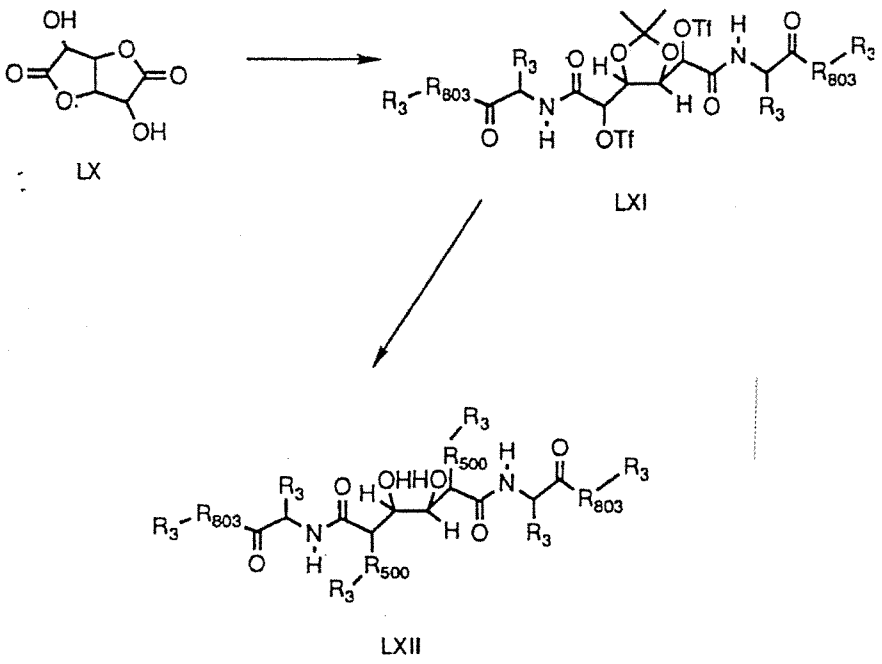
Exhibit 9 – Part 3 of 7

SCHEME 10



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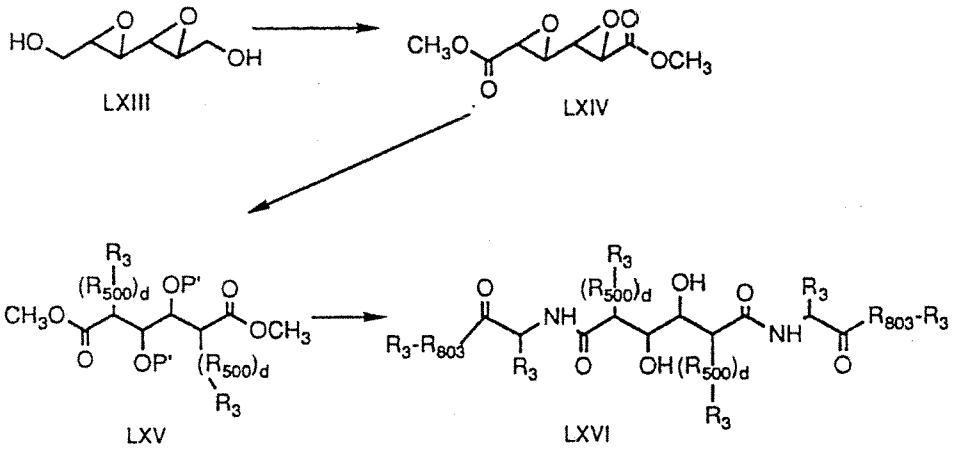

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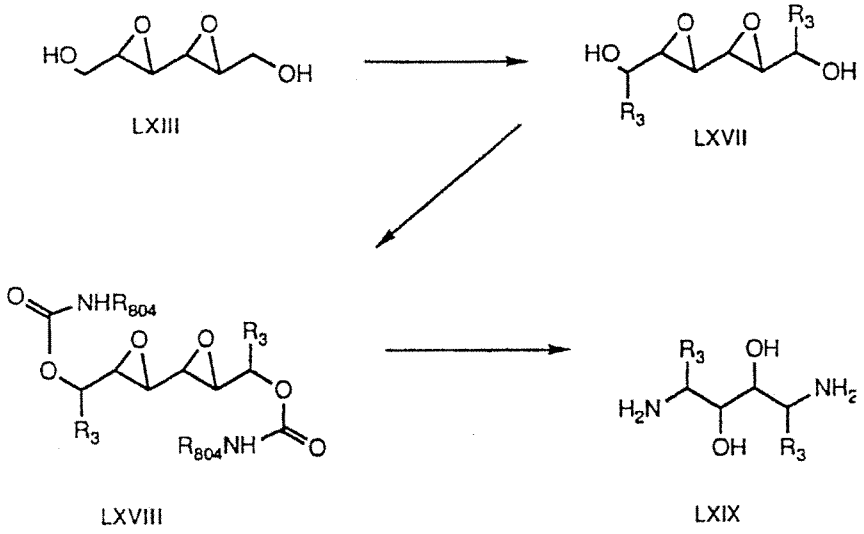
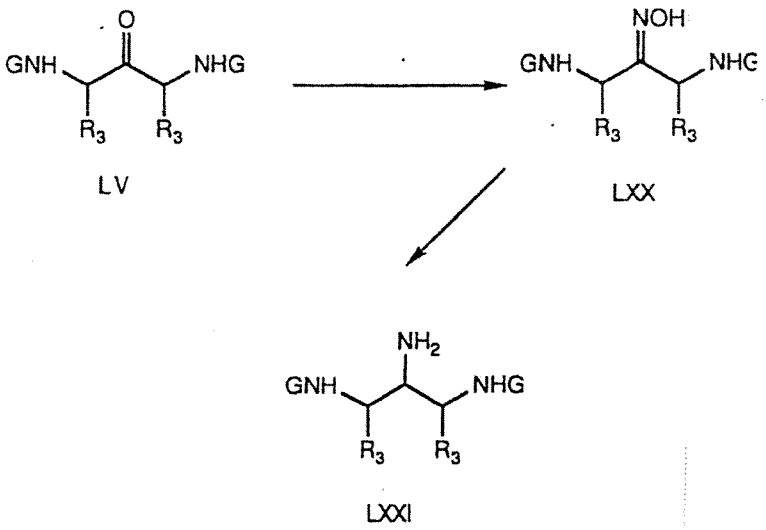


SCHEME 13



The following examples will serve to further illustrate preparation of the novel compounds of the invention.

Example 1

A. Bis-(2-phenylethyl)sulfide

A solution of 7.65 g (32 mmol) of sodium sulfide nonahydrate and 8.7 ml (64 mmol) of 2-bromoethylbenzene in 150 ml of 1:1 tetrahydrofuran:methanol was heated at reflux under inert atmosphere. After 24 h, the solution was allowed to cool and concentrated in vacuo to give the crude desired compound.

B. Bis-(2-phenylethyl)sulfone

A solution of the resultant compound of Example 1A (32 mmol) in 100 ml of methanol and 50 ml of water was cooled to 0° C and treated with 29 g (42 mmol) of OXONE. The resulting mixture was stirred at ambient temperature for 6 h, partitioned between dichloromethane and water, and the aqueous layer was washed with dichloromethane. The combined organic layers were concentrated in vacuo, taken up in dichloromethane, washed with water, dried over $MgSO_4$, and concentrated to give 7.57 g (87%) of the desired compound (R_f 0.24, 25% ethyl acetate in hexane) as a pure white solid, m.p. 98-99° C. ^1H NMR ($CDCl_3$) δ 3.1-3.2 (m, 8 H), 7.15-7.2 (m, 4 H), 7.25-7.35 (m, 6 H). Mass spectrum $(M + NH_4)^+$ = 292.
Anal. Calcd. for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61; S, 11.68. Found: C, 70.07; H, 6.63; S, 11.44.

Example 2

Bis-(2-phenylethyl)sulfoxide.

A solution of 7.25 mmol of the resultant compound of Example 1A in 40 ml of methanol and 10 ml of water was cooled to 0° C and treated with 2.23 g (3.63 mmol) of OXONE. After being stirred at 0° C for 2.5 h, the solution was partially concentrated in vacuo, diluted with water, extracted with three portions of chloroform, dried over $MgSO_4$, and concentrated. Flash chromatography using 30% ethyl acetate in chloroform gave 1.37 g (73%) of the desired compound (R_f 0.30, 30% ethyl acetate in chloroform) as a pure white solid, m.p. 70-71° C. ^1H NMR ($CDCl_3$) δ 2.8-3.0 (m, 4 H), 3.0-3.2 (m, 4 H), 7.2-7.4 (m, 10 H). Mass spectrum: $(M+H)^+$ = 259.
Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.38; H, 7.02; S, 12.41. Found: C, 74.26; H, 7.04; S, 12.16.

Example 3A and 3B

1,5-Diphenyl-3-pentanone (3A) And 1,5-Diphenyl-3-pentanol (3B).

A mixture of 1.00 g (4.27 mmol) of dibenzylidene acetone and 0.15 g of 10% palladium on carbon in 150 ml of methyl cellusolve was shaken under 4 atm. of hydrogen for 2 h. The solution was filtered and concentrated in vacuo. Flash chromatography using 10-20% ethyl acetate in hexane gave 0.60 g (59%) of 1,5-diphenyl-3-pentanone (R_f 0.43, 20% ethyl acetate in hexane) as a colorless oil and 0.29 g (28%) of 1,5-diphenyl-3-pentanol (R_f 0.36) as a white solid, m.p. 43-45° C. 1,5-Diphenyl-3-pentanone: ^1H NMR ($CDCl_3$) δ 2.71 (t, J = 7 Hz, 4 H), 2.89 (t, J = 7 Hz, 4 H), 7.1-7.3 (m, 10 H). Mass spectrum $(M+NH_4)+$ = 256.
Anal. Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.39; H, 7.63.
1,5-Diphenyl-3-pentanol: ^1H NMR ($CDCl_3$) δ 1.39 (d, J = 5 Hz, 1 H), 1.7-1.9 (m, 4 H), 2.6-2.9 (m, 4 H), 3.68 (m, 1 H), 7.1-7.3 (m, 10 H). Mass spectrum $(M+NH_4)^+$ = 258.
Anal. Calcd. for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.89; H, 8.18.

Example 4

1,3-Diphenoxy-2-propanol.

According to the procedure of Piantadosi et. al. (*J. Med. Chem.*, **1976**, 19, 222) a solution of 4.0 ml (45 mmol) of phenol in 30 ml of dioxane was treated with 0.95 g (24 mmol) of powdered sodium hydroxide and heated to reflux. Upon dissolution of the solid, the brown, refluxing solution was treated dropwise with 1.69 ml (22 mmol) of epichlorohydrin over a period of 10 min. After being heated at reflux for 5 h, the solution was cooled, concentrated in vacuo, taken up into ether, washed with several portions of water, dried over $MgSO_4$, and concentrated. Recrystallization from 2-propanol gave 1.87 g (35%) of the desired compound (R_f 0.33, 30% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 2.58 (d, J = 5 Hz, 1 H), 4.16 (dd, J = 10, 6 Hz, 2 H), 4.17 (dd, J = 10, 6 Hz, 2 H), 4.40 (sextet, J = 6 Hz, 1 H), 6.9-7.0 (m, 6 H), 7.2-7.35 (m, 4 H). Mass spectrum $(M+NH_4)^+$ = 262.

Example 5

1,3-Diphenoxyacetone.

A solution of 0.44 ml (6.2 mmol) of dimethylsulfoxide in 25 ml of dichloromethane was cooled under inert atmosphere to -63° C, treated with 2.3 ml (4.6 mmol) of oxalyl chloride (2M in dichloromethane), and stirred for 15 min. A solution of 0.75 g (3.1 mmol) of the resultant compound of Example 4 in 10 ml of dichloromethane was subsequently added, the solution was stirred for 30 min, and 1.73 ml (12.4 mmol) of triethylamine was added. After stirring for an additional 15 min, the solution was quenched with 10% aqueous citric acid, poured into a mixture of 1:1 ether:hexane and 10% citric acid, extracted with ether, washed with aqueous brine, dried over $MgSO_4$, and concentrated to a yellow oil. Purification by flash chromatography using 20% ethyl acetate in hexane gave 0.62 g (83%) of the desired compound as a white, crystalline solid, m.p. 55-57° C. ^1H NMR ($CDCl_3$) δ 4.89 (s, 4 H), 6.92 (m, 4 H), 7.02 (m, 2 H), 7.30 (m, 4 H). Mass spectrum $(M+NH_4)^+$ = 260.

Example 6

A. 3-Hydroxy-5-phenyl-1-pentene.

Vinylmagnesium Bromide (120 mmol, 1 M) in ether was added to 80 ml of dry tetrahydrofuran and cooled under inert atmosphere to 0° C. Hydrocinnamaldehyde (8.0 ml, 61 mmol) was added dropwise, and the solution was stirred for 10 min, quenched cautiously with saturated aqueous ammonium chloride, extracted with ether, washed with saturated brine, dried over $MgSO_4$, and concentrated to give 9.82 g (98.6%) of the crude desired product.

B. 3-(t-Butyldimethylsilyloxy)-5-phenyl-1-pentene.

A solution of the resultant compound of Example 6A (9.82 g, 60.6 mmol) and 8.2 g (120 mmol) of imidazole in 30 ml of dimethylformamide was treated with cooling (cold water bath) with 10 g (66 mmol) of t-butyldimethylsilyl chloride and stirred at ambient temperature. After 1 h, the solution was diluted with 1:1 ether:hexane, washed with three portions of water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using 3% ethyl acetate in hexane gave 13.2 g (79%) of the desired compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.04 (s, 3 H), 0.07 (s, 3 H), 0.90 (s, 9 H), 1.81 (m, 2 H), 2.66 (m, 2 H), 4.16 (q, J = 6 Hz, 1 H), 5.07 (dt, J = 10, 1 Hz, 1 H), 5.18 (dt, J = 17, 1 Hz, 1 H), 5.84 (ddd, J = 17, 10, 6 Hz, 1 H), 7.1-7.3 (m, 5 H). Mass spectrum: $(M+H)^+$ = 277.

C. 2-(t-Butyldimethylsilyloxy)-4-phenylbutyraldehyde.

A solution of 0.81 g (2.93 mmol) of the resultant compound of Example 6B in 20 ml of dichloromethane and 10 ml of methanol was cooled to -78° C. A mixture of ozone in air was bubbled through the solution until a blue color persisted. Air was bubbled through the solution to discharge excess ozone, and the solution was treated with dimethylsulfide. After being stirred overnight at ambient temperature, the solution was diluted with dichloromethane, washed with water, dried over $MgSO_4$, and concentrated in vacuo to give 0.81 g (100%) of the crude desired product.

D. (Z)-Methyl 4-(t-Butyldimethylsilyloxy)-6-phenyl-2-hexenoate.

A suspension of 120 mg (3.0 mmol) of sodium hydride (60% suspension in oil) in 20 ml of tetrahydrofuran was cooled to 0° C and treated with a solution of 937 mg (2.95 mmol) of bis(2,2,2-trifluoroethyl)(methoxycarbonylmethyl)phosphonate in 5 ml of tetrahydrofuran. The resulting solution was stirred for 10 min at 0° C, treated with a solution of 2.93 mmol of the resultant compound of Example 6C in 5 ml of tetrahydrofuran, and stirred at ambient temperature for 1 h. The solution was subsequently

quenched with aqueous ammonium chloride, extracted with ether, washed with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using 3% ethyl acetate in hexane gave 578 mg (59%) of the desired compound. ^1H NMR ($CDCl_3$) δ 0.02 (s, 3 H), 0.08 (s, 3 H), 0.90 (s, 9 H), 1.83 (m, 2 H), 2.64, (ddd, J = 13, 11, 6 Hz, 1 H), 2.77 (ddd, J = 13, 11, 6 Hz, 1 H), 3.70 (s, 3 H), 5.38 (br q, J = 7 Hz, 1 H), 5.72 (dd, J = 11, 1 Hz, 1 H), 6.21 (dd, J = 11, 8 Hz, 1 H), 7.15-7.3 (m, 5 H). Mass spectrum $(M+H)^+$ = 335.

E. (Z)-4-(t-Butyldimethylsilyloxy)-6-phenyl-2-hexenoic Acid.

A solution of 567 mg (1.69 mmol) of the resultant compound of Example 6D in 13 ml of dioxane was cooled to 0° C, treated with 6.5 ml (3.2 mmol) of 0.5 M aqueous lithium hydroxide, and stirred at ambient temperature for 24 h. The resulting solution was poured into chloroform/1 N HCl, separated, dried over $MgSO_4$, and concentrated to give the desired product. ^1H NMR ($CDCl_3$) δ 0.04 (s, 3 H), 0.09 (s, 3 H), 0.91 (s, 9 H), 1.88 (m, 2 H), 2.66, (m, 1 H), 2.78 (m, 1 H), 5.31 (br q, J = 7 Hz, 1 H), 5.78 (dd, J = 12, 1 Hz, 1 H), 6.34 (dd, J = 12, 8 Hz, 1 H), 7.15-7.3 (m, 5 H). Mass spectrum $(M+H)^+$ = 321.

F. (Z)-N-(3-Methylbutyl)-4-(t-butyldimethylsilyloxy)-6-phenyl-2-hexenamide.

A solution of the resultant compound of Example 6E (225 mg, 0.70 mmol) and 0.85 ml of 4-methylmorpholine in 15 ml of dichloromethane was cooled to 0° C and treated with 0.10 ml (0.77 mmol) of isobutyl chloroformate. The resulting solution was stirred for 10 min, treated with 0.089 ml (0.77 mmol) of isoamylamine, and stirred at ambient temperature for 2 h. The solution was subsequently diluted with dichloromethane, washed sequentially with 10% aqueous citric acid and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Flash chromatography using 15% ethyl acetate in hexane gave 245 mg (90%) of the desired compound as an oil. ^1H NMR ($CDCl_3$) δ 0.04 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 0.92 (d, J = 7 Hz, 6 H), 1.41 (br q, J = 7 Hz, 2 H), 1.63 (heptet, J = 7 Hz, 1 H), 1.86 (m, 2 H), 2.63 (m, 1 H), 2.78 (m, 1 H), 3.30 (m, 2 H), 5.50 (br q, 1 H), 5.59 (dd, J = 11, 1 Hz, 1 H), 5.98 (dd, J = 11, 8 Hz, 1 H), 7.15-7.3 (m, 5 H). Mass spectrum $(M+H)^+$ = 391.

G. (Z)-N-(3-Methylbutyl)-4-hydroxy-6-phenyl-2-hexenamide.

A solution of 58.7 mg (0.151 mmol) of the resultant compound of Example 6F in 1 ml of tetrahydrofuran was treated with 0.18 ml (0.18 mmol) of tetra-n-butylammonium fluoride (1 M in tetrahydrofuran). After being stirred for 1 h, the solution was concentrated in vacuo. Flash chromatography using 60% ethyl acetate in chloroform gave 26.9 mg (65%) of the desired compound as an oil. ^1H NMR ($CDCl_3$) δ 0.93 (d, J = 7 Hz, 6 H), 1.43 (q, J = 7 Hz, 2 H), 1.63 (heptet, J = 7 Hz, 1 H), 1.93 (m, 2 H), 2.80 (m, 2 H), 3.32 (m, 2 H), 4.58 (m, 1 H), 5.69 (br, 1 H), 5.73 (dd, J = 12, 1 Hz, 1 H), 6,19 (dd, J = 12, 6 Hz, 1 H), 7.15-7.3 (m, 5 H). Mass spectrum $(M+H)^+$ = 276.

Example 7

A. N-(3-Methylbutyl)-2-(1-(t-butyldimethylsilyloxy)-3-phenylpropyl)-cyclopropane-1-carboxamide.

The resultant compound of Example 6F was treated with diiodomethane and diethylzinc according to the procedure of Ito (*Organic Synthesis*, 1980, *59*, 113) to give the desired compound.

B. N-(3-Methylbutyl)-2-(1-hydroxy-3-phenylpropyl)-cyclopropane-1-carboxamide.

Using the procedure of Example 6G with the resultant compound of Example 7A gave the desired compound.

Example 8

A. cis-N-(3-Methylbutyl)-4-(t-butyldimethylsilyloxy)-6-phenyl-2-hexenamide-2,3-oxide.

A solution of 235 mg (0.59 mmol) of the resultant compound of Example 6F and 270 mg (1.25 mmol) of m-chloroperbenzoic acid in 5 ml of dichloromethane was allowed to stand at ambient temperature for 6 d. The resulting solution was diluted with ether, washed sequentially with 10% aqueous $Na_2S_2O_3$ and aqueous NaOH then with saturated brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using 20% ethyl acetate in hexane gave the desired compound as a ca. 2:1 mixture of diastereomers. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 3 H), 0.13 (s, 3 H), 0.90 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H), 0.96 (s, 9 H), 1.29 (br q, J = 7 Hz, 2 H), 1.58 (heptet, J = 7 Hz, 1 H), 1.82 (m, 2 H), 2.60 (m, 1 H), 2.76 (m, 1 H), 3.16 (m, 2 H), 3.35 (td, J = 8, 5 Hz, 1 H), 3.51 (d, J = 5 Hz, 1 H), 5.98 (br, 1 H), 7.15-7.3 (m, 5 H). Mass spectrum $(M+H)^+$ = 406.
Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 3 H), 0.07 (s, 3 H), 0.90 (d, J = 7 Hz, 6 H), 0.91 (s, 9 H), 1.27 (br q, J = 7 Hz, 2 H), 1.56 (heptet, J = 7 Hz, 1 H), 1.99 (m, 2 H), 2.73 (m, 1 H), 2.84 (m, 1 H), 3.09 (m, 1 H), 3.11 (dd, J = 8, 4 Hz, 1 H), 3.20 (m, 1 H), 3.41 (dt, J = 9, 6 Hz, 1 H), 3.51 (d, J = 4 Hz, 1 H), 5.81 (br, 1 H), 7.2-7.35 (m, 5 H). Mass spectrum $(M+H)^+$ = 406.

B. cis-N-(3-Methylbutyl)-4-hydroxy-6-phenyl-2-hexenamide-2,3-oxide.

Using the procedure of Example 6G separately with the major and minor diastereomers of Example 8A gave, after flash chromatography using 60% ethyl acetate in chloroform, 90% and 86% yields of the desired compounds, respectively. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H), 1.29 (br q, J = 7 Hz, 2 H), 1.57 (heptet, J = 7 Hz, 1 H), 1.89 (m, 2 H), 1.96 (d, J = 4 Hz, 1 H), 2.69 (m, 1 H), 2.80 (m, 1 H), 3.03 (m, 1 H), 3.19 (dd, J = 8, 5, Hz, 1 H), 3.22 (m, 1 H), 3.35 (m, 1 H), 3.58 (d, J = 5 Hz, 1 H), 6.01 (br, 1 H), 7.15-7.3 (m, 5 H). Mass spectrum $(M+H)^+$ = 292.
Minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H), 1.26 (m, 2 H), 1.55 (heptet, J = 7 Hz, 1 H), 2.02 (m, 2 H), 2.47 (d, J = 3 Hz, 1 H), 2.77 (m, 1 H), 2.85 (m, 1 H), 3.11 (m, 1 H), 3.13 (dd, J = 9, 5 Hz, 1 H), 3.24 (m, 2 H), 3.56 (d, J = 5 Hz, 1 H), 5.96 (br, 1 H), 7.2-7.35 (m, 5 H). Mass spectrum $(M+H)^+$ = 292.

Example 9

Di-(2-phenylethyl)phosphine Oxide

To a solution of 25 mmol of (2-phenyl)ethylmagnesium bromide in 25 ml of diethyl ether was added dropwise with cooling (ice bath) 0.92 ml (7.14 mmol) of diethyl phosphite. The resulting solution was heated at reflux for 2 h, cooled, and treated with aqueous ammonium chloride. The product was extracted with ether, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using ethyl acetate gave 1.23 g (64%) of the desired compound (R_f 0.64, 10% methanol in chloroform) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 2.0-2.2 (m, 4 H), 2.85-3.1 (m, 4 H), 6.89 (dm, J = 455 Hz, 1 H), 7.15-7.4 (m, 10 H). Mass spectrum $(M+H)^+$ = 259.

Example 10

A. 2-(t-Butyloxycarbonylamino)-1,5-diphenylpent-3-ene.

A solution of 15.1 g (54.5 mmol) of the resultant compound of Example 6A and 38 ml (220 mmol) of diisopropylethylamine in 450 ml of dry dichloromethane was cooled under N_2 atmosphere in an acetone/ice bath and treated dropwise with 8.5 ml (110 mmol) of methanesulfonyl chloride. The solution was stirred for 7 min after addition was complete, then was quenched with 400 ml of 10% citric acid. The bath was removed, and the mixture was extracted with 800 ml of ether. The organic layer was washed sequentially with 500 ml of water and 300 ml of saturated brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude mesylate as an off-white solid. To a flame-dried 3-neck 1000 mL flask equipped with an internal low-temperature thermometer was added 1.45 g (16 mmol) of anhydrous cuprous cyanide. The flask was then charged with 500 ml of anhydrous tetrahydrofuran. The suspension was cooled under N_2 altmosphere in a dry ice/acetone bath. A solution of phenylmagnesium bromide (55 ml, 165 mmol) in ether (3M) was added via syringe. The bath was removed, and the resulting beige suspension was warmed with stirring by use of a water bath. As the internal temperature reached -5° C, the solid began to dissolve, and the solution began to turn darker. By the time the internal temperature reached -1° C, the solution was homogenous, and was immediately recooled by placement of the flask in a dry ice/acetone bath. As the internal temperature reached -65° C, addition of a solution of the above crude mesylate in 75 ml of tetrahydrofuran was added via cannula. The resulting solution was stirred at *ca.* -70° C for 15 min. The bath was then removed, and the solution was immediately treated with 100 ml of saturated aqueous ammonium chloride followed by 300 ml of ether. As the mixture warmed, 100 ml of 1 N NH_4OH was added, and the mixture was stirred under air atmosphere for several hours while the aqueous layer turned dark blue. The mixture was then extracted with 500 ml of ether. The organic layer was washed with saturated brine and concentrated in vacuo without drying to give a yellow oil. The combined aqueous layers were extracted with 500 ml of additional ether, which was added to the above oil. The resulting solution was washed with saturated brine, dried over $MgSO_4$, and concentrated to a yellow oil. The oil was taken up in 100 ml of dichloromethane, treated with 50 g of silica gel, and concentrated in vacuo until the residue was a freely flowing solid. The solid was placed on top of a 60 mm column containing 300 g of silica gel and eluted sequentially with 1200 ml of hexane (to bring out biphenyl formed as a side product) followed by 5000 ml of 5% ethyl acetate in hexane. Combination of the pure fractions gave 11.95 g (65%) of the desired compound. ^1H NMR ($CDCl_3$, major isomer) δ 1.40 (s, 9 H), 2.7-2.9 m, 2 H), 3.32 (d, J = 7 Hz, 2 H), 4.4 (br, 2 H), 5.43 (dd, J = 15, 6 Hz, 1 H), 5.64 (dt, J = 15, 7 Hz, 1 H), 7.0-7.3 (m, 10 H).

B. 2-(t-Butyloxycarbonylamino)-1,5-diphenylpent-3-ene-3,4-oxide.

A solution of 11.71 g (34.75 mmol) of the resultant compound of Example 10A in 200 ml of dichloromethane was treated with 15 g (174 mmol) of solid sodium bicarbonate, cooled to 0° C, and treated with 24 g (69 mmol) of m-chloroperbenzoic acid (50%). The resulting suspension was sealed with a septum and stirred in a cold room (5° C) for three days. The resulting mixture, which contained much precipitate, was decanted into a 1000 ml flask. The white residue was broken up and washed out with 400 ml of 10% sodium thiosulfate solution and 300 ml of ether. The two-phase mixture was stirred for 2 hours, and the layers were separated. The organic layer was washed sequentially with 200 ml portions of 2 M NaOH, water, and saturated brine. The combined aqueous layers were extracted with 200 ml of ether, which was washed sequentially with 50 ml of water and 50 mL of aqueous brine, combined with the original organic phase, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was taken up in 100 ml of dichloromethane, treated with 50 g of silica gel, and concentrated in vacuo until the residue was a freely flowing solid. The solid was placed on top of a 60 mm column containing 300 g of silica gel and eluted sequentially with 1000 ml of 5% ethyl acetate in hexane followed by 3500 ml of 12% ethyl acetate in hexane. Concentration of the combined fractions gave 9.36 g (76%) of the desired compound (ca. 4:1 mixture of diastereomers) as an oil which solidified upon standing.

C. 4-Azido-2-(t-butyloxycarbonylamino)-1,5-diphenyl-3-hydroxypentane.

A solution of 9.12g (25.84 mmol) of the resultant compound of Example 10B, 7.0 g (140 mmol) of lithium azide, and 1.73 g (32 mmol) of ammonium chloride in 75 ml of dimethylformamide and 7.5 ml of water was heated in an oil bath at 70° C for 32 hours. After being allowed to cool, the resulting solution was treated with 1000 ml of 1:1 ether/hexane and 800 ml of water. The layers were separated, and the aqueous layer was extracted with 500 ml of additional 1:1 ether/hexane. The combined organic layers were washed sequentially with 400 ml of water and 200 ml of saturated brine, dried over $MgSO_4$, and concentrated in vacuo to a solid. The solid was taken up in 100 ml of dichloromethane, treated with 50 g of silica gel, and concentrated in vacuo until the residue was a freely flowing solid. The solid was placed on top of a 60 mm column containing 300 g of silica gel and eluted sequentially with 1000 ml of 10% ethyl acetate in hexane, 1000 ml of 15% ethyl acetate in hexane, and 2000 ml of 25% ethyl acetate in hexane. Concentration of the fractions gave 9.26 g (91%) of the desired compound as a *ca.* 4:1 mixture of diastereomers. ^1H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 2.78 (m, 1 H), 2.89 (m, 1 H), 3.13 (m, 1 H), 3.29 (m, 1 H), 3.41 (m, 1 H), 3.53 (m, 1 H), 3.80 (m, 1 H), 4.06 (m, 1 H), 4.83 (m, 1 H), 7.2-7.35 (m, 10 H). Mass spectrum $(M+H)^+$ = 338.

Example 11

4-Amino-2-(t-butyloxycarbonylamino)-1,5-diphenyl-3-hydroxypentane.

A rapidly stirring suspension of 10 mg of 10% palladium on carbon in 0.3 ml of methanol was treated under inert atmosphere with 60 mg (0.95 mmol) of solid ammonium formate. After 3 min, a solution of 52 mg (0.13 mmol) of the resultant compound of Example 10C in 0.4 ml of methanol was added. The resulting mixture was stirred for 2 h, diluted with methanol and 1 N ammonium hydroxide, filtered through Celite, and concentrated in vacuo. The residue was treated with 1 N NaOH, extracted with two portions of chloroform, dried over sodium sulfate, and concentrated. Flash chromatography using 7.5% methanol in chloroform gave 37 mg (76%) of the desired compound (R_f 0.38, 2.5% methanol/2% isopropylamine in chloroform) as a white solid, m.p. 134-135° C. ^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H), 2.50 (dd, J = 13, 10 Hz, 1 H), 2.8-3.1 (m, 4 H), 3.41 (br d, J = 7 Hz, 1 H), 4.11 (br q, J = 8 Hz, 1 H), 4.83 (br d, J = 9 Hz, 1 H), 7.15-7.35 (m, 10 H). Mass spectrum $(M+H)^+$ = 370.
Anal. Calcd. for $C_{22}H_{30}N_2O_3 \cdot 0.15H_2O$: C, 70.81; H, 8.18; N, 7.51. Found: C, 70.89; H, 8.15; N, 7.43.

Example 12

2,4-Diamino-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 11 (18 mg, 0.049 mmol) was treated with 1 ml of 4 M HCl in dioxane, stirred for 0.5 h at ambient temperature, and concentrated in vacuo. The residue was partitioned between chloroform and aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated to provide the desired compound (R_f 0.12, 10% methanol in chloroform) as a white solid, m.p. 106-107° C. ^1H NMR ($CDCl_3$) δ 2.51 (dd, J = 13, 10 Hz, 1 H), 2.67 (dd, J = 13, 9 Hz, 1 H), 2.85-3.0 (m, 2 H), 3.19 (m, 1 H), 3.38 (m, 2 H), 7.15-7.35 (m, 10 H). Mass spectrum: $(M + H)^+$ = 271.

Example 13

2,4-Bis-((methyl)sulfonyl)amino-1,5-diphenyl-3-hydroxypentane.

A solution of the resultant compound of Example 12 (0.049 mmol) and 0.032 ml (0.29 mmol) of 4-methylmorpholine in 1 ml of dichloromethane was cooled to 0° C and treated with 0.008 ml (0.10 mmol) of methanesulfonyl chloride. After 0.5 h, the solution was washed with 10% aqueous citric acid, dried over Na_2SO_4, and concentrated. Flash chromatography using 5% methanol in chloroform gave 2.6 mg (13%) of the desired compound. ^1H NMR ($CDCl_3$) δ 2.16 (s, 3 H), 2.34 (s, 3 H), 2.93 (m, 4 H), 3.41 (d, J = 4 Hz, 1 H), 3.7-3.8 (m, 2 H), 3.92 (m, 1 H), 5.06 (d, J = 9 Hz, 1 H), 5.42 (d, J = 9 Hz, 1 H), 7.2-7.4 (m, 10 H). Mass spectrum $(M+NH_4)^+$ = 444.

Example 14

2-Hydroxy-1,3-di(N-phenylamino)propane.

A mixture of 0.25 ml (2.74 mmol) of aniline, 0.107 ml (1.37 mmol) of epichlorohydrin, and 60.4 mg (1.51 mmol) of sodium hydroxide in 2 ml of dimethylformamide was heated at 110° C for 20 h. The solvent was removed in vacuo and the residue was purified by flash chromatography using 5% ethyl acetate in chloroform to give 21 mg (6%) of the desired compound (R_f 0.63, 40% ethyl acetate in chloroform). ^1H NMR ($CDCl_3$) δ 3.21 (dd, J = 13, 8 Hz, 2 H), 3.37 (dd, J = 13, 4 Hz, 2 H), 4.13 (m, 1 H), 6.65-6.8 (m, 6 H), 7.15-7.3 (m, 6 H). Mass spectrum $(M+H)^+$ = 243.

Example 15

2-Hydroxy-1,3-di(S-phenylthio)propane.

Using the procedure of Example 4 but replacing phenol with thiophenol gave, after flash chromatography using 10% ethyl acetate in hexane, the desired compound (1.21 g, 56%, R_f 0.20, 10% ethyl acetate in hexane) as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.77 (d, J = 4 Hz, 1 H), 3.05 (dd, J = 14, 7 Hz, 2 H), 3.20 (dd, J = 14, 5 Hz, 2 H), 3.82 (m, 1 H), 7.15-7.4 (m, 10 H). Mass spectrum $(M+NH_4)^+$ = 294.

Example 16

A. 2-(2-Phenylethyl)-4-phenylbut-1-ene.

A suspension of 1.59 g (4.45 mmol) of methyltriphenylphosphonium bromide in 100 ml of tetrahydrofuran was cooled to -78° C, treated with 2.2 ml (4.5 mmol) of n-butyllithium, warmed to 0° C, and recooled to -78° C. The resulting solution was treated via cannula with a solution of 1.59 g (4.45 mmol) of 1,5-diphenyl-3-pentanone in 20 ml of tetrahydrofuran. After being allowed to stir at ambient temperature for 2 h, the solution was diluted with hexane, washed sequentially with water and saturated brine, dried over $MgSO_4$, and concentrated in vacuo. The mixture was purified by flash chromatography to give 0.90 g (86%) of the desired compound as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.37 (t, J = 8 Hz, 4 H), 2.76 (t, J = 8 Hz, 4 H), 4.81 (s, 2 H), 7.15-7.3 (m, 10 H). Mass spectrum $(M+NH_4)^+$ = 254.
Anal. Calcd for $C_{18}H_2O$: C, 91.47; H, 8.53. Found: C, 90.93; H, 8.56.

B. 2-(2-Phenylethyl)-4-phenylbut-1-ene-1,2-oxide.

A solution of 107 mg (0.453 mmol) of the resultant compound of Example 16A in 2 ml of dichloromethane was treated with 150 mg (0.68 mmol) of m-chloroperbenzoic acid (80%). After being stirred for 40 min, the solution was treated with 10% aqueous sodium thiosulfate, stirred for 1 h, partitioned between ethyl acetate and aqueous NaOH, washed sequentially with water and saturated brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography using 10% ethyl acetate in hexane to give 133 mg (99%) of the desired compound (R_f 0.25, 10% ethyl acetate in hexane) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.95 (m, 4 H), 2.60 (s, 2 H), 2.71 (t, J = 9 Hz, 4 H), 7.15-7-3 (m, 10 H). Mass spectrum $(M+NH_4)^+$ = 270.

Anal. Calcd. for $C_{18}H_{20}O \cdot 0.3H_2O$: C, 83.88; H, 8.06. Found: C, 83.62; H, 7.94.

Example 17

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

Using the procedure of Example 10A but replacing phenylacetaldehyde with N-benzyl-N-(benzyloxycarbonyl)phenylalaninal gave, after flash chromatography using 20% ethyl acetate in hexane, 45 mg (30%) of the desired compound. ^1H NMR (d_6-DMSO, 100° C) δ 1.32 (s, 9 H), 2.54 (dd, J = 14, 7 Hz, 1 H), 2.62 (dd, J = 14, 7 Hz, 1 H), 2.77 (dd, J = 14, 7 Hz, 1 H), 2.83 (dd, J = 14, 7 Hz, 1 H), 4.04 (br pentet, J = 7 Hz, 1 H), 4.20 (d, J = 16 Hz, 1 H), 4.33 (d, J = 16 Hz, 1 H), 4.48 (br q, J = 7 Hz, 1 H), 5.03 (AA', 2 H), 5.44 (dd, J = 16, 6 Hz, 1 H), 5.61 (dd, J = 16, 7 Hz, 1 H), 7.0-7.4 (m, 20 H). Mass spectrum $(M+H)^+$ = 591.

B. 2-(N-Benzyl-N-(benzyloxycarbonyl)amino)-5-(t-butyloxycarbonylamino)-3,4-dihydroxy-1,6-diphenyl-3-hexane.

A solution of 40 mg (0.068 mmol) of the resultant compound of Example 17A in 1 ml of tetrahydrofuran was treated sequentially with 0.034 ml (0.0034 mmol) of osmium tetroxide (2.5% in t-butanol) and 20 mg (0.14 mmol) of 4-methylmorpholine-N-oxide. After 20 h, the solution was treated with 10% $Na_2S_2O_3$, stirred for 15 min, diluted with ether, washed with two portions of 10% $Na_2S_2O_3$, one portion of water, and one portion of saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography using 30% ethyl acetate in hexane gave the desired compound (R_f 0.43, 30% ethyl acetate in hexane) as a 2:1 mixture of diastereomers. Mass spectrum $(M+H)^+$ = 625.

Example 18

2-(N-Benzylamino)-5-(t-butyloxycarbonylamino)-3,4-dihydroxy-1,6-diphenyl-3-hexane.

Ammonia (ca. 3 ml) was condensed into a precooled (-78° C) mixture of excess sodium metal in 2 ml of tetrahydrofuran. A solution of 25 mg (0.040 mmol) of the resultant compound of Example 17B in 1 ml of tetrahydrofuran was added, and the resulting solution was stirred for 10 min, quenched with saturated aqueous ammonium chloride, allowed to warm to ambient temperature, extracted with ether, dried over Na_2SO_4, and concentrated to give the crude desired product. Mass spectrum: $(M+H)^+$ = 491.

Example 19

5-Amino-2-(N-benzylamino)-3,4-dihydroxy-1,6-diphenyl-3-hexane Dihydrochloride.

The resultant compound of Example 18 (18.5 mg, 0.038 mmol) was treated with 1 ml of 4 M HCl in dioxane. After 1 h, the solution was concentrated in vacuo to give the desired compound.

Example 20

1,5-Diphenyl-3-hydroxy-3-(hydroxymethyl)pentane.

Using the procedure of Example 17B with 166 mg (0.70 mmol) of the resultant compound of Example 16A gave, after purification by flash chromatography using 40% ethyl acetate in hexane, 114 mg (60%) of the desired compound (R_f 0.27, 50% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$) δ 1.77 (t, J = 6 Hz, 1 H), 1.89 (m, 4 H), 1.91 (s, 1 H), 2.70 (m, 4 H), 3.59 (d, J = 6 Hz, 2 H), 7.15-7.35 (m, 10 H). Mass spectrum $(M+NH_4)^+$ = 288.
Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.19; H, 8.06.

Example 21

A. 1,1-Di(phenoxymethyl)ethene.

A solution of 2.0 ml (22.7 mmol) of phenol in 40 ml of dioxane was heated to reflux and treated with 0.96 g (23.8 mmol) of sodium hydroxide. After the solid had dissolved, the solution was treated dropwise over a period of 15 min with 1.25 ml (10.8 mmol) of 2-chloromethyl-3-chloro-1-propene. The resulting solution was heated at reflux for 6 h, allowed to cool, and concentrated in vacuo. The residue was taken up in ether, washed with several portions of water, dried over $MgSO_4$, and concentrated to a yellow liquid. Flash chromatography using 10% ethyl acetate in hexane gave 1.72 g (65%) of the desired compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.63 (m, 4 H), 5.35-5.45 (m, 2 H), 6.9-7.0 (m, 6 H), 7.25-7.35 (m, 4 H). Mass spectrum $(M + NH_4)^+$ = 258.

B. 1,1-Di(phenoxymethyl)ethene-1,2-oxide.

A solution of 0.74 g (3.1 mmol) of the resultant compound of Example 21A in 15 ml of dichloromethane was treated with 0.52 g (6.2 mmol) of sodium bicarbonate, cooled to 0° C, and treated with a solution of 0.8 g (4.6 mmol) of m-chloroperbenzoic acid (80%). The resulting solution was stirred at ambient temperature for 16 h, treated with aqueous sodium bisulfite, stirred for 30 min, extracted with dichloromethane, washed sequentially with 1 N NaOH, water, and saturated brine, and dried over $MgSO_4$. Concentration of the solution gave an oil which was purified by flash chromatography using 10% ethyl acetate in hexane to give 0.44 g (56%) of the desired compound (R_f 0.50, 10% ethyl acetate in hexane). ^{1}H NMR ($CDCl_3$) δ 3.02 (s, 2 H), 4.26 (AA', 4 H), 6.9-7.0 (m, 6 H), 7.25-7.35 (m, 4H). Mass spectrum $(M+NH_4)^+$ = 274.

Example 22

N-(3-Methylbutyl)-5-(t-butyloxycarbonylamino)-6-phenyl-3-(phenylmethyl)-4-hydroxyhexanamide

Using the procedures of Evans et. al. (*J. Org. Chem.* 1985, *50*, 4615) with the resultant compound of 11B and isoamylamine gave the desired compound.

Example 23

A. 2,2-Dimethyl-4,5-di-(2-phenyl-1-oxoethyl)-1,3-dioxolane.

A solution of 7.5 g (20.5 mmol) of N,N,N′,N′,-tetramethyl-O,O′-isopropylidene-d-tartaric diamide (Briggs, et. al., *J. Chem. Soc. Perkin Trans. I*, 1985, 795) in 150 ml of tetrahydrofuran was treated over a period of 20 min with 41 ml (82 mmol) of benzylmagnesium chloride. The resulting solution was stirred overnight at ambient temperature, poured over ice/saturated ammonium chloride, extracted with ethyl acetate, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using 20% ethyl acetate in hexane gave 0.83 g (12%) of the desired compound as an oil. ^1H NMR ($CDCl_3$) δ 1.45 (s, 6 H), 3.94 (s, 4 H), 4.70 (s, 2 H), 7.2-7.4 (m, 10 H). Mass spectrum $(M+H)^+$ = 339.

B. 3,4-Dihydroxy-1,6-diphenylhexan-2,5-dione.

The resultant compound of Example 23A (100 mg, 0.3 mmol) was treated with 10 ml of 80% aqueous acetic acid, heated at reflux for 5 min, allowed to cool, and concentrated in vacuo. The crude product was purified by flash chromatography using 20% ethyl acetate in hexane to give 65 mg (74%) of the desired compound (R_f 0.15, 30% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 2.39 (d, J = 5 Hz, 1 H), 2.81 (d, J = 3 Hz, 1 H), 3.89 (d, J = 15 Hz, 2 H), 4.13 (d, J = 15 Hz, 2 H), 4.40 (br t, J = 3 Hz, 1 H), 4.66 (m, 1 H), 7.15-7.5 (m, 10 H). Mass spectrum $(M+H)^+$ = 299.

Example 24

1,6-Diphenyl-2,3,4,5-tetrahydroxyhexane.

According to the procedure of Achmatowicz and Wicha (*Tetrahedron Lett.*, 1987, *28*, 2999) the resultant compound of Example 23A was treated with sodium borohydride in ethanol and deprotected according to the procedure of 23B to give the desired compound as a mixture of stereoisomers.

Example 25

A. 2,2-Dimethyl-4,5-di-(2-phenyl-1-(N-hydroxyimino)ethyl)-1,3-dioxolane.

A solution of the resultant compound of Example 23A (0.5 g, 1.5 mmol) in 10 ml of pyridine was treated with 0.22 g (3.2 mmol) of hydroxylamine hydrochloride and stirred overnight at ambient temperature. The resulting solution was partitioned between ethyl acetate and water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using 10% ethyl acetate in hexane gave 0.53 g (92%) of the desired compound as an apparent 4:1:1 mixture of isomers. ^1H NMR ($CDCl_3$, major isomer) δ 1.40 (s, 6 H), 3.70 (d, J = 14 Hz, 2 H), 3.83 (d, J = 14 Hz, 2 H), 4.56 (s, 2 H), 7.15-7.35 (m, 10 H). Mass spectrum $(M+H)^+$ = 369.

B. 3,4-Dihydroxy-1,6-diphenylhexan-2,5-dione Dioxime

The resultant compound of Example 25A was deprotected according to the procedure of 23B to give the desired compound.

Example 26

3,4-Dihydroxy-1,6-diphenylhexan-2,5-dione Dimethyl Dioxime

Using the procedures of Example 25A and 25B but replacing hydroxylamine hydrochloride with methoxyamine hydrochloride gave the desired compound.

Example 27

3,4-Dihydroxy-1,6-diphenylhexan-2,5-dione Dihydrazide

Using the procedures of Example 25A and 25B but replacing hydroxylamine hydrochloride with hydrazine hydrate gave the desired compound.

Example 28

Bis-(1-phenylbut-2-yl)sulfoxide

Using the procedures of Example 1A and Example 2 but replacing (2-bromoethyl)benzene with (2-bromobut-1-yl)benzene gave the desired compound.

Example 29

A. (2-Phenylethyl)-(1-fluoro-2-phenylethyl)sulfide.

According to the procedure of McCarthy et. al. (*J. Amer. Chem. Soc.* **1985**, *107*, 735), the resultant compound of Example 2 was treated with diethylaminosulfur trifluoride in dichloromethane to give the desired compound.

B. (2-Phenylethyl)-(1-fluoro-2-phenylethyl)sulfoxide.

Using the procedure of Example 2 with the resultant compound of Example 29A gave the desired compound.

Example 30

A. O-Benzoyl-N,N-di-(2-phenylethyl)hydroxylamine.

According to the procedure of Vaouanc et. al. (*Synthesis*, 1985, 807), N,N-di-(2-phenylethyl)amine was treated with bis(diphenylphosphinyl)peroxide to give the desired compound.

B. N,N-Di-(2-phenylethyl)hydroxylamine.

According to the procedure of Vaouanc et. al. (*Synthesis*, 1985, 807), the resultant compound of Example 30A was treated with sodium ethoxide to give the desired compound. ^{1}H NMR ($CDCl_3$) δ 2.9-3.0 (m, 8 H), 5.62 (br s, 1 H), 7.15-7.3 (m, 10 H). Mass spectrum: $(M + H)^+ = 242$.

Example 31

1,5-Diphenyl-3-pentanone Oxime.

Using the procedure of Example 25A with 1,5-diphenyl-3-pentanone gave the desired compound.

Example 32

3-Amino-1,5-Diphenylpentane.

According to the procedure of Feuer and Braunstein (*J. Org. Chem.* 1969, *34*, 1817), the resultant compound of Example 31 was treated with borane to give the desired compound.

Example 33

N-(1,5-Diphenylpent-3-yl)hydroxylamine.

A solution of 0.37 g (1.55 mmol) of 1,5-diphenyl-3-pentanone in 20 ml of 2-propanol was treated with 0.22g (3.1 mmol) of hydroxylamine hydrochloride and 0.31 g (4.7 mmol) of anhydrous sodium acetate. After being stirred for 10 min, the mixture was treated with 0.20 g (3.2 mmol) of sodium cyanoborohydride and stirred at ambient temperature for 16 h. After concentration in vacuo, the residue was taken up in ethyl acetate, washed sequentially with aqueous $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography using 40% ethyl acetate in chloroform gave 121 mg (31%) of the desired compound (R_f 0.16, 30% ethyl acetate in chloroform) as a white solid, m.p. 54-55°C. ^{1}H NMR ($CDCl_3$) δ 1.7-1.85 (m, 2 H), 1.85-2.0 (m, 2 H), 2.6-2.75 (m, 4 H), 2.90 (pentet, J = 6 Hz, 1 H), 5.22 (br, 2 H), 7.1-7.35 (m, 10 H). Mass spectrum $(M+H)^+ = 256$.

Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.82; H, 8.39; N, 5.50.

Example 34

A. N-Methyl-N-methoxy-2-hydroxy-3-phenylpropanamide.

A solution of 2.0 g (12 mmol) of phenyllactic acid, 1.17 g (12 mmol) of N,O-dimethylhydroxylamine hydrochloride, and 1.78 g (13 mmol) of 1-hydroxybenzotriazole in 20 ml of dimethylformamide was treated sequentially with 2.77 ml (25 mmol) of 4-methylmorpholine and 2.53 g (13 mmol) of N-ethyl-N'-(dimethylaminoethyl)carbodiimide. After being stirred at ambient temperature overnight, the solution was diluted with ethyl acetate; washed sequentially with water, 10% citric acid, aqueous $NaHCO_3$, and saturated brine; dried over $MgSO_4$; and concentrated in vacuo to give 2.5 g (100%) of the crude desired compound. ^1H NMR ($CDCl_3$) δ 2.85 (dd, J = 14, 7 Hz, 1 H), 3.08 (dd, J = 14, 4 Hz, 1 H), 3.23 (s, 3 H), 3.72 (s, 3 H), 4.62 (m, 1 H), 7.2-7.3 (m, 5 H). Mass spectrum $(M+H)^+$ = 210.

B. N-Methyl-N-methoxy-2-fluoro-3-phenylpropanamide.

The resultant compound of Example 34A (0.5 g, 2.4 mmol) in 5 ml of dichloromethane was treated with 0.63 ml (4.8 mmol) of diethylaminosulfur trifluoride and stirred at ambient temperature. After 16 h, the solution was quenched with water, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography using 20% ethyl acetate in hexane gave 210 mg (42%) of the desired compound. ^1H NMR ($CDCl_3$) δ 3.1-3.2 (m, 2 H), 3.21 (s, 3 H), 3.68 (s, 3 H), 5.37 (dm, J = 50 Hz, 1 H), 7.2-7.4 (m, 5 H). Mass spectrum $(M+NH_4)^+$ = 229.

C. 1,5-Diphenyl-2-fluoro-3-pentanone.

A solution of 200 mg (0.1 mmol) of the resultant compound of Example 34B in 3 ml of tetrahydrofuran was treated with 0.36 ml (0.36 mmol) of 2-phenylethylmagnesium bromide and stirred at ambient temperature for 16 h. The resulting solution was treated with water, extracted with ethyl acetate, washed sequentially with aqueous ammonium chloride, water, and saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography using 5% ethyl acetate in hexane gave 108 mg (44%) of the desired compound (R_f 0.60, 15% ethyl acetate in hexane) as an oil. ^1H NMR ($CDCl_3$) δ 2.5-3.3 (m, 6 H), 4.96 (ddd, J = 50, 8, 4 Hz, 1 H), 7.1-7.3 (m, 10 H). Mass spectrum $(M+NH_4)+$ = 274, $(M+NH_4+H_2O)^+$ = 290.

Example 35

2,4-Bis-(N-acetylamino)-1,5-diphenyl-3-hydroxypentane..

A suspension of 0.037 mmol of the resultant compound of Example 12 in 1 ml of aqueous $NaHCO_3$ was cooled to 0 °C and treated with 0.04 ml of acetic anhydride. After being stirred for 40 min, the solution was extracted with dichloromethane. The organic phase was washed with saturated brine, dried over Na_2SO_4, and concentrated. The crude material was recrystallized from dichloromethane/ethyl acetate to give the desired compound (R_f 0.7, 10% methanol in chloroform, 90% yield) as a white solid, m.p. 125-126 °C. Mass spectrum: $(M+H)^+$ = 355.

Example 36

A. 4-(t-Butyloxycarbonylamino)-3-hydroxy-5-phenyl-1-pentene.

A solution of 10.25 g (36.7 mmol) of N-(t-butyloxycarbonyl)phenylalanine methyl ester in 60 ml of toluene was cooled to -78° C under inert atmosphere and treated dropwise over a period of 45 min with 35 ml (52.5 mmol) of diisobutylaluminum hydride in toluene. The resulting solution was stirred for 5 min, treated with 200 ml (200 mmol) of vinylmagnesium bromide, and allowed to warm to 0° C for 16 h. The solution was subsequently quenched cautiously with methanol, treated with aqueous Rochelle salts, stirred for a few min, and filtered. The residue was digested several times with ethyl acetate and filtered; and the combined filtrates were washed with saturated brine, dried over MgSO4, and concentrated. Silica gel chromatography using 20% ethyl acetate in hexane gave 5.46 g (54%) of the pure desired compound.

B. 4-Benzyl-3-(t-butyloxycarbonyl)-2,2-dimethyl-5-vinyloxazolidine.

A solution of 5.00 g (18.0 mmol) of the resultant compound of Example 36A and 17 ml (180 mmol) of 2-methoxypropene in 50 ml of dichloromethane was cooled to 0° C and treated with 0.21 g (0.83 mmol) of pyridinium p-toluenesulfonate. After several h at ambient temperature, the solution was treated with aqueous $NaHCO_3$, extracted with dichloromethane, dried over $MgSO_4$, and concentrated. Flash chromatography using 8% ethyl acetate in hexane gave 5.29 g (92%) of the desired compound as an oil.

C. 4-Benzyl-3-(t-butyloxycarbonyl)-2,2-dimethyloxazolidine-5-carboxaldehyde.

A solution of 5.28 g (16.7 mmol) of the resultant compound of Example 36B in 60 ml of dichloromethane and 30 ml of methanol was cooled to -78° C and treated with a stream of ozone in air until a blue color persisted. Dry nitrogen was bubbled through the solution until the blue color was discharged, and the resulting solution was transferred via cannula to a precooled (-45° C) suspension of 4.5 g of zinc metal in 4.5 ml of acetic acid, 100 ml of water, and 100 ml of methanol. The resulting mixture was stirred for 5 min, allowed to warm to ambient temperature over 2.5 h, quenched with saturated brine, extracted twice with dichloromethane, dried over $MgSO_4$, and concentrated. Flash chromatography using 30% ethyl acetate in hexane gave 4.41 g (83%) of the desired compound as an oil which crystallized. ^1H NMR ($CDCl_3$) δ 1.52 (s, 9 H), 1.54 (br, 6 H), 2.8 (br, 1 H), 3.3 (br, 1 H), 4.19 (br, 1 H), 4.42 (br, 1 H), 7.2-7.35 (m, 5 H), 9.65 (br, 1 H). Mass spectrum: $(M+H)^+ = 320$.

D. (cis)-Methyl 3-(4-Benzyl-3-(t-butyloxycarbonyl)-2,2-dimethyloxazolidin-5-yl)propenoate.

A suspension of 0.21 g (5.2 mmol) of sodium hydride (60% dispersion in mineral oil) in 15 ml of dry tetrahydrofuran was cooled to 0° C, treated with 1.52 g (4.8 mmol) of bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate in 5 ml of tetrahydrofuran, stirred for 10 min at 0° C, treated with a solution of 1.0 g (3.13 mmol) of the resultant compound of Example 36C in 5 ml of tetrahydrofuran, and stirred at ambient temperature for 1 h. The resulting solution was quenched with aqueous NH_4Cl, extracted with ether, washed with saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography using 15% ethyl acetate in hexane gave 0.82 g (69%) of the desired compound. Mass spectrum: $(M+H)^+ = 376$.

E. (cis)-3-(4-Benzyl-3-(t-butyloxycarbonyl)-2,2-dimethyloxazolidin-5-yl)propenoic Acid.

A solution of 218 mg (0.58 mmol) of the resultant compound of Example 36D in 4.6 ml of dioxane was treated with 2.3 ml (1.2 mmol) of. 0.5M aqueous lithium hydroxide. After 2 h, the solution was diluted with chloroform, acidified with 1 N HCl, partitioned, and the aqueous layer was washed with additional chloroform. The combined organic layers were dried over $MgSO_4$ and concentrated to give the desired compound as a colorless oil.

F. (cis)-N-(3-Methylbutyl)-3-(4-benzyl-3-(t-butyloxycarbonyl)-2,2-dimethyl-oxazolidin-5-yl)propenamide.

According to the mixed anhydride procedure of Example 6F, the resultant compound of Example 36E was coupled to isoamylamine to give 251 mg (100%) of the desired compound as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (d, J = 7 Hz, 6 H), 1.41 (t, J = 7 Hz, 2 H), 1.51 (s, 9 H), 1.57 (s, 6 H), 1.62 (heptet, J = 7 Hz, 1 H), 2.9-3.4 (m, 4 H), 3.96 (m, 1 H), 5.20 (m, 1 H), 5.7-6.1 (m, 3 H), 7.15-7.3 (m, 5 H). Mass spectrum: $(M+H)^+$ = 431.

G. (cis)-N-(3-Methylbutyl)-5-amino-4-hydroxy-6-phenyl-2-hexenamide.

A solution of 48 mg (0.11 mmol) of the resultant compound of Example 36F in 1 ml of dichloromethane was treated with 1 ml of trifluoroacetic acid. After being stirred for 1.75 h, the solution was concentrated in vacuo, taken up in 3 ml of 2:1 tetrahydrofuran:water, stirred for 45 min, treated with solid K_2CO_3, extracted with chloroform, dried over $MgSO_4$, and concentrated to give 21 mg (64%) of the desired compound. ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 7 Hz, 6 H), 1.43 (m, 2 H), 1.63 (heptet, J = 7 Hz, 1 H), 2.9-3.1 (m, 3 H), 3.33 (m, 2 H), 4.50 (m, 1 H), 5.36 (dd, J = 12, 2 Hz, 1 H), 5.43 (br, 1 H), 6.22 (dd, J = 12, 6 Hz, 1 H), 7.2-7.35 (m, 5 H). Mass spectrum: $(M+H)^+$ = 291.

Example 37

(cis)-N-(3-Methylbutyl)-5-(acetylamino)-4-hydroxy-6-phenyl-2-hexenamide.

A solution of 28.2 mg (0.092 mmol) of the resultant compound of Example 36G in 1 ml of dichloromethane was cooled to 0° C and treated sequentially with 0.010 ml (0.092 mmol) of 4-methylmorpholine and 0.087 ml (0.092 mmol) of acetic anhydride. After being stirred at ambient temperature for 1 h, the solution was partitioned between dichloromethane and water, dried over Na_2SO_4, and concentrated. Flash chromatography using 5% methanol in chloroform gave the desired compound (R_f 0.15, 5% methanol in chloroform). ^{1}H NMR ($CDCl_3$) δ 0.92 (d, J = 7 Hz, 6 H), 1.42 (q, J = 7 Hz, 2 H), 1.62 (heptet, J = 7 Hz, 1 H), 1.94 (s, 3 H), 2.92 (dd, J = 13, 7 Hz, 1 H), 2.99 (dd, J = 13, 5 Hz, 1 H), 3.32 (m, 2 H), 4.38 (m, 1 H), 4.43 (m, 1 H), 5.74 (dd, J = 12, 2 Hz, 1 H), 5.75 (br, 1 H), 6.07 (br, 1 H), 6.13 (dd, J = 12, 5 Hz, 1 H), 6.90 (d, J = 4 Hz, 1 H), 7.2-7.35 (m, 5 H). Mass spectrum: $(M+H)^+$ = 333.

Example 38

2,4-Bis-(((N,N-dimethylamino)sulfamoyl)amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 12B (0.1 mmol) was dissolved in 1 ml of dichloromethane and treated sequentially with 0.5 mmol of triethylamine and 0.2 mmol of (N,N-dimethyl)aminosulfamoyl chloride. After being stirred for 3 h, extractive workup gave the desired compound.

Example 39

2,4-Bis-(N-(aminocarbonyl)amino)-1,5-diphenyl-3-hydroxypentane.

A solution of 0.1 mmol of the resultant compound of Example 12B and 0.2 mmol of sodium hydroxide in 1 ml of water was treated with 0.3 mmol of potassium cyanate. After being heated to 60° C for 1 h, the solution was cooled, extracted with chloroform, dried over Na_2SO_4, and concentrated to give the desired compound.

Example 40

Di-(2-phenylethyl)phosphinic Acid.

The resultant compound of Example 9 (250 mg, 0.97 mmol) was added to 10 ml of 5.25% sodium hypochlorite. The resulting solution was stirred vigorously for 1 h, acidified, extracted with chloroform, washed with 1 N HCl and saturated brine, dried over $MgSO_4$, and concentrated in vacuo to give 217 mg (82%) of the desired compound (R_f 0.12, 20% methanol in chloroform) as a glass. ^1H NMR ($CDCl_3$) δ 2.0-2.1 (m, 4 H), 2.9-3.0 (m, 4 H), 7.15-7.4 (m, 10 H). Mass spectrum $(M+H)^+$ = 275.

Example 41

A. 3-(Azidomethyl)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 10C with 242 mg (0.96 mmol) of the resultant compound of Example 16B gave, after silica gel chromatography using 16% ethyl acetate in hexane, 259 mg (84%) of the desired compound. ^1H NMR ($CDCl_3$) δ 1.78 (s, 3 H), 1.90 (m, 4 H), 2.69 (m, 4 H), 3.41 (s, 2 H), 7.2-7.35 (m, 10 H). Mass spectrum: $(M+NH_4)^+$ = 313.

B. 3-(Aminomethyl)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 11 with 158 mg (0.536 mmol) of the resultant compound of Example 41A gave, after silica gel chromatography using 2.5% methanol/2% isopropylamine in chloroform, 116 mg (81%) of the desired compound (R_f 0.36, 2.5% methanol/2% isopropylamine in chloroform) as a white solid, m.p. 104-106° C. ^1H NMR ($CDCl_3$) δ 1.1-1.5 (br, 2 H), 1.81 (m, 4 H), 2.70 (m, 6 H), 7.15-7.35 (m, 10 H). Mass spectrum: $(M+H)^+$ = 270.
Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 83.56; H, 8.99; N, 5.88.

Example 42

2,8-Dimethyl-5-hydroxynonane

A solution of 5.63 g (33 mmol) of 2,8-dimethylnonan-5-one in 150 ml of methanol was cooled to 0° C and treated with 0.8 g (21 mmol) of sodium borohydride. After 1 h, the solution was quenched with 1 N HCl; diluted with 1:1 hexane/ether; washed sequentially with 1 N NaOH, water, and saturated brine; dried over $MgSO_4$; and concentrated in vacuo. Flash chromatography using 10% ethyl acetate in hexane gave 2.30 g (40%) of the desired compound (R_f 0.36, 20% ethyl acetate in hexane) as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 7 Hz, 6 H), 0.89 (d, J = 7 Hz, 6 H), 1.1-1.6 (m, 10 H), 3.56 (m, 1 H).

Example 43

A. 2-Benzyl-2-ethoxycarbonyl-1,3-dithiane.

A solution of 3.0 g (15.6 mmol) of 2-ethoxycarbonyl-1,3-dithiane in 40 ml of dry tetrahydrofuran was cooled under inert atmosphere to -78° C and treated with 7.5 ml (15.6 mmol) of n-butyllithium. The resulting solution was warmed to -25° C, stirred for 20 min, recooled to -78° C, treated with 1.8 ml (15.6 mmol) of benzyl chloride, and stirred at ambient temperature for 16 h. After quenching with aqueous ammonium chloride, the mixture was extracted with ether, washed sequentially with water, aqueous sodium thiosulfate, and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using 5% ethyl acetate in hexane gave 3.9 g (88%) of the desired compound. ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3 H), 1.85 (qt, J = 14, 3 Hz, 1 H), 2.11 (dm, J = 14 Hz, 1 H), 2.69 (dt, J = 14, 4 Hz, 2 H), 3.23 (ddd, J = 14, 12, 3 Hz, 2 H), 3.38 (s, 2 H), 4.27 (q, J = 7 Hz, 2 H), 7.25-7.35 (m, 5 H). Mass spectrum $(M+NH_4)^+$ = 300.

B. Ethyl 2,2-Difluoro-3-phenylpropanoate.

A solution of 0.50 g (1.76 mmol) of the resultant compound of Example 43A in 15 ml of acetonitrile was cooled to 0° C and treated with a solution of 1.8 g (10.5 mmol) of N-bromosuccinimide in 15 ml of acetonitrile and 2 ml of water. After being stirred for 5 min, the solution was added to 1:1 hexane/dichloromethane, washed sequentially with aqueous sodium bisulfite/sodium bicarbonate, water, and saturated brine, dried over $MgSO_4$, and concentrated to give 0.30 g of crude ethyl 3-phenylpyruvate. The crude residue was taken up in 3 ml of dry dichloromethane, treated with 0.83 ml (6.3 mmol) of diethylaminosulfur trifluoride, and stirred at ambient temperature for 3 d. The resulting solution was cooled to 0° C, quenched cautiously with water, extracted with dichloromethane, washed sequentially with water, aqueous sodium bicarbonate, and saturated brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using 5% ethyl acetate in hexane gave 72 mg (25%) of the desired compound. ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3 H), 3.38 (t, J_{H-F} = 16 Hz, 2 H), 4.24 (q, J = 7 Hz, 2 H), 7.25-7.35 (m, 5 H). Mass spectrum $(M+NH_4)^+$ = 232.

C. 2,2-Difluoro-1,5-diphenyl-3-pentanone.

A solution of 70 mg (0.33 mmol) of the resultant compound of Example 43B in 3 ml of tetrahydrofuran was cooled to -78° and treated with 0.33 ml (0.33 mmol) of (2-phenylethyl)magnesium bromide (1 M in tetrahydrofuran). The resulting solution was allowed to warm to ambient temperature for 1 h, quenched with acetic acid in tetrahydrofuran, taken up in ethyl acetate, washed sequentially with aqueous ammonium chloride, water, and saturated brine, dried over $MgSO_4$, and concentrated. Flash chromatography using 2% ethyl acetate in hexane gave 5.2 mg (6%) of the desired compound (R_f 0.71, 20% ethyl acetate in hexane). ^1H NMR ($CDCl_3$) δ 2.92 (t, J = 7 Hz, 2 H), 3.31 (t, J = 16 Hz, 2 H), 4.38 (t, J = 7 Hz, 2 H), 7.1-7.35 (m, 10 H). Mass spectrum $(M+NH_4)^+$ = 292, $(M+NH_4+H_2O)^+$ = 308.

Example 44

Ethyl 2,2-Difluoro-3-hydroxy-5-phenylpentanoate.

According to the procedure of Thaisrivongs et. al. (*J. Med. Chem.*, **1986**, *29*, 2080), ethyl bromodifluoroacetate was condensed with hydrocinnamaldehyde to give the desired compound.

Example 45

2,2-Difluoro-3-hydroxy-5-phenylpentanoic Acid.

Using the procedure of Example 6E with the resultant compound of Example 44 gave the desired compound.

Example 46

N-(3-Methylbutyl)-2,2-difluoro-3-hydroxy-5-phenylpentanamide.

Using the procedure of Example 6F with the resultant compound of Example 45 gave the desired compound.

Example 47

N-(3-Methylbutyl)-2,2-difluoro-3-oxo-5-phenylpentanamide.

According to the procedure of Thaisrivongs et. al. (*J. Med. Chem.*, 1986, *29*, 2080), the resultant compound of Example 46 was treated with dimethylsulfoxide and oxalyl chloride to give the desired compound.

Example 48

Dibenzyl 5,9-Diaza-6,8-dibenzyl-4,10-dioxo-7-hydroxy-3,3,11,11-tetramethyltridecanedicarboxylate.

The resultant compound of Example 12 (0.1 mmol) was dissolved in 1 ml of dichloromethane and treated sequentially with 0.5 mmol of triethylamine and 0.2 mmol of 3-benzyloxycarbonyl-2,2-dimethyl-propanoyl chloride (Matsushita, et. al., Heterocycles, 22, 1403 (1984). After being stirred for 3 h, extractive workup gave the desired compound.

Example 49

5,9-Diaza-6,8-dibenzyl-4,10-dioxo-7-hydroxy-3,3,11,11-tetramethyltridecanedicarboxylic Acid.

Using the procedure of Example 11 with the resultant compound of Example 48 gave the desired compound.

Example 50

1,3-Di-(4-nitrophenoxy)-2-propanol.

A solution of 1 g (7.2 mmol) of 4-nitrophenol, 0.28 ml (3.6 mmol) of epichlorohydrin, and 0.16 g (3.96 mmol) of sodium hydroxide in 2 ml of dimethylformamide was heated at 110° C for 1 h. The solvent was removed in vacuo, and the residue was purified by flash chromatography using chloroform to give 0.97 g (81%) of the desired compound (R_f 0.42, 40% ethyl acetate in chloroform). ^{1}H NMR ($CDCl_3$) δ 2.54 (d, 5 Hz, 1 H), 4.28 (dd, J = 10, 6 Hz, 2 H), 4.29 (dd, J = 10, 5 Hz, 2 H), 4.50 (br sextet, J = 6 Hz, 1 H), 7.0-7.05 (m, 4 H), 8.2-8.3 (m, 4 H). Mass spectrum $(M+NH_4)^+$ = 352.

Example 51

1,5-Diphenyl-3-((methoxy)methoxy)pentane.

A solution of 101 mg (0.42 mmol) of 1,5-diphenyl-3-pentanol, 0.18 ml (1.0 mmol) of ethyldiisopropylamine, and 0.063 ml (0.84 mmol) of chloromethyl methyl ether in 1 ml of dichloromethane was allowed to stand for 16 h. The resulting solution was taken up in ethyl acetate, washed sequentially with 10% aqueous citric acid, water, and saturated sodium bicarbonate, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography using 10% ethyl acetate in hexane gave 109 mg (92%) of the desired compound (R_f 0.51, 25% ethyl acetate in hexane) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.88 (m, 4 H), 2.70 (m, 4 H), 3.44 (s, 3 H), 3.64 (pentet, J = 6 Hz, 1 H), 4.70 (s, 2 H), 7.15-7.3 (m, 10 H). Mass spectrum $(M+NH_4)^+$ = 302.

Example 52

A. 2,2-Di-(3-phenylpropyl)-1,3-dithiane.

A solution of 1.0 g (4.2 mmol) of 2-(3-phenylpropyl)-1,3-dithiane in 25 ml of dry tetrahydrofuran was cooled to -78° C and treated with 3.23 ml (4.2 mmol) of *sec*-butyllithium. The resulting solution was stirred at -25° C for 20 min, recooled to -78° C, and treated with 0.64 ml (4.2 mmol) of 1-bromo-3-phenylpropane. After being stirred at -78° C for 15 min, the solution was allowed to stir overnight at ambient temperature. The solution was partitioned between ether and aqueous ammonium chloride, and the organic layer was washed sequentially with water, 1 M sodium bisulfite, and saturated brine, dried over $MgSO_4$, and concentrated in vacuo to give the desired compound. ^{1}H NMR ($CDCl_3$) δ 1.65-1.9 (m, 9 H), 2.18 (m, 1 H), 2.55-2.75 (m, 6 H), 2.78 (t, J = 8 Hz, 1 H), 3.40 (t, J = 6 Hz, 1 H), 7.1-7.35 (m, 10 H). Mass spectrum $(M+H)^+$ = 357.

B. 1,7-Diphenylheptan-4-one.

A solution of the resultant compound of Example 52A (1.6 g (4.5 mmol) in 20 ml of acetonitrile was cooled to 0° C and treated dropwise with a solution of 4.8 g (27 mmol) of N-bromosuccinimide in 15 ml of acetonitrile and 15 ml of water. The resulting solution was stirred for 1.5 h, extracted with dichloromethane, washed sequentially with 1 M sodium bisulfite, aqueous sodium bicarbonate, and saturated brine; dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography using 7% ethyl acetate in hexane gave 0.56 g

(93%) of the desired compound (R_f 0.33, 10% ethyl acetate in hexane) as an oil. ^1H NMR ($CDCl_3$) δ 1.90 (pentet, J = 7 Hz, 4 H), 2.39 (t, J = 7 Hz, 4 H), 2.61 (t, J = 7 Hz, 4 H), 7.15-7.3 (m, 10 H). Mass spectrum $(M+H)^+$ = 267.

Example 53

1,7-Diphenylheptan-4-ol.

Using the procedure of Example 42 with the resultant compound of Example 52 gave, after silica gel chromatography using 15% ethyl acetate in hexane, the desired compound (R_f 0.23, 30% ethyl acetate in hexane) as an oil. ^1H NMR ($CDCl_3$) δ 1.4-1.8 (m, 8 H), 2.62 (br t, 4 H), 3.63 (m, 1 H), 7.15-7.3 (m, 10 H). Mass spectrum $(M + NH_4)^+$ = 286.

Example 54

A. (Z)-(4-(t-Butyldimethylsilyloxy)-6-phenyl-2-hexenoyl)-Val-Val Amide.

A solution of the resultant compound of Example 6E (57 mg, 0.18 mmol) and 0.022 ml of 4-methylmorpholine in 3 ml of dichloromethane was cooled to 0 °C and treated with 0.026 ml (0.19 mmol) of isobutyl chloroformate. The resulting solution was stirred for 10 min, treated with a solution of 41 mg (0.19 mmol) of H-Val-Val-NH_2 in 1.5 ml of dimethylformamide, and stirred at ambient temperature for 2 h. The solution was subsequently diluted with ethyl acetate, washed sequentially with 10 % aqueous citric acid and aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. Flash chromatography using 60% ethyl acetate in chloroform gave 53 mg (57%) of the desired compound as a 1:1 mixture of diastereomers.

B. (Z)-(4-Hydroxy-6-phenyl-2-hexenoyl)-Val-Val Amide.

A solution of 13 mg (0.025 mmol) of the resultant compound of Example 54A in 0.5 ml of tetrahydrofuran was treated with 0.065 ml (0.065 mmol) of tetra-n-butylammonium fluoride (1 M in tetrahydrofuran). After being stirred for 16 h, the solution was concentrated in vacuo. Flash chromatography using 7.5% methanol in chloroform gave the desired compound, m.p. 147-149 °C, as a 1:1 mixture of diastereomers (R_f 0.15, 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+$ = 403.
Anal. Calcd. for $C_{22}H_{33}N_3O_4 \cdot 0.5H_2O$: C, 64.05; H, 8.31; N, 10.19. Found: C, 63,84; H, 7.65; N, 10.06.

Example 55

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

A solution of 39 mg (0.16 mmol) of Cbz-Val-OH, 52 mg (0.14 mmol) of the resultant compound of Example 11, and 23 mg (0.17 mmol) of 1-hydroxybenzotriazole in 2 ml of dimethylformamide was treated with 0.019 ml (0.17 mmol) of 4-methylmorpholine, cooled to 0 °C, and treated with 33 mg (0.17 mmol) of N-ethyl-N'-(dimethylaminopropyl)carbodiimide hydrochloride. After being stirred at ambient temperature overnight, the solution was diluted with ethyl acetate, washed sequentially with 10% citric acid, water, and aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. Separation of the desired compounds by

flash chromatography using methanol in chloroform gave 80 mg (95%) of the desired compound (R_f 0.40, 10% methanol in chloroform) as a white solid, m.p. 187-187.5° C. Mass spectrum $(M+H)^+$ = 604.

Example 56

A. 2-Amino-4-azido-1,5-diphenyl-3-hydroxypentane Hydrochloride.

The resultant compound of Example 10C (25 mg, 0.063 mmol) was treated with 1 ml of 4 M HCl in dioxane, stirred for 0.5 h at ambient temperature, and concentrated in vacuo to give the desired compound.

Example 57

Acetyl-Val-Val Amide of 2-Amino-4-azide-1,5-diphenyl-3-hydroxypentane.

A solution of 18 mg (0.069 mmol) of Ac-Val-Val-OH, 0.063 mmol of the resultant compound of Example 56, and 10 mg (0.076 mmol) of 1-hydroxybenzotriazole in 0.5 ml of dimethylformamide was treated sequentially with 0.015 ml (0.14 mmol) of 4-methylmorpholine and 15 mg (0.076 mmol) of N-ethyl-N'-(dimethylaminoethyl)carbodiimide. After being stirred at ambient temperature overnight, the solution was diluted with ethyl acetate, washed sequentially with aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated in vacuo to give the desired compound.

Example 58

(2N)-Acetyl-Val-Val Amide of 2,4-Diamino-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 11 with 0.063 mmol of the resultant compound of Example 57 gave, after silica gel chromatography using 7.5% methanol in chloroform, 15.3 mg (48%) of the desired compound.

Example 59

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

A solution of 8.5 mg (0.033 mmol) of Ac-Val-Val-OH, 15.3 mg (0.030 mmol) of the resultant compound of Example 58, and 8 mg (0.059 mmol) of 1-hydroxybenzotriazole in 1 ml of dimethylformamide was treated sequentially with 0.0045 ml (0.04 mmol) of 4-methylmorpholine and 6.5 mg (0.034 mmol) of N-ethyl-N'-(dimethylaminoethyl) carbodiimide. After being stirred at ambient temperature overnight, the solution was diluted with ethyl acetate, washed sequentially with 10% aqueous citric acid, aqueous $NaHCO_3$ and water, and concentrated in vacuo to a solid which was triturated with 1:1 chloroform:methanol, filtered, washed with 1:1 chloroform:methanol, and air-dried to give the desired compound as a white solid, m.p. 271-272.5° C. Mass spectrum $(M+H)^+$ = 751.

Anal. Calcd. for $C_{41}H_{62}N_6O_7 \cdot H_2O$: C, 64.04; H, 8.39; N, 10.93. Found: C, 63.89; H, 8.02; N, 10.82.

Example 60

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

A solution of the resultant compound of Example 59 (0.056 mmol) in 10 ml of acetone was cooled to 0° C and treated with 5 drops of aqueous chromic acid. After 1.25 h, the solution was quenched with 2-propanol and aqueous $NaHCO_3$, filtered through Celite, extracted with 10% methanol in chloroform, and concentrated in vacuo. Flash chromatography using 7.5% methanol in chloroform gave 3.7 mg (9%) of the desired compound (R_f 0.39, 10% methanol in chloroform). Mass spectrum $(M+H)^+$ = 749.

Example 61

A. 4-Azido-2-(t-butyloxycarbonylamino)-1,5-diphenyl-3-pentanone.

Using the procedure of Example 60 with the resultant compound of Example 5C gave the desired compound.

B. 4-Azido-2-(t-butyloxycarbonylamino)-1,5-diphenyl-3-methylenepentane.

Using the procedure of Example 16A with the resultant compound of Example 61A gave the desired compound.

C. 2-Amino-4-azido-1,5-diphenyl-3-methylenepentane Hydrochloride.

Using the procedure of Example 56 with the resultant compound of Example 61B gave the desired compound.

D. Cbz-Val Amide of 2-Amino-4-azido-1,5-diphenyl-3-methylenepentane.

Using the procedure of Example 55 with the resultant compound of Example 61C gave the desired compound.

E. Cbz-Val Amide of 3-Amino-2-(1-azido-2-phenylethyl)-4-phenyl-1-butene-1,2-epoxide.

Using the procedure of Example 16B with the resultant compound of Example 61D gave the desired compound.

Example 62

5-((N-Acetyl-valinyl-valinyl)amino)-2-(N-benzylamino)-3,4-dihydroxy-1,6-diphenyl-3-hexane.

A solution of 10 mg (0.04 mmol) of Ac-Val-Val-OH, 0.039 mmol.of the resultant compound of Example 19, and 6 mg (0.044 mmol) of 1-hydroxybenzotriazole in 1 ml of dichloromethane and 0.4 ml of dimethylformamide was treated with 0.009 ml (0.08 mmol) of 4-methylmorpholine, cooled to 0° C, and treated with 9 mg (0.047 mmol) of N-ethyl-N'-(dimethylaminoethyl)carbodiimide. After being stirred at ambient temperature overnight, the solution was diluted with ethyl acetate, washed sequentially with aqueous $NaHCO_3$ and water, dried over Na_2SO_4, and concentrated in vacuo. Separation of the desired compounds by flash chromatography using 6% methanol in chloroform gave 3.0 mg (13%) of the less polar diastereomer (R_f 0.33, 10% methanol in chloroform), m.p. 154-156° C, and 4.1 mg (17%) of the more polar diastereomer (R_f 0.28), m.p. 121-124° C. Mass spectrum (for each diastereomer): $(M+H)^+$ = 631.

Example 63

Cbz-val Amide of 2-Amino-4-azido-1,5-diphenyl-3-hydroxy-3-(hydroxymethyl)pentane.

Using the procedure of Example 17B with the resultant compound of Example 61D gave the desired compound.

Example 64

A. 2,2-Dimethyl-4,5-di-(1-hydroxy-2-phenylethyl)-1,3-dioxolane.

According to the procedure of Achmatowicz and Wicha (*Tetrahedron Lett.*, 1987, *28*, 2999) the resultant compound of Example 23 was treated with sodium borohydride in ethanol to give the desired compound as a mixture of stereoisomers.

B. 2,2-Dimethyl-4,5-di-(1-(Cbz-valinyl)oxy-2-phenylethyl)-1,3-dioxolane.

Using the procedure of Example 55 with the resultant compound of Example 64B and replacing 1-hydroxybenzotriazole with 4-dimethylaminopyridine gave the desired compound.

C. 2,5-Di-(Cbz-valinyl)oxy-3,4-dihydroxy-1,6-diphenylhexane.

The resultant compound of Example 64C was treated with 1 ml of 80% aqueous acetic acid, heated at reflux for 5 min, allowed to cool, and concentrated in vacuo to give the desired compound.

Example 65

2-(t-Butyloxycarbonylamino)-4-(Cbz-leucinyl-asparaginylamino)-1,5-diphenyl-3-hydroxypentane.

Using the procedure of Example 55 but replacing Cbz-Val-OH with Cbz-Leu-Asn-OH gave, after silica

gel chromatography using methanol/ chloroform, the desired compound (R_F 0.4; 2.5% methanol/ 2% isopropylamine/chloroform) in 98% yield, m.p. 192-193.5° C. Mass spectrum $(M+H)^+$ = 732.
Anal. Calcd for $C_{40}H_{53}N_5O_8$: C, 65.64; H, 7.30; N, 9.57. Found: C, 65.31; H, 7.43; N, 9.52.

Example 66

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

Using the procedure of Example 55 but replacing Cbz-Val-OH with Cbz-Asn-OH gave, after silica gel chromatography using methanol/ chloroform, the desired compound (R_F 0.4; 2.5% methanol/ 2% isopropylamine/chloroform) in 7-4% yield, m.p. 216-217° C. Mass spectrum $(M + H)^+$ = 619.

Example 67

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

Using the procedure of Example 11 with the resultant compound of Example 66 gave, after silica gel chromatography using methanol/ isopropylamine/ chloroform, the desired compound (R_F 0.3; 2.5% methanol/ 2% isopropylamine/ chloroform) in 95% yield. Mass spectrum $(M+H)^+$ = 519.

Example 68

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

Using the procedure of Example 55 but replacing Cbz-Val-OH with Cbz-Asn-OH and replacing the resultant compound of Example 11 with the resultant compound of Example 67 gave, after silica gel chromatography using methanol/ chloroform, the desired compound (R_F 0.4; 2.5% methanol/ 2% isopropylamine/ chloroform) in 75% yield, m.p. 234-236° C (dec). Mass spectrum $(M+H)^+$ = 767.
Anal. Calcd for $C_{41}H_{46}N_6O_9 \cdot 0.75H_2O$: 63.10; H, 6.14; N, 10.77. Found: C, 63.03; H, 6.03; N, 10.50.

Example 69

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

Using the procedure of Example 56 with the resultant compound of Example 55 gave, after silica gel chromatography using methanol/ isopropylamine/ chloroform, the desired compound (R_F 0.3; 2.5% methanol/ 2% isopropylamine/ chloroform) in 100% yield, m.p. 158-160° C. Mass spectrum $(M+H)^+$ = 504.

Example 70

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

Using the procedure of Example 55 but replacing the resultant compound of Example 11 with the resultant compound of Example 69 gave, after silica gel chromatography using methanol/ chloroform, the desired compound (R_F 0.4; 2.5% methanol/ 2% isopropylamine/ chloroform) in 98% yield. m.p. 198-200° C. Mass spectrum $(M+H)^+$ = 737.
Anal. Calcd. for $C_{43}H_{52}N_4O_7 \cdot 0.5H_2O$: C, 69.24; H, 7.16; N, 7.51. Found: C, 69.40; H, 7.29; N, 7.47.

Example 71

A. N-Boc-valinyl-valine benzyl ester.

Boc-Val-OH (2.86 g, 13.2 mmol) was coupled to valine benzyl ester p-toluenesulfonate (5.0 g, 13.2 mmol) using the procedure of Example 55 to give 5.41g, (100%) of the desired product (R_F 0.15; 20% ethyl acetate in hexane) as a colorless gum. Mass spectrum $(M+H)^+$ = 407.

B. N-(5-Carbomethoxypentanoyl)-valinyl-valine benzyl ester.

The resultant compound of Example 71A (0.50 g, 1.23 mmol) was deprotected according to the procedure of Example 56 and coupled to adipic acid monomethyl ester (0.21 g, 1.28 mmol) using the mixed anhydride procedure of Example 54A to give, after flash chromatography using 40% ethyl acetate in chloroform, 0.53 g (96%) of the desired compound.

C. N-(5-Carbomethoxypentanoyl)-valinyl-valine.

A mixture of the resultant compound of Example 71B (0.53 g, 1.18 mmol) and 100 mg of 10% palladium on carbon in 30 ml of methanol was stirred under one atmosphere of hydrogen. After 5 h, the mixture was filtered through Celite and concentrated to give 0.40 g (93%) of the desired compound as a solid.

D. 2-Azido-4-((5-carbomethoxypentanoyl)-valinyl-valinyl)amino-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 71C (91 mg, 0.25 mmol) was coupled to the resultant compound of Example 56 (0.25 mmol) using the carbodiimide coupling procedure of Example 55 to give, after flash chromatography using 60% ethyl acetate in chloroform, 104 mg (64%) of the desired compound (R_f 0.32, 75% ethyl acetate in chloroform). Mass spectrum $(M+H)^+$ = 637.

Example 72

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

Using the procedure of Example 11 with the resultant compound of Example 71D gave, after flash chromatography using 5% methanol in chloroform, the desired compound (R_f 0.28, 10% methanol in

chloroform) in 63% yield. Mass spectrum $(M+H)^+$ = 611.
Anal. Calcd. for $C_{34}H_{50}N_4O_6 \cdot 4H_2O$: C, 59.80; H, 8.56; N, 8.20. Found: C, 60.08; H, 7.36; N, 8.21.

Example 73

A. N-(6-(Benzyloxycarbonylamino)hexanoyl)-valinyl-valine methyl ester.

N-(6-(Benzyloxycarbonylamino)hexanoic acid was coupled to Val-Val methyl ester using the mixed anhydride procedure of Example 54A to give the desired compound.

B. N-(6-(Benzyloxycarbonylamino)hexanoyl)-valinyl-valine.

The resultant compound of Example 73A was hydrolyzed according to the procedure of Example 6E to give the desired compound. Mass spectrum $(M+H)^+$ = 464.

C. 2-(N-(6-Benzyloxycarbonylamino)hexanoyl)-valinyl-valinyl-amino)-4-(N-(5-carbomethoxypentanoyl)-valinyl-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

The resultant compound of Example 73B (37 mg, 0.079 mmol) was coupled to the resultant compound of Example 72 (48 mg, 0.079 mmol) using the carbodiimide coupling procedure of Example 55 to give, after flash chromatography using 4% methanol in chloroform, 31 mg (37%) of the desired compound (R_f 0.19, 5% methanol in chloroform). Mass spectrum $(M+H)^+$ = 1056.
Anal. Calcd. for $C_{58}H_{85}N_7O_{11} \cdot 3.5H_2O$: C, 62.23; H, 8.28; N, 8.76. Found: 62.12; H, 7.33; N, 8.75.

Example 74

2-(N-(6-(Benzyloxycarbonylamino)hexanoyl)-valinyl-valinyl-amino)-4-(N-(5-carboxypentanoyl)-valinyl-valinyl-amino)-1,5-diphenyl-3-hydroxypentane.

A solution of 31 mg (0.029 mmol) of the resultant compound of Example 73C in 5 ml of dioxane was treated with 1 ml of 0.5 M aqueous lithium hydroxide. After being stirred for 24 h at ambient temperature, the solution was concentrated in vacuo, diluted with ethyl acetate and 1 M hydrochloric acid, stirred for 2 h, and separated. The organic phase was washed with water, allowed to evaporate slowly to a small volume. The mixture was then filtered to give the desired compound as a solid.

Example 75

Cbz-Val Amide of 3-Amino-2-hydroxy-5-methyl-1-phenoxyhexane.

Cbz-valine was coupled to 3-amino-2-hydroxy-5-methyl-1-phenoxyhexane (J. Med. Chem. 1987, *30*, 1609) using the carbodiimide coupling procedure of Example 55 to give the desired compound.

Example 76

Cbz-Val Amide of 3-Amino-2-hydroxy-5-methyl-1-(phenylthio)hexane.

Cbz-valine was coupled to 3-amino-2-hydroxy-5-methyl-1-(phenylthio)hexane (J. Med. Chem. **1987**, *30*, 1609) using the carbodiimide coupling procedure of Example 55 to give the desired compound.

Example 77

Cbz-Val Amide of 3-Amino-2-hydroxy-5-methyl-1-(phenylsulfonyl)hexane.

Cbz-valine was coupled to 3-amino-2-hydroxy-5-methyl-1-(phenylsulfonyl)hexane (J. Med. Chem. **1987**, *30*, 1609) using the carbodiimide coupling procedure of Example 55 to give the desired compound.

Example 78

A. 3-(Benzyloxycarbonylamino)-3-methylbutanoic Acid.

A solution of 2,2-dimethyl-3-carbomethoxypropionic acid (LeMaul, Bull. Soc. Chim. Fr., 828 (1965), 20 g, 0.125 mol), diphenylphospholrylazide (34.3 g, 0.125 mol) and triethylamine was heated in toluene (150 ml) at 100° C for 2 h. After cooling to 5° C, the toluene solution was washed successively with 0.5 M HCl, aqueous $NaHCO_3$ and brine. Evaporation of the dried solution gave a residue which was chromatographed on silica gel eluting with 60/40 hexaneether. There was obtained 13 g of methyl 3-isocyanato-3-methyl-butanoate as a mobile liquid. A solution of this material in toluene (20 ml) was treated with benzyl alcohol (13 ml) and the resulting mixture heated at reflux for 40 h. Evaporation of the toluene left a residue which was dissolved in methanol (125 ml) and then treated with a solution of NaOH (6.6 g, 0.165 mol) in 22 ml of water. After 5 h, the reaction mixture was partially evaporated, washed with ether and acidified with 6N HCl. Extraction with methylene chloride and evaporation gave 21 g of the desired product. NMR (300 MHz, $CDCl_3$): 1.42 (s,6H), 2.78 (s,2H), 5.08 (s,2H).

B. Cbz-((β,β-di-Me)-β-Ala)-Leu-OCH_3.

A 4.0 g sample of 3-benzyloxycarbonylamino-3-methylbutanoic acid was coupled to leucine methyl ester hydrochloride using the mixed anhydride procedure described in Example 6F. Purification of the crude product by silica gel chromatography gave the desired compound.

C. Cbz-((β,β-di-Me)-β-Ala)-Leu-OH.

To a 0° C solution of Cbz-((β,β-di-Me)-β-Ala)-Leu-OMe (3.63 mmol) in dioxane (15 ml) was added a solution of lithium hydroxide (0.174 g, 4.15 mmol) in water (7.5 ml). After stirring for 1 h at 0-5° C, the reaction mixture was diluted with cold water and extracted 2X with ether. The aqueous portion was acidified with 6N HCl and extracted with ether. The organic extract was washed with brine and evaporated to give the desired compound.