Journal of Organometallic Chemistry, 423 (1992) 281–305
Elsevier Sequoia S.A., Lausanne
JOM 22190

Conjugate addition of organocuprates to γ-methyl-δ-oxy-α,β-enones. Influence of the alkoxy substituent on the diastereoselection

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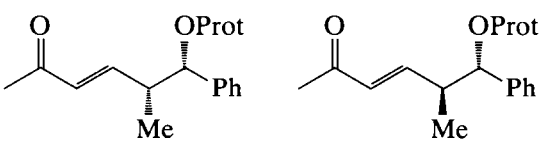
(Received June 6, 1991)

Abstract

The stereochemistry of the conjugate addition of cuprates to the title compounds is mainly governed by the γ-methyl group, but the alkoxy substituent also plays a role.

The conjugate addition of cuprates on γ-substituted-α,β-enones has been the subject of several studies [1]. We consider here the case in which an additional protected hydroxy group in the δ position may alter the diastereofacial preference arising from the effect of the γ-methyl group. The substrates we used were of type **1** (*syn*) and **2** (*anti*):

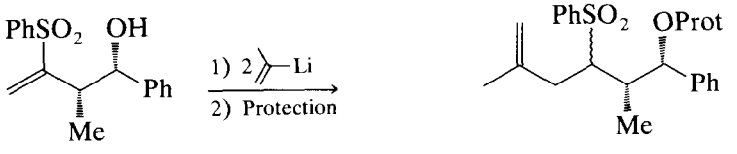


1 **2** (Prot = protecting group)

They were prepared in a few steps from the vinyl sulfone **3** (100% *syn*) [2] as depicted in Schemes 1–3.

The free alcohol **4a** was obtained in 99% yield, and protected *in situ* by treatment with triethylchlorosilane to give **4b** (85%), or with β-methoxyethoxymethyl chloride in the presence of diisopropylethylamine [3] to give **4c** (99%). Derivatives **4** were obtained as a mixture of two diastereomers (1.5/1).

For the preparation of the *anti* derivatives **2**, the free alcohol **4a** was oxidized with pyridinium chlorochromate [4] in large excess to the corresponding ketone **5**, which was reduced with lithium tri(s-butyl)borohydride [5] (L-Selectride) to the

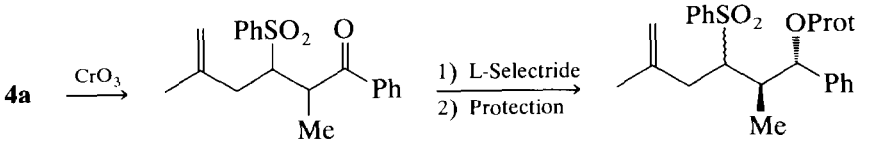


3

4a Prot = H
4b Prot = $SiEt_3$
4c Prot = MEM = $CH_2OCH_2CH_2OMe$

Scheme 1

desired alcohol **6a** [6] (Scheme 2):

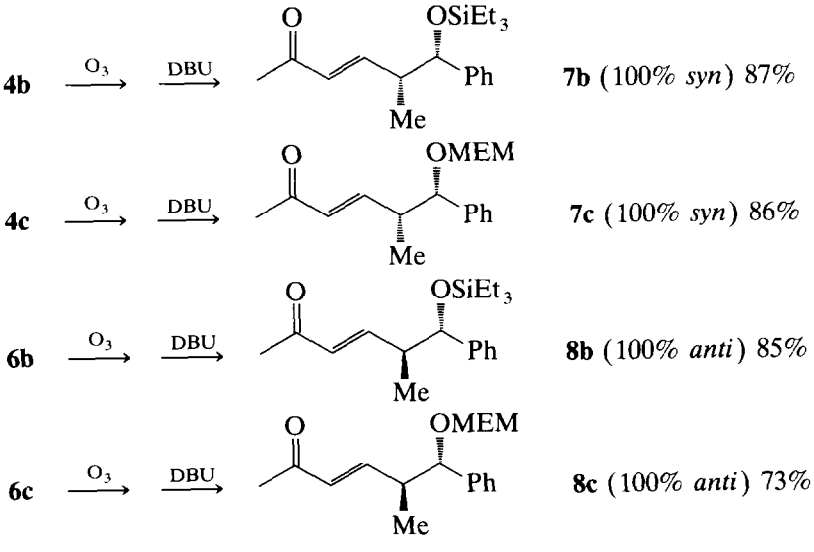


5

6a Prot = H 93%
6b Prot = $SiEt_3$
6c Prot = MEM
= $CH_2OCH_2CH_2OMe$

Scheme 2

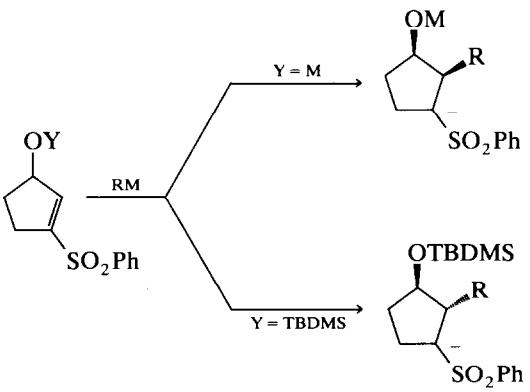
The excellent stereoselectivity of this reduction is apparent for ketones **8**, since as for **4a**, two diastereomers are present in the case of both **5** and **6a**. Alcohol **6a** was then protected as the triethyl silyl ether [7] **6b** in 98% yield or as the MEM ether **6c** [3] in 99% yield. Ozonolysis of **4b, 4c, 6b, 6c**, followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) [8], gave the corresponding enones (col-



Scheme 3

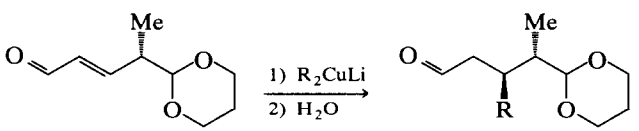
umn chromatography on silica converted traces of the *Z* enones into the pure *E* isomers) [9].

Several examples of the influence of a γ-methyl group on the addition of cuprates to enals, enones and enesters [1] have been reported but they usually involved cyclic substrates. In the latter cases (see, for example, ref. 1g) a γ-alkylated cyclohexenone undergoes addition of a cuprate by an *anti* process. Fuchs [10] observed that the steric outcome of the 1,4 addition of organolithium or magnesium reagents to α,β-ethylenic γ-oxy-sulfones depends strongly on the nature of the oxy-substituent: a free hydroxyl promotes syn addition by chelation, whereas a bulky silyloxy moiety induces *anti* addition (steric control) (eq. 1):



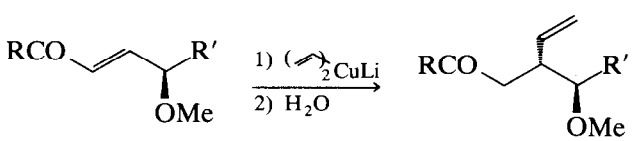
(1)

In reaction with open-chain, Honda [11] observed a 85/15 *anti/syn* ratio in the example shown in eq. 2, and this was explained in terms of a modified Felkin–Anh model (eq. 2).



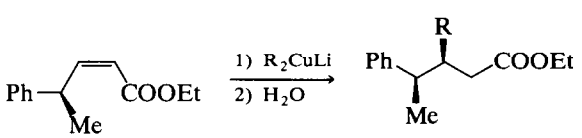
(2)

Roush et al. [12] showed that when a γ-alkoxy group is present in place of methyl, there is again *anti* addition (eq. 3):



(3)

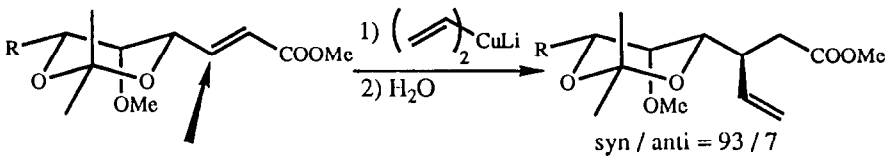
Thus, *anti* addition is the favoured pathway, and there are only scattered examples of cases in which *syn*-addition occurs, specifically in the case of *Z* homocinnamic esters, as shown by Yamamoto et al. [1d,13] (eq. 4):



Major Isomer (4)

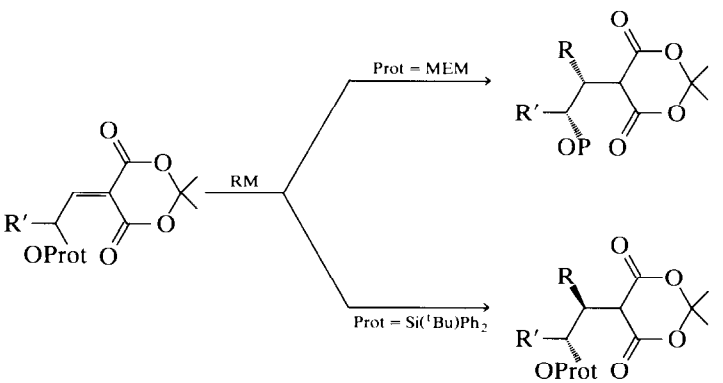
or when the conformation is blocked, leading to approximation to a cyclic case, as

reported by Nicolaou et al. [14] (eq. 5):



(5)

With open-chain species the nature of the protecting group is again very important, as shown by the following example in which a MEM ether promotes chelation [1e,15], whereas a bulky silyloxy group has the opposite effect (steric effect) (eq. 6):



(6)

Similarly Isobe et al. [16] have proposed a transition state in which a remote oxygenated function, δ to a vinyl sulfone, directs an incoming nucleophile to an approach opposite to that which would be favoured by the effect of a γ oxygenated function (eq. 7):

(7)

The objective of our present study was to find out whether δ oxygenated substrates **7b, 7c, 8b, 8c** would show steric interactions or chelating ability that might improve

Table 1

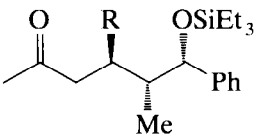
Addition of lithio cuprates to **7b** and **8b**

Entry	Substrate	Cuprate	T (°C)	Time (h)	Product	Yield (%)	Ratio *anti / syn*
1	**7b**	Me_2CuLi	−10	0.5	**9a**	83	> 99/1
2		Bu_2CuLi	−30	0.5	**9b**	81	> 95/5
3		Ph_2CuLi	0	4	**9c**	81	> 99/1
4	**8b**	Me_2CuLi	−10	0.5	**10a**	80	89/11
5		Bu_2CuLi	−30	0.5	**10b**	80	77/23
6		Ph_2CuLi	0	16	**10c**	36	67/33

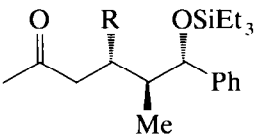
or override the steric influence of the γ-methyl substituent. We use the terms *anti*- or *syn*-addition to denote the cases in which the incoming R group approaches in the *syn* or *anti* position respectively, with respect to this methyl group.

Addition of dialkyl cuprates to silylated substrates 7b and 8b

The reactions were performed with lithiocuprates containing LiBr in ether. The results are shown in Table 1; the indicated stereochemistries of the products were as depicted below:



9a R = Me
9b R = Bu
9c R = Ph



10a R = Me
10b R = Bu
10c R = Ph

From the results it is apparent that *anti* addition is the main outcome and that the *syn* substrate **7b** behaves more stereoselectively than the *anti* one **8b**, so that the silyloxy group, although in a δ position, has a definite influence on the diastereofacial selection. For the *anti* substrate **8b** this effect is more pronounced for the bulkier cuprates (entries 4–6), which points to a steric effect of the silyloxy moiety.

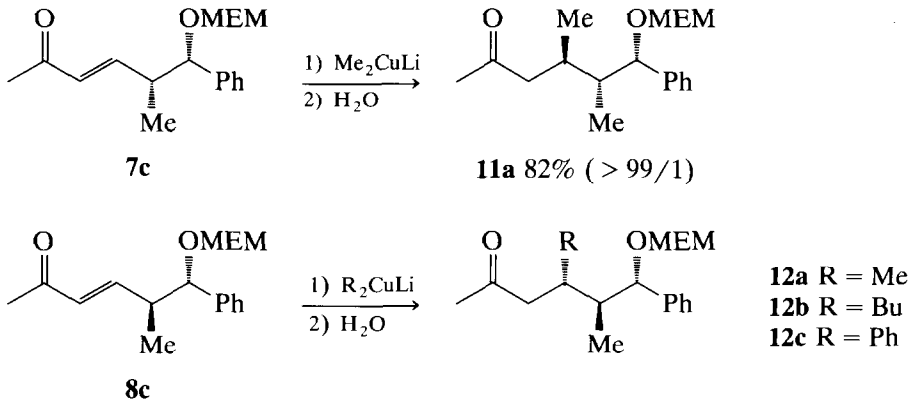
In order to decide whether this influence is purely steric or arised from the chelating ability of the oxygen atom, we decided to test the influence of added trimethylsilyl chloride in the reaction mixture. This reagent is well known not only to accelerate conjugate additions [17–23], but also to inhibit internal chelation of cuprates with polyfunctional enones as a consequence of this acceleration. This effect was revealed by A.B. Smith III [22] and in our laboratories [23].

For **7b** (*syn*), an *anti* addition of the cuprate is favoured by the steric effect of both methyl and silyloxy groups, the chelating effect of the latter acting in the opposite direction. For **8b** (*anti*) the steric effect of the two groups are competing and the chelating effect of the silyloxy moiety favours *anti* addition. In the first case, addition of trimethylsilyl chloride should not alter the outcome of the reaction, whereas in the second a fall in the stereoselectivity would indicate that a chelation effect operates when TMSCl is absent. The results are shown in Table 2.

Table 2

Effect of added Me_3SiCl on the addition of lithium dimethyl cuprate to enones **7b** and **8b**

Substrate	Product	TMSCl	Yield (%)	Ratio *anti* / *syn*
7b	**9a**	+	84	> 99/1
7b	**9a**	−	83	> 99/1
8b	**10a**	+	83	79/21
8b	**10a**	−	80	89/11



Scheme 4

For **8b**, the higher ratio of *syn* attack (21/79) in the presence of Me_3SiCl (compared with 11/89) supports the view that a weak chelation of the cuprate by the silyloxy group is possible. In an effort to obtain compounds **10a–c**, in high purity, we sought to improve the chelating power of the oxygenated substituent. This can be done either by using a free alcohol, or a MEM ether, as discussed above [10,15]. Cleavage of silyl ethers **7b** and **8b** by acetic acid/THF/water, gives the corresponding alcohols **8b** and **8d** in 95 and 98% yield. However our attemps to add cuprates to these hydroxy enones failed, and we turned to the MEM ethers **7c** and **8c** (Scheme 4 and Table 3).

As was expected, the chelating effect of the MEM was not strong enough to override the effect of the γ methyl group in the case of **7c** (100% *anti* addition), but **8c** now behaves much more stereoselectively than its silyloxy analogue **8b**. This is evidence for the beneficial effect of a chelating ether in the γ position; it is more pronounced with a smaller cuprate. The yields are also improved, because the reactions are much faster and allow to use of lower temperatures. Following up these observations we tried higher order cuprates [24], known to react even faster but they did not bring about any significant improvement in the diastereoselection: R = Bu at −80°C yields 88% of **12b** in a 92/8 ratio; R = Ph at −80°C yields 95% of **12c** in a 87/13 ratio.

Trapping of the enolates derived from conjugate addition is well documented [25–29] and has been used in the α,β-bis alkylation of enones. When enolates derived from **7b** and **8b** are treated with iodomethane in the presence of HMPT, the corresponding saturated ketones **13a** and **14a** are formed (Table 4).

Table 3

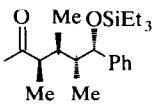
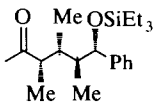
Addition of cuprates to enones **8c**

Cuprate	T (°C) [a]	Product	Yield (%) [a]	Ratio *anti / syn*	[a]
Me_2CuLi	−30 (−10)	**12a**	97 (80)	> 99/1	(89/11)
Bu_2CuLi	−60 (−30)	**12b**	88 (80)	91/9 [b]	(77/23)
Ph_2CuLi	−80 to −40 (0)	**12c**	72 (36)	88/12 [c]	(67/33)

[a] Conditions and results for **8b** → **10** shown in parentheses. [b] Ratio 99/1 after chromatography. [c] Ratio 90/10 after chromatography.

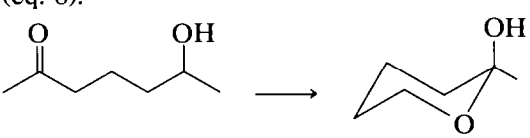
Table 4

Conjugate addition of lithium dimethylcuprate to enones **7b** and **8b**, followed by hydrolysis or methylation

Substrate	Quench	Product	Yield (%)	Diast. ratio [a]
7b	H_2O	**9a**	83	> 99/1
7b	MeI	 **(13a)**	81	> 98/2
8b	H_2O	**10a**	80	89/11
8b	MeI	 **(14a)**	83	89/11

[a] Determined by GLC.

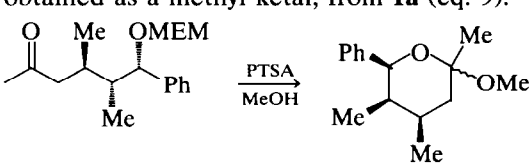
Trapping by iodomethane is evidently extremely stereoselective, since **13a** and **14a** are obtained with isomeric ratios analogues to those obtained by protonation, irrespective of the initially *syn* or *anti* nature of the enone. In order to establish the stereochemistry of products **7–14**, we took advantage of the spontaneous cyclisation of δ-hydroxyketones to give six membered ring hemiketals, in which the hydroxy group generally adopts an axial configuration owing to the anomeric effect (eq. 8).



(8)

Cleavage of silyl ethers **9a, 9b, 9c, 10a, 13a**, and **14a** by tetrabutylammonium fluoride [7] did not give the desired heterocycles, but hydrolysis with a mixture of acetic acid THF, and water [30,31] was successful (Table 5).

Since it was impossible to separate the two diastereoisomers in the case of **10** (77/23) and **10c** (67/33), these compounds were not hydrolyzed. The cyclisation generates a new chiral centre, which is unique for all compounds except **16a**, for which depending on the procedure used for hydrolysis, mixtures of two epimers, in ratios ranging from 50/50 to 100/0, were obtained. A structural assignment was made in the latter case). For the MEM ethers, deprotection by zinc bromide [3] was unsuccessful, and titanium tetrachloride [3] led to decomposition: we finally used (in the *syn* series), *p*-toluene-sulfonic acid in methanol [1e], but **18a** was then obtained as a methyl ketal, from **1a** (eq. 9).

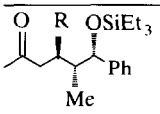
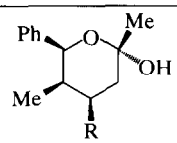
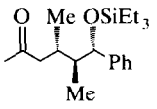
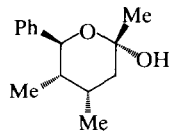
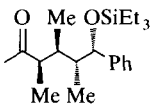
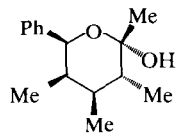
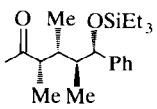
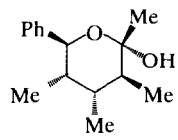


(9)

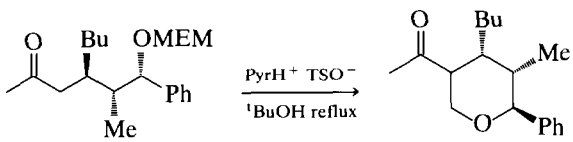
11a **18a** 89% (1 isomer)

Table 5

Hydrolysis of silyl ethers **9**, **10**, **13**, **14** to hydroxytetrahydropyrans

Substrate		Product		Yield (%)
	**9a** R = Me **9b** R = Bu **9c** R = Ph		**15a** R = Me **15b** R = Bu **15c** R = Ph	66 85 98
	**10a**		**16a**	70
	**13a**		**17a**	66
	**14a**		**17b**	80

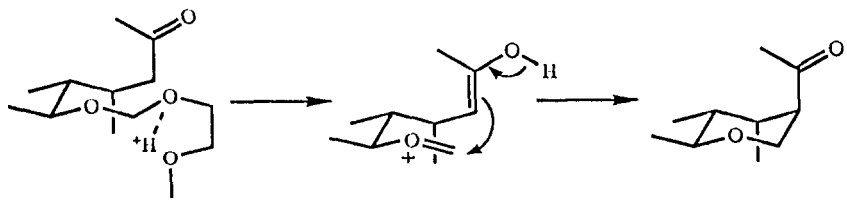
In the *anti* series, only **12b** could be hydrolyzed satisfactorily. The earlier methods failed, as did the use of trimethylsilyl iodide, but pyridinium tosylate in boiling tert-butanol brought about deprotection. However an unexpected cyclisation product was obtained (eq. 10):



12b **19b** 79%
2 isomers: 75/25

(10)

We can account for its formation in terms of the following mechanism (eq. 11):



(11)

Acetals and MEM ethers bearing a vinylsilane, allylsilane, or enoxysilane moiety are known to undergo analogous cyclisations, when treated with a Lewis acid [32], but we are aware of no previous example of a free ketone behaving similarly. The generality of this process is under study. The difficulty encountered in the hydrolysis of MEM ethers led us to conclude that the structures of **12a** and **12c** were analogous to that of **12b**, as deduced from **19b**.

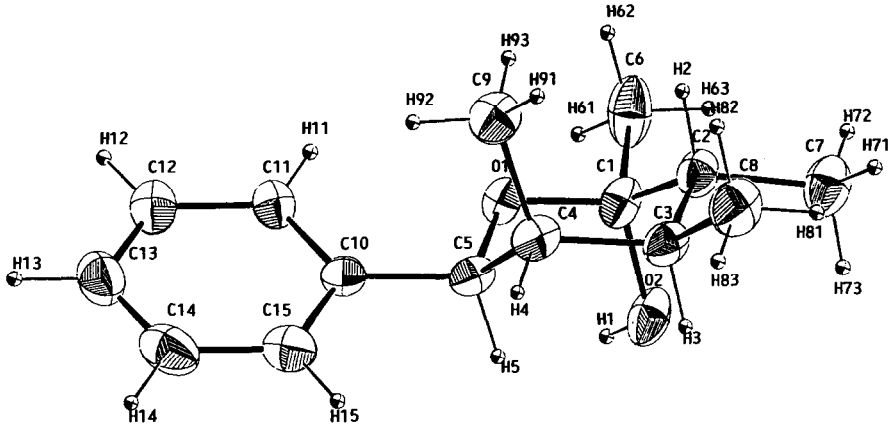
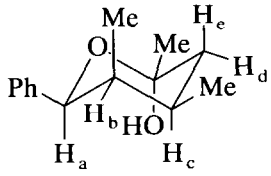


Fig. 1. ORTEP view of compound **17a**.

X-Ray structure were determined for **17a** (Fig. 1) and **17b** (Fig. 2).

Taking account of the fact in all other cases the tetrahydropyran ring adopts a chair conformation with an equatorial phenyl group, NMR spectroscopy allowed structural elucidation.



15a

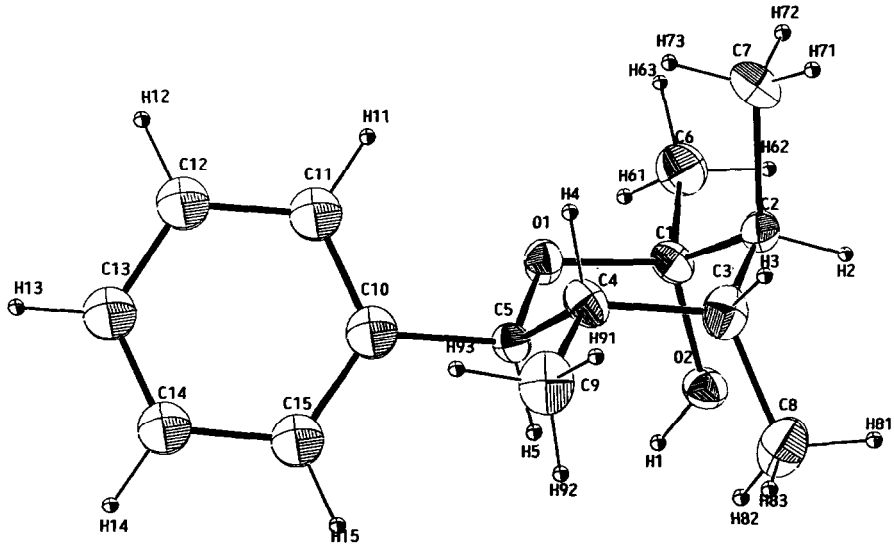
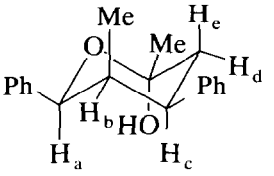


Fig. 2. ORTEP view of compound **17b**.

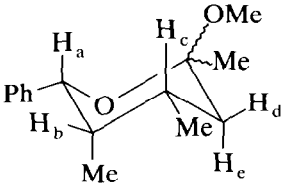
For H_c ($\delta = 2.4$ ppm) $J(H_cH_e) = 12.7$ Hz is indicative of an axial position for Hc. $J(H_cH_d) = J(H_cH_b) = 4.07$ Hz shows H_b to be in an equatorial position, as confirmed by $J(H_aH_b) = 2.5$ Hz. **15b**. No significant signals are obtained. The structure is assigned by analogy with that of **14a**.



15c

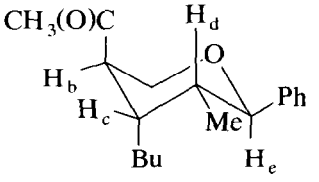
For H_c ($\delta = 3.70$ ppm) the value of $H(H_cH_e)$ of 13.3 Hz shows that H_c is in axial position, and the fact that $J(H_cH_d) = J(H_cH_b) = 4.1$ Hz, shows H_b to be in equatorial position. For H_a ($\delta = 5.42$ ppm) the value of $J(H_aH_b)$ of 2.5 Hz confirms the preceding assignment.

The structure of **16a** was deduced from that of **17b**.



18a

In **18a** H_c is axial ($J(H_cH_e) = 12.5$ Hz) and H_b equatorial $J(H_cH_d) = J(H_cH_b) = 4.1$ Hz. Thus the cuprate addition has taken place in an *anti* fashion (even though the actual configuration at the acetal carbon was not assigned)



major isomer

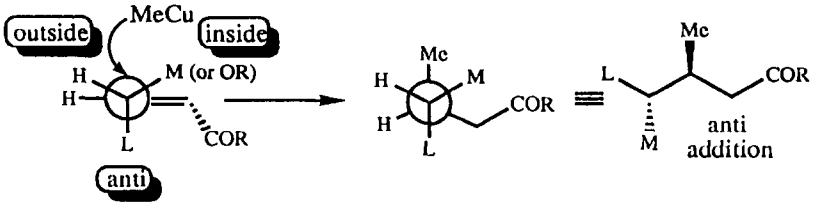
19b

For **19b** irradiation of CH_3, H_d (d 2.14 ppm) shows a diaxial coupling of 10.27 Hz with H_e (δ 4.17 ppm) and an axial–equatorial relationship with H_c, $J(H_dH_c) = 4.4$ Hz. H_b ($\delta = 2.45$ ppm) gives a broad multiplet, L = 11.96 Hz, which rules out axial–axial coupling.

Discussion

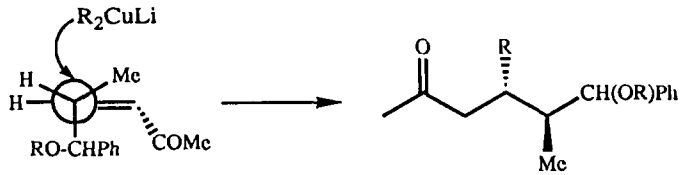
Various models have been proposed to account for the steric outcome of nucleophilic additions to activated C=C double bonds [33] bearing alkoxy or alkyl groups in the γ position [1d,12a,34–36]. Particularly relevant are the calculations by Dorigo and Morokuma [35] who considered the conjugate addition of alkylcop-

per reagents on substituted enals or enesters, and devised a general scheme in which, for E unsaturated systems the major product arises from attack on a conformer in which the larger group lies in *anti* position, while the medium one (m) (or an oxygenated one) is "inside" (eq. 12):



(12)

In our case Me and CHOR(Ph) groups should have rather similar electron donating effects which favour their *anti* position and stabilize the enone moiety, but the larger PhCH(OR) group will occupy it more satisfactorily and the methyl thus adopts an inside rather than outside position, resulting in an *anti* addition pathway (eq. 13).



(13)

Our results fit with this model provided the γ alkoxy group is not taken into account, and indeed, whatever its nature ($OSiR_3$ or MEM) its role can be neglected in the case of the *syn* substrate. In the *anti* series, however, one has to take account of the chelating ability of this group, which is weak ($OSiR_3$) or moderate (OMEM). In order to chelate, it must leave the *anti* position which will henceforth be occupied by the larger remaining substituent (methyl). Thus two pathways, leading to opposite stereoselectivities, are possible (Fig. 3; Met denotes a metal centre).

To the extent that as the chelation operates, the system is made more rigid, and a pseudo-cyclised model can be drawn (Fig. 4).

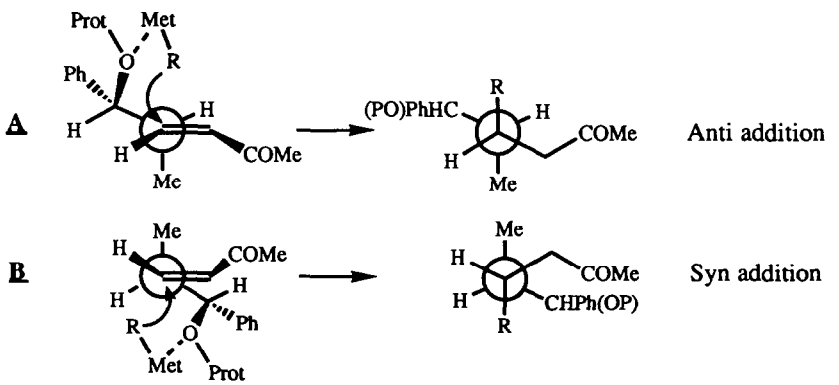


Fig. 3. Chelate model for *anti* enone.

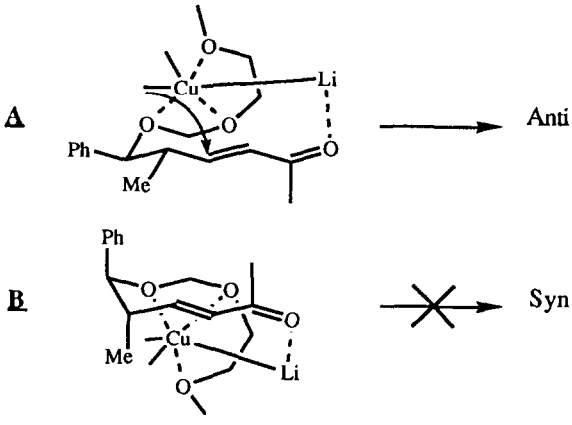


Fig. 4. Pseudo-cyclised model for *anti* enone.

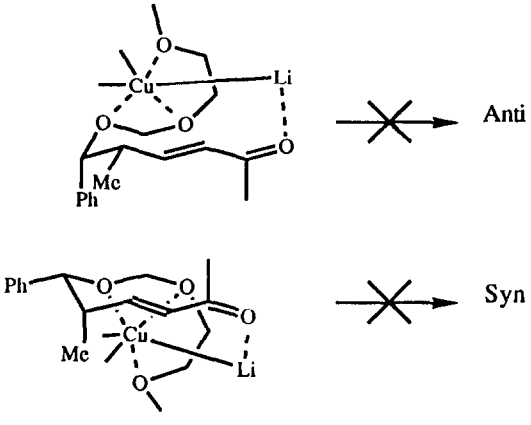


Fig. 5. Pseudo-cyclised model for *syn* enone.

Model **B** is highly improbable because of the axial positions of both the phenyl and methyl substituents, the latter preventing approach of the cuprate. In contrast, model **A** allows an easy *anti* addition, and is thus preferred.

In the *syn* series, such a pseudo-cyclic model cannot be involved because, whatever configuration is chosen one subsituent is always axial (Fig. 5). Thus, in this case, only the Morokuma model is applicable, and chelation is not possible.

The stereochemistry of the enolate capture fits the general pattern observed when allylic strain is the major factor [37,39]. The alkylation takes place on the

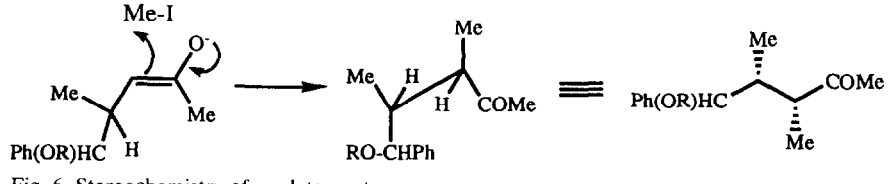


Fig. 6. Stereochemistry of enolate capture.

Table 6

Crystallographic data for **17a** and **17b**

	17a	**17b**
Formule	$C_{15}H_{22}O_2$	$C_{15}H_{22}O_2$
Mol. weight, g	234.34	234.34
Crystal system	tetragonal	tetragonal
Space group	$I4_1/a$	$P\bar{4}2_1/c$
a, Å	23.808(8)	14.865(5)
b, Å	23.808(8)	14.865(5)
c, Å	9.767(3)	13.076(4)
V, Å^3	5536	2889
Z	16	8
$F(000)$	2048	1024
D_c, g/cm^3	1.125	1.077
μ (Mo-K_α), cm^{-1}	0.68	0.65
Crystal size, mm	1.00×0.28×0.31	0.80×0.58×0.18
2θ	2–40°	2–40°
Reflections measured	1254	741
Reflections used	892($I > 1.5\sigma(I)$)	656($I > 1.5\sigma(I)$)
R; R_w [a]	0.046; 0.044	0.085; 0.071
l.s. parameters	160	125
r.m.s. shift/e.s.d. (last ref.)	0.17	0.20

[a] $R_w = [\Sigma w (F_o - F_c)^2 / \Sigma w F_o^2]^{1/2}$

face opposite to the larger group (CHOH(Ph)) with the allylic C–H bond lying in the plane of the C=C double bond (Fig. 6).

The diastereoselectivity observed is excellent in all cases studied.

Summary

A γ-methyl group exerts the dominant effect in the conjugate addition of a cuprate on a γ-methyl-δ-oxy-α,β-enone, leading to pure *anti*-addition to the *syn* substrate, whereas for the *anti* substrate, a chelating group on oxygen (MEM) definitely assists *anti* addition. The *syn* enone reacts exclusively according to the Morokuma model, whereas the *anti* enone exhibits a chelate effect and fits better with the Isobe model. In both cases, capture of the enolate by iodomethane is stereoselective, so that four contiguous substituted carbons can be created from the initial two, with good stereoselectivity.

X-Ray studies

Intensity data were collected at room temperature on a Philips PW 1100 diffractometer using graphite monochromated Mo-K_α radiation. Crystal data and details of the data collection are listed in Table 6. For each compound, the accurate cell dimensions and orientation matrix were obtained from least squares refinements of the setting angles of 25 well defined reflections. No decay in the intensities of two standard reflections was observed during the course of data collection. The usual corrections for Lorentz and polarization effects were applied.

Computations were performed by use of CRYSTALS [40] adapted to a Microvax-II computer. Scattering factors and corrections for anomalous dispersion were ap-

Table 7

Main bond lengths (Å) and angles (deg) for $C_{15}H_{22}O_2$, compound **17a**

O(1)–C(1)	1.420(5)	O(1)–C(5)	1.424(5)
C(1)–C(2)	1.533(6)	C(1)–O(2)	1.418(5)
C(1)–C(6)	1.526(6)	C(2)–C(3)	1.525(6)
C(2)–C(7)	1.569(6)	C(3)–C(4)	1.534(6)
C(3)–C(8)	1.522(6)	C(4)–C(5)	1.517(5)
C(4)–C(9)	1.524(6)	C(5)–C(10)	1.511(5)
C(10)–C(11)	1.376(5)	C(10)–C(15)	1.383(6)
C(11)–C(12)	1.389(6)	C(12)–C(13)	1.354(7)
C(13)–C(14)	1.368(7)	C(14)–C(15)	1.385(7)
C(5)–O(1)–C(1)	115.1(3)	C(2)–C(1)–O(1)	111.4(3)
O(2)–C(1)–O(1)	109.1(4)	O(2)–C(1)–C(2)	107.8(4)
C(6)–C(1)–O(1)	104.2(3)	C(6)–C(1)–C(2)	113.0(4)
C(6)–C(1)–O(2)	111.4(4)	C(3)–C(2)–C(1)	112.5(4)
C(7)–C(2)–C(2)	111.8(4)	C(7)–C(2)–C(3)	112.1(4)
C(4)–C(3)–C(2)	111.1(4)	C(8)–C(3)–C(2)	112.4(4)
C(8)–C(3)–C(4)	112.2(4)	C(5)–C(4)–C(3)	108.8(4)
C(9)–C(4)–C(3)	113.9(4)	C(9)–C(4)–C(5)	111.5(4)
C(4)–C(5)–O(1)	110.0(4)	C(10)–C(5)–O(1)	107.5(3)
c(10)–C(5)–C(4)	114.9(4)	C(11)–C(10)–C(5)	122.2(4)
C(15)–C(10)–C(5)	119.4(4)	C(15)–C(10)–C(11)	118.4(4)
C(12)–C(11)–C(10)	120.4(4)	C(13)–C(13)–C(11)	120.7(5)
C(14)–C(13)–C(12)	119.8(5)	C(15)–C(14)–C(13)	120.1(5)
C(15)–C(15)–C(10)	120.6(5)		

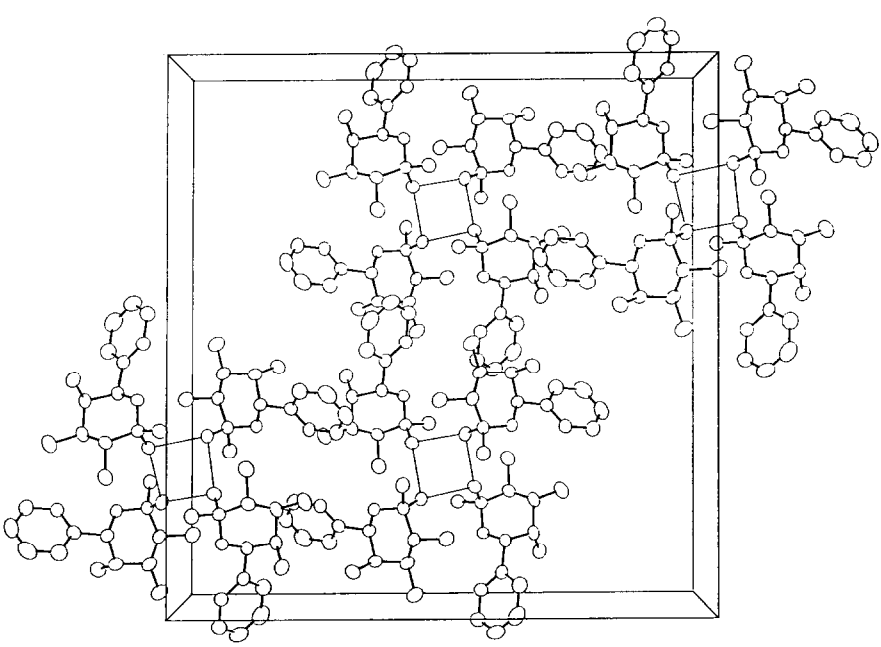


Fig. 7. Packing diagram for compound **17a**.

Table 8

Fractional parameters for $C_{15}H_{22}O_2$, compound **17a**

Atom	x	y	z	U_{eq}	U_{iso}
O(1)	0.4200(1)	0.3845(1)	0.0072(3)	0.0608	
C(1)	0.4235(2)	0.3277(2)	0.0507(5)	0.0665	
C(2)	0.3673(2)	0.3069(2)	0.1078(5)	0.0675	
C(3)	0.3180(2)	0.3214(2)	0.0145(5)	0.0665	
C(4)	0.3198(2)	0.3833(2)	−0.0286(5)	0.0643	
C(5)	0.3770(2)	0.3958(2)	−0.0902(4)	0.0596	
O(2)	0.4376(1)	0.2935(1)	−0.0631(4)	0.0748	
C(6)	0.4703(2)	0.3278(2)	0.1574(6)	0.0891	
C(7)	0.3692(2)	0.2427(2)	0.1440(6)	0.0887	
C(8)	0.2617(2)	0.3052(2)	0.0769(6)	0.0918	
C(9)	0.3057(2)	0.4242(2)	0.0866(5)	0.0805	
C(10)	0.3848(2)	0.4555(2)	−0.1389(4)	0.0593	
C(11)	0.4248(2)	0.4906(2)	−0.0835(5)	0.0691	
C(12)	0.4306(2)	0.5453(2)	−0.1313(6)	0.0833	
C(13)	0.3968(3)	0.5651(2)	−0.2316(6)	0.0918	
C(14)	0.3568(2)	0.5309(3)	−0.2880(5)	0.0943	
C(15)	0.3507(2)	0.4762(2)	−0.2419(5)	0.0845	
H(1)	0.465(2)	0.305(2)	−0.098(5)		0.11(2)

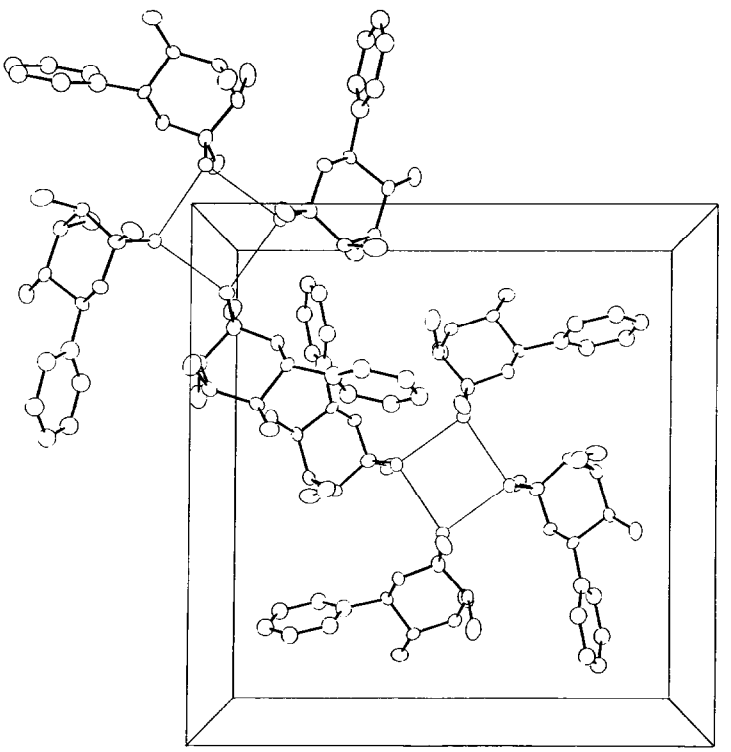


Fig. 8. Packing diagram for compound **17b**.

Table 9

Main bond lengths (Å) and bond angles (deg) for $C_{15}H_{22}O_2$, compound **17b**

O(1)–C(1)	1.43(1)	O(1)–C(5)	1.45(1)
C(1)–C(2)	1.54(1)	C(1)–O(2)	1.42(1)
C(1)–C(6)	1.50(2)	C(2)–C(3)	1.56(1)
C(2)–C(7)	1.56(2)	C(3)–C(4)	1.51(2)
C(3)–C(8)	1.53(2)	C(4)–C(5)	1.51(1)
C(4)–C(9)	1.52(2)	C(5)–C(10)	1.50(1)
C(10)–C(11)	1.37(1)	C(10)–C(15)	1.39(1)
C(11)–C(12)	1.39(1)	C(12)–C(13)	1.38(1)
C(13)–C(14)	1.33(1)	C(14)–C(15)	1.40(1)
C(5)–O(1)–C(1)	115.1(8)	C(2)–C(1)–O(1)	112.3(9)
O(2)–C(1)–O(1)	109.3(8)	O(2)–C(1)–C(2)	106.6(9)
C(6)–C(1)–O(1)	104.7(9)	C(6)–C(1)–C(2)	114.7(10)
C(6)–C(1)–O(2)	109.2(9)	C(3)–C(2)–C(1)	112.0(9)
C(7)–C(2)–C(1)	111.9(10)	C(7)–C(2)–C(3)	108.1(10)
C(4)–C(3)–C(2)	109.8(9)	C(8)–C(3)–C(2)	112.4(9)
C(8)–C(3)–C(4)	117.0(11)	C(5)–C(4)–C(3)	110.8(8)
C(9)–C(4)–C(3)	112.2(10)	C(9)–C(4)–C(5)	110.1(10)
C(4)–C(5)–O(1)	110.9(8)	C(10)–C(5)–O(1)	105.0(8)
C(10)–C(5)–C(4)	115.8(8)	C(11)–C(10)–C(5)	119.7(11)
C(15)–C(10)–C(5)	120.9(10)	C(15)–C(10)–C(11)	119.5(9)
C(12)–C(11)–C(10)	120.1.9)	C(13)–C(12)–C(11)	119.3(9)
C(14)–C(13)–C(12)	121.1(9)	C(15)–C(14)–C(13)	120.4(10)
C(14)–C(15)–C(10)	119.6(9)		

plied [41]. Solution of the structure was accomplished by a combination of direct (SHELXS [42]) and standard Fourier techniques. An absorption correction was applied (DIFABS [43]). For compound **17a**, all non-hydrogen atoms were refined anisotropically. For compound **17b**, because of the poor data to variables ratio, the phenyl carbon atoms were kept isotropic, and refined with an overall refinable isotropic thermal parameter. For both compounds hydrogen atoms were placed in calculated positions, and their coordinates calculated after each cycle. They were allocated an isotropic thermal parameter 20% higher than that of the carbons to which they were bonded. Tables 7–10 lists the main bond lengths and angles and fractional parameters for the two compounds.

Figures 7 and 8 show that capitals of both compounds consist of hydrogen bonded tetramers: O_2–$O_2' = 2.83$ Å for **17a**, and 2.79 Å for **17b**. Full tables of anisotropic thermal parameters and lists of calculated and observed structure factors are available from the authors.

Experimental

^1H and ^{13}C NMR spectra were recorded on a JEOL FX 90 Q or a Brucker AC 200, or a JEOL GSMX 400 apparatus ($CDCl_3$; δ ppm from TMS). GLC analyses were performed on a Carlo Erba chromatograph G1 and 2150, using a 3 m glass column (10% SE 30 on silanized chromosorb G 80/100 mesh or carbowax 20H) and a 25 m capillary glass column (OV 101). The gas chromatograph was coupled

Table 10

Fractional parameters for $C_{15}H_{22}O_2$, compound **17b**

Atom	x	y	z	U_{eq}	U_{iso}
O(1)	0.3775(4)	0.2716(5)	0.0688(5)	0.0499	
C(1)	0.4680(7)	0.3038(8)	0.0673(8)	0.0538	
C(2)	0.5361(7)	0.2288(8)	0.0426(8)	0.0515	
C(3)	0.5071(8)	0.1721(7)	−0.0521(9)	0.0592	
C(4)	0.4104(7)	0.1425(7)	−0.0403(9)	0.0513	
C(5)	0.3498(7)	0.2223(7)	−0.0219(7)	0.0396	
O(2)	0.4770(5)	0.3698(5)	−0.0110(6)	0.0510	
C(6)	0.4808(9)	0.348(1)	0.1694(9)	0.0740	
C(7)	0.5493(9)	0.163(1)	0.135(1)	0.0828	
C(8)	0.5329(9)	0.217(1)	−0.153(1)	0.0828	
C(9)	0.3775(9)	0.0892(8)	−0.132(1)	0.0739	
C(10)	0.2526(7)	0.2012(6)	−0.005(1)		0.076(2)
C(11)	0.2249(8)	0.1686(6)	0.0877(9)		0.076(2)
C(12)	0.1344(8)	0.1481(6)	0.1039(8)		0.076(2)
C(13)	0.0735(7)	0.1609(6)	0.0255(9)		0.076(2)
C(14)	0.0997(8)	0.1921(6)	−0.0651(9)		0.076(2)
C(15)	0.1903(8)	0.2127(6)	−0.0828(9)		0.076(2)
H(1)	0.436(9)	0.407(9)	−0.03(1)		0.21(6)

to Hitachi D 2000 integrator. Melting points were taken on a Büchi SMP-20 apparatus, and are uncorrected.

(1S,2S*,3R*S*)-1-Phenyl-2,5 dimethyl-3-phenylsulfonyl-hex-5-en-1-ol (**4a**).* To a solution of isopropenyllithium (33 mmol, 25 ml, 1.32 *N* in ether) in 25 ml of THF at −60°C under nitrogen was added a solution of **3** (11 mmol, 3.34 g) in 15 ml of THF. The mixture was allowed to warm to −30°C and the reaction monitored by TLC. Hydrolysis with saturated aqueous NH_4Cl was followed by extraction with ether (50 ml). The aqueous phase was extracted three times with 20 ml ether. The combined organic phases were washed with 15 ml of water, 15 ml of 0.1 *M* aqueous HCl, and 15 ml of brine, then dried over $MgSO_4$. Chromatography on silica (cyclohexane/ethyl acetate 80/20, as eluant) yielded 3.76 g (99%) of **4a** (two diastereoisomers 69/31). Major isomer: ^{1}H NMR (200 MHz): 0.98 (s, 3H), 1.5 (d, 3H, $J = 7.1$ Hz), 2.2 to 2.6 (m, 3H), 2.75 (s, 1H(OH)), 2.90 (ddd, 1H, $J = 11.0 \times 2.8 \times 1.8$ Hz), 4.62 (s, 1H), 4.75 (s, 1H), 5.3 (d, 1H, $J = 8.2$ Hz), 7.15 to 7.8 (m, 10H). ^{13}C NMR: 143.4, 139.7, 139.4, 133.2, 128.8, 128.2, 127.9, 127.6, 126.9, 114.6, 76.3, 63.3, 41.7, 36.4, 20.6, 10.5.

Oxidation of alcohols

*2,5-Dimethyl-1-phenyl-3-phenylsulfonyl-hex-5-ene-1-one (**5**).* To a vigorously stirred solution of **4a** (2.73 mmol, 940 mg) in 20 ml of dichloromethane under nitrogen at 0°C was pyridinium chlorochromate (14.82 mmol, 3.2 g). After 1.5 h and again after 3 h were added 100 mg of fresh pyridinium chlorochromate. The reaction was complete in 5 h. Ether was added to precipitate the chromous salts, and after trituration and filtration through a plug of Celite, the filtrate was purified by chromatographs on SiO_2 (eluent, dichloromethane) to give **5** as an oil (896 mg, 96%). ^{1}H NMR (200 MHz) of one diastereoisomer: 1.50 (s, 3H), 1.52 (d, 3H, $J = 7.0$ Hz), 2.5 (m, 2H), 3.9 (m, 2H), 4.68 (s, 1H), 4.72 (s, 1H), 7.35 to 7.95 (m,

10H). ^{13}C NMR (two diastereoisomers): 200.8, 200.3, 140.3, 140.2, 139.3, 138.7, 136.8, 135.4, 133.7, 133.6, 133.1, 132.6, 129.0, 128.8, 128.6, 128.4, 128.1, 115.0, 114.1, 64.1, 62.3, 41.1, 39.1, 36.4, 33.1, 21.4, 13.9, 12.5.

Reduction of ketone **5**

(1S,2R*,3R*S*)-1-phenyl-2,5-dimethyl-3-phenylsulfonyl-hex-5-ene-1-ol* ***(6a)***. Sodium tri(s-butyl)borohydride (2.4 mmol, 2.4 ml of a 1 *N* THF solution) was added to 5 ml of THF at −80°C followed by a solution of **5** (1.9 mmol, 650 mg) in 3 ml of THF. The mixture thickened and became yellow. It was kept at −75°C for 1 h, then at −20°C for 1 h, and subsequently hydrolyzed at 0°C by addition of ethanol (1.4 ml), then water (0.5 ml), 6 *N* aqueous sodium hydroxide (0.9 ml), and hydrogen peroxide (1.36 ml) (exothermic reaction). The mixture was extracted with ether (3 ml). The aqueous phase was saturated with potassium carbonate, and extracted three times with ether (5 ml). The combined organic phases were washed with water (2 × 10 ml), hydrochloric acid (0.1 *N*, 10 ml), then brine (2 × 10 ml), and dried over $MgSO_4$. The solvents were evaporated and isobutanol is removed under vacuum (10^{-2} torr). The product was chromatographed on SiO_2 (eluent: 80/20 cyclohexane/ethyl acetate) to give **6a** as white crystals 607 mg (93%). ^{13}C NMR (two diastereomers): 144.1, 143.0, 142.2, 140.4, 140.0, 139.5, 133.7, 133.6, 129.3, 129.2, 128.9, 128.8, 128.7, 128.5, 128.4, 128.0, 126.9, 126.7, 114.9, 114.1, 76.6, 76.2, 61.0, 60.8, 41.8, 39.0, 36.7, 32.7, 21.6, 21.4, 12.0, 11.8.

Protection of the hydroxy function

As a triethylsilyloxy derivative: (1S,2R*,3R*S*)-1-phenyl-1-triethylsilyloxy-2,5-dimethyl-3-phenylsulfonyl-hex-5-ene* ***(6b)***. To a solution of **6a** (1.22 mmol, 419 mg) in DMF (5 ml) were successively added imidazole (1.69 mmol, 108 mg), triethylchlorosilane (1.79 mmol, 0.3 ml), and 10 mg of 4-dimethylaminopyridine. The reaction was monitored by TLC, and when reaction was complete the mixture treated with water (10 ml) and ether 920 ml). The aqueous phase was extracted 4 times with ether (10 ml). The combined organic phases were washed 5 times with brine (10 ml) and dried over $MgSO_4$. The solvents were evaporated, and the crude product chromatographed on SiO_2 (eluent: 90/10 cyclohexane/ethyl acetate) to give **6b** as an oil (547 mg, 98%). ^{13}C NMR (two diastereoisomers): 144.1, 142.6, 141.6, 140.6, 140.4, 139.7, 133.4, 133.1, 129.0 to 126.5 no resolution, 114.4, 113.7, 78.0, 60.5, 60.1, 42.8, 39.7, 36.8, 32.1, 22.0, 21.1, 11.9, 11.0, 6.8, 6.7, 5.2, 5.0.

As a MEM ether: ***6c***. To a solution of **6a** (4.94 mmol, 1.70 g) in dichloromethane (40 ml) under nitrogen was added diisopropylethylamine (5.14 mmol, 0.9 ml) and β-methoxyethoxymethyl chloride (5.22 mmol, 0.6 ml). The mixture was stirred for 24 h then treated with saturated aqueous sodium carbonate (10 ml). The aqueous phase was extracted 3 times with dichloromethane (10 ml) and combined organic phases were washed with aqueous of ammonium chloride until slightly acidic, then dried over $MgSO_4$. The solvent was evaporated under vacuum and residue chromatographed on SiO_2 (eluent: 70/30 cyclohexane/ethylacetate) to give **6c** is as an oil (2.04 g, 98%). ^1H NMR (200 MHz) one diastereoisomer: 0.86 (d, 3H, $J = 7.1$ Hz), 1.58 (s, 3H), 2.5 to 2.9 (m, 4H), 3.39 (s, 3H), 3.5 (m, 4H), 4.0 to 5.0 (m, 5H), 7.05 to 7.95 (m, 10H). ^{13}C NMR: 141.6, 140.0, 133.2, 128.8, 128.6, 128.3, 127.9, 127.4, 126.6, 113.7, 94.1, 81.5, 71.5, 67.6, 60.8, 58.8, 38.1, 32.0, 21.6, 11.7.

(1S,2S*,3R*S*)-1-Phenyl-1-triethylsilyloxy-2,5-dimethyl-3-phenylsulfonyl-hex-5-ene (**4b**) (Products **4b** and **4c** were obtained similarly).* ^{1}H NMR (200 MHz) (two diastereoisomers): 0.4 (m, 6H), 0.7–0.9 (m, 12H), 1.25 + 1.45 (2d, 3H, J = 6.8 + 6.0 Hz), 2.3–3.1 (m, 4H), 4.39 + 4.42 (2d, 1H, J = 9.0 + 9.0 Hz), 4.7–4.9 (4s, 2H), 7.0–7.8 (m, 10H). ^{13}C NMR (two diastereoisomers): 144.4, 142.7, 141.9, 140.3, 140.1, 133.4, 133.3, 129.2, 129.1, 128.9, 128.5, 128.4, 128.0, 127.5, 115.0, 114.3, 77.4, 62.2, 61.6, 43.2, 40.1, 37.1, 31.9, 22.1, 20.5, 12.0, 11.9, 6.9, 6.8, 5.2, 5.1.

(1S,2S*,3R*S*)-1-Methoxyethoxymethylenoxy-1-phenyl-2,5-dimethyl-3-phenylsulfonyl-hex-5-ene (**4c**).* ^{1}H NMR (200 MHz) (one diastereoisomer): 0.89 (s, 3H), 1.56 (d, 3H, J = 7 Hz), 1.95 (m, 1H), 2.4 (m, 2H), 2.7 (m, 1H), 3.38 (s, 3H), 3.5 (m, 4H), 5.58–4.77 (m, 4H), 5.26 (d, 1H, J = 10.3 Hz), 7.3–7.7 (m, 10H). ^{13}C NMR (one diastereoisomer): 141.0, 140.2, 140.1, 133.5, 129.2, 128.8, 128.6, 128.5, 128.4, 115.3, 94.1, 81.5, 71.9, 67.4, 62.1, 59.2, 40.9, 36.9, 20.6, 12.2.

Ozonolysis desulfonation

(5R,6S*)-5-Methyl-6-phenyl-6-triethylsilyloxy-hex-3-en-2-one (**7b**).* A solution of **4b** (0.44 mmol, 201.5 mg) in 6 ml dichloromethane was cooled to −80°C and a stream of ozone (5% in O_2) bubbled through until a blue colour persisted. The mixture was then treated at −50°C with a large excess of dimethyl sulphide, and the temperature then allowed to rise to 0°C, and kept at that temperature for 1 h and then allowed to warm to 15°C, and 0.1 ml DBU was added. The desulfonation was monitored by TLC. When reaction was complete water (6 ml) and ether (30 ml) were added, and the aqueous phase was extracted 5 times with ether (5 ml). The combined organic phases were washed with water (10 ml) and brine (10 ml) they dried over $MgSO_4$. After removal of the solvents under vacuum, the residue was chromatographed on SiO_2 (eluent 90/10 cyclohexane/ethyl acetate) to give **7b** (134 mg 96%) as an oil (found: C, 71.87; H, 9.52. $C_{19}H_{30}O_2Si$ calc.: C, 71.70; H, 9.43%). ^{1}H NMR (200 MHz): 0.5 (m, 6H), 0.88 (m, 9H), 1.02 (d, 3H, J = 6.7 Hz), 2.17 (s, 3H), 2.6 (dddq, 1H, J = 7.5 × 5.4 × 1.2 × 6.7 Hz), 4.63 (d, 1H, J = 5.4 Hz), 5.95 (dd, 1H, J = 16.2 × 1.2 Hz), 6.75 (d, 1H, J = 16.2 × 7.5 Hz), 7.1 to 7.4 (m, 5H). ^{13}C NMR: 198.5, 150.3, 142.9, 131.1, 127.9, 127.4, 126.6, 78.1, 45.5, 26.6, 14.2, 6.8, 4.9.

(5R,6S*)-5-Methyl-6-methoxyethoxymethylenoxy-6-phenylhex-3-ene-2-one (**7c**) (These enone, and **8b** and **8c**, were obtained similarly).* Yield 86% (oil) (found: C, 70.08; H, 8.34. $C_{17}H_{24}O_4$ calc.: C, 69.88; H, 8.22%). ^{1}H NMR (200 MHz): 1.12 (d, 3H, J = 6.80 Hz), 2.18 (s, 3H), 2.74 (m, 1H), 3.4 (s, 3H), 3.42–3.64 (m, 3H), 3.85 (m, 1H), 4.66 (m, 3H), 5.96 (d, 1H, J = 16.2 Hz), 6.70 (dd, 1H, J = 16.2 × 7.4 Hz), 7.15–7.45 (m, 5H). ^{13}C NMR: 198.5, 149.5, 139.6, 131.3, 128.6, 128.0, 127.6, 93.6, 81.2, 71.9, 67.5, 59.1, 43.3, 26.9, 15.0.

(5S,6S*)-5-Methyl-6-phenyl-6-triethylsilyloxyhex-3-en-2-one (**8b**).* Yield 85% (oil) (found: C, 71.82; H, 9.49. $C_{19}H_{30}O_2Si$ calc.: C, 71.70, H, 9.43%). ^{1}H NMR (200 MHz): 0.48 (m, 6H), 0.85 (m, 9H), 0.95 (d, 3H, J = 6.8 Hz), 2.21 (s, 3H), 2.60 (m, 1H), 4.51 (d, 1H, J = 6.5 Hz), 6.00 (dd, 1H, J = 16.2 × 1.1 Hz), 6.89 (dd, 1H, J = 16.2 × 7.7 Hz), 7.15–7.35 (m, 5H). ^{13}C NMR: 198.4, 150.4, 143.2, 131.3, 128.0, 127.5, 126.6, 78.8, 45.6, 26.6, 15.9, 6.7, 4.9.

(5S,6S*)-5-Methyl-6-methoxyethoxymethylenoxy-6-phenyl-hex-3-en-2-one (**8c**).* Yield 73% (oil). m/z NICI NH_3 291 (M − H) 248, 201, 185, 141, 112. ^{1}H NMR (400 MHz): 0.95 (d, 3H, J = 6.87 Hz), 2.26 (s, 3H), 2.70 (m, 1H), 3.38 (s, 3H)

3.40–3.60 (m, 3H), 3.80 (m, 1H), 4.50 (d, 1H, $J = 7.7$ Hz), 4.57 (AB system 2H), 6.08 (dd, $J = 15.95 \times 0.83$ Hz), 6.91 (dd, 1H, $J = 15.95 \times 7.97$ Hz), 7.20–7.40 (m, 5H). ^{13}C NMR: 198.7, 150.4, 139.6, 131.2, 128.3, 128.0, 127.6, 93.1, 81.6, 71.6, 67.2, 59.0, 43.5, 26.9, 16.4.

Addition of cuprates to enones

To a suspension of the complex $CuBr \cdot Me_2S$ (3.81 mmol, 784 mg) in 10 ml of ether at -50°C under nitrogen was added a 1.2 *N* solution of methyllithium in ether (7.62 mmol, 6.35 ml). The temperature was raised to 0°C until a clear solution was obtained, and then a solution of 1.6 mmol of the enone in 7 ml of ether was added at -30°C, and the temperature allowed to rise slowly to -10°C. The mixture was treated with a solution of ammonium chloride in concentrated aqueous ammonia (4/1) then stirred in air. The aqueous phase was extracted 3 times with ether (10 ml) and the combined organic phases were washed with the NH_4Cl/NH_3 solution until colorless, then with brine, and finally dried over $MgSO_4$. The solvent was evaporated under vacuum and a sample of the residue subjected/GLC and NMR spectroscopic examination to establish the isomeric ratio. The product was chromatographed on SiO_2 (eluent: 90/10 cyclohexane/ethylacetate).

For reactions in the presence of Me_3SiCl once the cuprate was formed, one equivalent of Me_3SiCl was added at -70°C, followed by the enone. The temperature was allowed to rise slowly to -10°C, and the subsequent procedure was as above.

(4R,5R*,6S*)-4,5-Dimethyl-6-phenyl-6-triethylsilyloxyhexan-2-one* ***(9a)***. Yield 83% (oil), d.r. 100/0 (found: C, 71.78; H, 9.99. $C_{20}H_{34}O_2Si$ calc.: C, 71.86; H, 10.18%. ^{1}H NMR (200 MHz): 0.50 (m, 6H), 0.78–1.00 (m, 15H), 1.63 (m, 1H), 1.95 (m, 1H), 2.00 (s, 3H), 2.10 (m, 1H), 2.45 (m, 1H), 4.58 (d, 1H, $J = 6.1$ Hz), 7.15–7.40 (m, 5H). ^{13}C NMR: 208.9, 144.7, 128.1, 127.3, 126.8, 77.8, 46.93, 46.88, 30.5, 30.1, 19.4, 10.7, 6.9, 5.1.

(4R,5R*,6S*)-4-Butyl-5-methyl-6-phenyl-6-triethylsilyloxy-hexan-2-one* ***(9b)***. Yield 81% (oil), d.r. > 95/5. ^{1}H NMR (200 MHz): 0.50 (m, 6H), 0.75–1.00 (m, 15H), 1.00–1.40 (m, 6H), 1.75–2.45 (m, 7H), 4.46 (d, 1H, $J = 7$ Hz), 7.10–7.40 (m, 5H). ^{13}C NMR: 208.9, 144.5, 128.1, 127.4, 127.0, 78.7, 45.4, 42.7, 34.6, 32.8, 30.0, 29.4, 22.8, 14.1, 10.7, 6.9, 5.1.

(4R,5R*,6S*)-4,6-Diphenyl-5-methyl-6-triethylsilyloxy-hexan-2-one* ***(9c)***. Yield 81%, d.r. 100/0. ^{1}H NMR (200 MHz): 0.48 (m, 6H), 0.84 (m, 9H), 0.90 (d, 3H, $J = 6.0$ Hz), 1.84 (s, 3H), 1.97 (m, 1H), 2.68 (s, 1H), 2.71 (d, 1H, J = 3.6 Hz), 3.24 (m, 1H), 4.53 (d, 1H, $J = 3.7$ Hz), 7.10–7.60 (m, 10H). ^{13}C NMR: 208.8, 145.1, 144.4, 128.7, 128.3, 128.1, 127.1, 126.6, 126.5, 76.3, 47.6, 46.8, 43.5, 30.4, 10.4, 7.0, 5.3

(4S,5S*,6S*)-4,5-Dimethyl-6-phenyl-6-triethylsilyloxy-hexan-2-one* ***(10a)***. Yield 80%, d.r. 89/11.liquid. ^{1}H NMR (200 MHz): 0.46 (m, 6H), 0.60 (d, 3H, $J = 7$ Hz), 0.77–1.00 (m, 12H), 1.75 (m, 1H), 2.1 (s, 3H), 2.12–2.25 (m, 3H), 4.42 (d, 1H, $J = 7.4$ Hz), 7.10–7.40 (m, 5H). ^{13}C NMR: 208.4, 144.3, 127.9, 127.3, 127.0, 78.2, 46.2, 46.1, 30.1, 28.7, 18.7, 11.6, 6.8, 5.0.

(4S,5S*,6S*)-4-Butyl-5-methyl-6-phenyl-6-triethylsilyloxyhexan-2-one* ***(10b)***. Yield 80%, d.r. 77/23 (found: C, 73.38; H, 10.63. $C_{23}H_{40}O_2Si$ calc.: C, 73.40; H, 10.64%). ^{1}H NMR (200 MHz), 0.50 (m, 6H), 0.60 (d, 3H, $J = 7.2$ Hz), 0.70–1.40

(m, 18H), 1.89 (m, 1H), 2.14 (s, 3H), 2.10–2.60 (m, 3H), 4.45 (d, 1H, $J = 7.4$ Hz), 7.10–7.40 (m, 5H). ^{13}C NMR: 209.1, 144.5, 128.0, 127.2, 126.9, 78.5, 45.4, 42.2, 32.9, 32.5, 29.5, 22.9, 22.7, 14.1, 11.5, 6.6, 5.0.

(4S,5S*,6S*)-4,6-Diphenyl-5-methyl-6-triethylsilyloxyhexan-2-one (**10c**).* Yield 36%, d.r. = 67/33. ^{1}H NMR (200 MHz): 0.44 (m, 6H), 0.69 (d, 3H, $J = 7$ Hz), 0.85 (m, 9H), 1.84 + 1.96 (2s, 0.67H + 0.33H), 2.09 (m, 1H), 2.60–2.90 (m, 2H), 3.5 (m, 1H), 4.47 + 4.52 (2d, 0.67H + 0.33H, J = 6.48 Hz and 3.81 Hz), 7.00–7.65 (m, 10H). ^{13}C NMR: 208.6, 148.9, 144.4, 144.1, 143.5, 129 to 126.1 no resolution, 76.4, 47.6, 47.4, 46.8, 44.6, 43.6, 41.3, 30.4, 27.2, 11.8, 10.4, 7.0, 5.3, 5.2.

Addition to MEM protected enones

The procedure was as described for the silyloxy protected enones. The temperature was kept at -60°C in the case of **11a** and **12b** at -30°C in the case of **12a**, and -70°C in the case of **12c**.

(4R,5R*,6S*)-4,5-Dimethyl-6-methoxyethoxymethylenoxy-6-phenylhexan-2-one (**11a**).* Yield 82%, d.r. = 100/0. ^{1}H NMR (200 MHz): 0.90 (d, 3H, $J = 6.5$ Hz), 0.96 (d, 3H, $J = 7$ Hz), 1.77 (m, 1H), 1.95 (m, 1H), 2.00 (s, 3H), 2.00–2.20 (m, 1H), 2.47 (dd, 1H, $J = 15.2 \times 2.6$ Hz), 3.38 (s, 3H), 3.43–3.60 (m, 3H), 3.83 (m, 1H), 4.54 (d, 1H, $J = 6.1$ Hz), 4.60 (2d, 1H, $J = 14.75$ Hz), 7.15–7.35 (mm, 5H). ^{13}C NMR: 208.7, 141.3, 128.4, 127.7, 127.6, 93.7, 81.1, 71.9, 67.5, 59.1, 46.6, 44.9, 30.6, 30.1, 19.0, 11.0.

(4S,5S*,6S*)-4,5-Dimethyl-6-methoxyethoxymethylenoxy-6-phenylhexan-2-one (**12a**).* Yield 97%, one diastereomer. *m/z* (PICI NH_4^+) 326 ($M + NH_4^+$) 203, 185, 145. ^{1}H NMR (400 MHz): 0.53 (d, 3H, $J = 6.88$ Hz), 0.95 (d, 3H, $J = 6.88$ Hz), 1.85 (m, 1H), 2.16 (s, 3H), 2.23 + 2.60 (AB system: 1H + 1H), 2.68 (m, 1H), 3.34 (s, 3H), 3.43 (m, 2H), 3.50 + 3.83 (XY system: 1H + 1H), 4.32 (d, 1H, $J = 9.34$ Hz), 4.53 + 4.55 (2d, 2H, $J = 15.4$ Hz), 7.20–7.40 (m, 5H). ^{13}C NMR: 209.2, 141.0, 128.2, 127.9, 127.7, 93.1, 80.7, 71.7, 67.5, 59.0, 45.1, 44.1, 30.7, 28.5, 18.5, 11.3.

(4S,5S*,6S*)-4-Butyl-5-methyl-6-methoxyethoxymethylenoxy-6-phenyl-hexan-2-one (**12b**).* Two diastereomers 91/9. After chromatography on SiO_2 (eluent: 70/30 cyclohexane/ethyl acetate) the d.r. was $> 99/1$. ^{1}H NMR (400 MHz): 0.50 (d, 3H, $J = 6.87$ Hz), 0.89 (m, 3H), 1.15–1.35 (m, 6H), 2.00 (m, 2H), 2.16 (s, 3H), 2.23 (m, 1H), 2.55 (m, 2H), 3.34 (s, 3H), 3.41 (m, 2H), 3.49 + 3.82 (XY system: 1H + 1H), 4.31 (d, 1H, $J = 9.07$ Hz), 4.53 + 4.56 (2d, 1H + 1H, $J = 18.7$ Hz), 7.20–7.40 (m, 5H). ^{13}C NMR: 209.3, 141.3, 128.2, 127.8, 127.6, 93.2, 80.8, 71.7, 67.4, 59.0, 44.4, 40.2, 32.9, 31.8, 30.7, 29.6, 22.9, 14.1, 11.1.

(4S,5S*,6S*)-4,6-Diphenyl-5-methyl-6-methoxyethoxymethylenoxy-hexan-2-one (**12c**).* Two diastereomers 82/18, yield 72%, d.r. = 90/10 after chromatography as above. ^{1}H NMR (400 MHz): 0.58 (d, 1H, $J = 7.15$ Hz), 2.02 (s, 3H), 2.17 (qm, 1H, $J = 7.15$ Hz), 2.79 and 2.97 (AB system, 2H), 3.34 (s, 3H), 3.42 (m, 2H), 3.53 (m, 1H), 3.76 (dt, 1H, $J = 11.55 \times 4.13$ Hz), 3.84 (m, 1H), 4.41 (d, 1H, $J = 8.25$ Hz), 4.48 and 4.61 (XY system, 2H).

Trapping of the enolates by iodomethane

The conjugate addition was carried out as described above with 1.38 mmol of enone and 2.19 mmol of cuprate and a solution of iodomethane (6 ml) in THF (7 ml) and HMPA (7 ml) was then added at -10°C during 1 h. Work-up was similar to that described for the enones. The d.r. ratio was measured for the crude

product, which was then chromatographed on SiO_2 (eluent: 90/10 cyclohexane/ethyl acetate).

(3R,4S*,5R*,6S*)-3,4,5-Trimethyl-6-phenyl-6-triethylsilyloxyhexan-2-one* ***(13a)***. Yield 81%, d.r. > 98/2. ^{1}H NMR (200 MHz): 0.50 (m, 6H), 0.63 (d, 3H, J = 6.8 Hz), 0.76–1.05 (m, 15H), 2.00 (s, 3H), 2.25 (m, 1H), 2.60 (m, 2H), 4.65 (d, 1H, J = 5.95 Hz), 7.10–7.40 (m, 5H). ^{13}C NMR: 212.1, 144.9, 128.0, 126.8, 126.3, 74.9, 48.8, 45.4, 35.4, 28.1, 12.9, 10.6, 8.5, 7.0, 5.1.

(3S,4R*,5S*,6S*)-3,4,5-Trimethyl-6-phenyl-6-triethylsilyloxy-hexane-2-one* ***(14a)***. Yield 83%, d.r. 89/11. ^{1}H NMR (200 MHz): 0.50 (m, 6H), 0.60 (d, 3H, J = 6.8 Hz), 0.80–0.90 (m, 9H), 0.96 (d, 3H, J = 6.7 Hz), 0.98 (d, 3H, J = 7.0 Hz), 1.8 (m, 2H), 2.13 (s, 3H), 2.90 (m, 1H), 4.68 (d, 1H, J = 6.3 Hz), 7.15–7.35 (m, 5H). ^{13}C NMR: 213.4, 143.6, 128.2, 128.0, 127.4, 76.9, 49.4, 44.6, 36.8, 29.3, 14.4, 12.9, 11.7, 7.0, 5.3.

Deprotection of silyl ethers, cyclisation.

The protected ketone (1 mmol) was stirred with 25 ml of a 3/1/1 mixture of THF, acetic acid, and water. If no reaction was observed after 12h, one drop of concentrated sulphuric acid was added. The reaction was followed by TLC or GLC. The mixture was treated until neutral with aqueous sodium carbonate and extracted twice with ether (20 ml). The combined organic phases were washed with brine and dried over $MgSO_4$, and solvents evaporated. The residue was chromatographed on SiO_2 (eluent: 80/20 cyclohexane/ethylacetate). The hemiketals crystallized spontaneously.

(2S,4R*,5R*,6S*)-2,4,5-Triméthyl-6-phenyltetrahydropyran-2-ol* ***(15a)***. Yield 66%, m.p.: 94°C. ^{1}H NMR: 0.50 (d, 3H, J = 6.9 Hz), 0.94 (d, 3H, J = 6.9 Hz), 1.40–1.70 (m, 2H), 1.52 (s, 3H), 1.82 (m, 1H(OH)), 2.4 (qtd, 1H, J = 6.9 × 4.07 × 12.7 Hz), 5.2 (d, 1H, J = 2.5 Hz), 7.20–7.40 (m, 5H). ^{13}C NMR: 142.3, 128.1, 126.7, 126.0, 96.7, 75.4, 38.8, 37.3, 30.9, 30.1, 19.5, 4.7.

(2S,4R*,5R*,6S*)-2,5-Dimethyl-4-butyl-6-phenyl-tetrahydropyran-2-ol* ***(15b)***. Yield 85%. White crystals, becoming stick before melting. ^{1}H NMR (200 MHz): 0.49 (d, 3H, J = 7 Hz), 0.92 (m, 3H), 1.10–1.50 (m, 7H), 1.50 (s, 3H), 1.65 (dd, 1H, J = 13.6 × 4.1 Hz), 1.75–2.32 (m, 3H), 5.18 (d, 1H, J = 2.4 Hz), 7.10–7.40 (m, 5H). ^{13}C NMR: 142.3, 128.1, 126.7, 126.0, 96.7, 75.4, 36.8, 36.0, 35.2, 30.9, 29.1, 23.1, 14.3, 4.8.

(2S,4R*,5R*,6S*)-2,5-Dimethyl-4,6-diphenyltetrahydropyran-2-ol* ***(15c)***. Yield 98%, white crystals, becoming sticky before melting (found: C, 80.87; H, 7.81. $C_{19}H_{22}O_2$ calc.: C, 80.80; H, 7.85%). ^{1}H NMR (200 MHz): 0.38 (d, 3H, J = 7 Hz), 1.57 (s, 3H), 1.90 (dd, 1H, J = 13.1 × 4.1 Hz), 2.00–2.20 (m, 3H), 3.69 (dt, 1H, J = 1.33 × 4.1 Hz), 5.42 (d, 1H, J = 2.5 Hz), 7.10–7.40 (m, 10H). ^{13}C NMR: 143.8, 141.9, 128.5, 128.2, 127.7, 126.9, 126.0, 96.7, 75.2, 40.6, 32.9, 31.2, 5.5.

(2S,4S*,5S*,6S*)-2,4,5-trimethyl-5-phenyltetrahydropyran-2-ol* ***(16a)***. Yield 70%, m.p.: 68–70 °C (found: C, 76.22; H, 9.13. $C_{14}H_{20}O_2$ calc.: C, 76.30; H, 9.15%). ^{1}H NMR (200 MHz): 0.7 (d, 3H, J = 6.9 Hz), 0.93 (d, 3H, J = 6.8 Hz), 1.45 (s, 3H), 1.61 (s, 1H, OH), 1.80 (m, 1H), 2.05 (m, 1H), 4.60 (d, 1H, J = 10.3 Hz), 7.20–7.60 (m, 5H).

(2S,3R*,4S*,5R*,6S*)-2,3,4,5-Tetramethyl-6-phenyltetrahydropyran-2-ol* ***(17a)***. Yield 66%, m.p.: 127 °C. ^{1}H NMR (200 MHz): 0.55 (d, 3H, J = 7 Hz), 0.95 (d, 3H, J = 7 Hz), 1.05 (d, 3H, J = 7 Hz), 1.50 (s, 3H), 1.55 (dd, 1H, J = 10.2 × 7 Hz),

1.75–2.20 (m, 3H), 5.20 (d, 1H, $J = 2.3$ Hz), 7.20–7.40 (m, 5H). ^{13}C NMR: 142.4, 128.1, 126.7, 126.0, 98.9, 74.6, 40.4, 39.0, 36.3, 28.7, 17.9, 13.9, 5.6.

(2S,3S*,4R*,5S*,6S*)-2,3,4,5-Tetramethyl-6-phenyltetrahydropyran-2-ol (17b).* Yield 80%, m.p.: 105 °C. ^1H NMR (200 MHz): 0.58 (d, 3H, $J = 6.9$ Hz), 1.05 (d, 3H, $J = 6.4$ Hz), 1.10 (d, 3H, $J = 6.2$ Hz), 1.43 (s, 3H), 1.70–2.07 (m, 4H), 4.63 (d, 1H, $J = 10.4$ Hz), 7.20–7.40 (m, 5H). ^{13}C NMR: 141.6, 128.5, 127.9, 127.5, 106.3, 78.5, 37.4, 36.5, 24.1, 16.8, 16.7, 14.7, 14.5.

(4R,5R*,6S*)-2-Methoxy-2,4,5-trimethyl-6-phenyltetrahydropyran-2-ol (18a).* *p*-Toluenesulfonic acid monohydrate (55 mg, 2 equiv.) was added with stirring to a solution of **12b** (0.115 mmol, 35.5 mg) in methanol (3.5 ml). The reaction was complete after 5 days. The mixture was neutralized with sodium carbonate, the methanol was evaporated and the mixture extracted 3 times with ether (10 ml). The combined organic phases were washed twice with water (10 ml), then with 0.1 *N* aqueous HCl, and finally with brine, and dried over $MgSO_4$. The solvents were removed under vacuum and the residue chromatographed on silica (eluent: 90/10 cyclohexane/ethyl acetate) to give 23.9 mg (89%) of **18a** as an oil. ^1H NMR (200 MHz): 0.51 (d, 3H, $J = 7.1$ Hz), 0.93 (d, 3H, $J = 6.9$ Hz), 1.20 + 1.50 (m, 1H + 1H), 1.44 (s, 3H), 1.80 (m, 1H), 2.4 (qtd, 1H, $J = 7 \times 4.1 \times 12.5$ Hz), 3.19 (s, 3H), 4.83 (d, 1H, $J = 2.5$ Hz), 7.20–7.40 (m, 5H). ^{13}C NMR: 142.2, 128.1, 126.6, 125.9, 99.0, 74.9, 48.1, 38.5, 38.3, 29.8, 24.0, 19.5, 4.9.

(2S,3S*,4R*,5S*)-2-Phenyl-3-methyl-4-butyl-5-acetyltetrahydropyran (19b).* To a solution of **12b** (0.78 mmol, 272 mg) in t-butanol (15 ml) was added dry pyridinium tosylate (7.97 mmol, 2.00 g). The mixture was refluxed and the reaction monitored by TLC and GLC. The solvent was evaporated under vacuum, and ether (15 ml) and water (15 ml) are added to the residue. The aqueous phase was extracted 4 times with ether (10 ml). Subsequent work-up was then as described for **18d**. Chromatography on silica (eluent: 80/20 cyclohexane/ethyl acetate gave **19b** (169 mg, 79%) as a yellow oil. *m/z* (PICI NH_3): 292 ($M + NH_4^+$), 275, 257, 239, 187. ^1H NMR (400 MHz): 0.71 (d, 3H, $J = 7$ Hz), 0.96 (m, 3H), 1.18–1.70 (m, 7H), 0.96 (m, 3H), 1.18–1.70 (m, 7H), 2.14 (qdd, 1H, $J = 7 \times 4.95 \times 10.3$ Hz), 2.34 (s, 3H), 2.42 (m, 1H), 3.97 (dd, 1H, $J = 12.47 \times 2.93$ Hz), 4.17 (d, 1H, $J = 10.3$ Hz), 4.32 (d, 1H, $J = 12.5$ Hz), 7.20–7.40 (m, 5H). ^{13}C NMR: 210.0, 140.8, 128.3, 127.8, 127.1, 81.7, 63.6, 51.2, 37.0, 35.8, 30.2, 28.7, 25.0, 22.8, 15.0, 14.1.

Acknowledgements

We thank the CNRS for financial support (URA 473) the Rhône Poulenc company for a grant to one of us (G.C.), Mrs M. Baudry for the preparation of many starting materials, and Mrs Veillet-Lavallée for typing the manuscript.

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