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Addressing the Competition Between Intramolecular Acyl and Beta Ring Cleavage in β- Lactones

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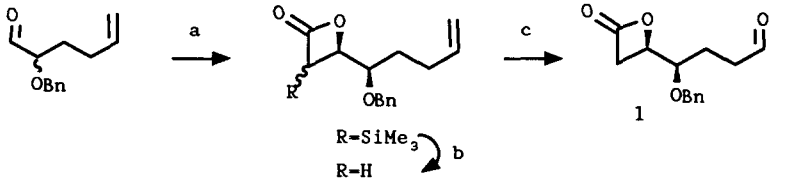
Abstract: A series of β-lactone derivatives containing both acyl- and β-cleavage nucleophiles has been prepared and ring-cleaved. Reaction outcome is both Lewis acid- and structure-dependent. © 1997 Elsevier Science Ltd.

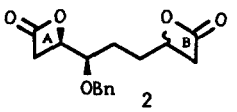
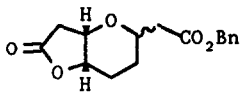
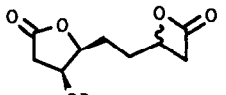
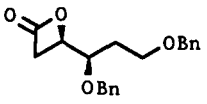
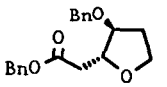
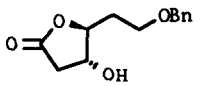
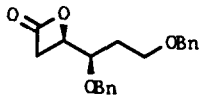
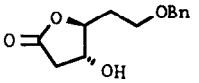
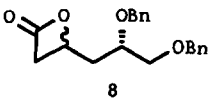
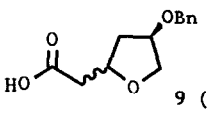
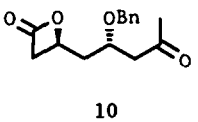
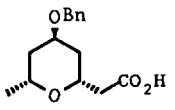
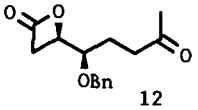
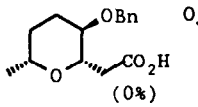
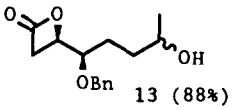
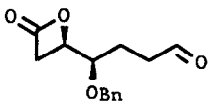
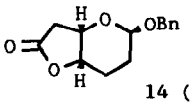
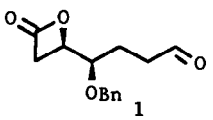
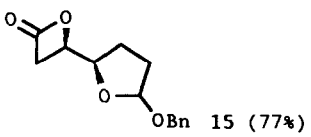
A number of recent studies has focused on Lewis acid mediated intramolecular ring opening reactions of β-lactones by pendant benzyloxy[1,2] and other[3] groups. Depending on the position of the benzyloxy group on the C-4 side chain, either acyl- or β-cleavage can occur. As of this writing, there has been no reported study which has addressed the competition between these two types of reactions. Focusing on this theme, we prepared a series of β-lactone derivatives containing both acyl- and β-cleavage nucleophiles (Table 1).

In most cases, stereoselective β-lactonizations were achieved by chelation-controlled 2+2 cycloaddition of TMS-ketene to the appropriate α- or β-benzyloxy aldehyde using the conditions of Romo and Zemribo.[4] Carbonyl-bearing substrates (see entries 5-8) were prepared from the appropriate enal by 2+2 cycloaddition followed by alkene ozonolysis. The preparation of compound **1** (Scheme 1) is representative. A second, cycloaddition of TMS-ketene to **1** ($BF_3.OEt_2$, -78°C) provided a route to the bis-β-lactone **2** (see entry 1) as a 1:1 mixture of diastereomers.



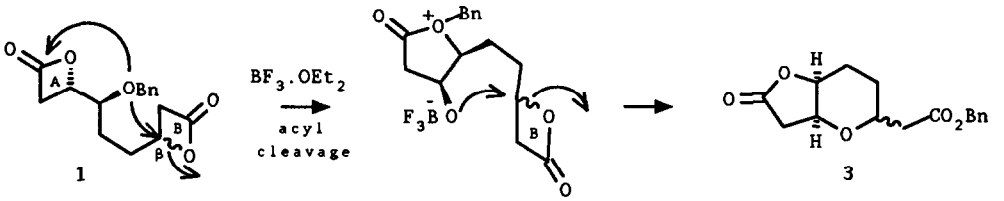
Scheme 1. [a]TMS-ketene, $MgBr_2.OEt_2$, CH_2Cl_2, -60°C; [b]$KF.2H_2O$, CH_3CN (90% 2 steps); [c]O_3, MeOH; Me_2S (73%).

Table 1. Reactions of β-Lactone Derivatives **1**, **2**, **5**, **8**, **10**, and **12**

Entry	Substrate	Conditions[a]	Product(s)/(yield)[b]
1	 2	A	 3 (55%) +  4 (20%)
2	 5	A	 6 (43%) +  7 (41%)
3	 5	B	 7 (86%)
4	 8	C	 9 (77%)
5	 10	D	 11 (70%)
6	 12	D	 (0%) +  13 (88%)
7	 1	A	 14 (56%)
8	 1	E	 15 (77%)

[a]Conditions A: $BF_3.OEt_2$, CH_2Cl_2, -5°C; B: $TiCl_4$, CH_2Cl_2, -78°C; C: $TiCl_4$, CH_2Cl_2, -50°C; D: TMSOTf, Et_3SiH, CH_2Cl_2, -55°C; E: TMSOTf, CH_2Cl_2, -55°C;
[b]All yields refer to purified products.

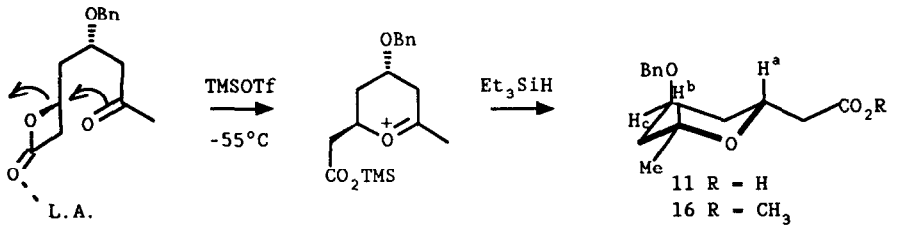
The bis-β-lactone **2** (entry 1) offered an interesting initial study, as the benzyloxy group was positioned to open ring **A** by acyl cleavage, or ring **B** by β-cleavage. On treatment with $BF_3.OEt_2$ in CH_2Cl_2 at ice-bath temperature, a mixture of compounds **3**[5] and **4** was formed. Other Lewis acids gave either no reaction (TMSOTf) or a complex mixture of products ($TiCl_4$). Formation of compound **3** presumably results from a tandem sequence of acyl cleavage of ring **A** followed by β-cleavage of ring **B** (Scheme 2). Benzyl group transfer following step 1 accounts for the minor product, benzyl ether **4**. The inertness of product **4** to $BF_3.OEt_2$ indicated that it is not an intermediate to structure **3**.



Scheme 2

The reason for selective acyl cleavage in bis-β-lactone **2** was not clear. Arguably, β-cleavage could have been impeded on steric grounds. In being positioned closer to ring **A**, the benzyloxy group would be a bulkier nucleophile when attacking ring **B** than it would be attacking ring **A**. Treatment of dibenzyloxy compound **5**[6] with $BF_3.OEt_2$ at -5°C (see entry 2) resulted in a 1:1 mixture of β- and acyl cleavage products **6** and **7**, respectively, providing some validation for the steric argument. However, with $TiCl_4$ at -78°C (entry 3), acyl cleavage was overwhelmingly favored, suggesting that in this system there is a kinetic preference for this mode of ring opening. Interestingly, with compound **8**[7] (entry 4), δ-lactone formation by acyl cleavage was not observed. Instead, β-cleavage occurred exclusively, giving the tetrahydrofuranacetic acids **9**.[8]

We next turned our attention to ketones as internal nucleophiles. As expected, treatment of compound **10** (entry 5) with TMSOTf at -55°C in the presence of triethylsilane gave tetrahydropyran **11** as a single diastereomer. Once again, there was no evidence of acyl cleavage. These results are consistent with a mechanism involving β-cleavage of the lactone ring by the ketone group, followed by stereoselective axial hydride addition to the oxy-stabilized carbonium ion generated (Scheme 3). Product stereochemistry was readily determined by an NOE difference experiment. Irradiation of H(a) in methyl ester **16**[9] caused a positive NOE in H(b) but not H(c). Similar treatment of compound **12** (entry 6) gave an unexpected result. In this case β-cleavage is presumably too sterically hindered, and ketone reduction is the only course available.



Scheme 3

An interesting observation was made during an initial attempt to prepare the bis-β-lactone **2** from aldehyde **1**. When reaction with TMS-ketene was attempted at ice-bath temperature, aldehyde **1** did not undergo cycloaddition, but instead rearranged to the bicyclic structure **14** in a sequence of steps beginning with acyl cleavage. When TMSOTf was used, acyl cleavage was subdued, but benzyl acetal **15** was the only product. The application of some of these findings is in progress.

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References and notes

1. (a) Mead, K. T.; Samuel, B. *Tetrahedron Lett.* **1988**, *29*, 6573; (b) Mead, K. T.; Yang, H.-L. *J. Org. Chem.* **1990**, *55*, 2991.
2. (a) Zemribo, R.; Champ, M. S.; Romo, D. *SynLett* **1996**, 278; (b) Arrastia, I.; Lecea, B.; Cossio, F. P. *Tetrahedron Lett.* **1996**, *37*, 245.
3. Mead, K. T.; Pillai, S. K. *Tetrahedron Lett.* **1993**, *34*, 6997.
4. By conducting all $MgBr_2$-promoted cycloadditions at -60°C, both α- and β-chelation control was found to be at least 98% diastereoselective. See: Zemribo, R.; Romo, D., *Tetrahedron Lett.* **1995**, *36*, 4159.
5. The ^{1}H-NMR spectrum of compound **3** was consistent with the assigned structure; IR (neat): 1733 and 1783 cm^{-1}; HRMS: 291.1232 calculated for $C_{16}H_{18}O_5$ $(M+H)^+$, 291.1238 found.
6. Compound **5** was prepared by $MgBr_2$-promoted 2+2 cycloaddition of TMS-ketene to 2,4-dibenzyloxy butanal. See reference 4.
7. Compound **8** was prepared as a 1:1 mixture of diastereomers by 2+2 cycloaddition of TMS-ketene to 3,4-dibenzyloxy butanal ($SnCl_4$, -78°C). Cycloaddition was not observed with $MgBr_2.OEt_2$.
8. Use of $BF_3.OEt_2$ resulted in a mixture of acids **9** (39%) and their corresponding benzyl esters (46%).
9. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.40 (5H, m), 4.56 (1H, d, J=12.0 Hz), 4.50 (1H, d, J=12.0 Hz), 4.26 (1H, *Ha*, m), 3.95 (1H, *Hb*, m), 3.85 (1H, *Hc*, m), 3.69 (3H, s), 2.56 (1H, dd, J=15.0, 7.8 Hz), 2.39 (1H, dd, J=15.0, 5.7 Hz), 1.94 (1H, ddd, J=13.8, 2.7, 2.4 Hz), 1.84 (1H, ddd, J=13.8, 3.0, 2.1 Hz), 1.40 (1H, ddd, J=12.3, 2.7, 2.4 Hz), 1.32 (1H, ddd, J=12.6, 3.0, 2.7 Hz), 1.14 (3H, d, J=6.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 171.70, 138.81, 128.35, 127.55, 127.45, 71.27, 70.06, 68.84, 68.45, 51.56, 41.26, 37.27, 34.85, 21.80

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