Supplementary Material (ESI) for Organic and Biomolecular Chemistry

Supplementary Information

Asymmetric Three- and [2+1]-Component Conjugate Addition Reactions for the Stereoselective Synthesis of Polysubstituted Piperidinones

Stephen G. Davies,* Paul. M. Roberts and Andrew D. Smith

Department of Organic Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, UK, OX1 3TA

e-mail: steve.davies@chem.ox.ac.uk

Experimental

General Experimental

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of nitrogen via standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. *n*-Butyllithium was used as a solution in hexanes at the molarity stated. All other solvents and reagents were used as supplied (Analytical or HPLC grade), without prior purification. Reactions were dried with $MgSO_4$. Thin layer chromatography (t.l.c.) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) or where stated on a Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (*J*) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C multiplicities were assigned using a DEPT sequence. In all cases, the reaction diastereoselectivity was assessed by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted. Low resolution mass spectra (*m/z*) were recorded on VG MassLab 20-250 or Micromass Platform 1 spectrometers

and high resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer or on a Waters 2790 Micromass LCT Exact Mass Electrospray Ionisation Mass Spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ESI) using partial purification by HPLC with methanol:acetonitrile:water (40:40:20) as eluent. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g/100 ml. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford.

Representative Procedure 1

LDA (1M, 1.1eq) was added dropwise to a stirred solution of the requisite β-amino ester (1eq) in anhydrous THF at -78˚C under nitrogen and after 10 minutes was allowed to warm to 0˚C. After thirty minutes, the enolate solution was recooled to -78˚C, prior to the addition of a conjugate acceptor (1eq) in anhydrous THF via cannula. After 15 minutes the solution was warmed to 0˚C for two hours before cooling to -78˚C and the addition of saturated aqueous ammonium chloride. After warming to rt, the resultant solution was partitioned between brine and 1:1 DCM/Et_2O, the organic extracts were dried, filtered and concentrated *in vacuo* before purification by column chromatography.

Representative Procedure 2

n-Butyllithium (1.55eq) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (1.6eq) in anhydrous THF at -78˚C and stirred for thirty minutes under nitrogen. A solution of the α,β-unsaturated ester in anhydrous THF was added dropwise *via* cannula and stirred at -78˚C for two hours before the addition of another α,β-unsaturated carbonyl component. After ten minutes, the reaction was warmed to 0˚C for two hours before cooling to -78˚C and the addition of saturated aqueous ammonium chloride. After warming to rt, the resultant solution was partitioned between brine and 1:1 DCM/Et_2O, and the organic extracts dried, filtered and concentrated *in vacuo* before purification by column chromatography.

Representative Procedure 3

$Pd(OH)_2$ / C (50% by mass) was added to a solution of the substrate in degassed MeOH and the resultant black suspension stirred under a hydrogen atmosphere (5atm) for 16 hours. After depressurisation, the reaction mixture was filtered through a plug of celite (eluent MeOH), concentrated *in vacuo* and the residue purified by column chromatography on silica gel.

Preparation of 1-*tert*-butyl-5-methyl (2*S*,3*S*,1'*R*,α*S*)-2-{1'-phenyl-(1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-pentanedioate 13 and 1,7-di-*tert*-butyl (2*S*,3*S*,1'*R*,α*S*)-2-{1'-phenyl-(1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-5-oxo-heptanedioate 14

Following representative procedure 1, LDA (2.0M, 2.64mmol, 1.32ml), **11** (2.4mmol, 1.0g) in THF (5ml) and methyl cinnamate (2.4mmol, 390mg) gave, after column chromatography on silica gel (hexane:Et_2O 15:1 to 10:1), **13** (408mg, 30%) as a mixture of diastereoisomers (66% d.e.). Recrystallisation (hexane:Et_2O) gave **13** as white blocks and as a single diastereoisomer; $[\alpha]_D^{24}$ +30.4 (c 1.0, $CHCl_3$); $C_{38}H_{43}NO_4$ requires C 79.0; H 7.5; N, 2.4%; found C 78.7; H 7.5; N, 2.3%; ν_{max} (KBr) 3027, 2933 (C-H), 1741, 1722 (C=O), 1146 (C-O); δ_H (500MHz, $CDCl_3$) 1.01 (3H, d, *J*7.0, C(α)*Me*), 1.26 (9H, s, OC*(Me)$_3$*), 2.42 (1H, dd, $J_{4A,4B}$16.0, $J_{4A,3}$3.4, C(4)H_A), 2.94 (1H, dd, $J_{4B,4A}$16.0, $J_{4B,3}$12.0, C(4)H_B), 3.09 (1H, app dt, $J_{3,4B}$12.0, $J_{3,4A;3,2}$3.5, C(3)*H*), 3.32 (3H, s, CO_2Me), 3.47 (1H, dd, $J_{2,1'}$11.9, $J_{2,3}$3.9, C(2)*H*), 3.58 (1H, AB, *J*14.2, NCH_A), 4.05 (1H, AB, *J*14.2, NCH_B), 4.21 (1H, q, *J*7.0, C(α)*H*), 4.30 (1H, d, $J_{5,4}$11.9, C(1')*H*), 7.05-7.44 (20H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 16.5 (C(α)*Me*), 28.0 (OC*(Me)$_3$*), 32.4 (*C(4)*H_2), 40.3 (*C(3)*H), 51.1 (NCH_2), 51.3 (O*Me*), 54.2, 57.2, 62.8 (*C(2)*H, *C(1')*H and *C(α)*H), 80.7 (O*C*$(Me)_3$), 126.4, 126.5, 126.7, 127.6, 127.8, 128.2, 128.4, 129.0, 129.6 ($Ph_{o/m/p}$), 136.8, 140.2, 141.7, 144.2 (Ph_{ipso}), 171.8, 172.6 (*C*=O); *m/z* APCI$^+$ 578.4, (MH^+, 75%), 522.1 (MH^+-C_4H_8, 10%). The mother liquors were further purified by column chromatography to give the minor diastereoisomer of unknown absolute configuration as a white foam (13mg, 1%); ν_{max} 3030, 2978 (C-H), 1738, 1721 (C=O), 1151 (C-O); δ_H (300MHz, $CDCl_3$) 0.84 (9H, s, OC*(Me)$_3$*), 0.91 (3H, d, *J*7.0, C(α)*Me*), 2.01 (1H, dd, $J_{4A,4B}$16.6, $J_{4A,3}$2.9, C(4)H_A), 2.69 (1H, dd, $J_{4B,4A}$16.6, $J_{4B,3}$12.8, C(4)H_B), 3.24 (1H, dd, $J_{2,1'}$11.7, $J_{2,3}$3.0, C(2)*H*), 3.58 (3H, s, CO_2Me), 3.78 (1H, AB, *J*13.5, NCH_A), 4.00 (1H, d, *J*11.7, C(1')*H*), 4.16-4.25 (2H, m, C(α)*H* and C(3)*H*), 4.30 (1H, AB, *J*13.5, NCH_B), 6.99-7.71 (20H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 14.0 (C(α)*Me*), 27.2 (OC*(Me)$_3$*), 32.7 (*C(4)*H_2), 38.7

(*C(2)*H), 50.9 (N*C*H$_2$), 51.3, 55.0, 55.2, 59.7 (O*Me*, *C(3)*H, *C(*1')H and *C(α)*H), 80.2 (O*C*(Me)$_3$), 126.5, 126.9, 127.3, 127.7, 127.9, 128.2, 128.4, 128.7, 129.3, 129.8 (*Ph*$_{o/m/p}$), 139.1, 139.7, 142.7 (*Ph*$_{ipso}$), 171.3, 173.1 (*C*=O); *m/z* APCI$^+$ 578.4, (MH$^+$, 100%), 600.7 (MNa$^+$, 10%). Further elution gave **14** (121mg, 15%) as a white foam; $C_{43}H_{51}NO_5$ requires C, 78.0; H, 7.8; N, 2.1%; found C, 77.7; H, 7.7; N, 2.1%; $[\alpha]_D^{23}$ +27.0 (c 1.0, $CHCl_3$); ν_{max} (KBr) 2978 (C-H), 1722 (C=O), 1147 (C-O); δ_H (500MHz, $CDCl_3$) 1.02 (3H, d, *J*6.8, C(α)*Me*), 1.28 and 1.38 (2 x 9H, s, OC*(Me)$_3$*), 2.57 (1H, dd, $J_{4A,4B}$17.2, $J_{4A,3}$2.8, C(4)*H$_A$*), 2.94 (2H, s, C(6)*H$_2$*), 3.12-3.16 (1H, m, C(3)*H*), 3.23 (1H, dd, $J_{4B,4A}$17.2, $J_{4B,3}$11.5, C(4)*H$_B$*), 3.46 (1H, dd, $J_{2,1'}$11.8, $J_{2,3}$3.7, C(2)*H*), 3.60 (1H, AB, *J*14.2, NC*H$_A$*), 4.08 (1H, AB, *J*14.2, NC*H$_B$*), 4.23 (1H, q, *J*6.8, C(α)*H*), 4.28 (1H, d, $J_{1',2}$11.8, C(1')*H*), 7.02-7.44 (20H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 16.4 (C(α)*Me*), 27.9, 28.0 (OC*(Me)$_3$* x 2), 39.2 (*C(3)*H), 41.0, 50.4, 51.1 (*C(4)*H$_2$, *C(6)*H$_2$ and N*C*H$_2$), 54.2, 57.1, 62.9 (*C(2)*H, *C(*1')H, *C(α)*H), 80.7, 81.5 (2 x O*C*(Me)$_3$), 126.5, 126.6, 126.7, 127.7, 127.8, 128.2, 128.3, 128.6, 129.0, 129.7 (*Ph*$_{o/m/p}$), 136.8, 140.1, 141.7, 144.3 (*Ph*$_{ipso}$), 166.1, 172.0 (2 x *C*O$_2$C(Me)$_3$), 201.2 (*C(5)*=O); *m/z* APCI$^+$ 662.4 (MH$^+$, 100%), 684.0 (MNa$^+$, 15%).

X-ray crystal structure determination for 13

Data were collected using an Enraf-nonius DIP2000 diffractometer with graphite monochromated Mo-kα radiation using standard procedures at 100K. The structure was solved by direct methods, full matrix and least-squares refinement with non-hydrogen atoms in anisotropic approximation. Hydrogen atoms were placed in calculated positions and included in the final refinement with fixed positional and thermal parameters. A total of 388 parameters were refined. A three term Chebychev polynomial was used as the weighting scheme. All crystallographic and refinement calculations were carried out using CRYSTALS.[35]

X-ray crystal structure data for **13** [$C_{38}H_{43}NO_4$]: M = 577.76, orthorhombic, space group P 21 21 21, a = 11.2640(2) Å, b = 16.6340(3) Å, c = 17.0480(2) Å, V = 3194.2 Å^3, Z = 4, μ = 0.07 mm^{-1}, colourless block, crystal dimensions = 0.4 x 0.4 x 0.5 mm^3. A total of 3793 unique reflections were measured for 1.81 < 2θ < 26.78 and 3618 reflections were used in the refinement. The final parameters were wR_2 = 0.031 and R_1 = 0.025 [I>3σ(I)]. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC634494. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Preparation of *tert*-butyl (2*S*,3*S*,1'*R*,α*S*)-2-(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-5-oxo-5-(4'',4''-dimethyl-oxazolidin-2''-one)pentanoate 15

Following representative procedure 1, LDA (2.0M, 1.10mmol, 0.55ml), **11** (1.0mmol, 415mg) in THF (5ml) and *N*-cinnamoyl-4,4-dimethyl-oxazolidin-2-one (0.95mmol, 233mg) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 3:1), **15** (322mg, 49%) as a colourless oil (78% d.e.); Data for major diastereoisomer; ν_{max} (film) 3061, 2976 (C-H), 1733, 1717, 1693 (C=O), 1143 (C-O); δ_H (500MHz, $CDCl_3$) 0.72, 0.89 (2 x 3H, s, C(4'')*Me*$_2$), 1.13 (3H, d, *J*6.8, C(α)*Me*), 1.56 (9H, s, OC*(Me)*$_3$), 3.00 (2H, ABq, *J*8.3, C(5'')*H*$_2$), 3.34 (1H, dd, $J_{4A,4B}$17.3, $J_{4A,3}$4.5, C(4)*H*$_A$), 3.54 (1H, app dt, $J_{3,4B}$10.5, $J_{3,4A;3,2}$4.0, C(3)*H*), 3.60 (1H, AB, *J*14.5, NC*H*$_A$), 3.67 (1H, dd, $J_{2,1'}$11.8, $J_{2,3}$3.5, C(2)*H*), 4.07 (1H, AB, *J*14.5, NC*H*$_B$), 4.16 (1H, dd, $J_{4B,4A}$17.3, $J_{4B,3}$10.5, C(4)*H*$_B$), 4.30 (1H, q, *J*6.8, C(α)*H*), 4.80 (1H, d, $J_{1',2}$11.8, C(1')*H*), 7.02-7.51 (20H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 17.1, 24.1, 24.5 (C(α)*Me*, C(4'')*Me*$_2$), 28.1 (OC*(Me)*$_3$), 36.0 (*C(4)*H_2), 40.6 (*C(2)*H), 51.2 (N*C*H_2), 54.7, 58.1, 63.6 (*C(3)*H, *C(1')*H and *C(α)*H), 60.2 (*C(4'')*Me_2), 75.0 (*C(5'')*H_2), 80.9 (O*C*$(Me)_3$), 126.2, 126.4, 126.5, 127.5, 127.7, 128.1, 128.2, 128.3, 128.9, 129.7 (*Ph*$_{o/m/p}$), 137.2, 140.5, 142.7, 144.1 (*Ph*$_{ipso}$), 153.9, 171.8, 172.6 (*C*=O); *m/z* APCI$^+$ 661.6 (MH^+, 75%), 682.9 (MNa^+, 10%); HRMS (CI^+) $C_{42}H_{49}N_2O_5$ requires 661.3341; found 661.3647.

Preparation of *tert*-butyl (2*S*,3*S*,1'*R*,4''*S*,α*S*)-2-(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-5-oxo-5-(4''-benzyl-oxazolidin-2''-one)-pentanoate 17

Following representative procedure 1, LDA (2.0M, 1.06mmol, 0.53ml), **11** (0.96mmol, 400mg) in THF (5ml) and (*S*)-*N*-cinnamoyl-4-benzyl-oxazolidin-2-one **16** (0.96mmol, 295mg) in THF (5ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 5:1), **17** (432mg, 62%) as a white foam (86% d.e.); $[\alpha]_D^{22}$ +51.8 (c 1.0, $CHCl_3$); ν_{max} (KBr) 2977 (C-H), 1782, 1718, 1702 (C=O), 1147 (C-O); δ_H (500MHz, $CDCl_3$) 1.06 (3H, d, *J*6.8, C(α)*Me*), 1.46 (9H, s, OC*(Me)*$_3$), 2.37 (1H, dd, $J_{A,B}$13.5, $J_{A,4''}$9.6, C(4'')C*H*$_A$Ph), 2.78 (1H, dd, $J_{B,A}$13.5, $J_{B,4''}$3.1, C(4'')C*H*$_B$Ph), 2.91 (1H, dd, $J_{4A,4B}$17.4, $J_{4A,3}$4.8, C(4)*H*$_A$), 3.26-3.30 (1H, m, C(3)*H*), 3.52 (1H, dd, $J_{2,1'}$11.8, $J_{2,3}$3.5, C(2)*H*), 3.57 (1H, AB, *J*14.2, NC*H*$_A$), 3.86 (1H, dd, $J_{4B,4A}$17.4, $J_{4B,3}$10.6, C(4)*H*$_B$), 4.02-4.10 (2H, m, C(5'')*H*$_2$), 4.05 (1H, AB, *J*14.2, NC*H*$_B$), 4.20 (1H, q, *J*6.8, C(α)*H*), 4.36-4.40 (1H, m, C(4'')*H*), 4.45 (1H, d, *J*11.8, C(1')*H*), 6.96-7.42 (25H, m, *Ph*); δ_C (50MHz,

$CDCl_3$) 16.9 (C(α)*Me*), 28.2 (OC*(Me)$_3$*), 34.7 (*C(4)*H_2), 37.4 (C(4")*C*H_2Ph), 40.5 (*C(2)*H), 51.2 (N*C*H_2), 54.7, 54.9, 57.7, 63.6 (*C(3)*H, *C(1')*H, *C(4")*H and *C(α)*H), 65.8 (*C(5")*H_2), 81.1 (O*C*(Me)$_3$), 126.5, 127.1, 127.7, 127.8, 128.3, 128.4, 128.8, 129.1, 129.4, 129.8 (*Ph*$_{o/m/p}$), 135.2, 137.4 140.5, 142.9, 144.2 (*Ph*$_{ipso}$), 153.4, 171.7, 171.9 (*C*=O); *m/z* APCI$^+$ 723.7 (MH^+, 100%), 745.6 (MNa^+, 35%); HRMS (CI^+) $C_{47}H_{51}N_2O_5$ requires 723.3798; found 723.3794.

Using 1.6eq of enolate; following representative procedure 1, LDA (2.0M, 1.28mmol, 0.64ml, 1.7eq), **11** (1.20mmol, 500mg, 1.6eq) in THF (5ml) and **16** (0.75mmol, 230mg, 1.0eq) in THF (5ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 5:1), **17** as a white foam (449mg, 83%, 86% d.e.).

Preparation of *tert*-butyl (2*S*,3*S*,1'*R*,4"*S*,α*S*)-2-(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-methoxyphenyl)-5-oxo-5-(4"-benzyl-oxazolidin-2"-one)-pentanoate 22

Following representative procedure 1, LDA (2.0M, 1.58mmol, 0.8ml), **11** (1.4mmol, 600mg) in THF (5ml) and (*S*)-*N*-*p*-methoxycinnamoyl-4-benzyl-oxazolidin-2-one **19** (1.4mmol, 486mg) in THF (5ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 8:1 to 5:1) **22** (632mg, 57%) as a white foam (88% d.e.); $C_{48}H_{52}N_2O_6$ requires C, 76.6; H, 7.0; N, 3.7%; found C, 76.3; H, 7.4; N, 3.7%; $[\alpha]_D^{22}$ +53.0 (c 1.0, $CHCl_3$); ν_{max} 2970 (C-H), 1777, 1718, 1700 (C=O), 1512 (OMe bend), 1251 (Ph-O), 1147 (C-O); δ_H (500MHz, $CDCl_3$) 1.05 (3H, d, *J*6.8, C(α)*Me*), 1.48 (9H, s, OC*(Me)$_3$*), 2.38 (1H, dd, $J_{A,B}$13.5, $J_{A,4"}$9.4, C(4")C$H_A$$CH_B$Ph), 2.79 (1H, dd, $J_{B,A}$13.5, $J_{B,4"}$3.2, C(4")CH_ACH_BPh), 2.89 (1H, dd, $J_{4A,4B}$17.3, $J_{4A,3}$4.8, C(4)H_A), 3.22 (1H, app dt, $J_{3,4B}$10.5, $J_{3,2;3,4A}$4.2, C(3')*H*), 3.48 (1H, dd, $J_{2,1'}$11.8, $J_{2,3}$3.5, C(2)*H*), 3.57 (1H, AB, *J*14.3, NCH_A), 3.75 (3H, s, O*Me*), 3.81 (1H, dd, $J_{4A,4B}$17.3, $J_{4B,3}$10.5, C(4)H_B), 3.98-4.06 (3H, m, C(5")H_2 and NCH_B), 4.19 (1H, q, *J*6.8, C(α)*H*), 4.34-4.39 (1H, m, C(4")*H*), 4.43 (1H, d, *J*11.8, C(1')*H*), 6.75 (2H, m, Ph(3)*H* and Ph(5)*H* C_6H_4OMe), 6.94-6.97 (2H, m, *Ph*), 6.99 (2H, m, Ph(2)*H* and Ph(6)*H* C_6H_4OMe), 7.15-7.42 (18H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 16.8 (C(α)*Me*), 28.1 (OC*(Me)$_3$*), 34.9 (*C(4)*H_2), 37.3 (C(4")*C*H_2), 39.7 (*C(2)*H), 51.0 (N*C*H_2), 54.8, 54.9, 55.1, 57.6, 63.4 (*C(3)*H, *C(1')*H, *C(4")*H, *OMe* and *C(α)*H), 65.7 (*C(5")*H_2), 81.0 (O*C*(Me)$_3$), 126.4, 127.0, 127.5, 127.7, 128.2, 128.3, 128.6, 128.7, 129.0, 129.3, 129.7 (*Ph*$_{o/m/p}$), 135.0, 135.1, 137.3, 140.4, 144.1 (*Ph*$_{ipso}$), 158.0 (*Ph(4)* C_6H_4OMe), 153.2, 171.7, 171.9 (*C*=O); m/z APCI$^+$ 774.8 (MH^+, 100%).

Preparation of *tert*-butyl (2*S*,3*S*,1'*R*,4''*S*,α*S*)-2-(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-5-oxo-5-(4''-phenyl-oxazolidin-2''-one)-pentanoate 23

Following representative procedure 1, LDA (2.0M, 2.12mmol, 1.06ml) **11** (1.92mmol, 800mg) in THF (10ml) and (*S*)-*N*-cinnamoyl-4-phenyl-oxazolidin-2-one **20** (2.4mmol, 390mg) in THF (10ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 5:1), **23** (710mg, 52%) as a white foam (92% d.e.); $C_{46}H_{48}N_2O_5$ requires C, 77.9; H, 6.8; N, 3.95%; found C, 77.95; H, 6.9; N, 3.8%; ν_{max} (KBr) 2976 (C-H), 1782, 1719, 1705 (C=O), 1147 (C-O); $[\alpha]_D^{22}$ +68.0 (c 1.0, $CHCl_3$); δ_H (500MHz, $CDCl_3$) 1.05 (3H, d, *J*6.8, C(α)*Me*), 1.49 (9H, s, OC*(Me)$_3$*), 2.89 (1H, dd, $J_{4A,4B}$17.0, $J_{4A,3}$4.9, C(4)H_A), 3.19 (1H, app dt, $J_{3,4B}$10.4, $J_{3,4A;3,2}$3.9, C(3)*H*), 3.50 (1H, dd, $J_{2,1'}$11.9, $J_{2,3}$3.1, C(2)*H*), 3.57 (1H, AB, *J*14.2, NCH_A), 3.95 (1H, dd, $J_{4B,4A}$17.0, $J_{4B,3}$10.4, C(4)H_B), 4.04 (1H, dd, $J_{5''A,5''B}$8.7, $J_{5''A,4''}$3.9, C(5'')H_A), 4.06 (1H, AB, *J*14.2, NCH_B), 4.21 (1H, q, *J*6.8, C(α)*H*), 4.45 (1H, d, $J_{1',2}$11.9, C(1')*H*), 4.51 (1H, t, *J*8.7, C(5'')H_B), 5.11 (1H, dd, $J_{4'',5''B}$8.7, $J_{4'',5'A}$3.9, C(4'')*H*), 6.79-7.40 (25H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 16.7 (C(α)*Me*), 28.2 (OC*(Me)$_3$*), 34.4 (*C(4)*H_2), 40.6 (*C(2)*H), 51.1 (N*C*H_2), 54.6, 57.4, 57.5, 63.4 (*C(3)*H, *C(1')*H, *C(4'')*H and *C(α)*H), 69.7 (*C(5'')*H_2), 81.1 (O*C*(Me)$_3$), 125.1, 126.4, 126.5, 127.6, 127.8, 128.0, 128.2, 128.3, 128.8, 129.1, 129.7 (*Ph*$_{o/m/p}$), 137.2, 138.6, 140.4, 142.5, 144.2 (*Ph*$_{ipso}$), 153.6, 171.4, 171.9 (C=O); *m/z* APCI$^+$ 709.7 (MH^+, 100%), 731.7 (MNa^+, 15%), 653.7 (MH^+-C_4H_8, 5%).

Preparation of *tert*-butyl (2*S*,3*S*,1'*R*,4''*S*,α*S*)-2-(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-5-oxo-5-(4''-phenyl-5'',5''-dimethyl-oxazolidin-2''-one)-pentanoate 24

Following representative procedure 1, LDA (2.0M, 1.53mmol, 0.76ml), **11** (1.44mmol, 600mg) in THF (5ml) and (*S*)-*N*-cinnamoyl-4-phenyl-5,5-dimethyloxazolidin-2-one **21** (2.4mmol, 390mg) in THF (5ml) gave, purification by column chromatography on silica gel (hexane:Et_2O 3:1) **24** (502mg, 75%) as a white foam (90% d.e.); ν_{max} (KBr) 3028, 2976 (C-H), 1777, 1723 (C=O), 1147 (C-O); $[\alpha]_D^{22}$ +42.5 (c 1.0, $CHCl_3$); δ_H (500MHz, $CDCl_3$) 0.86 (3H, s, C(5'')*Me$_A$*), 1.04 (3H, d, *J*6.8, C(α)*Me*), 1.48 (9H, s, OC*(Me)$_3$*), 1.54 (3H, s, C(5'')*Me$_B$*), 2.91 (1H, dd, $J_{4A,4B}$17.0, $J_{4A,3}$5.2, C(4)H_A), 3.22 (1H, ddd, $J_{3,4B}$10.2, $J_{3,4A}$5.2, $J_{3,2}$3.1, C(3)*H*), 3.44 (1H, dd, $J_{2,1'}$11.9, $J_{2,3}$3.1, C(2)*H*), 3.52 (1H, AB, *J*14.3, NCH_A), 3.90 (1H, dd, $J_{4B,4A}$17.0, $J_{4B,3}$10.3, C(4)H_B), 4.01 (1H, AB, *J*14.3, NCH_B), 4.16 (1H, q, *J*6.8, C(α)*H*), 4.46 (1H, d, *J*11.9, C(1')*H*), 4.80 (1H, s,

C(4")*H*), 6.68-6.72 (2H, m, *Ph*), 6.99-7.50 (23H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 16.8 (C(α)*Me*), 23.8, 28.8 (C(5")Me_2), 28.2 (OC*(Me)*$_3$), 34.9 (*C(4)*H_2), 40.6 (*C(2)*H), 51.1 (N*C*H_2), 54.7, 57.7, 63.5, 66.9 (*C(3)*H, *C(1')*H, *C(4")*H and *C(α)*H), 81.1, 82.0 (O*C*(Me)$_3$ and *C(5")*Me_2), 125.8, 126.4, 127.6, 127.8, 127.9, 128.3, 128.4, 128.5, 129.1, 129.8 ($Ph_{o/m/p}$), 135.9, 137.2, 140.5, 142.9, 144.2 (Ph_{ipso}), 153.1, 171.6, 171.9 (*C*=O); *m/z* APCI$^+$ 738.0 (MH^+, 50%), 681.5 (MH^+-C_4H_8, 75%); HRMS (CI^+) $C_{48}H_{53}N_2O_5$ requires 737.3954; found 737.3943.

Cleavage Reaction to give 1-*tert*-butyl-5-methyl (2*S*,3*S*,1'*R*,α*S*)-2-{1'-phenyl-(1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-pentanedioate 13

To a stirred solution of **24** (100mg, 0.136mmol) in THF (5ml) at -78˚C was added a solution of butyllithium (2.5M, 0.338mmol, 2.5eq) in MeOH (1ml) prepared at 0˚C. The resultant mixture was stirred at -78˚C for ten minutes and then warmed to rt overnight. The reaction was quenched by the addition of pH7 phosphate buffer solution (5ml), partitioned between brine and Et_2O (3 x 80ml), dried and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane: Et_2O 3:1) gave **13** (76mg, 97%) with identical spectroscopic properties as described earlier. Further elution gave the SuperQuat auxiliary (22mg, 85%).

Cleavage Reaction to give *tert*-butyl (2*S*,3*S*,1'*R*,1''*S*,α*S*)-2-{1'-phenyl-(1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-4-(1''-benzyl-2''-hydroxyethylcarbamoyl)-butanoate 25

To a stirred solution of **17** (200mg, 0.28mmol) in THF (5ml) at –78˚C was added a solution of butyllithium (2.5M, 0.69mmol, 2.5eq) in MeOH (2ml) prepared at 0˚C. The resultant mixture was stirred at –78˚C for ten minutes and then warmed to rt overnight before the addition of pH7 phosphate buffer solution (5ml), the solution partitioned between brine and Et_2O (3 x 80ml), dried and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane: Et_2O 3:1) gave **13** (46mg, 29%) which was spectroscopically identical to that obtained previously; a more polar fraction yielded **25** (107mg, 56%); ν_{max} (KBr) 3028, 2976 (C-H), 1723, 1654 (C=O), 1147 (C-O); $[\alpha]_D^{22}$ +18.9 (c 1.0, $CHCl_3$); δ_H (500MHz, $CDCl_3$) 1.08 (3H, d, *J*6.9, C(α)*Me*), 1.36 (9H, s, OC*(Me)*$_3$), 2.38 (1H, dd, $J_{4A,4B}$15.2, $J_{4A,3}$3.9, C(4)H_A), 2.49 (1H, dd, $J_{A,B}$13.8, *J*6.9, NCHC$H_A$$CH_B$Ph), 2.57 (1H, dd, $J_{B,A}$13.8, *J*7.3, NCHCH_ACH_BPh), 2.65 (1H, br s, O*H*), 2.74 (1H, dd, $J_{4B,4A}$15.2, $J_{4B,3}$11.8, C(4)H_B), 3.22 (1H, app dt, $J_{3,4B}$11.8, $J_{3,4A;3,2}$3.7, C(3)*H*), 3.26 (1H, dd, $J_{A,B}$11.0, *J*5.0,

NCHCH_ACH$_B$OH), 3.33 (1H, dd, $J_{B,A}$11.0, *J*3.3, NCHCH$_A$CH_BOH), 3.55 (1H, dd, $J_{2,1'}$11.8, $J_{2,3}$3.8, C(2)*H*), 3.65 (1H, AB, *J*14.2, NCH_A), 3.80-3.84 (1H, m, NC*H*CH$_A$CH$_B$), 4.13 (1H, AB, *J*14.2, NCH_B), 4.30 (1H, q, *J*6.9, C(α)*H*), 4.38 (1H, d, *J*11.8, C(1')*H*), 5.27 (1H, d, *J*7.7, N*H*), 7.03-7.08 (4H, m, *Ph*), 7.20-7.49 (21H, m, *Ph*); δ_C (125MHz, $CDCl_3$) 16.3 (C(α)*Me*), 27.9 (OC*(Me)$_3$*), 34.9 (*C*(4)H$_2$), 36.4 (NCH*C*H$_2$Ph), 41.0 (*C*(2)H), 51.0 (N*C*H$_2$), 52.3, 54.0, 57.0, 62.8 (*C*(3)H, *C*(1')H, N*C*HCH$_2$Ph and *C*(α)H), 63.4 (NCH*C*H$_2$OH), 80.8 (O*C*(Me)$_3$), 126.3, 126.5, 126.6, 127.6, 127.7, 127.8, 128.1, 128.3, 128.4, 128.9, 129.0, 129.6 ($Ph_{o/m/p}$), 136.7, 137.5, 140.0, 141.5, 144.2 (Ph_{ipso}), 171.6, 172.0 (*C*=O); *m/z* APCI$^+$ 697.9 (MH$^+$, 100%), 720.0 (MNa$^+$, 20%); HRMS (CI$^+$) $C_{46}H_{53}N_2O_4$ requires 697.4005; found 697.4014.

Preparation of (4*S*,5*S*,6*R*)-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 26 (from 13)

Following Representative Procedure 3, Pd(OH)$_2$ on C (60mg) and **13** (120mg, 0.20mmol) in MeOH (5ml) gave, after purification by column chromatography on silica gel (hexane:EtOAc 5:1), **26** as a white solid (56mg, 80%); $[\alpha]_D^{21}$ -17.4 (c 0.65, $CHCl_3$); ν_{max} (KBr) 3387 (NH), 2978 (C-H), 1711 (C=O$_{ester}$), 1654 (C=O$_{lactam}$), 1167 (C-O); δ_H (500MHz, C_6D_6) 0.85 (9H, s, OC*(Me)$_3$*), 2.57 (1H, dd, $J_{3A,3B}$17.3, $J_{3A,4}$5.5, C(3)H_A), 2.88 (1H, m, C(4)*H*), 2.92 (1H, dd, $J_{5,4}$5.5, $J_{5,6}$5.0, C(5)*H*), 3.60 (1H, dd, $J_{3B,3A}$17.3, $J_{3B,4}$13.2, C(3)H_B), 4.30 (1H, d, $J_{6,5}$5.0, C(6)*H*), 6.92 (1H, br s, N*H*), 6.98-7.19 (10H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 27.4 (OC*(Me)$_3$*), 32.5 (*C(3)*H$_2$), 40.9 (*C(5)*H), 51.8 (*C(4)*H), 59.0 (*C(6)*H), 80.7 (O*C*(Me)$_3$), 126.5, 127.2, 127.3, 128.2, 128.5, 128.6 ($Ph_{o/m/p}$), 138.3, 140.0 (Ph_{ipso}), 168.7, 172.6 (*C*(2) and *C*O$_2$C(Me)$_3$); *m/z* APCI$^+$ 352.1 (MH$^+$, 10%), 374.1 (MNa$^+$, 20%), 296.1 (MH$^+$-C$_4$H$_8$, 100%); HRMS (CI$^+$) $C_{22}H_{26}NO_3$ requires 352.1920; found 352.1913.

Preparation of (4*S*,5*S*,6*R*)-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 26 (from 17)

Following Representative Procedure 3, Pd(OH)$_2$ on C (75mg) and **17** (150mg, 0.21mmol) in MeOH (5ml) gave, after purification by column chromatography on silica gel (hexane:EtOAc 5:1), **25** as a white solid (50mg, 76%) with identical spectroscopic properties to that above.

Preparation of (4*S*,5*S*,6*R*)-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 26 (from 24)

Following Representative Procedure 3, $Pd(OH)_2$ on C (75mg) and **24** (200mg, 0.27mmol) in MeOH (5ml) gave, after purification by column chromatography on silica gel (hexane:EtOAc 5:1), **25** as a white solid (80mg, 84%) with identical spectroscopic properties to that previously described.

Preparation of *tert*-butyl (2*R*,3*S*,1'*S*,4''*S*,α*R*)-2-(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-5-oxo-5-(4''-benzyl-oxazolidin-2''-one)-pentanoate 28

Following Representative Procedure 2, *n*-BuLi (2.5M, 2.47mmol, 0.98ml), (*R*)-*N*-benzyl-*N*-α-methylbenzylamine (500mg, 2.36mmol) in THF (5ml), *tert*-butyl cinnamate (438mg, 2.15mmol) in THF (3ml) and (*S*)-4-benzyl-oxazolidin-2-one (660mg, 2.15mmol) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 6:1), **28** (590mg, 38%) as a white foam and as an inseparable mixture of diastereoisomers (85% d.e.), also containing (*S*)-4-benzyl-oxazolidin-2-one (12:1:1); ν_{max} (film) 2975 (C-H), 1782, 1728, 1702 (C=O), 1142 (C-O); $[\alpha]_D^{22}$ +18.3 (c 1, $CHCl_3$); δ_H (500MHz, $CDCl_3$) 1.19 (3H, d, *J*6.8, C(α)*Me*), 1.62 (9H, s, OC*(Me)$_3$*), 2.50 (1H, dd, $J_{A,B}$13.5, $J_{A,4''}$9.5, C(4")C$H_A$$CH_B$Ph), 2.99 (1H, dd, $J_{B,A}$13.5, $J_{B,4''}$3.2, C(4")C$H_A$$CH_B$Ph), 3.31 (1H, dd, $J_{4A,4B}$17.7, $J_{4A,3}$7.3, C(4)H_A), 3.38 (1H, dd, $J_{4B,4A}$17.7, $J_{4B,3'}$7.7, C(4)H_B), 3.51 (1H, dd, $J_{2,1'}$11.4, $J_{2,3}$5.3, C(2)*H*), 3.53 (1H, d, *J*14.8, NCH_A), 3.52-3.57 (1H, m, C(3)*H*), 3.75 (1H, d, *J*14.8, NCH_B), 4.07 (1H, q, *J*6.8, C(α)*H*), 4.09-4.17 (2H, m, C(5")H_2), 4.25 (1H, d, *J*11.4, C(1')*H*), 4.53-4.58 (1H, m, C(4")*H*), 6.81-6.83 (2H, m, *Ph*), 7.06-7.47 (23H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 19.5 (C(α)*Me*), 28.2 (OC*(Me)$_3$*), 37.4, 39.5 (*C(4)*H_2, *C(4")C*H_2Ph), 40.3 (*C(2)*H), 51.4 (N*C*H_2), 52.4, 55.0, 60.7, 63.9 (*C(3)*H, *C(1)*H, *C(4)*H and *C(α)*H), 66.0 (*C(5")*H_2), 81.0 (O*C*(Me)$_3$), 126.5, 126.8, 127.3, 127.4, 127.6, 128.0, 128.2, 128.4, 128.5, 128.9, 129.4, 129.5 (*Ph*$_{o/m/p}$), 135.1, 136.7, 139.2, 141.6, 144.9 (*Ph*$_{ipso}$), 153.3, 171.3, 171.8 (*C*=O); *m/z* APCI$^+$ 723.8 (MH^+, 10%), 667.6 (MH^+-C_4H_8, 30%); HRMS (CI^+) $C_{47}H_{50}N_2O_5Na$ requires 745.3617; found 745.3669.

Preparation of (4*S*,5*R*,6*S*)-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 29

Following Representative Procedure 3, $Pd(OH)_2$ on C (75mg) and **28** (150mg, 0.21mmol, 85% d.e.) in MeOH (5ml) gave, after purification by column chromatography on silica gel (hexane:EtOAc 2:1), **29** (50mg, 68%); ν_{max} (film) 3424 (NH), 1717 (C=O$_{ester}$), 1670 (C=O$_{lactam}$); $[\alpha]_D^{23}$ +135.7 (c 1, $CHCl_3$); δ_H (500MHz, C_6D_6) 0.80 (9H, s, OC(Me)$_3$), 2.25 (1H, dd, $J_{3A,3B}$17.8, $J_{3A,4}$10.9, C(3)H_A), 2.76 (1H, dd,

$J_{3B,3A}$17.8, $J_{3B,4}$5.7, C(3)H_B), 3.05 (1H, dd, $J_{5,4}$11.2, $J_{5,6}$5.8, C(5)*H*), 3.15-3.22 (1H, m, C(4)*H*), 4.51 (1H, dd, $J_{6,5}$5.8, $J_{6,NH}$3.0, C(6)*H*), 6.78-7.05 (10H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 27.2 (OC(*Me*)$_3$), 36.6 (*C(4)*H), 38.6 (*C(3)*H$_2$), 51.6 (*C(5)*H), 56.9 (*C(6)*H), 81.4 (O*C*(Me)$_3$), 127.0, 127.1, 127.6, 128.4, 128.7 ($Ph_{o/m/p}$), 138.7, 142.4 (Ph_{ipso}), 169.1, 171.1 (*C(2)* and *C*O$_2$C(Me)$_3$); *m/z* APCI$^+$ 352.2 (MH$^+$, 20%), 296.2 (MH$^+$-C_4H_8, 100%); HRMS (CI$^+$) $C_{22}H_{26}NO_3$ requires 352.1920; found 352.1915.

Preparation of (4*R*,5*S*,6*R*)-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 29

Following Representative Procedure 3, $Pd(OH)_2$ on C (50mg) and **31** (100mg) in MeOH (3ml) gave, after purification by column chromatography on silica gel (hexane:EtOAc 2:1), **29** (38mg, 80%); $[\alpha]_D^{23}$ -129.4 (c 1, $CHCl_3$).

Preparation of *tert*-butyl (2*S*,3*R*,1'*R*,4''*S*,α*S*)-2-(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-5-oxo-5-(4''-benzyl-oxazolidin-2''-one)-pentanoate 31

Following Representative Procedure 2, *n*-BuLi (2.5M, 2.47mmol, 0.98ml, 1.15eq), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (500mg, 2.36mmol, 1.1eq) in THF (5ml), *tert*-butyl cinnamate (438mg, 2.15mmol, 1.0eq) in THF (3ml) and (*S*)-4-benzyl-oxazolidin-2-one (660mg, 2.15mmol, 1.0eq) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 6:1), β-amino ester **11** (312mg, 35%) and **31** (434mg, 28%) as a mixture of diastereoisomers (50% d.e.). Repeated chromatographic purification resulted in diastereoisomeric enrichment of the major diastereoisomer (90% d.e.); Data for major diastereoisomer; ν_{max} (KBr) 2974 (C-H), 1783, 1726, 1700 (C=O), 1142 (C-O); δ_H (400MHz, C_6D_6) 1.20 (3H, d, *J*6.8, C(α)*Me*), 1.69 (9H, s, OC*(Me)$_3$*), 2.18 (1H, dd, $J_{A,B}$13.2, $J_{A,4''}$10.4, C(4'')CH_ACH_BPh), 2.91 (1H, app t, *J*8.4, C(5'')H_A), 3.04 (1H, dd, $J_{B,A}$13.2, $J_{B,4''}$3.0, C(4'')CH_ACH_BPh), 3.31-3.38 (2H, m, C(4)H_A and C(5'')H_B), 3.54 (1H, AB, *J*14.4, NCH_A), 3.67-3.80 (4H, m, C(4)H_B, C(2)*H,* C(3)*H* and NCH_B), 3.84-3.90 (1H, m, C(4'')*H*), 4.18 (1H, q, *J*6.8, C(α)*H*), 4.25 (1H, d, *J*11.7, C(1')*H*), 6.80-6.83 (2H, m, *Ph*), 6.99-7.34 (23H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 19.8 (C(α)*Me*), 28.2 (OC*(Me)$_3$*), 37.9, 39.6 (*C(4)*H$_2$, C(4'')*C*H$_2$Ph), 51.1 (N*C*H$_2$), 40.0, 52.2, 55.2, 61.1, 64.1 (*C(3)*H, *C(2)*H, *C(1')*H, *C(4'')*H and *C(α)*H), 66.0 (*C(5'')*H$_2$), 80.9 (O*C*(Me)$_3$), 126.1, 126.4, 126.7, 127.2, 127.3, 127.5, 127.7, 127.9, 128.1, 128.8, 128.9, 129.4, 130.5

($Ph_{o/m/p}$), 135.4, 136.6, 139.0, 141.5, 145.0 (Ph_{ipso}), 153.2, 171.2, 171.8 (*C*=O); *m/z* APCI$^+$ 723.4 (MH^+, 10%), 667.6 (MH^+-C_4H_8, 30%); HRMS (CI^+) $C_{47}H_{51}N_2O_5$ requires 723.3798; found 723.3823.

Preparation of (*E*)-cinnamyl-malonic acid diethyl ester 32[1]

n-Butyllithium (2.5M, 0.91ml, 2.24mmol), was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (500mg, 2.31mmol) in anhydrous THF (5ml) at -78˚C and stirred for thirty minutes under nitrogen. A solution of the dimethyl phenylallylidenemalonate in anhydrous THF (5ml) was added dropwise *via* cannula and stirred at -78˚C for two hours before the addition of saturated aqueous ammonium chloride. After warming to rt, the resultant solution was partitioned between brine and 1:1 DCM/Et_2O, the organic extracts were dried, filtered and concentrated *in vacuo*. Purification by column chromatography on silica gel (hexane:Et_2O 12:1), **32** (63mg, 16%) as a colourless oil; δ_H (200MHz, $CDCl_3$) δ_H 1.27 (6H, t, *J*7.1, OCH_2CH_3 x 2), 2.80 (2H, app td, $J_{3,2;3,4}$7.6, $J_{3,5}$1.3, C(3)H_2), 3.50 (1H, t, $J_{2,3}$7.6, (C(2)H), 4.21 (4H, q, *J*7.1, OCH_2CH_3 x 2), 6.16 (1H, dt, $J_{4,3}$7.6, $J_{4,5}$15.8, C(4)H), 6.49 (1H, br d, $J_{5,4}$15.8, C(5)H), 7.19-7.36 (5H, m, Ph).

Preparation of 1-*tert*-butyl-5-ethyl (2*S*,3*R*,1'*R*,α*S*)-2-{(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-4-ethoxycarbonyl-pentanedioate 34

Following Representative Procedure 2, *n*-BuLi (2.5M, 2.24mmol, 0.89ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (500mg, 2.30mmol) in THF (5ml), *tert*-butyl cinnamate (234mg, 1.15mmol) in THF (3ml) and diethyl benzylidenemalonate (571mg, 2.30mmol) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 6:1) **34** as a hygroscopic white foam (617mg, 81%); ν_{max} (film) 2978 (C-H), 1757, 1732 (C=O), 1141 (C-O); $[\alpha]_D^{24}$ –29.3 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 0.72 (3H, t, *J*7.1, OCH_2CH_3), 1.06 (3H, d, *J*6.8, C(α)*Me*), 1.25 (3H, t, *J*7.1, OCH_2CH_3), 1.66 (9H, s, $CO_2C(Me)_3$), 3.32 (1H, dd, $J_{3,4}$12.0, $J_{3,2}$1.0, C(3)*H*), 3.44 (1H, AB, *J*14.4, NCH_A), 3.55 (1H, dd, $J_{2,1'}$12.2, $J_{2,3}$1.0, C(2)*H*), 3.62-3.66 (3H, m, OCH_2CH_3 and C(4)*H*), 3.83 (1H, AB, *J*14.4, NCH_B), 4.02 (1H, dq, $J_{A,B}$10.7, $J_{A,CH3}$7.1, OCH_ACH_3), 4.11 (1H, q, *J*6.8, C(α)*H*), 4.17 (1H, dq, $J_{B,A}$10.7, $J_{B,CH3}$7.1, OCH_BCH_3), 4.72 (1H, d, *J*12.2,

[1] S. Raucher, K-W. Chan and D. S. Jones, *Tetrahedron Lett.*, **1985**, *25*, 6261.

C(1')*H*), 6.94-6.98 (2H, m, *Ph*), 7.14-7.37 (18H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 13.4, 14.1 ($OCH_2C\mathit{H_3}$), 17.5 (C(α)*Me*), 28.3 ($CO_2\mathit{C}(Me)_3$), 43.6 (*C(3)*H), 51.3 (NCH_2), 54.1, 57.0, 58.1 (*C(4)*H, *C(2)*H, and *C(α)*H), 60.9, 61.3 (OCH_2CH_3), 64.1 (*C(1')*H), 81.2 ($CO_2\mathit{C}(Me)_3$), 126.2, 126.3, 126.7, 127.3, 127.7, 127.9, 128.3, 128.8, 129.1, 130.5 ($Ph_{o/m/p}$), 137.2, 140.6, 142.4, 144.7 (Ph_{ipso}), 167.7, 167.9, 171.9 ($\mathit{C}O_2C(Me)_3$ and $\mathit{C}O_2Et$ x 2); *m/z* APCI$^+$ 664.7 (MH^+, 100%), 608.3 (MH^+-C_4H_8, 10%); HRMS (CI^+) $C_{42}H_{50}NO_6$ requires 664.3638; found 664.3642.

Preparation of (3*S*,4*R*,5*S*,6*R*)-3-ethoxycarbonyl-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 35

Following Representative Procedure 3, $Pd(OH)_2$ on C (75mg), **34** (150mg, 0.23mmol) in MeOH (5ml) gave, after purification by column chromatography on silica gel (Et_2O:hexane 2:1), **35** (78mg, 81%) as a colourless oil; ν_{max} (film) 3311 (NH), 2977 (C-H), 1723, 1666 (C=O), 1153 (C-O); $[\alpha]_D^{23}$ –72.1 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 0.92 (9H, s, $CO_2C\mathit{(Me)_3}$), 1.06 (3H, t, *J*7.1, $OCH_2C\mathit{H_3}$), 3.15 (1H, app t, $J_{5,4;5,6}$4.5, C(5)*H*), 3.93 (1H, dd, $J_{4,3}$12.7, $J_{4,5}$3.9, C(4)*H*), 4.03-4.13 (2H, m, $OC\mathit{H_2}CH_3$), 4.65 (1H, d, *J*12.7, C(3)*H*), 5.09 (1H, d, $J_{6,5}$5.2, C(6)*H*), 6.13 (1H, br s, N*H*), 7.23-7.37 (10H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 13.9 ($OCH_2C\mathit{H_3}$), 27.4 ($CO_2C\mathit{(Me)_3}$), 44.6, 49.8, 52.0 and 58.8 (*C(3)*H, *C(4)*H, *C(5)*H and *C(6)*H), 61.3 (OCH_2CH_3), 81.1 ($CO_2\mathit{C}(Me)_3$), 126.4, 127.6, 127.7, 128.3, 128.6, 128.7 ($Ph_{o/m/p}$), 137.8, 138.1 (Ph_{ipso}), 168.8, 170.0 (*C(2)*=O, $\mathit{C}O_2C(Me)_3$ and $\mathit{C}O_2Et$); *m/z* APCI$^+$ 424.2 (MH^+, 5%), 446.0 (MH^+, 100%), 368.1 (MH^+-C_4H_8, 20%); HRMS (CI^+) $C_{25}H_{30}NO_5$ requires 424.2124; found 424.2126.

Preparation of 1-*tert*-butyl-5-ethyl (2*S*,3*S*,1'*R*,α*S*)-2-{(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-4-ethoxycarbonyl-pentanedioate 36

Following representative procedure 1, LDA (2.0M, 0.53mmol, 0.27ml), **11** (200mg, 0.48mmol) in THF (5ml) and diethyl benzylidenemalonate (120mg, 0.48mmol) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 10:1), **36** (105mg, 33%) as a colourless oil and as an inseparable 8:1 mixture with diethyl benzylidenemalonate; ν_{max} (film) 2977 (C-H), 1754, 1731(C=O), 1140 (C-O); δ_H (400MHz, $CDCl_3$) 0.68 (3H, t, *J*7.3, $OCH_2C\mathit{H_3}$), 1.13 (3H, d, *J*6.8, C(α)*Me*), 1.28 (3H, t, *J*7.3, $OCH_2C\mathit{H_3}$), 1.66 (9H, s, $CO_2C\mathit{(Me)_3}$), 3.42 (1H, AB, *J*14.9, $NC\mathit{H_A}$), 3.51 (1H, AB, *J*14.9, $NC\mathit{H_B}$), 3.54-3.61 (2H, m, C(3)*H* and C(2)*H*), 3.64-3.69 (2H, m, $OC\mathit{H_2}CH_3$), 3.89 (1H, d, *J*12.2, C(4)*H*), 4.06 (1H, d, *J*11.5, C(1')*H*),

3.98 (1H, q, *J*6.8, C(α)*H*), 4.14-4.23 (2H, m, OC*H*$_2$CH$_3$), 7.08-7.33 (20H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 13.4, 14.0, 19.9 (OCH$_2$*C*H$_3$ x 2 and C(α)*Me*), 28.2 (CO$_2$C*(Me)$_3$*), 44.1, 49.4 (*C(3)*H and *C(2)*H), 51.2 (NCH$_2$), 56.1 (*C(4)*H), 61.1, 61.6 (O*C*H$_2$CH$_3$ x 2), 63.8 (*C(1')*H), 81.0 (CO$_2$*C*(Me)$_3$), 126.0, 126.3, 127.0, 127.1, 127.2, 127.4, 127.9, 128.0, 128.8, 129.4, 130.2, 130.5 (*Ph*$_{o/m/p}$), 135.2, 135.7, 141.4, 145.1 (*Ph*$_{ipso}$), 167.5, 167.8, 171.5 (*C*O$_2$C(Me)$_3$ and *C*O$_2$Et x 2); *m/z* APCI$^+$ 664.3 (MH$^+$, 100%), 686.6 (MNa$^+$, 10%), 608.6 (MH$^+$-C$_4$H$_8$, 5%); HRMS (CI$^+$) $C_{42}H_{50}NO_6$ requires 664.3638; found 664.3644.

Preparation of (3*S*,4*S*,5*S*,6*R*)-3-ethoxycarbonyl-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 37

Following Representative Procedure 3, Pd(OH)$_2$ on C (50mg), **36** (100mg, 0.13mmol) in MeOH (10ml) gave, after purification by column chromatography on silica gel (Et$_2$O:hexane 2:1), **37** (52mg, 91%) as a colourless oil; ν_{max} (film) 3309 (NH), 2979 (C-H), 1725, 1670 (C=O), 1159 (C-O); $[\alpha]_D^{23}$ –61.8 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 0.78 (9H, s, CO$_2$C*(Me)$_3$*), 1.09 (3H, t, *J*7.1, OCH$_2$C*H*$_3$), 3.47 (1H, d, *J*$_{3,4}$11.8, C(3)*H*), 3.54 (1H, dd, *J*$_{5,4}$12.8, *J*$_{5,6}$5.8, C(5)*H*), 3.78 (1H, app t, *J*$_{4,3;4,5}$12.3, C(4)*H*), 4.06-4.16 (2H, m, OC*H*$_2$CH$_3$), 5.06 (1H, dd, *J*$_{6,5}$5.8, *J*$_{6,NH}$3.6, C(6)*H*), 6.50 (1H, br s, N*H*), 7.11-7.41 (10H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 13.9 (OCH$_2$*C*H$_3$), 27.0 (CO$_2$C*(Me)$_3$*), 39.3, 50.5, 56.8 and 57.5 (*C(3)*H, *C(4)*H, *C(5)*H and *C(6)*H), 61.4 (O*C*H$_2$CH$_3$), 81.7 (CO$_2$*C*(Me)$_3$), 127.3, 127.5, 128.1, 128.5, 128.6 (*Ph*$_{o/m/p}$), 138.0, 139.9 (*Ph*$_{ipso}$), 167.3, 168.3, 169.2 (*C(2)*=O, *C*O$_2$C(Me)$_3$ and *C*O$_2$Et); *m/z* APCI$^+$ 424.2 (MH$^+$, 35%), 446.1 (MNa$^+$, 30%), 368.2 (MH$^+$-C$_4$H$_8$, 100%); HRMS (CI$^+$) $C_{25}H_{30}NO_5$ requires 424.2124; found 424.2127.

Preparation of 1-*tert*-butyl-5-methyl (2*S*,3*R*,1'*R*,α*S*)-2-{(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-bromophenyl)-4-methoxycarbonyl-pentanedioate 38

Following Representative Procedure 2, *n*-BuLi (2.5M, 2.18mmol, 0.89ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (500mg, 2.30mmol) in THF (3ml) and *tert*-butyl cinnamate (234mg, 1.15mmol) in THF (3ml) and dimethyl 4-bromobenzylidenemalonate (515mg, 1.72mmol) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et$_2$O 8:1), **38** (512mg, 63%) as a white foam; ν_{max} (KBr) 2974 (C-H), 1761, 1737 (C=O), 1141 (C-O); $[\alpha]_D^{24}$ –21.6 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 1.00 (3H, d, *J*6.8, C(α)*Me*), 1.58 (9H, s, OC*(Me)$_3$*), 3.18 (3H, s, CO$_2$*Me*), 3.23 (1H, dd, *J*$_{3,4}$11.6, *J*$_{3,2}$1.5, C(3)*H*), 3.43 (1H, dd, *J*$_{2,1'}$12.2, *J*$_{2,3}$1.5, C(2)*H*), 3.45 (1H, AB, *J*14.4, NC*H*$_A$), 3.57-3.61 (4H, m, CO$_2$*Me* and C(4)*H*), 3.78

(1H, AB, *J*14.4, NC*H*$_B$), 4.07 (1H, q, *J*6.8, C(α)*H*), 4.57 (1H, d, *J*12.2, C(1')*H*), 6.73-6.77 (2H, m, *Ph*), 7.04-7.07 (2H, m, *Ph*), 7.14-7.34 (15H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 17.3 (C(α)*Me*), 28.2 (CO_2C*(Me)$_3$*), 43.1 (*C(2)*H), 51.0 (N*C*H$_2$), 52.1, 52.7 (CO_2*Me* x 2), 53.8, 56.5, 57.9 (*C(3)*H, *C(4)*H, and *C(α)*H), 63.9 (*C(1')*H), 81.6 (CO_2C(Me)$_3$), 120.8 (*Ph(4)* C_6H_4Br), 126.4, 127.4, 127.7, 128.0, 128.2, 129.1, 130.3, 133.1 (*Ph*$_{o/m/p}$), 137.1, 140.4, 143.2, 144.6 (*Ph*$_{ipso}$), 167.7, 167.9, 171.7 (CO_2C(Me)$_3$ and CO_2Me x 2); *m/z* APCI$^+$ 714 (MH$^+$, 100%), 660 (MH$^+$-C_4H_8, 10%); HRMS (CI$^+$) $C_{40}H_{45}NBr^{79}O_6$ requires 714.2430, found 714.2444.

Preparation of 1-*tert*-butyl-5-methyl (2*S*,3*R*,1'*R*,α*S*)-2-{(1'-(3,4-dimethoxyphenyl)-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-(4-bromophenyl)-4-methoxycarbonyl-pentanedioate 39

Following Representative Procedure 2, *n*-BuLi (2.5M, 1.47mmol, 0.59ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (321mg, 1.51mmol) in THF (3ml) and *tert*-butyl 3-(3,4-dimethoxyphenyl)-prop-2-enoate (200mg, 0.76mmol) in THF (2ml) and dimethyl 4-bromobenzylidenemalonate (341mg, 1.14mmol) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 8:1), **39** (412mg, 70%) as a white foam; ν_{max} (KBr) 2953 (C-H), 1761, 1737 (C=O), 1141 (C-O); $[\alpha]_D^{24}$ -7.1 (c 1.0, $CHCl_3$); δ_H (400MHz, C_6D_6) 1.17 (3H, d, *J*6.8, C(α)*Me*), 1.54 (9H, s, OC*(Me)$_3$*), 2.77 (3H, s, CO_2*Me*), 3.35 (3H, s, O*Me*), 3.42 (6H, s, CO_2*Me* and O*Me*), 3.57 (1H, d, $J_{2,1'}$12.1, C(2)*H*), 3.64 (1H, AB, *J*14.8, NC*H*$_A$), 3.70 (1H, d, $J_{3,4}$12.0, C(3)*H*), 3.68 (1H, AB, *J*14.8, NC*H*$_B$), 3.99 (1H, d, $J_{4,3}$12.0, C(4)*H*), 4.32 (1H, q, *J*6.8, C(α)*H*), 4.92 (1H, d, $J_{1',2}$12.1, C(1')*H*), 6.51-6.56 (2H, m, Ph(2)*H*, Ph(5)*H*, $C_6H_3(OMe)_2$), 6.70 (1H, m, Ph(6)*H* $C_6H_3(OMe)_2$), 6.92- 6.95 (2H, m, *Ph*), 7.05-7.40 (12H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 18.1 (C(α)*Me*), 28.3 (CO_2C*(Me)$_3$*), 43.3 (*C(4)*H), 50.5 (N*C*H$_2$), 52.1, 52.6 (CO_2*Me* x 2), 55.4, 55.8 (O*Me*), 54.2, 56.6, 59.0 (*C(2)*H, *C(3)*H, and *C(α)*H), 64.3 (*C(1')*H), 81.6 (CO_2C(Me)$_3$), 110.3, 113.2 (*Ph(2)*, *Ph(5)* $C_6H_3(OMe)_2$), 120.8 (*Ph(4)* C_6H_4Br), 123.0, 126.4, 126.5, 127.7, 127.9, 128.2, 128.9 (*Ph*$_{o/m/p}$), 129.4 (*Ph*$_{ipso}$), 130.4, 131.0 (*Ph*$_{o/m/p}$), 140.9, 141.1, 144.5 (*Ph*$_{ipso}$), 147.9, 148.1 (*Ph(3)*, *Ph(4)*[$C_6H_3(OMe)_2$]), 167.8, 167.9, 172.0 (CO_2C(Me)$_3$ and CO_2Me x 2); *m/z* (ES$^+$) 774.3 (MH$^+$, 80%); HRMS (CI$^+$) $C_{42}H_{49}N^{79}BrO_8$ requires 774.2642, found 774.2664.

Preparation of 1-*tert*-butyl-5-methyl (2*S*,3*R*,1'*R*,α*S*)-2-{(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-methyl-4-methoxycarbonyl-pentanedioate 40

Following Representative Procedure 2, *n*-BuLi (1.6M, 2.24mmol, 1.40ml) and (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (500mg, 2.30mmol, 2.0eq) in THF (5ml) and *tert*-butyl cinnamate (234mg, 1.15mmol) in THF (3ml) and dimethyl ethylidenemalonate (273mg, 1.73mmol) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 7:1), **40** (439mg, 67%) as a yellow oil (88%d.e.); ν_{max} (film) 2976 (C-H), 1754, 1736 (C=O), 1143 (C-O); $[\alpha]_D^{24}$ +12.1 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 1.01 (3H, d, *J*7.3, C(3)*Me*), 1.07 (3H, d, *J*6.9, C(α)*Me*), 1.53 (9H, s, OC*(Me)$_3$*), 2.35-2.39 (1H, m, C(3)*H*), 3.18-3.23 (2H, m, C(2)*H* and C(4)*H*), 3.51 (3H, s, CO_2Me), 3.55 (1H, AB, *J*14.5, NCH_A), 3.60 (3H, s, CO_2Me), 3.89 (1H, AB, *J*14.5, NCH_B), 4.20 (1H, q, *J*6.9, C(α)*H*), 4.38 (1H, d, *J*11.9, C(1')*H*), 7.15-7.39 (15H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 16.0, 17.4 (C(α)*Me* and C(3)*Me*), 28.3 (CO_2C*(Me)$_3$*), 33.3 (*C(3)*H), 51.0 (N*C*H_2), 51.9, 52.3, 52.4 (*C(2)*H, CO_2Me x 2 and *C(4)*H), 58.1, 62.2 (*C(α)*H and *C(1')*H), 80.8 ($CO_2C(Me)_3$), 126.4, 127.5, 127.8, 128.2, 129.0, 129.7, 130.0 (*Ph*$_{o/m/p}$), 137.0, 140.5, 144.6 (*Ph*$_{ipso}$), 168.8, 169.1, 172.0 (*C*O_2C(Me)$_3$ and *C*O_2Me x 2); *m/z* APCI$^+$ 574.3 (MH^+, 100%), 596.2 (MNa^+, 20%), 518.2 (MH^+-C_4H_8, 10%); HRMS (CI^+) $C_{35}H_{44}NO_6$ requires 574.3169; found 574.3177.

Preparation of 1-*tert*-butyl-5-ethyl (2*S*,3*R*,1'*R*,α*S*)-2-{(1'-phenyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-cinnamyl-4-ethoxycarbonyl-pentanedioate 41 and (*E*)-cinnamyl-malonic acid diethyl ester 32

Following Representative Procedure 2, *n*-BuLi (2.5M, 1.24mmol, 0.49ml), (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (250mg, 1.18mmol) in THF (5ml) and *tert*-butyl cinnamate (219mg, 1.07mmol) in THF (3ml) and diethyl phenylallylidenemalonate (265mg, 1.07mmol, 1.0eq) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 12:1), (*E*)-cinnamyl-malonic acid diethyl ester **32** as a yellow oil (54mg, 19%) and **41** (472mg, 64%) as a white foam (82% d.e.); Data for major diastereoisomer **41**; ν_{max} (KBr) 2976 (C-H), 1751, 1732 (C=O), 1143 (C-O); $[\alpha]_D^{24}$ +49.3 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 0.99 (3H, d, *J*6.8, C(α)*Me*), 1.10. 1.16 (2 x 3H, t, *J*7.1, OCH_2CH_3), 1.52 (9H, s, CO_2C*(Me)$_3$*), 3.02 (1H, m, C(3)*H*), 3.41 (1H, d, $J_{4,3}$6.5, C(4)*H*), 3.51 (1H, dd, $J_{2,1'}$11.4, $J_{2,3}$6.7, C(2)*H*), 3.57 (1H, AB, *J*14.5, NCH_A), 3.95-4.15 (5H, m, OCH_2CH_3 x 2 and NCH_B), 4.22 (1H, q, *J*6.8, C(α)*H*), 4.32 (1H, d, $J_{1',2}$11.4, C(1')*H*), 5.88 (1H, d, *J*15.8, C=C*H*Ph), 5.99 (1H, dd, *J*15.8, *J*9.9, C*H*=CHPh), 7.00-7.03 (2H, m, *Ph*), 7.12-7.37 (18H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 14.0 (OCH_2CH_3), 17.3 (C(α)*Me*), 28.2 (CO_2C*(Me)$_3$*), 44.4 (*C(3)*H), 51.1 (N*C*H_2), 51.8, 54.1, 57.7 (*C(2)*H, *C(4)*H and *C(α)*H), 60.9, 61.2 (OCH_2CH_3 x 2), 63.2 (*C(1')*H), 81.1

($CO_2C(Me)_3$), 126.2, 126.3, 126.4, 127.0, 127.3, 127.8, 128.0, 128.1, 128.9, 130.0, 131.4 ($Ph_{o/m/p}$, *C*H=*C*HPh), 137.0, 137.5, 140.4, 144.6 (Ph_{ipso}), 167.9, 168.0, 172.1 ($CO_2C(Me)_3$ and CO_2Et x 2); *m/z* APCI$^+$ 690.4, (MH^+, 100%); HRMS (CI^+) $C_{44}H_{52}NO_6$ requires 690.3795, found 690.3790.

Preparation of 1-*iso*-propyl-5-ethyl (2*S*,3*R*,1'*S*,α*S*)-2-{(1'-methyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-cinnamyl-4-ethoxycarbonyl-pentanedioate 42

Following Representative Procedure 2, *n*-BuLi (2.5M, 1.21mmol, 0.48ml, 1.15eq) and (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (250mg, 1.18mmol, 1.1eq) in THF (5ml) and *iso*-propyl crotonate (135mg, 1.06mmol, 1.0eq) in THF (3ml) and diethyl phenylallylidenemalonate (285mg, 1.06mmol, 1.0eq) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et_2O 10:1) gave a mixture of products. The least polar fraction gave (*E*)-cinnamyl-malonic acid diethyl ester **32** (42mg, 15%) and **42** (404mg, 63%) as a colourless oil (85% d.e.) which was recrystallised (EtOAc:hexane) to give **42** as clear blocks (297mg, 46%); m.p. 121˚C (EtOAc:hexane); $[\alpha]_D^{24}$ +5.0 (c 1.0, $CHCl_3$); $C_{38}H_{47}NO_6$ requires C, 74.4; H, 7.7, N, 2.3%; found C, 74.1, H, 7.8, N, 2.15%; ν_{max} (KBr) 2970 (C-H), 1748, 1734, 1717 (C=O), 1174 (C-O); δ_H (400MHz, $CDCl_3$) 1.14-1.30 (18H, m, C(α)*Me*, OCH_2CH_3 x 2, $OCH(Me)_2$ and C(1')*Me*), 2.64 (1H, app t, $J_{2,1';2,3}$7.6, C(2)*H*), 3.08 (1H, ddd, $J_{3,CH=CHPh}$9.9, $J_{3,2}$7.6, $J_{3,4}$5.8, C(3)*H*), 3.35 (1H, app quin, $J_{1',Me;1',2}$7.0, C(1')*H*), 3.64 (1H, AB, *J*14.4, NCH_A), 3.75-3.79 (2H, m, NCH_B and C(2)*H*), 3.98 (1H, q, *J*6.9, C(α)*H*), 4.03-4.20 (4H, m, OCH_2CH_3 x 2), 4.98 (1H, sept, *J*7.2, $OCH(Me)_2$), 5.90 (1H, d, *J*15.9, CH=C*H*Ph), 6.26 (1H, dd, *J*15.9, *J*9.9, C*H*=CHPh), 7.18-7.44 (15H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 13.2, 16.2, 16.6, 21.6, 21.9 (OCH_2CH_3 x 2, C(1')*Me*, C(α)*Me* and $OCH(Me)_2$), 43.3 (*C(3)*H), 50.1 (NCH_2), 54.2, 54.5, 54.6, 58.7 (*C(2)*H, *C(4)*H, *C(1')*H and *C(α)*H), 61.0, 61.4 (OCH_2CH_3 x 2), 68.1 ($OCH(Me)_2$), 126.3, 126.6, 127.4, 127.9, 128.3, 128.4, 128.9 ($Ph_{o/m/p}$ and CH=C*H*Ph), 137.1 (C*H*=CHPh), 141.0, 144.0, 144.6 (Ph_{ipso}), 168.1, 168.6, 172.6 ($CO_2CH(Me)_2$ and CO_2Et x 2); *m/z* APCI$^+$ 614.4 (MH^+, 100%), 636.1 (MNa^+, 10%).

Preparation of 1-*iso*-propyl-5-ethyl (2*S*,3*R*,1'*S*,α*S*)-2-{(1'-methyl-1'-*N*-benzyl-*N*-α-methylbenzylamino)-3-phenyl-4-ethoxycarbonyl-pentanedioate 43

Following Representative Procedure 2, *n*-BuLi (2.5M, 1.21mmol, 0.48ml, 1.15eq) and (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (250mg, 1.18mmol, 1.1eq) in THF (5ml) and *iso*-propyl crotonate (135mg, 1.06mmol,

1.0eq) in THF (3ml) and diethyl benzylidenemalonate (261mg, 1.06mmol, 1.0eq) in THF (2ml), gave after purification by column chromatography on silica gel (hexane:Et_2O 10:1), **43** (324mg, 52%) as a yellow oil (78% d.e.), which crystallised on standing to give **43** as clear blocks (230mg, 37%); m.p. 59˚C; ν_{max} (KBr) 2980 (C-H), 1755, 1731 (C=O), 1171 (C-O); $[\alpha]_D^{23}$ +42.0 (c 0.25, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 0.93 (3H, t, *J*7.1, OCH_2CH_3), 1.08 (3H, d, *J*6.8, C(1')*Me*), 1.21-1.29 (12H, m, C(α)*Me*, OCH_2CH_3 and $OCH(Me)_2$), 2.90 (1H, dd, $J_{2,1'}$9.2, $J_{2,3}$5.5, C(2)*H*), 3.43 (1H, dq, $J_{1',2}$9.2, $J_{1',Me}$6.8, C(1')*H*), 3.63 (2H, m, NCH_2), 3.68 (1H, dd, $J_{3,4}$9.4, $J_{3,2}$5.5, C(3)*H*), 3.80-3.88 (2H, m, OCH_2CH_3), 3.90 (1H, q, *J*6.9, C(α)*H*), 3.97 (1H, d, $J_{4,3}$9.4, C(4)*H*), 4.01-4.15 (2H, m, OCH_2CH_3), 4.99 (1H, sept, *J*6.2, $OCH(Me)_2$), 7.04-7.37 (15H, m, *Ph*); δ_C (50MHz, $CDCl_3$) 13.6, 13.9, 15.4, 17.4, 21.7, 22.0 (OCH_2CH_3 x 2, C(1')*Me*, C(α)*Me* and $OCH(Me)_2$), 43.7 (*C(3)*H), 49.6 (NCH_2), 55.3, 55.6, 56.7, 59.5 (*C(2)*H, *C(4)*H, *C(1')*H and *C(α)*H), 61.0, 61.4 (OCH_2CH_3 x 2), 68.2 ($OCH(Me)_2$), 126.4, 126.5, 126.8, 127.8, 128.0, 128.8, 129.0 ($Ph_{o/m/p}$), 140.9, 141.2, 143.7 (Ph_{ipso}), 168.0, 168.3, 172.7 ($CO_2CH(Me)_2$ and CO_2Et x 2); *m/z* APCI$^+$ 588.3, (MH^+, 100%), 610.3 (MNa^+, 5%); HRMS (CI^+) $C_{36}H_{46}NO_6$ requires 588.3325, found 588.3320.

Preparation of (3*S*,4*R*,5*S*,6*R*)-3-methoxycarbonyl-4,6-diphenyl-5-*tert*-butoxycarbonyl-piperidin-2-one 44

Following Representative Procedure 3, $Pd(OH)_2$ on C (75mg), **38** (150mg, 0.21mmol) in MeOH (5ml), gave, after purification by column chromatography on silica gel (Et_2O:hexane 2:1), **44** as an off white solid (78mg, 90%); ν_{max} (KBr) 3436 (NH), 2922 (C-H), 1724, 1661 (C=O), 1154 (C-O); $[\alpha]_D^{24}$ –69.2 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 0.91 (9H, s, $CO_2C(Me)_3$), 3.15 (1H, app t, $J_{5,4;5,6}$4.5, C(5)*H*), 3.62 (3H, s, CO_2Me), 3.95 (1H, dd, $J_{4,3}$12.7, $J_{4,5}$3.9, C(4)*H*), 4.66 (1H, d, $J_{3,4}$12.7, C(3)*H*), 5.09 (1H, d, $J_{6,5}$5.1, C(6)*H*), 6.28 (1H, br s, N*H*), 7.23-7.39 (10H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 27.4 ($CO_2C(Me)_3$), 44.4, 49.7, 52.1, 52.5 and 58.7 (*C(3)*H, *C(4)*H, *C(5)*H, *C(6)*H and CO_2Me), 81.2 ($CO_2C(Me)_3$), 126.4, 127.4, 127.7, 128.4, 128.6, 128.7 ($Ph_{o/m/p}$), 137.7, 138.1 (Ph_{ipso}), 168.6, 168.8, 170.5 (*C(2)*, $CO_2C(Me)_3$ and CO_2Me); *m/z* APCI$^+$ 410.2 (MH^+, 100%), 432.2 (MH^+, 40%), 354.2 (MH^+-C_4H_8, 50%); HRMS (CI^+) $C_{24}H_{28}NO_5$ requires 410.196748; found 410.197534.

Preparation of (3*S*,4*R*,5*S*,6*R*)-3-methoxycarbonyl-4-methyl-5-*tert*-butoxycarbonyl-6-phenyl-piperidin-2-one 45

Following Representative Procedure 3, $Pd(OH)_2$ on C (75mg) and **40** (150mg, 0.26mmol) in MeOH (5ml) gave, after purification by column chromatography on silica gel (Et_2O:hexane 2:1), **45** as a colourless oil (70mg, 78%); ν_{max} (film) 3421 (NH), 1741, 1717 (C=O_{ester}), 1654 (C=O_{lactam}), 1155 (C-O); $[\alpha]_D^{23}$ +1.9 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 1.08 (3H, d, *J*6.8, C(4)*Me*), 1.15 (9H, s, $CO_2C(Me)_3$), 2.75 (1H, dqd, $J_{4,3}$11.9, $J_{4,Me}$6.8, $J_{4,5}$4.4, C(4)*H*), 2.94 (1H, app t, $J_{5,4;5,6}$4.5, C(5)*H*), 3.73 (1H, d, $J_{3,4}$11.9, C(3)*H*), 3.80 (3H, s, CO_2Me), 4.90 (1H, d, $J_{6,5}$5.0, C(6)*H*), 6.22 (1H, br s, N*H*), 7.09-7.38 (5H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 17.7 (C(4)*Me*), 27.7 ($CO_2C(Me)_3$), 33.8 (*C(4)*H), 51.2 (*C(5)*H), 52.6 and 52.7 (*C(3)*H and CO_2Me), 58.1 (*C(6)*H), 81.5 ($CO_2C(Me)_3$), 126.3, 128.4, 128.7 ($Ph_{o/m/p}$), 137.9 (Ph_{ipso}), 168.5, 168.9, 171.2 (*C(2)*, $CO_2C(Me)_3$ and CO_2Me); *m/z* APCI$^+$ 348.2 (MH^+, 30%), 370.1 (MNa^+, 50%), 292.2 (MH^+-C_4H_8, 100%); HRMS (CI^+) $C_{19}H_{26}NO_5$ requires 348.1811; found 348.1813.

Preparation of (3*S*,4*R*,5*S*,6*R*)-3-ethoxycarbonyl-4-hydrocinnamyl-5-*tert*-butoxycarbonyl-6-phenyl-piperidin-2-one 46

Following Representative Procedure 3, $Pd(OH)_2$ on C (50mg), **41** (100mg, 0.14mmol) in MeOH (5ml) gave, after purification by column chromatography on silica gel (hexane:EtOAc 5:1), **46** as an off white solid (52mg, 80%); ν_{max} (KBr) 3343 (NH), 2977 (C-H), 1726 (C=O_{ester}), 1678 (C=O_{lactam}), 1150 (C-O); $[\alpha]_D^{24}$ –17.0 (c 1.0, $CHCl_3$); δ_H (400MHz, $CDCl_3$) 1.19 (9H, s, $CO_2C(Me)_3$), 1.29 (3H, t, *J*7.1, OCH_2CH_3), 1.59-1.65, 1.74-1.79 (2 x 1H, m, $PhCH_2CH_2$), 2.58-2.71 (2H, m, C(4)*H* and $PhCH_ACH_B$), 2.82-2.88 (1H, m, $PhCH_ACH_B$), 3.16 (1H, app t, *J*4.4, C(5)*H*), 3.73 (1H, d, *J*11.8, C(3)*H*), 4.25 (2H, q, *J*7.1, OCH_2CH_3), 4.85 (1H, d, *J*4.8, C(6)*H*), 6.04 (1H, br s, N*H*), 7.14-7.41 (10H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 14.1 (OCH_2CH_3), 27.8 ($CO_2C(Me)_3$), 32.8, 34.1 ($PhCH_2CH_2$), 38.5 (*C(4)*H), 48.1 (*C(5)*H), 52.4 (*C(3)*H), 58.2 (*C(6)*H), 61.6 (OCH_2CH_3), 81.6 ($CO_2C(Me)_3$), 126.2, 126.4, 128.1, 128.5, 128.6, 128.8 ($Ph_{o/m/p}$), 138.1, 141.0 (Ph_{ipso}), 168.4, 168.8, 170.8 (*C(2)*, $CO_2C(Me)_3$ and CO_2Et); *m/z* APCI$^+$ 452.0 (MH^+, 30%), 474.2 (MNa^+, 25%), 396.2 (MH^+-C_4H_8, 100%); HRMS (CI^+) $C_{27}H_{34}NO_5$ requires 452.2437, found 452.2441.

Preparation of (3*S*,4*R*,5*S*,6*S*)-3-ethoxycarbonyl-4-hydrocinnamyl-5-*iso*-propoxycarbonyl-6-methyl-piperidin-2-one 47

Following Representative Procedure 4, $Pd(OH)_2$ on C (50mg) and **42** (100mg, 0.16mmol) in MeOH (5ml) gave, after purification by column chromatography on silica gel (Et_2O:hexane 2:1), **47** as a colourless oil (46mg, 75%); R_f (0.20); $[\alpha]_D^{23}$ -78.4 (c 1.0, $CHCl_3$); ν_{max} (KBr) 3205 (NH), 2980 (C-H), 1728 ($C{=}O_{ester}$), 1661 ($C{=}O_{lactam}$), 1186 (C-O); δ_H (400MHz, $CDCl_3$) 1.23-1.28 (12H, m, OCH_2CH_3, $OCH(Me)_2$ and C(6)H_3), 1.54-1.65 (1H, m, C(4)CH_A), 1.68-1.77 (1H, m, C(4)CH_B), 2.44-2.51 (1H, m, C(4)*H*), 2.53-2.60 (1H, m, $C(4)CH_2CH_A$), 2.77-2.84 (1H, m, $C(4)CH_2CH_B$), 2.93 (1H, app t, $J_{5,4;5,6}$4.0, C(5)*H*), 3.51 (1H, d, *J*11.4, C(3)*H*), 3.75-3.81 (1H, m, C(6)*H*), 4.21 (2H, q, OCH_2CH_3), 5.11 (1H, sept, *J*6.2, $OCH(Me)_2$), 6.48 (1H, br s, N*H*), 7.12-7.30 (5H, m, *Ph*); δ_C (100MHz, $CDCl_3$) 14.1, 19.1, 21.9, 22.0 (OCH_2CH_3, *C(6)*H_3 and $OCH(Me)_2$), 32.8, 34.2 ($C(4)CH_2CH_2Ph$), 38.3, 45.9, 49.3, 52.5 (*C(3)*H, *C(4)*H, *C(5)*H, *C(6)*H), 61.5 (OCH_2CH_3), 68.5 ($OCH(Me)_2$), 126.1, 128.1, 128.5 ($Ph_{o/m/p}$), 141.0 (Ph_{ipso}), 168.0, 169.7, 170.9 (*C(2)*, $CO_2CH(Me)_2$ and CO_2Et); *m/z* APCI$^+$ 376.2 (MH^+, 100%), 398.1 (MNa^+, 40%), 354.2 (MH^+-C_4H_8, 50%); HRMS (CI$^+$) $C_{21}H_{30}NO_5$ requires 376.2124; found 376.2125.