A New Synthesis of Lactones: Application to (±)-Mevalonolactone

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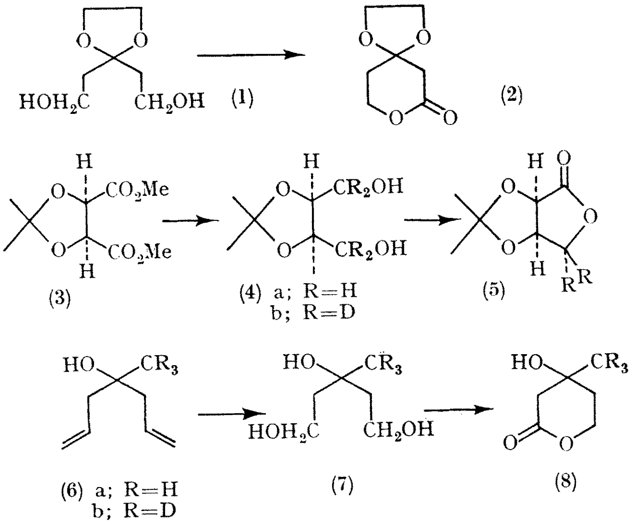
Summary Silver carbonate on celite converts primary 1,4-, 1,5-, and 1,6- diols into the corresponding lactones in high yield.

Although γ-butyrolactone can be obtained from butane-1,4-diol by dehydrogenation,[1] very few syntheses of lactones from diols by oxidation have been reported.[2,3]

It has been found that silver carbonate on celite in boiling benzene is a neutral oxidizing agent which transforms primary or secondary alcohols into aldehydes or ketones in very high yield.[4]

We report on the use of this reagent for the synthesis of γ-, δ-, and even ε-lactones from the corresponding diols. For instance hexane-1,6-diol (1·217 g.; 10·2 mmoles) in benzene (300 ml.) are heated under reflux for 17 hr. with silver carbonate–celite reagent (57 g.)[4] (100 mmoles of active compound). The course of the reaction is followed by t.l.c. When it is over, the solid is filtered off and the colourless solution is evaporated. The residue is pure ε-hexanolactone (g.l.c.). The yield is nearly quantitative.

In the same way, γ-butyrolactone (52%) and δ-valerolactone (90%) have been prepared from butane-1,4-diol and pentane-1,5-diol, respectively. Functional groups which are sensitive to acids are unaffected by silver carbonate.



(1) (2)

(3) (4) a; R=H b; R=D (5)

(6) a; R=H b; R=D (7) (8)

Thus the diol (1),[5] obtained by reduction with $LiAlH_4$ of the ethylene acetal of dimethyl acetonedicarboxylate, upon treatment with silver carbonate–celite, leads to the lactone (2), purified by preparative t.l.c. (yield 60%). The i.r. and n.m.r. spectra as well as the microanalysis agree with structure (2).

In the same way, the diol (4a), obtained by reduction with lithium aluminium hydride of dimethyl isopropylidene-*O*-2,3-*meso*-tartrate (3)[6] is converted into (±)-isopropylidene-2,3-erythronic acid lactone (5a), m.p. 61—62°, by the silver carbonate–celite reagent.

Reduction of (3) with $LiAlD_4$ leads to the deuteriated alcohol (4b) which is oxidized as above giving the deuteriated lactone (5b) m.p. 61—62° (quartet in n.m.r. spectrum, due to the AB system, δ 4·84 p.p.m., J 2·2 Hz., $CDCl_3$).

Finally, (±)-mevalonic acid lactone was synthesized in the following way: the tertiary alcohol (6a), from ethyl acetate and allylmagnesium bromide, was ozonized in methylene chloride. Subsequent reduction of the crude ozonide with lithium aluminium hydride in tetrahydrofuran led to the triol (7a). This triol, oxidized with silver carbonate–celite, gave (±)-mevalonolactone (8a), purified by high-vacuum distillation, identical in all respects with an authentic sample, in an overall yield from (7a) of 74%.

In the same way, deuteriated acetic acid, treated first with dihydropyran, and a trace of hydrochloric acid, then with allylmagnesium bromide, gave the deuteriated tertiary alcohol (6b). Ozonolysis, reduction of the crude ozonide, and subsequent oxidation of the resulting triol gave deuteriated (±)-mevalonolactone (8b). With the exception of the methyl signal, n.m.r. spectra of (8a) and (8b) are superimposable.†

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† Microanalysis, n.m.r., and i.r. data are consistent with the structures shown.

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