Enantioselective Intramolecular Michael Addition of Nitronates onto Conjugated Esters: Access to Cyclic γ -Amino Acids with up to Three Stereocentres

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General

^1H NMR spectra were recorded in either deuterated chloroform (CDCl_3) or methanol (MeOD), using a Bruker DPX 250 (250 MHz) spectrometer, a Bruker DPX 400 (400 MHz) spectrometer or a Bruker Nanobay 400 (400 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million using the abbreviations: s, singlet; d, doublet;; dd, double doublet; t, triplet; q, quartet; m, multiplet. All coupling constants were rounded to the nearest 0.5 Hz.

^{13}C NMR spectra were recorded at 63 MHz or 100 MHz in deuterated chloroform (CDCl_3) or methanol (MeOD) on a Bruker DPX 250, DPX 400 or Nanobay 400 respectively. Chemical shifts (δ) are quoted in parts per million.

Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer as a thin film. The absorptions are quoted in wavenumbers (cm^{-1}).

Mass spectrometry data was recorded on either a VG Autospec mass spectrometer using chemical ionisation (CI) conditions using gaseous ammonia as the ionising source, or a Thermo Scientific LTQ Orbitrap XL using electrospray ionisation (ESI) conditions.

Specific optical rotations ($[\alpha]_D$) were recorded at the sodium D line in chloroform and are quoted in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Solution concentrations (c) are given in the units of $10^{-2} \text{ g mL}^{-1}$.

Readings were taken using a Perkin-Elmer 341 polarimeter.

Melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected.

Thin layer chromatography (tlc) was performed on Merck aluminium backed plates coated with 0.2 mm silica gel 60F₂₅₄. The spots were visualised using UV light (254 nm) and then permanent staining by solutions of Permanganate. Column chromatography was carried out using silica gel 60 (40-63 μm). HPLC analysis was determined on an Agilent Technologies 1200 Series HPLC, using a ratio of hexanes and propan-2-ol as the eluent, using either a Chiralpak AD-H column

(0.46 cm ø X 25 cm) or a Chrialcel OD column (0.46 cm ø X 25 cm), detection by UV at 210 nm or 254 nm.

X-ray data was collected on a Oxford Gemini S-ultra defractometer using K α (λ = 1.54180 Å) radiation.

Anhydrous solvents were supplied as Sureseal® bottles by Aldrich. All chemicals were supplied by Aldrich, Fisher and Acros and were used as supplied unless otherwise stated.

Compound numbering within this supporting information continue from the manuscript.

Substrate synthesis via Wittig reaction:

General nitration procedure A

To a solution of bromo-compound (1 eq.) in dimethyl formamide (0.1 M) was added sodium nitrite (1.5 eq.), this solution was stirred until TLC analysis showed the consumption of the majority of the bromo-compound. The reaction was then poured into ice cold water, extracted with diethyl ether, the aqueous phase was washed with diethyl ether, the combined organic layers were dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the crude nitro compound.

Ethyl 6-nitrohexanoate (**14**)

Following general procedure **A**, ethyl 6-bromo hexanoate (15.0 g, 67.08 mmol) gave crude product as a light yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 3/17) afforded the title compound as a clear colourless oil (6.60 g, 52 %, 34.88 mmol). ^1H NMR (250 MHz, CDCl_3) 1.23-1.29 (3 H, t, $J = 7.5$ Hz, H-8), 1.37-1.49 (2 H, m, H-3), 1.63-1.75 (2 H, m, H-4), 1.98-2.10 (2 H, m, H-2), 2.30-2.36 (2 H, t, $J = 7.5$ Hz, H-5), 4.09-4.18 (2 H, q, $J = 7.5$ Hz, H-7), 4.37-4.42 (2 H, t, $J = 7.5$ Hz, H-1); ^{13}C NMR (62.8 MHz, CDCl_3) 14.2, 24.1, 25.7, 27.1, 33.8, 60.4, 75.4, 173.6; IR (cm^{-1}) 2936 (w), 1957 (w), 1730 (s), 1552 (s), 1436 (w), 1376 (m), 1180 (m), 1096 (m), 1032 (m); HRMS required for ($\text{C}_8\text{H}_{16}\text{NO}_4^+$) 190.1079; found 190.1078.

6-Nitrohexanal (**15**)

To a solution of ethyl-6-nitrohexanoate **14** (6.60 g, 34.88 mmol) in anhydrous DCM (250 mL) at -78°C was added DIBAL-H (3.8 mL, 38.37 mmol, 1M solution in hexanes). After 1 hour at -78°C TLC analysis showed consumption of starting material. The reaction was quenched with aqueous hydrochloric acid (1M, 50 mL) and water (100 mL), and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford crude the title compound as a light yellow oil, which was used without further purification. ^1H NMR (250 MHz, CDCl_3) 1.37-1.49 (2 H, m, H-3), 1.60-1.75 (2 H, m, H-4), 1.98-2.10 (2 H, m, H-2), 2.46-2.52 (2 H, dt, $J = 2.5$ & 7.5 Hz, H-5), 4.37-4.43 (2 H, t, $J = 7.5$ Hz, H-1), 9.78 (1 H, t, $J = 2.5$ Hz, H-6); ^{13}C NMR (62.8 MHz, CDCl_3) 21.2, 25.8, 27.2, 43.4, 75.4, 201.7.

(E)-Ethyl 8-nitrooct-2-enoate (1)

To a solution of crude 6-nitrohexanal **15** (1.41 g, 9.71 mmol) in dichloromethane (100 mL) was added in one portion (carbethoxymethylene)triphenylphosphorane (3.87 g, 10.68 mmol). The reaction mixture was left to stir for 18 hours, quenched with saturated ammonium chloride (50 mL), the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the crude product as a viscous yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) afforded the title compound as a light yellow oil (1.43 g, 68 %, 6.64 mmol). ^1H NMR (250 MHz, CDCl_3) 1.32 (3 H, t, $J = 7.5$ Hz, H-10), 1.38-1.60 (4 H, m, H-3&4), 1.97-2.09 (2 H, m, H-2), 2.17-2.33 (2 H, m, H-5), 4.11-4.20 (2 H, q, $J = 7.5$ Hz, H-9), 4.39 (2 H, t, $J = 7.5$ Hz, H-1), 5.78-5.86 (1 H, dt, $J = 2.5$ & 15 Hz, H-7), 6.87-6.99 (1 H, dt, $J = 7.5$ & 15 Hz, H-6); ^{13}C NMR (62.8 MHz, CDCl_3) 14.3, 25.8, 27.1, 27.3, 31.7, 60.3, 75.5, 121.9, 148.2; IR (cm^{-1}) 3418 (m), 2934 (s), 1958 (w), 1717 (s), 1654 (s), 1550 (s), 1463 (m), 1435 (m), 1369 (s), 1308 (s), 1268 (s), 1155 (s), 1117 (m), 1096 (m), 1044 (s), 983 (s), 865 (w), 736 (w), 711 (w); HRMS required for $(\text{C}_{10}\text{H}_{18}\text{NO}_4^+)$ 216.1236; found 216.1235.

(E)-methyl 8-nitrooct-2-enoate (16a)

To a solution of crude 6-nitrohexanal **15** (0.64 g, 4.44 mmol) in dichloromethane (20 mL) was added in one portion (carbmethoxymethylene)triphenylphosphorane (1.63 g, 4.88 mmol). The reaction mixture was left to stir for 18 hours, quenched with saturated ammonium chloride (10 mL) and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the crude product as a viscous yellow oil. Purification by column chromatography (silica

gel, diethyl ether/hexane, 1/3) afforded the title compound as a clear colourless oil (0.61 g, 68 %, 3.02 mmol). ^1H NMR (250 MHz, CDCl_3) 1.38-1.52 (4 H, m, H-3 & 4), 1.97-2.09 (2 H, quin, $J = 7.5$ Hz, H-2), 2.19-2.28 (2 h, dq, $J = 1$ & 7.5 Hz, H-5), 3.73 (3 H, s, H-9), 4.36-4.42 (2 H, t, $J = 7.5$ Hz), 5.79-5.87 (1 H, dt, $J = 2.5$ & 15 Hz, H-7), 6.88-7.00 (1 H, dt, $J = 7.5$ & 12.5 Hz, H-6); ^{13}C NMR (62.8 MHz, CDCl_3) 25.8, 27.1, 27.3, 31.7, 51.5, 75.5, 121.4, 148.5; IR (cm^{-1}) 2948 (s), 2861 (m), 1716 (s), 1657 (s), 1556 (s), 1434 (s), 1384 (m), 1311 (m), 1273 (m), 1198 (m), 1120 (m), 1041 (m), 984 (m), 862 (w), 719 (w), 614 (w); HRMS required for ($\text{C}_9\text{H}_{16}\text{NO}_4^+$) 202.1079; found 202.1078.

(*E*)-benzyl 8-nitrooct-2-enoate (16b)

To a solution of crude 6-nitrohexanal **15** (0.77 g, 5.28 mmol) in dichloromethane (20 mL) was added in one portion (carbbenzoxymethylene)triphenylphosphorane (2.38 g, 5.81 mmol). The reaction mixture was left to stir for 18 hours, quenched with saturated ammonium chloride (10 mL) and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the product as a crude viscous yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) afforded the title product as a clear colourless oil (0.77 g, 53 %, 2.79 mmol). ^1H NMR (250 MHz, CDCl_3) 1.38-1.52 (4 H, m, H-3 & 4), 1.96-2.08 (2 H, quin, $J = 7.5$ Hz, H-2), 2.19-2.28 (2 h, dq, $J = 1$ & 7.5 Hz, H-5), 4.35-4.41 (2 H, t, $J = 7.5$ Hz), 5.18 (2 H, s, H-9) 5.84-5.91 (1 H, dt, $J = 2.5$ & 15 Hz, H-7), 6.92-7.04 (1 H, dt, $J = 7.5$ & 12.5 Hz, H-6), 7.31-7.40 (5 H, m, H-10); ^{13}C NMR (62.8 MHz, CDCl_3) 25.8, 27.1, 27.3, 31.6, 66.2, 75.5, 121.6, 128.3, 128.6, 149.0; IR (cm^{-1}) 2932 (s), 2860 (m), 1715 (s), 1653 (s), 1556 (s), 1496 (m), 1455 (m), 1433 (m), 1380 (s), 1265 (s), 1182 (s), 1118 (m), 1015 (m), 909 (w), 740 (m), 698 (s), 603 (w); HRMS required for ($\text{C}_{15}\text{H}_{19}\text{NaNO}_4$) 300.1212; found 300.1217.

(*E*)-ethyl 2-methyl-8-nitrooct-2-enoate (**16c**)

To a solution of crude 6-nitrohexanal **15** (0.54 g, 3.70 mmol) in dichloromethane (20 mL) was added in one portion ethyl 2-(triphenylphosphoranylidene)propanoate (1.48 g, 4.07 mmol). The reaction mixture was left to stir for 18 hours, quenched with saturated ammonium chloride (100 mL) and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the crude product as a viscous yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) afforded the title compound as a clear colourless oil (0.48 g, 57 %, 2.09 mmol). ^1H NMR (250 MHz, CDCl_3) 1.27-1.33 (3 H, t, $J = 7.5$ Hz, H-11), 1.36-1.58 (4 H, m, H-3&4), 1.83 (3 H, t, $J = 1$ Hz, H-8), 1.98-2.09 (2 H, q, $J = 7.5$ Hz, H-2), 2.16-2.24 (2 H, q, $J = 7.5$ Hz, H-5), 4.15-4.23 (2 H, q, $J = 7.5$ Hz, H-10), 4.36-4.42 (2 H, t, $J = 7.5$ Hz, H-1), 6.69-6.75 (1 H, dt, $J = 1$ & 7.5 Hz, H-6); ^{13}C NMR (62.8 MHz, CDCl_3) 12.4, 14.3, 21.9, 26.0, 27.2, 27.9, 28.3, 60.5, 75.5, 141.1; IR (cm^{-1}) 2933 (m), 1706 (s), 1648 (w), 1552 (s), 1436 (w), 1383 (w), 1261 (m), 1175 (w), 1133 (m), 1096 (m), 1028 (w), 747 (w); HRMS required for ($\text{C}_{11}\text{H}_{19}\text{NaNO}_4$) 252.1212; found 252.1211.

Substrate synthesis via Horner-Wadsworth or Still-Gennari reaction

6-bromo hexanal (**17**)

To a solution of ethyl-6-bromohexanoate **13** (1.34 g, 6.02 mmol) in dichloromethane (250 mL) at -78 °C was added DIBAL-H (6.6 mL, 6.62 mmol, 1M solution in hexanes). After 1 hour at -78 °C TLC analysis showed consumption of starting material. The reaction was quenched with aqueous hydrochloric acid (1M, 50 mL) and water (100 mL) and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude title compound as a light yellow oil, which was used without further purification. ¹H NMR (250 MHz, CDCl₃) 1.37-1.49 (2 H, m, H-3), 1.60-1.75 (2 H, m, H-4) 1.98-2.10 (2 H, quin, *J* = 7.5 Hz, H-2), 2.46-2.52 (2 H, dt, *J* = 2.5 & 7.5 Hz, H-5), 4.37-4.43 (2 H, t, *J* = 7.5 Hz, H-1), 9.78 (1 H, t, *J* = 1.0 Hz, H-6).

(*Z*)-ethyl 8-bromooct-2-enoate (**18a**)

To a solution of ethyl [bis(2,2,2-trifluoroethoxy)phosphoryl]acetate (3.0 g, 9.03 mmol) in tetrahydrofuran (60 mL) at -78°C was added, 18-crown-6-ether (7.96 g, 30.01 mmol) and KHMDS (18 mL, 9.03 mmol). This solution was stirred for 10 minutes at -78°C before the addition of the crude 6-bromo hexanal **17** (1.08 g, 6.02 mmol). The resulting mixture was left to stir overnight. After this time the reaction was quenched with aqueous ammonium chloride (20 mL), the aqueous layer was washed with diethyl ether (2 x 25 mL) and the combined organic fractions dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude product as a yellow oil, Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) afforded the title compound as a clear colourless oil (0.75 g, 50 %, 3.01 mmol). ¹H NMR (250 MHz, CDCl₃) 1.26-1.32 (3 H, t, *J* = 7.5 Hz, H-10), 1.42-1.54 (4 H, m, H-3&4), 1.83-1.94 (2 H, m, H-2), 2.63-2.72 (2 H, m, H-5), 3.38-3.44 (2 H, t, *J* = 7.5 Hz, H-1), 4.13-4.21 (2 H, q, *J* = 7.5 Hz, H-9), 5.75-5.81 (1 H, dt, *J* = 2.5 &

12.5 Hz, H-7), 6.15-6.26 (1 H, dt, $J = 7.5$ & 12.5 Hz, H-6); ^{13}C NMR (62.8 MHz, CDCl_3) 14.3, 27.8, 28.1, 28.7, 32.5, 33.8, 59.9, 120.1, 149.9, 168.8; IR (cm^{-1}) 2979 (s), 2932 (s), 2857 (s), 1714 (s), 1643 (s), 1444 (m), 1414 (s), 1386 (m), 1364 (w), 1184 (s), 1095 (w), 914 (w), 820 (m), 730 (w), 643 (w), 561 (w); HRMS required for ($\text{C}_{10}\text{H}_{18}\text{BrO}_2$) 249.0490; found 249.0485 (^{79}Br), 251.0464 (^{81}Br).

(Z)-ethyl 8-nitrooct-2-enoate (19a)

Following general procedure **A**, (Z)-ethyl 8-bromooct-2-enoate **18a** (0.74 g, 2.97 mmol) gave the crude product as a yellow oil, purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) gave the title compound as a clear colourless oil (0.32 g, 50 %, 1.49 mmol). ^1H NMR (250 MHz, CDCl_3) 1.26 (3 H, t, $J = 7.5$ Hz, H-10), 1.37-1.63 (4 H, m, H-3&4), 1.98-2.10 (2 H, quin, $J = 7.5$ Hz, H-2), 2.63-2.73 (2 H, dq, $J = 2.5$ & 7.5 Hz, H-5), 4.12-4.21 (2 H, q, $J = 7.5$ Hz, H-9), 4.36-4.42 (2 H, t, $J = 7.5$ Hz, H-1), 5.76-5.82 (1 H, dt, $J = 12.5$ & 2.5 Hz, H-7), 6.14-6.24 (1 H, dt, $J = 7.5$ & 10.0 Hz, H-6); ^{13}C NMR (62.8 MHz, CDCl_3) 14.3, 25.8, 27.1, 28.1, 28.4, 59.9, 75.6, 120.4, 149.3, 166.8; IR (cm^{-1}) 2981 (m), 2932 (m), 2861 (m), 2359 (w), 2340 (w), 1715 (s), 1643 (m), 1549 (s), 1435 (m), 1415 (m), 1384 (m), 2289 (w), 1186 (s), 1095 (w), 1034 (m), 822 (m), 737 (m), 668 (w), 615 (w); HRMS required for ($\text{C}_{10}\text{H}_{17}\text{NNaO}_4$) 238.1055; found 238.1050.

Horner-Wadsworth Olefination – General Procedure B

To a suspension of NaH (1.2 eq.) in tetrahydrofuran (0.2 M) at 0°C was added a solution of the phosphonoacetate (1.2 eq.) in tetrahydrofuran dropwise. This solution was left to stir for 15 minutes, or until effervescence ceased, before the addition of a solution of 6-bromo hexanal **17** (1 eq.) in tetrahydrofuran. This solution was left to warm to room temperature overnight. The reaction was then quenched with aqueous ammonium chloride, extracted with diethyl ether, the

aqueous layer was washed with diethyl ether, and the combined organic fractions were dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the crude olefination product.

(E)-Ethyl 2-benzyl-8-bromooct-2-enoate and (Z)-Ethyl 2-benzyl-8-bromooct-2-enoate (18b)

Following general procedure **B** ethyl 2-(diethoxyphosphoryl)-3-phenylpropanoate (2.5 g, 7.95 mmol) gave a crude mixture of products as a light yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) gave a mixture of the title compounds as a clear colourless oil (1.21 g, 46 %, 3.62 mmol). ^1H NMR (250 MHz, CDCl_3) 1.21-1.31 (3 H, m), 1.40-1.49 (4 H, m), 1.79-1.94 (2 H, m), 2.25-2.51 (2 H, m), 3.35-3.43 (2 H, m), 3.58-3.69 (2 H, d), 4.07-4.19 (2 H, m), 5.88-5.94 & 6.88-6.94 (1 H, t, $J = 7.5$ Hz & 7.5 Hz); ^{13}C NMR (62.8 MHz, CDCl_3) 14.2, 24.1, 27.6, 27.8, 27.9, 28.5, 28.7, 29.3, 32.4, 32.5, 33.6, 33.8, 34.1, 40.5, 60.2, 60.6, 126.0, 126.1, 128.2, 128.3, 128.3, 128.8, 143.2, 143.4.

(E)-Ethyl 2-benzyl-8-nitrooct-2-enoate and (Z)-Ethyl 2-benzyl-8-nitrooct-2-enoate (19b)

Following general procedure **A**, a mixture of (*E*)-ethyl 2-benzyl-8-bromooct-2-enoate and (*Z*)-ethyl 2-benzyl-8-bromooct-2-enoate **18b** (1.21 g, 3.62 mmol) gave a crude mixture of products as a yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) gave pure title compounds as clear colourless oils. (**E**)-**18b** (0.16 g, 14 %, 0.52 mmol) and (**Z**)-**18b** (0.22 g, 20 %, 0.72 mmol). (**E**)-**18b** ^1H NMR (250 MHz, CDCl_3) 1.20-1.26 (3 H, t, $J = 7.5$ Hz, H-12), 1.31-1.56 (4 H, m, H-3 & 4), 1.91-2.02 (2 H, quin, $J = 7.5$ Hz, H-2), 2.24-2.33 (2 H, q, $J = \text{H-5}$), 3.68 (2 H, s, H-8), 4.11-4.19 (2 H, q, $J = 7.5$ Hz, H-11), 4.30-4.36 (2 H, t, $J = 7.5$ Hz, H-1), 6.86-6.92 (1 H, t, $J = 7.5$ Hz, H-6), 7.13-7.29 (5 H, m, H-9); ^{13}C NMR (62.8 MHz, CDCl_3) 14.1, 22.7, 26.0, 27.1, 27.9, 28.5, 31.6, 32.4, 60.6, 75.4, 126.0, 128.2, 128.3, 142.9; IR (cm^{-1}) 2979

(m), 2933 (s), 2860 (m), 1707 (s), 1644 (m), 1600 (m), 1551 (s), 1494 (m), 1452 (m), 1382 (m), 1266 (m), 1190 (m), 1125 (s), 1078 (m), 910 (w), 736 (s), 699 (s), 614 (w); HRMS required for (C₁₇H₂₃NaNO₄) 328.1525; found 328.1515. **(Z)-18b** ¹H NMR (250 MHz, CDCl₃) 1.16-1.22 (3 H, t, *J* = 7.5 Hz, H-12), 1.33-1.54 (4 H, m, H-3 & 4), 1.94-2.05 (2 H, quin, *J* = 7.5 Hz, H-2), 2.45-2.54 (2 H, q, *J* = H-5), 3.58 (2 H, s, H-8), 4.07-4.15 (2 H, q, *J* = 7.5 Hz, H-11), 4.32-4.38 (2 H, t, *J* = 7.5 Hz, H-1), 5.85-5.91 (1 H, t, *J* = 7.5 Hz, H-6), 7.14-7.30 (5 H, m, H-9); ¹³C NMR (62.8 MHz, CDCl₃) 14.1, 22.7, 26.0, 27.1, 27.9, 28.5, 31.6, 32.4, 60.6, 75.4, 126.0, 128.2, 128.3, 142.9; IR (cm⁻¹) 2979 (m), 2929 (s), 2859 (m), 1711 (s), 1642 (m), 1602 (m), 1551 (s), 1494 (m), 1452 (m), 1379 (m), 1228 (m), 1188 (m), 1129 (s), 1075 (m), 910 (w), 736 (s), 699 (s), 614 (w); HRMS required for (C₁₇H₂₃NaNO₄) 328.1525; found 328.1514.

(Z)-Methyl 2-(*N*-*tert*-butoxycarbonyl)-amino-8-bromooct-2-enoate (18c)

Following general procedure **B** methyl [(*tert*-butoxycarbonyl)amino] (dimethoxyphosphoryl)acetate (1.80 g, 6.06 mmol) gave the crude product as a light yellow oil.

Purification by column chromatography (silica gel, diethyl ether/hexane, 3/7) gave the title product as a clear colourless oil (0.70 g, 33 %, 2.00 mmol). ¹H NMR (400 MHz, CDCl₃) 1.47 (9 H, s, H-10), 1.47-1.50 (4 H, m, H-3 & 4), 1.85-1.88 (2 H, m, H-2), 2.54-2.56 (2 H, m, H-5), 3.39-3.41 (2 H, t, *J* = 7.5 Hz, H-1), 3.82 (3 H, s, H-12), 6.56 (1 H, br s, *N*-H), 6.68 (1 H, br s, H-6); ¹³C NMR (100 MHz, CDCl₃) 27.9, 28.0, 28.3, 28.8, 32.6, 33.7, 68.0, 80.3, 153.3, 164.7; IR (cm⁻¹) 3416 (m), 2976 (s), 2932 (s), 2858 (m), 1724 (s), 1706 (s), 1511 (s), 1436 (s), 1367 (s), 1242 (s), 1161 (s), 1048 (m), 1021 (m), 896 (w), 833 (w), 801 (w), 770 (w), 773 (m), 645 (w), 561 (m); HRMS required for (C₁₄H₂₄BrNNaO₄) 372.0786; found 372.0783 (⁷⁹Br) and 374.0762 (⁸¹Br).

(Z)-Methyl 2-(*N*-*tert*-butoxycarbonyl)-amino-8-nitrooct-2-enoate (19c)

Following general procedure **A**, (Z)-methyl 2-(*N*-*tert*-butoxycarbonyl)-amino-8-bromooct-2-enoate **18c** (0.70 g, 2.00 mmol) gave the crude product as a yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 2/3) gave the title compound as a clear colourless oil (0.21 g, 34 %, 0.67 mmol). ^1H NMR (400 MHz, CDCl_3) 1.40-1.50 (4 H, m, H-3 & 4), 1.48 (9 H, s, H-10), 2.00-2.04 (2 H, m, H-2), 2.21-2.26 (2 H, q, $J = 7.5$ Hz, H-5), 3.78 (3 H, s, H-12), 4.37-4.41 (2 H, t, $J = 7.5$ Hz, H-1), 6.10 (1 H, br s, *N*-H), 6.51-6.54 (1 H, t, $J = 7.5$ Hz, H-6)); ^{13}C NMR (100 MHz, CDCl_3) 25.9, 27.0, 27.4, 27.8, 27.9, 28.1, 28.2, 52.3, 60.4, 75.5, 136.0, 165.3; IR (cm^{-1}) 2978 (m), 2933 (m), 1790 (w), 1726 (s), 1713 (s), 1658 (m), 1555 (s), 1494 (s), 1436 (m), 1368 (s), 1247 (s), 1163 (s), 1047 (m), 1026 (m), 914 (w), 842 (w), 775 (w); HRMS required for ($\text{C}_{14}\text{H}_{24}\text{N}_2\text{NaO}_6$) 339.1532; found 339.1527.

(Z)-Methyl 2-(*N*-benzylcarbonyl)-amino-8-bromooct-2-enoate (18d)

Following general procedure **B** methyl 2-(((benzyloxy)carbonyl)amino) (dimethoxyphosphoryl)acetate (1.80 g, 5.43 mmol) gave the crude product as a light yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 3/7) gave the title compound as a clear colourless oil (0.49 g, 24 %, 1.28 mmol). ^1H NMR (400 MHz, CDCl_3) 1.47-1.51 (4 H, m, H-3 & 4), 1.86-1.89 (2 H, m, H-2), 2.55-2.61 (2 H, m, H-5), 3.39-3.42 (2 H, t, $J = 7.5$ Hz, H-1), 3.81 (3 H, s, H-12), 6.81-6.83 (2 H, br s, H-6 & *N*-H), 7.34-7.38 (5 H, m, H-10); ^{13}C NMR (100 MHz, CDCl_3) 27.9, 28.0, 28.8, 32.6, 33.7, 52.3, 66.9, 128.2, 128.3, 128.6, 164.4; IR (cm^{-1}) 3405, (m), 2934 (s), 2856 (m), 1730 (s), 1711 (s), 1664 (m), 1517 (s), 1436 (s), 1408 (m), 1333 (m), 1216 (s), 1043 (m), 949 (w), 843 (w), 766 (m), 739 (m), 698 (m), 642 (w), 593 (w), 560 (w); HRMS required for ($\text{C}_{17}\text{H}_{22}\text{BrNNaO}_4$) 406.0630; found 406.0626 (^{79}Br).

(Z)-Methyl 2-(*N*-benzylcarbonyl)-amino-8-nitrooct-2-enoate (**19d**)

Following general procedure **A**, (*Z*)-methyl 2-(*N*-benzylcarbonyl)-amino-8-bromooct-2-enoate **18d** (0.49 g, 1.28 mmol) gave the crude product as a yellow oil.

Purification by column chromatography (silica gel, diethyl ether/hexane, 2/3) gave the title compound as a clear colourless oil (0.19 g, 42 %, 0.54 mmol). ^1H NMR (400 MHz, CDCl_3) 1.35-1.42 (2 H, m, H-3), 1.47-1.54 (2 H, m, H-4), 1.94-2.01 (2 H, m, H-2), 2.19-2.24 (2 H, m, H-5), 3.75 (3 H, s, H-12), 4.32-4.36 (2 H, t, $J = 7.5$ Hz, H-1), 5.14 (2 H, s, H-9), 6.31 (1 H, br s, *N*-H), 6.58-6.61 (1 H, t, $J = 7.5$ Hz, H-6), 7.32-7.37 (5 H, m, H-10); ^{13}C NMR (100 MHz, CDCl_3) 25.9, 27.0, 27.4, 28.0, 52.4, 67.4, 75.5, 128.1, 128.2, 128.3, 128.6, 136.0, 154.1, 165.0; IR (cm^{-1}) 2951 (s), 2860 (m), 2253 (w), 1729 (s), 1709 (s), 1657 (m), 1553 (s), 1501 (s), 1454 (s), 1383 (m), 1231 (s), 1145 (w), 1108 (m), 1048 (s), 912 (m), 847 (w), 772 (m); HRMS required for ($\text{C}_{17}\text{H}_{22}\text{N}_2\text{NaO}_6$) 373.1376; found 373.1369.

Synthesis of (*E*)-ethyl-5,5-dimethyl-8-nitrooct-2-enoate (**25**)

Ethyl 6-(tert-butyldiphenylsilyloxy)-3-methylhex-2-enoate (20) was synthesised following the

procedure by Esumi T.; Zhao, M.; Kawakami, T.; Fukumoto, M.; Toyota, M. & Fukuyama, Y. *Tetrahedron Lett.*, **2008**, 2692.

Ethyl 6-(tert-butyldiphenylsilyloxy)-3,3-dimethylhexanoate (21)

To a suspension of copper(I)iodide (4.71 g, 24.74 mmol) in diethyl ether (12.5 mL) was added methyl lithium (30.9 mL 49.49 mmol) at 0 °C and the solution was stirred for 10 minutes. The

solvent was removed under reduced pressure at 0 °C and dichloromethane (5 mL) was added. The solution was stirred for 5 min at 0 °C and the solvent was removed under reduced pressure at 0 °C. To the residue was added pre cooled dichloromethane (150 mL) and the mixture was cooled to -78 °C. To this cooled solution was added trimethylsilyl chloride (3.1 mL, 24.74 mmol) drop-wise and ethyl 6-(tert-butyldiphenylsilyloxy)-3-methylhex-2-enoate **20** (5.08 g, 12.37 mmol) in dichloromethane (25 mL). The mixture was allowed to warm to 0 °C gradually and the reaction was quenched by the addition of a mixture of aqueous ammonium chloride and 28% ammonium hydroxide (1:1). The mixture was extracted with diethyl ether (3 x 100 mL), the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude compound as a light yellow oil. Purification by column chromatography (silica gel, ethyl acetate/hexane, 1/9) gave the title compound as a clear colourless oil (4.22 g, 80 %, 9.88 mmol). ¹H NMR (250 MHz, CDCl₃) 0.98 (6 H, s, H-7), 1.05 (9 H, s, H-1), 1.20-1.26 (3 H, t, *J* = 7.5 Hz, H-12), 1.27-1.36 (2 H, m, H-6), 1.49-1.58 (2 H, m, H-5), 2.17 (2 H, s, H-9), 3.61-3.67 (2 H, t, *J* = 7.5 Hz, H-4), 4.05-4.14 (2 H, q, *J* = 7.5 Hz, H-11), 7.34-7.42 (6 H, m, H-3), 7.65-7.68 (4 H, m, H-3); ¹³C NMR (62.8 MHz, CDCl₃) 14.1, 14.3, 26.9, 27.2, 27.4, 38.3, 46.2, 59.9, 64.5, 127.6, 129.5, 135.6; IR (cm⁻¹) 3069 (w), 2957 (s), 2895 (m), 1731 (s), 1471 (m), 1427 (m), 1306

(w), 1235 (m), 1111 (s), 1034 (w), 939 (w), 823 (m), 739 (m), 702 (s), 613 (m), 504 (s); HRMS required for (C₂₆H₃₈NaO₃Si) 449.2488; found 449.2482.

Ethyl 6-hydroxy-3,3-dimethylhexanoate (**22**)

Ethyl 6-(*tert*-butyldiphenylsilyloxy)-3,3-dimethylhexanoate **21** (4.22 g, 9.88 mmol) was dissolved in tetrabutyl ammonium fluoride (12 mL, 11.86 mmol) and stirred at room temperature overnight. This solution was concentrated under reduced pressure to give the crude product as a light yellow oil. Purification by chromatography (silica gel, ethyl acetate/hexane, 1/3) gave the title compound as a clear colourless oil (1.42 g, 76 %, 7.43 mmol). ¹H NMR (250 MHz, CDCl₃) 1.01 (6 H, s, H-5), 1.23-1.29 (3 H, t, *J* = 7.35 Hz, H-9). 1.33-1.40 (2 H, m, H-3), 1.52-1.64 (3 H, m, H-2 & O-H), 2.21 (2 H, s, H-6), 3.61-3.67 (2 H, t, *J* = 7.5 Hz, H-1), 4.08-4.16 (2 H, q, *J* = 7.5 Hz, H-8); ¹³C NMR (62.8 MHz, CDCl₃) 14.7, 27.8, 27.9, 33.5, 38.3, 46.3, 60.4, 63.9, 172.8; IR (cm⁻¹) 3400 (m), 2958 (s), 2872 (m), 1731 (s), 1466 (m), 1368 (m), 1308 (m), 1231 (m), 1124 (m), 1056 (m), 1031 (m); HRMS required for (C₁₀H₂₁O₃⁺) 189.1483; found 189.1485.

Ethyl 6-bromo-3,3-dimethylhexanoate (**23**)

To a solution of ethyl 6-hydroxy-3,3-dimethylhexanoate **22** (1.42 g, 7.43 mmol) in diethyl ether (50 mL) was added carbon tetrabromide (6.17 g, 18.59 mmol) and triphenyl phosphine (5.07 g, 19.33 mmol). This solution was stirred for 1 hour, quenched with aqueous ammonium chloride, extracted with ether, the aqueous phase was washed with diethyl ether (2 x 15 mL), the combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to afford the crude compound as a light yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) gave the title compound as a clear colourless oil (2.23 g, 94 %, 7.00 mmol). ¹H NMR (250 MHz, CDCl₃) 1.01 (6 H, s, H-5), 1.23-1.29 (3 H, t, *J* = 7.5 Hz, H-9), 1.41-1.48 (2 H, m, H-3), 1.81-1.93 (2 H, m, H-

2), 2.19 (2 H, s, H-6), 3.36-3.42 (2 H, t, $J = 7.5$ Hz, H-1), 4.08-4.16 (2 H, q, $J = 7.5$ Hz, H-8); ^{13}C NMR (62.8 MHz, CDCl_3) 14.8, 27.8, 28.3, 33.5, 34.7, 40.9, 46.3, 60.4, 172.5; IR (cm^{-1}) 2960 (m), 1730 (s), 1468 (m), 1367 (m), 1301 (w), 1228 (m), 1133 (m), 1037 (m), 934 (w), 670 (m), 560 (w); HRMS required for ($\text{C}_{10}\text{H}_{19}\text{BrNaO}_2$) 273.0466; found (Br^{79}) 273.0473 and (Br^{81}) 275.0452.

Ethyl 6-nitro-3,3-dimethylhexanoate (**24**)

Following general procedure **A**, 6-bromo-3,3-dimethylhexanoate **23** (2.23 g, 7.00 mmol) gave the crude product as a yellow oil.

Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) gave the title compound as a clear colourless oil (0.55 g, 36 %, 2.51 mmol). ^1H NMR (250 MHz, CDCl_3) 1.02 (6 H, s, H-5), 1.23-1.29 (3 H, t, $J = 7.5$ Hz, H-9), 1.36-1.44 (2 H, m, H-3), 1.97-2.09 (2 H, m, H-2), 2.21 (2 H, s, H-6), 4.08-4.16 (2 H, q, $J = 7.5$ Hz, H-8), 4.34-4.40 (2 H, t, $J = 7.5$ Hz, H-1); ^{13}C NMR (62.8 MHz, CDCl_3) 14.7, 22.9, 27.7, 33.4, 38.3, 46.0, 60.6, 76.5; IR (cm^{-1}) 2963 (m), 1727 (s), 1575 (m), 1552 (s), 1466 (w), 1369 (m), 1333 (w), 1231 (m), 1125 (m), 1032 (m); HRMS required for ($\text{C}_{10}\text{H}_{19}\text{NaNO}_4$) 240.1212; found 240.1214.

6-Nitro-3,3-dimethylhexanal

To a solution of ethyl 6-nitro-3,3-dimethylhexanoate **24** (0.55 g, 2.51 mmol) in dichloromethane (10 mL) at -78 °C was added DIBAL-H (2.8 mL, 2.76 mmol, 1M solution in hexanes). After 1 hour at -78 °C TLC analysis showed consumption of starting material. The reaction was quenched with aqueous hydrochloric acid (1M, 50 mL) and water (100 mL), the aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the crude product as a light yellow oil, which was used without further purification. ^1H NMR (250 MHz, CDCl_3) 1.09 (6 H, s, H-5), 1.37-1.43 (2 H, m, H-3), 1.98-2.05 (2

H, m, H-2), 2.30-2.32 (2 H, d, $J = 5.0$ Hz, H-6), 4.34-4.40 (2 H, t, $J = 7.5$ Hz, H-1), 9.82-9.86 (1 H, t, $J = 5.0$ Hz, H-7).

(E)-Ethyl 5,5-dimethyl-8-nitrooct-2-enoate (25)

To a solution of crude 6-nitro-3,3-dimethylhexanal (~0.43 g, 2.51 mmol) in dichloromethane (15 mL) was added in one portion (carbethoxymethylene)triphenylphosphorane (1.00 g, 2.76 mmol). The reaction mixture was left to stir for 18 hours, quenched with saturated ammonium chloride (10 mL), the aqueous layer was extracted with dichloromethane (2 x 10 mL). The combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the crude product as a viscous yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane 1/3) afforded the title compound as a clear colourless oil (0.32 g, 53 %, 1.33 mmol). ^1H NMR (250 MHz, CDCl_3) 0.94 (6 H, s, H-5), 1.24-1.33 (5 H, m, H-3 & 11), 1.93-2.05 (2 H, m, H-2), 2.10-2.14 (2 H, dd, $J = 2.5$ & 10 Hz, H-6), 4.15-4.24 (2 H, q, $J = 7.5$ Hz, H-10), 4.33-4.39 (2 H, t, $J = 7.5$ Hz, H-1), 5.79-5.86 (1 H, dt, $J = 2.5$ & 15 Hz, H-8), 6.87-7.00 (1 H, app. quin, $J = 7.5$ Hz, H-7); ^{13}C NMR (62.8 MHz, CDCl_3) 14.7, 22.8, 27.1, 34.0, 38.6, 45.0, 60.7, 76.4, 124.3, 145.8 ; IR (cm^{-1}) 2959 (m), 2359 (s), 2340 (m), 1717 (s), 1653 (w), 1552 (s), 1465 (w), 1368 (m), 1269 (m), 1197 (m), 1141 (w), 1043 (w), 986 (w), 668 (w); HRMS required for ($\text{C}_{12}\text{H}_{22}\text{NO}_4^+$) 244.1549; found 244.1543.

Synthesis of (*E*)-ethyl 4-(3-nitropropoxy)but-2-enoate (*E*)-29

Methyl 6-bromo-3-oxahexanoate was synthesized according to literature procedure. See Maruyama, T.; Asada, M.; Shiraishi, T.; Egashira, H.; Yoshida, H.; Maruyama, T.; Ohuchida, S.; Nakai, H.; Hondo, K.; Toda, M. *Bioorg. Med. Chem.* **2002**, 10, 975.

Methyl 6-nitro-3-oxahexanoate 27 was synthesized using general procedure **A**, where methyl 6-bromo-3-oxahexanoate **26** (0.976 g, 4.6 mmol) gave the title compound as a yellow oil which was purified by flash column chromatography (Ethyl Acetate : Hexanes, 3:7) to yield pure methyl 6-nitro-3-oxahexanoate **27** (0.163 g, 18%) as a clear, colourless oil. ^1H NMR (250MHz, CHCl_3) : 4.58 (2H, t, $J = 7.5$, H-1), 4.09 (2H, s, H-4), 3.76 (3H, s, H-5), 3.65 (2H, t, $J = 5$ Hz, H-3), 2.31 (2H, m, H-2). ^{13}C NMR (62.5 MHz, CHCl_3) : 170.63, 72.31, 68.11, 67.60, 51.87, 27.41 HRMS expected for ($\text{C}_6\text{H}_{11}\text{NNaO}_5$) 200.0535; found 200.0525

(*E*)-ethyl 4-(3-nitropropoxy)but-2-enoate (*E*)-29 and (*Z*)-ethyl 4-(3-nitropropoxy)but-2-enoate (*Z*)-29. To a solution of methyl 6-nitro-3-oxahexanoate **27** (0.163 g, 0.85 mmol) in anhydrous

DCM (25 mL) at -78 °C was added DIBAL-H (0.94 mL, 0.94 mmol, 1M solution in hexanes). After 1 hour at -78 °C TLC analysis showed consumption of starting material. The reaction was quenched with aqueous hydrochloric acid (1M, 15 mL) and water (15 mL), and the aqueous layer was extracted with dichloromethane (2 x 25 mL). The combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure to afford crude 2-(3-nitropropoxy)acetaldehyde (0.120 g). This product was used directly in the subsequent Wittig reaction. To a solution of crude 2-(3-nitropropoxy)acetaldehyde (0.120 g, 0.8 mmol) in dichloromethane (20 mL) was added in one portion (carbmethoxymethylene)triphenylphosphorane (0.322 g, 0.9 mmol). The reaction mixture was left to stir for 18 hours, quenched with saturated ammonium chloride (10 mL) and the aqueous layer was extracted with dichloromethane (2 x 15 mL). The combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure to afford a crude mixture of (*E*)-ethyl 4-(3-nitropropoxy)but-2-enoate and (*Z*)-ethyl 4-(3-nitropropoxy)but-2-enoate as a yellow oil. The mixture was purified by flash column chromatography (Ethyl Acetate : Hexanes, 1 : 3) to give the pure title compounds as clear, colourless oils (0.058 g and 0.033 g of *E*- and *Z*- respectively, 55%). ¹H NMR (*E*)-ethyl 4-(3-nitropropoxy)but-2-enoate (**E**-29 (250MHz, CHCl₃) : 6.93 (1H, dt, *J* = 5 Hz & 17.5 Hz, H-5), 6.03 (1H, dt, *J* = 2.5 Hz and 15 Hz, H-6), 4.53 (2H, t, *J* = 7.5 Hz, H-4), 4.22 (2H, q, *J* = 7.5 Hz, H-7), 4.12 (2H, m, H-3), 3.58 (2H, t, *J* = 7.5 Hz, H-1), 2.30 (2H, m, H-2), 1.28 (3H, br, H-8). ¹³C NMR (62.5 MHz, CHCl₃) : 143.58, 121.47, 72.57, 69.63, 66.89, 60.51, 31.61, 22.68, 14.25. ¹H NMR (*Z*)-ethyl 4-(3-nitropropoxy)but-2-enoate (**Z**-29 (250MHz, CHCl₃) : 6.30 (1H, m, H-5), 5.82 (1H, dt, *J* = 2.5 & 12.5 Hz, H-6), 4.55 (4H, m, H-1 and H-4), 4.17 (2H, q, *J* = 7.5 Hz, H-7), 2.28 (2H, m, H-2), 1.27 (3H, t, *J* = 7.5 Hz, H-8). ¹³C NMR (62.5 MHz, CHCl₃) : 147.52, 119.92, 72.70, 68.99, 66.66, 60.33, 27.54, 14.24. HRMS required for (C₉H₁₆NO₅⁺) 218.1028; found 218.1019.

Racemic reaction

General racemic reaction. General procedure C

To a solution of the nitro- α,β -unsaturated ester (1 eq.) in solvent (0.3 M concentration), was added cesium fluoride (2 eq.) and the resulting solution stirred for 48 h. The solution was concentrated under reduced pressure and purified by column chromatography.

General organocatalysis reaction. General procedure D

To a solution of the nitro- α,β -unsaturated ester (1 eq.) in solvent (0.5 M concentration), was added bifunctional organocatalyst **C** (0.1 eq.). The resulting solution was stirred for 7 days, concentrated under reduced pressure and purified by column chromatography.

Ethyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)acetate ((+)-2)

Following general procedure **D**, using catalyst **C**, in acetonitrile (0.25 mL), (*E*)-ethyl-8-nitrooct-2-enoate **1** (161.5 mg, 0.75 mmol) gave the crude product as a yellow oil. Purification by column chromatography (silica gel,

diethyl ether/hexane, 1/3) gave the title product as a clear colourless oil (140.0 mg, 0.65 mmol, 87 %). The enantiomeric excess was determined by HPLC analysis (25 °C) after DIBAL-H reduction to **30** and benzoyl protection to **32** to be 95.6%. $[\alpha]_D^{23} +22.5$ ($c = 1.04$, CHCl_3); ^1H NMR (250 MHz, CDCl_3) 1.13-1.45 (3 H, m, Cyc-H), 1.73-2.00 (4 H, m, Cyc-H), 2.15-2.50 (4 H, m, H-7 & Cyc-H), 4.09-4.17 (2 H, q, $J = 7.5$ Hz, H-9), 4.31-4.40 (1 H, dt, $J = 2.5$ & 12.5 Hz, H-1 (*trans*-isomer(major))), 4.71-4.77 (*cis*-isomer(minor)); ^{13}C NMR (62.8 MHz, CDCl_3) 14.2, 21.4, 22.9, 24.3, 24.6, 27.3, 28.1, 30.1, 35.3, 35.5, 37.4, 37.8, 60.6, 60.7, 85.2, 89.6; IR (cm^{-1}) 2939 (s), 2863 (m), 1731 (s), 1547 (s), 1450 (m), 1370 (s), 1349 (m), 1291 (m), 1244 (m), 1223 (m), 1176 (s), 1112 (m), 1028 (m), 970 (w), 900 (w), 856 (w), 736 (w); HRMS required for ($\text{C}_{10}\text{H}_{18}\text{NO}_4^+$) 216.1236; found 216.1232.

Methyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)acetate ((+)-**3**)

Following general procedure **D**, using catalyst **C**, in acetonitrile (0.25 mL), (*E*)-methyl 8-nitrooct-2-enoate **16a** (161.5 mg, 0.75 mmol) gave the crude product as a yellow oil. Purification by column chromatography (silica gel, diethyl

ether/hexane, 1/3) gave the title compound as a clear colourless oil (85.5 mg, 0.43 mmol, 57 %). The enantiomeric excess was determined by HPLC analysis (25 °C) after DIBAL-H reduction to **30** and benzoyl protection to **32** to be 96.4%. $[\alpha]_D^{23} +21.5$ ($c = 1.01$, CHCl_3); ^1H NMR (250 MHz, CDCl_3) 1.13-1.56 (3 H, m, Cyc-H), 1.74-1.99 (4 H, m, Cyc-H), 2.16-2.45 (4 H, m, H-7 & Cyc-H), 3.67 (3 H, s, H-9), 4.32-4.42 (1 H, dt, $J = 2.5$ & 15 Hz, H-1 (*trans*)), 4.71-4.77 (*Cis* bridge); ^{13}C NMR (62.8 MHz, CDCl_3) 21.4, 22.8, 24.2, 24.6, 27.3, 28.1, 30.1, 30.3, 31.9, 35.0, 35.4, 37.1, 37.7, 51.7, 51.8, 85.2, 89.6, 172.0; IR (cm^{-1}) 2942 (s), 2862 (m), 1737 (s), 1556 (s), 1434 (m), 1354 (m), 1292 (m), 1245 (m), 1170 (m), 1112 (m), 1004 (m), 971 (w), 914 (w), 855 (w), 735 (s), 648 (w); HRMS required for ($\text{C}_9\text{H}_{15}\text{NaNO}_4$) 224.0899; found 224.0901.

Benzyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)acetate ((+)-4)

Following general procedure **D**, using catalyst **C**, in acetonitrile (0.25 mL), (*E*)-benzyl 8-nitrooct-2-enoate **16b** (161.5 mg, 0.75 mmol) gave the crude product as a yellow oil. Purification by column

chromatography (silica gel, diethyl ether/hexane, 1/3) gave the title compound as a clear colourless oil (138.0 mg, 0.50 mmol, 66 %). The enantiomeric excess was determined by HPLC analysis (25 °C) after DIBAL-H reduction to **30** and benzoyl protection to **32** to be 98.0%. $[\alpha]_D^{23} +20.5$ ($c = 0.91$, CHCl₃); ¹H NMR (250 MHz, CDCl₃) 1.05-1.96 (7 H, m, Cyc-H), 2.19-2.29 (2 H, m, Cyc-H), 2.35-2.58 (2 H, m, Cyc-H), 4.29-4.40 (1 H, dt, $J = 5$ & 12.5 Hz, H-1(trans ring bridge)), 4.68-4.74 (cis ring bridge), 5.10 (2 H, s, H-9), 7.25-7.39 (5 H, m, H-10); ¹³C NMR (62.8 MHz, CDCl₃) 14.1, 21.4, 22.7, 22.8, 24.2, 24.5, 27.2, 28.0, 30.1, 30.3, 31.6, 31.8, 35.2, 35.4, 37.3, 37.7, 66.4, 66.5, 85.1, 89.5, 128.2, 128.3, 128.3, 128.6; IR (cm⁻¹) 2940 (s), 2861 (m), 2255 (w), 1736 (s), 1547 (s), 1454 (m), 1415 (w), 1374 (m), 1220 (m), 1165 (s), 1110 (m), 1002 (m), 911 (s), 826 (w), 734 (s), 697 (m), 648 (m); HRMS required for (C₁₅H₁₉NaNO₄) 300.1212; found 300.1216.

Ethyl 2-((1*R*,2*S*)-5,5-dimethyl-2-nitrocyclohexyl)acetate ((+)-9)

Following general procedure **D**, using catalyst **C**, in acetonitrile (0.25 mL), (*E*)-ethyl 5,5-dimethyl-8-nitrooct-2-enoate **25** (121.6 mg, 0.50 mmol) gave the crude product as yellow oil. Purification by column chromatography

(silica gel, diethyl ether/hexane, 1/3) gave the title compound as a clear colourless oil (92.6 mg, 0.38 mmol, 76 %). The enantiomeric excess was determined by HPLC analysis (25 °C) after DIBAL-H reduction to **31** and benzoyl protection to **33** to be 96.0%. $[\alpha]_D^{23} +40.9$ ($c = 1.54$, CHCl₃); ¹H NMR (250 MHz, CDCl₃) 0.96 (3 H, s, H-5 or 6), 1.05 (3 H, s, H-5 or 6), 0.97-1.15 (1 H, m, Cyc-H), 1.22-1.28 (3 H, t, $J = 7.5$ Hz, H-12), 1.26-1.36 (1 H, m, Cyc-H), 1.52-1.73 (2 H, m,

Cyc-H), 2.08-2.21 (3 H, m, H-9 & Cyc-H), 2.32-2.39 (1 H, dd, $J = 2.5$ & 15.0 Hz), 2.55-2.71 (1 H, m, Cyc-H), 4.07-4.19 (2 H, m, H-11), 4.24-4.35 (1 H, m, H-1); ^{13}C NMR (62.8 MHz, CDCl_3) 14.2, 24.2, 24.5, 26.3, 28.1, 30.4, 32.1, 32.6, 33.9, 36.6, 36.9, 37.3, 39.3, 43.1, 43.3, 60.6, 90.0, 171.5; IR (cm^{-1}) 2955 (s), 1735 (s), 1546 (s), 1464 (m), 1371 (m), 1341 (m), 1251 (m), 1186 (s), 1142 (m), 1095 (w), 1034 (m), 910 (w), 873 (w), 756 (s), 734 (s); HRMS required for ($\text{C}_{12}\text{H}_{21}\text{NaNO}_4$) 266.1368; found 266.1362.

Ethyl 2-((3*R*,4*S*)-4-nitrotetrahydro-2*H*-pyran-3-yl)acetate **8.**

Prepared according to general procedure X, (*E*)-ethyl 4-(3-nitropropoxy)but-2-enoate X (0.05 g, 0.23 mmol) gave the crude product as a yellow oil, which upon flash column chromatography (Ethyl acetate : Hexanes, 1 : 4) afforded ethyl 2-((3*R*,4*S*)-4-nitrotetrahydro-2*H*-pyran-3-yl)acetate **8** as a clear colourless oil (0.034 g, 69%). The enantiomeric excess was determined by HPLC analysis (25 °C) to be 92%. ^1H NMR (400MHz, CHCl_3) : 4.28 (2H, m, H-6), 4.14 (2H, m, H-7), 3.69 (1H, dt, $J = 2.5$ & 12.0 Hz, H-5), 3.42 (1H, t, $J = 11$ Hz, H-1), 3.12 (1H, m, ring-H), 2.72 (2H, m, H-4), 2.41 (1H, m, ring-H), 2.18 (2H, dd, $J = 6.5$ & 16.9 Hz, H-2), 1.28 (3H, t, $J = 7.1$ Hz, H-8). ^{13}C NMR (100 MHz, CDCl_3) : 172.1, 72.2, 68.6, 60.8, 47.7, 42.4, 29.9, 14.2. HRMS required for ($\text{C}_9\text{H}_{16}\text{NO}_5^+$) 218.1028; found 218.1018

(*R*)-Ethyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)propanoate ((+)-5**)**

Following general procedure **D**, using catalyst **C**, in acetonitrile (0.25 mL),

(*E*)-ethyl 2-methyl-8-nitrooct-2-enoate **16c** (172.0 mg, 0.75 mmol) gave the

crude product as a yellow oil. Purification by column chromatography (silica

gel, diethyl ether/hexane, 1/3) gave the title compound as a clear colourless oil (91.7 mg, 0.40

mmol, 53 %). The enantiomeric excess was determined by HPLC analysis (25 °C) to be 94%.

[Chiralcel OD column (0.46 cm $\varnothing$ X 25 cm) hexanes/2-propanol = 49/1; flow rate = 0.3 mL/min;

detection wavelength = 210 nm] tR 19.56 min (*R*-1*S*,2*R*); tR 20.42 min (*S*-1*R*,2*S*). $[\alpha]_D^{23} +14.3$ ($c = 0.95$, CHCl₃); ¹H NMR (250 MHz, CDCl₃) 1.10-1.13 (3 H, d, $J = 7.5$ Hz, H-8), 1.23-1.29 (3 H, t, $J = 7.5$ Hz, H-11), 1.22-1.38 (1 H, m, Cyc-H), 1.63-2.03 (4 H, m, Cyc-H), 2.25-2.32 (1 H, m, Cyc-H), 2.41-2.62 (2 H, m, H-7 & Cyc-H), 4.10-4.19 (2 H, q, $J = 7.5$ Hz, H-10), 4.38-4.48 (1 H, dt, $J = 2.5$ & 10 Hz, H-1); ¹³C NMR (62.8 MHz, CDCl₃) 9.8, 14.2, 14.7, 24.3, 24.5, 24.6, 25.0, 25.2, 32.0, 32.9, 39.4, 39.6, 42.4, 44.2, 60.5, 60.7, 87.8, 88.6, 174.5; IR (cm⁻¹) 2940 (s), 2863 (s), 2339 (w), 1732 (s), 1547 (s), 1450 (m), 1375 (m), 1300 (m), 1195 (s), 1140 (s), 1054 (m), 1020 (w), 855 (w), 734 (m); HRMS required for (C₁₁H₁₉NaNO₄) 252.1212; found 252.1207.

(*R*)-Ethyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)-3-phenylpropanoate ((+)-6)

Following general procedure **D**, using catalyst **C**, in acetonitrile (0.25 mL), (*E*)-ethyl 2-benzyl-8-nitrooct-2-enoate (**E**)-**19b** (95.4 mg, 0.31 mmol) gave the crude product as yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 1/3) gave the title compound as a clear

colourless oil (50.0 mg, 0.16 mmol, 52 %). The enantiomeric excess was determined by HPLC analysis (25 °C) to be >99%. [Chiralcel OD column (0.46 cm ø X 25 cm) hexanes/2-propanol = 47.5/2.5; flow rate = 0.5 mL/min; detection wavelength = 210 nm] tR 13.90 min (*R*-1*S*,2*R*); tR 15.40 min (*S*-1*R*,2*S*). $[\alpha]_D^{23} +12.9$ ($c = 1.00$, CHCl₃); ¹H NMR (250 MHz, CDCl₃) 1.08-1.14 (3 H, t, $J = 7.5$ Hz, H-12), 1.23-1.43 (3 H, m, Cyc-H), 1.79-2.05 (4 H, m, Cyc-H), 2.27-2.32 (1 H, m, Cyc-H), 2.43-2.52 (1 H, m, Cyc-H), 2.58-2.65 (1 H, dt, $J = 2.5$ & 12.5 Hz, H-7), 2.72-2.79 (1 H, dd, $J = 2.5$ & 12.5 Hz, H-8), 2.90-3.00 (1 H, dd, $J = 12.5$ & 12.5 Hz, H-8), 3.98-4.06 (2 H, q, $J = 7.5$ Hz, H-11), 4.52-4.63 (1 H, dt, $J = 5$ & 12.5 Hz, H-1), 7.13-7.28 (5 H, m, H-9); ¹³C NMR (62.8 MHz, CDCl₃) 14.1, 14.2, 23.7, 24.2, 24.5, 24.7, 24.9, 25.2, 25.9, 31.8, 32.0, 33.0, 35.4, 42.2, 43.2, 47.0, 48.6, 60.7, 87.9, 88.7, 126.4, 126.5, 128.4, 128.5, 128.9, 129.1; IR (cm⁻¹) 2939 (s), 1729 (s), 1602 (w), 1547 (s), 1494 (m), 1453 (m), 1370 (s), 1327 (m), 1213 (s), 1171 (s), 1095 (w),

1031 (m), 903 (w), 860 (w), 753 (s); HRMS required for (C₁₇H₂₃NaNO₄) 328.1525; found 328.1520.

(R)-Ethyl 2-(*tert*-butoxyaminocarbonyl)-2-((1*R*,2*S*)-2-nitrocyclohexyl)acetate ((-)-10)

Following general procedure **D**, using catalyst **C**, in acetonitrile (0.25 mL), (Z)-methyl 2-(*N*-*tert*-butoxycarbonyl)-amino-8-nitrooct-2-enoate **19c** (50.0 mg, 0.16 mmol) gave the crude product as a yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 3/7) gave the title compound as a clear colourless oil (5.4 mg, 0.02 mmol, 11 %). The enantiomeric excess was determined by HPLC analysis (25 °C) to be >99%. [Chiralcel OD column (0.46 cm ø X 25 cm) hexanes/2-propanol = 47.5/2.5; flow rate = 0.5 mL/min; detection wavelength = 210 nm] tR 29.56 min (*R*-1*S*,2*R*); tR 32.62 min (*S*-1*R*,2*S*). $[\alpha]_D^{23}$ -7.7 (*c* = 0.36, CHCl₃); ¹H NMR (250 MHz, CDCl₃) 1.18-1.36 (4 H, m, Cyc-H), 1.44-1.46 (9 H, m, H-10), 1.73-1.96 (3 H, m, Cyc-H), 2.26-2.70 (2 H, m, Cyc-H), 3.76-3.79 (3 H, d, *J* = 7.5 Hz, H-12), 4.31-4.51 (2 H, m, Cyc-H), 5.05-5.22 (1 H, m, Cyc-H); ¹³C NMR (62.8 MHz, CDCl₃) 14.2, 24.1, 24.3, 24.4, 24.5, 24.4, 25.6, 26.9, 28.2, 28.3, 32.2, 33.0, 42.4, 52.6, 52.7, 55.5, 60.4, 80.4, 85.5, 86.2; IR (cm⁻¹) 3367 (m), 2929 (m), 2358 (s), 2339 (m), 1714 (s), 1549 (s), 1502 (w), 1367 (w), 1261 (w), 1162 (m), 1051 (w), 668 (m); HRMS required for (C₁₄H₂₄NaN₂O₆) 339.1532; found 339.1528

(R)-Methyl 2-(benzyloxyaminocarbonyl)-2-((1*R*,2*S*)-2-nitrocyclohexyl)acetate ((-)-7)

Following general procedure **D**, using catalyst **C**, (Z)-methyl 2-(*N*-benzylcarbonyl)-amino-8-nitrooct-2-enoate **19d** (48.1 mg, 0.14 mmol) gave the crude product as a yellow oil. Purification by column chromatography (silica gel, diethyl ether/hexane, 3/7) gave the title compound as a clear colourless oil (29.3 mg, 0.08 mmol, 61 %). The enantiomeric excess was

determined by HPLC analysis (25 °C) to be 95%. [Chiralcel OD column (0.46 cm ø X 25 cm) hexanes/2-propanol = 19/1; flow rate = 1 mL/min; detection wavelength = 210 nm] tR 30.74 min (*R*-1*S*,2*R*); tR 44.29 min (*S*-1*R*,2*S*). $[\alpha]_D^{23}$ -6.0 (*c* = 0.98, CHCl₃); ¹H NMR (250 MHz, CDCl₃) 1.20-1.21 (2 H, d, *J* = 2.5 Hz, Cyc-H), 1.24-1.55 (3 H, m, Cyc-H), 2.25-2.73 (2 H, m, Cyc-H), 3.75-3.78 (3 H, m, *J* = 7.5 Hz, H-12), 4.37-4.61 (2 H, m, Cyc-H), 5.09-5.16 (2 H, m, H-9), 5.34-5.52 (1 H, m, N-H), 7.31-7.38 (5 H, m, H-10); ¹³C NMR (62.8 MHz, CDCl₃) 24.1, 24.3, 24.4, 25.4, 32.1, 33.0, 42.5, 43.3, 52.7, 52.9, 55.8, 67.4, 67.5, 85.6, 86.1, 128.3, 128.3, 128.6, 136.0; IR (cm⁻¹) 3361 (m), 2924 (m), 2845 (w), 1724 (s), 1547 (s), 1524 (m), 1339 (w), 1261 (w), 1216 (m), 1068 (m), 746 (w); HRMS required for (C₁₇H₂₂NaN₂O₆) 373.1376; found 373.1371.

General reduction to alcohol procedure E

To a solution of the nitro cyclohexyl ester (1 eq.) in dichloromethane (0.06 M) at -78°C, was added DIBAL-H (4 eq., 1M solution in hexanes), the reaction was left to warm to room temperature overnight. The reaction was quenched with aqueous hydrochloric acid (1M) and water, the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water, dried over MgSO₄, filtered and concentrated under reduced pressure to afford the nitro cyclohexyl alcohol, which was purified by column chromatography.

2-((1*R*,2*S*)-2-nitrocyclohexyl)ethanol ((+)-30)

Following general procedure E, ethyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)acetate ((+)-2) (85.5 mg, 0.42 mmol) gave the crude product as a light yellow oil.

Purification by column chromatography (silica gel, ethyl acetate/hexane, 2/3)

afforded the title compound as white crystalline needles (57.4 mg, 79 %, 0.33 mmol). $[\alpha]_D^{23}$ +26.8 (*c* = 0.94, CHCl₃); MP - 59.1-59.6 °C; ¹H NMR (250 MHz, CDCl₃) 0.99-1.15 (1 H, m, Cyc-H), 1.23-1.50 (3 H, m, H-7 & Cyc-H), 1.54-1.67 (1 H, m, H-7), 1.73-2.27 (6 H, m, Cyc-H), 3.58-3.75

(2 H, m, H-8), 4.23-4.33 (1 H, dt, $J = 5.0$ & 12.5 Hz, H-1); ^{13}C NMR (62.8 MHz, CDCl_3) 24.3, 24.7, 29.8, 32.1, 35.4, 37.8, 59.6, 91.3; IR (cm^{-1}) 3302 (m), 2938 (m), 2863 (m), 1545 (s), 1451 (m), 1366 (s), 1296 (w), 1248 (w), 1197 (w), 1090 (w), 1048 (m), 1005 (m), 850 (w), 733 (w), 670 (w); HRMS required for ($\text{C}_8\text{H}_{16}\text{O}_3\text{N}^+$) 174.1130; found 174.1123.

2-((1*R*,2*S*)-5,5-dimethyl-2-nitrocyclohexyl)ethanol ((+)-31)

Following general procedure E, ethyl 2-((1*R*,2*S*)-5,5-dimethyl-2-nitrocyclohexyl)acetate ((+)-9) (92.6 mg, 0.38 mmol) gave the crude product as a light yellow oil. Purification by column chromatography (silica gel, ethyl acetate/hexane, 2/3) afforded the title compound as a clear colourless oil (73.1 mg, 95 %, 0.36 mmol). $[\alpha]_D^{23} +26.6$ ($c = 0.98$, CHCl_3); ^1H NMR (250 MHz, CDCl_3) 0.96 (3 H, s, H-5 or 6), 1.03 (3 H, s, H-5 or H-6), 1.00-1.09 (1 H, m, Cyc-H), 1.16-1.47 (3 H, m, H-9 & Cyc-H), 1.50-1.68 (3 H, m, H-9 & Cyc-H), 1.88 (1 H, br s, O-H), 2.05-2.12 (2 H, m, H-8 & Cyc-H), 2.26-2.42 (1 H, m, Cyc-H), 3.56-3.73 (2 H, m, H-10), 4.11-4.26 (1 H, m, H-1); ^{13}C NMR (62.8 MHz, CDCl_3) 24.4, 28.3, 32.3, 33.5, 35.7, 36.9, 43.0, 59.6, 91.7; IR (cm^{-1}) 3369 (m), 2949 (s), 1545 (s), 1457 (m), 1373 (m), 1266 (w), 1173 (w), 1045 (m), 865 (w), 751 (w); HRMS required for ($\text{C}_{10}\text{H}_{19}\text{NaNO}_3$) 224.1263; found 224.1256.

General benzoyl protection procedure F

To a solution of the nitro cyclohexyl alcohol (1 eq.) in dichloromethane (0.03 M) was added benzoyl chloride (1.5 eq.) and pyridine (1.5 eq.). The solution was stirred for 1 hour and quenched with aqueous ammonium chloride. The aqueous layer was washed with dichloromethane; the combined organic layers were washed with water, dried over MgSO_4 , filtered and concentrated under reduced pressure to afford the benzoate, which was purified by column chromatography.

2-((1*R*,2*S*)-2-nitrocyclohexyl)ethyl benzoate ((+)-32)

Following general procedure **F**, 2-((1*R*,2*S*)-2-nitrocyclohexyl)ethanol **((+)-30)** (71.3 mg, 0.41 mmol) gave the crude product as a light yellow oil. Purification by column chromatography (silica gel, diethyl

ether/hexane, 1/4) afforded the title product as a clear colourless oil (88.7 mg, 78 %, 0.32 mmol). Enantiomeric excess was determined by HPLC analysis (25 °C). [Chiralpak AD-H column (0.46 cm ø X 25 cm) hexanes/2-propanol = 19/1; flow rate = 0.4 mL/min; detection wavelength = 210 nm] tR 30.76 min (1*R*,2*S*); tR 33.66 min (1*S*,2*R*). $[\alpha]_D^{23} +8.9$ ($c = 2.6$, CHCl₃); NMR (250 MHz, CDCl₃) 1.03-1.19 (1 H, m, Cyc-H), 1.25-1.49 (3 H, m, Cyc-H), 1.55-1.97 (6 H, m, H-7 & Cyc-H), 2.05-2.30 (3 H, m, H-6 & Cyc-H), 4.25-4.46 (3 H, m, H-1 & H-8), 7.42-7.51 (3 H, m, H-10), 8.01-8.06 (2 H, m, H-10); ¹³C NMR (62.8 MHz, CDCl₃) 22.0, 22.2, 24.3, 24.7, 27.0, 27.4, 28.4, 29.7, 31.5, 32.1, 36.0, 38.2, 61.9, 62.6, 86.1, 91.0, 128.5, 128.5, 128.9, 129.6, 130.2, 130.6; IR (cm⁻¹) 2938 (m), 2860 (w), 1718 (s), 1545 (s), 1450 (m), 1374 (w), 1315 (m), 1274 (s), 1175 (w), 1113 (m), 1069 (w), 1025 (w), 712 (s); HRMS required for (C₁₅H₁₉NNaO₄) 300.1212; found 300.1206.

2-((1*R*,2*S*)-5,5-dimethyl-2-nitrocyclohexyl)ethyl benzoate ((+)-33)

Following general procedure **F**, 2-((1*R*,2*S*)-5,5-dimethyl-2-nitrocyclohexyl)ethanol **((+)-31)** (73.1 mg, 0.36 mmol) gave the crude product as a light yellow oil. Purification by column chromatography

(silica gel, diethyl ether/hexane, 1/4) afforded the title compound as a clear colourless oil (88.6 mg, 82 %, 0.29 mmol). Enantiomeric excess was determined by HPLC analysis (25 °C). [Chiralpak AD-H column (0.46 cm ø X 25 cm) hexanes/2-propanol = 24/1; flow rate = 0.5 mL/min; detection wavelength = 210 nm] tR 23.10 min (1*R*,2*S*); tR 24.23 min (1*S*,2*R*). $[\alpha]_D^{23} +6.1$ ($c = 1.2$, CHCl₃); NMR (400 MHz, CDCl₃) 0.96 (3 H, s, H-5 or 6), 1.00 (3 H, s, H-5 or H-6),

1.03-1.06 (1 H, m, Cyc-H), 1.24-1.32 (1 H, m, Cyc-H), 1.50-1.62 (2 H, m, H-8 & H-9), 1.68-1.73 (1 H, m, Cyc-H), 1.83-1.87 (1 H, m, H-9), 2.07-2.13 (2 H, m, Cyc-H), 2.35-2.43 (1 H, m, Cyc-H), 4.17-4.24 (1 H, m, H-1), 4.28-4.36 (2 H, m, H-10), 7.41-7.47 (3 H, m, H-12), 8.02-8.05 (2 H, m, H-12); ^{13}C NMR (100 MHz, CDCl_3) 24.3, 28.3, 30.3, 31.5, 32.2, 34.1, 36.9, 42.8, 61.8, 91.4, 128.4, 128.5, 128.9, 130.2, 130.6, 162.4; IR (cm^{-1}) 2952 (w), 2360 (w), 1785 (s), 1718 (s), 1686 (s), 1598 (w), 1544 (m), 1451 (m), 1423 (w), 1324 (w), 1275 (s), 1212 (s), 1172 (m), 1072 (w), 1039 (s), 1016 (s), 995 (s), 777 (w), 706 (s), 615 (w); HRMS required for ($\text{C}_{17}\text{H}_{23}\text{NNaO}_4$) 328.1525; found 328.1521.

Absolute configuration determined by Nef reaction and comparison of products optical rotation with literature value.

(*R*)-Ethyl 2-(2-oxocyclohexyl)acetate ((+)-34)

To a solution of ethyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)acetate **((+)-2)** (0.11 g, 0.53 mmol) in ethanol (2.5 mL) was added sodium ethoxide (0.14 g, 2.12 mmol). This solution was stirred for one hour before the addition of a solution of aqueous hydrochloric acid/ethanol (1:1(1M, 5.3 mL: ethanol 5.3 mL)), after a further 10 minutes of stirring the reaction was diluted with water (5 mL) and extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with water, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product as a light yellow oil. Purification by column chromatography (silica gel, ethyl acetate/hexane, 1/9) afforded the title compound as a clear colourless oil (42.0 mg, 43 %, 0.23 mmol). $[\alpha]_D^{23} +17.5$ ($c = 1.00$, MeOH) (lit. -7.0 [(*S*)-ethyl 2-(2-oxocyclohexyl)acetate] Hiroi, K.; Achiwa, K.; Yamada, S.; *Chem. Pharm. Bull.*; **1972**; 20; 246), ^1H NMR (250 MHz, CDCl_3) 1.23-1.29 (3 H, t, $J = 7.5$ Hz, H-10), 1.33-1.50 (1 H, m, Cyc-H), 1.64-1.93 (3 H, m, Cyc-H), 2.08-2.19 (3 H, m, H-7 & Cyc-H), 2.35-2.42 (2 H, m,

Cyc-H), 2.72-2.94 (2 H, m, H-6 & H-7), 4.09-4.18 (2 H, q, $J = 7.5$ Hz, H-9); ^{13}C NMR (62.8 MHz, CDCl_3) 14.6, 25.6, 28.2, 34.3, 34.9, 42.2, 47.5, 60.8, 173.0, 211.5; IR (cm^{-1}) 2933 (m), 2860 (w), 1733 (s), 1711 (s), 1448 (w), 1367 (w), 1346 (w), 1276 (w), 1165 (m), 1130 (w), 1028 (w); HRMS required for ($\text{C}_{10}\text{H}_{17}\text{O}_3$) 185.1178; found 185.1172.

General Raney nickel cyclisation procedure F

To a solution of the nitro compound in ethanol (0.1 M) was added Raney Nickel (1 Spatula), the solution was placed under an atmosphere of hydrogen (1 atm.) after flushing the system with argon until TLC showed the reaction was complete. Toluene (Same volume as ethanol) was added to the solution and heated to complete cyclisation. After TLC showed the reaction had gone to completion, the mixture was filtered through a pad of Celite, concentrated under reduced pressure and purified by column chromatography.

(3*S*,3*aR*,7*aS*)-3-methyl-hexahydro-1*H*-indol-2(3*H*)-one, racemic ((±)-35)

Following general procedure F, racemic ethyl 2-(2-nitrocyclohexyl)propanoate ((±)-5) (121.0 mg, 0.53 mmol), gave the crude product which was purified by column chromatography (silica gel, ethyl acetate/hexane, 2/3) afforded the title compound as a white crystalline solid (26.8 mg, 0.17 mmol, 33 %). MP – 91.1-91.8 °C; ^1H NMR (400 MHz, CDCl_3) 1.06-1.08 (3 H, d, $J = 7.5$ Hz, H-8), 1.13-1.17 (1 H, m, Cyc-H), 1.25-1.35 (3 H, m, Cyc-H), 1.65-1.70 (1 H, m, Cyc-H), 1.78-1.91 (2 H, m, Cyc-H), 2.03-2.12 (2 H, m, Cyc-H), 2.35-2.42 (1 H, m, H-7), 3.16-3.23 (1 H, dt, $J = 5.0$ & 12.5 Hz), 6.35 (1 H, br s, N-H); ^{13}C NMR (100 MHz, CDCl_3) 9.7, 24.4, 24.8, 25.7, 31.2, 40.5, 47.9, 57.4, 182.2; IR (cm^{-1}) 3245 (w), 2930 (m), 2856 (w), 1696 (s), 1449 (w), 1376 (w), 1270 (w), 1101 (w), 755 (w); HRMS required for ($\text{C}_9\text{H}_{16}\text{NO}^+$) 154.1226; found 154.1223.

(3R,3aR,7aS)-3-methyl-hexahydro-1H-indol-2(3H)-one, chiral ((+)-35)

Following general procedure **F**, (*R*)-ethyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)propanoate **((+)-5)** (67.6 mg, 0.29 mmol), gave the crude product which was purified by column chromatography (silica gel, ethyl acetate/hexane,

2/3) afforded the title compound as a white crystalline solid (5.2 mg, 0.03 mmol, 12 %). $[\alpha]_D^{23} +17.7$ ($c = 0.1$, CHCl_3); MP – 91.2-91.9 °C; ^1H NMR (400 MHz, CDCl_3) 1.15-1.17 (3 H, d, $J = 7.5$ Hz, H-8), 1.22-1.38 (6 H, m, Cyc-H), 1.83-1.89 (3 H, m, Cyc-H), 1.98-2.08 (2 H, m, H-7 & Cyc-H), 2.96-3.01 (1 H, dt, $J = 5.0$ & 12.5 Hz), 5.79 (1 H, br s, N-H); ^{13}C NMR (100 MHz, CDCl_3) 12.5, 24.5, 26.0, 27.4, 30.8, 42.6, 52.6, 58.6, 180.7; IR (cm^{-1}) 3243 (m), 2926 (s) < 2862 (m), 2364 (m), 1707 (s), 1655 (s), 1381 (m), 1260 (s), 1075 (s), 867 (w), 800 (s); HRMS required for ($\text{C}_9\text{H}_{16}\text{NO}^+$) 154.1226; found 154.1224.

Determination of absolute configuration was by nitro reduction and cyclisation to the lactam and ^1H NMR analysis compared to literature values. Kojima, M.; Tomioka, Y.; *Chem. Pharm. Bull.*; **1976**, *24*, 1613. Conformation of relative configuration of this lactam was determined by x-ray crystallography (see page S87).

(3aR,7aS)-3-benzyl-hexahydro-1H-indol-2(3H)-one, racemic ((±)-36)

Following general procedure **F**, racemic ethyl 2-(2-nitrocyclohexyl)-3-phenylpropanoate **((±)-6)** (77.7 mg, 0.25 mmol), gave the crude product which was purified by column chromatography (silica gel, ethyl

acetate/hexane, 2/3) afforded the title compound as a white crystalline solid (20.6 mg, 0.09 mmol, 36 %). MP – 102.8-103.2 °C; ^1H NMR (400 MHz, CDCl_3) 0.93-1.40 (6 H, m, Cyc-H), 1.55-2.01 (3 H, m, Cyc-H), 2.26-2.32 (1 H, m, Cyc-H), 2.64-2.91 (2 H, m, Cyc-H), 3.14-3.18 (1 H, dd, $J = 4$ & 7.5 Hz, H-1), 5.92 (1 H, br s, N-H), 7.10-7.26 (5 H, m, H-9); ^{13}C NMR (100 MHz, CDCl_3) 24.3, 24.3, 25.7, 25.9, 26.1, 27.8, 30.7, 31.9, 34.7, 48.5, 49.0, 50.2, 57.7, 58.5, 126.1, 128.3,

128.4, 128.9, 129.2, 139.7, 179.4; IR (cm⁻¹) 3273 (m), 2929 (s), 2857 (m), 2375 (w), 1699 (s), 1437 (w), 1381 (w), 1275 (w), 1099 (w), 749 (w), 700 (w); HRMS required for (C₁₅H₂₀NO⁺) 230.1539; found 230.1539.

(3*R*,3*aR*,7*aS*)-3-benzyl-hexahydro-1*H*-indol-2(3*H*)-one, chiral ((-)-36)

Following general procedure **F**, (*R*)-Ethyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)-3-phenylpropanoate **(+)-6** (50.0 mg, 0.16 mmol), gave the crude product which was purified by column chromatography (silica gel, ethyl acetate/hexane, 2/3) afforded the title compound as a white crystalline solid (10.7 mg, 0.05 mmol, 29 %). [α]_D²³ -5.7 (*c* = 0.4, CHCl₃); MP – 102.5-103.1 °C; ¹H NMR (400 MHz, CDCl₃) 0.98-1.09 (1 H, m, Cyc-H), 1.13-1.36 (3 H, m, Cyc-H), 1.35-1.47 (2 H, m, Cyc-H), 1.63-1.66 (1 H, m, Cyc-H), 1.74-1.77 (1 H, m, Cyc-H), 1.94-1.98 (1 H, m, Cyc-H), 2.33-2.39 (1 H, m, H-7), 2.72-2.77 (1 H, dd, *J* = 7.5 & 12.5 Hz, H-8), 2.92-2.98 (1 H, dt, *J* = 5.0 & 12.5 Hz, H-1), 3.21-3.25 (1 H, dd, *J* = 5.0 & 12.5 Hz, H-8); ¹³C NMR (100 MHz, CDCl₃) 24.3, 25.7, 27.9, 30.7, 34.7, 49.0, 50.2, 58.5, 126.1, 128.4, 129.2, 139.7, 179.3; IR (cm⁻¹) 3273 (m), 2929 (s), 2857 (m), 2375 (w), 1699 (s), 1437 (w), 1381 (w), 1275 (w), 1099 (w), 749 (w), 700 (w); HRMS required for (C₁₅H₂₀NO⁺) 230.1539; found 230.1540.

Ethyl 2-((1*R*,2*S*)-2-aminocyclohexyl)acetate (37)

To a solution of ethyl 2-(2-nitrocyclohexyl)acetate (100.0 mg, 0.46 mmol) in ethanol (8 mL) was added Raney Nickel (one spatula), the solution was hydrogenated until TLC showed the reaction was complete. The reaction mixture was filtered through a pad of Celite, concentrated under reduced pressure and purified by column chromatography (silica gel, methanol/dichloromethane, 1/19) the title compound as a yellow oil (43.7 mg, 0.25 mmol, 54 %). ¹H NMR (400 MHz, CDCl₃) 1.01-1.08 (1 H, m, Cyc-H), 1.16-1.34 (1

H, m, Cyc-H), 1.24-1.27 (3 H, t, $J = 7.5$ Hz, H-10), 1.41-1.46 (1 H, m Cyc-H), 1.55-1.79 (3 H, m, Cyc-H), 1.87-1.90 (1 H, m, Cyc-H), 2.06-2.45 (4 H, m, H-7 & Cyc-H), 2.66-2.71 (1 H, dd, $J = 2.5$ & 10 Hz, H-1), 4.10-4.16 (2 H, q, $J = 7.5$ Hz, H-9); ^{13}C NMR (100 MHz, CDCl_3) 14.2, 25.5, 25.7, 31.7, 36.8, 38.7, 42.5, 54.7, 60.2, 173.5; IR (cm^{-1}) 3367 (m), 2925 (s), 2854 (m), 1729 (s), 1576 (w), 1447 (m), 1370 (m), 1288 (m), 1239 (m), 1029 (m), 933 (w), 859 (w); HRMS required for ($\text{C}_{10}\text{H}_{20}\text{NO}_2^+$) 186.1489; found 186.1485.

Ethyl 2-((1*R*,2*S*)-2-((*S*)-2-(benzyloxycarbonyl)-3-methylbutanamido)cyclohexyl)acetate ((-)-

38)

To a solution of ethyl 2-((1*R*,2*S*)-2-aminocyclohexyl)acetate **37** (43.7 mg, 0.25 mmol) in dichloromethane (5 mL) was added hydroxybenzotriazole (40.5 mg, 0.30 mmol) and carbobenzyloxy-L-valine (75.4 mg, 0.30 mmol), this solution was cooled to 0 °C and stirred for 10 minutes before the addition of dicyclohexylcarbodiimide (72.0 mg, 0.35 mmol). This solution was left to warm to room temperature over night. The solution was filtered through a pad of celite and concentrated under reduced pressure to afford the crude product as a light yellow oil. Purification by column chromatography (silica gel, ethyl acetate/hexane, 3/7) the title compound as a crystalline solid (80.6 mg, 84 %, 0.21 mmol). $[\alpha]_D^{23} -15.4$ ($c = 0.5$, CHCl_3); MP – 147.8-148.2 °C; ^1H NMR (400 MHz, CDCl_3) 0.87-0.89 (3 H, d, $J = 7.5$ Hz, H-6 or 7), 0.93-0.95 (3 H, d, $J = \text{H-6 or H-7}$), 1.10-1.36 (6 H, m, H-18 & Cyc-H), 1.54-1.82 (4 H, m, Cyc-H), 1.93-1.96 (1 H, m, Cyc-H), 2.04-2.14 (2 H, m, H-5 & Cyc-H), 2.30-2.49 (1 H, m, H-4), 3.48-3.78 (2 H, m, H-15), 3.94-3.98 (1 H, m, H-17), 4.06-4.12 (2 H, m, H-9 & H-17), 5.06-5.12 (2 H, m, H-2), 5.48-5.60 (1 H, m, N-H), 6.35-6.37 (1 H, m, N-H), 7.28-7.40 (5 H, m, H-1); ^{13}C NMR (100 MHz, CDCl_3) 14.2, 17.5, 17.7, 19.2, 19.4, 25.1, 25.4, 30.7, 30.9, 32.1, 33.6, 38.6, 39.2, 48.1, 53.2, 60.4, 60.5, 60.6, 67.0, 128.0, 128.1, 128.5, 136.3, 156.5, 171.0, 172.9, 173.8; IR (cm^{-1}) 3293 (m), 2928 (m), 1724 (m),

1689 (s), 1643 (s), 1534 (s), 1452 (w), 1385 (w), 1340 (w), 1285 (m), 1245 (s), 1177 (w), 1116 (w), 1038 (m), 697 (w); HRMS required for (C₂₃H₃₅N₂O₅⁺) 419.2540; found 419.2536.

(*R*)-2-((1*R*,2*S*)-2-nitrocyclohexyl)propan-1-ol (39**)**

Following general procedure **D**, (*R*)-ethyl 2-((1*R*,2*S*)-2-nitrocyclohexyl)propanoate **(+)-5** (50.0 mg, 0.22 mmol) gave the crude product which was purified by column chromatography (silica gel, ethyl acetate/hexane, 3/7) to afford the title compound as a clear colourless oil (31.4 mg, 76 %, 0.17 mmol). ¹H NMR (400 MHz, CDCl₃) 0.85-0.87 (3 H, d, *J* = 7.5 Hz, H-8), 1.05-1.15 (1 H, m, Cyc-H), 1.22-1.39 (2 H, m, Cyc-H), 1.58-1.64 (2 H, m, H-7 & Cyc-H), 1.73-1.80 (2 H, m, Cyc-H & O-H), 1.85-1.98 (2 H, m, Cyc-H), 2.24-2.32 (2 H, m, H-6 & Cyc-H), 3.45-3.54 (2 H, m, H-9), 4.43-4.50 (1 H, dt, *J* = 5.0 & 12.5 Hz, H-1); ¹³C NMR (100 MHz, CDCl₃) 10.5, 14.8, 23.4, 24.5, 24.7, 25.2, 32.3, 32.8, 35.6, 36.1, 41.1, 64.8, 65.6, 88.7; IR (cm⁻¹) 3368 (m), 2938 (s), 2359 (w), 1547 (s), 1450 (m), 1376 (m), 1248 (w), 1038 (m), 894 (w), 734 (m), 668 (w).

(*R*)-2-((1*R*,2*S*)-2-nitrocyclohexyl)propanoic acid (40**)**

To a solution of (*R*)-2-((1*R*,2*S*)-2-nitrocyclohexyl)propan-1-ol **39** (30.0 mg, 0.16 mmol) in acetone (2 mL) at 0 °C was added Jones reagent ((1 mL, 0.24 mmol) <http://www.organic-chemistry.org/chemicals/oxidations/jones-reagent.shtm>).

This solution was stirred overnight while warming to room temperature, excess isopropanol was added and the mixture was stirred for 10 minutes. The mixture was filtered, diluted with hydrochloric acid (2 M, 1 mL) and extracted with diethyl ether (5 mL). The aqueous layer was washed with diethyl ether (3 x 5 mL), the combined organic layers were washed with brine (15 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product. Purification by column chromatography (silica gel, ethyl acetate/hexane, 2/3) afforded the title compound as a clear colourless oil (29.0 mg, 90 %, 0.14 mmol). ¹H NMR (400 MHz,

CDCl₃) 1.13-1.15 (3 H, d, $J = 7.5$ Hz, H-8), 1.24-1.40 (3 H, m, Cyc-H), 1.72-1.80 (2 H, m, Cyc-H), 1.85-2.01 (2 H, m, Cyc-H), 2.27-2.31 (1 H, m, Cyc-H), 2.50-2.65 (2 H, m, H-7 & Cyc-H), 4.40-4.46 (1 H, dt, $J = 5.0$ & 12.5 Hz, H-1); ¹³C NMR (100 MHz, CDCl₃) 9.5, 22.7, 24.3, 24.6, 25.0, 31.6, 32.0, 32.8, 39.3, 42.2, 87.7, 180.3; IR (cm⁻¹) 2942 (s), 2864 (m), 1712 (s), 1547 (s), 1453 (m), 1375 (m), 1299 (w), 1242 (m), 1142 (m), 1113 (w), 1053 (w), 988 (w), 900 (w), 863 (w), 735 (w); HRMS required for (C₉H₁₅O₄NNa) 224.0899; found 224.0894.

(S)-Methyl 3-methyl-2-((R)-2-((1R,2S)-2-nitrocyclohexyl)propanamido)butanoate ((+)-41)

To a solution of (*R*)-2-((1*R*,2*S*)-2-nitrocyclohexyl)propanoic acid **40** (35.0 mg, 0.17 mmol) in dichloromethane (6 mL) was added, L-Valine methyl ester hydrochloride (32.1 mg, 0.19 mmol), *N*-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (40.1 mg, 0.21 mmol), diisopropylethyl amine (37 μ L, 0.21 mmol) and dimethyl amino pyridine (2 mg, 0.02 mmol). The mixture was stirred for 24 hours, was then acidified with aqueous sodium hydrogen sulphate extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate (20 mL) and brine (20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give the crude product. Purification by column chromatography (silica gel, ethyl acetate/hexane, 1/4) gave the title compound as a clear colourless oil (11.9 mg, 22 %, 0.04 mmol). $[\alpha]_D^{23} +6.0$ ($c = 0.4$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) 0.91-0.95 (6 H, dd, $J = 7.5$ & 12.0 Hz, H-12 & H-13), 1.10-1.12 (3 H, d, $J = 7.5$ Hz, H-8), 1.22-1.33 (3 H, m, Cyc-H), 1.75-1.77 (1 H, m, Cyc-H), 1.84-1.93 (3 H, m, H-6 & Cyc-H), 2.14-2.21 (1 H, m, H-11), 2.28-2.42 (3 H, m, H-7 & Cyc-H), 3.73 (3 H, s, H-15), 4.42-4.49 (1 H, dt, $J = 5.0$ & 12.5 Hz, H-1), 4.53-4.56 (1 H, dd, $J = 5.0$ & 7.5 Hz, H-10), 5.91-5.93 (1 H, m, N-H); ¹³C NMR (100 MHz, CDCl₃) 10.2, 17.8, 19.0, 24.3, 24.6, 24.8, 31.2, 32.3, 40.6, 43.9, 40.6, 43.9, 52.2, 56.8, 88.1, 172.4, 173.7; IR (cm⁻¹) 3323 (w), 2939 (m), 2869 (m), 2360 (m), 2340 (w), 1742 (m), 1657 (m), 1546 (s), 1450 (m), 1371 (m),

1308 (w), 1264 (w), 1203 (m), 1154 (m), 897 (w), 734 (w); HRMS required for ($\text{C}_{15}\text{H}_{27}\text{O}_5\text{N}_2^+$)
315.1914; found 315.1913.

NMR Data

Improvement of dr of (+)-2 over time by NMR study

X-Ray Crystal Structure and Associated Data for Compound X

All H atoms were located in difference Fourier maps but were placed geometrically after each cycle of the refinement at a distance of 0.95 Å from the connected atom. Isothermal temperature factors at 1.2 x u iso of the attached atom.

Data collection: *CrysAlis CCD* (Oxford Diffraction, 2006); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2006); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SIR92* (Altomane *et al.*, 1994); program(s) used to refine structure; *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS*.

Formula	C ₉ H ₁₅ N ₁ O ₁
M_r	153.22
Crystal habit	colourless block
Crystal dimensions /mm	0.10 x 0.15 x 0.30
Crystal system	monoclinic
Space group	$P 2_1$
T / K	295(1)
$a / \text{\AA}$	5.3337(3)
$b / \text{\AA}$	8.4781(5)
$c / \text{\AA}$	10.0357(6)
$\alpha / ^\circ$	90
$\beta / ^\circ$	99.050(6)
$\gamma / ^\circ$	90
$V / \text{\AA}^3$	448.16(5)
Z	2
$\lambda / \text{\AA}$	0.71073
μ / mm^{-1}	0.578
$\rho_{\text{calc}} / \text{Mg m}^{-3}$	1.135
$R(F), {}_wR(F)$	0.0321, 0.0376

asymmetric unit with ellipsoids drawn at 50% probability

view along *a* axis showing hydrogen bonding interactions (as dotted lines) between N1 and O11 of neighbouring molecules