Exhibit 9 – Part 6 of 7

Example 244

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

A solution of 3-(aminomethyl)pyridine (12 µl, 0.11 mmol) in 0.5 ml of nitromethane was cooled to -20° C and treated with 0.23 ml (0.12 mmol) of a 0.5 M solution of carbonyl bis(N-methyl)imidazole triflate (Rappoport, et. al., *J. Am. Chem. Soc.* **1989**, *111*, 6856) in nitromethane. After 30 min, the solution was treated with a solution of 50 mg (0.08 mmol) of the resultant compound of Example 240 in 1.0 ml of dimethylformamide and 26 µL (0.24 mmol) of 4-methylmorpholine. The resulting solution was stirred at 0° C for 1 h, concentrated in vacuo, partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography using 3% methanol in chloroform to provide 40 mg (65 %) of the desired compound (R_f 0.4, 10% methanol in chloroform) as a white solid, m.p. 205-206° C. Mass spectrum: $(M + H)^+ = 737$.

Example 245

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

Using the procedure of Example 163A but replacing nicotinyl chloride hydrochloride with isonicotinyl chloride hydrochloride and replacing valine benzyl ester p-toluenesulfonate with the resultant compound of Example 140 provided, after silica gel chromatography using 5% methanol in chloroform, the desired compound (90%, R_f 0.3, 10% methanol in chloroform) as a white solid, m.p. 256-258° C. Mass spectrum: $(M + H)^+ = 679$.

Example 246

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

The resultant compound of Example 223A was coupled to the resultant compound of Example 140 using the carbodiimide coupling procedure described in Example 55 to provide after silica gel chromatography using 3% methanol in chloroform, the desired compound (75%, R_f 0.2, 10% methanol in chloroform) as a white solid, 234-235° C. Mass spectrum: $(M + H)^+ = 735$.

Example 247

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

Using the procedure of Example 160D, the resultant compound of Example 161B was coupled to the resultant compound of Example 171 to provide, after silica gel chromatography using 5% methanol in chloroform, the desired compound (R_f 0.25, 10% methanol in chloroform) as a white solid, m.p. 207-208° C, in 32% yield. Mass spectrum: $(M + H)^+ = 769$.
Anal. Calcd for $C_{42}H_{52}N_6O_8 \cdot 1.25H_2O$: C, 63.74; H, 6.94; N, 10.62. Found: C, 63.70; H, 6.70; N, 10.54.

Example 248

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

The resultant Compound of Example 165B was coupled to the resultant compound of Example 171 using the carbodiimide coupling procedure of Example 160D to provide, after silica gel chromatography using 5% methanol in chloroform, the desired compound (R_f 0.21, 10% methanol in chloroform) as a white solid, m.p. 227-230° C (dec) in 47% yield. Mass spectrum: $(M + H)^+$ = 813.
Anal. Calcd for $C_{42}H_{64}N_6O_{10}\cdot 1.25H_2O$: C, 60.38; H, 8.02; N, 10.06. Found: C, 60.21; H, 7.78; N, 10.43.

Example 249

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

Using the procedure of Example 160D, the resultant compound of Example 161B was coupled to the resultant compound of Example 212 to provide, after silica gel chromatography using 3% methanol in chloroform, the desired compound (R_f 0.21, 5% methanol in chloroform) as a white solid, m.p. 175-178° C, in 66% yield. Mass spectrum: $(M + H)^+$ = 635.
Anal. Calcd for $C_{35}H_{46}N_4O_2\cdot 0.75H_2O$: C, 64.65; H, 7.38; N, 8.64. Found: C, 64.61; H, 7.16; N, 8.80.

Example 250

Bis-(2-(N-(Cbz-valinyl)amino)-3-phenylpropyl)sulfone.

The resultant compound of Example 155B was deprotected according to the procedure of Example 12 and coupled to Cbz-valine according to the procedure of Example 55. The crude mixture was diluted with ethyl acetate, washed sequentially with aqueous citric acid, water, aqueous $NaHCO_3$, and water. The solid in the organic layer was filtered, washed with ethyl acetate, and air-dried to a fine white powder, m.p. 259-260° C (dec) (67% yield). Mass spectrum: $(M + H)^+$ = 799.
Anal. Calcd for $C_{44}H_{54}N_4O_8S\cdot H_2O$: C, 64.69; H, 6.91; N, 6.86. Found: C, 64.42; H, 6.93; N, 7.51.

Example 251

(2S,3R,4S,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 (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane using the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography, the desired compound (R_f 0.65, 10% methanol in chloroform) as a white solid, m.p. 91-93° 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, 67.26; H, 8.30; N, 4.98.

Example 252

(2S,3S,4S,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 (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane using the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography, the desired compound (R_f 0.54, 10% methanol in chloroform) as a white solid, m.p. 75-77° C. Mass spectrum: $(M + H)^+$ = 867.

Example 253

(2S,3S,4S,5S,2'S,2"S)-2,5-Di-((2-hydroxy-3-methylpentanoyl)-amino)-3,4-dihydroxy-1,6-diphenylhexane.

L-2-Hydroxy-3-methylvaleric acid was coupled to the resultant compound of Example 171 using the diimide coupling procedure described in Example 55 to provide the desired compound (R_f 0.23, 10% methanol in chloroform) as a white solid, m.p. 226-230° C.
Anal. Calcd for $C_{30}H_{44}N_2O_6 \cdot 0.5H_2O$: C, 67.01; H, 8.44; N, 5.21. Found: C, 67.26; N, 8.30; N, 4.98.

Example 254

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

Using the procedures of Example 165 but replacing 4-(2-hydroxyethyl)morpholine with 3-(hydroxymethyl)-1-methylpiperidine provided the desired compound (R_f 0.30, 10% methanol in chloroform) as a white solid, m.p. 162-163. Mass spectrum: $(M + H)^+$ = 758.
Anal. Calcd for $C_{43}H_{59}N_5O_7 \cdot 0.5H_2O$: C, 67.34; H, 7.88; N, 9.13. Found: C, 67.40; H, 8.03; N, 8.69.

Example 255

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

Using the procedures of Example 165 but replacing 4-(2-hydroxyethyl)morpholine with 2-(hydroxymethyl)-1-methylpiperidine provided the desired compound (R_f 0.40, 10% methanol in chloroform) as a white solid, m.p. 160-161. Mass spectrum: $(M + H)^+$ = 758.
Anal. Calcd for $C_{43}H_{59}N_5O_7 \cdot 0.5H_2O$: C, 67.34; H, 7.88; N, 9.13. Found: C, 67.15; H, 7.77; N, 8.91.

Example 256

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

Using the procedure of Example 190C but replacing the resultant compound of Example 173 with the resultant compound of Example 140 provided the desired compound as a white solid, m.p. >260. Mass spectrum: $(M + H)^+ = 685$.
Anal. Calcd for $C_{37}H_{48}N_8O_4 \cdot 2H_2O$: C, 61.65; H, 7.27; N, 15.54. Found: C, 60.47; H, 6.70; N, 15.30.

Example 257

A. 2-(t-Butyloxycarbonyl)methyl-3-methylbutanoic Acid.

The resultant compound of Example 235B was hydroyzed according to the procedure of Example 6D except that excess 30% hydrogen peroxide was included in the reaction mixture to provide the crude desired compound.

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

The resultant compound of Example 257A was coupled to the resultant compound of Example 232 using the carbodiimide coupling procedure of Example 55 to provide, after silica gel chromatography using a gradient of 1-5% methanol in chloroform, the desired compound in 22% yield.

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

The resultant compound of Example 257B (45 mg) was treated with 1.5 ml of 2:1 dichloromethane/trifluoroacetic acid. After 4 h at ambient temperature, the solution was concentrated in vacuo to provide 28 mg (55%) of the desired compound as an off-white solid, m.p. 208-210 °C.

Example 258

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

Using the procedures of Example 223A and Example 223B but replacing 3-(3-pyridinyl)acrylic acid with 3-(2-pyridinyl)acrylic acid and replacing the resultant compound of Example 173 with the resultant compound of Example 140 provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound (35%, R_f 0.6, 10% methanol in chloroform) as a white solid, m.p. 216-218 °C. Mass spectrum: $(M + H)^+ = 735$

Example 259

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

Using the procedure of Example 226 but replacing (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane with the resultant compound of Example 140 and replacing t-butylisocyanate with benzylisocyanate provided, after silica gel chromatography using 3% methanol in chloroform, the desired compound (64%, R_f 0.7, 10% methanol in chloroform) as a white solid, m.p. 238-238.5° C. Mass spectrum: $(M + H)^+ = 735$

Example 260

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

A solution of 34 mg of triphosgene in 2 ml of tetrahydrofuran was cooled under N_2 atmosphere to -78° C and treated over a period of 2 min with a precooled (-78° C) solution of 80 mg of the resultant compound of Example 140 and 40 µl of 4-methylmorpholine in 1 ml of tetrahydrofuran. After 30 min, the solution was treated with a solution of 37 mg of 2-(aminomethyl)pyridine and 40 µl of 4-methylmorpholine in 1 ml of tetrahydrofuran. The resulting solution was allowed to warm to -10° C over a 2 hour period, after which it was concentrated in vacuo. Silica gel chromatography of the residue using a gradient of 3% methanol in chloroform-4.5% methanol/4.5% isopropylamine in chloroform provided 80 mg (64%) of the desired compound (R_f 0.46, 4.5% methanol/4% isopropylamine in chloroform) as a white solid, m.p. 198-199° C. Mass spectrum: $(M + H)^+ = 737$.

Example 261

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

Using the procedure of Example 260 but replacing 2-(aminomethyl)pyridine with 3-(aminomethyl)-pyridine provided, after silica gel chromatography using a gradient of 3% methanol in chloroform-4.5% methanol/4.5% isopropylamine in chloroform a 60% yield of the desired compound (R_f 0.3, 4.5% methanol/4% isopropylamine in chloroform) as a white solid, m.p. 238-239° C. Mass spectrum: $(M + H)^+ = 737$.

Anal. Calcd for $C_{42}H_{52}N_6O_6 \cdot H_2O$: C, 66.82; H, 7.21; N, 11.13. Found: C, 67.07; H, 6.98; N, 11.12.

Example 262

(2S,3S,4S,5S,2′S,2″S)-2,5-Di-((2-((methoxy)-methoxy)-3-methylpentanoyl)-amino)-3,4-dihydroxy-1,6-diphenylhexane.

Using the procedure of Example 253 but replacing L-2-hydroxy-3-methylvaleric acid with L-2-(-(methoxy)-methoxy)-3-methylvaleric acid provided, after silica gel chromatography using 20% ethyl acetate in hexane, the desired compound (88%, R_f 0.18, 20% ethyl acetate in hexane) as a white solid, m.p. 190-194° C. Mass spectrum: $(M + H)^+ = 617$.

Example 263

3,6-Diamino-2,8-dimethyl-5-hydroxy-4,4-difluorononane.

Using the procedures described in detail in Example 181, and replacing Boc-L-cyclohexylalaninal with Boc-L-leucinal provided the desired compound. Mass spectrum: M^+ = 238.

Example 264

3,6-Bis-(Cbz-valinyl-amino)-2,8-dimethyl-5-hydroxy-4,4-difluorononane.

Using the procedure described in Example 182, the product from Example 263 was coupled to Cbz-Val to give the desired compound (56%). Mass spectrum: $(M+H)^+$ = 705. ^1H NMR ($CDCl_3$) δ0.82 (m, 12H), 3.90 (m, 1H), 4.02 (m, 1H), 4.30 (m, 1H), 4.55 (m, 1H), 5.02 (s, 4H), 5.80 (br d, 1H), 7.20 (br d, 1H), 7.35 (m, 10H), 7.70 (br d, 1H).

Example 265

3,6-Bis-(Cbz-valinyl-amino)-2,8-dimethyl-5-oxo-4,4-difluorononane.

Using the procedure described in Example 183, the product from Example 264 was oxidized to provide the desired product (93%). Mass spectrum: $(M+H)^+$ = 703. ^1H NMR ($CDCl_3$): δ0.8 (m, 1,12H), 3.90 (m, 1H), 4.02 (m, 1H), 4.65 (m, 1H), 4.80 (m, 1H), 5.05 (s, 4H), 7.35 (m, 12H), 7.95 (br d, 1H), 8.42 (br d, 1H).

Example 266

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

Using the procedure described in Examples 181A and 181B but replacing Boc-L-cyclohexylalaninal with phenylalaninal provided the desired product. Mass spectrum: M^+ = 299.

B. 4(S)Benzyl-5(R)-(3′(3′,3′-difluoro-2′-oxo-1′-phenyl-propyl))-2-oxazolidinone.

The hydrolysis of the resultant compound of Example 266A by lithium hydroxide in aqueous dioxane provided the corresponding acid, which was condensed with N,O-dimethyl-hydroxylamine with EDAC to give the corresponding amide. The amide was dissolved in THF and reacted with 3 equivalents of benzylmagnesium chloride to give the desired compound (88%). Mass spectrum: M^+ = 345. ^1H NMR ($CDCl_3$) δ2.82 (dd, 1H), 33.0 (dd, 1H), 4.07 (m, 2H), 4.15 (m, 1H), 4.70 (m, 1H), 7.15-7.38 (m, 10H).

C. 2,5-Diamino-1,6-diphenyl-3,3-difluoro-4-hydroxyhexane.

Using the resultant compound from Example 266B and the procedures described in Example 181D, 181E, and 181F provided the desired compound. Mass spectrum: M^+ = 320.

Example 267

2,5-Bis-(Cbz-valinyl-amino)-1,6-diphenyl-3,3-difluoro-4-hydroxyhexane.

Using the resultant compound from Example 266C and the procedure described in Example 182, the desired product was obtained in 70% yield. Mass spectrum: $(M+H)^+$ = 787. ^1H NMR ($CDCl_3$) δ0.60-0.80 (m, 12H), 5.02 (s, 4H), 6.05 (br d, 1H), 6.95, 1H), 7.10-7.35 (m, 10H), 7.50 (br d, 1H), 7.95 (br d, 1H).

Example 268

2,5-Bis-(2-pyridyl-methoxycarbonyl-valinyl-amino)-1,6-diphenyl-3,3-difluoro-4-hydroxyhexane.

Using the resultant compound from Example 266C and the procedure described in Example 182, but replacing Cbz-Val with 2-pyridinyl-methoxycarbonyl-valine provided the desired compound in 74% yield. $(M+H)^+$ = 789, ^1H NMR ($CDCl_3$) δ0.60-0.75 (m, 12H), 1.75 (m, 1H), 1.88 (m, 1H), 3.80 (m, 2H), 4.62 (m, 1H), 4.80 (m, 1H), 5.08 (s, 2H), 5.10 (s, 2H), 6.10 (br d, 1H), 7.05-7.40 (m, 15H), 7.50 (br d, 1H), 7.80 (m, 2H), 8.0 (br d, 1H), 8.52 (m, 2H).

Example 269

5-(2-Pyridinyl-methoxycarbonyl-valinyl-amino)-2-amino-1,6-diphenyl-3,3-difluoro-4-hydroxyhexane.

Using the resultant compound from Example 266C and reacting with the p-nitrophenyl ester of 2-pyridinyl-methoxycarbonyl-valine in DMF provided the desired compound in 69% yield. Mass spectrum: $(M+H)^+$ = 555. ^1H NMR ($CDCl_3$) δ0.90(d, 3H), 1.0 (d, 3H), 2.15 (m, 1H), 2.45(m, 1H), 2.80-3.20 (m, 4H), 3.82 (m, 1H), 4.05 (m, 1H), 4.58 (m, 1H), 5.27 (s, 2H), 5.50 (br d, 1H), 6.50 (br d, 1H), 7.10-7.40 (m, 12H), 7.70 (m, 1H), 8.60 (d, 1H).

Example 270

2-(t-Butylacetyl-amino)-5-(2-pyridinyl-methoxycarbonyl-valinyl-amino)-1,6-diphenyl-3,3-difluoro-4-hydroxyhexane.

Reaction of the resultant compound from Example 269 with t-butylacetyl chloride in dichloromethane and 1.1 equivalent of triethylamine provided the desired compound in 77% yield. Mass spectrum: $(M+H)^+$ = 653. ^1H NMR ($CDCl_3$): δ0.80 (s, 9H), 0.82 (d, 3H), 0.93 (d, 3H), 1.83 (q, 2H), 2.12 (m, 1H), 2.70-3.20 (m, 4H), 3.80 (m, 1H), 3.95 (m, 1H), 4.55 (m, 1H), 4.80 (m, 1H), 5.20 (s, 2H), 5.35 (br d, 1H), 6.50 (br d, 1H), 7.10-7.35 (m, 13H), 7.70 (m, 1H), 8.60 (br d, 1H).

Example 271

2-(N-Propylsulfonylamino)-5-(2-pyridinyl-methoxycarbonyl-valinyl-amino)-3,3-difluoro-4-hydroxyhexane.

Reaction of the resultant compound from Example 269 and 1 equivalent of propane-sulfonyl chloride and 1.1 equivalent of triethylamine provided the desired product in 65% yield. Mass spectrum: $(M+H)^+$ = 661. ^1H NMR ($CDCl_3$) δ0.80 (d, 3H), 0.88 (m, 2H), 0.95 (d, 3H), 1.10 (t, 3H), 2.0 (m, 3H), 2.40 (m, 2H), 2.85-3.15 (m, 4H), 3.30 (m, 1H), 3.50 (m, 1H), 3.95 (m, 1H), 4.90 (m, 1H), 5.25 (m, 3H), 6.12 (br d, 1H), 7.20 (m, 12H), 7.70 (m, 1H), 8.60 (m, 1H).

Example 272

A. 4(S)-Benzyl-5(R)-(3′(3′,3′-difluoro-2′-hydroxy-1′-phenyl-propyl)-2-oxazolidinone.

To a solution of 1 gm of the resultant compound from Example 266B in 20 ml of dry THF was added two equivalents of DIBAH in toluene at -78° C. After 1 hr, the reaction was quenched by careful addition of water. The reaction mixture was acidified with 1N HCl and extracted with EtOAc (3 x 5 ml), washed with satd. brine and dried with anhy. Na_2SO_4. Concentration and purification by SiO_2 column chromatography (20% EtOAc/CH_2Cl_2) provided 850 mg of pure product. Mass spectrum: M^+ = 347. ^1H NMR ($CDCl_3$): δ2.05 (d, 1H), 2.80-3.10 (m, 4H), 4.20 (m, 1H), 4.30 (m, 1H), 4.70 (m, 1H), 5.0 (br s, 1H), 7.30 (m, 10H).

B. 5-Benzyloxycarbonylamino-3,3-difluoro-2,4-dihydroxy-1,6-diphenylhexane.

To a solution of 100 mg of the resultant compound from Example 272A in 5 ml of dioxane and 5 ml of water was added 226 mg of barium hydroxide octahydrate. After refluxing for 3 hr and cooled to RT, the solution was filtered and concentrated in *in vacuo*. The crude material was dissolved in CH_2Cl_2 and 1.2 equivalent of Cbz-NOS was added and the mixture was stirred at RT overnight. Concentration and purification by SiO_2 column chromatography (20% EtOAc/CH_2Cl_2) provided 120 mg of product. Mass spectrum: M^+ = 439.

Example 273

5-Cbz-valinyl-amino-3,3-difluoro-2,4-dihydroxy-1,6-diphenylhexane.

The resultant compound from Example 272B was deprotected by hydrogenolysis (Pd/C, H_2) and coupled to Cbz-Val-OH using the procedure described in Example 182 to provide the desired product (72%). Mass spectrum: $(M+H)^+$ = 539. ^1H NMR ($CDCl_3$): δ0.75 (d, 3H), 0.88 (d, 3H), 2.15 (m, 1H), 2.70-3.05 (m, 4H), 3.88 (m, 1H), 4.0-4.20 (m, 2H), 4.40 (m, 1H), 4.50 (m, 1H), 5.05 (s, 2H), 5.10 (d, 1H), 6.46 (br d, 1H), 7.30 (m, 15H).

Example 274

5-Cbz-valinyl-amino-3,3-difluoro-1,6-diphenyl-4-hydroxy-2-oxo-hexane.

Oxidation of the resultant compound from Example 273 with sodium dichromate in acetic acid provided

the desired product. ^{1}H NMR ($CDCl_3$): δ0.8 (d, 3H), 0.9 (d, 3H), 2.0 (m, 1H), 2.80 (m, 1H), 3.26 (m, 1H), 3.90 (m, 1H), 4.0 (br s, 3H), 5.0 (br s, 3H), 6.20 (br s, 1H), 7.25 (m, 15H).

Example 275

A. 4(S)-Benzyl-5(R)-(3′(3′,3′-difluoro-2′-methanesulfonyloxy-1′-phenyl-propyl)-2-oxazolidinone.

To a solution of 250 mg of the resultant product from Example 272A in 5 ml of CH_2Cl_2 was added 0.136 ml of triethylamine and 0.065 µl of methanesulfonyl chloride. After 2 hr at RT the mixture was poured into satd. brine and extracted with CH_2Cl_2 (3 x 30 ml), dried and concentrated. SiO_2 column chromatography (10% EtOAc/CH_2Cl_2) provided 203 mg of product. ^{1}H NMR ($CDCl_3$): δ2.32 (s, 3H), 2.80-3.30 (m, 4H), 4.27 (m, 1H), 4.72 (m, 1H), 5.02 (br s 1H), 5.25 (m, 1H), 7.30 (m, 10H).

B. 4(S)-Benzyl-5(R)-(3′(3′,3′-difluoro-1′-phenyl-trans-propenyl)-2-oxazolidinone.

To a solution of 200 mg of the resultant product from Example 275A in 10 ml of toluene as added 2 equivalent of DBU. After refluxing for 2 hr, cooled to RT the crude product was purified by SiO_2 column chromatography to provide 77 mg of product. ^{1}H NMR ($CDCl_3$): δ2.80-3.05 (m, 2H), 4.15 (m, 1H), 4.50 (m, 1H), 5.10 (br s, 1H), 6.20 (m, 1H), 7.05 (m, 1H), 7.30 (m, 10H).

C. 4(S)-Benzyl-5(R)-(3′(3′,3′-difluoro-1′-phenyl-propyl)-2-oxazolidinone.

The resultant compound from Example 275B was dissolved in 2 ml of methanol and stirred under hydrogen with 10% Pd/C as catalyst. After 15 minutes, filtration and concentration provided the desired product (100%). ^{1}H NMR ($CDCl_3$): δ2.30 (m, 2H), 2.80-3.00 (m, 4H), 4.20 (m, 1H), 4.32 (m, 1H), 7.30 (m, 10H).

D. 5-Benzyloxycarbonyl-valinyl-amino-3,3-difluoro-1,6-diphenyl-4-hydroxyhexane.

Opening of the oxazolidinone ring of the resultant compound from Example 275C with barium hydroxide and coupling to Cbz-Val-OH using the procedure of Example 182 provided the desired product (70%). ^{1}H NMR ($CDCl_3$): δ0.80 (d, 3H), 0.90 (d, 3H), 2.10 (m, 3H), 2.70 (m, 2H), 3.0 (m, 2H), 3.70 (m, 2H), 3.95 (m, 1H), 4.30 (m, 1H), 5.10 (br s, 2H), 5.15 (br d, 1H), 6.45 (br d, 1H), 7.10-7.40 (m, 15H).

Example 276

5-Benzyloxycarbonyl-valinyl-amino-3,3-difluoro-1,6-diphenyl-4-oxo-hexane.

Oxidation of the resultant compound from Example 275D using sodium dichromate in acetic acid provided the desired compound (70%). ^{1}H NMR ($CDCl_3$): δ0.82 (d, 3H), 0.90 (d, 3H), 2.05 (m, 1H), 2.35 (m, 2H), 2.80 (t, 2H), 2.90 (m, 1H), 3.30 (m, 1H), 3.90 (m, 1H), 5.10 (s, 2H), 5.12 (br d, 1H), 5.30 (m, 1H), 6.10 (br d, 1H), 7.10-7.35 (m, 15H).

Example 277

5-Cbz-valinyl-amino-3,3-difluoro-4-hydroxy-1,6-diphenyl-2-isobutylcarbonyloxy-hexane.

To a solution of the resultant compound from Example 273 in CH_2Cl_2 was added 2 equivalents of triethylamine and 1.5 equivalents of isovaleryl chloride. After 2 hr at RT, the mixture was poured into dil. HCl, extraction with EtOAc (3 x 50 ml), washed with satd. $NAHCO_3$ and brine, dried and concentrated. Purification by SiO_2 column chromatography (10% EtOAc/CH_2Cl_2) provided the desired product.

Example 278

5-Cbz-valinyl-amino-3,3-difluoro-4-hydroxy-1,6-diphenyl-2-isopropylamino-carbonyloxy-hexane.

To a solution of the resultant compound from Example 273 in CH_2Cl_2 was added 1.5 equivalent of isopropylisocyanate and excess DMAP. The solution was stirred at RT overnight. The reaction mixture was poured into dil. HCl and extracted with EtOAc (3 x 50 ml), washed with brine, dried and concentrated. Purification by SiO_2 column chromatography (15% EtOAc/CH_2Cl_2) provided the desired product.

Example 279

5-Cbz-valinyl-amino-3,3-difluoro-4-hydroxy-1,6-diphenyl-2-methoxy-hexane.

To the resultant compound of Example 272A was added 2.2 eq. of sodium hydride in DMF at 0 °C, followed by the addition of methyl iodide. After 2 h at RT, conc. and purified the product by silica gel column chromatography. The resultant product was hydrolyzed with barium hydroxide to open the oxazolidinone ring and coupled to Cbz-Val-OH using the procedure described in Example 182, to give the desired product.

Example 280

5-Cbz-valinyl-amino-3,3-difluoro-4-oxo-1,6-diphenyl-2-methoxy-hexane.

The resultant compound of Example 279 was oxidized with $Na_2Cr_2O_7$ in acetic acid to provide the desired product.

Example 281

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

A mixture of 171 µL (1.23 mmol) of triethylamine, 137 mg (1.23 mmol) of 2-mercaptopyridine and 200 mg (0.308 mmol) of the resultant compound of Example 196A in 1.0 mL of dry DMF was stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 42 cm silica gel column eluted with 50% ethyl acetate in hexane to give 211 mg (78.6% yield) of the title compound; FAB MS M/Z: 873 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure.

B. N,N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis(2'-pyridylthio)-2,5-diamino-3,4-hexanediol.

A solution of 200 mg (0.23 mmol) of the resultant compound of Example 281A in 7.0 mL of methanol containing 1 mL of 0.1 N aqueous hydrochloric acid was stirred at 40° C overnight. The solvent was evaporated under reduced pressure. The residue was dissolved in methylene chloride/methanol and the resultant solution was washed with aqueous sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give the title compound as a white powder; FAB MS M/Z: 833 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{42}H_{52}N_6O_8S_2$: C, 60.58; H, 6.29; N, 10.10. Found: C, 60.15; H, 6.29; N, 9.97.

Example 282

A. N, N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis-((1'-methyl-2'-imdazoyl)thio)-2,5-diamino-3,4-O-isopropylidenehexanediol.

To a solution of 196 mg (1.72 mmol) of 2-mercapto-1-methylimidazole and 280 mg (0.431 mmol) of the resultant compound of Example 196A in 1.5 mL of dry DMF was added 240 µL (1.72 mmol) of triethylamine. The resultant solution stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 35 cm silica gel column eluted with 10% isopropyl alcohol in toluene to give 287 mg (81% yield) of the title compound; FAB MS M/Z: 879 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure.

B. N,N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis-((1'-methyl-2'-imdazoyl)thio)-2,5-diamino-3,4-hexanediol

A solution of 280 mg (0.32 mmol) of the resultant compound of Example 282A in 7.0 mL of methanol containing 0.1 mL of concentrated aqueous hydrochloric acid was stirred at 40° C for 40 h. The solvent was evaporated under reduced pressure and methanol was added to the residue. The methanol was evaporated and the residue was treated with aqueous sodium bicarbonate solution. The precipitate which formed was filtered to give 148 mg of the title compound; FAB MS M/Z: 839 $(M+H)^+$, 861 $(M+Na)^+$. ^1H NMR (d_6-DMSO) δ 0.79 (d, 6H), 0.84 (d, 6H), 2.00 (m, 2H), 3.12 (d, 4H), 3.50 (s, 6H), 3.97 (dd, 2H), 4.08 (br dd, 2H), 5.0 (q, 4H), 5.44 (br m, 2H), 6.89 (d, 2H), 7.19 (d, 2H), 7.23 (d, 2H), 7.34 (m, 6H), 7.70 (d, 2H).

Example 283

N, N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis-(2'-pyrimidinylthio)-2,5-diamino-3,4-O-isopropylidenehexanediol

A mixture of 185 µL (1.335 mmol) of triethylamine, 150 mg (1.335 mmol) of 2-mercaptopyrimidine

(commercially available from Aldrich Chemical Co.) and 217 mg (0.333 mmol) of the resultant compound of Example 196A in 2.0 mL of dry DMF was stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 35 cm silica gel column eluted with 10% isopropyl alcohol in toluene to give 219 mg (75% yield) of the title compound; FAB MS M/Z: 875 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{43}H_{54}N_8O_8S_2$: C, 59.04; H, 6.18; N, 12.81. Found: C, 58.69; H, 6.20; N, 12.61.

B. N,N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis(2'-pyrimidinylthio)-2,5-diamino-3,4-hexanediol

A solution of the resultant compound of Example 283A (205 mg, 0.234 mmol) in 10.0 mL of methanol containing 0.10 mL of concentrated aqueous hydrochloric acid was stirred at 40° C for 7.5 h. The reaction mixture was stirred for approximately 64 h at ambient temperature. Additional methanolic hydrochloric acid (5 mL) was added and the reaction mixture was then stirred for 8 h at 40° C. The solvent was evaporated under reduced pressure and methanol was added to the residue. The methanol was evaporated. The residue was dissolved in chloroform and the resultant solution was washed with aqueous sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 198 mg of the crude product. The crude product was purified by flash chromatography on a 1.5 X 37 cm silica gel column eluted with 5% methanol in methylene chloride to give 28 mg (14% yield) of the title compound; FAB MS M/Z: 835 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{42}H_{52}N_6O_8S_2 + H_2O$: C, 56.33; H, 6.10; N, 13.14. Found: C, 56.47; H, 5.89; N, 13.13.

Example 284

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

A mixture of 190 µL (1.366 mmol) of triethylamine, 158 mg (1.23 mmol) of cyclohexylmercaptan and 222 mg (0.341 mmol) of the resultant compound of Example 196A in 3.0 mL of dry DMF was stirred at ambient temperature for 2 days. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 40 cm silica gel column eluted with 40% ethyl acetate in hexane to give 211 mg (78.6% yield) of the title compound; FAB MS M/Z: 883 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{47}H_{71}N_4O_8S_2$: C, 63.95; H, 7.94; N, 6.35. Found: C, 63.86; H, 8.00; N, 6.31.

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

A solution of the resultant compound of Example 284A (120 mg, 0.136 mmol) in 3.0 mL of trifluoroacetic acid was cooled in an ice bath. To the cooled solution was added 3 mL of water and the solution was stirred for 5 h at 0° C. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on a 1.0 X 37 cm silica gel column eluted with 20% ethyl acetate in methylene chloride, followed by 40% ethyl acetate in methylene chloride to give the title compound; FAB MS M/Z: 843 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{44}H_{66}N_6O_8S_2$: C, 62.71; H, 7.84; N, 6.65. Found: C, 62.69; H, 7.84; N, 6.64.

Example 285

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

A mixture of 204 µL (1.47 mmol) of triethylamine, 163 mg (1.47 mmol) of 4-mercaptopyridine and 239 mg (0.368 mmol) of the resultant compound of Example 196A, in 2.0 mL of dry DMF was stirred at 5° C for 1 h and at ambient temperature for 4 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 43 cm silica gel column eluted with 5% methanol in methylene chloride to give 220 mg (68.6% yield) of the title compound; FAB MS M/Z: 873 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{45}H_{56}N_6O_8S_2$: C, 61.86; H, 6.53; N, 9.62. Found: C, 61.49; H, 6.35; N, 9.57.

B. N,N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis-(4'-pyridylthio)-2,5-diamino-3,4-hexanediol

A solution of the resultant compound of Example 285A, in 5.0 mL of methanol containing 40µL of concentrated aqueous hydrochloric acid was stirred at 40° C for 2 days. While the reaction mixture was stirring additional aliquots (total 80 µL) of concentrated hydrochloric acid were added. The reaction mixture was allowed to stir over the weekend at ambient temperature and then another drop of concentrated hydrochloric acid was added. After stirring for a total of 4.5 days the solvent was evaporated under reduced pressure. Methanol was added to the residue and evaporated off under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 45 cm silica gel column eluted with 10% methanol in methylene chloride, followed by 20% methanol in methylene chloride . The material obtained from the column was treated with 10 mL of methanol containing 0.10 mL of concentrated aqueous hydrochloric acid at 40° C for 5.5 h. The solvent was evaporated under reduced pressure. Methanol was added to the residue and evaporated off under reduced pressure.The residue was dissolved in methylene chloride/methanol and the resultant solution was washed with dilute aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give 13 mg (6.2% yield) of the title compound; FAB MS M/Z: 833 $(M+H)^+$. ^1H NMR (CD_3OD) δ 0.91 (d, 6H), 0.93 (d, 6H), 2.01 (m, 2H), 3.20 (br m, 4H), 3.90 (d, 2H), 4.27 (m, 2H), 4.77 (m, 2H), 5.11 (s, 4H), 7.25-7.40 (m, 14H), 8.23 (d, 4H)..

Example 286

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

A solution of 157 mg (1.74 mmol) of t-butylmercaptan and 283 mg (0.435 mmol) of the resultant compound of Example 196A in 2.0 mL of dry DMF was cooled in an ice bath. To the cooled solution added 242 µL (1.74 mmol) of triethylamine. The resultant solution was allowed to warm slowly to ambient temperature and it was stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 35 cm silica gel column eluted with 20% ethyl acetate in hexane, followed by 40% ethyl acetate in hexane to give 173 mg. (48% yield) of the title compound; FAB MS M/Z: 831 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{43}H_{66}N_4O_8S_2$: C, 62.17; H, 7.95; N, 6.74. Found: C, 62.34; H, 8.02; N, 6.74.

B. N,N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis-(t-butylthio)-2,5-diamino-3,4-hexanediol

A solution of the resultant compound of Example 286B (173 mg, 0.208 mmol) in 3.0 mL of trifluoroacetic acid containing 0.4 mL of water was stirred at 0° C for 4.5 h. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 39 cm silica gel column eluted with 50% ethyl acetate in hexane to give 78 mg (47.5% yield) of the title compound; FAB MS M/Z: 791 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure.

Analysis calculated for $C_{40}H_{62}N_4O_8S_2$: C, 60.76; H, 7.85; N, 7.09. Found: C, 60.50; H, 7.93; N, 7.03.

Example 287

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

A solution of 283 mg (0.435 mmol) of the resultant compound of Example 196A, in 2.0 mL of dry DMF was cooled in an ice bath. To the cooled solution was added 108 mg (1.74 mmol) of ethylmercaptan followed by 242 µL (1.74 mmol) of triethylamine. The resultant solution was stirred at 0 °C for 4.5 h, allowed to warm slowly to ambient temperature and it was stirred at ambient temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 37 cm silica gel column eluted with 50% ethyl acetate in hexane to give 116 mg (34.5% yield) of the title compound; FAB MS M/Z: 775 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{39}H_{58}N_4O_8S_2$: C, 60.46; H, 7.49; N, 7.24. Found: C, 60.24; H, 7.33; N, 7.16.

B. N,N-Bis-(Cbz-valinyl)-(2R, 3R, 4R, 5R)-1,6-bis-(ethylthio)-2,5-diamino-3.4-hexanediol

A solution of the resultant compound of Example 287A (116 mg, 0.15 mmol) in 3.0 mL of trifluoroacetic acid containing 0.3 mL of water was stirred at 0 °C for 2.5 h. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on a 1.0 X 35 cm silica gel column eluted with 50% ethyl acetate in hexane to give the title compound; FAB MS M/Z: 735 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{36}H_{54}N_4O_8S_2$: C, 58.86; H, 7.36; N, 7.63. Found: C, 58.58; H, 7.33; N, 7.52.

Example 288

A. (6S,7R,8R,9S)-6,9-Di-((N-toluenesulfonyl)amino)-7,8-O-isopropylidenetetradecanediol

To a solution of 1.175 g (5.715 mmol) of cuprous bromide-dimethylsufide complex in 8 mL of anhydrous, oxygen-free THF at -40 °C was added 4.57 mL (11.43 mmol) of 2.5 M n-butyl lithium. The solution was stirred for 0.5 h at -40 °C and then cooled to -60 °C. A solution of (2S,3R,4R,5S)-1,2:5,6-diimino-3,4-O-isopropylidenehexanediol (703 mg, 1.43 mmol(Y.L. Merrer, et al, *Heterocycles*, 1987, *25*, 541-548)) in ~16 mL of anhydrous, oxygen-free THF was added. The solution was allowed to warm slowly to approximately -25 °C and stirred for 4 h at that temperature. The reaction mixture was treated with 10% concentrated ammonium hydroxide in saturated ammonium chloride solution and the aqueous mixture was extracted with diethyl ether. The organic solution was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.0 X 27 cm silica gel column eluted with 20% ethyl acetate in hexane to give 0.414 g (47.6% yield) of the title compound; DCI/NH_3 MS M/Z: 626 $(M+NH_4)^+$; The 300 MHz ^1H NMR spectrum was consistent with the assigned structure.

B. N,N-Bis-(Cbz-valinyl)-(2S, 3R, 4R, 5S)-6,9-diamino-7,8-O-isopropylidenetetradecanediol

The resultant compound of Example 288A, in 3 mL of anhydrous diethyl ether was added to ~75 mL of liquid ammonia and small pieces of sodium metal were added until a blue color persisted for 5 minutes.

The reaction was quenched with ammonium chloride and the ammonia was evaporated. The residue was dissolved in diethyl ether and the ether solution was washed with dilute aqueous ammonium hydroxide and brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the intermediate 6,9-diamino compound. The diamine (159 mg, 0.53 mmol) was dissolved in 5 mL of THF and the THF solution was cooled in an ice bath. To the cooled solution was added 532 mg (2.12 mmol) of N-carbobenzyloxyvaline, followed by 406 mg (2.12 mmol) of N-ethyl-N'-(dimethylaminopropyl)carbodiimide and 295 µL (2.12 mmol) of triethylamine. The reaction mixture was allowed to gradually warm to ambient temperature and was stirred at ambient temperature overnight. The solvent which had evaporated from the reaction mixture was replaced with 5 mL of THF and the mixture was stirred for 2 h. The reaction mixture was then diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a 1.5 X 35 cm silica gel column eluted with 30% ethyl acetate to to give 83 mg (20% yield) of the title compound; DCI/NH_3 MS M/Z: 784 $(M+NH_4)^+$, 767 $(M+H)^+$; The 300 MHz ^1H NMR spectrum is consistent with the assigned structure. Analysis calculated for $C_{43}H_{66}N_4O_8$: C, 67.36; H, 8.62; N, 7.31. Found: C, 67.68; H, 9.02; N, 7.27.

C. N,N-Bis-(Cbz-valinyl)-(6S, 7R, 8R, 9S)-6,9-diamino-7,8-tetradecanediol

A solution of the resultant compound of Example 288B (80 mg, 0.1 mmol) in 3.0 mL of trifluoroacetic acid containing 0.3 mL of water was stirred at 0 °C for 4.75 h. The solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on a 1.0 X 22 cm silica gel column eluted with 50% ethyl acetate in hexane to give 51 mg (45% yield) of the title compound; ^1H NMR ($CDCl_3$) δ 0.86 (t, 6H), 0.92 (d, 6H), 0.98 (d, 6H), 1.20-1.33 (br m, 12H), 1.51-1.61 (br m, 2H), 2.12-2.22 (m, 2H), 3.39 (br s, 1H), 3.55 (br s, 1H), 3.82-3.92 (m, 2H), 3.95 (dd, 2H), 5.10 (s, 4H), 5.10 (s, 4H), 5.20 (br d, 2H), 6.23 (d, 2H), 7.30-7.40 (m, 10H).Analysis calculated for $C_{40}H_{62}N_4O_8$: C, 66.12; H, 8.54; N, 7.71. Found: C, 66.04; H, 8.59; N, 7.70.

Example 289

A. (2S,3R,4R,5S)-1,6-Diphenyl-2,5-di-((N-toluenesulfonyl)amino)-3,4-O-isopropylidenehexanediol

To a stirred suspension of 411 mg (2.0 mmol) of CuBr-Me_2S in 2 mL of ether at 0 °C was added 3.08 ml (4.0 mmol) of 1.3 M phenyllithium in ether/cyclohexane. After 30 minutes, a suspension of 246 mg (0.50 mmol) of (2S,3R,4R,5S)-1,2:5,6-diimino-3,4-O-isopropylidenehexanediol (703 mg, 1.43 mmol (Y.L. Merrer, et al, *Heterocycles*, 1987, *25*, 541-548)) was added in 20 mL. After 80 minutes, the reaction mixture was quenched with 10% NH_4OH saturated with NH_4Cl. The ether layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. Chromatography of the residue on silica gel with 7:3/hexane:EtOAc afforded 280 mg (86.4%) of the title compound. MS m/z 649 $(M+H^+)$

B. N,N-Bis-(Cbz-valinyl)-(2S, 3R, 4R, 5S)-1,6-diphenyl-2,5-diamino-3,4-hexanediol

The resultant compound of Example 289A was converted to the title compound in a manner analogous to that described in Examples 288B and 288C.

Example 290

A. N,N-Bis-(Cbz-valinyl)-(2S, 3R, 4R, 5S)-1,6-di-(4-(methoxymethyloxy)phenyl)-2,5-diamino-3,4-hexanediol.

Using the procedures of Example 289, but subsituting 4-(methoxymethyloxy)phenyllithium for phenyllithium in Step A provided the desired product.

B. N,N-Bis-(Cbz-valinyl)-(2S, 3R, 4R, 5S)-1,6-di-(4-hydroxyphenyl)-2,5-diamino-3,4-hexanediol.

The resultant compound of Example 290A was hydrolyzed according to the procedure of Example 23B to provide the desired compound.

Example 291

2,4-Bis-(N-(Cbz-isoleucyl)amino)-1,5-diphenyl-3-hydroxypentane

The resultant compound of Example 12 (100 mg, 0.37 mmol), N-benzyloxycarbonyl-isoleucine p-nitrophenyl ester (428 mg, 1.1 mmol) and triethylamine (210 µL) were combined with 0.5 mL of dry acetonitrile and stirred together at ambient temperature for 0.5 h. Dry THF (1.0 mL) was added and the resultant solution was stirred at ambient temperature overnight. The reaction mixture was then diluted with 5 mL of THF and 5 mL of 3 M aqueous sodium hydroxide solution was added. The mixture was stirred at ambient temperature for 0.5 h and then it was extracted with 100 mL of methylene chloride. The organic solution was washed with 3 X 25 mL of 0.5 M aqueous sodium hydroxide solution and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue (319 mg) was dissolved in approximately 5 mL of chloroform and applied to a 1.0 X 40 cm column of 40 mesh silica gel. The column was eluted sequentially @ 5 p.s.i with 100 mL of chloroform, 100 mL of 0.5% methanol in chloroform and 100 mL of 1% methanol in chloroform to give 106 mg (37% yield) of the title compound: FAB MS M/Z: 765 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{45}H_{56}N_4O_7$: C, 70.65; H, 7.38; N, 7.32. Found: C, 70.35; H, 7.52; N, 7.21.

Example 292

2-(t-Butyloxycarbonylamino)-4-(N-(Cbz-isoleucyl)amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 11 (125 mg, 0.34 mmol), N-benzyloxycarbonyl-isoleucine p-nitrophenyl ester (196 mg, 0.51 mmol) and triethylamine (94 µL, 0.67 mmol) were combined with 1.0 mL of dry THF and stirred together at ambient temperature overnight. The reaction mixture was then heated at reflux temperature for 3 h. The cooled reaction mixture was then diluted with 5 mL of THF and 5 mL of 3 M aqueous sodium hydroxide solution was added. The mixture was stirred at ambient temperature for approximately 0.5 h. and was then diluted with chloroform. The chloroform solution was washed with 3 X 25 mL of 0.5 M aqueous sodium hydroxide solution and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue (227 mg) was taken up in approximately 5 mL of chloroform and applied to a 1.0 X 45 cm column of 40 mesh silica gel. The column was eluted @ 5-10 p.s.i. sequentially with 100 mL of chloroform, 100 mL of 0.5% methanol in chloroform and 100 mL of 1% methanol in chloroform to give 169 mg (81% yield) of the title compound; FAB MS M/Z: 618 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{36}H_{47}N_3O_6$: C, 69.99; H, 7.67; N, 6.80. Found: C, 69.26; H, 7.52; N, 6.61.

Example 293

A. 2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl α-bromoacetate.

The resultant compound of Example 70 (600 mg, 0.81 mmol) was dissolved in 8 mL of methylene chloride and 72 µL (0.9 mmol) of pyridine. The solution was cooled in an ice bath with stirring under a nitrogen atmosphere. α-Bromoacetyl bromide (181 mg, 0.9 mmol) was added in one portion and the ice bath was removed. The reaction mixture was stirred at ambient temperature for 3 h and then diluted with 150 mL of chloroform. The chloroform solution was washed with 150 mL of water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.

The residue (644 mg) was taken up in a mixture of chloroform and methanol and adsorbed onto approximately 1.5 g of 40 mesh silica gel *in vacuo* @ 40° C. The silica gel with the product adsorbed onto it was applied to a 1.0 X 40 cm column of 40 mesh silica gel and the column was eluted @ ~5 p.s.i. sequentially with 100 mL of chloroform and 100 mL of 1% methanol in chloroform to give 378 mg (55% yield) of the title compound; FAB MS M/Z: 859 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure.

B. 2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl (α-(4'-methyl-1'-piperazinyl)acetate

The resultant compound of Example 293A (175 mg, 0.204 mmol) and 1-methylpiperazine (44 mg, 0.44 mmol) were combined with 4 mL of freshly distilled THF and the reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 2 h. The reaction mixture was then concentrated under reduced pressure. The residue (218 mg) was taken up in appromimately 3 mL of 5% methanol in methylene chloride and applied to a 0.6 X 40 cm column of 40 mesh silica gel. The column was eluted @ ~10 p.s.i. sequentially with 50 mL of methylene chloride and 50 mL of 5% methanol in methylene chloride to give 170 mg (96% yield) of product. The product was dissolved in methylene chloride/methanol and adsorbed onto ~ 1g of 40 mesh silica gel. The silica gel containing the adsorbed product was applied to a 0.6 X 45 cm column of 40 mesh silica gel and the column was eluted @ ~10 p.s.i sequentially with 50 mL of methylene chloride, 50 mL of 0.5% methanol in methylene chloride, 50 mL of 1% methanol in methylene chloride, 50 mL of 2% methanol in methylene chloride, 50 mL of 3% methanol in methylene chloride, 50 mL of 4% methanol in methylene chloride and 50 mL of 5% methanol in methylene chloride to give 144 mg (82% yield) of the title compound; FAB MS M/Z: 877 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{50}H_{64}N_6O_8$: C, 68.47; H, 7.36; N, 9.58. Found: C, 68.32; H, 7.27; N, 9.54.

Example 294

2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl (α-1'-morpholinoacetate.

The resultant compound of Example 293A (198 mg, 0.231 mmol), and morpholine (43 mg, 0.5 mmol) were combined with 4 mL of freshly distilled THF and the reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 4 h. A drop of triethylamine was added and the reaction mixture was concentrated under reduced pressure. The residue (241 mg) was dissolved in methanol/methylene chloride and adsorbed onto ~ 500 mg of 40 mesh silica gel. The silica gel containing the adsorbed product was applied to a 0.6 X 40 cm column of 40 mesh silica gel and the column was eluted @ ~10 p.s.i. sequentially with 50 mL of chloroform, 50 mL of 1% methanol in chloroform, 50 mL of 2% methanol in chloroform and 50 mL of 3% methanol in chloroform to give 186 mg (93% yield) of the title compound; FAB MS M/Z: 864 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{49}H_{61}N_5O_9$: C, 68.11; H, 7.12; N, 8.11. Found: C, 67.99; H, 7.14; N, 8.09.

Example 295

A. 2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl 3-(chloromethyl)benzoate

The resultant compound of Example 70 (769 mg, 1.04 mmol) was combined with 3-(chloromethyl)-benzoyl chloride (395 mg, 2.09 mmol) and pyridine (165 mg, 2.09 mmol) in 10 mL of freshly distilled methylene chloride. The reaction mixture was stirred at ambient temperature under nitrogen for approximately 65 h and then diluted with 150 mL of chloroform. The chloroform solution was washed with 75 mL of water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue (1.59 g) was taken up in ~ 10 mL of methylene chloride and applied to a 1.5 X 45 cm column of 40 mesh silica gel. The column was eluted @ ~5 p.s.i. sequentially with 200 mL of methylene chloride, 200 mL of 0.5% methanol in methylene chloride and 200 mL of 1% methanol in methylene chloride to give 275 mg (30% yield) of the title compound; FAB MS M/Z: 889 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure.

B. 2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl 3-((4'-methyl-1'-piperazinyl)methyl)benzoate

The resultant compound of Example 295A (130 mg, 0.146 mmol) and 1-methylpiperazine (32 mg, 0.337 mmol) were combined with 4 mL of freshly distilled THF and the reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 2 h. The reaction mixture was then heated at reflux for 18 h under a nitrogen atmosphere and concentrated under reduced pressure. The residue (160 mg) was taken up in appromimately 2 mL of chloroform and applied to a 0.6 X 45 cm column of 40 mesh silica gel. The column was eluted @ 5-10 p.s.i. sequentially with 50 mL of methylene chloride, 50 mL of 1% methanol in methylene chloride, 50 mL of 2% methanol in methylene chloride, 50 mL of 3% methanol in methylene chloride, 50 mL of 4% methanol in methylene chloride and 50 mL of 5% methanol in methylene chloride to give 89 mg (60% yield) of the title compound; FAB MS M/Z: 953 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure. Analysis calculated for $C_{56}H_{68}N_6O_8$: C, 70.56; H, 7.19; N, 8.82. Found: C, 70.22; H, 7.13; N, 8.63.

Example 296

2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl 3-((1'-morpholino)methyl)benzoate

The resultant compound of Example 295A (133 mg, 0.15 mmol), and morpholine (26 mg, 0.30 mmol) were combined with 4 mL of freshly distilled THF and the reaction mixture was heated at reflux under a nitrogen atmosphere for 17 h. The reaction mixture was concentrated under reduced pressure. The residue (170 mg) was taken up in appromimately 1 mL of chloroform and applied to a 0.6 X 45 cm column of 40 mesh silica gel. The column was eluted @ 10 p.s.i. sequentially with 50 mL of chloroform, 50 mL of 1% methanol in chloroform, 50 mL of 2% methanol in chloroform and 50 mL of 3% methanol in chloroform to give 84 mg (60% yield) of the title compound; FAB MS M/Z: 940 $(M+H)^+$. Analysis calculated for $C_{55}H_{65}N_5O_9 + H_2O$: C, 68.94; H, 7.05; N, 7.31. Found: C, 69.15; H, 6.82; N, 7.27

Example 297

A. 4-(Chloromethyl)benzoyl chloride

Benzoic acid (20.0 g, 117 mmol) was suspended in 100 mL of freshly distilled methylene chloride with stirring under a nitrogen atmosphere. Approximately 2 drops of DMF was added to the suspension, followed by the dropwise addition of oxalyl chloride (29.7 g, 234 mmol) over a 0.5 h period. The reaction mixture was stirred at ambient temperature for 17 h. The reaction mixture was then concentrated in vacuo @ 45-50° C. Toluene (30 mL) was three times added to the residual oil and removed by azeotropic distillation. The oil was then distilled under reduced pressure to give 20.8 g (94% yield) of the title compound; b.p. 139-149° C (12 mm Hg); 1H NMR (CDCl3) d 4.63 (s, 2H), 7.54 (d, 2H), 8.12 (d, 2H).

B. 2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl 4-(chloromethyl)benzoate

The resultant compound of Example 70 (1.3 g, 1.76 mmol) was combined with 4-(chloromethyl)benzoyl chloride (1.0 g, 5.3 mmol) and pyridine (418 mg, 5.3 mmol) in 10 mL of freshly distilled methylene chloride. The reaction mixture was heated at reflux under nitrogen for approximately 10 h and then diluted with 150 mL of chloroform. The chloroform solution was washed with 75 mL of water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue (2.1 g) was taken up in ~ 10 mL of chloroform and applied to a 1.8 X 45 cm column of 40 mesh silica gel. The column was eluted @ ~5 p.s.i. sequentially with 200 mL of methylene chloride, 250 mL of 0.5% methanol in methylene chloride and 600 mL of 1% methanol in methylene chloride to give 721 mg (46% yield) of the title compound; FAB MS M/Z: 889 $(M+H)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure.

C. 2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl 4-((4'-methyl-1'-piperazinyl)methyl)benzoate

The resultant compound of Example 297B (200 mg, 0.225 mmol) and 1-methylpiperazine (45 mg, 0.45 mmol) were combined with 5 mL of freshly distilled THF and the reaction mixture was heated at 45° C under a nitrogen atmosphere for approximately 64 h. The reaction mixture was concentrated under reduced pressure. The residue (245 mg) was taken up in appromimately 2 mL of chloroform and applied to a 0.6 X 40 cm column of 40 mesh silica gel. The column was eluted @ 10 p.s.i. sequentially with 50 mL of chloroform and 50 mL of 1% methanol in methylene chloride to give 106 mg (37% yield) of the title compound; FAB MS M/Z: 953 $(M+H)^+$. Analysis calculated for $C_{56}H_{68}N_6O_8 + H_2O$: C, 9.25; H, 7.26; N, 8.65. Found: C, 69.06; H, 7.00; N, 8.60.

Example 298

2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl 4-((1'-morpholino)methyl)benzoate

The resultant compound of Example 297B (200 mg, 0.225 mmol), and morpholine (39 mg, 0.45 mmol) were combined with 5 mL of freshly distilled THF and the reaction mixture was heated at 45° C under a nitrogen atmosphere for approximately 64 h. The reaction mixture was concentrated under reduced pressure. The residue (249 mg) was taken up in appromimately 2 mL of chloroform and applied to a 0.6 X 45 cm column of 40 mesh silica gel. The column was eluted @ ~10 p.s.i. sequentially with 50 mL of 1% methanol in methylene chloride, 50 mL of 2% methanol in methylene chloride, 50 mL of 3% methanol in methylene chloride and 50 mL of 4% methanol in methylene chloride to give 163 mg (76% yield) of the title compound; FAB MS M/Z: 940 $(M+H)^+$. Analysis calculated for $C_{55}H_{65}N_5O_9 + H_2O$: C, 68.94; H, 27.05; N, 7.31. Found: C, 68.84; H, 6.80; N, 7.29.

Example 299

A. 2,4-Bis(t-butyloxycarbonylamino)-1,5-diphenyl-3-pentanol

To a stirred solution of the resultant compound of Example 11 (1.0 g, 2.7 mmol) in 20 mL of dichloromethane was added 0.77 g of di-t-butyldicarbonate. After 1 hour, 4 drops of diisopropylethylamine was added, and after 30 minutes, the reaction mixture was concentrated under reduced pressure. Chromatrography of the residue on a 1.5 x 45 cm column of silica gel with 200 mL of chloroform and then 200 mL of 99:1/chloroform:methanol afforded 1.19 g (94%) of the title compound. DCI/IBU MS M/Z: 471 $(M+H)^+$. The 300 MHz ^1H NMR was consistent with the assigned structure.

B. 2,4-Bis-(t-butyloxycarbonyl)amino)-1,5-diphenyl-3-pentanone

Oxalyl chloride (380 mg, 3.0 mmol) was dissolved in 45 mL of freshly distilled methylene chloride and the solution was cooled to -78° C under a nitrogen atmosphere. DMSO (469 mg, 6.0 mmol) was added to the stirred solution, followed 5 minutes later by a solution of 1.18 g (2.5 mmol) of the resultant compound of Example 299A, in 20 mL of methylene chloride. After the reaction mixture was stirred for 50 min at -78° C, 1.75 mL (12.5 mmmol) of triethylamine was added. The reaction mixture was stirred for 5 min at -78° C and then allowed to warm to ambient temperature and stirred at ambient temperature for 1 h. The reaction mixture was diluted with 100 mL of chloroform, washed with 100 mL of brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure.The residue was taken up in ~ 10 mL of methylene chloride and applied to a 1.0 X 45 cm column of silica gel. The column was eluted @ 5-10 p.s.i. with 100 mL of methylene chloride and 100 mL of 1% methanol in methylene chloride to give 1.02 g (87% yield) of the title compound; DCI/NH3 MS M/Z: 486 $(M+NH4)+$, 469 $(M+H)+$.

C. 2,4-Bis-(t-butyloxycarbonylamino)-1,5-diphenyl-3-pentanone oxime

The resultant compound of Example 299B (217 mg, 0.46 mmol), hydroxylamine hydrochloride (48 mg, 0.69 mmol) and anhydrous pyridine (75 µL, 0.92 mmol) were added to 10 mL of methanol. The reaction mixture was stirred at ambient temperature under a nitrogen atmosphere for 18 h. Additional hydroxylamine hydrochloride (48 mg) and pyridine (75 µL) were added and the reaction mixture was stirred for 5 h. The reaction mixture was then concentrated under reduced pressure and the residue was dissolved in 100 mL of chloroform. The chloroform solution was washed with 50 mL of water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue (250 mg) was taken up in ~ 2 mL of methylene chloride and applied to a 0.6 X 45 cm column of silica gel. The column was eluted sequentially with 50 mL of methylene chloride, 50 mL of 1% methanol in methylene chloride and 50 mL of 2% methanol in methylene chloride to give 160 mg (72% yield) of the title compound; DCI/NH3 MS M/Z: 501 $(M+NH_4)^+$, 484 $(M+H)+$. Analysis calculated for $C_{27}H_{37}N_3O_5 + 0.5H_2O$: C, 5.77; H, 7.77; N, 8.52. Found: C, 66.11; H, 7.50; N, 8.66.

Example 300

2,4-Bis-(t-butyloxycarbonylamino)-1,5-diphenyl-3-aminopentane

The resultant compound of Example 299 (134 mg, 0.277 mmol), was dissolved in 20 mL of methanol. 10% Palladium on carbon (50 mg) and ammonium formate (350 mg, 5.5 mmol) were added and the reaction mixture was stirred at ambient temperature under one atmosphere of hydrogen for ~64 h. The reaction was incomplete at this time and 100 mg of 10% palladium on carbon and 200 mg ammonium formate were added. The reaction mixture was stirred at ambient temperature under one atmosphere of hydrogen for ~24 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in methanol and adsorbed onto ~ 500 mg of silica gel in vacuo @

45° C. The silica gel was applied to a 0.6 X 40 cm of silica gel and eluted @ 10 p.s.i. with 50 mL of 2% methanol in methylene chloride, 50 mL of 3% methanol in methylene chloride, and 150 mL of 5% methanol in methylene chloride to give 20 mg (15% yield) of the title compound; DCI/NH_3 MS M/Z: 470 $(M+H)^+$; ^1H NMR (CDCl3) δ7.35-7.00 (m, 10 H), 5.20 (d, 1H), 4.83 (d, 1H), 4.10 (m, 1H), 3.83 (m, 1H), 3.0-2.5 (m, 5H), 1.42 (s, 9H), 1.32 (s, 9H).

Example 301

2,2-Bis-(2'-phenyl-1'-(t-butoxycarbonylamino)-1'-ethyl)oxirane

Approximately 3 mmol of diazomethane was generated by standard procedures from N-methyl-N-nitroso-p-toluenesulfonamide (sold by Aldrich Chemical Co. under the tradename Diazald®) and distilled directly into a solution of the resultant compound of Example 289B (100 mg, 0.21 mmol) in 2 mL of THF. The solution was then diluted with 10 mL of methanol and ~13 mL of diethyl ether. The reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was protected from moisture by a drying tube containing calcium chloride. The solution was concentrated under reduced pressure and the residue (106 mg) was taken up in ~1 mL of methylene chloride. The methylene chloride solution was applied to a 0.6 X 45 cm column of silica gel preequilibriated with hexane. The column was eluted @ 10 p.s.i sequentially with 50 mL of hexane, 50 mL of 5% ethyl acetate in hexane, 50 mL of 10% ethyl acetate in hexane, 50 mL of 15% ethyl acetate in hexane, 50 mL of 20% ethyl acetate in hexane, 50 mL of 25% ethyl acetate in hexane, and 50 mL of 5% methanol in methylene chloride to give 24.5 g (24% yield) of the title compound; DCI/isobutane MS M/Z: 483 $(M+H)^+$.

Example 302

A. 2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentanone

To a cold (-78° C) solution of oxalyl chloride (93 mg, 0.73 mmol) in 11 mL of freshly distilled methylene chloride was added, with stirring, 103 μL (1.46 mmol) of DMSO. To this soltuion at -78° C after stirring for 5 minutes was added a solution of the resultant compound of Example 70 (450 mg, 0.61 mmol) in 5.5 mL of methylene chloride/DMSO (10:1). The reaction mixture was stirred at -78° C for ~50 min, triethylamine (426 μL, 3.0 mmol) was added and stirring was continued for 5 min at -78° C. The cold bath was removed and the reaction mixture was allowed to warm to ambient temperature. The reaction mixture was diluted with 150 mL of chloroform. The chloroform solution was washed with 100 mL of brine, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue was taken up in ~3 mL of chloroform and applied to a 1.0 X 45 cm column of silica gel. The column was eluted with 100 mL of chloroform and 100 mL of 0.5% methanol in chloroform to give 376 mg (84% yield) of the title compound; DCI/NH3 MS M/Z: 501 $(M+NH_4)^+$. The 300 MHz ^1H NMR spectrum was consistent with the assigned structure.

B. 2,2-Bis-(2'-phenyl-1'-(N-(Cbz-valinyl)amino)-1'-ethyl)oxirane

The resultant compound of Example 302A (370 mg, 0.5 mmol) was suspended in 50 mL of methanol at ambient temperature. THF was added (30 mL) until a solution was formed. Excess diazomethane was generated by standard procedures from N-methyl-N-nitroso-p-toluenesulfonamide (sold by Aldrich Chemical Co. under the tradename Diazold®) and distilled (in ~50 mL of diethyl ether) directly into the solution of the ketone. The reaction mixture was stirred at ambient temperature for 17 h and then concentrated *in vacuo* at 40° C. The residue (410 mg) was taken up in 2 mL of chloroform and applied to a 1.0 X 45 cm column of

silica gel preequilibrated with hexane. The column was eluted @~5 p.s.i. with 100 mL of methylene chloride, 100 mL of 1% methanol in methylene chloride, 100 mL of 2% methanol in methylene chloride and 100 mL of 3% methanol in methylene chloride to give 82 mg (22% yield) of the title compound; DCI/NH_3 MS M/Z: 749 $(M+H)^+$.

Example 303

A. Dimethyl-2,4-bis(phenylmethyl)-3-oxoglutarate

Dimethyl 2,4-bis(phenylmethylene)-3-oxo-glutarate (630 mg, 1.8 mmol) (C.H. Chen, et al, *J. Org. Chem.*, **1981**, *46*, 2752-2757) was dissolved in about 100 mL of methanol and 250 mg of 10% palladium on carbon was added. The reaction mixture was shaken at ambient temperature under 4 atmospheres of hydrogen for about 12 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue (750 mg) was taken up in ~15 mL of methylene chloride and applied to a 1.0 X 45 cm column of silica gel. The column was eluted @ 5 p.s.i. with 150 mL of methylene chloride to give 374 mg (58% yield) of the title compound. The 300 MHz ^1H NMR was consistent with the assigned structure.

B. Dimethyl-2,4-bis(phenylmethyl)-3-hydroxyglutarate

To a solution of the resultant compound of Example 303B (370 mg, 1.04 mmol) in 20 mL of methanol/THF (1:1) at ambient temperature under a nitrogen atmosphere was added 40 mg (1.04 mmol) of sodium borohydride. The reaction mixture was stirred at ambient temperature for 1 h and then concentrated under reduced pressure. The residue was co-evaporated with 2 X 10 mL of methanol. The residue (517 mg) was then taken up in methylene chloride and applied to a 1.0 X 45 cm column of silica gel. The column was eluted with 100 mL of methylene chloride, 100 mL of 0.5% methanol in methylene chloride and 100 mL of 1.0% methanol in methylene chloride to give two products. The title compound was recovered as the major product in 49% yield (182 mg); DCI/NH3 MS M/Z: 374 $(M+NH_4)^+$, 357 $(M+H)+$.

Example 304

A. 2,4-Bis-(phenylmethyl)-3-hydroxy-glutaric acid

The resultant compound of Example 303B (120 mg, 0.337 mmol) and lithium hydroxide monohydrate (30 mg, 0.71 mmol) were added to THF/water (4:1) and the solution was stirred for ~20 h at ambient temperature under a nitrogen atmosphere. The reaction mixture was diluted with 20 mL of THF and adjusted to neutral pH with strongly acidic ion exchange resin HCR-S (commercially available from Nalco Co.). The mixture was filtered through a millepore (0.45 μ) filter and the filtrate was concentrated under reduced pressure to give 120 mg of the title compound; DCI/NH3 MS M/Z: 346 $(M+NH_4)^+$.

B. N,N'-Bis-(1'-benzyloxycarbonyl-2'-methyl-1'-propyl)-2,4-bis(phenylmethyl)-3-hydroxy-glutaramide

To a stirred mixture of 2,4-bis(phenylmethyl)-3-hydroxy-glutaric acid (66 mg, 0.2 mmol) and valine benzyl ester (168 mg, 0.44 mmol) in DMF at 0°C was added diethyl cyanophosphonate (67 mg, 0.44 mmol) followed by triethylamine (123 mg, 0.88 mmol). The reaction mixture was stirred at 0°C under nitrogen for 0.5 h and then it was allowed to warm to ambient temperature. The reaction mixture was stirred at ambient temperature for 18 h and was then diluted with 100 mL of chloroform, washed with 100 mL of

water, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. The residue (1.6 g) was taken up in ~1 mL of methylene chloride and applied to a 0.6 X 45 cm column of silica gel. The column was eluted @ 10 p.s.i. with 100 mL of methylene chloride. The residue was then taken up in ~1 mL of methylene chloride and applied to a 0.6 X 40 cm columnm of silica gel. The column was eluted @ ~10 p.s.i. with 50 mL of methylene chloride, 50 mL of 1% methanol in methylene chloride and 2% methanol in methylene chloride to give 93 mg (65% yield) of the title compound; FAB MS M/Z: 707 $(M+H)^+$.

Example 305

N,N'-Bis-(1'-benzyloxycarbonyl-2'-methyl-1'-propyl)-2,3,4,5-tetrahydroxyadipamide

Valine benzyl ester p-tóluenesulfonate salt (10.6 g, 28 mmol) was partitioned between 200 mL of chloroform and 56 mL of 0.5 M aqueous sodium hydroxide solution. The organic layer was separated and washed with 75 mL of brine and 75 mL of 5% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure. Acetonitrile (25 mL) and mannosaccharodilactone (W.N. Haworth, et al, *J. Chem. Soc.*,1944, 217) (1.8 g, 10.3 mol) were added to the residue and the reaction mixture was heated at reflux under nitrogen for 10.5 h. The reaction mixture was allowed to cool to ambient temperature and stirred at ambient temperature for ~64 h. Acetonitrile (75 mL) was added followed by 25 mL of strongly acidic ion exchange resin (HCR-S) and the mixture was stirred at ambient temperature for 2 h. The resin was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was taken up in ~25 mL of methylene chloride and applied to a 2.8 X 55 cm column of silica gel. The column was eluted @ ~5 p.s.i with 250 mL of methylene chloride and 1 L of 5% methanol in methylene chloride to give 5.26 g (86% yield) of the desired product. The product (267 mg) was further purified by chromatography. It was dissolved in ~1 mL of methylene chloride and applied to a 0.6 X 45 cm column of silica gel. The column was eluted @~10 p.s.i. with 50 mL of methylene chloride and 100 mL of 2% methanol in methylene chloride to give 212 mg of the title compound: EI MS m/z 589 $(M+H^+)$; ^1H NMR δ 0.87 (d, 6H), 0.93 (d, 6H), 2.18-2.30 (m, 2H), 4.05 (t, 2H), 4.14 (d, 2H), 4.25 (dd, 2H), 4.58 (dd, 2H), 4.67 (d, 2H), 5.12-5.24 (dd, 4H), 7.30-7.40 (m, 8H), 7.62 (d, 2H).

Example 306

N,N'-Bis-(1'-benzyloxycarbonyl-2'-methyl-1'-propyl)-3,4-dihydroxy-2,5-bis(phenylmethyl)adipamide.

A solution of 100 mg (0.68 mmol) of 2,3:4,5-dianhydro-D-iditol (R.S. Tipson, et al, *Carbohydrate Research*, 1968, 7, 232-243) in 5 mL of dichloromethane and 1 mL of DMSO was added to a solution of 208 mg (1.64 mmol) of oxalyl chloride in 10 mL of dichloromethane which had been treated with 257 mg (3.28 mmol) of DMSO at -78 °C. After 15 minutes at this temperature 685 mg (6.8 mmol) of triethylamine was added and the resulting solution allowed to warm to room temperature. The resulting dialdehyde is purifed by chromatography on silica gel and then oxidized to dimethyl 2,3:4,5-diepoxyadipate according to the procedure of D.R. Williams, et al (Tetrahederon Letters, 1988, 5087-5090). The diepoxide is then treated with the cuprate reagent prepared from benzyl lithium and $CuBr\text{-}Me_2S$ or CuCN in an ethereal solvent such as tetrahydrofuran or diethyl ether, to afforded dimethyl 3,4-dihydroxy-2,5-bis(phenylmethyl)adipate. The resulting diol is then protected as the bis(t-butyldiphenylsilyl) ether by treatment with t-butyldiphenylsilyl chloride in DMF in the presence of imidazole. Saponification of the diester with LiOH in aqueous THF, followed by acidification and coupling to valine benzyl ester in the manner described in Example 304, followed by deprotection with tetrabutylammmonium fluoride in THF affords the title compound.

Example 307

A. N,N′-Bis-(1′-benzyloxycarbonyl-2′-methyl-1′-propyl)-2,3,4,5-tetrahydroxyadipamide, 3,4-O-isopropylidene

To a stirred solution of 5.00 g (8.49 mmol) of The resultant compound of Example 305, in 1000 mL of acetone was aded 3.3 mL of concentrated sulfuric acid. After 60 minutes at room temperature, the reaction mixture was diluted with 1 liter of dichloromethane and then neutralized with 8.3 mL of concentrated ammonium hydroxide. The precipitate was removed by filtration, the filtrate concentrated under reduced pressure, and the residue purified by chromatography on silica gel with a hexane/EtOAc gradient to afford 3.93 g (74 %) of the desired product.^{1}H NMR ($CDCl_3$) δ 7.35 (s, 10H), 5.18 (abq, 4H), 4.58 (dd, 2H), 4.33 (m, 2H), 4.20 (m, 2H), 2.22 (m, 2H), 1.41 (s, 6H), 0.90 (d, 6H), 0.94 (d, 6H).

B. N,N′-Bis-(1′-benzyloxycarbonyl-2′-methyl-1′-propyl)-2,5-bis(trifluoromethylsulfonyloxy)-3,4,-dihydroxyadipamide, 3,4-O-isopropylidene

To a stirred solution of 159 mg (0.253 mmol) of the resultant compound of Example 307A in 3 mL of dichloromethane at -15 °C was added 0.051 mL (0.63 mmol) of pyridine and then 0.094 mL (0.56 mmol) of triflic anhydride. After 2 h, the temperature had increased to -10 °C, and the reaction mixture was diluted with 100 mL of dichloromethane, and washed with saturated aqueous sodium bicarbonate. The separated organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel with 98:2/dichloromethane:methanol afforded 55 mg (24 %) of the title compound. FAB MS m/z 893 $(M+H)^+$.

C. N,N′-Bis-(1′-benzyloxycarbonyl-2′-methyl-1′-propyl)-2,5-phenylthio-3,4-dihydroxyadipamide, 3,4-O-isopropylidene

To a stirred solution of 50 mg (0.056 mmol) of the resultant compound of Example 307B, in 5 mL of acetonitrile was simultaneously added 62 mg (0.56 mmol) of thiophenol and 28 mg (0.28 mmol) of triethylamine. After 30 minutes at room temperature, the reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel with 98:2/dichloromethane:methanol afforded 30 mg (66 %) of the title compound. ^{1}H NMR ($CDCl_3$) δ 7.5-7.15 (m, 22 H), 5.16 (abq, 4H), 4.88 (s, 2H), 4.54 (dd, 2 H); 3.84 (s, 2 H), 2.15 (m, 2 H), 1.47 (s, 6 H), 0.78 (d, 12 H).

D. N,N′-Bis-(1′-benzyloxycarbonyl-2′-methyl-1′-propyl)-2,5-phenylthio-3,4-dihydroxyadipamide

A stirred solution of 27 mg (0.033 mmol) of the resultant compound of Example 307C in 2 mL of 4:1/acetonitrile:10% aqeuous HCl was heated at 45 °C for 3 hours.The cooled reaction mixtures was diluted with 75 mL of dichloromethane, and then washed with 50 mL of water and then 25 mL of pH 6 phosphate buffer.The separated organic phase was dried over magnesium sulfate and then concentrated under reduced pressure. Chromatography of the residue on silica gel with 95:5 to 85:15/dichloromethane:EtOAc afforded 6.5 mg of the desired compound. ^{1}H NMR ($CDCl_3$) δ 7.45-7.20 (m, 22 H), 5.19 (abq, 4H), 4.52 (dd, 2 H), 4.47 (dd, 2 H), 3.92 (d, 2 H), 3.88 (d, 2H), 2.19 (m, 2 H), 0.80 (d,6 H), 0.78 (d,6 H).

Example 308

2,4-Bis-(N-(Cbz-valinyl)amino)-1,5-diphenyl-3-pentyl 2-aminoacetate

To a stirred solution of 50 mg (0.058 mmol) of the resultant compound of Example 293A, in 1 mL of THF was added approximately ten equivalents of ammonia dissolved in THF. After 72 h, the reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel with a 97:3 to 93:7/dichloromethane:MeOH gradient afforded 6.6 mg (14 %) of the title compound. FAB MS m/z 794 $(M+H)^+$.^{1}H NMR ($CDCl_3$) δ 7.4-7.1 (m, 20 H), 5.08 (s, 4 H), 0.81 (d,3 H), 0.76 (d, 3 H), 0.66 (d 3 H), 0.62 (d 3 H).

Example 309

1-(1′-(N-(Cbz-valinyl)amino)-2′-cyclohexyl-1′-ethyl)-1-(2″-(N-(Cbz-valinyl)amino)-3″-methyl-1″,1″-difluoro-1″-butyl)-oxirane

To a solution of 16 mg (0.022 mmol) of the ketone product from Example 183 in 2 mL of THF was added 4 mL of an ethereal solution containing excess diazomethane. After 2 h at room temperature and 16 hours at - 20 °C, the solution was warmed to room temperature and concentrated under reduced pressure to afford 16 mg of the title compound. DCI/NH_3 MS,757 $(M+H^+)$, 774 $(M+NH_4^+)$.^{1}H NMR ($CDCl_3$) δ 7.37 (s, 5H), 7.34 (s, 5H), 5.98 (d 1 H), 5.83 (d, 1 H), 5.32 (d, 1 H), 5.2-5.0 (m, 5 H), 4.62-4.40 (m, 2 H), 4.03-3.90 (m, 2 H), 2.94 (bs, 1H), 2.78 (bs, 1H), 2.40-0.80 (m).

Example 310

N,N-Bis-(Cbz-valinyl)-(2S, 3S, 4S, 5S)-1,6-diphenyl-2,5-diamino-3,4-hexanediol

Oxidation of of 2,3:4,5-dianhydro-D-iditol (R.S. Tipson, et al, *Carbohydrate Research*, **1968**, *7*, 232-243) as described in Example 306, but substituting THF for the dichloromethane/DMSO mixture as solvent, affords a solution of the corresponding dialdehyde. This solution is then recooled to -78 °C, and treated with four equivalents (relative to the iditol) of phenylmagnesium bromide. The reaction mixture is then quenched with a pH 7 phosphate buffer and extracted into ethyl acetate, dried over sodium sulfate, and concentrated under reduced pressure. The resulting diol is treated with benzyl isocyanate, in the presence of either DMAP or diisopropylethylamine, in an inert solvent, such as benzene or THF. The resulting biscarbamate is then treated with 2 equivalents of NaH or potassium t-butoxide in THF. The resulting diol is then treated with hydrogen over a Pd catalyst in a solvent such as MeOH to afford (2S, 3S, 4S, 5S)-3,4-dihydroxy-1,6-diphenyl-hexane-2,5-diamine. This is then converted into the title compound by treatment with Cbz-valine p-nitrophenyl ester in THF in the presence of triethylamine.

Example 311

2-(N-Benzyl-N-(benzyloxycarbonyl)amino)-5-(t-butyloxycarbonylamino)-1,6-diphenyl-3-hexene-3,4-oxide.

A solution of 160 mg (0.27 mmol) of the resultant compound of Example 117A and 117 mg (0.54 mmol) of 3-chloroperoxybenzoic acid in 1 ml of dichloromethane was stirred at ambient temperature for 2 days. The resulting solution was diluted with dichloromethane, washed sequentially with aqueous sodium bicarbonate and saturated brine, dried over $MgSO_4$, and concentrated. Silica gel chromatography of the residue using 10% ethyl acetate in hexane provided 150 mg (92%) of the desired compound (R_f 0.50, 20% ethyl acetate in hexane) as an oil. Mass spectrum: $(M + H)^+$ = 607.

Example 312

2-Amino-5-(t-butyloxycarbonylamino)-1,6-diphenyl-3-hexene-3,4-oxide.

A mixture of the resultant compound of Example 311 (152 mg) and 50 mg of 10% palladium on carbon in 50 ml of methanol was shaken under 4 atmospheres of hydrogen for 1 day. The mixture was filtered and concentrated in vacuo to provide 92 mg (96%) of the desired compound. Mass spectrum: $(M + H)^+ = 383$.

Example 313

2,5-Di-(t-butyloxycarbonylamino)-1,6-diphenyl-3-hexene-3,4-oxide.

Using the procedure of Example 205 with the resultant compound of Example 312 provided the desired compound.

Example 314

2,5-Di-(t-butyloxycarbonylamino)-1,6-diphenyl-3-hydroxyhexane.

A solution of the resultant compound of Example 313 in tetrahydrofuran was treated at ambient temperature with 2 molar equivalents of lithium triethylborohydride (1.0 M in tetrahydrofuran). After 2 h, the solution was quenched with citric acid, extracted with ether, washed with dilute aqueous NaOH and saturated brine, dried over Na_2SO_4, and concentrated. Silica gel chromatography provided the desired compound.

Example 315

A. 4-Azido-2,5-di-(t-butyloxycarbonylamino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 10C with the resultant compound of Example 314 provided the desired compound.

B. 4-Amino-2,5-di-(t-butyloxycarbonylamino)-1,6-diphenyl-3-hydroxyhexane.

Using the procedure of Example 11 with the resultant compound of Example 315 provided the desired compound.

Example 316

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

Quinaldic acid was coupled to the resultant compound of Example 173 using the carbodiimide coupling procedure of Example 55 to provide the desired compound.

Example 317

(2S,3S,4S,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 210 provided the desired compound.

Example 318

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

Quinaldic acid was coupled to the resultant compound of Example 317 using the carbodiimide coupling procedure of Example 55 to provide the desired compound.

Example 319

(2S,3S,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 209 provided the desired compound.

Example 320

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

Quinaldic acid was coupled to the resultant compound of Example 319 using the carbodiimide coupling procedure of Example 55 to provide the desired compound.

Example 321

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

Indole-2-carboxylic acid was coupled to the resultant compound of Example 173 using the carbodiimide coupling procedure of Example 55 to provide the desired compound.

Example 322

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

Indole-2-carboxylic acid was coupled to the resultant compound of Example 317 using the carbodiimide coupling procedure of Example 55 to provide the desired compound.

Example 323

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

Indole-2-carboxylic acid was coupled to the resultant compound of Example 319 using the carbodiimide coupling procedure of Example 55 to provide the desired compound.

Example 324

(2S,3R,4R,5S,2′S,2″S)-2,5-Di-(N-(2-(1,2,3,4-tetrahydropyrrolo[3,4-b]indol-3-on-2-yl)-4-methylpentanoyl)-amino)-3,4-dihydroxy-1,6-diphenylhexane.

(1′S)-2-(1-Carboxy-3-methylbutyl)-1,2,3,4-tetrahydropyrrolo[3,4-b]indol-3-one lithium salt, prepared according to the procedure of Kempf et. al. (J. Org. Chem. **1990**, *55*, 1390) was coupled to the resultant compound of Example 171 using the carbodiimide coupling procedure of Example 160D to provide the desired compound.

Example 325

(2S,3R,4R,5S,2′S,2″S)-2,5-Di-(N-(2-(1,2,3,4-tetrahydropyrrolo[3,4-b]indol-3-on-2-yl)-3-methylbutanoyl)-amino)-3,4-dihydroxy-1,6-diphenylhexane.

(1′S)-2-(1-Carboxy-2-methylpropyl)-1,2,3,4-tetrahydropyrrolo[3,4-b]indol-3-one lithium salt, prepared according to the procedure of Kempf et. al. (J. Org. Chem. **1990**, *55*, 1390) was coupled to the resultant compound of Example 171 using the carbodiimide coupling procedure of Example 160D to provide the desired compound.

Example 326

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

Using the procedure of Example 201A but replacing L-valine methyl ester hydrochloride with the resultant compound of Example 171 and replacing benzyl bromoacetate with t-butylbromoacetate provided the desired compound.

Example 327

A. A. N, N-Di-(N-(t-butyloxy)carbonyl)-(2S, 3R, 4R, 5S)-1,2:5,6-diimino-3,4-O-isopropylidenehexanediol.

Using the procedure of Example 205 but replacing (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane with (2S,3R,4R,5S)-1,2:5,6-diimino-3,4-O-isopropylidenehexanediol (Y.L. Merrer, et al, *Heterocycles*, **1987**, *25*, 541-548) provided the desired compound.

B. (2S,3R,4R,5S)-2,5-Di-(N-((t-butyloxy)carbonyl)amino)-1,6-di-(2-formylphenyl)-3,4-O-isopropylidenehexanediol.

Using the procedure of Example 289A but replacing (2S,3R,4R,5S)-1,2:5,6-diimino-3,4-O-isopropylidenehexanediol with the resultant compound of Example 327A and replacing phenyllithium with lithium 1-(N-methyl-N-(dimethylaminoethyl)amino-1-(2-lithiophenyl)-methoxide (Tetrahedron Lett. **1983**, *24*, 5465) provided the desired compound.

C. (2S,3R,4R,5S)-2,5-Diamino-3,4-dihydroxy-1,6-di-(2-formylphenyl)-hexane Dihydrochloride.

Using the procedure of Example 12 with the resultant compound of Example 327B provided the desired compound.

Example 328

(1R,2R,3′S,3″S)-1,2-Dihydroxy-1,2-bis-(1,2,3,4-tetrahydroisoquinolin-3-yl)-ethane.

Using the procedure of Example 145A but replacing dihydrocinnamaldehyde and valine benzyl ester dihydrochloride with the resultant compound of Example 327C provided the desired compound.

Example 329

(1R,2R,3′S,3″S)-1,2-Dihydroxy-1,2-bis-(2-((t-butyl)amino)carbonyl-1,2,3,4-tetrahydroisoquinolin-3-yl)-ethane.

Using the procedure of Example 226 but replacing (2S,3R,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane with the resultant compound of Example 328 provided the desired compound.

Example 330

A. N-(t-Butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid.

Using the procedure of Example 205 but replacing (2S,3S,4S,5S)-2,5-diamino-3,4-dihydroxy-1,6-diphenylhexane with 1,2,3,4-tetrahydroisoquinoline-2-carboxylic acid provided the desired compound.

B. N-(t-Butyloxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid t-Butyl Amide.

The resultant compound of Example 330A was coupled to t-butylamine using the mixed anhydride coupling procedure described in Example 6F to provide the desired compound.

C. 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic Acid t-Butyl Amide Hydrochloride.

The resultant compound of Example 330B was deprotected according to the procedure of Example 12 to provide the desired compound.

D. 2,2-Dimethoxy-1,3-bis-(3-((t-butyl)amino)carbonyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-propane.

Using the procedure of Example 201A but replacing L-valine methyl ester hydrochloride with the resultant compound of Example 330C and replacing benzyl bromoacetate with 1,3-dibromo-2,2-dimethoxypropane (J. Org. Chem. **1981**, *46*, 2532) provided the desired compound.

E. 1,3-Bis-(3-((t-butyl)amino)carbonyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-propan-2-ol.

The resultant compound of Example 330D (0.05 mmol) was treated with 25 ml of 1:1 1 N HCl/tetrahydrofuran. After being stirred for 16 h, the solution was concentrated in vacuo. The residue was taken up in methanol and treated with excess sodium borohydride. After 1 h, the solution was quenched with aqueous ammonium chloride, partitioned between chloroform and aqueous NaOH, dried over Na_2SO_4, and concentrated to provide the desired compound.

Example 331

1,3-Bis-(3-((t-butyl)amino)carbonyl-decahydroisoquinolin-2-yl)-propan-2-ol.

Using the procedure of Example 211 with the resultant compound of Example 330E provided the desired compound.

Example 332