A New Synthesis of α-Methylene-γ-butyrolactones

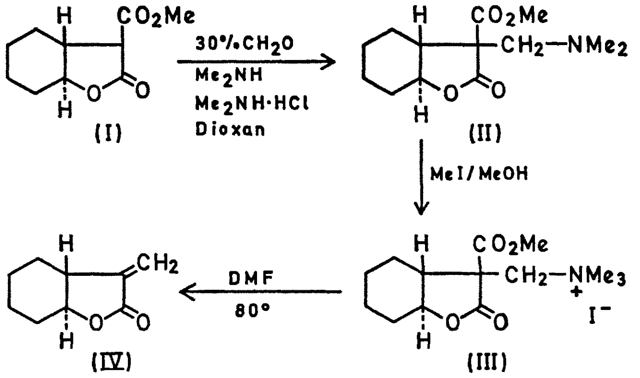
By E. S. BEHARE and R. B. MILLER*

(*Department of Chemistry, University of California, Davis, California* 95616)

Summary A high yield of α-methylene-γ-butyrolactones can be obtained by treatment of a 3-methoxycarbonyl-lactone successively with formaldehyde–dimethylamine hydrochloride, methyl iodide, and heating in dimethylformamide.

RECENTLY, Martin, Watts, and Johnson[1] reported a new synthesis of the α-methylene-γ-butyrolactone group, an important structural feature of many sesquiterpenes of biological importance.[2] We report our findings in an independently-developed but complementary synthetic route to the α-methylene-γ-butyrolactone group which provides a more satisfactory yield than those previously reported.[3–6]

We chose as our model 3-methoxycarbonyl-*trans*-octahydrobenzofuran-2-one (I) because conversion of this compound into the α-methylene-γ-butyrolactone (IV) by Marshall's procedure resulted in the poorest overall yield of the compounds he used (*ca.* 19%).† Compound (I) was



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† It should be noted that Marshall states in a footnote (ref. 5) that the decarboxylative deamination method of α-methylene-γ-lactone synthesis developed by van Tamelen and Bach (ref. 4) for their total synthesis of (±)-protolichesterinic acid afforded the desired α-methylenelactone (IV) in only 5% yield. This procedure would be analogous to the last step in the Johnson synthesis (ref. 1) of α-methylenebutyrolactones.

prepared by condensation of dimethyl sodiomalonate with cyclohexene oxide.[7] Treatment of compound (I) under Mannich reaction conditions with aqueous formaldehyde (30%), dimethylamine, and dimethylamine hydrochloride in dioxan resulted in a high yield of compound (II)‡ which was not purified for subsequent use. Compound (II) was then quaternized using a mixture of methyl iodide in methanol at room temperature overnight. After evaporation of the solvent at reduced pressure and washing the residue with anhydrous ether, an almost quantitative yield of the salt (III) was obtained. Heating the salt (III) overnight at 80° in dimethylformamide gave a high yield of desired product (IV) in a very pure form. The product crystallized on standing and was recrystallized from aqueous methanol as a white crystalline solid,§ m.p. 39—41°. The overall isolated yield based on compound (I) was 67%.

The last step in the sequence is thought to procede first by displacement of the carboxylate anion by iodide in a similar manner to the use of lithium iodide in cleavage of methyl esters,[8] followed by decarboxylation with concurrent β-elimination of trimethylamine.

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‡ All new compounds have suitable mass spectral analysis and n.m.r. and i.r. data consistent with the structures indicated.

§ Although Marshall (ref. 5) reports this compound as a liquid, the n.m.r. and i.r. data are in agreement with those reported by him and the mass spectrum is consistent with this structure.

[1] J. Martin, P. C. Watts, and Francis Johnson, *Chem. Comm.*, 1970, 27.

[2] For some recent examples see the work of S. M. Kupchan, Y. Aynehchi, J. M. Cassady, H. K. Schnoes, and A. L. Burlingame, *J. Org. Chem.*, 1969, **34**, 3867; S. M. Kupchan, R. J. Hemingway, D. Werner, and A. Karim, *ibid.*, pp. 3903, 3908.

[3] E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 1950, 230.

[4] E. E. van Tamelen and S. R. Bach, *J. Amer. Chem. Soc.*, 1955, **77**, 4683; 1958, **80**, 3079.

[5] J. A. Marshall and N. Cohen, *Tetrahedron Letters*, 1964, 1997; *J. Org. Chem.*, 1965, **30**, 3475.

[6] H. Minato and I. Horibe, *Chem. Comm.*, 1965, 531.

[7] S. Coffey, *Rec. Trav. chim.*, 1923, **42**, 287.

[8] For references and examples, see L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, 1967.