Improved procedure for Juliá–Colonna asymmetric epoxidation of α,β-unsaturated ketones: total synthesis of diltiazem and Taxol™ side-chain

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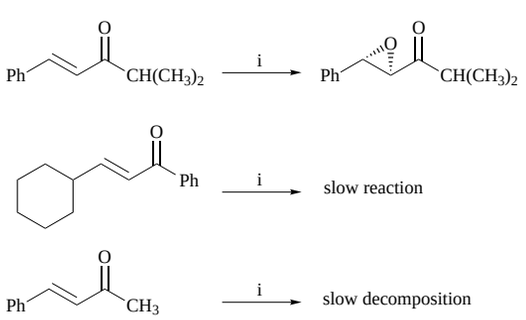
Poly-L-leucine catalyses the asymmetric epoxidation of enones 1–6 efficiently in a non-aqueous medium to provide the epoxy ketones 7–12 (70–91% yield; 80 to ≥95% ee). The strategy was used to make diltiazem 16 and the Taxol™ side chain 23 in single enantiomer form.

Introduction

The asymmetric epoxidation of α,β-unsaturated ketones is a topic of current interest. Recent publications have featured the use of lanthanide–bis(naphthol) complexes[1] and a magnesium bis(alkoxide) derived from (+)-diethyl tartrate[2] as interesting and useful methodology.

We have been interested for some time in developing and optimising an alternative procedure, namely the Juliá–Colonna asymmetric epoxidation of enones.[3] This oxidation reaction, as originally described, employs a three-phase system comprising of alkaline hydrogen peroxide, an organic solvent (such as hexane or toluene) and an insoluble polymer, for example poly-L-alanine or poly-L-leucine. Prior to use in the reaction, the polyamino acid catalyst had to be treated with the organic reaction solvent together with the alkaline hydrogen peroxide over a period of several hours so as to form a gel.

While the oxidation reaction often gave good yields of epoxy ketones with impressive optical purities, the reaction rates were often slow so that 24–72 h was normally the length of time required for completion of the reaction. In addition compounds sensitive to hydroxide were not viable starting materials. Another, more unexpected, restriction was that compounds with protons bonded to either the α′- or the α-carbon atoms were poor substrates, requiring extremely long reaction times, if they were oxidised at all (Scheme 1).



Scheme 1 *Reagents and conditions:* i, 30% aqueous H_2O_2, NaOH, hexane or toluene, immobilised poly-L-leucine (I-PLL), room temp., one week

Much of the tedium and many of the restrictions associated with the Juliá–Colonna oxidation procedure have been eliminated by the development of a non-aqueous, two-phase oxidation protocol which we report herein.[4]

Two phase poly-leucine oxidation of α,β-unsaturated ketones

The oxidation of chalcone **1** is effected very efficiently using the cheap, readily available oxidant urea hydrogen peroxide[5] (UHP) in tetrahydrofuran or *tert*-butyl methyl ether containing diazabicycloundecane (DBU), with immobilised poly-L-leucine[6] (I-PLL) as the insoluble catalyst. The epoxide **7** (85% yield, >95% ee) was obtained after only 20 min and no pre-treatment of the polypeptide catalyst with aqueous organic solvent was required. Under the new reaction conditions the polymer appears as a paste rather than gel.

Similarly alkene **2** furnished the corresponding epoxide **8** (85% yield, ≥98% ee), after only 2 h of reaction time. Even enones that were extremely poor substrates in the three-phase system (*e.g.* enones **3**, **4** and **5**) afforded the corresponding epoxides [compounds **9** (91% yield, 89% ee), **10** (70% yield, 80% ee) and **11** (76% yield, 94% ee)] over 3, 6 and 12 h respectively, employing the new conditions. The oxidation of enone **6**, to afford epoxy ketone **12**, was relatively slow (28 h)

1	$R^1 = R^2 = Ph$	**7**
2	$R^1 = CH{=}CHPh$; R^2 = naphthyl	**8**
3	R^1 = cyclohexyl; $R^2 = Ph$	**9**
4	$R^1 = Ph$; $R^2 = CH_3$	**10**
5	$R^1 = Ph$; $R^2 = Bu^t$	**11**
6	$R^1 = p\text{-}CH_3O\text{-}C_6H_4$; $R^2 = Bu^t$	**12**

but very efficient (≥90% yield) and highly enantioselective (≥96% ee).

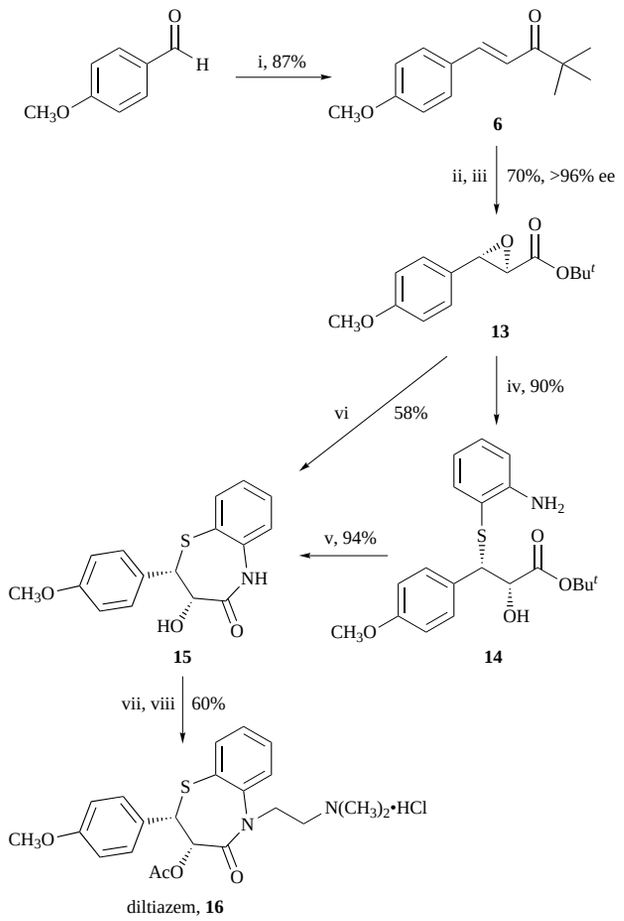
The work-up for the reaction is quite simple: the organic phase is decanted leaving the polymer in the reaction flask. The product is obtained from the organic phase after normal aqueous work-up, followed by flash chromatography. The catalyst can be recycled at least six times without detriment to the rate of oxidation or the optical purity of the product.

Synthesis of diltiazem

The potent blood pressure lowering agent diltiazem [(+)-(2*S*,3*S*)-*cis*-diltiazem hydrochloride] **16**, has been the focus of many syntheses.[7] However most syntheses of this commercially

important calcium channel blocker suffer from one of the following pitfalls: a large number of steps, low overall yield, and/or costly materials.

We now report a short total synthesis of diltiazem **16** from *p*-anisaldehyde in *ca.* 30% overall yield. Aldol condensation of cheap and commercially available *p*-anisaldehyde and pinacolone (3,3-dimethylbutan-2-one) provided enone **6** in 87% yield (Scheme 2) after Kugelrohr distillation; this unsaturated ketone was an excellent substrate in the new, two-phase asymmetric epoxidation protocol (*vide supra*). Thus large scale asymmetric epoxidation of enone **6** using I-PLL was straightforward and reproducible, providing ready access to large quantities of enantiomerically pure epoxy ketone **12** (90% yield, ⩾96% ee). In addition, it further substantiated our previous claims of the recyclable nature of the I-PLL.[4] Thus for each of three runs 4.0 g of enone **6** were epoxidised using the same 7.0 g batch of I-PLL catalyst. The reaction was not examined on a larger scale, but should be amenable to further scale-up based on previous research.[8] Note also that no loss in yield or ee was observed upon recycling the polyamino acid (I-PLL).



Scheme 2 *Reagents and conditions:* i, pinacolone, $NaOCH_3$, CH_3OH; ii, I-PLL, UHP, DBU, THF, 20 h; iii, KF, MCPBA, CH_2Cl_2; iv, *o*-aminothiophenol, toluene reflux; v, xylene reflux; vi, *o*-aminothiophenol, mesitylene; vii, 2-(dimethylamino)ethyl chloride, hydrochloride, K_2CO_3, EtOAc; viii, acetic anhydride, pyridine, DMAP

The isolated epoxide (1*S*,2*R*)-**12** was of such a quality that it was reacted on without further purification. Initial efforts concerning the requisite Baeyer–Villiger oxidation of **12** focused on the use of trifluoroperacetic acid. Following the prescribed conditions of Heaney *et al.*[5b] the epoxy ester **13** was formed, albeit in low yield (*ca.* 45%). Next we examined KF[9] and $NaHCO_3$ buffered MCPBA oxidation conditions and, gratifyingly, found the KF conditions to be far superior to the other methods, providing a 70% yield of epoxy ester **13**, from enone **6**. The structure of epoxy ester **13** was confirmed by an X-ray crystal structure determination (Fig. 1).

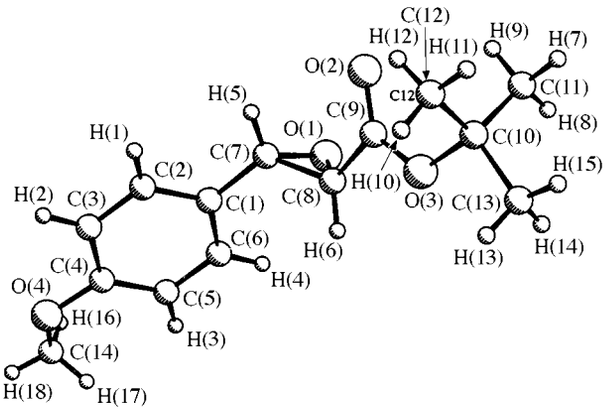


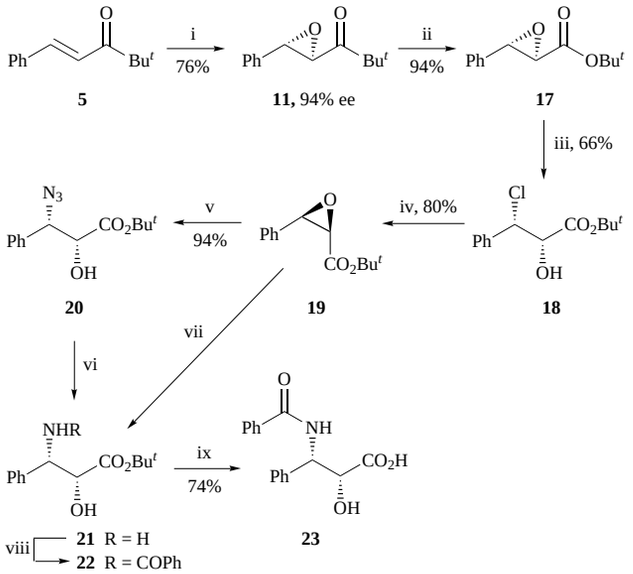
Fig. 1 Crystal structure of epoxy ester **13**

o-Aminothiophenol ring opening of epoxide **13** occurred with a rare example of retention of configuration upon nucleophilic attack at the stereogenic centre, providing alcohol **14** in 90% yield. The mechanism of this epoxy-ring opening reaction has been elaborated elsewhere.[7g,k] The reaction is effected in refluxing toluene for 18 h and is essentially quantitative. After removal of the toluene, *in vacuo*, high-grade product can be obtained by recrystallisation of the waxy yellow solid from a light petroleum and chloroform mixture. Dissolution of alcohol **14** in refluxing xylene furnished the well-documented diltiazem intermediate **15** in 94% yield, $[a]_D^{21}$ +57.6 (*c* 1.0, $CHCl_3$) {lit.,[7h] $[a]_D^{25}$ +55.2 (*c* 1.0, $CHCl_3$)}. Purification of the benzothiazepinone **15** could be effected by trituration of the crude product with a light petroleum–acetone mixture. The total synthesis of diltiazem **16** was completed using described alkylation and acetylation procedures.[7g] The absolute configuration and relative stereochemistry of the title compound was established unambiguously by correlation with ^{1}H NMR data, mp 206–208 °C, and $[a]_D^{20}$ +103.2 (*c* 1.0, CH_3OH) {lit.,[7g] mp 208–210 °C; $[a]_D^{20}$ +102.0 (*c* 1.0, CH_3OH)}. Note that, in a further simplification of the route to diltiazem, the reaction of *o*-aminothiophenol and epoxide **13** afforded the alcohol **15** directly (58%, not optimised) on heating in mesitylene for 36 h.

Synthesis of the side-chain of Taxol™

The synthesis of the phenylisoserine side-chain of Taxol™ is shown in Scheme 3. The requisite enone **5** is obtained simply and in high yield by condensation of benzaldehyde with pinacolone. The Juliá–Colonna epoxidation then proceeded at ambient temperature in the two-phase system to furnish the epoxide **11** in 76% yield and 94% ee. Recrystallisation of the epoxy ketone **11** increased the ee to 97%. Baeyer–Villiger oxidation of ketone **11** with MCPBA gave an excellent yield of the *tert*-butyl epoxycinnamate **17**.

Synthetic steps from a *trans*-epoxycinnamate to the phenylisoserine side-chain of Taxol™ are known in the literature (on the methyl ester) and we chose to follow the method documented by Srivastava *et al.*[10] Thus, treatment of **17** first with hydrogen chloride gas (to furnish chlorohydrin **18**) and then basic Amberlite resin afforded the *cis*-epoxide **19**. This allows a choice of methods to introduce the benzoyl functionality. In the first experiment, the azido alcohol **20** was prepared by heating the *cis*-epoxide **19** with sodium azide in aqueous methanol (Scheme 3). Conversion of the azido alcohol to the target molecule was initially accomplished as described by Denis *et al.*,[11] namely *O*-benzoylation followed by catalytic hydrogenation, wherein the benzoyl function migrated to the nitrogen. A simplified procedure involved hydrogenation of azide **20** to provide the amine **21**, followed by Schotten–Baumann benzoylation to give **22** and hydrolysis to afford the phenylisoserine **23**. Con-



Scheme 3 *Conditions and reagents:* i, I-PLL, UHP, DBU, 12 h; ii, MCPBA, CH_2Cl_2; iii, HCl (g), CH_2Cl_2; iv, Amberlite IRA-420 ($^-$OH), THF; v, NaN_3, MeOH, H_2O; vi, H_2, Pd/C, EtOAc; vii, NH_3, MeOH; viii, benzoyl chloride; ix, trifluoroacetic acid, CH_2Cl_2

cerned with the use of azide on a large scale we investigated alternative methodology. Attempted direct introduction of benzoylamino functionality into compound **19** by Ritter reaction, with benzonitrile as the nucleophile, was not successful: however we found that the amino alcohol **21** could be obtained directly from **19** by treatment of the epoxy ester with methanolic ammonia. Subsequent benzoylation led to isolation of (2*R*,3*S*)-*N*-benzoylphenylisoserine *tert*-butyl ester **22** in 49% yield from epoxide **19**. It is of note that the *tert*-butyl ester essentially overcomes the formation of the carboxamide which is the major product formed on using the ethyl ester in this pathway.[12]

The need to invert the configuration of the epoxide from *trans* to *cis* (**17**→**19**) renders this route longer than more direct approaches, such as the Sharpless aminohydroxylation of *trans*-cinnamate.[13] However it has been found that epimerisation takes place during the coupling reaction of an acetal protected phenylisoserine with the baccatin component to form Taxol™, and that the coupling is selective for the required epimer.[14] Thus only the configuration at C-3 of the phenylisoserine needs to be controlled. It is noteworthy, therefore, that one of the strengths of the polyleucine methodology is that either enantiomer of a particular epoxy ketone can be accessed by utilising the correct polyleucine. Thus enone **5** is converted into *ent*-**11** using immobilised poly-D-leucine and the usual two-phase oxidation conditions; the epoxide *ent*-**11** is an alternative intermediate for the construction of Taxol™ given the above-mentioned data of Denis *et al.* and the chemistry outlined in Scheme 3.

Summary and conclusion

The Juliá–Colonna oxidation of α,β-unsaturated ketones has been improved by the application of non-aqueous reaction conditions. Coupled with our recent finding of the broad scope of the oxidation to include enones having alkyl groups (*e.g. tert*-butyl groups) attached to the carbonyl unit, this new process provides easy access to useful targets. Thus enones **5** and **6** gave the Taxol™ side-chain and diltiazem precursors **11** and **12** respectively. The power and utility of our new two-phase asymmetric epoxidation system has been amply demonstrated.

Experimental

General

Flash column chromatography was carried out using silica gel (Merck 60, 40–63 μm). TLC was carried out on commercially available pre-coated plates (Merck silica gel 60 F254). Toluene, xylene (isomers + ethylbenzene, bp 137–144 °C) and mesitylene (bp 162–164 °C) were purchased from Aldrich Chemical Company. MCPBA (57–85% peracid, 7–10% acid, the rest water) was purchased from Aldrich. THF was distilled from sodium and benzophenone. Chiral HPLC was performed using a Chiralpak AD column, UV detector 254 nm, flow: 1.0 ml min^{-1}. Melting points were recorded with a Gallenkamp melting point apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer FT-IR Paragon 1000 infrared spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker AMX 400, Varian Gemini 2000 (300 MHz) or Bruker AC 200 spectrometers. Chemical shifts are quoted in parts per million; *J* values are in Hz. High and low resolution mass spectra were recorded with a VG Analytical 7070E Magnetic Sector and Fisons Instruments Trio-1000 Quadrapole mass spectrometers respectively. Optical rotations ($[\alpha]_D$) were measured with an Optical Activity PolAAr 2001 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalysis was carried out at the University of Liverpool and Butterworths. Light petroleum refers to the fraction with bp 40–60 °C.

3-Cyclohexyl-1-phenylprop-2-en-1-one 3

To a refluxing solution of lithium iodide (4.44 g, 33.2 mmol) and acetophenone (1.5 ml, 12.93 mmol) in dry diethyl ether (66.0 ml) was added cyclohexanecarbaldehyde (0.94 ml, 8.62 mmol) under N_2. The mixture was left for 12 h, at which time the solution was yellow–orange and a further 66.0 ml of diethyl ether was added. After 28 h, the reaction was quenched by the addition of aqueous HCl (30 ml, 2.0 M) and water (70.0 ml). This solution was extracted with diethyl ether (3 × 50 ml) and the combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (2% EtOAc–light petroleum graduated to 4% EtOAc–hexanes) to provide **3** (610 mg, 2.63 mmol, 30% yield) as white crystals, R_f 0.47 (10% EtOAc–light petroleum), mp 50.0–51.0 °C; ν_{max}(KBr)/cm^{-1} 1664.5 (C=O), 1615.4 (C=C); δ_H(400 MHz, $CDCl_3$) 1.14–1.42 (5H, m, cy), 1.64–2.00 (5H, m, cy), 2.19–2.34 (1H, m, cy), 6.83 [1H, d, *J* 16, C(O)C*H*=CH-cy], 7.00 [1H, dd, *J* 6.8 and 15.6, C(O)CH=C*H*-cy], 7.42–7.59 (3H, m, Ph), 7.90–8.00 (2H, m, Ph); δ_C(100 MHz, $CDCl_3$), 25.76 (CH_2), 25.90 (CH_2), 31.83 (CH_2), 40.97 (CH), 123.36 (CH), 128.39 (CH), 128.49 (CH), 132.45 (CH), 154.81 (CH), 154.81 (CH), 191.29 (C); *m*/*z* (EI) 214 (M^+), 105 ($PhCO^+$), 77 (Ph^+) (Found: C, 83.93; H, 8.48. $C_{15}H_{18}O$ requires C, 84.07; H, 8.47%).

(−)-3-Cyclohexyl-2,3-epoxy-1-phenylpropan-1-one 9

Immobilised poly-L-leucine (100 mg) was added to a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 equiv.), THF (0.8 ml) and urea hydrogen peroxide (27.1 mg, 0.289 mmol). This mixture was stirred for 15 min and then enone **3** (50 mg, 0.234 mmol, 1.0 equiv.) was added. After 3 h at room temp. the reaction was worked up by filtering off the poly-leucine and adding saturated aqueous ammonium chloride (25 ml). This solution was extracted with ethyl acetate (3 × 25 ml) and the combined organic layers dried ($MgSO_4$) and concentrated to furnish 48.9 mg (0.213 mmol, 91% yield, 89% ee) of a clear oil, R_f 0.30 (10% EtOAc–light petroleum); $[\alpha]_D^{22}$ −2.27 (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1691.3 (C=O); δ_H(300 MHz, $CDCl_3$) 1.10–2.00 (11H, m, cy), 2.97 [1H, dd, *J* 2.0 and 7.0, PhC(O)CH(O)C*H*(O)-cy], 4.10 [1H, d, *J* 2.0, PhC(O)C*H*(O)CH(O)-cy], 7.43–7.70 (3H, m, Ph), 7.95–8.15 (2H, m, Ph); δ_C(100 MHz, $CDCl_3$) 25.49 (CH_2), 25.51 (CH_2), 26.03 (CH_2), 28.88 (CH_2), 29.37 (CH_2), 39.90 (CH), 56.34 (CH), 63.91 (CH), 128.12 (CH), 128.17 (CH), 128.71 (CH), 133.56 (CH), 194.70 (C) (Found: M^+, 230.13047. $C_{15}H_{18}O_2$ requires for *M*, 230.13068); HPLC retention times: (10% EtOH in hexanes) 8.34 and 16.10 min.

trans-(−)-(3*R*,4*S*)-3,4-Epoxy-4-phenylbutan-2-one 10

Immobilised poly-L-leucine (100 mg) was added to THF (0.8

ml) followed by urea hydrogen peroxide (27.1 mg, 0.289 mmol, 1.2 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 equiv.). This mixture was stirred for 5 min and then enone **4** (35 mg, 0.234 mmol) was added. At 2 h and 4 h more UHP (0.5 equiv.) and DBU (0.6 equiv.) were added. After 6 h at room temp. the reaction was worked up by filtering off the poly-leucine and adding saturated aqueous ammonium chloride (25 ml). This solution was extracted with ethyl acetate (3 × 20 ml) and the combined organic layers dried ($MgSO_4$), concentrated and chromatographed to furnish **10** (27.2 mg, 0.17 mmol, 70% yield, 80% ee by HPLC), $[\alpha]_D^{19}$ −73.3 (*c* 1.0, $CHCl_3$) {lit.,[15] $[\alpha]_D^{25}$ −75.5 (*c* 2.2, $CHCl_3$), 98% ee}), as a clear oil, R_f 0.40 (light petroleum–EtOAc, 4:1); ν_{max}(neat)/cm^{-1} 3030, 1711, 1669, 1412, 1360, 1250; δ_H(200 MHz, $CDCl_3$) 7.35 (3H, m, Ph), 7.27 (2H, m, Ph), 4.00 [1H, d, *J* 1.8, H(O)CC=O], 3.49 [1H, d, *J* 1.8, PhC(O)H], 2.19 (3H, s, CH_3); δ_C(100 MHz, $CDCl_3$) 204.1 (C), 135.0 (C), 129.0 (CH), 128.6 (CH), 125.6 (CH), 63.4 (CH), 57.7 (CH), 24.7 (CH_3); HPLC retention times: (10% EtOH in hexanes) enone 9.6 min, epoxide (major) 10.3 min, epoxide (minor) 20.6 min.

trans-4,4-Dimethyl-1-(4-methoxyphenyl)pent-1-en-3-one 6 (diltiazem precursor)

To a 250 ml round bottom flask was added *p*-anisaldehyde (12.00 g, 88.1 mmol, 1.0 equiv.), pinacolone (12.50 g, 124.8 mmol, 1.42 equiv.), methanol (90.0 ml) and finally NaOMe (7.0 g, 129.6 mmol, 1.47 equiv.). The mixture was refluxed for 40 h, then quenched with saturated aqueous NH_4Cl and extracted three times with EtOAc. The combined organic extracts were dried, filtered and evaporated to provide 18.66 g of a mobile brown oil. Kugelrohr distillation provided 16.8 g (77.0 mmol, 87% yield) of pure enone **6**, as a slightly yellow oil, R_f 0.47 (light petroleum–ethyl acetate, 4:1); ν_{max}(neat)/cm^{-1} 2967, 2933, 1678, 1598, 1573, 1512, 1258; δ_H(200 MHz, $CDCl_3$) 7.65 (1H, d, *J* 15.5, C*H*=CHCO), 7.53 (2H, m, Ar), 7.01 (1H, d, *J* 15.5, CH=C*H*CO), 6.91 (2H, m, Ar), 3.84 (3H, s, OCH_3), 1.23 (9H, s, Bu^t); δ_C(75 MHz, $CDCl_3$) 204.1 (C), 161.3 (C), 142.5 (CH), 129.9 (CH), 127.6 (C), 118.4 (CH), 114.2 (CH), 55.2 (CH_3), 42.9 (C), 26.3 (CH_3); *m*/*z* (EI) 218 (M^+, 7%), 161 (100), 133 (16), 118 (4).

trans-(−)-(1*S*,2*R*)-4,4-Dimethyl-1,2-epoxy-1-(4-methoxyphenyl)pentan-3-one 12

To 7.0 g of I-PLL (immobilised poly-L-leucine) was added THF (50.0 ml), urea hydrogen peroxide (2.07 g, 21.98 mmol, 1.20 equiv.) and DBU (4.11 ml, 27.48 mmol, 1.5 equiv.). This mixture was stirred for 3–5 min and the enone **6** (4.01 g, 18.37 mmol, 1.0 equiv.) was added as a solution in 10 ml of THF. After 3 h more UHP (1.06 g, 11.3 mmol, 0.61 equiv.) and DBU (2.5 ml, 16.13 mmol, 0.88 equiv.) were added. After 28 h, TLC examination shows only a minute amount (≤5%) of the starting enone remaining. After work-up (see as described previously) the volatile components were removed under high vacuum. This provided 4.28 g (18.27 mmol, 99% crude yield) of a viscous oil. ^{1}H NMR spectroscopy showed this material to be ≥90% pure. This silica gel-sensitive epoxide can be chromatographed only when the eluent is doped with 1% Et_3N (gradient elution 2% EtOAc in hexanes→12% EtOAc in hexanes) furnishing the analytically pure epoxide in 70% yield. (We found the crude epoxide could be reacted further without purification.) R_f 0.40 (light petroleum–EtOAc, 4:1); $[\alpha]_D^{20}$ −263.4 (*c* 2.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 2978, 2839, 1700, 1612, 1502, 1518, 1401, 1234; δ_H(200 MHz, $CDCl_3$) 7.23 (2H, m, Ar), 6.90 (2H, m, Ar), 3.86 [1H, d, *J* 1.9, CH(O)C*H*C=O], 3.81 (3H, s, OCH_3), 3.76 [1H, d, *J* 1.9, C*H*(O)CHC=O], 1.29 (9H, s, Bu^t); δ_C(75 MHz, $CDCl_3$) 208.2 (C), 160.2 (C), 127.5 (C), 127.0 (CH), 114.2 (CH), 59.2 (CH), 59.0 (CH), 55.2 (CH_3), 43.4 (C), 25.6 (CH_3); *m*/*z* (EI) 234 (M^+, 20%), 150 (57), 149 (24), 135 (16), 121 (100), 91 (18), 77 (22), 57 (93), 41 (21) (Found: C, 72.02; H, 7.70. $C_{14}H_{18}O_3$ requires C, 71.76; H, 7.75%); HPLC retention times: (2.0% EtOH in hexanes) enone 13.4 min, epoxide (major) 23.2 min, epoxide (minor) 26.6 min.

Racemic 12. For comparison 4.0 g of enone **6** were epoxidized without I-PLL and provided 2.19 g (48% yield) of racemic epoxide **12** as a viscous oil after flash chromatography (eluent doped with 1% Et_3N). Racemic **12** solidified (mp 35–36 °C) and was recrystallised from light petroleum.

tert-Butyl (−)-(2*R*,3*S*)-2,3-epoxy-3-(4-methoxyphenyl)-propanoate 13

The crude (1*S*,2*R*)-epoxy ketone **12** (4.28 g, 18.27 mmol, ≥90% pure by ^{1}H NMR spectroscopy) was dissolved in CH_2Cl_2 (30.0 ml, distilled) and added to a 30 min prestirred solution of MCPBA (11.05 g, between 2.0 and 3.0 equiv.) and KF (7.97 g, 135.3 mmol, 7.5 equiv.) in CH_2Cl_2 (180.0 ml). After 24 h at 30 °C (oil bath), complete consumption of the ketone was indicated by TLC analysis. The reaction solution was filtered through a Celite-packed glass sinter funnel. The Celite/residue was rinsed with CH_2Cl_2 (2 × 70 ml) and the combined filtrates were dried ($MgSO_4$), filtered and concentrated to provide 3.59 g of crude epoxy ester. Flash chromatography (100% light petroleum→8% EtOAc in light petroleum, doped with 1% Et_3N) provided 3.20 g (12.8 mmol, 70% from enone **6**) of crystalline ester **13** (mp 53–55 °C). Using pure epoxy ketone **12** in the Baeyer–Villiger oxidation, the ester **13** was formed in 84% yield. A sample was recrystallised from light petroleum, R_f 0.46 (light petroleum–EtOAc, 4:1), mp 55–56 °C; $[\alpha]_D^{19}$ −155.6 (*c* 2.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2979, 2934, 2836, 1741, 1613, 1517; δ_H(200 MHz, $CDCl_3$) 7.21 (2H, m, Ar), 6.88 (2H, m, Ar), 3.97 [1H, d, *J* 1.8, CH(O)C*H*CO_2R], 3.80 (3H, s, OCH_3), 3.40 [1H, d, *J* 1.8, C*H*(O)CHCO_2R], 1.51 (9H, s, Bu^t); δ_C(75 MHz, $CDCl_3$) 167.4 (C), 160.2 (C), 127.3 (CH and C), 114.1 (CH), 82.5 (C), 57.5 (CH), 57.3 (CH), 55.3 (CH_3), 27.9 (CH_3); *m*/*z* (EI) 250 (M^+, 2%), 194 (34), 149 (23), 148 (31), 121 (42), 91 (15), 77 (22), 57 (100) (Found: C, 67.14; H, 7.17. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.26%).

tert-Butyl (+)-(2*S*,3*S*)-3-[(2-aminophenyl)thio]-2-hydroxy-3-(4-methoxyphenyl)propanoate 14

To the epoxy ester **13** (1.04 g, 4.17 mmol, 1.0 equiv.) under an inert atmosphere was added toluene (6.0 ml, dry) and 2-aminothiophenol (0.508 ml, 4.75 mmol, 1.14 equiv.) and the solution was refluxed for 17 h. Removal of the solvent provided a yellow waxy solid (1.76 g). The product can be recrystallised from a mixture of light petroleum and chloroform. Purification by flash chromatography (gradient elution 10% EtOAc in light petroleum→25% EtOAc in light petroleum) provided the alcohol **14** (1.42 g, 3.77 mmol, 90% yield). Recrystallisation from light petroleum–$CHCl_3$ gave long needle-like white crystals, R_f 0.30 (light petroleum–EtOAc, 2:1), mp 100.5–101.5 °C; $[\alpha]_D^{21}$ +133.2 (*c* 1.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3455, 3355, 2961, 2834, 1716, 1608; δ_H(300 MHz, $CDCl_3$) 7.24 (2H, m, Ar), 7.06 (2H, m, Ar), 6.77 (2H, m, Ar), 6.66 (1H, dd, *J* 1.1 and 8.0, Ar), 6.54 (1H, dt, *J* 1.2 and 7.7, Ar), 4.41 (1H, d, *J* 4.1, ArSC*H* or CHC*H*OH), 4.25 (1H, d, *J* 4.2, ArSC*H* or CHC*H*OH), 3.77 (3H, s, OCH_3), 1.41 (9H, s, Bu^t); δ_C(75 MHz, $CDCl_3$) 171.7 (C), 159.0 (C), 149.1 (C), 137.6 (CH), 131.9 (C), 130.3 (CH), 129.8 (CH), 118.5 (CH), 116.0 (C), 115.0 (CH), 113.5 (CH), 83.0 (C), 74.5 (CH), 56.5 (CH), 55.2 (CH_3), 27.8 (CH_3); *m*/*z* (EI) 375 (M^+, 1%), 244 (6), 195 (19), 149 (28), 125 (22), 124 (19), 121 (43), 57 (100) (Found: C, 63.87; H, 6.67; N, 3.78; S, 8.45. $C_{20}H_{25}NO_4S$ requires C, 63.97; H, 6.72; N, 3.73; S, 8.54%).

cis-(+)-(2*S*,3*S*)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one 15

Method A. Using the method of Schwartz *et al.*[7g] the amino ester **14** (350 mg, 0.932 mmol) was added to xylene (8.0 ml) and toluene-*p*-sulfonic acid (20 mg), under an atmosphere of N_2. A Dean–Stark trap was added and the reaction solution was refluxed for 18 h. After washing the reaction mixture with sat-

urated aqueous $NaHCO_3$ the organic layer was dried ($MgSO_4$), filtered and concentrated to give a yellow–brown solid. Flash chromatography (gradient elution 15% EtOAc in light petroleum→35% EtOAc in light petroleum) provided 144.7 mg (0.480 mmol, 52% yield) of pure benzothiazepinone as an off-white solid, mp 201.5–202.5 °C, $[\alpha]_D^{20}$ +58.4 (*c* 1.0, $CHCl_3$).

Method B. The neat amino ester **14** (350 mg, 0.932 mmol) was heated at 185 °C. The material melted and soon after (≤30 s) began to slowly effervesce (loss of *tert*-butyl alcohol). No further effervescence was noted after 40 min and heating was discontinued. Flash chromatography (as above) provided 143.2 mg (0.475 mmol, 51%) of pure benzothiazepinone as an off-white solid, mp 201.0–202.5 °C, $[\alpha]_D^{22}$ +57.6 (*c* 1.0, $CHCl_3$).

Method C. The amino ester **14** (198 mg, 0.527 mmol) was refluxed in xylene, under an atmosphere of nitrogen for 9 d. Removal of the solvent provided a light yellow solid which, after flash chromatography, provided 149.8 mg (0.497 mmol, 94% yield) of pure benzothiazepinone as a white solid, mp 201.0–202.5 °C, $[\alpha]_D^{22}$ +58.0 (*c* 1.0, $CHCl_3$).

Method D. Epoxy ester **13** (318.0 mg, 1.27 mmol), mesitylene (2.2 ml) and *o*-aminothiophenol (154 μl, 145.3 mmol, 1.14 equiv.) were heated at 115 ± 3 °C for 16 h. The temperature was then raised until the solution began to reflux. After 20 h (at reflux, note not optimised) none of the alcohol **14** remained (TLC). *In vacuo* removal of the solvent followed by flash chromatography provided the requisite benzothiazepinone 2.22 mg (0.737 mmol, 58%), mp 201–202 °C, $[\alpha]_D^{20}$ +58.6 (*c* 1.0, $CHCl_3$).

The crude benzothiazepinone **15**, from any of the above methods, could be precipitated with a variety of two-component solvent mixtures all containing light petroleum and either chloroform, acetone or ethyl acetate. For the purpose of data collection the crude product was purified by flash chromatography. All samples were pure by ^1H NMR spectroscopy, but were triturated with light petroleum–EtOAc (1:1) before optical rotations were measured.

R_f 0.30 (light petroleum–EtOAc, 1:1); ν_{max}(KBr)/cm^{-1} 3375, 1678; δ_H(300 MHz, $CDCl_3$) 8.90 (1H, s, HNCO), 7.68 (1H, dm, *J* 7.7, *o*-NHAr-*H*), 7.46 (2H, m, *p*-OCH_3Ar-*H*), 7.38 (1H, tt, *J* 1.5 and 7.7, *o*-NHAr-*H*), 7.22 (1H, tt, *J* 1.4 and 7.7, *o*-NHAr-*H*), 7.13 (1H, dm, *J* 8.0, *o*-NHAr-*H*), 6.77 (2H, m, *p*-OCH_3Ar-*H*), 5.08 (1H, d, *J* 6.9, ArSC*H*CHOH), 4.48 (1H, dd, *J* 6.9 and 9.6, ArSCHC*H*OH), 3.75 (3H, s, OCH_3), 3.05 (1H, d, *J* 9.6, ArSCHCHO*H*); δ_C(75 MHz, $CDCl_3$) 173.7 (C), 160.0 (C), 140.4 (C), 134.8 (CH), 131.2 (CH), 130.1 (CH), 127.5 (C), 127.0 (CH), 126.3 (C), 123.1 (CH), 113.7 (CH), 69.2 (CH), 57.4 (CH), 55.2 (CH_3); δ_H(300 MHz, [$^2H_6$]DMSO) 10.28 (1H, s, HNCO), 7.58 (1H, d, *J* 7.1, Ar), 7.39 (3H, m, Ar), 7.15 (2H, t, *J* 8.2, Ar), 6.87 (2H, d, *J* 8.7, Ar), 5.03 (1H, d, *J* 6.6, SC*H*CHOH), 4.68 (1H, d, SCHCHO*H*), 4.28 (1H, t, *J* 6.6, SCHC*H*OH), 3.74 (3H, s, OCH_3); δ_C(75 MHz, [$^2H_6$]DMSO) 172.5 (C), 159.0 (C), 141.9 (C), 133.8 (C), 130.9 (CH), 129.9 (CH), 128.4 (C), 126.2 (C), 125.5 (CH), 122.6 (CH), 113.3 (CH), 69.2 (CH), 57.4 (CH), 55.2 (CH_3) (Found: C, 63.60; H, 4.98; N, 4.69; S, 10.67. $C_{16}H_{15}NO_3S$ requires C, 63.77; H, 5.02; N, 4.65; S, 10.64%).

(1*S*,2*R*)-4,4-Dimethyl-1,2-epoxy-1-phenylpentan-3-one 11

Triphasic reaction. A mixture of 10 M aqueous NaOH (0.5 ml), poly-L-leucine (100 mg), (*E*)-4,4-dimethyl-1-phenylpent-1-en-3-one **5** (100 mg, 0.53 mmol) and hexane (2 ml) was stirred at room temperature for 8 h. During this time the poly-L-leucine swells, forming a gelatinous material. EDTA (5 mg, 0.013 mmol) was added, followed by aqueous H_2O_2 (27%, 1.3 ml). The mixture was allowed to warm to room temperature and was stirred for 16 h. Further 10 M aqueous NaOH (0.2 ml) and H_2O_2 (0.5 ml) were added and the reaction was stirred for another 24 h. The mixture was filtered and the poly-L-leucine washed with ethyl acetate (20 ml). (The poly-L-leucine can be recovered and reused.) The filtrate was washed with water (5 ml), brine (5 ml) and dried ($MgSO_4$). The solvent was evaporated to give the epoxide **11** (69 mg, 64%, 94% ee) as a white solid (when the reaction was repeated on a 7 g scale, an 83% ee was obtained, recrystallisation from pentane enhanced this to 97%), mp 72–76 °C; $[\alpha]_D^{20}$ −261.2 (*c* 1.05, CH_2Cl_2); ν_{max}(Nujol)/cm^{-1} 1706; δ_H($CDCl_3$, 400 MHz) 7.41–7.30 (5H, m), 3.85 (2H, s), 1.23 (9H, s); δ_C($CDCl_3$, 100 MHz) 208.14, 135.60, 128.91, 128.71, 125.61, 59.36, 59.13, 43.58, 25.70; *m*/*z* 204 (M^+), 91, 57 (Found: C, 76.31; H, 7.88. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%).

Biphasic reaction. Under the biphasic conditions (*vide supra*) the enone **5** was transformed into the epoxide **11** in 76% yield (94% ee).

(2*R*,3*S*)-*tert*-Butyl 2,3-epoxy-3-phenylpropanoate 17

A solution of the ketone **11** (3.35 g, 16.40 mmol) and 60% *m*-chloroperoxybenzoic acid (5.66 g, 32.80 mmol) in CH_2Cl_2 (100 ml) was heated under reflux for 4 d. The solution was cooled to room temperature and washed with 1 M aqueous NaOH (2 × 100 ml), water (50 ml) and brine (50 ml). The solution was dried ($MgSO_4$) and evaporated to give the ester **17** (3.39 g, 94%) as a white solid, mp 37–43 °C; ν_{max}(Nujol)/cm^{-1} 1739; δ_H($CDCl_3$, 200 MHz) 7.42–7.24 (5H, m), 4.04 (1H, d, *J* 2), 3.40 (1H, d, *J* 2), 1.52 (9H, s).

(2*R*,3*R*)-*tert*-Butyl 2,3-epoxy-3-phenylpropanoate 19

Hydrogen chloride gas was bubbled through a solution of the *trans*-epoxide **17** (3.35 g, 15.21 mmol) in dry CH_2Cl_2 (60 ml) at 0 °C for 30 min. The solvent was evaporated and the residue chromatographed (ethyl acetate–pentane, 1:9) to give (2*R*,3*S*)-*tert*-butyl 3-chloro-2-hydroxy-3-phenylpropanoate **18** (2.57 g, 66%), ν_{max}(neat)/cm^{-1} 3394, 1738; δ_H($CDCl_3$, 200 MHz) 7.60–7.35 (5H, m), 5.68 (1H, d, *J* 3), 4.42 (1H, dd, *J* 7 and 3), 3.34 (1H, d, *J* 7), 1.54 (9H, s). A solution of the chlorohydrin (2.50 g, 9.75 mmol) in dry THF (40 ml) under nitrogen was stirred over Amberlite IRA 420 (OH) (20 g) at room temperature overnight. The mixture was filtered, and the resin washed with THF (2 × 10 ml). The solvent was evaporated and the residue dissolved in diethyl ether (50 ml), washed with water (10 ml), dried ($MgSO_4$) and evaporated to give the *cis*-epoxide **19** (1.72 g, 80%) as a colourless liquid; ν_{max}/cm^{-1} 1750, 1718; δ_C($CDCl_3$, 200 MHz) 7.45–7.28 (5H, m), 4.22 (1H, d, *J* 5), 3.72 (1H, d, *J* 5), 1.18 (9H, s); *m*/*z* 220 (M^+), 164, 107, 91.

(2*R*,3*S*)-*tert*-Butyl 3-azido-2-hydroxy-3-phenylpropanoate 20

The epoxide **19** (648 mg, 2.94 mmol) was dissolved in methanol (16 ml), methyl formate (2.5 ml) and water (2 ml). Sodium azide (955 mg, 14.7 mmol) was added and the mixture heated to 60 °C under nitrogen for 20 h. After cooling to room temperature, the reaction was diluted with water (30 ml) and extracted with diethyl ether (3 × 20 ml). The organic extracts were washed with water (20 ml), brine (20 ml) and dried ($MgSO_4$). The solvent was evaporated to give the hydroxy azide **20** (729 mg, 94%) as a pale yellow oil which solidified on standing, ν_{max}(Nujol)/cm^{-1} 3477, 2108, 1732; δ_C($CDCl_3$, 200 MHz) 7.50–7.33 (5H, m), 4.78 (1H, d, *J* 4), 4.27 (1H, dd, *J* 7 and 4), 3.20 (1H, d, *J* 7), 1.50 (9H, s).

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine *tert*-butyl ester 22

A mixture of the azide **20** (1.54 g, 5.85 mmol) and palladium on carbon (5%, 250 mg) in ethyl acetate (20 ml) was stirred under an atmosphere of hydrogen at room temperature overnight. The mixture was filtered through Celite and washed with ethyl acetate (20 ml). To this solution was added saturated aqueous sodium hydrogen carbonate (20 ml). Benzoyl chloride (0.68 ml, 5.85 mmol) was added dropwise with vigorous stirring over 5 min. After a further 15 min, the organic phase was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 ml). The combined organic extracts were washed with 1 M hydrochloric acid (20 ml), water (20 ml), brine (20 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue crystallised from pentane to give the *N*-benzoyl-3-phenylisoserine *tert*-butyl ester **22** (1.69 g, 85%) as a white solid, mp 115–

117 °C, ν_{max}(Nujol)/cm^{-1} 3358, 1734, 1654; δ_H(400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8), 7.51–7.27 (8H, m), 7.02 (1H, d, *J* 9), 5.75 (1H, dd, *J* 9 and 2), 4.52 (1H, dd, *J* 6 and 2), 3.40 (1H, d, *J* 6), 1.48 (9H, s); δ_C(100 MHz, $CDCl_3$) 172.09, 166.75, 138.91, 134.35, 131.67, 128.65, 128.60, 127.72, 127.00, 126.85, 84.21, 73.43, 54.54, 27.83; *m*/*z* (CI) 342 (MH^+), 286 (Found: C, 70.18; H, 6.84; N, 4.09. $C_{20}H_{23}NO_4$ requires C, 70.36; H, 6.79; N, 4.10%).

As an alternative method, the *cis*-epoxide **19** (568 mg, 2.58 mmol) was dissolved in methanol (7.5 ml) in a screw top tube and the solution cooled to −25 °C. Ammonia gas was bubbled in to provide a saturated solution. The tube was sealed, allowed to warm to room temperature and then heated to 100 °C with stirring for 16 h. After cooling to room temperature, the tube was opened cautiously and the solvent evaporated. The crude amino alcohol was benzoylated as described above to give the *N*-benzoyl-3-phenylisoserine *tert*-butyl ester **22** (433 mg, 49%).

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine 23

A solution of the *tert*-butyl ester **22** and trifluoroacetic acid (5 ml) in CH_2Cl_2 (10 ml) was stirred at room temperature for 18 h. The solvent was evaporated and the residue crystallised from ethyl acetate (20 ml) to give the acid **23** (970 mg, 74%) as a white solid, mp 176–178 °C (lit.,[10] 175.5–177 °C); $[\alpha]_D^{20}$ −38.6 (*c* 1.05, EtOH) {lit.,[10] $[\alpha]_D$ −35.5 (*c* 1.07, EtOH)}; ν_{max}(Nujol)/cm^{-1} 3513, 3349, 1719, 1706, 1677, 1636; δ_H(400 MHz, [$^2H_6$]DMSO) 12.75 (1H, br), 8.56 (1H, d, *J* 9), 7.84 (2H, d, *J* 8), 7.58–7.20 (8H, m), 5.7–5.4 (1H, br), 5.48 (1H, dd, *J* 9 and 4), 4.38 (1H, d, *J* 4); δ_C(100 MHz, [$^2H_6$]DMSO) 173.34, 165.95, 140.16, 134.23, 131.31, 128.23, 127.94, 127.25, 127.07, 126.86, 73.48, 55.71; *m*/*z* (CI) 286 (MH^+), 268.

X-Ray crystal structure determination of epoxy ester 13

Data collection. A colourless prism crystal of $C_{14}H_{18}O_4$ having approximate dimensions of 0.250 × 0.150 × 0.250 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα radiation and a 12 kW rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 23 carefully centred reflections in the range $35.70 < 2\theta < 43.77°$ corresponded to an orthorhombic cell with dimensions: $a = 5.87(1)$ Å, $b = 8.85(2)$ Å, $c = 25.47(\frac{1}{3})$ Å, $V = 1324(6)$ Å^3, for $Z = 4$ and $M = 250.29$, D_c 1.256 g cm^{-3}. Based on the systematic absences of: *h*00: $h \neq 2n$, 0*k*0: $k \neq 2n$, 001: $l \neq 2n$, and the successful solution and refinement of the structure, the space group was determined to be: $P2_12_12_1$ (#19).

The data were collected at a temperature of −120 ± 1 °C using the ω scan technique to a maximum 2θ value of 50.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.53° with a take-off angle of 6.0°. Scans of (1.35 + 0.30 tan θ)° were made at a speed of 4.0° min^{-1} (in omega). The weak reflections [$I < 10.0\sigma(I)$] were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2 : 1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400.0 mm.

Data reduction. A total of 2799 reflections was collected. The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection indicating crystal and electronic stability (no decay correction was applied).

The linear absorption coefficient for Mo-Kα is 0.9 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarisation effects.

Structure solution and refinement. The structure was solved by direct methods.[16] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in the structure factor calculation in idealised positions ($d_{C-H} = 0.95$ Å), and were assigned isotropic thermal parameters which were 20% greater than the $B_{equivalent}$ value of the atom to which they were bonded. The final cycle of full-matrix least-squares refinement[17] was based on 2442 observed reflections [$I > 3.00\sigma(I)$] and 163 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of: $R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.034$, $R_w = [(\Sigma w(|F_o| - |F_c|)^2/\Sigma wF_o^2)]^{\frac{1}{2}} = 0.041$.

The standard deviation of an observation of unit weight[18] was 1.75. The weighting scheme was based on counting statistics and included a factor ($p = 0.03$) to downweight the intense reflections. Plots of $\Sigma w(|F_o| - |F_c|)^2$ *versus* $|F_o|$, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.13 and −0.17 e Å^{-3}, respectively.

Neutral atom scattering factors were taken from Cromer and Waber.[19] Anomalous dispersion effects were included in F_{calc}[20]; the values for $\Delta f'$ and $\Delta f''$ were those of Cromer.[21] All calculations were performed using the TEXSAN[22] crystallographic software package of Molecular Structure Corporation.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/152.

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