PERKIN 1 COMMUNICATION

Stereoselective epoxidation of electron poor dienes using poly(L-leucine)

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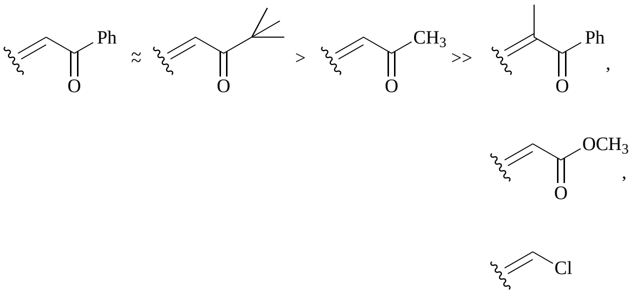
Poly(L-leucine) catalysed oxidation of dienes 2, 3, 10, 16 and 18 and the triene 17 furnishes the corresponding epoxides 4, 5, 11, 19, 21 and 20 respectively in good to excellent yield and in states of high optical purity. Some regioselective reactions of the saturated epoxy ketones 5 and 11 are described.

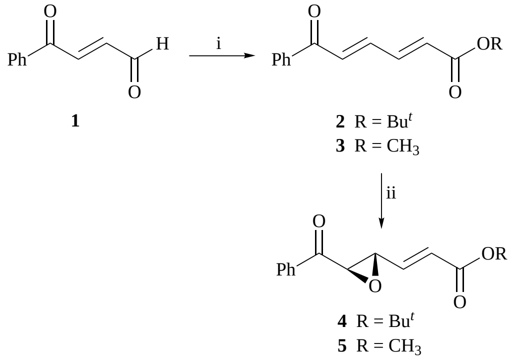
The stereoselective oxidation of chalcones using basic hydrogen peroxide and poly(L-leucine) was pioneered by Banfi *et al.*[1] We have shown that the original three-phase oxidation system could be applied to α,β-unsaturated ketones other than chalcones (1,3-diphenylprop-2-en-1-ones).[2] Use of a two-phase oxidation method considerably enhanced the rate of oxidation of chalcones and allowed the range of substrates to be extended further.[3]

α,β-Unsaturated esters as well as vinyl chlorides and electron rich alkenes are totally unreactive even under the new conditions. Less predictably α-methylchalcone [PhCH=C(CH_3)-COPh] is far less reactive than chalcone itself; the relative rates of oxidation of α,β-unsaturated carbonyl compounds can be ordered qualitatively as shown below.



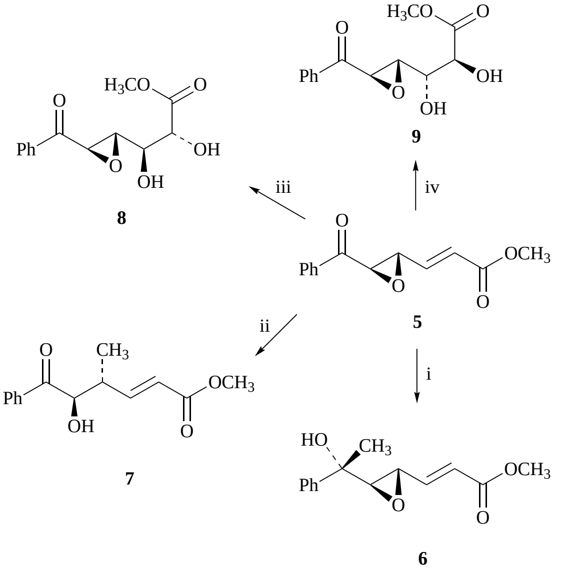
While the lack of reactivity of species such as cinnamate esters is disappointing, the marked difference in reactivity of different alkenes may be used to advantage in some circumstances.

For example keto esters **2** and **3** are readily prepared from the aldehyde **1** (Scheme 1) and are readily oxidised over a period of 5 h using urea hydrogen peroxide (UHP) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran under catalysis by poly(L-leucine) to give the epoxides **4** (95% yield, 90% ee) and **5** (90% yield, 90% ee) respectively. Use of poly(D-leucine) in the preparation of *ent*-**5** gives comparable results (91% yield, 95% ee).



Scheme 1 *Reagents and conditions:* i, $Ph_3P{=}CHCO_2R$, $PhCH_3$, 70%; ii, poly(L-leucine), urea hydrogen peroxide, DBU, THF, 90%

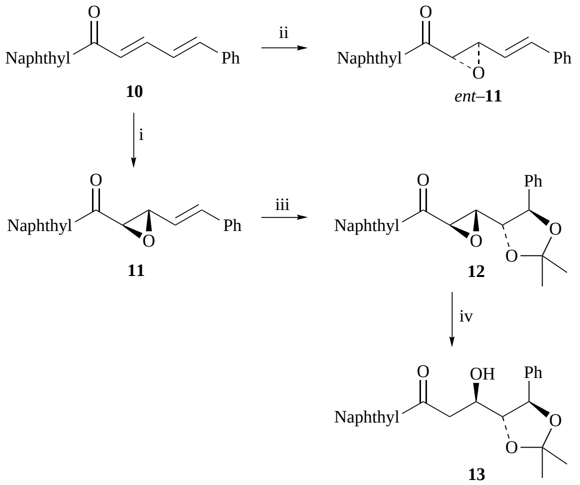
The optically active products are susceptible to attack at multiple points by other reagents; the ketone carbonyl group, the alkene moiety and the ester unit may be attacked in a chemoselective fashion. For example, reaction of the keto ester **5** with methylmagnesium chloride gives the tertiary alcohol **6** as the only stereoisomer (70% yield) (Scheme 2).



Scheme 2 *Reagents and conditions:* i, MeMgCl, THF, 71%; ii, MeLiCuCN, THF, 30%; iii, 'super' AD mix α, 58%; iv, 'super' AD mix β, 68%

In contrast, reaction of compound **5** with LiCuCNMe gave the epoxy-ring opened product **7** albeit in modest yield. Dihydroxylation of the alkene unit in compound **5** with *N*-methylmorpholine *N*-oxide and a catalytic amount of osmium tetraoxide gave an inseparable mixture of the diols **8** and **9** in the ratio 2 : 1. Good control over the introduction of the *cis*-diol unit is achieved using the 'super' AD mix preparations recommended by Sharpless *et al.*[4] (Scheme 2).

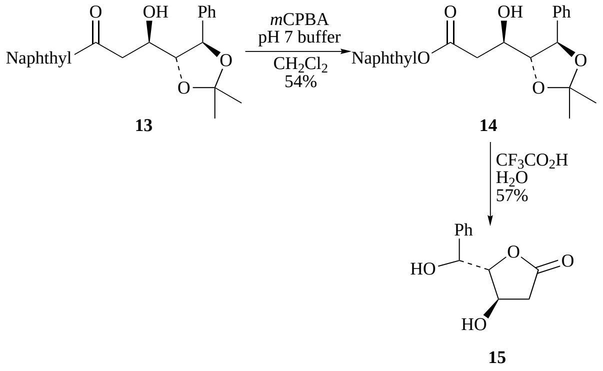
The asymmetric epoxidation of the dienone **10** (naphthyl refers to the 2-naphthyl isomer) gives the oxirane **11** with poly(L-leucine) and the enantiomer *ent*-**11** with poly(D-leucine) (Scheme 3).[5] Once again the differing reactivity of the alkene unit, the epoxide moiety and the carbonyl group may be used to advantage. Thus, *bis*-hydroxylation and acetonide formation, according to Sharpless's rules,[4,6] allows access to the compound **12**; reaction of this compound with higher order cuprate leads to opening of the three-membered ring and formation of the secondary alcohol **13**. The latter product was unexpected and



Scheme 3 *Reagents and conditions:* i, poly(L-leucine), urea hydrogen peroxide, DBU, THF, 85%, 96% ee; ii, poly(D-leucine), urea hydrogen peroxide, DBU, THF, 80%, 90% ee; iii, (a) AD mix-β, 95%, (b) for clarity (D-2,2′-dimethoxypropane, toluene-*p*-sulfonic acid (*p*-TSA, cat.), acetone, 92%; iv, MeLiCuCN, THF, 55%

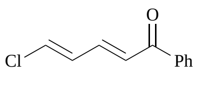
was characterised only after a full spectroscopic data set had been obtained.†

Subsequent oxidation of **13** under standard Baeyer–Villiger conditions gave the ester **14**, which was then treated with



aqueous trifluoroacetic acid to afford the γ-lactone **15** in 57% yield over two steps.‡

Finally, the chlorodiene **16**, the trienone **17** and alkylated dienone **18** were oxidised with urea–hydrogen peroxide under catalysis by poly(L-leucine) to furnish the epoxides **19** (57% yield, 86% ee), **20** (43% yield, 90% ee) and **21** (70% yield, 92% ee) with remarkable selectivity, emphasising the predictability and regioselectivity of the oxidation process on the basis of double bond reactivity as shown above.



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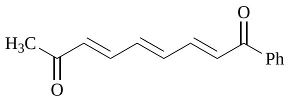

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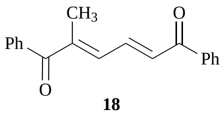

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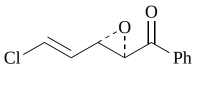

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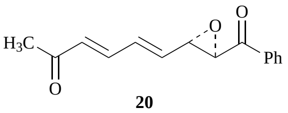

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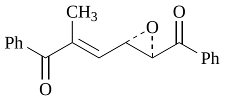

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Experimental

Procedure for the poly(L-leucine) oxidation of dienone ester 3

To a solution of the dienone **3** (3.96 mmol) in THF (13 cm^3) was added successively poly(L-leucine) (1.65 g), urea–hydrogen peroxide (447 mg, 4.8 mmol, 1.2 equiv.), and DBU (718 µl, 4.8 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature for 5 h after which time TLC analysis (50% ethyl acetate–light petroleum) indicated total consumption of starting material. The poly(L-leucine) was removed by suction filtration, washing with ethyl acetate. The filtrate was concentrated *in vacuo* and the resulting brown residue was purified by flash-column chromatography [light petroleum–ethyl acetate (70 : 30)] to yield the epoxide **5** as a colourless solid (90%), mp 58–59 °C; $[\alpha]_D^{23}$ −80.4 (*c* 1.15, CHCl$_3$) (Found: M$^+$, 232.07331. $C_{13}H_{12}O_4$ requires *M*, 232.07356); δ_H(300 MHz; CDCl$_3$) 3.71 (1H, dd, *J* 1.8 and 7.2, =CHC*H*O), 3.78 (3H, s, OCH$_3$), 4.24 (1H, d, *J* 1.8, CHOC=O), 6.28 (1H, d, *J* 15.7, =C*H*CO$_2$CH$_3$), 6.78 (1H, dd, *J* 7.2 and 15.7, =C*H*CHO), 7.49–7.54 (2H, m, 2 × ArC*H*), 7.62–7.67 (1H, m, ArC*H*), 8.01 (2H, d, *J* 7.0, 2 × ArC*H*); δ_C(75 MHz; CDCl$_3$) 51.90 (OCH$_3$), 56.94 (CHO), 58.67 (CHO), 125.64 (=CH), 128.44 (=CH), 129.02 (=CH), 134.26 (=CH), 135.35 (ArC), 142.20 (=CH), 165.69 (C=O), 192.63 (C=O); ν_{max}(thin film)/cm^{-1} 1722 (ester C=O), 1689 (ketone C=O), 1231 (epoxide); *m*/*z* (EI) 232 (M$^+$, 1%), 217 (M$^+$ − CH$_3$, 3), 201 (217 − O, 2), 105 (PhCO, 100).

Acknowledgements

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† $[\alpha]_D^{29}$ +50 (*c* 0.8, CHCl$_3$) (Found: MH$^+$, 377.174 81. $C_{24}H_{24}O_4$ requires *M*H, 377.175 29); δ_H(400 MHz; CDCl$_3$) 1.59 (3H, s, CH$_3$), 1.62 (3H, s, CH$_3$), 3.18 (1H, dd, *J* 3.1 and 17.4, C*H*H′), 3.21 (1H, s, OH, exchangeable with D$_2$O), 3.48 (1H, dd, *J* 9.0 and 17.4, CH*H*′), 3.88 (1H, dd, *J* 8.6 and 1.8, CHO), 4.36 (1H, approx. dt, *J* 9.0 and 2.5, C*H*OH), 5.17 (1H, d, *J* 8.6, CHO), 7.48 (7H, m, 6 × naphthyl-C*H*, 1 × Ar-C*H*), 7.91 (4H, m, ArC*H*), 8.40 (1H, s, naphthyl-C*H*); δ_C(75 MHz; CDCl$_3$) 26.92 (CH$_3$), 27.32 (CH$_3$), 43.01 (CH$_2$), 65.21 (CHOH), 78.78 (CHO), 85.55 (CHO), 109.52 [(CH$_3$)$_2$*C*], 123.67 (naphthyl-CH), 126.93, 127.87, 128.46 (Ph-CH), 128.59, 128.77, 129.68, 130.13 (naphthyl-CH), 132.53, 134.15, 135.85 (naphthyl-C), 137.92 (Ph-C), 199.50 (C=O); *m*/*z* (FAB$^+$) 377 (MH$^+$, 12%), 361 (MH$^+$ − O, 15), 319 [MH$^+$ − (CH$_3$)$_2$CO, 100], 301 [MH$^+$ − (CH$_3$)$_2$CO − H$_2$O, 46].

‡ (Found: 226.108 24. $C_{11}H_{12}O_4$ + NH$_4$ requires 226.107 93); δ_H(400 MHz; CD$_3$CN) 2.48 (1H, dd, *J* 1.9 and 17.6, C*H*H′), 2.82 (1H, dd, *J* 5.7 and 17.5, CH*H*′), 3.92 (1H, br s, OH, exchangeable with D$_2$O), 3.95 (1H, br s, OH, exchangeable with D$_2$O), 4.27 (1H, ddd, *J* 1.9, 4.2 and 5.8, C*H*OH), 4.57 (1H, dd, *J* 4.1 and 6.4, CHO), 5.08 (1H, d, *J* 6.4, C*H*OH), 7.43 (5H, m, 5 × ArC*H*); δ_C(100 MHz; CD$_3$CN) 39.28 (CH$_2$), 68.20 (CHOH), 71.55 (CHO), 86.52 (CHOH), 127.05 (ArCH), 127.80 (ArCH), 128.22 (ArCH), 140.50 (Ar*C*), 175.65 (C=O); *m*/*z* (CI) 226 (M + NH$_4$, 100%), 208 (M + NH$_4$ − H$_2$O, 44%).