Asymmetric hydrolysis of pro-chiral 3,3-disubstituted 2,4-diacetoxycyclohexa-1,4-dienes

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Asymmetric enzymatic hydrolysis of pro-chiral 3,3-disubstituted 2,4-diacetoxycyclohexa-1,4-dienes 2 affords in high yields optically pure 2,2-disubstituted 3-acetoxycyclohex-3-enones 1 (>98% ee). Under mild conditions *Candida cylindracea* **lipase (enzyme/substrate ratio = 2%) hydrolyses specifically the** *pro-S* **enol ester function of the pro-chiral starting material 2.**

Introduction

The ability of enzymes to react as specific and chiral catalysts covers a well defined area of organic research to which several books[1] and reviews[2] are devoted. These enzymatic procedures are now routinely used in organic synthesis. Enzymes are extremely versatile catalysts allowing chemoselective transformations of multifunctional compounds under mild conditions. Moreover, these experimental conditions (room temperature, pH ~ 7) minimise side-reactions such as racemization, isomerization, rearrangements or decomposition. Since enzymes provide a chiral environment, asymmetric reactions can be achieved very easily with good results. This is the reason why enzymes and microorganisms are now valuable catalysts for asymmetric synthesis. Hydrolytic enzymes such as lipases or esterases are among the most useful enzymes for enantioselective reactions.

While hydrolysis of classical esters has been widely described in the literature, there are few reports of the hydrolysis of enol esters. Ohta *et al.*[3] reported for the first time the kinetic resolution of enol acetates by enzymatic hydrolysis. They also developed a procedure for asymmetric protonation of an enol ester using microorganisms. However this last reaction suffers from two major limitations: first, a large amount of enzyme was required which results in a somewhat difficult work-up and second, the stereoselectivities obtained are in the range of 70–90% enantiomeric excess (ee). In this paper, we report the synthesis of the optically pure keto acetates **1** by enzymatic hydrolysis of the pro-chiral dienol diacetates **2** (Fig. 1). This hydrolysis uses the ability of enzymes to distinguish enantiotopic homomorphic groups linked to a quaternary prostereogenic centre in a pro-chiral substrate as shown in our preliminary note.[4]

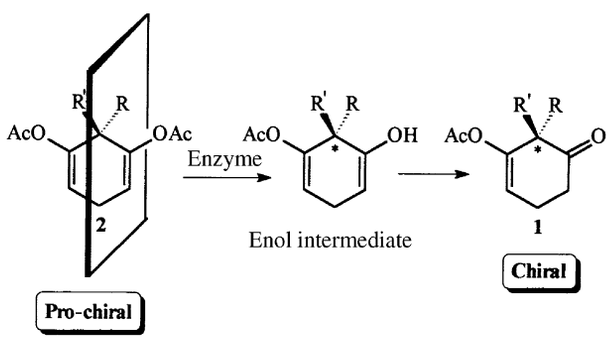
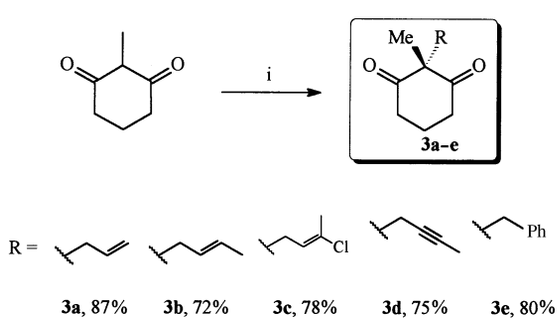
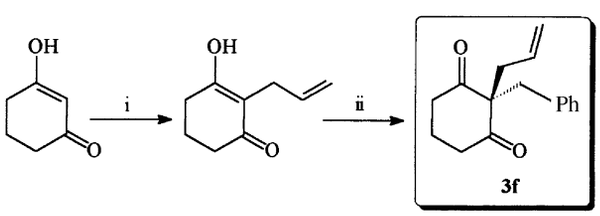


Fig. 1



Scheme 1 *Reagents:* i, NaOH, then RX (excess), room temp. (RT), 48 h (72–87%)



Scheme 2 *Reagents:* i, H_2O, Triton B (40% in MeOH), allyl bromide (69%); ii, H_2O, Triton B (40% in MeOH), benzyl bromide (55%)

Results and discussion

Synthesis

2,2-Disubstituted 1,3-diketones 3. The 1,3-diketones **3a–e** are easily obtained in high yield (Scheme 1) by alkylation of the commercially available 2-methylcyclohexane-1,3-dione with an alkyl halide (**3a**, **3d** and **3e** or **3b** and **3c**) in a basic aqueous medium. We synthesised the diketone **3f** substituted by two hindered unsaturated side-chains according to the procedure of T. Rajamannar *et al.*[5] Treatment of cyclohexane-1,3-dione first with allyl bromide and second with benzyl bromide afforded the desired ketone **3f** in satisfactory yield (Scheme 2).

Dienol diacetates 2. To the best of our knowledge no dienol diacetates **2** have been described in the literature. We prepared these compounds according to the synthesis developed by H. House *et al.*[6] for the preparation of mono enol acetate derivatives. By treatment of the 1,3-diketones **3** with acetic anhydride or isopropenyl acetate, we obtained a mixture containing the dienol diacetate **2** (*ca.* 60%), the keto acetate **1** (20–40%) and the starting diketone **3** (5–15%) (Scheme 3). A longer reaction time does not improve the overall yield of compound **2**. Instead, we observed degradation of the mixture and formation of tars. We decided to monitor the acetylation by gas chromatography (GC) and stopped the reaction when 50–60% of the dienol diacetate **2** was formed (Scheme 3). After work-

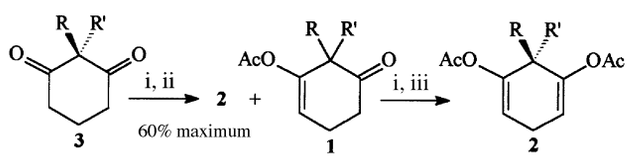
Table 1 Synthesis of the dienol diacetates **2**

Entry	Diacetate **2**	R′	R	Yield (%) from diketone **3**
1	**2a**	Me	$CH_2CH=CH_2$	69
2	**2b**	Me	$CH_2CH=CHCH_3$(*E*)	76
3	**2c**	Me	$CH_2CH=C(Cl)CH_3$(*E*)	36
4	**2d**	Me	$CH_2C\equiv CCH_3$	60
5	**2e**	Me	CH_2Ph	59
6	**2f**	$CH_2CH=CH_2$	CH_2Ph	79

Table 2 Preparation of the keto acetates **1** by asymmetric hydrolysis of the dienol diacetates **2** with *Candida cylindracea* lipase

	Diacetate **2**					Product		
Entry		Enzyme (IU)	*T*/°C	Reaction time	% Conversion	**1**	Yield (%)	Ee (%)
1	**2b**	110	40	24 h	20	**1b**		
2	**2b**	225	40	72 h	92	**1b**	70	>98 [a,b]
3	**2b**	540	40	69 h	96	**1b**	63	>98 [a,b]
4	**2b**	225	45	72 h	93	**1b**	70	>98 [a,b]
5	**2a**	225	24	74 h	95	**1a**	78	>98 [a]
6	**2a**	225	28	23 h	80	**1a**	75	>98 [a]
7	**2a**	225	32	14 h	87	**1a**	74	>98 [a]
8	**2a**	225	35	19 h	98	**1a**	80	>98 [a]
9	**2a**	225	40	14 h	100	**1a**	80	>98 [a]
10	**2c**	225	35	56 h	95	**1c**	73	>98 [a,b]
11	**2d**	360	35	40 h	95	**1d**	75	>98 [a]
12	**2e**	330	40	96 h	90	**1e**	62	>98 [a]
13	**2f**	360	38	10 days	60	**1f**	45	70 [a]

[a] The enantiomeric excess was determined with a chiral NMR shift reagent. [b] The enantiomeric excess was determined by chiral stationary phase GC.



Scheme 3 *Reagents:* i, Ac_2O (10 to 15 equiv.), PTSA, 140 °C, 1 to 3 h; ii, separation of compounds **1** and **2** from compound **3**; iii, purification (see text)

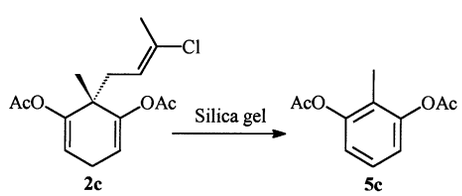


Fig. 2

up and chromatography on silica gel, the mixture of the enol acetates **1** and **2** was heated under the same experimental conditions to give a mixture of *ca*. 90% of the dienol diacetate **2** and 10% of the keto acetate **1**.

We applied different procedures for purification of the diacetates **2** depending on the nature of the substituents. The keto acetate **1** and the dienol diacetate **2** cannot be obtained analytically pure by flash chromatography. Therefore, the mixture of compounds **1** and **2** was treated with $LiBH_4$. The keto acetate **1** was reduced to the corresponding alcohol **4** while unchanged dienol diacetate **2** was easily obtained in a pure form after flash chromatography. This reduction step was used to purify the dienol diacetates **2a–d** and **2f** (Table 1). For compound **2e**, most of the product crystallised during work-up in the organic layer. The remaining diacetate **2e** was separated from **1e** by flash chromatography.

For the synthesis of compound **2c** bearing a chlorovinyl substituent, we observed, during the acetylation step, the formation of a by-product **5c** (Fig. 2). This derivative became the major compound when the reaction time was increased. Its formation results from acid-catalysed aromatisation of the six-membered ring [toluene-*p*-sulfonic acid (PTSA) was used to catalyse the acetylation] and loss of the ethylenic side-chain. Furthermore, flash chromatography of a crude product containing a mixture of compounds **1c**, **2c** and **5c** afforded only the keto acetate **1c** and the aromatic by-product **5c**. The silica gel was sufficient to aromatise the diacetate **2c** into compound **5c**. To prevent degradation of the dienol diacetate, the acetylation was monitored by GC and stopped as soon as a few percent of aromatic contaminant **5c** was detected. Purification by chromatography was thus performed on silica gel treated by an eluent (Et_2O–light petroleum) containing 3% of triethylamine. Under these conditions, we obtained a mixture of the diacetate **2c** and the keto acetate **1c** in an 80:20 ratio which led, after reduction and purification, to the dienol diacetate **2c** (*E* double bond stereochemistry) in 36% yield starting from diketone **3c** (Table 1). The dienol diacetates **2** were obtained in good yields (>60%) except for the chloro dienol diacetate **2c** (Table 1).

Enzymatic hydrolysis

Of the lipases and esterases available we used five enzymes to hydrolyse the dienol diacetates **2a–b** into the corresponding keto acetates. We first observed that *Rhizopus niveus* lipase and Porcine pancreas lipase are not catalysts for hydrolysis of these diacetates. However *Pseudomonas fluorescens* lipase and Hog liver esterase afforded the desired keto acetates but with low enantiomeric excess (ee < 30%). The best results were obtained with *Candida cylindracea* lipase (Fluka), the keto acetates **1a–b** being prepared in high yields (>70%) and with high enantiomeric excesses (>98%). A study with *Candida cylindracea* lipase, indicated that 1 mmol of the diacetate **2b** was hydrolysed under optimal conditions with 225 International Units (6.5 mg) of lipase corresponding to an enzyme/substrate ratio of 2% (Table 2, entry 2). An increase in the amount of enzyme used (5%) failed to improve the rate of hydrolysis (Table 2, entry 3). We observed that the reaction was very slow using a 1% ratio of enzyme/substrate (Table 2, entry 1). The optimum temperature for this enzymatic hydrolysis was in the range 40–45 °C (Table 2, entries 2, 4 and entries 5–9). We have shown that enzymatic hydrolysis with *Candida cylindracea* lipase of the dienol diacetate **2a** at 40 °C in phosphate buffer at pH 7, led to the corresponding (*S*)-keto acetate **1a** in 80% yield and an

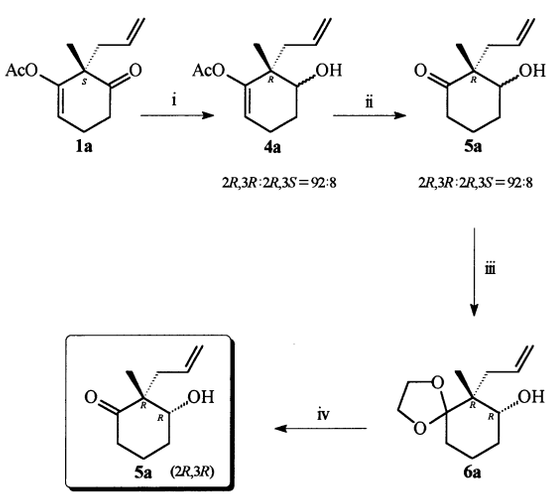
enantiomeric excess (ee) >98%[4] (Table 2, entry 9). Under these conditions, dienol diacetates **2b** and **2c** were hydrolysed into the corresponding optically pure keto acetates **1b** and **1c** (Table 2, entries 2, 10). Hydrolyses on a multigram scale (1–2 g) have also been performed on the dienol diacetates **2a**, **2b** and **2c** with similar results. Moreover, hydrolysis of the diacetate **2a** catalysed by the cheap acetone powder (Sigma) of *Candida cylindracea* (50% ratio enzyme to substrate) afforded the optically pure keto acetate **1a** in a 79% yield after 1 h at 35 °C. The hydrolysis of the diacetate **2a** could be also performed in the presence of an organic solvent (10% THF) or in a biphasic medium (toluene) without modifying the enantiomeric excess value.

The solid compounds (**2d–f**) were supernatant in an aqueous medium and, therefore, very difficult to hydrolyse under the previous conditions. Evaporation using an air flow of a solution of **2d–f** in dichloromethane afforded an oil which could be hydrolysed as previously described. Enzymatic hydrolysis of the dienol diacetates **2d** and **2e** provided the corresponding keto acetates **1d** and **1e** with ees higher than 98% and in good yield (Table 2, entries 11, 12). The hydrolysis of the dienol diacetate **2f** was slow. A 60% conversion was obtained after 10 days of incubation. Moreover, the asymmetric induction was lower (Table 2, entry 13).

The stereoselectivity for the hydrolytic process was always very high for the methyl series (**2a–e**). All the keto acetates were prepared with an ee >98%. The ee value was independent of the nature of the other substituents. However, in the case of compound **2f** with allyl and benzyl groups, the selectivity decreases, presumably because the binding pocket could not distinguish between the two.

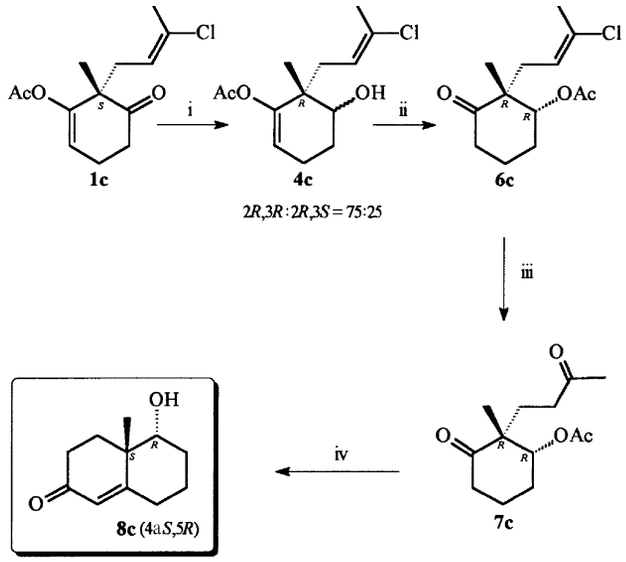
Determination of absolute configuration

The absolute configuration of products **1a** and **1c** was established as follows. The allyl keto acetate **1a** was transformed into the known (2*R*,3*R*)-ketol **5a**[7] in a 40% overall yield (Scheme 4).



Scheme 4 *Reagents:* i, $NaBH_4$, MeOH, −78 °C (93%); ii, MeLi, THF, −20 °C (72%); iii, ethylene glycol, PTSA, then chromatography (75%); iv, HCl (79%)

Treatment of **1a** with sodium borohydride in methanol afforded the hydroxy enol ester **4a** as a mixture of two diastereoisomers (2*R*,3*R*:2*R*,3*S* = 92:8). Using $LiBH_4$ in Et_2O, the diastereoisomeric ratio changed to 73:27 (2*R*,3*R*:2*R*,3*S*).[4] Addition of 3 equiv. of methyllithium to **4a** provided the ketol **5a**. Attempts at chromatographic separation of the two diastereoisomers of **5a** were unsuccessful. However, we observed that the two diastereoisomers were easily separated after protection of the ketone as a ketal (compound **6a**). The 2-methyl and 3-hydroxy groups of the major diastereoisomer of **6a** were shown to have a *trans* configuration by NOE correlation between 2-Me and 3-H (irradiation: 3-H; observed: Me NOE = 7%). Hydrolysis in an acidic medium afforded the ketol **5a**. By comparison with the



Scheme 5 *Reagents:* i, $LiBH_4$, MeOH, Et_2O, −10 °C (98%); ii, NaH, THF, 0 °C, then chromatography (62%); iii, $Hg(OAc)_2$, HCO_2H, RT (76%); iv, MeONa in MeOH, RT (40%)

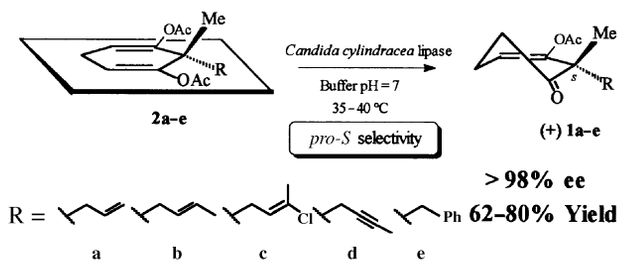


Fig. 3

literature,[7] the absolute configuration (2*R*,3*R*) was assigned to this compound. Following the correlation sequence, we assigned the *S* configuration to the starting keto acetate **1a**. The chloro keto acetate **1c** was transformed into the known bicyclic ketol **8c** (Scheme 5). In the first step, the ketone was reduced by lithium borohydride in diethyl ether to give the alcohol **4c** as a mixture of two diastereoisomers (75:25), treatment of which with sodium hydride provided the keto ester **6c**; deprotonation of the hydroxy group with MeONa afforded a sodium alkoxide which deprotected the enol ester function by intermolecular nucleophilic attack.[8] Thus, in a one-step procedure, we achieved the deprotection of the enol ester as well as the protection of the alcohol moiety. Treatment of compound **6c** with mercury acetate gave the 1,5-diketone **7c**, treatment of which with sodium methoxide induced intramolecular aldolisation to the known ketol **8c**. The relative configuration of **8c** was assigned by comparison of its ^1H and ^{13}C spectral data with literature values[9] whilst its 4*S*,5*R* configuration was established from its $[\alpha]_D$ value. Thus, we assigned the *S* configuration to the keto acetate **1c**.

For the dienol diacetates **2a** and **2c**, *Candida cylindracea* lipase hydrolysed specifically the *pro-S* enol ester function. By analogy, we assigned the same absolute configuration to the other keto acetates.

Conclusion

Optically pure keto acetates **1** were easily synthesised in good yields by enzymatic enantioselective hydrolysis (Fig. 3). Hydrolysis catalysed by *Candida cylindracea* lipase afforded the expected keto acetate **1** with very high ees and *pro-S* selectivity.

The *S* configuration of the quaternary stereogenic centre was assigned for the allyl and chloro keto acetates **1a** and **1c**. We

have also demonstrated the versatility of this methodology. Moreover, only a small amount of enzyme is required (ratio enzyme : substrate = 2%) and the work-up procedure is very easy. Applications of these chirons as useful intermediates in organic synthesis will be published in the near future.

Experimental

General

^{1}H NMR spectra were recorded on a Bruker A. C 200 (200 MHz) spectrometer for $CDCl_3$ solutions unless otherwise noted. *J* Values are given in Hz. ^{13}C NMR spectra were recorded on a Bruker A. C 200 (50 MHz) spectrometer for $CDCl_3$ solutions unless otherwise noted. IR spectra were obtained with a Perkin-Elmer 16 PC FT-IR spectrophotometer. Mass spectra were recorded on a JEOL JMS AX 500 mass spectrophotometer (EI: electronic impact; CI: chemical ionisation with Bu^{t}H). GC analyses were performed on a Hewlett Packard 5890-II gas chromatograph, using an HP-1 (5 m × 0.53 mm × 2.65 μm film) column for GC routine, HP-1 (25 m × 0.25 mm) column for diastereoisomer separation and FS-Hydrodex β-MT (25 m × 0.25 mm) Macherey-Nagel column for enantiomer separation. Flash chromatography was performed with Merck Kieselgel 60 (230–400 mesh ASTM) support, unless otherwise noted, with light petroleum (distillation temp. <60 °C)–diethyl ether mixtures as eluent. The progress of reactions was monitored by GC or by TLC (Et_2O–light petroleum = 1 : 1). Microanalyses were performed by INSA Laboratories, Rouen.

Enantiomeric excess determination

The enantiomeric excess was determined by ^{1}H NMR (200 MHz) spectroscopy, the spectra being recorded in the presence of a chiral NMR shift reagent: tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]praseodymium(III) (**1a**–**f**) or tris[3-(trifluoromethylhydroxymethylene)-(+)camphorato]-europium(III) (**1a**) or by a chiral stationary phase GC (**1b**,**c**).

Halogeno derivatives

1-Bromobut-2-yne.[10] A solution of but-2-yn-1-ol (5 g, 71 mmol) and pyridine (1 cm^3) in dry diethyl ether (20 cm^3) was stirred at RT for 5 min after which phosphorus tribromide (2.4 cm^3, 25 mmol) was added dropwise to it. Stirring was continued for 30 min after which the mixture was refluxed for 2 h; it was then treated with ice. The organic layer was separated, washed with 5% aq. $NaHCO_3$ and brine, dried ($CaCl_2$), filtered and evaporated. Distillation of the residue under reduced pressure gave the bromoacetylenic compound (5.76 g, 61%); δ_H(200 MHz, $CDCl_3$) 1.85 (t, *J* 2.5, 3 H) and 3.87 (q, *J* 2.5, 2 H); δ_C(50 MHz, $CDCl_3$) 3.7, 15.6, 74.3 and 83.5; ν_{max}/cm^{-1} 2320 and 2240; bp (0.8 mmHg) 58 °C.

1-Iodobut-2-ene (*E*/*Z* = 9 : 1). Commercial 1-chlorobut-2-ene (10 g, 0.11 mol) was added at RT to a solution of sodium iodide (50 g, 0.33 mol) in acetonitrile (200 cm^3) and the mixture stirred for 1 h. The suspension was then filtered and the acetonitrile layer was extracted with pentane. Concentration of the extract gave the iodo derivative (15.21 g, 76%); δ_H(200 MHz, $CDCl_3$) 1.61–1.67 (m, 3 H), 3.83–3.92 (m, 2 H) and 5.66–5.74 (m, 2 H); δ_C(50 MHz, $CDCl_3$) 6.8, 17.6, 128.9 and 129.7; *m*/*z* (EI) 38, 43, 55, 58, 127 and 182.

3-Chloro-1-iodobut-2-ene (*E*/*Z* = 9 : 1). To a solution of sodium iodide (50 g, 0.33 mol) in acetonitrile (200 cm^3) was added commercial 1,3-dichlorobut-2-ene (5 g, 40 mmol) and the stirring continued for 1 h. The mixture was filtered and the solution was extracted with pentane; the extract was then concentrated to afford the iodo compound (6.92 g, 80%); δ_H(200 MHz, $CDCl_3$) 1.52 (d, *J* 1.3, 3 H), 3.50 (d, *J* 8.4, 2 H) and 5.15 (tq, *J* 8.4, 1 H); δ_C(50 MHz, $CDCl_3$) 0.4, 26.2, 123.5 and 135.3; ν_{max}/cm^{-1} 1650; *m*/*z* (EI) 53, 89, 92, 127 and 216–218.

Synthesis of diketones

General procedure for alkylation in an alkaline medium. 2-Methylcyclohexane-1,3-dione (11.35 g, 90 mmol) was added to stirred aqueous sodium hydroxide (1 mol dm^{-3}; 90 cm^3, 90 mmol) at RT (room temp.). After 1 h, the halogeno derivative (135 mmol) was added dropwise to the mixture during 10 h. The mixture was then stirred at RT for 48 h after which the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (Et_2O–light petroleum = 20 : 100) to give the desired disubstituted diketone **3**.

2-Methyl-2-(prop-2-enyl)cyclohexane-1,3-dione 3a.[7] Product (13.0 g, 87%) prepared from allyl bromide; δ_H(200 MHz, $CDCl_3$) 1.20 (s, 3 H), 1.75–2.05 (m, 2 H), 2.48 (d, *J* 7.3, 2 H), 2.61 (t, *J* 6.5, 4 H), 4.97–5.07 (m, 2 H) and 5.44–5.65 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 17.2, 18.9, 37.7, 40.9, 64.6, 118.8, 132.0 and 209.3; ν_{max}/cm^{-1} 1730 and 1630 (Found: C, 72.35; H, 8.48. $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%).

2-Methyl-2-(but-2-enyl)cyclohexane-1,3-dione 3b. Product (11.68 g, 72%; *E*/*Z* = 9 : 1) prepared from 1-iodobut-2-ene; δ_H(200 MHz, $CDCl_3$) 1.17 (s, 2.7 H), 1.20 (s, 0.3 H), 1.57–1.60 (dd, *J* 6, *J* 1, 3 H), 1.70–2.10 (m, 2 H), 2.40–2.44 (d, *J* 7, 2 H), 2.55–2.75 (m, 4 H), 5.11–5.20 (m, 1 H) and 5.35–5.60 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 17.2, 17.3, 18.0, 37.4, 40.4, 65.1, 124.3, 129.3 and 209.3; ν_{max}/cm^{-1} 1725 and 1685; *m*/*z* (EI) 55, 109, 124, 152 and 180 (Found: C, 73.71; H, 8.52. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%).

2-Methyl-2-(3-chlorobut-2-enyl)cyclohexane-1,3-dione 3c. Product (15.07 g, 78%; *E*/*Z* 9 : 1) prepared from 3-chloro-1-iodobut-2-ene; δ_H(200 MHz, $CDCl_3$) 1.20 (s, 3 H), 1.75–2.10 (m, 2 H), 2.05 (d, *J* 1.2, 3 H), 2.45–2.80 (m, 6 H) and 5.23 (tq, *J* 7, *J* 1.2, 1 H); δ_C(50 MHz, $CDCl_3$) 17.1, 18.0, 26.1, 35.7, 37.5, 65.0, 119.4, 133.1 and 209.1; ν_{max}/cm^{-1} 1725 and 1690; *m*/*z* (CI) 127, 179 and 215–217 (Found: C, 61.61; H, 6.94. $C_{11}H_{15}ClO_2$ requires C, 61.54; H, 7.04%).

2-Methyl-2-(but-2-ynyl)cyclohexane-1,3-dione 3d. Product (12.03 g, 75%) prepared from 1-bromobut-2-yne; δ_H(200 MHz, $CDCl_3$) 1.20 (s, 3 H), 1.66 (t, *J* 2.5, 3 H), 1.85–1.96 (m, 2 H), 2.51 (q, *J* 2.5, 2 H) and 2.60–2.67 (m, 4 H); δ_C(50 MHz, $CDCl_3$) 2.9, 17.0, 20.7, 25.7, 37.9, 64.0, 74.5, 77.8 and 209.0; ν_{max}/cm^{-1} 2240 and 1700 (Found: C, 73.85; H, 7.93. $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92%); mp 51 °C.

2-Methyl-2-benzylcyclohexane-1,3-dione 3e.[5] Product (15.57 g, 80%) prepared from benzyl bromide; δ_H(200 MHz, $CDCl_3$) 1.26 (s, 3 H), 1.40–1.56 (m, 1 H), 1.63–1.79 (m, 1 H), 2.19–2.34 (m, 2 H), 2.44–2.58 (m, 2 H), 3.09 (s, 2 H), 6.97–7.02 (m, 2 H) and 7.15–7.24 (m, 3 H); δ_C(50 MHz, $CDCl_3$) 16.5, 21.8, 39.0, 43.6, 65.1, 126.8, 128.2, 129.7, 136.5 and 211.0; ν_{max}/cm^{-1} 1720 and 1690; *m*/*z* (EI) 91, 145, 173 and 216 (Found: C, 77.63; H, 7.50. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%); mp 43 °C.

General procedure for alkylation with Triton B

A 40% solution of benzyl(triethyl)ammonium hydroxide (Triton B) in MeOH (4.4 cm^3, 10 mmol) was added to a stirred solution of the diketone (10 mmol) in water (5 cm^3) followed by the halogeno derivative (12 mmol). The mixture was stirred at RT overnight after which it was filtered and the filtrate extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$) and evaporated to give the crude product which was purified by chromatography on silica gel to afford the alkylated diketone.

2-(Prop-2-enyl)cyclohexane-1,3-dione.[5] Product (1.05 g, 69%) prepared from allyl bromide; δ_H(200 MHz, $CDCl_3$) 1.77–2.20 (m, 2 H), 2.31–2.77 (m, 4 H and 0.15 × 2 H of non-enol form), 3.06 (d, *J* 4.4, 0.85 × 2 H of enol form), 3.50 (t, *J* 7, 0.15 H of non-enol form), 4.92–5.09 (m, 2 H), 5.70–5.93 (m, 1 H) and 9.0 (s, OH, 0.85 H of enol form); δ_C(50 MHz, $CDCl_3$) of enol form

20.7, 25.9, 32.71, 32.72, 113.9, 117.0, 136.2, 143.2 and 188.2; ν_{max}/cm^{-1} 3500 and 1590; *m*/*z* (EI) 55, 96, 137 and 152; mp 125 °C.

2-Benzyl-2-(prop-2-enyl)cyclohexane-1,3-dione 3f. Product (1.33 g, 55%) prepared from benzyl bromide; δ_H(200 MHz, $CDCl_3$) 1.05–1.21 (m, 1 H), 1.52–1.67 (m, 1 H), 1.96–2.11 (m, 2 H), 2.23–2.38 (m, 2 H), 2.61 (d, *J* 7.5, 2 H), 3.06 (s, 2 H), 4.97–5.06 (m, 2 H), 5.39–5.60 (m, 1 H), 6.94–6.98 (m, 2 H) and 7.14–7.24 (m, 3 H); δ_C(50 MHz, $CDCl_3$) 15.2, 40.8, 42.6, 44.2, 68.9, 119.2, 126.8, 128.3, 129.6, 132.2, 136.2 and 211.5; ν_{max}/cm^{-1} 1705 and 1680; *m*/*z* (CI) 225 and 243 (Found: C, 79.37; H, 7.56. $C_{16}H_{18}O_2$ requires C, 79.31; H, 7.49%); mp 62 °C.

Synthesis of dienol diacetates

2,4-Diacetoxy-3-methyl-3-(prop-2-enyl)cyclohexa-1,4-diene 2a: typical procedure. *Acetylation.*—A solution of the diketone **3a** (2 g, 12 mmol) and toluene-*p*-sulfonic acid (70 mg, 0.36 mmol) in acetic anhydride (12 cm^3, 120 mmol) was refluxed for 3 h with concurrent removal of the acetic acid formed during the acetylation by distillation. The solution was then cooled to RT and distilled under reduced pressure to remove most of the remaining acetic anhydride. The crude product was then added, at ice-bath temperature, to a mixture of pentane (100 cm^3) and saturated aq. Na_2CO_3 (100 cm^3). After the mixture had been stirred for 1 h at ice-bath temperature it was neutralised with Na_2CO_3, added portionwise. The layers were separated and the organic layer washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a mixture containing the diacetate **2a** (55%), the keto acetate **1a** (40%) and the starting diketone **3a** (5%). The unchanged diketone **3a** was separated from the mixture of enol esters **2a** and **1a** by flash chromatography (Et_2O–light petroleum = 15:100) to give a 52:48 ratio of diacetate **2a**:keto acetate **1a**. The mixture was recycled under the same experimental conditions to afford a 90:10 ratio of **2a**:**1a**.

Reduction.—Lithium borohydride (4.5 mg, 0.2 mmol) was added to a stirred solution of diacetate–keto acetate (**2a**:**1a** = 9:1) (1 g contained 85 mg, 0.41 mmol of keto acetate) in dry diethyl ether (50 cm^3) at 0 °C. Absolute methanol (0.1 cm^3) was then added to the mixture and stirring continued for 30 min (reaction monitored by GC). After this, the mixture was diluted with water and the aqueous layer was separated and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and evaporated to give a mixture of the diacetate **2a** and the alcohol **4a** in a quantitative yield. Flash chromatography on silica gel (Et_2O–light petroleum = 15:100) afforded the dienol diacetate **2a** (2.07 g, 69% from **3a**); δ_H(200 MHz, $CDCl_3$) 1.14 (s, 3 H), 2.16 (s, 6 H), 2.20 (d, *J* 7.2, 2 H), 2.87–2.92 (m, 2 H), 4.95–5.05 (m, 2 H), 5.47 (t, *J* 3.6, 2 H) and 5.65–5.85 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 21.1, 23.1, 24.5, 40.4, 43.2, 112.2, 116.9, 134.4, 146.8 and 169.0; ν_{max}/cm^{-1} 1745 and 1670–1640 (Found: C, 67.34; H, 7.29. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%).

This procedure was also used for the dienol diacetates **2b**–**d** and **2f**.

(*E*)-2,4-Diacetoxy-3-methyl-3-(but-2-enyl)cyclohexa-1,4-diene 2b. Product (2.41 g, 76%) prepared from **3b**; δ_H(200 MHz, $CDCl_3$) 1.10 (s, 3 H), 1.60 (dd, *J* 6, *J* 1, 3 H), 2.10 (d, *J* 7, 2 H), 2.13 (s, 6 H), 2.85 (m, 2 H), 5.30–5.50 (m, 2 H) and 5.46 (t, *J* 3.7, 2 H); δ_C(50 MHz, $CDCl_3$) 17.8, 20.8, 22.8, 24.3, 39.1, 43.1, 111.8, 126.5, 127.3, 146.9 and 168.6; ν_{max}/cm^{-1} 1760 and 1675; *m*/*z* (CI) 125, 163, 181, 223 and 265 (Found: C, 68.19, H, 7.63. $C_{15}H_{20}O_4$ requires C, 68.16, H, 7.63%).

(*E*)-2,4-Diacetoxy-3-methyl-3-(3-chlorobut-2-enyl)cyclohexa-1,4-diene 2c. Product (1.29 g, 36%) prepared from **3c**; δ_H(200 MHz, $CDCl_3$) 1.07 (s, 3 H), 1.92 (d, *J* 1, 3 H), 2.0 (s, 6 H), 2.20 (d, *J* 7, 2 H), 2.81 (t, *J* 3.7, 2 H), 5.30 (tq, *J* 7, *J* 1, 1 H) and 5.38 (t, *J* 3.7, 2 H); δ_C(50 MHz, $CDCl_3$) 20.6, 23.4, 24.4, 26.0, 35.0, 42.4, 112.0, 121.6, 131.0, 146.8 and 168.7; ν_{max}/cm^{-1} 1760 and 1670; *m*/*z* (CI) 179, 203, 221, 257, 263 and 299–301 (Found: C, 60.91; H, 6.80. $C_{15}H_{19}ClO_4$ requires C, 60.30; H, 6.41%).

2,4-Diacetoxy-3-methyl-3-(3-chlorobut-2-enyl)cyclohexa-1,4-diene 2d. Product (1.89 g, 60%) prepared from **3d**; δ_H(200 MHz, $CDCl_3$) 1.13 (s, 3 H), 1.74 (t, *J* 2.5, 3 H), 2.15 (s, 6 H), 2.35 (q, *J* 2.5, 2 H), 2.93 (t, *J* 3.6, 2 H) and 5.51 (t, *J* 3.6, 2 H); δ_C(50 MHz, $CDCl_3$) 3.5, 20.9, 21.6, 24.5, 27.3, 42.7, 75.2, 77.2, 112.4, 146.9 and 168.8; ν_{max}/cm^{-1} 2240, 1760 and 1680 (Found: C, 68.50; H, 7.07. $C_{15}H_{18}O_4$ requires C, 68.69; H, 6.92%); mp 60 °C.

2,4-Diacetoxy-3-benzyl-3-(prop-2-enyl)cyclohexa-1,4-diene 2f. Product (3.09 g, 79%) prepared from **3f**; δ_H(200 MHz, $CDCl_3$) 2.19 (s, 6 H), 2.25–2.34 (dt, *J* 22.5, *J* 3.7, 1 H), 2.66–2.77 (dt, *J* 22.5, *J* 3.9, 1 H), 2.36 (d, *J* 7, 2 H), 2.80 (s, 2 H), 4.91–5.00 (m, 2 H), 5.60 (dt, *J* 3.7, *J* 3.9, 2 H), 5.72–5.93 (m, 1 H) and 7.12–7.23 (m, 5 H); δ_C(50 MHz, $CDCl_3$) 21.3, 24.2, 40.2, 41.6, 48.8, 113.4, 116.9, 126.1, 127.5, 130.0, 134.3, 137.2, 144.1 and 168.0; ν_{max}/cm^{-1} 1760 and 1695; *m*/*z* (EI) 91, 151, 193, 235, 242, 284 and 326; mp 75 °C.

2,4-Diacetoxy-3-benzyl-3-methylcyclohexa-1,4-diene 2e. A solution of the diketone **3e** (2.7 g, 12.5 mmol) and PTSA (70 mg, 0.38 mmol) in acetic anhydride (13 cm^3, 125 mmol) was refluxed for 3.5 h with concurrent removal of the acetic acid formed during the reaction by distillation. Most of the remaining acetic anhydride was also then distilled off. The resulting crude product was added at ice-bath temperature to a mixture of pentane (100 cm^3) and saturated aq. Na_2CO_3 (100 cm^3). After the mixture had been stirred for 1 h at ice-bath temperature it was neutralised with Na_2CO_3, added portionwise. The organic layer was separated, filtered and washed with cold pentane and evaporated to afford the diacetate **2e** as a red solid. The red solid was filtered off on silica gel to afford white crystals of the diacetate **2e** (700 mg). The aqueous layer was extracted with pentane and the extracts were washed with brine, dried ($MgSO_4$) and concentrated to provide a mixture of the diacetate **2e** and the keto acetate **1e**. Crystallisation of this crude product from hexane provided the diacetate **2e** (500 mg) and chromatography of the remaining mixture gave further diacetate **2e** (560 mg).

The dienol **2e** diacetate (1.76 g) was obtained in a final yield of 59%; δ_H(200 MHz, $CDCl_3$) 1.35 (s, 3 H), 1.71 (s, 6 H), 1.96–2.07 (dt, *J* 22, *J* 3.4, 1 H), 2.33–2.44 (dt, *J* 22, *J* 4, 1 H), 2.83 (s, 2 H), 5.33 (dt, *J* 3.4, *J* 4, 2 H), 7.09–7.24 (m, 3 H) and 7.34–7.39 (m, 2 H); δ_C(50 MHz, $CDCl_3$) 20.6, 23.5, 24.4, 42.7, 45.3, 113.2, 126.0, 128.0, 130.6, 138.3, 146.5 and 168.1; ν_{max}/cm^{-1} 1750 and 1640; *m*/*z* (CI) 125, 199, 241, 259 and 301 (Found: C, 72.18; H, 6.90. $C_{18}H_{20}O_4$ requires C, 71.98; H, 6.71%); mp 100 °C.

General procedure for enzymatic hydrolysis

Liquid dienol diacetates 2a–c. *Candida cylindracea* lipase (36 IU per 1 mg; 6.25 mg, 225 IU) was added to a suspension of the diacetate **2** (1 mmol) in phosphate buffer KH_2PO_4–Na_2HPO_4 (0.1 mol dm^{-3}; 5 cm^3). The reaction was performed at pH 7 [with a pHstat to maintain the correct pH value by the addition of aq. NaOH (1 mol dm^{-3})] and at the desired temperature (maintained with the aid of a thermostatted bath; see Table 2). When the desired % conversion (monitored by GC) was obtained the mixture was extracted with Et_2O, and the extract dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residual oil was purified by chromatography on silica gel (eluent Et_2O–light petroleum = 0:100 to 5:100) to afford the keto acetate **1**. A 60 Å, >440 mesh silica gel was used for purification of the keto acetate **1a** and 100 Å, >440 mesh silica gel for the purification of the keto acetate **1b**.

(+)-(*S*)-3-Acetoxy-2-methyl-2-(prop-2-enyl)cyclohex-3-enone 1a. Product (165 mg, 80%); δ_H(200 MHz, $CDCl_3$) 1.15 (s, 3 H), 2.16 (s, 3 H), 2.25–2.55 (m, 6 H), 4.93–5.02 (m, 2 H), 5.50–5.67 (m, 1 H) and 5.68 (t, *J* 4.3, 1 H); δ_H(200 MHz, C_6D_6) 1.18 (s, 3 H), 1.64 (s, 3 H), 1.75–1.84 (m, 2 H), 2.12–2.28 (m, 3 H), 2.60 (dd, *J* 13, *J* 7.2, 1 H), 4.94–5.09 (m, 2 H), 5.51 (t, *J* 4.3, 1 H) and 5.68–5.90 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 20.3, 21.0, 22.2, 36.8, 40.9, 52.3, 115.1, 118.1, 133.8, 146.3, 170.3 and 210.6; ν_{max}/cm^{-1} 1750, 1730 and 1680–1630; *m*/*z* (EI) 43, 110, 125, 166, 167 and

208 (Found: C, 69.36; H, 7.42. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74%); $[\alpha]_{436}$ +21.1 [*c* 1 (CH_2Cl_2), 25 °C, ee >98%].

(*E*)-(+)-3-Acetoxy-2-methyl-2-(but-2-enyl)cyclohex-3-enone 1b (E). Product (156 mg, 70%); δ_H(200 MHz, $CDCl_3$) 1.12 (s, 3 H), 1.60 (dd, *J* 6, *J* 1, 3 H), 2.16 (s, 3 H), 2.10–2.55 (m, 6 H), 5.20–5.45 (m, 2 H) and 5.67 (t, *J* 4.2, 1 H); δ_C(50 MHz, $CDCl_3$) 17.8, 20.2, 20.9, 22.0, 36.9, 40.2, 52.4, 114.8, 125.7, 126.7, 148.4, 167.0 and 211.3; ν_{max}/cm^{-1} 1760, 1715 and 1680; *m*/*z* (EI) 55, 126, 168, 180 and 222 (Found: C, 70.50; H, 7.96. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.16%); $[\alpha]_{436}$ +66.0 [*c* 1 (CH_2Cl_2), 26 °C, ee >98%].

(*S*,*E*)-(+)-3-Acetoxy-2-methyl-2-(3-chlorobut-2-enyl)cyclohex-3-enone 1c. Product (186 mg, 73%); δ_H(200 MHz, $CDCl_3$) 1.18 (s, 3 H), 2.02 (d, *J* 1.2, 3 H), 2.16 (s, 3 H), 2.30–2.70 (m, 6 H), 5.25 (m, *J* 7, 1 H) and 5.70 (t, *J* 4.2, 1 H); δ_C(50 MHz, $CDCl_3$) 20.6, 21.0, 22.0, 26.2, 35.7, 36.3, 51.8, 114.7, 121.6, 132.3, 148.4, 169.0 and 210.6; ν_{max}/cm^{-1} 1760, 1720 and 1685; *m*/*z* (CI) 179, 215, 221 and 257–259 (Found: C, 61.11; H, 6.90. $C_{13}H_{17}ClO_3$ requires C, 60.82; H, 6.67%); $[\alpha]_{436}$ +22.4 [*c* 0.9 (CH_2Cl_2), 25 °C, ee >98%].

Solid dienol diacetates 2d–f

Dichloromethane (0.5 cm^3) was added to the dienol diacetate **2** (1 mmol) after which most of the former was evaporated with the aid of a compressed air stream. To the residual oil was added phosphate buffer KH_2PO_4–Na_2HPO_4 (0.1 mol dm^{-3}; 5 cm^3) and then *Candida cylindracea* lipase (9.1 mg, 330 IU). The reaction was performed at the desired temperature, maintained with the aid of a thermostatted bath (Table 2), at pH 7. After the mixture had been stirred for several hours (until the desired % conversion was obtained), it was extracted with CH_2Cl_2 and the extract dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (Et_2O–light petroleum = 5:100) to afford the keto acetate **1**. A 100 Å, >440 mesh silica gel was used to purify the keto acetate **1d**.

(+)-3-Acetoxy-2-methyl-2-(but-2-ynyl)cyclohex-3-enone 1d. Product (165 mg, 75%); δ_H(200 MHz, $CDCl_3$) 1.15 (s, 3 H), 1.73 (t, *J* 2.5, 3 H), 1.64 (s, 3 H), 1.75–2.12 (m, 2 H), 2.15–2.40 (m, 2 H), 2.40 (dd, *J* 12.5, *J* 2.5, 1 H), 2.70 (dd, *J* 12.5, *J* 2.5, 1 H) and 5.51 (t, *J* 4.3, 1 H); δ_C(50 MHz, $CDCl_3$) 3.3, 20.3, 20.8, 21.6, 26.7, 38.7, 51.7, 74.6, 78.0, 115.5, 147.7, 168.9 and 210.2; ν_{max}/cm^{-1} 2240, 1760, 1715 and 1680 (Found: C, 70;86; H, 7.08. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%); $[\alpha]_{436}$ +38.3 [*c* 1 (CH_2Cl_2), 25 °C, ee >98%].

(+)-3-Acetoxy-2-benzyl-2-methylcyclohex-3-enone 1e. Product (160 mg, 62%); δ_H(200 MHz, $CDCl_3$) 1.20 (s, 3 H), 1.60–1.95 (m, 2 H), 2.05–2.45 (m, 2 H), 2.20 (s, 3 H), 2.83–3.00 (m, *J* 13, 2 H), 5.62 (t, *J* 4.4, 2 H), 7.02–7.10 (m, 2 H) and 7.15–7.20 (m, 3 H); δ_H(200 MHz, C_6D_6) 1.27 (s, 3 H), 1.51–1.72 (m, 2 H), 1.68 (s, 3 H), 1.99–2.11 (m, 2 H), 2.70–3.11 (m, *J* 13, 2 H), 5.47 (t, *J* 4.5, 1 H) and 7.0–7.25 (m, 5 H); δ_C(50 MHz, $CDCl_3$) 19.9, 21.0, 22.8, 37.2, 43.0, 53.9, 116.0, 126.3, 126.7, 129.5, 136.9, 147.3, 169.0 and 211.8; ν_{max}/cm^{-1} 1760, 1710 and 1690; *m*/*z* (EI) 91, 125, 167, 216 and 258 (Found: C, 74.12; H, 6.93. $C_{16}H_{18}O_3$ requires C, 74.40, H, 7.02%); $[\alpha]_{436}$ +27.0 [*c* 0.98 (CH_2Cl_2), 25 °C, ee >98%].

(+)-3-Acetoxy-2-benzyl-2-(prop-2-enyl)cyclohex-3-enone 1f. Product (127 mg, 45%); δ_H(200 MHz, $CDCl_3$) 1.18–1.40 (m, 2 H), 1.55–1.75 (m, 1 H), 1.65 (s, 3 H), 1.92–2.05 (m, 1 H), 2.27–2.35 (dd, *J* 13.8, *J* 6, 1 H), 2.77 (m, *J* 13, 2 H), 4.95–5.12 (m, 2 H), 5.75 (t, *J* 4, 1 H), 5.81–6.03 (m, 1 H) and 7.02–7.20 (m, 5 H); δ_C(50 MHz, $CDCl_3$) 19.1, 21.4, 38.9, 41.2, 42.5, 58.4, 117.3, 118.4, 126.5, 127.9, 130.1, 133.2, 136.5, 145.3, 168.6 and 211.3; ν_{max}/cm^{-1} 1760, 1715 and 1680; *m*/*z* (EI) 91, 151, 242 and 284 (Found: C, 75.68; H, 6.95. $C_{18}H_{20}O_3$ requires C, 76.03; H, 7.09%); $[\alpha]_{436}$ +53.1 [*c* 0.7 (CH_2Cl_2), 25 °C, ee 70%].

Determination of absolute configuration

3-Acetoxy-2-methyl-2-(prop-2-enyl)cyclohex-3-enol 4a. A solution of the *S*-keto enol acetate **1a** (200 mg, 0.96 mmol) in MeOH (20 cm^3) was cooled to −78 °C and sodium borohydride (35 mg, 1.92 mmol) was added at the same temperature to it. The mixture was then stirred overnight after which 1 mol dm^{-3} hydrochloric acid (5 cm^3) was added to it. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 5 cm^3). The combined organic layer and extracts were dried ($MgSO_4$), and concentrated to provide the alcohol **4a** (188 mg, 93%) with a 92:8 *trans*/*cis* diastereoisomeric ratio (determined by GC). Major isomer (*trans*): δ_H(200 MHz, $CDCl_3$) 1.07 (s, 3 H), 1.70–1.80 (m, 2 H), 2.11 (s, 3 H), 2.05–2.35 (m, 4 H), 2.70 (s, OH), 3.70 (t, *J* 5.0, 1 H), 5.03–5.15 (m, 2 H), 5.30 (t, *J* 4.0, 1 H) and 5.83–6.05 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 20.0, 21.0, 22.8, 25.7, 38.8, 42.6, 73.9, 114.4, 117.3, 135.4, 150.1 and 169.6; ν_{max}/cm^{-1} 3460, 1750 and 1675–1640 (Found: C, 68.82, H, 8.59. $C_{12}H_{18}O_3$ requires C, 68.55, H, 8.63%).

(1*R*,2*R*)-3-(1,3-Dioxolan-2-yl)-2-methyl-2-(prop-2-enyl)cyclohexan-1-ol 6a

To a solution of the alcohol **4a** (185 mg, 0.9 mmol) in THF (15 cm^3) was added dropwise at −20 °C a solution of methyllithium in Et_2O (1.6 mol dm^{-3}; 1.7 cm^3, 2.7 mmol). The mixture was stirred for 1 h after which it was treated with water and then 1 mol dm^{-3} hydrochloric acid at −20 °C. The layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic layer and extracts were dried ($MgSO_4$) and evaporated to afford the ketol **5a** (109 mg, 72%) in a 92:8 diastereoisomeric ratio. The ketol **5a** (107 mg, 0.65 mmol) was added to a solution of ethylene glycol (1 cm^3, 13 mmol) and PTSA (5 mg, 0.03 mmol) in toluene (10 cm^3) and the mixture refluxed for 2 h in a Dean-Stark apparatus. Saturated aq. $NaHCO_3$ was then added to the mixture after which the aqueous layer was separated and extracted with Et_2O. The combined organic layers and extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the hydroxydioxolan **6a** in a 92:8 diastereoisomeric ratio. The *trans* major diastereoisomer (1*R*,2*R*) **6a** (103 mg, 75%) was obtained by flash chromatography (Et_2O–light petroleum, 5:100) on silica gel (60 Å, >440 mesh); δ_H(200 MHz, $CDCl_3$) 0.99 (s, 3 H), 1.48–1.76 (m, 6 H), 2.00 (dd, *J* 13.3, *J* 8.2, 1 H), 3.14 (t, *J* 10.2, OH), 3.60 (dt, *J* 10.2, *J* 3.1, 1 H), 3.84–4.00 (m, 4 H), 5.01–5.13 (m, 2 H) and 5.78–5.96 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 17.7, 19.0, 28.0, 30.1, 35.1, 44.9, 64.0, 65.3, 75.5, 112.9, 117.5 and 135.0; ν_{max}/cm^{-1} 3450 and 1640; *m*/*z* (CI) 195 and 213; *m*/*z* (EI) 55, 69, 86, 99, 108, 122, 139, 150, 194 and 212.

(2*R*,3*R*)-3-Hydroxy-2-methyl-2-(3-prop-2-enyl)cyclohexanone 5a[7]

A solution of the dioxolanol **6a** (120 mg, 0.6 mmol) in 3 mol dm^{-3} hydrochloric acid (4 cm^3) was stirred overnight after which it was extracted with CH_2Cl_2 (4 × 2 cm^3) and the extract dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (Et_2O–light petroleum, 20:100) to afford the (2*R*,3*R*) ketol **5a** (80 mg, 79%); δ_H(200 MHz, $CDCl_3$) 1.13 (s, 3 H), 1.60–2.11 (m, 4 H), 2.32–2.44 (m, 4 H), 2.70 (s, OH), 3.57 (dd, *J* 7.0, *J* 3.3, OH), 5.02–5.13 (m, 2 H) and 5.62–5.83 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 19.5, 20.5, 28.4, 36.4, 37.6, 54.1, 76.3, 117.7, 133.6 and 214.5; ν_{max}/cm^{-1} 3480, 1700 and 1640; *m*/*z* (CI) 151 and 169; *m*/*z* (EI) 55, 67, 81, 93, 109, 122, 135, 150 and 168 (Found: C, 71.53; H, 9.38. $C_{10}H_{16}O_2$ requires C, 71.39; H, 9.59%); $[\alpha]_D$ −31.6 (*c* 0.55, $CHCl_3$, 25 °C). {lit.,[7] (2*S*,3*S*) **5a**: $[\alpha]_D$ +32 (*c* 0.42, $CHCl_3$, 25 °C); (2*R*,3*S*) **5a**: $[\alpha]_D$ −4.7 (*c* 0.6, $CHCl_3$, 23 °C)}.

(*E*)-3-Acetoxy-2-methyl-2-(3-chlorobut-2-enyl)cyclohex-3-enol 4c

Lithium borohydride (25 mg, 1.15 mmol) and then methanol (0.5 cm^3) were added at −10 °C to a solution of the (*S*)-keto acetate **1c** (600 mg, 2.4 mmol) in dry diethyl ether (30 cm^3). The mixture was stirred for 2 h (reaction monitored by GC) after which distilled water and 1 mol dm^{-3} hydrochloric acid were

added to it. The aqueous layer was separated and extracted with Et_2O and the combined organic layer and extracts were washed with brine, dried ($MgSO_4$) and evaporated to provide the alcohol **4c** (609 mg, 98%) in a 75:25 *trans*/*cis* diastereoisomeric ratio (determined by GC); major isomer (*trans*); δ_H(200 MHz, $CDCl_3$) 0.99 (s, 3 H), 1.70–1.75 (m, 2 H), 2.01 (d, *J* 1.1, 3 H), 2.05 (s, 3 H), 2.00–2.52 (m, 5 H), 3.60 (m, 1 H), 5.25 (t, *J* 3.8, 1 H) and 5.65 (tq, *J* 7.0, *J* 1.1, 1 H); δ_C(50 MHz, $CDCl_3$) 20.1, 20.9, 22.8, 25.8, 26.2, 35.2, 43.0, 74.0, 115.5, 122.5, 132.0, 149.9 and 169.7; ν_{max}/cm^{-1} 3480, 1750 and 1675; *m*/*z* (EI) 127, 163, 169, 198, 216 and 258–260 (Found: C, 59.95; H, 7.81. $C_{13}H_{19}ClO_3$ requires C, 60.35; H, 7.40%).

(2*R*,3*R*,*E*)-3-Acetoxy-2-methyl-2-(3-chlorobut-2-enyl)cyclohexanone 6c

A solution of the alcohol **4c** (380 mg, 1.47 mmol) in THF (5 cm^3) was added at 0 °C to a suspension of sodium hydride (60% weight in oil; 65 mg, 1.65 mmol), freshly washed with THF (2 × 2 cm^3). The mixture was stirred for 30 min after which 1 mol dm^{-3} hydrochloric acid and diethyl ether (10 cm^3) were added to it. The aqueous layer was extracted with Et_2O and the combined organic layer and extracts were dried ($MgSO_4$) and concentrated to afford the ketone **6c** (323 mg, 85%) in a 75:25 *trans*/*cis* diastereoisomeric ratio. The major diastereoisomer (2*R*,3*R*)-*trans*-**6c** was purified by flash chromatography (Et_2O–light petroleum, 10:100; silica gel: 60 Å, >440 mesh) of the crude product (236 mg, 62%); δ_H(200 MHz, $CDCl_3$) 1.15 (s, 3 H), 1.80–2.05 (m, 4 H), 2.03 (d, *J* 1.0, 3 H), 2.05 (s, 3 H), 2.37–2.56 (m, 4 H), 4.90–4.96 (m, 1 H) and 5.30 (tq, *J* 7.0, *J* 1, 1 H); δ_C(50 MHz, $CDCl_3$) 20.0, 20.5, 20.8, 25.4, 26.2, 31.8, 37.2, 52.0, 77.8, 120.2, 132.6, 169.7 and 211.8; ν_{max}/cm^{-1} 1740, 1710 and 1665.

(2*R*,3*R*)-3-Acetoxy-2-methyl-2-(3-oxobutyl)cyclohexanone 7c

Mercury acetate (136 mg, 0.42 mmol) was added to a suspension of the ketone **6c** (100 mg, 0.38 mmol) in 80% formic acid (2 cm^3) at RT and the mixture stirred for 2 h. The suspension was then filtered and the filtrate concentrated *in vacuo* (evaporation of most of the formic acid). The residue was dissolved in Et_2O (5 cm^3) and concentrated. The crude product was purified by chromatography (Et_2O–light petroleum, 30:100) to provide the diketone **7c** (70 mg, 76%); δ_H(200 MHz, $CDCl_3$) 1.03 (s, 3 H), 1.63–2.16 (m, 6 H), 2.00 (s, 3 H), 2.10 (s, 3 H), 2.24–2.50 (m, 4 H) and 4.80–4.86 (m, 1 H); δ_C(50 MHz, $CDCl_3$) 19.0, 20.3, 20.9, 25.3, 28.7, 30.0, 37.4, 37.7, 51.7, 78.1, 170.0, 207.9 and 212.1; ν_{max}/cm^{-1} 1740 and 1705.

(4a*S*,5*R*)-5-Hydroxy-4a-methyl-2,3,4,4a,5,6,7,8-octahydronaphthalene-2-one 8c[9]

A solution of sodium methoxide (2 cm^3), prepared by dissolving sodium (700 mg, 30 mmol) in absolute methanol (10 cm^3), was added at RT to the diketone **7c** (110 mg, 0.51 mmol) and the mixture stirred for 1 h. A solution of brine was then added to the mixture and the methanol removed by evaporation under reduced pressure. The residue was dissolved in Et_2O and the solution washed with 1 mol dm^{-3} hydrochloric acid until neutral. The solution was then dried ($MgSO_4$) and concentrated to give the crude product which was purified by flash chromatography (AcOEt–light petroleum, 1:1) to afford the ketol **8c** (37 mg, 40%); δ_H(200 MHz, $CDCl_3$) 1.17 (s, 3 H), 1.10–1.50 (m, 11 H), 3.37–3.45 (dd, *J* 4.4, 1 H) and 5.75 (d, *J* 1.7, 1 H); δ_C(50 MHz, $CDCl_3$) 21.7, 23.1, 30.2, 31.9, 33.6, 34.1, 41.5, 78.2, 126.2, 168.5 and 199.6; ν_{max}/cm^{-1} 3415, 1655 and 1615; *m*/*z* (EI) 79, 91, 109, 124, 162 and 180 (Found: C, 72.81; H, 8.42. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%); mp 98 °C; $[\alpha]_D$ +110.2 (*c* 0.9, C_6H_6, 25 °C) {lit.,[9] (4*R*,5*S*) **8c**: $[\alpha]_D$ −111 (*c* 1.3, C_6H_6, 25 °C); (4*S*,5*S*) **8c**: $[\alpha]_D$ +203 (*c* 1.55, C_6H_6, 25 °C)}.

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