Exhibit 9 – Part 5 of 7

B. N-((2-Pyridinyl)methoxycarbonyl)-valine Lithium Salt.

Using the procedure of Example 160C with the resultant compound of Example 162A provided the desired compound.

C. 2-(N-((2-Pyridinyl)methoxycarbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 160C with the resultant compound of Example 162B provided, after silica gel chromatography using 2% methanol in chloroform, 119 mg (99%) of the desired compound28, 5% methanol in chloroform) as a white solid, m.p. 194-195° C. Mass spectrum: $(M + 1)^+$ = 738.
Anal. Calcd for $C_{42}H_{51}N_5O_7 \cdot 0.5H20$: C, 67.54; H, 7.02; N, 9.38. Found: C, 67.31; H, 7.00; N, 9.37.

Example 163

A. N-((3-Pyridinyl)carbonyl)-valine Benzyl Ester.

A solution of 2.44 g (6.44 mmol) of L-valine benzyl ester p-toluenesulfonate in 100 ml of dichloromethane was cooled under N_2 atmosphere to 0° C and treated sequentially with 1.15 g (6.44 mmol) of nicotinyl chloride hydrochloride and 2.8 ml (26 mmol) of 4- methylmorpholine. After being stirred at ambient temperature overnight, the resulting solution was diluted with 200 ml of diethyl ether, washed sequentially with water, aqueous $NaHCO_3$, and saturated brine, dried over Na_2SO_4, and concentrated in vacuo to give 2.09 g (95%) of the desired compound. ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 7 Hz, 3 H), 1.01 (d, J = 7 Hz, 3 H), 2.30 (m, 1 H), 4.83 (dd, J = 9, 5 Hz, 1 H), 5.20 (AA', 2 H), 6.67 (br d, 1 H), 7.37 (br s, 6 H), 8.11 (dd, J = 8, 2 Hz, 1 H), 8.74 (br, 1 H), 9.01 (s, 1 H).

B. N-((3-Pyridinyl)carbonyl)-valine.

A suspension of 0.16 g of 10% palladium on carbon in 20 ml of methanol was treated with a solution of 1.08 g (3.16 mmol) of the resultant compound of Example 163A in 10 ml of methanol. The resulting mixture was stirred vigorously under H_2 atmosphere for 4 h, filtered through Celite, and concentrated in vacuo to provide the desired compound as an off-white solid.

C. 2-(N-((3-Pyridinyl)carbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 160C with the resultant compound of Example 163B provided, after silica gel chromatography using 3% methanol in chloroform, 85 mg (72%) of the desired compound (R_f 0.21, 5% methanol in chloroform), m.p. 196-199° C. Mass spectrum: $(M + 1)^+$ = 708.
Anal. Calcd for $C_{41}H_{49}N_5O_6 \cdot 1.25H_2O$: C, 67.42; H, 7.11; N, 9.59. Found: C, 67.56; H, 6.91; N, 9.66.

Example 164

A. N-((4-Pyridinyl)carbonyl)-valine Benzyl Ester.

Using the procedure of Example 163A but replacing nicotinyl chloride hydrochloride with isonicotinyl chloride hydrochloride provided 2.32 g (97%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 3 H), 0.99 (d, J = 7 Hz, 3 H), 2.30 (m, 1 H), 4.82 (dd, J = 9, 5 Hz, 1 H), 5.22 (AA', 2 H), 6.75 (br d, 1 H), 7.38 (br s, 5 H), 7.63 (dd, J = 6, 2 Hz, 2 H), 8.76 (dd, J = 6, 2 Hz, 1 H).

B. N-((4-Pyridinyl)carbonyl)-valine.

Using the procedure of Example 163B with the resultant compound of Example 164A gave the desired compound.

C. 2-(N-((4-Pyridinyl)carbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 160C with the resultant compound of Example 164B provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound.

Example 165

A. N-((2-(4-Morpholinyl)ethyloxy)carbonyl)-valine Methyl Ester.

A solution of 1.04 g (6.60 mmol) of the resultant compound of Example 160A and 0.88 ml (7.25 mmol) of 4-(2-hydroxyethyl)morpholine in 30 mL of toluene was heated at reflux under N_2 atmosphere for 12 h. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography using 5% methanol in chloroform to give 1.41 g (71%) of the desired compound as an oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 2.16 (m, 1 H), 2.50 (br t, 4 H), 2.62 (t, J = 6 Hz, 2 H), 3.72 (t, J = 6 Hz, 4 H), 3.75 (s, 3 H), 4.20 (br t, 2 H), 4.37 (dd, J = 9, 5 Hz, 1 H), 5.25 (br d, 1 H).

B. N-((2-(4-Morpholinyl)ethyloxy)carbonyl)-valine Lithium Salt.

A solution of 77.7 mg (0.27 mmol) of the resultant compound of Example 165A in 1 ml of dioxane was treated with 1.04 ml (0.52 mmol) of 0.5 M aqueous lithium hydroxide. After being stirred for 2.5 h at ambient temperature, the resulting solution was treated with 0.26 ml (0.26 mmol) of 1 N aqueous HCl and concentrated in vacuo to provide the desired compound as a white solid.

C. 2-(N-((2-(4-Morpholinyl)ethyloxylcarbonyl)-valinyl-amino)-4-Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 160C with the resultant compound of Example 165B provided, after silica gel chromatography using 4% methanol in chloroform, 150 mg (94%) of the desired compound (R_f 0.34, 7.5% methanol in chloroform) as a white solid, m.p. 159-161 °C. Mass spectrum: $(M + 1)^+$ = 760.
Anal. Calcd for $C_{42}H_{57}N_5O_8 \cdot 0.75H20$: C, 65.22; H, 7.62; N, 9.05. Found: C, 65.19; H, 7.49; N, 9.08.

Example 166

A. N-((2-(1-Pyrrolidinyl)ethyloxy)carbonyl)-valine Methyl Ester.

Using the procedure of Example 165A but replacing 4-(2-hydroxyethyl)morpholine with 4-(2-hydroxyethyl)pyrrolidine provided, after silica gel chromatography using 6% methanol in chloroform, 1.14 g (80%) of the desired compound as an oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 1.80 (m, 4 H), 2.15 (m, 1 H), 2.57 (m, 4 H), 2.63 (t, J = 6 Hz, 2 H), 3.74 (s, 3 H), 4.20 (br t, 2 H), 4.28 (dd, J = 9, 5 Hz, 1 H), 5.30 (br d, 1 H).

B. N-((2-(1-Pyrrolidinyl)ethyloxy)carbonyl)-valine Lithium Salt.

Using the procedure of Example 165B with the resultant compound of Example 166A provided the desired compound as a white solid.

C. 2-(N-((2-(1-Pyrrolidinyl)ethyloxy)carbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 16°C with the resultant compound of Example 166B provided, after silica gel chromatography using 7.5% methanol in chloroform, 103 mg (63%) of the desired compound (R_f 0.13, 7.5% methanol in chloroform) as a white solid, m.p. 143-146° C. Mass spectrum: $(M + 1)^+$ = 744.
Anal. Calcd for $C_{42}H_{57}N_5O_7$: C, 67.81; H, 7.72; N, 8.89. Found: C, 68.20; H, 7.53; N, 8.89.

Example 167

A. N-((2-Furanyl)methoxycarbonyl)-valine Methyl Ester.

Using the procedure of Example 165A but replacing 4-(2-hydroxyethyl)morpholine with 2-furfuryl alcohol provided, after silica gel chromatography using 20% ethyl acetate in hexane, 0.91 g (70%) of the desired compound as an oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 2.15 (m, 1 H), 3.74 (s, 3 H), 4.29 (dd, J = 9, 5 Hz, 1 H), 5.07 (s, 2 H), 5.25 (br d, 1 H) 6.36 (m, 1 H), 6.42 (m, 1 H), 7.43 (m, 1 H).

B. N-((2-Furanyl)methoxycarbonyl)-valine.

Using the procedure of Example 165B with the resultant compound of Example 167A provided, after acidification and extraction into chloroform, the desired compound as a white solid.

C. 2-(N-((2-Furanyl)methoxycarbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 160C with the resultant compound of Example 167B provided the desired compound.

Example 168

A. N-(((1-Methyl)pyrrolidin-2-yl)methoxycarbonyl)-valine Methyl Ester.

Using the procedure of Example 165A but replacing 4-(2-hydroxyethyl)morpholine with 1-methyl-2-pyrrolidine-methanol provided, after silica gel chromatography using 5% methanol in chloroform, the desired compound as an oil. ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7 Hz, 3 H), 0.96 (d, J = 7 Hz, 3 H), 1.6-2.0 (m, 34 H), 2.15 (m, 1 H), 2.23 (td, J = 9, 8 Hz, 1 H), 2.40 (s, 3 H), 2.53 (m, 1 H), 3.03 (m, 1 H), 3.74 (s, 3 H), 4.00 (dd, J = 12, 6 Hz, 1 H), 4.17 (dd, J = 12, 5 Hz, 1 H), 4.28 (dd, J = 9, 5 Hz, 1 H), 5.27 (br d, 1 H).

B. N-(((1-Methyl)pyrrolidin-2-yl)methoxycarbonyl)-valine Lithium Salt.

Using the procedure of Example 165B with the resultant compound of Example 168A provided the desired compound as a white solid.

C. 2-(N-(((1-Methyl)pyrrolidin-2-yl)methoxycarbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 160C with the resultant compound of Example 168B provided, after silica gel chromatography using methanol in chloroform, the desired compound.

Example 169

A. N-(((1-Methyl)piperazin-4-yl)carbonyl)-valine Methyl Ester.

A solution of 0.86 g (5.47 mmol) of the resultant compound of Example 160A in 10 ml of dichloromethane was treated with 0.73 ml (6.6 mmol) of 1-methylpiperazine. The resulting solution was stirred at ambient temperature for 2.5 h, after which it was concentrated in vacuo. The residue was purified by silica gel chromatography using 5% methanol in chloroform to provide 1.40 g (100%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 0.91 (d, J = 7 Hz, 3 H), 0.95 (d, J = 7 Hz, 3 H), 2.13 (m, 1 H), 2.31 (s, 3 H), 2.41 (t, J = 5 Hz, 4 H), 3.43 (m, 4 H), 3.74 (s, 3 H), 4.46 (dd, J = 9, 5 Hz, 1 H), 4.93 (br d, 1 H).

B. N-(((1-Methyl)piperazin-4-yl)carbonyl)-valine Lithium Salt.

Using the procedure of Example 165B with the resultant compound of Example 169A provided the desired compound as a white solid.

C. 2-(N-(((1-Methyl)piperazin-4-yl)carbonyl)-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 160D but replacing the resultant compound of Example 160C with the resultant compound of Example 169B provided, after silica gel chromatography using 6% methanol in chloroform, 196 mg (98%) of the desired compound (R_f 0.15, 7.5% methanol in chloroform) as a white

solid, m.p. 175-176° C. Mass spectrum: $(M + 1)^+ = 729$.
Anal. Calcd for $C_{41}H_{56}N_6O_6 \cdot H_2O$: C, 65.93; H, 7.83; N, 11.25. Found: C, 65.58; H, 7.70; N, 11.14.

Example 170

A. N-((t-Butyloxy)carbonyl)-phenylalaninal.

A solution of 2.8 ml (40 mmol) of dry dimethylsulfoxide in 150 ml of dry dichloromethane was cooled under nitrogen atmosphere in a dry ice/chloroform bath (*ca.* -60° C). In a separate flask, a 2 M solution of 8oxalyl chloride in dichloromethane (15 ml, 30 mmol) was precooled to -60° C and then added via cannula. After 10 min, a solution of 5 g (20 mmol) of N-((t-butyloxy)carbonyl)-phenylalaninol in 30 ml of dry dichloromethane was added via cannula. The resulting solution was stirred at -60° C for 45 min, and was subsequently treated via syringe with 11 ml (80 mmol) of dry triethylamine. After being stirred for an additional 15 min at -60° C, the solution was quenched by addition of 10% aqueous citric acid, then immediately poured into a rapidly stirred mixture of 200 ml of 1:1 hexane:ether and 100 ml of 10% aqueous citric acid. The reaction flask was rinsed with ether which was added to the above mixture. The mixture was poured into a separatory funnel and the layers were separated. The aqueous layer was washed sequentially with dilute aqueous sodium bicarbonate and saturated brine, dried over $MgSO_4$, and concentrated in vacuo to provide the crude desired compound.

B. 2,5-Di-(N-((t-butyloxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

In a glove bag purged with argon, a 500 ml three-neck flask was charged with 27 g of $TiCl_3(DME)_2$ followed by 200 ml of anhydrous dimethoxyethane (DME). A separate flask was charged with 20 g of Zn-Cu couple and connected to one of the side necks of the three-neck flask with Gooch tubing. The flask was sealed with septa, removed from the glove bag, and outfitted under positive argon flow with an overhead mechanical stirrer. Under positive argon pressure, Zn-Cu was added in portions with vigorous stirring. After addition, the Gooch tubing was removed and replaced with a rubber septum. Stirring was continued while the flask was placed in an oil bath and heated to 85° C for 2.5 h. After being allowed to cool, the flask was placed in an ice bath while stirring was continued, and the mixture was treated via cannula with a solution of the resultant compound of Example 170A (20 mmol) in 20 ml of anhydrous dimethoxyethane. The progress of the reaction was monitered by tlc. After 1 h, the reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate. The filtrate was treated with saturated aqueous sodium bicarbonate, and air was bubbled through the suspension until it became white. The layers were separated, and the organic layer was washed with saturated brine, dried over $MgSO_4$, and concentrated to give 3.7 g of a light yellow solid. The solid was taken up in dichloromethane, treated with silica gel, and concentrated to a freely flowing powder. The powder was placed on the top of a silica gel column and eluted first with 70:30 hexane:ethyl acetate to bring off the more mobile product (R_f 0.26, 70:30 hexane:ethyl acetate) which contained two diastereomers (2S,3S,4S,5S and 2S,3R,4S,5S) followed by 60:40 hexane:ethyl acetate to bring off the less mobile product (R_f 0.10) which contained one major diastereomer (2S,3R,4R,5S).
(2S,3R,4R,5S)-2,5-Di-(N-((t-butyloxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane: m.p. 200-202° C. ^1H NMR δ 1.35 (s, 18 H), 2.87 (dd, J = 13, 7 Hz, 2 H), 2.98 (dd, J = 13, 7 Hz, 2 H),3.41 (m, 2 H), 3.76 (br q, J = 8 Hz, 2 H), 3.96 (m, 2 H), 4.77 (br d, J = 8 Hz, 2 H), 7.15-7.3 (m, 10 H). Mass spectrum: $(M + H)^+ = 501$.
Anal. Calcd for $C_{28}H_{40}N_2O_6 \cdot 0.5H_2O$: C, 65.99; H, 8.11; N, 5.50. Found: 65.96; H, 7.96; N, 5.49.

Example 171

(2S,3R,4R,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

(2S,3R,4R,5S)-2,5-Di-(N-((t-butyloxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane (2.7 g, 5.4 mmol) was treated with 200 ml of 6N aqueous hydrochloric acid and heated to 90° C until the solid had completely dissolved (30 min). The resulting solution was cooled, concentrated in vacuo, treated with saturated brine and 3N aqueous NaOH, extracted with chloroform, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography using 3% methanol/2% isopropylamine in chloroform provided the pure desired compound (R_f 0.40, 5% methanol/2% isopropylamine in chloroform) as a white solid, m.p. 86-89° C. ^1H NMR ($CDCl_3$) δ 2.72 (dd, J = 14, 9 Hz, 2 H), 2.92 (dd, J = 14, 6 Hz, 2 H), 3.03 (dd, J = 9, 5 Hz, 2 H), 3.69 (s, 2 H), 7.15-7.35 (m, 10 H). Mass spectrum: $(M + H)^+$ = 301.
Anal. Calcd for $C_{18}H_{24}N_2O_2 \cdot 0.25H_2O$: C, 70.91; H, 8.10; N, 9.19. Found: C, 70.52; H, 7.92; N, 8.93.

Example 172

A. N-((Cbz-valinyl)oxy)-succinimide

A suspension of 3.40 g (13.5 mmol) of Cbz-valine and 1.56 g (13.5 mmol) of N-hydroxysuccinimide in 200 ml of dichloromethane was treated with 2.86 g (14.9 mmol) of N-ethyl-N'-(dimethylaminopropyl) carbodiimide hydrochloride and stirred at ambient temperature for 4 h. The resulting solution was washed sequentially with 10% citric acid, aqueous $NaHCO_3$, and water; dried over Na_2SO_4, and concentrated in vacuo to provide 4.00 g (85%) of the desired compound.

B. (2S,3R,4R,5S)-2,5-Di-(N-(Cbz-valinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 28.7 mg (0.096 mmol) of the resultant compound of Example 171 in 1 ml of dioxane was treated with 139 mg (0.40 mmol) of the resultant compound of Example 172A and stirred at ambient temperature for 24 h. The resulting solution was treated with 0.5 ml of 3N NaOH, stirred for 15 min, extracted with two portions of 10% methanol in chloroform, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel using 3% methanol in chloroform to provide 42.4 mg (58%) of the desired compound (R_f 0.35, 5% methanol in chloroform) as a white solid, m.p. 231-232° C. Mass spectrum: $(M + H)^+$ = 767.
Anal. Calcd for $C_{44}H_{54}N_4O_8 \cdot 0.25H_2O$: C, 68.51; H, 7.12; N, 7.26. Found: C, 68.48; H, 7.11; N, 7.12.

Example 173

(2S,3R,4R,5S)-2,5-Di-(N-(valinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 71C with the resultant compound of Example 172B provided the desired compound (R_f 0.07, 10% methanol in chloroform) as a white solid, m.p. 205-207° C. Mass spectrum: $(M + H)^+$ = 499.
Anal. Calcd for $C_{28}H_{42}N_4O_4 \cdot 0.75H_2O$: C, 65.66; H, 8.56; N, 10.94. Found: C, 65.47; H, 7.93; N, 10.59.

Example 174

A. N-((4-Pyridinyl)methoxycarbonyl)-valine.

Using the procedure of Example 160C but adding twice the amount of 1M HCl provided the desired compound.

B. 2,4-Di-(N-((4-pyridinyl)methoxycarbonyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 174A (0.60 mmol) was coupled to the resultant compound of Example 12 (60 mg, 0.22 mmol) using the procedure of Example 55 except that the reaction was allowed to proceed for 2 days at ambient temperature. Silica gel chromatography using methanol/chloroform provided the desired compound (R_f 0.44, 10:1 chloroform:methanol) as a white solid, m.p. 158-159° C. Mass spectrum: $(M + H)^+ = 741$.
Anal. Calcd for $C_{41}H_{50}N_6O_7 \cdot 0.5H_2O$: C, 65.85; H, 6.87; N, 11.24. Found: C, 6.76; H, 65.67; N, 11.12.

Example 175

A. N-((3-Pyridinyl)methoxycarbonyl)-valine.

Using the procedure of Example 161B but adding twice the amount of 1M HCl provided the desired compound.

B. 2,4-Di-(N-((3-pyridinyl)methoxycarbonyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 174B but replacing the resultant compound of Example 174A (0.60 mmol) with the resultant compound of Example 175A gave, after silica gel chromatography using methanol/chloroform, the desired compound (R_f 0.53, 10:1 chloroform:methanol) as a white solid, m.p. 177-178° C. Mass spectrum: $(M + H)^+ = 741$.
Anal. Calcd for $C_{41}H_{50}N_6O_7 \cdot 0.5H_2O$: C, 65.85; H, 6.87; N, 11.24. Found: C, 66.09; H, 6.72; N, 11.24.

Example 176

A. N-((2-Pyridinyl)methoxycarbonyl)-valine.

Using the procedure of Example 162B but adding twice the amount of 1M HCl provided the desired compound.

B. 2,4-Di-(N-((2-pyridinyl)methoxycarbonyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 174B but replacing the resultant compound of Example 174A (0.60 mmol) with the resultant compound of Example 176A gave, after silica gel chromatography using methanol/chloroform, the desired compound as a white solid, m.p. 155-156° C. Mass spectrum: $(M + H)^+ = 741$.
Anal. Calcd for $C_{41}H_{50}N_6O_7 \cdot 0.5H_2O$: C, 65.85; H, 6.87; N, 11.24. Found: C, 65.89; H, 6.90; N, 11.24.

Example 177

2,4-Di-(N-(((3-pyridinyl)carbonyl)-valinyl)-amino)-1,5-diphenyl-3-hydroxypentane.

A solution of 15 mg (0.032 mmol) of the resultant compound of Example 140 and 0.01 ml (0.09 mmol) of 4-methylmorpholine in 2 ml of dichloromethane was cooled to 0 °C and treated with 12 mg (0.067 mmol) of nicotinyl chloride hydrochloride. The resulting solution was stirred at 0 °C for 1 h, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The residue was recrystallized from chloroform/ethyl acetate/hexane to afford the desired compound (R_f 0.40, 10% methanol in chloroform) as a white solid, m.p. 228-230. Mass spectrum: $(M + H)^+ = 679$.

Example 178

2,5-Di-(N-(((3-pyridinyl)carbonyl)-valinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 177 with the resultant compound of Example 173 provided the desired compound.

Example 179

2,5-Di-(N-((3-pyridinyl)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 177 but replacing the resultant compound of Example 140 with the resultant compound of Example 171 provided the desired compound.

Example 180

2,5-Di-(N-((4-pyridinyl)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 177 but replacing the resultant compound of Example 140 with the resultant compound of Example 171 and replacing nicotinyl chloride hydrochloride with isonicotinyl chloride hydrochloride provided the desired compound.

Example 181

A. Ethyl 4(S)-((t-Butyloxycarbonyl)amino)-5-cyclohexyl-2,2-difluoro-3(R,S)-hydroxypentanoate.

To a suspension of 1.2 g (17 mmol) of activated zinc in 5 ml of tetrahydrofuran under argon in a sonicating bath was added slowly a solution of 1.7 g (6.8 mmole) of Boc-L-cyclohexylalaninal and 2.34 ml

(18.4 mmole) of ethyl bromodifluoroacetate in 30 ml of tetrahydrofuran. After complete addition, the solution was sonicated for an additional 30 min. The mixture was then added to 1 M $KHSO_4$ and extracted with dichloromethane (3 x 100 ml), dried with Na_2SO_4, filtered and concentrated *in vacuo*. The residual oil was purified by silica gel column chromatography (15-30% ethyl acetate in hexane) to give 1.22 g (75%) of two diastereomers.

3(R) diastereomer: ^1H NMR ($CDCl_3$) δ 1.37 (t, 3H, J = 7.0 Hz), 1.46 (S, 9H), 4.35 (q, 2H, J = 7.0 Hz); m.p. 73-74.5° C.

Anal. ($C_{18}H_{31}NO_5F_2$) C,H,N.

3(S) diastereomer: ^1H NMR ($CDCl_3$) δ 1.37 (t, 3H, J = 7.5 Hz), 1.45 (S, 9H), 4.31 (q, 2H, J = 7.5 Hz); m.p. 115-117° C.

Anal. ($C_{18}H_{31}NO_5F_2$) C,H,N.

B. 2-Oxazolidinone derivative of Ethyl 4(S)-amino-5-cyclohexyl-2,2-difluoro-3(R)-hydroxypentanoate.

To 50 mg of the resultant 3(R) isomer of Example 181A was added 1 ml of 4 M HCl in dioxane. The solution was stirred at ambient temperature for 30 min. The concentrated residue was dissolved in dichloromethane and treated with 0.1 ml of triethylamine and excess phosgene in toluene (10% solution). After stirring at ambient temperature for 1 hr, the crude product was purified by silica gel column chromatography (10% ethyl acetate in hexane) to give 32 mg of desired compound. ^1H NMR ($CDCl_3$) d 1.38 (t, 3H, J = 7 Hz), 4.08 (m, 1H), 4.38 (q, 2H, J = 7 Hz), 4.58 (ddd, 1H, J = 4.5, 6.0, 15 Hz), 46.05 (br S, 1H). Anal. ($C_{14}H_{21}NO_4F_2$) C,H,N.

C. 4(S)-cyclohexylmethyl-5(R)-(4′(4′,4′-difluoro-3′-oxo-2′-methyl-butyl))-2-oxazolidinone.

The hydrolysis of 2.5 g of the resultant compound of Example 181B by lithium hydroxide in aqueous methanol provided 2.3 g of the corresponding carboxylic acid. The acid was dissolved in 40 ml of tetrahydrofuran and cooled to -78° C. To the vigorously stirred solution was added 18 ml of isopropyl lithium solution in pentane (12.4% by wt.). After 30 min, the solution was slowly warmed to 0° C and stirred for an additional 30 min. The reaction was carefully quenched with water and extracted with ethyl acetate (3 x 100 ml), dried and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (20% ethyl acetate in hexane) to give 1.36 g of desired product. ^1H NMR ($CDCl_3$) d 1.20 (t, 6H, J = 6.3 Hz), 3.17 (d of heptet, 1H, J = 1.8, 6.6 Hz), 4.06 (m, 1H), 4.62 (ddd, 1H, J = 4.5, 6.0, 20.4 Hz), 5.63 (br S, 1H). Anal. ($C_{14}H_{23}NO_3F_2$) C,H,N.

D. Oxime derivative of 4(S)-cyclohexylmethyl-5(R)-(4′(4′,4′-difluoro-3′oxo-2′-methyl-butyl))-2-oxazolidinone.

To a solution of 1.2 g of the resultant compound of Example 181C in 20 ml of ethanol was added 0.55 ml of pyridine and then 410 mg of hydroxyamine hydrochloride. The solution was heated to reflux for 5.5 hrs. The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography (10% EtOAc/CH_2Cl_2) to give 1.12 g of desired product. Mass spectrum: M^+ = 318.

E. 4(S)-Cyclohexylmethyl-5(R)-(4′(4′,4′-difluoro-3′-amino-2-methyl-butyl))-2-oxazolidinone.

To a solution of 1.1 g of the resultant compound of Example 181D in 40 ml of ethanol was added 0.5 g of activated Raney nickel. The reaction mixture was stirred vigorously under a hydrogen atmosphere for 2 h. The catalyst was filtered off and the filtrate concentrated to a oily residue. The crude product was purified by silica gel column chromatography (10% EtOAc/CH_2Cl_2) to give 550 mg of desired product. Mass spectrum: M^+ = 304.

F. 3,6-Diamino-7-cyclohexyl-5-hydroxy-4,4-difluoro-2-methylheptane.

To a solution of 150 mg of the resultant compound of Example 181E in 10 ml of dioxane and 10 ml of water was added 325 mg of barium hydroxide octahydrate. The reaction mixture was heated to reflux for 0.3 hrs. The suspension was cooled to ambient temperature and filtered and the solid was washed with ethyl acetate. The filtrate was washed with satd. brine and the aqueous phase was extracted with ethyl acetate (2 x 50 ml). The combined ethyl acetate solution was dried, filtered and concentrated to provide 130 mg of the desired product. Mass spectrum: $M^+ = 278$.

Example 182

3,6-Bis-(Cbz-valinyl-amino)-7-cyclohexyl-5-hydroxy-4,4-difluoro-2-methylheptane.

To a solution of 130 ml of the resultant compound of Example 181F in 10 ml of dimethylformamide was added at 0° C successively 230 mg of Cbz-valine, 220 mg of N-ethyl-N'-(dimethylaminopropyl) carbodiimide hydrochloride, 400 mg of 1-hydroxybenzotriazole and 0.16 ml of triethylamine. The solution was stirred at 0° C for 3 hrs and at ambient temperature for 12 hrs. The dimethylformamide was removed under vacuum and the residue was dissolved in 50 ml of ethyl acetate and washed with saturated. brine. The aqueous layer was extracted with ethyl acetate (2 x 50 ml) and dried, filtered and concentrated. The crude product was purified by silica gel column chromatography (2% MeOH/CH_2Cl_2) to give 220 mg of the desired compound (64%). Mass spectrum: $(M+H)^+ = 745$. ^1H NMR ($CDCl_3$) d 0.78-0.90 (m, 18H), 3.60 (m, 1H), 3.85 (m, 1H), 4.00 (m, 1H), 4.40 (m, 1H), 4.55 (m, 1H), 5.03 (S, 4H), 5.78 (d, 1H), 7.25-7.36 (m, 10H), 7.69 (d, 1H).

Example 183

3,6-Bis-(Cbz-valinyl-amino)-7-cyclohexyl-5-oxo-4,4-difluoro-2-methylheptane.

A solution of oxidant was prepared as follows: to 392 mg of sulfuric acid was added 5 ml of acetic acid and 298 mg of sodium dichromate. To a solution of 150 mg of the resultant compound of Example 182 in 10 ml of acetic acid was added 2 ml of the oxidant. After stirring at ambient temperature for 1 hr, the acetic acid was removed under vacuum and the residue was dissolved in 50 ml of ethyl acetate and washed with 30 ml of water. The aqueous layer was extracted with ethyl acetate (2 x 40 ml) and the combined ethyl acetate solution was dried, filtered and concentrated. The crude product was purified by silica gel column chromatography (10% EtOAc/CH_2Cl_2) to give 120 mg of the desired compound (80%). Mass spectrum: $(M+H)^+ = 743$. ^1H NMR ($CDCl_3$): d 0.85-0.98 (m, 18H), 3.90-4.02 (m, 2H), 460 (m, 1H), 5.35 (br d, 1H), 6.10 (br d, 1H), 6.20 (br d, 1H), 7.35 (m, 10H).

Example 184

3,6-Bis-(Cbz-0-methyl-serinyl-amino)-7-cyclohexyl-5-hydroxy-4,4-difluoro-2-methylheptane.

To a solution of 90 mg of the resultant compound of Example 181F in 7 ml of dimethylformamide was added at 0° C 164 mg of Cbz-0-methyl-serine, 160 mg of N-ethyl-N'-(dimethylaminopropyl) carbodiimide hydrochloride, 280 mg of 1-hydroxybenzotriazole and 0.11 ml of triethylamine. The solution was stirred at

0 °C for 3 hrs, then at ambient temperature for 19 hrs. The DMF was removed under vacuum and the residue was dissolved in 50 ml of ethyl acetate and washed with satd. $NaHCO_3$, then brine. The aqueous layer was extracted with EtOAc (2 x 50 ml) and dried, filtered and concentrated. The crude product was purified by silica gel column chromatography (82%) of the desired compound. Mass spectrum: $(M+H)^+ = 749$.

Example 185

3,6-Bis-(Cbz-0-methylserinyl-amino)-7-cyclohexyl-5-oxo-4,4-difluoro-2-methylheptane.

The resultant compound of Example 184 (60 mg) was oxidized using the procedure of Example 183 to give 40 mg of desired product. Mass spectrum: $(M+H) = 747$.

Example 186

3,6-Bis-(acetyl-0-methylserinyl-amino)-7-cyclohexyl-5-hydroxy-4,4-difluoro-2-methylheptane.

A solution was 50 mg of the resultant compound of Example 185 and 20 mg of 10% Pd/C was stirred vigorously under a hydrogen atmosphere. After 30 minutes, the catalyst was filtered off and the filtrate concentrated to give a colorless oil, which was dissolved in 2 ml of CH_2Cl_2. The solution was cooled to 0 °C, 0.03 ml of triethylamine and 0.01 ml of acetyl chloride were added. After 2 hrs, the solution was concentrated and the crude product purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to give 16 mg of the desired compound. Mass spectrum: $(M+H)^+ = 565$.

Example 187

Glycine Ester of 2,4-Bis-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane Acetate Salt.

Using the procedure of Example 95 with the resultant compound of Example 70 provided the desired compound.

Example 188

2,5-Di-(N-((t-butyloxy)carbonyl)amino)-3,4-dihydroxy-1,6-di-(4-thiazolyl)hexane.

Using the procedures of Example 170A and Example 170B but replacing N-((t-butyloxy)carbonyl)-phenylalaninol with N-((t-butyloxy)carbonyl)-(4-thiazolyl)-alaninol provided the desired compound.

Example 189

A. Benzyl 2-(1-morpholinyl)acetate.

A solution of 1.5 ml (17 mmol) of morpholine in 40 ml of dichloromethane was treated with 1 ml (6.3 mmol) of benzyl 2-bromoacetate. The resulting solution was stirred at ambient temperature for 16 h. The resulting solution was filtered and concentrated in vacuo. The residue was purified by silica gel chromatography using 3:1 chloroform:ethyl acetate to provide 1.35 g (91%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 2.59 (m, 4 H), 3.27 (s, 2 H), 3.77 (m, 4 H), 5.17 (s, 2 H), 7.3-7.4 (m, 5 H).

B. 2-(1-Morpholinyl)acetic Acid.

Using the procedure of Example 163B with the resultant compound of Example 189A provided the desired compound.

C. 2,5-Di-(N-((2-(1-morpholinyl)acetyl)-valinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 189B was coupled to the resultant compound of Example 173 using the coupling procedure of Example 55 provided, after silica gel chromatography using a gradient of 3-5% methanol in chloroform, the desired compound (R_f 0.31, 10% methanol in chloroform).

Example 190

A. Benzyl 2-(1-Imidazolyl)acetate.

A solution of 1.4 g (21 mmol) of imidazole and 1.0 ml (6.3 mmol) of benzyl 2-bromoacetate in 40 ml of dichloromethane was stirred at ambient temperature for 16 h. The resulting solution was washed with water, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromotography of the residue using 5% methanol in chloroform provided 1.22 g (89%) of the desired compound as an oil. ^{1}H NMR ($CDCl_3$) δ 4.73 (s, 2 H), 5.21 (s, 2 H), 6.96 (t, J = 1 Hz, 1 H), 7.11 (t, J = 1 Hz, 1 H), 7.36 (m, 5 H), 7.51 (br s, 1 H).

B. 2-(1-Imidazolyl)acetic Acid

The resultant compound of Example 190A was hydrogenolyzed according to the procedure of Example 163B except that water was added prior to filtration to solubilize the product. Removal of the solvent after filtration provided the desired compound.

C. 2,5-Di-(N-((2-(1-imidazolyl)acetyl)-valinyl-amino)-1,5-diphenyl-3,4-dihydroxypentane.

The resultant compound of Example 190B was coupled to the resultant compound of Example 173 using the carbodiimide coupling procedure described in Example 55 to give a crude mixture in which the product was soluble. The mixture was diluted with ethyl acetate, filtered, and the solid was washed sequentially with water and ethyl acetate. The residue was air-dried to provide the desired compound in 40% yield.

Example 191

A. 1-(2-Bromohexanoyl)-4-methylpiperazine.

Using the mixed anhydride procedure of Example 6F, 2-bromohexanoic acid was coupled to 1-methylpiperazine provide the desired compound.

B. 2,5-Di-(N-((2-(4-methylpiperazin-1-yl)carbonyl)pent-1-yl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 159A but replacing the resultant compound of Example 116A with the resultant compound of Example 191A and replacing O-benzylhydroxylamine hydrochloride with the resultant compound of Example 171 provided the desired compound.

Example 192

2,5-Di-(N-(2-methoxycarbonyl-3-phenylprop-1-yl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 159A but replacing O-benzylhydroxylamine hydrochloride with the resultant compound of Example 171 provided the desired compound.

Example 193

A. 4-(2-(Benzyloxycarbonyl)-3-methylprop-1-yl)-1,1-dioxo-1,4-thiazine.

According to the method of Kawaguchi, et. al. (*Agric. Biol. Chem.* 1987, *51*, 435), 3-sulfolene was ozonolyzed and aminated with L-valine benzyl ester p-toluenesulfonate to provide the desired compound.

B. 4-(2-Carboxy-3-methylprop-1-yl)-1,1-dioxo-1,4-thiazine.

The resultant compound of Example 193A was hydrogenolyzed according to the procedure of Example 163B to provide the desired compound.

C. 2,5-Di-(N-(2-(1,1-dioxothiazin-4-yl)-3-methylbutanoyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 193B was coupled to the resultant compound of Example 171 using the coupling procedure described in Example 160D to provide the desired compound.

Example 194

A. 4-(2-(Benzyloxycarbonyl)-3-methylprop-1-yl)morpholine.

According to the method of Kawaguchi, et. al. (*Agric. Biol. Chem.* **1987**, *51*, 435), 2,5-dihydrofuran was ozonolyzed and aminated with L-valine benzyl ester p-toluenesulfonate to provide the desired compound.

B. 4-(2-Carboxy-3-methylprop-1-yl)morpholine.

The resultant compound of Example 194A was hydrogenolyzed according to the procedure of Example 163B to provide the desired compound.

C. 2,5-Di-(N-(2-(morpholin-4-yl)-3-methylbutanoyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 194B was coupled to the resultant compound of Example 171 using the coupling procedure described in Example 160D to provide the desired compound.

Example 195

2,5-Di-(2-(1,1-dioxothiazin-4-yl)-3,4-dihydroxy-1,6-diphenylhexane.

According to the method of Kawaguchi, et. al. (*Agric. Biol. Chem.* **1987**, *51*, 435), 3-sulfolene was ozonolyzed and aminated with the resultant compound of Example 171 to provide the desired compound.

Example 196

A. N, N-Bis-(Cbz-valinyl)-(2S, 3R, 4R, 5S)-1,2:5,6-diimino-3,4-O-isopropylidenehexanediol

A solution of (2S,3R,4R,5S)-1,2:5,6-diimino-3,4-O-isopropylidenehexanediol (2.72 g, 12.7 mmol, Y.L. Merrer, et al, *Heterocycles*, 1987, *25*, 541-548)) and 3.51 g (14 mmol) of N-Cbz-valine in 30 mL of dry THF was cooled in an ice bath. To the cooled solution was added 2.684 g (14 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, followed by 1.95 mL (14 mmol) of triethylamine. The reaction mixture was stirred overnight in the ice bath. The reaction temperature was 10° C when the reaction mixture was diluted with ethyl acetate, washed with dilute aqueous sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a 5 X 30 cm silica gel column eluted with 50% ethyl acetate in hexane to give 1.20 g (26.3% yield) of the title compound; FAB MS M/Z: 651 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.96 (d, 6H), 1.03 (d, 6H), 1.33 (s, 6H), 2.15-2.28 (m, 2H), 2.48 (d, 2H), 2.58 (d, 2H), 2.74 (br s, 2H), 3.89 (br s, 2H), 4.27 (dd, 2H), 5.09 (s, 4H), 7.30-7.40 (m, 10H). Analysis calculated for $C_{35}H_{46}N_4O_8$: C, 64.62; H, 7.08; N, 8.62. Found: C, 64.35; H, 7.07; N, 8.41.

B. N, N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis(phenylthio)-2,5-diamino-3,4-O-isopropylidenehexanediol

To a slurry of 22.5 mg (0.564 mmol) of 60% sodium hydride in 1 mL of THF cooled in an ice bath, was added 87 µL (0.846 mmol) of thiophenol. The mixture was stirred for 0.5 h and then a solution of 92 mg

(0.141 mmol) of the resultant compound of Example 196A in 2.0 mL of DMF was added to the mixture at ambient temperature. The reaction mixture was stirred at ambient temperature overnight and then diluted with ethyl acetate and water. The aqueous mixture was extracted with ethyl acetate. The organic phase was concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.0 X 30 cm silica gel column eluted with 40% ethyl acetate in hexane to give 55 mg (45% yield) of the title compound; FAB MS M/Z: 871 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 6H), 0.96 (d, 6H), 1.32 (s, 6H), 2.10-2.21 (m, 2H), 2.88-2.98 (dd, 2H), 3.05-3.15 (dd, 2H), 3.95 (dd, 2H), 4.0 (br s, 2H), 4.11 (dd, 2H), 5.09 (s, 4H), 7.12-7.25 (m, 8H), 7.30-7.40 (m, 10H).

C. N,N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis(phenylthio)-2,5-diamino-3,4-hexanediol

A solution of the resultant compound of Example 196B (55 mg, 0.063 mmol) in 2.0 mL of trifluoroacetic acid containing 0.2 mL of water at 0° C was stirred for 4 h. The solvent was evaporated under reduced pressure and ethyl alcohol was added to the residue. The ethanol was removed under reduced pressure and the residue was purified by flash chromatography on a 1.0 X 35 cm silica gel column eluted with 40% methylene chloride in ethyl acetate to give 38 mg (73% yield)of the title compound; FAB MS M/Z: 831 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 0.89 (d, 6H), 0.97 (d, 6H), 2.10-2.20 (m, 2H), 3.08-3.20 (m, 2H), 3.66 (br s, 2H), 3.74 (br s, 2H), 3.92 (dd, 2H), 5.11 (s, 4H), 7.12-7.29 (m, 8H), 7.30-7.40 (m, 12H). Analysis calculated for $C_{44}H_{54}N_4O_8S_2$: C, 63.61; H, 6.50; N, 6.75. Found: C, 63.61; H, 6.57; N, 6.69.

Example 197

2,5-Di-(N-(Cbz-isoleucinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A mixture of 10 mg (0.033 mmol) of the resultant compound of Example 171 and 38.6 mg (0.10 mmol) of Cbz-isoleucine p-nitrophenyl ester in 0.2 ml of tetrahydrofuran was stirred at ambient temperature for 21 h. The resulting misture was diluted with 1 ml of tetrahydrofuran, treated with 0.5 ml of 3N NaOH, stirred for 45 min, extracted with chloroform, washed sequentially with 3N NaOH and saturated brine, dried over $MgSO_4$,and concentrated. The residue was purified on silica gel by eluting with 2% methanol in chloroform to provide 23 mg (86%) of the desired compound. Mass spectrum: $(M + H)^+ = 795$.

Example 198

2,5-Di-(N-(Cbz-alaninyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 197 but replacing Cbz-isoleucine p-nitrophenyl ester with Cbz-alaninyloxy-succinimide provided the desired compound. Mass spectrum: $(M + H)^+ = 711$.

Example 199

2,5-Di-(N-(Cbz-phenylalaninyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 197 but replacing Cbz-isoleucine p-nitrophenyl ester with Cbz-phenylalanine p-nitrophenyl ester provided the desired compound. Mass spectrum: $(M + H)^+ = 863$.

Example 200

2,5-Di-(N-(Cbz-leucinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 197 but replacing Cbz-isoleucine p-nitrophenyl ester with Cbz-leucine p-nitrophenyl ester provided the desired compound. Mass spectrum: $(M + H)^+ = 795$.

Example 201

A. N-((Benzyloxycarbonyl)methyl)-valine Methyl Ester.

A solution of 2.12 g (12.6 mmol) of L-valine methyl ester hydrochloride, 2.0 ml (12.6 mmol) of benzyl bromoacetate, and 3.5 ml (31 mmol) of 4-methylmorpholine in 100 ml of dioxane was heated at reflux for 4 h. After being allowed to cool, the solution was concentrated in vacuo and partitioned between ether and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Chromatography on silica gel using 20% ethyl acetate in hexane provided 0.77 g (22%) of the desired compound as a colorless oil (R_f 0.24, 20% ethyl acetate in hexane). ^1H NMR δ 0.95 (d, J = 7 Hz, 6 H), 1.96 (br, 1 H), 1.98 (octet, J = 7 Hz, 1 H), 3.08 (d, J = 6 Hz, 1 H), 3.43 (AA', 2 H), 3.71 (s, 3 H), 5.16 (s, 2 H), 7.36 (m, 5 H).

B. N-(Carboxymethyl)-valine Methyl Ester.

The resultant compound of Example 201A (0.7 g, 2.5 mmol) was hydrogenolyzed according to the procedure of Example to provide 0.49 g (100%) of the desired compound as a white solid.

C. N-((((4-Methyl)piperazinyl)carbonyl)methyl)-valine Methyl Ester.

Using the carbodiimide coupling procedure of Example , the resultant compound of Example 201B (466 mg, 2.46 mmol) was coupled to 1-methylmorpholine to provide, after chromatography on silica gel using 5% methanol in chloroform, 0.61 g (91%) of the desired compound as a colorless oil.

D. N-((((4-Methyl)piperazinyl)carbonyl)methyl)-valine.

A solution of 0.59 g (2.2 mmol) of the resultant compound of Example 201C in 16 ml of dioxane was treated with 8.7 ml (4.4 mmol) of 0.5M aqueous lithium hydroxide. The resulting solution was stirred at ambient temperature for 16 h, treated with 4.4 ml of 1M aqueous HCl, and concentrated in vacuo to provide the crude desired compound.

E. 1,5-Diphenyl-3-hydroxy-2-(N-(Cbz-valinyl)amino)-4-N-(N-((((4-methyl)piperazinyl)carbonyl)methyl)valinyl)amino-pentane.

The resultant compound of Example 201D (80 mg, 0.21 mmol) was coupled to the resultant compound of Example 69 (89 mg, 0.18 mmol) according to the procedure described in Example 55 to provide, after silica gel chromatography using 6% methanol in chloroform, the desired compound (R_f 0.16, 7.5% methanol

in chloroform) as a white solid, m.p. 74-76° C. Mass spectrum: $(M + H)^+$ = 743.
Anal. Calcd. for $C_{42}H_{58}N_6O_6 \cdot 0.5H_2O$: C, 67.09; H, 7.91; N, 11.18. Found: C, 67.16; H, 7.86; N, 10.87.

Example 202

A. Methyl 3-(4-Morpholinyl)propanoate.

A solution of 4.9 ml (56 mmol) of morpholine in 50 ml of dichloromethane was treated dropwise with 5.0 ml (56 mmol) of methyl acrylate. The resulting solution was allowed to stand at ambient temperature for 3 days, after which it was concentrated in vacuo to an oil. Chromatography on silica gel using 0.5% methanol/2% isopropylamine in chloroform provided 9.54 g (99%) of the desired compound as a colorless liquid.

B. 3-(4-Morpholinyl)propanoic Acid.

A solution of the resultant compound of Example 202A (8.35 g, 48.3 mmol) in 60 ml of dioxane was treated with 40 ml of water and 19.3 ml (58 mmol) of 3N aqueous NaOH. After being stirred for 4 h, the solution was treated with 58 ml (58 mmol) of 1N aqueous HCl and concentrated in vacuo to provide the crude desired compound.

C. (2S,3R,4R,5S)-3,4-Dihydroxy-2,5-di-(N-(N-(3-(4-morpholinyl)propanoyl)-valinyl)-amino-1,6-diphenylhexane.

The resultant compound of Example 202B (0.64 mmol) was coupled to the resultant compound of Example 173 (0.214 mmol) according to the procedure described in Example 55 to provide, after silica gel chromatography using 5% methanol in chloroform, 101.5 mg (61%) of the desired compound (R_f 0.17, 10% methanol in chloroform) as a white solid, m.p. 243-245° C (dec). Mass spectrum: $(M + H)^+$ = 781.
Anal. Calcd. for $C_{42}H_{64}N_6O_8 \cdot H_2O$: C, 63.14; H, 8.33; N, 10.52. Found: C, 63.20; H, 8.16; N, 11.21.

Example 203

(2S,3R,4R,5S)-3,4-Dihydroxy-2,5-di-(N-(N-(3-pyridylacetyl))-valinyl)-amino-1,6-diphenylhexane.

3-Pyridylacetic acid hydrochloride (117 mg, 0.68 mmol) was coupled to the resultant compound of Example 173 (113 mg, 0.226 mmol) according to the procedure described in Example 55 to provide, after silica gel chromatography using 10% methanol in chloroform, the desired compound (R_f 0.16, 10% methanol in chloroform). Mass spectrum: $(M + H)^+$ = 737.

Example 204

(2S,3S,4S,5S)- and (2S,3R,4S,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 171 with the more mobile mixture of compounds of Example 170B

provided a mixture of diamines which were separated by silica gel chromatography using 2% isopropylamine in chloroform containing sequential amounts of 1%, 2% and 5% methanol.
(2S,3S,4S,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane: R_f 0.40 (5% methanol/2% isopropylamine in chloroform), ^1H NMR ($CDCl_3$) δ 2.63 (dd, J = 14, 11 Hz, 2 H), 2.85 (dd, J = 14, 4 Hz, 2 H), 3.60 (dt, J = 11, 4 Hz, 2 H), 3.92 (d, J = 3 Hz, 2 H), 7.2-7.4 (m, 10 H).
(2S,3R,4S,5S)-2,5-Diamino-3,4-dihydroxy-1,6-diphenylhexane: R_f 0.23 (5% methanol/2% isopropylamine in chloroform), m.p. 115-119° C, ^1H NMR ($CDCl_3$) δ 2.46 (dd, J = 14, 9 Hz, 1 H), 2.61 (dd, J = 14, 11 Hz, 1 H), 3.02 (td, J = 9, 3 Hz, 1 H), 3.19 (dd, J = 14, 4 Hz, 1 H), 3.35-3.4 (m, 2 H), 3.51 (t, J = 9 Hz, 1 H), 3.76 (dd, J = 9, 3 Hz, 1 H), 7.2-7.4 (m, 10 H).

Example 205

(2S,3S,4S,5S)-2,5-Di-(N-((t-butyloxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 15 mg (0.05 mmol) of (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane in 0.5 ml of dichloromethane was treated with 24 mg (0.11 mmol) of di-t-butyldicarbonate and stirred at ambient temperature. After 16 h, the solution was concentrated in vacuo, and the residue was purified by silica gel chromatography using 30% ethyl acetate in hexane to provide 17 mg (68%) of the desired compound, m.p. 216-218° C. ^1H NMR δ 1.40 (s, 18 H), 2.97 (dd, J = 14, 5 Hz, 2 H), 3.20 (dd, J = 14, 5 Hz, 2 H), 3.22 (m, 2 H), 4.03 (m, 2 H), 4.35 (d, J = 5 Hz, 2 H), 4.41 (d, J = 9 Hz, 2 H), 7.2-7.3 (m, 10 H). Mass spectrum: $(M + H)^+$ = 501.

Example 206

(2S,3R,4S,5S)-2,5-Di-(N-((t-butyloxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 205 with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided the desired compound (R_f 0.32, 30% ethyl acetate in hexane), as a white solid, m.p. 208-212° C. ^1H NMR δ 1.33 (s, 9 H), 1.40 (s, 9 H), 2.67 (m, 1 H), 2.75-2.95 (m, 6 H), 3.47 (m, 2 H), 4.14 (m, 2 H), 4.58 (m, 1 H), 4.83 (br d, 1 H), 4.93 (br d, 1 H), 7.15-7.3 (m, 10 H).

Example 207

(2S,3R,4R,5S)-2,5-Di-(N-((4-morpholinyl)acetyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 189B (23.5 mg, 0.16 mmol) was coupled to 23.2 mg (0.077 mmol) of the resultant compound of Example 171 using the carbodiimide coupling procedure described in Example 55 to provide, after silica gel chromatography using 5% methanol in chloroform, the desired compound (R_f 0.4, 10% methanol in chloroform) as a white solid, m.p. 172-177° C, in 55% yield. Mass spectrum: $(M + H)^+$ = 555.
Anal. Calcd for $C_{30}H_{42}N_4O_6 \cdot 0.5H_2O$: C, 63.92; H, 7.69; N, 9.93. Found: C, 64.10; H, 7.58; N, 9.97.

Example 208

(2S,3R,4R,5S)-2,5-Di-(N-((2-pyridinyl)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Picolinic acid was coupled to the resultant compound of Example 171 using the carbodiimide coupling procedure described in Example 55 to provide, after chromatography on silica gel using 5% methanol in chloroform, 58 mg (60%) of the desired compound (R_f 0.6, 10% methanol in chloroform) as a white solid, m.p. 179-184° C. Mass spectrum: $(M + H)^+$ = 511.
Anal. Calcd for $C_{30}H_{30}N_4O_4 \cdot 0.5H_2O$: C, 69.35; H, 6.01; N, 10.78. Found: C, 69.15; H, 5.93; N, 10.53.

Example 209

(2S,3R,4S,5S)-2,5-Di-(N-(Cbz-valinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 172B with 25 mg (0.083 mmol) of (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided the desired compound (31%, R_f 0.3, 5% methanol in chloroform) as a white solid, m.p. 230-234° C. Mass spectrum: $(M + H)^+$ = 767.

Example 210

(2S,3S,4S,5S)-2,5-Di-(N-(Cbz-valinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Cbz-valine p-nitrophenyl ester was coupled to (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane using the procedure of Example 172B to provide the desired compound (R_f 0.42, 5% methanol in chloroform) as a white solid, m.p. 239-242° C in 86 % yield.

Example 211

(2S,3R,4R,5S)-2,5-Di-(N-((t-butyloxy)carbonyl)amino)-1,6-dicyclohexyl-3,4-dihydroxyhexane.

A mixture of 180 mg (0.36 mmol) of (2S,3R,4R,5S)-2,5-di-(N-((t-butyloxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane and 180 mg of 5% rhodium on carbon in 50 ml of methanol was shaken under 4 atmospheres of hydrogen for 24 h. The resulting mixture was filtered and concentrated in vacuo. The residue was purified by silica gel chromatography using 5% ethyl acetate in hexane to provide 120 mg (65%) of the desired compound (R_f 0.35, 30% ethyl acetate in hexane) as a white solid, m.p. 224-226° C. Mass spectrum: $(M + H)^+$ = 513.
Anal. Calcd for $C_{28}H_{52}N_2O_6$: C, 65.69; H, 10.22; N, 5.46. Found: C, 65.27; H, 10.16; N, 5.40.

Example 212

(2S,3S,4R,5S)-5-Amino-2-(N-((t-butyloxy)carbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 200 mg (0.67 mmol) of (2S,3S,4R,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane in 10

ml of dichloromethane was treated with 174 mg (0.8 mmol) of di-t-butyldicarbonate. After being allowed to stir overnight at ambient temperature, the solution was concentrated, and the residue was purified by silica gel chromatography using 10% methanol in chloroform to provide 180 mg (56%) of the desired compound along with 80 mg (20%) of the resultant compound of Example 206.

Example 213

(2S,3S,4R,5S)-2-(N-((t-Butyloxy)carbonyl)amino)-5-(N-(Cbz-valinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 212 was coupled to Cbz-valine using the carbodiimide coupling procedure of Example 55 to provide the desired compound (R_f 0.48, 5% methanol in chloroform) as a white solid, m.p. 178-182° C, in 88% yield. Mass spectrum: $(M + H)^+$ = 634.
Anal. Calcd for $C_{36}H_{47}N_3O_7 \cdot 0.5H_2O$: C, 67.27; H, 7.53; N, 6.54. Found: C, 67.18; H, 7.45; N, 6.71.

Example 214

A. N,N-Dimethylvaline.

A mixture of 2.5 g of L-valine, 0.5 g of 10% palladium on carbon, in 93 ml of methanol and 7 ml of formalin was shaken under 4 atmospheres of hydrogen. After 24 h, the solution was filtered and concentrated in vacuo to provide the crude desired compound.

B. (2S,3R,4R,5S)-2,5-Bis-(N-(N,N-dimethylvalinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 214A was coupled to the resultant compound of Example 171 using the carbodiimide coupling procedure of Example 55 to provide the desired compound (20%, R_f 0.3, 10% methanol in chloroform) as a white solid, m.p. 200-204° C. Mass spectrum: $(M + H)^+$ = 555.

Example 215

A. N-((2-Pyridinyl)methoxycarbonyl)-valine p-Nitrophenyl Ester.

A solution of 0.87 mmol of the resultant compound of Example 176A and 133 mg (0.96 mmol) of p-nitrophenol in 4 ml of tetrahydrofuran and 2 ml of dimethylformamide was treated with 183 mg (0.96 mmol) of N-ethyl-N'-(dimethylaminopropyl) carbodiimide hydrochloride and stirred at ambient temperature. After 4 h, the solvent was removed in vacuo, and the residue was partially purified by silica gel chromatography using 20% ethyl acetate in chloroform to give 0.34 mg of the desired compound contaminated with excess p-nitrophenol.

B. (2S,3R,4R,5S)-2,5-Di-(N-((2-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 230 mg of the crude resultant compound of Example 215A and 70 mg (0.23 mmol) of the

resultant compound of Example 171 in 1 ml of 1:1 tetrahydrofuran/dimethylformamide was stirred at ambient temperature for 16 h. The resulting solution was treated with aqueous $NaHCO_3$, stirred for 1 h, diluted with 5% methanol in chloroform, washed with aqueous $NaHCO_3$ until the washes were colorless, dried over Na_2SO_4, and concentrated. Chromatography on silica gel using 2% methanol in chloroform followed by 5% methanol in chloroform provided 140.6 mg (80%) of the desired compound (R_f 0.32, 10% methanol in chloroform) as a white solid, m.p. 196-200° C. Mass spectrum: $(M + H)^+ = 769$.
Anal. Calcd for $C_{42}H_{52}N_6O_8$: C, 65.61; H, 6.82; N, 10.93. Found: C, 65.68; H, 6.93; N, 10.95.

Example 216

(2S,3S,4S,5S)-2,5-Di-(N-((2-pyridinyl)methoxycarbonyl)valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 171 with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography using a gradient of 2-5% methanol in chloroform, the desired compound (R_f 0.32, 5% methanol in chloroform) as a white solid, m.p. 220-223° C, in 79% yield. Mass spectrum: $(M + H)^+ = 769$.
Anal. Calcd for $C_{42}H_{52}N_6O_8 \cdot 0.5H_2O$: C, 64.85; H, 6.87; N, 10.80. Found: C, 64.69; H, 6.84; N, 10.63.

Example 217

(2S,3R,4S,5S)-2,5-Di-(N-((2-pyridinyl)methoxycarbonyl)valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 171 with (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography using a gradient of 2-5% methanol in chloroform, the desired compound (R_f 0.23, 5% methanol in chloroform) as a white solid, m.p. 238-240° C, in 82% yield. Mass spectrum: $(M + H)^+ = 769$.
Anal. Calcd for $C_{42}H_{52}N_6O_8 \cdot 0.25H_2O$: C, 65.23; H, 6.84; N, 10.87. Found: C, 65.01; H, 6.89; N, 10.92.

Example 218

A. 2-(N-(t-Butyloxycarbonyl)aminomethyl)pyridine.

A solution of 21.2 g (97 mmol) of di-t-butyldicarbonate in 200 ml of dichloromethane was cooled to 0° C and treated in portions with 10 ml (97 mmol) of 2-(aminomethyl)pyridine. After being allowed to warm to ambient temperature and stirred overnight, the resulting solution was diluted with 100 ml of dichloromethane, washed with three 100 ml portions of water, dried over Na_2SO_4, and concentrated in vacuo to provide 19.8 g (98%) of the desired compound (R_f 0.28, 5% methanol in chloroform). ^1H NMR ($CCDl_3$) δ 1.47 (s, 9 H), 4.45 (d, J = 6 Hz, 2 H), 5.56 (br, 1 H), 7.18 (m, 1 H), 7.28 (d, J = 8 Hz, 1 H), 7.66 (td, J = 7, 2 Hz, 1 H), 8.53 (m, 1 H).

B. 2-((N-(t-Butyloxycarbonyl)-N-methylamino)methyl)pyridine.

A solution of 19.8 g (95 mmol) of the resultant compound of Example 218A in anhydrous tetrahydrofuran was cooled under N_2 atmosphere to 0° C and treated with 4.95 g (124 mmol) of sodium

hydride (60% dispersion in oil). The solution was stirred for 15 min, treated dropwise with 7.1 ml (114 mmol) of methyl iodide, stirred at ambient temperature for 2 h, and quenched cautiously with water. The resulting mixture was partitioned between ether and water, dried over Na_2SO_4, and concentrated. Chromatography on silica gel provided 14.9 g (70%) of the desired compound as a colorless oil.

C. 2-(N-methylamino)methyl)pyridine Dihydrochloride.

The resultant compound of Example 218B (3.05 g, 13.7 mmol) was treated with 30 ml of 4N HCl in dioxane and heated at 40° C for 0.5 h. The solvent was removed in vacuo to provide the crude desired compound as a light brown solid.

D. N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)valine Methyl Ester.

A mixture of 1.61 g (7.2 mmol) of the resultant compound of Example 218C and 1.14 g (7.2 mmol) of the resultant compound of Example 160A in 40 ml of dichloromethane was treated with 2 ml (18 mmol) of 4-methylmorpholine. After being stirred for 2 h, the solution was partitioned between dichloromethane and water, dried over Na_2SO_4, and concentrated. Chromatography on silica gel using 2% methanol in chloroform provided 1.94 g (96%) of the desired compound (R_f 0.32, 5% methanol in chloroform) as a colorless oil. ^1H NMR ($CCDl_3$) δ 0.93 (d, J = 7 Hz, 3 H), 0.97 (d, J = 7 Hz, 3 H), 2.16 (m, 1 H), 3.03 (s, 3 H), 3.72 (s, 3 H), 4.43 (dd, J = 8, 5 Hz, 1 H), 4.55 (s, 2 H), 6.15 (br, 1 H), 7.22 (dd, J = 8, 6 Hz, 1 H), 7.28 (d, J = 6 Hz, 1 H), 7.69 (br t, 1 H), 8.55 (d, J = 5 Hz, 1 H).

E. N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)valine p-Nitrophenyl Ester.

Using the procedures of Example 176A and Example 215A but replacing the resultant compound of Example 162A with the resultant compound of Example 218D provided the desired compound.

F. (2S,3R,4R,5S)-2,5-Di-(N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 215A with the resultant compound of Example 218E provided, after silica gel chromatography using a gradient of 2-5% methanol in chloroform, the desired compound (R_f 0.28, 5% methanol in chloroform) as a white solid, m.p. 108-111° C, in 85% yield. Mass spectrum: $(M + H)^+$ = 795.
Anal. Calcd for $C_{44}H_{58}N_8O_6 \cdot 1.25H_2O$: C, 64.65; H, 7.46; N, 13.71. Found: C, 64.35; H, 7.06: N, 13.58.

Example 219

(2S,3S,4S,5S)-2,5-Di-(N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 215A with the resultant compound of Example 218E and replacing the resultant compound of Example 171 with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography using a gradient of 1-5% methanol in chloroform, the desired compound (R_f 0.38, 5% methanol in chloroform) as a white solid, m.p. 110-112° C, in 75% yield. Mass spectrum: $(M + H)^+$ = 795.

Anal. Calcd for $C_{44}H_{58}N_8O_5 \cdot H_2O$: C, 65.00; H, 7.44; N, 13.78. Found: C, 64.61; H, 7.21; N, 13.60.

Example 220

(2S,3R,4S,5S)-2,5-Di-(N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 215A with the resultant compound of Example 218E and replacing the resultant compound of Example 171 with (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography using a gradient of 1-2% methanol in chloroform, the desired compound (R_f 0.36, 5% methanol in chloroform) as a white solid, m.p. 159-162° C, in 79% yield. Mass spectrum: $(M + H)^+ = 795$.
Anal. Calcd for $C_{44}H_{58}N_6O_8$: C, 66.48; H, 7.35; N, 14.09. Found: C, 66.31; H, 7.43; N, 13.95.

Example 221

2,4-Di-(N-((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 218D was hydrolyzed according to the procedure of Example 176A and coupled to the resultant compound of Example 12 according to the carbodiimide coupling procedure described in Example 55 to provide, after silica gel chromatography using 3% methanol in chloroform, the desired compound (53%, R_f 0.5, 10% methanol in chloroform) as a white solid, m.p. 70-72° C. Mass spectrum: $(M + H)^+ = 765$.

Example 222

(2S,3R,4R,5S)-2,5-Di-(N-(((2-pyridinyl)carbonyl)valinyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Picolinic acid was coupled to the resultant compound of Example 173 using the carbodiimide coupling procedure described in Example 55 to provide after silica gel chromatography using a gradient of 5-10% methanol in chloroform, the desired compound (R_f 0.16, 10% methanol in chloroform) as a white solid, m.p. 167-171° C, in 61% yield. Mass spectrum: $(M + H)^+ = 709$.
Anal. Calcd for $C_{40}H_{48}N_6O_6$: C, 67.78; H, 6.83; N, 11.86. Found: C, 67.81; H, 6.59; N, 11.78.

Example 223

A. 3-(3-Pyridinyl)propanoic Acid

A mixture of 3 g (20 mmol) of 3-(3-pyridinyl)acrylic acid and 0.3 g of 10% palladium on carbon in 150 ml of ethyl acetate was shaken under 4 atmospheres of hydrogen for 24 h. After filtration, the resulting solution was concentrated in vacuo to provide the desired compound.

B. (2S,3R,4R,5S)-2,5-Di-(N-(3-(3-pyridinyl)propanoyl)valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 223A was coupled to the resultant compound of Example 173 using the carbodiimide coupling procedure described in Example 55 to provide after silica gel chromatography using a gradient of 5-10% methanol in chloroform, the desired compound (R_f 0.1, 10% methanol in chloroform) as a white solid, m.p. 260-263° C, in 37% yield. Mass spectrum: $(M + H)^+$ = 765.

Example 224

(2S,3R,4R,5S)-3,4-Dihydroxy-2,5-di-(N-(N-(2-pyridylacetyl))-valinyl)-amino-1,6-diphenylhexane.

(2-Pyridyl)acetic acid was coupled to the resultant compound of Example 173 using the carbodiimide coupling procedure described in Example 55 to provide after silica gel chromatography using a gradient of 2-5% methanol in chloroform, the desired compound (41%, R_f 0.21, 5% methanol in chloroform) as a white solid, m.p. 208-213° C. Mass spectrum: $(M + H)^+$ = 737.

Example 225

A. N-((4-Pyridinyl)methoxycarbonyl)-valine p-Nitrophenyl Ester.

Using the procedures of Example 176A and Example 215A but replacing the resultant compound of Example 162A with the resultant compound of Example 160B provided the desired compound.

B. (2S,3R,4R,5S)-2,5-Di-(N-((4-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 215A with the resultant compound of Example 225A provided, after silica gel chromatography using a gradient of 2-5% methanol in chloroform, the desired compound (R_f 0.11, 10% methanol in Chloroform) as a white solid, m.p. 221-224° C in 48% yield. Mass spectrum: $(M + H)^+$ = 769.
Anal. Calcd for $C_{42}H_{52}N_6O_8 \cdot 0.5H_2O$: C, 64.85; H, 6.87; N, 10.80. Found: C, 64.91; H, 6.81; N, 10.80.

Example 226

(2S,3R,4S,5S)-2,5-Di-(N-(t-butylaminocarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 30 mg (0.1 mmol) of (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane in 1 ml of dichloromethane was treated with 25 µl (0.22 mmol) of t-butylisocyanate. The resulting solution was stirred at ambient temperature, diluted with dichloromethane, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Silica gel chromatography using a gradient of 1-3% methanol in chloroform provided 49 mg (98%) of the desired compound (R_f 0.4, 10% methanol in chloroform) as a white solid, m.p. 193-196° C. Mass spectrum: $(M + H)^+$ = 499.
Anal. Calcd for $C_{28}H_{42}N_4O_4 \cdot H_2O$: C, 65.09; H, 8.58; N, 10.84. Found: C, 65.17; H, 8.21; N, 10.77.

Example 227

(2S,3R,4S,5S)-2,5 Di-(N-(isopropylaminocarbonyl)amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 226 but replacing t-butylisocyanate with isopropylisocyanate provided the desired compound (R_f 0.24, 10% methanol in chloroform) as a white solid, m.p. 220-222° C, in 81% yield. Mass spectrum: $(M + H)^+$ = 471.
Anal. Calcd for $C_{26}H_{38}N_4O_4 \cdot 0.25H_2O$: C, 65.73; H, 8.17; N, 11.79.

Example 228

(2S,3S,4S,5S)-2,5-Di-(N-((4-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 215A with the resultant compound of Example 225A and replacing the resultant compound of Example 171 with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography using a gradient of 2-5% methanol in chloroform, the desired compound (35%, R_f 0.25, 10% methanol in chloroform) as a white solid, m.p. 190-193° C. Mass spectrum: $(M + H)^+$ = 769.

Example 229

A. N-((3-Pyridinyl)methoxycarbonyl)-valine p-Nitrophenyl Ester.

Using the procedures of Example 176A and Example 215A but replacing the resultant compound of Example 162A with the resultant compound of Example 161A provided the desired compound.

B. (2S,3S,4S,5S)-2,5-Di-(N-((3-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 215A with the resultant compound of Example 229A and replacing the resultant compound of Example 171 with (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography using a gradient of 5-10% methanol in chloroform, the desired compound (R_f 0.31, 10% methanol in chloroform) as a white solid, m.p. 202-207° C. Mass spectrum: $(M + H)^+$ = 769.

Example 230

(2S,3R,4S,5S)-2,5-Di-(N-((3-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 215A with the resultant compound of Example 229A and replacing the resultant compound of Example 171 with (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane provided, after silica gel chromatography us-

ing a gradient of 2-5% methanol in chloroform, the desired compound (31%, R_f 0.28, 10% methanol in chloroform) as a white solid, m.p. 212-216° C. Mass spectrum: $(M + H)^+$ = 769.

Example 231

(2S,3S,4R,5S)-2-(N-((t-Butyloxy)carbonyl)amino)-5-(N-((2-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 215B but replacing the resultant compound of Example 171 with the resultant compound of Example 212 provided, after silica gel chromatography using a gradient of 0-2% methanol in chloroform, the desired compound (R_f 0.57, 5% methanol in chloroform) as a white solid, m.p. 202-204° C, in 61% yield. Mass spectrum: $(M + H)^+$ = 635.

Example 232

(2S,3S,4R,5S)-2-Amino-5-(N-((3-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 231 (200 mg, 0.31 mmol) was treated with 20 ml of 4N HCl in dioxane. After being stirred at ambient temperature for 2 h, the solvent was removed in vacuo. The residue was partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Silica gel chromatography using a gradient of 2% methanol/2% isopropylamine in chloroform provided 40 mg (84%) of the desired compound.

Example 233

(2S,3S,4R,5S)-2-(N-Succinylamino)-5-(N-((3-pyridinyl)methoxycarbonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

A solution of 50 mg (0.93 mmol) of the resultant compound of Example 232 in 0.5 ml of dichloromethane was treated with 9.3 mg (0.93 mmol) of succinic anhydride. The resulting mixture was stirred overnight at ambient temperature and concentrated in vacuo to a solid which was washed with chloroform. The solvent was decanted to provide the desired compound (R_f 0.91, 1:1:1:1 ethyl acetate/n-butanol/water/acetic acid) as a white solid. Mass spectrum: $(M + H)^+$ = 635.

Example 234

A. N-(Chlorosulfonyl)-valine Methyl Ester.

A suspension of 15.3 g (90 mmol) of L-valine methyl ester hydrochloride in 45 ml of acetonitrile was treated with 22 ml (270 mmol) of sulfuryl chloride and heated at reflux for 16 h. The resulting light yellow solution was allowed to cool and concentrated in vacuo to a viscous oil. The oil was treated two times with acetonitrile followed each time by concentration in vacuo. The crude desired product was thus obtained as

a viscous oil.

B. N-((N-Methyl-N-((2-pyridinyl)methyl)amino)sulfonyl)-valine Methyl Ester.

A mixture of 13.7 mmol of the resultant compound of Example 218C and 3.17 g (13.7 mmol) of the resultant compound of Example 234A in 100 ml of dichloromethane was cooled to 0° C and treated with 6 ml of 4-methylmorpholine. The resulting solution stirred for 2 h, diluted with dichloromethane, washed with aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. Chromatography on silica gel using 30% ethyl acetate in chloroform provided 1.72 g (40%) of the desired compound as a colorless oil. ^1H NMR ($CCDl_3$, major rotamer) δ 0.95 (d, J = 7 Hz, 3 H), 1.03 (d, J = 7 Hz, 3 H), 2.12 (m, 1 H), 2.79 (s, 3 H), 3.76 (s, 3 H), 3.95 (dd, J = 8, 4 Hz, 1 H), 4.54 (AA', 2 H), 6.40 (d, J = 8 Hz, 1 H), 7.26 (m, 1 H), 7.35 (d, 6 Hz, 1 H), 7.71 (br t, 1 H), 8.59 (d, J = 4 Hz, 1 H). Mass spectrum: $(M + H)^+$ = 316.

C. N-((N-Methyl-N-((2-pyridinyl)methyl)amino)sulfonyl)-valine.

A solution of 200 mg (0.63 mmol) of the resultant compound of Example 234B in 2.5 ml of dioxane was treated with 2.5 ml of 0.5M LiOH. After being stirred overnight at ambient temperature, the solution was concentrated in vacuo at 30° C, diluted with dioxane and water, neutralized with 1M HCl, and concentrated in vacuo to provide the crude desired compound.

D. (2S,3R,4R,5S)-2,5-Di-(N-((N-Methyl-N-((2-pyridinyl)methyl)amino)sulfonyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 234C was coupled to the resultant compound of Example 171 using the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography using 2% methanol in chloroform, the desired compound (45%, R_f 0.5, 10% methanol in chloroform) as a white solid, m.p. 85-89° C. Mass spectrum: $(M + H)^+$ = 867.
Anal. Calcd for $C_{42}H_{58}N_8O_8S_2 \cdot H_2O$: C, 57.00; H, 6.83; N, 12.66. Found: C, 56.78; H, 6.56; N, 12.45.

Example 235

A. (4S)4-Benzyl-3-(3-methylbutanoyl)oxazolidine-2-one.

Using the procedure of Example 100A but replacing 4-(2-propyl)-oxazolidine-2-one with 4-benzyloxazolidine-2-one and replacing 4-methylpentanoyl chloride with isovaleryl chloride provided the desired compound.

B. (4S,2'S)-3-(2-(t-Butyloxycarbonyl)methyl-4-methylbutanoyl)-4-benzyloxazolidine-2-one.

Using the procedure of Example 100B with the resultant compound of Example 235A provided, after silica gel chromatography using 15% ethyl acetate in hexane followed by dichloromethane, the desired compound (R_f 0.35, 20% ethyl acetate in hexane) in 88% yield.

C. Benzyl (2S)-2-(t-Butyloxycarbonyl)methyl-4-methylbutanoate.

Using the procedure of Example 100C with the resultant compound of Example 235B provided, after silica gel chromatography using 6% ethyl acetate in hexane, the desired compound (R_f 0.43, 10% ethyl acetate in hexane) in 60% yield.

D. Benzyl (2S)-2-Carboxymethyl-4-methylbutanoate.

Using the procedure of Example 100D with the resultant compound of Example 235C provided the desired compound as a crude colorless oil.

E. Benzyl (2S)-2-(((N-Methyl-N-((2-pyridinyl)methyl)amino)carbonyl)methyl)-4-methylbutanoate.

The resultant compound of Example 235D was coupled to the resultant compound of Example 218C using the mixed anhydride coupling method described in Example 6F to provide, after silica gel chromatography using 60% ethyl acetate in chloroform, the desired compound (R_f 0.19, 60% ethyl acetate in chloroform) in 73% yield.

F. (2S)-2-(((N-Methyl-N-((2-pyridinyl)methyl)amino)(carbonyl)methyl)-4-methylbutanoic Acid.

The resultant compound of Example 235E was hydrogenolyzed according to the procedure described in Example 71C to provide the desired compound.

G. (2S,3R,4R,5S,2′S,2″S)-2,5-Di-(2-(((N-methyl-N-((2-pyridinyl)methyl)amino)carbonyl)methyl)-4-methylbutanoylamino)-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 235F was coupled to the resultant compound of Example 171 using the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography using 5% methanol in chloroform, the desired compound in 42% yield, m.p. 169-170 °C. Mass spectrum: $(M + H)^+$ = 793.

Anal. Calcd for $C_{46}H_{60}N_6O_6 \cdot 0.5H_2O$: C, 68.89; H, 7.67; N, 10.48. Found: C, 68.85; H, 7.80; N, 10.16.

Example 236

Ethyl 3-(2-Pyridinyl)acrylate.

A suspension of 0.43 g (10.7 mmol) of sodium hydride (60% dispersion in oil) in 60 ml of anhydrous tetrahydrofuran was cooled to 0 °C and treated with 2.1 ml (10.5 mmol) of triethylphosphonoacetate. The resulting solution was stirred for 10 min, treated with 1.0 ml (10.5 mmol) of pyridine-2-carboxaldehyde, heated at reflux for 2 h, and stirred overnight at ambient temperature. The resulting mixture was partitioned between ether and aqueous ammonium chloride, washed sequentially with water and saturated brine, dried over $MgSO_4$, and concentrated in vacuo. Chromatography on silica gel using 25% ethyl acetate in hexane provided 1.54 g (83%) of the desired compound as a colorless liquid. ^1H NMR ($CDCl_3$) δ 1.34 (t, J = 7 Hz, 3 H), 4.28 (q, J = 7 Hz, 2 H), 6.92 (d, J = 16 Hz, 1 H), 7.27 (ddd, J = 8, 5, 1 Hz, 1 H), 7.43 (d, J = 8 Hz, 1 H), 7.72 (m, 1 H), 8.65 (m, 1 H).

B. 3-(2-Pyridinyl)acrylic Acid.

The resultant compound of Example 236A was hydrolyzed according to the procedure of Example 176A to provide the desired compound.

C. (2S,3R,4R,5S)-2,5-Di-(N-(3-(2-pyridinyl)propenoyl)-valinyl-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedures of Example 223A and Example 223B but replacing 3-(3-pyridinyl)acrylic acid with the resultant compound of Example 236B provided the desired compound.

Example 237

(2S,3R,4R,5S)-2,5-Di-(N-(3-(2-pyridinyl)propanoyl)-valinyl-anino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedures of Example 223A and Example 223B but replacing 3-(3-pyridinyl)acrylic acid with 3-(2-pyridinyl)acrylic acid provided the desired compound (R_f 0.21, 10% methanol in chloroform). Mass spectrum: $(M + H)^+$ = 765.

Example 238

2,4-Di-(N-((2-(4-morpholinyl)ethyloxy)carbonyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 165B was coupled to the resultant compound of Example 12 using the carbodiimide coupling procedure of Example 160D to provide, after silica gel chromatography using 3% methanol in chloroform, the desired compound (R_f 0.6, 10% methanol in chloroform) in 66% yield as a white solid, m.p. 122-123° C. Mass spectrum: $(M + H)^+$ = 783.

Example 239

2-(Boc-valinyl-amino)-4-(Cbz-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Boc-valine was coupled to the resultant compound of Example 69 using the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography using 3% methanol in chloroform, the desired compound (82%, R_f 0.7, 10% methanol in chloroform) as a white solid, m.p. 184-184° C. Mass spectrum: $(M + H)^+$ = 703.

Anal. Calcd for $C_{40}H_{54}N_4O_7 \cdot 0.5H_2O$: C, 67.49; H, 27.79; N, 7.87. Found: C, 67.79; H, 7.63; N, 7.91.

Example 240

4-(Cbz-valinyl-amino)-2-(valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 12 with the resultant compound of Example 239 provided a crude hydrochloride salt which was partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Chromatography of the residue on silica gel using 3% methanol in chloroform provided in 89% yield the desired compound (R_f 0.5, 10% methanol in chloroform) as a white solid, m.p. 126-127°C. Mass spectrum: $(M + H)^+ = 603$.
Anal. Calcd for $C_{35}H_{46}N_4O_5 \cdot 1.5H_2O$: C, 66.75; H, 7.84; N, 8.90. Found: C, 66.88; H, 7.25; N, 8.79.

Example 241

A. N-((2-Thiazolyl)methoxycarbonyl)-valine Methyl Ester.

Using the procedure of Example 160B but replacing pyridine-4-methanol with 2-(hydroxymethyl)thiazole (Dondoni, et. al., *Synthesis*, 1987, 998; *Tetrahedron Lett.* 1983, *24*, 2901) provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound in 74% yield. Mass spectrum: $(M + H)^+ = 273$.

B. 2,4-Di-(N-((2-thiazolyl)methoxycarbonyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 241A was hydrolyzed according to the procedure of Example 176A and coupled to the resultant compound of Example 12 according to the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography using 3% methanol in chloroform, the desired compound (72%, R_f 0.7, 10% methanol in chloroform) as a white solid, m.p. 92-93°C. Mass spectrum: $(M + H)^+ = 751$.
Anal. Calcd for $C_{37}H_{46}N_6O_7S$: C, 59.18; H, 6.18; N, 11.20. Found: C, 60.42; H, 6.51; N, 10.61.

Example 242

4-(Cbz-valinyl-amino)-2-(N-((2-(1-imidazolyl)acetyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 190B was coupled to the resultant compound of Example 240 using the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography using 3% methanol in chloroform, the desired compound (70%, R_f 0.3, 10% methanol in chloroform.) Mass spectrum: $(M = H)^+ = 711$.

Example 243

4-(Cbz-valinyl-amino)-2-(N-((2-(1-morpholinyl)acetyl)-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 189B was coupled to the resultant compound of Example 240 using the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography using 3% methanol in chloroform, the desired compound (67%, R_f 0.5, 10% methanol in chloroform). Mass spectrum: $(M + H)^+ = 730$.