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Experimental Section

All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under dry argon or nitrogen. All solvents were purified before use. Ether and THF were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2), toluene and acetonitrile were distilled from CaH_2. Methanol was distilled from magnesium turnings.

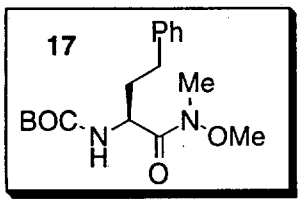
^1H NMR spectra were measured at 400 MHz on a Varian VNMR 400 instrument or at 500 MHz on a Varian Inova 500 instrument. Chemical shifts are reported in δ units with coupling constants reported in Hz. Residual chloroform (δ 7.26) or methanol (δ 4.87) was used as internal references for spectra measured in $CDCl_3$ or CD_3OD. ^1H NMR spectra measured in C_6D_6 were referenced against residual C_6D_5H (δ 7.15). Heterodecoupled ^{13}C NMR spectra were recorded at 125 or 100 MHz. Chemical shifts are reported relative the δ 77.0 ppm resonance of $CDCl_3$ or the δ 128.0 ppm resonance of C_6D_6 for spectra measured in these solvents.

High resolution mass spectra were measured at 70 eV on a Kratos GC/MS 80 RFA mass spectrometer at the Indiana University Mass Spectrometry Laboratory, on a VG 70-250-S manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory, or on a ZAB-SE mass spectrometer at the, School of Chemical Sciences, University of Illinois Mass Spectrometry Laboratory. (The latter instrument was purchased with funds provided by grants from the Division of Research Resources, National Institutes of Health (RR 01575), the National Science Foundation (PCM 8121494), and the National Institute of General Medical Sciences (GM 27029). We thank the staff of the Illinois Mass Spectrometry Laboratory for performing a number of mass spectral analyses for us). Chemical impact high resolution spectra (CI-HRMS) were run on a DCI probe with ammonia or methane as the reagent gas. Fast atom bombardment high resolution spectra (FAB-HRMS) were run at 6 KV accelerating voltage, and calibrated with CsI, using a matrix of 3-nitrobenzyl alcohol. Most FAB samples were doped with KCl in methanol. The atom gun utilized xenon gas with settings of 1 ma and 8 KV.

Infrared spectra were recorded using a Perkin-Elmer Specturm 1000 FT-IR Spectrophotometer. Optical rotations were measured on a Rudolph Autopol III polarimeter using a 1 mL capacity quartz cell with a 10 cm path length. Elemental analyses were performed by Robertson Microlit Laboratories, Inc,.

Madison , N.J., or by the Elemental Analysis Laboratory at the University of Michigan.

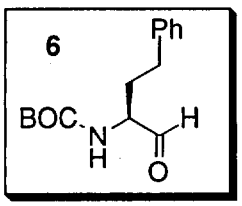
Analytical and semi-preparative HPLC separations were performed by using an HPLC system composed of two Rainin HXPL pumps (gradient), a Rheodyne 7125 injector, a Dynamax UV-C detector and a Shimadzu CR601 integrator. Analytical thin-layer chromatography (TLC) was performed by using plates coated with a 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Compounds were visualized by staining (and charring) of the TLC plates with a solution of ceric sulfate and ammonium molybdate in aqueous sulfuric acid or with a solution of *o*-vanillin in ethanol with acetic and sulfuric acid. Flash chromatography was performed as described by Still using Kieselgel 60 (230-400 mesh) silica gel.[1] Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by ^{1}H NMR analysis) for use in subsequent reactions.



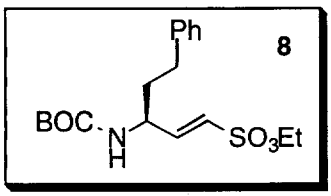
***N*-Methoxy-*N*-methyl *N'*-*tert*-Butoxycarbonyl-L-homophenylalanyl Amide (17).** To a 23 °C two phase mixture of L-homophenylalanine (1.61 g, 9.0 mmol) in 12 mL of a 1*N* NaOH solution, *tert*-butanol (15 mL) and water (18 mL) was added di-*ter*-butyl dicarbonate (2.54 g, 11.6 mmol) in one portion.[2] The pH of the solution was maintained to approximately 11 by addition of 1*N* NaOH (reaction became homogeneous) and the mixture was stirred at room temperature for 12 h. After dilution with of water (20 mL) and pentane (100 mL) pentane, the aqueous phase was separated, cooled to 0 °C and then acidified to pH 2-3 with 1 M $KHSO_4$ with vigorous stirring. This aqueous system was extracted with EtOAc (3 x 100 mL). The combined organic portions were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 2.48 g (98%) of crude N-Boc L-homophenylalanine which was used without further purification in the next step: ^{1}H NMR ($CDCl_3$, 400 MHz) d 7.25 (m, 5 H), 6.46 (bs, 1 H), 5.03 (d, J = 7.2 Hz, 1 H), 4.37 (m, 1 H), 2.73 (t, J = 7.6 Hz, 2 H), 2.21 (m, 1 H), 2.00 (m, 1 H), 1.46 (s, 9 H); IR ($CHCl_3$) 3460, 2550 (br), 1720, 1670, 1505, 1460, 1400, 1380, 1250, 1175, 1060, 1035, 860 cm^{-1}.

To a –5 °C solution of Boc-protected homophenylalanine (2.48 g, 8.9 mmol) and *N*-methyl morpholine (2.00 mL, 18.2 mmol) was added *iso*-butyl chloroformate (1.15 mL, 8.80 mmol).[3] After 30 min, *N*-*O*-dimethylhydroxylamine hydrochloride (900 mg, 9.20 mmol) was added. The reaction was

allowed to warm to 25 °C overnight, then was poured into H_2O (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 75 mL). The combined organic extracts were dried, filtered and concentrated *in vacuo* to yield a crude oil. Purification of the crude product by flash column chromatography using 2% MeOH/CH_2Cl_2 afforded the known[4] Weinreb amide **17** (2.30 g, 80% yield) as a clear oil: $[\alpha]_D^{26}$ = -8.0° (*c* 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.20 (m, 5 H), 5.29 (d, *J* = 0.6 Hz, 1 H), 4.68 (m, 1 H), 3.62 (s, 3 H), 3.16 (s, 3 H), 2.70 (m, 2 H), 2.02 (m, 1 H), 1.83 (m, 1 H), 1.45 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 155.6, 141.1, 128.5, 128.3, 125.9, 79.6, 61.5, 50.1, 34.6, 32.1, 31.7, 28.3; IR (neat) 3320 (broad), 3020, 3010, 2980, 2970, 1725, 1660, 1600, 1500, 1250, 1180, 1050, 1020, 1000, 870, 750, 700 cm^{-1}; HRMS calcd for $C_{17}H_{26}N_2O_4$ $(M+1)^+$ 323.1970, found 323.1963. *Anal.* Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H,8.13; N, 8.69. Found: C, 63.09; H, 8.03; N, 8.57.

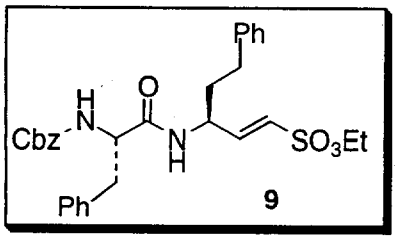


***N-tert*-Butoxycarbonyl-L-homophenylalaninal (6).** To a 0 °C solution of Weinreb amide **14** (2.19 g, 6.8 mmol) in THF (60 mL) was added $LiAlH_4$ (345 mg, 9.1 mmol). After 40 min, the reaction was quenched with $KHSO_4$ (2 g in 30 mL of H_2O) and then stirred for 2 h.[5] The mixture was diluted with Et_2O (50 mL) and the layers separated. The aqueous layer was extracted with Et_2O (3 x 50 mL) and the combined organic layers were washed with 1N HCl (2 x 50 mL), saturated aqueous $NaHCO_3$ (2 x 30 mL) and brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 1.67 g (89%) of the crude aldehyde **6** that was used directly in the next reaction. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (s, 1 H), 7.30-7.18 (m, 5 H), 5.08 (d, *J* = 5.2 Hz, 1H), 4.25 (m, 1 H), 2.71 (m, 2 H), 2.24 (m, 1 H), 1.84 (m, 1 H), 1.46 (s, 9 H).



Ethyl (3S)-N-t-butoxycarbonyl-3-amino-5-phenyl-pent-1-enyl sulfonate, (8): To a stirred solution of triethyl α-phosphonomethanesulfonate **7** (194 mg, 0.75 mmol) in THF (5 mL) at -78 °C was added BuLi (0.34 mL of a 2.2 M solution, 0.75 mmol). This mixture was stirrred for 15 min, then aldehyde **6** (196 mg, 0.74 mmol) was added as a solution in THF

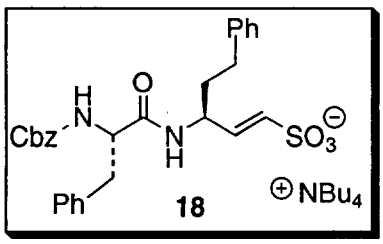
(3 mL). The reaction was allowed to warm slowly to room temperature overnight and was then quenched with pH 7 buffer. The mixture was extracted twice with CH_2Cl_2. The combined organics were dried and concentrated in vacuo. Chromatographic purification of the crude product (40% Et_2O-hexanes) gave vinyl sulfonate **8** as a white solid (160 mg, 59%): mp 66-69 °C; $[\alpha]_D^{20}$ 0° (c 1.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.15 (m, 5 H), 6.80 (dd, *J* = 5.2, 15.2 Hz, 1 H), 6.30 (d, *J* = 15.2 Hz, 1 H), 4.67 (d, *J* = 7.1 Hz, 1 H), 4.33 (m, 1 H), 4.15 (q, *J* = 7.1 Hz, 2 H), 2.69 (m, 2 H), 1.88 (m, 2 H), 1.44 (s, 9 H), 1.35 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 148.5, 140.2, 128.6, 128.3, 126.4, 124.7, 67.0, 50.7, 35.5, 31.9, 28.3, 28.2, 14.8; IR (neat) 3380, 2980, 1730-1680, 1520-1500, 1360, 1170, 1010, 920 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{18}H_{27}NO_5S$ (M^+), 369.1610, found 369.1596. *Anal.* Calcd for $C_{18}H_{27}NO_5S$: C, 58.51; H, 7.37; N, 3.79. Found: C, 58.70; H, 7.38; N, 3.86.



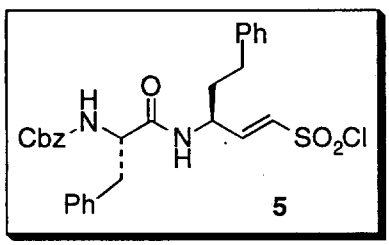
9

Ethyl (3S)-N-(N'-carbobenzyloxy-L-phenylalanyl)-3-amino-5-phenyl-pent-1-enyl sulfonate, (9, WRR-198): To a stirred solution of the BOC protected amine **8** (830 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) was added TFA (5 mL of a 50% solution in CH_2Cl_2). The mixture was stirred for 0.5 h, then the solvents were removed in vacuo. The residue was dissolved in DMF (10 mL) and N-Cbz-L-phenylalanine (672 mg, 2.25 mmol) was added. The reaction was cooled to 0 °C and *i*-Pr_2NEt (0.86 mL, 4.95 mmol), HOBT hydrate (335 mg, 2.48 mmol), and EDC (475 mg, 2.48 mmol) were added. The reaction was stirred overnight as the cooling bath warmed slowly to room temperature. The mixture was then poured into 1 : 1 ethyl acetate-hexanes and extracted once with 1 N HCl, once with brine, and once with saturated $NaHCO_3$. The organics were dried (Na_2SO_4) and concentrated to recover the vinyl sulfonate as a white solid (1 g, 81%): mp 160-161 °C; $[\alpha]_D^{20}$ +6.7 (c 8.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.18 (m, 13 H), 7.08 (d, *J* = 7.9 Hz, 2 H), 6.65 (dd, *J* = 4.9, 15.2 Hz, 1 H), 6.07 (d, *J* = 6.0 Hz, 1 H), 5.92 (d, *J* = 15.2 Hz, 1 H), 5.33 (d, *J* = 6.3 Hz, 1 H), 5.09 (m, 2 H), 4.60 (m, 1 H), 4.39 (m, 1 H), 4.15 (m, 2 H), 3.07 (m, 2 H), 2.57 (m, 2 H), 1.86 (m, 1 H), 1.76 (m, 1 H), 1.39 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 156.0, 147.1, 140.1, 135.9, 135.8, 129.1, 129.0, 128.7, 128.6, 128.34, 128.28, 128.1,

127.5, 126.4, 125.0, 67.3, 67.0, 56.6, 49.3, 38.2, 35.1, 31.7, 14.8; IR ($CHCl_3$) 3420, 3030, 2940, 1715, 1680, 1500, 1360, 1170 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{30}H_{34}N_2O_6S$ (M^+) 550.2137, found 550.2135. *Anal.* Calcd for $C_{30}H_{34}N_2O_6S$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.80; H, 6.54; N, 5.14.

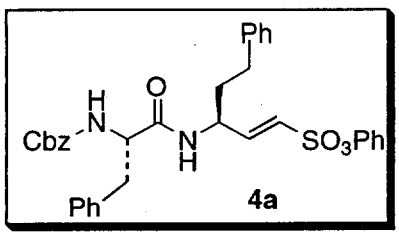


Tetrabutylammonium (3S)-*N*-(*N'*-Carbobenzyloxy-L-phenylalanyl)-3-amino-5-phenyl-pent-1-enylsulfonate, (18): To a stirred solution of the ethyl sulfonate **9** (216 mg, 0.39 mmol) in acetone (5 mL) was added tetrabutylammonium iodide (TBAI) (174 mg, 0.47 mmol). The reaction was heated at reflux for 2.25 h at which time TLC analysis showed the reaction to be incomplete. Additional TBAI (50 mg) was added and the reaction refluxed overnight. The mixture was then cooled and concentrated in vacuo. Purification of the crude product by silica gel chromatography (5% MeOH-CH_2Cl_2) gave the salt **18** (245 mg, 82%) as an off-white foam: $[\alpha]_D^{20}$ -1.3° (c 12.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.10 (m, 15 H), 6.82 (d, J = 5.3 Hz, 1 H), 6.42 (s, 2 H), 5.57 (d, J = 5.7 Hz, 1 H), 5.01 (m, 2 H), 4.57 (m, 1 H), 4.38 (m, 1 H), 3.24 (m, 8 H), 3.07 (m, 2 H), 2.58 (m, 2 H), 1.85 (m, 2 H), 1.61 (m, 8 H), 1.40 (m, 8 H), 0.96 (t, J = 7.1 Hz, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 141.6, 136.3, 134.7, 133.6, 129.4, 128.5, 128.4, 128.3, 128.2, 127.7, 126.7, 125.6, 66.6, 58.6, 56.3, 49.3, 38.4, 36.0, 31.9, 23.9, 19.6, 13.6; IR (neat) 3250, 2960, 1720, 1670, 1495, 1200, 1035 cm^{-1}; HRMS (FAB, Na^+) calcd for $C_{44}H_{65}N_3NaO_6S$ (M+ Na^+) 786.4492, found 786.4491.

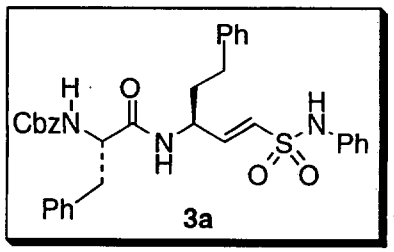


(3S)-N-(N'-Carbobenzyloxy-L-phenylalanyl)-3-amino-5-phenyl-pent-1-enyl sulfonyl chloride, (5): To a stirred solution of triphenylphosphine (132 mg, 0.50 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added sulfuryl chloride (45 μL, 0.55 mmol). The cooling bath was removed and the sulfonate salt **15** (192 mg, 0.25 mmol) was added as a solution in CH_2Cl_2 (2 mL). When TLC analysis showed the reaction to be complete, the mixture was concentrated *in vacuo*. Purification of the crude product by flash

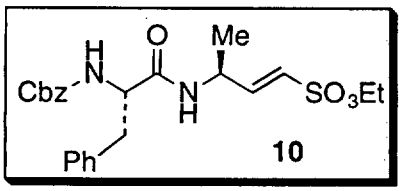
chromatography (5% ether-CH_2Cl_2) gave sulfonyl chloride **5** as a white solid (100 mg, 74%): mp 163-164 °C (d); $[\alpha]_D^{20}$ +11.3° (c 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.07 (m, 15 H), 6.74 (dd, *J* = 4.5, 15.1 Hz, 1 H), 6.23 (d, *J* = 14.8 Hz, 1 H), 5.79 (m, 1 H), 5.29 (m, 1 H), 5.23 (m, 2 H), 4.67 (m, 1 H), 4.34 (m, 1 H), 3.14-3.00 (m, 2 H), 2.61-2.52 (m, 2 H), 1.90 (m, 1 H), 1.79 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 147.8, 139.7, 135.8, 135.7, 133.6, 129.15, 129.11, 128.7, 128.6, 128.4, 128.3, 128.1, 127.7, 126.5, 67.4, 56.8, 48.9, 38.2, 34.9, 31.7; IR (neat) 3280, 1685, 1660, 1520, 1365, 1280, 1235, 1155 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{28}H_{29}ClN_2O_5S$ (M^+) 540.1486, found 540.15122. *Anal.* Calcd for $C_{28}H_{29}ClN_2O_5S$: C, 62.16; H, 5.40; N, 5.18. Found: C, 62.20; H, 5.31; N, 5.15.



Phenyl (3S)-N-(N'-carbobenzyloxy-L-phenylalanyl)-3-amino-5-phenyl-pent-1-enyl sulfonate, (4a, WRR-204): To a stirred solution of sulfonyl chloride **9** (95 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added a solution of phenol (19 mg, 0.21 mmol) and DBU (31 μL, 0.21 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 0.5 h at 0 °C, then was warmed to ambient temperature. One hour later, more phenol (19 mg, 0.21 mmol) and DBU (31 μL, 0.21 mmol) were added. After another hour, the mixture was poured into saturated $CuSO_4$ and extracted twice with CH_2Cl_2 . The combined organics were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude product by flash chromatography (30% ethyl acetate-hexanes) gave the phenyl sulfonate **4a** as a white solid (53 mg, 52%): mp 146-148 °C; $[\alpha]_D^{20}$ +17.2° (c 0.73, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.49-7.02 (m, 20 H), 6.51 (dd, *J* = 4.9, 15.1 Hz, 1 H), 6.03 (d, *J* = 15.1 Hz, 1 H), 5.90 (m, 1 H), 5.36 (m, 1 H), 5.10 (m, 2 H), 4.54 (m, 1 H), 4.38 (m, 1 H), 3.05 (m, 2 H), 2.50 (m, 2 H), 1.80-1.66 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 149.4, 148.7, 140.0, 135.9, 135.8, 129.8, 129.1, 129.0, 128.7, 128.6, 128.4, 128.2, 128.1, 127.6, 127.3, 126.4, 124.6, 122.6, 67.4, 56.7, 49.4, 38.2, 34.9, 31.6.; IR (neat) 3280, 1695, 1655, 1530, 1370, 1140 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{34}H_{34}N_2O_6S$ (M^+) 598.2137, found 598.2148. *Anal.* Calcd for $C_{34}H_{34}N_2O_6S$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.51; H, 5.85; N, 4.60.

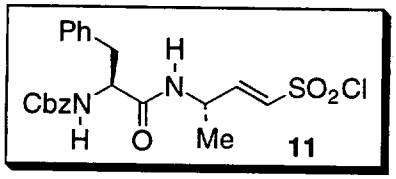


Phenyl (3S)-N-(N'-carbobenzyloxy-L-phenylalanyl)-3-amino-5-phenyl-pent-1-enyl sulfonamide, (3a, WRR-208): To a stirred solution of sulfonyl chloride **5** (63 mg, 0.116 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added aniline (23 μL, 0.26 mmol). The mixture was stirred for 1.75 h, then was diluted with ethyl acetate and poured into dilute HCl (pH 3). The organics were separated and the aqueous layer was further extracted twice with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude product by flash chromatography (15% ether-CH_2Cl_2) gave sulfonamide **3a** as a white solid (58 mg, 84%). mp 179-180 °C; $[\alpha]_D^{20}$ -9.1° (c 0.88, acetone); ^{1}H NMR (400 MHz, d_6-acetone) δ 8.68 (s, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.32-7.20 (m, 16 H), 7.17-7.05 (m, 4 H), 6.64 (dd, *J* = 5.3, 15.1 Hz, 1 H), 6.55 (d, *J* = 7.7 Hz, 1 H), 6.31 (d, *J* = 15.2 Hz, 1 H), 5.01 (m, 2 H), 4.57 (m, 1 H), 4.39 (m, 1 H), 3.10 (dd, *J* = 5.9, 13.6 Hz, 1 H), 2.93 (dd, *J* = 8.5, 13.8 Hz, 1 H), 2.57-2.48 (m, 2 H), 1.84 (m, 1 H), 1.73 (m, 1 H); ^{13}C NMR (100 MHz, d_6-acetone) δ 171.7, 146.2, 138.9, 138.4, 130.2, 130.0, 129.3, 129.2, 129.1, 129.0, 128.6, 128.5, 127.5, 126.7, 125.0, 121.3, 66.7, 57.5, 49.9, 38.8, 36.4, 32.4; IR (KBr) 3305, 1695, 1665, 1535, 1500, 1150 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{34}H_{35}N_3O_5S$ (M^+) 597.2297, found 597.2287. *Anal.* calculated for $C_{34}H_{35}N_3O_5S$: C, 68.32; H, 5.90; N, 7.03. Found: C, 68.02; H, 6.06; N, 6.78.



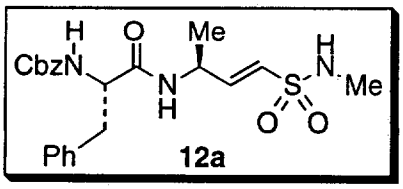
Ethyl (3S)-*N*-(*N*'-Carbobenzyloxy-L-phenylalanyl)-3-amino-but-1-enyl sulfonate, (10, WRR-179): To a stirred solution of triethyl phosphonomethanesulfonate **7** (95 mg, 0.36 mmol) in THF (1.5 mL) at -78 °C was added BuLi (0.15 mL of a 2.5 M solution, 0.38 mmol). Twenty minutes later, the known[6] dipeptide aldehyde Z-Phe-Ala-H (129 mg, 0.36 mmol) was added as a solution in THF (1.5 mL). The reaction was then allowed to stir overnight as the cooling bath warmed to room temperature. The mixture was poured into pH 7 buffer and extracted twice with CH_2Cl_2. The combined organics were dried ($MgSO_4$) and concentrated. Purification of the product by preparative thin layer chromatography (SiO_2; 50% ethyl acetate: hexanes) gave the sulfonate **10** as a colorless solid (124 mg, 75%): mp 85-87 °C; $[\alpha]_D^{20}$ +0.5° (c=2.02,

$CHCl_3$); ^1H NMR (500 MHz, $CDCl^3$) δ 7.37-7.25 (m, 8 H), 7.17 (d, *J* = 7.2, 2 H), 6.62 (dd, *J* = 4.7, 15.2, 1 H), 6.12 (d, *J* = 5.4, 1 H), 5.90 (d, *J* = 15.2, 1 H), 5.45 (d, *J* = 6.3, 1 H), 5.07 (s, 2 H), 4.65 (m, 1 H), 4.37 (m, 1 H), 4.13 (m, 1 H), 3.08 (dd, *J* = 6.5, 13.7, 1 H), 3.01 (dd, *J* = 8.2, 13.7 Hz, 1 H), 1.38 (d, *J* = 7.0 Hz, 3 H), 1.17 (d, *J* = 6.8, 3 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 170.4, 156.0, 148.2, 135.9, 129.0, 128.6, 128.1, 127.5, 124.2, 67.0, 56.5, 45.2, 38.5, 19.3, 14.8; IR (neat) 3290, 1700, 1660, 1540, 1360, 1170 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{23}H_{28}N_2O_6S$ (M^+), 460.1668, found 460.1670.



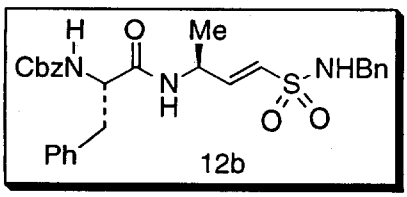
(3S)-N-(N'-Carbobenzyloxy-L-phenylalanyl)-3-amino-but-1-enyl-sulfonyl chloride, (11): To a stirred solution of ethyl sulfonate **10** (655 mg, 1.42 mmol) in acetone (10 mL) was added tetrabutylammonium iodide (1.6 g, 4.3 mmol).[7] The reaction was heated to reflux for 4 hours. The mixture was then cooled and concentrated in vacuo. Purification of the product by chromatography (SiO_2; gradient 5 to 10% MeOH: CH_2Cl_2) gave the tetrabutylammonium salt WRR-178 (940 mg, 98%).

To a stirred solution of Ph_3P (169 mg, 0.644 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added SO_2Cl_2 (57 μl, 0.708 mmol).[7] The cold bath was removed and the sulfonate salt (215 mg, 0.319 mmol) was added as a solution in CH_2Cl_2 (2 mL). The reaction was stirred for 1 h, then the mixture was concentrated in vacuo. Purification of the product by chromatography (SiO_2; 10% Et_2O: CH_2Cl_2) gave the sulfonyl chloride **11** as a white solid (130 mg, 90%): mp 138-141 °C; $[\alpha]_D^{20}$ -7.0° (c=3.59, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39-7.20 (m, 10 H), 6.73 (dd, *J* = 4.3, 14.8 Hz, 1 H), 6.25 (m, 2 H), 5.64 (m, 1 H), 5.08 (s, 2 H), 4.71 (m, 1 H), 4.42 (m, 1 H), 3.12 (dd, *J* = 5.6, 13.3 Hz, 1 H), 3.02 (dd, *J* = 8.9, 13.1 Hz, 1 H), 1.19 (d, *J* = 7.0 Hz Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 156.1, 148.8, 135.9, 135.8, 133.1, 129.2, 129.0, 128.8, 128.6, 128.3, 127.9, 127.6, 67.2, 56.7, 44.9, 38.7, 19.1; IR (neat) 3280, 1690, 1535, 1370 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{21}H_{24}ClN_2O_5S$ (MH^+) 451.1094, found 451.1111. *Anal.* Calcd. for $C_{21}H_{23}ClN_2O_5S$: C, 55.94; H, 5.14; N, 6.21. Found: C, 56.04; H, 5.19; N, 6.06.



12a

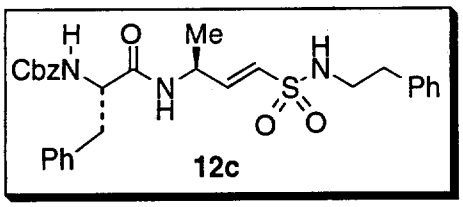
Methyl (3S)-N-(N'-Carbobenzyloxy-L-phenylalanyl)-3-amino-but-1-enyl sulfonate, (12a, WRR-206): To a stirred solution of sulfonyl chloride **11** (36 mg, 0.08 mmol) in CH_2Cl_2 (0.8 mL) at 0 °C was added methylamine (0.4 mL of a 40% aqueous solution). The reaction was stirred at 0 °C for 40 min. The mixture was then poured into water and extracted thrice with ethyl acetate. The combined organics were dried (Na_2SO_4) and concentrated. Purification of the crude product by preparative TLC (65% ethyl acetate-hexanes) gave the sulfonamide **12a** as a white solid (14 mg, 39%): mp 141-142 °C; $[\alpha]_D^{20}$ -1.30° (c 1.56, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36-7.18 (m, 10 H), 6.52 (dd, *J* = 4.8, 15.0 Hz, 1 H), 6.36 (d, *J* = 5.0 Hz, 1 H), 5.97 (d, *J* = 15.0 Hz, 1 H), 5.55 (d, *J* = 6.4 Hz, 1 H), 5.07 (s, 2 H), 4.64 (m, 2 H), 4.43 (m, 1 H), 3.06 (m, 2 H), 2.62 (s, 3 H), 1.19 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 156.1, 145.5, 136.1, 135.9, 129.2, 128.8, 128.6, 128.3, 128.0, 127.2, 126.5, 67.2, 56.4, 45.3, 38.4, 29.0, 19.7; IR (neat) 3300, 1700, 1665, 1540, 1330, 1250, 1155 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{22}H_{27}N_3O_5S$ (M^+) 445.1671, found 445.1692. *Anal.* calculated for $C_{22}H_{27}N_3O_5S$: C, 59.31; H, 6.11; N, 9.43. Found: C, 59.60; H, 6.18; N, 9.26.



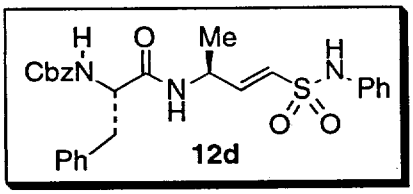
12b

Benzyl (3S)-*N*-(*N'*-Carbobenzyloxy-L-phenylalanyl)-3-amino-but-1-enyl sulfonamide, (12b, WRR-184): To a stirred solution of sulfonyl chloride **11** (61 mg, 0.135 mmol) in CH_2Cl_2 (1 mL) was added a solution of benzylamine (10 µl, 0.15 mmol) and DBU (23 µl, 0.15 mol) in CH_2Cl_2(1 mL). The mixture was stirred for 20 min, then the mixture was poured into saturated $CuSO_4$ and extracted twice with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and concentrated to give sulfonamide **12b** as a white solid (36 mg, 51%): mp 145-147 °C; $[\alpha]_D^{20}$ +2.1° (c 0.5, acetone);. ^1H NMR (400 MHz, d_6-acetone) δ 7.46-7.19 (m, 15 H), 6.57 (dd, *J* = 5.0, 15.2 Hz, 1 H), 6.52 (m, 2 H), 6.24 (d, *J* = 15.2 Hz, 1 H), 5.04 (A of AB, *J* = 12.7, 1 H), 4.99 (B of AB, *J* = 12.7 Hz, 1 H), 4.65 (m, 1 H), 4.41 (ddd, *J* = 5.9, 8.4, 8.5 Hz, 1 H), 4.16 (d, *J* = 6.3 Hz, 2 H), 3.16 (dd, *J* = 5.9, 13.8 Hz, 1H), 2.95 (dd, *J* = 8.5, 13.7 Hz, 1 H), 1.23 (d, *J* = 7.1, 3 H); ^{13}C NMR (100 MHz, d_6-acetone) δ 171.4, 156.9, 145.5, 139.0, 138.5, 130.2, 129.3,

129.2, 128.8, 128.64, 128.57, 128.2, 127.5, 66.8, 57.5, 47.5, 46.0, 39.1, 19.9; IR ($CHCl_3$) 3300, 1660, 1540, 1145 cm^{-1}; HRMS (CI, NH_3) Calcd for $C_{28}H_{32}N_3O_5S$ (MH^+) 522.2063, found 522.2074 m/z.

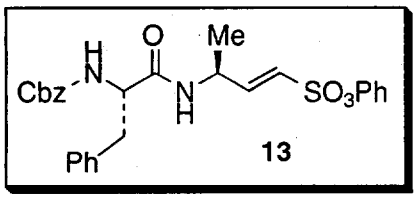


(2-Phenyl)-ethyl (3S)-N-(N'-carbobenzyloxy-L-phenylalanyl)-3-amino-but-1-enyl sulfonamide, (12c, WRR-186): To a stirred solution of sulfonyl chloride **11** (83 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added a solution of phenethylamine (25 µl, 0.20 mmol) and DBU (30 µl, 0.20 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred for 0.5 h, then was poured into saturated $CuSO_4$ and extracted twice with CH_2Cl_2 . The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the crude product by preparative TLC (30% Et_2O-CH_2Cl_2) gave sulfonamide **12c** as a clear viscous oil (45 mg, 47%): mp 155-157 °C; $[\alpha]_D^{20}$ +3.5° (c 0.58, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.14 (m, 15 H), 6.45 (dd, *J* = 4.7, 15.1 Hz, 1 H), 5.95 (d, *J* = 7.1 Hz, 1 H), 5.84 (dd, *J* = 1.3, 15.2 Hz, 1 H), 5.36 (d, *J* = 6.9 Hz, 1 H), 5.06 (s, 2 H), 4.60 (m, 1 H), 4.36 (m, 2 H), 3.22 (m, 2 H), 3.03 (dddd, *J* = 6.5, 13.6, 13.6, 13.7 Hz, 2 H), 2.83 (t, *J* = 6.7 Hz, 2 H), 1.14 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 156.0, 144.6, 137.8, 136.0, 135.9, 129.2, 128.9, 128.8, 128.6, 128.3, 128.1, 127.7, 126.9, 67.3, 56.4, 45.2, 44.1, 38.4, 36.1, 19.6; IR ($CHCl_3$) 3300, 1700, 1660, 1540, 1330, 1145 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{29}H_{33}N_3O_5S$ (M^+) 535.2141, found 535.2143. *Anal.* Calcd. for $C_{29}H_{33}N_3O_5S$: C, 65.03; H, 6.21; N, 7.84. Found C, 65.30; H, 6.30; N, 7.62.



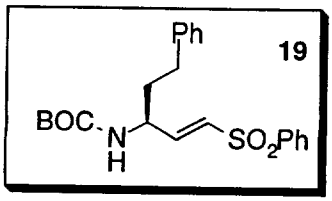
Phenyl (3S)-N-(N'-carbobenzyloxy-L-phenylalanyl)-3-amino-but-1-enyl sulfonamide, (12d, WRR-205): To a stirred solution of sulfonyl chloride **11** (69 mg, 0.153 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added aniline (42 µl, 0.46 mmol). Five minutes later, the mixture was diluted with CH_2Cl_2 and poured into saturated aqueous $CuSO_4$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and

concentrated. Purification of the crude product by preparative TLC (ethyl acetate-hexanes) gave sulfonamide **12d** as a white solid (51 mg, 66%): mp 144-145 °C; $[\alpha]_D^{20}$ -2.2° (c 0.93, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.06 (m, 15 H), 6.47 (dd, *J* = 5.1, 15.1 Hz, 1 H), 6.09 (d, *J* = 15.1 Hz, 1 H), 6.02 (m, 1 H), 5.49 (d, *J* = 6.3 Hz, 1 H), 5.07 (s, 2 H), 4.56 (m, 1 H), 4.37 (m, 1 H), 3.07-2.96 (m, 2 H), 1.07 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 146.1, 136.4, 136.1, 129.4, 129.2, 128.9, 128.6, 128.3, 128.0, 127.3, 127.2, 125.5, 121.8, 67.2, 56.4, 45.2, 38.5, 19.5; IR (neat) 3300, 1700, 1660, 1600, 1540, 1500, 1345, 1150 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{27}H_{29}N_3O_5S$ (M^+) 507.1828, found 507.1845 m/z. *Anal.* Calcd. for $C_{27}H_{29}N_3O_5S$: C, 63.89; H, 5.76; N, 8.28. Found: C, 63.95; H, 5.72; N, 8.06.

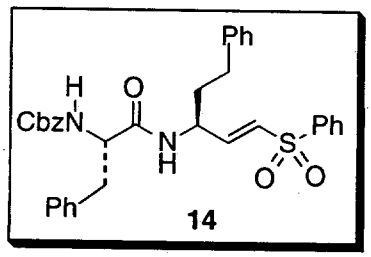


13

Phenyl (3S)-N-(N'-Carbobenzyloxy-L-phenylalanyl)-3-amino-but-1-enyl sulfonate, (13, WRR-199): To a stirred solution of sulfonyl chloride **11** (98 mg, 0.217 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added a solution of phenol (23 mg, 0.24 mmol) and DBU (36 µl, 0.24 mmol) in CH_2Cl_2 (1 mL). The reaction was allowed to warm slowly to room temperature over 2 h. The mixture was then poured into saturated $CuSO_4$ and extracted twice with CH_2Cl_2. The combined organics were dried (Na_2SO_4) and concentrated. Purification of the crude product by preparative TLC (1 : 1 ethyl acetate-hexanes) gave the phenyl sulfonate **13** as a white solid (56 mg, 51%): mp 138-139 °C; $[\alpha]_D^{20}$ -6.4° (c 1.09, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.12 (m, 15 H), 6.48 (dd, *J* = 4.8, 15.3 Hz, 1 H), 6.01 (d, *J* = 15.3 Hz, 1 H), 5.91 (d, *J* = 6.1 Hz, 1 H), 5.44 (d, *J* = 7.0 Hz, 1 H), 5.08 (s, 2 H), 4.58 (m, 1 H), 4.36 (m, 1 H), 3.10 (dd, *J* = 6.2, 13.6 Hz, 1 H), 2.96 (dd, *J* = 8.5, 13.5 Hz, 1 H), 1.10 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 156.0, 149.7, 149.4, 135.9, 129.8, 129.1, 129.0, 128.6, 128.4, 128.1, 127.6, 127.3, 123.9, 122.6, 67.3, 56.6, 45.4, 38.6, 19.2; IR (neat) 3300, 3070, 2940, 1700, 1665, 1545, 1380, 1250, 1150, 1030 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{27}H_{28}N_2O_6S$ 508.1668, found 508.1680. *Anal.* Calcd for $C_{27}H_{28}N_2O_6S$: C, 63.76; H, 5.55; N, 5.51. Found: C, 63.92; H, 5.61; N, 5.42.

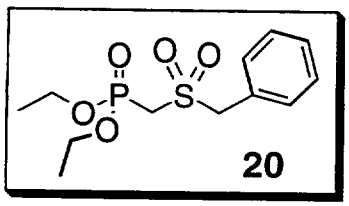


Phenyl (3S)-(*N*-*tert*-Butoxycarbonyl)-3-amino-5-phenylpent-1-enyl Sulfone (19). To a -10 °C solution of diethyl α-(phenylsulfonyl)methylphosphonate [8] (900 mg, 3.1 mmol) in THF (15 mL) was added NaH (80 mg, 3.30 mmol). After gas evolution had ceased (ca. 10 min), a -10 °C solution of Boc-homophenylalaninal **6** (710 mg, 2.60 mmol) in THF (10 mL) was added via cannula. The reaction was allowed to warm to 25 °C and stirred for a period of 1 h. The reaction was diluted with Et_2O (30 mL) then poured into brine (30 mL). The layers were separated and the organic layer was dried, filtered and concentrated *in vacuo* to yield a crude oil. Purification of the crude product by flash column chromatography using 40% EtOAc/-hexanes afforded vinyl sulfone **19** (750 mg, 78 % yield) as a clear oil: $[\alpha]_D^{26}$ = -1.0° (*c* 4.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.21 (m, 10H), 6.90 (dd, *J* = 15.1, 4.9 Hz, 1 H), 6.42 (d, *J* = 15.1 Hz, 1 H), 4.65 (s, 1 H), 4.38 (s, 1 H), 2.66 (m, 2 H), 1.75 (m, 2 H), 1.40 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 140.3, 140.1, 133.5, 130.5, 129.2, 128.5, 128.3, 127.5, 126.2, 80.0, 50.6, 35.8, 31.8, 28.2; IR (neat) 3440, 3060, 3025, 2980, 2920, 2860, 1720, 1500, 1450, 1370, 1320, 1250, 1150, 1090, 1050, 1030, 850 cm^{-1}; HRMS calcd for $C_{22}H_{27}NO_4S$ $(M)^+$ 401.1661, found 401.1655. *Anal.* Calcd for $C_{22}H_{27}NO_4S$: C, 65.81; H, 6.78; N, 3.49. Found: C, 65.90; H, 6.94; N, 3.37.



Phenyl (3S)-*N*-(*N'*-Carbobenzyloxy-L-phenylalanyl)-3-amino-5-phenylpent-1-enyl Sulfone (14). To a solution of vinyl sulfone **19** (340 mg, 0.92 mmol) in CH_2Cl_2 (2 mL) was added 1:1 TFA/CH_2Cl_2 (2 mL). After 1h, the reaction was concentrated *in vacuo* to yield the TFA salt of phenyl (3S)-3-amino-5-phenylpent-1-enyl sulfone as a light brown oil (380 mg, 99%), which was used in the next step without further purification: ^{1}H NMR (500 MHz, CD_3OD) δ 7.95-7.10 (m, 10 H), 6.94 (d, *J* = 15.2 Hz, 1 H), 6.88 (dd, *J* = 15.2, 7.4 Hz, 1 H), 4.89 (bs, 3 H), 3.97 (m, 1 H), 2.59 (m, 2 H), 2.10 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 140.9, 140.8, 140.5, 137.2, 135.3, 130.8, 129.8, 129.3, 129.0, 127.6, 52.1, 35.2, 32.1.

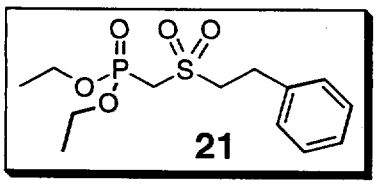
To a 0 °C solution of Cbz-Phe-OH (35 mg, 0.12 mmol), the above TFA salt (54 mg, 0.13 mmol), *N*-methyl morpholine (0.015 mL, 0.14 mmol) and 1-hydroxybenzotriazole (HOBt) (20 mg, 0.15 mmol) in DMF (2 mL) was added 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl) (30 mg, 0.16 mmol). The reaction was allowed to warm to 25 °C and stirred overnight. The reaction was diluted with EtOAc (15 mL) and then poured into saturated aqueous $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), 1 N HCl (2 x 20 mL), and brine then dried, filtered and concetrated *in vacuo* to yield a crude solid. Purification of the crude product by flash column chromatography using 40% EtOAc/hexanes afforded dipeptide vinyl sulfone **14** (69 mg, 97% yield) as a clear oil: $[\alpha]_D^{26}$ = +6.9° (*c* 0.9, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (m, 2 H), 7.62-7.53 (m, 3 H) 7.32-7.03 (m, 15 H), 6.76 (dd, *J* = 15.1, 4.9 Hz, 1 H), 6.05 (dd, *J* = 15.1, 1.4 Hz, 1 H) 5.97 (d, *J* = 7.4 Hz, 1 H), 5.25 (d, *J* = 6.7 Hz, 1 H), 5.05 (s, 2 H), 4.64 (m, 1 H), 4.30 (m, 1 H), 3.02 (m, 2 H), 2.95 (m, 2 H), 1.86 (m, 1 H), 1.72 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 155.9, 145.2, 140.2, 140.0, 136.0, 135.9, 133.5, 130.6, 129.3, 129.2, 128.8, 128.6, 128.59, 128.56, 128.3, 128.1, 127.6, 127.3, 67.3, 56.5, 49.2, 38.1, 35.4, 31.7; IR (neat) 3320, 3060, 3030, 2910, 2830, 1660, 1550, 1450, 1300, 1150, 1100, 750, 730, 700 cm^{-1}; HRMS calcd for $C_{34}H_{34}N_3O_5S$ $(M+1)^+$ 583.2267, found 583.2246. *Anal.* Calcd for $C_{34}H_{34}N_2O_5S$: C, 70.08; H, 5.88; N, 4.81. Found: C, 70.10; H, 6.07; N, 4.68.



Diethyl α-(Benzylsulfonyl)methylphosphonate (20). To a stirred solution of benzyl mercaptan (0.62 g, 5 mmole) and potassium bicarbonate (0.75 g, 7.5 mmole) in ethanol (15 mL) at room temperature was added diethyl iodomethanephosphonate (1.39 g, 5 mmole).[9] The mixture was stirred overnight at room temperature, then the solvent was removed under reduced pressure. The residue was partitioned between EtOAc (25 mL) and water (50 mL). The aqueous layer was extracted twice with EtOAc (25 mL x 2). The combined organic layer was washed with brine, saturated $NaHCO_3$, brine, 1 N HCl, and brine and dried over Na_2SO_4. The solvent was remove under reduce pressure, and the crude product was purified by flash chromatography (Et_2O) to give the sulfide

product (diethylphosphonomethyl benzyl sulfide) as a colorless oil (1.33 g, 97%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5 H), 4.18 (quint, J = 8.2 Hz, 4 H), 3.88 (s, 2 H), 2.55 (d, *J* = 13.5 Hz, 2 H), 1.34 (t, *J* = 8.2 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 129.3, 128.4, 127.2, 62.6 (d, *J* = 8.7 Hz), 36.9 (d, *J* = 3.8Hz), 23.0 (d, *J* = 198.5 Hz), 16.5 (d, *J* = 8.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.2.

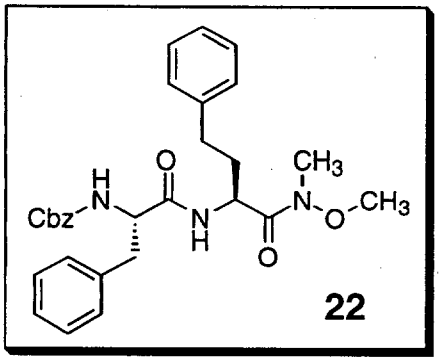
To a stirred solution of diethylphosphonomethyl benzyl sulfide (1.33g, 4.85 mmole) in a 1 : 1 : 1 mixture (30 mL) of CH_2Cl_2, acetonitrile, and water at room temperature was added $NaIO_4$ (4.15 g, 19.4 mmole) and $RuCl_3$ (0.101 g, 0.485 mmole).[10,11] The mixture was virgorously stirred for 15 min at room temperature. The mixture then was diluted with EtOAc (50 mL) and water (150 mL). The aqueous layer was extracted twice with EtOAc (50 mL x 2). The combined organic layer was washed with brine, saturated $NaHCO_3$, brine, 1N HCl, and brine and dried over Na_2SO_4. The EtOAc solution was then passed through a plug of silica gel, then concentrated under reduce pressure. Purification of the crude product by flash chromatography (ether) provided the α-sulfonyl phosphonate **20** as a yellowish solid (1.30 g, 88%): mp 43-44 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.54 (m, 5 H), 4.59 (s, 2 H), 4.22 (quint, *J* = 8.6 Hz, 4 H); 3.38 (d, *J* = 13.0 Hz, 2 H), 1.38 (t, *J* = 8.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 131.0, 129.2, 128.0, 63.8 (d, *J* = 6.4 Hz), 60.3, 47.8 (d, *J* = 139.2Hz), 16.3 (d, *J* = 6.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 11.5; IR (KBr) 2978, 1311, 1245, 1138, 1020, 799 cm^{-1}; HRMS (CI, NH3) calcd for $C_{12}H_{20}O_5PS$ (M+1): 307.0769, found 307.0760. *Anal.* Calcd. for $C_{12}H_{19}O_5PS$: C, 47.05; H, 6.25; found: C, 46.90; H, 6.13.



Diethyl α-(Phenethylsulfonyl)methylphosphonate (21). To a stirred solution of phenethyl mercaptan (0.69 g, 5 mmole) and potassium bicarbonate (0.75 g, 7.5 mmole) in ethanol (15 mL) at room temperature was added diethyl iodomethanephosphonate (1.39 g, 5 mmole).[9] The mixture was stirred overnight at room temperature, then was concentrated in vacuo. The residue was partitioned between EtOAc (25 mL) and water (50 mL). The aqueous layer was separated and extracted twice with EtOAc (25 mL x 2). The combined organic extracts were washed with brine, saturated $NaHCO_3$, 1N HCl, and brine and dried over Na_2SO_4. The crude product was purified by flash chromatography (Et_2O), giving

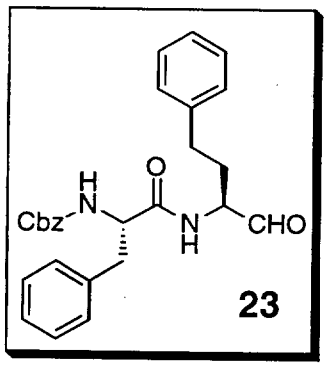
the product sulfide as a colorless oil (0.98 g, 68%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.40 (m, 5 H), 4.22 (m, 4 H), 3.08 (m, 4 H); 2.80 (d, J = 14.2 Hz, 2 H), 1.60 (t, J = 8.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 128.5, 128.4, 126.3, 62.6 (d, J = 8.7 Hz), 35.7 (d, J = 6.1Hz), 34.8 (d, J = 3.8 Hz), 25.4 (d, J = 198.4 Hz), 16.6 (d, J = 8.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.9; low resolution mass spec (CI, NH_3) cald. for $C_{13}H_{22}O_3PS$ (M+1): 289, found 289.

To a stirred solution of diethyl α-phosphonomethyl phenethylsulfide (310 mg, 1.08 mmole) in a 1 : 1 : 1 mixture (10 mL) of methylene chloride, acetonitrile, and water at room temperature was added $NaIO_4$ (0.92g, 4.3 mmole) and $RuCl_3$ (22.3 mg, 0.1076 mmole).[10,11] The mixture was virgorously stirred for 15 min at room temperature, then was diluted with EtOAc (50 mL) and water (150 mL). The aqueous layer was extracted twice with EtOAc (50 mL x 2). The combined organic layers were washed with brine, saturated $NaHCO_3$, 1 N HCl, and brine, and dried over Na_2SO_4. The EtOAc solution was then filtered through a plug of silica gel, and then concentrated in vacuo. Purification of the crude product by flash chromatography (30% EtOAc-hexanes) gave phosphonate **21** as a colorless oil (265 mg, 77%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.48 (m, 5 H), 4.30 (quint, J=8.4 Hz, 4 H), 3.75 (t, J = 7.6 Hz, 2 H), 3.56 (d, J = 12.8 Hz, 2 H), 3.24 (t, J = 7.6 Hz, 2 H), 1.44 (t, J = 8.4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 128.8, 128.5, 126.9, 63.7 (d, J = 8.7 Hz), 55.6, 50.6 (d, J = 184.1 Hz), 28.4, 16.4 (d, J = 4.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 12.3; IR (KBr): 2984, 1314, 1259, 1146, 1027, 968, 799 cm^{-1}; HRMS (CI, NH_3) caldd. for $C_{13}H_{22}O_5PS$ (M+1) 321.0926, found 321.0919. *Anal.* Calcd. for $C_{13}H_{21}O_5PS$ C: 48.74, H, 6.61; found: C, 48.62, H, 6.63.

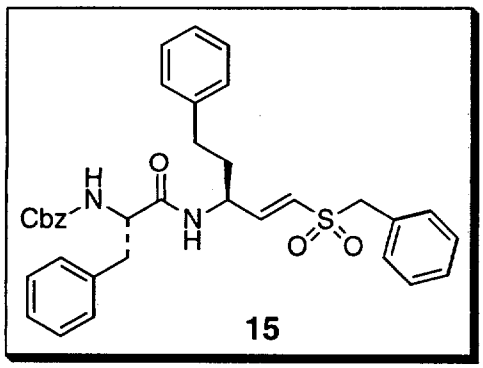


***N*-Methoxy-*N*-methyl (*N*'-Carbobenzyloxy-L-phenylalanyl-L-homophenylalanyl) Amide (22).** To a stirred solution of the BOC-protected homophenylalanine Weinreb amide **17** (830 mg, 2.25 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a solution of trifluoroacetic acid (5 mL, 50% in CH_2Cl_2). This mixture was stirred for 0.5 h, then solution was concentrated, first on the rotary evaporator, and then under high vaccum. The residue was dissolved in DMF (10 mL) and N-Cbz-L-phenylalanine (672 mg, 2.25 mmol) was added. The solution was cooled to 0 °C and

diisopropylethylamine (0.86 mL, 4.95 mmol), 1-hydroxybenzotriazole hydrate (335 mg, 2.48 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (475 mg, 2.48 mmol) were added. This mixture was stirred for 18 h as the bath warmed to ambient temperature. The resulting solution was poured into EtOAc (50 mL) and washed with brine, saturated $NaHCO_3$, 1N HCl, and brine and dried over Na_2SO_4. The crude product was purified by flash chromatography (30% EtOAc-hexanes) to give the dipeptide **22** as a white solid: mp: 110-111 °C; $[\alpha]_D^{20}$ -9.3° (c 0.27, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 7.08-7.40 (m, 15H), 6.60 (b, 1H), 5.36 (b,1H), 5.06 (dd, J=4.90 & 15.2 Hz, 2H), 4.49 (b, 1H), 4.52 (b, 1H), 3.61 (s, 3H), 3.14 (s, 3H), 3.07 (m, 2H), 2.60 (m, 2H), 2.03 (m, 1H), 1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 170.5, 155.7, 140.9, 136.2, 136.0, 129.3, 128.5, 128.4, 128.3, 128.0, 127.9, 126.8, 125.9, 67.0, 61.5, 56.0, 49.0, 38.5, 34.1, 31.6; IR (KBr) 3809, 3604, 2930, 1720, 1464, 1542, 1240, 698 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{29}H_{34}N_3O_5$ (M+1) 504.2498, observed 504.2518. *Anal.* Calcd. for $C_{29}H_{33}N_3O_5$: C, 69.17; H, 6.60; N, 8.34; found: C, 69.08; H, 6.83; N, 8.39.

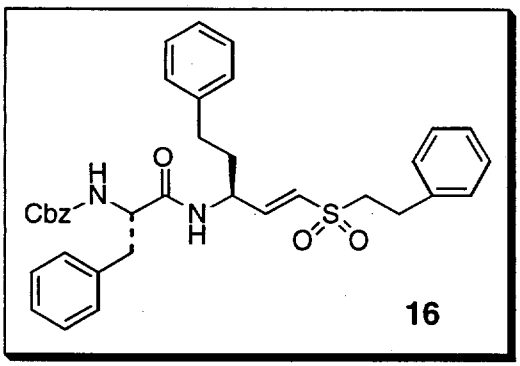


***N'*-Carbobenzyloxy-L-phenylalanyl-L-homophenylalaninal (23).** To a stirred solution of the dipeptidyl Weinreb amide **22** (1.64 g, 3.25 mmol) in THF (50 mL) at 0 °C was cautiously added $LiAlH_4$ (148 mg, 3.90 mmol). One hour later, the reaction was carefully quench with saturated potassium bisulfate at 0 °C. 1N Hydrochloric acid (100 mL, precooled to 0 °C) was slowly added. The mixture was extracted three times with ethyl acetate. The combined organics were washed once with brine, dried over Na_2SO_4, and concentrated in vacuo to give the aldehyde **23** (1.3 g, 90%) that was used immediately in subsequent reactions: ^1H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1 H), 7.10-7.38 (m, 15 H), 6.28 (b, 1 H), 5.20 (b,1 H), 5.11 (dd, J = 16.2 Hz, 2 H), 4.40 (m, 2 H), 3.12 (m, 4 H), 2.80 (m, 2 H), 2.20 (m, 1 H), 1.90 (m, 1 H).



15

Benzyl (3S)-*N*-(*N*'-Carbobenzyloxy-L-phenylalanyl)-3-amino-5-phenylpent-1-enyl Sulfone (15). To a stirred solution α-sulfonyl phosphonate **20** (40 mg, 0.13 mmol) in THF (30 mL) at -78 °C was slowly added n-BuLi (0.053 mL of a 2.47 M solution in hexane, 0.13 mmol). Twenty minutes later, N-CBZ protected dipeptidyl aldehyde **23** (58 mg, 0.13 mmol) in THF (10 mL) at -78 °C was slowly added. The reaction mixture was stirred for approximately 15 h as the cooling bath warmed to ambient temperature. The reaction was then quenched with pH 7 buffer and was diluted with water. The mixture was extracted three times with EtOAc. The combined organic layer was washed with brine, saturated $NaHCO_3$, 1 N HCl, and brine. The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude product by silica gel flash chromatography (1 : 1 EtOAc-hexanes) gave **15** as a white solid (48 mg, 62%): mp: 191-2 °C; $[\alpha]_D^{20}$ +6.8° (c 0.22, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.00-7.40 (m, 20 H), 6.42 (dd, *J* = 13.5, 6.6 Hz, 1 H), 5.99 (d, *J* = 13.5 Hz, 1 H), 5.84 (b, 1 H), 5.22 (b, 1 H), 5.11 (dd, *J* = 15.2 Hz, 2 H), 4.52 (m, 1 H), 4.38 (m, 1 H), 4.18 (s, 1 H), 3.02 (m, 2 H), 2.59 (m, 2 H), 1.70 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 152.1, 148.0, 149.6, 136.0, 135.9, 131.0, 130-126 (m), 67.3, 61.2, 56.5, 49.5, 38.2, 34.5, 31.2; IR (KBr) 3328,1685, 1655, 1542, 1313, 1125 cm^{-1}; HRMS (CI, NH_3) calcd. for $C_{35}H_{37}N_2O_5S$ (M+1) 597.2423, found 597.2408. *Anal.* Calcd. for $C_{35}H_{36}N_2O_5S$: C, 70.45; H, 6.08; N, 4.69. Found: C, 70.27; H, 6.39; N, 4.81.



16

Phenethyl (3S)-*N*-(*N*'-Carbobenzyloxy-L-phenylalanyl)-3-amino-5-phenylpent-1-enyl Sulfone (16). To a stirred solution of **21** (47 mg, 0.13 mmol) in THF (30 mL) at -78 °C was slowly added *n*-BuLi (0.050 mL of a 2.47 M solution in hexane, 0.125 mmol). Twenty minutes later, N-Cbz protected dipeptidyl aldehyde **23** (67 mg, 0.15 mmol) in THF (10 mL) at -78 °C was added dropwise. The reaction mixture was stirred for approximately 15 h as the cooling bath warmed to

room temperature. The reaction was then quenched with pH 7 buffer, diluted with water, and extracted with EtOAc (3x). The combined organic layers were washed with brine, saturated $NaHCO_3$, 1 N HCl, and brine, and then dried over Na_2SO_4. Purification of the crude product by flash chromatography (1 : 1 EtOAc- hexanes) gave **16** as a white solid (53 mg, 70%): mp 188-9 °C; $[\alpha]_D^{20}$ +7.2° (c 2.2, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.08-7.38 (m, 20 H), 6.68 (dd, *J* = 13.2, 6.8 Hz, 1 H), 5.99 (d, *J* = 13.2 Hz, 1 H), 5.82 (b, 1 H), 5.18 (b, 1 H), 5.12 (dd, *J* = 14.5 Hz, 2 H), 4.60 (m, 1 H), 4.38 (m, 1 H), 3.20 (m, 2 H), 3.08 (m, 4 H), 2.58 (m, 2 H), 1.89 (m, 1 H), 1.74 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 154.1, 147.4, 140.2, 137.5, 136.0, 135.8, 129.2, 129.0, 128.8, 128.7 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.4, 126.9, 126.4,, 67.9, 56.6, 56.2, 49.5, 38.0, 35.2, 32.0, 28.4; IR (KBr) 3316, 1686, 1656, 1523, 1288, 1125 cm^{-1}; HRMS (CI, NH_3) calcd. for $C_{36}H_{39}N_2O_5S$ (M+1) 611.2580, found 611.2589. *Anal.* Calcd. for $C_{36}H_{38}N_2O_5S$: C, 70.79; H, 6.27; N, 4.59. Found: C, 70.56; H, 6.53; N, 4.32.

Enzyme Inhibition Studies. Inhibitors were screened for effectiveness against cruzain, the *Trypanosoma cruzi* cathepsin L-like protease, using purified recombinant protein lacking the C terminal domain.[12] Cruzain (4 nM) was incubated with 1 nM to 10,000 nM inhibitor in 100 mM sodium acetate buffer (pH 5.5) and 10 mM DTT (buffer A) for 5 min at room temperature. Z-Phe-Arg-AMC (Bachem) (K_m = 1 μM) was added to a concentration of 20 μM in a final volume of 200 μL, and the increase in fluorescence (excitation at 355 nm and emission at 460 nm) was followed with an automated microtiter plate spectrofluorometer (Labsytems Fluoroskan II). Inhibitor stock solutions were prepared at 20 mM in DMSO, and serial dilutions were made in DMSO.[13] Controls were performed using enzyme alone, enzyme with DMSO and enzyme with a previously known, highly effective irreversible inhibitor, (Mu-Phe-HPhe-(CH=CHSO$_2$Ph), **1**, Arris Pharmaceuticals Inc., South San Francisco, CA)[4,14] with each assay set. Inhibitors which had IC_{50}'s of less than 1 μM were further analyzed. Inhibition data for other enzymes were determined similarly: papain (EC 3.4.22.2, Sigma) at 6 nM enzyme and 100 μM Z-Phe-Arg-AMC (K_m = 50 μM) in buffer A plus 1 μM EDTA and 0.1% Triton X 100 (buffer B); and cathepsin B (bovine spleen, EC 3.4.22.1, Sigma) at 10 nM enzyme and 100 μM Z-Phe-Arg-AMC (K_m = 110 μM) in buffer B.

Inhibition data for various vinyl sulfonamides vs. cruzain are summarized in Table 2, while inhibition data for vinyl sulfonates and vinyl sulfones vs. cruzain are summarized in Table 3.

Table 2: Inhibition of Cruzain by Vinyl Sulfonamides: % Enzyme Inhibition at Different Inhibitor Concentrations

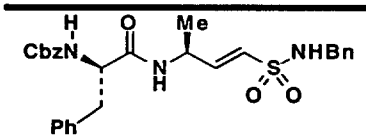
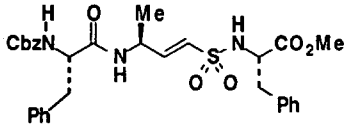
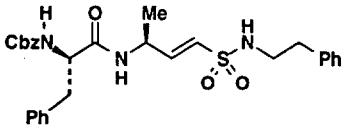
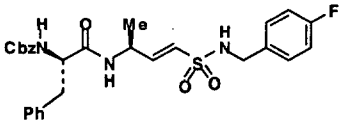
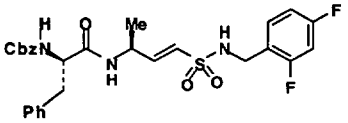
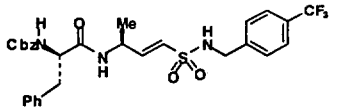
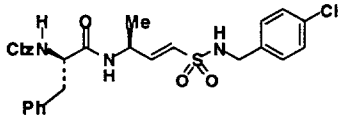
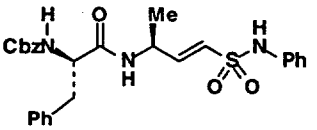
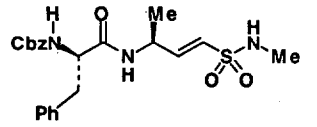
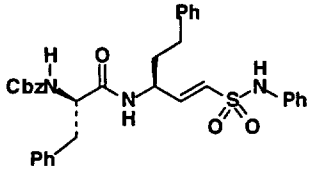
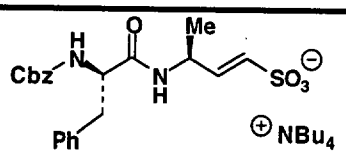
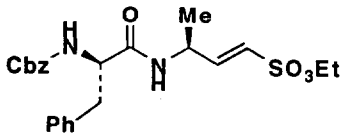
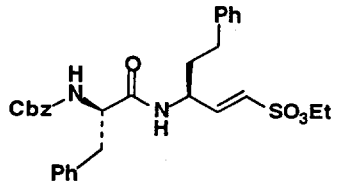
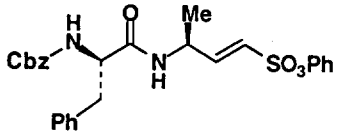
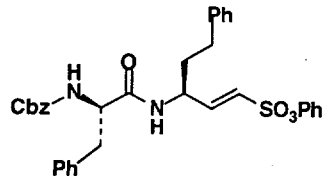
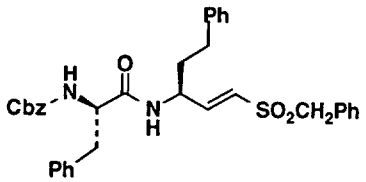
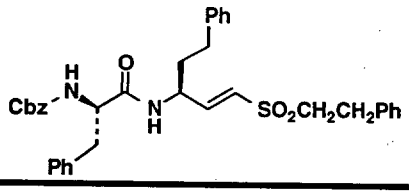
Structure	Comp.	Concentration (μM) 10	1	0.1	0.01
	**WRR-184 (12b)**	99	80	49	4
	**WRR-185**	97	88	41	1
	**WRR-186 (12c)**	95	79	20	8
	**WRR-196**	>99	87	20	2
	**WRR-197**	100	61	18	8
	**WRR-200**	100	80	25	5
	**WRR-201**	100	94	35	17
	**WRR-205 (12d)**	>99	97.4	54	14
	**WRR-206 (12a)**		95	44	3
	**WRR-208 (3a)**	0	>98	83	14

Table 3: Inhibition of Cruzain by Vinyl Sulfonates and Sulfones: % Inhibition at Different Inhibitor Concentrations

Structure	Comp.	Concentration (μM) 10	1	0.1	0.01	0.001
	**WRR-178**	81	58	9		
	**WRR-179 (10)**	97	90	53		
	**WRR-198 (9)**	100	>98	93	47	3
	**WRR-199 (13)**	100	100	98	95	58
	**WRR-204 (4a)**	100	100	>99	97	34
	**WRR-256 (15)**	100	100	>99	89	19
	**WRR-257 (16)**	100	96	95	70	11

Kinetic Assays of Irreversible Inhibitors. Kinetic analyses of the irreversible cysteine protease inhibitors were performed as follows.[13,15] Cruzain (2 nM) in 100 μL of assay buffer was added to inhibitor dilutions in 100 μL of 5 μM Z-Phe-Arg-AMC (K_m = 1 μM) in buffer A. Progress curves were obtained for 5 min at room temperature (less than 5% of substrate consumed) with ten-fold dilutions of inhibitor, starting at 10 μM. Inhibitor dilutions which gave simple exponential progress

curves over a wide range of k_{obs} were used to determine kinetic parameters. The value of k_{obs}, the rate constant for loss of enzyme activity, was determined from an equation for pseudo first order dynamics using UltraFit (Biosoft). When k_{obs} varied linearly with inhibitor concentration,[16] k_{ass} was determined by linear regression analysis.[13] If the variation was hyperbolic, indicating saturation inhibition kinetics, k_{inact} and K_i were determined from an equation describing a two step irreversible inhibitor mechanism ($k_{obs} = k_{inact}\,[I]_o/([I]_o + K_i^*(1 + [S]_o/K_m))$) and non linear regression analysis using UltraFit. K_i and k_{inact} were also deterimined from double reciprocal plots of k_{obs} vs. the inhibitor concentration when $r^2 > 0.95$; K_i and k_{inact} are the intersection of the x axis and the slope, respectively.[13] Apparent second order rate constants (k_{inact}/K_i) determined in this way were in good agreement with the kinetic constants (k_{ass} or k_{inact}/K_i) determined by the regression analyses. Kinetic constants for **3a**, **9**, **12b**, and **13-16** are summarized in Table 1 (see text of manuscript).

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(16) It was not possible to demonstrate saturation kinetics for many of the enzyme-inhibitor combinations, owing to the range of inhibitor concentrations that were studied. In the case of cruzain and **4a**, it was not possible to obtain k_{obs} data at inhibitor concentrations greater than 60 nM, whereas for cruzain and **15** the maximum inhibitor concentration that gave k_{obs} data was 200 nM. Accordingly, the majority of inhibition constants in Table 1 are reported as k_{ass} (see ref. 13).