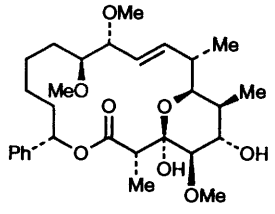
Synthesis of Substructures of Soraphen A: Formation of the Enolate of Benzyl Propionate

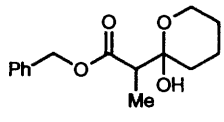
Bernard Loubinoux,[a] Jean-Luc Sinnes*,[a] and Anthony C. O'Sullivan[b]
[a] *Laboratoire de Chimie Organique 4, Faculté des Sciences, B.P. 239, 54506 Vandoeuvre-les-Nancy Cédex, France*
[b] *Ciba-Geigy AG, Crop Protection Division, CH-4002 Basle, Switzerland*

During the preparation of substructures of the fungicidal natural product soraphen A **1**, it was observed that the β-keto ester **12** was formed as the major product upon deprotonation of benzyl propionate with LDA. Studies of the stability of the enolate **13** showed that two mechanisms previously described for the decomposition of ester enolates cannot be operating in this example. A competition between deprotonation and condensation is proposed, which is in accord with the results described here and in the literature. The use of a *reactive* base is shown to provide good yields of the enolate **13**. In addition, temperature is shown to be another factor influencing the yield of **13**.

Soraphen A **1** is a macrolide isolated from the myxobacterium *Sorangium cellulosum* by Höfle and co-workers.[1] It was shown to possess potent fungicidal activity.[2] Although the molecule is amenable to total synthesis,[3] it was thought possible that the fungicidal activity of soraphen A could be invoked by simpler molecules. The structure **2**, shown alongside soraphen A, was



Soraphen A **1**



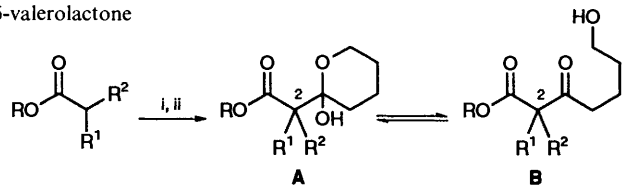
Model compound **2**

chosen because it contains the hemiacetal and phenyl functionality found in the bottom half of the soraphen molecule.[4] The reaction of ester enolates with lactones (Meinwald reaction[5]) was thought to be a simple and direct route to such compounds, as both esters and lactones can be either purchased or easily prepared. Furthermore, the reaction has been used for the synthesis of many natural products,[6] including efrotomycin[7] and pederin,[8] indicating the wide scope of the reaction.

Results and Discussion

Treatment of δ-valerolactone with the lithium enolates of the esters **3**–**7** resulted in the formation of the desired hemiacetals **2** and **8**–**11** (Table 1). The compounds exist as mixtures of slowly interconverting hemiacetal **A** and hydroxy ketone **B** tautomers.[4] The hydroxy ketone tautomers **B** are β-keto esters which undergo keto–enol tautomerisation[9] in addition to the opening and closure of the ring. The enols were not detected in the mixture by ^{1}H NMR spectroscopy, but the enolisation was apparent from the behaviour of compound **2**, which exists as a mixture of two hemiacetal diastereoisomers **2A**$_1$ and **2A**$_2$, epimeric at C-2, plus the hydroxy ketone tautomer **2B**. On dissolution of **2** in $CDCl_3$, a mixture of the three isomers **2A**$_1$, **2A**$_2$ and **2B** in a ratio of 25:28:47 was observed by ^{1}H NMR. The composition of the tautomeric mixture changed slowly, reaching equilibrium after *ca.* 24 h, with a final product ratio of 19:59:22. The tautomerisation was

Table 1 Reaction of the lithium enolate of the esters **3**–**7** with δ-valerolactone



A **B**

Reagents and conditions: i, LDA (1 equiv.), −78 °C, THF; ii, δ-valerolactone (1 equiv.), −78 °C

Esters	Products	A:B	Yield (%)
3	**8**	82:18	81
4	**9**	47:53	48
5	**10**	91:9	55
6	**2**	53:47	8
7	**11**	32:68	46

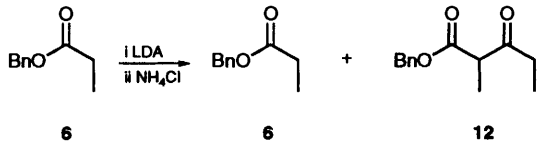
3, 8	R = Bu^t, R^1 = R^2 = H
4, 9	R = Bu^t, R^1 = Me, R^2 = H
5, 10	R = $PhCH_2$, R^1 = R^2 = H
6, 2	R = $PhCH_2$, R^1 = Me, R^2 = H
7, 11	R = $PhCH_2$, R^1 = R^2 = Me

not accelerated by the addition of [$^2H_5$]pyridine, but addition of a small amount of [$^2H_4$]acetic acid caused equilibrium to be reached in a few minutes. The equilibrium ratio of the hemiacetal and hydroxy ketone tautomers is dependent on the substitution pattern at C-2 as can be seen from Table 1. Increasing the number of methyl groups at this position favours the ring opened hydroxy ketone tautomers. These interconversions mirror the behaviour of soraphen A **1** itself,[10] although the tautomerisation in the latter case is very much slower, presumably because it is accompanied and encumbered by changes in ring conformation.

Attempted reaction of the enolates of 1- or 2-naphthyl propionate with δ-valerolactone under the standard conditions[5] was unsuccessful as only unchanged starting material was recovered, perhaps due to decreased reactivity of the enolates. More serious was the very low yield of compound **2** which is structurally the closest model of soraphen A **1** in this series. Only a small amount of the benzyl ester **6** was recovered, the main product being the Claisen condensation product **12**. The protocol described by Meinwald[5] was followed using a small excess of the ester **6** compared with LDA (lithium

diisopropylamide), however even equimolar amounts or a small excess of base led to low yields of **2**. It was surprising that such a seemingly trivial reaction should perform so poorly, and as **2** represents our most important target compound some effort was invested in improving its synthesis. An indirect approach failed. Attempted deprotection of the *tert*-butyl group of the ester **9** with trifluoroacetic acid resulted in rapid decomposition, presumably due to the lability of the hemiacetal moiety. Therefore, an investigation for the reason of the low yield of **2** in the Meinwald reaction was undertaken.

Formation of the Enolate of Benzyl Propionate.—It was readily found that the β-keto ester **12** did not arise as a by-product in the Meinwald reaction but that it was present in the enolate solution before the addition of δ-valerolactone. Addition of the benzyl propionate **6** to a solution of 1 equiv. of LDA in THF at *ca.* −60 °C in a conventional manner, followed by quenching with aqueous NH_4Cl led to recovery of **6** accompanied by large amounts of **12** (Scheme 1). Rather than

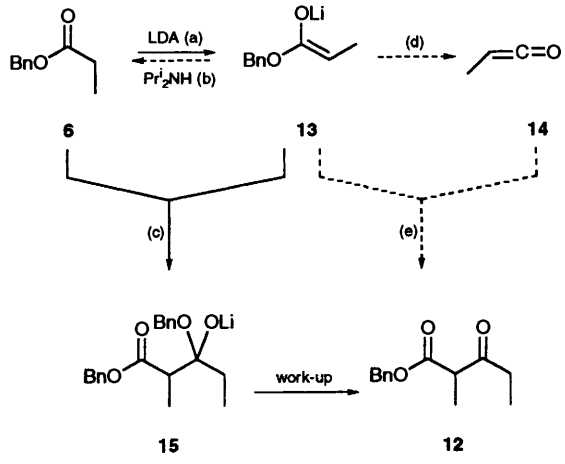


6 **6** **12**

Scheme 1

skirting the problem by optimising the reaction empirically, a systematic study of the origin of the unwanted Claisen condensation product **12** was undertaken in the expectation that an elucidation of the root of the problem would allow measures to be taken that may expand the scope of ester enolate formation and usage.

Problems with the formation of ester enolates have often been encountered, and the formation of by-products has been attributed to the instability of the enolate **13** as described below and shown in Scheme 2. Possible decomposition pathways are:



15 **12**

Scheme 2 Possible mechanisms for the formation of the β-keto ester **12** during the deprotonation of the ester **6**

1. Reversibility of ester deprotonation: this would entail the reprotonation of the enolate **13** with diisopropylamine (b),[11] followed by a condensation of the resultant **6** with another molecule of enolate **13** (c).

2. Formation of a ketene intermediate: here alkoxide would be eliminated (d) forming a ketene **14** which would combine with the enolate **13** (e) to form **12**. Enolate decomposition to ketene is a known process,[12] but temperatures of *ca.* 0 °C were required for the enolates described. This reaction has been much studied and even elaborated to a useful synthetic method.[13] The reaction of ketenes with enolates has also been described.[14]

To distinguish between these possible mechanisms the stability of the enolate **13** was examined. It was generated at −78 °C in a typical fashion by slow addition of benzyl propionate **6** in THF to a solution of LDA in THF–hexane at −78 °C. At this temperature samples were taken from the enolate solution using a syringe encased in solid CO_2[15] and quenched with aqueous NH_4Cl. The resultant mixtures were analysed by GC.

As can be seen from Table 2 (entries 1 and 2), the amount of β-keto ester **12** did not increase with time. The lithium enolate **13** is thus stable at −60 °C in THF. The β-keto ester **12**, or rather the adduct **15**, must be formed concomitantly with the enolate **13** (Scheme 2). Therefore, we conclude that the β-keto ester **12** arises from a rapid irreversible[16] ester–enolate (Claisen) condensation (c), which is fast enough to compete with ester deprotonation (a). This simple explanation has never been explicitly proposed as a cause of failure in enolate formation.

This mechanistic proposal is in accord with what is known about the effects of variation of the reaction parameters on the yields obtained from enolate reactions. For example, it can be surmised that the superiority of *tert*-butyl[17] (or even more hindered[18]) esters in enolate formation and reaction is not due to the stability of their enolates,[19] but rather to the stability of their carbonyl groups towards nucleophilic attack.[20] The unwanted Claisen reaction is thus slowed without the rate of ester deprotonation being greatly influenced. Similarly, the beneficial effects of an excess of base can be understood as being due to a more rapid rate of reaction (a) with no change in the rate of (c). Furthermore, the stability of the enolate **13** is incompatible with the two alternative mechanisms detailed above.

Effect of Base.—In the light of the conclusion drawn above, that the amount of the β-keto ester **12** formed during the deprotonation of **6** is determined by the relative rates of the two processes (a) and (c), it can be seen that the rate of (c) will not vary substantially with the base used, but that of (a) will be influenced considerably. Thus, the key to success in ester enolate formation is the use of a *reactive* base. The effect of a series of bases, commonly used for enolate formation, was examined. Again the low temperature quench method[15] was used to acquire the results shown in Table 2.

The enolate **13** is converted slowly into **12** in the presence of hexamethyldisilazane (entries 3 and 4). Hexamethyldisilazane (pK_a = 29.5)[21] is more acidic than diisopropylamine (pK_a = 34.4)[22] and it seems to cause a reprotonation [(b) in Scheme 2] of the enolate **13** (pK_a = *ca.* 24.5),[23] resulting in the formation of the ester **6** and eventually, through reaction of **6** with **13**, in the formation of **12**. Silylamides as bases have been described as unsuitable for the deprotonation of esters.[15,24]

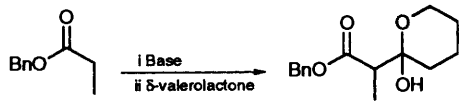
The basicity of lithium dialkylamides is increased by the presence of branching alkyl groups on the amine[21] which are electron donating. At the same time the reactivity of these bases is decreased by the steric hindrance of these additional alkyl groups.[21] LTMP[25] (lithium tetramethylpiperidide) is presumably so reactive[26] because it is more basic than LDA—tetramethylpiperidine has a pK_a of 37.0[22] in comparison with 34.4[22] for that of Pr$^i_2$NH—and at the same time it is less sterically hindered than the equally substituted Bu$^t_2$NLi (pK_a Bu$^t_2$NH *ca.* 38)[22] because the alkyl groups are bound in a ring.[27]

Having shown LTMP to be a superior base for formation of the enolate **13**, the Meinwald condensation of **13** with δ-valerolactone was repeated with this base. It was gratifying to find that a good yield of the desired condensation product **2** was formed (Table 3). Also, when the enolate **13** was used in

Table 2 Amount (%) of the β-keto ester **12** formed after different reaction times (min)

			12 (Yield %)						
Entry	Base	*t*/min	5	10	15	30	60	90	120
1	LDA		31	35	32	30	35	30	34
2	LTMP		3	5	4	4	5	6	5
3	$LiN(SiMe_3)_2$		15	22	26	34	49	56	—
4	$NaN(SiMe_3)_2$		32	36	48	52	57	53	—

Table 3 Effect of base and temperature on the yield of compound **2**

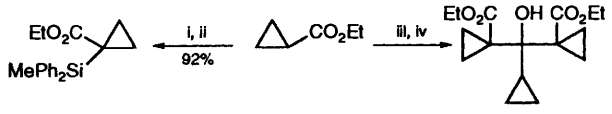


6 **2**

Base	Temp. of enolate preparation (°C)	Yield (%)
LDA	−78	8
LDA	−100	50
LTMP	−78	60

condensation reactions with other more substituted lactones[28] the yield of the desired condensation product was consistently higher when LTMP rather than LDA was used as a base.

Effect of Temperature.—An additional factor which may influence the yield of **13** can be understood from the work of Prieto *et al.*[29] who have shown that ethyl cyclopropanecarboxylate **16** can be deprotonated with LDA at −100 °C and subsequently silylated, whereas the same ester **16** led only to the condensation product **18** when deprotonation was attempted at −78 °C.[30]



17 **16** **18**

Scheme 3 Effect of temperature on the formation of the enolate of **16**. *Reagents and conditions:* i, LDA, THF, −100 °C; ii, $MePh_2SiCl$; iii, LDA, THF, −78 °C; iv, Me_3SiCl.

The effect of temperature on enolate formation was examined for the reaction of benzyl propionate **6**. Addition of **6** to a solution of LDA at −100 °C followed by warming to −78 °C and addition of δ-valerolactone led to **2** in 50% yield in comparison to 8% when the enolate was prepared at −78 °C. Clearly the two competing reactions (a) and (c) have very different thermodynamic parameters and the low temperature has a beneficial effect in suppressing the formation of the β-keto ester **12**.

Variation in Yields.—Although in every experiment conducted the enolate **13** was stable at −70 °C after addition of the ester **6** to a solution of LDA or LTMP (Table 2), there were differences in the proportion of the enolate **13** formed during addition of the ester **6** to the solution of base. The level of **12** varied between 8 and 35% with LDA and between 3 and 16% with LTMP, but remained constant once addition was complete. Clearly there are factors operating which this work cannot account for but which probably relate to the complex nature of the mechanism of enolate formation. Although the formation of lithium enolates is one of the most commonly used procedures in organic synthesis, the mechanism of this reaction is poorly understood, and as far as we can ascertain no studies of the rate of ketone or ester deprotonations have been published. It seems that complexation and decomplexation steps are involved in the mechanism[31–35] and that the reaction is very rapid. Under such circumstances a variation in the rate of ester deprotonation can be expected.

Conclusions

We propose that during the deprotonation of benzyl propionate **6** the β-keto ester **12** is formed by a Claisen condensation [(c) in Scheme 2] which competes with ester deprotonation [(a) in Scheme 2]. Consequently, the rate of (a) relative to (c) can be increased by the use of a more reactive base, as was demonstrated with the use of LTMP which afforded a much higher yield of **2** than LDA. In addition, the observation of Prieto[29] was confirmed that low temperatures (−100 °C) have a positive effect on the yield of the enolate **13**.

The compounds **2** and **8–11** were inactive as fungicides when tested against a series of plant pathogens.† Similarly, they were inactive as inhibitors of acetyl coenzyme A carboxylase at concentrations up to 300 times the IC_{50} value of Soraphen A,‡ which is known to exert its fungicidal effect through inhibition of this enzyme.[36]

Experimental

General.—NMR spectra were measured in $CDCl_3$ with tetramethylsilane as internal standard on a Varian Unity 500 (500 MHz ^1H), a Bruker 250 (250 MHz ^1H) or a Varian XL 300 (75 MHz ^{13}C) spectrometer. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. Capillary GC using a packed Supelco SE-54 (0.25 μm) fused silica capillary column (30 m, 0.25 mm ID) was performed with Carlo Erba HRGC 5160 Mega Series. Dry tetrahydrofuran (THF) was freshly distilled from sodium–benzophenone prior to use. Temperatures were measured internally using an Ebro TTX 690 thermometer protruding through a septum into the reaction flask. Glassware was flame-dried and cooled under nitrogen. TLC analyses were performed using Merck pre-coated silica 60F254 plates. Column chromatography was carried out on Merck silica gel 60 (230–400 Mesh).

tert-*Butyl Esters* **8** *and* **9** *and Benzyl Esters* **10**, **2** *and* **11**.—*General procedure.* Under an argon atmosphere BuLi (1.6 mol dm^{-3} in hexane; 37.5 cm^3, 60 mmol) was added slowly to a solution of diisopropylamine (10.2 cm^3, 72 mmol) in dry THF (30 cm^3) at 0 °C. The mixture was stirred for 45 min and then cooled to −78 °C, when a solution of *tert*-butyl acetate (8.35 g, 72 mmol) in dry THF (30 cm^3) was added slowly to it. After 1 h at −78 °C a solution of δ-valerolactone (6 g, 60 mmol) in dry

† We thank Dr. Roland Zeun (Ciba) and his colleagues for screening these compounds.

‡ The tests described here were performed by Michelle Moreau, Susan Schenk and Jacqueline Schmidt, Ciba, Basle.

THF (24 cm^3) was added slowly to this mixture, which was then stirred at this temp. for 2 h. The reaction mixture was quenched with acetic acid (12 cm^3) dissolved in dry THF and allowed to warm to room temp. It was then diluted with Et_2O and poured into water. After separation of the layers the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, dried (K_2CO_3) and concentrated. Chromatography of the residue on silica gel (EtOAc–hexane, 1:5) yielded the product mixture **8A** and **B** (10.5 g, 81%); *m/z* (CI) 215 $[M - H]^-$ and 197 $[M - H - H_2O]^-$; $\nu_{max}(CHCl_3)/cm^{-1}$ 3610 and 3450 (OH) and 1730 and 1710 (CO).

tert-*Butyl* (2′-*hydroxytetrahydropyran*-2′-*yl*)*acetate* **8A**. δ_H(500 MHz) 1.39–1.64 (m, 3′-H_2 and 4′-H_2), 1.48 (s, Bu^{t}O), 1.70 (m, 5′-H_{eq}), 1.90 (ddddd, *J* 13.5, 13.5, 13.5, 4.5 and 4.5, 5′-H_{ax}), 2.47 (d, *J* 15, 2-H), 2.53 (d, *J* 15, 2-H), 3.63 (m, 6′-H_{eq}), 3.98 (ddd, *J* 5, 10 and 10, 6′-H_{ax}) and 5.02 (d, *J* 2.5, OH); δ_C 171.8 (C-1), 94.7 (C-2′), 81.9 (*C*Me_3), 61.3 (C-6′), 45.9 (C-2), 35.0 (C-3′), 28.1 (Me), 25.1 (C-5′) and 18.6 (C-4′).

tert-*Butyl* 7-*hydroxy*-3-*oxoheptanoate* **8B**. δ_H(500 MHz) 1.39–1.64 (m, 5-H_2 and 6-H, OH), 1.48 (s, Bu^{t}O), 2.59 (t, *J* 7.5, 4-H_2), 3.35 (s, 2-H_2) and 3.63 (m, 7-H_2); δ_C 203.4 (C-3), 166.6 (C-1), 62.3 (C-7), 50.6 (C-2), 42.5 (C-4), 31.9 (C-6), 28.0 (Me) and 19.5 (C-5).

tert-*Butyl esters* **9**. Distillation with kugelrohr (150 °C, 0.1 mbar) yielded the products **9** in 48% yield; *m/z* (CI) 229 $[M - H]^-$ and 127 $[M - H - HCO_2C_4H_9]^-$, $\nu_{max}(CHCl_3)/cm^{-1}$ 3620 and 3460 (OH) and 1740 and 1710 (CO) (Found: C, 62.5; H, 9.5. $C_{12}H_{22}O_4$ requires C, 62.6; H, 9.6%).

tert-*Butyl* 2-(2′-*hydroxytetrahydropyran*-2′-*yl*)*propionate* **9A**. Diastereoisomer **9A**$_1$: δ_H(500 MHz) 1.20 (d, *J* 7.5, Me), 1.47 (s, Bu^{t}O), 1.50–1.73 (m, 3′-H_2 and 4′-H_2), 1.86 (m, 5′-H_2), 2.48 (q, *J* 7.5, 2-H), 3.60 (m, 6′-H_{eq}), 3.98 (m, 6′-H_{ax}) and 4.73 (d, *J* 2.5, OH). Diastereoisomer **9A**$_2$: δ_H(500 MHz) 1.18 (d, *J* 7.5, Me), 1.47 (s, Bu^{t}O), 1.50–1.73 (m, 3′-H_2 and 4′-H_2), 1.86 (m, 5′-H_2), 2.48 (q, *J* 7.5, 2-H), 3.60 (m, 6′-H_{eq}), 3.98 (m, 6′-H_{ax}) and 4.25 (d, *J* 2.5, OH).

tert-*Butyl* 7-*hydroxy*-2-*methyl*-3-*oxoheptanoate* **9B**. δ_H(500 MHz) 1.3 (d, *J* 7.5, Me), 1.47 (s, Bu^{t}O), 1.50–1.73 (m, 5-H_2, 6-H_2 and OH), 2.53 (ddd, *J* 17.5, 7.5 and 7.5, 4-H), 2.64 (ddd, *J* 17.5, 7.5 and 7.5, 4-H), 3.43 (q, *J* 7.5, 2-H) and 3.64 (t, *J* 7.5, 7-H_2).

Benzyl esters **10**. Chromatography on silica gel (EtOAc–hexane 1:3) yielded the product mixture **10A** and **B** in 55% yield; $\nu_{max}(CHCl_3)/cm^{-1}$ 3610 and 3490 (OH) and 1745 and 1720 (CO) (Found: C, 67.2; H, 7.3. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2%).

Benzyl (2′-*hydroxytetrahydropyran*-2′-*yl*)*acetate* **10A**. δ_H(500 MHz) 1.40–1.70 (m, 3′-H_2 and 4′-H_2), 1.76 (m, 5′-H_{eq}), 1.90 (m, 5′-H_{ax}), 2.59 (d, *J* 16, 2-H), 2.70 (d, *J* 16, 2-H), 3.63 (m, 6′-H_{eq}), 3.98 (ddd, *J* 4, 10 and 10, 6′-H_{ax}), 4.72 (d, *J* 2, OH), 5.15 (d, *J* 12, C*H*Ph), 5.23 (d, *J* 12, C*H*Ph) and 7.29–7.40 (m, ArH); δ_C 172.1 (C-1), 129.5 (Ar), 94.8 (C-2′), 66.8 (*C*H_2Ph), 61.4 (C-6′), 45.2 (C-2), 35.0 (C-3′), 25.1 (C-5′) and 18.6 (C-4′).

Benzyl 7-*hydroxy*-3-*oxoheptanoate* **10B**. δ_H(500 MHz) 1.40–1.70 (m, 5-H_2 and 6-H_2, OH), 2.58 (t, *J* 8, 4-H_2), 3.50 (s, 2-H_2), 3.62 (m, 7-H_2), 5.19 (m, C*H*$_2$Ph) and 7.29–7.40 (m, ArH); δ_C 203.4 (C-3), 167.0 (C-1), 135.5 (ArC), 67.2 (*C*H_2Ph), 62.3 (C-7), 49.2 (C-2), 42.7 (C-4), 31.9 (C-6) and 19.5 (C-5).

Benzyl esters **2**. Chromatography on silica gel (EtOAc–hexane 1:6) yielded the products **2** (8%) and **12** (84%); *m/z* (FD) 265 $(M + H)^+$; $\nu_{max}(CHCl_3)/cm^{-1}$ 3620 and 3480 (OH) and 1750 and 1720 (CO) (Found: C, 68.6; H, 7.9. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%).

Benzyl 2-(2′-*hydroxytetrahydropyran*-2′-*yl*)*propionate* **2A**. Diastereoisomer **2A**$_1$: δ_H(500 MHz) 1.21 (d, *J* 7.5, Me), 1.45–1.68 (m, 3′-H_2 and 4′-H_2), 1.86 (m, 5′-H_2), 2.69 (q, *J* 7.5, 2-H), 3.63 (m, 6′-H_{eq}), 3.97 (m, 6′-H_{ax}), 4.42 (d, *J* 2.5, OH), 5.55 (d, *J* 12.5, C*H*Ph), 5.59 (d, *J* 12.5, C*H*Ph) and 7.29–7.40 (m, ArH); δ_C 176.7 (C-1), 96.9 (C-2′), 66.5 (*C*H_2Ph), 61.3 (C-6′), 48.6 (C-2), 32.0 (C-3′), 25.2 (C-5′), 18.6 (C-4′) and 12.6 (Me). Diastereoisomer **2A**$_2$: δ_H(500 MHz) 1.27 (d, *J* 7.5, Me), 1.45–1.68 (m, 3′-H_2 and 4′-H_2), 1.86 (m, 5′-H_2), 2.70 (q, *J* 7.5, 2-H), 3.63 (m, 6′-H_{eq}), 3.97 (m, 6′-H_{ax}), 4.71 (d, *J* 5, OH), 5.55 (d, *J* 12.5, C*H*Ph), 5.59 (d, *J* 12.5, C*H*Ph) and 7.29–7.40 (m, ArH); δ_C 174.4 (C-1), 96.6 (C-2′), 66.6 (*C*H_2Ph), 61.4 (C-6′), 49.7 (C-2), 31.4 (C-3′), 25.1 (C-5′), 18.6 (C-4′) and 11.7 (Me).

Benzyl 7-*hydroxy*-2-*methyl*-3-*oxoheptanoate* **2B**. δ_H(500 MHz) 1.34 (d, *J* 5, OH), 1.37 (d, *J* 7.5, Me), 1.45–1.68 (m, 5-H_2 and 6-H_2), 2.48 (ddd, *J* 17.5, 7.5 and 7.5, 4-H), 2.58 (ddd, *J* 17.5, 7.5 and 7.5, 4-H), 3.58 (m, 2-H and 7-H_2), 5.54 (d, *J* 12.5, C*H*Ph), 6.03 (d, *J* 12.5, C*H*Ph) and 7.29–7.40 (m, ArH); δ_C 205.7 (C-3), 170.4 (C-1), 67.1 (*C*H_2Ph), 62.3 (C-7), 52.9 (C-2), 41.0 (C-4), 31.9 (C-6), 19.5 (C-5) and 12.8 (Me).

Benzyl 2-*methyl*-3-*oxopentanoate* **12**. δ_H(250 MHz) 1.03 (t, *J* 7, CH_2CH_3), 1.37 (d, *J* 7, $CHCH_3$), 2.50 (m, CH_2), 3.59 (q, *J* 7, CH), 5.19 (s, CH_2Ph) and 7.35 (m, ArH).

Benzyl esters **11**. Chromatography on silica gel (EtOAc–hexane 1:3) yielded the product mixture **11A** and **B** in 46% yield; *m/z* (CI) 277 $(M - H)^-$; $\nu_{max}(CHCl_3)/cm^{-1}$ 3620 and 3500 (OH) and 1730 and 1715 (CO).

Benzyl 2-(2′-*hydroxytetrahydropyran*-2′-*yl*)-2-*methylpropionate* **11A**. δ_H(500 MHz) 1.38 (s, Me), 1.52 (m, 5′-H), 1.59 (m, 3′-H_2 and 4′-H_2), 1.71 (m, 5′-H), 3.65 (m, 6′-H_{eq}), 4.00 (t, *J* 5, 6′-H_{ax}), 4.82 (d, *J* 2.5, OH); 5.53 (s, CH_2Ph) and 7.32–7.42 (m, ArH).

Benzyl 7-*hydroxy*-2,2-*dimethyl*-3-*oxoheptanoate* **11B**. δ_H(500 MHz) 1.39 (s, Me), 1.43 (m, 6-H_2), 1.60 (m, 5-H_2), 2.11 (s, OH), 2.40 (t, *J* 7.5, 4-H_2), 3.55 (t, *J* 7.5, 7-H_2), 5.17 (s, CH_2Ph) and 7.32–7.42 (m, ArH); δ_C 207.9 (C-3), 173.5 (C-1), 67.1 (*C*H_2Ph), 62.3 (C-7), 55.7 (C-2), 37.6 (C-4), 32.0 (C-6), 22.0 (Me) and 19.8 (C-5).

Low Temperature Investigation of the Stability of the Lithium Enolate of Benzyl Propionate **13**.—Under an argon atmosphere, a solution of benzyl propionate (658 mg, 4 mmol) in dry THF (2 cm^3) was added slowly to a solution of base (4 mmol) at −78 °C. At different times (see Table 2) samples (*ca.* 1 cm^3) were taken from the enolate solution using a syringe encased in solid CO_2. These samples were put in a cold flask (−78 °C) under argon, quenched with saturated aqueous NH_4Cl (0.4 cm^3) and allowed to warm to room temp. The mixture was then diluted with Et_2O (1 cm^3) and analysed by GC. The retention times for the benzyl alcohol, benzyl propionate and β-keto ester were 5.2, 9.1 and 15.5 min, respectively.

Synthesis of Benzyl 2-(2′-*Hydroxytetrahydropyran*-2′-*yl*)-*propionate* **2** *with LTMP*.—Under an argon atmosphere BuLi (1.6 mol dm^{-3} in hexane; 2.5 cm^3, 4 mmol) was added slowly to a solution of 2,2,6,6-tetramethylpiperidine (565 mg, 4 mmol) in dry THF (5 cm^3) at 0 °C. The mixture was stirred for 45 min at 0 °C and then cooled to −78 °C, when a solution of benzyl propionate (656 mg, 4 mmol) in dry THF (2 cm^3) was added slowly to it. After 45 min at −78 °C a solution of δ-valerolactone (400 mg, 4 mmol) in dry THF (2 cm^3) was added slowly to this mixture, which was then stirred for 2 h before being quenched with saturated aqueous NH_4Cl (1 cm^3) and allowed to warm to room temp. It was then diluted with Et_2O and washed with water. After separation of the layers, the aqueous layer was extracted with EtOAc and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc–toluene 1:4) yielded the benzyl esters **2** (633 mg, 60%).

Synthesis of Benzyl 2-(2′-*Hydroxytetrahydropyran*-2′-*yl*)-*propionate* **2** *with LDA at* −100 °C.—Under an argon atmosphere BuLi (1.6 mol dm^{-3} in hexane; 3.8 cm^3, 6.09 mmol)

was added slowly to a solution of diisopropylamine (0.86 cm^3, 6.09 mmol) in dry THF (8 cm^3) at 0 °C. The mixture was stirred for 30 min at this temp. and then cooled to −100 °C when a solution of benzyl propionate (1 g, 6.09 mmol) in dry THF (3 cm^3) was added slowly to it. After 15 min at −100 °C the mixture was allowed to warm to −78 °C, when a solution of δ-valerolactone (609 mg, 6.09 mmol) in dry THF (2 cm^3) was added slowly to it. The mixture was stirred at −78 °C for 5 h after which it was quenched with saturated aqueous NH_4Cl (2 cm^3) and allowed to warm to room temp. The mixture was then extracted with Et_2O and the extract washed with water and dried (Na_2SO_4). Concentration under reduced pressure followed by chromatography of the residue on silica gel (EtOAc–toluene 1:4) yielded the benzyl esters **2** (796 mg, 50%).

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