The Sharpless Asymmetric Aminohydroxylation Reaction: Optimising Ligand/Substrate Control of Regioselectivity for the Synthesis of 3- and 4-Aminosugars

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Electronic Supplementary Information

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General experimental

1. Melting points were determined using a Reichert heating stage with microscope and are uncorrected.

2. Infrared absorption spectra were obtained using a Perkin Elmer 1600 Fourier Transform Infrared spectrometer as a thin film between 0.5 cm sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}) and the appearance of bands are expressed as s = strong and br = broad.

3. ^{1}H Nuclear magnetic resonance spectra were recorded using a Bruker AC200 (200.1 MHz), Bruker AVANCE DPX200 (200 MHz), Bruker AVANCE DPX300 (300.1 MHz), or Bruker DPX400 (400.1 MHz) spectrometer at 300K unless otherwise stated. Spectra were recorded in deuteriochloroform unless otherwise stated. Data is expressed as parts per million downfield shift from tetramethylsilane with either tetramethylsilane or chloroform as an internal standard and is reported as chemical shift (δ), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet with descriptors obs = obscured, br = broad), coupling constant (*J* Hz) and assignment. All multiplicities and coupling constants are apparent.

4. ^{13}C Nuclear magnetic resonance spectra were recorded using a Bruker AC200 (50.3 MHz), Bruker AVANCE DPX200 (50 MHz), Bruker AVANCE DPX300 (75.5 MHz), or Bruker DPX400 (100.4 MHz) spectrometer with complete proton decoupling at 300K unless otherwise stated. Spectra were recorded in deuteriochloroform unless otherwise stated. The chemical shifts are reported relative to chloroform (δ 77.3) and are expressed as chemical shift (δ), where numbers in brackets following the chemical shift refer to the number of carbon atoms contributing to the signal. FIDs were manipulated prior to Fourier transformation applying an exponential line broadening function to improve the signal to noise ratio.

5. Low resolution electron impact mass spectra were recorded on either an AEI model Kratos MS902 double focusing mass spectrometer with an accelerating voltage of 8000V and using electron impact (EI) ionisation mode at 70eV, or a Finnegan PolarisQ ion trap mass spectrometer using electron impact ionisation mode at 40 or 70 eV. High resolution electron impact mass spectra were recorded on a VC Autospec mass spectrometer operating at 70 eV. Low resolution electrospray mass spectra were recorded on a Finnegan LCQ mass spectrometer. High resolution electrospray mass spectra were recorded on a Bruker ApexII Fourier Transform Ion Cyclotron Resonance mass spectrometer with a 7.0 T magnet, fitted with an off-axis Analytica electrospray

source (University of New South Wales, Sydney) or a Finnegan MAT 900XL (University of Queensland, Brisbane). Major fragments are quoted as x (assignment), where x is the mass to charge ratio. High resolution mass spectra were recorded at a nominal resolution of 8000 to 9000.

6. Chiral Analytical High Performance Liquid Chromatography (HPLC) was carried out on a Waters Gradient system consisting of two 510 pumps, a 490E programmable multi-wavelength detector at 220, 254 and 270 nm, a 410 differential refractometer, and a U6K injector. All retention times are reported at 470 nm and calculations were based on peak areas at 470 nm. Data was acquired and processed using Millenium software (Version 3.05.01). Separation was carried out using the indicated solvents on a Daicel Chiralcel OD-H (25 cm x 4.6 mm ID, 5 μm particle size) or a Daicel Chiralpak AD-H (25 cm x 4.6 mm ID, 5 μm particle size) column with a flow rate of 0.5 ml/min.

7. Analytical High Performance Liquid Chromatography (HPLC) was carried out on a Waters Associates system consisting of a 6000A pump, a 440 absorbance detector at 254 nm, an R410 differential refractometer, and a U6K injector. All retention times are reported at 254 nm. Spectra were recorded using a BBC-Metrawatt/Goerz SE 120 chart recorder. Separation was carried out using the indicated solvents on a Jones Chromatography Zorbax Sil column (25 cm x 4.6 mm ID, 5 μm particle size).

8. Preparative High Performance Liquid Chromatography (HPLC) was carried out on a Waters Associates system consisting of a 510EF pump, an Isco 226 absorbance monitor at 254 nm, an R403 differential refractometer, and a U6K injector. All retention times are reported at 254 nm. Spectra were recorded using a BBC-Metrawatt/Goerz SE 120 chart recorder. Separation was carried out using the indicated solvents on an RT1 Zorbax Sil column (25 cm x 21.2 mm ID, 7 μm particle size).

9. Optical rotations α were measured using an Optical Activity PolAAr 2001 Automatic polarimeter with the sodium D line (589 nm) at ambient temperature. Optical rotations were recorded in dichloromethane unless otherwise stated and run in a 0.25 dm cell. Specific rotations $[\alpha]_D$ are expressed in units of dm^{-1} g^{-1} cm^3 and concentrations are reported as *c* g solute/100 cm^3 solution.

10. Analytical thin layer chromatography was performed using aluminium backed pre-coated silica gel plates (Merck Kieselgel 60 F254). Compounds were visualised by short wave ultra-violet fluorescence or by staining with acidified ethanolic solution of anisaldehyde, alkaline potassium permanganate solution or phosphomolybdic acid and ceric sulfate in sulfuric acid.

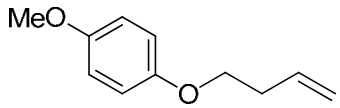
11. Flash chromatography was performed using Merck Kieselgel 60 (230-400 mesh) with the indicated solvents. Solvent compositions are mixed v/v as specified.

12. Reagents were used as received except where there is an indication to the contrary in the experimental text. Solvents and reagents were purified according to the methods of Perrin, Perrin and Amarego.[1] The term "brine" refers to saturated aqueous sodium chloride solution.

13. Reaction temperatures were controlled using dry ice/acetone (-78 °C), ice/water (0 °C) cooling baths, or using a Lauder ETK50 cooler.

Experimental procedures and spectroscopic data

1-But-3-enyloxy-4-methoxy-benzene 24.[2]

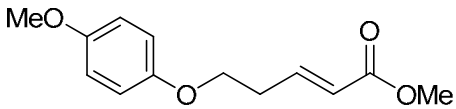


24

General Mitsunobu procedure:[3]

To a stirred solution of 3-buten-1-ol (0.506 g, 7.02 mmol) in tetrahydrofuran (25 ml) at room temperature was added *p*-methoxyphenol (8.60 g, 6.93 mmol, 1.0 eq) and triphenylphosphine (2.36 g, 9.00 mmol, 1.3 eq). Following addition of diethyl azodicarboxylate (1.53 ml, 9.72 mmol, 1.4 eq), the mixture was heated at reflux for 15 minutes then cooled and concentrated to afford a brown oil. Purification by flash chromatography (5% diethyl ether/hexane) afforded pure **24** as a colourless oil (1.21 g, 97%). R_f = 0.24 (5% diethyl ether/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.84 (4H, s, 4 Ar<u>H</u>), 5.86 (1H, ddt, *J* = 17.1, 6.8, 6.8 Hz, C<u>H</u>=CH_2), 5.17-5.01 (2H, m, CH=C<u>H</u>$_2$), 3.92 (2H, t, *J* = 6.7 Hz, OC<u>H</u>$_2$$CH_2$), 3.72 (3H, s, OC<u>H</u>$_3$), 2.47 (2H, ddt, *J* = 6.7, 6.7, 1.3 Hz, OCH_2C<u>H</u>$_2$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 154.3, 153.5, 135.0, 117.3, 116.0 (2C), 115.0 (2C), 68.3, 56.1, 34.2; **IR** (thin film): 1642 (s, C=C), 1510 cm^{-1}.

5-(4-Methoxy-phenoxy)-pent-2-enoic acid methyl ester 9a.[4]



9a

General cross metathesis procedure:[5]

A solution of methyl acrylate (30.3 μl, 0.336 mmol, 1.9 eq) and Grubbs' second generation catalyst (7.50 mg, 0.00883 mmol, 5 mol%) in dichloromethane (1 ml) was stirred at room temperature under a nitrogen atmosphere. 1-but-3-enyloxy-4-methoxy-benzene **24** (31.6 mg, 0.177 mmol) in dichloromethane (0.5 ml + 0.2 ml wash) was added and the mixture was heated at reflux for 3.5 h, then cooled and concentrated. Purification by flash chromatography (8% ethyl acetate/hexane) afforded unsaturated ester **9a** as a clear oil (37.7 mg, 90%). R_f = 0.34 (20% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 7.04 (1H, dt, *J* = 15.7, 6.8 Hz, CH_2C<u>H</u>=CH), 6.82 (4H, s, 4 Ar<u>H</u>), 5.95 (1H, dt, *J* = 15.7, 1.6 Hz, CH_2CH=C<u>H</u>), 4.02 (2H, t, *J* = 6.4 Hz, OC<u>H</u>$_2$$CH_2$), 3.76 (3H, s,

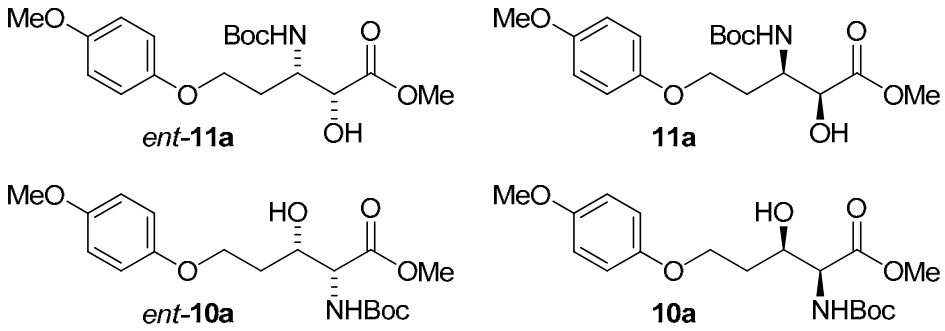
OC<u>H</u>$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 2.65 (2H, ddt, *J* = 6.7, 6.5, 1.5 Hz, OCH$_2$C<u>H</u>$_2$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 167.1, 154.4, 153.1, 145.5, 123.3, 116.0 (2C), 115.1 (2C), 67.0, 56.1, 51.9, 32.5; **IR** (thin film): 1727 (s, br, C=O), 1660 (s, C=C) cm^{-1}.

(2*R*,3*S*)-3-*tert*-Butoxycarbonylamino-2-hydroxy-5-(4-methoxy-phenoxy)-pentanoic acid methyl ester *ent*-**11a**

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-hydroxy-5-(4-methoxy-phenoxy)-pentanoic acid methyl ester 11a

(2*R*,3*S*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-5-(4-methoxy-phenoxy)-pentanoic acid methyl ester *ent*-**10a**

(2*S*,3*R*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-5-(4-methoxy-phenoxy)-pentanoic acid methyl ester 10a



General AA procedure 1 (substrate soluble in n-propanol):

i) Using (DHQ)$_2$PHAL

See experimental section main article.

ii) Using (DHQD)$_2$PHAL

General AA procedure 1 was followed using (DHQD)$_2$PHAL (8.80 mg, 0.0113 mmol, 5 mol%) and (2*E*)-5-(4-methoxy-phenoxy)-pent-2-enoic acid methyl ester **9a** (50.0 mg, 0.212 mmol) with stirring at room temperature for 1 h to afford a 20:1 mixture of regioisomers **11**:**10**. Purification (as for part **i**) afforded pure **11a** as a white solid (63.3 mg, 81%, 96% ee (Chiralcel OD-H (as above): ret. time 22.5 (major – **11a**), 37.5 (minor – *ent*-**11a**) min)). **$[\alpha]_D$** = +61 (c 0.63, CH_2Cl_2). All other spectral data as for *ent*-**11a**.

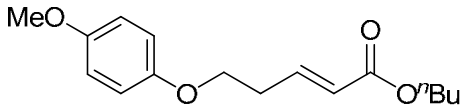
iii) Using (DHQ)$_2$AQN

General AA procedure 1 was followed using (DHQ)$_2$AQN (5.50 mg, 0.00642 mmol 5 mol%) (2*E*)-5-(4-methoxy-phenoxy)-pent-2-enoic acid methyl ester **9a** (30.9, 0.131 mmol) with stirring at room temperature for 24 h to afford a 1:5 mixture of regioisomers **11**:**10**. Purification (as for part **i**), followed by preparative HPLC (Zorbax Sil, 3% isopropyl alcohol/hexane) afforded *ent*-**10a** contaminated with a trace of **11**, the mixture being a clear oil (27.7 mg, 57%, 68% ee (Chiralcel OD-H, as above: ret. time 21.6 (minor – **10a**), 23.2 (minor – **11a**), 24.4 (major – *ent*-**10a**), 37.0 (minor – *ent*-**11a**) min)). R_f = 0.13 (30% ethyl acetate/hexane); **^{1}H n.m.r.** (400 MHz, $CDCl_3$): δ 6.87-6.83 (4H, m, 4 ArH), 5.44 (1H, d, *J* = 9.0 Hz, NH), 4.48 (1H, d (br), *J* = 7.2 Hz, CH(OH)), 4.38 (1H, d, *J* = 9.2 Hz, CH(NH)), 4.19-4.10 (2H, m, OCH_2CH_2), 3.80 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 2.94 (1H, s (br), OH), 2.07-1.98 (2H, m, OCH_2CH_2), 1.47 (9H, s, $C(CH_3)_3$); **^{13}C n.m.r.** (100 MHz, $CDCl_3$): δ 171.7, 156.1, 154.1, 152.5, 115.7 (2C), 114.6 (2C), 80.1, 70.6, 66.5, 57.9, 55.7, 52.5, 33.1, 28.3 (3C); **IR** (thin film): 3440 (s, br, OH, NH), 1740 (s, C=O), 1710 (s, C=O), 1508 cm^{-1}; **LRMS** (EI): *m/z* = 369 (M^+, 28%), 270 (100); **HRMS** (EI): calc. for $C_{18}H_{27}NO_7$ 369.1788 found 369.1783.

iv) Using (DHQD)$_2$AQN

General AA procedure 1 was followed using (DHQD)$_2$AQN (5.8 mg, 0.00677 mmol, 5 mol%) and (2*E*)-5-(4-methoxy-phenoxy)-pent-2-enoic acid methyl ester **9a** (30.5 mg, 0.129 mmol) with stirring at room temperature for 1 h to afford a 1:5 mixture of regioisomers **11**:**10**. Purification (as for part **iii**) afforded **10a** contaminated with a trace of **11**, the mixture being a clear oil (27.6 mg, 58%, 89% ee (Chiralcel OD-H, as above: ret. time 20.9 (major – **10a**), 23.0 (minor – **11a**), 25.2 (minor – *ent*-**10a**), 38.1 (minor – *ent*-**11a**) min)). All other spectral data as for *ent*-**10a**.

(2*E*)-5-(4-Methoxy-phenoxy)-pent-2-enoic acid *n*-butyl ester 9b.



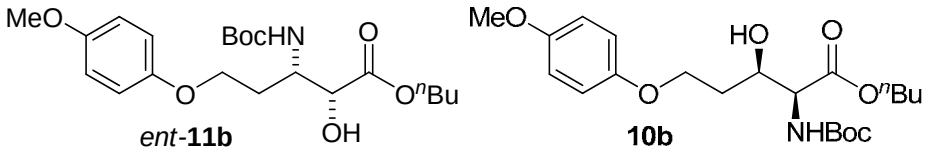
9b

The general cross metathesis procedure was followed using 1-but-3-enyloxy-4-methoxy-benzene **24** (0.304 g, 1.71 mmol), *n*-butyl acrylate (0.361 ml, 2.52 mmol, 1.5 eq) and Grubbs' second generation catalyst (71.3 mg, 0.0840 mmol, 5 mol%). The mixture was heated at reflux for 7 h, after which dimethylsulfoxide (5 ml) was added and the mixture was allowed to cool to room temperature, stirred for 12 h, then concentrated. Purification by flash chromatography (10% ethyl

acetate/hexane) afforded pure (*E*)-**9b** as a clear oil (0.387 g, 81%). R_f = 0.19 (10% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 7.02 (1H, dt, *J* = 15.7, 6.9 Hz, CH_2CH=CH), 6.83 (4H, s, 4 ArH), 5.95 (1H, dt, *J* = 15.7, 1.6 Hz, CH_2CH=CH), 4.14 (2H, t, *J* = 6.6 Hz, $OCH_2(CH_2)_2CH_3$), 4.03 (2H, t, *J* = 6.4 Hz, OCH_2CH_2CH=CH), 3.77 (3H, s, OCH_3), 2.66 (2H, ddt, *J* = 6.7, 6.5, 1.6 Hz, OCH_2CH_2), 1.68-1.61 (2H, m, $CH_2CH_2CH_3$), 1.45-1.34 (2H, m, CH_2CH_3), 0.94 (3H, t, *J* = 7.2 Hz, CH_2CH_3)**; ^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 166.4, 154.0, 152.7, 144.6, 123.3, 115.6 (2C), 114.6 (2C), 66.6, 64.2, 55.6, 32.1, 30.7, 19.1, 13.7; **IR** (thin film): 1709 (s, C=O), 1659 (s, C=C), 1506 cm^{-1}; **LRMS** (EI) : *m/z* = 278 (M^+, 38%), 99 (100); **HRMS** (EI): calc. for $C_{16}H_{22}O_4$ 278.3360, found 278.1520.

(2*R*,3*S*)-3-*tert*-Butoxycarbonylamino-2-hydroxy-5-(4-methoxy-phenoxy)-pentanoic acid *n*-butyl ester *ent*-**11b**

(2*S*,3*R*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-5-(4-methoxy-phenoxy)-pentanoic acid *n*-butyl ester 10b



i) Using (DHQ)$_2$PHAL

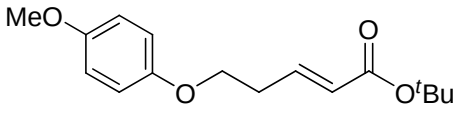
General AA procedure 1 was followed using $(DHQ)_2PHAL$ (5.80 mg, 0.00745 mmol, 5 mol%) and (2*E*)-5-(4-methoxyphenoxy)-pent-2-enoic acid *n*-butyl ester **9b** (40.3 mg, 0.145 mmol) with stirring at room temperature for 26 h to afford a to afford a 9:1 mixture of regioisomers **11**:**10**. Purification by flash chromatography (column 1: 15% methanol/dichloromethane, column 2: 20% ethyl acetate/hexane) afforded unreacted alkene **9b** (7.2 mg, 18%) as well as β-amino product *ent*-**11b** as a clear oil (37.9 mg, 64%, 99% ee (Chiralcel OD-H, 7.5% isopropyl alcohol/hexane: ret. time 26.4 (minor – **11b**), 30.2 (major – *ent*-**11b**) min)). **$[\alpha]_D$** = -30 (c 0.28, CH_2Cl_2). R_f = 0.14 (20% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.87-6.77 (4H, s, 4 ArH), 4.88 (1H, d, *J* = 9.7 Hz, NH), 4.35-4.20 (2H, m (obs), CH(NH), CH(OH)), 4.17 (2H, t, *J* = 6.7 Hz, $OCH_2(CH_2)_2CH_3$), 4.00 (2H, t, *J* = 6.1 Hz, OCH_2CH_2CH(NH)), 3.74 (3H, s, OCH_3), 3.38 (1H, d, *J* = 4.1 Hz, OH), 2.16-1.96 (2H, m, OCH_2CH_2CH(NH)), 1.73-1.58 (2H, m, CH_2CH_3), 1.47-1.25 (11H, m, $C(CH_3)_3$, CH_2CH_3), 0.92 (3H, t, *J* = 7.3 Hz, CH_2CH_3); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): 173.5, 155.3, 153.9, 152.9, 115.7 (2C), 114.6 (2C), 79.6, 72.3, 66.1, 65.7, 55.7, 50.6, 32.2, 30.4, 28.1 (3C), 19.0, 13.7; **IR** (thin film):

3348 (s, br, OH, NH), 1740 (s, C=O), 1508 cm^{-1}; **LRMS** (+ESI): *m/z* = 845 (2M+Na, 34%), 434 (M+Na, 100); **HRMS** (+ESI): calc. for $C_{21}H_{33}NO_7Na$ 434.2155, found 434.2149.

ii) Using (DHQD)$_2$AQN

General AA procedure 1 was followed using $(DHQD)_2AQN$ (6.20 mg, 0.00723 mmol, 5 mol%) and (2*E*)-5-(4-methoxyphenoxy)-pent-2-enoic acid *n*-butyl ester **9b** (41.0 mg, 0.147 mmol) with stirring at room temperature for 2 h to afford an approximately 1:2 mixture of regioisomers **11**:**10**. Purification by flash chromatography (column 1: 5% methanol/dichloromethane, column 2: 15% ethyl acetate/hexane) afforded α-amino isomer **10b** as a clear oil (18.1 mg, 30%, 87% ee (Chiralcel OD-H, solvent system as for part (i): ret. time 20.5 (major – **10b**), 22.2 (minor – *ent*-**10b**) min)). **$[\alpha]_D$** = +7 (c 1.81, CH_2Cl_2). R_f = 0.09 (5% methanol/dichloromethane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.81 (4H, s, 4 ArH), 5.48 (1H, d, *J* = 9.3 Hz, NH), 4.46 (1H, s (br), CH(OH)), 4.32 (1H, d, *J* = 9.5 Hz, CH(NH)), 4.18 (2H, t (obs), *J* = 6.6 Hz, $OCH_2CH_2CH(NH)$), 4.16-4.07 (2H, m (obs), $OCH_2(CH_2)_3CH_3$), 3.77 (3H, s, OCH_3), 2.79 (1H, s (br), OH), 2.07-1.95 (2H, m, $OCH_2CH_2CH(NH)$), 1.72-1.58 (2H, m, $CH_2CH_2CH_3$), 1.46 (9H, s, $C(CH_3)_3$), 1.46-1.30 (2H, m (obs), CH_2CH_3), 0.93 (3H, t, *J* = 7.3 Hz, CH_2CH_3); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): 171.6, 156.4, 154.5, 152.8, 115.8 (2C), 115.0 (2C), 80.3, 71.1, 66.8, 65.8, 58.3, 56.0, 33.5, 30.8, 28.6 (3C), 19.3, 14.0; **IR** (thin film): 3420 (s, br, OH, NH), 1742 (C=O), 1717 (s, C=O), 1510 cm^{-1}; **LRMS** (+ESI): *m/z* = 434 (M+Na, 100%); **HRMS** (+ESI): calc. for $C_{21}H_{33}NO_7Na$ 434.2155, found 434.2150.

(2*E*)- 5-(4-Methoxy-phenoxy)-pent-2-enoic acid *tert*-butyl ester 9c.



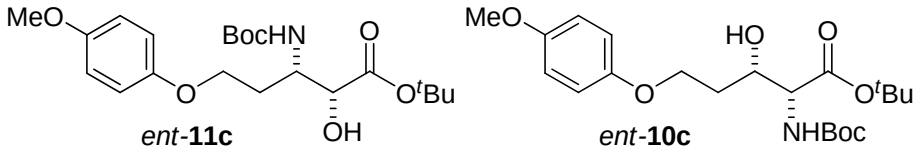
9c

The general cross metathesis procedure was followed using *tert*-butyl acrylate (82.3 μl, 0.562 mmol, 2.0 eq), Grubbs' second generation catalyst (14.3 mg, 0.0168 mmol, 6 mol%), and 1-but-3-enyloxy-4-methoxy-benzene **24** (51.2 mg, 0.287 mmol). The mixture was heated at reflux for 4 h, then cooled for addition of dimethylsulfoxide[6] (60.0 μl, 0.846 mmol, 50 mol% w.r.t. catalyst). The mixture was stirred for 48 h at room temperature, then concentrated. Purification by flash chromatography (5% ethyl acetate/hexane) afforded pure (*E*)-**9c** as a clear oil (71.7 mg, 90%). R_f = 0.19 (10% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.92 (1H, dt, *J* = 15.7, 6.9 Hz, CH_2CH=CH), 6.81 (4H, s, 4 ArH), 5.86 (1H, dt, *J* = 15.7, 1.5 Hz, CH_2CH=CH), 4.00 (2H, t, *J* = 6.5 Hz, OCH_2CH_2), 3.75 (3H, s, OCH_3), 2.62 (2H, ddt, *J* = 6.6, 6.5, 1.5 Hz, OCH_2CH_2), 1.48 (9H, s,

C(C<u>H</u>$_3$)$_3$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 165.9, 154.2, 153.0, 143.5. 125.3, 115.8 (2C), 114.9 (2C), 80.5, 67.0, 55.9, 32.2, 28.3 (3C); **IR** (thin film): 1712 (s, C=O), 1654 (s, C=C) cm^{-1}; **LRMS** (EI): *m/z* = 278 (M^+, 42%), 124 (100); **HRMS** (EI): calc. for $C_{16}H_{22}O_4$ 278.1518, found 278.1511.

(2*R*,3*S*)-3-*tert*-Butoxycarbonylamino-2-hydroxy-5-(4-methoxy-phenoxy)-pentanoic acid *tert*-butyl ester ***ent*-11c**

(2*R*,3*S*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-5-(4-methoxy-phenoxy)-pentanoic acid *tert*-butyl ester ***ent*-10c**



i) Using (DHQ)$_2$PHAL

General AA procedure 1 was followed using $(DHQ)_2PHAL$ (3.8 mg, 0.00488 mmol, 5 mol%) and (2*E*)-5-(4-methoxy-phenoxy)-pent-2-enoic acid *tert*-butyl ester **9c** (25.8 mg, 0.0927 mmol) with stirring at room temperature for 1 h to afford a 6:1 mixture of regioisomers **11**:**10**. Purification by flash chromatography (column 1: 5% methanol/dichloromethane, column 2: 20% ethyl acetate/hexane) afforded unreacted alkene **9c** (5.1 mg, 20%), dihydroxylated product (4.10 mg, 14%), as well as β-amino isomer ***ent*-11c** as a clear oil (21.3 mg, 56%, 96% ee (Chiralcel OD-H, 5% isopropyl alcohol/hexane: ret. time 21.8 (minor – **11c**), 29.6 (major – ***ent*-11c**) min)). **$[\alpha]_D$** = -40 (c 0.6, CH_2Cl_2). R_f = 0.17 (40% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.88-6.78 (4H, m, 4 Ar<u>H</u>), 4.81 (1H, d, *J* = 10.0 Hz, N<u>H</u>), 4.36-4.23 (1H, m, C<u>H</u>(NH)), 4.13-4.10 (1H, m, C<u>H</u>(OH)), 4.00 (2H, t, *J* = 5.7 Hz, OC<u>H</u>$_2$CH$_2$), 3.76 (3H, s, OC<u>H</u>$_3$), 3.23 (1H, d, *J* = 4.1 Hz, O<u>H</u>), 2.10-2.00 (2H, m, OCH$_2$C<u>H</u>$_2$), 1.49 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.37 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 172.5, 155.1, 153.9, 153.0, 115.7 (2C), 114.6 (2C), 83.5, 79.3, 72.4, 65.9, 55.7, 50.4, 32.7, 28.3 (3C), 27.8 (3C); IR (thin film): 3393 (s, br, OH, NH), 1717 (s, C=O) 1510 cm^{-1}; **LRMS** (+ESI): *m/z* = 845 (2M+Na, 95%), 434 (M+Na, 100); **HRMS** (EI): calc. for $C_{21}H_{33}NO_7$ 411.2257, found 411.2264.

ii) Using (DHQ)$_2$AQN

General AA procedure 1 was followed using $(DHQ)_2AQN$ (3.8 mg, 0.00443 mmol, 5 mol%) and (2*E*)-5-(4-methoxy-phenoxy)-pent-2-enoic acid *tert*-butyl ester **9c** (25.2 mg, 0.0905 mmol) with

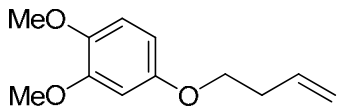
stirring at room temperature for 1 h to afford a 1:1.2 mixture of regioisomers **11**:**10**. Purification as for part (i) afforded unreacted alkene **9c** (2.9 mg, 12%).

A second fraction afforded dihydroxylated product (2.2 mg, 8%).

A third fraction afforded pure β-amino product *ent*-**11c** (13.4 mg, 36%, 74% ee (Chiralcel OD-H, as for part (i): ret. time 21.6 (minor – **11c**), 30.9 (major – *ent*-**11c**) min), $[\alpha]_D$ = -29 (c 0.11, CH_2Cl_2).

A fourth fraction afforded pure α-amino product *ent*-**10c** as a yellow oil (16.0 mg, 43%, 51% ee (Chiralcel OD-H, as for part (i): ret. time 24.0 (minor – **10c**), 26.9 (major – *ent*-**10c**) min)). **$[\alpha]_D$** = -10 (c 0.21, CH_2Cl_2)). R_f = 0.16 (20% ethyl acetate/hexane); **^{1}H n.m.r.** (400 MHz, $CDCl_3$): δ 6.84 (4H, s, 4 Ar<u>H</u>), 5.32 (1H, d, *J* = 8.8 Hz, N<u>H</u>), 4.40-4.34 (1H, m, C<u>H</u>(OH)), 4.21 (1H, d, *J* = 9.0 Hz, C<u>H</u>(NH)), 4.17-4.00 (2H, m, OC<u>H</u>$_2$CH$_2$), 3.77 (3H, s, OC<u>H</u>$_3$), 2.69 (1H, s (br), O<u>H</u>), 2.01-1.97 (2H, m, OCH$_2$C<u>H</u>$_2$), 1.49 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.46 (9H, s, C(C<u>H</u>$_3$)$_3$;**^{13}C n.m.r.** (100 MHz, $CDCl_3$): δ 171.3, 157.1, 155.1, 153.6, 116.3 (2C), 115.4 (2C), 82.9, 80.4, 71.5, 67.0, 58.8, 56.1, 41.6, 28.5 (3C), 28.2 (3C); **IR** (thin film): 3441 (s, br, OH, NH), 1717 (s, C=O), 1508 cm^{-1}; **LRMS** (+ESI): *m/z* = 845 (2M+Na, 57%), 434 (M+Na, 100); **HRMS** (EI): calc. for $C_{21}H_{33}NO_7$ 411.2257, found 411.2256.

4-But-3-enyloxy-1,2-dimethoxy-benzene 25.[7]



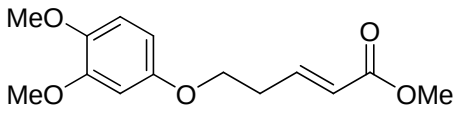
25

Method 1 (*Mitsunobu etherification*):

The general Mitsunobu procedure was followed using 3-buten-1-ol (0.200 g, 2.77 mmol), 3,4-dimethoxyphenol (1.12 g, 7.26 mmol, 2.6 eq), triphenylphosphine (1.46 g, 5.54 mmol, 2.0 eq) and diisopropyl azodicarboxylate (1.09 ml, 5.55 mmol, 2.0 eq). The mixture was heated at reflux for 17 h, then allowed to cool and concentrated. Purification by flash chromatography (10% ethyl acetate/hexane) afforded pure **25** as a clear oil (0.408 g, 71%). R_f = 0.25 (10% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.75 (1H, d, *J* = 8.7 Hz, ArC6-<u>H</u>), 6.51 (1H, d, *J* = 2.8 Hz, ArC3-<u>H</u>), 6.38 (1H, dd, *J* = 8.7, 2.8, ArC5-<u>H</u>), 5.89 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz, C<u>H</u>=CH$_2$), 5.21-5.05 (2H, m, CH=C<u>H</u>$_2$), 3.95 (2H, t, *J* = 6.7 Hz, OC<u>H</u>$_2$CH$_2$), 3.83 (3H, s, OC<u>H</u>$_3$), 3.81 (3H, s, OC<u>H</u>$_3$), 2.51 (2H, dtt, *J* = 6.7, 6.7, 1.4 Hz, C<u>H</u>$_2$CH=CH$_2$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$):

δ 153.4, 149.8, 143.4, 134.4, 116.8, 111.8, 103.8, 100.9, 67.6, 56.3, 55.7, 33.6; **IR** (thin film): 1610 (C=C), 1595 cm^{-1}.

(2*E*)-5-(3,4-Dimethoxy-phenoxy)-pent-2-enoic acid, methyl ester 9d



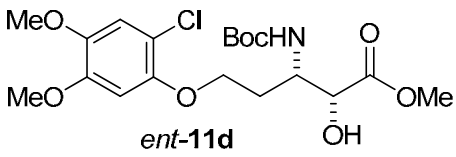
9d

The general cross metathesis procedure was followed using methyl acrylate (190 μl, 2.11 mmol, 2.0 eq), Grubbs' second generation catalyst (44.0 mg, 0.0518 mmol, 5.0 mol%) and 4-but-3-enyloxy-1,2-dimethoxy-benzene **25** (0.220 g, 1.07 mmol) with heating at reflux for 19 h. Purification by flash chromatography (20% ethyl acetate/hexane) afforded pure **9d** as an off-white solid (0.266 g, 94%, mp 33-37 °C). R_f = 0.18 (20% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.99 (1H, dt, *J* = 15.7, 6.9 Hz, CH_2CH=CH), 6.71 (1H, d, *J* = 8.7 Hz, ArC5-H), 6.46 (1H, d, *J* = 2.8 Hz, ArC2-H), 6.32 (1H, dd, *J* = 8.7, 2.8 Hz, ArC6-H), 5.91 (1H, dt, *J* = 15.8, 1.5 Hz, CH_2CH=CH), 3.97 (2H, t, *J* = 6.3 Hz, OCH_2CH_2), 3.79 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.68 (3H, s, $COOCH_3$), 2.60 (2H, ddt, *J* = 6.5, 6.5, 1.5 Hz, OCH_2CH_2); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 166.5, 153.0, 149.7, 144.9, 143.5, 122.7, 11.7, 103.6, 100.8, 66.2, 56.2, 55.6, 51.2, 31.9; **IR** (thin film): 1720 (s, C=O), 1659 (w, C=C) cm^{-1}; **LRMS** (EI): *m/z* = 266 (M^+, 7.5%), 113 (100); 113 (100); **HRMS** (+ESI): calc. for $C_{14}H_{18}O_5Na$ 266.1052, found 289.1048.

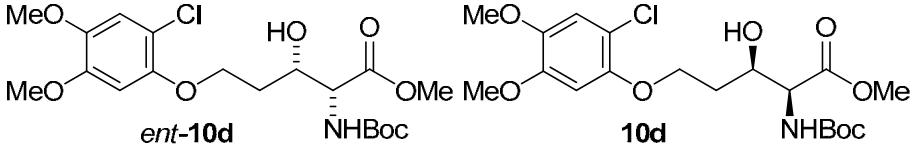
(2*R*,3*S*)-3-*tert*-Butoxycarbonylamino-5-(2-chloro-4,5-dimethoxy-phenoxy)-2-hydroxy-pentanoic acid, methyl ester *ent*-11d

(2*R*,3*S*)-2-*tert*-Butoxycarbonylamino-5-(2-chloro-4,5-dimethoxy-phenoxy)-3-hydroxy-pentanoic acid methyl ester *ent*-10d

(2*S*,3*R*)-2-*tert*-Butoxycarbonylamino-5-(2-chloro-4,5-dimethoxy-phenoxy)-3-hydroxy-pentanoic acid methyl ester 10d



ent-**11d**



ent-**10d** **10d**

(i) Using (DHQ)$_2$PHAL

General AA procedure 1 was followed using (DHQ)$_2$PHAL (6.10 mg, 0.00783 mmol, 5 mol%) and (2*E*)-5-(3,4-dimethoxy-phenoxy)-pent-2-enoic acid, methyl ester **9d** (39.8 mg, 0.149 mmol) with stirring at room temperature for 19 h to afford a to afford a 15:1 mixture of regioisomers **11**:**10**. Purification by flash chromatography (25% ethyl acetate/hexane) afforded pure β-amino isomer *ent*-**11d** as a clear oil (42.8 mg, 66%, 98% ee (Chiralpak AD-H, 20% isopropyl alcohol/hexane: ret. time 23.0 (minor – **11d**), 24.9 (major – *ent*-**11d**)). **[α]$_D$** = -36 (c 0.70, CH_2Cl_2). R_f = 0.40 (70% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.87 (1H, s, ArH), 6.62 (1H, s, ArH), 4.99 (1H, d, *J* = 9.5 Hz, NH), 4.40-4.29 (2H, m, CH(NH), CH(OH)), 4.10 (2H, t, *J* = 6.2 Hz, OCH_2CH_2), 3.86 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.29 (1H, s (br), OH), 2.24-2.06 (2H, m, OCH_2CH_2), 1.38 (9H, s, $C(CH_3)_3$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 173.8, 155.5, 148.4, 148.3, 144.2, 114.4, 113.4, 101.6, 79.6, 72.4, 68.1, 56.5, 56.3, 52.8, 50.8, 32.1, 28.2 (3C); **IR** (thin film): 3366 (s, br, OH, NH), 1740 (s, C=O), 1709 (s, C=O) cm^{-1}; **LRMS** (+ESI): *m/z* = 891 ($(C_{19}H_{28}{}^{37}ClNO_8)_2Na$, 60%) 889 ($C_{38}H_{56}{}^{35}Cl^{37}ClN2O_{16}Na$, 78), 458 ($C_{19}H_{28}{}^{37}ClNO_8Na$, 34), 456 ($C_{19}H_{28}{}^{35}ClNO_8Na$, 100); **HRMS** (+ESI): calc. for $C_{19}H_{28}{}^{35}ClNO_8Na$ 456.1401, found 456.1400.

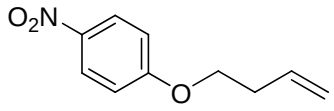
(ii) Using (DHQ)$_2$AQN

General AA procedure 1 was followed using (DHQ)$_2$AQN (6.60 mg, 0.00770 mmol, 5 mol%) and (2*E*)-5-(3,4-dimethoxy-phenoxy)-pent-2-enoic acid, methyl ester **9d** (39.5 mg, 0.148 mmol) with stirring at room temperature for 19 h to afford a 1:7 mixture of regioisomers **11**:**10**. Purification by flash chromatography (25% ethyl acetate/hexane) followed by preparative HPLC (Zorbax Sil, 8% isopropyl alcohol/hexane: ret. time 26 (major – *ent*-**10d**), 29 (minor – **11**) min)) afforded α-amino isomer *ent*-**10d** as a white solid (38.9 mg, 61%, mp 75-79 °C, 92% ee (Chiralpak AD-H, solvent system as for part (i): ret. time 34.7 (minor – **10d**), 37.6 (major – *ent*-**10d**)). **[α]$_D$** = -7.9 (c 1.6 CH_2Cl_2). R_f = 0.50 (70% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 6.87 (1H, s, ArH), 6.58 (1H, s, ArH), 5.43 (1H, d, *J* = 9.2 Hz, NH), 4.52 (1H, d (br), *J* = 9.1 Hz, CH(OH)), 4.37 (1H, d (br), *J* = 9.5 Hz, CH(NH)), 4.28-4.21 (1H, m, $OCH_AH_BCH_2$), 4.14 (1H, dt, *J* = 8.9, 4.0 Hz, $OCH_AH_BCH_2$) 3.86 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.20 (1H, s (br), OH), 2.19-2.07 (1H, m, $OCH_2CH_AH_B$), 2.04-1.96 (1H, m, $OCH_2CH_AH_B$), 1.46 (9H, s, $C(CH_3)_3$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 171.5, 156.1, 148.4, 147.9, 144.1, 113.7, 113.4, 100.5, 80.1, 70.7, 68.6, 58.0, 56.5, 56.3, 52.5, 33.2, 28.2 (3C); **IR** (thin film): 3427 (s, br, OH, NH), 1744 (s, C=O), 1709 (s, C=O), 1506 cm^{-1}; **LRMS** (+ESI): *m/z* = 458 ($C_{19}H_{28}{}^{37}ClNO_8Na$, 41%), 456 ($C_{19}H_{28}{}^{35}ClNO_8Na$, 100); **HRMS**: (+ESI) calc. for $C_{19}H_{28}{}^{35}ClNO_8Na$ 456.1401, found 456.1405.

(iii) Using (DHQD)$_2$AQN

General AA procedure 1 was followed using (DHQD)$_2$AQN (6.50 mg, 0.00758 mmol, 5 mol%) and (2*E*)-5-(3,4-dimethoxy-phenoxy)-pent-2-enoic acid, methyl ester **9d** (40.0 mg, 0.150 mmol) with stirring at room temperature for 19 h to afford a to afford a 1:7 mixture of regioisomers **11**:**10**. Purification as for part (i) afforded α-amino isomer **10d** as a white solid (48.7 mg, 75%, 93% ee (Chiralpak AD-H, solvent system as for part (i): ret. time 34.1 (major – **10d**), 37.8 (minor – *ent*-**10d**)). $[\alpha]_D$ = +8.9 (c 1.7, CH_2Cl_2). All other data as for *ent*-**10d**.

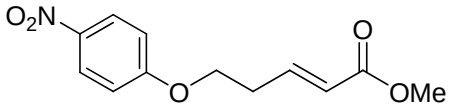
1-But-3-enyloxy-4-nitro-benzene 26. [8]



26

The general Mitsunobu procedure was followed using 3-buten-1-ol (0.250 g, 3.47 mmol) and 4-nitrophenol (1.45 g, 10.4 mmol, 3.0 eq). The mixture was heated at reflux for 1.5 h, allowed to cool, then concentrated to afford a pale orange oil. Purification by flash chromatography (15% ethyl acetate/hexane) afforded **26** as a clear oil (0.671 g, 100%). R_f = 0.40 (15% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 8.20 (2H, m, 2 Ar<u>H</u>), 6.95 (2H, m, 2 Ar<u>H</u>), 5.89 (1H, ddt, *J* = 17.1, 10.3, 6.6 Hz, C<u>H</u>=CH_2), 5.25-5.10 (2H, m, CH=C<u>H</u>$_2$), 4.11 (2H, t, *J* = 6.7 Hz, OC<u>H</u>$_2$$CH_2$), 2.59 (2H, dtt, *J* = 6.7, 6.7, 1.4 Hz, OCH_2C<u>H</u>$_2$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 163.9, 141.4, 133.6, 125.8 (2C), 117.6, 114.4 (2C), 67.9, 33.2; **IR** (thin film): 1609 (s, C=C), 1593 (s, NO_2) cm^{-1}; **LRMS** (EI): *m/z* = 194 (M+H, 100%), 193 (M^+, 95), 177 (M-O, 30).

(2*E*)-5-(4-Nitro-phenoxy)-pent-2-enoic acid, methyl ester 9e



9e

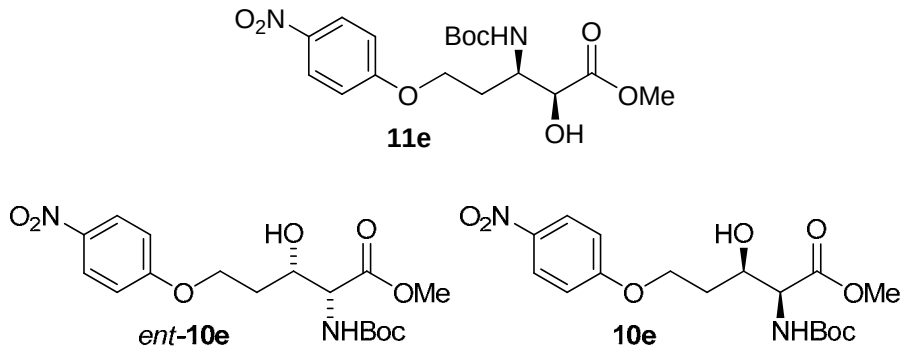
The general cross metathesis procedure was followed using methyl acrylate (1.18 ml, 13.1 mmol, 2.0 eq), Grubbs' second generation catalyst (0.279 g, 0.329 mmol, 5.0 mol%) and 1-but-3-enyloxy-4-nitro-benzene **26** (1.27 g, 6.57 mmol) with heating at reflux for 114 h. Purification by flash chromatography (10% ethyl acetate/hexane) afforded pure **9e** as a pale brown solid (1.45 g, 88%, mp 45-48 °C). R_f = 0.23 (25% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 8.14-8.00 (2H, m, 2 Ar<u>H</u>), 6.96 (1H, dt (obs), *J* = 15.7, 6.9 Hz, CH_2C<u>H</u>=CH), 6.92-6.74 (2H, m, 2 Ar<u>H</u>), 5.92

(1H, dt, *J* = 15.7, 1.5 Hz, $CH_2CH=C\underline{H}$), 4.12 (2H, t, *J* = 6.3 Hz, $OC\underline{H_2}CH_2$), 3.67 (3H, s, $OC\underline{H_3}$), 2.68 (2H, dtt, *J* = 6.7, 6.5, 1.5, $OCH_2C\underline{H_2}$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 166.5, 163.5, 143.9, 141.6, 125.9 (2C), 123.5, 114.4 (2C), 66.6, 51.5, 31.6; **IR** (thin film): 1720 (s, C=O), 1593 (s, NO_2), 1512 cm^{-1}; **LRMS** (EI): *m/z* = 252 (M+H, 31%) 251 (M^+, 7.5), 234 (M-OH, 100); **HRMS** (EI): calc. for $C_{12}H_{13}NO_5$ 251.0794, found 251.0790.

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-hydroxy-5-(4-nitro-phenoxy)-pentanoic acid, methyl ester 11e

(2*R*,3*S*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-5-(4-nitro-phenoxy)-pentanoic acid methyl ester *ent*-**10e**

(2*S*,3*R*)-2-*tert*-Butoxycarbonylamino-3-hydroxy-5-(4-nitro-phenoxy)-pentanoic acid, methyl ester 10e



General AA procedure 2 **(substrate insoluble in n-propanol):**

i) Using (DHQD)$_2$PHAL

To a stirring solution of *tert*-butyl carbamate (56.3 mg, 0.481 mmol, 3.1 eq) in *n*-propanol (0.6 ml) at room temperature was added a solution of sodium hydroxide (18.4 mg, 0.460 mmol, 2.9 eq) in water (1.2 ml). To this mixture was added 1,3-dichloro-5,5-dimethylhydantoin (62.6 mg, 0.318 mmol, 2.0 eq), followed by a solution of $(DHQD)_2PHAL$ (6.20 mg, 0.00796 mmol, 5 mol%) in *n*-propanol (0.6 ml), then (2*E*)-5-(4-nitro-phenoxy)-pent-2-enoic acid methyl ester **9e** (39.4 mg, 0.157 mmol). To this mixture was added potassium osmate dihydrate (3.10 mg, 0.00841 mmol, 5 mol%). The resulting mixture was stirred at room temperature for 4 h before the reaction was quenched with sodium sulfite (0.160 g, 1.27 mmol, 8.1 eq), diluted with water (5 ml) and extracted into ethyl acetate (3 x 10 ml). The combined organic layers were dried, filtered and concentrated to afford a 30:1 mixture of regioisomers **11**:**10**. Purification by flash chromatography (column 1: 5% methanol/dichloromethane, column 2: 25% ethyl acetate/hexane, increasing to 100% ethyl acetate)

afforded **11e** as a clear oil (42.9 mg, 71%, >95% ee). **$[\alpha]_D$** = +73 (c 1.7, CH_2Cl_2). R_f = 0.085 (25% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 8.20-8.17 (2H, m, 2 ArH), 6.98-6.93 (2H, m, 2 ArH), 4.82 (1H, d, *J* = 9.8 Hz, NH), 4.38-4.23 (2H, m, CH(NH), CH(OH)), 4.15 (2H, t, *J* = 5.9 Hz, OCH_2CH_2), 3.81 (3H, s, OCH_3), 3.27 (1H, s (br), OH), 2.20-2.05 (2H, m, OCH_2CH_2), 1.36 (9H, s, $C(CH_3)_3$); **^{13}C n.m.r.** (75 MHz, $CDCl_3$): δ 173.7, 163.8, 155.3, 141.6, 125.9 (2C), 114.5 (2C), 79.9, 72.3, 65.6, 53.0, 50.1, 31.8, 28.3 (3C); **IR** (thin film): 3389 (s, br, OH, NH), 1740 (s, C=O), 1709 (s, C=O), 1593 (s, NO_2), 1514 cm^{-1}; **LRMS** (+ESI): *m/z* = 407 (M+Na, 100%); **HRMS** (+ESI): calc. for $C_{17}H_{24}N_2O_8Na$ 407.1425 found 407.1425.

ii) Using (DHQ)$_2$AQN

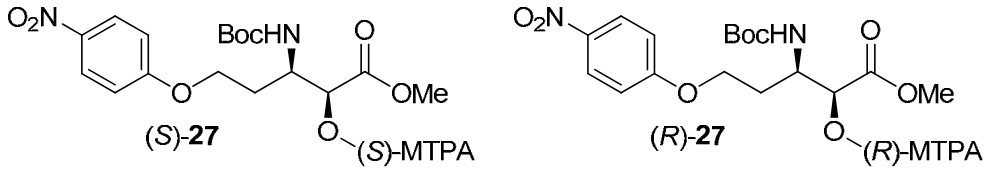
General AA procedure 2 was followed using $(DHQ)_2AQN$ (6.60 mg, 0.00793 mmol, 5 mol%) and (2*E*)-5-(4-nitro-phenoxy)-pent-2-enoic acid methyl ester **9e** (40.4 mg, 0.161 mmol) with stirring at room temperature for 11 h to afford a to afford a 1:7 mixture of regioisomers **11**:**10**. Purification by flash chromatography (column 1: as above; column 2: 2.5% methanol/dichloromethane) afforded pure *ent*-**10e** as a clear oil (46.6 mg, 75%, >90% ee). **$[\alpha]_D$** = -12 (c 2.3, CH_2Cl_2). R_f = 0.11 (30% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 8.21-8.13 (2H, m, 2 ArH), 6.99-6.91 (2H, m, 2 ArH), 5.39 (1H, d, *J* = 8.9 Hz, NH), 4.45-4.35 (2H, m, CH(NH), CH(OH)), 4.31-4.12 (2H, m, OCH_2CH_2), 3.78 (3H, s, OCH_3), 2.30 (1H, s (br), OH), 2.08-1.98 (2H, m, OCH_2CH_2), 1.45 (9H, s, $C(CH_3)_3$); **^{13}C n.m.r.** (100 MHz, $CDCl_3$): δ 171.6, 163.6, 156.1, 141.7, 125.9 (2C), 114.5 (2C), 80.4, 69.1, 65.5, 57.8, 52.7, 33.0, 28.1 (3C); **IR** (thin film): 3427 (s, br, OH, NH), 1736 (s, C=O), 1712 (s, C=O), 1593 (NO_2), 1506 cm^{-1}; **LRMS** (+ESI): *m/z* = 407 (M+Na, 100%); **HRMS** (+ESI): calc. for $C_{17}H_{24}N_2O_8Na$ 407.1425 found 407.1425.

iii) Using (DHQD)$_2$AQN

General AA procedure 2 was followed using $(DHQD)_2AQN$ (6.80 mg, 0.00793 mmol, 5 mol%) and (2*E*)-5-(4-nitro-phenoxy)-pent-2-enoic acid methyl ester **9e** (40.0 mg, 0.159 mmol), with the exception that the potassium osmate dihydrate catalyst was added prior to addition of substrate **9e**. The mixture was stirred at room temperature for 8 h to afford a to afford a 1:8 mixture of regioisomers **11**:**10**. Purification by flash chromatography (column 1: 3% methanol/dichloromethane; column 2: 25% ethyl acetate/hexane) afforded pure **10e** as a clear oil (30.6 mg, 50%, ee n.d.). **$[\alpha]_D$** = +19 (c 1.2, CH_2Cl_2). All other spectral data as for *ent*-**10e**.

(*S*)-MTPA derivative (*S*)-27

(*R*)-MTPA derivative (*R*)-27



General procedure for the preparation of MTPA esters:

(*S*)-MTPA ester (*S*)-27:

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-2-hydroxy-5-(4-nitro-phenoxy)-pentanoic acid, methyl ester **11e** (8.50 mg, 0.0221 mmol) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (6.80 mg, 0.0290 mmol, 1.3 eq) were stirred in dichloromethane (0.9 ml) at room temperature. To this solution was added 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (9.40 mg, 0.0490 mmol, 2.2 eq) and 4-(dimethylamino)pyridine (0.60 mg, 0.00491 mmol, 0.22 eq). The mixture was sonicated at 0 °C for 5 h, during which time a white precipitate formed. The mixture was filtered through celite and concentrated. Purification by flash chromatography (40% ethyl acetate/hexane) afforded pure (*S*)-MTPA derivative (*S*)-**27** as a pale yellow oil (2.10 mg, 16%). **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 8.21-8.17 (2H, m, 2 *p*-NO_2Ar<u>H</u>), 7.71-7.68 (2H, m, 2 Ar<u>H</u>), 7.47-7.41 (3H, m, 3 Ar<u>H</u>), 6.95-6.87 (2H, m, 2 *p*-NO_2Ar<u>H</u>), 5.31 (1H, d, *J* = 1.8 Hz, C<u>H</u>(O-MTPA)), 4.59 (1H, d, *J* = 7.3 Hz, N<u>H</u>), 4.57-4.49 (1H, m, C<u>H</u>(NH), 4.02 (2H, t, *J* = 6.1 Hz, OC<u>H_2</u>CH_2), 3.81 (3H, s, CO_2C<u>H_3</u>), 3.64 (3H, d, *J* = 1.1 Hz, $C(CF_3)OC$<u>H_3</u>), 2.01-1.71 (2H, m, OCH_2C<u>H_2</u>), 1.37 (9H, s, $C(C$<u>H_3</u>$)_3$).

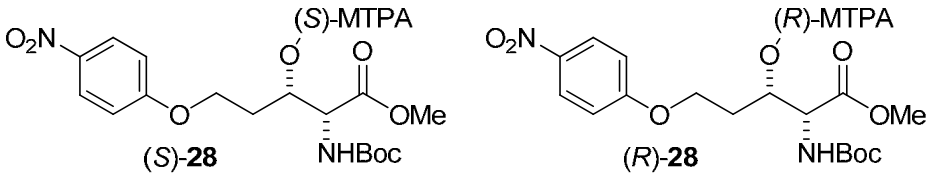
(*R*)-MTPA ester (*R*)-27:

The general procedure for the preparation of MTPA esters was followed using (2*S*,3*R*)-3-*tert*-butoxycarbonylamino-2-hydroxy-5-(4-nitro-phenoxy)-pentanoic acid, methyl ester **11e** (8.10 mg, 0.0211 mmol) and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (7.40 mg, 0.0316 mmol, 1.5 eq) with sonication at 0 °C for 5 h. Purification by flash chromatography (40% ethyl acetate/hexane) afforded pure (*R*)-MTPA derivative (*R*)-**27** as a pale yellow oil (2.00 mg, 16%). **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 8.21-8.17 (2H, m, 2 *p*-NO_2Ar<u>H</u>), 7.61-7.58 (2H, m, 2 Ar<u>H</u>), 7.46-7.39 (3H, m, 3 Ar<u>H</u>), 6.96-6.87 (2H, m, 2 *p*-NO_2Ar<u>H</u>), 5.35 (1H, d, *J* = 2.2 Hz, C<u>H</u>(O-MTPA)), 4.73 (1H, d, *J* = 10.0 Hz, N<u>H</u>), 4.62-4.55 (1H, m, C<u>H</u>(NH), 4.15-4.09 (2H, m, OC<u>H_2</u>CH_2), 3.77 (3H, s,

$CO_2C\underline{H}_3$), 3.58 (3H, d, *J* = 0.76 Hz, $C(CF_3)OC\underline{H}_3$), 2.17-1.92 (2H, m, $OCH_2C\underline{H}_2$), 1.37 (9H, s, $C(C\underline{H}_3)_3$).

(*S*)-MTPA derivative (*S*)-28

(*R*)-MTPA derivative (*R*)-28



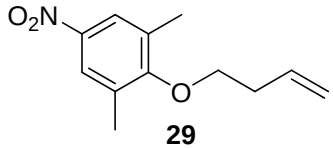
(*S*)-MTPA ester (*S*)-28:

The general procedure for the preparation of MTPA esters was followed using (2*R*,3*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-5-(4-nitro-phenoxy)-pentanoic acid methyl ester *ent*-**10e** (6.90 mg, 0.0180 mmol) and (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (6.40 mg, 0.0273 mmol, 1.5 eq) with sonication at 0 °C for 5 h. Purification by flash chromatography (30% ethyl acetate/hexane) afforded pure (*S*)-MTPA derivative (*S*)-**28** as a pale yellow oil (2.6 mg, 24%). **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 8.23-8.17 (2H, m, 2 *p*-$NO_2Ar\underline{H}$), 7.46-7.26 (5H, m, 5 $Ar\underline{H}$), 6.96-6.85 (2H, m, 2 *p*-$NO_2Ar\underline{H}$), 5.83 (1H, dt, *J* = 6.8, 2.0 Hz, $C\underline{H}$(O-MTPA)), 5.08 (1H, d, *J* = 9.4 Hz, $N\underline{H}$), 4.64 (1H, d, *J* = 9.3 Hz, $C\underline{H}$(NH), 4.05-3.95 (1H, m, $OC\underline{H}_AH_BCH_2$), 3.84-3.73 (1H, m (obs), $OCH_A\underline{H}_BCH_2$), 3.77 (3H, s, $CO_2C\underline{H}_3$), 3.52 (3H, d, *J* = 1.3 Hz, $C(CF_3)OC\underline{H}_3$), 2.20-2.13 (2H, m, $OCH_2C\underline{H}_2$), 1.45 (9H, s, $C(C\underline{H}_3)_3$).

(*R*)-MTPA ester (*R*)-28:

The general procedure for the preparation of MTPA esters was followed using (2*R*,3*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-5-(4-nitro-phenoxy)-pentanoic acid methyl ester *ent*-**10e** (4.30 mg, 0.0112 mmol) and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (3.41 mg, 0.0146 mmol, 1.3 eq) with sonication at 0 °C for 5 h. Purification by flash chromatography (30% ethyl acetate/hexane) afforded pure (*R*)-MTPA derivative (*R*)-**28** as a pale yellow oil (1.1 mg, 16%). **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 8.23-8.17 (2H, m, 2 *p*-$NO_2Ar\underline{H}$), 7.46-7.26 (5H, m, 5 $Ar\underline{H}$), 6.96-6.85 (2H, m, 2 *p*-$NO_2Ar\underline{H}$), 5.84 (1H, t, *J* = 6.8 Hz, $C\underline{H}$(O-MTPA)), 5.05 (1H, d, *J* = 9.5 Hz, $N\underline{H}$), 4.64 (1H, d, *J* = 10.9 Hz, $C\underline{H}$(NH), 4.13-4.01 (2H, m, $OC\underline{H}_2CH_2$), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.46 (3H, d, *J* = 1.2 Hz, $C(CF_3)OC\underline{H}_3$), 2.32-2.23 (2H, m, $OCH_2C\underline{H}_2$), 1.45 (9H, s, $C(C\underline{H}_3)_3$).

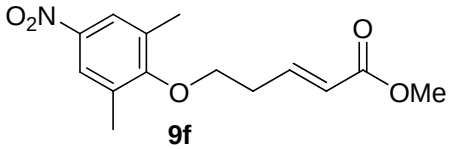
2-But-3-enyloxy-1,3-dimethyl-5-nitro-benzene 29.



29

The general Mitsunobu procedure was followed using 3-buten-1-ol (0.108 g, 1.50 mmol) and 2,6-dimethyl-4-nitrophenol (0.249 g, 1.49 mmol, 1.0 eq). The mixture was heated at reflux for 16 h, allowed to cool, then concentrated to afford a pale orange oil. Purification by flash chromatography (column 1: 15% ethyl acetate/hexane, column 2: 5% diethyl ether/hexane) afforded pure **29** as a yellow oil (0.298 g, 90%). R_f = 0.30 (25% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 7.80 (2H, s, 2 Ar<u>H</u>), 5.90 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, C<u>H</u>=CH_2), 5.20-5.05 (2H, m, CH=C<u>H</u>$_2$), 3.82 (2H, t, *J* = 6.6 Hz, OC<u>H</u>$_2$$CH_2$), 2.54 (2H, ddt, *J* = 13.3, 6.7, 1.3 Hz, OCH_2C<u>H</u>$_2$), 2.28 (6H, s, 2 C<u>H</u>$_3$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 161.5, 143.4, 134.3, 132.4 (2C), 124.2 (2C), 117.5, 71.9, 34.8, 16.6 (2C); **IR** (thin film): 1641 (s, C=C), 1589 (s, NO_2) cm^{-1}; **LRMS** (EI): *m/z* = 222 (M+H, 45%), 221 (M^+, 30), 55 (100); **HRMS** (EI): calc. for $C_{12}H_{15}NO_3$ 221.1052, found 221.1051.

5-(2,6-Dimethyl-4-nitro-phenoxy)-pent-2-enoic acid, methyl ester 9f.

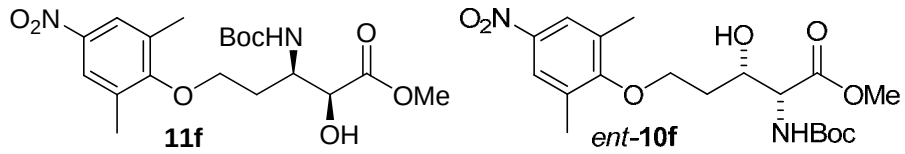


9f

The general cross metathesis procedure was followed using methyl acrylate (0.245 ml, 2.72 mmol, 2.0 eq), Grubbs' second generation catalyst (57.7 mg, 0.0680 mmol, 5.0 mol%) and 2-but-3-enyloxy-1,3-dimethyl-5-nitro-benzene **29** (0.299 g, 1.35 mmol) with heating at reflux for 72 h. Purification by flash chromatography (10% ethyl acetate/hexane) afforded pure **9f** as a pale yellow solid (0.250 g, 66%, mp 56-61 °C). R_f = 0.23 (20% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 7.87 (2H, m, 2 Ar<u>H</u>), 7.06 (1H, dt, *J* = 15.7, 7.1 Hz, CH_2C<u>H</u>=CH), 5.98 (1H, dt, , *J* = 15.7, 1.5 Hz, CH_2CH=C<u>H</u>), 3.93 (2H, t, *J* = 6.4 Hz, OC<u>H</u>$_2$$CH_2$), 3.72 (3H, s, OC<u>H</u>$_3$), 2.71 (2H, ddt, *J* = 13.4, 6.4, 1.5, OCH_2C<u>H</u>$_2$), 2.31 (6H, s, 2 C<u>H</u>$_3$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 166.5, 161.1, 144.6, 143.5, 132.3 (2C), 124.2 (2C), 123.5, 70.5, 51.5, 33.0, 16.6 (2C); **IR** (thin film): 1722 (s, C=O), 1659 (s, C=C), 1593 (s, NO_2), cm^{-1}; **LRMS** (EI): *m/z* = 280 (M+H, 19%), 202 (M-CH_3NO_3, 100); **HRMS** (EI): calc. for $C_{14}H_{17}NO_5$ 279.1107, found 279.1105.

(2*S*,3*R*)-3-*tert*-Butoxycarbonylamino-5-(2,6-dimethyl-4-nitro-phenoxy)-2-hydroxy-pentanoic acid, methyl ester 11f

(2*R*,3*S*)-2-*tert*-Butoxycarbonylamino-5-(2,6-dimethyl-4-nitro-phenoxy)-3-hydroxy-pentanoic acid methyl ester *ent*-**10f**



(i) Using (DHQD)$_2$PHAL

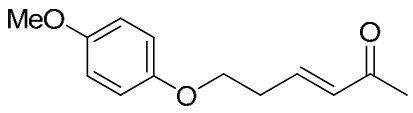
General AA procedure 1 was followed using (DHQD)$_2$PHAL (5.60 mg, 0.00716 mmol, 5 mol%) and 5-(2,6-dimethyl-4-nitro-phenoxy)-pent-2-enoic acid, methyl ester **9f** (39.1 mg, 0.129 mmol) with stirring at room temperature for 7 h. Purification by flash chromatography (column 1: 5% methanol/dichloromethane, column 2: 25% ethyl acetate/hexane) afforded a 3:1 mixture of regioisomers **11**:**10** (34.4 mg, 65%). The regioisomers were separated by preparative HPLC (Zorbax Sil, 30% isopropyl alcohol/hexane: ret. time 31 (major - **11**), 28 (minor – **10**) min)) to afford β-amino isomer **11f** as an orange oil (13.4 mg, 25%, 93% ee (Chiralpak AD-H, 7.5% isopropyl alcohol/hexane: ret. time 21.4 (major – **11f**), 30.9 (minor – *ent*-**11f**)). **[α]$_D$** = +36 (c 1.3, CH_2Cl_2). R_f = 0.65 (70% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 7.90 (2H, s, 2 Ar$\underline{H}$), 4.84 (1H, d, *J* = 10 Hz, N$\underline{H}$), 4.43 (1H, dt, *J* = 9.8, 4.6 Hz, C$\underline{H}$(NH)), 4.26 (1H, d, *J* = 5.0 Hz, C$\underline{H}$(OH)), 3.96 (1H, m, OC$\underline{H}_A$H$_B$CH$_2$), 3.81 (3H, s, OC$\underline{H}_3$), 3.81-3.77 (1H, m, OCH$_A$$\underline{H}_BCH_2$), 3.28 (1H, d, *J* = 5.1 Hz, O$\underline{H}$), 2.32 (6H, s, 2 C$\underline{H}_3$), 2.22-2.13 (1H, m, OCH$_2$C$\underline{H}_A$H$_B$), 2.09-1.99 (1H, m, OCH$_2$CH$_A$$\underline{H}_B$), 1.40 (9H, s, C(C$\underline{H}_3$)$_3$); **^{13}C n.m.r.** (75 MHz, $CDCl_3$): δ 174.1, 161.5, 155.6, 143.8, 132.7 (2C), 124.5 (2C), 80.1, 72.7, 69.2, 53.3, 50.5, 33.2, 28.5 (3C), 16.8 (2C); **IR** (thin film): 3395 (s, br, OH, NH), 1742 (s, C=O), 1713 (s, C=O), 1518 cm^{-1}; **LRMS** (+ESI): *m/z* = 435 (M+Na, 100%); **HRMS**: (+ESI) calc. for $C_{19}H_{28}NO_8Na$ 435.1743, found 435.1738.

(ii) Using (DHQ)$_2$AQN

General AA procedure 1 was followed using (DHQ)$_2$AQN (6.60 mg, 0.00770 mmol, 6 mol%) and 5-(2,6-dimethyl-4-nitro-phenoxy)-pent-2-enoic acid, methyl ester **9f** (39.1 mg, 0.129 mmol) with stirring at room temperature for 7 h. Purification by flash chromatography (column 1: 5% methanol/dichloromethane, column 2: 25% ethyl acetate/hexane) afforded a 1:10 mixture of regioisomers **11**:**10** (29.8 mg, 56%). The regioisomers were separated by preparative HPLC

(Zorbax Sil, 30% isopropyl alcohol/hexane: ret. time 28 (minor - **11**), 31 (major – **10**) min)) to afford α-amino isomer *ent*-**10f** as an orange oil (13.3 mg, 25%, 91% ee (Chiralpak AD-H, 6% isopropyl alcohol/hexane: ret. time 29.4 (minor –**10f**), 31.0 (major – *ent*-**10f**)). **$[\alpha]_D$** = -11 (c 1.3, CH_2Cl_2). R_f = 0.19 (30% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 7.90 (2H, s, 2 ArH), 5.41 (1H, d, *J* = 10 Hz, NH), 4.53 (1H, m, CH(OH)), 4.40 (1H, d, *J* = 8.5 Hz, CH(NH)), 4.06-3.95 (2H, m, OCH_2CH_2), 3.8 (3H, s, OCH_3), 2.35 (6H, s, 2 CH_3), 2.21-1.75 (1H, s (br, obs), OH), 2.07-2.01 (2H, m, OCH_2CH_2), 1.45 (9H, s, $C(CH_3)_3$); **^{13}C n.m.r.** (75 MHz, $CDCl_3$): δ 172.0, 161.2, 156.4, 144.0, 132.6 (2C), 124.6 (2C), 80.6, 70.7, 70.0, 58.2, 53.0, 34.4, 28.6 (3C), 16.8 (2C); **IR** (thin film): 3421 (s, br, OH, NH), 1747 (s, C=O), 1713 (s, C=O), 1520 cm^{-1}; **LRMS** (+ESI): *m/z* = 435 (M+Na, 60%); **HRMS**: (+ESI) calc. for $C_{19}H_{28}NO_8Na$ 435.1743, found 435.1738.

(2*E*)-6-(4-Methoxy-phenoxy)-hex-3-en-2-one 15.

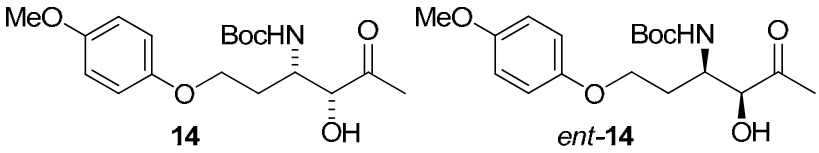


15

The general cross metathesis procedure was followed using 1-but-3-enyloxy-4-methoxy-benzene **24** (0.105 g, 0.589 mmol), methyl vinyl ketone (98.1 μl, 1.18 mmol, 2.0 eq) and Grubbs' second generation catalyst (25.0 mg, 0.0294 mmol, 5 mol%). The mixture was heated at reflux for 20 h, allowed to cool to room temperature, then concentrated. Purification by flash chromatography (20% ethyl acetate/hexane) afforded pure unsaturated ketone **15** as a pale brown oil (0.108 g, 83%). R_f = 0.18 (20% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.85 (1H, dt (obs), *J* = 16.1, 6.8 Hz, CH_2CH=CH), 6.80 (4H, s, 4 ArH), 6.15 (1H, dt, *J* = 16.1, 1.5 Hz, CH_2CH=CH), 4.01 (2H, t, *J* = 6.3 Hz, OCH_2CH_2), 3.73 (3H, s, OCH_3), 2.64 (2H, ddt, *J* = 6.6, 6.3, 1.5 Hz, CH_2CH=CH), 2.23 (3H, s, C(O)CH_3); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 198.5, 154.2, 152.8, 144.1, 133.1, 115.7 (2C), 114.8 (2C), 66.8, 55.8, 32.5, 27.0; **IR** (thin film): 1680 (s, C=O), 1628 (s, C=C) cm^{-1}; **LRMS** (EI): *m/z* = 220 (M^+, 95%), 163 (100); **HRMS** (EI): calc. for $C_{13}H_{16}O_3$ 220.1099, found 220.1095.

(2*R*,3*S*)-{2-Hydroxy-1-[2-(4-methoxy-phenoxy)-ethyl]-3-oxo-butyl}-carbamic acid *tert*-butyl ester 14

(2*S*,3*R*)-{2-Hydroxy-1-[2-(4-methoxy-phenoxy)-ethyl]-3-oxo-butyl}-carbamic acid *tert*-butyl ester *ent*-**14**



(i) Using (DHQ)$_2$PHAL (*buffered*)

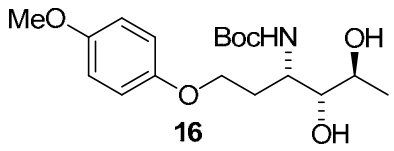
General AA procedure 1 was followed using (DHQ)$_2$PHAL (83.6 mg, 5 mol%)) and (2*E*)-6-(4-methoxy-phenoxy)-hex-3-en-2-one **15** (1.01 g, 4.59 mmol), with the exception that sodium hydrogen carbonate (1.14 g, 13.6 mmol, 3.0 eq) was also added. The mixture was stirred at room temperature for 20 min and following the standard work-up, afforded a >15:1 mixture of regioisomers. Purification by flash chromatography (2 columns: 20% ethyl acetate/hexane) afforded β-amino isomer **14** as a white solid (0.985 g, 61%, mp 72-77 ºC, 90% ee (Chiralcel OD-H, 20% isopropyl alcohol/hexane: ret. time 17.6 (major - **14**), 20.0 (minor – *ent*-**14**)). **$[\alpha]_D$** = -94 (c 0.99, CH_2Cl_2). R_f = 0.29 (40% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 6.90-6.78 (4H, m, 4 ArH), 4.71 (1H, d, *J* = 10.1 Hz, NH), 4.51 (1H, m, CH(NH)), 4.20 (1H, d, *J* = 2.5 Hz, CH(OH)), 4.02 (2H, t, *J* = 5.9 Hz, OCH_2CH_2), 3.82 (1H, d, *J* = 4.0 Hz, OH), 3.75 (3H, s, OCH_3), 2.32 (3H, s, $C(O)CH_3$), 2.10 (2H, dt, *J* = 6.7, 6.2 Hz, OCH_2CH_2)), 1.36 (9H, s, $C(CH_3)_3$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 208.5, 155.8, 154.3, 153.2, 116.1 (2C), 115.0 (2C), 80.1, 65.8, 56.0, 49.6, 33.1, 28.4 (3C), 25.7; **IR** (thin film): 3406 (s, br, OH, NH) , 1715 (s, C=O) cm^{-1}; **LRMS** (+ESI): *m/z* = 376 (M+Na, 77%), 360 (100); **HRMS** (EI): calc. for $C_{18}H_{27}NO_6Na$ 376.1736, found 376.1743.

***(ii) Using (DHQD)$_2$PHAL* (buffered)**

General AA procedure 1 was followed using (DHQD)$_2$PHAL (5.50 mg, 5 mol%)) and (2*E*)-6-(4-methoxy-phenoxy)-hex-3-en-2-one **15** (30.0 mg, 0.136 mmol), with the exception that sodium hydrogen carbonate (34.4 mg, 0.409 mmol, 3.0 eq) was also added. The mixture was stirred at room temperature for 25 min and following the standard work-up, afforded a 6.5:1 mixture of regioisomers. Purification by flash chromatography (2 columns: 20% ethyl acetate/hexane) afforded β-amino isomer *ent*-**14** as a white solid (30.3 mg, 63%, 93% ee (Chiralcel OD-H, 20% isopropyl

alcohol/hexane: ret. time 17.5 (minor - **14**), 20.0 (major – *ent*-**14**)). $[\alpha]_D$ = +92 (c 2.1, CH_2Cl_2). All other spectral data as for **14**.

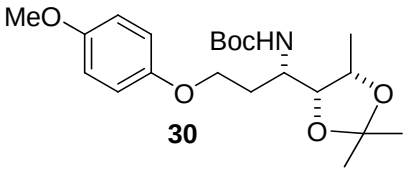
(1*S*,2*R*,3*S*)-{2,3-Dihydroxy-1-[2-(4-methoxy-phenoxy)-ethyl]-butyl}-carbamic acid *tert*-butyl ester 16



16

To a stirred solution of (2*R*,3*S*)-{2-hydroxy-1-[2-(4-methoxy-phenoxy)-ethyl]-3-oxo-butyl}-carbamic acid *tert*-butyl ester **14** (0.514 g, 1.45 mmol) in diethyl ether (141 ml) at room temperature was added a solution of zinc borohydride in ether (approx. 0.16 *M*, 88.1 ml, 14.1 mmol, 10 eq). The resulting solution was stirred for 20 min, then water (24 ml) was added and the mixture stirred until effervescence ceased. Hydrochloric acid (1 *M*, 24 ml) was added and the mixture extracted with ethyl acetate (2 x 20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated. The crude product was purified by flash chromatography (40% ethyl acetate/hexane) to afford pure **16** as an oily white solid (0.399 g, 77%, mp 55-62 °C). **$[\alpha]_D$** = -21 (c 5.5, CH_2Cl_2). **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 6.80 (4H, s, 4 ArH), 5.08 (1H, d, *J* = 9.2 Hz, N<u>H</u>), 4.26 (1H, s (br), O<u>H</u>), 4.14 (1H, m, C<u>H</u>(NH)), 3.98 (2H, t, *J* = 6.1 Hz, OC<u>H</u>$_2$CH$_2$), 3.74 (3H, s, OC<u>H</u>$_3$), 3.50 (1H, m, C<u>H</u>(OH)CH$_3$), 3.27 (1H, d (br), *J* = 8.0 Hz, CH(NH)C<u>H</u>(OH)), 2.99 (1H, s (br), O<u>H</u>), 2.00 (2H, dt, *J* = 6.1, 6.0 Hz, OCH$_2$C<u>H</u>$_2$), 1.41 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.27 (3H, d, *J* = 6.2 Hz, CH(OH)C<u>H</u>$_3$); **^{13}C n.m.r.** (75 MHz, $CDCl_3$): δ 157.9, 154.5, 153.0, 116.1 (2C), 115.1 (2C), 80.8, 78.6, 67.8, 66.4, 55.1, 49.2, 32.3, 28.7 (3C), 19.7; **IR** (thin film): 3385 (s, br, OH, NH), 1685 (s, C=O) cm^{-1}; **LRMS** (+ESI): *m/z* = 733 (2M+Na, 40%), 378 (M+Na, 100); **HRMS** (+ESI): calc. for $C_{18}H_{29}NO_6Na$ 378.1893, found 378.1892.

(1*S*,4*R*,5*S*)-[3-(4-Methoxy-phenoxy)-1-(2,2,5-trimethyl-[1,3]dioxolan-4-yl)-propyl]-carbamic acid *tert*-butyl ester 30

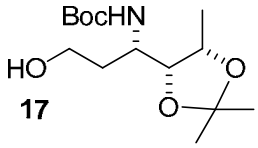


30

To a stirred solution of (1*S*,2*R*,3*S*)-{2,3-dihydroxy-1-[2-(4-methoxy-phenoxy)-ethyl]-butyl}-carbamic acid *tert*-butyl ester **16** (0.120 g, 0.338 mmol) in dichloromethane (1.4 ml) at 0 °C was

added 2-methoxypropene (84.0 μl, 0.877 mmol, 2.6 eq) and 10-camphorsulfonic acid (7.95 mg, 0.0342 mmol, 0.10 eq). The mixture was stirred at 0 °C for 3 h, at which time additional 2-methoxypropene (20 μl, 0.209 mmol, 0.62 eq) and 10-camphorsulfonic acid (~2 mg, 0.00861 mmol, 0.026 eq) were added. Further 2-methoxypropene (50 μl, 0.522 mmol, 1.5 eq) was added after 2 h and the mixture was allowed to warm to room temperature, stirred for 14 h, then diluted with dichloromethane (10 ml) and washed with sodium hydrogen carbonate solution (sat., aq., 10 ml). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (20% ethyl acetate/hexane) to afford pure **30** as an off-white solid (0.115 g, 86%, mp 48-55 °C). $[\alpha]_D$ = -9.4 (c 1.6, CH_2Cl_2). R_f = 0.63 (50% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 6.85 (4H, s, 4 ArH), 4.85 (1H, d, *J* = 8.0 Hz, NH), 4.37 (1H, dq, *J* = 6.6, 6.7 Hz, CH(O)CH_3), 4.13 (1H, m, CH(O)CH(O)CH_3), 3.99 (2H, t, *J* = 6.3 Hz, OC$H_2$$CH_2$), 3.88 (1H, m, CH(NH)), 3.76 (3H, s, OCH_3), 2.01 (2H, m, OCH_2CH_2), 1.50 (3H, s, C(CH_3)$_A$(CH_3)$_B$), 1.41 (9H, s, C(CH_3)$_3$), 1.35 (3H, s, C(CH_3)$_A$(CH_3)$_B$), 1.28 (3H, d, *J* = 6.5 Hz, CH(O)CH_3); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 155.4, 154.0, 153.2, 115.8 (2C), 114.8 (2C), 107.6, 79.4, 78.8, 73.5, 65.9, 55.9, 47.6, 34.8, 28.5 (3C), 27.3, 24.7, 15.2; **IR** (thin film): 3453, 3362 (s, br, NH), 1720 (s, C=O) cm^{-1}; **LRMS** (EI): *m/z* = 813 (2M+Na, 7%), 418 (M+Na, 100); **HRMS** (+ESI): calc. for $C_{21}H_{33}NO_6Na$ 418.2206, found 418.2201.

(1*S*,4*R*,5*S*)-[3-Hydroxy-1-(2,2,5-trimethyl-[1,3]dioxolan-4-yl)-propyl]-carbamic acid *tert*-butyl ester 17

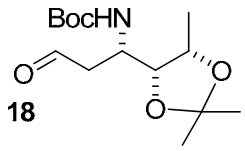


17

To a 0 °C stirred solution of (1*S*,4*R*,5*S*)-[3-(4-methoxy-phenoxy)-1-(2,2,5-trimethyl-[1,3]dioxolan-4-yl)-propyl]-carbamic acid *tert*-butyl ester **30** (0.385 g, 0.973 mmol) in a mixture of acetonitrile (16 ml) and water (4 ml) was added ceric ammonium nitrate (1.34 g, 2.44 mmol, 2.5 eq). The mixture was stirred 0 °C for 25 min then quenched with sodium hydrogen carbonate solution (sat., aq., 20 ml) and allowed to warm to room temperature. The mixture was extracted with dichloromethane (3 x 15 ml) and the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (30% ethyl acetate/hexane) to afford pure alcohol **17** as a brown solid (0.227 g, 81%, mp 86-89 °C). $[\alpha]_D$ = +5.3 (c 3.1 CH_2Cl_2). R_f = 0.23 (40% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 4.86 (1H, d, *J* = 8.8 Hz, NH), 4.38 (1H, dq, *J* = 6.7, 6.6 Hz, CH(O)CH_3), 4.02 (1H, dd, *J* = 7.1, 1.6 Hz,

C<u>H</u>(O)CH(O)CH_3), 3.84 (1H, t (br), *J* = 9.3 Hz, C<u>H</u>(NH)), 3.75-3.56 (3H, m, C<u>H_2</u>OH, O<u>H</u>), 1.77-1.67 (1H, m, C<u>H_A</u>$H_B$$CH_2$OH), 1.63-1.54 (1H, m, CH_A<u>H_B</u>CH_2OH), 1.49 (3H, s, C(C<u>H_3</u>)$_A$(CH_3)$_B$), 1.43 (9H, s, C(C<u>H_3</u>)$_3$), 1.34 (3H, s, C(CH_3)$_A$(C<u>H_3</u>)$_B$), 1.26 (3H, d, *J* = 6.6 Hz, CH(O)C<u>H_3</u>); **^{13}C n.m.r.** (75 MHz, $CDCl_3$): δ 157.2, 107.7, 80.4, 79.5, 73.6, 58.4, 46.4, 38.1, 28.6 (3H), 27.2, 24.4, 15.0; **IR** (thin film): 3452 (s), 3373 (s, br), 1690 (s, C=O), 1504 cm^{-1}; **LRMS** (+ESI): *m/z* = 601 (2M+Na, 7%), 312 (M+Na, 100); **HRMS** (+ESI): calc. for $C_{14}H_{27}NO_5Na$ 312.1787, found 312.1788.

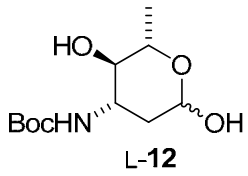
(1*S*,4*R*,5*S*)-[3-Oxo-1-(2,2,5-trimethyl-[1,3]dioxolan-4-yl)-propyl]-carbamic acid *tert*-butyl ester 18



18

To a stirred solution of alcohol **17** (29.2 mg, 0.101 mmol) and TEMPO (1.62 mg, 0.0104 mmol, 0.10 eq) in dichloromethane (0.1 ml) at room temperature under a nitrogen atmosphere was added bis-acetoxyiodobenzene (36.7 mg, 0.114 mmol, 1.1 eq). The resulting mixture was stirred at room temperature for 4 h, then diluted with dichloromethane (5 ml), washed with sodium thiosulfate solution (sat., aq., 5 ml), and the aqueous layer re-extracted with dichloromethane (3 x 5 ml). The combined organic layers were washed with sodium hydrogen carbonate solution (sat., aq., 5 ml), dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (40% ethyl acetate/hexane) to afford pure aldehyde **18** as a pale yellow oil (24.4 mg, 84%). **[α]$_D$** = +40 (c 1.1, CH_2Cl_2). R_f = 0.25 (40% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 9.75 (1H, t, *J* = 1.8 Hz, C<u>H</u>O), 4.93 (1H, d, *J* = 7.3 Hz, N<u>H</u>), 4.38 (1H, dq, *J* = 6.6, 6.6 Hz, C<u>H</u>(O)CH_3), 4.14-4.07 (2H, m, C<u>H</u>(NH), C<u>H</u>(O)CH(O)CH_3) 2.70-2.67 (2H, m, C<u>H_2</u>CHO), 1.48 (3H, s, C(C<u>H_3</u>)$_A$(CH_3)$_B$), 1.41 (9H, s, C(C<u>H_3</u>)$_3$), 1.31 (3H, s, C(CH_3)$_A$(C<u>H_3</u>)$_B$), 1.30 (3H, d, *J* = 6.8 Hz, CH(O)C<u>H_3</u>); **^{13}C n.m.r.** (75 MHz, $CDCl_3$): δ 200.8, 155.2, 107.9, 80.1, 78.2, 73.4, 48.7, 46.0, 28.6 (3C), 27.2, 24.5, 14.8; **IR** (thin film): 1718 (s, C=O), 1504 cm^{-1}; **LRMS** (+ESI): *m/z* = 310 (M+Na, 55%); **HRMS** (+ESI): calc. for $C_{14}H_{25}NO_5Na$ 310.1630, found 310.1639.

(2*S*,3*R*,4*S*)-(3,6-Dihydroxy-2-methyl-tetrahydro-pyran-4-yl)-carbamic acid *tert*-butyl ester (*N*-*tert*-butoxycarbonyl-L-acosamine) L-12



L-**12**

To a stirring solution of (1*S*,4*R*,5*S*)-[3-oxo-1-(2,2,5-trimethyl-[1,3]dioxolan-4-yl)-propyl]-carbamic acid *tert*-butyl ester **18** (24.4 mg, 0.0849 mmol) in a mixture of dioxane (1.5 ml) and water (0.26 ml) was added Dowex® 50W ion exchange resin (25.0 mg, 1 mg/mg aldehyde). The mixture was stirred at room temperature for 20 h, with further Dowex® 50W being added after 4 h and 17 h (50.0 mg and 100 mg respectively). After 20 h, the resin was filtered off, washed with diethyl ether (20 ml), and washings dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (60% ethyl acetate/hexane) to afford a 1.2:1 mixture of α-L-**12** and β-L-**12** as a white solid (13.4 mg, 64%, mp 90-120 °C). $\mathbf{[\alpha]_D}$ = -61 (c 0.48, CH_2Cl_2). R_f = 0.16 (60% ethyl acetate/hexane). **^{1}H n.m.r.** (300 MHz, **MeOD**): δ 5.21 (1H, d, *J* = 3.0 Hz, OC$\underline{H}_\alpha$(OH)), 4.83 (1H, dd, *J* = 9.7, 2.0 Hz, OC$\underline{H}_\beta$(OH)), 3.98-3.84 (2H, m, C$\underline{H}_\alpha$(CH_3), C$\underline{H}_\alpha$(NH)), 3.58-3.49 (1H, m, C$\underline{H}_\beta$(NH)), 3.40-3.35 (1H, m, C$\underline{H}_\beta$(CH_3)), 2.99 (1H, dd, *J* = 9.7, 9.6 Hz, C$\underline{H}_\alpha$(OH)), 2.97 (1H, dd, *J* = 9.4, 9.4 Hz, C$\underline{H}_\beta$(OH)), 2.27 (1H, ddd, *J* = 12.6, 4.6, 2.0 Hz, C$\underline{H}_{A\beta}H_BCH$(OH)), 2.03 (1H, ddd, *J* = 13.0, 4.6, 1.1 Hz, C$\underline{H}_{A\alpha}H_BCH$(OH)), 1.64 (1H, ddd, *J* = 12.6, 12.6, 3.5 Hz, $CH_A\underline{H}_{B\alpha}CH$(OH)), 1.50 (9H, s, C(C$\underline{H}_{3\alpha}$)$_3$), 1.49 (9H, s, C(C$\underline{H}_{3\beta}$)$_3$), 1.52-1.41 (1H, m (obs), $CH_A\underline{H}_{B\beta}CH$(OH)), 1.32 (3H, d, *J* = 6.2 Hz, C$\underline{H}_{3\beta}$), 1.26 (3H, d, *J* = 6.2 Hz, C$\underline{H}_{3\alpha}$); **^{13}C n.m.r.** (75 MHz, MeOD): δ 156.4 (2 $\underline{C}$=O), 96.0 (O$\underline{C}_\beta$H(OH)), 92.9 (O$\underline{C}_\alpha$H(OH)), 81.0 (2 $\underline{C}$(CH_3)$_3$), 78.1 (C(NH)$\underline{C}_\alpha$H(OH)), 76.9 (C(NH)$\underline{C}_\beta$H(OH)), 75.6 ($\underline{C}_\beta$H(CH_3)), 70.3 ($\underline{C}_\alpha$H(CH_3)), 54.6 ($\underline{C}_\beta$H(NH)), 51.2 ($\underline{C}_\alpha$H(NH)), 41.2 ($\underline{C}_\beta H_2$), 39.1 (($\underline{C}_\alpha H_2$), 29.6 (2 C($\underline{C}H_3$)$_3$), 19.4 (2 CH_3); **IR** (thin film): 3385 (s, br, OH, NH), 1684 (s, C=O) cm^{-1}; **LRMS** (+ESI): *m/z* = 499 (2M+Na-H_2O, 100%), 270 (M+Na, 31); **HRMS** (+ESI): calc. for $C_{11}H_{21}NO_5Na$, 270.1317 found 270.1320.

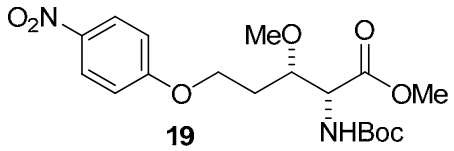
^{1}H n.m.r. (200 MHz, **$CDCl_3$**): δ 5.30 (1H, s (br), OC$\underline{H}_\alpha$(OH)), 4.87 (1H, ddd, *J* = 9.3, 5.7, 2.1 Hz, OC$\underline{H}_\beta$(OH)), 4.68 (1H, d, *J* = 6.5 Hz, N$\underline{H}_\beta$), 4.58 (1H, d, *J* = 6.8 Hz, N$\underline{H}_\alpha$), 4.01-3.84 (4H, m, 2 CH(NH)CH(O$\underline{H}$), C$\underline{H}_\alpha$(CH_3), C$\underline{H}_\alpha$ (NH)), 3.70-3.53 (1H, m, C$\underline{H}_\beta$(NH)), 3.44-3.30 (2H, m, C$\underline{H}_\beta$(CH_3)), OCH(O$\underline{H}_\beta$)), 3.09-2.97 (2H, m, 2 C(NH)C$\underline{H}$(OH)), 2.88 (1H, s (br), OCH(O$\underline{H}_\alpha$)), 2.20 (1H, ddd, *J* = 12.4, 4.7, 2.1 Hz, C$\underline{H}_{A\beta}H_BC$(OH)), 2.07 (1H, ddd, *J* = 12.8, 4.6, 1.1 Hz, C$\underline{H}_{A\alpha}H_BC$(OH)), 1.61 (1H, ddd, *J* = 12.7, 3.4, 1.9 Hz, $CH_A\underline{H}_{B\alpha}C$(OH)), 1.48-1.41 (1H, m (obs),

$CH_A\underline{H}_{B\beta}C(OH)$), 1.45 (18H, s, 2 $C(C\underline{H}_3)_3$), 1.33 (3H, d, *J* = 6.1 Hz, $C\underline{H}_{3\beta}$), 1.27 (3H, d, *J* = 6.2 Hz, $C\underline{H}_{3\alpha}$).

Silver(I) Oxide

To a stirred solution of silver(I) nitrate (12.7 g, 74.8 mmol) in water (50 ml) at 70 °C was added a 70 °C solution of sodium hydroxide (3.00 g, 75.0 mmol) in water (50 ml). A dark brown precipitate formed and the suspension was stirred at 70 °C for 20 min, then the water was decanted off. The dark brown solid was filtered off and washed with water (2 x 25 ml), acetone (2 x 25 ml), then diethyl ether (2 x 15 ml) before drying at the pump, then over potassium hydroxide in a vacuum dessicator overnight to afford pure silver(I) oxide (8.36 g, 96%) as a fine brown powder. The compound was stored in the dark in a dessicator.

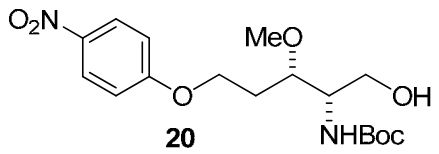
(2*S*,3*S*)-2-*tert*-Butoxycarbonylamino-3-methoxy-5-(4-nitro-phenoxy)-pentanoic acid methyl ester 19



19

To a stirred solution of (2*R*,3*S*)-2-*tert*-butoxycarbonylamino-3-hydroxy-5-(4-nitro-phenoxy)-pentanoic acid methyl ester *ent*-**10e** (0.500 g, 1.30 mmol) in a acetonitrile (1.4 ml) and methyl iodide (1.4 ml) at room temperature was added dried, freshly prepared silver(I) oxide (0.602 g, 2.60 mmol, 2.0 eq). The suspension was stirred in the dark at room temperature for 68 h, with further silver(I) oxide (0.500 g, 2.16 mmol, 1.7 eq) and methyl iodide (1.0 ml) being added after 63 h. The mixture was then filtered, washing with ethyl acetate (50 ml), and the solution was concentrated. Purification by flash chromatography (30% ethyl acetate/hexane) afforded pure **19** as a yellow oil (0.444 g, 86%). $\mathbf{[\alpha]_D}$ = -23 (c 1.7, CH_2Cl_2). R_f = 0.24 (30% ethyl acetate/hexane); **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 8.22-8.17 (2H, m, 2 Ar$\underline{H}$), 7.01-6.95 (2H, m, 2 Ar$\underline{H}$), 5.26 (1H, d, *J* = 10.2 Hz, N$\underline{H}$), 4.38 (1H, d, *J* = 9.7 Hz, C$\underline{H}$(NH)), 4.15 (2H, t, J = 5.8 Hz, $OC\underline{H}_2CH_2$), 4.02 (1H, m, C$\underline{H}(OCH_3)$), 3.78 (3H, s, C(O)$OC\underline{H}_3$), 3.32 (3H, C(H)$OC\underline{H}_3$), 2.10-1.99 (2H, m, $OCH_2C\underline{H}_2$), 1.44 (9H, s, $C(C\underline{H}_3)_3$); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 172.1, 164.1, 156.4, 142.0, 126.3 (2C), 114.9 (2C), 80.6, 78.5, 65.3, 59.1, 56.4, 52.9, 31.3, 28.7 (3C); **IR** (thin film): 3404 (s, br, NH), 1751 (s, C=O), 1713 (s, C=O) cm^{-1}; **LRMS** (+ESI): *m/z* = 421 (M+Na, 100%); **HRMS** (+ESI): calc. for $C_{18}H_{26}N_2O_8Na$ 421.1581, found 421.1585.

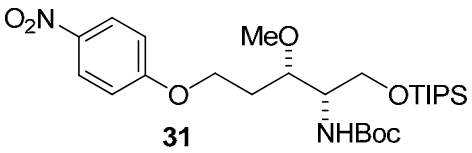
(1*S*,2*S*)-[1-Hydroxymethyl-2-methoxy-4-(4-nitro-phenoxy)-butyl]-carbamic acid *tert*-butyl ester 20



20

To a stirred solution of (2*S*,3*S*)-2-*tert*-butoxycarbonylamino-3-methoxy-5-(4-nitro-phenoxy)-pentanoic acid methyl ester **19** (14.8 mg, 0.0371 mmol) in tetrahydrofuran (0.75 ml) at room temperature was added lithium borohydride (1.62 mg, 0.0744 mmol, 2.0 eq) The mixture was stirred at room temperature for 4 h, with additional lithium borohydride (3.00 mg, 0.138 mmol, 3.7 eq) being added over this time. The reaction mixture was then concentrated, diluted with water (5 ml) and extracted with ethyl acetate (3.5 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (50% ethyl acetate/hexane) to afford alcohol **20** as a yellow solid (13.5 mg, 98%, mp 103-105 °C). $\mathbf{[\alpha]_D}$ = +17 (c 1.7, CH_2Cl_2). R_f = 0.24 (50% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, $CDCl_3$): δ 8.21-8.18 (2H, m, 2 Ar<u>H</u>), 6.98-6.94 (2H, m, 2 Ar<u>H</u>), 5.02 (1H, s (br), N<u>H</u>), 4.16 (2H, t, J = 5.8 Hz, OC<u>H</u>$_2$CH$_2$), 3.77-3.67 (4H, m, C<u>H</u>(OCH$_3$), C<u>H</u>(NH), C<u>H</u>$_2$OH), 3.41 (3H, s, OCH$_3$), 2.09-1.96 (3H, m, OCH$_2$C<u>H</u>$_2$), O<u>H</u>), 1.44 (9H, s, C(C<u>H</u>$_3$)$_3$); **^{13}C n.m.r.** (75 MHz, $CDCl_3$): δ 164.0, 156.7, 141.9, 126.2 (2C), 114.8 (2C), 80.1, 78.0, 65.4, 64.2, 58.9, 54.3, 30.6, 28.6 (3C); **IR** (thin film): 3420 (s, br, OH, NH), 1710 (s, C=O), 1517 cm^{-1}; **LRMS** (+ESI): *m/z* = 763 (2M+Na, 25%), 393 (M+Na, 100); **HRMS** (+ESI): calc. for $C_{17}H_{26}N_2O_7Na$ 393.1638, found 393.1637.

(1*S*,2*S*)-[2-Methoxy-4-(4-nitro-phenoxy)-1-triisopropylsilanyloxymethyl-butyl]-carbamic acid *tert*-butyl ester 31

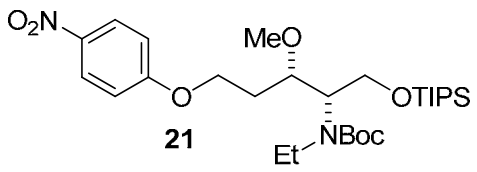


31

To a stirring solution of (1*S*,2*S*)-[1-hydroxymethyl-2-methoxy-4-(4-nitro-phenoxy)-butyl]-carbamic acid *tert*-butyl ester **20** (0.152 mg, 0.410 mmol) in dimethylformamide (0.30 ml, 2 ml/g alcohol) at room temperature was added imidazole (69.8 mg, 1.03 mmol, 2.5 eq), followed by chlorotriisopropylsilane (132 μl, 0.617 mmol, 1.5 eq). The mixture was stirred for 4 h, then diluted with ethyl acetate (5 ml), washed with ammonium chloride solution (sat., aq., 5 ml), and the

aqueous layer re-extracted with ethyl acetate (2 x 5 ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (20% ethyl acetate/hexane) to remove residual imidazole, affording the desired TIPS ether **31** contaminated with a small amount of triisopropylsilanol (0.234 g). This mixture was not separated but carried on to the next step. **^{1}H n.m.r.** (200 MHz, $CDCl_3$): δ 8.20-8.16 (2H, m, 2 Ar$\underline{H}$), 6.98-6.92 (2H, m, 2 Ar$\underline{H}$), 4.82 (1H, d, *J* = 7.7 Hz, N$\underline{H}$), 4.15 (2H, m, OC$\underline{H}_2$CH$_2$), 3.88-3.63 (4H, m, C$\underline{H}$(OCH$_3$), C$\underline{H}$(NH), C$\underline{H}_2$OSi), 3.40 (3H, s, OC$\underline{H}_3$), 2.09-1.97 (2H, m, OCH$_2$C$\underline{H}_2$), 1.43 (9H, s, C(C$\underline{H}_3$)$_3$), 1.17-0.95 (21 H, m, Si(C$\underline{H}$(C$\underline{H}_3$)$_2$)$_3$)); **^{13}C n.m.r.** (50 MHz, $CDCl_3$): δ 164.2, 156.1, 141.8, 126.1 (2C), 114.7 (2C), 79.6, 75.5, 65.6, 62.4, 59.0, 54.1, 30.8, 28.6 (3C), 18.2 (6C), 12.2 (3C).

(1*S*,2*S*)-Ethyl-[2-methoxy-4-(4-nitro-phenoxy)-1-triisopropylsilanyloxymethyl-butyl]-carbamic acid *tert*-butyl ester 21



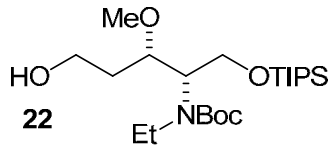
21

Potassium hydride 30% suspension in oil was washed three times with pentane, then treated with a solution of iodine in tetrahydrofuran (0.3 *M*) until the purple iodine colour persisted. The mixture was allowed to stand for 30 min, then the liquid decanted and the solid washed with a further two portions of tetrahydrofuran and dried overnight.

To a stirred solution of TIPS ether **31** (0.190 g, 0.361 mmol) in tetrahydrofuran (3.2 ml) at –20 °C was added dried, recrystallised[9] 18-crown-6 (0.154 g, 0.583 mmol, 1.6 eq) and purified potassium hydride (20.7 mg, 0.516 mmol, 1.4 eq). The suspension was stirred for 10 minutes then ethyl iodide (41.3 ml, 0.516 mmol, 1.4 eq) was added. The mixture was stirred at –20 °C for 3 h then quenched with ammonium chloride solution (sat., aq., 5 ml) and extracted with ethyl acetate (3 x 10 ml). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to afford pure **21** as a pale yellow oil (0.173 g, 86%). **$[\alpha]_D$** = +5.6 (c 1.4, CH_2Cl_2). R_f = 0.32 (15% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, 330 K, $CDCl_3$): δ 8.16-8.12 (2H, m, 2 Ar$\underline{H}$), 6.96-6.91 (2H, m, 2 Ar$\underline{H}$), 4.22-4.14 (2H, m, OC$\underline{H}_2$CH$_2$), 3.95-3.78 (4H, m, C$\underline{H}$(OCH$_3$), C$\underline{H}$(NEt), C$\underline{H}_2$OSi), 3.36 (3H, s, OC$\underline{H}_3$), 3.36-3.24 (2H, m (obs), NC$\underline{H}_2$CH$_3$), 2.04-1.96 (2H, m, OCH$_2$C$\underline{H}_2$), 1.44 (9H, s, C(C$\underline{H}_3$)$_3$), 1.12 (3H, t, *J* = 6.9 Hz, NCH$_2$C$\underline{H}_3$), 1.05 (18H, s, 3 CH(C$\underline{H}_3$)$_2$), 1.07-1.03 (3H, m (obs), 3 C$\underline{H}$(CH$_3$)$_2$); **^{13}C**

n.m.r. (75 MHz, 330 K, $CDCl_3$): δ 164.3, 156.1, 142.0, 126.1 (2C), 114.8 (2C), 79.5, 77.7, 65.9, 62.5, 61.6, 59.1, 41.3, 31.3, 28.7 (3C), 18.2 (6C), 15.1, 12.4 (3C); **IR** (thin film): 1689 (s, C=O), 1593, 1517 cm^{-1}; **LRMS** (+ESI): *m/z* = 577 (M+Na, 100%); **HRMS** (+ESI): calc. for $C_{28}H_{50}N_2O_7SiNa$ 577.3281, found 577.3265.

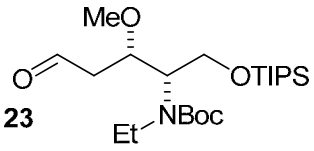
(1*S*,2*S*)-Ethyl-(4-hydroxy-2-methoxy-1-triisopropylsilanyloxymethyl-butyl)-carbamic acid tert-butyl ester 22



22

To a stirred solution of (1*S*,2*S*)-ethyl-[2-methoxy-4-(4-nitro-phenoxy)-1-triisopropylsilanyloxymethyl-butyl]-carbamic acid *tert*-butyl ester **21** (50.0 mg, 0.0901 mmol) at room temperature in ethyl acetate (0.55 ml) was added palladium on carbon (10% w/w, 5.75 mg, 0.00541 mmol, 6 mol%). The resulting suspension was stirred under hydrogen for 4 h, at which time further palladium catalyst was added (3.90 mg, 0.00367mmol, 4 mol%). The mixture was stirred for 2 h, then acetic anhydride (15.0 μl, 0.159 mmol, 1.8 eq) was added and the mixture maintained under hydrogen for 1.5 h, then filtered through celite, washing with ethyl acetate (30 ml). The solution was concentrated and redissolved in a mixture of acetonitrile (1.5 ml), sodium hydrogen carbonate solution (sat., aq., 0.15 ml), and water (0.15 ml), then cooled to 0 °C for the addition of ceric ammonium nitrate (81.9 mg, 0.149 mmol, 1.7 eq). The mixture was stirred at 0 °C for 30 min, with further ceric ammonium nitrate (20.0 mg, 0.0365 mmol, 0.4 eq) added at 15 minutes. The reaction was quenched with sodium thiosulfate solution (sat., aq., 5 ml) and extracted with ethyl acetate (5 x 15 ml). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to afford pure **22** as a pale yellow oil (31.1 mg, 80%). $\mathbf{[\alpha]_D}$ = -7.6 (c 2.7, CH_2Cl_2). R_f = 0.26 (30% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, 330 K, $CDCl_3$): δ 3.98 (1H, m, C<u>H</u>(NEt)), 3.89 (2H, d, *J* = 6.0 Hz, C<u>H</u>$_2$OSi), 3.76 (2H, t, *J* = 5.9 Hz, C<u>H</u>$_2$OH), 3.72 (1H, dt (obs), *J* = 5.8, 5.8 Hz, C<u>H</u>(OMe)), 3.40 (3H, s, OC<u>H</u>$_3$), 3.30 (2H, m, NC<u>H</u>$_2$CH$_3$), 1.97 (1H, s (br), O<u>H</u>), 1.78 (2H, ddt, *J* = 5.9, 5.9, 1.6 Hz, C<u>H</u>$_2$CH$_2$OH), 1.46 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.14 (3H, t, *J* = 7.0 Hz, NCH$_2$C<u>H</u>$_3$), 1.08 (18H, s, 3 CH(C<u>H</u>$_3$)$_2$), 1.07 (3H, m (obs), 3 C<u>H</u>(CH$_3$)$_2$); **^{13}C n.m.r.** (50 MHz, 330 K, $CDCl_3$): δ 156.3, 80.1, 79.6, 62.6, 62.2, 60.7, 58.9, 41.6, 34.1, 28.9 (3C), 18.3 (6C), 15.0, 12.5 (3C); **IR** (thin film): 3447 (s, br, OH), 1693 (s, C=O) cm^{-1}; **LRMS** (+ESI): *m/z* = 889 (2M+Na, 13%), 456 (M+Na, 100); **HRMS** (+ESI): calc. for $C_{22}H_{47}NO_5SiNa$ 456.3117, found 456.3110.

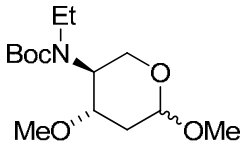
(1*S*,2*S*)-Ethyl-(2-methoxy-4-oxo-1-triisopropylsilanyloxymethyl-butyl)-carbamic acid *tert*-butyl ester 23



23

To a stirring solution of alcohol **22** (31.1 mg, 0.0717 mmol) in dichloromethane (0.7 ml) was added Dess-Martin periodinane (45.6 mg, 0.108 mmol, 1.5 eq). The suspension was stirred in the dark for 2 h, with additional periodinane (10.0 mg, 0.0237 mmol, 0.33 eq) added after 1.5 h. The reaction was quenched with a mixture of saturated aqueous solutions of sodium hydrogen carbonate and sodium thiosulfate (4:1, 4 ml) and extracted into dichloromethane (3 x 15 ml). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to afford aldehyde **23** as a clear and colourless oil (26.8 mg, 87%). $[\alpha]_D$ = 0 (c 1.2, CH_2Cl_2). R_f = 0.37 (10% ethyl acetate/hexane); **^{1}H n.m.r.** (300 MHz, 330 K, $CDCl_3$): δ 9.82 (1H, t, *J* = 1.9 Hz, OHC), 4.12 (1H, dt, *J* = 5.5, 5.4 Hz, CH(OCH$_3$)), 4.00-3.86 (3H, m, CH(NEtBoc), CH$_2$OSi), 3.37 (3H, s, OCH$_3$), 3.39-3.22 (2H, m (obs), NCH$_2$CH$_3$), 2.70 (1H, ddd, J = 16.8, 5.3, 1.5 Hz, OHCCH$_A$H$_B$CH(OCH$_3$)), 2.61 (1H, ddd, *J* = 16.8, 6.6, 2.0 Hz, OHCCH$_A$H$_B$ CH(OCH$_3$)), 1.46 (9H, s, C(CH$_3$)$_3$), 1.13 (3H, t, J = 7.0 Hz, NCH$_2$CH$_3$), 1.10-1.07 (3H, m (obs), 3 CH(CH$_3$)$_2$), 1.09 (18H, s, 3 CH(CH$_3$)$_2$); **^{13}C n.m.r.** (50 MHz, 330 K, $CDCl_3$): δ 200.7, 156.2, 79.9, 76.6, 62.5, 62.0, 58.9, 46.3, 41.3, 28.8 (3C), 18.3 (6C), 15.1, 12.4 (3C); **IR** (thin film): 1726 (s, C=O), 1695 (s, C=O) cm^{-1}; **LRMS** (+ESI): *m/z* = 454 (M+Na, 100%); **HRMS** (+ESI): calc. for $C_{22}H_{45}NO_5SiNa$ 454.2960, found 456.2950.

(3*S*,4*S*)-(4,6-Dimethoxy-tetrahydro-pyran-3-yl)-ethyl-amine (methyl 2,4-dideoxy-4-(*N*-Boc-ethylamino)-3-*O*-methyl-L-*threo*-pentopyranoside) L-13



L-13

To a stirred solution of (1*S*,2*S*)-ethyl-(2-methoxy-4-oxo-1-triisopropylsilanyloxymethyl-butyl)-carbamic acid *tert*-butyl ester **23** (26.8 mg, 0.0622 mmol) in distilled methanol (1.2 ml) at 0 ºC was added hydrochloric acid in dioxane (4 *M*, 17 μl, 0.0684 mmol, 1.1 eq). The mixture was stirred at 0 ºC for 1 h, then at –10 ºC for 16 h, at which time the reaction was quenched with triethylamine (30

μl). The solvent was removed by evaporation the crude product purified by flash chromatography (30% ethyl acetate/hexane) to afford pure L-**13** as a white solid (10.2 mg, 56%). $[\alpha]_D$ = -21.8 (c 0.11, CH_2Cl_2). R_f = 0.5 (30% ethyl acetate/hexane). **^{1}H n.m.r.** (300 MHz, 330 K, $CDCl_3$): δ 4.74 (1H, dd, *J* = 3.4, 1.5 Hz, OC$\underline{H}_\alpha$(OCH_3)), 4.35 (1H, d, *J* = 8.0 Hz, OC$\underline{H}_\beta$(OMe)), 3.97 (2H, m, 2 C$\underline{H}$(OCH_3)), 3.87-3.79 (4H, m, 2 C$\underline{H}_2$O), 3.51 (2H, m, 2 C$\underline{H}$(N), 3.46 (3H, s, OCHOC$\underline{H}_{3\beta}$), 3.36 (3H, s, OCHOC$\underline{H}_{3\alpha}$), 3.33 (6H, s, 2 OC$\underline{H}_3$), 3.29-2.21 (4H, m (br), 2 C$\underline{H}_2CH_3$), 2.32 (1H, dd, *J* = 4.9, 2.2 Hz, C$\underline{H}_{A\beta}H_B$), 2.27 (1H, dd, *J* = 4.9, 1.6 Hz, C$\underline{H}_{A\alpha}H_B$), 1.58-1.48 (1H, m (obscured), $CH_A\underline{H}_{B\alpha}$), 1.48 (9H, s, C(C$\underline{H}_{\alpha 3}$)$_3$), 1.47 (9H, s, C(C$\underline{H}_{\beta 3}$)$_3$), 1.47-1.43 (1H, m (obscured), $CH_A\underline{H}_{B\beta}$), 1.31 (6H, m, 2 $CH_2C\underline{H}_3$); **LRMS** (+ESI): *m/z* = 312 (M+Na, 100%); **HRMS** (+ESI): calc. for $C_{14}H_{27}NO_5Na$ 312.1782, found 312.1786.

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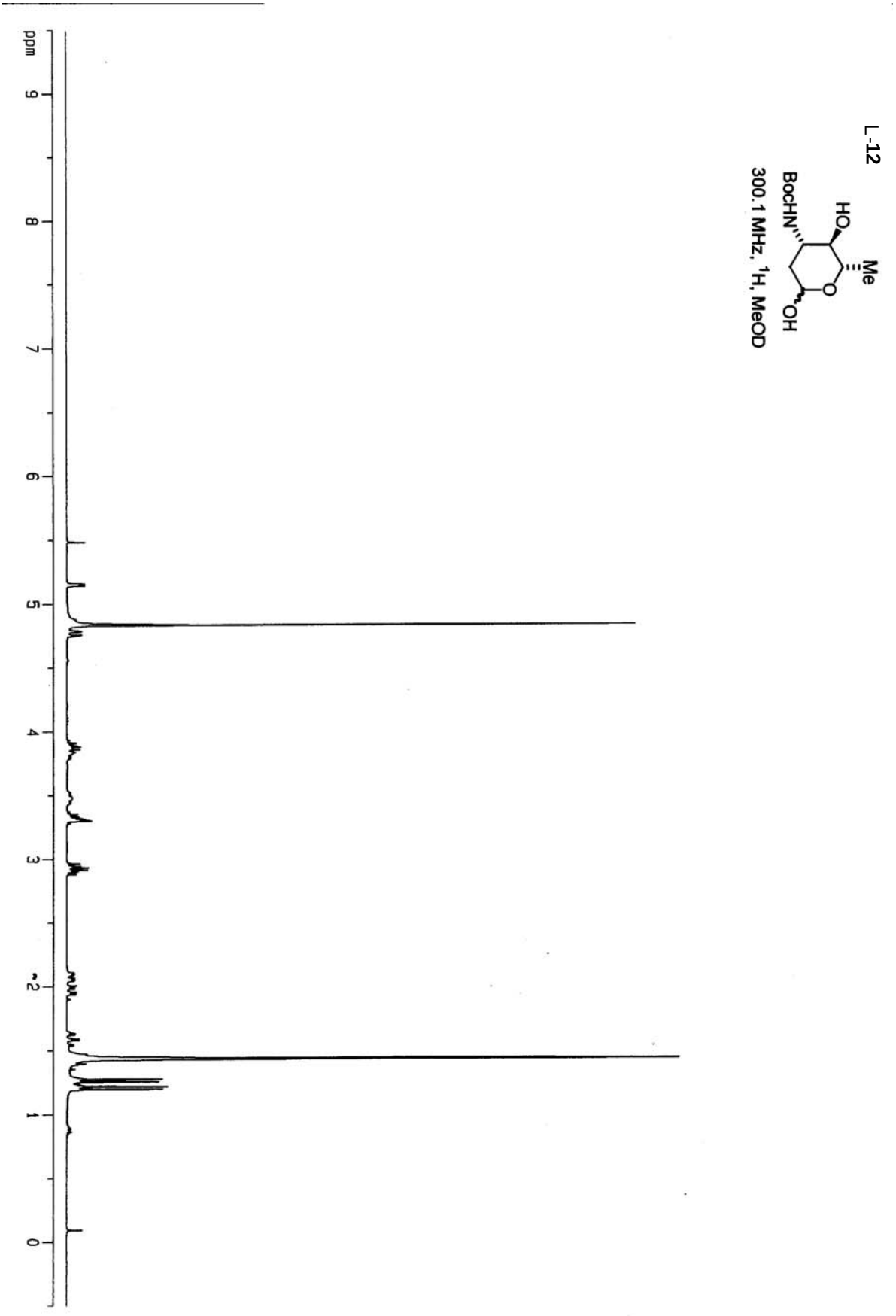
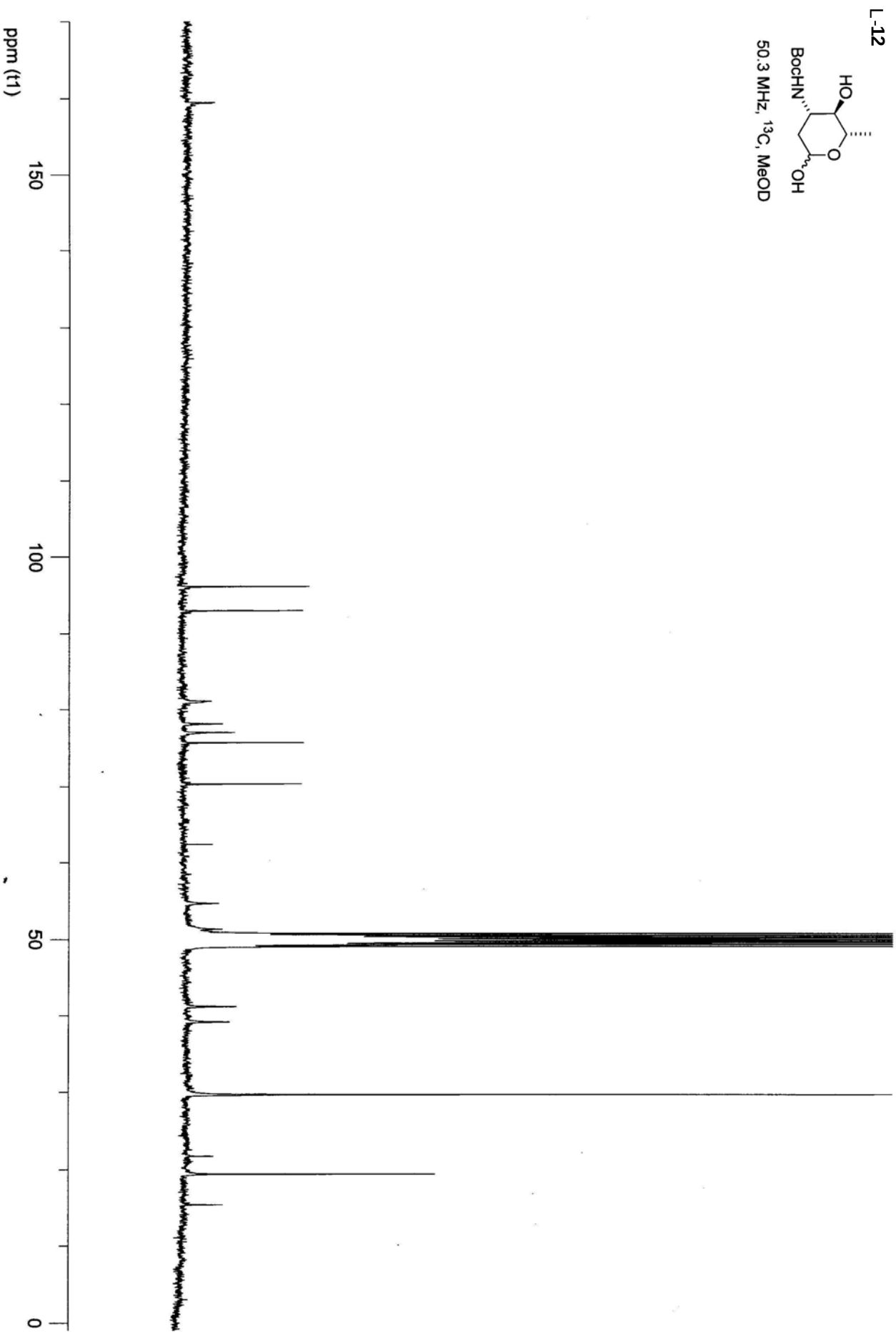
^{1}H and ^{13}C NMR spectra

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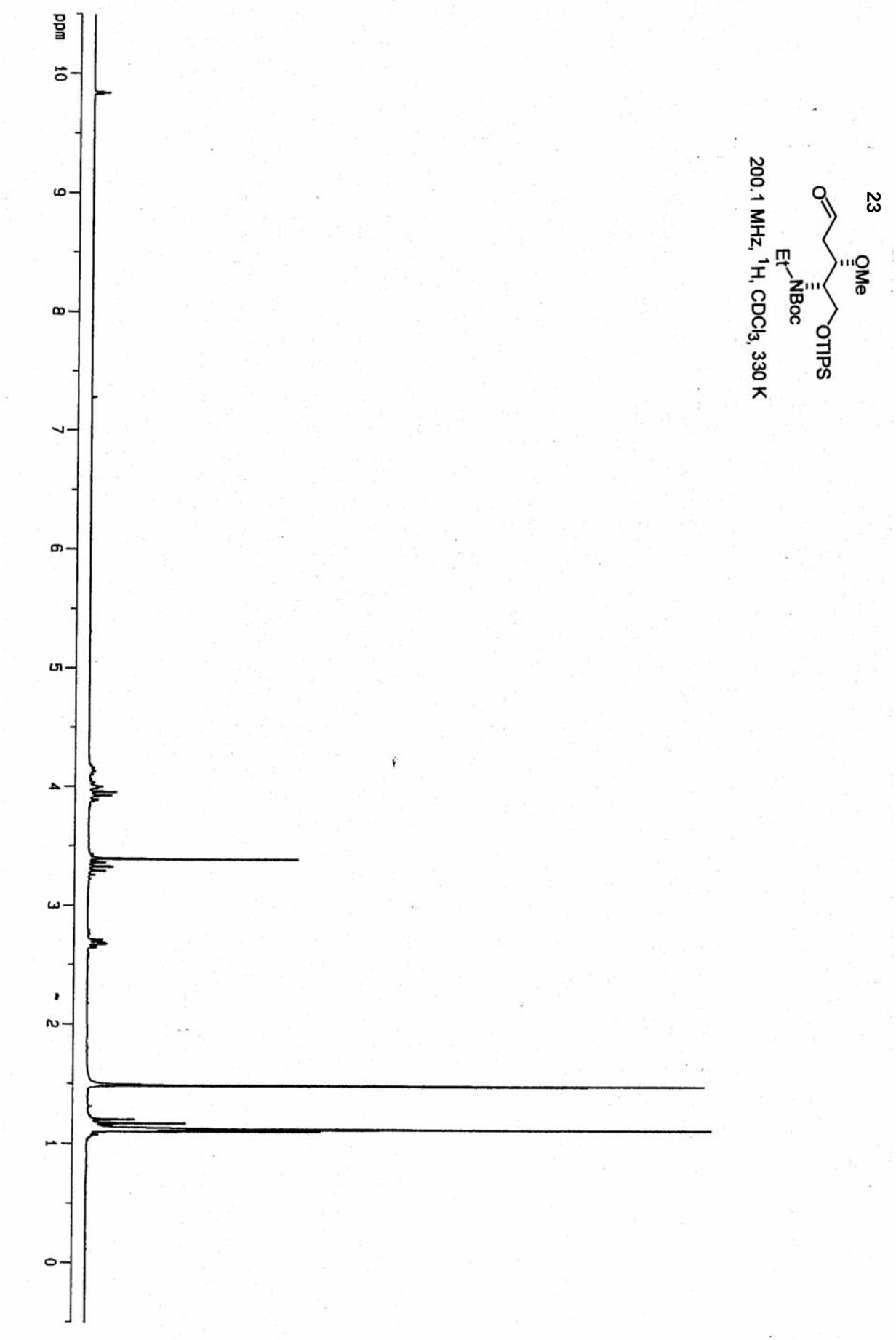
50
0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2
1
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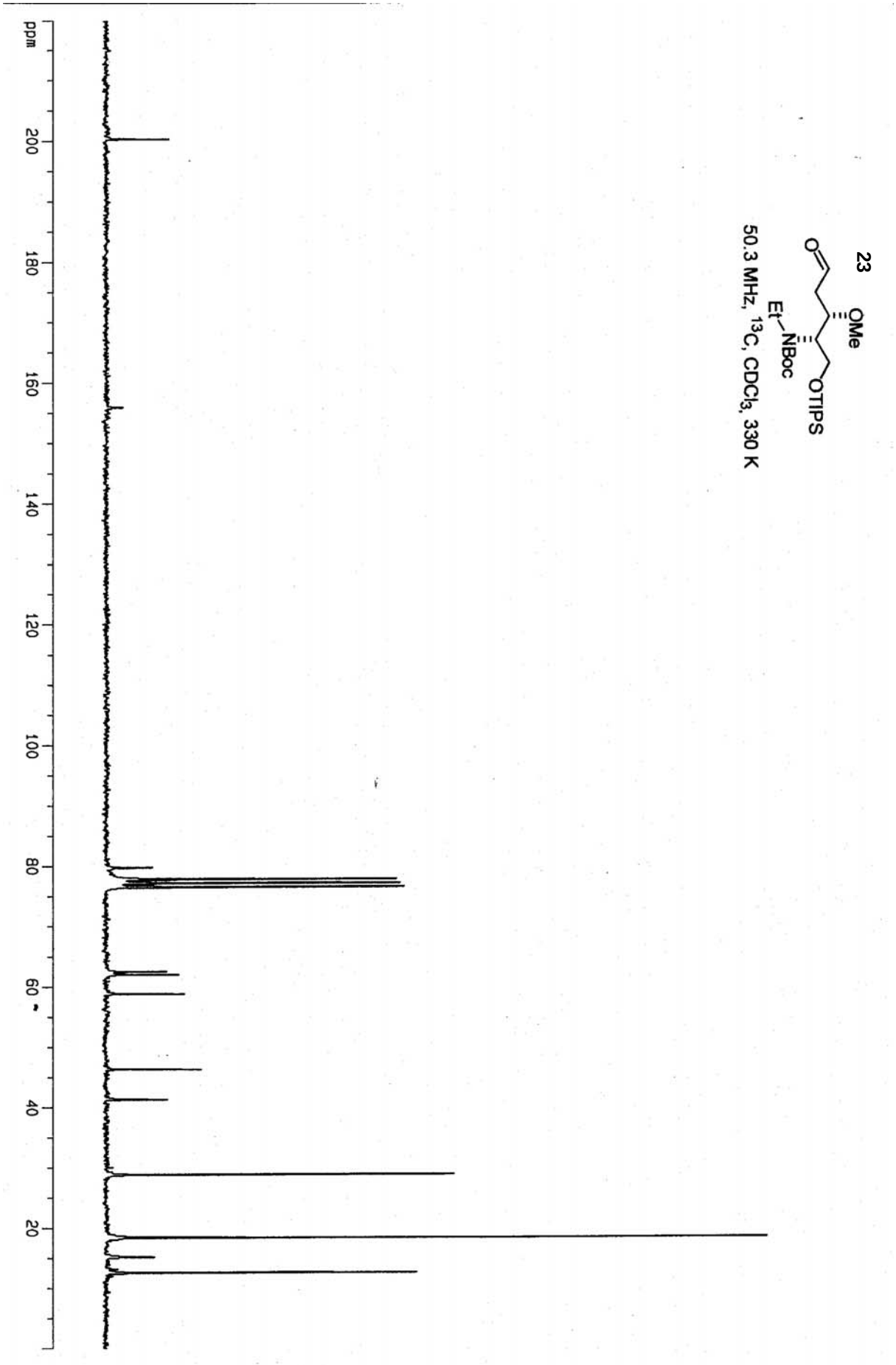
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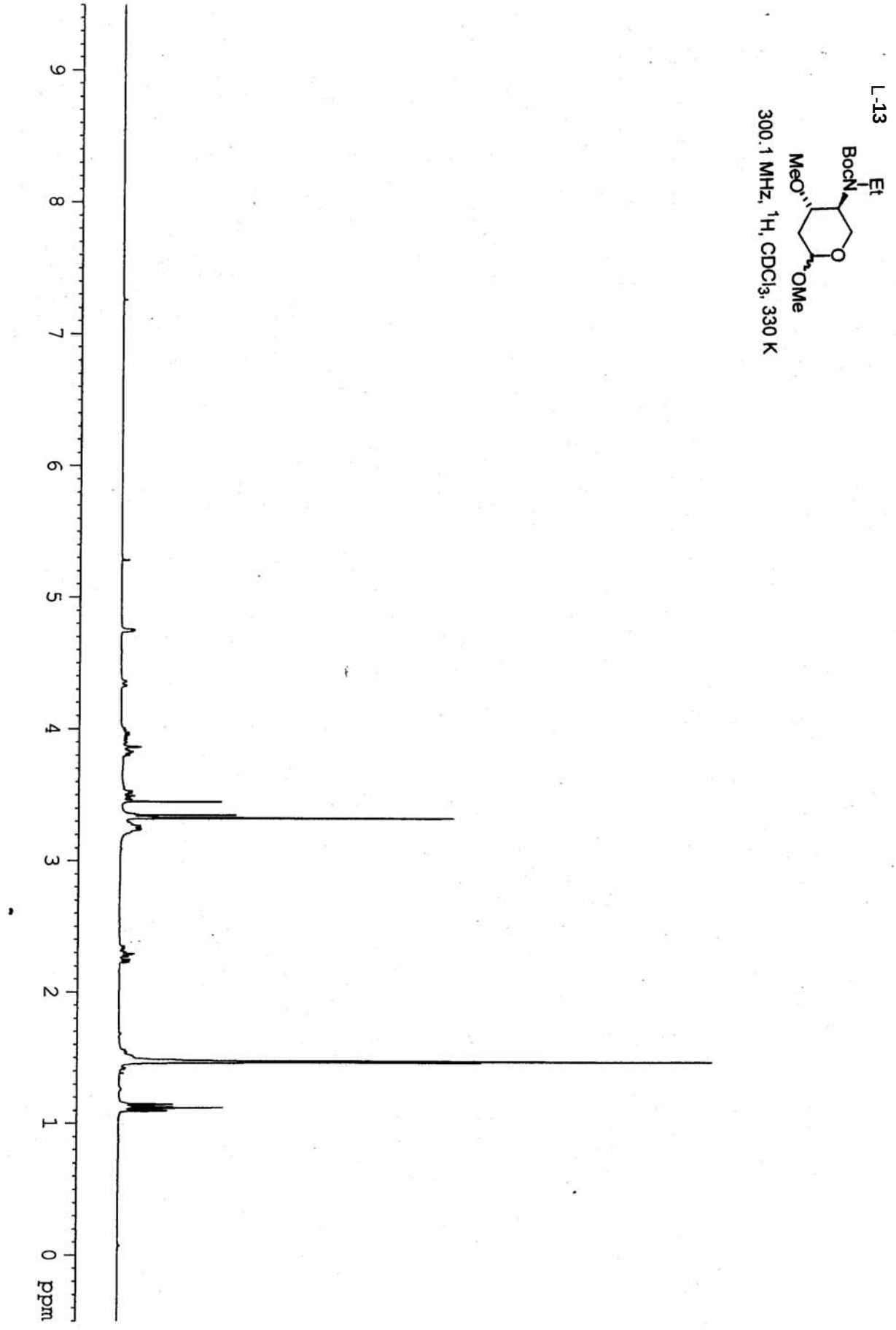
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2
1
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