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Iodocyclisation Studies on Unsaturated α-Hydroxy Esters

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Abstract: Iodocyclisation of ethyl 2-hydroxyhex-5-enoate **1** and the homologous hept-6-enoate **4** under thermodynamic or kinetic conditions gave the novel tetrahydrofurans **2/3** and tetrahydropyrans **5/6** respectively. In contrast, ethyl 2-hydroxypent-4-enoate **7** gave iodolactones **9** and **10** in good yield, rather than the expected cyclic ether **8**. Oxygen-18 studies revealed that the mechanism of iodolactonisation of **7** is dependent upon the reaction conditions employed.

Oxygen containing heterocycles including tetrahydrofurans, tetrahydropyrans as well as both γ- and δ-lactones are components of a diverse range of biologically important natural products. The stereocontrolled construction of these moieties is of considerable current interest.[1] Recently we have described the enantioselective synthesis of a series of unsaturated α-hydroxy acids using a combination of organometallic chemistry and biotransformations.[2] Derivatives of these α-hydroxy acids have potential as intermediates for the synthesis of oxygen containing heterocycles e.g. *via* electrophilic-mediated intramolecular cyclisations. Iodine has been widely used to effect such cyclisations and the stereochemical outcome of the reactions has been studied on a range of substrates.[3] During investigations into the iodocyclisation of unsaturated α-hydroxy esters we obtained some unexpected results which are now reported.

Results and Discussion

Substituted tetrahydropyrans and tetrahydrofurans have been prepared by iodocyclisation of unsaturated alcohols. Optimum reaction conditions involve treatment of the unsaturated alcohol with iodine in anhydrous acetonitrile to achieve thermodynamic control and with the addition of a mild base for kinetic control.[4] Ethyl 2-hydroxyhex-5-enoate **1** and ethyl 2-hydroxyhept-6-enoate **4** were cyclised under both sets of conditions giving the novel 5-*exo* and 6-*exo* heterocycles **2/3** and **5/6** respectively in good yields (Scheme 1). Each pair of diastereomers was readily separated by flash chromatography and the structures of all the products were confirmed by NMR spectroscopy including nOe studies.

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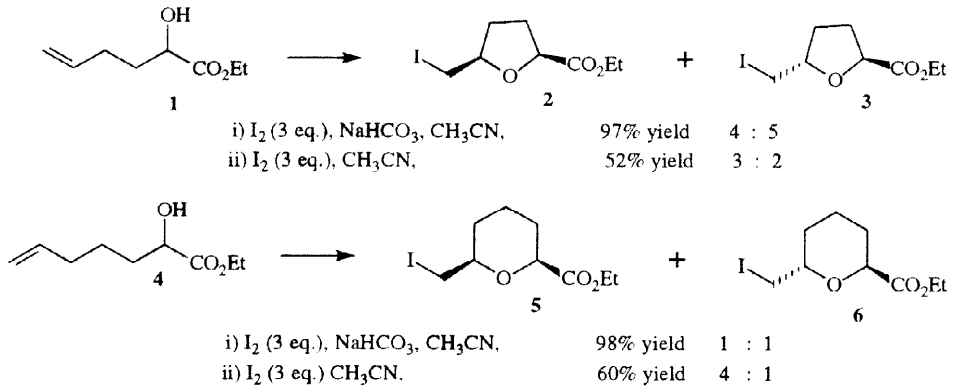
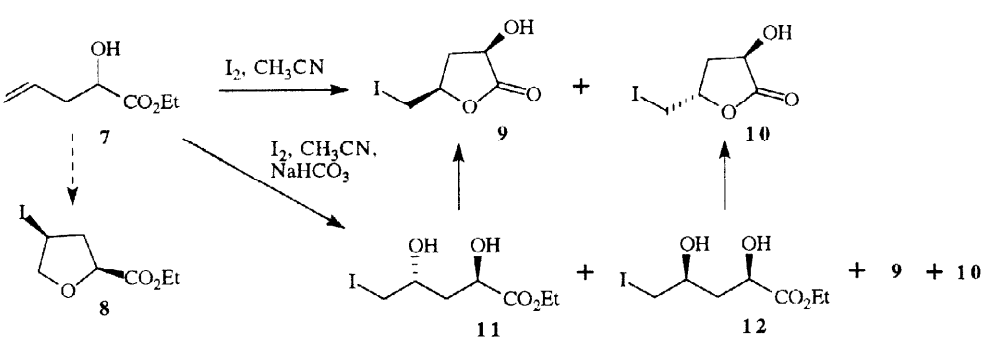


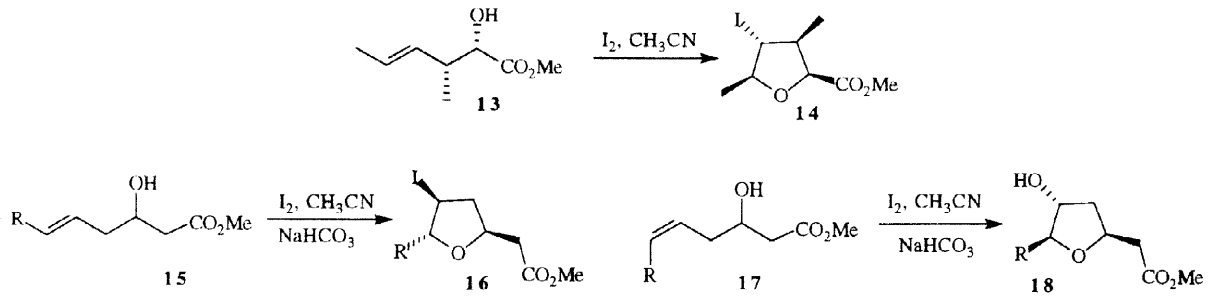
Scheme 1

We then turned our attention to cyclisation of the shorter unsaturated ester, ethyl 2-hydroxypent-4-enoate **7**. Although Galatsis *et al.* have reported that 4-*exo* ring closure may occur,[5] cyclisation of β,γ-unsaturated alcohols to iodotetrahydrofurans is far more common.[6] Thus, iodocyclisation of ethyl 2-hydroxypent-4-enoate **7** might reasonably be expected to give substituted tetrahydrofuran **8** (Scheme 2). However, treatment of **7** with iodine in dry acetonitrile gave solely a 2:1 mixture of the *syn*- and *anti*-lactones **9** and **10** which were separated by flash chromatography and their structures confirmed by ^{1}H- and ^{13}C-NMR as well as nOe studies. When water was added to the reaction mixture, a similar ratio of lactones **9** and **10** was obtained but in higher overall yield (80% compared with 50% yield under anhydrous conditions). Iodolactonisation of **7** also occurred with iodine in acetonitrile in the presence of base but in this case a mixture of the *anti* and *syn* ethyl 2,4-dihydroxy-5-iodopentanoates **11** and **12** as well as lactones **9** and **10** were formed initially. On standing, diols **11** and **12** cyclised to lactones **9** and **10**.



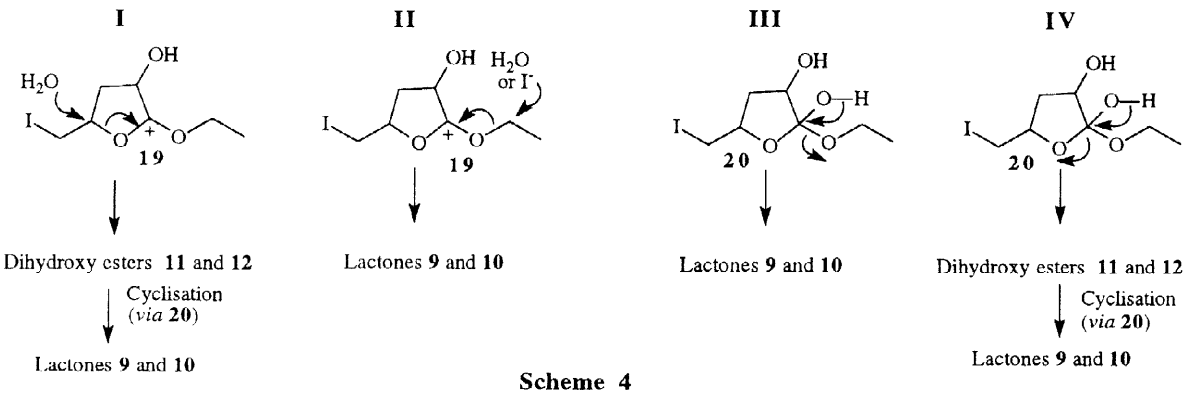
Scheme 2

Although the iodolactonisation of γ,δ-unsaturated esters is precedented,[7] the reaction has been reported to be slow and indeed Bartlett and Myerson demonstrated that iodocyclisation of α-hydroxy ester **13** gives exclusively the tetrahydrofuran **14**, no lactones were detected (Scheme 3).[8] Interestingly, Knight and co-workers have shown that treatment of (*E*)-3-hydroxy alkenoates **15** with iodine and sodium hydrogen carbonate gave mainly the expected iodo-tetrahydrofurans **16** whereas the (*Z*)-isomers **17** gave exclusively the hydroxy-tetrahydrofurans **18**.[9] It was proposed that formation of the hydroxylated products involved participation of the ester functionality.



Scheme 3

Mechanisms to account for the observed products from iodolactonisation of hydroxy ester **7** are proposed in Scheme 4. Attack of the ester group on the iodonium functionality gives the stabilised cation **19** which may react in four ways. Water may be incorporated at C-4 (pathway **I**) to give diols **11** and **12** which then cyclise to the lactones, alternatively *O*-alkyl fission would lead directly to lactones **9** and **10** (pathway **II**). Nucleophilic attack of water on the cation at C-1 would give orthoester **20**, a precursor to lactones **9** and **10** either directly by elimination of ethoxide (pathway **III**) or *via* the diols (pathway **IV**). The mechanisms of iodocyclisation in the presence and absence of base were investigated using oxygen-18 labelling studies.



Scheme 4

First, hydroxy ester **7** was treated with iodine (3 equivalents) in acetonitrile in the presence of $H_2{}^{18}O$ (95% enriched) giving lactones **9** and **10**. The *anti* lactone **10** showed a 78% incorporation of ^{18}O (by MS) located solely in the carbonyl oxygen (^{13}C-NMR, δ176.86 and δ176.90, in *ca.* 3.5:1 ratio corresponding to ^{18}O and ^{16}O carbonyl groups respectively) no isotope shift was apparent for the signal at δ67.4 assigned to C-5 or for any of the other signals. The *syn* lactone **9** had 85% incorporation of ^{18}O also located solely in the carbonyl group (^{13}C-NMR, δ176.79 and δ176.83, in *ca.* 7:1 ratio corresponding to ^{18}O and ^{16}O carbonyl groups respectively), no isotope shift was apparent for the signal at δ68.82 assigned to C-5 or for any of the other signals. Since diols **11** and **12** are apparently not intermediates in this reaction, it may be concluded that pathway **III** is favoured. Treatment of **7** with iodine (3 equivalents) in dry acetonitrile then quenching with $H_2{}^{18}O$ gave lactones **9** and **10** directly with no incorporation of oxygen-18 by MS or ^{13}C-NMR spectroscopy which is consistent with pathway **II**.

Oxygen-18 studies were also used to investigate the mechanism of iodolactonisation of **7** in the presence of base whereby diols **11** and **12** are initially formed (*via* pathways **I** or **IV**) then cyclise on standing to lactones **9** and **10**. Treatment of **7** with iodine (3 equivalents) and sodium hydrogen carbonate in dry acetonitrile and work up with $H_2{}^{18}O$ gave the diols which cyclised to lactones **9** and **10**. It was apparent from ^{13}C-NMR spectroscopy that there was a good incorporation of oxygen-18 solely into the carbonyl group of the lactones indicating that pathway **IV** predominates in this case. Hence it is apparent that the precise mechanism of the reaction is very much dependent on the conditions employed.

These investigations shed further light on the apparently conflicting results on halocyclisation described in the literature. Kočovský and Tureček have shown that bromolactonisation of a steroidal γ,δ-unsaturated ester with hypobromous acid in $H_2{}^{18}O$ leads to incorporation of oxygen-18 into the carbonyl group of the resultant lactone and thus proceeds *via* an analogous mechanism to pathway **III** (Scheme 4).[10] In contrast, Bartlett[8] and Jager[11] have suggested that the slow rate and high stereoselectivity observed in iodolactonisation of β-substituted-γ,δ-unsaturated esters with iodine in *dry* acetonitrile are consistent with a rate-determining dealkylation of a cationic intermediate (i.e. analogous to pathway **II**). Both sets of results are in good agreement with our observations on the iodolactonisation of hydroxy ester **7** in the presence of $H_2{}^{18}O$ or under anhydrous conditions followed by the addition of $H_2{}^{18}O$.

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