Journal of

The Chemical Society,

Chemical Communications

NUMBER 24/1972 20 DECEMBER

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# α-Hydroxymethylation of γ- and δ-Lactones: a New Synthesis of α-Methylene-γ-butyrolactones

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*Summary* The direct high yield α-hydroxymethylation of the *trans*-bicyclic lactone (I) and δ-valerolactone, and an efficient three-step synthesis of the *trans*-α-methylene-γ-butyrolactone (III) are described.

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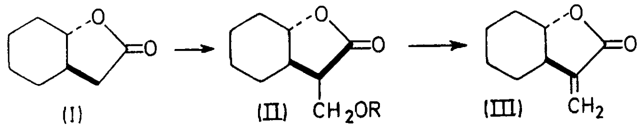
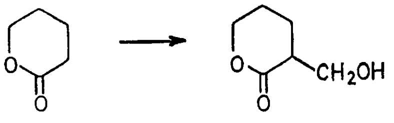
The α-methylene-γ-butyrolactone structural unit is found in many naturally occurring cytotoxic sesquiterpene lactones which have been isolated during the search for antitumor agents from plant sources,[1] and its synthesis has recently received much attention.[2] However, none of the many synthetic schemes permits access *via* direct α-hydroxymethylation of the γ-butyrolactone system, despite the ready availability of the appropriate lactone precursors. The method described here is applicable to δ-lactones; other methods are not applicable to the six-membered ring lactones.[2c–e]



(I) (II) (III)

a; R = H
b; R = $MeSO_2$
c; R = $p$-$MeC_6H_4{\cdot}SO_2$

In connection with other work on the total syntheses of sesquiterpenes possessing both the α-methylene γ and δ units (*e.g.* vernolepin)[3] we required a procedure for the introduction of the α-methylene unit from lactone precursors, and we report the direct conversion of a γ-butyrolactone into an α-hydroxymethyl-γ-butyrolactone [*e.g.* (I) → (IIa)] with lithium di-isopropylamide to form the lactone enolate[4] which is efficiently trapped with formaldehyde. To a solution of lithium di-isopropylamide (1·2 equiv.) in anhydrous tetrahydrofuran (THF) at −78° was slowly added a solution of lactone (I) (1 equiv.) in THF. After 30 min the mixture was warmed to −20° and gaseous formaldehyde in nitrogen was passed in. After an additional 30 min, the reaction was quenched by the addition of 10% HCl. Work-up afforded the butyrolactone (IIa) (>95%),† which was converted into the mesylate (IIb) ($MeSO_2Cl$–pyridine) and thence (refluxing pyridine) into the known *trans*-α-methylene-γ-butyrolactone (III) [$\nu_{max}$ (film) 1771 and 1674 cm$^{-1}$; $\delta(CDCl_3)$ 6·04 (d, *J* 3 Hz, $C{=}CH_2$), 5·35 (d, *J* 3 Hz, $C{=}CH_2$), 3·45—3·95 (br, CHO) p.p.m.]. The overall yield from (I) to (III) was *ca.* 80%. In addition, conversion of (IIa) into tosylate (IIc), m.p. 112—112·5°,



(IV) (V)

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† Satisfactory analytical and/or spectral data were obtained for all compounds.

followed by refluxing of (IIc) in pyridine afforded (III) in *ca.* 75% overall yield from (IIa).

In view of the lack of methods for the construction of the α-methylene-δ-valerolactone system, we applied the direct hydroxymethylation procedure to δ-valerolactone (IV). Treatment of (IV) with lithium di-isopropylamide as already described, followed by treatment with formaldehyde at −20° afforded the α-hydroxymethyl-δ-valerolactone (V) (> 95%).

We acknowledge support by the Research Corporation and a Public Health Service Research Grant from the National Cancer Institute, (to P.A.G.), and a postdoctoral fellowship from the Science Development Program of the National Science Foundation (to K.H.).

(*Received, 2nd October* 1972; *Com.* 1690.)

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