A New Synthetic Method for Exocyclic Methylene αβ-Unsaturated γ-Lactones and Synthesis of (±)-Isoalantolactone

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THE exocyclic methylene αβ-unsaturated γ-lactone function is a most common grouping in various naturally-occurring sesquiterpenic lactones. The synthesis of this grouping was recently achieved by Marshall and Cohen,[1] and they synthesized (±)-alantolactone[2] by their method. As we had also taken an interest in the synthesis of this lactonic grouping, the paper of Marshall and Cohen prompted us to report our new method.

When α-formyl-lactone[3] (II), which was derived from *cis*-octahydrobenzofuran-2-one (I), was reduced with sodium borohydride in methanol, it gave an oily α-methylol-lactone (III), b.p. 120°/0·2 mm. (bath temp.) [ν_{max} (film) 1760 cm.$^{-1}$] in 55—60% yield. Compound (III) was also obtained on hydrogenation of (II) with 10% palladium–charcoal or Adams' catalyst in ethanol in 45—50% yield.

When the tosylate, m.p. 98—99°, of (III) was refluxed in pyridine for 4 hrs., or when the tosylation product of (III) was immediately refluxed without isolation of the tosylate for 6 hrs., there

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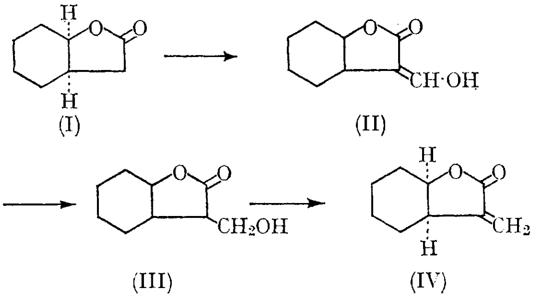
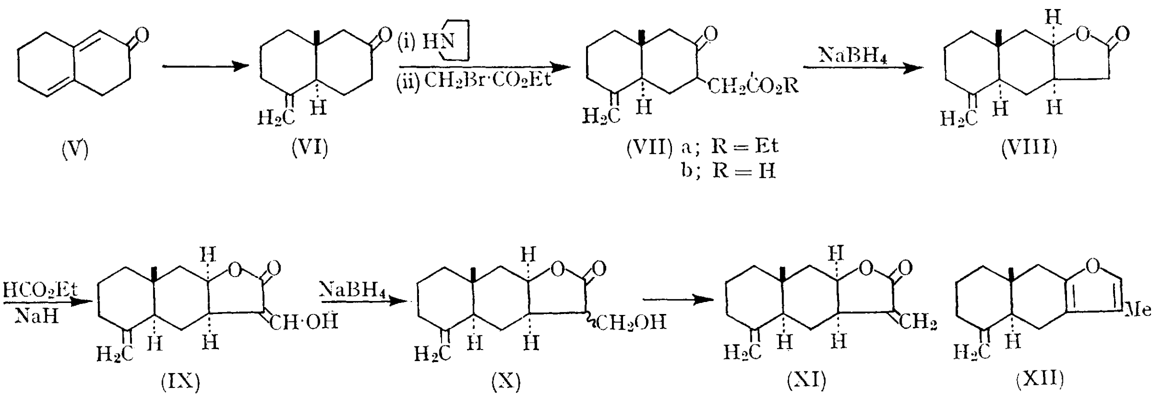
[1] J. A. Marshall and N. Cohen, *Tetrahedron Letters*, **1964**, 1997; J. A. Marshall, N. Cohen, and K. R. Arenson, *J. Org. Chem.*, 1965, **30**, 762.

[2] J. A. Marshall and N. Cohen, *J. Amer. Chem. Soc.*, 1965, **87**, 2773.

[3] F. Korte and K. H. Büchel, *Angew. Chem.*, 1959, **71**, 709; F. Korte and K. H. Büchel, *Chem. Ber.*, 1960, **93**, 1025.

was obtained 3-methyleneoctahydrobenzofuran-2-one[1] (IV), b.p. 60°/0·1 mm. (bath temp.) [ν_{max} (film) 1763, 1670, 1271, 1130, 978, 965, and 814 cm.$^{-1}$, λ_{max} 211 mμ (ϵ 4600)], in 45—50% yield. This procedure is very simple and efficient for syntheses of high-molecular-weight compounds having this functional group. Next, we applied this method to the synthesis of a sesquiterpenic lactone, racemic isoalantolactone (XI).





For this purpose, we used as the starting material *trans*-5-methylene-9-methyl-2-decalone[4] (VI), which was synthesized from (V) for synthesis of racemic atractylon (XII) by our group.

Alkylation of (VI) with ethyl bromoacetate *via* the Stork enamine procedure and hydrolysis of the reaction product (VIIa) afforded an oily keto-carboxylic acid (VIIb) (ν_{max} 1705, 1644, and 885 cm.$^{-1}$) in 49% overall yield. The compound (VIIb) was reduced with sodium borohydride in methanol to give the lactone (VIII), m.p. 103—105° (ν_{max} 1765, 1646, 898, and 889 cm.$^{-1}$) in 66% yield.

The lactone (VIII) was treated with ethyl formate and sodium hydride in dry ether to give the sodium salt of (IX), which was acidified with hydrochloric acid in ether to afford α-formyl-lactone (IX) in 63% yield. Reduction of (IX) with sodium borohydride in methanol afforded an oily hydroxy-lactone (X) (ν_{max} 3600, 3498, 1756, 1650, and 890 cm.$^{-1}$) in 59% yield. When the tosylation product of (X) with tosyl chloride in pyridine was refluxed for 6 hrs. in pyridine, it gave racemic isoalantolactone (XI), m.p. 93—94° (ν_{max} 1754, 1669, 1644, 1262, 966, and 890 cm.$^{-1}$), which was shown to be identical with isoalantolactone* by comparison of the infrared spectra. Additional confirmation of identity was provided by gas-chromatographic retention times.

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[4] H. Minato and T. Nagasaki, *Chem. Comm.*, 1965, 377.