A New Synthesis of α-Methylene Lactones

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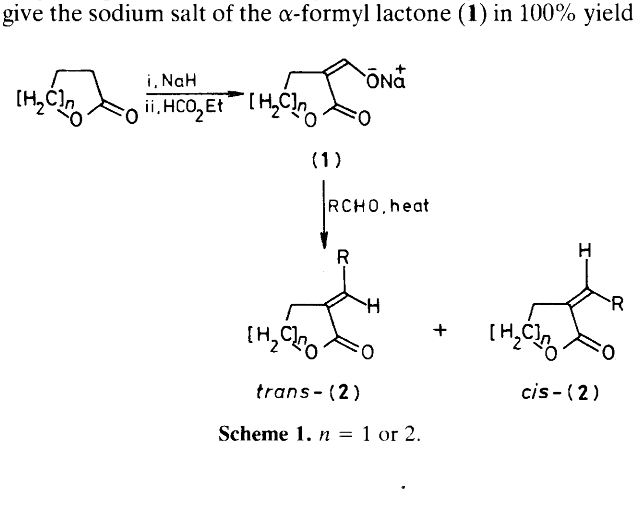
The α-formylation of γ- and δ-lactones and the high yield conversion into their respective α-methylene γ- and δ-lactones are described.

The α-methylene-γ-butyrolactone structural unit is a structural feature common to a large number of biologically important sesquiterpenes and the development of synthetic routes to this entity has commanded considerable attention.[1] However, many of the methods used have the disadvantage of either low yields or being multi-step, and often a further drawback has been their inapplicability to δ-lactones.[2] Herein we report a novel two-step reaction sequence for the insertion of an α-methylene or substituted α-methylene unit into either γ-butyrolactone or δ-valerolactone, which proceeds in uniformly high yield.

The α-methylene function can be introduced in two quite simple steps (Scheme 1); formylation[3] of the parent lactone to give the sodium salt of the α-formyl lactone (**1**) in 100% yield, followed by refluxing the latter under nitrogen, with an aldehyde, for periods varying from 3 to 18 h (see Table 1). Work-up of the α-methylene lactones (**2**) was accomplished by filtration, removal of the solvent under reduced pressure, and passage of the resulting solution through a Kieselgel pad, with dichloromethane as solvent. The substituted methylene lactones were purified by removal of the solvent under reduced pressure, addition of 6 M hydrochloric acid, and extraction with diethyl ether. Final purification was accomplished by either distillation or recrystallisation.

The reaction with benzaldehyde and propionaldehyde resulted in the formation of a mixture of the corresponding α-*trans*- and α-*cis*-(substituted ylidene)-γ-butyrolactones. Although separation of the individual isomers proved impossible, their relative ratio could be determined by ^{1}H n.m.r. data. The olefinic proton of the α-*trans*-benzylidene-γ-

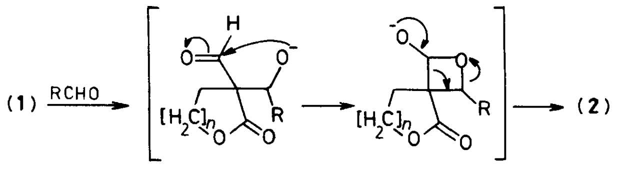


Scheme 1. n = 1 or 2.

Table 1. Preparation of α-methylene lactones (**2**).

Compound (**2**)[a] n	R	Solvent[b]	Reaction time	Ratio *trans* : *cis*	% Yield
1	H	THF	3 h		98
1	Ph	THF + HMPA	18 h	3 : 1	67
1	Et	Dioxane + HMPA	18 h	1.7 : 1	81
2	H	THF	18 h		80

[a] All compounds gave satisfactory microanalytical and spectral data.
[b] THF = tetrahydrofuran, HMPA = hexamethylphosphoramide [2 equiv. of HMPA with respect to (**1**)].



Scheme 2

butyrolactone resonates as a triplet at δ 7.40 compared with the corresponding *cis* isomer where the olefinic proton appears as a triplet at δ 7.20. The olefinic proton of the α-*trans*-ethylidene-γ-butyrolactone resonates at δ 6.56 as a triple triplet, while the corresponding *cis* isomer shows a triple triplet at δ 6.13.

The reaction scheme may be best explained by formyl transfer from carbon to oxygen followed by elimination of carboxylate anion,[4] as outlined in Scheme 2.

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