New Synthesis of α-Methylenebutyrolactones

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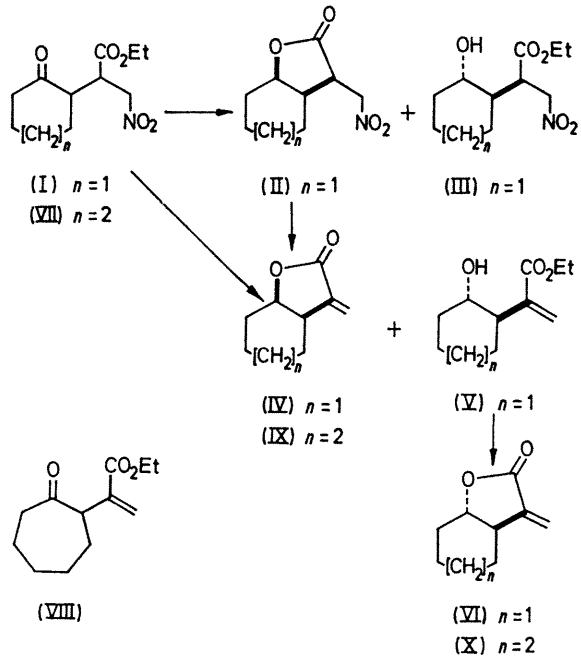
Summary An efficient three-step synthesis of α-methylenebutyrolactones consisting of enamine formation, Michael addition to ethyl β-nitroacrylate, and borohydride reduction with simultaneous lactonization and elimination of the nitro-group, is described.

THE perhydroazulene sesquiterpene lactones are a large class of natural products containing a number of asymmetric centres and, frequently, an α-methylenebutyrolactone fused to the cycloheptane ring. The complexity of these terpenes requires that any synthesis include an efficient method for introducing the lactone moiety. Methods for the synthesis of α-methylenebutyrolactones[1,2] have drawbacks; they require several steps, give poor overall yields, or need a nucleophilic epoxide opening. The use of a cycloheptene oxide leads to ambiguities with respect to both the stereochemistry of epoxidation and the regiospecificity of epoxide opening. We report a new method which is based on alkylation of an appropriate cycloalkanone and thus ensures regiospecificity.

The morpholine enamine of cyclohexanone[3] underwent Michael addition to ethyl β-nitroacrylate[4] to yield the adduct (I) (81% after hydrolysis). Reduction of (I) in methanol with excess of $NaBH_4$ for 1 h at 0° gave, in nearly quantitative yield, a 50 : 50 mixture of *cis*-nitromethyllactone (II) and *trans*–hydroxy ester (III). Treatment of (II) with di-isopropylamine (1 equiv.) at room temperature in chloroform caused smooth elimination[5] of nitrous acid and gave the known[2] *cis*-α-methylenebutyrolactone (IV) in high yield. Alternatively, borohydride reduction in methanol at 0° followed by heating under reflux for 10 h effected reduction, lactonization, and elimination in one step and



yielded a mixture of *cis*-lactone (IV) (45%), and *trans* unsaturated hydroxy-ester (V) (40%). Ester (V) was saponified to the known[2] corresponding acid, m.p. 84—85° (lit.,[2] 84·5—85·5°), and thence to *trans*-α-methylenebutyrolactone (VI) *via* dicyclohexylcarbodi-imide-induced lactonization.[2]

Similarly, the morpholine enamine of cycloheptanone reacted with ethyl β-nitroacrylate to give a mixture of adduct (VII) (49%) and elimination product (VIII) (21%). Borohydride reduction of (VII) gave an 86 : 14 mixture of the known[2] *cis*- and *trans*-α-methylenebutyrolactones (IX) and (X) (91%).

To optimize the yield of either the *cis* or the *trans* product, the action of various reducing agents would have to be examined; work on this is in progress.

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