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

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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 MgSO₄. Thin layer chromatography (t.l.c.) was performed on aluminium sheets coated with 60 F₂₅₄ silica. Sheets were visualised using iodine, UV light or 1% aqueous KMnO₄ solution. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX 400 (¹H: 400 MHz and ¹³C: 100.6 MHz) or where stated on a Bruker AMX 500 (¹H: 500 MHz and ¹³C: 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. ¹³C multiplicities were assigned using a DEPT sequence. In all cases, the reaction diastereoselectivity was assessed by peak integration of the ¹H 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, NH₃), 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 cm² 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/Et₂O, 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-methylbenzyllamine (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/Et₂O, 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 (2S,3S,1’R,αS)-2-{1’-phenyl-(1’-N-benzyl-N-α-methylbenzylamino)-3-phenyl-pentanedioate 13 and 1,7-di-tert-butyl (2S,3S,1’R,αS)-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$_2$O 15:1 to 10:1), 13 (408mg, 30%) as a mixture of diastereoisomers (66% d.e.). Recrystallisation (hexane:Et$_2$O) gave 13 as white blocks and as a single diastereoisomer; [α]$_D^{24}$ +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%; $v$$_{max}$ (KBr) 3027, 2933 (C-H), 1741, 1722 (C=O), 1146 (C-O); $\delta$$_H$ (500MHz, CDCl$_3$) 1.01 (3H, d, $J$ 7.0, C($\alpha$)Me), 1.26 (9H, s, OC(Me)$_3$), 2.42 (1H, dd, $J_{4A,4B}$16.0, $J_{4A,3.4}$, C(4)H$_4$), 2.94 (1H, dd, $J_{4B,4A}$16.0, $J_{4B,3.12}$, C(4)H$_B$), 3.09 (1H, app dt, $J$ 3,4B 12.0, $J$ 3,4A;3,23.5, C(3)H), 3.32 (3H, s, CO$_2$Me), 3.47 (1H, dd, $J$ 2,1’11.9, $J$ 2,33.9, C(2)H), 3.58 (1H, AB, $J$ 14.2, NC$_A$H)$_A$, 4.05 (1H, AB, $J$ 14.2, NCH$_A$), 4.21 (1H, q, $J$ 7.0, C($\alpha$)H), 4.30 (1H, d, $J$ 11.7, C(1’)H), 4.30 (1H, AB, $J$ 13.5, NCH$_B$), 7.05-7.44 (20H, m, Ph); $\delta$$_C$ (50MHz, CDCl$_3$) 16.5 (C($\alpha$)Me), 28.0 (OC(Me)$_3$), 32.4 (C(4)H$_2$), 40.3 (C(3)H), 51.1 (NCH$_2$), 51.3 (OMe), 54.2, 57.2, 62.8 (C(2)H), C(1’)H and C($\alpha$)H), 80.7 (OC(Me)$_3$), 126.4, 126.5, 126.7, 127.6, 127.8, 128.2, 128.4, 129.0, 129.6 ($Ph_{o/m/p}$), 136.8, 140.2, 141.7, 144.2 ($Ph_{ipso}$), 171.8, 172.6 (C=O); $m/z$ APCI$^+$ 578.4, (MH$^+$, 75%), 522.1 (MH$^+$-C$_4$H$_8$, 10%). The mother liquors were further purified by column chromatography to give the minor diastereoisomer of unknown absolute configuration as a white foam (13mg, 1%); $v$$_{max}$ 3030, 2978 (C-H), 1738, 1721 (C=O), 1151 (C-O); $\delta$$_H$ (300MHz, CDCl$_3$) 0.84 (9H, s, OC(Me)$_3$), 0.91 (3H, d, $J$ 7.0, C($\alpha$)Me), 2.01 (1H, dd, $J_{4A,4B}$16.6, $J_{4A,3.2}$, C(4)H$_A$), 2.69 (1H, dd, $J_{4B,4A}$16.6, $J_{4B,3.12}$, C(4)H$_B$), 3.24 (1H, dd, $J_{2A,1.17}$, $J_{2B,3.0}$, C(2)H), 3.58 (3H, s, CO$_2$Me), 3.78 (1H, AB, $J$ 14.2, NC$_B$H)$_B$, 6.99-7.71 (20H, m, Ph); $\delta$$_C$ (50MHz, CDCl$_3$) 14.0 (C($\alpha$)Me), 27.2 (OC(Me)$_3$), 32.7 (C(4)H$_2$), 38.7
(C(2)H), 50.9 (NCH2), 51.3, 55.0, 55.2, 59.7 (OMe, C(3)H, C(1)H and C(α)H), 80.2 (OC(Me)3), 126.5, 126.9, 127.3, 127.7, 127.9, 128.2, 128.4, 128.7, 129.3, 129.8 (Pho/m/p), 139.1, 139.7, 142.7 (Phipso), 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; C43H51NO5 requires C, 78.0; H, 7.8; N, 2.1%; found C, 77.7; H, 7.7; N, 2.1%; [α]D23 +27.0 (c 1.0, CHCl3); v max (KBr) 2978 (C-H), 1722 (C=O), 1147 (C-O); δH (500MHz, CDCl3) 1.02 (3H, d, J6.8, C(α)Me), 1.28 and 1.38 (2 x 9H, s, OC(Me)3), 2.57 (1H, dd, J4A,AB17.2, J4A,32.8, C(4)HA), 2.94 (2H, s, C(6)H2), 3.12-3.16 (1H, m, C(3)H), 3.23 (1H, dd, J4B,4A17.2, J4B,311.5, C(4)HB), 3.46 (1H, dd, J2,1'11.8, J2,3,3.7, C(2)H), 3.60 (1H, AB, J14.2, NCH3), 4.08 (1H, AB, J14.2, NCH9), 4.23 (1H, q, J6.8, C(α)H), 4.28 (1H, d, J1'211.8, C(1')H), 7.02-7.44 (20H, m, Ph); δC (50MHz, CDCl3) 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)H2, C(6)H2 and NCH2), 54.2, 57.1, 62.9 (C(2)H, C(1')H, C(α)H), 80.7, 81.5 (2 x OC(Me)3), 126.5, 126.6, 126.7, 127.7, 127.8, 128.2, 128.3, 128.6, 129.0, 129.7 (Pho/m/p), 136.8, 140.1, 141.7, 144.3 (Phipso), 166.1, 172.0 (2 x CO2C(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-nnonius 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 [C38H43NO4]: 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 Å3, Z = 4, μ = 0.07 mm−1, colourless block, crystal dimensions = 0.4 x 0.4 x 0.5 mm3. 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 wR2 = 0.031 and R1 = 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 (2S,3S,1'R,αS)-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:Et₂O 3:1), 15 (322mg, 49%) as a colourless oil (78% d.e.);

Data for major diastereoisomer; \( \nu_{\text{max}} \) (film) 3061, 2976 (C-H), 1733, 1717, 1693 (C=O), 1143 (C-O); \( \delta_H \) (500MHz, CDCl₃) 0.72, 0.89 (2 x 3H, s, C(4'')Me₂), 1.13 (3H, d, J₆.₈, C(α)Me), 1.56 (9H, s, OC(Me)₃), 3.00 (2H, ABq, J₈.₃, C(5'')H₂), 3.34 (1H, dd, \( J_{4A,4B} \) 17.3, \( J_{4A,3.4.5} \), C(4)H₄a), 3.54 (1H, app dt, J₃,4B 10.5, J₃,2₄ 10.5, C(3)H), 3.60 (1H, AB, J₁₄.₅, NCH₃a), 3.67 (1H, dd, J₂,₃.₄.₅ 11.8, J₂,₃ 3.5, C(2)H), 4.07 (1H, AB, J₁₃,1₄.₂ 11.8, C(1')H), 7.02-7.51 (20H, m, Ph); \( \delta_C \) (50MHz, CDCl₃) 17.1, 24.1, 24.5 (C(α)Me, C(4'')Me₂), 28.1 (OC(Me)₃), 36.0 (C(4)H₂), 40.6 (C(2)H), 51.2 (NCH₃), 54.7, 58.1, 63.6 (C(3)H, C(1')H and C(α)H), 60.2 (C(4'')Me₂), 75.0 (C(5'')H₂), 80.9 (OC(Me)₃), 126.2, 126.4, 126.5, 127.5, 127.7, 128.1, 128.2, 128.3, 128.9, 129.7 (Ph₉₉₉₉), 137.2, 140.5, 142.7, 144.1 (Phipso), 153.9, 171.8, 172.6 (C=O); \( m/z \) APCI⁺ 661.6 (MH⁺, 75%), 682.9 (MNa⁺, 10%); HRMS (Cl⁺) C₄₂H₄₉N₂O₅ requires 661.3341; found 661.3647.

Preparation of tert-butyl (2S,3S,1'R,4''S,αS)-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:Et₂O 5:1), 17 (432mg, 62%) as a white foam (86% d.e.); [α]D ²² 1+51.8 (c 1.0, CHCl₃); \( \nu_{\text{max}} \) (KBr) 2977 (C-H), 1782, 1718, 1702 (C=O), 1147 (C-O); \( \delta_H \) (500MHz, CDCl₃) 1.06 (3H, d, J₆.₈, C(α)Me), 1.46 (9H, s, OC(Me)₃), 2.37 (1H, dd, \( J_{AB} \) 13.5, \( J_{AA} \) 9.6, \( C(4'')CH₄Ph \)), 2.78 (1H, dd, \( J_{BA} \) 13.5, \( J_{BB} \) 3.1, \( C(4'')CH₄Ph \)), 2.91 (1H, dd, \( J_{4A,4B} \) 17.4, \( J_{4A,4B} \) 4.8, \( C(4)H₄ \)), 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, J₁₄.₂, NCH₃a), 3.86 (1H, dd, \( J_{4B,4A} \) 17.4, \( J_{4B,3} \) 10.6, \( C(4)H₄ \)), 4.02-4.10 (2H, m, C(5'')H₂), 4.05 (1H, AB, J₁₄.₂, NCH₃b), 4.20 (1H, q, J₆.₈, C(α)H), 4.36-4.40 (1H, m, C(4'')H), 4.45 (1H, d, J₁₄.₂, C(1')H), 6.96-7.42 (25H, m, Ph); \( \delta_C \) (50MHz,
CDCl₃) 16.9 (C(α)Me), 28.2 (OC(Me)₃), 34.7 (C(4)H₂), 37.4 (C(4")CH₂Ph), 40.5 (C(2)H), 51.2 (NCH₂), 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")H₂), 81.1 (OC(Me)₃), 126.5, 127.1, 127.7, 128.3, 128.4, 128.8, 129.1, 129.4, 129.8 (Pho/m/p), 135.2, 137.4, 140.5, 142.9, 144.2 (Phipso), 153.4, 171.7, 171.9 (C=O); m/z APCI⁺ 723.7 (MH⁺, 100%), 745.6 (MNa +, 35%); HRMS (CI +) C₄₇H₅₁N₂O₅ 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:Et₂O 5:1), 17 as a white foam (449mg, 83%, 86% d.e.).

Preparation of tert-butyl (2S,3S,1'R,4"S,αS)-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:Et₂O 8:1 to 5:1) 22 (632mg, 57%) as a white foam (88% d.e.); C₄₈H₅₂N₂O₆ requires C, 76.6; H, 7.0; N, 3.7%; found C, 76.3; H, 7.4; N, 3.7%; [α]D²² +53.0 (c 1.0, CHCl₃); ν max 2970 (C-H), 1777, 1718, 1700 (C=O), 1512 (OMe bend), 1251 (Ph-O), 1147 (C-O); δH (500MHz, CDCl₃) 1.05 (3H, d, J₆.8, C(α)Me), 1.48 (9H, s, OC(Me)₃), 2.38 (1H, dd, J₉.9, J₄₂₂₄.₉, C(4")CH₂CH₂Ph), 2.79 (1H, dd, J₉.9, J₄₂₂₄.₉, C(4")CH₂CH₂Ph), 2.89 (1H, dd, J₉.9, J₄₂₂₄.₉, C(4")CH₂CH₂Ph), 3.22 (1H, app dt, J₃.₄, J₉.9, C(3')H), 3.48 (1H, dd, J₉.9, J₉.9, C(3')H), 3.57 (1H, AB, J₁₄.₃, NCH₂), 3.75 (3H, s, OMe), 3.81 (1H, dd, J₉.₉, J₉.₉, 1.1, 1.1, C(1')H), 6.75 (2H, m, Ph(3)H and Ph(5)H C₆H₄OMe), 6.94-6.97 (2H, m, Ph), 6.99 (2H, m, Ph(2)H and Ph(6)H C₆H₄OMe), 7.15-7.42 (18H, m, Ph); δC (50MHz, CDCl₃) 16.8 (C(α)Me), 28.1 (OC(Me)₃), 34.9 (C(4)H₂), 37.3 (C(4")CH₂), 39.7 (C(2)H), 51.0 (NCH₂), 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")H₂), 81.0 (OC(Me)₃), 126.4, 127.0, 127.5, 127.7, 128.2, 128.3, 128.6, 128.7, 129.0, 129.3, 129.7 (Pho/m/p), 135.0, 135.1, 137.3, 140.4, 144.1 (Phipso), 158.0 (Ph(4) C₆H₄OMe), 153.2, 171.7, 171.9 (C=O); m/z APCI⁺ 774.8 (MH⁺, 100%).
Preparation of tert-butyl (2S,3S,1'R,4''S,αS)-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 46H48N2O5 requires C, 77.9; H, 6.8; N, 3.95%; found C, 77.95; H, 6.9; N, 3.8%; v max (KBr) 2976 (C-H), 1782, 1719, 1705 (C=O), 1147 (C-O); [α]D +68.0 (c 1.0, CHCl3); δH (500MHz, CDCl3) 1.05 (3H, d, J6.8, C(α)Me), 1.49 (9H, s, OC(Me)3), 2.89 (1H, dd, J4A,4B17.0, J4A,3.4.9, C(4)H4), 3.19 (1H, app dt, J3,4B10.4, J3,23.9, C(3)H), 3.50 (1H, dd, J2,1'11.9, J2,33.1, C(2)H), 3.57 (1H, AB, J14.2, C(5'')H4), 4.21 (1H, q, J6.8, C(α)H), 4.45 (1H, d, J1',211.9, C(1')H), 5.11 (1H, dd, J4'',5'B8.7, J4'',5'A3.9, C(4'')H), 6.79-7.40 (25H, m, Ph); δC (50MHz, CDCl3) 16.7 (C(α)Me), 28.2 (OC(Me)3), 34.4 (C(4)H2), 40.6 (C(2)H), 51.1 (NCH2), 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'')H2), 81.1 (OC(Me)3), 125.1, 126.4, 126.5, 127.6, 127.8, 128.0, 128.2, 128.3, 128.8, 129.1, 129.7 (Pho/mp), 137.2, 138.6, 140.4, 142.5, 144.2 (Phipso), 153.6, 171.4, 171.9 (C(O)); m/z APCI + 709.7 (MH+, 100%), 731.7 (MNa+, 15%), 653.7 (MH+-C4H8, 5%).

Preparation of tert-butyl (2S,3S,1'R,4''S,αS)-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-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.); v max (KBr) 3028, 2976 (C-H), 2976, 2923 (C-H), 1777, 1723 (C(O), 1147 (C-O); [α]D +42.5 (c 1.0, CHCl3); δH (500MHz, CDCl3) 0.86 (3H, s, C(5'')MeA), 1.04 (3H, d, J6.8, C(α)Me), 1.48 (9H, s, OC(Me)3), 1.54 (3H, s, C(5'')MeB), 2.91 (1H, dd, J4A,4B17.0, J4A,3.5.2, C(4)H4), 3.22 (1H, ddd, J5,4B10.2, J5,5A5.2, J5,23.1, C(3)H), 3.44 (1H, dd, J2,1'11.9, J2,33.1, C(2)H), 3.52 (1H, AB, J14.3, NCH4), 3.90 (1H, dd, J4B,4A17.0, J4B,3.10.3, C(4)H4), 4.01 (1H, AB, J14.3, NCH4), 4.16 (1H, q, J6.8, C(α)H), 4.46 (1H, d, J11.9, C(1')H), 4.80 (1H, s,
C(4")H, 6.68-6.72 (2H, m, Ph); δ_C (50MHz, CDCl3) 16.8 (C(α)Me), 23.8, 28.8 (C(5")Me2), 28.2 (OC(Me)3), 34.9 (C(4')H), 40.6 (C(2')H), 51.1 (NCH2), 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 (OC(Me)3 and C(5")Me2), 125.8, 126.4, 127.6, 127.8, 127.9, 128.3, 128.4, 128.5, 129.1, 129.8 (Ph&m, 135.9, 137.2, 140.5, 142.9, 144.2 (Phipso), 153.1, 171.6, 171.9 (C=O); m/z APCI+ 738.0 (MH+, 50%), 681.5 (MH+-C4H8, 75%); HRMS (CI+) C48H53N2O5 requires 737.3954; found 737.3943.

Cleavage Reaction to give 1-tert-butyl-5-methyl (2S,3S,1'R,αS)-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 Et2O (3 x 80ml), dried and concentrated in vacuo. Purification by column chromatography on silica gel (hexane: Et2O 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 (2S,3S,1"R,1"S,αS)-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 Et2O (3 x 80ml), dried and concentrated in vacuo. Purification by column chromatography on silica gel (hexane: Et2O 3:1) gave 13 (46mg, 29%) which was spectroscopically identical to that obtained previously; a more polar fraction yielded 25 (107mg, 56%); \nu_max (KBr) 3028, 2976 (C-H), 1723, 1654 (C=O), 1147 (C-O); [α]_D^{22} +18.9 (c 1.0, CHCl3); δ_H (500MHz, CDCl3) 1.08 (3H, d, J6.9, C(α)Me), 1.36 (9H, s, OC(Me)3), 2.38 (1H, dd, J4.8,15.2, J4.3,3.9, C(4)HA), 2.49 (1H, dd, J3.7,13.8, J6.9, J6.9, NCHCH3CH2Ph), 2.57 (1H, dd, J3.7,13.8, J7.3, NCHCH3CH2Ph), 2.65 (1H, br s, OH), 2.74 (1H, dd, J4.8,15.2, J4.3,11.8, C(4)HA), 3.22 (1H, app dt, J3.7,11.8, J3.7,3.7, C(3)H), 3.26 (1H, dd, J3.7,11.0, J5.0,
NCHCH₃CH₂OH, 3.33 (1H, dd, J₈,₇ 11.0, J₃,₂ 3.3, NCHCH₃CH₂OH), 3.55 (1H, dd, J₆,₅ 11.8, J₃,₂ 3.3, NCHCH₃CH₂OH), 3.65 (1H, AB, J₂,₁ 14.2, NCHCH₃CH₂OH), 4.13 (1H, AB, J₁₄.₂, NCHCH₃CH₂OH), 4.30 (1H, q, J₆.₉, C(α)H), 4.38 (1H, d, J₁₁.₈, C(1')H), 5.27 (1H, d, J₇.₇, NH), 7.03-7.08 (4H, m, Ph), 7.20-7.49 (21H, m, Ph); δC (125MHz, CDCl₃) 16.3 (C(α)Me), 27.9 (OC(Me)₃), 34.9 (C(₄)H₂), 36.4 (NCHCH₃CH₂Ph), 41.0 (C(2)H), 51.0 (NCH₂), 52.3, 54.0, 57.0, 62.8 (C(3)H), C(1')H, NCHCH₂Ph and C(α)H), 63.4 (NCHCH₂OH), 80.8 (OC(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 (Pho/m/p), 136.7, 137.5, 140.0, 141.5, 144.2 (Phips), 171.6, 172.0 (C=O); m/z APCI⁺ 697.9 (MH⁺, 100%), 720.0 (MNa⁺, 20%); HRMS (CI⁺) C₄₆H₅₃N₂O₄ requires 697.4005; found 697.4014.

Preparation of (4S,5S,6R)-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%); [α]D²¹ -17.4 (c 0.65, CHCl₃); νmax (KBr) 3387 (NH), 2978 (C-H), 1711 (C=O ester), 1654 (C=O lactam), 1167 (C-O); δH (500MHz, C6D6) 0.85 (9H, s, OC(Me)₃), 2.57 (1H, dd, J₃A,₃B 17.3, J₃A,₄ 13.2, C(3)HA), 2.88 (1H, m, C(4)H), 2.92 (1H, dd, J₃₄,₅₅ 17.3, J₃₅,₆ 5.0, C(5)H), 3.60 (1H, dd, J₃₅,₃₆ 17.3, J₃₆,₄ 13.2, C(3)HB), 4.30 (1H, d, J₆,₅ 5.0, C(6)H), 6.92 (1H, br s, NH), 6.98-7.19 (10H, m, Ph); δC (50MHz, CDCl₃) 27.4 (OC(Me)₃), 32.5 (C(3)H₂), 40.9 (C(5)H), 51.8 (C(4)H), 59.0 (C(6)H), 80.7 (OC(Me)₃), 126.5, 127.2, 127.3, 128.2, 128.6 (Pho/m/p), 138.3, 140.0 (Phips), 168.7, 172.6 (C(2) and CO₂C(Me)₃; m/z APCI⁺ 352.1 (MH⁺, 10%), 374.1 (MNa⁺, 20%), 296.1 (MH⁺-C₄H₈, 100%); HRMS (CI⁺) C₂₂H₂₆NO₃ requires 352.1920; found 352.1913.

Preparation of (4S,5S,6R)-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), 26 as a white solid (50mg, 76%) with identical spectroscopic properties to that above.

Preparation of (4S,5S,6R)-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 (2R,3S,1'S,4''S,αR)-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$_2$O 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); $\nu_{\text{max}}$ (film) 2975 (C-H), 1782, 1728, 1702 (C=O), 1142 (C-O); $[\alpha]_{D}^{22}$ +18.3 (c 1, CHCl$_3$); $\delta$H (500MHz, CDCl$_3$) 1.19 (3H, d, $J_{6,H,\alpha}$Me), 1.62 (9H, s, OC(Me)$_3$), 2.50 (1H, dd, $J_{A,B}$13.5, $J_{A,4''}$9.5, C(4'')CH$_2$Ph), 2.99 (1H, dd, $J_{B,A}$13.5, $J_{B,4''}$3.2, C(4'')CH$_2$Ph), 3.31 (1H, dd, $J_{B,4''}$3.2, C(4'')CH$_2$Ph), 3.38 (1H, dd, $J_{A,B}$13.5, $J_{A,4''}$9.5, C(4'')CH$_2$Ph), 3.51 (1H, dd, $J_{2,1''}$11.4, $J_{2,3''}$5.3, C(2)H), 3.53 (1H, d, $J_{14.8}$, NC(4)H), 3.53-3.57 (1H, m, C(3)H), 3.75 (1H, d, $J_{14.8}$, NC(3)H), 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); $\delta$C (50MHz, CDCl$_3$) 19.5 (C(α)Me), 28.2 (OC(Me)$_3$), 37.4, 39.5 (C(4)H$_2$, C(4'')CH$_2$Ph), 40.3 (C(2)H), 51.4 (NCH$_2$), 52.4, 55.0, 60.7, 63.9 (C(3)H, C(1')H, C(4)H and C(qH)), 66.0 (C(5'')H$_2$), 81.0 (OC(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$_8$H$_8$, 30%); HRMS (CI$^+$) C$_{47}$H$_{50}$N$_2$O$_5$Na requires 745.3617; found 745.3669.

Preparation of (4S,5R,6S)-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%); $\nu_{\text{max}}$ (film) 3424 (NH), 1717 (C=O$_{\text{ester}}$), 1670 (C=O$_{\text{lactam}}$); $[\alpha]_{D}^{23}$ +135.7 (c 1, CHCl$_3$); $\delta$H (500MHz, C$_6$D$_6$) 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,
Preparation of (4R,5S,6R)-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 (2S,3R,1'R,4''S,\(\alpha\)S)-2-(1'-phenyl-1'-N-benzyl-N-\(\alpha\)-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-\(\alpha\)-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\(_2\)O 6:1), \(\beta\)-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; \(\nu_{\text{max}}\) (KBr) 2974 (C-H), 1783, 1726, 1700 (C=O), 1142 (C-O); \(\delta_H\) (400MHz, CD\(_2\)Cl\(_2\)) 1.20 (3H, d, J6.8, C(\(\alpha\))Me), 1.69 (9H, s, OC(Me)\(_3\)), 2.18 (1H, dd, \(J_{A,B}^{13.2}, J_{A,A'}^{10.4}\), C(4'')CH\(_2\)CHPh), 2.91 (1H, app t, \(J_{8.4}\), C(5'')H\(_2\)), 3.04 (1H, dd, \(J_{B,A}^{13.2}, J_{B,B'}^{3.0}\), C(4'')CH\(_2\)CHPh), 3.31-3.38 (2H, m, C(4)H\(_2\) and C(5'')H\(_2\)), 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, J6.8, C(\(\alpha\))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); \(\delta_C\) (100MHz, CDCl\(_3\)) 19.8 (C(\(\alpha\))Me), 28.2 (OC(Me)\(_3\)), 37.9, 39.6 (C(4)H\(_2\), C(4'')CHPh), 51.1 (NCH\(_2\)), 40.0, 52.2, 55.2, 61.1, 64.1 (C(3)H, C(2)H, C(1')H, C(4'')H and C(\(\alpha\))H), 66.0 (C(5'')H\(_2\)), 80.9 (OC(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/hipso), 153.2, 171.2, 171.8 (C=O); m/z APCI+ 723.4 (MH+, 10%), 667.6 (MH+-C4H8, 30%); HRMS (CI+) C47H51N2O5 requires 723.3798; found 723.3823.

### Preparation of (E)-cinnamyl-malonic acid diethyl ester 32

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/Et2O, the organic extracts were dried, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (hexane:Et2O 12:1), 32 (63mg, 16%) as a colourless oil; δH (200MHz, CDCl3) δH 1.27 (6H, t, J7.1, OCH2CH3 x 2), 2.80 (2H, app td, J3,2,3.4, J3,5,1.3, C(3)H2), 3.50 (1H, t, J2,3.7, C(2)H), 4.21 (4H, q, J7.1, OCH2CH3 x 2), 6.16 (1H, dt, J4,3,7.6, J4,5,15.8, C(4)H), 6.49 (1H, br d, J5,4,15.8, C(5)H), 7.19-7.36 (5H, m, Ph).

### Preparation of 1-tert-butyl-5-ethyl (2S,3R,1'R,αS)-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:Et2O 6:1) 34 as a hygroscopic white foam (617mg, 81%); νmax (film) 2978 (C-H), 1757, 1732 (C=O), [α]24 D −29.3 (c 1.0, CHCl3); δH (400MHz, CDCl3) 0.72 (3H, t, J7.1, OCH2CH3), 1.06 (3H, d, J6.8, C(α)Me), 1.25 (3H, t, J7.1, OCH2CH3), 1.66 (9H, s, CO2C(Me)3), 3.32 (1H, dd, J3,4,12.0, J3,2,1.0, C(3)H), 3.44 (1H, AB, J14.4, NCHA), 3.55 (1H, dd, J2,3,12.2, J2,3,10.0, C(2)H), 3.62-3.66 (3H, m, OCH2CH3 and C(4)H), 3.83 (1H, AB, J14.4, NCHA), 4.02 (1H, dq, J11,10.7, J11,12.2, OCH2CH3), 4.11 (1H, q, J6.8, C(α)H), 4.17 (1H, dq, J11,10.7, J11,12.2, OCH2CH3), 4.72 (1H, d, J12.2, 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); δC (50MHz, CDCl₃) 13.4, 14.1 (OCH₂C₃H₇), 28.3 (CO₂C(Me)₃), 43.6 (C(3)H), 51.3 (NCH₂), 54.1, 57.0, 58.1 (C(4)H, C(2)H, and C(α)H), 60.9, 61.3 (OCH₂CH₃), 64.1 (C(1')H), 81.2 (CO₂C(Me)₃), 126.2, 126.3, 126.7, 127.3, 127.7, 127.9, 128.3, 128.8, 129.1, 130.5 (Ph₁/m/p), 137.2, 140.6, 142.4, 144.7 (Phᵢpsɔ), 167.7, 167.9, 171.9 (CO₂C(Me)₃ and CO₂Et x 2); m/z APCI⁺ 664.7 (MH⁺, 100%), 608.3 (MH⁺-C₄H₈, 10%); HRMS (CI⁺) C₄₂H₅₀NO₆ requires 664.3638; found 664.3642.

Preparation of (3S,4R,5S,6R)-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 (Et₂O:hexane 2:1), 35 (78mg, 81%) as a colourless oil; νmax (film) 3311 (NH), 2977 (C-H), 1723, 1666 (C=O), 1153 (C-O); [α]D²³ –72.1 (c 1.0, CHCl₃); δH (400MHz, CDCl₃) 0.92 (9H, s, CO₂C₃H₇), 1.06 (3H, t, J₇.1, OCH₂C₃H₇), 3.15 (1H, app t, J₅.₄,₅,₆₄.₅, C(5)H), 3.93 (1H, dd, J₄.₃₁₂.₇, J₄₅₃₉, C(4)H), 4.03-4.13 (2H, m, OCH₂CH₃), 4.65 (1H, d, J₁₂.₇, C(3)H), 5.09 (1H, d, J₆₅₅₂, C(6)H), 6.13 (1H, br s, NH), 7.23-7.37 (10H, m, Ph); δC (50MHz, CDCl₃) 13.9 (OCH₂C₃H₇), 27.4 (CO₂C(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 (OCH₂CH₃), 81.1 (CO₂C(Me)₃), 126.4, 127.6, 127.7, 128.3, 128.6, 128.7 (Ph₁/m/p), 137.8, 138.1 (Phᵢpsɔ), 168.8, 170.0 (C(2)=O, CO₂C(Me)₃ and CO₂Et); m/z APCI⁺ 424.2 (MH⁺, 5%), 446.0 (MH⁺, 100%), 368.1 (MH⁺-C₄H₈, 20%); HRMS (CI⁺) C₂₅H₃₀NO₅ requires 424.2124; found 424.2126.

Preparation of 1-tert-butyl-5-ethyl (2S,3S,1'R,αS)-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 benzyldienemalonate (120mg, 0.48mmol) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et₂O 10:1), 36 (105mg, 33%) as a colourless oil and as an inseparable 8:1 mixture with diethyl benzyldienemalonate; νmax (film) 2977 (C-H), 1754, 1731(C=O), 1140 (C-O); δH (400MHz, CDCl₃) 0.68 (3H, t, J₇.3, OCH₂CH₃), 1.13 (3H, d, J₆.₈, C(α)Me), 1.28 (3H, t, J₇.₃, OCH₂CH₃), 1.66 (9H, s, CO₂C(Me)₃), 3.42 (1H, AB, J₄₁₉.₉, NCH₃), 3.51 (1H, AB, J₄₁₉.₉, NCH₃), 3.54-3.61 (2H, m, C(3)H and C(2)H), 3.64-3.69 (2H, m, OCH₂CH₃), 3.89 (1H, d, J₁₂.₂, C(4)H), 4.06 (1H, d, J₁₁.₅, C(1')H),
3.98 (1H, q, J6.8, C(α)H), 4.14-4.23 (2H, m, OCH₂CH₃), 7.08-7.33 (20H, m, Ph); δC (50MHz, CDCl₃) 13.4, 14.0, 19.9 (OCH₂CH₃ x 2 and C(α)Me), 28.2 (CO₂C(Me)₂), 44.1, 49.4 (C(3)H and C(2)H), 51.2 (NCH₂), 56.1 (C(4)H), 61.1, 61.6 (OCH₂CH₃ x 2), 63.8 (C(I')H), 81.0 (CO₂C(Me)₂), 126.0, 126.3, 127.0, 127.1, 127.2, 127.4, 127.9, 128.0, 128.8, 129.4, 130.2, 130.5 (Pho/m/p), 135.2, 135.7, 141.4, 145.1 (Phipso), 167.5, 167.8, 171.5 (CO₂C(Me)₂ and CO₂Et x 2); m/z APCI + 664.3 (MH⁺, 100%), 686.6 (MNa +, 10%), 608.6 (MH⁺-C₄H₈, 5%); HRMS (CI+) C₄₂H₅₀NO₆ requires 664.3638; found 664.3644.

Preparation of (3S,4S,5S,6R)-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 (Et₂O:hexane 2:1), 37 (52mg, 91%) as a colourless oil; νmax (film) 3309 (NH), 2979 (C-H), 1725, 1670 (C=O), 1159 (C-O); [α]D²³ –61.8 (c 1.0, CHCl₃); δH (400MHz, CDCl₃) 0.78 (9H, s, CO₂C(Me)₃), 1.09 (3H, t, J7.1, OCH₂CCH₃), 3.47 (1H, d, J3.411.8, C(3)H), 3.54 (1H, dd, J5.412.8, J5.65.8, C(5)H), 3.78 (1H, app t, J4.34.512.3, C(4)H), 4.06-4.16 (2H, m, OC₂H₂CH₃), 5.06 (1H, dd, J5.65.8, J6.6NH₃.6, C(6)H), 6.50 (1H, br s, NH), 7.11-7.41 (10H, m, Ph); δC (50MHz, CDCl₃) 13.9 (OCH₂CCH₃), 27.0 (CO₂C(Me)₂), 39.3, 50.5, 56.8 and 57.5 (C(3)H, C(4)H, C(5)H and C(6)H), 61.4 (OCH₂CH₃), 81.7 (CO₂C(Me)₂), 127.3, 127.5, 128.1, 128.5, 128.6 (Pho/m/p), 138.0, 139.9 (Phipso), 167.3, 168.3, 169.2 (C(2)=O, CO₂C(Me)₂ and CO₂Et); m/z APCI + 424.2 (MH⁺, 35%), 446.1 (MNa⁺, 30%), 368.2 (MH⁺-C₄H₈, 100%); HRMS (CI+) C₂₅H₃₀NO₅ requires 424.2124; found 424.2127.

Preparation of 1-tert-butyl-5-methyl (2S,3R,1'R,αS)-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:Et₂O 8:1), 38 (512mg, 63%) as a white foam; νmax (KBr) 2974 (C-H), 1761, 1737 (C=O), 1141 (C-O); [α]D²⁴ –21.6 (c 1.0, CHCl₃); δH (400MHz, CDCl₃) 1.00 (3H, d, J6.8, C(α)Me), 1.58 (9H, s, OC(Me)₂), 3.18 (3H, s, CO₂Me), 3.23 (1H, dd, J3.411.6, J3.21.5, C(3)H), 3.43 (1H, dd, J2.112.2, J2.51.5, C(2)H), 3.45 (1H, AB, J14.4, NC₂H₄), 3.57-3.61 (4H, m, CO₂Me and C(4)H), 3.78
Supplementary Material (ESI) for Organic and Biomolecular Chemistry
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(1H, AB, J14.4, NCH3), 4.07 (1H, q, J6.8, C(α)H), 4.57 (1H, d, J12.2, C(1')H), 6.73-6.77 (2H, m, Ph), 7.04-7.07 (2H, m, Ph), 7.14-7.34 (15H, m, Ph); \( \delta_{\text{C}} \) (50MHz, CDCl3) 17.3 (C(α)Me), 28.2 (CO2C(Me)3), 43.1 (C(2)H), 51.0 (NCH3), 52.1, 52.7 (CO2Me 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 (CO2C(Me)3), 120.8 (Ph(4) C8H4Br), 126.4, 127.4, 127.7, 128.0, 128.2, 129.1, 130.3, 133.1 (Pho/m/p), 137.1, 140.4, 143.2, 144.6 (Phipso), 167.7, 167.9, 171.7 (CO2C(Me)3 and CO2Me x 2); \( m/z \) APCI+ 714 (MH+, 100%); HRMS (CI+) C40H45NBr79O6 requires 714.2430, found 714.2444.

Preparation of 1-tert-butyl-5-methyl (2S,3R,1’R,αS)-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:Et2O 8:1), 39 (412mg, 70%) as a white foam; \( \nu_{\text{max}} \) (KBr) 2953 (C-H), 1761, 1737 (C=O), 1141 (C-O); \([\alpha]_{\text{D}}^{24} = -7.1 \) (c 1.0, CHCl3); \( \delta_{\text{H}} \) (400MHz, C6D6) 1.17 (3H, d, J6.8, C(α)Me), 1.54 (9H, s, OC(Me)3), 2.77 (3H, s, CO2Me), 3.35 (3H, s, OMe), 3.42 (6H, s, CO2Me and OMe), 3.57 (1H, d, J2,1:12.1, C(2)H), 3.64 (1H, AB, J14.8, NCH3), 3.70 (1H, d, J3,4:12.0, C(3)H), 3.99 (1H, d, J4,3:12.0, C(4)H), 4.32 (1H, q, J6.8, C(α)H), 4.92 (1H, d, J1,2:12.1, C(1’)H), 6.51-6.56 (2H, m, Ph(2)H, Ph(5)H, C6H3(OMe)2), 6.70 (1H, m, Ph(6)H C6H3(OMe)2), 6.92-6.95 (2H, m, Ph), 7.05-7.40 (12H, m, Ph); \( \delta_{\text{C}} \) (50MHz, CDCl3) 18.1 (C(α)Me), 28.3 (CO2C(Me)3), 43.3 (C(4)H), 50.5 (NCH3), 52.1, 52.6 (CO2Me x 2), 55.4, 55.8 (OMe), 54.2, 56.6, 59.0 (C(2)H, C(3)H, and C(α)H), 64.3 (C(1’)H), 81.6 (CO2C(Me)3), 110.3, 113.2 (Ph(2), Ph(5) C8H4(OMe)2), 120.8 (Ph(4) C8H4Br), 123.0, 126.4, 126.5, 127.7, 127.9, 128.2, 128.9 (Pho/m/p), 129.4 (Phipso), 130.4, 131.0 (Pho/imp), 140.9, 141.1, 144.5 (Phipso), 147.9, 148.1 (Ph(3), Ph(4)[C8H4(OMe)2]), 167.8, 167.9, 172.0 (CO2C(Me)3 and CO2Me x 2); \( m/z \) (ES+) 774.3 (MH+, 80%); HRMS (CI+) C42H49N79BrO6 requires 774.2642, found 774.2664.

Preparation of 1-tert-butyl-5-methyl (2S,3R,1’R,αS)-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 ethylenedimalonate (273mg, 1.73mmol) in THF (2ml) gave, after purification by column chromatography on silica gel (hexane:Et2O 7:1), 40 (439mg, 67%) as a yellow oil (88%d.e.); ν<sub>max</sub> (film) 2976 (C-H), 1754, 1736 (C=O), 1143 (C-O); [α]<sub>D</sub><sup>24</sup> +12.1 (c 1.0, CHCl₃); δ<sub>H</sub> (400MHz, CDCl₃) 1.01 (3H, d, J<sub>7.3</sub>, C(3)Me), 1.07 (3H, d, J<sub>6.9</sub>, C(α)Me), 1.53 (9H, s, OC(Me)<sub>3</sub>), 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, CO₂Me), 3.55 (1H, AB, J<sub>14.5</sub>, NC<sub>HA</sub>), 3.60 (3H, s, CO₂Me), 3.89 (1H, AB, J<sub>14.5</sub>, NC<sub>HB</sub>), 4.20 (1H, q, J<sub>6.9</sub>, C(α)H), 4.38 (1H, d, J<sub>11.9</sub>, C(1')H), 7.15-7.39 (15H, m, Ph); δ<sub>C</sub> (50MHz, CDCl₃) 16.0, 17.4 (C(α)Me and C(3)Me), 28.3 (CO₂C(Me)<sub>3</sub>), 33.3 (C(3)H), 51.0 (NCH₂), 51.9, 52.3, 52.4 (C(2)H, CO₂Me x 2 and C(4)H), 58.1, 62.2 (C(α)H and C(1')H), 80.8 (CO₂C(Me)<sub>3</sub>), 126.4, 127.5, 127.8, 128.2, 129.0, 129.7, 130.0 (Ph<sub>o</sub>/m/p), 137.0, 140.5, 144.6 (Ph<sub>ipso</sub>), 168.8, 169.1, 172.0 (CO₂C(Me)<sub>3</sub> and CO₂Me x 2); m/z APCI<sup>+</sup> 574.3 (MH<sup>+</sup>, 100%), 596.2 (MNa<sup>+</sup>, 20%), 518.2 (MH<sup>+</sup>-C₄H₈, 10%); HRMS (CI<sup>+</sup>) C₃₅H₄₄NO₆ requires 574.3169; found 574.3177.

Preparation of 1-tert-butyl-5-ethyl (2S,3R,1'R,αS)-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:Et2O 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<sub>max</sub> (KBr) 2976 (C-H), 1751, 1732 (C=O), 1143 (C-O); [α]<sub>D</sub><sup>24</sup> +49.3 (c 1.0, CHCl₃); δ<sub>H</sub> (400MHz, CDCl₃) 0.99 (3H, d, J<sub>6.8</sub>, C(α)Me), 1.10. 1.16 (2 x 3H, t, J<sub>7.1</sub>, OCH₂CH₃), 1.52 (9H, s, CO₂C(Me)<sub>3</sub>), 3.02 (1H, m, C(3)H), 3.41 (1H, d, J<sub>4.6.5</sub>, C(4)H), 3.51 (1H, dd, J<sub>1.14</sub>, J<sub>2.6.7</sub>, C(2)H), 3.57 (1H, AB, J<sub>14.5</sub>, NCH₃), 3.95-4.15 (5H, m, OCH₂CH₃ x 2 and NCH₃), 4.22 (1H, q, J<sub>6.8</sub>, C(α)H), 4.32 (1H, d, J<sub>J1.2</sub>;11.4, C(1')H), 5.88 (1H, d, J<sub>15.8</sub>, C=CHPh), 5.99 (1H, dd, J<sub>15.8</sub>, J<sub>9.9</sub>, CH=CHPh), 7.00-7.03 (2H, m, Ph), 7.12-7.37 (18H, m, Ph); δ<sub>C</sub> (50MHz, CDCl₃) 14.0 (OCH₂CH₃), 17.3 (C(α)Me), 28.2 (CO₂C(Me)<sub>3</sub>), 44.4 (C(3)H), 51.1 (NCH₂), 51.8, 54.1, 57.7 (C(2)H, C(4)H and C(α)H), 60.9, 61.2 (OCH₂CH₃ x 2), 63.2 (C(1')H), 81.1...
(CO₂C(Me)₃), 126.2, 126.3, 126.4, 127.0, 127.3, 127.8, 128.0, 128.1, 128.9, 130.0, 131.4 (Phᵦᵦᵦᵦ, CH=CHPh), 137.0, 137.5, 140.4, 144.6 (Phᵦᵦᵦᵦᵦ), 167.9, 168.0, 172.1 (CO₂C(Me)₃ and CO₂Et x 2); m/z APCI⁺ 690.4, (MH⁺, 100%); HRMS (CI⁺) C₄₄H₅₂NO₆ requires 690.3795, found 690.3790.

Preparation of 1-iso-propyl-5-ethyl (2S,3R,1'S,αS)-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:Et₂O 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); [α]D²⁴ +5.0 (c 1.0, CHCl₃); C₃₈H₄₇NO₆ requires C, 74.4; H, 7.7, N, 2.3%; found C, 74.1, H, 7.8, N, 2.15%; νmax (KBr) 2970 (C-H), 1748, 1734, 1717 (C=O), 1174 (C-O); δH (400MHz, CDCl₃) 1.14-1.30 (18H, m, C(α)Me, OCH₂C₃H₃ 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, J₃,CH-C₃H₃ 9.9, J₃,7.6, J₃,4.5.8, C(3)H), 3.35 (1H, app quin, J₁',Me;1',2 7.0, C(1')H), 3.64 (1H, AB, J₁₄.₄, NCH₄), 3.75-3.79 (2H, m, NCH₂ and C(2)H), 3.98 (1H, q, J₆.₉, C(α)H), 4.03-4.20 (4H, m, OCH₂CH₃ x 2), 4.98 (1H, sept, J₇.₂, OCH(Me)₂), 5.90 (1H, d, J₆.₉, CH=CHPh), 6.26 (1H, dd, J₁₅.₉, J₉.₉, CH=CHPh), 7.18-7.44 (15H, m, Ph); δC (50MHz, CDCl₃) 13.2, 16.2, 16.6, 21.6, 21.9 (OCH₂CH₃ x 2, C(1')Me, C(α)Me and OCH(Me)₂), 43.3 (C(3)H), 50.1 (NCH₂), 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 (OCH₂CH₃ x 2), 68.1 (OCH(Me)₂), 126.3, 126.6, 127.4, 127.9, 128.3, 128.4, 128.9 (Phᵦᵦᵦᵦ and CH=CHPh), 137.1 (CH=CHPh), 141.0, 144.0, 144.6 (Phᵦᵦᵦᵦᵦ), 168.1, 168.6, 172.6 (CO₂CH(Me)₂ and CO₂Et x 2); m/z APCI⁺ 614.4 (MH⁺, 100%), 636.1 (MNa⁺, 10%).

Preparation of 1-iso-propyl-5-ethyl (2S,3R,1'S,αS)-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,
1.0 eq) in THF (3 ml) and diethyl benzylidene malonate (261 mg, 1.06 mmol, 1.0 eq) in THF (2 ml), gave after purification by column chromatography on silica gel (hexane:Et₂O 10:1), 43 (324 mg, 52%) as a yellow oil (78% d.e.), which crystallised on standing to give 43 as clear blocks (230 mg, 37%); m.p. 59 °C; \( \nu_{\text{max}} \) (KBr) 2980 (C-H), 1755, 1731 (C=O), 1171 (C-O); \( [\alpha]_D^{23} +42.0 \) (c 0.25, CHCl₃); \( \delta \) (400 MHz, CDCl₃) 0.93 (3H, t, \( J = 7.1 \), OCH₂C₆H₃), 1.08 (3H, d, \( J = 6.8 \), C(1')Me), 1.21-1.29 (12H, m, C(\( \alpha \))Me, OCH₂C₆H₃ and OCH(Me)₂), 2.90 (1H, dd, \( J_{1',2} = 9.2, J_{1',6} = 6.8 \), C(1'H)) 3.63 (2H, m, NCH₂), 3.68 (1H, dd, \( J = 3,4 = 9.4, J = 3,2 = 5.5 \), C(3'H)), 3.80-3.88 (2H, m, OCH₂CH₃), 3.90 (1H, q, \( J = 6.9 \), C(\( \alpha \))H), 3.97 (1H, d, \( J = 4,3 = 9.4 \), C(4'H)), 4.01-4.15 (2H, m, OCH₂CH₃), 4.99 (1H, sept, \( J = 6.2 \), OCH(Me)₂), 7.04-7.37 (15H, m, Ph); \( \delta \)C (50 MHz, CDCl₃) 13.6, 13.9, 15.4, 17.4, 21.7, 22.0 (OCH₂C₆H₃ x 2, C(1')Me, C(\( \alpha \))Me and OCH(Me)₂), 43.7 (C(3)H), 49.6 (NCH₂), 55.3, 55.6, 56.7, 59.5 (C(2)H), C(3)H, C(1')H and C(\( \alpha \))H), 61.0, 61.4 (OCH₂C₆H₃ 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 (CO₂CH(Me)₂ and CO₂Et x 2); m/z APCI⁺ 588.3, (MH⁺, 100%), 610.3 (MNa⁺, 5%); HRMS (CI⁺) C₃₆H₄₆NO₆ requires 588.3325, found 588.3320.

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

Following Representative Procedure 3, Pd(OH)₂ on C (75 mg), 38 (150 mg, 0.21 mmol) in MeOH (5 ml), gave, after purification by column chromatography on silica gel (Et₂O:hexane 2:1), 44 as an off white solid (78 mg, 90%); \( \nu_{\text{max}} \) (KBr) 3436 (NH), 2922 (C-H), 1724, 1661 (C=O), 1154 (C-O); \( [\alpha]_D^{24} +69.2 \) (c 1.0, CHCl₃); \( \delta \) (400 MHz, CDCl₃) 0.91 (9H, s, CO₂C(Me)₃), 3.15 (1H, app t, \( J_{5,4,5,6,4,5} = 12.7 \), C(5)H), 3.62 (3H, s, CO₂Me), 3.95 (1H, dd, \( J_{4,3} = 12.7, J_{5,3} = 3.9, C(4)H \)), 4.66 (1H, d, \( J_{5,4} = 12.7, C(3)H \)), 5.09 (1H, dd, \( J = 6,5, J = 5,1.1 \), C(6)H), 6.28 (1H, br s, NH), 7.23-7.39 (10H, m, Ph); \( \delta \)C (100 MHz, CDCl₃) 27.4 (CO₂C(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 CO₂Me), 81.2 (CO₂C(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), CO₂C(Me)₃ and CO₂Me); m/z APCI⁺ 410.2 (MH⁺, 100%), 432.2 (MH⁺, 40%), 354.2 (MH⁺-C₄H₈, 50%); HRMS (CI⁺) C₂₄H₂₈NO₅ requires 410.196748; found 410.197534.
Preparation of (3S,4R,5S,6R)-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 (Et₂O:hexane 2:1), 45 as a colourless oil (70mg, 78%); νmax (film) 3421 (NH), 1741, 1717 (C=O ester), 1654 (C=O lactam), 1155 (C-O); [α]D²³ +1.9 (c 1.0, CHCl₃); δ_H (400MHz, CDCl₃) 1.08 (3H, d, J6.8, C(4)Me), 1.15 (9H, s, CO₂C(Me)₃), 2.75 (1H, dqd, J₄,311.9, J₄,Me6.8, J₄,54.4, C(4)H), 2.94 (1H, app t, J₅,4;5,64.5, C(5)H), 3.73 (1H, d, J₃,411.9, C(3)H), 3.80 (3H, s, CO₂Me), 4.90 (1H, d, J₆,55.0, C(6)H), 6.22 (1H, br s, NH), 7.09-7.38 (5H, m, Ph); δ_C (100MHz, CDCl₃) 17.7 (C(4)Me), 27.7 (CO₂C(Me)₃), 33.8 (C(4)H), 51.2 (C(5)H), 52.6 and 52.7 (C(3)H and CO₂Me), 58.1 (C(6)H), 81.5 (CO₂C(Me)₃), 126.3, 128.4, 128.7 (Pho/mp), 137.9 (Phipso), 168.5, 168.9, 171.2 (C(2), CO₂C(Me)₃ and CO₂Me); m/z APCI⁺ 348.2 (MH⁺, 30%), 370.1 (MNa⁺, 50%), 292.2 (MH⁺-C₄H₈, 100%); HRMS (CI⁺) C₁₉H₂₆NO₅ requires 348.1811; found 348.1813.

Preparation of (3S,4R,5S,6R)-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%); νmax (KBr) 3343 (NH), 2977 (C-H), 1726 (C=O ester), 1678 (C=O lactam), 1150 (C-O); [α]D²⁴ –17.0 (c 1.0, CHCl₃); δ_H (400MHz, CDCl₃) 1.08 (3H, d, J6.8, C(4)Me), 1.15 (9H, s, CO₂C(Me)₃), 1.19 (9H, s, CO₂C(Me)₃), 1.29 (3H, t, J7.1, OCH₂C(H₃)), 1.59-1.65, 1.74-1.79 (2 x 1H, m, PhCH₂CH₂), 2.58-2.71 (2H, m, C(4)H and PhCH₂CH₂), 2.82-2.88 (1H, m, PhCH₂CH₂), 3.16 (1H, app t, J4.4, C(5)H), 3.73 (1H, d, J11.8, C(3)H), 4.25 (2H, q, J7.1, OCH₂CH₂), 4.85 (1H, d, J4.8, C(6)H), 6.04 (1H, br s, NH), 7.14-7.41 (10H, m, Ph); δ_C (100MHz, CDCl₃) 14.1 (OCH₂CH₂), 27.8 (CO₂C(Me)₃), 32.8, 34.1 (PhCH₂CH₂), 38.5 (C(4)H), 48.1 (C(5)H), 52.4 (C(3)H), 58.2 (C(6)H), 61.6 (OCH₂CH₂), 81.6 (CO₂C(Me)₃), 126.2, 126.4, 128.1, 128.5, 128.6, 128.8 (Pho/mp), 138.1, 141.0 (Phipso), 168.4, 168.8, 170.8 (C(2), CO₂C(Me)₃ and CO₂Et); m/z APCI⁺ 452.0 (MH⁺, 30%), 474.2 (MNa⁺, 25%), 396.2 (MH⁺-C₄H₈, 100%); HRMS (CI⁺) C₂₇H₃₄NO₅ requires 452.2437, found 452.2441.
Preparation of (3S,4R,5S,6S)-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 (Et₂O:hexane 2:1), 47 as a colourless oil (46mg, 75%); Rᶠ (0.20); [α]D²³ -78.4 (c 1.0, CHCl₃); ν_max (KBr) 3205 (NH), 2980 (C-H), 1728 (C=O ester), 1661 (C=O lactam), 1186 (C-O); δ_H (400MHz, CDCl₃) 1.23-1.28 (12H, m, OCH₂C₆H₅, OCH(Me)₂ and C(6)H₃), 1.54-1.65 (1H, m, C(4)CH₄), 1.68-1.77 (1H, m, C(4)CH₂), 2.44-2.51 (1H, m, C(4)H), 2.53-2.60 (1H, m, C(4)CH₂CH₃), 2.77-2.84 (1H, m, C(4)CH₂CH₂), 2.93 (1H, app t, J₅,₆ 4.0, C(5)H), 3.51 (1H, d, J₄,₅ 4.0, C(3)H), 3.75-3.81 (1H, m, C(6)H), 4.21 (2H, q, OC₃H₂CH₃), 5.11 (1H, sept, J₆,₂ 6.2, OCH(Me)₂), 6.48 (1H, br s, NH), 7.12-7.30 (5H, m, Ph); δ_C (100MHz, CDCl₃) 14.1, 19.1, 21.9, 22.0 (OCH₂CH₃, C(6)H₃ and OCH(Me)₂), 32.8, 34.2 (C(4)CH₂CH₂Ph), 38.3, 45.9, 49.3, 52.5 (C(3)H, C(4)H, C(5)H, C(6)H), 61.5 (OCH₂CH₃), 68.5 (OCH(Me)₂), 126.1, 128.1, 128.5 (Ph₉₉, Ph₉₉), 141.0 (Ph₉₉), 168.0, 169.7, 170.9 (C(2), CO₂CH(Me)₂ and CO₂Et); m/z APCI⁺ 376.2 (MH⁺, 100%), 398.1 (MNa⁺, 40%), 354.2 (MH⁺-C₄H₈, 50%); HRMS (CI⁺) C₂₁H₃₀NO₅ requires 376.2124; found 376.2125.