i.e. with the highest σ-orbital, will migrate preferentially. As σ (C-H) has a higher energy than σ (C-C), pathway A is favored. For stronger Lewis acids the electronic effect is no longer so important, and the steric effect, i.e. the relative strain of the conformers **18a - c** gains in emphasis. Conformers **18a** and **b** both have an "inside" methyl group and are thus disfavored with respect to **18c**. This rationalizes the product ratios in the last three runs in Table 2 in which the proportion of **20** + **21** versus **19** is steadily increased.



Scheme 5: Relative Migratory Aptitudes of H and the Diastereotopic Me-Groups (Total Yields of 19 + 20 + 21 > 92%).

Solvent	LA	19	20	21
Et_2O	$MgBr_2$	81	7	12
Toluene	$MgBr_2$	86	4	10
CCl_4	$MgBr_2$	73	9	18
CH_2Cl_2	$MgBr_2$	89	3	8
CH_2Cl_2	$TiCl_4$	74	5	21
CH_2Cl_2	$SnCl_4$	71	6	23
CH_2Cl_2	$FeBr_3$	65	8	27
CH_2Cl_2	$AlBr_3$	36	18	46

Table 2: Influence of Solvent and Lewis Acid (LA) on the Product Ratio 19 / 20 / 21 (5°C).

References and Notes:

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6. Nicolaou, K.C.; Lysenko, Z. *J. Am. Chem. Soc.* **1977**, 99, 3185.
7. (Point Group $P2_{1/c}$, a = 12.0091 ± 0.0051, b = 22.0685 ± 0.0084, c = 16.0596 ± 0.0067 Å; α = γ = 90°, β = 92.493° (± 0.034), V = 4252.13 Å^3, ρ = 1.334 g/cm^3, Rw = 0.0615, Syntex-R-3-Diffractometer, Graphite-Monochromator, SHELLX-Program-System, R = 0.0747, Rw = 0.0648).
   Further details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Centre on quoting the full journal citation.

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