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

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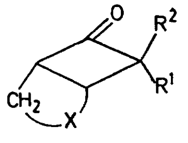
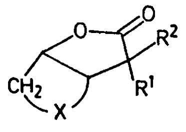
Summary α-Methylene-γ-lactones have been synthesized by oxidation of readily available halogenomethylcyclobutanones and treatment of the product lactones with diazabicyclononene.

THE biological activity of compounds possessing the α-methylene-γ-lactone unit fused to other alicyclic rings[1] has stimulated a search for synthetic routes to such species. 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]

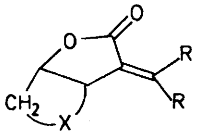


(1)

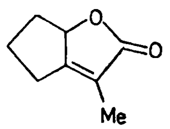


(2)

a; R^1 = Me; R^2 = Br; X = -CH=CH-
b; R^1 = Me; R^2 = Br; X = $-[CH_2]_2-$
c; R^1 = Me; R^2 = Br; X = $-[CH_2]_3-$
d; R^1 = Me; R^2 = Cl, X = $-[CH_2]_2-$
e; R^1 = Pr^i; R^2 = Br; X = -CH=CH-
f; R^1 = Br; R^2 = Me; X = $-[CH_2]_2-$



(3)



(4)

a; R = H; X = -CH=CH-
b; R = H; X = $-[CH_2]_2-$
c; R = H; X = $-[CH_2]_3-$
d; R = Me; X = -CH=CH-

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 keten 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 alkylhalogenoketens 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 chloromethyllactone (**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 bromoisopropylketen 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 αβ-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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