The Total Synthesis of Ustiloxin D and Considerations on the Origin of Selectivity of the Asymmetric Allylic Alkylation

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Figure S1. HPLC Traces of Natural Ustiloxin D and **59**

Experimental Procedures. All reactions were carried out in flame-dried glassware sealed with a rubber septum under an argon atmosphere. Liquids and solutions were transferred *via* syringe or stainless steel cannula. The reaction solvents THF, Et₂O, toluene and benzene were distilled over sodium metal, CH₂Cl₂, CH₃CN, NEt₃, iPr₂NEt and pyridine were distilled over calcium hydride and anhydrous DMF in AcroSeal bottles were used without further purification. Flash chromatography was carried out using ICN silica gel 32-63 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed using EM 0.25mm silica gel 60 F₂₅₄ glass plates. TLC plates were visualized using UV fluorescence and by one or more of the following: ceric ammonium molybdate, potassium permanganate, ninhydrin, vanillin and iodine. Optical rotation was measured on a digital polarimeter using a sodium lamp at the indicated temperature. Infrared spectra were recorded on a FT-IR spectrometer and are reported in wavenumbers (cm⁻¹). ¹H NMR spectra were recorded on a 500MHz and 400 MHz spectrometer and are reported in ppm using the solvent resonance as an internal standard (CHCl₃=7.26 ppm, CD₂HOD=3.30 ppm, CD₂HS(O)CD₃=2.49 ppm, DOH=4.67 ppm). Data are reported as: δ shift (s= singlet, d=doublet, t=triplet, q=quartet, m=multiplet, b=broad, J=coupling constant in Hz, integration). Proton decoupled ¹³C NMR spectra were recorded on a 500 MHz and 400 MHz spectrometer and are reported in ppm using the solvent resonance as an internal standard (CDCl₃=77.0 ppm, CD₃OD=49.0 ppm, DMSO=39.5 ppm, 1,4-dioxane=66.5 ppm).

3-Acetoxy-4-hydroxybenzaldehyde (5). 3,4-Dihydroxybenzaldehyde (3.9 g, 28 mmol, 1 equiv, pretreated with activated charcoal in methanol-ethyl acetate mixture, filtered through celite and solvents removed) was suspended in 39 mL THF and cooled to 0 °C. Sodium hydroxide solution (35 mL, 70 mmol, 2.5 equiv, 2 N solution in water) was added dropwise, followed by a dropwise addition of acetic anhydride (3.2 mL, 34 mmol, 1.2 equiv). The reaction mixture was allowed to stir for 20 min then it was diluted with ethyl acetate. The reaction was acidified by addition of concentrated hydrochloric acid (2.5 mL) and pH 2.5 phosphate buffer (20 mL). THF was removed under reduced pressure, and the reaction mixture was filtered through a pad of celite and rinsed with ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the crude product was purified by silica gel chromatography. Byproduct 3,4-diacetoxybenzaldehyde was eluted using 100/1 chloroform/methanol with 0.5% triethylamine. Main product fractions were eluted using 70/1 to 50/1 chloroform/methanol, followed by 10/1 chloroform/methanol to elute 3-acetoxy-4-hydroxybenzaldehyde **5** (4.38 g, 24.3 mmol, 86%) (pale-yellow solid) was obtained along with 503 mg (2.26 mmol, 8%) of 3,4-diacetoxybenzaldehyde and 217 mg (1.57 mmol, 6%) of 3,4-dihydroxybenzaldehyde. All spectral properties matched literature values.¹

¹ Buchanan, J. G.; Hill, D. G.; Wightman, R. H.; Boddy, I. K.; Hewitt, B. D. *Tetrahedron* **1995**, *51*, 6033.

3-Acetoxy-4-benzyloxybenzaldehyde (6). Potassium carbonate (24.55 g, 177.6 mmol, 4 equiv) was added to DMF (250 mL) and cooled to 0 °C. Benzyl iodide was added dropwise (11.1 mL, 88.8 mmol, 2 equiv) followed by dropwise addition of a solution of **5** (8.0 g, 44.4 mmol, 1 equiv in 100 mL DMF) *via* an addition funnel. An additional 100 mL DMF was used to rinse the addition funnel.

Reaction was complete after 30 min at which time pH 2.5 buffer was added (450 mL) followed by water (500 mL) and then concentrated HCl (10 mL) to produce a solution of pH~4. An additional 500 mL water diluted the mixture and this was extracted with (4 × 500 mL) diethyl ether. These extracts were subsequently dried over anhydrous Na₂SO₄ and the volatiles removed under reduced pressure. The crude oil was loaded onto a silica gel column. Excess benzyl iodide was eluted using a gradient of 10/1 to 5/1 hexanes/ethyl acetate, followed by elution with 3/1 to obtain **6** (11.5 g, 42.5 mmol, 96%) as a white solid. All spectral properties matched literature values.²

(4R,5R)-5-(3-Acetoxy-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-(carboxylic acid methyl ester) (9). Molecular sieves (3Å, 1.24 g, dried overnight in 300 °C oven), anhydrous sodium sulfate (68 mg, 0.479 mmol, 0.2 equiv), 5-methoxy-2-(4-methoxyphenyl)-oxazole **8** (489 mg, 2.38 mmol, 1 equiv), **6** (775 mg, 2.87 mmol, 1.2 equiv) and (*S*)-2,2'-bis(3,5-di-*tert*-butyl-2-hydroxybenzilideneamino)-1,1'-binaphthyl aluminum chloride³ **7** (177 mg, 0.239 mmol, 0.1 equiv) were

added to an argon purged flame dried flask. After purging with argon, silver hexafluoroantimonate (very hygroscopic!) (85.5 mg, 0.249 mmol, 0.11 equiv) was added quickly followed again by an argon purge. Toluene (2.2 mL) was added and the reaction was wrapped in aluminum foil and stirred at room temperature for 25 h in a closed environment. Toluene (0.5 mL) was added at the four-hour point to keep the reaction stirring, because the product was not very soluble and the reaction mixture solidified. The reaction mixture was directly loaded onto a short silica gel column and all compounds were eluted using ethyl acetate and 2/1 chloroform/methanol. The crude material was purified using silica gel chromatography. (*S*)-2,2'-Bis(3,5-di-*tert*-butyl-2-hydroxybenzilideneamino)-1,1'-binaphthyl was eluted using 9/1 hexanes/ethyl acetate, followed by 3-acetoxy-4-benzyloxybenzaldehyde which eluted with 4/1 hexanes/ethyl acetate. Trace amounts of the *trans* compound (*4S,5R*)-5-(3-acetoxy-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-(carboxylic acid methyl ester) **10** eluted with 1/1 hexanes/ethyl acetate and 1/2 to 1/4 hexanes/ethyl acetate eluted the product **9** (1.11 g, 2.34 mmol, 99%). Enantioselectivity was determined to be 96% *ee* using Chiralpak AS column eluting with 15% ethanol in hexanes. The major isomer eluted at 16.07 min and the minor isomer eluted at 25.95 min. *R*_f=0.2 (1/1 hexanes/ethyl acetate); **IR** (film) 1756 m, 1645 m, 1609 m, 1514 s, 1455 w, 1346 w, 1303 w, 1259 s, 1200 s, 1171 s, 1122 m, 1084 m, 1026 m, 910 w, 840 w, 743 w, 693 w; **¹H NMR** (500

² Haensel, R.; Su, T-L.; Schulz, J. *Chem. Ber.* **1977**, *110*, 3664.

³ Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem. Int. Ed.* **2001**, *40*, 1884-1888.

MHz, CDCl_3) δ 8.00 (dd, $J=2, 7$ Hz, 2H), 7.34-7.28 (mult, 5H), 7.06 (dd, $J=2, 8$ Hz, 1H), 6.98 (d, $J=2$ Hz, 1H), 6.93 (dd, $J=2, 7$ Hz, 2H), 6.91 (d, $J=8$ Hz, 1H), 5.80 (d, $J=11$ Hz, 1H), 5.20 (d, $J=11$ Hz, 1H), 5.06 (s, 2H), 3.84 (s, 3H), 3.26 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (125.5 MHz, CDCl_3) δ 164.9, 168.7, 166.2, 162.6, 150.2, 140.0, 136.3, 130.5, 128.9, 128.5, 127.9, 127.0, 124.8, 120.9, 119.1, 113.8, 113.4, 81.9, 74.0, 70.5, 55.3, 51.9, 20.5; HRMS calculated for $\text{C}_{27}\text{H}_{25}\text{NO}_7$ ($\text{M}+\text{H}$): 476.1704, found (MALDI): 476.1705.

(4*S*,5*R*)-5-(3-Acetoxy-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-(carboxylic acid methyl ester) (10). *cis*-Oxazoline **9** (688 mg, 1.45 mmol, 1 equiv) was dissolved in dichloromethane (10 mL) at ambient temperature. 1,8-Diazabicyclo[5.4.0]undec-7-ene (43 μL , 0.29 mmol, 0.2 equiv) was added and the reaction mixture stirred for 2.5 h. The reaction was diluted with dichloromethane and then neutralized using 0.5 N-hydrochloric acid. The layers were separated and the

aqueous layer was extracted twice more with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate. Solvent was removed under reduced pressure and the crude material was purified on silica gel chromatography. *trans*-Oxazoline **10** was eluted using 3/1 to 2/1 hexanes/ethyl acetate (599 mg, 1.26 mmol, 87%), followed by recovered **9** (50.4 mg, 0.106 mmol, 7%) which eluted with 1/1 hexanes/ethyl acetate. $R_f=0.3$ (1/1 hexanes/ethyl acetate); ^1H NMR (400 MHz, CDCl_3) δ 8.00 (d, $J=8$ Hz, 2H), 7.47-7.62 (mult, 5H), 7.20 (d, $J=8$ Hz, 1H), 7.1- (s, 1H), 7.00 (d, $J=8$ Hz, 1H), 6.93 (d, $J=8$ Hz, 2H), 5.81 (d, $J=8$ Hz, 1H), 5.11 (s, 2H), 4.78 (d, $J=8$ Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.27 (s, 3H).

(4*S*,5*R*)-5-(3-Acetoxy-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-methyl-oxazolidine-4-carboxylic acid methyl ester (11). Toluene-azeotroped **10** (54.4 mg, 0.114 mmol, 1 equiv) was dissolved in dichloromethane (1 mL) at ambient temperature. Freshly distilled (from calcium hydride) methyl trifluoromethanesulfonate (15 mL, 0.13 mmol, 1.2 equiv) was added and the reaction was stirred 2h. Toluene was added and all solvent was removed under reduced pressure. The material was resuspended in dichloromethane (1 mL) at 0 $^\circ\text{C}$. Saturated

sodium bicarbonate solution (1 mL) and sodium borohydride (9.3 mg, 0.25 mmol, 2 equiv) were added all at once with vigorous stirring. Bubbling ensued and the reaction was stirred 15 min before being diluted with dichloromethane and water. The layers were separated and the aqueous layer was extracted twice more with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 . Solvent was removed under reduced pressure and the crude material was purified using silica gel chromatography. The desired **11** and the over-reduced 3-(3-acetoxy-4-benzyloxyphenyl)-3-hydroxy-2-benzylmethylaminopropionic acid methyl ester **14** eluted together using 4/1 hexanes/ethyl acetate and 48.3 mg of the mixture was obtained and the yields were 62 % and 24 % respectively, as determined by the integration of ^1H NMR spectrum. Recovered **10** (3.5 mg, 0.0074 mmol, 6%) was obtained by eluting with 2/1 to 1/2 hexanes/ethyl acetate.

5-(3-Acetoxy-4-benzyloxyphenyl)-1-(4-methoxyphenyl)-3-methyloxazolidine-4-carboxylic acid methyl ester **11**. $R_f=0.8$ (1/1 hexanes/ethyl acetate); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.49 (d, $J=8$ Hz, 2H), 7.40-6.91 (mult, 8H), 6.90 (d, $J=8$ Hz, 2H), 5.32 (d, $J=7$ Hz, 1H), 5.07 (s, 2H), 5.00 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.38 (d, $J=7$ Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H).

3-(3-Acetoxy-4-benzyloxyphenyl)-3-hydroxy-2-benzylmethylaminopropionic acid methyl ester **14**. $R_f=0.8$ (1/1 hexanes/ethyl acetate); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.38-7.27 (mult, 5H), 7.22 (d, $J=8$ Hz, 2H), 7.12 (dd, $J=2, 8$ Hz, 1H), 7.01 (d, $J=2$ Hz, 1H), 6.90 (d, $J=8$ Hz, 1H), 6.87 (d, $J=8$ Hz, 2H), 5.04 (s, 2H), 4.80 (d, $J=10$ Hz, 1H), 4.29 (br, 1H), 3.80 (s, 3H), 3.79 (d, $J=10$ Hz, 1H), 3.59 (s, 3H), 3.55 (d, $J=13$ Hz, 1H), 3.25 (d, $J=10$ Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H).

(4S,5R)-3-(3-Acetoxy-4-benzyloxyphenyl)-3-hydroxy-2-methylaminopropionic acid methyl ester (12). Oxazolidine **11** and the over-reduced **14** (133 mg, 0.271 mmol, 1 equiv) were dissolved in THF (10 mL) at 0 °C and 0.1 N oxalic acid solution (10 mL) was added. The reaction mixture was stirred overnight at 4 °C. THF was removed under reduced pressure and the reaction mixture was diluted with ethyl acetate. Saturated sodium bicarbonate

solution was added until the pH of the solution was 8. The layers were separated and the aqueous layer was extracted twice more with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude material was purified using silica gel column chromatography. 4-Methoxybenzaldehyde and the over reduced byproduct **14** eluted with 4/1 hexanes/ethyl acetate. The desired product **12** (81.2 mg, 0.217 mmol, 80%) eluted with 100% ethyl acetate and 10/1 ethyl acetate/methanol. $R_f=0.3$ (ethyl acetate); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.40-7.26 (mult, 5H), 7.14 (dd, $J=2, 8$ Hz, 1H), 7.03 (d, $J=2$ Hz, 1H), 6.59 (d, $J=8$ Hz, 1H), 5.07 (s, 2H), 4.51 (d, $J=8$ Hz, 1H), 3.55 (s, 3H), 3.16 (d, $J=8$ Hz, 1H), 2.37 (s, 3H), 2.24 (s, 3H).

(4S,5R)-3-(3-Acetoxy-4-benzyloxyphenyl)-2-(benzyloxycarbonylmethylamino)-3-tert-butyldimethylsilyloxypropionic acid methyl ester (13). Amino alcohol **12** (77.8 mg, 0.208 mmol, 1 equiv) was dissolved in acetonitrile (2 mL) at ambient temperature. Sodium bicarbonate (91.0 mg, 1.08 mmol, 5 equiv) was added followed by addition of benzyl chloroformate (45 μL , 0.32 mmol, 1.5 equiv). The reaction was stirred for 4 h and then diluted with ethyl acetate. Water was added and the

layers were separated. The aqueous layer was extracted twice more with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude material was purified using silica gel column chromatography. The product was obtained by eluting with a gradient of 9/1 to 2/1 hexanes/ethyl acetate. 3-(3-Acetoxy-4-benzyloxyphenyl)-2-(benzyloxycarbonylmethylamino)-3-hydroxypropionic acid methyl ester (97.8 mg, 0.193 mmol, 93%) was obtained. $R_f=0.4$ (1/1 hexanes/ethyl acetate); $^1\text{H NMR}$ (500 MHz, $\text{DMSO}-d_6$, 22 °C) δ 7.39-7.02 (mult, 5H), 5.95 (br, 1H), 5.22-4.85 (mult, 6H), 3.56 (3.59)

(s, 3H), 2.96 (2.92) (s, 3H), 2.23 (2.22) (s, 3H); $^1\text{H NMR}$ (500 MHz, DMSO- d_6 , 70 °C) δ 7.40-7.08 (mult, 5H), 7.52 (br, 1H), 5.19-4.84 (mult, 6H), 3.56 (s, 3H), 2.97 (s, 3H), 2.20 (s, 3H); **MS** calculated for $\text{C}_{28}\text{H}_{29}\text{O}_8\text{N}$ ($\text{M}+\text{Na}$): 530, found (ESI): 530. The chemical shifts in parentheses are the shifts for the minor rotamer.

3-(3-Acetoxy-4-benzyloxyphenyl)-2-(benzyloxycarbonylmethylamino)-3-hydroxypropionic acid methyl ester (97.8 mg, 0.193 mmol, 1 equiv) was dissolved in pyridine (1 mL) at ambient temperature. *tert*-Butyldimethylsilyl chloride (182 mg, 1.21 mmol, 6 equiv) and silver nitrate (202 mg, 1.19 mmol, 6 equiv) were added and the reaction mixture was stirred for 17 h. Pyridine was removed under reduced pressure and the reaction mixture was directly loaded onto a silica gel column. Elution with a gradient of 19/1 to 6/1 hexanes/ethyl acetate afforded **13** (109 mg, 0.175 mmol, 91%). $R_f=0.6$ (1/1 hexanes/ethyl acetate) $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 7.38-6.85 (mult, 13H), 5.34-4.77 (mult, 6H), 3.66 (3.63) (s, 3H), 3.10 (3.12) (s, 3H), 2.23 (2.24) (s, 3H), 0.84 (0.83) (s, 9H), 0.01 (-0.01) (s, 3H), -0.23 (-0.24) (s, 3H). The chemical shifts in parentheses are the shifts for the minor rotamer.

(4S,5R)-2-(Benzyloxycarbonylamino)-3-(3-benzyloxy-4-hydroxyphenyl)-3-(tert-butyldimethylsilyloxy)propionic acid methyl ester (4). Fully protected **13** (109 mg, 0.175 mmol, 1 equiv) was dissolved in THF (3 mL) and methanol (0.5 mL) at 0 °C. Potassium *tert*-butoxide (1 M solution in THF) (265 μL , 0.265 mmol, 1.5 equiv) was added and the reaction was stirred for 10 min. The reaction was diluted with ethyl acetate and neutralized by adding pH 2.5 phosphate buffer (2 mL). The layers

were separated. The aqueous layer was extracted twice more with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude material was purified using silica gel column chromatography. The product was obtained by eluting with 5/1 hexanes/ethyl acetate giving **4** (96.1 mg, 0.166 mmol, 95%). $R_f=0.5$ (1/1 hexanes/ethyl acetate); $^1\text{H NMR}$ (500 MHz, DMSO- d_6) δ 7.47-6.66 (mult, 13H), 5.22-4.79 (mult, 6H), 3.60 (3.58) (s, 3H), 3.06 (3.00) (s, 3H), 0.80 (s, 9H), -0.02 (-0.03) (s, 3H), -0.28 (-0.27) (s, 3H). The chemical shifts in parentheses are the shifts for the minor rotamer.

Carbonic acid-1-ethyl-1-methylallyl ester methyl ester (16). 3-Methylpent-1-ene-3-ol (1.97 mL, 16.5 mmol, 1 equiv) was dissolved in THF (30 mL) at 0 °C. Butyl lithium (1.6 M solution in hexanes) (11.5

mL, 18.4 mmol, 1.1 equiv) was added dropwise and the reaction mixture was stirred for 30 min. Methyl chloroformate (1.9 mL, 25 mmol, 1.5 equiv) was added dropwise and the reaction was gradually warmed to room temperature and stirred at room temperature for 4 h. The reaction was acidified by the addition of 1 N hydrochloric acid, and the organic products were extracted three times with ether. The combined organic layers were dried over anhydrous MgSO_4 . Solvents were carefully removed under reduced pressure, and the product was distilled under reduced pressure. Product **16** distilled at 58 °C, 5 mm Hg (2.19 g, 13.9 mmol, 84%). $R_f=0.8$ (5/1 hexanes/ethyl acetate); **IR** (film) 2976 w, 1752 m, 1442 w, 1275 s, 1134 w, 993 w, 943 w, 871 w, 794 w; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ

5.99 (dd, $J=12, 20$ Hz, 1H), 5.22 (d, $J=12$ Hz, 1H), 5.18 (d, $J=20$ Hz, 1H), 3.72 (s, 3H), 1.86 (q, $J=8$ Hz, 2H), 1.57 (s, 3H), 0.91 (t, $J=8$ Hz, 3H); ^{13}C NMR (125.5 MHz, CDCl_3) δ 153.7, 140.6, 114.0, 84.6, 53.8, 32.3, 22.2, 7.7;

Carbonic acid methyl ester-3-methylpent-2-enyl ester (17).

3-Methylpent-2-en-1-ol⁴ (1.49 g, 14.9 mmol, 1 equiv) was diluted with dichloromethane (50 mL) at 0 °C. 4-Dimethylaminopyridine (2.55 g, 20.8 mmol, 1.4 equiv) was added followed by methyl chloroformate (1.38 mL, 17.9 mmol, 1.2 equiv). The reaction was allowed to warm to room temperature and stirred 10 h. 1N HCl solution (100 mL) was added and the layers were separated. The aqueous layer was then extracted with dichloromethane (3 $\times$ 50 mL). The combined organic layers were dried over anhydrous MgSO_4 . After careful removal of the solvent under reduced pressure, **17** was distilled under reduced pressure (104 °C, 30 mmHg) (1.84 g, 11.6 mmol, 78%). $R_f=0.8$ (5/1 hexanes/ethyl acetate); IR (film) 2972 s, 1801 s, 1750 s, 1445 s, 1381 m, 1270 s, 1089 m, 949 m, 793 s; ^1H NMR (400 MHz, CDCl_3) δ 5.34 (t, $J=10$ Hz, 1H), 4.64 (d, $J=10$ Hz, 2H), 3.76 (s, 3H), 2.14 (q, $J=8$ Hz, 2H), 1.01 (t, $J=8$ Hz, 3H); ^{13}C NMR (125.5 MHz, CDCl_3) δ 155.7, 145.4, 117.3, 64.1, 54.5, 24.9, 22.7, 12.8;

3-[3-(1-Ethyl-1-methylallyloxy)-4-methoxyphenyl]acrylic acid methyl ester (21).

Phenol **20** (50.1 mg, 0.241 mmol, 1 equiv), (*1S,2S*)-1,2-bis(2-diphenylphosphinobenzoyl)-aminocyclohexane⁵ **19** (8.2 mg, 0.012 mmol, 0.05 equiv) and tris(dibenzylideneacetone)dipalladium(0)-chloroform⁶ (2.5 mg, 0.0024 mmol, 0.01 equiv) were dissolved in dichloromethane (degassed by bubbling argon for 20 min) (0.5 mL) at room temperature. **16** (77.3 mg, 0.489 mmol, 2 equiv) was added as a solution in dichloromethane (1.5 mL). The reaction was complete within 30 min and the reaction mixture was loaded onto a silica gel column. **21** (68.1 mg, 0.235 mmol, 97%, 25%*ee*) was obtained upon elution with 15/1 to 3/1 hexanes/ethyl acetate. $R_f=0.7$ (2/1 hexanes/ethyl acetate); $R_t=16.0$ min (major isomer), 17.5 min (minor isomer), Chiralpak AD (1 mL/min, 1% isopropyl alcohol/heptane); ^1H NMR (400 MHz, CDCl_3) δ 7.58 (d, $J=16$ Hz, 1H), 7.23 (s, 1H), 7.15 (d, $J=12$ Hz, 1H), 6.86 (d, $J=12$ Hz, 1H), 6.21 (d, $J=16$ Hz, 1H), 6.07 (dd, $J=12, 20$ Hz, 1H), 5.20 (d, $J=12$ Hz, 1H), 5.14 (d, $J=20$ Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 1.93-1.76 (mult, 2H), 1.38 (s, 3H), 1.00 (t, $J=8$ Hz, 3H).

3-[3-(1-Ethyl-1-methylallyloxy)-4-methanesulfonyloxyphenyl]acrylic acid methyl ester (23).

This compound was synthesized in a similar manner to **21** starting from **22** (30.1 mg, 0.111 mmol, 1 equiv). Adduct **23** (11.6 mg, 0.0327 mmol, 29%, 10%*ee*) was obtained upon elution with 10/1 to 2/1 hexanes/ethyl acetate followed by recovered starting material

⁴ Sen, S. E.; Ewing, G. J. *J. Org. Chem.* **1997**, 62, 3529-3536.

⁵ Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, 114, 9327-9343.

⁶ Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, 65, 253-266.

23 (21.5 mg, 0.0790 mmol, 71%). R_f =0.5 (2/1 hexanes/ethyl acetate); R_t =10.9 min (minor isomer), 11.3 min (major isomer), Chiralpak AD (1 mL/min, 10% isopropyl alcohol/heptane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.57 (d, J =16 Hz, 1H), 7.36-7.29 (mult, 2H), 7.16 (d, J =12 Hz, 1H), 6.30 (d, J =12 Hz, 1H), 6.07 (dd, J =12, 20 Hz, 1H), 5.29 (d, J =12 Hz, 1H), 5.21 (d, J =20 Hz, 1H), 3.79 (s, 3H), 3.20 (s, 3H), 1.93-1.80 (mult, 2H), 1.45 (s, 3H), 0.99 (t, J =8 Hz, 3H).

3-{3-(1-Ethyl-1-methylallyloxy)-4-[2-(trimethylsilyl)ethoxymethoxy]phenyl}acrylic acid methyl ester (25). This compound was synthesized in a similar manner to **21** starting from **24** (72.1 mg, 0.222 mmol, 1 equiv). Adduct **25** (78.9 mg, 0.194 mmol, 87%, 18%*ee*) was obtained upon elution with 20/1 to 4/1 hexanes/ethyl acetate followed by recovered starting material **24** (2.9 mg, 0.0894 mmol, 4%). R_f =0.7 (2/1

hexanes/ethyl acetate); R_t =8.7 min (major isomer), 9.2 min (minor isomer), Chiralpak AD (1 mL/min, 1% isopropyl alcohol/heptane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.57 (d, J =16 Hz, 1H), 7.24 (d, J =2 Hz, 1H), 7.12 (d, J =2 Hz, 1H), 7.11 (s, 1H), 6.23 (d, J =16 Hz, 1H), 6.08 (dd, J =16, 20 Hz, 1H), 5.24 (s, 2H), 5.20 (d, J =12 Hz, 1H), 5.15 (d, J =20 Hz, 1H), 3.79 (s, 3H), 3.76 (d, J =8 Hz, 1H), 3.74 (d, J =12 Hz, 1H), 1.91-1.74 (mult, 2H), 1.36 (s, 3H), 0.98 (t, J =8 Hz, 3H), 0.96 (dd, J =8, 8 Hz, 2H), 0.00 (s, 9H).

3-[3-(1-Ethyl-1-methylallyloxy)-4-methoxymethoxyphenyl]acrylic acid methyl ester (27). Using **16**: This compound was synthesized in a similar manner to **21** starting from **26** (53.2 mg, 0.223 mmol, 1 equiv). Adduct **27** (67.5 mg, 0.211 mmol, 94%, 20%*ee*) was obtained upon elution with 20/1 to 3/1 hexanes/ethyl acetate.

Using **17**: Phenol **26** (52.3 mg, 0.223 mmol, 1 equiv), (*1S,2S*)-1,2-bis(2-diphenylphosphinobenzoyl)aminocyclohexane **19** (7.7 mg, 0.011 mmol, 0.05 equiv) and tris(dibenzylideneacetone)dipalladium(0)-chloroform (2.3 mg, 0.0022 mmol, 0.01 equiv) were dissolved in dichloromethane (degassed by bubbling argon for 20 min) (0.5 mL) at room temperature. Carbonate **16** (70.6 mg, 0.446 mmol, 2 equiv) was added as a solution in dichloromethane (1.5 mL). The reaction was complete within 30 min and the reaction mixture was loaded onto a silica gel column. Adduct **27** (31.4 mg, 0.0981 mmol, 44%, 82%*ee*) was obtained upon elution with 20/1 to 3/1 hexanes/ethyl acetate followed by recovered starting material **26** (28.7 mg, 0.120 mmol, 54%). R_f =0.6 (2/1 hexanes/ethyl acetate); R_t =29.3 min (minor isomer), 31.6 min (major isomer), Chiralcel OJ (0.5 mL/min, 0.8% isopropyl alcohol/heptane); R_t =16.8 min (major isomer), 18.4 min (minor isomer), Chiralpak AD (0.9 mL/min, 1% isopropyl alcohol/heptane); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.57 (d, J =16 Hz, 1H), 7.23 (s, 1H), 7.11-7.04 (mult, 2H), 6.23 (d, J =16 Hz, 1H), 6.07 (dd, J =12, 20 Hz, 1H), 5.20 (d, J =12 Hz, 1H), 5.15 (d, J =20 Hz, 1H), 3.79 (s, 3H), 3.52 (s, 3H), 1.92-1.75 (mult, 2H), 1.37 (s, 3H), 0.99 (t, J =8 Hz, 3H).

(2*S*,3*S*)-2-Azido-3-[3-(1-ethyl-1-methylallyloxy)-4-methoxymethoxyphenyl]-3-hydroxypropionic acid methyl ester (29). Using **16**: This compound was synthesized in a similar manner to **21** starting from **28** (16.2 mg, 0.0545 mmol, 1 equiv). Adduct **29** (17.5 mg, 0.0461 mmol, 85%, 22%*ee*) was obtained upon elution with 10/1 to 1/1 hexanes/ethyl acetate followed by recovered starting material **28** (0.5 mg, 0.0017 mmol, 3%).

Using **17**: This compound was synthesized in a similar manner to **27** starting from **28** (16.2 mg, 0.0545 mmol, 1 equiv) and **17**. Adduct **29** (2.28 mg, 0.0060 mmol, 11%, 80%*ee*) was obtained upon elution with 10/1 to 1/1 hexanes/ethyl acetate followed by recovered starting material **28** (12.0 mg, 0.0403 mmol, 74%). R_f =0.7 (1/1 hexanes/ethyl acetate); R_t =12.5 min (major isomer), 13.0 min (minor isomer), Chiralpak AD (0.9 mL/min, 10% isopropyl alcohol/heptane); ^1H NMR (400 MHz, CDCl_3) δ 7.96-6.92 (mult, 3H), 6.13-6.03 (mult, 1H), 5.18 (s, 2H), 5.22-5.10 (mult, 1H), 4.90 (d, J =8 Hz, 1H), 4.02 (d, J =8 Hz, 1H), 3.80 (s, 3H), 3.56 (s, 3H), 1.91-1.73 (mult, 2H), 1.38 (s, 3H), 0.99 (t, J =8 Hz, 3H).

General Procedure for: 2-(Benzyloxycarbonyl-methylamino)-3-[4-benzyloxy-3-(1-ethyl-1-methylallyloxy)phenyl]-3-(tert-butyldimethylsilyloxy)-propionic acid methyl ester (30). Phenol **4** (1 equiv) was dissolved in dichloromethane (1.5 mL, degassed by bubbling argon for 20 min) at room temperature. (*1*S*,2*S**)-1,2-Bis(2-diphenylphosphinobenzoyl)aminocyclohexane **19** (0.5 equiv) and tris(dibenzylideneacetone)dipalladium(0)-chloroform

adduct (0.1 equiv) were added. The carbonate precursor to the π -allyl Pd complex (5 equiv) was added as a 200 μL solution in dichloromethane. After 2 h, the reaction mixture was loaded directly onto a silica gel column. Excess π -allyl precursor and dibenzylideneacetone were eluted using 20/1 hexanes/ethyl acetate. Desired product **30** eluted with 10/1 hexanes/ethyl acetate, followed by recovered **4** which eluted with 4/1 hexanes/ethyl acetate. R_f =0.5 (5/1 hexanes/ethyl acetate); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.75-7.19 (mult, 13H), 6.31-6.22 (mult, 1H), 5.60 (5.53) (d, J =5 Hz, 1H), 5.42-5.05 (mult, 5H), 3.91 (3.87) (s, 3H), 3.34 (3.18) (s, 3H), 2.00-1.90 (mult, 2H), 1.47 (1.51) (s, 3H), 1.14 (t, J =9 Hz, 3H), 1.09 (1.08) (s, 9H), 0.28 (0.27) (s, 3H), 0.01 (-0.01) (s, 3H). The NMR chemical shifts in parentheses are the shifts for the minor rotamer.

Using **16**: **30** was prepared according to the above General Procedure from **16** (8.7 mg, 0.0550 mmol, 5 equiv) to afford **30** (3.4 mg, 0.00514 mmol, 78%).

Using **17**: **30** was prepared according to the above General Procedure from **17** (8.7 mg, 0.0550 mmol, 5 equiv) to afford **30** (0.4 mg, 0.000659 mmol, 10%).

Using **31**: **30** was prepared according to the above General Procedure from **31** (8.7 mg, 0.0335 mmol, 5 equiv) to afford **30** (1.0 mg, 0.00151 mmol, 24%).

Using **34**: **30** was prepared according to the above General Procedure from **34** (3.6 mg, 0.00510 mmol, 1 equiv) to afford **30** (0.5 mg, 0.000755 mmol, 15%).

Carbonic acid (Z)-3-methyl-pent-2-enyl ester 2,2,2-trichloro-ethyl ester (31). 3-Methylpent-2-en-1-ol (750 mg, 7.49 mmol, 1 equiv) was diluted with dichloromethane (15 mL) at 0 °C. 2,2,2-Trichloroethyl chloroformate (1.56 mL, 11.2 mmol, 1.5 equiv) was added followed by pyridine (727 μ L, 8.99 mmol, 1.2 equiv). The reaction was complete immediately and saturated NH_4Cl solution (10 mL) was added and the layers were separated. The aqueous layer was then extracted with dichloromethane (3×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After careful removal of the solvent under reduced pressure, the crude mixture was loaded onto a silica gel column. Using a gradient of 20/1 pentane/diethyl ether to 100% diethyl ether, **31** was obtained (2.04 g, 7.42 mmol, 99%). $R_f=0.8$ (5/1 hexanes/ethyl acetate); **IR** (film) 2970 m, 1759 s, 1668 w, 1447 m, 1389 m, 1279 s, 1238 s, 1124 w, 1062 w, 945 w, 901 w, 818 m, 727 m; **^1H NMR** (500 MHz, CDCl_3) δ 5.33 (t, $J=10$ Hz, 1H), 4.72 (s, 3H), 4.67 (d, $J=7$ Hz, 2H), 2.10 (q, $J=8$ Hz, 2H), 1.73 (s, 3H), 0.98 (t, $J=7.5$ Hz, 3H); **^{13}C NMR** (125.5 MHz, CDCl_3) δ 153.9, 146.3, 116.9, 94.4, 76.6, 65.2, 25.0, 22.9, 12.9;

Phosphoric acid dimethyl ester (Z)-3-methyl-pent-2-enyl ester (32). 3-Methylpent-2-en-1-ol (347 mg, 3.47 mmol, 1 equiv) was diluted with dichloromethane (10 mL) at 0 °C. Pyridine (672 μ L, 8.32 mmol, 2.4 equiv) was added followed by phosphorochloridic acid dimethyl ester (1.2 mL, 10.4 mmol, 3.0 equiv). The reaction was allowed to warm to room temperature and stirred 1.5 h. 1N HCl solution (10mL) was added and the layers were separated. The aqueous layer was then extracted with dichloromethane (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After careful removal of the solvent under reduced pressure, the crude mixture was loaded onto a silica gel column. Using a gradient of 1/1 pentane/diethyl ether to 100% diethyl ether, **32** was obtained (279 mg, 1.34 mmol, 38%). $R_f=0.15$ (5/1 hexanes/ethyl acetate); **IR** (film) 2965 s, 1668 w, 1450 m, 1380 w, 1283 s, 1187 m, 1042 s, 987 s, 847 s, 751 w; **^1H NMR** (500 MHz, CDCl_3) δ 5.15 (t, $J=7$ Hz, 1H), 3.55 (s, 3H), 3.55 (d, $J=9$ Hz, 2H), 3.52 (s, 3H), 1.90 (q, $J=7.5$ Hz, 2H), 1.55 (s, 3H), 0.79 (t, $J=8$ Hz, 3H); **^{13}C NMR** (125.5 MHz, CDCl_3) δ 144.8, 118.1, 63.4, 53.7, 24.5, 22.4, 18.0, 12.4; **HRMS** calculated for $\text{C}_8\text{H}_{17}\text{O}_4\text{P}$ ($\text{M}+\text{Na}$): 231.0762, found (ESI): 231.0768.

Chloro-3-methylpent-2-enyl formate (73). This compound was synthesized following the procedure for the synthesis of chloro-2-trimethylsilylethyl formate⁷. 3-Methylpent-2-ene-1-ol (50.5 mg, 0.504 mmol, 1 equiv) was dissolved in toluene (0.3 mL) at ambient temperature. Potassium carbonate (70.9 mg, 0.513 mmol, 1 equiv) was added followed by phosgene (20% solution in toluene) (370 μ L, 0.699 mmol, 1.4 equiv). The reaction was stirred for 1.5 h and then argon was bubbled for 5 min to blow away excess phosgene. The reaction mixture was filtered through a pad of anhydrous magnesium sulfate, and rinsed with ether. Ether was carefully removed under reduced pressure, and

⁷ Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.

the remaining toluene solution of chloro-3-methylpent-2-enyl formate **73** was used directly without characterization for the next reaction. $R_f=0.9$ (5/1 hexanes/ethyl acetate).

2-(Benzyloxycarbonylmethylamino)-3-[4-benzyloxy-3-(3-methylpent-2-enyloxycarbonyloxy)phenyl]-3-(tert-butyldimethylsilyloxy)propionic acid methyl ester (34**)**. Phenol **4** (5.4 mg, 0.0093 mmol, 1 equiv) was dissolved in dichloromethane (0.2 mL) at 0 °C. Diisopropylethylamine (8 μ L, 0.046 mmol, 5 equiv) was added followed by **73** (0.7 M solution in toluene) (40 μ L, 0.028 mmol, 3 equiv).

The reaction was allowed to warm to room temperature and stirred for 20 h. The reaction was diluted with dichloromethane and saturated sodium bicarbonate solution was added. The product was extracted three times with dichloromethane and the combined organic layers were dried over anhydrous MgSO_4 . After removal of the solvent under reduced pressure, the crude product was purified using silica gel column chromatography. Using a gradient of 5/1 to 2/1 hexanes/ethyl acetate, **34** (3.9 mg, 0.0055 mmol, 59%) was obtained. $R_f=0.6$ (2/1 hexanes/ethyl acetate); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.40-6.75 (mult, 13H), 5.33-4.65 (mult, 7H), 3.67 (3.62) (s, 3H), 3.10 (3.11) (s, 3H), 2.11-2.05 (mult, 2H), 1.72 (s, 3H), 0.97 (0.96) (t, $J=8$ Hz, 3H), 0.84 (0.82) (s, 9H), 0.00 (-0.02) (s, 3H), -0.24 (-0.26) (s, 3H); **MS** calculated for $\text{C}_{39}\text{H}_{51}\text{O}_9\text{NSi}$ ($\text{M}+\text{Na}$): 728, found (ESI): 728. The NMR chemical shifts in parentheses are the shifts for the minor rotamer.

(4S,5R)-5-(4-Benzyloxy-3-hydroxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-(carboxylic acid methyl ester) (40**)**. Fully protected **10** (950 mg, 2.00 mmol, 1 equiv) was dissolved in THF (30 mL) and methanol (6 mL) at 0 °C. Potassium carbonate (332 mg, 2.40 mmol, 1.2 equiv) was added and the reaction was allowed to warm to room temperature and stirred overnight. Most of the solvent was removed under reduced pressure, and the reaction was resuspended in dichloromethane.

pH 2.5 Phosphate buffer was added until the yellow color disappeared (about 12 mL) and the layers were separated. The aqueous layer was extracted twice more with dichloromethane and the combined organic layers were dried over anhydrous Na_2SO_4 . After the removal of the solvent under reduced pressure, the products were purified using silica gel column chromatography. Using a gradient of 2/1 to 1/2 hexanes/ethyl acetate, **40** (769 mg, 1.78 mmol, 89%) was obtained followed by the *cis* isomer, (4*R*,5*R*)-5-(4-benzyloxy-3-hydroxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-(carboxylic acid methyl ester) (41.5 mg, 0.0957 mmol, 5%). $R_f=0.4$ (2/1 benzene/ether); **IR** (film) 3028 w, 2952 w, 1739 m, 1637 m, 1609 m, 1512 s, 1452 w, 1421 w, 1339 m, 1257 s, 1228 s, 1171 s, 1130 w, 1084 m, 1025 m, 913 w, 842 w, 743 w, 696 w; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.96 (dd, $J=2, 7$ Hz, 2H), 7.38-7.31 (mult, 5H), 6.94 (d, $J=2$ Hz, 1H), 6.88 (d, $J=7$ Hz, 2H), 6.87 (d, $J=8$ Hz, 1H), 6.81 (dd, $J=2, 8$ Hz, 1H), 6.32 (s, 1H), 5.73 (d, $J=7.5$ Hz, 1H), 5.07 (s, 2H), 4.73 (d, $J=7.5$ Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H); $^{13}\text{C NMR}$ (125.5 MHz, CDCl_3) δ 171.4, 165.2, 162.5, 146.4, 146.1, 136.0, 133.0, 130.4,

128.6, 128.3, 127.6, 119.1, 117.5, 113.6, 112.3, 112.2, 82.8, 76.4, 71.0, 55.3, 52.7; **HRMS** calculated for $C_{25}H_{25}NO_6$ (M+H): 434.1598, found (MALDI): 434.1592.

(4S,5R)-5-[3-(Benzyloxy-4-)-1-(1S)-ethyl-1-methylallyloxy)-phenyl]-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (41b).

Phenol **40** (827 mg, 1.91 mmol, 1 equiv) was dissolved in dichloromethane (degassed by bubbling argon for 20 min) (8 mL) at room temperature. (*1R,2R*)-1,2-bis(2-diphenylphosphinobenzoyl)aminocyclohexane **19** (331 mg, 0.480 mmol, 0.25 equiv) and tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (99.5 mg, 0.0961 mmol, 0.05 equiv) were added. Carbonic acid-1-ethyl-1-methylallyl ester methyl ester **16** (907 mg, 5.73 mmol, 3 equiv) was added dropwise over 10 min. The reaction turned yellow. When **16** was fully consumed, the reaction color changed to orange. A subsequent aliquot of **16** (50 μ L, 0.3 mmol, 0.15 equiv) was added when the color change was observed. (About one addition every 5 min over 20 min were necessary.) Though the reaction appeared to stop after one hour, the contents were further stirred for two additional hours and then were directly loaded onto a silica gel column. A gradient of 10/1 to 5/1 hexanes/ethyl acetate eluted excess **16** and dibenzylideneacetone. The product **41b**, (837 mg, 1.55 mmol, 81%, 27%*de*) eluted with 2/1 hexanes/ethyl acetate and recovered starting material **40** (130 mg, 0.282 mmol, 15%) was obtained upon elution with 1/2 hexanes/ethyl acetate. R_f =0.4 (2/1 hexanes/ethyl acetate); R_t =31.6 min (major isomer **41b**), 37.4 min (minor isomer **41a**), Chiralpak AD (0.9 mL/min, 80% ethanol/hexane); **IR** (film) 2969 w, 2935 w, 1740 m, 1641 m, 1609 m, 1576 w, 1512 s, 1454 w, 1434 w, 1420 w, 1307 w, 1258 s, 1224 m, 1170 s, 1133 w, 1082 m, 1026 w, 1008 w, 920 w, 842 w, 772 w, 740 w, 697 w; **¹H NMR** (500 MHz, $CDCl_3$) δ 7.96 (dd, J =2, 9 Hz, 2H), 7.42 (d, J =9 Hz, 1H), 7.35 (t, J =7.5 Hz, 2H), 7.29 (t, J =7.5 Hz, 1H), 6.93-6.90 (mult, 2H), 6.91 (d, J =9 Hz, 2H), 6.01 (dd, J =12, 18 Hz, 1H), 5.71 (d, J =7 Hz, 1H), 5.06 (s, 2H), 5.05-5.00 (mult, 2H), 4.70 (d, J =7 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 1.83-1.71 (mult, 2H), 1.23 (s, 3H), 0.91 (t, J =7.5 Hz, 3H); **¹³C NMR** (100 MHz, $CDCl_3$) δ 171.4, 165.1, 162.4, 152.0, 146.2, 142.9, 137.1, 132.0, 130.4, 128.3, 127.6, 127.1, 120.2, 120.1, 119.2, 114.8, 114.5, 113.6, 83.6, 82.7, 76.6, 71.0, 55.2, 52.6, 34.1, 21.1, 8.2; **HRMS** calculated for $C_{31}H_{33}NO_6$ (M+H): 516.2381, found (MALDI): 516.2385.

(4S,5R)-5-[4-Benzyloxy-3-((1S,2S)-1-ethyl-2,3-dihydroxy-1-methylpropoxy)phenyl]-4,5-dihydrooxazole-4-carboxylic acid methyl ester (42d).

Terminal alkene **41b** (779 mg, 1.51 mmol, 1 equiv), potassium carbonate (210 mg, 1.52 mmol, 1 equiv), sodium bicarbonate (256 mg, 3.05 mmol, 2 equiv), potassium ferricyanide(III) (1.49 g, 4.54 mmol, 3 equiv) were charged in a flask. (DHQD)₂PYR (266 mg, 0.302 mmol, 0.2 equiv) was added as a solution in *tert*-butyl alcohol (7.5 mL), followed by potassium osmate dihydrate (28.1 mg, 0.0763 mmol, 0.05 equiv) in water (7.5 mL). The reaction was stirred at room temperature for 3 days. Sodium sulfite (2.27 g) was added

and the reaction was stirred for 30 min. The products were extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 . After removal of the solvent under reduced pressure, the crude material was purified using silica gel column chromatography. Recovered starting material **41b** (118 mg, 0.227 mmol, 15%) eluted using 3/1 hexanes/ethyl acetate. The desired product **42d** (614 mg, 1.12 mmol, 74%, 78%*de*) was obtained by elution with a gradient of 1/1 to 1/4 hexanes/ethyl acetate. $R_f=0.3$ (1/2 hexanes/ethyl acetate); **IR** (film) 3483 m, 2940 m, 1742 m, 1634 s, 1608 s, 1579 w, 1511 s, 1505 s, 1455 w, 1436 w, 1422 w, 1377 w, 1259 s, 1224 m, 1171 s, 1133 m, 1083 m, 1026 m, 842 w, 749 w, 698w; **¹H NMR** (400 MHz, CDCl_3) δ 8.01 (d, $J=12$ Hz, 2H), 7.45-7.23 (mult, 5H), 6.96 (d, $J=12$ Hz, 2H), 7.08-6.90 (mult, 3H), 5.76 (d, $J=8$ Hz, 1H), 5.09 (s, 2H), 4.74 (d, $J=8$ Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.60-3.76 (mult, 3H), 1.97-1.79 (mult, 1H), 1.68-1.45 (mult, 1H), 1.19 (s, 3H), 0.98 (t, $J=8$ Hz, 3H); **¹³C NMR** (100 MHz, CDCl_3) δ 171.4, 165.2, 162.6, 152.7, 143.9 (144.0), 135.7, 132.5 (135.6), 130.4, 128.7, 128.6, 128.4, 127.7 (127.9), 122.3 (122.9), 121.6 (121.8), 119.1, 113.8, 87.3 (86.8), 82.5, 76.6 (75.4), 74.1, 71.2 (71.3), 62.6 (62.5), 55.4, 29.5 (29.3), 19.7 (19.9), 8.4; **HRMS** calculated for $\text{C}_{31}\text{H}_{35}\text{NO}_8$ ($\text{M}+\text{Na}$): 572.2255, found (MALDI): 572.2269. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4S,5R)-5-{4-Benzoyloxy-3-[(1S,2R)-1-(carboxyhydroxymethyl)-1-methylpropoxy]phenyl}-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (43). Diol **42d** (481 mg, 0.876 mmol, 1 equiv) was dissolved in dichloromethane (22 mL) at 0 °C. Saturated sodium bicarbonate solution (22 mL) was added followed by the addition of potassium bromide (20.4 mg, 0.171 mmol, 0.2 equiv), 2,2,6,6-tetramethyl-1-

piperidinyloxy, free radical (TEMPO) (28.1 mg, 0.180 mmol, 0.2 equiv). Sodium hypochlorite solution (commercial bleach, 5.25% by weight, 1.5 mL, 1.1 mmol, 1.2 equiv) was added with vigorous stirring. The reaction was complete within 20 min. Saturated sodium sulfite solution was added to quench excess oxidant. The layers were separated and the aqueous layer was extracted twice more with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was directly used for the next oxidation reaction without further characterization. $R_f=0.8$ (1/2 hexanes/ethyl acetate).

The crude aldehyde was dissolved in *tert*-butyl alcohol (47 mL) and 2-methyl-2-butene (18 mL) at room temperature. Sodium chlorite (913 mg, 8.08 mmol, 9.2 equiv, ~80% tech grade) and sodium phosphate monobasic hydrate (836 mg, 6.06 mmol, 6.9 equiv) were dissolved in water (16 mL) and added as an aqueous solution. After stirring for 20 min, pH 2.5 phosphate buffer was added and the layers were separated. The aqueous layer was extracted twice with chloroform. The combined organic layers were dried over anhydrous Na_2SO_4 . After removal of the solvent, the crude product was purified using silica gel column chromatography. TEMPO eluted first with 1/1 hexanes/ethyl acetate. **43** (494 mg, 0.876 mmol, quant.) started to elute using 1/2 hexanes/ethyl acetate and continued to elute until elution with 10/1 chloroform/methanol. $R_f=0.5$ (5/1 chloroform/methanol); **IR** (film) 3478 w, 2953 m, 2566 w, 1742 s, 1634 s,

1609 s, 1511 s, 1505 s, 1455 m, 1309 m, 1259 s, 1224 s, 1173 s, 1131 m, 1086 m, 1026 m, 949 w, 919 w, 842 w, 753 m, 698 w; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.99 (d, $J=12$ Hz, 2H), 7.47-7.31 (mult, 5H), 6.95 (d, $J=12$ Hz, 2H), 7.03-6.91 (mult, 3H), 5.78 (d, $J=8$ Hz, 1H), 5.12 (5.14) (s, 2H), 4.75 (d, $J=8$ Hz, 1H), 4.33 (4.26) (br, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 2.02-1.72 (mult, 2H), 1.23 (1.25) (s, 3H), 1.03 (t, $J=8$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 171.3, 165.3, 162.7, 152.2, 143.2, 135.2, 132.8, 130.5, 128.8, 128.7, 128.5, 128.1, 127.9 (127.7), 122.3, 122.2 (121.6), 118.9, 113.8 (113.6), 86.7 (86.4), 82.4, 76.5, 74.5, 71.2 (71.1), 55.4, 52.8, 28.9, 19.8 (19.2), 8.0 (7.6); **HRMS** calculated for $\text{C}_{31}\text{H}_{35}\text{NO}_9$ ($\text{M}+\text{H}$): 564.2228, found (MALDI): 564.2220. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4*S*,5*R*)-5-(4-Benzoyloxy-3-((1*S*)-1-[(*R*)-(tert-butoxycarbonylmethylcarbamoyl)hydroxymethyl]-1-methylpropoxy}phenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (44). Free acid **43** (285 mg, 0.506 mmol, 1 equiv) and glycine *tert*-butyl ester hydrochloride (132 mg, 0.788 mmol, 1.5 equiv) were dissolved in acetonitrile

(20 mL) at room temperature. Benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (450 mg, 1.02 mmol, 2 equiv) was added, followed by the addition of diisopropylethylamine (440 μL , 2.53 mmol, 5 equiv). After stirring for 1 hour, more glycine *tert*-butyl ester hydrochloride (39.3 mg, 0.234 mmol, 0.5 equiv), BOP reagent (112 mg, 0.253 mmol, 0.5 equiv) and diisopropylethylamine (88 μL , 0.51 mmol, 1 equiv) were added. The reaction was further stirred for another 2.5 h and then diluted with ethyl acetate. Phosphate buffer (pH 2.5) was added and the layers were separated. The aqueous layer was extracted twice more with ethyl acetate and the combined organic layers were washed twice with saturated sodium bicarbonate solution, once with brine, and dried over anhydrous sodium sulfate. After the removal of the solvent under reduced pressure, the crude product was purified using silica gel column chromatography. Using a gradient of 2/1 to 1/2 hexanes/ethyl acetate, **44** (300 mg, 0.443 mmol, 88%) was obtained. $R_f=0.5$ (1/1 hexanes/ethyl acetate); **IR** (film) 3363 w, 2976 w, 2930 w, 1741 s, 1672 m, 1641 m, 1609 m, 1512 s, 1455 w, 1434 w, 1367 w, 1257 s, 1224 m, 1169 s, 1134 m, 1082 m, 1026 w, 1009 w, 843 w, 750 w, 698 w; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.97 (dd, $J=2, 7$ Hz, 2H), 7.74 (t, $J=6$ Hz, 1H), 7.37-7.32 (mult, 5H), 7.07 (d, $J=2$ Hz, 1H), 6.99 (dd, $J=2, 8.5$ Hz, 1H), 6.94 (d, $J=7.5$ Hz, 2H), 6.91 (d, $J=8.5$ Hz, 1H), 5.73 (d, $J=7.6$ Hz, 1H), 5.03 (dd, $J=10, 22$ Hz, 2H), 4.71 (4.72) (d, $J=7.5$ Hz, 1H), 4.26 (4.18) (d, $J=3.5$ Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.57 (dd, $J=6, 18$ Hz, 1H), 3.36 (dd, $J=5.5, 18$ Hz, 1H), 1.95 (mult, 1H), 1.80 (mult, 1H), 1.36 (s, 9H), 1.24 (1.42) (s, 3H), 0.98 (t, $J=7$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 172.2 (171.1), 168.4, 165.2, 162.6, 152.6 (151.4), 143.9, 135.8 (135.6), 132.7 (132.6), 130.4, 128.9, 128.7 (128.5), 127.7 (127.9), 122.4, 120.5 (121.7), 119.1 (119.8), 113.8, 113.6 (113.4), 86.1 (87.0), 82.5 (82.4), 81.6 (81.9), 76.8, 72.9 (74.8), 71.2 (71.1), 55.4, 52.8, 41.6 (41.7), 28.5 (28.9), 27.9, (28.0), 18.9 (19.3), 8.0 (7.6); **HRMS** calculated for $\text{C}_{37}\text{H}_{44}\text{N}_2\text{O}_{10}$ ($\text{M}+\text{Na}$): 699.2888, found (MALDI): 699.2905. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4*S*,5*R*)-5-(4-Benzoyloxy-3-((1*S*)-1-[(*R*)-(tert-butoxycarbonylmethyl-carbamoyl)-trifluoromethanesulfonyloxy-methyl]-1-methyl-propoxy}-phenyl)-2-(4-methoxy-phenyl)-4,5-dihydro-oxazole-4-carboxylic acid methyl ester (45). Alcohol **44** (1.23 mg, 1.81 mmol, 1 equiv) was dissolved in dichloromethane (45 mL) at -20 °C. Pyridine (1.5 mL, 19 mmol, 10 equiv) was added

followed by the addition of trifluoromethanesulfonic anhydride (914 μ L, 5.43 mmol, 3 equiv). Temperature was carefully maintained at -20 °C over 8 h. The reaction was then diluted with dichloromethane and saturated sodium bicarbonate solution was added and warmed to room temperature. The layers were separated and the aqueous layer was extracted twice more with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄. After the removal of the solvent under reduced pressure, the crude triflate was purified using silica gel column chromatography. Byproduct and pyridine eluted using 3/1 hexanes/ethyl acetate, followed by the desired triflate (1.17 g, 1.45 mmol, 80%), which eluted with a gradient of 3/1 to 2/1 hexanes/ethyl acetate. Recovered starting material **44** (164 mg, 0.242 mmol, 13%) eluted using 1/2 hexanes/ethyl acetate. **45** was used without further characterization. R_f =0.6 (1/1 hexanes/ethyl acetate).

(4*S*,5*R*)-5-(3-((1*S*)-1-[(*S*)-Azido-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (46). Triflate **45** (1.17 g, 1.45 mmol, 1 equiv) was dissolved in 1,3-dimethyl-3,4,5,6-tetrahydro-2(*H*)-pyrimidinone (DMPU) (6 mL). Lithium azide

(1.05 g, 12.0 mmol, 8.3 equiv, 56% by weight dispersed in DMPU) was added and the reaction was stirred at room temperature for 2 d. The reaction was loaded directly onto a silica gel column and eluted with 1/2 hexanes/ethyl acetate to remove most of the reaction solvent, DMPU. The product fractions were concentrated and the crude product was purified using silica gel column chromatography. Trace amount of the recovered triflate eluted using a gradient of 3/4/2 to 3/8/4 hexanes/benzene/ether. The product **46** (711 mg, 1.01 mmol, 70%) eluted using a gradient of 3/8/4 to 0/2/1 hexanes/benzene/ether. R_f =0.6 (2/1 benzene/ether, developed twice); **IR** (film) 3359 w, 2972 w, 2116 s, 1742 m, 1682 w, 1652 w, 1607 m, 1514 s, 1370 m, 1259 s, 1223 m, 1168 m, 1080w, 1026 w, 843 w, 770 w; **¹H NMR** (500 MHz, CDCl₃) δ 7.98 (d, J =9 Hz, 2H), 7.39-7.33 (mult, 6H), 7.05 (d, J =2 Hz, 1H), 7.03 (dd, J =2, 9 Hz, 1H), 6.96-6.91 (mult, 1H), 6.92 (dd, J =2, 7 Hz, 2H), 5.75 (d, J =7.5 Hz, 1H), 5.04 (5.07) (d, J =2 Hz, 2H), 4.73 (d, J =7.5 Hz, 1H), 4.33 (4.28) (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.72 (3.71) (dd, J =5.5, 9.5 Hz, 1H), 3.61 (3.54) (dd, J =5.5, 18 Hz, 1H), 1.90-1.82 (mult, 1H), 1.79-1.70 (mult, 1H), 1.39 (1.41) (s, 9H), 1.30 (1.20) (s, 3H), 0.95 (0.96) (t, J =7.5 Hz, 3H); **¹³C NMR** (100

MHz, CDCl₃) δ 171.4, 168.4, 167.8, 165.2, 162.6, 152.3 (150.9), 143.5, 136.0, 132.3, 130.4, 128.8, 128.7, 128.4 (128.3), 127.8, 122.9 (123.0), 121.8 (121.9), 121.5, 119.1, 113.7, 113.6, 85.7 (85.9), 82.5, 81.9 (82.0), 70.9, 68.8 (69.2), 55.4, 52.8, 41.6 (41.8), 29.2, 27.9, 20.3 (20.1), 8.0 (8.3); **HRMS** calculated for C₃₇H₄₃N₅O₉ (M+H): 702.3133, found (MALDI): 702.3163. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(2S,3R)-3-(3-((1S)-1-[(S)-Azido-(*tert*-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy)-4-benzyloxyphenyl)-3-hydroxy-2-methylaminopropionic acid methyl ester (47). Oxazoline **46** (297 mg, 0.423 mmol, 1 equiv) was dissolved in dichloromethane (4.5 mL) at room temperature. Methyl

trifluoromethanesulfonate (57 μ L, 0.50 mmol, 1.2 equiv, freshly distilled from calcium hydride) was added and the reaction was stirred at room temperature for 1 h. Toluene was added and the reaction mixture was azeotroped. The reaction mixture was redissolved in dichloromethane (4.5 mL) at 0 °C. Saturated sodium bicarbonate solution (4.5 mL) and sodium borohydride (32.4 mg, 0.856 mmol, 2 equiv) were added at once with vigorous stirring, accompanied by bubbling. After 15 min, the layers were separated and the aqueous layer was extracted twice more with dichloromethane. The combined organic layers were dried over anhydrous Na₂SO₄. After the removal of the solvent under reduced pressure, the crude products were purified using silica gel column chromatography. Using a gradient of 3/1 to 3/2 hexanes/ethyl acetate, the desired (4*S*,5*R*)-5-(3-((1*S*)-1-[(*S*)-azido-(*tert*-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy)-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-methyloxazolidine-4-carboxylic acid methyl ester was obtained as a mixture with the over-reduced product, (2*S*,3*R*)-3-(3-((1*S*)-1-[(*S*)-azido-(*tert*-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy)-4-benzyloxyphenyl)-3-hydroxy-2-[(4-methoxybenzyl)methylamino]propionic acid methyl ester (251 mg combined). Using 1/2 hexanes/ethyl acetate, starting material **46** (29.7 mg, 0.0416 mmol, 10%) was recovered. *R*_f=0.8 (1/2 hexanes/ethyl acetate). The NMR spectrum of this compound was too complex to be analyzed due to the presence of multiple oxazolidine diastereomers.

The mixture of (4*S*,5*R*)-5-(3-((1*S*)-1-[(*S*)-azido-(*tert*-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy)-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-methyloxazolidine-4-carboxylic acid methyl ester and the over-reduced (2*S*,3*R*)-3-(3-((1*S*)-1-[(*S*)-azido-(*tert*-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy)-4-benzyloxyphenyl)-3-hydroxy-2-[(4-methoxybenzyl)methylamino]propionic acid methyl ester (251 mg combined) was dissolved in THF (15 mL) at room temperature. 0.1 N Oxalic acid solution (12 mL) was added and the reaction was allowed to stir overnight. After removal of THF at reduced pressure, aqueous 1 N HCl (2 mL) was added and the reaction mixture was washed with ether to remove *p*-methoxybenzaldehyde. The aqueous layer was then made basic to pH paper using saturated sodium bicarbonate solution. The products were extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure and purified by elution with 2/1 hexanes/ethyl acetate separated the

over-reduced byproduct and some remaining *p*-methoxybenzaldehyde. Using a gradient of 1/2 hexanes/ethyl acetate to 100% ethyl acetate to 10/1 chloroform/ethyl acetate, the desired **47** (154 mg, 0.257 mmol, 61% over 2 steps) was obtained. $R_f=0.4$ (ethyl acetate); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.44-7.29 (mult, 6H), 7.07-6.86 (mult, 3H), 5.05 (5.02) (s, 2H), 4.53 (d, $J=8$ Hz, 1H), 4.29 (4.33) (s, 1H), 3.77-3.64 (3.21-3.18) (mult, 2H), 3.58 (3.59) (s, 3H), 3.53 (3.52) (s, 3H), 2.40 (s, 3H), 1.91-1.75 (mult, 2H), 1.39 (1.41) (s, 9H), 1.30 (1.20) (s, 3H), 1.00 (0.97) (t, $J=8$ Hz, 3H). The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4*S*,5*R*)-5-(3-((1*S*)-1-[(*S*)-((2*S*)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (52**).**

Azide **46** (684 mg, 0.974 mmol, 1 equiv) was dissolved in THF (8 mL) and water (2 mL) at room temperature. Trimethylphosphine ($\text{P}(\text{Me})_3$) (2.9 mL,

2.9 mmol, 4 equiv, 1 M solution in THF) was added and the reaction was allowed to stir 4 h. THF was removed under reduced pressure. Ethyl acetate and saturated sodium bicarbonate solution were added. The layers were separated and the aqueous layer was extracted twice more with ethyl acetate. The combined organic layers were washed once with brine and dried over anhydrous Na_2SO_4 . Solvents were removed under reduced pressure and the crude product was loaded onto a silica gel column. The desired amine **52** (498 mg, 0.737 mmol, 76%) eluted using a gradient of 25/1 to 5/1 chloroform/methanol. $R_f=0.2$ (1/2 hexanes/ethyl acetate); **IR** (film) 3375 w, 2976 w, 2935 w, 1743 s, 1674 m, 1645 m, 1609 m, 1511 s, 1506 s, 1455 w, 1367 w, 1305 w, 1257 s, 1223 m, 1170 s, 1082 w, 1026 w, 1008 w, 843 w, 741 w, 698 w; $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.97 (d, $J=9$ Hz, 2H), 7.73 (7.81) (br, 1H), 7.37-7.32 (mult, 5H), 7.24-7.23 (mult, 1H), 7.04-7.02 (mult, 2H), 6.92 (d, $J=9$ Hz, 2H), 5.74 (d, $J=7$ Hz, 1H), 5.02 (5.05) (s, 2H), 4.72 (d, $J=7.5$ Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.64 (s, 2H), 1.91 (mult, 1H), 1.77 (mult, 1H), 1.39 (1.42) (s, 9H), 1.25 (1.69) (s, 3H), 0.93 (1.02) (t, $J=7.5$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 173.2 (173.0), 171.5, 168.9, 165.2, 162.6, 152.4, 144.1, 136.1, 132.2 (132.3), 130.4, 128.7, 128.6, 128.4 (128.3), 127.8, 121.0 (122.2), 121.2 (121.3), 119.2, 113.8, 113.5 (113.4), 86.4, 82.6, 81.6 (81.8), 70.9, 60.6, 55.4, 52.8, 41.7, 28.6 (29.5), 28.0, 19.9 (19.6), 8.1 (8.2); **HRMS** calculated for $\text{C}_{37}\text{H}_{45}\text{N}_3\text{O}_9$ ($\text{M}+\text{H}$): 676.3228, found (MALDI): 676.3218. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4*S*,5*R*)-5-(3-((1*S*)-1-((2*S*)-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl)-1-methylpropoxy)-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (54). Amine **52** (490 mg, 0.724 mmol, 1 equiv) and azidovaline⁸ **53** (157 mg, 1.09 mmol, 1.5 equiv) were dissolved in acetonitrile (7 mL) at room temperature. BOP reagent (642 mg, 1.45

mmol, 2 equiv) and diisopropylethylamine (460 μ L, 2.64 mmol, 4 equiv) were added and the reaction was stirred for 9 h. The reaction was diluted with ethyl acetate and saturated sodium bicarbonate solution was added. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed once with brine and dried over anhydrous Na_2SO_4 . Solvents were removed under reduced pressure, and the crude product was loaded onto a silica gel column. The desired product, **54** (599 mg, 0.713 mmol, 98%) was obtained upon elution with 1/1 to 1/2 hexanes/ethyl acetate. $R_f=0.5$ (1/2 hexanes/ethyl acetate); **IR** (film) 3373 w, 2970 w, 2930, 2099 m, 1741 s, 1672 s, 1609 m, 1512 s, 1455 w, 1368 w, 1257 s, 1222 m, 1170 s, 1127 w, 1082 w, 1026 m, 1008 w, 844 m, 742 w, 698 w; **^1H NMR** (500 MHz, CDCl_3) δ 7.95 (d, $J=8.5$ Hz, 2H, 7.43-7.22 (mult, 7H), 7.03 (d, $J=1.5$ Hz, 1H), 7.07-6.94 (mult, 1H), 6.91 (d, $J=8.5$ Hz, 1H), 6.90 (d, $J=8.5$ Hz, 2H), 5.73 (5.72) (d, $J=7.5$ Hz, 1H), 5.21-5.02 (mult, 1H), 5.11 (5.12) (s, 2H), 4.79 (4.99) (d, $J=9$ (8) Hz, 1H), 4.70 (d, $J=7.5$ Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.67-3.62 (mult, 2H), 2.32-2.25 (mult, 1H), 2.00-1.94 (1.70-1.64) (mult, 1H), 1.78-1.71 (1.64-1.54) (mult, 1H), 1.35 (1.38) (s, 9H), 1.25 (1.17) (s, 3H), 0.99 (0.98) (d, $J=7$ Hz, 3H), 1.01 (0.88) (t, $J=6.5$ Hz, 3H), 0.86 (d, $J=7$ Hz, 3H); **^{13}C NMR** (125.5 MHz, CDCl_3) δ 171.4, 169.3, 169.2 (168.9), 168.5 (168.2), 165.2, 162.6, 151.7, 143.6 (143.5), 136.1 (135.7), 132.4 (132.2), 130.4, 128.9, 128.7, 128.5, 128.1, 127.4, 123.4, 122.0, 120.9, 119.9 (119.1), 113.8, 113.3, 85.4 (86.1), 82.5, 81.7 (81.8), 76.7 (76.6), 71.0 (70.5), 58.2 (58.9), 55.4, 52.8, 41.8 (42.1), 31.8 (31.9), 30.1 (28.7), 27.9 (28.0), 20.1 (20.5), 19.5, 17.1 (17.2), 8.4 (8.3); **HRMS** calculated for $\text{C}_{42}\text{H}_{52}\text{N}_6\text{O}_{10}$ ($\text{M}+\text{H}$): 801.3817, found (MALDI): 801.3794. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(2*S*,3*R*)-3-(3-((*IS*)-1-[(*S*)-((2*S*)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy)-4-benzyloxyphenyl)-3-hydroxy-2-methylaminopropionic acid methyl ester (55). Oxazoline **54** (579 mg, 0.687 mmol, 1 equiv) was dissolved in dichloromethane (12 mL) at room temperature. Methyl trifluoromethanesulfonate (freshly distilled from

⁸ Hackeng, T. M.; Griffin, J. H.; Dawson, P. E. *Proc. Natl. Acad. Sci. USA* **1999**, 96, 10068-10073.

calcium hydride) (95 μ L, 0.84 mmol, 1.2 equiv) was added and the reaction was stirred for 2 h. Toluene was added and the reaction mixture was azeotroped and dried under high vacuum (0.5 mmHg). The residue was dissolved in dichloromethane (20 mL) at 0 °C. Saturated sodium bicarbonate solution (20 mL) and sodium borohydride (51.5 mg, 1.36 mmol, 2 equiv) were added at once with vigorous stirring. After 10 min, the layers were separated, and the aqueous layer was extracted twice more with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified using silica gel column chromatography. The desired (4*S*,5*R*)-5-(3-{(1*S*)-1-[(*S*)-((2*S*)-2-azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-methyloxazolidine-4-carboxylic acid methyl ester (549 mg, 0.672 mmol) was obtained upon elution with 2/1 to 1/1 hexanes/ethyl acetate. R_f =0.8 (1/2 hexanes/ethyl acetate), followed by the recovered starting material **54** (37.7 mg, 0.0471 mmol, 7%).

(4*S*,5*R*)-5-(3-{(1*S*)-1-[(*S*)-((2*S*)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-methyloxazolidine-4-carboxylic acid methyl ester (549 mg, 0.672 mmol) was dissolved in THF (20 mL) at room temperature. Oxalic acid (0.1 N solution in water) (16 mL) was added and the reaction was stirred for 9 h. THF was removed under reduced pressure, and chloroform and saturated sodium bicarbonate solution were added. The layers were separated and the aqueous layer was extracted twice more with chloroform. The combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude products were purified using silica gel column chromatography. Using 1/1 hexanes/ethyl acetate, *p*-methoxybenzaldehyde and the over-reduced product that had formed in the methylation step eluted. The desired product **55** (334 mg, 0.470 mmol, 68% over 2 steps) was obtained upon elution with a gradient of 1/4 hexanes/ethyl acetate, 100% ethyl acetate and 20/1 chloroform/methanol. R_f =0.2 (1/2 hexanes/ethyl acetate); ^1H NMR (500 MHz, CD_3OD) δ 7.50-7.46 (mult, 2H), 7.32-7.41 (mult, 3H), 7.16 (7.12) (d, J =2 Hz, 1H), 7.01-7.07 (mult, 1H), 6.98 (6.96) (d, J =2 Hz, 1H), 5.15 (s, 2H), 4.81 (4.88) (s, 1H), 4.65 (d, J =7Hz, 1H), 3.74-3.41 (mult, 2H), 3.35 (d, J =7.5 Hz, 1H), 2.31 (s, 3H), 2.20-2.13 (mult, 1H), 2.09-2.04 (1.81-1.76) (mult, 1H), 1.87-1.83 (1.72-1.67) (mult, 1H), 1.40 (1.44) (s, 9H), 1.34 (1.35) (s, 3H), 0.96 (1.01) (t, J =6.5 (7.5) Hz, 3H), 0.96 (d, J =6.5 Hz, 3H), 0.92 (d, J =6.5 Hz, 3H). The chemical shifts in parentheses are the shifts for the minor diastereomer.

(2*S*,3*R*)-3-(3-{(1*S*)-1-[(*S*)-((2*S*)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-2-(benzyloxycarbonylmethylamino)-3-hydroxypropionic acid (56**).** Methyl ester **55** (71.2 mg, 0.104 mmol, 1 equiv) was dissolved in THF (6 mL) at 0 °C. Lithium hydroxide (3 mL, 0.3 mmol, 3 equiv, 0.1 N solution in water) was added and the reaction was stirred for 1.5 h at 0 °C. At this point, TLC showed complete

methyl ester hydrolysis, so benzyl chloroformate (45 μ L, 0.32 mmol, 3 equiv) was added and the reaction was stirred for one additional hour. The reaction was diluted with chloroform and pH 2.5 aqueous phosphate buffer was added. The layers were separated and the aqueous layer was extracted twice more with chloroform. The combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified using silica gel column chromatography. Excess benzyl chloroformate was eluted using 1/1 hexanes/ethyl acetate, and the desired product **56** (59.4 mg, 0.0725 mmol, 70%) was obtained upon elution with a gradient of 25/1 to 4/1 chloroform/methanol. $R_f=0.6$ (5/1 chloroform/methanol); **IR** (film) 3374 br, 2971 w, 2935 w, 2099 m, 1740 w, 1669 s, 1507 m, 1454 w, 1392 m, 1368 m, 1304 w, 1258 m, 1221 m, 1154 s, 1050 m, 1026 s, 1005 s, 848 w, 824 w, 766 w, 699 w; **^1H NMR** (500 MHz, DMSO-d_6 , 85 $^\circ\text{C}$) δ 7.92 (br, 1H), 7.49-7.10 (mult, 8H), 6.93 (br, 1H), 5.08 (5.13) (s, 2H), 4.93 (4.89) (s, 1H), 4.79 (br, 1H), 3.76-3.54 (mult, 5H), 2.85 (2.86) (s, 3H), 2.03-2.12 (mult, 1H), 1.93-1.84 (mult, 1H), 1.78-1.69 (mult, 1H), 1.35 (1.38) (s, 9H), 1.20 (1.27) (s, 3H), 0.95-0.81 (mult, 9H); **^{13}C NMR** (125.5 MHz, DMSO-d_6 , 85 $^\circ\text{C}$) δ 168.7, 168.3, 168.0, 164.7, 162.9, 155.3, 142.5, 137.5, 136.8, 127.8, 127.7, 127.3, 127.1, 126.5, 125.8, 121.9, 113.2, 84.1, 83.7, 80.1, 70.2, 68.0, 57.7, 30.3, 29.7, 28.4, 27.5, 27.4, 27.2, 27.1, 19.2, 18.4, 17.7, 7.8, 7.4; **HRMS** calculated for $\text{C}_{42}\text{H}_{54}\text{N}_6\text{O}_{11}$ ($\text{M}+\text{Na}$): 841.3743, found (MALDI): 841.3749. The chemical shifts in parentheses are the shifts for the minor diastereomer.

2S,3R-3-(3-((1S)-1-[(S)-((2S)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy)-4-benzyloxyphenyl)-2-(benzyloxycarbonylmethylamino)-3-hydroxypropionic acid (57**).** Azide **56** (49.9 mg, 0.0609 mmol, 1 equiv) was dissolved in THF (0.6 mL) and water (0.15 mL) at room temperature. Trimethylphosphine (240 μ L, 0.240

mmol, 4 equiv, 1 M solution in THF) was added and the reaction was stirred for 10 h. Solvents were removed under reduced pressure, and the remaining reaction mixture was loaded directly onto a silica gel column. Using a gradient of 25/1 to 5/1 chloroform/methanol, **57** (34.9 mg, 0.0440 mmol, 72%) was obtained. The two diastereomers showed different R_f values on TLC but could not be separated. $R_f=0.5$ (major isomer) (5/1 chloroform/methanol), $R_f=0.4$ (minor isomer) (5/1 chloroform/methanol); **IR** (film) 3363 br,s, 2976 m, 2935 m, 1742 m, 1674 s, 1606 m, 1505 m, 1455 w, 1386 m, 1367 m, 1311 w, 1258 m, 1222 m, 1155 s, 1122 w, 1049 w, 1026 m, 1003 m, 947 w, 848 w, 824 w, 752 m, 698 m; **^1H NMR** (500 MHz, DMSO-d_6 , 80 $^\circ\text{C}$) δ 7.87 (br, 1H), 7.44-7.20 (mult, 8H), 6.95 (br, 1H), 5.01 (5.13) (s, 2H), 4.97 (s, 1H), 4.66 (br, 1H), 3.67-3.55 (mult, 2H), 3.37 (d, $J=4$ Hz, 1H), 2.73 (2.91) (s, 3H), 2.01-2.04 (mult, 1H), 1.83-1.74 (mult, 2H), 1.36 (1.38) (s, 9H), 1.19 (1.26) (s, 3H), 0.93 (d, $J=7$ Hz, 3H), 0.90 (0.80) (t, $J=7$ Hz, 3H), 0.85 (d, $J=6.5$ Hz, 3H); **^{13}C NMR** (125.5 MHz, DMSO-d_6 , 80 $^\circ\text{C}$) δ 172.0, 171.4, 169.0, 168.1, 150.9, 142.8, 136.8, 135.5, 127.8, 127.2, 126.6, 125.9, 122.4, 121.8, 113.1, 83.2, 80.1, 72.1, 70.1, 65.6, 63.7, 58.7, 30.6, 28.1, 27.5, 27.4, 27.2, 19.2, 18.6, 16.6, 7.4; **HRMS** calculated for $\text{C}_{42}\text{H}_{56}\text{N}_4\text{O}_{11}$ ($\text{M}+\text{Na}$): 815.3838,

found (MALDI): 815.3829. The chemical shifts in parentheses are the shifts for the minor diastereomer.

{[15-Benzyloxy-10-(benzyloxycarbonylmethylamino)-3-ethyl-11-hydroxyl-7-isopropyl-3-methyl-6,9-dioxo-2-oxa-5,8-diaza-bicyclo[10.3.1]hexadeca-[(16),12,14-triene-4-carbonyl]amino}acetic acid *tert*-butyl ester (58). 7-Azabenzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) (21.4 mg, 0.0410 mmol, 3 equiv), DMF (5 mL) and

diisopropylethylamine (12 μ L, 0.069 mmol, 5 equiv) were charged in a flame dried flask at room temperature. Amino acid **57** (10.7 mg, 0.0135 mmol) in DMF (0.3 mL) was added slowly using a syringe pump (0.3 mL/h). When the addition was complete, the reaction was stirred for another 1 h and then diluted with ether. Water was added and the layers were separated. The aqueous layer was extracted twice with ether. The combined organic layers were dried over anhydrous Na_2SO_4 . After the removal of the solvent, the crude material was purified using silica gel column chromatography. Using a gradient of 2/1 to 1/2 hexanes/ethyl acetate, **58** (6.5 mg, 0.0084 mmol, 69%) was obtained. Some starting amino acid **57** (1.0 mg, 0.0013 mmol, 9%) was recovered from the rinse of the syringe. R_f =0.4 (1/2 hexanes/ethyl acetate); **IR** (film) 3406 w, 3333 m, 2956 m, 1925 m, 2848 m, 1793 w, 1661 s, 1525 m, 1505 m, 1455 m, 1367 m, 1260 m, 1223 m, 1155 s, 1124 w, 1075 w, 998 w, 959 w, 845 w, 809 w, 734 w, 696 w; **^1H NMR** (500 MHz, DMSO-d_6 , 70 $^\circ\text{C}$) δ 7.99 (t, J =6 Hz, 1H), 7.94 (d, J =6.5 Hz, 1H), 7.46-7.30 (mult, 7H), 7.12 (d, J =8.5 Hz, 1H), 6.94 (d, J =8.5 Hz, 1H), 5.48 (br, 1H), 5.16-5.01 (mult, 3H), 4.91 (d, J =10 Hz, 1H), 4.62 (d, J =10 Hz, 1H), 4.38 (d, J =8.5 Hz, 1H), 3.85 (dd, J =6.5, 17 Hz, 1H), 3.76 (dd, J =5, 17 Hz, 1H), 2.13-2.08 (mult, 1H), 2.02-1.96 (mult, 1H), 1.96-1.88 (mult, 1H), 1.42 (s, 9H), 1.11 (s, 3H), 0.95 (t, J =8 Hz, 3H), 0.75 (d, J =7 Hz, 3H), 0.73 (d, J =7 Hz, 3H); **^{13}C NMR** (125.5 MHz, DMSO-d_6 , 70 $^\circ\text{C}$) δ 170.5, 170.0, 168.8, 168.4, 168.1, 168.0, 155.7, 151.7, 151.5, 143.7, 143.6, 136.9, 136.7, 134.7, 134.6, 127.8, 127.2, 126.8, 123.7, 123.6, 123.2, 121.9, 114.7, 84.0, 83.8, 80.3, 70.4, 70.1, 69.8, 69.4, 68.7, 68.5, 65.7, 63.9, 60.1, 59.8, 58.9, 58.6, 58.1, 42.0, 41.6, 30.7, 29.7, 27.6, 27.4, 27.3, 27.1, 19.3, 18.6, 18.6, 17.4, 17.4, 7.9, 7.8; **HRMS** calculated for $\text{C}_{42}\text{H}_{54}\text{N}_4\text{O}_{10}$ ($\text{M}+\text{Na}$): 797.3732, found (MALDI): 797.3749.

C2-*epi*-Ustiloxin D *tert*-butyl ester (74).

Macrocycle **58** (10.2 mg, 0.0132 mmol, 1 equiv) was dissolved in methanol (1 mL) at room temperature. 5% Palladium on carbon (5.0 mg, 50% weight of substrate, purchased from Acros) was added and a hydrogen balloon was set. After 5.5 h, hydrogen was released and the reaction mixture was concentrated. The crude material was purified by directly loading onto a

silica gel column. Using a gradient of 20/1 to 10/1 chloroform/methanol, C2-*epi*-

Ustiloxin D *tert*-butyl ester **74** (5.8 mg, 0.011 mmol, 80%) was obtained. $R_f=0.2$ (5/1 chloroform/methanol); **IR** (film) 3300 m, 2975 m, 2935 m, 1747 m, 1652 s, 1538 m, 1520 s, 1456 w, 1388 w, 1369 m, 1286 m, 1224 m, 1157 m, 1133 w, 1116 w, 1063 w, 961 w, 887 w, 844 w, 755 m; **¹H NMR** (500 MHz, CD₃OD) δ 7.16 (dd, $J=2, 8$ Hz, 1H), 7.03 (br, 1H), 6.90 (d, $J=8.5$ Hz, 1H), 4.65 (s, 1H), 4.46 (d, $J=9$ Hz, 1H), 3.97 (d, $J=7.5$ Hz, 1H), 3.61 (d, $J=18$ Hz, 1H), 3.83 (d, $J=18$ Hz, 1H), 3.17 (d, $J=9$ Hz, 1H), 2.33 (s, 3H), 2.31-2.24 (mult, 1H), 2.16-2.09 (mult, 1H), 2.04-1.96 (mult, 1H), 1.45 (s, 9H), 1.38 (s, 3H), 1.41 (t, $J=7.5$ Hz, 3H), 0.82 (d, $J=7$ Hz, 3H), 0.81 (d, $J=7.5$ Hz, 3H); **¹³C NMR** (125.5 MHz, CD₃OD) δ 175.2, 171.7, 171.4, 170.0, 152.1, 143.6, 134.0, 124.6, 123.2, 118.6, 85.7, 82.8, 75.5, 73.3, 61.2, 61.0, 42.9, 34.5, 31.0, 29.6, 28.3, 22.8, 19.4, 18.4, 8.5; **HRMS** calculated for C₂₇H₄₂N₄O₈ (M+Na): 573.2895, found (MALDI): 573.2898.

C2-*epi*-Ustiloxin D (59). C2-*epi*-Ustiloxin D *tert*-butyl ester **74** (3.4 mg, 0.0062 mmol, 1 equiv) was dissolved in THF (0.5 mL) at room temperature. Lithium hydroxide (0.5 mL, 0.05 mmol, 9 equiv, 1 N solution in water) was added and the reaction was stirred for 8 h. The reaction mixture was acidified by the addition of aqueous 1 N HCl (about 3 drops) and the solvent was removed under reduced pressure. The crude

product was purified using a Sep-Pak C18. The Sep-Pak column was activated prior to use by pre-treating with 5 mL methanol followed by 15 mL water. The crude compound was loaded using water. Water (3 mL) was run to elute all the inorganic salts. The desired compound C2-*epi*-Ustiloxin D **59** (2.6 mg, 0.0053 mmol, 85%) was eluted using 1/1 water/methanol (6 mL). $R_f=0.5$ (1/2 chloroform/methanol); $[\alpha]_D^{23}$ -90.8° (c 0.33, H₂O); **IR** (KBr) 3411 s, 2966 w, 2935 w, 1657 s, 1610 m, 1517 m, 1463 w, 1385 m, 1287 m, 1220 w, 1155 w, 1113 m, 1073 s, 962 w, 794 w, 783 w; **¹H NMR** (500 MHz, D₂O) δ 6.98 (dd, $J=2, 8.5$ Hz, 1H), 6.88 (d, $J=8.5$ Hz, 1H), 6.67 (br, 1H), 4.63 (s, 1H), 4.53 (d, $J=9.5$ Hz, 1H), 3.84 (d, $J=9$ Hz, 1H), 3.69 (d, $J=9.5$ Hz, 1H), 3.56 (s, 2H), 2.54 (s, 3H), 2.10 (dq, $J=7.5, 21.5$ Hz, 1H), 1.72 (dq, $J=7.5, 21.5$ Hz, 1H), 1.60 (mult, 1H), 1.31 (s, 3H), 0.99 (t, $J=7.5$ Hz, 3H), 0.63 (d, $J=6.5$ Hz, 3H), 0.53 (d, $J=7$ Hz, 3H); **¹³C NMR** (125.5 MHz, D₂O) δ 175.9, 170.5, 170.4, 165.7, 150.8, 142.1, 130.1, 123.1, 122.2, 118.6, 72.9, 68.7, 68.3, 59.8, 59.6, 43.4, 32.0, 28.4, 23.1, 18.1, 17.7, 6.8; **HRMS** calculated for C₂₃H₃₄N₄O₈ (M+H): 495.2449, found (MALDI): 495.2453.

(4*S*,5*R*)-5-[3-(Benzyloxy-4-)-1-(*IR*)-ethyl-1-methylallyloxy]phenyl]-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (41a).

Phenol **40** (3.51 g, 8.09 mmol, 1 equiv) was dissolved in dichloromethane (degassed by bubbling argon for 20 min) (30 mL) at room temperature. (*IS*, 2*S*)-1,2-bis(2-diphenylphosphinobenzoyl)aminocyclohexane **60** (335.4 mg, 0.486 mmol, 0.06 equiv) and tris(dibenzylideneacetone)-dipalladium(0)-chloroform adduct (167.7 mg, 0.162 mmol, 0.02 equiv) were added. Carbonic acid-1-ethyl-1-methylallyl ester methyl ester **16** (4.0 mL, 24.3 mmol, 3 equiv)

was added dropwise over 1 min. The reaction turned yellow. When **16** was fully consumed, the reaction color changed to orange. Subsequent aliquots of **16** (333 μ L, 2.11 mmol, 0.25 equiv) were added every 10 min over 40 min as this color change to orange was observed. The catalyst had ceased to react after 1 h and the crude mixture was loaded directly to a silica gel column. A gradient of 10/1 to 5/1 hexanes/ethyl acetate eluted excess **16** and dibenzylideneacetone. The product **41a**, (3.14 g, 6.09 mmol, 70%, 26%*de*) eluted with 2/1 hexanes/ethyl acetate and recovered starting material **40** (1.07 g, 2.47 mmol, 30%) was obtained upon elution with 1/2 hexanes/ethyl acetate. R_f =0.4 (2/1 hexanes/ethyl acetate); R_t =31.6 min (minor isomer **41b**), 37.4 min (major isomer **41a**), Chiralpak AD (0.9 mL/min, 80% ethanol/hexane); **IR** (film) 2937 w, 2358 w, 1738 m, 1640 m, 1608 m, 1511 m, 1453 w, 1371 w, 1306 w, 1255 s, 1223 m, 1169 s, 1132 m, 1080 m, 1024 m, 921 w, 841 w, 738 w, 696 w; **¹H NMR** (400 MHz, $CDCl_3$) δ 7.97 (d J=9 Hz, 2H), 7.42 (d J=7 Hz, 2H), 7.35 (t J=8 Hz, 2H), 7.29 (d J=7 Hz, 1H), 7.06 (d J=2 Hz, 1H), 6.91 (d J=9 Hz, 2H), 6.95-6.85 (m, 2H), 6.02 (dd J=11, 18 Hz, 1H), 5.72 (d J=7 Hz, 1H), 5.06 (s, 2H), 5.03 (d J=11 Hz, 1H), 5.03 (d J=12 Hz, 1H), 4.71 (d J=7 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 1.86-1.68 (m, 2H), 1.33 (s, 3H), 0.92 (t J=7 Hz, 3H); **¹³C NMR** (100 MHz, $CDCl_3$) δ 171.5, 165.2, 162.5, 152.1, 146.2, 143.0, 137.1, 132.1, 130.4, 128.4, 127.7, 127.2, 120.3, 120.1, 119.3, 114.8, 114.6, 113.6, 83.7, 82.8, 76.7, 71.0, 55.3, 52.7, 34.2, 21.0, 8.3; **HRMS** calculated for $C_{31}H_{33}NO_6$ (M+H): 516.2381, found (FAB): 516.2356.

(4S,5R)-5-[4-Benzyloxy-3-((1R,2S)-1-ethyl-2,3-dihydroxy-1-methylpropoxy)phenyl]-4,5-dihydrooxazole-4-carboxylic acid methyl ester (42a**).** Terminal alkene **41a** (4.15 g, 8.05 mmol, 1 equiv), potassium carbonate (1.11 g, 8.05 mmol, 1 equiv), sodium bicarbonate (1.35 g, 16.1 mmol, 2 equiv), potassium ferricyanide(III) (7.95 g, 24.2 mmol, 3 equiv) were charged in a flask. (DHQD)₂PYR (1.42 mg, 1.61

mmol, 0.2 equiv) was added as a solution in *tert*-butyl alcohol (41 mL), followed by potassium osmate dihydrate (148.3 mg, 0.402 mmol, 0.05 equiv) in water (41 mL). The reaction was stirred at room temperature for 4.5 days. Sodium sulfite (12.07 g, 95.7 mmol, 12 equiv) was added and the reaction was stirred for 1 h before diluting the mixture with water (250 mL). The aqueous layer was extracted with ethyl acetate (3 $\times$ 150 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 . After removal of the solvent under reduced pressure, the crude yellow foam was purified using silica gel column chromatography. Recovered starting material **41a** (708.3 mg, 1.37 mmol, 17%) eluted using a gradient of 2/1 to 1/1 hexanes/ethyl acetate. The desired product **42a** (3.18 g, 5.79 mmol, 72%, 66%*de*) was obtained by elution with a gradient of 1/2 to 1/10 hexanes/ethyl acetate to 100% ethyl acetate. R_f =0.3 (1/2 hexanes/ethyl acetate); **IR** (film) 3460 w, 2940 w, 1738 m, 1634 m, 1609 m, 1512 s, 1258 s, 1171 s, 1132 m, 1083 m, 1026 m, 842 w, 742 w, 698 w; **¹H NMR** (400 MHz, $CDCl_3$) δ 7.96 (d J=9 Hz, 2H), 7.42-7.29 (m, 5H), 7.06-6.88 (m, 3H), 6.91 (d J=9 Hz, 2H), 5.74 (d J=6 Hz, 1H), 5.06 (s, 3H), 4.72 (d J=8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.66 (d J=8 Hz, 2H), 2.46 (2.39) (d J=6 Hz, 1H), 1.91-1.78 (m, 1H), 1.62-1.57 (1.51-1.46) (m, 1H), 1.15 (s, 3H), 0.93 (t J=7 Hz, 3H); **¹³C NMR** (100 MHz, $CDCl_3$) δ 165.2, 162.6, 152.7, 144.0

(143.9), 135.6 (135.7), 132.6, 130.4, 128.7, 128.6, 128.4, 127.9 (127.7), 122.9 (122.3), 121.8 (121.6), 119.2, 113.8, 86.8 (87.3), 82.5, 76.6 (75.4), 74.1, 71.1 (71.3), 62.5 (62.6), 55.4, 52.8, 29.3 (29.5), 14.1, 8.4; **HRMS** calculated for $C_{31}H_{35}NO_8$ ($M+Na$): 550.2421, found (FAB): 550.2454. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4S,5R)-5-{4-Benzoyloxy-3-[(1R,2R)-1-(carboxyhydroxymethyl)-1-methylpropoxy]phenyl}-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (61). Diol **42a** (3.18 g, 5.79 mmol, 1 equiv) was dissolved in dichloromethane (130 mL) at 0 °C. Saturated sodium bicarbonate solution (130 mL) was added followed by the addition of potassium bromide (138.1 mg, 1.16 mmol, 0.2 equiv), 2,2,6,6-tetramethyl-1-

piperidinyloxy, free radical (TEMPO) (181.3 mg, 1.16 mmol, 0.2 equiv). Sodium hypochlorite solution (9.9 mL, 7.53 mmol, 1.3 equiv, commercial bleach, 5.25% by weight) was added with vigorous stirring. After 15 min, saturated sodium sulfite solution was added to quench excess oxidant. The layers were separated and the aqueous layer was extracted with chloroform (3 × 40 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was directly used for the next oxidation reaction without further characterization. $R_f=0.8$ (1/2 hexanes/ethyl acetate).

The crude aldehyde was dissolved in *tert*-butyl alcohol (393 mL) and 2-methyl-2-butene (150 mL) at room temperature. Sodium chlorite (6.02 g, 53.3 mmol, 9.2 equiv, ~80% tech grade) and sodium phosphate monobasic hydrate (5.51 g, 40.0 mmol, 6.9 equiv) in water (140 mL) was added all at once. After stirring for 1 h, pH 2.5 phosphate buffer (500 mL) and ethyl acetate (200 mL) were added and the layers were separated. The aqueous layer was extracted with chloroform (3 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . After removal of the solvent, the crude product was purified using silica gel column chromatography. TEMPO eluted first with 1/1 hexanes/ethyl acetate. Desired compound **61** (3.11 g, 5.52 mmol, 95%) started to elute using a gradient of 1/4 hexanes/ethyl acetate to 100% ethyl acetate followed by 5/1 to 2/1 chloroform/methanol. $R_f=0.5$ (5/1 chloroform/methanol); **IR** (film) 2952 w, 1742 m, 1634 m, 1609 m, 1513 s, 1456 w, 1259 s, 1172 s, 1122 m, 1084 m, 1024 m, 842 w, 744 m, 698 w; **1H NMR** (500 MHz, $CDCl_3$) δ 7.94 (d $J=7$ Hz, 2H), 7.44-7.26 (m, 5H), 7.02 (d $J=16$ Hz, 2H), 6.99-6.88 (m, 3H), 5.72 (br, 1H), 5.08 (br, 2H), 4.71 (br, 1H), 4.24 (d $J=22$ Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 2.00-1.65 (m, 2H), 1.20 (s, 3H), 0.97 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.7, 165.6, 162.9, 152.6, 143.7, 135.9, 132.8, 130.8, 129.0, 127.9, 121.9, 119.3, 114.0, 86.7, 82.8, 76.7, 71.4, 55.7, 53.1, 29.3, 20.0, 19.5, 14.5, 8.4; **HRMS** calculated for $C_{31}H_{35}NO_9$ ($M+H$): 564.2228, found (FAB): 564.2252.

(4*S*,5*R*)-5-(4-Benzyloxy-3-((1*R*)-1-[(*R*)-(tert-butoxycarbonylmethylcarbamoyl)hydroxymethyl]-1-methylpropoxy}phenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (62). Free acid **61** (3.11 g, 5.52 mmol, 1 equiv) and glycine *tert*-butyl ester hydrochloride (1.11 g, 6.63 mmol, 1.2 equiv) were dissolved in acetonitrile

(55 mL) at room temperature. Benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) (3.66 g, 8.28 mmol, 1.5 equiv) was added, followed by the addition of diisopropylethylamine (3.85 mL, 22.1 mmol, 4 equiv). After stirring for 1.5 h, more glycine *tert*-butyl ester hydrochloride (462.7 mg, 2.76 mmol, 0.5 equiv), BOP reagent (1.22 g, 2.76 mmol, 0.5 equiv) and diisopropylethylamine (962 μ L, 5.52 mmol, 1 equiv) were added. The reaction was further stirred for another 5 h and then diluted with ethyl acetate (75 mL) before quenching with water (75 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 $\times$ 75 mL). The organics were pooled washed with saturated sodium bicarbonate solution (200 mL) and with brine (200 mL), and dried over anhydrous Na₂SO₄. After the removal of the solvent under reduced pressure, the crude product was purified using silica gel column chromatography. Using a gradient of 2/1 to 1/2 hexanes/ethyl acetate, **62** (3.58 g, 5.29 mmol, 96%) was obtained. *R*_f=0.5 (1/1 hexanes/ethyl acetate); **IR** (film) 3359 w, 2976 w, 1741 s, 1641 m, 1609 m, 1512 s, 1368 m, 1257 s, 1170 s, 1082 m, 1027 m, 844 m, 746 w; **¹H NMR** (500 MHz, CDCl₃) δ 7.92 (dd *J*=2, 9 Hz, 2H), 7.71 (7.65) (t *J*=6 Hz, 1H), 7.36-7.29 (m, 5H), 7.03-6.90 (m, 3H), 6.87 (d *J*=6 Hz, 2H), 5.70 (t *J*=7 Hz, 1H), 5.02 (dd *J*=2, 10 Hz, 2H), 4.67 (d *J*=7 Hz, 1H), 4.26 (4.40) (d *J*=2 Hz, 1H), 4.13 (4.25) (d *J*=4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.70 (dd *J*=5, 8 Hz, 1H), 3.52 (3.31) (dd *J*=6, 18 Hz, 1H), 1.95-1.88 (1.83-1.77) (m, 1H), 1.78-1.69 (m, 1H), 1.32 (1.38) (s, 9H), 1.19 (s, 3H), 0.98 (t *J*=7 Hz, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 172.0 (170.9), 168.2, 164.9, 162.4, 151.2 (152.3), 143.6 (143.5), 135.6 (135.4), 132.3 (132.2), 130.1, 128.6 (128.5), 128.3, 127.5 (127.7), 122.1, 120.3, 119.5, 118.8, 113.5, 113.4 (113.2), 86.6 (85.8), 82.3 (82.2), 81.4 (81.6), 76.4, 74.6 (72.7), 70.9 (70.8), 55.2, 52.6, 41.4, 40.1, 39.8 (39.9), 39.6 (39.4), 28.3 (28.6), 27.7 (27.8), 18.7 (19.0), 7.4 (7.8); **HRMS** calculated for C₃₇H₄₄N₂O₁₀ (M+Na): 677.3074, found (FAB): 677.3080; The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4*S*,5*R*)-5-(3-((1*R*)-1-[(*S*)-Azido-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (63). Secondary alcohol **62** (3.58 g, 5.29 mmol, 1 equiv) was dissolved in dichloromethane (133 mL) at -20 °C. Pyridine (4.3 mL, 52.9 mmol, 10 equiv)

was added followed by the addition of trifluoromethanesulfonic anhydride (2.67 mL, 15.9 mmol, 3 equiv). Temperature was carefully maintained at -20 °C over 22 h. The

reaction was quenched with saturated sodium bicarbonate solution (75 mL) and warmed to room temperature. The layers were separated and the aqueous layer was extracted with chloroform (3 × 75 mL). The combined organic layers were dried over anhydrous Na₂SO₄. After the removal of solvent under reduced pressure, the crude triflate was purified using silica gel column chromatography. A byproduct and pyridine eluted using 3/1 hexanes/ethyl acetate, followed by the desired triflate (3.32 g, 4.10 mmol, 78%), which eluted with a gradient of 3/1 to 1/1 hexanes/ethyl acetate. Recovered starting material **62** (422.5 mg, 0.624 mmol, 12%) eluted using 1/2 hexanes/ethyl acetate. The triflate was used without further characterization. R_f=0.6 (1/1 hexanes/ethyl acetate).

The triflate (3.32 g, 4.10 mmol, 1 equiv) was dissolved in 1,3-dimethyl-3,4,5,6-tetrahydro-2(*H*)-pyrimidinone (DMPU) (20 mL). Solid lithium azide (prepared by lyophilizing an aqueous solution—**CAUTION**: Potential for explosion) (1.61 g, 32.8 mmol, 8 equiv) was added and the reaction was stirred at room temperature for 2.5 days. The reaction was loaded directly onto a silica gel column and eluted with 1/2 hexanes/ethyl acetate to remove most of the reaction solvent, DMPU. The product fractions were concentrated and the crude product was purified using silica gel column chromatography. Trace amount of the recovered triflate eluted using 1/4/2 hexanes/benzene/ether. The product **63** (2.06 g, 2.94 mmol, 72%) eluted using 1/8/4 hexanes/benzene/ether. R_f=0.6 (2/1 benzene/ether, developed twice); **IR** (film) 3364 w, 2978 w, 2116 s, 1739 m, 1665 m, 1609 m, 1506 m, 1513 m, 1368 m, 1257 s, 1224 s, 1170 s, 1082 m, 1027 m, 843 w, 749 w, 699 w; **¹H NMR** (400 MHz, CDCl₃) δ 7.96 (dt J=2, 9 Hz, 2H), 7.41-7.28 (m, 6H), 7.06-6.91 (m, 3H), 6.91 (dt J=3, 9 Hz, 2H), 5.75 (d J=7 Hz, 1H), 5.05 (d J=10 Hz, 2H), 4.72 (dd J=3, 7 Hz, 1H), 4.33 (4.28) (s, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.71 (dd J=5, 7 Hz, 1H), 3.57 (dd J=5, 11 Hz, 1H), 1.89-1.79 (m, 1H), 1.81-1.73 (m, 1H), 1.41 (1.39) (s, 9H), 1.2 (1.3) (s, 3H), 0.96 (0.95) (t, J=7 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 171.5, 168.3 (168.4), 167.4 (167.8), 165.2, 162.6, 152.9 (152.4), 143.4 (143.5), 136.0, 132.3 (132.2), 130.4, 128.7 (128.8), 128.4, 127.8, 122.9, 121.9 (121.8), 121.5, 119.1, 113.8 (113.5), 85.9 (85.7), 82.5, 82.0 (81.9), 70.9, 69.1 (68.8), 55.4, 52.8, 41.8 (41.6), 29.2, 28.0, 20.3 (20.1), 8.3 (8.0); **HRMS** calculated for C₃₇H₄₃N₅O₉ (M+H): 702.3133, found (FAB): 702.3165. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4*S*,5*R*)-5-(3-((1*R*)-1-((*S*)-((2*S*)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl)-1-methylpropoxy)-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (75). Azide **63** (2.06 g, 2.94 mmol, 1 equiv) was dissolved in THF (21 mL) and water (8 mL) at room temperature.

Trimethylphosphine (1 M solution in THF) (8.8 mL, 8.8 mmol, 4 equiv) was added and the reaction was allowed to stir 24 h. THF was removed under reduced pressure. Ethyl acetate (80 mL) and saturated sodium bicarbonate solution (80 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with brine (80 mL) and dried over anhydrous Na₂SO₄. Solvents were removed under reduced pressure and the crude product was

loaded onto a silica gel column. Trace impurities were eluted using 1/2 hexanes/ethyl acetate followed by the desired amine (1.54 g, 2.28 mmol, 78%). Polarity was increased to 1/4 then 5/1 chloroform/methanol to complete elution of **75**. $R_f=0.2$ (1/2 hexanes/ethyl acetate); **IR** (film) 3368 w, 2978 w, 1739 m, 1641 w, 1609 w, 1512 s, 1368 w, 1256 s, 1169 s, 1082 m, 1026 w, 843 w, 749 w; **^1H NMR** (500 MHz, CDCl_3) δ 7.96 (dd $J=1$, 9 Hz, 2H), 7.83 (7.72) (t $J=6$ Hz, 1H), 7.40-7.24 (m, 5H), 7.04-6.90 (m, 3H), 6.91 (dd $J=1$, 8 Hz, 2H), 5.73 (d $J=8$ Hz, 1H), 5.01 (5.05) (s, 2H), 4.72 (dd $J=2$, 7 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80-3.75 (m, 1H), 3.68-3.59 (m, 1H), 1.92-1.87 (m, 1H), 1.83 (br, 2H), 1.83-1.73 (m, 1H), 1.41 (1.38) (s, 9H), 1.25 (1.17) (s, 3H), 1.01 (0.93) (t $J=7$ Hz, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 173.0 (173.2), 171.5, 168.9, 165.2, 162.6, 153.1, 152.4, 144.0 (144.1), 136.1, 132.3 (132.2), 130.4, 128.6 (128.7), 128.4 (128.3), 127.8, 122.2 (121.4), 121.0 (121.2), 119.2, 113.8, 113.5 (113.4), 86.4, 82.5 (82.6), 81.6 (81.8), 76.6, 70.9, 60.2 (60.6), 55.4, 52.8, 41.7, 29.6 (28.6), 28.0, 19.6 (19.9), 8.2 (8.1); **HRMS** calculated for $\text{C}_{37}\text{H}_{45}\text{N}_3\text{O}_9$ ($\text{M}+\text{H}$): 676.3228, found (FAB): 676.3236. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(4*S*,5*R*)-5-(3-((*IR*)-1-[(*S*)-((2*S*)-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy)-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-4,5-dihydrooxazole-4-carboxylic acid methyl ester (64**).** Amine **75** (679 mg, 1.00 mmol, 1 equiv) and Boc-valine (326 mg, 1.50 mmol, 1.5 equiv) were dissolved in acetonitrile (10 mL) at room temperature. BOP reagent (889 mg, 2.01 mmol, 4 equiv)

and diisopropylethylamine (700 μL , 4.02 mmol, 2 equiv) were added and the reaction was stirred 1 h. The reaction was diluted with ethyl acetate (50 mL) and saturated sodium bicarbonate solution (50 mL) was added. The layers were separated and the aqueous layer extracted with ethyl acetate (2 $\times$ 50 mL). The combined organic layers were washed once with brine (30 mL) and dried over anhydrous Na_2SO_4 . Solvents were removed under reduced pressure and the crude product was loaded onto a silica gel column. Trace impurities were removed eluting with 2:1 hexanes/ethyl acetate. The desired product **64** (911.9 mg, 1.04 mmol, quant.) was obtained upon elution with 1/1 to 1/2 hexanes/ethyl acetate. $R_f=0.6$ (1/5 hexanes/ethyl acetate); **IR** (film) 3371 m, 2975 m, 1743 s, 1664 s, 1610 m, 1512 s, 1456 w, 1367 m, 1257 s, 1170 s, 1083 w, 1026 s, 1009 m, 845 w, 750 w, 700 w; **^1H NMR** (500 MHz, CDCl_3) δ 7.98 (dd $J=2$, 9 Hz, 2H), 7.49-7.33 (m, 6H), 7.09-6.97 (m, 3H), 6.95 (dd $J=1$, 9 Hz, 2H), 5.75 (dd $J=3$, 7 Hz, 1H), 5.58 (5.53) (d $J=8$ Hz, 1H), 5.18 (5.24) (d $J=9$ Hz, 2H), 4.77 (4.96) (d $J=9$ Hz, 1H), 4.73 (d $J=7$ Hz, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.75-3.70 (m, 1H), 3.65-3.57 (m, 1H), 3.48-3.41 (m, 1H), 1.83-1.77 (2.01-1.92) (m, 1H), 1.71-1.66 (m, 1H), 1.41 (1.38) (s, 9H), 1.29 (1.22) (s, 3H), 0.98 (t $J=7$ Hz, 3H), 0.92 (d $J=7$ Hz, 3H), 0.88 (d $J=7$ Hz, 3H); **^{13}C NMR** (125.5 MHz, CDCl_3) δ 171.8, 170.6, 169.1, 167.9 (168.1), 164.7, 162.1, 155.5, 135.7, 129.9, 128.3 (128.2), 127.7 (127.9), 127.1, 122.9, 118.6, 113.3, 113.0, 85.7 (86.2), 82.0, 81.1, 79.1, 76.1, 70.4, 58.2, 54.9, 52.3, 41.5 (41.3), 39.8 (40.0), 39.5 (39.6), 39.3 (39.1), 30.2, 27.8 (27.4), 19.7 (19.8), 18.8, 17.4, 7.9; **HRMS** calculated for $\text{C}_{47}\text{H}_{62}\text{N}_4\text{O}_{12}$

(M+Na): 897.4262, found (FAB): 897.4275. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(2*S*,3*R*)-3-(3-((1*R*)-1-[(*S*)-((2*S*)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-3-hydroxy-2-methylaminopropionic acid methyl ester (65). Oxazoline **64** (911.9 mg, 1.04 mmol, 1 equiv) was dissolved in dichloromethane (20 mL) at room temperature. Methyl trifluoromethanesulfonate (141.5 μ L, 1.25 mmol,

1.2 equiv, freshly distilled from calcium hydride) was added and the reaction was stirred for 2 h. Toluene was added and the reaction mixture was azeotroped and dried under high vacuum (0.5 mmHg). The residue was dissolved in dichloromethane (30 mL) at 0 °C. Saturated sodium bicarbonate solution (30 mL) and sodium borohydride (78.7 mg, 2.08 mmol, 2 equiv) were added at once with vigorous stirring. Bubbling ensued and after 15 min, the layers were separated. The aqueous layer was extracted with dichloromethane (2 $\times$ 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and the solvent removed under reduced pressure to leave a white foam. The crude product was purified using silica gel column chromatography. The desired (4*S*,5*R*)-5-(3-((1*R*)-1-[(*S*)-((2*S*)-2-azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-methyloxazolidine-4-carboxylic acid methyl ester (759 mg, 0.852 mmol, 82%) was obtained upon elution with 2/1 to 1/1 hexanes/ethyl acetate. *R*_f=0.8 (1/2 hexanes/ethyl acetate).

(4*S*,5*R*)-5-(3-((1*S*)-1-[(*S*)-((2*S*)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl]-1-methylpropoxy}-4-benzyloxyphenyl)-2-(4-methoxyphenyl)-3-methyloxazolidine-4-carboxylic acid methyl ester (759 mg, 0.852 mmol) was dissolved in THF (28 mL) at room temperature. Oxalic acid (22 mL, 2.17 mmol, 2.5 equiv, 0.1 N solution in water) was added and the reaction was stirred 12 h. THF was removed under reduced pressure, and dichloromethane (50 mL) and saturated sodium bicarbonate solution (15 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (3 $\times$ 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude products were purified using silica gel column chromatography. Using 1/1 hexanes/ethyl acetate, *p*-methoxybenzaldehyde and the over-reduced product that had formed in the methylation step eluted. The desired product **65** (591 mg, 0.764 mmol, 90%, 74% over 2 steps) was obtained upon elution with a gradient of 1/4 hexanes/ethyl acetate, 100% ethyl acetate and 20/1 chloroform/methanol. *R*_f=0.2 (1/2 hexanes/ethyl acetate); IR (film) 3347 br, 2971 w, 2358 m, 1672 m, 1510 s, 1368 m, 1259 m, 1161 s, 1015 m, 750 w; ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.29 (m, 5H), 7.14-6.86 (m, 3H), 5.17 (d, *J*=11 Hz, 1H), 5.07 (5.11) (s, 2H), 5.03 (t, *J*=7 Hz, 1H), 4.81 (4.92) (d, *J*=8 Hz, 1H), 3.88-3.83 (4.35-4.32) (m, 1H), 3.73 (3.75) (s, 3H), 3.53 (d, *J*=2 Hz, 1H), 3.45-3.30 (m, 1H), 3.23 (3.13) (d, *J*=5 Hz, 1H), 2.36 (s, 3H), 1.76-1.64 (1.90-1.78) (m, 2H), 1.38 (1.35) (s, 9H), 1.25 (1.22) (s, 3H), 0.96 (t, *J*=7 Hz, 3H), 0.90 (d, *J*=7 Hz, 3H),

0.86 (d, $J=7$ Hz, 3H); ^{13}C NMR (125.5 MHz, CDCl_3) δ 171.8, 170.3, 169.4, 168.5 (168.9), 155.8, 143.4, 128.6 (128.8), 128.5 (127.7), 124.1, 122.3, 121.2, 112.9, 97.5, 86.4, 81.5, 80.2 (80.3), 79.7, 75.1, 71.0, 70.4, 62.9, 60.1, 58.8, 52.5, 52.1, 51.8, 42.1 (41.9), 38.1, 35.1, 31.1, 30.5, 28.6, 28.2 (28.0), 26.6, 19.3 (20.0), 17.8; HRMS calculated for $\text{C}_{40}\text{H}_{60}\text{N}_4\text{O}_{11}$ ($\text{M}+\text{H}$): 773.4337, found (FAB): 773.4345. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(2S,3R)-3-(3-((1R)-1-((2S)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl)-1-methylpropoxy)-4-benzyloxyphenyl)-2-(benzyloxycarbonylmethylamino)-3-hydroxypropionic acid (76). Methyl ester **65** (591 mg, 0.764 mmol, 1 equiv) was dissolved in THF (40 mL) at 0 °C. Lithium hydroxide (0.1 N solution in water) (19.1 mL, 1.91 mmol, 2.5

equiv) was added and the reaction was stirred for 3 h at 0 °C. At this point, TLC showed complete methyl ester hydrolysis, so benzyl chloroformate (327 μL , 2.29 mmol, 3 equiv) was added and the reaction was stirred for 3 h. At this time, an additional aliquots of benzyl chloroformate were added (109 μL , 0.764 mmol, 1 equiv) every 1h over 2h. After stirring one additional hour, the reaction was diluted with dichloromethane (50 mL) and pH 2.5 phosphate buffer was added (100 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified using silica gel column chromatography. Excess benzyl chloroformate was eluted using 1/2 hexanes/ethyl acetate, and the desired product **76** (420 mg, 0.470 mmol, 62%) was obtained upon elution with a gradient of 25/1 to 10/1 chloroform/methanol. $R_f=0.6$ (5/1 chloroform/methanol); IR (film) 3332 br, 2974 m, 2937 m, 2256 w, 1668 s, 1505 s, 1455 w, 1391 w, 1367 m, 1302 w, 1257 m, 1220 m, 1158 s, 1026 m, 1007 m, 850 w, 823 w, 770 m, 699 w; ^1H NMR (500 MHz, $\text{DMSO}-d_6$, 80 °C) δ 7.98-7.55 (m, 1H), 7.46 (dd, $J=7$, 17 Hz, 1H), 7.39-6.90 (m, 6H), 5.16 (5.02) (s, 2H), 4.89-4.64 (m, 3H), 3.85 (d, $J=27$ Hz, 1H), 3.74-3.50 (m, 2H), 2.90 (s, 3H), 1.90-1.64 (m, 2H), 1.38 (s, 18H), 1.21 (s, 3H), 0.89-0.83 (m, 6H); ^{13}C NMR (125.5 Hz, $\text{DMSO}-d_6$, 80 °C) δ 171.6, 169.0, 168.7, 167.9, 155.0, 150.6, 142.6, 136.6, 135.1, 127.8, 127.1, 126.5, 123.0, 121.6, 113.2, 84.6, 80.2, 77.8, 70.1, 65.6, 63.9, 57.8, 29.7, 28.4, 27.8, 27.6, 27.4, 27.2, 18.7, 17.6, 7.9; HRMS calculated for $\text{C}_{47}\text{H}_{64}\text{N}_4\text{O}_{13}$ ($\text{M}+\text{Na}$): 915.4368, found (FAB): 915.4408. The chemical shifts in parentheses are the shifts for the minor diastereomer.

(2S,3R)-3-(3-((1R)-1-((S)-((2S)-2-Azido-3-methylbutyrylamino)-(tert-butoxycarbonylmethylcarbamoyl)methyl)-1-methylpropoxy)-4-benzyloxyphenyl)-2-(benzyloxycarbonylmethylamino)-3-hydroxypropionic acid (66). Carbamate **76** (200 mg, 0.224 mmol, 1 equiv) was dissolved in dichloromethane (2.6 mL) and cooled to 0°C. Pre-chilled trifluoroacetic acid was added (640

μL) was added and the reaction stirred for 4 h. At this time, the reaction mixture was diluted with pre-chilled dichloromethane (50 mL) and poured into saturated sodium bicarbonate solution (50 mL) at 0°C. The emulsion was filtered through a pad of Celite and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organics were washed once with brine (20 mL) before drying them over anhydrous Na₂SO₄. Solvents were removed under reduced pressure, and the crude loaded onto a silica gel column. Trace impurities eluted using 50/1 chloroform/methanol and then a gradient of 25/1 to 2/1 chloroform/methanol eluted **66** (148 mg, 0.186 mmol, 83%) was obtained. The two diastereomers showed different R_f values on TLC but could not be separated. R=0.5 (major isomer) (5/1 chloroform/methanol), R_f=0.4 (minor isomer) (5/1 chloroform/methanol); **IR** (film) 3364 br, s, 3064 w, 2972 m, 2256 w, 2128 w, 1742 m, 1673 s, 1505 m, 1470 w, 1455 w, 1392 m, 1368 m, 1307 w, 1258 m, 1221 m, 1154 s, 1050 m, 1026 s, 1004 s, 847 w, 825 w, 765 m, 698 w, 666 w, 623 w; **¹H NMR** (500 MHz, DMSO-d₆, 80 °C) δ 7.83 (7.90) (br, 1H), 7.45 (dd, J=5, 7 Hz, 1H), 7.37-7.16 (m, 4H), 6.93 (7.11) (br, 2H), 5.07 (5.13) (s, 2H), 4.94 (s, 1H), 4.68 (br, 1H), 3.60 (3.69) (dd, J=6, 17.5 Hz, 2H), 3.13 (3.31) (d, J=4.5 Hz, 1H), 2.86 (2.75) (s, 3H), 2.07-1.98 (m, 1H), 1.83-1.74 (1.67-1.60) (m, 2H), 1.38 (1.36) (s, 9H), 1.27 (1.20) (s, 3H), 0.88 (0.92) (d, J=7 Hz, 3H), 0.82 (0.90) (t, J=6 Hz, 3H), 0.78 (d, J=7 Hz, 3H); **¹³C NMR** (125.5 MHz, DMSO-d₆, 80 °C) δ 173.1, 172.5, 190.0, 168.1, 150.6, 142.7 (142.8), 136.8, 135.3, 127.8, 127.2, 126.6, 122.8, 121.7, 113.3, 84.2, 80.2 (80.1), 72.1 (72.3), 70.1 (70.0), 65.5, 63.9, 57.7, 30.5 (30.7), 28.6, 27.6, 27.4 (27.2), 27.0, 18.7, 16.3, 8.0; **HRMS** calculated for C₄₂H₅₆N₄O₁₁ (M+Na): 815.3838, found (FAB): 815.3798. The chemical shifts in parentheses are the shifts for the minor diastereomer.

[[15-Benzyloxy-10-(benzyloxycarbonylmethylamino)-3-ethyl-11-hydroxyl-7-isopropyl-3-methyl-6,9-dioxo-2-oxa-5,8-diazabicyclo[10.3.1]hexadeca-[(16),12,14-triene-4-carbonyl]amino}acetic acid tert-butyl ester (67). 7-Azabenzotriazol-1-yloxy-tris(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) (253.4 mg, 0.486 mmol, 3 equiv), DMF (56 mL) and diisopropylethylamine (141 μL, 0.808

mmol, 5 equiv) were combined. Amino acid **66** (128.1 mg, 0.162 mmol, 1 equiv) in DMF (6 mL) was added slowly using a syringe pump (0.4 mL/h). When the addition was complete, the syringe was rinsed with DMF (5 mL) and added over 1 h. The mixture was

stirred for one additional hour and then was diluted with diethyl ether (60 mL) and quenched with water (60 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 60 mL). The combined organic layers were washed once with brine (30 mL) and dried over anhydrous Na₂SO₄. After removal of solvents under reduced pressure, the crude material was purified using silica gel column chromatography. Using a gradient of 3/2 to 1/2 hexanes/ethyl acetate, **67** (66 mg, 0.0852 mmol, 56%) was obtained. Some starting amino acid **66** (7.3 mg, 0.00921 mmol, 6%) was recovered from the syringe used for the slow addition. R_f =0.4 (1/2 hexanes/ethyl acetate); **IR** (film) 3319 br, 2971 m, 1660 s, 1504 m, 1261 m, 1222 m, 1154 s, 1026 m, 738 w; **¹H NMR** (500 MHz, DMSO-*d*₆, 80 °C) δ 8.01 (7.93) (t, *J*=5.5 Hz, 1H), 7.76 (7.86) (d, *J*=8 Hz, 1H), 7.45 (dd, *J*=2.5, 7.5 Hz, 2H), 7.39-7.21 (m, 5H), 7.08 (7.12) (d, *J*=8.5 Hz, 1H), 6.98 (6.93) (d, *J*=9 Hz, 1H), 5.67 (s, 1H), 5.16-5.01 (m, 3H), 4.88 (4.92) (d, *J*=9.5 Hz, 1H), 4.62 (4.65) (d, *J*=10 Hz, 1H), 4.55 (4.39) (d, *J*=9 Hz, 1H), 3.96 (3.91) (t, *J*=8 Hz, 1H), 3.83 (3.85) (d, *J*=6 Hz, 1H), 3.78 (3.75) (dd, *J*=6, 11 Hz, 1H), 1.99-1.91 (2.08-2.17) (m, 1H), 1.99 (br, s, 1H), 1.62-1.56 (1.88-1.82) (m, 1H), 1.42 (s, 9H), 1.13 (s, 3H), 0.96 (0.80) (t, *J*=7.5 Hz, 3H), 0.76 (d, *J*=7 Hz, 3H), 0.74 (d, *J*=7 Hz, 3H); **¹³C NMR** (125.5 MHz, DMSO-*d*₆, 80 °C) δ 170.5, 170.0, 168.8 (168.4), 168.1 (168.0), 155.7, 151.7 (151.5), 143.8 (143.6), 136.9 (136.7), 134.7 (134.6), 127.8, 127.2 (126.8), 123.2 (123.6), 121.9, 114.9, 83.8 (84.0), 80.3, 70.2 (70.1), 69.1 (68.7), 65.8, 64.0, 60.0, 58.6, 57.9 (58.2), 54.2, 41.3 (40.9), 29.2, 27.6, 27.4 (27.3), 27.1, 22.4, 18.6 (18.7), 18.4, 17.4, 7.9; **HRMS** calculated for C₄₂H₅₄N₄O₁₀ (M+H): 775.3918, found (FAB): 775.3914. The chemical shifts in parentheses are the shifts for the minor diastereomer.

Ustiloxin D *tert*-butyl ester (77). Macrocycle **67** (53.0 mg, 0.0684 mmol, 1 equiv) was dissolved in methanol (2 mL) at room temperature. 5% Palladium on carbon (21.8 mg, 0.0103 mmol, 0.15 equiv, purchased from Acros) was added and a hydrogen balloon was attached. After 2 h, the hydrogen source was removed and the reaction mixture was concentrated. The crude material was purified

by directly loading onto a silica gel column. Using a gradient of 1/2 hexanes/ethyl acetate then a gradient of 25/1 to 10/1 chloroform/methanol, ustiloxin D *tert*-butyl ester **77** (32.9 mg, 0.0597 mmol, 87%) was obtained. R_f =0.2 (5/1 chloroform/methanol); **IR** (film) 3287 br, s, 2971 m, 2219 w, 1748 w, 1732 w, 1643 s, 1537 s, 1369 s, 1286 s, 1222 m, 1157 s, 1132 m, 1114 m, 1062 w, 1033 w, 960 w, 888 w, 844 w, 755 m; **¹H NMR** (500 MHz, CD₃OD) δ 7.04 (6.95) (dd, *J*=2, 8 Hz, 1H), 6.96 (6.91) (br, 1H), 6.78 (6.72) (d, *J*=8.5 Hz, 1H), 4.65 (4.54) (s, 1H), 4.42 (4.35) (d, *J*=8 Hz, 1H), 3.92 (3.86) (d, *J*=7.5 Hz, 1H), 3.72 (3.73) (d, *J*=2 Hz, 2H), 3.13 (3.08) (d, *J*=8 Hz, 1H), 2.23 (s, 3H), 2.04-1.92 (2.22-2.12) (m, 1H), 2.00-1.90 (m, 1H), 1.94-1.84 (1.64-1.56) (m, 1H), 1.33 (s, 9H), 1.27 (1.16) (s, 3H), 1.03 (0.90) (t, *J*=6.5 Hz, 3H), 0.73 (d, *J*=7 Hz, 3H), 0.70 (d, *J*=7 Hz, 3H); **¹³C NMR** (125.5 MHz, CD₃OD) δ 182.0, 174.3, 171.9, 171.8 (171.7), 169.9, 152.1 (152.0), 143.6 (143.9), 133.6 (133.9), 124.7, 123.2, 118.6 (118.0), 95.9, 85.7, 85.4, 82.8, 75.1, 72.2, 61.2, 60.7, 42.9, 34.4 (34.6), 29.6 (29.9), 28.3, 19.4, 18.4, 8.8 (8.5); **HRMS**

calculated for $C_{27}H_{42}N_4O_8$ (M+H): 551.3081, found (FAB): 551.3076. The chemical shifts in parentheses are the shifts for the minor diastereomer.

Ustiloxin D (1). Ustiloxin D *tert*-butyl ester **77** (7.4 mg, 0.0134 mmol, 1 equiv) was dissolved in THF (1.4 mL) at room temperature. Lithium hydroxide (1 N solution in water) (1.4 mL, 0.14 mmol, 10 equiv) was added and the reaction was stirred for 5 h. The reaction mixture was acidified by the addition of 1 N HCl (about 20 drops) and the solvent was removed under reduced pressure.

The crude product was purified using a Sep-Pak C18. The Sep-Pak column was activated prior to use by pre-treating with 5 mL of methanol followed by 15 mL of water. The crude compound was loaded using water. Water (3 mL) was run to elute all the inorganic salts. The desired compound ustiloxin D **1** (6.2 mg, 0.0125 mmol, 94%) was eluted using 1/1 water/methanol (6 mL). Analytical reverse phase HPLC indicated that the product was a 2:1 mixture of ustiloxin D **1**: C2-*epi*-ustiloxin D **59**. Rt = 7.2 min (minor isomer), 9.6 min (major isomer) Waters Xterra M8 phenyl (1 mL/min, 5% acetonitrile/water containing 0.05% trifluoroacetic acid). These were separated preparatively using conditions identical to the analytical run. $R_f=0.5$ (1/2 chloroform/methanol); $[\alpha]_D^{25} = -49.7^\circ$ (c 0.35, H_2O), natural ustiloxin D: $[\alpha]_D^{20} = -48.8^\circ$ (c 0.5 H_2O); IR (KBr) 3421 br, s, 2930 w, 1654 m, 1389 w, 1070 br, s, 800 w; 1H NMR (500 MHz, D_2O) δ 7.01 (dd, $J=2, 8.5$ Hz, 1H), 6.90 (d, $J=8$ Hz, 1H), 6.84 (br, s, 1H), 4.60 (d, $J=9.5$ Hz, 1H), 3.90 (d, $J=10$ Hz, 1H), 3.74 (d, $J=9$ Hz, 1H), 3.67 (s, 2H), 2.57 (s, 3H), 1.97 (dq, $J=7, 21$ Hz, 1H), 1.69 (m, 1H), 1.53 (s, 3H), 1.52 (dq, $J=7.3, 21$ Hz, 1H), 0.91 (t, $J=7.5$ Hz, 3H), 0.67 (d, $J=7$ Hz, 3H), 0.59 (d, $J=7$ Hz, 3H); ^{13}C NMR (125.5 MHz, D_2O) δ 171.2, 171.1, 166.3, 151.0, 142.7, 130.7, 124.0, 122.7, 119.1, 86.0, 73.1, 69.0, 60.2, 59.5, 32.4, 29.1, 21.3, 18.5, 18.1, 8.1; HRMS calculated for $C_{23}H_{34}N_4O_8$ (M+H): 495.2455, found (FAB): 495.2463.

SAMPLE DEC. & VT
 date Mar 19 2002 dfrq 499.751
 solvent CDC13 dn H1
 file exp 30
 ACQUISITION 499.751 dm 0
 sfrq 499.751 dm 0
 tn H1 dnm 200
 at 4.000 dmf C
 np 6400 dseq 200
 sw 8000.0 dres 1.0
 fb 4000 homo n
 bs 4 dfrq2 DEC2 0
 tpwr 58 dn2 0
 pw 5.0 dpwr2 1
 al 0 ddf2 0
 tof 0 ddf2 0
 nt 100 dnm2 n
 ct 20 dmf2 C
 alock n dseq2 200
 gain not used dres2 1.0
 FLAGS n homo2 n
 il n PROCESSING
 in n wifile
 dp y wifile
 hs nn proc ft
 DISPLAY 131072 f
 sp -1501.3 math
 wp 8000.0 wfft
 vs 0 weft
 sc 250 wexp
 wc 0 wnt
 hzmm 0.13 wft
 is 74.06
 rfl 1501.3
 rfp 0
 th 7
 ins 3.000
 nm cdc ph

12 10 8 6 4 2 0 -2 ppm

SAMPLE DEC. & VT
 date Apr 12 2002 dfreq 499.751
 solvent CDC13 dn H1
 file exp 30
 ACQUISITION 499.751
 sfrq 499.751 dm 0
 tn H1 dnm 200
 at 4.000 dmf C
 np 64000 dseq 200
 sw 8000.0 dres 1.0
 fb 4000 homo n
 bs 4
 tpwr 60 dfreq2 DEC2 0
 pw 10.0 dn2
 dl 0 dpwr2 1
 tof 0 dof2 0
 nt 100 dmf2 n
 ct 20 dnm2 C
 alock n dmf2 200
 gain not used dseq2
 dres2
 i1 n homo2 1.0
 in n
 dp y
 hs nm
 DISPLAY -100.1 ft
 sp wp 5197.1 fn 131072
 vs 150 math
 SC 250 weff
 WC 0 wexp
 hzmm 0 wbs
 is 0.35 wnt
 rfl 250.28
 rfp 1501.3
 th 0
 ins 7
 nm cdc ph 3.000

9

PROTON PARAMETERS: CDCL3

EXP1 PULSE SEQUENCE: STD1H

DATE 03-01-02

SOLVENT CDCL3

FILE CDCL3

Pulse Sequence: s2pu1
Solvent: CDCl3
Ambient temperature
INOVA-500 "ui500"
PULSE SEQUENCE
Pulse 29.0 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
16 Repetitions
OBSERVE H1, 499.7485827 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 6 min, 48 sec

) Pulse Sequence: szpu1
Solvent: CDCl3
Ambient temperature
INOVA-500 "u1500"
PULSE SEQUENCE
Pulse 29.0 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
64 repetitions
OBSERVE H1, 499.7485838 MHz
DATA PROCESSING
F1 size 131072
Total time 1 hr, 6 min, 48 sec

Pulse Sequence: szpu1
Solvent: CDCl3
Ambient temperature
INOVA-500 "ui500"
PULSE SEQUENCE
Pulse 29.0 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7485823 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 6 min, 48 sec

Pulse Sequence: szpu1
Solvent: CDCl3
Ambient temperature
INOVA-500 "ui500"
PULSE SEQUENCE
Pulse: 60.0 degrees
Acq. time: 4.000 sec
Width: 8000.0 Hz
48 repetitions
OBSERVE H1, 499.7485830 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 6 min, 48 sec

16

EXP1 PULSE SEQUENCE: STD1H
DATE 05-03-01
SOLVENT CDCL3
FILE CDCL3

17

EXP1 PULSE SEQUENCE: STD1H
DATE 09-07-99
SOLVENT CDCL3
FILE CDCL3

EXP1 PULSE SEQUENCE: STD1H
DATE 09-13-99
SOLVENT CDCL3
FILE CDCL3

EXP1 PULSE SEQUENCE: STD1H
DATE 09-09-99
SOLVENT CDCL3
FILE CDCL3

```
EXP 1 PULSE SEQUENCE: STD1H
DATE 09-09-99
SOLVENT CDCL3
FILE CDCL3
```

```
EXP1  PULSE SEQUENCE
DATE  10-15-99
SOLVENT  CDCL3
FILE    CDCL3
```

STD 1H

Pulse Sequence: s2pu1
Solvent: DMSO
Ambient temperature
INNOVA-500 "u1500"
PULSE SEQUENCE
Pulse 29.0 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
16 repetitions
OBSERVE H1, 499.7509450 MHz
DATA PROCESSING
FT size 131072
Total time 1 hr, 6 min, 48 sec

SAMPLE DEC. & VT
 date Apr 22 2004
 solvent CDC13
 file ACQUISITION
 title 499.751
 sfrq 499.751
 tn H1
 at 4.000
 np 64000
 sw 8000.0
 fb 4000
 bs 4
 tpwr 60
 pw 10.0
 dl 0
 tof 0
 nt 1000
 ct 32
 alock n
 gain not used
 flags
 il n
 in n
 dp y
 hs n
 DISPLAY nm
 sp -100.0
 wd 5197.3
 vs 160
 sc 0
 wc 250
 hzmm 0.25
 is 277.10
 rfi 5141.8
 rfp 3628.2
 th 4
 ins 1.000
 nm cdc ph
 dfreq 499.751
 dn H1
 dpr 30
 dot 0
 dm nmn
 dmm C
 dmf 200
 dseq 1.0
 dres n
 homo
 DEC2
 dfreq 0
 dn2
 dpwr2 1
 dot2 0
 dm2 n
 dmf2 C
 dseq2 200
 dres2 1.0
 homo2 n
 PROCESSING
 wfile
 y proc
 fn ft
 math 131072
 werr
 wexp
 wbs
 wnt
 wft

```

exp1 szpu1
SAMPLE
date 4 2002
solvent Mar CDC13
file exp
ACQUISITION
sfrq 499.751
tn H1
at 4.000
np 64000
sw 8000.0
fb 4000
bs 4
tpwr 58
pw 5.0
d1 0
tof 0
nt 100
ct 20
atlock n
gain not used
FLAGS
il n
in n
dp n
hs n
SP DISPLAY -0.0
WP 3998.0
VS 100
SC 0
WC 250
hzmm 15.99
is 214.36
rfl 1501.3
th 0
ins 7
nm cdc ph 1.000
DEC. & VT
dfrq 499.751
dn H1
dpwr 30
dof 0
dm nnn
dmm c
dmf 200
dseq 1.0
dres n
homo DEC2
dfrq2 0
dn2 0
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2 1.0
dres2 n
homo2
PROCESSING
wfile ft
proc fn 131072
math f
werr weft
wexp wbs
wnt wft

```

Solvent: CDCl₃
Ambient temperature
INOVA-500 "41500"
PULSE SEQUENCE
Pulse 63.5 degrees
Acq. time 4.000 sec
Width 8000.0 Hz
1000 repetitions
OBSERVE H1, 499.7485825 MHz
DATA PROCESSING
FT size 65536
Total time 1 hr, 6 min, 48 sec

40

Solvent: CDCl₃
Ambient temperature
INOVA-500 "41500"

Pulse: 60.0 degrees
Acq. time: 4.000 sec
Width: 8000.0 Hz
16 repetitions
OBSERVE: H1, 499.7485824 MHz
DATA PROCESSING
FT size: 131072
Total time: 1 hr, 6 min, 48 sec

47

nm cdc ph

```

expt  stdh
SAMPLE
date Nov 11 2002
solvent CDCl3
file exp
ACQUISITION
sfrq 400.114
tn H1
at 4.002
np 40000
sw 4937.5
fb not used
bs 4
tpwr 60
pw 7.0
dl 0.500
tof 0
nt 100
ct 28
atlock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -80.2
wp 4161.1
vs 150
sc 0
wc 250
h2mm 2.80
is 500.00
rfl 3384.6
rfp 2836.8
th 20
ins 2.000
nm cdc ph
DEC. & VT
dfrq 400.114
dn H1
dpwr 30
dof 0
dm nmh
dmf C
200
PROCESSING
wtfile
proc ft
not used

```

61
 Ar = *p*MeOPh

```

exp1 s2pu1
SAMPLE Nov 14 2002
date CDC13
solvent exp
file ACQUISITION
sfrq 499.751
tn H1
at 4.000
np 64000
sw 8000.0
fb 4000
bs 4
tpwr 60
pw 10.0
dl 0
tof 0
nt 100
ct 52
a1ock n
gain not used
FLAGS n
il n
in n
dp y
hs n
DISPLAY -100.1
sp 5197.3
wp 150
vs 0
sc 250
wc 0
hzm 0.38
is 945.44
rf1 2741.0
rfp 1244.4
th 3.000
ins nm
cdc ph
DEC. & VT 499.751
dfrq H1
dn 30
dpwr 0
dof 0
dm nm
dmm 200
dmf 200
dseq 1.0
dres n
homo DEC2
dfrq2 0
dn2 1
dpwr2 0
dof2 n
dm2 n
dmm2 200
dseq2 1.0
dres2 n
homo2 n
PROCESSING
wfile ft
proc fn
math 131072
werr werr
wexp wexp
wbs wbs
wnt wnt
wft

```

```

exp1 std1h
SAMPLE      DEC. & VT
date Nov 18 2002      dfrq 400.114
solvent CDCl3         dn    H1
file exp             dpwr 30
ACQUISITION          dof   0
sfrq 400.114        dm    nmh
tn H1               dmf    c
at 4.002             PROCESsing
np 40000             wtfile ft
sw 4997.5            proc   not used
fb not used          fn
bs 4                 wfrf 60
tpwr 60              wefr 7.0
pw 7.0               wexp 0
dl 0.500             wbs 0
tof 0                wnt 12
nt 100               ct 12
ct 12                atlock n
gain not used        flags n
in n                 in n
dp y                 display
SP -80.2             sp
WP 4161.1            wp
VS 150               vs
SC 0                 SC
WC 250               WC
h2mm 0.28            h2mm
is 500.00             is
f1 3384.2            f1
f2 2896.8            f2
th 20                th
ins 1.000            ins
nm cdc ph            nm

```

Ar = *p*MeOPh **75**

```

exp1 s2pu1
SAMPLE
date Nov 26 2002
solvent CDCl3
file exp
ACQUISITION
sfreq 499.751
in H1
at 4.000
nd 64000
sw 8000.0
f2 4000
bs 4
tpwr 60
pw 10.0
d1 0
tof 0
nt 100
ct 84
alock n
gain not used
flags n
i1 n
in n
dp y
hs n
DISPLAY
sp -100.1
wp 5197.3
vs 150
sc 0
wc 250
h2mm 2.40
is 1108.19
rf1 2430.9
rfp 1024.5
th 7
ins 1.000
nm cdc ph
DEC. & VT
dfreq 499.751
dn H1
dpr 30
dof 0
dm nmn
dmm c
dmf 200
dseq 1.0
dres n
homo
dfreq2 0
dn2
dpwr2 1
dof2 0
dm2 n
dmm2 c
dmf2 200
dseq2 1.0
dres2 n
homo2
PROCESSING
wftile y
proc fn
ft 131072
math
werr
wexp
wbs
wnt
wft

```

```

exp1 s2pu1
SAMPLE
date Nov 27 2002
solvent CDC13
file exp
ACQUISITION
sfrq 499.751
tn H1
at 4.000
np 64000
sw 8000.0
fb 4000
bs 4
tpwr 4
pw 10.0
d1 0
tof 0
nt 100
ct 24
alock n
gain not used
flags n
il n
in n
dp n
hs n
DISPLAY -100.1
sp WP 5197.3
vs SC 150
sc 0
wc 250
h2mm 0.52
is 1239.64
rfl 3143.1
rfl 3618.2
th 7
ins 1.000
nm cdc ph

```

```

DEC. & VT
dfrq 499.751
dn H1
dpwr 30
dof 0
dm nm
dmf c
dseq 200
dres 1.0
homo n
DEC2
dfrq2 0
dn2 0
dpwr2 1
dof2 0
dm2 n
dmf2 c
dmf2 200
dseq2 1.0
dres2 n
homo2 n
PROCESSING
wfile ft
fn 131072
proc f
math wft
werr werr
wexp wexp
wbs wbs
wnt wnt

```

[illegible]

```

exp1 szpu1
SAMPLE 4 2002 DEC. & VT 499.753
date Dec 4 2002
solvent DMSO
file exp
ACQUISITION
sfrq 499.753
tn H1
at 4.000
np 64000
sw 8000.0
fb 4000
bs 4
tpwr 60
pw 10.0
di 0
tof 0
nt 100
ct 32
a1ock n
gain not used
FLAGS
il n
in n
dp n
hs y
DISPLAY -100.1
sp WP 5197.4
wp VS 150
vs SC 0
wc WC 250
hzmz 0.41
is 1056.94
rf1 2755.4
rfp 1244.4
th 7
ins 2.000
nm cdc ph
DEC. & VT 499.753
dfrq dn H1
dn 30
dpwr 0
do 0
dm mn
dmn mn
dmf 200
dseq 200
dres 1.0
homo n
temp 80.0
DEC2
dfrq2 0
dn2 0
dpwr2 1
dof2 0
dm2 n
dmn2 c
dmf2 200
dseq2 1.0
dres2 n
homo2 n
PROCESSING
wfile ft
proc fn 131072
math f
wfft wft

```

exp1 s2pul

SAMPLE		DEC. & VT	
date	Dec 5 2002	dfrq	499.753
solvent	DMSO	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	499.753	dm	nmn
tn	H1	dmm	c
at	4.000	dmf	200
np	64000	dseq	
sw	8000.0	dres	1.0
fb	4000	homo	n
bs	4	temp	80.0
tpwr	60	dfrq2	0
pw	10.0	dn2	
d1	0	dpwr2	1
tof	0	dof2	0
nt	1000	dm2	n
ct	24	dmm2	c
alock	n	dmf2	200
gain	not used	dseq2	
flags	not used	dres2	1.0
il	n	homo2	n
in	n		
dp	y	wtfile	
hs	nm	proc	ft
DISPLAY		fn	131072
sp	-100.1	math	f
wp	5197.4	weir	
vs	150	wexp	
sc	0	wbs	
WC	250	wnt	
h2mm	0.46		
is	1211.09		
rfl	2754.6		
rflp	1244.4		
th	7		
ins	9.000		
nm	cdc		
	ph

Chemical structure of compound **77**, a complex molecule featuring a benzene ring with a hydroxyl group and a methoxy group, and a side chain containing a carbamate and a carboxylate group.