

Free Radical Chemistry of Lactones: Ring Contractions and Expansions

David Crich,^{*,†} Athelstan L. J. Beckwith,^{*,‡}
G. Fredrick Filzen,[†] and Robert W. Longmore[‡]

Department of Chemistry (M/C 111)
University of Illinois at Chicago
845 W. Taylor Street, Chicago, Illinois 60607-7061
Research School of Chemistry
The Australian National University
Canberra, ACT 0200, Australia

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The β -(acyloxy)alkyl, or Surzur/Tanner,¹ rearrangement (**1** \rightarrow **2**, X = CR) is the archetypal radical ester migration.² Of



more recent vintage are the parallel β -(phosphatoxy)alkyl (**1** \rightarrow **2**, X = P(OR)₂),³ β -(nitroxy)alkyl (**1** \rightarrow **2**, X = NO),⁴ and β -(sulfonatoxy)alkyl (**1** \rightarrow **2**, X = SO₂R)⁴ migrations. In these reactions, in benzene solution, the ester group migrates intramolecularly, in a nondissociative manner with a broad spectrum of rate constants, through either of two competing pathways involving polarized three-center-three-electron and five-center-five-electron transition states (Figures 1 and 2, respectively). In the extreme case, when appropriate stabilizing groups and/or solvents are present, both pathways probably converge on a caged radical cation/anion pair as intermediate.⁵ Halo- or selenolactonization followed by tin hydride mediated dehalogenation, or deselenation, is a common synthetic protocol.⁶ During dehalogenation, in principle, the intermediate radical might undergo the β -(acyloxy)alkyl migration resulting in either ring expansion or ring contraction depending on the disposition (exo or endo) of the initial radical and the relative stabilities of the two radicals (Scheme 1). To our knowledge, only one example of such a process (**3** \rightarrow **4**, 72%) has been described in

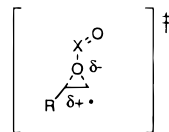


Figure 1.

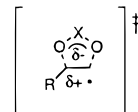
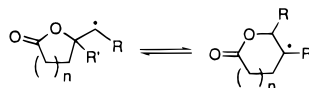
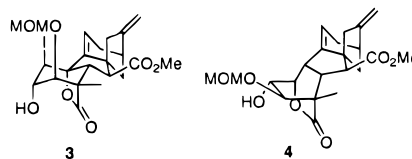


Figure 2.

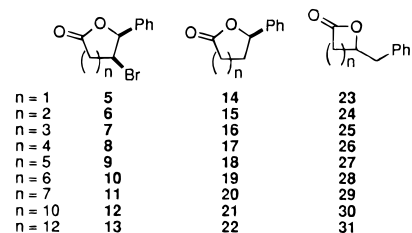
Scheme 1



the literature.⁷ That such rearrangements have not been observed more frequently is probably due to the high concentrations of tin hydride normally employed and the presumably low migration rate constants. As such the use of low stannane concentrations or syringe pump techniques should reveal a whole new class of rearrangements and, through comparison of lactones of differing ring size, potentially provide valuable information on the stereoelectronic requirements for both the three-center-three-electron and five-center-five-electron shifts and eventual ion pair intermediates.



A series of bromolactones (**5**–**13**) was conveniently prepared by cyclization of the corresponding seco-acids according to the Yamaguchi protocol.⁸ Each was heated to reflux in benzene



(4.7 mM) and treated dropwise with 1.3 equiv of tributyltin hydride (31 mM) and 5 mol % AIBN over 10 h. Analysis of the crude reaction mixtures by ¹H-NMR spectroscopy gave the ratios of reduced to rearranged products in Table 1. Inspection of Table 1 reveals that all lactones but one (**5**) undergo the anticipated ring contraction, although with varying efficiency.⁹ This variation may be discussed in terms of the conformation, Z or E, of the various lactones. Equally, the relative difference in strain between the initial and rearranged radicals, as well as at the transition state, needs to be taken into consideration in

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(9) We recognize that for experiments conducted with syringe pump additions the stationary concentrations of stannane may not be totally reproducible from experiment to experiment and so hesitate to derive precise relative rates from the data in Table 1.

[†] University of Illinois at Chicago.

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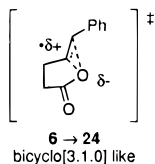
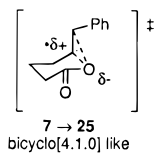
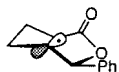
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Table 1. Lactone Contractions

entry	substrate	ring size	product ratio ^a
1	5	5 → 4	14/23 = 100/0
2	6	6 → 5	15/24 = 1/2.4
3	7	7 → 6	16/25 = 0/100
4	8	8 → 7	17/26 = 1/1.2
5	9	9 → 8	18/27 = 1.3/1
6	10	10 → 9	19/28 = 2.0/1
7	11	11 → 10	20/29 = 1/1
8	12	14 → 13	21/30 = 1.2/1
9	13	16 → 15	22/31 = 1.2/1

^a Product ratios are measured on the crude mixtures which were devoid of other products except those derived from tributyltin hydride.

**Figure 3.****Figure 4.****Figure 5.**

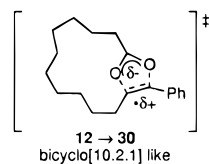
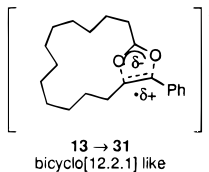
each case. Five-, six-, and seven-membered lactones are constrained to the high-energy *E*-conformation and therefore must rearrange (contract) by the three-electron-three-center mechanism (Figure 1), whereas eight- and larger ring lactones¹⁰ are able to adopt the *Z*-conformation common¹¹ to simple esters. The failure of **5** to rearrange (Table 1, entry 1) is clearly related to the strain inherent in four-membered ring lactones as well as in the bicyclo[2.1.0]pentane-like transition state required for the contraction. The large difference in contraction of **6** and **7** (Table 1, entries 2 and 3) is of some interest. Differential strain in the transition states (Figures 3 and 4, respectively) is probably insufficient to account for the large discrepancy in rates. A comparison of calculated strain energies¹² for five-, six- and seven-membered lactones suggests that **6** would rearrange more rapidly than **7** if reduction in strain at the ground state were the determining factor. It seems likely that the very rapid contraction of **7** is in large part due to a favorable, low-energy half-chair conformer in which the singly occupied p-orbital of the derived radical is ideally oriented, that is, preorganized, to interact with the scissile β -C–O bond (Figure 5). We also draw attention to the fact that in this conformation the singly occupied p-orbital is periplanar with the scissile β -C–O thus removing any barrier associated with rotation from the normal perpendicular conformation¹³ of β -alkoxyalkyl radicals. The work of Huisgen, Clossen, and Wiberg suggests that eight- and nine-membered lactones exist as mixtures of the *E*- and *Z*-conformers

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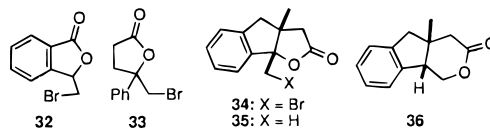
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**Figure 6.****Figure 7.**

but that larger rings are predominantly *Z*.^{10–12} Thus, for the 14- and 16-membered lactones studied (**12** and **13**, Table 1, entries 8 and 9), the ring contractions are best rationalized as occurring via the five-center-five-electron pathway and so bicyclo[13.3.0]tetradecane and bicyclo[15.3.0]hexadecane-like transition states (Figures 6 and 7), respectively.

In the medium-sized rings (**9**, **10**, **11**), the observed ratios must reflect the complex interplay between transannular strain, the *E/Z*-ratios of substrate and product, and the crossover between three- and five-center mechanisms. Further work with oxygen-labeled substrates is needed to clarify matters here, and this will be undertaken and reported on in due course.

We have also briefly investigated the radical expansion of γ - to δ -lactones. Of the three substrates prepared **32–34**, only one (**34**) underwent rearrangement resulting in the ratio **35:36**¹⁴ = 5.1:1. When this reaction was conducted in *tert*-butyl alcohol as solvent, the ratio improved to **35:36** = 1.1:1, consistent with a polar transition state for migration (Figure 1) and earlier solvent effects in the β -(acyloxy)alkyl rearrangement.^{2c–e} The failure of **32** to undergo ring expansion on treatment with Bu₃SnH is attributed to the orthogonal nature of the “migrating” bond and the π -cloud of the benzene ring; that of **33** can probably be understood on similar grounds. On the other hand, in **34**, the scissile C–O bond overlaps nicely with the benzene π -system enabling benzylic stabilization of the developing radical at the transition state.



In conclusion, it has been demonstrated that lactones do indeed undergo radical rearrangements. Synthetic chemists practicing halolactonization/radical dehalogenation sequences, and their seleno equivalents, can probably avert the possibility of such rearrangements by working in the presence of catalytic diphenyl diselenide.¹⁵

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Supporting Information Available: Listings of characterization data (¹H and ¹³C-NMR and mass spectra) for compounds **5–36** (12 pages). See any current masthead page for ordering and Internet access instructions.

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