Synthesis of Bicyclic α-Methylene-γ-lactones involving Stereocontrolled Introduction of an Homoallylic Acyloxy Group

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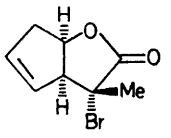
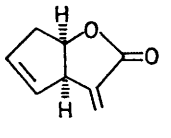
Summary Syntheses of 6-*endo*- (VI) and 6-*exo*-acetoxy-4-methylene-2-oxabicyclo[3.3.0]oct-7-en-3-one (XI) from readily available bromolactones (I) and (VII) have been accomplished through formation and dehydrohalogenation of intermediate iodoacetates.

We have recently described the synthesis of the bromomethyl-lactone (I) and its conversion into the bicyclic

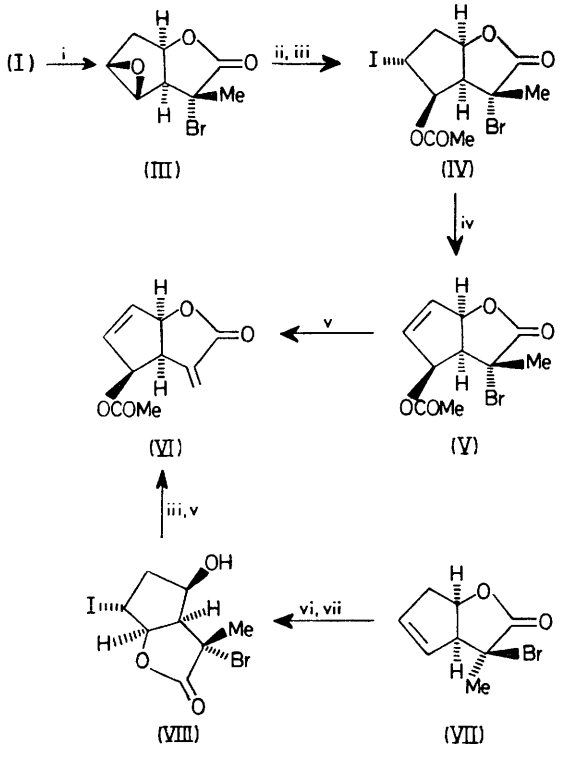


(I)



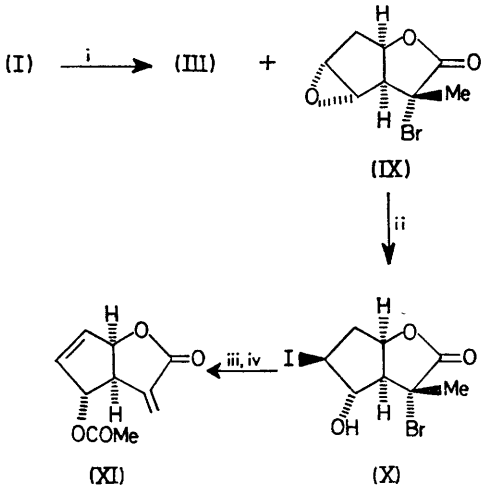
(II)

α-methylene-γ-lactone (II).[1] We now report that the halogenolactone group in (I) can confer regioselectivity upon reactions occurring at the transannular olefinic double bond. We have taken advantage of this to introduce an acyloxy group at the position homoallylic to the developing *exo*-methylene group; that this relationship of acyloxy and *exo*-methylene functions accentuates the potential cytotoxicity of such simple molecules is well documented.[2]



SCHEME 1. i, $ClC_6H_4CO_3H$-*m*, C_6H_{14}, $NaHCO_3$; ii, HI, H_2O, AcOH; iii, Ac_2O, C_5H_5N; iv, Et_3N, C_6H_6, reflux 10 h; v, Et_3N, C_6H_6, reflux 90 h; vi, OH^-; vii, CO_2, KI_3.

Treatment of the lactone (I) with *m*-chloroperoxybenzoic acid in hexane led to exclusive formation of the *endo*-epoxide (III)[3] (Scheme 1) owing, presumably, to favourable interaction of the peracid and the lactone ring;[4] the directive role of the bromine atom is of secondary but significant importance.[5] Ring opening of this epoxide with aqueous hydroiodic acid took place specifically, with nucleophilic attack occurring at C-7 to give, after acetylation, the iodoacetate (IV) in almost quantitative yield. The required double dehydrohalogenation was performed optimally with triethylamine in hot benzene. Loss of HI to give the lactone (V) preceded dehydrobromination and formation of the *exo*-methylene lactone (VI).†



SCHEME 2. i, $ClC_6H_4CO_3H$-*m*, $CHCl_3$, $NaHCO_3$; ii, HI, H_2O, AcOH; iii, Ac_2O, C_5H_5N; iv, Et_3N, C_6H_6, reflux 90 h.

A complimentary route to lactone (VI), as a development of recent work by Grieco *et al.*,[6] involved hydrolysis of the bromolactone (VII), iodolactonization of the resulting hydroxy acid to give the iodohydrin (VIII), followed by acetylation and dehydrohalogenation (Scheme 1). This route did not give high yields in the early stages.

Peracid treatment of the lactone (I) under conditions favouring *exo*-epoxidation[5] led to a mixture of (III) and (IX) in the ratio 4:1, from which (IX) was obtained by chromatography over silica. Specific epoxy ring-opening was again achieved using hydroiodic acid, furnishing the iodohydrin (X) (Scheme 2) from which the lactone (XI) was obtained in excellent yield.

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† Attempted dehydrohalogenations using the commonly employed diazabicyclononene led to extensive decomposition.

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[3] Assignment of configuration to the isomeric epoxides (III) and (IX) is dealt with in a separate publication: S. M. Ali, and S. M. Roberts, *J.C.S. Perkin I*, in the press.
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