α-Carboxylation of Lactones: a General Route to α-Methylene Lactones

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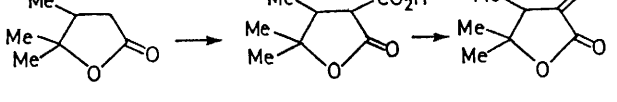
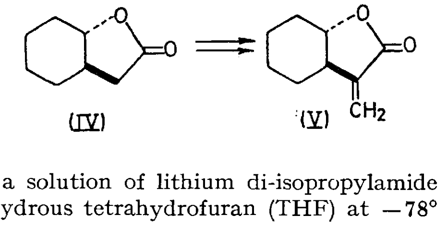
Summary The high yield α-carboxylation of γ- and δ-lactones, and the conversion into their respective α-methylene γ- and δ-lactones are described.

A general method for carboxylation of α-anions of lactones should constitute an attractive route to α-methylene γ- and δ-lactones [*e.g.* (I) → (II) → (III)], which represent structural units found in many naturally occurring cytotoxic sesquiterpenes.[1] Despite considerable effort by Johnson[2] and others,[3] methods employed for the introduction of the α-methylene function in both five and six-membered ring lactones have been unsatisfactory. We describe a general method for carboxylation of lactone enolates which permits the synthesis of both α-methylene γ- and δ-lactones. The procedure complements the recently reported general methods for construction of the α-methylene lactone structural unit, namely: α-hydroxymethylation of lactones[4] and the reductive amination of α-formyl lactones.[5]

We have found that the α-carboxylic acid function can be introduced into readily available γ- and δ-lactones by reaction of the corresponding lactone enolate with carbon dioxide. To a solution of lithium di-isopropylamide (1·3 mmol) in anhydrous tetrahydrofuran (THF) at −78° was

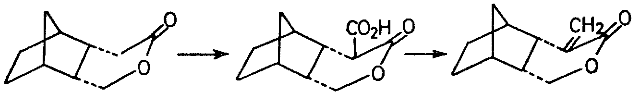


(I) (II) (III)



(IV) (V)

very slowly added a THF solution of lactone (I) (1·0 mmol). The solution of the α-lithiated lactone was warmed to −25° and anhydrous carbon dioxide was passed into the reaction vessel for 15 min. The reaction was quenched by the addition of 10% HCl. Purification afforded the crystalline butyrolactone (II)† in 75% yield which was identical in all respects with a sample prepared by an alternative procedure.[6]



(VI) (VII) (VIII)

Conversion of (II) into the α-methylene-γ-butyrolactone (III) was accomplished by heating (II) (1·1 mmol) in the presence of diethylamine (5·5 mmol) and 37% aqueous formaldehyde (1·0 ml) for 30 min followed by the addition of sodium acetate (100 mg) and glacial acetic acid (1·0 ml), and further heating for 15 min. There was obtained a 95% yield of the α-methylene-γ-butyrolactone (III) [ν_{max} ($CHCl_3$) 1768 and 1665 cm^{-1}; δ (CCl_4) 1·18 (s, 3H, Me), 1·16 (d, 3H, *J* 7 Hz, CHMe), 1·43 (s, 3H, Me), 2·78 (m, 1H, C*H*Me), 5·40 (d, *J* 3 Hz, 1H), and 6·08 (d, *J* 3 Hz, 1H)]. Similarly, the *trans*-lactone (IV) was converted into the *trans*-α-methylene lactone (V) which was identical in all respects with a sample previously prepared in our laboratory.[4] The potential of this 'α-methyleneation sequence' was demonstrated as follows: α-carboxylation of the δ-lactone (VI)[7] afforded a 95% yield of (VII) (m.p. 101—102°) which underwent smooth conversion (90%) into the α-methylene-δ-lactone (VIII).

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

[1] S. M. Kupchan, M. A. Eakin and A. M. Thomas, *J. Medicin. Chem.*, 1971, **14**, 1147.

[2] Johnson has demonstrated that γ-lactones undergo α-carboxylation upon treatment with methyl methoxymagnesium carbonate (J. Martin, P. C. Watts, and F. Johnson, *Chem. Comm.*, 1970, 27). This step, however, is not applicable to six membered δ-lactones. For other methods which are not applicable to six membered ring lactones see: E. S. Behare and R. B. Miller, *Chem. Comm.*, 1970, 402; J. W. Patterson and J. E. McMurry, *ibid.*, 1971, 488.

[3] E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 1950, 230; E. E. van Tamelen and S. R. Bach, *J. Amer. Chem. Soc.*, 1958, **80**, 3079; J. A. Marshall and N. Cohen, *J. Org. Chem.*, 1965, **30**, 3475; H. Minato and I. Horibe, *Chem. Comm.*, 1965, 531.

[4] P. A. Grieco and K. Hiroi, *J.C.S. Chem. Comm.*, 1972, 1317.

[5] Personal communication from C. R. Hutchinson and A. D. Harmon (University of Connecticut) *Tetrahedron Letters*, in the press.

[6] P. Boldt, W. Thielecke, and J. Etzemüller, *Chem. Ber.*, 1969, **102**, 4157.

[7] P. A. Grieco and M. Meyers, unpublished results. The synthesis of lactone (VI) will be reported in due course.