

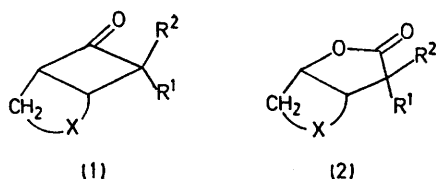
Three-step Synthesis of α -Methylene- γ -lactones through Formation and Oxidation of Substituted Cyclobutanones

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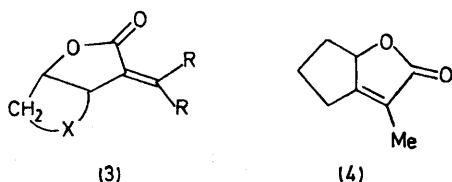
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Summary α -Methylene- γ -lactones have been synthesized by oxidation of readily available halogenomethylcyclobutanones and treatment of the product lactones with diazabicyclononene.

THE biological activity of compounds possessing the α -methylene- γ -lactone unit fused to other alicyclic rings¹ has stimulated a search for synthetic routes to such species.



- a; $R^1 = \text{Me}$; $R^2 = \text{Br}$; $X = -\text{CH}=\text{CH}-$
 b; $R^1 = \text{Me}$; $R^2 = \text{Br}$; $X = -[\text{CH}_2]_2-$
 c; $R^1 = \text{Me}$; $R^2 = \text{Br}$; $X = -[\text{CH}_2]_3-$
 d; $R^1 = \text{Me}$; $R^2 = \text{Cl}$; $X = -[\text{CH}_2]_2-$
 e; $R^1 = \text{Pr}^i$; $R^2 = \text{Br}$; $X = -\text{CH}=\text{CH}-$
 f; $R^1 = \text{Br}$; $R^2 = \text{Me}$; $X = -[\text{CH}_2]_2-$



- a; $R = \text{H}$; $X = -\text{CH}=\text{CH}-$
 b; $R = \text{H}$; $X = -[\text{CH}_2]_2-$
 c; $R = \text{H}$; $X = -[\text{CH}_2]_3-$
 d; $R = \text{Me}$; $X = -\text{CH}=\text{CH}-$

One present method involves construction of the requisite γ -lactone, and introduction of functionality into the α -position with subsequent modification furnishing the α -methylene group.² Occasionally the γ -lactone has been formed by Baeyer-Villiger oxidation of a cyclobutanone.³

¹ S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Medicin. Chem.*, 1971, **14**, 1147; K. H. Lee, R. Meck, C. Piantadosi, and E. S. Huang, *ibid.*, 1973, **16**, 299; G. A. Howie, P. E. Manni, and J. M. Cassady, *ibid.*, 1974, **17**, 840; A. Rosowsky, N. Papathanasopoulos, H. Lazarus, G. E. Foley, and E. J. Modest, *ibid.*, p. 674; W. Herz and I. Wahlberg, *J. Org. Chem.*, 1973, **38**, 2485; K. H. Lee, T. Ibuka, and M. Kozuka, *Tetrahedron Letters*, 1974, 2287.

² P. A. Grieco, *Synthesis*, 1975, 67; R. B. Miller and R. D. Nash, *Tetrahedron*, 1974, **30**, 2961; R. B. Miller and E. S. Behase, *J. Amer. Chem. Soc.*, 1974, **96**, 8102; D. Caine and G. Hasenhuettl, *Tetrahedron Letters*, 1975, 743; J. A. Marshall and W. R. Snyder, *J. Org. Chem.*, 1975, **40**, 1656.

³ P. A. Grieco and K. Hiroi, *Tetrahedron Letters*, 1974, 3467; P. A. Grieco, N. Marinovic, and M. Miyashita, *J. Org. Chem.*, 1975, **40**, 1670.

⁴ W. T. Brady, R. Roe, E. F. Hoff, and F. H. Parry, *J. Amer. Chem. Soc.*, 1970, **92**, 146; W. T. Brady and R. Roe, *ibid.*, p. 4618.

⁵ A. E. Green, J. C. Muller, and G. Ourisson, *J. Org. Chem.*, 1974, **39**, 186.

⁶ J. A. Marshall and N. Cohen, *J. Org. Chem.*, 1965, **30**, 3475.

The need to derivatize the γ -lactone can be circumvented by introduction of the required functionality at an earlier stage; we report that this can be accomplished by cycloaddition of an appropriately substituted ketene and an olefin followed by oxidation of the α -substituted cyclobutanone so formed to give the desired α -substituted γ -lactone.

It is known that cycloaddition of various alkylhalogenoketenes to cyclic olefins can be controlled so that the required *exo*-halogenocyclobutanones (**1a—e**) are formed preferentially.⁴ Side products are removed readily by distillation or chromatography.

Oxidation of the ketones (**1a—d**) with peroxyacetic acid or *m*-chloroperoxybenzoic acid proceeded to give the γ -lactones (**2a—d**) respectively, specifically in high yield. The bromomethyl-lactones (**2a—c**) readily eliminated HBr on treatment with diazabicyclononene in boiling toluene,⁵ to give the corresponding α -methylene- γ -lactones (**3a—c**), respectively, in 60—80% yield. The lactones (**3a—c**) displayed the characteristic signals of an α -methylene group in the ¹H n.m.r. spectra.⁶ The chloromethyl-lactone (**2d**) forms the lactone (**3b**) more slowly, but in equally good yield, under the same conditions.

The α -isopropylidene- γ -lactone (**3d**) was prepared from bromoisopropylketene in a similar manner. However, the relatively slow rate of oxidation of the ketone (**1e**) led to a poor yield of the lactone (**2e**) owing to concurrent epoxidation of the double bond. As expected compound (**2f**) gave only the $\alpha\beta$ -unsaturated lactone (**4**) on treatment with base.⁵

The above route is applicable to the construction of α -methylene- γ -lactones possessing *cis*-fused five- and six-membered, saturated and unsaturated rings and the potential of this method for the synthesis of naturally occurring α -methylene- γ -lactones is under investigation.

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