Synthesis of Pyroglutamic Acid Derivatives via Double Michael Reactions of Alkynones

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Supporting Information

Contents	Page
General Information	S1
Preparation of Alkynones	S2
Preparation of Tethered Diacids	S3
Double Michael Reactions	S4
Preparation of 19–22	S9
Stereochemical Determinations	S12
NMR Spectra of New Compounds	S13

General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH₂Cl₂ and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.¹ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra

1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl_3 . ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl_3 at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl_3 at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135° . ^{19}F NMR spectra were recorded on a Bruker ARX250 (235 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) of CFCl_3 . High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer using the fast atom bombardment (FAB) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound.

Preparation of Alkynones

The known alkynones **3a**,² **3b**,³ **3c**,⁴ **3d**,⁵ **3e**,⁶ **3f**,² and **3g**⁷ were all prepared by the addition of ethynyl magnesium bromide to $\text{Ar}-\text{CHO}$ the appropriate aldehyde, followed by oxidation of the resulting propargylic alcohol with activated manganese dioxide.

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7. Alvarez-Ibarra, C.; Csáky, A. G.; Martín Ortega, E.; Jesús de la Morena, M.; Quiroga, M. L. *Tetrahedron Lett.* **1997**, 38, 4501–4052.

Preparation of Tethered Diacids

Diethyl *N*-(2-carbethoxyacetyl)-*N*-(4-methoxyphenyl)aminomalonate (**7a**)

To a vigorously stirred mixture of the amine **23**⁸ (1.00 g, 3.56 mmol) in CH₂Cl₂ (4 mL) and saturated aqueous Na₂CO₃ solution (4 mL) at room temperature was added ethyl malonyl chloride (0.61 mL, 4.47 mmol) in one portion. The mixture was stirred for 1 h and then partitioned between saturated aqueous NaHCO₃ solution (30 mL) and CH₂Cl₂ (30 mL). The aqueous layer was separated and extracted with CH₂Cl₂ solution (3 x 50 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo* to leave the *amide* **7a** (1.39 g, 98%) as a brown oil. IR (film) 2983, 2938, 2840, 1742 (C=O), 1672 (C=O), 1510, 1250, 1034, 843 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.41 (2H, dm, *J* = 8.9 Hz, ArH), 6.88 (2H, d, *J* = 8.9 Hz, ArH), 5.55 (1H, s, CHN), 4.23-4.09 (6H, m, 3 x CO₂CH₂CH₃), 3.82 (3H, s, OCH₃), 3.24 (2H, s, CH₂C=O), 1.29-1.14 (9H, m, 3 x CO₂CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 166.9 (2 x C), 165.6 (2 x C), 159.9 (C), 131.9 (C), 130.7 (2 x CH), 114.5 (2 x CH), 64.3 (CH), 62.0 (2 x CH₂), 61.2 (CH₂), 55.4 (CH₃), 41.4 (CH₂), 14.0 (CH₃), 13.8 (2 x CH₃); HRMS (ES) Exact mass calcd for C₁₉H₂₆NO₈ [M+H]⁺: 395.1653, found: 395.1654.

Dimethyl *N*-(2-carbethoxyacetyl)-*N*-(4-methoxyphenyl)aminomalonate (**7b**)

To a vigorously stirred mixture of the amine **24** (3.00 g, 11.8 mmol)⁹ in CH₂Cl₂ (11 mL) and saturated aqueous Na₂CO₃ solution (11 mL) at room temperature was added methyl malonyl chloride (1.57 mL, 14.2 mmol) over 1 min. The mixture was stirred for 4 h, and a further portion of methyl malonyl chloride (0.65 mmol, 5.92 mmol) was added. After stirring for another 1 h, the reaction was partitioned between saturated aqueous NaHCO₃ solution (20 mL) and CH₂Cl₂ (20 mL). The aqueous layer was separated and extracted with CH₂Cl₂ solution (3 x 50 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo* to leave the *amide* **7b** (4.00 g, 96%) as a brown oil. IR (film) 3004, 2954, 2843, 1747 (C=O), 1671 (C=O), 1509, 1436, 1249, 1218, 1167; ¹H NMR (360 MHz, CDCl₃) δ 7.38 (2H, dm, *J* = 8.3 Hz, ArH), 6.89 (2H, dm, *J* = 8.3 Hz, ArH), 5.54 (1H, s, CHN), 3.82 (3H, s,

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9. Tombor, Z.; Greff, Z.; Nyitrai, J.; Kajtár-Peredy, M. *Liebigs Ann. Org. Bioorg. Chem.* **1995**, *5*, 825–836.

OCH₃), 3.72 (6H, s, 2 x OCH₃), 3.69 (3H, s, OCH₃), 3.26 (2H, s, CH₂C=O); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.3 (C), 166.8 (C), 165.9 (2 x C), 159.9 (C), 131.8 (C), 130.4 (2 x CH), 114.6 (2 x CH), 64.1 (CH), 55.4 (CH₃), 52.8 (2 x CH₃), 52.3 (CH₃), 41.1 (CH₂); HRMS (ES) Exact mass calcd for C₁₆H₂₀NO₈ [M+H]⁺: 353.1183, found: 353.1183.

Double Michael Reactions: General Procedure

To a stirred solution of the appropriate tethered diacid (0.20 mmol), KO^tBu (4.7 mg, 0.04 mmol) and the appropriate metal salt (0.04 mmol) in CH₂Cl₂ (0.5 mL) at room temperature was added a solution of the appropriate alkynone (0.22 mmol) in CH₂Cl₂ (0.5 mL) *via* cannula dropwise over 1 min. The reaction was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the double Michael product.

(±)-(3R,4R)-3,5,5-Tricarbethoxy-1-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)pyrrolidin-2-one (8). The title compound was prepared according to the General Procedure from tethered diacid **7a** (79 mg, 0.20 mmol), alkynone **3a** (29 mg, 0.22 mmol) and Ni(acac)₂ (10.8 mg, 0.04 mmol) and purified by column chromatography (20:1 CH₂Cl₂/Et₂O) to give a yellow oil (80 mg, 76%) as an 18:1 inseparable mixture of diastereomers.

Trituration with Et₂O, followed by recrystallization from Et₂O/hexane gave colorless crystals suitable for X-ray diffraction. m.p 101–102 °C; IR (film) 3047, 2980, 1733 (C=O), 1713 (C=O), 1674 (C=O), 1509, 1249, 1053, 803, 778 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.97-7.95 (2H, m, ArH), 7.63-7.57 (1H, m, ArH), 7.51-7.47 (2H, m, ArH), 7.16 (2H, d, *J* = 8.9 Hz, ArH), 6.87 (2H, d, *J* = 8.9 Hz, ArH), 4.37-4.24 (4H, m, 2 x OCH₂CH₃), 4.18-4.06 (3H, m, OCH₂CH₃ and CH₂CH), 3.80 (3H, s, OCH₃), 3.64 (1H, d, *J* = 11.3 Hz, CHC=O), 3.61 (1H, dd, *J* = 16.7, 4.7 Hz, CH₂CH), 3.02 (1H, dd, *J* = 16.7, 9.1 Hz, CH₂CH), 1.31-1.26 (6H, m, 2 x OCH₂CH₃), 1.06 (3H, t, *J* = 7.0 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 196.4 (C), 170.1 (C), 168.4 (C), 167.9 (C), 166.1 (C), 159.2 (C), 136.1 (C), 133.5 (CH), 129.3 (2 x CH), 129.1 (C), 128.7 (2 x CH), 128.1 (2 x CH), 114.0 (2 x CH), 75.4 (C), 62.8 (CH₂), 62.4 (CH₂), 61.9 (CH₂), 55.4 (CH₃), 52.7 (CH), 40.3 (CH), 39.1 (CH₂), 14.0 (CH₃), 14.0 (CH₃), 13.6 (CH₃); HRMS (ES) Exact mass calcd. for C₂₈H₃₂NO₉ [M+H]⁺: 526.2072, found: 526.2069.

(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-4-[2-(4-chlorophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (9). The title compound was prepared according to the General Procedure from tethered diacid **7a** (79 mg, 0.20 mmol), alkynone **3b** (36 mg, 0.22 mmol) and Mg(OTf)₂ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH₂Cl₂/Et₂O) to give a yellow oil (68 mg, 61%) as a 14:1 inseparable mixture of diastereomers. IR (film) 2983, 2940, 2841, 1743 (C=O), 1673 (C=O), 1510, 1250, 1035, 844 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.91 (2H, dm, *J* = 8.5 Hz, ArH), 7.46 (2H, dm, *J* = 8.5 Hz, ArH), 7.15 (2H, dm, *J* = 9.0 Hz, ArH), 6.87 (2H, dm, *J* = 9.0 Hz, ArH), 4.42-4.25 (4H, m, 2 x OCH₂CH₃), 4.21-4.07 (3H, m, OCH₂CH₃ and CH₂CH), 3.79 (3H, s, OCH₃), 3.63 (1H, d, *J* = 11.4 Hz, CHC=O), 3.58 (1H, dd, *J* = 16.3, 4.7 Hz, CH₂CH), 2.93 (1H, dd, *J* = 16.4, 9.2, CH₂CH), 1.29 (3H, t, *J* = 7.1 Hz, OCH₂CH₃), 1.28 (3H, t, *J* = 7.1 Hz, OCH₂CH₃), 1.05 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 195.4 (C), 170.0 (C), 168.4 (C), 167.9 (C), 166.1 (C), 159.2 (C), 140.0 (C), 134.4 (C), 129.5 (2 x CH), 129.3 (2 x CH), 129.0 (2 x CH and C), 114.1 (2 x CH), 75.3 (C), 62.9 (CH₂), 62.5 (CH₂), 61.9 (CH₂), 55.4 (CH₃), 52.5 (CH), 40.3 (CH), 39.1 (CH₂), 14.1 (CH₃), 14.0 (CH₃), 13.5 (CH₃); HRMS (ES) Exact mass calcd. for C₂₈H₃₁ClNO₉ [M+H]⁺: 560.01682, found: 560.1683.

(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-1-(4-methoxyphenyl)-4-[2-(4-nitrophenyl)-2-oxoethyl]pyrrolidin-2-one (10). The title compound was prepared according to the General Procedure from tethered diacid **7a** (79 mg, 0.20 mmol), alkynone **3c** (39 mg, 0.22 mmol) and Ni(acac)₂ (10.8 mg, 0.04 mmol) and purified by column chromatography (25% EtOAc/petrol) to give a yellow oil (88 mg, 77%).

IR (film) 2936, 2849, 1734 (C=O), 1717 (C=O), 1604, 1526, 1511, 1348, 1249, 1223, 1026 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.35 (2H, dm, *J* = 8.9 Hz, ArH), 8.15 (2H, dm, *J* = 8.9 Hz, ArH), 7.14 (2H, dm, *J* = 9.0 Hz, ArH), 6.88 (2H, dm, *J* = 9.0 Hz, ArH), 4.39-4.23 (4H, m, 2 x OCH₂CH₃), 4.18-4.05 (3H, m, OCH₂CH₃ and CH₂CH), 3.80 (3H, s, OCH₃), 3.66 (1H, dd, *J* = 16.3, 4.6 Hz, CH₂CH), 3.64 (1H, d, *J* = 11.4 Hz, CHC=O), 2.97 (1H, dd, *J* = 16.3, 9.2 Hz, CH₂CH), 1.31 (3H, t, *J* = 7.1 Hz, OCH₂CH₃), 1.30 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 1.04 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 195.4 (C), 169.6 (C), 168.2 (C), 167.8 (C), 166.0 (C), 159.3 (C), 150.5 (C), 140.3 (C), 129.3 (2 x CH), 129.2 (2 x CH), 128.9 (C), 123.9 (2 x CH), 114.1 (2 x CH), 75.2 (C), 63.0 (CH₂), 62.6 (CH₂), 62.0 (CH₂), 55.4 (CH₃), 52.2 (CH), 40.2 (CH), 39.6 (CH₂), 14.1 (CH₃), 14.0 (CH₃), 13.5 (CH₃); HRMS (ES) Exact mass calcd. for C₂₈H₃₁N₂O₁₁ [M+H]⁺: 571.1922, found: 571.1923.

(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-1-(4-methoxyphenyl)-4-[2-(4-methoxyphenyl)-2-oxoethyl]pyrrolidin-2-one (11).

The title compound was prepared according to the General Procedure from tethered diacid **7a** (79 mg, 0.20 mmol), alkynone **3d** (35 mg, 0.22 mmol) and Mg(OTf)₂ (12.9 mg, 0.04 mmol) and purified by column chromatography (25% EtOAc/petrol) to give a yellow oil (77 mg, 69%) as a 10:1 inseparable mixture of diastereomers. IR (film) 2981, 2937, 2840, 1734 (C=O), 1717 (C=O), 1679 (C=O), 1600, 1511, 1249, 1171, 1026 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.94 (2H, dm, *J* = 9.0 Hz, ArH), 7.15 (2H, dm, *J* = 9.1 Hz, ArH), 6.95 (2H, dm, *J* = 9.0 Hz, ArH), 6.87 (2H, dm, *J* = 9.1 Hz, ArH), 4.39-4.22 (4H, m, 2 x OCH₂CH₃), 4.18-4.03 (3H, m, OCH₂CH₃ and CH₂CH), 3.88 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.64 (1H, d, *J* = 11.3 Hz, CHC=O), 3.57 (1H, dd, *J* = 16.3, 4.6 Hz, CH₂CH), 2.91 (1H, dd, *J* = 16.3, 9.3 Hz, CH₂CH), 1.28 (3H, t, *J* = 7.1 Hz, OCH₂CH₃), 1.27 (3H, t, *J* = 7.1 Hz, OCH₂CH₃), 1.05 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 194.9 (C), 170.2 (C), 168.4 (C), 167.9 (C), 166.1 (C), 163.7 (C), 159.2 (C), 130.4 (2 x CH), 129.3 (2 x CH), 129.2 (2 x C), 114.0 (2 x CH), 113.8 (2 x CH), 75.4 (C), 62.8 (CH₂), 62.4 (CH₂), 61.8 (CH₂), 55.5 (CH₃), 55.4 (CH₃), 52.7 (CH), 40.5 (CH), 38.7 (CH₂), 14.1 (CH₃), 14.0 (CH₃), 13.5 (CH₃); HRMS (ES) Exact mass calcd. for C₂₉H₃₄NO₁₀ [M+H]⁺: 556.2177, found: 556.2175.

(±)-(3*R*,4*R*)-3,5,5-Tricarbethoxy-4-[2-(4-fluorophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (12).

The title compound was prepared according to the General Procedure from tethered diacid **7a** (79 mg, 0.20 mmol), alkynone **3e** (30 mg, 0.22 mmol) and Mg(OTf)₂ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH₂Cl₂/Et₂O) to give a yellow oil (81 mg, 75%) as a 15:1 inseparable mixture of diastereomers. IR (film) 2982, 2937, 2840, 1735 (C=O), 1718 (C=O), 1691 (C=O), 1597, 1511, 1249, 1230, 1158 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.02-7.98 (2H, m, ArH), 7.17 (2H, dm, *J* = 8.7 Hz, ArH), 7.15 (2H, dm, *J* = 9.0 Hz, ArH), 6.87 (2H, d, *J* = 9.0 Hz, ArH), 4.39-4.21 (4H, m, 2 x OCH₂CH₃), 4.17-4.03 (3H, m, OCH₂CH₃ and CH₂CH), 3.80 (3H, s, OCH₃), 3.63 (2H, d, *J* = 11.4 Hz, CHC=O), 3.58 (1H, dd, *J* = 16.4, 4.6 Hz, CH₂CH), 2.93 (1H, dd, *J* = 16.4, 9.3 Hz, CH₂CH), 1.29 (3H, t, *J* = 7.1 Hz, OCH₂CH₃), 1.28 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 1.05 (3H, t, *J* = 7.2 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 195.0 (C), 170.0 (C), 168.3 (C), 167.9 (C), 166.0 (C), 165.9 (C, d, *J*_F = 255.0 Hz), 159.2 (C), 132.5 (C, d, *J*_F = 2.9 Hz), 130.8 (2 x CH, d, *J*_F = 9.4 Hz), 129.3 (2 x CH), 129.0 (C), 115.8 (2 x CH, d, *J*_F = 21.9 Hz), 114.0 (2 x CH), 75.3 (C), 62.4 (CH₂), 62.8 (CH₂), 61.9 (CH₂), 55.3 (CH₃), 52.5 (CH), 40.3 (CH), 39.0 (CH₂), 14.0 (CH₃), 13.9 (CH₃),

13.5 (CH₃); ¹⁹F NMR (235 MHz, CDCl₃) δ -104.6; HRMS (ES) Exact mass calcd. for C₂₈H₃₁FNO₉ [M+H]⁺: 544.1977, found: 544.1976.

(±)-(3R,4R)-3,5,5-Tricarbethoxy-1-(4-methoxyphenyl)-4-[2-(2-naphthyl)-2-oxoethyl]pyrrolidin-2-one (13). The title compound was prepared according to the General Procedure from tethered diacid **7a** (79 mg, 0.20 mmol), alkynone **3f** (40 mg, 0.22 mmol) and Mg(OTf)₂ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH₂Cl₂/Et₂O) to give a yellow oil (79 mg, 69%) as an 8:1

inseparable mixture of diastereomers. IR (film) 2981, 2935, 2848, 1735 (C=O), 1716 (C=O), 1687 (C=O), 1511, 1249, 1214, 1025 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.66-8.63 (1H, m, ArH), 8.04-8.02 (1H, m, ArH), 7.96-7.94 (1H, m, ArH), 7.90-7.88 (1H, m, ArH), 7.64-7.51 (3H, m, ArH), 7.18 (2H, dm, *J* = 9.0 Hz, ArH), 6.88 (2H, dm, *J* = 9.0 Hz, ArH), 4.40-4.09 (7H, m, 3 x OCH₂CH₃ and CH₂CH), 3.80 (3H, s, OCH₃), 3.68 (1H, dd, *J* = 17.0, 4.9 Hz, CH₂CH), 3.67 (1H, d, *J* = 11.3 Hz, CHC=O), 3.16 (1H, dd, *J* = 17.0, 8.9 Hz, CH₂CH), 1.29 (3H, t, *J* = 7.1 Hz, OCH₂CH₃), 1.25 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 1.09 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 200.0 (C), 170.1 (C), 168.5 (C), 168.0 (C), 166.1 (C), 159.2 (C), 134.5 (C), 134.0 (C), 133.3 (CH), 130.1 (C), 129.2 (2 x CH and CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 126.6 (CH), 125.8 (CH), 124.2 (CH), 114.0 (2 x CH), 73.4 (C), 62.8 (CH₂), 62.4 (CH₂), 61.9 (CH₂), 55.3 (CH₃), 52.9 (CH), 42.3 (CH₂), 40.7 (CH), 14.0 (2 x CH₃), 13.6 (CH₃); HRMS (ES) Exact mass calcd. for C₃₂H₃₄NO₉ [M+H]⁺: 576.2228, found: 576.2231.

(±)-(3R,4R)-3,5,5-Tricarbomethoxy-1-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)pyrrolidin-2-one (14). The title compound was prepared according to the General Procedure from tethered diacid **7b** (71 mg, 0.20 mmol), alkynone **3a** (29 mg, 0.22 mmol) and Mg(OTf)₂ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH₂Cl₂/Et₂O) to give a yellow oil (58 mg, 60%) as a 10:1 inseparable mixture of diastereomers.

IR (film) 2954, 1740 (C=O), 1716 (C=O), 1687 (C=O), 1511, 1435, 1248, 830 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.96-7.93 (2H, m, ArH), 7.63-7.57 (1H, m, ArH), 7.51-7.47 (2H, m, ArH), 7.15 (2H, dm, *J* = 8.9 Hz, ArH), 6.89 (2H, dm, *J* = 8.9 Hz, ArH), 4.10 (1H, ddd, *J* = 11.3, 8.4, 5.1 Hz, CH₂CH), 3.67 (1H, d, *J* = 11.3 Hz, CH=O), 3.83 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.69 (3H, s, OCH₃), 3.55 (1H, dd, *J* = 17.2, 5.1 Hz, CH₂CH), 3.07 (1H, dd, *J* = 17.2, 8.4 Hz, CH₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 196.4 (C), 169.9 (C), 168.8 (C), 168. x CH), 128.0 (2 x CH),

125.0 (C), 114.1 (2 x CH), 75.6 (C), 55.3 (CH₃), 53.2 (CH₃), 53.1 (CH₃), 52.8 3 (C), 166.5 (C), 159.3 (C), 136.0 (C), 133.5 (CH), 129.2 (2 x CH), 128.8 (C), 128.7 (2 (CH₃), 52.5 (CH), 40.4 (CH), 38.9 (CH₂); HRMS (ES) Exact mass calcd. for C₂₅H₂₆NO₉ [M+H]⁺: 501.1868, found: 533.1875.

(±)-(3R,4R)-3,5,5-Tricarbomethoxy-4-[2-(4-bromophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (15). The title compound was prepared according to the General Procedure from tethered diacid **7b** (71 mg, 0.20 mmol), alkynone **3f** (46 mg, 0.22 mmol) and Mg(OTf)₂ (12.9 mg, 0.04 mmol) and purified by column chromatography (20:1 CH₂Cl₂/Et₂O) to give a yellow oil (68 mg, 60%) as a 10:1 inseparable mixture of diastereomers.

IR (film) 2953, 2924, 2844, 1740 (C=O), 1716 (C=O), 1690, 1585, 1511, 1249 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.82 (2H, d, *J* = 8.5 Hz, ArH), 7.64 (2H, d, *J* = 8.5 Hz, ArH), 7.14 (2H, dm, *J* = 9.0 Hz, ArH), 6.88 (2H, dm, *J* = 9.0 Hz, ArH), 4.08 (1H, ddd, *J* = 11.4, 8.6, 5.1 Hz, CH₂CH), 3.83 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.68 (3H, s, OCH₃), 3.67 (1H, d, *J* = 11.4 Hz, CH=O), 3.51 (1H, dd, *J* = 17.0, 5.1 Hz, CH₂CH), 3.00 (1H, dd, *J* = 17.0, 8.6 Hz, CH₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 195.6 (C), 169.8 (C), 168.8 (C), 168.3 (C), 166.6 (C), 159.4 (C), 134.7 (C), 132.1 (2 x CH), 129.6 (2 x CH), 129.3 (2 x CH), 128.9 (C), 128.8 (C), 114.2 (2 x CH), 75.5 (C), 55.4 (CH₃), 53.3 (CH₃), 53.2 (CH₃), 53.0 (CH₃), 52.4 (CH), 40.4 (CH), 38.9 (CH₂); HRMS (ES) Exact mass calcd. for C₂₅H₂₅BrNO₉ [M+H]⁺: 561.0707, found: 561.0706.

(±)-(3R,4R)-3,5,5-Tricarbomethoxy-4-[2-(4-fluorophenyl)-2-oxoethyl]-1-(4-methoxyphenyl)pyrrolidin-2-one (16). The title compound was prepared according to the General Procedure from tethered diacid **7b** (71 mg, 0.20 mmol), alkynone **3e** (30 mg, 0.22 mmol) and Ni(acac)₂ (10.8 mg, 0.04 mmol) and purified by column chromatography (20:1 CH₂Cl₂/Et₂O) to give a yellow solid (59 mg, 59%) as a 10:1 inseparable mixture of diastereomers.

m.p. 146–147 °C; IR (CHCl₃) 2955, 2924, 2847, 1741 (C=O), 1716 (C=O), 1689 (C=O), 1597, 1510, 1249, 1231, 1158 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.00–7.96 (2H, m, ArH), 7.18–7.13 (4H, m, ArH), 6.88 (2H, d, *J* = 9.0 Hz, ArH), 4.08 (1H, ddd, *J* = 11.3, 8.6, 5.1 Hz, CH₂CH), 3.82 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.80 (3H, s, OCH₃), 3.67 (1H, d, *J* = 11.3 Hz, CHC=O), 3.52 (1H, dd, *J* = 16.9, 5.1 Hz, CH₂CH), 3.01 (1H, dd, *J* = 16.9, 8.6 Hz, CH₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 194.9 (C), 169.8 (C), 168.7 (C), 168.2 (C), 166.6 (C), 165.9 (C, d, *J*_F = 255.5 Hz), 159.3 (C), 132.5 (C, d, *J*_F = 2.8 Hz), 130.8 (2 x CH, d, *J*_F = 9.4 Hz), 129.2 (2 x

CH), 128.8 (C), 115.8 (2 x CH, d, $J_F = 22.0$ Hz), 114.2 (2 x CH), 75.5 (C), 55.3 (CH₃), 53.2 (CH₃), 53.1 (CH₃), 52.9 (CH₃), 52.4 (CH), 40.4 (CH), 38.8 (CH₂); ¹⁹F NMR (235 MHz, CDCl₃) δ -104.4; HRMS (ES) Exact mass calcd. for C₂₅H₂₅FNO₉ [M+H]⁺: 519.1773, found: 533.1777.

(±)-(3*R*,4*R*)-3,5,5-Tricarbomethoxy-1-(4-methoxyphenyl)-4-[2-(1-naphthyl)-2-oxoethyl]pyrrolidin-2-one (17). The title compound was prepared according to the General Procedure from tethered diacid **7b** (71 mg, 0.20 mmol), alkynone **3f** (40 mg, 0.22 mmol) and Ni(acac)₂ (10.8 mg, 0.04 mmol) and purified by column chromatography (20:1 CH₂Cl₂/Et₂O) to give a yellow oil (72 mg, 67%) as a 15:1

inseparable mixture of diastereomers. IR (film) 2935, 2849, 2360, 1739 (C=O), 1715 (C=O), 1607, 1510, 1435, 1364, 1250 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.61 (1H, d, $J = 7.8$ Hz, ArH), 8.04 (1H, d, $J = 8.3$ Hz, ArH), 7.93-7.88 (2H, m, ArH), 7.65-7.51 (3H, m, ArH), 7.17 (2H, d, $J = 9.1$ Hz, ArH), 6.89 (2H, d, $J = 9.1$ Hz, ArH), 4.21 (1H, ddd, $J = 11.3, 8.3, 5.6$ Hz, CH₂CH), 3.84 (3H, s, OCH₃), 3.81 (3H, s, OCH₃), 3.77 (3H, s, OCH₃), 3.72 (3H, s, OCH₃), 3.69 (1H, d, $J = 11.3$ Hz, CHC=O), 3.59 (1H, dd, $J = 17.4, 5.6$ Hz, CH₂CH), 3.23 (1H, dd, $J = 17.4, 8.3$ Hz, CH₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 200.0 (C), 169.8 (C), 168.9 (C), 168.3 (C), 166.6 (C), 159.2 (C), 134.4 (C), 133.9 (C), 133.4 (CH), 130.0 (C), 129.1 (2 x CH), 128.8 (C), 128.4 (CH), 128.2 (CH), 127.9 (CH), 126.6 (CH), 125.7 (CH), 124.2 (CH), 114.2 (2 x CH), 75.6 (C), 55.3 (CH₃), 53.2 (2 x CH₃), 52.9 (CH₃), 52.6 (CH), 42.2 (CH₂), 40.7 (CH); HRMS (ES) Exact mass calcd. for C₂₉H₂₈NO₉ [M+H]⁺: 533.1759, found: 533.1759.

Diethyl *N*-(2-carbethoxy-5-oxohexanoyl)-*N*-(4-methoxyphenyl)aminomalonate (19) and diethyl 2-[*N*-(2-carbethoxyacetyl)-*N*-(4-methoxyphenyl)amino]-2-(3-oxobutyl)malonate (20)

Using Mg(OTf)₂: To a stirred solution of the tethered diacid **7a** (79 mg, 0.20 mmol), KO^tBu (4.7 mg, 0.04 mmol) and Mg(OTf)₂ (12.9 mg, 0.04 mmol) in CH₂Cl₂ (1 mL) at room temperature was added methyl vinyl ketone (20 μ L, 0.22 mmol). The reaction was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane→50% EtOAc/hexane) gave the *Michael adduct* **19** (48 mg, 52%) as a pale yellow oil.

Using Ni(acac)₂: To a stirred solution of the tethered diacid **7a** (79 mg, 0.20 mmol), KO^tBu (4.7 mg, 0.04 mmol) and Ni(acac)₂ (10.8 mg, 0.04 mmol) in CH₂Cl₂ (1 mL) at room temperature was added

methyl vinyl ketone (20 μ L, 0.22 mmol). The reaction was stirred at room temperature for 16 h and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane $\rightarrow$ 50% EtOAc/hexane) gave the *Michael adduct* **19** (10 mg, 11%) as a pale yellow oil followed by the *Michael adduct* **20** (28 mg, 30%) as a pale yellow oil.

Data for **19**:

IR (film) 2983, 2938, 2908, 1741 (C=O), 1716 (C=O), 1668 (C=O), 1509, 1250, 1180, 1031 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.36 (2H, br s, ArH), 6.87 (2H, d, J = 8.3 Hz, ArH), 5.44 (1H, s, NCH), 4.28-4.00 (4H, m, 3 x OCH_2CH_3), 3.81 (3H, s, OCH_3), 3.46 (1H, dd, J = 8.1, 6.3 Hz, CHCH_2), 2.60-2.43 (2H, m, CHCH_2CH_2), 2.12 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.10-2.05 (2H, m, CHCH_2), 1.26 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.25 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.16 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 207.7 (C), 169.6 (C), 169.1 (C), 165.9 (C), 165.4 (C), 159.9 (C), 131.9 (C), 131.2 (CH), 130.3 (CH), 114.5 (2 x CH), 64.9 (CH), 62.0 (2 x CH_2), 61.3 (CH_2), 55.4 (CH_3), 47.6 (CH), 40.1 (CH_2), 29.8 (CH_3), 23.1 (CH_2), 14.0 (CH_3), 13.9 (CH_3), 13.8 (CH_3); HRMS (ES) Exact mass calcd. for $\text{C}_{23}\text{H}_{32}\text{NO}_9$ $[\text{M}+\text{H}]^+$: 466.2072, found: 466.2070.

Data for **20**: IR (film) 2982, 2939, 2841, 1741 (C=O), 1671 (C=O), 1509, 1366, 1248, 1031, 843 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.36 (2H, dm, J = 9.0 Hz, ArH), 6.91 (2H, dm, J = 9.0 Hz, ArH), 4.19 (2H, q, J = 7.2 Hz, OCH_2CH_3), 4.19 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.12 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.83 (3H, s, OCH_3), 3.11 (2H, s, EtO_2CCH_2), 2.63-2.59 (2H, m, $\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 2.17-2.13 (2H, m, $\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 2.06 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 1.28 (6H, t, J = 7.1 Hz, 2 x OCH_2CH_3), 1.21 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 206.6 (C), 167.6 (2 x C), 167.4 (C), 167.0 (C), 160.0 (C), 131.5 (2 x CH), 131.4 (C), 114.6 (2 x CH), 71.2 (C), 62.0 (2 x CH_2), 61.1 (CH_2), 55.5 (CH_3), 42.4 (CH_2), 38.5 (CH_2), 29.9 (CH_3), 28.9 (CH_2), 14.0 (2 x CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd. for $\text{C}_{23}\text{H}_{32}\text{NO}_9$ $[\text{M}+\text{H}]^+$: 466.2072, found: 466.2072.

($\pm$)-(3*R*,4*R*)-4-Benzyl 3,5,5-tricarbethoxy-1-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)pyrrolidin-2-one (21**)**

To a solution of the double Michael product **8** (53 mg, 0.10 mmol) in THF (1 mL) at room temperature was added NaH (60% dispersion in mineral oil, 40 mg, 0.10 mmol) in one portion, followed by BnBr

(18 μ L, 0.15 mmol). The mixture was stirred at room temperature for 5 h, quenched with H₂O (10 mL), and extracted with EtOAc (3 x 10 mL), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane→33% EtOAc/hexane) gave the *benzylated pyrrolidinone 21* (41 mg, 67%) as a yellow oil. IR (film) 2982, 2936, 2904, 1741 (C=O), 1706 (C=O), 1510, 1249, 1070, 1030, 913 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.94-7.91 (2H, m, ArH), 7.59 (1H, t, *J* = 7.4 Hz, ArH), 7.48 (2H, app t, *J* = 7.6 Hz, ArH), 7.32 (5H, br s, ArH), 7.19 (2H, dm, *J* = 8.9 Hz, ArH), 6.83 (2H, dm, *J* = 8.8 Hz, ArH), 4.31-4.25 (2H, m, OCH₂CH₃), 4.15-3.91 (5H, m, 2 x OCH₂CH₃ and CH₂CH), 3.79 (3H, s, OCH₃), 3.64 (1H, dd, *J* = 18.2, 10.8 Hz, CH₂CH), 3.64 (1H, d, *J* = 14.1 Hz, CH₂Ph), 3.24 (1H, d, *J* = 14.1 Hz, CH₂Ph), 3.10 (1H, dd, *J* = 18.2, 4.0 Hz, CH₂CH), 1.35 (3H, t, *J* = 7.2 Hz, OCH₂CH₃), 1.00-0.95 (6H, m, 2 x OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 196.4 (C), 172.0 (C), 169.9 (C), 167.4 (C), 167.1 (C), 159.1 (C), 136.4 (C), 135.4 (C), 133.2 (CH), 131.0 (2 x CH), 130.4 (2 x CH), 129.3 (C), 128.6 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.3 (CH), 113.7 (2 x CH), 75.7 (C), 62.3 (CH₂), 61.9 (CH₂), 61.7 (CH₂), 58.6 (C), 55.3 (CH₃), 40.4 (CH), 37.4 (CH₂), 36.7 (CH₂), 14.1 (CH₃), 13.6 (2 x CH₃); HRMS (ES) Exact mass calcd. for C₃₅H₃₈NO₉ [M+H]⁺: 616.2541, found: 616.2538.

(±)-(4R)-5,5-Dicarbethoxy-1-(4-methoxyphenyl)-4-(2-oxo-2-phenylethyl)pyrrolidin-2-one (22)

A solution of double Michael product **8** (53 mg, 0.10 mmol) in DMF (1 mL) was heated to 110 °C for 72 h. After cooling to room temperature, the mixture was partitioned between H₂O (15 mL) and EtOAc (15 mL). The aqueous layer was separated and extracted with EtOAc (2 x 15 mL), and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/hexane→33% EtOAc/hexane) gave the *decarboxylated pyrrolidinone 22* (27 mg, 60%) as a yellow oil. IR (film) 2981, 2936, 2838, 1730 (C=O), 1687 (C=O), 1511, 1294, 1248, 1031, 690 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.96 (2H, d, *J* = 7.3 Hz, ArH), 7.63-7.59 (1H, m, ArH), 7.52-7.47 (2H, m, ArH), 7.17 (2H, dm, *J* = 8.9 Hz, ArH), 6.88 (2H, dm, *J* = 8.9 Hz, ArH), 4.40-4.26 (2H, m, OCH₂CH₃), 4.19-4.03 (2H, m, OCH₂CH₃), 3.80 (3H, s, OCH₃), 3.80-3.70 (1H, m, CH₂CH), 3.54 (1H, dd, *J* = 17.2, 3.9 Hz, PhCOCH₂), 3.02-2.94 (2H, m, CH₂CON and PhCOCH₂), 2.40 (1H, dd, *J* = 16.7, 11.1 Hz, CH₂CON), 1.30 (3H, t, *J* = 7.1 Hz, OCH₂CH₃), 1.06 (3H, t, *J* = 7.1 Hz, OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 196.4 (C), 172.0 (C), 169.9 (C), 167.4 (C), 167.1 (C), 159.1 (C), 136.4 (C), 135.4 (C), 133.2 (CH), 131.0 (2 x CH), 130.4 (2 x CH), 129.3 (C), 128.6 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.3 (CH), 113.7 (2 x CH), 75.7 (C), 62.3 (CH₂), 61.9 (CH₂), 61.7 (CH₂), 58.6 (C), 55.3 (CH₃), 40.4 (CH), 37.4 (CH₂), 36.7 (CH₂), 14.1 (CH₃), 13.6 (2 x CH₃); HRMS (ES) Exact mass calcd. for C₂₅H₂₆NO₆ [M+H]⁺: 442.1771, found: 442.1768.

OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 196.7 (C), 114.1 (2 x CH), 62.5 (CH₂), 62.3 (CH₂), 60.4 (C), 55.4 (CH₃), 39.8 (CH₂), 36.7 (CH), 35.6 (CH₂), 14.2 (CH₃), 13.6 (CH₃); HRMS (ES) Exact mass calcd. for C₂₅H₂₈NO₇ [M+H]⁺: 454.1860, found: 454.1863.

Stereochemical Determinations

- The relative stereochemistry of **8** was determined by X-ray crystallography. Crystal structure deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 638217
Note – there is a small degree of disorder associated with one of the geminal diester groups (see CIF file for details).

- The relative stereochemistries of the remaining double Michael products **9–17** were assigned by analogy.

NMR Spectra of New Compounds

195.402

169.626

168.236

167.774

166.034

159.316

150.478

140.336

129.316

129.231

128.911

123.924

114.077

77.508

77.000

76.491

75.194

62.967

62.591

62.045

55.372

52.236

40.187

39.617

14.103

14.047

13.513