Stereocontrol in a one-pot procedure for anionic oxy-Cope rearrangement followed by intramolecular aldol reaction

Alistair P. Rutherford,[a] Cameron S. Gibb,[a] Richard C. Hartley *[a] and Jonathan M. Goodman[b]

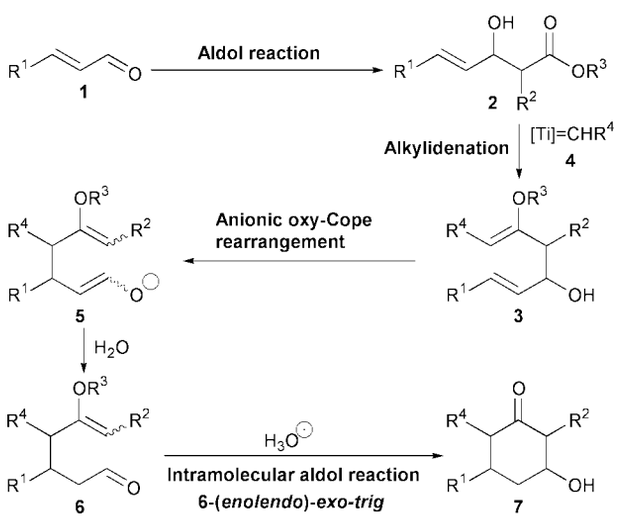
[a] *Department of Chemistry, University of Glasgow, Glasgow, UK G12 8QQ*
[b] *Department of Chemistry, Lensfield Road, Cambridge, UK CB2 1EW*

Received (in Cambridge, UK) 19th December 2000, Accepted 23rd March 2001
First published as an Advance Article on the web 18th April 2001

Racemic β-hydroxycyclohexanones with up to three chiral centres have been synthesized in a stereocontrolled way using the novel anionic oxy-Cope (AOC) rearrangement of acyclic enol ethers. The first examples of compounds containing an aldehyde and an enol ether in a 1,5 relationship are reported. Stereocontrol in the cyclisation of these compounds by a 6-(*enolendo*)-*exo-trig* intramolecular aldol reaction has been studied: there is high stereoselectivity for an axial hydroxy group in the product β-hydroxycyclohexanones. AM1 calculations show that there is a stabilising electrostatic attraction between the oxygen atom of the axial C-3 hydroxy group and the electron-poor carbon at C-1 in the intermediate oxonium ions. ≥87% of AOC rearrangement occurs *via* a chair-like transition state giving rise to the 5,6-*anti* stereochemistry of the β-hydroxycyclohexanones. Trapping the enolate product of AOC rearrangement with oxygen gives fragmentation *via* a 1,2-dioxetane.

Introduction

We have been developing a general method for the stereocontrolled synthesis of polyfunctionalised ring systems using four key reactions: the aldol reaction, Takai alkylidenation, a novel anionic oxy-Cope (AOC) rearrangement of acyclic enol ethers and a new intramolecular aldol reaction (Scheme 1).[1]



Scheme 1

The starting α,β-unsaturated aldehyde **1** has one piece of stereochemical information, the *E* double bond geometry. The aldol reaction then introduces up to two chiral centres in a controlled way. The aldol reaction is chosen as the first step because it is reliable and has efficient diastereoselective and enantioselective versions.[2]

The second key step is the conversion of ester **2** into enol ether **3** using a titanium(IV) alkylidene reagent **4**. Titanium alkylidene reagents **4** developed by Tebbe[3] and by Grubbs[4] are limited to methylenation ($R^4 = H$), while those developed by Petasis[5] can only be generated if R^4 does not allow β-elimination (*i.e.* R^4 = H, aryl, $SiMe_3$). However, Takai[6,7] and, more recently, Takeda[8] have reported methods of generating titanium(IV) alkylidenes in a way that tolerates β-hydrogen atoms. Furthermore, their reagents convert esters into enol ethers with good *Z*-selectivity. Thus, the alkylidenation step may introduce further stereochemical information.

The third key step is AOC rearrangement of enol ether **3** to give enolate **5**. This moves the stereochemical information into positions that are less accessible by 'direct' synthesis, and it may also increase the stereochemical complexity of the system. The AOC rearrangement of rigid cyclic substrates is well known to give high levels of stereocontrol and is widely used.[9] Our method employs the rarer AOC rearrangement of acyclic substrates.[10] Prior to our work, only five examples of AOC rearrangement of enol ethers had been reported;[11–13] all were cyclic and only two had our 1,3-relationship between the enol ether and the oxyanion.[12,13] Enolate **5** is quenched with water to give the novel aldehyde–enol ether **6**. Compounds containing an aldehyde and an enol ether in a 1,5 relationship were unknown prior to our work.

The fourth key step is acid-induced carbocyclisation[14] of aldehyde **6** to give a β-hydroxycyclohexanone **7** producing up to two new chiral centres. 6-(*enolendo*)-*exo-trig* cyclisation of enol ethers onto aldehydes is new. However, since our communication[1] similar reactions of enol ethers with ketones have been reported.[15] Similar 6-(*enolendo*)-*exo-trig* intramolecular aldol reactions[16] are some of the most important synthetic (*e.g.* the Robinson annulation) and biological transformations (*e.g.* aromatic ring formation in polyketide synthesis). However, there had been no systematic study of the stereochemical aspects of this highly favoured process prior to the work that we report here. There were reports where the orientation of the 3-hydroxy group had been determined by face selectivity on a carbocycle present in the reactant,[17] but reported stereoselectivities in the formation of monocyclic β-hydroxycyclohexanones varied from only axial,[15,18,19] to mostly equatorial.[19,20]

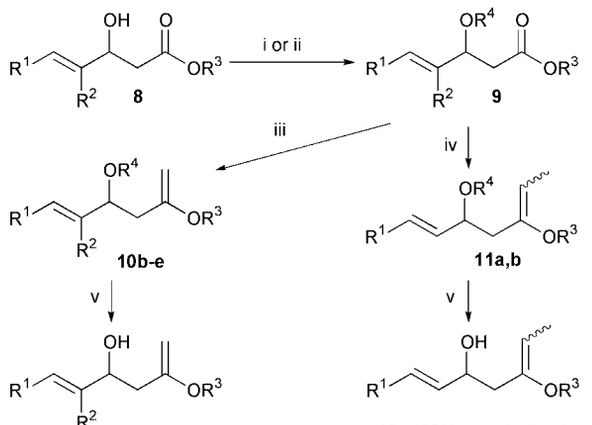
We here give full details of our first studies[1] on the route outlined in Scheme 1. We wished to determine whether acyclic enol ethers **3** would undergo AOC rearrangement; whether the acid-induced cyclisation would be selective for an axial or for an equatorial 3-hydroxy in β-hydroxycyclohexanone **7**; whether there would be good control of the 5,6-relative stereochemistry

DOI: 10.1039/b010138i

of cyclohexanones **7**, which is set up in the AOC rearrangement; and whether the bifunctional aldehydes **6** could be isolated. By choosing racemic substrates **3** (R^2 = H) that had only one chiral centre, we avoided the complex issue of the orientation of the oxyanion during AOC rearrangement.

Results and discussion

We synthesised a range of substrates **12** and **13** for the AOC rearrangement by the route shown in Scheme 2. Reaction of



a R^1 = Ph, R^2 = H, R^3 = Et, R^4 = TMS
b R^1 = Ph, R^2 = H, R^3 = Pr^i, R^4 = TBDMS
c R^1 = Pr^n, R^2 = H, R^3 = Pr^i, R^4 = TES
d R^1 = Ph, R^2 = H, R^3 = Ph, R^4 = TMS
e R^1 = H, R^2 = Bu^n, R^3 = Ph, R^4 = TMS

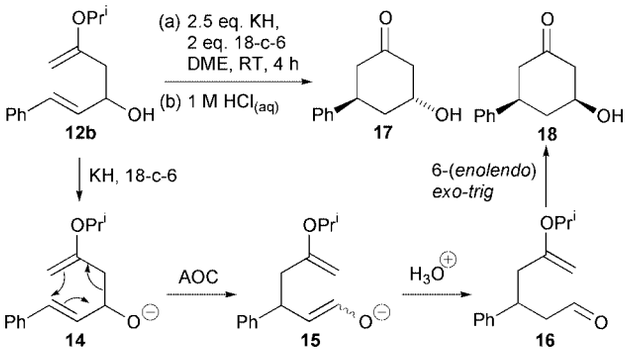
Scheme 2 *Reagents and conditions*: i, TBDMSCl or TESCl, $EtNPr^i_2$, DMF; ii, TMSCl, $EtNPr^i_2$, THF or CH_2Cl_2; iii, $TiCl_4$, TMEDA, Zn, CH_2Br_2, THF; iv, $TiCl_4$, TMEDA, Zn, CH_3CHBr_2, THF; v, TBAF, THF.

cinnamaldehyde with the appropriate lithium enolates gave aldols **8a** and **8b** in close to quantitative yield. The aliphatic aldol **8c** was made from (*E*)-hex-2-enal in 89% yield. The aldols **8d** and **8e** were made in 82% and 43% yield respectively by Mukaiyama reaction[21] between 1-phenoxy-1-trimethylsilyloxyethylene[22] and the appropriate aldehyde. The use of Mukaiyama conditions is necessary as β-lactones are formed in aldol reactions using phenyl esters.[23] Indeed, Schick and co-workers[24] have used related indium-mediated Reformatsky reaction as a method for the synthesis of β-lactones.

Alkylidenation of β-hydroxyesters **8** using a modification[7,25] of Takai's procedure[6] failed, so the aldols **8** were protected as silyl ethers **9**. Methylenation then gave enol ethers **10**, while ethylenation gave mixtures of *Z* and *E* enol ethers **11** with the *Z* isomers predominating (81–85% *Z*). Much higher *Z*-selectivity has been observed in the ethylenation of esters having a branch alpha to the carbonyl group.[6,26] It is noteworthy that even the trimethylsilyl group is stable to Takai alkylidenation. The trimethylsilyl ethers were carried through all steps with no purification after work-up.

Removal of the silyl protecting groups gave alcohols **12** and **13** in 18–52% overall yield from the corresponding aldols. The *E* and *Z* isomers of enol ethers **13a** and **13b** were separated in order to study their rearrangement products. The double bond geometries were assigned from the chemical shifts of $RC(OR^3)$=$CHCH_3$ in the ^{13}C NMR spectra as described by Strobel *et al.*[27] *Z*-enol ethers have δ_C = 109.5 and 110.6 ppm respectively, while δ_C = 93.7 and 94.8 ppm for *E*-enol ethers.

Initially, we attempted to rearrange and cyclise alcohols **12b** and **12c** so that we could determine the diastereoselectivity in the cyclisation step. isopropyl enol ether **12b** reacted with potassium hydride and 18-crown-6 (18-c-6) in DME to give alkoxide **14** which underwent AOC rearrangement to enolate **15** (Scheme 3). This was quenched with aqueous hydrochloric acid

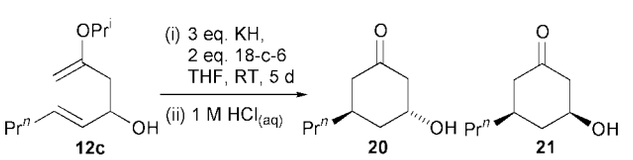


Scheme 3

to generate the desired aldehyde **16** which cyclised under these acid conditions to give a 95 : 5 ratio of 3,5-*anti*- and 3,5-*syn*-β-hydroxycyclohexanones[28] **17** and **18** (no dehydration). The crude mixture was not amenable to chromatography so pure β-hydroxycyclohexanone **17** was obtained in 43% yield by crystallisation. Dehydration of the crude mixture of products from rearrangement of alcohol **12b** gave 5-phenylcyclohex-2-enone[29] **19** in 61% yield.

The above rearrangement–cyclisation and the rearrangements of enol ethers **13** that follow gave crude product mixtures with 80–100% mass balance after work-up. The ^1H NMR spectra showed that the desired β-hydroxycyclohexanones were essentially the only products and the characteristic olefinic signals (δ 5–6 ppm) for the starting 1,5-dienes were absent. In each case, the ratio of isomers was determined by integration of the C*H*OH signal in the ^1H NMR spectrum of the crude mixture. Structural assignment is described below.

A much longer reaction time was required for the rearrangement of aliphatic alcohol **12c**. Acid-induced cyclisation then gave a 51% isolated yield of a 90 : 10 mixture of 3,5-*anti*- and 3,5-*syn*-β-hydroxycyclohexanones **20** and **21** (Scheme 4).



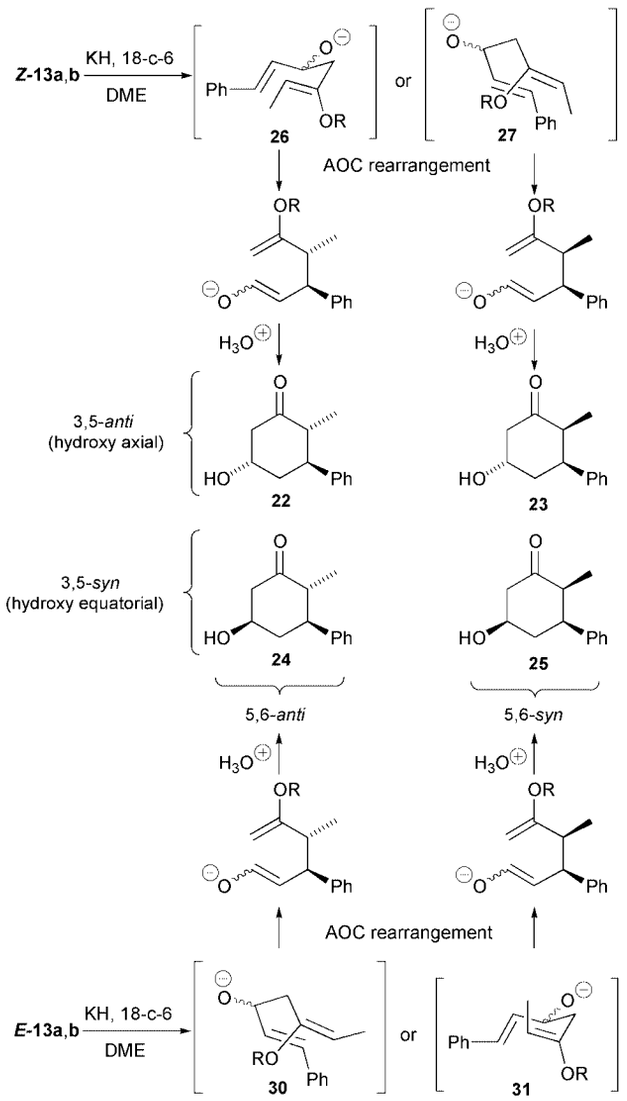
Scheme 4

We concluded from the above cyclisations that there is a strong preference for the formation of an axial hydroxy group in the product β-hydroxycyclohexanones. An explanation for this selectivity is given below.

We next examined control of the 5,6-relative stereochemistry † of β-hydroxycyclohexanones **7** (R^2 = H) by the AOC rearrangement (Scheme 1).

The 5,6-*anti*-β-hydroxycyclohexanones **22** and **24** were the major products when *Z* enol ethers ***Z*-13a** and ***Z*-13b** were rearranged and cyclised (Scheme 5, Table 1). We presume that the 5,6-*anti* isomers arise from AOC rearrangement *via* chair-like conformation **26**; if this is so, then 87–89% of the reaction proceeds *via* this conformation. Similarly, we believe that the 5,6-*syn*-β-hydroxycyclohexanones **23** and **25** arise from rearrangement *via* boat-like conformation **27**. The orientation

† For ease of comparison with the 3,5-disubstituted cyclohexanones, the substituents of the trisubstituted cyclohexanones are considered to be at positions 3, 5 and 6. The latter compounds would be named as 2,3,5-trisubstituted cyclohexanones according to IUPAC nomenclature.



Scheme 5 a R = Et, b R = Pr^{i}.

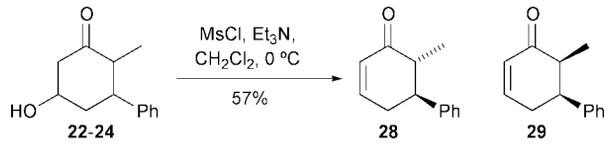
Table 1 Products from AOC rearrangement of alcohols **13**

Reactant	Ratio of products (%)[b]				
	22	**23**	**24**	**25**	**28** : **29**
***Z*-13a**	74	12	13	[a]	1
***Z*-13b**	78	11	10	[a]	1
***E*-13a**	24	66	9		1
***E*-13b**	24	67	8		1

[a] Not detected and expected to be <1%. [b] Ratio of products as determined by ^{1}H NMR spectroscopy of the crude mixture after work-up.

of the oxyanion is unknown, but recent evidence suggests that it is axial.[26] The major isomer **22** was isolated by crystallisation in 31% yield from the rearrangement–cyclisation of enol ether ***Z*-13b**. Unfortunately, dehydration of alcohol **22** proceeded with epimerisation to give an 87 : 13 mixture of cyclohexenones **28** and **29** (Scheme 6). Under the same conditions, the crude mixture from rearrangement–cyclisation of enol ether ***Z*-13b** gave the same 87 : 13 ratio of cyclohexenones **28** and **29** in 57% yield (Scheme 6).

We confirmed that the 5,6 stereochemistry reflects whether the transition state of AOC rearrangement is chair-like or boat-like and is not the result of epimerisation. When enol ether ***Z*-13a** was rearranged and quenched with 1 M DCl in D_2O the label was incorporated only at C-4 of β-hydroxycyclohexanone

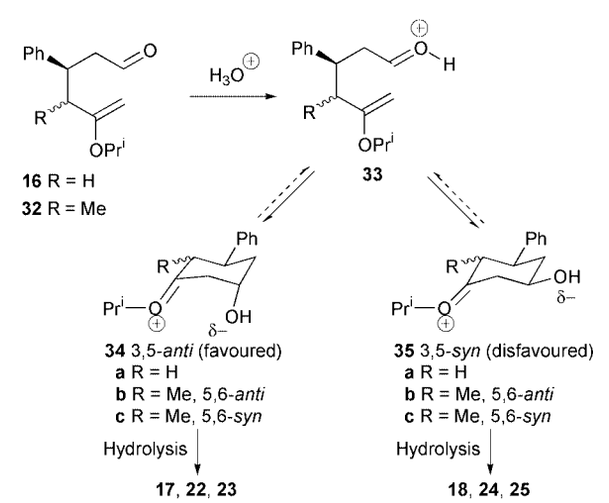


Scheme 6

22. This was evident from loss of couplings to C*H*OH and C*H*Ph, and a reduction in the size of the signal for the C-4 methylene in the ^{1}H NMR spectrum of the product **22**. The doublet due to the methyl group showed no trace of collapse to a singlet and the C-2 protons were unaffected. The lack of deuterium incorporation at C-2 confirms that cyclisation is faster than protonation of the enol ether, a result that mirrors kinetic studies of base-catalysed intramolecular aldol reactions.[30]

E Enol ethers ***E*-B13a** and ***E*-13b** gave the 5,6-*syn* isomer **23** as the major product of rearrangement, presumably as a result of rearrangement *via* chair-like conformation **31** (Scheme 5). However, substantial amounts of 5,6-*anti* isomer **22** were also formed, indicating that the boat-like conformation **30** competes. The C*H*OH signal of the all *syn* isomer **25** in the ^{1}H NMR spectrum overlaps sufficiently with that of its C-6 epimer **24** to prevent the ratio of **24** : **25** from being determined accurately. We estimate that the ratio of **24** : **25** is 3 : 5 since the 5,6-*anti* isomers **22** and **24** should be produced in the same ratio by rearrangement of either *E* or *Z* enol ethers **13**.

In all the above cyclisations, there is a strong preference for the formation of an axial hydroxy group (*i.e.* 3,5-*anti* stereochemistry) in the product β-hydroxycyclohexanones. The aldehydes **16** and **32** produced by aqueous quench of the AOC rearrangement of isopropyl enol ethers **12b** and **13b** might become protonated to give oxonium ions **33** (Scheme 7), which



Scheme 7

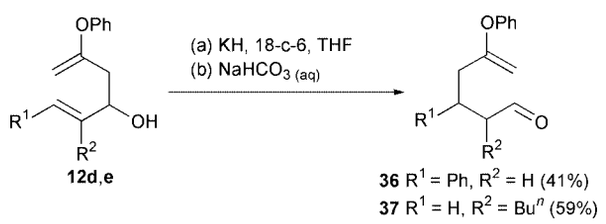
would undergo intramolecular aldol reactions to give the 3,5-*anti* oxonium ions **34**, and 3,5-*syn* oxonium ions **35**. Hydrolysis of 3,5-*anti* oxonium ions **34** would then give the favoured β-hydroxycyclohexanones **17**, **22** and **23**, while hydrolysis of 3,5-*syn* oxonium ions **35** would give β-hydroxycyclohexanones **18**, **24** and **25**. MM2 calculations as implemented in MacroModel version 5.5[31,32] show that there is a modest thermodynamic preference for 3,5-*anti*-β-hydroxycyclohexanones **17**, **22** and **23** with an axial hydroxy group over the corresponding 3,5-*syn* β-hydroxycyclohexanones **18**, **24** and **25** with an equatorial hydroxy group (Table 2, entries 1–3). The preference is lower than that observed experimentally and AM1 calculations[33] carried out using MOPAC version 7[34] indicate that the 3,5-*syn*-β-hydroxycyclohexanones **18**, **24** and **25** are lower in energy (Table 2, entries 4–6). However, AM1

Table 2 MM2 and AM1 calculations

Method of calculation	3,5-*anti* (axial OH)		3,5-*syn* (equatorial OH)		Ratio at 0 °C 3,5-*anti* : *syn*
	Compound	kJ mol^{-1}	Compound	kJ mol^{-1}	
MM2	**17**	21.16	**18**	22.84	68 : 32
MM2	**22**	26.35	**24**	28.17	69 : 31
MM2	**23**	39.55	**25**	41.19	67 : 33
AM1	**17**	−325.4	**18**	−328.6	20 : 80
AM1	**22**	−337.6	**24**	−340.6	21 : 79
AM1	**23**	−330.1	**25**	−336.0	7 : 93
AM1	**34a**	334.2	**35a**	343.4	98 : 2
AM1	**34b**	320.4	**35b**	331.5	99 : 1
AM1	**34c**	324.4	**35c**	334.5	99 : 1

calculations strongly favour oxonium ions **34** with an axial hydroxy group over the corresponding oxonium ions **35** with an equatorial hydroxy group. The Mulliken population analysis suggests that there is a positive charge on C-1 and a partial negative charge on the oxygen atom of the hydroxy group, so there should be an electrostatic interaction between these two centres. When the hydroxy group is equatorial the distance between C-1 and the oxygen atom of the hydroxy group is about 3.7 Å, while this distance is only approximately 2.5 Å for an axial hydroxy group. Thus, the electrostatic interaction in 3,5-*anti* oxonium ions **34** would be stronger than that in 3,5-*syn* oxonium ions **35** and probably accounts for the greater stability of the 3,5-*anti* configuration. Stabilisation of the intermediate 3,5-*anti* oxonium ions **34** could lead to the observed preference for β-hydroxycyclohexanones **17**, **22** and **23**. It seems likely that the rate of hydrolysis of oxonium ions **34** and **35** would be similar. The calculated thermodynamic preference for 3,5-*anti* oxonium ions **34** could, therefore, lead to the observed preference for β-hydroxycyclohexanones **17**, **22** and **23**, provided the ratio of **34** : **35** is thermodynamically controlled. If, however, this ratio is kinetically controlled (*i.e.* ions **34** and **35** do not equilibrate), it is likely that there will still be a preference for β-hydroxycyclohexanones **17**, **22** and **23**, because the interactions which lead to the thermodynamic preference for the 3,5-*anti* stereochemistry should be partially present in the transition state for its formation; thus, there will be a kinetic preference for the 3,5-*anti* oxonium ions **34** and the cyclohexanones **17**, **22** and **23** derived from them.

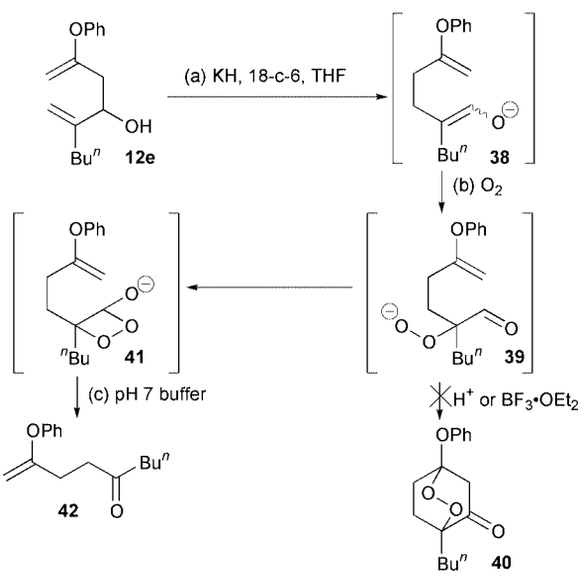
The bifunctional intermediates **6** (Scheme 1) are interesting in that they contain both a nucleophilic enol ether and an electrophilic aldehyde group. Alkyl enol ethers proved too nucleophilic to allow the isolation of such intermediates, but alcohols **12d** and **12e** underwent AOC rearrangement followed by alkaline quench to give phenyl enol ethers–aldehydes **36** and **37** that could be isolated (Scheme 8). Recently, the relative rates



Scheme 8

of enolate protonation and intramolecular reaction between an enolate and an aldehyde have been studied.[30] Compounds **36** and **37** may prove useful for similar studies of acid-induced aldol reactions.

Finally, we wished to test whether our method could be used to make cyclic peroxides that would be potential antibiotics. The 1,2,4-trioxane component of artemisinin is known to be responsible for its antimalarial activity, and other cyclic peroxides have antifungal activity.[35] We hoped that quenching the enolate **38** resulting from AOC rearrangement of alcohol **12e** with oxygen[12,36] would give aldehyde **39**, which would cyclise upon acid quench to give compound **40** (Scheme 9).



Scheme 9

Unfortunately, aldehyde **39** fragments (presumably *via* 1,2-dioxetane **41**) to give ketone **42**, which could be isolated in 71% yield when a neutral quench was used. Autooxidation of enolisable carbonyl groups in protic solvents is well known,[37] but regiocontrol can be problematic and multiple fragmentations can occur. Since our oxygenation–fragmentation occurs at low temperature (perhaps limiting multiple fragmentation) and the position of the enolate is determined by the AOC rearrangement, the reaction could be synthetically useful. Recently, a similar fragmentation of a peroxide derived from a potassium enolate has been exploited in gibberellin synthesis.[38]

Stereochemical assignment

The spectroscopic data for the 3,5-*anti*-β-hydroxycyclohexanone **17** correspond to that reported by Fleming and co-workers[28] and the 3,5-*syn* diastereomer **18** was identified in the ^{1}H NMR spectrum of the crude mixture by comparison with their data for the 3,5-*syn* compound **18**. The ^{1}H NMR signal for C*H*OH of 3,5-*anti*-β-hydroxycyclohexanone **20** is a narrow multiplet of approximately 16 Hz, showing no large axial–axial couplings.

The 3,5-*anti*,5,6-*anti*-β-hydroxycyclohexanone **22** was isolated and its stereochemistry determined by ^{1}H NMR spectroscopy (see Fig. 1 and Table 3). The rows in Table 3 show the unadjusted coupling constants measured from the signal at the chemical shift shown. The signal for *CH*OH is a 2.9 Hz quintet, confirming that it is equatorial and the hydroxy group

Table 3 Selected ^{1}H NMR data for cyclohexanone **22**

δ	Assignment	H^2	$H^{2'}$	H^3	H^4	$H^{4'}$	H^5	H^6	Me
2.77	H^2		14.1	3.0	—	—	—	—	—
2.62	$H^{2'}$	14.1		[a]	—	—	—	—	—
4.59	H^3	2.9	2.9		2.9	2.9	—	—	—
2.13–2.19	H^4	—	—	[a]		[a]	[a]	—	—
2.13–2.19	$H^{4'}$	—	—	[a]	[a]		[a]	—	—
3.13	H^5	—	—	—	9.1	7.5		11.8	—
2.64	H^6	—	—	—	—	—	11.9		6.6
0.84	Me	—	—	—	—	—	—	6.5	

[a] Coupling constant could not be determined; — indicates no coupling.

Table 4 Selected ^{1}H NMR data for cyclohexanone **43**

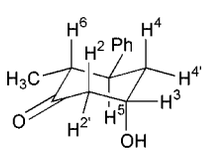
δ	Assignment	H^2	$H^{2'}$	H^3	H^4	$H^{4'}$	H^5	H^6	Me
2.74	H^2		14.5	3.7	—	—	—	—	—
2.38	$H^{2'}$	14.6		4.9	—	—	—	—	—
4.40	H^3	[a]	[a]		[a]	[a]	—	—	—
2.29	H^4	—	—	2.5		13.5	10.9	—	—
1.96	$H^{4'}$	—	—	4.5	13.7		3.5	—	—
3.71	H^5	—	—	—	11.0	4.3		4.3	—
2.70	H^6	—	—	—	—	—	[a]		[a]
0.88	Me	—	—	—	—	—	—	7.2	

[a] Coupling constant could not be determined; — indicates no coupling.

Table 5 Selected ^{1}H NMR data for cyclohexanone **44**

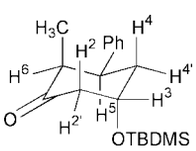
δ	Assignment	H^2	$H^{2'}$	H^3	H^4	$H^{4'}$	H^5	H^6	Me
2.58	H^2		12.2	12.2	—	—	—	—	—
2.76	$H^{2'}$	13.0		4.9	—	2.2	—	—	—
3.95	H^3	10.9	4.8		10.9	4.8	—	—	—
2.04	H^4	—	—	10.7		12.9	12.9	—	—
2.20	$H^{4'}$	—	[a]	[a]	[a]		[a]	—	—
2.38	H^5	—	—	—	12.3	3.3		12.3	—
2.52	H^6	—	—	—	—	—	[a]		[a]
0.78	Me	—	—	—	—	—	—	6.4	

[a] Coupling constant could not be determined; — indicates no coupling.



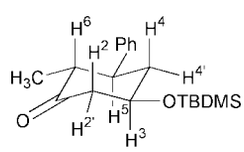
22

Fig. 1



43

Fig. 2



44

Fig. 3

is axial. The signals for H^5 and H^6 show a large axial–axial coupling to each other, confirming the 5,6-*anti* stereochemistry.

Isomers **23** and **24** could not be isolated by chromatography or crystallisation, but silylation of the product mixture from rearrangement of *Z*-enol ether **13** followed by exhaustive chromatography gave samples of the silylated derivatives **43** and **44**. The stereochemistry of each isomer was assigned using ^{1}H NMR spectroscopy (see Fig. 2 and Table 4, Fig. 3 and Table 5). In each case, the connectivity was established by irradiating the signals for C*H*OTBDMS (leading to simplification of the signals for H^2, $H^{2'}$, H^4 and $H^{4'}$) and the methyl group (leading to the signal for H^6 collapsing to a doublet). In each case, the signal for H-6 was partly obscured and when the methyl group was irradiated, one line of the doublet was coincident with a neighbouring signal, so $J_{5,6}$ is determined from the signal for H-5. Averaging two or more similar couplings leads to minor discrepancies in the coupling constants measured from different signals.

The signal for C*H*OTBDMS of silyl ether **43** is a narrow multiplet and $J_{2,3}$, $J_{2',3}$, $J_{4,3}$ and $J_{4',3}$ are all less than 5 Hz. Thus, the silyloxy group is axial. $J_{5,6}$ is 4.3 Hz, allowing us to assign the 5,6-*syn* stereochemistry. The signal for C*H*OTBDMS of silyl ether **44** shows large axial–axial couplings to H^2 and H^4, confirming that the silyloxy group is equatorial. $J_{5,6}$ is large, confirming the 5,6-*anti* stereochemistry.

Unfortunately, treatment of the silyl derivatives with TBAF generated a mixture of isomers, presumably by a fluoride induced retro-aldol process. However, the assignment of the stereochemistry of the silyl ethers allows us to identify the corresponding alcohols in the crude mixture produced by rearrangement–cyclisation because the ^{1}H NMR signal for C*H*OTBDMS in each silyl derivative was the same shape

and almost the same chemical shift as the C*H*OH of the corresponding alcohol.

Conclusion

We have synthesised racemic β-hydroxycyclohexanones with up to three chiral centres in a stereocontrolled way using the novel AOC rearrangement of acyclic enol ethers. We have isolated the first examples of compounds containing an aldehyde and an enol ether in a 1,5 relationship. We have studied stereocontrol in the novel 6-(*enolendo*)-*exo-trig* intramolecular aldol reaction between enol ethers and aldehydes and shown that the reaction favours the formation of an axial hydroxy group. We have shown that the 5,6-relative stereochemistry of β-hydroxycyclohexanones is controlled by the AOC rearrangement and ⩾87% of AOC rearrangement occurs *via* a chair-like transition state. Finally, we have observed an oxidative fragmentation of an enolate prepared by AOC rearrangement.

Experimental

All reactions were carried out under an atmosphere of nitrogen, using oven-dried glassware. All solutions were added *via* syringe unless otherwise stated. THF, ether and DME were freshly distilled from sodium–benzophenone. Dichloromethane, hexane and all amines were distilled from CaH_2 prior to use. DMF was distilled from BaO or from calcium hydride and was stored over 4 Å MS. Petroleum ether refers to the fraction boiling at 40–60 °C. Cinnamaldehyde was distilled. 18-Crown-6 was dried by azeotrope with toluene. Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Purification by column chromatography was carried out using Fisher Matrex™ silica gel, mesh size 35–70 μm, Fluka basic alumina Brockmann grade III or Aldrich neutral alumina Brockmann grade III mesh size ~150 as the stationary phase. Melting points are uncorrected. IR spectra were recorded using a Nicolet Impact 410 FTIR spectrometer. NMR spectra were recorded using Bruker AM-200SY, AM-360 and DPX-400 spectrometers. Chemical shifts are given in ppm relative to tetramethylsilane using residual $CHCl_3$ as an internal standard (7.26 ppm). *J* Values are given in Hz. The multiplicities of ^{13}C nuclei were determined using the DEPT pulse sequence. Mass spectra were recorded on a JEOL JMS700 spectrometer. Combustion analysis was carried out using a Carlo-Erba 1106 elemental analyser.

Ethyl (*E*)-3-hydroxy-5-phenylpent-4-enoate 8a[39]

Ethyl acetate (11.1 cm^3, 113.6 mmol) in dry THF (230 cm^3) was added to a stirred solution of LDA [made from butyllithium (1.0 mol dm^{-3} solution in THF, 113.5 cm^3, 113.5 mmol) and diisopropylamine (14.9 cm^3, 113.5 mmol)]. After 40 min (*E*)-cinnamaldehyde (14.3 cm^3, 113.4 mmol) was added. Stirring continued for 20 min, then the mixture was poured into aqueous hydrochloric acid (200 cm^3, 1 mol dm^{-3}). The layers were separated and the aqueous phase extracted with ether (2 × 200 cm^3). The combined organic extracts were washed with aqueous hydrochloric acid (100 cm^3) and saturated aqueous sodium bicarbonate solution (100 cm^3). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give the aldol **8a** as a yellow oil (23.43 g, 106.4 mmol, 94%), sufficiently pure for the silyl protection reaction; δ_H(200 MHz, $CDCl_3$) 7.40–7.19 (5H, m, Ph), 6.65 (1H, dd, *J* 16.0 and 1.2, PhC*H*=), 6.21 (1H, dd, *J* 16.0 and 6.0, PhCH=C*H*), 4.89–4.64 (1H, br m, C*H*OH), 4.18 (2H, q, *J* 6.0, OCH_2CH$_3$), 2.62–2.59 [2H, m, CH(OH)CH_2] and 1.26 (3H, d, *J* 6.0, OCH$_2$CH_3).

Isopropyl (*E*)-3-hydroxy-5-phenylpent-4-enoate 8b[40]

In the same way, isopropyl acetate (11.5 cm^3, 98.2 mmol), LDA [*ex* butyllithium (1.6 mol dm^{-3} solution in THF, 61.2 cm^3, 97.9 mmol) and diisopropylamine (9.9 g, 12.8 cm^3, 97.9 mmol)], and (*E*)-cinnamaldehyde (12.3 cm^3, 97.5 mmol) gave aldol **8b** (23.63 g, 103%) as a pale yellow oil, sufficiently pure for the silyl protection reaction; R_f (alumina, 1 : 1 ether–hexane) 0.21; ν_{max}(thin film)/cm^{-1} 3449 br s (OH), 2981 m, 2935 w, 1726 s (C=O), 1495 m, 1374 w, 1107 m, 966 m, 818 m and 751 s; δ_H(400 MHz, $CDCl_3$) 7.37–7.21 (5H, m, Ph), 6.64 (1H, d, *J* 16.0, PhC*H*=), 6.21 (1H, dd, *J* 16.0 and 6.0, PhCH=C*H*), 5.06 (1H, sep, *J* 6.4, OC*H*Me$_2$), 4.74–4.68 (1H, br m, C*H*OH), 3.26 (1H, d, *J* 4.2, OH), 2.63 [1H, dd, *J* 16.0 and 4.8, CH(OH)C*H*^{A}H^B], 2.58 [1H, dd, *J* 16.0 and 7.4, CH(OH)CH^A*H*^{B}] and 1.24 (6H, d, *J* 6.4, OCH*Me*$_2$); δ_C(100 MHz, $CDCl_3$) 171.7 (C), 136.5 (C), 130.6 (CH), 130.1 (CH), 128.6 (CH), 127.8 (CH), 126.5 (CH), 68.9 (CH), 67.9 (CH), 41.9 (CH_2) and 21.8 (CH_3); *m*/*z* (EI) 234.1 ($M^{+\bullet}$, 25%), 174.1 (40), 133.1 (100) (Found: M^+, 234.1256, $C_{14}H_{18}O_3$ requires *M*, 234.1256).

Isopropyl (*E*)-3-hydroxyoct-4-enoate 8c

In the same way, isopropyl acetate (7.2 cm^3, 61 mmol), LDA [*ex* 38.2 cm^3 of a 1.6 mol dm^{-3} solution of butyllithium in hexane and 8.0 cm^3, 61.1 mmol of diisopropylamine] and (*E*)-hexenal (7.1 cm^3, 61 mmol) gave the *aldol* **8c** as a pale yellow oil (12.68 g, 103%) sufficiently pure for the silyl protection reaction. A pure sample was obtained by column chromatography on silica using 1 : 1 ether–hexane as eluent to give a colourless oil (89%), R_f (silica, 1 : 1 ether–hexane) 0.42; ν_{max} (thin film) 3448 s br (OH), 2961 s, 2932 s, 1732 s (C=O), 1468 m, 1108 m and 966 m; δ_H(400 MHz, $CDCl_3$) 5.68 (1H, dt, *J* 15.2 and 6.8, CH$_2$C*H*=), 5.45 (1H, dd, *J* 15.2 and 6.8, CH$_2$CH=C*H*), 5.02 (1H, sep, *J* 6.4, C*H*Me$_2$), 4.45 (1H, m, C*H*OH), 2.51–2.45 [2H, m, CH(OH)CH_2], 1.97 (2H, dt, *J* 7.4 and 6.8, CH_2CH=), 1.36 (2H, sex, *J* 7.2, CH$_3$CH_2), 1.22 (6H, d, *J* 6.4, CH*Me*$_2$) and 0.86 (3H, t, *J* 7.2, CH_3CH$_2$); δ_C(100 MHz, $CDCl_3$) 172.3 (C), 132.8 (CH), 131.1 (CH), 69.4 (CH), 68.5 (CH), 42.3 (CH_2), 34.6 (CH_2), 22.6 (CH_2), 22.2 (CH_3) and 14.0 (CH_3); *m*/*z* (CI) 218.2 [$(M + NH_4)^+$, 45%], 200.0 ($-H_2O$, 52), 183.1 (100) [Found (EI): M^+, 200.1413. $C_{11}H_{20}O_3$ requires *M*, 200.1412].

Phenyl (*E*)-3-hydroxy-5-phenylpent-4-enoate 8d

$BF_3{\cdot}OEt_2$ (11.2 cm^3, 0.09 mol) was added to a stirred solution of (*E*)-cinnamaldehyde (11.5 cm^3, 0.09 mol) in dry CH_2Cl_2 (200 cm^3) over 0.5 h at −78 °C under nitrogen. After stirring for 30 min at −78 °C, 1-phenoxy-1-trimethylsiloxyethylene[22] (19 g, 0.09 mol, approx. 70% pure) was added, over 30 min and stirring was continued at −78 °C for 30 min. The temperature was allowed to rise to −30 °C over 30 min and stirring was continued for a further 3 h. The mixture was then poured into pH 7 phosphate buffer (200 cm^3) and warmed to room temperature. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 cm^3), the organic washings were combined, dried ($MgSO_4$) and concentrated to give *ester* **8d** as needles (8.25 g, 43%‡). R_f (DCM) 0.13; mp 99–101 °C; ν_{max} (KBr) 3447 (OH), 1737 (C=O), 1489 (C=C), 1195, 1145, 743 and 690 cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.35–6.99 (10H, m, 2 × *Ph*), 6.65 (1H, d, *J* 15.9, =C*H*Ph), 6.23 (1H, dd, *J* 15.9 and 6.2, =C*H*CHOH), 4.77 (1H, m, C*H*OH), 2.84 (2H, d, *J* 6.7, CH_2) and 2.76 (1H, br s, O*H*); δ_C(100 MHz) 170.6 (C), 150.3 (C), 136.2 (C), 131.1 (CH), 129.6 (CH), 129.5 (2 × CH), 128.6 (2 × CH), 127.9 (CH), 126.5 (2 × CH), 126.0 (CH), 121.4 (2 × CH), 68.9 (CH) and 41.7 (CH_2); *m*/*z* 268 (5, $M^{+\bullet}$), 175 (49, $M^{+\bullet}$ − PhO$^\bullet$), 157 (16.4, $M^{+\bullet}$ − PhO$^\bullet$ and H_2O), 133 (96), 115 (29) and 94 (100, PhOH) (Found: C 75.91, H 5.91%. $C_{17}H_{16}O_3$ requires C 76.12, H 5.97%).

Phenyl 3-hydroxy-4-methyleneoctanoate 8e

Aldol **8e** (17.73 g, 82%) was prepared from 2-butylacrolein

‡ Based on the aldehyde.

(11.5 g, 87 mmol) using the method described for **8d** as an oil. R_f (DCM) 0.10; ν_{max}(thin film) 3458 (OH), 2956, 2931, 1760 (C=O), 1650 (C=C), 1594 (aromatic ring) and 1493 (aromatic ring) cm^{-1}; δ_H(200 MHz; $CDCl_3$) 7.42–7.04 (5H, m, *Ph*), 5.17 (1H, s, =CH*H*), 4.96 (1H, s, =C*H*H), 4.62 (1H, dd, *J* 7.6 and 5, C*H*OH), 2.93–2.74 (2H, m, CH_2C(O)), 2.30–1.97 (2H, m, =CCH_2), 1.93 (1H, d, *J* 1.6, O*H*), 1.67–1.15 (4H, m, MeCH_2-CH_2) and 0.93 (3H, t, *J* 7.0, *Me*); *m/z* (CI) 249 (100, M + H^+), 231 (45, M + H^+ − H_2O) and 94 (61, PhOH) [Found: (M + H)$^+$, 249.1489. $C_{15}H_{21}O_3$ requires *M* + *H*, 249.1488].

Isopropyl (*E*)-3-(*tert*-butyldimethylsilyloxy)-5-phenylpent-4-enoate 9b

Ester **8b** (8.90 g, 38.0 mmol) was dissolved in dry DMF (80 cm^3) and diisopropylethylamine (20.0 cm^3, 114.9 mmol), then TBDMSCl (11.55 g, 76.6 mmol) were added. After 17 h the mixture was poured into saturated aqueous sodium bicarbonate solution (100 cm^3) and extracted with ether (2 × 100 cm^3). The combined ethereal extracts were washed with aqueous hydrochloric acid solution (2 × 100 cm^3, 1.1 mol dm^{-3}) then brine (100 cm^3) and dried over magnesium sulfate. The solvent was removed under reduced pressure to give, after chromatography on silica gel using 10 : 1 hexane–ether as eluent, the *silyl ether* **9b** as a pale yellow oil (12.95 g, 37.2 mmol, 98%); R_f (alumina, 1 : 1 ether–hexane) 0.76; ν_{max}(thin film)/cm^{-1} 2930 s, 2886 s, 1736 s (C=O), 1495 m, 1472 m, 1374 m, 1257 w, 965 m, 840 m, 777 m, 746 m and 693 m; δ_H(400 MHz, $CDCl_3$) 7.38–7.24 (5H, m, Ph), 6.58 (1H, d, *J* 16.0, PhCH=), 6.21 (1H, dd, *J* 16.0 and 6.8, PhCH=C*H*), 5.02 (1H, sep, *J* 6.4, C*H*Me_2), 4.78 (1H, dd, *J* 12.8 and 6.8, CHOSi), 2.61 [1H, dd, *J* 14.4 and 7.6, CH(OSi)CH^AH^B], 2.50 [1H, dd, *J* 14.4 and 5.2, CH(OSi)-CH^AH^B], 1.26 (3H, d, *J* 6.4, CHMe^AMe^B), 1.23 (3H, d, *J* 6.4, CHMe^AMe^B), 0.75 (9H, s, $SiCMe_3$), −0.08 (3H, s, SiMe^AMe^B) and −0.10 (3H, s, SiMe^AMe^B); δ_C(100 MHz, $CDCl_3$) 170.5 (C), 136.6 (C), 131.7 (CH), 129.8 (CH), 128.5 (CH), 127.6 (CH), 126.4 (CH), 70.7 (CH), 67.8 (CH), 44.2 (CH_2), 25.8 (CH_3), 21.87 (CH_3), 21.82 (CH_3), 18.1 (C), −4.2 (CH_3) and −5.0 (CH_3); *m/z* (CI, NH_3) 366 [(M + NH_3)$^+$], 234 (100) [Found: (M + NH_3)$^+$ 366.2459, $C_{20}H_{36}O_3Si$ requires $M + NH_3$ 366.2464].

Isopropyl (*E*)-3-triethylsilyloxyoct-4-enoate 9c

In the same way, *ester* **8c** (11.0 g, 54.9 mmol), diisopropylethylamine (28.7 cm^3, 165.0 mmol) and triethylsilyl chloride (TESCl) (18.4 cm^3, 110.0 mmol) in dry DMF (110 cm^3) gave *silyl ether* **9c** as a pale yellow oil (23.27 g) which was used in the Takai reaction without further purification. A pure sample was obtained by column chromatography on silica gel using 10 : 1 hexane–ether as eluent to give a colourless oil (88%); ν_{max}(thin film)/cm^{-1} 2956 s, 2877 s, 1735 s (C=O), 1466 w, 1374 m, 968 m and 744 m; δ_H(400 MHz, $CDCl_3$) 5.57 (1H, dt, *J* 15.3 and 6.8, CH_2C*H*=), 5.39 (1H, ddt, *J* 15.3 ,7.2 and 1.2, CH_2CH=C*H*), 4.94 (1H, sep, *J* 6.4, C*H*Me_2), 4.49 (1H, br dt, *J* 7.2 and 6.4, C*H*OSi), 2.46 [1H, dd, *J* 14.4 and 7.6, CH(OSi)CH^AH^B], 2.33 [1H, dd, *J* 14.4 and 6.0, CH(OSi)CH^AH^B], 1.93 (2H, br q, *J* 7.2, CH_2CH=), 1.34 (2H, sex, *J* 7.2, CH_3CH_2), 1.18 (3H, d, *J* 6.4, CHMe^AMe^B), 1.17 (3H, d, *J* 6.4, CHMe^AMe^B), 0.89 (9H, t, *J* 8.0, $SiCH_2CH_3$), 0.84 (3H, t, *J* 7.2, CH_3CH_2) and 0.54 (6H, q, *J* 8.0, $SiCH_2CH_3$); δ_C(100 MHz, $CDCl_3$) 171.0 (C), 132.6 (CH), 131.7 (CH), 71.1 (CH), 67.9 (CH), 44.7 (CH_2), 34.5 (CH_2), 22.6 (CH_2), 22.2 (CH_3), 22.1 (CH_3), 14.0 (CH_3), 7.1 (CH_3) and 5.2 (CH_2); *m/z* (CI) 315.3 [(M + H)$^{+\cdot}$ 7%], 285.2 (20), 183.2 (100) [Found: (M + H)$^+$, 315.2352, $C_{17}H_{34}O_3Si$ requires *M* + *H*, 315.2355].

(5*E*)-2-Isopropoxy-4-triethylsilyloxynona-1,5-diene 10c

Titanium tetrachloride (13.9 cm^3, 127.2 mmol) was added slowly to THF (100 cm^3) under nitrogen at 0 °C. To the resulting bright yellow suspension was added TMEDA (38.4 cm^3, 254.4 mmol) to give an orange–brown suspension. The mixture was stirred at 0 °C for 20 min, then zinc powder (18.7 g, 286.2 mmol, preactivated by sequential washing with 5% aqueous hydrochloric acid, water, acetone and ether) mixed with a small amount of lead(II) chloride (~20 mg) was added. An exotherm occurred and the mixture turned a grey–blue colour. The ice bath was removed and the suspension stirred for 40 min, over which time a dark green colour developed. The mixture was then re-cooled in an ice bath and a solution of the *ester* **9c** (9.98 g, 31.8 mmol) and dibromomethane (4.9 cm^3, 70.0 mmol) in THF (5 cm^3) was added dropwise. After addition was complete the ice bath was removed and the reaction mixture stirred for 17 h (the suspension turned dark brown–black after ~20 min at rt). The reaction mixture was then re-cooled with an ice bath, and saturated potassium carbonate (40 cm^3) solution was added *via* syringe. The resulting thick black slurry was stirred for a further 15 min, then poured into ether (200 cm^3). The reaction vessel was washed repeatedly with ether and the combined washings were then passed through a short column of basic alumina to filter off the solid formed during the quench. After washing the filtrate with additional ether, the combined washings were dried and concentrated under reduced pressure. The residue was treated with hexane, and the insoluble white precipitate formed on concentration was filtered off by passing the hexane solution through a short column of basic alumina. The precipitate was washed with additional hexane and the combined washings concentrated under reduced pressure to give a pale yellow oil (8.46 g, 85%) containing the *enol ether* **10c** and a small amount of TMEDA. This was used without further purification in the deprotection reaction. A pure sample was obtained as a colourless oil by chromatography on basic alumina using hexane as eluent, R_f (alumina, hexane) 0.63; ν_{max}(thin film)/cm^{-1} 2956 s, 2876 s, 1655 m, 1459 m, 1370 m, 1005 m and 741 m; δ_H(400 MHz, $CDCl_3$) 5.53 (1H, dt, *J* 15.2 and 6.4, CH_2C*H*=), 5.40 (1H, ddt, *J* 15.2, 6.8 and 1.2, CH_2CH=C*H*), 4.28 (1H, q, *J* 6.8, C*H*OSi), 4.17 (1H, sep, *J* 6.0, C*H*Me_2), 3.88 (1H, d, *J* 1.6, =CH^AH^B), 3.81 (1H, d, *J* 1.6, =CH^AH^B), 2.29 [1H, dd, *J* 13.6 and 6.8, CH(OSi)CH^AH^B], 2.12 [1H, dd, *J* 13.6 and 6.4, CH(OSi)CH^AH^B], 2.03–1.89 (2H, m, CH_2CH=), 1.37 (2H, sex, *J* 7.2, CH_3CH_2), 1.22 (3H, d, *J* 6.0, CHMe^AMe^B), 1.19 (3H, d, *J* 6.0, CHMe^AMe^B), 0.94 (9H, t, *J* 8.0, $SiCH_2CH_3$), 0.88 (3H, t, *J* 7.2, CH_3CH_2) and 0.58 (6H, q, *J* 8.0, $SiCH_2CH_3$); δ_C(100 MHz, $CDCl_3$) 158.5 (C), 133.4 (CH), 130.6 (CH), 83.6 (CH_2), 71.8 (CH), 68.5 (CH), 45.7 (CH_2), 34.6 (CH_2), 22.8 (CH_2), 22.2 (CH_3), 21.7 (CH_3), 14.1 (CH_3), 7.2 (CH_3) and 5.3 (CH_2); *m/z* (EI) 312.2 ($M^{+\bullet}$, 11%), 213 (100) (Found: M^+, 312.2487. $C_{18}H_{39}O_2Si$ requires *M*, 312.2485).

(1*E*,5*Z*)-3-(*tert*-Butyldimethylsilyloxy)-5-isopropoxy-1-phenylhepta-1,5-diene 11b

In the same way as above for **10c**, a solution of the *ester* **9b** (4.00 g, 11.5 mmol) and 1,1-dibromoethane (2.3 cm^3, 25 mmol) in THF (3 cm^3) was added to the suspension formed from titanium tetrachloride (5.0 cm^3, 8.7 mmol), TMEDA (13.9 cm^3, 91.8 mmol), activated zinc powder (6.75 g, 103 mmol) and lead(II) chloride (~10 mg) in THF (15 cm^3). The reaction was stirred for 4 h, then worked-up as above to give a pale yellow oil (3.37 g). Chromatography on basic alumina using hexane as eluent gave a 15 : 85 *E*–*Z* mixture of *enol ethers* **11b** as an oil (2.45 g, 59%). The NMR data given are for the major *Z isomer*; R_f (alumina, hexane) 0.71; ν_{max}(thin film)/cm^{-1} 2956 m, 2929 m, 2857 m, 1679 w, 1494 m, 1369 m, 1254 m, 1196 m, 1115 m and 838 m; δ_H(360 MHz, $CDCl_3$) 7.38–7.22 (5H, m, Ph), 6.53 (1H, d, *J* 15.9, PhCH=), 6.26 (1H, dd, *J* 15.9 and 5.8, PhCH=C*H*), 4.73 (1H, q, *J* 6.7, =C*H*Me), 4.42 (1H, br q, *J* 6.6, CHOSi), 4.10 (1H, sep, *J* 6.1, C*H*Me_2), 2.36 [1H, br dd, *J* 14.2 and 6.7, CH(OSi)CH^AH^B], 2.28 [1H, dd, *J* 14.6 and 6.6, CH(OSi)-CH^AH^B], 1.57 (3H, d, *J* 6.7, =CH*Me*), 1.21 (3H, d, *J* 6.1, CHMe^AMe^B), 1.20 (3H, d, *J* 6.1, CHMe^AMe^B), 0.92 (9H, s,

$SiCMe_3$), 0.08 (3H, s, SiMe^AMe^B) and 0.07 (3H, s, SiMe^AMe^B); δ_C(90 MHz, $CDCl_3$) 149.3 (C), 137.2 (C), 132.9 (CH), 128.43 (CH), 127.1 (CH), 126.31 (CH), 126.26 (CH), 109.5 (CH), 71.1 (CH), 68.8 (CH), 41.8 (CH_2), 25.8 (CH_3), 22.5 (CH_3), 22.3 (CH_3), 18.2 (C), 10.6 (CH_3), −4.6 (CH_3) and −5.0 (CH_3); *m*/*z* (EI+) 360.2 ($M^{+\bullet}$, 2%), 247.2 (100) (Found: M^+, 360.2487. $C_{22}H_{36}O_2Si$ requires *M*, 360.2485).

(1*E*)-5-Isopropoxy-1-phenylhexa-1,5-dien-3-ol 12b

In the same way as for **10c**, a solution of the *ester* **9b** (13.0 g, 37.3 mmol) and dibromomethane (5.8 cm^3, 82.1 mmol) in THF (5 cm^3) was added to the mixture formed from titanium tetrachloride (16.4 cm^3, 149.2 mmol), TMEDA (45.0 cm^3, 298.4 mmol), zinc powder (21.9 g, 335.7 mmol) and lead(II) chloride (~20 mg) in THF (150 cm^3). Stirring was continued for 17 h, whereupon the reaction mixture was worked up as described to give the crude *enol ether* **10b** as a pale yellow oil (9.35 g, 27.0 mmol). Tetrabutylammonium fluoride (67.5 cm^3 of a 1.0 mol dm^{-3} solution in THF) and 4 Å molecular sieves (12.2 g) were added. After stirring for 2.5 h, the reaction mixture was poured through filter paper into saturated sodium bicarbonate solution (50 cm^3). The layers were separated and the aqueous phase extracted with ether (2 × 50 cm^3). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a dark brown oil. The *alcohol* **12b** was obtained as a pale yellow oil (3.52 g, 41% over two steps) after column chromatography on alumina, using 1 : 1 ether–hexane as eluent; R_f (alumina, 1 : 1 ether–hexane) 0.46; ν_{max}(thin film)/cm^{-1} 3415 br s (OH), 2976 s, 2922 sm, 1653 s (enol ether C=C), 1619 m, 1495 m, 1291 m, 1001 m, 965 m, 801 m, 749 s and 693 m; δ_H(400 MHz, $CDCl_3$) 7.39 (2H, d, *J* 7.2, *o*-Ph), 7.32 (2H, t, *J* 7.2, *m*-Ph), 7.24 (1H, t, *J* 7.2, *p*-Ph), 6.65 (1H, d, *J* 16.0, PhCH=), 6.26 (1H, dd, *J* 16.0 and 6.4, PhCH=C*H*), 4.54–4.51 (1H, m, C*H*OH), 4.29 (1H, sep, *J* 6.0, C*H*Me$_2$), 4.05 (1H, d, *J* 2.0, =CH^AH^B), 3.99 (1H, d, *J* 2.0, =CH^AH^B), 2.87 (1H, d, *J* 3.6, OH), 2.45 [1H, dd, *J* 14.0 and 4.4, CH(OH)CH^AH^B], 2.36 [1H, dd, *J* 14.0 and 8.0, CH(OH)-CH^AH^B], 1.28 (3H, d, *J* 6.0, CHMe^AMe^B) and 1.27 (3H, d, *J* 6.0, CHMe^AMe^B); δ_C(100 MHz, $CDCl_3$) 157.7 (C), 136.8 (C), 131.3 (CH), 129.6 (CH), 128.6 (CH), 127.3 (CH), 126.3 (CH), 84.1 (CH_2), 70.6 (CH), 68.7 (CH), 43.5 (CH_2), 21.44 (CH_3) and 21.37 (CH_3); *m*/*z* (CI) 233.2 [(M + H)$^+$, 15%)], 215.2 (40), 173.1 (100) [Found: (M + H)$^+$, 233.1541. $C_{15}H_{21}O_2$ requires *M* + *H*, 233.1542].

(5*E*)-2-Isopropoxynona-1,5-dien-4-ol 12c

Tetrabutylammonium fluoride (52 cm^3 of a 1.0 mol dm^{-3} solution in THF) and 4 Å MS (10 g) were added to the crude *enol ether* **10c** (8.02 g, 25.6 mmol). The orange solution was stirred for 2.5 h, then poured through filter paper into saturated sodium bicarbonate solution (50 cm^3), washing the sieves with ether. The layers were separated and the aqueous phase extracted with ether (2 × 50 cm^3). The combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure to give a dark brown oil. The *alcohol* **12c** was obtained as a pale yellow oil (1.91 g, 38%) after column chromatography on alumina, using 1 : 1 ether–hexane as eluent, R_f (alumina, 1 : 1 ether–hexane) 0.61; ν_{max}(thin film)/cm^{-1} 3399 br s (OH), 2960 s, 2929 s, 1654 m, 1294 m, 1121 m and 799 m; δ_H(400 MHz, $CDCl_3$) 5.67 (1H, dtd, *J* 15.2, 6.8 and 0.8, CH_2C*H*=), 5.44 (1H, ddt, *J* 15.2, 6.8 and 1.2, CH_2CH=C*H*), 4.25 (1H, sep, *J* 6.0, C*H*Me$_2$), 4.25–4.20 (1H, m, C*H*OH), 3.96 (1H, d, *J* 1.6, =CH^AH^B), 3.92 (1H, d, *J* 1.6, =CH^AH^B), 2.49 (1H, d, *J* 3.2, OH), 2.29 [1H, dd, *J* 14.0 and 3.8, CH(OH)CH^AH^B], 2.20 [1H, dd, *J* 14.0 and 8.4, CH(OH)CH^AH^B], 1.99 (2H, br q, *J* 7.2, CH_2CH=), 1.38 (2H, sex, *J* 7.2, CH_3CH_2), 1.23 (3H, d, *J* 6.0, CHMe^AMe^B), 1.22 (3H, d, *J* 6.0, CHMe^AMe^B) and 0.88 (3H, t, *J* 7.2, CH_3CH$_2$); δ_C(100 MHz, $CDCl_3$) 158.6 (C), 132.2 (CH), 131.9 (CH), 84.3 (CH_2), 71.3 (CH), 69.2 (CH), 44.2 (CH_2), 37.4 (CH_2), 22.7 (CH_2), 22.0 (CH_3), 21.9 (CH_3) and 14.1 (CH_3); *m*/*z* (CI) 199.2 [(M + H)$^+$, 95%], 101.1 (100) [Found (EI): M^+, 198.1617. $C_{12}H_{22}O_2$ requires *M*, 198.1620].

(1*E*)-5-Phenoxy-1-phenylhexa-1,5-dien-3-ol 12d

Diisopropylethylamine (8.04 cm^3, 46 mmol) then chlorotrimethylsilane (5.84 cm^3, 46 mmol) were added to a solution of *ester* **8d** (8.25 g, 30.7 mmol) in dry CH_2Cl_2 (150 cm^3) with stirring at 0 °C under nitrogen. Stirring was continued for 13 h at room temperature. Hexane was added to the mixture which was then filtered and concentrated to give the *silyl ether* **9d**. Takai methylenation followed by deprotection in the same way as described for enol ether **12a** gave *alcohol* **12d** (1.80 g, 25%) as a pale yellow oil. R_f (DCM) 0.63; ν_{max}(thin film)/cm^{-1} 3384 (OH), 1640 (C=C), 1592 (aromatic ring), 1491 (aromatic ring) and 1218; δ_H(200 MHz; $CDCl_3$) 7.43–7.02 (10H, m, 2 × *Ph*), 6.70 (1H, d, *J* 15.8, =C*H*Ph), 6.31 (1H, dd, *J* 15.8 and 6.1, =C*H*CHOH), 4.78–4.63 (1H, m, C*H*OH), 4.25 (1H, d, *J* 1.8, =C*H*H), 4.02 (1H, d, *J* 1.8, =CH*H*), 2.66 (1H, dd, *J* 12.9 and 4.6, CH^AH^B), 2.58 (1H, dd, *J* 12.9 and 7.9, CH^AH^B) and 2.31 (1H, br s, O*H*); δ_C(50 MHz) 159.8 (C), 154.8 (C), 136.6 (C), 131.1 (CH), 130.5 (CH), 129.6 (2 × CH), 128.5 (2 × CH), 127.6 (CH), 126.5 (2 × CH), 124.4 (CH), 121.1 (2 × CH), 91.0 (CH_2), 70.4 (CH) and 42.4 (CH_2); *m*/*z* (EI) 266 (3, $M^{+\bullet}$), 248 (6, $M^{+\bullet} - H_2O$), 173 (10), 155 (8) and 133 (100) (Found: M^+, 266.1306. $C_{18}H_{18}O_2$ requires *M*, 266.1305).

5-Methylene-2-phenoxynon-1-en-4-ol 12e

Enol ether **12e** was prepared using the method described for preparation of **12d**: *alcohol* **8e** (17.0 g, 68.5 mmol) gave *silyl ether* **9e** (18.5 g) as a red oil. A portion of the *ester* **9e** (13.1 g, 41.2 mmol) then gave *enol ether* **12e** (2.20 g, 18% over 3 steps) as a pale yellow oil. R_f (DCM) 0.71; ν_{max}(thin film)/cm^{-1} 3450 (OH), 2954, 2929, 1645 (C=C), 1593 (aromatic ring) and 1493 (aromatic ring); δ_H(360 MHz; $CDCl_3$) 7.35–7.03 (5H, m, *Ph*), 5.15 (1H, s, (HO)HCC=CH*H*), 4.91 (1H, s, (HO)HCC=C*H*H), 4.45 (1H, dd, *J* 8.6 and 3.6, C*H*OH), 4.21 (1H, d, *J* 1.4, PhOC=C*H*H), 3.98 (1H, d, *J* 1.4, PhOC=CH*H*), 2.61 (1H, dd, *J* 14.3 and 3.6, CH^AH^{B}CHOH), 2.44 (1H, dd, *J* 14.3 and 8.6, CH^AH^B), 2.37 (1H, br s, OH), 2.18–1.98 (2H, m, =CCH_2), 1.52–1.26 (4H, m, MeCH_2CH_2) and 0.91 (3H, t, *J* 7.2, *Me*); δ_C(100 MHz) 160.5 (C), 154.8 (C), 150.9 (C), 129.6 (2 × CH), 124.4 (CH), 121.1 (2 × CH), 109.4 (CH_2), 90.5 (CH_2), 72.5 (CH), 41.1 (CH_2), 31.4 (CH_2), 30.1 (CH_2), 22.6 (CH_2) and 14.0 (CH_3); *m*/*z* (CI) 247 (43, M + H$^+$), 229 (100, M + H$^+$ − H_2O), 169 (29), 153 (34) and 135 (65) [Found: (M + H)$^+$, 247.1700. $C_{16}H_{23}O_2$ requires 247.1702].

(1*E*,5*ZE*)-5-Ethoxy-1-phenylhepta-1,5-dien-3-ol 13a

Aldol **8a** (23.43 g, 106.4 mmol) was dissolved in THF (100 cm^3), chlorotrimethylsilane (16.0 cm^3, 125.4 mmol) and diisopropylethylamine (19.8 cm^3, 125.4 mmol) were added and the reaction was stirred at rt for 17 h. The bulk of the amine hydrochloride salt formed during the reaction was filtered off and the precipitate washed with hexane. The combined washings were concentrated under reduced pressure, and the process repeated to remove the remaining salt. The *silyl ether* **9a** was obtained as a yellow oil (22.54 g, 77.0 mmol, 72%). In the same way as for *enol ether* **11b**, a solution of the crude *ester* **9a** (7.54 g, 25.8 mmol) and 1,1-dibromoethane (5.7 cm^3, 63 mmol) in THF (5 cm^3) was added to the suspension formed from titanium tetrachloride (12.5 cm^3, 114 mmol), TMEDA (34.4 cm^3, 228 mmol), activated zinc powder (16.8 g, 257 mmol) and lead(II) chloride (~10 mg) in THF (50 cm^3). The reaction was stirred for 4 h, then worked-up as above to give the *enol ether* **11a** as a yellow oil (5.25 g, 17.2 mmol, 67%). The oil was dissolved in a solution of TBAF in THF (18.0 cm^3, 1.0 mol dm^{-3}) and the mixture stirred for 1 h. Work-up as above gave a yellow oil

which was chromatographed on basic alumina using 1 : 1 hexane–ether as eluent to give the *alcohols* **13a** as a pale yellow oil (2.06 g, 8.87 mmol, 25% over 3 steps). Repeated chromatography was required to obtain a sample of each isomer free from the other.

(1*E*,5*Z*)-5-Ethoxy-1-phenylhepta-1,5-dien-3-ol, *Z*-13a. R_f (alumina, 1 : 1 hexane–ether) 0.57; ν_{max}(thin film)/cm^{-1} 3409 br m (OH), 2977 m, 2915 m, 2863 m, 1670 m (enol ether C=C), 1494 m, 1448 m, 1193 m, 966 m, 743 m and 694 m; δ_H(400 MHz, $CDCl_3$) 7.38 (2H, d, *J* 7.2, *o*-Ph), 7.31 (2H, t, *J* 7.2, *m*-Ph), 7.23 (1H, t, *J* 7.2, *p*-Ph), 6.65 (1H, d, *J* 16.0, PhCH=), 6.26 (1H, dd, *J* 16.0 and 4.4, PhCH=C*H*), 4.81 (1H, q, *J* 6.4, =C*H*Me), 4.48–4.43 (1H, m, C*H*OH), 3.87–3.75 (2H, m, OCH_2CH_3), 2.56 (1H, d, *J* 2.8, OH), 2.46 [1H, dd, *J* 14.4 and 4.0, CH(OH)CH^AH^B], 2.30 [1H, dd, *J* 14.4 and 8.4, CH(OH)CH^AH^B], 1.64 (3H, d, *J* 6.8, =CH*Me*) and 1.29 (3H, t, *J* 7.0, OCH_2CH_3); δ_C(100 MHz, $CDCl_3$) 151.4 (C), 136.8 (C), 131.4 (CH), 129.8 (CH), 128.5 (CH), 127.5 (CH), 126.4 (CH), 109.5 (CH), 70.5 (CH), 68.5 (CH_2), 40.5 (CH_2), 15.4 (CH_3) and 10.5 (CH_3); *m*/*z* (EI) 232.2 ($M^{+\bullet}$, 5%), 133.1 (100) (Found: M^+, 232.1463. $C_{15}H_{20}O_2$ requires *M*, 232.1463).

(1*E*,5*E*)-5-Ethoxy-1-phenylhepta-1,5-dien-3-ol, *E*-13a. R_f (alumina, 1 : 1 hexane–ether) 0.60; ν_{max}(thin film)/cm^{-1} 3458 br s (OH), 2861 w, 1668 m (enol ether C=C), 1495 w, 1226 w, 1103 w, 963 w and 748 w; δ_H(360 MHz, $CDCl_3$) 7.37 (2H, d, *J* 7.2, *o*-Ph), 7.31 (2H, t, *J* 7.2, *m*-Ph), 7.23 (1H, t, *J* 7.2, *p*-Ph), 6.63 (1H, d, *J* 15.9, PhCH=), 6.26 (1H, dd, *J* 15.9 and 6.1, PhCH=C*H*), 4.58 (1H, q, *J* 6.8, =C*H*Me), 4.55–4.48 (1H, partly obscured m, C*H*OH), 3.74–3.66 (2H, m, OCH_2CH_3), 2.75 (1H, br d, *J* 3.0, OH), 2.48 [2H, m, CH(OH)C$H^A$$H^B$], 1.62 (3H, d, *J* 6.8, =CH*Me*) and 1.29 (3H, t, *J* 7.0, OCH_2CH_3); δ_C(90 MHz, $CDCl_3$) 153.0 (C), 137.0 (C), 131.7 (CH), 129.6 (CH), 128.5 (CH), 127.4 (CH), 126.4 (CH), 93.7 (CH), 71.2 (CH), 62.0 (CH), 37.5 (CH_2), 14.7 (CH_3) and 11.8 (CH_3); *m*/*z* (EI) 232 ($M^{+\bullet}$, 7%), 133 (100) (Found: M^+, 232.1464. $C_{15}H_{20}O_2$ requires *M* 232.1463).

(1*E*,5*EZ*)-5-Isopropoxy-1-phenylhepta-1,5-dien-3-ol, 13b

In the same way as above for **12c**, *silyl ether* **11b** (2.40 g, 6.66 mmol) was dissolved in a solution of TBAF in THF (18.1 cm^3, 1.1 mol dm^{-3}). 4 Å MS were added and the mixture stirred for 2 h. Work-up as above gave a yellow oil which was chromatographed on basic alumina using 1 : 1 hexane–ether as eluent to give the *alcohols* as a pale yellow oil (1.45 g, 5.9 mmol, 88%). Repeated chromatography was required to obtain a sample of each isomer free from the other.

(1*E*,5*Z*)-5-Isopropoxy-1-phenylhepta-1,5-dien-3-ol, *Z*-13b. R_f (alumina, 2 : 1 petroleum ether–ether) 0.61; ν_{max}(thin film)/cm^{-1} 3425 br m (OH), 2974 m, 1678 m, 1494 m, 1449 m, 1196 m, 1113 m, 965 m, 747 m and 693 m; δ_H(360 MHz, $CDCl_3$) 7.39 (2H, d, *J* 7.2, *o*-Ph), 7.31 (2H, t, *J* 7.2, *m*-Ph), 7.24 (1H, t, *J* 7.2, *p*-Ph), 6.63 (1H, d, *J* 15.9, PhCH=), 6.26 (1H, dd, *J* 15.9 and 6.1, PhCH=C*H*), 4.87 (1H, q, *J* 6.7, =C*H*Me), 4.49–4.41 (1H, m, C*H*OH), 4.17 (1H, sep, *J* 6.1, C*H*Me$_2$), 2.57 (1H, br d, *J* 2.5, OH), 2.45 [1H, dd, *J* 14.4 and 4.1, CH(OH)CH^AH^B], 2.29 [1H, dd, *J* 14.4 and 8.5, CH(OH)CH^AH^B], 1.63 (3H, d, *J* 6.7, =CH*Me*), 1.25 (3H, d, *J* 6.1, CHMe^AMe^B) and 1.22 (3H, d, *J* 6.1, CHMe^AMe^B); δ_C(90 MHz, $CDCl_3$) 149.7 (C), 136.8 (C), 131.4 (CH), 129.7 (CH), 128.4 (CH), 127.4 (CH), 126.4 (CH), 110.6 (CH), 70.5 (CH), 69.8 (CH), 40.6 (CH_2), 22.4 (CH_3), 22.2 (CH_3) and 10.7 (CH_3); *m*/*z* (CI) 247.2 [$(M + H)^+$, 9%], 229.2 (90), 187.2 (100) [Found: $(M + H)^+$, 247.1697. $C_{16}H_{23}O_2$ requires *M* + *H*, 247.1698].

(1*E*,5*E*)-5-Isopropoxy-1-phenylhepta-1,5-dien-3-ol, *E*-13b. R_f (alumina, 2 : 1 petroleum ether–ether) 0.69; δ_H(400 MHz, $CDCl_3$) 7.38 (2H, d, *J* 7.2, *o*-Ph), 7.26 (2H, t, *J* 7.2, *m*-Ph), 7.23 (1H, t, *J* 7.2, *p*-Ph), 6.63 (1H, d, *J* 15.9, PhCH=), 6.24 (1H, dd, *J* 15.9 and 6.1, PhCH=C*H*), 4.58 (1H, q, *J* 6.8, =C*H*Me), 4.53–4.48 (1H, m, C*H*OH), 4.25 (1H, sep, *J* 6.0, C*H*Me$_2$), 2.88 (1H, d, *J* 3.7, OH), 2.48 [1H, dd, *J* 14.3 and 4.6, CH(OH)CH^AH^B], 2.43 [1H, dd, *J* 14.4 and 7.4, CH(OH)CH^AH^B], 1.62 (3H, d, *J* 6.8, =CH*Me*), 1.23 (3H, d, *J* 6.0, CHMe^AMe^B) and 1.22 (3H, d, *J* 6.0, CHMe^AMe^B); δ_C(90 MHz, $CDCl_3$) 151.1 (C), 137.0 (C), 131.7 (CH), 129.6 (CH), 128.4 (CH), 127.4 (CH), 126.4 (CH), 94.8 (CH), 71.3 (CH), 67.7 (CH), 37.5 (CH), 21.9 (CH_3), 21.8 (CH_3) and 11.9 (CH_3).

(3*SR*,5*SR*)-3-Hydroxy-5-phenylcyclohexanone[28] 17

Alcohol **12b** (500 mg, 2.15 mmol) and 18-crown-6 (1.14 g, 4.30 mmol) in DME (4 cm^3) were added with stirring to a suspension of potassium hydride (617 mg of 35% suspension in mineral oil, 5.38 mmol) in DME (6 cm^3). After stirring for 4 h, the mixture was poured into cold aqueous hydrochloric acid (25 cm^3, 1 mol dm^{-3}). The mixture was stirred for 15 min at 0 °C, then allowed to warm to room temperature over 15 min. After an additional 15 min at rt, ether (50 cm^3) was added and the layers separated. The aqueous phase was extracted with ether (10 cm^3) and the combined organic extracts were washed with hydrochloric acid (10 cm^3), water (10 cm^3) and brine (10 cm^3). Solvent removal under reduced pressure yielded a yellow solid (402 mg, 80% w/w). Purification by trituration with ether gave the cyclohexanone[28] **17** as an amorphous solid (215 mg, 43%); δ_H(360 MHz, $CDCl_3$) 7.35–7.19 (5H, m, Ph), 4.60 [1H, qn, *J* 3.0, C*H*(OH)], 3.57 [1H, tt, *J* 12.2 and 4.1, C*H*(Ph)], 2.69–2.51 [4H, m, $CH_2C(O)CH_2$], 2.35–2.19 (1H, br s, OH), 2.21 [1H, m with large doublet splitting, *J* 14.0, CH(Ph)CH_{eq}H$_{ax}$] and 2.06 [1H, distorted ddd, *J* 14.1, 12.2 and 2.4, CH(Ph)CH$_{eq}$$H_{ax}$].

New data: δ_C(100 MHz, $CDCl_3$) 209.7 (C), 143.7 (C), 128.7 (CH), 126.7 (2 × CH), 68.3 (CH), 48.7 (2 × CH_2), 39.2 (CH_2) and 38.2 (CH).

5-Phenylcyclohex-2-enone[29] 19

Crude alcohols **17** and **18** (211 mg, 1.11 mmol) were dissolved in DCM (10 cm^3) and treated with methanesulfonyl chloride (0.1 cm^3, 1.2 mmol) and triethylamine (0.62 cm^3, 4.4 mmol). Work-up as for compound **28** gave the cyclohexenone **19** as a yellow oil[29] (117 mg, 61%). A pure sample was obtained as a solid in 34% yield after further chromatography using DCM as eluent; δ_H(400 MHz, $CDCl_3$) 7.40–7.24 (5H, m, Ph), 7.06 [1H, ddd, *J* 10.0, 6.0 and 2.8, C*H*=CHC(O)], 6.13 [1H, d br d, *J* 10.0 and 2.8, CH=C*H*C(O)], 3.36 (1H, ddt, *J* 12.4, 10.4 and 5.2, C*H*Ph), 2.72–2.61 [3H, m, C(O)CH_2 and =CHCH_{eq}H$_{ax}$] and 2.54 (1H, ddt, *J* 18.8, 10.8 and 2.4, =CHCH$_{eq}$$H_{ax}$).

(3*SR*,5*RS*)-3-Hydroxy-5-(*n*-propyl)cyclohexanone 20

Potassium hydride (173 mg of a 35% suspension in mineral oil, 1.50 mmol) was washed with hexane (3 × 4 cm^3) to remove oil and then suspended in dry THF (1.5 cm^3) under nitrogen. To the suspension was added a solution of *alcohol* **12c** (100 mg, 0.50 mmol) and 18-crown-6 (269 mg, 1.00 mmol) in THF (1 cm^3) with stirring at rt. The resulting dark brown mixture was stirred for 5 days, whereupon it was poured into cold (ice bath) aqueous hydrochloric acid (5 cm^3, 1 mol dm^{-3}) with vigorous stirring. The mixture was stirred at 0 °C for 10 min, then the ice bath was removed and stirring continued for an additional 15 min. Ether (10 cm^3) was then added and the layers separated. The aqueous phase was extracted with ether (2 × 10 cm^3) and the combined organic extracts were dried over magnesium sulfate. Solvent removal under reduced pressure yielded the *alcohols* **20** and **21** (54 mg, 69%) as a brown oil. This was washed quickly through a short column of neutral alumina with ether to give a pure sample of a 90 : 10 *anti*–*syn* mixture of isomers as a yellow oil (40 mg, 51%); data for the major isomer

20: ν_{max}(thin film)/cm^{-1} 3423 brs (OH), 2958 s, 2928 s, 1708 s (C=O), 1413 m, 1292 m, 1236 m, 1095 m, 1062 m, 1037 m and 970 m; δ_H(360 MHz, $CDCl_3$) 4.50–4.44 (1H, m, C*H*OH), 2.54 [1H, dd, *J* 14.2 and 3.7, CH(OH)CH_{ax}H$_{eq}$C(O)], 2.50–2.40 [2H, m, CH(OH)CH$_{ax}$$H_{eq}$C(O)CH$_{ax}$$H_{eq}$], 2.30–2.21 (1H, m, C*H*Pr), 2.03–1.96 [2H, m, CH(Pr)CH_{ax}H$_{eq}$C(O) and CH(OH)-CH$_{ax}$$H_{eq}$CH(Pr)], 1.89 (1H, br s, OH), 1.56 [1H, ddd, *J* 13.9, 11.4 and 2.5, CH(OH)CH$_{eq}$$H_{ax}$CH(Pr)], 1.40–1.25 (4H, m, MeCH_2CH_2) and 0.91–0.88 (3H, m, Me); δ_C(90 MHz, $CDCl_3$) 210.4 (C), 68.4 (CH), 49.1 (CH_2), 47.7 (CH_2), 38.5 (CH_2), 38.0 (CH_2), 32.4 (CH), 19.7 (CH_2) and 14.0 (CH_3); *m*/*z* (EI) 156 (M$^{+\bullet}$, 45%), 113 (52), 96 (90), 69 (100) (Found: M$^+$, 156.1150. $C_9H_{16}O_2$ requires *M*, 156.1150).

(3*SR*,5*SR*,6*RS*)-3-Hydroxy-6-methyl-5-phenylcyclohexanone 22

Potassium hydride (1.16 g of 35% suspension in mineral oil, 10.15 mmol) was washed with hexane (3 × 2 cm^3) to remove oil and then suspended in dry 1,2-dimethoxyethane (DME) (15 cm^3) under nitrogen. To the suspension was added a solution of *alcohol* **13b** (85% *Z*, 1 g, 4.06 mmol) and 18-crown-6 (2.15 g, 8.12 mmol), in DME (5 cm^3) with stirring at rt. The resulting dark brown mixture was stirred for 3 h, whereupon it was poured into cold (ice bath) aqueous hydrochloric acid (50 cm^3, 1 mol dm^{-3}) with vigorous stirring. The mixture was stirred for 15 min at 0 °C, then allowed to warm to room temperature over 15 min. After an additional 15 min at rt, ether (50 cm^3) was added and the layers separated. The aqueous phase was extracted with ether (10 cm^3) and the combined organic extracts were washed with hydrochloric acid (10 cm^3), water (10 cm^3) and brine (10 cm^3). Solvent removal under reduced pressure yielded a brown solid (757 mg, 91% w/w). Purification was achieved by trituration with cold ether to give *cyclohexanone* **22** as a white solid (150 mg, 31%); mp 156–157 °C (Found: C 76.4; H 7.9, $C_{13}H_{16}O_2$ requires C 76.4; H 7.9%); ν_{max}(KBr)/cm^{-1} 3369 br (OH), 1713 vs (C=O), 1492 m, 1452 m, 1230 m, 1015 m, 753 m and 700 s; δ_H(360 MHz, $CDCl_3$) 7.36–7.22 (5H, m, Ph), 4.59 [1H, qn, *J* 2.9, C*H*(OH)], 3.13 [1H, ddd, *J* 11.8, 9.1 and 7.5, C*H*(Ph)], 2.77 [1H, dd, *J* 14.1 and 3.0, C(O)CH$_{eq}$$H_{ax}$], 2.64 [1H, partly obscured dq, *J* 11.9 (by irradiation of Me) and 6.6, C*H*Me], 2.62 [1H, d with poorly resolved smaller couplings, *J* 14.1, C(O)CH_{eq}H$_{ax}$], 2.19–2.13 (2H, m, CH(Ph)CH_2), 1.94 (1H, br s, OH), 0.84 (3H, d, *J* 6.5, Me); δ_C(90 MHz, $CDCl_3$) 210.92 (C), 143.15 (C), 128.70 (CH), 127.43 (CH), 126.75 (CH), 68.92 (CH), 50.63 (CH), 49.05 (CH_2), 46.50 (CH), 40.58 (CH_2) and 11.99 (CH_3); *m*/*z* (EI) 204 (M$^{+\bullet}$, 62%), 186 (M$^{+\bullet}$ − H_2O, 29), 91 (100), 77 (Ph, 49) (Found: M$^+$, 204.1151. $C_{13}H_{16}O_2$ requires *M*, 204.1150).

(5*SR*,6*SR*)-6-Methyl-5-phenylcyclohex-2-enone 28

The crude *alcohols* **22**–**24** (241 mg, 1.18 mmol) were dissolved in DCM (10 cm^3) under nitrogen and cooled in an ice bath. Methanesulfonyl chloride (0.1 cm^3, 1.18 mmol) was added in one portion, then triethylamine (0.7 cm^3, 4.72 mmol) was added dropwise. The resulting solution was stirred for 15 min then poured into water (10 cm^3) and the layers separated. The organic phase was washed with hydrochloric acid (10 cm^3, 1.1 mol dm^{-3}) then brine (10 cm^3) and dried over magnesium sulfate. Concentration under reduced pressure followed by column chromatography on silica using DCM as eluent gave the *cyclohexenones* as a pale yellow oil (125 mg, 57%), containing a 13 : 87 mixture of *syn* and *anti* isomers **29** and **28**; data for *anti* isomer **28**: R_f (silica, DCM) 0.79; ν_{max}(thin film)/cm^{-1} 3029 w, 2970 w, 2929 w, 2877 w, 1676 vs (C=O), 1494 m, 1454 m, 1388 m, 1232 m, 769 m, 748 m and 702 s; δ_H(400 MHz, $CDCl_3$) 7.30–7.10 (5H, m, Ph), 6.97 [1H, ddd, *J* 10.0, 4.8 and 2.8, C*H*=CHC(O)], 6.12 [1H, br d, *J* 10.0, CH=C*H*C(O)], 2.97 (1H, ddd, *J* 12.8, 9.6 and 6.0, CHPh), 2.69 (1H, dq, *J* 12.8 and 6.8, CHMe), 2.65–2.55 (2H, m, CH_2) and 0.94 (3H, d, *J* 6.8, Me); δ_C(100 MHz, $CDCl_3$) 201.3 (C), 148.2 (CH), 142.8 (C), 129.3 (CH), 128.7 (CH), 127.4 (CH), 126.9 (CH), 48.6 (CH), 46.8 (CH), 34.9 (CH_2) and 12.5 (CH_3); *m*/*z* (EI) 186.1 (M$^{+\bullet}$, 40%), 118.1 (100) (Found: M$^+$, 186.1044, $C_{13}H_{14}O$ requires *M*, 186.1045).

5-Phenoxy-3-phenylhex-5-enal 36

A solution of **12d** (0.10 g, 0.38 mmol) and 18-crown-6 (0.20 g, 0.74 mmol) in dry THF (1 cm^3) was added to a flask containing potassium hydride (0.11 g of a 35% dispersion in mineral oil prewashed with dry hexane 4 × 2 cm^3), in dry THF (5 cm^3) under nitrogen. The resulting mixture was stirred for 2 h at room temperature then poured into aqueous saturated sodium bicarbonate (50 cm^3). The product was extracted into ether (2 × 50 cm^3) and dried ($MgSO_4$). Purification by chromatography on alumina, eluting with hexane–ether (20 : 1), gave *aldehyde* **36** as an oil (41 mg, 41%). R_f (hexane–ether, 5 : 1) 0.40; ν_{max}(thin film)/cm^{-1} 2924, 1724 (C=O), 1634 (C=C), 1592 (aromatic ring), 1491 (aromatic ring) and 1218; δ_H(200 MHz; $CDCl_3$) 9.63 (1H, t, *J* 2.0, C*H*O), 7.30–6.83 (10H, m, 2 × *Ph*), 3.97 (1H, d, *J* 1.8, =CH*H*), 3.78 (1H, d, *J* 1.8, =C*H*H), 3.64 (1H, broad qn, *J* 7.6, C*H*Ph), 2.82 (1H, ddd, *J* 16.7, 6.2 and 1.9, C*H*^{A}H^{B}CHO), 2.73 (1H, ddd, *J* 16.7, 8.4 and 2.1, CH^A*H*^{B}CHO) and 2.54 [2H, d, *J* 7.7, =C(OPh)CH_2CHPh]; δ_C(50 MHz) 201.8 (CH), 160.4 (C), 154.8 (C), 142.9 (C), 129.5 (2 × CH), 128.6 (2 × CH), 127.5 (2 × CH), 126.6 (CH), 124.4 (CH), 121.0 (2 × CH), 90.3 (CH_2), 49.3 (CH_2), 41.3 (CH_2) and 37.7 (CH); *m*/*z* (CI) 267 (100, M + H$^+$), 249 (22) and 173 (M + H$^+$ − HOPh) [Found: (M + H)$^+$, 267.1386. $C_{18}H_{19}O_2$ requires *M*, 267.1385].

5-Formyl-2-phenoxynon-1-ene 37

Aldehyde **37** was prepared (0.10 g, 59%) as an oil from *hexadienol* **12e** (0.17 g, 0.69 mmol) using the method described for synthesis of **36**. R_f (hexane–ether 5 : 1) 0.43; ν_{max}(thin film)/cm^{-1} 2930, 1725 (C=O), 1593 (aromatic ring), 1491 (aromatic ring), 1220 and 693; δ_H(360 MHz; $CDCl_3$) 9.63 (1H, d, *J* 2.5, C*H*O), 7.35–7.00 (5H, m, *Ph*), 4.15 (1H, s, =C*H*H), 3.94 (1H, s, =CH*H*), 2.40–2.36 (1H, m, C*H*CHO), 2.32–2.27 (2H, m, =CCH_2), 2.00–1.94 (2H, m, =CCH$_2$CH_2), 1.79–1.64 (2H, m, PrCH_2), 1.53–1.46 (2H, m, EtCH_2), 1.34–1.26 (2H, m, MeCH_2) and 0.90 (3H, t, *J* 7.2, *Me*); δ_C(50 MHz) 205.0 (CH), 162.3 (C), 155.1 (C), 129.5 (2 × CH), 124.0 (CH), 120.9 (2 × CH), 89.0 (CH_2), 51.0 (CH), 31.5 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 26.0 (CH_2), 22.7 (CH_2) and 13.8 (CH_3); *m*/*z* (EI) 246 (5, M$^{+\bullet}$), 229 (14), 183 (23), 149 (32), 94 (45) and 43 (100) (Found: M$^+$, 246.2019. $C_{16}H_{22}O_2$ requires *M*, 246.2026).

2-Phenoxynon-1-en-5-one 42

A solution of *alcohol* **12e** (0.10 g, 0.41 mmol) and 18-crown-6 (0.21 g, 0.82 mmol) in dry THF (1 cm^3) was added to a flask containing potassium hydride (0.14 g of a 35% dispersion in mineral oil prewashed with dry hexane 4 × 2 cm^3) in dry THF (5 cm^3). The resulting mixture was stirred for 1.5 h at room temperature, then cooled to −78 °C and dry oxygen gas was bubbled through the solution over 30 min. pH 7 phosphate buffer (15 cm^3) was then added dropwise to the mixture and the solution was then allowed to warm to room temperature. The organic phase was separated and the aqueous phase was extracted with ether (2 × 25 cm^3). The ethereal extracts were combined, dried ($MgSO_4$) and concentrated. Chromatography on alumina, eluting with hexane–ether (10 : 1), gave *ketone* **42** as an oil (71 mg, 71%). R_f [alumina, hexane–ether (10 : 1)] 0.27; ν_{max}(thin film)/cm^{-1} 2958, 2930, 2871, 1715 (C=O), 1657 (C=C), 1638, 1592 (aromatic ring), 1490 (aromatic ring) and 1220; δ_H(360 MHz; $CDCl_3$) 7.35–7.00 (5H, m, *Ph*), 4.17 (1H, d, *J* 1.8, =C*H*H), 3.93 (1H, d, *J* 1.8, =CH*H*), 2.73 (2H, t, *J* 7.2, =CCH$_2$CH_2 or =CCH_2), 2.56 (2H, t, *J* 7.2, =CCH$_2$CH_2 or =CCH_2), 2.45 (2H, t, *J* 7.5, PrCH_2), 1.65–1.53 (2H, m, EtCH_2),

1.37–1.26 (2H, m, MeCH_2) and 0.90 (3H, t, *J* 7.7, *Me*); δ_C(50 MHz) 210.1 (C), 162.0 (C), 155.1 (C), 129.5 (2 × CH), 124.0 (CH), 120.7 (2 × CH), 89.0 (CH_2), 42.6 (CH_2), 40.1 (CH_2), 29.6 (CH_2), 28.2 (CH_2), 22.3 (CH_2) and 13.8 (CH_3); *m*/*z* (EI) 232 ($M^{+\bullet}$, 9%) and 147 (100) [Found (CI): $(M + H)^+$, 233.1544. $C_{15}H_{21}O_2$ requires $(M + H^+)$ 233.1541].

(3*RS*,5*SR*,6*SR*)- and (3*RS*,5*SR*,6*RS*)-3-*tert*-Butyldimethylsilyloxy-6-methyl-5-phenylcyclohexanone, 43 and 44

A mixture of *alcohols* **22**–**24** (776 mg, 3.7 mmol) was dissolved in dry DMF (10 cm^3) under nitrogen. Diisopropylethylamine (1.2 cm^3, 6.7 mmol) then *tert*-butyldimethylsilyl chloride (468 mg, 3.1 mmol) were added at 0 °C. The reaction mixture was allowed to warm to room temperature and then left to stir over three days (~60 h). The mixture was then poured into saturated aqueous sodium bicarbonate solution (20 cm^3). The aqueous phase was separated and extracted with ether (2 × 10 cm^3). The combined organic extracts were washed with aqueous hydrochloric acid (2 × 10 cm^3, 1 mol dm^{-3} solution) then brine (10 cm^3) and dried ($MgSO_4$). Concentration under reduced pressure gave a mixture of the unprotected *alcohol* **22**, its TBDMS ether, and *silyl ethers* **43** and **44**. Separation of the two diastereoisomers was achieved by column chromatography followed by preparative TLC.

(3*RS*,5*SR*,6*SR*)-3-*tert*-Butyldimethylsilyloxy-6-methyl-5-phenylcyclohexanone 43. Spectral data for **43**: ν_{max}(thin film)/cm^{-1} 2954, 2929, 2856, 1714 (C=O); δ_H(360 MHz, $CDCl_3$) 7.37–7.13 (5H, m, Ph), 4.40 [1H, m, Σ*J* ~16, C*H*(OTBDMS)], 3.71 [1H, dt, *J* 11.0 and 4.3, C*H*(Ph)], 2.74 [1H, dd, *J* 14.5 and 3.7, C(O)C$H_{ax}$$H_{eq}$], 2.70 [1H, dq partly obscured, C*H*Me], 2.38 [1H, dd, *J* 14.6 and 4.9, C(O)C$H_{eq}$$H_{ax}$], 2.29 [1H, ddd, *J* 13.5, 10.9 and 2.5, CH(Ph)C$H_{ax}$$H_{eq}$], 1.96 [1H, ddd, *J* 13.7, 4.5 and 3.5, CH(Ph)C$H_{ax}$$H_{eq}$], 0.88 (3H, d, *J* 7.2, CH*Me*), 0.84 (9H, s, Si^{t}Bu), 0.03 (3H, s, Si*Me*^{A}Me^B), −0.01 (3H, s, SiMe^A-*Me*^{B}); *m*/*z* (EI) 261 ($M^{+\bullet}$ − ^{t}Bu$^\bullet$, 20%), 157 (100) [Found (CI): $(M + NH_3)^+$ 336.2345. $C_{19}H_{34}NO_2Si$ requires $M + NH_3$, 336.2359].

(3*RS*,5*SR*,6*RS*)-3-*tert*-Butyldimethylsilyloxy-6-methyl-5-phenylcyclohexanone 44. Spectral data for **44**: ν_{max}(thin film)/cm^{-1} 2956 m, 2856 m, 1715 vs (C=O), 1376 m, 1254 m, 1095 s, 777 m and 700 m; δ_H(360 MHz, $CDCl_3$) 7.40–7.15 (5H, m, Ph), 3.95 [1H, tt, *J* 10.9 and 4.8, C*H*(OTBDMS)], 2.76 [1H, ddd, *J* 13.0, 4.9 and 2.2, C(O)C$H_{eq}$$H_{ax}$], 2.58 [1H, t, *J* 12.2, C(O)-C$H_{ax}$$H_{eq}$], 2.52 [1H, dq partly obscured, C*H*Me], 2.38 [1H, td, *J* 12.3 and 3.3, C*H*(Ph)], 2.20 [1H, doublet with poorly-resolved smaller couplings, *J* approx. 13.0, CH(Ph)C$H_{ax}$$H_{eq}$], 2.04 [1H, td, *J* 12.9 and 10.7, CH(Ph)C$H_{ax}$$H_{eq}$], 0.87 (9H, s, Si^{t}Bu), 0.78 (3H, d, *J* 6.4, CH*Me*), 0.06 (3H, s, Si*Me*^{A}Me^B), 0.05 (3H, s, SiMe^A*Me*^{B}); *m*/*z* (EI) 261 ($M^{+\bullet}$ − ^{t}Bu$^\bullet$, 7%), 157 (38), 31 (100) [Found (CI): $(M + H)^+$, 319.2090. $C_{19}H_{31}O_2Si$ requires $M + H$, 319.2093].

Acknowledgements

University of Glasgow for a scholarship for A. P. R., Loudon bequest for supporting C. S. G.

References

1 A. P. Rutherford, C. S. Gibb and R. C. Hartley, *Tetrahedron Lett.*, 1998, **39**, 685.
2 For a review see: A. S. Franklin and I. Paterson, *Contemp. Org. Synth.*, 1994, 317.
3 F. N. Tebbe, G. W. Parshall and G. S. Reddy, *J. Am. Chem. Soc.*, 1978, **100**, 3611.
4 T. R. Howard, J. B. Lee and R. H. Grubbs, *J. Am. Chem. Soc.*, 1980, **102**, 6876; K. A. Brown-Wensley, S. L. Buchwald, L. Cannizzo, L. Clawson, S. Ho, D. Meinhardt, J. R. Stille, D. Straus and R. H. Grubbs, *Pure Appl. Chem.*, 1983, **55**, 1733.
5 N. A. Petasis and S.-P. Lu, *Tetrahedron Lett.*, 1995, **36**, 2393 and refs. 1–3 therein.
6 T. Okazoe, K. Takai, K. Oshima and K. Utimoto, *J. Org. Chem.*, 1987, **52**, 4410.
7 K. Takai, Y. Kataoka, J. Miyai, T. Okazoe, K. Oshima and K. Utimoto, *Org. Synth.*, 1996, **73**, 73.
8 Y. Horikawa, M. Watanabe, T. Fujiwara and T. Takeda, *J. Am. Chem. Soc.*, 1997, **119**, 1127.
9 For a review see: L. A. Paquette, *Tetrahedron*, 1997, **53**, 13971.
10 N. Greeves and W.-M. Lee, *Tetrahedron Lett.*, 1997, **35**, 6445 and refs. 10 and 11 therein; E. Lee, Y. R. Lee, B. Moon, O. Kwon, M. S. Shim and J. S. Yun, *J. Org. Chem.*, 1994, **59**, 1444; S.-Y. Wei, K. Tamooka and T. Nakai, *Tetrahedron*, 1993, **49**, 1025; L. A. Paquette and G. D. Maynard, *J. Am. Chem. Soc.*, 1992, **114**, 5018.
11 L. A. Paquette, D. T. DeRussy and R. D. Rogers, *Tetrahedron*, 1988, **44**, 3139; L. A. Paquette, J. Reagan, S. L. Schreiber and C. A. Teleha, *J. Am. Chem. Soc.*, 1989, **111**, 2331; R. E. Maleczka, Jr. and L. A. Paquette, *J. Org. Chem.*, 1991, **56**, 6538.
12 L. A. Paquette, D. T. DeRussy, N. A. Pegg, R. T. Taylor and T. M. Zydowsky, *J. Org. Chem.*, 1989, **54**, 4576.
13 L. A. Paquette, T. M. Morwick, J. T. Negri and R. D. Rogers, *Tetrahedron*, 1996, **52**, 3075.
14 For a review of carbocyclisations see: R. C. Hartley and S. T. Caldwell, *J. Chem. Soc., Perkin Trans. 1*, 2000, 477.
15 H. Ohtake, X.-L. Li, M. Shiro and S. Ikegami, *Tetrahedron*, 2000, **56**, 7109.
16 J. E. Baldwin and M. J. Lusch, *Tetrahedron*, 1982, **38**, 2939.
17 Examples include: J. R. Bull and J. H. S. Borry, *J. Chem. Soc., Perkin Trans. 1*, 1994, 913; I. Shiina, H. Iwadare, M. Saitoh, N. Ohkawa, T. Nishimura and T. Mukaiyama, *Chem. Lett.*, 1995, 781; T. Mukaiyama, I. Shiina, K. Kimura, Y. Akiyama and H. Iwadare, *Chem. Lett.*, 1995, 229; Y. Tsuda, Y. Sakai, T. Sano and J. Toda, *Chem. Pharm. Bull.*, 1991, **39**, 1402.
18 K. Tadano, S. Kanazawa, K. Takao and S. Ogawa, *Tetrahedron*, 1992, **48**, 4283.
19 H. Fukase and S. Horii, *J. Org. Chem.*, 1992, **57**, 3642.
20 M.-H. Filippini, R. Faure and J. Rodriguez, *J. Org. Chem.*, 1995, **60**, 6872.
21 T. Mukaiyama, *Org. React.* (*N. Y.*), 1982, **28**, 238.
22 N. Sloughi and G. Rousseau, *Synth. Commun.*, 1987, **17**, 1.
23 C. Wedler, A. Kunath and H. Schick, *J. Org. Chem.*, 1995, **60**, 758.
24 H. Schick, R. Ludwig, K. Kleiner and A. Kunath, *Tetrahedron*, 1995, **51**, 2939.
25 M. Mortimore and P. Kocienski, *Tetrahedron Lett.*, 1988, **29**, 3357.
26 A. P. Rutherford and R. C. Hartley, *Tetrahedron Lett.*, 2000, **41**, 737.
27 M. P. Strobel, C. G. Andrieu, D. Paquer, M. Vazeux and C. C. Pham, *Nouv. J. Chim.*, 1980, **4**, 101.
28 A route to these β-hydroxycyclohexanones is known: I. Fleming, R. Henning, D. C. Parker, H. E. Plaut and P. E. J. Sanderson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 317.
29 M. J. Aurell, P. Gavina and R. Mestres, *Tetrahedron*, 1994, **50**, 2571.
30 J. P. Richard and R. W. Nagorski, *J. Am. Chem. Soc.*, 1999, **121**, 4763.
31 N. L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127.
32 F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **11**, 440.
33 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
34 J. J. P. Stewart, *J. Comput. Aided Mol. Des.*, 1990, **4**, 1.
35 K. J. McCullough, *Contemp. Org. Synth.*, 1995, **3**, 225.
36 L. A. Paquette and R. C. Thompson, *J. Org. Chem.*, 1993, **58**, 4952.
37 J. Zabicky, *The Chemistry of the Carbonyl Group*, Wiley, New York, 1970, Vol. 2, pp. 81–87.
38 L. N. Mander and D. J. Owen, *Tetrahedron*, 1997, **53**, 2137.
39 S. Matsubara, N. Tsuboniwa, Y. Morizawa, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1984, 3242.
40 K. Inomata, T. Kawahara and T. Mukaiyama, *Chem. Lett.*, 1974, 245.