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Medium ring stereocontrol in the functionalisation of eight-membered lactones

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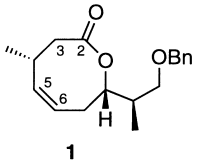
Abstract

Medium ring lactones with up to three substituents have been prepared as single diastereoisomers via Claisen rearrangement. Application of medium ring stereocontrol to a γ,δ-unsaturated eight-membered ring lactone prepared by this route enabled the overall diastereoselective functionalisation of all but one of the ring positions. A comparison of the ring-induced selectivity was made with that of the corresponding acyclic hydroxy ester which exhibited an overall reversal of stereoselectivity. This methodology provides access to highly substituted polyketide fragments.

Keywords: asymmetric induction; lactones; stereocontrol; oxygenation.

Medium rings exhibit well-defined conformational preferences[1] which lead to impressive diastereoselectivity in the functionalisation of these systems.[2–5] Substrate control of functionality has been widely exploited in asymmetric synthesis.[6] However, the facial selectivity for medium rings is less predictable than for smaller ring substrates, and less attention has been focused in this area. Medium ring systems form the core of many natural products and the reliable stereoselective functionalisation of such rings is therefore an important and desirable aim. We report here the diastereoselective functionalisation of the unsaturated eight-membered lactone **1** and the comparison of these results with the corresponding acyclic hydroxy ester **2**.



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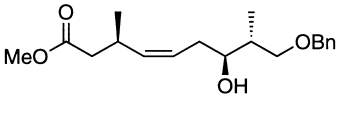

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The lactone **1** has been synthesised via the Claisen rearrangement of a ketene acetal prepared by in situ thermal selenoxide elimination from a seleno acetal.[7] Reaction of **1** with potassium carbonate in

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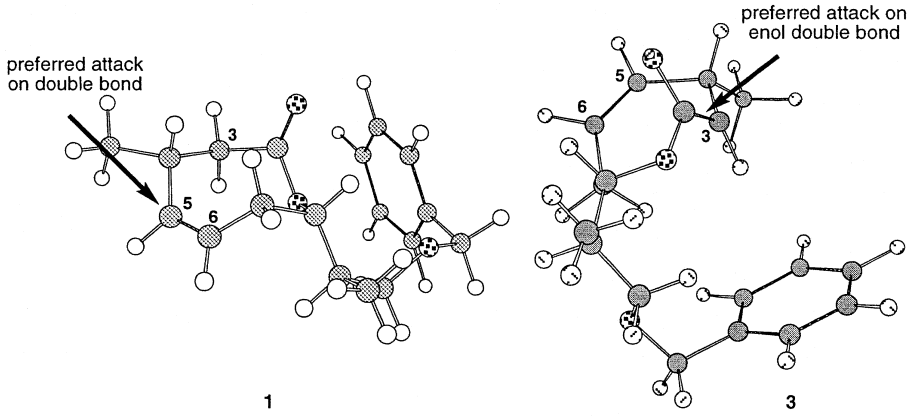


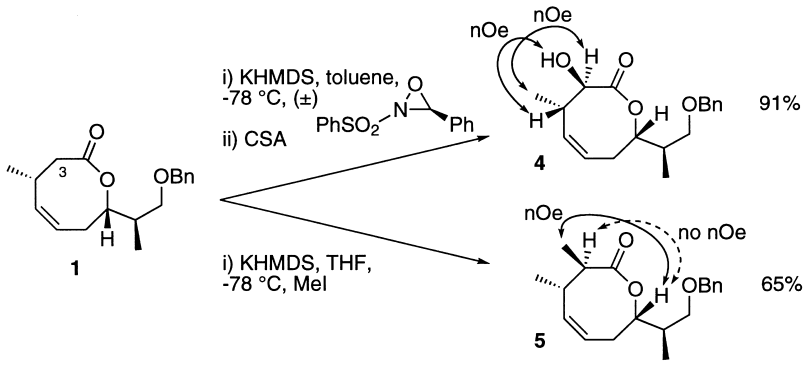
Figure 1. Global minima of the lactone **1** and the enol **3** calculated using Macromodel®. Molecular modelling was carried out with in vacuo simulation

methanol gave quantitative conversion to the methyl ester **2**. The preferred conformation of the lactone was determined via a Monte Carlo[8] conformational search using the MM2 forcefield[9] in Macromodel® version 5.5.[10] The global minimum clearly shows that the β-face (as drawn) is more exposed owing to the cup-like conformation adopted by the lactone ring and should, therefore, be attacked preferentially (Fig. 1). Similar modelling was carried out on the enol **3** of the lactone **1**; the global minimum of the enol shows that the β-face of the enol double bond is more exposed to electrophilic attack at C-3.

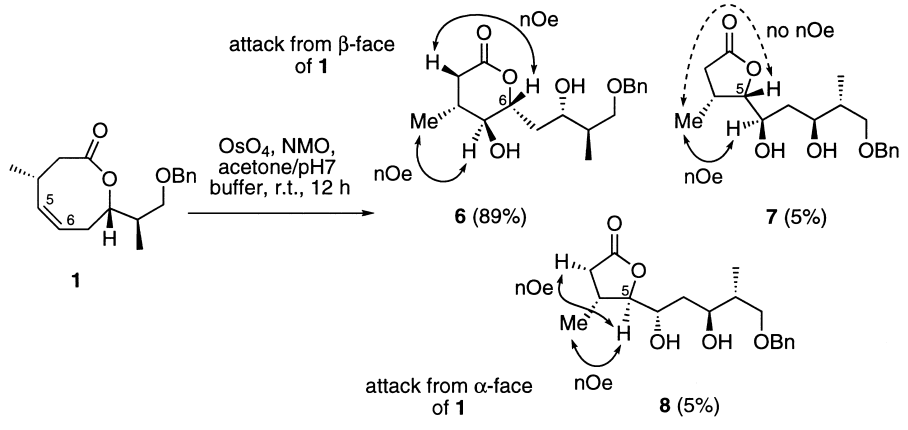
C-3 functionalisation. Functionality at C-3 could be introduced through enolate formation and subsequent reaction with an electrophile. Certain enolates of eight-membered lactones have been found to be relatively unstable to elimination to the ketene, and formation of the enolate itself can be extremely substrate-dependent.[11] Hydroxylation of the lactone **1** was accomplished by oxidation of the potassium enolate (formed by use of KHMDS in toluene) with the Davis oxaziridine,[12] followed by a camphorsulfonic acid quench at −78°C, which gave the hydroxylactone **4** in 91% yield.† When a saturated ammonium chloride solution was used to quench the reaction at the same temperature the yield was reduced to 61%. Methylation of the lactone at C-3 was effected using KHMDS in THF to generate the potassium enolate. Subsequent addition of methyl iodide gave the methyl-substituted lactone **5** in 65% yield. Under the same conditions with toluene as solvent, an inferior yield of 20% was obtained. Both reactions afforded single diastereomers, the stereochemistries of which were assigned by ^{1}H NMR nOe experiments (Scheme 1).

C-5–C-6 functionalisation. Dihydroxylation of the double bond of the lactone **1** was effected by treatment with a catalytic quantity of osmium tetroxide and 4 equivalents of *N*-methylmorpholine-*N*-oxide in acetone:pH7 buffer, 4:1.[13] The initial dihydroxylation products underwent in situ translactonisation to give a mixture of diols (Scheme 2). The observed facial selectivity was approximately 19:1 in favour of attack from the β-face of the lactone (as drawn) in agreement with the modelling prediction. The major product, following ring-contraction, was the six-membered ring lactone **6**. The structures of the lactones were assigned through ^{1}H NMR and IR evidence; the carbonyl stretching frequencies of the lactones **7** and **8** occurred at 1770 cm^{-1} which is characteristic of five-membered ring lactones. ^{1}H NMR COSY experiments also confirmed the ring sizes through assignment of the C-6 protons as *endo*- or *exo*-cyclic. The relative configurations of the lactones were confirmed via ^{1}H NMR nOe enhancements.

† Full characterisation (^{1}H NMR, COSY, ^{13}C NMR, IR, microanalysis) was obtained on compounds **2**, **4**, **6**, **9** and **10**; (^{1}H NMR, COSY, ^{13}C NMR, IR, mass spectrometry) on compounds **5**, **7**, **8**, and **11**.

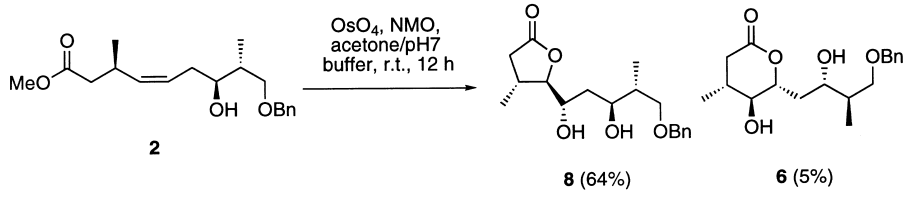


Scheme 1. C3 functionalisation of the lactone **1** with nOe evidence for product stereochemistry



Scheme 2. Dihydroxylation of the lactone **1** with nOe evidence for assignment of stereochemistry of the products **6**, **7** and **8**

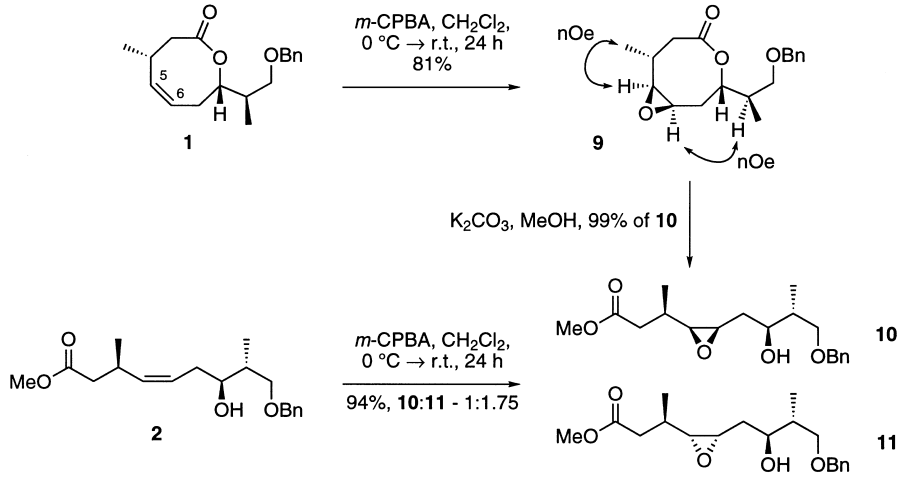
By contrast, the methyl ester **2** predominantly gave the five-membered lactone **8** when subjected to the same osmylation conditions, with a small amount of **6** also being observed (Scheme 3). Presumably, direction of attack to the α-face of **2** is mediated by the homoallylic OH group.[14,15] The reversal of selectivity complements the near exclusive attack from the β-face observed upon dihydroxylation of the lactone **1**. No six-membered lactone was formed following attack on the α-face of **2**. In contrast to the formation of the six-membered lactone following dihydroxylation of the β-face of the lactone **1**, the corresponding dihydroxylation of the α-face of **2** afforded only five-membered ring products. This observation may reflect an unfavourable conformation for cyclisation of the acyclic precursor to the (unobserved) six-membered product.



Scheme 3. Dihydroxylation of the methyl ester **2**

Epoxidation of the unsaturated lactone **1** was carried out using *m*-CPBA in CH_2Cl_2. The epoxide **9** was isolated as a single diastereomer in 81% yield. The configuration of the epoxide was again determined by ^{1}H NMR nOe enhancements to be the product of attack on the β-face of the olefin, as

predicted. The epoxylactone was opened with methanolic potassium carbonate to give the epoxyester **10** in quantitative yield. This sequence is to be compared with the epoxidation of the acyclic olefin **2** which gave a mixture of epoxides **10** and **11**, the identities of which were confirmed by comparison with the spectra of **10** prepared via lactone epoxidation/ring opening (Scheme 4). Interestingly, the overall selectivity of functionalisation was again reversed for the methyl ester compared with the lactone. The ratio of products **10**:**11** was 1:1.75, a lower selectivity for epoxidation of **2** from the α-face than that of dihydroxylation.



Scheme 4. Epoxidation of the lactone **1** and methyl ester **2**

Conclusion. The conformational preference of the lactone **1** enabled highly diastereoselective functionalisation at the C-3, C-5 and C-6 positions. The stereochemistries of all products were unambiguously determined via nOe experiments. High facial selectivity was observed for reaction of the lactone double bond compared with the acyclic methyl ester **2** which showed a reversal of diastereoselectivity. This powerful methodology enables reliable functionalisation of eight-membered lactones at all of the available ring positions. Investigation is ongoing into highly functionalised fragments of this type, which may serve as precursors for polyketides and other natural products.

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