Efficient Asymmetric Synthesis of the Vasopeptidase Inhibitor BMS-189921

Janak Singh,* David R. Kronenthal, Mark Schwinden, Jollie D. Godfrey,
Rita Fox, Edward J. Vawter, Bo Zhang, Thomas P. Kissick, Bharat Patel,
Omar Mneimne, Michael Humora, Chris G. Papaioannou, Walter Szymanski,
Michael K. Y. Wong, Chien K. Chen, James E. Heikes, John D. DiMarco,
Jun Qiu, Rajendra P. Deshpande, Jack Z. Gougoutas and Richard H. Mueller

Supporting Information

Experimental: ^1H NMR spectra were recorded on a JOEL FX 270 MHz spectrometer using TMS as internal standard and ^{13}C NMR were recorded at 68 MHz. Optical rotations were recorded at ambient temperature. HPLC analysis results are described as area percent (AP).

N-(Benzyloxycarbonyl)- α -phosphono-glycine trimethyl ester **2** and (S)-2-(acetylthio)benzenepropanoic acid **16** are commercially available from Aldrich Chemical Company and Davos Chemical corporation respectively.

Part I: Synthesis of (S)- α -aminoazepinone **6b** via enantioselective reduction of enamide **3**.

2,6-Dinitro-2, 6-dimethyl-3-heptanol (1).

Acrolein (71.6 mL, 1.07 mol) was added to a mixture of 2-nitropropane (480 mL, 5.36 mol) and Et₃N (14.9 mL, 0.11 mol) under an argon atmosphere. (Caution for scaleup: The reaction is strongly exothermic and it is advisable to add acrolein slowly and use an ice bath to keep the temperature around 20 °C). After 20 h the

mixture was washed with 1N HCl (600 mL). The light blue organic phase was washed further with aqueous NaHCO₃ (350 mL), brine (200 mL), dried over Na₂SO₄, filtered and concentrated under vacuum at 35 °C. The oil was dissolved in heptane (200 mL) and evaporated. This process was repeated and the light blue solid was dissolved in toluene (500 mL) at 60 °C and allowed to cool slowly to 20 °C. After standing overnight, the product was filtered, washed with hexane/toluene (1:2, 40 mL) and dried under vacuum to yield 96.8 g of product **1** as a white solid HPLC AP 99.5.¹ The mother liquor was diluted with hexane (200 mL) and cooled to 0 °C. After 30 minutes the solid was isolated as above to give 72.6 g (AP 98.3) of **1**, combined yield = 68%. ¹H NMR (270 MHz, CDCl₃) δ, 1.3 – 1.7 (m, 2 H), 1.69 (s, 3 H), 1.7 (s, 3 H), 1.74 (s, 3 H), 1.76 (s, 3 H), 2.0 – 2.2 (m, 1 H), 2.38 – 2.40 (m, 1 H), 2.48 – 2.6 (m, 1 H). ¹³C NMR (68 MHz, CDCl₃) δ, 20.3, 23.8, 25.8, 26.1, 26.8, 75.5, 86.8, 91.1. IR (KBr) 3530, 1539, 1530 cm⁻¹; Anal. Calcd for C₉H₁₈N₂O₅: C, 46.15; H, 7.74; N, 11.96; Found: C, 46.13; H, 7.83; N, 12.03.²

(z)-6-Methyl-6-nitro-2-[[[(phenylmethoxy)carbonyl]amino]-2-heptanoic acid, methyl ester (3).

1,8-Diazabicyclo[5.4.0]undec-7-ene (69.5 mL, 0.455 mole) was added dropwise to a solution of (d,l)-Cbz-α-phosphonoglycine trimethylester (54.8 g, 165 mmol) in CH₂Cl₂ (270 mL). precooled to –20 °C under a nitrogen atmosphere.³ The mixture

¹ HPLC method: Column: YMC S3 ODS 6.0 x 150.0; Solvent A: 100% 0.2% aqueous H₃PO₄. Solvent B: 90% CH₃CN in water. Gradient: 10% to 100% B in 30 min; flow rate 1.5 ml/min; wave length 205 nm. R_t of **1** 21.4 min.

² Rosini, G.; Marotta, E.; Ballini, R.; Petrini, M. *Synthesis*, **1986**, 237.

³ (a). Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis*, **1984**, 53. (b). Kazmaier, U. *Tetrahedron Lett.*, **1996**, 37, 5351. (c). Cis geometry of olefin **3** was confirmed by single crystal x-ray analysis. Coordinates

was stirred for 5 minutes and a solution of carbinol **1** (38.7 g, 165 m mole) in CH₂Cl₂ (150 mL) was added slowly via a cannula. Additional CH₂Cl₂ (100 mL) was used to transfer the residual material. The temperature was maintained at –20 °C during the addition. The mixture was allowed to warm to 0 °C and stirred for 5 h below 5 °C and at 20 °C for 1 h. The reaction was complete by HPLC analysis.⁴ The solution was concentrated under vacuum at 35 °C and the resulting oil was dissolved in EtOAc (500 mL) and washed consecutively with 1 N HCl (400 mL), saturated aqueous NaHCO₃ (200 mL), 10% NaHSO₄ (200 mL) and brine (200 mL). The solution was dried (MgSO₄), and stirred with charcoal (2 g activated carbon) for 0.5 h. The mixture was filtered through a silica gel pad (60 g) and the product eluted with EtOAc (1 l). The solvent was evaporated to give 62.7 g (yield ~99%) of olefin **3** (AP 89; contains 7% E-isomer). ¹H NMR (500 MHz, CDCl₃) δ, 1.56 (s, 6 H), 2.05 – 2.09 (m, 2 H), 2.15 – 2.2 (m, 2 H), 3.8 (s, 3 H), 5.1 (s, 2 H), 6.3 (bs, 1 H), 6.5 (t, 1 H, J = 7.4), 7.3 – 7.4 (m, 5 H). olefinic proton in the minor *trans* isomer at 6.8 ppm (t, 1 H, J = 7.5 Hz). ¹³C NMR (68 MHz, CDCl₃) δ, 24.2, 26.2, 39.2, 53.0, 68.0, 88.2, 126.3, 128.6, 128.8, 128.9, 129.1, 135.3, 136.4, 154.4, 165.2. IR ((KBr) 3325, 1719, 1661 cm⁻¹. MS (ESI) M – H = 349. Anal. calcd for C₁₇H₂₂N₂O₆: C, 58.28; H, 6.33; N, 8.0; Found: C, 58.17; H, 6.55; N, 8.14.^{3c}

from the X-ray determinations have been deposited in the Cambridge Crystallographic Database and can be obtained upon request to the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

⁴ HPLC method same as in footnote 1: R_t phosphonate **2**, 15.6 min; **1**, 18.7 min; Z and E-alkenes, 23.3 and 24.5 min.

(*S*)-6-Methyl-6-nitro-2-[[(*phenylmethoxy*)carbonyl]amino]heptanoic-acid, methyl ester (**4a**).

A solution of enamidoester **3** (274 g, 0.761 mole) in MeOH (1330 mL, preparged with argon gas) in an Ace Glass pressure vessel was sparged with argon gas for 0.5 h while stirring. Chiral catalyst (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)-benzene(cyclooctadiene)rhodium(I)trifluoromethane-sulfonate (0.245 g, 0.339 x 10⁻³ mole)⁵ was added and the vessel was evacuated and pressurized to 40 psi three times with H₂. The reactor was then pressurized with H₂ to 40 psi and stirring was continued at ambient temperature for 17 h. The reaction was monitored by ¹H NMR, which indicated more than 50% remaining starting material **3**. A second batch (0.274 g) of the catalyst was added and the hydrogenation was continued for an additional 24 h. ¹H NMR indicated that the reaction was complete. The solvent was evaporated to give 254.8 g of dark oil. The oil was dissolved in EtOAc – n-hexane (1:1, 500 mL) and passed through a pad of silica gel (12.5 x 15 cm). The product was eluted with of EtOAc – n-hexane (1:1, 2.7 l). Fractions containing product were evaporated to furnish 263 g (quantitative yield) of the ester **4a**. HPLC ee = 99.4%.⁶ ¹H NMR (270 MHz, CDCl₃) δ, 1.3 – 1.5 (m, 1 H), 1.68 (s, 3 H), 1.70 (s, 3 H), 1.70 – 1.8 (m, 2 H), 1.9 – 2.1 (m, 3 H), 3.9 (s, 3 H), 4.48 – 4.58 (m, 1 H), 5.3 (s, 2 H), 5.5 – 5.6 (broad d, 1

⁵ Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.*, **1993**, *115*, 101125.

⁶ (a). HPLC method same as in footnote 1: R_t product **4a** 24.1 min. (b). Chiral HPLC was conducted on Chiralcel OD-R 4.6 x 250 mm, 10 μm, mobil phase 3:2 H₂O:CH₃CN, column temperature 35 °C, flow rate 0.5 ml/min., UV wave length 210 nm. A reference sample of the R-enantiomer (**i**) was prepared by the reduction of enamidoester (**3**) with catalyst of opposite chirality [H₂, ((COD) Rh-(R,R) Et-DuPHOS)OTf, MeOH, 40 psi] in 98% yield, ee 99.7%.

H), 7.5 (s, 5 H). ^{13}C NMR (68 MHz, CDCl_3) δ , 17.5 19.9, 25.3, 26.0, 32.4, 40.0, 52.3, 53.3, 60.3, 66.9, 87.8, 128.0, 128.1, 128.4, 136.1, 155.8, 172.6. MS (ESI) $M + \text{H}_2\text{O} = 370$. $[\alpha]_{\text{D}} = -7.6$ ($c = 1$, 95% EtOH). Anal. calcd for $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_6 \cdot 0.065 \text{H}_2\text{O}$: C, 57.75; H, 6.88; N, 7.93, H_2O , 0.33; Found: C, 57.42; H, 6.93; N, 7.83, H_2O , 0.33.

(*S*)-6-Methyl-6-amino-2-[[(*phenylmethoxy*)carbonyl]amino]heptanoic-acid, methylester (**4b**).

Acetyl chloride (110 mL, 1.55 mol) was added dropwise over 0.5 h to a solution of nitroester **4a** (54.6 g, 155 moles) in MeOH (800 mL) pre-cooled to 0 °C under an argon atmosphere. The internal temperature of the reaction mixture was maintained between 0 to 12 °C. Zn dust (132 g, 2.02 mole) was added portionwise while keeping the temperature at 0 to 12 °C.⁷ After the addition was complete the mixture was warmed to 55 °C and stirring was continued for 2 h. HPLC⁸ showed complete absence of the starting material **4a**. The mixture was cooled to ambient temperature, filtered and solvent was evaporated under vacuum at 35 °C. The resulting white slurry was dissolved in H_2O (500 mL) and the pH of the solution was adjusted to 1.1 with conc. HCl (20 mL). The cloudy solution was washed with EtOAc (3 x 350 mL). The aqueous layer containing the HCl salt of **4b** was concentrated under vacuum and the semi-solid was redissolved in water (500 mL) and washed with MTBE (2 x 200 mL). The aqueous layer was cooled to 0 °C and basified with cold conc. aq NH_4OH (120 mL) to raise the pH to 10.7. The milky

⁷ (a). Bryce, M. R.; Gardiner, J. M.; Hursthouse, M. B.; Short, R. L. *Tetrahedron Lett.* **1987**, 34, 577. (b). Adams, J. P.; Box, D. S. *J. Chem. Soc., Perkin Trans. I*, **1999**, 749.

⁸ HPLC method same as in footnote 1: R_t product 12.5 min.

solution was extracted with CH₂Cl₂ (3 x 250 mL). The organic extract was dried by stirring over MgSO₄, filtered and evaporated in vacuum to give 46.1 g (yield 85%) of the aminoester **4b** as a light yellow liquid. ¹H NMR (270 MHz, CDCl₃) δ, 1.2 (s, 6 H), 1.5 (br s, 4 H), 1.7 – 1.8 (m, 1 H), 1.9 (m, 1 H), 2.1 (br s, 2 H), 3.9 (s, 3 H), 4.5 – 4.6 (m, 1 H), 5.2 (s, 2 H), 5.5 – 5.6 (m, 1 H), 7.5 (s, 1 H). ¹³C NMR (68 MHz, CDCl₃) δ, 20.2, 30.0, 33.2, 44.0, 49.7, 52.3, 53.8, 67.0, 128.1, 128.2, 136.2, 155.9, 173.0. MS (ESI) M + H = 321, M – H = 319.

*N*⁶-[2-(1,1-Dimethylethoxy)-2-oxoethyl]-6,6-dimethyl-*N*²-[(phenyl-methoxy)-carbonyl]-L-lysine, methyl ester (**5a**).

Diisopropylethyl amine (68.8 mL, 395 mmol) was added to a solution of aminoester **4b** (42.5 g, 132 mmol) in CH₃CN (650 mL) at 20 °C under a nitrogen atmosphere. The solution was stirred and *t*-butyl bromoacetate (21.8 mL, 145 mmol) was introduced. The reaction was complete after 20 h as evidenced by HPLC.⁹ Aqueous KHSO₄ (10%, 640 mL) was added to the stirring reaction mixture to give a precipitate. The mixture was filtered and the filtrate was evaporated under vacuum at 40 °C to remove CH₃CN. The aqueous solution (pH 2.3) was washed with heptane (400 mL). The aqueous layer was basified with 5 N aqueous NH₄OH to pH 10.6. The milky solution was extracted with CH₂Cl₂ (3 x 350 mL). The combined organic extracts were washed with brine (350 mL) and dried by stirring overnight over MgSO₄. The mixture was filtered and the filtrate was evaporated on a rotary evaporator. The resulting oil was redissolved in EtOAc (200 mL) and filtered through a pad of silica gel (70 g). The product was eluted with EtOAc (600 mL) and the solvent was evaporated to provide 63.6 g of aminodiester **5a** (yield 92%). ¹H NMR (270 MHz, CDCl₃) δ, 1.0 (s, 6 H), 1.3 – 1.4 (m, 4 H), 1.5 (s, 9 H), 1.6 – 1.8 (m, 2 H), 3.2 (s, 2 H), 3.7 (s, 3 H), 4.3 – 4.4 (m,

⁹ HPLC method same as in footnote 1: R_t product 16.0 min.

1 H), 5.1 (s, 2 H), 5.3 (m, 1 H), 7.4 (s, 5 H). ^{13}C NMR (68 MHz, CDCl_3) δ , 19.6, 26.0, 28.0, 33.0, 40.1, 44.5, 51.5, 52.3, 53.4, 53.6, 66.9, 81.6, 127.8, 128.0, 128.4, 136.1, 155.8, 171.2, 172.8. IR (neat) 3390, 1730 cm^{-1} . $[\alpha]_{\text{D}} = -10$ ($c = 1$, CH_3OH). MS (ESI) $M + H = 437$, $M - H = 435$, $2M + H = 973$. Anal. calcd for $\text{C}_{23}\text{H}_{36}\text{N}_2\text{O}_6$: C, 63.28; H, 8.31; N, 6.42; Found: C, 63.23; H, 8.49; N, 6.66.

*N*⁶-[2-(1,1-Dimethylethoxy)-2-oxoethyl]-6,6-dimethyl-*N*²-[(phenylmethoxy)-carbonyl]-*L*-lysine, monohydrochloride (HCl salt of **5b**).

A solution of LiOH monohydrate (5.3 g, 136 mmol) in H_2O (160 mL) was added to a solution of aminodiester **5a** (53.9 g, 124 mmol) in THF (780 mL) and water (100 mL) stirring at 0 °C under nitrogen gas atmosphere. After 3.5 h, 1N HCl (20 mL) was added to adjust the pH to 10.4. The mixture was concentrated under vacuum to a cloudy aqueous solution. It was treated with 1N HCl (180 mL) to bring the pH to 2.6. Solid NaCl (80 g) was added to this solution. The resulting milky aqueous solution was extracted with CH_2Cl_2 (3 x 350 mL). The organic solution was dried over MgSO_4 , filtered and evaporated under vacuum to furnish 57.1 g (yield 93.4%) of the hydrochloride salt of **5b**. ^1H NMR (270 MHz, CDCl_3) δ , 1.4 (s, 6 H), 1.5 (m, 2 H), 1.6 (s, 9 H), 1.9 (br s, 4 H), 3.8 (br s, 2 H), 4.4 (m, 1 H), 5.2 (s, 2H), 6.2 – 6.23 (d, 1 H, $J = 9.6$ Hz), 7.4 (br s, 5 H), 9.7 (br s, 1 H). ^{13}C NMR (68 MHz, CDCl_3) δ , 19.0, 22.8, 23.0, 27.8, 32.6, 38.3, 53.4, 54.0, 60.5, 66.5, 84.4, 127.8, 127.9, 128.3, 136.7, 156.0, 165.9, 175.5. $[\alpha]_{\text{D}} = -7.0$ ($c = 1.0$, CH_3OH).

(*S*)-Hexahydro-2,2-dimethyl-7-oxo-6-[[[(phenylmethoxy)carbonylamino] - 1*H*-azepine-1-acetic acid, 1,1-dimethylethyl ester (**6a**).

1-Hydroxybenzotriazole monohydrate (HOBT, 19.9 g, 130 mmol) was added to a solution of aminoacid hydrochloride **5b** (51.8 g, 113 mmol) in CH₃CN (1.05 l) at 20 °C under a nitrogen atmosphere. Diisopropylethyl amine (21.6 mL, 124 mmol) was added dropwise and then 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 26.0 g, 136 mmol) was introduced. After 2 h HPLC¹⁰ analysis indicated the completion of the reaction. The orange red solution was concentrated at 35 °C. The residue was taken up in EtOAc (700 mL) and washed with HCl (1N, 300 mL), aqueous NaHCO₃ (2 x 300 mL) and brine (200 mL). The solution was dried over MgSO₄, filtered and concentrated in vacuum. The dark red oil was dissolved in a mixture (1:8) of EtOAc and hexane (500 mL) and filtered through a pad of silica gel (150 g). The product was eluted with mixture (1:8) of EtOAc and hexane (5 x 500 mL). The first four fractions were combined and solvent was removed under vacuum to obtain 42.0 g of product **6a** (yield 92%). ¹H NMR (270 MHz, CDCl₃) δ, 1.3 (s, 3 H), 1.4 (s, 3 H), 1.5 (s, 9 H), 1.5 – 1.7 (m, 1 H), 1.8 – 2.0 (m, 4 H), 2.1 – 2.2 (m, 1 H), 3.8 – 4.3 (AB q, 2 H, J = 18 Hz), 4.6 - 4.8 (m, 1 H), 5.1 (s, 2 H), 6.2 (m, 1 H), 7.4 (br s, 5 H). ¹³C NMR (68 MHz, CDCl₃) δ, 20.1, 27.9, 28.0, 30.4, 30.5, 30.7, 30.8, 40.0, 47.5, 53.2, 55.8, 58.8, 60.4, 66.5, 81.4, 127.9, 128.4, 136.7, 155.5, 169.2, 172.6, . IR (KBr) 3405, 3335, 1724, 1740 cm⁻¹. Anal. calcd for C₂₂H₃₂N₂O₅: C, 65.32; H, 7.97; N, 6.93; Found: C, 65.12; H, 8.02; N, 6.79. [α]_D = -16.0 (c = 1.0, CH₃OH).

(*S*)-6-Aminohexahydro-2,2-dimethyl-7-oxo-1*H*-azepine-1-acetic acid, 1,1-dimethylethyl ester (**6b**).

Pd(OH)₂ (0.395 g) was added to a solution of **6a** (3.95 g, 9.7 mmol) in 50 mL MeOH. The reaction mixture was stirred under hydrogen atmosphere from a balloon. The hydrogenolysis was complete after 4 h (TLC: Silica gel, EtOAc, R_f of **6b** = 0.1 and **6a** = 0.8).¹¹ The catalyst was filtered through a Celite pad and the

¹⁰ HPLC method same as in footnote 1: R_t product **6a** 26.3 min., **5b** 14.1 min and HOBT 5.0 min.

¹¹ HPLC method same as in footnote 1: R_t of **6b** = 10.7 min.

filtrate was evaporated. The residue was taken up in EtOAc and evaporated to remove residual MeOH. The crystalline product was dried under vacuum to give 2.59 g (yield 97.9%) of **6b**, mp 73-75 °C (recrystallized from EtOAc/hexane; m.p. 84-85 °C). HPLC¹¹ AP (205 nm) 98.0, chiral HPLC¹² ee (210 nm) 95.5. ¹H NMR (270 MHz, CDCl₃) δ, 1.3 (s, 3 H), 1.4 (s, 3 H), 1.5 (s, 9 H), 1.5 – 1.7 (m, 1 H), 1.8 – 1.95 (m, 5 H), 2.3 (br s, 2 H), 3.7 – 3.8 (dd, 1 H, J = 4 Hz, 13 Hz), 3.9 – 4.3 (AB q, 2 H, J = 17 Hz). ¹³C NMR (68 MHz, CDCl₃) δ, 20.0, 27.8, 28.0, 30.0, 32.2, 40.0, 53.4, 57.1, 58.2, 80.9, 169.4, 176.6. IR (KBr) 3500, 1742, 1620 cm⁻¹. mp 73 – 75 °C. MS (ESI) M + H = 271, 2 M + H = 541. Anal. calcd for C₁₄H₂₆N₂O₃: C, 61.61; H, 9.71; N, 10.27; H₂O 0.92; Found: C, 61.28; H, 9.68; N, 10.09; H₂O 0.71 (K.F.). [α]_D = + 7.3 (c = 1.0, EtOAc).

(S)-6-Aminohexahydro-2,2-dimethyl-7-oxo-1*H*-azepine-1-acetic acid, 1,1-dimethylethyl ester, methanesulfonate (1:1) (**6c**).

A solution of methanesulfonic acid in EtOAc (1.0 M, 2.05 mL, 2.05 mmol) was added to a solution of **6b** (0.541 g, 2.0 mmol, ee 95.5%) in 4 mL of EtOAc at ambient temperature under an argon atmosphere. Seed crystals of the salt **6c** were added and the mixture was gently stirred magnetically in an ice-bath. Copious crystals were obtained within a few minutes. After 3 h the solid was filtered and the residue in the flask was transferred to the funnel with a portion of the first filtrate. The product was washed with 2 ml of ice-cold EtOAc and dried under vacuum for 1.5 h to give salt **6c** (0.556 g, 75.9% yield) as birefringent crystals, mp 151 °C (dec.), chiral HPLC ee (210 nm, 99.5%.¹² ¹H NMR (270 MHz, CDCl₃) δ, 1.3 (s, 3 H), 1.4 (s, 3 H), 1.5 (s, 9 H), 1.5 – 1.7 (m, 1 H), 1.8 – 1.95 (m, 5 H), 2.3 (br s, 2 H), 3.7 – 3.8 (dd, 1 H, J = 4 Hz, 13 Hz), 3.9 – 4.3 (AB q, 2 H, J = 17 Hz). ¹³C NMR (68 MHz, CDCl₃) δ, 20.0, 27.8, 28.0, 30.0, 32.2, 40.0, 53.4, 57.1, 58.2, 80.9, 169.4, 176.6. IR (KBr) 3500, 1742, 1620 cm⁻¹. mp 73 – 75 °C. MS (ESI) M

¹² Chiral HPLC for azepinone **6b**. Chiral column Crownpak CR+, 4.0 x 150 mm, 5 μm, mobile phase 85:15 aqueous HClO₄ (pH 1.5)/MeOH, flow rate 1.0 ml/min., UV wavelength 210 nm.

+ H = 271, 2 M + H = 541. Anal. calcd for C₁₄H₂₆N₂O₃: C, 61.61; H, 9.71; N, 10.27; H₂O 0.92; Found: C, 61.28; H, 9.68; N, 10.09; H₂O 0.71 (K.F.). [α]_D = + 7.3 (c = 1.0, EtOAc).

This salt was converted back to the free base **6b** in nearly quantitative yield by neutralization of its aqueous solution with NaOH, extraction with CH₂Cl₂, drying (MgSO₄) and evaporation of the solvent.

Part II: Synthesis of (S)- α -aminoazepinone **6b** via dynamic resolution of racemic α -aminoazepinone **15b**.

N-(1,1-Dimethyl-2-propynyl)glycine, 1,1-dimethylethyl ester (**8**).

t-Butylbromoacetate (98%, 37.1 g, 186.5 mmol) was added to a solution of wet 1,1-dimethylpropargyl amine (90%, 43.0 g, 466 mmol) in THF (100 mL) and the mixture was stirred at 20 °C. The reaction was complete after 20 h (TLC: Silica gel, EtOAc/hexane 1:4, R_f of **8** 0.4 and t-butylbromoacetate 0.6, visualized by UV and p-anisaldehyde/heat). Solvent was evaporated on a rotary evaporator and the resulting mixture of white solid (HBr salt of 1,1-dimethylpropargyl amine) and oil was treated with hexane (50 mL) and filtered. The filter cake was washed with hexane (150 mL) and the filtrate was extracted with 10% KHSO₄ (150 mL). The pH of aqueous layer was 3.5. The organic layer was extracted further with 10% KHSO₄ (3 x 60 mL) until the pH of the aqueous layer was below 1.5. The aqueous extracts were combined and washed with hexane (2 x 50 mL). Methyl-t-butyl ether (MTBE, 100 mL) was added the aqueous layer stirred at 20 °C and conc. NH₄OH (19 mL) was added dropwise to pH 10.5. The aqueous layer was separated and extracted with MTBE (3 x 50 mL). The organic extracts were

combined and washed with brine (20 mL) and dried by stirring over MgSO_4 for 0.5 h. The mixture was filtered and the solvent was evaporated under vacuum. The oily product was dried under pump vacuum to give 34.75 g (yield 94.6%) of ester **8**. ^1H NMR (270 MHz, CDCl_3) δ , 1.39 (s, 6H), 1.48 (s, 9H), 1.78 (br s, 1H), 2.28 (s, 1H), 3.42 (s, 2H); ^{13}C NMR (CDCl_3 , 68 MHz) δ , 28.6, 29.9, 47.4, 49.8, 70.8, 81.7, 172.0; IR (CH_2Cl_2 film) 3302, 1736 cm^{-1} ; MS (ESI) $M + H = 198$; Anal. calcd for $\text{C}_{11}\text{H}_{19}\text{N}_1\text{O}_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.68; H, 9.67; N, 7.07.

(Z)-3-Bromo-2-[[*(1,1*-dimethylethoxy)carbonyl]amino]-2-propenoic acid, methyl ester (**11**).

A dry, 1-l flask equipped with a magnetic stir bar and an argon inlet was charged with N-BOC-L-serine methyl ester **9** (50.0 g, 227 mmol) and anhydrous CH_2Cl_2 (500 mL). The mixture was stirred until homogeneous. The solution was cooled to 0°C , and methanesulfonyl chloride (18 mL, 232 mmol) was added over 2-3 min. Triethylamine (95 mL, 681 mmol) was added slowly over 30 min such that the internal temperature never exceeded 6°C . The mixture was stirred at 0°C for 30 min and then was allowed to warm to room temperature over 1 h. After stirring for 30 min. the reaction was complete by TLC (silica gel, 1:1 hexane:EtOAc; **9** $R_f = 0.28$, **10** $R_f = 0.74$; R_f of intermediate mesylate = 0.36; KMnO_4 for visualization). The mixture was washed with 0.5M KHSO_4 (200 ml diluted with 75 ml H_2O and 2 x 200 ml without dilution), sat. NaHCO_3 , (200 mL), and brine (200 mL). The organic layer was dried (MgSO_4) and concentrated under vacuum to approximately 250 mL. The orange solution was diluted with anhydrous

CH₂Cl₂ to 500 mL and charged into a dry flask equipped with a magnetic stir bar and an argon inlet. N-Bromosuccinimide (38.4 g, 216 mmol) was added and the mixture was stirred for 1 h at room temperature. The mixture was cooled to 0 °C and triethylamine (16 mL, 114 mmol) was added slowly over 10 min such that the internal temperature remained below 6 °C. Stirring was continued for 1 h. The mixture was concentrated in vacuum to an oil/solid mixture, which was concentrated from MTBE (2 x 100 mL) to remove CH₂Cl₂. The residue was dissolved in MTBE (500 mL) and washed successively with 0.5M KHSO₄ (2 x 100 mL), half-saturated NaHCO₃ (2 x 100 mL) and brine (100 mL). The solution was dried with MgSO₄, filtered and concentrated under vacuum such that about 30 mL MTBE still remained in the product. The solution was stirred mechanically and cooled to 0 °C. Hexane was added slowly to cloudiness and then seed crystals of **11** were added; the product began to crystallize. The remaining hexane (900 mL total) was added slowly over 20 min. The suspension was cooled slowly over 1 h to –20 °C and then placed in a –20 °C freezer for 5 h. The mixture was filtered cold, and the solids were washed with 3% MTBE/hexane (2 x 40 mL) and air-dried for 30 min to provide **11** (47.5 g, 75% yield; mp 59 °C) as a white solid. The mother liquor was concentrated to an oil which was crystallized from 6 mL MTBE and 180 mL hexane as above to provide a second crop of **11** (3.8 g, 6% yield; total yield 81%). ¹H NMR (270 MHz, CDCl₃) δ, 1.48 (s, 9H), 3.82 (s, 3H), 6.22 (br s, 1H), 6.88 (s, 1H); ¹³C NMR (68 MHz, CDCl₃) δ, 28.2, 53.0, 81.9, 109.3, 132.4, 151.8, 163.0; IR (KBr) 3232, 1739, 1715 cm⁻¹; MS (ESI) M + H = 280, M – H = 278; mp 59 °C; Anal. calcd for C₉H₁₄NO₄Br: C, 38.53; H, 5.05; N, 5.00; Br 28.53. Found: C, 38.46, H, 5.09; N, 4.87; Br, 28.86.¹³

¹³ (a). Miossec; R. Danion-Bougot; D. Danion, *Synthesis*, **1994**, 1171. (b). Yamada, M.; Nakao, K.; Fukui, T.; Nunami, K. *Tetrahedron*, **1996**, 52, 5751.

(Z)-6-[[[(1,1-Dimethylethoxy)acetyl]amino]-2-[[[(1,1-dimethylethoxy)-carbonyl]amino]-6-methyl-2-hepten-4-ynoic acid, methyl ester, methanesulfonic acid salt (**12a**).

Triethylamine (600 mL) and ester **8** (74 g, 375 mmol) were added consecutively to bromide **11** (100 g, 357 mmol) at 15 °C. The contents were stirred to homogeneity and then Pd(Ph₃P)₄ (1 g, 0.9 mmol) and CuI (1.44 g, 7.6 mmol) were added.^{13a} In 10 min, the reaction temperature rose slowly to 22 °C. The mixture was cooled to 15 °C. After 2 h additional Pd(Ph₃P)₄ (1 g, 0.9 mmol) was added, and the reaction mixture was stirred for 1 h. After 8.5 h the mixture was diluted with MTBE (600 mL) and stirred for 30 min. The mixture was filtered through a medium-frit funnel, and the solids were washed with MTBE (3 x 100 mL). The filtrate was concentrated in vacuum to an oil. The oil was dissolved in MTBE (700 mL), and the solution was extracted with 1M aqueous KHSO₄ (4 x 200 mL; 2 x 100 mL) while performing TLC analyses (40% EtOAc/hexane; silica gel plate) of the MTBE layer after each extraction to ensure adequate extraction of **12** (R_f = 0.28). The aqueous extracts were combined and cooled to 10 °C. The pH was adjusted to 8 with 50% aqueous NaOH (50 mL) while maintaining the internal temperature at <25 °C. The resulting aqueous/oily mixture was diluted with saturated aqueous NaCl (200 mL) and then extracted with EtOAc (3 x 400 mL). The combined EtOAc layers were treated with MgSO₄ and decolorizing carbon (Norit A; 21 g) and stirred for 30 min. The mixture was filtered through Celite, and the solids were washed with EtOAc (2 x 250 mL). The filtrate was concentrated in vacuum to give the enyne ester **12** as an oil. The oil was dissolved in IPA (250 mL) and

concentrated in vacuum to an oil (167 g). The oil was dissolved in isopropyl alcohol (IPA, 2.1 L) by warming and then the solution was cooled to 20 °C. With stirring, methanesulfonic acid (12.3 mL, 190 mmol) was added slowly over 15 min. Seed crystals of **12a** were added, and the mixture was stirred for 5 min; the product crystallized. Additional methanesulfonic acid (10.0 mL, 154 mmol) was added over approximately 5 min. After 5 h the mixture was filtered and the solid was washed with IPA (2 x 250 mL) and air-dried overnight to give 140 g of **12a** (yield 79%) as off-white crystals, mp 156-58 °C dec, HPLC AP 100.¹⁴ The combined filtrates were concentrated to 450 g of a solid/liquid mixture. The mixture was heated to 60 °C with stirring to dissolve all solids and the heating bath was removed. Seeds of **12a** were added at 50 °C and the mixture allowed to cool and stir overnight. The resulting slurry was filtered and the solid was washed with 50:50 IPA/MTBE (2 x 125 mL) and air-dried for 2.5 h to yield a second crop of **12a** (15.2 g, yield 9%; HPLC AP 100; combined yield 88%) as white crystals. ¹H NMR (270 MHz, CD₃OD) δ, 1.48 (s, 9H), 1.53 (s, 9H), 1.71 (s, 6H), 2.68 (s, 3H), 3.79 (s, 3H), 4.06 (s, 2H), 6.12 (s, 1H); ¹³C NMR (68 MHz, CD₃OD) δ, 26.2, 28.3, 28.5, 39.3, 45.4, 53.0, 55.9, 81.5, 82.7, 85.1, 96.7, 105.5, 137.9, 152.8, 165.5, 166.9; IR (KBr) 3236, 1740, 1615 cm⁻¹; MS (ESI) M + H = 397, M – H = 395; mp 156-58 °C (dec., effervescence); Anal. Calcd for C₂₀H₃₂N₂O₆•1.0 CH₃SO₃H: C, 51.21; H, 7.37; N, 5.69; S, 6.51. Found: C, 51.11; H, 7.21; N, 5.56; S, 6.59.

¹⁴ HPLC method same as in footnote 1 at wavelength 220 nm. R_t **11** 18.2 min and **12** 15.1 min.

*1,7-Diaza-6,6-dimethyl-1,2,8-octanetricarboxylic acid, 2-methyl-1,8-bis(1,1-dimethylethyl) ester, methanesulfonic acid salt (**13c**).*

Rh-C (5%, 13.5 g) was added to a solution of **12a** (135.2 g, 276.5 mmol) in MeOH (1350 mL) at 0 °C. The vessel was purged with H₂ and the mixture was then stirred vigorously under 1 atmosphere of H₂ gas. After 7 h, the reaction was allowed to warm to room temperature over 30 min. The reaction was filtered through Celite, and the Celite was washed with MeOH (3 x 200 mL). The combined filtrate was concentrated to an oil, which was dissolved in IPA (200 mL) and evaporated again to give a solid (136.86 g). The solid was redissolved in IPA (400 mL) with stirring at 50 °C to give a hazy solution that was allowed to cool to 20 °C, and then MTBE (500 mL) was added. Seed crystals of **13a** were added, and the product began to crystallize. Additional MTBE (600 mL) was added slowly over 20 min and the slurry was stirred for 4 h. The slurry was filtered, and the product was washed with MTBE (200 mL) and air-dried overnight to provide **13a** [118.2 g, yield 86%; AP (210 nm) 100]¹⁵ as a white solid. The mother liquor was concentrated and the solid was recrystallized with the same procedure as above using IPA (56 mL) and MTBE (150 mL) to provide a second crop of **13a** (9.9 g, yield 7%; AP 100, total yield 93%). ¹H NMR (270 MHz, CD₃OD) δ, 1.33 (s, 6H), 1.43 (s, 9H), 1.52 (s, 9H), 1.4 – 1.85 (m, 6H), 2.69 (s, 3H), 3.7 (s, 3H), 3.87 (s, 2H), 4.12 (m, 1H); ¹³C NMR (68 MHz, CD₃OD) δ, 21.1, 23.2, 28.2, 28.6, 32.6, 38.4, 39.5, 43.3, 52.6, 54.5, 61.1, 80.6, 85.1, 158.1, 167.2, 174.6; IR (KBr) 3386, 1750, 1724, 1709 cm⁻¹; MS (ESI) M + H = 403, M – H =

¹⁵ HPLC method same as in footnote 1: R_f of **12** 15.4 min, **13** 14.3 min.

401; mp 153 °C; Anal. Calcd for C₂₁H₄₂N₂O₉S: C, 50.58; H, 8.49; N, 5.62; S, 6.43. Found: C, 50.59; H, 8.55; N, 5.56; S, 6.47; HPLC AP (205 nm) ~100.

Hexahydro-2,2-dimethyl-6-[[[(1,1-dimethylethoxy)carbonyl]amino]-7-oxo-1H-azepine-1-acetic acid, 1,1-dimethylethyl ester (15a).

A mixture of **13c** (126.7 g, 254.0 mmol), THF (1270 mL) and H₂O (120 mL) was cooled to 0 °C. A solution of LiOH•H₂O (22.4 g, 533.5 mmol) in H₂O (280 mL) was added slowly over 30 min such that the internal temperature of the stirring mixture never exceeded 2.5 °C. The container of LiOH solution was rinsed with H₂O (20 mL), and the rinse was added slowly to the reaction mixture.¹⁶ After 5 h the pH of the reaction was adjusted to 8.7 with 1M HCl (100 mL). THF was removed under vacuum, and the aqueous solution was washed with MTBE [(2 x 200 mL); 3.47 g of the starting material **13c** was recovered from these washings]. The pH of the aqueous layer was adjusted to 5 with 1M HCl (180 mL). CH₂Cl₂ (860 mL) was added, and the aqueous layer was saturated with solid NaCl. The pH of the mixture was further adjusted to 3 with 1M HCl (170 mL), and the aqueous layer was further saturated with solid NaCl. The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 200 mL). The combined CH₂Cl₂ layers were dried (MgSO₄) and concentrated such that 1 L CH₂Cl₂ remained. This solution of HCl salt **14** was charged into a 2-L flask equipped with a mechanical stirrer and an argon inlet. HOBt monohydrate (39.6 g, 292.7 mmol) was

¹⁶ HPLC method: Column: YMC S3 ODS 4.6 x 50; Solvent A: 100% 0.2% aqueous H₃PO₄. Solvent B: 90% CH₃CN in water. Gradient: 10% to 100% B in 10 min; flow rate 2.5 ml/min; wave length 205 nm. R_t of **13a** 4.3 min. and **14** 3.5 min.

introduced and then DIPEA (49 mL, 262.9 mmol) was added dropwise over 10 min. EDC (60.8 g, 317 mmol) was added and the mixture was stirred at room temperature for 2 h.¹⁷ The CH₂Cl₂ was removed in vacuum, and the residue was dissolved in EtOAc (200 mL) and concentrated. The material was taken up in a mixture of EtOAc (1200 mL), 1M HCl (800 mL), and H₂O (800 mL). The organic layer was washed with saturated NaHCO₃ (2 x 600 mL), brine (1 x 600 mL) and then dried (MgSO₄). The solution was filtered and evaporated in vacuum and the product was dried under high vacuum overnight to provide **15a** (69.06 g, 73% overall yield from **13c**, yield 76% based on recovered **13c**), HPLC AP (210 nm) 99.1. ¹H NMR (270 MHz, CDCl₃) δ, 1.38 (s, 3H), 1.42 (s, 9H), 1.48 (s, 12H), 1.5 – 2.18 (m, 6H), 3.85 – 4.30 (AB q, 2H, J = 18 Hz), 4.55 (m, 1H), 5.87 (d, 1H, J = 8 Hz); ¹³C NMR (68 MHz, CDCl₃) δ, 19.9, 27.7, 28.1, 30.4, 30.7, 39.7, 47.2, 52.4, 58.4, 78.8, 80.9, 154.7, 168.5, 172.1; IR (KBr) 3435, 3341, 1717, 1708, 1632 cm⁻¹; MS (ESI) M + H = 371, M – H = 369; mp 110 °C; Anal. Calcd for C₁₉H₃₄N₂O₅: C, 61.60; H, 9.25; N, 7.56. Found: C, 61.39, H, 9.42; N, 7.47.

6-Aminohexahydro-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid, 1,1-dimethylethyl ester (15b).

To a solution of ester **15a** (14.81 g, 40.0 mmol) in 100 mL MeOH was added dropwise MSA (5.58 mL, 58.08 mmol) and the mixture was stirred overnight. An aqueous solution of NaHCO₃ was added to the mixture and MeOH was evaporated under vacuum. The mixture was acidified with aqueous 10% KHSO₄ to pH 1.5 and washed with MTBE. The aqueous portion was saturated with NaCl and basified with aqueous NaOH to pH 10.7. The product was extracted three times

¹⁷ HPLC method same as in footnote 1: R_t of **14** 12.4 min and **15a** 24.4 min.

with CH₂Cl₂, dried (MgSO₄) and evaporated. The residue was dissolved in EtOAc and evaporated again and dried under vacuum to give 9.35 g (yield 84%) of racemic ester **15b**, HPLC AP (210 nm) 93.4. The ¹NMR of this compound was identical to that of the optically active compound **6b**.

(S)-6-Aminohexahydro-2,2-dimethyl-7-oxo-1*H*-azepine-1-acetic acid, 1,1-dimethylethyl ester (**6b**). (via dynamic resolution)

A 500-mL, three-necked, round-bottomed flask equipped with thermocouple, overhead stirrer, and nitrogen inlet was charged with (1*R*)-(-)-10-camphorsulfonic acid (19.56 g, 84.3 mmol, 0.9 equiv) and 2-hydroxy-5-nitrobenzaldehyde (0.783 g, 4.7 mmol, 0.05 equiv). A solution of compound **15b** (25.33 g, 93.7 mmol) in toluene (170 mL) was added resulting in a temperature rise to 50°. The mixture was stirred at 60° for ~48 h while monitoring the e.e. of the slurry.¹² The mixture was cooled slowly to room temperature and filtered. The product was washed with pre-chilled (15-25°) n-butyl acetate (3 x 75 mL) and dried under vacuum to afford 37.5 g (80.7%) of the (*R*)-CSA salt of **6b** with e.e. >99%.¹²

Aqueous NaOH (1*N*, 9.2 mL, 9.2 mmol) was added to a solution of this salt (4.38 g, 8.71 mmol) in CH₂Cl₂ (44 mL) containing H₂O (26 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 44 mL). The organic layers were combined, dried (MgSO₄) and evaporated under vacuum. The residue was dried under vacuum to give 2.59 g (yield quantitative) of the amino ester **6b**, HPLC AP (210 nm) 99.1. The product made by this dynamic resolution method

was identical to the compound **6b** prepared by the method described in part I above.

Part III. Conversion of (S)- α -aminoazepinone **6b** to BMS-189921

[S-(R,R*)]-6-[[2-(Acetylthio)-1-oxo-3-phenylpropyl]amino]hexahydro-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid, 1,1-dimethylethyl ester (**17**).*

A solution of (S)- α -aminoazepinone **6b** (0.781 g, 2.8 mmol,) in CH₂Cl₂ (11 ml) was cooled in an ice-bath and powdered acid **16** (0.641 g, 2.86 mmol) was added. A clear solution was obtained within several minutes. EDC (0.642 g, 3.351 mmol) was added and the mixture was stirred for 2.5 h.¹⁸ The solvent was evaporated and the residue was taken up in EtOAc (25 mL) and 1 N HCl (15 mL). The aqueous layer was separated and extracted with EtOAc (25 mL). The combined organic extracts were washed successively with 1 N HCl (2 x 15 mL), brine (15 mL), saturated aqueous NaHCO₃ (2 x 10 mL) and brine (10 mL). The solution was dried (Na₂SO₄) and evaporated to give 1.32 g (yield 93%) of **17** as a white foam. HPLC, AP (205 nm) 95.7; Diastereomeric purity (220 nm) 97.9%. Chiral HPLC ee = 97.8. ¹H NMR (270 MHz, CDCl₃) δ , 1.3 (s, 3 H), 1.4 (s, 3 H), 1.5 (s, 9 H), 1.4 (m, 1 H, masked), 1.8 – 2.0 (m, 4 H), 2.1 (m, 1 H), 2.3 (s, 3 H), 2.9 – 3.4 (m, 2 H), 3.9 – 4.3 (AB q, 2 H, J = 17.6 Hz), 4.3 (m, 1 H), 4.6 – 4.7 (m, 1 H), 7.2 – 7.3 (m, 5 H), 7.4 (d, 1 H, J = 5.9 Hz). ¹³C NMR (68 MHz, CDCl₃) δ , 20.1, 28.2, 28.4, 30.1, 30.8, 31.0, 37.3, 40.4, 47.8, 48.7, 52.6, 59.2, 81.7, 127.1, 128.7, 129.6, 138.0, 169.3, 169.6, 172.6, 194.7. IR (KBr) 3500, 3385, 1744, 1692, 1630 cm⁻¹. MS (ESI) M + H = 477, Anal. Calcd for C₂₅H₃₆N₂O₅S•0.4 H₂O: C, 62.06; H, 7.67; N, 5.79; S, 6.63; H₂O, 1.43; Found: C, 62.28; H, 7.63; N, 5.75; S, 6.44; H₂O, 1.49. [α]_D = - 48.9 (c = 1.0, EtOAc).

¹⁸ (a). HPLC method same as in footnote 1: R_t 27.2. (b). HPLC conditions for diastereomeric purity: Solvent A: 90% 0.2% aqueous H₃PO₄ and 10% MeOH. Solvent B: 90% MeOH and 10% MeOH. 72% B isocratic; flow rate 1.5 ml/min; wave length 220 nm.

[S-(R,R*)]-6-[[2-(Acetylthio)-1-oxo-3-phenylpropyl]amino]hexahydro-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (18).*

Trifluoroacetic acid (9.0 mL, 126.0 mmol) was added to a solution of diester **17** (3.75 g, 7.88 mmol) in CH₂Cl₂ (30 mL). After 5 h HPLC showed starting material **17** AP 0.3.¹⁹ Na₂HPO₄•H₂O (8.4 g, 59.1 mmol) dissolved in 50 mL H₂O was added to the reaction mixture chilled in an ice-bath. The pH of the mixture dropped to 1.4 (pH meter) and was adjusted to 2.9 with 10 N NaOH. The layers were separated and the organic layer was washed with a solution of NaH₂PO₄ (0.5 g) in 25 mL of H₂O after adjusting its pH to 2.9 with conc. HCl. The layers were separated and the aq. layers were backwashed with CH₂Cl₂ (5 mL). The combined organic layers were dried (Na₂SO₄), and evaporated. The residue was dissolved in CH₂Cl₂ (6 mL) and heptane (24 mL) was added slowly with stirring over 20 min. The resulting mass of crystals was stirred overnight, filtered, washed with CH₂Cl₂/heptane 1:9, and heptane, and dried under vacuum to give 3.08 g (93% yield) of the acid **18** as colorless crystals,¹⁹ mp 160-61 °C, HPLC AP (205 nm) 95.2; AP **17** 0.5; HPLC for the diastereomeric purity: AP (220 nm) 98.9. ¹H NMR (270 MHz, CDCl₃) δ, 1.35 (s, 3 H), 1.45 (s, 3 H), 1.4 (m, 1 H), 1.8 – 2.2 (m, 5 H), 2.9 – 3.4 (m, 2 H), 3.9 – 4.4 (AB q, 2 H, J = 17.6 Hz), 4.2 – 4.3 (m, 1 H), 4.7 – 4.8 (m, 1 H), 7.2 – 7.3 (m, 5 H), 7.35 (d, 1 H, J = 5.9 Hz). ¹³C NMR (68 MHz, CDCl₃) δ, 20.2, 27.9, 29.7, 30.4, 30.7, 36.8, 39.8, 46.8, 48.3, 52.2, 59.3, 126.8, 128.4, 129.3, 137.6, 169.3, 172.9, 174.9, 194.6. IR (KBr) 3315, 1755, 1702, 1622 cm⁻¹. MS (ESI) M + H = 421; Anal. calc for C₂₁H₂₈N₂O₅ S•0.1 H₂O: C, 59.72; H, 6.73; N, 6.63; S, 7.59, H₂O, 0.43; Found: C, 59.29, H, 6.61; N, 6.55; S, 7.56, H₂O, 0.1 (KF). [α]_D = - 46.6 (c = 0.7, CHCl₃).

¹⁹ Structure of the acid **18** was confirmed by single crystal x-ray analysis. Coordinates from the X-ray determinations have been deposited in the Cambridge Crystallographic Database and can be obtained upon request to the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

[S-(R,R*)]-Hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (BMS-189921).*

DL-dithiothreitol (0.049 g, 0.32 mmol) was added to a suspension of **18** (2.67 g, 6.35 mmol) in methanol (8.5 mL).²⁰ The suspension was sparged with argon for 15 min, cooled to 1°C, and kept under argon atmosphere. In an addition funnel 1N NaOH (25.4 mL, 25.4 mmol) was sparged with argon for 20 min and then added to the reaction mixture over 20 min such that the internal temperature did not exceed 5°C. After 30 min the ice bath was removed to allow the mixture to warm to room temperature over 1 h.²² A pH probe and a reflux condenser were attached to the reaction flask. The mixture was acidified with previously sparged 3N HCl solution to pH 6. The mixture was warmed to 40°C and seed crystals of BMS-189921 were added, and the mixture was further acidified with stirring to pH 2. At this point, the product crystallized. The resulting slurry was stirred at 40°C for 30 min and then allowed to cool to room temperature over 1 h. The product was filtered and washed with distilled water (~35 mL) until the water wash tested negative for chloride with AgNO₃ solution. The product was air-dried for 30 min and then washed with MTBE (2 x 5 mL) and hexane (2 x 5 mL), air-dried, and finally dried under high vacuum overnight to give BMS-189921 (2.21 g, 92% yield) as a white solid.²¹ ¹H NMR (270 MHz, CDCl₃) δ, 1.37 (s, 3 H), 1.4 (s, 3 H),

²⁰ (a). Robl, J. A.; Sulsky, R.; Sieber-McMaster, E.; Ryono, D. E.; Cimarusti, M. P.; Simpkins, L. M.; Karanewski, D. S.; Chao, S.; Asaad, M. M.; Seymour, A. A.; Fox, M.; Smith, P. L.; Trippodo, N. C. *J. Med. Chem.*, **1999**, 42, 305. (b). Kronenthal, D. R.; Deshpande, R. P. Patent US 644810, Sept. 3, 2002.

²¹ HPLC method same as in foot note 16: R_t **18** 6.2 min and BMS-189921 6.0 min. Reference samples of enantiomer **ii** and diastereomers **iii** and **iv** were prepared from the corresponding precursors by methods similar to the synthesis of BMS-189921.

1.5 (m, 1 H), 1.9 – 2.1 (m, 6 H), 3.0 – 3.3 (m, 2 H), 3.6 – 3.7); (m, 1 H), 4.0 – 4.3 (AB q, J = 18 Hz, 2 H), 4.76 – 4.8 (m, 1 H), 7.2 – 7.3 (m, 5 H), 7.78 (d, 1 H, J = 5.9 Hz). ^{13}C NMR (68 MHz, CDCl_3) δ , 20.3, 28.1, 29.8, 30.8, 39.9, 41.4, 44.8, 46.9, 52.3, 59.5, 127.1, 128.6, 129.6, 137.7, 171.4, 173.2, 174.3. IR (KBr) 3500, 1748, 1715, 1620 cm^{-1} . mp 174 $^{\circ}\text{C}$. MS (ESI) $M + H = 379$, $M - H = 377$. Anal. calc. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_4\text{S}$: C, 60.30; H, 6.92; N, 7.40; S, 8.47. Fd. C, 60.25; H, 6.96; N, 7.25; S, 8.61. $[\alpha]_{\text{D}} = -17.6$ ($c = 1.0$, CHCl_3), Chiral HPLC AP, ee ~99.0.

Part IV. Reference samples of the byproducts disulfide **19** and azalactone (i) (footnote 17) were prepared by the following procedures:

[R-(R,S*)]-Hexahydro-6-[(2-mercapto-1-oxo-3-phenylpropyl)-amino]-2,2-dimethyl-7-oxo-1H-azepine-1-acetic acid (**19**).*

A solution of NaHCO_3 (0.89 g, 10.57 mmol) in H_2O (65 mL) and THF (5 mL) was stirred at 20 $^{\circ}\text{C}$. BMS-189921 (1.00g, 2.64 mmol) was added, and the mixture was stirred for 15 min for complete dissolution. O_2 was bubbled through the solution for 30 min, and the solution was stirred under an O_2 atmosphere. When necessary, the pH was adjusted to 7.5 with 0.5N HCl. Oxygen was bubbled through the solution for an additional 4 h, and the solution was stirred under an O_2 atmosphere for an additional 18 h. The solution was acidified to pH 2.0 with 6.0N HCl and extracted with ethyl acetate (2 x 100 mL). The combined extracts were washed once with sat. aq. NaCl (50 mL), dried with MgSO_4 , filtered, and concentrated in vacuum to give a solid. The solid was evaporated twice from

hexane and dried under high vacuum to give 1.00 g (100% yield) of disulfide **19** as a white solid. m.p. 110 °C, ¹H NMR (270 MHz, CDCl₃) δ, 1.35 (s, 6H), 1.4 (s, 6H), 1.7 - 2.1 (m, 12H), 2.9 - 3.05 (m, 2H), 3.1 - 3.25 (m, 2H), 3.78 (t, J = 7.5 Hz, 2H), 3.95 - 4.1 (ABq, J = 16.8 Hz, 4H), 4.7 - 4.9 (m, 2H), 7.1 - 7.3 (m, 10H), 7.6 (d, J = 7.5 Hz), 9.6 (bs, 2H) ; IR (KBr) 3490, 1738, 1626 cm⁻¹; MS (ESI): M - H = 1507.

TFA salt of azalactone (i) (footnote 17):

[S-(R,R*)]-[[4-[1-(Acetylthio)-2-phenylethyl-4,5-dihydro-5-oxo-4-oxazolyl]-1,1-dimethylbutyl]amino]acetic acid, trifluoroacetate (1:2).*

Compound **17** (3.23 g, 7.69 mmol) was dissolved in TFA (7 mL) and stirred at ambient temperature under an argon atmosphere. After 72 h the TFA was evaporated. The residue was dissolved in MTBE (4 mL), and hexane (30 mL) was added until no more precipitate was formed. The supernatant layer was decanted, and the residue, a colored oil, was washed with hexane (2 x 10 mL) and dried under vacuum to give 5.15 g (97.5% yield) of the TFA salt of (i) as a rose-colored oil. ¹H NMR (270 MHz, CDCl₃) δ, 1.55 (s, 6 H), 1.55 - 1.9 (m, 6 H), 2.35 (s, 3 H), 2.9 - 3.1 (m, 2 H), 3.2 - 3.35 (m, 2 H), 3.9 - 4.13 (d of ABq, 2 H, J = 3.7 and 16 Hz), 4.3-4.4 (t, 1 H, J = 3.5 Hz), 4.55 - 4.7 (m, 1 H), 7.04 (m, 1 H), 7.21 - 7.36 (m, 5 H), 11.0 (bs, 3 H); ¹³C NMR (68 MHz, CDCl₃) δ, 20.4, 26.2, 26.4, 32.8, 37.6, 40.6, 42.3, 49.2, 53.8, 89.7, 128.1, 129.5, 129.8, 130.0, 137.8, 172.7, 173.1, 173.2, 196.9. MS (ESI) M + H = 421, M + TFA + H = 535; M - H = 419, M + TFA - H = 533; [α]_D = -51.2 (c = 1.86, THF).