Ketone-directed peracid epoxidation of cyclic alkenes

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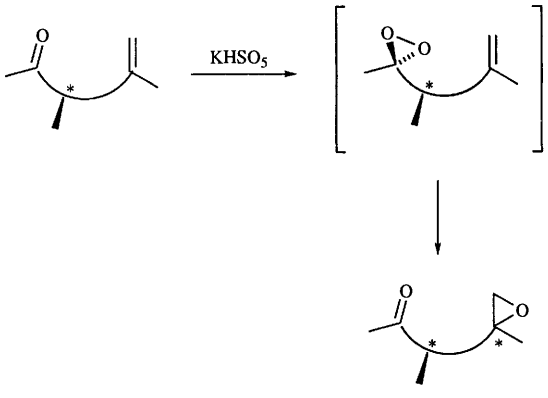
Ketone carbonyl groups are shown to direct the peracid epoxidation of cyclic alkenes with greater selectivity than that displayed by esters. An ^{18}O labelling study is used to show that a dioxirane intermediate is not involved in these reactions.

Introduction

Directing effects due to coordination of a reagent to functionality in the substrate are of great importance in controlling relative stereochemistry during organic transformations.[1] One of the earliest such directing effects was described in 1957, when Henbest discovered that cyclohex-2-en-1-ol was converted almost exclusively to the *syn*-epoxide product upon treatment with *meta*-chloroperbenzoic acid (MCPBA), presumably due to hydrogen bonding between the peracid and the substrate's hydroxy group.[2] Since that time, many other functional groups have been shown to be capable of directing peracid epoxidation.[1,3]

We have recently begun a study of the intramolecular dioxirane epoxidation reaction (Scheme 1), as a method for

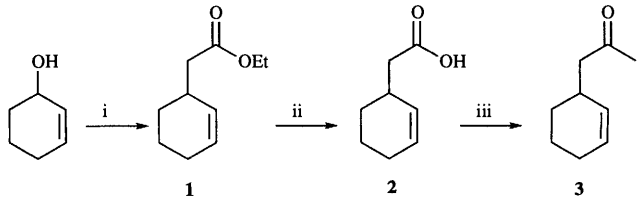


Scheme 1

effecting *ketone*-directed epoxidation. In attempting to prepare reference samples of diastereoisomeric mixtures using peracids, we discovered that the ketone carbonyl group can exert a stronger directing effect than might be expected simply on the basis of its hydrogen bonding ability. Here we describe in full[4] our investigations of this directing effect with various ketones, including mechanistic studies employing an ^{18}O labelled carbonyl group.

Results and discussion

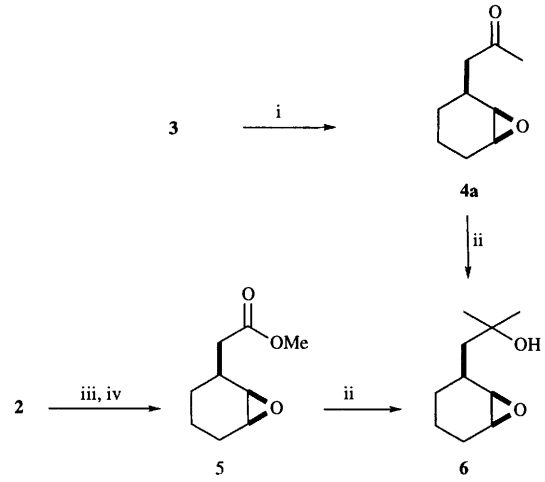
As the first substrate to be tested for our intramolecular epoxidation study, we prepared ketone **3**, where intramolecular epoxidation can occur only *syn* to the side-chain. Synthesis of **3** (Scheme 2) began with an orthoester Claisen rearrangement[5] of cyclohex-2-en-1-ol to give a mixture of the



Scheme 2 *Reagents and conditions:* i, $MeC(OEt)_3$, $MeCH_2CO_2H$, 140 °C; ii, MeOH, NaOH, 37%; iii, MeLi, Me_3SiCl, 85%

ester **1** and 2-acetoxycyclohexene.[6] Direct separation of these compounds was not attempted; rather, ester hydrolysis was performed on the mixture, allowing subsequent removal of cyclohex-2-en-1-ol from the acid **2** by simple acid–base manipulations. Conversion of the acid **2** to the methyl ketone **3** was accomplished under conditions reported by Rubottom.[7]

Epoxidation of **3** was carried out using MCPBA in dichloromethane in an attempt to obtain authentic samples of both the *syn*- and the *anti*-epoxides for spectroscopic comparison. We were surprised to find that this reaction yielded only one epoxide, product **4a** by analysis of the ^1H and ^{13}C NMR spectra of the crude reaction mixture (Scheme 3). The



Scheme 3 *Reagents and conditions:* i, MCPBA, CH_2Cl_2, 61%; ii, MeLi, THF, 45%; iii, I_2, CH_3CN; iv, NaOMe, MeOH, 57%

relative stereochemistry of **4a** was determined as *syn* by a set of correlation experiments. Iodolactonisation of acid **2** and opening of the lactone with sodium methoxide yielded the known[8] epoxy ester **5**. The ester **5** and the ketone **4a** were treated separately with methyllithium and were found to yield the same tertiary alcohol **6**.

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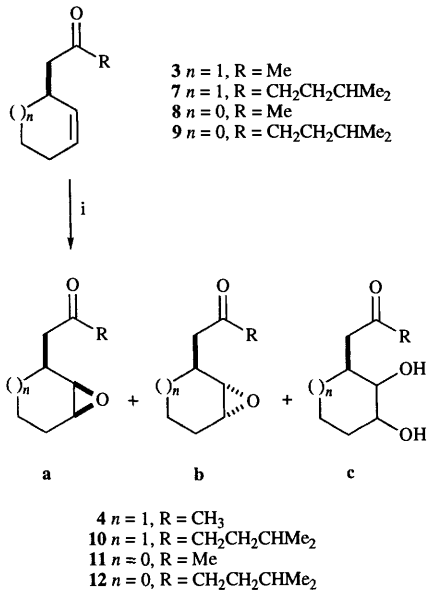


Scheme 4 *Reagents and conditions:* i, MCPBA, solvent (see Table 1)

Table 1 MCPBA epoxidation of keto alkenes **3** and **7–9**

Entry	Substrate	Product	Solvent[a]	Product ratio **a**:**b**:**c**	Yield of **a** (%)
1	**3**	**4**	CH_2Cl_2	**a** only	61
2	**3**	**4**	Et_2O	**a** only	55
3	**7**	**10**	CH_2Cl_2	4:0:1	45
4	**7**	**10**	Et_2O	4:0:1	50
5	**8**	**11**	CH_2Cl_2	5:1:0	83
6	**8**	**11**	Et_2O	10:1:0	24
7	**9**	**12**	CH_2Cl_2	9:2:0	78
8	**9**	**12**	Et_2O	9:1:0	50

[a] Where CH_2Cl_2 was used as solvent, an equal volume of saturated aqueous sodium hydrogen carbonate was also employed.

A number of other cyclic ketoalkenes **7–9** (Scheme 4) were prepared in a similar way to **3**, by reacting acid **2** or commercially available 2-(cyclopent-2-enyl)acetic acid with the appropriate alkyllithium reagent. The results of peracid epoxidation are shown in Table 1. The relative configuration of the major epoxide products **10a** and **11a** was assigned by a correlation experiment similar to that in Scheme 3; the relative stereochemistry of **12a** and **12b** is assumed in view of the similarity of their ^{1}H NMR spectra to those of **11a** and **11b**, respectively. For the five-membered ring epoxides **11** and **12**, the diastereoisomeric ratio was measured by integration of the epoxide proton resonances, distinct for the two isomers in the crude ^{1}H NMR spectrum. In the epoxidation of alkene **7**, the *anti*-epoxide **10b** was not observed. The crude ^{1}H NMR spectra indicated the presence of diol **10c**, which presumably arises from facile hydrolysis of **10b** with neighbouring group participation from the ketone carbonyl (*vide infra*). Since diol **10c** can potentially also arise from hydrolysis of the *syn*-isomer **10a**, an estimate of the diastereoselectivity of the epoxidation of **7** made by measurement of the ratio of **10a** to **10c** must be regarded as a lower limit.

It has been noted several times previously that carbonyl groups are capable of directing peracid epoxidations, with examples including carbamates,[8] amides[9,10] and esters,[8,9] as well as scattered instances of ketone direction.[11] For comparison purposes, some literature data on the stereoselectivity of epoxidation of structurally similar carbamates, amides and esters are given in Fig. 1. By examination of the data in Table 1, it can be seen that the *syn*-selectivity observed for ketones is usually lower than for amides and carbamates, but in

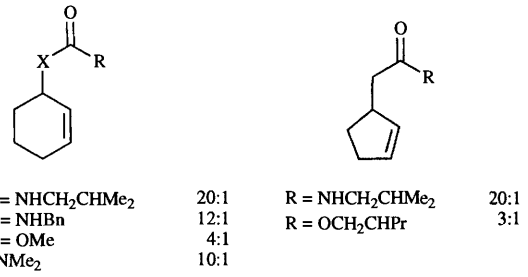
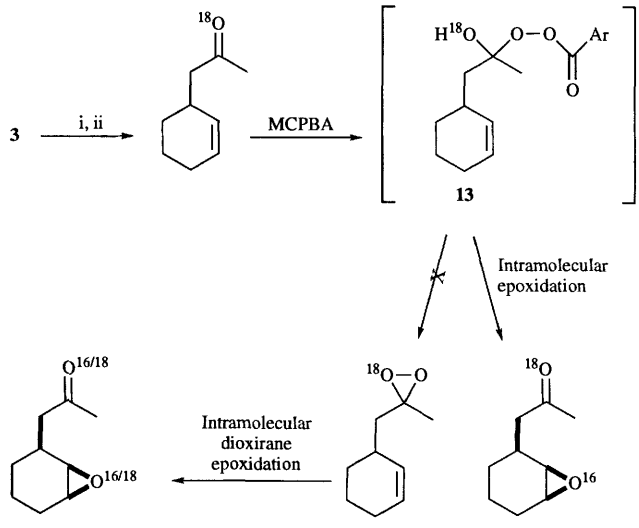


Fig. 1 *syn*:*anti* epoxide ratios for peracid epoxidation in dichloromethane (refs. 8 and 9)

all cases higher than for the corresponding ester. Interestingly, use of diethyl ether as solvent results in higher selectivity than with dichloromethane, the reverse of the situation for hydroxy-directed epoxidation.[12]

To explain the *syn*-selectivity observed for amides and carbamates, Kocovsky[8] proposed that hydrogen bonding of the substrate carbonyl to the peracid hydroxy was playing an important role. This idea is consistent with his observation that esters, possessing a less basic carbonyl group, display much lower selectivity. This proposed mode of hydrogen bonding is effectively the reverse of the well known mode of hydrogen bonding for hydroxy-directed peracid epoxidation.[1,13] The importance of hydrogen bonding in determining the stereoselectivity for our ketone substrates was tested by performing the epoxidation of **3** in a range of solvents, including protic solvents such as methanol or *tert*-butyl alcohol. In these solvents, hydrogen bonding between substrate and reagent would be expected to be reduced considerably; indeed, the *syn*-stereoselectivity of MCPBA epoxidation of cyclopent-3-en-1-ol is known to fall markedly when methanol is used as solvent rather than dichloromethane.[14] However, no formation of the *anti*-epoxide **4b** (or the diol **4c**) was ever observed for peracid epoxidation of **3** in a variety of solvents (dichloromethane, ether, benzene, methanol or *tert*-butyl alcohol). Thus, our ketones display higher selectivity than might be expected based on consideration of hydrogen bonding effects.

An alternative explanation for the high stereoselectivity involves the possibility of addition of the peracid to the carbonyl group (Scheme 5). This is identical to the first step of



Scheme 5 *Reagents and conditions:* i, $HC(OMe)_3$, MeOH, cat. TsOH, molecular sieves, reflux, 100%; ii, $H_2{}^{18}O$, THF, cat. H_2SO_4, 100%

the Baeyer–Villiger reaction, a process which does not generally occur for simple acyclic alkyl ketones (*e.g.* acetone) with MCPBA due to the poor migratory aptitude of the primary alkyl group.[15] Indeed, acetone has been shown to react with

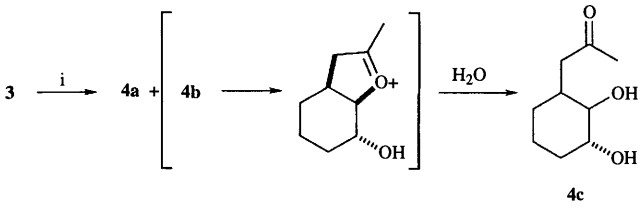
peracetic acid to provide a species capable of alkene epoxidation;[15] this intermediate was postulated to be either the carbonyl oxide or the dioxirane.[15] As indicated in Scheme 5, the dioxirane mechanism can be tested by ^{18}O labelling of the ketone carbonyl. Assuming little or no stereocontrol in the addition to the carbonyl group, the ^{18}O label would be expected to be distributed equally between the two diastereotopic oxygens of the dioxirane, either of which is capable geometrically of undergoing intramolecular transfer to the alkene. A dioxirane mechanism would therefore distribute the ^{18}O label between the ketone and epoxide groups in the product. The presence of ^{18}O label can readily be detected either by mass spectrometry or by the slight upfield ^{13}C shift[16] (typically *ca.* 0.03 to 0.04 ppm for an epoxide[17]) observed for adjacent carbons. A sample of ^{18}O labelled ketone **3** was prepared by hydrolysis of the derived dimethoxy ketal with $H_2{}^{18}O$ (Scheme 5). Label incorporation was confirmed by mass spectrometry (M^+ 140). When this labelled ketone was epoxidised with MCPBA in either dichloromethane or diethyl ether, no transfer of ^{18}O label to the ring epoxide was observed by ^{13}C NMR or mass spectrometric analysis. Specifically, in the ^{13}C spectrum of **4a** (100 MHz, $CDCl_3$) obtained from epoxidation of ^{18}O labelled **3**, there was no evidence of the doubling of the epoxide resonances (at δ 55.1 and 53.5) that would be expected for an $^{18}O/^{16}O$ mixture. Two carbonyl peaks (at δ 207.91 and 207.85) were observed, however, presumably due to partial exchange of the carbonyl ^{18}O with $H_2{}^{16}O$. Also, a mass spectral fragment due to the cyclohexyl epoxide ring at *m/z* 97 was observed, but no corresponding peak for the ^{18}O labelled compound at *m/z* 99. The possibility of a dioxirane intermediate in this epoxidation process can therefore be excluded.

Two other possible explanations for the role of the ketone carbonyl in directing the epoxidation remain. First, as proposed by Murray,[15] a carbonyl oxide may be involved. Alkene epoxidation by carbonyl oxides is known and can be accompanied by scrambling of alkene geometry, thus distinguishing it from dioxirane epoxidation.[18] Such loss of stereospecificity is, of course, not possible for the cyclic alkenes employed here. A second explanation is that the tetrahedral intermediate **13** is capable of effecting intramolecular epoxidation, a process consistent with the results of our labelling experiment. Precedent for alkene epoxidation by species similar to **13** can be obtained from the work of Rebek on α-hydroperoxy ethers,[19] and from the studies of α-silyloxy peroxy esters by Saito.[20]

Other epoxidation reagents

Several other common epoxidation reagents were reacted with **3** in order to ascertain the generality of the ketone directing effect. The *syn*-epoxide **4a** was again the exclusive product when magnesium monoperoxyphthalate hexahydrate (MMPP)[21] was used as the oxidant. This reaction is carried out in ethanol, again suggesting that hydrogen bonding does not play a role in influencing the stereoselectivity. Ketone **8** was also epoxidised using MMPP and afforded a 7:1 ratio of *syn*- to *anti*-epoxides **11a**:**11b**. It is reasonable to assume that the directing effect with MMPP operates by a mechanism similar to that with MCPBA.

Dimethyldioxirane, clearly incapable of converting the ketone **3** to a tetrahedral intermediate of type **13**, was studied next. Our first experiments using an isolated solution of dimethyldioxirane (DMDO)[22] in acetone interestingly afforded epoxide **4a** and diol **4c** in a 1:1 isolated ratio. The diol presumably arises from the facile opening of the *anti*-epoxide **4b** by neighbouring group participation from the ketone carbonyl (Scheme 6), and its stereochemistry is tentatively assigned on this basis. The mechanism of formation of diol **4c** was also investigated using ^{18}O labelled ketone. Mass spectrometry revealed substantial transfer of ^{18}O label to one of the hydroxy groups of the diol, since the fragment in the EI spectrum due to

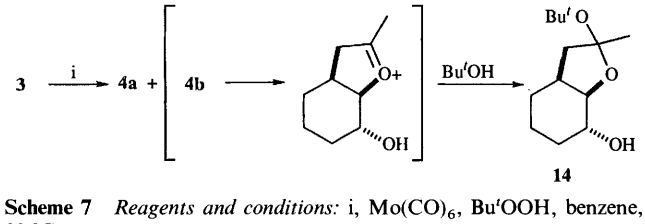


4c

Scheme 6 *Reagents and conditions:* i, DMDO, acetone–CH_2Cl_2

loss of the $MeCOCH_2$ side chain was observed at *m/z* 116. The corresponding peak due to the unlabelled diol **4c**, at *m/z* 114, was not significant. This seems to indicate that the mechanism of formation of **4c** is indeed as suggested in Scheme 6. Given that DMDO solution has found application to the epoxidation of acid sensitive substrates due to its neutral nature,[23] it is perhaps surprising that this hydrolysis of the *anti*-epoxide occurs so readily. The DMDO solution used for this reaction had been dried with anhydrous potassium carbonate and stored over powdered molecular sieves prior to use; it was later discovered that, when the DMDO solution used was dried only with potassium carbonate, the expected two diastereoisomeric epoxide products **4a** and **4b** were obtained in a 2.5:1 ratio. It is therefore likely that the presence of a small amount of the potentially Lewis acidic molecular sieves in the reaction mixture was responsible for promoting the diol formation observed originally. The difference between the measured ratio of epoxides and the ratio of *syn*-epoxide to diol observed using the DMDO solutions dried in different ways may reflect an actual change in the diastereoselectivity of the epoxidation process, but it is more likely that the diol **4c**, as mentioned earlier, can arise also by hydrolysis of the *syn*-epoxide **4a**, and so selectivity measured based on the diol represents a lower limit.

Ketone **3** was subjected to epoxidation with $Mo(CO)_6$–Bu^tOOH in benzene at reflux, conditions under which Pearson has demonstrated that esters can direct the stereochemistry of epoxidation reactions.[24] A 3:2 mixture of *syn*-epoxide **4a** and cyclic ketal **14** was observed in the crude ^1H NMR spectrum. Ketal **14**, the stereochemistry of which is again tentatively assigned based on the proposed mechanism for its formation, probably arises from intramolecular ring opening of the *anti*-epoxide **4b**, followed by trapping of the oxonium ion intermediate by *tert*-butyl alcohol solvent (Scheme 7). Little



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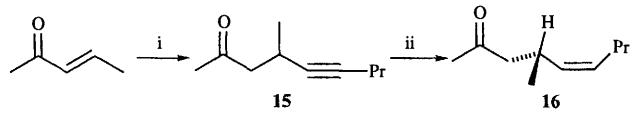
Scheme 7 *Reagents and conditions:* i, $Mo(CO)_6$, Bu^tOOH, benzene, 80 °C

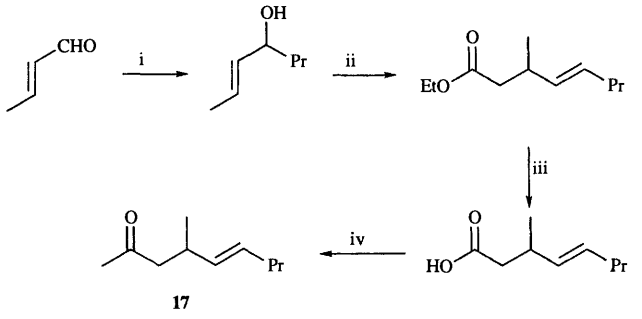
stereoselectivity was again observed for epoxidation of the cyclopentene **8** under these [$Mo(CO)_6$–Bu^tOOH] conditions, a 3:2 mixture of **11a** and **11b** being evident in the crude ^1H NMR spectra.

Epoxidation of acyclic systems

Control of the diastereoselectivity of epoxidation of acyclic ketoalkenes is of greater interest, since the product epoxy ketones can be transformed into oxygen-containing heterocycles *via* intramolecular opening of the epoxide by the carbonyl group.[25] First to be prepared were substrates with the same tether length and position of asymmetric centre as the cyclic alkenes studied previously. The alkyne **15**, prepared by copper-mediated conjugate addition[26] of pentynyllithium to pent-2-en-3-one, was envisaged to be a precursor to either the corresponding *E*- or *Z*-alkene by choice of appropriate



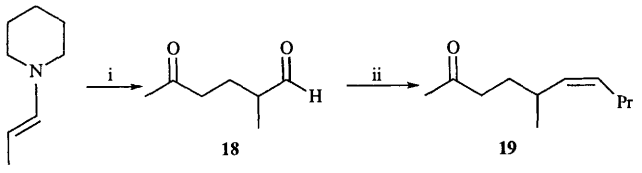
Scheme 8 *Reagents and conditions:* i, PrC≡CLi, CuI, TMSI, 10%; ii, H_2, Lindlar cat. (92%)



Scheme 9 *Reagents and conditions:* i, PrMgCl, Et_2O, 78%; ii, $MeC(OEt)_3$, propionic acid, 100%; iii, NaOH, MeOH, 75%; iv, MeLi, Me_3SiCl, THF, 40%

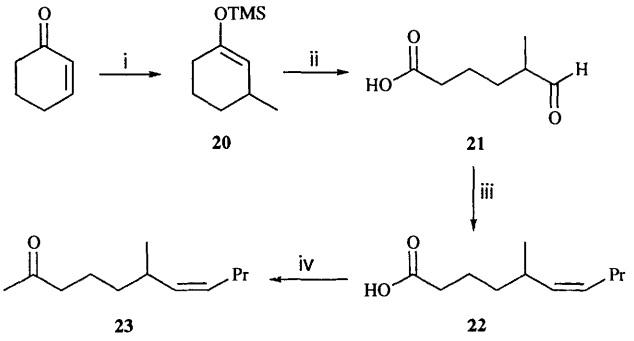
reduction method; indeed, Lindlar hydrogenation to afford *Z*-isomer **16** proceeded smoothly (Scheme 8). However, attempted formation of the *E*-alkene **17** by dissolving metal reduction could not be achieved cleanly, so compound **17** was prepared by an orthoester Claisen route (Scheme 9) similar to that used to provide **3**. The *Z*-alkene **16** was expected to have a marked ground state preference, due to avoidance of $A_{1,3}$-strain,[27] for a conformation where the hydrogen at the asymmetric centre eclipses the alkene propyl substituent (as shown in Scheme 8). This conformational preference, were it to be carried through to the epoxidation transition state, would ensure differentiation of the diastereotopic alkene faces with the ketone side chain effectively held over one of the two. However, MCPBA epoxidation of **16** in dichloromethane or in ether afforded essentially a 1:1 mixture of the possible diastereoisomeric epoxides. Less surprisingly, the *E*-isomer **17**, lacking the $A_{1,3}$-strain conformational lock, also afforded a mixture of diastereoisomers.

The main reason for the lack of selectivity for the *Z*-alkene **16** was considered to be that the tether between the ketone and alkene was too short to allow the intramolecular epoxidation process to occur without considerable deviation from the preferred ($A_{1,3}$-strain) conformation. As well as reducing the energy difference between the competing diastereoisomeric transition states for intramolecular epoxidation, this would slow intramolecular epoxidation relative to background intermolecular epoxidation by MCPBA. In either case, the consequence would be low stereoselectivity. The *Z*-alkene **19** with an extra methylene group was therefore prepared (Scheme 10) by addition of the piperidine enamine of propanal



Scheme 10 *Reagents and conditions:* i, Methyl vinyl ketone, 0 °C–room temp., 15% oxalic acid; ii, $Ph_3P(CH_2)_3Me^+Br^-$, NaHMDS, PhMe, −78 °C, 85%

to methyl vinyl ketone followed by hydrolysis[28] and Wittig olefination of the resulting keto aldehyde **18**. The tether was also extended still further (Scheme 11): organocopper addition to cyclohexenone and trapping of the enolate with chlorotrimethylsilane[29] gave **20** which was immediately ozonolysed[30] to give acid **21**. Wittig olefination followed by methyllithium addition to the resulting acid **22** yielded the required ketone



Scheme 11 *Reagents and conditions:* i, MeLi, CuI, TMSCl, TMEDA, THF; ii, O_3, Me_2S, −78 °C, 41% over the two steps; iii, $Ph_3P(CH_2)_3Me^+Br^-$, NaHMDS, PhMe, −78 °C, 80%; iv, MeLi, Me_3SiCl, THF, 61%

23. However, epoxidation of **19** or **23** with MCPBA still provided approximately a 1:1 diastereoisomeric mixture in each case. Since models suggest that intramolecular epoxidation is possible for **19** or **23** whilst accommodating the preferred conformation about the alkene–asymmetric centre bond, it seems likely that direct and non-stereoselective intermolecular epoxidation by MCPBA is responsible for the low selectivity. A more flexible tether would indeed be expected to slow any intramolecular process relative to intermolecular MCPBA epoxidation. Finally, epoxidation of **19** or **23** with DMDO was examined, and again was found to be non-stereoselective.

Conclusions

We have shown that the peracid epoxidation of cyclic alkenes **3** and **7–9** is directed by the ketone carbonyl group, and have ruled out the involvement of a dioxirane using ^{18}O labelling. For the synthetically more interesting acyclic alkenes, however, peracid epoxidation occurs non-stereoselectively. The main problem is that direct, intermolecular epoxidation by the peracid competes with any intramolecular process and so a reagent system needs to be developed where background epoxidation in the absence of a ketone is minimal. The Oxone® system used by Curci and others[31] to generate dioxiranes from ketones would appear to fulfil this criterion, and we are indeed currently investigating the intramolecular version of this process. Our work to date has shown that this apparently simple reagent system is in fact rather complex, with several important and interdependent variables, and details of this will be reported elsewhere.

Experimental

General

All NMR spectra were recorded in $CDCl_3$ on a JEOL GX 270 or JEOL EX 400 spectrometer. *J* Values are given in Hz. Multiplicities in ^{13}C spectra were determined by DEPT experiments. IR spectra were recorded on a Perkin-Elmer 1605 FTIR spectrometer. Mass spectra were recorded under EI conditions unless otherwise stated. EI and CI (isobutane) spectra were recorded on VG 7070B, VG 12-253 or VG ZAB-E instruments. FAB spectra (from *meta*-nitrobenzyl alcohol) were recorded on a VG AutoSpec machine.

Microanalyses were performed in the School of Chemistry, University of Bath. Diethyl ether (referred to throughout as ether) and THF were distilled from sodium–benzophenone ketyl; toluene from sodium; and dichloromethane from phosphorus pentoxide. Petrol refers to light petroleum, bp 60–80 °C, which was redistilled prior to use. All commercial reagents were used without further purification unless stated otherwise in the appropriate text. Flash column chromato-

graphy[32] was performed using Matrex silica Si. Where appropriate, the silica was neutralised by flushing it once with a 1% solution of triethylamine in the appropriate eluent.

Cyclohex-2-enylacetic acid 2

A solution of cyclohex-2-en-1-ol (5 g, 51 mmol) and propionic acid (1 cm^3) in triethyl orthoacetate (100 cm^3) was heated to 140 °C for 16 h, any ethanol formed being distilled away from the reaction. The reaction mixture was then allowed to cool and diluted with ethyl acetate. The organics were washed successively with HCl (2 mol dm^{-3}), saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and evaporated, to yield a mixture of ethyl ester **1** and 2-acetoxycyclohexene (6.9 g) as an orange oil. Sodium hydroxide solution (1 mol dm^{-3}; 60 cm^3) was added to a stirred solution of this mixture (6.9 g) in methanol (60 cm^3). On completion, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was discarded. The aqueous layer was acidified with HCl (1 mol dm^{-3}) and extracted twice with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and the solvent evaporated to yield the acid **2** (2.66 g, 37%) as a dark oil (Found: C, 68.5; H, 8.7. $C_8H_{12}O_2$ requires C, 68.6; H, 8.6%); ν_{max}(film)/cm^{-1} 2931, 2674, 1700, 1409, 1291, 1050, 957 and 725; δ_H(270 MHz) 5.73 (1 H, m), 5.55 (1 H, dd, *J* 10.0, 2.0), 2.60 (1 H, m), 2.36–2.31 (2 H, m), 2.00–1.48 (4 H, m) and 1.36–1.13 (2 H, m); δ_C(67.5 MHz) 178.9 (s), 129.8 (d), 128.4 (d), 40.5 (t), 32.1 (d), 28.8 (t), 24.9 (t) and 20.9 (t); *m/z* 140 (M^+), 122 ($M^+ - H_2O$), 94 ($M^+ - H_2O - CO$), 81 and 80.

General procedure for the preparation of ketones 3, 7, 8 and 9 from the parent acid by alkyllithium addition

A solution of the acid **2** or cyclopent-2-enylacetic acid (Aldrich) (1.85 mmol) in THF (15 cm^3) under nitrogen was treated rapidly with alkyllithium (4 equiv.) at 0 °C and the mixture left to stir. When the reaction was complete it was quenched with freshly distilled chlorotrimethylsilane (5 cm^3, 40 mmol) and allowed to warm to room temperature. Hydrochloric acid (1 mol dm^{-3}; 15 cm^3) was then added and the solution stirred for 20 min. The mixture was extracted three times with ether, the combined organics washed with water, dried (Na_2SO_4) and evaporated to yield a yellow oil. Flash chromatography (10% ether–petrol) gave the ketone.

1-Cyclohex-2-enylpropan-2-one 3. Yield 85%; ν_{max}/cm^{-1} 2910, 1720, 1350 and 1150; δ_H(400 MHz) 5.68 (1 H, dq, *J* 10.0, 3.0), 5.47 (1 H, ddd, *J* 10.1, 4.7, 2.3), 2.57 (1 H, m), 2.42 (2 H, dd, *J* 16.2, 6.7), 2.37 (1 H, dd, *J* 16.2, 7.9), 2.21 (3 H, s), 1.98–1.93 (2 H, m), 1.78 (1 H, m), 1.67 (1 H, m), 1.53 (1 H, m) and 1.19 (1 H, m); δ_C(100 MHz) 208.1 (s), 130 (d), 127.8 (d), 49.9 (t), 31.0 (d), 30.3 (q), 28.8 (t), 24.9 (t) and 20.9 (t); *m/z* 138 (M^+), 95 ($M^+ - CH_3CO$), 80 and 43 (Found: M^+, 138.1069. $C_9H_{14}O$ requires *M*, 138.1045).

1-Cyclohex-2-enyl-5-methylhexan-2-one 7. Yield 54%; ν_{max}/cm^{-1} 2926, 2869, 1710, 1467, 1383, 1366, 1252, 1060 and 842; δ_H(400 MHz) 5.68 (1 H, m), 5.48 (1 H, m), 2.40–2.36 (2 H, m), 1.96 (1 H, m), 1.80–1.43 (6 H, m), 1.26–1.12 (4 H, m), 0.88 (3 H, d, *J* 10.1) and 0.87 (3 H, d, *J* 10.4); δ_C(100 MHz) 210.8 (s), 130.6 (d), 127.8 (d), 49.02 (t), 41.5 (t), 32.6 (t), 31.1 (d), 28.9 (t), 27.9 (d), 22.6 (t), 22.3 (q) and 21.0 (t); *m/z* 194 (M^+), 123 ($M^+ - C_5H_{11}$) and 81 (Found: M^+, 194.1667. $C_{13}H_{22}O$ requires *M*, 194.1671).

1-Cyclopent-2-enylpropan-2-one 8. Yield 71%; ν_{max}/cm^{-1} 2951, 1710 and 1362; δ_H(270 MHz) 5.74 (1 H, dq, *J* 5.7, 2.2), 5.62 (1 H, m), 3.10 (1 H, m), 2.52 (1 H, dd, *J* 16.5, 6.8), 2.42 (1 H, dd, *J* 16.5, 7.9), 2.36–2.05 (2 H, m), 2.13 (3 H, s) and 1.44–1.13 (2 H, m); δ_C(100 MHz) 209.0 (s), 133.9 (d), 131.2 (d), 49.9 (t), 40.9 (d), 31.7 (t), 30.2 (q) and 29.8 (t); *m/z* 124 (M^+), 123 ($M^+ - 1$), 108 ($M^+ - O$) and 67 (Found: M^+, 124.0873. $C_8H_{12}O$ requires *M*, 124.0888).

1-Cyclopent-2-enyl-5-methylhexan-2-one 9. Yield 64%; ν_{max}/cm^{-1} 2955, 1715, 1467, 1366 and 719; δ_H(400 MHz) 5.74 (1 H, m), 5.62 (1 H, m), 3.09 (1 H, m), 2.49 (1 H, dd, *J* 16.1, 6.8), 2.41 (1 H, dd, *J* 14.7, 7.8), 2.32 (1 H, m), 2.12 (1 H, m), 1.56–1.50 (4 H, m), 1.48–1.23 (3 H, m) and 0.88 (6 H, d, *J* 6.4); δ_C(100 MHz) 210.9 (s), 134.0 (d), 131.0 (d), 48.9 (t), 41.1 (d), 32.6 (t), 31.8 (t), 29.9 (t), 27.7 (t), 22.6 (d) and 22.3 (q); *m/z* 180 (M^+), 109 ($M^+ - C_5H_{11}$), 81 and 67 (Found: M^+, 180.1490. $C_{12}H_{20}O$ requires M, 180.1514).

General epoxidation procedures

With MCPBA. A stirred solution of the alkene (0.34 mmol) in a mixture of CH_2Cl_2 (1 cm^3) and saturated aqueous sodium hydrogen carbonate (1 cm^3) was treated portionwise with MCPBA (50%; 0.68 mmol) under nitrogen. When reaction was complete, water (4 cm^3) was added, followed by solid Na_2SO_3 (until no more O_2^{2-} was present as indicated by Merck semi-quantitative peroxide papers). The mixture was diluted with ether and the organic layer separated, washed successively with saturated aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4) and evaporated to give the crude product.

(1R*,2S*,3R*)-1-(2,3-*Epoxycyclohexyl*)*propan*-2-*one* **4a**. Reaction of alkene **3** with MCPBA by the general procedure above, followed by flash chromatography (20% EtOAc–petrol) afforded the epoxide **4a** (61%) as a colourless oil; ν_{max}/cm^{-1} 2935, 1715, 1441, 1363, 1258, 1180 and 860; δ_H(270 MHz) 3.14 (1 H, dt, *J* 4.0, 0.7), 3.08 (1 H, dd, *J* 4.0, 2.3), 2.70 (1 H, m), 2.50–2.30 (2 H, m), 2.10 (3 H, s) and 1.90–1.00 (6 H, m); δ_C(67.5 MHz) 210 (s), 55.1 (d), 53.5 (d), 46.7 (t), 30.5 (d), 30.1 (q), 25.0 (t), 23.5 (t) and 19.3 (t); *m/z* (CI) 155 (MH^+), 137 (M – OH) and 97 (Found: MH^+, 154.0991. $C_9H_{14}O_2$ requires MH, 154.0994).

(1R*,2S*,3R*)-1-(2,3-*Epoxycyclohexyl*)-5-*methylhexan*-2-*one* **10a**. Reaction of alkene **7** with MCPBA by the general procedure above afforded a *ca.* 4:1 mixture of **10a** and **10c** according to ^1H NMR analysis of the crude reaction mixture (peaks for **10c** at *ca.* δ 3.6). Flash chromatography (20% EtOAc–petrol) afforded the epoxide **10a** (45%) as a colourless oil; ν_{max}/cm^{-1} 2920 and 1700; δ_H(400 MHz) 3.17 (1 H, m), 3.10 (1 H, m), 2.71 (1 H, dd, *J* 19.1, 9.3), 2.46–2.35 (2 H, m), 1.90–1.75 (2 H, m), 1.49 (1 H, m), 1.08 (1 H, m), 0.89 (3 H, s) and 0.87 (3 H, s); δ_C(100 MHz) 210.5, 55.3, 53.3, 45.8, 41.6, 32.6, 30.2, 27.7, 25.1, 23.6, 22.3 and 19.4; *m/z* 210 (M^+), 167, 139, 97, 81 and 67 (Found: M^+, 210.1665. $C_{13}H_{22}O_2$ requires *M*, 210.1619).

(1R*,2S*,3R*)-1-(2,3-*Epoxycyclopentyl*)*propan*-2-*one* **11a**. Reaction of alkene **8** with MCPBA by the general procedure above afforded a 5:1 mixture of **11a** and **11b** according to ^1H NMR analysis of the crude mixture (epoxide peaks for **11b** at δ 3.43 and 3.29). Flash chromatography (20% EtOAc–petrol) afforded the epoxide **11a** (83%) as a colourless oil; ν_{max}/cm^{-1} 2960, 1710 and 1350; δ_H(400 MHz) 3.44 (2 H, s), 2.72 (1 H, dd, *J* 18.0, 7.9), 2.58 (1 H, dd, *J* 17.7, 6.1), 2.37 (1 H, m), 2.16 (3 H, s), 2.01 (1 H, m), 1.74–1.55 (2 H, m) and 0.94 (1 H, m); δ_C(100 MHz) 208.0 (s), 59.3 (d), 57.3 (d), 44.8 (t), 35.1 (d), 30.3 (t), 27.3 (q) and 24.6 (t); *m/z* 140 (M^+), 122 ($M^+ - H_2O$) and 83 (Found: M^+, 140.0847. $C_8H_{12}O_2$ requires *M*, 140.0837).

(1R*,2S*,3R*)-1-(2,3-*Epoxycyclopentyl*)]-5-*methylhexan*-2-*one* **12a** *and its* anti-*isomer* **12b**. Reaction of alkene **9** with MCPBA by the general procedure above afforded a 9:2 mixture of **12a** and **12b** according to ^1H NMR analysis of the crude product mixture. Flash chromatography (20% EtOAc–petrol) afforded the epoxides **12a** (78%) and **12b** (2%), as colourless oils. The discrepancy between the crude and isolated ratios of these compounds is due to their volatility. Less polar, **12a**; ν_{max}/cm^{-1} 2956, 1711, 1266, 853 and 736; δ_H(400 MHz) 3.43 (1 H, m), 3.42 (1 H, m), 2.68 (1 H, dd, *J* 17.6, 7.8), 2.55 (1 H, dd, *J* 17.6, 6.3), 2.45–2.16 (4 H, m), 1.99 (1 H, m), 1.72–1.44 (5 H, m), 0.88 (1 H, s) and 0.77 (1 H, s); δ_C(100 MHz) 210.6 (s), 59.3 (d), 57.3 (d), 43.8 (t), 41.2 (t), 35.1 (d), 32.6 (t), 27.7 (d), 27.3 (t),

24.6 (t) and 22.3 (q); *m/z* 196 (M^+), 140 and 83 (Found: M^+, 196.1507. $C_{12}H_{20}O_2$ requires *M*, 196.1463).

More polar, **12b**; δ_H(400 MHz) 3.45 (1 H, d, *J* 2.4), 3.30 (1 H, d, *J* 2.4), 2.69 (1 H, m), 2.41 (2 H, t, *J* 7.3), 2.35 (1 H, d, *J* 15.6), 2.33 (1 H, d, *J* 17.1), 1.96 (1 H, m), 1.61–1.44 (5 H, m), 1.20 (1 H, m) and 0.89 (6 H, d, *J* 6.4); δ_C(100 MHz) 208.0 (s), 59.8 (d), 56.6 (d), 43.8 (t), 41.1 (t), 34.3 (d), 32.6 (t), 27.7 (d), 25.2 (t), 24.5 (t) and 22.3 (q).

With MMPP: epoxidation of 3 and 8. A stirred solution of alkene (0.3 mmol) in ethanol (3 cm^3) was treated portionwise with MMPP (0.3 mmol) under nitrogen and the mixture stirred overnight. The mixture was diluted with H_2O and extracted three times with CH_2Cl_2. The combined organics were washed successively with saturated aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated.

Epoxidation of **3** afforded exclusively **4a** (73%), identical by ^1H and ^{13}C NMR to the sample prepared using MCPBA.

Epoxidation of **8** produced a 7:1 ratio of **11a**:**11b** by ^1H NMR analysis of the crude mixture. Flash chromatography (20% EtOAc–petrol) provided **11a** (50%), identical by ^1H and ^{13}C NMR to the sample prepared using MCPBA.

With $Mo(CO)_6$–TBHP: epoxidation of 3 and 8. *tert*-Butyl hydroperoxide (3 mol dm^{-3} solution in 2,2,4-trimethylpentane; 0.3 cm^3, 0.9 mmol) and hexacarbonylmolybdenum (10 mg, 0.036 mmol, 0.1 equiv.) were added to a stirred solution of alkene (0.36 mmol) in benzene (3 cm^3). The mixture was heated at reflux until the reaction was complete (TLC). The mixture was then cooled and water was added. The organics were separated and the aqueous layer was extracted three times with ether. The combined organic extracts were washed with saturated aqueous sodium sulfite, dried ($MgSO_4$) and evaporated to give the crude product.

Epoxidation of alkene **3** by the above procedure resulted in a 3:2 mixture of epoxide **4a** and ketal **14** according to analysis of the crude ^1H NMR. Flash chromatography (20% EtOAc–petrol) afforded epoxide **4a** (30%) and ketal **14** (18%). Less polar **4a**, identical by ^1H NMR to the sample obtained by MCPBA epoxidation.

More polar **14**; ν_{max}/cm^{-1} 3420, 2978, 2934, 1456, 1362, 1190, 1119, 1007 and 870; δ_H(400 MHz) 3.94 (1 H, t, *J* 6.4), 3.73 (1 H, m), 2.61 (1 H, m), 2.05 (1 H, dd, *J* 13.4, 7.6), 1.81–1.58 (2 H, m), 1.56 (1 H, s), 1.53–1.25 (5 H, m) and 1.24 (9 H, s); δ_C(100 MHz) 110.7 (s), 83.7 (d), 79.5 (s), 70.7 (d), 40.7 (t), 36.3 (d), 29.5 (t), 26.6 (q), 26.3 (t), 24.6 (q) and 18.9 (t); *m/z* 155 ($M^+ - Bu^tO$), 137 ($M^+ - Bu^tOH - H_2O$), 73 (Bu^tO) and 43 (CH_3CO) (Found: $M^+ - Bu^tO$, 155.1050. $C_9H_{15}O_2$ requires $M - Bu^tO$, 155.1072).

Epoxidation of alkene **8** by the above procedure resulted in a 3:2 mixture of epoxides **11a**:**11b** according to analysis of the crude ^1H NMR. Flash chromatography (20% EtOAc–petrol) afforded **11a** (25%) and **11b** (16%), identical by ^1H NMR to the samples obtained by MCPBA epoxidation.

Epoxidation of 3 with dimethyldioxirane: preparation of 4b and 4c. Dimethyldioxirane[22] (*ca.* 0.1 mol dm^{-3} solution in acetone; 0.5 cm^3, 0.05 mmol) was added to a solution of the ketone **3** (6 mg, 0.04 mmol) in CH_2Cl_2 (1 cm^3). After 2 min the solvent was evaporated to give a film which was analysed by ^1H NMR and then subjected to flash chromatography (20% EtOAc–petrol) on neutralised silica. When the dimethyldioxirane solution had been dried with anhydrous potassium carbonate and stored over 4 Å molecular sieves, the crude ^1H NMR showed a 1:1 mixture of *syn*-epoxide **4a** and diol **4c**. Flash chromatography yielded epoxide **4a** (3 mg, 50%) and diol **4c** (3 mg, 50%). Less polar, epoxide **4a**, identical by ^1H NMR to the sample prepared by MCPBA epoxidation of **3**.

More polar, diol **4c**; ν_{max}/cm^{-1} 3397 and 1703; δ_H(400 MHz) 3.59–3.52 (2 H, m), 2.79 (1 H, dd, *J* 16.8, 6.4), 2.63–2.57 (2 H, m), 2.34 (1 H, dd, *J* 17.1, 6.7), 2.18 (3 H, s), 1.94 (1 H, m) and 1.63–1.30 (4 H, m); δ_C(100 MHz) 209.5, 75.3, 70.7, 42.6, 34.4, 31.6, 30.5, 28.5 and 19.5; *m/z* 172 (M^+), 154 ($M - H_2O$), 114 and 96 (Found: M^+, 172.1119. $C_9H_{16}O_3$ requires *M*, 172.1099).

When the dimethyldioxirane solution had been dried only with anhydrous potassium carbonate, the crude ^1H NMR showed a 2.5:1 mixture of *syn*-epoxide **4a** and *anti*-epoxide **4b**. Flash chromatography yielded epoxides **4a** (30%) and **4b** (11%). Less polar, epoxide **4a**, identical by ^1H NMR to the sample prepared by MCPBA epoxidation of **3**.

More polar, *anti*-epoxide **4b**; δ_H(400 MHz) 3.15 (1 H, pent, *J* 1.8), 2.84 (1 H, d, *J* 3.7), 2.51 (2 H, dd, *J* 15.0, 7.0), 2.37 (1 H, m), 2.18 (3 H, s), 2.05 (1 H, dt, *J* 15.0, 4.3), 1.70–1.60 (2 H, m), 1.39–1.24 (2 H, m) and 0.77 (1 H, m); δ_C(100 MHz) 207.5, 56.0, 52.6, 47.5, 30.4, 30.2, 26.7, 24.4 and 17.0; *m/z* 154 (M^+), 97, 70, 58 and 43 (Found: M^+, 154.1005. $C_9H_{14}O_2$ requires *M*, 154.0994).

Correlation experiments to prove *syn*-stereochemistry: general procedure for the reaction of ketones 4a, 10a and 11a with alkyllithiums

The alkyllithium reagent [1 equiv. in ether (methyllithium) or petrol (isopentyllithium[33])] was added to a solution of the appropriate ketone (0.13 mmol) in THF (0.25 cm^3) at 0 °C under nitrogen. After one hour the reaction was allowed to warm to room temperature. Saturated aqueous sodium hydrogen carbonate was added to the reaction and the aqueous layer was extracted with CH_2Cl_2. The organics were separated, dried and the solvent evaporated. The residue was flash chromatographed on neutralised silica to give the alcohols in fair yields.

Tertiary alcohol 6, derived from 4a and methyllithium. Yield 45%; ν_{max}/cm^{-1} 3400; δ_H(270 MHz) 3.24 (1 H, t, *J* 3.3), 3.19 (1 H, dt, *J* 1.5, 3.7), 2.06 (1 H, m), 1.87–1.80 (3 H, m), 1.51–1.36 (3 H, m), 1.29 (3 H, s) and 1.28 (3 H, s); δ_C(67.5 MHz) 56.5, 54.0, 46.9, 30.6, 29.4, 27.4, 23.7 and 19.6; *m/z* (CI) 171 (MH^+), 153 ($M - H_2O$) and 97.

Tertiary alcohol derived from 10a and isopentyllithium. Yield 45%; ν_{max}/cm^{-1} 3424, 2934 and 911; δ_H(400 MHz) 3.13–3.06 (2 H, m), 1.92 (1 H, m), 1.73–1.64 (2 H, m), 1.50 (1 H, s), 1.71–0.97 (15 H, m), 0.78 (6 H, d, *J* 6.4) and 0.77 (6 H, d, *J* 6.9); δ_C(100 MHz) 74.8 (s), 56.8 (d), 54.0 (d), 43.0 (t), 42.9 (t), 37.8 (t), 36.6 (t), 32.8 (t), 32.5 (t), 30.4 (d), 28.6 (d), 27.5 (t), 23.8 (t), 22.7 (q) and 19.9 (t); *m/z* (FAB) 283 (MH^+), 265 ($M - OH$), 211 and 81.

Tertiary alcohol derived from 11a and methyllithium. Yield 33%; ν_{max}/cm^{-1} 3430; δ_H(400 MHz) 3.50 (1 H, s), 3.44 (1 H, s), 2.16 (1 H, m), 2.01 (1 H, dd, *J* 13.2, 7.8), 1.82 (1 H, dd, *J* 14.2, 7.3), 1.73–1.55 (4 H, m), 1.29 (3 H, s), 1.27 (3 H, s) and 0.98 (1 H, m); δ_C(100 MHz) 71.0 (s), 60.6 (d), 57.4 (d), 44.7 (t), 36.0 (d), 30.6 (q), 29.4 (q), 27.4 (t) and 26.5 (t); *m/z* (CI) 157 (MH^+), 139 ($M - OH$), 121, 83 and 73.

Preparation of the tertiary alcohols from the appropriate epoxy methyl ester and alkyllithium

The ester **5** was prepared as described by Kocovsky.[8] The corresponding 5-membered ring methyl ester was prepared in the same way.

The alkyllithium (1 equiv.) was added to a solution of the appropriate ester (0.13 mmol) in THF (0.25 cm^3) under a nitrogen atmosphere at −78 °C. After one hour the reaction was allowed to warm to room temperature. Saturated aqueous sodium hydrogen carbonate was added to the reaction and the aqueous layer was extracted with CH_2Cl_2. The organics were separated, dried and the solvent evaporated. The reaction gave good yields of tertiary alcohol, identical in all cases by ^1H and ^{13}C NMR to those prepared by addition of alkyllithiums to the ketones.

Ketone 3, ^{18}O labelled. Trimethyl orthoformate (1 cm^3, 1 mmol) was added to a solution of the ketone **3** (10 mg, 0.07 mmol) in methanol (1 cm^3) with several crystals of toluene-*p*-sulfonic acid and flame dried 4 Å molecular sieves under nitrogen. The reaction was heated to reflux for 150 min. The

mixture was then diluted with saturated aqueous sodium hydrogen carbonate and extracted three times with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and the solvents evaporated to give the crude ketal (13 mg, 98%), as an oil; δ_H(270 MHz) 5.69 (2 H, s), 3.20 (6 H, s), 2.40–0.80 (9 H, m) and 1.30 (3 H, s).

^{18}O Labelled water (Aldrich, 95 atom% ^{18}O; 0.147 cm^3, 7 mmol) and 98% sulfuric acid (1 drop from a small capillary tube) were added to a solution of the crude dimethyl ketal (143 mg, 0.7 mmol) in THF (2.5 cm^3) under nitrogen. After 1 h triethylamine (1 cm^3, 7 mmol) was added and the mixture stirred for a further 5 min before being subjected to flash chromatography on neutralised silica (10% EtOAc–petrol), to yield ^{18}O labelled ketone (83 mg, 76%). Evidence for label incorporation was provided by mass spectrometry (*m/z* 140) and ^{13}C NMR analysis of a *ca.* 1:1 mixture of this labelled product with unlabelled ketone (two carbonyl resonances observed, at δ 208.399 and 208.344).

(*Z*)-4-Methylnon-5-en-2-one 16. Butyllithium (2.5 mol dm^{-3} solution in hexanes; 26.5 cm^3, 66.25 mmol) was added to pent-1-yne (5 cm^3, 62 mmol) in ether (22 cm^3) at −78 °C under nitrogen. The mixture was stirred for 15 min and then added to a suspension of CuI (12.5 g, 66 mmol) in ether (160 cm^3), also under nitrogen at −78 °C. After 40 min iodotrimethylsilane (11 cm^3, 77 mmol) was added to the deep brown mixture and after a further 5 min pent-3-en-2-one (3.5 cm^3, 35.6 mmol) in ether (20 cm^3) was also introduced into the reaction. The mixture was stirred at −78 °C for a further 6 h then allowed to warm to room temperature whilst stirring overnight. Pyridine (16 cm^3) was added to complex out the copper salts followed after 3 h by HCl (2 mol dm^{-3}; 165 cm^3). The resulting suspension was filtered over Celite, the organics were separated and the aqueous layer extracted twice with ether. The combined organics were washed successively with HCl (2 mol dm^{-3}), saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and the solvent evaporated. Flash chromatography of the residue (17% EtOAc–petrol) afforded alkyne **15** (700 mg, 10%), as a very volatile oil; δ_H(270 MHz) 2.90 (1 H, t sextet, *J* 7.0, 2.2), 2.61 (1 H, dd, *J* 16.1, 7.3), 2.44 (1 H, dd, *J* 16.1, 7.0), 2.15 (3 H, s), 2.08 (2 H, dt, *J* 7.1, 2.2), 1.46 (2 H, sextet, *J* 7.3), 1.14 (3 H, d, *J* 7.0) and 0.93 (3 H, t, *J* 7.3); δ_C(67.5 MHz) 207.0, 83.4, 80.7, 50.9, 30.4, 22.4, 21.9, 21.3, 20.6 and 13.3.

A solution of **15** (670 mg, 4.40 mmol) in dry hexane (100 cm^3) containing quinoline (24 cm^3) was charged with Lindlar catalyst (134 mg) and hydrogenated at 1 atm for 20 min. The reaction was then filtered on a Celite–sodium sulfate pad, washing through with ether (400 cm^3). The filtrate was evaporated under reduced pressure to give a yellow liquid which was pre-adsorbed onto silica gel (Merck 9385) prior to purification by flash chromatography (10% ether–petrol) to afford **16** (621 mg, 92%), as a pale yellow, sweet-smelling liquid; ν_{max}/cm^{-1} 2959, 1716, 1456, 1359, 1167 and 734; δ_H(400 MHz) 5.31 (1 H, dt, *J* 10.7, 7.3), 5.15 (1 H, br t, *J* 10.0), 3.01 (1 H, m), 2.37 (2 H, d, *J* 7.0), 2.11 (3 H, s), 2.08–1.98 (2 H, m), 1.42–1.30 (2 H, m), 0.97 (3 H, d, *J* 6.7) and 0.90 (3 H, t, *J* 7.3); δ_C(100 MHz) 208.3 (s), 134.2 (d), 129.2 (d), 51.1 (t), 30.5 (q), 29.4 (t), 28.2 (d), 22.8 (t), 21.1 (q) and 13.7 (q); *m/z* 154 (M^+), 139 ($M^+ - CH_3$), 111, 69 and 43 (Found: M^+, 154.1374. $C_{10}H_{18}O$ requires *M*, 154.1358).

(*E*)-3-Methyloct-4-enoic acid. Propylmagnesium chloride (2 mol dm^{-3} solution in ether; 50 cm^3, 100 mmol) was added to a stirred solution of *trans*-but-2-enal (8 cm^3, 100 mmol) in ether (50 cm^3) under nitrogen at 0 °C. After the addition the reaction was allowed to warm to room temp. When completed the reaction was diluted with HCl (2 mol dm^{-3}; 30 cm^3) and water (50 cm^3). The organics were separated and the aqueous layer extracted three times with ether. The combined organics were washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$) and the solvent evaporated to yield crude hept-2-en-4-ol (8.98 g, 78%). A solution of this crude hept-2-en-4-ol (8.98 g, 79 mmol) and propionic acid (1 cm^3) in triethyl orthoacetate (200 cm^3) was heated at 140 °C for 8 h. The reaction was allowed to cool to room temperature and was then diluted with ethyl acetate and washed twice with HCl (2 mol dm^{-3}), saturated aqueous sodium hydrogen carbonate and brine. The organic layer was dried and the solvent evaporated to yield crude ethyl (*E*)-3-methyloct-4-enoate (14.55 g, 100%). Sodium hydroxide (1 mol dm^{-3} aqueous solution; 80 cm^3) was added to this crude ethyl ester (14.55 g, 79 mmol) in methanol (80 cm^3) and the mixture stirred rapidly for 24 h. The reaction was then diluted with CH_2Cl_2 and water, the organic layer separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organics were discarded. The aqueous layer was acidified (2 mol dm^{-3} HCl) and extracted three times with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and the solvent evaporated to yield (E)-3-*methyloct*-4-*enoic acid* (9.29 g, 75%); ν_{max}/cm^{-1} 2929, 1710, 1410, 1294 and 969; δ_H(270 MHz) 5.48–5.30 (2 H, m), 2.63 (1 H, sept, *J* 7.0), 2.4 (2 H, dd, *J* 6.3, 0.9), 1.97 (2 H, q, *J* 7.0), 1.36 (2 H, hex, *J* 7.3), 1.06 (3 H, d, *J* 6.8) and 0.88 (3 H, t, *J* 7.3); δ_C(67.5 MHz) 179.1 (s), 133.9 (d), 129.7 (d), 41.8 (t), 34.5 (t), 33.4 (d), 22.5 (t), 20.4 (q) and 13.5 (q); *m/z* 156 (M^+), 138 ($M^+ - H_2O$), 127 ($M^+ - CO$), 113 ($M^+ - CO_2$) and 81 (Found: M^+, 156.1159. $C_9H_{16}O_2$ requires *M*, 156.1150).

(*E*)-4-Methylnon-5-en-2-one 17. Following the general procedure described earlier (for the preparation of **3**, **7**, **8** and **9**), (*E*)-3-methyloct-4-enoic acid was treated with methyllithium to afford the ketone **17** (40%); ν_{max}/cm^{-1} 2959, 1716, 1456, 1362 and 969; δ_H(400 MHz) 5.40 (1 H, dt, *J* 15.3, 6.4), 5.30 (1 H, dd, *J* 15.5, 6.9), 2.65 (1 H, septet, *J* 7.0), 2.43 (1 H, dd, *J* 15.6, 7.0), 2.34 (1 H, dd, *J* 15.6, 7.0), 2.11 (3 H, s), 1.93 (2 H, q, *J* 7.3), 1.34 (2 H, sextet, *J* 7.3), 0.99 (3 H, d, *J* 6.7) and 0.86 (3 H, t, *J* 7.3); δ_C(100 MHz) 208.5 (s), 134.4 (d), 129.1 (d), 51.1 (t), 34.5 (t), 32.8 (d), 22.5 (t), 20.1 (q) and 13.5 (q); *m/z* 154 (M^+), 139 ($M^+ - CH_3$), 111, 97, 81, 69 and 43 (Found: M^+, 154.1353. $C_{10}H_{18}O$ requires *M*, 154.1368).

(*Z*)-5-Methyldec-6-en-2-one 19. Sodium hexamethyldisilazide (1 mol dm^{-3} solution in THF; 39 cm^3, 39 mmol) was added to a stirred suspension of butyl(triphenyl)phosphonium bromide (15.56 g, 39 mmol) in toluene (250 cm^3), under nitrogen. The deep red mixture was cooled to −78 °C and a solution of aldehyde **18**[28] (5 g, 39 mmol) in toluene (150 cm^3) was added. After 30 min the reaction was warmed to room temperature and stirred for another 30 min before being quenched with water. The organic layer was separated and the aqueous layer was extracted with ether. The combined organics were washed with water, dried ($MgSO_4$) and the solvent evaporated. Flash chromatography of the residue (5% EtOAc–petrol) afforded **19** (5.1 g, 85%); ν_{max}/cm^{-1} 2958, 1718, 1457 and 1165; δ_H(400 MHz) 5.33 (1 H, dt, *J* 11.0, 7.3), 5.06 (1 H, tt, *J* 10.5, 1.5), 2.43–2.36 (3 H, m), 2.11 (3 H, s), 2.00–1.93 (2 H, m), 1.63 (1 H, m), 1.44–1.32 (3 H, m), 0.94 (3 H, d, *J* 6.4) and 0.89 (3 H, t, *J* 7.3); δ_C(100 MHz) 209.3 (s), 135.3 (d), 129.3 (d), 41.8 (d), 31.7 (t), 31.1 (q), 29.9 (t), 29.5 (t), 22.9 (t), 21.4 (q) and 13.8 (q); *m/z* 168 (M^+), 150 ($M^+ - H_2O$), 125, 110, 95, 81 and 43 (Found: M^+, 168.1475. $C_{11}H_{20}O$ requires *M*, 168.1514).

(*Z*)-5-Methyldec-6-enoic acid 22. Sodium hexamethyldisilazide (1 mol dm^{-3} solution in THF; 15.5 cm^3, 15.5 mmol) was added to a stirred suspension of butyl(triphenyl)phosphonium bromide (6.2 g, 15.5 mmol) in toluene (90 cm^3), under nitrogen. The deep red mixture was cooled to −78 °C, and a solution of aldehyde **21**[30] (1.1 g, 7.75 mmol) in toluene (60 cm^3) was added. After 30 min the reaction was warmed to room temperature and stirred for another 30 min before being quenched with water. The organic layer was separated and the aqueous layer extracted with ether. The combined organic fractions were discarded. The aqueous layer was acidified with HCl (2 mol dm^{-3}) and extracted three times with ether. The combined organics were dried ($MgSO_4$) and the solvent evaporated. Flash chromatography of the residue (40% EtOAc–petrol +

1% AcOH) afforded acid **22** (1.12 g, 80%); ν_{max}/cm^{-1} 3427, 1709, 1411 and 909; δ_H(400 MHz) 5.32 (1 H, dt, *J* 11.0, 7.3), 5.10 (1 H, tt, *J* 11.0, 1.5), 2.43 (1 H, m), 2.32 (2 H, t, *J* 7.5), 2.02–1.96 (2 H, m), 1.65–1.52 (2 H, m), 1.41–0.95 (4 H, m), 0.93 (3 H, d, *J* 6.4) and 0.89 (3 H, t, *J* 7.3); δ_C(100 MHz) 180.3 (s), 135.7 (d), 128.8 (d), 36.8 (t), 34.2 (t), 31.4 (d), 29.5 (t), 22.9 (t), 22.7 (t), 21.3 (q) and 13.8 (q); *m*/*z* 184 (M^+), 141, 128, 110, 97 and 81 (Found: M^+, 184.1461. $C_{11}H_{20}O_2$ requires *M*, 184.1463).

(*Z*)-6-Methylundec-7-en-2-one 23. Following the general procedure described earlier (for the preparation of **3**, **7**, **8** and **9**), treatment of acid **22** with methyllithium afforded ketone **23** (61%); ν_{max}/cm^{-1} 2957, 1719, 1460, 1358 and 1164; δ_H(400 MHz) 5.27 (1 H, dtt, *J* 10.9, 7.3, 0.6), 5.07 (1 H, tt, *J* 11.0, 1.5), 2.43–2.38 (1 H, m), 2.35 (2 H, t, *J* 7.0), 2.08 (3 H, s), 1.99–1.92 (2 H, m), 1.55–1.44 (2 H, m), 1.37–1.21 (2 H, m), 1.16–1.07 (1 H, m), 0.89 (3 H, d, *J* 6.4) and 0.86 (3 H, t, *J* 7.3); δ_C(100 MHz) 209.1 (s), 135.8 (d), 128.6 (d), 43.8 (t), 36.9 (t), 31.4 (d), 29.7 (q), 29.5 (t), 22.9 (t), 21.8 (t), 21.2 (q) and 13.7 (q); *m*/*z* 182 (M^+), 164 ($M^+ - H_2O$), 124, 95, 81 and 43 (Found: M^+, 182.1703. $C_{12}H_{22}O$ requires *M*, 182.1671).

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