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Ring-opening of lactones with enolate nucleophiles: a simple access to functionalised β-ketoesters, β,δ-diketoesters and β-ketosulfoxides

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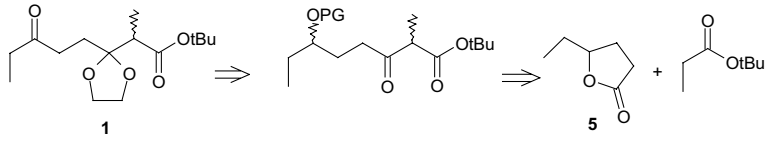
Abstract—γ-, δ- and ε-Lactones are readily opened by stabilised carbanions to the corresponding bis- or tris-silyl ethers, which can be selectively cleaved to 5- 6- or 7- silyloxy-3-ketoesters, 3,5-diketoesters, or 2-ketosulfoxides.

β-Polyketoesters[1] and β-ketosulfoxides[2] are versatile building blocks in synthesis. They are generally prepared by acylation of the corresponding stabilised carbanion nucleophiles using esters,[1,3,4] Weinreb amides,[5] or anhydrides.[6] As a part of our studies directed toward the total synthesis of Pamamycin-607,[7] the preparation of ketone **1** prompted us to explore the chemistry of carbanion additions to the carbonyl group of lactones (Scheme 1). This sequence was thought to be a simple and direct route to such a diketoester equivalent, as both propionate and lactone can be purchased.

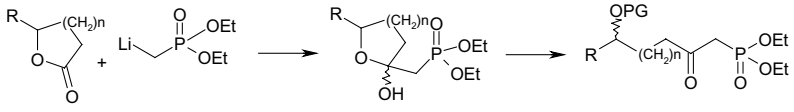
Surprisingly, whereas the condensation of stabilised anions on γ- and δ-lactones leading to the corresponding cyclic hemiketals (Meinwald procedure) is well-documented,[8] trapping of the open keto form by selective protection of the alkoxide function is only described when methylphosphonates are used as carbanion sources (Scheme 2).[9]

One paper also mentioned very briefly the condensation of the dilithiated dianion of enone–esters **3** on δ-valerolactone **2** to give ω-hydroxy-diketoesters **4** (Scheme 3).[8e]

Herein, we describe the application of Hoffmann's sequence[9] using ester enolates as nucleophiles on different lactones and its extension to the preparation of very



Scheme 1.



Scheme 2.

Keywords: Lactone ring-opening; Ketosulfoxides.
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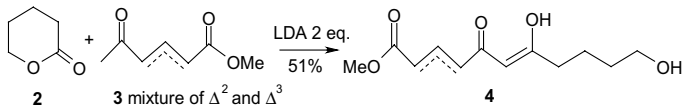
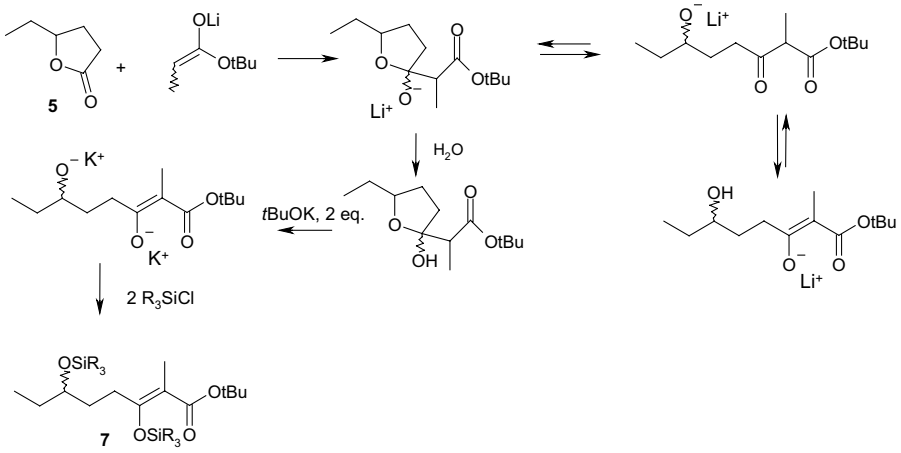


Scheme 3.



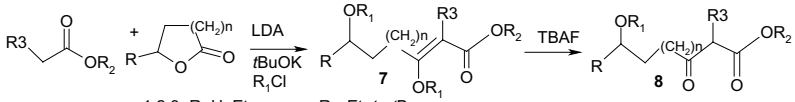
Scheme 4.

useful 5-(or 6)-silyloxy-β,δ-diketoesters and β-ketosulfoxides. In order to prepare ketone **1**, we first studied the addition of *tert*-butyl propionate to γ-caprolactone **5**. The lithium enolate of the ester, formed by deprotonation using 1 equiv of LDA in THF, adds smoothly to the lactone to produce a hemiketal, which exists as an equilibrium mixture of its cyclic and open-chain isomers (Scheme 4).

According to Hoffmann, the open-chain form is favored by forming the lithium or potassium dianion, either by adding a second equivalent of base to the previous reaction mixture, or by hydrolysing and treating the resulting crude hemiketal with 2 equiv of base.

Unfortunately, in contrast with Hoffmann's ketophosphonates, treatment of the potassium open-chain

Table 1. Ring-opening of lactones **2**–**4** with lithium enolate anions[10]



Entry	Lactones	Lithium enolate	Silyl protecting group	Isolated yield of bis-silyl compound **7** (%)	Overall yields (%)
1		Ethyl acetate	TBDMS	62	57
2		*tert*-Butyl acetate	TBDMS	85	**79**
3			TBDPS	78	71
4	**5**	*tert*-Butyl propionate	TBDMS	86	**82**
5			TBDPS	79	**75**
6		Ethyl acetate	TBDMS	68	61
7			TBDPS	61	55
8	**2**	*tert*-Butyl acetate	TBDMS	87	**80**
9		*tert*-Butyl propionate	TBDMS	90	**82**
10			TBDPS	61	54
11		Ethyl acetate	TBDMS	52	48
12			TBDPS	40	33
13	**6**	*tert*-Butyl acetate	TBDMS	85	**77**

dianion with 1 equiv of a bulky silylating agent does not result in regioselective protection of the hydroxyl group. A mixture of hemiketal, mono- and bis-silylated products is obtained. This suggests that β-ketoester enolates are more reactive towards silylating agents than the corresponding β-ketophosphonate enolates. However, when 2 equiv of silylating reagent are used together with the potassium dianion (produced from the ketal by reaction with potassium *tert*-butoxide), the bis-silylated adduct **7** is obtained cleanly and can be purified by silica gel chromatography. The resulting silyl enol ether is surprisingly stable under acidic conditions. Thus, various Brønsted or Lewis acidic conditions either gave no conversion or, under harsh conditions, led to concomitant deprotection of both silyl groups followed by an unwanted cyclisation reaction. Selective deprotection of the silyl enol ether was achieved using 1 equiv of TBAF in THF at 0 °C or rt, affording the β-ketoester **8** cleanly in high yield (>90%).

This reaction sequence has been extended to δ-valerolactone **2** and ε-caprolactone **6** using *tert*-butyl propionate and acetate as well as ethyl acetate. The reaction proceeds more efficiently with *tert*-butyl acetate (Table 1, entries 2, 8, 13) than with ethyl acetate (Table 1, entries 1, 6, 11). The less hindered ester is known to give side-products derived from self-condensation of the ester enolate.[8a] Additionally, if acetates are used, the intermediate bis-silylated derivatives **7** are less stable and the silyl enol ethers are partially cleaved during silica gel chromatography.

The deprotection of compounds **5** by 1 equiv of TBAF is equally selective, and neither secondary nor primary silyloxy groups resulting from the opening of the various lactones are cleaved in the process. Thus compounds **8** are obtained smoothly and in good yield. The results are listed in Table 1.

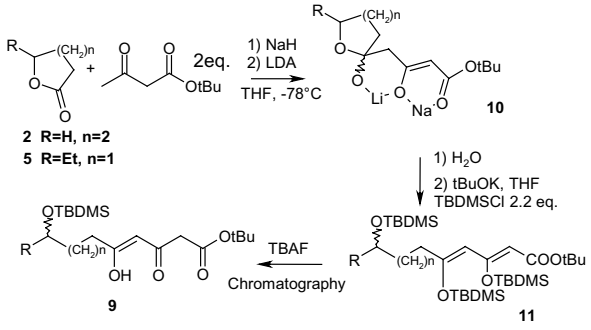
While this procedure works well for ester enolates, extension to the preparation of silyloxy-β,δ-diketoesters **9** and β-ketosulfoxides **12** results in slightly lower yields (Scheme 5 and Table 2).

In contrast with compounds **4**, hydrolysis of lithium hemiketalides **10** led to mixtures of hemiketals and their corresponding open-chain form (Table 2, entries 2, 4).

Whereas the conversion of lithium hemiketalides **10** to the corresponding tris-silylated derivatives **11** was good, the purification of crude material gave mixtures of compounds **9** and **11** even when alkaline treatment (NEt_3 5%) of silica gel was performed before the chromatography.

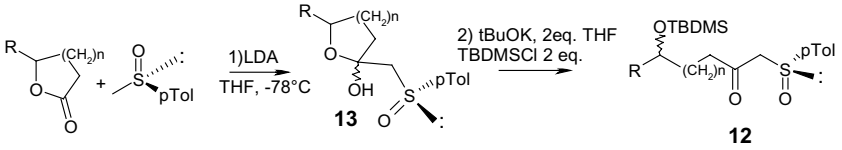
In the case of lactone ring-opening using a methylsulfoxide carbanion, hemiketals **13** were nicely isolated from crude material where no open-ring form can be detected and subsequent treatment with 2 equiv of *t*-BuOK and 2 equiv of TBDMSCl led directly to β-ketosulfoxides **12** after purification (Table 2, entries 1, 3). While only 1 equiv of TBDMSCl should be enough to convert hemiketals **13** to β-ketosulfoxides **12**, we noticed that overall yields were better when using excess of silylating agent.

In summary, γ-, δ- and ε-lactones are readily opened by stabilised carbanions to the corresponding bis- or tris-silyl ethers, which can be selectively cleaved to 5-, 6-, or 7- silyloxy-3-ketoesters, -3,5-diketoesters, or 2-ketosulfoxides. It is the first example of preparation of β-ketosulfoxides from the corresponding lactones.



Scheme 5.

Table 2. Ring-opening of lactones **2** and **5** with methyl-*para*-tolylsulfoxide and *tert*-butyl acetoacetate anions[11]



Entry	Lactones	Lithium enolate	Overall yields of **9** or **12** (%)
1		Methyl-*p*-tolyl sulfoxide	45
2		*tert*-Butyl acetoacetate[a]	40
	5		
3		Methyl-*p*-tolyl sulfoxide	60
4		*tert*-Butyl acetoacetate[a]	55
	2		

[a] Two equivalents of *tert*-butyl acetoacetate dianion are used, excess of *tert*-butyl acetoacetate is removed from crude mixture by distillation.

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10. *Typical procedure for β-ketoester preparation. Lactone opening*: a solution of diisopropylamine (1.63 g, 16.13 mmol, 1.05 equiv) in 20 mL anhydrous THF under argon is cooled to −78 °C and *n*-butyllithium (1.6 M in hexanes, 10 mL, 16 mmol, 1.05 equiv) is added slowly. After 15 min at −78 °C, a solution of *tert*-butyl propionate (2 g, 15.36 mmol, 1 equiv) in 10 mL anhydrous THF is added dropwise via cannula. After another 30 min a solution of γ-caprolactone **5** (1.75 g, 15.36 mmol, 1 equiv) in 10 mL anhydrous THF is also added slowly via cannula. The reaction is stirred at −78 °C for 2 h and quenched by addition of 2 mL of methanol. The reaction mixture is hydrolysed with 50 mL of saturated ammonium chloride solution and extracted with 3×50 mL of ethyl acetate. The combined organic layers are dried over magnesium sulfate, filtered and the solvents are removed in vacuo to afford a yellowish oil. The crude hemiketal is dissolved in 30 mL anhydrous THF at room temperature under argon and potassium *tert*-butoxide (3.13 g, 27.94 mmol, 2.1 equiv) is added in small portions to avoid heating of the reaction mixture. After 15 min of stirring at rt, *tert*-butylchlorodimethylsilane (4.21 g, 27.94 mmol, 2.1 equiv) is added and the reaction is stirred for another 10 min. The reaction mixture is diluted with 50 mL of water and extracted with 3×50 mL of ethyl acetate. The organic layers are dried over magnesium sulfate, filtered and the solvents are removed under reduced pressure to afford 6.05 g of the crude product as a viscous yellow oil, which is purified by flash chromatography on silica gel (*n*-hexane–ethyl acetate 50:1). The pure bis-silylated product **7** is obtained as colourless very viscous oil (5.93 g, 86%).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.61 (m, 1H), 2.67–2.50 (m, 2H), 1.75 (s, 3H), 1.72–1.58 (m, 2H), 1.52–1.42 (m, 2H), 1,48 (s, 9H), 0.96 (s, 9H), 0.89 (s, 9H), 0.87 (t, J = 7.5 Hz, 3H), 0.20 (s, 3H), 0.18 (s, 3H), 0.04 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 163.2, 110.3, 79.3, 73.4, 34.6, 31.3, 29.9, 28.3, 25.8, 18.3, 13.4, 9.2, −4.5.
Silyl enol ether deprotection: the bis-silylated adduct **7** (3 g, 6.35 mmol, 1 equiv) obtained following the previous procedure is dissolved in 40 mL THF and cooled to 0 °C, followed by a slow dropwise addition of TBAF (1 M solution in THF, 6.35 mL, 6.35 mmol, 1 equiv). After completion of the reaction, the reaction mixture is diluted with 100 mL of saturated ammonium chloride solution and extracted with 3×50 mL of ethyl acetate. The combined organic layers are washed with 50 mL water and 50 mL of brine, dried on magnesium sulfate and filtered. Evaporation of the solvents under reduced pressure affords a yellow oil, which is purified by flash chromatography on silica gel (*n*-hexane–diethyl ether 20:1). The β-ketoester **8** is obtained as a colourless viscous oil (2.14 g, 95%).
^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.63 (m, 1H), 3.43 (q, J = 7 Hz, 1H), 2.74–2.44 (m, 2H), 1.84–1.60 (m, 2H), 1.52–1.42 (m, 2H), 1.45 (s, 9H), 0.89 (s, 9H), 0.86 (t, J = 7.5 Hz, 3H), 0.05 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.5, 169.8, 81.6, 72.4, 53.9, 37.0, 29.9, 29.6, 27.9, 25.9, 18.1, 12.8, 9.6, −4.5.
11. *Typical procedure for β-ketosulfoxide preparation*: a solution of diisopropylamine (1.01 g, 10 mmol, 1 equiv) in 20 mL anhydrous THF under argon is cooled to −78 °C and *n*-butyllithium (1.6 M in hexanes, 6.25 mL, 10 mmol, 1 equiv) is added slowly. After 30 min at −78 °C, a solution of (+)-methyl-*p*-tolyl sulfoxide (1.54 g, 10 mmol, 1 equiv) in 10 mL anhydrous THF is added dropwise via cannula. After 1 h a solution of δ-valerolactone **2** (1 g, 10 mmol, 1 equiv) in 10 mL anhydrous THF is also added slowly via cannula. The reaction is stirred at −78 °C for 2 h and quenched by addition of 5 mL of methanol. The reaction mixture is hydrolysed with 50 mL of saturated ammonium chloride solution and extracted with 3×50 mL of ethyl acetate. The combined organic layers are dried over magnesium sulfate, filtered and the solvents are removed in vacuo to afford a white oil corresponding to hemiketal **13**.
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53 and 7.36 (A_2X_2, 4H aromatics, J = 8 Hz), 5.5 (d, 1H, 2.5 Hz), 3.82 (m, 2H), 3.03 and 2.78 (AB, 2H, J = 13 Hz), 2.4 (s, 3H), 1.78 (m, 2H), 1.44 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).
The α-sulfinyl-hemiketal **13** was dissolved in 100 mL anhydrous THF at room temperature under argon and potassium *tert*-butoxide (2.5 g, 22.2 mmol, 2 equiv) is added in small portions to avoid heating of the reaction mixture. After 45 min of stirring at rt, when potassium *tert*-butoxide is completely dissolved, *tert*-butylchlorodimethylsilane (3.34 g, 22.2 mmol, 2 equiv) is added and the reaction is stirred for another 10 min. The reaction mixture is diluted with 50 mL of water and extracted with 3×50 mL of ethyl acetate. The organic layers are dried over magnesium sulfate, filtered and the solvents are removed under reduced pressure to afford 4.55 g of the crude product as a viscous yellow oil. The product is purified by gradient chromatography on demetallated silica gel[12] using *n*-hexane–ethyl acetate 6:1 as eluent. The pure product **12** is obtained as viscous yellow oil (1.95 g, 64%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (d, 4H aromatics, J = 8 Hz), 3.8 (dd AB, 2H, J = 5.5 Hz), 3.6 (t, 2H, J = 14 Hz), 2.52 (q, 2H, J = 8 Hz), 2.4 (s, 3H), 1.6 (m, 2H), 1.46 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.5, 142.1, 139.1, 130.1, 124.1, 68.1, 62.6, 62.6, 44.7, 31.9, 25.9, 21.4, 19.6, 18.3.
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