Preferential Formation of Five-membered Rings in Two Claisen Cyclisations

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α-Lithiations of the acetoxy groups of **1** and **2** lead to Claisen cyclisations in which five-membered rings are formed much faster than six-membered rings; this selectivity is opposite to that of aldol condensations.

Lithium bis(trimethylsilyl)amide induces intramolecular Claisen condensations of α-acetoxy esters to γ-lactones and of α-mono- or α,α-di-substituted β-acetoxy esters to δ-lactones; without an α-substituent in the β-acetoxy esters the α,β-elimination becomes the predominant reaction.[1,2] Both five- and six-membered ring lactones can thus be prepared in this way and the question arises which ring size is the preferred. Intramolecular competition between the two cyclisation modes is possible in triester **1**. This compound was synthesized† and a solution of it (1.40 g) in tetrahydrofuran (THF) was added dropwise to 2.5 equiv. of lithium bis(trimethylsilyl)amide in THF (−78 °C). After 2 h the cold reaction mixture was poured onto dilute hydrochloric acid. The crude product (1.12 g) was separated into acidic (0.85 g) and neutral components (0.20 g) by partition between diethyl ether and aqueous sodium hydrogen carbonate. The acidic fraction consisted mainly of the tetronic acid **3** (73% yield, tautomeric mixture). Capillary column GLC and ^{1}H NMR analysis‡ of crude **4** obtained by *O*-acetylation of crude **3** (Scheme 1) showed that any six-membered ring lactone

† Diethyl 3,3-dimethyl-2-hydroxybutanedioate was prepared as described[3] (with some modifications in the workup) and then acetylated with acetyl chloride (25 equiv., reflux, 17 h) to give **1** in a purity exceeding 99% (capillary column GLC). The NMR spectra confirmed the structure and the high purity.

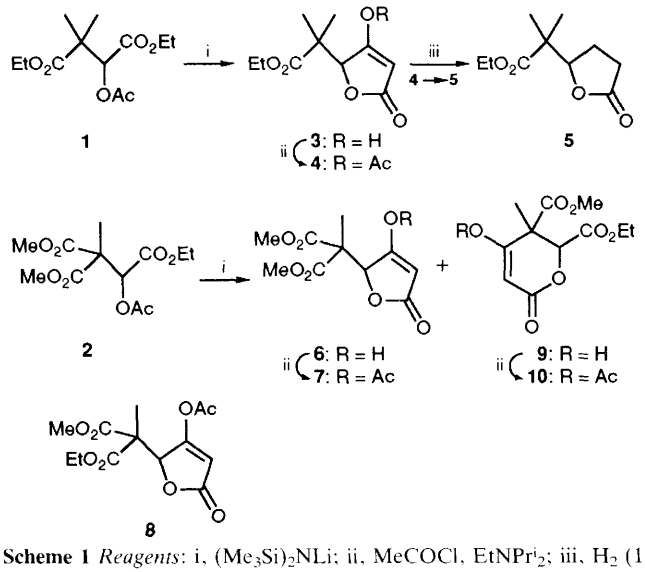
‡ *Selected spectroscopic data*: ^{1}H NMR spectra of **4**, **7**, **8**, and **10** (270 MHz) were run on $CDCl_3$ solutions using $SiMe_4$ as internal reference. Electron impact mass spectra (70 eV) are presented as *m/z* (relative abundance).

Compound **4**, ^{1}H NMR: δ 1.11 (s, 3H), 1.31 (t, 3H, *J* 7.1 Hz), 1.36 (s, 3H), 2.25 (s, 3H), 4.21 (10 resonances, 2H), 5.19 (d, 1H, *J* 1.5 Hz) and 6.18 (d, 1H, *J* 1.5 Hz).

Compound **7**, ^{1}H NMR: δ 1.43 (s, 3H), 2.25 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 5.63 (d, 1H, *J* 1.5 Hz) and 6.21 (d, 1H, *J* 1.5 Hz). MS: 43 (100), 69 (18), 115 (24), 145 (16), 175 (10), 213 (10) and 244 (18), M^+ = 286 lacking.

Compound **8**, ^{1}H NMR: δ 1.28 (t, 3H, *J* 7.1 Hz), 1.44 (s, 3H), 2.25 (s, 3H), 3.81 (s, 3H), 4.23 (9 resonances, 2H), 5.61 (d, 1H, *J* 1.5 Hz) and 6.21 (d, 1H, *J* 1.5 Hz). MS: 43 (100), 69 (17), 115 (16), 129 (12), 159 (19), 189 (16), 213 (9), 227 (5) and 258 (30), M^+ = 300 lacking.

Compound **10**, ^{1}H NMR: δ 1.31 (t, 3H, *J* 7.0 Hz), 1.44 (s, 3H), 2.23 (s, 3H), 3.82 (s, 3H), 4.28 (q, 2H, *J* 7.1 Hz), 5.41 (s, 1H) and 6.27 (s, 1H). MS: 43 (100), 69 (19), 85 (11), 112 (9), 117 (14), 126 (26), 127 (14), 173 (19), 185 (9) and 258 (8), M^+ = 300 lacking.



Scheme 1 *Reagents*: i, $(Me_3Si)_2NLi$; ii, MeCOCl, $EtNPr^i_2$; iii, H_2 (1 atm), PtO_2, Et_2O

present must amount to less than 1%. In dilute solution in $CDCl_3$ **3** was a 3 : 1 mixture of keto and enol forms (^1H NMR), but in more concentrated solutions the ratio was 1 : 1 (^{13}C NMR, *cf.* ref. 2). The structure was proved by a two-step reduction[4] to **5** (Scheme 1), which was indistinguishable (^1H NMR) from a sample of **5** prepared by condensing[5] succinic anhydride with ethyl lithioisobutyrate, followed by reduction of the resulting keto ester acid with sodium borohydride and lactonisation.

In an attempt to favour the ring-closure to δ-lactone, we turned to the tetraester **2**. This compound can give a δ-lactone by reaction of the α-lithiated acetoxy group with any one of the two *methyl* ester functions, or give a γ-lactone by reaction with one *ethyl* ester function. Compound **2** was synthesised in three steps.§ The base-induced ring-closure of **2** (0.85 g) and workup were carried out as for **1**. The crude product (0.73 g) was separated as above into an acidic (0.47 g) and a neutral fraction (0.19 g). *O*-Acetylation (Scheme 1) of the acidic fraction gave a mixture of three enol acetates (GLC ratios 73 : 15 : 12; ^1H NMR ratios 78 : 15 : 7). Chromatography on silica gel and characterisation by electron impact mass and ^1H NMR spectroscopy showed that the major component was **7**, that the 15% component was the transesterification product **8**, and that the minor component was the six-membered ring compound **10**.‡ As expected, the NMR spectra of **8** and **10** are similar and the only diagnostically useful difference is the splitting of the two strongly shifted 1H-signals. In **8** there is an allylic coupling of ^4J 1.5 Hz, whereas in **10** the two protons are seen as singlets. Clear differences in the mass spectra‡ support the conclusion that **8** and **10** are structural isomers rather than stereoisomers. Both compounds consist of a strongly predominant stereoisomer; the relative configurations have not been studied.

In summary, the intramolecular Claisen condensations of **1** and **2** proceed with five-/six-membered ring selectivities of >100 : 1 and *ca.* 10 : 1, respectively. The main reactions, leading to **3** and **6**, respectively, belong to Baldwin's category 5-(enol-*endo*)-*exo*-*trig* ring closures.[7] Such reactions are regarded as disfavoured whereas the corresponding 6-(enol-*endo*)-*exo*-*trig* reactions are regarded as favoured (*e.g.* in aldol condensations[7]). Evidently, our intramolecular Claisen condensations do not follow this generalisation.¶

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§ The sodium enolate of dimethyl methylmalonate (NaH, Et_2O) was *C*-acylated with ethoxalyl chloride (reflux, 1 h) and the resulting α-keto ester (79%, *cf.* ref. 6) then reduced with zinc dust in acetic acid (23 °C, 17 h). After filtration and evaporation of excess acetic acid, the crude hydroxy ester was acetylated with acetyl chloride (25 equiv. reflux, 16 h) to give **2**, which was purified by silica gel chromatography and distillation (47% overall yield; purity >97%, capillary column GLC). The NMR spectra confirmed the structure and the high purity.

¶ A referee considered the five- and six-membered ring tetrahedral intermediates (denoted 5T and 6T, respectively) formed in the competing ring-closing steps and assumed that 'the torsional strain is probably higher in 6T than in 5T (full substitution on adjacent carbon atoms). Consequently if transition states resemble their intermediates it is possible that formation of 6T could be slower, leading to the observed result'.