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Stereoselective Conjugate Addition of Organolithium and Organocopper Reagents to δ-Oxygenated α,β-Unsaturated Carbonyl Systems Derived from Glyceraldehyde Acetonide

John Leonard, Soad Mohialdin, Darrell Reed, Gary Ryan and Philip A. Swain*

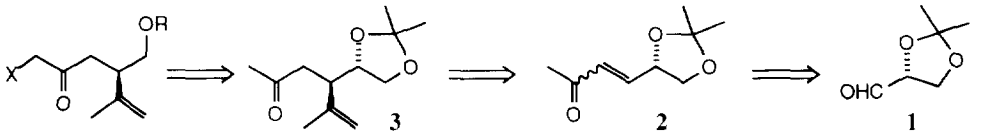
Department of Chemistry, University of Salford, Salford M5 4WT, U.K.

e-mail address: j.leonard@chemistry.salford.ac.uk

This paper is dedicated to Professor Hans Suschitzky on the occasion of his 80th birthday

Abstract: Addition reactions of organolithium and organocopper reagents to δ-oxygenated α,β-unsaturated carbonyls, derived from glyceraldehyde acetonide, have been studied. In most cases there is a strong preference for conjugate addition of the organometallic reagent. Organocopper reagents react with *anti* stereoselectively, whereas most organolithium reagents react with *syn* stereoselectivity, except for phenyllithium which is unusual.[1]

Glyceraldehyde acetonide **1** is an easily accessible chiral synthon which is available in its *R*-form from D-mannitol or from ascorbic acid in its *S*-form.[2,3] The aldehyde readily undergoes Wittig-type reactions with stabilised phosphoranes and phosphonates, providing a useful source of chiral α,β-unsaturated carbonyl compounds, such as enone **2**.[4] Our original interest in studying the diastereoselectivity of conjugate additions to enones derived from glyceraldehyde was associated with synthetic studies towards the right-hand portion of the marine cembrenolide lophotoxin.[1a] We needed a synthetic method that would provide us with an acyclic system, bearing an isopropenyl substituent at a chiral centre β-to a carbonyl group (Scheme 1). We also wanted to be able to prepare such compounds enantiomerically pure and in either enantiomeric form. We thought that these objectives could be achieved *via* a diastereoselective conjugate addition of an organometallic isopropenyl reagent to enone **2**.



Potential cembrenolide precursor - each individual enantiomer required

Diastereoselective conjugate addition

Glyceraldehyde acetonide - either enantiomer available

Scheme 1

During our initial studies with isopropenyl reagents we noticed some interesting regiochemical and stereochemical preferences and we therefore decided to broaden the scope of the study to incorporate a variety of different reagents and substrates.

Prior to our studies, several groups had carried out conjugate addition reactions on δ-oxygenated-α,β-unsaturated systems derived from carbohydrates.[5-8] In the main, copper-lithium reagents were found to give addition compounds with a high degree of *anti* stereoselectivity, and a Felkin-type transition state was proposed to account for this.[7] However, using similar substrates, allylic reagents and sulfur stabilised carbanions were found to give *syn* addition products selectively and this was not easily rationalised.[9] Cha and Lewis reported that Me_2CuLi reacted with enone **2**, derived from glyceraldehyde, with modest *anti* diastereoselectivity and we therefore expected other copper-lithium reagents to react with the same diastereoisomeric preference.[10]

RESULTS AND DISCUSSION

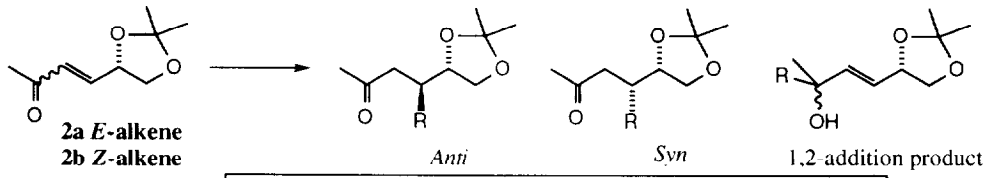
1. Addition of organometallic reagents to E and Z (5S)-5,6-(O-Isopropylidene)hex-3-en-2-one **2**

E and *Z* (5*S*)-5,6-(O-isopropylidene)hex-3-en-2-ones **2a** and **2b** were prepared by the reaction of glyceraldehyde acetonide with 1-triphenylphosphoranylidene-2-propanone.[4] The ratio of *E* and Z geometric isomers obtained depends on the solvent and the temperature of the reaction. We found that almost pure *E* isomer can be prepared easily by a 'one-pot' mannitol diacetonide diol cleavage-Wittig procedure,[4a] but for early studies we wanted to compare the reactions of the individual geometrical isomers. Thus, a 2:1 (*E*:*Z*) mixture of enones was obtained by carrying out the Wittig reaction in methanol at 0°C and the isomers were separated by preparative HPLC.

Initially various organocopper reagents were generated from isopropenyllithium and reacted with separate *E* and *Z* enones **2a** and **2b** in diethyl ether (Table 1). With each of the copper reagents only 1,4-addition products were isolated and there was a clear preference for the *anti* addition product. The reactions were slightly more selective at -100°C than at -78°C, but the difference was not significant enough to warrant the extra experimental difficulties of maintaining the lower temperature. Both enone geometrical isomers were found to react in the same stereochemical sense and although the *Z*-alkene reacted with somewhat higher stereoselectivity than the *E*-isomer, the difference was not great, and the remaining studies were therefore carried out on the *E*-isomer which is easier to prepare.[4a]

The reactions of normal cuprates (R_2CuLi) with the enones were disappointing in terms of both stereoselectivity and yield. However, higher order cuprates reacted more cleanly and with better stereoselectivity.[11] Perhaps the most surprising feature of these results was that isopropenyl copper (RCu), prepared by combining equimolar amounts of CuI and isopropenyl lithium, was the reagent of choice, in terms of both yield and stereoselectivity. This type of reagent is normally quite unreactive towards enones unless a Lewis acid is added, but in this case 1,4 addition products were formed exclusively in 80% isolated yield. Neither the incorporation of TMS-Cl or $BF_3.Et_2O$ in the reaction mixtures appeared to have any significant effect on the diastereoisomer ratios of the reaction products. When ^{n}butyl copper reagents were added to enone **2a** we were surprised to find that the stereoselectivity of the reaction was reversed, although the preference for the *syn* addition product was low.

The fact that reaction of monocopper reagents with enones **2** were highly effective indicated that the enones were particularly susceptible to conjugate addition and we therefore decided to investigate their reactions with some lithium reagents. When isopropenyllithium was reacted with enone **2**, the 1,4-addition product was the major regioisomer (19:1 ratio). The diastereoisomer selectivity for this reaction was also extremely high, but in the opposite direction to that observed with the organocopper reagent, with the *syn* isomer predominating in a ratio of 36:1. Butyllithium also reacted to give a high ratio of the *syn* conjugate addition product (15:1 ratio), but the preference for conjugate addition was not as pronounced (2.5:1 ratio). A surprising result in this series was that phenyllithium gave mainly 1,2-addition product (10:1 ratio) and although the stereoselectivity of the conjugate addition was low, the major isomer was the *anti* isomer. This result is even more curious when it is compared to the reaction of phenyllithium with extended enone **16a**, which gives almost exclusively conjugate addition products (see below).



R = MeC=CH$_2$	**3a**	**4a**	**5a**
R = Bu	**3b**	**4b**	**5b**
R = Me	**3c**	**4c**	**5c**

Scheme 2

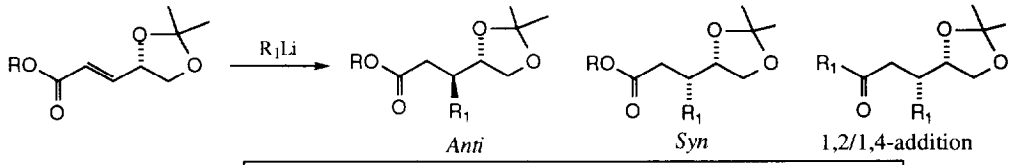
Enone	Temp°C	Solvt.	R	Reagent	1,4:1,2	Yield	ANTI	SYN
Z	-100	Et_2O	$CH_2(Me)C$-	R_2CuLi	1:0	60%	4	1
Z	-100	Et_2O	$CH_2(Me)C$-	$R_2CuCNLi_2$	1:0	73%	7	1
Z	-100	Et_2O	$CH_2(Me)C$-	R-Cu	1:0	80%	8	1
Z	-78	Et_2O	$CH_2(Me)C$-	R-Cu/ TMSCl	1:0	75%	6	1
Z	-78	Et_2O	$CH_2(Me)C$-	R-Cu/ $BF_3.Et_2O$	1:0	75%	6	1
E	-100	Et_2O	$CH_2(Me)C$-	RCu	1:0	80%	5	1
E	-100	Et_2O	$CH_2(Me)C$-	R_2CuLi	1:0	60%	3	1
E	-78	Et_2O	^{n}Bu	RCu	1:0	70%	1	1.5
E	-78	Et_2O	^{n}Bu	R_2CuLi	1:0	50%	1	3
E	-78	Et_2O	$CH_2(Me)C$-	RLi	19:1	60%	1	36
E	-78	Et_2O	^{n}Bu	RLi	2.5:1	76%	1	15
E	-78	THF	^{n}Bu	RLi	1:0	60%	1	4
E	-78	THF	Ph	RLi	1:10	76%	2	1

Table 1 - Addition of organometallic reagents to enone **2a** and **2b**.

2. Addition of organolithium reagents to methyl and ethyl E (4S)-4,5-(O-isopropylidene)pent-2-enoates ***6a/b***

Ethyl and methyl (*E*)(4*S*)-4,5-(O-isopropylidene)pent-2-enoates were readily prepared in either enantiomeric form, from D-mannitol *bis*-acetonide or ascorbic acid acetonide, by diol cleavage followed by the *in-situ* trapping of glyceraldehyde acetonide with either ethyl or methyl(triphenylphosphoranylidene) acetate.[4a]

Considering the unusual behaviour of **2a** and **2b** towards organometallic reagents, we decided to extend the study to include enoates **6a** and **6b**. When we attempted to react them with copper reagents extensive decomposition occurred and the study was therefore restricted to organolithium reagents. Methyl-, ^{n}butyl-, and isopropenyl-lithium reagents were reacted with the methyl and ethyl esters **6a** and **6b**, using both diethyl ether and THF as solvents, at -78 °C, and the results are summarised in Table 2.



6-12a R = Me
6-12b R = Et

R_1 = MeC=CH_2	**7 a,b**	**8 a,b**	**9**
R_1 = Bu	**10 a,b**	**11 a,b**	**12**
R_1 = Me	**13 a,b**	**14 a,b**	**15**

Scheme 3

RO	Temp°C	Solvt.	R	Reagent	1,4:1,2/1,4	Yield	ANTI	SYN
MeO	-78	Et_2O	MeC=CH_2	RLi	2:1	71%	0	1
EtO	-78	Et_2O	MeC=CH_2	RLi	3:1	65%	1	5
MeO	-78	Et_2O	^{n}Bu	RLi	>20:1	73%	0	1
EtO	-78	Et_2O	^{n}Bu	RLi	>20:1	66%	0	1
EtO	-78	Et_2O	^{n}Bu	RLi/LiBr	>20:1	67%	0	1
†MeO	-78	Et_2O	Me	RLi	5:1	†72%	0	1
EtO	-78	Et_2O	Me	RLi	6:1	70%	0	1
†MeO	-78	THF	MeC=CH_2	RLi	1:5*	†72%	<1	4
†EtO	-78	THF	MeC=CH_2	RLi	1:4*	†65%	<1	4
MeO	-78	THF	^{n}Bu	RLi	10:1	66%	0	1
EtO	-78	THF	^{n}Bu	RLi	4:1	66%	0	1
EtO	-78	THF	^{n}Bu	RLi/LiBr	1.5:1	66%	0	1
†MeO	-78	THF	Me	RLi	1:2	†69%	0	1
EtO	-78	THF	Me	RLi	2:1	67%	0	1

†Product contains some starting material.

*Products also contain some bis-1,2/1,4-addition product.

Table 2 - Addition of organolithium reagents to enoates **6a** and **6b**

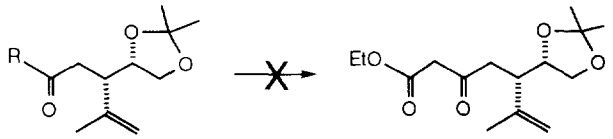
There are two striking general features of the reactions. Firstly, although some *bis*-1,2/1,4 addition product (**9**, **12**, **15**) was always formed, no mono-1,2- addition product was ever isolated, indicating that 1,4-addition is strongly favoured over 1,2 addition. Secondly, the reactions are highly *syn* stereoselective, with only traces of *anti* 1,4- addition product ever being isolated. The solvent used for the reactions was found to have a significant influence. In general, the 1,4-mono addition product (**8**, **11**, **14**) were favoured when ether was the solvent, whereas the proportion of *bis*-1,2/1,4-addition product increased when THF was used. We thought that the concentration of lithium bromide in the lithium reagent might be influential, but adding extra

lithium bromide to the butyllithium reactions appeared to have little effect. Changes to the ester group or the lithium reagent did result in small changes in the product ratio.

From a practical viewpoint, these reactions are very easily carried out on a multi-gram scale; with ether as the solvent they are of synthetic utility for preparing chiral mono *syn* 1,4- addition products (**8**, **11**, **14**) as single diastereoisomers. In contrast to the enone reactions, the butyllithium additions were particularly selective on the enoates. In some cases chromatographic separation of the mono and *bis*- addition products was difficult, but simple $NaBH_4$/MeOH treatment as part of the work-up converted the ketone to a much more polar secondary alcohol, which was very easily separated from the ester.

3. *Addition of organolithium reagents to (4E, 6S)-ethyl and methyl 6,7-(O-isopropylidene)-3-oxohept-4-enoate* ***16a/b***

For our synthetic studies towards diterpenoids, we had intended to convert the isopropenyl substituted esters or ketones, prepared as above, into an extended 1,3-dicarbonyl system (Scheme 4). Although various well precedented methods were attempted for this interconversion, none was successful and we therefore turned our attention to the more speculative possibility of adding organometallic reagents, in a conjugate fashion, to the unsaturated ketoester **16a**, which was readily prepared by one of two procedures. Initially, enone **2a** was extended by reaction of its kinetic enolate with ethyl cyano formate. On a large scale **16a** was conveniently prepared directly from D-mannitol *bis*-acetonide by $Pb(OAc)_4$ diol cleavage, followed by *in-situ* aldehyde trapping with the phosphorane derived from ethyl-4-chloroacetoacetate.[4a]



R = Me or OMe

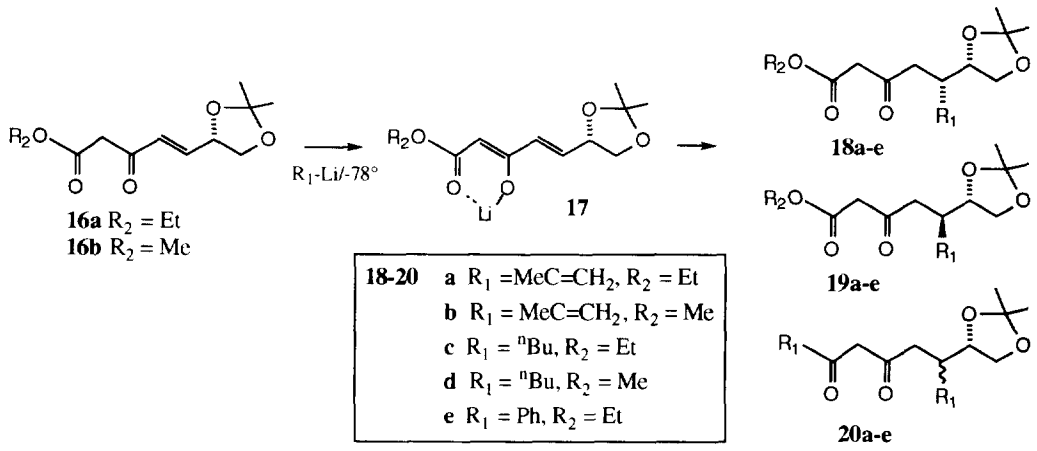
Scheme 4

The NMR spectra of **16a** and **16b** showed that they exist in solution as ~1:1 mixtures of the keto and enol forms and we anticipated problems in carrying out reactions with basic reagents. We were initially concerned that there are potentially a number of different ways in which organolithium reagents could react with the system: as a base; by addition to the ketone carbonyl; by addition to the ester carbonyl, or by conjugate addition etc. Taking these potential problems into account, we initially attempted to react the compounds with various copper-based reagents, but the reactions did not proceed cleanly. Eventually, after carrying out a series of experiments we discovered that, under carefully-controlled conditions, organolithium reagents would indeed add cleanly in a conjugate fashion to enones **16a** and **16b**.

Our initial study concentrated on the addition of isopropenyllithium to **16a**. A complex product mixture, including some starting material, was obtained when one equivalent of isopropenyllithium was reacted in THF at -78°C. Enolisation of the system will lead to depletion of the reagent, but we anticipated that if

enolate **17** was formed, it might itself be susceptible to conjugate addition. Two equivalents of the lithium reagent were therefore employed and this indeed led to conjugate addition products in up to 82% yield. A negligible quantity of 1,2-ester addition product was isolated, but the ratio of *syn* and *anti* isomers was at best 4:1, with the *syn* diastereoisomer predominating. This was a surprisingly low isomer ratio when compared with that of 36:1 for the addition of isopropenyllithium to enone **2a**. When the ester group in the starting material was changed from ethyl to methyl there was a surprising dramatic change in the outcome of the reaction and the major product became the *bis*-1,2/1,4-addition product **20a**. The nature of the solvent was also found to be important, most reactions being much cleaner in THF than in ether.

In order to evaluate the generality of this conjugate addition reaction we decided to investigate the use of other lithium reagents. ^{n}Butyllithium was again used as an example of a simple primary alkyllithium but the reaction was by no means as clean. Although the major products were those of conjugate addition, a high proportion of 1,2/1,4-addition product **20c** was produced and the *syn:anti* ratio was less pronounced. There were also several minor by-products, including the deconjugated enone, formed by deprotonation at C-6. Phenyllithium added very cleanly, in a conjugate manner, to **16a** in THF and negligible addition to the ester was observed. The stereoselectivity of the process was also high (*ca.* 12:1), but we were intrigued to discover that the major isomer was **19e**, with *anti* stereochemistry (see Table 3).



18-20 **a** R_1 = MeC=CH_2, R_2 = Et
b R_1 = MeC=CH_2, R_2 = Me
c R_1 = ^{n}Bu, R_2 = Et
d R_1 = ^{n}Bu, R_2 = Me
e R_1 = Ph, R_2 = Et

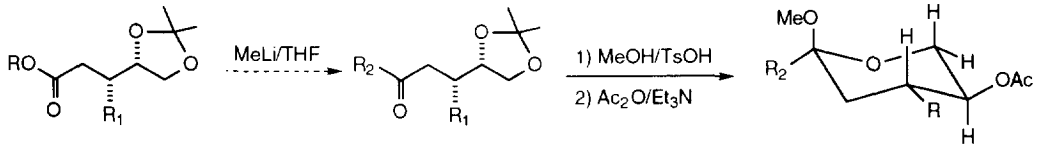
Scheme 5

R_2	Temp°C	Solvt.	R_1	Reagent	1,4:1,2/1,4	Yield	ANTI	SYN
EtO	-78	THF	MeC=CH_2	RLi	>20:1	82%	1	4
MeO	-78	Et_2O	MeC=CH_2	RLi	1:20	60%	1	1
EtO	-78	THF	^{n}Bu	RLi	3:1	66%	2	1
EtO	-78	Et_2O	^{n}Bu	RLi	6:1	55%	1	2
MeO	-78	THF	^{n}Bu	RLi	>10:1	60%	1	1
EtO	-78	THF	Ph	RLi	>20:1	66%	12	1
EtO	-78	Et_2O	Ph	RLi	>20:1	49%	5	1

Table 3 - Addition of organolithium reagents to enoates **16a** and **16b**

4. Determination of the relative configurations of the conjugate addition products

The reaction sequences used to determine the stereochemistry of the conjugate addition products were themselves interesting,[12] and will be discussed in detail in a separate full paper. For any of the ketone products with *syn* stereochemistry, hydrolysis of the isopropylidene group in acidic methanol provided a six-membered ring methyl acetal, as a single anomer, in high yield (Scheme 6). Following acetylation of the free alcohol the 300 MHz ^{1}H NMR spectra of the tetrahydropyrans were virtually first order. In each case an antiperiplanar sequence of protons attached to C-4, C-5 and C-6 was easily identified. This confirmed that the ring substituents were *trans* to one another and that the original addition products therefore had *syn* stereochemistry. In order to determine the relative stereochemistry of the ester products, they were correlated with the corresponding methyl ketones by treatment with methyllithium. The β-ketoesters could also be correlated with the methyl ketones by hydrolysis and decarboxylation on treatment with lithium hydroxide in THF/water.



Scheme 6

5. Stereoselectivity of the conjugate addition reactions

Several groups have attempted to devise a universal model to account for the stereoselectivity of addition reactions to γ-alkoxy-α,β-unsaturated systems. However, there are several unusual anomalies and none of the models proposed so far are really satisfactory. Roush originally suggested a modified Felkin-Ahn-type model,[7] with the small group (H) adopting the 'inside' position, to account for the more common *anti* addition of cuprates to γ-alkoxy-α,β-unsaturated systems. We and other workers in the field initially adopted this model and we suggested a lithium co-ordinated modification to account for the *syn* selectivity of lithium reagents (Figure 1).[1a] Morokuma *et al.*[13] and Bernardi *et al.*[14] have attempted to devise universal models to account for the observed stereoselectivities of conjugate additions to γ-alkoxy-α,β-unsaturated systems through molecular mechanics studies, but their conclusions differ. Meanwhile, Yamamoto *et al.* have suggested several models to account for the results of their wide ranging studies on the reactions of simple γ-alkoxy-α,β-unsaturated systems.[18] They suggest that some cuprates react preferentially *via* a π-complex, and that this may be responsibel for their unusual stereoselectivity.

We wanted to explain the strong preference of lithium reagents for conjugate addition, as well as the observed stereochemical preferences and we thought the two features might be. We thought that modelling the ground-state conformation of the molecules might provide some insight. Thus, MM2 calculations using

Macromodel[15] suggest that conformations in which the γ-oxygen almost overlaps the 'inside' position of the alkene bond (Figure 2) are highly preferred. Studies in the carbohydrate field also suggest that an oxygen atom overlapping with the π-system of an enone causes a lowering of its LUMO energy.[16] If this arrangement is indeed stable and reactive, it may well be retained in the transition state, with lithium reagents being directed by co-ordination with the δ-oxygen (co-ordination with the γ-oxygen may also be possible), while copper reagents (which may react *via* electron transfer) may prefer to attack from the least hindered face, away from the isopropylidene ring. Clearly other complications such as chelation could alter the conformation of the molecule in the transition state, but the arrangement with the γ-oxygen overlapping the π system does appear to be highly favoured and has indeed been used to account for stereoselection in other types of reaction.[17]

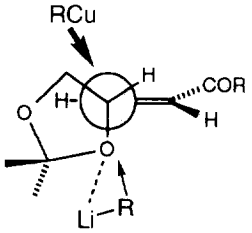


Figure 1

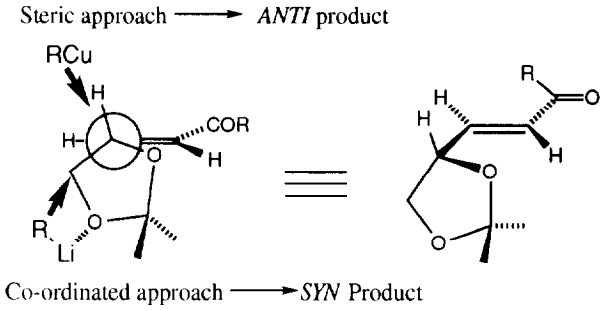


Figure 2

The extended system **16a** retains the preference for conjugate addition although the stereoselectivity is less predictable.

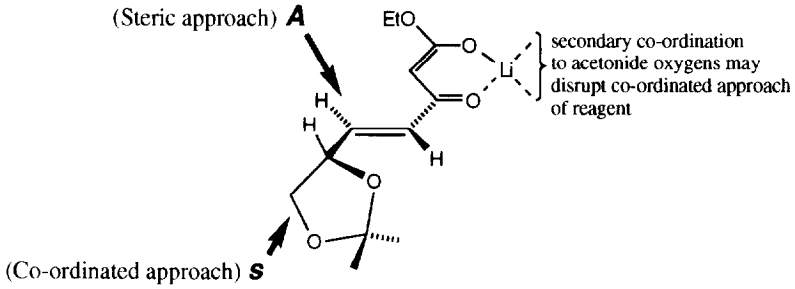


Figure 3

It could be that the ability of the isopropylidene oxygens to direct the approach of the lithium reagent is diminished in **17** because of intermolecular chelation with the lithium 1,3-dicarbonyl enolate, and that steric controlled approach, leading to *anti* addition, therefore becomes more prominent. For isopropenyl lithium *syn* (co-ordinated) addition is still predominant, although the selectivity is diminished, but phenyllithium adds with high selectivity for the *anti* product (Figure 3). It may be that chelation is negligible in this case, either because of the bulk of the phenyl anion, or because it is a softer nucleophile.

Overall, there is no universal model to account for the array of observed selectivities for additions of nucleophiles to γ-alkoxy-α,β-unsaturated systems and it may well be that different types of reagent react preferentially *via* different conformations.

The methods described here can be used to access a range of enantiomerically pure δ-oxygenated carbonyl synthons with a chiral centre of predictable stereochemistry at the γ-position. Unusual regiochemical and stereochemical preferences have been observed which are not easily explained by any simple universal model at present.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Melting point determinations were carried out on an electrothermal apparatus and were recorded uncorrected. Infra-red absorption spectra were run either neat (for liquids) or as nujol mulls (for solids) on a Perkin-Elmer 1710 FT-IR instrument or a Perkin-Elmer 297 grating spectrophotometer. ^{1}H NMR spectra were recorded, at 300 MHz a Bruker AC-300 instrument, as solutions in deuterochloroform, unless stated otherwise. Chemical shifts are referenced to tetramethylsilane and *J* values are rounded to the nearest 0.5 Hz. Where '~' precedes the multiplicity of a signal an apparent multiplicity is implied which is made up of non-equivalent couplings. Mass spectra were recorded at low resolution on a VG 12-553 instrument or a Finnigan 4500 instrument and at high resolution on a VG ZAB-E instrument or a Kratos Concept 1-S instrument. Mass spectra were recorded under chemical ionisation (CI) conditions using ammonia as the reagent gas. All organolithium reagents were titrated prior to use. After aqueous work-up of reaction mixtures, organic solutions were routinely dried with anhydrous magnesium sulphate and "evaporation" or "evaporated", refers to removal of solvent on a rotary evaporator. Thin layer chromatography was carried out using Merck Kieselgel 60 F_{254} glass backed plates. The plates were visualised by the use of a UV lamp, or by dipping in a solution of vanillin in ethanolic sulphuric acid, followed by heating. Silica gel 60 (particle sizes 40-63 μ) supplied by E.M. Merck was employed for flash chromatography.

Isopropenyl lithium solution

Isopropenyllithium was prepared by sonicating a mixture of isopropenyl bromide (5.6ml, 63mmol) and lithium dispersion (1.7g, 245mmol) in diethyl ether (100ml), under argon, for 3h. After allowing the red precipitate to to settle, the isopropenyllithium solution was transfered to a clean dry flask, under an atmosphere of argon by cannulation.

General experimental procedure for the addition of monocopper reagents (RCu) to (5S)-5,6-(O-isopropylidene)hex-3-en-2-one **2** *- (Method A)*

To a stirred suspension of CuI (450mg, 2.36mmol) in ether (30ml), under N_2 at -60°C, was added a solution of the lithium reagent (isopropenyl-, butyl- or phenyl-) (2.36mmol). The temperature was allowed to rise to -30°C for 30min, then cooled to -100°C (or -78°C) before adding a solution of *(5S)-5,6-(O-isopropylidene)hex-3-en-2-one* **2** (100mg, 0.59mmol). After 2h at -100°C (or -78°C), aqueous NH_4Cl (30ml) was added to the mixture and it was then extracted with ether (3 x 25ml). The combined organic extracts were dried and evaporated.

The ratio of products formed was determined by gc and gc/ms, and they were isolated by flash chromatography (light petroleum/ethyl acetate).

General experimental procedure for the addition of cuprate reagents (R_2CuLi) to (5S)-5,6-(O-isopropylidene)hex-3-en-2-one **2** *- (Method B)*

The procedure was identical to Method A, except that CuI (225mg, 2.18mmol) was used.

General experimental procedure for the addition of higher order cuprate reagents ($R_2CuCNLi_2$) to (5S)-5,6-(O-ispropylidene)hex-3-en-2-one **2** *- (Method C)*

The procedure was identical to Method A, except that CuCN (195mg, 2.18mmol) was used.

General experimental procedure for the addition of organolithium reagents (RLi) to (5S)-5,6-(O-isopropylidene)hex-3-en-2-one **2** *- (Method D)*

To a stirred solution of the lithium reagent (isopropenyl-, butyl- or phenyl-) (2.36mmol) in diethyl ether (or THF) (30ml), under N_2 at -78°C, was added a solution of (5S)-5,6-(O-isopropylidene)hex-3-en-2-one **2** (100mg, 0.59mmol) in diethyl ether (or THF) (10ml). After 2h, aqueous NH_4Cl (30ml) was added to the mixture and it was then extracted with ether (3 x 25ml). The combined organic extracts were dried and evaporated. The ratio of products formed was determined by gc and gc/ms, and they were isolated by flash chromatography (light petroleum/ethyl acetate).

Products from addition reactions of isopropenyl reagents to (5S)-5,6-(O-isopropylidene)hex-3-en-2-one. (See Table 1 for details of yields and product distributions).

(4R, 5S)-4-Isopropenyl-5,6-(O-isopropylidene)hexan-2-one (anti addition product) ***3a.***

ν_{max}/cm^{-1} 3080, 2990, 2930, 1720, 1645; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, s, CC*H*$_3$), 1.37 (3H, s, CC*H*$_3$), 1.68 (3H, br. s, H_2C=C C*H*$_3$), 2.12 (3H, s, COC*H*$_3$), 2.52 (1H, dd, *J* 15 and 8 C*H*$_2$CO), 2.70 (1H, m, CH_2CHCHO), 2.82 (1H, dd, *J* 15 and 5 C*H*$_2$CO), 3.60 (1H, ~br. t, C*H*$_2$O), 3.90-4.04 (2H, m, CHC*H*$_2$O, CH_2CHO), 4.80 (2H, br. s, C=C*H*$_2$); m/z (NH_3 CI) 230 ([M + NH_4]$^+$, 5%), 213 ([M + H]$^+$, 100%), 151 (21), 101 (12); Found [M + H]$^+$ 213.1490. $C_{12}H_{21}O_3$ requires, 213.1493.

(4S, 5S)-4-Isopropenyl-5,6-(O-isopropylidene)hexan-2-one (syn addition product) ***4a.***

ν_{max}/cm^{-1} 2930, 1718, 1210; δ_H (300 MHz, $CDCl_3$) 1.30 (3H, s, CC*H*$_3$), 1.37 (3H, s, CC*H*$_3$), 1.74 (3H, br. s, H_2C=C C*H*$_3$), 2.10 (3H, s, COC*H*$_3$), 2.48 (1H, dd, *J* 16.5, 5.5, C*H*$_2$CO), 2.57 (1H, dd, *J* 16.5, 8.5, C*H*$_2$CO), 2.85 (1H, m, CH_2CHCH), 3.59 (1H, ~t, *J* 7.5, CHC*H*$_2$O), 3.89 (1H, dd, *J* 8.0, 6.5, CHC*H*$_2$O), 4.13 (2H, ~q, *J* 8, 8, 7.5, CH_2CHO), 4.72 (1H, br. s, C=C*H*$_2$), 4.84 (1H, br. s, C=C*H*$_2$); m/z (NH_3 CI) 213 ([M + H]$^+$, 30%), 197 (36), 156 (42), 155 (100%), 137 (65); Found [M + H]$^+$ 213.1487. $C_{12}H_{21}O_3$ requires, 213.1491.

Products from the addition of ^{n}butyllithium to (5S)-5,6-(O-isopropylidene)hex-3-en-2-one (See Table 1 for details of yields and product distributions).

(4S, 5S)-4-Butyl-5,6-(O-isopropylidene)hexan-2-one (1,4 anti addition product) ***3b***

ν_{max}(neat)/cm^{-1} 2940, 1710, 1458, 1370, 1210; δ_H (300 MHz, $CDCl_3$) 0.85 (3H, t, $(CH_2)_3CH_3$), 1.15-1.30 (6H, m, $(CH_2)_3CH_3$), 1.29 (3H, s, C(C*H*$_3$)$_2$), 1.34 (3H, s, C(C*H*$_3$)$_2$), 2.07 (1H, m, 4-H), 2.14 (3H, s, COC*H*$_3$), 2.36 (1H, dd, $J_{3a,3b}$ 17, $J_{3a,4}$ 6.5, 3-H$_a$), 2.57 (1H, dd, $J_{3a,3b}$ 17, $J_{3b,4}$ 5.5, 3-H$_b$), 3.53 (1H, ~t, *J* 6.5, 6-H), 3.91-4.03 (2H, m, 6-H and 5-H); *m/z* (NH_3, CI), 246 ([M + NH_4]$^+$, 30%), 229 ([M + H]$^+$, 70%), 171 (100%). Found [M + NH_4]$^+$ 246.2065. $C_{13}H_{28}O_3N$ requires 266.2069.

(4S, 5S)-4-Butyl-5,6-(O-isopropylidene)hexan-2-one (1,4 syn *addition product)* ***4b***

ν_{max}(neat)/cm^{-1} 2850, 1710, 1450, 1370, 1210; δ_H (300 MHz, $CDCl_3$) 0.81 (3H, t, $(CH_2)_3CH_3$), 1.15-1.25 (6H, $(CH_2)_3CH_3$), 1.25 (3H, s, C(C*H*$_3$)$_2$), 1.32 (3H, s, C(C*H*$_3$)$_2$), 2.09 (3H, s, COC*H*$_3$), 2.18-2.35 (2H, m, 4-H and 3-H$_a$), 2.46 (1H, dd, $J_{3a,3b}$ 19, $J_{3b,4}$ 8, 3-H$_b$), 3.51 (1H, t, $J_{6a,6b}$ 8, $J_{5,6a}$ 8, 6-H$_a$), 3.86 (1H, dd, $J_{6a,6b}$ 8, $J_{5,6b}$ 6.5, 6-H$_b$), 4.08 (1H, ~ q, 5-H), *m/z* (NH_3, CI) 246 ([M + NH_4]+, 30%), 229 (70%), 171 (100%). Found [M + NH_4]$^+$ 246.2070. $C_{13}H_{28}O_3N$ requires 266.2069.

(2S)-1,2-(O-isopropylidene)-5-methylnon-3-en-4-ol (1,2 addition product) ***5b***

ν_{max}(neat)/cm^{-1} 3450, 2950; δ_H (300 MHz, $CDCl_3$) 0.86 (3H, t, $(CH_2)_3CH_3$), 1.16-1.35 (6H, $(CH_2)_3CH_3$), 1.37 (3H, s, $C(CH_3)_2$), 1.40 (3H, s, $C(CH_3)_2$), 1.59 (3H, s, CCH_3), 3.55 (1H, ~t, OCH_2CHO), 4.06 (1H, dd, *J* 8, 6, OCH_2CHO), 4.48 (1H, ~ q, OCH_2CHO), 5.62 (1H, dd, *J* 16, 7.5, HC=CHCH0), 5.84 (1H, br. d, *J* 16, CCH=CH); *m/z* (NH_3, CI) 246 ([M + NH_4]+, 85%), 229 ([M + H]$^+$, 20%), 228 (100%), 211 (75), 188 (93).

Products from the addition of phenyllithium to (5S)-5,6-(O-isopropylidene)hex-3-en-2-one.

(4S,5S)-5,6-(O-isopropylidene)-4-phenylhexan-2-one (syn adduct) ***4c*** *(3 mg, 2%).*

ν_{max} (neat)/cm^{-1} 2933, 1716, 1454, 1370, 1216; δ_H (300 MHz) 1.26 (3H, s, $C(CH_3)_2$), 1.29 (3H, s, $C(CH_3)_2$), 2.06 (3H, s, $COCH_3$), 2.87 (1H, dd (distorted), $J_{3a,3b}$ 17, $J_{3a,4}$ 8, 3-H_a), 2.93 (1H, dd (distorted), $J_{3a,3b}$ 17, $J_{3b,4}$ 6.5, 3-H_b), 3.42 (1H, m, 4-H), 3.50 (1H, ~t, $J_{6a,6b}$ 8, $J_{5,6a}$ 8, 6-H_a), 3.87 (1H, dd, $J_{6a,6b}$ 8, $J_{5,6b}$ 6.5, 6-H_b), 4.29 (1H, m, 5-H), 7.17-7.37 (5H, m, Ph); *m/z* (NH_3, CI) 266 ([M + NH_4]$^+$, 50%), 249 ([M + H]$^+$, 100%), 231 (30%), 191 (60%); Found [M + NH_4]$^+$ 266.1752. $C_{15}H_{24}O_3N$ requires 266.1756.

(4R,5S)-5,6-(O-isopropylidene)-4-phenylhexan-2-one (anti adduct) ***3c*** *(7 mg, 5%)*

ν_{max} (neat)/cm^{-1} 2986, 1710, 1371, 1216; δ_H (300 MHz) 1.33 (3H, s, $C(CH_3)_2$), 1.41 (3H, s, $C(CH_3)_2$), 2.03 (3H, s, $COCH_3$), 2.79 (1H, dd, $J_{3a,3b}$ 16.5, $J_{3a,4}$ 9.5, 3-H_a), 3.08 (1H, dd, $J_{3a,3b}$ 16.5, $J_{3b,4}$ 4.5, 3-H_b), 3.24 (1H, ~td, $J_{3a,4}$ 9.5, $J_{4,5}$ 9, $J_{4,3b}$ 4.5, 4-H), 3.53 (1H, dd, $J_{6a,6b}$ 8, $J_{5,6a}$ 6.5, 6- H_a) 3.69 (1H, dd, $J_{6a,6b}$ 8, $J_{5,6b}$ 6, 6-H_b), 4.17 (1H, m, 5-H), 7.2-7.5 (5H, m, Ph), *m/z* (NH_3, CI) 266 ([M + NH_4]$^+$, 30%), 249 ([M + H]$^+$, 100%), 231 (30%), 191 (60%); Found [M + NH_4]$^+$ 266.1758. $C_{15}H_{24}O_3N$ requires 266.1756.

(5S)-5,6-(O-isopropylidene)-2-phenylhex-3-en-2-ol (1,2 adduct) (~4:1 mixture at C-2) ***5c****, (94 mg, 70%)*

ν_{max} (neat)/cm^{-1} 3441, 2934, 2877, 1493, 1447, 1215; δ_H (300 MHz, $CDCl_3$) 1.36 (3H, s, $C(CH_3)_2$), 1.39 (3H, s, $C(CH_3)_2$), 1.63 (3H, s, CCH_3), 3.57 (1H, ~t, *J* 8, 7.5, 6-H_a), 4.09 (1H, dd, $J_{6a,6b}$ 8, $J_{6b,5}$ 7, 6-H_b), 4.53 (1H, ~q, 5-H), 5.66-5.78 (1H, m, 4-H), 6.09 (1H, br. d, *J* 16, 3-H), 7.20-7.50 (5H, m, Ph), *m/z* (NH_3, CI) 266 ([M + NH_4]$^+$, 10%), 248 (40), 231 (50), 208 (30), 173 (100%); Found [M$^+$] 248.1419. $C_{15}H_{20}O_3$ requires 248.1412.

General method for addition of RLi reagents to (4S)-4,5-(O-isopropylidene)pent-2-enoates ***6a/b*** *- (Method E).*

To a stirred solution of (4S)- methyl or ethyl 4,5-(O-isopropylidene)pent-2-enoate (0.54mmole) in diethyl ether or THF (10ml) at -78°C, was added R-Li (0.59mmole) over 10 minutes. When no starting material remained, as indicated by tlc (*ca* 2-3h), saturated aqueous NH_4Cl (25ml) was added and the mixture was extracted with ethyl acetate (3 x 25ml). The combined organic extracts were dried and evaporated, the residue was analysed using gc/gc-m.s, and the components were separated by flash chromatography [light petroleum/ethyl acetate].

Reaction of methyl 4,5-(O-isopropylidene)pent-2-enoate ***6a*** *with isopropenyllithium in diethyl ether.*

Reaction according to Method E provided: (3*S*,4*S*)-methyl 3-isopropenyl-4,5-(O-isopropylidene)pentanoate (1,4 *syn* adduct) **8a** (56mg, 46%) and (5*S*,6*S*) 5-isopropenyl-6,7-(O-isopropylidene)-2-methyl-1-hepten-3-one (1,2-1,4 adduct) **9** (32mg, 25%).

Reaction of methyl 4,5-(O-isopropylidene)pent-2-enoate ***6a*** *with isopropenyl lithium in THF.*

Reaction according to Method E provided: Starting material (20mg, 20%), together with a mixture of isopropenyl addition products (65mg, ~52%). This mixture comprised (5S,6S)-5-isopropenyl-6,7-(O-isopropylidene)-2-methyl-1-hepten-3-one (1,2-1,4-adduct) **9**, (3*S*,4*S*)-methyl 3-isopropenyl-4,5-(O-isopropylidene)pentanoate (1,4 syn adduct) **8a** and 3-hydroxy-3-isopropenyl-6,7-(O-isopropylidene)-2-methylhepta-1,4-diene (bis-1,2-addition product), in a ratio of 5:1:1.

(3S,4S)-Methyl 3-isopropenyl-4,5-(O-isopropylidene)pentanoate (1,4 syn adduct) ***8a****.*

ν_{max}/ cm^{-1} (neat), 2975, 2945, 1730, 1670, 1430; δ_H (300 MHz, CDC_{13}): 1.31 (3H, s, CCH_3), 1.37 (3H, s, CCH_3), 1.75 (3H, br. s, $H_2C=CCH_3$), 2.41 (2H, ~d, *J* 7, $COCH_2$), 2.81 (1H, ~q, *J* 8, 7 and 7, CH_2CHCHO), 3.61 (3H, s, CH_3O), 3.61 (1H, m, CH_2O), 3.91 (1H, dd, *J* 8 and 6, CH_2O), 4.14 (1H, ~q, *J* 7, 6 and 6, CHO),

4.75 (1H, d, *J* 1, H_2C=), 4.85 (1H, sharp m, H_2C=); m/z (NH_3, CI) 229 ([M + H]$^+$, 100%), 193 (93), 171 (55), 153 (27), 135 (29), 101 (89); Found: [M + H]$^+$, 229.1440. $C_{12}H_{21}O_4$ requires 229.1439.

(5S,6S)-5-Isopropenyl-6,7-(O-isopropylidene)-2-methylhept-1-en-3-one (1,2-1,4 adduct) ***9.***

ν_{max}/ cm^{-1} (neat), 2990, 2925, 1705, 1670, 1640, 1500, 1370; δ_H (300 MHz, $CDCl_3$): 1.29 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 1.75 (3H, br. s, H_2C=CCH_3), 1.82 (3H, br. s, H_2C=CCH_3), 2.69-2.78 (1H, m, CH_2CHCHO), 2.82-2.91 (2H, m, COCH_2), 3.60 (1H, ~t, *J* 8 and, CHOCH_2O), 3.91 (1H, dd, *J* 8 and 6, CHCH_2O), 4.10-4.20 (1H, m, CHOCH_2O), 4.70 (1H, br. s, H_2C=CCH$_3$), 4.81 (1H, sharp m, H_2C=CCH$_3$), 5.74 (1H, sharp m, H_2C=C(CH$_3$)CO), 5.79 (1H, s, H_2C=C(CH$_3$)CO); m/z (NH_3, CI) 256 ([M + NH_4]$^+$, 31%), 239 ([M + H]$^+$, 100), 221 (7.3), 181 (84.3); Found: [M + H]$^+$, 239.1654. $C_{14}H_{23}O_3$ requires 239.1646.

3-Hydroxy-3-isopropenyl-6,7-(O-isopropylidene)-2-methylhepta-1,4-diene (bis-1,2-adduct).

ν_{max}/ cm^{-1} (neat) 3450 (broad), 2975, 2925, 2850, 1660, 1640; δ_H (300 MHz, $CDCl_3$) 1.37 (3H, s, CCH$_3$), 1.39 (3H, s, CCH_3), 1.58 (1H, br. s, OH), 1.68 (6H, sharp m, 2 x H_2C=CCH_3), 3.57 (1H, ~t, *J* 8 and, CHCH_2O), 4.07 (1H, dd, *J* 8 and 6, CHCH_2O), 4.56 (1H, m, CHOCH_2), 4.94-4.95 (2H, sharp m, H_2C=CCH$_3$), 5.00 (1H, br. s, H_2C=CCH_3), 5.02 (1H, br. s, H_2C=CCH$_3$), 5.74 (1H, dd, *J* 15 and 7, CH=CHCHO), 6.13 (1H, dd, *J* 15 and 1, CH=CHCH); m/z (NH_3, CI) 256 ([M + NH_4]$^+$, 25%), 238 (14), 221 (100), 198 (41), 180 (19), 164 (89), 101 (79), 95 (77); Found [M + NH_4]$^+$, 256.1957. $C_{14}H_{26}NO_3$ requires 256.1959.

Reaction of ethyl 4,5-(O-isopropylidene)pent-2-enoate with isopropenyl lithium in diethyl ether.

Reaction according to Method E provided an inseparable mixture of (3*S*,4*S*)-ethyl 3-isopropenyl-4,5-(O-isopropylidene)pentanoate (1,4 *syn* adduct) **8b** and (5S,6S)-5-isopropenyl-6,7-(O-isopropylidene)-2-methyl-1-hepten-3-one (1,2-1,4 adduct) **9**, in a ratio of 2.5:1. The ester could be isolated following reduction of the mixture with $NaBH_4$ as described below.

Reaction of ethyl 4,5-(O-isopropylidene)pent-2-enoate ***6a*** *with isopropenyllithium in THF.*

Reaction according to Method E provided: Starting material (22mg, 20%), together with a mixture of isopropenyl addition products (58mg, ~45%). This mixture comprised (5*S*,6*S*) 5-isopropenyl-6,7-(O-isopropylidene)-2-methyl-1-hepten-3-one (1,2-1,4-adduct) **9**, (3*S*,4*S*) ethyl 3-isopropenyl-4,5-(O-isopropylidene) pentanoate (1,4 syn adduct) **8b** and (6S)-3-hydroxy-3-isopropenyl-6,7-(O-isopropylidene)-2-methylhepta-1,4-diene (bis-1,2-addition product), in a ratio of 5:1:1.

Isolation of (3S,4S)-ethyl 3-isopropenyl-4,5-(O-isopropylidene)pentanoate ***8b.***

To a stirred suspension of sodium borohydride (19mg, 0.5mmole), in absolute ethanol (2ml), at room temperature was added a solution of the ketone/ester mixture **8b/9** (96mg, *ca* 0.4mmole) in absolute ethanol (10ml). After 2.5 hours the pH of the mixture was adjusted to 7 by dropwise addition of glacial acetic acid. The solvent was then evaporated and the residue was purified by flash chromatography [light petroleum/ethyl acetate (9:1)] to provide:

(3S,4S)-ethyl 3-isopropenyl-4,5-(O-isopropylidene) pentanoate ***8b*** *(58mg, 61%).*

ν_{max}/cm^{-1} (neat) 3060, 2975, 2920, 1730, 1640; δ_H (300 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7, CH_3CH$_2$O), 1.31 (3H, s, CCH_3), 1.38 (3H, s, CCH_3), 1.68 (3H, br. s, H_2C=CCH_3), 2.40 (2H, ~d, *J* 7, COCH_2), 2.82 (1H, ~q, *J* 7, 7 and 6.5, CH_2CHCCHO), 3.62 (1H, ~t, *J* = 8 and 7 OCH_2CH), 3.91 (1H, dd, *J* 8 and 6 OCH_2CH), 4.08 (2H, q, *J* 7, CH$_3$CH_2O), 4.14 (1H, ~q, *J* 7, 6.5, and 6, CHCHOCH$_2$), 4.76 (1H, br. s, H_2C=), 4.87 (1H, sharp m, H_2C=); m/z (NH_3, CI): 260 ([M + NH_4]$^+$, 10%), 243 ([M + H]$^+$, 100%), 185 (55), 174 (39), 157 (45); Found: [M + H]$^+$ 243.1602. $C_{13}H_{22}O_4$ requires, 243.1595, and

(5S,6S)-3-hydroxy-5-isopropenyl-6,7-(O-isopropylidene)-2-methyl-1-heptene (23mg, 24%).

ν_{max}/ cm^{-1} (neat), 3500 (broad), 2950, 1640 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (3H, s, CCH_3), 1.37 (3H, s, CCH_3), 1.69 (3H, sharp m, H_2C=CCH_3), 1.73-1.79 (3H, m, H_2C=CCH_3), 2.17-2.25 (0.5H, m), 2.32-2.40 (0.5H, m, CH_2CHCHO), 2.50-2.60 (0.5H, m, CH_2CHCHO), 3.25-3.31 (0.5H, m, OCH_2CHO), 3.41-3.49

(0.5H, m, OCH_2CHO), 3.90-4.10 (3H, m, CHOH, OCH_2CHO, OCH$_2$CHO, OCH_2CHO) 4.78-4.97 (4H, m, 2 x H_2C=C), m/z (NH_3, CI): 241 ([M + H]$^+$, 30%), 223 (30), 187 (80), 169 (100%),101 (90); Found [M + H]$^+$ 241.1802. $C_{14}H_{25}O_3$ requires 241.1804.

Reactions of ethyl and methyl 4,5-(O-isopropylidene)pent-2-enoate ***6a*** *and* ***6b*** *with "butyllithium.*

Reactions were carried out according to Method E using 1M "butyllithium in hexane, except as noted, and the results are summarised in Table 4. Only *syn* 1,4-addition products and 1,2/1,4-addition products were isolated from the reactions. The ratio of products was determined by gc and gc-ms.

				Product Ratios		
Ester	**Method**	**Solvent**	**Yield**	**15**	**12a/b**	**9a/b**
OMe	A	Et_2O	96mg, 73%	1	>20	-
OMe	reverse addition†	Et_2O	96mg, 73%	1	>20	-
OMe	A	THF	87mg, 66%	1	10	-
OEt	A	Et_2O	85mg, 66%	1	>20	-
OEt	A + LiBr	Et_2O	85mg, 66%	1	20	-
OEt	A	THF	86mg, 66%	1	4	-

† A solution of the enoate in Et_2O was added to BuLi solution (~1M in hexane) in Et_2O.

Table 4

(3R,4S)-Methyl 3-butyl-4,5-(O-isopropylidene) pentanoate (1,4 syn adduct) ***11a***

ν_{max}/ cm^{-1} (neat), 2940, 2920, 2870, 1735, 1450 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 0.85 (3H, t, CH_3CH$_2$), 1.23 (6H, m, butyl CH_2), 1.29 (3H, s, CCH_3), 1.34 (3H, s, CCH_3), 2.16 (2H, m, COCH_2CH), 2.30-2.40 (1H, m, CH$_2$CHCHO), 3.55 (1H, ~t, J 8 and 8, CHCH_2O), 3.62 (3H, s, CH_3O), 3.91 (1H, dd, J 8 and 6.5, CHCH_2O), 4.08 (1H, ~q, J 7, 7 and 6.5, CHOCH$_2$O); m/z (NH_3, CI) 262 ([M + NH_4]$^+$, 5%), 245 ([M + H]$^+$, 100%), 229 (14), 187 (90%); Found [M + H]$^+$, 245.1750. $C_{13}H_{25}O_4$ requires 245.1753.

(3R,4S)-Ethyl 3-butyl-4,5-(O-isopropylidene) pentanoate (1,4 syn adduct) ***11b****.*

ν_{max}/ cm^{-1} (neat), 2950, 2850, 1730, 1460; d_H (300 MHz): 0.85 (3H, t, CH_3CH$_2$CH$_2$), 1.23 (t, 3H, J 7, CH_3CH$_2$O), 1.25-1.30 (6H, m, butyl CH_2), 1.30 (3H, s, CCH_3), 1.36 (3H, s, CCH_3), 2.10-2.20 (2H, m, COCH_2CH), 2.30-2.40 (1H, m, CH$_2$CHCHO), 3.58 (1H, ~t, J 8 and 8, CHCH_2O), 3.88 (1H, dd, J 7 and, CHCH_2O), 4.08 (2H, q, CH$_3$CH_2O), 4.22 (1H, m, CHOCH$_2$); m/z (NH_3, CI) 276 ([M + NH_4]$^+$, 4%), 259 ([M + H]$^+$, 95%), 243 (45), 201 (100%); Found [M + H]$^+$ 259.1913. $C_{14}H_{27}O_4$ requires 259.1909.

(2R,3S)-3-"Butyl-1,2-(O-isopropylidene)-5-nonanone (1,2-1,4-adduct) ***12****.*

ν_{max}/ cm^{-1} (neat), 2975, 2850, 1710, 1435; δ_H (300 MHz, $CDCl_3$) 0.86-0.88 (6H, m, 2 x CH_3CH$_2$), 1.26 (10H, m, 2 x butyl CH_2), 1.31 (3H, s, CCH_3), 1.37 (3H, s, CCH_3), 1.53 (2H, m, CH$_2$CH_2CO), 2.15 (2H, m, COCH_2CH), 2.22-2.50 (1H, m, CH$_2$CHCHO), 3.58 (1H, ~t, J 8 and 8, CHOCH_2O), 3.94 (1H, dd, J 8 and 7, CHOCH_2O), 4.10 (1H, ~q, J ~7, OCHCH$_2$O); m/z (NH_3, CI) 288 ([M + NH_4]$^+$, 2%), 271 ([M + H]$^+$, 60%), 255 (15), 213 (100%); Found [M + H]$^+$ 271.1907. $C_{16}H_{31}O_3$ requires 271.2273.

Reactions of ethyl and methyl 4,5-(O-isopropylidene) pent-2-enoate with methyllithium.

Reactions were carried out according to Method E using 1M methyllithium in hexane, except as noted, and the results are summarised in the Table 5. Only *syn* 1,4-addition products and 1,2/1,4-addition products were isolated from the reactions. The ratio of products was determined by gc and gc-ms.

				Product Ratios		
Ester	**Method**	**Solvent**	**Yield**	**16**	**13a/b**	**11a/b**
OMe	A	Et_2O	78mg, 72%†	1	5	-
OMe	A	THF	75mg, 69%†	2	1	-
OEt	A	Et_2O	76mg, 70%	1	6	-
OEt	A	THF	73mg, 67%	1	2	-

† Product contains some starting material (~10%)

Table 5

(3R,4S)-Methyl 3-methyl-4,5-(O-isopropylidene) pentanoate (1,4 syn adduct) ***13a.***

ν_{max}/ cm^{-1} (neat), 2990, 2860, 1720, 1450; δ_H (300 MHz, $CDCl_3$): 0.96 (3H, d, *J* 6, CH_3CH), 1.31 (3H, s, CCH_3), 1.38 (3H, s, CCH_3), 2.16 (2H, m, COCH_2CH + CH$_2$C*H*CHO), 2.37 (1H, dd, *J* 10 and 4, COCH_2CH), 3.61 (1H, ~t, *J* 7, CHOCH_2O), 3.65 (3H, s, CH_3O), 3.95 (1H, dd, *J* 8 and 7, CHOCH_2O), 4.04 (1H, ~q, *J* 7, 7 and, C*H*OCH$_2$O); m/z (NH_3, CI) 220 ([M + NH_4]$^+$, 3%), 203 ([M + H]$^+$, 100%), 187 (19), 145 (91); Found [M + H]$^+$ 203.1279. $C_{10}H_{19}O_4$ requires 203.1283.

(3R,4S)-Ethyl 3-methyl-4,5-(O-isopropylidene) pentanoate (1,4 syn adduct) ***13b.***

ν_{max}/ cm^{-1} (neat), 2990, 2865, 1720, 1445; δ_H (300 MHz, $CDCl_3$) 0.97 (3H, d, *J* 7, CH_3CH), 1.23 (3H, t, CH_3CH$_2$O), 1.37 (3H, s, CCH_3), 1.42 (3H, s, CCH_3), 2.15 (2H, m, COCH_2CH + CH$_2$C*H*CHO), 2.37 (1H, dd, *J* 10 and 5.5, COCH_2CH), 3.65 (1H, dd, *J* 8 and 7, CHCH_2O), 3.93 (1H, dd, *J* 8 and 6.5, CHCH_2O) 4.10-4.30 (3H, m, C*H*OCH$_2$ + CH$_3$CH_2O); m/z (NH_3, CI) 234 ([M + NH_4]$^+$, 3%), 217 ([M + H]$^+$, 100%), 201 (80), 159 (81); Found [M + H]$^+$ 217.1429. $C_{11}H_{21}O_4$ requires 217.1439.

(2R,3S) 3-Methyl-1,2-(O-isopropylidene)-5-hexanone (1,2-1,4-adduct) ***15.***

ν_{max}/ cm^{-1} (neat), 2950, 2850, 1720, 1430; δ_H (300 MHz, $CDCl_3$) 0.90 (3H, d, *J* 6, CH_3CH), 1.31 (3H, s, CCH_3), 1.38 (3H, s, CCH_3), 2.13 (3H, s, CH_3CO), 2.22-2-32 (2H, m, COCH_2CH + CH$_2$C*H*CHO), 2.52 (1H, dd, *J* 11 and 8, COCH_2CH), 3.60 (1H, ~t, *J* 7 and 7, CHCH_2O), 3.94 (1H, dd, *J* 8 and 6.5, CHCH_2O), 3.99 (1H, ~q, *J* 7, 6.5 and 6.5, C*H*OCH$_2$); m/z (NH_3, CI) 204 ([M + NH_4]$^+$, 3%), 187 ([M + H]$^+$, 50%), 171 (15), 129 (100%); Found [M + H]$^+$ 187.1333. $C_{10}H_{19}O_3$ requires 187.1334.

*General method for addition of organolithium reagents to (4E, 6S)-ethyl or methyl 6,7-(*O*-isopropylidene)-3-oxohept-4-enoate - (Method F).*

To a stirred solution of the appropriate organolithium reagent (0.88mmol) in THF (25ml), under argon, at -78°C was added (4*E*,6*S*)-ethyl 6,7-(*O*-isopropylidene)-3-oxohept-4-enoate **16a** (100mg, 0.41mmol) in tetrahydrofuran (10ml). When the reaction appeared to be complete by tlc (~1h), saturated ammonium chloride solution (25ml) was added and the mixture was allowed to warm to room temperature. The mixture was then extracted with dichloromethane (3 x 10ml), and the combined extracts were washed with brine (10ml), dried and evaporated. The residue was purified by flash chromatography (light petroleum-ethyl acetate).

Addition of isopropenyllithium to (4E, 6S)-ethyl 6,7-(O-isopropylidene)-3-oxohept-4-enoate ***16a.***

When the enoate (100mg) was reacted with isopropenyllithium (0.8M in ether, 1.05ml, 0.88mmol), according to Method F, the following products were obtained:

(5S,6S)-Ethyl-(6,7-O-isopropylidene)-3-oxo-5-isopropenylheptanoate (1,4 syn *product)* ***18a*** *(77mg, 66%)*

ν_{max}(neat)/cm^{-1} 2985, 1742, 1718, 1660, 1370 1244, 1060; δ_H (300 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7, CH_3CH$_2$O), 1.28 (3H, s, C(CH_3)$_2$), 1.32 (3H, s, C(CH_3)$_2$), 1.66 (3H, s, H$_2$C=CCH_3), 2.60 (1H, dd, $J_{4a,4b}$ 15, $J_{4a,5}$ 8, 4-H_a), 2.64-2.69 (1H, m, 5-H), 2.87 (1H, dd, $J_{4a,4b}$ 15, $J_{4b,5}$ 4.5, 4-H_b), 3.41 (2H, s, 2-H_2), 3.59 (1H, ~t, *J* ~8, 7-H_a), 3.90-4.02 (2H, m, 6-H, 7H_b), 4.13 (2H, q, *J* 7, CH$_3$CH_2O), 4.78 (2H, br. s, C=CH_2); *m/z* (NH_3,

CI) 302 ([M + NH_4]$^+$, 85%), 285 ([M + H]$^+$, 80%), 227 (90%), 101 (100%); Found [M + H]$^+$ 285.1701. $C_{15}H_{25}O_5$ requires 285.1702.

(5R,6S)-Ethyl (6,7-O-isopropylidene)-3-oxo-5-isopropenylheptenoate (1,4 anti *product)* ***19a*** *(19mg, 16%)* ν_{max} (neat)/cm^{-1} 2986, 1739, 1642, 1414, 1119, 1061, 702; δ_H (300 MHz) 1.24 (3H, t, *J* 7, C*H*$_3$CH$_2$O), 1.30 (3H, s, C(C*H*$_3$)$_2$), 1.37 (3H, s, C(C*H*$_3$)$_2$), 1.76 (3H, s, H$_2$C=CC*H*$_3$), 2.64 (1H, dd (distorted), $J_{4a,4b}$ 17, $J_{4a,5}$ 5.5, 4-H$_a$), 2.73 (1H, dd (distorted), $J_{4a,4b}$ 17, $J_{4b,5}$ 8.5, 4-H$_b$), 2.88 (1H, m, 5-H), 3.41 (2H, s, 2-H$_2$), 3.60 (1H, t, $J_{7a,7b}$ 8, $J_{6,7a}$ 8, 7-H$_a$), 3.90 (1H, dd, $J_{7a,7b}$ 8, $J_{6,7b}$ 6.5, 7-H$_b$), 4.15 (1H, m, 6-H), 4.17 (2H, q, *J* 7, CH$_3$C*H*$_2$O), 4.74 (1H, br. s, C=C*H*$_2$), 4.86 (1H, br. s, C=C*H*$_2$); *m/z* (NH$_3$, CI) 302 ([M + NH_4]$^+$ 85%), 285 ([M + H]$^+$, 80%), 227 (100%), 101 (80%); Found [M + H]$^+$ 285.1696. $C_{15}H_{25}O_5$ requires 285.1702.

Addition of "butyllithium to (4E, 6S)-ethyl 6,7-(O-isopropylidene)-3-oxohept-4-enoate ***16a****.*

When the enoate (100mg) was reacted with "butyllithium (1.5M in hexane, 0.6ml, 0.84mmol), according to Method F, the following products were obtained. Chromatographic separation of the products was quite difficult because of co-elution with several minor by-products.

*(5S,6S)-Ethyl-(6,7-O-isopropylidene)-5-butyl-3-oxoheptanoate (1,4-*anti *product)* ***19c*** *(40mg, 33%)* ν_{max}(neat)/cm^{-1} 2986, 2934, 1745, 1717, 1650, 1371, 1218; δ_H (300 MHz, $CDCl_3$) 0.87 (3H, ~t, C*H*$_3$(CH$_2$)$_3$), 1.15-1.30 (6H, m, (C*H*$_2$)$_3$CH$_3$), 1.28 (3H, s, C(C*H*$_3$)$_2$), 1.33 (3H, s, C(C*H*$_3$)$_2$), 2.12 (1H, m, 5-H), 2.47 (1H, dd, $J_{4a,4b}$ 17, $J_{4a,5}$ 6, 4-H$_a$), 2.65 (1H, dd, $J_{4a,4b}$ 17, $J_{4b,5}$ 6, 4-H$_b$), 3.46 (s, 2H, 2-H$_2$), 3.53 (1H, dd, $J_{7a,7b}$ 8, $J_{6,7a}$ 7, 7-H$_a$), 3.93 (1H, ~q, $J_{6,7a}$ 8, $J_{6,7b}$ 7, $J_{5,6}$ 7, 6-H), 4.02 (1H, dd, $J_{7a,7b}$ 8, $J_{6,7b}$ 7, 7-H$_b$), 4.17 (2H, q, CH$_3$C*H*$_2$O); *m/z* (NH$_3$, CI) 318 ([M + NH_4]$^+$, 100%), 301 ([M + H]$^+$, 25%), 260 (50), 243 (45); Found [M + NH_4]+ 318.2240. $C_{16}H_{32}NO_5$ requires 318.2280.

*(5R,6S)-Ethyl-(6,7-O-isopropylidene)-5-butyl-3-oxoheptanoate (1,4-*syn *product)* ***18c*** *(20mg, 16%)* ν_{max}(neat)/cm^{-1} 2950, 1745, 1717, 1650; δ_H (300 MHz, $CDCl_3$) 0.83 (3H, ~t, C*H*$_3$(CH$_2$)$_3$), 1.15-1.30 (6H, m, (C*H*$_2$)$_3$CH$_3$), 1.27 (3H, s, C(C*H*$_3$)$_2$), 1.34 (3H, s, C(C*H*$_3$)$_2$), 2.26 (1H, m, 5-H), 2.41 (1H, dd, $J_{4a,4b}$ 17, $J_{4a,5}$ 6.5, 4-H$_a$), 2.59 (1H, dd, $J_{4a,4b}$ 17, $J_{4b,5}$ 6, 4-H$_b$), 3.41 (s, 2H, 2-H$_2$), 3.54 (1H, ~t, $J_{7a,7b}$ 8, $J_{6,7a}$ ~7.5, 7-H$_a$), 3.88 (1H, dd, $J_{7a,7b}$ 8, $J_{6,7b}$ 6.5, 7-H$_b$), 4.08-4.14 (1H, m, 6-H), 4.14 (2H, q, CH$_3$C*H*$_2$O); *m/z* (NH$_3$, CI) 318 ([M + NH_4]$^+$, 50%), 301 ([M + H]$^+$, 10%), 260 (70), 243 (100); Found [M + H]+ 301.2016. $C_{16}H_{29}O_5$ requires 301.2015.

Addition of phenyllithium to (4E, 6S)-ethyl 6,7-(O-isopropylidene)-3-oxohept-4-enoate ***16a****.*

When the enoate (100mg) was reacted with phenyllithium (1.75M in hexane, 0.56ml, 0.88mmol), according to Method F, the following products were obtained.

(5R,6S)-Ethyl 6,7-(O-isopropylidene)-5-phenyl-3-oxoheptanoate (1,4 anti *product)* ***19e*** *(80 mg, 60%)* ν_{max}(neat)/cm^{-1} 3029, 2935, 1742, 1717, 1603, 1454, 1370; δ_H (300 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7, C*H*$_3$CH$_2$O), 1.32 (3H, s, C(C*H*$_3$)$_2$), 1.40 (3H, s, C(C*H*$_3$)$_2$), 2.88 (1H, dd, $J_{4a,4b}$ 16, $J_{4a,5}$ 8, 4-H$_a$), 3.19 (1H, dd, $J_{4a,4b}$ 16, $J_{4b,5}$ 5, 4-H$_b$), 3.27 (1H, m, 5-H), 3.34 (2H, ~br. s, H$_2$-2), 3.53 (1H, dd, $J_{7a,7b}$ 8.5, $J_{7a,6}$ 6.5, 7-H$_a$), 3.70 (1H, dd, $J_{7a,7b}$ 8.5, $J_{7b,6}$ 6, 7-H$_b$), 4.10 (2H, q, *J* 7, CH$_3$C*H*$_2$O), 4.15-4.22 (1H, m, 6-H), 7.1-7.3 (5H, m, Ph); *m/z* (NH$_3$, CI) 338 ([M + NH_4]+, 20%), 321 ([M + H]$^+$, 8%), 280 (20), 260 (100%), 202 (40); Found [M + NH_4]$^+$ 338.1971. $C_{18}H_{28}NO_5$ requires *m/z* 338.1967.

(5S,6S)-Ethyl 6,7-(O-isopropylidene)-5-phenyl-3-oxoheptanoate (1,4 syn *product)* ***18e*** *(8mg, 6%)* ν_{max}(neat)/cm^{-1} 2985, 1742, 1718, 1660, 1370, 1244; δ_H (300 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7, C*H*$_3$CH$_2$O), 1.26 (3H, s, C(C*H*$_3$)$_2$), 1.29 (3H, s, C(C*H*$_3$)$_2$), 3.02-3.05 (2H, m, 4-H$_2$), 3.37 (2H, s, 2-H$_2$), 3.46 (1H, m, 5-H), 3.48 (1H, ~t, $J_{7a,6}$ 8, $J_{7a,7b}$ 8, 7-H$_a$), 3.87 (1H, dd, $J_{7a,7b}$ 8, $J_{6,7b}$ 6.5, 7-H$_b$), 4.10 (2H, q, *J* 7, CH$_3$C*H*$_2$O), 4.27-4.36

(1H, m, 6-H), 7.1-7.3 (5H, m, Ph); *m/z* (NH_3, CI) 338 ($[M+NH_4]^+$, 75%), 280 (80), 263 (100%), 101 (50); Found $[M+NH_4]^+$ 338.1953, $C_{18}H_{28}NO_5$ requires 338.1967.

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