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Asymmetric Metal-Catalysed Epoxidation of Electron-Deficient Olefins

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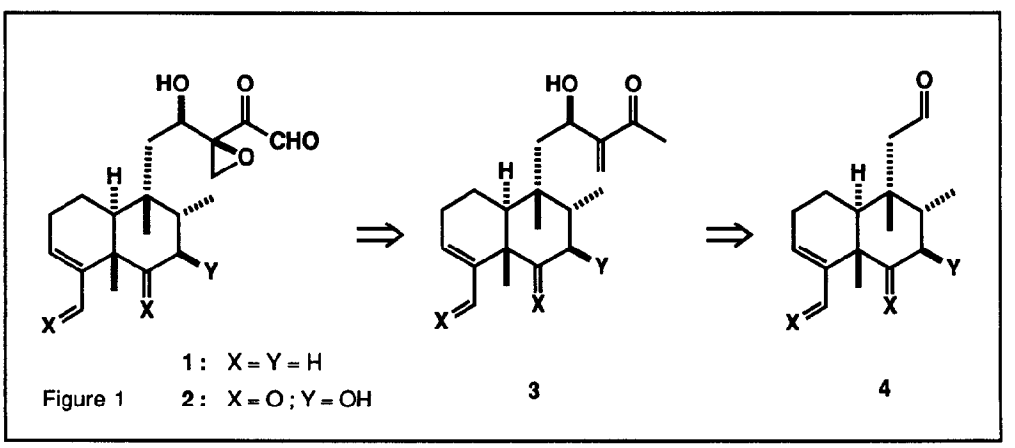
Abstract: *The SYN diastereospecific epoxidation of acyclic β-hydroxyketones (β-hydroxyacrylates) and cyclic β-hydroxyketones using titanium and vanadium catalysts is reported. Some initial results on the asymmetric epoxidation of these systems using the Sharpless titanium-tartrate catalyst are also described.*

The clerodane diterpenes clerocidin **1** [1] and terpenticin **2** [2] possess a side-chain almost unique to this class of natural products [3], which incorporates four oxygen atoms connected to five carbon centres (Figure 1). The crucial and only stereochemical feature in this side-chain is a *syn*-epoxy-alcohol group. We envisionned that such a functionalised side-chain could be produced by a stereospecific epoxidation of a β-hydroxyenone precursor **3**, itself readily accessible from the aldehyde **4** by a Baylis-Hillman reaction [4]. In order to develop a suitable methodology for the former transformation, we decided to investigate in detail various epoxidation conditions for the stereoselective conversion of the model β-hydroxyenone **5** to the *syn*-epoxide **6** (Table 1).



1 : X = Y = H
2 : X = O ; Y = OH

3

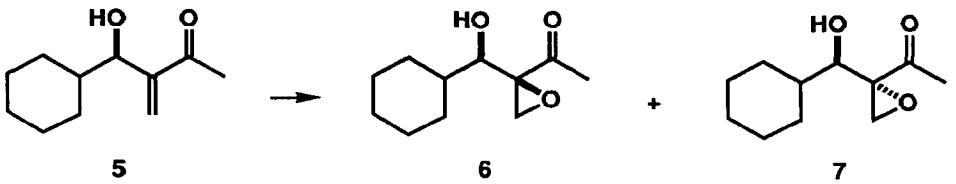
4

Figure 1

In this paper [5], we report some of our results towards the successful realisation of this objective, as well as the first applications of the Sharpless titanium-catalysed epoxidation reaction

to effect kinetic resolution of electron-deficient olefins with moderate to good enantiomeric excess [6].

Table 1. Stereoselective epoxidation of the model compound.



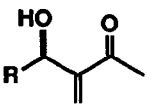
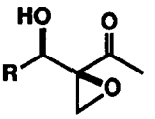
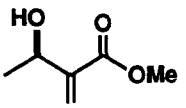
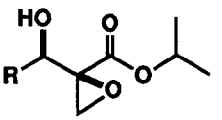
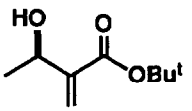
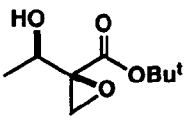
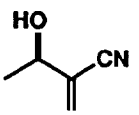
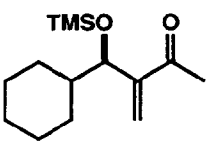
5 6 7

Entry	Conditions	Yields	6 / 7 [a]
1	H_2O_2 / NaOH / MeOH / 0°C	76%	40 : 60
2	TBHP / NaOH / MeOH / - 40°C	70%	33 : 67
3	BQBr [b] / CHP [c] / Tol / NaOH / - 20°C	78%	40 : 60
4	^{t}BuOOLi / THF / -78°C to 20°C	[d]	-
5	mCPBA / CH_2Cl_2 / 20°C / 3 days	No reaction	
6	Ti $(OPr^i)_4$ / TBHP / CH_2Cl_2 / - 15°C	78%	> 99 : < 1
7	VO $(acac)_2$ / TBHP / C_6H_6 / - 20°C	76%	> 99 : <1

[a] ratios determined by 250 MHz and 400 MHz NMR. [b] BQBr = benzyl quininium bromide. [c] CHP = cumyl hydroperoxide. [d] decomposition of the substrate took place.

Enones such as **5** are electron-deficient systems and their epoxidation is typically accomplished using nucleophilic oxidants under basic conditions [7]. Therefore, we initiated our studies using such reagents. The results - displayed in Table 1 - were disappointing. A 2 : 3 mixture of *syn*- and *anti*-epoxy-alcohols **6** and **7** was typically obtained, regardless of the reagent or the conditions employed (Table 1, Entries 1 - 4). Despite the possible directing effect of the

Table 2. Titanium - catalysed epoxidation of electron - deficient olefins

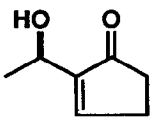
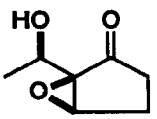
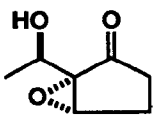
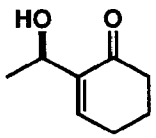
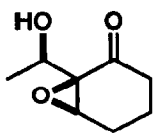
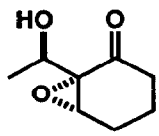
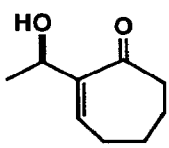
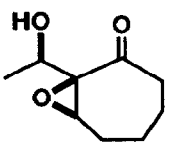
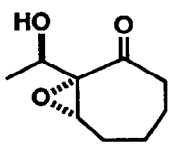
Entry	Substrate	Product	Yields
1	 8	 a. R = Me b. R = Et c. R = Pr^i	63% 72% 70%
2	 9		81%
3	 10		78%
4	 11	**No reaction**	
5	 12	**No reaction**	

hydroxyl function, no reaction was observed with mCPBA (Table 1, Entry 5) owing to the electron-poor character of the carbon-carbon double bond of these systems.

However, much to our surprise [8], epoxidation using titanium tetraisopropoxide/TBHP [9] or vanadyl acetylacetonate/TBHP [10] proceeded smoothly, giving only the *syn*-epoxy-alcohol 6 in excellent yield (Table 1, Entries 6 and 7).

In view of the complete lack of reactivity of these catalysts towards simple enones, this observation is highly unusual and prompted a detailed investigation of this reaction in order to delineate the structural features required in the substrates for their successful epoxidation.

Table 3. Epoxidation of cyclic β-hydroxyenones

Entry	Substrate	Condition	Products		Yields
1			 + 		
	13	**A**	>99	<1	73%
		B	10	1	87%
2			 + 		
	14	**A**	>99	<1	82%
		B	10	1	91%
		C	4	1	70%
		D	>99	<1	92%
3			 + 		
	15	**A**	>99	<1	68%
		B	8	1	83%

A = $Ti(OPr^i)_4$ /TBHP / CH_2Cl_2 / -15°C. **B** = TBHP / MeOH / NaOH / 0°C. **C** = H_2O_2 / MeOH / NaOH / 0°C. **D** = $VO(acac)_2$ / TBHP / CH_2Cl_2 / -20°C

In all the acyclic cases examined so far (Table 2), except in Entries 4 and 5 where no reaction was observed, **only the syn-epoxy-alcohol was produced using the Ti(IV) catalyst** [11]. The stereoselectivity was remarkably unaffected by the size of the substituent R (Table 2, entries 1a - 1c). The catalyst also tolerated an ester functionality. In the case of the methyl ester **9** (Table 2, entry 2) transesterification accompanied epoxidation and the *syn*-isopropyl-epoxy-ester was produced as the sole product. This side-reaction could be easily suppressed by employing the *tert*-butyl ester **10** (Table 2, entry 3). Interestingly, base-catalysed epoxidation of the β-hydroxyester **10** (MeOH / NaOH / H_2O_2) did not afford the desired material. Only the product resulting from the addition of methanol onto the carbon-carbon double bond could be isolated, though in poor yield. Although the Sharpless epoxidation is successful with β-hydroxyenones and β-hydroxyacrylates, no reaction is observed with the corresponding nitrile (Table 2, entry 4) and the starting material is recovered unchanged [12]. **Similarly, no epoxidation takes place if the hydroxyl function is blocked** (Table 2, entry 5) confirming that an initial coordination of the hydroxyl group to the metal-catalyst is required for subsequent reaction to ensue.

Cyclic substrates were next examined (Table 3). Again, the titanium and vanadium catalysts gave consistently high levels of *syn*-stereoselectivity. However, the fate of the cyclic systems under Weitz-Scheffer conditions [13] differed markedly from the analogous acyclic cases. **Indeed, while acyclic β-hydroxyenones afforded preferentially the *anti*-isomer, though in a modest 2 : 3 ratio, cyclic β-hydroxyenones gave predominantly the *syn*-isomer** (Table 3, condition B). This selectivity, not only depends on the reaction conditions (Table 3, conditions **B** and **C**) but also never reaches [14] the exquisite levels obtained with the titanium or vanadium catalysts (Table 3, conditions **A** and **D**).

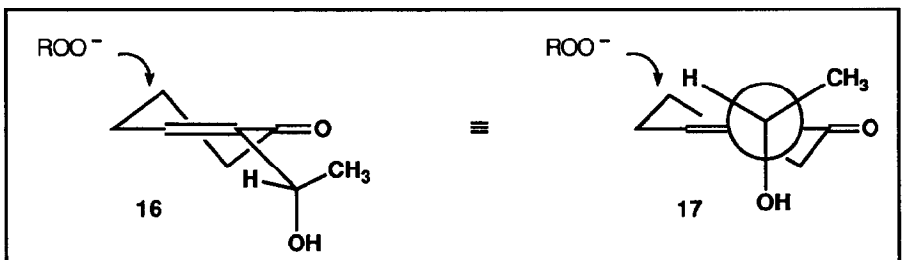


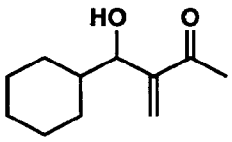
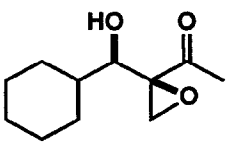
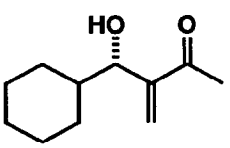
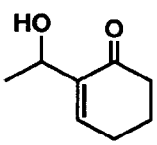
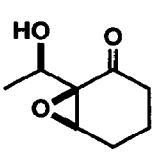
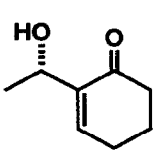
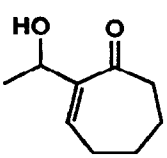
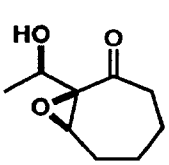
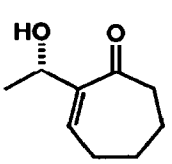
Figure 2

It has been previously reported that the titanium-catalysed epoxidation of 1,1-disubstituted allylic alcohols was highly *erythro*-selective [15]. Somehow, the carbonyl oxygen of the β-hydroxyenones and β-hydroxyacrylates appears to be involved in these reactions, enhancing the *syn*-selectivity [16]. In the case of cyclic systems, the high *syn*-selectivity observed under Weitz-Scheffer conditions can be rationalised by considering two factors: the stereochemical bias favouring axial attack on a cyclic enone [17] by a nucleophile and a preferred ground-state

conformation of the allylic alcohol portion [18] of the molecule in which the C-O bond of the alcohol function is parallel to the π-system of the enone moiety (Figure 2).

Interestingly, kinetic resolution using the titanium-tartrate procedure leads to the corresponding optically active epoxides/β-hydroxyenones in moderate to good enantiomeric excess (Table 4). It is remarkable that the cyclic β-hydroxyenone **14** affords high e.e. of the desired *syn*-epoxide after 50% conversion (Entry 2, condition **A**). In sharp contrast, only poor asymmetric induction is achieved in the epoxide product derived from the acyclic β-hydroxyenone **5** (Entry 1). **Remarkably, at 75% conversion, the recovered seven-membered ring enone proved to be at least 75% optically pure** (Entry 3, $k_f/k_s = 4$).

Table 4. Asymmetric epoxidation of electron-deficient olefins

Entry	Substrate	Condition	Products		
1				+	
	5	**A**	18 % ee[(a)]		13 % ee[(b)]
2				+	
	14	**A**	78 % ee[(a)]		50 % ee[(b)]
		B	19 % ee[(a)]		88 % ee[(b)]
3				+	
	15	**B**	20 %ee[(a)]		75 % ee[(b)]

A = $Ti(OPr^i)_4$ / (-) - DET / TBHP / CH_2Cl_2 / - 15°C / 50% conversion. **B** = $Ti(OPr^i)_4$ / (-) - DET / TBHP / CH_2Cl_2 / -15°C / 75% conversion. (a) = ee determined by ^1H NMR (250 MHz / 400 MHz) using chiral shift reagent [Eu(hfc)$_3$]. (b) = ee determined by HPLC using a Pirkle 1A column

Similarly, the six-membered enone gives an epoxide of poor e.e. **but the unreacted starting material now possesses a significant optically purity of 88% e.e.** (Entry 2, condition **B**, $k_f/k_s = 5$). So far, only the acyclic system has not yet yielded good levels of asymmetric induction. Although these enantiomeric excesses are still far from the exquisite levels obtained for the epoxidation of simple allylic alcohols, they are nevertheless the **first reported examples of asymmetric epoxidations and kinetic resolutions of electron-deficient olefins using the Sharpless procedure.** The optically active epoxides and β-hydroxyenones are useful synthetic materials [19], the chemistry of which is now being investigated in our laboratory, in conjunction with possible improvements of the asymmetric induction levels.

In summary, we have shown for the first time that the epoxidation of electron-deficient olefins using titanium and vanadium catalysts gave smoothly the *syn*-epoxides. A free hydroxyl group and a ketone or ester function - but not a nitrile - are required by these catalysts for a successful reaction to take place. Kinetic resolution of acyclic and cyclic β-hydroxyenones can be realised, though the latter proved to be better substrates for the chiral titanium catalyst, leading to decent levels of asymmetric induction.

Acknowledgments: Financial support for this research by the Science and Engineering Research Council is gratefully acknowledged. Awards from The Royal Society and The Nuffield Foundation are highly appreciated. We are extremely grateful to Dr B Taylor and Mr P Tyson (NMR) and Mr H Adams (X-ray) for their enthusiastic contribution.

Experimental Section

^{1}H NMR spectra were recorded on a Perkin Elmer R-34 (220 MHz), Bruker 250 (^{1}H 250 MHz and ^{13}C 62.9 MHz) and Bruker WH400 (^{1}H 400 MHz and ^{13}C 100 MHz) spectrometers. Chemical shifts are reported in ppm downfield from tetramethylsilane. Mass spectral data were collected on a Kratos MS25 instrument in either chemical ionisation (CI) or electron impact (EI) mode. IR spectra were recorded using a Perkin Elmer 684 spectrometer in $CHCl_3$ solution Thin layer chromatography was performed on Merck 0.2 mm aluminium-backed TLC plates and visualised using ultra-violet light followed by development with alkaline $KMnO_4$ solution. Column chromatography was performed using Merck silica gel 60 (230-400 mesh) under pressure. Ethyl acetate and petroleum ether (40-60°C) were distilled prior to use and THF dried by the Na/benzophenone ketyl method. The following terms are used for the ^{1}H NMR spectra: bm = broad multiplet, qq = quartet of quartets, bs = broad singlet, td = triplet of doublets. The β-hydroxyenones **8a** [20], **8b** [20], **8c** [21] and **14** [22], the β-hydroxyacrylates **9** [23] and **10** [23] and the β-hydroxynitrile **11** [20] were prepared according to the literature procedures.

3-Methylene-4-hydroxy-4-cyclohexyl-butan-2-one 5.

To a stirred solution of cyclohexane carboxaldehyde (12.3 g, 0.11 mol) and 3-hydroxyquinuclidine (1.27 g, 0.01 mol), in 10 mL of dichloromethane, was added dropwise, at room temperature and

under nitrogen, 7.0 g of methyl vinyl ketone (0.1 mol) over a period of 8h. After stirring for a further 12h, the colourless, viscous, liquid obtained was flashed through a pad of silica gel (eluant : ethyl acetate). Concentration followed by distillation under reduced pressure gave pure 5 (9.3 g, 51%), as a colourless oil (b.p 92-94°C, 0.2 mmHg). IR ($CHCl_3$) 3400, 2840, 1660, 1360, 1250, 1125, 1075, 1015, 970, 950 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.14 (s, 1 H), 5.92 (d, J = 1.1 Hz, 1 H), 4.07 (t, J = 7.4 Hz, 1 H), 2.74 (d, J = 7.9 Hz , 1 H), 2.37 (s, 3 H), 1.94-0.87 (m, 11 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 200.7, 150.0, 126.5, 76.9, 42.5, 30.1, 28.3, 26.5, 26.3, 26.1, 25.9; MS, CI : 200 (M^++NH_4); Anal. Calcd for C $_{11}H_{18}O_2$: C, 72.53; H, 9.89; Found: C, 72.51; H, 10.19.

3-Methylene-4-cyclohexyl-4-(trimethylsilyloxy)-butan-2-one 12.

A cold (0°C) solution of 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one (0.5 g, 2.8 mmol) and pyridine (0.35 g, 4.4 mmol) in dichloromethane (15 mL) was treated dropwise with trimethylsilylchloride (0.46 g, 4.2 mmol) and stirred for 2h (0°C). After addition of 5 mL of an aqueous copper sulphate solution and stirring for 30 min at room temperature, the organic layer was separated, washed with saturated sodium bicarbonate, dried over anhydrous potassium carbonate and the solvent removed *in vacuo*, giving the title product **12** (0.57 g, 82 %) as a colourless liquid. IR ($CHCl_3$) 2910, 2850, 1670, 1420, 1375, 1315, 1245, 1200, 1080, 1015, 910, 900, 835 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.12 (bs, 1 H), 6.01 (t, J = 1.2 Hz, 1 H), 4.47 (q, J = 1.2, 4.8 Hz, 1 H), 2.32 (s, 3 H), 1.75-0.80 (m, 11 H), 0.02 (s, 9 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 199.1, 151.6, 125.4, 72.9, 43.5, 30.0, 26.9, 26.4, 26.3, 26.2, -0.1; M.S. *m/z* (M^+) calcd 254.1718, obsd 254.1702.

2-(1-Hydroxyethyl)-2-cyclopenten-1-one 13.

To a stirred solution of 2-cyclopenten-1-one (2.0 g, 24 mmol) and acetaldehyde (1.6 g, 36 mmol) in dichloromethane (60 mL), at -20°C, under argon, was added dropwise diethylaluminium iodide (28 mL, 28 mmol, 1M solution in toluene). On completion of the addition and stirring for a further 2h at -20°C, diethyl ether (30 mL) was added, followed by 25 mL of a 0.2 M aqueous HCl solution. The organic layer was separated and the aqueous phase further extracted with diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil which was purified by column chromatography (silica gel, 1: 2 ethyl acetate : petroleum ether) giving the title compound **13** (1.7 g, 60 %) as a colourless oil. IR ($CHCl_3$) 3450, 3000, 1710, 1685, 1630, 1520, 1440, 1400, 1370, 1295, 1230, 1080, 1050, 1000, 980, 920, 880 cm^{-1}, ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (m, J = 1.5, 3.0 Hz, 1 H), 4.63 (m, J = 1.5, 6.8 Hz, 1 H), 3.34 (b, 1 H), 2.63 (m, 2 H), 2.46 (m, 2 H), 1.40 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.8, 157.0, 148.9, 63.6, 35.2, 26.4, 21.6; MS *m/z* (M^+) calcd 126.0681, obsd 126.0696.

2-(1-Hydroxyethyl)-2-cyclohepten-1-one 15.

To a cooled (-20°C) solution of 2-cyclohepten-1-one (1.09 g, 10 mmol) and acetaldehyde (0.66 g, 15 mmol) in 50 mL of dichloromethane was added dropwise, under argon, 12 mL of

diethylaluminium iodide (12 mmol, 1M solution in toluene). After stirring for a further 2h, the reaction mixture was diluted with 30 mL of diethyl ether followed by the addition of 20 mL of a 0.2M aqueous HCl solution. The organic layer was separated and the aqueous phase extracted using diethyl ether (2 x 30 mL). The ethereal extract was washed with brine (40 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. The crude reaction product was purified by column chromatography (silica gel, ethyl acetate : petroleum ether 1: 4) to give compound **15** (0.84 g, 54 %) as a colourless oil. IR ($CHCl_3$) 3500, 3000, 2970, 2860, 1695, 1660, 1520, 1450, 1410, 1380, 1230, 1200, 1115, 1055, 1020, 925, 880 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 6.71 (td, *J* = 1.1, 6.3 Hz, 1 H), 4.51 (m, *J* = 1.0, 1.8, 6.6 Hz, 1 H), 2.60 (m, 2 H), 2.44 (m, 2 H), 1.85-1.70 (m, 4 H), 1.33 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 206.2, 145.7, 141.3, 69.0, 43.1, 27.5, 24.9, 22.4, 21.4; M.S. *m/z* (M^+) calcd 154.0994, obsd 154.1000.

***Syn*-2-(cyclohexyl-hydroxymethyl)-1,2-epoxybutan-3-one 6 and *anti*-2-(cyclohexyl-hydroxymethyl)-1,2-epoxybutan-3-one 7** (Table 1, entry 1).

To a cold (0°C) solution of 3-methylene-4-hydroxy-4-cyclohexylbutan-2-one **5** (7.50 g, 41 mmol) in 50 mL of methanol was added dropwise 10 mL of a 30% aqueous hydrogen peroxide (0.1 mol) solution followed by 9 mL of a 2 M aqueous sodium hydroxide solution (18 mmol). After stirring for a further 3h, 30 mL of water were added. Extraction of the resulting suspension with diethyl ether (3 x 80 mL), drying of the combined ethereal extract (Na_2SO_4) and removal of the solvent *in vacuo* afforded a colourless oil containing the two diastereoisomeric epoxides (*syn*: *anti* = 2 : 3), which were separated by column chromatography (silica gel, petroleum ether : ethyl acetate, 6 : 1).

***Syn*-2-(cyclohexyl-hydroxymethyl)-1,2-epoxybutan-3-one 6** (2.50 g, 30%), colourless oil. IR ($CHCl_3$) 3540, 2920, 2850, 1705, 1445, 1360, 1110, 1020, 960, 890, 870 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.01 (AB, *J* = 5.1 Hz, 2H), 3.00 (q, *J* = 8.0, 9.8 Hz, 1 H), 2.75 (d, *J* = 9.8 Hz, 1 H), 2.08 (s, 3 H), 2.05-0.90 (m, 11 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.3, 78.3, 61.5, 49.7, 41.4, 29.3, 29.1, 26.3, 25.9, 25.7, 24.4; MS (EI) *m/z* 180 (M^+-H_2O), (CI) 216 (M^++NH_4). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.66; H, 9.09. Found: C, 66.52; H, 9.33.

***Anti*-2-(cyclohexylhydroxymethyl)-1,2-epoxybutan-3-one** (3.8 g, 46%), colourless solid, m.p. 36-37°C (from n-hexane). IR ($CHCl_3$) 3550, 2910, 2850, 1710, 1445, 1360, 1110, 1020, 960, 890, 870 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 3.91 (q, *J* = 5.8, 9.0 Hz, 1 H), 3.14 (AB, *J* = 5.0 Hz, 2 H), 2.10 (s, 3 H), 1.90-0.80 (m, 12 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 207.2, 73.5, 64.2, 48.4, 41.1, 29.9, 28.2, 26.2, 26.1, 25.9, 24.7; MS *m/z* (EI) 180 (M^+-H_2O) (CI) 216 (M^++NH_4). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.66; H, 9.09. Found: C, 66.59; H, 9.11.

Epoxidation of 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one 5 at -40°C (Table 1, entry 2).

To a cold (-40°C) solution of 3-methylene-4-cyclohexyl-4-hydroxy-butan-2-one **5** (0.2 g, 1.1 mmol) in methanol (5 mL) was added dropwise *tert*-butyl hydroperoxide (1.1 mL, 3.3 mmol, 3 M solution in 2,2,4-trimethylpentane) followed by sodium hydroxide (0.3 mL, 0.6 mmol, 2 M

solution). The reaction was stirred at -40°C for 4h and quenched by the addition of 3 mL of water. The resulting suspension was extracted with diethyl ether (3 x 10 mL). The combined ethereal extracts were washed with brine (10 mL), dried (Na_2SO_4) and the solvents removed *in vacuo* to give a mixture of the *syn*- and *anti*-epoxy-alcohols **6** and **7** (0.15 g, 70%, ratio 1: 2).

Phase Transfer Catalysed Epoxidation of 5 (Table 1, entry 3).
To a solution of 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one **5** (0.18 g, 1 mmol), benzyl quininium bromide (0.03 g, 0.06 mmol), and cumyl hydroperoxide (0.21 g, 1.1 mmol) in toluene (10 ml) at -20°C was added NaOH (0.04 mL, 6M, 0.24 mmol). The reaction mixture was stirred at -20°C for 30 h. The organic layer was separated, washed with water (5 mL) and dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* gave a mixture of the *syn*- and *anti*-epoxides (ratio 2 : 3) in 78% yield (0.15 g).

Epoxidation of 5 Using Lithium *tert*-butylhydroperoxide (Table 1, entry 4).
To a cooled (-78°C) THF solution (4 mL) of *tert*-butyl hydroperoxide (0.77 mL, 2.3 mmol, 3 M solution in 2,2,4-trimethylpentane) was added under argon 1.06 mL of butyllithium (1.7 mmol, 1.6 M solution in hexanes). After 5 min, 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one **5** (0.2 g, 1.1 mmol) in THF (2 mL) was introduced. The reaction mixture was allowed to warm to room temperature and stirred for a further 16 h before solid sodium sulphite was added. After 15 min, the mixture was diluted with diethyl ether (10 mL), filtered through Celite and the filtrate concentrated *in vacuo*. Examination of the reaction product by NMR and TLC indicated that a complex mixture of products had formed.

mCPBA Epoxidation of 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one 5 (Table 1, entry 5).
To a stirred solution of 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one **5** (0.2 g, 1.1 mmol) in dichloromethane (12 mL), at 0°C, was added mCPBA (0.47 g, 2.7 mmol). The reaction was stirred at room temperature and monitored by TLC. No epoxide was formed after three days.

Titanium (IV) Isopropoxide-Catalysed Epoxidation of 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one 5 (Table 1, entry 6).
General Procedure for Titanium-Catalysed Epoxidations
Powdered, activated 4A molecular sieves were added to dry dichloromethane (5 mL) and the mixture cooled to -20°C, under an argon atmosphere. After addition of $Ti(OPr^i)_4$ (31 mg, 33 µl, 0.11 mmol) and 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one **5** (0.2 g, 1.1 mmol. dissolved in 1 mL of dichloromethane), and stirring for 20 min, *tert*-butyl hydroperoxide (0.73 mL, 2.2 mmol, 3 M solution in 2,2,4-trimethyl pentane) was introduced over a period of 10 min. The reaction was warmed to -15°C, stirred overnight and quenched by the addition of 1 mL of water followed by stirring for 30 min. The organic layer was separated and the aqueous phase extracted with dichloromethane (3 x 5 mL). The combined organic extracts were washed with brine (6 mL),

dried over $MgSO_4$ and the solvents removed *in vacuo* to give the crude *syn*-epoxide **6**. No *anti*-epoxide could be detected in the crude NMR spectrum. Purification by column chromatography (silica gel, 1: 5 ethyl acetate : light petroleum) yielded the pure *syn*-epoxy-alcohol **6** (0.17 g, 78 %).

Vanadyl Acetylacetonate-Catalysed Epoxidation of 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one 5 (Table 1, entry 7).
To a cold (0°C) solution of 3-methylene-4-cyclohexyl-4-hydroxybutan-2-one **5** (0.2 g, 1.1 mmol) in dry benzene (8 mL) was added vanadyl acetylacetonate (0.06 g, 0.22 mmol), producing a green solution which was stirred for 20 min. before dropwise addition of *tert*-butyl hydroperoxide (0.73 mL, 2.2 mmol of a 3M solution in 2,2,4-trimethylpentane) over 10 min. The resultant red solution was stirred for 10 h at room temperature and the colour changed to yellow-brown. The reaction mixture was washed with water (4 mL), brine (4 mL) and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* followed by purification on silica gel (ethyl acetate : petroleum ether 1 : 3) gave 0.16 g (76 %) of the pure *syn*-epoxide **6**.

***Syn*-3-methylene epoxy-4-hydroxy-pentan-2-one** (Table 2, entry 1a).
(63 %), colourless oil. IR ($CHCl_3$) 3580, 3000, 2910, 1705, 1400, 1360, 1230, 1195, 1100, 1070, 1025, 950, 915, 885 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (m, J = 6.3 Hz, 1 H), 3.04 (AB, J = 4.8 Hz, 2 H), 2.60 (d, J = 6.3 Hz, 1 H), 2.08 (s, 3 H), 1.30 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 66.3, 63.2, 49.0, 24.5, 18.7; MS *m/z* (EI) 112 (M^+-H_2O).

***Syn*-3-methylene epoxy-4-hydroxy-hexan-2-one** (Table 2, entry 1b).
(72 %), colourless oil. IR ($CHCl_3$) 1710 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 3.58 (q, J = 3.8, 9.1 Hz), 1 H), 3.05 (AB, J = 4.8 Hz, 2 H), 2.62 (b, 1 H), 2.08 (s, 3 H), 1.73 (m, J = 13.8, 7.5, 4.0 Hz, 1 H,), 1.55 (m, J = 13.8, 9.1, 7.3 Hz, 1 H), 1.01 (t, J = 6.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 72.9, 62.4, 49.6, 26.4, 24.6, 10.1; MS *m/z* (EI) 126 (M^+-H_2O).

***Syn*-3-methylene epoxy-4-hydroxy-5-methyl-hexan-2-one** (Table 2, entry 1c). Prepared according to the general method described for the epoxidation of **5**. (70 %), colourless oil. IR ($CHCl_3$) 3540, 2960, 1700, 1465, 1390, 1360, 1230, 1180, 1100, 1035, 870 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 3.01 (AB, J = 5.0 Hz, 2 H), 2.99 (q, J = 5.1, 9.3 Hz, 1 H), 2.80 (b, 1 H), 2.09 (s, 3 H), 2.01 (m, J = 5.2, 6.5, 6.8 Hz, 1 H), 1.00 (d, J = 6.5 Hz, 3 H), 0.93 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.2, 78.8, 61.8, 49.7, 31.9, 24.5, 19.0, 18.5; MS *m/z* (EI) 140 (M^+-H_2O).

Isopropyl *syn*-2-methylene epoxy-3-hydroxy-butanoate (Table 2, entry 2).
To a cold (-15°C) solution of methyl-3-methylene-4-hydroxybutanoate **9** (0.2 g, 1.5 mmol) in dichloromethane (8 mL) was added 4A molecular sieves followed by 0.84 mL of titanium (IV) isopropoxide (0.88 g, 3.1 mmol). After stirring for 30 min, *tert*-butyl hydroperoxide (1.1 mL, 3.3 mmol 3M solution in 2,2,4-trimethylpentane) was introduced over a period of 10 min. The

reaction mixture was stirred for a further 30h, before being diluted with dichloromethane (12 mL). Water was added and the mixture stirred vigorously at room temperature for 30 min. The organic layer was separated and the aqueous phase extracted twice with dichloromethane (20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and the solvents removed *in vacuo* to give the crude *syn*-epoxide. The pure isopropyl *syn*-2-methylene epoxy-3-hydroxybutanoate was obtained by filtration of the crude product through silica (1: 5 ethyl acetate : petroleum ether) (0.22 g, 81 %), colourless oil. IR ($CHCl_3$) 3000, 1730, 1520, 1420, 1375, 1280, 1225, 1200, 1140, 1090, 1030, 1015, 930 850 cm-1 ; ^1H NMR (250 MHz, $CDCl_3$) δ 5.12 (m, *J* = 6.1 Hz, 1 H), 4.15 (m, *J* = 0.4, 6.6 Hz, 1 H), 3.10 (AB, *J* = 5.8 Hz, 2 H), 2.53 (bd, *J* = 0.4 Hz, 1 H), 1.34 (d, *J* = 6.6 Hz, 3 H), 1.29 (d, *J* = 6.5 Hz, 3 H), 1.28 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (62.9 MHz $CDCl_3$) δ 168.9, 69.6, 65.5, 58.8, 49.3, 21.5, 18.5; MS *m/z* (CI) 192 (M^++NH_4), 175 (M^++H). Anal. Calcd for $C_8H_{14}O_4$: 55.17; H, 8.05. Found: C, 55.09; H, 7.79.

***tert*-butyl *syn*-2-methylene epoxy-3-hydroxybutanoate** (Table 2, entry 3).
0.43 g (78 %), colourless liquid . IR ($CHCl_3$) 3560, 2980, 2930, 1730, 1395, 1370, 1295, 1260, 1160, 1135, 1090, 1030, 925, 835 cm^{-1}; ^1H NMR (250 MHz, ($CDCl_3$) δ 4.10 (m, *J* = 5.5, 6.2 Hz, 1 H), 3.07 (AB, *J* = 5.8 Hz, 2 H), 2.49 (d, *J* = 5.5 Hz, 1 H), 1.50 (s, 9 H), 1.33 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.3, 83.0, 65.6, 59.1, 49.3, 27.8, 18.6; MS *m/z* (M^+-Me) calcd 173.0814, obsd 173.0817.

***Syn*-2-(1-hydroxy-ethyl)-2,3-epoxy-2-cyclopentan-1-one** (Table 3, entry 1, condition **A**). (73 %), colourless oil. IR ($CHCl_3$) 3570, 3000, 2940, 1745, 1530, 1425, 1370, 1230, 1200, 1075, 1040, 930, 865 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 4.35 (q, *J* = 6.5 Hz, 1 H), 3.91 (m, 1 H), 2.49 (b, 1 H), 2.48-1.92 (m, 4 H), 1.23 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 190.1, 65.1, 61.8, 61.5, 32.3, 22.1, 18.0; MS *m/z* (M^+) calcd 142.0630, obsd 142.0626.

***Syn*-2-(1-hydroxyethyl)-2,3-epoxy-2-cyclohexan-1-one** (Table 3, entry 2, condition **A**). (82 %), colourless oil. IR ($CHCl_3$) 3560, 3000, 2950, 1710, 1515, 1370, 1275, 1230, 1200, 1070, 1000, 920, 850 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 4.33 (q, *J* = 6.2 Hz, 1 H), 3.64 (t, *J* = 2.0 Hz, 1 H), 2.64-2.53 (m, 1 H), 2.38 (b, 1 H), 2.35-1.62 (m, 5 H), 1.23 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 206.7, 63.1, 62.6, 58.1, 37.5, 23.0, 18.0, 17.5; MS *m/z* (M^+) calcd 155.0708, obsd 155.0696.

***Syn*-2-(1-hydroxy-ethyl)-2,3-epoxy-2-cycloheptan-1-one** (Table 3, entry 3, condition **A**). (68 %), colourless oil. IR ($CHCl_3$) 3520, 3000, 2940, 1685, 1520, 1450, 1420, 1230, 1200, 1075, 980, 925, 890 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 3.83 (bq, *J* = 6.5 Hz, 1 H), 3.35 (d, *J* = 6.0 Hz, 1 H), 2.91 (b, 1 H), 2.77 (m, *J* = 4.0, 10.5, 13.3 Hz, 1 H), 2.47-2.25 (m, 2 H), 1.93-1.65 (m, 4 H), 1.30 (d, *J* = 6.4 Hz, 3 H), 1.10 (m, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 213.1, 68.9, 67.6, 59.5, 41.2, 27.0, 24.0, 23.0, 19.0; MS *m/z* (M^+-H_2O) calcd 152.0847, obsd 152.842.

General procedure for the base-catalysed epoxidation of cyclic β-hydroxy enones (Table 3, condition **B**).

To a cold solution (0°C) of 2-(1-hydroxyethyl)-2-cyclohexen-1-one **14** (280 mg, 2 mmol) in 5 mL of methanol was added dropwise 1.3 mL of *tert*-butylhydroperoxide (4 mmol, 3 M solution in 2,2,4-trimethylpentane) followed by 0.5 mL of an aqueous sodium hydroxide solution (1 mmol, 2 M). The reaction mixture was stirred for a further 4h. Water (3 mL) was then added and the mixture extracted with diethyl ether (3 x 10 mL). The ethereal extract was washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was filtered through silica gel (1 : 1 ethyl acetate : petroleum ether). The resulting oil (0.28 g, 91 %) was shown to contain the *syn*- and *anti*-epoxy-alcohols in a 10 : 1 ratio.

Vanadyl Acetylacetonate-Catalysed Epoxidation of 2-(1-hydroxy-ethyl)-2-cyclohexen-1-one 14 (Table 3, entry 2, condition D).

To a cold (-20°C) solution of 2-(1-hydroxyethyl)-2-cyclohexen-1-one **14** (0.2 g, 1.4 mmol) in 5 mL of dichloromethane was added vanadyl acetylacetonate (0.074 g, 0.28 mmol). The green solution which resulted was stirred for 20 min. then *tert*-butyl hydroperoxide (0.93 mL, 2.8 mmol, 3 M solution in 2,2,4-trimethylpentane) was added dropwise over a period of 10 min. The red solution was stirred at -20°C for 12 h and quenched by the addition of 3 mL of water. The organic layer was separated and the aqueous phase extracted with dichloromethane (2 x 5 mL). The organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and the solvents removed *in vacuo*. Purification by column chromatography (silica gel, 1 : 2 ethyl acetate : petroleum ether) afforded 0.2 g (92 %) of the pure *syn*-epoxy-alcohol.

General Procedure for the kinetic Resolutions (Table 4).

To a cold (-20°C) suspension of crushed 4A molecular sieves in 4 mL of dichloromethane were added sequentially, $Ti(OPr^i)_4$ (31 µl, 31 mg, 0.11 mmol), (-)-diethyl tartrate (22 µl, 27 mg, 0.13 mmol), and 3-methylene-4-hydroxy-4-cyclohexylbutan-2-one **5** (0.2 g, 1.1 mmol) dissolved in 1 mL of dichloromethane. The resulting mixture was stirred for 30 min followed by the addition of *tert*-butylhydroperoxide (0.73 mL, 2.2 mmol, 3 M solution in 2,2,4-trimethylpentane) over a period of 10 min. The reaction was then warmed to -15°C and stirred for 4h before being quenched by the addition of 1 mL of water. After stirring for 30 min. the organic layer was separated and the aqueous phase was extracted with dichloromethane (2 x 5 mL). The combined organic extracts were stirred with aqueous $FeSO_4$ (5 mL), washed with brine (5 mL) and dried over $MgSO_4$. Concentration gave a 1:1 mixture of starting hydroxyenone **5** and *syn*-2-(cyclohexyl-hydroxy-methyl)-1,2-epoxy-butan-3-one **6** which were separated by reverse phase HPLC (C18 column, 2 : 3 acetonitrile : water). The optical purity of the recovered enone was determined by HPLC on chiral support (Pirkle 1A, hexane : isopropanol) as well as by using the chiral shift reagent: Eu(hfc)3 and found to be 13% whereas that of the epoxide was found to be 18 % (confirmed by formation of Mosher esters and integration of HPLC trace (Dynamax silica column, 19:1 hexane : ethyl acetate). A similar procedure was applied for the other resolutions.

References and Notes

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7 In this context, it is important to remember the beautiful work done by Jackson (**a.** Ashwell, M.; Clegg, W.; Jackson, R. W. *J. Chem. Soc., Perkin Trans I*, **1991**, 897. **b.** Ashwell, M.; Jackson, R. W.; Kirk, J. M. *Tetrahedron*, **1990**, *46*, 7429.) on the directed epoxidation of β-hydroxysulfones using $LiOOBu^t$. Transposition of these reaction conditiond to our case, however, lead to the formation of the Baeyer-Villiger product in extremely low yield, accompanied by extensive decomposition. We are very grateful to Dr. R. Jackson for pointing out to us the need - and the great sensitivity - of this reaction to be performed at the right temperature. This parameter varies considerably from substrate to substrate.

8 In light of the well-known ability of titanium and vanadium complexes to coordinate to hydroxyl functions, the thought of using these metals to effect the desired directed-epoxidation occurred to us quite early on. However, the electron-poor nature of the carbon-carbon double bond of the β-hydroxyenones coupled with the absence of reports on the ability of these metals to epoxidise electron-deficient systems left us with little doubt that the chances of success were, at best, slim.

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11 The vanadium-catalysed epoxidations proved to be more capricious to handle than the titanium ones. Despite this slight drawback, again only the *syn*-epoxy-alcohol is produced with complete diastereocontrol. The oxidation of other electron-deficient olefins using various metal catalysts will be reported elsewhere.

12 We have no reasonable explanation to offer at this stage for the particular behaviour of the acrylonitrile derivative.

13 Weitz, E.; Scheffer, A. *Ber.*, **1921**, *54*, 2327.

14 For a synthetic application of our observation, see: Marson, C. M.; Benzies, D. W. M.; Hobson, A. D.; Adams, H.; Bailey, N. A. *J. Chem. Soc., Chem. Commun.*, **1990**, 1516.

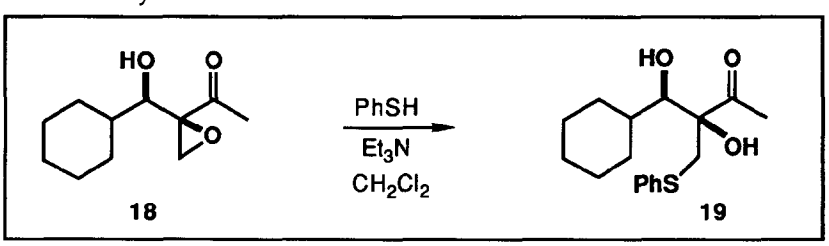
15 Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1981**, *103*, 6237.

16 It is possible that a six-membered titanium chelate, involving both the hydroxyl and the carbonyl oxygen atoms, is implicated in these reactions. Intramolecular oxygen transfer *via* a boat-like transition-state may then lead to the observed *syn*-epoxide. However, it is worth remembering that these titanium alkoxides are very dynamic systems and that such an intermediate may not be the most reactive species in the mixture. It is also interesting to note that all these reactions proceed more slowly than the epoxidations of the corresponding simple allylic alcohols. Such a chelate may actually be responsible for the decrease in the rate of the reaction. An alternative explanation is to assume that, under the influence of the metal, the carbonyl function will rotate out of conjugation. The substrate then becomes a reasonable electron-rich system and usual epoxidation takes place. This argument is, however, difficult to transpose to the cyclic enone cases.

17 Wu, Y.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.*, **1987**, *109*, 5560.

18 Such an arrangement allows the interaction between the σ^* antibonding orbital of the C-O bond and the carbon-carbon π-orbital resulting, not only in further stabilisation during the attack by the nucleophile, but also in an increased facial-discrimination (A different conformation has been proposed for electrophilic attack on allylic alcohols: Houck, K. N. *J. Am. Chem. Soc.*, **1984**, *106*, 3880). In this context, it is noteworthy that base-catalysed epoxidation of the hydroxyl-protected cyclic β-hydroxyenone **14** gave a 5 : 1 ratio of *syn*- to *anti*-epoxide. This observation rules out any significant participation of hydrogen-bonding in these Weitz-Scheffer epoxidation.

19 For example, ring-opening of epoxide **18** using thiophenol-triethylamine proved to be highly regioselective, giving the diastereomerically pure *syn*-diol **19**. Such functionalised diols are difficult to obtain by other routes.



18 19

20 Amri, H.; Villieras, J. *Tetrahedron Lett.*, **1986**, *27*, 4307.

21 Baylis, A. B.; Hillman, M. E. D. German Patent No 2155113, **1972**, [CA **1972**, *77*, 341749].

22 Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.*, **1981**, *54*, 274.

23 Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl.*, **1983**, *22*, 795.